1-1-2009

Human analogues of rodent spatial pattern association, separation, and completion memory tasks

Meera Paleja
Ryerson University

Follow this and additional works at: <http://digitalcommons.ryerson.ca/dissertations>

Part of the [Cognition and Perception Commons](#)

Recommended Citation

Paleja, Meera, "Human analogues of rodent spatial pattern association, separation, and completion memory tasks" (2009). *Theses and dissertations*. Paper 490.

This Thesis is brought to you for free and open access by Digital Commons @ Ryerson. It has been accepted for inclusion in Theses and dissertations by an authorized administrator of Digital Commons @ Ryerson. For more information, please contact bcameron@ryerson.ca.

RF
469
P35
2009

HUMAN ANALOGUES OF RODENT SPATIAL PATTERN ASSOCIATION, SEPARATION,
AND COMPLETION MEMORY TASKS

by

Meera Paleja, B.Sc. (Hons.) York University, Toronto, June 2007

A thesis

presented to Ryerson University

in partial fulfillment of the requirements for the degree of

Master of Arts

in the Program of

Psychology

Toronto, Ontario, Canada, 2009

© Meera Paleja, 2009

I hereby declare that I am the sole author of this thesis.

I authorize Ryerson University to lend this thesis to other institutions or individuals for the purposes of scholarly research.

I further authorize Ryerson University to reproduce this thesis by photocopying or by other means, in total or in part, at the request of other institutions or individuals for the purpose of scholarly research.

Human Analogues of Rodent Spatial Pattern Association, Separation, and Completion

Memory Tasks

Master of Arts, October 2009

Meera Paleja

Psychology

Ryerson University

Spatial pattern association (SPA), separation (SPS), and completion (SPC) have been shown to be dependent on distinct subfields of the hippocampus in rodents, but these processes have not been assessed using analogous paradigms in humans. In this thesis I developed three computerized tasks analogous to well-established rodent tasks used to assess these processes. Participants showed improved performance across trials in the SPA task, indicating increasing familiarity with the environment. Participants showed performance differences that were dependent on the amount of demand on the subprocesses used in SPS and SPC, specifically, poorer performance with decreasing separation distance between target and foil in the SPS task, and poorer performance with decreasing number of wall cues in the SPC task. These results support sensitivity of the tasks to these subprocesses in humans. These tasks set the stage for valuable future directions including the use of these tasks with imaging and clinical populations.

Acknowledgments

Over the course of my M.A. studies, I have been privileged to have had the support and guidance of a number of people. First and foremost, I could not have done this without my parents, who taught me the importance of education and hard work, and also made me aware of how fortunate I am to be able to pursue my goals with relatively few boundaries. Ba taught me the importance of enjoying life, smiling, and always making an effort to connect with others, no matter how busy or stressed out I might be. Raj and Radha taught me that life is about more than what you read about in books and journal articles. In their words, it's not enough to know all about the human brain- you have to be able to use yours.

Thanks to my labmates, Ronak and Maddy, who were able to provide insight into my project, ask relevant and important questions, and really made me think about what I was doing on a larger scale. Also, thanks to them for putting up with my hogging the testing room. Thank you to the lab research assistants, Adina and Vanessa, who helped me get the participants I needed in the nick of time.

To my committee member Julia Spaniol, thank you for your suggestions, insight, and perspective into my project.

Finally and most importantly, thanks to my advisor Todd Girard, for his limitless patience, attention to detail, and knowledge. I feel privileged to be your student and look forward to working with you in the years ahead.

Table of Contents

Introduction.....	1
Spatial Memory and the Hippocampus	1
Virtual Human Analogues of Rodent Spatial Memory Tasks.....	4
Hippocampal Anatomy	6
Spatial Memory Subprocesses	8
Summary	19
Main Thesis Objective	19
Methods and Results	22
Participants	22
General Experimental Paradigm	23
Experiment 1 Procedure	25
Experiment 1 Results	28
Experiment 2 Procedure	31
Experiment 2 Results	32
General Discussion	37
SPA.....	37
SPS	39
SPC	40
Limitations and Future Directions	43
Conclusions	45
References.....	47

List of Figures

Figure 1. Abstract fractal patterns on Arena walls.

Figure 2. Pattern Association task.

Figure 3. Pattern Separation task from Experiment 1.

Figure 4. Pattern Completion task.

Figure 5. Pattern Separation task from Experiment 2.

Figure 6. Pattern Association mean accuracy across bins of 7 trials For Experiments 1 and 2.

Figure 7. Pattern Separation task accuracy in Experiment 1 (original) and Experiment 2.

Figure 8. Pattern Completion mean accuracy in Experiments 1 and 2.

While the hippocampus has long been renowned for its general role in spatial memory in rodents and humans, recent research has identified the importance of specifically considering subprocesses of spatial memory. In this thesis, I first provide an overview of the hippocampus' role in episodic memory more generally and spatial memory in particular. I then discuss the relevance of virtual analogues of rodent spatial memory tasks and how they have been used to study spatial memory in humans. The general anatomic features of the hippocampus are discussed, as they are useful for understanding relations between hippocampal subregions and spatial memory subprocesses. Then various memory-related functions of the hippocampus are considered, particularly spatial memory and the subprocesses of pattern separation, association, and completion as well as rodent evidence, computational models, and human studies examining the neural correlates of these tasks. The main objective of my thesis is the development of human analogues of various rodent tasks that have been shown to be sensitive to hippocampal subprocesses in rodents.

Spatial Memory and the Hippocampus

Explicit memory refers to forms of memory accompanied by conscious awareness and includes both semantic (fact-based) and episodic (event-based) memory. The hippocampi are bilateral structures in the medial-temporal lobe (MTL) that are highly involved in various aspects of long-term explicit memory, including both semantic and episodic memory.

To the extent that episodic memory is defined as memory for a personal event in a particular spatial-temporal context, spatial memory is integral to forming a coherent episode and hence a critical component of episodic memory. Remembering the spatial context of events and being able to navigate and form a "cognitive map," or an allocentric, viewer-independent mental representation that allows one to remember and navigate a spatial environment (O'Keefe &

Nadel, 1978), is essential for day-to-day functioning. For example, spatial memory is required to remember where one parked one's car and also to navigate the route one uses to get to one's workplace. Various lines of evidence support the notion of hippocampal involvement in spatial memory in both rodents and humans.

One seminal study found that hippocampally lesioned rats performed poorer than controls on the Morris Water Maze task, a well-established measure of spatial memory. In this task, rats are submerged into a pool of opaque water and must search to find a hidden platform under the surface to escape. Then, placed in a random starting location, they must use distal cues from the room to assess their whereabouts in order to relocate the platform more efficiently on subsequent trials. Rats with hippocampal lesions were significantly worse at acquiring the location of the platform than rats with superficial cortical lesions, sham surgery, and no surgery (Morris et al., 1982).

The finding of hippocampal involvement in spatial memory has also been extended to humans. One study found that the gray matter volume of the right hippocampus correlated positively with years of experience as a taxi driver (Maguire et al., 2003). Results further suggested that larger hippocampi may result from increased duration and frequency of use of spatial information, as opposed to navigational expertise per se. A subsequent study found that a former taxi driver with Alzheimer's disease and bilateral hippocampal damage was unable to navigate around streets in London with which he had much prior experience. Specifically, using a virtual reality driving simulator, he was only able to find a location when he could take commonly used roads, but not when he was required to use an alternate, uncommon route (Maguire, Nannery, & Spiers, 2006). Therefore, it seems that the hippocampus is required for facilitating flexible navigation even in places learned long ago.

One viewpoint is that spatial memory, including memory for object-location or location-location associations, is just a special case of more general contextual memory, or the ability to form associations between various aspects of the environment. Specifically, the hippocampus is important for spatial memory because it is involved in forming relations between objects and locations (Eichenbaum, 2000).

Another view about the nature of the hippocampus' role in spatial memory is that the hippocampus functions to support a "cognitive map" (O'Keefe & Nadel, 1978). According to this view, the spatial arrangement of the environment is stored in the hippocampus as a map and the hippocampus is important for both the formation and storage of these maps. Initial support for this view came from the finding that certain "place cells" in the hippocampus of freely moving rats fired maximally when rats were in certain locations. These neurons are thought to be involved in the encoding of these specific spatial locations (O'Keefe & Dostrovsky, 1971).

Rolls (1996) suggested that primates, including humans, possess analogous "spatial view" cells in the CA3 subregion of the hippocampus that is related to the more sophisticated visual system of primates. Thus, he suggests one major function of the primate hippocampus is to associate spatial locations with objects in the environment. In other words, there is no need for the primate to actually visit the place, as rats would have to do. Rather, simply viewing an object at some location is adequate for the formation of object-place memories that can lead to a later recall of the location of the object observed. In this sense, spatial memory abilities in rats and humans to some extent are distinct, given that the two species have evolved quite differently. Nonetheless, rodent studies have done much to illuminate understanding of human spatial memory and its underlying neural correlates, indicating much evolutionary continuity in spatial

memory abilities overall. The use of analogous tasks with humans and rodents will assist in identifying the limits of this evolutionary continuity in spatial memory.

Virtual Human Analogues of Rodent Spatial Memory Tasks

Rodent studies have played a critical and invaluable role in illuminating the nature of memory processes mediated by the hippocampus. Work with rodents allows the use of experimental designs and manipulations that could not be implemented in human populations for ethical or practical reasons. Specifically, the experimental induction of lesions has allowed researchers to gain a greater understanding of the neural substrates essential for particular spatial memory tasks.

One advantage of lesion studies in rodents is that they provide experimental control that imaging and lesion studies in humans cannot. For instance, they allow researchers to lesion a particular region and thus assess more definitively if it is necessary for a particular task and also which regions are not. Neuroimaging studies in humans differ from rodent lesion studies in that they tell us what brain regions are *involved* during a task, not which areas are *necessary*. To this end, one benefit of imaging studies is that they may reveal involved regions not evident or not studied using lesion work. A limitation of studying lesions in humans is that the damage typically does not occur to a circumscribed region making data much more difficult to interpret. Furthermore, it is often not possible to compare pre- and post-lesion performance in humans due to ethical and practical reasons. In this regard, among others, rodent studies remain informative and useful for understanding brain-behaviour relations.

However, a key issue surrounding rodent studies is the generalizability of findings to human populations, specifically, the extent to which neural regions implicated in rodents when performing certain tasks are also implicated in humans. In recent years, a number of researchers

have made efforts to address this limitation by designing spatial memory tasks that closely parallel those used with rodents. These analogous tasks allow for the formulation and testing of hypotheses concerning expected neural activation in humans during task performance. According to this line of thinking, human spatial memory tasks that are a close approximation of rodent tasks that require certain brain regions should involve similar or identical neural regions in humans. Thus, the design of tasks that resemble rodent tasks is the first step to delineating the neural regions involved when humans engage in these tasks. One major advantage of using analogues of rodent tasks is that they enable us to bridge the well-established, well-controlled, and finer-grained studies conducted with rodents with human studies. Although the regions involved in humans may end up being dissimilar from those involved in rodent tasks, rodent tasks provide a useful "starting point" to predict neural correlates of analogous spatial memory tasks in humans.

In an attempt to more closely emulate tasks used in the rodent spatial memory literature, a number of different computerized analogues of rodent spatial memory tasks have been developed for use with human populations in recent years (e.g. Astur et al., 2005; Canovas, Espinola, Iribarne, & Cimadevilla, 2008; Hanlon et al., 2006; Jacobs, Laurance, & Thomas, 1997; Jacobs, Thomas, Laurance, & Nadel, 1998; Laurance et al., 2002; Livingstone & Skelton, 2007; Shipman & Astur, 2006; Shore et al., 2001; Skelton, Ross, Nerad, & Livingstone, 2006; Thomas, Hsu, Laurance, Nadel, & Jacobs, 2001). These tasks involve three-dimensional computerized virtual environments that participants navigate through, typically using a joystick or keyboard. For instance, Canovas et al. (2008) developed a virtual version of the rodent cheeseboard maze. In this computerized task, participants were presented with a room full of boxes and asked to discover hidden rewards as efficiently as possible. Jacobs et al. (1998) developed a computer

program called CG-Arena that resembled the dry-land version of the Morris water maze, which they used to assess place learning. Virtual versions of the Morris water maze have also been developed and used in conjunction with fMRI. These studies report hippocampal activation during the virtual maze, suggesting convergence across species for the involvement of the hippocampus in the Morris water maze task (Astur et al., 2005; Shipman & Astur, 2008). These tasks have also been used to assess spatial memory deficits in clinical populations associated with hippocampal dysfunction, including traumatic brain injury (Livingstone & Skelton, 2007; Skelton et al., 2006) and schizophrenia (Hanlon et al., 2006).

These tasks have been useful in providing cross-species convergence of hippocampal function and dysfunction in spatial memory tasks. However, this thesis is innovative in developing human analogues to assess more specific subprocesses of spatial memory. This direction is important because recent theoretical and empirical work indicates that spatial memory may be better understood in terms of its subprocesses that differentially involve unique subregions of the hippocampus in rodents.

Hippocampal Anatomy

Although the general role of the hippocampus in spatial memory has been well-established, recent studies have identified functional dissociations among hippocampal subregions. To fully appreciate these dissociations, an understanding of hippocampal anatomy is useful and important.

The MTL includes the region of forebrain along the ventromedial surface of the temporal lobe. In addition to the hippocampus, it includes the amygdala and parahippocampal gyrus, which contains the parahippocampal, perirhinal, and entorhinal cortices (Sweatt, 2004). The name hippocampus derives from the Greek word meaning seahorse, because of its curved shape

in the coronal view (Duvernoy, 2005). The anterior end of the hippocampus is adjacent to the amygdala and there are strong interconnections between these two structures. The fornix extends from the posterior end of the hippocampus and primarily connects it directly with subcortical regions (Sweatt, 2004). The central location of the hippocampus in the brain is ideal when considering its role in integrating converging multimodal sensory information.

The hippocampus is divided into subregions based on differences in cellular morphology, connectivity and development. Hippocampal subregions are labeled by CA fields, where CA refers to *cornu ammonis* in Latin, meaning ram's horn. They are so named because of their curved shape. Subregions of the hippocampus include the dentate gyrus (DG), CA1, CA2, CA3 and CA4. CA1 and CA3 are the largest and most easily identified subfields in the hippocampus. In terms of information processing, the CA1 neurons are the main output to the fornix. The main input into the hippocampus is the entorhinal cortex, via which two projection pathways terminate onto hippocampal pyramidal neurons: a primary one to DG and second to CA1 (Duvernoy, 2005).

Two cortical projection pathways that converge onto the hippocampus are the dorsal and ventral visual streams (Duvernoy, 2005). The dorsal stream is often referred to as the "where/action" path. This stream is essential for indicating where in space an object is located as well as guiding interactions with that object. The dorsal stream preferentially connects to a polysynaptic intrahippocampal path that travels from the entorhinal cortex to the dentate gyrus and then to the CA3 and finally CA1 subfield. In contrast, the ventral stream is often referred to as the "what/perceptual path" and is important for identifying or recognizing an object. This stream preferentially connects to a direct perforant path from the entorhinal cortex to the CA1 subfield (Duvernoy, 2005). Thus, the hippocampus appears to be integrating information about

both what an object is as well as where it is located, indicating that it plays an important role in processing and remembering the spatial location of objects in the environment. Further, the different subfields of the hippocampus also appear to have differential functional relevance.

Spatial Memory Subprocesses

Rodent studies and computational models suggest different subprocesses of spatial memory may be preferentially dependent on different hippocampal subfields. In a review, Kesner and Hopkins (2006) categorize spatial memory tasks into the subprocesses of pattern separation, pattern association, and pattern completion.

It is important to note that there is conceptual overlap among these subprocesses of spatial pattern separation, association, and completion. Specifically, while they all surround the concept of associative memory, pattern separation probes more precisely into places and times as individual components, while pattern completion probes the ability to not only recognize a well-learned association but fill in partial or incomplete information. These processes are described in further detail in the following sections.

Pattern Separation

Pattern separation is the process of transforming similar memories into different nonoverlapping representations (Bakker, Kirwan, Miller, & Stark, 2008). In other words, pattern separation involves the orthogonalization of both objects and events in the environment spatially and temporally. The hippocampus appears to be involved in separating events in space and time so that one event can be remembered as distinct from another event (Kesner & Hopkins, 2006). Spatial pattern separation is important for remembering where something happened. In order to support contextual processing and thus episodic memory, it is necessary to be able to optimally

separate stimuli in the environment in space, allowing us to form unique representations of the places where events occur.

Pattern Separation in Rats. Gilbert, Kesner, and Lee (2001) showed that spatial pattern separation may be dependent on a different subfield than spatial-temporal pattern separation. For spatial pattern separation, a delayed-matching-to-place task was used. Rats were trained to displace an object covering a food well that was baited. At test, they were to choose between two identical objects, one of which covered the same well as the sample object (correct) or a second that covered a different unbaited well (incorrect). Difficulty was manipulated by increasing or decreasing the distance between the two objects. The further apart the two objects, the easier it was to discriminate between them. For the spatial-temporal order pattern separation task, a radial arm maze was used. A sequence of eight arms was presented to the animal by sequentially opening each door one at a time to allow access to the food reward at the end of the arm. On the choice phase, doors for two of the arms were presented and the rat had to enter the arm that had occurred earlier in the sequence to get a reward. Similar to the spatial task, as the temporal distance in the sequence between the two choice arms decreased, the difficulty increased. The results showed that DG lesions in rats resulted in a deficit on the spatial task but not the spatial-temporal task, whereas CA1 lesions resulted in a deficit on the spatial-temporal task but not spatial task. These findings indicate that DG may be more important for spatial pattern separation, while the CA1 may be more important for temporal pattern separation.

In a subsequent study, the same spatial pattern separation task was used with rats with CA3 lesions (Gilbert & Kesner, 2006). These rats all showed a uniform deficit compared to controls across all conditions. The authors suggested deficits in this spatial pattern separation task in CA3-lesioned rats could be indicative of a spatial working-memory deficit rather than the

involvement of CA3 in spatial pattern separation. Specifically, DG lesions in rats showed graded deficits across separation conditions (performing at chance at the two closest separations, and identical to preoperative performance and controls at the two furthest distances), showing that the DG lesions disrupted the ability to discriminate between spatial locations as opposed to the working memory demands of the task. Conversely, the proportionally poorer performance of the CA3 lesioned rats shows, according to the authors, that their deficits are more likely to be due to a spatial working memory deficit that affects performance equally across separation conditions. However, this could also just be a result of some other general deficit that impairs even more basic task performance, for instance, a general spatial learning deficit. It is important to note that these findings do not preclude the possibility that CA3 is also involved in pattern separation.

Both rodent studies and computational models implicate the DG as crucial for pattern separation in the hippocampus. Spatial pattern separation is impaired with dorsal DG lesions and spared with dorsal CA1 lesions (Goodrich-Hunsaker, Hunsaker, & Kesner, 2008). This result is in line with computational models that suggest the DG orthogonalizes input by removing redundant information before it reaches the CA3 cells (Becker, 2005; Rolls, 1996).

The role of CA3 in pattern separation is less clear-cut. According to O'Reilly and McClelland's model (1994), CA3 might act to store representations already separated by the DG. Leutgeb, Leutgeb, Moser and Moser (2007) suggest that a dual set of mechanisms involving the DG and CA3 are involved in pattern separation. When there is only a slight change in the environment at a fixed location, pattern separation occurs in the DG and CA3. Specifically, cortical inputs change their pattern of correlated activity in the DG and the cells in the DG begin firing at different rates. This disambiguation of firing patterns is transferred to the CA fields via sparse connections between granule cells in the DG and pyramidal cells in the CA fields.

Connections between granule cells in the DG and CA3 pyramidal cells may allow for these uncorrelated firing patterns to transfer to the CA3 cells. These firing patterns lead to the disambiguation of memories in the hippocampus. When there are greater changes in the environment, pattern separation involves an independent cell population in CA3. Others have also suggested the process CA3 engages in might differ as a function of environmental change (e.g. Lee, Yoganarasimha, Rao, & Knierim, 2004; Leutgeb & Leutgeb, 2007; Vazdarjanova & Guzowski, 2004). Further study is needed to fully understand the role of CA3 in pattern separation in rodents. Nonetheless, it seems clear that slightly different aspects of spatial pattern separation depend upon the DG and CA3 cell fields.

Pattern Separation in Humans. The hippocampus appears to play a critical role in spatial pattern separation in humans too. Hopkins and Kesner (1993) found impairment of hypoxic participants with hippocampal atrophy on a geographical spatial distance task where participants were asked during the study phase to remember cities on a map of New Brunswick. During the test phase, participants were presented with two cities and asked to indicate which one was the furthest east. Spatial distances were manipulated, with 0, 2, 4, or 6 cities from the study phase in between the two test cities presented. The hypoxic subjects performed on a gradient corresponding to the spatial separation but poorer on all conditions compared to controls. Given that hypoxia tends to preferentially affect the CA1 subregion (Duvernoy, 2005), this indicates that the CA1 subregion may be important for spatial pattern separation in humans. However, subfield-specific damage was not assessed in this study. Therefore, we can only conclude that the hippocampus appears to play a role in spatial pattern separation in humans.

Moreover, the hippocampus appears to be more important than other MTL structures for pattern separation. Kirwan & Stark (2007) administered a continuous recognition task to

participants in a high-resolution functional magnetic resonance imaging (fMRI) scanner. In a continuous recognition paradigm, on each trial, a presented object might be new, a repetition of an object viewed previously, or a slightly altered version of a previously viewed object (i.e., a lure). Participants were asked to state whether the object was new, old, or similar to an object they had seen previously. Pattern separation was inferred by participants successfully discriminating a lure from an old object. In other words, they had to identify it as a “similar” object. This “similar” option was important because calling a lure “new” could just mean the participant never encoded the original variation of this cue. Identifying a lure as “similar” meant they could correctly identify they had seen something similar before, but had successfully “separated” the two as distinctive stimuli, despite their similarities. Activity in the hippocampus, unlike the parahippocampus, successfully discriminated between correctly identified true stimulus repetitions, correctly rejected presentations of lure stimuli, and false alarms to similar lures. There were no differences in subregional involvement when subjects engaged in pattern separation. In other words, the pattern of activity in CA1, CA3/DG and the subiculum were similar.

Bakker, Kirwan, Miller and Stark (2008) used high-resolution fMRI to measure hippocampal activity during a memory encoding task. Subjects viewed pictures of everyday objects. Similar to Kirwan & Stark (2007), a continuous repetition paradigm was used in which a presented object might be new, a repetition of an object viewed previously, or a slightly altered version of a previously viewed object, a lure. To parallel the rodent literature, an incidental encoding, rather than intentional encoding paradigm was utilized by asking participants to make an indoor/outdoor object judgment with no indication that they would later be given a memory test, rather than old/new/similar memory judgment. They hypothesized that if pattern separation

was taking place in a certain subregion, the lure would be treated more like a new stimulus than a repetition, as measured by fMRI. Specifically, if the subregion is engaging in pattern separation, the subregion should show similar activity to the presentation of the lure as it did to the initial presentation of the similar stimulus. They found activity demonstrating a strong bias toward pattern separation that was limited to the CA3/DG region. Even though the resolution used was very high (1.5mm) for fMRI, it was still not possible to confidently isolate CA3 from the DG and thus, they referred to it as a single region. Interestingly, this task produced findings of subregional involvement that paralleled findings in rodent literature, that is, a bias for pattern separation in the DG/CA3, while the former study did not show any subregional differences.

Both of the aforementioned studies employed similar paradigms, with a few important distinctions that could account for the dissimilar findings. First, pattern separation was operationalized differently. Kirwan and Stark (2007) used behavioural measures to infer this process, while Bakker et al. (2008) used neural activation to infer this process. Second, the former study assessed regions involved during encoding, while the latter assessed regions involved at retrieval. Third, Bakker et al. (2008) used incidental encoding in an attempt to more closely emulate rodent tasks. To our knowledge, these are the only studies that have examined the hippocampal subregions involved in pattern separation in humans. Although these tasks assess pattern separation, they differ from the well-established rodent paradigms that support differential subregional functions. Thus, the human analogue developed in this thesis will be useful for further subregional interrogation of human spatial memory and for drawing cross-species comparisons.

Pattern Association

In addition to pattern separation, pattern association is also necessary for remembering events, as it allows us to associate components of the environment or event with each other. The hippocampus and its subregions support the formation of arbitrary associations, including paired-associate learning. Spatial pattern association involves the binding of associations between objects/events with places, as well as among places (i.e., as required to construct a cognitive map). The hippocampus in rats and humans is critically involved in processing information associated with learning and subsequent retrieval of object-location (place) associations (Kesner & Hopkins, 2006).

According to his computational model of the role of memory in the CA3 subregion, Rolls (1996) suggests that a CA3 auto-associative network is responsible for the formation and storage of arbitrary associations. According to this model, the intrinsic, recurrent connectivity within CA3 allows various elements of an episode to be automatically integrated into a unified representation. In other words, the CA3 functions like its own network because of its recurrent connectivity within itself, making associations between various stimuli in the environment.

Pattern Association in Rats. In a recent study, Kesner, Hunsaker, and Warthen (2008) found that CA3 lesions disrupted the ability of rats to support arbitrary associations. For example, these rats were unable to associate an object and its spatial location. This finding could not be accounted for by lack of motivation or a deficit in working memory. Further, CA3-lesioned rats were only impaired on an episodic (different object-place associations at every trial) memory version of the task and unimpaired when the task was nonepisodic (same object-place association at every trial), suggesting the importance of the CA3 subregion in forming arbitrary

associations between objects and spatial locations. This finding is consistent with the computational model proposed by Rolls (1996), mentioned previously.

Gilbert and Kesner (2002) trained rats on a successive discrimination go/no go task to examine object-place paired associate learning. Two paired associates were used. A particular object (A) in one particular location (1) was reinforced, and another object (B) in a different location (2) was also reinforced. Mispairs, such as object A in location 2, were not reinforced. If the object was presented in its correctly paired location, the rat should displace the object to receive a reward, but if the object was in a mispaired location, the rat was to withhold displacing it. CA3-lesioned rats were impaired in associating an object with a spatial location, but not in associating an object with something without a spatial component, such as an odor. This suggests that the CA3 is important for paired-associate learning for spatial associations but not for nonspatial associations. A subsequent study from the same lab with a similar paradigm found that CA1-lesioned and DG-lesioned rats were not impaired in learning the paired association, while the CA3-lesioned rats were, suggesting the importance of the CA3 subregion, but not CA1 or DG in object-place paired-associate learning (Gilbert & Kesner, 2003).

Pattern Association in Humans. Memory for paired associations between objects and locations can be considered to rely on intact spatial pattern association processes, and numerous studies have examined paired-associate learning in humans (Kesner & Hopkins, 2006). In one such study by Stepankova, Fenton, Pastalkova, Kaline, and Bohbot (2004) participants were shown up to six objects on the floor of a circular curtained area for 10s. Then, participants were asked to mark off locations on a map of the area where the objects were located. They were also asked to put the objects back in their original locations. Right-hippocampal lesioned participants performed poorly compared to normal controls. In addition, there was an increased magnitude of

deficit with an increasing number of object-locations, suggesting the hippocampus plays a role in paired association memory in humans. However, the role of hippocampal subregional involvement in pattern association has not been systematically studied.

Pattern Completion

Pattern completion is also critical to episodic memory as it allows us to make inferences when given partial spatial information. Spatial pattern completion allows us to recall or generate well-established knowledge based on partial or incomplete spatial information. Computational models have suggested one potential mechanism for retrieval of episodic memory is pattern completion. According to this notion, an auto-associative network retrieves patterns of activity, or memories, based on partial or degraded information or cues (Kesner & Hopkins, 2006). For example, pattern completion might allow us to infer the location of our car in a parking lot when the cars surrounding it have changed or gone, and we can no longer use them as cues to locate our car. In this situation, we may use cues such as other cars, or landmarks such as lamp posts, trees, or the road to locate our car. In this case, the subset of available cues leads to the retrieval of a complete memory of where the car is located. The CA3 subregion appears to act as an auto-associator, and thus forms and stores episodic memories. The extensive recurrent collateral connectivity of the CA3 subregion allows for the retrieval of the entirety of the memory, based on the activation of a portion of the representation (i.e., a cue or subset of cues; Rolls, 1996; Rolls, 1997).

Pattern Completion in Rats. Gold and Kesner (2005) used a delayed matching-to-place task on rats with CA3 lesions. During the sample phase, rats removed a covering of a food well that could appear in one of five possible spatial locations. At the choice phase, rats were to find the same well with the proximal block removed and thus, needed to relocate it using the four

distal, extramaze cues provided in the room. After they reached stable performance, rats were then given lesions to the CA3 subregion. Subsequently they were tested on the same task, but with zero, one, two, three, or all four extramaze cues missing. In order to find the correct well efficiently, rats presumably have to mentally "fill in" or complete the arrangement of extramaze cues. Rats with CA3 lesions were impaired in pattern completion as indicated by a disproportionate linear increase in errors in comparison to controls as the number of available cues was reduced. This provides evidence for the role of CA3 in spatial pattern completion in rodents.

Nakazawa and colleagues (2002) ablated the *N*-methyl-D-aspartate (NMDA) receptor gene in the CA3 subregion of rodents. These rodents performed equivalent to controls on the Morris water maze task when all extramaze cues were present. However, when three out of the four extramaze cues were removed, control rodents showed the same level of recall as in the full-cue condition, whereas the mutant rodents were severely impaired on the task. Therefore, CA3 appears to be important for spatial pattern completion in rodents.

Pattern Completion in Humans. Ryan, Alhoff, Whitlow, and Cohen (2000) and Ryan and Cohen (2004) examined relational processing in normal controls and hippocampal amnesia patients. Participants were shown a scene, and later, participants examined a similar, but slightly altered scene. For instance, in an altered scene, an object may be moved to a different location in the scene or removed entirely. Eye-tracking equipment indicated that normal participants tended to spend more time looking at the area of the scene that was altered (the area where the object was originally presented) compared to unaltered areas of the scene at both short and long delays. This increased looking indicates they had knowledge that something was previously there and that a representation of this was activated. In other words, they were engaging in a process that

could be considered pattern completion. At short delays, the amnesic participants performed similarly to controls. That is, they spent an increased amount of time looking at the altered area of the scene. However, at long delays, the amnesic patients spent less time looking at the altered area of the scene compared to controls, suggesting an issue with the spatial pattern completion process. This study provides evidence for hippocampal involvement in spatial pattern completion. However, one issue with viewing this study as assessing pattern completion is that it does not involve a “well-learned” environment, posited to be a crucial component of pattern completion (Kesner & Hopkins, 2006).

Few studies have examined subregional hippocampal involvement in pattern completion in humans. In addition to pattern separation, the study mentioned previously by Bakker et al. (2008) examined subregional correlates of pattern completion. Because pattern completion involves well-established representations, images of common objects (e.g. rubber duck) were used. In this case, pattern completion was operationalized as the processing of a similar lure (e.g., rubber duck viewed from a different orientation) like a repetition of the original stimulus. In particular, if a brain region was involved in pattern completion, it should respond as though the similar lure is a repeated stimulus. This approach is based on the assumption that if a similar object is processed as a repetition, then the responsive brain region is preserving the overlap/similarities between the two. It is involved in completing or realizing a representation of the same or similar object based on partial visual information to what was previously seen (e.g., because of the differing orientation). A bias towards pattern completion was observed in various MTL regions, including the CA1, but not the CA3.

Summary

In summary, animal lesion studies have shown that spatial pattern separation, association, and completion subprocesses are differentially dependent on DG, CA1, and CA3. Rodent studies and computational models have shown that CA3 appears to be important for spatial pattern association and spatial pattern completion, and possibly spatial pattern separation. DG appears to be preferentially involved in spatial pattern separation. The sole human study examining the neural correlates of pattern separation and completion found DG/CA3 to be involved in the former, and CA1 to be involved in the latter (Bakker et al., 2008). To our knowledge, subregional involvement in pattern association has not been assessed in human studies. It is premature to conclude that these apparent discrepancies in subfield-processing relations reflect species differences. Indeed, the rodent studies are based on lesion methodology; whereas the human findings are based on a single fMRI study. In addition, the rodent tasks are based on memory for locations, whereas the human paradigm assessed processing of common objects. Moreover, it is only very recently that subfield-level analysis of human neuroimaging data has been possible and current methods remain unable to parse out the DG from the CA3 subregion in humans. If neural involvement of rodents and humans is identical, we would expect DG to be preferentially involved in spatial pattern separation in humans. Since current imaging techniques are unable to obtain isolated DG versus CA3 activation, human analogues of a rodent pattern separation behavioural task offers the potential to provide insight into processes to which even modern imaging remains blind.

Main Thesis Objective

This thesis addresses two main gaps in the literature. First, while human analogues of rodent spatial memory tasks have been developed, none have been developed that isolate spatial

pattern association, separation, and completion in particular. Second, while tasks assessing spatial pattern association, separation, and completion in humans have been developed, none have been developed that are directly analogous to rodent tasks. Thus, the objective of the current project is to develop virtual human analogues of rodent tasks assessing these subprocesses. As in the rodent tasks, task sensitivity to these processes will be assessed in terms of differences in performance in response to increasing task demands related to the subprocesses.

The development of these tasks will lead to future imaging work that will allow us to examine the neural correlates of these tasks and assess whether they correspond to those involved in rodents. Similar neural involvement in rodents and humans would be indicative of similar neural processes in both species when performing similar tasks, and would provide evidence for the applicability of rodent spatial memory tasks assessing these subprocesses to humans. In addition, similar neural involvement will provide further support for evolutionary continuity in hippocampal cognitive function in humans and rodents (Kesner & Hopkins, 2006).

The current study has three specific goals:

1. In a virtual analogue of the rodent spatial pattern association (SPA) task, I aim to demonstrate learning over trials. Specifically, participants should show increasing accuracy and decreasing latency as the trials progress if they are learning over trials.
2. In a virtual spatial pattern separation (SPS) task, I aim to demonstrate my task's sensitivity to separation manipulations. If my task is sensitive to separation manipulations, accuracy should decrease as the distance between target and foil decrease.
3. In a virtual analogue to a rodent task assessing pattern completion (SPC), I aim to demonstrate my task's sensitivity to cue removal manipulations. If this task is sensitive to

the removal of distal cues, accuracy should decrease and latency increase as the number of surrounding/distal cues in the environment decrease.

Participants

Sixty-two young adults in total were recruited from the Psychology Participant Pool (undergraduate students; both Experiments 1 and 2) and on-campus advertisement (community participants; only in Experiment 2). Exclusionary criteria included lack of fluency in English, non-normal vision, having a psychological disorder, or being on medication that could affect performance. On the basis of these exclusionary criteria, seven participants were excluded. Eight additional participants were excluded for not completing the tasks, the task being overwritten, or being administered incorrectly by the experimenter. Therefore, data from 47 diverse participants is presented.

One participant from Experiment 1 had their spatial pattern association data overwritten and thus only 10 people were included in the SPA analysis for this Experiment. Further, one participant from Experiment 2 also had their SPA data overwritten, and thus only 30 participants were included in the SPS analysis for Experiment 2. Both these participants' data were included in the spatial pattern separation and spatial pattern completion tasks.

Sixteen undergraduate students participated in Experiment 1 (13 female, M age = 21.47 years, SD = 4.69, age range = 18-36 years). I initially planned to run 10 participants and then check the data to monitor performance. Thus, eleven of these participants completed the original version of the spatial pattern separation task. Then I ran five participants on a modified version that appeared more promising (summarized below). Experiment 1 results suggested medium-sized effects for the spatial pattern association task and spatial pattern separation task, with larger effects for spatial pattern completion. Therefore, I used Cohen's standard effect size of $f = .25$ for an estimated minimum medium-sized effect for a repeated-measures ANOVA with 3 levels of

difficulty, $\alpha = .05$, and power = .85, which yields a recommended sample size of $N = 31$.

Therefore, 31 healthy participants were run in Experiment 2 (22 female, M age = 22.87, SD = 4.54, age range = 18-42 years). Eleven of these were community participants with a mean education level of 16 years (SD = 1.79 years).

General Experimental Paradigm

One contrast between the human tasks and analogous rodent tasks is that participants in human tasks are given verbal instruction about general task demands, rather than being given multiple training phases (e.g., learning to displace objects to obtain food rewards, etc.) as rodents are. However, the mnemonic content being assessed remained analogous. All tasks were performed in a circular computer-generated (CG) arena with brick walls (<http://web.arizona.edu/~arg/data.html>; Jacobs et al., 1997). Each meter is represented by 10 units, based on the length of one stride (10 units) as appearing equivalent to 1 meter on the screen (Jacobs et al., 1997). The arena had a diameter of 92 units and was housed in a 500 x 500 x 100 unit room. The wall had a height of 8 units. The external walls were purple, the ceiling gray, and the floor gray. Each wall had a different picture of a fractal pattern on it that was difficult to verbalize (i.e. did not resemble any common objects that could be easily verbalized) and was similar in colour to the others (Figure 1). The use of non-verbalizable stimuli in this task is in line with Steckler and Muir's (1995) suggestion to design tasks with abstract stimuli that cannot be easily verbalized when comparing humans and non-humans in order to minimize verbal processes.

Figure 1. Abstract fractal patterns on Arena walls.

Of primary importance was the assessment of the sensitivity of performance to difficulty manipulations thought to place increasing demands on the subprocesses of interest. In other words, these manipulations allowed some assessment of the tasks' construct validity.

The tasks were always administered in the following order: SPA, SPS, and SPC. The SPA task was a baseline task to ensure participants became familiar with the virtual environment and with navigation through the arena. Since SPC involves the retrieval of well-established information (Kesner & Hopkins, 2006), it is important to ensure that the participants were familiar with the virtual environment before they engaged in this task. Therefore, the SPC task was administered last. There were three fixed but random sequences for the ordering of trials for each task to minimize the likelihood that the results were due to a particular sequence of target

(and foil) locations. Participants were randomly assigned to one of these three different sequences.

Experiment 1 Procedure

The spatial pattern tasks were designed so that the tasks and virtual environment were as similar as possible, with only subtle variations in task demands to assess the subprocesses of pattern separation, association, and completion. Extra-maze cues (Figure 1) were provided on the walls of the virtual room to allow for the allocentric spatial processing required of these tasks.

Spatial pattern association. During the sample phase, a 5 by 5 unit green square was presented in one of 20 pre-determined spatial locations in the arena. The participant was required to use the arrow keys to navigate to and situate themselves on the green square. Once they reached it, they were required to press the space bar to take them into a 5-s delay followed by the choice phase. During the choice phase, the participant was placed in the centre of the arena in a random start orientation and required to navigate to the spatial location that had been marked in the sample phase, this time in the absence of a visible target (Figure 2).

Figure 2. Pattern Association task

Thus, the participant was required to use only extra-maze cues as a guide. If the participant did not find the location within 45 s, a new trial would begin. Because the correct location was no longer indicated by the presence of the green square, the participant had to use extra-maze cues to code for its location. Twenty one study-test pairs of trials were presented.

Spatial pattern separation. The SPS task was modeled after the rat cheeseboard task used by Gilbert et al (2001). A delayed-matching-to-place task was used. In the sample phase, the participant was presented with a green square located in one of 20 pre-determined spatial locations in the CG Arena identical to the study phase for the SPA task. The participant started in the centre of the arena facing north. Using the arrow keys, he/she was required to move to the green square on the floor of the arena. Once the participant was situated on it, they pressed the space bar to take them into the next phase. In the choice phase, participants were allowed to choose between two objects that were identical to the study object. One of these objects was placed in the study location (correct choice) and the other was placed in a different location (incorrect choice; Figure 3).

Figure 3. Pattern Separation task from Experiment 1.

Participants were required to discriminate the correct allocentric location based on its spatial relation to extra-maze cues. To make a selection, they navigated to one of the green squares, situated themselves on it, and then pressed the space bar. The trial ended after a choice was made. There were three possible distances presented pseudorandomly that separated the foil from the correct object (10, 20, or 30 area units from the centre of the target to the centre of the foil). Twenty-one study-test pairs were presented overall, across which the relative position of the foil was counterbalanced (i.e., N, E, S, W sides).

Spatial pattern completion. This version of the delayed-matching-to-place task was modeled after the cheeseboard task used by Gold and Kesner (2005). Each trial had a sample phase and choice phase. The sample phase was identical to that in the SPA and SPS tasks. That is, the participant started from a designated starting position in the centre of the arena facing north and the participant traveled to the green square placed on the floor of the arena. In the choice phase, the object was removed and after a 5-s delay the participant was allowed to explore the maze until he/she reached the same (correct) spatial location or a maximum of 45s, as in the association task (Figure 4). The main difference between this task and the SPA task was that the number of extra-maze cues (four, two, or zero) available was manipulated. These three possible cue conditions were repeated seven times each in a random presentation sequence across trials. In addition, the participant had a random starting orientation in each choice phase requiring allocentric spatial memory. In total, there were 21 study-test pairs.

Figure 4. Pattern Completion Task.

Sample

Choice

Experiment 1 Results

SPA. Accuracy in this task was calculated by a score of 1 for a trial when the participant did find the target in the allotted time and a score of 0 when they did not. This was averaged for each trial across participants. The SPA task appeared to produce a learning curve, with 20% of participants finding the target at trial 1 and 67% by trial 21. However, a linear trend analysis of the accuracy data across the 21 trials indicates no linear trend, $F(1,18) = 1.186, p = .308, MSE = 0.189$, partial $\eta^2 = .073$. Further, there was no quadratic trend across all 21 trials, $F(1,18) = 1.056, p = .318, MSE = 0.344$, partial $\eta^2 = 0.055$.

A further ANOVA was conducted to minimize trial-by-trial noise by using 3 bins of 7 trials (trials 1-7, 8-14, and 15-21). This analysis revealed no significant differences in accuracy between the three bins, $F(2, 18) = 0.537, p = .594, MSE = 0.044$, partial $\eta^2 = 0.056$. However, there appears to be a visible trend that failed to reach significance. Latency was also analyzed in bins of 7 to assess whether participants found the targets faster as the trials progressed. This analysis found no differences in latency between the three bins, $F(2, 18) = 1.328, p = .290, MSE = 30.930$, partial $\eta^2 = 0.129$.

Although significant differences were not revealed in these analyses, the medium and large effect sizes for accuracy and latency led us to suspect that using a larger sample may bring out these differences. Therefore, this task was not modified further with the expectation that the larger sample in Experiment 2 might produce differences between the conditions that we did not find with this relatively smaller sample.

SPS. A repeated-measures ANOVA with foil distance as the levels of the independent variable and accuracy as the dependent variable showed no difference between the three foil distance conditions, $F(2, 20) = 1.613, p = .224, MSE = 0.019$, partial $\eta^2 = 0.139$.

Since average accuracy on this task was very high for a separation of 10 units ($M = .789$), 20 units ($M = .753$), and 30 units ($M = .855$), and this task did not produce significant differences in accuracy **between** the three foil separation conditions, a small sample ($N = 5$) was tested on a modification of this task that was hypothesized to increase the difficulty of the task. This task had the same requirements with three modifications. First, the targets were made smaller. The square during the sample phase was now 2 by 2 units rather than 5 by 5 units. The second modification was that the stimuli during the choice phase were two circles rather than squares in order to discourage the use of angle cues in other words, the relation of the edges of the square to other edges in the room in making a judgment. Since circles have no straight edges, using these cues during the test phase would be impossible. Further, changing the target from square to circle between study and test ensured the participant was placing an emphasis on remembering the *location* of the target, rather than the target itself. The third modification was that the target and foil were closer together in all three distance manipulations by a factor of 2 in order to increase difficulty (separations of 5, 10, and 15 area units). The participant was instructed to go to the circle that appeared in the same location as the square had been presented in the study phase.

A repeated-measures ANOVA of this altered task again showed no differences in accuracy between the three foil distance conditions, $F(2, 8) = 0.028, p = .972, MSE = 0.070$, partial $\eta^2 = 0.007$. Although there appeared to be a decline in accuracy for all three separation conditions in the modified task ($M_{\text{separation1}} = .733, SD_{\text{separation1}} = .148, M_{\text{separation2}} = .743, SD_{\text{separation2}} = .344, M_{\text{separation3}} = .771, SD_{\text{separation3}} = .163$) versus the original task, t tests revealed no difference at the closest separation ($t(14) = 0.574, p = .575, d = 0.378$), the intermediate separation ($t(14) = 0.070, p = .945, d = 0.033$), or the furthest separation ($t(14) = 1.132, p = .277, d = 0.578$). While it was possible these differences were not found because the modified task was underpowered, I still decided to create a new task that could produce larger differences between conditions for Experiment 2 (below). An analysis of latency also did not show differences between conditions, and therefore is not included in detail here.

SPC. Accuracy was calculated in this task similarly as for the SPA task, where participants were given a score of 1 for a trial in which they found the target in the allotted time, and a score of 0 when they did not. A repeated-measures ANOVA with number of wall cues missing as the levels of the independent variable and accuracy as the dependent variable was significant, $F(2, 20) = 12.222, p < .001, MSE = 0.018$, partial $\eta^2 = 0.550$. Follow-up paired samples t -tests confirmed differences in accuracy between all three conditions, with higher accuracy in the 0 cues missing condition versus the 2 cues missing condition, $t(10) = 2.622, p = .026, d = 0.791$ and higher accuracy on the 2 cues missing versus 4 cues missing conditions, $t(10) = 2.622, p = .026, d = 0.791$.

Latency was also analyzed to see if participants took longer to find a target when fewer cues were available versus when more cues were available. A repeated-measures ANOVA with latency as the dependent variable also found significant differences between conditions, $F(2, 20)$

$= 17.768, p < .001, MSE = 21.059$, partial $\eta^2 = 0.640$. Paired-samples t tests showed a difference approaching significance with shorter latency in the zero cues missing condition versus two cues missing condition, $t(10) = -2.211, p = .051, d = 0.667$, and a slower latency for the two cues missing versus four cues missing conditions, $t(10) = -4.254, p = .002, d = 1.283$.

Thus the results show differential accuracy between the three cue conditions and differential latency between at least two of the three conditions with the other approaching significance.

Experiment 2 Procedure

Since significant differences between the three conditions were not seen in SPS, a modified task with an increased number of foils was used on another set of 31 participants. Specifically, during the study phase, three distractors in addition to the target were used, rather than one. This increase in the overall task difficulty was aimed at allowing for more room for variation across performance levels. SPA and SPC were also administered, but unmodified, as a cross-validation of the Experiment 1 findings for these two tasks in a separate sample.

Modified SPS Task. A delayed-match-to-sample for spatial location task was used. Participants were presented with a green square located in one of 20 pre-determined spatial locations in the CG Arena. The participant started in the centre of the arena facing north. Using the arrow keys, they were required to move to a green square on the floor of the arena. Once the participant was situated on it they pressed the space bar to take them into the next phase. In the choice phase, participants started at a random orientation and were allowed to choose between four green circles arranged in a square formation. One of these circles was placed in the study location (target, correct choice). The others were placed to complete three remaining corners of the arrangement (foils, incorrect choices). Participants were required to discriminate the correct

allocentric location of the target based on its spatial relation to extra-maze cues. To make a selection, they navigated to one, situated themselves on it and then pressed the space bar. The trial ended after a choice was made (Figure 5). There were three possible distances between the target and the furthest foil (2.83, 5.66, and 8.49 area units), which were presented in a pseudorandom sequence. Twenty-one study-test pairs were presented overall, across which the relative position of the foils were counterbalanced (i.e., equal representation of N, E, S, W sides).

Figure 5. Pattern Separation task from Experiment 2.

Experiment 2 Results

SPA. Again, the SPA task produced a learning curve, with 37% of participants finding the target at trial 1 and 74% by trial 21. Unlike in Experiment 1, a linear trend analysis showed a linear trend across trials, $F(2, 58) = 8.439, p = .009, MSE = .205, \text{partial } \eta^2 = .070$.

A further ANOVA using 3 bins of 7 trials (trials 1-7, 8-14, and 15-21) revealed a significant difference in accuracy between the three bins, $F(2, 58) = 5.352, p = .007, MSE = .037, \text{partial } \eta^2 = .156$. Follow-up paired t tests revealed greater performance on Bin 3 versus Bin 1, $t(29) = 2.975, p = .015, d = 0.474$, and Bin 2 versus Bin 1, $t(29) = 2.975, p = .006, d = 0.543$, but no difference between Bin 3 and Bin 2, $t(29) = 0.512, p = .612, d = 0.094$.

Accuracy and latency for each bin in Experiment 1 versus 2 were compared using an independent-samples t test to ensure there were no significant differences between these identical

tasks. As expected, there were no differences in accuracy nor latency for any of the bins ($p \geq .144$ for all conditions). Mean accuracy for Experiment 1 and 2 is presented in Figure 6.

Figure 6. Mean Accuracy Across Bins of 7 Trials For Experiments 1 and 2. Bin 1, 2, and 3 refer to bins of trials 1-7, 8-14, and 15-21 respectively (error bars represent standard error).

Latency was also assessed to see if participants became faster at locating the target as the task progressed. An ANOVA comparing latency of 3 bins of 7 trials found significant differences between the bins, $F(2, 58) = 8.002, p = .001, MSE = 41.739, \text{partial } \eta^2 = 0.216$. Follow-up paired-samples t tests found significant differences between bin 1 and bin 2 $t(29) = 4.021, p < .001, d = 0.734$ as well as bin 1 and bin 3 $t(29) = 2.770, p = .010, d = 0.506$, but not between bin 2 and bin 3 $t(29) = -0.764, p = .451, d = 0.139$.

SPS. A repeated-measures ANOVA with foil distance as the levels of the independent variable and accuracy as the dependent variable revealed that the modified task was successful in demonstrating a difference among the three foil separation conditions, $F(2, 60) = 5.028, p = .010, MSE = 0.031, \text{partial } \eta^2 = 0.144$. Follow-up paired samples t tests revealed lower accuracy for a

separation of 2.83 area units than for separation of 5.66 area units, $t(30) = -2.997, p = .005, d = 0.538$ and lower accuracy for a separation of 2.83 area units than for 8.49 area units, $t(30) = -2.377, p = .024, d = 0.436$. There was, however, no difference in accuracy for a separation of 5.66 and 8.49 area units, $t(30) = 0.878, p = .387, d = 0.158$. Overall, this new SPS task was more effective at producing accuracy differences between the separation levels than the original SPS task, at least between the two closest target-foil distances.

Accuracy was compared between Experiment 1 and 2 using three independent samples t tests in order to assess whether a significant drop in accuracy was achieved through the modifications made on this task. A significant drop in accuracy was found at the shortest separation, $t(40) = 7.027, p < .001, d = 2.264$, the intermediate separation, $t(40) = 4.604, p < .001, d = 1.067$, and the largest separation, $t(32.132) = 8.776, p < .001, d = 2.664$. Therefore, this latest task showed significantly lower accuracy in all separation conditions compared to the original task (Figure 7).

Figure 7. Pattern separation task mean accuracy in Experiment 1 (original) and Experiment 2. Levels of separation 1, 2, and 3 represent 10, 20, and 30 units respectively for Experiment 1. For Experiment 2, level of separation 1, 2, and 3 represent 2.83, 5.66, and 8.49 area units respectively (error bars represent standard error).

Furthermore, polynomial trend analyses revealed both a linear trend, $F(1,30) = 5.648, p = .024, MSE = .025$, partial $\eta^2 = .158$, as well as a quadratic trend, $F(1, 30) = 4.589, p = .040, MSE = .036$, partial $\eta^2 = .133$, across levels of separation.

SPC. Accuracy varied across cue missing conditions, $F(2, 60) = 12.021, p < .001, MSE = .034$, partial $\eta^2 = .286$. In particular, performance was more accurate for the zero cues missing versus two cues missing condition, $t(30) = 2.98, p = .006, d = .535$ as was the zero cues missing versus the four cues missing condition, $t(30) = 5.495, p < .001, d = .987$. In contrast to Experiment 1, the higher accuracy in the two cues missing condition versus four cues missing conditions just failed to reach statistical significance although there was a medium effect size, $t(30) = .0993, p = .078, d = .328$ (Figure 8).

Figure 8. Pattern completion mean accuracy in Experiments 1 and 2 (error bars represent standard error).

Latency also differed across cue conditions, $F(2, 60) = 23.140, p < .001, MSE = 38.396$, partial $\eta^2 = 0.435$. Specifically, there was a shorter latency for the zero cues missing versus two cues missing condition, $t(30) = -4.399, p = .004, d = 0.563$ and shorter latency for the two cues missing versus four cues missing condition, $t(30) = -3.542, p = .001, d = 0.636$.

Independent-samples *t* tests were used to assess whether there was a significant difference in accuracy and latency between conditions in Experiment 1 and 2. These analyses, as expected, found no significant differences for accuracy or latency for the conditions (all $ps \geq .364$).

General Discussion

The objective of this thesis was to develop human analogues of rodent tasks that have been shown to be sensitive to hippocampal subprocesses in rodents. I developed three novel computer-generated virtual-maze tasks analogous to rodent tasks used to evaluate pattern association, separation, and completion in humans. The use of the CG-Arena allowed us to create a computer-generated virtual environment that was visually similar to that used in rodent tasks. Further, it enabled us to specify parameters that allowed us to create analogous tasks, as well as closely parallel the difficulty manipulations used in rodent tasks. Performance on these tasks varied according to the difficulty manipulation condition (separation distance for SPS and number of wall cues missing for SPC) suggesting these tasks may be sensitive to the same subprocesses assessed in rodents.

In the SPA task, participants showed improved performance across trials. In the SPS task, sensitivity to separation of target and foils was evidenced by increased accuracy with increasing separation distance conditions. Furthermore, participants' performance was dependent on the number of extra-maze cues in the SPC task. I will discuss these findings and their implications for this study in more detail below, as well as possible future directions incorporating these tasks.

SPA

Participants showed what appeared to be a learning curve, with an increased number of participants who found the target by the last trial versus the first trial. However, there was only a significant linear trend in Experiment 2 and not in Experiment 1. This may have reflected some inherent differences between the samples for Experiment 1 and Experiment 2 that affected outcome. For instance, Experiment 1 included only undergraduate students, while Experiment 2 included undergraduate students, graduate students, and community participants. In the future, a

diverse sample that includes undergraduate students, graduate students, and community participants may be more representative of the general population. An even more plausible explanation for the different findings between experiments is the smaller sample size of participants in Experiment 2. The identical effect sizes between Experiment 1 and 2 indicate that Experiment 1 did not show a significant result similar to Experiment 2 due to a lack of power. Overall, however, participants seemed to be learning to find the targets more accurately and quickly over trials. Importantly, an analysis comparing bins of 7 trials found no significant differences in accuracy or latency between SPA in Experiment 1 versus Experiment 2, suggesting performance on this task is similar across both experiments. Further, there appeared to be some improvement in accuracy and latency across bins in Experiment 2, indicating participants were improving at the task over time. Since there was no significant improvement between Bins 2 and 3, participants were not improving much across trials beyond trial 15. Therefore, it seems the 21 trials we have for this task were sufficient in producing gains in performance.

Results were consistent with our goals for the SPA task. The learning curve and improved performance across bins may reflect the participants' increasing familiarity with the room, including the wall cues that help the participant gauge their location relative to the target, as well as improved strategy. This former component is critical for the later SPC task, given that spatial pattern completion requires a 'well-learned' environment. Although we did not set criteria for what constitutes a well-learned environment, the ordering of the tasks with SPC always completed last was to ensure the environment was well-learned.

SPS

In Experiment 1 of the SPS task, participants did not show differences in accuracy between any of the three separations. An altered task was created that used two circles rather than squares and a decrease in separation distance for all three separations. This task also did not show differences between any of the levels of separation, although it did result in an overall decrease in accuracy. In Experiment 2, participants were presented with four circles during the sample phase (one target and three foils) as opposed to two circles (one target and one foil). With this modification, participants did show differential accuracy between two of the three conditions (with the third marginally significant), and lowered overall accuracy. Therefore, four major changes were made that differentiated the original SPS task from the final version: the target and foils were resized to make them smaller, targets and foils were circles rather than squares during the choice phase, the distance between the target and foils was decreased, and the number of foils were increased. The final task was more successful at producing differences in accuracy between the separation conditions than the previous two versions.

The finding that the final task produced accuracy differences between two of the three levels of separation could be

explained in a number of ways. It is possible that in the first version of the task, the locations were quite easy to discriminate from one another due to the large targets and large distances between them. This is evidenced by the high accuracy rates for this task at all separation conditions. Therefore, the three distances did not require or incite intense pattern separation processes. Arguably, at closer distances, a "heavier" reliance on the pattern separation process is required to successfully discriminate between spatial locations. This rationale was the basis for the creation of the modified task in Experiment 1. However, this task also did not

produce differences between spatial separations. At this point, a slight deviation from the rodent literature was required and the three-foil task in Experiment 2 was developed. This task did produce more statistically significant differences in accuracy between separation conditions than the previous two tasks. Presumably, the final task engaged heavier pattern separation processing, as indicated by differences in accuracy based on distance of separation in the final SPS task. Performance on the latest SPS task is more sensitive to separation between the target and foils than were the previous two versions. Therefore, this version of the task is a good measure of spatial pattern separation.

SPC

Performance on the SPC task in both Experiment 1 and 2 showed differences between wall cue missing conditions in latency and accuracy. Specifically, as the number of cues on the walls decreased, accuracy decreased and latency increased. Experiment 1 showed differences in accuracy and latency between all cue missing conditions with accuracy decreasing and latency increasing as wall cues were eliminated. Experiment 2 showed differences in accuracy between two of the three conditions and an accuracy difference that just failed to reach significance between two cues missing and all four cues missing. In other words, as the number of wall cues in this task decreased, accuracy also decreased for two of the three conditions. Consistent with Experiment 1, Experiment 2 showed an increase in latency as wall cues were removed. Therefore, it appears that the SPC task produced differences in latency and accuracy between the cue missing conditions. This indicates performance on this task was reliant on the number of cues in the environment.

Our findings for the SPC task are consistent with findings in rodents for similar tasks. Using an identical paradigm to the SPC task used in the current study, Gold and Kesner (2005)

found that there was an increase in number of errors that was dependent on number of cues available. Specifically, rodents searched fewer incorrect locations for the reward when there were more extra-maze cues available. In another study using the same rodent task, unoperated control rats and CA3-lesioned rats were highly reliant on visual extra-maze cues in order to successfully solve a SPC task (Kirwan, Gilbert, & Kesner, 2005). Therefore, findings from the present study are in line with rodent studies that found differences in performance as a function of available cues.

Jacobs et al. (1998) developed a similar task to our SPC task also using CG-Arena. In this task, participants learned the location of an invisible target on the arena floor through several acquisition trials. The test phase had four cycles with two trials each. During trial 1 of each cycle, they were to find the invisible target on the first trial while all cues were present. During trial 2 of each cycle, the participants were to find the invisible target when one or more wall cues were missing. If the participant did not find the target in three minutes, the trial ended and went on to the next trial. The location of the target remained consistent across trials. There were no differences in time to locate the target between the conditions when zero (the baseline acquisition condition where all cues were present), one, two, or three distal cues were eliminated. However, locating the target under these conditions took significantly less time compared to locating the target when all four cues were missing. This differed from our findings, since we found significant differences in latency between all three of our cue missing conditions (zero missing, two missing, and all four missing). Accuracy was not assessed in the Jacob et al. (1998) study.

One important distinction between the task used by Jacob et al. (1998) and ours is that our target could appear in one of many different spatial locations, unlike their target, which was consistently in the same position across trials. This might explain the discrepant findings

between their task and ours, specifically that performance on our task was more sensitive to the number of wall cues available compared to their task. Perhaps the position of their target became so well-learned that subtle variations in the presence of distal cues had no effect on the time it took to find the target. Participants were somewhat reliant on distal cues, as indicated by impaired performance when all four cues were removed. In our task, the location of the target was new on every trial. Together, these findings indicate that participants might be more reliant on distal cues when first learning a spatial location, and less reliant as they have more experience navigating to that location. Moreover, our target location varied on every trial, which would qualify it more as “episodic-like” and dependent on the hippocampus compared to their nonepisodic task.

Another difference between our task and the one developed by Jacobs et al. (1998) is that we reported accuracy as well as latency differences in our task, while the task developed by Jacobs et al. (1998) only provided an assessment of latency to reach the target. Although their task follows the traditional procedure used in the Morris Water Maze task, our task more closely parallels recent rodent literature directly assessing spatial pattern completion in rodents. In this regard, our task yielded significant differences in both accuracy and latency based on cue availability, indicating sensitivity to these manipulations in humans as in rats. Furthermore, our task was specifically aimed at creating a human analogue of a rodent SPC task, whereas Jacobs et al. (1998) did not explicitly state that their objective was to assess spatial pattern completion. Rather it seemed they aimed to assess the impact of distal cue removal on place-learning strategy more generally.

Limitations and Future Directions

This study aimed to develop human analogues of rodent SPA, SPS, and SPC tasks. Although task parameters were adequately developed, there were some limitations to our study. First, we did not look at sex differences in spatial navigation, despite a large literature on differential spatial navigation strategies and overall performance on spatial memory tasks in males and females (Canovas et al., 2008). Furthermore, previous video game experience was not taken into account, which could affect performance on this task.

Also, the verbal instructions given to our human participants may have posed different cognitive demands than the incidental learning that takes place in rodents. Arguably the processes required to perform a task when given verbal instructions may differ from learning task demands incidentally. A future study employing an incidental-learning paradigm would address this limitation.

Other future directions of research will employ fMRI to assess whether the spatial-pattern tasks involve differential hippocampal subfields in humans as established with findings from animal models. Animal and computational models have identified DG as important for spatial pattern completion (e.g. Becker, 2005; Gilbert & Kesner, 2006; Gilbert, Kesner, & Lee, 2001; Goodrich-Hunsaker, Hunsaker, & Kesner, 2008; Rolls, 1996). Similarly, the sole human study examining subregional hippocampal involvement in pattern separation has identified preferential involvement of the DG/CA3 region (Bakker et al., 2008). Thus, in the context of our task, we expect conditions that require greater pattern separation processes to elicit more DG/CA3 activity than those that require less separation. Specifically, we expect DG/CA3 activity will increase with decreasing separation of target and foil.

The sole human study that has examined hippocampal subfield involvement in nonspatial pattern completion found preferential activity in CA1 as opposed to DG/CA3 (Bakker et al., 2008). This finding is contrary to both animal studies as well as computational models that predict CA3 involvement in learning of arbitrary associations and pattern completion when space is a component (Kesner & Hopkins, 2006; Rolls, 1996; Rolls, 1997). Clearly, the study of hippocampal involvement in pattern completion in humans requires further study. Thus, an imaging study using our SPC task that more closely models the rodent paradigm might produce findings that are more consistent with the rodent literature. Otherwise, it might corroborate Bakker et al.'s (2008) findings and thereby suggest species differences in performing these similar tasks. In addition, we might predict increasing activity as a function of the degree of pattern completion processes that are required to complete a task. For example, in line with the current behavioural results, greater subregional activity might be expected in response to decreasing cue availability in our SPC task.

In addition to the findings of differential subregional involvement in different spatial pattern tasks, dissociations have been found with respect to subregional involvement in spatial pattern tasks versus spatial-temporal tasks. Specifically, numerous rodent studies have implicated the CA1 subregion as being preferentially important compared to DG and CA3 in temporal pattern association, separation, and completion (e.g. Gilbert, Kesner, & Lee, 2001; Hoang & Kesner, 2008; Kesner & Hopkins, 2006; Weiss, Bouwmeester, Power, & Disterhoft, 1999). Therefore, a future direction will include the development of human analogues of rodent spatial-temporal pattern tasks. Further, these tasks could be administered in a single imaging study along with the spatial pattern tasks to identify subregional dissociations. Based on the framework

established in the rodent literature, we predict preferential CA3 involvement of the spatial pattern tasks, and preferential CA1 involvement of the spatial-temporal pattern tasks.

Functional dissociations between subregions are also of clinical relevance. That is, certain clinical disorders show preferential damage to particular hippocampal subfields and sparing of other subfields. For instance, histology studies have indicated that the CA1 subfield appears to be relatively spared in Schizophrenia, while abnormalities are predominantly seen in CA3 (Benes, 1999; Harrison, 2004). This pattern of damage contrasts with that found in various other disorders including Alzheimer's disease and hypoxia, which preferentially affect the CA1 subfield (Duvernoy, 2005; Mueller, Stables, Du, et al., 2007). Research demonstrating disparate hippocampal pathology in different disorders suggests that the pattern of memory deficits between disorders may also be unique. Thus, future research using the tasks developed here may provide means to further understand commonalities and differences across conditions associated with hippocampal dysfunction.

Conclusions

In sum, in this thesis I developed tasks analogous to the well-established rodent paradigms measuring spatial pattern association, separation, and completion. The CG-Arena was used to create tasks that were close analogues of rodent tasks. First, it allowed us to provide a similar visual environment to that used in rodent tasks. Second, it allowed us to manipulate separation distances between targets, spatial location of targets, and the presence/absence of the surrounding wall cues in the virtual environment among many other parameters to create conditions that closely paralleled those used in rodent tasks. Subjects showed performance differences that were dependent on the difficulty manipulations used in these tasks. Specifically, differential performance based on separation distance in the SPS task, and differential

performance based on the number of wall cues in the SPC task. The varying performance across conditions suggests these tasks may be sensitive to these subprocesses. Furthermore, we attempted to minimize the use of verbalization of wall cues by using fractal patterns rather than common objects.

This work provides a foundation for various avenues of future research. Imaging studies in humans might strengthen the findings from computational models and animal models that predict preferential activity of a particular subregion when engaged in a particular spatial pattern subprocess. Furthermore, dissociations in subregional involvement between spatial and spatial-temporal subprocesses can be examined. The development of these tasks may shed light in certain clinical disorders that have been shown to be associated with selective damage or sparing of certain hippocampal subregions. Therefore, the human analogues of rodent spatial pattern association, separation, and completion tasks may illuminate functional differences in subregion-specific hippocampally mediated spatial memory subprocesses and set the stage for valuable future research directions.

References

- Astur, R.S., St. Germain, S.A., Baker, E.K., Calhoun, V., Pearlson, G.D., & Constable, R.T. (2005). fMRI hippocampal activity during a virtual radial arm maze. *Applied Psychophysiology and Biofeedback*, 30, 307-317.
- Bakker, A., Kirwan, C.B., Miller, M. & Stark, C.E.L. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science*, 319, 1640-1643.
- Becker, S. (2005). A computational principle for hippocampal learning and neurogenesis. *Hippocampus*, 15, 722-738.
- Benes, F. M. (1999). Evidence for altered trisynaptic circuitry in schizophrenic hippocampus. *Biological Psychiatry*, 46(5), 589-599.
- Canovas, R., Espinola, M., Iribarne, L., & Cimadevilla, J.M. (2008). A new virtual task to evaluate human place learning. *Behavioural Brain Research*, 190, 112-118.
- Duvernoy, H.M. (Eds) (2005). *The Human Hippocampus: Functional Anatomy, Vascularization, and Serial Sections with MRI* (3rd ed). New York: Springer.
- Eichenbaum, H. (2000). Hippocampus: Mapping or memory? *Current Biology*, 10, 785-787.
- Gilbert, P.E. & Kesner, R.P. (2002). Role of the rodent hippocampus in paired-associate learning involving associations between a stimulus and a spatial location. *Behavioral Neuroscience*, 116, 63-71.
- Gilbert, P.E. & Kesner, R.P. (2003). Localization of function within the dorsal hippocampus: The role of the CA3 subregion in paired-associate learning. *Behavioral Neuroscience*, 117, 1385-1394.
- Gilbert, P.E. & Kesner, R.P. (2006). The role of the dorsal CA3 hippocampal subregion in spatial working memory and pattern separation. *Behavioral Brain Research*, 169, 142-149.

- Gilbert, P.E., Kesner, R.P., & DeCoteau, W.E. (1998). Memory for spatial location: Role of the hippocampus in mediating spatial pattern separation. *The Journal of Neuroscience*, 18, 804-810.
- Gilbert, P.E., Kesner, R.P., & Lee, I. (2001). Dissociating hippocampal subregions: A double dissociation between dentate gyrus and CA1. *Hippocampus*, 11, 626-636.
- Gold, A.E., & Kesner, R.P. (2005). The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. *Hippocampus*, 15, 808-814.
- Goodrich-Hunsaker, N.J., Hunsaker, M.R., & Kesner, R.P. (2008). The interactions and dissociations of the dorsal hippocampus subregions: How the dentate gyrus, CA3, and CA1 process spatial information. *Behavioral Neuroscience*, 122, 16-26.
- Hanlon, F.M., Weisend, M.P., Hamilton, D.A., Jones, A.P., Thoma, R.J., Huang, M. et al. (2006). Impairment on the hippocampal-dependent virtual Morris water maze task in schizophrenia. *Schizophrenia Research*, 87, 67-80.
- Harrison, P. J. (2004). The hippocampus in schizophrenia: A review of the neuropathological evidence and its pathophysiological implications. *Psychopharmacology*, 174(1), 151-162.
- Hoang, L.T. & Kesner, R.P. (2008). Dorsal hippocampus, CA3, and CA1 lesions disrupt temporal sequence completion. *Behavioral Neuroscience*, 122, 9-15.
- Hopkins, R.O. & Kesner, R.P. (1993). Memory for temporal and spatial distances for new and previously learned geographical information in hypoxic subjects. *Society for Neuroscience Abstracts* 19, 1284 Washington, DC.
- Jacobs, W.J., Laurance, H.E., Thomas, K.G.F. (1997). Place learning in virtual space I: Acquisition, overshadowing, and transfer. *Learning and Motivation*, 28, 521-541.

- Jacobs, W.J., Thomas, K.G.F., Laurance, H.E., & Nadel, L. (1998). Place learning in virtual space. *Learning and Motivation*, 29, 288-308.
- Kesner, R.P. & Hopkins, R.O. (2006). Mnemonic functions of the hippocampus: A comparison between animals and humans. *Biological Psychology*, 73, 3-18.
- Kesner, R.P., Hunsaker, M.R., & Warthen, M.W. (2008). The CA3 subregion of the hippocampus is critical for episodic memory processing by means of relational encoding in rats. *Behavioral Neuroscience*, 122, 1217-1225.
- Kirwan, C.B., Gilbert, P.E., & Kesner, R.P. (2005). The role of the hippocampus in the retrieval of a spatial location. *Neurobiology of Learning and Memory*, 83(1), 65-71.
- Kirwan, C.B. & Stark, C.E.L. (2007). Overcoming interference: An fMRI investigation of pattern separation in the medial temporal lobe. *Learning and Memory*, 14, 625-633.
- Laurance, H.E., Thomas, K.G.F., Newman, M.C., Kaszniak, A.W., Nadel, L., & Jacobs, W.J. (2002). Older adults map novel environments but do not place learn: Findings from a computerized spatial task. *Aging, Neuropsychology, and Cognition*, 9, 85-97.
- Lee, I., Yoganarasimha, D., Rao, G., & Knierim, J.J. (2004). Comparison of population coherence of place cells in hippocampal subfields CA1 and CA3. *Nature*, 430, 456-459.
- Leutgeb, J.K., Leutgeb, S., Moser, M., & Moser, E.I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science*, 315, 961-966.
- Livingstone, S.A. & Skelton, R.W. (2007). Virtual environment navigation tasks and the assessment of cognitive deficits in individuals with brain injury. *Behavioral Brain Research*, 183, 21-31.
- Maguire, E.M., Nannery, R., & Spiers, H.J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain*, 129, 2894-2907.

- Maguire, E.M., Spiers, H.J., Good, C.D., Hartley, T., Frackowiak, R.S.J., & Burgess, N. (2003). Navigation expertise and the human hippocampus: A structural brain imaging analysis. *Hippocampus*, 13, 250-259.
- Morris, R.G., Garrud, P., Rawlins, J.N., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, 297, 681-683.
- Mueller, S.G., Stables, L., Du, A.T., Schuff, N., Truran, D., Cashdollar, N. et al. (2007). Measurement of hippocampal subfields and age-related changes with high resolution MRI at 4 T. *Neurobiology of Aging*, 28, 719-726.
- Nakazawa, K., Quirk, M.C., Chitwood, R.A., Watanabe, M., Yeckel, M.F., Sun, LD. et al. (2002). Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science*, 297, 211-218.
- O'Keefe, J. & Dostrovsky, J. (1971). The hippocampus as a spatial map: Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, 34, 171-175.
- O'Keefe, J. & Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. New York: Oxford University Press.
- O'Reilly, R.C. & McClelland, J.L. (1994). Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. *Hippocampus*, 4, 661-682.
- Rolls, E.T. (1996). A theory of hippocampal function in memory. *Hippocampus*, 6, 601-620.
- Rolls, E.T. (1997). An attractor network in the hippocampus: Theory and neurophysiology. *Learning and Memory*, 14, 714-731.
- Rosenbaum, S.R., Priselac, S., Kohler, S., Black, S.E., Gao, F., Nadel, L. & Moscovitch, M. (2000). Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nature Neuroscience*, 3, 1044-1048.

- Ryan, J.D., Alhoff, R.R., Whitlow, S., & Cohen, N.J. (2000). Amnesia is a deficit in relational memory. *Psychological Science*, 11, 454-461.
- Ryan, J.D. & Cohen, N.J. (2004). Processing and short-term retention of relational information in amnesia. *Neuropsychologia*, 42, 497-511.
- Shipman, S.L. & Astur, R.S. (2008). Factors affecting the hippocampal BOLD response during spatial memory. *Behavioral Brain Research*, 187, 433-441.
- Shore, D.I., Stanford, L., MacInnes, W.J., Klein, R.M., & Brown, R.E. (2001). Of mice and men: Virtual Hebb-Williams mazes permit comparison of spatial learning across species. *Cognitive, Affective, and Behavioral Neuroscience*, 1, 83-89.
- Skelton, R.W., Ross, S.P., Nerad, L., & Livingstone, S.A. (2006). Human spatial navigation deficits after traumatic brain injury shown in the arena maze, a virtual Morris water maze. *Brain Injury*, 20, 189-203.
- Stepankova, K., Fenton, A.A., Pastalkova, E., Kaline, M., & Bohbot, V.D. (2004). Object-location memory impairment in patients with thermal lesions to the right or left hippocampus. *Neuropsychologia*, 42, 1017-1028.
- Sweatt, J.D. (2004). Hippocampal function in cognition. *Psychopharmacology*, 174, 99-110.
- Thomas, K.G.F., Hsu, M., Laurance, H.E., Nadel, L., & Jacobs, W.J. (2001). Place learning in virtual space III: Procedures and their application to fMRI and clinical neuropsychology. *Behavior Research Methods, Instruments, and Computers*, 33, 21-37.
- Vazdarjanova A. & Guzowski, J.F. (2004). Differences in hippocampal neuronal population responses to modifications of an environmental context: Evidence for distinct, yet complimentary, functions of CA3 and CA1 ensembles. *The Journal of Neuroscience*, 24, 6489-6496.

④B1-61-308