17

Discriminative Avoidance Learning: A Model System

MICHAEL GABRIEL

Discriminative learning occurs when particular stimuli predict outcomes important to the learner. Thus, for example, animals readily learn to obtain reward or to avoid pain in the presence of stimuli that predict the efficacy of responding, and they learn to remain inert in the presence of nonpredictive stimuli.

This important form of learning is not only profoundly useful to the learner, it also affords a valuable scientific tool for analyses of the neural bases of learning processes. Discriminative training procedures bring about the acquisition of discriminative brain activity, i.e., different patterns of neuronal activity in response to the differentially predictive stimuli. Electrophysiological mapping can be used to identify the neurons and circuits that exhibit discrimination between these categories of stimuli. Documentation of the acquisition rates and latencies of discriminative neuronal activity and the effects of brain lesions can yield an analysis of the brain substrates of discrimination learning.

In this chapter, an application of this strategy to the analysis of discriminative active avoidance learning in rabbits is described. The results indicate a critical involvement of cingulate cortex and limbic thalamus in this learning, and they document the learning-relevant neural circuit activity and information flow.

Cingulate Cortical and Limbic Thalamic Involvement in Learning and Memory

The limbic thalamus is defined as the anterior, medial dorsal, and other thalamic nuclei that contain neurons that project to cingulate cortex. The involvement of this thalamocortical system in learning and memory processes is supported by numerous studies over the past four decades. Cingulate cortical, limbic thalamic, and related diencephalic ablations in a variety of species impair the acquisition of active avoidance behavior (Pribram and Fulton, 1954; Peretz, 1960; McClearly, 1961; Moore, 1964; Gabriel et al., 1989, 1991a; Lubar, 1964; Lubar and Perachio, 1965; Eckersdorf, 1974), aversive Pavlovian conditioning of autonomic responses (Chapter 13 of this volume), and reward-based instrumental learning (Markowitsch, 1982; Kessler et al., 1982; Aggleton and Mishkin, 1983; Pribram et al., 1962; Isserhof et al., 1982; Irle and Markowitsch, 1982; Zola-Morgan and Squire, 1985; Staubli et al., 1987), including many tasks that require spatial encoding for their solution (Meunier et al., 1991; Aggleton and Mishkin, 1985; Greene and Naranjo, 1986; Holmes et al., 1983; Meunier et al., 1991; Markowska et al., 1989; Murray et al., 1989; Stokes and Best, 1988; Chapter 16 of this volume).

Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook
Brent A. Vogt and Michael Gabriel, Editors

In addition, studies of memory performance in patients with damaged cingulate cortices have implicated the retrosplenial region of posterior cingulate cortex and limbic thalamus in the mediation of human memory processes (Victor et al., 1971; Squire, 1987; Chapter 18 of this volume), and studies of metabolic activity during cognitive performance have demonstrated an active involvement of anterior cingulate cortex in a variety of memory-related task performances by humans (e.g., Pardo et al., 1990).

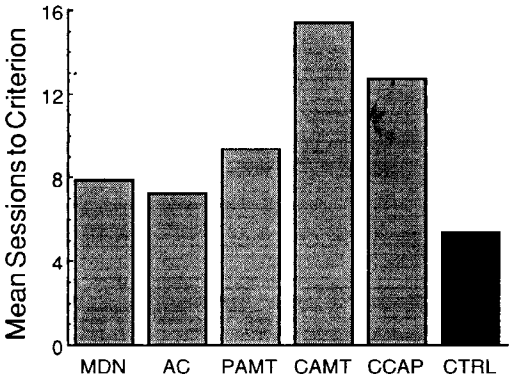


FIGURE 17.1. Mean number of training sessions required for completion of the avoidance learning criterion in controls (CTRL), rabbits with bilateral thermocoagulation lesions in medial dorsal nucleus (MDN), fiber-sparing ibotenic acid lesions in anterior cingulate cortex (AC), partial bilateral electrolytic lesions in MD and anterior thalamic nuclei (PAMT), complete bilateral electrolytic lesions of MD and anterior thalamic nuclei (CAMT), and bilateral lesions in the anterior and posterior cingulate cortex (CCAP). The means in all lesion groups excepting group AC were significantly greater than the control mean ($p < .05$), and the difference between the AC and CTRL means approached significance ($p = .086$).

Lesions and Discriminative Avoidance Learning in Rabbits

Discriminative avoidance training was administered as the rabbits occupied a large activity wheel designed for aversive conditioning of small animals (Brogden and Culler, 1936). The rabbits learned to step in response to a 0.5 sec tone—a positive conditioned stimulus (CS) or CS+—in order to avoid a brief shock to the footpads, delivered via the grid floor of the apparatus 5 sec after tone onset if no response was made. They also learned to ignore a different tone, a negative conditioned stimulus or CS−, which did not predict shock.

For convenience, the thalamocortical system of reciprocally interconnected anterior cingulate cortical and medial dorsal (MD) thalamic neurons is referred to here as the *anterior circuit,* and the system formed by neurons of posterior cingulate cortex and anterior group of thalamic nuclei is referred to as the *posterior circuit.* Bilateral electrolytic and aspirative lesions, which damaged both the anterior and posterior circuits (at either the cortical or thalamic levels), were severely detrimental to acquisition of avoidance responses, as shown in Figure 17.1 (Gabriel et al., 1983, 1989, 1991a). All but 3 of the 14 rabbits in two experiments with lesions in both circuits failed to reach the acquisition criterion of two consecutive days in which the percentage of avoidance responses exceeded the percentage of responses to the CS− by at least 60. In both studies the average frequency of avoidance responses (responses during the 5 sec CS+ and shock interval) reached approximately 30%, as compared with 85% in controls. No abnormalities of mobility in the testing apparatus were seen in these rabbits, indicating that the learning deficit was not secondary to a motoric disturbance. The average latencies and durations of the unconditioned response (UR) to the shock in rabbits with lesions did not differ significantly from the averages in controls, thus providing evidence that reduced sensitivity to the shock did not engender the learning deficits.

In other studies, decelerative cardiac rate orienting responses to novel auditory stimuli occurred at normal or enhanced magnitudes in rabbits with cingulate cortical and limbic thalamic lesions (Buchanan, 1988; Buchanan and Powell, 1982; Chapter 13 of this vol-

ume), indicating that these lesions did not interfere with sensory reception of the CS. The totality of these observations is consistent with the hypothesis that the impairments of discriminative avoidance learning in the rabbits with lesions were due to a disruption of associative processes rather than to a sensory, motor, or motivational deficit.

Acquisition and performance of the avoidance response were not impaired by bilateral electrolytic lesions of the dorsal and posterior subicular complex (Gabriel et al., 1987) or the dorsal and posterior hippocampus (Kang et al., 1990). Moreover, acquisition and performance were unaffected by bilateral lesions of the deep cerebellar nuclei in rabbits that were incapable of acquiring Pavlovian eyeblink and nictitating membrane conditioned responses (CRs; Steinmetz et al., 1991). These results indicate that the acquisition of discriminative avoidance behavior is governed by a circumscribed neural circuitry that is distinct from circuitries involved in mediating oculomotor CRs.

Unit Recording Studies: A General Overview

Methodology

Limbic thalamic and cingulate cortical involvement in the mediation of discriminative avoidance learning indicated by the foregoing effects of lesions is corroborated by extensive studies of the multi- and single-unit correlates of acquisition and performance. Each rabbit in these studies underwent aseptic surgical implantation of four to six fixed-position electrodes for the recording of unit activity and an intracerebral electroencephalogram (EEG). The electrodes were made from insulated stainless-steel-pin electrodes. The recording surfaces were formed by removing insulation from the tips, which ranged from 10 to 50 μm and had electrical impedances of 500 kΩ to 2 MΩ. Leads soldered to each electrode were soldered to the contacts of a miniature connector attached to the skull with dental acrylic. The neuronal records from each electrode were fed into a field-effect transistor, which served as a high impedance source-follower located a short distance (about 2.5 cm) from the brain recording sites. The transistor outputs fed via shielded cable were split, one limb entering preamplifiers with band-width appropriate for unit recording (gain = 100,000, ½ amplitude cutoffs as 500 and 8000 Hz) and the other limb entering preamplifiers for EEG recording (gain = 8000, ½ amplitude cutoffs at 0.2 and 60 Hz). The unit activity records were subjected to a second stage of active band-pass filtering (½ amplitude cutoffs at 600 and 8000 Hz, roll-off = 18 dB per octave) to remove residual EEG frequencies. The records were then fed into Schmitt triggers, which were adjusted by computer to yield a mean rate of output pulses within limits of 95 to 165 pulses per second. With this criterion, typically, the largest spikes present in each record were sampled. In addition, the integral of the unit records was recorded, following procedures described by Buchwald et al. (1973). The band-pass filter outputs were half-wave rectified and integrated with time constants for the rise and fall of the integrators of 15 and 75 msec, respectively. The Schmitt trigger data provided an index of the discharge frequency of the largest spikes on each record, whereas the integrated unit activity measured the energy fluctuations of the entire record, including activity below the triggering thresholds. The Schmitt trigger pulses were counted and the integrator and field-potential signals digitized on each trial (CS presentation) for 1.0 sec, 0.3 sec before CS onset, and 0.7 sec after CS onset. A digital value was stored for each measure and electrode every 10 msec during the sampling interval. These data were written to magnetic tape after each trial. In addition, averages of the behavioral data, unit histograms, integrated activity, and field potentials were stored on disk and continuously displayed on a VT100 graphics terminal as they were

formed during the training sessions. The stored averages were subsequently submitted to analysis of variance.

Large amplitude, discrete single-unit spikes, which could be electronically isolated during both locomotion and immobility, were sampled separately throughout all training trials and during the post-trial period, to obtain information on single-unit correlates of acquisition and performance. In some studies, multiunit records containing large amplitude spikes were fed from as many as four channels into the Brain-Wave Systems, Inc., Workstation, allowing the extraction and analysis of single-spike waveforms from the multiunit records (Fig. 17.2).

Premotor Single-Unit Activity

Observations made to date indicate that substantial proportions of the single units recorded in the anterior and posterior circuits in trained rabbits, at both cortical and thalamic levels, exhibit premotor firing patterns. About 50% of the thalamic cells and 30% of the cortical cells show firing frequency increases that begin after the onset of the CS+ and reach a maximum in anticipation of CR performance (Fig. 17.2*H, I, J, M*-cluster 1).

An exceptional pattern has been found consistently in the MD thalamic nucleus, wherein many cells decrease their firing rate in anticipation of response output (Fig. 17.2*J;* 2*M*-cluster 2). Also, some instances of inverted discharge patterns have been found in anterior cingulate cortex.

Of considerable interest is the question of whether the premotor neuronal discharges in cingulate cortex and limbic thalamus occur in untrained rabbits or whether they are a product of neuronal plasticity induced by the conditioning procedure. Many more premotor cells were found during the session in which the learned response was first performed at asymptotic levels, compared to the number of such cells found during the first conditioning session or during the session in which significant behavioral discrimination between CS+ and CS− was first performed. These results are consistent with the idea that the premotor discharges are context-dependent products of learning rather than hard-wired patterns invariably associated with locomotion.

Response-predictive firing patterns of single neurons in primate cingulate cortex that are remarkably similar to the patterns seen in rabbit cingulate cortex have been reported to occur during performance in a cued reaction-time task (Shima et al., 1991). Other results providing elaboration of the premotor functions of cingulate cortical cells are reviewed in Chapters 12 to 14 of this volume.

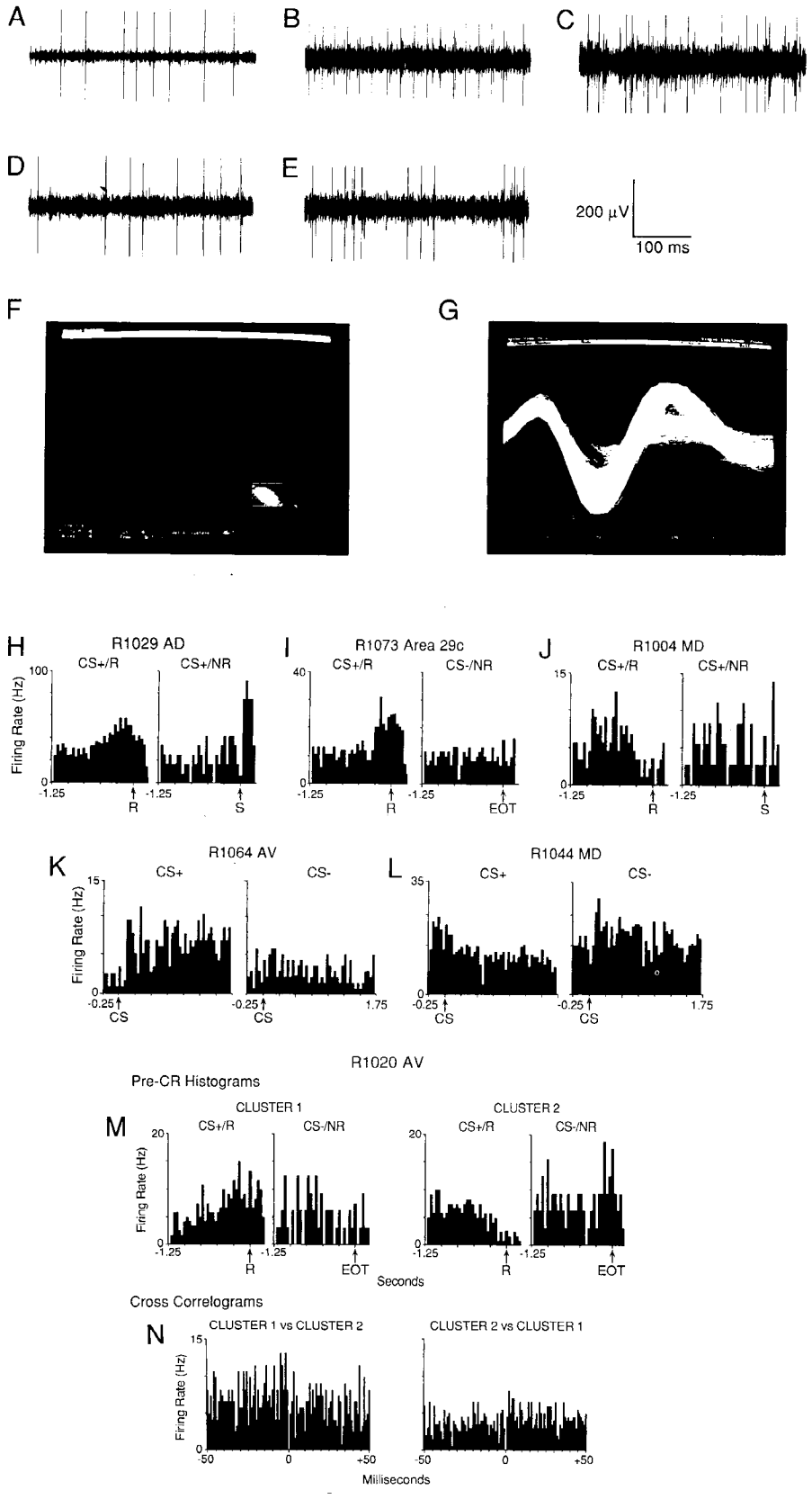
Activity Evoked by Conditioned Stimuli

General Properties of the Tone-Evoked Neuronal Activity

Before and after conditioning, the CSs elicit in posterior circuit structures a triphasic multiunit discharge pattern consisting of a brief latency discharge increment from 15 to 20 msec after CS onset, an inhibitory firing pause from 40 to 70 msec, and an second firing increment from 80 msec until 300 to 500 msec after the CS. Anterior circuit areas exhibit a similar triphasic profile, although the inhibitory pause is greatly attenuated in these areas and in some posterior circuit areas, such as the anterior dorsal (AD) thalamic nucleus. The inhibitory pause could be related to the presence of small and presumably inhibitory interneurons. For example, the effect is robust in the anterior ventral (AV) nucleus, which exhibits more interneurons than the AD nucleus (Vogt, 1985).

Training-Induced Changes of Tone-Elicited Discharges

An involvement of the anterior and posterior circuits in learning and memory is indicated by the occurrence of changes in the tone-


A
B
C
D
E
200 μV
100 ms
F
G
H
R1029 AD
CS+/R
CS+/NR
Firing Rate (Hz)
100
0
-1.25
R
S
I
R1073 Area 29c
CS+/R
CS-/NR
40
EOT
J
R1004 MD
15
K
R1064 AV
CS+
CS-
-0.25
CS
1.75
L
R1044 MD
35
R1020 AV
Pre-CR Histograms
CLUSTER 1
CLUSTER 2
M
20
Seconds
Cross Correlograms
N
CLUSTER 1 vs CLUSTER 2
CLUSTER 2 vs CLUSTER 1
-50
0
+50
Milliseconds

elicited discharges or training-induced neuronal activity (TIA), which develops during discriminative avoidance learning. There are two kinds of TIA, excitatory and discriminative:

1. *Excitatory* TIA is defined as increased multiunit firing elicited by the CSs during conditioning, relative to activity elicited during a pretraining session in which the CSs and the shock unconditioned stimulus (US) are presented in an unpaired manner.
2. *Discriminative* TIA is defined as greater firing frequencies in response to CS+ than in response to the CS−.

The two forms of TIA, illustrated in Figure 17.3, represent *associative* neuronal plasticity because they depend on the pairing or association of the CSs and the US. However, the two forms of TIA are independent and dissociable, as indicated later. The ability to document TIA makes feasible the goal of brain-mapping in order to discover the dynamic neuronal antecedents of the learned behavior.

Both forms of TIA occur in all cingulate cortical and limbic thalamic areas in the third excitatory phase of the triphasic discharge profiles beginning 80 to 100 msec after the onsets of the CSs. In addition, both forms of TIA occur, in certain areas, in the excitatory initial component of the triphasic discharge, 10 to 25 msec after CS onset. For example, discriminative TIA was found in the brief latency component of anterior cingulate area 24 multiunit discharges throughout training (Gabriel and Orona, 1982), and brief latency discriminative TIA has been documented in the AV thalamic nucleus in asymptotically trained rabbits (Foster et al., 1980).

Distinctive Functions of the Anterior and Posterior Circuits

Theoretical Orientation

Comparisons of TIA and effects of lesions of the anterior and posterior circuit struc-

FIGURE 17.2. Representative multiunit records *(A–E)* sampled at high rates. The four-dot clusters enclosed in rectangles in *F* indicate sets of sampled spikes having similar waveshapes. The clusters were obtained by displaying the dots for the peak height (plotted on the vertical axis) and valley depth (plotted on the horizontal axis) measures for record *C* in anterior cingulate cortex. The superimposed waveforms associated with each cluster *(G)* are shown.

Histograms indicating cingulate cortical and limbic thalamic single-unit activity related to the onset of the CS+ and CS− and to the avoidance responses (R) are shown in *H–M*. Each bar of the histograms indicates the average firing rate (in hertz) for the cell during a 40 msec interval, and the labels (e.g., R1029) indicate the subject code number. Illustrated, respectively, are premotor discharges of AD thalamic *(H)* and area 29c cells *(I)*, a cell exhibiting a decrease in firing frequency in anticipation of the avoidance response *(J)*, a common finding in the MD thalamic nucleus. The right-hand histograms in *H–J* represent the cell's firing on trials in which no response occurred and thus a shock (S) was delivered, or on CS− trials the trial terminated uneventfully (EOT) 5 sec after CS onset. In *K* and *L* are shown, respectively, a cell exhibiting discriminative TIA in the AV thalamic nucleus and a cell showing inverse discrimination with a greater firing rate to the CS− than to the CS+, common in the MD nucleus. The letter *M* illustrates two AV units from the same electrode exhibiting, respectively, increased and decreased firing in anticipation of R.

The cross-correlograms of these two units are shown in *N*. For each correlogram the first member of the pair (cluster 1 vs cluster 2) is the plotted spike, and the second member is the reference spike. For each firing of the reference spike (represented implicitly at the 0 time reference at the center of the plot), plotted spike firings are tallied in preceding and following 40 msec bins. The left-hand correlogram indicates that firings of the spike exhibiting premotor excitation (cluster 1) tend to precede firings of the spike exhibiting reduced premotor firing (cluster 2), whereas the opposite relationship is indicated by the right-hand correlogram.

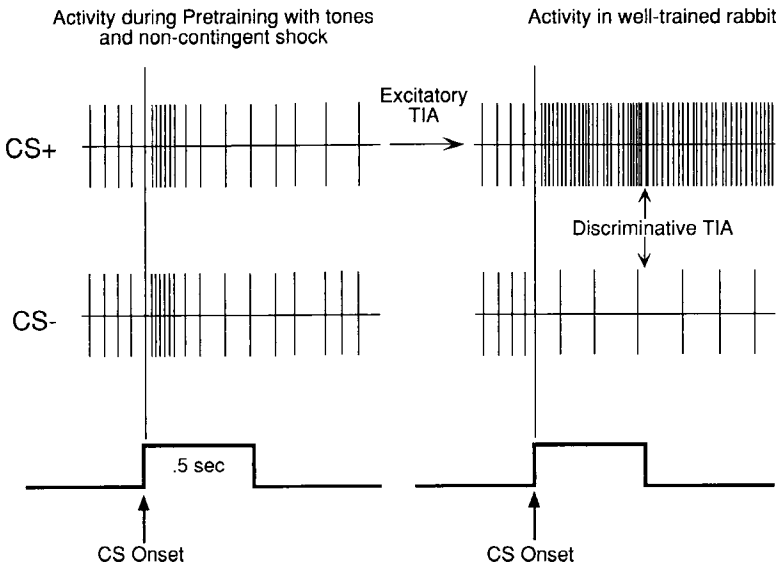


FIGURE 17.3. Two forms of training-induced neuronal activity (TIA). Excitatory TIA, illustrated by the comparison of the left-hand and right-hand traces, refers to an increment of CS-elicited neuronal excitation during training relative to the excitation that occurs during pretraining with tones and unpaired US presentations. Discriminative TIA, illustrated by the comparison of the upper and lower right-hand traces, refers to the development during training of significantly different neuronal firing profiles in response to the CS+ and CS−, respectively.

tures have begun to yield a characterization of the distinct functions of these two circuits. A theoretical schema is described here to provide a framework for considering these results.

As will be shown, the excitatory and discriminative TIA that develops in anterior circuit structures is rapidly acquired and quite flexible. Rapid acquisition characterized activity in both the anterior cingulate and MD thalamic nuclei, relative to their cortical and thalamic counterparts in the posterior circuit. The property of flexibility is based on the observation that TIA in anterior cingulate cortex is more readily modified in response to new CS and US relationships than TIA in posterior cingulate cortex. These characteristics foster the hypothesis that anterior circuit activity reflects the operation of a mnemonic *recency* system, a conception that is similar to the concept of a working memory system, applied by others to the functioning of anterior circuit structures (e.g., Goldman-Rakic, 1990).

In contrast, the TIA in the posterior circuit develops more gradually than in the anterior circuit, and it is not readily altered, once acquired. Instead, this circuit is specialized for the maintenance and retention of TIA. The TIA exhibited by neurons of posterior cingulate cortex is retained even after TIA in the anterior circuit is altered and as new behavior emerges following reversal of the CS and US relationships. On the basis of these properties, the posterior circuit is hypothesized to constitute a mnemonic *primacy* system. The term *primacy* denotes that primary or original encodings are retained in this system even after more recent information is encoded by the recency system. The empirical results that provide the bases for the distinction between neural mnemonic recency and primacy systems are reviewed in next section.

Rates of Development and Decline of Training-Induced Neuronal Activity

The combined neuronal activity recorded in layers 5 and 6 of posterior cingulate cortical

areas 29b,c (Fig. 17.4, row 1) developed discriminative TIA in an early stage of learning (i.e., during the first session of conditioning) when the CS+ first predicted the occurrence of the shock. In contrast, discriminative TIA in the upper layers (1 to 4) of area 29b,c developed late in training during the session in which the learning criterion was met. When the neuronal records of the superficial and deep layers were pooled, the early-forming discriminative TIA present in the deep layers was obscured by the upper layer records, which did not exhibit discriminative TIA in the first training session. Therefore, by virtue of the pooling of the data, the overall average discharges of area 29 neurons exhibited a somewhat retarded development of discriminative TIA: The TIA first became significant in the session in which behavioral discrimination first occurred (Fig. 17.4, row 3). In contrast, discriminative TIA in all layers of anterior cingulate cortical area 24 developed rapidly (in the first conditioning session; Fig. 17.4, fourth row; Gabriel and Orona, 1982). As in area 29, some of the neuronal records of area 24 also exhibited late-developing discriminative TIA (Orona and Gabriel, 1983), but the early- and late-developing discriminations in area 24 were not clearly segregated in the cortical layers.

One study provided evidence that the early-developing discriminative TIA in the deep layers of area 29 may be relayed from anterior circuit neurons of area 24. Rabbits with fiber-sparing ibotenic acid lesions in area 24 exhibited only the late variety of discrimination in area 29 (Gabriel et al., 1991a, Fig. 17.5). Thus, early and late development of discriminative TIA may be intrinsic to the anterior and posterior circuits, respectively. This hypothesis raises the further possibility, for which no data currently exist, that the late-developing discriminative TIA exhibited by some area 24 neuronal records is relayed to area 24 from area 29.

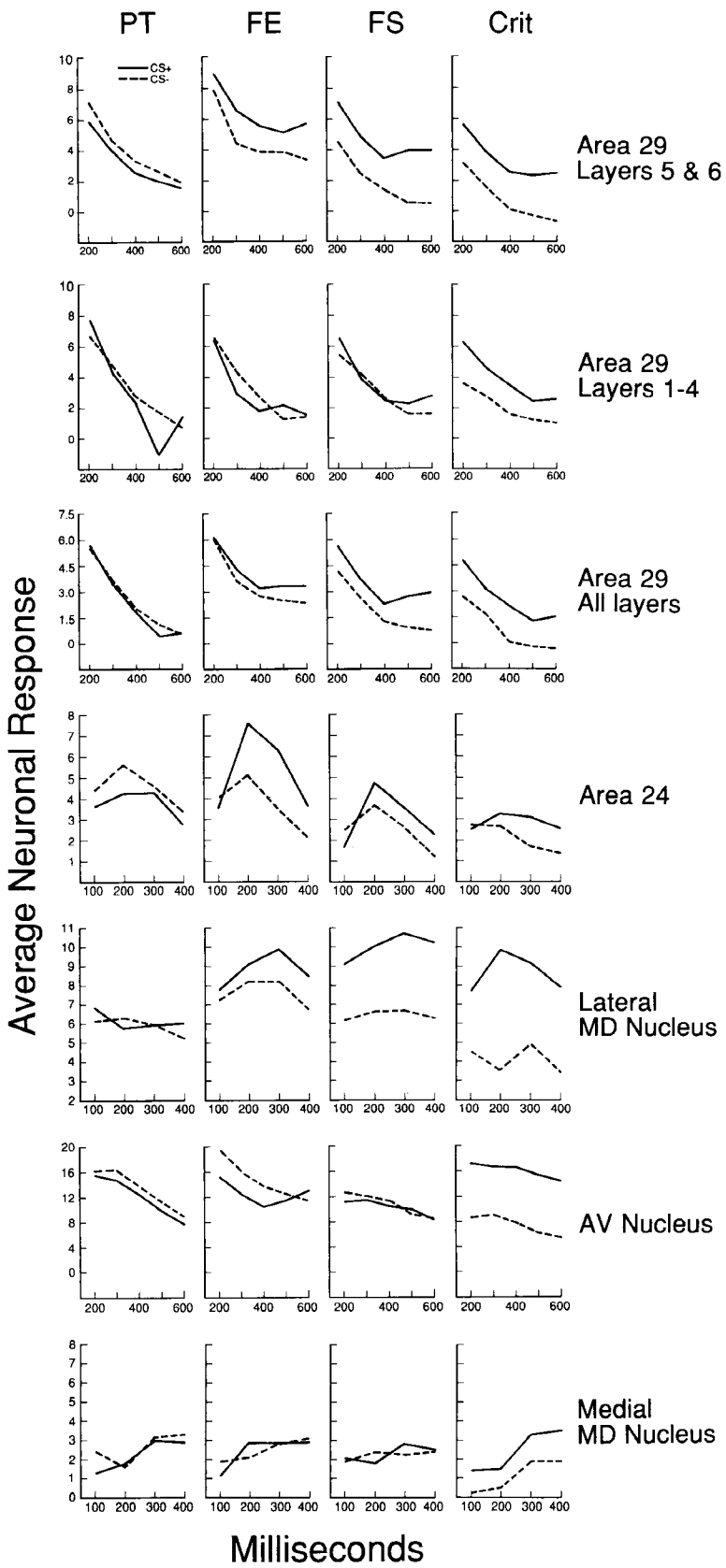
Massive discriminative TIA predominantly in the lateral division of the MD nucleus (Groenewegen, 1988) developed in the session of the first significant behavioral discrimination (Fig. 17.4, row 5), whereas AV thalamic neurons did not discriminate until the session in which the criterion of behavioral discrimination was met, well after the development of significant behavioral discrimination (Fig. 17.4, row 6). Neither significant discriminative nor excitatory TIA was found in the medial division of the MD nucleus (Fig. 17.4, row 7). These findings at both cortical and thalamic levels provided the first indication that anterior circuit neurons develop discriminative TIA faster than posterior circuit neurons.

In addition to differences in the onset of discrimination during training, excitatory TIA in anterior cingulate cortex declined rapidly after reaching a maximum early in training (Fig. 17.4, row 4). Also, a dramatic loss of discharge magnitude occurred in the MD nucleus during overtraining sessions that followed the attainment of criterion (Orona and Gabriel, 1983). A gradual reduction of the average discharge magnitude in later training stages also occurred in cortical and thalamic neuronal records of the posterior circuit, but this reduction was much less pronounced than the reduction seen in the anterior circuit structures.

In summary, the first occurrence of discriminative TIA and the decline of excitatory TIA in anterior circuit structures precede these changes in posterior circuit structures during the course of behavioral acquisition: The changes in anterior cingulate cortex occur in earlier stages of behavioral acquisition than they do in posterior cingulate cortex. Similarly, the changes occur first in the MD nucleus and later in the AV nucleus.

Effects of Restricted Lesions

Findings indicating a more rapid development and decline of TIA in anterior rather than in posterior circuit structures during the course of behavioral acquisition suggest that the principal contribution of anterior circuit neurons to the learned discrimination occurs at an earlier stage of training than does the


PT
FE
FS
Crit
CS+
CS-
Area 29
Layers 5 & 6
Area 29
Layers 1-4
Area 29
All layers
Area 24
Lateral
MD Nucleus
AV Nucleus
Medial
MD Nucleus
Average Neuronal Response
Milliseconds

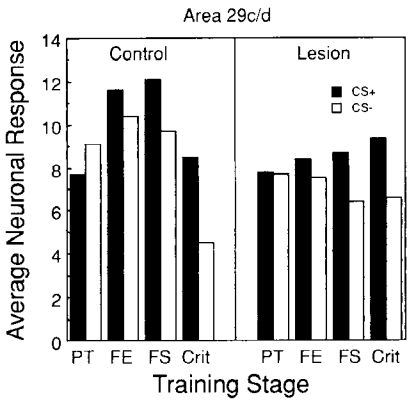


FIGURE 17.5. Average integrated unit discharge magnitudes in the first 400 msec after CS+ and CS− onset in area 29c,d in controls and in rabbits with ibotenic acid lesions of area 24. The values were normalized relative to the pre-CS baseline. Data are shown in four stages of behavioral acquisition (pretraining session, PT; first exposure session, FE; first significant behavioral discrimination, FS; and criterial behavioral discrimination learning, Crit). These results show an absence of the early training-stage development of excitatory TIA in area 29c,d in rabbits with lesions in area 24b, a result suggesting that early discrimination in area 29c,d is relayed from area 24b.

contribution of neurons of the posterior circuit.

The lesion results described earlier demonstrate virtual abolition of acquisition after cingulate cortical or limbic thalamic lesions, which included components of both anterior and posterior thalamocortical circuits. Lesions confined to either the anterior or posterior circuit yielded moderate yet statistically reliable performance impairments, the nature of which depended on which circuit was disrupted. Lesions in anterior cingulate or MD nucleus moderately retarded acquisition (Gabriel et al., 1989, 1991a). Averages of six to eight daily training sessions were needed before rabbits with these lesions completed the criterial stage of training, rather than the three to four sessions taken by intact controls (Fig. 17.1). As in the case of the larger lesions, the retarded acquisition was due to a reduced frequency of avoidance responses, not an inability to withhold responding to the CS−. Performance levels attained by the rabbits with these lesions during and following the criterial sessions were equivalent to those of controls.

In contrast, rabbits with lesions of the cortical or thalamic component of the posterior circuit attained criterion at normal rates. Yet, performance worsened relative to that of the controls during training beyond criterion, and significant performance deficits were found during overtraining, first session of extinction training, and reacquisition training given after the completion of extinction (Gabriel et al., 1983, 1987; Fig. 17.6).

Consideration of the contrasting effects of lesions in the anterior and posterior circuits fosters the hypothesis that anterior circuit processes contribute principally to behavioral acquisition. The anterior circuit contribution declines as training continues after criterion is reached. The posterior circuit contribution develops gradually during training and reaches its maximum during and after criterion, as the anterior circuit contribution wanes. This hypothesis is illustrated graphically in Figure 17.7. Note however that this hypothesis requires qualification by virtue of the moderate impairments that followed the discrete, single-circuit lesions. The rather good residual performance

FIGURE 17.4. Average magnitude of multiunit discharges in response to the CS+ and CS−, respectively, during various stages of behavioral acquisition (pretraining session, PT; first exposure session, FE; first significant behavioral discrimination, FS; criterial behavioral discrimination learning, Crit). Each panel shows the multiunit firing frequency in consecutive intervals of 100 msec following onset of the CS+ and CS−, normalized relative to the pre-CS baseline. Different patterns of development of excitatory and discriminative TIA are shown. Row 1: area 29b,c,d layers 5 and 6; row 2: area 29b,c,d layers 1 to 4; row 3: all layers of area 29b,c,d; row 4: all layers, area 24b; row 5: lateral division of MD nucleus; row 6: the AV nucleus; row 7: the medial division of the MD nucleus.

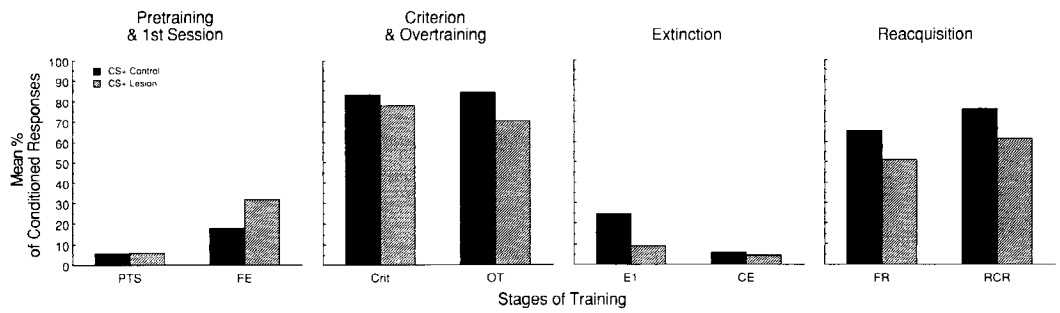


FIGURE 17.6. Average percentage of avoidance responses performed following CS+ during stages of behavioral acquisition and postcriterial performance by controls (dark bars) and by rabbits with lesions in the anterior thalamus or area 29c/d (light bars). These areas constitute the "posterior circuit." These data show the modest but statistically reliable attenuations of avoidance response frequency in rabbits with lesions during late stages of overtraining (OT), the first session of extinction training (E1), and during the first and criterial session of reacquisition (FR and RCR, respectively). No significant effects were found during the pretraining session (PT) or during criterial behavioral discrimination learning (Crit) and complete extinction (CE) sessions. Performance was significantly elevated in rabbits with lesions during the first exposure session (FE).

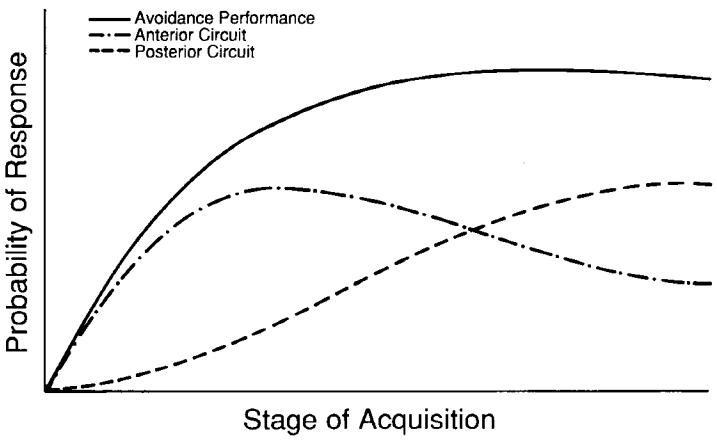


FIGURE 17.7. Theoretical illustration indicating the preferential involvement of anterior circuit processes in the early stages of behavioral acquisition and the preferential involvement of the posterior circuit processes in the later stages of acquisition. Avoidance response performance is proposed to be a product of the summation of coding processes in the anterior and posterior circuits.

capabilities exhibited by rabbits with these lesions suggest a degree of functional redundancy. The anterior circuit alone can support a reduced level of avoidance performance in well-trained rabbits, and the posterior circuit alone can support acquisition, albeit a moderately retarded acquisition.

Reversibility of Discriminative Training-Induced Neuronal Activity

TIA During Standard Reversal Learning

Several previous reports concerned the neuronal correlates of reversal learning, wherein the rabbits acquired the discriminative avoidance response to asymptotic levels and then received reversal training with the CS+ and CS− interchanged. The tonal frequency of the CS+ during original learning was used as the CS− for reversal training, and the frequency of the original CS− was used as the CS+ (Gabriel et al., 1977, 1980a; Orona et al., 1982).

During reversal training the rabbits learned to perform avoidance responses to the former CS− and to suppress responding to the former CS+. The fundamental question raised by these studies was if *neuronal reversal* learning would occur with behav-

ioral reversal learning. That is, would neurons of the anterior and posterior circuits exhibit discriminative TIA appropriate to the reversal problem—greater neuronal discharges to the former CS− than to the former CS+—during the course of reversal learning.

The results showed that the neuronal records in various anterior and posterior circuit areas varied:

1. In relation to the occurrence of an "old habit" effect at the outset of reversal training (i.e., an enhanced expression during the first session of reversal training of the discriminative TIA that had developed during original learning)
2. In relation to the occurrence of reversal of discriminative TIA during behavioral reversal learning

Figure 17.8 shows average neuronal records exhibiting old habit effects at the outset of reversal learning. These included layers 5 and 6 of posterior cingulate cortical area 29b/c (Fig. 17.8*A*), AV nucleus (Fig. 17.8*B*), lateral division of the MD nucleus (Fig. 17.8*C*), and combined records of area 32 and lateral agranular (insular) projection field of the MD nucleus dorsal to the rhinal sulcus (Fig. 17.8*E;* Uylings and Van Eden, 1991). The exceptional cases in this regard were the records obtained in anterior cingulate cortical area 24b, the only one of the monitored anterior or posterior circuit areas that did not exhibit a statistically reliable old habit effect (Fig. 17.8*D*).

Anterior and posterior circuit areas also differed substantially in relation to the occurrence of TIA reversal (i.e., the development of discriminative TIA appropriate to the reversal task), as shown in Figure 17.8. Reversal was exhibited by the neuronal records of the AV and MD thalamic nuclei (Figs. 17.8*B* and 8*C*) and in anterior cingulate cortical area 24b (Fig. 17.8*D*). Reversal of TIA did not occur during standard reversal training in the cortical areas that exhibited the most pronounced old habit effects at the outset of reversal training (areas 29b/c, 32, and insular cortex, Fig. 17.8*A* and 17.8*E* respectively). Particularly striking was the retention of the original discriminative TIA exhibited by neurons in posterior cingulate cortical area 29b/c. The original discriminative TIA occurred not only during the first reversal training sessions but even during later sessions in which the rabbits' behavior exhibited discrimination appropriate to the reversal problem. For these records, the most that was achieved was a neutrality, wherein the CS+ and CS− elicited equal and minimal neuronal firing as the rabbits exhibited mastery of the reversal problem.

TIA in Postreversal Noncontingent Sessions

These studies have shown that cingulate cortical and limbic thalamic excitatory TIA in several anterior and posterior circuit areas reach a maximum or peak magnitude during acquisition and decline in magnitude as training progresses. This feature of the activity will be discussed later. Here, however, it is relevant to point out that the decline of the TIA in well-trained rabbits could arguably provide an explanation for the failure of the training-induced discharges in certain areas of anterior and posterior cingulate cortex to exhibit reversal in the final stages of reversal learning. It could be argued that reversal of the discriminative TIA is not seen in these areas because the CS elicited discharges are of too low a magnitude to exhibit a difference between CS+ and CS−.

To assess this possibility it was reasoned that the discharges could be enhanced by presenting occasional noncontingent footshocks during training to rabbits performing reversal discrimination at asymptotic levels. Discriminative TIA not seen during standard sessions might emerge as a result of shock-induced discharge enhancement. The results confirmed the original conclusion: The records of the AV and lateral MD nuclei and anterior cingulate area 24, which exhibited discriminative TIA appropriate to the reversal problem under standard training conditions, exhibited significantly enhanced discriminative TIA appropriate to the reversal problem during the noncontingent shock sessions (Fig. 17.9, rows 2, 4, and 6). Also,

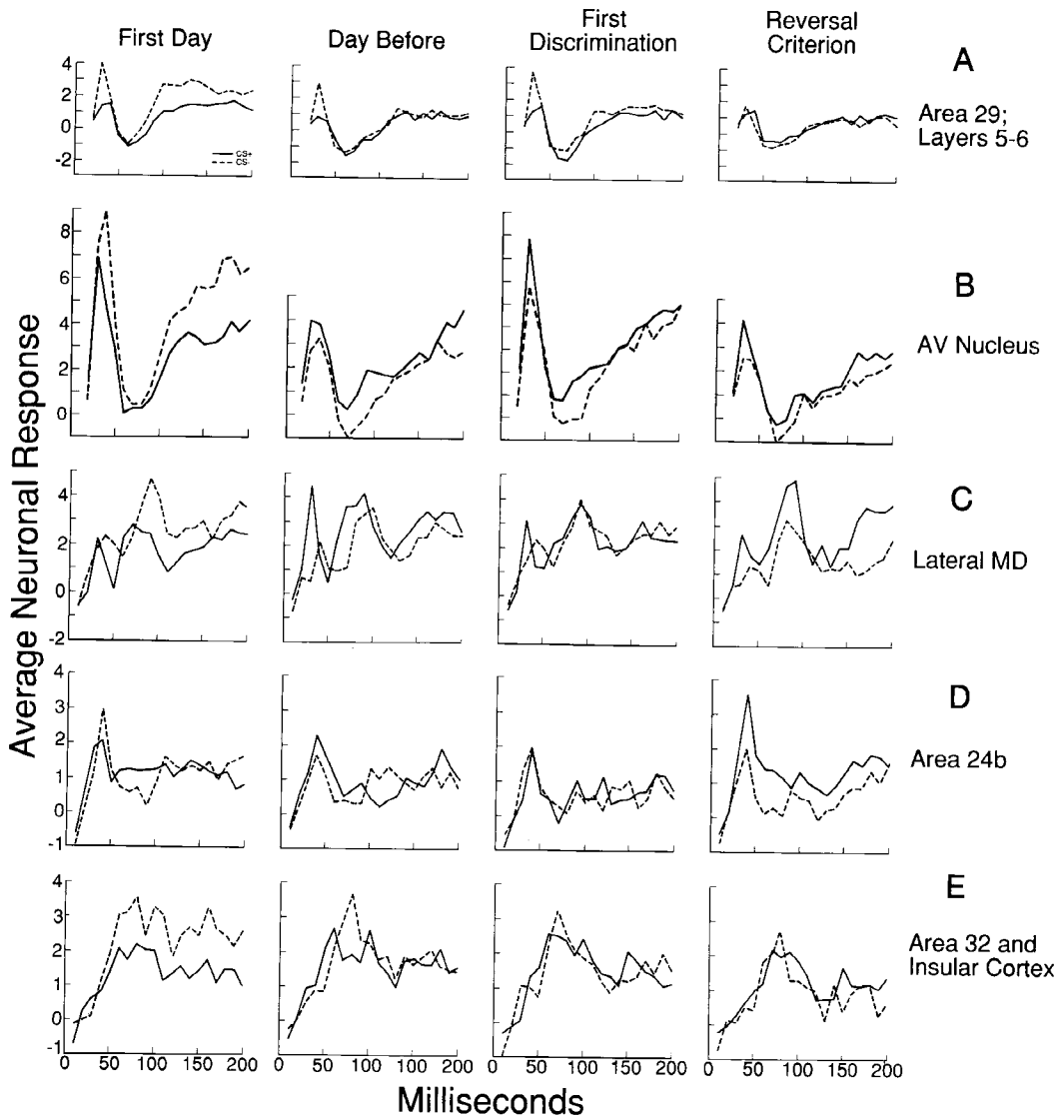


FIGURE 17.8. Average magnitude of multiunit neuronal discharges in cingulate cortex and limbic thalamus during four stages of reversal learning, the first session of reversal training, the session before the first significant behavioral reversal, the session in which the first significant behavioral reversal occurred, and the session in which the criterion of reversal learning was attained. The neuronal activity is plotted in the form of standard scores indicating the frequency of multiunit firing normalized with respect to the pre-CS baseline, following CS+ and CS−, in 20 consecutive 10 msec intervals after CS onset. Shown is activity in layers 5 and 6 of area 29c/d (*A*); AV nucleus (*B*); lateral division of MD nucleus (*C*); area 24b (*D*); and combined records of prefrontal area 32 and the lateral "insular" cortical projection field of the MD nucleus (*E*), which in rabbits surrounds the rhinal sulcus.

neurons in area 32 and insular cortex that did not exhibit significant discriminative TIA appropriate to either the original or the reversal problem during criterial performance of the reversal problem did exhibit the reverse discrimination during the noncontingent shock sessions (Fig. 17.9, row 5). Remarkably, area 29b,c, which exhibited a large old-habit effect in the early stages of reversal learning and no discriminative TIA

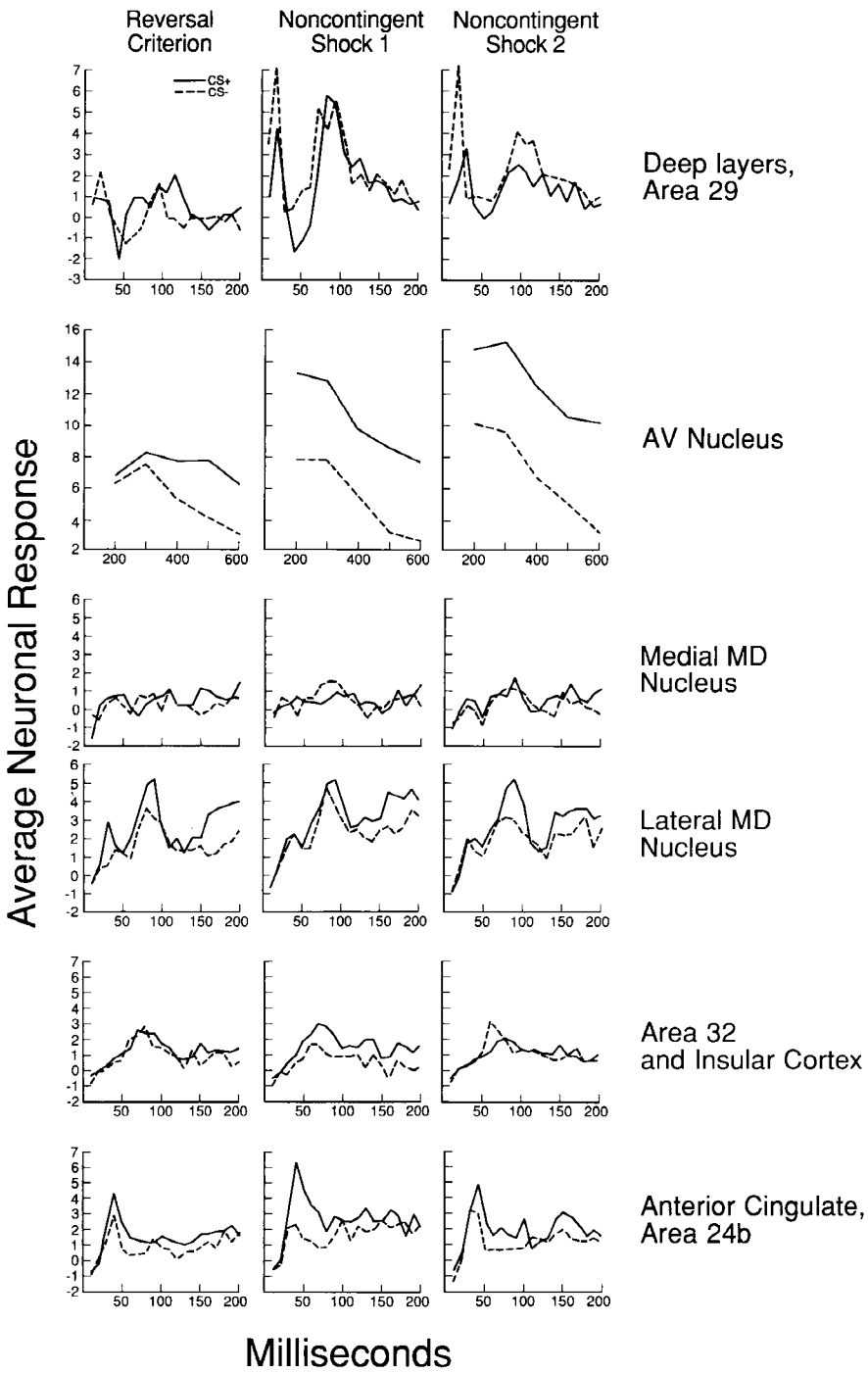


FIGURE 17.9. Average neuronal discharges recorded in cingulate cortex during the criterial session of reversal learning and during two additional training sessions in which standard training was accompanied by the presentation of unpaired footshock presentations. The neuronal activity is plotted in the form of standard scores normalized with respect to the pre-CS baseline in 20 consecutive 10 msec intervals after CS+ and CS− onset, or, for AV nucleus, in 6 consecutive intervals of 100 msec after CS+ and CS− onset. Activity related to reversal learning is shown for deep layers 5 and 6 of area 29c/d; the AV nucleus; medial MD nucleus; lateral MD nucleus; combined records of the lateral cortical projection field of the MD nucleus surrounding the rhinal sulcus and prefrontal area 32; and area 24b.

at the end of reversal learning, showed a reemergence of the old habit effect in response to the noncontingent shocks (Fig. 17.9, row 1).

To summarize, the discriminative TIA in anterior cingulate cortex and in the AV and lateral MD nuclei appears to be reversible, during the course of reversal learning. This is not true of posterior cingulate cortical discriminative TIA, which remains appropriate to the originally learned discrimination throughout reversal learning. The reversibility of discriminative TIA in anterior circuit structures and the retention of discriminative TIA in posterior cingulate cortex are features of the data compatible with the attribution to the anterior and posterior circuits, respectively, of recency and primacy system functions.

It should be noted that the reversibility exhibited by AV thalamic discriminative TIA constitutes an exception to the attribution of primacy functions to the posterior circuit. These results argue for allocation of the primacy and recency functions only to the cortical components of the anterior and posterior circuits. The related thalamic areas may perform a more general variety of significance coding not confined to this functional distinction in all respects.

Irreversibility of Posterior Cingulate Cortical Training-Induced Neuronal Activity: The Engram Trapped?

The available data indicate that the irreversibility of discriminative TIA is quite unique to posterior cingulate cortical neurons. Neuronal records found in regions that project to the posterior cingulate cortex, including the AV thalamic nucleus and anterior cingulate cortex, do not exhibit a persistent old-habit effect. Extensive recordings have not been made in the regions of the subicular complex which project to posterior cingulate cortex, but the available data indicate that little or no discriminative TIA develops in records of the subicular complex during behavioral acquisition (Poremba and Gabriel, 1991). This renders unlikely the possibility that the irreversible discriminative TIA is projected from the subiculum to the posterior cingulate cortex. These results are consistent with the possibility that fundamental biophysical and biochemical changes (i.e., engrams) underlying the irreversible TIA occur locally in posterior cingulate cortex.

Manipulation of Conditioned Stimulus Duration

Functional specificity of the anterior and posterior circuits was indicated by studies of the effects of varied CS duration (Sparenborg and Gabriel, 1992). Three values of CS duration (200, 500, and 5000 msec) were presented in a counterbalanced order, each for three consecutive training sessions after rabbits were trained to criterion using the standard 500 msec CSs. In all cases the interval from CS onset to US onset was 5000 msec.

Effects in Area 24

Significantly greater excitatory TIA occurred in area 24b of anterior cingulate cortex in response to the 200 msec CS+ than in response to the 5000 msec CS+. Excitatory TIA magnitude in response to the standard (500 msec) CS+ was intermediate between the TIA elicited by the 200 and 5000 msec stimuli (Fig. 17.10, row 1). There thus occurred an inverse covariation of discharge magnitude and CS duration. This inverse covariation was due largely to changes in response to the CS+, as constant discharges of minimal amplitude were elicited by CS− of varied duration. The neuronal records of the AV and MD nuclei were not significantly related to the CS duration variable, as shown in Figure 17.10 (rows 2 and 3).

The increased TIA elicited by the brief duration CS may provide a means to compensate for a possible loss of salience of the brief CS due to its curtailed duration. Such compensation may be needed to maintain an effective mnemonic representation of the brief CS.

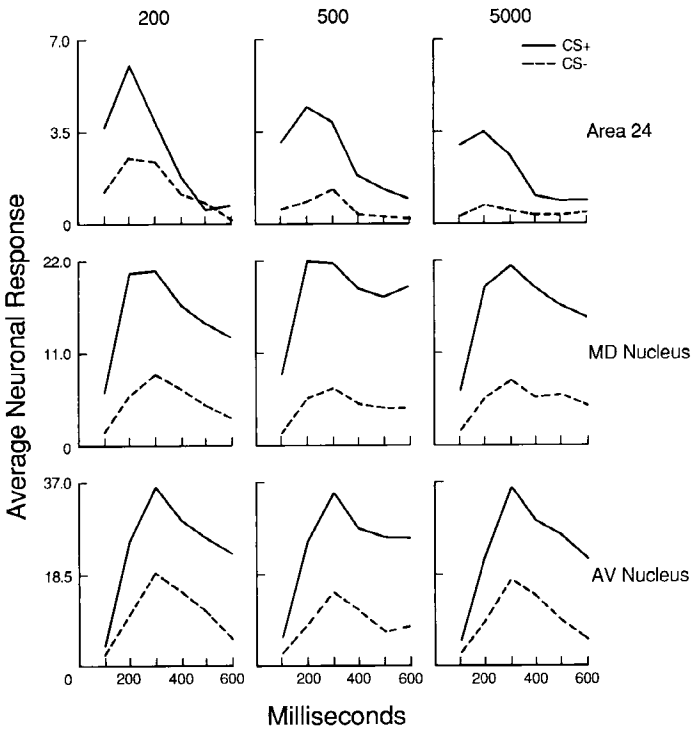


FIGURE 17.10. Average multiunit spike frequency recorded in well-trained rabbits in area 24b, MD nucleus and in AV nucleus during separate training sessions in which the standard 0.5 sec CS+ and CS− experienced during behavioral acquisition were presented, or in which brief (200 msec) or long (5000 msec) CSs were presented. In all cases, the interval from CS onset to shock presentation on nonavoidance trials was 5000 msec. The neuronal activity is plotted in the form of standard scores normalized with respect to the pre-CS baseline. Activity following CS+ and CS− is shown in six consecutive 100 msec intervals after CS onset.

EFFECTS IN AREA 29

The overall average neuronal records of posterior cingulate cortical area 29c/d were not significantly affected by CS duration. However, effects of CS duration were observed when neuronal records of area 29c/d were segregated into subsets exhibiting, respectively, early- and late-developing discriminative TIA, as described earlier. The late-discriminating records exhibited compensatory encoding similar to that shown by the records of area 24 (i.e., the difference between discharges elicited by the CS+ and the CS− increased as CS duration decreased; Fig. 17.11). In contrast, the average discharges of posterior cingulate records that exhibited early-developing discrimination were not monotonically related to CS duration. Instead these discharges were governed by CS novelty. Significantly greater discharges were elicited by the novel 200 and 5000 msec durations than by the familiar 500 msec duration (i.e., the duration that was used throughout the course of CR acquisition; Fig. 17.12).

That the early-discriminating posterior cingulate cortical records exhibited sensitivity to the unexpected CS durations clearly implicates the involved neuronal population in the "tracking" of CS duration for relatively long periods of time (days and weeks). That is, the involved neurons had to "remember" the duration of the original CS in order to respond to the novelty of the two test CS durations. These results are in accord with the hypothesis that posterior cingulate neuronal circuits participate in a mnemonic primacy system. This primacy-related activity was not found in anterior cingulate cortex.

BEHAVIORAL RELEVANCE OF THE DURATION-RELATED NEURONAL ACTIVITY

The coexistence of two neuronal populations in area 29, one of which enhances its discharges in response to significant cues that are abbreviated and a second that at the same time responds to the novelty of abbreviated as well as lengthened cues, may seem paradoxical. The first of these results may

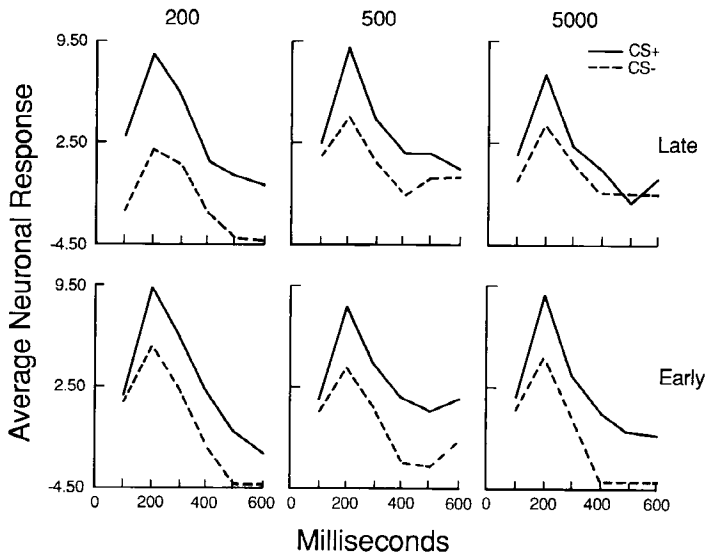


FIGURE 17.11. Average multiunit spike frequency recorded in well-trained rabbits in posterior cingulate cortical area 29c/d during separate counterbalanced sets of three training sessions in which the standard 0.5 sec CSs during behavioral acquisition were presented, or in which brief (200 msec) or long (5000 msec) CSs were presented. In all cases, the interval from CS onset to shock presentation on nonavoidance trials was 5000 msec. The neuronal activity following CS onset in the form of standard scores normalized with respect to the pre-CS baseline is shown in six consecutive 100 msec intervals after CS onset.

The data are averaged over the three days in which a given CS duration was presented. The upper panels show data for neuronal records that exhibited late-developing discriminative TIA and the lower panels show the data of records which exhibited early-developing discriminative TIA during behavioral acquisition. An inverse correlation of TIA and CS duration occurred in the late-discriminating records, and enhanced discharges in response to the novel 200 and 5000 msec CS durations (i.e., the durations not used during acquisition), relative to the familiar 500 msec training duration, occurred in the early-discriminating records.

reflect processes that ensure that the CS is detected and performance of the avoidance response maintained despite the brief CS duration. The second, novelty-detection function, is associated in many testing situations with a decreased probability of behavioral output.

In fact, the performance of avoidance responses was inversely related to CS duration: Rabbits made significantly fewer CRs to the 200 msec CS than to the 500 msec CS, and they made significantly fewer CRs to the 500 msec CS than to the 5000 msec CS. This indicates that the continuing presence of the CS during the interval from CS onset to US onset is an important factor determining the probability that an avoidance response will occur (Fig. 17.13). In contrast, the rabbits exhibited a significantly reduced incidence of avoidance responding in the first session with the novel 5000 msec CS than they did in the second and third consecutive sessions with the same CS where they exhibited significantly higher levels.

These behavioral results suggest that the novelty detection function putatively characterizing the activity of the early-discriminating neurons had behavioral consequences in the avoidance task. However, the postulated performance-enhancing function of the late-discriminating neurons did not have detectable behavioral consequences. If such a function exists, it did not succeed in boosting the performance of the avoidance behavior in response to the brief CS to the same level exhibited by the behavioral responses elicited by the long CS. It is however, possible, that the performance loss

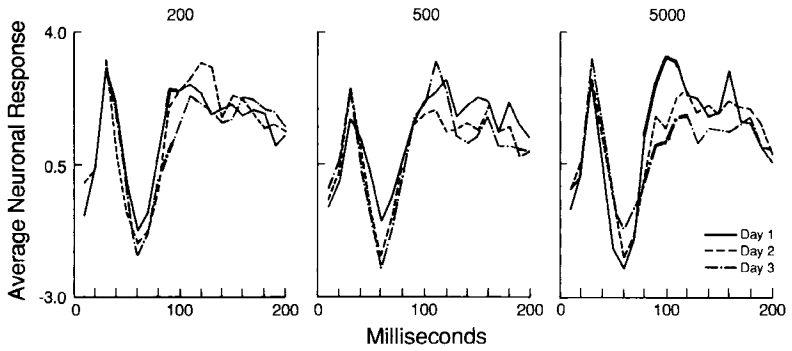


FIGURE 17.12. Average multiunit spike frequency exhibited by early-discriminating multiunit records of posterior cingulate cortical area 29c/d during separate counterbalanced sets of three avoidance training sessions administered to trained rabbits. Within each set of three sessions, the CSs were presented for 200 or 5000 msec or for the standard duration of 500 msec experienced during behavioral acquisition. Activity following CS+ and CS− is shown in 20 consecutive 10 msec intervals after CS onset. The three plots in each panel show the data recorded during each of three consecutive sessions (days) in which the same CS duration was used. There is a modest but statistically reliable drop from the first to the third day in the average discharge magnitude for the novel 200 and 5000 msec CS durations, but no change over days in the discharges elicited by the familiar 500 msec duration used for original training. The significant reductions of firing frequency over days occurred in the intervals from 90 to 120 msec after CS onset.

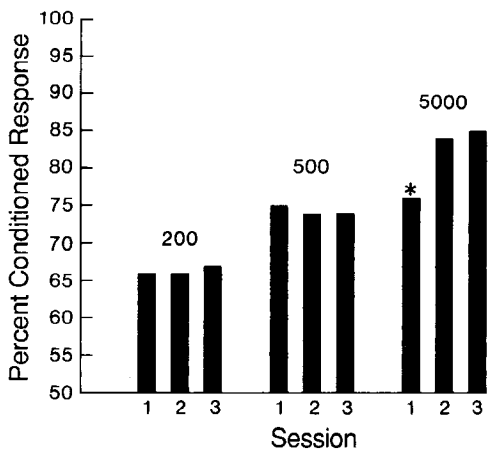


FIGURE 17.13. Average percentage of conditioned responses during separate counterbalanced sets of three training sessions administered to trained rabbits. In each set of three sessions the CSs were presented for 200 or 5000 msec, or, for the standard duration of 500 msec experienced during behavioral acquisition. The results indicated the presence of a highly significant overall covariation between the CS duration and performance. However, the presentation of the novel 5000 msec CS (*) did not immediately elevate performance to the high level ultimately associated with that duration.

in response to the brief CS would have been more severe than the actual loss if this function did not exist.

Manipulation of Conditioned Stimulus Probability

Effects in Cingulate Cortex

Differences between anterior and posterior cingulate cortical TIA emerged in relation to the manipulation of the relative incidence or "probability" of the CSs (Stolar et al., 1989). Rabbits received standard discriminative avoidance training to asymptotic levels after which they experienced, in a counterbalanced order, training sessions with either frequent or rare CS+ presentations. In the rare CS+ sessions, the CS+ occurred on 20% (24/120) of the trials and the CS− occurred on 80% (96/120) of the trials. This relationship was reversed in the frequent CS+ sessions.

Discriminative TIA in anterior cingulate area 24b was subordinated to the effects of the probability manipulation: Greater average discharges occurred in response to the

rare CS+ than to the frequent CS−, and, greater average discharges occurred in response to the rare CS− than to the frequent CS+ (Fig. 17.14, row 1). Also, the enhanced discharges to the rare CSs exceeded significantly discharges recorded during standard training sessions in which the two stimuli were presented equally often. The neuronal discharges of area 24b did not differentiate the neuronal discharges elicited by the frequent and equiprobably presented CSs.

The unique sensitivity to rare but not frequent CSs of area 24b neurons is suggestive, again, of a kind of compensatory encoding, which ensures that rare significant stimuli receive adequate mnemonic encoding in order to bridge the rather broad temporal gap between their successive occurrences. Insofar as this compensatory encoding is an immediate response to the introduction of the rare CS, it can be viewed as a manifestation of mnemonic recency encoding.

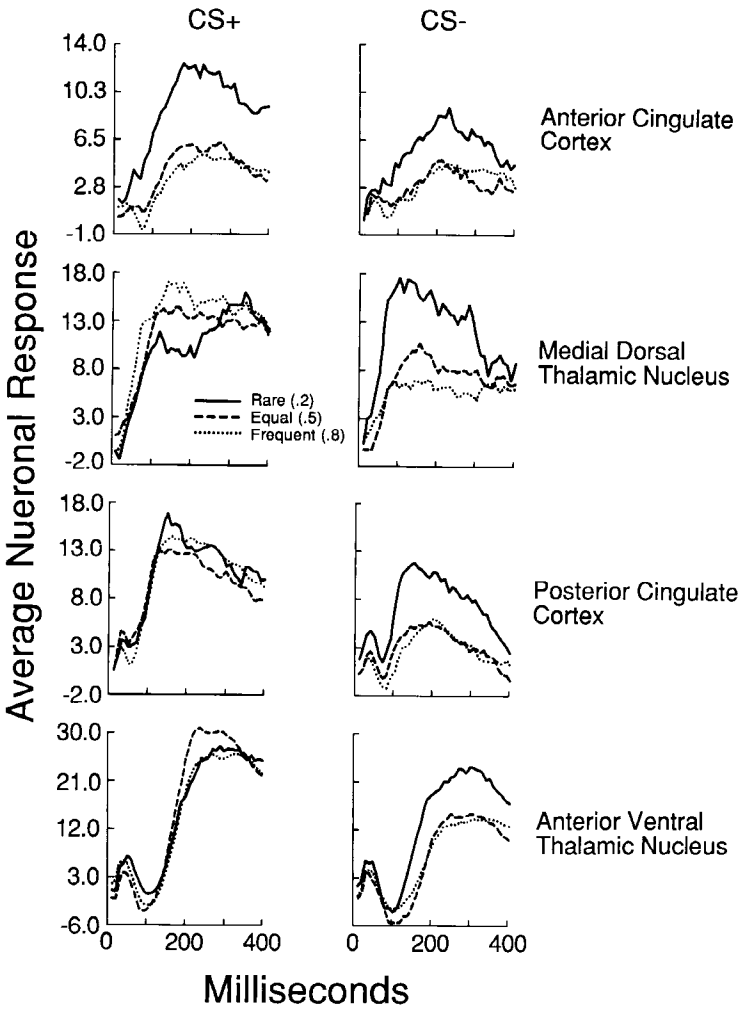


FIGURE 17.14. Average integrated unit activity in response to the CS+ and CS− in trained rabbits given sessions in which the CSs were presented equally often (equal); the CS+ was presented rarely (on 20% of the training trials) and the CS− was presented frequently (on 80% of the training trials); or the CS− and CS+ were presented rarely and frequently as defined in the previous choice. The neuronal activity is plotted in the form of standard scores normalized with respect to the pre-CS baseline for 40 consecutive 10 msec intervals following CS onset.

Unlike area 24b neurons, which were particularly responsive to rare CSs, posterior cingulate cortical area 29b,c neurons exhibited discharge enhancement in response to the rare and frequent CS+, relative to the equiprobable control CS+ (Fig. 17.14, row 3, left panel). The rare and frequent CS+ conditions were less familiar than the equiprobable CS+ control condition because the control condition operated throughout acquisition, whereas the rare and frequent conditions were newly experienced in single-test sessions.

The discharge enhancement to both the rare and the frequent CS+ in posterior cingulate cortex reflects the encoding and detection of deviation from expectancies developed during the history of training. The effects of CS+ incidence on posterior cingulate cortical neuronal populations are similar to the results indicating governance of posterior cingulate cortical activity by familiarity and novelty in the previously described studies of CS duration effects. Both sets of data are compatible with the hypothesis that posterior cingulate circuits are involved in the production of a primacy-based representation of the standard CSs formed during the course of acquisition and in the comparison of the unexpected CS conditions to the primacy-based representation.

In sum, the discharges of anterior and posterior cingulate neurons differ in relation to the historical scope of events that influence them. Anterior cingulate discharges are controlled by an abbreviated history (events in a given training session), whereas posterior cingulate discharges are controlled by a prolonged history (events spanning several training sessions).

Effects in Limbic Thalamus

The AV thalamic neuronal discharges were significantly reduced in response to both the rare and frequent CS+, relative to the discharges elicited by the equiprobable CS+ (Fig. 17.14, row 4, left panel). This pattern was the inverse of the pattern exhibited by posterior cingulate neuronal discharges that were enhanced by the rare and the frequent CS+ relative to the equivalent moderate discharges elicited by the equiprobable CS+. The number of MD thalamic records available for these analyses was small (n = 4), and thus the results did not attain statistical significance. However, trends of the data suggested that MD thalamic average discharges were suppressed in response to the rare CS+ relative to the control CS+, but were unaltered by the frequent CS+ (Fig. 17.14, row 2, left panel). This pattern was also the inverse of the pattern exhibited by anterior cingulate neurons that were enhanced by the rare CS+ relative to the equivalent moderate discharges elicited by the frequent and equiprobable CS+.

These data corroborated other studies that indicated an inverse covariation of elicited neuronal discharges in cingulate cortex and limbic thalamus. For example, lesions of the dorsal subiculum, an origin of projecting fibers to posterior cingulate cortex, significantly attenuated the TIA in posterior cingulate cortex and enhanced the TIA in the AV thalamic nucleus (Gabriel et al., 1987). The important point is, however, that regardless of the direction of the change, the pattern of thalamic discharges differentiated the various CS+ probability conditions in exactly the same manner as did the pattern of discharges in corresponding areas of cingulate cortex. Thus thalamic and cortical neurons of the anterior circuit differentiated the rare CS+ from the frequent and equiprobable CS+; thalamic and cortical neurons of the posterior circuit differentiated the rare and frequent CS+ from the equiprobable CS+. As argued in "Effects in Cingulate Cortex," the different effects of CS+ probability are compatible with the hypothesis that the anterior and posterior circuits are preferentially involved, respectively, in mnemonic recency and primacy encoding processes.

Before leaving the topic of CS probability, it should be noted that the unique effects of CS probability in the anterior and posterior circuits seem to apply exclusively to the CS+. The cortical and thalamic neurons in

both circuits exhibited dramatically enhanced discharges to the rare CS− relative to the discharges elicited by both frequent and equiprobable CS−. These data suggest that rare presentation of a CS− can disrupt the processes that contribute to discriminative TIA by limiting the neuronal discharges elicited by the CS−. The disruption of these processes may be mediated by neural events that are different from those that mediate the distinctive anterior and posterior circuit differentiation of the rare and frequent CS+.

One clue to the distinctive response to the rare CS− is provided by a study demonstrating that the local 6-hydroxydopamine-engendered depletion of norepinephrine (NE) either in posterior cingulate cortex or the anterior thalamus eliminated discharge increments in response to a rarely presented CS− and in response to a white noise stimulus never previously presented in the training environment (Sparenborg and Gabriel, 1992). These results raise the possibility that NE is involved in the production of the discharge enhancements engendered by the rare CS− and other unexpected events.

Neuronal Activity in Deafferented Networks: Tracking Down the Origins of Training-Induced Neuronal Activity

Limbic Circuit Interactions and Subcortical Synaptic Plasticity

Cortical and Thalamic Deafferentation and Training-Induced Neuronal Activity

Studies of excitatory and discriminative TIA in key deafferented brain areas have proved useful for determining the origins of TIA. Combined anterior and MD thalamic lesions that blocked behavioral acquisition abolished virtually all cingulate cortical CS-driven unit activity (Gabriel et al., 1989), and lesions restricted to either the anterior or MD thalamic nuclei blocked TIA in corresponding areas of cingulate cortex (Gabriel et al., 1983, 1989; Fig. 17.15).

In contrast, damage induced in the cere-

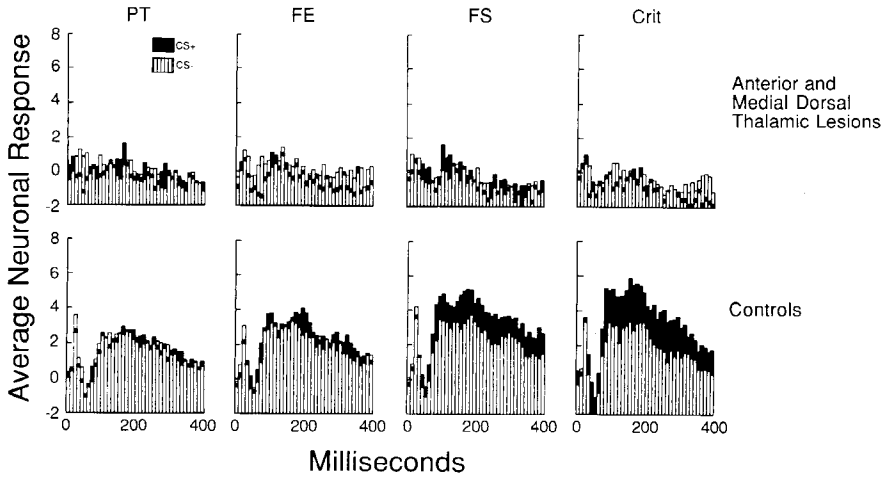


Figure 17.15. Average multiunit spike frequency in area 29 during four stages of behavioral acquisition in rabbits with combined anterior and medial thalamic lesions and in surgical controls. The neuronal activity is plotted in the form of standard scores normalized with respect to the pre-CS baseline for 40 consecutive 10 msec intervals following CS onset. The thalamic lesions essentially eliminated all training-induced activity in area 29. Pretraining session, PT; first exposure session, FE; first significant behavioral discrimination, FS; criterial behavioral discrimination learning, Crit.

bral cortical areas that project to limbic thalamus (anterior cingulate cortex, posterior cingulate cortex, subiculum) do not at all attenuate limbic thalamic TIA. Indeed, such lesions *enhance* thalamic TIA (Gabriel et al., 1987, 1991a; Fig. 17.16). That thalamic TIA develops in rabbits with cingulate cortical and hippocampal formation lesions supports the hypothesis that cingulate cortical and hippocampal formation afferents are not essential for limbic thalamic TIA. To our knowledge, other areas of the cerebral cortex do not contain neurons that project directly to the limbic thalamic nuclei. Auditory cortex has been shown unessential for auditory frequency discrimination in cats (e.g., Neff and Diamond, 1958). Therefore, although indirect routes of influence from nonauditory areas of cerebral cortex are possible, it is unlikely that inputs from the cerebral cortex are necessary for the development of limbic thalamic TIA during learning.

These findings indicate the importance of limbic thalamus as an essential source of

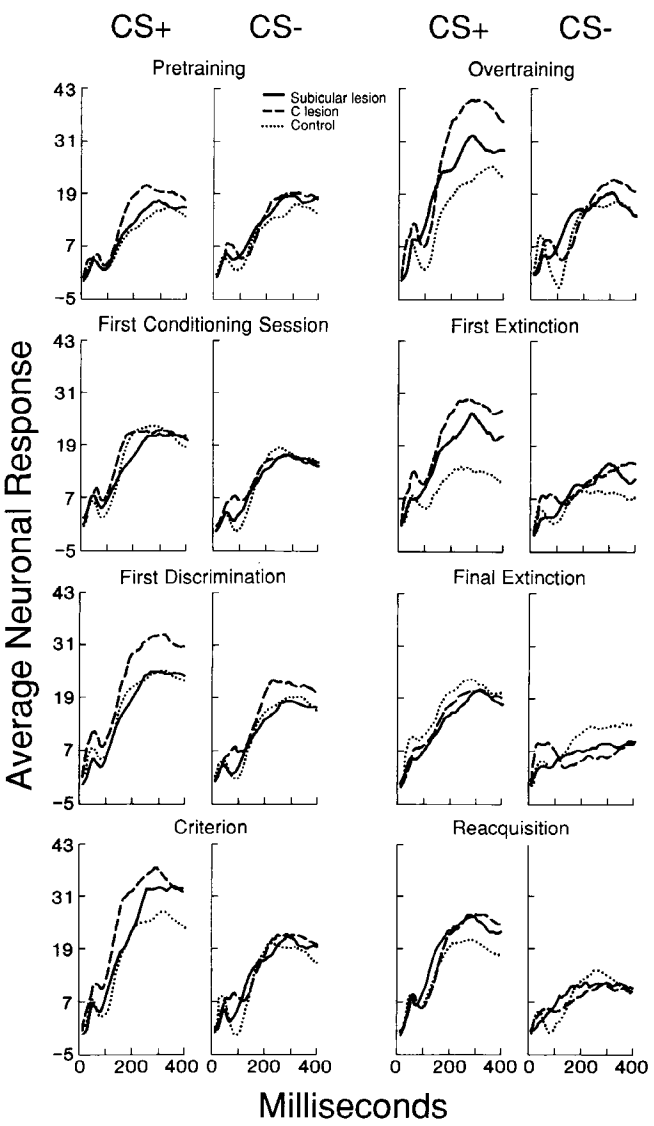


FIGURE 17.16. Average AV integrated unit discharges elicited by CS+ and CS− during training stages in separate groups of rabbits with bilateral electrolytic lesions of the dorsal and posterior subicular complex (solid lines), area 29b,c,d (dashed lines), or in surgical controls (dotted lines). The neuronal activity is plotted in the form of standard scores normalized with respect to the pre-CS baseline for 40 consecutive 10 msec intervals following CS onset. The elicited discharges in the rabbits with lesions were enhanced significantly, relative to controls, in the late stages of training (criterion, overtraining, and extinction).

TIA. Cingulate cortical TIA is dependent on input from the limbic thalamus, whereas limbic thalamic TIA does *not* require input from cingulate cortical or hippocampal formation neurons. Thus, virtually all cue-elicited activation of cingulate cortical neurons is accomplished by limbic thalamic input.

The dependence of cortical TIA on thalamic afferents does not mean that cingulate cortical TIA is a passive replication of limbic thalamic TIA. That this is not the case is indicated by the clear differences between the TIA in cingulate cortex and the limbic thalamus described previously, such as the fading of anterior cingulate cortical TIA as MD thalamic TIA increases during acquisition or the irreversibility of posterior cingulate cortical discriminative TIA exhibited concurrently with the development of reversed anterior thalamic discriminative TIA, during reversal learning.

These findings give rise to the following hypotheses regarding the origins of cingulate cortical and limbic thalamic TIA. Limbic thalamic excitatory and discriminative TIA is a product of subcortical training-induced synaptic plasticity, which develops independently of inputs from the cerebral cortex. The projection of limbic thalamic TIA to cingulate cortex is necessary for the exhibition of TIA in cingulate cortex. However, thalamic TIA projected to cingulate cortex is significantly modulated by training-induced synaptic plasticity that is intrinsic to cingulate cortex.

Subcortical Origins of Limbic Thalamic Training-Induced Neuronal Activity

These considerations raise a question concerning the identity of the subcortical afferents to the limbic thalamus that are involved in the production of limbic thalamic TIA. The following text reviews results of studies investigating the effects of manipulations of several relevant afferents.

AV thalamic excitatory and discriminative TIA developed normally during acquisition in rabbits that had received 6-hydroxydopamine microinfusions that reduced AV thalamic NE levels to 4% of control levels (Sparenborg and Gabriel, 1992, Fig. 17.17). Responsiveness of AV thalamic neuronal populations to unexpected stimuli was significantly reduced as a result of the depletion of anterior thalamic NE, and NE depletion profoundly attenuated posterior cingulate cortical TIA (Sparenborg and Gabriel, 1992). However, NE did not appear to be involved in the basic development of TIA in the AV nucleus.

Bilateral electrolytic lesions, which transected the mamillothalamic tract (Mtt), reduced the magnitude of tone-elicited discharges and eliminated the development of

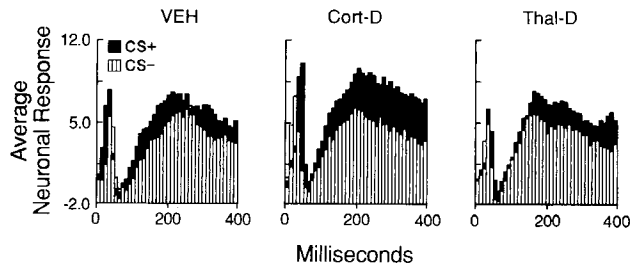


Figure 17.17. Average AV thalamic multiunit spike frequency histograms during performance in combined criterion sessions of discriminative avoidance conditioning in rabbits with 6-hydroxydopamine-induced depletion of NE in the posterior cingulate cortex (Cort-D), anterior thalamus (Thal-D), and in saline injected controls (VEH). The neuronal activity is plotted in the form of standard scores normalized with respect to the pre-CS baseline. Activity following CS+ and CS− is shown in 40 consecutive 10 msec intervals after CS onset. Neither cortical nor thalamic depletion of NE hindered the development of excitatory or discriminative TIA in AV nucleus.

acquisition-related excitatory TIA in the AV nucleus (Gabriel et al., 1992; Fig. 17.18). These results suggested a role of mamillothalamic synaptic transmission in production of AV thalamic excitatory TIA and the training-stage-related peaks of TIA. Preliminary data reported by Gabriel et al. (1988) suggested that the Mtt transections were associated with retardation of behavioral acquisition. However, now that all of the data have been collected, it has become evident that rabbits with the bilateral Mtt lesions exhibited exactly the same behavioral deficit, illustrated in Figure 17.6, as exhibited by rabbits with lesions in other components of the posterior circuit (posterior cingulate cortex, anterior thalamus): loss of performance efficiency following a normal behavioral acquisition.

The possibility that cholinergic fibers originating in the midbrain dorsal tegmentum are involved in the production of limbic thalamic excitatory TIA is suggested by the profound reduction of TIA amplitude in the AV nucleus and posterior cingulate cortex and by the severe reduction of avoidance responding following systemic administration to well-trained rabbits of scopolamine hydrobromide (Henzi et al., 1990; Fig. 17.19). The dependence of these effects on the central action of scopolamine was indicated by the absence of behavioral or neuronal effects of scopolamine methylbromide, which does not cross the blood-brain barrier.

Working Model for Limbic Thalamic Excitatory Training-Induced Neuronal Activity

It has been shown that electrical stimulation of the dorsal tegmental cholinergic group of nuclei, which project massively to limbic thalamus (e.g., Hallenger et al., 1987; Hoover and Baisden, 1980), can induce a prolonged enhancement of anterior thalamic synaptic responsiveness to mamillary body

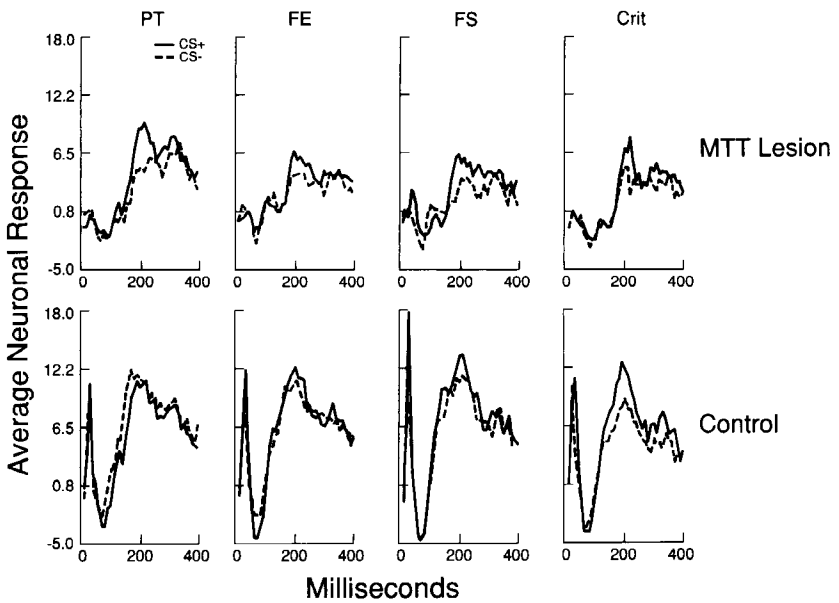


Figure 17.18. Average AV thalamic multiunit spike frequency following CS+ and CS− during the pretraining session (PT), first exposure session (FE), first significant behavioral discrimination (FS), and criterial behavioral discrimination learning (Crit). Data are shown for rabbits with bilateral electrolytic lesions of the mamillothalamic tract (MTT), and in surgical controls. The neuronal activity is plotted in the form of standard scores normalized with respect to the pre-CS baseline for 40 consecutive 10 msec intervals following CS onset. Overall AV discharge magnitude and excitatory TIA is absent in rabbits previously undergoing mamillothalamic tract transection.

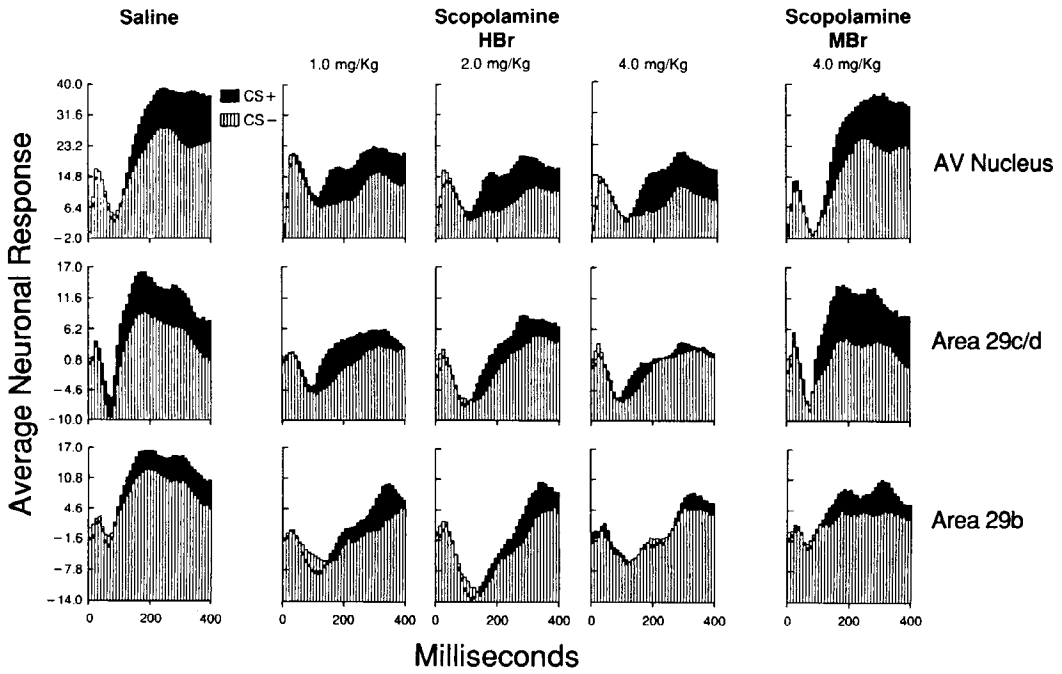


FIGURE 17.19. Average integrated unit discharges elicited by CS+ and CS− in well-trained rabbits during sessions in which systemic counterbalanced injections of scopolamine hydrobromide (HBr; 1.0, 2.0, or 4.0 mg/kg), scopolamine methylbromide (MBr; 4.0 mg/kg), or saline were given prior to the daily training session. The data were obtained from the AV nucleus and areas 29c/d and 29b. The results show significant reduction of the elicited discharges in these areas following scopolamine hydrobromide injection at all doses.

stimuli (Paré et al., 1989). Moreover, m2 muscarinic acetylcholine receptor binding is specifically increased with the development of TIA in the AV nucleus (Vogt et al., 1991). These findings raise the possibility that Mtt and cholinergic afferents from the midbrain tegmentum cooperate to induce anterior thalamic excitatory TIA (see Fig. 17.20). The TIA could be so produced as follows: Temporally correlated mamillary and tegmental afferents induce up regulation of muscarinic receptors presynaptic on Mtt axon terminals. These receptors enhance the release of the Mtt excitatory neurotransmitter. Work suggests the presence of muscarinic receptors localized to Mtt axon terminals in the AV nucleus (Sikes and Vogt, 1987).

Subcortical Origins of Limbic Thalamic Discriminative Training-Induced Neuronal Activity

It is interesting to note that the Mtt transections and scopolamine hydrobromide injections altered limbic thalamic excitatory TIA, but these manipulations did not affect discriminative TIA. That is, even though the increased discharge magnitudes resultant from exposure to the conditioning task (i.e., excitatory TIA) were eliminated by these treatments, the AV thalamic neurons nevertheless continued to exhibit greater discharge magnitudes in response to the CS+ than in response to the CS−. These findings indicate independence of excitatory and discriminative TIA (i.e., that discriminative TIA is not a product of the synaptic plasticities that induce excitatory TIA). None of the results obtained to date have indicated which afferents may be critical for the discriminative TIA in limbic thalamus.

Findings of this and other projects have demonstrated that discriminative TIA develops in the medial division of the medial geniculate nucleus, the thalamic relay of the auditory transmission pathway (e.g., Gabriel et al., 1976; Ryugo and Weinberger, 1978;

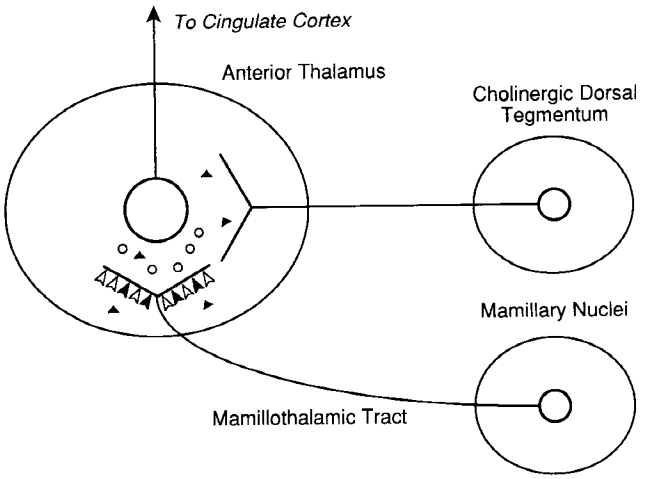


FIGURE 17.20. The hypothetical roles of cholinergic and mamillothalamic afferents in production of anterior thalamic training-induced excitation. Coactivation of mamillothalamic and tegmental cholinergic inputs results in the increased numbers of m2 receptors on the terminals of mamillothalamic axons. TIA is due to the consequent increased release of the mamillothalamic neurotransmitter release.

Birt et al., 1979). Moreover, medial geniculate neurons appear to be necessary for differential aversive conditioning of decelerative cardiac responses (Jarrell et al., 1986), and auditory cortex appears to contribute to differential cardiac CRs in later stages of acquisition (Teich et al., 1988). These results raise the possibility that medial geniculate neurons, and possibly auditory cortical neurons in the later training stages, contribute to limbic thalamic discriminative TIA. Such a contribution would have to be made via indirect routes as projections from auditory cortex or from the medial geniculate nucleus to the limbic thalamus have not been found.

Neurons in certain divisions of the medial geniculate nucleus project to amygdaloid nuclei and surrounding areas (LeDoux et al., 1985, 1986). One study suggests that these projections may be a component of the pathway that carries discriminative TIA to the limbic thalamus: Bilateral electrolytic lesions affecting several amygdaloid nuclei blocked behavioral acquisition and eliminated the development of excitatory and discriminative TIA in the AV and MD thalamic nuclei (Poremba and Gabriel, 1991; Fig. 17.21). Direct projections from the amygdala to the limbic thalamus, which could mediate the information flow suggested by these data, are not known. Projections from the basolateral amygdala to the MD thalamic nucleus terminate in the medial division of the MD nucleus (Krettek and Price, 1977a,b), not a site of TIA. However, this information flow could be mediated by projections from amygdaloid areas to the cholinergic tegmentum (e.g., Hopkins and Holtstege, 1978). As documented in "Working Model for Limbic Thalamic Excitatory Training-Induced Neuronal Activity," this area represents the origin of an extensive projection to both the AV and MD nuclei. Other as yet uninvestigated subcortical regions contain neurons that project to limbic thalamus and thus could modulate limbic thalamic TIA. These include the medial pretectal nucleus, the rostrolateral reticular thalamic nucleus, and the dorsal raphe nucleus (Sikes and Vogt, 1987; Poremba et al., 1993).

Limbic Circuit Interactions: Hippocampal and Cingulate Cortical Contributions to Limbic Thalamic Training-Induced Neuronal Activity

PROLOGUE

Afferents from cingulate cortex and hippocampal formation are not essential for limbic thalamic TIA. However, the projections from these areas significantly modulate thalamic TIA. In this section are described the attributes of the thalamic activity that are governed by the cortical inputs. These attributes are referred to as training-stage-related peaks of TIA. Description of the training-stage-related peaks is followed by data that indicate the modulatory role of the

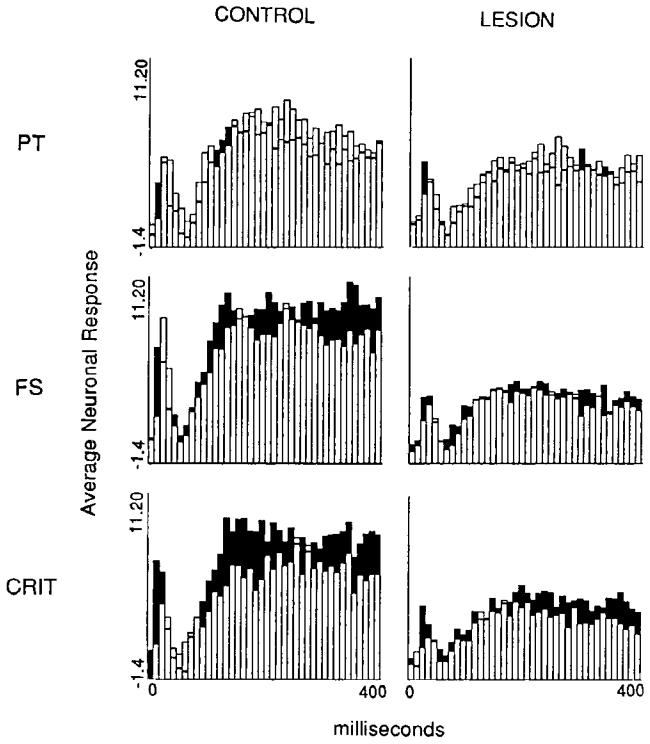


FIGURE 17.21. Average AV thalamic multiunit spike frequency following CS+ and CS− during the pretraining session (PT), first significant behavioral discrimination (FS), and criterion behavioral discrimination learning (CRIT). Data are shown for rabbits with bilateral electrolytic lesions of the amygdaloid complex and in surgical controls. The data indicate that overall AV thalamic discharge magnitude, training-induced excitation, and training-induced discrimination between CS+ and CS− are absent in the AV thalamic nuclei in rabbits with amygdaloid lesions.

cortical afferents, the importance of NE in governing these attributes, and a special involvement of AD thalamic neurons in the governance of TIA in other anterior thalamic nuclei. Finally an interpretation of the functional significance of these circuit interactions is provided.

Training-Stage-Related Peaks of Training-Induced Neuronal Activity: Limbic Thalamic Products of Hippocampal Modulation

The TIA in various limbic thalamic nuclei and in layers of posterior cingulate cortex exhibited peak amplitudes in the early, intermediate, or late stage of behavioral acquisition. The TIA amplitude in each area declined as training continued beyond the stage in which the peaks occurred (Gabriel et al., 1991b).

AD thalamic TIA exhibited a massive peak in the very first session of conditioning (Fig. 17.22, row 1, second panel from left), measured relative to the discharges recorded on the preceding day during pretraining with tones and unpaired shock presentations (Fig. 17.22, row 1, first panel on the left). The discharges elicited during training sessions that followed the first training session declined progressively during subsequent training stages (Fig. 17.22, row 1, third and fourth panels from left). Similarly, TIA recorded in the parvocellular division of the AV (AVp) nucleus and from the lateral dorsal (LD) thalamic nucleus reached a peak during the session in which behavioral discrimination between CS+ and CS− first occurred and declined thereafter (Fig. 17.22, rows 2 and 4, third panel from the left). TIA of the magnocellular AV (AVm) nucleus and the anterior medial (AM) nucleus did not reach peak magnitude until criterial (asymptotic) behavioral discrimination was attained (Fig. 17.22, rows 3 and 5, fourth panel). Distinct peaks of TIA were also observed in different layers of posterior cingulate cortex (Fig. 17.23), suggesting that projections of the various thalamic nuclei preferentially activate neurons in particular layers of posterior cingulate cortex.

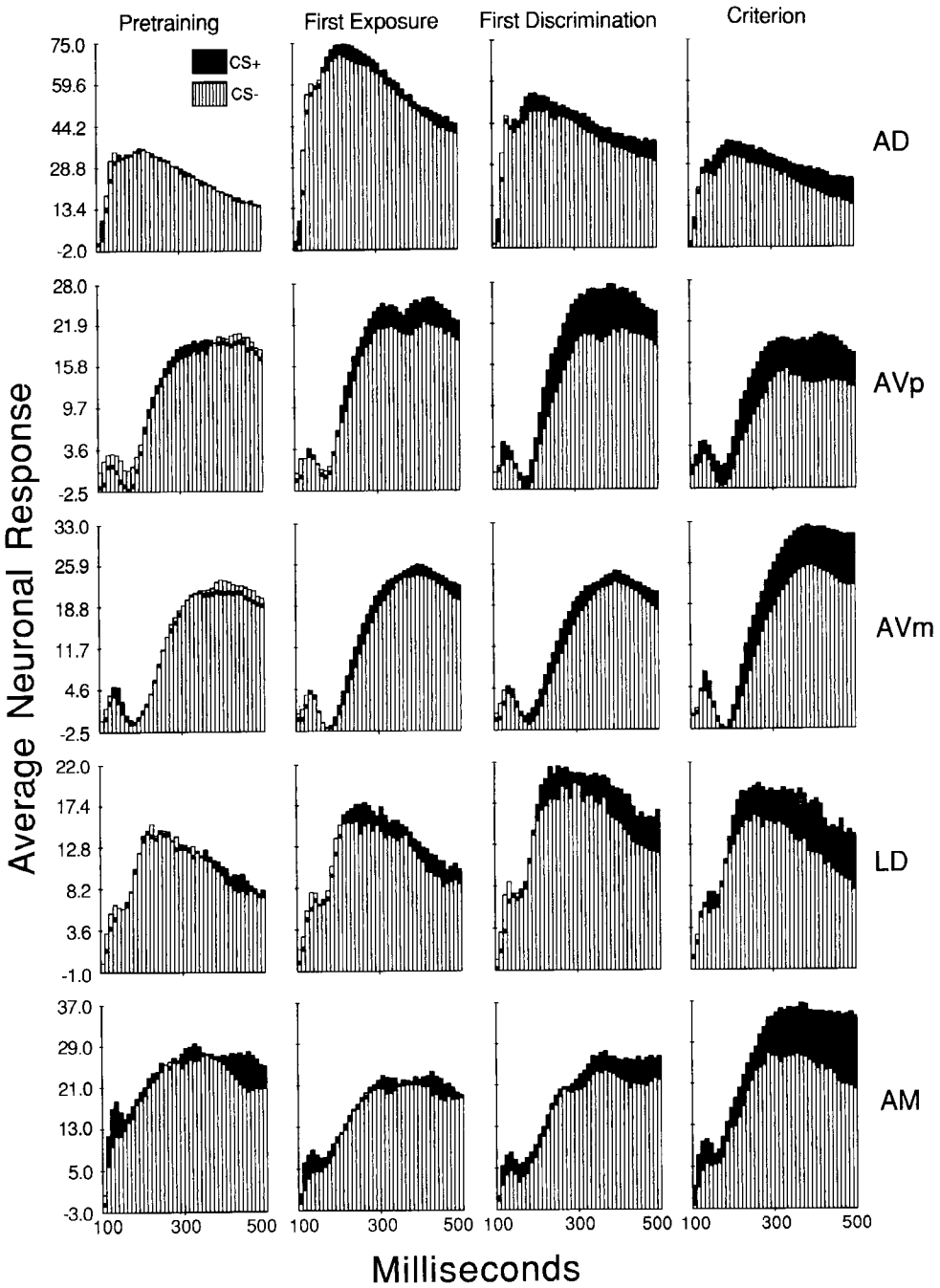


FIGURE 17.22. Average integrated unit discharges elicited by CS+ and CS− in trained rabbits during pretraining, first exposure, first discrimination, and criterion. The data were obtained from the anterodorsal (AD), parvocellular division of the anteroventral (AVp), magnocellular anteroventral (AVm), laterodorsal (LD), and anterior medial (AM) thalamic nuclei. These results demonstrate in the various areas for which data are shown separate training-stage-related peaks of training-induced excitation.

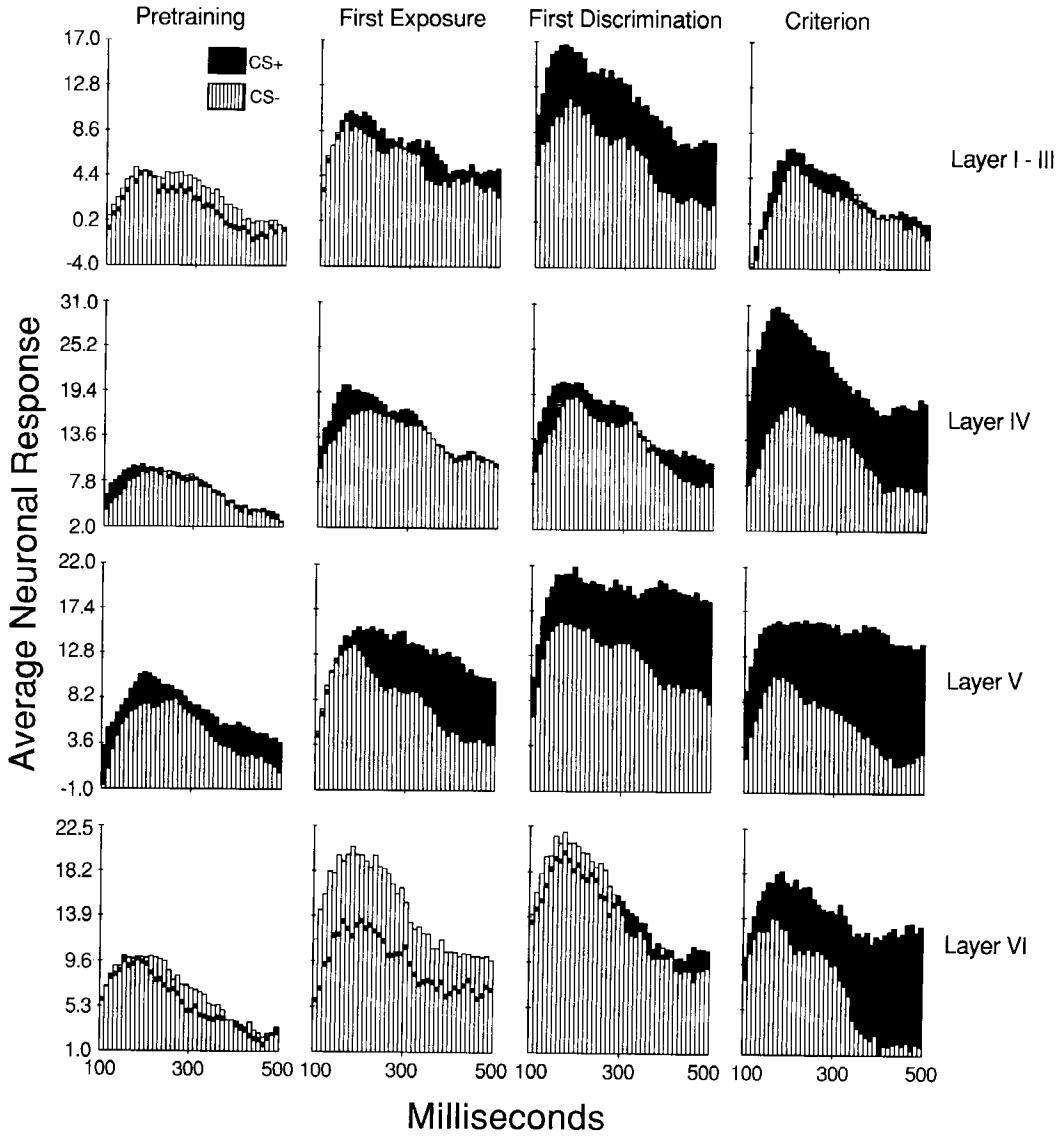


FIGURE 17.23. Average integrated unit discharges elicited by CS+ and CS− in trained rabbits during pretraining, first exposure, first discrimination, and criterion. The data were obtained from four layers of area 29c/d. These results demonstrate in the various layers separate training-stage-related peaks of training-induced excitation, as also shown (Fig. 17.22) in the thalamic projection nuclei of area 29.

MODULATION OF THE PEAKS OF TRAINING-INDUCED NEURONAL ACTIVITY BY CINGULATE CORTICAL, HIPPOCAMPAL, AND NORADRENERGIC INFLUENCES

As previously indicated, the magnitude of excitatory and discriminative TIA in the AV nucleus was increased relative to control records, in rabbits given bilateral electrolytic lesions of the dorsal and posterior subicular complex before training (Fig. 17.16; Gabriel et al., 1987). The lesion-related enhancement of the activity of the AV nucleus was not evident during preliminary training or in the early training stages, but rather emerged in asymptotically trained rabbits. Excitatory

TIA in the AV nuclei of rabbits with subicular lesions increased progressively during training to criterion, exceeded significantly the excitatory TIA magnitude in control subjects, and exceeded the TIA in controls during performance at criterion. TIA in the rabbits with lesions continued to increase as training beyond criterion was given, whereas the TIA in controls declined during the postcriterial sessions. The absence of the declining phase of the TIA effectively eliminated the stage-specific peak exhibited by the AV thalamic control records. In other words, the AV thalamic peak of TIA was abolished in rabbits with these lesions. Lesions of posterior cingulate cortex (Gabriel et al., 1987) and 6-hydroxydopamine-induced depletion of posterior cingulate cortical NE (Sparenborg and Gabriel, 1992) produced essentially the same effects on AV thalamic TIA as did subicular lesions. That is, the declining phase of the AV thalamic excitatory TIA was eliminated; TIA increased during the progress of the postcriterial training sessions. These results suggest that NE-mediated information flow from posterior cingulate cortex to the anterior thalamus, in conjunction with information flow from the subiculum to the anterior thalamus, is necessary for the post-peak decline and thus the temporal "sculpting" of the AV thalamic TIA peak in intact rabbits.

Preliminary results of an ongoing study suggest that combined bilateral electrolytic lesions of the dorsal and posterior subiculum and posterior cingulate cortex have effects on anterior thalamic TIA that are similar to those which followed the single lesions of these two areas: enhancement of AV thalamic TIA and the interference with the late-stage decline of AV thalamic TIA. This finding eliminates the hypothesis that the thalamic TIA enhancements were due to an increased excitation of the AV nucleus by neurons in the spared cortical area (the posterior cingulate or subiculum) in the rabbits with single lesions.

The study of the combined lesion effects has also provided preliminary data on the effects of these limbic cortical lesions on the unique TIA recorded in the AD nucleus. Available AD thalamic neuronal records (n = 3) in rabbits with the combined lesions exhibited as in controls a massive increment of CS-elicited activity in the initial session of conditioning, relative to the discharges during the unpaired shock and tone presentations given on the preceding day. However, the records in rabbits with lesions (Fig. 17.24) did not exhibit the dramatic decline of AD thalamic excitatory TIA seen in controls (Fig. 17.22, upper panels) during training sessions that followed the first session. These results suggest that subicular and posterior cingulate lesions interfere with the training-

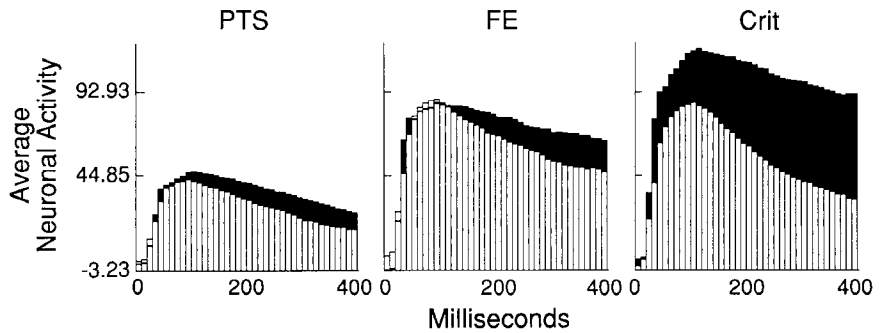


FIGURE 17.24. Average AD thalamic integrated unit activity following onset of CS+ and CS− in the pretraining session (PTS), first exposure session (FE), and criterial behavioral discrimination learning (Crit) in rabbits with lesions of the dorsal and posterior subicular complex and posterior cingulate cortex. The neuronal activity is plotted in the form of standard scores normalized with respect to the pre-CS baseline for 40 consecutive 10 msec intervals following CS onset.

stage-related peak in the AD nucleus in a manner similar to the interference with the AV peak by preventing the postpeak decline of TIA amplitude.

This suggests that hippocampal formation governance of the training-stage-related peaks is a product of information flow from subiculum to posterior cingulate cortex and to the mamillary nuclei and anterior thalamus via fornix projections. The information flow along these routes is apparently responsible for the suppression of the elicited discharges in the limbic thalamic nuclei during training stages that precede and follow the stage in which the peak of TIA is expressed. Thus, the flow of information from the hippocampal formation and posterior cingulate cortex is essential for inhibitory "temporal sculpting" of the training-stage-related peaks.

Remarkably, retrograde tracing studies using the enzyme *Phaseolus vulgaris* leucoagglutinin indicate that the connectional patterns of the Mtt could indeed support the separate governance of the training-stage-related peaks. Separate regions of the mamillary nuclei give rise to distinct projections to the anterior nuclei which exhibit separate peaks, the AD, AVp, AVm, and AM nuclei (Seki and Zyo, 1984; Hayakawa and Zyo, 1989). Moreover, studies using (*Phaseolus vulgaris* leucoagglutinin) indicate distinct linked subregions of the subicular complex and anterior thalamus that could be involved in subicular complex control of the stage-related thalamic peaks (Van Groen and Wyss, 1990a,b). Note also, however, that cingulate cortical efferents reach the anterior thalamus via direct corticothalamic projections that course through the internal capsule (Vogt, 1985). Therefore, the contribution of posterior cingulate cortical lesions to anterior thalamic TIA are realized by a different system of projecting fibers than are the contributions of the subiculum.

To summarize, the development of excitatory and discriminative TIA in the limbic thalamus does not depend on inputs from the hippocampal formation or cingulate cortex. However, efferents from these areas are important and perhaps essential sources of the AV thalamic training-stage-related peaks of TIA. Lesions in these areas interfere with the peaks in the AD and AV thalamic nuclei (and possibly in other limbic nuclei not yet studied in rabbits with lesions) by preventing the pre- and postpeak suppression of TIA.

Limbic Thalamic Training-Induced Neuronal Activity and Unexpected Stimuli

The interpretation of the training-stage-related peaks of thalamic TIA is aided by consideration of preliminary studies of the effects of unexpected stimuli on neuronal activity and behavior in the avoidance task. The subicular complex lesions, which enhanced the amplitude of AV thalamic excitatory TIA, were also associated with an increase in behavioral responsiveness. Rabbits with these lesions produced more frequent CS-elicited locomotions than did the controls during training sessions in which unexpected task events and contingencies occurred, including the first exposure to conditioning (when the rabbits first experienced the pairing of the CS+ with shock) and the first session of extinction training (when the CS+ was not followed by shock, after several training sessions in which these two stimuli were paired). It is important to note the specificity of the response overproduction to the sessions with unexpected stimuli: The rabbits with lesions did not overrespond during standard training sessions in which only familiar stimulus contingencies occurred (Fig 17.25).

These findings suggest that the behavior of rabbits with subicular lesions is characterized by a certain rigidity, insofar as such animals seem to fail to detect alterations of the task stimulus contingencies and/or they fail to exhibit normal suppression of their behavior in response to these alterations. This basic result has been observed in a variety of experimental settings throughout the history of studies of the effects of hippocampal lesions on behavioral acquisition and performance (Nadel et al., 1975; Gabriel et al., 1980b; Isaacson, 1982).

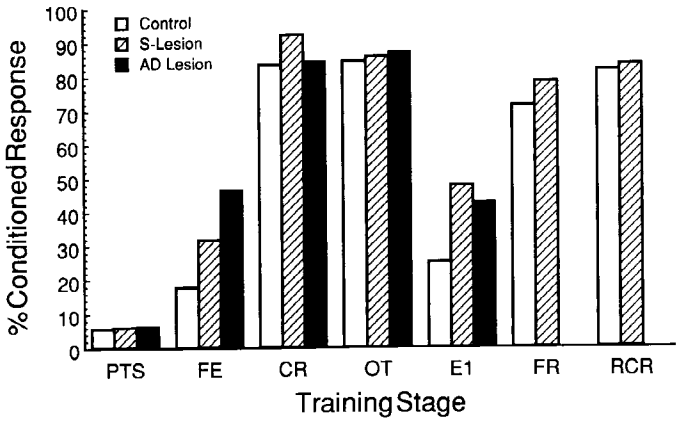


FIGURE 17.25. Average percentage of conditioned responses performed during various stages of behavioral acquisition in controls and in rabbits with lesions of the dorsal and posterior subicular complex (S-lesion) and in rabbits with lesions of the AD nucleus. The results show that these lesions enhanced the incidence of avoidance response performance during the first exposure session (FE) and the first session of extinction (E1). No significant effects of the lesions were found during the pretraining session (PTS), criterial performance (CR), overtraining (OT), or during the first or criterial sessions of reacquisition (FR and RCR, respectively).

The indications that subicular damage enhanced AV thalamic TIA and rendered the rabbits insensitive to task changes led to the following hypotheses:

1. Subicular efferents driven by hippocampal novelty-detection processes suppress limbic thalamic TIA in response to unexpected events in the training environment.
2. The suppression of the thalamic TIA is the cause of novelty-induced suppression of the behavior (Gabriel et al., 1986).

In order to test these hypotheses, rabbits with hippocampal lesions and controls were given standard training sessions followed by extinction training (CSs presented with no shock). During extinction, either the standard CSs or unexpected stimuli were presented. Several unexpected stimulus conditions were employed, in a counterbalanced order. For brevity, the discussion here will concern two of these conditions, which seemed to yield the essential results yielded by the full set of conditions. In one condition, the "novel context" condition, extinction with the standard CSs was given with the addition of "contextual" changes consisting of a novel odor (wintergreen) and reduced illumination in the learning chamber. In the second condition, the "novel CS" condition, a single 0.5 sec tone having an auditory frequency not heard during training replaced the standard CS+ and CS−. The foregoing hypotheses fostered the predictions that behavioral responding and AV thalamic TIA would be suppressed more quickly in the novel extinction tests than in the standard extinction test.

As expected, the rabbits made significantly fewer CRs during extinction in the novel conditions than with the standard stimuli (Fig. 17.26, upper panel). Previous work had also shown that visuospatial and tactile alterations of the conditioning apparatus hasten the extinction of the avoidance response (Gabriel and Vogt, 1970).

The TIA recorded in the AV nucleus was also reduced in both the novel tone and novel context extinction sessions, relative to TIA in the standard extinction session. However, the reduction of TIA occurred in the second and third 20-trial blocks of extinction trials, whereas the novelty-induced suppression of behavioral responding occurred in the very first 20-trial block of extinction trials. AV

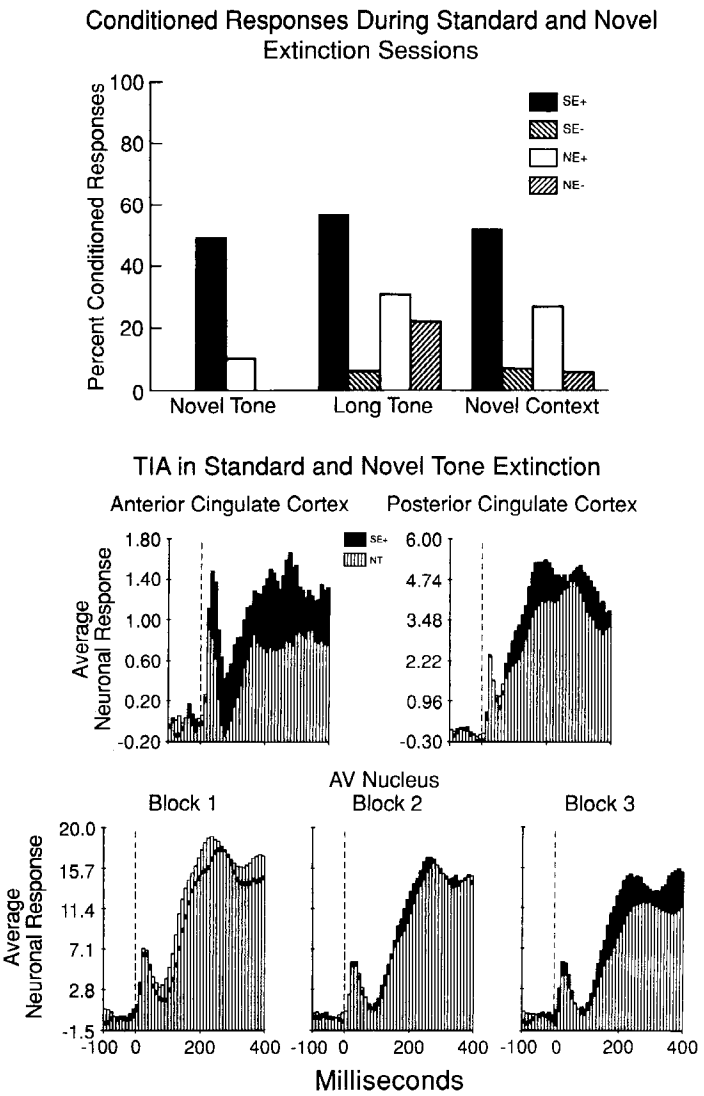


FIGURE 17.26. Behavioral and neuronal data obtained during standard and novel extinction sessions presented to well-trained rabbits. Standard extinction consisted of presentation of the CSs used for training, without footshock. Novel extinction consisted of either a novel tone session (presentation without shock, of a tone of different auditory frequency than either CS used during training), a long tone session (presentation during extinction of 5000 msec CSs rather than the 500 msec CSs used during acquisition), or a novel context session (presentation of the standard CSs without shock and with altered olfactory cues and luminance in the conditioning chamber).

The upper panel indicates that significantly fewer responses were made during novel extinction sessions (NE) than during standard extinction (SE+). The middle panels show significant suppression of anterior cingulate neuronal activity (left middle panel) during extinction with the novel tone (NT) when compared with the activity elicited during extinction with the standard CS+ (SE+). No significant change of posterior cingulate cortical neuronal activity (right middle panel) occurred during extinction with the NT, relative to extinction with the standard CS+. The lower panels show that the AV thalamic multiunit activity was not significantly altered during the first two of three consecutive blocks of 20 extinction trials with the NT+ when compared with the activity elicited during three blocks of SE. In all cases, the neuronal activity is plotted in the form of standard scores indicating the magnitude of integrated multiunit activity normalized with respect to the pre-CS baseline in 40 consecutive 10 msec intervals after CS onset. Similar neuronal results were found for the long tone and novel context conditions.

thalamic TIA was not altered significantly in the first two blocks of extinction trials with unexpected stimuli relative to TIA in the standard extinction sessions (Fig. 17.26, lower panels). These results thus conclusively rule out the hypotheses that engendered this study by demonstrating that the suppression of limbic thalamic activity is not the condition in the brain that is responsible for novelty-induced suppression of behavior.

As in the case of the AV thalamic neuronal activity, the activity in posterior cingulate cortex was not immediately altered by presentation of unexpected stimuli during the extinction sessions (Fig. 17.26, row 2, right-hand panel). Indeed, the only area in which there occurred a significant and immediate alteration (suppression) of neuronal firing in response to extinction training with unexpected stimuli relative to standard extinction training was anterior cingulate cortical area 24 (Fig. 17.26, row 2, left-hand panel). The relative intransigence of posterior cingulate cortical and AV thalamic neurons in response to the unexpected stimulus conditions and the immediate response to the unexpected stimuli exhibited by area 24 neurons is in keeping with the aforementioned characterization of the anterior and posterior circuits as mnemonic recency and primacy circuits, respectively. The sensitivity exhibited in this study by anterior cingulate cortical neurons to novel and incongruous stimulus events is consistent with conclusions based on metabolic mapping studies with human subjects using positron emission tomography (e.g., Pardo et al., 1990; see also Chapter 18 of this volume).

The foregoing results suggest that the training-stage-related peaks of TIA which characterized posterior circuit CS-elicited activity are not much influenced by unexpected stimuli. This is consistent with the hypotheses that these neurons participate in a mnemonic primacy circuit that maintains its encodings in spite of changes in task-relevant stimuli. However, other observations indicate that this conclusion may not provide a complete description of posterior circuit activity in relation to unexpected stimuli. Preliminary data of an ongoing study have indicated that the neurons of the AD nucleus are uniquely sensitive to the novel context treatment, i.e., AD neuronal discharges elicited by standard CS were significantly enhanced (and behavioral output was suppressed) during extinction with the novel contextual stimuli, relative to the activity during standard extinction. These and several other findings reviewed later suggest that the cells of the AD nucleus are involved in a distinct circuitry that is concerned with the detection of novelty. The AD cells cannot thus be considered to participate in the primacy coding functions attributed to AV thalamic cells. Additional information relevant to the specific functions of AD cells is presented in "Functional Affinity of the Anterodorsal Nucleus and Hippocampal Formation."

In addition to the exceptional case represented by the AD thalamic neurons, presentation of scattered white noise stimuli during standard conditioning in trained rabbits significantly activated the firing of AV thalamic and posterior cingulate cortical cells. These activations were norepinephrine dependent in that they were significantly attenuated in rabbits with 6-hydroxydopamine-induced local depletion of norepinephrine (Sparenborg and Gabriel, 1992; Fig. 17.27). The massive activations by white noise were accompanied by hyperfrequent, brief-latency conditioned responding rather than behavioral suppression typically induced by unexpected stimuli.

It may seem incongruous that posterior circuit neurons presumed to participate in a stable mnemonic primacy coding process nonetheless respond dramatically to the presentation of an unexpected (scattered) white noise stimulus. It is likely that neurons in other limbic and perhaps nonlimbic thalamic sites are also activated by white noise. Note, however, that the behavioral and neuronal effects of white noise presentations did not typify a novelty response, as novel stimuli typically engender suppression of behavior in the avoidance paradigm. Instead, the activity elicited by white noise may have re-

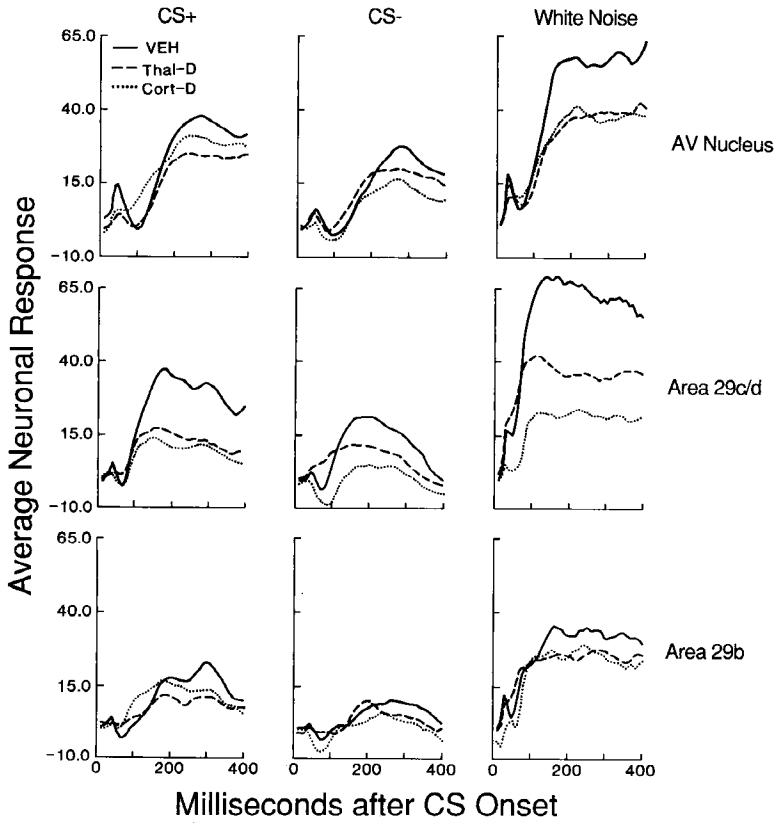


FIGURE 17.27. Average AV nucleus, areas 29c/d and 29b integrated unit discharges during performance of trained rabbits in a standard training session in which a novel white noise stimulus was presented at the same intensity (85 dB) as the standard CS+ and CS−, approximately every tenth trial. Data are plotted separately for the three stimulus types, for rabbits with 6-hydroxydopamine-induced depletion of NE in the posterior cingulate cortex (Cort-D), anterior thalamus (Thal-D), and in saline injected controls (VEH). Activity following CS+ and CS− is shown in 40 consecutive 10 msec intervals after CS onset.

flected the operation of a program for flight in response to a stimulus innately classified as threatening by rabbits.

Thus, in sum, the data suggest that anterior thalamic TIA contributes to the production of a mnemonic primacy code. A hypothesis is presented later which states that this TIA specifically retrieves the learned behavior while minimizing interference due to other learned associations. However, the subtle TIA patterns evident during standard training can be overridden by massive norepinephrine-dependent activation of limbic thalamic cells in response to innate threat stimuli. This massive activation can impel the vigorous and rapid performance of the avoidance response.

Functions of the Training-Stage-Related Peaks

Topographic Neuronal Pattern for Retrieval

The peaks of TIA collectively result in a distinctive topographic distribution of CS-elicited excitation in cingulate cortex. For example, in a well-trained rabbit, maximal excitation occurs in layers and cortical pro-

jection fields accessed by axon terminals of AVm and AM neurons, whereas minimal excitation occurs in the partially overlapping but distinct cingulate cortical layers and fields accessed by LD, AD, and AVp neurons. The distribution of excitation is quite different in moderately trained rabbits, which exhibit maximal excitation in the LD and AVp nuclei and in related cortical layers and fields, and the distribution in moderately trained rabbits differs from that in novices, which exhibit maximal excitation in the AD nucleus and related cortical layers and fields. These facts suggest the following tentative working hypotheses.

The topographic distribution of excitation in a particular stage of training is a unique product of the training situation and the level of training. The only way to produce a particular topographic excitation pattern in the brain is to present the CS+ to a rabbit located in the training situation and previously trained to the requisite level. As such, the topographic patterns are, de facto, a neuronal code for the spatiotemporal context of the learning situation. The various patterns thus uniquely code the spatiotemporal learning context (i.e., the background stimuli that identify the training situation, the particular CS presented, and the amount of accrued training).

The occurrence of the topographic patterns means that different discrimination problems concurrently engaged will activate different thalamocortical cytoarchitectures. Thus, the topographic patterns could serve to differentiate within the brain different discrimination problems practiced concurrently. The physical separation of excitation patterns relevant to different discriminative habits could foster "retrieval specificity" (i.e., the attachment of learned responses to the specific circumstances of training). This could in turn minimize retroactive and proactive interference (i.e., the tendency for responses acquired in one setting to occur in other settings in which they are not appropriate).

Support for a role of the posterior circuit in mediating retrieval specificity is provided by a number of studies (reviewed by Jaffard et al., 1991) that indicate that lesions of the mamillary nuclei (which would abolish the training-stage-related peaks) increase the susceptibility of animals to mnemonic interference effects. For example, mice given ibotenic acid and electrolytic lesions of the mamillary nuclei and controls were trained sequentially to discriminate between pairs of arms in a radial maze (Beracochea et al., 1989). Different groups received discriminative training on 2, 4, or 6 pairs of arms prior to retention testing. Retention performance deteriorated significantly more in the mice with lesions than in controls as the number of preexposed pairs of arms increased, suggesting a greater amount of retroactive interference in the mice with lesions.

The retrieval specificity hypothesis is currently being evaluated by training rabbits in both the avoidance and the drinking tasks, the onset of training in one task being offset by a few days from the onset of training in the other task. Two different topographic retrieval patterns should be evident in the same animal on the same day during performance in the two tasks. With intact hippocampi (and thus intact retrieval patterns), rabbits should be able to perform efficiently in the two tasks even under conditions of cue reversal (i.e., when the predictive cue in one task is the nonpredictive cue in the other and vice versa). However, the maintenance of distinct topographic patterns and efficient performance in each task should be severely disrupted in rabbits with hippocampal damage.

Topographic Retrieval Pattern and Hippocampal Processing

The involvement of the topographic patterns in retrieval processes is in all likelihood not limited to avoidance learning. Instead, and in keeping with cingulate cortical involvement in both appetitive and aversive learning situations, as discussed in the first section of this chapter, it is likely that the topographic

patterns occur generally in learning situations governed by interactions of hippocampal, cingulate cortical, and limbic thalamic circuitry. The patterns are thus implicated putatively in the operation of "hippocampal" mnemonic processes variously referred to as memory (Mishkin et al., 1984), working memory (Olton et al., 1979), declarative memory (Cohen, 1984); cognitive mapping (O'Keefe and Nadel, 1978), and others (i.e., processes believed to be dependent on the integrity of medial temporal lobe structures). The hypothesis offered here is not in conflict with these characterizations of the medial temporal lobe memory system. It is however, preferentially compatible with theories that maintain the following:

1. The mnemonic functions of the hippocampal system emerge from the interactions between medial temporal lobe, cingulate cortical, and diencephalic limbic circuits.
2. These interactions are fundamentally important for context-based retrieval of stored information.

It is important to note that the topographic patterns of TIA are not essential for *all* retrieval. Rabbits with hippocampal lesions learn and perform the avoidance task. Studies of the effects of cingulate cortical and hippocampal formation lesions reviewed earlier indicate that this normal acquisition and performance is accomplished on the basis of massive limbic thalamic discharges, which are undifferentiated topographically with respect to the training stage (i.e., the topographic retrieval pattern is degraded or nonexistent in rabbits with hippocampal lesions). Instead, the topographic patterns are produced by the hippocampal modulation of the limbic thalamus and thus are part and parcel of the special retrieval processes mediated by hippocampal circuitry. These processes are not necessary for basic response acquisition and performance, but they are necessary, as discussed earlier, for performance in memory tasks that place a heavy burden on retrieval specificity, such as tasks that require subjects to use contextual information in multitask situations—to match behavioral programs with the cues presented.

The hippocampus is well positioned via its connections with entorhinal cortex to have access to multimodal relational and configural properties of the environment, represented by these areas. It is proposed here that the chief role of hippocampal processing is "data fusion" or the boiling down of these complex properties into simple representations that can be encoded in the mnemonic recency and primacy circuits and that can be used for retrieval of information stored in these circuits. Here it is proposed that the training-stage-related peaks of TIA in the limbic thalamus represent an outcome of this data fusion process, which allows the rabbit to be sensitive to subtle changes of the spatiotemporal context.

These hypotheses are supported by the data presented in "Modulation of the Peaks of Training-Induced Neuronal Activity by Cingulate Cortical, Hippocampal, and Noradrenergic Influences" indicating degradation of the topographic retrieval pattern in rabbits with hippocampal damage, and a specific insensitivity of rabbits with hippocampal lesions to changes in the contextual stimuli of the training situation: Such rabbits suppressed their behavior normally in response to the novel CS but failed to suppress performance in response to the novel context (Fig. 17.28). Furthermore, multiunit records of the CA1 subfield of the hippocampus showed discharge specificity to the novel context manipulation in the form of a marked suppression of firing in response to the standard CS when they were presented in the novel context. In contrast, a clear suppression of firing was not found in response to the novel CS (Fig. 17.29). Thus the novel CS and novel context manipulations serve to illustrate a dissociation between the simple unexpected stimuli that can be detected and used for behavioral suppression by cingulate cortex and limbic thalamus alone and the more complex stimulus patterns that require the hippocampal data fusion mechanism for their detection.

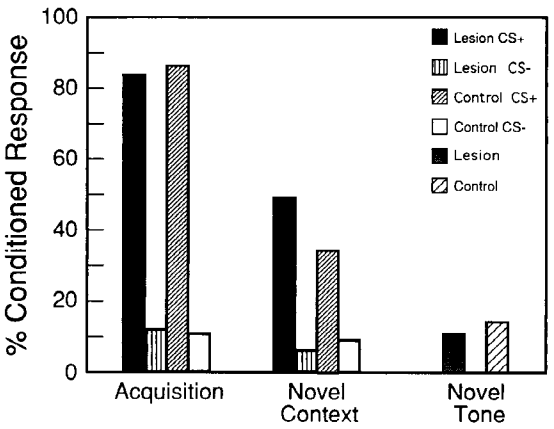


FIGURE 17.28. The percentage of conditioned responses elicited during a standard acquisition session and during the novel tone and novel context extinction sessions are plotted for rabbits with bilateral electrolytic lesions of the dorsal and posterior hippocampus and for surgical controls. The results show that extinction with a novel tone suppresses behavioral responding equally in rabbits with lesions and in controls. However, extinction in a novel context only succeeds in suppressing the behavior of intact rabbits.

FUNCTIONAL AFFINITY OF THE ANTERODORSAL NUCLEUS AND HIPPOCAMPAL FORMATION

Several findings suggest that AD thalamic neurons act in close cooperation with hippocampal formation neurons in the governance of excitatory TIA in other limbic thalamic nuclei. First, AD and hippocampal neurons exhibit similar patterns of TIA during learning—massive excitatory TIA in the first conditioning session and decline of the TIA as training continues beyond the first session. This pattern, shown in Figure 17.22 (row 1 panels) for AD neuronal records, is shown in Figure 17.30 for hippocampal records. Second, subicular and AD nuclear lesions have virtually identical behavioral effects; i.e., the frequency of avoidance responses increased significantly in rabbits with these lesions during training sessions with unexpected stimulus contingencies (the first sessions of conditioning and extinction), as described in "Limbic Thalamic Training-Induced Neuronal Activity and Unexpected Stimuli" (Kubota and Gabriel, 1993; Fig. 17.25). This response-overproduction contrasts with the response reductions produced by anterior thalamic lesions centered in the AV and/or MD nuclei. Third, AD thalamic TIA, which declines in the late stages of acquisition, was enhanced during exposure to the novel context extinction test (but not during exposure to the novel CS test), suggesting an involvement of AD thalamic neurons in the processing of complex but not simple novelty.

These results implicate AD neurons uniquely in the hippocampal functions of complex novelty detection and novelty-induced suppression of performance. It is suggested here that the failure of novelty detection and behavioral suppression because of disruption of circuitry involving the hippocampal formation and AD thalamic neurons is fundamentally a result of the disruption of the topographic retrieval patterns formed by the limbic thalamic training-stage-related peaks of TIA. AD and subicular axons converge in posterior cingulate cortex. Posterior cingulate lesions, like AD and subicular lesions, disrupt the topographic patterns by blocking the declining phase of AV thalamic TIA. Therefore, it is likely that posterior cingulate cortical efferent information flow is modulated by convergent subicular and AD thalamic afferents in posterior cingulate cortex to shape the rising and declining phases of the training-stage-related thalamic peaks.

Theoretical Synthesis

A theoretical working model (Gabriel, 1990) and a preliminary computational version of the model (Gabriel and Schmajuk, 1990) attempt to integrate the behavioral and neuronal data of this project. Here this model

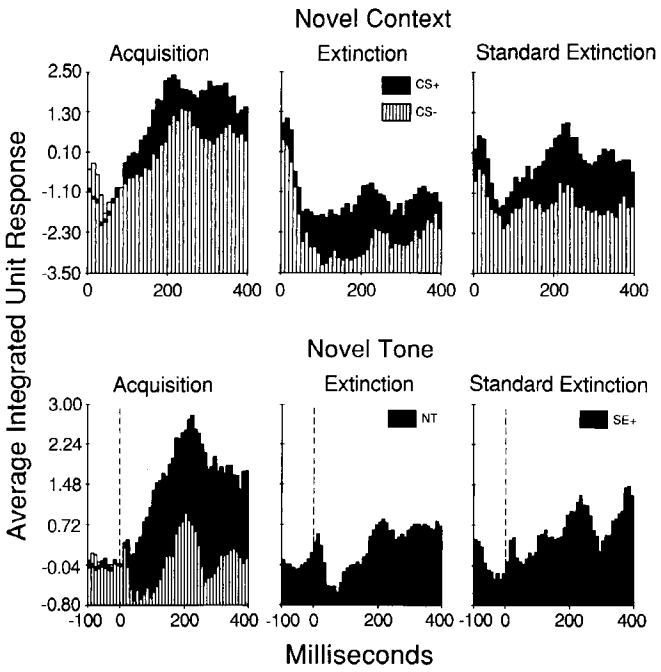


FIGURE 17.29. The average integrated neuronal activity in response to CS+ (dark bars) and CS− (light bars) are plotted in 40 consecutive 10 msec intervals after CS onset, for the CA1 subfield of the dorsal hippocampus. Data obtained during sessions of standard acquisition in well-trained rabbits, extinction with an unexpected stimulus, and standard extinction (SE) are shown, respectively, in the three panels in each row. The upper panels show data of the novel context extinction session and related control sessions, whereas the lower row shows data from the novel tone (NT) session and related control sessions. Upper panel data are normalized relative to the pre-CS baseline, and CS onset is indicated at the leftmost abscissa position. Lower panels show average "raw" scores, including the pre-tone baseline. CS onset in these panels is shown by dashed lines. These results indicate that the onset of novel and standard extinction greatly diminished the discharges of CA1 neurons. In addition, the novel context condition (but not the NT condition) induced a pronounced inhibitory or "off"-type discharge of the CA1 cells in response to the CS.

is summarized and updated to incorporate the new findings described in this chapter (see Fig. 17.31). The model specifies the distinct functions and associated neural circuitry that operate during discrimination learning and performance. Two fundamental neural computations identified by the model are motor priming, the principal function of striatal motor areas, and event processing, the principal function of limbic cortex and thalamus.

Motor Priming

It is proposed that the learned response of locomotion is *primed* or made ready when a trained rabbit is placed into the conditioning apparatus. The background contextual stimuli of the experimental environment acquire the capacity to elicit the priming of locomotion during the course of conditioning. By this view the priming of locomotion is a neural preparatory response conditioned to the background stimuli. The idea that background stimuli in conditioning environments importantly modulate conditioned behavior has been well established since the time of Pavlov and has received substantial attention (see volume edited by Balsam and Tomie, 1985). In addition to the priming of the learned behavior, the motor priming system provides the neural signals to lower

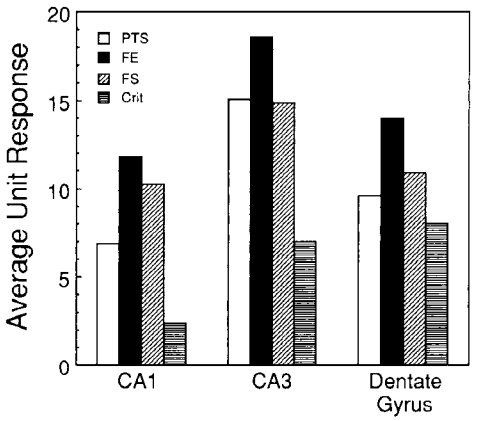


FIGURE 17.30. Average integrated unit discharges elicited by CS+ and CS− in trained rabbits during the pretraining session (PTS), first exposure session (FE), first significant behavioral discrimination (FS), and criterial behavioral discrimination learning (Crit) in three subfields of the dorsal hippocampus. Each bar represents the average discharge magnitude in the form of standard scores normalized with respect to the pre-CS baseline for 400 msec following CS onset. These results show that hippocampal areas exhibit dramatic increases in the first conditioning session, relative to the discharges in the preceding PTS with tone and unpaired shock presentation.

brainstem structures that initiate the locomotory response. This response initiation function is signified by the uppermost large arrow in Figure 17.31.

Event Processing

The background stimuli prime locomotion, but they do not determine the precise moment of its elicitation. That moment is determined by the activity of the limbic event processing system activity. The premotor activities of cingulate cortical neurons projected to the striatum represent command volleys that trigger the output of the already primed response (see pathway 7, Fig. 17.31). The command volleys represent the end products of limbic system event processing. They are regarded not as hard-wired, prelocomotory volleys but rather as products of neural learning processes (i.e., neuronal plasticity). Thus a principal brain modification underlying discriminative avoidance learning is the "construction" of cingulate cortical command volleys and the plasticity that makes these volleys contingent on the external presence of the learning context and the CS+.

The timing of the cingulate cortical command volleys is responsible for the coordination of response output with key events such as the CS+ and the shock US. Sites in which cingulate cortical efferent projections of command volleys could be involved in initiating conditioned locomotion include the striatum, motor cortex, zona incerta, and deep layers of the superior colliculus (Vogt, 1985; Groenewegen et al., 1990; Alexander et al., 1990).

The operation of the event-processing system begins outside of the limbic system, with the formation of discriminative TIA in structures of the auditory projection pathway (the medial and dorsal divisions of the medial geniculate nucleus). The neurons in these nuclei act as a peripheral adaptive filter that classifies auditory afferents as engendered by either associatively significant or nonsignificant external events. The afferent flow of information through the medial geniculate complex responsible for discriminative TIA is indicated by the large arrow and the box labeled "Sensory Input" in the lower right of Figure 17.31.

The pathway whereby discriminative TIA flows from the sensory filtering nuclei of the medial geniculate complex to the limbic thalamic nuclei has not been established. Possible intermediary relays are listed in the box labeled "Sensory Input" in Figure 17.31. Findings discussed in "Subcortical Origins of Limbic Thalamic Discriminative Training-Induced Neuronal Activity" indicate that relays in and/or in the vicinity of the amygdaloid nuclei provide an important intermediary. It is proposed that the amygdaloid projections to the cholinergic dorsal tegmentum (laterodorsal and pedunculopontine tegmental nuclei in Fig. 17.31) is the principal trajectory of input to the limbic thalamus, as indicated in the lower left of

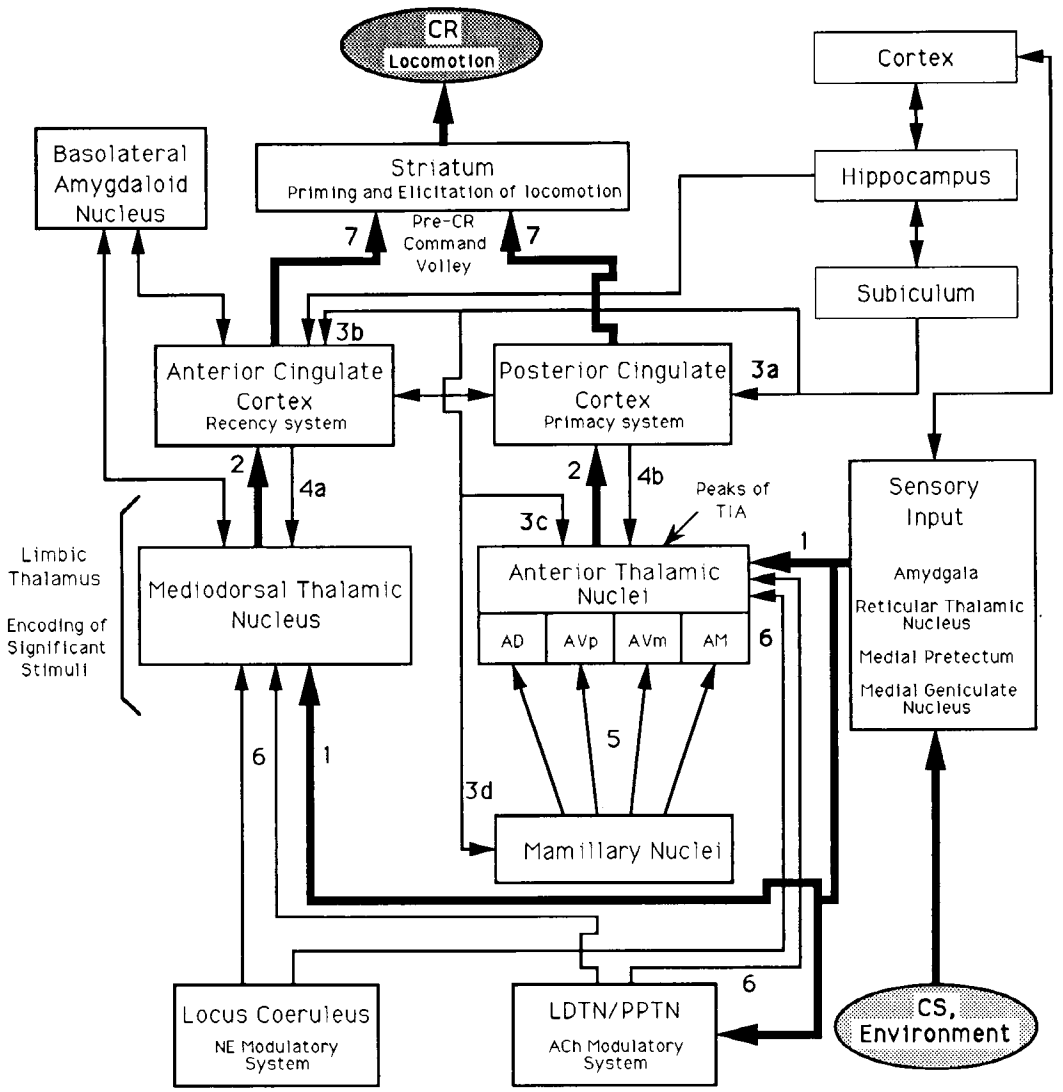


FIGURE 17.31. Theoretical model of the neural circuitry and information flow underlying discriminative avoidance learning. The wide lines indicate major information flows involved in triggering CR output, and thin lines represent modulatory influences that are involved in the development of training-induced excitation (TIA_1) and training-induced discrimination (TIA_2). Information enters the system through sensory pathways, and synaptic plasticity subserving TIA_2 is elaborated in the medial geniculate nucleus. CS-elicited activity progresses via connection 1 to the anterior and MD thalamic nuclei via possible synaptic relays in the reticular thalamic nucleus, medial pretectum, or amygdaloid complex. Anterior cingulate, MD, and basolateral amygdaloid circuitry participate in mnemonic recency functions, whereas posterior cingulate cortex, anterior thalamic, and hippocampal formation circuitry participate in mnemonic primacy functions.

In the anterior thalamus the discriminative discharges undergo modulation as a result of inputs from brainstem cholinergic cell groups (connection 6), hippocampal formation (connection 3c), cingulate cortex (connections 4a and b), and mamillary nuclei (connection 5). The modulation brings about TIA_1 as well as separate training-stage-related peaks of TIA_1 in distinct anterior thalamic nuclei. The peaks produce a cue-driven topographic pattern of excitation projected via connection 2 to separate layers of cingulate cortex. The topographic pattern is proposed to represent the neuronal coding of the spatio-

Figure 17.31 (pathway 1). As documented in "Distinctive Functions of the Anterior and Posterior Circuits," the anterior circuit (anterior cingulate cortex and MD thalamus) and posterior circuit (posterior cingulate cortex and anterior thalamus) subserve mnemonic recency and primacy functions, respectively.

Input to the thalamic components of these two circuits from the cholinergic tegmentum produces excitatory TIA (i.e., the increased thalamic cell discharges in trained rabbits compared with discharges during noncontingent pretraining). In addition, inputs from the hippocampal formation via cingulate cortex (pathways 3a, 3b, 4a, and 4b) and via the mamillary nuclei (pathways 3d and 5) converge with the tegmental inputs in anterior thalamus to construct the topographically distinct training-stage-related peaks of excitatory TIA in the various anterior thalamic nuclei and layers of the posterior cingulate cortex. It is proposed that the peaks of TIA considered collectively represents the mnemonic primacy code. The topography of the pattern changes during behavioral acquisition, however, a particular pattern at a given stage of training specifies that the CS+ has been presented in the training environment. This pattern thus constitutes a retrieval pattern in that it signifies that conditions are appropriate for the performance of an avoidance response. As a primacy system neuronal code, the pattern is very stable, thus providing an "historical" mnemonic template for the detection of change. The specificity of the retrieval patterns to the particular spatiotemporal context that defines the learning situation permits the rabbits to detect changes in the learning context and to perform concurrently several discriminative problems with minimal interference.

If input patterns match the primacy circuit retrieval pattern, cells in cingulate cortex that project to the striatal structures of the motor priming system produce a command volley that calls forth the learned response. If a match does not occur hippocampal efferents suppress performance and activate recency encoding processes in anterior cingulate cortex.

The topographic retrieval patterns are a product of hippocampal modulation of limbic thalamus and cingulate cortex. The patterns thus account for properties of the mammalian memory system that have been regarded in other theories as uniquely hippocampal. Hippocampal damage deletes the topographic patterns and the "hippocampal" mnemonic properties, leaving intact nontopographic excitatory TIA, which is adequate for the mediation of basic acquisition of the avoidance behavior. Thus, mnemonic functions, which are preserved in animals with hippocampal lesions (such as instrumental avoidance learning), are products of basic cingulate cortical and limbic diencephalic encoding processes devoid of the hippocampal topographic patterns. This conception is thus at odds with other theories that contend that basic classical and instrumental learning are provinces of a "habit" system or a "procedural" learning system, proposed to exist entirely outside of the limbic domain.

Acknowledgments

The research reported here and preparation of the manuscript was supported by grants from the National Institutes of Health Program in the Neurological Basis of Cognition and by the National Science Foundation Center for the Neurobiology of Learning and Memory, University of Illinois. Thanks are due to Amy Poremba, Yasuo Kubota, and Eunjoo Kang for their assistance in the reported research and in preparation of the manuscript.

temporal learning context essential for CR retrieval. If the retrieval pattern is elicited by the CS+ in a trained rabbit, command volleys of pre-CR cingulate cortical neuronal activity relayed to striatal motor structures via connection 7 trigger output of the learned behavior. Anterodorsal, AD; parvocellular division of anteroventral, AVp; magnocellular division of anteroventral, AVm; anteromedial, AM; laterodorsal tegmental nucleus, LDTN; pedunculopontine tegmental nucleus, PPTN.

References

Aggleton JP, Mishkin M (1983): Memory impairments following restricted medial thalamic lesions in monkeys. *Exp Brain Res* 52:199–209

Aggleton JP, Mishkin M (1985): Mamillary body lesions and visual recognition in the monkey. *Exp Brain Res* 58:190–197

Alexander GE, Crutcher MD, DeLong MR (1990): Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res* 85:119–146

Balsam PD, Tomie A, eds (1985): *Context and Learning,* Hillsdale, NJ: Erlbaum

Beracochea DJ, Aloui F, Jaffard R (1989): Impairment of memory in a delayed non-matching to place task following mamillary body lesions in mice. *Exp Brain Res* 34:147–154

Birt D, Nienhuis R, Olds M (1979): Separation of associative from non-associative short latency changes in medial geniculate and inferior colliculus during differential conditioning and reversal in rats. *Brain Res* 167:129–138

Brogden WJ, Culler FA (1936): A device for motor conditioning of small animals. *Science* 83:269

Buchanan SL (1988): Mediodorsal thalamic lesions impair differential heart rate conditioning. *Exp Brain Res* 73:320–328

Buchanan SL, Powell DA (1982): Cingulate cortex: Its role in pavlovian conditioning. *J Comp Physiol Psychol* 96:755–774

Buchwald J, Holstein SB, Weber DS (1973): Multiple-unit recording: Technique, interpretation, and experimental applications. In: *Bioelectric Recording Techniques: Part A, Cellular Processes and Brain Potentials,* Thompson RF, Patterson MM, eds. New York: Academic Press, p 242

Cohen NJ (1984): Preserved learning capacity in amnesia: Evidence for multiple memory systems. In: *The Neuropsychology of Memory.* Squire LR, Butters N, eds. New York: Guilford Press, pp 83–103

Eckersdorf B (1974): The effects of lesions in the posterior part of the gyrus cinguli on the conditioned defensive response of active avoidance in cats. *Acta Physiol Pol* 2:105–114

Foster K, Orona E, Lambert RW, Gabriel M (1980): Early and late acquisition of discriminative neuronal activity during differential conditioning in rabbits: Specificity within the laminae of cingulate cortex and the anteroventral thalamus. *J Comp Physiol Psychol* 94:1069–1086

Gabriel M (1990): Functions of anterior and posterior cingulate cortex during avoidance learning in rabbits. *Prog Brain Res* 85:467–483

Gabriel M, Foster K, Orona E (1980a): Interaction of the laminae of cingulate cortex and the anteroventral thalamus during behavioral learning. *Science* 208:1050–1052

Gabriel M, Foster K, Orona E, Saltwick SE, Stanton M (1980b): Neuronal activity of cingulate cortex, anteroventral thalamus and hippocampal formation in discriminative conditioning: Encoding and extraction of the significance of conditional stimuli. *Prog Psychobiol Physiol Psychol* 9:125–232

Gabriel M, Kubota Y, Henzi V, Swanson D (1992): Mamillothalamic tract lesions eliminate training-induced excitation in the anteroventral thalamic nucleus during learning in rabbits. In preparation

Gabriel M, Kubota Y, Shenker J (1988): Limbic circuit interactions during learning. In: *Information Processing by the Brain,* Markowitsch H, ed. Toronto: Hans Huber, pp 39–63

Gabriel M, Kubota Y, Sparenborg S, Straube K, Vogt B (1991a): Effects of cingulate cortical lesions on avoidance learning and training-induced unit activity in rabbits. *Exp Brain Res* 86:585–600

Gabriel M, Lambert RW, Foster K, Orona E, Sparenborg S, Maiorca R (1983): Anterior thalamic lesions and neuronal activity in the cingulate and retrosplenial cortices during discriminative avoidance behavior in rabbits. *Behav Neurosci* 97:675–696

Gabriel M, Miller J, Saltwick SE (1976): Multiple unit activity of the rabbit medial geniculate nucleus in conditioning, extinction, and reversal. *Physiol Psychol* 4:124–134

Gabriel M, Miller J, Saltwick SE (1977): Unit activity in cingulate cortex and the anteroventral thalamus of the rabbit during differential conditioning, extinction, and reversal. *J Comp Physiol Psychol* 91:423–433

Gabriel M, Orona E (1982): Parallel and serial processes of the prefrontal and cingulate cortices during behavioral learning. *Brain Res Bull* 8:781–785

Gabriel M, Schmajuk N (1990): Neural and computational models of limbic system interaction during avoidance learning and performance in rabbits. In: *Learning and Computational Neuroscience: Foundations of Adaptive Networks,*

Gabriel M, Moore J, eds. Cambridge, MA: MIT Press, Bradford Division

Gabriel M, Sparenborg SP, Kubota Y (1989): Anterior and medial thalamic lesions, discriminative avoidance learning and cingulate cortical neuronal activity in rabbits. *Exp Brain Res* 76:441–457

Gabriel M, Sparenborg S, Stolar N (1986): An executive function of the hippocampus: Pathway selection for thalamic neuronal significance code. In: *The Hippocampus* Issacson RL, Pribram K, eds. New York: Plenum, Vol 4, pp 1–39

Gabriel M, Sparenborg S, Stolar N (1987): Hippocampal control of cingulate cortical and anterior thalamic information processing during learning in rabbits. *Exp Brain Res* 67:131–152

Gabriel M, Vogt J (1970): Incubation of avoidance CRs in the rabbit produced by increase over time to in stimulus generalization to apparatus stimuli. *Behav Neurol Biol* 7:113–125

Gabriel M, Vogt BA, Kubota Y, Poremba A, Kang E (1991b): Training-stage-related neuronal plasticity in limbic thalamus and cingulate cortex during learning in rabbits: A possible key to mnemonic retrieval. *Behav Brain Res* 46:175–185

Goldman-Rakic PS (1990): Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. *Prog Brain Res* 85:325–337

Greene E, Naranjo JN (1986): Thalamic role in spatial memory. *Behav Brain Res* 19:123–131

Groenewegen HJ (1988): Organization of the afferent connections of the medial dorsal nucleus in the rat, related to the medial dorsal-prefrontal topography. *Neuroscience* 24:379–431

Groenewegen HJ, Berendse HW, Wolters JG, Lohman AHM (1990): The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: Evidence for a parallel organization. *Prog Brain Res* 85:95–118

Hallenger AE, Levey A, Lee H, Rye D, Wainer B (1987): The origins of cholinergic and other subcortical afferents to the thalamus in the rat. *J Comp Neurol* 262:105–124

Hayakawa T, Zyo K (1989): Retrograde double labelling study of the mamillothalamic and the mamillotegmental projections in the rat. *J Comp Neurol* 284:1–11

Henzi V, Kubota Y, Gabriel M (1990): Scopolamine but not haloperidol disrupts training-induced neuronal activity in cingulate cortex and limbic thalamus during learning in rabbits. *Brain Res* 518:107–114

Holmes EJ, Butters N, Jacobson S, Stein BM (1983): An examination of the effects of mamillary-body lesions on reversal learning set in monkeys. *Physiol Psychol* 11:159–165

Hoover DB, Baisden RH (1980): Localization of putative cholinergic neurons innervating the anteroventral thalamus. *Brain Res Bull* 5:518–524

Hopkins DA, Holtstege G (1978): Amygdaloid projections to the mesencephalon, pons and medulla oblongata in the cat. *Exp Brain Res* 32:529–574

Irle E, Markowitsch HJ (1982): Single and combined lesions of the cat's thalamic mediodorsal nucleus and the mamillary bodies lead to severe deficits in the acquisition of an alternation task. *Behav Brain Res* 6:147–165

Isaacson RA (1982): *The Limbic System,* 2nd ed. New York: Plenum.

Isserhof A, Rosvold HE, Galkin TW, Goldman-Rakic PS (1982): Spatial memory impairments following damage to the medial dorsal nucleus of the thalamus in rhesus monkeys. *Brain Res* 232:97–113

Jaffard R, Beracochea D, Cho Y (1991): The hippocampal-mamillary system: Anterograde and retrograde amnesia. *Hippocampus* 1:275–278

Jarrell TW, Romanski LM, Gentile CG, McCabe PM, Schneiderman N (1986): Ibotenic acid lesions in the medial geniculate region prevent the acquisition of differential Pavlovian conditioning of bradycardia to acoustic stimuli in rabbits. *Brain Res* 382:199–203

Kang E, Kubota Y, Poremba A, Gabriel M (1990): Hippocampal lesions, limbic cortical and thalamic training-induced unit activity, avoidance conditioning and response to different forms of novelty in rabbits. *Soc Neurosci Abstr* 113(19):264

Kessler J, Markowitsch HJ, Otto B (1982): Subtle but distinct impairments of rats with chemical lesions of the thalamic medial dorsal nucleus, tested in a radial arm maze. *J Comp Physiol Psychol* 96:712–720

Krettek JE, Price J (1977a): The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. *J Comp Neurol* 171:157–192

Krettek JE, Price J (1977b): Projections from the amygdaloid complex to the cerebral cortex and

thalamus in the rat and cat. *J Comp Neurol* 172:687–722

Kubota Y, Gabriel M (1993): Avoidance learning and limbic circuit neuronal activity in rabbits with lesions of the anterior dorsal thalamic nucleus. Submitted

LeDoux JE, Iwata J, Pearl D, Reis DJ (1986): Disruption of auditory but not visual learning by destruction of intrinsic neurons in the medial geniculate body of the rat. *Brain Res* 371:395–399

LeDoux JE, Ruggerio DA, Reis DJ (1985): Projections to the subcortical forebrain from anatomically defined regions of the medial geniculate body in the rat. *J Comp Neurol* 242:182–213

Lubar JF (1964): Effect of medial cortical lesions on the avoidance behavior of the cat. *J Comp Physiol Psychol* 58:38–46

Lubar JF, Perachio AA (1965): One-way and two-way learning and transfer of an active avoidance response in normal and cingulectomized cats. *J Comp Physiol Psychol* 60:46–52

Markowitsch HJ (1982): Retention performance of a learned delayed alternation task after chemical lesions of the cat's medial dorsal nucleus. *Behav Brain Res* 4:263–277

Markowska AL, Olton DS, Murray EA, Gaffan D (1989): A comparative analysis of the role of fornix and cingulate cortex in memory: Rats. *Exp Brain Res* 74:187–201

McClearly RA (1961): Response specificity in the behavioral effects of limbic system lesions in the cat. *J Comp Physiol Psychol* 54:605–613

Meunier M, Jaffard R, Destrade C (1991): Differential involvement of anterior and posterior cingulate cortices in spatial discrimination learning in a T-maze in mice. *Behav Brain Res* 44:133–143

Mishkin M, Malamut B, Bachevalier J (1984): Memories and habits: Two neural systems. In: *Neurobiology of Learning and Memory,* Lynch G, McGaugh JL, Weinberger NM, eds. New York: Guilford Press, pp 65–77

Moore (1964): Effects of some rhinencephalic lesions on conditioned avoidance behavior in cats. *J Comp Physiol Psychol* 57:65–71

Murray EA, Davidson M, Gaffan D, Olton DS, Suomi S (1989): Effects of fornix transection and cingulate cortical ablation on spatial memory in rhesus monkeys. *Exp Brain Res* 74:173–186

Nadel L, O'Keefe J, Black A (1975): Slam on the brakes: A critique of Altman, Brunner and Bayer's response inhibition model of hippocampal function. *Behav Biol* 14:151–162

Neff WD, Diamond IT (1958): The neural basis of auditory discrimination. In: *Biological and Biochemical Bases of Behavior,* Harlow HF, Woolsey CN, eds. Madison: University of Wisconsin Press, pp 101–126

O'Keefe JO, Nadel L (1978): *The Hippocampus as a Cognitive Map.* Oxford: Oxford University Press

Olton DS, Becker JT, Handelmann GE (1979): Hippocampus, space and memory. *Behav Brain Sci* 2:313–365

Orona E, Foster K, Lambert RW, Gabriel M (1982): Cingulate cortical and anterior thalamic neuronal correlates of the overtraining reversal effect. *Behav Brain Res* 4:133–154

Orona E, Gabriel M (1983): Multiple-unit activity of the prefrontal cortex and medial dorsal thalamic nucleus during acquisition of discriminative avoidance behavior in rabbits. *Brain Res* 263:295–312

Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990): The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proc Natl Acad Sci USA* 87:256–259

Paré D, Steriade M, Deschenes M, Bouhassira D (1989): Prolonged enhancement of anterior thalamic synaptic responsiveness by stimulation of a brain-stem cholinergic group. *J Neurosci* 10:20–33

Peretz E (1960): The effects of lesions of the anterior cingulate cortex on the behavior of the rat. *J Comp Physiol Psychol* 53:540–548

Poremba A, Gabriel M (1991): Amygdala lesions block acquisition of discriminative active avoidance learning in rabbits. *Soc Neurosci Abstr* 130(18):325

Poremba A, Kubota Y, Gabriel M (1993): Afferent connections of the anteroventral nucleus in the rabbit identified using WGA-HRP retrograde transport. Submitted

Pribram KH, Fulton JF (1954): An experimental critique of the effects of anterior cingulate ablations in monkeys. *Brain* 77:34–44

Pribram KH, Wilson WA Jr, Connors J (1962): Effects of lesions of the medial forebrain on alternation behavior of rhesus monkeys. *Exp Neurol* 6:36–47

Ryugo DK, Weinberger NM (1978): Differential plasticity of morphologically distinct neuron populations in medial geniculate body of the cat during classical conditioning. *Behav Biol* 22:275–301

Seki M, Zyo K (1984): Anterior thalamic affer-

ents from the mamillary body and the limbic cortex in the rat. *J Comp Neurol* 229:242–256

Shima K, Aya K, Mushiake H, Inase M, Aizawa H, Tanji J (1991): Two movement-related foci in the primate cingulate cortex observed in signal-triggered and self-paced forelimb movements. *J Neurophysiol* 65:188–202

Sikes RW, Vogt BA (1987): Afferent connections of anterior thalamus in rats: Sources and association with muscarinic acetylcholine receptors. *J Comp Neurol* 256:538–551

Sparenborg SP, Gabriel M (1992): Local norepinephrine depletion and learning-related neuronal activity in cingulate cortex and anterior thalamus of rabbits. *Exp Brain Res,* in press.

Squire LR (1987): *Memory and the Brain.* New York: Oxford University Press

Staubli U, Schottler F, Nejat-Bina D (1987): Role of dorsomedial thalamic nucleus and piriform cortex in processing of olfactory information. *Behav Brain Res* 25:117–129

Steinmetz J, Gabriel M, Sears L, Kubota Y, Poremba A, Kang E (1991): Cerebellar interpositus nucleus lesions disrupt classical nictitating membrane conditioning but not discriminative avoidance learning in rabbits. *Behav Brain Res* 45:71–80

Stokes KA, Best PJ (1988): Mediodorsal thalamic lesions impair radial maze performance in the rat. *Behav Neurosci* 102:294–300

Stolar N, Sparenborg S, Donchin E, Gabriel M (1989): Conditional stimulus probability and activity of hippocampal, cingulate cortical and limbic thalamic neurons during avoidance conditioning in rabbits. *Behav Neurosci* 103:919–934

Teich AH, McCabe PM, Gentile CG, Jarrell TW, Winters RW, Liskowsky DR, Schneiderman N (1988): Role of auditory cortex in the acquisition of differential heart rate conditioning. *Physiol Behav* 44:405–412

Uylings HBM, Van Eden CG (1991): Quantitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. *Prog Brain Res* 85:31–62

Van Groen T, Wyss JM (1990a): The connections of the presubiculum and parasubiculum of the rat. *Brain Res* 518:227–243

Van Groen T, Wyss JM (1990b): The postsubicular cortex in the rat: Characterization of the fourth region of the subicular complex and its connections. *Brain Res* 529:165–177

Victor M, Adams RD, Collins GH (1971): *The Wernicke-Korsakoff Syndrome.* Philadelphia: Davis

Vogt BA (1985): Cingulate cortex. In: *Cerebral Cortex,* Peters A, Jones EG, eds. New York: Plenum, Vol 4, pp 89–149

Vogt BA, Gabriel M, Vogt LJ, Poremba A, Jensen E, Kubota Y, Kang E (1991): Muscarinic$_2$ receptor binding increases in anterior thalamus and cingulate cortex during discriminative avoidance learning. *J Neurosci* 11:1508–1514

Zola-Morgan S, Squire LR (1985): Amnesia in monkeys after lesions of the medial dorsal nucleus of the thalamus. *Ann Neurol* 17:558–564