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"Somatic Sensory Responses in the Rostral Sector of the Posterior Group (POm) and in the Ventral Posterior Medial Nucleus (VPM) of the Rat Thalamus: Dependence on the Barrel Field Cortex"

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Somatic Sensory Responses in the Rostral Sector of the Posterior Group (POm) and in the Ventral Posterior Medial Nucleus (VPM) of the Rat Thalamus: Dependence on the Barrel Field Cortex

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ABSTRACT

The projection from the whiskers of the rat to the S-I (barrel) cortex is segregated into two separate pathways—a lemniscal pathway relayed by the ventral posterior medial nucleus (VPM) to cortical barrels, and a paralemniscal pathway relayed by the rostral sector of the posterior complex (POm) to the matrix between, above, and below barrels. Before investigating how the barrel cortex integrates these sensory pathways, it is important to learn more about the influence of the various inputs to the two thalamic nuclei. Based on the greater density of descending versus ascending projections to POm, it seemed likely that corticofugal inputs play an important role in the sensory activity of POm. To test this, the responses of POm and VPM cells to sensory stimuli were measured before, during, and after suppression of the S-I cortex. S-I was suppressed by application of magnesium or by cooling; the status of the barrel cortex was assessed continuously by an electrocorticogram. All VPM cells (n = 8) responded vigorously to whisker movement even when the barrel cortex was profoundly depressed. In contrast, all POm cells (n = 9) failed to respond to whisker movement once the barrel cortex became depressed, typically about 25 minutes after the start of cortical cooling or magnesium application. POm cells regained responsiveness about 30 minutes after the cessation of cortical cooling or the washoff of magnesium. These findings indicate that the transmission of sensory information through the lemniscal pathway occurs independently of the state of cortex, whereas transmission through the paralemniscal pathway depends upon the state of the cortex itself.

Key words: vibrissa, receptive field, latency, barrel, trigeminal

The two pathways from the whiskers to cortex in the rodent offer a good opportunity to study the cortical integration of parallel sensory pathways. The first is a "lemniscal" pathway relayed by the principal trigeminal nucleus and the thalamic ventral posterior medial nucleus (VPM) to layer IV barrels in cortex (Woolsey and Van der Loos, '70; Welker, '71; Killackey, '73; Jensen and Killackey, '87). The second is a "paralemniscal" pathway relayed by the rostral zone of the thalamic posterior complex (POm) to the septal regions above, below, and between barrels (Lu and Lin, '86; Lin et al., '87; Koralek et al., '88; Lu, '88).

As a step toward determining how the two pathways are integrated by the cortex, an earlier study compared and contrasted the responses of cells in VPM and POm to whisker movements (Diamond et al., '92). For the typical VPM cell, one whisker (or at most two) forms the "center receptive field," producing a strong response at a short latency (4–7 ms). For the typical POm cell, several whiskers yield nearly an equal response, the strongest at a latency of greater than 15 ms. The significant differences between POm and VPM cell responses raise the question of the sensory inputs to the thalamus. The short-latency response of VPM cells to one or two whiskers can be attributed to the input from the trigeminal complex, in particular from the principal trigeminal nucleus (Smith, '73; Peschanski, '83; Friedberg et al., '91; Chiaia et al., '91). It is not as easy to

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explain the response properties of POm cells. The fact that POm receives a denser projection from from the barrel cortex (Hoogland et al., '87, '88; Welker et al., '88; Nothias et al., '88; Fabri and Burton, '91) than from the trigeminal complex (Chiaia et al., '91) suggests a particularly strong influence from the cortex.

Here we have examined the role of corticofugal inputs by measuring the responses of VPM and POm cells to whisker movement before, during, and after suppression of the barrel cortex. During cortical suppression, VPM cells maintained a strong sensory response. Under the same conditions, POm cells showed a profound reduction in spontaneous and evoked activity. Thus, ascending inputs are not sufficient by themselves to bring POm neurons to threshold; barrel cortex itself makes an essential contribution to the sensory activity of POm cells under our recording conditions. The different relationship of POm and VPM to the cortex may provide a clue to the function of paralemniscal sensory pathways.

MATERIALS AND METHODS

Preparation

Male Long-Evans rats weighing 250–350 g were anesthetized with an i.p. injection of urethane (1.5 g/kg) and placed in a Narashige stereotaxic apparatus after the ear bars were coated with a local anesthetic gel. Body temperature was maintained at 36–37° C under thermistor control. The scalp was injected with lidocaine, the skin was incised in the midsagittal plane, and the temporal muscle was retracted. The opening made in the skull extended from 2 to 7 mm lateral to the midline and from 1 to 4 mm caudal to bregma. This exposed the surface of almost all the S-I (barrel) cortex with little exposure of other cortical regions (Hall and Lindholm, '74). A small opening was made in the dura to advance the thalamic microelectrode.

During surgery and the subsequent recording session the spontaneous rate of respiration typically was 80–90/min. Rats had flaccid muscles, an absence of coordinated vibrissae movement, and little, if any, withdrawal from a firm hindlimb pinch. At the end of the experiment the rat was given a lethal dose of Nembutal and perfused through the heart with a 250 ml rinse of 0.1 M phosphate-buffered saline followed by 4% buffered paraformaldehyde.

Identification of POm and VPM

Microelectrode tracks through POm and VPM were reconstructed from 75-μm-thick sections cut in the frontal plane and stained with cresyl violet. POm is located medial and dorsal to VPM (see Fig. 2), lateral to the central lateral nucleus (CL), and ventral to the lateral posterior nucleus (LP). The band of POm cells lying immediately dorsal and medial to VPM responds to snout and face stimulation. Cells increasingly dorsal and medial, bordering CL and LP, respond to stimulation of the limbs and trunk. Overall, the body representation in POm seems to be a mirror image of that in the ventral posterior nucleus, reflected about the POm/VPM border (Diamond et al., '92).

POm is referred to here as the "rostral sector of the posterior group" to distinguish it from a caudal sector. Caudal PO in the rat (including the area called "posterior intralaminar nucleus" by LeDoux et al., '87) lies immediately posterior to VPM and POm and is intercalated between the pretectal area and medial geniculate nucleus. Caudal PO differs from POm on several grounds. Unlike POm, caudal PO receives convergent somatic and auditory input (LeDoux et al., '87). Caudal PO projects densely to S-II but only sparsely to the S-I barrel field (Carvell and Simons, '87; Spreafico et al, '87). In contrast, POm projects more densely to the barrel field than to S-II (Koralek et al., '88).

Recording

Recordings from the barrel cortex served two purposes. First, the electrocorticogram (ECoG), together with the rate of respiration and the reflex status, provided information about the depth of anesthesia. This is an important variable since the sensory response of cortical and thalamic cells systematically varies with anesthetic depth (Armstrong-James and George,'88; Armstrong-James and Callahan, '91; Friedberg et al., '91). Secondly, the ECoG allowed monitoring of the suppression and subsequent recovery of barrel field neuronal activity.

The ECoG was recorded from the barrel cortex with a tungsten microelectrode with a 10 μm tip (A-M Systems Inc.) at a depth of 1,000 μm below the pia. The signal was filtered twice, first at a band pass of 1–60 Hz and then at a band pass of 0.1–32 Hz. The trace was digitized at 100 points per second and displayed on a computer monitor on-line. In some cases a Fast Fourier Transform was performed on the digitized trace to determine the strongest frequencies. Prior to the period of cortical suppression, the ECoG trace exhibited a peak-to-peak amplitude of about 150 μV and a predominant frequency of 3–7 Hz (Fig. 1). The subjects were in anesthetic stage III-3 (Guedel, '20; Kubicki, '68; Friedberg et al., '91), as evaluated by the ECoG together with the respiration rate and the reflex status. If the subject entered stage III-2 during the recording session (if the whiskers began to move in a coordinated way, for example) a supplement of urethane was given (10% of the original dose).

To record neuronal responses in the thalamus a carbon fiber microelectrode (Armstrong-James and Millar, '79) electrolytically sharpened to a tip diameter of less than 1 μm (Armstrong-James and Millar, '80) with an impedance at 1 KHz of 0.7–1.0 MΩ was used. The microelectrode was advanced vertically through the neocortex and hippocampus to reach the thalamus. Action potentials were isolated by a time-amplitude window discriminator (Bak Electronics, Inc.) and monitored on a digital storage oscilloscope (Nicolet). Continual comparison of spike waveforms triggering the acceptance pulse with the initially stored action potential waveform ensured isolation of a single cell's activity over the course of the recording, which could last up to 2½ hours.

Whisker stimulation

As the electrode passed through POm or VPM the whiskers contralateral to the recording site were brushed and the rest of the body stimulated by hand-held probes after each 10–20 μm advance. Activity evoked by displacement of individual whiskers was collected as soon as a responsive single unit was isolated. The whisker stimulator was positioned just below a whisker 10 mm from the base of the whisker. The stimulator consisted of a hooked wire tip held in place by a glass capillary glued to a piezoelectric ceramic wafer. The piezoelectric wafer was deflected by a computer-gated electrical current. The stimulus was a 300 μm trapezoidal up-down movement of the wire tip with rise and fall times of 0.5 ms and a total stimulus duration of 3

ms. In each block of trials the stimulus was presented 50 times at 1 Hz, as in previous studies (Armstrong-James and Fox, '87; Diamond et al., '92).

Using peristimulus time histograms (PSTHs), the cell response to deflection of single whiskers was measured on-line. Although several whiskers within the receptive field of a POm cell usually produced a qualitatively similar response, it was possible to combine the measures of response magnitude and response latency to identify the whisker that evoked the greatest response at the shortest latency, and this was defined as the most effective whisker, or center receptive field (see Diamond et al., '92).

When the receptive field included the trunk or limbs the appropriate stimuli were brush strokes, taps with a wooden applicator, light pressure, joint rotation, etc. Nociceptive inputs to thalamic cells were not tested. Responses to limb stimulation were analyzed quantitatively in two cases in which the piezoelectric stimulator was set up to indent the skin of the forelimb and hindlimb (see Results).

Thalamic recording sites were marked by passing a DC current of 3 μA for 10 seconds (electrode tip positive). This produced a spheroidal lesion of roughly 100 μm diameter, which was apparent in histological sections (Fig. 2).

Thalamic response to cortical suppression

At the outset of the recording session the receptive field of the cluster of cells at the cortical barrel field recording site was mapped. The leads from this electrode were then switched and the signal was amplified and filtered to produce a digitized on-line ECoG trace. Periodically this same electrode was used to record cortical multiunit activity.

Once the receptive field of a well-isolated thalamic cell was mapped the response of this cell to stimulation of its center receptive field was measured periodically for the remainder of the experiment—one block of 50 stimulus trials was presented every 3–4 minutes. During the first set of stimulus blocks the cortex was normal. After completion of these "control" blocks, a test for the influence of barrel cortex on the thalamus was carried out by measuring the sensory response of the thalamic cell while inactivating the cortex. The suppression was initiated at 0 minutes in all figures.

Two different methods were used to inactivate the barrel cortex. When examined separately, no difference was found between the data collected with the two methods; therefore, these two groups of experiments will be considered together. In eight subjects the cortex was suppressed by exposure to a magnesium solution (magnesium sulfate dissolved to a concentration of 4% in 0.1 M buffered phosphate at pH 7.4). This solution was warmed to 37°C and repeatedly applied to the dura. To allow cortical recovery, the magnesium solution was replaced with a bath of 37°C artificial cerebrospinal fluid (CSF) (Eagle's minimum essential medium; GIBCO), which was flushed repeatedly over the cortex. In nine subjects the cortex was suppressed by exposure to a continous flow of cold artificial CSF. The artificial CSF was cooled to 4°C before being applied, and the temperature of the reservoir in contact with the dura was 14°C. To allow recovery, the cortex was bathed in warm artificial CSF (37°C).

To test for the possibility of direct effects on the thalamus, in one case (in which cell activity was not recorded) temperatures in the barrel cortex and in the VPM/POm region of the thalamus were monitored with a 0.4-mm-diameter needle thermoprobe (Cole-Parmer) during the standard cooling procedure. The cortex equilibrated at 18–21°C and at the same time the thalamus equilibrated near 35°C.

Inactivation of the barrel cortex, defined as a reduction of at least 50% in the peak-to-peak amplitude of the ECoG, occurred about 30 minutes after the onset of cooling or exposure to magnesium (see Fig. 1). After the ECoG became inactive, the cooling or magnesium treatment was maintained for an additional 15 minutes so that five blocks of data could be collected from the thalamic unit deprived of its cortical input. Thus, the mean total period of suppression was 42 minutes (standard error 5 minutes). The suppression treatment was then terminated. A return of the ECoG waveform to 75% of presuppression amplitude was used as an operational definition of functional recovery of the cortex (Fig. 1). The time required for recovery ranged from 30 to 90 minutes (mean recovery period was 65 minutes), and there was considerable variability in this parameter among different subjects (standard error 12 minutes).

Data analysis

During the experiment the timing of action potentials relative to the stimulus was viewed on-line (MI²) and stored on a hard disk for further analysis using our own software. To calculate the response latency, response magnitude, and response probability, the level of spontaneous activity had to be measured and subtracted from the activity occuring after the stimulus. To estimate "spontaneous activity," the number of spikes occuring in the 100 ms preceding the stimulus was counted. In previous experiments under the same conditions, the mean value across 50 trials was 22.0 spikes for POm cells and 25.8 spikes for VPM cells, corresponding to spontaneous firing rates of 4.4 and 5.2 spikes per second, respectively (Diamond et al., '92). The mean number of spikes occuring spontaneously in each 2 ms bin could then be calculated. The next step was to plot a PSTH with 2 ms bins showing spikes recorded in the 100 ms following the stimulus (that is, from $t = 0$ to $t = 100$ ms) for each block of 50 trials. Within that histogram, the "response period" was defined as the interval bracketed by the first and last bins containing at least five times the number of spontaneous spikes expected in a single bin during spontaneous activity. For example, if 30 spikes occurred in the 100 ms period preceding the stimulus, yielding an expected value of 0.6 spikes per bin, then the response period would be defined as the poststimulus interval bracketed by bins containing three or more spikes. The probability that a bin would contain three "spontaneous" spikes is low (about 1 in 126, assuming that the number of spikes occuring spontaneously in a single bin follows a Poisson distribution). The "response magnitude" was then calculated as the number of spikes occurring in the response period, after the number of spikes expected to occur spontaneously within that period was subtracted. The "response probability" was the percent of trials in which a spike was recorded during the response period. In each of the 50 trials, the time of the first event within the response period was calculated and the median of these values was taken as the "latency." The median rather than the modal latency was used because the PSTHs of many POm cells had highly variable latencies with no mode.

For every thalamic neuron, the level of activity (response magnitude, response probability, and spontaneous activity) at each time point after the start of cortical suppression was

computed as a percent of the average level of activity during the "control" period (4 to 5 blocks of stimuli prior to the onset of cortical suppression). To apply statistical tests for the effect of cortical suppression, the first step was to form two separate groups, POm cells and VPM cells. Then, the average activity for the groups at each time point after the start of suppression was compared to the average activity during the "control" period. Two tests were applied: a one-tailed t-test (assuming normal distributions) and a nonparametic Wilcoxon signed rank. For all data points the level of significance (at the criterion of $P < 0.05$) was equivalent in the two tests.

Experimental design: general considerations

Of the entire set of thalamic cells studied, a total of 17 met four strict criteria: 1) the thalamic cell showed a sensory response during 4 to 5 control blocks of stimuli; 2) the same thalamic cell was discriminated continually during the entire period of cortical suppression, including a 15 minute period of cortical inactivation (very low amplitude ECoG activity); 3) following the period of cortical suppression, the same thalamic cell was studied continually during the recovery of cortex, or during an additional 30 minute period of cortical suppression; 4) any sudden changes seen in the thalamic cell's sensory activity were related to changes in cortical activity—as measured by the ECoG and by cortical multiunit activity (i.e., the change in the thalamic cell's activity was not explained by injury). Thus, one thalamic neuron was excluded from the analysis because it suddenly lost spontaneous and evoked activity immediately after the onset of cortical cooling; the change in the thalamic cell's activity occurred long before any changes in cortical activity were apparent. Twelve thalamic cells were excluded as soon as doubts arose during the recording session that the same single unit was being discriminated continually. Of 17 cells included in the analysis, 13 were studied while the cortex was allowed to recover from the 15 minute period of profound depression. The other four cells were studied continuously during an additional 30 minute period of cortical suppression; the barrel cortex was not permitted to recover.

Studies measuring the effect of cortical suppression often sample one group of cells when the cortex is normal and a second group after the cortex is inactivated. This design was not used for two reasons. First, the change in thalamic activity over time (from the onset until the termination of cortical suppression) was of interest. Second, as will be shown shortly, it would have been impossible to locate and study POm cells once the barrel cortex was depressed. The suppression-recovery cycle was induced only once in each animal because the usual assumption that the barrel cortex returns to the normal condition after "recovery" from a period of inactivation may not be valid (see Discussion). Therefore, only a single cell could be studied quantitatively in each animal. This design made it difficult to collect a large sample of cells. However, it will become apparent that the difference between POm and VPM cells was so robust that a sample of just 17 cells was sufficient to distinguish the properties of the two nuclei.

RESULTS

The main findings concern the sensory responses of thalamic cells during suppression of the barrel cortex. Before that evidence is presented, the direct effects of suppression on cortical activity will be summarized.

Relationships among cortical suppression, ECoG, and cortical multiunit activity

The ECoG was recorded in every experiment in order to monitor the status of the barrel cortex. Four ECoG traces recorded in case 14 are shown in the left column of Figure 1. In the "control" period prior to cortical suppression (uppermost ECoG trace), the record displayed a peak-to-peak amplitude of about 150 μv and a dominant frequency of 3–4 Hz (Fast Fourier Transform not illustrated). The time-matched cortical multiunit recording is shown on the upper right. The center receptive field whisker was stimulated and 50 trials were collected. The cortical cells responded briskly with a latency of 10 ms.

Once the control recordings were complete, the barrel cortex was bathed with a solution containing 4% magnesium sulfate. The first noticeable change in cortical activity occurred about 8 minutes later (Fig. 1, second trace from the top), when the ECoG exhibited a series of high-amplitude waves. (Cortical multiunit activity was not collected at this time.) About 50 minutes after the magnesium application the ECoG indicated significant cortical depression (Fig. 1, second trace from the bottom). At this time cortical multiunit activity was eliminated, as indicated by the time-matched PSTH devoid of spikes. At 63 minutes the magnesium bath was removed and replaced with a bath of 37°C artificial CSF. Although barrel cortex gradually regained activity, there was a persistent broadening and slowing of ECoG waves. This is apparent in the bottom ECoG trace, recorded 70 minutes after removal of the magnesium bath. Failure of the ECoG to return precisely to the normal pattern even 60–90 minutes after the removal of the suppressing agent was characteristic of most experiments. The accompanying PSTH shows that cortical responses to whisker displacement had returned.

Normal sensory responses of POm and VPM cells

After the brains were sectioned and stained with cresyl violet, nine recording sites were identified in POm and the other eight in VPM. An example of a recording site in POm, from case 14, is shown in Figure 2. The response of all thalamic cells to stimulation of the center receptive field whisker was measured prior to inactivation of the cortex. Among those cells located in POm the average latency to stimulation of the center receptive field whisker was 15.3 ms and the average response magnitude was 34 spikes in 50 trials. Among those cells located in VPM the average latency was 6.0 ms and the average response magnitude was 76 spikes in 50 trials. These results are similar to those of a prior study that used a larger sample of cells (Diamond et al., '92).

Effect of cortical suppression on POm cells

Cells with vibrissal receptive fields. The effect of cortical suppression on the thalamic cell in case 14 is shown in Figure 3. The thalamic recording site was subsequently identified in POm (Fig. 2). This cell was studied concurrently with the cortical recordings shown in Figure 1. Five blocks of stimuli were presented to the center receptive field whisker, E1, prior to the application of magnesium to the barrel cortex. In these control blocks the mean latency was 18 ms and the mean response magnitude 46 spikes. At 0

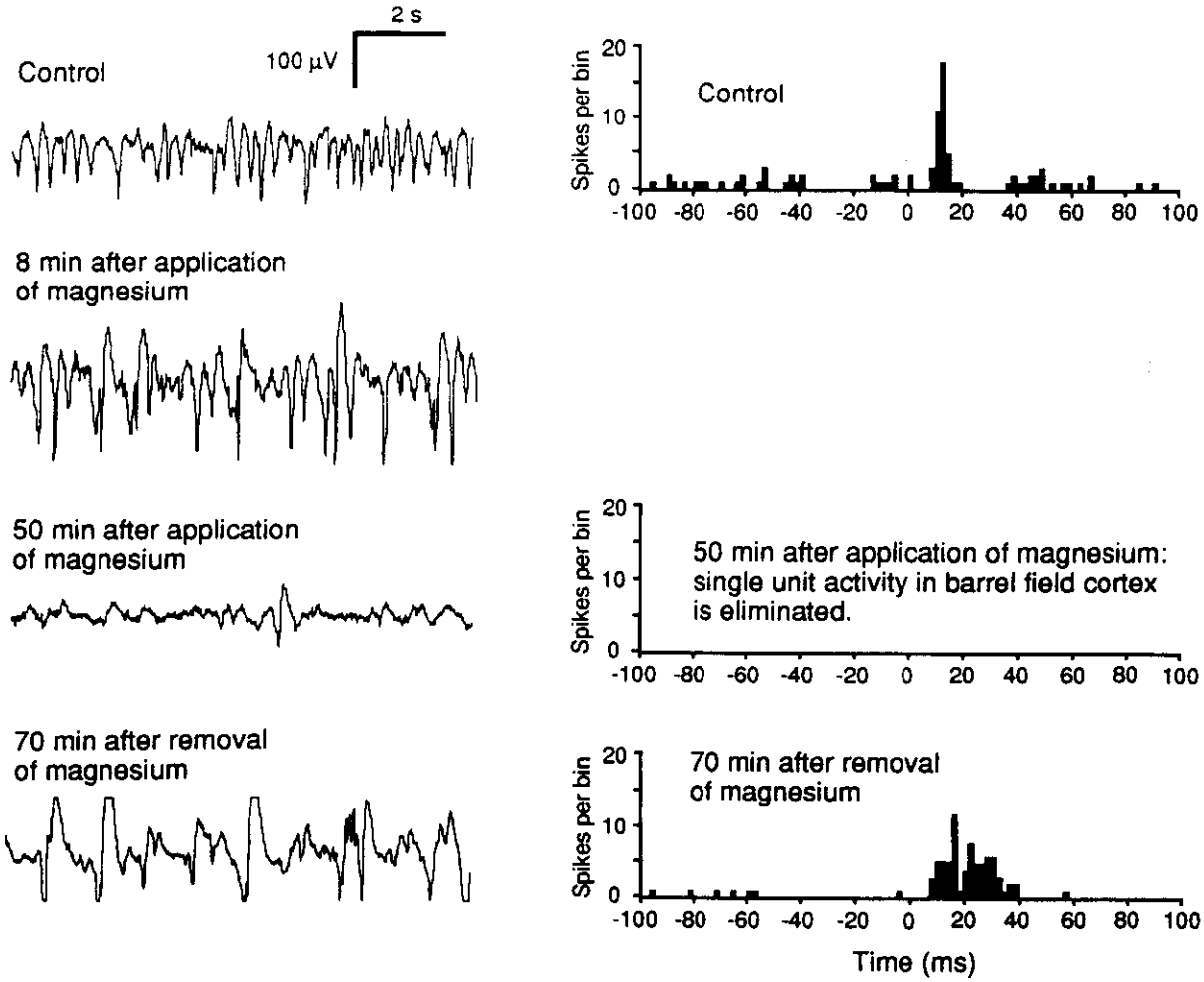

Fig. 1. **Effect of magnesium application on the barrel cortex ECoG and multiunit activity in a typical experiment, case 14.** The column on the **left** shows barrel cortex electrocorticogram (ECoG) traces. The peristimulus time histograms (PSTHs) to the **right** show multiunit activity recorded from the same cortical site immediately after storage of the ECoG trace. **Top:** the "control" state prior to cortical suppression. The ECoG displayed a peak-to-peak amplitude of 100–150 μv. The PSTH at this time revealed a robust response to whisker displacement. The whisker stimulus was at 0 ms. **Second from top**: 8 minutes after application of magnesium. High-amplitude waves of 250–300 μV were apparent in the ECoG trace. No PSTH was recorded at this time. **Third from top:** 50 minutes after application of magnesium. ECoG activity was depressed. Cortical multiunit spontaneous and evoked activity were eliminated. **Bottom:** 70 minutes after removal of magnesium. The ECoG trace showed substantial but not complete recovery; there remained some slowing of the waveform. There was recovery of cortical multiunit activity although the final PSTH was not identical to the first PSTH.

minutes, 2 minutes after completion of the control blocks, the surface of the cortex was bathed in a 4% magnesium sulfate solution. Within 10 minutes the response of the thalamic cell to whisker movement began to increase (Fig. 3A). The 15 minute period of elevated responsiveness occurred simultaneously with the high-amplitude waves seen in the ECoG (Fig. 1, second trace). By 20 minutes the POm cell began to show a progressive decrease both in evoked activity (Fig. 3A,B) and in spontaneous activity (Fig. 3C). Nearly complete inactivation of the barrel cortex (Fig. 1, third trace) occurred about 50 minutes after the initial exposure to magnesium. The magnesium treatment was maintained for an additional 15 minutes during which time five additional blocks of whisker stimulation were presented.

At 63 minutes the magnesium solution was replaced with artificial CSF. All measures of the POm cell's activity remained depressed for at least 30 minutes. In 120–135 minutes (57–72 minutes after the removal of the magnesium), the POm cell's activity began to return to normal. The experiment was terminated at 135 minutes, when the amplitude and waveform of the ECoG approached normal (Fig. 1, bottom trace).

The effects of cortical suppression on the timing of thalamic activity are revealed by averaging together the PSTHs from sets of stimulus blocks (Fig. 3D). During the initial 15 minutes of cortical magnesium exposure, when the ECoG recorded from the barrel cortex exhibited high-amplitude waves, the whisker-evoked response of this POm cell increased slightly above the control response (this is most visible in the poststimulus interval 22-36 ms). During the period 47–62 minutes after magnesium application, the POm cell lost all sign of evoked activity. Some spontaneous activity remained. Finally, a robust response reminiscent of

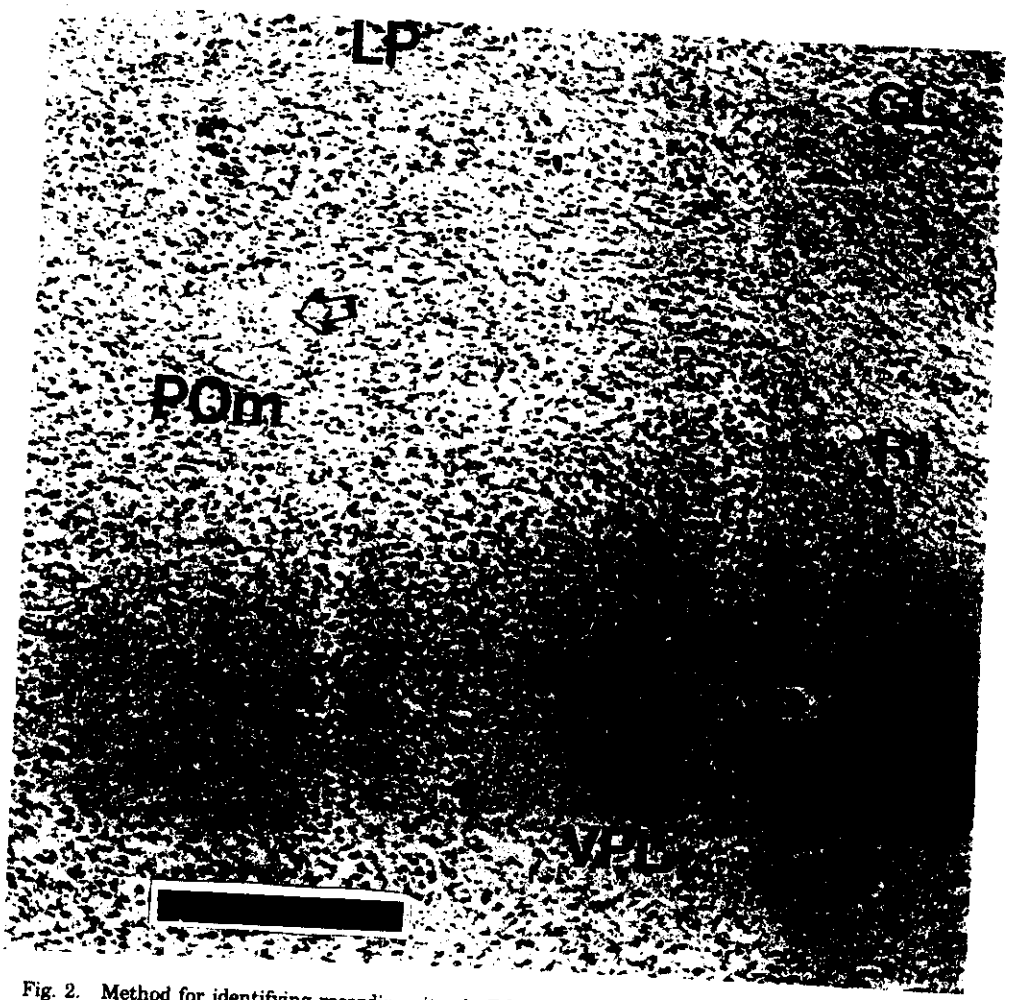

Fig. 2. Method for identifying recording sites in POm and VPM. The arrow indicates an electrolytic lesion made at the POm recording site in case 14. GL, lateral geniculate nucleus; LP, lateral posterior nucleus; POm, rostral subdivision of the posterior group; Rt, reticular nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus. Scale bar = 0.5 mm.

the control response was recorded during the period from 120–135 minutes, 55–70 minutes after removal of the magnesium bath (final PSTH in Fig. 3D). The effect of cortical suppression and recovery on this cell was typical of all POm cells with trigeminal receptive fields.

Cells with receptive field on the limbs. To determine whether the dependence on S-I cortex might hold true for POm cells representing body regions other than the whisker pad, one cell with receptive field on the forelimb and one cell with receptive field on the hindlimb were studied.

The outcome of cortical inactivation was equivalent for these two cells, and the results of the forelimb cell (case 28) are illustrated in Figure 4. The center receptive field of the cell was the glabrous skin on the medial aspect of digit 3. The stimulator was positioned to indent the skin and four blocks of 50 stimuli were presented with the cortex in the normal condition. In these control blocks the mean latency was 27 ms and the mean response magnitude was 22 spikes. The cortical cooling procedure was then initiated (0 minutes). Immediately the evoked response magnitude began to climb (Fig. 4A), although some of this increase was related to a decrease in the rate of spontaneous activity (Fig. 4C; recall that evoked response is the difference between total activity and spontaneous activity). Within 15 minutes of the onset of cortical cooling all measures of the POm cell's activity, spontaneous and evoked, began to decrease rapidly. At 30 minutes the ECoG displayed sluggish, low-amplitude waves similar to those shown in the third ECoG trace of Figure 1. The cooling of cortex was maintained for an additional 15 minutes so that five blocks of data could be collected while the cortex was inactive. At 45 minutes the cooling was terminated and warm artificial CSF was substituted. Within a few minutes the activity of the POm cell, spontaneous and evoked, began to recover. This corresponded to the recovery of activity in the ECoG. In 120–135 minutes the response of this POm to forelimb stimulation was similar to that of the control period (Fig. 4A and B). Spontaneous activity also recovered (Fig. 4C). The ECoG trace approached the normal pattern at this time.

As in case 14, the PSTHs from sets of stimulus blocks were averaged together to highlight the effects of cortical suppression on the timing of activity in the thalamus (Fig. 4D). During the set of five control blocks, the PSTH of the POm cell revealed a high rate of spontaneous activity and a dispersed response with an onset at approximately 20 ms

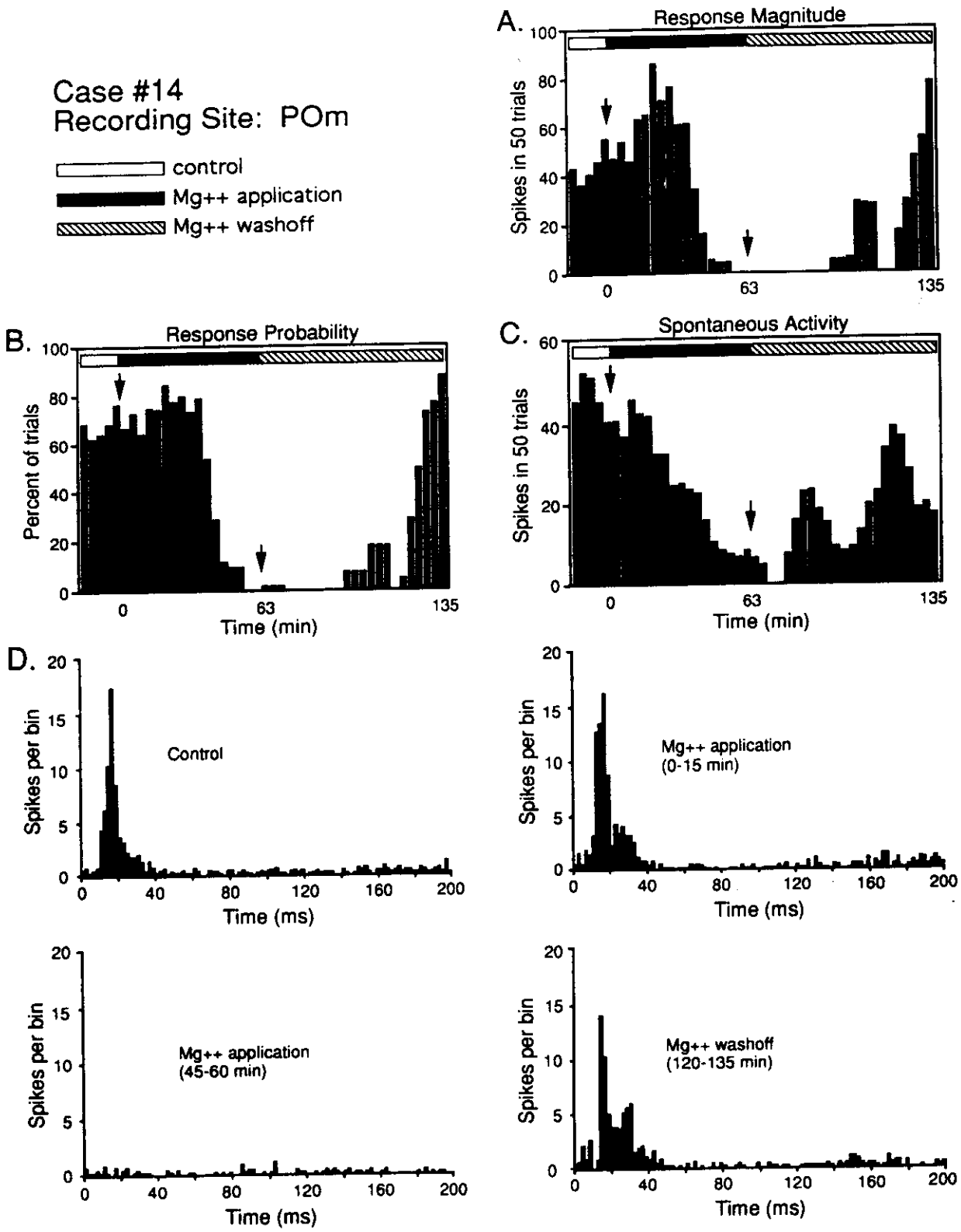
Case #14
Recording Site: POm
control
Mg++ application
Mg++ washoff
A.
Response Magnitude
Spikes in 50 trials
B.
Response Probability
Percent of trials
C.
Spontaneous Activity
Spikes in 50 trials
Time (min)
D.
Control
Spikes per bin
Time (ms)
Mg++ application
(0-15 min)
Mg++ application
(45-60 min)
Mg++ washoff
(120-135 min)

Figure 3

poststimulus and a peak at roughly 36–40 ms. During the initial 15 minutes of cortical cooling, the rate of spontaneous activity was noticeably depressed; however, the stimulus-evoked volley appears to have become more tightly clustered. During the period 30–45 minutes after the start of cortical cooling, there was a greatly diminished response, but there appear to have been a few evoked spikes. Finally, 75–90 minutes after the end of cortical cooling, the POm cell produced a robust response (final PSTH in Fig. 4D) comparable to that recorded during the control period 2½ hours earlier.

Summary of POm cells. To verify that the response to cortical suppression of the entire group of POm single units followed the pattern of the two cells described above, the data from nine separate cases were averaged (Fig. 5). Recall that in most experiments the ECoG trace exhibited high-amplitude waves approximately 10 minutes after application of the cortical suppressant (e.g., Fig. 1). As might be expected, then, Figure 5 shows that shortly after the initiation of cortical suppression the POm cells exhibited a marked increase in evoked activity. Specifically, in the third block of stimuli (at 9 minutes in Fig. 5A) the average evoked response magnitude of the population was 66% greater than during the control period (although not significantly different from the control response; $P < 0.05$). In this same block of stimuli the rate of spontaneous activity dropped to 45% of the control rate (Fig. 5C). The complementary changes in response magnitude and spontaneous activity suggest that increased cortical activity (the cortical bursting often noted prior to cortical depression) produced increased sensory responsiveness in POm, but decreased spontaneous activity. Of course, the two measures are not independent, since spontaneous activity was subtracted from total activity to give response magnitude. Still, this elevated response magnitude was not merely an artefact, as will become apparent in the PSTHs (Fig. 5D).

After the brief period of elevated response, the evoked response of the population diminished to a level of about 70–80% of the control response and remained at this plateau for 15 minutes (Fig. 5A). The POm cells then underwent a progressive decline in evoked response beginning at 27 minutes. At this time, the response magnitude was 40% of the control value, and the reduction in response remained significant ($P < 0.05$) through 45 minutes. The decrease in the cells' activity is also apparent in the plots of response probability and spontaneous activity (Fig. 5B,C). At 45 minutes response magnitude, response probability, and spontaneous activity had declined to between 5 and 20% of control levels. The plots are "reset" after 45 minutes so that 0 minutes designates the washoff of magnesium from the cortical surface, or the re-warming of the cortex. The recovery of the POm cells' activity began within a few minutes. The response magnitude remained significantly depressed ($P < 0.05$) until 24 minutes after the start of the cortical recovery, at which time the response magnitude was, on average, 52% of the control response. The time course of the recovery of response probability and spontaneous activity was similar to that of response magnitude.

The PSTHs in Figure 5D were collected before, during, and after cortical inactivation. Each plot was generated by merging and averaging PSTHs from the 9 studied POm cells. The first PSTH is from the control period, before the suppression of barrel cortex. Evoked activity in this PSTH began about 10 ms poststimulus, reached a peak at 12–18 ms, and continued until approximately 60 ms. The next PSTH in Figure 5D was compiled in the first 10 minutes after completion of the control blocks. In agreement with Figures 3A, 4A, and 5A, this PSTH demonstrates that an increase in evoked activity occurred shortly after application of the cortical suppressant. The inset—generated by subtracting the control PSTH from the second PSTH—reveals elevated activity in bins at 28–58 ms poststimulus.

The third PSTH shows POm activity recorded 30–45 minutes after application of the cortical suppressant. The rate of spontaneous activity was lower than in the two preceding PSTHs (compare 100–200 ms). A response to the stimulus can be detected approximately 20 ms after the stimulus, but it is greatly reduced in comparison to the control response. The final PSTH shows the recovery of POm activity 60–75 minutes after the removal of the cortical suppressant. At this time cells in POm exhibited a clear response to the stimulus that resembled the response during the control period.

Correlation between cortical activity and POm multiunit activity. Further observations confirmed the strong correlation between cortical activity and POm activity. The activity of the cluster of neurons surrounding the single unit being discriminated was monitored through the oscilloscope and the audio speaker. Whenever a POm single unit was silenced or depressed due to cortical inactivation, the surrounding cells were equally depressed. In no case was robust spontaneous or evoked activity recorded from a POm cell cluster simultaneously with the silencing of the discriminated single unit. In some cases there was a complete absence of activity at the recording site during the period of maximal cortical inactivation. In that situation, the viability of the thalamic cells could only be ensured by their subsequent recovery. The recovery of the POm single unit always occurred simultaneously with the recovery of the surrounding neurons.

Effect of cortical suppression on VPM cells

Two representative cells with vibrissal receptive fields. In comparison to the cases just described, suppression of

Fig. 3. Effect of suppression of barrel cortex on a typical POm cell with a vibrissal receptive field. This thalamic cell was recorded in case 14, as were the cortical data shown in Figure 1. Plots A–C show the evoked and spontaneous activity of the POm cell. On the x-axis, 0 minutes is starting time of cortical magnesium application. This is also indicated by the first arrow on the graph. The second arrow indicates the magnesium washoff at 63 minutes. **A.** Response magnitude initially increased during the time when the ECoG exhibited high-amplitude waves. Later, response magnitude fell to nought coincident with the loss of cortical activity. After the washoff of magnesium sulfate from the cortical surface, the POm cell's response magnitude recovered, albeit unevenly. **B.** After reaching a plateau slightly above the control level, response probability decreased rapidly. Following a period with 0% response probability, there was a recovery beginning about 30 minutes after the washoff of magnesium from the cortical surface. **C.** Spontaneous activity showed a gradual decrease as cortical activity diminished, and an uneven recovery matching the return of cortical activity. **D.** Averaged PSTHs of the POm cell from the indicated periods of time. The onset of the whisker stimulus is at 0 ms in these and in all PSTHs. During the first 15 minutes after application of magnesium to the cortex, the evoked activity of this POm cell appears to have increased slightly. During the period 45–60 minutes after the application of magnesium all evoked sensory activity appears to have been eliminated, while some spontaneous activity remained. Finally, during the period 120–135 minutes, 57–72 minutes after the washoff of magnesium, the evoked activity returned.

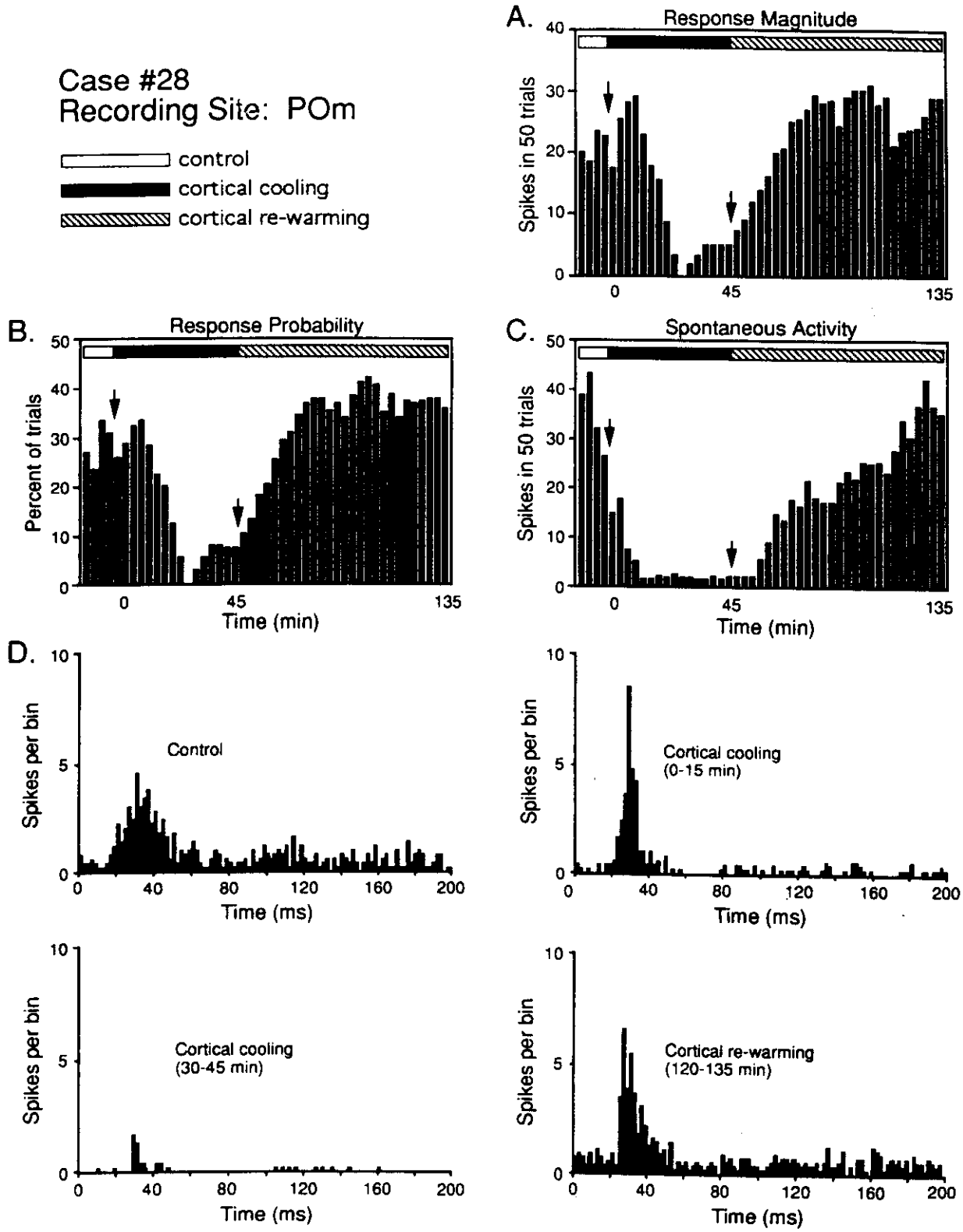

Fig. 4. Effect of suppression of cortical activity on a POm cell with a forelimb receptive field. The labeling of the plots follows the conventions of Figure 3. Barrel cortex was cooled from 0 to 45 minutes, and the response of the thalamic cell is described in the text.

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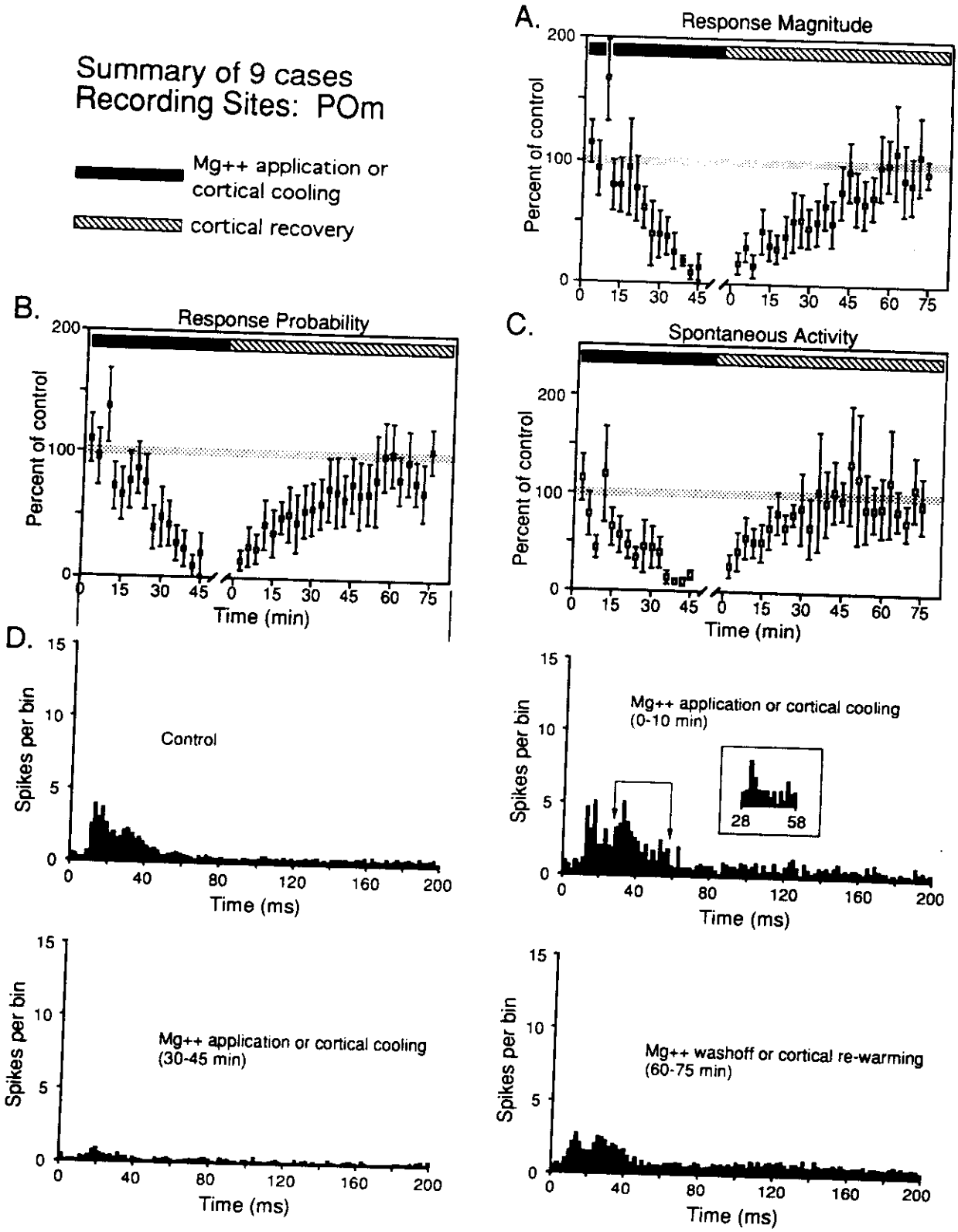

Figure 5 (see p. 76)

the barrel field cortex led to only minor changes among those cells subsequently localized in VPM. A good example is case 42 (Fig. 6). The center receptive field of the neuron was whisker E4. Before cooling the cortex, four blocks of whisker stimuli were presented during which the average latency was 6.2 ms and the average response magnitude was 55 spikes. A solution of cold artificial CSF (4°C) was then applied to the barrel cortex. Response magnitude and response probability remained at high levels during the entire period in which cortex was cooled (Fig. 6A,B). This is in spite of the fact that from 30–45 minutes the ECoG exhibited a significant diminuition in wave amplitude, and cortical multiunit activity was eliminated. The rate of spontaneous activity decreased slightly (Fig. 6C); however, the rebound in spontaneous activity (20 minutes) suggests that the initial decrease could have been part of a cyclical fluctuation.

The PSTHs in Figure 6D indicate that this VPM cell continued to respond vigorously to whisker movement throughout the initial period of cortical suppression (0–15 minutes) and the final period of cortical suppression (30–45 minutes). An interesting observation is that when the cortex was inactivated the response latency of the VPM cell increased by 2 ms. This was not uncommon among VPM cells; four cells exhibited a slight but consistent increase in latency (2–4 ms), and four cells showed no change. An increase in latency was not correlated with a change in the level of spontaneous or evoked activity.

After 45 minutes of cooling the barrel cortex was rewarmed. Examining the portion of the histogram after 100 ms, it is clear that the rate of spontaneous activity increased during the cortical recovery, consistent with Figure 6C. Aside from this, the effect of the recovery of the barrel cortex on the PSTHs of the VPM cell was minimal.

Case 15 is selected to show changes in the activity level of a VPM cell that seemed to occur independently of the state of the cortex (Fig. 7). The center receptive field of the cell was whisker D6. Prior to cortical suppression four blocks of stimuli were presented to whisker D6; the average latency was 4 ms and the average response magnitude was 89 spikes in 50 trials. At 0 minutes, a solution of 4% magnesium sulfate was applied to the surface of the barrel cortex. The thalamic cell showed a modest decrease in response magnitude (Fig. 7A) lasting for about 20 minutes. The apparent decrease in response magnitude may be explained partly by a significant increase in spontaneous activity (Fig.7C). One might at first assume that the increase in spontaneous activity was related to cortical suppression. However, at 15 minutes, while the cortex was still exposed to magnesium, the rate of spontaneous activity began to decrease rapidly. Moments later (24 minutes) the rate of spontaneous activity once again climbed. Just before the removal of the magnesium (33 minutes) the spontaneous activity again began to fall, and continued to fall as the barrel cortex recovered. The unpredictablility of these fluctuations suggests that they were not determined by the state of the cortex.

Independently of these moment-to-moment shifts in the rate of spontaneous activity, the VPM cell maintained a brisk response to whisker movement. This is indicated by the fact that the cell consistently fired in reply to over 80% of stimulus presentations even during the time span when the barrel field ECoG was depressed (Fig. 7B). The consistency of the cell's response is confirmed by the PSTHs shown in Figure 7D. As the cortex changed from the normal to the depressed state (20–35 minutes) there was no consistent change in the sensory responses of the VPM cell. Similarly, the recovery of the cortex (60–75 minutes) had no marked effect on the sensory response of the thalamic cell.

Summary of VPM cells. The averaged data from the eight VPM cells (Fig. 8) show that the general trend was to maintain an even rate of activity during the course of cortical suppression. Plots in Figure 8A–C show the effect on VPM cells of 60 minutes of cortical cooling or magnesium exposure. Because only four VPM cells were studied during cortical recovery, averaged recordings from this period are not presented.

In contrast to the POm cells, there was no period of "hyperexcitability" during the first 10 minutes after application of the cortical suppressant (Fig. 8A; compare with Fig. 5A). Response magnitude decreased by about 15% during magnesium exposure or cortical cooling. However, at no time during the period of cortical suppression did the response magnitude (Fig. 8A) or the response probability (Fig. 8B) differ significantly from the control value ($P < 0.05$).

It should be emphasized that the population's high degree of variability in spontaneous activity (Fig. 8C) is not due to two classes of VPM cells, one that showed an increase in spontaneous activity during cortical suppression and one that showed a decrease. Rather, the rate of spontaneous activity of individual VPM cells changed markedly over time, and these changes were not consistently positive or negative—they seemed to be random fluctuations. This can be appreciated in Figures 6C and 7C. The average value of spontaneous activity during cortical suppression never differed signficantly from the control value ($P < 0.05$).

The PSTHs in Figure 8D were collected before and during cortical suppression. Each plot was generated by merging PSTHs from the eight studied VPM cells. The scale of the plots is the same as in Figure 5D, revealing the

Fig. 5 (on page 75). The data from the group of nine POm cells reveal the loss and recovery of activity. The graphs are based on nine cells studied for 45 minutes or more after the application of the cortical suppressant, and seven cells studied for 75 minutes or more of cortical recovery (two cells were studied for shorter periods). In parts A–C all measurements of evoked and spontaneous activity were calculated as a fraction of control response in individual cases and then averaged; standard errors of the mean are given. The horizontal shading corresponds to 100% of the control level. **A.** Response magnitude. Note the evidence for POm hyperexcitability about 10 minutes after the application of magnesium or the onset of cortical cooling. After the brief period of hyperexcitability, a plateau in response level is evident, followed by a progressive decline through 45 minutes. The recovery of the barrel cortex led to a progressive increase in POm responsiveness. **B.** Response probability. At about 10 minutes, the POm cells tended to respond to a higher percent of stimulus trials than during the control period (not significant); this was followed by a decline in response probability. The subsequent recovery in response probability was monotonic. **C.** Spontaneous activity initially decreased, recovered, and then decreased again as the barrel cortex became depressed. The recovery of spontaneous activity was similar to that of response magnitude and response probability. **D.** Averaged PSTHs from the indicated periods of time. During 0–10 minutes the sensory response of the POm cells increased markedly. This is especially evident in the interval 28–58 ms poststimulus, indicated by the arrows. The inset shows the increase above the control PSTH in this interval. During the period 30–45 minutes after the start of cortical cooling or magnesium application, there was a minimal sensory response. Finally, during the period 60–75 minutes after the magnesium washoff or cortical rewarming the evoked activity returned to near the control level.

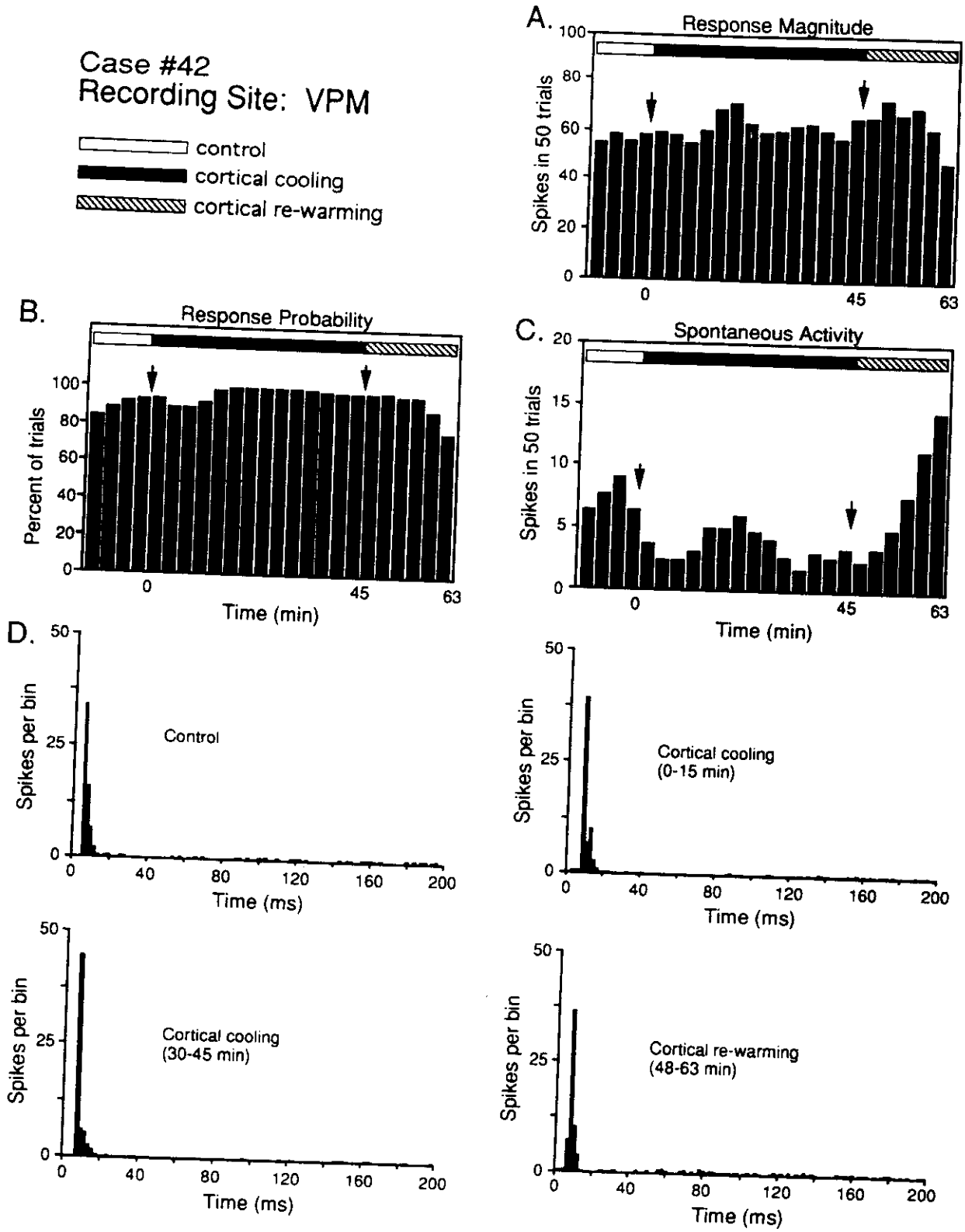

Fig. 6. Effect of suppression of barrel cortex on a typical VPM cell, case 42. The format follows Figures 3 and 4. The cortex was cooled at 0–45 minutes and then rewarmed. See the text for a description of the activity of the thalamic cell.

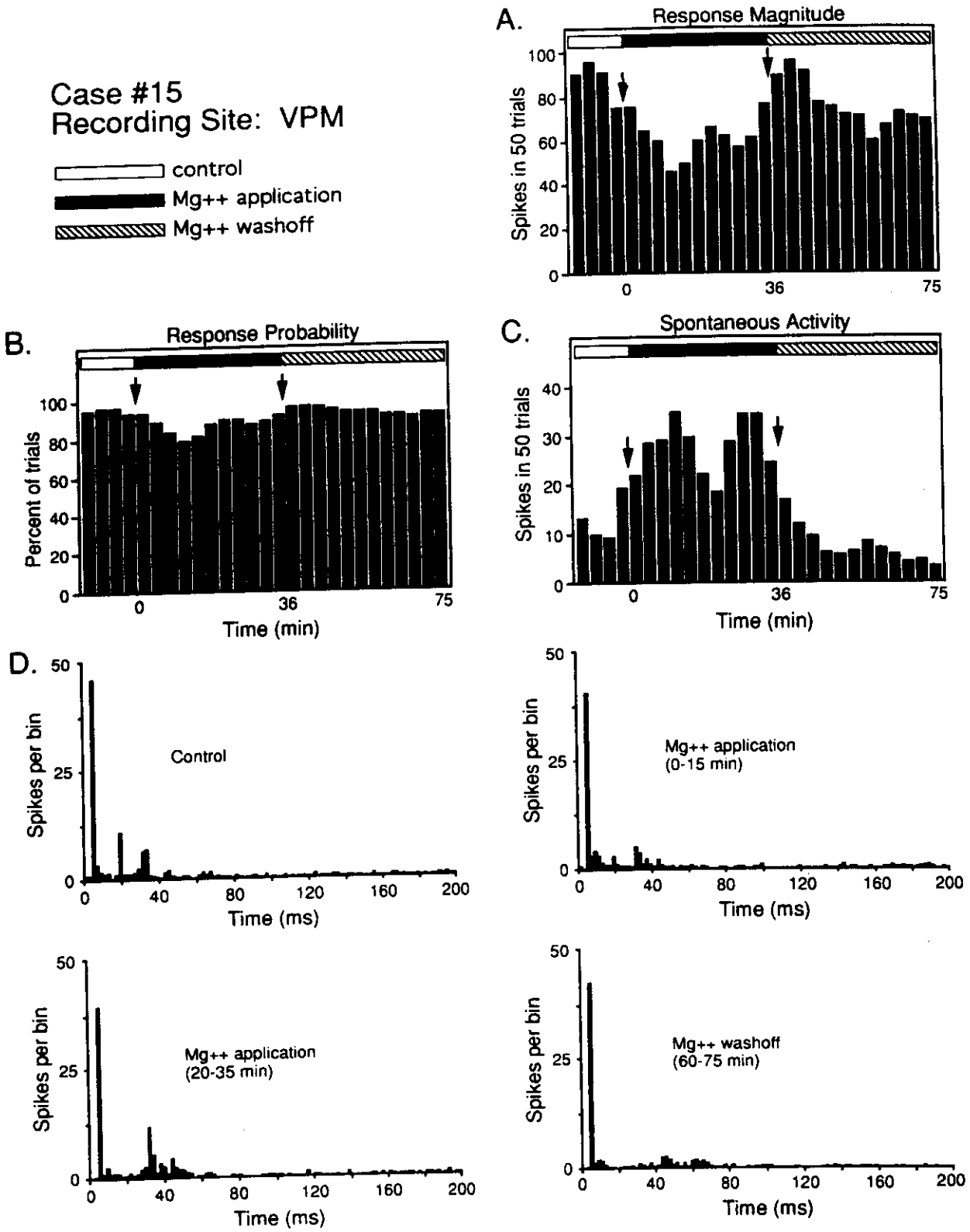

Fig. 7. Fluctuations in the activity of a VPM cell during the course of cortical suppression, case 15. The format follows Figures 3, 4, and 6. Magnesium was applied to the cortex at 0–36 minutes, and then washed off. See the text for additional information.

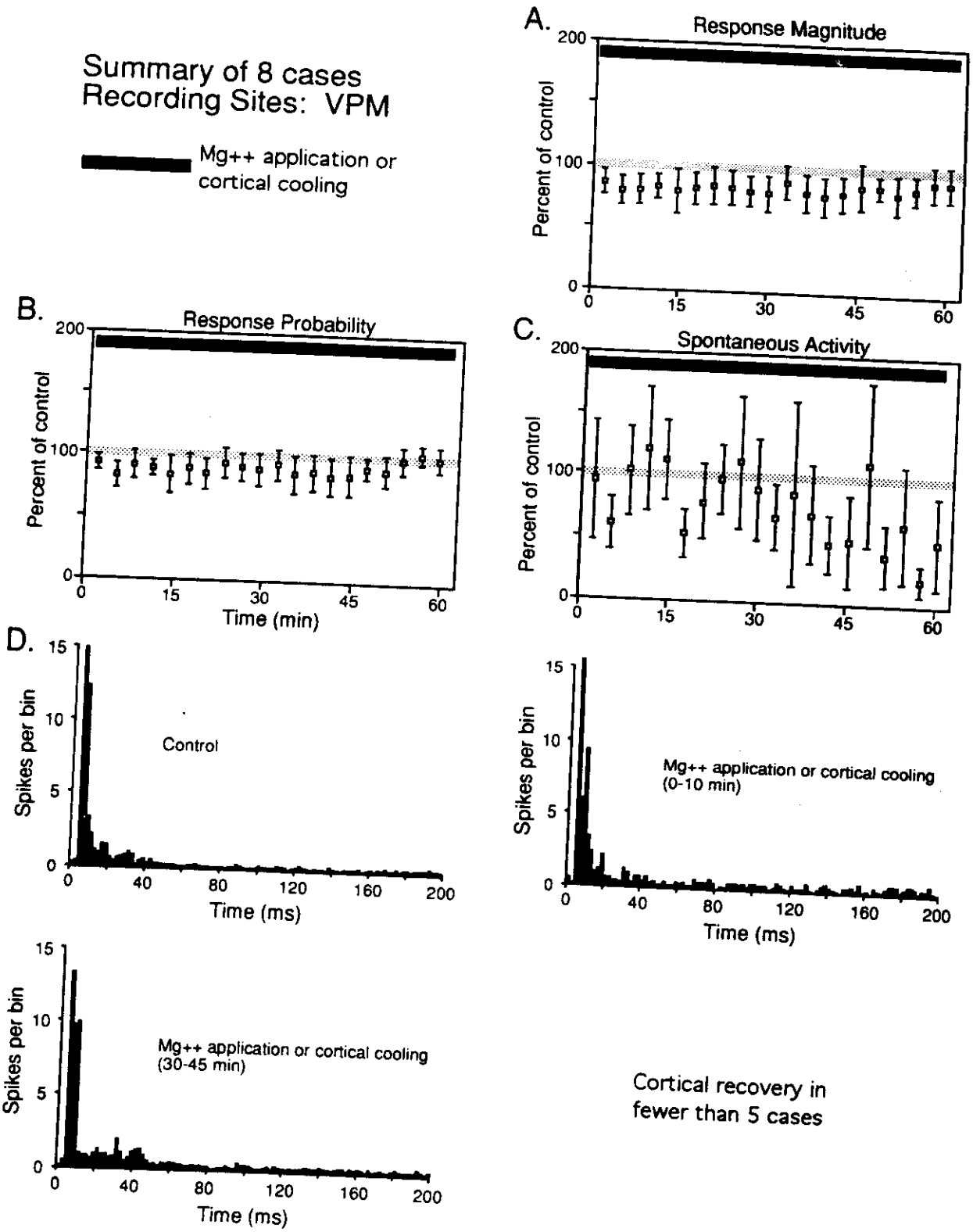

Fig. 8. The data from the group of eight VPM cells show that evoked and spontaneous activity remained robust during the course of cortical suppression. The labeling of the plots follows the conventions of Figure 5. **A–D:** The graphs are based on eight cells studied for 36 minutes or more, seven cells for 45 minutes or more, and five cells for 60 minutes or more. The data recorded during the recovery of cortex are not shown because only four of eight VPM cells were studied during cortical recovery. The findings are described in the text.

shorter latency and the more clustered response of VPM cells in comparison to POm cells. The chief result is that during the initial 10 minute period after the control blocks, and during the period 30–45 minutes after application of the cortical suppressant, the response of the VPM cells was robust. Cortical suppression did not seem to have a marked depressive effect on these VPM cells.

Correlation between cortical activity and VPM multiunit activity. The activity of the cluster of neurons surrounding the single unit being discriminated was monitored through the oscilloscope and the audio speaker at VPM recording sites as well as at POm recording sites. A consistent observation was that the cluster of VPM cells neighboring the recorded single unit exhibited robust spontaneous and evoked activity during the interval when the barrel cortex was silenced or depressed. This supports the idea that VPM activity was weakly, if at all, correlated with cortical activity.

Direct comparison of POm and VPM

Since these experiments used a single thalamic recording electrode, it was not possible to measure simultaneously the effect of cortical suppression on POm cells and VPM cells. However, the opportunity to compare directly POm and VPM arose when the thalamic single unit remained responsive to whisker stimulation throughout the 15 minute period of cortical inactivity. In four of these cases, cortex was suppressed for an additional 30 minutes. Once it became clear that the thalamic cell remained highly responsive to whisker stimulation, a small electrolytic lesion was made to mark this thalamic recording site. While the barrel cortex remained inactive, the microelectrode was withdrawn in 50 μm steps. The strength of the multiunit response to brush strokes across the whisker pad was noted after each step of the eletrode. There was invariably a clear change in the characteristics of the recorded cells with just a small step of the electrode—cells above a certain depth showed minimal spontaneous and evoked activity. After the brain tissue had been processed histologically, the microelectrode track and recording sites were plotted in relation to the boundaries of thalamic nuclei. From this analysis it was apparent that the shift from active to inactive cells corresponded to a step across the boundary from VPM into POm. These results offer more direct evidence that POm cells were unresponsive to whisker movement at the same time that VPM cells were responsive.

DISCUSSION

The main finding of this study is that the somatosensory responses of POm cells were dependent upon the functional integrity of the S-I barrel field. Two techniques—magnesium and cooling—were used to inactivate the barrel cortex[1] and, independently of the method of cortical suppression, POm cells exhibited a loss followed by a recovery of spontaneous and evoked activity coincident with the inactivation and recovery of barrel cortex activity. In contrast, VPM cells maintained an almost constant level of activity during the course of cortical suppression.[1]

[1]In pilot experiments, a third technique—application of lidocaine to the cortex—effectively eliminated activity in POm but not in VPM; however, this technique was abandoned because it produced seizures.

Methods of suppressing the barrel cortex

Our observations on the effect of cooling on cortical activity are consistent with those of Mosely et al. ('72). They found that about 6–8 minutes into a cycle of cooling, cells in cat sensory-motor cortex exhibited a brief episode of bursting, repetitive firing. The bursting can be attributed to a slight depolarization of the resting membrane potential (Pierau et al., '69). Brief episodes of bursting activity may account for the high-amplitude ECoG spikes we observed in most experiments during the first 10 minutes of cooling. Mosely et al. ('72) found that when the temperature dropped below 25°C the electrical activity of cortical cells ceased, probably due to reversible inactivation of the Na-K pump. They note that some activity was evident in the ECoG even when single unit spike activity was silenced; our observation is nearly identical. Their observation that no cortical cells recovered if cooled to below 18°C raises the possibility that our cooling protocol may have caused long-term or permanent damage to some cortical cells. This could explain why the ECoG trace and cortical multiunit activity seldom replicated the precooling control records after the cortex was re-warmed.

We believe that cooling depressed cortical activity without directly affecting the thalamus. POm and VPM are separated from the barrel cortex by a large volume of tissue, which includes the lateral posterior and lateral geniculate nuclei of the thalamus, the hippocampus, the corpus callosum, and the internal capsule. This intervening tissue more than 2 mm thick—most of which has a separate blood supply from subcortical arteries—would be expected to insulate POm and VPM from direct effects of cooling. In one experiment that followed the normal cooling protocol (see Materials and Methods) the temperature in the thalamus reached 35°C when the cortex was cooled to 18-21°C. At these temperatures action potential generation and conduction in the cortex would be reversibly blocked whereas electrical activity in the thalamus would remain normal (Mosely et al., '72).

Application of 4% magnesium sulfate depressed cortical activity as effectively as did cooling. Its mechanism of action presumably includes blockade of calcium channels. Magnesium never induced siezures nor did it produce epileptiform activity in the cortex. However, like the cooling technique, magnesium exposure often led to a brief episode of high-amplitude waves in the ECoG that preceded cortical depression (Fig. 1). Whether produced by magnesium or by cooling, such episodes of high-amplitude waves in the ECoG were accompanied by an increased firing rate in POm cells. This transient hyperexcitability of POm is apparent in Figures 3, 4, and 5.

While it is difficult to prove that magnesium never entered the thalamus, the experimental records show that hippocampal pyramidal neurons lying between the barrel cortex and thalamus exhibited a normal level of spontaneous activity. Moreover, the comparison between POm and VPM serves as a simple test for direct effects on the thalamus: since POm and VPM are located equidistant from the barrel cortex, any simple diffusion of magnesium should infiltrate the two thalamic nuclei at the same concentration. The fact that all VPM cells remained responsive during cortical suppression argues that magnesium did not directly suppress the thalamus during recordings from POm.

Facilitatory influence of the cortex on VPM

Most investigators agree that the S-I cortex exerts a modest facilitatory influence on transmission of information through VPM (e.g., Waller and Feldman, '67; Albe-Fessard et al., '83). For example, in cats electrical stimulation of S-I cortex immediately preceding nerve stimulation can decrease the response latency of VPM cells (Andersen et al., '72). This is consistent with our observation that in four of eight cases the latency of VPM cells increased slightly during cortical suppression (e.g., Fig. 6). A latency shift could occur if elimination of a facilitatory cortical influence allowed the VPM cell to become hyperpolarized by several millivolts.

The idea of a facilitatory descending influence on the ventral posterior nucleus (VP) was reached in two studies that used an experimental design similar to ours (Yuan et al., '85, '86). In the first study the authors examined the effect of cortical suppression with lidocaine on the discharge of VP single units in rats anesthetized with chloral hydrate. Their method was to present an electrocutaneous stimulus at frequencies ranging from 1 to 50 Hz 30 minutes after application of lidocaine. When the stimulus frequency was 20 Hz, cortical suppression led to a 50% reduction in VP response. Cortical suppression had a significant effect when the stimulus frequency was as low as 5 Hz. However, when the stimulus frequency was 1 Hz, cortical suppression led to only about a 10% decrease in VP response, which was not statistically significant. In a study on restrained unanesthetized rats, Yuan et al. ('86) used 4% magnesium sulfate to suppress the barrel cortex. The authors again found that cortical suppression significantly reduced responsiveness to 20 Hz electrocutaneous stimulation. When the stimulus frequency was 1 Hz, cortical suppression led to a reduction of approximately 20% in the VP cells' response, but this decrease was not statistically significant.

The present results are consistent with those outlined above. With a 1 Hz natural stimulus (whisker displacement), we found that 30 minutes after the start of cortical suppression, the response magnitude of VPM cells had decreased 18% on average compared to the presuppression values (see Fig. 8A), but the reduction was not statistically significant ($P < 0.05$).

We used a low-frequency stimulus in order to avoid the complications of interpretation arising from high-frequency repetitive stimulation. At electrocutaneous stimulation rates of 20 Hz, VPM cells can recruit discharges of cells in the thalamic reticular nucleus (Andersen et al., '64), producing sustained inhibition of VPM (Shosaku, '86). Any comparison of the influence of the barrel cortex on POm and VPM would be further complicated by the fact that POm cells are not able to follow repetitive stimuli presented at more than 1 Hz (Diamond et al., '92).

One report described increased sensory responses in VP after S-I extirpation, but this was based only on activity occurring 80–270 ms after the cutaneous stimulus (Angel and Clarke, '75).

Two routes from barrel cortex to VPM

The barrel cortex could facilitate transmission through VPM in two ways, the first being through direct synaptic contact on the dendrites of VPM cells. Most corticothalamic axons in VPM terminate as small boutons (Hoogland et al., '87, '88; Welker et al., '88). The source of this descending projection has been described as a mixture of layer V and VI cells (Wise and Jones, '77; Chmielowska et al., '89), however, with retrograde tracer injections carefully restricted to VPM it has recently been shown that cells in upper layer VI are the main if not exclusive source (Good and Killackey, '91; our own unpublished observations). We can therefore gain some insight into the direct cortical influence on sensory transmission through VPM by considering the information conveyed to VPM by layer VI cells. Cells in layer VI of the barrel field exhibit a low response magnitude to whisker deflection in comparison to cells in other layers (Armstrong-James and Fox, '90). Layer VI cells begin to fire at latencies of 15 ms or more, and thus are among the last cells activated in a cortical column. VPM cells fire at latencies of about 6 ms and the bulk of the response is complete before layer VI cells even begin to discharge (e.g., Figs. 6–8; also see Armstrong-James and Callahan, '91; Friedberg et al., '91; Diamond et al., '92). The relative timing indicates that cortical layer VI cells could hardly influence the VPM volley evoked by the most recent stimulus.

The second way in which the cortex can influence sensory transmission through VPM is through the reticular nucleus. The functional significance of the cortical projection to the reticular nucleus is complicated by the different cell types in the reticular nucleus: one type is excited by cortical activity and the other type is inhibited (Angel, '83). Therefore one cannot be certain whether 1) cortical activity excites the reticular nucleus, causing it to inhibit VPM, or 2) cortical activity inhibits the reticular nucleus, thereby releasing VPM. The net cortical effect on the reticular nucleus probably varies with behavioral state (Angel, '83). In the present discussion, perhaps the most important consideration is that the cortical projection to the reticular nucleus originates in layer VI. Due to the relative timing of evoked activity in VPM and layer VI of cortex, the sensory signal associated with a single stimulus would be transmitted through VPM before the reticular nucleus could be engaged by the cortex.

In summary, S-I cortex may facilitate transmission through VPM (directly or through the reticular nucleus) but the nature of the facilitation needs to be carefully defined: the corticofugal volley evoked by a brief stimulus may condition the response of VPM cells to the subsequent stimulus, but the timing of the descending volley precludes it affecting transmission of information through VPM related to the most recent stimulus. This mode of cortical influence departs sharply from that seen in POm.

Dependence of POm on barrel cortex

Through what mechanism did cortical inactivation disable the flow of sensory information through POm? One possibility is that suppression interrupted the ascending flow of information through the trigeminal complex. Although this cannot be ruled out, there are several lines of evidence against it. First, the sparseness of the trigeminal projection to POm makes it seem unlikely that POm is strongly influenced by the ascending sensory pathway. Several investigators were unable to detect a projection from the trigeminal nuclei to POm (reviewed by Nothias et al., '88). Only recently has a weak projection been established: POm is the target of about 7% of the cells in principal trigeminal nucleus and 17% of cells in spinal trigeminal nucleus (Chiaia et al., '92). Second, although the

cortex has been shown to have mixed facilitatory and inhibitory effects on the trigeminal nuclei (Woolston et al., '83), elimination of the descending cortical influence does not prevent sensory transmission through the trigeminal nuclei (review by Dubner et al., '78). Finally, if sensory transmission through the trigeminal nuclei were seriously compromised by cortical suppression, one would expect to have seen a more profound loss of activity among VPM cells.

The remaining possibility is that, to produce a sensory response, POm cells require direct excitation from the cortex. The density of the projection from S-I cortex to POm (Hoogland et al., '87, '88; Nothias et al., '88; Welker et al., '88; Fabri and Burton, '91) is consistent with a strong cortical influence. Also consistent is a series of studies that revealed the characteristics of cortical terminals in POm (Hoogland et al., '87, '88; Welker et al., '88). Corticothalamic axons in the mouse were filled by Phaseous vulgaris-leucoagglutinin (PHA-L) (we assume that the same results would be obtained in other rodents). By performing electron microscopy on serial sections through synapses, it was shown that axon terminals in POm—but not in VPM—were large glomerular endings, closely resembling the glomerular terminals in VPM arising from the principal trigeminal nucleus. Some terminals in POm reached 10 μm in diameter, enveloping the dendritic membrane and making repeated contacts throughout their appositions. The authors concluded that the arrangement of these "giant" corticothalamic terminals "seems to allow the cortex to hold a powerful synaptic grip over... PO neurons" (Hoogland et al., '88, p. 160).

This synaptic grip may permit the cortex to convey sensory activity directly to POm. Due to a monosynaptic input from VPM (White,'79; Frost and Caviness, '80; White and Hersch, '82; Chmielowska et al., '89), the layer Vb cells that project to POm (Hoogland et al., '87; Good and Killackey, '91) have a brisk response to whisker movement at a latency preceding that of POm cells (Armstrong-James et al., 1987; Armstrong-James and Fox, '90). Each sensory response in POm could derive from a volley in the corticofugal fibers. Alternatively, the cortex could merely exert a strong facilitatory effect, allowing POm cells to be activated by ascending inputs from the trigeminal complex. The present results do not rule out the "sensory drive" hypothesis or the "facilitation" hypothesis (or a combination). In either case, the sensory activity of POm cells depends on the activity of the barrel cortex.

Functional significance of the cortico-thalamo-cortical loop

One clue to the possible function of POm comes from the pattern of thalamocortical projections. Axons from VPM terminate in cortical barrels whereas axons from POm terminate in a "complementary" pattern between, above, and below the layer IV barrels (Koralek et al., '88). Although it is known that the surround receptive field of a barrel neuron is generated in large part by intracortical relays arising from neighboring barrels (Armstrong-James et al., '91), the circuit through which neighboring barrels communicate is unclear. However, if the targets of POm—the septal cells—are elements in this circuit, then POm is well positioned to influence the communication between columns. To illustrate our interpretation, Figure 9 indicates the pattern of thalamocortical projections and the timing of sensory activity. After whisker D1 is displaced (0

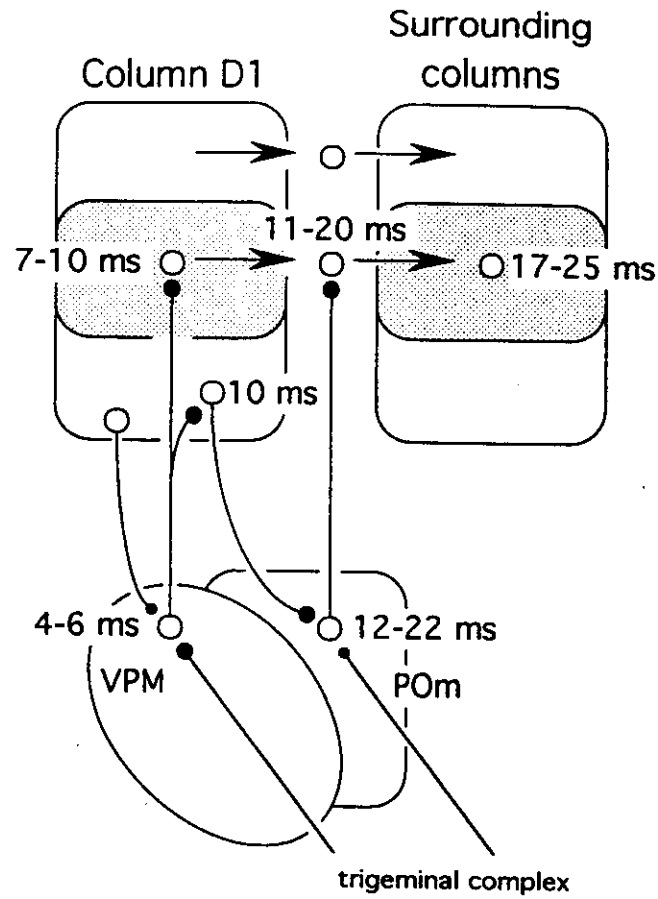

Fig. 9. Schema to show the timing of activity in selected circuits of the somatic sensory system. Cell bodies are unfilled circles. Dense projections are indicated by large filled circles, less dense projections by smaller filled circles. The horizontal spread of activity across the cortex is indicated by arrows, but the anatomical pathway is not known. POm (rostral subdivision of the posterior group) may contribute to the excitation of cells in the septum around cortical column D1, thereby regulating the spread of activity to neighboring columns. Latency data are from Armstrong-James and Callahan ('91), Armstrong-James and Fox ('90), Armstrong-James et al. ('91), and Diamond et al. ('92). See text for description. VPM, ventral posterior medial nucleus.

ms), the trigeminal complex activates cells in the D1 barreloid of VPM (4–6 ms). VPM activates cells in layer IV (7–10 ms) and layer Vb (10 ms) of cortical column D1. Cells in POm respond about 12–22 ms after the whisker movement—at this time cells in the septum surrounding cortical column D1 also are active (11–20 ms).

A layer Vb pyramidal cell could receive input on its dendrites from numerous sources (in addition to VPM) including: local and distant ipsilateral cortical regions, the contralateral cortex, midline thalamic nuclei, brain-stem noradrenergic nuclei, and forebrain cholinergic nuclei. All these influences are integrated and "fed back" to POm, which in turn projects between cortical columns. It seems unlikely that POm inhibits the cortex, since POm contains few if any GABAergic cells, and since few of the cortical cells receiving POm input are GABAergic (Lin et al., '85). Rather, when POm cells are active they may "prime" the cells intercalated between cortical columns, in this way enhancing the spread of activity betweeen columns. On the

other hand, under experimental or behavioral conditions when POm cells are suppressed, the communication between cortical columns may in turn be suppressed. Thus, we favor the idea that the descending control over POm permits the barrel cortex itself to control the spread of activity between columns.

Significance of lemniscal and paralemniscal pathways

The present results would be more general if there were "lemniscal" and "paralemniscal" pathways in the somatosensory system of other species, and in other sensory modalities. The problem of course is to identify thalamic nuclei that are analogous to VPM and POm of the rat. In species other than rodents, "rods" of large VPM cells project to layer IV of S-I; a matrix of smaller VPM cells also projects to S-I, but avoids layer IV (Penny et al., '82; Rausell and Jones, '91a,b). These rods may be analagous to VPM barreloids in the rat—the lemniscal pathway—while the matrix may be analogous to POm in the rat—the paralemniscal pathway (see Discussion in Diamond et al., '92).

In the visual system one might identify the lateral geniculate as a "lemniscal pathway." Cells in the lateral geniculate are modulated by corticofugal inputs, but are not dependent on the striate cortex for their sensory response (Koch, '87; Sillito and Murphy, '88). In monkeys the visual response of cells in the pulvinar is eliminated by lesion of the striate cortex but not by lesions of the superior colliculus (Bender, '83). The pulvinar projects to the visual cortex but avoids layer IV, the target of the lateral geniculate; the pulvinar receives input from layer V of the cortex whereas the lateral geniculate receives input from layer VI (Diamond et al., '91). These distinctions between the lateral geniculate and the pulvinar are reminiscent of the distinctions between VPM and POm. This suggests that the pulvinar nucleus may serve a "paralemniscal" function in the visual pathway, and that certain principles may govern the cortical integration of parallel sensory pathways regardless of the sensory modality.

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