ELSEVIER

An analysis of independence and interactions of brain substrates that subserve multiple attributes, memory systems, and underlying processes

Raymond P. Kesner[*] and Jason Rogers

Department of Psychology, University of Utah, Salt Lake City, UT 84112, USA

Abstract

It is proposed that memory is organized into event-based, knowledge-based, and rule-based memory systems. Furthermore, each system is composed of the same set of multiple attributes and characterized by a set of process oriented operating characteristics that are mapped onto multiple neural regions and interconnected neural circuits. Based on this theoretical model of memory, it is possible to investigate the independence and interaction among brain regions between any two systems for any of the proposed attributes or processes. This applies also to the investigation of independence and interactions between any two attributes within a system and between processes associated with a system for any of the proposed attributes. In this article, research evidence is presented to suggest that there are both dissociations and interactions between the hippocampus and caudate nucleus in mediating spatial and response attributes within the event-based memory system, between the hippocampus and the parietal cortex in subserving the spatial attribute within the event-based and knowledge-based memory systems, and between the hippocampus and the prefrontal cortex in subserving the spatial attribute within the event-based and rule-based memory systems.
© 2004 Elsevier Inc. All rights reserved.

1. Introduction

In order to address the question whether multiple brain systems can operate independently of each other or whether there must always be cooperative or competitive interactions among multiple brain systems, it is necessary to provide a theoretical context for evaluating the role of multiple brain systems in subserving a complex variety of processes that are involved in the processing of different forms, domains or attributes of information. An overall view of a theoretical framework that can be used to analyze the above-mentioned question will be described first, followed by a discussion of the importance of determining the processes and attributes associated with each task or set of tasks that are selected for analysis. This will be followed by the elaboration of a more detailed analysis of the independence and interactions between: (a) the hippocampus and caudate nucleus within the context of an event-based memory system for spatial and response attributes, (b) the hippocampus and parietal cortex within the context of a comparison between the event-based memory system and the knowledge-based memory system for the spatial attribute, and (c) the hippocampus and medial prefrontal cortex within the context of a comparison between the event-based memory system and the rule-based memory system for the spatial attribute.

The proposed theoretical model of memory is organized into event-based, knowledge-based, and rule-based memory systems. Each system is composed of the same set of multiple attributes or forms of memory, characterized by a set of process oriented operating characteristics and mapped onto multiple neural regions

---
[*] Corresponding author. Fax: 1-801-581-5841.

E-mail address: rpkesner@behsci.utah.edu (R.P. Kesner).

and interconnected neural circuits. For more detail see Kesner (1998, 2002).

On a psychological level (see Fig. 1), the event-based memory system provides for temporary representations of incoming data concerning the present, with an emphasis upon data and events that are usually personal or egocentric and that occur within specific external and internal contexts. The emphasis is upon the processing of new and current information. During initial learning great emphasis is placed on the event-based memory system, which will continue to be of importance even after initial learning in situations where unique or novel trial information needs to be remembered. This system is akin to episodic memory (Tulving, 1983).

The knowledge-based memory system provides for more permanent representations of previously stored information in long-term memory and can be thought of as one's general knowledge of the world. The knowledge-based memory system would tend to be of greater importance after a task has been learned given that the situation is invariant and familiar. The organization of these attributes within the knowledge-based memory system can take many forms and are organized as a set of attribute-dependent cognitive maps and their interactions that are unique for each memory. This system is akin to semantic memory (Tulving, 1983).

The rule-based memory system receives information from the event-based and knowledge-based systems and integrates the information by applying rules and strategies for subsequent action. In most situations, however, one would expect a contribution of all three systems with a varying proportion of involvement of one relative to the other.

The three memory systems are composed of the same forms, domains or attributes of memory. Even though there could be many attributes, the most important attributes include *space, time, response, sensory-perception,* and *reward value* (*affect*). In humans a *language* attribute is also added. A spatial (space) attribute within this framework involves memory representations of places or relationships between places. It is exemplified by the ability to encode and remember spatial maps and to localize stimuli in external space. Memory representations of the spatial attribute can be further subdivided into specific spatial features including allocentric spatial distance, egocentric spatial distance, allocentric direction, egocentric direction, and spatial location. A temporal (time) attribute within this framework involves memory representations of the duration of a stimulus and the succession or temporal order of temporally separated events or stimuli. A response attribute within this framework involves memory representations based on feedback from motor responses (often based on proprioceptive and vestibular cues) that occur in specific situations as well as memory representations of stimulus–response associations. A reward value (affect) attri-

MEMORY AT THE PSYCHOLOGICAL LEVEL			
ATTRIBUTES	EVENT-BASED MEMORY SYSTEM PROCESSES	KNOWLEDGE-BASED MEMORY SYSTEM PROCESSES	RULE-BASED MEMORY SYSTEM PROCESSES
place	1. Selective filtering of interference of temporary memory representations, labeled	1. Selective attention and selective filtering associated with permanent memory representations of familiar information	
time	**PATTERN SEPARATION**		1. The selection of strategies and rules for maintaining or manipulating information
language	2. Short-term and intermediate-term memory for new information partly based on **PATTERN ASSOCIATION**	2. Perceptual memory	for subsequent action.
response	3. Consolidation or elaborative rehearsal of new information partly based on	3. Long-term storage based on **PATTERN ASSOCIATIONS**	2. Short-term or working memory for new and familiar information
affect	**PATTERN ASSOCIATION**		
sensory-perceptual	4. Retrieval of familiar information based on flexibility, action, and **PATTERN COMPLETION**	4. Retrieval of familiar information based on flexibility and action	

Fig. 1. Memory at the psychological level as a function of attributes and processes for the event-based, knowledge-based, and rule-based memory systems.

bute within this framework involves memory representations of reward value, positive or negative emotional experiences, and the associations between stimuli and rewards. A sensory-perceptual attribute within this framework involves memory representations of a set of sensory stimuli that are organized in the form of cues as part of a specific experience. Each sensory modality (olfaction, auditory, vision, somatosensory, and taste) has its own memory representations and can be considered to be part of the sensory-perceptual attribute component of memory. A language attribute within this framework involves memory representations of phonological, lexical, morphological, syntactical, and semantic information. The attributes within each memory system can be organized in many different ways and are likely to interact extensively with each other even though it can be demonstrated that these attributes do in many cases operate independent of each other.

Within each system attribute information is processed in different ways based on different operational characteristics. For the event-based memory system, specific processes involve: (a) selective filtering or attenuation of interference of temporary memory representations of new information and is labeled pattern separation, (b) short-term and intermediate-term memory for new information partly based on pattern associations, (c) consolidation or elaborative rehearsal of new informa-

tion partly based on pattern associations, and (d) retrieval of new information based on flexibility, action, and pattern completion.

For the knowledge-based memory system, specific processes include: (a) selective attention and selective filtering associated with permanent memory representations of familiar information, (b) perceptual memory and (c) long-term memory storage based on pattern associations, and (d) retrieval of familiar information based on flexibility and action.

For the rule-based memory system, the major processes include the selection of strategies and rules for maintaining or manipulating information for subsequent action as well as short-term or working memory for new and familiar information.

On a neurobiological level (see Fig. 2) each attribute maps onto a set of neural regions and their interconnected neural circuits. For example, within the event-based memory system it has been demonstrated that in animals and humans: (a) the hippocampus supports memory for spatial and temporal attribute information, (b) the caudate mediates memory for response attribute information, (c) the amygdala subserves memory for reward value (affect) attribute information, and (d) the perirhinal and extrastriate visual cortex support memory for visual object attribute information as an example of a sensory-perceptual attribute.

	MEMORY AT THE NEUROBIOLOGICAL LEVEL		
	EVENT-BASED MEMORY SYSTEM	KNOWLEDGE-BASED MEMORY SYSTEM	RULE-BASED MEMORY SYSTEM
ATTRIBUTES	BRAIN REGIONS	BRAIN REGIONS	BRAIN REGIONS
place	hippocampus (H,M,R)	parietal cortex (H,M,R)	lateral prefrontal cortex (H,M) Infra/pre-limbic cortex (R)
time	hippocampus (H,M,R)	dorsal prefrontal (H,M); anterior cingulate (R)	dorsal prefrontal (H,M) anterior cingulate (R)
language	hippocampus (H)	posterior parietal cortex; Wernicke's area, Broca's area (H)	lateral prefrontal cortex (H)
response	caudate (H,M,R)	pre-motor, supplementary motor cortex (H,M) precentral cortex (R), cerebellum (H,M,R)	pre-motor, supplementary motor cortex (H,M) precentral cortex (R), cerebellum (H,M,R)
affect	amygdala (H,M,R)	orbital-frontal cortex (H,M,R)	orbital-frontal cortex (H,M,R) agranular insular cortex (R)
sensory- perceptual	perirhinal (objects) (H,M,R)	Inferotemporal cortex (H,M) TE 2 cortex (R)	lateral prefrontal cortex (H,M) infra/pre-limbic cortex (R)

H = humans, M = monkeys, R = rats

Fig. 2. Memory at the neurobiological level as a function of attributes and brain regions for the event-based, knowledge-based, and rule-based memory systems.

Evidence supportive of the above-mentioned mapping of attributes onto specific brain regions is based in part on the use of paradigms that measure the short-term or working memory process based on performance within matching or non-matching-to-sample, delayed conditional discrimination or continuous recognition memory of single or lists of items tasks; the consolidation and retrieval process based on learning and retention of a variety of behavioral tasks; the pattern separation process based on performance within category memory or discrimination tasks. For a detailed presentation of the research to support the above-mentioned statements see Kesner (1998).

Within the knowledge-based memory system, it has been demonstrated that in animals and humans: (a) the posterior parietal cortex supports memory for spatial attributes, (b) the dorsal and dorso-lateral prefrontal cortex and/or anterior cingulate support memory for temporal attributes, (c) the pre-motor, supplementary motor, and cerebellum in monkeys and humans and precentral cortex and cerebellum in rats support memory for response attributes, (d) the orbital prefrontal cortex supports memory for reward value (affect) attributes, and (e) the inferotemporal cortex in monkeys and humans and TE2 cortex in rats subserves memory for sensory-perceptual attributes, e.g., visual objects. Evidence supportive of the above mentioned mapping of attributes onto specific brain regions is based in part on the use of paradigms that measure the perceptual memory process based on performance within a repetition priming or a discrimination performance paradigm, the attention process by measuring performance within selective attention and stimulus binding tasks, the long-term storage and retrieval process by measuring learning and retention in a variety of behavioral tasks. For a detailed presentation of the research to support the above-mentioned statements see Kesner (1998).

Within the rule-based memory system it can be shown that different subdivisions of the prefrontal cortex support different attributes. For example: (a) the dorso-lateral and ventro-lateral prefrontal cortex in monkeys and humans and the infralimbic and prelimbic cortex in rats support spatial and visual object attributes, (b) the pre-motor and supplementary motor cortex in monkeys and humans and precentral cortex in rats support response attributes, (c) the dorsal, dorso-lateral, and mid-dorso-lateral prefrontal cortex in monkeys and humans and anterior cingulate in rats mediate primarily temporal attributes, and (d) the orbital prefrontal cortex in monkeys and humans and agranular insular cortex in rats support affect attributes. Evidence supportive of the above-mentioned mapping of attributes onto specific brain regions is based in part on the use of paradigms that measure the use of rules within short-term memory based on performance within matching or non-matching-to-sample, delayed condi-

tional discrimination or continuous recognition memory of single or lists of items tasks, temporal ordering of information, and sequential learning, as well as paradigms that measure the use of rules in cross-modal switching, reversal learning, paired-associate, and problem solving tasks. For a detailed presentation of the research to support the above-mentioned statements see Kesner (2002).

Given the complexity of the nature of memory representations and the multitude of processes associated with learning and memory associated with any specific task, it is clear that prior to analyzing the neural circuits that support mnemonic processing, one must determine which attributes and which systems and associated underlying processes are essential for memory analysis of the proposed task. A few examples will suffice. For example, if one assumes that the hippocampus supports the processing of the spatial attribute within the event-based memory system, then any task that minimizes the importance of the spatial attribute and emphasizes the importance of reward value, response and sensory-perceptual attributes are not likely to involve the hippocampus. Also, tasks that concern retention of well-learned spatial information or short-term spatial memory are not likely to involve the hippocampus. Acquisition of a cue preference task based on reward value–place associations is likely to produce interactions among the amygdala, hippocampus, orbital-frontal cortex, and parietal cortex. Acquisition of an object–place association is likely to involve interactions among the hippocampus, perirhinal cortex, parietal cortex, inferotemporal cortex, and medial prefrontal cortex. However, performance of a previously learned matching-to-sample task for spatial information is likely to involve primarily the hippocampus and medial prefrontal cortex, for response information primarily the caudate nucleus and prefrontal cortex, for reward value information primarily amygdala and orbital-frontal cortex, and for visual object information primarily perirhinal cortex and prefrontal cortex.

2. Event-based memory system-spatial and response attributes: Hippocampus and caudate nucleus

2.1. Short-term and intermediate-term working memory process

With respect to spatial attribute information, it can be shown that using paradigms that measure a short-term or intermediate working memory process based on performance within matching or non-matching-to-sample, delayed conditional discrimination or continuous recognition memory of single or lists of items tasks, short and intermediate working memory for spatial information is impaired in rats and monkeys with bilateral

hippocampal damage and humans with right hippocampal damage (Hopkins, Kesner, & Goldstein, 1995a; Kesner, 1990; Olton, 1983, 1986; Parkinson, Murray, & Mishkin, 1988; Pigott & Milner, 1993; Smith & Milner, 1981). In contrast, for rats with caudate nucleus lesions and humans with caudate nucleus damage due to Huntington's disease (HD), there are no deficits for short- or intermediate-term spatial location information (Colombo, Davis, & Volpe, 1989; Cook & Kesner, 1988). There are, however, profound deficits for short-term memory for a right or left turn response or a list of hand motor movement responses (Cook & Kesner, 1988; Duncan-Davis, Filoteo, Kesner, & Roberts, 2003; Kesner, Bolland, & Dakis, 1993; Kesner & Filoteo, 1998). In contrast, for rats, monkeys, and humans with hippocampus lesions there are no deficits for short-term memory for a right or left turn response or a list of hand motor movement responses (Hopkins et al., 1995a; Kesner et al., 1993). These data suggest that there is a double dissociation between the caudate nucleus and the hippocampus in terms of short- or intermediate-term processing of response vs. place attributes.

In addition, it should be noted that for rats, monkeys, and humans, caudate nucleus lesions produce deficits in tasks like delayed response, delayed alternation, and delayed matching to position (Divac, Rosvold, & Szwarcbart, 1967; Dunnett, 1990; Oberg & Divac, 1979; Partiot et al., 1996; Sanberg, Lehmann, & Fibiger, 1978). One salient feature of delayed response, delayed alternation, and delayed matching to position tasks is the maintenance of spatial orientation to the baited food well relative to the position of the subject's body often based on proprioceptive and vestibular feedback. These data suggest that the caudate nucleus plays an important role in short-term memory representation for the feedback from a motor response feature of response attribute information.

With respect to specific spatial features, such as allocentric spatial distance, egocentric spatial distance, and spatial location, it has been shown in both rats and humans with bilateral hippocampal damage, that there are severe deficits in short-term or intermediate-term memory for these spatial features (Kesner & Hopkins, unpublished; Long & Kesner, 1996, 1998), whereas caudate nucleus lesions do not produce a deficit for spatial location information. In a recent study of the direction feature of the spatial attribute, the effect of hippocampus and caudate nucleus lesions was investigated (DeCoteau, Hoang, Huff, Stone, & Kesner, 2004). In this experiment a new delayed-match-to-sample task was designed to assess short-term memory for direction information in rats. To minimize the use of visuospatial cues, all testing was performed in the dark. During the task's study phase, rats traversed a maze arm oriented in one of three directions. Following a delay period, a test phase was presented that required a choice between the study phase direction (correct) and a foil direction (incorrect). Once rats reached a learning criterion they were given probe trials. Results of the probe trials suggested that, when correctly solving the original task, normal animals (1) favor the use of direction rather than turning response information, and (2) utilize vestibular feedback. Rats were then given hippocampus, medial caudate nucleus or cortical control lesions. The results are shown in Fig. 3 and indicate that unlike control animals, rats with hippocampus and medial caudate nucleus lesions exhibited marked impairments when retested. All rats were able to learn a less mnemonic, direction discrimination task. These results suggest that the hippocampus and medial caudate nucleus interact with each other either because the task can be solved by using a direction or response strategy or because both brain regions process ideothetic information, a necessary component to trigger required support processes associated with short- or intermediate-term memory for direction information.

2.2. Consolidation and pattern association process

The hippocampus also plays a role in the acquisition or learning of new spatial information requiring the consolidation of spatial attributes. This is readily observable in the acquisition of an object–place or odor–place paired-associate task, a spatial navigation task in a water maze, dry-land version of the water maze,
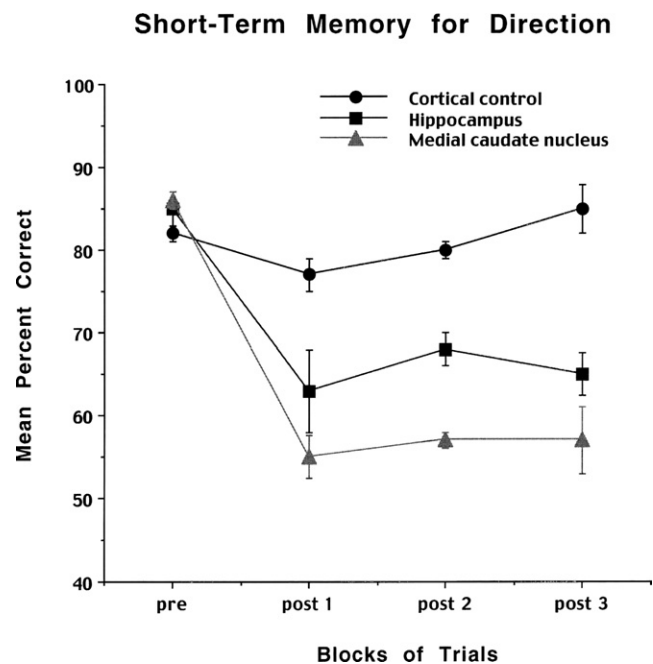

Fig. 3. Mean percent correct and standard error based on a short-term memory for direction task for the cortical control, hippocampus, and medial caudate nucleus lesion groups as a function of pre- and post-surgery blocks of trials (100 trials/block).

eight-arm radial maze, plus maze, and inhibitory avoidance tasks requiring an association of a painful stimulus with a specific spatial location, in that rats with hippocampal lesions are markedly impaired in these tasks (DeCoteau & Kesner, 2000; Gilbert & Kesner, 2002; Kesner, 1990; McDonald & White, 1993; Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978; Packard & McGaugh, 1996). Furthermore, for the acquisition of the object–place and object–odor tasks there is regional specificity in that only dorsal CA3, but not CA1 or dentate gyrus, lesions produce a deficit (Gilbert & Kesner, 2003). It has also been shown that post-trial disruption of normal hippocampal function with, for example, electrical brain stimulation, results in time-dependent memory impairments for spatial information (Kesner & Wilburn, 1974). These effects reveal that the hippocampus is involved in short- or intermediate-term consolidation processes, because the gradients are usually short within minutes to a few hours. Whether the hippocampus promotes the transfer of spatial information to the knowledge-based system or whether the hippocampus promotes the consolidation of information already processed in the knowledge-based system still needs to be resolved. Based on research with animals it has been assumed that the basal ganglia, including the caudate nucleus, mediates the consolidation and learning of stimulus–response associations or habits (Mishkin & Petri, 1984; Phillips & Carr, 1987). Support for this idea comes from the findings that visual pattern discrimination and concurrent visual object discriminations are disrupted in monkeys with either putamen or tail of the caudate lesions, but lesions of the hippocampus do not result in any deficits in these tasks (Mishkin, 1982; Wang, Aigner, & Mishkin, 1990). It should be noted, however, that monkeys with lesions in the tail of the caudate do not have difficulty in remembering previously learned concurrent visual object discriminations, but they are impaired only in learning a new set of concurrent visual objects.

It has been suggested in rats that the caudate nucleus is involved in sensory–motor integration including learning and consolidation of stimulus–response associations usually defined by tasks in which a particular motor response is reinforced in the presence of a single cue or tasks that require a consistent choice of direction or consistent choice to initiate or withhold responding (Phillips & Carr, 1987; McDonald & White, 1993). Support for this idea comes from a large number of studies indicating that damage to the caudate nucleus impairs brightness discrimination (Schwartzbaum & Donovick, 1968), tactile discrimination (Colombo et al., 1989), conditional visual discrimination (Reading, Dunnett, & Robbins, 1991), right/left maze discrimination (Cook & Kesner, 1988), runway learning (Kirkby, Polgar, & Coyle, 1981), eight-arm maze learning (reference memory or non-varying component of the task)

(Colombo et al., 1989; Packard & White, 1990); and cued radial arm maze and cued Morris water maze learning (Packard & White, 1990; Whishaw, Mittleman, Bunch, & Dunnett, 1987). In this latter task, only an approach response to the correct visual cue location is required. In contrast, rats with hippocampal lesions are not impaired in the above-mentioned tasks (McDonald & White, 1993). There is some evidence for regional specificity, since in a conditional visual discrimination (fast vs. slow frequency of light flashes) task using a choice bar press response, only ibotenic acid lesions of the lateral, but not the medial caudate resulted in an impairment in the acquisition of the task, suggesting that the lateral caudate is necessary for the acquisition of response rules to perform accurately on a conditional visual discrimination task (Reading et al., 1991). A similar impairment in learning a stimulus–response association (enter an arm on an eight-arm maze if cued by a light) following lateral caudate lesions was reported by McDonald and White (1993). Similar results have been shown to characterize HD patients with caudate lesions in that they are impaired in acquisition and learning of a variety of motor tasks (Heindel, Salmon, Shults, Walicke, & Butters, 1989; Martone, Butters, Payne, Becker, & Sax, 1984).

Even though it is clear that the hippocampus and caudate nucleus can operate independent of each other, by selecting the appropriate task such as the plus maze and a simple learning task involving the use of both spatial and response attributes, it is not surprising that competition and cooperation between the two systems can emerge from the heretofore description of dissociations between the caudate nucleus and the hippocampus. As an example, it has been shown that based on probe tests, when rats learn that one location is correct in a plus maze, they first learn to use a spatial strategy, but with continued training they shift to a response strategy. Manipulations of the hippocampus with the use of lidocaine (a local anesthetic) blocked the expression of place learning without affecting response learning, whereas lidocaine injections into the caudate nucleus did not affect place learning, but disrupted response learning (Packard & McGaugh, 1996). These results suggested that the hippocampus and caudate nucleus can operate independent of each other. However, in additional research Packard (1999) has shown that post-trial injections of glutamate in the hippocampus postpone the shift from place to response, whereas post-trial injections of glutamate into the lateral caudate nucleus facilitate the shift to a response strategy, suggesting the possibility of competitive interactions between the hippocampus and the caudate nucleus. Further support of the idea of potential competitive interactions between the hippocampus and the caudate nucleus has been reviewed by Packard and Knowlton (2002).

2.3. Pattern separation process

It can be demonstrated that single cells within the hippocampus are activated by most sensory inputs, including vestibular, olfactory, visual, auditory, and somatosensory as well as higher-order integration of sensory stimuli (Cohen & Eichenbaum, 1993). The question of importance is whether these sensory inputs have a memory representation within the hippocampus. Thus far, it appears that short-term memory for odor or visual object information is not altered by lesions of the hippocampus (Aggleton, Hunt, & Rawlins, 1986; Jackson-Smith, Kesner, & Chiba, 1993; Kesner et al., 1993; Mumby, 2001; Otto & Eichenbaum, 1992), implying that sensory-perceptual information is not represented in memory within the hippocampus. One possible role for the hippocampus in processing all sensory information might be to provide for sensory markers to demarcate a spatial location, so that the hippocampus can more efficiently mediate spatial information. It is, thus, possible that one of the main process functions of the hippocampus is to encode and separate spatial locations from each other. This would ensure that new highly processed sensory information is organized within the hippocampus and enhances the possibility of remembering and temporarily storing one place as separate from another place. It is assumed that this is accomplished via pattern separation of spatial information, so that spatial locations can be separated from each other and spatial interference is reduced. This process is akin to the idea that the hippocampus is involved in orthagonalization of sensory input information (Rolls, 1989), in representational differentiation (Myers, Gluck, & Granger, 1995), and indirectly in the utilization of relationships (Cohen & Eichenbaum, 1993).

To assess this function rats were trained in a *spatial* task. In this task rats were required to remember a spatial location dependent upon the distance between the study phase object and an object used as a foil. More specifically, during the study phase an object that covers a baited food well was randomly positioned in 1 of 15 possible spatial locations on a cheese board (dry-land version of a water maze containing a large number of food wells). Rats exited a start box and displaced the object in order to receive a food award and were then returned to the start box. On the ensuing test phase rats were allowed to choose between two objects that were identical to the study phase object. One object was baited and positioned in the previous study phase location (correct choice), the other (foil) was unbaited and placed in a different location (incorrect choice). Five distances (min = 15 cm, max = 105 cm) were randomly used to separate the foil from the correct object. Following the establishment of a criterion of 75% correct averaged across all separation distances, rats were given either large (dorsal and ventral) hippocampal or cortical control lesions dorsal to the dorsal hippocampus. Following recovery from surgery the rats were retested. The results indicate that whereas control rats matched their pre-surgery performance for all spatial distances, hippocampal lesioned rats displayed impairments for short (15–37.5 cm) and medium (60 cm) spatial separations, but performed as well as controls when the spatial separation was long (82.5–105 cm). The fact that the hippocampal lesioned group was able to perform the task well at large separations indicates that the deficits observed at the shorter separations were not the result of an inability to remember the rule. The results suggest that the hippocampus may serve to separate incoming spatial information into patterns or categories by temporarily storing one place as separate from another place. It can be shown that the ability to remember the long distances was not based on an egocentric response strategy, because if the study phase was presented on one side of the cheese board and the test originated on the opposite side, the hippocampal lesioned rats still performed the long distances without difficulty. Furthermore, the hippocampal lesioned group had no difficulty discriminating between two short distances. It is clear that in this task it is necessary to separate one spatial location from another spatial location. Hippocampal lesioned rats cannot separate these spatial locations very well, so that they can perform the task only when the spatial locations are far apart (Gilbert, Kesner, & Lee, 2001). Similar deficits have been observed for new geographical information in patients with hippocampal damage due to an hypoxic episode (Hopkins & Kesner, 1993).

Does spatial pattern separation based on spatial interference play a role in the acquisition (consolidation) of a variety of hippocampal-dependent tasks? A few examples will suffice. Because rats are started in different locations in the standard water maze task, there is a great potential for interference among similar and overlapping spatial patterns. Thus, the observation that hippocampal lesioned rats are impaired in learning and subsequent consolidation of important spatial information in this task could be due to difficulty to separate spatial patterns resulting in enhanced spatial interference. Support for this idea comes from the observation of Eichenbaum, Stewart, and Morris (1990) who demonstrated that when fimbria-fornix lesioned rats are trained on the water maze task from only a single starting position (less spatial interference) there are hardly any learning deficits, whereas training from many different starting points resulted in learning difficulties. In a somewhat similar study it was shown that total hippocampal lesioned rats learned or consolidated rather readily that only one spatial location was correct on an eight-arm maze (Hunt, Kesner, & Evans, 1994). In a different study, McDonald and White (1995) used a place preference procedure in an eight-arm maze. In this

procedure food is placed at the end of one arm and no food is placed at the end of another arm. In a subsequent preference test normal rats prefer the arm that contained the food. In this study fornix lesioned rats acquired the place preference task as quickly as controls, if the arm locations were opposite each other, but the fornix lesioned rats were markedly impaired, if the locations were adjacent to each other. Clearly, it is likely that there would be greater spatial interference when the spatial locations are adjacent to each other rather than far apart. Thus, spatial pattern separation can play a role in the acquisition of new spatial information.

Is the hippocampus involved in all forms of pattern separation or is it specific for spatial and temporal pattern separation? Could the caudate nucleus be involved in subserving response, but not spatial pattern separation? From a theoretical perspective, Robbins and Brown (1990) have suggested that the caudate nucleus plays a role in response selection within egocentric space, such that responses are organized with reference to the current position of the body and limbs and the target of the intended movement. Thus, discrete responses occur in a vector space and the more overlap in the direction, extent, and form of the movement, the more the response patterns need to be separated from each other.

To address these questions a new task was developed using a delayed-match-to-sample for motor response task to assess memory for motor responses in rats with control, hippocampal, and caudate nucleus lesions utilizing a cheeseboard maze. It is assumed that selection of the appropriate motor response in this short-term memory task is based on proprioceptive and vestibular feedback. All testing was conducted in complete darkness. Behavior was monitored using an infrared camera. A start box was positioned in the center of the maze facing a randomly determined direction on each of 8 daily trials. Trials consisted of a sample phase followed by a choice phase. On the sample phase, a phosphorescent object was randomly positioned to cover a baited food well in 1 of 5 equally spaced positions around the circumference of the maze forming a 180° arc 60 cm from the start box. One position was directly in front of the box, the remaining positions were 45° and 90° to each side of center. On each trial, the start box door was opened, the animal exited the box, displaced the object to receive a food reward, and returned to the box. The box was then rotated to face a different direction. The food well in the same position relative to the start box was baited and an identical phosphorescent object was positioned to cover the food well. A second identical phosphorescent object was positioned to cover a different unbaited food well. On the ensuing choice phase, the animal was allowed to choose between the two objects. The object that covered the food well in the same position relative to the start box as the object in the sample phase was the correct choice and the second foil object

was the incorrect choice. The rat must remember the motor response made on the sample phase and make the same motor response on the choice phase to receive a reward. Four separations of 45°, 90°, 135°, and 180° were randomly used to separate the correct object from the foil object during the choice phase. The results are shown in Fig. 4 and indicate that hippocampal lesioned rats match the performance of controls across all separations. However, rats with caudate nucleus lesions are impaired across all separations. Thus, the results suggest that the caudate nucleus, but not the hippocampus, support pattern separation for motor response information based in part on proprioceptive and vestibular inputs. Additional research supports the idea that the caudate is involved in response pattern separation. In this experiment rats with quinolinic acid lesions of the medial or lateral caudate and controls were tested for performance of a previously learned auditory conditional response association task. The task involved the selection of two possible responses (reaching up on top of an object vs. pushing away an object) when presented
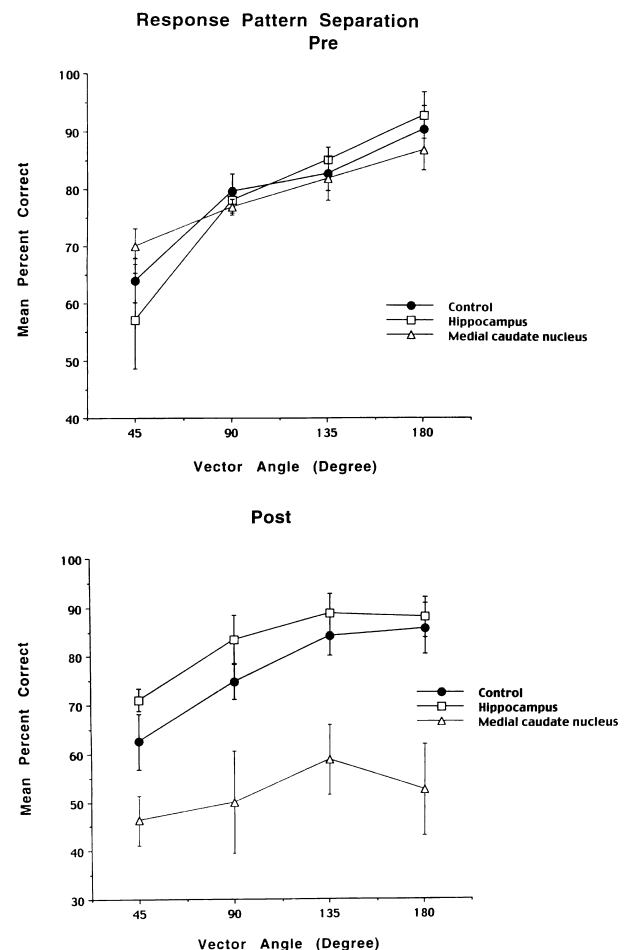

Fig. 4. Mean percent correct and standard error based on a response pattern separation task for control, hippocampus, and caudate lesion groups as a function of vector angle (degrees).

with one of two different tones. Results indicated that lesions of either the medial or lateral caudate produced a sustained deficit in the auditory conditional response association task. Only the lateral caudate lesioned rats exhibited transient motor problems immediately following surgery, but these problems did not interfere with the execution of the appropriate responses. In the present task it is assumed that the two required responses overlap to a great extent in a limited vector space such that there is heightened interference between responses based in part on proprioceptive and vestibular feedback. Normal rats do not have difficulty in separating the two responses, but rats with either medial or lateral caudate lesions cannot separate the responses very well and thus they have difficulty in performing the conditional auditory-response task (Adams, Kesner, & Ragozzino, 2001). Thus, it appears that both the medial and lateral caudate are involved in response selection and response separation within egocentric space. Thus, it appears that there are both dissociations and interactions between the hippocampus and caudate nucleus in mediating spatial and response attributes, respectively within the event-based memory system. Clearly, dissociations and interactions can also be observed between other attributes within the event-based memory system, such as spatial and affect attributes involving the hippocampus and amygdala, affect and visual object attributes involving the hippocampus and perirhinal cortex, as well as temporal and spatial attributes within subregions of the hippocampus (Brown & Aggleton, 2001; Gilbert et al., 2001; Gilbert & Kesner, 2003; Kesner, 1998; Kesner & Gilbert, 2001).

3. Event-based memory vs. knowledge-based memory for the spatial attribute: Hippocampus and parietal cortex

Just as interactions may occur across attributes within a memory system, interactions may also occur across memory systems. For example, with regard to spatial information, interactions may occur between the event-based system and knowledge-based system. Specifically, interactions may occur between the hippocampus and the parietal cortex (PC). In general, it is suggested that the hippocampus and PC operate independently with regard to intrinsic processes (such as episodic vs. perceptual memory), but they are more likely to interact during learning and retention of especially spatial information.

3.1. Episodic vs. perceptual memory

Although the hippocampus and PC are not directly linked anatomically (Burwell, 2000; Lavenex & Amaral, 2000; Witter et al., 2000), it appears that both regions process spatial information. They can, however, operate

independently with respect to the intrinsic processes performed by that region. One might expect hippocampal lesions to impair spatial short-term and intermediate-term memory, or episodic memory (a component of event-based memory, see above), whereas PC lesions may impair perceptual memory (a component of knowledge-based memory). Indeed, a double dissociation exists between the hippocampus and PC in regards to perceptual memory vs. short-term memory (STM) or working memory (WM) for spatial information. Keane, Gabrieli, Mapstone, Johnson, and Corkin (1995) reported that a patient with occipital-lobe damage (extending into PC) showed a deficit in perceptual priming but had not effect on recognition memory, whereas a patient with bilateral medial temporal-lobe damage (including hippocampus) had a loss of recognition memory, but no loss of perceptual memory. Recently, Chiba, Jackson, and Kesner (2002) tested hippocampal and PC lesioned rats on two versions of a spatial continuous recognition task. These authors demonstrated that rats with lesions of the PC disrupted perceptual memory (continuous reinforcement condition), whereas lesions of the hippocampus disrupted spatial working memory (differential reinforcement condition). Furthermore, Kesner (2000b) reported that lesions of the PC, but not the hippocampus, disrupted positive priming (a component of perceptual memory) for spatial locations (Kesner, unpublished observations). Thus, the hippocampus and PC can operate independent of each other, suggesting the possibility for parallel processing.

3.2. Acquisition and retention

Despite clear instances where the hippocampus and PC can operate independent of each other, data indicate that the hippocampus and PC can interact during new learning and retention of spatial information. Bilateral lesions of the hippocampus or PC result in impaired learning and retention of a spatial navigation task in a water maze or a dry-land version of the water maze (DiMattia & Kesner, 1988; Kesner, Farnsworth, & Kametani, 1992). Save, Poucet, Foreman, and Thinus Blanc (1992) reported that during a reaction-to-change task, lesions to either the hippocampus or PC result in decreased reaction to a spatial change, but intact exploration for a non-spatial change, such as changing of a visual object. Additional visual cues separate from or close to the location of the target stimulus (a rat) had no effect on either lesion groups; both failed to re-explore when the target stimulus had been removed. Furthermore, using a multiple-object scene discrimination task, DeCoteau and Kesner (1998) showed that lesions of the hippocampus and PC disrupted both spatial and spatial/object discriminations, whereas both lesions were unimpaired on object discriminations. Finally, lesions of the hippocampus or PC disrupt learning of object–place

paired-associates (Gilbert & Kesner, 2002; Long, Mellem, & Kesner, 1998). Clearly from these data it appears that both the hippocampus and PC participate in acquisition and retention of spatial information.

A disconnection procedure was employed to test the potential interactions between the hippocampus and PC (for similar procedures, see Warburton, Baird, Morgan, Muir, & Aggelton, 2001). In this approach, unilateral lesions were made to either the hippocampus or PC. In one group, unilateral lesions were made in contralateral hemispheres and in the second group lesions were made in the same hemisphere. An assumption made is that the right and left hemispheres operate in parallel. Crossed lesions (i.e., unilateral lesions in contralateral hemispheres), therefore, would disrupt communication within each of the two hemispheres, thus disconnecting the two brain regions. It was hypothesized that if the hippocampus and PC interact, then crossed lesioned animals should be markedly impaired compared to animals with lesions on the same side.

Following recovery from surgery, animals were trained on an object–place paired-associate task (for details see Gilbert & Kesner, 2002). Two paired-associates were reinforced which consist of one particular object (A) in one particular location (1) and a different object (B) in a different location (2). Rats should learn that if an object is presented in its paired location then the rat should displace the object to receive a reward (Go). However, the rat should withhold displacing the object if it is not in its paired location (No-Go). Difference scores calculated from the latencies between Go/No-Go stimuli assessed learning; increased latencies indicate better learning (since animals learn not to run during non-rewarded trials, hence "No-Go"). The data are shown in Fig. 5. Animals with crossed lesions are considerably more impaired than animals with lesions on the same side, that is, animals with crossed lesions have a lower latency difference score, thus indicating that they failed to learn the object–place associations. Subsequent tests (not shown) indicate that all animals learned simple discriminations (objects and places). From these data it can be concluded that the hippocampus and PC are likely to interact with each other during new learning of object–place paired-associates.

What still needs to be determined is the qualitative nature and the temporal dynamics of the interaction. In terms of the qualitative representation of spatial information, it has been suggested that the PC processes the spatial location of objects in an egocentric framework based on the relationship between the organism and appropriate object or objects in the external environment (Andersen, 1999; Chen, Lin, Barnes, & McNaughton, 1994; Colby, 1999). In contrast, the hippocampus processes the spatial location of objects in an allocentric framework based on the relative position of objects in the external environment (Morris et al., 1982;
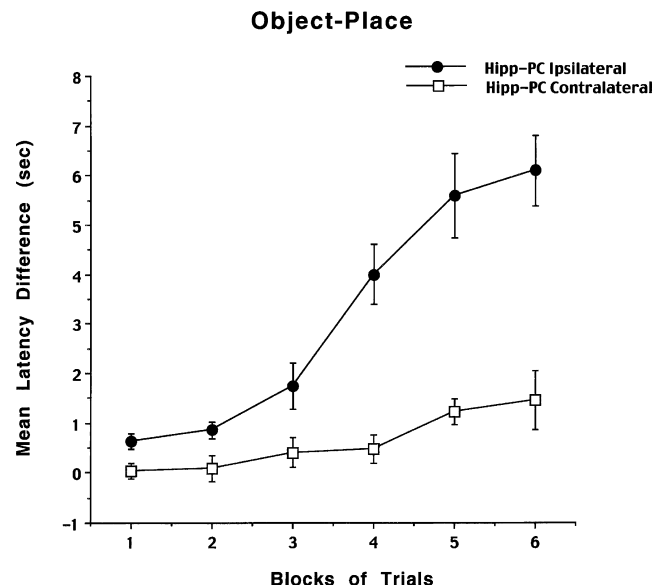

Fig. 5. Mean latency difference (sec) and standard error based on an object–place paired-associate task for the hippocampus (Hipp) and parietal cortex (PC) lesioned group with both lesions on the same side (ipsilateral) and Hipp and PC lesioned group with the Hipp lesion on one side and PC lesion on the other side (contralateral) as a function of blocks of trials (60 trials/block).

O'Keefe, 1979; Rolls, 1999). However, both the PC and the hippocampus mediate learning and retention of tasks that have been suggested to emphasize primarily allocentric information, such as the water maze spatial navigation, the reaction to a spatial change, and the object–place paired-associate tasks. The hippocampus and PC are also both involved in processing of ideothetic information (one form of egocentric information) based on self-motion and vestibular inputs (Berthoz, 1999; Bures et al., 1999; Chen & Nakamura, 1998; Whishaw, McKenna, & Maaswinkel, 1997). Thus, it appears that both the hippocampus and PC process egocentric and allocentric information, but it is possible that the hippocampus places proportionally a greater emphasis on allocentric and PC places proportionally a greater emphasis on egocentric spatial processing. The emphasis on egocentric and allocentric processing of spatial information would suggest the possibility that short-term spatial information is first encoded in the PC in an egocentric framework to guide action and then processed in long-term memory in the hippocampus in an allocentric framework (Burgess, Jeffery, & O'Keefe, 1999; Save & Poucet, 2000). This model suggests that long-term memory for spatial information resides in the hippocampus, a view also championed by Nadel and Moscovitch (1997). Some support for this view comes from the finding of long-term retrograde amnesia gradients (for a review see Nadel & Moscovitch, 1997).

There are, however, other views of possible temporal relationships between the hippocampus and PC. Some

models assume that the long-term store is located in the PC and not in the hippocampus. Then, it is assumed that new information is first processed in the PC and if a mismatch between current input and long-term store occurs, then information is transferred for further processing in the hippocampus followed by consolidation and transfer back to PC (Save & Poucet, 2000). Alternatively, the information could first be processed in the hippocampus and then transferred to the PC. Finally, other models assume parallel processing of information with information processed independently in both PC and hippocampus followed by subsequent transfer of information to PC. The data that have been presented thus far do not differentiate among these views of temporal interactions between the hippocampus and PC, but there are some data that support the idea that information is first processed in the hippocampus and then transferred to the PC. Izquierdo et al. (1997) showed that injections of AP5 (a glutamate antagonist) or muscimol (a GABA agonist) injected into the hippocampus or amygdala 0 min after inhibitory avoidance training produce retrograde amnesia, whereas the same injections into the entorhinal cortex or parietal cortex produce retrograde amnesia only 180 min after inhibitory training. Furthermore, using CNQX (an AMPA antagonist) injected into the amygdala or hippocampus 1 day after training, entorhinal cortex 1 or 31 days after training, and parietal cortex 1, 31 or 60 days after training temporarily disrupts retrieval of learned information. These data suggest that during learning the hippocampus is first involved followed by activation of the PC and during retrieval the information is stored in long-term memory primarily in the PC. Thus, it appears that the hippocampus and PC can operate independently with regard to intrinsic processes (such as episodic vs. perceptual memory), but they are more likely to interact during learning, and retention of spatial information.

It is important to note that there are likely to be other types of interactions between the event-based memory and knowledge-based memory for other attributes, such as for example between the perirhinal cortex and inferotemporal cortex with respect to the sensory-perceptual (visual object) attribute (Murray & Bussey, 1999). Also, there are likely to be dissociations and interactions between other attributes within the knowledge-based memory system, such as spatial locations and visual object involving the parietal cortex and inferotemporal cortex (Mishkin & Ungerleider, 1982).

4. Event-based memory vs. rule-based memory for the spatial attribute: Hippocampus and medial prefrontal cortex

With respect to spatial attribute information, one might expect a dissociation between the hippocampus and medial prefrontal cortex, especially prelimbic and infralimbic cortex, in any new learning task that involves spatial information in that the animals need to learn new event-based or episodic spatial information as well as spatial rules. One example will suffice. Winocur and Moscovitch (1990) trained rats with prefrontal cortex or hippocampus lesions on two maze problems in a Hebb–Williams maze. They showed that prefrontal cortex lesioned rats have difficulty in learning the maze, but also have difficulty transferring the information to a new maze suggesting a problem with learning of the rules associated with successful learning of the maze. In contrast, hippocampal lesions showed savings for memory of the general skill of maze learning, but had poor recall of the learning experience.

It has been suggested that the hippocampus mediates memory for past events within a relatively short time frame (short-term or intermediate-term) (Kesner, 1990; Olton, 1983). Thus, as a consequence of damage to the hippocampus, one would expect severe difficulty in remembering relatively new spatio-temporal information that would, in turn, create a problem in using memory for the future based on memories necessary to plan or anticipate future events. In contrast, it has been suggested that the prefrontal cortex mediates memory for future events, given that memory for the past within either a short or long time frame is not based on temporal order. One might then expect a dissociation between the prefrontal cortex and hippocampus in spatial tasks that could be solved using both prospective and retrospective codes. To test this idea sham-operated rats or animals with medial prefrontal cortex or hippocampus lesions were tested in a task that provided an opportunity for rats to utilize retrospective and prospective memory codes, while remembering items (spatial locations) within short or long lists (Kametani & Kesner, 1989; Kesner, 1989). More specifically, on any one trial a rat was presented with 2, 4, 6, 8, or 10 items (spatial locations) on a 12-arm radial maze followed 15 min later by two win-shift tests comprising a choice between a place previously visited and a novel place. Each animal was given a total of 20 trials with 8 tests for each point of interpolation or each list length (2, 4, 6, 8, or 10). During learning, rats show an increase in errors as the number of places to be remembered is increased from 2 to 6 to 8 reflecting the use of a retrospective memory code (the ability to remember the spatial locations previously visited). These rats also show a decrease in errors as the number of places is increased from 8 to 10 reflecting the use of a prospective memory code (the ability to anticipate the spatial locations that have not yet been visited). Results indicate that sham-operated animals display an increase in errors as a function of point of interpolation or set size (2–8 items) followed by a decrease in errors with a set size of 10 items suggesting the use of both retrospective and prospective memory

codes. In contrast, animals with medial prefrontal cortex lesions made few errors for short list lengths, but a large number of errors for the longer list lengths, reflecting an inability to shift from a retrospective to a prospective memory code, whereas animals with hippocampus lesions made errors across all list length, reflecting a deficit in utilizing both retrospective and prospective strategies. It is likely that the hippocampus lesioned rats were not able to use a prospective strategy, because they were not able to remember spatial information needed to initiate a prospective strategy. It should be noted that more recently it has been shown that in certain situations, it is possible to obtain increased single cell activity in the hippocampus reflecting the use of a prospective code (Ferbinteanu & Shapiro, 2003; Frank, Brown, & Wilson, 2000). The role of the prefrontal cortex in potentially triggering this prospective code has not yet been investigated.

There is good evidence that the prefrontal cortex plays an important role in short-term memory, especially in a delayed matching- or non-matching-to-sample tasks where a correct choice response for a stimulus (e.g., object or spatial location) is required after a delay period (Delatour & Gisquet-Verrier, 1996; Floresco, Seamans, & Phillips, 1997; Fuster, 2001; Izaki, Maruki, Hori, & Nomura, 2001; Porter, Burk, & Mair, 2000). Strong electrophysiological correlates can be identified during a short-term delay period within the prefrontal cortex in non-human primates in delayed-choice tasks (Constantinidis, Franowicz, & Goldman-Rakic, 2001; Rainer, Asaad, & Miller, 1998). The rodent medial prefrontal cortex also plays an equivalent role in tasks where a delayed choice response to stimuli is required and lesions of the medial prefrontal cortex impair performance in delayed-choice tasks (Delatour & Gisquet-Verrier, 1996; Shaw & Aggleton, 1993). Thus, based on the above-mentioned studies it has been suggested that the prefrontal cortex as part of the event-based memory system is involved in mediating short-term memory for many attributes including spatial attribute information.

In contrast, a large number of studies indicate that short-term memory is spared, whereas intermediate-term memory is relatively impaired with damage to the hippocampal system both in humans (Eichenbaum, 2000; Eichenbaum, Otto, & Cohen, 1994; Holdstock, Shaw, & Aggleton, 1995; Kesner & Hopkins, 2001; Scoville & Milner, 1957) and animals (Alvarez, Zola-Morgan, & Squire, 1994; Clark, West, Zola, & Squire, 2001; Eichenbaum, 2000; Eichenbaum et al., 1994; Mishkin, 1978; Steele & Morris, 1999). The relatively intact short-term memory with hippocampal dysfunction in the above literature, however, is in contrast to the computational models of the hippocampus, since those models suggest that the hippocampus mediate short-term memory mainly by virtue of the recurrent collaterals in CA3 area (Granger, Wiebe, Taketani, & Lynch,

1996; Kesner & Rolls, 2001; Wiebe, Staubli, & Abros-Ingerson, 1997).

Thus, based on the above-mentioned studies it has been suggested that the hippocampus as part of the event-based memory system is primarily involved in mediating intermediate-term memory and perhaps short-term memory for spatial attribute information. Lee and Kesner (2003) examined the dynamic interactions between the prefrontal cortex and hippocampus by first training rats on a delayed non-matching-to-place task on a radial eight-arm maze requiring memory for a single spatial location following short-term (i.e., 10 s) delays. After reaching criterion rats were prepared with an axon-sparing lesion of the dorsal hippocampus combined with reversible inactivation of the medial prefrontal cortex, or vice versa, within a subject. The rats were then retested at 10 s delays. The results showed that inactivating either the medial prefrontal cortex or the dorsal hippocampus produced an initial deficit in short-term (i.e., 10 s) spatial working memory, which eventually improved over time to a normal level of performance. This suggests that inactivating one of these structures initially affected the short-term working memory system, but a compensatory adjustment was made to achieve normal performance. Therefore, it seems that the dorsal hippocampus and medial prefrontal cortex normally process short-term memory for spatial information in parallel, which may explain the null-effect of hippocampal damage on short-term memory in previous literature (Alvarez et al., 1994; Clark et al., 2001; Eichenbaum, 2000; Eichenbaum et al., 1994; Holdstock et al., 1995; Jarrard, 1993; Kesner & Adelstein, 1989; Kesner & Hopkins, 2001; Kesner & Novak, 1982; Mishkin, 1978; Porter et al., 2000; Scoville & Milner, 1957; Steele & Morris, 1999; Winocur, 1992). It also supports the computational models that have proposed the role of the dorsal hippocampus in short-term memory (Granger et al., 1996; Kesner & Rolls, 2001; Wiebe et al., 1997). After the system becomes stabilized presumably as a result of a compensatory mechanism in the absence of one structure, this compensatory structure might be sufficient for normal performance when information needs to be stored for only seconds. The rats were then exposed to both a 10 s delay (short-term memory) and a 5-min delay (intermediate-term memory). The results indicated that the dorsal hippocampus lesioned rats were impaired for the 5 min, but not the 10 s delays, whereas the medial prefrontal cortex lesioned rats showed no impairment at either the 10 s or 5 min delays. In this situation, the dorsal hippocampus became a necessary structure for spatial working memory following an intermediate-term delay (i.e., 5 min), whereas the medial prefrontal cortex failed to show compensation for this time window, suggesting a unique function for the dorsal hippocampus in the time range longer than short term (Alvarez et al., 1994; Clark et al., 2001; Eichenbaum,

2000; Eichenbaum et al., 1994; Holdstock et al., 1995; Jarrard, 1993; Kesner & Adelstein, 1989; Kesner & Hopkins, 2001; Kesner & Novak, 1982; Mishkin, 1978; Porter et al., 2000; Scoville & Milner, 1957; Steele & Morris, 1999; Winocur, 1992). The rats were then retested with 10 s and 5 min delays following a combination of lesion of the dorsal hippocampus with inactivation of the medial prefrontal cortex or lesion of the medial prefrontal cortex and inactivation of the dorsal hippocampus. Inactivating both regions at the same time resulted in a severe impairment of short-term and intermediate memory for spatial information suggesting that one of the structures needs to function properly for intact processing of short-term or intermediate-term spatial memory. Thus, the two regions interact with each other to ensure the processing of spatial information across a dynamic temporal range including both short-term and intermediate-term memory. The current results provide compelling evidence indicating that a mnemonic time-window is a critical factor in dissociating the function of the hippocampal system from that of the medial prefrontal cortex in a delayed-choice task. That is, the dorsal hippocampus and medial prefrontal cortex appear to process spatial memory in parallel within a short-term range, whereas the dorsal hippocampal function becomes more essential once the critical time-window requires spatial memory for a time period exceeding that range.

A previous disconnection experiment (Floresco et al., 1997) showed that the interaction between the hippocampus and medial prefrontal cortex is necessary for rats to perform a spatial working memory task with a 30-min delay. However, the Lee and Kesner (2003) results demonstrate that the medial prefrontal cortex might not be necessary for an intermediate- or long-term delayed response when only a simple rule (i.e., win-shift) is applied to a very small number of trial-unique items (i.e., two different arms per trial in our task). Once a task requires prospective coding (Rainer, Rao, & Miller, 1999) of a sequence of several spatial items during an intermediate-term delay (i.e., 30 min in Floresco et al., 1997), based on memory of previously coded items (i.e., during sample phase), the interactive communication between the hippocampus and medial prefrontal cortex might become intensified (Floresco et al., 1997), thus resulting in a performance deficit with even one of the communicating partners disabled (Ragozzino, Adams, & Kesner, 1998). That is, the interaction between the "past" (hippocampus) and the "future" (prefrontal cortex) may need the intimate prefrontal cortex–hippocampal interaction especially when those items need to be organized sequentially with a significant amount of delay. Such prospective coding based on retroactive search in memory might be very difficult in the Lee and Kesner (2003) experiment, since the animals had no prediction, during a delay period, on which side's adjacent arm to a study arm would be chosen as a test arm.

Therefore, further investigation is needed to determine whether the hippocampal–prefrontal cortex interaction is mainly for proactively guiding and temporally integrating sequential responses (Fuster, 2001; Miller, 2000; Seamans, Floresco, & Phillips, 1995). Thus, it appears that there are important dissociations and interactions between the medial prefrontal cortex and hippocampus with respect to the spatial attribute in the context of rule learning vs learning of the specifics of a spatial situation, prospective vs. retrospective coding, and temporal dynamics of short-term and intermediate-term memory. There are likely to be other types of interactions between the event-based memory and rule-based memory for other attributes, such as for example between the amygdala and orbital-frontal cortex with respect to the affect attribute (Schoenbaum, Setlow, & Ramus, 2003). Also, there are likely to be dissociations and interactions between other attributes within the rule-based memory system, such as spatial and affect involving the dorsolateral (monkeys and humans) and prelimbic and infralimbic (rats) cortex and orbito-frontal cortex (Kesner, 2000a).

5. Summary

In summary, it is proposed that memory is organized into event-based, knowledge-based, and rule-based memory systems. Furthermore, each system is composed of the same set of multiple attributes and characterized by a set of process oriented operating characteristics that are mapped onto multiple neural regions and interconnected neural circuits. Based on this theoretical model of memory, it is possible to investigate the independence and interaction among brain regions between any two systems for any of the proposed attributes or processes. This applies also to the investigation of independence and interactions between any two attributes within a system and between processes associated with a system for any of the proposed attributes. In this paper we have presented research evidence to suggest that there are both dissociations and interactions between the hippocampus and caudate nucleus in mediating spatial and response attributes, respectively, within the event-based memory system. Clearly, dissociations and interactions can also be observed between other attributes within the event-based memory system, such as spatial and affect attributes involving the hippocampus and amygdala, affect and visual object attributes involving the hippocampus and perirhinal cortex, as well as temporal and spatial attributes within subregions of the hippocampus.

Evidence has also been presented to suggest that there are both dissociations and interactions between the hippocampus and the parietal cortex in subserving the spatial attribute within the event-based and knowledge-based memory systems. Furthermore, dissociations and

interactions can also be observed between the event-based and knowledge-based memory systems for different attributes, such as the visual object attribute involving the perirhinal and inferotemporal cortex and between other attributes within the knowledge-based memory system, such as spatial and visual object involving the parietal cortex and inferotemporal cortex.

Evidence has also been presented to suggest that there are both dissociations and interactions between the hippocampus and the prefrontal cortex in subserving the spatial attribute within the event-based and rule-based memory systems. Furthermore, dissociations and interactions can also be observed between the event-based and rule-based memory systems for different attributes, such as the affect attribute involving the amygdala and orbital-frontal cortex and interactions between other attributes within the rule-based memory system, such as spatial and affect involving the dorso-lateral (monkeys, humans) and prelimbic and infralimbic (rats) frontal cortex and orbito-frontal cortex.

Thus, there are many brain regions that can be studied to uncover the nature of their interactions and independence of each other in the context of the complexity of the neural representation of memory.

References

Adams, S., Kesner, R. P., & Ragozzino, M. E. (2001). Role of the medial and lateral caudate-putamen in mediating an auditory conditional response association. *Neurobiology of Learning and Memory, 76*, 106–116.

Aggleton, J. P., Hunt, P. R., & Rawlins, J. N. P. (1986). The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. *Behavioural Brain Research, 19*, 133–146.

Alvarez, P., Zola-Morgan, S., & Squire, L. R. (1994). The animal model of human amnesia: Long-term memory impaired and short-term memory intact. *Proceedings of the National Academy of Sciences of the United States of America, 91*, 5637–5641.

Andersen, R. A. (1999). Multimodal integration for the representation of space in the posterior parietal cortex. In N. Burgess, K. J. Jeffery, & J. O'Keefe (Eds.), *The hippocampal and parietal foundations of spatial cognition* (pp. 90–103). New York: Oxford University Press.

Berthoz, A. (1999). Hippocampal and parietal contribution to topokinetic and topographic memory. In N. Burgess, K. J. Jeffery, & J. O'Keefe (Eds.), *The hippocampal and parietal foundations of spatial cognition*. Oxford: Oxford University Press.

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience, 2*, 51–61.

Bures, J., Fenton, A. A., Kaminsky, Y., Rossier, J., Sacchetti, B., & Zinyuk, L. (1999). Dissociation of exteroceptive and ideothetic orientation cues: Effect on hippocampal place cells and place navigation. In N. Burgess, K. J. Jeffery, & J. O'Keefe (Eds.), *The hippocampal and parietal foundations of spatial cognition* (pp. 167–185). Oxford: Oxford University Press.

Burgess, N., Jeffery, K. J., & O'Keefe, J. (1999). Integrating hippocampal and parietal functions: A spatial point of view. In N. Burgess, K. J. Jeffery, & J. O'Keefe (Eds.), *The hippocampal and parietal foundations of spatial cognition* (pp. 3–32). Oxford: Oxford University Press.

Burwell, R. (2000). The parahippocampal region: corticocortical connectivity. In H. E. Scharfman, M. P. Witter, & R. Schwarcz (Eds.), *The parahippocampal region* (pp. 25–42). New York: The New York Academy of Sciences.

Chen, L. L., Lin, L.-H., Barnes, C. A., & McNaughton, B. L. (1994). Head-direction cells in the rat posterior cortex: II. Contributions of visual and ideothetic information to the directional firing. *Experimental Brain Research, 101*, 24–34.

Chen, L. L., & Nakamura, K. (1998). Head-centered representation and spatial memory in rat posterior parietal cortex. *Psychobiology, 26*, 119–127.

Chiba, A., Jackson, P., & Kesner, R. P. (2002). Two forms of spatial memory: A double dissociation between the parietal cortex and the hippocampus in the rat. *Behavioral Neuroscience, 5*, 874–883.

Clark, R. E., West, A. N., Zola, S. M., & Squire, L. R. (2001). Rats with lesions of the hippocampus are impaired on the delayed nonmatching-to-sample task. *Hippocampus, 11*, 176–186.

Cohen, N. J., & Eichenbaum, H. B. (1993). *Memory, amnesia, and hippocampal function*. Cambridge: MIT Press.

Colby, C. L. (1999). Parietal cortex constructs action-oriented spatial representations. In N. Burgess, K. J. Jeffery, & J. O'Keefe (Eds.), *The hippocampal and parietal foundations of spatial cognition* (pp. 104–126). New York: Oxford University Press.

Colombo, P. J., Davis, H. P., & Volpe, B. T. (1989). Allocentric spatial and tactile memory impairments in rats with dorsal caudate lesions are affected by preoperative behavioral training. *Behavioral Neuroscience, 103*, 1242–1250.

Constantinidis, C., Franowicz, M. N., & Goldman-Rakic, P. S. (2001). The sensory nature of mnemonic representation in the primate prefrontal cortex. *Nature Neuroscience, 4*, 311–316.

Cook, D., & Kesner, R. P. (1988). Caudate nucleus and memory for egocentric localization. *Behavioral Neural Biology, 49*, 332–343.

DeCoteau, W. E., Hoang, L., Huff, L., Stone, A., & Kesner, R. P. (2004). Effects of the hippocampus and medial caudate nucleus lesions on memory for direction information in rats. *Behavioral Neuroscience, 118*, 540–545.

DeCoteau, W., & Kesner, R. P. (1998). Effects of hippocampal and parietal cortex lesions on the processing of multiple-object scenes. *Behavioral Neuroscience, 112*, 68–82.

DeCoteau, W., & Kesner, R. P. (2000). A double dissociation between the rat hippocampus and medial caudoputamen in processing two forms of knowledge. *Behavioral Neuroscience, 114*, 1096–1108.

Delatour, B., & Gisquet-Verrier, P. (1996). Prelimbic cortex specific lesions disrupt delayed-variable response tasks in the rat. *Behavioral Neuroscience, 110*, 1282–1298.

DiMattia, B., & Kesner, R. P. (1988). Spatial cognitive maps: Differential role of parietal cortex and hippocampal formation. *Behavioral Neuroscience, 102*, 471–480.

Divac, I., Rosvold, H. E., & Szwarcbart, M. K. (1967). Behavioral effects of selective ablation of the caudate nucleus. *Journal of Comparative and Physiological Psychology, 63*, 184–190.

Duncan-Davis, J. D., Filoteo, J. V., Kesner, R. P., & Roberts, J. W. (2003). Recognition memory for hand positions and spatial locations in patients with Huntington's disease: Differential visuospatial memory impairment. *Cortex, 39*, 239–253.

Dunnett, S. B. (1990). Role of prefrontal cortex and striatal output systems in short-term memory deficits associated with ageing, basal forebrain lesions, and cholinergic-rich grafts. *Canadian Journal of Psychology, 44*, 210–232.

Eichenbaum, H. (2000). A cortical–hippocampal system for declarative memory. *Nature Review Neuroscience, 1*, 41–50.

Eichenbaum, H., Otto, T., & Cohen, N. J. (1994). Two functional components of the hippocampal memory system. *Behavioral and Brain Sciences, 17*, 449–518.

Eichenbaum, H., Stewart, C., & Morris, R. G. M. (1990). Hippocampal representation in spatial learning. *Journal of Neuroscience, 10*, 331–339.

Ferbinteanu, J., & Shapiro, M. L. (2003). Prospective and retrospective memory coding in the hippocampus. *Neuron, 40*, 1227–1239.

Floresco, S. B., Seamans, J. K., & Phillips, A. G. (1997). Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *Journal of Neuroscience, 17*, 1880–1890.

Frank, L. M., Brown, E. N., & Wilson, M. (2000). Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron, 27*, 169–178.

Fuster, J. M. (2001). The prefrontal cortex—an update: Time is of the essence. *Neuron, 30*, 319–333.

Gilbert, P. E., & Kesner, R. P. (2002). Role of the rodent hippocampus in paired-associate learning involving associations between a stimulus and a spatial location. *Behavioral Neuroscience, 116*, 63–71.

Gilbert, P. E., & Kesner, R. P. (2003). Localization of function within the dorsal hippocampus: The role of the CA3 subregion in paired-associate learning. *Behavioral Neuroscience, 117*, 1385–1394.

Gilbert, P. E., Kesner, R. P., & Lee, I. (2001). Dissociating hippocampal subregions: A double dissociation between dentate gyrus and CA1. *Hippocampus, 11*, 626–636.

Granger, R., Wiebe, S. P., Taketani, M., & Lynch, G. (1996). Distinct memory circuits composing the hippocampal region. *Hippocampus, 6*, 567–578.

Heindel, W. C., Salmon, D. P., Shults, C. W., Walicke, P. A., & Butters, N. (1989). Neuropsychological evidence for multiple implicit memory systems: A comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *Journal of Neuroscience, 9*, 582–587.

Holdstock, J. S., Shaw, C., & Aggleton, J. P. (1995). The performance of amnesic subjects on tests of delayed matching-to-sample and delayed matching-to-position. *Neuropsychologia, 33*, 1583–1596.

Hopkins, R. O., & Kesner, R. P. (1993). Memory for temporal and spatial distances for new and previously learned geographical information in hypoxic subjects. *Society for Neuroscience Abstracts, 19*, 1284.

Hopkins, R. O., Kesner, R. P., & Goldstein, M. (1995a). Item and order recognition memory for words, pictures, astract pictures, spatial locations, and motor responses in subjects with hypoxic brain injury. *Brain and Cognition, 27*, 180–201.

Hunt, M. E., Kesner, R. P., & Evans, R. B. (1994). Memory for spatial location: Functional dissociation of entorhinal cortex and hippocampus. *Psychobiology, 22*, 186–194.

Izquierdo, I., Quillfeldt, J. A., Zanatta, M. S., Quevedo, J., Schaeffer, E., Schmitz, P. K., & Medina, J. H. (1997). Sequential role of hippocampus and amygdala, entorhinal cortex and parietal cortex in formation and retrieval of memory for inhibitory avoidance in rats. *European Journal of Neuroscience, 9*, 786–793.

Izaki, Y., Maruki, K., Hori, K., & Nomura, M. (2001). Effect of rat medial prefrontal cortex temporal inactivation on a delayed alternation task. *Neuroscience Letters, 315*, 129–132.

Jackson-Smith, P., Kesner, R. P., & Chiba, A. A. (1993). Continuous recognition of spatial and nonspatial stimuli in hippocampal lesioned rats. *Behavioral and Neural Biology, 59*, 107–119.

Jarrard, L. E. (1993). On the role of the hippocampus in learning and memory in the rat. *Behavioral and Neural Biology, 60*, 9–26.

Kametani, H., & Kesner, R. P. (1989). Retrospective and prospective coding of information: Dissociation of parietal cortex and hippocampal formation. *Behavioral Neuroscience, 103*, 84–89.

Keane, M., Gabrieli, J., Mapstone, H., Johnson, K., & Corkin, S. (1995). Double dissociation of memory capacities after bilateral occipital-lobe or medial temporal-lobe lesions. *Brain, 118*, 1129–1148.

Kesner, R. P. (1989). Retrospective and prospective coding of information: Role of the medial prefrontal cortex. *Journal of Experimental Brain Research, 74*, 163–167.

Kesner, R. P. (1990). Learning and memory in rats with an emphasis on the role of the hippocampal formation. In R. P. Kesner & D. S. Olton (Eds.), *Neurobiology of comparative cognition* (pp. 179–204). Hillsdale, NJ: Erlbaum.

Kesner, R. P. (1998). Neurobiological views of memory. In J. L. Martinez & R. P. Kesner (Eds.), *The Neurobiology of Learning and Memory* (pp. 361–416). San Diego, CA: Academic Press.

Kesner, R. P. (2000a). Subregional analysis of mnemonic functions of the prefrontal cortex in the rat. *Psychobiology, 28*, 219–228.

Kesner, R. P. (2000b). Behavioral analysis of the contribution of the hippocampus and parietal cortex to the processing of information: Interactions and dissociations. *Hippocampus, 10*, 483–490.

Kesner, R. P. (2002). Memory neurobiology. *Encyclopedia of the human brain* (Vol. 2, pp. 783–796). San Diego: Academic Press.

Kesner, R. P., & Adelstein, T. B. (1989). Equivalent spatial location memory deficits in rats with medial septum or hippocampal formation lesions and patients with dementia of the Alzheimer's type. *Brain and Cognition, 9*, 289–300.

Kesner, R. P., Bolland, B. L., & Dakis, M. (1993). Memory for spatial locations, motor response, and objects: Triple dissociation among the hippocampus, caudate nucleus, and extrastriate visual cortex. *Experimental Brain Research, 93*, 462–470.

Kesner, R. P., Farnsworth, G., & Kametani, H. (1992). Role of parietal cortex and hippocampus in representing spatial memory. *Cerebral Cortex, 1*, 367–373.

Kesner, R. P., & Filoteo, J. V. (1998). Nonprimate models of motor and cognitive functions associated with Huntington's disease. In A. I. Troster (Ed.), *Memory in neurodegenerative disease: Biological, cognitive and clinical perspectives* (pp. 21–35). Cambridge University Press.

Kesner, R. P., & Gilbert, P. E. (2001). Process oriented view of amygdala and hippocampus: Mediation of reward value and spatial location information. In P. E. Gold & W. T. Greenough (Eds.), *Memory consolidation: Essays in honor James L. McGaugh* (pp. 249–273). Washington, DC: American Psychological Association.

Kesner, R. P., & Hopkins, R. O. (2001). Short-term memory for duration and distance in humans: Role of the hippocampus. *Neuropsychology, 15*, 58–68.

Kesner, R. P., & Novak, J. M. (1982). Serial position curve in rats: Role of the hippocampus. *Science, 218*, 173–175.

Kesner, R. P., & Rolls, E. T. (2001). Role of long-term synaptic modification in short-term memory. *Hippocampus, 11*, 240–250.

Kirkby, R. J., Polgar, S., & Coyle, I. R. (1981). Caudate nucleus lesions impair the ability of rats to learn a simple straight-alley task. *Perceptions and Motor Skills, 52*, 499–502.

Lavenex, P., & Amaral, D. (2000). Hippocampal-neocortical interaction: A hierarchy of associativity. *Hippocampus, 10*, 420–430.

Lee, I., & Kesner, R. P. (2003). Time-dependent relationship between the dorsal hippocampus and the prefrontal cortex in spatial memory. *Journal of Neuroscience, 23*, 1517–1523.

Long, J. M., & Kesner, R. P. (1996). The effects of dorsal vs. ventral hippocampal, total hippocampal, and parietal cortex lesions on memory for allocentric distance in rats. *Behavioral Neuroscience, 110*, 922–932.

Long, J. M., & Kesner, R. P. (1998). Effects of hippocampal and parietal cortex lesions on memory for egocentric distance and spatial location information in rats. *Behavioral Neuroscience, 112*, 480–495.

Long, J., Mellem, J., & Kesner, R. (1998). The effects of parietal cortex lesions on an object/spatial location paired-associate task in rats. *Psychobiology, 26*, 128–133.

Martone, M., Butters, N., Payne, M., Becker, J., & Sax, D. S. (1984). Dissociations between skill learning and verbal recognition in amnesia and dementia. *Archives of Neurology, 41*, 965–970.

McDonald, R. J., & White, N. M. (1993). A triple dissociation of systems: hippocampus, amygdala, and dorsal striatum. *Behavioral Neuroscience, 107*, 3–22.

McDonald, R. J., & White, N. M. (1995). Hippocampal and nonhippocampal contributions to place learning in rats. *Behavioral Neuroscience, 109*, 579–593.

Miller, E. K. (2000). The prefrontal cortex and cognitive control. *Nature Review Neuroscience, 1*, 59–65.

Mishkin, M. (1982). A memory system in the monkey. *Philosophical Transactions of the Royal Society of London B, 298*, 85–95.

Mishkin, M., & Petri, H. L. (1984). Memories and habits: Some implications for the analysis of learning and retention. In L. R. Squires & N. Butters (Eds.), *Neuropsychology of memory* (pp. 287–296). New York: Guilford Press.

Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not separate removal of the amygdala and hippocampus. *Nature, 273*, 297–298.

Mishkin, M., & Ungerleider, L. G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behavioral Brain Research, 6*, 57–77.

Morris, R. G. M., Garrud, J. N. P., Rawlins, J. N. P., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature, 297*, 681–683.

Myers, C. E., Gluck, M. A., & Granger, R. (1995). Dissociation of hippocampal and entorhinal function in associative learning: A computational approach. *Psychobiology, 23*, 116–138.

Mumby, D. G. (2001). Perspectives on object-recognition memory following hippocampal damage: Lessons from studies in rats. *Behavioural Brain Research, 127*, 159–181.

Murray, E. A., & Bussey, T. J. (1999). Perceptual-mnemonic functions of the perirhinal cortex. *Trends in Cognitive Science, 3*, 142–151.

Nadel, L., & Moscovitch, M. (1997). Consolidation, retrograde amnesia and the hippocampal formation. *Current Opinion Neurobiology, 7*, 217–227.

O'Keefe, J. (1979). A review of the hippocampal place cells. *Progress in Neurobiology, 13*, 419–439.

Oberg, R. G. E., & Divac, I. (1979). Cognitive functions of the neostriatum. In I. Divac & R. G. E. Oberg (Eds.), *The neostriatum* (pp. 291–313). Oxford: Pergamon.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map.* Oxford: Clarendon Press.

Olton, D. S. (1983). Memory functions and the hippocampus. In W. Seifert (Ed.), *Neurobiology of the hippocampus.* New York: Academic Press.

Olton, D. S. (1986). Hippocampal function and memory for temporal context. In R. L. Isaacson & K. H. Pribram (Eds.), *The Hippocampus* (Vol. 3). New York: Plenum Press.

Otto, T., & Eichenbaum, H. (1992). Complementary roles of the orbital prefrontal cortex and the perirhinal-entorhinal cortices in an odor-guided delayed-nonmatching-to-sample task. *Behavioral Neuroscience, 106*, 762–775.

Packard, M. G. (1999). Glutamate infused post-training into the hippocampus or caudate-putamen differentially strengthens place and response learning. *Proceedings of the National Academy of Sciences of the United States of America, 96*, 12881–12886.

Packard, M. G., & Knowlton, B. J. (2002). Learning and memory functions of the basal ganglia. *Annual Review in Neuroscience, 25*, 563–593.

Packard, M. G., & McGaugh, J. L. (1996). Inactivation of the hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of Learning and Memory, 65*, 65–72.

Packard, M. G., & White, N. M. (1990). Lesions of the caudate nucleus selectively impair "Reference Memory" acquisition in the radial maze. *Behavioral Neural Biology, 53*, 39–50.

Parkinson, J. K., Murray, E. A., & Mishkin, M. (1988). A selective mnemonic role for the hippocampus in monkeys: Memory for the location of objects. *Journal of Neuroscience, 8*, 4159–4167.

Partiot, A., Verin, M., Pillon, B., Teixeira-Ferreira, C., Agid, Y., & Dubois, B. (1996). Delayed response tasks in basal ganglia lesions in man: Further evidence for a striato-frontal cooperation in behavioural adaptation. *Neuropsychologia, 34*, 709–721.

Phillips, A. G., & Carr, G. D. (1987). Cognition and the basal ganglia: A possible substrate for procedural knowledge. *Canadian Journal of Neurology & Science, 14*, 381–385.

Pigott, S., & Milner, B. (1993). Memory for different aspects of complex visual scenes after unilateral temporal- or frontal-lobe resection. *Neuropsychologia, 31*, 1–15.

Porter, M. C., Burk, J. A., & Mair, R. G. (2000). A comparison of the effects of hippocampal or prefrontal cortical lesions on three versions of delayed non-matching-to-sample based on positional or spatial cues. *Behavioural Brain Research, 109*, 69–81.

Ragozzino, M. E., Adams, S., & Kesner, R. P. (1998). Differential involvement of the dorsal anterior cingulate and prelimbic/infra-limbic areas of the rodent prefrontal cortex in spatial working memory. *Behavioral Neuroscience, 112*, 293–303.

Rainer, G., Asaad, W. F., & Miller, E. K. (1998). Selective representation of relevant information by neurons in the primate prefrontal cortex. *Nature, 393*, 577–579.

Rainer, G., Rao, S. C., & Miller, E. K. (1999). Prospective coding for objects in primate prefrontal cortex. *Journal of Neuroscience, 19*, 5493–5505.

Reading, P. J., Dunnett, S. B., & Robbins, T. W. (1991). Dissociable roles of the ventral, medial and lateral striatum on the acquisition and performance of a complex visual stimulus–response habit. *Behavioural Brain Research, 45*, 147–161.

Robbins, T. W., & Brown, V. J. (1990). The role of the striatum in the mental chronometry of action: A theoretical review. *Reviews in the Neurosciences, 2*, 181–213.

Rolls, E. (1989). Functions of neuronal networks in the hippocampus and neocortex in memory. In J. H. Byrne & W. O. Berry (Eds.), *Neural models of plasticity: Theoretical and empirical approaches.* New York: Academic Press.

Rolls, E. T. (1999). Spatial view cells and the representation of place in the primate hippocampus. *Hippocampus, 9*, 467–480.

Sanberg, P. R., Lehmann, J., & Fibiger, H. C. (1978). Impaired learning and memory after Kainic acid lesions of the striatum: A behavioral model of Huntington's disease. *Brain Research, 149*, 546–551.

Save, E., & Poucet, B. (2000). Hippocampal–parietal cortical interactions in spatial cognition. *Hippocampus, 10*, 491–499.

Save, E., Poucet, B., Foreman, N., & Thinus Blanc, C. (1992). Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal formation. *Behavioral Neuroscience, 106*, 447–456.

Schoenbaum, G., Setlow, B., & Ramus, S. J. (2003). A systems approach to orbitofrontal cortex function: Recordings in rat orbitofrontal cortex reveal interactions with different learning systems. *Behavioral Brain Research, 146*, 19–29.

Schwartzbaum, J. S., & Donovick, P. J. (1968). Discrimination reversal and spatial alternation associated with septal and caudate dysfunction in rats. *Journal of Comparative Physiological Psychology, 65*, 83–92.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry, 20*, 11–21.

Seamans, J. K., Floresco, S. B., & Phillips, A. G. (1995). Functional differences between the prelimbic and anterior cingulate regions of rat prefrontal cortex. *Behavioral Neuroscience, 109*, 1063–1073.

Shaw, C., & Aggleton, J. P. (1993). The effects of fornix and medial prefrontal lesions on delayed non-matching-to-sample by rats. *Behavioural Brain Research, 54*, 91–102.

Smith, M. L., & Milner, B. (1981). The role of the right hippocampus in the recall of spatial location. *Neuropsychologia, 19*, 781–793.

Steele, R. J., & Morris, R. G. M. (1999). Delay-dependent impairment of a matching-to-place task with chronic and intrahippocampal infusion of the NMDA-antagonist D-AP5. *Hippocampus, 9*, 118–136.

Tulving, E. (1983). *Elements of episodic memory*. Oxford: Clarendon Press.

Wang, J., Aigner, T., & Mishkin, M. (1990). Effects of neostriatal lesions on visual habit formation in rhesus monkeys. *Society for Neuroscience Abstracts, 16*, 617.

Warburton, E. C., Baird, A., Morgan, A., Muir, J. L., & Aggelton, J. P. (2001). The conjoint importance of the hippocampus and anterior thalamic nuclei for allocentric spatial learning: Evidence from a disconnection study in the rat. *Journal of Neuroscience, 21*, 7323–7330.

Whishaw, I. Q., McKenna, J. E., & Maaswinkel, H. (1997). Hippocampal lesions and path integration. *Current Opinions in Neurobiology, 7*, 228–234.

Whishaw, I. Q., Mittleman, G., Bunch, S. T., & Dunnett, S. B. (1987). Impairments in the acquisition, retention and selection of spatial navigation strategies after medial caudate-putamen lesions in rats. *Behavioural Brain Research, 24*, 125–138.

Wiebe, S. P., Staubli, U. V., & Abros-Ingerson, J. (1997). Short-term reverberant memory model of hippocampal field CA3. *Hippocampus, 7*, 656–665.

Winocur, G. (1992). A comparison of normal old rats and young adult rats with lesions to the hippocampus or prefrontal cortex on a test of matching-to-sample. *Neuropsychologia, 9*, 769–781.

Winocur, G., & Moscovitch (1990). Hippocampal and prefrontal cortex contributions to learning and memory: Analysis of lesion and aging effects on maze learning in rats. *Behavioral Neuroscience, 104*, 544–551.

Witter, M., Naber, P., van Haeften, T., Machielsen, W., Rombouts, S., Barkhof, F., Scheltens, P., & Lopes da Silva, F. (2000). Cortico-hippocampal communication by way of parallel parahippocampal-subicular pathways. *Hippocampus, 110*, 398–410.