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Posterior Cingulate Cortex and Spatial Memory: A Microlimnology Analysis

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The neurobiology of cingulate cortex is like a dog. Each of the four areas of study—anatomy, physiology, chemistry, and behavior—forms one of the dog's legs. No one notices it when we are simply sitting still, but if we get together and try to get up and run, it is clearly a three-legged dog. An understanding of the contributions of area 29 neurons to the control of behavior is only now beginning to emerge, and it is becoming clear to us that this circuitry makes a unique contribution to memory processes; one that includes, but is not limited to, the spatial domain. Our experiments over the past 10 years have shown that circuitry in area 29 exerts a powerful influence in the spatial guidance of behavior. Its contribution bears family resemblances both to posterior parietal cortex and to the hippocampal formation. On closer scrutiny there are important differences between effects of damage to area 29 and its cortical relatives. Our goals for this chapter are threefold. First, we provide a description of the deficit in spatial navigation that follows damage to area 29 in rats. Second, we compare and contrast this deficit with the effects of damage to the hippocampal formation, posterior parietal cortex, or area 24. Third, we will present new data exploring the functional relationship that area 29 has with other cortical and thalamic areas.

Behavioral Paradigm

Our first experiment involving area 29 followed logically from our prior work on the analysis of behavior of rats with damage to components of the hippocampal system, which includes the hippocampal formation, entorhinal cortex, subicular cortices, and interconnecting fiber systems. Most of the hippocampal experiments were designed to address one of two points: the nature of the mnemonic processes dependent on hippocampal circuitry or the functional anatomy of the essential circuitry for the hippocampal memory system. The most useful behavioral task in respect to both projects was the place navigation task developed by Richard Morris (1981); the use of this task was grounded firmly in prior theoretical and empirical work (O'Keefe and Nadel, 1978). In the 1980s, the task became rather popular. In 1980, the first presentation using Morris's place navigation task to examine effects of brain damage or drugs was made at the annual meeting of the Society for Neuroscience (Sutherland et al., 1980).

In the typical case, the task involves a circular pool (1.5 m diameter) of room-temperature water. The inside walls of the pool are white, and the water is rendered opaque with powdered milk or nontoxic paint. A small escape platform is placed

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somewhere in the pool; its top surface is barely covered by the opaque water. Thus, the goal is invisible and the only way that a rat can reliably swim directly to it is by learning the topographical relationship between the goal and at least some of the cues located outside the pool. Unlike many other tasks that assess spatial memory skills, this task cannot be solved by means of one of the other nonspatial mapping strategies. For example, the rat cannot reliably find the goal by means of swimming according to some sequence of movements (say, turn left 90°, swim forward 0.5 m), since each swim is started from one of the four cardinal compass points according to a random sequence. Nor can the rat be successful if it uses only one exteroceptive cue, adopting a consistent trajectory in relationship to only this particular cue; this strategy would only work if there was some local landmark associated with the goal or if the rat swam from a constant start location and could line up with some distal target that was in the same direction as the goal. The correct solution to the task requires the rat to appreciate that the meaning of each distal cue is ambiguous; that is, whether to swim toward, away from, to the left of, or in another direction depends on the cue's current relationship to at least one other cue in the situation. According to our analysis, solutions to problems of this sort require the formation of *configural associations* among events (Sutherland and Rudy, 1989). These three spatial strategies, the mapping, movement sequence, and cue guidance strategies, require that the rat use sensory and motor information in three different ways, and, importantly, they depend on different learning and memory systems. We will say little more about the nonmapping, nonconfigural strategies except to note that neither area 29 nor the hippocampal system is importantly involved.

Role of the Hippocampal System

There is now a fairly consistent experimental literature demonstrating that damage to the hippocampal system prevents animals from solving tasks that require the use of a mapping strategy (Morris et al., 1982; O'Keefe et al., 1975; Sutherland et al., 1982) but does not abolish the use of nonmapping strategies. The mapping strategy is impaired after bilateral damage to any of the components of the hippocampal system, including CA1, CA3, dentate gyrus, perforant path, entorhinal cortex, subicular cortex, and fornix (Hoesing et al., 1991; Morris et al., 1990; Sutherland and Rodriguez, 1989; Sutherland et al., 1983; Whishaw, 1987). As we will show later in this chapter, hippocampal damage impairs the use of the spatial mapping strategy even in a preoperatively familiar environment, but the magnitude of the impairment declines as the interval between initial training and damage increases. Thus, "older" spatial memories are less resistant to disruption. To summarize a large body of work by many investigators, the hippocampal contribution to spatial processing is responsible for the following:

1. It involves all of its principal anatomical subcomponents
2. It is limited to a certain type of map-based or configural-association-based spatial information
3. It is necessary for initial learning
4. It diminishes in importance, apparently, with the passage of time from initial learning.

If one considers that the hippocampal system creates and is involved in storing representations of at least recent experience in such a way that the animal can use cue *relationships* to guide its behavior, then it is reasonable to inquire about the sources of the hippocampal system's information and the route by which it is engaged in the control over behavior. Since both the initial acquisition and retention of spatial map performance requires an intact hippocampal system, then a connected anatomical region whose integrity is not necessary for acquisition and retention performance cannot be a part of the essential circuit for this mnemonic system. Without going into detail, if we apply this crude criterion to existing data

we can rule out the following subcortical areas: neostriatum, nucleus accumbens, anterior and mediodorsal thalamic areas, cerebellum, medial septal area, mamillary complex, amygdala, lateral geniculate nuclei, habenular complex, and claustrum. Likewise, we can rule out the following cortical areas: anterior cingulate area 24, all of frontal cortex including motor cortex, most of somatosensory cortex, perirhinal cortex, temporal cortex (area 41), and visual cortex (area 17). To date, we have found only two circumscribed zones outside of the hippocampal formation that may be considered essential: area 29 and, for want of a better term, posterior parietal cortex (i.e., a region between 3 and 6 mm posterior to the bregma and from the lateral border of cingulate cortex to the dorsal bank of the rhinal sulcus). As a caution, from previous experiments using aspiration lesions, one cannot rule out a contribution from fibers passing through these regions. We believe that distributed among these two regions and the hippocampal system are to be found the necessary circuitry for creating the representations of exteroceptive and movement information that form the bases for spatial mapping and other configural associations, temporary storage of these representations, transformation of these representations into output to motor circuitry, and permanent storage of this configural information. Our working hypothesis is that area 29 circuitry participates in all of these processes. We will not develop arguments supporting this position based on the wealth of new and old anatomical data as these have been presented clearly in other chapters in this volume. Instead we will present evidence from the behavior of rats with area 29 damage in spatial memory tasks.

One advantage of using the place navigation task is that data collection and analysis can proceed automatically using a microcomputer-based tracking system. On every trial of testing several measures of the rat's swim path are gathered as shown in Figure 16.1. Except under unusual conditions these measures are strongly correlated; that is, if a group of animals exhibits long swim path lengths, then escape latency and directional error will be high and the proportion of swimming in the correct quadrant will not be reliably different from 25%. Therefore, for brevity and simplicity, in the following experiments the data presentation has been limited to one measure of performance in each experiment, although across experiments the reader will have the opportunity to see that performance on all of the measures is impaired by cingulate cortex damage.

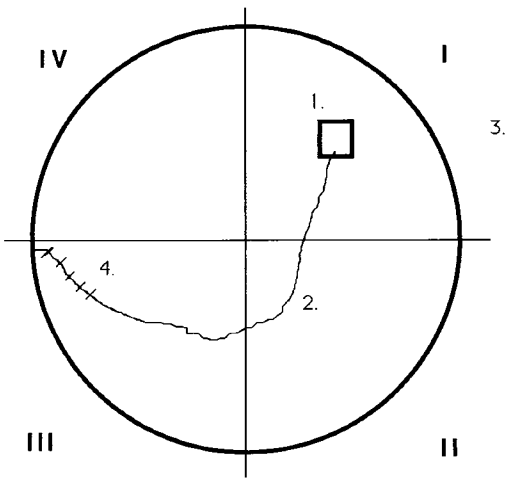

FIGURE 16.1. Measures of place navigation performance: 1, Time to find the platform; 2, swim path length; 3, proportion of path length in correct quadrant; 4, heading error at 5 points at path start. These calculations are performed automatically for each trial.

Spatial Reference Memory: Acquisition

A distinction that is made frequently in the spatial memory literature is between those tasks that depend heavily on working and those that depend on reference memory processes. A simple definition is that a task depends on spatial working memory if, in order to successfully complete a trial, the animal must remember a list of locations that were encountered earlier in the trial. For

example, in a maze task performance depends importantly on working memory if the animal must keep track of which arms it has just visited. In contrast, if the goal is always in the same location from trial to trial, independent of where the animal has been on any particular trial, then the task depends upon reference memory. Thus, in working memory spatial information has a trial-specific or episode-specific nature, whereas in reference memory spatial information is useful across trials and episodes. As we have characterized the system that includes area 29, bilateral damage should impair performance that depends on the spatial map strategy, regardless of whether the task has a working memory component. Experiments by others using mice, rats, and monkeys strongly imply that area 29 is not essential for certain kinds of nonmapping spatial reference memory. In these experiments cingulate-damaged subjects were not impaired (Markowska et al., 1988; Murray et al., 1989) or even facilitated (Meunier and Destrade, 1988) in solving spatial problems. It is important to note that in every case in which spatial learning was spared in these experiments the task clearly could be solved by adopting either a movement sequence strategy (Hebb-Williams maze, Meunier and Destrade, 1988) or a cue guidance strategy (Markowska et al., 1988; Murray et al., 1989). Furthermore, Meunier and Destrade (1988) demonstrated that their paradoxical "facilitation" of learning occurred after cingulate damage induced by the passage of nonspecific electrolytic current but did not occur if selective cytotoxin lesions were made at the same locations (see later for further discussion of this issue).

For a few readers some articles may make the relationship between cingulate circuitry and spatial memory seem less clear. But on our reading of the literature and considering our own experimental results, we believe that this functional relationship is coming into sharper focus. At this point it is worthwhile to review our (Sutherland et al., 1988) findings on acquisition of spatial reference memory in the place navigation task after bilateral aspiration of area 29. These lesions included virtually all of the zones of area 29; in some rats a posterior piece of area 29d and area 29a are spared. For all testing there is a two-week interval between surgery and behavioral testing. Training in the swimming pool is conducted typically over 5 to 10 consecutive days. Figure 16.2 presents the average time taken to find the hidden platform, which for this experiment was always positioned in the center of the southeast quadrant of the pool. For comparison, the performance of a group of rats that had selective damage to the hippocampal formation by means of multiple microinjections of colchicine into the dentate gyrus is included (for details, see Sutherland, 1985; Sutherland et al., 1983). Throughout training both lesion groups differed significantly from controls in escape latency and all other measures of performance, but the two lesion groups are similar to each other. Minimally from these data we can conclude that elements in area 29 are essential to successful performance in a reference memory task if the animal is required to adopt a spatial mapping strategy.

Spatial Working Memory: Acquisition

We modified the training procedure in the place navigation task to place a greater burden for successful performance on working and short-term memory. The platform was moved to a new hiding place each training session, but for all of the trials of that session the hidden platform remained in the same place. Importantly, there were very short intertrial intervals. The rats received 16 trials each session arranged in trial couplets; that is, there was a very short interval (<1 sec) between the end of odd numbered trials and the beginning of even numbered trials and much longer intervals (>120 sec) between even and odd trials. In the spatial reference memory task, the intertrial interval was always greater than 2 min. Thus, if

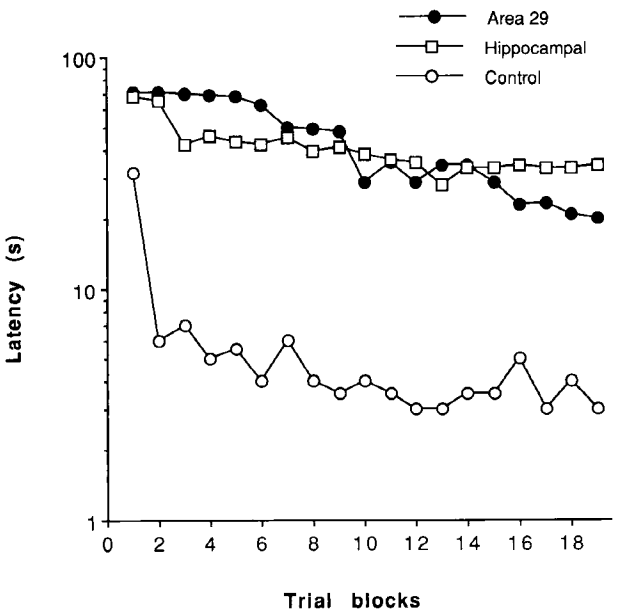

FIGURE 16.2. Mean latency to find the hidden platform during acquisition of navigation to a fixed goal location. Modified with permission of the *Journal of Neuroscience* from Sutherland et al. (1988).

"rapid forgetting" of information is the fundamental defect, as has been suggested for animals with damage to certain other limbic structures, this procedure should detect it in rats with area 29 damage. Normal rats learn to search around the pool on the first trial of each session until they collide with the platform and for the rest of the trials of the session they return directly to that new correct location (Whishaw, 1987). We have also presented for comparison the performance of rats with anterior cingulate aspirations that included all of area 24 and most of area 32 either alone or in combination with area 29 aspirations.

Figure 16.3 depicts the mean number of swim path directional errors committed by controls and area 29 and area 24 lesion rats. An error is scored whenever a rat's swim path strayed more than 9 cm from a straight line between the start location and the goal. The three groups with cingulate damage made more errors than did the controls during acquisition. The performance of rats with damage to anterior cingulate cortex was superior to that of rats with combined damage or damage to area 29 alone. Over the initial 20 days of training the combined and area 29 lesion groups did not differ significantly from each other.

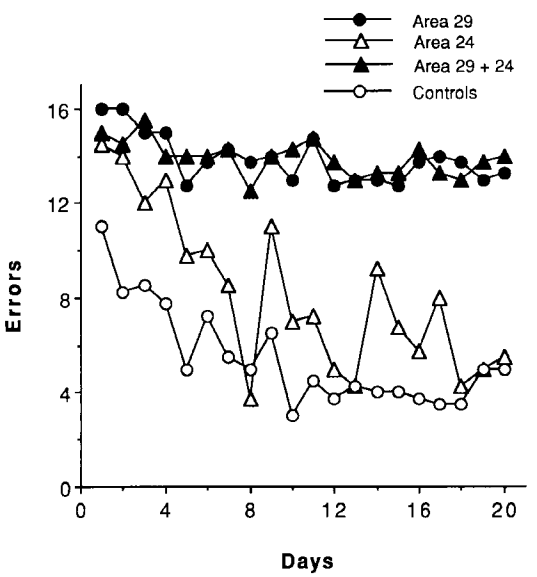

FIGURE 16.3. Mean number of trajectory errors each day during the first 10 days of postoperative acquisition of navigation to the hidden platform in the moving location version. Modified with permission of the *Journal of Neuroscience* from Sutherland RJ, et al. (1988).

Figure 16.4 shows mean escape latency for each of the 16 daily trials at the end of an additional 20 days of training for the area 24, area 29, and control groups. As can be seen, the rats with area 24 damage alone

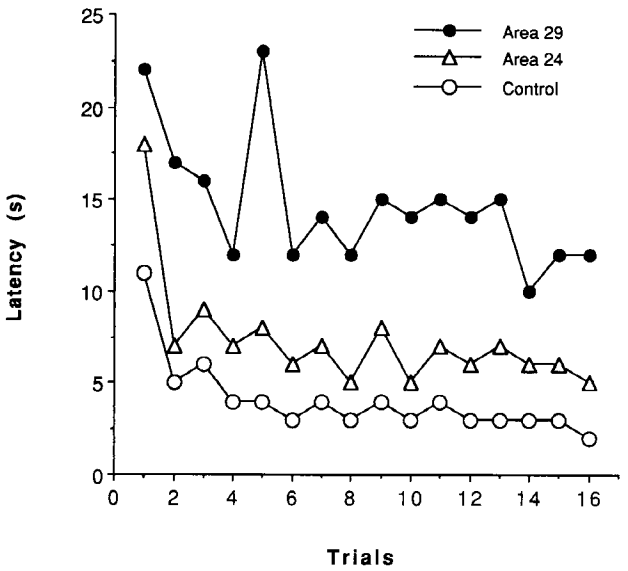

FIGURE 16.4. Mean latency to find the hidden platform for the 16 trials of a session after 20 days of training in the moving location version. Modified with permission of the *Journal of Neuroscience* from Sutherland et al. (1988).

were performing similarly to control rats. Importantly, these two groups showed statistically significant decreases in latency between the first and second trial. These rats demonstrate one-trial place learning (Whishaw, 1987). In contrast, the rats with area 29 damage and combined damage showed only a modest improvement in latency; gradually improving across many trials. Note the lack of beneficial effect of the very short intervals between trials.

Thus, from this moving platform version of the place navigation task the following is clear:

1. A robust, long-lasting impairment is produced by area 29 damage.
2. Area 24 makes a detectable, but nonessential, contribution to performance.
3. Providing very short retention intervals between trials does not ameliorate the area 29 deficit.

Spatial Reference and Working Memory: Retention

In other experiments we have shown that preoperative training in place navigation can differentially affect performance by different lesion groups; especially lesions of the hippocampal system versus the subcortical targets of hippocampal efferents (Sutherland and Rodriguez, 1989). Damage to the target regions did not reliably disrupt navigation to the hidden platform in preoperatively trained rats, despite the fact that similar damage to these structures (mamillary nuclei, anterior thalamic nuclei, or nucleus accumbens) in different rats markedly impaired acquisition. Damage to the hippocampal system produces a clear impairment in place navigation even if the rats have been preoperatively trained (Schenk and Morris, 1985; Sutherland, 1985; Sutherland and Rodriguez, 1989; Whishaw, 1987). This implies that no single target region for fornix fibers is in the necessary output route for hippocampal circuitry to affect behavior, nor do any of them provide necessary perceptual or motor information to the hippocampal system.

Logically, preoperative training in the place navigation task could affect postoperative performance and thereby ameliorate an impairment in several ways:

1. The rats could benefit solely from retaining the "procedural" aspects of the task, for example, remembering which spatial strategy is applicable to the problem.

2. They could retain the information about the layout of important objects in the environment.

3. They could retain the specific information about exactly where in the environment the goal is located.

This third option would obviously only improve performance in our spatial reference memory task.

If, as we have suggested, area 29 is part of the essential circuitry interfacing a spatial mapping system with perceptual systems and movement, then a clear prediction is that none of these sources of amelioration due to preoperative training will abolish the impairment produced by area 29 aspiration. Our data strongly support this position; that is, even if rats are trained before area 29 ablation to locate the hidden platform in a fixed location in the pool (reference memory version) or to locate the platform in a new location each session (working memory version), they show a clear navigational deficit.

Figure 16.5 depicts the mean escape latency for control and area 29 damaged rats during postoperative testing. Both groups had received six days of preoperative training with the hidden platform located in the same fixed location as they experienced during postoperative testing. Figure 16.6 presents the same measure from two different groups of rats who had received preoperative training on the moving platform version of the task. In the case of both of these experiments, all rats had achieved a very similar accurate level of performance by the end of preoperative training. As is apparent from the data both control groups demonstrated very good retention of place navigation. Both area 29 damaged groups are impaired relative to controls. If, however, one compares the performance of these two lesion groups to area 29 damaged groups that are preoperatively naive (Figs. 16.2, 16.3, and 16.4), two points should be noted. First, the preoperatively trained groups have superior performance; they achieve an asymptotic level after fewer trials. Second, the level of final performance is essentially the same in naive and pretrained groups. Thus, the use of whatever nonmapping strategies area 29 damaged rats can acquire is facilitated by preoperative training in both working and reference memory procedures, but this preoperative training does not allow the rats postoperatively to swim directly to the correct region of the pool.

For those interested in anterior cingulate cortex, note that in an earlier article (Suther

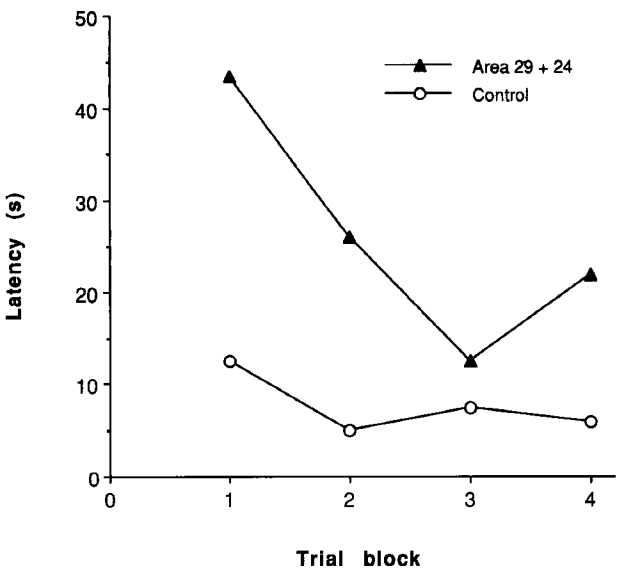

FIGURE 16.5. Mean latency to find the hidden platform in a fixed location after surgery. All rats were trained preoperatively to navigate to the same location. Modified with permission of the *Journal of Neuroscience* from Sutherland et al. (1988).

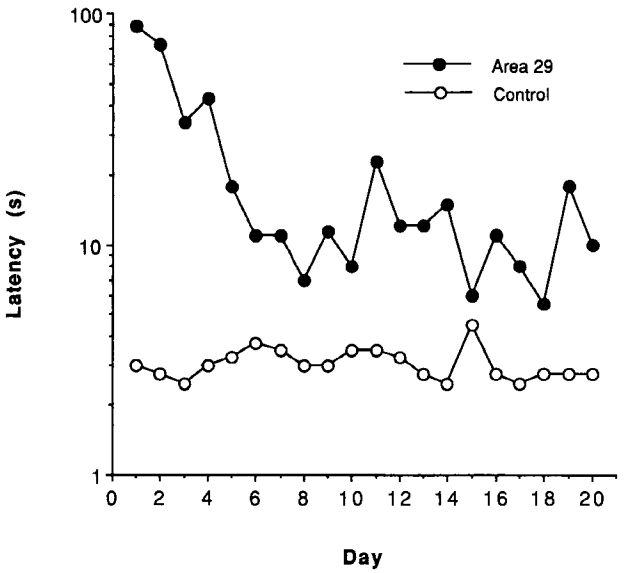

FIGURE 16.6. Mean latency to find the hidden platform in the moving location version (after surgery). All rats had been trained preoperatively in this version. Modified with permission of the *Journal of Neuroscience* from Sutherland et al. (1988).

land, 1985) we described the effects of preoperative training on performance of rats with area 24 aspiration in the reference memory version of the place navigation task. These rats are not reliably different from controls. That is, they are able to navigate directly to the goal location. We may infer from this observation and current considerations that an intact area 29 is necessary for behavioral expression of the mapping strategy even if this information had been well established prior to damage. Furthermore, regardless of how the area 29 contribution makes contact with motor systems, it is not indirectly via its connections with area 24.

Retrograde Gradient?

Work with rats and monkeys (Sutherland et al., 1987; Zola-Morgan and Squire, 1990) has provided some experimental support for the clinically derived hypothesis (Milner, 1959) that the hippocampal formation has a temporally limited, consolidating role in permanent memory formation. We have found that the interval of time between preoperative training and hippocampal damage affects the magnitude of the impairment of postoperative performance. Longer intervals are associated with less impairment. These data were collected using the single, fixed platform location in the place navigation task. So far we have examined intervals of 0, 1, 4, 8, 12, and 100 weeks. Although place navigation is not entirely normal after hippocampal damage even with 12- or 100-week intervals, performance is much better than at 0, 1, or 4 weeks.

The retrograde gradient observed after hippocampal damage allows a test of one hypothesis concerning area 29. If the *only* contribution of circuitry in area 29 to spatial mapping performance is to provide input to or convey output from the hippocampal system, then it is reasonable to predict that the cingulate impairment will similarly decline in magnitude with increasing intervals between preoperative training and ablation. In our view of the area 29 contribution, unlike the steep retrograde gradient seen after damage to the hippocampal formation, the gradient should be more or less flat after area 29 damage; preoperative training clearly facilitates achieving the postoperative asymptotic performance level but additional time between training and damage should have no effect.

Figure 16.7 presents the results of varying the interval of time between training and

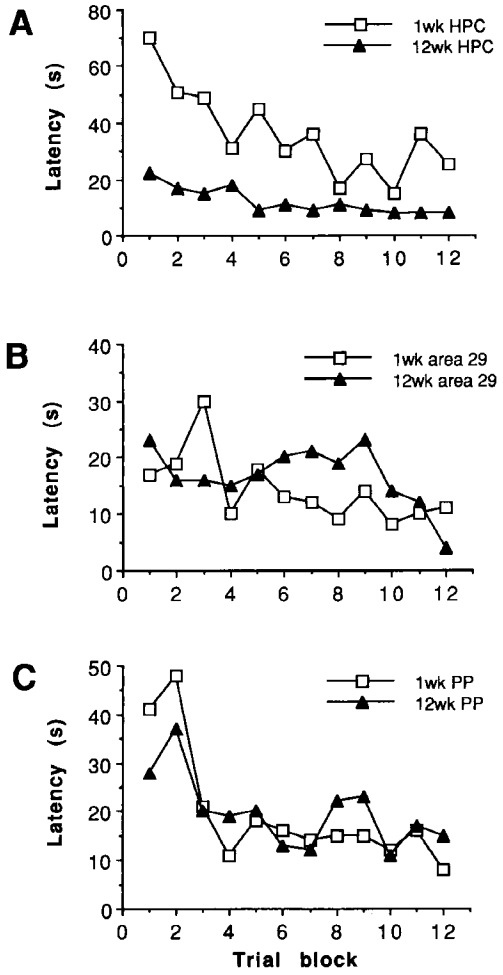

FIGURE 16.7. Mean latency to find the hidden platform in the fixed location version after damage to the hippocampus (HPC; *A*), area 29 *(B)*, or posterior parietal (PP) cortex *(C)*. All rats had been preoperatively trained to navigate to the fixed location 1 or 12 weeks before surgery.

damage. The figure depicts postoperative performance by rats with 1- or 12-week training-damage intervals. For comparison, the results are included from similar procedures using groups of rats with damage to the hippocampus or posterior parietal cortex. The most important new features of these data are that the longer intervals between training and surgery are associated with superior performance after hippocampal damage (Fig. 16.7*A*), but not after area 29 (Fig. 16.7*B*) or posterior parietal damage (Fig. 16.7*C*). Whatever specific contributions area 29 or the posterior parietal area make to place navigation, they are expressed equivalently when rats are navigating using cues that became familiar recently or long ago. This clearly contrasts with the specific contribution of the hippocampal formation.

To show that the impairment after area 29 or posterior parietal aspiration cannot be due to a change in the aversive motivation of our task, to a general inability to control swimming, or to a general inability to use visual cues, Figure 16.8 is presented. This figure demonstrates that both area 29 and posterior parietal aspiration groups can swim accurately to a solid black escape platform that protrudes 6 cm above the surface of the water.

At this juncture, it is worth noting that the pattern of results we have generated is consistent with the following notions:

1. Circuitry in the posterior parietal region participates in representing stimulus information, including both exteroceptive and movement-related cues. The absence of such representations obviously would prevent usage of a mapping strategy, even in the most familiar environments.
2. Area 29 circuitry participates in the transformation of mapping relevant information into a code that can interface with movement systems.
3. Both areas may act as long-term or permanent storage sites for mapping related information.

Anatomical Considerations: Fibers of Passage

We have been discussing the behavioral effects of area 29 aspiration without positing which neural elements damaged by the ablations are responsible for the spatial impairment. Implicit in the preceding discussion has been the idea that the effects are not due simply to interrupting fibers passing through the region. That possibility is not without precedent. Meunier and Destrade (1988) discovered that their effects of nonselective

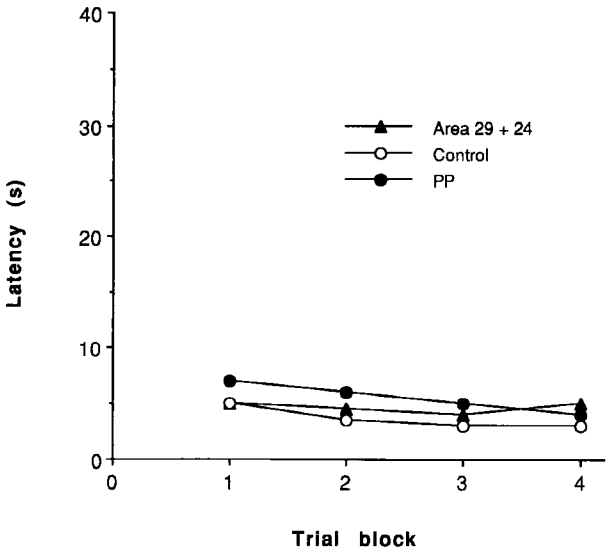

FIGURE 16.8. Mean latency to find a visible, black platform. Posterior parietal, PP.

damage to area 29 in mice, involving paradoxical facilitation of Hebb-Williams maze performance, did not occur when they spared the fibers of passage, including the cingulum bundle, using a cytotoxin lesion. To address the issue of fibers of passage, we employed a selective, excitatory amino acid cytotoxin, quisqualic acid. In this experiment, area 29 was completely aspirated in one hemisphere and in the other hemisphere there was either no damage or quisqualic acid was injected at six sites within area 29. Rats were also included with bilateral aspiration of area 29. If all of the effects we have been examining are produced by interrupting fibers of passage, then the performance of rats receiving cytotoxin injections should be similar to that of rats with only unilateral aspirations. If the effects are attributable to damage to area 29 neurons, then the performance of the rats receiving cytotoxin injections should be similar to that of rats with bilateral aspirations of area 29.

Fortunately for the interpretation of the results of this experiment, unilateral area 29 aspiration causes little disruption of acquisition of place navigation, far less than bilateral aspiration as shown in Figure 16.9. In addition, the similarity in performance between the cytotoxin-treated rats and those receiving bilateral aspiration is clear; the difference between them is not statistically significant. Both of these groups differed significantly from the control and unilateral damaged groups. The control and unilateral groups did not significantly differ from each other.

The results of this experiment are consistent with the idea that the intrinsic area 29 neurons make a significant contribution to spatial mapping. A significant contribution from fibers passing through the region could not be detected, nor was there a hint of a trend that would indicate a contribution.

Parenthetically, a second issue was also addressed concerning fibers passing in the vicinity of area 29. If one inspects the trajectory of fibers connecting entorhinal cortex with hippocampal formation via the perforant path, there is a clear danger of inadvertent damage to a dorsal portion during aspiration of the posterior part of area 29. We are not convinced that all surgeons in previous experiments (present volume contributors excluded) have managed to leave the perforant path intact. This is a possible trivial explanation for the similarity in the lesion effects in area 29 and hippocampal formation. In order to assess this issue we measured perforant path-dentate-evoked potentials in 10 rats with unilateral area 29 aspirations after complet-

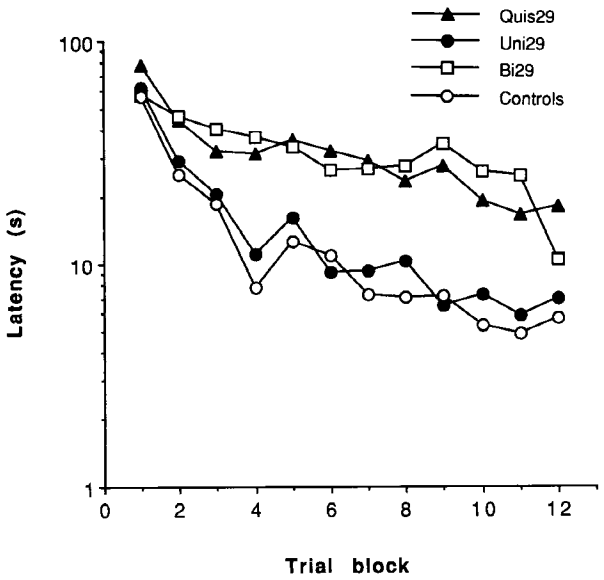

FIGURE 16.9. Mean latency to find the hidden platform (fixed location version) for rats with unilateral (Uni29) or bilateral (Bi29) area 29 aspiration or unilateral aspiration together with contralateral area 29 injections of quisqualic acid (Quis29).

ing their behavioral testing. The perforant path in rats under urethane anaesthesia was stimulated with single pulses of intensities ranging between 50 and 500 μA, and field excitatory postsynaptic potentials and population spike areas were measured in the hilus. The collected input and output functions were obtained in the hemispheres ipsilateral and contralateral to the area 29 aspiration. In every case we were able to confirm that the perforant path was intact; furthermore, there was no evidence for neither a rightward shift of the input and output curve in any measure of the evoked potential nor a lower asymptote for any measure in the hemisphere ipsilateral to area 29 aspiration.

Anatomical Considerations: Critical Components

Subfields

As is clear from preceding chapters, the zones that make up area 29 are characterized by a rich variation in afferent and efferent connections. Is there evidence for a functional distinction between zones in relation to their contribution to place navigation? In the aspiration and cytotoxin lesion experiments discussed earlier, essentially all of areas 29d and 29c were destroyed. Given the marked differences in connections that these two areas have with, for example, thalamic nuclei or regions of the visual system, as an initial comparison we prepared two groups of rats. Both received unilateral aspiration of all of area 29. In addition, one group received injections of quisqualic acid aimed at more dorsal and lateral sites (i.e., centered on area 29d) and the other group received injections centered on area 29c. In addition, the injections into area 29d included more posterior cortex and more cortical damage in total than injections into area 29c. Figures 16.10 and 16.11 reveal the results. Both groups have a clear impairment, similar in magnitude to bilateral aspirations. As can be seen in Figure 16.10, however, there were no differences between these two groups, either in rate of acquisition or in final place navigation performance. Neither group was able to learn to navigate to the correct location within the pool. Consistent with this conclusion are the data presented in Figure 16.11 (for comparison we have added the data from rats with the other kinds of area 29 lesions). These data indicate the percentage

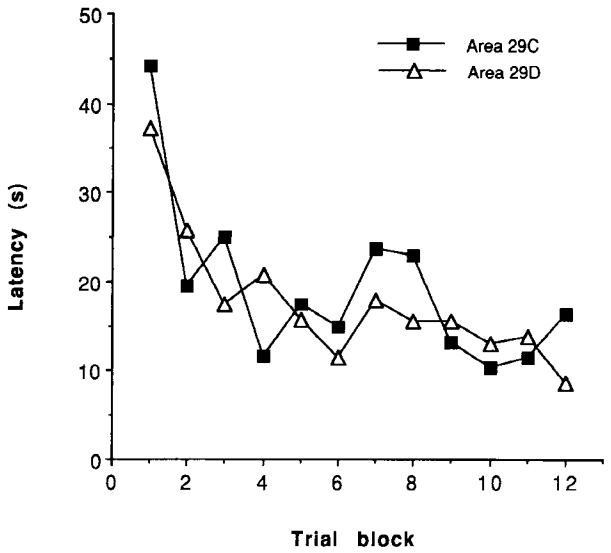

FIGURE 16.10. Mean latency to find the hidden platform (fixed location version) after unilateral area 29 aspiration plus contralateral quisqualic acid lesions in areas 29c or 29d.

of swim path distances in the goal quadrant of the pool during a 30 sec probe trial with the platform removed from the pool. For all rats the probe trial was conducted after the completion of training. Statistical analyses of quadrant preference revealed that only two of the groups preferred to search for the platform in the correct quadrant (i.e., the control rats and the rats that had sustained only unilateral damage to area 29). All of the other groups, which includes all of the groups that have any form of bilateral area 29 damage, distributed their swim search approximately evenly throughout the four quadrants, averaging about 25% (random level) in the correct quadrant.

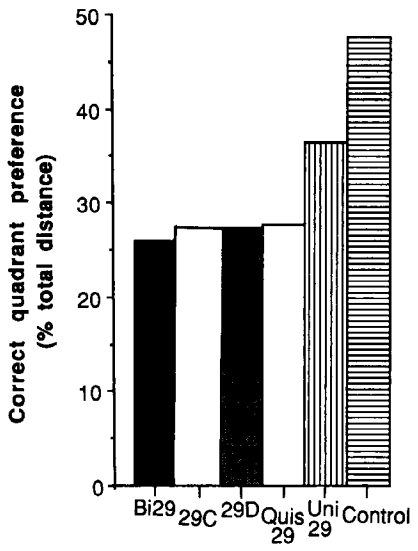

FIGURE 16.11. Mean proportion of swim path length in the correct quadrant during a 30 sec probe trial with the platform removed from the pool. For definitions to abbreviations, see legend to Figure 16.9. (Random level is 25%.)

Thus, using these methods we failed to dissociate the contributions of areas 29c and 29d to place navigation. Two reasons for this failure come immediately to mind: The extent of unintended damage to neighboring zones masked a functional difference, or both 29c and 29d play essential, albeit not necessarily similar, roles in place navigation processes. We are continuing to explore this issue.

Hippocampal Connections

A second way of discovering which components are important to place navigation is a "crossed lesion" approach. First, we can take advantage of our previous findings that unilateral damage to area 29 has little impact on place navigation acquisition. Second, we have shown that unilateral damage to the hippocampal system, neocortex, or anterior

thalamic area do not block acquisition of place navigation. Anatomical tracing techniques have uncovered a wealth of connections between components of the hippocampal system and area 29. Assuming that the preponderance of these connections is ipsilateral, then one can test the idea that it is these connections that are important for place navigation using a combined lesion strategy. Specifically, we prepared rats with unilateral neurotoxin damage to the hippocampal formation (see Sutherland and McDonald, 1990, for technique) and, in addition, all of area 29 was unilaterally aspirated. In one-half of the rats, area 29 was removed in the same hemisphere (ipsilateral lesion) and in the other half in the opposite hemisphere (crossed lesion). If the connections between the hippocampus and area 29 are critical, then a disconnection in both hemispheres (albeit at different points) should be more deleterious to navigation than making exactly the same damage at two points within the same hemisphere, since one entire hippocampal-area 29 circuit will be intact.

The results in this experiment are clear. As shown in Figure 16.12, the mean swim distance during acquisition of place navigation using the hidden platform in a single fixed location is presented for control rats and rats with crossed or ipsilateral hippocampal and area 29 lesions. Consistent with the idea that the hippocampal formation and area 29 make an integrated contribution to place navigation, we find that the crossed lesion group is significantly impaired relative to the control and ipsilateral lesion groups. The asymptotic level of performance of the crossed lesion group is similar to that of the bilateral area 29, whereas the ipsilateral combined lesion group reached the same asymptotic performance as the control group and the unilateral area 29 aspiration group. This confirms that hippocampal connections with area 29 are indeed critical in acquisition of place navigation.

Anterior Thalamic Connections

We have employed the same crossed lesion strategy described in the previous section to examine the importance of anterior thalamic connections with area 29. The same parameters, which are described in detail in Sutherland and Rodriguez (1989), were used for electrolytic anterior thalamic lesions. Briefly, these lesions include damage to both anteroventral and anterodorsal nuclei, but spare lateral thalamic nuclei, nucleus reuniens, and mediodorsal nuclei, but, of

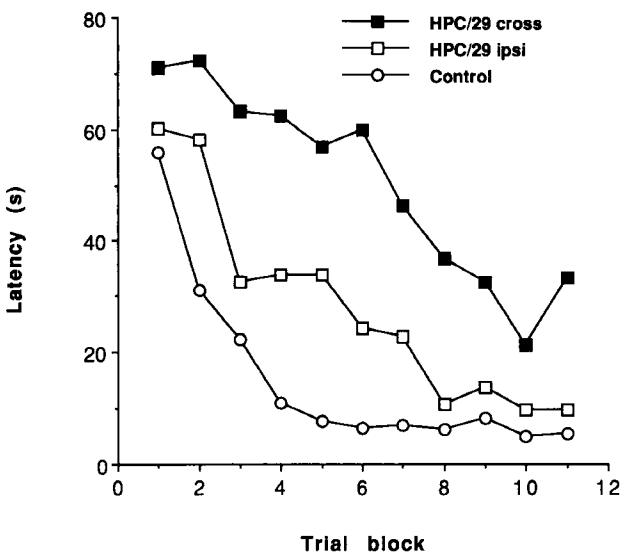

FIGURE 16.12. Mean swim path length on each trial in computer pixel units after crossed or ipsilateral (ipsi) hippocampal (HPC) and area 29 damage.

course, interrupt the fibers of passage. We prepared rats with unilateral anterior thalamic lesions and, in addition, unilateral aspiration of area 29 either in the same or opposite hemispheres.

The results unfortunately are not as clear as with combined hippocampal and area 29 damage, nonetheless they are qualitatively similar. As shown in Figure 16.13, crossed lesions produce a significantly greater impairment than do ipsilateral lesions, although the performance difference is not as great as we would wish for an unambiguous interpretation. We suggest that these data provide direct evidence that the connections between the anterior thalamus and area 29 provide information that is important for spatial mapping. One possibility for the smaller separation in the performance of crossed vs. ipsilateral lesion groups is that, in contrast to the hippocampal connections, there is a more substantial complement of functionally important fibers connecting area 29 with the contralateral thalamus.

Taken together, the results from the crossed lesion experiments are consistent with the idea that the interaction between the hippocampal formation, anterior thalamic area, and area 29 is a critical basis for the acquisition of spatial map information. An important additional piece of information that we wish to have is the result of a disconnection experiment involving thalamic nuclei and hippocampal formation. Does the utilization of spatial map information require the integration of thalamic and hippocampal representations?

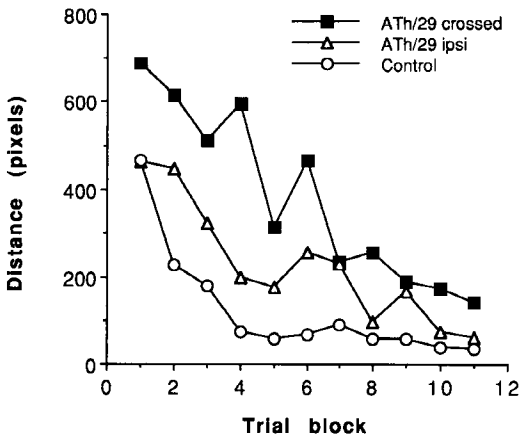

FIGURE 16.13. Mean swim path length on each trial in computer pixel units after crossed or ipsilateral (ipsi) anterior thalamic (ATh) and area 29 damage.

Relationship to a Hippocampal Memory System

In other contexts (Sutherland and Rudy, 1989; 1991) we have developed the argument that the hippocampal formation's contribution to spatial mapping is a special case of a more general role in learning and memory. Hippocampal circuitry is always necessary in the formation and initial storage of information used to solve spatial map problems. But problems requiring a spatial map representation by no means exhaust the list of behavioral contexts for which hippocampal circuitry is essential. In our view, the key element of a spatial map problem that makes it depend on the hippocampal formation is the ambiguity of each of the stimulus elements in the environment. The animal must use information from two or more elements of the situation in order to infer the correct path or select the appropriate movement. Faced with the same element on different occasions the animal must make different responses depending on that element's relationship to some other aspect of the situation. Thus, in our words, the animals must learn about *configural* relationships to respond appropriately. The hippocampal formation is the key component of the *configural association* system. In behavioral contexts in which the correct response can be selected unambiguously on the basis of information about a single element, the representation of information in the hippocampal formation is not essential. In our terminology, learning in these situations depends on the acquisition of *simple associations.*

We have developed several behavioral tests of the configural association idea (see,

for example, Alvarado and Rudy, 1991; Rudy and Sutherland, 1989; Sutherland and McDonald, 1990; Sutherland et al., 1989), and in each case we have found impaired performance after neurotoxic hippocampal damage whenever learning or remembering the correct solution to the task depends on acquiring or retaining a configural association (but see Whishaw and Tomie, 1990). Importantly, the impairments are produced regardless of whether the task requires the rat to adopt a spatial mapping strategy. Adding a mapping requirement to a task is sufficient, but not necessary, to make it depend on the hippocampal formation.

The existence of extensive projections from components of the hippocampal system to area 29, the demonstrations from Gabriel's laboratory of the dependence of discriminative unit activity in area 29 on inputs from the subiculum (Gabriel and Sparenborg, 1986), and our demonstration of the importance for spatial mapping of the connections of the hippocampus and area 29 using the crossed lesion method are all prima facie evidence that area 29 is part of the configural association system. Our place navigation results are consistent with the ideas that area 29 is important in the following:

1. The initial acquisition of configural associations by virtue of input from sensory and motor systems
2. Allowing an interface between configural representations and movement systems
3. Possibly being a basis for long-term or permanent storage of configural information

An alternative view that we cannot now rule out is that area 29 contributes exclusively spatial information, as has been suggested for the hippocampal formation (O'Keefe and Nadel, 1978; Nadel, 1991). We would, however, like to consider two relevant points. First, human amnesic syndromes are not limited to spatial information nor is the acquisition of spatial information by amnesics with hippocampal damage impaired to a greater degree than is the nonspatial information (Cave and Squire 1991). At face value at least, the study of patient R. B., who sustained histologically confirmed, selective damage to the hippocampus, is also relevant. The data indicate that R. B. had clinically significant amnesia not limited to spatial information (Zola-Morgan et al., 1989). On these grounds alone it is very likely that area 29 is provided with information based on its input from the hippocampal system that is not adequately characterized as necessarily spatial. Likewise, there is no indication in the impaired memory performance by the patient with retrosplenial amnesia described by Valenstein et al. (1987) that the deficits can be ascribed to poor spatial memory. Second, we have some preliminary results from rats with area 29 lesions that, if confirmed, are more directly relevant to this issue. One very simple, nonspatial configural task involves a *negative patterning discrimination.* In this task rats must learn to resolve a discrimination involving a light, tone, and a compound stimulus composed of the light and tone. The rats are rewarded for pressing a lever in the presence of either the light or tone alone, but never rewarded for responding when the light and tone occur together. Since the meaning of each stimulus element is ambiguous unless its relationship to the other is appreciated, by definition, this discrimination requires a configural solution. Normal rats learn to lever press rapidly during either stimulus alone and withhold responding during the stimulus compound. We have already demonstrated that an intact hippocampal formation is necessary to learn and retain a negative patterning discrimination (Rudy and Sutherland, 1989; Sutherland and McDonald, 1990). Our preliminary data suggest that the same is true for area 29. The animals with area 29 damage that we have so far tested failed to learn or retain the discrimination.

We suggest therefore that area 29 should be viewed as part of a memory system that makes a contribution that is more general than it is specific to spatial mapping alone. Its contribution may best be characterized as

linking components of a memory system that creates and stores representations of environments and movements in such a way that responses may be guided by the relationships among cues, be they spatial, temporal, or more abstract relationships.

The data reviewed in this chapter show the following:

1. Area 29 neurons are important for memory performance.
2. They act in concert with the hippocampal system and with the anterior thalamic area.
3. They are equally important for acquisition and retention performance in a mapping task.
4. They make a contribution that is independent of the working memory versus reference memory distinction or the distinction between recent versus remote memory.

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References

Alvarado M, Rudy JW (1991): Hippocampal lesions impair acquisition of the transverse patterning problem but not of simple discriminations. *Soc Neurosci Abstr* 17:131

Cave CB, Squire LR (1991): Equivalent impairment of spatial and nonspatial memory following damage to the human hippocampus. *Hippocampus* 1:329–340

Gabriel M, Sparenborg S (1986): Anterior cingulate cortical neuronal correlates of conditioning blocked in rabbits with posterior cingulate cortical lesions. *Soc Neurosci Abstr* 12:518

Hoesing JM, Skelton RW, Evanson J, Sutherland RJ (1991): Does learning produce long-lasting changes in perforant path-dentate evoked potentials? *Soc Neurosci Abstr* 17:483

Markowska AL, Olton DS, Murray EA, Gaffan D (1988): A comparative analysis of the role of fornix and cingulate cortex in memory: Rats. *Exp Brain Res* 74:187–201

Meunier M, Destrade C (1988): Electrolytic but not ibotenic acid lesions of the posterior cingulate cortex produce transitory facilitation of learning in mice. *Behav Brain Res* 27:161–172

Milner B (1959): The memory defect in bilateral hippocampal lesions. *Psychiatr Res Rep* 11:43–52

Morris RGM (1981): Spatial localization does not require the presence of local cues. *Learn Motiv* 12:239–260

Morris RGM, Garrud P, Rawlins JNP, O'Keefe J (1982): Place navigation impaired in rats with hippocampal lesions. *Nature (London)* 297:681–683

Morris RGM, Schenk FS, Tweedie F, Jarrard LE (1990): Ibotenate lesions of hippocampus and/or subiculum: Dissociating components of allocentric spatial learning. *Eur J Neurosci* 2:1016–1028

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 (1991): The hippocampus and space revisited. *Hippocampus* 1:221–229

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

O'Keefe J, Nadel L, Keightly S, Kill D (1975): Fornix lesions selectively abolish place learning in the rat. *Exp Neurol* 48:152–166

Rudy JW, Sutherland RJ (1989): The hippocampal formation is necessary for rats to learn and remember configural discriminations. *Behav Brain Res* 34:97–109

Schenk F, Morris RGM (1985): Dissociation between components of spatial memory in rats after recovery from the effects of retrohippocampal lesion. *Exp Brain Res* 58:11–28

Sutherland RJ (1985): The navigating hippocampus: An individual medley of space, memory and movement. In: *Electrophysiology of the Archicortex,* Buzsaki G, Vanderwolf CH, eds. Budapest: Akadémiai Kiadó, pp 255–279

Sutherland RJ, Arnold KA, Rodriguez AJ (1987): Anterograde and retrograde effects on place memory after limbic or diencephalic damage. *Soc Neurosci Abstr* 13:1066

Sutherland RJ, Kolb B, Whishaw IQ (1982): Spatial mapping: Definitive disruption by hippocampal or medial frontal cortex damage. *Neurosci Lett* 31:271–276

Sutherland RJ, McDonald RJ (1990): Hippocampus, amygdala, and memory deficits in rats. *Behav Brain Res* 37:57–79

Sutherland RJ, McDonald RJ, Hill CR, Rudy JW (1989): Damage to the hippocampal formation in rats selectively impairs the ability to learn cue relationships. *Behav Neurol Biol* 52:331–356

Sutherland RJ, Rodriguez AJ (1989): The role of the fornix/fimbria and some related subcortical structures in place learning and memory. *Behav Brain Res* 32:265–277

Sutherland RJ, Rudy JW (1989): Configural association theory: The role of the hippocampal formation in learning, memory, and amnesia. *Psychobiology* 17:129–144

Sutherland RJ, Rudy JW (1991): Exceptions to the rule of space. *Hippocampus* 1:250–252

Sutherland RJ, Whishaw IQ, Kolb B (1980): Abnormalities in EEG and spatial performance following intrahippocampal injections of neurotoxins. *Soc Neurosci Abstr* 6:565

Sutherland RJ, Whishaw IQ, Kolb B (1983): A behavioural analysis of spatial localization following electrolytic, kainate- or colchicine-induced damage to the hippocampal formation in the rat. *Behav Brain Res* 7:133–153

Sutherland RJ, Whishaw IQ, Kolb B (1988): Contributions of cingulate cortex to two forms of spatial learning and memory. *J Neurosci* 8:1863–1872

Valenstein E, Bowers D, Verfaellie M, Heilman KM, Day A, Watson RT (1987): Retrosplenial amnesia. *Brain* 110:1631–1646

Whishaw IQ (1987): Hippocampal granule cell and CA3–4 lesions impair formation of a place learning-set in the rat and induce reflex epilepsy. *Behav Brain Res* 24:59–72

Whishaw IQ, Tomie J (1990): Rats with hippocampal removals can learn simple, conditional and tactile discriminations using odor and tactile cues. *Soc Neurosci Abstr* 16:606

Zola-Morgan SM, Squire LR (1990): The primate hippocampal formation: Evidence for a time-limited role in memory storage. *Science* 250:288–290

Zola-Morgan S, Squire LR, Amaral DG (1989): Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to the CA1 field of the hippocampus. *J Neurosci* 6:2950–2967