

1 Behavioral Dynamics of Episodic Memory

When we think of an individual memory, many of us think of an episodic memory. We conjure up rich recollections of sequences of events from our recent or remote past that play out in our minds as if we were reliving the experience. For example, I can remember walking our dog Ollie in the snow on the morning that I wrote this paragraph on January 20, 2010. I remember some of my actions in putting on his leash, stepping out the back door and walking along our back path to the street. I remember distinct points of view, for example as I walked up the hill and then as I turned to see our cat following us. I remember some of the twists and turns in my path as we walked around piles of plowed snow or as Ollie investigated patches of yellow. I remember the movement of our neighbor's cat as it ran out of our way, and I remember how Ollie barked and ran toward the neighbor's cat. As demonstrated by this example, the term *episodic memory* refers to the memory of specific events occurring at a specific place and time. In this book, the term *remember* is used to specifically describe the retrieval of an episodic memory. As described below, episodic memory is contrasted with many other types of memory, including memory for general facts and world knowledge (semantic memory) and memory for how to do things (procedural memory).

By no means do I remember every moment in time from my walk. I did not encode some events, and others were rapidly forgotten. However, my episodic memory contains many detailed representations of the dynamics of the episode—including my location, my point of view, the type and speed of my actions. With some thought, I can remember many segments of a detailed pathway through time and space. Like the snow under my feet, my episodic memory retained mental footprints showing where I faced, where I turned, and even how fast I moved. I can retrieve my memory on the basis of these imprints in my memory, as if retracing my path by matching my foot to each footprint. This path of footprints through the snow with its features of direction and speed, and the associated actions, will be described here as a spatio-temporal trajectory or episodic trajectory. The traces left in my memory are not just discrete footprints but the continuous trace of my full body moving through

three-dimensional space, as well as the continuous traces of other moving agents including our dog and our cat. A more accurate analogy may be the streaks of movement in a long-exposure photograph, where a movement appears as an unbroken, fluid arc. I will argue that episodic memory contains segments of the spatiotemporal trajectories from our prior experience. My memories of this morning are most vivid, but I can also recollect portions of episodes from the more distant past, with actions, point of view, and segments of trajectories. I can mentally relive many segments of my past life.

This book will focus on the brain mechanisms of episodic memory. On the behavioral level, I will focus on the capacity to encode and retrieve segments of spatiotemporal trajectories from personal experience, including the time and location of individual events such as encounters with other agents or items. On the biological level, I will focus on the dynamical properties of neurons in the brain regions implicated in episodic memory, presenting a model of how the cellular properties of these neurons could underlie the mechanisms of episodic memory.

This is an exciting time of progress in our understanding of the brain dynamics of episodic memory. Recent experimental discoveries have provided new insights, elucidating new details about how our brains might encode and retrieve spatiotemporal trajectories. These recent discoveries include the discovery of “grid cells” in the entorhinal cortex of rats foraging through open spaces, the discovery of cellular rhythms in individual neurons in entorhinal cortex that could underlie these grid cells, the discovery of “splitter cells” that appear selective for different sequences through the same location, and also the discovery of patterns of neural activity that appear to reflect the “replay” of previous movements through the environment. These discoveries provide for the first time a framework for understanding the encoding and retrieval of episodic memory not just as discrete snapshots of past time but as a dynamic replay of spatiotemporal trajectories. These breakthroughs also help to resolve some puzzling paradoxes of scientific findings over the past several decades.

Definition of Episodic Memory

In the domain of psychological research, episodic memory was first defined by Endel Tulving (Tulving, 1972). At that time, a number of cognitive researchers were focused on studying memory as a single, monolithic process. In contrast, researchers today acknowledge the existence of multiple memory systems.

Before Tulving, there were many writers who described different aspects of memory function. However, Tulving had an influential effect in focusing academic research on differences between the recollection of a specific sensory experience at a specific place and time versus the retrieval of a piece of factual evidence from general knowledge. Tulving first developed the term *episodic memory* as a contrast to the concept

of semantic memory (Tulving, 1972, 1983, 1984, 2001; Baddeley, 2001). The term *semantic memory* was developed by Quillian (Collins and Quillian, 1969) to describe memory for facts and general knowledge about the world. For example, remembering that Stockholm is the capital of Sweden would be considered a semantic memory, as opposed to remembering a specific trip to visit relatives in Stockholm, which would be an episodic memory. Episodic memory was later contrasted with other forms of memory such as knowing how to do things, referred to as *procedural* or *implicit memory* (Cohen and Squire, 1980; Cohen and Eichenbaum, 1993), and with actively keeping recent information in mind, known as *working memory* (Baddeley and Hitch, 1974; Baddeley, 2001).

Over the years, the definition of episodic memory has matured to include many features accepted by the vast majority of neuroscientists and psychologists (though there are still some features that are controversial). There is general acceptance of the statement that the form of the retrieval query directed at the episodic system is “What did you do at time T in place P?” (Tulving, 1984). Tulving’s definition also includes the capacity for mental time travel to past episodes, to replay them from memory as if reliving them (Tulving, 1983; Eichenbaum and Cohen, 2001; Tulving, 2002). These features of episodic memory fit well with subjective experience and the particular example that I presented above.

Tulving focuses on mental time travel as the mental voyage from the current time to the past episode being remembered, and his perspective differs from the focus presented here in that he does not focus as much on the mental time travel within the past episode itself. In fact, he states that his model

...describes a “snapshot view” of episodic memory: It focuses on conditions that bring about a slice of experience frozen in time which we identify as “remembering.” The recursive operation [...] produces many snapshots whose orderly succession can create the mnemonic illusion of the flow of past time. (Tulving, 1984, p. 231)

This description differs from how I will describe the retrieval process. In particular, it suggests a discrete rather than a continuous flow of retrieval and suggests that a retrieval act (ecphory) is required for each discrete snapshot, rather than a retrieved memory being extended in the dimension of time. This runs contrary to elements of personal experience, such as my memory of my dog lunging toward the neighbor’s cat as a complete fluid movement (a continuous motion rather than a snapshot).

Thus, I argue that the process of mental time travel goes beyond forming associations of single items with a single, static behavioral context of location and time and involves encoding of continuous segments of a spatiotemporal trajectory. This requires specific machinery on a cellular and circuit level. I will present models of the cellular dynamics of episodic memory that allow us to relive a sequence of events as segments of a spatiotemporal trajectory with an explicit sense of position in continuous space

and duration in continuous time and an explicit reexperience of factors such as head direction and the direction of movements.

Other features of episodic memory have been elaborated by other researchers such as Martin Conway (2009). Conway reviews data showing that episodic memories have a perspective, either consisting of the point of view of the person retrieving the memory (a “field” perspective) or a third-person observer perspective (Nigro and Neisser, 1983; Robinson and Swanson, 1993; Conway, 2009). The description below will show how the field view of episodic memory could arise from the functional role of neurons that respond on the basis of current head direction. Conway also points out that visual episodic memories represent short time slices of experience (Anderson and Conway, 1993; Williams et al., 2008) with beginning and end points often related to the achievement of specific goals. This is related to other experimental work showing some consistencies in how humans parse their experience into separate events (Zacks and Tversky, 2001; Zacks et al., 2001; Agam et al., 2005). This conception of short time slices of experience is consistent with the model presented here of episodic memories as containing segments of spatiotemporal trajectories.

Episodic Memory as a Spatiotemporal Trajectory

To further illustrate the concept of episodic memory as a spatiotemporal trajectory, I will provide another specific example. Episodic memory allows me to remember different events that I experience each day in the same work environment and to recall these in detail after a few hours or days. The example in figure 1.1A shows my memory of the start of one specific day at Boston University. At location 1 in the figure, I park my car in one of many spots in the Warren Towers parking garage. I then walk along Cummington Street and pass one of my graduate students, Jim Heys, on the street outside the Science and Engineering library (location 2). I continue down the street to my office in the Center for Memory and Brain at location 3, where I speak with my wife, Chantal Stern, and then later with another graduate student, Mark Brandon. After meeting with Mark, I go back up the street for a brief meeting in the Biomedical Engineering Building (location 4). Then I walk back down the street and enter the Life Science and Engineering Building at location 5, where I greet one of my postdoctoral fellows, Nathan Schultheiss.

As shown in the figure, my episodic memory of my day includes segments from a continuous spatiotemporal trajectory shown with a dashed line that passes between different buildings. The trajectory includes my sense of absolute location but contains more than just location. I can remember my point of view at individual moments, so there is a clear directional component. I can also remember the timing of the trajectory, such as my speed of walking or the timing of events when I stayed in one location. Thus, it is a spatiotemporal trajectory. The spatiotemporal trajectory or episodic

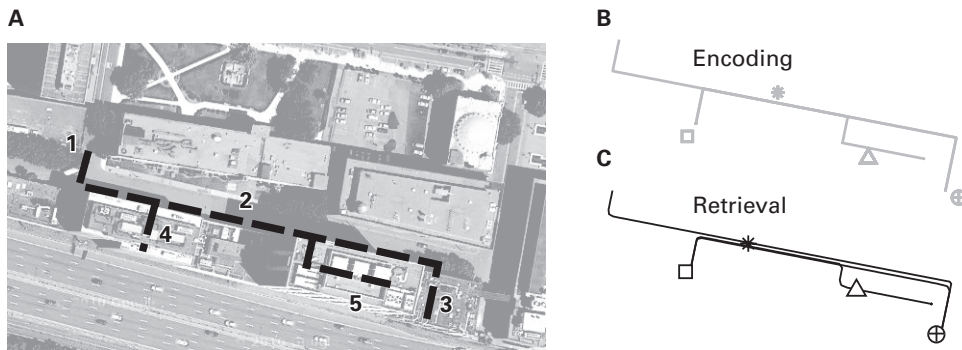


Figure 1.1

Example of episodic memory as a spatiotemporal trajectory. (A) My spatiotemporal trajectory (dashed black line) through the Boston University campus, including encounters with people at different positions. (B) The encoded trajectory is shown in gray with symbols representing the events of meeting people at different positions (asterisk, circle, plus sign, square, triangle). (C) The episodic memory model can correctly retrieve the spatiotemporal trajectory (black) and retrieve the events of meeting people encountered at specific positions (symbols).

trajectory forms a framework for the association of individual events or items. Different positions along the episodic trajectory are associated with individual events involving interacting with specific people. Figure 1.1B shows the spatiotemporal trajectory during encoding as a gray line. The events are symbolized by different symbols at different positions along the spatiotemporal trajectory (for example, the asterisk indicates meeting Jim, the circle marks the meeting with Chantal, the plus sign indicates meeting with Mark).

Consistent with Tulving's definition of episodic memory as involving mental time travel, I have the capability to remember segments of the overall episodic memory in sequential order as if reliving the experience. The complete sequential recollection of the whole episode is represented by a black line in figure 1.1C that retraces the full trajectory. My recollection includes walking speed and point of view at individual locations along the trajectory and includes retrieval of the events at salient positions along the trajectory. Recollection of the full trajectory requires considerable mental focus. However, as an alternative I can relive one isolated segment and then jump back in time to remember an earlier segment.

I have simulated the mechanisms described here in a computer program implementing a mathematical model of brain dynamics that effectively encodes and retrieves spatiotemporal trajectories. The model of brain dynamics was trained on the gray line representing the location, speed, and direction along the encoded trajectory, and then, cued by the starting position in the parking lot, the computer model generated the

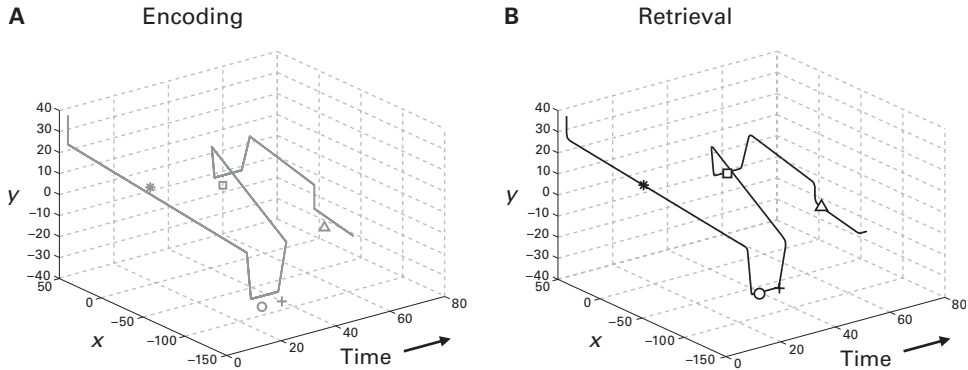


Figure 1.2

Spatiotemporal trajectory in dimensions of both space and time during encoding (A) and retrieval (B). (A) The trajectory changes in both time and space (x and y dimensions) when walking, for example, when passing Jim on the street (asterisk). The trajectory evolves in only time when I am stationary in one location and experience different events, for example, when speaking with Chantal (circle) and Mark (plus sign) at different times in my office. (B) The model generates retrieval of an extended trajectory cued from the location where I parked my car. Retrieval matches the previously experienced trajectory through time and space, including the time and location of the events of meeting people (asterisk, circle, plus, etc.). With different cues, retrieval can start from arbitrary locations or events and select specific trajectory segments.

black line in the figure, showing that the model can effectively retrieve the full spatiotemporal trajectory as well as the location and time of individual events along the trajectory.

To illustrate the role of time in a spatiotemporal trajectory, figure 1.2 plots the same spatiotemporal trajectory in a different way, showing the dimension of time as well as the coordinates of location. In the plot of the spatiotemporal trajectory, different walking speeds result in different slopes of the spatiotemporal trajectory. The model of brain dynamics effectively retrieves both the time intervals and spatial location properties, so that the line indicating retrieval matches the line indicating the original encoded trajectory.

The model of brain dynamics that retrieved the trajectories in the figures contains representations of many of the neurophysiological properties of neurons that have been discovered in recent experimental data. For example, the model includes grid cells and time cells. The elements contributing to this model of brain dynamics will be described in detail, including both the anatomical components and the physiological data. The primary focus of subsequent sections will be describing how neural circuits can encode and retrieve an episode as a spatiotemporal trajectory along with associated events. Thus, my goal is to write the book I described in the preface. The

book I was seeking when first learning about memory, a book that describes how populations of neurons could encode and retrieve a complex spatiotemporal trajectory of behavior.

Note that episodic trajectories are not necessarily limited to the dimensions of physical time and space. When I recall walking between the buildings at Boston University, I also remember my thoughts about the environment. As I walked past my graduate student, I remember thinking about his experimental project on the resonance frequencies of entorhinal neurons. When I spoke to my student Mark, I remember discussing his data on drug infusions that alter grid cell firing. Thus, the episodic trajectory includes additional segments that incorporate features of sensory experience as well as trajectories through internal thought. These can all be incorporated into a multidimensional feature array (or vector) representing the state experienced at a particular time and place, and this multidimensional feature array (vector) can be encoded and retrieved with mechanisms analogous to those used for a trajectory defined only in physical space and time. This has been described as a memory space, in contrast to pure physical space (Eichenbaum et al., 1999). This point will be addressed further in the subsequent text.

A Model of Episodic Memory

As noted above, this book focuses on presenting a model of episodic memory as a spatiotemporal trajectory. The description of episodic memory as a spatiotemporal trajectory immediately puts specific demands on the model. By the definition of episodic memory, the model must address the encoding and retrieval of the place and time of the episode. In addition, the model must address the encoding and retrieval of a viewpoint and the direction of action during specific events in the episodic memory. In the model presented here, the components of time, space, and action are bound together in the manner of physics. The following chapters of the book will provide detailed descriptions of the individual components of the model, but a basic overview is useful as a guide for explaining the significance of different sets of data.

Consider my arrival in my office at the Center for Memory and Brain. Chantal came to my door to say that our paper on sequence retrieval was accepted by the *Journal of Neuroscience*. Then, after about an hour, my graduate student Mark Brandon came to the door to report on his recording data showing grid cell firing patterns altered by muscimol infusions. A short time later, I walked out of my office and back up the street to the Biomedical Engineering Department. When I came out of that building, I walked back along the exact same segment of street that I traversed in the morning, but this time entered the door into the Life Science and Engineering Building. All of these elements need to be coded in the episodic memory.

In the model, my position in time and space is coded by the relative timing of rhythmic activity in different populations of neurons. Rhythmic activity of neurons is described in chapter 2. The representation of my trajectory through space and time is determined by the nature of inputs that change the relative timing of rhythmic peaks in activity, as described in chapter 3. The model depends on the fact that rhythms at slightly different frequencies will shift in timing relative to each other. In the absence of inputs, the relative timing of rhythms with different frequencies will evolve according to time alone, as described in chapter 3, allowing items to be linked with specific points in time coded by populations of neurons, as described in chapters 4 and 5. Thus, as I sat in my office, I could encode the duration of the interval between speaking with Chantal and speaking with Mark. When I left the Center for Memory and Brain to walk to the Biomedical Engineering Department, the trajectory shifted in space. My own sense of direction and movement speed provided a velocity signal that could drive the rhythmic frequency of different populations of neurons. The shift in frequency proportional to velocity meant that the relative timing of these other rhythms could code my location in space, as described in chapter 3. Thus, the code of relative timing can be altered by different inputs that describe the sequential movement of the trajectory through space and time. In addition, the encoding of individual events requires associating the relative timing of population activity with specific items, events, or actions at individual positions along the trajectory, as described in chapters 4 and 5.

During retrieval, one component of the spatiotemporal trajectory is activated as a cue—for example, a memory of entering the Center for Memory and Brain. This activates the relevant rhythms. These rhythms then shift a small amount in relative timing to retrieve the time interval until part of the population pattern activates an association with the event of speaking with Chantal. The rhythms shift a larger amount before a different part of the population pattern retrieves the association with the event of speaking to Mark. Eventually, the recollection reaches the time of leaving the Center for Memory and Brain, and this activates a memory of the direction and speed of movement leaving the center and turning left to walk to the Biomedical Engineering Department. This shifts the frequency of rhythms coding location, causing them to update the internal representation of location in the memory. In this manner, the spatiotemporal trajectory is recreated from the starting cue, and the individual events and actions along the trajectory are reactivated. The subsequent chapters will focus on the neural mechanisms for this process.

Brain Systems for Episodic Memory

Now that I have described the behavioral properties of episodic memory, with an emphasis on encoding and retrieval of spatiotemporal trajectories, we must consider

data suggesting specific brain mechanisms for episodic memory. We cannot fully understand episodic memory if we only consider data on a behavioral level. Thus, the work presented here focuses on a reductionist approach to the understanding of episodic memory. The behavior must be linked not only to the anatomical structures but to the cellular physiology within these structures and the role of particular chemicals acting as neurotransmitters and neuromodulators. Later chapters will address how the cellular properties of individual neurons and the effect of modulators such as acetylcholine may be involved in episodic memory function. However, studying the cellular mechanisms of episodic memory requires first having some sense of what brain structures are involved in episodic memory.

Where in the brain should we look for the cellular dynamics of episodic memory function? Human data provide some answers about the specific anatomical structures involved in episodic memory. Often the first source of information for localizing function in the brain arises from studies of the effects of brain damage. The brain damage can be accidental due to head trauma, or the damage can be deliberate as part of a medical treatment. The first case I will discuss involves a medical treatment that had an unexpected result.

I once met a man who had entirely lost his capacity for episodic memory. His name was Henry Molaison. To preserve his anonymity when he was alive, older journal articles refer to him only as patient HM. I met him when he came to Massachusetts General Hospital in Boston to have an anatomical scan using magnetic resonance imaging to show the specific damage to his brain that caused this loss of episodic memory. My wife was one of the postdoctoral fellows collecting the scanning data, so I accompanied her, along with our infant daughter, Simone. Henry Molaison was 68 years old at the time. He was tall and broad shouldered with a wide face and forehead. He was gregarious and talkative, though when I was first introduced to him he simply said hello, without saying "Nice to meet you." He had learned to avoid saying such things because he knew that he could not remember if he had just spoken to the individual 5 minutes previously.

In response to questions about his past, he very rapidly fell into detailed descriptions of memories from his youth, describing his work in a factory making electric motors, winding the wires around the central core of each little motor. When I met him, Henry used a walker with an attached basket filled with crossword puzzle books and issues of *Reader's Digest*. Before he went into the scanner, I saw him reading a sensationalistic story in *Reader's Digest* about doctors delivering a baby in China. It was the woman's second child, and laws in China restrict couples to one birth. We briefly discussed the details of this somewhat dramatic story before patient HM went into the scanner. After about 15 minutes, he was taken out of the scanner, and I said, "That was a sad story you were reading, wasn't it?" He looked at me blankly, clearly not remembering anything of our previous conversation. "You know, the story about

the doctors in China?" I pointed at the *Reader's Digest*, where he had placed a bookmark on the story. He opened the *Reader's Digest* and, without saying anything, started reading the story again at the beginning, clearly having no recollection of any part of the previous conversation, though I had a clear episodic memory of those events.

This story gives a notion of patient HM's behavioral impairment. He could carry on a conversation, keeping track of the context of recent comments. This indicated the preservation of his working memory. He knew the meaning of most words, indicating the preservation of his semantic memory. He could rapidly unfold his collapsible walker, indicating the preservation of his procedural memory. He could remember some episodes from before his surgery, indicating he does not have loss of memory for all events from before surgery (known as retrograde amnesia) though he had difficulty remembering events shortly before his surgery, suggesting partial retrograde amnesia. Most strikingly, he demonstrated an inability to form memories for new events in his life after the surgery. This is often described as complete anterograde amnesia.

He was more patient and friendly than one normally would expect of a 68-year-old man waiting to have a scan in a hospital—I could not help feeling that his personality was more like a 27-year-old man. This was his age when a neurosurgeon in Hartford, Connecticut, performed the brain surgery that resulted in his loss of ability to form new episodic memories. He could remember events from his childhood, suggesting that episodic memories occurring some time before his surgery were preserved, but the surgery appeared to block the formation of new episodic memories.

The selective behavioral impairment of patient HM provides one piece of evidence supporting the existence of multiple memory systems (Eichenbaum and Cohen, 2001). Surprisingly, most people do not have a strong intuition about the existence of multiple different types of memory function. In colloquial conversation, we use the same word "remember" for a variety of functions. We talk about remembering the name of the capital of Sweden (semantic memory), or remembering the start of a spoken sentence (working memory), or remembering how to ski (procedural memory), or remembering our first search for articles on memory (episodic memory). However, in these examples, the same word is being used to describe very different types of memory that depend on distinct brain systems. As noted above, Endel Tulving first defined episodic memory as a contrast to semantic memory, or memory for general knowledge of the world (Tulving, 1983, 1984, 2001). As described below, short-term memory for the start of a sentence is separate from long-term episodic memory. In addition, extensive data show a distinction between episodic memory and memory for motor skills learned by the procedural memory system, such as the ability to ski or to ride a bicycle, which shows a dependence on brain systems unaffected in patient HM (Cohen and Squire, 1980; Eichenbaum and Cohen, 2001).

As a child, patient HM suffered from intractable epilepsy—regular seizures would disrupt his life daily, and drugs could not control the seizure activity. Finally, as a last resort, a neurosurgeon named William Scoville removed the regions of patient HM's brain where the seizures appeared to be starting. The surgeon entered through two openings on each side of the forehead, lifting bone flaps that gave him access to the inside and bottom surface of each temporal lobe (ventromedial surface). He then cut the tissue from the ventromedial surface, removing structures on both sides of the brain that included the anterior two-thirds of the hippocampus, the entire entorhinal cortex, and parts of the perirhinal and parahippocampal cortices as well as the amygdala and white matter (fiber) connections of these regions. The lesion that Scoville created in patient HM is shown in figure 1.3 (Scoville and Milner, 1957; Corkin et al., 1997). The anatomy is described further in chapters 2 and 5.

Patient HM was not the only case of anterograde amnesia from bilateral excision of the medial temporal lobe. The original article by Scoville and Milner described several other cases, but these other cases were schizophrenics in whom other

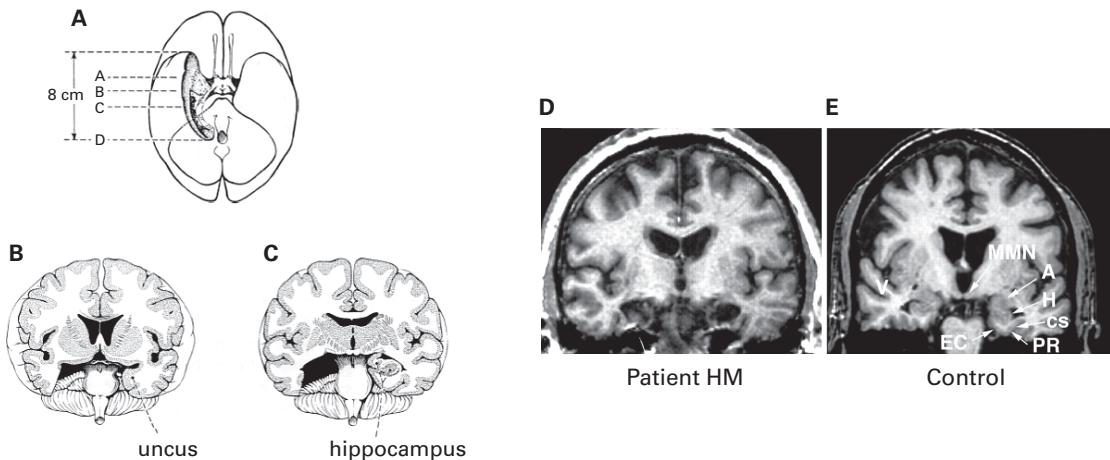


Figure 1.3

Damage to the brain of patient HM. (A) Ventral (bottom) surface of brain showing location of removal of hippocampus, entorhinal cortex and other structures. (B and C) Brain cross-sections showing areas removed on both sides in patient HM. Each figure shows the damage on the left and illustrates the area that is missing on the right. (D) Anatomical scan of the brain of patient HM, showing absence of the anterior hippocampus and entorhinal cortex on both sides of the brain. (E) Comparison scan of a different brain with intact structures, including hippocampus (H), entorhinal cortex (EC), perirhinal cortex (PR), amygdala (A), medial mammillary nucleus (MMN), collateral sulcus (cs), ventricle (v). Reprinted with permission from Scoville and Milner, 1957 (A–C) and Corkin et al., 1997 (D, E).

behavioral disorders partially obscured the nature of the memory impairment, which is strikingly specific in patient HM. The neurosurgeon Wilder Penfield at the Montreal Neurological Institute performed a similar surgery unilaterally in a patient which resulted in profound anterograde amnesia due to previous atrophy of the hippocampus on the contralateral side (Penfield and Milner, 1958).

The damage to the brain of patient HM was very extensive. However, more selective damage to the hippocampus has been shown to impair memory function also. Complications during surgery (hypoxia) has caused selective damage to subregions of the hippocampus in some subjects (Rempel-Clower et al., 1996). These subjects have amnesic effects that are somewhat less severe than those of patient HM, but they still demonstrate impairments of episodic memory in quantitative tests of human memory that allow a more sensitive measure of these differences in memory capabilities.

Tests of Episodic Memory

Whereas patient HM's deficit would be clear to anyone who spoke to him for a reasonable period of time, comparing deficits across patients cannot be done on the basis of anecdotes such as the one above. The description of his disorder gives a general sense of what memory function he retained (he could remember individual topics during a conversation, and he could remember facts about the world and memories from the distant past). These aspects of spared function can be described using the terms working memory and semantic memory, respectively, but this general description of the disorder does not provide a clear quantitative assessment of the individual dimensions of memory function.

I remember a feeling of disappointment as an undergraduate when I first read the literature on human memory function. I had expected descriptions of the mechanisms for memory recollection that had all the richness of my own episodic memories with trajectories and viewpoints and complex visual scenes. However, I primarily found quantitative studies of human verbal memory function that focused on the encoding and recall of lists of single words or groups of letters. I should mention that this was the year before Tulving's book on episodic memory was published in 1983.

However, despite their initial dryness to a student, these studies using specific human memory tasks provide an important quantification of human memory function in a consistent, standardized manner. Memory tasks include standard clinical tests used in neuropsychological evaluation of patients, such as the Wechsler Memory Scale, described below. In addition, considerable research has utilized individual memory tests, described below, that provide a larger continuous scale for measuring memory function. These latter tests also allow quantification of the effect of numerous other factors on memory function in humans, including conditions of encoding as well as effects of drugs. These tasks vary in presentation modality and timing of different components but share some features. Here I will describe some standard tests of

memory that directly test episodic memory, such as free recall and cued recall, as well as tests that address aspects of other memory systems. My description is focused not on the general use of these tests but on what they say about the selectivity of effects of neural damage on different aspects of memory function. In addition, the effect of drugs on performance in these tasks will be discussed in more detail in chapter 6.

Neuropsychological Tests

Neuropsychological tests focus on assessing the behavioral symptoms of brain damage or disease. The Wechsler Memory Scale has been used in a variety of neuropsychological testing situations, including the initial studies of patient HM. This task contains a battery of different memory tasks focused on different components of memory function. Any behavioral task will put demands on multiple different memory systems, but some require episodic memory function more strongly than others. The Wechsler Memory Scale includes a test of story recall, in which a paragraph is read to participants and they are scored on how well they retrieve components of this story. This requires elements of semantic memory and working memory but clearly also tests episodic memory. Patient HM was severely impaired on paragraph recall. Patient HM also showed striking deficits in other tests on the Wechsler Memory Scale that required encoding and retrieval of items from an episode (Scoville and Milner, 1957; Corkin, 1984) such as the free recall of words from a list or cued recall of paired associates (both tasks are described in more detail below). In the list of difficult paired associates, patient HM could retrieve none of the second words in each pair. While this provides a general overview of memory impairment, the Wechsler Memory Scale has relatively small numbers of items in each component of the task. This allows it to give a broad qualitative measure of memory function but does not give much quantitative detail. For example, the test includes a list of 20 word pairs for testing paired associate learning, whereas focused paired associate learning tasks might use 64 or more (see below). Thus, the Wechsler Memory Scale can distinguish between a college undergraduate and patient HM but might not distinguish between two amnesics with slightly differing memory capacities.

Numerous other multicomponent tasks have been developed for neuropsychological research, including the California Verbal Learning Task (CVLT). This task also provides a consistent assessment which can be relatively rapidly applied across a large number of patients. However, similar to the Wechsler Memory Scale, the CVLT has a paucity of numbers within the individual components of the task. The mini-mental state examination is an even shorter test that is often used as an initial screen for dementia—for example, in studies of patients with Alzheimer's disease.

Free Recall

Better quantitative data are available from individual laboratory tests of free recall that have larger numbers of words than the Wechsler Memory Scale and can give a detailed quantitative assessment of individual components of memory function. In a free recall

task, participants sit with an examiner in a testing room and hear or see a sequential presentation of a series of single words during an encoding period. Subsequently, during a separate retrieval period, they are asked to say as many words on the list as they can remember in any order, either immediately after the end of the list (immediate free recall) or after a delay period of varying length with intervening distraction (delayed free recall). Thus, the task has two separate behavioral components that occupy extended periods of time. In the encoding period, participants are presented with the individual words. In the retrieval period, they must generate the words that were on the list. (Note that these longer periods of encoding and retrieval during a behavioral task differ from possible rapid changes between dynamics of encoding and retrieval in the brain.) In an immediate free recall test, normal participants usually show a much greater probability for recall of words at the end of the list. This is called the “recency” effect and appears to involve short-term memory. In contrast, retrieval of words from the start of the list in immediate free recall and from the entire list in delayed free recall is believed to require episodic memory.

Remarkably, only in the past few decades have the fields within cognitive science accepted the existence of multiple different memory systems. One of the first distinctions was between short-term memory and long-term episodic memory, as supported by cognitive data in patients with amnesia caused by Korsakoff’s syndrome. Korsakoff’s syndrome results from insufficient levels of the vitamin thiamine in the diet, causing neurological damage to structures including the medial mammillary nuclei and anterior thalamus. Baddeley and Warrington (Baddeley and Warrington, 1970) tested patients with Korsakoff’s syndrome as well as some with hippocampal damage in an immediate free recall task. Multiple tests allowed plotting of a serial position curve, in which the probability of recall is plotted for words at different positions in the encoded list. As shown in figure 1.4, the control participants in the task showed a normal recency effect with enhanced retrieval of words from the end of the list. The amnesic patients showed a similar recency effect with normal retrieval for words at the end of the list. However, the amnesics showed a dramatic reduction in retrieval of words from the start of the list relative to control participants, indicating a selective loss of long-term episodic memory but not short-term memory.

Thus, the serial position curve shows similar responses to recent stimuli in both controls and amnesics, with a clear decrease in performance on earlier portions of the curve in amnesics. The figure demonstrates the impairment of delayed free recall (long-term memory) in amnesics with sparing of recency (short-term memory). Patient HM and other hippocampal patients show a similar pattern of deficits (Corkin, 1984; Graf et al., 1984). For example, patient RB had a lesion selective to a subregion of the hippocampus termed CA1 caused by hypoxia during surgery. In tests of the free recall of ten words from the middle of a fifteen-word list, patient RB only recalled 10 percent of the words whereas controls recalled about 40 percent (Graf et al., 1984). This

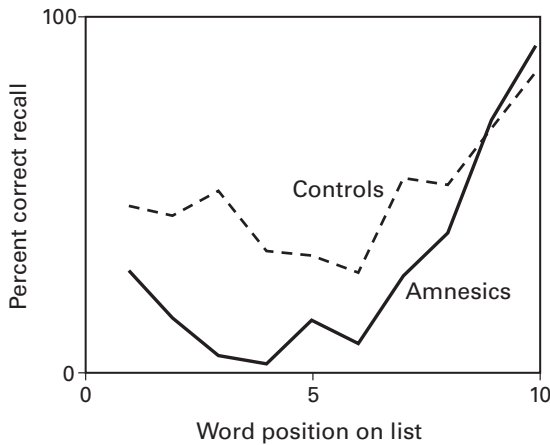


Figure 1.4

Serial position curves for control participants (dashed line) and amnesics (solid line) showing percent correct recall of words based on their presentation time during encoding at different serial positions in the list.

indicates a selective effect of hippocampal damage on long-term episodic memory. The separation of short-term memory from long-term episodic memory is further supported by the existence of a different group of patients with a different locus of damage (e.g., the parietal lobe) showing a selective loss of short-term memory relative to long-term episodic memory (Warrington and Shallice, 1969; Shallice and Warrington, 1970).

In the popular media, there is sometimes confusion about the difference between long-term and short-term memory. For example, in the film *Memento* the main character has a memory impairment similar to patient HM that is referred to as a short-term memory problem, but the character displays normal short-term memory function as defined in the psychology literature. This confusion arises because medial temporal lobe damage spares semantic memory and some long-term episodic memory from before the damage and sparing of short-term memory in patient HM. The confusion could be alleviated by using the label intermediate term episodic memory to describe the loss of encoding of new episodic memories in patient HM, despite the sparing of old episodic memories that he consolidated before the damage.

As noted above, the impairment of delayed free recall is similar in the different types of amnesia arising from either hippocampal damage or Korsakoff's syndrome, though the anatomical basis appears to be very different. In particular, Korsakoff's amnesia is associated with atrophy of the mammillary nuclei and the anterior thalamus (Vann and Aggleton, 2004). Other sources of damage to these regions have also

been shown to cause amnesia, including two rather unusual cases in which damage was caused by sharp objects entering the brain through the nose, including a miniature fencing foil and a pool cue (Vann and Aggleton, 2004) that damaged the mammillary nuclei and anterior thalamus. Physiological data suggest that the role of these structures could involve the coding of speed and head direction by the activity of neurons in the mammillary nuclei (Blair et al., 1998) and anterior thalamus (Taube, 1995). The model presented here shows how the input from these regions would be essential to the encoding of spatiotemporal trajectories for episodic memory.

The verbal free recall task seems quite far from a model of spatiotemporal trajectories in episodic memory. However, it is clearly a test of episodic memory, so the relationship to spatiotemporal trajectories is worth evaluating. A free recall task focuses on a restricted subspace of the spatiotemporal trajectory, defined in the dimension of time by the start and end of testing and defined in space by the testing room. In fact, most free recall tasks divide time into testing on individual lists, and participants must limit their free recall to words presented in the most recent list.

The subjects in a free recall task experience a full spatiotemporal trajectory as they walk into the building for their experiment, find the appropriate room, and learn about the testing rules. If they were tested on their recall of the approach to the room, they could just as easily describe memories of this approach as they describe memories of individual words in the test. During the free recall task, the participants experience a wide dimensionality of individual words that could be seen as excursions into multiple dimensions of orthography and semantics. Thus, the trajectory does not just involve the dimensions of time and physical space but also involves movement through other dimensions of what has been termed a memory space (Eichenbaum et al., 1999). Multiple dimensions of sensory experience and internal thought are a constant component of episodic experience. Participants are likely to have heard some of the same words in the free recall task during a conversation earlier that day, but they are asked to ignore these previous multidimensional memories because they fall outside of the temporal segment of memories experienced within the subspace defined by the free recall task. In free recall, no temporal order is required in the response. Even though retrieval of a series of words involves an excursion along a spatiotemporal trajectory of previous experience, most experimenters will only score the individual words recalled. In a sense, this collapses the time dimension of the retrieved spatiotemporal trajectory onto a plane of verbal dimensions defining only the words. However, some free recall experiments will sample the temporal domain by keeping information about order of retrieval (Howard and Kahana, 2002) or specifically requiring the serial recall of the words (Burgess and Hitch, 1999), constraining retrieval to recreate the spatiotemporal trajectory in the same temporal order.

In addition to damage to brain regions, administration of different types of drugs can have a profound effect on memory performance in these tasks. For example, drugs

that block the activity of acetylcholine receptors or enhance GABA receptor activity can strongly impair the encoding of new words in this task, while sparing the recall of previously learned words. Drug effects on episodic memory are reviewed in more detail in chapter 6.

Cued Recall

In a cued recall or paired associates task, participants sit in a testing room and hear or see sequential presentation of a series of pairs of words, for example, *barber* followed by *crumb*, then *razor* followed by *tact*, then *vulture* followed by *aspirin*. They are then given the first word of each pair and asked to say or type the second word of the pair. For example, they would be given the word *razor* and should respond with the word *tact*. This task also shows strong impairments in amnesic patients with hippocampal damage. Patient HM was not able to learn a single paired associate from the unrelated list in the Wechsler Memory Scale (Scoville and Milner, 1957). Even patients with much more selective damage affecting only subregions of the hippocampal formation such as region CA1 show significant quantitative impairments on this task (Rempel-Clower et al., 1996). For example, patient RB has damage restricted to region CA1 of the hippocampus. When tested three times sequentially on a list of ten unrelated paired associates, patient RB only recalled 3.7 pairs out of 30 while controls recalled correct associations over 20 times (Zola-Morgan et al., 1986). Cued recall does not completely ignore the order of encoding as in free recall but focuses on retrieval of very short temporal segments of an episode.

Richness of Episodic Detail

Tasks such as free recall and cued recall test the episodic memory for the specific event of seeing a particular word at a particular time and a particular place. However, they do not test the full richness of detail about an episode from real life. More recently, specific behavioral scoring methods have been developed to fully quantify the richness of detail in human episodic recollection (Levine et al., 2002) by scoring the amount of contextual detail internal to specific remembered episodes. These techniques show significant reductions in the recall of internal details from an episodic memory after lesions of the hippocampus and parahippocampal cortices (Steinvorth et al., 2005; Kirwan et al., 2008). In contrast to the impairment of richness of detail in episodic memory, hippocampal and parahippocampal lesions have less effect on long-term semantic memory (Steinvorth et al., 2005). Interestingly, recent data show that lesions of the medial temporal cortices also cause significant impairments in the description of future or imagined episodes (Hassabis et al., 2007; Schacter and Addis, 2007). These data on richness of detail support the notion that the hippocampus and parahippocampal cortices create a detailed representation of a complex spatiotemporal trajectory on which a range of detailed items and events can be fastened. The loss of

this spatiotemporal trajectory impairs the ability to retrace a trajectory and access the relevant details and even impairs the ability to imagine walking along a future trajectory and experiencing events and viewpoints along that future trajectory.

Spatial Memory

Given the focus of this text on the encoding of spatiotemporal trajectories in episodic memory, perhaps the most relevant quantitative data for this model concerns the learning of visual mazes by patient HM. In the time of initial testing on patient HM, one available task used an array of metal pegs on a board and a metal stylus. Participants were required to put the stylus on the pegs and learn by trial and error the winding path between the start and finish pegs with wrong responses detected by a click. In an average of 25 trials, normal participants can learn to contact only the 28 correct pegs between start and finish, but patient HM did not reduce his number of errors in 215 trials (Milner et al., 1968). I interpret this as evidence for his difficulty in remembering the spatiotemporal sequence of correct pegs encountered on a given trial. On a dramatically shortened task with 8 pegs in an array of 20, patient HM did show a reduction in errors over several days, indicating a capacity for learning over extended training that could reflect learning in semantic memory or procedural memory. This slow semantic learning is consistent with the ability of patient HM to draw a floor map of the house he lived in after his surgery after he had lived there for eight years (Milner et al., 1968). This could indicate the slow updating of neocortical semantic memory over time in contrast to rapid learning of new spatial memories. Recent studies on patients with unilateral thermal lesions of the hippocampus performed for treatment of epilepsy show striking impairments in memory for the spatial location of objects. Participants were shown one to six objects in an arena and asked to mark the locations or replace the objects. Right hippocampal lesions caused significant impairments relative to controls even for the location of a single object (Bohbot et al., 1998; Stepankova et al., 2004).

Recognition Tasks

In a recognition task, participants are usually presented with a list of single words during the encoding period. Subsequently, their recognition of these words can be tested by presenting word pairs containing one novel word and one word presented during encoding. Participants must choose the word presented during encoding. For example, participants might see the words *horse*, *bone*, *church*, *snow* during encoding. Then, during recognition testing, they would be asked to indicate the familiar word in a series of word pairs, such as the pair *horse*, *glove*. As an alternative test of recognition, participants might be presented with single words and requested to indicate whether the word is old or new. Considerable research has focused on characterizing aspects of memory function retained in humans with hippocampal damage. This

remains an active and controversial area of ongoing research. In general, amnesics with hippocampal damage perform better on recognition tasks than on free recall or paired associate tasks, but this might reflect sparing of just one mechanism for recognition.

Considerable research has focused on the possibility of two separate mechanisms involved in recognition memory. During the recognition period, participants might explicitly retrieve a detailed episodic memory of hearing a word (recollection) or they might base their response on a vague sense of the greater familiarity of one word versus another (familiarity). This was initially tested by Tulving using what is known as the “remember–know” paradigm. Participants were told to rate the confidence of their response by responding with “remember” for recollection and “know” for familiarity. More recently, these mechanisms have been tested based on participants’ rating their confidence in their recognition judgment. Many researchers and models have proposed that hippocampal circuits are required for recognition based on recollection, but not for recognition based on a general sense of familiarity (Norman and O’Reilly, 2003; Fortin et al., 2004; Yonelinas et al., 2005; Eichenbaum et al., 2007). However, amnesics with hippocampal damage show impairments on recognition memory tasks including both “remember” and “know” responses (Manns et al., 2003). Full review of the extensive research and controversies in this area would require a separate book. This book primarily focuses on mechanisms that would be involved in recognition judgments based on recollection. In this task, if a subject can recollect a segment of a spatiotemporal trajectory containing the word, he or she will give a “remember” (recollection) response.

Comparison with Short-Term Memory Tests

The data on the serial position curve above show sparing of short-term memory during impairment of long-term memory. Similarly, damage to the hippocampus and adjacent cortical structures does not affect the articulatory loop for holding information in working memory. This can be seen by the preserved performance of patients with hippocampal damage in the digit span task. In this task, participants are presented with sequences of numbers and requested to repeat them back (without an interfering task) at the end of the sequence. Typically, participants are very effective at repeating lists of numbers up to seven digits long but begin to make errors with longer lists, particularly when there are ten or more digits in the list. Participants with hippocampal damage show normal memory span (they can usually repeat back six or seven digits effectively, similar to normal participants; Cave and Squire, 1992). Patient HM had a memory span of six digits after his operation (Milner et al., 1968), and patient PB with anterograde amnesia from unilateral left hippocampectomy combined with atrophy of the right hippocampus had a forward digit span of nine (Penfield and Milner, 1958). Amnesics usually show significant impairments on longer, supraspan

lists, suggesting the necessity for use of hippocampal circuits once working memory capacity has been exceeded.

The Brown-Peterson task provided initial behavioral evidence for a short-term memory process with rapid decay that was distinct from long-term episodic memory. In this task, participants are presented with groups of three words or three consonants (called trigrams). For example, the experimenter might say “YQM” and the subject repeats this. After each trigram, the subject must count backward by threes from different starting numbers. Then after 3, 9, or 18 seconds, they must repeat the trigram that was presented to them. This task has traditionally been described as a test of short-term memory. However, participants such as patient HM show some reductions of performance on this task (Corkin, 1984), indicating a potential role for the hippocampus or parahippocampal cortices in this type of task despite the short retention interval. The presence of a distractor task during the delay in this task appears to be important as it may prevent holding of information by active maintenance in the neocortex and thereby require the use of hippocampal circuits for episodic memory. This type of task emphasizes the importance of developing a model that can directly address task variables and data from individual tasks rather than attempting to summarize the behavior in multiple individual tasks in terms of a small number of discrete verbal categories.

Functional Imaging Studies

As described here, the attribution of behavioral function to specific brain regions draws on a long history of neuropsychological work involving effects of localized brain damage on behavioral function. Patient HM and other patients with localized damage to the hippocampus and adjacent areas were influential in focusing memory research on these regions. Though some of this research may seem old, research on the neural mechanisms of other cognitive functions such as language have an even longer history that extends back to the work of neurologists in the mid-nineteenth century.

Given this long history, the use of functional imaging techniques in humans presents a very recent addition to the field. When the technique of positron-emission tomography (PET) became available for measuring the activity of brain regions by measuring uptake of radioactive glucose or oxygen, studies of memory focused on finding activation of the hippocampus. Initial studies analyzed PET activation during verbal memory tasks such as word stem completion based on recall (Squire et al., 1992; Buckner et al., 1995) or retrieval of episodic versus semantic paired associates (Fletcher et al., 1995), but these studies did not show robust activation of the hippocampal formation. In contrast, PET activation during encoding of faces showed greater regional cerebral blood flow in the hippocampus (Grady et al., 1995; Haxby et al., 1996).

A later imaging technique involved measuring changes in blood oxygenation and flow associated with neural activity using functional magnetic resonance imaging (fMRI). The first demonstration of hippocampal activation using fMRI was obtained with a study using encoding of complex visual scenes for subsequent postscan recognition (Stern et al., 1996). Participants in this study showed robust differences in activation in the posterior hippocampus and parahippocampal gyrus between encoding of different visual scenes and repeated presentation of a single visual scene. This effect was replicated in a later study using the same techniques (Gabrieli et al., 1997). Refinement of fMRI techniques allowed measurement of event-related activity associated with individual stimuli. These techniques showed differences in hippocampal and parahippocampal fMRI signal associated with stimuli that were later remembered versus those that were forgotten in a subsequent memory task, both for complex visual images (Brewer et al., 1998) and for word stimuli (Wagner et al., 1998). Subsequent studies showed that both types of stimuli could activate hippocampal regions, with greater left hippocampal activation for word stimuli versus bilateral coding for pictures (Kirchhoff et al., 2000). Interestingly, most imaging studies show greater activation of posterior hippocampal regions with encoding (Stern et al., 1996; Greicius et al., 2003), consistent with rat lesion studies suggesting the dorsal hippocampus may be more strongly involved in episodic memory (Moser and Moser, 1998). Dorsal hippocampus in rats is analogous to posterior hippocampus in humans. High resolution imaging studies analyzing the function of individual hippocampal subregions (Bakker et al., 2008) will be discussed further in chapter 5.

Studies have also demonstrated the involvement in encoding of episodic memory of a broader circuit of regions beyond the hippocampus and parahippocampal structures, including the inferior prefrontal cortex, the parietal cortex, and the retrosplenial cortex. One study used a virtual world in which subjects received items from individuals in different locations of the virtual world and were later tested for their memory of the items and the individuals (Burgess et al., 2001). Results support a model in which the location of events is coded by parahippocampal and hippocampal structures with translation to head centered coordinates by parietal cortex (Burgess et al., 2001; Byrne et al., 2007). The retrosplenial activity appears to correlate with the recall of specific spatial locations from memory (Epstein et al., 2007b; Epstein et al., 2007a), rather than with more general perception of spatial scenes mediated by parahippocampal cortices. The involvement in spatial processing is consistent with retrosplenial neural responses based on head direction in rats (Cho and Sharp, 2001). Imaging studies have also shown correlates of sustained entorhinal cortex activity during encoding with subsequent cued recall performance (Fernandez et al., 1999). In a delayed match to sample task, entorhinal activity during the delay period after the sample period correlated with subsequent long-term recognition memory for the sample stimulus (Schon et al., 2004; Schon et al., 2005). These studies support the

proposal that cellular mechanisms of persistent spiking in entorhinal cortex may contribute to encoding of episodic memories as described later.

Episodic-like Memory in Animals

Our capacity to remember episodes in our lives provides a profound and highly valued aspect to our existence, allowing us the capacity to relive events in our lives. We value the ability to relive a proud moment such as a graduation or the birth of a child. We expect and in many cases require that we will remember a meeting with a coworker or a visit to a family member. We start to question our mental capabilities if we forget an episode, and we question the capabilities of others if they forget an episode that we remember. Thus, the memory for episodes is an essential component of human behavior.

The richness and complexity of human episodic memory have led some researchers to argue that episodic memory and mental time travel are a purely human capacity (Tulving, 1983, 1984; Suddendorf and Corballis, 1997; Tulving, 2001) whereas others argue that animals have this capacity as well (Clayton et al., 2003; Dere et al., 2006). The personal experience of animals is beyond experimental test, as they cannot provide a description of consciously reliving the richness of detail in a recollection of a prior event. However, behavioral data provide a compelling argument that many of the capacities for episodic memory shown in humans can be found in animals (Dere et al., 2006). This has led to the development of behavioral tasks testing what is referred to as “episodic-like memory” in animals (Fortin et al., 2002; Clayton et al., 2003; Fortin et al., 2004; Dere et al., 2006). Studies on episodic-like memory in animals provide an important opportunity to perform experiments for testing the brain mechanisms of episodic memory.

As described in chapter 2, electrophysiological recordings from animals show phenomena that support the existence of mental time travel along previously experienced trajectories (Skaggs and McNaughton, 1996; Johnson and Redish, 2007). In addition, many of the qualitative anatomical (Amaral and Witter, 1989) and physiological (Halliwell, 1986, 1989) properties of neural circuits observed in human cortical structures are also found in other mammals. Thus, it is reasonable to conclude that the cellular dynamics mediating episodic memory in humans are also present in animals, even if there is a difference in the quantity of experimental data on episodic memory available from other species. This section will review some of the available behavioral data indicating the presence of episodic memory in animals.

Birds

Some of the most compelling data on episodic-like memory in animals come from research on birds such as the scrub jay, which demonstrate remarkable episodic