Fornix Lesions Impair Context-Related Cingulothalamic Neuronal Patterns and Concurrent Discrimination Learning in Rabbits (*Oryctolagus cuniculus*)

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Cingulothalamic neurons develop topographic patterns of cue-elicited neuronal activity during discrimination learning. These patterns are context-related and are degraded by hippocampal lesions, suggesting that hippocampal modulation of cingulothalamic activity results in the expression of the patterns, which could promote the retrieval of context-appropriate responses and memories. This hypothesis was tested by training rabbits (*Oryctolagus cuniculus*) with fornix lesions concurrently on two discrimination tasks (approach and avoidance) in different contexts. Because the same conditioned stimuli were used for both tasks, contextual information was critical for overcoming intertask interference during concurrent task acquisition. The lesions degraded the topographic patterns and significantly impaired concurrent learning, suggesting that hippocampal–cingulothalamic interactions and the resulting topographic patterns are critical for processing contextual information needed to defeat interference.

Important memory-related processes are subserved by interactions of hippocampal and anterior thalamic neurons (Aggleton & Brown, 1999; Beracochea, Jaffard, & Jarrard, 1989; Gabriel, Foster, Orona, Saltwick, & Stanton, 1980; Gabriel & Sparenborg, 1986; Gabriel & Talk, 2001; Golob & Taube, 1997; Mizumori, Cooper, Leutgeb, & Pratt, 2001). Studies of multisite neuronal activity recorded during discriminative avoidance learning have elucidated these interactions. Neurons in the limbic (anterior and medial dorsal) thalamic nuclei and related areas of the cingulate cortex develop distinctive firing profiles in response to a shock-predictive tone conditional stimulus (CS+) compared with profiles elicited by a different, negative conditional stimulus (CS−). The differential firing develops as subjects learn to step in response to the CS+ to avoid a scheduled footshock and to ignore the CS−, which does not predict the footshock. Discriminative avoidance learning is severely impaired in subjects with lesions of the cingulate cortex or the limbic thalamic nuclei (Gabriel, 1993).

An intriguing feature of posterior cingulate cortical and anterior thalamic (cingulothalamic) neuronal activity concerns its variation over the course of behavioral learning and with respect to cytoarchitecture. Neurons in different posterior cingulate cortical layers and anterior thalamic nuclei exhibit peak firing rates to the CS+ in particular stages of discriminative avoidance learning. Different

layers and nuclei have "preferred" learning stages, that is, stages of behavioral learning in which the neurons are maximally responsive to the CS+ (Gabriel, Vogt, Kubota, Poremba, & Kang, 1991). These learning-stage-related peaks of firing are lost or severely degraded in subjects with hippocampal lesions (Gabriel, Sparenborg, & Stolar, 1987; Kang & Gabriel, 1998). However, the basic discriminative neuronal responses and behavioral learning remain intact in subjects with lesions, indicating that the peaks are not essential for learning.

The fact that different areas develop CS-elicited firing peaks at different stages of learning means that at any given stage of learning, there exists a distinctive areal or topographic distribution of CS-elicited neuronal activation. The particular areas that exhibit a peak response in an early stage of learning are different from the areas that exhibit peaks in intermediate stages of learning, and these areas in turn differ from those that exhibit peaks in the final stages of learning. Thus, the topographic pattern changes systematically during acquisition. It follows from the foregoing that different task-specific topographic patterns will be observed in subjects performing concurrently in two discriminative tasks, an implication recently confirmed in a study of concurrent discriminative approach and avoidance learning (Freeman, Cuppernell, Flannery, & Gabriel, 1996a). In other words, the changing topographic pattern is task- or context-related. It uniquely reflects the particular task being practiced. For simplicity, the changing topographic pattern is henceforth referred to as the *context-related pattern*.

The foregoing findings have led us to propose that when trained subjects enter particular learning environments, the background contextual stimuli initiate hippocampal efferents that prime the context-related topographic pattern. The primed pattern is expressed when specific retrieval cues, such as the CS+, are presented. The pattern, in turn, aids retrieval of context-appropriate memory and learned response output (Gabriel, 1993). This mechanism would be especially helpful when mnemonic interference is

high. In the extreme case, when identical CSs are used in different tasks, as in the aforementioned study, the successful generation of context-specific patterns is critical for the retrieval of context-appropriate behavior and memory.

An extensive literature has implicated the hippocampus in processing contextual information (for reviews, see Anagnostaras, Gale, & Fanselow, 2001; Gabriel, 1993; Maren, 2001; Myers & Gluck, 1994). For example, subjects with hippocampal lesions do not exhibit conditioned fear responses to contextual stimuli. Of interest, the subjects exhibiting these deficits showed no impairment in learning to respond to a discrete conditional stimulus, suggesting that they had a specific context-processing deficit rather than a more general associative-learning deficit. Other studies have shown that subjects trained in one context exhibit performance decrements when tested in a different context, indicating that a dependency of the learned response on the learning context is established during acquisition. Subjects with hippocampal damage exhibit no such performance decrements (Freeman, Weible, Rossi, & Gabriel, 1997; Penick & Solomon, 1991).

Here, we test the hypothesis that hippocampal efferents prime the cingulothalamic context-related pattern via fornix fiber projections to the anterior thalamus. In this view, fornix lesions are expected to disrupt the context-related pattern and impair concurrent acquisition of discriminative instrumental approach and avoidance behavior when each task is administered using the same CSs in different learning contexts. The loss of the context-related pattern should not impair the learning of a single task, as in this situation contextual information is not essential for response retrieval.

Method

Subjects and Surgical Procedures

The subjects were 44 male New Zealand white rabbits (*Oryctolagus cuniculus*), weighing 1.5–2.0 kg at the time of their delivery by the supplier (Myrtle's Rabbitry Inc., Thompson Station, TN). All of the rabbits contributed behavioral and neuronal data to the analyses. Seven days after their arrival in the Beckman Institute Vivarium at the University of Illinois at Urbana–Champaign, the rabbits were placed on a moderately restricted diet (1 cup of Purina rabbit chow daily) to prevent obesity. Each rabbit was anesthetized for stereotaxic surgery using a subcutaneous injection (1 mg/kg of body weight) of a solution containing 60 mg/ml of ketamine hydrochloride and 8 mg/ml of xylazine. Electrolytic lesions of the fornix were induced using electrodes fabricated from stainless steel pins coated with Epoxylite. The insulation was removed from 0.7–0.8 mm of the tips to uncover a conductive surface. The coordinates and durations of current passage were as follows: AP 1.0 mm posterior to bregma, ML 1.25, DV 6.0, 50 s; and ML 2.5, DV 6.3, 50 s. Rabbits in the control group underwent the same surgical procedures with electrodes lowered into the fornix but no current passage. During surgery, six chronically indwelling fixed-position stainless steel microelectrodes were implanted for the recording of multi-unit and single-unit neuronal activity during learning. The target sites for recording electrodes were as follows: anterior cingulate cortex (AP 3.5 mm anterior to bregma, ML 0.8, DV 3.5), posterior cingulate cortex (AP 4.0 mm posterior to bregma, ML 0.8, DV 1.5), anterior ventral thalamic nucleus (AP 2.0 mm posterior to bregma, ML 2.3, DV 7.0), anterior dorsal thalamic nucleus (AP 2.5 mm posterior to bregma, ML 2.5, DV 6.0), medial dorsal (MD) thalamic nucleus (AP 4.6 mm posterior to bregma, ML 1.5, DV 8.0), and CA1 of the hippocampus (AP 5.0 mm posterior to bregma, ML 5.0, DV 2.5). Anterior cingulate cortical and MD thalamic neurons have not been shown to exhibit the context-related pattern and are

therefore not presented here. After at least 1 week for recovery from surgery, the rabbits were placed on a restricted regimen of 100 cc of water daily. They were given at least 1 week to adjust to this regimen before training. Water consumption was monitored during each training session, and the remainder of the 100-cc daily allotment was given (in the rabbits' home cages) 2 hr after training.

Discriminative Approach Learning

The rabbits were trained while they occupied a cubical metal chamber, which provided electrical shielding and sound attenuation. Within the chamber, the rabbits occupied a Plexiglas restrainer that allowed free head movement. Two pure tones (1 kHz or 8 kHz; duration = 500 ms; 85 dB re 20 μN/m^2; rise time = 3 ms) were assigned as positive and negative conditional stimuli (CS+ and CS−). The assignments were counterbalanced with respect to rabbits. During training, the onset of the CS+ was followed after 4 s by insertion of the drinking spout through an opening in the chamber wall. Head extension of 4 cm was the instrumental response required to reach the inserted spout. A water reward of 3 ml was dispensed automatically, immediately following oral contact with the spout. CS− presentation was also followed by spout insertion and spout contact responses were recorded, but no reward was dispensed. Instead, oral contact with the spout produced immediate retraction of the spout. The intervals between CS presentations (intertrial intervals) were 8 s, 13 s, 18 s, or 23 s. These intervals occurred in an irregular sequence.

Prior to training, the rabbits received daily acclimation sessions, that is, exposure to the conditioning chamber and water spout. Sixty spout insertions at irregular intervals were given during these sessions until the rabbits reached a criterion of at least 45 spout contact responses in a session. After the acclimation sessions, the rabbits were given two preliminary training sessions to obtain neuronal and behavioral records in response to the experimental stimuli in the absence of the critical learning contingencies for comparison with data of later training sessions. In the first preliminary training session, the tones to be used as CSs were presented 60 times each without spout insertion or water reward. In the second session, the tone CSs and water spout were presented in an explicitly unpaired manner. The rabbits could obtain water reward for spout contact responses. Following preliminary training, the rabbits were given daily training sessions (as described above) consisting of 120 trials (60 each with the CS+ and CS−) in an irregular order.

Discriminative Avoidance Learning

All rabbits received training while they occupied a rotating wheel apparatus designed for the instrumental conditioning of small animals (Brogden & Culler, 1936). The apparatus, similar to a rodent exercise wheel, consisted of two Plexiglas sides (each 0.50 in. [1.27 cm] thick, 30 in. [76.2 cm] in diameter) interconnected by a series of brass bars (0.19 in. [0.48 cm] diameter, 6 in. [15.24 cm] length) spaced 1 in. [2.54 cm] apart around the circumference of the wheel. The bars served as the grid floor of the wheel. The same pure tones used as the CSs during approach learning were used as the CSs for avoidance learning, with reversal of predictive values as described above. A 1.5-mA constant current shock delivered to the rabbits' footpads through the grid floor of the wheel served as an unconditional stimulus (US). The US had a maximum duration of 0.5 s and was terminated by wheel rotation. Prior to avoidance learning, rabbits were given two pretraining sessions to obtain neuronal and behavioral records in response to the experimental stimuli in the absence of the critical learning contingencies for comparison with data of later sessions. In the first pretraining session, the rabbits received 120 CS presentations (60 with each CS) in an irregular order. In the second pretraining session, 120 CS presentations were given along with explicitly unpaired presentations of the US. Regular discriminative avoidance learning sessions consisted of 120 presentations of the tone CS (60 with each CS) in an irregular order.

Onset of the CS+ was followed after 5 s by the US. Locomotion after the CS+ prevented the scheduled US. The CS− was never followed by the US. The rabbits learned to step in the rotating wheel in response to the CS+ and to ignore the CS−.

Partial Acquisition Group

The approach and avoidance tasks differ greatly in the amount of training needed for acquisition. Approach learning requires several (six to seven, on average) daily sessions of training before any significant discriminative learning occurs, whereas significant discrimination in the avoidance tasks is seen, typically, on the 1st or 2nd day of training. Thus, it was necessary to initiate approach training in advance of avoidance learning, thus delaying the concurrent phase of training until preliminary discriminative behavioral acquisition in the approach task occurred. If the two tasks had been initiated simultaneously, avoidance learning would have been completed by most rabbits prior to any approach learning. To avoid this problem, we trained the rabbits in the partial acquisition group (control $n = 10$, lesion $n = 17$) to a lenient criterion in the approach task (the first session in which the percentage of spout contact responses on CS+ trials exceeded the percentage of spout contact responses on CS− trials by at least 25%). Concurrent discriminative avoidance learning sessions were then introduced and alternated with continuing approach learning sessions, one session each day. The acoustic stimuli (CS+ and CS−) used during avoidance learning were identical to those used during approach learning, except that their predictive values were reversed. That is, the tone that had been assigned as the CS+ for approach learning was used as the CS− for avoidance learning and the tone that had been assigned as the CS− for approach learning was used as the CS+ for avoidance learning. Concurrent approach and avoidance learning continued until rabbits achieved a criterion that yielded asymptotic performance in each task. The criteria required that the percentage of spout contact responses on CS+ trials exceed the percentage of spout contact responses on CS− trials by at least 50% for the approach task and by at least 60% for the avoidance task. These criteria had to be met in two consecutive training sessions.

Full Acquisition Group

Intriguingly, the context-related cingulothalamic patterns are present only during behavioral acquisition. The neuronal responses and the context-related patterns wane during postasymptotic performance of the discrimination (Foster, Orona, Lambert, & Gabriel, 1980; Freeman, Cuppernell, Flannery, & Gabriel, 1996b). Studies of the effects of lesions have shown that cingulothalamic processing becomes irrelevant to performance in well-trained subjects (Hart, Poremba, & Gabriel, 1997). These results suggested that hippocampal modulation of the context-related pattern may contribute to context-appropriate retrieval only during concurrent acquisition of the tasks but not during continuing performance of well-trained subjects. To test this hypothesis, we used an additional full acquisition group (control $n = 10$, lesion $n = 7$) that received approach training until they reached asymptotic performance levels before beginning concurrent learning in the approach and avoidance tasks. A finding of a lesion-related disruption of performance during concurrent training in rabbits fully trained in the initial task, and therefore no longer exhibiting topographic patterns, would be negative for our hypothesis.

Asymptotic performance was achieved by training the rabbits to the previously mentioned approach learning criterion (50% more frequent responses to the CS+ than to the CS−). Thus, in contrast to the partial acquisition group, rabbits in the full acquisition group were allowed to acquire the first (approach) task fully before beginning the concurrent learning of the second (avoidance) task. After attaining required levels of performance in the discriminative approach task, the rabbits received continuing concurrent approach and avoidance learning sessions as described previously for the partial acquisition group. Concurrent approach

and avoidance learning continued until the rabbits attained the same performance criteria (described above) required of the partial acquisition group.

Analysis of the Behavioral Data

The behavioral data were submitted to a factorial repeated-measures analysis of variance (ANOVA) using the 2V program (BMDP Statistical Software; SPSS, Chicago) with the following dependent measures: (a) the number of sessions required to attain the first significant discrimination (FS) and the criterion in the approach and avoidance learning tasks, (b) the percentage of trials in which a conditioned response (CR) was made in response to the CS+ and the CS−, and (c) discrimination scores calculated by subtracting the percentage of CS− trials with a CR from the percentage of CS+ trials with a CR.

Improvement scores were calculated by subtracting the discrimination score for a given session from the discrimination score from the following training session. The improvement scores reflected the change in discriminative performance from one session to the next. To compare improvement scores in the approach and avoidance tasks, we correlated the scores from the two tasks for various epochs of training.

Collection of the Neuronal Data

The neuronal records were passed from the recording electrodes to a field-effect transistor (FET) that served as a high-impedance source follower located approximately 2.5 cm from the recording sites in the brain. The FET outputs were fed into a preamplifier appropriate for unit recording (gain = 40,000, 0.5 amplitude cutoffs at 500 and 8000 Hz). The records were subjected to a second stage of active band-pass filtering (0.5 amplitude cutoffs at 600 and 8000 Hz, roll off = 18 dB/octave). The records were then fed to Schmitt triggers with voltage thresholds set to allow triggering at a mean rate of 110–190 spikes per second. With this setting, the larger spikes were sampled from each record. In addition, the band-pass filter outputs were half-wave rectified and integrated. The Schmitt trigger data provided an index of the firing frequency of the larger spikes, whereas integrated activity measured the fluctuations of the entire record, including activity below the triggering thresholds. Schmitt trigger pulses were counted and the integrator signals digitized on each trial (CS presentation) for 1.0 s, from 0.3 s before the CS onset to 0.7 s after the CS onset. A digital value was stored for each measure and electrode every 10 ms throughout the 1 s sampling interval.

Analysis of the Neuronal Data

Rabbits in the full acquisition group did not exhibit lesion-induced learning impairments. Thus, the analysis of the neuronal data was restricted to rabbits in the partial acquisition group. The neuronal data, consisting of the spike frequency or integrated activity in each of the one hundred 10-ms intervals (30 before and 70 after CS onset) were averaged across trials in each training session. Separate averages were constructed for the CS+ and CS−. The averaged scores in each of the forty 10-ms intervals following CS onset were normalized with respect to the 30 pre-CS intervals using the z-score transformation, which involves subtracting the mean value in the 30 pre-CS intervals from each of the 40 post-CS intervals and dividing the difference by the standard deviation of the pre-CS interval values. Thus, each of the 40 z scores following CS onset represented the average change of neuronal activity stated in units of pre-CS variability. Because z scores calculated in this way are sensitive to the mean and standard deviation of the baseline (pre-CS) neuronal activity, any lesion-induced change in baseline neuronal activity could affect the outcome of group comparisons. To eliminate this possibility, we submitted the baseline statistics for each brain region to ANOVAs. In no case were significant group differences found.

The z scores were submitted to a factorial repeated-measures ANOVA including factors of training session (described below), CS (CS+ and CS−), and post-CS interval (40 consecutive 10-ms recording intervals following the onset of the CS). For both tasks, the session variable had seven levels. For approach learning, the analysis included data from the pretraining session, the session of FS discrimination (i.e., the session immediately preceding the initiation of concurrent avoidance learning), and the next five approach learning sessions (CT1–CT5) that were presented concurrently with avoidance learning. For avoidance learning, the analysis included the pretraining session and the first six avoidance learning sessions (CT1–CT6). Because the rabbits were always given approach training first followed by concurrent approach and avoidance training sessions, all of the avoidance training sessions took place under concurrent training conditions. Corrections of the F tests because of violations of the sphericity assumption of the repeated-measures analysis were performed as needed, following the procedure of Huynh and Feldt (1976). Factors yielding significant F ratios were further analyzed using simple effects tests, following Winer (1962).

Histology

After the completion of training, euthanasia was administered via an overdose of sodium pentobarbital followed by transcardial perfusion with normal saline and 10% formalin. The brains were frozen and sectioned at 40 μm, and the sections were photographed while still wet (Fox & Eichman, 1959). After drying, the sections were stained with a metachromatic Nissl and myelin stain using formol thionin (Donovick, 1974). Photographs and stained sections were used to assess the lesions and to verify electrode placement. Two rabbits had incomplete transection of the fornix and were excluded from the analyses, yielding final samples of 14 control rabbits and 21 rabbits with lesions in the partial acquisition group and 10 control rabbits and 7 rabbits with lesions in the full acquisition group. As shown in Figure 1, the lesions were centered in the fibers exiting the septal pole of the hippocampus, which form the descending columns of the fornix.

Results

Partial Acquisition Group

Fornix lesions did not affect the mean number of approach training sessions needed to attain the required moderate level of approach performance (FS) prior to the concurrent phase of training (see Figure 2), $F(1, 33) = 0.04$, $p < .84$. In contrast, both approach and avoidance learning were significantly retarded during the concurrent phase of training in rabbits with lesions. The rabbits with lesions required significantly more training sessions than controls to improve from the FS session to criterial (asymptotic) performance, $F(1, 33) = 5.27$, $p < .05$. Five of the 21 rabbits with lesions did not attain the approach learning criterion within the allotted 20 concurrent approach training sessions. None of the control rabbits failed to attain the approach learning criterion. The rabbits with lesions also required significantly more training sessions than controls to reach the criterion of avoidance learning, $F(1, 33) = 6.23$, $p < .05$. No rabbits failed to attain the avoidance learning criterion.

The percentage of trials in which CRs were performed in response to the CS+ and the CS− is shown in Figure 3. A lesion-induced impairment in avoidance learning was suggested by an interaction of the group, training stage and stimulus factors, which approached significance in the partial acquisition group, $F(6, 204) = 2.14$, $p < .07$. Individual comparisons showed that (a) the CR percentage performed in response to the CS+ was signifi-
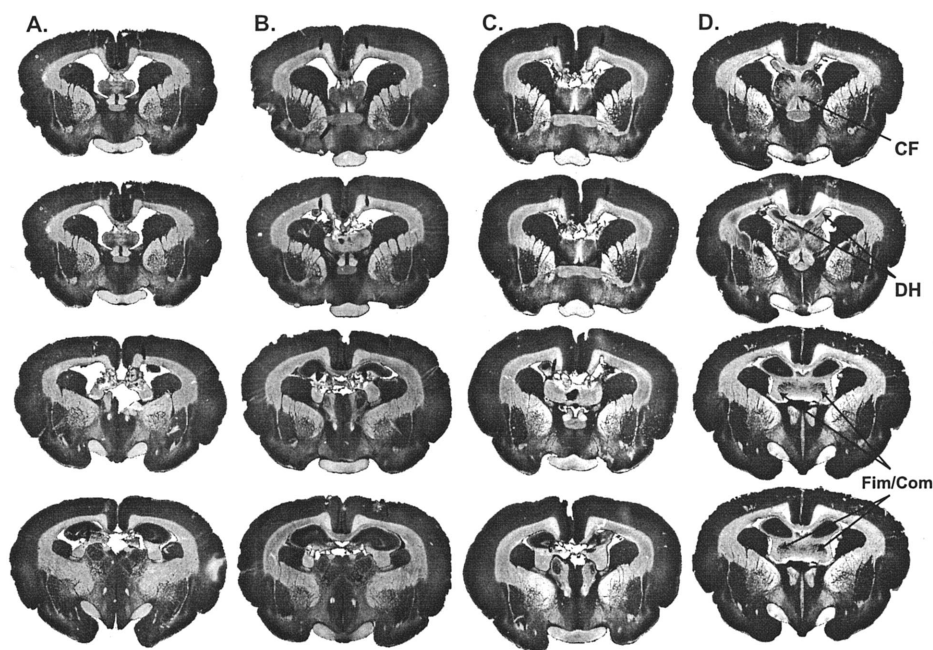

Figure 1. Photographs of coronal sections from three representative rabbits with fornix lesions (Columns A, B, and C). Equivalent sections from a control rabbit are shown in Column D. The descending columns of the fornix (CF), the anterior dorsal hippocampus (DH), and the fimbria and ventral hippocampal commissure (Fim/Com) are shown. Tracks from recording probes are visible in some of the sections.
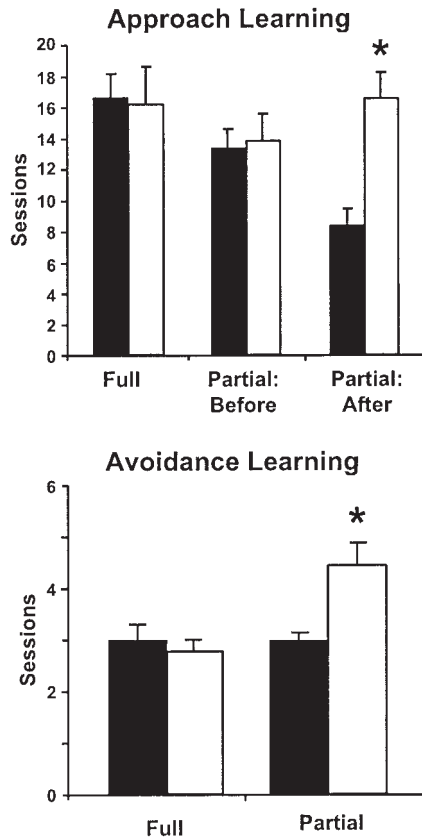
Approach Learning

Avoidance Learning

Figure 2. Average (± *SE*) number of sessions required for attainment of the discriminative approach criteria (upper plot) and avoidance criteria (lower plot) for control rabbits (solid bars) and rabbits with lesions (open bars). The data of rabbits in the full acquisition group (Full), which were trained to a criterion that yielded asymptotic performance, are shown on the left of each plot. Rabbits in the partial acquisition group were trained to a moderate level of approach performance before concurrent training (Partial: Before). Continuing approach training was given concurrently with avoidance training until the rabbits attained criteria indicating asymptotic performance in both tasks. The number of sessions required to reach these criteria are shown for approach (Partial: After) and avoidance learning (Partial). * *p* < .05.

cantly greater in controls than in rabbits with lesions during concurrent training session CT4 (*p* < .05) and (b) the CR percentage in controls in response to the CS− declined significantly during concurrent training sessions CT4, CT5, and CT6 compared with CT1 (all *p*s < .05), whereas no significant decline in CR percentage to the CS− occurred during these sessions in rabbits with lesions.

Analysis of CR performance during discriminative approach learning also indicated a learning impairment in rabbits with lesions, as indicated by a significant interaction of the group, training stage, and stimulus factors, *F*(2, 66) = 4.44, *p* < .05 (see Figure 3). Because the rabbits approached the drinking spout on CS+ trials, at the outset of training, discriminative approach learning consisted primarily of learning to omit responses to the CS− (Smith, Freeman, Nicholson, & Gabriel, 2002). Consistent with this, the percentage of responses to the CS− of control rabbits

declined significantly during concurrent training sessions CT2– CT6, relative to the CR percentage in the first concurrent training session (CT1; *p* < .05 all comparisons). In contrast, no significant decline in responding to the CS− occurred in rabbits with lesions during these sessions. Thus, as during avoidance learning, the rabbits with lesions failed to show a progressive increase in behavioral discrimination in terms of reduced responding to the CS− during concurrent training.

Discrimination scores, obtained by subtracting the percentage of CS− trials in which a CR was performed from the percentage of CS+ trials in which a CR was performed, were calculated for consecutive training sessions preceding and following the onset of concurrent training. The interaction of the training stage and group factors in the analysis of the discrimination scores for approach learning (see Figure 4) approached significance, *F*(10, 330) = 2.29, *p* < .06. Individual comparisons showed that controls and rabbits with lesions exhibited significant discrimination in the approach task before concurrent training was initiated. However,
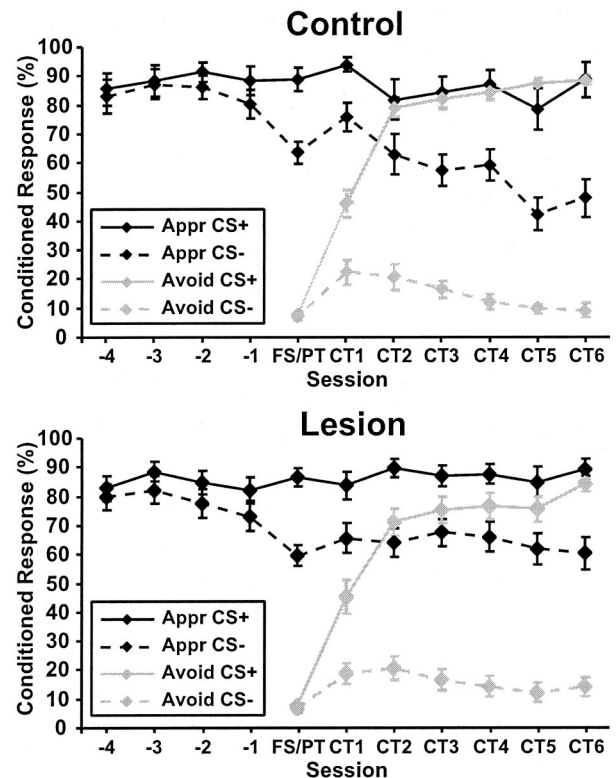

Figure 3. Average (± *SE*) percentage of trials in which a conditioned response was made in response to the CS+ (solid lines) and the CS− (dashed lines) for rabbits in the partial acquisition group. Data are shown for approach (Appr; black) and avoidance learning (Avoid; gray) in control rabbits (upper plot) and rabbits with lesions (lower plot). Approach training data are shown for the four sessions preceding the initiation of concurrent training (−4 through −1), the session of first significant discrimination (FS), and the first six concurrent approach training sessions (CT1–CT6). Concurrent avoidance training sessions were introduced after the session of FS. Avoidance training data are shown for pretraining (PT) and the first six concurrent avoidance training sessions (CT1–CT6). CS = conditioned stimulus.

Approach Learning: Partial Acquisition Group
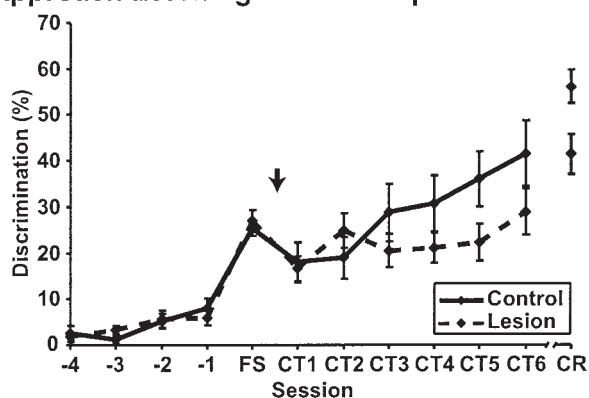
Avoidance Learning: Partial Acquisition Group
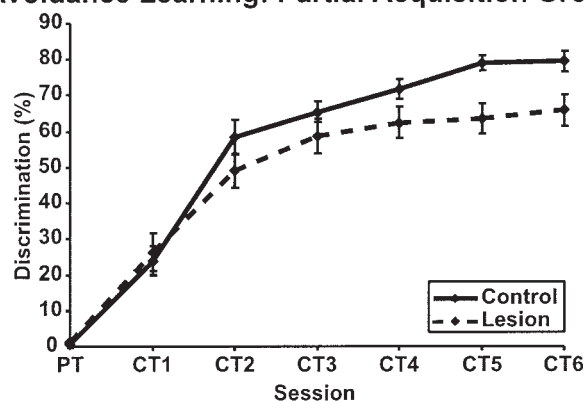
Figure 4. Average (± *SE*) discrimination scores during concurrent approach (upper plot) and avoidance (lower plot) training for rabbits in the partial acquisition group. In the approach plot, data are shown for the four sessions preceding the session of first significant behavioral discrimination (FS; −4 through −1), the session of FS, and the first six concurrent approach training sessions (CT1–CT6). Data are also shown for the criterial session (CR), which occurred several sessions after CT6 in many subjects. Approach performance declined when concurrent training was initiated following FS, indicated by an arrow. In the avoidance plot, data are shown for pretraining (PT) and the first six concurrent avoidance training sessions (CT1–CT6). Because avoidance training was initiated after approach training had begun, all avoidance training sessions were given under concurrent training conditions.

control rabbits continued to improve after concurrent training was introduced, whereas rabbits with lesions showed no improvement for several training sessions.

Discriminative performance declined in the approach task when concurrent training was initiated, that is, performance dropped significantly from the FS session in the approach task to the first concurrent training session (CT1; $p < .05$). After CT1, however, controls resumed their improvement. Discrimination scores for concurrent approach training sessions CT5 and CT6 were significantly greater than for the FS session ($p < .05$). In contrast, the rabbits with lesions showed no improvement during the same training sessions. Furthermore, the discrimination scores of controls in the approach task were significantly greater than those of rabbits with lesions during concurrent training sessions CT5 and CT6 ($p < .05$).

The discriminative performance in the approach task of rabbits with lesions did eventually improve beyond the level reached before concurrent training. This improvement was noted during the session of criterion attainment ($p < .05$). Nevertheless, the discriminative performance of the rabbits with lesions remained significantly below that of controls ($p < .05$).

The analysis of discrimination scores for avoidance learning showed that during concurrent avoidance learning, rabbits with lesions exhibited reduced discrimination, during asymptotic performance, relative to controls (see Figure 4). This was indicated by a significant interaction of the group and training stage factors, $F(6, 204) = 2.27$, $p < .05$. Individual comparisons indicated that the discrimination scores of control rabbits exceeded significantly those of rabbits with lesions in concurrent training sessions CT5 and CT6 ($p < .05$ in both instances).

Full Acquisition Group

Rabbits in the full acquisition group were given discriminative approach training until they attained a strict criterion that yielded asymptotic performance before concurrent training of the avoidance task began. Thus, unlike rabbits in the partial acquisition group, rabbits in the full acquisition group acquired the approach and avoidance behaviors one at a time, first the approach task (before concurrent training) and then the avoidance task (during concurrent training).

In contrast to the partial acquisition group, the full acquisition lesion and control groups did not differ in the number of sessions required to attain the criterion in either task (see Figure 2): approach task, $F(1, 15) = 0.03$, $p < .87$; avoidance task, $F(1, 12) = 0.25$, $p < .64$. No effects of the lesions were found in the percentage of trials in which an approach or avoidance CR was made in response to the CS+ and CS− before or during concurrent training. For both tasks, the interactions of the training stage, stimulus, and group factors were not significant: approach task, $F(8, 104) = 0.18$, $p < .95$; avoidance task, $F(4, 40) = 1.31$, $p < .29$.

The analysis of discrimination scores (see Figure 5) showed no significant effects of the lesions on concurrent performance in the discriminative approach task. Remarkably, rabbits with lesions exhibited significantly greater discrimination scores than controls during discriminative avoidance learning, as indicated by the main effect of the group factor, $F(1, 10) = 7.90$, $p < .05$. This result, discussed below, is consistent with previous findings of enhanced learning in subjects with hippocampal formation lesions (Isaacson, Douglas, & Moore, 1961; Kang & Gabriel, 1998; Packard, Hirsh, & White, 1989).

Approach and Avoidance: Correlations in the Partial Acquisition Group During Concurrent Acquisition

The finding that concurrent learning was impaired in the partial acquisition group with lesions may have been due to greater intertask interference during concurrent learning than during single-task learning. If such interference occurred, then performance improvement in one of the concurrent tasks should have been associated with a lack of improvement or deterioration in the other task in rabbits with lesions. To assess this possibility, we correlated session-to-session improvement scores during the partial acquisition group's concurrent approach learning with their

Approach Learning: Full Acquisition Group
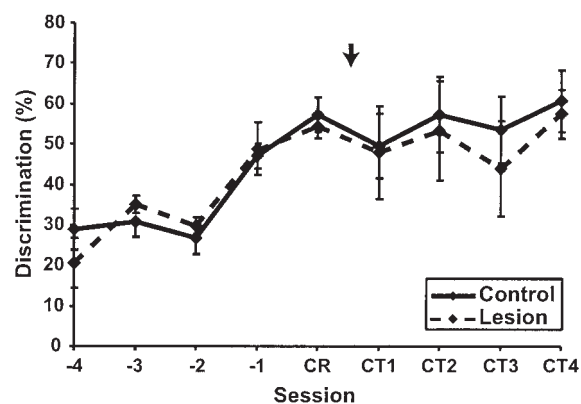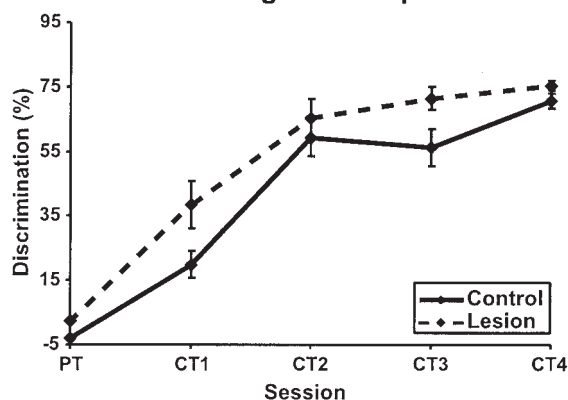

Avoidance Learning: Full Acquisition Group

Figure 5. Average (± *SE*) discrimination scores during concurrent approach (upper plot) and avoidance (lower plot) training of rabbits in the full acquisition group. Approach training data are shown for the four sessions preceding the criterial session (CR; −4 through −1), the CR, and the first four concurrent approach training sessions (CT1–CT4). Concurrent avoidance training sessions were introduced after CR, indicated by an arrow. Avoidance training data are shown for pretraining (PT) and the first four concurrent avoidance training sessions (CT1–CT4). Because avoidance training was initiated after approach training had begun, all avoidance training sessions were given under concurrent training conditions.

comparable improvement scores during avoidance learning. The improvement scores were obtained by subtracting the discrimination score of each rabbit in a given concurrent training session from the score obtained in the following concurrent training session in the same task. Larger differences indicated greater between-session improvement. The rabbits frequently reached asymptotic performance in one of the tasks (approach or avoidance) within a few sessions of the onset of concurrent training. At asymptote, the rabbits' performance ceased to improve and the corresponding improvement scores were near zero. Thus, analysis of the improvement scores was limited to the first four concurrent training sessions.

Improvement scores for each task were computed and correlated. For example, scores reflecting the improvement from the first to the second concurrent training session in the approach task were correlated with comparable scores in the avoidance task.

Similarly, scores reflecting the improvement from the second to the third sessions, the third to the fourth sessions, and so on through the first four concurrent approach and avoidance training sessions were correlated. These correlations reflected the degree to which improvement in one task was associated with improvements (or decrements) in the other task. In addition, the improvement scores for the initial avoidance training stages (first and second avoidance training sessions) were correlated with the average improvement scores for the first four concurrent approach training sessions. These correlations reflected the degree to which rapid improvements early in avoidance training were associated with improvements (or decrements) persisting several sessions into concurrent approach training. The converse correlation, improvement during early approach sessions with the first four avoidance sessions, could not be computed because rabbits learned the avoidance task very rapidly, thus curtailing in many rabbits the range of sessions in which improvement could be measured.

In rabbits with lesions, large improvement scores in one task were associated with small improvements (or decrements) in discriminative performance in the other task (see Figure 6). Scores reflecting the improvement (or decrement) from the first to the second concurrent training sessions in the approach and avoidance training of rabbits with lesions showed a significant negative correlation ($r = -.52$, $p < .05$). This correlation was not present in controls ($r = -.04$, $p < .90$). Indeed, the improvement in the avoidance task was negatively correlated with improvement throughout the early sessions of approach learning in rabbits with lesions. Scores reflecting the improvement (or decrement) from the first to the second concurrent avoidance training session were negatively correlated with the average of the improvement scores for the first four concurrent approach training sessions ($r = -.56$, $p < .01$). This correlation was not present in controls ($r = -.13$, $p < .69$). The remaining correlations were not significant.

Discriminative Training-Induced Neuronal Activity

During discriminative instrumental learning, neurons throughout the cingulothalamic circuit develop discriminative responses, that is, they become more responsive to the CS+ than to the CS− (for a review, see Gabriel, 1993). These discriminative responses have been proposed to encode the associative significance of the CSs, and they are independent of the context-related pattern, which has been proposed to be involved in context-based retrieval of the task-appropriate response (Gabriel et al., 1991). In the present study and others, damage to the hippocampus or related structures did not disrupt the significance coding (discriminative) function of cingulothalamic neurons (Freeman et al., 1997; Gabriel, Sparenborg, & Stolar, 1987; Kang & Gabriel, 1998). As in Freeman et al.'s (1997) study, the rabbits with fornix lesions in the present study exhibited discriminative neuronal responses in both tasks, despite the fact that the predictive value of the tones was reversed (i.e., the approach CS+ was the avoidance CS−, and the avoidance CS+ was the approach CS−). Thus, the neurons reversed their discriminative responses to the same conditional stimuli on alternating days, and hippocampal input was not needed for this relatively complex significance coding function.
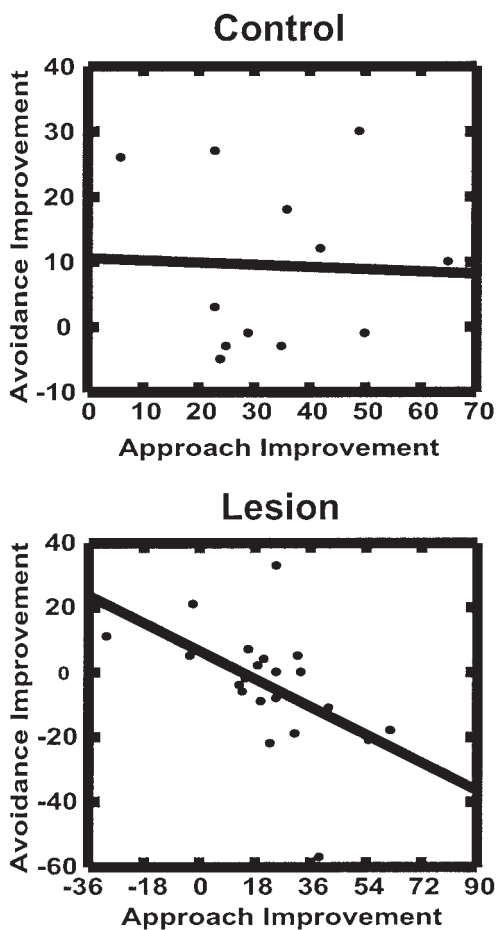
Control

Lesion

Figure 6. Improvement scores (%) reflecting the change in discriminative performance from one session to the next are plotted for control rabbits (upper plot) and rabbits with lesions (lower plot). The plotted improvement scores reflect the change in discriminative performance from the first to the second concurrent training sessions in each task. These scores showed significant negative correlation in lesion but not control subjects (see Results section).

Context-Related Pattern of Cingulothalamic Neuronal Activity

As explained in the introduction, the context-related pattern of neuronal activity arises from the fact that each cingulothalamic region (layer, nucleus) exhibits a peak of training-induced neuronal activity in a particular stage of behavioral acquisition (Gabriel et al., 1991). Neuronal response magnitudes initially increase over training sessions, but the response magnitudes decline with continued training. The inflection point when the increase stops and the decrease begins is different for the different areas. Thus, at any given stage of training there is a unique distribution, or topographic pattern, of neuronal excitation across the various regions of the cingulothalamic circuitry. The topographic patterns are context specific insofar as they differ across the approach and avoidance tasks (Freeman et al., 1996a). A lesion-induced disruption of the topographic patterns under the same conditions that disrupted context-specific learning (i.e., the partial acquisition

condition) would support the hypothesis that the topographic patterns promote the disambiguation of similar learning contexts that require different behavioral responses.

The analysis of the neuronal data was aimed at determining whether these context-related patterns are a product of hippocampal input to the cingulothalamic circuitry. If so, the expected rise and fall of the neuronal response should be lost or degraded in rabbits with fornix lesions. If the rise and fall of the response is lost or degraded in multiple areas over several concurrent approach and avoidance training sessions, then it follows that the context-related pattern is also lost or degraded. Thus, our testing strategy involved the detection during the concurrent phase of training of (a) a significant increase in the neuronal response during the initial training sessions in each task and (b) a significant drop in the response magnitude from the session of the peak response to a later session. Previous studies have shown that hippocampal or subicular damage eliminated the falling phase of the neuronal response during training in several cingulothalamic areas (Gabriel et al., 1987; Kang & Gabriel, 1998).

Anterior Ventral Thalamic Neuronal Activity

Neuronal data recorded in the parvocellular division of the anterior ventral thalamic nucleus suggested that the lesions disrupted the rise and fall of neuronal response magnitude during concurrent approach learning (see Figure 7). Controls ($n = 7$) exhibited the expected training-related rise and subsequent fall in neuronal response magnitudes, whereas the rabbits with lesions ($n = 17$) did not: interaction of the stage, CS, 10-ms post-CS interval, and group factors for integrated activity, $F(174, 3828) = 1.79$, $p < .05$. Individual comparisons indicated that in controls, the neuronal responses to the CS+ were significantly increased during concurrent training session CT3 relative to the pretraining (1 interval) and FS sessions (3 intervals; all $ps < .05$). The neuronal response declined during concurrent training session CT5 relative to FS (2 intervals), CT1 (8 intervals), and CT3 (5 intervals). In contrast, the average neuronal response of rabbits with lesions was significantly increased during CT2 (10 intervals), CT3 (18 intervals), CT4 (20 intervals), and CT5 (13 intervals), all relative to pretraining (all $ps < .05$). However, in replication of previous studies with hippocampal formation lesions (Gabriel et al., 1987; Kang & Gabriel, 1998), there was no fall in the neuronal response magnitude during later training sessions in the rabbits with lesions. The absence of a rise followed by a fall of these anterior thalamic responses is consistent with the hypothesis that context-related pattern was disrupted in the rabbits with lesions.

Anterior Dorsal Thalamic Neuronal Activity

The data recorded in the anterior dorsal thalamus during concurrent avoidance learning also indicated a disruption of the context-related pattern (see Figure 8). Analysis of the data indicated that control rabbits developed the expected rise and subsequent fall in the magnitude of neuronal responses, but rabbits with lesions did not: interaction of the stage, CS, and group factors for spike frequency, $F(6, 102) = 2.40$, $p < .05$. Individual comparisons indicated that the neuronal responses of control rabbits increased in magnitude during the first concurrent training session (CT1) relative to pretraining ($p < .05$), and they continued to
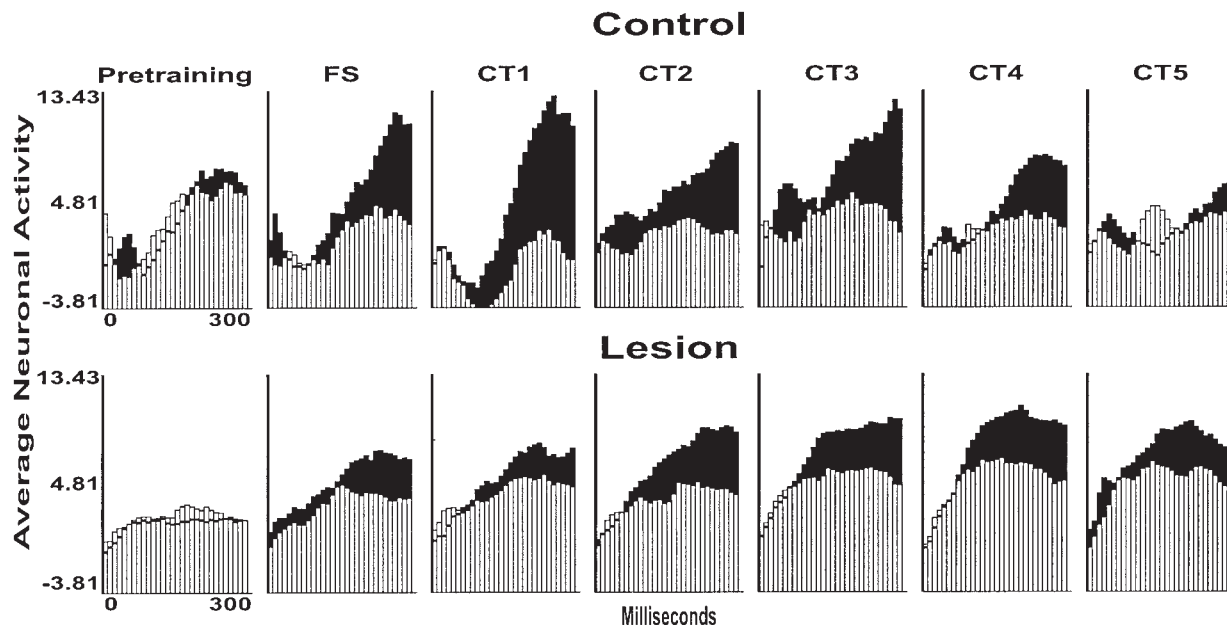
Figure 7. Average integrated unit activity recorded in the parvocellular division of the anterior ventral thalamic nucleus during discriminative approach learning. The data, in the form of z scores normalized with respect to a 300-ms pre-conditioned stimulus (CS) baseline, are shown in 30 consecutive 10-ms intervals following the onset of the CS+ (solid) and CS− (open). Data of control rabbits (top row) and rabbits with lesions (bottom row) are shown for pretraining with explicitly unpaired tone and reinforcement presentations, the session of first significant behavioral discrimination (FS), and the next five concurrent approach training sessions (CT1–CT5).

increase until they reached peak magnitude during session CT3, relative to CT1 and pretraining (all $ps < .05$). Although the response magnitudes did not show a significant decline relative to session CT3, they were not significantly increased during sessions CT4–CT6, relative to CT1 (all $ps > .05$). In contrast, rabbits with lesions exhibited increased responses throughout concurrent training (CT1–CT6) relative to pretraining (all $ps < .05$).

Posterior Cingulate Cortical Neuronal Activity: Layer 4

Neuronal data recorded in Layer 4 of the posterior cingulate cortex during concurrent avoidance learning are shown in Figure 9. Control rabbits exhibited the expected increase and subsequent decline in the magnitude of neuronal responses, but rabbits with lesions did not, as indicated by a significant interaction of the stage and group factors for integrated activity, $F(6, 54) = 3.46, p < .01$. Individual comparisons indicated that control rabbits developed increased neuronal responses during the FS session and concurrent training session CT1 relative to pretraining, followed by decreased responses during sessions CT4 and CT5 relative to CT1 and CT2 (all $ps < .05$). The neuronal responses of rabbits with lesions did not exhibit a significant change in magnitude across training sessions (all $ps > .05$).

Posterior Cingulate Cortical Neuronal Activity: Layer 5

Analysis of the data recorded in Layer 5 of the posterior cingulate cortex during discriminative avoidance learning suggested a disruption of the context-related pattern in rabbits with lesions (see Figure 10). The interaction of the stage and group factors ap-

proached significance for spike frequency (control $n = 11$, lesion $n = 16$), $F(6, 150) = 2.16, p < .08$. Individual comparisons indicated that control rabbits developed increased neuronal responses during concurrent training sessions CT2 through CT4, followed by decreased responses during CT5 (relative to CT1; $p < .05$) and CT6 (relative to CT1–CT4; all $ps < .05$). Rabbits with lesions developed increased responses during CT2, CT4, and CT5 relative to pretraining ($p < .05$), but they did not exhibit a significant decline in the responses.

Other Cingulothalamic Brain Regions

A significant rise followed by a decline in response magnitude, indicative of the context-related pattern, was not found in all of the cingulothalamic regions examined, particularly during discriminative approach learning. The neuronal response magnitudes in several brain regions during approach learning were quite small, in both lesion and control rabbits, relative to the responses seen in the current and previous studies of the context-related pattern during avoidance learning (Gabriel et al., 1991). For example, anterior dorsal thalamic neuronal responses averaged 3.4 z scores above the mean during approach learning, compared with 20.8 during avoidance learning. Neuronal responses in the posterior cingulate cortex (Layers 4 and 5) were similarly dampened. Responses of this magnitude cannot exhibit the large changes needed to observe the context-related pattern, and the analysis of these data did not reveal any significant changes in response magnitudes across training sessions. The reduced response magnitudes observed in the approach task were likely due to the lower motivational strength of
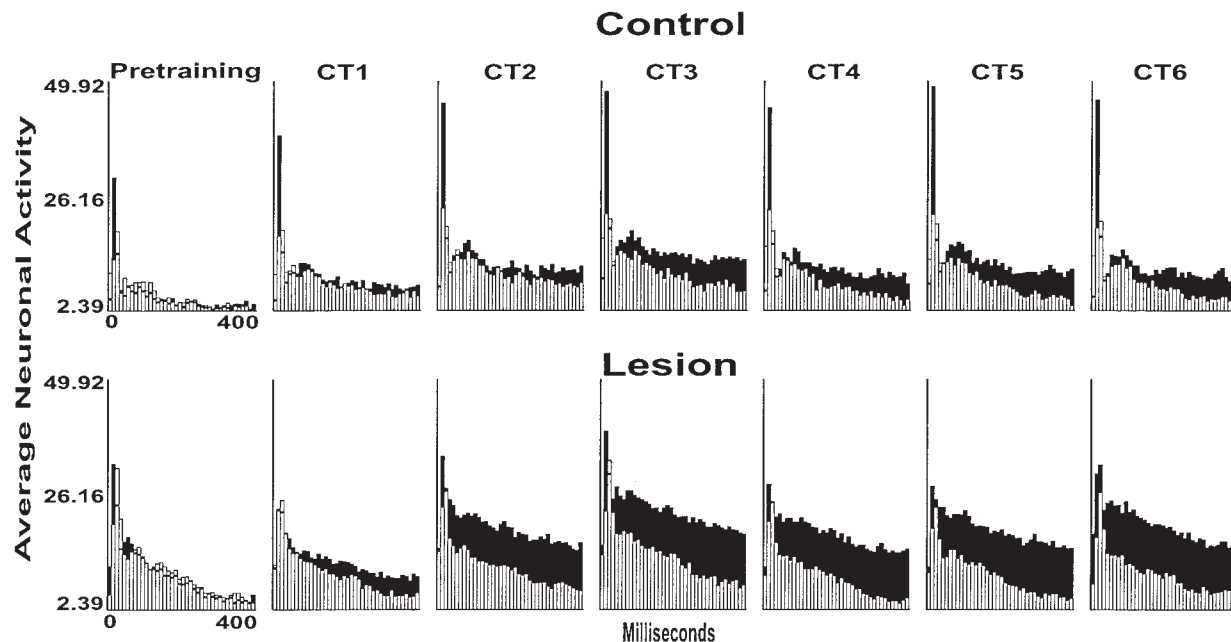
Figure 8. Average spike frequency recorded in the anterior dorsal thalamic nucleus during discriminative avoidance learning. The data, in the form of *z* scores normalized with respect to a 300-ms pre-conditioned stimulus (CS) baseline, are shown in 40 consecutive 10-ms intervals following the onset of the CS+ (solid) and CS− (open). Data of control rabbits (top row) and rabbits with lesions (bottom row) are shown for pretraining with explicitly unpaired tone and reinforcement presentations and the first six concurrent avoidance training sessions (CT1–CT6).

the water reward, relative to the footshock used in the avoidance task (Smith, Monteverde, Schwartz, Freeman, & Gabriel, 2001). Neuronal responses in the magnocellular division of the anterior ventral thalamic nucleus also did not exhibit the context-related pattern. This was likely due to the relatively small number of records obtained for this brain region.

Discussion

Summary of Results and Conclusions

Fornix lesions disrupted the context-related pattern of cingulothalamic neuronal activity, and they impaired concurrent acquisition of discriminative instrumental approach and avoidance responses. These results are consistent with the hypothesis that the context-related pattern serves as a neural code that can mediate context-appropriate behavior in learning situations, in which the discrete cues, per se, such as CSs, are not clearly indicative of the required response. Moreover, the results confirm previous findings that the context-related pattern expressed in the cingulothalamic circuit depends on hippocampal input. Given additional evidence of a role of the hippocampus in processing of contextual information (Bouton, 1990; Gabriel et al., 1991; Hayman, Chakraborty, Anderson, & Jeffery, 2003; Hirsh, 1974; Kim & Fanselow, 1992; Phillips & LeDoux, 1992; Winocur, Rawlins, & Gray, 1987) as well as findings indicating that hippocampal neurons exhibit unique response patterns in different environments (Kubie & Rank, 1983), we interpret the current findings as indicating that the hippocampus integrates all of the information that defines a given

learning context and uses that information to generate a neural context code. This code is activated by extant contextual stimuli whenever subjects reenter a familiar learning situation. On the basis of the hippocampal code, hippocampal efferents modulate neuronal responses in the cingulothalmic circuit to generate a context-related pattern of cue-elicited neuronal activity. The context-related pattern, which occurs very early in the time series following CS onset, enhances the retrieval of context-appropriate behavior. Several important features of the data and theoretical account are elaborated in the following paragraphs.

Interference and Memory Retrieval

The mechanism under consideration would confer special advantages in learning situations characterized by high interference, such as in the present experiment, in which the same cues call forth different discriminative behaviors depending on the learning context. This situation in particular places a high premium on subjects' ability to use contextual information to disambiguate different learning situations and to retrieve context-appropriate behavior.

There is a long tradition in experimental psychology that identifies proactive and retroactive interference as an extremely important factor underlying failures of the memory system in humans and animals (reviewed by Bjork, 2003). Here, we propose that cooperative hippocampal and cingulothalamic functional interactions represent key neurologic adaptations to the problem of interference.

During concurrent training in this study, the same acoustic stimuli governed two behavioral discriminations administered in
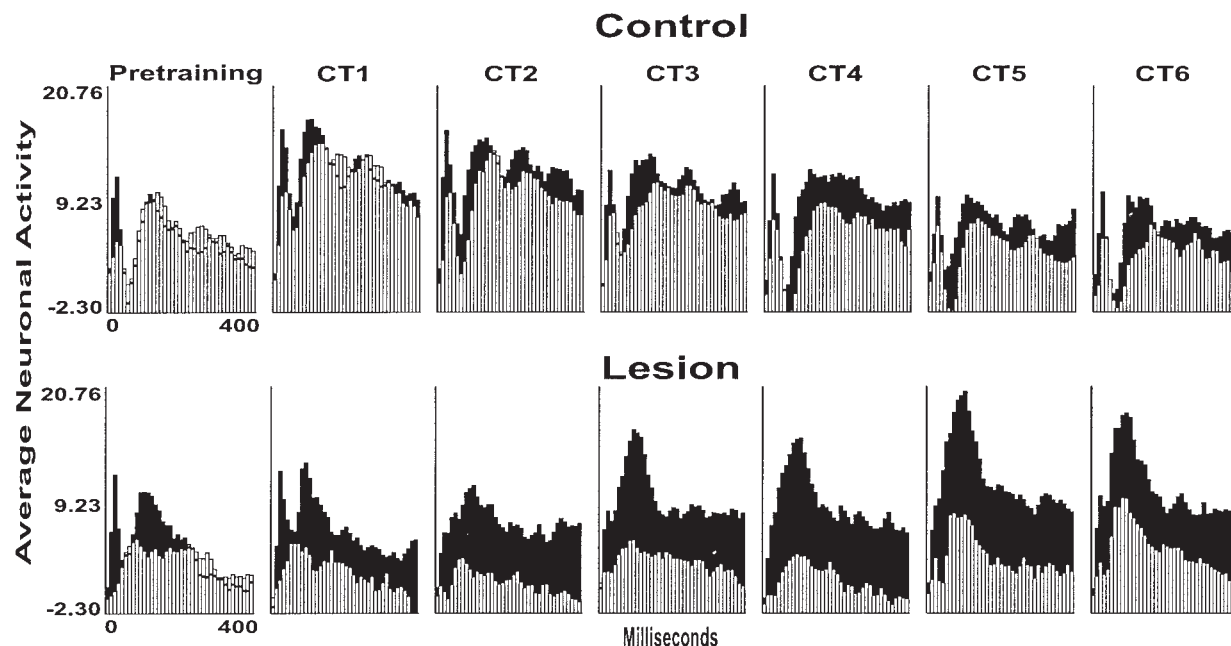
Figure 9. Average integrated unit activity recorded in Layer 4 of the posterior cingulate cortex during discriminative avoidance learning. The data, in the form of z scores normalized with respect to a 300-ms pre-conditioned stimulus (CS) baseline, are shown in 40 consecutive 10-ms intervals following the onset of the CS+ (solid) and CS− (open). Data of control rabbits (top row) and rabbits with lesions (bottom row) are shown for pretraining with explicitly unpaired tone and reinforcement presentations and the first six concurrent avoidance training sessions (CT1–CT6).

different training contexts. The status of each stimulus as CS+ or CS− was reversed between the tasks for each rabbit. Thus, for example, in the avoidance training context, a given tone elicited a locomotory response whereas the same tone elicited the withholding of a head-extension response in the approach training context. Similarly, the complementary tone elicited withholding of a locomotory response in the avoidance context and head extension in the approach context. This situation likely engendered interference insofar as the behavioral response to a given CS acquired in one of the contexts would likely be elicited wholly or in part by the same CS in the other context, thus leading to a deficit in retrieval of context-appropriate behavior. It is important to note that subjects can use contextual information to overcome the deleterious effects of interference. Contextual information allows subjects to behave conditionally by producing one behavior or the other in response to the same CS, depending on the operative context. Unable to make full use of contextual information for their concurrent acquisition, the rabbits given fornix lesions that degraded their context-specific patterns were significantly impaired during the concurrent phase of their training. Consistent with this account, performance in the low interference condition of single-task acquisition and performance of a well-learned discrimination were not affected by the lesions.

Specificity of the Impairment to the Acquisition Phase of Concurrent Learning

The lesion-induced impairment occurred only during concurrent training after partial acquisition of the single discriminative approach response. Thus, the impairment was limited to concurrent

acquisition. No impairment was seen in rabbits given concurrent training after the discriminative approach response had been learned fully to asymptotic levels. Also, no lesion-related impairments were found during acquisition of the behaviors individually, for example, during the initial phase of approach learning prior to concurrent training in this study or during discriminative avoidance learning in rabbits with hippocampal, entorhinal cortical, or subicular complex lesions in previous studies (Freeman et al., 1997; Gabriel et al., 1987; Kang & Gabriel, 1998).

Correlational analysis showed that the rabbits with lesions in the partial acquisition group were unable to exhibit concurrent session-to-session improvement in both tasks during acquisition, whereas such learning did occur in controls. In rabbits with fornix lesions, improvement in one of the tasks was associated with an absence of improvement or deterioration in the other task. Because all of the rabbits eventually learned both tasks, these results suggested that even though the tasks were presented concurrently, the two behaviors were acquired in series in the rabbits with lesions. Also consistent with this idea is the finding that the lesions did not impair concurrent performance when one task was fully learned before concurrent training was introduced.

The observation that the lesion-induced impairment in our study was restricted to the acquisition phase of concurrent learning is consistent with previous findings that the context-related pattern is expressed only during acquisition in a given task and diminishes and disappears in highly trained subjects (Freeman et al., 1996a; Gabriel, 1993). These results are further corroborated by findings that show that lesions of the cingulothalamic circuit, which block
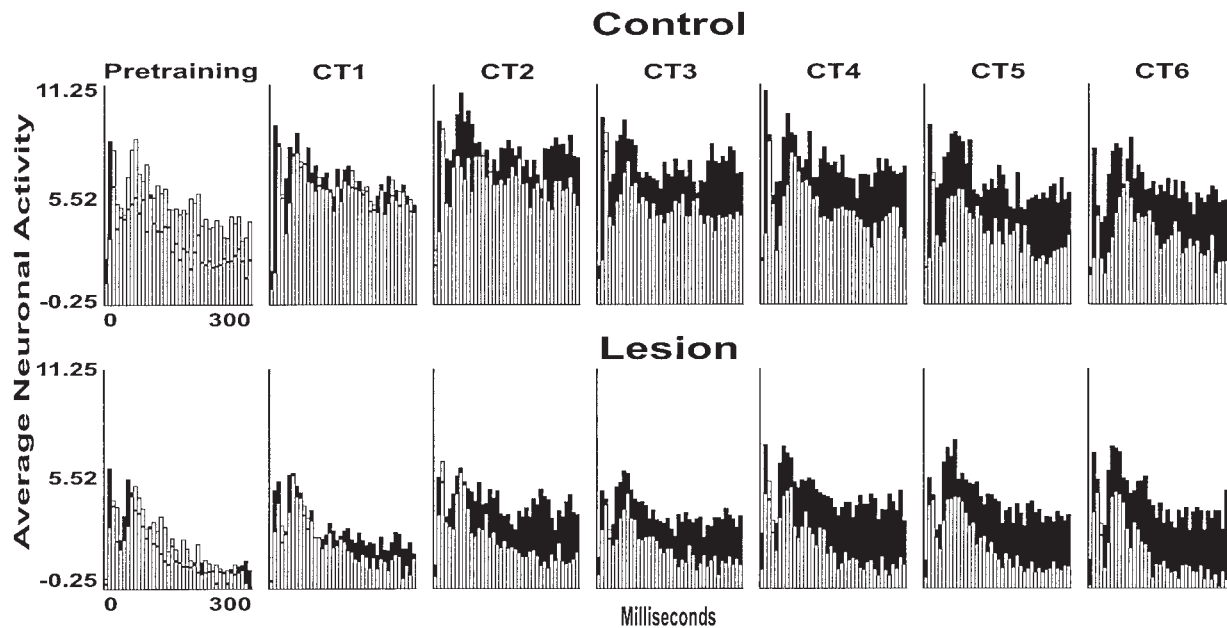
Figure 10. Average spike frequency recorded in Layer 5 of the posterior cingulate cortex during discriminative avoidance learning. The data, in the form of *z* scores normalized with respect to a 300-ms pre-conditioned stimulus (CS) baseline, are shown in 30 consecutive 10-ms intervals following the onset of the CS+ (solid) and CS− (open). Data of control rabbits (top row) and rabbits with lesions (bottom row) are shown for pretraining with explicitly unpaired tone and reinforcement presentations and the first six concurrent avoidance training sessions (CT1–CT6).

acquisition of discriminative avoidance behavior, do not impair retention of this behavior when they are administered after substantial overtraining (Hart et al., 1997). These results indicate that the cingulothalamic circuitry becomes irrelevant to discriminative performance in highly overtrained subjects. The specificity of the effects of the fornix lesions to the acquisition phase of concurrent learning is in accord with studies of other hippocampus-dependent forms of learning. For example, hippocampal *N*-methyl-D-aspartate receptor blockade impaired radial maze acquisition but not performance in previously trained subjects (Shapiro & O'Connor, 1990). These findings and the findings of the present studies thus suggest that the advantage conferred by the hippocampal context code is transient and limited to learning situations characterized by ample mnemonic interference. Presumably, learning an individual task can be mediated entirely by extrahippocampal circuitry. Moreover, considerable evidence indicates that substantial training, or the passage of time following training, promotes neural coding of habits and memories within nonhippocampal and noncingulothalamic circuitries (Freeman & Gabriel, 1999; Hart, Poremba, & Gabriel, 1997; Squire & Zola-Morgan, 1991; Teyler & DiScenna, 1986). Consistent with this idea, Gisquet-Verrier and Schenk (1994) reported that contextual cues significantly facilitated the retrieval of a previously learned avoidance response in rats given hippocampal lesions before training and tested 21 days after initial acquisition.

A word of caution is needed regarding the effects of the fornix lesions used in this study. Our intent was to test the specific hypothesis that information flow from the hippocampus to the cingulothalamic circuitry, mediated by the fornix, is involved in

supporting performance in high interference concurrent discrimination learning. Our finding that the fornix lesions altered cingulothalamic patterns and concurrent learning as predicted vindicates this strategy. However, other circuitry could also be involved. For example, fornix lesions do not disrupt flow from the hippocampus via the subicular complex to the posterior cingulate cortex. Moreover, the fornix lesions could alter processing in other areas of fiber termination (e.g., septum, hypothalamus). Additional convergent studies using different approaches to disconnection are needed to address this issue.

Relationships to Other Accounts

Pattern separation. The notion that hippocampal processes engender patterning in other brain areas that allow contextual information to be used in the service of mnemonic retrieval has much in common with theories that attribute to the hippocampus a prime role in pattern separation (Gilbert, Kesner, & Lee, 2001; McClelland, McNaughton, & O'Reilly, 1995; Rolls, 1996). *Pattern separation* refers to a hypothetical process whereby well-differentiated neural representations are engendered in response to similar and thus confusable retrieval cues to foster retrieval of context-appropriate behavior. In the present study, rabbits with fornix lesions were particularly susceptible to interference due to the use of the same CSs in two concurrently trained discrimination tasks. Thus, the degraded context-related pattern and the associated interference seen in rabbits with lesions are suggestive of a failure of pattern separation.

The hippocampus and context. The results as interpreted above are concordant with the view that the hippocampus is a functional module of the brain that carries out the encoding of learning situations or contexts (Gabriel, 1993; Gabriel, Foster, Orona, Saltwick, & Stanton, 1980; Gabriel & Sparenborg, 1986; Gabriel & Talk, 2001). In this view, hippocampal processes yield a neural code that identifies the multidimensional stimulus configurations that constitute particular learning contexts. All aspects of contexts are coded, including multimodal exteroceptive and interoceptive background and temporally discrete stimuli, as well as the spatial and temporal relations among these stimuli. It is proposed further that the hippocampal code is produced when subjects enter a new learning context, and it is automatically distributed to multiple functional modules of the brain, including the cingulothalamic circuitry. These modules incorporate the contextual information into their own computations during learning. On reintroduction to the learning situation, the context code is again activated and distributed, enabling the recipient modules to process the ensuing events in a context-appropriate manner.

Past work has demonstrated that cingulothalamic training-induced neuronal activity is context related and hippocampus dependent (see the introduction). We argue here that the context-related pattern is a manifestation of the hippocampal context code, which occurs in the cingulothalamic circuitry as a result of hippocampal modulation. The pattern supports the retrieval of task-appropriate behavior by minimizing between-task interference during concurrent learning.

The idea that a fundamental computation of the hippocampus involves the encoding of contextual stimuli present in a learning situation, and the relations among them, is a common theme of varied theoretical accounts of hippocampal function (e.g., Cohen & Eichenbaum, 1994; Gabriel, 1993; Gabriel et al., 1980; Gabriel et al., 1986; Mizumori et al., 2001; Rudy & Sutherland, 1995). In support of this view are many findings that demonstrate hippocampal involvement in the mnemonic coding of learning situations, places, or contexts (Leutgeb, Kjelstrup, Treves, Moser, & Moser, 2003; Markus et al., 1995; Mizumori et al., 2001; Mizumori, Ragozzino, Cooper, & Leutgeb, 1999; Morris, Garrud, Rawlins, & O'Keefe, 1982; Nadel, Willner, & Kurz, 1985; Smith, Munoz, Turner, & Mizumori, 2003; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000).

With respect to the coding of conditioning contexts, it has been shown that the strength of the association between CS and CR is diminished in proportion to the extent that the original learning context has been changed (Gabriel & Vogt, 1972). It follows that all detectable features of the context are coded and incorporated into the habit structure during conditioning. The idea that the hippocampus is essential for this coding is supported by studies that show that conditioned fear responses to contextual stimuli are abolished in subjects with hippocampal damage (Holt & Maren, 1999; Kim & Fanselow, 1992; McAlonan, Wilkinson, Robbins, & Everitt, 1995; Phillips & LeDoux, 1992, 1994; but see Gisquet-Verrier, Dutrieux, Richer, & Doyere, 1999). The implication of these findings is that any arbitrary change of the conditioning context will diminish CR retrieval. This idea is supported by studies that show that damage to the entorhinal cortex, which is closely related to the hippocampus, disrupts the exquisite sensitivity of CRs and context-related associative neuronal activity to contextual stimuli (Freeman et al., 1997).

Spatial processing. Visuospatial information is, typically, a prominent component of learning contexts. Therefore, participation of the hippocampus in the acquisition of behavior guided by visuospatial stimuli, as well as the neurophysiological phenomenon of hippocampal place coding, can be viewed as representing processes that are closely related to the hippocampal contextual processing posited here. The anterior thalamus and posterior cingulate cortex have been implicated in spatial learning, and neurons in these regions exhibit spatial and directional firing (Cho & Sharp, 2001; Harker & Whishaw, 2002; Mizumori, Miya, & Ward, 1994; Mizumori & Williams, 1993; Taube, 1995). Consistent with the present results, these results suggest that the hippocampus, anterior thalamus, and posterior cingulate cortex are parts of a highly coordinated functional circuit. This idea recently received support from studies showing highly context-specific neuronal responses throughout this circuitry during spatial learning (Smith, Kolarick, & Mizumori, 2002; Smith et al., 2003). Moreover, hippocampal–anterior thalamic interactions have been implicated in episodic memory (i.e., memory for events that occurred in a particular spatiotemporal context; Aggleton & Brown, 1999; Tulving, 1993). Consistent with this notion, the present results indicate a critical role of hippocampal–cingulothalamic interactions in linking a particular place, or context, with the events, such as conditioning contingencies, that occur therein.

Topographic patterns and behavior. It is necessary to address the notion that the cingulothalamic neuronal activity may be directly related to particular behaviors being acquired in the learning situation. It should be noted that very similar topographic patterns develop during acquisition of two highly distinct behavioral responses, the approach response of head extension and the avoidance response of locomotion. This observation argues against a direct correlation of the neuronal activity with either of these behaviors. The topograhic patterns are based on the neuronal activity from 100–300 ms after CS onset, whereas the learned behavioral response recorded in our studies have an average latency of 2,000–3,500 ms. Thus, the topographic patterns represent early stimulus processing and are not involved directly in production of behavioral CRs. This point is corroborated by studies that showed no difference in CS+ discharge on success and failure trials in the magnocellular and parvicellular divisions of the AV nucleus and four layers of Area 29c/d and 29b (Kang & Gabriel, 1991). The present account regards the early responses as giving rise to the context-specific topographic patterns of activation that promote the retrieval of context-appropriate behavior. In this view, the early response amplitudes in a particular area are not expected to predict success or failure on a particular trial. It is not the amplitude of the response per se but the patterning of amplitudes across areas that is relevant to production of the context-appropriate CR. Note, however, that about half of all recorded cingulothalamic single neurons do exhibit incremental firing rates beginning 400 ms before the behavioral CR (Kubota, Wolske, Poremba, Kang, & Gabriel, 1996). We interpret these increases as directly contributory to CR output.

Several studies have shown that learning and performance can actually be enhanced in subjects with hippocampal damage (Gabriel et al., 1987; Isaacson et al., 1961; Kang & Gabriel, 1998; Packard et al., 1989). Consistent with these results, rabbits with lesions in the full acquisition group of this study exhibited significantly enhanced behavioral responding to the CS+ (e.g., see

Figure 5). On the hypothesis espoused here, such enhancements are due to the enhancement of cingulothalamic discriminative discharges found in subjects with hippocampal formation lesions (e.g., Results, Gabriel et al., 1987; Kang & Gabriel, 1998). The enhanced discharges result from the attenuation of the topographic patterns in subjects with lesions. Thus, rather than restricted discriminative discharges in limited cingulothalamic areas, as found in controls, many of the areas exhibit the CS+/CS− discrimination, throughout training, in subjects with lesions. In other words, the benefit of the topographic activation in relation to pattern separation has a cost: reduction of the magnitude and anatomical scope of the basic neuronal discrimination in intact subjects.

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