Bachelor Degree Project

THE HIPPOCAMPAL DEPENDENCE OF LONG-TERM DECLARATIVE MEMORY

Bachelor Degree Project in Cognitive Neuroscience
Basic level 15 ECTS
Spring term 2015

Rodrigo Alvarez Svahn

Supervisor: Daniel Broman
Examiner: Joel Parthemore

Abstract

Investigations into the neural correlates of memory have found the hippocampus to be a crucial structure for long-term declarative memories, but the exact nature of this contribution remains under debate. This paper covers three theories concerned with how the hippocampus is involved in long-term memory, namely the Standard Consolidation Model, the Multiple-Trace Theory, and the Distributed Reinstatement Theory. According to the Standard Consolidation Model, long-term declarative memories (both episodic and semantic) are dependent on the hippocampus for a limited time during which the memories undergo a process of consolidation, after which they become dependent on the neocortex. In contrast, the Multiple-Trace Theory argues that detailed and context-specific episodic (but not semantic) memories remain dependent on the hippocampus indefinitely. While both the aforementioned theories posit that memories are initially dependent on the hippocampus, the Distributed Reinstatement Theory does not. Advocates of this theory propose that several memory systems compete for the encoding of a memory, and that the hippocampus usually is the dominant system. However, it is also suggested that the other (unspecified) memory systems can overcome the hippocampal dominance through extensive and distributed learning sessions. In this paper, findings from both human and rodent studies focusing on the hippocampus are reviewed and used to evaluate the claims made by each theory on a systems level.

Keywords: hippocampus, retrograde amnesia, standard consolidation model, multiple-trace theory, distributed reinstatement theory

Table of Contents

Introduction

The brain's capacity to store previously encountered information and to vividly recreate past experiences is truly extraordinary. The ability to form and sustain memories is part of everyday life, and something most people might take for granted. While some may jokingly state that they have incredibly awful memory, the truth is that they are capable of storing an immense amount of information. These people are able to study and retain information to prepare for a test, remember parts of their childhood, and form long-lasting relationships with people based on their past memories with them. In light of all the things our memory function allows us to do, it becomes apparent how devastating a loss of this ability can be. Although there is still much left to learn, scientific investigations into various kinds of memory loss and the specific damage required to produce them have given us some insight into the workings of memory. This paper will focus on scientific investigations into how a region known as the hippocampus contributes to memory.

Studies within the domain of memory are conducted very frequently, and may be of great importance. Expanding our current knowledge of how the human brain obtains, stores, and retrieves knowledge could have several beneficial consequences. With the knowledge of how memory traces are formed and strengthened comes the potential of devising new optimized study programs and ways of teaching. Additionally, such knowledge could aid the development of beneficial clinical interventions for different kinds of memory disorders. For such reasons, it is very important to continuously improve our understanding of the workings of memory. If, and more hopefully when, the day comes that a theory is able to account for the hippocampal involvement in memory, we are likely have taken one step further in the aforementioned directions.

Even though we do not yet have a complete picture of how the hippocampus is involved in long-term memory formation and storage, scientific research has still uncovered much of

how memory is supported by the brain over the years. In the middle of the 20th century, Brenda Milner and Wilder Penfield carried out several experiments on patients who displayed memory impairments after undergoing unilateral temporal lobectomy. In most cases, the patients were left with only a mild, material-specific memory impairment (Milner, Squire, & Kandel, 1998). Eventually, Milner and Penfield (1955) reported having encountered two patients exhibiting severe, enduring, and generalized memory impairments after the surgery (Milner & Penfield, 1955). One of these patients (P.B.) underwent a left temporal lobectomy in two stages, and it was only after the second stage during which the uncus, hippocampus, and hippocampal gyrus were removed that a severe memory loss was observed (Milner & Penfield, 1955). Upon P.B.'s death some years later, the autopsy revealed an extensive, long-standing atrophy of the right hippocampus, with no other significant abnormality being observed in the rest of the right temporal lobe (Milner et al., 1998). Thus, upon removal of P.B.'s left temporal lobe, he was deprived of hippocampal function bilaterally. This indicated the importance of intact hippocampal function for normal memory performance.

Subsequently, Milner examined the now famous patient H.M., who underwent bilateral medial temporal lobe (MTL) resection (including the hippocampus) as a means to alleviate his epileptic seizures, leaving him with a severe memory impairment without any apparent loss of other cognitive abilities (Scoville & Milner, 1957). He could neither form new memories nor remember some events prior to his surgery (Squire & Wixted, 2011). The memory deficit observed in H.M. after the surgery has been the subject of extensive and some of the most important research on human memory.

Milner and Scoville never claimed that the hippocampal lesions were exclusively responsible for H.M.'s memory loss (Milner et al., 1998). However, they had not come across amnesia following focal, bilateral removal of the amygdala and uncus (Scoville & Milner, 1957), and thus attention was drawn towards the hippocampus. While ties between the

hippocampus and memory function had been made, brain lesions resulting in impaired memory performance had not been limited to the hippocampus alone (Zola-Morgan, Squire, & Amaral, 1986). Therefore, the importance of the hippocampus in normal memory function could not be fully established. However, a few decades after the discovery of H.M., Zola-Morgan et al. (1986) reported observations of long-lasting memory impairments in a patient (R.B.) with bilateral damage limited to the CA1 field of the hippocampus. R.B.'s memory impairment was not as severe as that of H.M.'s, which suggested that while the hippocampus was crucial for fully intact memory performance, other structures within the MTL also contributed to memory. Subsequent research in primates further established the importance of structures within the MTL (hippocampus and the parahippocampal, entorhinal, and perirhinal cortices) for the normal functioning memory (Squire & Zola-Morgan, 1991). Today, it is believed that the severity of H.M.'s memory impairment depends not only on the hippocampal damage, but that the surgical removal included the hippocampal region as well as the perirhinal and entorhinal cortices (Milner et al., 1998).

Studies with patient H.M. eventually led to the now generally accepted notion of memory not being a single, unitary entity. For example, a study by Milner (as cited in Milner et al., 1998) found that H.M. could learn a new motor skill through a mirror-drawing task without knowledge of ever having performed the task, contributing to the idea of there being multiple, anatomically separate memory systems in the brain. Further findings in other amnesic patients corroborated this idea. By employing a mirror-reading task, Cohen and Squire (1980) elaborated upon Milner's mirror-drawing task by showing that learning in amnesic patients was not restricted to perceptual-motor information, but included pattern-analyzing skills as well.

Importantly, it appeared as though H.M. (and R.B.) could still remember facts and events from a time remote to the surgery, meaning that the medial temporal lobes could not be

the ultimate long-term memory storage site (Squire & Wixted, 2011). Instead, the neocortex has been proposed to be the final repository for remote memories (i.e., long-term memories of remote times; Zola-Morgan & Squire, 1990). Today, there is still disagreement about the exact contribution of the hippocampus and other medial temporal lobe structures to remote memory. Some argue that the hippocampus plays a permanent role in the retention of long-term memories, while others mean that it has only a temporary role. In this paper, three leading theories regarding hippocampal involvement in long-term memory formation and storage will be reviewed. These are: the Standard Consolidation Model, the Multiple-Trace Theory, and the Distributed Reinstatement Theory. The reason why these three theories were chosen is quite simple. The largest ongoing debate is between the Standard Consolidation Model and the Multiple-Trace theory, so it was only natural for these two to be included. As for the Distributed Reinstatement Theory, it provides such a different account of long-term memory formation and storage (see below), that it adds an interesting contrast to the other two theories.

Before describing the different theories and what evidence there is in support and opposition of them, different kinds of memory and patterns of memory loss (amnesia) will be defined. When evaluating the theories, findings from both human subjects and rodents in the existing literature will be reviewed, with the focus being on the hippocampal dependence of long-term declarative memory. The main interests of this paper with regards to findings from human subjects are lesion studies and neuroimaging studies investigating episodic memory. Studies of contextual fear conditioning and spatial memory will be included in the section about findings from rodents. This is because they open for the possibility of experimentally testing a memory's contextual specificity, meaning that they can be used to evaluate the aforementioned theories. Concluding the paper will be a discussion of the compatible and contradictory findings between the theories.

Separate Memory Systems

Evidence from lesion studies have converged over the years to suggest that memory does not consist of a single system. Memory as a whole can be divided into short-term and long-term memory. Short-term memory allows for the maintenance of small quantities of information over a few seconds, whereas long-term memory makes it possible to retain larger quantities of information over an extended period of time (Baddeley, Eysenck, & Anderson, 2015). Long-term memory can be further divided into implicit or nondeclarative memory and explicit or declarative memory. The former refers to memories that are not readily available for conscious recollection (e.g. knowing how to ride a bicycle), and the latter to memories that can be consciously retrieved (Adlam, Patterson, & Hodges, 2009). A distinction between such memories was made by the philosopher Gilbert Ryle in 1949 before the work with H.M. had fueled empirical research into the existence of multiple memory systems (Milner et al., 1998). Ryle (1949) distinguished between the ability of knowing how (knowing how to play chess), and the ability of knowing that (knowing the rules of chess). Furthermore, it has been suggested that there are multiple separable long-term declarative memory systems (semantic, episodic, and autobiographical memory, see below). This notion was derived from observations of some brain damaged patients exhibiting much more severe impairments of episodic memory (memory of personally experienced events) than semantic memory (memory for factual information), and other patients exhibiting the opposite pattern, with episodic memory being more spared than semantic memory (Baddeley et al., 2015).

Semantic Memory

Semantic memory refers to our knowledge about the world; it includes knowledge of such things as the number of days in a week, the capital of a certain country, and the meaning of words and phrases (Baddeley et al., 2015). This kind of memory is impersonal, as it is not dependent on personal experience (Tulving, 2002). The capital of Sweden is Stockholm

regardless of someone's experience with it, or lack thereof. A loss of semantic knowledge means that information about the meanings and functions of words and objects can no longer be retrieved (Baddeley et al., 2015). A popular depiction of such a loss is found in the novel *One Hundred Years of Solitude* written by Nobel Prize winner Gabriel Garcia Marquez before the syndrome was identified in neurology (Rascovsky, Growdon, Pardo, Grossman, & Miller, 2009). Marquez describes how a fictitious town is struck by an insomnia plague, resulting in the inhabitants gradually losing their memories. In the article by Rascovsky et al. (2009), a comparison is made between the symptoms described in the book, and the symptoms displayed by a patient of theirs (S.D.). Interestingly, Marquez's description of semantic memory loss is strikingly similar to the impairments observed in patient S.D. (Rascovsky et al., 2009).

Episodic Memory

The episodic memory system stores context-specific, detailed events that one has personally experienced (Tulving, 2002), e.g. family vacations and your first kiss. There is disagreement, however, on the exact requirements for what constitutes an episodic memory or an episodic memory system. Tulving (1972), who coined the term, likens episodic memory to a form of mental time travel. He argues that our episodic memory system allows us not only to mentally travel back in time so as to allow us to "relive" a past event, but to travel forward in time as well. Imagine making dinner plans for next week. Episodic memory makes it possible to remember having made those plans, and to appropriately plan for that day.

Furthermore, Tulving (2002) suggests that there are three central components that make up the episodic memory system. These are: a sense of subjective time, autonoetic awareness, and a self. Autonoetic awareness, which Tulving firmly believes to be uniquely human, refers to the ability to be aware of the subjective time during which an episode was experienced, a kind of temporal "tag" (Tulving, 2002). This means that it helps us keep track of where we are

located in time, and allows for distinguishing between the past, the present, and the future. Autonoetic awareness is also described as the ability to be conscious of the existence of a self, making it possible to separate the recollection of a personal experience from that of a general fact (Tulving & Markowitsch, 1998). As mentioned above, autonoetic awareness is thought to be a distinctively human ability. However, there have been findings of nonhuman animals, for example scrub jays (Clayton & Dickinson, 1998) and chimpanzees (Osvath & Karvonen, 2012), exhibiting memory capabilities that largely reflect a capacity for episodic memory, showing that Tulving's notion of episodic memory may not be restricted solely to humans.

A different interpretation by Baddeley et al. (2015) involves three central components of an episodic memory system as well, though the components thought to be required are not the same. They argue that the first requirement of such a system is that it encodes a distinct experience in such a way that it can be distinguished from other, similar experiences. The second component is a means of storing episodes in a stable way (Baddeley et al., 2015). The third and final required component proposed by Baddeley et al. (2015) is a method to scan the system, and subsequently retrieve the memory in question. Thus, exactly what constitutes an episodic memory system is still under debate. However, a discussion of the nature of the system itself is not within the scope of this thesis. Episodic memory will therefore be referred to in accordance with its core definition; i.e. contextually-detailed memory for personally experienced events.

Spatial/Schematic Memory

Moscovitch et al. (2005) argue that a distinction can, and must, be made between contextually rich episodic memories and gist-like episodic memories. They suggest that spatial memories consisting of great perceptual-spatial detail can be likened to episodic memories. These kinds of spatial/episodic memories allow for re-experiencing of a given environment, and have been suggested to be the spatial equivalent of mental time travel

(Moscovitch et al., 2005). Futhermore, they propose that less detailed schematic spatial memories correspond to semantic memories. As such, it has been argued that carefully designed protocols testing detailed and schematic spatial memory in animals can be used as a replacement for studying episodic and semantic memory in humans (Winocur, Moscovitch, & Bontempi, 2010). Testing episodic memory through spatial memory tasks is conceivable as spatial memory makes up part of the spatiotemporal requirement for the recollection of a detailed autobiographical episode. Nonetheless, this has not been settled conclusively (Sutherland, Sparks, & Lehmann, 2010).

Autobiographical Memory

Autobiographical memory refers to personal knowledge or memory for personally experienced events (Conway & Pleydell-Pearce, 2000). Confusion may arise when reviewing the literature, as autobiographical memory is often used interchangeably with episodic memory. However, an autobiographical memory must not necessarily be episodic. For example, even though the memory one has of a friend's face is autobiographic, it is equally non-episodic as the memory one has of a famous face, (Zola-Morgan, Cohen, & Squire, 1983). This kind of memory is semantic, but still classifies as autobiographical knowledge.

Personal semantic memory. The semantic component of autobiographical memory has been termed personal semantic memory, which includes personal facts pertaining to one's own life (Herfurth, Kasper, Schwarz, Stefan, & Pauli, 2010). Such memories do not have to be directly linked to a specific spatiotemporal context, as in the case of the name of a certain childhood friend (Herfurth et al., 2010). Nevertheless, they can be coupled to a spatiotemporal context; one can have knowledge of the fact that a personal event has happened, without being able to actually experience a detailed recollection of the event (Tulving, Schacter, McLachlan & Moscovitch, 1988).

Amnesia

A wide range of studies have been conducted on patients exhibiting various memory impairments with the hopes of uncovering the brain regions vital for certain types of memory. While human subjects can suffer brain damage due to several different etiologies, focal circumscribed lesions to a single region in the brain seldom occur naturally. Nevertheless, when such rare cases come about, it opens for the possibility to gain insight into the importance of a specific area. The hippocampus and the surrounding medial temporal lobes have been of special interest when investigating long-term declarative memory. Observations of amnesia following damage to the hippocampus and MTL has led to several theories (including the three described in this paper) of hippocampal function and its role in memory. Impaired functioning of long-term declarative memory is commonly divided into two groups, namely anterograde and retrograde amnesia.

Anterograde Amnesia

Anterograde amnesia (AA) is a general term referring to the inability to acquire new memories after the onset of damage; it can refer to the inability to form new episodic memories, the inability to learn new factual information in a normal fashion, or both (Frankland & Bontempi, 2005). While patients with AA are unable to form new memories, they can remember facts and events learned prior to the cause of amnesia.

There is general consensus about the MTL being necessary for the formation of new declarative memories (Frankland & Bontempi, 2005), meaning that damage to this area should result in AA for both episodic and semantic information. This pattern of memory loss has been found in two patients with almost complete bilateral damage to the MTL (Bayley & Squire, 2005). However, a subsequent study using the same two subjects found some degree of intact semantic learning (Bayley, O'Reilly, Curran, & Squire, 2008). This opens for the possibility that factual learning (and perhaps retention of factual information) can be

supported by structures outside of the MTL, and that MTL damage can result in AA for only episodic memory (Frankland & Bontempi, 2005).

Retrograde Amnesia

Retrograde amnesia (RA) describes the inability to retrieve memories acquired before the onset of damage (Frankland & Bontempi, 2005), and can come in two different forms; it is either temporally graded or ungraded. Temporally graded RA refers to cases in which only memories of more recent time periods are lost, with memories acquired more remote to the onset of damage being relatively spared (Squire & Alvarez, 1995). The degree of temporal gradient differs in each case, it is not fixed. Ungraded RA, on the other hand, refers to cases where memories from all past time periods are equally lost (Squire & Alvarez, 1995). Ungraded RA is sometimes called nongraded RA or RA with a flat gradient.

Early observations of temporally graded RA led to the idea of memory consolidation, a process by which memories over time become strengthened enough to be permanently stored in the brain (Nadel, Hupbach, Gomez, & Newman-Smith, 2012). For example, in the beginning of the 20th century, Burnham (1903) wrote about the loss of recent memory:

> The fixing of an impression depends upon a physiological process. It takes time for an impres[s]ion to become so fixed that it can be reproduced after a long interval; for it to become part of a permanent store of memory considerable time may be necessary (p. 392).

Findings of temporally graded RA combined with the groundbreaking studies of patient H.M. and his memory impairments caused by extensive MTL damage eventually led to the idea of systems level memory consolidation (Nadel, Winocur, Ryan, & Moscovitch, 2007). According to this view, memories are initially stored in the hippocampal system, but gradually become dependent on other systems such as the neocortex through a process of consolidation (Frankland & Bontempi, 2005).

Standard Consolidation Model

One influential view embracing the idea of systems consolidation is the Standard Consolidation Model (SCM) proposed by Alvarez and Squire (1994). They argue for a process of memory consolidation during which a given declarative memory initially dependent on the hippocampus gradually becomes consolidated in, and ultimately dependent on, the neocortex. They further argue that different separable cortical areas are not only specialized for the processing of certain types of information, but that each specialized area stores a specific kind of information as well. It follows then that damage to the area responsible for processing a certain type of information should result in that component being erased from already established memories (Squire & Wixted, 2011). This has been shown to be true for damage to area V4, responsible for processing information about color, which leads to a deficit known as achromatopsia. Patients with achromatopsia can no longer process information about color, and memories once encoded in color are now retrieved in black and white (Squire & Wixted, 2011).

Alvarez and Squire (1994) suggest that the formation of long-term declarative memories is dependent on the binding together of the cortical sites involved in the initial processing of the memory. Furthermore, the MTL are thought to be directly involved in linking together the different cortical sites, and thus in maintaining the coherence of the memory (Reber, Alvarez, & Squire, 1997). More specifically, an experience is thought to be encoded in parallel by both the neocortex and the MTL and to be bound together through hippocampal-cortical connections (Frankland & Bontempi, 2005). Reactivation of the hippocampal network elicits activity in the cortical sites, which causes the connections between the cortical sites to be strengthened (Frankland & Bontempi, 2005). Eventually, the cortico-cortical connections are strengthened enough to support a coherent memory without the hippocampus (Alvarez & Squire, 1994), a process that can take several years to be completed (Squire & Wixted, 2011).

Thus, upon completion of the consolidation process, the neocortex is thought to stand as the permanent storage-site for long-term declarative memories (Squire & Alvarez, 1995).

No distinction is made between semantic and episodic memories within the SCM; they are thought to be represented equally within the brain (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006). This means that all long-term declarative memories eventually become independent of the MTL, irrespective of their nature. Following this premise, damage to the hippocampus and the surrounding MTL should lead to temporally graded retrograde amnesia for both semantic and episodic memory (Squire & Alvarez, 1995). In addition, since the MTL are suggested to be critical for the consolidation process, some degree of anterograde amnesia should be observed as well. Nevertheless, impairments of anterograde amnesia will not be the focus of this thesis.

Multiple-Trace Theory

Introduced by Nadel and Moscovitch (1997), the Multiple-Trace Theory (MTT) was presented as an opposing theory to the SCM. The theory is built on a similar premise as the SCM, namely that cortical plasticity (experience-dependent changes in cortical function and/or structure) is necessary for the long-term representation of hippocampus-based memories (Winocur et al., 2010). Nevertheless, they disagree about the exact nature of this plasticity, as well as to how the hippocampus is involved.

According to MTT, both semantic and episodic memories are initially dependent on the integrity of the hippocampus, but differ in terms of hippocampal dependence over time (Nadel & Moscovitch, 1997). On the one hand, as a semantic memory becomes stabilized, hippocampal involvement gradually diminishes until the memory can finally be supported by neocortical structures alone. On the other hand, episodic memories are thought to always be dependent on the hippocampus. Furthermore, when an episodic memory is retrieved it is simultaneously re-encoded (Moscovitch et al., 2006). Consequently, a new memory trace is

created within the hippocampus each time a memory is retrieved; having been retrieved more times, older memories are more widely distributed in the hippocampus (Moscovitch et al., 2006).

The formation of multiple traces comes with a major advantage. Nadel, Samsonovich, Ryan, and Moscovitch (2000) argue that there is an additive effect of all traces on memory retrieval. They propose that each trace may independently trigger retrieval, so a failure in retrieval is only possible when every single trace of a memory fails. As a result of a more wide distribution of traces and the independence of each trace, more extensive damage to the hippocampus is required to affect older episodic memories (Moscovitch et al., 2006).

While certainly of interest, the age of the memory is not the most important factor in determining the supporting brain regions. This goes directly against SCM in that SCM predicts that older memories are mediated solely by neocortical regions (Alvarez & Squire, 1994), while newer memories are dependent on the hippocampus (Teng & Squire, 1999). Instead, MTT suggests that memories are always dependent on the hippocampus as long as they retain rich contextual details of the past events, no matter how old they are (Moscovitch et al., 2006). When such details are lost, neocortical areas may alone support the retrieval. However, since the very definition of an episodic memory requires detailed recollection, the retrieved memory can no longer be considered to be episodic in nature (St-Laurent, Moscovitch, Tau, & McAndrews, 2011).

Nevertheless, the age of the memory can in fact still be of some importance within the framework of MTT. Due to a gradual process of decay, memories may lose details as they age (Nadel et al., 2000). This means that enough degradation of a memory trace eliminates the contextual details, resulting in neocortical areas taking over the responsibility for maintaining the now schematic-like memory.

Semantic memories do not necessarily have contextual ties, and can be likened to the schematic versions of episodic memories; thus, semantic memories are thought to be mediated by areas within the neocortex (Winocur & Moscovitch, 2011). Furthermore, advocates of MTT support the idea of semantic memories being derived from episodic memories (see Winocur et al., 2010). This view holds that even semantic knowledge is initially connected to the contextual details present at encoding. A more detailed explanation of how this idea is expressed within the framework of MTT will be provided in the following section on the Transformation Hypothesis.

The Transformation Hypothesis

Recently, Winocur et al. (2010) presented an extension of the MTT called the Transformation Hypothesis, where they argue for the dynamic nature of memory. The idea is that as a memory gradually stops being dependent on the hippocampus, and instead starts relying on extrahippocampal structures, the very nature of the memory changes (Winocur & Moscovitch, 2011). More specifically, when extrahippocampal structures take over, rich details and contextual features are lost. What is left is the gist of the memory (Winocur & Moscovitch, 2011).

The Transformation Hypothesis states that almost all declarative memories, including semantic memories, rely on the hippocampus upon acquisition (Winocur et al., 2010). However, as the experiencer encounters the same information time after time, statistical regularities among the different experiences are identified (Winocur & Moscovitch, 2011). To illustrate this point, consider the following example by Winocur et al. (2010): When learning what the word “dog” means, the word is originally linked to the context during which it was first learned. As one has further experiences with dogs, they become connected to more episodes. This is where calculations of statistical regularities extract the general features

common to each episode. Now, contextual details are no longer necessary for retrieving the meaning of "dog"; the memory has become schematic.

The above example serves to show how semantic memory can depend on episodic memory. The semantic knowledge one has of the word "dog" is, at least in this case, inferred from several episodes. The overlapping information consistent across all episodes becomes generalized into a semantic memory trace. Consequently, an episodic memory can become semanticized (Winocur & Moscovitch, 2011). Hippocampal involvement diminishes during this process, and when the memory has become semantic/schematic, the hippocampus is no longer necessary for retrieval.

The dynamic nature of memory is emphasized during and after completion of the consolidation process. The SCM suggests a linear process of consolidation, where a consolidated memory now dependent on neocortical structures is an exact copy of the original memory (Winocur et al., 2010). In contrast, the Transformation Hypothesis proposes that there are two different versions of the same memory (Winocur, Moscovitch, & Sekeres, 2013). At first, there is only the context-specific original memory. As the consolidation process begins, a second, schematic version of the memory starts being outlined. This second version is not an exact copy of the original memory, for it does not contain the same amount of contextual details. Additionally, these two separate versions of the same memory can co-exist (Winocur, Moscovitch, & Sekeres, 2013).

The dynamic relationship between the two types of memory becomes apparent when considering the nature of their co-existence. Winocur et al. (2010) argue that only one of the memories is dominant at a given time, and that the gist-like schematic memory often prevails with regards to older memories. However, they further propose that when implementing a reminder, the context-specific memory may be reinstated as the dominant version. The switch from schematic dominance to specific dominance is accompanied by a change in the neural

structures supporting retrieval (Winocur et al., 2010). The former version is supported by extrahippocampal structures, while the latter version depends on the hippocampus. Contrary to the core arguments of SCM, this suggests that the hippocampus may again resume responsibility for retrieval, even after consolidation is complete (Winocur, Moscovitch, & Sekeres, 2013).

As for the effects of brain damage on memory function, MTT makes three central predicitions. First, damage to the hippocampus and the surrounding MTL should impair the function of episodic memory more severely than that of semantic memory (Moscovitch et al., 2006). Second, the extent of RA for autobiographical episodes depends on the extent of hippocampal damage (Moscovitch et al., 2006). Third, complete loss of hippocampal function leads to ungraded RA for autobiographical episodic memory (Moscovitch et al., 2006). Therefore, findings of temporally graded RA for episodic memory can still be consistent with MTT, as long as hippocampal damage is not complete.

Distributed Reinstatement Theory

The Distributed Reinstatement Theory (DRT) formulated by Sutherland et al. (2010) is a more recent theory of how memories can become independent of the hippocampus, and argues against the traditional notion of a systems level consolidation process. DRT is partly a dual-store model, where it is thought that various (unspecified) memory systems encode information independently of each other (Sutherland et al., 2010). It is suggested that these memory systems interactively compete for the responsibility of encoding and storing the representation of a memory, and that the hippocampus usually is dominant (Driscoll, Howard, Prusky, Rudy, & Sutherland, 2005). Furthermore, the formation of a memory in the hippocampus inhibits other memory systems from encoding information about that experience (Driscoll et al., 2005). As long as the hippocampus is intact, it interferes with the establishment of memories in non-hippocampal memory systems (Sutherland et al., 2010).

This idea has been termed overshadowing (Sutherland, Lehmann, Spanswick, Sparks, & Melvin, 2006), and for that reason this theory has also been referred to as Overshadowing Theory (e.g. in Winocur, Moscovitch, & Sekeres, 2013). The concept of overshadowing dates back to Pavlov, but in his case the idea pertains to associations between compound conditioned stimuli; the effect of the stronger stimulus overshadows the effect of the weaker stimulus (Pavlov, 1927). Sutherland et al. (2010) argue that Pavlov's use of the concept is analogous to their notion of the activity of the more dominant hippocampal memory system overshadowing the activity of another separate memory system.

Since the hippocampus acts as an inhibitor, a non-hippocampal system should be able to establish and support retrieval of a new memory by itself if the hippocampus is inactivated (Sutherland et al., 2010). This idea is derived from findings of hippocampal damage resulting in retrograde, but not anterograde, amnesia (Sutherland et al., 2006). However, the nature of a memory supported by a non-hippocampal memory system is most likely different in nature from a memory supported by the hippocampus (Sutherland et al., 2010). Any specifics regarding exactly how memory representations may differ between systems are not given.

While the hippocampus is usually the dominant memory system, Sutherland et al. (2006) argue that it is possible for non-hippocampal memory systems to resist the overshadowing exercised by the intact hippocampus. It is not the quality (MTT) nor the age (SCM) of the memory that is thought to determine hippocampal dependence, but instead the learning parameters (Sutherland et al., 2010). Specifically, it is hypothesized that distributed learning sessions, as opposed to a single session, can help form strong representations of an experience in both the hippocampal and the non-hippocampal system (Sutherland & Lehmann, 2011). In this way, a memory can still be retrieved after hippocampal damage if extensive learning has taken place, whereas ungraded RA would be expected in the absence of extensive experience. Additionally, findings of any intact version of a memory (e.g.

semanticized instead of contextually detailed) or intact capability for some kind of new learning after hippocampal damage are consistent with DRT. Ungraded RA without any intact version of the memory is inconsistent with DRT only if extensive learning has taken place. Unfortunately, exactly how much learning that is needed for a non-hippocampal system to be able to overcome the hippocampal overshadowing is not specified.

It is important to note that DRT is a model that has been tested exclusively in animals due to the necessary freedom to manipulate experimental procedures.

Evidence from Human Subjects

As seen above, each theory predicts differential involvement of the hippocampus and the surrounding MTL in the retention of memories as well as different variations of RA depending on the implicated brain areas and the extent of damage within each area (Alvarez & Squire, 1994; Nadel & Moscovitch, 1997; Sutherland et al., 2010). This means that the activity of these regions upon retrieval of a memory should differ depending on factors such as age or quality, and that the observed impairments should depend on the time and location of the damage. Studies of retrograde amnesia, as well as neuroimaging studies, are used to test the predictions made by the different theories. In this section, data from human subjects and whether support is found for MTT or the SCM will be reviewed. Since MTT and the SCM make similar predictions with regards to semantic memory, this section will focus on studies of episodic memory. Note again that the DRT has currently only been tested in rodents, and will therefore not be featured in this section.

Lesion Studies of Retrograde Amnesia

One influential case in research on RA has been that of patient K.C., who suffered a severe closed head injury due to a motorcycle accident in 1981 (Rosenbaum et al., 2005). Subsequent analysis of the damage conducted by Rosenbaum et al. (2005) revealed a general cortical atrophy, as well as abnormalities in the hippocampal formation and the

parahippocampal gyrus. The former was shown to be largely necrotic bilaterally, with severe atrophy of the remaining non-necrotic tissue. Because of the general cortical atrophy, volumetric ratings of medial temporal lobe and related limbic structures were obtained from K.C. and five controls to assess proportionate or disproportionate loss of volume in each area. The largest disproportional volume reductions were found bilaterally in the hippocampus and parahippocampal gyrus (which includes the entorhinal, perirhinal, and parahippocampal cortex; Rosenbaum et al., 2005). Additional regions that suffered from disproportionate reduction in volume included the left amygdala and mammillary bodies, bilateral septal area, caudate nucleus, and posterior and anterior parts of the thalamus (Rosenbaum et al., 2005). Overall, the right hemisphere of the brain was affected to a lesser degree than the left.

Patient K.C. had greatly impaired memory functions, with equally severe anterograde amnesia for semantic and episodic memory. In contrast, his retrograde amnesia was far worse for episodic memory; he could not remember any personally experienced events, but his semantic knowledge acquired prior to the accident was relatively intact (Tulving, 2002). This pattern can be interpreted as favoring MTT over the SCM, as the former claims that only episodic, not semantic, memories are perpetually dependent on the hippocampus. The latter would predict temporally graded RA equal for both episodic and semantic memory, as no distinction between the two types of memory is made. However, K.C. was also shown to be able to recall some remote spatial memories (that make up part of the spatiotemporal characteristics of episodic memory; Rosenbaum et al., 2000). This has been suggested to imply either that the hippocampus is not necessary for retrieval of remote spatial memories (and thus not all aspects of episodic memory), or that some very small portion of the hippocampus is still functional, and enough to mediate remote spatial (and episodic) memories by itself (Rosenbaum et al., 2005). The latter has been shown to be possible; a patient with developmental amnesia and a bilateral hippocampal volume loss of over 50% has

been shown to be able to remember detailed autobiographical episodes (Maguire, Vargha-Khadem, & Mishkin, 2001).

Both these alternatives can conform to MTT. First, the necessity of an intact hippocampus in retrieval of a remote spatial memory depends on the complexity of the memory. MTT would hold that the retrieved memory should be schematic and contain few contextual details if the hippocampus is not intact. Second, MTT states that a remote episodic/complex spatial memory should have established more traces within the hippocampus. More extensive damage would thus be required for the elimination of such a memory. In the latter case, MTT could still be consistent with the retrieved memory being complex and rich in detail, as the damage has not been extensive enough to eliminate older memories. Nevertheless, the study by Rosenbaum et al. (2000) showed that K.C.'s remote spatial memory loss was similar in nature to that of his episodic memory impairment, i.e., contextual details had been lost, and the retrieved memories were more general and schematic. As such, the findings are in favor of MTT.

While the study by Rosenbaum et al. (2005) found that damage to the hippocampus and the surrounding MTL was the determining factor in K.C.'s memory deficit, it could not be settled conclusively that the observed neocortical damage did not contribute significantly to it. A subsequent study by Rosenbaum et al. (2008) sought to investigate the respective contributions of lesions restricted to the MTL and MTL lesions extending to neocortical structures to impairments of remote autobiographical memory in four patients. They hypothesized that if autobiographical episodic memory was affected more severely than personal semantic memory by complete bilateral damage to the MTL, then recall of autobiographical events would have to be dependent on the degree of damage to the MTL, irrespective of the degree of neocortical damage. Such findings would support MTT. In contrast, if a temporal gradient would be found for both episodic and semantic aspects, and be

related to neocortical damage independently of MTL damage, support would be found for the SCM.

The results showed that the two patients with most damage to extrahippocampal structures within the MTL and neocortical structures exhibited the mildest retrograde episodic memory impairments (Rosenbaum et al., 2008). Additionally, the patient with most hippocampal damage bilaterally, and equally or less extensive extrahippocampal MTL and neocortical damage than the other patients, showed the greatest remote episodic memory loss. No deficit of personal semantic memory was observed in any of the patients (Rosenbaum et al., 2008). These results strongly favor MTT over the SCM.

Another study using similar tests to those used by Rosenbaum et al. (2000) also found intact remote spatial memory function in a patient (E.P.) with complete bilateral damage to the hippocampus caused by viral encephalitis (Teng & Squire, 1999). These results, however, were interpreted as being consistent with the SCM, and seen as evidence for memories not being permanently stored in the hippocampus (Teng & Squire, 1999). A difference between these two studies is that Rosenbaum et al.'s (2000) conclusion of patient K.C.'s remote spatial memory being schematic came partly from him providing a sketch map which was lacking in landmark inclusions. In the study by Teng and Squire (1999), patient E.P. declined to try providing a sketch.

E.P. has also been found to have intact remote episodic memory as compared to controls (Reed & Squire, 1998), which further supports the SCM. Furthermore, two additional subjects in the same study successfully recollected autobiographical episodes, the characteristics of which matched those recollected by controls. The fourth subject (G.T.) displayed grave RA covering the entire life span, something that Reed and Squire (1998) ascribe to G.T.'s damage extending more into the lateral temporal cortex than that of the other patients.

Further support for the SCM is found in that damage limited to the hippocampal formation has been shown to produce temporally graded RA (Bayley, Hopkins, & Squire, 2003; Reed & Squire, 1998; Rempel-Clower, Zola, Squire, & Amaral, 1996). However, there is no consensus on exactly what constitutes the hippocampal formation; it has been suggested to include the hippocampus proper, dentate gyrus, and subiculum by some (Moscovitch et al., 2006; Haist, Gore, & Mao, 2001), while others (Rempel-Clower et al., 1996) define it as including the aforementioned areas with the addition of entorhinal cortex. This becomes problematic when considering that the entorhinal cortex has been demonstrated to be important for memory consolidation (see Haist et al., 2001), and that most studies do not specify what the concept entails when they refer to the hippocampal formation.

Contrasting the above results are the findings by Cipolotti et al. (2001), that damage limited to the hippocampus can produce ungraded RA for autobiographical episodic memories. These findings are predicted by MTT, but cannot be explained by the SCM. A central premise of MTT is that of permanent hippocampal involvement in the retention of contextual details, and it has been argued that many studies of RA do not adequately investigate such features. Indeed, Nadel et al. (2000) have criticized many findings of temporally graded RA for insufficient testing of the amount of contextual details provided in episodic memory reports.

In answer to this criticism, Kirwan, Bayley, Galván, and Squire (2008) conducted a study designed to be more sensitive to the amount of details per memory report. They found that while patients with MTL damage were impaired in the recollection of recent episodic autobiographical memories, recollection of remote memories was completely intact. While the results obtained by Kirwan et al. (2008) support the SCM, there are other similar studies that favor MTT (Addis, Moscovitch, & McAndrews, 2007; St-Laurent, Moscovitch, Levine, & McAndrews, 2009; St-Laurent et al., 2011).

In a recent article, St-Laurent, Moscovitch, Jadd, & McAndrews (2014) further argued for the importance of testing the perceptual richness of memory reports provided by patients with MTL damage. In this study, they adopted a novel, more naturalistic way of testing the perceptual richness of autobiographical memories. Patients with damage to the MTL were found to produce less perceptual details in their episodic memory reports than did controls, as predicted by MTT (St-Laurent et al., 2014). However, many of the patients included in the study by St-Laurent et al. (2014) had damage extending beyond the MTL to the anterior temporal lobe. This damage included the temporal pole, the amygdala, the anterior hippocampus, rhinal cortex, lateral temporal cortex, and parts of the parahippocampal cortex (St-Laurent et al., 2014). Thus, it cannot be ruled out that impairment of these areas contributed to the remote memory loss. Indeed, the SCM holds that damage to areas beyond the MTL is needed for impairment of remote memory and ungraded RA, and such indications have been found (Bright et al., 2006; Kirwan et al., 2008; Squire & Bayley, 2007).

While studies of patients with hippocampal damage exhibiting RA are highly useful to evaluate and test the SCM and MTT, the evidence is far too divided for one of the theories to be refuted. To obtain a more complete picture, a wider range of studies are required.

Neuroimaging Studies of Healthy Subjects

Another way to assess the validity of MTT and the SCM is through neuroimaging studies where the activity of various regions in the brain is measured during memory retrieval. Initial neuroimaging studies reported no significant activation of the MTL during retrieval of episodic memories (Schacter & Wagner, 1999) when using positron emission tomography (PET; Shallice et al., 1994; Tulving et al., 1994). However, a later study using event-related functional magnetic resonance imaging (fMRI) was able to provide evidence for the hippocampus being selectively involved in episodic memory retrieval (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000). It has been suggested that the difference in the

obtained results stems from the design limitations imposed by using PET (Buckner, 2000). In the PET studies, the trials were necessarily sequenced close to each other and the data equated (Buckner, 2000). Thus, if hippocampal activity is increased during episodic memory retrieval but decreased during semantic memory retrieval, no significant results will be obtained if the data is equated. In contrast, Eldridge et al. (2000) were able to collect data from each trial independently by using fMRI.

Since then, several studies have measured hippocampal activity during retrieval of episodic memories from different time periods. According to the SCM, hippocampal involvement should decrease as the remoteness of a retrieved memory is increased (Moscovitch et al., 2006). Contrary to this, MTT predicts that the hippocampus should be equally activated during retrieval of detailed episodic memories across all time periods, and that it is vividness of recall, not the age of the memory, that determines the level of hippocampal activation (Moscovitch et al., 2006).

Supporting the SCM are findings of temporally graded hippocampal and MTL activation in response to retrieval of recent and remote memories (Niki & Luo, 2002; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003). Piefke et al. (2003) instructed 20 healthy subjects to recall 20 detailed autobiographical episodes from childhood (up to 10 years of age) and 20 detailed autobiographical episodes from the last five years. The participants prepared six detailed and descriptive sentences for each memory, which served as stimulus throughout the subsequent fMRI scanning during memory retrieval. A significant increase in hippocampal activation was observed only during retrieval of recent autobiographical episodes, as compared to remote episodes and baseline (Piefke et al., 2003). However, it has been argued that the study conducted by Piefke et al. (2003) did not control for vividness or number of details (Nadel et al., 2007). It can therefore not be concluded whether or not the retrieved memories were episodic in nature. Niki and Luo (2002) investigated MTL activation during

retrieval of autobiographical episodes by having subjects recollect places they had visited either approximately 7 years back, or during the last 2 years. A temporal gradient of MTL activation was found, and additional analysis eliminated the amount of details as the determining factor (Niki & Luo, 2002). Importantly, there is no mention of hippocampal activity in neither condition, so nothing concrete about the specific involvement of the hippocampus can be inferred.

An interesting finding of temporally graded activation of the hippocampus was obtained by Maguire and Frith (2003). Using fMRI, they found a lateral asymmetry of hippocampal activation in response to recent and remote memories; the left hippocampus showed significant activation in response to autobiographical memories across the lifespan, whereas the level of activity of the right hippocampus decreased with the remoteness of the memories. The right hippocampus was active during retrieval of autobiographical episodes that were up to 30 years old, after which it was deactivated (Maguire & Frith, 2003). The implications of these findings for MTT and the SCM are somewhat vague. On the one hand, MTT is consistent with the permanent activation of the left hippocampus during autobiographical memory retrieval, but it is inconsistent with the gradual decrease (and ultimately the deactivation) in right hippocampal activity when remoteness of the memories increased (Maguire & Frith, 2003). On the other hand, the SCM is consistent with the gradually decreasing activation of the right hippocampus as a function of memory remoteness, but is inconsistent with the finding that it could take up to 30 years for the hippocampal involvement to diminish fully (Maguire & Frith, 2003). Thus, it can be hard to determine whether the aforementioned findings support or oppose one of the theories more than the other.

In general, a larger number of neuroimaging studies seem to support MTT in that significant hippocampal/MTL activation has been observed irrespective of the age of the memory (Nadel, Campbell, & Ryan, 2007; Ryan et al., 2001; Rekkas & Constable, 2005;

Steinvorth, Corkin, & Halgren, 2006; Viard et al., 2010; Viard et al., 2007). For example, Rekkas and Constable (2005) measured MTL activation in subjects recalling recent (2.5 days) and remote (mean remoteness 8 years) memories. They found that the MTL (including the hippocampus) was significantly activated during both conditions. In fact, greater MTL activity was observed when subjects retrieved remote memories than when they recalled recent memories. Unlike the aforementioned study by Piefke et al. (2003), Rekkas and Constable (2005) did not interview the subjects before the fMRI scanning procedure. They suggest that a prescan interview might cause subjects to subsequently re-experience the prescan recollection instead of the original event itself. Therefore, it is possible that a prescan interview might reduce the temporal gradient (Rekkas & Constable, 2005). Nevertheless, Piefke et al. (2003) still found a temporal gradient in hippocampal activation during recollection of recent and remote memories. Their findings are contrasted by the evidence obtained in the study by Rekkas and Constable (2005), where significant hippocampal activity was observed irrespective of remoteness, where the temporal interval between the retrieved memories was (supposedly) held constant.

In place of remoteness, vividness and recollective quality have been suggested to modulate the activation of MTL structures, including the hippocampus (Addis, Moscovitch, Crawley, & McAndrews, 2004; Svoboda, McKinnon, & Levine, 2006). Indeed, a study by Gilboa, Winocur, Grady, Hevenor, and Moscovitch (2004) also found vividness to be most strongly correlated to hippocampal activity. In addition, they found that whereas retrieval of remote memories was associated with activity along the rostrocaudal hippocampal axis, retrieval of recent memories was associated with activity in the anterior hippocampus. Gilboa et al. (2004) argue that these findings might clarify why circumscribed lesions to the hippocampus can result in different types of RA. If the rostrocaudal axis is damaged, remote episodic memory becomes impaired. However, if the anterior hippocampus is damaged,

temporally graded RA is to be expected. Nevertheless, these findings show that the hippocampus is involved in episodic memory retrieval across all time periods, which is not consistent with the SCM.

Evidence from Rodents

Aside from studies conducted with human subjects, it can also be useful to study nonhuman animals in order to uncover the importance of various brain structures for memory. One advantage of such studies is the freedom of inducing experimental lesions and studying their impact on memory performance (Sutherland et al., 2010). In addition, since the lesions are experimentally induced, the locus, extent, and time of induction can be carefully monitored and controlled. Being able to control such factors makes it highly useful to study prospectively recent and remote memories in experimental animals (Squire & Bayley, 2007). Some suggest that contextually rich or impoverished spatial memories can be seen as analogues of episodic and semantic memory, respectively, in both human and nonhuman animals (Moscovitch et al., 2005; Winocur, Moscovitch, & Sekeres, 2013). Spatial memory makes up part of the spatiotemporal aspect that pertains to successful episodic memory retrieval, and is studied extensively in rodents. Furthermore, because contextual details are crucial for vivid recall of past experiences, contextual fear conditioning is used to measure the hippocampal dependence of context-specific memories. However, as Sutherland et al. (2010) point out, we currently do not know whether or not nonhuman animals (in this case rats) have some form of memory analogous to human episodic memory. Nevertheless, Sutherland et al. (2010) are still optimistic towards the use of experimental animals and argue that while the nature of the memory itself can be difficult to determine, it is possible to study whether temporary inactivation or permanent lesions to specific brain regions leads to temporally graded or ungraded RA. In this section, studies of memory in rodents, the most extensively

studied nonhuman animal in memory research (Sutherland et al., 2010), will be reviewed and the findings set up against the SCM, MTT, and DRT.

Contextual Fear Conditioning

One commonly used protocol when examining the role of the rodent hippocampus in memory is contextual fear conditioning, where the rat is conditioned to pair an aversive stimulus with the context in which the stimulus is given (Sparks, Spanswick, Lehmann, & Sutherland, 2013). Subsequently, the rat elicits a fear response when it is placed in that same context but with the absence of any aversive stimulus. This differs slightly from classical fear conditioning where the aversive stimulus is paired with another simple neutral stimulus (e.g. a tone); contextual fear conditioning employs polymodal stimulus, while classical fear condition uses unimodal stimulus (Kim & Fanselow, 1992). A fear response is measured through freezing, i.e., the lack of any movement aside from breathing (Wang, Teixeira, Wheeler, & Frankland, 2009). In studies investigating hippocampal contributions to recent and remote memory in rodents, lesions are induced at different points in time before or after the learning session is complete, after which their performance is evaluated (Broadbent & Clark, 2013).

Investigations into the long-term role of the hippocampus in memory through contextual fear conditioning have yielded some inconsistent results (Sutherland et al., 2010; Winocur et al., 2010). For example, an early study by Kim and Fanselow (1992) showed that rats receiving hippocampal lesions only 1 day after training exhibited no contextual fear response. However, those rats that received hippocampal lesions 7, 14, or 28 days after training retained contextual fear memories. Additionally, they showed that fear response towards a tone (non-context) was unaffected by the lesions in the same rats. It was concluded that the hippocampus plays a significant role only in the retention of recently acquired contextual fear memories, but not those acquired remotely nor non-contextual fear memories (Kim &

Fanselow, 1992). These findings are not consistent with MTT, which would predict permanent hippocampal involvement in context-specific memories.

Other studies have obtained similar results. For example, Winocur, Sekeres, Binns, and Moscovitch (2013) found that rats induced with hippocampal lesions 1 day post-training exhibited no significant response on tests of contextual fear. Those induced with hippocampal lesions 28 days after training showed similar and significant fear responses to both recent and remote memories. The same pattern has been observed in other studies following hippocampal lesions 1-28 days (Winocur, Frankland, Sekeres, Fogel, & Moscovitch, 2009), 1-42 days (Wang et al., 2009), and 1-50 days (Anagnostaras, Maren, & Fanselow, 1999) post-training. These findings indicate that the hippocampus has a time-limited role in memory, contrary to predictions made by MTT.

However, such findings of a temporal gradient in contextual fear conditioning may not be as clear cut as they seem. As in most debates of remote memory, it has been argued that the nature of a memory changes with time; recent fear memories have been suggested to be context-dependent, and remote fear memories context-independent (Winocur et al., 2010). To test this idea, some studies of contextual fear conditioning manipulate the context in which the rats are tested. For example, rats are first conditioned in a given context. Their fear response is subsequently tested at both a recent and a remote time period in either the same context (CXT-S) or a different context (CXT-D). What differs between the two contexts are the specific cues (spatial, temporal and local) present in that environment, while the more general features (e.g., a box with a grid floor) are common to both contexts (Rosenbaum, Winocur, & Moscovitch, 2001).

A study by Winocur, Moscovitch, and Sekeres (2007) found that control rats exhibited a significantly stronger fear response in CXT-S than in CXT-D at short delays (1 day). However, at long delays (28 days) the same rats now showed a stronger response in CXT-D,

equal to that in CXT-S. This was interpreted as contextual specificity diminishing over time, leading to the more general features common to both contexts (instead of only the specific cues present in CXT-S) eliciting a fear response (Winocur et al., 2007). In contrast to controls, rats with hippocampal lesions exhibited the same poor degree of fear response in CXT-S and CXT-D at both short and long delays, supporting the idea that the hippocampus mediates context-sensitive memories (Winocur et al., 2007). While such findings argue for a time-limited role of the hippocampus in memory, this pertains only to memories that do not contain a certain level of contextual specificity and detail.

According to Winocur et al. (2007), these findings argue against a simple consolidation process of memory, and instead favor a transformation account whereby the nature of a memory changes with the passage of time. Thus, support is found for the extended MTT-Transformaton Hypothesis. This support is further corroborated by similar findings from studies of contextual fear conditioning, indicating a selective role for the hippocampus in mediating context-specific memories (Wiltgen & Silva, 2007; Wiltgen et al., 2010; Winocur, Sekeres et al., 2013). In addition, there is evidence for the dynamic interplay between memory systems proposed by MTT, and against the linear consolidation process proposed by the SCM. This evidence comes from studies showing that a contextual fear memory that is independent of the hippocampus can become hippocampus-dependent again and disrupted by hippocampal damage once it has been reactivated (Debiec, LeDoux, & Nader, 2002; Winocur et al., 2009).

For example, Winocur et al. (2009) found that using the fear-conditioning chamber as a reminder allowed the retrieved memory to recover its contextual specificity. In contrast, when using a reminder other than the fear-conditioning chamber (different context), the reinstated memory contained only the more general characteristics of the original memory. Reinstating the memory in the former way made it more likely to be affected by hippocampal lesions than

when reinstating it in the latter way (Winocur et al., 2009). The above findings have been argued to indicate that established memories can switch between hippocampal and non-hippocampal dependence through different reminders, and that contextual features can be reinstated in a semanticized memory (Winocur, Moscovitch, & Sekeres, 2013). As mentioned above, this is inconsistent with the linear consolidation process proposed by the SCM, but consistent with the dynamic relationship between memory systems proposed by MTT.

In conflict with MTT are findings from a study where rats with hippocampal lesions were able to express context-specific fear memories (Wang et al., 2009). However, it was also observed that the memories were very fragile and highly susceptible to disruption, and it was concluded that the hippocampus is necessary for stronger representations of context-specific memories in the long-term. Additionally, there are studies of contextual fear conditioning showing that the contextual complexity of the memory determines hippocampal involvement, where the findings are inconsistent with MTT. For example, a study by Broadbent and Clark (2013) found that damage to the dorsal hippocampus significantly impaired contextual fear conditioning in rats, even when the lesion was induced 100 days after training. While MTT predicts permanent hippocampal involvement in contextually rich memories, it is also thought that partial lesions to the hippocampus do not impair remote memories, only those acquired recently (Moscovitch et al., 2006). The findings obtained by Broadbent and Clark (2013) show that partial hippocampal damage can lead to impairments of remote context-specific memories, and are thus not consistent with MTT.

In a review by Sutherland et al. (2010) it was concluded that in many studies using contextual fear conditioning to investigate the hippocampal dependence of context-specific memories, only partial damage to the hippocampus was induced. Indeed, there have been studies where lesions have been selectively induced to the dorsal (Anagnastoras et al., 1999; Broadbent & Clark, 2013; Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998; Kim &

Fanselow, 1992; Lehmann, Lacanilao, & Sutherland, 2007; Sutherland, O'Brien, & Lehmann, 2008) and ventral (Sutherland et al., 2008) portion of the hippocampus. Of the aforementioned studies, three found ungraded RA after partial hippocampal damage (Broadbent & Clark, 2013; Lehmann et al., 2007; Sutherland et al., 2008).

Whereas such results are incompatible with MTT, they can conform to DRT. According to DRT, information is acquired independently by various memory systems; while the hippocampal memory system is usually dominant, other memory systems can assume dominance if the hippocampus is disrupted (Sutherland et al., 2010). Thus, in the cases described above, it is hypothesized that other memory systems have taken over the responsibility of mediating the memories. Since the information each memory system encodes and supports is supposedly different from that mediated by others (Sutherland et al., 2010), findings of ungraded RA for context-specific memories following partial lesions to the hippocampus are consistent with DRT.

Another way in which the hippocampus can be overshadowed by other memory systems is by manipulating the learning parameters. For example, Lehmann et al. (2009) demonstrated that by implementing repeated contextual fear-conditioning sessions, and distributing these over both hours and days, context-specific memories can be represented without the hippocampus. They exposed rats to 11 sessions of contextual fear conditioning, where the rats received mild foot-shocks in a specific context, spanning over 6 days (repeated learning condition). Additionally, the rats were simultaneously trained 10 times in another context, where no shocks were administered (control condition). 72 hours after the last sessions, the rats received complete hippocampal lesions (Lehmann et al., 2009). In the same study, another group of rats were exposed to the same number of shocks (12), but during a single learning session. Lesions were induced 7-10 days after training to match the time span between the first conditioning session and surgery in the repeated learning condition. They

found that hippocampal lesions resulted in extensive RA in rats that underwent a single learning session, which is consistent with findings from earlier studies (Lehmann et al., 2009). However, rats that underwent repeated learning sessions had intact memory for contextual fear conditioning after complete hippocampal damage.

These findings clearly go against MTT, while favoring DRT. The findings obtained by Lehmann et al. (2009) are also inconsistent with the SCM, which posits that memories become independent of the hippocampus through a prolonged process of consolidation. The aforementioned findings show that memories can become independent of the hippocampus through repeated and distributed learning sessions, even at relatively short delays (Sutherland et al., 2010). The findings obtained by Lehmann et al. (2009) have been replicated in a similar study by Lehmann and McNamara (2011). Further support for DRT can be found in a study by Sparks et al. (2013), where it was demonstrated that increasing the amount of context-shock pairings during a single learning session had no effect on the hippocampal dependence of contextual fear memories. Additionally, it has been found that it is possible for rodents with hippocampal damage to have intact contextual fear conditioning (Wiltgen, Sanders, Anagnostaras, Sage, & Fanselow, 2006). It is not clear exactly which non-hippocampal systems support certain versions of a memory, but it has been suggested that the basolateral amygdala can take over dominance of contextual fear memories (Biedenkapp & Rudy, 2009). Furthermore, it has been found the anterior cingulate cortex is important for remote contextual fear memory, but not recent (Frankland, Bontempi, Talton, Kaczmakrek, & Silva, 2004).

Spatial Memory

An additional way to assess memory performance in rodents is through tests of spatial memory. One frequently used protocol is the Morris Water-Maze, a task where the rat is placed in a pool of water and needs to find a specific platform which allows it to escape from the water (Morris, 1981). Studies using the original or modified versions of the water-maze

have yielded results that seem to favor MTT; both recent and remote memory have been equally impaired following hippocampal lesions. For example, Broadbent, Squire, and Clark (2006) induced reversible hippocampal lesions (using the drug lidocaine) in rats either immediately or 30 days after training. They found that spatial memory was impaired in both groups. Moreover, when rats induced with lesions immediately after training recovered from the drug infusion, and the drug no longer had any effect, memory performance returned to normal and the rats performed equal to controls (Broadbent et al., 2006). In another water-maze study using four navigational beacons, rats received sham lesions or lesions to the hippocampus two months after completing training (Clark, Broadbent, & Squire, 2007). While the hippocampal-lesioned rats performed at chance, controls performed significantly better. Additionally, indications that the control rats used the beacons to navigate were found. In contrast, rats with hippocampal lesions did not use the beacons at all, indicating that impairments following hippocampal lesions may not be restricted to spatial memory alone (Clark et al., 2007). Both aforementioned studies also conform to DRT; as no extensive and prolonged learning took place, non-hippocampal memory systems were inhibited by the hippocampal involvement, and the memory could thus not be established outside of the hippocampus. Therefore, removal or inactivation of the hippocampus should abolish the memory entirely.

One argument for the lack of temporally graded RA in studies using the water-maze is that learning usually takes place for a short period of time when the animals are of adult age; in contrast, human studies (where temporally graded RA if found more often) usually focus on spatial knowledge learned during a prolonged period of time, starting in childhood (Clark, Broadbent, & Squire, 2005b). This possibility was tested by Clark et al. (2005b), who trained 21-days old rats in the water-maze until they were 90-days old young adults (69 days of training). 100 days after completing the training, rats underwent surgical removal of the

hippocampus. These rats performed poorly (chance level) on retention tasks of the water-maze, while controls performed well (Clark et al., 2005b). Thus, even with extensive and prolonged training, hippocampal lesions can still result in impaired remote spatial memory. Such findings are not only inconsistent with SCM, but DRT as well; DRT argues that repeated and distributed learning sessions should allow a memory to become independent of the hippocampus.

Additional studies, using other tasks than the water-maze, have also investigated how extensive experience in an environment affects spatial memory retention after damage to the hippocampus. Winocur, Moscovitch, Fogel, Rosenbaum, and Sekeres (2005) demonstrated that rats reared for three months in a complex environment (and thus having extensive experience in it) retained allocentric spatial representations of it after hippocampal damage. These results were interpreted as support for the notion that more schematic memories, in this case map-like allocentric representations, can be independent of the hippocampus; as such, the findings are consistent with MTT (Winocur et al., 2005). Furthermore, the above findings are also consistent with DRT in that extrahippocampal structures were able to mediate a different representation of the memory independently of the hippocampus after extensive and distributed learning.

The findings obtained by Winocur et al. (2005) were corroborated in a subsequent study by Winocur, Moscovitch, Rosenbaum, and Sekeres (2010), also based on rearing rats in a complex environment. They found that preoperative rearing of as little as two weeks was enough to sustain allocentric spatial memories of the learned environment after hippocampal damage. In addition, the hippocampal-lesioned rats exhibited impairments in flexible use of the preoperatively learned information (Winocur et al., 2010). In contrast, rats that were reared postoperatively for three months did not have intact spatial representations of the learned environment, and performed as poorly as did hippocampal rats that had not been

reared in the environment at all. Lastly, it was also found that all groups exhibited some degree of spatial learning, and that the postoperatively learned information was similar in nature to the retained schematic memories learned preoperatively (Winocur et al., 2010). These findings provide further support for MTT; the spatial memories that could be retained and the information that could be learned after damage to the hippocampus was schematic and not as cohesive as the spatial memories that can be formed and retained by the intact brain (Winocur et al., 2010). These results also provide support for DRT, for the same reasons described above. However, even though remote spatial memories were intact after hippocampal damage, as predicted by SCM, they appeared to be different than spatial memories mediated by the hippocampus. Thus, SCM is inconsistent with the above findings.

In general, it seems as though tasks of spatial memories in rodents seldom yield support for SCM. Most studies show either that RA for spatial memory is ungraded (Sutherland et al., 2010) or that the intact capability for remote spatial memory after hippocampal lesions is different than in the intact brain (Winocur et al., 2010). One exception is a study by Kitamura et al. (2012), where it was indicated that neither the retrieval of remote spatial memories nor the quality of a memory is dependent on the hippocampus. This supports the SCM, and is highly inconsistent with MTT. Additional evidence against MTT comes from findings of partial hippocampal damage resulting in ungraded RA for spatial memories (Clark, Broadbent, & Squire, 2005a; Martin, Hoz, & Morris, 2005). However, the same findings are also inconsistent with the SCM, which predicts temporally graded RA following hippocampal damage.

Discussion

Whether damage to the MTL and the hippocampus proper leads to temporally graded or ungraded RA is still hotly debated. Due to naturally acquired lesions in most cases not being limited to the hippocampus, it has been problematic to determine if the observed impairments

are due to damage to the hippocampus itself or other implicated areas (Cipolotti et al., 2001). Additionally, differences in testing parameters and different interpretations of the same results can lead to reports of temporally graded or ungraded RA for the same patient. This has been shown to be true for patient H.M., with the initial study reporting temporally graded RA covering only three years (Scoville & Milner, 1957). In contrast, Corkin (2002) reports that while H.M. could remember instances from his childhood, some appeared to be semanticized and not autobiographical in nature. In another subsequent study, H.M.'s memory impairment was suggested to have no temporal gradient (Steinvorth, Levine, & Corkin, 2005). In light of these changing interpretations, it has been suggested that the methods of measuring RA have gradually become more refined (Sutherland et al. 2010).

Evidence in favor of both MTT and the SCM can be found in human lesion studies investigating patterns of RA following damage to the hippocampus and adjacent structures in the MTL. However, many findings of temporally graded RA for autobiographical episodes have been criticized for inadequate control over the quality and number of details (i.e. vividness) pertaining to the recollected events (Gilboa et al., 2004; Nadel et al., 2000). While this issue has been addressed and controlled for in a study by Kirwan et al. (2008), where a temporal gradient was found nonetheless, adequate testing of perceptual richness continues to be stressed. Indeed, St-Laurent et al. (2014) recently devised a test where subjects with unilateral MTL epilepsy were presented with short film clips (perceptually rich content) and written narratives describing the scenarios in the film clips (perceptually poor content) in a laboratory setting. In addition to providing memory reports for both contents, subjects were also required to recall autobiographical episodes that took place at least 1 year prior. The perceptual richness of all three types of memory reports was then compared, and a similar deficit in perceptual details was observed in the retrieval of autobiographical memories and film clips. While the study by St-Laurent et al. (2014) used patients with damage to the MTL,

this protocol should be possible to use when investigating the neural activity during episodic and semantic memory retrieval in healthy subjects.

Findings of temporally ungraded RA after hippocampal/MTL damage that seemingly favor MTT have been criticized as well. It has been suggested that lesions should result in ungraded RA only when the damage extends beyond the MTL into neocortical areas (Bright et al., 2006). Thus, proponents of the SCM have argued that in many cases of ungraded RA following MTL damage there might be damage to neocortical areas underlying the more extensive memory impairment (Kirwan et al., 2008). In light of the criticism directed towards both the SCM and MTT, more comprehensive analyses of intact and damaged neural tissue as well as impaired and unimpaired function of certain brain regions in subjects with brain damage need to be conducted. Additionally, more protocols that adequately test perceptual richness need to be designed, and better control over factors such as vividness of recall needs to be exerted.

Adequate testing of vividness of recall in neuroimaging studies has been stressed as well (Gilboa et al., 2004). Indeed, most neuroimaging studies are in line with MTT in that equal activation of the hippocampus has been observed during retrieval of both recent and remote autobiographical episodes, and that the quality of the memory seems to determine hippocampal dependence (Svoboda et al., 2006). As these studies measure neural activity in healthy subjects, a clear distinction can be made between the activity observed in the MTL (and the hippocampus proper) and neocortical regions. Thus, neuroimaging studies where the pattern of activity favors MTT cannot be criticized in the same manner as the lesion studies where temporally ungraded RA has been found following damage to the MTL.

Overall, the more recent data from human lesion studies and neuroimaging seems to favor MTT over the SCM. Only two neuroimaging studies appear support the SCM; however, one (Piefke et al., 2003) did not control for details, and in the other (Niki & Luo, 2002) there

was no mention of the hippocampus proper. While there are many findings from lesions studies thought to support the SCM, such findings are becoming increasingly criticized. In addition to the criticism raised above, findings of very remote memory loss following hippocampal damage is inconsistent with the SCM. Within the framework of the SCM, such findings can only be explained if the consolidation process is yet to be completed. However, many have argued that it is highly improbable for a process of memory consolidation to be so lengthy, and that several decades should be enough to completely consolidate a memory (Evans, Breen, Antoun, & Hodges, 1996; Moscovitch et al., 2006; Sanders & Warrington, 1971). Interestingly though, in the study by Maguire and Frith (2003) where a lateral asymmetry of hippocampal activation was found during retrieval of recent and remote memories, the right hippocampus ceased to be activated after as long as 30 years. Therefore, an extended period of consolidation should not be regarded a complete impossibility.

While the SCM receives support from human lesion studies where hippocampal damage has led to temporally graded RA, it has proven difficult to experimentally replicate such findings in animal models (Sutherland et al., 2010; Tayler & Wiltgen, 2013). Indeed, when controlling for contextual details, rodent studies of contextual fear conditioning do not yield support for the SCM. Similarly, findings of temporally graded RA for tasks requiring spatial memory after lesions to the rodent hippocampus are sparse (the exception being the study by Kitamura et al., 2012). While these two tasks were the only ones reviewed in this paper, Sutherland et al. (2010) have pointed out that ungraded RA following substantial hippocampal damage is observed in an increasing number of tasks (e.g. in picture discrimination memory, shock-probe conditioning, and fear-potentiated startle memory). With the SCM facing increasing difficulties accounting for findings in both the human and rodent literature, it has been suggested that a future revision of the theory may be worth considering (Sutherland et al., 2010).

Meanwhile, MTT fares better against the findings from both humans and rodents. While not only receiving increasing support from lesion studies, neuroimaging results are also highly consistent with the theory. Certainly, the majority of neuroimaging studies find that the hippocampus is significantly activated during retrieval of both recent and remote episodic memories. In contrast, retrieval of remote semantic memories does not elicit significant activation of the hippocampus (Haist et al., 2001), and the activity of the hippocampus upon retrieval of semantic memories has been shown to decrease with the remoteness of the memory (Smith & Squire, 2009). Both patterns of activation during retrieval of episodic and semantic memories are predicted by MTT, while the SCM receives support only from the activation patterns of semantic memory retrieval.

Plenty of additional support for MTT is found in tasks of contextual fear conditioning and spatial memory in rodents. Rodents with experimentally induced lesions to the hippocampus after contextual fear conditioning retain a fear memory of the general features of the learned context. In contrast, control rats exhibit a stronger fear response when exposed to the learned context than they do when placed in a different context with the same general features. This suggests that the intact hippocampus allows for distinguishing between contexts and that semanticized memories can be retained without it, as argued by MTT. Analogous findings have been obtained in tasks of spatial memory, namely that hippocampal lesions result in temporally ungraded RA for more detailed memories, but more general map-like memories can remain intact.

However, MTT faces problems with findings of ungraded RA following only partial hippocampal damage, as it is predicted that partial damage should abolish only more recent memories. Therefore, even though many reports of hippocampal damage leading to ungraded RA can be found, not all are consistent with MTT (Sutherland et al., 2010). This issue naturally applies to human lesion studies as well, but has been addressed by Addis et al.

(2007), who state that intact remaining tissue does not necessarily equal intact functionality. While indications of intact tissue having decreased functionality have been found (Addis et al., 2007), this may not always be the case. Thus, partial hippocampal damage resulting in ungraded RA can generally be seen as being at odds with MTT.

Seemingly, many of the findings supporting MTT can also conform to DRT, since both theories argue that some memories can survive hippocampal damage, though the nature of those memories are different than that of memories mediated by the hippocampus. Thus, aforementioned findings of intact schematic memory retrieval after damage to the hippocampus are equally consistent with DRT as they are with MTT. However, there are some key differences between the two theories. Two examples are that partial hippocampal damage resulting in ungraded RA is not inconsistent with DRT, and that according to DRT, memories remain dependent on the memory system that was involved in their formation (Winocur, Moscovitch, & Sekeres, 2013). Thus, findings of equally severe and temporally ungraded RA following both partial and complete hippocampal lesions are inconsistent with MTT but consistent with DRT (Lehmann et al., 2007; Sutherland et al., 2008). Additionally, in line with the central premise of DRT, studies of both contextual fear conditioning (Lehmann et al., 2009) and spatial memory (Winocur et al., 2005) have found that extensive and distributed learning leads to the formation of a memory representation outside of the hippocampus. Lehmann et al. (2009) showed that a detailed context-specific representation of a memory could be retained even after complete hippocampal damage, while the study by Winocur et al (2005) found that the surviving memories were more schematic. While both these findings are consistent with DRT, the findings obtained by Lehmann et al. (2009) are incompatible with MTT, which states that context-specific memories are always mediated by the hippocampus.

Opposing the predictions made by DRT, however, are findings hippocampal lesions resulting in ungraded RA for spatial memory following extensive experience in the Morris water-maze (Clark et al., 2005b). According to DRT, the extensive training period (100 days) should have allowed a non-hippocampal memory system to form a representation of the memory, allowing for the retention of that memory after disruption of the hippocampus. Additional evidence against DRT comes from a study by Winocur, Sekeres et al. (2013), where rats received both a single session of contextual fear conditioning and 8 days of training in the water-maze, and subsequently received lesions to the hippocampus. Hippocampal-lesioned rats exhibited temporally graded RA for contextual fear conditioning, but ungraded RA for the spatial memory task. This pattern is inconsistent with DRT, which predicts ungraded RA for both tasks (Winocur, Moscovitch, & Sekeres, 2013). Such a differential pattern could be consistent with DRT if distributed and repeated learning had taken place in one of the tasks, but in this case a single session of contextual fear conditioning allowed for the retention of a schematic memory after hippocampal lesions. In contrast, spatial memory was abolished after hippocampal lesions, even with 8 days of spatial memory training before surgery (Winocur, Sekeres et al., 2013). Therefore, the results are incompatible with DRT.

As emphasized earlier in the paper, DRT has currently only been tested experimentally in animal models. Difficulties arise when trying to apply the theory to human lesion studies and findings of RA for episodic autobiographical memories, as it can be virtually impossible to know the manner in which an episode encoded by a patient 40 years prior was learned. Arguably, episodic events are not encoded through distributed learning sessions, as each learning experience could be viewed as a separate event. However, it has been suggested that reiteration of similar information across several learning sessions could count as distributed learning of an episode, and lead to the establishment of a memory in a non-hippocampal

memory system (Sutherland et al., 2010). This could explain findings of temporally graded RA in humans following damage to the hippocampus, as intact memories supposedly overcame the hippocampal overshadowing through repeated retrieval and learning (Sutherland et al., 2010). This suggestion is similar to ideas found in MTT, namely that retrieval of an episode creates additional traces within the hippocampus, and that statistical regularities among experiences can be calculated and lead to the formation of a schematic or semanticized version of a memory in neocortical structures.

Apart from the suggestion that reiteration of episodic information can lead to the formation of memories outside of the hippocampus, DRT has not been discussed much in relation to specific patterns of RA for episodic memory in humans following hippocampal damage. One human lesion study that has been discussed in relation to DRT is a study by Maguire, Nannery, and Spiers (2006), who investigated RA for a spatial memory task in a patient with bilateral damage to the hippocampus. The subject was a former London taxi driver with roughly 40 years of experience, and the task was to virtually navigate a car through the streets of London. Since the routes had been learned 40 years prior, the task exclusively tested remote spatial memory (Maguire et al., 2006).

The study found that the subject was able to navigate through routes he likely had more experience with (arterial roads), but not those he had traveled less frequently (non-arterial roads). While these results were interpreted as supporting MTT at the time (Maguire et al., 2006), they have later been argued to support DRT as well (Sutherland et al., 2010). This is because the findings indicate that more experience with certain routes allowed representations of them to be formed and retained outside of the hippocampus, while memory for routes that were not reiterated as much remained dependent on the hippocampus and were eliminated after hippocampal damage (Sutherland et al., 2010).

As noted above, studies with human subjects need to be more carefully controlled to be able to account for inconsistent findings and to adequately test the predictions made by the different theories. Similar issues can be found in the methodology used in animal studies as well. Just as with human studies, it has been stressed that contextual specificity must be sufficiently tested and controlled for, as MTT makes a critical distinction between contextual and non-contextual memories (Winocur et al., 2010). Other problems may be found with the different ways in which lesions are experimentally induced. For example, while temporary inactivations (e.g., as used by Broadbent et al., 2006) are excellent tools when wanting to investigate the effects of hippocampal lesions induced at different points in time, information about the duration, extent/spread, and potential long-term effects of the inactivation is often lacking (Sutherland et al., 2010). Therefore, a clear definition of the optimal experimental parameters to be used when selectively disabling a specific region in the brain is needed (Sutherland et al., 2010). For a recent review of the current procedures used when inducing temporary inactivations, see Gulbrandsen and Sutherland (2014).

Perhaps the most pressing issue facing the use of animal models to investigate human declarative memory is the viability of considering certain types of memory in animals to be analogous to episodic and semantic memory in humans. As mentioned earlier in the paper, MTT holds that contextually specific and schematic memories are analogous to episodic and semantic memory, respectively (Winocur, Moscovitch, & Sekeres, 2013). In addition, since it is thought that both contextual fear memories and spatial memories can be retrieved with both context-specific or schematic information (Winocur, Sekeres et al., 2013), it is argued that spatial memory (Moscovitch et al., 2005) and contextual fear conditioning (Winocur, Moscovitch, & Sekeres, 2013) can be used to adequately test episodic and semantic memory in animals. However, it is believed that humans and animals use different strategies to solve the same task (Clark & Squire, 2010). For example, solving visual discrimination tasks

requires the MTL in humans, but the basal ganglia in monkeys, as monkeys use habit learning to solve such tasks (Clark & Squire, 2010). Thus, the memory tasks used in animal studies must be designed to adequately test their human counterpart, as using the same task in both species does not necessarily employ the same kind of memory in both species. Simply stating that contextually specific and schematic memories require the same systems and strategies between species might be insufficient.

A more tentative approach is that of Sutherland et al. (2010), who state that it is more suitable to simply use animal models to assess whether hippocampal lesions produce temporally graded or ungraded RA for any given task. When basing experiments on such a premise, the nature of the task itself is not the main interest, and no inferences about analogous memory systems can be drawn. However, this is only a viable option when evaluating theories such as DRT, where the nature of the memory is not of special interest. Using animal studies to evaluate MTT requires analogous testing of human episodic and semantic memory, as the quality and nature of the memory is of thought to be of utmost importance. Despite difficulties bridging the gap between human and animal memory, animal models have proven highly useful historically (Clark & Squire, 2013). Therefore, although it is important to remain careful when using animal models of human amnesia, one should remain positive of their usefulness.

Conclusion

The first aim of this paper was to investigate how the hippocampal dependence of long-term declarative memory is taken into consideration by the Multiple-Trace Theory, the Distributed Reinstatement Theory, and the Standard Consolidation Model. The second aim was to examine the current literature (human and rodent) for evidence favoring and opposing the three theories. In general, much support can be found for MTT in both the human and rodent literature. Nevertheless, there are some findings that are inconsistent with the theory,

especially from human lesion studies investigating the effects of hippocampal damage on remote memory. DRT, having been experimentally tested only in rodents, has been discussed very little in relation to findings from human subjects. This is because it can be difficult to assess the validity of DRT with results from conventional human lesion studies of retrograde amnesia for episodic memory following hippocampal damage. In the rodent literature, however, there is much support to be found for the theory. Meanwhile, the SCM faces significantly more hurdles, being opposed by a substantial amount of evidence from studies with both humans (especially neuroimaging studies) and rodents. For the most part, the SCM seems to have increasing difficulties accounting for more novel findings of hippocampal involvement in remote memory. Therefore, it has proposed that a revision of the theory might be in place.

References

Addis, D. R., Moscovitch, M., Crawley, A. P., & McAndrews, M. P. (2004). Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. *Hippocampus*, *14*(6), 752–762. doi:10.1002/hipo.10215

Addis, D. R., Moscovitch, M., & McAndrews, M. P. (2007). Consequences of hippocampal damage across the autobiographical memory network in left temporal lobe epilepsy. *Brain*, *130*(9), 2327–2342. doi:10.1093/brain/awm166

Adlam, A. L., Patterson, K., & Hodges, J. R. (2009). "I remember it as if it were yesterday": Memory for recent events in patients with semantic dementia. *Neuropsychologia*, *47*(5), 1344–1351. doi:10.1016/j.neuropsychologia.2009.01.029

Alvarez, P., & Squire, L. R. (1994). Memory consolidation and the medial temporal lobe: A simple network model. *Proceedings of the National Academy of Sciences*, *91*, 7041–7045. doi:10.1073/pnas.91.15.7041

Anagnostaras, S. G., Maren, S., & Fanselow, M. S. (1999). Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: Within-subjects examination. *The Journal of Neuroscience*, *19*(3), 1106–1114. Retrieved from http://www.jneurosci.org/content/19/3/1106.long

Baddeley, A., Eysenck, M. W., & Anderson, M. C. (2015). *Memory* (2nd ed.). London: Psychology Press.

Bayley, P. J., Hopkins, R. O., & Squire, L. R. (2003). Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. *Neuron*, *38*(1), 135–144. doi:10.1016/S0896-6273(03)00156-9

Bayley, P. J., O'Reilly, R. C., Curran, T., & Squire, L. R. (2008). New semantic learning in patients with large medial temporal lobe lesions. *Hippocampus*, *18*(6), 575–583. doi:10.1002/hipo.20417

Bayley, P. J., & Squire, L. R. (2005). Failure to acquire new semantic knowledge in patients with large medial temporal lobe lesions. *Hippocampus*, *15*(2), 273–80. doi:10.1002/hipo.20057

Biedenkapp, J. C., & Rudy, J. W. (2009). Hippocampal and extrahippocampal systems compete for control of contextual fear: Role of ventral subiculum and amygdala. *Learning & Memory*, *16*, 38–45. doi:10.1101/lm.1099109

Bright, P., Buckman, J., Fradera, A., Yoshimasu, H., Colchester, A. C., & Kopelman, M. D. (2006). Retrograde amnesia in patients with hippocampal, medial temporal, temporal lobe, or frontal pathology. *Learning & Memory*, *13*(5), 545–557. doi:10.1101/lm.265906

Broadbent, N. J., & Clark, R. E. (2013). Remote context fear conditioning remains hippocampus-dependent irrespective of training protocol, training-surgery interval, lesion size, and lesion method. *Neurobiology of Learning and Memory,106*, 300–308. doi:10.1016/j.nlm.2013.08.008

Broadbent, N. J., Squire, L. R., & Clark, R. E. (2006). Reversible hippocampal lesions disrupt water maze performance during both recent and remote memory tests. *Learning & Memory*, *13*(2), 187–191. doi:10.1101/lm.134706

Buckner, R. L. (2000). Neural origins of 'I remember'. *Nature Neuroscience*, *3*(11), 1068–1069. doi:10.1038/80569

Burnham, W. H. (1903). Retroactive amnesia: Illustrative cases and a tentative explanation. *The American Journal of Psychology*, *14*, 118–132. doi:10.2307/1412310

Cipolotti, L., Shallice, T., Chan, D., Fox, N., Scahill, R., Harrison, G., . . . Rudge, P. (2001). Long-term retrograde amnesia… the crucial role of the hippocampus. *Neuropsychologia*, *39*(2), 151–172. doi:10.1016/S0028-3932(00)00103-2

Clark, R. E., Broadbent, N. J., & Squire, L. R. (2005a). Hippocampus and remote spatial memory in rats. *Hippocampus, 15*(2), 260–272. doi:10.1002/hipo.20056

Clark, R. E., Broadbent, N. J., & Squire, L. R. (2005b). Impaired remote spatial memory after hippocampal lesions despite extensive training beginning early in life. *Hippocampus, 15*(3), 340–346. doi:10.1002/hipo.20076

Clark, R. E., Broadbent, N. J., & Squire, L. R. (2007). The hippocampus and spatial memory: Findings with a novel modification of the water maze. *Journal of Neuroscience, 27*(25), 6647–6654. doi:10.1523/JNEUROSCI.0913-07.2007

Clark, R. E., & Squire, L. R. (2010). An animal model of recognition memory and medial temporal lobe amnesia: History and current issues. *Neuropsychologia, 48*(8), 2234–2244. doi:10.1016/j.neuropsychologia.2010.02.004

Clark, R. E., & Squire, L. R. (2013). Similarity in form and function of the hippocampus in rodents, monkeys, and humans. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 10365–10370. doi:10.1073/pnas.1301225110

Clayton, N. S., & Dickinson, A. (1998). Episodic-like memory during cache recovery by scrub jays. *Nature, 395*(6699), 272–274. doi:10.1038/26216

Cohen, N. J., & Squire, L. R. (1980). Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of knowing how and knowing that. *Science, 210*, 207–210. doi:10.1126/science.7414331

Conway, M. A., & Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychological Review, 107*(2), 261–288. doi:10.1037//0033-295X.107.2.261

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nature Reviews Neuroscience, 3*(2), 153–160. doi:10.1038/nrn726

Debiec, J., LeDoux, J. E., & Nader, K. (2002). Cellular and systems reconsolidation in the hippocampus. *Neuron*, *36*(3), 527–538. doi:10.1016/S0896-6273(02)01001-2

Driscoll, I., Howard, S. R., Prusky, G. T., Rudy, J. W., & Sutherland, R. J. (2005). Seahorse wins all races: Hippocampus participates in both linear and non-linear visual discrimination learning. *Behavioural Brain Research*, *164*(1), 29–35. doi:10.1016/j.bbr.2005.05.006

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: A selective role for the hippocampus during retrieval. *Nature Neuroscience*, *3*(11), 1149–1152. doi:10.1038/80671

Evans, J. J., Breen, E. K., Antoun, N., & Hodges, J. R. (1996). Focal retrograde amnesia for autobiographical events following cerebral vasculitis: A connectionist account. *Neurocase*, *2*(1), 1–11. doi:10.1080/13554799608402383

Frankland, P. W., & Bontempi, B., (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience*, *6*(2), 119–130. doi:10.1038/nrn1607

Frankland, P. W., Bontempi, B., Talton, L. E., Kaczmarek, L., & Silva, A. J. (2004). The involvement of the anterior cingulate cortex in remote contextual fear memory. *Science*, *304*(5672), 881–883. doi:10.1126/science.1094804

Frankland, P. W., Cestari, V., Filipkowski, R. K., McDonald, R. J., & Silva, A. J. (1998). The dorsal hippocampus is essential for context discrimination but not for contextual conditioning. *Behavioral Neuroscience*, *112*(4), 863–874. doi:10.1037/0735-7044.112.4.863

Gilboa, A., Winocur, G., Grady, C. L., Hevenor, S. J., & Moscovitch, M. (2004). Remembering our past: Functional neuroanatomy of recollection of recent and very remote personal events. *Cerebral Cortex*, *14*(11), 1214–1225. doi:10.1093/cercor/bhh082

Gulbrandsen, T. L., & Sutherland, R. J. (2014). Temporary inactivation of the rodent hippocampus: An evaluation of the current methodology. *Journal of Neuroscience Methods, 225,* 120–128. doi:10.1016/j.jneumeth.2014.01.015

Haist, F., Gore, J. B., & Mao, H. (2001). Consolidation of human memory over decades revealed by functional magnetic resonance imaging. *Nature Neuroscience, 4*(11), 1139–1145. doi:10.1038/nn739

Herfurth, K., Kasper, B., Schwarz, M., Stefan, H., & Pauli, E. (2010). Autobiographical memory in temporal lobe epilepsy: Role of hippocampal and temporal lateral structures. *Epilepsy & Behavior*, *19*(3), 365–371. doi:10.1016/j.yebeh.2010.07.012

Kim, J. J., & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science*, *256*(5057), 675–677. doi:10.1126/science.1585183

Kirwan, C. B., Bayley, P. J., Galván, V. V., & Squire, L. R. (2008). Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe. *Proceedings of the National Academy of Sciences*, *105*(7), 2676–2680. doi:10.1073/pnas.0712155105

Kitamura, T., Okubo-Suzuki, R., Takashima, N., Murayama, A., Hino, T., Nishizono, H., . . . Inokuchi, K. (2012). Hippocampal function is not required for the precision of remote place memory. *Molecular Brain, 5*(5), 1–8. doi:10.1186/1756-6606-5-5

Lehmann, H., Lacanilao, S., & Sutherland, R. J. (2007). Complete or partial hippocampal damage produces equivalent retrograde amnesia for remote contextual fear memories. *European Journal of Neuroscience*, *25*(5), 1278–1286. doi:10.1111/j.1460-9568.2007.05374.x

Lehmann, H., & McNamara, K. C. (2011). Repeatedly reactivated memories become more resistant to hippocampal damage. *Learning & Memory*, *18*(3), 132–135. doi:10.1101/lm.2000811

Lehmann, H., Sparks, F. T., Spanswick, S. C., Hadikin, C., McDonald, R. J., & Sutherland, R. J. (2009). Making context memories independent of the hippocampus. *Learning & Memory, 16*(7), 417–420. doi:10.1101/lm.1385409

Maguire, E. A., & Frith, C. D. (2003). Lateral asymmetry in the hippocampal response to the remoteness of autobiographical memories. *The Journal of Neuroscience*, *23*(12), 5302–5307. Retrieved from http://www.jneurosci.org/content/23/12/5302.long

Maguire, E. A., Nannery, R., & Spiers, H. J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain*, *129*(11), 2894–2907. doi:10.1093/brain/awl286

Maguire, E. A., Vargha-Khadem, F., & Mishkin, M. (2001). The effects of bilateral hippocampal damage on fMRI regional activations and interactions during memory retrieval. *Brain*, *124*, 1156–1170. doi:10.1093/brain/124.6.1156

Martin, S. J., Hoz, L. D., & Morris, R. G. (2005). Retrograde amnesia: neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding. *Neuropsychologia*, *43*(4), 609–624. doi:10.1016/j.neuropsychologia.2004.07.007

Milner, B., & Penfield, W. (1955). The effect of hippocampal lesions on recent memory. *Transactions of the American Neurological Association*, *80*, 42–48.

Milner, B., Squire, L. R., & Kandel, E. R. (1998). Cognitive neuroscience and the study of memory. *Neuron*, *20*, 445–468. doi:10.1016/S0896-6273(00)80987-3

Morris, R. G. (1981). Spatial localization does not require the presence of local cues. *Learning and Motivation*, *12*(2), 239–260. doi:10.1016/0023-9690(81)90020-5

Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A., & Rosenbaum, R. S. (2006). The cognitive neuroscience of remote episodic, semantic and spatial memory. *Current Opinion in Neurobiology*, *16*, 179–190. doi:10.1016/j.conb.2006.03.013

Moscovitch, M., Rosenbaum, R. S., Gilboa, A., Addis, D. R., Westmacott, R., Grady, C., . . . Nadel, L. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *Journal of Anatomy, 207*(1), 35-66. doi:10.1111/j.1469-7580.2005.00421.x

Nadel, L., Campbell, J., & Ryan, L. (2007). Autobiographical memory retrieval and hippocampal activation as a function of repetition and the passage of time. *Neural Plasticity, 2007*, 90472. doi:10.1155/2007/90472

Nadel, L., Hupbach, A., Gomez, R., & Newman-Smith, K. (2012). Memory formation, consolidation and transformation. *Neuroscience and Biobehavioral Reviews, 36*(7), 1640–1645. doi:10.1016/j.neubiorev.2012.03.001

Nadel, L., & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinion in Neurobiology, 7*(2), 217–227. doi:10.1016/S0959-4388(97)80010-4

Nadel, L., Samsonovich, A., Ryan, L., & Moscovitch, M. (2000). Multiple trace theory of human memory: Computational, neuroimaging, and neuropsychological results. *Hippocampus, 10*, 352–368. doi:10.1002/1098-1063(2000)10:4<352::AID-HIPO2>3.3.CO;2-4

Nadel, L., Winocur, G., Ryan, L., & Moscovitch, M. (2007). Systems consolidation and hippocampus: Two views. *Debates in Neuroscience, 1*, 55–66. doi:10.1007/s11559-007-9003-9

Niki, K., & Luo, J. (2002). An fMRI study on the time-limited role of the medial temporal lobe in long-term topographical autobiographic memory. *Journal of Cognitive Neuroscience, 14*(3), 500–507. doi:10.1162/089892902317362010

Osvath, M., & Karvonen, E. (2012). Spontaneous innovation for future deception in a male chimpanzee. *PLOS One, 7*(5), e36782. doi:10.1371/journal.pone.0036782

Pavlov, I. (1927). *Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex.* (G. V. Anrep, Trans.). London: Oxford University Press.

Piefke, M., Weiss, P. H., Zilles, K., Markowitsch, H. J., & Fink, G. R. (2003). Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain*, *126*, 650–668. doi:10.1093/brain/awg064

Rascovsky, K., Growdon, M. E., Pardo, I. R., Grossman, S., & Miller, B. L. (2009). 'The quicksand of forgetfulness': semantic dementia in One Hundred Years of Solitude. *Brain*, *132*, 2609–2616. doi:10.1093/brain/awp100

Reber, P. J., Alvarez, P., & Squire, L. R. (1997). Reaction time distributions across normal forgetting: searching for markers of memory consolidation. *Learning & Memory*, *4*(3), 284–290. doi:10.1101/lm.4.3.284

Reed, J. M., & Squire, L. R. (1998). Retrograde amnesia for facts and events: Findings from four new cases. *The Journal of Neuroscience*, *18*(10), 3943–3954. Retrieved from http://www.jneurosci.org/content/18/10/3943.long

Rekkas, P. V., & Constable, R. T. (2005). Evidence that autobiographic memory retrieval does not become independent of the hippocampus: An fMRI study contrasting very recent with remote events. *Journal of Cognitive Neuroscience*, *17*(12), 1950–1961. doi:10.1162/089892905775008652

Rempel-Clower, N. L., Zola, S. M., Squire, L. R., & Amaral, D. G. (1996). Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *The Journal of Neuroscience*, *16*(16), 5233–5255. Retrieved from http://www.jneurosci.org/content/16/16/5233.long

Rosenbaum, R. S., Köhler, S., Schacter, D. L., Moscovitch, M., Westmacott, R., Black, S. E., . . . Tulving, E. (2005). The case of K.C.: Contributions of a memory-impaired person to

memory theory. *Neuropsychologia*, *43*(7), 989–1021. doi:10.1016/j.neuropsychologia.2004.10.007

Rosenbaum, R. S., Moscovitch, M., Foster, J. K., Schnyer, D. M., Gao, F., Kovacevic, N., . . . Levine, B. (2008). Patterns of autobiographical memory loss in medial-temporal lobe amnesic patients. *Journal of Cognitive Neuroscience*, *20*(8), 1490–1506. doi:10.1162/jocn.2008.20105

Rosenbaum, R. S., Priselac, S., Köhler, 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*(10), 1044–1048. doi:10.1038/79867

Rosenbaum, R. S., Winocur, G., & Moscovitch, M. (2001). New views on old memories: Re-evaluating the role of the hippocampal complex. *Behavioural Brain Research*, *127*, 183–197. doi:10.1016/S0166-4328(01)00363-1

Ryan, L., Nadel, L., Keil, K., Putnam, K., Schnyer, D., Trouard, T., & Moscovitch, M. (2001). Hippocampal complex and retrieval of recent and very remote autobiographical memories: Evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus*, *11*(6), 707–714. doi:10.1002/hipo.1086

Ryle, G. (1949). *The concept of mind*. London: Hutchinson's University Library.

Sanders, H. I., & Warrington, E. K. (1971). Memory for remote events in amnesic patients. *Brain*, *94*(4), 661–668. doi:10.1093/brain/94.4.661

Schacter, D. L., & Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*, *9*(1), 7–24. doi:10.1002/(SICI)1098-1063(1999)9:1<7::AID-HIPO2>3.0.CO;2-K

Schmolck, H., Kensinger, E. A., Corkin, S., & Squire, L. R. (2002). Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. *Hippocampus*, *12*(4), 520–533. doi:10.1002/hipo.10039

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, *20*(1), 11–21. doi:10.1136/jnnp.20.1.11

Shallice, T., Fletcher, P., Frith, C. D., Grasby, P., Frackowiak, R. S., & Dolan, R. J. (1994). Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature*, *368*(6472), 633–635. doi:10.1038/368633a0

Smith, C. N., & Squire, L. R. (2009). Medial temporal lobe activity during retrieval of semantic memory is related to the age of the memory. *The Journal of Neuroscience*, *29*(4), 930–938. doi:10.1523/JNEUROSCI.4545-08.2009

Sparks, F. T., Spanswick, S. C., Lehmann, H., & Sutherland, R. J. (2013). Neither time nor number of context-shock pairings affect long-term dependence of memory on hippocampus. *Neurobiology of Learning and Memory*, *106*, 309–315. doi:10.1016/j.nlm.2013.05.008

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: A neurobiological perspective. *Current Opinion in Neurobiology*, *5*, 169–177. doi:10.1016/0959-4388(95)80023-9

Squire, L. R., & Bayley, P. J. (2007). The neuroscience of remote memory. *Current Opinion in Neurobiology*, *17*, 185–196. doi:10.1016/j.conb.2007.02.006

Squire, L. R., & Wixted, J. T. (2011). The cognitive neuroscience of human memory since H.M. *Annual Review of Neuroscience, 34*, 259–258. doi:10.1146/annurev-neuro-061010-113720

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, *253*(5026), 1380–1386. doi:10.1126/science.1896849

St-Laurent, M., Moscovitch, M., Levine, B., & McAndrews, M. P. (2009). Determinants of autobiographical memory in patients with unilateral temporal lobe epilepsy or

excisions. *Neuropsychologia*, *47*(11), 2211–2221. doi:10.1016/j.neuropsychologia.2009.01.032

St-Laurent, M., Moscovitch, M., Tau, M., & McAndrews, M. P. (2011). The temporal unraveling of autobiographical memory narratives in patients with temporal lobe epilepsy or excisions. *Hippocampus*, *21*(4), 409–421. doi:10.1002/hipo.20757

Steinvorth, S., Corkin, S., & Halgren, E. (2006). Ecphory of autobiographical memories: An fMRI study of recent and remote memory retrieval. *Neuroimage*, *30*(1), 285–298. doi:10.1016/j.neuroimage.2005.09.025

Steinvorth, S., Levine, B., & Corkin, S. (2005). Medial temporal lobe structures are needed to re-experience remote autobiographical memories: Evidence from H.M. and W.R. *Neuropsychologia*, *43*(4), 479–496. doi:10.1016/j.neuropsychologia.2005.01.001

Sutherland, R. J., & Lehmann, H. (2011). Alternative conceptions of memory consolidation and the role of the hippocampus at the systems level in rodents. *Current Opinion in Neurobiology*, *21*(3), 446–451. doi:10.1016/j.conb.2011.04.007

Sutherland, R. J., Lehmann, H., Spanswick, S. C., Sparks, F. T., & Melvin, N. R. (2006). Growth points in research on memory and hippocampus. *Canadian Journal of Experimental Psychology - Revue Canadienne de Psychologie Experimentale*, *60*(2), 166–174. doi:10.1037/cjep20060016

Sutherland, R. J., O'Brien, J., & Lehmann, H. (2008). Absence of systems consolidation of fear memories after dorsal, ventral, or complete hippocampal damage. *Hippocampus*, *18*(7), 710–718. doi:10.1002/hipo.20431

Sutherland, R. J., Sparks, F. T., & Lehmann, H. (2010). Hippocampus and retrograde amnesia in the rat model: A modest proposal for the situation of system consolidation. *Neuropsychologia*, *48*(8), 2357–2369. doi:10.1016/j.neuropsychologia.2010.04.015

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: A meta-analysis. *Neuropsychologia*, *44*(12), 2189–2208. doi:10.1016/j.neuropsychologia.2006.05.023

Tayler, K. K., & Wiltgen, B. J. (2013). New methods for understanding systems consolidation. *Learning & Memory*, *20*(10), 553–557. doi:10.1101/lm.029454.112

Teng, E., & Squire, L. R. (1999). Memory for places learned long ago is intact after hippocampal damage. *Nature*, *400*, 675–677. doi:10.1038/23276

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of memory* (pp. 381–403).

Tulving, E. (2002). Episodic memory: From mind to brain. *Annual Review of Psychology*, *53*, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Tulving, E., Kapur, S., Markowitsch, H. J., Craik, F. I., Habib, R., & Houle, S. (1994). Neuroanatomical correlates of retrieval in episodic memory: Auditory sentence recognition. *Proceedings of The National Academy of Sciences*, *91*(6), 2012–2015. doi:10.1073/pnas.91.6.2012

Tulving, E., & Markowitsch, H. J. (1998). Episodic and declarative memory: Role of the hippocampus. *Hippocampus*, *8*(3), 198–204. doi:10.1002/(SICI)1098-1063(1998)8:3<198::AID-HIPO2>3.3.CO;2-J

Tulving, E., Schacter, D. L., McLachlan, D. R., & Moscovitch, M. (1988). Priming of semantic autobiographical knowledge: A case study of retrograde amnesia. *Brain and Cognition*, *8*(1), 3–20. doi:10.1016/0278-2626(88)90035-8

Viard, A., Lebreton, K., Chételat, G., Desgranges, B., Landeau, B., Young, A., . . . Piolino, P. (2010). Patterns of hippocampal-neocortical interactions in the retrieval of episodic autobiographical memories across the entire life-span of aged adults. *Hippocampus*, *20*(1), 153–165. doi:10.1002/hipo.20601

Viard, A., Piolino, P., Desgranges, B., Chételat, G., Lebreton, K., Landeau, B., . . . Eustache, F. (2007). Hippocampal activation for autobiographical memories over the entire lifetime in healthy aged subjects: An fMRI study. *Cerebral Cortex, 17*(10), 2453–2467. doi:10.1093/cercor/bhl153

Wang, S. H., Teixeira, C. M., Wheeler, A. L., & Frankland, P. W. (2009). The precision of remote context memories does not require the hippocampus. *Nature Neuroscience*, *12*(3), 253–255. doi:10.1038/nn.2263

Wiltgen, B. J., Sanders, M. J., Anagnostaras, S. G., Sage, J. R., & Fanselow, M. S. (2006). Context fear learning in the absence of the hippocampus. *The Journal of Neuroscience, 26*(20), 5484–5491. doi:10.1523/JNEUROSCI.2685-05.2006

Wiltgen, B. J., & Silva, A. J. (2007). Memory for context becomes less specific with time. *Learning & Memory*, *14*(4), 313–317. doi:10.1101/lm.430907

Wiltgen, B. J., Zhou, M., Cai, Y., Balaji, J., Karlsson, M. G., Parivash, S. N., . . . Silva, A. J. (2010). The hippocampus plays a selective role in the retrieval of detailed contextual memories. *Current Biology*, *20*(15), 1336–1344. doi:10.1016/j.cub.2010.06.068

Winocur, G., Frankland, P. W., Sekeres, M., Fogel, S., & Moscovitch, M. (2009). Changes in context-specificity during memory reconsolidation: Selective effects of hippocampal lesions. *Learning & Memory, 16*(11), 722–729. doi:10.1101/lm.1447209

Winocur, G., & Moscovitch, M. (2011). Memory transformation and systems consolidation. *Journal of the International Neuropsychological Society*, *17*(5), 766–780. doi:10.1017/S1355617711000683

Winocur, G., Moscovitch, M., & Bontempi, B. (2010). Memory formation and long-term retention in humans and animals: Convergence towards a transformation account of hippocampal–neocortical interactions. *Neuropsychologia, 48*(8), 2339–2356. doi:10.1016/j.neuropsychologia.2010.04.016

Winocur, G., Moscovitch, M., Fogel, S., Rosenbaum, R. S., & Sekeres, M. (2005). Preserved spatial memory after hippocampal lesions: Effects of extensive experience in a complex environment. *Nature Neuroscience*, *8*(3), 273–275. doi:10.1038/nn1401

Winocur, G., Moscovitch, M., Rosenbaum, R. S., & Sekeres, M. (2010). An investigation of the effects of hippocampal lesions in rats on pre- and postoperatively acquired spatial memory in a complex environment. *Hippocampus*, *20*(12), 1350–1365. doi:10.1002/hipo.20721

Winocur, G., Moscovitch, M., & Sekeres, M. (2007). Memory consolidation or transformation: Context manipulation and hippocampal representations of memory. *Nature Neuroscience*, *10*(5), 555–557. doi:10.1038/nn1880

Winocur, G., Moscovitch, M., & Sekeres, M. J. (2013). Factors affecting graded and ungraded memory loss following hippocampal lesions. *Neurobiology of Learning and Memory, 106*, 351–364. doi:10.1016/j.nlm.2013.10.001

Winocur, G., Sekeres, M. J., Binns, M. A., & Moscovitch, M. (2013). Hippocampal lesions produce both nongraded and temporally graded retrograde amnesia in the same rat. *Hippocampus*, *23*(5), 330–341. doi:10.1002/hipo.22093

Zola-Morgan, S., Cohen, N. J., & Squire, L. R. (1983). Recall of remote episodic memory in amnesia. *Neuropsychologia, 21*(5), 487–500. doi:10.1016/0028-3932(83)90005-2

Zola-Morgan, S., & Squire, L. (1990). The primate hippocampal formation: Evidence for a time-limited role in memory storage. *Science*, *250*(4978), 288–90. doi:10.1126/science.2218534

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *The Journal of Neuroscience*, *6*(10), 2950–2967. Retrieved from http://www.jneurosci.org/content/6/10/2950.full.pdf+html