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Activity in Rostral Motor Cortex in Response to Predictable Force-Pulse Perturbations in a Precision Grip Task

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Boudreau, Marie-Josée and Allan M. Smith. Activity in rostral motor cortex in response to predictable force-pulse perturbations in a precision grip task. J Neurophysiol 86: 1079–1085, 2001. The purpose of this investigation was to characterize the discharge of neurons in the rostral area 4 motor cortex (MI) during performance of a precision grip task. Three monkeys were trained to grasp an object between the thumb and index finger and to lift and hold it stationary for 2–2.5 s within a narrow position window. The grip and load forces and the vertical displacement of the object were recorded on each trial. On some trials a downward force-pulse perturbation generating a shear force and slip on the skin was applied to the object after 1.5 s of static holding. In total, 72 neurons were recorded near the rostral limit of the hand area of the motor cortex, located close to the premotor areas. Of these, 30 neurons were examined for receptive fields, and all 30 were found to receive proprioceptive inputs from finger muscles. Intracortical microstimulation applied to 38 recording sites evoked brief hand movements, most frequently involving the thumb and index finger with an average threshold of 12 μA. Slightly more than one-half of the neurons (38/72) demonstrated significant increases in firing rate that on average began 284 ± 186 ms before grip onset. Of 54 neurons tested with predictable force-pulse perturbations, 29 (53.7%) responded with a reflexlike reaction at a mean latency of 54.2 ± 16.8 ms. This latency was 16 ms longer than the mean latency of reflexlike activity evoked in neurons with proprioceptive receptive fields in the more caudal motor cortex. No neurons exhibited anticipatory activity that preceded the perturbation even when the perturbations were delivered randomly and signaled by a warning stimulus. The results indicate the presence of a strong proprioceptive input to the rostral motor cortex, but raise the possibility that the afferent pathway or intracortical processing may be different because of the slightly longer latency.

INTRODUCTION

The cortical control of natural precision grasping movements has been investigated for more than 30 yr (Hepp-Reymond and Wiesendanger 1972; Lawrence and Kuypers 1968; Smith et al. 1975). It is now clear that precision grasping is the result of a distributed control process involving both central sensorimotor structures (Cadoret and Smith 1997; Dugas and Smith 1992; Hepp-Reymond et al. 1978, 1989, 1994; Lemon 1993; Picard and Smith 1992a,b; Salimi et al. 1999) and peripheral afferents (Johansson and Westling 1984; Westling and Johansson 1984). However, the execution of the precision grip seems to be critically dependent on the primary motor cortex (Brochier et al. 1999; Lawrence and Kuypers 1968; Schieber and Poliakov 1998). Through its direct projections to motoneurons supplying the intrinsic and extrinsic muscles of the hand, the primary motor cortex (MI or Brodmann’s area 4) can directly influence all the muscles involved in grasping (Lemon 1993). The important contribution of motor cortex to the control of relatively independent finger movements has been well supported by the combined contribution of electrophysiological studies in primates (Clough et al. 1968; Lemon 1993; Muir and Lemon 1983), clinical observations on the effects of lesions (Lawrence and Hopkins 1976; Lawrence and Kuypers 1968; Passingham 1988; Penfield and Rasmussen 1950) and from more recent reversible cortical inactivation experiments in primates (Brochier et al. 1999; Schieber and Poliakov 1998). The direct supraspinal action on the spinal motoneurons is essential for the ability to move the fingers independently (Lawrence and Kuypers 1968), a characteristic feature of almost all hand skills. The initiation of a precision grip involves establishing a finger configuration that accurately matches the size of the object (Jeannerod 1984, 1986), but that ultimately requires the fine control of the grip forces between thumb and index finger. Johansson and Westling (1984) demonstrated the importance of this fine control in the grasping, lifting, and holding of small objects. These authors (Johansson and Westling 1984; Westling and Johansson 1984) and others (Cadoret and Smith 1996) have shown that the grip force used during a grasping task is accurately scaled to the weight and frictional properties of the hand-held object. The precise control of finger forces is most likely exerted by the primary motor cortex since the contribution of this area to the production of pinch force has been repeatedly found in a variety of neurophysiological studies in awake monkeys and for different tasks (Bennett and Lemon 1996; Hepp-Reymond et al. 1978; Lemon et al. 1996; Maier et al. 1993; Muir and Lemon 1983; Picard and Smith 1992a,b; Smith et al. 1975).

According to Strick and Preston (1982a,b), the motor cortex in new world primates (squirrel monkeys) contains two spatially separate motor representations of the digits and wrist that can be defined on the basis of their somatosensory afferent input. These authors observed that the cutaneous inputs were located in the caudal part of the hand representation in motor
cortex, whereas the proprioceptive inputs were located in the rostral part of the hand representation area. Picard and Smith (1992a,b), in their studies of awake old world monkeys, reported that a high proportion of neurons in caudal motor cortex responded to cutaneous stimulation from the glabrous skin of the hand, and they suggested that this region was important for adjusting grip forces to the digit/surface friction of grasped objects. These authors mainly recorded from the caudal motor cortex in the bank of the central sulcus where a preponderance of cutaneous afferents from the volar fingers and palm are found. However, they implied that the more rostral regions on the surface near the lip of the central sulcus with a higher percentage of proprioceptive afferents might also be important. The present experiment was designed to supplement the study of Picard and Smith (1992b) and to further characterize the neurons of the most rostral part of the primary motor cortex during the precision grip task. Particular attention was given to the dominant presence of proprioceptive afferents to neurons in this area. The input-output properties of neurons were carefully examined, and the modulation of the neuronal activity in response to a readily predictable perturbation during the task performance was studied.

METHODS

Subjects and motor task

Three female monkeys (macaca fascicularis) weighing between 2.8 and 3.5 kg were used in these experiments. Although the area 6, premotor cortex (PM) was also explored in two animals, in this paper we will focus only on motor cortex. One of the three animals was also a subject in a muscimol inactivation experiment (Brochier et al. 1999). The experimental procedures and the task were the same as in the preceding paper (Boudreau et al. 2001). Briefly the monkeys were trained to grasp a metal tab between the thumb and index finger that was attached to the instrumented armature of a linear motor. The animal was required to hold the object within a vertical position window of 12–25 mm. The linear motor generated a force of 0.6 N to simulate an object weighing approximately 60 g. Occasionally some neurons were tested with weight simulations of 30, 60, and 100 g. The computer-controlled object measured both the horizontal force exerted by the fingers (grip force) and the vertical lifting (load force) and the movement of the object in the vertical axis.

Force-pulse perturbations

On separate blocks of trials, a brief (100-ms) downward force-pulse perturbation was applied to the object during the stationary holding phase to produce an additional downward shear force on the fingers. This perturbation was usually delivered 1.5 s after the onset of the tone indicating that the object had entered the position window and was therefore predictable after the first trial. The force of the perturbation was 1.0 N for two monkeys and 3.5 N for the other monkey. The perturbation force was adjusted to produce a downward object displacement of several millimeters. If unopposed, the perturbations were strong enough to displace the manipulandum from the position window, resulting in a loss of reward for the monkey. The monkey had to resist the perturbation by stiffening the wrist and fingers to maintain the metal tab within the boundaries of the position window. For two monkeys, the testing procedures began with a block of unperturbed control trials followed by a block of consecutively perturbed trials and then followed by a second block of unperturbed control trials to extinguish the behavioral expectancy of the perturbation in subsequent conditions. On some occasions, for the third monkey, an additional block of trials consisting of random combina-

tions of 75% perturbed and 25% unperturbed trials were presented. In this condition, a warning flash delivered 800 ms prior to the perturbation preceded all force-pulse perturbation trials. Both the control and perturbed conditions were always applied to a tonic resistive force of 0.6 N and a grasping surface covered with 32-grit sandpaper.

Surgical preparation

Following previously published procedures (Espinoza and Smith 1990; Evarts 1965), a circular stainless steel recording chamber 18 mm diam was implanted stereotaxically over the hand representation of the primary motor and premotor cortices contralateral to the trained hand under sterile surgical conditions.

Recording procedures

After a postoperative recovery period, recording sessions were conducted on a daily basis while the monkey performed the grasping task. If the activity of a cell was judged to be task related, the cell discharge was recorded in different conditions. Whenever possible after data collection, each cell was carefully examined to identify the receptive field (RF) by stimulating the skin with air puffs or a camel hair bush or by passively moving the hand or digits about different joints when the monkey was as quiescent and relaxed as possible. Moreover, for almost every recording site, intracortical microstimulation (ICMS) was carried out to identify the output property of the region. The ICMS consisted of a 100-ms train of 0.2-ms cathodal pulses delivered at 300 Hz through a constant-current isolation unit. The maximum applied intensity was 45 μA. The ICMS threshold corresponded to the lowest current intensity required to evoke a discrete visible movement of the fingers or wrist. The RF and ICMS were also used to map the extent of the thumb and index finger representation in the recorded area.

Histological analysis and reconstruction of recording sites

To confirm the location of the recorded cells, electrolytic lesions were made in the three monkeys by passing current through the recording microelectrode sites (25–50 μA for 20 s). These electrolytic marking lesions were produced at three stereotaxically chosen penetrations within the recording chamber. At the conclusion of experimentation, the animals were killed with an overdose of pentobarbital sodium and perfused transcardially with 0.9% saline followed by 4% paraformaldehyde. After the brains had been removed, visible markers were applied to the cortical surface at the penetration sites, and the brains were photographed. The brains were immersed in a solution of sucrose (20%, 4°C) for 24 h for cryoprotection before freezing (−80°C). Frozen sections (40 μm thick) were cut in a parasagittal plane and were stained with cresyl violet. The location of electrode penetrations and the recording sites were reconstructed from the lesion coordinates.

Statistical analysis

The cellular discharge, grip force, load force, and vertical displacement of the object were recorded in blocks of 25–35 trials under both perturbed and unperturbed conditions. The onset time of neuronal activity related to the task was defined as a 100-ms change in discharge that was at least 2 SDs greater than the mean activity, calculated during a similar 100-ms control period occurring 0.8 s before the grip onset. Either a t-test or an ANOVA was used to determine whether the prehensile force and neuronal discharge frequency were significantly altered by the test conditions. The reflexlike responses to the perturbation were determined by comparing the mean firing frequency during the 100 ms before and after the perturbation onset with a t-test (P ≤ 0.05).
RESULTS

A total of 72 motor cortical neurons in 3 monkeys were found to be active in the grasping task. This rather low yield was due to the fact that the primary purpose of the study was to examine the activity of neurons of the ventral and dorsal premotor area. Fifty-four of the 72 neurons were tested for responses to the perturbation, and the receptive fields were identified for 30 of 30 neurons tested.

Location of the recorded neurons

The histological analysis, based on the electrolytic marking lesions and electrode tracks in the cortex, indicated that these neurons were clustered in the rostral hand representation of area 4 motor cortex at a distance of about 3.0 mm from the central sulcus close to the ventral premotor cortex. The boundary between the motor cortex and the premotor cortex was established on the basis of cytoarchitectonic criteria distinguishing area 4 from area 6 (Sessle and Wiesendanger 1982). These included the higher density of large pyramidal cells in layer V of primary motor cortex area and the low current threshold required for eliciting movements with ICMS in this area compared with the relatively lower incidence of motor reactions to ICMS in the premotor cortex. This region was nevertheless rostral to the area explored by Rosen and Asanuma (1972). The rostral recording zone did not appear to overlap even the most rostral region recorded by Picard and Smith (1992a,b), which was either within the central sulcus or close to it. Figure 1 shows the approximate surface location of task-modulated cells for the three monkeys. All cells were recorded at an estimated depth of 0.5–2.5 mm below the cortical surface.

Responses to microstimulation and identification of receptive fields

ICMS performed at 38 penetration sites within the recording area evoked movements from 37 sites at thresholds varying from 4 to 30 μA (average threshold of 12 ± 7 μA, mean ± SD). These clear ICMS responses contrast with a lower incidence in adjacent premotor areas. Most of the responses were brief, unambiguous, short-latency movements frequently involving the thumb and forefinger rather than the wrist. At 23 sites, independent movements of the thumb were observed, whereas 13 sites yielded movements in the other fingers. Only one stimulation site evoked movement of the wrist.

The responses to cutaneous and proprioceptive stimuli were examined for a total of 30 neurons. All of these 30 neurons were responsive to proprioceptive stimulation, which involved a displacement of the digits, particularly the thumb as well as tapping and stretching intrinsic and extrinsic hand muscles. Movements of the thumb activated 19/30 neurons, whereas only 5 were related to the displacement of the index finger, and the remaining 6 neurons were related to the movement of several fingers. No RFs were associated with either wrist or elbow movements. As reported by Picard and Smith (1992a), passive movement in a single direction activated most of these cells (26/30) with proprioceptive RFs. However, four cells responded to stimulation applied in two opposite directions such as either flexion/extension (3/4) or adduction/abduction (1/4).

FIG. 1. Surface distribution of recording sites in the thumb and index areas of the rostral primary motor cortex for monkeys 1, 2 (left hemisphere), and 3 (right hemisphere). AS, arcuate sulcus; CS, central sulcus; MI, primary motor cortex; PM, premotor cortex. The broken line running mediolaterally indicates the border between premotor and primary motor cortex.

Input-output relationship

The relationship between the input-output properties of the motor cortex cells examined in this experiment was derived from 30 neurons that had well-defined RFs recorded in a region from which a clear ICMS response could be evoked. For 13 neurons the ICMS evoked movements in the same location on
the hand as the proprioceptive receptive field. Seven neurons received their input from muscle groups acting in one direction and ICMS-produced activity in the opposite direction. In the 10 remaining neurons the afferent input came from groups of muscles concurrently active during the task performance, but acting at different fingers than the muscles activated by ICMS (Espinoza and Smith 1990). These results generally extend the close relation between afferent input and efferent cortical output described by Rosen and Asanuma (1972) to the rostral limit of area 4.

Activation patterns

The discharge of neurons active during the task were examined for common features and grouped into the three categories, phasic, phasic-tonic, and tonic, on the basis of established patterns observed earlier in motor cortex (Hepp-Reymond et al. 1978; Smith et al. 1975). The relative proportion of each activation pattern in the rostral motor cortex was similar to the caudal zone according to unpublished data from Picard and Smith. In both zones most task-related neurons were active during the dynamic phase of the task and the proportion of phasic, phasic-tonic, and tonic neurons was similar (61, 29, and 10% for the rostral zone compared with 52, 23, and 11.2% for the caudal zone, respectively).

Pregrip activity

A substantial number of the rostral motor cortex neurons (38/72 or 52.7%) demonstrated a significant increase in their activity before the grip onset. Some neurons (7/72, or 9.7%) also showed an activity change even before the hand began moving toward the grasping tab. The onset of neuronal activity change was on average 284 ± 186 ms before grip onset. This pregrip activity onset in the rostral motor cortex was later than the pregrip activity for neurons found in premotor areas that on average show activity changes 392 ms in the ventral PM and 378 ms in the dorsal PM (Boudreau et al. 2001). Figure 2 illustrates a rostral motor cortex cell with an activity change prior to the grip onset. As seen from the raster, the onset and duration of pregrip activity in this particular cell varied from trial to trial and appeared to be related to the opening of the hand in preparation for grasping.

Responses to the perturbation

Of 72 task-modulated cells, 54 were tested with the perturbation. From these, 53/54 cells were tested with consecutive unsignaled perturbations, and 9 were also tested with a warning stimulus signaling the impending perturbation. One cell was tested in the signaled condition only.

TRIGGERED REACTIONS. All three monkeys demonstrated a stereotyped, reflexlike, grip force increase and upward movement generated at the wrist to maintain the object within the position window. These triggered reactions were immediately and invariably present after the perturbation at a latency of 50–100 ms, and they disappeared as soon as the perturbation was withdrawn.

More than one-half of the cells (29/54) responded to the perturbation with reflexlike responses. In 26 cells the perturbation resulted in an increased discharge frequency. In the majority of these cells, the increase in firing frequency was of sharp onset and could be accurately measured from a peri-
stimulus activity histogram. An example of these reflexlike reactions is illustrated in Fig. 3. Figure 3 also shows the activity histogram both for signaled and unsignaled perturbations. As observed in the caudal motor cortex (Picard and Smith 1992b), a few rostral tonically active neurons (3/27) exhibited an inhibition of their discharge in response to the perturbation. These three cells all had proprioceptive input from finger muscles.

The response latency to the force-pulse perturbation was calculated from a peristimulus time histogram synchronized on the perturbation onset with a binwidth of 5 ms, which showed that all cells responded within 100 ms after the perturbation. Figure 4 shows the broad distribution of response latencies in rostral motor cortex with a mean latency of 54.2 ± 16.8 ms. The mean latency of neurons in rostral motor cortex was significantly longer ($P = 0.009$) than similar responses in the caudal motor cortex (43.17 ± 17.24 ms) previously reported by Picard and Smith (1992b), but similar to those measured in the ventral (55 ± 16.9 ms) and dorsal (54.5 ± 17.4 ms) premotor cortex (Boudreau et al. 2001). A further comparison of neurons limited only to those with proprioceptive RFs in the rostral zone showed a longer response latency (54.2 ± 16.8 ms) to the perturbation than the 8/16 neurons with proprioceptive RFs in the caudal zone (38.7 ± 16.4 ms) that was unexpected.

PREPARATORY RESPONSES. The force-pulse perturbations were always applied at the same time on each trial and therefore were highly predictable, allowing the animals to develop an appropriate preparatory strategy. In anticipation of the forthcoming perturbation, two strategies emerged. One consisted of either increasing the grip force before the perturbation onset to
attenuate the object slip, and the second was simply to hold the object higher within the position window. Frequently the animal opted for a combination of both strategies. The animals generally started their anticipatory grip force increase once the object position was stabilized in the holding phase of the task. Unfortunately the warning stimulus used to assist the animal in discriminating perturbed from unperturbed trials did not appear to have any additional effect on either the anticipatory grip forces or object displacement strategies.

Despite a preparatory grip force increase associated with the perturbations, no neurons showed any change in discharge frequency prior to the force-pulse perturbation. Moreover, the warning stimulus did not produce any observable enhancement of the neuronal activity in the rostral motor cortex.

**DISCUSSION**

The present study examined the modulation of the neurons in the rostral hand region of the primary motor cortex during performance of a precision grip task. Two main observations were reported. The first observation was that all 30 hand-related cells tested for receptive fields in this region had proprioceptive inputs from hand muscles. The second observation was that more than one-half the neurons in the rostral motor cortex responded to the perturbation but at a longer latency than neurons with proprioceptive receptive fields in the caudal motor cortex. No neurons showed any preparatory activity in anticipation of the perturbation.

**Proprioceptive afferents**

All task-modulated cells examined for receptive fields in this study were responsive to proprioceptive inputs from intrinsic and extrinsic hand muscles. Moreover the rostral motor cortex from which these cells were recorded was more anterior than the region recorded by Picard and Smith (1992a). However, this area appeared to be a pure hand representation region as indicated by the fact that the responses to ICMS were limited to the fingers. The predominance of proprioceptive afferents to this area is in agreement with earlier observations by Strick and Preston (1982b) on rostral area 4 in *Saimiri sciureus* monkeys. If the results of the present study are combined with those of Picard and Smith (1992a,b), there is clear evidence of a rostrocaudal gradient in afferent submodality as suggested by Strick and Preston (1982a,b). Even within the rostral zone of Picard and Smith, a minority of neurons with cutaneous receptive fields were found, whereas the present study found no cutaneous fields further rostrally. These data further support the notion that cutaneous and proprioceptive afferents are segregated within motor cortex.

**Modulation of neuronal activity related to the perturbation**

**TRIGGERED REACTIONS.** The downward force-pulse perturbation elicited short-latency responses in some rostral motor cortex neurons similar to those reported for caudal motor cortex by Picard and Smith (1992b). Moreover, like observations have also been reported by other authors (Evarts 1973; Evarts and Fromm 1981; Johansson et al. 1988) for perturbations applied during wrist movements. In addition, like the neurons in the caudal motor cortex (Picard and Smith 1992b), the response latency of the rostral motor cortex neurons was short enough to suggest their participation in long-latency reflexes (Evarts 1973; Evarts and Fromm 1981; Evarts and Tanji 1976; Lee and Tatton 1982; Macefield et al. 1996a). It has been proposed that motor cortical neurons, activated by feedback from cutaneous and proprioceptive receptors in response to the perturbations contribute, directly or indirectly, to the reflex grip force increases observed 50–100 ms after object slip or load increase (Cole and Abbs 1988; Dugas and Smith 1992; Johansson and Westling 1984, 1988; Picard and Smith 1992b). However, Macefield and colleagues (1996b) suggested that tactile afferents of the skin were the only receptors in the hand responsible for a latency early enough to trigger a grip force change at a latency of <100 ms. In contrast, our results suggest that the proprioceptive afferents could play a role in these triggered responses. The fact that a substantial number of the cells in the present study had proprioceptive RFs and responded to the perturbation within 100 ms supports this view. However, the mean response latency of neurons receiving proprioceptive afferents in the rostral motor cortex was significantly longer ($P < 0.005$) than the mean response latency of neurons receiving proprioceptive afferents in the caudal motor cortex. These results suggest that there might be two pathways to the primary motor cortex or possibly an additional intracortical relay for proprioceptive afferents to the rostral cortex. Otherwise, the proportion of responsive neurons in the rostral zone (53.7%) was not significantly lower than the proportion of responsive neurons found in the caudal zone (61%) of the primary motor cortex (Picard and Smith 1992b).

That is, cells receiving cutaneous afferents were not more responsive to the force-pulse perturbation than cells receiving proprioceptive afferents, suggesting that both sensory afferents could make an important contribution to the grip force adjustments following sudden load force changes.

Although the force-pulse perturbations were associated with a preparatory behavior, no neurons in the rostral hand representation of primary motor cortex showed any anticipatory change in activity before the perturbation. The absence of the neuronal preparatory response to the predictable perturbation was not surprising since very few neurons in the caudal motor cortex (Picard and Smith 1992b), ventral and dorsal premotor cortex (Boudreau et al. 2001), ventral circumflex cortex and supplementary motor area (Cadoret and Smith 1997) showed any activity changes in preparation for the perturbation. This suggests that the motor and premotor areas either are not, or are only weakly, involved in these preparatory mechanisms. Instead, the preparatory responses to the perturbation appear to be more closely related to cerebellar activity where a substantial number of the cells show an increase in activity prior to the perturbation compared with the same period in the control condition (Dugas and Smith 1992; Monzéé and Smith 2000).

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