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Correlations Between Activity of Motor Cortex Cells and Arm Muscles During Operantly Conditioned Response Patterns

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Summary. Monkey motor cortex cells were recorded during isolated, isometric contractions of each of four representative arm muscles — a flexor and extensor of wrist and elbow — and comparable response averages computed. Most cells were coactivated with several of the muscles; some fired the same way with all four and others with none. Results suggest that many precentral cells have a higher order relation to muscles than motoneurons.

Operantly reinforced bursts of cell activity were associated with coactivation of specific muscles, called the cell's "motor field"; the most strongly coactivated muscle was usually the one whose isolated contraction had evoked the most intense unit activity. During active elbow movements most cells fired in a manner consistent with their isometric patterns, but clear exceptions were noted. Differential reinforcement of unit activity and muscle suppression was invariably successful in dissociating correlations.

The strength of each unit-muscle correlation was assessed by the relative intensity of their coactivation and its consistency under different response conditions. Several cells exhibited the most intense coactivation with the same muscle during all conditions. Thus, intensity and consistency criteria usually agreed, suggesting that strong correlations so determined may operationally define a "functional relation".

However, correlations in the sense of covariation are neither necessary nor sufficient evidence to establish anatomical connections. To test the possibility of direct excitatory connections we stimulated the cortex, but found lowest threshold responses in distal muscles, even from points where most cells had been strongly correlated with proximal muscles. Post-spike averages of rectified EMG activity provided scant evidence for cell-related fluctuations in firing probabilities of any muscles.

Key words: Motor cortex cells — Muscles — Correlations — Operant conditioning — Monkey

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In contrast to our relatively detailed knowledge of the neural organization of sensory systems, at least from receptors to cortex, we know comparatively little about the functional organization of cells in motor systems. Our greater understanding of the hierarchical relations between cells in sensory systems derives largely from the ease of characterizing their receptive fields by stimulating an adequate set of receptors. A comparable analysis of motor system organization would involve observation of central cells during isolated activation of an appropriate set of specific muscles. This study represents a first attempt to examine the relations of individual motor cortex cells to a representative set of four arm muscles, and to test the consistency of the observed unit-muscle correlations under different response patterns.

Functional connections between precentral motor cortex cells and motoneurons have been clearly confirmed by the effects of cortical ablation (Kuypers, 1960) and cortical stimulation with increasing degrees of refinement (Asanuma and Rosén, 1972; Chang *et al.*, 1947; Woolsey *et al.*, 1951). Individual motoneurons appear to receive convergence of monosynaptic connections from "colonies" of cortical cells distributed in overlapping regions (Landgren *et al.*, 1962; Phillips and Porter, 1964). While these studies have elucidated the degree of convergence from many pyramidal tract (PT) cells to single motoneurons, none has revealed the degree of divergence of single PT cells onto different motoneurons. The two extreme possibilities are that a PT cell projects specifically to motoneurons of only a single muscle, or that a PT cell projects widely to motoneurons of many muscles, with varying synaptic potency. The observed consequences of cortical ablation and stimulation are all compatible with either possibility, so long as PT cells are appropriately distributed in intermingled regions.

Studies of precentral cell activity in awake monkeys performing specific motor responses have further confirmed their functional relations to muscle activity. In monkeys performing a reaction time response, activity of related PT cells typically changes prior to the movement and covaries in latency with muscle activity (Evarts, 1966; Luschei *et al.*, 1971). In monkeys trained to perform wrist movements against different loads, Evarts (1967, 1968) and Humphrey *et al.* (1970) observed that activity of precentral PT cells was more strongly correlated with the force exerted than with the position of the wrist. These observations suggest a functional relation between PT cell and motoneuron activity, but since the responses involved coordinated activity of many muscles they were not designed to reveal which specific muscles a given cortical cell may influence. To investigate the correlation between activity of precentral cells and specific arm muscles, and to determine the stability of such correlations in a variety of behaviors, we recorded their activity during different reinforced response patterns.

Our primary objective was to document the activity of precentral cells during isolated contractions of each of four representative arm muscles, a flexor and extensor of both wrist and elbow. With the monkey's left arm held semi-prone in a cast we reinforced isometric bursts of electromyographic (EMG) activity in each of the muscles. Under isometric conditions the position of the wrist and elbow was held constant and torque developed about these joints can be considered proportional to rectified EMG activity (Basmajian, 1973). In addition to isolated EMG bursts, we also reinforced bursts of unit activity in the same cortical cell and ob-

served correlated muscle activity. In some cases unit-muscle correlations were also observed under additional conditions, such as active and passive elbow movements. Finally, in some experiments we tested the stability of the observed unit-muscle correlation by making operant reinforcement contingent on dissociation of the correlation. Our results suggest that precentral cells have more complex and variable relations to muscles than simple and consistent covariation with a single muscle, and that observations during a variety of responses are necessary to determine the strongest unit-muscle correlations.

Methods

Recording

Experiments were performed with two fluid-deprived rhesus monkeys (*Macaca mulatta*) seated in a primate restraint chair inside an IAC 400 sound attenuating chamber. During recording sessions the monkey's head was restrained and fruit juice could be dispensed directly into its mouth. The monkey's arm could be held semi-prone in a molded cast pivoted at the elbow, allowing measurable flexion and extension of the elbow joint but no gross movement of the wrist. The cast could also be locked in place (elbow at 90°; wrist at 180°), rendering muscle contractions isometric. EMG activity of flexor carpi radialis (FCR), extensor carpi radialis (ECR), biceps (B) and triceps (T) was recorded through pairs of braided stainless steel wires (BWR 09.6, Bergen Wire Rope Company, Lodi, N.J.) permanently implanted in each muscle and led subcutaneously to a connector fixed to the skull. Implanted EMG electrodes assured consistent sampling of the same muscles from day to day and permitted meaningful comparisons of the degree of activation of a muscle under different response conditions.

Activity of single precentral units was recorded with tungsten microelectrodes advanced with a remotely controlled hydraulic microdrive (Trent Wells) held in a bone-fixed adapter allowing exploration of a 20-mm diameter circular area of cortex. Most units were characterized with respect to PT projection on the basis of an antidromic response to each of three shock at 500/sec through a bipolar electrode permanently implanted at posterior 2, lateral 2. The location of all units was confirmed to be in area 4 of precentral cortex (Fig. 1C).

Conditioning

Prior to unit recording sessions, each monkey was trained in several behavioral situations with fruit juice reinforcement. 1. It was reinforced for sitting quietly during passive manipulation of the arm. This permitted characterization of cell responses to passive joint movements and cutaneous stimulation in the absence of active resistance. 2. With its arm held semi-prone in the movable cast, the monkey was reinforced for active flexions and extensions of the elbow in a vertical plane between stops at elbow angles of 90° and 70°. 3. With the arm cast locked in place at 90° elbow angle, the monkey was reinforced for isolated contraction of each of the individual arm muscles with simultaneous suppression of the other three muscles. The unit-muscle correlations were documented most completely in one monkey, but results and conclusions were confirmed in the other monkey as well.

Patterns of unit and muscle activity were detected and reinforced with an electronic activity integrator (Fig. 1B). The activity integrator had several input channels which accepted voltage signals (v_i) proportional to the recorded activity (e_i) of each element, namely, rectified EMG activity of implanted muscles and pulses triggered from the cortical cell's action potentials. Each input voltage, v_i, was multiplied by a weighting factor, a_i, whose algebraic sign and amplitude were determined by a polarity switch and gain control for each channel. The sum of the weighted input voltages was temporally integrated with a parallel resistor-capacitor network, with a passive decay constant of 50—100 msec. When this integrator voltage reached a threshold level set by a Schmitt trigger, the feeder delivered 0.1 ml of apple juice, and a relay reset the integrator voltage to zero for approximately 500 msec.

The use of the activity integrator can be illustrated by the procedure for differentially conditioning isolated activity in a specific muscle. If isolated biceps activity was desired, the weighting factor for that channel was made positive so that biceps activity drove the integrator toward the reinforcement level. To condition simultaneous suppression of the other three

muscles, the weighting factors on these channels were made negative so their activity drove the integrator voltage away from reinforcement level and prevented reinforcement. To eliminate unit activity from the reinforcement contingency, the weighting factor for that channel was made zero. At the beginning of a reinforcement period the monkey typically emitted simultaneous bursts of EMG activity in several arm muscles every 2—3 sec. The gains were then set to reinforce approximately half of these burst responses. As the monkey emitted a greater proportion of reinforced bursts the gains were continually adjusted to differentially reinforce only the closest approximations to the required pattern. Terminal performance typically consisted of repeated bursts of EMG activity in the reinforced muscle with negligible coactivation of the other three. After recording 50—100 responses with a given muscle, the procedure was repeated with each of the other three muscles. After approximately 8 weeks of training one monkey could reliably contract each of the four muscles in isolation in a given session; the time required to shape isolated activity in a given muscle decreased to a few minutes.

In addition to food reinforcement the monkey also received continuous visual feedback from a meter which was illuminated and activated during the reinforcement periods. The meter's needle deflection was proportional to the integrator voltage and the extreme rightward position corresponded to reinforcement level. Since reinforcement was consistently correlated with rightward deflections, such deflections could become a conditioned reinforcer. During reinforcement of isolated muscle activity, a set of colored lights indicated which muscle was being reinforced and the amplified EMG activity of the reinforced muscle was audible to the monkey.

In a typical session, after a precentral unit was isolated and characterized with respect to PT projection and sensory responses the first reinforced response patterns were isolated activity of individual muscles. The order in which muscles were reinforced varied from day to day. After a complete set of isolated muscle bursts was obtained for a unit, the monkey was reinforced for other responses, such as unit bursts and/or elbow movements.

Data Analysis

A 7-channel FM tape system recorded precentral cell activity, EMGs of the four arm muscles, elbow position during passive and active movements, a delayed trigger pulse 1 sec after the occurrence of each reinforced response pattern, and voice. Averages of 50—100 reinforced responses were computed with a Nuclear Chicago Data Retrieval Computer. By playing the tape backwards and triggering the averager from the delayed pulses we computed response averages of full-wave rectified EMG activity of each muscle and time histograms of unit activity over a 2-sec analysis interval straddling the reinforced response. To facilitate comparison of the relative amount of EMG activity under each behavioral condition, the gains and numbers of trials in the averages were the same for each condition unless otherwise noted. Usually the response patterns were sufficiently repeatable from trial to trial, so that the averages were typical of the single trials. Averages of responses which varied substantially are noted by an asterisk.

The response averages defined both the temporal and spatial aspects of the total response pattern. Temporally, the isometric responses consisted of a burst of activity in one or more elements (muscle or unit), which typically lasted 300—1000 msec. Spatially the response pattern involved activation of different elements during the bursts, with different relative intensities. The total response pattern was separated into the *reinforced pattern*, comprising the responses of elements whose activity was included in the reinforcement contingency, and the *correlated pattern* observed in the remaining elements, whose activity was not reinforced. (In the figures the reinforced elements are labeled + or —, indicating that activation or suppression was reinforced; the correlated elements are indicated by 0.)

In this study the term unit-muscle correlation refers to instances in which a burst of activity in one element (unit or muscle) was consistently associated with a correlated pattern in the other. The unit-muscle correlation is called positive when the two elements were consistently coactivated, negative when one was suppressed while the other was activated, or complex when one exhibited an activation-suppression sequence during bursts of the other.

To determine whether these units had any detectable effect on the activity of the recorded arm muscles we also computed post-spike averages of rectified EMG activity. By triggering

the averager from action potentials of the cortical unit and summing rectified EMG activity in the subsequent 31-msec interval, we looked for evidence that the cortical unit affected the firing probability of any motor units constituting the multi-unit EMG records.

Results

We observed 181 precentral cells in the monkey trained to isometrically contract contralateral arm muscles; 23 units were recorded during repeated isometric activity of one or more muscles. Ten units were recorded during the requisite number of isolated bursts of EMG activity (at least 50) in each of the four arm muscles. The relative location of these units in the precentral gyrus is shown in Fig. 1C. Table 1 summarizes the major type of response pattern observed under each behavioral condition for the cells documented with all four muscles; Table 2 indicates response patterns of eight additional cells recorded with two or three

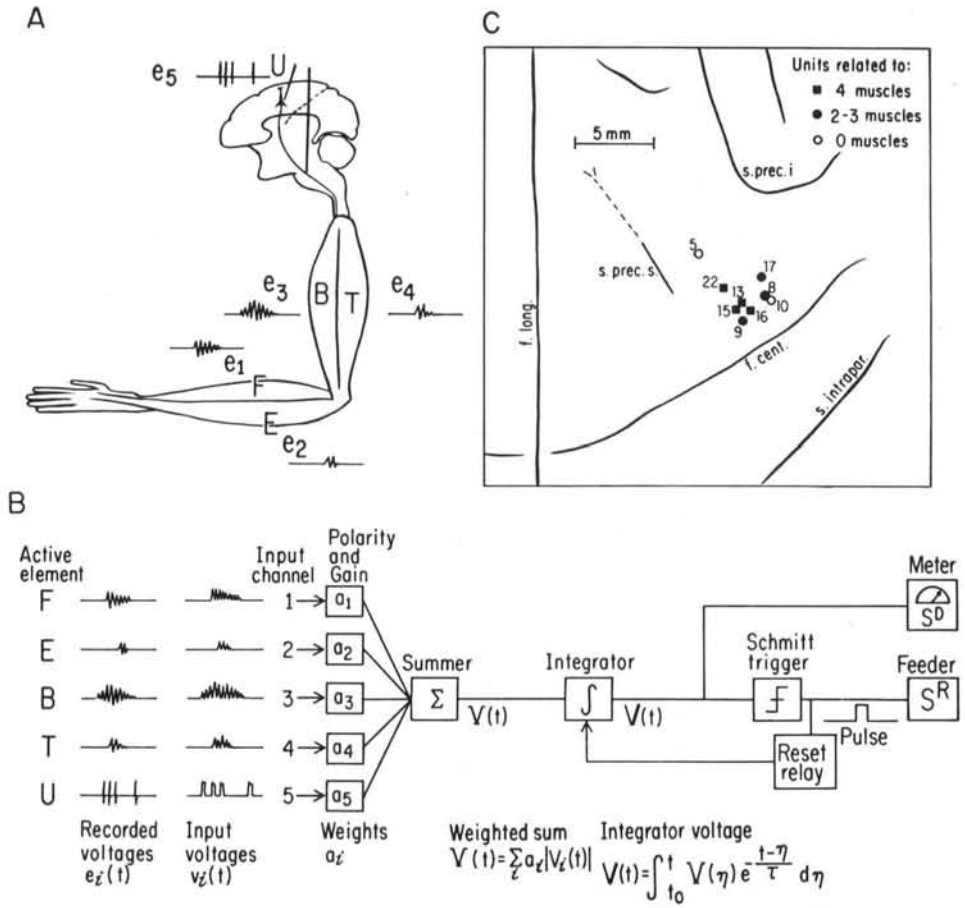

Fig. 1. (A) Schematic diagram of monkey showing typical voltages (e_i) recorded from precentral unit (U) and four arm muscles: F flexor carpi radialis, E extensor carpi radialis, B biceps, T triceps. (B) Major components of the activity integrator circuit used to reinforce response patterns under isometric conditions. (C) Location of recorded cells in precentral gyrus. Position of the 20-mm diameter recording mount was marked after perfusion with India ink tracks at four extreme coordinates; electrode tracks were located within the polar coordinate system of the mount. Cells are numbered as in text and in Table 1. *F. cent.* central fissure, *f. long.* longitudinal fissure, *s. prec. s.* superior precentral sulcus, *s. prec. i.* inferior precentral sulcus

Table 1. Responses of precentral cortex cells. Summary of response patterns of precentral units under different behavioral conditions obtained from response averages. These units were observed with isolated activity in each of the four arm muscles: flexor carpi radialis (F), extensor carpi radialis (E), biceps (B), and triceps (T). "PT" indicates antidromic response latency (msec) to PT stimulation. Blanks indicate that observation of the response was not attempted.

Isometric responses were recorded with the arm fixed in the cast; entries under muscles indicate whether unit activity transiently increased (+) or decreased (—) or both (—/+), or was unchanged (0) with respect to isolated activity of each muscle. Parentheses indicate a weak effect, and /+ indicates that unit activity followed muscle peak. Under $U+$ the table indicates which muscles were coactivated with reinforced unit bursts, in order of decreasing relative strength. Column $U+/M-$ indicates cases in which differential reinforcement of unit activity and muscle suppression was attempted and successful (S). The Elbow Movement columns indicate the predominant unit response in relation to active and passive flexions and extensions of the elbow with the arm in the cast. Natural stimulation indicates responses to passive joint movements and cutaneous stimulation with the arm out of the cast

Unit	PT	Isometric responses						Elbow Movements				Natural stimulation
								Active		Passive		
		FCR	ECR	BIC	TRC	U+	U+/M—	Flxn	Extn	Flxn	Extn	(arm out of cast)
5		0	0	0	0	none				0	0	shoulder mvt
8		+	0	+	0	B, F, E	S	+	0	0	+	elbow ext; wrist flxn
9	0.9	0	0	+	+	T, F, E	S	—	+	(+)	+	elbow flxn and extn
10	0.8	0	0	0	0	none						shoulder flxn
13	none	—/+	—/+	—/+	—/+					+	—	elbow flxn
15a	1.1	/+	+	(—)/+	+	T, F	S	—/(+)	+	—	+	elbow extn
15b	none	/(+)	+	/+	0					0	+	elbow extn
16	0.9	+/—	—/+	+	+	B, T	S	+	—	+	—	elbow flxn
17	0.9	0	0	—	(+)							shoulder flxn and hair
22	1.0	—	—	—	—					+		elbow flxn and face

Table 2. Responses of additional precentral units observed with isolated contractions of two or three muscles. Same convention as Table 1. Responses were evaluated from averages of at least 50 bursts; those in brackets were evaluated from at least 10 bursts

Unit	PT	Isometric responses FCR	ECR	BIC	TRC	Natural stimulation
14	none	0		+/—	0	elbow flxn
21	none	0		0	+	elbow extn
1			+	+		elbow flxn
2				+/—	+	elbow flxn, hair
6		—	0			wrist extn
7		0	+			elbow extn, wrist extn, shoulder flxn
18	0.9		+	+	[+]	elbow extn, shoulder extn, wrist flxn
19	1.0			—	0	elbow extn, shoulder flxn

muscles. These tables are incomplete due largely to deterioration of unit isolation or behavioral performance before all observations could be made. Since each cell exhibited a different set of relations under the response conditions, the response pattern of each unit is best considered separately. The 10 units observed with all four muscles are grouped according to whether they fired in relation to some of the muscles (4 units), all four of the muscles (4), or none of the muscles (2).

Units Related to Specific Muscles

Four units modified their activity in relation to isometric bursts of two or three of the four arm muscles. Of these, unit 8 was documented under the most complete set of response conditions and exhibited a relatively simple and self-consistent set of unit-muscle correlations. Figure 2 illustrates the isometric response patterns for this cell. After an initial shaping period for each response condition the monkey repeatedly emitted the reinforced response pattern, as illustrated. Unit 8 was most intensely and consistently coactivated with biceps bursts (Fig. 2C). The response average shows that unit activity increased well before biceps activity and reached a peak firing rate of 45 imp/sec, approximately coincident with the biceps peak. Unit 8 also showed some activity in relation to flexor carpi radialis (FCR) bursts (Fig. 2A), although this activity was more variable and less intense than that accompanying biceps bursts. Reinforced bursts of extensor carpi radialis (ECR), with slight coactivation of FCR, was accompanied by negligible unit activity (Fig. 2B). Triceps bursts, accompanied by some wrist muscle activity, evoked extremely weak and variable unit activity (Fig. 2D). Thus, in relation to isometric muscle contractions unit 8 exhibited the most intense and consistent correlated response with isolated biceps bursts and a weaker response with FCR.

When bursts of unit activity were reinforced with no contingency on muscle activity, operant unit bursts were accompanied repeatedly by EMG activity, predominantly in biceps and to a lesser degree in both wrist muscles (Fig. 2E). Thus, the unit-muscle correlation with biceps and FCR seen during isolated muscle bursts was present again, but in addition ECR was now also coactivated.

To test whether the previously observed unit-muscle correlations could be dissociated, the next schedule differentially reinforced bursts of unit activity accompanied by successively less muscle activity. After about 15 min of shaping,

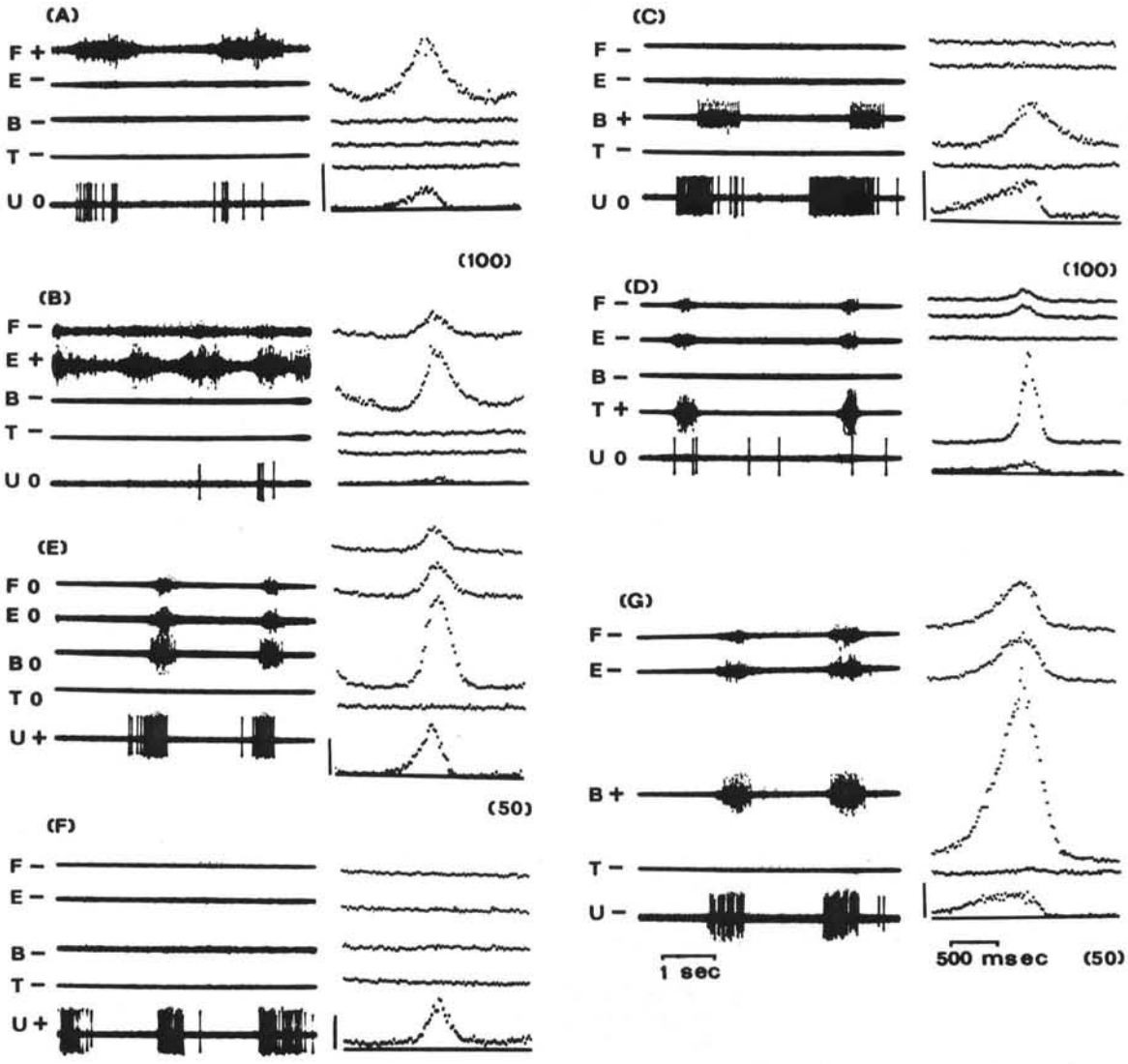

Fig. 2. Operantly conditioned response patterns of unit 8 and four arm muscles under isometric conditions. Raw trials at left show successive response on a 5-sec sweep; response averages at right show averages of indicated number of successive responses on a 2-sec sweep. Muscles and unit are labeled as in Fig. 1. A "+" or "—" indicates that activity of that element drove the integrator voltage toward (+) or away (—) from reinforcement level; a "0" denotes activity not included in the reinforcement contingency. (A—D) Relation of unit 8 to isolated bursts of EMG activity in each arm muscle; FCR (A), ECR (B), biceps (C) and triceps (D). Averages A—D each comprise 100 responses and show EMG activity at same vertical scale, except for reduction of D by one half. (E) Operant unit bursts reinforced with no contingency on the muscles. (F) Responses when operant unit bursts and simultaneous muscle suppression were reinforced. (G) Responses when isolated biceps activity and unit suppression were reinforced. Averages E—G comprise 50 responses and show EMG activity at the same scale. In this and subsequent figures time histograms of unit activity are shown with zero baseline and vertical bars calibrating firing rate of 50 imp/sec

involving approximately 100 reinforced responses and an equal number of unreinforced responses, the monkey repeatedly fired the unit in bursts without any measurable EMG activity (Fig. 2F). Surprisingly, this training did not take appreciably more time than required for shaping isolated EMG bursts. The reverse

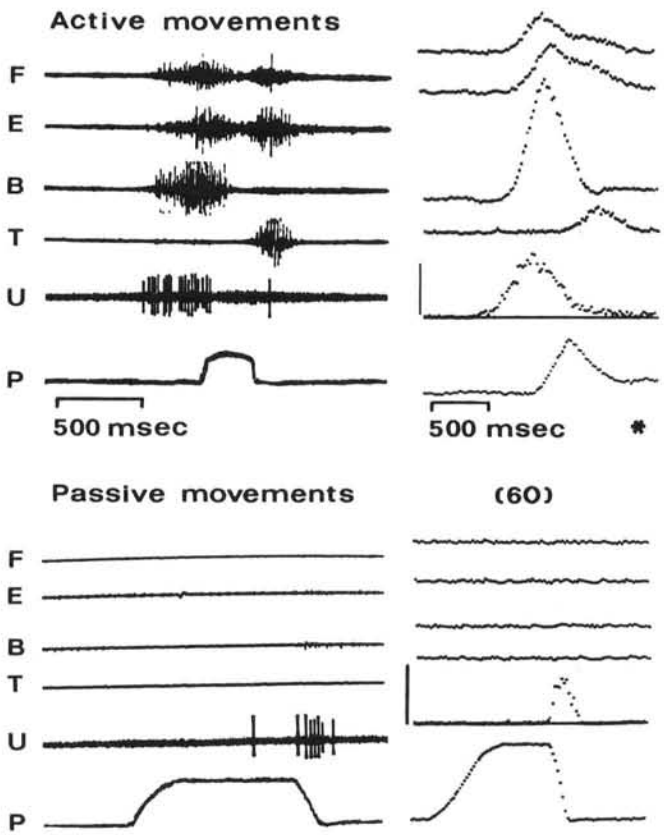

Fig. 3. Responses of unit 8 and muscles during active and passive elbow movement with arm in cast. Position shown with flexion upwards. Single trial shown at left, and averages over 60 responses at right with EMGs at same gain. This cell responded before active elbow flexion and during passive elbow extension. In this and subsequent figures, asterisk under response average denotes some variability in responses constituting the average

dissociation, namely unit suppression during isometric biceps activity, was less successful. After 25 min of shaping, responses consisted of intense biceps bursts accompanied by wrist muscle activity and some unit activity (Fig. 2G). Comparison of response averages with Fig. 2E reveals a net change in the reinforced direction but incomplete unit suppression.

During active elbow movements this cell exhibited a response pattern consistent with the isometric unit-muscle correlations: it fired strongly with biceps during active flexion and negligibly with triceps during active extension (Fig. 3). Both wrist muscles were also coactivated during elbow flexions and extensions. With passive movements of the arm cast (Fig. 3) the cell was driven repeatedly by passive elbow extension, with essentially no activity in any muscles (except for a very slight biceps response, probably due to the stretch reflex).

To summarize the unit-muscle correlations observed for unit 8, the predominant correlation was with the biceps (cf. Table 1); this appeared during B+, U+, and active flexion, but could be dissociated during U+/M—. This unit also showed a less intense coactivation with the wrist flexor under conditions F+, U+ and active flexion. A moderate correlation with ECR appeared only during U+ and active flexion, but not during E+. Finally, this unit displayed negligible coactivation with the triceps muscle under any condition.

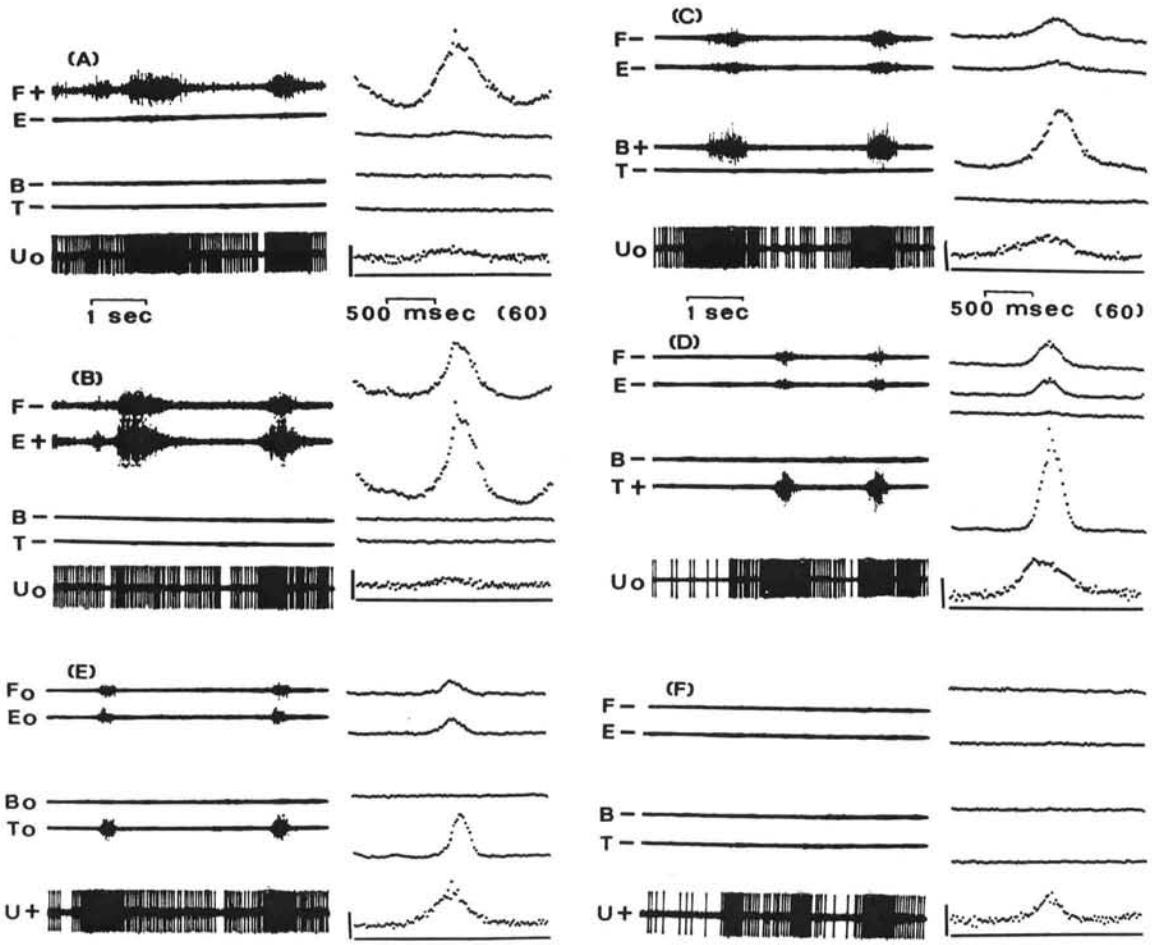

Fig. 4. Isometric response patterns of unit 9 and arm muscles. Examples of successive responses are shown at left and averages over 60 responses at right with identical gains. Reinforced response patterns consisted of isolated muscle activity (A—D), operant unit bursts (E) and unit bursts with muscle suppression (F). This PT cell fired most intensely and most consistently with the triceps muscles

The second cell that was predominantly correlated with only two arm muscles was unit 9, an identified PT cell (Fig. 4). This unit had a relatively high tonic firing rate. Its activity increased most strongly with triceps bursts (Fig. 4D), moderately with biceps bursts (Fig. 4C) and negligibly with bursts of FCR and ECR (Fig. 4A, B). When operant bursts of the unit were reinforced, the most intense correlated EMG response appeared in triceps, although both wrist muscles were also coactivated (Fig. 4E). Differential reinforcement of unit activity and muscle suppression was also successful with this cell (Fig. 4F).

The responses of unit 9 during active elbow movements (Fig. 5) were only partially consistent with the isometric pattern. Consistent with the isometric unit-triceps correlation, the cell fired before active elbow extension (confirmed more convincingly in single trials than the response average). However, in contrast to the increased unit activity seen during isometric biceps bursts, activity of this cell was clearly and consistently suppressed with active flexion. The response average in Fig. 5 shows that unit suppression began prior to biceps and wrist

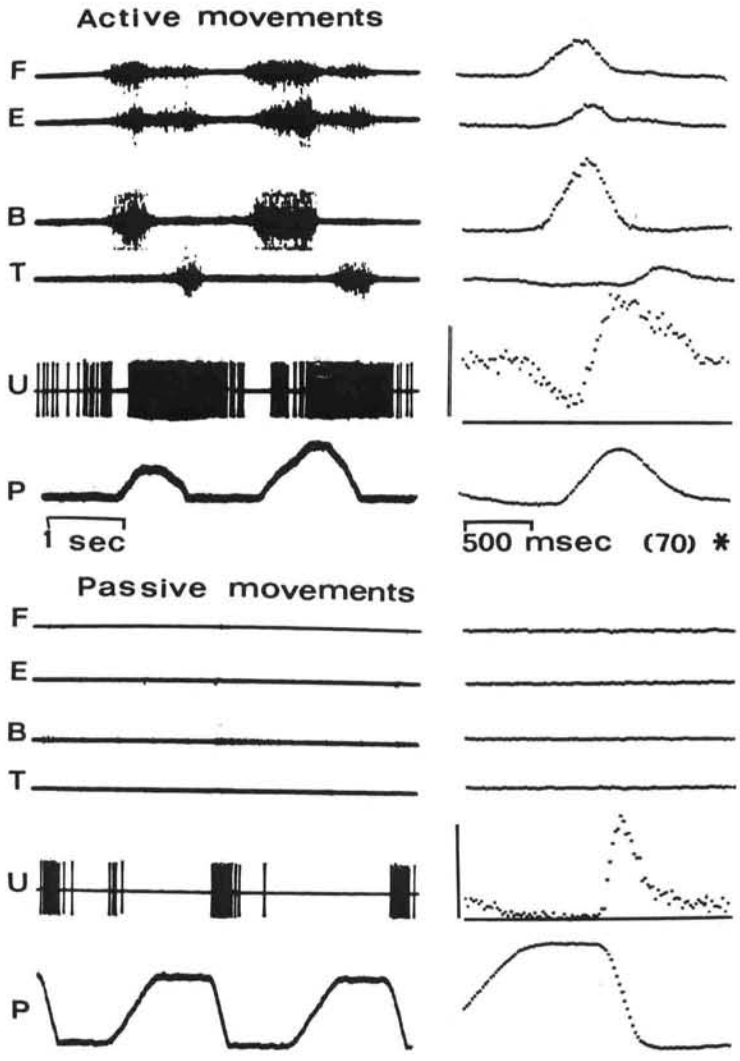

Fig. 5. Responses of unit 9 during active and passive elbow movements. This cell fired in relation to both active and passive extension and was consistently suppressed before active flexion

muscle activity and was strongest approximately 100 msec before the peak muscle activity. This cell also exhibited a clear phasic response to passive elbow extension and a slight response to passive flexion.

Thus the set of unit-muscle correlations exhibited by unit 9 showed a strong and consistent correlation with triceps (under T+, U+, and active extension). The unit-biceps correlation was least consistent; it was moderately positive under B+, did not appear under U+, and was clearly negative during active flexion. Correlations with the wrist muscles were negligible during isometric muscle bursts and moderate during U+ and active flexion.

A third cell whose activity was modulated with only two of the four muscles was unit 17, a PT cell which exhibited weak suppression during biceps bursts, weak facilitation during triceps bursts, and negligible response with either wrist muscle. This was the only cell with a positive covariation with only one of the four muscles (and a negative covariation with its antagonist).

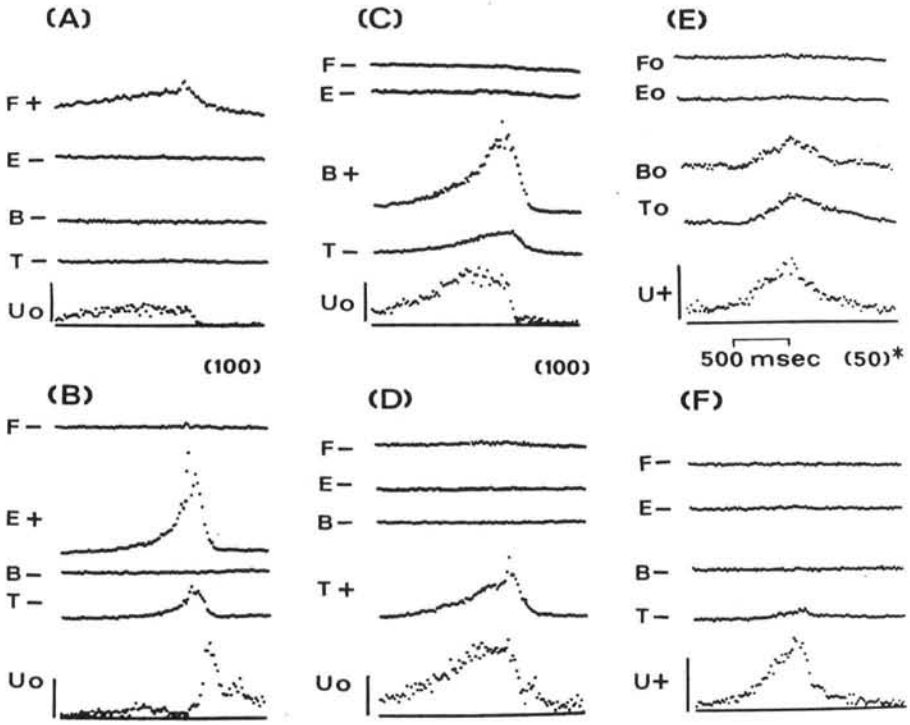

Fig. 6. Responses of unit 16 under isometric conditions. This PT cell was coactivated most strongly with biceps and triceps. Averages for (A—D) comprise 100 trials; for (E) and (F) 50 trials

Units Related to all Four Muscles

Of the four units that showed some activity in relation to isometric contractions of all four muscles, two exhibited different response patterns with each muscle. One of these, unit 16, was a PT cell that exhibited a simple burst response in association with both biceps and triceps, and a more complex response in association with the wrist muscles (Fig. 6). With both biceps and triceps the unit fired in a ramp-shaped burst which preceded and resembled the respective EMG activity (Fig. 6C, D). With FCR the unit activity consisted of a relatively weak burst followed by consistent suppression. With the ECR, the unit was suppressed before the muscle activity, and sharply activated after the peak muscle response. These reciprocal unit patterns with respect to wrist flexor and extensor were seen consistently in each of the single trials as well as in the response average.

When operant bursts of unit 16 were reinforced the correlated muscle activity appeared in both biceps and triceps (Fig. 6E). However, in this case the response average is not typical of each single trial: in some trials the biceps was more active, in others the triceps, and in some, both muscles were coactivated with the unit. As with previous cells, when the differential schedule was imposed the monkey readily suppressed all muscle activity and generated relatively intense isolated unit bursts (Fig. 6F).

During active elbow movements unit 16 showed a strong excitatory response preceding active flexion and a clear suppression of activity preceding active extension (Fig. 7) — in contrast to the excitation seen during isometric triceps

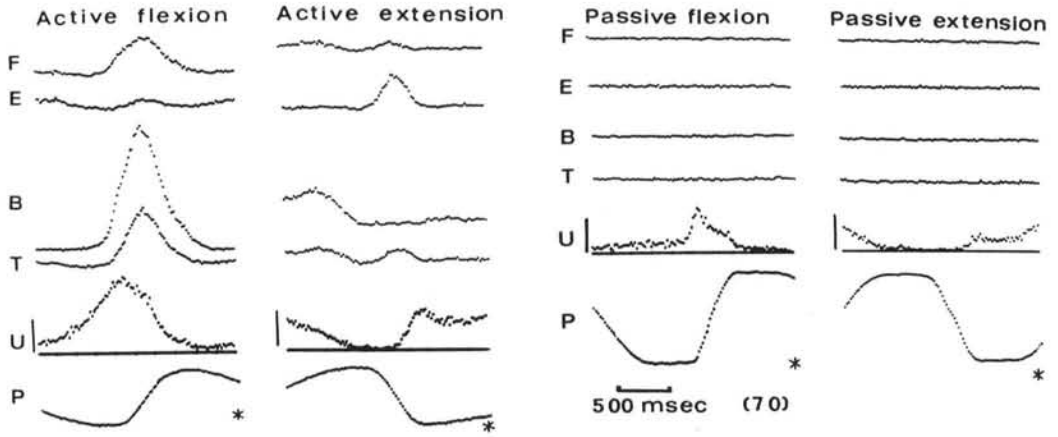

Fig. 7. Responses of unit 16 during active and passive movements. This cell fired with flexion and was suppressed with extension under both active and passive conditions

bursts. This unit responded to passive movements in the same direction as active movements: it was excited by passive flexion and suppressed during passive extension.

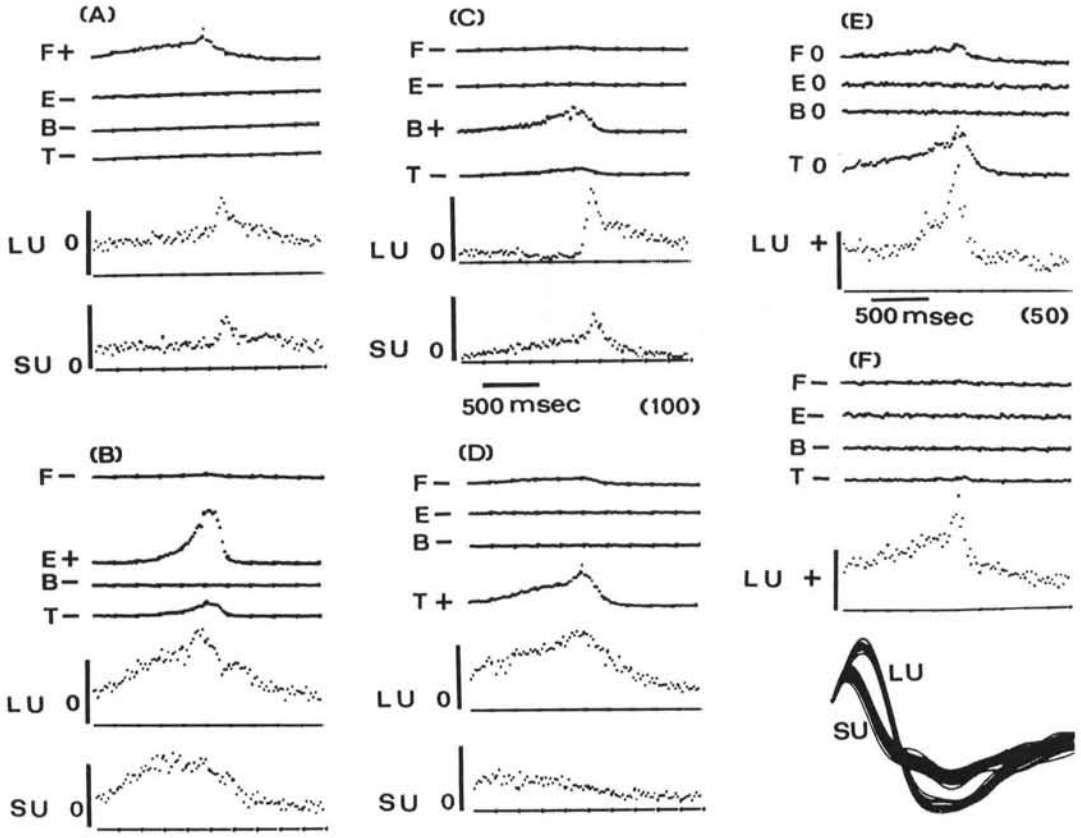

Fig. 8. Responses of units 15a and 15b under isometric conditions. During isolated muscle responses, activities of two simultaneously recorded cells could be separately counted: a large PT unit (*LU* = 15a) and a small non-PT unit (*SU* = 15b). Superimposed action potentials of both units on a fast sweep are shown at lower right. Isolation of small unit was unreliable during operant bursts of large in E and F. For A to D, N = 100; for E and F, N = 50

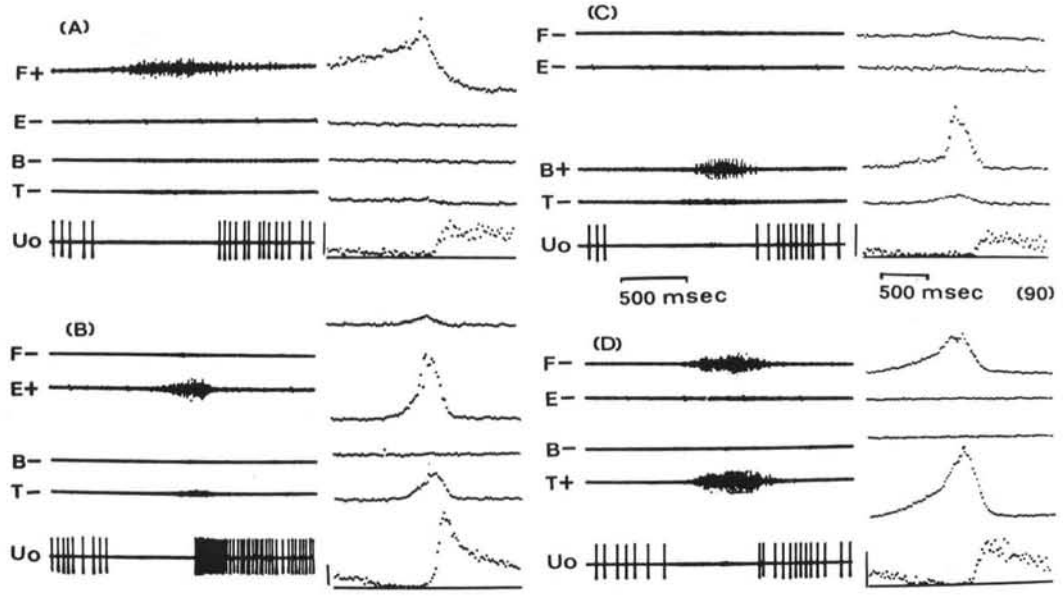

Fig. 9. Responses of unit 13 during isolated muscle bursts. This non-PT cell exhibited the same pattern during bursts of all muscles: suppression with EMG onset and activation during termination of EMG activity

Thus, cell 16 showed the most consistent unit-muscle correlations with biceps as seen in B+, U+ and active flexion. The unit-triceps correlation was less consistent, being positive during T+, U+ and active flexion, but negative during active extension. The correlated pattern of this unit to isometric contractions of the wrist muscles can best be summarized as "complex" and reciprocal.

Another cell related in some way to all four muscles was unit 15a (Fig. 8, LU). This PT cell fired prolonged bursts before and throughout isolated contractions of both extensor muscles (Fig. 8B, D); in relation to the two flexor muscles unit 15a fired a brief burst *after* the peak of the muscle bursts (Fig. 8A, C). Operant bursts of this cell were accompanied by triceps activity and weak FCR activity (Fig. 8E), but could be dissociated from both (Fig. 8F). In this session a smaller, non-PT cell (15b = SU) was simultaneously recorded and sufficiently well isolated during muscle responses to be electronically separated. This neighboring cell fired in a pattern remarkably similar to that of unit 15a for all muscles except triceps. Both units were readily driven by passive elbow extension. Consistent with its isometric responses, unit 15a also fired during active elbow extension.

Two precentral cells were related to isometric bursts of all four muscles in the same way. Unit 22 was a PT cell whose activity was suppressed with each of the four muscles. Unit 13, which did not respond to PT stimulation at intensities effective for other cells, exhibited the same complex sequence of suppression followed by facilitation with each muscle (Fig. 9). The overall response pattern of unit 13 was the same with each muscle, but appeared most intensely with ECR. For all four muscles unit activity was suppressed preceding and up to peak muscle activity, after which the unit became transiently active as muscle activity dropped. This pattern did not appear correlated with feeding, since it occurred with each muscle burst whether or not the response was reinforced. Unit 13 also responded to passive elbow flexion but unfortunately was not observed during active elbow movements.

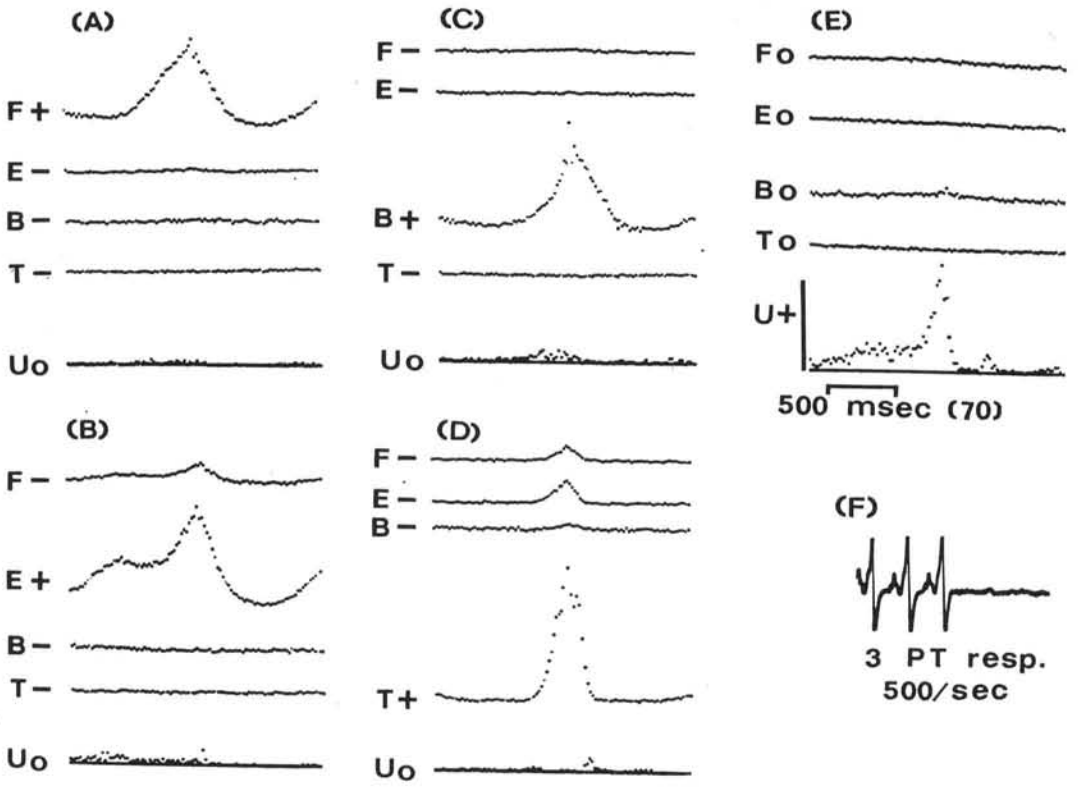

Fig. 10. Responses of unit 10 under isometric conditions. This PT cell was not coactivated with any of the four arm muscles, either during muscle bursts (A—D) or during operant unit bursts (E). (F) Several superimposed responses of unit to trains of three PT shocks at 500 imp/sec

Units Unrelated to Isometric Muscle Contractions

Two of the cells (units 5 and 10) did not respond during repeated isometric contraction of any of the four muscles; furthermore, operant bursts of these units were not accompanied by any measured muscle activity. Both units could be driven by passive shoulder movements. Of the two, unit 10 is the more remarkable since it was identified as a PT cell and was recorded within 0.5 mm of unit 8 and within 3 mm of five other cells strongly related to elbow and wrist muscle activity (Fig. 1C). As shown in Fig. 10, this cell exhibited essentially no response in relation to isometric bursts of any of the four muscles. When unit bursts were reinforced the cell reached average peak firing rates of 55 imp/sec without any correlated EMG activity in any of the four arm muscles, even though the latter were not included in the reinforcement contingency. The fact that this unit responded to passive shoulder movements suggests that it might have been correlated with proximal muscles whose activity was not monitored.

EMG Responses Evoked by Electrical Stimulation of the Cortex

To test the possibility of a functional connection between the recorded cells and muscles, we sometimes stimulated the cortex through the microelectrode at the recording site at the end of the experiment. For example, after recording from unit 8 we tested the EMG responses evoked by a train of four shocks (0.4 msec biphasic) at 500/sec at the same cortical point. Trains were repeatedly presented

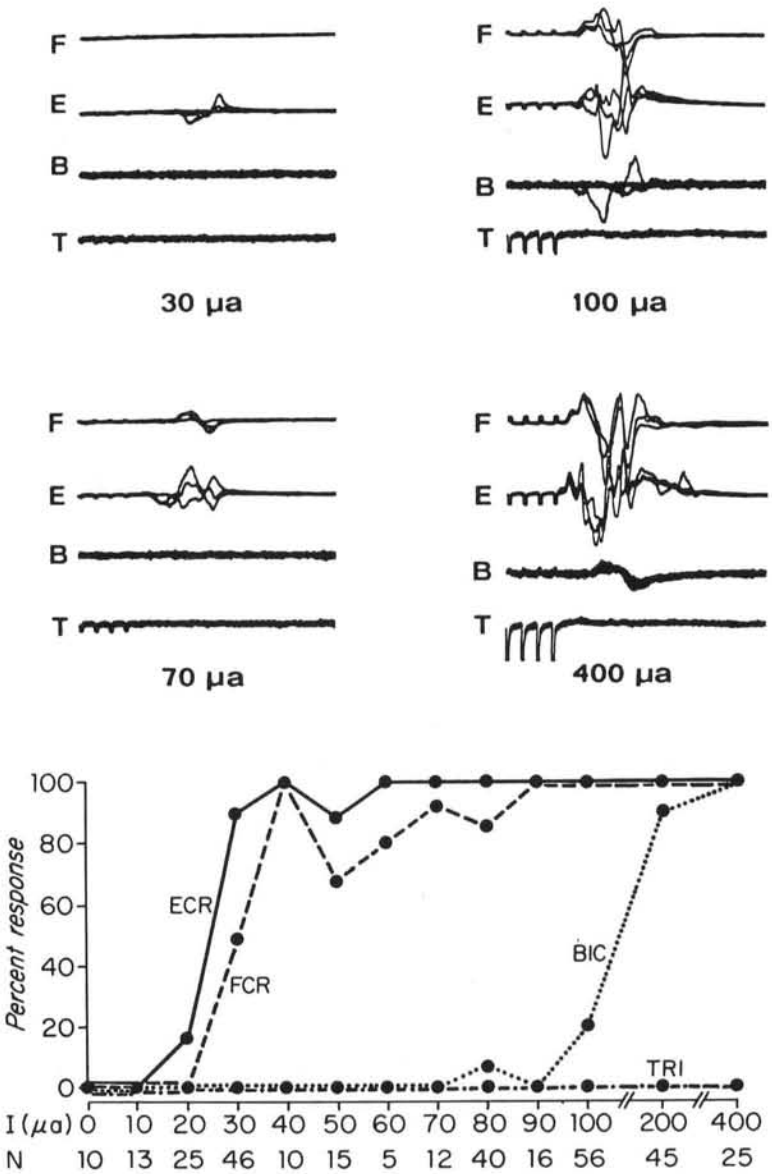

Fig. 11. Muscle responses to cortical stimulation at the point where unit 8 was recorded. Trains of four cortical shocks were presented at different stimulus intensities. Samples at top show three superimposed responses, with gains for biceps and triceps 2.5 times those for FCR and ECR. Time scale is given by 2-msec interval between stimulus artifacts. Graph plots percent of N stimulus trains which evoked any response in each muscle, as function of stimulus intensity (I) in μA. N = total number of trains presented, with animal at rest

at increasing intensities from 10 to 400 μA (Fig. 12). The threshold response occurred in ECR at a stimulus intensity of 20 μA (4 responses in 25 repetitions) and occurred more consistently at 30 μA (41 responses in 46 repetitions). The 30-μA stimulus evoked simultaneous responses in FCR (19/46). Only at intensities of 100 μA did the stimuli evoke any response in biceps (11/56). At 400 μA the biceps responded repeatedly; at this intensity the response latency was 8 msec for wrist muscles and 10 msec for biceps. These observations were made while the monkey was quiescent; during active or passive arm movements, responses to cortical

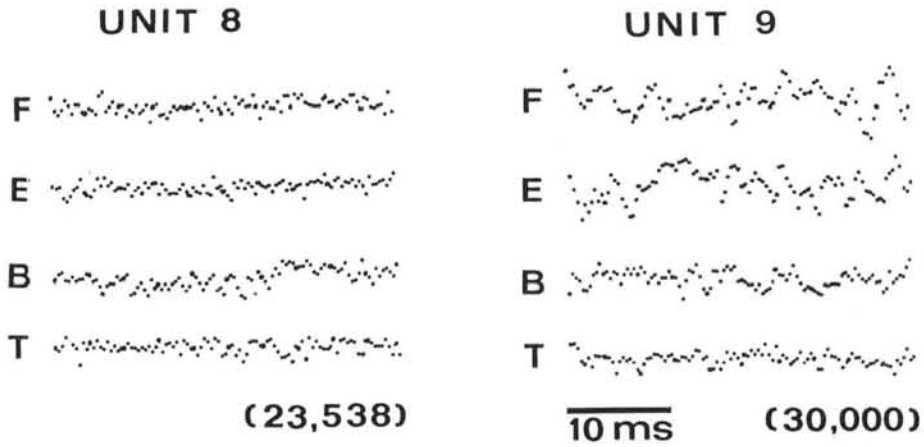

Fig. 12. Post-spike averages of rectified EMG activity for units 8 and 9. Each 31-msec sweep was triggered from indicated number of action potentials of the cortical cell during isometric response conditions. Each dot represents a 0.31-msec bin

stimulation could be substantially potentiated. These four muscles exhibited the same relative thresholds to electrical stimulation at other cortical points, where cells had been most consistently coactivated with proximal muscles.

Post-Spike EMG Averages

As a further test for functional connections, we computed post-spike averages of rectified EMG activity for units 8, 9, 15a, 15b and 16 to detect any possible effects of the cortical cell on the firing probabilities of motor units in the muscle. For most cells, averages of large numbers of sweeps (between 20000 and 30000) failed to demonstrate clear transient changes in EMG activity in any of the muscles synchronized with the cortical unit spike. Figure 12 shows the post-spike EMG average of units 8 and 9 compiled from the isometric response patterns. None of the muscles exhibit a convincing fluctuation in activity with a time course resembling a post-synaptic potential. A barely perceptible increase in mean biceps activity occurred at 22 msec for unit 8; however, since this could conceivably be related to a bias toward sampling at the onset of EMG bursts, when biceps activity was increasing, it cannot be unambiguously interpreted.

Discussion

Precentral Unit Activity Correlated with Isolated Muscle Bursts

For purposes of analysis, the set of isolated contractions in flexors and extensors of wrist and elbow represents a mutually exclusive, "orthogonal" set of response patterns designed to determine whether a given motor cortex cell was related to activation of one or more of these muscle groups. It should be noted, however, that the term "isolated muscle activity" in this context is meant to include the probable coactivation of synergistic muscles, but exclude the coactivation of other recorded muscles, at least to the extent illustrated. Of the ten cells observed in relation to a sufficient number of isolated contractions in all four arm muscles, eight units changed their activity in relation to more than one muscle and two were not related to any (Table 1). The unit-muscle correlations were more

often positive (11 cases) than negative (6 cases) or complex (7 cases). The observation that most units were consistently related to several muscles rather than one suggests that some precentral cells may have a higher order relationship to muscle groups than do motoneurons. The simplest set of unit-muscle relations was that of cell 17, which was activated with triceps, inhibited with biceps and unrelated to wrist muscles. However, this was the only cell exhibiting such a simple and reciprocal relationship to antagonistic muscles of only one joint. Other cells fired with antagonists of the same joint (units 9 and 16) or with muscles of more than one joint (units 8, 13, 15a, 15b and 16). Two units (13 and 22) exhibited the same pattern with all four muscles, suggesting that they were more strongly related to the occurrence of the response than to which muscle was being activated. Alternatively, these cells may have been correlated with a common component of each reinforced response, such as reinforcement. However, a simple relation to feeding is unlikely since unreinforced EMG bursts were accompanied by the same unit response as reinforced bursts.

Although our sample is too limited to deduce the general nature of the relation of precentral cells to isolated contraction of individual muscles, these patterns clearly suggest a higher order relation than a one-to-one correlation with specific muscles (or even with groups of synergistic muscles); furthermore, our results indicate that cells in the same cortical region can exhibit quite different sets of correlations with the same set of muscles.

Temporally the burst patterns of cortical units during isometric EMG bursts were commonly of two types. The first type broadly overlapped the EMG burst, often had a similar time course, but temporally preceded EMG activity (Figs. 2A, C; 4C, D; 6A, C, D; 8B, D). The second type did not increase until muscle activity had peaked and exhibited maximal firing rates as muscle activity was decreasing (Figs. 6B; 8A, C; 9); sometimes the latter bursts were preceded by unit suppression as EMG activity increased. If these two patterns are functionally related to EMG responses, the former would be expected of cells involved in turning muscle activity on and the latter of cells turning muscle activity off. Some units exhibited one type of burst with one muscle and the other with its antagonist (units 15a, 15b, 16), as if involved in turning one on and the antagonist off. In other cases the same type of burst pattern was seen with both of the antagonist muscles acting at a joint (units 9, 16, 13). The second type of burst pattern may also represent a response to sensory input from receptors activated as the muscle relaxes.

Muscle Activity Correlated with Operant Unit Bursts: Motor Fields

By making reinforcement contingent on unit bursts and allowing contraction of muscles to occur freely, we determined which muscles the monkey would coactivate with operant bursts of these same cortical cells. In a previous study with the monkey's limbs unrestrained, operant bursts of different precentral cells were associated with different types of movements, from generalized and variable movements for some cells, through specific and repeatable movements of specific joints for others, to no observable movements for some (Fetz and Baker, 1973). In the present study unit bursts were reinforced with the contralateral arm held in an isometric cast and correlated EMG responses proved considerably more repeatable from one burst to the next. It is noteworthy that each of the units in a

relatively restricted area of motor cortex was associated with correlated bursts in different sets of muscles and two cells were associated with no muscle activity (Table 1 and cf. Figs. 2E, 4E, 6E, 8E, 10E). This confirms the observation that muscle responses correlated with operant unit bursts may be quite different for neighboring precentral cells and supports the concept of a "motor field" defined as the set of muscles coactivated with operant bursts of the cell (Fetz, 1974).

It is instructive to compare the unit-muscle correlations observed when unit bursts were reinforced with those observed when isolated muscle contraction was reinforced. For both cells 8 and 9 the muscle that was most strongly coactivated with operant unit bursts (biceps and triceps, respectively) was the one muscle of the four whose isolated contraction evoked the most intense and consistent unit activity. However, the motor field of these cells also included other muscles which were less consistently correlated with the unit under other behavioral conditions (e.g., ECR for unit 8). Thus, the motor field may include more muscles than those optimally associated with the unit in other situations. It is noteworthy that operant bursts of two cells in the same cortical region occurred without any recorded muscle activity (units 5 and 10), and these units were not active during isolated bursts of any of the four muscles.

Unit and Muscle Activity During Active and Passive Movements

During active flexions and extensions of the elbow with the arm in the cast, most unit-muscle correlations were consistent with those seen during isometric responses. For example, cell 8 fired with biceps during active flexion as well as during isometric biceps bursts and operant unit bursts. Of more interest, some unit-muscle correlations were not consistent under all conditions. Cell 9, for example, was activated with biceps under isometric conditions (Fig. 4C) but was clearly inhibited with biceps during active flexion (Fig. 5). This suggests that the correlations seen during isometric contractions do not always predict the pattern seen during active movements. In both discrepant cases (units 9 and 16) the unit was coactivated with both biceps and triceps under isometric conditions but fired reciprocally during active flexions and extensions of the elbow.

One objective of documenting relations of a motor cortex unit to a set of independent muscles was to see whether the relation of that unit to a more complex response, involving a combination of the muscles, is simply a proportional combination of its relations to each individual muscle. Such would be the case if the motor system were a linear system, for which superposition of responses held. The fact that this was not consistently observed suggests a sufficient degree of complexity to preclude generalizations from one set of response conditions to another.

In addition to firing with active movements, many precentral cells can also be activated by sensory stimulation (Albe-Fessard and Liebeskind, 1966; Fetz and Baker, 1969; Goldring and Ratcheson, 1972; Rosén and Asanuma, 1972). All of these cells responded in a repeatable fashion to passive movement of one or more contralateral joints, usually including the elbow. The responses of motor cortex cells during active and passive movements of the same joint may be compared to determine whether the cell's sensory input has any consistent relation to the possible motor output with which the cell is related. In agreement with previous

observations (Fetz and Baker, 1969; Goldring and Ratcheson, 1972) the cells recorded in these monkeys showed a variety of relationships between responses during active and passive movements; some units responded during active and passive movement of the joint in the same direction (units 16 and 15a); others responded during active movement in one direction and passive movements in the opposite direction (unit 8). Thus, we found no predominant input-output relation for precentral cells related to elbow movements.

Unit-Muscle Correlations and Functional Connections

The basic observations in these experiments concerned correlations (in the sense of coactivation) between activity of a motor cortex cell and four specific arm muscles. Since some of these cells potentially had functional connections with motoneurons of these muscles, it is useful to reconsider the logical relations between correlated activity and anatomical connections. Obviously, a temporal correlation between two elements does not provide convincing evidence for a functional connection. Since a precentral cell and muscle could be coactivated during a given response without being connected, a temporal correlation is not *sufficient* to establish a functional connection. Conversely, a precentral cell and muscle could be independently activated in spite of a direct synaptic connection, since the synaptic effects of one precentral cell are surely subthreshold (Clough *et al.*, 1968; Landgren *et al.*, 1962; Phillips and Porter, 1964; Preston and Whitlock, 1961); thus, a consistent temporal correlation is not even a *necessary* consequence of a functional connection. Despite such deductions there remains an intuitive inclination to expect that activity of connected elements would tend to be correlated. The degree to which this is the case for motor cortex cells and muscles could be empirically investigated only by employing independent measures of temporal correlations and functional connections.

Strength of Temporal Correlations

The "strength" of a unit-muscle correlation could be considered proportional to both the intensity and consistency of their coactivation under different behavioral conditions. Intensity refers to the relative amount of coactivation of the unit and muscle during a given response condition. Consistency is proportional to the number of different behavioral conditions in which it appears. In the present context, these response conditions include isolated muscle contractions, operant unit bursts, or movements involving the muscle. The unit-muscle correlations would be most consistent if they appeared under all conditions (e.g., unit 9-triceps), less consistent if they appeared under some (e.g., unit 9-ECR) and least consistent if they were positive under one condition and negative under another (e.g., unit 9-biceps).

Although the intensity and consistency critera were defined independently, our data suggest a significant relationship. Units 9 and 15a showed the most consistent unit-muscle correlations with triceps, and units 8 and 16 with biceps. In each case the muscle that exhibited the most consistent correlation under various behavioral conditions was also the one most strongly active in association with operant unit bursts, and was usually the one whose isolated contraction evoked the most intense correlated unit activity. This suggests that intensity and consistency are themselves consistent criteria for strong correlations.

A particularly powerful test of the consistency of an observed correlation is to directly reinforce its dissociation. If differential reinforcement of activity in one element and suppression of the other is readily successful, the previous correlation could be considered weaker than if the dissociation proves impossible. All precentral cells tested in this study could be dissociated from their correlated muscle activity by differentially reinforcing simultaneous suppression of EMG activity. At the least, this suggests that the muscle activity was not necessary to generate unit activity and conversely that unit activity was not sufficient to generate muscle activity (a point readily confirmed when spontaneous or evoked cell activity occurred without muscle activity).

On the other hand, failure to dissociate a correlation must be cautiously interpreted as evidence for strong correlations, since there are several potential explanations. The dissociation might be physiologically impossible, as in the case of a prepotent connection. Except for the neuromuscular junction, such obligatory connections are relatively rare in the central nervous system and do not appear to exist at the corticomotoneuronal junction. Alternatively, failure to dissociate a correlation may also be related to behavioral causes, such as lack of motivation or insufficient shaping. The unsuccessful attempt to condition muscle activity and unit suppression (Fig. 2G) was made after 7 h of prior conditioning involving numerous reinforcements, when the rate of responding was clearly deteriorating; this suggests that failure to achieve complete unit suppression may be related to fatigue or satiation. Since failure to dissociate a correlation depends significantly on behavioral factors, it can be invoked as evidence for a "strong" correlation only if these behavioral conditions are controlled or constant.

The above criteria for the strength of a unit-muscle correlation all involve examination of the intensity and consistency of the covariation under different behavioral conditions. One could argue that strong correlations in this sense operationally define a "functional relationship". Nevertheless, such correlations can never prove the existence of functional connections. To test whether cortical cells synaptically contact a motoneuron, it becomes necessary to resort to more direct physiological tests, such as electrical stimulation, or more sensitive cross-correlation techniques.

Connections Tested by Cortical Stimulation

Short latency muscle or motoneuron responses evoked by electrical stimulation of cortex can provide evidence for an anatomical connection between the two. When we stimulated at points where these cells were recorded, the lowest threshold responses occurred in distal muscles, although short latency biceps responses appeared at intensities five times greater. Since most of the cells in this area had the strongest correlation with proximal muscles, a discrepancy exists between the behaviorally correlated muscles and the electrically evoked muscles. This discrepancy can be understood by recalling that the effects of electrical stimulation depend on the synaptic potency of connections as well as the relative number of stimulated cells with connections to specific muscles. It is quite possible that a minority of cells with potent excitatory connections to distal motoneurons could produce a lower threshold response than a majority with weaker excitatory or mixed effects on proximal motoneurons, when all are stimulated electrically. Yet

recording would reveal the majority of cells in the region to have strongest correlations with proximal muscles. Such a possibility is consistent with the observation that cortical stimulation evokes relatively large EPSPs in motoneurons of distal muscles and weaker or mixed PSPs in proximal motoneurons (Clough *et al.*, 1968; Landgren *et al.*, 1962; Phillips and Porter, 1964). Furthermore, electrical stimulation may synaptically recruit cortical cells at a distance via intracortical connections or axon collaterals of thalamocortical cells. Thus, the functional relations of a cortical area as revealed by the most common unit-muscle correlations need not be identical to those suggested by threshold responses to electrical stimulation.

Connections Tested by Post-Spike Averages

A more specific method of documenting synaptic connections of a single cell is suggested by the technique of Mendell and Henneman (1971). By averaging the membrane potentials of motoneurons following action potentials in a single IA afferent fiber they observed that each afferent fiber produced EPSPs in virtually every homonymous motoneuron. If PT cells make similar ubiquitous connections on motoneurons of even one muscle, and if the postsynaptic potentials have any effect on firing probability, it should be feasible to demonstrate statistically a transient change in firing probability of motor units following the cortical cell's spikes. Since unitary synaptic potentials are relatively small (Porter and Hore, 1969), their effect could only be seen by averaging EMG activity following a sufficiently large number of action potentials. Several cells in this study were strongly correlated with specific muscles, in the sense of consistently covarying with those muscles; however, on a finer level of temporal resolution the post-spike average failed to reveal a clear transient modulation of muscle activity with a time course expected for postsynaptic potentials.A gradual increase in firing probability seen in some cases may be due to a slight bias toward sampling at the onset of bursts when EMG activity is increasing, and cannot be unambiguously attributed to direct synaptic connections. More convincing evidence of transient facilitation of wrist muscles has recently been found for precentral cells related to wrist movements (Fetz and German, unpublished observations) which have more potent synaptic connections. Similarly, Woody and Black-Cleworth (1973) have reported transient changes in facial muscle activity following cortical intracellular stimulation. Thus, post-spike averages have proven effective for documenting synaptic connections of individual cells.

Conclusions

Rather than document many cells in relation to a single movement, we chose to study each cell in relation to a set of different responses, including isolated contractions of four arm muscles. Consequently, comparatively fewer cells could be completely documented. Nevertheless, their relation to a representative set of muscles was clearly established. On the basis of these results we would anticipate that a more extensive study will reveal classes of motor cortex cells whose relation to muscles are analogous to the relation of sensory cortex cells to receptors. Some precentral cells may have a relatively simple and direct relation to activation of specific muscles acting at one joint (e.g., unit 17). Others may covary in relation to a more extensive set of muscles including antagonists, or muscles acting at

different joints (like units 8, 9, 15a and 16). Still higher order cells may show the same response pattern with every muscle (units 13, 22), possibly being more concerned with the generation of the response than its topography. Finally, cells unrelated to any of the recorded muscles (units 5 and 10) may either be related to unrecorded muscles or have more subtle functions yet to be determined. Characterizing more cells in relation to isolated contractions of a comparable set of muscles would appear to be a useful strategy for investigating the functional organization of motor cortex.

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