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A Study of Hippocampal Structure-function Relations Along the Septo-temporal Axis

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Abstract

This study examined structural-functional differences along the septo-temporal axis of hippocampus using radial-maze tasks that involved two different memory processes (reference memory (RM), working memory (WM)), and the utilization of two kinds of information (spatial vs. nonspatial cue learning). In addition, retention of the nonspatial cue task was tested nine weeks following completion of acquisition, and the rats then underwent discrimination reversal training. Ibotenic acid lesions limited to either the dorsal pole, intermediate area, or ventral pole had minimal effects on acquisition of the complex place and cue discrimination tasks. The one exception was that rats with lesions confined to the dorsal third of hippocampus made more WM errors on the spatial task (but not the cue task) early in training. Selective lesions of the three hippocampal regions had no effects on either long-term retention or reversal of the nonspatial cue discrimination task. In contrast, rats that had all of the hippocampus removed were severely impaired in learning the spatial task, making many RM and WM errors, while on the nonspatial cue task the impairment was limited to WM errors. Further analysis of the WM errors made in acquisition showed that rats with complete lesions were significantly more likely on both the spatial and nonspatial cue tasks to reenter arms that had been baited and visited on that trial compared to arms that had not been baited. A similar pattern of errors emerged for complete hippocampal lesioned rats during reversal discrimination. This pattern of errors suggests that in addition to an impairment in handling spatial information, complete removal of hippocampus also interferes with the ability to inhibit responding to cues that signal reward under some conditions but not under others.

The finding that selective lesions limited to the intermediate zone of the hippocampus produce no impairment in either working memory ('rapid place learning') or reference memory in our radial maze tasks serve to limit the generality of the conclusion of Bast et al. (2009) that the intermediate area is needed for behavioral performance based on rapid learning about spatial cues.

Keywords

learning; memory; spatial vs. nonspatial cue learning; working vs reference memory; rat

Introduction

Recent research has served to clarify the nature and extent of the differences in structure and function of the hippocampus along the longitudinal or septo-temporal axis. Rather than discrete subdivisions making up the major components as found along the transverse axis (dentate gyrus, pyramidal fields CA 3 – CA1), the differences along the septo-temporal axis are best characterized as being in the form of gradients (Bast, 2007; Bast et al., 2009; Cenquizca and Swanson, 2006, 2007). Thus, for spatial information, research findings indicate that neurons in the dorsal or septal pole have discrete receptive fields that respond to specific locations within the environment (so-called ‘place cells’) (Muller, 1996; O’Keefe and Dostrovsky, 1971; O’Keefe and Nadel, 1978), while as one moves along the intermediate third of the hippocampus and to the ventral pole region, place cells gradually decrease in number and are replaced by cells that are more sensitive to larger and less accurate place fields (Brun et al., 2008; Jung et al., 1994; Maurer et al., 2005; McNaughton et al., 2006;). Anatomically, cortical and subcortical inputs project to different hippocampal areas along the axis as one moves from the septal to the ventral poles with the septal (dorsal) area receiving visuospatial inputs from the dorsolateral entorhinal cortex and more ventral hippocampus being the recipient of fibers from ventromedial entorhinal cortex and subcortical inputs from hypothalamus and amygdala (Hargreaves et al., 2005; McNaughton et al., 2006). Projections from hippocampus also differ along the septo-temporal gradient (Amaral and Witter, 1989; Amaral and Lavenex, 2006; Cenquizca and Swanson, 2007; Witter and Amaral, 2004). It has been proposed that these anatomical connections form three overlapping domains, with a dorsal pathway from the septal third innervating primarily the retrosplenial area and anterior cingulate cortex, a ventral area with strong reciprocal hypothalamic and amygdala connections, and with the intermediate and ventral areas having outputs to medial prefrontal cortical areas and subcortical sites like the mediodorsal striatum. (See Bast et al., 2009, Cenquizca and Swanson, 2006, 2007, and Fanselow and Dong, 2010 for a more detailed discussion of the underlying anatomical differences and functional implications.)

Given the structural differences along the septo-temporal axis described above, and the recently reported differences in gene expression (Fanselow and Dong, 2010), it is not too surprising that lesions to dorsal or ventral halves of the hippocampus have been found to have differential effects on a number of behaviors (Bannerman, et al., 2004; Davidson, et al., 2009, 2010; Kjelstrup et al., 2002; McDonald et al. 2006; Moser and Moser, 1998; Moser et al., 1993; Nadel, 1968; Pothuizen et al. 2004.) In an especially important paper by Bast, et al. (2009), selective lesions involving each of the three septo-temporal regions were used together with recordings of neuronal activity in dorsal hippocampus and a water maze task that requires rapid place learning. The results were interpreted as supporting the view that the intermediate region of hippocampus “... likely combines anatomical links to visuospatial information with links to behavioral control through medial prefrontal cortex and subcortical sites” (p. 731). Further, it was suggested that the underlying anatomical bases for the rapid one-trial learning paradigm used in this research may have different anatomical bases from those mediating incremental learning that occurs over many trials and days where the same location is always correct.

In the research reported here, rats with selective lesions of the hippocampus limited to either the dorsal pole, intermediate area, the ventral pole, or including all of hippocampus were trained and tested on an incremental 8-arm radial maze task that was designed to require the utilization of two kinds of information (spatial vs. nonspatial cue learning) and two different memory processes (reference memory (RM), and working memory (WM)) (see Jarrard, 1983, 1993; Jarrard et al., 2004). In the spatial version of the task, the eight arms of the radial maze differed in their spatial location within the room. There were obvious extramaze cues that remained constant over trials, and diffuse lighting was provided by a bank of florescent bulbs. In the nonspatial intramaze cue task, different textured inserts were placed on the arms in a random order over trials, and lighting was provided by a single incandescent light bulb and reflector located directly over the center of the maze. In order to obtain information regarding the two memory processes, a limited baiting procedure was employed in which for any one animal the same four arms and four cue inserts were baited with a reward over trials and were considered correct when visited; choices of the remaining four arms and four cue inserts were never baited and when visited were incorrect (RM error). Repeating choices of arms or cues that had already been chosen within a trial (WM errors) could be divided into repeating arms (or cues) that were correct but had already been visited on that trial (WMC), and repeated entries into arms (or repeated choices of cues) that had never been baited for that rat (WMI). Thus, for both the spatial and the nonspatial cue versions of the task, the error data provided information regarding RM, WMC, and WMI. The two versions of the radial maze task (spatial vs. nonspatial cue task) place comparable demands on the subjects in a number of ways, and appear to be of equal difficulty since control rats learn both tasks at essentially the same rate.

A theoretical question of considerable importance centers around the long-term retention of information learned following damage to the hippocampus and related hippocampal formation structures. Since rats that have had the hippocampus removed are impaired in learning most spatial tasks, testing long-term retention of spatial learning is generally not feasible. However, rats with similar lesions often learn nonspatial cue tasks as well as controls (Jarrard, 1993). Thus, an important question is whether long-term retention of a nonspatial cue task learned postoperatively will be remembered as well as in control animals. In the present study rats underwent 10 days of retention testing on the nonspatial cue task 9 weeks following the completion of acquisition training and testing. Since the hippocampus was removed before acquisition, one would assume the information will be in long-term storage presumably in neocortex (McClelland et al., 1995; O'Reilly and Rudy, 2001).

The specific learning and memory functions performed by the hippocampus are a topic of longstanding interest. Much evidence (see Eichenbaum and Cohen, 2001; Squire, 2004 for reviews) establishes a role for the hippocampus in (a) the encoding and retrieval of spatial information, and (b) the formation and recall of memories about events and facts (i.e. declarative memory). However, some findings suggest that the hippocampus may also be involved with certain types of associative processes. Morris (2006) noted that several recent accounts converge on the idea that the hippocampus functions to resolve 'predictable ambiguities' such as those that exist when a specific stimulus is associated with different outcomes dependent on the presence or absence of another cue. In what may be the simplest

example of this type of deficit, interference with the structural or functional integrity of the hippocampus is often accompanied by an impaired ability to withhold responding to cues that have been appetitively reinforced under one set of circumstances but nonreinforced under other conditions. In particular, it appears that rats with all of the hippocampus removed are like normal rats in that they will quickly learn to respond to cues that are associated with appetitive reinforcement. However, such hippocampal-lesioned rats are impaired in inhibiting their responding when those same cues are no longer reinforced (for reviews, see Chan et al., 2001; Davidson and Jarrard, 2004).

The present study was also designed to compare lesions that remove all of the hippocampus with lesions confined to the dorsal, intermediate, and ventral segments in ability to withhold responding to 'predictably ambiguous' cues in the radial maze. That is, if complete or subtotal hippocampal lesions disrupt the ability to inhibit responding to previously rewarded, but currently nonrewarded cues, then one would expect that lesioned rats would exhibit more WMC errors compared to WMI errors. WMC errors involve revisiting cues that are no longer baited because the reward in that arm has already been collected on that trial. Thus, to avoid making WMC errors, the rats would have to inhibit responding to cues in the maze that have been associated with reward, and this is the type of inhibition that has been proposed to depend on the hippocampus. WMI errors involve revisiting arms within a trial that were never baited. Therefore, avoiding WMI errors does not require rats to refrain from responding to previously rewarded cues, and WMI errors would not involve interference with any hippocampal-dependent inhibition of responding to previously reinforced cues.

The above inhibitory hypothesis was also tested in a different way. The experiment concluded with a test in which the identity of rewarded and nonrewarded nonspatial cues used in training were reversed during testing. In this test, rats had to learn to avoid entering arms with cues that were baited during acquisition and retention testing because those arms were not baited during reversal testing. At the same time, the rats had to learn to enter arms with cues that had not been rewarded during training because those cues are now associated with reward during reversal testing. If complete or subtotal hippocampal lesions interfere with inhibition of responding to previously rewarded cues, then lesioned rats should have more difficulty compared to controls in learning to refrain from responding to previously rewarded, but now nonrewarded cues during reversal testing.

Previous research reported impaired reversal learning by animals with aspiration lesions of the hippocampus (Berger & Orr, 1983; Weikart & Berger, 1986). We also reported that rats with ibotenate lesions of the complete hippocampus showed impaired discrimination reversal learning based on their inability to withhold responding to previously rewarded cues (Davidson & Jarrard, 2004). However, all of these studies employed Pavlovian discrimination and reversal tasks which required animals to learn about discrete auditory and visual cues. Whether reversal learning in our radial maze task would be similarly impaired by complete or subtotal hippocampal lesions has not been investigated. There are extrahippocampal projections from the intermediate and ventral pole regions of hippocampus to brain areas more involved in controlling motor responses (medial prefrontal cortex, subcortical structures like the striatum) (Swanson, 2000), and this suggests there may

be differential effects on reversal learning among the different groups with subtotal hippocampal lesions.

In the proposed experiments we examined structure-function differences along the septo-temporal axis of hippocampus using radial-maze tasks that involved the utilization of two different kinds of information (spatial vs. nonspatial cue learning) and two memory processes (reference memory and working memory). The rats were then tested for retention of the nonspatial cue task after 9 weeks, and this was followed by reversal learning.

Materials and Methods

Subjects

Forty-two naïve, male rats were used in this experiment. The Sprague-Dawley rats, purchased from Harlan, weighed 250 – 300 g at the time of surgery. They were maintained under a 12:12 h light/dark cycle (0700 – 1900) at a temperature of 22 C and were housed in individual cages for the duration of the experiment. All procedures were in accordance with the standards established in the Guide for Care and Use of Laboratory Animals, and approved by the Institutional Animal Care and Use Committee of Washington and Lee University.

Apparatus

The animals were trained on one of two eight-arm radial mazes located in separate rooms. One radial maze (Lafayette Instrument Company) had 8 similar arms (10 × 70 cm) that radiated from a central platform (34 cm in diameter), clear Plexiglas walls (20 × 30 cm) that extended from the platform, and at the end of each arm a food well that could not be seen from the central platform. The second radial maze had a central platform (34 cm in diameter), eight similar arms (9 × 89 cm) and walls (5.5 × 88 cm) of Plexiglas that extended from the central platform. Small holes (1.2 cm in diameter and 0.5 cm deep) in the floor at the end of each arm served as food wells. Florescent lighting in both rooms used during testing on the spatial version of the task served to maximize extramaze room cues (rack of cages, cabinets, table, curtain on one wall, location of experimenter).

In the cue version of the task, for both radial mazes there were eight removable inserts of different materials (e.g., carpet, screen wire, sandpaper, cloth, etc.) mounted on plywood that covered the surface of the arms. Lighting in the rooms during testing on the intramaze cue task consisted of a single light bulb with a reflector directly over the maze. This lighting arrangement served to maximize the details of the intramaze cues on the maze and minimize room cues.

Surgical and Histological Procedures

The rats were randomly assigned to five groups matched on pre-operative body weight. In addition to rats assigned to a Control Group (operated and unoperated), the lesioned groups included a Dorsal Hippocampal Group (DH), Intermediate Hippocampal (IH), Ventral Hippocampal (VH), and a Complete Hippocampal Group (CH). The surgical lesions were made with multiple focal injections of small amounts of the axon-sparing neurotoxin,

ibotenic acid (IBO) (Tocris Bioscience) (see Jarrard, 1989, 2002). Stereotaxic coordinates for the different lesions and amount of IBO injected at each site are given in Table 1. The rats were anesthetized with intraperitoneal injections of a combination of sodium pentobarbital and chloral hydrate, and placed in a stereotaxic apparatus with bregma and lambda being level. An incision was made in the scalp, and a bone flap overlying the area to be lesioned was removed. Injections of IBO were made with a 5- μ l Hamilton syringe mounted on the stereotaxic frame and held in a Kopf microinjector unit (model 5000). A small diameter glass micropipette was glued onto the end of the needle of the syringe in order to minimize damage to the overlying cortex. The IBO was dissolved in phosphate buffered saline (pH 7.4) at a concentration of 10 mg/ml. As shown in Table 1, injections ranging from 0.05 μ l to 0.10 μ l were made over 1 min at each site.

Following behavioral testing, all rats were administered an overdose of the anesthetic and were perfused transcardially with a mixture of buffered physiological saline followed by a 10% formaldehyde solution. The brains were removed from the skull, embedded in egg yolk, and cryoprotected in a 30% solution of sucrose-formalin. Subsequently, the brains were cut on a microtome into 40- μ m sections with every fifth section being saved for histology. A cresyl violet stain was used to determine cell loss and gliosis resulting from the lesions.

The extent of the damage to the hippocampus in the various groups was determined using an Olympus microscope together with a SPOT RT camera and associated software system. Beginning with the most rostral section showing CA3 hippocampal cells (approximately -1.8 from bregma), each of the approximately 26 stained sections through the hippocampus was captured and imported onto a computer screen. The area of the hippocampus (CA1 – CA3, dentate gyrus, alveus, adjacent fimbria) that was normal appearing was traced manually for each section in both control and lesioned animals. The total volume of the remaining hippocampus on both sides was determined for each animal, and the percent of damage to hippocampus was subsequently calculated for each of the 4 lesioned groups using the total volume of the hippocampus in control rats.

General Behavioral Testing Procedures

Acquisition of the Place and Cue Task—Thirty days following surgery the rats were placed on a limited food deprivation schedule and were handled approximately 5 min each day for 5 days. Body weight was reduced during this period to approximately 85% of ad libitum weight, with a 1.5% gain being permitted during each week of preliminary and acquisition training. In order for the animals to become familiar with the reward that was to be used as reinforcement during training, several 45 mg sucrose pellets (P.J. Noyes Company) were placed in a small glass dish in the home cage starting the second day of handling.

The second week of preliminary training involved habituation to the testing room, radial maze, and the handling procedure. Several sucrose pellets were placed on each of the 8 arms and the platform of the radial maze, and the rats were placed in pairs on the maze for 3 min. On one trial the room lighting and maze was arranged for the spatial task; the second trial involved placing the 8 cues on the arms and having only the central light bulb for lighting.

Starting the second day, the rats were exposed individually for 3 min to each of the two task arrangements, and several sucrose pellets were placed halfway down each arm and on the platform. On subsequent days the order of exposure to the two tasks was counterbalanced so that by Day 5 the rats had equal exposure to both the spatial and intramaze cue versions of the radial maze. On Days 4 and 5 only a single pellet was placed at the end of each arm for each version of the task.

On each day of training, the rats received 2 trials on each version of the task (spatial and intramaze cue). The order of testing of the two tasks was counterbalanced over days. In the spatial task, four of the similar eight arms were designated as correct for that animal (and baited with a single sucrose pellet) and were consistently baited for that rat on all subsequent trials. In the cue version of the task, four of the eight intramaze cues were designated as correct for each rat (and thus consistently baited), and four cues were never baited. The spatial location of the cues on the arms was changed in a random order from trial to trial. At the beginning of a trial, the rat was placed on the platform in the center of the maze, and remained on the maze until either the 4 correct (baited) arms or cues were visited, until a total of 16 choices were made, or until 5 min. had elapsed.

For both the spatial and cue tasks the experimenter recorded the arms entered and the total time required to choose the four correct arms (or cues). The animals were tested in squads of 4 rats. After the first few trials, the rats were making choices with minimal delay, and the intertrial intervals for each task was approximately 15 min. The animals received training trials 5 days each week for 5 weeks and thus a total of 50 trials on each task.

Retention—Following acquisition training the animals had ad libitum access to food for 9 weeks during which body weight was recorded on 2 successive days each week. At the end of this period, body weight was again reduced for each rat to approximately 85% of the weight obtained at the end of the 9 weeks. Retention testing consisted of 2 trials on the intramaze cue task each day for 7 days with the 4 previously designated correct cues again being reinforced. As during training, a rat remained on the maze until either the 4 correct cues were chosen, until a total of 16 choices were made, or until 5 min. had elapsed.

Reversal Training—During reversal each of the 4 cues that had not been correct were now reinforced with a single sucrose pellet while the previously correct cues were not reinforced. As during retention testing, each rat received two trials each day. Testing was continued for 10 days.

Results

Histology

Coronal sections at 5 anterior-posterior levels through the hippocampus are presented in Figure 1 for a control and a representative rat from each of the 4 lesion groups. For the CH Group the total amount of damage to hippocampus averaged 95% of that found in controls with a range from 93% to 100%. The cell loss within hippocampus included most of the pyramidal neurons in fields CA1-CA3 and the hilar and granule cells of the dentate gyrus. Atrophy of any remaining hippocampus was apparent in all rats as shown for the CH rat in

Figure 1. Further, there was considerable shrinkage of the fimbria, and the remaining axons were displaced and located along the dorsal and lateral edges of the thalamus as shown in Figure 1. The spared hippocampal cells in the CH rat shown in the figure are located in the posterior-dorsal area and are few in number. There was occasional extrahippocampal damage to the subiculum in this group, especially in the ventral subiculum, but this was usually unilateral and limited in amount.

The selective lesions in DH, IH, and VH Groups all show a loss of CA1-CA3 pyramidal cells and dentate granular cells in the intended areas (see Figure 1). Estimates of the amount of damage in the dorsal hippocampus (DH Group) averaged 36% of the total hippocampus with a range from 28% to 45%. This lesion is similar in terms of amount of damage to hippocampus as that found in the IH Group (average of 37%; range from 32% to 43%), and the VH Group (average of 39%; range of 34% to 42%). There was minimal damage to structures and areas outside of hippocampus. The one exception was some damage to ventral subiculum in several rats but as in the CH Group this cell loss was small in amount.

Behavior

Mixed design Analyses of Variance (ANOVA) were used to evaluate number of reference memory (RM) and working memory (WM) errors with Group (CH, DH, IH, VH, and Controls) as a between-subjects factor and Cue Type (spatial and nonspatial), WM Error Type (WMC and WMI), and Blocks of trials, as within-subjects factors. Newman-Keuls tests were used to further evaluate significant main effects and interactions.

Acquisition—Figure 2 shows the mean number of reference memory (RM) errors made by each group (CH, DH, IH, VH, and Control) during acquisition of both the spatial task (left panel) and nonspatial cue task. RM errors decreased for all groups during training with spatial and with nonspatial cues. However, on the spatial learning task, the decrease in RM errors was less for rats with CH lesions compared with the rats in the other lesion groups and controls. No differences between groups were observed when RM performance was based on nonspatial cues. This pattern of results yielded a significant main effect of Block ($F(4,136) = 170.07, p < .01$), and significant Cue Type $\times$ Group ($F(4, 34) = 9.65, p < .01$) and Block $\times$ Cue Type $\times$ Group ($F(16, 136) = 1.86, p < .05$, interactions. Subsequent Newman-Keuls tests showed that rats with CH lesions differed significantly from Controls and from rats with VH lesions on Block 4 of training with spatial cues and differed significantly from controls, VH-lesioned and rats with IH lesions on Block 5 of the spatial cue task. No group differed significantly from any other on any block of the training with nonspatial cues.

The mean number of total working memory (WM) errors for each group during training on the spatial and nonspatial tasks is shown in Figure 3. With both spatial and nonspatial cues, total WM errors started out and remained higher over the course of training for rats with CH lesions compared to rats in the other groups. In addition, WM errors with spatial cues were also elevated at the outset of training for rats with DH lesions compare to rats other than those with CH lesions. These effects resulted in significant main effects of Group ($F(4, 34) = 36.36, p < .01$) and Block ($F(4, 136) = 64.07, p < .01$) as well as significant Group $\times$ Block ($F(16, 136) = 5.37, p < .01$), Group $\times$ Cue Type ($F(4, 34) = 2.92, p < .05$), and Group $\times$

Block x Cue Type ($F(16,136) = 2.83, p < .01$) interactions. Newman-Keuls tests confirmed that on the spatial cue task rats with CH lesions made significantly more WM errors than each of the other groups on Blocks 1, 2, and 5 of training and made significantly more errors than rats with VH lesions on Block 3 of that task (all $ps < .05$). In addition, rats with DH lesions made significantly more errors compared to controls and to rats with VH lesions on the first block of training with spatial cues ($ps < .05$). Newman-Keuls tests also confirmed that on the nonspatial task, rats with CH lesions made significantly more errors on Block 1 compared to each of the other groups ($ps < .05$) and made significantly more errors on Block 2 than controls and rats with VH lesions. No other differences among groups were significant on any block during training with either type of cue. In addition, separate ANOVAs were used to compare performance on spatial and nonspatial tasks of each lesion group with controls. For rats with CH lesions, the analysis yielded a significant Group x Cue Type interaction ($F(1, 16) = 5.34, p < .05$), and Newman-Keuls test confirmed that CH-lesioned rats made more errors with spatial cues than with nonspatial cues ($p < .05$), whereas this difference was not significant for controls. This comparison between Cue Types did not reveal significant differences for any other lesion group.

We also analyzed the type of WM errors made by each lesion group and controls by comparing the number errors made when rats returned to arms that had been, but were no longer, baited on a given trial (i.e., WMC errors), and with the number of errors made when rats returned to arms that were never baited (i.e., WMI). The data of primary interest in this analysis are shown in Figure 4. Collapsed across all blocks of training, the figure shows that rats with CH lesions made more WMC and WMI errors compared to each of the other groups with both spatial and nonspatial cues. ANOVA obtained a significant main effect of Error Type ($F(1,34) = 22.71, p < .01$) that interacted significantly with Group ($F(4, 34) = 3.65, p < .05$). The Error Type x Group x Block interaction did not achieve significance, nor did any interaction involving Error Type with Cue Type reach significance. Newman-Keuls tests showed that rats with CH lesions made significantly more WMC than WMI errors on both the spatial ($p < .05$) and the nonspatial cue ($p < .05$) tasks. Differences in WMC and WMI errors were not significant for any other group on either task.

Retention

Beginning 9 weeks after the end of acquisition training, all rats were tested for retention of learning about nonspatial cues, for which there were no differences among the groups when training was completed (see Block 5 data in Figures 3 and 4). Reference memory and working memory errors on the first block of retention testing (prior to the opportunity for substantial relearning of the maze problem) was largely the same for all lesion conditions. This was also found across all seven two-trial blocks of retention testing. That is, RM errors, total WM errors, and WMC and WMI errors increased for all groups about the same amount on the first block of retention testing compared to the last block of training. ANOVAs comparing the numbers of each type of error on these two blocks obtained a significant main effects of Block (smallest $F(1, 29) = 4.65, p < .05$ for WMC errors). However, none of these ANOVAs obtained significant main effects or interactions involving Group. Additional ANOVAs comparing each type of error for all groups on all Blocks 1–7 of testing obtained similar outcomes, with each analysis yielding a significant main effect of Block (smallest

$F(6, 24) = 2.50, p < .05$, for total WM errors), and no significant main effects or interactions involving Group. These findings in retention testing indicate that there were no differential effects on forgetting of the nonspatial cue information for the groups.

Reversal Training

To test the effects of each lesion on reversal training with nonspatial cues, pellets were no longer presented with the four cues that had been associated with reward during training and retention testing. They were presented instead with the four cues that had been nonrewarded during those phases of the experiment. Not surprisingly (see Figure 5), RM errors increased dramatically at the beginning of reversal training compared to the end of retention testing. However, RM errors during reversal differed little as a function of group. An ANOVA comparing RM errors on the first block of reversal training to those observed on the last block of retention testing obtained only a significant main effect of Block ($F(1, 27) = 408.06, p < .01$). The main effect of Group and the Group $\times$ Block interaction failed to achieve significance. The same statistical outcome was obtained when RM errors were analyzed during Blocks 1–5 of reversal training (i.e., only the main effect of Block ($F(4, 108) = 23.46, p < .01$ was significant).

Reversal training had a different effect on WM errors. Figure 6 shows that while total WM errors increased for all groups on the first block of reversal training, the magnitude of this increase was much larger for rats with CH lesions compared to the other groups. Each of these latter groups (i.e., DH, VH, IH, and controls) showed a lower and similar number of total WM errors on the first block of reversal training. An ANOVA used to evaluate these data obtained significant main effects of Group ($F(4, 27) = 5.45, p < .01$) and Block ($F(1, 27) = 159.31, p < .01$), as well as a significant Group $\times$ Block interaction ($F(4, 27) = 6.65, p < .01$). Newman-Keuls tests found that while total WM errors did not differ significantly among the groups at the end of retention testing, on the first block of reversal training the group with CH lesions exhibited significantly more total WM errors compared to each of the other groups ($ps < .05$). Comparison of total WM errors among the groups over all 5 blocks of reversal training yielded significant main effects of Group ($F(4, 27) = 11.30, p < .01$) and Block ($F(4, 108) = 68.02, p < .01$), and a significant Group $\times$ Block interaction ($F(16, 108) = 3.26, p < .01$). Newman-Keuls tests showed that over all of reversal training rats with CH-lesions exhibited more total WM errors than the DH, VH, IH, and control groups ($ps < .05$), while total WM errors among these latter groups did not differ significantly.

WMC and WMI errors were also compared for each group during reversal training. The data from the last block of retention testing are depicted on the left side of the dashed line in each panel of Figure 7, whereas the data shown on the right side of the dashed line in each panel represent errors during each block of reversal training. Thus, the data shown for reversal training in left panel of Figure 7 depicts the tendency for rats to revisit arms on a trial that contained nonspatial cues that had been associated with reward during training and retention testing, but were no longer rewarded during reversal training (now WMI errors). The data shown for reversal training in the right panel of Figure 7 depicts the tendency for rats to return to arms already visited on a given trial that contained nonspatial cues that were not

associated with reward during training and retention testing but were rewarded during reversal training (now WMC errors).

As can be seen in Figure 7, at the end of retention testing none of the groups exhibited more than a minimal number of WMC or WMI errors. However, when reversal training began WMI errors (left panel of Figure 7) increased as the rats tended to revisit arms with cues that were associated with pellets during training and retention testing, even though those cues were no longer associated with reward during reversal training. This effect was especially pronounced for rats that had CH lesions. A rather different pattern of reversal performance is shown in the right panel of Figure 7. Here, all groups showed a similar small increase in WMC errors on the first block of reversal training indicating a tendency to revisit arms with nonspatial cues that were previously non-rewarded in training and retention testing but were rewarded during reversal. Differences between groups did not emerge until the second block of reversal training, when rats with CH lesions exhibited more WMC errors compared to rats in each of the other groups. This delayed increase in errors indicates that after the previously non-rewarded cues became associated with reward during reversal training, rats with CH lesions had more difficulty in refraining from responding to those cues compared to rats in each of the other treatment conditions.

An ANOVA comparing errors at the end of retention testing with those observed on the first Block of reversal training obtained significant main effects of Group, Block, and Error Type (smallest $F(4, 27) = 5.45$, $p < .01$, for Group) and significant Group x Block, Group x Error Type, Block x Error Type, and Group x Block x Error Type interactions (smallest $F(4, 27) = 4.12$, $p < .01$, for Group x Error Type). Newman-Keuls tests showed that the Groups did not differ significantly at the end of retention testing with respect to either WMC or WMI errors. However, on the first block of reversal training rats with CH lesions exhibited significantly more WMI errors to cues that were previously rewarded but were no longer rewarded compared to each of the other lesioned groups and controls ($ps < .05$). In contrast, no differences in WMC errors were found among any of the groups on the first block of reversal training based on cues that were previously nonrewarded but currently rewarded. An ANOVA used to evaluate performance over all Blocks 1–5 of reversal training yielded significant main effects of Group, Block, and Error Type (smallest $F(4, 27) = 11.30$, $p < .01$, for Group) and significant Group x Block, Block x Error Type, and Group x Block x Error Type interactions (smallest $F(16, 108) = 3.26$, $p < .01$, for Group x Block). Newman-Keuls test revealed that rats with CH-lesions showed significantly more WMI errors to nonspatial cues previously rewarded but currently nonrewarded ($ps < .05$) on both Blocks 1 and 2. Newman-Keuls tests also showed that on Block 2 of reversal training, CH-lesioned rats exhibited significantly more WMC errors ($ps < .05$) than each of the other groups based on revisiting arms with previously nonrewarded but currently rewarded nonspatial cues.

Discussion

Histological analysis of the lesions in the three selective lesion groups indicated that the extent of the cell loss was similar for rats in the DH, IH, and VH Groups (e.g., 36, 37, 39%, respectively) with the lesions varying only in location within hippocampus. Even though there are the differences in afferent and efferent connections for the dorsal pole, intermediate

area, and ventral pole described in the INTRODUCTION, the effect of these lesions on acquisition and performance of the complex place and cue discrimination tasks was generally minimal. The one exception was that rats with lesions confined to the dorsal hippocampus (DH) were impaired on the spatial task (but not the cue task) on the first block of 10 trials, making significantly more working memory errors. Given that the dorsal hippocampus is the area of greatest concentration of 'place cells' with discrete receptive fields that respond to specific locations within the environment (Muller, 1996; O'Keefe and Nadel, 1978), this impaired performance on the place task early in training is not too surprising. It is worth noting that (with the above exception) none of the selective lesion groups differed from controls in either the types of errors made in acquisition or in subsequent retention and reversal testing.

Bast, et al. (2009) reported that the intermediate zone of the hippocampus was needed for behavioral performance requiring rapid place learning in the water maze where the platform location changed each day. However, the intermediate area was not necessary in an incremental reference-memory version of the task that involved multiple trials in the same location over several days. We also found that damage confined to the intermediate hippocampus produced no impairment in reference memory on the spatial version of the radial maze task – a task that involved reinforcing the same spatial arms on multiple trials over many days. Thus, assuming that encoding the location of baited arms in the radial maze depends on an incremental learning process similar to that involved in learning the location of a hidden platform in a water maze, the results of the present study are consistent with the hypothesis that the intermediate hippocampus is not needed for incremental learning about spatial cues. We also found that reference memory (e.g., incremental learning) based on nonspatial cues failed to be impaired following lesions of the intermediate hippocampus. This latter finding is not surprising given that the present results, together with other findings, indicate that reference memory with nonspatial cues is not affected even following removal of the entire hippocampus (Jarrard, 1983, 1993; Jarrard, Bowring, & Davidson, 2004).

In discussing the findings that the intermediate zone of the hippocampus was needed for rapid learning about spatial cues, Bast et al. (2009) advanced the hypothesis that damage to the intermediate hippocampus impaired the ability of rats to translate place learning into "... appropriate search and approach behavior (similar to the task of returning to a novel place where you parked your car)" (p. 731). We suggest that spatial working memory performance in our radial maze task also requires rats to translate learning about spatial cues into appropriate search and approach behavior. Specifically, avoidance of errors in the radial maze task requires rats to rapidly encode the outcome of visiting one location in the radial maze and to use that information to identify and approach baited arms that had not been visited earlier in the trial. Despite this apparent conceptual similarity, we found no evidence that either spatial or nonspatial working memory performance in the radial maze depended on the structural integrity of the intermediate segment of the hippocampus. Thus, it would seem that the effects of damage to the intermediate hippocampus observed in the water maze task may not extend to the behavioral expression of rapid learning about either spatial or nonspatial cues in the radial maze.

In agreement with other research findings, rats that had all of the hippocampus removed (CH Group) were especially impaired in handling spatial information, making many RM and WM errors on the spatial version of the task. In contrast, in the same rats RM performance on the nonspatial cue task was unaffected but nonspatial WM performance *was* especially impaired early in training. So, how is one to interpret the increase in WM errors that were found on both the spatial and nonspatial cue tasks following complete removal of the hippocampus? In our view, this indicates that the complete hippocampus is necessary for correct performance based on the rapid encoding of both spatial and nonspatial information.

Damage limited to each of the septo-temporal regions (dorsal, intermediate, ventral) had minimal effects on incremental learning – only when all of hippocampus was removed was learning in the radial maze adversely affected. (As noted above, an exception was the difficulty found in DH rats but this was limited to early in training and only on the spatial version of the task.) It has been found that even with complete removal of hippocampus, slow learning of an incremental version of the water maze task can occur (Morris et al., 1990; Whishaw and Jarrard, 1996). Obviously, task difficulty is an important variable to consider when trying to determine whether or not the necessary spatial information can be utilized following removal of the hippocampus. In those cases where spatial learning is possible without a hippocampus, it is assumed that the necessary storage of learning and relevant information occurs in the neocortex (McClelland et al., 1995; Nadel and Moscovitch, 1997). From the neocortex there are a number of routes other than through hippocampus by which the relevant information can eventually come into contact with behavioral control systems (Swanson, 2000).

Our present findings also have implications for understanding the nature of the rapid, hippocampal-dependent, associative learning process suggested above. With both spatial and nonspatial cues, WM performance in the radial maze depended on the ability of rats to refrain from returning to arms that had already been visited within a trial. In addition to making more overall WM errors compared to controls and rats with subtotal hippocampal lesions, we found that rats with total hippocampal damage were significantly more likely to revisit arms that had been previously baited on a trial (i.e., making WMC errors) compared to arms that had not been baited (WMI errors). This outcome was obtained with both spatial and nonspatial cues. Thus, at least part of the deficit in the expression of rapid learning in behavioral performance might be attributed to a reduced ability to inhibit responding to previously rewarded, but currently nonrewarded, spatial and nonspatial cues. (See the review by Davidson and Jarrard, 2004 for a more complete description of this kind of inhibitory learning.) The above deficit may also be seen as a specific example of a deficit found in rats without a hippocampus in the ability to resolve a ‘predictable ambiguity’ (Morris, 2006) that occurs when a single cue (e.g., an arm insert or spatial location in our radial maze) is associated with one outcome (food reward) under some conditions (during an initial visit) but not under other circumstances (as on a second visit during the same trial).

Testing for retention of the postoperatively learned nonspatial cue task was carried out nine weeks following the end of acquisition. The general pattern of results obtained for all lesion and control groups was that both nonspatial RM and WM errors increased on the first block of testing relative to the last block of acquisition training, and then performance recovered

over the remaining retention trials. Thus, retention of nonspatial RM and WM was not impaired for rats with complete or any of the subtotal lesions relative to controls. Comparison of WMC and WMI errors for all groups supported the same conclusion. These findings provide further support for the view that the necessary and underlying changes at the neuronal level for this kind of incremental learning must occur and be represented outside of hippocampus -- presumably in neocortex (McClelland et al., 1995).

In addition to obtaining information regarding inhibitory learning in the various groups by analyzing the types of working-memory errors made in acquisition, the experiment concluded with reversal training where previously rewarded and nonrewarded nonspatial cues were reversed. Because error rates were low and the groups did not differ at the end of retention testing, we were able to test the effects of each lesion type on reversal learning under conditions where concerns about differential savings of previous learning among the groups were minimized. As one might expect, at the outset of discrimination reversal the rats persisted in choosing arms with cues that had previously been correct but were not now baited. We found that RM performance was similarly affected for all groups throughout reversal training; however, this was not the case for WM performance. At the outset of discrimination reversal testing, rats with complete hippocampal lesions made more WM errors compared to each of the other lesion groups and this difference persisted, although nonsignificantly, across several blocks of reversal training. The results indicated that compared to each of the other lesion groups, rats with complete hippocampal removal made more WMI errors during reversal; that is, they continued to revisit the arms with cues that had been but were no longer correct. The tendency to make WMC errors in reversal (i.e., revisit arms that were baited during reversal, but had been previously unbaited during training and retention testing) did not differ for rats with complete hippocampal lesions relative to the other groups at the beginning of reversal training. However, after several trials of reversal, the CH rats were found to make more WMC errors compared to the other groups.

Given the pattern of errors made by rats without a hippocampus in original acquisition, the errors in reversal are what one would expect if the animal had a problem with learned inhibition. That is, rats with complete hippocampal lesions tended to persist in responding to previously rewarded and now nonrewarded cues, and began to exhibit a tendency to revisit rewarded arms during reversal training despite the fact that reward in those arms had already been collected. It is important to point out that neither lesions of the septal pole, intermediate hippocampus, nor ventral pole resulted in rats differing from controls in learning to switch responding to nonspatial cues when the reinforcement contingencies were changed. Thus, even though projections from the intermediate and ventral pole regions are more closely connected to prefrontal cortex and subcortical structures like striatum (Cenquizca & Swanson, 2007), reversal learning involving choices of nonspatial cues failed to be differentially affected.

In a modified 8-arm radial maze procedure that involved choosing a different 4 arms that were illuminated each day, McDonald, et al. (2006) reported that large neurotoxin lesions of the dorsal and ventral hippocampus did not affect acquisition but that subsequent reversal of the correct, baited arms resulted in an enhanced ability to reverse in rats with ventral lesions.

The facilitated reversal compared to controls was interpreted as support for the ventral lesions having interfered with acquisition of a context-specific inhibitory association normally accrued during original learning of the visual discrimination. Such an interpretation generally supports the view that the hippocampus plays a role in learned inhibition (Chan, et al., 2001; Davidson and Jarrard, 2004). Both the nature and extent of the lesions and the very different behavioral testing procedures used in this research prevent direct comparisons with the present experiment but do suggest a need for further research.

It is interesting that the selective lesions limited to the three hippocampal regions (dorsal, intermediate, ventral) had minimal effects on learning and memory in our tasks, while removal of all of hippocampus resulted in major impairments in handling spatial information and in learned inhibition. A similar lack of effects of partial lesions (dorsal vs. ventral) was recently reported by Lehmann et al. (2010) using a fear-potentiated startle procedure but rats with complete hippocampal lesions showed a significant deficit. While each of the three septo-temporal regions have distinctive patterns of afferents and efferents, it is important to note that the underlying neuronal circuitry suggests there are a number of possible routes for interaction (Fanslow and Dong, 2010). Certainly, as the amount of damage to hippocampus is increased one would expect greater involvement of the different regions. There have been a number of experiments designed to study the effects of varying overall amount of damage to hippocampus and location of damage within the structure (Broadbent et al., 2004; Moser et al., 1993, 1995). In one of the earlier studies Moser, et al. (1993) found that at least 20% of dorsal hippocampus had to be lesioned for performance to be impaired on the Morris water maze, while damage to almost all the ventral half of hippocampus was required for performance to be affected. More recently, Broadbent, et al. reported that 30 – 50% damage to the dorsal area and greater than 50% to the ventral area were needed for impaired spatial impairment in the water maze, while on a different task 75 – 100% damage to hippocampus was required for impaired object recognition. Given the major differences between the behavioral testing procedures used in these and other studies as compared to the incremental testing procedures employed in our study, and the fact that we were primarily interested in location of the damage within hippocampus while keeping total amount of damage similar, it is difficult to make meaningful comparisons. However, it would be interesting to know what performance measures on our radial maze tasks would be more affected as location within the hippocampus is varied while amount of damage is increased.

The present findings using selective ibotenate lesions of hippocampus limited to different regions along the septo-temporal axis (dorsal pole, the intermediate region, ventral pole) show an overall lack of effects on incremental reference-memory tasks in acquisition, retention, and reversal learning of two equally complex discrimination tasks designed to require the utilization of spatial vs. nonspatial cue information and two different memory processes (reference memory, working memory). The one exception was that damage to the dorsal pole of the hippocampus resulted in a selective impairment only on the spatial but not the nonspatial task. Further, the impairment was limited to the first 10 trials. While reference memory performance was in general agreement with the idea that incremental learning processes do not depend on the structural integrity of the intermediate hippocampus, the present findings also indicate that WM performance, which would seem to be based on the expression in performance of rapid learning within a trial, was unaffected following lesions

of the intermediate hippocampus. Thus, at present, the generality of the finding that behavioral performance based on rapid learning depends on the intermediate zone of the hippocampus (see Bast et al., 2009) cannot be extended to performance of the limited baiting radial maze procedure used in the present study.

In contrast with the selective lesions described above, removal of all of hippocampus was followed by an inability to utilize the spatial information required to learn the spatial task while having minimal adverse effects on utilization of the intramaze cue information. Interpretation of the pattern of error data obtained on both the spatial and nonspatial cue tasks suggests that in addition to an impairment in spatial learning and memory, complete removal of the hippocampus also interferes with the ability to inhibit responding to cues that signal reward under some conditions but not under others.

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Figure 1.

Photomicrographs of coronal sections at five anterior-posterior (AP) levels for a control animal (left) and a representative rat from each of the four lesion groups. Abbreviations are as follows: Complete Hippocampus (CH), Dorsal (DH), Intermediate (IH), and Ventral Hippocampus (VH) Group. The AP stereotaxic levels are approximate and are taken from Paxinos and Watson (1989).

Figure 2.

The figure depicts mean reference memory (RM) errors with spatial cues (left panel) and nonspatial cues (right panel) over all five, 10-trial blocks of training, for rats that received lesions of the complete hippocampus (CH), lesions limited to the dorsal (DH), the ventral (VH) or the intermediate (IH) hippocampal regions, and for control rats (C) with an intact hippocampus. Alphabetic indicators (a,b,c,d,e) correspond to each group (see legend) and denote groups that differ significantly ($p < .05$) on a given block. Vertical bars depict standard error of the mean (SEM).

Figure 3.

The figure depicts mean working memory (WM) errors with spatial cues (left panel) and nonspatial cues (right panel) over all five, 10-trial blocks of training, for rats that received lesions of the complete hippocampus (CH), lesions limited to the dorsal (DH), the ventral (VH) or the intermediate (IH) hippocampal regions, and for control rats (C) with an intact hippocampus. Alphabetic indicators (a,b,c,d,e) correspond to each group (see legend) and denote groups that differ significantly ($p < .05$) on a given block.) Vertical bars depict standard error of the mean (SEM).

Figure 4.

The figure depicts mean working memory correct (WMC) and working memory incorrect (WMI) errors with spatial cues (left panel) and nonspatial cues (right panel) over all of training, for rats that received lesions of the complete hippocampus (CH), lesions limited to the dorsal (DH), the ventral (VH) or the intermediate (IH) hippocampal regions, and for control rats (C) with an intact hippocampus. * denotes a significant difference ($p < .05$) between WMC and WMI errors. Vertical bars depict standard error of the mean (SEM).

Figure 5.

The figure depicts mean reference memory (RM) errors with nonspatial cues over the last block of retention testing (left of the vertical dashed line) and over each block of reversal training, for rats that received lesions of the complete hippocampus (CH), lesions limited to the dorsal (DH), the ventral (VH) or the intermediate (IH) hippocampal regions, and for control rats (C) with an intact hippocampus. Vertical bars depict standard error of the mean (SEM).

Figure 6.

The figure depicts mean working memory (WM) errors with nonspatial cues over the last block of retention testing (left of the vertical dashed line) and over each block of reversal training, for rats that received lesions of the complete hippocampus (CH), lesions limited to the dorsal (DH), the ventral (VH) or the intermediate (IH) hippocampal regions, and for control rats (C) with an intact hippocampus. Alphabetic indicators (a,b,c,d,e) correspond to each group (see legend) and denote groups that differ significantly ($p < .05$) on a given block. Vertical bars depict standard error of the mean (SEM).

Figure 7.

The left panel of the figure depicts mean working memory correct (WMC) errors on the last block of retention testing (left of the dashed line) and mean working memory incorrect (WMI) errors on each block of reversal training. The right panel of the figure depicts mean WMI errors on the last block of retention testing (left of the dashed line) and mean WMC errors on each block of reversal training. All errors are with nonspatial cues for rats that received lesions of the complete hippocampus (CH), lesions limited to the dorsal (DH), the ventral (VH) or the intermediate (IH) hippocampal regions, and for control rats (C) with an intact hippocampus. Alphabetic indicators (a,b,c,d,e) correspond to each group (see legend) and denote groups that differ significantly ($p < .05$) on a given block. Vertical bars depict standard error of the mean (SEM).

Table 1Stereotaxic coordinates ^a for hippocampal lesion groups

Group Designation	AP (–)	ML (+/–)	DV (–)	Volume of IBO (in ul)
DH	2.4	1.0	3.0	0.05
	3.1	1.4	2.4	0.05
	3.1	3.0	2.7	0.10
	4.0	2.5	2.3	0.05
	4.0	3.6	2.5	0.05
IH	4.9	3.4	3.2	0.05
	4.9	4.8	4.0	0.05
	5.7	4.1	3.4	0.06
	5.7	5.0	4.3	0.07
	5.7	5.0	5.3	0.07
VH	4.4	4.4	6.7	0.05
	4.4	4.4	7.2	0.07
	4.9	4.8	6.5	0.05
	4.9	4.8	7.0	0.07
	5.7	5.4	6.0	0.06
CH	Injections were made at 30 sites (see Jarrard et al., 2004)			

Note: Abbreviations are as follows: DH, dorsal hippocampus; IH, intermediate hippocampus;

VH, ventral hippocampus; IBO, ibotenic acid.

^aBregma was used as the reference point to determine AP and ML sites, while all DV injections were calculated from dura at AP –5.2, ML +/- 4.1.