Fine Control of Operantly Conditioned Firing Patterns of Cortical Neurons

E. M. SCHMIDT, J. S. MCINTOSH, L. DURELLI, AND M. J. BAK [1]

Laboratory of Neural Control, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20014

Chronic recording microelectrodes were implanted in the hand–arm area of the precentral gyrus of three *Macca mulatta* monkeys. The firing patterns of individual and combined units were operantly conditioned with either a four- or an eight-target random tracking task. Neurons were considered "conditioned" only if the performance was significantly different from control runs. Conditioning occurred in 77% (37 of 48) of the single units and 65% (15 of 23) of the combined units. The activity of conditioned neurons was associated with specific hand or limb movements, whereas the activity of unconditioned neurons was either uncorrelated with any movement made by the monkey or correlated with seldom-made movements. Performance was measured in terms of information outflow rate to compare different task parameters. The best performance of 3.85 bits/s was obtained with a four-target, 0.5 s hold-time task. This compared to 4.29 bits/s when the same task was performed with a manipulandum and wrist movement. Monkeys were able to exert fine control of the firing rate of cortical neurons and to change rapidly from one rate to another on visual command.

INTRODUCTION

Transmission of information from the nervous system to devices outside the body may be a method for operating a very elegant prosthesis (10) or for controlling neuromuscular stimulators (13) that could activate paralyzed muscles of a paraplegic. Assuming that long-term connections

Abbreviations: IOR—information outflow rate; PT—pyramidal tract; EMG—electromyogram.

[1] Dr. Durelli is a visiting scientist from Clinia Neurologica, Universita di Torino, Torino, Italy. His current address is Clinica Neurologica, Universita di Sassari, Viale S. Pietro 10, 07100 Sassari, Italy.

can be made to the nervous system, one is then confronted with the question of at what rate can information be transmitted from the system. Applying information theory (20) to manual target tracking, Klemmer (11) found that human subjects can transmit information at the rate of 3.5 bits/s on an eight-target task. Török and Hammond (22) evaluated a similar task in humans using single motor unit electromyogram (EMG) as the control signal and found an information outflow rate of about 1 bits/s.

Operant conditioning techniques were utilized by a number of investigators (5–9, 12, 23, 24) to produce transient increases or decreases in the firing rate of precentral cortical neurons. Wyler and Prim (25) used conditioning techniques to change phasic firing patterns of a single cortical neuron to more tonic patterns. In a previous study (18) we showed that a monkey can be conditioned to alternate the firing rate of single precentral cortical neurons between two frequency zones on command. Chronic recording from the same neuron for several days allowed repeated conditioning runs with the same parameters. Task performance continued to improve during these repeated trials. The refinement in performance indicated that the monkey might be able to produce finer control over the firing patterns of operantly conditioned neurons than previous tasks had required. The present study was undertaken to determine if fine control of neuronal firing patterns could be achieved and also to determine the information outflow rate of cortical neurons.

Throughout this paper, reference will be made to "conditioning" of individual neurons. However, what appears to be conditioned in these experiments is a movement, and the neuron under study is correlated with that movement.

MATERIALS AND METHODS

Three *Macaca mulatta* monkeys were initially trained to move a handle whose position was indicated by one of eight red annular cursor lights. The desired handle position was indicated by one of eight green target lights. When the red annulus surrounded the desired target light for a specific hold time, a fruit juice reward was delivered to the monkey. At the time of reward, the target light was turned off for a period of 260 ms before the next target light was illuminated. If the target was not matched and held for the required time within 8 s of the presentation, an error was registered and the next target light in the sequence was then illuminated. Each "run" consisted of a block of 40 trials, where each trial consisted of the pseudorandom presentation of one of the eight target lights. A run included five presentations of each target. The maximum time of a run was 5.3 min if all targets were missed. Typical runs were completed in 3.5

min. The same sequence of light presentations was used for each run. Task control and data processing were conducted with a PDP-12 computer.

When the monkey was performing consistently at or above a 95% reward rate, 11 or 12 chronic microelectrodes were implanted in the hand–arm area of the precentral motor cortex contralateral to the trained arm. Details of the electrode construction and implantation techniques were described elsewhere (15–17). Head restraint devices were attached to two of the monkeys at the time of electrode implantation.

After recovery from surgery, the monkeys were placed daily in a primate chair consisting of neck and waist restraints and, in two cases, head restraints. Except for these minimal restraints, the monkey was free to make arm and body movements during the cell conditioning sessions. The handle on which the monkey had been trained was removed and the position of the red annulus was then controlled by the firing rate of a cortical neuron recorded from one of the chronic microelectrodes. The amplified, bandpass-filtered (600-Hz to 6-kHz) neuroelectric activity from an electrode was discriminated (2) and all accepted spikes from a single neuron were displayed, in their entirety, by an analog delay device (1) to verify single-unit recording. Each accepted spike triggered a generator that produced a pulse of constant amplitude and width. This pulse was applied to a Krohn–Hite Model 3322R low-pass filter, whose response to single pulses is shown in Fig. 1A for three different filter cutoff frequencies. The output of the filter was passed through a variable-gain amplifier prior to the A-to-D converter that activated the appropriate light. The lag time of the cursor light movement produced by the filter is shown in Fig. 1B for a step change in firing frequency between zones 1 and 4 for three different filter cutoff frequencies. The response is symmetrical for both increases and decreases in firing rate. The transformation between neuronal firing rate and cursor light position was usually adjusted to utilize the full firing range of the neuron being conditioned.

Two different types of tasks were utilized during cell conditioning runs. One task required the monkey to accumulate a prescribed length of time on-target prior to a reward without necessarily remaining within the target window. The other task required that the monkey match the cursor light to the target position and hold it on-target continuously for a prescribed time in order to obtain a reward. The total time for each target light presentation was limited, and if the cursor and target lights were not matched to the desired criterion, that trial was terminated and a new random target light presented. The position of the cursor light was recorded at 20-ms intervals so that times at all light positions could be calculated. Usually after four runs, a "control" run was conducted by turning off the target and cursor lights and determining the number of
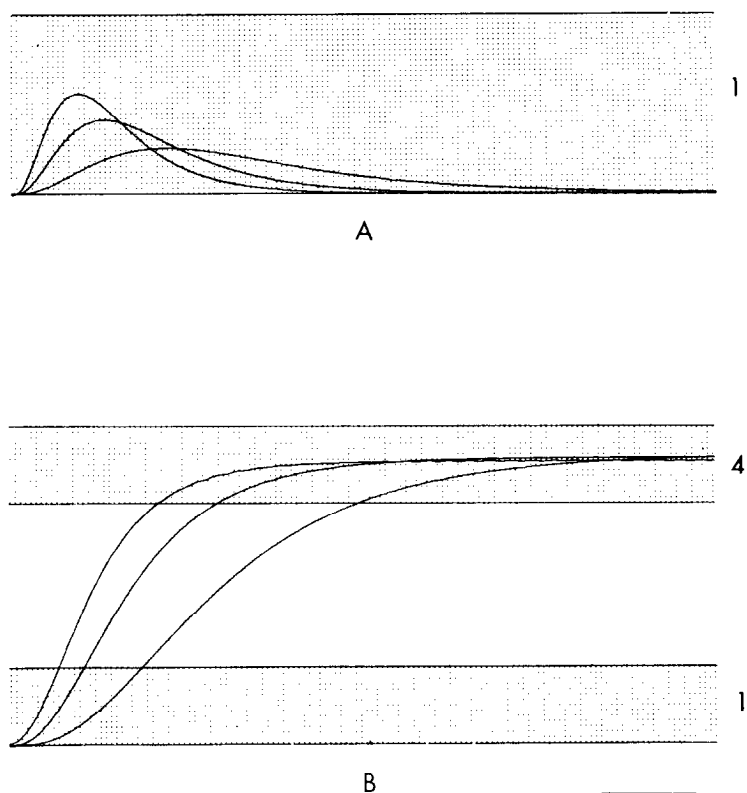
Fɪɢ. 1. A—The impulse response of the Krohn–Hite Model 3322R low-pass RC filter for 1.5-, 2.5-, and 3.5-Hz cutoff frequencies used to smooth the neuronal spike trains. The highest cutoff frequency produces the fastest response. The shaded region corresponds to target zone 1. B—The time response of the cursor position for a step change in firing frequency from 0 to 23.5 spikes/s for the three filter cutoff frequencies in A, which moved the cursor from target zone 1 to 4. Time calibration = 0.2 s.

trials that were rewarded by random movements while still recording the accompanying neuronal activity from the cell under study. During the control run, many trials were terminated because the maximum time allowed for a target was exceeded. A cell was classified as conditioned if the number of rewarded trials on the control run was less than the value determined from the four preceding conditioning runs at the 0.01 level of confidence with a single-sided t-test.

The performance for each run was measured in terms of the percentage of correct trials and the information outflow rate (IOR). Information theory defines the amount of infomation in a random sequence of targets

as

$$I = \log_2 (N_T) \text{ bits,}$$

where I = information in bits and N_T = number of different targets.

For four random targets the information content of each target is two bits, and for eight targets it is three bits. The IOR is a measure of the information input to the system and the time required to perform a correct response. It is defined as follows:

$$\text{IOR} = C \times I / \sum_{i=1}^{n} (t_i - T_H),$$

where C = number of correct responses, n = number of trials per run, t_i = time from target presentation to reward, T_H = hold time on-target, and $t_i - T_H$ = time to target. Each missed target transmitted zero information yet required 8 s to complete, which is included in the time calculation for IOR. The hold time on-target is subtracted from t_i so that changes in the IOR with different hold times measure the differences in difficulty of the task.

RESULTS

The chronic microelectrodes used in this study recorded well-defined single-unit activity from the same neuron for periods of 1 to 108 days. Excluding the one neuron that was recorded from for 108 days, the average period in which conditioning was attempted with individual neurons was 3.12 days (SD 3.98). At times, multiunit activity was recorded that could be separated into the activity of two single units and conditioning was attempted with each one. When the activity on an individual electrode could not be reliably separated into single-unit activity, conditioning runs were conducted with "combined-unit recordings" of the two or three largest units picked up by the electrode. The activity of neurons meeting the requirements of being conditioned was always associated with specific repeatable limb movements. These movements were refined as conditioning continued with a given neuron, and at times became almost imperceptible. The activity of neurons not conditioned at a statistically significant level was unrelated to a host of movements produced by the monkey. The movement relationship became quite evident with one monkey that had been used for cortical cell conditioning for approximately 14 months. After working with the same shoulder-related neuron for 6 weeks, the contingency was shifted to a neuron that was related to finger extension. During the first run, of 40 random target presentations, the monkey started making finger movements and diminished shoulder movements. Within 30 min, the control of precise firing rate of the contingent neuron was greatly improved, accompanied only by finger movements.

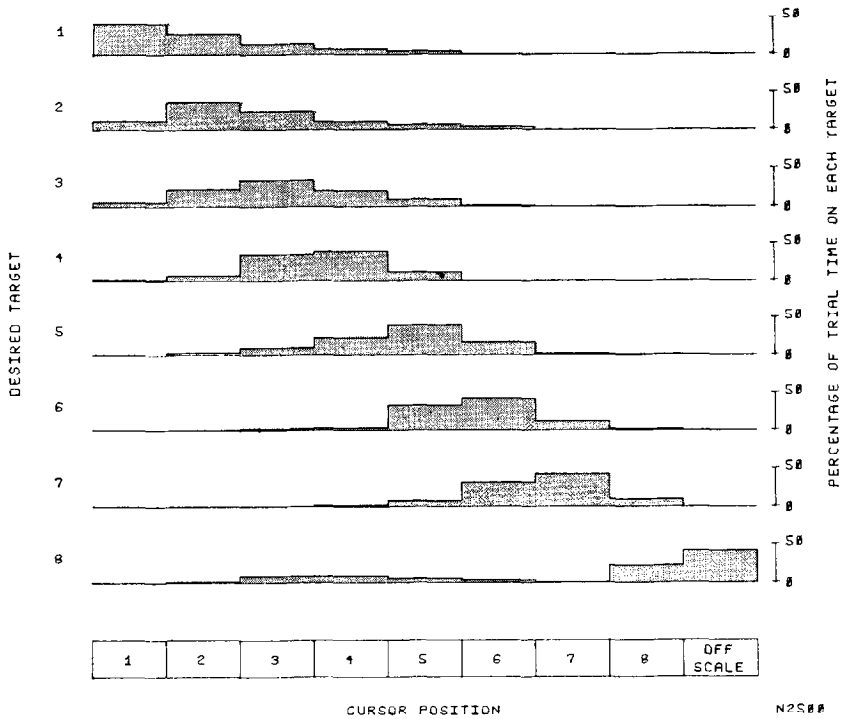*Accumulated Time On-Target, Eight-Target Task.* The first task

FIG. 2. Firing rate distributions of a conditioned cortical pyramidal tract neuron for the eight different targets. The firing frequency was divided into eight equal zones to activate the appropriate cursor light. The range of each cursor position was 4.83 spikes/s. Firing rates greater than 38.6 spikes/s went off-scale and were included in the last bin of the histograms.

required the monkey to adjust the firing rate of the contingent neuron within a narrow range and accumulate 1 s on-target within 8 s to receive a reward. An example of the distribution of cursor light positions produced by a conditioned pyramidal tract neuron is shown in Fig. 2 for the 40 random targets of one run, all of which were rewarded. As the target changed randomly from positions 1 through 8, the distribution of cursor light positions followed the target position. At times when target 8 was illuminated, the monkey increased the firing rate of the contingent neuron above the level for target zone 8, thus driving the cursor light off-scale and eliminating visual feedback about the actual cursor light position. On some runs, this loss of visual feedback for high rates was prevented by incorporating a limiter in the electronics for the cursor light position. This enlarged target zone 8 to include all off-scale firing rates, making the task more symmetrical because target zone 1 was effectively limited at zero frequency when the neuron was not firing. The incorporation of the limiter
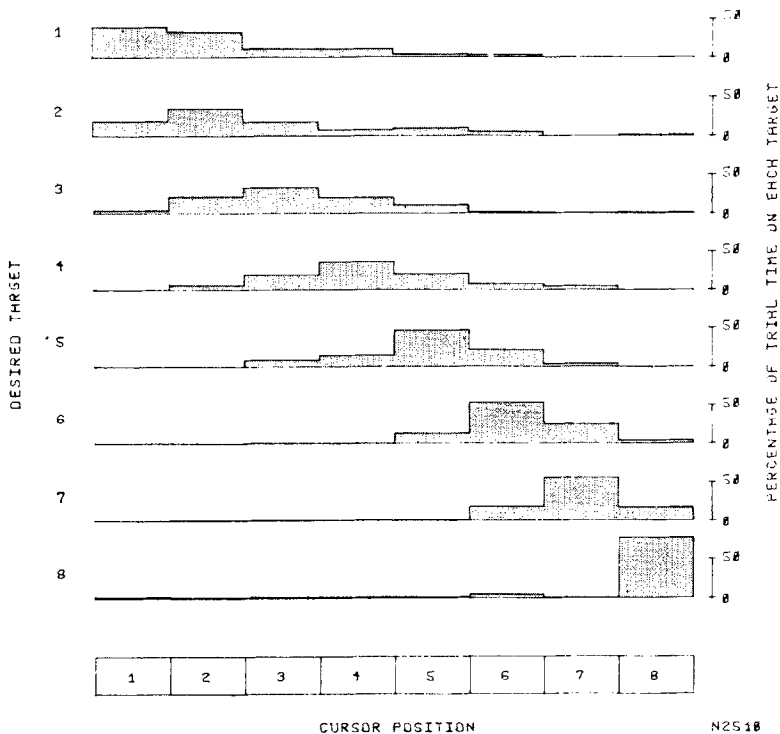
FIG. 3. Similar to Fig. 2, but with the addition of a limiter that shifted all off-scale responses to target zone 8.

was analogous to incorporating mechanical stops in a handle movement task. Figure 3 illustrates the cursor light distribution, for the same pyramidal tract neuron shown in Fig. 2, with the limiter circuit. Trials for target zone 8 were the ones mainly affected by the limiter circuit, resulting in 79% of the trial time being spent in zone 8 compared to 24% when the limiter was not present.

Figure 4 shows the combined results of four runs on the distribution of times to target zone 8 with and without the limiter. The time to target was computed from the time to reward minus the 1-s accumulated time on-target. Without the limiter, a considerable portion of each trial was spent off-scale with no visual feedback. This resulted in an oscillation about target 8 and required more total time to accumulate the 1 s on-target. When the limiter was active and target 8 appeared, the monkey would make a vigorous movement, rapidly changing the firing rate of the contingent neuron. This was in contrast to the subtle and slower changes in movement that were made for the other targets, and for target 8 when the limiter was off. This performance difference is again analogous to that with and without mechanical stops in a manual tracking task.
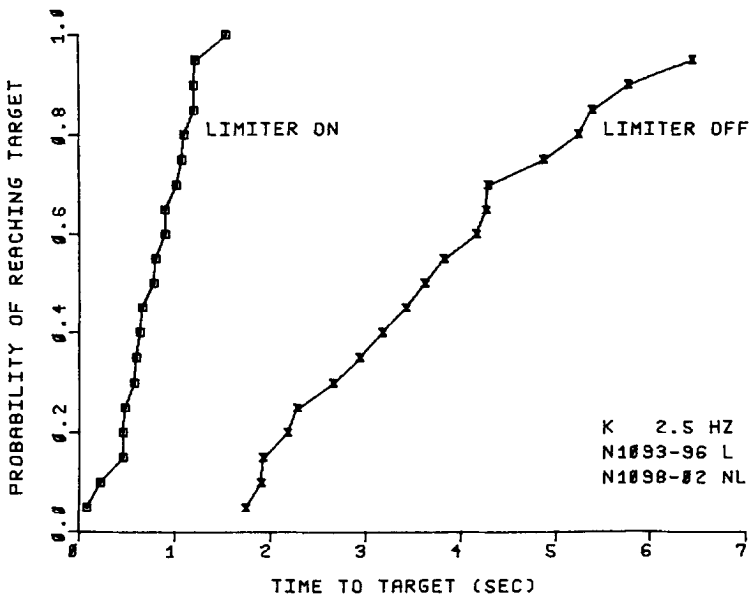
FIG. 4. Distribution of times to reach target zone 8 with and without the limiter for four separate runs (five trials at target 8 each run).

Some neurons could be turned off with specific limb positions. Thus when target 1 was illuminated, the monkey would rapidly assume a position that silenced the contingent neuron. Even though the neuron could also be turned off by very subtle changes in muscular activity, the monkey tended to make the more exaggerated movement that was associated with silence of the contingent neuron, again analogous to a mechanical stop in the "off" direction.

The best performance of a monkey on the eight target task was evaluated for 0.5, 0.76, and 1 s of accumulated time on-target. At 0.5 s, the IOR was 3.57 bits/s for the best performance. As the time on-target was increased to 0.76 s, the IOR dropped to 2.63 bits/s. Further increasing the time on-target to 1 s reduced the IOR to 2.45 bits/s. The average time to target for the best performance of each neuron was 3.44 s (SD 1.28). The minimum average time to target achieved with an individual neuron was 0.84 s. The performance varied greatly during the daily recording sessions depending on how eager the monkey was to perform the task. On the day of the best performance, the IOR varied from 0.85 to 2.45 bits/s (mean 1.54 SD 0.59) on the 1 s accumulated hold task. The percentage of re-warded trials varied from 28.5 to 100% (mean 94.5, SD 6.4). For the sake of comparison, a control run with the same neuron resulted in an IOR

TABLE 1

Information Outflow Rates (IOR) in Bits per Second[a]

Task	Hold time (s)		
	0.5	0.76	1
Eight-target, accumulated hold			
Handle	6.19 (20)[b]	5.61 (20)	4.48 (20)
Neuron	3.57 (8.1)	2.63 (8.1)	2.45 (8.1)
Filter (Hz)	2.5	2.5	2.5
Correct (%)	100	100	100
Four-target, continuous hold			
Handle	4.29 (13.3)	4.19 (13.3)	4.18 (13.3)
Neuron	3.85 (5.4)	1.78 (5.4)	1.01 (5.4)
Filter (Hz)	2.5	2.5	2.0
Correct (%)	100	100	95
Eight-target, continuous hold			
Handle	5.20 (20)	4.73 (20)	4.28 (20)
Neuron	1.93 (3.4)	1.06 (3.4)	0.71 (3.4)
Filter (Hz)	1.5	1.5	1.5
Correct (%)	97.5	95	77.5

[a] Best performances obtained with the different tasks by the contingent neuron or by handle movement with wrist flexion or extension. When the handle task was performed, the filter was not used for smoothing the signal.

[b] The values in parentheses are the theoretical maximum values of the IOR assuming a reaction time of 150 ms and the appropricate filter delay.

of 0.16 bits/s with 32.5% of the trials rewarded due to random fluctuations in firing rate associated with random movements.

Spike Train Smoothing. The ability to record from the same neuron for many days with the chronically implanted electrodes provided the opportunity to measure the tracking performance when some of the parameters used to generate the cursor light position from the cell firing rate were varied. The filter used to smooth the pulse train generated by cell firing (see Methods) was varied in cutoff frequency from 1.5 to 3.5 Hz, which had only a minor effect on the performance of the monkey measured by the IOR on the accumulated time on-target task. With the continuous hold task, a slight improvement in performance occurred with the lowest filter frequency. However, insufficient data were obtained for different filter frequencies to adequately evaluate this parameter on the continuous hold task.

The theoretical upper limit for the IOR is the information content of each target divided by the sum of the reaction time and filter delay. Assum-
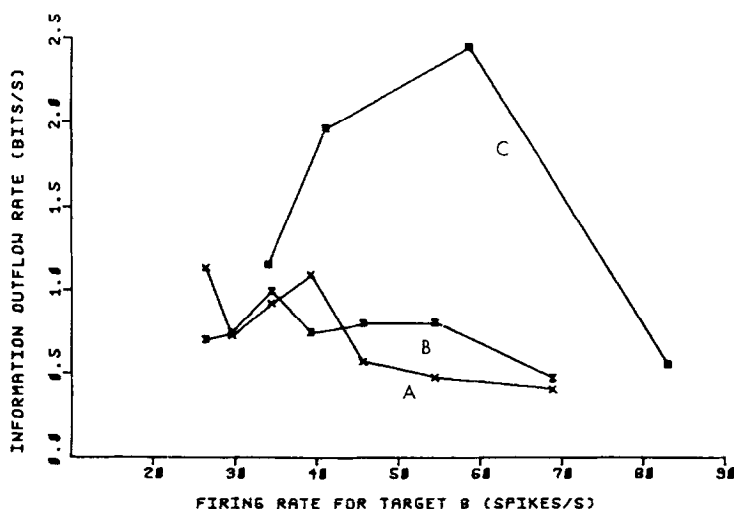
Fɪɢ. 5. Effects of conversion gain between neuronal firing rate and cursor light position on information outflow rate for three different neurons. Curves A and B were obtained early in the experiment, and curve C was obtained 14 months after the implantation of the recording electrodes.

ing a reaction time of 150 ms and average filter delay of 315 ms with the 3.5 Hz filter cutoff frequency, results in an upper limit on the IOR for the eight-target task of 6.45 bits/s. Reducing the cutoff frequency of the filter to 1.5 Hz increases the filter delay to 730 ms and limits the maximum IOR to 3.4 bits/s. The choice of filter cutoff frequency has to be a compromise between two conflicting conditions. If the cutoff frequency is too low, the maximum IOR will be limited by the response of the filter and not by the performance of the monkey. On the other hand, if the cutoff frequency is too high, the spike train will not be adequately smoothed and the cursor will move off-target and again limit the IOR for the continuous on-target hold task. Included in Table 1 are the theoretical upper limits of the IOR for the different tasks and parameters utilized.

Conversion from Firing Rate to Cursor Position. The effect of variation in the transfer function from firing rate to cursor light position was investigated with three conditioned neurons. Figure 5, curves A and B, illustrates the effect of changing the neuronal firing frequency required to reach target 8 for two neurons recorded 2 months after neuronal conditioning began. As the firing frequency for target 8 was increased above 40 spikes/s, the monkey had some difficulty firing cell A at the higher rates, which degraded the performance. There was an indication with cell B that lowering the frequency for target 8 also degraded the performance. A

third neuron, recorded 15 months after the initial implant, when the monkey was very accustomed to the conditioning task, was also evaluated at a number of different firing frequencies for target 8. The results are shown as curve C in Fig. 5. For this neuron, the best performance was near 60 spikes/s for target zone 8. When higher frequencies were required for zone 8, a number of targets were missed and the performance was degraded. At firing rates below 60 spikes/s for target zone 8, the performance was also degraded.

Changing the relationship between cell firing rate and cursor light position in effect changed two parameters. The first parameter was the firing frequency to reach a specific target and the second was the width of each target. The variation in firing frequency that would remain within one target zone can be determined by dividing the firing frequency for target 8 by the number of targets. At the lowest frequency tested (Fig. 5) the target width was 3.3 spikes/s, and at the highest frequency the target width increased to 10.4 spikes/s. The target width for the best performance in Fig. 5C was 7.3 spikes/s at the peak of the curve.

Four-Target Task. The next task utilized with the monkeys was deemed more difficult, in that a continuous on-target hold of 0.5, 0.76, or 1 s was required for a reward. To compensate for the increased difficulty, the number of targets was reduced to four, doubling the width of each target zone. This allowed more modulation of the contingent neuron while still remaining on-target. A run still consisted of 40 trials, but now each target was presented 10 times. Each rewarded target now contained only two bits of information rather than the three bits for the eight-target task. The best performance achieved on a 0.5 s continuous hold, four-target task was 100% correct with an IOR of 3.85 bits/s, which corresponds to an average time to target of 0.52 s. Increasing the continuous on-target hold time to 0.76 s reduced the IOR to 1.78 bits/s with no errors. Further increasing the hold time to 1 s reduced the best performance to 92.5% with an IOR of 1.01 bits/s. The average time to target for only the rewarded trials was futher increased to 1.33 s. The decrease in the IOR and the increase in the time to target, as the required on-target hold time increased, were due to variations in firing rate that moved the cursor prematurely off-target, requiring a reinitiation of the hold timing.

Eight-Target Continuous Hold Task. When the monkeys were working well at the four-target continuous hold task, the number of targets was increased to eight and hold times of 0.5, 0.76, and 1 s were evaluated. The best performance on the 0.5 s continuous on-target hold was 1.93 bits/s, with only one of the 40 targets missed. The average time to target for the rewarded trials was 1.35 s. Increasing the continuous hold time to 0.76 s reduced the IOR to 1.06 bits/s, with two errors, and increased the average
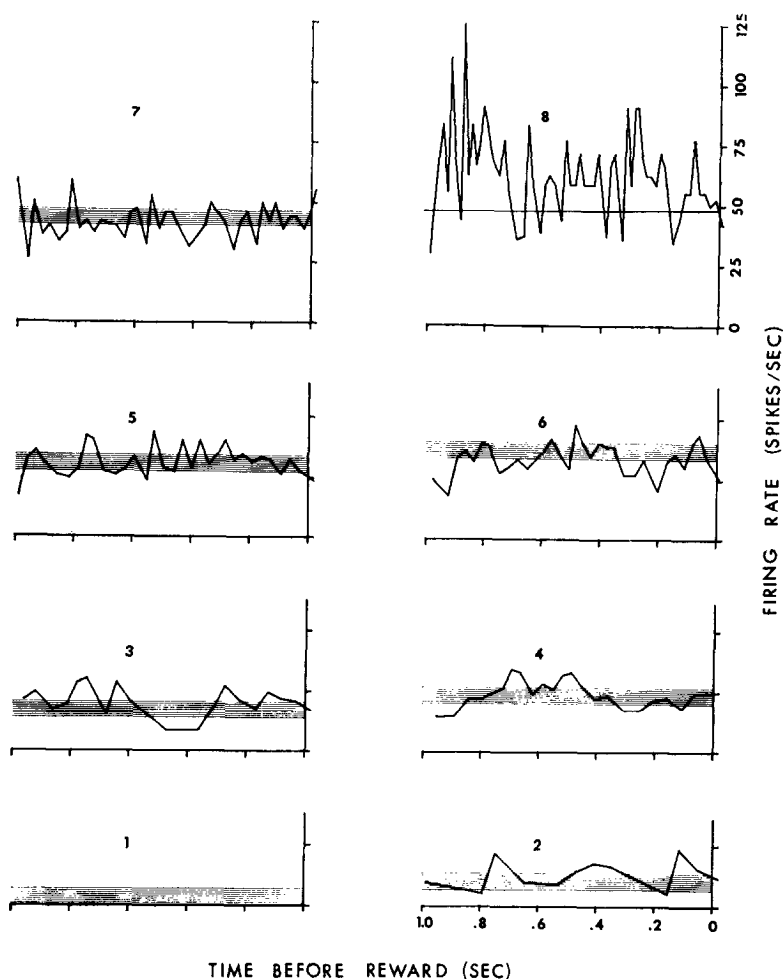
FIG. 6. Instantaneous firing rate of a conditioned cortical pyramidal tract neuron for the eight different targets. The task required a continuous hold on-target of 0.76 s for a reward. Each trace shows the activity 1 s prior to the reward. A limiter was used on target 8 which placed all rates greater than 47.5 spikes/s in zone 8. Smoothing of the instantaneous rate (cutoff frequency, 1.5 Hz) kept rapid excursions within the target window. The shaded areas show the width of the target window.

time to target for the rewarded trials to 2.45 s. Further increasing the hold to 1 s reduced the IOR to 0.71 bits/s and increased the errors to nine, but decreased the average time to target for rewarded trials to 1.9 s. The decrease in time to target was due to the elimination of the nine trials that were terminated at 8 s without a reward but that were attained with times to target longer than 2 s on the 0.76 s hold time task.

Although the feedback to the monkey was derived from the smoothed firing rate of the contingent neuron, the instantaneous firing rate was relatively stable for each target position. Figure 6 illustrates the firing rate of a pyramidal tract neuron, associated with shoulder musculature, for 1 s preceding the reward on the eight different targets. When target 1 was illuminated, the monkey moved its hand to the waist region and relaxed
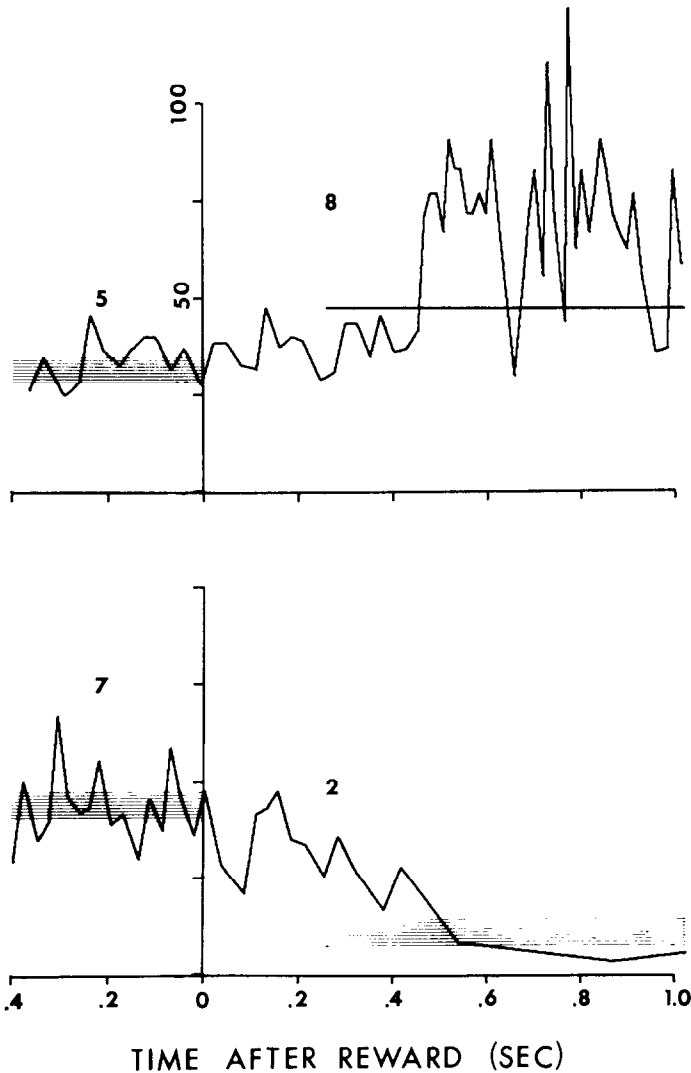

TIME AFTER REWARD (SEC)

FIG. 7. Similar to Fig. 6, except the instantaneous rate is shown for 0.4 s before and 1 s after two rewarded trials. The target and cursor lights were off for a period of 0.26 s while the monkey received a reward.

the shoulder, which was associated with no neural activity from the contingent cell. For all other targets, the monkey grasped the edge of the neck restraint plate, which was 33 cm from his body axis. Modulation of the neuron was accomplished by almost isometric contraction of the deltoid and biceps muscles. When the higher-numbered targets were presented, which required higher firing rates, the intensity of shoulder contraction as seen on a video monitor appeared to increase. The limiter circuit for target zone 8 was utilized in this run. When target 8 was presented, the monkey made what appeared to be a maximal contraction of the shoulder region, which produced a very high discharge rate of the contingent neuron. The instantaneous firing rate became much more erratic; however, the filtered and limited firing rate remained within zone 8. When target 7 was illuminated the firing rate became much more uniform in order to remain within the target window. Figure 7 shows the change in firing rate of this neuron before and after the reward to illustrate how rapidly firing rate could be modified when a new target was illuminated. Clearly the monkey could continuously modulate this neuron from zero to maximal rate in a finely controlled fashion.

Neuron Identification. A pyramidal tract (PT) electrode was implanted in one monkey 13 months after the initial implantation of the cortical electrodes. Only two single units were available at that time and both were identified as PT neurons with antidromic latencies of 1.2 and 1.3 ms. Both of these units were well conditioned. The chronic electrodes were fabricated with a length of approximately 1.5 mm, such that when they were implanted the tips would be approximately in layer V of the precentral cortex. Because of the electrode placement, a number of the units conditioned were probably PT neurons.

Removal of Feedback. Tests were conducted to determine if, after the monkey learned the task of controlling the cursor light position, a sense of effort was developed that would allow removal of the visual feedback of cell firing rate. The performance on a normal run of 0.76 s accumulated time on-target was 100% correct with an IOR of 2.31 bits/s. On the first run when the red cursor light, indicating cell firing rate, was turned off, the performance dropped to 80% correct with an IOR of 0.58 bits/s. Some trials on targets 5, 6, and 7 were missed. During this run, the monkey made shoulder movements similar to those on a normal run. The performance on a control run, when no lights were present, was 42.5% correct with an IOR of 0.21 bits/s. The next two runs were normal, with visual feedback provided. Performance returned to 100% correct with an IOR of 2.39 bits/s. Removal of the red cursor light on the next run caused the performance to fall to 42.5% correct and an IOR of 0.21 bits/s. The monkey no longer made shoulder movements when only the cursor light was turned

off, behaving as if it were a control run. On subsequent attempts at turning off the cursor light, following normal runs, the performance was always similar to that on a control run.

Summary of Results. Each day of neuronal conditioning consisted, on the average, of 18.7 runs (SD 5.9). Single and combined neurons that were classified as conditioned reached a significant level of performance after an average of 2.2 runs (SD 1.4). The minimum number of runs conducted with neurons classified as unconditioned was four, but the average number of runs conducted with these units was 9.6 (SD 5.5). Neuronal conditioning was attempted with 71 different recordings from single units, or combined units from a given electrode, in three monkeys. A total of 48 different individual neurons was tested, and of these 37 were successfully conditioned. The activity of conditioned neurons was always associated with specific movements of the contralateral hand or arm. The activity of single units not conditioned either was uncorrelated with the animals' movements, and the monkey was therefore unable to perform the eight-target tracking task at a significant level, or less often, was associated with rarely made movements. The monkeys performed the tracking task by finely controlling the discharge rate of the contingent neuron rather than firing the neuron in a series of bursts to stay near or on-target. Combined-unit recordings were obtained fom 23 different groups of neurons, and of these 15 combined units were conditioned.

Table 1 lists the best performances obtained with the four- and eight-target tasks. For comparison, all tasks were also conducted with a handle that controlled the cursor light position by flexion or extension of the wrist. The best performance of each conditioned neuron on the eight-target accumulated time task, averaged for all units, was an 85.88% correct response rate (SD 9.52) with an IOR of 0.79 bits/s (SD 0.31). The best performance achieved with any neuron was 3.57 bits/s on the eight-target, 0.5 s accumulated time task.

DISCUSSION

Utilizing a multiple-target tracking task for operantly conditioning the firing patterns of precentral cortical neurons, we were able to successfully condition 77% (37 of 48) of the individual neurons and 65% (15 of 23) of the combined units tested. The activity of the conditioned neurons was associated with specific repeatable limb movements. The activity of the single neurons not conditioned at a statistically significant level was unrelated to a host of movements produced by the monkey. Thus it appears that we are conditioning movements that are related to the firing pattern of the contingent neuron under study. With the combined units that were not conditioned, another possibility arises to explain failures. If the indi-

vidual activity of the two or three combined units varied reciprocally with a movement, then the overall firing rate would remain relatively constant. Evarts (3) saw a number of reciprocally related neurons in the motor cortex of monkeys. The percentages of unconditioned single units and combined units were similar, which would suggest that reciprocal cells were infrequently encountered.

Varying degrees of success at conditioning the firing rate of cortical neurons have been reported by different investigators (6, 18, 23, 25). Fetz and Baker (6) found that 64.7% of the precentral cortical neurons they tested could be conditioned for increased or decreased firing rates. For conditioned neurons the average time to reach the terminal plateau level of firing rates was 6.5 min. Schmidt et al. (18) reported that 78.9% of the neurons tested could be conditioned to fire within two different frequency bands. Wyler and Fetz (23) conditioned 98% of the neurons tested for increased or decreased firing rates and spent at least 1 h with neurons that were not conditioned. More recently, Wyler and Prim (25) were able to condition all neurons tested with a paradigm requiring the monkey to fire the neurons at interspike intervals between 30 and 60 ms. With our multiple-target task experiment, we were able to condition 77% of the single neurons and 65% of the combined units. The average time to reach a significant level of performance was about 8 min (2.2 runs). The average time spent with unconditioned neurons was approximately 35 min (9.6 runs). Differences in task requirements, length of attempted conditioning time, and neuron selection undoubtedly are factors in reported success rates for cell conditioning.

The chronic electrodes were fabricated such that when they were implanted the tips would be approximately in layer V of the precentral cortex. A number of the units conditioned were probably PT neurons. In one monkey, near the end of the study, a PT-stimulating electrode was implanted. Both units that were conditioned while the stimulating electrode was in place were PT neurons over which the monkey had excellent control. Further studies are required to determine the percentages of projecting and nonprojecting neurons from the precentral cortex that can be conditioned.

The present experiment was undertaken to determine if tonic firing rates could be conditioned to any of eight possible levels and then rapidly changed on command to a new level. The target window width varied from 3 to 12 spikes/s, but most runs were with a window width of about 6 spikes/s. The performance was evaluated by calculating an information outflow rate (IOR) which took into account the information content of the task and the speed with which it was performed. The maximum IOR on the eight-target task of 3.57 bits/s was achieved with the accumulated

time on-target of 0.5 s. As the time required on-target increased, the IOR decreased, indicating that the task difficulty increased when longer periods of tonic firing were required. When the eight-target task required a continuous hold on-target of 0.5 s, the IOR decreased to roughly half the value obtained with the accumulated time on-target task. As the continuous hold time on-target increased to 1 s, the IOR decreased to less than one-third the value obtained with the 1 s accumulated time task. Reducing the number of targets to four, which doubled the target width, doubled the IOR on the 0.5 s continuous hold time task. The increased IOR occurred even though the information content of each target was reduced from three to two bits.

When the task was performed at the 100% level, the average time to target could be obtained by dividing the information content of each target by the IOR. For the eight-target, 0.5 s continuous hold task, the average time to target was 1.55 s. With the four-target task, the average time to target was reduced to 0.55 s. The reduction in time to target was due mainly to the wider target zones, which resulted in fewer overshoots and driftings off-target during the hold phase.

The IORs shown in Table 1 were the maximum values observed with these monkeys. The way the task was constructed required complete concentration on the task for 1 to 5 min. An error on 1 or 2 of the 40 trials presented each run would affect the resultant IOR. For example, if the IOR was 2 bits/s on the four-target task and one trial was missed, the IOR would decrease to 1.66 bits/s. Missing two trials would further reduce the IOR to 1.41 bits/s, assuming that all other trials were completed in 1 s. The incorporation of fewer trials per run would probably increase the maximum IORs obtainable because shorter periods of complete concentration on the task would be required. If a true random sequence of target presentations were used for each run, one would have to be concerned that each run was of the same difficulty. Using the same sequence of targets in each run overcomes the problem of variation in difficulty on different runs. However, the possibility of predicting the next target as the length of the sequence shortens must be considered. Because of these problems, we used the same sequence of 40 target presentations in each run, which we assume was sufficiently long to minimize the possibility of the monkey predicting the next target position.

The filter used to smooth the spike train appeared to have little effect on performance over the range of 1.5 to 3.5 Hz for the eight-target accumulated time task. Cutoff frequencies less than 1.5 Hz would limit the maximum IOR to values less than 3.57 bits/s, which was produced by one of the monkeys. With the eight-target continuous hold task, performance was slightly improved with the 1.5 Hz cutoff frequency. The

maximum observed IOR on this task was 1.93 bits/s. A somewhat lower cutoff frequency could have been used before the monkey's performance was limited by the filter response. An optimum filter would result in an IOR somewhat between 2 and 3.5 bits/s. An additional problem arises as the filter cutoff frequency is decreased. The filter introduces a time delay between the change in neuronal firing rate and the change in resultant cursor light position. As the cutoff frequency is decreased, the delay becomes greater. At some point, the delayed feedback will adversely affect the monkey's performance. Thus the optimum filter must sufficiently smooth the spike train to remain within the desired target window and yet not limit the IOR either due to delayed feedback or by a slow filter response.

In a previous study (19) we concluded that the motor cortex was involved in specifying the muscles to be activated for a specific task and not the level of force produced by the muscles. This was based on the weak relationship, found in only a few cortical neurons, between cortical discharge frequency and force output. Also, recruitment of additional cortical neurons was not observed as the force output was increased. These results were probably influenced by the specific task employed and the use of the resultant output force produced on the manipulandum rather than the actual state of a muscle. In the present study, using operant conditioning techniques, modulation of cortial neurons was accompanied by either changes in limb position, variations in isometric force, or combinations of these manipulations. Using operant techniques, we found that the monkey can recruit different cortical neurons and smoothly modulate their activity. From these observations, we conclude that some motor cortex neurons may be involved in specifying the level of activity in specific muscles, which is the same as Evarts's (4) earlier conclusion. The ordered activity of populations of cortical neurons, as observed by Porter and Lewis (14), is consistent with our observation that activity can be finely controlled at low firing rates. However, when correlations are made between cortical neuronal activity and output parameters of the animal, such as position, force, rate of change of force, etc., caution should be exercised, because these parameters may not directly measure the state of a specific muscle or muscles associated with the cortical neuron.

A possible future application of the work discussed may be for controlling devices external to the body, such as artificial limbs or neuromuscular stimulators for paraplegics. One requirement for these applications is providing long-term connections to the nervous system. To date, there has been some success in this area. Neuronal activity is still being recorded from one monkey 24 months after chronic implantation of the microelectrodes. Activity from what we believed was the same neuron was obtained

for 3.5 months. The second requirement is that signals obtained from these chronic connections can be used by the subject for control of a device external to the body. By measuring the information outflow rate (IOR) for a four- or an eight-target random tracking task, we found that for a 0.5 s on-target task a monkey approached the rates obtainable when the same task was done with a manipulandum and wrist movements. As the required time on-target increased, the performance with a neuron decreased and the performance with the wrist task remained relatively constant. Normal movements require the participation of many cortical neurons whose rates are smoothed by the motoneuron and muscle. Undoubtedly, this integrative action plays a major role in finer control of muscular output compared to the fine control of the firing rate of a cortical neuron. IORs from 0.71 to 3.85 bits/s were achieved with the different task requirements. Klemmer (11) found that human subjects could transmit information at the rate of 2.6 bits/s with a four-target discrete tracking task. With eight targets the IOR increased to 3.5 bits/s, and with 32 targets it further increased to 4.2 bits/s. Klemmer concluded that the maximum IOR with this type of task was near 4.2 bits/s. His task required the subject to position a hand-held cursor within $\frac{1}{4}$ in. of the target center and then press down slightly to indicate he was on-target. We obtained somewhat greater IORs when the monkey performed the tracking task by positioning a handle that moved the cursor. Part of the difference in performance might be attributed to physical differences in the task; however, some of the difference was probably due to using monkeys that were trained at the task for many months and knew that correct performance was their means of obtaining fluid intake. We also found that increasing the number of targets inceased the IOR with the handle task. When the cortical neuron was used for controlling the cursor position, the IOR decreased when the number of targets was increased from four to eight. Therefore to maximize IORs with cell firing, and our specific task, fewer than eight targets should be used. Even though the monkey can finely control the firing rate of a single cortical neuron, finer control and larger IORs can be obtained with hand movements.

Török and Hammond (22), in a somewhat similar eight-target task, using human subjects and single motor unit signals for control, achieved an IOR of 1 bit/s. Our overall results were similar; however, one monkey achieved a much higher IOR, which may have been due to differences in the tasks and the methods of processing the signals or may reflect better control obtainable from cortical neurons. To test these two alternatives, Thomas et al. (21) repeated our task with human subjects and single-unit EMGs. The best performance of a human subject on the eight-target, 1 s accumulated time on-target task was 2.73 bits/s, whereas the monkey

368 SCHMIDT ET AL.

produced 2.45 bits/s, indicating that single-unit EMG and single-unit cortical signals are quite comparable as a signal source in terms of information outflow rate. The choice between these two sources of control signals must be made in terms of long-term recordability and the number of possible independent information channels. Due to the intrinsic recruitment order of motor units in a muscle, only one channel of information appears feasible from a single muscle. When the number of possible muscle sites are limited, such as in the case of a paraplegic, cortical signals may be the ultimate choice. Further experiments are required to determine IORs when multiple cortical recordings are used to provide simultaneous independent channels of information.

REFERENCES

1. BAK, M. J., AND E. M. SCHMIDT. 1977. An analog delay circuit for on-line visual confirmation of discriminated neuroelectric signals. *IEEE Trans. Biomed. Eng.* **24**: 69–71.
2. BAK, M. J., AND E. M. SCHMIDT. 1977. An improved time-amplitude window discriminator. *IEEE Trans. Biomed. Eng.* **24**: 486–489.
3. EVARTS, E. V. 1967. Representation of movements and muscles by pyramidal tract neurons of the precentral motor cortex. Pages 215–253 in M. D. YAHR and P. PURPURA, Eds., *Neurophysiological Basis of Normal and Abnormal Motor Activities*. Raven Press, New York.
4. EVARTS, E. V. 1969. Activity of pyramidal tract neurons during postural fixation. *J. Neurophysiol.* **32**: 375–385.
5. FETZ, E. E. 1969. Operant conditioning of cortical unit activity. *Science* **13**: 955–958.
6. FETZ, E. E., AND M. A. BAKER. 1973. Operantly conditioned patterns of precentral unit activity and correlated responses in adjacent neurons and contralateral muscles. *J. Neurophysiol.* **36**: 179–204.
7. FETZ, E. E., AND D. V. FINOCCHIO. 1971. Operant conditioning of specific patterns of neural and muscular activity. *Science* **174**: 431–435.
8. FETZ, E. E., AND D. V. FINOCCHIO. 1975. Correlations between activity of motor cortex cells and arm muscles during operantly conditioned response patterns. *Exp. Brain Res.* **23**: 217–240.
9. FETZ, E. E., AND A. R. WYLER. 1973. Operantly conditioned firing patterns of epileptic neurons in the monkey motor cortex. *Exp. Neurol.* **40**: 586–607.
10. FRANK, K. 1968. Some approaches to the technical problem of chronic excitation of peripheral nerve. *Ann. Otol. Rhinol. Laryngol.* **77**: 761–771.
11. KLEMMER, E. T. 1956. Discrete tracking in one and two dimensions. U.S. Air Force AFCRC-TN-56-2.
12. OLDS, J. 1965. Operant conditioning of single unit responses. 23rd Int. Congr. Physiol. Sci., Tokyo, pp. 372–380.
13. PECKHAM, P. H., AND J. T. MORTIMER. 1977. Restoration of hand function in the quadriplegic through electrical stimulation. Pages 83–95 in F. T. HAMBRECHT AND J. B. RESWICK, Eds., *Functional Electrical Stimulation: Applications in Neural Prosthesis*. Marcel Dekker, New York.
14. PORTER, R., AND M. McD. LEWIS. 1975. Relationship of neuronal discharges in

CORTICAL CONDITIONED FIRING PATTERN

the precentral gyrus of monkeys to the performance of arm movements. *Brain Res.* **98**: 21–36.

15. SALCMAN, M., AND M. J. BAK. 1973. Design, fabrication and in vivo behavior of chronic recording intracortical microelectrodes. *IEEE Trans. Biomed. Eng.* **20**: 253–260.

16. SALCMAN, M., AND M. J. BAK. 1976. A new chronic recording intracortical microelectrode. *Med. Biol. Eng.* **14**: 42–50.

17. SCHMIDT, E. M., M. J. BAK, AND J. S. MCINTOSH. 1976. Long-term chronic recording from cortical neurons. *Exp. Neurol.* **52**: 496–506.

18. SCHMIDT, E. M., M. J. BAK, J. S. MCINTOSH, AND J. S. THOMAS. 1977. Operant conditioning of firing patterns in monkey cortical neurons. *Exp. Neurol.* **54**: 467–477.

19. SCHMIDT, E. M., R. G. JOST, AND K. K. DAVIS. 1975. Reexamination of the force relationship of cortical cell discharge patterns with conditioned wrist movements. *Brain Res.* **83**: 213–223.

20. SHANNON, C. E., AND W. WEAVER. 1949. *The Mathematical Theory of Communication.* University of Illinois Press, Urbana.

21. THOMAS, J. S., E. M. SCHMIDT, AND F. T. HAMBRECHT. 1978. Facility of motor unit control during tasks defined directly in terms of unit behavior. *Exp. Neurol.* **59**: 384–395.

22. TÖRÖK, Z., AND P. H. HAMMOND. 1971. On the performance of single motor units as sources of control signals. Proc. Inst. Mech. Eng. Conf., Human Locomotor Engineering, University of Sussex.

23. WYLER, A. R., AND E. E. FETZ. 1974. Behavioral control of firing patterns of normal and abnormal neurons in chronic epileptic cortex. *Exp. Neurol.* **42**: 448–464.

24. WYLER, A. R., E. E. FETZ, AND A. A. WARD, JR. 1974. Effects of operantly conditioning epileptic unit activity on seizure frequencies and electrophysiology of neocortical experimental foci. *Exp. Neurol.* **44**: 113–125.

25. WYLER, A. R., AND M. M. PRIM. 1976. Operant conditioning of tonic neuronal firing rates from single units in monkey motor cortex. *Brain Res.* **117**: 498–502.