NIH Public Access
Author Manuscript
Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2010 August 1.

Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2009 August 1; 33(5): 774–781. doi:10.1016/j.pnpbp.2009.03.037.

The Role of the CA3 Hippocampal Subregion in Spatial Memory: A Process Oriented Behavioral Assessment

Paul E. Gilbert[1,2] and **Andrea M. Brushfield**[1]

[1]Department of Psychology, San Diego State University, San Diego CA

[2]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego CA

Abstract

Computational models, behavioral data, and electrophysiological data suggest that the CA3 subregion of the hippocampus may support multiple mnemonic processes critical to the formation and subsequent retrieval of spatial memories. Multiple researchers have proposed that the CA3 subregion contains an autoassociative network in which synaptic connections between CA3 neurons that represent different components of a memory are strengthened via recurrent collateral connections. As a result, it has been suggested that the CA3 autoassociative network may support multiple processes including the formation of spatial arbitrary associations, temporary maintenance of spatial working memory, and spatial pattern completion. In addition, the CA3 subregion has been suggested to be involved in spatial pattern separation. The separation of patterns is hypothesized to be accomplished based on the low probability that any two CA3 neurons will receive mossy-fiber input synapses from a similar subset of dentate gyrus cells. The separation of patterns also may be enhanced by competitive inhibition within CA3 and dentate gyrus. This review will focus on the mnemonic processes supported by CA3 neurons and how these processes may facilitate the encoding and retrieval of spatial information. Although there is growing evidence indicating that the hippocampus plays a role in the processing of nonspatial information as well, the scope of the present review will focus on the role of the CA3 subregion in spatial memory.

Keywords

CA3; Spatial Memory; Pattern Completion; Pattern Separation; Arbitrary Association ; Hippocampus

Introduction

Since the early 1960s, the hippocampus has been one of the most studied structures in the mammalian brain. Based on many years of research, the hippocampus has been determined to be highly involved in learning and memory. Although a great deal of progress has been made in understanding how the hippocampus processes information and what types of information

© 2009 Elsevier Inc. All rights reserved.

Please address all correspondence to Dr. Paul Gilbert, San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, 6363 Alvarado Court, Suite 103, San Diego, CA 92120. Tel: (619) 594-7409; Fax: (619) 594-3773; Email: pgilbert@sciences.sdsu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

the hippocampus may process, there is still debate as to the precise function of this structure. As discussed in a recent publication by Manns and Eichenbaum (2005), early descriptions of the hippocampal formation suggested that information was serially processed through the hippocampal subregions via a trisynaptic loop (Lorente De No´, 1933; Ramon y Cajal, 1995). Information was suggested to enter via entorhinal cortex projections to dentate gyrus with serial projections from the dentate gyrus to the CA3 subregion, which projects serially to the CA1 subregion. The CA1 subregion has projections to the subiculum that in turn has projections back to entorhinal cortex to complete the trisynaptic loop. Based on this idea, a lesion or damage to any anatomical component of the trisynaptic loop would cause the serial processing loop to fail resulting in hippocampal dysfunction. Early studies tested rats with lesions in dentate gyrus, CA3, or CA1 on a working memory version of the radial eight-arm maze. The results demonstrated that a lesion to the dentate gyrus (Emerich and Walsh, 1989; McLamb et al., 1988; Tilson et al., 1987, Walsh et al., 1986), CA1 (Davis et al., 1987; Davis et al., 1986; Davis and Volpe, 1989), or CA3 (Handelmann and Olton, 1981; Jarrard, 1983) all resulted in deficits similar to complete hippocampal lesions. Rats with lesions of dentate gyrus (Nanry et al., 1989; Sutherland et al., 1983), CA1 (Auer et al., 1989; Block, 1999; Nunn et al., 1994; Olsen et al., 1994; Whishaw et al., 1994), or CA3 (Sutherland et al., 1983) also showed deficits comparable to complete hippocampal lesions on the Morris water maze. Therefore, early behavioral studies involving selective lesions to hippocampal subregions suggested that a lesion to any subregion results in a deficit similar to a complete hippocampal lesion. These data could be considered support for the existence of a trisynaptic loop. However, more recent anatomical studies discussed below have demonstrated that the hippocampal anatomical connections are not serial but rather there are projections from entorhinal cortex to each hippocampal subregion (Amaral and Witter, 1995; Witter, 1993). Based on the hippocampal architecture and connectivity, recent models and behavioral studies have demonstrated that the various subregions of the hippocampus may support specific processing functions (Bennett et al., 1994; Gilbert and Kesner, 2003, 2006; Gilbert et al., 2001; Gold and Kesner, 2005; Granger et al., 1996; Guzowski et al., 2004; Hasselmo and McClelland, 1999; Hasselmo et al., 2002; Jensen and Lisman, 1996; Kesner and Hopkins, 2006; Kesner and Rolls, 2001; Kesner et al., 2000; Kesner et al. 2004; Kesner et al., 2005; Lee and Kesner, 2002, 2003, 2004a, 2004b; Lee et al., 2004; Lee et al., 2005b; Leutgeb, et al., 2004; Lisman, 1999; Marr, 1971; McClelland and Goddard, 1996; McNaughton and Morris, 1987; McNaughton and Nadel, 1989; Mizumori et al., 1999; O'Reilly and McClelland, 1994; Rogers et al., 2006; Rolls, 1989, 1996; Rolls and Kesner, 2006; Samsonovich and McNaughton, 1997; Samura and Hattori, 2005; Shapiro and Olton, 1994; Tanila, 1999; Treves, 2004; Treves and Rolls, 1992, 1994; Vazdarjanova and Guzowski, 2004; Wallenstein and Hasselmo, 1997; Wiebe et al., 1997). In addition, recent research has shown that the mnemonic processes supported by each hippocampal subregion can be functionally dissociated using behavioral and electrophysiological measures (Gilbert and Kesner, 2003, 2006; Gilbert et al., 2001; Hunsaker et al., 2006; Jerman et al., 2006; Kesner and Hopkins, 2006; Kesner et al., 2000; Kesner et al., 2004; Lee and Kesner, 2004a, 2004b; Lee et al., 2005a; Lee et al., 2005b; Leutgeb et al., 2004; Rolls and Kesner, 2006; Vazdarjanova and Guzowski, 2004). This review will focus on the mnemonic processes supported by CA3 neurons and how these processes may facilitate the encoding of spatial information. Although there is growing evidence indicating that the hippocampus plays a role in the processing of nonspatial information as well, the scope of the present review will focus on the role of the CA3 subregion in spatial memory.

Basic Hippocampal Anatomy

For a complete review of hippocampal anatomy, please see Amaral and Witter (1995). The main input into the hippocampal system is from entorhinal cortex, which receives inputs from multiple cortical regions and all sensory modalities. The cortical inputs that terminate on the superficial layers (I, II, and III) of the entorhinal cortex comprise the primary inputs to the

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

hippocampus (Witter, 1993). In the rat, the cortical inputs to the superficial layers of entorhinal cortex originate in the olfactory domain of the telencephalon, perirhinal cortex, and pre- and parasubiculum. The entorhinal cortex then projects directly to the dentate gyrus, CA3, and CA1 subregions (Amaral and Witter, 1995; Witter, 1993). Cells in layer II of entorhinal cortex project primarily to the dentate gyrus and also to CA3/2. The projections that terminate in the CA1 region originate in layer III of the entorhinal cortex. The primary projection of the entorhinal cortex is to the DG. The connections between entorhinal cortex, DG, and CA3 are generally reported to be feed-forward (Ishizuka et al., 1990; Witter, 1993). The DG granular neurons project to CA3 pyramidal neurons via mossy fiber projections. The neurons that comprise CA3, in turn, project to CA1 neurons via the Schaffer collaterals. Recurrent collateral connections exist within both the DG and CA3 that serve to interconnect neurons within these respective regions. The DG recurrent pathway includes a layer of excitatory interneurons, the hilus, which interconnects granule cells and a layer of inhibitory interneurons that provide recurrent inhibition. The CA3 subregion has extensive interconnections among the principal cells via a recurrent collateral fiber system (Amaral and Witter, 1995). The primary output from the hippocampus to neocortex originates in CA1 and projects to subiculum, entorhinal cortex, and parahippocampal structures (Witter, 1993). In addition to the projections originating in CA1, projections out of Ammon's horn originate in CA3. Swanson and Cowan (1977) report that the septal region of CA3 projects to dorsal subiculum, parasubiculum, and the cingulate. Many researchers have reported that CA3 projects to the lateral and medial septal nuclei (Amaral and Witter, 1995; Gaykema et al., 1991; Risold and Swanson, 1997). The lateral septum then has projections to the medial septum (Jakab and Leranth, 1995), which in turn projects to subiculum and eventually entorhinal cortex (Amaral and Witter, 1995; Jakab and Leranth, 1995).

One of the most prominent features of the CA3 subregion cytoarchitecture is that there are extensive interconnections among the principal cells via a recurrent collateral fiber system forming an autoassociative network (Amaral and Witter, 1995). Multiple researchers have suggested that the hippocampus, and specifically the CA3 subregion of the hippocampus, contains an autoassociative network that may support a number of mnemonic processes including the formation of arbitrary associations, pattern completion, and working memory (Alvarez and Squire, 1994; Bennett et al., 1994; Bunsey and Eichenbaum, 1993; Granger et al., 1996; Gluck and Myers, 1997; Hasselmo et al., 1996; Jensen and Lisman, 1996; Kesner et al., 2000; Marr, 1971; McClelland and Goddard, 1996; McNaughton and Nadel, 1989; Redish et al., 2001; Rolls, 1996; Rolls and Kesner, 2006; Treves and Rolls, 1992, 1994; Wallenstein and Hasselmo, 1997; Wiebe et al., 1997). The term autoassociative means that synaptic connections between neurons that represent different components of a memory are strengthened. The CA3 subregion of the hippocampus is considered an autoassociative network because of the aforementioned recurrent excitatory connections and synaptic modification among CA3 neurons6 (Rolls and Kesner, 2006). For detailed descriptions of autoassociative networks see Hertz et al. (1991), Rolls and Treves (1998), and Rolls and Deco (2002). CA3 also receives converging inputs from multiple input pathways; for example, perforant path inputs from the entorhinal cortex, mossy fiber inputs from the dentate gyrus, and its own outputs fed back as inputs via the recurrent collaterals (Amaral and Witter, 1995). Most of the synaptic connections embedded in those different pathways in CA3 are modifiable in their strength (Marr, 1971;Treves and Rolls, 1994). The aforementioned anatomical and physiological characteristics inspired many theoretical and computational models to assign specific processes to CA3 (Hasselmo and McClelland, 1999; Hasselmo et al., 2002; Jensen and Lisman, 1996; Kesner et al., 2000; Kesner et al., 2005; Lisman, 1999; Marr, 1971; McNaughton and Nadel, 1989; O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2000; Rolls, 1996; Rolls and Kesner, 2006; Samsonovich and McNaughton, 1997; Shapiro and Olton, 1994; Treves and Rolls, 1992; Treves and Rolls, 1994; Wiebe et al., 1997).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Spatial Arbitrary Associations

The CA3 autoassociative network has been suggested to be responsible for the formation of arbitrary associations or paired associate learning (Bennett et al., 1994; Gilbert and Kesner, 2003; Hasselmo and McClelland, 1999; Kesner et al., 2000; Kesner et al., 2005; McNaughton and Nadel, 1989; Rolls 1996; Rolls and Kesner, 2006; Wallenstein and Hasselmo, 1997; Wiebe et al., 1997). For example, Rolls and Kesner (2006) suggest that information from parietal cortex regarding the location of an object may be associated with information from temporal cortex regarding the identity of the object see also (Rolls, 1996). Therefore, CA3 could enable the organism to remember a particular object and its location. To test this hypothesis, Gilbert and Kesner (2003) trained rats with CA3, CA1, or dentate gyrus lesions on a successive discrimination go/no-go task to examine object-place paired associate learning. This task has been shown to be sensitive to complete hippocampal lesions (Gilbert and Kesner, 2002). In this task, two paired-associates were reinforced that consisted of one particular object (A) in one particular location (1) and a different object (B) in a different location (2). Mispairs that were not reinforced included object (A) in location (2) and object (B) in location (1). Rats should learn that if an object was 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 was not in its paired location (No-Go). In a second task, rats were trained on a successive discrimination go/no-go task to examine odor-place paired-associate learning. In this task, the same procedure was used, except that rats needed to learn that when an odor was presented in its paired location the rat should dig in sand mixed with the odor to receive a reward. The results indicate that relative to controls, rats with CA3 lesions were impaired in learning both the object-place and odor-place paired associations (Gilbert and Kesner, 2003). However, rats with lesions to the dentate gyrus or CA1 hippocampal subregions matched the performance of controls. Thus, the results suggest that the CA3 subregion of the dorsal hippocampus contains a mechanism to support the formation of object-place and odor-place arbitrary associations. A recent study also demonstrated that CA3 lesions disrupt learning of an object-trace-place task where a short delay was implemented between the presentation of the object paired-associate and the spatial location (Hunsaker et al., 2006). Wallenstein et al. (1998) developed a computational model demonstrating that the CA3 recurrent collateral network may be capable of associating temporally discontiguous events.

In support of the CA3 subregion in paired-associate memory, a recent study has shown CA3 N-methyl-D-asparate receptor involvement in associative memory recall (Nakazawa et al., 2002). As electrophysiological evidence for a role of CA3 in forming object-place associations, Rolls et al. (1989) have recorded cells in the monkey hippocampus (CA3 and CA1) that combine information regarding an object and its position in space. A recent study using a viral vector to temporally control a focal deletion of the NR1 gene demonstrated that the learning of novel associations between specific contexts was dependent on CA3 NMDA receptors (Rajji et al., 2006). In this task, rats were presented with two different odors each mixed with sand and placed in small digging cups. The rats were then simultaneously presented with each odor in two different contexts. In one context, the rat was required to dig in the cup containing one of the odors and in the other context the rat was required to dig in the other odor cup. Therefore, to receive a reward, the rat must learn to associate one odor with one context and the other odor with the other context. Deletions of the NR1 gene in the CA3 subregion of dorsal hippocampus were shown to disrupt learning of the odor-context associations but did not affect expression of previously learned associations (Rajji et al., 2006). A previously published study by Gilbert and Kesner (2004) also showed that hippocampal lesions, including the CA3 subregion, do not completely abolish retrieval of previously learned object-place associations but rather result in a 8 transient deficit. Therefore, the CA3 subregion of the hippocampus may be necessary for the formation of novel arbitrary associations but may play only a limited role in the retrieval of previously learned associations.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Although the CA3 subregion may support the formation of novel arbitrary associations involving a spatial component, rats with large lesions to the dorsal and ventral hippocampus, including the CA3 subregion, have been shown to learn a nonspatial object-odor paired associate task as readily as controls (Gilbert and Kesner, 2002). In addition, humans, nonhuman primates, pigeons, and rodents with hippocampal lesions have been reported to display normal learning of nonspatial paired associations involving odor-odor (Bunsey and Eichenbaum, 1995,1996; Li et al., 1999), object-object (Bingman et al., 1999; Cho and Kesner, 1995; Murray et al., 1993; Petrides, 1990), visual-response (Petrides, 1997; Winocur, 1992; Wise and Murray, 1999), and auditory-visual (Jarrard and Davidson, 1990) associations. However, some researchers have reported impaired visual-visual (Ridely et al., 1995; Sutherland et al., 1989) and visual-auditory (Honey et al., 1998) paired-associate learning in animals with hippocampal damage. Therefore, the majority of the existing data suggest that the rodent hippocampus, and particularly the CA3 subregion, is involved in the formation of arbitrary associations when a stimulus must be associated with a spatial location. However, the CA3 subregion of the hippocampus may not be necessary for the formation of all arbitrary associations.

Spatial Working Memory

Many researchers have suggested that the CA3 autoassociative network also may be involved in temporarily maintaining working memory representations (Gilbert and Kesner, 2006; Granger et al., 1996; Jensen and Lisman, 1996; Kesner et al., 2000; Kesner et al., 2004; Kesner and Rolls, 2001; Lee and Kesner, 2002, 2003; Lee et al., 2005b; McClelland and Goddard, 1996, O'Reilly and McClelland, 1994; Rolls, 1996; Rolls and Kesner, 2006; Shapiro and Olton, 1994; Treves and Rolls, 1992; Wiebe et al., 1997). Rolls and Kesner (2006) suggest that the excitatory recurrent collateral network can implement a short-term memory by maintaining the firing of neurons in the recurrent connections (see also Rolls, 1996). It is suggested that a stable short-term attractor can maintain a spatial location across a considerable delay or until a different input pushes the attractor to maintain a new spatial location (Rolls and Kesner, 2006). Wiebe and colleagues (1997) suggest that the dense recurrent connectivity within the CA3 subregion could serve as a "holding memory" that would be capable of maintaining short-term memory representations.

Using a classic paradigm originally developed by Olton et al. (1979), researchers tested rats with CA3 lesions on a task designed to measure both spatial working and reference memory using the radial eight-arm maze (Handelmann and Olton, 1981; Jarrard, 1983). On this task, four arms on the maze always contained a food reward, whereas the remaining four arms never contained food. On each trial, the animal was placed in the center of the maze and was allowed to traverse the arms until all of the food was collected. Repeated entries into reward arms were scored as working memory errors, whereas entries into non-reward arms were considered reference memory errors. The data indicated that rats with CA3 lesions committed significantly more spatial working memory errors compared to controls (Handelmann and Olton, 1981; Jarrard, 1983). A more recent study by Lee and Kesner (2003) examined the effects of CA3 subregional lesions on a delayed nonmatching-to-place task using a radial 8-arm maze. During the sample phase of the task, each rat was allowed to visit a randomly chosen arm and then return to the center platform. Following a 10 s delay, the rat was presented with two adjacent arms. One arm was the same arm visited on the sample phase and the second was a new arm. The rat was required to select the new arm to receive a food reward. CA3 lesions disrupted acquisition of the task with short 10 s delays; however, CA3 was not necessary for task performance with intermediate (5 min) or long (24 hr) delays (Lee and Kesner, 2003). Another recent study conducted by Gilbert and Kesner (2006) tested rats with CA3 lesions on a delayed-match-to-sample for spatial location task. On each trial, an object covered a baited food well in one of fifteen spatial locations along a row of food-wells perpendicular to the start box. Once the rat exited the start box, displaced the object to receive a food reward and then returned to

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

the start box, the same food well was then quickly re-baited, an identical object was positioned to cover the food well and another identical object was positioned in a different location along the row of food wells covering 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 same food well as the object in the sample phase was the correct choice and the second foil object was the incorrect choice. Five spatial separations (15–105 cm) were randomly used to separate the correct object from the foil object during the choice phase. Following surgery, rats with CA3 lesions were significantly impaired relative to controls across all spatial separations, suggesting that CA3 lesions impaired working memory. Chronic glucocorticoid exposure or chronic stress, which results in increased glucocorticoid levels, has been shown to result in significant atrophy of the CA3 pyramidal neurons within the hippocampus (Bodnoff et al., 1995; Kant, 1993; Shors and Dryver, 1992; Stein-Behrens et al., 1994; Watanabe et al., 1992). Similar to neurotoxin lesion studies, rats treated with chronic glucocorticoids or exposed to chronic stress also show impairments in spatial working memory (Bardgett et al., 1994; Luine et al., 1994; Shors and Dryver, 1992; Szuran et al., 1994).

Electrophysiological data also suggest that the CA3 subregions may be involved in working memory. Researchers have recorded units in CA3 that showed a preferential increase or decrease in firing rate during the delay period of a delayed-response task (Cahusac et al., 1989; Colombo et al., 1998; Watanabe and Niki, 1985). Similar findings also have been reported in the CA3 and CA1 regions in rats on a delayed-match-to-position task (Hampson et al., 1993). Using behavioral and electrophysiological techniques, Lee and Kesner (2002) showed that NMDA receptors in the CA3 subregion are involved in the acquisition of spatial working memory. Therefore, multiple studies have provided behavioral and electrophysiological data suggesting that the CA3 hippocampal subregion may maintain short-term working memory spatial representations.

Spatial Pattern Completion

The CA3 autoassociative network has been suggested to support pattern completion. Marr (1971) suggested that the recurrent collateral system in CA3 might be capable of completing stored patterns of information during retrieval based on partial or incomplete input to the hippocampus, termed the collateral effect. More recent models have been generated to describe how the CA3 autoassociative network may support pattern completion (Guzowski et al., 2004; Kesner, et al., 2005; Lee et al., 2004; McNaughton and Nadel, 1989; Mizumori et al., 1989; O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2000; Rolls, 1996; Rolls and Kesner, 2006; Samura and Hattori, 2005; Treves, 2004). Rolls and Kesner (2006) argue that a fundamental property of the CA3 recurrent collateral network is that recall can be symmetric, meaning that the entire memory may be retrieved from any part. Therefore, if an incomplete retrieval cue is given, the autoassociative network is capable of retrieving the original pattern via the recurrent collaterals, resulting in pattern completion.

Until recently, few behavioral or electrophysiological studies had been conducted to examine the role of the CA3 subregion in spatial pattern completion. Gold and Kesner (2005) trained rats on a delayed-matching-to-sample for spatial location task involving systematic manipulations of four available spatial cues to examine spatial pattern completion. During the sample phase, the rats were allowed to displace an object to receive a food reward in one of five spatial locations on a cheeseboard apparatus. On the ensuing choice phase, the rats were required to return to the same spatial location without the aid of the visual object. Therefore, the rat must rely on the spatial cues to locate the same location on the maze. On some trials, all four spatial cues were available. However, on other trials, one, two, three, or all four cues were removed. The removal of the cues used to encode the sample phase location was hypothesized to increase the amount of pattern completion necessary to retrieve the location

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

of the sample phase object on the choice phase. The results indicated that control rats displayed pattern completion across all manipulations of the spatial cues. However, rats with CA3 lesions showed impaired pattern completion as evidenced by a linear increase in errors as the number of available cues was reduced on the choice phase (Gold and Kesner, 2005). A somewhat similar study was conducted by Nakazawa and colleagues (2002) who investigated pattern completion in genetically engineered mice that lacked the NMDA receptor gene in the CA3 subregion. The mutant mice were able to perform a spatial reference memory task in the Morris water maze when all spatial cues were present; however, retrieval of the platform location was impaired when a portion of the extramaze cues were removed.

Lee et al. (2005b) also examined the role of the CA3 subregion in delayed memory for a temporal sequence of spatial locations using a newly devised apparatus termed the “Tulum Maze.” On this task, each rat was required to remember four different spatial sections of the maze sequentially presented during the sample phase. Each section was cued by a unique object that was specifically associated with a location within the section during the sample phase. Then following a brief 15 s delay, the animal was required to revisit the location within a particular section of the maze in the absence of the cued object. Lesions of the CA3 subregion impaired memory for the first three spatial sections visited on the sample phase but not the most recently visited section. Lee and colleagues (2005b) suggest that the task requires spatial pattern completion because the animal must remember a target location without the cued object that marked the location during encoding.

Electrophysiological studies also have provided evidence for the role of the CA3 subregion in spatial pattern completion. Studies have reported that some cells in CA3 respond when a monkey’s view of a particular part of space is briefly obscured by a curtain or darkness (Robertson et al., 1998; Rolls, 1996). This pattern of firing may reflect a completion of the scene in the absence of the visual input. Similar findings also have been reported in rats (Samsonovitch and McNaughton, 1997). In a study conducted by Lee et al. (2004), firing activity of CA3 and CA1 place cells was recorded concurrently in freely moving rats. The animals were placed on a circular track surrounded by both local and distal cues. During the training sessions, the cue configurations were held constant; however, on testing sessions the cue configurations were rotated in opposite directions (counterclockwise and clockwise, respectively) producing varying degrees of mismatch. When the animals were exposed to stable environments, a backward shift was observed across laps in CA1, but not CA3. When cue configurations were altered, both CA3 and CA1 displayed shifting responses; however, the amount of time required to produce a shift varied across sessions. Backward shifts in CA3 place field locations were observed when there was a high degree of mismatch between cue configurations during the first exposure; whereas, CA1 place fields exhibited a delay in shifting response. On the second day of testing the opposite results were observed. CA1 place field locations displayed a backward shift; whereas, CA3 place fields did not demonstrate a significant shift in location. These results suggest that CA3 may flexibly support the rapid acquisition of novel spatial representations. Further, CA3 representations were more coherent than CA1 as degrees of mismatch among environments increased, thus supporting the role of CA3 in pattern completion. In another recent study, Vazdarjanova and Guzowski (2004) allowed rats to explore two environments with each exploration period separated by 30 min. The time course of activations of neuron ensembles in both CA3 and CA1 were measured using a new immediate-early gene-based brain-imaging method (Arc/H1a catFISH). Rats exposed to the same environment during each exploration period showed a high degree of overlap among CA3 and CA1 ensembles. When cue configurations (either local or distal) were altered in similar environments, CA3 ensembles exhibited a greater overlap than those observed in CA1, supporting a pattern completion processes in CA3 (Vazdarjanova and Guzowski, 2004). Therefore, the results of the aforementioned studies provide behavioral and

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

electrophysiological data suggesting that the CA3 hippocampal subregion may support spatial pattern completion.

Spatial Pattern Separation

Based on characteristics of the mossy fiber system, researchers suggest that pattern separation also may be a function of the dentate gyrus and its mossy fiber projections to CA3 (Bischofberger et al., 2006; Gilbert and Kesner, 2006; Gilbert et al., 1998; Gilbert et al., 2001; Kesner and Hopkins, 2006; Kesner et al., 2004; O'Reilly and McClelland, 1994; Rolls and Kesner, 2006; Rolls, 1989, 1996; Shapiro and Olton, 1994; Treves and Rolls, 1992). Pattern separation is described as a mechanism for separating partially overlapping patterns of activation so that one pattern may be retrieved as separate from other patterns. Pattern separation is facilitated by sparse connections in the mossy-fiber system, which connects dentate gyrus granular cells to CA3 pyramidal neurons (Rolls, 1989, 1996). The separation of patterns is accomplished based on the low probability that any two CA3 neurons will receive mossy-fiber input synapses from a similar subset of dentate gyrus cells. The mossy-fiber inputs to CA3 from dentate gyrus are suggested to be essential during learning and may influence which CA3 neurons will fire based on the distributed activity in the dentate gyrus (Rolls and Kesner, 2006). The cells of the dentate gyrus are suggested to act as a competitive learning network with Hebb-like modifiability to reduce redundancy and produce sparse, orthogonal outputs. O'Reilly and McClelland (1994) suggest that the separation of patterns is enhanced by lateral inhibition within CA3. This assumption is described as a competitive "k-Winner-take-all" (kWTA) activation function. The lateral inhibition and the sparse connections are proposed to function contemporaneously to assure that an approximately constant (k) number of neurons in CA3 that receive the excitatory input become active. These "k" neurons are described as the neurons that have an excitatory level that exceeds the inhibitory input level of the inhibitory interneurons. The model suggests that the entorhinal cortex to dentate gyrus perforant pathway may dominate during encoding and hence, enhance pattern separation. In contrast, the direct one-stage pathway from entorhinal cortex to CA3 may be the preferential processing pathway during retrieval (O'Reilly and McClelland, 1994). In support of the role of the dentate gyrus in encoding, a recent study conducted in mice showed that the mossy-fibers projections to CA3 are essential for the encoding of spatial information but are not necessary for retrieval (Lassalle et al., 2000). Lee and Kesner (2004a,b) also have shown that the mossy fiber input to CA3 is critically involved in encoding of spatial information in rats, but may not be involved in retrieval. The study also showed that the perforant path input to CA3 from entorhinal cortex may support retrieval of spatial information, but is not necessary for encoding (Lee & Kesner, 2004a,b).

Rolls (1996) notes multiple characteristics of the mossy-fiber projection system that may promote pattern separation in the mossy fiber system and hence, efficient information storage in CA3. First, mossy-fiber synapses are very large and terminate close to the soma of the CA3 pyramidal neurons in the pyramidal layer. Therefore, the mossy-fiber synapses will be relatively powerful in activating the CA3 cell. The projections from layer II of entorhinal cortex to CA3 terminate in the lacunosum moleculare layer of the CA3 pyramidal cells, which is much further from the soma. Second, the firing activity of granule cells within the dentate gyrus is sparse (Jung and McNaughton, 1993) and coupled with the small number of connections to CA3 cells may produce a sparse signal that may be transformed into an even sparser signal in CA3. It also has been demonstrated that the place fields of dentate gyrus cells (Mizumori et al., 1990) and specifically granular cells (Jung and McNaughton, 1992) are small and highly reliable which may support the role of dentate gyrus in pattern separation. In addition, the mossy-fibers, demonstrate nonassociative plasticity (Brown et al., 1989), which may enhance the signal-to-noise ratio such that the mossy-fiber cell would produce a nonlinearly amplified current in the CA3 cell. Due to this type of plasticity in the dentate, a particular stimulus such

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

as spatial location, across subsequent presentations would be likely to activate the same population of CA3 neurons, which may result in economical storage because one CA3 cell could be used in different memories (Rolls, 1996).

Behavioral studies have suggested that the dentate gyrus may support spatial pattern separation (Gilbert et al., 2001); however, until recently no behavioral studies have examined the role of the CA3 subregion in spatial pattern separation. A recent study (Gilbert and Kesner, 2006) tested rats with CA3 lesions on a delayed-match-to-sample pattern separation task developed by Gilbert and colleagues (Gilbert et al., 1998, 2001). On each trial, an object covered a baited food well in one of fifteen spatial locations along a row of food-wells perpendicular to the start box. Once the rat exited the start box, displaced the object to receive a food reward and returned to the start box, the same food well was then quickly re-baited, an identical object was positioned to cover the food well and another identical object was positioned in a different location along the row of food wells covering 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 same food well as the object in the sample phase was the correct choice and the 15 second foil object was the incorrect choice. Five spatial separations (15–105 cm) were randomly used to separate the correct object from the foil object during the choice phase. Following surgery rats with CA3 lesions were significantly impaired relative to controls across all spatial separations suggesting that CA3 lesions may impair spatial pattern separation as well as spatial working memory (Gilbert and Kesner, 2006). A study by Tanila (1999) offered cellular recording evidence for the existence of a pattern separation mechanism for generating separate representations in CA3 based on overlapping inputs. In this study, neuronal ensembles were recorded while rats explored two visually identical rectangular environments connected by a hidden door and received electrical stimulation of the lateral hypothalamus as reinforcement for visiting particular locations in the environment. During the first recording session, the rat was allowed to explore the first environment. Then the door to the second environment was opened allowing the rat to enter the second environment for a 5 min recording session. The rat was then placed in a bucket for a 5 min period before another recording session in the second environment followed by a recording session in the first environment. Finally, the rat was allowed to re-explore the second environment following a 90-degree rotation of the environment relative to its original position in the room. It was shown that CA3 place cells were able to maintain distinct representations of two visually identical environments and selectively reactivate either one of the representation patterns depending on the experience of the rat. These data provide further evidence for the role of dentate gyrus and CA3 in spatial pattern separation. In addition, McNaughton et al. (1989) have shown that following colchicine-induced lesions of the dentate gyrus, there is a significant decrease in reliability in CA3 and CA1firing. Therefore, if the CA3 and CA1cells display less reliability following dentate gyrus lesions, the cells may not be forming accurate representations of space due to decreased efficiency in pattern separation.

In a more recent study, Leutgeb et al. (2004) conducted cellular recordings in CA3 and CA1 while rodents were exposed to various contextual conditions. Animals were placed in geometric shaped enclosures with varying degrees of similarity and were allowed to explore for food. The enclosures were distributed into three different rooms. The amount of overlap in CA1 varied as a function of the degree of geometric similarity. As similarity increased, the amount of overlap in activation patterns increased. Conversely, as contexts became less similar, the amount of overlap decreased. In contrast, CA3 place cells were able to maintain separate patterns of activation regardless of the degree of geometric similarity. The firing characteristics in CA3 resembled those in CA1; however, the firing was sparse in CA3, suggesting that CA3 may support pattern separation or the orthogonalization of similar activity patterns into distinct representations.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Based on the aforementioned electrophysiological data, it appears that the CA3 subregion of the hippocampus may support both pattern separation (Leutgeb et al., 2004) and pattern completion as mentioned in the previous section of this review (Lee et al., 2004). The results of these two studies may be viewed as contradictory and lead to the question of how the CA3 subregion could support two disparate functions (see Guzowski et al., 2004 for a discussion). A resolution to this apparent disparity has been proposed by Vazdarjona and Guzowski (2004). The time course of activations of neuron ensembles in both CA3 and CA1 were measured using a new immediate-early gene-based brain-imaging method (Arc/H1a catFISH). According to Vazdarjona and Guzowski (2004), CA3 appears to support different processing functions, pattern completion and pattern separation, depending on manipulations of the environment. In the task, rats were allowed to explore two environments with each exploration period separated by approximately 30 min. Rats exposed the same environment during each exploration period showed a high degree of overlap among CA3 and CA1 ensembles. When cue configurations (either local or distal) were altered in similar environments, CA3 ensembles exhibited a greater overlap than those observed in CA1, suggesting that CA3 may support pattern completion as discussed previously. However, when exposed to alterations to both local and distal cues in two completely different environments, CA3 ensembles exhibited a lower overlap than those observed in CA1, suggesting that CA3 also may support a pattern separation. Coupled with the findings from Leutgeb and colleagues (2004) and Lee and colleagues (2004), these studies suggest that CA3 may flexibly shift between pattern completion and pattern separation in a competitive and discontinuous manner depending on environmental conditions and task demands (Guzowski et al., 2004). Since attractor networks, such as CA3, respond nonlinearly to input patterns (Rolls and Treves, 1998), pattern completion may occur with minimal changes to sensory inputs; however, when changes to sensory inputs are increased, pattern separation may occur (Guzowski et al., 2004). This may be accomplished by an inherent threshold mechanism existing in the CA3 subregion (Kesner et al., 2004). When input patterns are dissimilar enough, CA3 may support pattern separation. However, CA3 may instead support pattern completion when input patterns are not sufficient enough to cross the threshold. O'Reilly and McClelland (1994) proposed a computational model of hippocampal function demonstrating how the hippocampus may be capable of supporting both processes and how the structure may minimize the trade-off between pattern completion and pattern separation. The competition between pattern separation and pattern completion has been modeled as a sigmoidal function (McClelland and Goddard, 1996; O'Reilly and McClelland, 1994). Guzowski et al. (2004) suggest that one possible role of place cell representations is to learn different adaptive responses to the same stimuli based on different contextual information. As reviewed by Knierim (2003), place cells can remap in a familiar environment with sufficient alterations in the environment or changes in the required behavior of the animal. Guzowski et al. (2004) suggest that this remapping may reflect pattern separation and may allow the animal to generate independent representations of behavioral contingencies in a particular context to reduce the chance of engaging in an inappropriate behavioral response. However, if every small change in an environment resulted in remapping and the creation of a new representation, pattern separation may be disruptive to CA3 function (Guzowski et al., 2004). Therefore, pattern separation may be tempered by pattern completion to reconstruct the original representation from a degraded input while ignoring small irrelevant alterations in the context (Guzowski et al., 2004). This multiple processing capability of CA3 may provide an efficient means for storing and subsequently retrieving memory representations.

Summary

Based on the hippocampal architecture and connectivity, behavioral and electrophysiological studies have demonstrated that the various subregions of the hippocampus may support specific processing functions. In addition, recent research has shown that the mnemonic processes supported by each hippocampal subregion can be functionally dissociated. Computational

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

models, behavioral data, and electrophysiological data suggest that the CA3 subregion of the hippocampus may support multiple mnemonic processes critical to the formation of accurate spatial memories. It has been suggested that the CA3 recurrent collateral network may support the formation of spatial arbitrary associations, temporary maintenance of spatial working memory, and spatial pattern completion. In addition, based on the low probability that any two CA3 neurons will receive mossy-fiber input synapses from a similar subset of dentate gyrus cells and competitive inhibition, the CA3 subregion has been suggested to be involved in spatial pattern separation. Thus, the CA3 subregion may facilitate the accurate encoding and subsequent retrieval of spatial memories by supporting mnemonic processes to 1) associate a stimulus with a spatial location, 2) separate partially overlapping patterns of activation so that one spatial location can be retrieved as separate from other spatial locations, and 3) retrieve a spatial memory based on partial or incomplete input.

Acknowledgements

The authors would like to thank Dr. Raymond Kesner for his technical advice on the manuscript and for his excellent collaborations.

References

Alvarez P, Squire LR. Memory consolidation and the medial temporal lobe: a simple network model. Proc Natl Acad Sci USA 1994;91:7041–7045. [PubMed: 8041742]

Amaral, DG.; Witter, MP. The hippocampal formation. In: Paxinos, G., editor. The rat nervous system. San Diego: Academic Press; 1995. p. 443-493.

Auer RN, Jensen ML, Whishaw IQ. Neurobehavioral deficit due to ischemic brain damage limited to half of the CA1 sector of the hippocampus. J Neurosci 1989;9:1641–1647. [PubMed: 2723745]

Bardgett ME, Taylor GT, Csernansky JG, Newcomer JW, Nock B. Chronic corticosterone treatment impairs spontaneous alternation behavior in rats. Behav Neural Biol 1994;61:186–190. [PubMed: 8204085]

Bennett MR, Gibson WG, Robinson J. Dynamics of the CA3 pyramidal neuron autoassociative memory network in the hippocampus. Philos Trans R Soc Lond B Biol Sci 1994;343:167–187. [PubMed: 8146234]

Bingman VP, Strasser R, Baker C, Riters LV. Paired-associate learning is unaffected by combined hippocampal and parahippocampal lesions in homing pigeons. Behav Neurosci 1998;112:533–540. [PubMed: 9676971]

Bischofberger J, Engel D, Frotscher M, Jonas P. Timing and efficacy of transmitter release at mossy fiber synapses in the hippocampal network. Pflugers Arch 2006;453:361–372. [PubMed: 16802161]

Block F. Global ischemia and behavioral deficits. Prog Neurobiol 1999;58:279–295. [PubMed: 10341364]

Bodnoff SR, Humphreys AG, Lehman JC, Diamond DM, Rose GM, Meaney MJ. Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. J Neurosci 1995;15:61–69. [PubMed: 7823152]

Brown, TH.; Ganong, AH.; Kairiss, EW.; Keenan, CL.; Kelso, SR. Long-term potentiation in two synaptic systems of the hippocampal brain slice. In: Byrne, JH.; Berry, WO., editors. Neural models of plasticity. San Diego: Academic Press; 1989. p. 266-306.

Bunsey M, Eichenbaum H. Critical role of the parahippocampal region for paired-associate learning in rats. Behav Neurosci 1993;107:740–747. [PubMed: 8280384]

Bunsey M, Eichenbaum H. Selective damage to the hippocampal region blocks long-term retention of a natural and nonspatial stimulus-stimulus association. Hippocampus 1995;5:546–556. [PubMed: 8646281]

Bunsey M, Eichenbaum H. Conservation of hippocampal memory function in rats and humans. Nature 1996;379:255–257. [PubMed: 8538790]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Cahusac PM, Miyashita Y, Rolls ET. Responses of hippocampal formation neurons in the monkey related to delayed spatial response and object-place memory tasks. Behav Brain Res 1989;33:229–240. [PubMed: 2757782]

Cho YH, Kesner RP. Relational object association learning in rats with hippocampal lesions. Behav Brain Res 1995;67:91–98. [PubMed: 7748506]

Colombo M, Fernandez T, Nakamura K, Gross CG. Functional differentiation along the anterior-posterior axis of the hippocampus in monkeys. J Neurophysiol 1998;80:1002–1005. [PubMed: 9705488]

Davis HP, Baranowski JR, Pulsinelli WA, Volpe BT. Retention of reference memory following ischemic hippocampal damage. Physiol Behav 1987;39:783–786. [PubMed: 3602133]

Davis HP, Tribuna J, Pulsinelli WA, Volpe BT. Reference and working memory of rats following hippocampal damage induced by transient forebrain ischemia. Physiol Behav 1986;37:387–392. [PubMed: 3749297]

Davis, HP.; Volpe, BT. Memory performance after ischemia or neurotoxin damage of the hippocampus. In: Squire, LR.; Lindenlaub, E., editors. Biology of memory. New York: Schattauer-Verlag, Stuttgart; 1989. p. 477-507.

Emerich DF, Walsh TJ. Selective working memory impairments following intradentate injection of colchicine: attenuation of the behavioral but not the neuropathological effects by gangliosides GM1 and AGF2. Physiol Behav 1989;45:93–101. [PubMed: 2727146]

Gaykema RP, van der Kuil J, Hersh LB, Luiten PG. Patterns of direct projections from the hippocampus to the medial septum-diagonal band complex: anterograde tracing with phaseolus vulgaris leucoagglutinin combined with immunohistochemistry of choline acetyltransferase. Neurosci 1991;43:349–360.

Gilbert PE, Kesner RP. Role of the rodent hippocampus in paired-associate learning involving associations between a stimulus and a spatial location. Behav Neurosci 2002;116:63–71. [PubMed: 11895184]

Gilbert PE, Kesner RP. Localization of function within the dorsal hippocampus: the role of the CA3 subregion in paired-associate learning. Behav Neurosci 2003;117:1385–1394. [PubMed: 14674856]

Gilbert PE, Kesner RP. Memory for objects and their locations: the role of the hippocampus in retention of object-place associations. Neurobiol Learn Mem 2004;81:39–45. [PubMed: 14670357]

Gilbert PE, Kesner RP. The role of the dorsal CA3 hippocampal subregion in spatial working memory and pattern separation. Behav Brain Res 2006;169:142–149. [PubMed: 16455144]

Gilbert PE, Kesner RP, DeCoteau WE. Memory for spatial location: role of the hippocampus in mediating spatial pattern separation. J Neurosci 1998;18:804–810. [PubMed: 9425021]

Gilbert PE, Kesner RP, Lee I. Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. Hippocampus 2001;11:626–636. [PubMed: 11811656]

Gluck MA, Myers CE. Psychobiological models of hippocampal function in learning and memory. Annu Rev Psychol 1997;48:481–514. [PubMed: 9046567]

Gold AE, Kesner RP. The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. Hippocampus 2005;15:808–814. [PubMed: 16010664]

Granger R, Wiebe SP, Taketani M, Lynch G. Distinct memory circuits composing the hippocampal region. Hippocampus 1996;6:567–678. [PubMed: 9034846]

Guzowski JF, Knierim JJ, Moser EI. Ensemble dynamics of hippocampal regions CA3 and CA1. Neuron 2004;44:581–584. [PubMed: 15541306]

Hampson RE, Heyser CJ, Deadwyler SA. Hippocampal cell firing correlates of delayed-match-to-sample performance in the rat. Behav Neurosci 1993;107:715–739. [PubMed: 8280383]

Handelmann GE, Olton DS. Spatial memory following damage to hippocampal CA3 pyramidal cells with kainic acid: impairment and recovery with preoperative training. Brain Res 1981;217:41–58. [PubMed: 7260619]

Hasselmo ME, Bodelon C, Wyble BP. A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. Neural Comput 2002;14:793–817. [PubMed: 11936962]

Hasselmo ME, McClelland JL. Neural models of memory. Curr Opin Neurobiol 1999;9:184–188. [PubMed: 10322183]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Hasselmo ME, Wyble BP, Wallenstein GV. Encoding and retrieval of episodic memories: role of cholinergic and GABAergic modulation in the hippocampus. Hippocampus 1996;6:693–708. [PubMed: 9034856]

Hertz, J.; Krogh, A.; Palmer, RG. An introduction to the theory of neural computation. Wokingham: Addison-Wesley; 1991.

Honey RC, Watt A, Good M. Hippocampal lesions disrupt an associative mismatch process. J Neurosci 1998;18:2226–2230. [PubMed: 9482806]

Hunsaker MR, Thorup JA, Welch T, Kesner RP. The Role of CA3 and CA1 in the Acquisition of an Object-Trace-Place Paired-Associate Task. Behav Neurosci 2006;120:1252–1256. [PubMed: 17201469]

Ishizuka N, Weber J, Amaral DG. Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. J Comp Neurol 1990;295:580–623. [PubMed: 2358523]

Jakab, RL.; Leranth, C. Septum. In: Paxinos, G., editor. The rat nervous system. Vol. 2nd ed.. San Diego: Academic Press; 1995. p. 405-442.

Jarrard LE. Selective hippocampal lesions and behavior: effects of kainic acid lesions on performance of place and cue tasks. Behav Neurosci 1983;97:873–889. [PubMed: 6651962]

Jarrard LE, Davidson TL. Acquisition of concurrent conditional discriminations in rats with ibotenate lesions of hippocampus and subiculum. Psychobiol 1990;18:68–73.

Jensen O, Lisman JE. Hippocampal CA3 region predicts memory sequences: accounting for the phase precession of place cells. Learn Mem 1996;3:279–287. [PubMed: 10456097]

Jerman T, Kesner RP, Hunsaker MR. Disconnection analysis of CA3 and DG in mediating encoding but not retrieval in a spatial maze learning task. Learn Mem 2006;13:458–464. [PubMed: 16882862]

Jung MW, McNaughton BL. Spatial selectivity of unit activity in the hippocampal granular layer. Hippocampus 1993;3:165–182. [PubMed: 8353604]

Kant GJ. Effects of psychoactive drugs or stress on learning, memory, and performance as assessed using a novel water maze task. Pharmacol Biochem Behav 1993;44:287–295. [PubMed: 8446662]

Kesner RP, Gilbert PE, Wallenstein GV. Testing neural network models of memory with behavioral experiments. Curr Opin Neurobiol 2000;10:260–265. [PubMed: 10753789]

Kesner RP, Hopkins RO. Mnemonic functions of the hippocampus: a comparison between animals and humans. Biol Psychol 2006;73:3–18. [PubMed: 16473455]

Kesner RP, Hunsaker MR, Gilbert PE. The role of CA1 in the acquisition of an object-trace-odor paired associate task. Behav Neurosci 2005;119:781–786. [PubMed: 15998199]

Kesner RP, Lee I, Gilbert P. A behavioral assessment of hippocampal function based on a subregional analysis. Rev Neurosci 2004;15:333–351. [PubMed: 15575490]

Kesner RP, Rolls ET. Role of long-term synaptic modification in short-term memory. Hippocampus 2001;11:240–250. [PubMed: 11769307]

Knierim, JJ. Hippocampal remapping: implications for spatial learning and navigation. In: Jeffery, KJ., editor. The neurobiology of spatial behavior. Oxford, England: Oxford Press; 2003. p. 226-239.

Lassalle JM, Bataille T, Halley H. Reversible inactivation of the hippocampal mossy fiber synapses in mice impairs spatial learning, but neither consolidation nor memory retrieval, in the Morris navigation task. Neurobiol Learn Mem 2000;73:243–257. [PubMed: 10775494]

Lee I, Kesner RP. Differential contribution of NMDA receptors in hippocampal subregions to spatial working memory. Nat Neurosci 2002;5:162–168. [PubMed: 11780144]

Lee I, Kesner RP. Differential roles of dorsal hippocampal subregions in spatial working memory with short versus intermediate delay. Behav Neurosci 2003;117:1044–1053. [PubMed: 14570553]

Lee I, Kesner RP. Encoding versus retrieval of spatial memory: double dissociation between the dentate gyrus and the perforant path inputs into CA3 in the dorsal hippocampus. Hippocampus 2004a;14:66–76. [PubMed: 15058484]

Lee I, Kesner RP. Differential contributions of dorsal hippocampal subregions to memory acquisition and retrieval in contextual fear-conditioning. Hippocampus 2004b;14:301–310. [PubMed: 15132429]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Lee I, Rao G, Knierim JJ. A double dissociation between hippocampal subfields: differential time course of CA3 and CA1 place cells for processing changed environments. Neuron 2004;42:803–815. [PubMed: 15182719]

Lee I, Hunsaker MR, Kesner RP. The role of hippocampal subregions in detecting spatial novelty. Behav Neurosci 2005a;119:145–153. [PubMed: 15727520]

Lee I, Jerman TS, Kesner RP. Disruption of delayed memory for a sequence of spatial locations following CA1- or CA3-lesions of the dorsal hippocampus. Neurobiol Learn Mem 2005b;84:138–147. [PubMed: 16054848]

Leutgeb S, Leutgeb JK, Treves A, Moser MB, Moser EI. Distinct ensemble codes in hippocampal areas CA3 and CA1. Science 2004;305:1295–1298. [PubMed: 15272123]

Li H, Matsumoto K, Watanabe H. Different effects of unilateral and bilateral hippocampal lesions in rats on the performance of radial maze and odor-paired associate tasks. Brain Res Bull 1999;48:113–119. [PubMed: 10210177]

Lisman JE. Relating hippocampal circuitry to function: recall of memory sequences by reciprocal dentate-CA3 interactions. Neuron 1999;22:233–242. [PubMed: 10069330]

Lorente De No´ R. Studies on the structure of the cerebral cortex: I. The area entorhinalis. J Psychol Neurol 1933;45:381–438.

Luine V, Villegas M, Martinez C, McEwen BS. Repeated stress causes reversible impairments of spatial memory performance. Brain Res 1994;639:167–170. [PubMed: 8180832]

Manns JR, Eichenbaum H. Time and treason to the trisynaptic teachings: theoretical comment on Kesner et Al. (2005). Behav Neurosci 2005;119:1140–1143. [PubMed: 16187843]

Marr D. Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci 1971;262:23–81. [PubMed: 4399412]

McClelland JL, Goddard NH. Considerations arising from a complementary learning systems perspective on hippocampus and neocortex. Hippocampus 1996;6:654–665. [PubMed: 9034852]

McLamb RL, Mundy WR, Tilson HA. Intradentate colchicine disrupts the acquisition and performance of a working memory task in the radial arm maze. Neurotoxicol 1988;9:521–528.

McNaughton BL, Barnes CA, Meltzer J, Sutherland RJ. Hippocampal granule cells are necessary for normal spatial learning but not for spatially-selective pyramidal cell discharge. Exp Brain Res 1989;76:485–496. [PubMed: 2792242]

McNaughton BL, Morris RGM. Hippocampal synaptic enhancement and information storage within a distributed memory system. Trends Neurosci 1987;10:408–415.

McNaughton, BL.; Nadel, L. Hebb-marr networks and the neurobiological representation of action in space. In: Gluck, MA.; Rumelhart, DE., editors. Neuroscience and connectionist theory. Erlbaum: Hillsdale; 1989. p. 1-63.

Mizumori SJ, McNaughton BL, Barnes CA, Fox KB. Preserved spatial coding in hippocampal CA1 pyramidal cells during reversible suppression of CA3c output: evidence for pattern completion in hippocampus. J Neurosci 1989;9:3915–3928. [PubMed: 2585060]

Mizumori SJ, Perez GM, Alvarado MC, Barnes CA, McNaughton BL. Reversible inactivation of the medial septum differentially affects two forms of learning in rats. Brain Res 1990;528:12–20. [PubMed: 2245328]

Mizumori SJ, Ragozzino KE, Cooper BG, Leutgeb S. Hippocampal representational organization and spatial context. Hippocampus 1999;9:444–451. [PubMed: 10495025]

Murray EA, Gaffan D, Mishkin M. Neural substrates of visual stimulus-stimulus association in rhesus monkeys. J Neurosci 1993;13:4549–4561. [PubMed: 8410203]

Nanry KP, Mundy WR, Tilson HA. Colchicine-induced alterations of reference memory in rats: role of spatial versus non-spatial task components. Behav Brain Res 1989;35:45–53. [PubMed: 2803543]

Nakazawa K, Quirk MC, Chitwood RA, Watanabe M, Yeckel MF, Sun LD, Kato A, Carr CA, Johnston D, Wilson MA, Tonegawa S. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science 2002;297:211–218. [PubMed: 12040087]

Nunn JA, LePeillet E, Netto CA, Hodges H, Gray JA, Meldrum BS. Global ischemia: hippocampal pathology and spatial deficits in the water maze. Behav Brain Res 1994;62:41–54. [PubMed: 7917032]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Olsen GM, Scheel-Kruger J, Moller A, Jensen LH. Relation of spatial learning of rats in the Morris water maze task to the number of viable CA1 neurons following four-vessel occlusion. Behav Neurosci 1994;108:681–690. [PubMed: 7986362]

Olton DS, Becker JT, Handelmann GH. Hippocampus, space, and memory. Brain and Behav Sci 1979;2:313–365.

O'Reilly RC, McClelland JL. Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. Hippocampus 1994;4:661–682. [PubMed: 7704110]

O'Reilly RC, Rudy JW. Computational principles of learning in the neocortex and hippocampus. Hippocampus 2000;10:389–397. [PubMed: 10985278]

Petrides M. Nonspatial conditional learning impaired in patients with unilateral frontal but not unilateral temporal lobe excisions. Neuropsychologia 1990;28:137–149. [PubMed: 2107458]

Petrides M. Visuo-motor conditional associative learning after frontal and temporal lesions in the human brain. Neuropsychologia 1997;35:989–997. [PubMed: 9226660]

Rajji T, Chapman D, Eichenbaum H, Greene R. The role of CA3 hippocampal NMDA receptors in paired associate learning. J Neurosci 2006;26:908–915. [PubMed: 16421310]

Ramon y Cajal, S. Histology of the nervous system. Oxford, England: Oxford University Press; 1995.

Redish AD, Battaglia FP, Chawla MK, Ekstrom AD, Gerrard JL, Lipa P, Rosenzweig ES, Worley PF, Guzowski JF, McNaughton BL, Barnes CA. Independence of firing correlates of anatomically proximate hippocampal pyramidal cells. J Neurosci 2001;21:RC134. [PubMed: 11222672]

Ridley RM, Timothy CJ, Maclean CJ, Baker HF. Conditional learning and memory impairments following neurotoxic lesion of the CA1 field of the hippocampus. Neurosci 1995;67:263–275.

Risold PY, Swanson LW. Connections of the rat lateral septal complex. Brain Res Rev 1997;24:115–195. [PubMed: 9385454]

Robertson RG, Rolls ET, Georges-Francois P. Spatial view cells in the primate hippocampus: effects of removal of view details. J Neurophysiol 1998;79:1145–1156. [PubMed: 9497397]

Rogers JL, Hunsaker MR, Kesner RP. Effects of ventral and dorsal CA1 subregional lesions on trace fear conditioning. Neurobiol Learn Mem 2006;86:72–81. [PubMed: 16504548]

Rolls, ET. Functions of neuronal networks in the hippocampus and neocortex in memory. In: Byrne, JH.; Berry, WO., editors. Neural models of plasticity: Theoretical and empirical approaches. New York: Academic Press; 1989. p. 240-265.

Rolls ET. A theory of hippocampal function in memory. Hippocampus 1996;6:601–620. [PubMed: 9034849]

Rolls ET, Kesner RP. A computational theory of hippocampal function, and empirical tests of the theory. Prog Neurobiol 2006;79:1–48. [PubMed: 16781044]

Rolls ET, Miyashita Y, Cahusac PM, Kesner RP, Niki H, Feigenbaum JD, Bach L. ippocampal neurons in the monkey with activity related to the place in which a stimulus is shown. J Neurosci 1989;9:1835–1845. [PubMed: 2723752]

Rolls, ET.; Treves, A. Neural Networks and Brain Function. Oxford, England: Oxford University Press; 1998.

Rolls, ET.; Deco, G. Computational Neuroscience of Vision. Oxford, England: Oxford University Press; 2002.

Samsonovich A, McNaughton BL. Path integration and cognitive mapping in a continuous attractor neural network model. J Neurosci 1997;17:5900–5920. [PubMed: 9221787]

Samura T, Hattori M. Hippocampal memory modification induced by pattern completion and spike-timing dependent synaptic plasticity. Int J Neural Syst 2005;15:13–22. [PubMed: 15912579]

Shapiro, ML.; Olton, DS. Hippocampal function and interference. In: Schacter, DL.; Tulving, E., editors. Memory systems. London: MIT Press; 1994. p. 141-146.

Shors TJ, Dryver E. Stress impedes exploration and the acquisition of spatial information in the eight-arm radial maze. Psychobiology 1992;20:247–253.

Stein-Behrens B, Mattson MP, Chang I, Yeh M, Sapolsky R. Stress exacerbates neuron loss and cytoskeletal pathology in the hippocampus. J Neurosci 1994;14:5373–5380. [PubMed: 8083742]

Swanson LW, Cowan WM. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. J Comp Neurol 1977;172:49–84. [PubMed: 65364]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Sutherland RJ, McDonald RJ, Hill CR, Rudy JW. Damage to the hippocampal formation in rats selectively impairs the ability to learn cue relationships. Behav Neural Biol 1989;52:331–356. [PubMed: 2590146]

Sutherland RJ, Whishaw IQ, Kolb B. A behavioural analysis of spatial localization following electrolytic, kainate- or colchicine-induced damage to the hippocampal formation in the rat. Behav Brain Res 1983;7:133–153. [PubMed: 6830648]

Szuran T, Zimmermann E, Welzl H. Water maze performance and hippocampal weight of prenatally stressed rats. Behav Brain 1994;65:153–155.

Tanila H. Hippocampal place cells can develop distinct representations of two visually identical environments. Hippocampus 1999;9:235–246. [PubMed: 10401639]

Tilson HA, Rogers BC, Grimes L, Harry GJ, Peterson NJ, Hong JS, Dyer RS. Time-dependent neurobiological effects of colchicine administered directly into the hippocampus of rats. Brain Res 1987;408:163–172. [PubMed: 2885066]

Treves A. Computational constraints between retrieving the past and predicting the future, and the CA3-CA1 differentiation. Hippocampus 2004;14:539–556. [PubMed: 15301433]

Treves A, Rolls ET. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus 1992;2:189–199. [PubMed: 1308182]

Treves A, Rolls ET. Computational analysis of the role of the hippocampus in memory. Hippocampus 1994;4:374–391. [PubMed: 7842058]

Vazdarjanova A, Guzowski JF. Differences in hippocampal neuronal population responses to modifications of an environmental context: evidence for distinct, yet complementary, functions of CA3 and CA1 ensembles. J Neurosci 2004;24:6489–6496. [PubMed: 15269259]

Watanabe Y, Gould E, Cameron HA, Daniels DC, McEwen BS. Phenytoin prevents stress- and corticosterone-induced atrophy of CA3 pyramidal neurons. Hippocampus 1992;2:431–435. [PubMed: 1308199]

Watanabe T, Niki H. Hippocampal unit activity and delayed response in the monkey. Brain Res 1985;325:241–254. [PubMed: 3978418]

Wallenstein GV, Eichenbaum H, Hasselmo ME. The hippocampus as an associator of discontiguous events. Trends Neurosci 1998;21:317–323. [PubMed: 9720595]

Wallenstein GV, Hasselmo ME. Functional transitions between epileptiform-like activity and associative memory in hippocampal region CA3. Brain Res Bull 1997;43:485–493. [PubMed: 9250622]

Walsh TJ, Schulz DW, Tilson HA, Schmechel DE. Colchicine-induced granule cell loss in rat hippocampus: selective behavioral and histological alterations. Brain Res 1986;398:23–36. [PubMed: 3801898]

Whishaw IQ, Rod MR, Auer RN. Behavioral deficits revealed by multiple tests in rats with ischemic damage limited to half of the CA1 sector of the hippocampus. Brain Res Bull 1994;34:283–289. [PubMed: 8055352]

Wiebe SP, Staubli UV, Ambros-Ingerson J. Short-term reverberant memory model of hippocampal field CA3. Hippocampus 1997;7:656–665. [PubMed: 9443061]

Winocur G. Conditional learning in aged rats: evidence of hippocampal and prefrontal cortex impairment. Neurobiol Aging 1992;13:131–135. [PubMed: 1542374]

Wise SP, Murray EA. Role of the hippocampal system in conditional motor learning: mapping antecedents to action. Hippocampus 1999;9:101–117. [PubMed: 10226772]

Witter MP. Organization of the entorhinal-hippocampal system: a review of current anatomical data. Hippocampus 1993;3:33–44. [PubMed: 8287110]