OPERANT CONTROL OF SINGLE UNIT ACTIVITY AND CORRELATED MOTOR RESPONSES

Eberhard E. Fetz

Operant conditioning of neural activity promises to be a useful technique for studying the functional consequences of neural responses; it provides a direct method of eliciting patterns of activity in specific neural elements and thereby determining whether such patterns may be correlated with specific behavioral responses. Other participants in this conference have operantly conditioned spontaneous or evoked field potentials generated in various neural structures and have noted behavioral correlates of these potentials. We have operantly conditioned patterns of activity in single motor cortex cells in awake rhesus monkeys, and have studied the correlated motor responses.

Olds was the first to report the possibility of operantly conditioning patterns of unit activity. In his initial studies he used medial forebrain bundle (MFB) stimulation to reinforce patterns of cell activity in restrained rats tranquilized with meprobamate (Olds and Olds, 1961). Units were chosen for conditioning if their firing rates were below two impulses per second and if they did not respond directly to MFB stimulation. Olds reported that under these circumstances "paleocortical" units were easier to condition than "neocortical" units. He reported a variety of possible unit responses. Some units increased their firing rate by bursting more frequently when reinforcement was contingent on cell activity. Others fired at a high tonic rate after repeated MFB stimulations, suggestive of seizure discharges. A third group of units responded directly to MFB stimulation, but only when it occurred after prior unit activity. (The possibility remains that such units received a sub-threshold facilitation from MFB and that when the cell was sufficiently depolarized to fire spontaneously the MFB stimulation could also evoke responses.) In a subsequent study Olds used food to reinforce activity of hippocampal and "mid-brain tegmental" units in awake rats (Olds, 1962; Olds, 1967). To eliminate movement artifacts and reduce the possibility that cell activity was evoked by gross movement, reinforcement

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was not delivered unless recorded movement artifacts were absent for two seconds prior to the burst of neural activity. In most cases the implanted probes picked up multiple unit activity which could be recorded and conditioned over several days. Olds reported that such activity could be brought under control of a discriminative stimulus. Unit activity recorded from other probes near the conditioned cells was usually found to correlate positively with rate changes of the conditioned units. Bursts of pontine cells were often associated with slight movements of eyes and head which escaped detection by the movement monitor; bursts of some hippocampal units were associated with movements of the nose or whiskers. In these pioneering studies Olds anticipated many of the issues involved in operant conditioning of neural activity.

More recently, David Hiatt has continued these investigations in Olds' laboratory by operantly conditioning unit responses in five different brain regions in the rat (Hiatt, 1972). Upon reinforcing increased firing rates with food or MFB stimulation, Hiatt found that a greater proportion of cerebellar and brain stem units could be conditioned to augment their rates than could units in hippocampus, midbrain or superior colliculus. "Control units" recorded simultaneously from other electrodes underwent similar rate changes, suggesting a relatively generalized correlated response. As discussed below, Hiatt also attempted unit conditioning in rats paralyzed with gallamine triethiodide, with some success. In a final set of experiments Hiatt made reinforcement contingent on decreases as well as increases in activity and also presented noncontingent reinforcement; these experiments suggested that noncontingent MFB stimulation often increased cell (and motor) activity, so that it was necessary to compare the effects of contingent reinforcement with pseudoconditioning rates rather than with preconditioning rates. Hiatt also documented a variety of motor responses associated with periods of high and low unit activity. As discussed below, many of Hiatt's observations are similar to our own.

Our studies derived from an interest in the role of motor cortex cells in control of movement. In initial studies, in collaboration with Dr. Mary Ann Baker, we allowed the monkey relatively free movement of his limbs in order to observe whether operantly conditioned bursts of activity of specific precentral cells might be correlated with specific limb movements (Fetz and Baker, 1973). More recently, in studies in collaboration with Dr. Dom V. Finocchio, we monitored EMG activity under isometric conditions, with the contralateral arm fixed in a cast, and were able to include EMG as well as unit activity in the reinforcement contingency (Fetz and Finocchio, 1971).

These studies provide a situation in which the neural elements whose activity is reinforced have a relatively direct and well-documented relation to motor responses. Anatomically, the axons of many precentral cells are known to project via the pyramidal tract (PT) to the spinal cord, where they synapse on motoneurons and interneurons (Kuypers, 1960). Physiologically, the synaptic efficacy of these connections has been amply demonstrated;

electrical stimulation of motor cortex and PT is particularly potent in exciting motoneurons of distal muscles (Asanuma and Rosen, 1972; Chang *et al.*, 1947; Phillips and Porter, 1964; Porter, 1970, 1973; Preston and Whitlock, 1961). Behaviorally, these cells have been observed to modify their activity prior to a well-timed motor response (Evarts, 1967; Humphrey *et al.*, 1970; Luschei *et al.*, 1971; Fetz and Finocchio, 1971). These observations suggested that precentral cells may be causally involved in generating movements and led us to expect that operant reinforcement of motor cortex cells might elicit specific correlated motor responses.

MOTOR CORTEX UNIT CONDITIONING

In our initial studies, the reinforced response pattern was a transient change in the firing rate of a single precentral cell. The most commonly reinforced pattern was a transient increase in firing rate, or "operant burst", which was reinforced on a DRH schedule (differential reinforcement of high rates). With some of these cells we also reinforced a transient decrease in rate on a DR0 schedule (differential reinforcement of zero activity).

The conditioning of operant unit bursts will be used to illustrate many of the procedures and problems involved in these studies. To reinforce patterns of cell activity we used an "activity integrator" (AI) consisting of a parallel RC voltage integrator connected to a Schmitt trigger which set a "reinforcement level" for triggering the feeder. In its most general form the AI had several inputs, each of which could accept a separate voltage signal proportional to the activity of a unit or a muscle (Figure 1). Each of these input voltages could be added to or subtracted from the integrator voltage, and each could be made to contribute more or less to the net integrator voltage through a variable gain control on each channel. In its simplest mode of operation the AI reinforced high rates of unit activity by summing voltage pulses triggered from the cell's action potentials. The gain was adjusted so that on the average the integrator voltage fluctuated at some level (proportional to the firing rate) below the reinforcement level, and only transient peaks of activity drove the integrator voltage to the reinforcement level. As the unit rates increased, the gain could be reduced so that ever higher rates were required to trigger the feeder. In practice the gain was continually adjusted to keep reinforcement rates at approximately 10 to 25 per minute. This procedure required the experimenter to decrease the gain as firing rates went up and increase the gain if the rates suddenly dropped. If the reinforcement level was set too low, maximum response differentiation would not be achieved (Notterman and Mintz, 1965) and reinforcements would be delivered too frequently; if the level was set too high the animal could stop responding altogether due to loss of reinforcement.

In addition to food reinforcement, the monkey had continuous visual feedback in the form of a meter which was illuminated during reinforcement

periods and whose needle deflection was proportional to the integrator voltage. Reinforcement level of the AI corresponded to the extreme rightward position on the meter scale; thus, rightward deflections of the meter needle could become a secondary reinforcer for appropriate responses. To test whether monkeys actually discriminated the meter changes we occasionally started a conditioning period with the meter activated but the feeder turned off. Experienced monkeys initially increased unit rates during such a period, but after a few minutes their responses extinguished. Whether the effective discriminative stimulus (S^D) was illumination or deflection remains untested. Hiatt (1972) reported similar observations with a light as S^D; by presenting this S^D as a "discriminative probe" Hiatt could test for

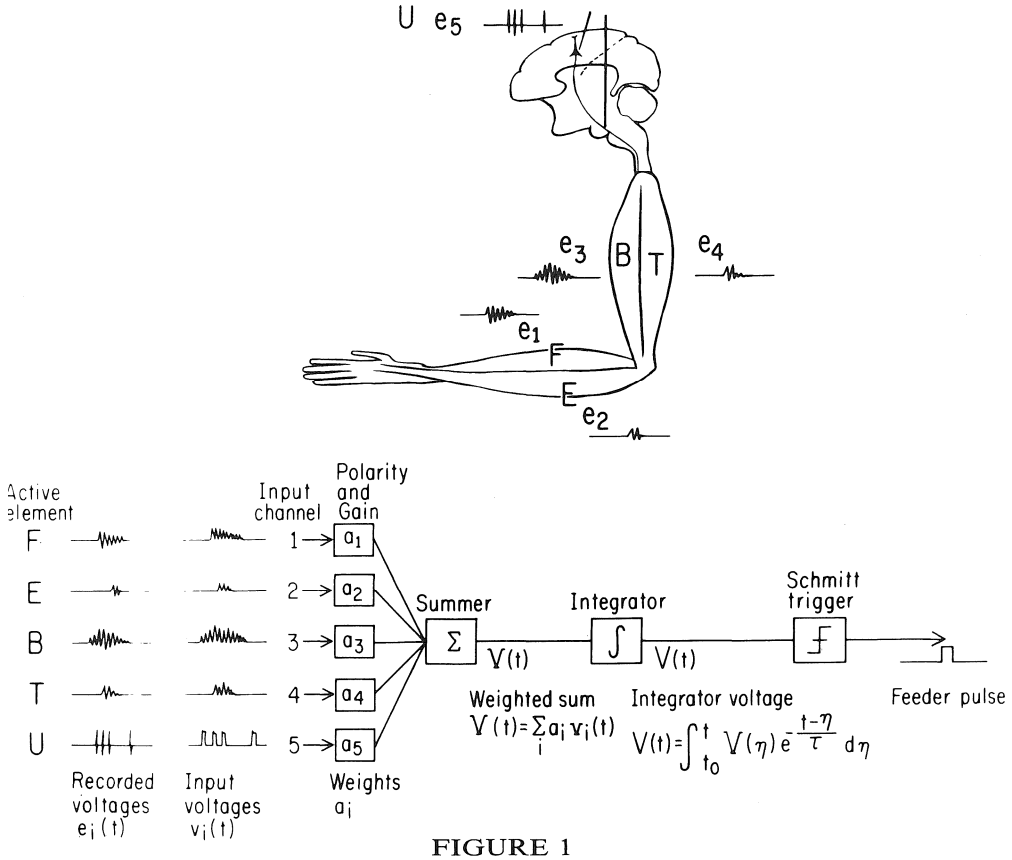


FIGURE 1

General form of activity integrator used to reinforce patterns of cell and muscle activity, with separate inputs for activity of each element. Top shows diagrammatically the recording of unit activity in precentral cortex and EMG activity in contralateral muscles. Input voltages (v_i) are proportional to recorded activity of each element (e_i) and are multiplied by a weighting factor (a_i), then summed. The weighted sum is temporally integrated and when this integrated voltage reaches a reinforcement level set by the Schmitt trigger, the feeder discharges. Polarity of each weighting factor determines whether that element drives the integrator toward or away from reinforcement level; magnitude of each weighting factor determines the relative contribution of that element to the integrator voltage, and can be modified continually during shaping of response patterns (From Fetz and Finocchio, 1971).

conditioned responding without the confounding effects of intracranial stimulation.

The main features of a typical DRH conditioning session are illustrated in Figure 2. During the 12-minute preconditioning period, unit firing rates remained approximately steady at 2.8 $\pm$ 0.9 impulses per second (mean $\pm$ standard deviation). During the first DRH period (DRH-1) apple juice reinforcement was delivered for transient increases in rates, and the meter was illuminated and activated. Initially, relatively low-frequency bursts occurred sporadically but after several minutes they became more intense and recurred more frequently. After about four minutes, average unit activity had reached a new plateau level of 15.4 $\pm$ 4.6 impulses per second. Following each DRH period, we introduced an extinction (SΔ) period to determine whether rates would again revert to preconditioning levels. Average rates did drop during extinction, but not all the way to preconditioning levels. In subsequent DRH periods rates again increased, with the highest average rates obtained during DRH-3. Firing rates were not directly proportional to the reinforcement rates (upper graph), suggesting that increases in unit rates were not unconditioned consequences of reinforcement, as might be the case if the unit responded to reinforcing stimuli or during feeding behavior. The relatively low firing rates at the beginning of the DRH period can be attributed to "acquisition" of the response. (The sudden drop in rate during the last minute of DRH-3 illustrates one of the hazards of advancing the reinforcement criteria too rapidly. As rates increased during DRH-3, the reinforcement level was raised so rapidly that the rate of reinforcements decreased; initially this elicited greater firing rates but beyond a certain point the animal stopped responding altogether.)

The firing pattern of this cell during the first three periods of the session is illustrated in the dot rasters below the graph (Figure 2). These show continuous one-minute samples of activity from the preconditioning period, DRH-1 and SΔ-1. To illustrate the differentiation of operant bursts during the DRH-1 period, we sampled the reinforced bursts at intervals of every 20 seconds throughout the first reinforcement period, and aligned these bursts on successive lines of the dot rasters (Figure 3, top). Early in the period reinforced bursts were relatively weak and brief, in contrast to the longer and more intense bursts occurring at the end of DRH-1. Examples of successive operant bursts occurring during the plateau level of firing in DRH-1 are shown in the lower dot raster display in Figure 3. The time histogram illustrates the mean firing rate for 200 operant bursts during this session, and shows that the peak rate during these bursts attained 60-70 impulses per second. This "response average" also shows that the predominant activity occurred before the feeder discharge, and that there was no increase in activity immediately subsequent to feeder discharge.

To determine the degree to which activity of other cortical units was correlated with that of the reinforced cell, we often positioned the

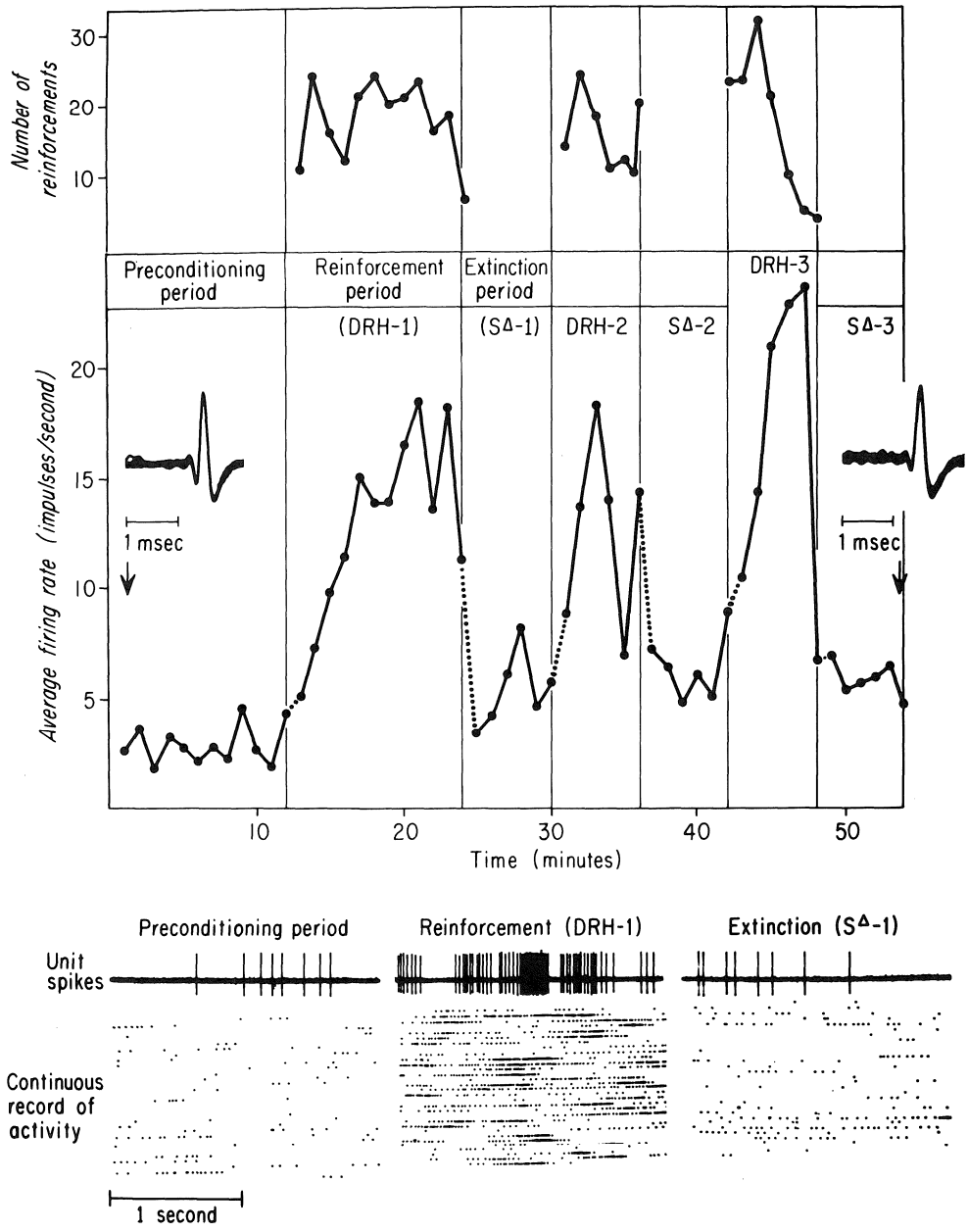


FIGURE 2

Typical unit conditioning session in which a precentral unit was differentially reinforced for high rates. Superimposed action potentials of cell are shown in insets from beginning and end of session (arrows). Firing rate is plotted in successive 1-min averages in middle graph; number of reinforcements delivered per minute is plotted at top. At bottom are samples of unit activity from first three periods; dot rasters show one continuous minute of activity in successive 2-sec sweeps. (From Fetz and Baker, 1973.)

microelectrode so that action potentials of two adjacent cells could be monitored simultaneously and separated electronically into individual pulse trains for each unit. For most unit pairs, when one of the two cells was reinforced for high rates the overall average firing rate of the adjacent cell usually increased also. Olds and Hiatt also reported increases in average rates of "control cells" recorded from adjacent probes during reinforced

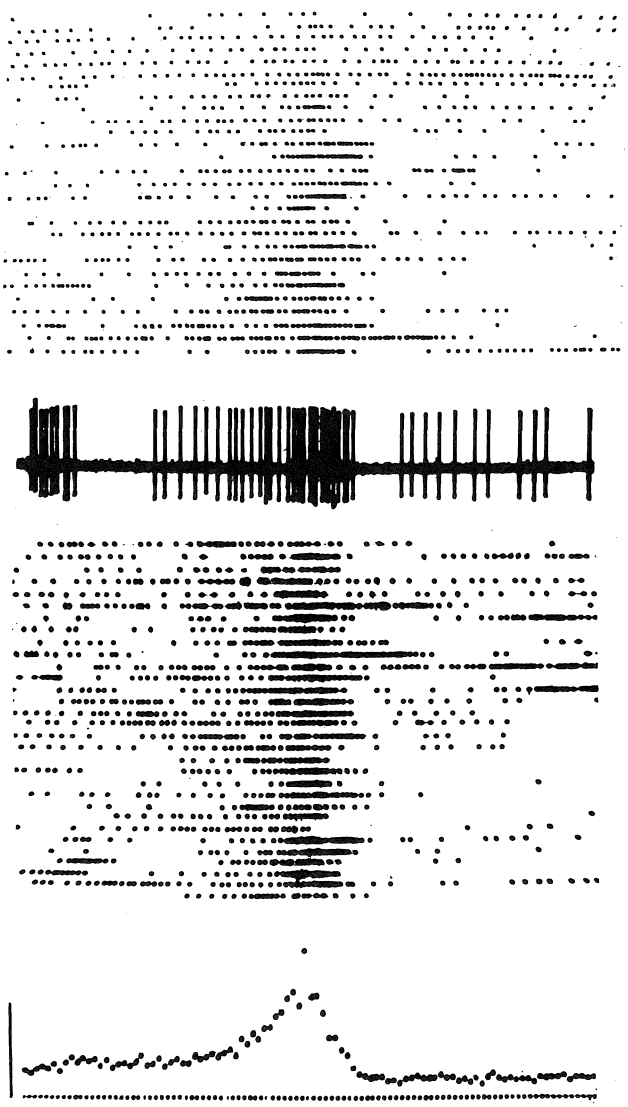


FIGURE 3

Examples of operant unit bursts from session in Figure 2. Duration of each sweep is 2 sec. Top dot rasters show bursts which triggered feeder, sampled approximately every 20 sec from beginning of DRH-1, to show increases in intensity of successive bursts. Spike train illustrates typical operant burst. Dot rasters below illustrate successive operant bursts which trigger feeder at end of DRH-1. Time histogram at bottom is "response average" over 200 unit bursts; peak marks point at which feeder discharged. Vertical bar represents firing rate of 50 per sec.

increases in the experimental units (Olds, 1967; Hiatt, 1972). When we examined the response averages computed from the operant bursts of the reinforced cell, we often found that the adjacent unit exhibited a correlated pattern of activity such as another simple burst (4 cases) or a more complex pattern involving suppression as well as facilitation (3 cases); in some sessions the adjacent unit exhibited no correlated fluctuation in rate with the burst of the reinforced unit (3 cases). In sessions in which two units initially showed correlated activity, the rates could also be differentially conditioned by making reinforcement contingent on simultaneous suppression of one unit with increased activity of the other (Fetz and Baker, 1973).

In view of expectations that neighboring cortical cells would be involved in the same responses, it seems remarkable to find adjacent units whose activity is independent. An example of a pair of relatively independent

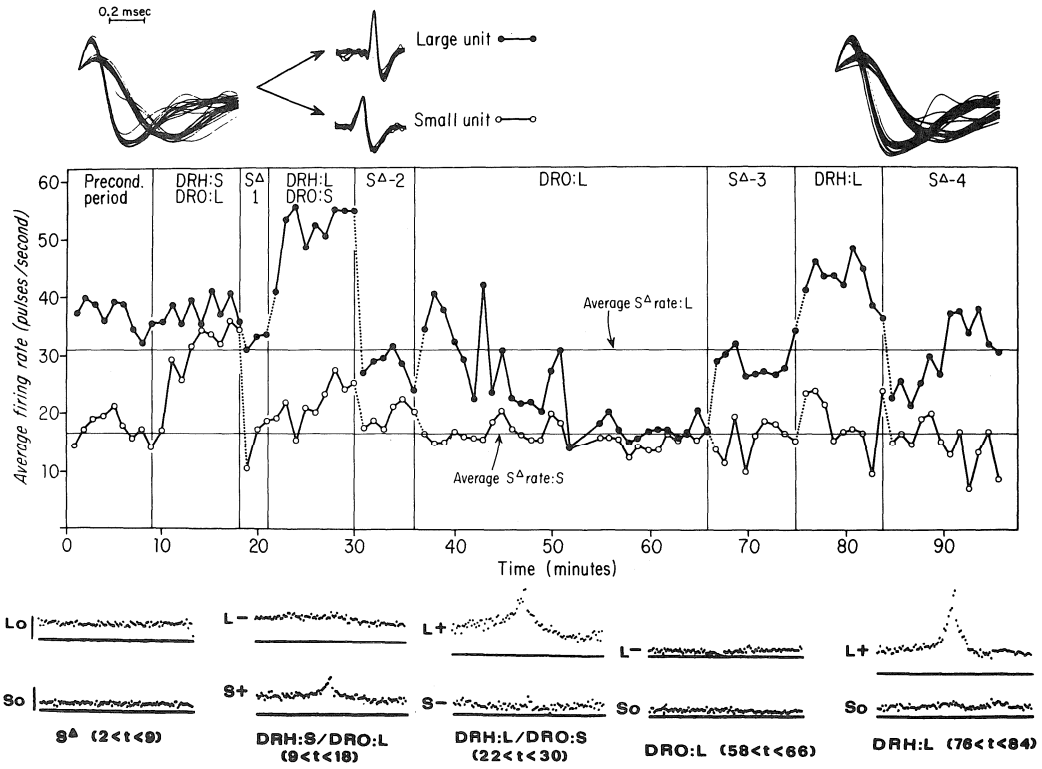


FIGURE 4

Double unit conditioning session in which large and small units were independently controlled. Samples of unit action potentials at top show a fast sweep triggered from both units and separate action potentials corresponding to separate pulse trains used during conditioning. Graph plots 1-min averages of firing rates during different behavioral periods (see text); horizontal lines indicate average time-out rates for both units. Response averages at bottom give time histograms of large and small unit activity during the 2-sec intervals around feeder discharge for each behavioral period. Vertical bars calibrate 50 per sec for all averages (From Fetz and Baker, 1973).

precentral units is illustrated in Figure 4. The points illustrated by this session can be made most simply by considering the behavioral periods in the reverse order in which they occurred during the session. During the last reinforcement period (DRH:L) we reinforced high rates of firing of the large unit with no contingency on the small. Note that large-unit rates increased with negligible change in small-unit rates; this independence was seen both in the 1-minute averages of rates in the graph and in the response average computed around the operant bursts of the large unit (bottom of Figure 4).

During the preceding behavioral period (DR0:L) the large unit was reinforced for low rates. (This was accomplished by feeding pulses from the unit into a negative-polarity input channel of the activity integrator so that pulses from the large unit drove the integrator voltage away from the reinforcement level. To drive the integrator voltage toward the reinforcement level in the absence of unit activity, we introduced regular pulses from a pulse generator into another channel with positive polarity.) At the beginning of this DR0 period the monkey actually increased firing rates—a response pattern which was commonly observed at the beginning of the DR0 periods. Although increased rates were inappropriate for this schedule, they can be understood in terms of the animal's prior reinforcement history. All monkeys in these experiments were initially trained on DRH schedules and were exposed much more to DRH conditioning than to DR0; thus, the illumination of the meter and presentation of reinforcement would presumably be a strong discriminative stimulus for DRH. (An additional set of lights was introduced as a discriminative stimulus for DRH and DR0 but apparently was not effective in this session.) After 12 minutes on DR0 the monkey did suppress unit firing rates below extinction levels and sustained this suppression until SΔ-3, during which rates reverted to time-out levels. Thus the firing rates of this unit could be bidirectionally conditioned, further confirming that rate changes were operants rather than respondents. The second point of interest is that during the DR0:L period the adjacent small unit fired relatively independently, both in the one-minute averages plotted in the graph and in the response averages below.

Considering finally the first two behavioral periods of this session, we see that average rates of either the small unit or the large could be increased without comparable changes in the other. The schedules employed in these periods reinforced differential rates for the two units, *i.e.*, high rates in one associated with low rates in the other. For example, in DRH:L/DR0:S, reinforcement was delivered when the large unit increased its rates while the small unit decreased its rates. (Pulses from the large unit went into a positive-polarity input, driving the integrator voltage toward reinforcement level; pulses from the small unit went into a negative-polarity input, driving the integrator voltage away from reinforcement level.) Firing rates during these differential schedules indicate that the schedules were more successful in increasing average rates of the unit on DRH than in decreasing average rates of the unit on DR0. However, exposure to these schedules was

relatively brief and it seems probable, on the basis of more recent observations, that prolonged differential conditioning might have produced suppression of rates in the unit on DR0. Behavioral analysis of this session would have been simpler had the schedules been presented in reverse order; as it stands, the session leaves open the possibility that initial periods may have influenced performance in later periods. For example, one could imagine that the prior DRH:L/DR0:S period may have conditioned responses involving low rates of the small unit and resulted in similar responses being emitted during the subsequent DRH:L period. However, in light of more recent observations we would find such interactions between different periods of a session improbable. Such ambiguities can be avoided in future work by proceeding from simpler to more complex schedules.

MOTOR RESPONSES CORRELATED WITH OPERANT UNIT BURSTS

To determine whether operant bursts of specific motor cortex cells were associated with specific movement, we allowed the monkey relatively free movement of arms and legs while visually observing his responses through a one-way mirror or a closed-circuit TV monitor. Such observation permitted qualitative characterization of motor responses which accompanied operant bursts of precentral cells, and indicated that for different units these burst-correlated responses fell into three classes.

(1) Generalized and *variable* movements accompanied operant bursts of some cells. These movements often involved more than one limb and were so variable from one burst to the next that it was impossible to determine whether any specific component of the generalized response was repeatedly correlated with unit bursts. Although generalized, such movements usually were associated only with unit bursts and did not continue between bursts.

(2) *Specific* movements involving excursion of one or a few joints in a contralateral limb repeatedly accompanied operant bursts of some cells. In some cases the movements were relatively generalized and variable at the beginning of DRH conditioning, but after 10 to 30 minutes of DRH conditioning a sufficient number of components dropped out until finally operant bursts were repeatedly associated with relatively slight excursions of one specific joint.

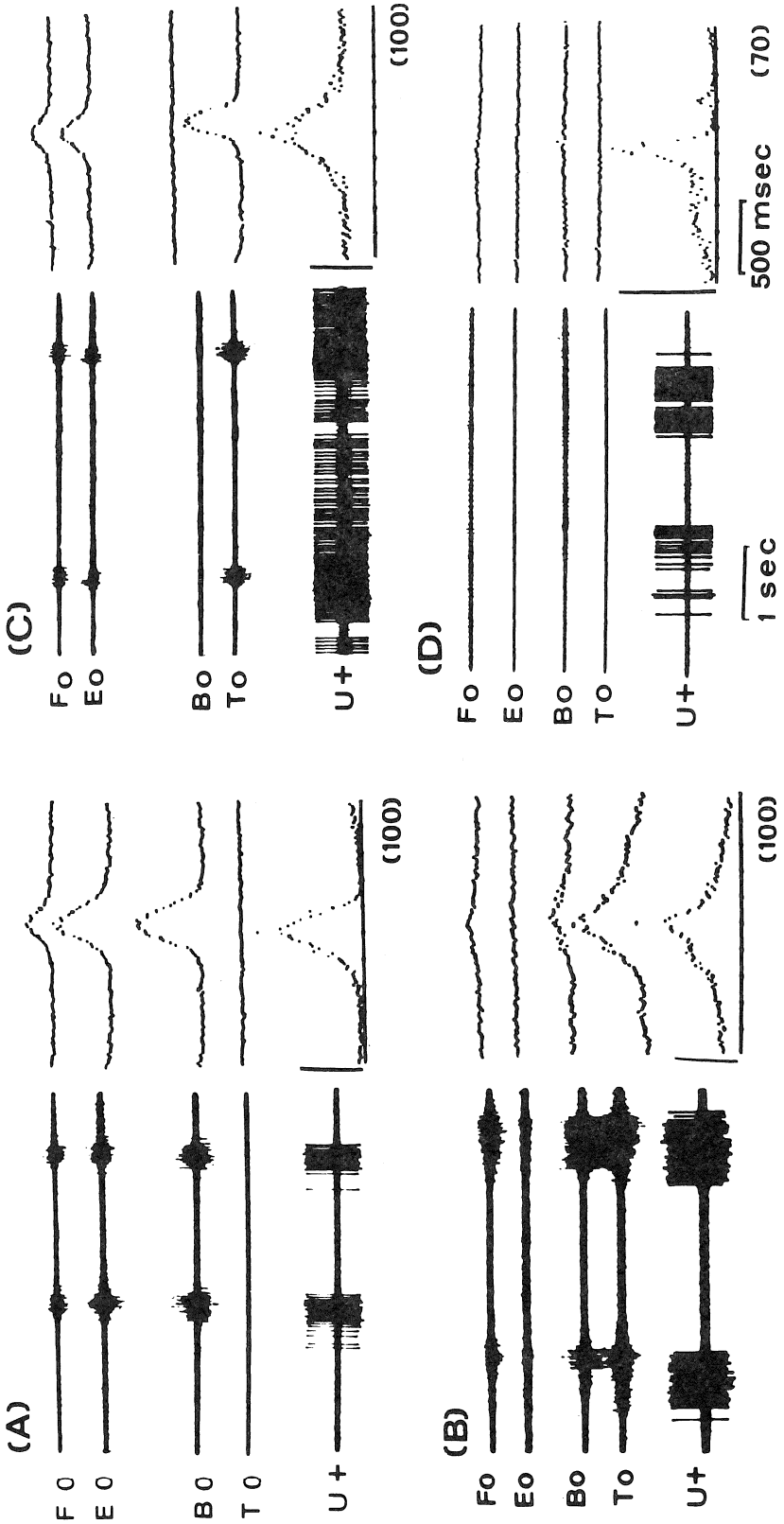
(3) *No* observable movements were seen with bursts of some precentral units. Such cases were typified by relatively little or no motor activity at the beginning of the DRH periods, and the monkey repeatedly generated operant bursts without any observable movement.

While visual observations are relatively qualitative, they do indicate that different movements are associated with different cells and that the monkey did not simply adopt the strategy of making generalized responses which might have activated many precentral cells.

To better quantify the muscle activity associated with operant bursts, we recorded EMG activity of representative muscles of the contralateral limb. Under conditions of free limb movement, surface EMG electrodes proved unusable since the monkey's first movements were invariably directed at tearing the electrodes off. A more successful approach involved electrodes implanted in the belly of specific muscles and led subcutaneously to a connector on the skull. Such electrodes did not impair movements or generate artifacts; furthermore, once implanted, they allowed easy and repeatable monitoring of specific limb muscles. The muscle activity associated with operant bursts typically occurred as a burst of EMG activity, with a time course similar to that of the unit burst. Under conditions of free limb movement the relative amount of EMG activity in each muscle could be quite variable from one unit burst to the next. However, with the arm held in an isometric cast the correlated muscle activity was usually more consistent from one operant burst to the next. Under both conditions we found it convenient to average the rectified EMG activity over 50 to 100 reinforced unit bursts to obtain a response average of the associated muscle activity. The time course of these response averages indicated that the average EMG burst overlapped to a great extent with the average unit burst; usually the onset and peak of the unit burst preceded the onset and peak, respectively, of the EMG burst.

To illustrate the fact that different patterns of muscle activity accompanied operant bursts of different cells, Figure 5 shows unit bursts and correlated EMG activity for four cells recorded within 3 millimeters of each other in the motor cortex of the same monkey. In each case reinforcement was contingent only on operant bursts of the unit, not on any muscle activity. The data samples show that the monkey generated an operant unit burst and a correlated burst of isometric EMG activity in specific arm muscles approximately every two seconds. It is clear that a different set of muscles became active with operant bursts of each unit. Bursts of Cell A were repeatedly associated with EMG activity in biceps and both wrist muscles; Cell B was predominantly correlated with triceps and biceps; Cell C with triceps and wrist muscles; and Cell D fired in bursts without any correlated EMG activity. Thus, the relative amount of EMG activity in each arm muscle was different for each motor cortex cell.

To facilitate discussion, we can define the set of muscles whose activity is temporally correlated with operant bursts of a precentral cell as that cell's behavioral "motor field". Such a concept is tentatively proposed as the motor analog of the sensory receptive field of cells in sensory systems. In each case the "field" is the locus of peripheral elements (muscles or receptors) whose activity is correlated with activity of a central neuron. In a similar way, Schiller and Stryker (1972) have used the term "motor field" to denote the magnitude and direction of the saccades optimally correlated with bursts of superior colliculus cells. In their experiments the set of burst-correlated saccades was obtained from a larger set of spontaneously


(A)
F O
E O
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T O
U +
(100)
(B)
Fo
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Eo
Bo
To
U+
(100)
(D)
Fo
Eo
Bo
To
U+
(70)
500 msec
1 sec

occurring saccades. Clearly, operant conditioning of unit bursts could be a more direct method of eliciting a cell's motor field.

In order to assess the relative merits of operantly conditioning unit activity as a technique for investigating the relationship between motor cortex cells and movements, we can contrast the strategy of reinforcing cell activity and observing correlated motor responses with the technique of reinforcing specific movements and observing correlated cell activity. In the latter approach monkeys were trained to repeat certain simple stereotyped movements, such as flexion and extension of the wrist, in which the parameters of position and force could be quantified and brought under experimental control. Relating cell activity to repeatable response patterns with measurable mechanical parameters offers distinct advantages if the object is to document quantitatively the role of various cells in a standard response. The power of this approach is fully realized when one of the response parameters can be systematically varied independently of the others, thereby resolving the question of which parameter a given cell may be most strongly related to (Evarts, 1968; Humphrey *et al.*, 1970; Brooks *et al.*, 1972). However, the fruitfulness of this approach depends on the experimenter's skill in isolating cells that are related to the pretrained motor response. Even in precentral cortex where cells with similar outputs are presumably congregated together, the proportion of units unrelated to a specific response can be relatively high.

In discussing this problem, Evarts (1968) pointed out that documenting the relation of precentral "motor" cortex cells to one specific movement is analogous to documenting the relation of postcentral "sensory" cortex cells to one specific stimulus. In each case some cortical units may be directly related to the peripheral event (movement or stimulus); others will be indirectly related, and the remainder will be unrelated. Determining which peripheral events are optimally associated with each unit is relatively straightforward in the sensory system: one can test a variety of stimuli to find the modalities and receptive fields of those stimuli which most effectively drive the postcentral cells. Analogously, in the motor system one could in principle search for that motor pattern with which a given precentral cell may be most strongly correlated by training the animal to

FIGURE 5

Muscle responses correlated with operant bursts of four different precentral cells in the same monkey. With his arm placed in an isometric cast, EMG activity was recorded from flexor carpi radialis (F), extensor carpi radialis (E), biceps (B) and triceps (T). Unit activity was reinforced (U+) with no contingency on muscles. Samples at left illustrate two successive responses in a 5-sec interval. Response averages at right represent averages of full-wave rectified EMG activity and time histograms of unit activity over the designated number of responses (vertical calibration bar equals 50 impulses per sec). Units B, C, and D were identified as PT cells on the basis of a short-latency antidromic response; unit A was not tested. All cells were located within 3 mm of each other. (From Fetz *et al.*, in press.)

make an exhaustive repertoire of movements, and ascertaining the ones in which the cell is optimally involved. However, the problems of anticipating and training all potentially relevant motor response patterns are prohibitive. A more practical and direct strategy would be to reinforce the activity of each cell isolated by the microelectrode and observe the correlated responses. Without constraints imposed by the measuring apparatus the animal would be free to emit any number of motor responses, whether or not they involve a specific joint. Under unrestrained conditions, however, these responses can be characterized only qualitatively. In our experiments, a convenient compromise between totally unrestrained, unquantifiable movements and measurable but predetermined responses is the isometric situation in which the position is held constant and force can be measured (or assumed proportional to rectified EMG activity); in the isometric cast the animal remains free to contract any set of muscles in association with the reinforced unit bursts. Under these conditions operant reinforcement of motor cortex cells elicited different "motor fields" for different cells (Figure 5).

The analogy between motor field and receptive field implied above is limited by a crucial difference: whereas stimulation of the receptive field provides relatively secure evidence for a synaptic pathway from the peripheral receptors to the sensory cortex cell, reinforcing activity of a motor cortex cell and observing correlated muscle activity does not provide conclusive evidence for a functional connection. The problem is that the operational definition of the motor field involves a behavioral response in which elements may be temporally correlated without any underlying physiological connection. By a functional connection we mean an anatomical pathway from the motor cortex cell to motoneurons, whereby the activity of the former synaptically influences the activity of the latter. The way to experimentally confirm such a synaptic connection—in principle if not in practice—is to stimulate the cortical cell and observe the synaptic potentials generated in various motoneurons. Such a procedure would define what we might call the cell's physiological "muscle field"—namely, those muscles whose motoneurons are synaptically affected by activity of that cell. This muscle field actually represents a closer analog of the concept of a sensory receptive field, because activation of the responding elements (muscles) is mediated by a physiological connection. Unfortunately, stimulating a cortical cell in isolation (presumably with an intracellular microelectrode) and measuring synaptic responses of various motoneurons is prohibitively difficult. However, Asanuma and Rosen (1972) have suggested a practical approximation to this procedure involving intracranial microstimulation near a specific set of cells combined with observation of muscle responses. The muscles affected by microstimulation near a cell will differ from those influenced by that cell alone (*i.e.*, its physiological muscle field) to the extent that the extracellular stimulation would excite other neural elements in addition to the given cortical cell.

TEMPORAL CORRELATIONS AND FUNCTIONAL CONNECTIONS

Having made the operational distinction between the set of muscles temporally correlated with operant bursts of a cell (behavioral motor field) and the set of muscles whose motoneurons are functionally connected with that cell (physiological muscle field), it is meaningful to consider their possible relation. The basic observable in chronic recording experiments is the correlation between the activity of two elements, such as a cortical cell and a contralateral muscle. From such observed correlations one would like to make deductions concerning possible functional connections. However, it is clear that the observation of a temporal correlation between two elements during a specific response pattern is not convincing evidence for a functional connection. First of all, a temporal correlation in a single behavioral situation is not *sufficient* evidence to establish a functional connection; a given unit and muscle could be coactivated during a given response pattern without any synaptic connection between the two. In fact, strong correlations can be produced by behavioral procedures such as overtraining until responses recur in a repeatable stereotyped pattern. Furthermore, a temporal correlation is not even a *necessary* consequence of functional connections. A motor cortex cell could be synaptically connected to a motoneuron, but as long as its synaptic influences can be overriden by other connections on the motoneuron, the activity of the two need not be invariantly correlated. Consequently, if the temporal correlations observed in a given behavioral situation are neither necessary nor sufficient evidence for functional connections, we must consider what additional observations, if any, might be possible to help establish or disprove the existence of such connections.

Considering first the basic observable in a behavioral situation—namely, the correlation between activities of two elements—we can assess the strength or stability of such a correlation by several observations. First, in a given behavioral situation—*i.e.*, when one particular response is repeatedly reinforced—we can examine the *variability* of the correlation from one response to the next. If the reinforced response recurs in a repeatable manner, those correlated responses which also recur in a repeatable fashion could be considered to be more strongly correlated than any associated responses whose amplitude and duration varied. When the amplitude or duration of the reinforced response varies from trial to trial, those correlated responses whose amplitude and duration vary proportionately would be more strongly correlated than any whose activity fluctuated independently. In our experience operant bursts of a precentral unit were sometimes consistently proportional to EMG bursts in some specific muscles, while bursts of other muscles were more variably correlated. Another kind of variability in the correlated activity occurs when the intensity of the correlated response changes gradually and systematically throughout the

session. In some experiments activity which appeared initially correlated with the reinforced response eventually dropped out after numerous repetitions of the response. Such associated activity is obviously weakly correlated. Presumably the rate at which such associated responses drop out is a function of their variability from one reinforced response to the next; the more variable their correlation with the reinforced response, the more variable their correlation with the reinforcer, and the less likely they are to be sustained by the reinforcement. This phenomenon would seem to be relatively unreliable as a method of eliminating superstitious components of the correlated response pattern; nevertheless, when such spontaneous dissociation occurs, it certainly can be interpreted as reflecting a weak correlation.

The second test of the strength of a correlation would be to examine the activity of the correlated elements under a variety of *different behavioral conditions*. The correlation would be strong if the activity of the two elements continued to be correlated when either one or the other is reinforced, or when a motor response involving either element is reinforced. In recent studies we reinforced isolated contractions in specific arm muscles and observed unit-muscle correlations under various response patterns (Fetz and Finocchio, 1971). The activity of one precentral cell in relation to the isolated activity of four different arm muscles, a flexor and an extensor of the wrist and of the elbow, is illustrated in Figure 6. This unit fired most strongly in conjunction with the biceps bursts, but also became active with bursts of flexor carpi radialis (FCR). Negligible unit activity accompanied bursts of the extensor muscles: triceps and extensor carpi radialis (ECR). Correlations appearing under these behavioral conditions can be compared with those occurring when operant bursts of the cell were reinforced; with no contingency on the muscles, operant bursts of this cell were accompanied by activity in biceps and *both* wrist muscles (Figure 7E). Thus, for biceps and FCR the unit-muscle correlations appeared when either the muscle or the unit was reinforced; for ECR the correlation appeared only when the unit was reinforced, suggesting a weaker correlation between ECR and the unit.

Two additional behavioral conditions in which this unit was observed were active and passive elbow movements (see Figure 2 in Fetz and Finocchio, 1971). When the monkey actively flexed the elbow, the unit fired in association with biceps and both wrist muscles; when he actively extended the elbow the unit did not fire with activity of triceps and both wrist muscles. Again, these observations suggest a stronger correlation with biceps than with the other muscles. When the elbow was passively moved, the unit was driven by passive extension, but not flexion. During the passive extension EMG activity was virtually absent. These observations suggest that observed correlations are as much a function of the behavioral conditions as of any underlying physiological connection. Those correlations which appear during a variety of reinforced response patterns could be considered stronger than those which appear with only a few.

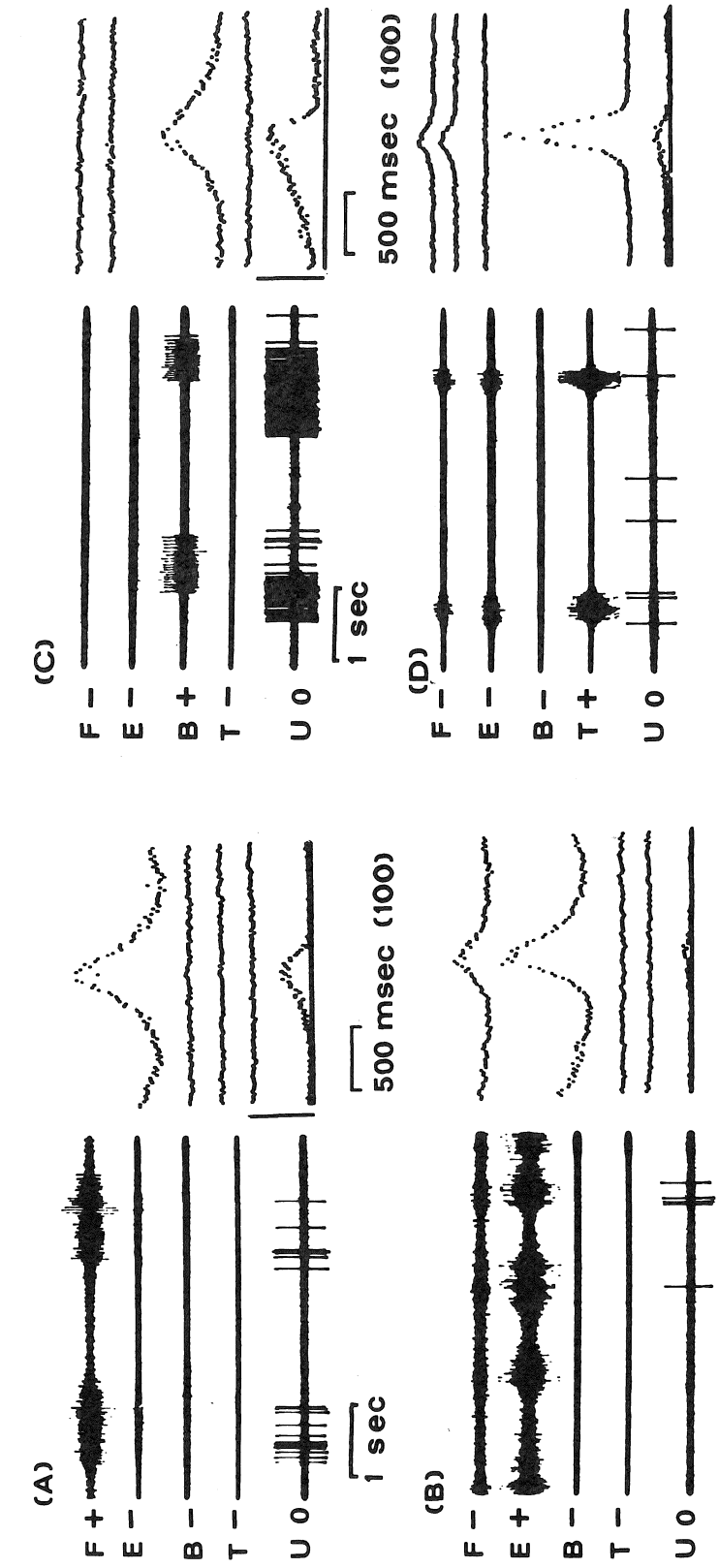

FIGURE 6

Relation of precentral cell to isolated activity in four arm muscles. With his arm held in an isometric cast, the monkey was given reinforcement for isolated contraction of flexor carpi radialis (A), extensor carpi radialis (B), biceps (C), and triceps (D). Each sample at left shows two successive responses on a 5-sec sweep. Response averages over 100 successive responses are shown at right. Vertical bar equals 50 impulses per sec (Partly from Fetz and Finocchio, 1971).

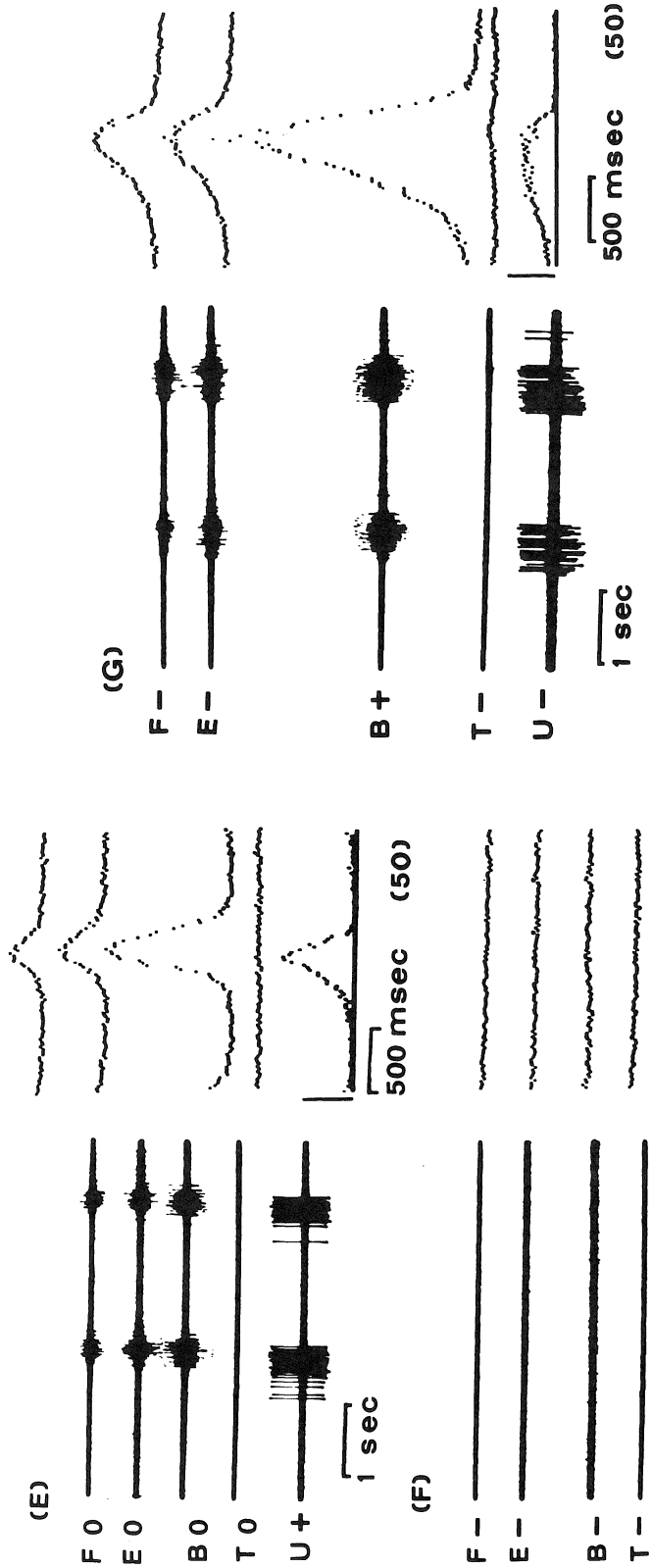

FIGURE 7

Dissociation of EMG from unit activity for cell of Figure 6. Same convention as Figure 6 except response averages include 50 responses. Scale is same for E-G, but different from Figure 6. (E) reinforcing operant bursts of precentral cell with no contingency on muscles; (F) reinforcing operant burst of cell and muscle suppression; (G) reinforcing biceps activity and suppression of unit and other muscles (Partly from Fetz and Finocchio, 1971).

A third and particularly potent test of the stability of an observed correlation is to directly reinforce its *dissociation.* If activity of one of the two elements can be suppressed during continued activity of the other, their correlation is clearly weaker than if the dissociation is impossible. In the above example, when the monkey was given reinforcement for operant bursts of the cell during suppression of all EMG activity, he readily learned to generate this response pattern (Figure 7F). This would indicate that muscle activity was not necessary to generate the unit activity. Such dissociation of correlated muscle activity has been successful in every case in which the monkey was required to fire a precentral cell and suppress the previously correlated muscles. While successful dissociation demonstrates that the two elements need not be invariantly correlated, it still does not disprove the possibility of a functional connection; such a connection could still exist but the synaptic effects of the cortical cell could be overridden by influences mediated by other connections during the dissociated response. One might expect that an existing connection would make dissociation more difficult, but this remains to be proven. On the other hand, if an attempted dissociation fails, there are two types of explanation. The dissociation may be physiologically impossible, as would be the case with a prepotent synaptic connection. However, failure may also be related to behavioral causes such as lack of motivation or insufficient shaping. For the cell in Figure 7, the reverse dissociation, namely suppression of unit activity during intense bursts of biceps activity, was not obtained. Before interpreting this as evidence that unit activity was necessary for biceps contraction, it is important to note that this schedule was imposed after seven hours of conditioning and the monkey's responses were recurring relatively infrequently, suggesting that fatigue or satiation could also account for the inability to perform the required pattern. Thus, failure to shape a dissociation can be considered evidence of a strong correlation only if behavioral explanations for the failure are eliminated.

The above criteria for strong correlations involve examination of the stability of the correlation (1) during spontaneous variations in successive responses under any one behavioral condition, (2) during different reinforced response patterns, and (3) during reinforced dissociation. Since all these approaches involve observations of correlations, they can never prove the existence of functional connections. In order to test whether a functional connection exists between the two correlated elements, one must employ some sort of direct physiological procedure. Two such tests, commonly used in acute physiological experiments, can also be adopted in chronic experiments. First, by blocking the possible anatomical connection between the two elements, one can test whether such a connection is necessary for their coactivation. Secondly, by electrically stimulating one element and measuring the response of the other, one can directly demonstrate the existence of a physiological connection.

One could test whether a specific pathway is involved in mediating the

interaction between two elements by *blocking conduction* in that pathway. A surgical or electrolytic lesion can often be used to eliminate a specific pathway, but such a lesion is permanent. More reversible methods, such as anesthetic block or cold block, are less specific in effect but offer the important advantage that function can be restored and the procedures can be repeated many times with the same preparation (Brooks *et al.*, 1972). In cases where the possible functional pathway involves muscle activity, a neuromuscular blocking agent can often be used to reversibly eliminate motor responses. When such direct interventions abolish the correlated activity, one can conclude that the eliminated pathway was a functional connection necessary for the correlation.

In considering the relation between motor cortex cells and movements it is clear that a causal relationship may exist in either direction. Since many precentral cells can be driven by stimulating peripheral receptors (Albe-Fessard and Liebeskind, 1966; Fetz and Baker, 1969; Rosen and Asanuma, 1972), one must consider the possibility that the monkey activated the reinforced cells through movements which stimulated such receptors. To some extent, the relative timing of unit and muscle activity suggests that unit activity preceded EMG activity. Although their overlap is greater than their separation, the onset and peak of the unit bursts typically preceded the onset and peak respectively of the EMG by 20 to 100 msec. This relative timing is consistent with other studies in which movements were reinforced and motor cortex cells were found to modulate their firing rates up to 100 msec before the recorded EMG activity (Evarts, 1967, 1968; Humphrey *et al.*, 1970; Luschei *et al.*, 1971; Fetz and Finocchio, 1971). Thus, even though precentral cells may respond to peripheral stimulation under passive conditions, they can also be activated by central pathways prior to a voluntary response. In the case of operant bursts, the increased cell activity occurring prior to any recorded EMG activity could not be due to sensory feedback from such peripheral responses. However, the possibility remains that some of the unit activity later in the burst could be sustained by afferent impulses. The degree to which sensory input contributes to sustained precentral unit activity might be directly investigated by blocking the afferent pathway or blocking neuromuscular transmission. While we have not performed these interventions in these experiments, Taub and Berman (1968) have trained bilaterally deafferented monkeys to emit motor responses, indicating that some motor centers can be activated without sensory feedback.

Hiatt (1972) investigated the question of whether motor responses mediated conditioned unit activity, by paralyzing rats with gallamine triethiodide (Flaxedil) while continuing to reinforce increased rates with MFB stimulation. Gallamine alone decreased or abolished activity in about half the units. Of the testable cells, one-third continued to exhibit increased responding during the discriminative stimulus after paralysis. Increased responding was maintained in one of six cerebellar units and in all five of the

brain stem units (recorded in five different animals), but in none of the seven units in other areas. Hiatt concluded that those units which the rat did not activate under paralysis had been driven by "feedback excitation from conditioned movements". Such a possibility could have been confirmed by testing whether the cells responded to passive movements or to cutaneous stimulation. Again, before reaching firm conclusions concerning physiological connections on the basis of response failures, it is important to recognize alternative behavioral explanations. In experiments employing neuromuscular blocking agents and artificial respiration it is always possible that these procedures might alter the state of the animal so drastically that he would not respond. The fact that responding under paralysis was sustained in brain stem units in Hiatt's study, as well as autonomic responses in other studies, suggests that some operants can continue to be emitted when muscles are paralyzed. The optimal experimental design would employ an operant which survives paralysis in the same experiment as the abolished operant, to show that the latter was not lost for behavioral reasons.

A second method of directly demonstrating a pathway between two elements employs *electrical stimulation* of one to evoke responses in the other. An invariant, short-latency response would indicate a relatively direct connection. In our experiments, after recording the activity of cells correlated with specific muscles, we sometimes stimulated motor cortex through the microelectrode at the same point. This usually evoked a short latency (15 msec) response in the muscles which had been behaviorally correlated with the unit; however, other arm muscles sometimes responded at even lower thresholds. For example, the unit in Figures 6 and 7 was optimally correlated with biceps in the behavioral situations. Electrical stimulation at this cortical point produced the lowest threshold responses in the wrist muscles; only at higher intensity did biceps become active. This suggests that the neural elements stimulated electrically had more potent synaptic connections to distal muscle motoneurons than to proximal muscle motoneurons, as measured by relative threshold (see also Phillips and Porter, 1964; Porter, 1973). The fact that reinforcing operant bursts evoked correlated activity in a different set of muscles than did electrically stimulating the cortex at the same point (*i.e.*, the fact that the behavioral motor field is different from the Asanuma approximation to the physiological muscle field) is readily understood when one realizes that neither method involves activation of one cortical cell in isolation; the additional elements involved may be quite different under each condition and can readily explain the difference between the associated muscle activities. Discrepancies between responses correlated with unit activity in a behavioral situation and responses evoked by electrical stimulation have been observed in other cortical areas as well (Luschei *et al.*, 1971; Towe, 1973). A closer congruence has been reported between saccades correlated with superior colliculus unit bursts and eye movements evoked by electrical stimulation at

the same point (Schiller and Stryker, 1972). Even though the relative amount of muscle activity evoked by electrical stimulation may not be identical in detail with the relative amount of muscle activity accompanying operant bursts, electrical stimulation can nevertheless demonstrate the existence of a functional connection.

OPERANT CONDITIONING OF EPILEPTIC CELLS

In addition to the above studies on the relation of motor cortex cells to movements, we have also used operant reinforcement of unit activity to investigate the degree of synaptic control over the firing patterns of epileptic cells. In the monkey a chronic epileptogenic focus can be produced by subpial injection of alumina cream in pre- and postcentral cortex. After four to eight weeks the local EEG exhibits typical sharp-wave patterns and most cells in the region are firing in abnormal high-frequency bursts. Such a focus can also precipitate generalized seizures. In collaboration with Dr. Allen Wyler we investigated the degree to which a monkey could learn to control the firing rates and firing patterns of spontaneously bursting cells near an alumina focus.

As shown in Figure 8, the predominant firing pattern of these cells was a high-frequency burst which recurred with a remarkably stereotyped temporal pattern in which the first interspike interval was consistently longer than intervals in the rest of the bursts. Properties of these so-called long first interval (LFI) bursts have been documented by Calvin *et al.* (1968) and by Wyler *et al.* (1973). Besides occurring spontaneously, LFI bursts may also be antidromically evoked by a single shock to the pyramidal tract, suggesting that the burst-generating mechanism is a pacemaker within the cell (Wyler *et al.*, 1973). In addition to the LFI bursts, these cells also occasionally fired in a more tonic "regular" pattern typical of normal precentral cells. During regular firing, interspike intervals were usually longer than even the first intervals of the bursts, as shown by the interspike interval histogram in Figure 8B. This feature allowed us to generate separate pulse trains for spikes which occurred during bursts and for spikes which occurred during regular activity. This enabled us to continuously monitor the proportion of spikes which occurred in bursts for any time interval (*e.g.*, 100 sec); this ratio, called the epileptic index (EI), typically ranged between 80 and 99 percent for the cells in this study. On-line generation of separate pulse trains for spikes in bursts and spikes in regular activity also allowed us to reinforce these two modes of activity differentially (Fetz and Wyler, 1973). Thus, in addition to reinforcing increases and decreases in total rate on DRH and DR0 schedules, respectively, we could also differentially reinforce regular activity (DRR) or burst activity (DRB). To reinforce regular activity, pulses from regular spikes drove the AI toward reinforcement level while pulses from burst spikes drove the AI away from

reinforcement level (Figure 9). To differentially reinforce burst activity, the input polarities for these pulses were reversed.

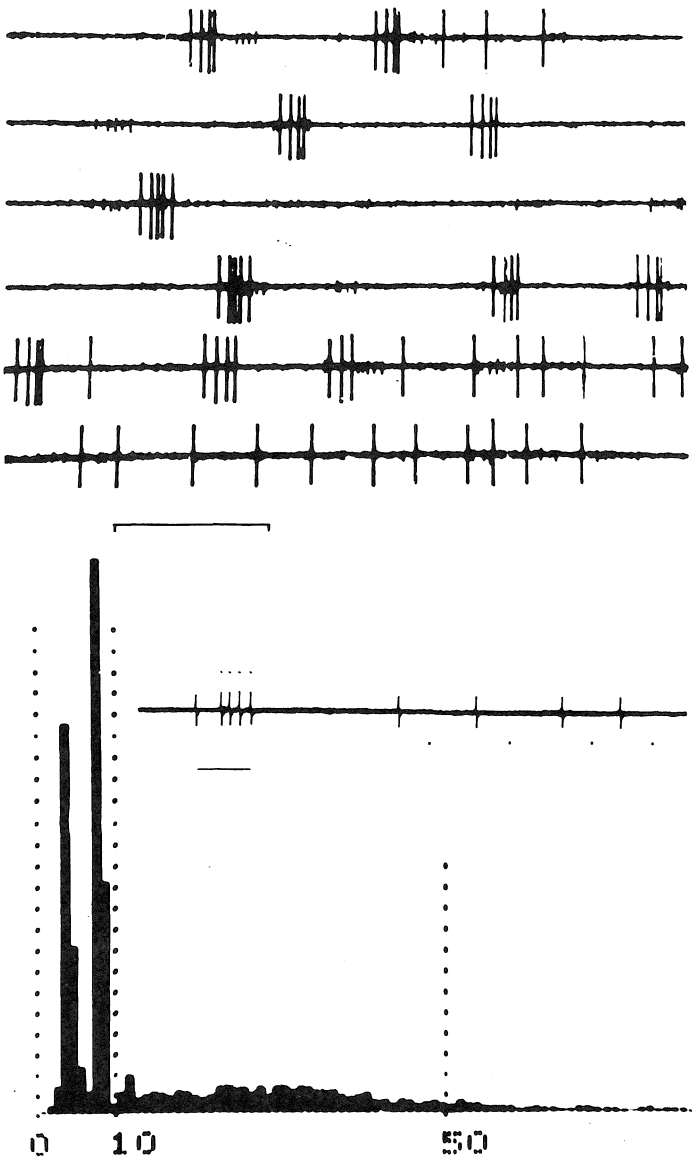

FIGURE 8

Examples of firing patterns of precentral PT cells near a chronic alumina focus. Top illustrates continuous record of activity in successive sweeps. Bottom shows interspike interval histogram of cell activity including both burst and regular firing modes. First two histogram peaks represent intervals occurring during LFI bursts; distribution above 10 msec represents intervals occurring during regular firing (From Fetz and Wyler, 1973).

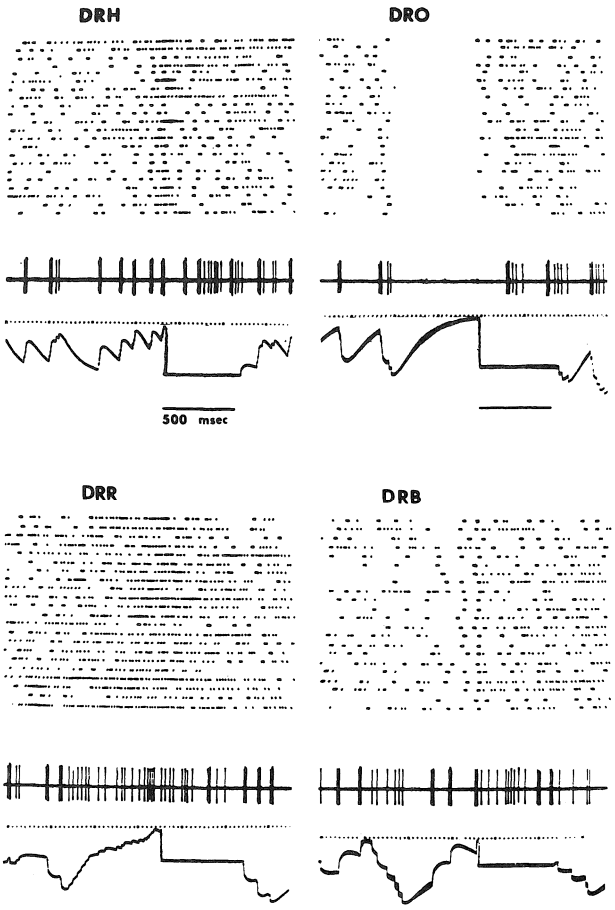

FIGURE 9

Samples of reinforced firing patterns of one epileptic unit recorded during four different behavioral schedules. For each section a single spike train is shown with corresponding trajectory of the AI below (reinforcement level indicated by dotted line). Clumped spikes represent LFI bursts and single spikes represent "regular" firing. Dot rasters show samples of successive responses which triggered the feeder, with LFI bursts shown by fused dots. During DRH (top left) all spikes drove AI toward reinforcement level; during DR0 (top right) all spikes drove AI away from reinforcement level, while the multivibrator pulses drove AI toward reinforcement level in the absence of unit activity. During DRR (bottom left) pulses from regular spikes drove AI toward reinforcement level while pulses from burst spikes drove AI away. During DRB (bottom right) burst pulses drove AI toward reinforcement level and regular pulses drove AI away from reinforcement level (From Fetz and Wyler, 1973).

To summarize our results, the monkey readily learned to increase total rates of all conditioned epileptic cells under DRH schedules. Up to a point, rate increases occurred without any consistent change in the EI, meaning that the number of bursts increased in proportion to the total number of spikes. In some cases, increases in total rates were accompanied by a slight drop in the EI, indicating that relatively more regular activity was emitted. When the monkey was given reinforcement for low rates he could produce prolonged pauses in cell activity (Figure 9). In some cases these recurred sufficiently frequently to decrease total average rates; in other cases intervening periods of higher activity precluded any decrease in average rate. Nevertheless, examination of DR0 responses showed that pauses in cell activity were consistently followed by a burst pattern rather than by regular activity, suggesting that suppression of cell firing enhanced the burst-generating mechanism.

When the monkey was given reinforcement differentially for regular activity on DRR he reduced the epileptic index in two ways: he decreased the absolute number of bursts per second and also increased the number of regular spikes per second; the latter predominated, producing a concomitant increase in total rate (Figure 9). This suggests that sufficiently high synaptic drive on the cell could produce a suppression or occlusion of the burst-generating mechanism. Giving the monkey differential reinforcement for burst activity produced transient periods in which bursts recurred more often, along with a drop in total activity (Figure 9). However, net increases in average epileptic index under DRB conditions were not consistently obtained in a limited exposure to this schedule in this study.

These results indicate that a monkey with an epileptogenic alumina focus could demonstrate some synaptic control over firing rates and firing patterns of cells whose predominant mode of activity was a high-frequency burst pattern. Although we did not monitor the EEG in these experiments, we have since observed that epileptic bursts in cells tend to correlate with sharp waves in the EEG, while regular firing is often associated with a desynchronized EEG. This suggests that it may be feasible to train epileptic patients to control the number of interictal EEG spikes with appropriate "biofeedback". It remains to be documented whether continued training of interictal unit or EEG patterns modifies susceptibility to generalized seizures as has been shown for sensorimotor rhythm training (Sterman and Friar, 1972).

SUMMARY

In summary, we have reviewed experiments on operant conditioning of single-unit activity and have considered this technique as a way of eliciting correlated behavioral responses. When operant bursts of precentral "motor" cortex cells were reinforced under conditions of relatively free limb

movement, various types of correlated motor responses were visually observed, from generalized and variable activity, through specific movements of specific joints, to no movements at all. Under isometric conditions operant bursts were often correlated with EMG bursts in specific muscles of the contralateral limb; these bursts broadly coincided with precentral unit bursts. The set of muscles coactivated with operant bursts of a unit—defined as the cell's "motor field"—could be different for different cells in the same cortical region.

The nature of the functional connection between a precentral unit and the motoneurons of the correlated muscles was considered in detail; this connection is difficult to assess on the basis of correlations observed in a specific behavioral situation. Additional means of assessing the "strength" of a correlation between unit and muscle were proposed, including the degree of covariation from one reinforced response to the next, the appearance of the correlation under different behavioral conditions, and its resistance to operantly reinforced dissociation. Ultimately, observation of temporal correlations in a behavioral situation is neither necessary nor sufficient evidence for the existence of a functional connection in the physiological sense. To determine whether anatomical connections exist between the correlated elements, one must employ additional physiological techniques such as stimulation and ablation.

Operant conditioning techniques have also proved successful in controlling the firing pattern of epileptic cells in a monkey with a chronic alumina focus. In cells near the focus, the monkey could modify not only overall firing rates but also a relative amount of epileptic burst activity.

REFERENCES

ALBE-FESSARD AND LIEBESKIND, 1966.

Albe-Fessard, D. and Liebeskind, J. Origine des messages somato-sensitifs activant les cellules du cortex moteur chez le singe. *Exp. Brain Res.*, 1:127-146, 1966.

ASANUMA AND ROSEN, 1972.

Asanuma, H. and Rosen, I. Topographical organization of cortical efferent zones projecting to distal forelimb muscles in the monkey. *Exp. Brain Res.*, 14:243-256, 1972.

BLACK, 1972.

Black, A.H. The operant conditioning of central nervous system electrical activity. In: *The Psychology of Learning and Motivation, Vol.* 6, (G.H. Bower, Ed.). New York, Academic Press, 1972. pp. 47-95.

BROOKS ET AL., 1972.

Brooks, V.B., Adrien, J., and Dykes, R.W. Task-related discharge of neurons in motor cortex and effects of dendate cooling. *Brain Res.*, 40:85-88, 1972.

CALVIN ET AL., 1968.

Calvin, W.H., Sypert, G.W., and Ward, A.A. Structured timing patterns within bursts from epileptic neurons in undrugged monkey cortex. *Exp. Neurol.*, 21:535-549, 1968.

CHANG ET AL., 1947.

Chang, H.T., Ruch, T.C., and Ward, A.A., Jr. Topographical representation of muscles in motor cortex of monkeys. *J. Neurophysiol.*, 10:39-56, 1947.

EVARTS, 1967.

Evarts, E.V. Representation of movements and muscles by pyramidal tract neurons of the precentral motor cortex. In: *Neurophysiological Basis of Normal and Abnormal Motor Activities* (M.D. Yahr and D.P. Purpura, Eds.). Hewlett, Raven Press, 1967. pp. 215-251.

EVARTS, 1968.

Evarts, E.V. Relation of pyramidal tract activity to force exerted during voluntary movement. *J. Neurophysiol.*, 31:14-27, 1968.

FETZ, 1969.

Fetz, E.E. Operant conditioning of cortical unit activity. *Science*, 163:955-958, 1969.

FETZ AND BAKER, 1969.

Fetz, E.E. and Baker, M.A. Response properties of precentral neurons in awake monkeys. *Physiologist*, 12:223, 1969.

FETZ AND BAKER, 1973.

Fetz, E.E. and Baker, M.A. Operantly conditioned patterns of precentral unit activity and correlated responses in adjacent cells and contralateral muscles. *J. Neurophysiol.*, 36:179-204, 1973.

FETZ AND FINOCCHIO, 1971.

Fetz, E.E. and Finocchio, D.V. Operant conditioning of specific patterns of neural and muscular activity. *Science*, 174:431-435, 1971.

FETZ AND WYLER, 1973.
Fetz, E.E. and Wyler, A.R. Operantly conditioned firing patterns of epileptic neurons in motor cortex of chronic monkey. *Exp. Neurol.*, 40:586-607, 1973.

FETZ ET AL., IN PRESS.
Fetz, E.E., Finocchio, D.V., and Baker, M.A. Motor fields of precentral cells elicited by operant reinforcement of unit activity. In: *Control of Posture and Locomotion* (R.B. Stein, Ed.). New York, Plenum Press, in press.

FOX AND RUDELL, 1970.
Fox, S.S. and Rudell, A.P. Operant controlled neural event: Functional independence in behavioral coding by early and late components of visual cortical evoked response in cats. *J. Neurophysiol.*, 33:548-561, 1970.

HARRISON AND MORTENSEN, 1962.
Harrison, V.F. and Mortensen, O.A. Identification and voluntary control of single motor unit activity in the tibialis anterior muscle. *Anat. Rec.*, 144:109-116, 1962.

HIATT, 1972.
Hiatt, D.E. *Investigations of Operant Conditioning of Single Unit Activity in the Rat Brain.* Ph.D. Thesis, California Institute of Technology, Pasadena, 1972.

HUMPHREY ET AL., 1970.
Humphrey, D.R., Schmidt, E.M., and Thompson, W.D. Predicting measures of motor performance from multiple cortical spike trains. *Science*, 170:758-762, 1970.

KUYPERS, 1960.
Kuypers, H.G. Central cortical projections to motor and somato-sensory cell groups. An experimental study in the rhesus monkey. *Brain*, 83:161-184, 1960.

LUSCHEI ET AL., 1971.
Luschei, E.S., Garthwaite, C.R., and Armstrong, M.E. Relationship of firing patterns of units in face area of monkey precentral cortex to conditioned jaw movements. *J. Neurophysiol.*, 34:552-561, 1971.

NOTTERMAN AND MINTZ, 1965.
Notterman, J.M. and Mintz, D.E. *Dynamics of Response*, New York, Wiley, 1965.

OLDS, 1965.
Olds, J. Operant conditioning of single unit responses. (23rd Int. Cong. Physiol. Sci.) *Excerpta Med. Int. Cong. Ser.*, 87:372-380, 1965.

OLDS, 1967.
Olds, J. The limbic system and behavioral reinforcement. *Prog. Brain Res.*, 27:144-164, 1967.

OLDS AND OLDS, 1961.
Olds, J. and Olds, M.E. Interference and learning in paleocortical systems. In: *Brain Mechanisms and Learning* (J.F. Delafresnaye, Ed.). Oxford, Blackwell, 1961. pp. 153-187.

PHILLIPS AND PORTER, 1964.
Phillips, C.G. and Porter, R. The pyramidal projection to motoneurones of some muscle groups of the baboon's forelimb. *Prog. Brain Res.*, 12:222-245, 1964.

PORTER, 1970.
Porter, R. Early facilitation at corticomotoneuronal synapses. *J. Physiol. (London)*, 207:733-745, 1970.

PORTER, 1973.
Porter, R. Functions of the mammalian cerebral cortex in movement. *Prog. Neurobiol.*, 1:2-51, 1973.
PRESTON AND WHITLOCK, 1961.
Preston, J.B. and Whitlock, D.G. Intracellular potentials recorded from motoneurons following precentral gyrus stimulation in primates. *J. Neurophysiol.*, 24:91-100, 1961.
ROSEN AND ASANUMA, 1972.
Rosen, I. and Asanuma, H. Peripheral afferent inputs to the forelimb area of the monkey motor cortex: Input-output relations. *Exp. Brain Res.*, 14:257-273, 1972.
ROSENFELD, 1970.
Rosenfeld, J.P. *Operant Control of a Neural Event Evoked by a Stereotyped Behavior.* Ph.D. Thesis, University of Iowa, 1970.
SCHILLER AND STRYKER, 1972.
Schiller, P.H. and Stryker, M. Single-unit recording and stimulation in superior colliculus of the alert rhesus monkey. *J. Neurophysiol.*, 35:915-924, 1972.
SKINNER, 1938.
Skinner, B.F. *The Behavior of Organisms: An Experimental Analysis.* New York, Appleton-Century Crofts, 1938.
STERMAN AND FRIAR, 1972.
Sterman, M.B. and Friar, L. Suppression of seizures in an epileptic following sensorimotor EEG feedback training. *Electroencephalogr. Clin. Neurophysiol.*, 33:89-95, 1972.
TAUB AND BERMAN, 1968.
Taub, E. and Berman, A.J. Movement and learning in the absence of sensory feedback. In: *The Neuropsychology of Spatially Oriented Behavior* (S.J. Freeman, Ed.). Homewood, Dorsey, 1968.
TOWE, 1973.
Towe, A.L. Motor cortex and the pyramidal system. In: *Efferent Organization and Integration of Behavior* (J. Maser, Ed.). New York, Academic Press, 1973. pp. 67-97.
WYLER ET AL., 1973.
Wyler, A.R., Fetz, E.E., and Ward, A.A., Jr. Spontaneous firing patterns of epileptic neurons in motor cortex of chronic monkey. *Exp. Neurol.*, 40:567-585, 1973.