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FRAMING SPATIAL COGNITION: NEURAL REPRESENTATIONS OF PROXIMAL AND DISTAL FRAMES OF REFERENCE AND THEIR ROLES IN NAVIGATION

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Knierim JJ, Hamilton DA. Framing Spatial Cognition: Neural Representations of Proximal and Distal Frames of Reference and Their Roles in Navigation. *Physiol Rev* 91: 1245–1279, 2011; doi:10.1152/physrev.00021.2010.—The most common behavioral test of hippocampus-dependent, spatial learning and memory is the Morris water task, and the most commonly studied behavioral correlate of hippocampal neurons is the spatial specificity of place cells. Despite decades of intensive research, it is not completely understood how animals solve the water task and how place cells generate their spatially specific firing fields. Based on early work, it has become the accepted wisdom in the general neuroscience community that distal spatial cues are the primary sources of information used by animals to solve the water task (and similar spatial tasks) and by place cells to generate their spatial specificity. More recent research, along with earlier studies that were overshadowed by the emphasis on distal cues, put this common view into question by demonstrating primary influences of local cues and local boundaries on spatial behavior and place-cell firing. This paper first reviews the historical underpinnings of the "standard" view from a behavioral perspective, and then reviews newer results demonstrating that an animal's behavior in such spatial tasks is more strongly controlled by a local-apparatus frame of reference than by distal landmarks. The paper then reviews similar findings from the literature on the neurophysiological correlates of place cells and other spatially correlated cells from related brain areas. A model is proposed by which distal cues primarily set the orientation of the animal's internal spatial coordinate system, via the head direction cell system, whereas local cues and apparatus boundaries primarily set the translation and scale of that coordinate system.

I. INTRODUCTION

The experimental analysis of spatial navigation has occupied a special place in the history of experimental psychology and has been a central component of contemporary research on the neurobiology of learning, memory, and cognition. Few issues in the literature on spatial navigation have been the subject of more intense study and debate than the question of how navigation to a particular location is achieved and the related question of what is learned when navigation to a particular place is reinforced. By far, the most popular spatial task used to study these questions is the Morris water task (152), which has become the standard task to assess learning and memory impairments in rodents as the result of lesions, pharmacological manipulations, or genetic engineering. Despite its prevalence, it is still not known precisely how rats and mice solve this task. What exactly is learned during training? What interoceptive and exteroceptive cues are most important? How do the procedural aspects of the task interact with the cognitive (spatial) aspects of the task? The operational simplicity of this task belies the complexity of how the brain actually solves it. Perceptual systems, memory systems, motivational/reward systems, and motor systems all must interact to produce the learned behavior. The spatial memory component of the task depends critically on an intact hippocampal system. Despite the wealth of knowledge about the place-related firing of hippocampal place cells, it is still not known precisely how the firing of place cells contributes to the animal's learning and performance of spatial tasks.

The purpose of the present review is to address one component of these critical issues. Ever since the earliest studies of rat spatial behavior and the subsequent discovery of place cells in the hippocampus, the distal cues in an environment have been assigned a privileged role as providing the most critical information for the construction and use of mental representations of space. As reviewed below, this viewpoint was established in large part because early researchers intentionally diminished the salience of local cues, to ensure that the behavior of the subjects could not be explained by simple sensory responses to the local cues. As a consequence of this experimental strategy, intramaze cues, such as the boundaries of an apparatus and the local objects and surface textures, came to be considered as providing minimal information in supporting the formation and use of "cognitive mapping" strategies to solve spatial tasks. A number of findings in the past 20 years, from both behavioral and neurophysiological experiments, are forcing a reevaluation of the dominant role of distal cues. These studies have shown that local apparatus boundaries and cues can often override distal cues in controlling both behavior and neural representations of space. This review will present the historical reasons for the initial emphasis on the dominance of distal cues and the more recent evidence that overturns this dogma. We will argue that distal cues have a predominant role in setting the orientation of an animal's spatial representation, via their profound impact on the head direction cell system, rather than defining specific spatial locations. For the latter, local boundaries and self-motion cues (path integration) appear to play the dominant role. (A detailed discussion of the powerful role of self-motion cues is beyond the scope of this review, which focuses instead on the relative roles of proximal and distal exteroceptive cues. For reviews of the influence of interoceptive cues, the reader is referred to References 142 and 248. We suggest that the issue of how external landmarks control place cells and spatial navigation is best thought of as a process of coordinate system alignment, whereby an internal coordinate system embodied by grid cells of the medial entorhinal cortex must be aligned, scaled, and oriented to an external coordinate system that corresponds to the world outside the head. We will present a functional anatomical model of how head direction cells are controlled by distal landmarks to set the orientation of the grid cell coordinate system and boundary cells are controlled by the local apparatus walls or borders to set the *phase* (horizontal offset) of the grid cell coordinate system. The grid cell phase and orientation then determine the location and orientation of place cells in the hippocampus (through computational mechanisms that are under intense investigation but not well understood) (40, 143, 198, 216).

For the purposes of this review, we shall operationally define distal and proximal cues according to the common working definitions in laboratory experiments; that is, distal cues are the cues on the walls of the lab or otherwise removed from the behavioral apparatus, whereas proximal cues are those cues that are part of the apparatus itself. Because the proximal-distal axis is a continuum, some cues are inherently ambiguous by these definitions. These cases will be discussed as they come up in the review, as they can prove instructive for thinking about the relative roles of cues that are closer or farther from the animal, and about the roles of different brain areas and neurons that are selectively controlled by these sets of cues.

II. BEHAVIORAL ANALYSES OF SPATIAL LEARNING

A. Overview

The broad goal of the first component of the review is to survey the historical and contemporary literature on spatial navigation. Emphasis is given to data and theory regarding the control of spatial navigation by exteroceptive visual stimuli; however, contrast with other forms of control is provided where appropriate and expository. This approach is not intended to deny the significance of other forms of navigation that depend solely on nonvisual exteroceptive or interoceptive (e.g., kinesthetic) sources of control with respect to either the exceedingly rich spatial navigation capabilities of human and nonhuman animals, or the theoretical importance of these forms of control and related behaviors. The framework we wish to advance here is primarily concerned with how visual aspects of the environment are involved in the control of navigation to a goal location and the firing characteristics of individual neurons in the neural circuits that have been implicated in this behavior. In particular, we promote the idea that spatial navigation in commonly used laboratory tasks involves combined control by distal visual cues beyond the apparatus boundary and cues provided by the apparatus itself. We refer to these sources of control as frames of reference (70, 161, 227, 239, 269) and propose that distal cue and apparatus frames of reference interact such that navigation is directed toward relative locations in the apparatus rather than locations defined directly by the extra-apparatus landmarks. We constrain application of this approach to tasks for which the apparatus does not disambiguate precise spatial locations, primarily because the most commonly used laboratory tasks fall neatly into this category, including the Morris water task and other popular dry-land maze and open field tasks commonly employed in the study of head direction cells, grid cells, and place cells. We argue that distal cues provide critical information for orientation in apparatus frames of reference and serve to disambiguate geometrically similar locations in the apparatus (e.g., corners, walls, or locations that are equidistant from a symmetrical boundary). Prior to discussing the contemporary data that have motivated this view, we first describe some historical antecedents and highlight findings relevant to the general issue of control by distal room and apparatus cues.

B. Sensory Processes and Sources of Control

It is generally recognized that navigation from one location to another can be achieved using a variety of distinct strategies that rely on different forms of interoceptive or exteroceptive cues, as was evident in the earliest laboratory studies on complex maze learning in the rat. Following the earlier work of Small (213), Watson (244) attempted to systematically identify the means by which rats negotiated complex mazes consisting of numerous choice points and dead ends. Rats were virtually unimpaired at negotiating a Hampton Court Maze when they were made anosmic, blind, deaf, had their vibrissae removed, or experienced a variety of manipulations of tactile and visual stimuli. On the basis of these findings, Watson (244) concluded that a kinesthetic sense was all that was required to learn mazes, claiming that "vision plays no part in the maze association," and rats that partially solved the maze on the basis of visual information "were not using visual stimuli in any critically discriminative way." Somewhat inconsistent with these conclusions were the findings obtained in one of Watson's own experiments designed to evaluate control of navigation by distal visual cues that lay outside the boundaries of the maze. After rats were well-trained, the maze was rotated such that the features of the maze, as well as interoceptive sources of control, were put into conflict with distal cues. Watson found that performance of normal rats, as well as rats that were anosmic or deaf, was disturbed by rotation of the maze, whereas performance of blinded rats was not disturbed, indicating that visual information beyond the boundaries of the maze contributed to maze navigation.

Although the effects of maze rotation on performance observed by Watson were not always replicated (62, 86), disruptions in performance when the maze was rotated relative to extramaze stimuli were the most common observations. The later work of Carr (23), Higginson (86), Gengerelli (62), Vincent (240), Honzik (92, 93), Dennis (41), and Wherry (246) drew attention to the importance of considering control by visual information as well as other modalities (e.g., olfactory and tactile) to understanding maze performance, and in some cases demonstrated that vision was the dominant sense involved in maze learning (93). Walthall (241) demonstrated that heterogeneity in the visual distal cue environment facilitated learning, and Carr (23) noted that when simpler mazes with no boundary walls were employed, rats tended to navigate to the location of reinforcement in the room frame of reference, providing early evidence that rats could learn the position of a goal relative to extramaze cues under certain circumstances.

C. What Is Learned?

The early emphasis on basic sensory modalities involved in maze navigation quickly expanded to include a diverse and influential set of arguments regarding what rats learned in mazes. Response learning, for example, involves learning to perform specific motor responses, usually 90° turning responses (left/right). With the use of this strategy, complex mazes such as the Hampton Court Maze (244) would require learning complex sequences of responses, whereas simple mazes used in later work (e.g., the T-maze) would require learning a single response. Stimulus-response (S-R) approaches argued that responses, including turning responses and more general approach/avoidance tendencies, become associated with interoceptive and/or exteroceptive stimuli (96–98, 107, 200, 255). Central to this idea was the formation of S-R associations, which allow particular stimuli to control particular responses. Several researchers also highlighted the importance of a general sense of direction in maze navigation (36, 95, 178, 179), which was most frequently considered in terms of orientation toward and movement in the direction of a particular location associated with reinforcement. Dashiell, for example, noted that rats prefer movement along straight paths in the direction of current movement (36, 39), but they also develop obvious tendencies to move in the general direction of the goal box in complex and simple mazes (35, 37, 243). Although visual cues can contribute to this type of orientation (38), this ability was not shown to be critically dependent on visual information provided by cues outside the maze (37, 243) or other stimuli inside the maze (37, 38), leading Dashiell to emphasize the importance of intraorganism cues in orientation.

The ability to learn the spatial layout of an environment, including the location of goals, is commonly referred to as place learning. This was a central feature of Tolman's cognitive mapping theory (236), which emphasized that rats (and humans) possess a natural tendency to form cognitive maps of what is present in the environment and where the elements of the environment (e.g., cues, goals) are located in relation to one another. Once formed, a cognitive map can be utilized to guide navigation, including situations in which previously available paths to a goal are blocked or novel shortcuts to a goal are made available (237). For example, Tolman, Ritchie, and Kalish (237) first trained rats to navigate a path that consisted of several 90° turns to arrive at a goal location. The initial path required the animals to navigate away from the goal location. Subsequently, when a number of novel pathways radiating from a central platform were made available, the animals chose a pathway that allowed direct navigation to the goal location. A prominent visual source of control outside the maze included a dimly lit lamp adjacent to the goal. Although the precise nature of the control provided by this stimulus was not investigated, support for the broader idea that rats will take novel shortcuts to a particular location in the environment, rather than following a novel path similar to the path established through training, was emphasized. It was recognized that this ability could not have emerged from cues within the maze but must have been based on other cues in the environment, of which the light as well as other cues beyond the maze boundaries were prime candidates (93, 237). At the time, the major theoretical alternatives to spatial learning as characterized by Tolman were variants of response-learning theories, and S-R theorists argued that these data could reasonably be explained in terms of approach behaviors directed toward the light stimulus positioned above the goal box. Furthermore, some studies failed to obtain evidence of shortcut-taking in the rat, leading Wilcoxon and Waters (255) to question the generality of a strong spatial disposition in rats.

In 1946, Tolman et al. (238) lamented that although numerous studies had been conducted to address the basic means by which rats solve maze problems, none had convincingly demonstrated that one form of solution was dominant or preferred over others, and more problematic, researchers tended to argue on the basis of equivocal data that maze learning only involved one type of solution to the exclusion of others. Moreover, although considerable attention had been devoted to response learning and place learning, prior studies, according to Tolman, had not convincingly distinguished response and place strategies. To address this issue, Tolman et al. (238) trained rats to either perform a particular response (e.g., always perform a right turn) or to navigate to a specific spatial location in the room independent of the particular responses that were involved. A simple plus maze with two distinct start locations (S1 and S2) and two possible goal (food) locations (F1 and F2) was employed in this experiment **(FIG. 1)**, allowing the various solutions of interest to be contrasted more easily than in complex mazes. The animals in the Response group were trained to perform a right turn at the center of the maze, such that they would be reinforced at F1 when released from S1 and reinforced at F2 when released from S2. Thus the spatial location of reinforcement varied from trial to trial, but the response at the choice point was consistent. In the Place group, the spatial location of reinforcement was held constant, but the motor response varied from trial to trial [e.g., S1→F1 (right turn), S2→F1 (left turn)]. Rats in the Place group learned to navigate to the particular place in the room much more readily than rats in the Response group learned to perform a particular motor response. This result stood in obvious contrast to the basic preference for kinesthetic solutions outlined by Watson as well as the explanations offered by S-R associative theorists. The apparent preference of rats to learn where to navigate independently of specific motor responses, which Tolman et al. (238) termed a place disposition, appeared to support the notion that rats learned to navigate to a particular spatial location in the environment.

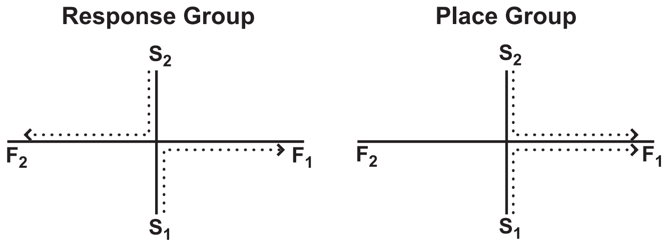

FIGURE 1. Diagram of the apparatus used by Tolman, Ritchie, and Kalish (238) to contrast response and place learning. Two start locations (S_1 and S_2) and two goal locations (food boxes, F_1 and F_2) were used throughout training. Start locations and/or food locations were changed from trial to trial so that performance of particular responses (left or right) or navigation to a particular place was reinforced. For example, a rat trained to perform a right turn response (Response Group) would be trained to navigate to F_1 when released from S_1, and to navigate to F_2 from S_2, as indicated by dotted lines in the *left panel*. This strategy required the animals to navigate to different places on each trial. A rat trained to navigate to location F_1 (Place Group) would be trained to navigate to F_1 when released from either S_1 or S_2, as indicated by the dotted lines in the *right panel*. This strategy required animals to perform different motor responses from trial to trial.

Blodgett, McCutchan, and Mathews (12) noted that the apparent place disposition demonstrated by Tolman et al. (238) might reflect learning to move in the direction of reinforcement rather than navigation to a particular position in the room. Note that the term *direction* as used here does not refer to a magnetic compass direction, but direction of movement relative to other, presumably visual, environmental cues. Tolman et al. (238) discussed interchangeably the disposition to navigate to a particular position and the disposition to orient toward the position where reinforcement is located in the environment. These types of behavioral dispositions could, of course, be distinct, with one involving the capacity to recognize particular locations and the other involving orienting and moving in the direction of a particular location, with no explicit representation of the target location itself. To contrast the relative influence of response, place, and directional strategies, Blodgett et al. (12) rotated and/or repositioned a T-maze from trial to trial and systematically manipulated the reinforced arm such that specific types of responding would reliably result in reinforcement **(FIG. 2)**. For the response-only groups, reinforcement was always located on the same arm of the maze, and because the maze was repositioned and rotated for each trial, the place and direction of reinforcement varied such that the particular turning response (left for some rats, right for others) was the only response that reliably resulted in reinforcement. For the direction-only groups, navigation in a particular direction in the room and apparatus was reinforced. The reinforced arm (left or right) and the precise location of reinforcement in the room varied from trial to trial, making the directional response the only response that always resulted in reinforcement. Finally, for the place-only group, reinforcement was always located in the same place in the room regardless of the apparatus position. The reinforced arm (left or right) and the direction of reinforcement in the room and maze varied from trial to trial; thus navigating to the same spatial location in the room was the only response that always resulted in rein-

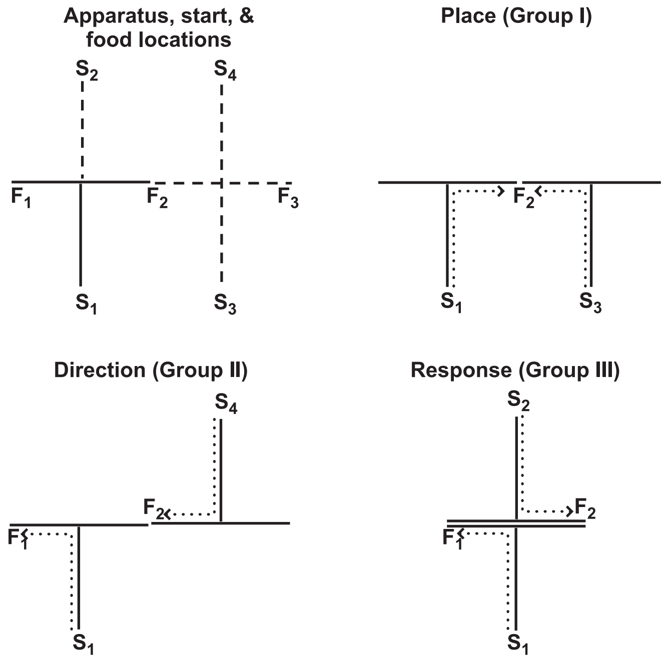

FIGURE 2. Diagram of the T-maze locations and orientations used by Blodgett, McCutchan, and Mathews (12) to contrast place, response, and direction learning. The T-maze was translated and/or rotated from trial to trial and could occupy four locations in the room. The *top left panel* illustrates the T-maze in one location (solid lines) and the other three possible positions (dashed lines). There were four possible start locations (S_1, S_2, S_3, and S_4) and three possible reinforcement locations (F_1, F_2, and F_3). The maze position and orientation and the start and/or food locations were changed from trial to trial so that particular responses, navigation to a particular place, or navigation in a particular direction were reinforced. Examples of specific conditions among three groups are illustrated. One condition from the place group (*top right*) involved translating the maze between two positions from trial to trial. Rats were released from S_1 or S_3, and reinforced for navigating to F_2, requiring different responses and navigation in opposite directions. One condition from the direction group (*bottom left*) involved translating and rotating the maze from trial to trial. When released from S_1, navigation to F_1 was reinforced. When released at S_4, navigation to F_2 was reinforced. This required the animal to navigate in the same direction in the room and apparatus, but to navigate to different locations and perform different responses from trial to trial. One condition from the response group (*bottom right*) involved translating and rotating the maze from trial to trial. If released at S_1, navigation to F_1 was reinforced, and when released from S_2, navigation to F_2 was reinforced. This required the animal to perform the same response (left turn) while navigating to different places and in different directions from trial to trial. Rats learned the direction and response tasks more readily than the place task.

forcement. The direction and response groups made the fewest errors, whereas the place group committed the most errors. Based on this outcome, Blodgett et al. (12) concluded that the relative contribution of place information to performance in the T-maze is negligible compared with response and directional information. They suggested that the apparent place disposition reported by Tolman et al. (238), when the maze remained stationary, can reasonably be explained in terms of directional responding rather than navigation to a particular position in the room. The findings of Blodgett et al. (12) highlighted the need to distinguish navigation to places and movement in a particular direction; however, these observations did not have a considerable impact during the years immediately following their report. Recently, D. M. Skinner and colleagues have replicated the findings of Blodgett et al. in the T-maze and extended this line of work to include open field environments, other maze preparations, and the neurobiological bases of these forms of responding. The findings from these experiments are discussed below in section II*D6*.

The work of Wilcoxon and Waters (255) and Scharlock (200) further highlighted the distinction between visual control in terms of spatial relationships among items in the environment and observer, and control in the form of moving toward particular stimuli. Using a T-maze, Scharlock (200) trained rats to reliably navigate to a goal arm and then altered the distance between prominent distal room cues (e.g., lights) and reinforcement locations (at the ends of the T-maze). He observed that some rats stopped precisely where the food cup was located in the apparatus, whereas others ran over the food cup, falling off the end of the maze arm. Scharlock (200) concluded that the latter rats were simply approaching one or more distal visual cues, whereas the former rats were learning precisely where the food cup should be found. Viewed another way, the animals learned to orient toward the goal location; however, some animals primarily navigated by approaching distal cues while others also made use of cues from the maze to terminate movement along the chosen trajectory.

Around this time, an influential paper by Restle (186) highlighted problems with the basic conceptual framework that had driven research on maze learning for several decades. Restle argued, convincingly, that the either/or approach to the place versus response debate was specious, because animals are capable of either form of navigation and environmental conditions determine the tendency to utilize a particular strategy. For example, in well-lit environments, animals tend to utilize a place strategy, whereas in dimly lit environments they tend to utilize a response strategy. Restle's paper in many respects represented the end of an era, at least with respect to the prevailing place versus response debate. In the years following Restle's paper, the literature on spatial learning and navigation, without a compelling theoretical motivation, was relatively inactive compared with the preceding decades.

D. Contemporary Spatial Navigation Tasks (1980–2010)

During the 1970s and early 1980s, several major events reinvigorated the study of navigation and interest in place navigation in particular. In 1971, O'Keefe and Dostrovsky (168) described hippocampal place cells that increased their firing rates in a spatially selective manner and suggested a possible neurobiological basis for Tolman's cognitive maps. The subsequent publication of *The Hippocampus as a Cognitive Map* (169) by O'Keefe and Nadel represented a successful application of cognitive principles to the neurobiological bases of spatial navigation. It is difficult to overstate the influence this book had on the subsequent surge of interest in spatial navigation and its neurobiological bases that continues to grow. A major limitation of earlier maze studies was the difficulty in unambiguously distinguishing different types of responding without introducing complex training procedures. The discovery of place cells and the apparent linkages between spatial navigation and the hippocampus motivated the desire to unambiguously measure place navigation, and appropriate tasks were needed for this enterprise. The development of tasks such as the radial arm maze and, more importantly, the Morris water task (152) provided critical methodologies to investigate the psychological and neurobiological bases of spatial navigation.

1. *Emergence of critical tasks and methods for measurement of place navigation*

Tasks and associated apparatus that allowed rodents to clearly demonstrate that they could acquire information about specific spatial locations emerged in the 1970s and 1980s (reviewed in Ref. 76). The radial arm maze (174) was one such task that was widely and effectively used by researchers interested in spatial learning. On a given trial, rodents are required to keep track of which of several goal locations (arms) they had already visited, as repeat visits to an arm went unrewarded. This requirement prompted Olton et al. (172) to suggest that efficient performance, in addition to a specific spatial learning and memory process, involved a strong working memory component that they proposed was critically dependent on the hippocampus. In contrast, O'Keefe and Nadel (169) had identified the hippocampus as the central structure in their cognitive mapping system, and demonstrations that performance in the radial arm maze critically depend on spatial information provided by distal cues was soon forthcoming. Suzuki, Augineros, and Black (228) utilized three manipulations to determine whether topographical relationships among distal visual cues were critically involved in the control of navigation (see **FIG. 3**). With the use of a radial eight-arm maze, rats were trained to visit the ends of four arms baited with food. The other four arms were unbaited. After training, the set of distal visual cues was rotated, partially removed, or reconfigured (transpositioned) so that the topographical relationships among cues did not match the relationships present during training. When the cues were rotated, the behavioral patterns of the animals (arm entries) rotated by a commensurate amount. Deletion/removal of some cues did not disrupt navigation, suggesting that a subset of cues and their topographical relations were sufficient to control behavior. Transposition of cues, in contrast, resulted in clear disruptions of performance. Collectively, these observations are consistent with the notion that the topographical relationships among distal cues are critically involved in the control of behavior in the radial arm maze (but see Refs. 52 and 128). Although this pattern of observations nicely illustrates the role of distal cues in control of behavior, it does not provide information about the distinction between navigation to precise locations relative to the distal cue reference frame and orientation and movement in the direction of reinforcement within the distal cue and local apparatus reference frames. Perhaps more importantly, although convincing demonstrations of the role of spatial information processing in the radial arm maze had been provided (99, 100, 228), it is, nonetheless, difficult to completely eliminate the working memory component of the standard radial arm maze. Although the radial arm maze is still widely used today to study spatial navigation, as are other dry maze preparations (7–9, 211), the desire to measure spatial navigation unambiguously and the fact that dry mazes generally require a considerable amount of training and effort on the part of the experimenter led to the preference for use of a more elegant and unambiguous method to measure spatial navigation, the Morris water task.

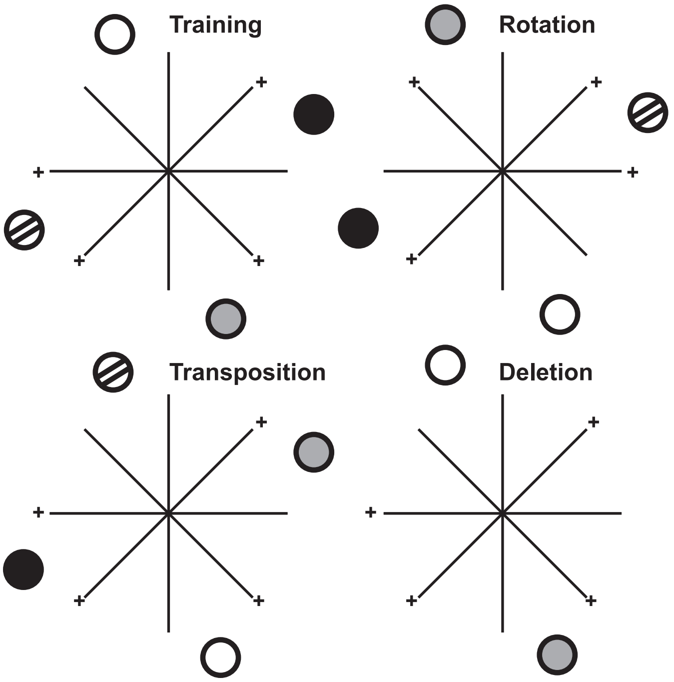

FIGURE 3. Diagrams of an eight-arm radial maze illustrating the types of distal cue manipulations used by Suzuki, Augineros, and Black (228). Reinforced (baited) arms are indicated by +. Four distinct distal cues are represented by circles. After training (*top left*), the critical manipulations involved rotating the distal cues (*top right*), transposing the distal cues (*bottom left*), and systematically removing (deleting) distal cues (*bottom right*).

Over the past three decades, the Morris water task (152, 153, 224, 247) has become a model, almost ubiquitous, behavioral task for the measurement of place navigation and learning. In this task, rats are trained to navigate to a hidden escape platform in a circular pool of cool, opaque water. In its most frequently used version, the platform remains in a fixed spatial location relative to the distal visual environment, and animals are released from four equally spaced points around the perimeter wall of the pool. These placements render simple motor responses ineffective and increase the likelihood that subjects swim in all parts of the pool and sample views of the room from all sectors. Furthermore, there are no cues inside the pool that indicate the location of the platform; the boundaries of the apparatus provide the only prominent and stable local cue, although the circular pool does not disambiguate spatial locations. A rat that has mastered this task will take fairly direct trajectories to the platform from each start point. If the platform is removed (for a probe trial), the rat will persist in searching where the platform was previously located. In contrast, if the platform location is moved from trial to trial, the search patterns in a probe trial are roughly distributed evenly throughout the environment, without notable preferences for any particular location (152). The Morris water task offered a simple way to measure place learning and memory in a behavioral context that did not involve a strong working memory component, required less training than other tasks (including the radial arm maze), and was less ambiguous with respect to interpreting the nature of the processes underlying performance. A casual literature search of the number of papers reporting the use of the Morris water task reveals that it has undoubtedly been the most popular behavioral task for rodents for almost three decades, and its popularity appears to be increasing.

2. Evidence for control of navigation in the Morris water task by distal visual cues

On the basis of the basic procedures, apparatus, and behavioral observations, it is generally agreed that animals learn to navigate to the platform based on its fixed spatial relationship to the available distal visual cues **(TABLE 1)**. When distal cues are systematically rotated, transpositioned, or removed, a similar pattern of results to that obtained in the radial arm maze (228) is observed in the Morris water task. Rotation of the distal cues results in a corresponding rotation of orientation and search in the water task (141, 259), although evidence that distance to the pool wall is an important cue has also been presented (73, 140, 245). Furthermore, deletion of single cues or a subset of cues does not typically disrupt behavior provided that a sufficiently rich distal cue environment remains. For example, water task performance by well-trained rats does not appear to be disrupted by distal cue removal provided that at least two cues remain (180, 190). This observation is consistent with the idea that the spatial relationships among distal cues are critical for accurate spatial navigation in this task; however, the generality of this particular observation is not clear. Individual distal cues have been shown to exert significant control over behavior (43, 193), and in some studies a single distal cue has been shown to be sufficient for learning and performance comparable to that observed with a rich constellation of distal visual cues (58) (J. R. Keith, personal communication). Furthermore, direct experience with spatial relationships among distal cues does not appear to be necessary in order for a set of cues to control navigation in the water task (24). Nonetheless, the general consensus among researchers who utilize this task (and certainly

Table 1. *Quotations through the years demonstrating the standard notion of the prominence of distal landmarks in the control of spatial navigation and place cell firing*

Year: Quote
1981: ". . . rats can rapidly learn to locate an object that they can never see, hear, or smell provided it remains in a fixed spatial location relative to distal room cues." (152) (p. 239)
1991: "With regard to place learning, one of the most sensitive assessments of hippocampal system damage involves the Morris water maze. Rats learn to swim to the locus of an invisible escape platform from various starting positions, guided solely by distal visual (place) cues." (31) (p.266)
1994: "The [water maze] task requires rats to find a particular location in space solely by means of visual cues external to the apparatus." (22) (p. 496)
1994: "When, for example, a rat is exploring a radial-arm maze, place cells in its hippocampus respond to places defined in relation to objects in the environment outside the maze (for example, lighting fixtures, cabinets, and racks of cages)." (22) (p. 498)
1997: "Most investigators agree that PCs [place cells] fire in relation to the constellation of distal, visual stimuli in the environment, such as posters on a curtain surrounding a maze." (85) (p. 20)
1998: "One strategy was based entirely on cues that surrounded the pool, and could have involved information about the geometric relationship between the platform and a set of these cues. In other words, rats used a cognitive map to define the position of the platform." (176) (p. 77)
2000: "When released at random locations around the pool, the mouse must use contextual (spatial) cues—markings on the walls of the room in which the pool is located—to find the platform." (105) (p. 1267)
2009:"The only cues available are outside the pool, so the rat must learn the relation between several cues in the room and the platform's location." (120) (p. 174)

Reference numbers are given in parentheses.

among the general neuroscience community) is that rats learn to navigate to the platform based on its fixed spatial relationship to the constellation of distal visual cues. Following the early descriptions of the spatial firing characteristics of place cells in the hippocampus (167, 168), subsequent demonstrations that rats with hippocampal lesions are impaired at place navigation in the Morris task (151, 225) and do not react normally to changes in the spatial configuration of cues (261) further strengthened the belief that navigation in the water task critically depends on the spatial relationships among distal cues and the escape platform.

3. *Experience viewing distal cues and behavioral flexibility in the Morris water task*

Learning and performance in the Morris water task are robust in the face of departures from the basic procedures described in section II*D1*. For example, releasing subjects from a subset, even just one, of the possible start locations still produces evidence for place learning with enough trials, such that, if rats are released from other start locations, they can swim directly to the escape platform (152). Thus rats can learn to execute a trajectory to the platform from a release point that was never used in training, which conforms to the idea that rats form spatial cognitive maps of the environment and can compute novel paths to a goal. Subsequently, however, Sutherland et al. (223) demonstrated that accurate navigation requires that the subject has previously visited the vicinity of the novel start location as part of a swim trajectory leading to escape from the water. Using a Plexiglas barrier and/or a curtain to bisect the pool, these authors systematically controlled experience swimming through and viewing distal cues through the part of the pool containing the novel release point. The broad conclusion based on the outcome of these manipulations was that such experience was critical for the rat to navigate to the platform from the novel release point, and that rats learn to navigate to the escape platform within a range of familiar views of the distal cue environment experienced during training. Matthews and Best (139) questioned this interpretation, suggesting that a generalization decrement on test trials when the Plexiglas partition was removed could account for the lack of accurate trajectories from novel release points. When the partition was slowly faded over several trials (by moving it from the center to the periphery of the pool), Matthews and Best found that rats were able to escape faster than rats for which the partition was abruptly removed, even though rats in the faded condition had not swam in the region of the pool near the novel release point during fading. Rats in the faded condition that performed at median levels tended to navigate to the center of the familiar region of the pool first before taking a direct trajectory to the platform and had slightly longer latencies than rats with unrestricted access to all parts of the pool. Overall, these observations suggest that a generalization decrement could account for a considerable proportion of the effect reported by Sutherland et al., but also suggest that navigation from a novel release point may still not reach the degree of accuracy achieved with unconstrained access to the environment during training.

Hamilton, Driscoll, and Sutherland (77) replicated the manipulations of Sutherland et al. (223) in humans using a virtual (computerized) variant of the water task in which access to any region of the pool could be restricted without introducing a visible partition. The results were identical to the findings of Sutherland et al. (223) in that restricting access to a region of the virtual pool resulted in poorer performance from a novel release point within the restricted region compared with participants who had experience navigating through all parts of the virtual pool while on a path to the platform. Because a visible barrier was not used, the results obtained in humans cannot be accounted for exclusively by a generalization decrement. Furthermore, consistent with the idea that rats learn to execute particular trajectories learned during training, Whishaw and Mittleman (249) demonstrated that when rats fail to locate the platform on their initial trajectory, they frequently return to the release location and attempt the same trajectory again. In the context of these observations, it is important to note that performance in the Morris water task is multifaceted and involves processes related to the computation and execution of trajectories to the escape platform as well as search behaviors that can be focused at locations where reinforcement is expected. As such, researchers generally recognize the need to distinguish between processes involved in navigation between locations (getting there) and recognizing particular locations (knowing where) in tasks like the Morris water task (223, 249, 250).

The idea that learning in the water task involves learning the location of the platform relative to the available cues was captured well in the perceptual matching model of Wilkie and Palfrey (256). This mathematical/computational model learned to recognize the spatial location of the platform by storing a perceptual memory of the view of the available distal cues from the platform and attempting to systematically reduce the difference between the current view and the remembered view from the platform. Sutherland et al. (226) reasoned that if rats learn the location of the platform on the basis of its fixed spatial relationship to a constellation of distal cues, then experience viewing the distal cues from the platform location should facilitate subsequent swim training to the same platform location. They reported a modest benefit of platform placement experience, and Keith and McVety (106) later provided additional evidence consistent with this type of latent spatial learning in the Morris water task in the form of reduced escape latencies following platform placement. Chew et al. (29) pointed out, however, that animals do not typically take direct trajectories to the platform during the trials immediately after platform placement experience. Thus, while a reduction in escape latency suggests that platform placement experience leads to some improvement, the fact that animals do not execute direct trajectories to the platform precludes the strong conclusion that the ability to navigate to the precise spatial location of the platform was learned. Sutherland et al. (223) further demonstrated that nearly all of the information necessary for place navigation performance is acquired during swimming, not during time spent on the platform. When rats are on the platform, they clearly sample the cues around the room, rearing and rotating often (particularly during early training) (73). Limiting this type of experience, however, appears to have only subtle disruptive effects on performance, whereas limitations on the ability to view cues while swimming to the platform causes larger disruptions in acquisition of place navigation (4, 133, 223). Thus, taken together with the data described above, it appears that information acquired while rats are swimming toward the platform is critical; information obtained while on the platform can contribute modestly to later performance (226), but it is not essential to learning (but see Ref. 43 regarding individual differences in latent spatial learning in the water task).

4. Control of navigation by room and apparatus reference frames

Although the observations described in section II*D3* indicate that experience gained during navigation to the escape platform in the Morris water task is more critical than information gained while at the platform itself, the basic idea that rats learn to navigate to the platform on the basis of its fixed spatial relationship to the available distal cues certainly was not weakened by these observations, and this view continues to be the preferred characterization of how rats solve the water task. The fact that the platform is in a fixed spatial relationship to distal visual stimuli is, however, neither sufficient to conclude that animals learn to navigate to a precise location in the water task defined by these cues, nor does it rule out the possibility that animals learn to move in the direction of the platform within the room and pool. Following a preliminary study by Weisend et al. (245), Hamilton et al. (74) addressed this issue in the Morris water task. Rats were trained to swim to a hidden escape platform that remained in the same location throughout training. The pool was then repositioned in the room such that the absolute spatial location of the platform in the room was centered in the opposite quadrant of the pool. A single, no-platform probe trial was run with the pool in the shifted position **(FIG. 4)**. If a rat was trained with the pool in position 1 and the platform in location B, moving the pool to position 2 for the no-platform probe trial put the location of the platform in the room reference frame (location B) into conflict with the location of the platform in the apparatus reference frame (location C). (Hamilton et al. referred to locations B and C as the absolute and relative locations, respectively.) The probe results showed that rats swam directly to and persisted in searching at the relative (pool-based) location, as if they were directly trained to navigate to this location. In contrast, rats treated the absolute (room-based) location as if it were a novel, untrained location.

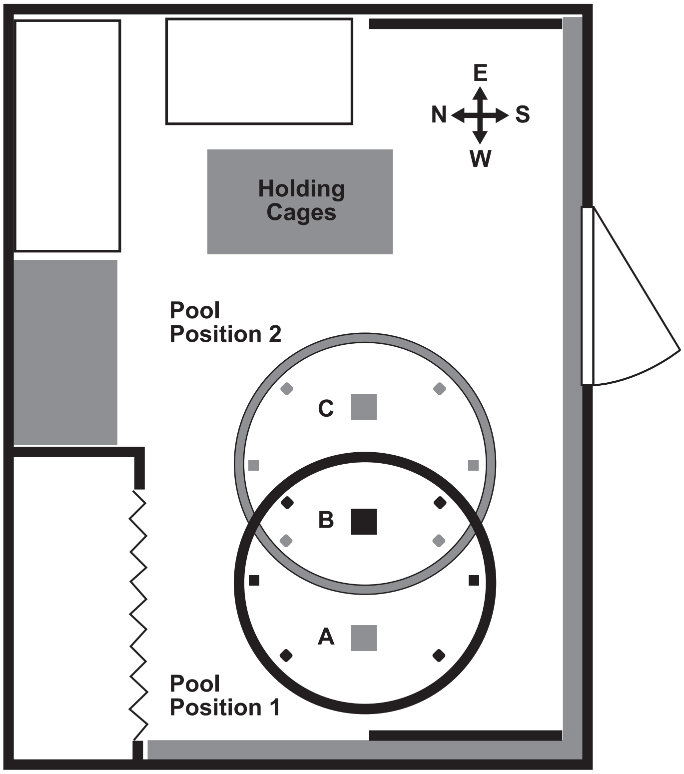

FIGURE 4. Layout of the room used in the experiments of Hamilton and colleagues showing the two locations where the pool could be positioned in the room. Pool positions 1 (black) and 2 (gray) represent the same pool positions used by Hamilton et al. (72–74) and Akers et al. (1, 2). Each pool position was separated by 75 cm (the radius of the pool). During training, the platform was typically located at the black rectangle labeled *B*; the gray rectangles (locations *A* and *C*) mark comparison locations (relative/opposite) used for probe trial analyses. The small circles (SW, SE, NW, and NE) represent release points used during training trials, and the rectangles (north-most and south-most points) represent release points used during no-platform probe trials. Black indicates release points for pool position 1, and gray indicates release points used for pool position. [From Akers et al. (1).]

The preference for navigation to relative locations in the apparatus described above has been demonstrated in a broad range of procedural variants of the Morris water task. These include limited training (8 trials), extensive training (240 trials) (73, 74), brief (5 s) and longer (30 s) experience on the platform at the end of each trial (74), as well as when the platform is relocated every four trials (73) in a moving platform variant of the water task (221, 247). The preference has also been demonstrated in preweanling rats (1) and in humans in a virtual variant of the Morris water task (75). Hamilton et al. (73) also found a weak preference for navigation to the relative location after a single platform placement experience.

Importantly, rats can learn to navigate to the absolute location if explicitly trained to do so using methods similar to those used in dry maze tasks (12, 94, 211, 222). In one experiment, the pool was relocated on each trial and the escape platform either remained in the same relative location in the pool or the same spatial location in the distal cue reference frame. Both adult (73) and preweanling (2) rats learned to navigate to the relative location faster than they learned to navigate to the absolute location, although both young and adult rats were eventually able to perform both tasks equally well. One interpretation of this outcome is that the pool is the dominant reference frame for the rat, and training the rat to navigate to the absolute location in the room requires a manipulation that reduces the influence of the pool. When the platform occupies different relative locations in the pool on each trial, the predictiveness of the pool reference frame is reduced, thereby allowing the room reference frame to dominate. Hamilton and co-workers (72, 73) further evaluated this idea, attempting to reduce control by the apparatus reference frame by filling the pool nearly to the top with water. Under this condition, rats displayed a modest preference for the absolute location of the platform in the room reference frame over the relative location in the apparatus reference frame, and the rate of learning was reduced compared with situations in which the pool wall is a prominent visual cue. Hamilton et al. (72) later showed that preference for the absolute location in the room was transient, and with more training rats switch to a preference for navigation to the relative location. This type of manipulation has not been used extensively, so the generality of these observations and the features of this manipulation that result in a preference for absolute place navigation are not well-established. For example, using a water T-maze, Whyte et al. (251) performed a similar manipulation, but failed to observe a preference for navigating to a location in the room reference frame by reducing control by the apparatus. The differences in results in the Morris water task and the water T-maze may be related to differences in how effective this type of manipulation is at reducing apparatus control in these tasks, and examination of these differences may yield important clues regarding the role of the apparatus in control of behavior.

It is important to acknowledge that complete elimination of the apparatus as a frame of reference in the Morris water task is practically impossible, as the water task requires an effective boundary to preclude escape from the pool at the boundary. Thus a small amount of the pool wall remained visible in the studies by Hamilton and co-workers (72, 73). These authors suggested that the shift from a preference for navigation to the absolute location to a preference for navigation to the relative location could have resulted from an increasing amount of control over behavior by the apparatus over the course of training; that is, if the apparatus provided only weak control early during training, animals navigated primarily on the basis of the distal visual cues. As the apparatus gained more control, navigation began to be controlled by both room and apparatus cues. One way to conceptualize this pattern is to consider the types of visual information involved in the control of navigation. Distance and direction (orientation) information may be utilized in any navigation situation; however, the sources of this information and how the information is used vary with the situation. In the standard water task, direction (orientation) information is provided by the distal cues. This type of information cannot be provided by the apparatus because it contains no polarizing features that provide an orientation signal. The apparatus could, however, provide distance information. For example, rats could learn the distance of the platform from the pool wall. If direction information from distal cues and distance information from the apparatus are combined, the animal could orient and move in a particular direction from a specific location and expect the platform to be encountered at a particular distance from the pool wall. In contrast, if the distal cues provide both distance and direction information, it would be possible to navigate to a precise location within the room reference frame. The observation that reducing the pool wall as a cue, or explicitly reducing control by the pool via training procedures, results in navigation to a location within the room reference frame provides strong support for this conceptualization.

Taking advantage of the capabilities of a computerized, virtual Morris water task for humans which allows greater control over the environment, Hamilton et al. (75) systematically evaluated the effect of reducing the size of the apparatus (pool wall), ranging from an apparatus boundary wall that was a prominent visual cue to a condition with no visual apparatus boundary. There were two major observations. First, there was a preference for navigation to the relative location of the platform in the pool in all conditions where a boundary was detectable, whereas a preference for navigation to the precise location of the platform in the room reference frame was only observed when there was no visible apparatus boundary. Second, the proportion of participants who learned to take direct trajectories to the platform decreased as the size of the pool wall was reduced, with the worst performance observed in the condition with no detectable apparatus boundary. This outcome is contrary to what would be expected if the distal cues were the major source of control related to place navigation. The apparent primacy of control by local apparatus reference frames in rat and human variants of the water task is reminiscent of the observation that spatially ambiguous geometries that provide a local reference frame may gain considerable control over behavior, even when conspicuous landmarks that provide unambiguous information regarding locations are present (26; see also Refs. 27 and 28 for recent theoretical commentary on the geometric module). The work of Pearce and colleagues (83, 177) has shown that if the apparatus geometry is capable of disambiguating spatial locations, these cues appear to be the prominent source of control relative to other features. These basic phenomena have also been demonstrated in human participants in virtual navigation tasks (183, 184).

The work of Doeller and Burgess (47, 48) on control by boundaries in human virtual navigation nicely illustrates that boundaries play an important role in the type of navigation involved in the Morris water task. The virtual environments used by these researchers differed, however, from those used by Hamilton et al. (75) in one major respect that is important for the current discussion. The distal cue environment used by Doeller and Burgess was sufficiently far away (rendered at infinity) from the local apparatus reference frame such that the size of the distal cues did not change as the participant moved in the apparatus. Thus the distal cues could only provide orientation information, but provided no signal regarding distance that could be used in isolation to determine precise spatial locations. Nonetheless, participants were able to navigate directly to a goal location within the local apparatus reference frame. The distal cue environment used by Hamilton et al. was arranged such that the size of the distal visual cues changed dramatically as participants moved through the virtual pool. Thus the distal visual cues alone could have provided useful distance and direction information. Nonetheless, the distal cues appear to have primarily contributed to navigation by providing orientation information, even though they could have provided sufficient information to control navigation to a particular location independently of the local apparatus reference frame.

5. Influence of local and distal frames of reference in the water task: sequential or simultaneous?

Based on the collective findings from rats and humans, Hamilton et al. (75) suggested that navigation in the water task and related tasks could involve *1*) distinct, sequential processes controlled by the distal room cues and apparatus cues (from the pool) and/or *2*) a simultaneous interaction between the two sources of control. With respect to the first possibility, they proposed that navigation to the relative location in the pool when the pool is repositioned involves a movement vector, in which the directionality of the trajectory is controlled by the distal room cues and subsequent search for the platform is controlled based on distance from the pool wall. With respect to the second possibility, they proposed that the primary function of the distal cues is to disambiguate locations within the pool reference frame; thus the movement vector would involve selection of direction and distance relative to the local apparatus reference frame. Under this view, subjects learn to navigate to a particular location in the pool based on distal room cues that disambiguate locations within the local apparatus reference frame, rather than learning to navigate to a particular location within the room reference frame. These explanations are not necessarily mutually exclusive, and it may prove difficult to distinguish them experimentally. For example, rats show a preference, albeit weak, for navigation to a precise location within the local apparatus reference frame after platform placement alone (i.e., with no experience actually swimming along a trajectory to the platform). Platform placement does not provide experience swimming to the platform; thus these data cannot be explained in terms of the animals learning to swim in a particular direction in the room and apparatus. The preference for the relative location in the apparatus suggests that during platform placement rats learned the location of the platform within the apparatus rather than its location in the room reference frame. Furthermore, in the experiment described above in which Hamilton et al. (73) moved the pool between four different locations and kept the platform in the same relative location in the pool, the rate of learning was comparable to what is observed in the standard water task where the platform and pool remained in a fixed location relative to the room reference frame. When tested with the pool in a novel position in the room, rats showed a clear preference for the relative location in the pool. It is important to note that these procedures do not allow a single, reliable directional response to be learned, and are, therefore, more consistent with the idea that distal cues serve the function of disambiguating the local apparatus reference frame rather than supporting a pure directional response. Similarly, in the standard water task, it is not possible to solve the task by learning a single directional response relative to the room reference frame because multiple release points are utilized. Thus the totality of the findings from the water task experiments of Hamilton et al. most strongly support the conclusion that rats learn to navigate to locations in the local apparatus reference frame rather than learning single directional responses in which the directionality of the response trajectories are controlled exclusively by the distal room cues. Nonetheless, these observations do not rule out the possibility that local apparatus and distal cue reference frames control behavior independently. For example, rats could learn multiple, distinct directional responses from each release point, and/or pool position in the moving pool manipulation, that are conditionally controlled by stimuli that reliably distinguish release points (and/or pool positions).

The idea that rats might initially orient in the direction of the platform and then search at an appropriate distance from the pool wall sequentially was partially motivated by data obtained in a cued variant of the water task. Hamilton, Rosenfelt, and Whishaw (78) trained rats to navigate to an escape platform marked by a conspicuous, proximal, visual cue with a typical constellation of prominent distal visual cues also present. These authors noted that shortly after rats began swimming in the direction of the cued platform they engaged in head-scanning prior to swimming more or less directly to the platform. They also observed that this head-scanning was accompanied by alterations in swim kinematics, the most clear being a momentary reduction in swim velocity followed by acceleration to the platform. Tests with the cued platform removed or relocated revealed that the initial trajectory (~1–2 ft.) was directed toward the trained spatial location of the platform. If the platform was absent, the subsequent portion of the swim was inaccurate; however, if the platform was present but in a novel location, rats would first swim in the direction of the trained location, then swim directly to the cued platform. This led these authors to suggest that distal and proximal cues control distinct sequential aspects of navigation. Consistent with this interpretation, when the rats were tested with novel distal cues, the initial trajectory was disrupted even though the cued platform was present and the rats had already mastered the cued navigation task in a different environment. Applied to the hidden platform task, this sequential control hypothesis suggests that the distal cue reference frame controls initial orientation and the local apparatus reference frame controls subsequent aspects of the trajectory. Hamilton et al. (74) performed the pool relocation experiments described above with a conspicuous cue marking the escape platform. During a test trial, the pool was repositioned and the cued platform was either placed in the absolute location in the room or in the relative location in the pool. Surprisingly, rats tested with the platform in the absolute location did poorly and either navigated toward the relative location of the platform (i.e., in the opposite direction from where the cue was located for the test) or were otherwise disrupted, whereas rats tested with the cued platform in the relative location swam directly to the platform. Collectively, these observations strongly support the idea that distal cues control initial orientation and proximal cues control subsequent aspects of behavior on a given trial.

Results obtained in humans are also consistent with the notion of sequential control by room and apparatus cues (75). In one study, participants were trained to navigate to a hidden platform in a fixed spatial location in the virtual Morris water task while the location of eye fixation in the virtual environment was obtained (250 Hz) as participants navigated to the platform. Participants who learned to take direct trajectories to the platform consistently sampled distal room cues during the early aspects of the swim (0–25% of the total path length), after which they looked directly at the precise location in the pool where the platform was located. In contrast, participants who failed to solve the task by taking direct trajectories to the goal tended to look almost exclusively within the pool reference frame, which contained no disambiguating spatial information. The sequential control of navigation to a hidden platform in human and rodent variants of the Morris water task may represent specific examples of a more general situation where directionality of the initial trajectory is selected based on distal cues, and subsequent control is provided by local features of the environment closer in proximity to the goal. We reiterate that this sequential hypothesis and the idea that distal cues disambiguate the local apparatus reference frame are both supported by empirical data (72–74) and although the preponderance of the data support the latter, neither should be ruled out at this point. Furthermore, because these important frames of reference do not change location relative to one another in typical procedures, another possibility is that animals and humans also make use of spatial location information provided solely by distal cues. We emphasize the fact that the preferences described above are only demonstrable in test situations where some manipulation of the frames of reference is performed; therefore, the data should be interpreted to indicate that navigation to the relative location in the apparatus is preferred. The conclusion that animals and humans do not learn the spatial location of goals relative to distal cues alone cannot be supported with these data. Additionally, there are alternative explanations that warrant further consideration in future research. One idea to be explored is that, when navigation is associated with a room-based frame of reference, it is based primarily on the geometric boundaries of the room, rather than on the distances to configurations of individual landmarks. Another explanation is the view-based matching account suggested by Cheung et al. (28) (see also Ref. 27). Under this view, the critical process is not one of recognizing a particular place relative to distal cues alone, but rather matching the perceived view of salient features of the environment, as viewed from the platform, which would include the pool wall. When the pool is repositioned for test trials, the relative position in the pool would most closely match the view from the platform location used during training compared with any other location in the pool, although some generalization decrement may be expected. View-based matching can account for a great deal of data obtained in the rodent and human experiments described here. It is not clear, however, how such an approach would account for the dynamic changes in stimulus control during an individual trial. Although there are clear differences among these alternative accounts, it is perhaps most important to emphasize that these explanations represent an important departure from the generally accepted view that rats learn to navigate to a hidden escape platform in the Morris water task based on its fixed spatial relationship to the available distal room cues and, more generally, the idea that distal cues provide the only (or most) important source of control of spatial behavior.

6. Control of navigation in dry maze and open field tasks by room and apparatus cues

As noted above, the distinction between place and direction highlighted by Blodgett et al. in the T-maze (12) did not have a considerable impact in the years immediately following its publication. Recently, however, D. M. Skinner and colleagues have replicated and extended the work of Blodgett et al. to address the relative influence of direction and place in dry mazes (e.g., T-maze, plus-maze), open field environments that are commonly used in electrophysiology studies, as well as related water tasks (e.g., water T-maze)

(94, 211, 212, 222, 251, 260). In their initial report, Skinner et al. (211) replicated the original work of Blodgett et al. (12) in the T-maze, showing that responding based on direction was learned more readily than navigation to a location in the room. They also extended this pattern of observations to a square open field environment that was moved between two locations throughout training (FIG. 5). All rats were started in the middle of one side of the open field, and two potential sites of reinforcement were located in the corners of the opposite side. For rats in the Direction group, navigation in a particular direction within the apparatus and room reference frames was reinforced. The apparatus positions, release points, and sites of reinforcement were arranged such that animals navigated in a consistent direction, but navigated to different locations in the room and performed different turning responses on each trial. In each of two Place groups, navigation to a location in the room reference frame was reinforced. In these groups, the apparatus positions in the room, the release points, and the sites of reinforcement were arranged such that animals navigated in different directions and performed different turning responses on successive trials. Rats in the direction group reached criterion in significantly fewer training trials than rats in one of the place conditions (Place 1, **FIG. 5**); however, one of the place groups learned as well as the direction group (Place 2, **FIG. 5**). The same patterns of data for the Direction, Place 1, and Place 2 groups were also obtained in both dry (211) and water (251) T-mazes.

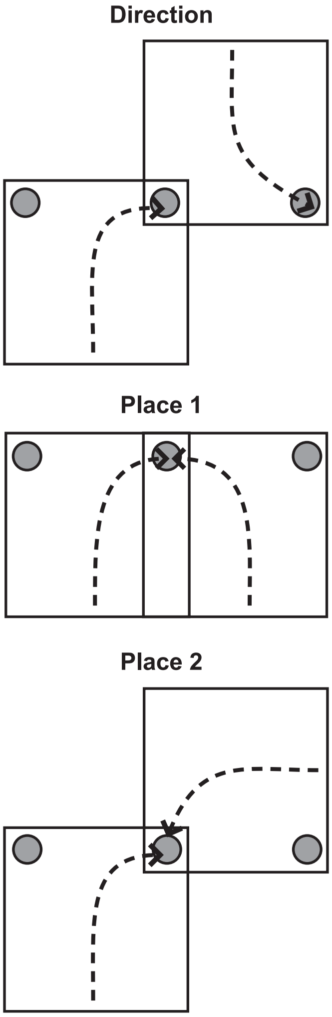

FIGURE 5. Diagram of the direction, place 1, and place 2 conditions utilized by Skinner et al. (211). The squares represent the boundaries of a single square open field that was positioned in one of two locations in the room. The gray circles indicate potential locations of reinforcement. In each condition, the apparatus was moved (translated) between the two possible positions for each trial. The dotted lines indicate the paths from the release point to the reinforced location for each apparatus position. In the direction condition, navigation in the direction of reinforcement within the apparatus and room was reinforced. In the place 1 and place 2 conditions, navigation to a particular location in the room regardless of the apparatus position was reinforced. Rats learned the direction and place 2 tasks much faster than the place 1 task.

The work of Skinner et al. has since been focused on attempting to elucidate the factors that influence successful place navigation. Ritchie, Aeschliman, and Pierce (188) noted that place navigation could not be distinguished from other forms of responding if the animal could not discriminate the starting points from trial to trial. Similarly, Skinner and colleagues (94, 211, 222) suggested that the release locations were more distinctive in the Place 2 condition, in which successful place navigation was obtained, compared with the Place 1 condition. The ease with which starting locations are discriminated may be related to similarities among the local views of the cues from the release points, but may also be related to differences in interoceptive cues, such as those involved in path integration during performance of the maze and transport to/from the home cages and maze. For example, Skinner et al. (211) noted that release points that are sufficiently far apart so as to be easily discriminated based on visual cues also involve more distinctive paths from the animals' holding cage to the various release points, and both signals appear to be important for successful solution of the Place 2 problem. Recently, Skinner et al. (212) have demonstrated that the distinctiveness of the initial orientations at the release points may be more important than the distinctiveness of the release locations. For example, if a T-maze is translated (e.g., east-west) and the start point is in the same location in the apparatus (e.g., south), the initial orientations for each maze position are similar (e.g., toward the north). In contrast, when the T-maze is rotated, the initial direction of movement as well as the direction of movement in the reinforced arm are more distinctive. Of course, rather than promoting true place navigation, it is also possible that distinctiveness among the release points could promote the development of multiple, distinct directional responses that are brought under the conditional control of information that distinguishes the start points (e.g., distance, visual distinctiveness, path integration). Explanations of this type are difficult to rule out with the presently available data, especially given that a single release point is used for each apparatus position, which would require that only two distinct directional responses would need to be learned.

One observation from an experiment using variations on a standard plus maze provides some support for the idea that navigation to a particular location within the apparatus is important in dry maze tasks. In one group of rats, Horne et al. (94) used a single plus-maze that was translated between two positions in the room (e.g., east-west). A single release location in the maze was used (e.g., south), and reinforcement was always located at the same place in the room (e.g., in the right arm when the maze was in the west position, and in the left arm when the maze was in the east position). In this condition, the rate of learning was considerably slower compared with all other conditions that were evaluated. Another condition involved using the same apparatus positions (e.g., along the same east-west axis); however, instead of using a single plus-maze, a double plus-maze that occupied both positions of the single plus-maze simultaneously was used. The location of reinforcement and start locations were the same as in the single maze condition, which meant that the location of reinforcement was always located in the center of the two mazes (same relative location in the apparatus), as well as being located in the same spatial location in the room reference frame. Rats in this condition met criterion during training faster than all other conditions for which reinforcement occupied different relative locations in the apparatus, but was located in the same place in the room. One explanation for this observation is that in the single plus-maze condition, the relative location of reinforcement in the apparatus differs from trial to trial, whereas the location within the apparatus is the same from trial to trial for the double plus-maze.

The work of Skinner and colleagues indicates that distal cues control the selection of a trajectory to a goal location within an ambiguous apparatus; however, the contribution of information from the apparatus, or cues within the apparatus, when it is translated or rotated within the room have not been systematically evaluated. Biegler and Morris (8, 9) developed a task designed to allow for independent assessment of control of navigation by distal cues and local landmarks in a dry open field that provides some data relevant to the issue of combined control by distal cues and local, intra-apparatus cues. In several experiments, Biegler and Morris trained rats to navigate to a feeder (F+) within a square apparatus, the location of which was predicted based on its fixed distance and direction from a conspicuous landmark. A second landmark indicated the location of a feeder that did not allow access to food (F−), and the apparatus was surrounded by a set of distal cues (white and black curtains) that provided orientation information. The primary manipulation in these experiments was the stability of the landmarks relative to the distal and apparatus cues from trial to trial. Only when the landmark that predicted the location of food remained in a fixed spatial location was the rats' search behavior focused at the location of reinforcement (F+), whereas when the location of the landmark varied it exerted little control over search behavior at the reinforcement location (see Ref. 176 for a similar approach using a single local cue in the water task). Interestingly and unexpectedly, when the landmarks that remained in a fixed location during training were removed during test trials, the control of search behavior by distal cues alone was shown to be quite weak. One possibility suggested by Biegler and Morris (7) is that distal cues and the local landmark cues work synergistically to control behavior, with the distal cues providing direction information and the local landmark providing a distance signal. This interpretation and the data on which it is based fit nicely with the idea that distal cues do not provide an exclusive source of control over spatial behavior, and suggest that distal and local cues can provide distinct sources of control in dry land navigation tasks. As Biegler and Morris (7) emphasize, distal orientation cues are not likely to provide a signal capable of resolving precise locations within the apparatus but can provide orientation information, whereas local features of the environment provide a more precise signal for localizing specific locations. The experiments conducted by Biegler and Morris have not been repeated with translation of the apparatus within the distal room reference frame as a manipulation; however, based on the available data, we would expect apparatus translation to result in navigation to the location predicted by the local landmarks and apparatus with directionality determined by distal cues, rather than navigation to the precise location exclusively within the distal room reference frame.

Although there are important methodological differences between the Morris water task studies and the dry maze and open field studies described above, and additional work is needed to better understand the relative contributions of room and apparatus reference frames in these tasks, it is most important for the purposes of the present review to emphasize *1*) the compelling demonstrations that navigation in the direction of reinforcement within the apparatus dominates over navigation to locations defined exclusively by the room reference frame, and *2*) the high degree of consistency between these observations and the data obtained in the Morris water task using comparable procedures. That similar phenomena are reliably observed in a wide variety of navigation tasks and methodological variations on these tasks (e.g., apparatus, motivation) indicates that the predominance of navigation based primarily on the local apparatus reference frame, or cues within this reference frame, holds considerable generality. Furthermore, because the predominance of the local reference frame has been demonstrated in dry maze and open field tasks such as those that are commonly utilized in physiology experiments, it is reasonable to assume that the physiology data obtained during goal-directed behavior and exploration in dry mazes and open fields involves similar preferences for navigation based on the local apparatus reference frame.

E. Summary

A growing body of data from studies using a broad range of apparatus and procedures, including dry land mazes, open fields, the Morris water task in rodents, and virtual navigation tasks in humans, give cause to question the common belief that spatial navigation in standard laboratory tasks involves navigation to precise spatial locations based exclusively or primarily on spatial information provided by distal visual cues. The early studies by Blodgett et al. (12) demonstrated that rats learn to navigate in the direction of reinforcement in room and apparatus reference frames more readily than they learn to navigate to precise spatial locations defined only by the room reference frame. The later work of Skinner and colleagues (94, 211, 212, 222, 251, 260) replicated and extended these findings in dry and water T-mazes as well as in open field environments, and identified some conditions in which learning to navigate to a single spatial location in the room reference frame were supported. Dudchenko (49) also studied the cues used by rats to perform an alternation task on the T-maze and reported only a modest influence of distal cues. The work of Weisend et al. and Hamilton et al. (1, 2, 72–75, 245) in the Morris water task established the basic importance of both distal cue and apparatus reference frames to the control of navigation in this commonly used task. The precise means by which local apparatus and distal cue reference frames interact are still not well understood. However, the manner in which control of navigation is achieved by these sources of information is currently being investigated by several laboratories. At this stage in our understanding of these types of control, it is important to emphasize that the hypothesized processes and sources of control are not mutually exclusive, and may combine in complex ways in the service of behavior (12, 186, 227). Given the similarity between recent physiological data and the behavioral data reviewed here, combined behavioral and physiological investigations will likely be influential in our understanding of how room and apparatus reference frames interact.

III. NEUROPHYSIOLOGY OF REPRESENTATIONS OF PLACE

A. Overview

Ever since the discovery of the spatially selective firing of rat hippocampal neurons by O'Keefe and Dostrovsky in 1971 (168), numerous studies have attempted to discover the types of information used by the hippocampus to generate the robust firing of these place cells. Recapitulating the development of thought regarding the control of spatial behavior (described in the first part of this review), early work on place cells suggested the primacy of distal cues over proximal cues in the control of place fields (162, 167). Evidence of intramaze cue control was overshadowed by the strong control by extramaze cues when the two sets of cues were rotated relative to one another. Furthermore, when the extramaze cues were rearranged in ways that disrupted their topographical relationships, place fields were disrupted, as was the rat's spatial performance (228). These results led to the standard, "textbook" notion that place fields were primarily defined by the constellation of extramaze cues that the animal senses at a particular location in a room.

Over the past 15 years, a number of discoveries have converged to remove distal cues from their privileged position as the major source of input controlling the firing of place cells. One set of studies demonstrated that self-motion cues and path integration strategies were critical, perhaps primary, sources of information controlling place fields and hippocampus-dependent navigation (142, 169, 248). This review will not cover these studies, but other articles have reviewed this material (142, 248). This review instead covers a second set of studies that have shown that local, apparatus-based cues, when made as salient as the distal cues, can exert strong control over the place cells. These apparatus cues can be surface textures (either visual or tactile) or apparatus boundaries. In parallel, physiological recordings of brain areas that are connected with the hippocampus have revealed an assortment of interacting cell types that suggest a division of function for how intra- and extramaze cues control the spatial representations of the hippocampus. We will argue that the primary source of spatial input to the hippocampus is a path integration computation embodied by grid cells of the medial entorhinal cortex (MEC) (71, 143, 166). The spatial framework embodied by grid cells exists as an internal, cognitive representation of location in the complete absence of exteroceptive cues, but it requires input from these cues to remain stable relative to the external world (71). The primary role of distal cues is to *1*) provide a global context signal that, in conjunction with local cues, allows the animal to recognize a familiar environment and 2) set the orientation of the internally generated MEC grid relative to the external world. For the latter operation, the distal cues implement this control not directly on the grid cells, but rather they directly control the preferred firing directions of the head direction (HD) cell system (in conjunction with idiothetic input from vestibular and other sources; Refs. 144, 145, 218–220). The HD system, in turn, sets the orientation of the grids. It is also necessary to align the grids in the *x*-*y* plane relative to the external world (i.e., align the phase of the grids). The most prominent cues for this translational alignment of the grid are the boundaries of the local apparatus itself (165). Boundary cells in the MEC, subiculum, presubiculum, and parasubiculum may have the necessary properties to perform this process, as well as for stretching the grid to conform to the geometry of the apparatus (5, 13, 132, 199, 215). Thus, rather than directly defining locations that cause place cells to fire selectively, the distal cues have a powerful, but largely indirect, role in terms of neural circuitry.

A cautionary word about the unit-recordings studies reviewed here is appropriate. In our descriptions of some studies, we state the numbers of cells that were reported to have behaved in certain ways when environmental cues were manipulated. When interpreting these numbers (and indeed numbers from all such neurophysiological studies, especially of highly flexible and plastic structures such as the hippocampus), one should always be mindful that the results typically combined the data from different animals and from different recording sessions. Neurons from different animals can respond differently to the same experimental manipulation, as the result of subtle differences in how the experiments were run, different training histories or experiences of the animals, differences in cell sampling, intrinsic differences between individuals, and so on. Even the same neuron can respond differently to repetitions of the same manipulation. Moreover, the results of these experiments are rarely black and white; there are usually exceptions to the main results in any experiment. Although modern, multichannel recording technologies help to overcome this limitation, with the ability to record many neurons simultaneously and develop a snapshot of neural ensemble activity within a single individual and a single session, this caveat still holds when these multichannel recordings are combined across data sets. Thus, in the following sections, we emphasize the overall pattern of results that each experiment demonstrates, rather than the precise numbers of cells that were controlled, for example, by local or global cues in a particular experiment. Important details about how individual subjects differed or how results changed over time can be found in a number of the original references.

B. Early Studies of Place Cells Emphasized the Dominance of Distal Cues

O'Keefe and Dostrovsky's (168) original report of place units in the hippocampus was a brief, anecdotal description of a small number of cells that fired selectively at a particular location. Rats were placed on a 24 × 36 cm surface, and hippocampal units were recorded as the rat moved on the surface. This report demonstrated that these cells were sensitive to multiple sensory modalities and that they fired to a conjunction of both spatial and nonspatial cues. For example, one cell fired only when the rat was in a particular location on the apparatus and when the investigator was lightly restraining the rat by hand. Importantly, the tone was set regarding the relative unimportance of local apparatus cues when they reported that the spatial firing fields were not affected by rotating the apparatus; that is, the place fields stayed in the same location relative to the room frame of reference, rather than rotating to remain bound to the apparatus frame of reference. This result was taken as evidence that the spatially correlated firing was not an artifact of the cell's responsiveness to an uncontrolled, discrete sensory cue located at the spot where the place field occurred.

Subsequent studies reinforced the notion that place cells were controlled by distal cues. O'Keefe's (162) first detailed description of place cells tested explicitly whether place cells fired as a response to a particular sensory cue at the location of the cell's place field on the apparatus. Replacing an arm of a three-arm maze with a new arm, interchanging the arms, and covering the arms with Perspex or cardboard had no strong effect on the spatial firing preferences of 13/14 neurons. Thus the cells could not have been firing solely or primarily in response to a local cue on the maze. Other anecdotal observations reinforced the notion that the cells fired relative to the distal-cue frame of reference. Although maze rotations were performed only rarely, because the rotations of the radially asymmetric three-arm maze were disturbing to the animal, one cell was described that kept its place field relative to the distal cues after a few repetitions of maze rotation. In contrast, a dentate gyrus neuron held its place field in a corner of the rat's home box when the box was rotated, following the local frame of reference of the box over the room frame of reference. Similarly, Kubie and Ranck (123) showed that place fields remained bound to the distal frame of reference when a radial eight-arm maze was rotated, but they were controlled by the local, apparatus frame of reference when a walled apparatus was rotated. O'Keefe (164) interpreted these results to show that local cues cannot be the sole determinant of place-cell selectivity, and that distal cues dominate in elevated mazes. This distal-cue dominance was critical for the initial demonstration that place cells were not simply responsive to local sensory cues that were present at a particular location, but were instead computing a higher-order property controlled by remote stimuli.

The control by distal cues was tested further in experiments in which both the apparatus and sets of controlled stimuli on curtains surrounding the maze were rotated independently. As shown previously, place fields were not controlled by rotation of a T-maze, but they followed the rotation of the curtain containing controlled distal cues (167). When all four distal cues were removed, most cells lost their special specificity (although numerous subsequent studies have shown that place fields can maintain themselves in the absence of external cues; see below). When one or two cues were removed, most cells still maintained their firing fields, suggesting that they were not responsive to any particular sensory cue. A few cells were disrupted by this cue removal, which indicated that these cells might be sensitive to individual distal cues. An alternative explanation, however, is that the hippocampus underwent a "global remapping" as a result of the environmental change in the sessions when these cells were recorded, which would not have been detected without the simultaneous recording of multiple place cells.

The dominance of distal cues was demonstrated further by O'Keefe and Speakman (170) in a study in which rats performed a spatial memory task on a plus maze. Controlled cues on a curtain enclosing the maze were rotated in between trials, and the rats were trained to go to a reward site on one arm determined by the location of the controlled cues. The place fields were controlled strongly by the rotation of the controlled cues. Weaker influences of the static background cues (such as uncontrolled laboratory room cues outside the curtained enclosure or cues on the maze itself) were also observed, such that some cells fired strongest only to a particular configuration of the controlled cues on the curtains and the static background cues. When the controlled cues were entirely removed after placing the rat on the start arm of the maze and allowing it to orient itself, the rats were able to perform the task based on their memory of the cue locations, and the place cells maintained their firing fields in the same locations relative to where the cues used to be **(FIG. 6)**. Importantly, when the controlled cues were entirely removed before the rat was placed on the maze, thus preventing the rat from orienting itself relative to the cues, the place fields maintained locations on the plus maze that were at the proper radial distance from the center of the maze but that occurred on unpredictable arms, as if the cells lost their directional anchor. The most important aspect of this finding was that the rat's behavioral choice was strongly correlated with the location of the place field. That is, if the place field was on the west arm during normal trials and the reward arm was the north arm, the rat would choose the south arm in the cue-removal trials if the place field was present on the east arm and would choose the east arm if the place field was present on the north arm. This result showed that *1*) the place fields could maintain a coherent spatial representation even in the absence of the controlled cues, *2*) the controlled cues appeared to set the orientation of this representation, and *3*) the animal's behavioral choice was correlated with (and potentially guided by) this representation.

The work of Muller, Kubie, Ranck, and colleagues (157, 158) helped to fortify the notions that place fields represented a legitimate spatial signal and that this signal was controlled by distal cues. O'Keefe's work demonstrated

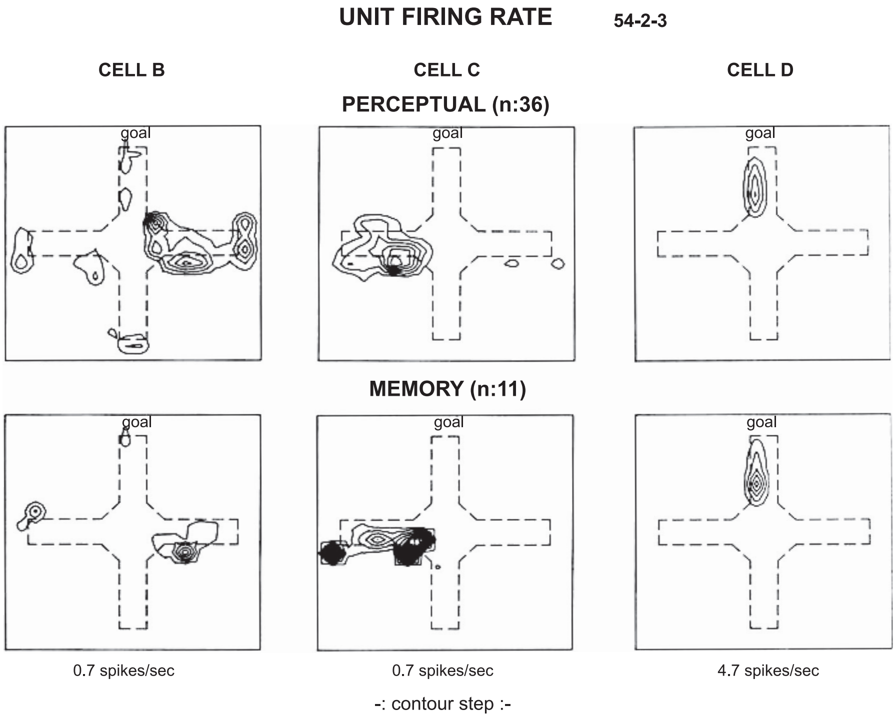

FIGURE 6. Place cells maintain spatial selectivity in the absence of controlling distal cues. Three cells are shown during a spatial learning task on a plus maze (170). The top row shows the firing locations of the cells as a contour map when controlled distal cues were present on the curtains surrounding the maze (perceptual trials). The cues were rotated between trials, and the rats were required to visit a goal arm that rotated along with the cues. The contour maps were aligned such that the variable goal arm was placed at the top of the figure, and the place fields are seen to be sharply tuned relative to the goal arm and the distal cues. The bottom row shows the firing locations when the distal cues were removed after the rat was placed on the maze (memory trials). The sharply defined contour maps show that the cells maintained place fields under these conditions, and that the locations of the place fields were consistent with the locations when the distal cues were present. [From O'Keefe and Speakman (170), with kind permission from Springer Science + Business Media.]

convincingly that the spatial correlate of place cells was not a simple artifact of spatially inhomogeneous, local sensory cues that drive the place cell at a given location. However, another possibility was that the cells might encode a particular motor action or behavioral variable that was correlated with space. Although this seemed unlikely from O'Keefe's data, the spatially inhomogeneous behavior of rats during spatial maze performance made this concern linger. Muller, Kubie, and Ranck (157, 158) developed a recording environment that minimized this concern by training the rat to forage for randomly scattered food in an enclosed chamber (typically a cylinder or square) with only a single polarizing cue card. The rat spent most of its time in motion as it searched for the food pellets, and there were no obvious behaviors that were biased to occur at any particular location in the chamber. Nonetheless, robust place fields were recorded under these conditions in all parts of the chamber. When the cue card was rotated between trials, the place fields rotated by a similar amount, suggesting that the cue card, at the periphery of the chamber, acted like the distal cues of earlier studies (123, 167) in controlling the firing of place cells. It is important to note that the potential influence of local cues on the floor was intentionally deemphasized by replacing the paper that lined the floor of the chamber before each session. Although this procedure helped to clearly demonstrate that local cues on the floor were not necessary to fire place cells (as the cells maintained their firing fields even when the paper was changed), it prevented a measurement of how strongly the local cues could control place fields when the local cues were put in conflict with the cue card on the wall.

The cue card used by Muller and colleagues was a large, very salient visual landmark that exerted strong control over place fields. A series of studies showed that other intra-apparatus cues, such as three-dimensional objects, could control place fields if the objects were placed at the periphery of the chamber. When 2 or 3 objects were located near the center of the cylinder, only 2 of 52 place cells were consistently controlled by a coherent rotation of the set of objects (32). However, when the same objects were placed in a row near the periphery, or placed as an isosceles triangle at the periphery, place fields were as strongly controlled by rotation of the objects as by rotation of a peripheral cue card (32). Interestingly, when the objects were arranged as an equilateral triangle at the periphery, 23/29 cells were controlled by a 120° rotation of the object set (33), showing that information about object identity was available to disambiguate the symmetrical geometry of the rotation. These objects at the periphery could exert control over the place fields even in blind rats, as long as the animal came in physical contact with at least one of them (195). When two objects in the center of a cylinder were rotated 90° as a rigid set, in the presence of a stable cue card along the walls, fields far from the objects were largely unaffected, whereas fields near the objects underwent a local remapping (126). When an object was replaced with a novel object, the place fields were mostly unaffected. These data reinforced the notion that distal cues are more important than proximal cues in orienting place fields. Even though a white cue card on the wall and the objects along the wall were local cues, in the sense that the rat had physical access to them and could sniff, touch, and taste them, the findings that they only controlled the place fields when they were located at the periphery of the chamber were consistent with the view that distal cues had preferential control of place fields over proximal cues.

A special case of a peripheral local cue showing control over place fields was the demonstration of such control by a goal (or reward) location (15). In this study, rats found water reward at one of five cups on a square platform (at each corner and in the middle). The platform was surrounded by a black curtain that masked external cues. The majority of place fields were located at individual reward cup locations; for example, one cell would fire selectively at the reward location at the SW corner but fire less (or not at all) at the other four reward locations. This preference could be interpreted as the place field map over-representing important locations (see also Refs. 53, 85, 89, 118, 119). When the reward cups were selectively baited, the baited locations became overrepresented, and place fields moved from one location to another as the reward site moved. This result could occur either if the cells were selectively encoding the goal location or if the reward cup was acting as a polarizing cue to orient the spatial representation. The reward cups were primarily at the periphery of the apparatus. As in the studies investigating discrete objects (discussed above), it is possible that the control by the reward site was critically dependent on the peripheral location, but this possibility was not tested. In contrast, Speakman and O'Keefe (217) failed to find strong control of the place fields by reward locations in an environment with controlled distal cues on the curtains surrounding a plus maze. In this study, the large majority of place fields remained bound to the controlled, distal landmarks. Lenck-Santini et al. (127) also failed to find control by a goal location in a Y-maze, even in the absence of salient distal cues. Thus the ability of reward sites to control place fields may depend, in part, on whether the goal locations represent the most peripheral orientation cue in the environment, whether there are other cues present that have stronger control over the orientation of the place cell map, or other factors such as the behavioral parameters of the task.

A number of early studies pointed dramatically to the fact that local cues had the potential to influence place fields as strongly as distal cues in animals with damage to the hippocampus and related circuitry. Miller and Best (147) recorded place cells on an eight-arm radial maze in control animals and in animals with lesions of the entorhinal cortex, which is the dominant source of cortical input to the hippocampus. In control animals, 26/26 place cells maintained their firing fields relative to the distal room cues when the 8-arm maze was rotated between trials. In contrast, only 1/17 place cells in EC-lesioned animals maintained their fields relative to the distal cues and 5/17 fields rotated with the 8-arm maze (i.e., these fields were bound to the local frame of reference). The remaining 11 cells either lost their fields or rotated their fields to an arm that was not predicted by either the local or distal reference frames. Fornix lesions also revealed a significant control by local cues (5/29 cells), although the majority of fields were controlled by distal cues (16/29). Similar results with fornix-lesioned animals were reported by Shapiro et al. (202), in which place fields tended to rotate with the maze and in which covering the maze surface with black cardboard tended to obliterate the fields. Hill and Best (87) recorded place fields from blind and deaf rats and showed that place fields were present in these animals, but 11/15 cells were controlled by local cues when the 6-arm radial maze was rotated. The remaining four cells fired in the same location in the room following maze rotation. However, when the rats were disoriented by 2–3 Hz spinning for 30 s before they were replaced on the maze, the fields of these cells followed local maze cues. Thus these experiments suggested either *1*) that local cues had a potential influence over place fields in normal animals but that this influence was completely overshadowed by the stronger distal cues and was unmasked only in lesioned animals (and animals whose sensory experience was severely limited), or 2) that these animals developed a compensatory mechanism to anchor their spatial representations to the local frame of reference, a tendency that is not present in normal animals.

The main results of the early experiments on place cells indicated that they were controlled more strongly by distal cues over local cues. O'Keefe (164) cautioned that these results did not imply that local cues were inherently incapable of promoting a spatial signal: "nondirectional local cues (olfactory and tactile) could be ruled out as the *sole* determinants of place cell firing by substitution of a different arm for the usual arm (p. 231)." The emphasis on "*sole* determinants" shows that he recognized that local cues could have a significant influence on place cell firing. Indeed, O'Keefe's (162) description of "misplace" cells, cells that fired in a particular location only when an unexpected stimulus occurred there or when an expected stimulus was absent, showed a convincing influence of local cues. Furthermore, in interpreting their results regarding the relative influence of controlled cues versus static background cures, O'Keefe and Speakman (170) stated: "A map of the enclosure is constructed on the basis of the invariant features of the environment, in this case, most probably on the basis of the *shape and texture of the maze*, the colour of the curtains, etc. Early in training the static background cues and the controlled cues are incorporated into this representation… (p. 26; emphasis added)." In spite of these comments, the results showing control by distal cues in the early experiments were so influential that, in combination with the behavioral data reviewed earlier, it became commonplace in the experimental literature and in textbooks to equate a hippocampus-dependent spatial representation or spatial behavior with control by distal cues. This assumption was made explicit in early computational models of place fields (84, 201, 204, 270). These models used variations of the same basic architecture. The sensory information about distal cues formed the input to the model, which learned a set of weights from these inputs onto an output cell such that the output cell fired in a single location (i.e., the output cell developed a place field). These early models formalized the idea that place cells derived their preferred firing locations by a triangulation procedure in which the angles and distances to a set of distal cues defined a location where the cell received maximal excitation.

C. The Importance of Local Cues: The Tide Turns

One obvious difficulty in interpreting the early experiments was that they did not necessarily equate the perceptual or behavioral salience of the proximal and distal cues when cue manipulations were performed. These studies were motivated by the question of whether place fields constituted a high-order, cognitive representation, or whether they could be explained as a simple response to a particular sensory stimulus. The demonstration that rotation of the apparatus had a minor influence over the place fields compared with rotation of the extramaze cues was crucial for demonstrating that the place signal was not tied specifically to a local stimulus or behavior that happened to be correlated with a particular spatial location, a result that would have been considered trivial. Rather, place fields were more likely the result of higher-order, cognitive processing. A new picture of the potential influence of local cues began to emerge when investigators intentionally increased the salience of the local cues. Young et al. (265) recorded place cells on a plus maze with different textured cue inserts on the arms of the maze (modeled after Ref. 173), with no prominent distal cues on the walls. The cues were rearranged after each arm entry, and the rat had to visit each cue type (ignoring the location of the cue) in a win-shift, working memory protocol. A three-way ANOVA revealed significant main effects of location, cue, and radial distance on the maze arm, as well as all possible interactions. Thus, in a task with no salient, distal cues and an explicitly nonspatial performance requirement, the intramaze cues exerted a significant degree of control over the firing of the cells. Nonetheless, there was a paucity of cells that fired to the cues alone (with no interaction with location or radial distance), even though the cues were the only important variable for successful task performance. It is unclear whether these results demonstrated a dysfunctional spatial mapping system under conditions in which the only salient sensory cues (i.e., the local cues) were in constant flux, or whether they indicated the encoding of nonspatial variables when these variables were important for task performance (as argued by the authors). If the latter interpretation were correct, one might have expected a higher proportion of cells that responded to the cues alone. Nonetheless, the results clearly showed that in normal rats, local, intramaze cues could have a powerful influence on place cells, as was shown earlier in animals with lesions (87, 147, 201).

Just as the early papers stacked the deck in favor of distal cues, the Young et al. (265) study stacked the deck in favor of local cues. The question remained whether the local cues could exert an influence over distal cues when they were matched in salience and placed in conflict with each other. Shapiro and co-workers (203, 229) investigated this critical issue using the same style plus maze as in the Young et al. (265) paper, but they included salient distal cues in the environment and a standard working memory protocol in which the rats had to visit each arm of the maze without repetition for each trial. Unlike the Young study, in which the local cues were scrambled after each arm visit, the rats ran multiple trials in which the cues were in a standard, stable configuration, intermixed with probe sessions in which *1*) the local and distal cue sets were rotated relative to each other (double rotation), *2*) the local cues were scrambled, *3*) the distal cues were scrambled, or *4*) individual cues were manipulated to test for control by single cues. These investigators found a mixture of results, in that some place fields were controlled by the distal cues, others by the local cues, and others showed remapping responses. Although more cells followed the distal cues (41/144) than the local cues (22/144) in the double-rotation sessions, this study showed a major influence of local cues even in the presence of salient distal cues.

In a very similar experiment, Brown and Skaggs (16) provided striking evidence for a dominance of local cues over distal cues in control of place fields. On the first day of experience in the double-rotation condition, place fields were controlled strongly by the local cues, even though salient distal cues were present. A significant influence of the distal cues was shown by the large number of place fields that remapped, but the number of place cells that rotated their firing fields as predicted by the rotation of the distal cues was no more than that predicted by chance. In subsequent days, two of four rats continued to show dominance by local cues, and two of four rats switched to a combination of distal-cue control and partial remapping. Whereas Tanila et al. (229) argued that both local and distal cues could control individual cells of a simultaneously recorded ensemble, Brown and Skaggs (16) suggested that such split control was due only to chance effects of partial remapping, as some cells that remapped happened to form place fields by chance at a location predicted by the rotation of the nondominant cue set. Regardless of the interpretation of the data in terms of such ensemble discordance, Brown and Skaggs (16) showed that the local frame of reference could dominate over the distal frame of reference, in conditions where both frames of reference contained salient cues. A similar conclusion was reached by Renaudineau et al. (185), who performed a double rotation of salient distal cues and local objects located at the periphery of a platform. The majority of cells remapped their place fields, but most of the cells that maintained fields after the double rotation were controlled by the local objects (especially those cells with place fields close to the objects).

Knierim (109) showed a dominance of local cues in some animals in a double-rotation paradigm on a circular track. The track was divided into four 90° segments covered by four different surface textures, similar to Shapiro et al. (203), as well as a standard array of distal cues on the walls. This paper showed that, when the proximal and distal cues were rotated opposite to each other, split representations occurred more than expected by chance (as determined by a Monte Carlo simulation). Thus, in agreement with Tanila et al. (229), both local and distal frames of reference could exert control over the hippocampal representation simultaneously. A number of individual cells showed split place fields in the double-rotation session, as one subfield rotated to follow the proximal cues and another subfield rotated to follow the distal cues. This split control was sometimes dynamic, as some cells were initially controlled by one set of cues in the initial laps of the double-rotation session and then switched their firing locations to (or developed new subfields at) locations predicted by the other set of cues. Animals showed strong individual differences in which set of cues dominated. Some animals were controlled strongly by local cues, others by distal cues, and others showed more split representations. Lee et al. (125) found a striking difference between the CA1 and CA3 regions in terms of the overall coherence of their spatial representations in the double-rotation sessions. Whereas CA1 place field ensembles were more likely to form split representations, with equal proportions of cells controlled by local as by global cues (in addition to a majority of cells that remapped or responded ambiguously), the CA3 place field representations were more coherent (reflecting the pattern-completion properties of the CA3 recurrent collateral system) and were controlled by the local cues. Overall, these results showed that salient local cues could exert a powerful control over place fields in normal rats, even dominating over distal cues, overturning the dogma that place fields were controlled exclusively (or primarily) by distal cues (16, 109, 125, 185, 203).

Bures, Fenton, and colleagues designed a variety of tasks in which the animal moved on a platform that was constantly rotating relative to the distal cues (18, 19, 57). In some versions, the rats had to learn to stay out of a segment of the platform to avoid shock. Under certain conditions, the animals showed that they could keep track simultaneously of where they were located in both the platform and room reference frames (19, 57). In one variation, the rats were "place-clamped," such that whenever they moved on the platform, the platform moved in the opposite direction to make the rats remain in the same location relative to the distal room cues. With this conflict between distal cues and idiothetic/substratal cues, place fields were disrupted (18). In another experiment, rats were trained to release food from an overhead dispenser by navigating to an unmarked goal location. In probe tests when the platform was constantly rotated, some place cells maintained fields in the platform reference frame, others maintained fields in the room reference frame, and others fired in a conjunctive manner, only when the platform and room were aligned to their initial relative orientations (269; see also Refs. 69 and 170). Thus, even though the platform contained no intentionally salient landmarks, place cells could maintain firing relative to the platform (presumably on the basis of path integration mechanisms with a contribution of subtle, local cues) (142, 196, 248). Intriguingly, analyses of the variability in firing among different passes through a place field suggest that animals can dynamically switch between local-cue and distal-cue dominated representations on the order of a second, suggesting perhaps that the reference frames are under the control of an attention-like process (56; see also Refs. 108 and 159).

D. Rotation Versus Translation Manipulations

As described above, most experiments that have tested the relative influence of local and distal cues have performed rotational manipulations on the cues. The tacit assumption of these studies was that the manner in which the cues were manipulated was not an important factor in interpreting how strongly the different reference frames control the place fields. However, a number of studies that have performed manipulations in which the cues were translated relative to each other, rather than rotated, have proven this assumption false.

O'Keefe (163) reported anecdotally that place fields responded in a mixed fashion when a small platform, upon which the rat was located, was moved to different locations in the experimental room. A small number of place cells fired only when the rat was in a particular location in the room, as predicted by a model of place fields being controlled primarily by distal cues. However, many cells maintained their place fields in the frame of reference of the platform itself, firing in a single location on the platform regardless of where the platform was located in the room. "Since these fields were not affected by rotation of the platform and are therefore not sensitive to intramaze cues, these findings suggest that the significant extra-apparatus cues may not be very specific but may serve instead to identify parts of the apparatus relative to the room (e.g., this is the corner of the platform nearest the wall or this is the arm of the maze farthest from the light)" (163). Similar anecdotal observations were made by O'Keefe and Burgess (165). The effects of such apparatus translations on place fields were investigated quantitatively by Knierim and Rao (117) in an experiment in which rats ran on a circular or rectangular track that was moved to various locations within the recording room. In each case, the standard location was centered in the middle of a circular curtain-enclosed space, with typical spatial cues on the curtains. There were no salient cues on the tracks themselves. The circular track was shifted 48 cm in the *z*-axis (vertically), returned to the standard location, and then shifted to the east and to the west (in each case 33 cm from the center of the room). In all sessions, the overwhelming majority of place fields maintained their firing fields on the track itself, ignoring the three-dimensional location of the track in the room. When the distal cues were rotated in 45° increments in subsequent sessions with the track returned to the center of the room, the place fields rotated their preferred firing locations by the same amount as the cues. Thus this experiment demonstrated a robust dissociation between weak control by the distal cues when the track was translated relative to the cues versus strong control when the cues were rotated relative to the track. Similar findings were observed with the rectangular track, which could be shifted in the room to 4 completely nonoverlapping locations. As with the circular track, the overwhelming majority of place cells maintained their firing fields at the same location of the track, regardless of the location of the track in the room. Three cells appeared to fire in the same location of the room, as they shifted their firing locations on the track to maintain a stable place field relative to the distal cues (as well as showing an interaction with sensitivity to location on the track). However, these cells represented a very small fraction of the population of cells recorded in this experiment.

Siegel et al. (208) followed up on this study by recording from place cells while the rats performed a spatial learning task that was conceptually similar to the Morris water task. Rats foraged for food randomly on a square platform, and when a tone sounded, they were required to navigate to an unmarked location on the platform to release more food pellets that scattered on the platform from an overhead dispenser (192). At two time points, one early in training and one a few days later, the platform was shifted by half of its length in the room (analogous to the Morris water task shift of Ref. 74, reviewed above). In this manipulation, half of the platform was in the same location in the room frame of reference after the shift, and the other half of the platform was in a new location in the room. Thus cells in the overlap region had the opportunity to express place fields in either reference frame when the platform was shifted. Many more cells remapped in this experiment compared with the track-shift experiments of (117), indicating an interaction between local and distal reference frames. However, of the cells that did not remap, the firing fields were four to six times more likely to be controlled by the platform (i.e., the fields shifted in the room along with the platform) than by the room cues **(FIG. 7)**. Although the fields tended to shift less than the platform itself, demonstrating an effect of the room cues, the shift was more aligned with the platform reference frame than the room reference frame. The rat's behavioral choices were ambiguous in the platform-shift sessions; nonetheless, the place-field results are consistent with the behavioral results of Hamilton et al. (74) that the local frame of reference dominated over the distal frame in controlling the rats' internal spatial representations.

A more complex study by Gothard et al. (70) also showed control by local cues in a landmark navigation task. Rats exited a movable start box and navigated to a goal location defined by two prominent, local landmarks that shifted position as a rigid pair. In different versions of the task, the goal landmarks were either rotated and translated or just translated. Prominent stable landmarks along the walls of the 3.5-m-diameter recording arena served as peripheral, room-based cues. Of 448 CA1 cells recorded, 227 had an identifiable behavioral correlate. Less than half of the cells (45%) were defined as "classic" place cells that fired relative to the static, peripheral cues. In contrast, 55% of the cells fired in relation to either the moving goal location/landmarks (10%) or to the moving start/end box (20% as the rat moved into the box, 16% as the rat moved out of the box, and 8% when the rat was in the box). Follow-up studies demonstrated a dynamic transition between a start-box reference frame and a static-background reference frame as the rat ran on a linear track in which the start and end positions varied along the track and a goal location was fixed on the other end of the track (68, 69). Thus these studies demonstrated complex interactions between the room-based reference frame and behaviorally relevant, local-cue-based reference frames in the control of place fields.

E. The Importance of Geometric Boundaries

A major breakthrough in understanding the determinants of place-cell spatial selectivity was a paper by O'Keefe and Burgess (165), in which the geometry of a recording chamber was manipulated by changing the length of each wall of a rectangular box. Box shapes included a small square (61 × 61 cm), a horizontally aligned rectangle (61 × 122 cm), a vertically aligned rectangle (122 × 61 cm), and a large square (122 × 122 cm). Many place fields were controlled strongly by the walls in these manipulations, sometimes stretching or compressing their fields along the axis in which the box was stretched or compressed. These authors developed a model of place field formation in which the inputs to place cells were hypothesized "boundary-vector cells" (BVCs), which fired whenever the rat was at a certain distance and allocentric bearing to a boundary in the environment (6, 82). Place fields were formed as the conjunction of the firing of a number of input BVCs, which caused the place cell to fire in a single, restricted location. Although it

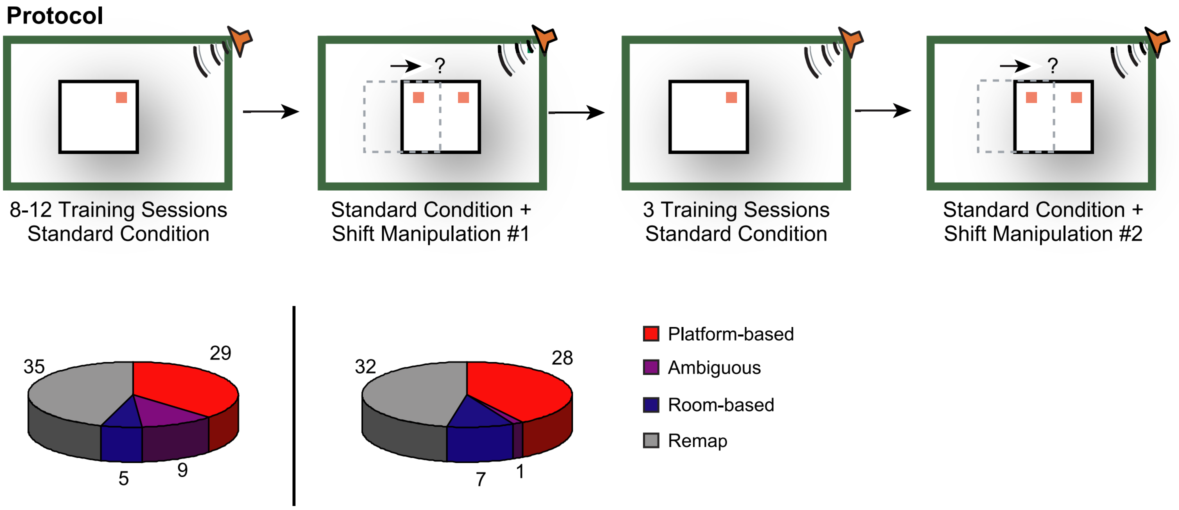

FIGURE 7. Place cells are more strongly controlled by local, platform cues than by distal cues in a spatial task. *Top*: protocol. Rats were trained for 8–12 sessions to go to an unmarked location (orange square) on a square platform when a tone sounded, to release food from an overhead dispenser. On the first test day, rats performed the task with the platform in the standard location in the room, and then the platform was shifted in the room. Analogous to Hamilton et al. (74), rats had to choose to go to the goal location either in room-based or platform-based reference frames. The platform shift manipulation was repeated after 3 more days of training in the standard condition. *B*: place field results. After the first shift manipulation (left pie chart), the majority of place fields remapped between the standard and shift conditions (gray). Of the cells that did not remap, fields were almost 6 times more likely to shift with the platform (red) than to remain in the room reference frame (blue). Similar results were obtained in the second shift manipulation (right pie chart). [Modified from Siegel et al. (208).]

was not known at the time if these cells actually existed in the brain, the model made predictions about how manipulation of the walls or barriers of a chamber would affect the firing of place cells, and these predictions were impressively accurate (20, 82, 131) (see also Refs. 157 and 189 for further studies on the influence of barriers on place cells).

F. Hippocampal Inputs: Head Direction Cells, Grid Cells, and Boundary Cells

To summarize the results reviewed so far, distal cues strongly control the firing of place cells when the distal cues or the behavioral apparatus are rotated relative to each other and when there are few salient local cues on the apparatus (162), at least in open, elevated mazes (123). However, when the local cues are made more salient and rotated relative to the distal cues, the results are more variable. In some cases the distal cues still dominate, but the local cues exert a significant control over the place fields (203). In other cases, the local cues actually dominate over the distal cues (16, 109, 125, 185). When the apparatus is translated to different locations relative to the room and to the distal cues, the place fields are more strongly controlled by intra-apparatus cues than by the distal cues, even if the intra-apparatus cues are not particularly salient (117, 163, 208). In the translation studies, it is conceivable that the apparatus boundaries were the dominant cues that determined the firing location of the place fields, rather than the configuration of distal cues on the walls (165). Why is the influence of distal cues on place field firing locations dependent on whether the apparatus is rotated versus translated relative to the cues? To answer this question, it is not sufficient to record from only the hippocampal place cells themselves. The hippocampus is many synapses removed from the primary sensory neurons and cortical areas that are directly affected by the manipulation of the external cues. One must understand the nature of the representations that actually provide the input to the hippocampus, and how these inputs are affected by these manipulations. We now discuss three types of hippocampal input cells: head direction cells, grid cells, and boundary cells.

1. Head direction cells

Head direction cells were discovered by Ranck (182, 233, 234) in the dorsal presubiculum (also known as the postsubiculum), a brain area that has strong inputs to the entorhinal cortex. A number of other areas were subsequently found to contain head direction cells, including the lateral mammillary nucleus, the anterior dorsal thalamic nucleus, the lateral dorsal thalamic nucleus, the striatum, the retrosplenial cortex, the medial entorhinal cortex, and perhaps the hippocampus itself (10, 25, 130, 149, 194, 230, 253, 263). These cells fire selectively when the animal's head is pointed in a particular direction in an allocentric frame of reference, regardless of the orientation of the head relative to the body (231). Head direction cells integrate angular velocity signals from the vestibular system, specifically, the horizontal semicircular canals, as well as from secondary sources such as optic flow and motor efference copy, to maintain a preferred firing direction as the animal moves through the environment (144, 154, 209, 220, 235, 266). This system of cells is thought to serve as an internal compass—not a geomagnetic compass, but one based primarily on the integration of self-motion cues. Unlike place cells, which can remap to unpredictable locations between environments, head direction cells appear to maintain a high degree of coherence in their relative firing preferences across environments. That is, if one head direction cell has a preferred firing direction 90° clockwise to the preferred firing direction of another head direction cell, these cells will maintain their 90° difference in all environments, even if the absolute directions change between environments (232, 263, 272).

Early investigations of head direction cells showed that they, like place cells, were controlled by the rotation of distal cues when local cues were not prominent (65, 66, 234). Under some conditions, the head direction cells were controlled most strongly by vestibular and other idiothetic cues, similar to place fields (11, 81, 112–114). In contrast to place cells, however, head direction cells are controlled by distal cues even when local cues are made more salient. Yoganarasimha et al. (263) recorded simultaneously from place cells of the hippocampus and head direction cells of the thalamus during the double-rotation manipulation, as rats ran on a circular track with salient local textures and with salient distal cues on the curtains surrounding the track. Whereas place cells in this study formed split representations like those seen in previous studies (109, 125), the head direction cells always maintained a completely coherent representation of head direction that was controlled strongly by the rotation of the distal cues. In another study, when a circular or square track was translated in an environment, the head direction cells did not change their firing directions when the tracks were in different parts of the room (262). However, when the distal cues were rotated, the tuning curves of the head direction cells rotated accordingly. A compelling indication of the dominance of distal cues over head direction cells came from a study by Zugaro et al. (272). When three objects were placed at the periphery of a high-walled, cylindrical arena, head direction cells were controlled strongly by rotation of the objects (similar to place fields) (32, 33). When the walls of the arena were removed, however, allowing the rat to see the curtains along the room walls, the three objects lost control of the head direction cell firing directions. Thus the objects only had control over the head direction cells when they were the most distal cues available to the rat; when the room curtains were visible to serve as a more distal backdrop, rotation of the objects was completely ineffective in controlling the head direction cells (see also Ref. 271). There are special cases in which local apparatus cues can control the head direction cells. Head direction cells can be controlled by changes in the orientation of an open behavioral apparatus when the apparatus is directionally polarized (e.g., a T-maze) and when there are no salient distal cues (50). If the geometry of an enclosed apparatus is strongly polarized, then the geometry can control the head direction cells even in the presence of distal cues (30). In general, however, the strong control over head direction cells by the most distal cues in an environment reinforces the notion that distal cues are particularly important for setting the orientation or direction of an animal's spatial map, as the perception of these cues does not change much as an animal moves around an environment, and they can therefore serve as an accurate, reliable anchor for an animal's sense of direction (169, 197). For precisely the same reason, however, distal cues are less appropriate to define with a high degree of precision the individual locations in an environment.

2. *Grid cells*

The major cortical inputs to the hippocampus originate in the MEC and lateral entorhinal cortex (LEC). Whereas LEC neurons display little spatial selectivity (80, 264), MEC neurons display an exquisitely regular, periodic firing pattern that forms a hexagonal (or triangular) grid on the surface of a recording environment (71). These grid cells are thought to be the major component of a path-integration system, whereby velocity cues (based primarily on self-motion) are integrated in two dimensions to continuously update a representation of the animal's position on a two-dimensional plane (60, 71, 143, 166; but see Ref. 122). The firing of grid cells is controlled by the rotation of a salient cue card in a standard recording environment (71). However, like place cells (114, 128, 136, 181, 207, 254), MEC neurons maintain their firing patterns in darkness (71) and can also be controlled by idiothetic cues when these cues are placed in conflict with external cues (81). A subset of grid cells is sensitive to the animal's head direction. These grid × head direction cells are comingled with simple head direction cells in layers III-VI of MEC (194), and the MEC receives a strong projection from areas that contain head direction cells, such as the postsubiculum and the retrosplenial cortex (257). Grid cells have also been reported in the presubiculum and parasubiculum, although they are most prominent in layer II of the MEC, which projects to the DG and CA3 regions of the hippocampus (13). The spatial firing patterns of MEC cells are tightly coupled to the firing of hippocampal place cells and thalamic head direction cells (81).

MEC grids are strongly affected by manipulations of the environmental walls. When a square box is stretched in one dimension, the spacing between the grid vertices is stretched in that dimension and slightly compressed in the orthogonal dimension (5). When the box is stretched in both dimensions, thus creating a larger square, the grid scaling expands in both dimensions [although this effect may only occur when the stretched environment is relatively novel, as Hafting et al. (71) reported only weak effects of scaling when grid cells were recorded in two familiar arenas of different sizes]. Thus distortions of the boundaries of the environment can cause distortions of the underlying pattern of grid cell firing. The boundaries appear to act as an anchor of the grids in the horizontal plane. If the walls of a small, square enclosure are removed while the animal is inside the enclosure, the grid cells shift their firing locations as the animal explores the larger enclosure in which it now finds itself (199). These results suggest that the grids were bound to the walls of the small box and that they shifted to align with the walls of the large box when the small box walls were removed.

3. *Boundary cells*

The influence of apparatus boundaries may be mediated by a class of cells in the MEC and subiculum that fire when the animal is at (or at a specific distance from) a particular boundary (132, 199, 215). These cells are reminiscent of the BVCs predicted by O'Keefe and Burgess (165), although it is not clear whether they have all of the properties required of the BVC model. Boundary cells may also be located in the parasubiculum and presubiculum, which contain cells that fire along the walls in an enclosed environment (13, 80). However, manipulations were not performed to test explicitly whether these latter cells were controlled by the boundaries, as was done in the prior studies of boundary cells in MEC and subiculum (132, 199, 215).

G. Different Roles Played by Hippocampal Afferents in Orienting/Aligning the Map

With an understanding of the properties of neurons that are afferent to the hippocampal place cells (head direction cells, grid cells, and boundary cells), one is in a better position to understand the functional roles played by local and distal cues in controlling the firing locations of place cells and the behavioral choices of animals in spatial tasks. The regular, hexagonal firing of MEC grid cells (even in the dark) suggests that the grids represent a path-integration-based spatial framework that is internally coherent and maintains itself in the absence of external sensory information (60, 63, 71, 143, 166). Like place cells and head direction cells (81, 110, 113, 114), the network of grid cells presumably maintains this internal coherence even when the representation becomes decoupled from any external reference frame. The grids can thus be considered as a self-consistent, internal coordinate system that must be associated and bound to the coordinate frame of the external world, in order for the internal frame to serve as a useful means of navigating and learning about the relationships among external objects and items. The binding of the grids to the external world can be characterized in three ways, according to the geometric notion of affine transformations **(FIG. 8)**: *1*) translation, in

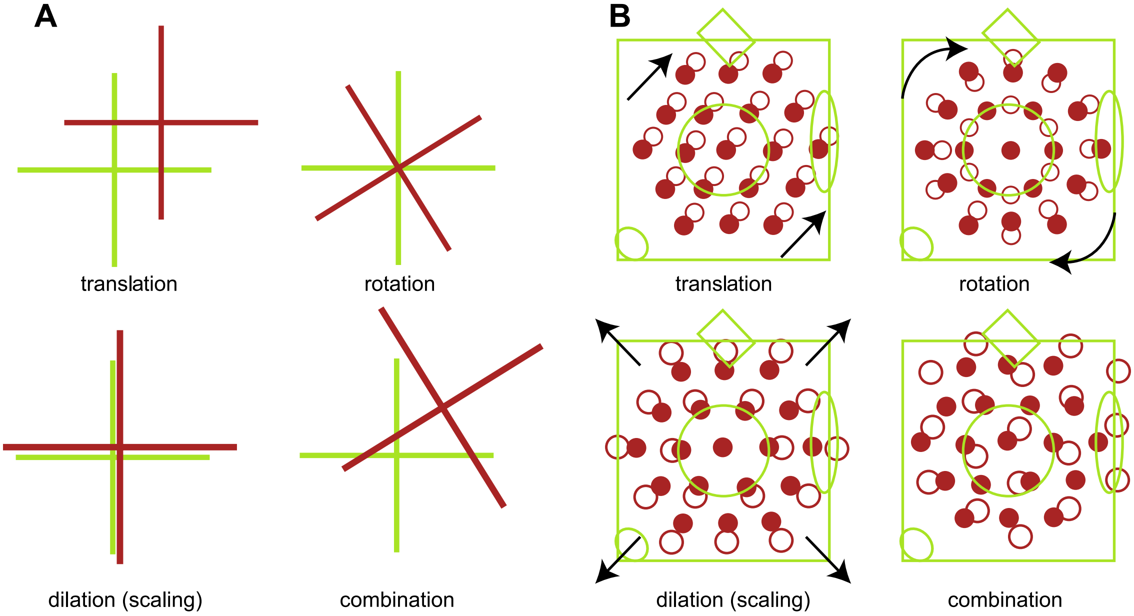

FIGURE 8. *A*: affine transformations of two coordinate systems. *B*: the grid cells (red) can be considered an internal coordinate system that must be aligned with the coordinate system of the external world (green, representing a circular platform in a square room with distal cues on the walls) via translation, rotation, dilation, or a combination.

which the grids are shifted relative to the external boundaries and landmarks (61); *2*) rotation, in which the grids are rotated relative to the external landmarks and boundaries (61, 71); and *3*) dilation, in which the grids are scaled (5). Local and distal cues can have different degrees of influence on all three of these planar transformations of the grid fields (and hippocampal place fields) relative to the external cues. Anatomical considerations suggest the following hierarchy that determines how each cue set affects the grids and place fields **(FIG. 9)**. The head direction signal appears to be initiated in a subcortical circuit composed of the lateral mammillary nucleus (LMN) and the dorsal tegmental nucleus of Gudden (206, 231). Head direction cells of the LMN project to the anterior dorsal thalamic nucleus, which projects to the postsubiculum, which projects to MEC. All of these regions contain head direction cells, with the postsubiculum and MEC also containing cells that carry conjunctive spatial and head direction signals (21, 194, 205). The postsubiculum may be the location where the internally coherent, idiothetic-based head direction system becomes bound to the distal cues in the environment (67). We suggest that this binding is the principal route by which distal cues ultimately influence the precise firing locations of hippocampal neurons. Head direction cells, bound to the distal cues, set the orientation of the MEC grids relative to the external world; in turn, the grids set the orientation of the spatial representations of the hippocampal place cells.

In contrast to rotational binding, the binding of the grids to the external world via translation and dilation is proposed to be mediated by boundary cells (13, 132, 199, 215). Once again, the head direction cell system plays a critical role, this time in disambiguating boundaries (e.g., distinguishing the north boundary from the east boundary) and allowing the boundary cells to fire selectively at a particular boundary rather than to the entire circumference of the environment (20, 163). The boundary cells are hypothesized to bind the grids to the external world by setting the phase and (in some situations) the scale of the grids (5, 61, 199, 215). [Note that there is an independent, anatomically determined scaling of grids along the dorsoventral axis of the MEC that is independent of size or shape of the particular environment (5, 17, 71).] Once the grid is bound to the external world (phase set by apparatus boundaries and orientation set by head direction cells), the downstream place fields of the hippocampus are set accordingly. In this model, the place cells do not receive a major direct input from constellations of distal cues. Rather, the influence of these cues derives from their influences on grid cells, boundary cells, and head direction cells. Thus the spatial firing of place cells does not primarily encode or represent constellations of distal cues directly. Instead, these cells represent an internally generated, spatial map that can be specific to individual contexts (14, 102, 111, 123, 137) and can incorporate individual items and events into that framework in the support of episodic memory (115, 134, 169). Insofar as the distal cues are processed as individual items in an environment or are components of environmental boundaries, these cues can become incorporated into the spatial representation (perhaps via the LEC). This influence may explain the apparent control of some place cells by individual distal cues (167, 203). However, the spatial representations embodied by place cells and grid cells exist largely independent of, and

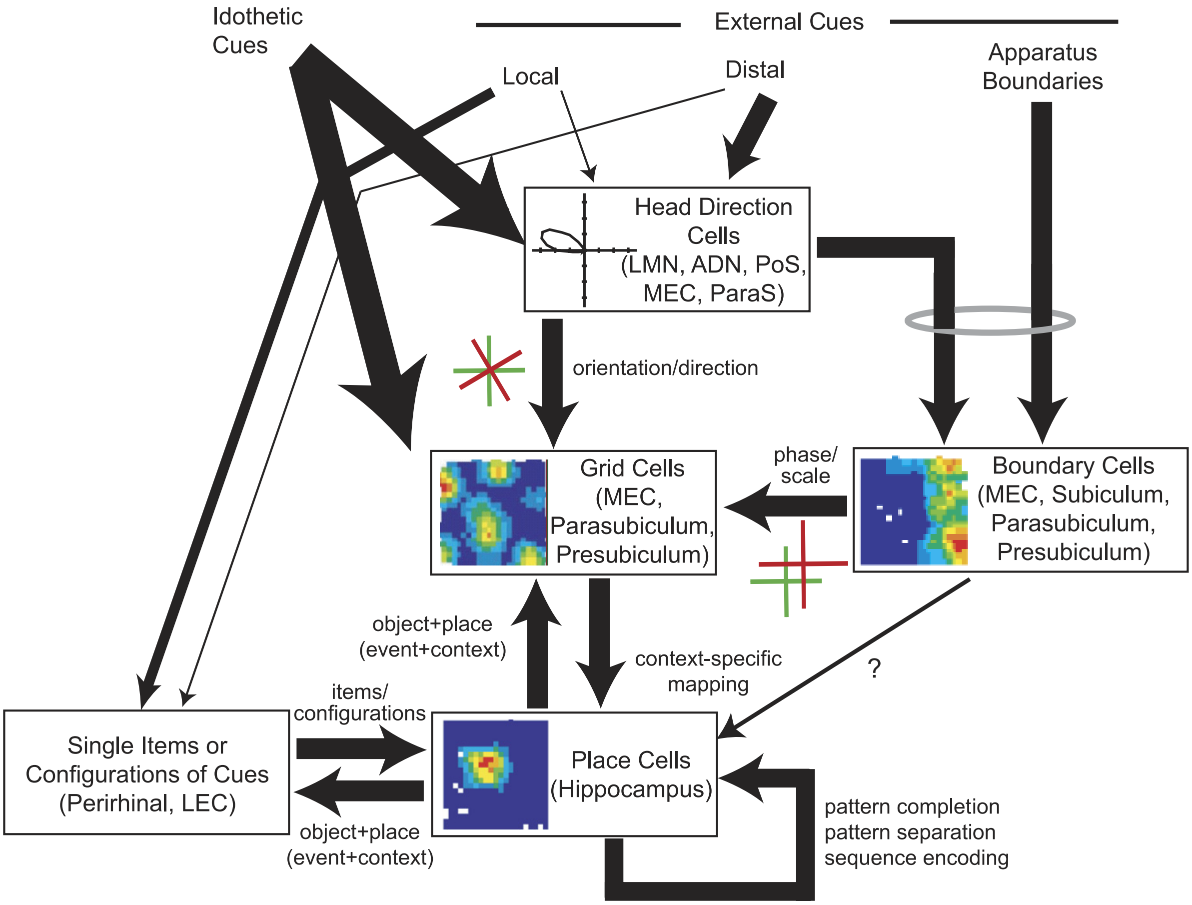

FIGURE 9. Flow chart showing hypothesized relationships between local cues, distal cues, and physiological cell types in the control of neural spatial representations. Head direction cells and grid cells are presumed to be updated primarily by idiothetically driven, path integration mechanisms (not reviewed here). Distal cues are primarily used to orient the head direction cell system, which is an internally coherent representation that integrates angular velocity signals to continuously update a directional signal. The head direction cells set the orientation of the grid cells of the MEC and subicular regions and also disambiguate apparatus and environmental boundaries (i.e., disambiguate the north wall from the east wall) so that boundary cells can fire selectively at a single boundary. The boundary cells are used to phase-align and scale the grids to the environment (they may also directly influence place cells). Place cells derive their spatial firing from grid cells, and thus they are controlled by the distal cues and apparatus boundaries via these input cells. The major functions of place cells are to create context-specific, spatial representations (3, 160, 214); to perform the mnemonic operations of pattern completion and pattern separation (138, 146, 171, 191); and to store representations of event sequences (45, 59, 104, 124, 175, 210). Information about specific local and distal cues can be incorporated into the place-cell representation via the lateral entorhinal cortex, and then fed back to the grid cells via backprojections from the hippocampus to aid in map alignment between the areas and to send conjunctive item plus context representations back to the neocortex for potential use as an organizing framework for episodic memory (115, 121, 134, 169).

prior to, the incorporation of these distal cues into the representation.

This model leads to ways of interpreting a number of place field studies and behavioral studies. Cressant et al. (34) recorded place fields on a T-maze and rotated the maze by either 90° or 45°. When the maze was rotated 90°, place fields were maintained on the arm that was in the same location in the room, rather than on the same arm of the maze itself. When the maze was rotated 45°, the place fields underwent a global remapping. The explanation supported by the above model is that the distal cues had primary control over the head direction cell system, and that the results on place fields were secondary to the head direction control. In both 90° and 45° rotations, the head direction cells presumably kept their preferred firing directions relative to the distal cues (263, 272). When the T-maze was rotated 90°, the boundaries of the arms at the same locations in the room were oriented the same as in the initial session. Thus, if the MEC grid cells were oriented by the head direction cells and phase-locked to the boundaries, the downstream place cells would maintain the same firing locations relative to the room. When the T-maze was rotated 45°, however, there would be a conflict between the head direction cells and the orientation of the boundaries. Such a conflict might cause the grids to shift unpredictably, thereby inducing hippocampal remapping of the T-maze. [Another explanation, according to the BVC model (20, 82), is that the hypothetical BVCs would fire very differently when the boundaries of the T-maze are rotated relative to the distal cues.] A prediction of these models is that translation of the T-maze to different room locations would cause the place cells to maintain their fields in the maze frame of reference, as the boundaries and the head direction cells maintain the same relationship in this condition. The results of Knierim and Rao (117) and Yoganarasimha et al. (262) strongly support this prediction.

A similar explanation can be given for the finding of place field hysteresis when a three-arm radial maze was rotated in small increments relative to room cues (46, 187). When the maze was rotated clockwise, place fields tended to follow the rotation of the maze, until the point where the maze geometry approached the original orientation (i.e., as the maze rotation approaches 120°), whereupon the fields "snapped" back to their original location relative to distal cues. When the maze was then rotated in the opposite direction, the place fields rotated with the maze again, until the maze rotations approached 120°. The important point is that the place fields showed a hysteresis effect [a similar hysteresis was seen when the geometry of a walled enclosure was gradually transformed from a circle to a square (129)]. At certain locations in the middle of the clockwise and counterclockwise rotation sequence, the orientation of the maze relative to the room cues was identical. However, the location of the place field on the maze depended more on the recent history (how was the maze oriented and where did the place field fire on the previous trial) than on the absolute orientation of the maze relative to the distal room cues. This result can be explained by the room cues determining which arm was closest to the original orientation of the maze and orienting/aligning the spatial representation to the boundaries of that arm, with an orientation bias to match the most recent trials when the maze rotation was ambiguous. When the maze rotated back to the original orientation, the directional/spatial system reset back to the original orientation.

This model can also account for the tendency of place fields on a rectangular track to stay bound to the room frame of reference when a flat or tilted track was rotated 90° or 180° (116). Place fields fired at the same location relative to the room when the flat rectangular track was rotated 180°. Under these conditions, the geometry of the track did not discriminate the two orientations (although there were polarizing cues on the apparatus that housed the track). When the track was tilted ~45° in the z-axis, such that the rat had to climb up one long side of the rectangle and down the other long side, cells either remapped or were maintained relative to the room reference frame (ignoring the z-axis) when the tilted track was rotated 180°. Thus the addition of tilt caused a partial remapping, but did not endow the track with control of the place fields that did not remap (but see Ref. 101). When the flat track was rotated 90°, partial remapping occurred, but the cells that did not remap were still controlled by the room reference frame. Note that the cells did not fire in the same x,y location relative to the room cues, because the rotation of the rectangle placed the corners of the track, for example, in slightly different x,y coordinates. However, cells that fired at the NW corner in the normal orientation also fired at the NW corner (defined relative to the room) in the 90°-rotated orientation, as predicted by O'Keefe (163). The 90° rotation is geometrically equivalent to a distortion of the rectangle, with a compression of the long axis and an expansion of the short axis. Thus similar to the distortion of place fields and grid cells when a box is transformed (5, 165), it appears that the place field map was stretched to conform to the distortion of the rectangle, oriented by the distal cues, rather than being rotated to follow the geometry of the track. In contrast, when the apparatus is a rectangular box with walls, the place field map can rotate with the box (103, 123). In these cases, one would predict that the head direction cells were controlled by the framework of the box because the walls were the most prominent distal cues, and the head direction cells caused the hippocampal place cell map to rotate as well.

This model also can account for the behavioral results, described in the first part of this review, that showed a lack of influence of distal cues in controlling the rats' behavior under certain conditions. These results were interpreted as showing that rats use a directional strategy over a place strategy. Another interpretation of these results is that the rats were indeed using a spatial mapping strategy, but that the map was more strongly bound to the local frame of reference of the behavioral apparatus itself, rather than to the global frame of reference defined by room cues. Thus, when Blodgett et al. (12) shifted the T-maze to new locations in the room, it is likely that the hippocampal representation also shifted with the T-maze [with perhaps some degree of partial remapping (117, 163, 208, 262).] If this supposition is true, then the rat would be able to solve Blodgett's "directional" task using a spatial strategy tied to the frame of reference of the T-maze (i.e., go to a particular place on the maze, rather than a particular place in the room).

A similar explanation holds for the Morris water task shift experiments of Hamilton et al. (74). If one assumes that the place fields seen in a water task (90) act similarly to the place fields of the platform-shift experiments of Siegel et al. (208), then sufficient information would be retained in the hippocampal map for the rat to solve the task based on swimming to a location in the pool frame of reference (based on distances from the pool wall and orientation information from room cues) rather than a direction. Indeed, directional information (strictly defined) is not adequate to solve this task, as the animal has to swim in somewhat different directions to reach the escape platform depending on its starting point. Pure directional information can only inform the rat within 180° of the proper direction to swim. Rather, rats must localize themselves in the pool to calculate the precise direction needed to navigate to the goal. On the assumption that the directional signal is carried by the head direction cell system, it is noteworthy that attempts to tie the bearing of the head direction cell system directly to animals' behavioral choices have produced mixed results (51, 64, 155, 156). It seems likely that the animals tend to use their hippocampal spatial systems to solve these tasks, even when a directional strategy is possible. The head direction system plays an important role in orienting this spatial representation, but the animals do not appear to reliably use the head direction signal and a pure directional strategy to solve the task directly.

H. Local Cues Are Involved in Both Spatial and Nonspatial Computations in Hippocampus

With respect to local apparatus cues, this review is mainly concerned with the role of such cues in establishing and calibrating the spatial firing of place cells relative to external landmarks. However, it is clear that local cues can influence place fields in other ways. Objects or stimuli can be incorporated into the hippocampal spatial representation so as to encode the individual items that occupy a particular location (79, 150, 162, 189, 258). This information may come from the LEC, which does not contain cells with strong spatial or directional tuning but which does contain cells that fire when the animal investigates objects or individual items (42, 80, 242, 267, 268). According to this view, the hippocampus combines a spatial signal from the MEC with an object-related (or event-related) signal from the LEC to create conjunctive object + place (item + source; event + context) representations that are essential for the formation and long-term encoding of episodic memories (115, 134). Examples of such object-selective firing are many. O'Keefe's original studies described "misplace" cells as cells that fired at a specific location either when the animal encountered an unexpected object there or failed to encounter an expected object or reward (162). We have already described the controversial issue of whether goal locations can orient the spatial map (15, 127, 217). Other studies have addressed the issue of whether goal locations themselves are specifically encoded into the spatial map. Some studies have shown that goal or reward locations are overrepresented (15, 88, 89, 118, 119). Other studies, however, have failed to demonstrate such an overrepresentation (91, 162, 208). A number of studies have shown that hippocampal cells respond to local objects or discrete stimuli. In cases where the animal occupies different locations in the recording environment, this signal is almost always shown to ride on top of an underlying, spatial signal, in agreement with the idea that the nonspatial stimuli are being incorporated into a spatial map (121, 135, 150, 252, 258). In some cases, the incorporation of the nonspatial information occurs in conjunction with a learning task related to the objects or stimuli (121, 150).

A complete review of such nonspatial inputs onto place cells is beyond the scope of this review. However, the incorporation of local objects into the hippocampal spatial representation leads to the question of when should a local cue be considered a nonspatial object, to be incorporated into a spatial map, versus a spatial landmark that can provide location information? This question cannot be answered purely on the properties of the object itself. The best way to approach this question is to consider that the same stimulus can be used in both ways, presumably by different processing circuits in the hippocampal system. An analogy to the visual system is instructive (44). A motion signal can be used by the dorsal visual stream to calculate the movement of an object in the visual field. However, the same motion signal can also be used by the ventral stream to create representations of shape (structure from motion). Similarly, local objects may be used by some parts of the hippocampal circuit to help orient a spatial map under certain conditions and by other parts to incorporate significant nonspatial information into the spatial map. To understand these questions in more detail, we must continue our investigation into areas both upstream and downstream of the hippocampus proper. The nature of hippocampal representations and coding cannot be understood solely by manipulating operationally defined "local and distal" cues and recording only the CA1 and CA3 pyramidal cells that reside many synapses away from the sensory periphery. It is essential to understand the representations encoded by the brain areas that constitute the inputs to the hippocampus. What is explicitly represented by the firing of grid cells, boundary cells, and object cells? How are these representations changed by our manipulation of environmental cues? How do the changes to the hippocampal input change the hippocampal representations, and what computational rules can be inferred by this transformation? Only by understanding hippocampal processing at this level will we begin to understand the computational functions of the hippocampus, and how this brain area underlies our ability to both navigate flexibly and to form declarative memories.

IV. SUMMARY AND CONCLUDING COMMENTS

It is not usually a straightforward task to bridge behavior and neural processing, especially in a task as complex as the Morris water task and related navigation tasks. Animals and humans can utilize a diverse set of behavioral and cognitive strategies, sometimes employing more than one strategy simultaneously. Neuroscientists like to cleanly parcel out different brain structures and assign them to specific, behaviorally separable functions. However, numerous brain areas are engaged and required in any particular behavior, and any particular brain area is likely to be involved in a number of behaviors that we define operationally as being distinct. With these caveats in mind, the present review attempts to bridge behavioral analyses of the Morris water task and other navigation tasks with physiological findings of spatial representations in the hippocampus and related regions. Accumulating evidence demonstrates the inadequacy of the prevailing (although not universal) view that spatial navigation in a diverse range of tasks and spatial firing in the hippocampus are controlled primarily by the constellation of distal cues in an environment. Prior work has already demonstrated conclusively the importance of self-motion cues and path integration in navigation and in the firing of hippocampal place cells (54, 55, 142, 148, 248), but distal cues are still thought (and taught) by many to be the primary source of exteroceptive sensory input controlling these processes. We have attempted to review how this notion became ingrained, and how more recent behavioral experiments and neurophysiological discoveries have removed the distal cues from their privileged status. We wish to emphasize, emphatically, that nothing in this review should be taken as an argument that distal cues are unimportant in controlling spatial navigation or hippocampal place cells. The data overwhelmingly demonstrate the importance of these cues. However, the nature of this control is more complex than simple notions that animals solve navigation tasks, and place cells define locations, primarily by learning locations in a frame of reference defined by constellations of distal cues. Instead, distal cues appear to be mainly involved in binding the orientation of a spatially coherent, internal, cognitive representation of an environment to the external world. This binding is primarily accomplished through the HD system. Individual distal cues can also influence place cells directly, perhaps through the lateral entorhinal cortex, but the major effect appears to be via the grid cell and HD cell systems of the medial entorhinal pathway. The importance of local boundaries in controlling behavior and place cells demonstrates that it is imperative to consider the local apparatus framework in understanding both how animals solve spatial learning tasks as well as how hippocampal representations are formed. An animal can use a cognitive mapping strategy to solve the Morris water task, the T-maze, or any other spatial task, even if the map is based on the local frame of reference rather than the global frame of reference (i.e., it can be a map of the rat's location in the pool, not exclusively or primarily a map of the rat's location in the room). Animals can simultaneously keep track of their locations in more than one reference frame (57). Thus it is not a question of whether animals use a local or global frame of reference; they can use both. However, when these frames of reference are put in conflict with each other, the local frame can dominate, especially when the conflict involves a translational shift rather than a rotational shift. The convergence of data from both behavioral and neurophysiological experiments provides hope that we are progressing toward the goal of being able to understand spatial navigation in the Morris water task and other commonly used laboratory tasks in terms of the neurobiological mechanisms that underlie performance.

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