Conditional Selection of Contra- and Ipsilateral Forelimb Movements by the Dorsal Premotor Cortex in Monkeys

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Kurata K. Conditional selection of contra- and ipsilateral forelimb movements by the dorsal premotor cortex in monkeys. J Neurophysiol 103: 262–277, 2010. First published November 4, 2009; doi:10.1152/jn.91241.2008. It has been suggested that the dorsal premotor cortex (PMd) may contribute to conditional motor behavior. Thus when a selection is instructed by arbitrary conditional cues, it is possible that the unilateral PMd affects behavior, regardless of which arm, contra- or ipsilateral, is to be used. We examined this possibility by recording neuronal activity and injecting muscimol into the caudal PMd (PMdc) of monkeys while they were performing a reaching task toward visuospatial targets with either the right or left arm, as instructed by low-frequency or high-frequency tone signals. Following the injection of a small amount of muscimol (1 µL; 5 µg/µL) into the unilateral PMdc, monkeys exhibited two major deficits in behavioral performance: 1) erroneous selection of the arm not indicated by the instruction (selection errors) and 2) no movement initiation in response to a visuospatial target cue serving as a trigger signal for reaching within the reaction time limit (movement initiation errors). Errors were observed following unilateral muscimol injection into both right and left PMdc, although selection errors occurred with significantly greater frequency in the arm contralateral to the injection site. By contrast, movement initiation errors were more commonly observed in left-arm trials, regardless of whether the right or left PMdc was inactivated. Notably, errors rarely occurred following a ventral PM muscimol injection. These results suggest that the left and right PMdc cooperate to transform conditional sensory cues into appropriate motor output and can affect both contra- and ipsilateral body movement.

INTRODUCTION

We frequently make behavioral selections based on arbitrarily conditioned sensory cues, such as the colors of traffic lights. Although many brain areas participate in such sensorimotor integration, the dorsal premotor cortex (PMd) of monkeys has been demonstrated to play an important role in the selection and execution of conditional motor behavior guided by arbitrary color (Halsband and Passingham 1985; Kurata and Hoffman 1994; Kurata and Wise 1988; Passingham 1985a,b) and tone (Kurata 1993) cues. In response to conditional sensory (auditory or visual) signals that instruct forthcoming movements, a number of neurons in the PMd exhibit sustained changes in activity, termed set-related activity (Hoshi and Tanji 2006; Kurata and Wise 1988). Neurons in the PMd also exhibit movement-related activity in response to sensory (visual, auditory, and somatosensory) trigger signals for movement initiation (Kurata and Tanji 1986; Weinrich and Wise 1982). Further, when the PMd was reversibly inactivated by injection of muscimol, monkeys showed selective deficits in performing a motor task with conditional color cues instructing target locations (Kurata and Hoffman 1994). By contrast, the same monkeys did not exhibit such deficits following PMd injection when the same movements were instructed by visual cues directly indicating the target locations or when the ventral PM (PMv) was inactivated (Kurata and Hoffman 1994). In parallel to these findings in monkeys, the human PMd has been reported to be preferentially activated by visual and auditory instruction signals that were arbitrarily associated with motor responses (Iacoboni et al. 1998; Kurata et al. 2000). Although these studies focused on the involvement of the PMd in conditional motor behavior performed by an upper limb contralateral to the region, the PMd of both hemispheres could also be activated by the conditional cues, such as color and tone cues, especially when they are nonspatial and thus independent of hemispheric specificity in neural processing. Supporting this idea, the neurons in the PMd are known to be associated with forelimb movements not only contra- but also ipsilateral to the cerebral hemisphere in monkeys (Cisek et al. 2003; Hoshi and Tanji 2006) and humans (Iacoboni et al. 1998; Kurata et al. 2000).

Similar to the findings in the PMd, the PMv and the primary motor cortex (MI) also contain neurons with set- and movement-related activity related not only to contralateral but also to ipsilateral forelimb movements (Cisek et al. 2003; Evarts 1966; Hoshi and Tanji 2006; Kurata 2007). In contrast to the PMd, the PMv has been suggested to be involved more in processing visuospatial information for an impending forelimb movement (Hoshi and Tanji 2006; Kakei et al. 2001; Kurata 2007; Kurata and Hoshi 2002; Tanji et al. 1987) and in prism adaptation (Kurata and Hoshi 1999) than in conditional motor behavior (Kurata and Hoffman 1994). Recently, we examined the laterality of movement-related neuronal activity in the PMv and MI because laterality may indicate stages in the visuospatial transformation for reaching (Kurata 2007). We found that whereas neuronal activity closely related to motor coordinates (termed M-type) had a preference for reaching movements with the arm contralateral to the hemisphere where the activity was recorded, most of neuronal activity reflecting visual space (termed V-type) had less laterality. Accordingly, we suggest that the bilaterality of V-type neuronal activity does not necessarily contribute to motor control of both arms and that the activity may represent an earlier stage of the visuomotor transformation.

Consistent with the observed bilateral neuronal activity, the PMd and PMv in monkeys are reciprocally connected with various cortical motor areas, not only of the ipsilateral but also of the contralateral hemisphere (Boussaoud et al. 2005; Cavada
and Goldman Rakic 1989; Leichnetz 1986; Marconi et al. 2003; Zarei et al. 2006). In humans, it has been reported that transcranial magnetic stimulation of the PMd changes excitability of the PMd and MI of the contralateral hemisphere (Bestmann et al. 2008; Koch et al. 2006, 2007; Mochizuki et al. 2004), most likely via callosal connections (Di Lazzaro et al. 1999; Ferbert et al. 1992). Corresponding to these results, functional magnetic resonance imaging studies have demonstrated that the bilateral PMd was activated when conditional cues were applied to perform movements (Iacoboni et al. 1998; Kurata et al. 2000).

Although laterality of set- and movement-related neuronal activity in the MI, PMd, and PMv has been investigated using visuospatial cues (Cisek et al. 2003; Hoshi and Tanji 2006), it is not yet known whether neuronal firing in the PMd and PMv displays laterality when conditional auditory cues instruct selection of either the right or left arm. Furthermore, little is known regarding how lateralized neuronal activity contributes to conditional arm selection. We hypothesized that when instructions for arm selection are given conditionally by auditory cues, crucial information for the required behavior is processed in the PMd and may then be conveyed to the contralateral hemisphere, where final motor commands are generated to control the specified arm. Our first objective was to record and analyze the laterality of set- and movement-related activity in the PMd and PMv when conditional auditory cues were given to instruct which arm should be moved. These cues consisted of differently pitched tones emanating from the same locations and were considered appropriate as conditional cues, given that neuronal activity in PM neurons is affected not only by visuospatial cues and eye positions during task performances (Boussaoud and Wise 1993; Boussaoud et al. 1993; Pesaran et al. 2006), but also by auditory discrimination (Lemus et al. 2009). Tightly linked to the first aim, our second aim was to compare the behavioral effects of muscimol injection into either the PMd or PMv on conditional selection of the arm contra- or ipsilateral to the injected hemisphere. Muscimol, a potent γ-aminobutyric acid type A receptor agonist, was injected unilaterally into the PMd or PMv of the monkeys to examine whether focal, unilateral inactivation of one of the motor areas would affect the conditional selection of contra-, ipsi-, or bilateral forelimb movements. The optimal locations for muscimol injection were selected based on dense concentrations of neurons exhibiting reaching-related activity. In this study, we present data from two monkeys whose movement-related neuronal activity in the PMv and the MI has been reported elsewhere (Kurata 2007). However, the main body of data on neuronal activity in the PMd, on arm selection and on movement initiation errors before (including neuronal recording sessions) and after muscimol injection into the PMd and PMv, is reported here for the first time.

METHODS

Subjects and apparatus

All experiments were approved by the Animal Research Committee of Hirosaki University, Japan. Experiments were conducted in compliance with the Guide for the Care and Use of Mammals in Neuroscience and Behavioral Research by the Committee on Guidelines for the Use of Animals in Neuroscience and Behavioral Research (National Research Council, Washington, DC).

We used two male Japanese monkeys (Macaca fuscata, 5.5–8.2 kg). The two monkeys were the same monkeys 1 and 2 as in our previous study (Kurata 2007). The monkeys sat comfortably in a primate chair. Two key switches, made of 5 × 10-cm acrylic plates, were symmetrically placed at the ends of the right and left armrests to hold the keys. The keys and armrests were positioned 20 cm below the animal’s eyes. They faced a 21-in. cathode ray tube (CRT) screen. The screen was placed 30 cm away from the monkey’s eyes and the vertical center of the screen was aligned with the monkey’s head and body. The screen was covered with a transparent touch panel that monitored the position of the monkey’s hand on the screen by detecting local pressure. The position of the monkey’s hand on the touch screen was sampled at 500 Hz through an eight-channel, 12-bit A/D converter, and the data were stored on a laboratory computer. A loudspeaker was placed under the CRT screen for presentation of auditory cues. An apparatus with two pairs of 4 × 4-cm wedge prisms (10° to the left or right) was placed 6 cm away from the monkey’s eyes as described previously (Kurata 2007; Kurata and Hoshi 1999, 2002). Eye movements were monitored using an infrared oculometer system (R21CA, RMS, Hirosaki, Japan). The infrared light was presented by the oculometer and reflected by a half mirror placed in a 6-cm space between the monkey’s eyes and the prism holder. The monkeys were free to move their eyes at any time during a trial. An opaque barrier immediately below a spout for juice rewards blocked the view to their arms until a reaching arm was seen through the prisms and prevented the mirror from being displaced or broken by the monkeys.

Behavioral task

The monkeys were trained to make quick reaching movements toward a target with the right or left hand. A trial began when the monkey used both hands to depress the keys (Fig. 1B). Then, 500 ms after trial initiation, either a 300-Hz or 1-kHz tone was randomly selected and presented to instruct the monkey to prepare for a right or left arm movement, and the trials were termed Insc-R and Insc-L trials, respectively. Within 1.5–3.0 s after the auditory instruction signal (termed the preparation period), a blue rectangular target appeared on

![FIG. 1. Experimental design. A: cortical map showing the forelimb areas of the dorsal and ventral premotor cortices (PMd, PMv) and primary motor cortex (MI). AS, arcuate sulcus; CS, central sulcus. B: temporal sequence of behavioral events. In the trial, right-arm use for reaching was instructed by the low auditory cue (Insc-R trial). In each trial, there was an auditory instruction signal for either the right or left arm. After a preparation period, a visuospatial target was pseudorandomly selected from 9 possible locations that were common in the 3 prism conditions and it was presented to the monkeys in a behavioral sequence shown in B (see Fig. 1 in Kurata 2007 for the target locations). The presentation of the target served as a trigger signal (TS) for movement initiation. If the monkey initiated a movement using the instructed arm within reaction time limit (500 ms for neuronal recording sessions and 800 ms for muscimol injection sessions) and successfully hit the target on the screen, a drop of juice was given as a reward.](http://jn.physiology.org/)
the 21-in. monitor with a touch sensor; this served as a trigger signal (TS) to initiate a movement. If the monkey released the hold key with the instructed arm (movement onset) within 500 ms after target presentation (the reaction time limit during neuronal recording sessions), reached the touch screen within 500 ms of the movement onset, and hit the correct target, then a drop of juice (0.1 mL) was delivered as a reward. During muscimol injection sessions, the reaction time limit was set at 800 ms, given that reaction time was frequently longer than the preinjection control periods (see RESULTS). When the monkey released one or both of the hold keys during the preparation period before the target presentation or failed to release the key on the instructed side, the trial was aborted and the monkey was required to initiate a trial over again. The onset of arm movement was detected by the release of either the left or the right key. The reaction time (RT) was defined as the period between the appearance of the target and movement onset. The movement time (MT) was defined as the period between movement onset and contact with the screen by the instructed arm. The monkeys were outfitted with prisms that shifted the image of the target 10° to either the left or right, or were allowed to view the target normally. During each trial, the instruction signal for either a right- or left-arm movement was pseudorandomly selected and a target was also pseudorandomly selected from among nine visual locations that were common under the three prism conditions (cf. Fig. 1C of Kurata 2007). The task was performed in a block of 200 trials under each prism condition. During the trial block, data were evenly sampled for the nine target locations and the two arms.

**Surgery and neuronal and EMG recordings**

After completion of the behavioral training, the monkeys were surgically prepared under aseptic conditions using nitrous oxide and isoflurane anesthesia, following induction with ketamine hydrochloride (8 mg/kg, administered intramuscularly [im]) and atropine sulfate. Four head-restraining bolts and one rectangular stainless steel recording chamber (27 × 27 mm) were implanted in the skull over the left hemisphere of each monkey. The chamber was centered at anterior 12.0 mm and lateral 18.0 mm, according to the Horsley–Clarke stereotaxic frame. Antibiotics and analgesics were used to prevent postsurgical infection and pain. For monkey 1, another recording chamber was implanted in the skull over the right hemisphere after completion of neuronal recording and muscimol injection in the left hemisphere.

After complete recovery from the surgery (>7 days), we recorded neuronal activity in the PMd, PMv, and the MI (Fig. 1A) in each monkey during performance of the behavioral task. The monitored areas were selected based on the central and arcuate sulci, the superior precentral dimple, and the arcuate spur observed during surgery. We confirmed by histological reconstruction that the areas covered the proximal forelimb representations of the PMd, PMv, and MI (Genti-lucci et al. 1988; Kurata and Hoshi 2002; Kurata and Tanji 1986). For the single-unit recordings, we used glass-insulated Elgiloy microelectrodes (1.0–1.5 MΩ at 333 Hz) inserted through the dura mater using a hydraulic microdrive (MO95; Narishige, Tokyo). Electrode signals were amplified, filtered, and sorted (multichannel processor and multiprobe detector [MSD]; Alpha-Omega, Nazareth, Israel). The MSD was used to sort spikes, allowing up to three isolated neurons to be recorded simultaneously.

We also bilaterally sampled electromyographic (EMG) activity with wire electrodes from the anterior deltoid, trapezius, supraspinatus, infraspinatus, pectoralis major, rhomboid, thoracic paravertebral, biceps, and triceps brachii muscles. The EMG data were band-pass filtered between 20 Hz and 5 kHz and were sampled at 100 Hz through an A/D converter on a laboratory computer.

**Muscimol microinjection**

After completion of neuronal recording from the PMv, PMd, and MI, 1.0 μL of muscimol was injected into either the PMv or PMd in daily sessions. Injection sites were selected on the basis of the density of movement-related neurons with directional selectivity (see RESULTS). Muscimol injection was performed as in previously published work (Kurata and Hoffman 1994; Kurata and Hoshi 1999). Briefly, we prepared muscimol (concentration: 5 μg/μL; Sigma) dissolved in 0.1 M phosphate buffer (pH 7.4). Using an electric pump for microdialysis (CMA/100, Carnegie Medicin, Stockholm, Sweden), muscimol (1.0 μL) was injected at a rate of 0.1 μL/min through thin stainless steel tubing inserted into the unilateral hemisphere of the cerebral cortex by the same hydraulic microdrive used for the microelectrodes. The system enabled us to inject muscimol at known coordinates within the recording chamber.

**Neuronal and EMG data analysis**

Our database included only those neurons for which activity was stably recorded during >100 trials under each of the three prism conditions. The significance level of all statistical tests (Systat for Windows, version 8.0.2, SPSS, Chicago, IL) was P < 0.01, unless described otherwise. Raster displays and peri-event histograms with 20-ms bin width of recorded neuronal activity were aligned with the onsets of the auditory instruction signals and the onsets of contra- and ipsilateral arm movements for each target under each prism condition. To analyze neuronal activity during the preparation period, we determined the mean discharge rate and its SD during the preparation period (1.5–3.0 s) and during the interval between the trial initiation and the instruction signal onset (preinstruction control period, 0.5 s). If the neuron exhibited a sustained increase in activity following the instruction signal and the activity significantly differed from the preinstruction control period (ANOVA, P < 0.01), then the activity was defined as set related. We also statistically compared set-related activity following the auditory signals instructing the right and left forelimbs to examine laterality.

The data from the first 10 trials during adaptation to the prisms were not used for quantitative analysis of movement-related activity because it was essential to obtain data after readaptation to the prisms in each condition. To define movement-related neuronal activity, we calculated the mean discharge rate and the SD of the neuron during the RT and compared it with those of the same neuron during the interval of 0.5 to 1.5 s before target presentation (premovement control period). If the neuron increased its activity before movement onset after a target was presented and its activity exceeded 2.56 SD (P < 0.01) during the RT in at least two consecutive bins (40 ms) of at least three of the nine histograms in the no-prism condition, using the contra- or ipsilateral arm, then the activity was tentatively considered movement related. During recording, we also examined the visual response of the neurons. For this purpose, a visual stimulus identical to the target was presented in optionally selected trials under different prism conditions. The test visual stimulus was presented 200 ms after trial initiation for 100 ms at selected target positions where the neuron activity changed during the RT (see Kurata 2007 for details).

After the neuronal activity was judged to be movement related, the time when the activity first exceeded the threshold value was defined as the onset of neuronal activity. After the earliest onset of neuronal activity was obtained from the peri-event histogram, the mean discharge rate between the onset of neuronal activity and movement onset during the RT in each trial was calculated. When the neuronal activity did not exceed the threshold in the peri-event histogram, the mean discharge rate between target presentation and movement onset in each trial was calculated. The values during the RT were used for subsequence quantitative and statistical analyses. We also calculated the mean discharge rate during the MT and used the values for subsequent analyses.

Using the mean discharge rates during the preparation period, RT, and MT, we examined the latency of the neuronal activity. For set-related activity, data from equal numbers of Ins-R and Ins-L trials under the no-prism condition were used. For movement-related activity during RT
and MT, we first selected neuronal data from a comparable number of trials at each of nine target locations under the no-prism condition only and then combined the data from the different targets during either Ins-R or Ins-L trials for subsequent analyses. The values before and during arm movements contra- and ipsilateral to the recorded hemisphere (contra and ipsi, respectively) were used to calculate the laterality index (LI) to determine the selectivity of each neuronal activity

\[
LI = \frac{\text{Contra} - \text{Ipsi}}{\text{Contra} + \text{Ipsi}}
\]

An LI value of 1.0 indicates that the neuronal activity was associated with contralateral arm movements only. An LI value of \(-1.0\) shows movement-related neuronal activity immediately before and during ipsilateral arm movements only. Neuronal activity with an LI value of 0 is equally active immediately before and during contra- and ipsilateral arm movements. When the neuronal activity associated with contralateral movements is 50% greater than that associated with ipsilateral movements, the LI would be 0.20. Using ANOVA, we statistically compared laterality by examining the discharge rates during contra- versus ipsilateral movements for each neuron during the preparation period, RT, and MT, after matching sampling numbers for the targets and the arm used (see Figs. 3 and 4). Bilateral activity was defined as the situation in which there was no statistically significant difference in the discharge rate between contra- and ipsilateral forelimb movements (ANOVA, \(P > 0.01\)). When the neuronal activity showed a statistically significant difference (\(P < 0.01\)), the activity was as defined contra- or ipsilateral, depending on the positive or negative LI value, respectively. For each set- and movement-related activity, the contra- or ipsilateral arm that exhibited a higher absolute LI value during the sampling period was termed the preferred arm and the other, the nonpreferred arm. We rectified the digitized EMG activity and analyzed it in the same manner as the neuronal activity.

Behavioral analysis and terminology

The following five parameters of task performance were defined and analyzed statistically: 1) reaction time: the time between TS and movement onset (defined as the time when a key switch was released by the right or left hand); 2) movement time: the time between movement onset and first contact with the touch screen, when an instructed key was released; 3) premature movement: movement initiation during the preparation period before TS presentation; 4) selection error: key release (i.e., initiation of reaching) within the RT limit by a hand other than that signaled by the instruction; and 5) movement initiation error: no movement initiation in response to the TS during the RT limit: the monkey released neither the right nor the left key within the RT limit.

After the tubing for injection was inserted in a single location in the cerebral cortex, the parameters were sampled in the following periods: 1) immediately before injection (preinjection period, \(~30\) min), during which \(>100\) trials under each prism condition were recorded; and 2) during and immediately after injection (postinjection period, \(~60\) min), during which prism conditions were switched every \(100\) trials. The difference in each behavioral parameter between two of the three sampling periods was compared by ANOVA with Scheffé post hoc comparison.

**Histology**

When all the experiments were completed, electrolytic marking lesions were produced by passing \(20 \mu A\) of cathodal DC through the microelectrodes for 15 s. Nine or 10 days later, the monkeys were deeply anesthetized with pentobarbital (50 mg/kg, im) and were transcardially perfused with saline, followed by a fixative containing 3.7% formaldehyde in 0.1 M phosphate buffer (pH 7.4), followed by formalin solutions with 10 and 30% sucrose in 0.1 M phosphate buffer (pH 7.4). After marking the location of the recording chamber with five pins at known electrode coordinates, the brain was removed from the skull and photographed. Later, it was sectioned serially at 50 \(\mu m\) in the frontal plane using a freezing microtome.

**RESULTS**

**EMG activity during task performance**

EMG analyses showed that shoulder muscles were movement related, but no systematic change in activity was detected during the other task periods. Of the muscles recorded, the right and left anterior deltoid muscles were prime movers for reaching (see Table 1 of Kurata 2007). Figure 2 shows the EMGs of the right and left anterior deltoid muscles aligned at movement onset of the left and right arms in monkey 1. During preparation periods, activity of the two muscles was stable and did not exhibit constant changes. Immediately before reaching

<table>
<thead>
<tr>
<th>Monkey 1: L-hemisphere</th>
<th>Set</th>
<th>B</th>
<th>I</th>
<th>Mvt-RT</th>
<th>B</th>
<th>I</th>
<th>Mvt-MT</th>
<th>B</th>
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<tbody>
<tr>
<td>PMd</td>
<td>17</td>
<td>8</td>
<td>12</td>
<td>35</td>
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<td>22</td>
<td>29</td>
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<td>PMv</td>
<td>5</td>
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<td>0</td>
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<td>30</td>
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<td>31</td>
<td>16</td>
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<td>MI</td>
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<td>Monkey 1: R-hemisphere</td>
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<td>PMd</td>
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<td>Monkey 2: L-hemisphere</td>
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<td>7</td>
<td>28</td>
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<td>Three hemispheres</td>
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<td>PMd</td>
<td>38 (54)</td>
<td>17 (24)</td>
<td>16 (23)</td>
<td>63 (54)</td>
<td>14 (13)</td>
<td>28 (27)</td>
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<tr>
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<td>8 (11)</td>
<td>101 (54)</td>
<td>61 (32)</td>
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<td>23 (16)</td>
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<tr>
<td>MI</td>
<td>32 (48)</td>
<td>19 (29)</td>
<td>15 (23)</td>
<td>105 (61)</td>
<td>34 (20)</td>
<td>34 (20)</td>
<td>98 (67)</td>
<td>21 (14)</td>
<td>27 (18)</td>
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*Set, set-related activity; Mvt-RT and Mvt-MT, movement-related activity during reaction time and movement time, respectively. Numbers in parentheses indicate percentages of the classified activity in each area. The data of movement-related activity in the PMv and MI were taken were taken from two of three monkeys shown in Kurata (2007) are presented again for comparative purposes only.
movements during RT, the anterior deltoid muscle of the instructed arm changed its activity and the muscle was also active during MT. The laterality indexes (see METHODS) of the muscle were 0.82 and 0.76 during RT and 0.77 and 0.69 during MT in monkeys 1 and 2, respectively. The laterality index of other muscles ranged from −0.02 (paravertebral muscle) to 0.92 (pectoralis major; see Table 1 of Kurata 2007). In all the muscle activity we recorded, no constant change occurred during the preparatory period.

Set- and movement-related neuronal activity in the motor areas

Neuronal activity was recorded from 197, 294, and 268 neurons in the PMd, PMv, and MI, respectively, from three hemispheres of the two monkeys. Of these, 63 PMd, 99 PMv, and 73 MI neurons with set-related activity and 105 PMd, 191 PMv, and 173 MI neurons with movement-related activity were well isolated long enough for their classification by quantitative analyses (Table 1). Figure 3 shows three representative set-related activities recorded in the left PMd of monkey 1. The neuron in Fig. 3A increased activity following an auditory signal instructing contralateral (right) arm movements and the same neuron decreased its discharge rate when ipsilateral (left) arm movements were instructed. The difference in mean discharge rate of the set-related activity between the two preparation periods (right and left) was statistically significant (ANOVA, P < 0.01) and the set-related activity was defined as I-type. As shown in these representative neurons, we did not observe phasic short-latency activity in response to auditory signals (cue- or signal-related activity). Similar to set-related activity, movement-related activity was statistically classified as C-, B-, or I-type (Fig. 4). Table 1 shows numbers of C-, B-, and I-types of set- and movement-related neurons recorded in the PMd, PMv, and MI of the two monkeys.

Figure 5 shows histograms of the LI values of set- and movement-related activity classified as contra-, bi-, and ipsilateral activities in the PMd, PMv, and MI of the two monkeys (three hemispheres). A majority of the PMd and MI set-related activities were classified as C-type, whereas B-type set-related neurons comprised a majority in the PMv (Fig. 5, Table 1). Differences in the numbers of each classified set-related activity in the three motor areas of the hemispheres were statistically significant (Pearson’s chi-square test, P < 0.01). On the other hand, a majority of movement-related activity was classified as C-type during both RT and MT. The differences in the numbers of each classified movement-related activity in the three motor areas of the hemispheres were not statistically significant (Pearson’s chi-square test, P > 0.01). Figure 6 shows the histograms of magnitudes for C-, B-, and I-types of set- and movement-related activity in the three motor areas. The differences in each classified set- and movement-activity magnitude between the motor areas were not statistically significant (ANOVA, P > 0.01).

Location of neuronal activity and selection of muscimol injection sites

Figure 7 shows the two-dimensional distributions of set- and movement-related neurons in the PMd, PMv, and MI of the left hemisphere in monkey 1 (see also Fig. 8 of Kurata 2007 for movement-related activity in the PMv and MI of monkey 2). Neurons with set- and movement-related activity were distributed similarly in the PM and MI and formed two foci in the PM. One of them was located in the PMd, in a caudal region

FIG. 2. Electromyographic (EMG) activity (top and bottom parts for summed and individual activities in each panel, respectively) of the right and left anterior deltoid muscles of monkey 1. The EMG activities during Ins-R and Ins-L trials and the resultant histograms were aligned at movement onset of the right (right panels) or left arms (left panels). The anterior deltoid muscle was the primary muscle used for reaching. IS, instruction signal; TS, trigger signal; Hit, the first contact with the screen by the forelimb on the instructed side.
laterally adjacent to the superior precentral sulcus (SPS). Thus the main body of the location area should be termed the caudal PMd (PMdc) (Hoshi and Tanji 2006) lateral to the SPS, although a part of the PMdc immediately caudal to the genu of the arcuate sulcus was not included in this study (cf. Cisek et al. 2003; Hoshi and Tanji 2006; Luppino et al. 2001). Another focus was located in the PMv, caudal to the genu of the arcuate sulcus and lateral to the arcuate spur. We recorded a number of set-related neurons in the MI (Table 1), primarily located in its proximal representation. Figure 7 also shows the distribution of the set- and movement-related neurons with laterality preference. In the three motor regions, the neurons with different laterality (C-, B-, and I-types) were distributed in parallel with the density of the total classified neurons (Fig. 7, A and B). We could not discern any tendency toward clustering from a surface view. The classified neurons were recorded primarily in layers III and V and were intermingled, without any particular tendency for the locations.

The bottom of Fig. 7 shows the muscimol injection sites in the PMdc and PMv. In the two areas, injections were made in the region forming a focus of set- and movement-related neurons. Some sites, distant from the regions with a dense collection of set- and movement-related neurons, were selected for control injections of muscimol or saline. In the other hemispheres, distributions of the set- and movement-related neuronal activities were similar and muscimol injection sites were similarly selected (Fig. 7). To avoid cortical damage by injection, fewer than ten injection sites were selected in the PMdc or PMv and muscimol was not injected more than once at the same spot.

Effects of muscimol on conditional arm selection
Because muscimol was injected into the cerebral cortex after neuronal recording was completed in each hemisphere, we used behavioral data during the neuronal recording as the control for the muscimol experiments. In daily sessions of

FIG. 3. Three representative types of set-related activity recorded in the left PMd of monkey 1. In each panel, the raster display and histogram were aligned with right and left instruction signal onsets (IS-R and IS-L, respectively). Set-related activities were higher before (A) the right (contralateral, defined as C-type), (B) left (ipsilateral, I-type), and (C) both arm movements (B-type). TS, trigger (target) signal onset; Mvt, movement onset; and Hit, hit the touch screen.
neuronal recording, the monkeys performed correctly on 97.1–98.5% of 2,000–3,000 task trials (Table 2). Mean frequencies of trial performance by monkeys 1 and 2 were 14.4 and 12.1/min (4.17 and 4.96 s per trial), respectively. The errors consisted of premature key release during the preparation period (0–0.2%), selection errors during the RT limit (1.0–1.9%), or no movement initiation within the RT limit (0.2–0.8%), also referred to as movement initiation errors. The overall error rates, including all three types of errors, by monkeys 1 and 2 were 2.1/1000 and 1.7/1000, respectively.

We judged that muscimol was effective when the total error number exceeded the mean + 1.96SDs following muscimol injection. In daily muscimol injection sessions, control behavioral data, consisting of 400 trials under the three prism conditions for >40 min, were monitored and recorded after the tube for injection was inserted in the cerebral cortex at one of the selected sites (Fig. 7), but before muscimol was injected. When the error rates were not more than 2.2% (9 of 400 trials) during the preinjection periods, then it was judged that the monkey’s performance was similar to that during the neuronal recording session and 1 μL of muscimol was injected at the spot. If the monkey exhibited more than ten errors during the 400 preinjection trials, muscimol was not injected at the spot and the daily session was aborted.
Figure 8, A and B shows typical effects of muscimol at two injection sites in the left PMdc of monkey 1 (sites C and G in Fig. 7, respectively). The second trace of Fig. 8A indicates a trial in which the conditional auditory cue instructed the monkey to move his right arm (Ins-R trial), contralateral to the injected hemisphere. However, the monkey incorrectly initiated movements with his left arm. The onset of the error movement is indicated by a red “L” letter. This type of error was termed a selection error. In Fig. 8A, trials with selection errors are shown by red horizontal lines. Of the 11 successive trials shown in Fig. 8A, selection errors were observed during three Ins-R trials, although the other six Ins-R trials and two Ins-L trials were performed correctly. After muscimol injection at site G (Fig. 8B), the monkey showed selection errors during the Ins-R and Ins-L trials (marked by a blue line and the “R” letter). In addition, he failed to initiate forelimb movements within the reaction time limit (800 ms) indicated by the pink lines and pink diamonds (Fig. 8B). This type of error was termed a movement initiation error. Figure 8C shows cumulative histograms of selection errors and movement initiation errors during Ins-R and Ins-L trials following muscimol injection at site C in the PMdc of monkey 1. Note that the monkey made no errors prior to the injection. When muscimol was injected in the left PMdc, selection errors in the Ins-R trials were most frequent, but selection errors in the Ins-L trials and movement initiation errors by both right and left arms were also observed (Fig. 8C). Despite these behavioral errors, the two monkeys performed the task continuously and without gross behavioral disruption following muscimol injections. Mean frequencies of trial performance were similar for the two monkeys throughout the pre- and postinjection periods and differences in trial frequency (trial number per minute) between pre- and postinjection periods were not statistically significant (ANOVA, \( P > 0.05 \)) between the two monkeys. Error types as a percentage of total errors are also shown in Fig. 8C.

Quantitative analyses of behavioral errors following muscimol injection into the PMdc

For quantitative analyses, behavioral data from effective injection locations in the PMdc (see METHODS) were integrated and are shown in Fig. 9 and Table 2. The top panels of Fig. 9 show the time course of behavioral performance before and after muscimol injection into the PMdc. Very few minimal errors were observed during the preinjection period when the injection needle was lowered into the cerebral cortex prior to muscimol injection. Following PMdc muscimol injections (top panels of Fig. 9), both selection errors and movement initiation errors occurred more frequently than during the preinjection period (Scheffé, \( P < 0.05 \)). Selection errors increased following inactivation of the PMdc, regardless of whether it was in the right or left hemisphere. However, after inactivation of the...
left PMdc (top left and right panels of Fig. 9), selection errors in Ins-R trials were significantly more frequent than were those in Ins-L trials (Pearson’s chi-square test, \( P < 0.05 \)). By contrast, muscimol injection into the right PMdc of monkey 1 (top middle panel of Fig. 9) induced significantly higher numbers of selection errors in Ins-L trials than in Ins-R trials (Pearson’s chi-square test, \( P < 0.05 \)). Thus unilateral muscimol injection into the PMdc induced more selection errors in the trials that required selection of the arm contralateral to the injected PMdc, regardless of whether the inactivated PMdc was in the right or left hemisphere.

Movement initiation errors occurred in both Ins-R and Ins-L trials after muscimol injection into the right and left PMdc of monkey 1, but this error type was observed only in Ins-L trials following the left PMdc inactivation of monkey 2 (Fig. 9 and Table 2). In both monkeys, movement initiation errors were significantly more frequent in the trials requiring use of the left arm (Pearson’s chi-square test, \( P < 0.05 \)), regardless of whether the right or left PMdc was inactivated. During PMdc inactivation, the monkeys sometimes released the key during the preparation period (termed premature movement initiation in Table 2), but these errors were considerably less common than the two major error types and showed no statistically significant laterality preference (Pearson’s chi-square test, \( P > 0.05 \)).

During PMdc inactivation sessions, the number of trials performed was similar for both monkeys throughout the pre- and postinjection periods and differences in trial frequency (trial number per minute) between pre- and postinjection periods were not statistically significant (Pearson’s chi-square test, \( P > 0.05 \)). Means and SDs of reaction times (RTs) before and after muscimol injections into the PMdc are listed in Table 3. RT was compared by three-way ANOVA, when the following three conditions were used as factors: 1) correct and error trials, 2) pre- and postinjection periods, and 3) left and right hands. The difference in RT between correct and selection error trials was statistically significant (\( P < 0.01 \)), whereas the difference between pre- and postinjection periods was not (\( P > 0.01 \)). The RT for the right hand was significantly shorter than that for the left (\( P < 0.01 \)).

In contrast to the case with PMdc injections, we did not observe increases in any error type following muscimol injections into the PMv (bottom panels of Fig. 9 and Table 2). Differences in the number of each type of behavioral error between the pre- and postinjection periods were not statistically significant (Pearson’s chi-square test, \( P > 0.05 \)).

**DISCUSSION**

Three major new findings arise from the current experiments. First, local unilateral inactivation of the PMdc by muscimol induced deficits in the selection of right- and left-arm reaching movements when the required selections were directed by conditional auditory cues. These selection errors
were most frequently observed when the arm contralateral to the injected hemisphere was instructed by the cues; these deficits were also occasionally observed in the arm ipsilateral to the injected hemisphere, but much less frequently than in the contralateral arm. Second, PMdc inactivation induced failures to initiate reaching movements during the required RT limit (800 ms). Third, such errors were rarely observed following PMv inactivation. Each of these results will be subsequently discussed in separate sections. Because we made thorough recordings of task-related activity from the PMdc, PMv, and

**FIG. 7.** A: locations of classified set-related neurons, according to laterality preferences (C-, B-, or I-types), recorded in the PMdc, PMv, and MI of monkey 1. Neuronal activity was classified according to activity during preparation periods and reaction time periods (see METHODS). The filled circles show the locations of neurons, with the size of the circle reflecting the number of cells recorded in the track. Short horizontal bars indicate that no classified neuron was recorded in the track. The interrupted oblique line in the panel indicates the borderline between the MI and PM, determined by the cytoarchitectonic boundary between areas 4 and 6 and intracortical microstimulation (see METHODS). B: locations of the C-, B-, and I-types of movement-related neurons. Other details are the same as in A. C: injection sites of muscimol (1.0 μL) into the PMdc and PMv. AS, arcuate sulcus; CS, central sulcus; Prin, principal sulcus; SPS, superior precentral sulcus.
In the present study, arm selection was instructed by conditional auditory cues. In response to the auditory cues, a number of neurons in cortical motor areas exhibited sustained activity changes during the movement preparation period following cue presentation (set-related activity). These motor areas also reflected movement-related changes in neuronal activity. We found that a majority of PMdc neurons with set- and movement-related activity were densely packed (Fig. 8), it is reasonable to conclude that inactivation of the neuronal activity in the PMdc was a causal factor in the observed behavioral deficits.

Unilateral PMdc inactivation affected motor behavior in the selection of not only contra- but also ipsilateral forelimb movements, as instructed by the conditional auditory cues. Because the most prominent effects on selection errors occurred after muscimol injections into the PMdc contralateral to the arm moved, the loss of neuronal activity specific (or at least preferential) for contralateral arm movements might contribute to the higher frequency of selection errors by the contralateral arm. In contrast, the intact PMdc in the other hemisphere, which also exhibits set-related activity specific to its contralateral arm, would be able to exert normal control over its contralateral arm (i.e., ipsilateral to the injected hemisphere). Selection errors by the arm ipsilateral to the injected PMdc could also be explained by preferential inactivation of the neurons controlling that (ipsilateral) arm. The results of our study suggest that, in parallel with laterality of neuronal activity observed during the preparation period and movement execution, the selection of either the right or left arm may rely on a delicate balance or interaction of activity in the PMdc of both hemispheres connected by cross-callosal projections. Because we injected muscimol in only one hemisphere, it is possible that the PMdc in the opposite hemisphere may not have fully compensated for the inactivated PMdc and that
the selection errors may be attributed to the loss of net balance between interhemispheric inhibition and facilitation.

Consistent with our current findings, when the human PMd was unilaterally excited using transcranial magnetic stimulation, the PMd exerted state-dependent causal influences on activity in the contralateral MI and PMd (Bestmann et al. 2008). Using paired-pulse transcranial magnetic stimulation, callosal connections between the primary motor cortices (MIs) of the two hemispheres were found to contribute to interhemispheric inhibition (Di Lazzaro et al. 1999; Wahl et al. 2007) and facilitation responses (Hanajima et al. 2001) evoked by the contralateral MI. Although it has been suggested that callosal connections between the motor areas of the two hemispheres are important for bimanual coordination and learning of bimanual motor skills (Bonzano et al. 2008; de Guise et al. 1999; Diedrichsen et al. 2003; Eliassen et al. 2000), our main results shed new light on the functional connectivity between the premotor cortices of the two hemispheres. In addition, we found that laterality in the neuronal activities and effects of muscimol on arm selection were similar in the right and left PMd. Thus it appears that no clear dominance between the
Deficits in movement initiation following PMdc inactivation

We observed frequent movement initiation errors following muscimol injections into the PMdc, but not the PMv. In contrast to selection errors, movement initiation errors were significantly more frequent during left-arm trials than during right-arm trials, regardless of whether the right or left PMdc was inactivated. Movement initiation errors in the left-arm trials following inactivation of the right (contralateral) PMdc may be ascribed to similar mechanisms as those discussed for selection errors. Two possible explanations can be offered for movement initiation errors observed in left-arm trials after muscimol injection into the left (ipsilateral) PMdc. First, inactivation of movement-related (and perhaps set-related) neuronal activity specific for the ipsilateral arm could have reduced downstream motor control of this arm. The second possibility is that, under baseline conditions, activity in the left PMdc exerts excitatory effects, via callosal projections, on cortical motor areas in the right hemisphere that control the left arm, and these are then eliminated following left PMdc inactivation. In any case, these data suggest that in both hemispheres the PMdc interacts and cooperates during execution of arm movements as well as in arm selection.

Although more behavioral errors occurred following PMdc inactivation compared with baseline conditions, the overall error rate remained low (2.9–4.9% of total trials; see Fig. 9 and Table 2). These apparently minor effects of PMdc inactivation might be due to the small volume of muscimol used (1 μL), which was previously reported to inactivate a cortical area about 2.0 mm in diameter (Kurata and Hoffman 1994; Martin 1991). Given that neurons exhibiting set- and movement-
related activity were distributed in a much wider area (Fig. 7), it is likely that only part of the PMdc involved in the conditional motor behavior was inactivated by the injection. Thus much higher error rates may have been observed had the entire PMdc displaying relevant neuronal activity been inactivated. The development of novel optical techniques for precise spatial and temporal control of specific neuronal subpopulations (Zhang et al. 2007) will be of considerable help in dissecting the roles of local neural circuits in various aspects of sensorimotor integration and motor control.

Specificity of the PMdc in controlling conditional motor behavior

In contrast to PMdc inactivation, when muscimol was injected into the PMv, conditional selection errors were considerably less common. Although both the PMdc and PMv displayed relatively similar set- and movement-related neuronal activity (see Table 1), the effects of muscimol inactivation of these areas on motor behavior were distinct and dissociable.

What might be the significance of the specific effects of PMd inactivation? One possibility is that this specificity results from the loss of a major pathway for processing conditional motor behavior. We did not test this directly, but it is important to note that cortical areas other than the PMdc may contribute to conditional motor behavior. Such areas include the prefrontal and posterior parietal cortices, which are connected to the PMdc and contain neurons that display sustained activity changes in response to instruction signals necessary for decision making (Cisek and Kalaska 2005; Genovesio et al. 2005; Hoshi and Tanji 2000, 2002, 2004, Luppino et al. 2001; Pesaran et al. 2008; Quian Quiroga et al. 2006; Wallis and Miller 2003). Moreover, it has been reported that these areas were activated during conditional motor learning in humans (Deiber et al. 1997), suggesting that plastic changes necessary for conditional learning occur across a broad frontoparietal network. It is likely that the frontoparietal network also plays an important role in conditional motor behavior in nonhuman primates. The specific effects of PMdc inactivation were apparent immediately after muscimol injection but faded over time, suggesting that the PMdc plays a major role in the observed behavioral deficits.

The second possible explanation for the sharp contrast in the effects of PMdc versus PMv inactivation may lie in differences in their sources of afferent input, particularly from the parietal cortex and thalamic nuclei. The PMdc and PMv receive differential input from the dorsal and ventral parts of the posterior parietal cortex, respectively (Schmahmann and Pandya 2006), and thus these parietal inputs may convey specific conditional versus spatial information for motor behavior to be processed in the PMdc and PMv, respectively. Regarding the motor thalamus, the PMdc receives inputs from the oral and caudal parts of ventral lateral nucleus (VLo and VLc), whereas the main source of thalamic input to the PMv is area X and the ventral posterior lateral nucleus (Kurata 1994, 2005; Matelli et al. 1989; Schall and Strick 1984). However, it has been demonstrated that monkeys with large anterior thalamic lesions, including in the ventral anterior nucleus and the anterior part of the VLo, were severely impaired at relearning a conditional motor task (Canavan et al. 1989). Accordingly, inputs from the rostral motor thalamic nuclei to the PMdc may play a prominent role in conditional motor behavior.

Possible auditory pathways to the PMdc

In this and previous studies (Kurata 1993; Weinrich and Wise 1982), PMdc neurons responded to auditory instruction signals with sustained changes in activity, termed set-related activity. How does auditory input gain access to the PMdc? Although no direct pathways exist from cortical auditory areas to the PMdc in monkeys, auditory inputs may be relayed through multiple corticocortical connections or via subcortical connections such as the basal ganglia and cerebellum. In the cerebral cortex of monkeys, dual corticocortical auditory pathways projecting from temporal auditory areas to the frontal cortex have been proposed, analogous to what has been observed for visual processing pathways (Rauschecker and Tian 2000). According to this scheme, the dorsal and ventral auditory pathways correspond to “where” and “what” streams. The primary auditory cortex projects to the surrounding specialized auditory areas: the anterolateral (AL), middle lateral (ML), caudolateral (CL), and caudomedial (CM) areas (Tian et al. 2001). The caudal auditory areas (CM and CL) then project to the parietal cortex, constituting the dorsal auditory pathway suggested by Barnes and Pandya (1992). The PMd receives direct and indirect projections from the posterior parietal cortex, which contains neurons that respond to a variety of auditory stimuli (Grunewald et al. 1999; Linden et al. 1999; Strianne et al. 1996), and from the prefrontal cortex (Dum and Strick 2005; Romanski et al. 1999). In the posterior parietal cortex, an eye-centered reference frame is encoded not only by visual but also by auditory inputs (Cohen and Andersen 2000). The auditory cues used in our study instructed which arm should be used and the “what” content could be conveyed through the dorsal pathway (Kurata 1991; Pandya and Kuypers 1969). Alternatively, the conditional information may have been transmitted using the ventral pathway that projects to the prefrontal cortex. The prefrontal cortex, in turn, may then relay essential conditional information to the PMdc.

Comparison of neuronal activity with previous studies

Laterality of neuronal activity in the cortical motor areas has been reported previously. Our results are generally consistent with previous studies (Cisek et al. 2003; Cramer et al. 1999; Evarts 1966; Kim et al. 1993a,b; Kollias et al. 2001; Tanji et al. 1988). However, a wide range of results has been reported that is most likely explained by differences in the particular behavioral tasks used. With respect to set-related activity, Cisek et al. (2003) reported that during an instructed delay period, 90 PMd neurons responded to visuospatial cues for future targets and, of these, 19 (21%), 3 (3%), and 55 (61%) of the 90 neurons were tuned to target locations with contralateral, ipsilateral, and both arms, respectively. Of the 55 neurons tuned to both arms, 16, 35, and 4 neurons seemed to correspond well to the C-, B-, and I-types of neurons, respectively, described in our study (cf. Figs. 10 and 13 of Cisek et al. 2003). Thus 35 (39%), 35 (39%), and 7 (8%) of the 90 PMd neurons described by Cisek et al. (2003) could be classified as C-, B- and I-types, respectively, according to the criteria we outline in the present study. Cisek et al. (2003) also reported that, in contrast to the PMd, only 7% of MI set-related neurons showed bilateral tuning with tuning to the target location. These percentages are consistent with those reported in our study (Table 1). It should be noted, however, that in the study
by Cisek et al. (2003), monkeys performed the task with either the right or left arm in discrete trial blocks and the instruction cue indicated the visuospatial location of a target to be reached but was not specific for which arm was to be used. In another study, Hoshi and Tanji (2006) reported that about 20% of 825 PMd neurons exhibited responses to visual instruction cues for arm selection (cf. Fig. 5C of Hoshi and Tanji 2006), and 12 and 8% of the 825 PMd neurons exhibited preference for contra- and ipsilateral arms, respectively. However, it is not clear how these neuronal subpopulations relate to the C-, B-, and I-types described in the present study. Hoshi and Tanji (2006) also reported that a vast majority of PMv neurons showed location-selective activity in response to visuospatial instruction cues, but not to arm use (cf. Fig. 4, B and D of Hoshi and Tanji 2006). Accordingly, studies of set-related activity from several laboratories, including ours, suggest that the PMd is more specialized for translating arbitrary conditional cue information into preparation and execution of both contra- and ipsilateral arm movement.

As for movement-related activity, reported differences in laterality between studies are most likely a result of differences in recording sites and behavioral tasks and may depend on whether the required movements involved primarily the proximal or the distal part of the limb or both. When use of the distal part of a forelimb was required, it has been commonly observed in monkeys and humans that the contralateral MI was strongly activated and the ipsilateral MI was only weakly activated (Cisek et al. 2003; Cramer et al. 1999; Kim et al. 1993a,b; Kollias et al. 2001; Tanji et al. 1988). Cisek et al. (2003) reported similar findings in MI, where movement-related activity was observed using a task with whole-arm reaching movements that mainly involved the proximal arm. Ipsilateral MI cells were active much more frequently during proximal limb movements, especially when bimanual movements were performed (Donchin et al. 1998; Kazennikov et al. 1999; Kermadi et al. 1998). These reports support the view of Brinkman and Kuypers (1973) that the ipsilateral MI plays a role in the control of the arm, but not of distal hand and finger movements.

With respect to neuronal responses to auditory cues in the PM, Lemus et al. (2009) recently reported that the PMv participated in decision-making processes by discriminating between two different pitches that were presented as sample and match signals during a trial. Although we observed no behavioral deficits following muscimol injections into the PMv, it is likely that the injected muscimol did not spread to the far ventral part of the PMv where Lemus et al. (2009) found neuronal activity reflecting auditory discrimination. Further studies will be necessary to address whether muscimol inactivation of this part of the ventral PMv produces impairments in auditory discrimination.

REFERENCES


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