Systems consolidation, transformation and reorganization: Multiple Trace Theory, Trace Transformation Theory and their Competitors

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Abstract

We review the literature on systems consolidation by providing a brief history of the field to place the current research in proper perspective. We cover the literature on both humans and non-humans, which are highly related despite the differences in techniques and tasks that are used. We argue that understanding the interactions between hippocampus and neocortex (and other strurctures) that underlie systems consolidation, depend on appreciating the close correspondence between psychological and neural representations of memory, as postulated by Multiple Trace Theory and Trace Transformation Theory. We end by evaluating different theories of systems consolidation in light of the evidence we reviewed and suggest that the concept of systems consolidation, with its central concern with the time-limited role the hippocampus plays in memory, may have outlived its usefulness. We sggest replacing it with a program of research on the psychological processes and neural mechanisms that underlie changes in memory across the lifetime – a natural history of memory change.

"The fixing of an impression depends on a physiological process. It takes time for an impression to become so fixed that it can be reproduced after a long interval; for it to become part of the permanent store of memory considerable time may be necessary. This we may suppose is not merely a process of making a permanent impression upon the nerve cells, but also a process of association, of organization of the new impressions with the old ones" (Burnham, 1904).

"One other incident in the early 1970s left me pondering the adequacy of the levels account of memory. I had gone to Montreal to visit my friend Morris Moscovitch, who was spending the year in Brenda Milner's lab. While I was talking to Morris, Brenda popped her head around the door to say hello and to apologize that she could not chat, as she was already late for a meeting. "However," she said, "my amnesic patients have no trouble perceiving and comprehending events, they are clearly capable of processing to deep semantic levels—yet they don't remember things. How does that fit with your theory?" "Sorry, can't stay," she added, leaving me to worry about the undeniable problem raised by her question. It may therefore be necessary to concede that something else plays a necessary role in memory beyond adequate depth and elaboration of processing. The most obvious candidate for this further ingredient is consolidation, a process with no cognitive correlates as far as I can tell that presumably proceeds automatically after the cognitive processes associated with depth and elaboration. In light of the many investigations carried out on the celebrated amnesic patient HM, and also in light of current studies in neuroscience (Alvarez & Squire, 1994; Corkin, 2002, 2013; Dudai, 2004; Eichenbaum, 2004; Nadel & Moscovitch, 1997), it seems likely that such further processing is carried out by interactions between the hippocampus and relevant areas of the cerebral cortex. (Craik, 2020)."

"Our model of consolidation postulates that the medial temporal lobe region maintains coherence within an ensemble of neocortical sites until such time as the coherence of these sites becomes an intrinsic property of the ensemble. It is our view that during this lengthy process certain aspects of memory for the original event are forgotten while those that remain are strengthened. But it would be simplistic to suggest that any biological change is responsible for consolidation lasting as long as several years, as indicated by the data from retrograde amnesia. Rather, this time period, during which the medial temporal region maintains its importance. Is filled with external

events (such as repetitions and activities related to original learning) and internal processes (such as rehearsal and reconstruction). These influence the fate of as-yet unconsolidated information through remodeling the neural circuitry underlying the original representation. The selection of which elements of memory are forgotten and which survive and are strengthened depends on how these elements are affected by: 1) the particular events intervening between learning and retention; and 2) how the elements fit into the organism's pre-existing knowledge. During memory consolidation some elements of memory are incorporated into pre-existing schemata; others might form the basis of new schemata; still others will be lost.

"These ideas differ from the view that memories are fixed entities, traces of past experience uninfluenced by subsequent prior events, and changed only by slow erosion. Memory consolidation by our view is not a relentlessly gradual of passive process. The ideas developed here fit more comfortably with a view of memory as a dynamic process, which changes over time through reorganization and assimilation to pre-existing memories, and which is affected by subsequent memory-storage episodes. This view has precedents in the work of Bartlett (1932), and Rumelhart and Norman (1978) and in psychoanalytic theory (see for example, Feldman, 1977). It should be clear that we view consolidation as subserving just this sort of dynamism in memory." (Squire et al., 1984, pp.205-206).

Introduction

The issues raised by these quotations concern the relation between consolidation and cognition. Reluctantly, Craik (2020) concedes that consolidation is a physiological process, devoid of cognitive correlates, mediated by the hippocampus, or by hippocampal-neocortical interactions, and comes into play automatically only after all the heavy cognitive work has been done. Burnham (1904), pointedly argues against this view of consolidation, but does not indicate how

psychological and physiological processes are related to one another. Squire et al. (1984) address Burnham's point and provide a general solution without specifying how such consolidation processes might be realized neurologically other than appeal to large structures, the medial temporal lobes and neocortex. Moreover, they view consolidation as a unidirectional process with a clear beginning and end; only ‘’as yet unconsolidated information" is susceptible to the active dynamism of memory that shape and determine detail retention or loss before stabilization is achieved.

Despite Burnham's plea to consider psychological changes alongside neural ones, and Squire et al. elaborating on it (in print, if not in the lab), research on systems consolidation has been concerned almost exclusively with changes in neural representation with little, if any regard, for the changes in psychological representation that might accompany them. In this review we take up the challenge of relating psychological and neural processes to one another, beyond retention and loss, to explain the nature of systems consolidation, and argue that we cannot understand one without the other.

We begin with a brief historical review to introduce the concepts around which we will organize the issues we address. Placing the current state of the field in historical context reveals some of the conditions that shaped our thinking, and continues to do so.

History and nomenclature

The history of memory consolidation dates back to the beginnings of memory research in the late 19th early 20th century when the term was fist coined by Müller and Pilzecker (1900) to describe the process by which memories become stabilized and resistant to interference or disruption (Lechner et al. 1999). Using associations between pairs of nonsense syllables, Muller and

Pilzecker conducted an extensive series of experiments to show that a short time after learning, typically about ten minutes, associative memories become resistant to the interfering effects of other stimuli. These ideas on memory consolidation were soon linked to effects of lesions on memory in humans (Burnham, 1904; Korsakoff, 1889; Ribot, 1882) such that memory loss following brain damage was observed to follow a temporal gradient, with memories for recent events being more affected than memory for remote events. It took time to consolidate memories, but once consolidated, they were resistant to disruption by neurological insult (see Lechner et al., 1999; McGaugh, 2000). Though related, the time scales of evidence from the psychological laboratory and neurological clinic were orders of magnitude apart, suggesting that different mechanisms mediated them.

A review of a large series of cases on the effects of brain damage on recent and remote memory by Russell (1948) corroborated these early clinical observations, and helped initiate the modern era of consolidation research. In 1949, Hebb proposed his synaptic strength theory of memory formation, providing a plausible neurobiological mechanism for memory consolidation. He hypothesized that memories were represented/mediated by neuronal cell assemblies. These cell assemblies were formed by increasing synaptic strength through reverberation of interconnected neurons which were activated by co-occurring aspects of an experience. Reactivating the cell assembly by stimulating some of its neurons gives rise to a memory of the event that initially led to the assembly's formation. Disrupting the reverberation before the synapses were sufficiently strengthened prevented the formation of a cell assembly and the memory it supported.

Synaptic strengthening among local neuronal networks over short intervals is at the heart of most current theories of *cellular consolidation* (but see Gallistel, 2020; Gallistel & Matzel, 2013) for another view). Rather than reverberation, however, it is now believed that an experience-initiated

cascade of intracellular, and extracellular, molecular mechanism leads to strengthening of a Hebb synapse and memory formation (Kandel et al., 2014). Cellular consolidation is a relatively rapid process, lasting on the order of minutes to hours. Disrupting consolidation before it is completed leads to memory loss.

Cell assemblies that represent memory are now construed as memory *engrams*, a term coined by Semon (Semon, 1904, 1921; also see Schacter, 1982; Schacter, Eich & Tulving, 1978) to refer to the lasting physical changes that accompany an event or experience. He distinguished it from *ecphory*, the process by which a retrieval cue interacts with the engram to yield a memory (Josselyn et al., 2015, 2017; Josselyn & Tonegawa, 2020; Tonegawa et al., 2015). The engram provides the initial, dormant substrate that makes memory possible, but a memory does not exist until ecphory has occurred (Moscovitch et al., 2016). Like Bartlett (see below), Semon thought that memories were dynamic, being modified in the process of retrieval, and becoming engrams themselves which can strengthen or add to previously related engrams (precursor of Multiple Trace Theory). According to Semon, engrams did not reside in a single cell or location, but rather were distributed among the neural elements that mediated that particular experience or event. The processes underlying cellular consolidation are believed to be common to all engrams, but the type of memory that the engrams can potentially represent will vary depending on the neurons forming the engram and their projections. These engrams, and their precursors, constitute the beginning of *systems consolidation*.

Beginning in the 1920s, Lashley, Hebb's mentor, embarked on a neurological search for engrams by ablating different parts of the cortex in rats and studying their effects on memory for mazes (Lashley, 1950). Because lesion size, rather than lesion location, determined the extent of

memory loss, Lashley concluded, in accord with Semon, that memories were distributed throughout the cortex.

It was Hebb's student, Brenda Milner, working in collaboration with Penfield and Scoville, who discovered the crucial role that the medial temporal lobes, and the hippocampus in particular, played in memory formation and consolidation. They found that damage to the medial temporal lobes, particularly the hippocampus, caused a severe and lasting anterograde amnesia and a temporally graded retrograde amnesia of about three years in one of their patients, HM, with more remote memories being preserved, consistent with observations by Ribot and Korsakoff more than a half century earlier, and Russell and Nathan more recently (Milner & Penfield, 1955; Penfield & Milner, 1958; Scoville & Milner, 1957). Memory loss, however, primarily involved declarative memory which includes both episodic memory and semantic memory, leaving other forms of memory, such as procedural memory and priming, relatively preserved (Moscovitch, 1982, 1995, 2012; Squire, 2009).

Milner's findings, and subsequent research with other amnesic patients, laid the groundwork for our knowledge of *systems consolidation* which is typically far more prolonged than cellular consolidation, lasting years or even decades, and is concerned with the organization of engrams, and their distributed representations, across neorcortical and other networks. Systems consolidation is the term adopted for the process by which memory engrams extend to new neural locations and in parallel cease to depend on structures that subserved their acquisition. It should be noted that this definition is not free of the theoretical suppositions (see Box 1), some which we will question.

Standard Consolidation Theory (SCT)

Based on these findings, and adapting the theoretical frameworks we noted, investigators proposed what has come to be known as the Standard (Systems) Consolidation Theory (SCT). According to SCT, the hippocampus binds into a hippocampal-neocortical ensemble (memory trace or engram) the neuronal pattern that underlies the content and experience of an event. The sparsely-coded hippocampal neurons in this ensemble serve as a pointer or index to the distributed neocortical representations of the engram (Teyler & Rudy, 2007; Teyler & DiScenna, 1986). At retrieval, an internally generated or externally driven cue interacts with the hippocampal index which, in turn, reactivates the ensemble to yield an episodic memory of the event. Over time, and guided/reinforced by the hippocampus, the links among the neocortical elements of the ensemble are strengthened to the point that they can be reactivated without hippocampal input. This marks the end of the consolidation process, at which point memories are retrieved directly from neocortex and independently of the hippocampus (Moscovitch, 1995; Moscovitch & Winocur, 1992; Squire & Alvarez, 1995).

Typically, theory and experiments on systems consolidation have focused on the process by which memories become independent of the hippocampus and come to rely on neocortex. The figure in Box 1 captures this element of SCT well, but it also helps us identify less obvious elements which reveal the set of premises underlying SCT. Some have been stated explicitly, but others are assumed implicitly, yet play a major role (see Box 1).

BOX 1. Premises of Standard Consolidation Theory (SCT)

Figure 1. captures the elements of SCT and its modified version well. Using it, we identify less obvious, yet nonetheless major premises underlying SCT some of which are clearly stated in the theory, but some of which are implicit but play major role.

(i) (ii)

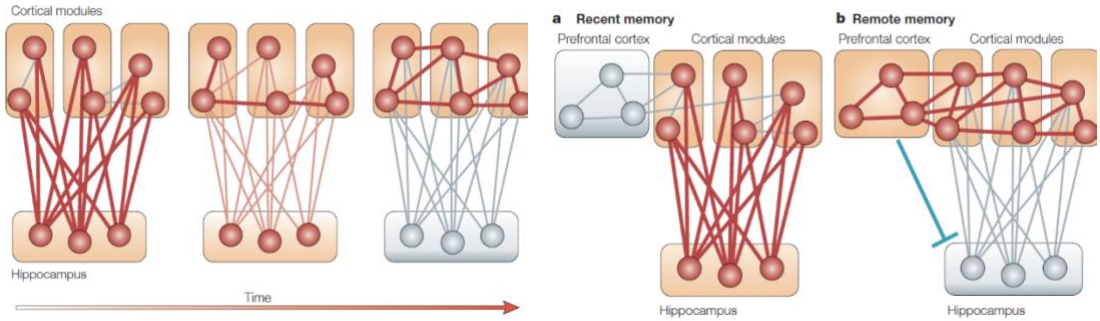

Figure 1. (i) Traditional Standard Consolidation Model. Hippocampal-neocortical connections formed at encoding are weakened with time as neocortical connections are strengthened. (ii) Modified Model in which hippocampal neocortical connections mediating recent memory are replaced by pre-frontal neocortical connections for remote memories, accompanied by frontal inhibition of hippocampal connections.

1. *Binding hub:* The hippocampus binds co-activated neocortical (and other neurons) that represent the experience of an event into a hippocampal-neocortical ensemble (memory trace or engram).
2. *Index/pointer:* The hippocampus acts as an index or pointer, and possibly a spatial scaffold, whose activation reinstates the event in memory.
3. *Initiation:* Memory consolidation begins with the presentation of the to-be-remembered event.
4. *Gateway:* The hippocampus is the gateway to neocortical representation of declarative memory.
5. *Strengthening of neocortical connections:* With time, and replay, the neocortical connections to each other are strengthened until they are so bound to one another so that activating any of the

components can reactivate the entire ensemble without help from the hippocampus. Alternatively, connections to prefrontal cortex are also strengthened. Concurrently, hippocampal binding is diminished. It is these processes that constitute *systems consolidation.*

6. *Time-limited*: The role of the hippocampus in reactivating the neocortical component of memory trace is time-limited. As a result, there is a *temporal gradient* of retrograde amnesia with recently acquired, but not fully consolidated memories, being more vulnerable to disruption than more remote, consolidated memories.

7. *Equivalence:* All declarative memories, whether episodic (context-specific) or semantic (context-general), undergo the same process.

8. *Comparability:* The neocortical elements mediating episodic memories remain unchanged throughout the consolidation process. Except for strengthening of connections among the neocortical elements and loosening those to the hippocampus, the episodic memory represented in neocortex retains its characteristics, whether or not it is dependent on the hippocampus for retention and retrieval.

9. *Substitution:* Post-consolidation retrieval can be implemented either by activating one of the neocortical elements directly, leading to re-activation of the entire ensemble, much like Hebb's cell assembly. Alternatively, activation of the neocortical elements which represent the content of the memory may be mediated by another neocortical structure (see prefrontal cortex in the above fiure) which plays a role comparable to the hippocampus, effectively substituting for it once consolidation is completed. The primary candidate is the ventro-medial prefrontal (vmPFC) cortex.

10. *Unidirectional:* Systems consolidation is unidirectional, proceeding from the hippocampus to neocortex.

11. *Stability:* Systems consolidation and memory dynamism end when stable cortical traces are created. Once consolidated, memories remain stable. Retrieving memories does not make them more susceptible to interference or loss.

Premise 8 (Comparability) needs elaboration. In the interest of simplicity, the figure captured one aspect of the standard theory but, in the process, eliminated a more nuanced view of memory as dynamic even by proponents of SCT. Perhaps a better way of stating Premise 8 is that memories still dependent on the hippocampus are fundamentally similar to those that can be retained or retrieved independently of it. In short, they retain their episodic characteristics throughout the consolidation process.

Basic principles of systems consolidation: A neuro-psychological representational perspective

In reviewing the evidence regarding systems consolidation, we show that only the first two premises, and possibly the fifth, survive scrutiny. The rest either need to be abandoned or modified and SCT along with them. The discerning/attentive reader will note that the first two premises describe what is the consensus view regarding hippocampal function in encoding, retention and retrieval of recently acquired episodic memories.

1. Our **first principle** is that the hippocampus retains its function in representing episodic memories and does not relinquish it to other structures over time. Whether the memory is recent or remote does not matter. Although this view was controversial when we first proposed it in 1997 (Nadel & Moscovitch, 1997), it has gained traction, not only because we believe it accords

with the evidence on systems consolidation that has accumulated since then (see below), but also because of evidence of hippocampal involvement in a variety of other functions including imagining fictitious scenes and scenarios, and imagining the future (Addis et al. 2007b;Addis & Schacter, 2012; Addis, 2020; Hassabis et al., 2007; Maguire & Hassabis, 2011; Maguire & Mullally, 2013; Moscovitch et al., 2016; Viard, Desgranges, Eustache & Piolino, 2012). It seems implausible that if the hippocampus is implicated in imagining the future, it would not also be implicated in reliving the past, no matter how remote. Indeed, it is telling that research on hippocampal involvement in imagining the future, including solving future problems, was initiated by individuals, such as Maguire and Addis, who were among the proponents of the idea that the hippocampus was implicated in remote memory as much as in recent memory.

2. These observations on hippocampal involvement in memory lead to our **second principle** which is that systems consolidation is not a unidirectional time-dependent process. Consolidation involves more than a process of selection, of 'pruning' event details and of relinquishing retained information to other neural locations. Instead, we suggest that memories are always in flux, and throughout their "lives" there are potentially multiple interactive forms of event representations (Sekeres et al., 2017, 2018a; Winocur & Moscovitch, 2011). The passage of time, as well as task demands at encoding and retrieval dictate the strength or dominance of each of these representations and determine what form of a memory would be preferentially expressed.
3. Our **third principal** is that each of these psychological forms of representations is supported by distinct neurobiological substrates and processes, and their interactions drive memory dynamics (Robin & Moscovitch, 2017; Sekeres et al., 2018a; Winocur & Moscovitch, 2011). Our view is that these processes, and the distributed neural substrates that mediate them, are implicated in memory formation, organization and expression from the very beginning, and thus diverges from

the idea that the hippocampus is the gateway to systems consolidation (contra Premse 4) (Gilboa & Moscovitch, submitted). As such, systems consolidation is not the mere relinquishing of hippocampal involvement to the neocortex over time, (in fact, for some memories that may never occur) but a dynamic process of hippocampal-neocortical interactions that determine the organization and expression of memory that begins even before acquisition (contra premise 3) and continues for a lifetime.

What then changes with systems consolidation? SCT is correct that there are changes in neural representation with time and experience. Our contention is that these changes are accompanied by corresponding changes in psychological representations. We also will provide evidence that there are parallel multiple forms of neural-psychological memory representations at all stages, from acquisition to retention to retrieval of recent and remote memories. As noted above, each of these representations are subject to change with time and experience, the extent to which any representation is expressed at a given time being determined by conditions that exist at retrieval, such as task demands, goals, and motivation, as well as prior knowledge.

The evidence we present accords with a more general principle: the *principle of functional-neural isomorphism* which states that "representations that differ from one another must necessarily be mediated by different structures (collections of neurons), and representations mediated by different structures must necessarily differ in some fundamental way from one another (Moscovitch et al., 2016, pp. 109)." Its corollary is that there is *neural-psychological representation correspondence,* namely that each type of representation is mediated by its corresponding structure and vice-versa (Gilboa & Moscovtich, submitted). If episodic memory is mediated by the hippocampus, this relationship should hold regardless of whether the memory occurred recently or long ago. Conversely, these principles suggest that if there is a change in the

mediating structure, such as sometimes occurs as memories age, there should also be a change in the nature of the psychological representation.

Now for the evidence.

Early Challenges to SCT

Since its inception following Milner's reports (Milner & Penfield, 1955; Penfield & Milner, 1958; Scoville & Milner, 1957, Penfield, 1974), SCT in its various iterations guided research on systems memory consolidation in rodents and humans, and provided the framework for interpreting the results. Despite its success and the advances in knowledge it fostered (Squire et al., 2015), troubling findings emerged which challenged some of these premises. Studying rodents, Misanin et al. (1968) noted that retrieving already consolidated memories made them vulnerable to disruption for a short time after retrieval, suggesting that consolidated memories are not as stable at SCT assumes (contra Premise 11) (Hardt et al., 2009; Miller & Matzel, 2006; Nader & Hardt, 2009; Sara, 2000ab; Squire, 2006; see Nadel & Sederberg, *in press*).

Sanders and Warrington (1971) reported memory deficits following hippocampal lesions in humans that extended for decades, some covering a lifetime, suggesting that the role of the hippocampus is not time-limited (contra premise 6). Even when not so prolonged, the extent of retrograde amnesia often lasted years suggesting, as Craik (2020), Burnham (1904) and Squire et al., (1984) surmised, that more than mere neurobiological strengthening of neocortical connections was involved. Following Tulving (1972) proposal of a distinction between episodic and semantic memory, Kinsbourne and Wood, (1975) noted that amnesia primarily affected episodic memories, while relatively sparing semantic memory, suggesting that consolidation does not treat all declarative memories equivalently (contra premise 7). Likewise, cognitive map

theory (O'Keefe & Nadel, 1978), one of the most influential theories of hippocampal function, does not assume an expiry date for the dependence of allocentric spatial representations on the hippocampus. If, however, cognitive maps do change with time, what is the nature of that change, and what is its neural substrate?

Recent Challenges to SCT

SCT successfully withstood these challenges both with respect to episodic and semantic memory (Squire, 1992; Squire & Alvarez, 1995) and to spatial memory (Rosenbaum et al., 2000; Teng & Squire, 1999, Rosenbaum et al., 2004a,b; 2005,b; see review in Rosenbaum et al., 2001) until the late 1990s and early 2000s. By then, new evidence on the functional neuroanatomy and interaction of the medial temporal lobes and prefrontal cortex, and on neurobiological basis of consolidation in rodents, revived these same critiques, which now took their toll on some of the premises underlying SCT. Equally important were the development of alternative theoretical frameworks that not only could accommodate the new data, but stimulate and guide research in new directions that expanded our understanding of hippocampal function and its interaction with neocortex. As much of this ground has been covered extensively (for most recent reviews, see Kandel et al., 2014; Moscovitch et al., 2016; Sekeres et al., 2018; Squire et al., 2015), we will only review it briefly here, and focus on the most recent empirical and theoretical developments.

Multiple Trace Theory

Although SCT could account for the temporally-graded retrograde amnesia for semantic memory following MTL damage, it had more difficulty in dealing with observations of severe and temporally extensive retrograde amnesia, sometimes encompassing a lifetime, for episodic memories of autobiographical events. In humans, *episodic memory* refers to recollection of a

particular event and the experiences that accompany it, so that one effectively travels mentally back in time and relive the event by reinstating the context in which it occurred (Suddendorf & Corballis, 1997, 2007; Tulving, 1985, 2001, 2002). By comparison, *semantic memory* refers to general knowledge about the world and oneself without regard to the context in which the memory was acquired. A hallmark of episodic memory is that it is rich in perceptual, temporal, sequential and other contextual details that enable one to re-experience an event, whereas semantic memory is concerned only with general knowledge devoid of the contextual details that accompanied its acquisition (Moscovitch et al., 2016). Likewise, in non-human species, contextual specificity is considered to be the hallmark of episodic-like memory, whereas semantic-like memories were considered to be context general (Sekeres et al., 2018; Winocur & Moscovitch, 2011; Winocur et al., 2010).

Building on Kinsbourne and Wood's (1975) and Warrington and Weiskrantz's (1970) observations and ideas, and on Moscovitch and Winocur's (1992; Moscovitch, 1994) Component Process Model, Nadel and Moscovitch (1997) proposed that the MTL, and hippocampus in particular, is needed for the retention and retrieval of episodic memories in perpetuity. To account for suggestive evidence that the extent and severity of retrograde amnesia for episodic memories is related to the size of the MTL lesion (Fujii et al., 2000), Nadel and Moscovitch proposed that each time a memory is retrieved, it is re-encoded as a separate, sparsely-distributed trace in the hippocampus along with the new context in which retrieval occurs (Nadel et al., 2000). These multiple traces are more numerous, and more widely distributed for older memories that have had more opportunities for retrieval than did newer memories. As a result, older memories are more resistant than newer memories to the effects of hippocampal damage, leading to a temporal gradient of retrograde amnesia; extensive damage would affect even the

oldest memories. The re-encoding of retrieved memories was based on the idea that the hippocampus is a "stupid" memory system that obligatorily encodes all information in conscious awareness, whether externally presented or internally generated (Moscovitch, 1992, 1995, 2008). Being stupid, the hippocampus lacks thematic and possibly even temporal organization beyond that afforded by mere contiguity over short intervals.

If memory is to be "intelligent" and serve the myriad functions to which it is put, the hippocampus depends on other structures. Chief among these structures is the prefrontal cortex (PFC), areas of which are recruited and act as "working-with-memory" structures (Moscovitch, 1992, 1994; Moscovitch & Winocur, 1992). At encoding they direct attention to relevant information and also bring relevant knowledge to bear on perception to ensure that some measure of goal-directed control is exerted. At retrieval, in response to an internally-generated or externally-presented cue, the PFC initiates and directs search to recover those hippocampal engrams which cannot be activated directly by these cues; the PFC monitors the memory that is retrieved to ensure that it is consistent with the goals of the task and with other knowledge and memories. The PFC then places the retrieved memories in a coherent sequence if the memory is temporally extended beyond the close proximity of one item with another. These extrahippocampal structures are implicated during retrieval of both recent and remote memories.

Semantic memory representations, on the other hand, do not rely for retention and retrieval on the specific circumstances/context that accompanied their acquisition. They are presumed to be derived from extraction of statistical regularities across neocortical representations related to their content or by assimilation to representations of prior knowledge, a process that may be prolonged (McClelland et al., 1995). Once formed, however, semantic memories are resistant to hippocampal damage, consistent with both MTT and SCT.

The differential effects of hippocampal lesions on remote episodic and semantic memory suggest that it is not the memory's age, but the nature of the memory that distinguishes memories whose retention and retrieval are dependent on the hippocampus from those that are not. The hippocampus's role with respect to episodic memory is not time-limited (contra premise 6), but continues over the life of the memory. In agreement with SCT, MTT acknowledges that semantic memories, unlike episodic memories, do become independent of the hippocampus with time, suggesting that systems consolidation is not equivalent for all declarative memory (contra premise 7).

Having a plausible, alternative theoretical framework to SCT led to a burgeoning of studies on systems consolidation. Investigators began to examine recent and remote memories in patients with memory disorders from a new perspective, placing as much weight on psychological changes as on neural ones. This approach also informed functional neuroimaging studies in neurologically intact people (see Sekeres et al., 2018a). Comparable studies were conducted in non-human species, usually rodents. At first, most of these studies used classical lesion methods (Sutherland et al., 2010; Winocur et al., 2010) but later came to rely increasingly on newly developed neurobiological techniques that allowed for more precise tracking of the engrams that supported recent and remote memories, and provided greater control over them (Jasnow et al., 2017; Josselyn & Tonegawa, 2020; Sekeres et al., 2018).

Because a major distinction between SCT and MTT concerned differences in the fate of episodic and semantic memory, new psychological tests were devised that were sensitive to those differences (Kopelman et al., 1989; Kopelman & Marsh, 2018; Levine et al., 2002; Piolino et al., 2003, 2009; Renoult et al, 2020) enabling investigators to track them over time. To track memories over long time intervals, investigators examined autobiographical memory and

memory for public events and personalities, and distinguished between episodic and semantic contributions to them (Moscovitch et al., 2005, 2006; Sekeres et al., 2016, 2018; Squire et al., 2015; Kopelman, 2019). With respect to autobiographical memory, one can test the two aspects separately as the Autobiographical Memory Inventory does by asking people to name personal facts they know about themselves at different times in their life (name of high school they attended) and by recounting an episode that occurred at different times (Kopelman et al., 1989). Another strategy is to ask people to provide narratives of episodes that occurred at different times and then score the narrative separately for details unique to the event (intrinsic/episodic) from details that were more general or tangential (external/semantic) (Autobiographical Interview: Levine et al., 2002). Some tests were a hybrid of both approaches (Piolino et al., 2003, 2009).

The scoring that was devised for testing autobiographical memory was also adapted to score complex, video narratives. In a seminal study, St-Laurent et al. (2009) modified the AI interview technique (Levine et al., 2002) to test memory for short, video clips in patients with unilateral medial temporal lobe epilepsy and lobectomy. The pattern of performance in recalling recently-viewed video clips resembled that of recalling remote autobiographical events. In both cases, the patients were especially impaired on details that captured the perceptual aspects of the clip and the event, but less so, if at all, on the central aspects that captured the gist of the event. Their memory for external, semantic aspects, was relatively well-preserved (St-Laurent et al., 2011, 2014). In a follow-up, fMRI study, St-Laurent et al. (2016) showed that the patients' impoverished memory for perceptual details was associated with reduced activation in posterior neocortex which was linked to the hippocampus. That activation was reduced, but not eliminated, suggests that the remaining tissue was sufficient to support gist and semantics.

Comparable approaches were devised to examine spatial memory, with findings that were consistent with the views described above. Following hippocampal damage or dysfunction, memory for coarse (schematic) spatial layouts, routes, vector distances, and relative location was retained for highly familiar environments acquired long ago, enabling navigation in them (Rosenbaum et al., 2000; Teng & Squire, 1999). By comparison, memory was deficient for finer details of layout, and for perceptual details of non-salient landmarks and scenes along a route (Herdman et al., 2015; Hirshhorn et al., 2012a, b; Rosenbaum et al., 2000, 2001, 2005), preventing the person to re-experience the environment in rich detail much as they could not do so for past events.

The new evidence that emerged was consistent, for the most part, with MTT. Compromised hippocampal function led to a reduction in episodic aspects of recent and remote memories, whether for events or for environments, across the lifespan, with relative sparing of semantic or schematic aspects. This pattern of impoverished contextual details specific to an episode or location, with retention of general, non-specific information was observed in patients with extensive hippocampal damage whether caused by excisions or trauma (Sekeres et al., 2018; Wincour & Moscovitch, 2011), by infection by herpes simplex (Fujii et al., 2019) or by autoimmune disorders (Argyropoulos & Butler, 2020; Argyropoulos et al., 2019; Lad et al., 2019; Miller et al., 2020), by dementia (Piolino et al., 2009), by amnestic mild cognitive impairment (Murphy et al., 2008) or atrophy and dysfunction in normal aging (Levine et al., 2002; Viard et al., 2007), by accelerated long term forgetting and epilepsy (Butler & Zeman, 2008), by electroconvulsive therapy (ECT, Lomas et al., 2021) and by psychiatric disorders such as depression (Söderlund et al., 2014; Williams, et al., 2007) and schizophrenia (McLeod et al., 2006; Herold et al. 2015).

The same pattern is also observed with damage restricted to the CA1 (Bartsch et al., 2011; Bartsch & Butler, 2013) and CA3 (Miller et al., 2020) subfields of the hippocampus and pre-subiculum, to its output pathways, such as the fornix (Poreh et al., 2006; Gilboa et al**.,** 2006b) or to structures, such as retrosplenial cortex (Summerfield et al., 2009; Vann et al., 2009; Foster et al., 2013) and diencephalon (Kopelman, 1989, 1999), that receive projections from the hippocampus to form part of the extended hippocampal system.

A similar picture emerged from studies on animal models. Typically, hippocampal damage or disruption, whether caused by surgical lesions, pharmacological intervention, or optogenetic and transgenic techniques, led to retrograde memory loss without a temporal gradient, as long as context-specificity determined performance (Sekeres et al., 2018; Sutherland & Lehmann, 2011; Sutherland et al., 2010). This pattern was observed in a variety of paradigms, such as contextual fear conditioning (Jasnow et al., 2017; Sekeres et al., 2018a; Wiltgen & Silva, 2007; Winocur et al., 2007), socially-acquired preference tasks (Winocur et al., 2007), water maze and cross maze tasks (Winocur et al., 2013), regardless of whether they were based on positive or negative reinforcement (Winocur et al., 2007). There also were studies in which a temporal gradient was observed (Kim & Fanselow, 1992; Winocur, 1990), but as we shall see, this occurred not because the initial memories became consolidated in neocortex but because their context-specificity declined (Winocur et al., 2013), turning them into context-general memories, or their representation was altered (Jasnow et al., 2017; Wiltgen et al., 2010; Wiltgen & Tanaka, 2013; Winocur et al., 2010), making them more compatible with neocortical than hippocampal function (contra premise 8).

Although the consensus favoured MTT, proponents of SCT countered that temporally extensive loss of episodic memory only occurred when damage extended beyond the hippocampus (Squire

& Bayley 2007; Squire et al., 2015; Lah & Miller, 2008), a critique that does not apply to work an animal models where location of lesions or disruption can be controlled . In addition, they claimed that the patients' impaired anterograde memory made them lose track of their own narratives causing them to go on tangents when recounting their memories, making performance suffer (Dede et al., 2016). Providing them with appropriate guidance, returns performance to normal.

With respect to lesion location, we noted that temporally extensive retrograde episodic memory loss occurs even when lesions are restricted to the hippocampus, or even just to its subfields, and output pathways (see above). As for the deficit being attributed to amnesic patients losing track of their narrative, temporally extensive deficits in episodic memory are observed even in studies using the Autobiographical Interview (Levine et al, 2002), a test that consists of a structured interview that probes the participants' memories should their narrative be curtailed or derailed (Rosenbaum et al., 2008, 2009; Sheldon & Levine, 2016, 2018; Sheldon et al., 2019). Admittedly, probing leads to improved performance, but it does so in both patients and controls, without narrowing the gap between them. Moreover, even when remote autobiographical memory is tested using recognition, patients with damage to the hippocampal system are impaired at recognizing details (Gilboa et al., 2006b).

Neither of these objections to MTT from proponents of SCT, however, apply to functional neuroimaging studies that assess the differential involvement of the hippocampus in retrieving recent and remote episodic memories in neurologically intact humans (Cabeza & St. Jacques, 2007; Maguire et al., 1999; Svoboda et al., 2006;). Nor do these objections apply to comparative animal studies, particularly with rodents, where past experience and lesion size and location can be controlled far better than it is in humans. As predicted by MTT, functional neuroimaging

studies of autobiographical memory overwhelmingly show that the hippocampus is activated by recollection of vivid, detailed context-specific memories from across the lifespan, the extent of activation being modulated by episodic richness rather than memory age (Moscovitch et al., 2005, 2016; Sekeres et al., 2018). When episodic detail and richness are not taken into account, there is the expected reduction in hippocampal activation with memory as it ages (Boccia et al., 2020; Gilboa et al., 2004). From the earliest neuroimaging studies on remote memory (Addis et al., 2004; Gilboa et al., 2004; Maguire, 2001; Maguire et al., 1999, 2001; Ryan et al., 2000; see reviews in Cabeza & St. Jacques, 2007; Svoboda et al., 2006) to the most recent (see reviews in Sekeres et al., 2018; Sheldon & Levine, 2016, 2018; Sheldon et al., 2019), it was clear that the hippocampus, however, does not act alone (Cabeza & Moscovitch, 2013; Moscovitch et al, 2016) but is co-activated with a set of structures which include the precuneus, retrospelinal and parahippocampal cortex, and the ventromedial prefrontal cortex, along with the postero-lateral parietal cortex, which together form an autobiographical memory or recollection network (Ranganath & Ritchey, 2012; Ritchey & Cooper, 2020; Rugg & Vilberg, 2013;). Each node in this network is likely activated by different aspects of the episodic memory e.g., precuneus by imagery (Fletcher et al., 1996; Shallice et al., 1994), retrosplenial and parahippocampal cortex by spatial information (Epstein, 2008; Epstein & Baker, 2019; Vann et al., 2009), vmPFC by schemas related to the content of the memory (Gilboa & Marlatte, 2017), and the parietal cortex by attention (Ciaramelli et al., 2008; Cabeza et al., 2008, 2012; Cabeza & Moscovitch, 2013), number of details (Vilberg & Rugg, 2008, 2009, 2012), the subjective sense of re-experiencing (Richter et al., 2016; Simons et al., 2008), multimodal integration (Bonnici et al., 2016), or the processes needed to retrieve (Fletcher, 1998 a, b) and monitor it (e.g. vmPFC; Gilboa et al., 2006b, Moscovitch et al., 2016).

To date, all the neuroimaging studies on autobiographical memory had participants either answer true- false questions or mentally relive the events while being scanned, followed by extensive off-line narratives which were scored for details. Capitalizing on advances in fMRI denoising, Gilmore et al (2021) had participants narrate memories acquired on the day of scanning to those acquired 5-10 years earlier. Compared to a control condition, they found a decline in posterior hippocampal activation accompanied over that period accompanied by a comparable decline in functional connectivity between the hippocampus and neocortical regions implicated in memory. There was no change in anterior hippocampal activation. Although the authors conclude that this evidence supports SCT as the role of the hippocampus seems time-limited, a closer examination of the data suggests that the findings are more in accord with MTT/TTT. Internal details (see below) also decline during that period,with the drop being most prominenet for activity and object which account for about half the number of details. Thus, as predicted by MTT/TTT, changes in hippocampal activation correspond to changes memory representation, with posterior hippocampus and the posterior neocortical structures implicated in representing details and the anterior hippocampus implicate in representing the gist of the event (see below, p.28).

More investigations are needed to determine the precise contribution of the extra-hippocampal regions. Transcranial magnetic stimulation (TMS) has proven to be a useful tool in this regard. A recent study using TMS to interfere with the function of the precuneus led to a reduction in perceptual aspects of the autobiographical memory (Hebscher, et al., 2020). Conversely, stimulation of mPFC led to reduced false memories in the Deese-Roediger-McDermott (Deese, 1959, Roediger & McDermott, 1995) paradigm (Berkers et al., 2017; see also Chadwick et al, 2016, for the role of the temporal pole) presumably reflecting reduced activation of prior knowledge that biases episodic (detailed) encoding in this paradigm. Likewise, TMS stimulation

of the parietal cortex can enhance memory formation and retrieval (Wang et al., 2014) or diminish the subjective sense of remembering (Yazar et al., 2014)

Critique of MTT

To get its point across, MTT focused on one salient issue, the continued involvement of the hippocampus in remote episodic, but not semantic, memory. In doing so, it neglected many other issues, some of which are highlighted in the quotation from one of its proponents (Nadel) at the beginning of this chapter (Squire et al., 1984). Thus, while MTT differentiated between episodic and semantic memory, it did not consider the kind of qualitative changes that memories of even single episodes undergo. As well, by treating episodic and semantic memory dichotomously, MTT ignored the highly interactive, and interdependent nature of the two. With respect to transition from episodic to semantic memory, MTT did not consider mechanisms other than the extraction of statistical regularities among events, fueled perhaps by repeated retrieval of episodes either voluntarily or through off-line replay during sleep (Wilson & McNaughton, 1994) or rest (Dinkelman & Born, 2010; Dudai et al., 2015; Kim, Gulati, & Ganguly, 2019). With a focus on the hippocampus, it did not consider the contribution of other structures that operate in concert with the hippocampus in encoding, retention and retrieval of episodic memory, and that operate independently of it in the case of "consolidated" memories. Even with respect to the hippocampus, the field at the time tended to treat it as a unitary structure, rather than as highly differentiated one, a view that is now prevalent and figures prominently in current research on recent and remote memory (Maguire & Mullaly, 2013; Robin & Moscovitch, 2017; Sekeres et al., 2018; Zeidman & Maguire, 2016). Most importantly, MTT paid little heed to the dynamic nature of memory (Bartlett, 1932; Squire et al., 1984) that continues to play

increasingly larger roles in contemporary theories of memory (Schacter, 2011, 2012a,b; Schacter et al., 2012).

These can all be construed as errors of omission that can be rectified without violating any of the basic tenets of MTT. One set of findings, however, is problematic: The size of hippocampal lesions is not related to the extent of retrograde memory loss, in either humans (Winocur et al., 2010; Winocur & Moscovitch, 2011) or rodents (Sutherland et al., 2010, 2020). We take up this issue at the end of the next section.

Trace Transformation Theory (TTT): Details, gist, schema, and semantics

By questioning some of the basic assumptions of SCT, MTT succeeded, despite its limitations, not only in accounting for some troubling data and stimulating new investigations, but also in opening up the field of systems consolidation to new theories which we review and evaluate at the end of the chapter. Here, we focus on one of them, Trace Transformation Theory (TTT; Winocur et al., 2007, 2010; Winocur & Moscovitch, 2011; Sekeres et al., 2018). It builds on MTT's foundations but extends its scope to deal with some of MTT's limitations while integrating new findings on memory consolidation with advances in knowledge of medial temporal lobe and neocortical function, and their interaction in recent and remote memory.

In its most recent version (Robin & Moscovitch, 2017; Sekeres et al., 2018), TTT incorporated recent developments on the distinctions between gist, schema and semantics, and their neural correlates. Whereas full-blown episodic memories are rich in detail unique to the event (e.g. what everyone at the birthday party wore, how the cake looked and tasted), some episodic memories retain only the *gist* of the event, which effectively is a summary of its central elements, without the peripheral, incidental details (Reyna & Brainerd, 1995). One way of thinking about

detailed memories and gist is that they vary in granularity from fine to coarse-grained, and as such have been postulated to be represented preferentially by the posterior and anterior hippocampus, respectively (Brunec et al., 2018; Poppenk & Moscovitch, 2011; Poppenk et al., 2013; Moser et al., 2008; Robin, 2018; Robin & Moscovitch, 2017; Strange et al., 2014). While gist retains a measure of contextual specificity, schemas are more general still, referring to what is common across a series of similar events (what happens at a typical birthday party) and have been proposed to be mediated by the vmPFC (Ghosh et al., 2014; Gilboa & Marlatte, 2017; Tse et al., 2007, 2011; Wang and Morris, 2010). Semantics refers to the conceptual aspect of an event (what "birthday party" means – a celebration of one's date of birth) that does not include what typically transpires at the event, and implicates a different network of structures, with the anterior and lateral temporal, and inferior, lateral frontal, cortex playing central roles (Lambon Ralph, 2014; Lambon Ralph & Patterson, 2008; Lambon Ralph et al., 2017; Martin, 2016; Martin et al., 2014).

According to TTT, these different representations related to an episode can be encoded into memory concurrently, can co-exist with one another in memory, and can interact dynamically with each other, supporting one another in some instances, competing in others, and, in still other instances, transforming from one into the other and back again (contra premises 10 & 11; Sekeres et al., 2018; Robin & Moscovitch, 2017). The variants that are expressed are determined by a variety of factors, including the age of the memory and the demands of the task. The important point is that whichever variant is expressed, it is accompanied by co-activation of its corresponding neural structure, and vice-versa (Moscovitch et al., 2016; Sekeres et al., 2018), according to a principle of Neural-Psychological Representational Correspondence (NPRC; Gilboa & Moscovitch, submitted).

While incorporating these new developments, TTT accepts MTT's basic premise that as long as episodic memories remain detailed and context-specific, they will continue to depend on the hippocampus for retention and retrieval. With age and experience, however, some episodic memories, likely the majority, will be transformed into variants of the original or will express some aspects of the original while de-emphasizing others. Some will retain or express the gist of the episode with few, contextual details while others may retain just the general schema without any episodic remnant; some may be forgotten entirely, while others may remain detailed, but the details themselves may be modified by prior knowledge and subsequent experiences (Robin & Moscovtich, 2017; Sekeres et al.,2016, 2018; Squire et al., 1984; Winocut & Moscovitch, 2011). In accord with the principles enunciated earlier, especially that of NPRC, TTT posits that the nature of the transformed memory determines how it will be represented neurally and, conversely, if neural representations change, so will the nature of the memory that is represented and/or the processes that operate on it (Gilboa & Moscovitch, submitted)[1].

Findings and conclusions from human studies on the role of the hippocampus and neocortex in systems consolidation are remarkably consistent with those from the animal studies. Animal studies can exert the level of control and neurobiological interventions not afforded to human studies. Human studies, on the other hand, can draw on conceptual advances about the nature of memory, sophisticated behavioural testing and neurological techniques, from structural to functional neuroimaging of healthy and neurologically impaired people across the lifespan. By

[1] Consideration of the full implication of the NPRC principle, and the evidence that semantic and schematic memory traces are already created at the time of encoding (Hebscher et al., 2019b), has led Gilboa and Moscovitch (submitted) to suggest that the concept of systems consolidation itself might be a misnomer. Instead, multiple memory traces may be formed concurrently, and expressed differentially depending on factors such as task demands at encoding and retrieval; time and subsequent experiences influence synaptic strengthening or pruning of each of these traces and determine the way they interact with each other. While a full discussion of this possibility is beyond the scope of the present chapter, much of the data on systems consolidations described below is also consistent with it.

complementing one another, studies on humans and animals produce a synergy that benefits both of them and, as we shall see, produce converging evidence that advances our knowledge of systems consolidation. We address the recent non-human animal research first before turning to the human research.

Systems consolidation in non-human animals: Recent evidence

Context-specific and context-general memories in systems consolidation: separable neural substrates, their co-existence and interaction as evidenced from studies using lesions, early gene expression and optogenetic stimulation and inhibition.

Winocur, Moscovitch and their colleagues (Winocur et al., 2007, 2011) put the hypotheses derived from TTT to a stringent test using two paradigms, contextual fear conditioning (Kim and Fanselow, 1992) and socially acquired food preferences (Winocur, 1990), that had served as early pillars supporting SCT in the animal literature. In contextual fear conditioning, the rodent (typically rat or mouse) experiences an aversive event (shock) in a distinctive context. The extent to which the rodent freezes in fear when reintroduced to that context is a measure of its memory for it. In socially-acquired food preferences, rats choose the food that they smelled on the breath of a conspecific over a novel food. Initial tests showed that hippocampal lesions at short (within a day) and long (days or weeks) delays following acquisition in either test produces a temporally graded effect such that recent, but not remote memories, are lost. Similar results were obtained with other paradigms (for review see Winocur et al., 2010). Subsequent studies showed that remote memories were mediated by extra-hippocampal neocortical structures, particularly the medial prefrontal cortex (mPFC), which included the anterior cingulate cortex (ACC) (Frankland et al, 2006; for review see Frankland & Bontempi, 2005).

These results were interpreted in accordance with SCT as it was assumed that performance at remote intervals was driven by what was effectively the same memory as at recent intervals (premise 8). Based on TTT, Winocur et al. (2007, 2011) challenged this assumption and predicted, instead, that different kinds of memories were expressed at each time point: a context-specific one at the recent interval and a transformed one that lost its contextual specificity at the remote point. To assay context specificity, they tested animals in the same context as at acquisition (training context) or in a different one (novel context) that bore a general similarity to the first. Consistent with their prediction, they found that neurologically intact rats froze only in the training context at short delays but in both context at long delays. They concluded that a context-specific memory at short delays generalized over time. Next, they showed that animals that received hippocampal lesions at short delays did not freeze in either context, whereas those that received the lesions at long delays froze in both, confirming that the recent context specific memory was dependent on the hippocampus and that the remote, generalized memory was not, likely being dependent on the mPFC (contra premise 8).

These findings were corroborated by other investigators (Wiltgen & Silva, 2007; Wiltgen et al., 2010) and extended to show that damage to mPFC had the reverse effect – damage shortly after acquisition had little effect on performance, but eliminated the generalized memory at long delays, with rats freezing now only in the training context but not in the novel one (Frankland & Bontempi, 2005; Jasnow et al., 2017). The latter finding suggests, in accord with TTT, that both memories co-existed, albeit mediated by different structures, and that one of them dominates. Removing one, allows the other to emerge or be expressed (For review, see Jasnow et al., 2017). To eliminate freezing entirely in either context, both the hippocampus and mPFC have to be lesioned (Einarsson et al., 2015). The co-existence of different representations of the memory,

context-specific and context-general, and competition between them may also explain why optogenetic suppression (deactivation) of the hippocampus at remote time points eliminates freezing at first, but prolonging the suppression restores the generalized memory and leads to freezing in both contexts (Goshen et al., 2011), the latter effect being replicated by chemo-suppression which has a longer time course (Einarsson et al., 2015).

The distinction between schema and gist, formulated for humans, does not have a clear counterpart in studies on non-human species, yet some data on the differential effects of disrupting the ventral and dorsal hippocampus (homologues of anterior and posterior hippocampus in humans) suggests that such a distinction would be useful. Cullen et al. (2015) found that pharmacological inactivation of ventral CA1 at the remote interval eliminated freezing in a novel, but not the training context. They concluded that the ventral hippocampus, like the mPFC, is necessary for expression of a more generalized memory, with the dorsal hippocampus mediating the context specific memory. This formulation accords with TTT's proposal that the anterior and posterior hippocampus in humans, the homologues of ventral and dorsal hippocampus in rodents, mediate gist and richly detailed episodic memories, respectively. We will have more to say about the role of schema in memory, and its distinction from gist in rodents, when we consider how each type of memory develops.

Studies on hippocampal activation using immediate early gene expression and optogenetics provide converging evidence to support TTT's formulation of recent and remote memory in rodents. Using expression of c-FOS. Sekeres et al. (2018b) found greater activation of the hippocampus relative to mPFC in context fear conditioning at short delays when the memory was context specific, but the reverse at long delays when memory was context-general. The distinction between context-specific and context-general memories, and the co-existence of the

two at each time point, is supported by evidence the hippocampus was always more activated in the same, than different context, but the mPFC was equally activated in both contexts (contra premise 9). In a related study, Wiltgen et al. (2010) using IEG for Arc, c-fos, and zif268, showed that the extent to which the dorsal hippocampus showed greater activation in the training than novel context was related to the rodents' performance in both the recent and remote memory condition. Those with larger differences tended to freeze more in the training than novel context, and were more susceptible to the effects of dorsal hippocampal lesions, attesting to the specificity of their memory even at the remote timepoint, in line with the observation in humans of greater hippocampal activation for vivid, richly detailed episodic memories at remote time points.

Further exploring this phenomenon, Tayler et al. (2013) tagged cells that were active during memory acquisition (engram cells) and examined them shortly after training and again several weeks later. They found that the pattern of activated cells remained stable in the neocortex, but changed in the hippocampus consistent with evidence of loss of specificity and increased generalization with time. In particular, activation was diminished in the dentate gyrus (DG), a region supporting pattern separation processes needed for memory specificity and distinctiveness, but increased in CA3, a region subserving pattern completion which is implicated in generalizations underlying gist. This interpretation was confirmed by Guo et al. (2018) who showed that inhibition of CA3 by DG engram cells underlies context specificity. The progressive decline of this inhibition over time leads to memory generalization which can be reversed by enhancing the inhibition.

Reactivating hippocampal engram cells by optogenetic stimulation in contextual fear conditioning revives memories in mouse infantile amnesia induced by neurogenesis (Guskjolen

et al., 2018), in drug induced retrograde amnesia in adult mice (Einarsson et al., 2015), and in mice models of Alzheimer's Disease (Roy et al., 2016). On the other hand, optogenetic stimulation of mPFC engrams in a contextual fear conditioning paradigm is not effective shortly after learning when the engram, though formed, is not yet viable and remains "silent", but is effective two weeks later when the engram has become viable and the memory is more generalized (Kitamura et al., 2017). Whether or not mPFC engram cells can be activated early may depend not on the time since acquisition, but on whether or not they need to compete with hippocampal engrams. De Sousa et al. (2019) selectively reactivated cells in retrosplenial cortex during sleep the day after contextual fear conditioning. This led to accelerated contextual generalization in recently acquired memories and greater mPFC engagement coupled with decreased hippocampal dependence during retrieval. Importantly, increased mPFC activity following retrosplenial stimulation only occurred when the hippocampus was deactivated. The rapid generalization of memories that are cortically dependent is consistent with the NPRC principle (Gilboa and Moscovitch, submitted) and with idea that rapid cortical learning occurs at encoding but requires large-scale cortico-cortical network activity to be viable and compete for expression with hippocampal memory engrams (Hebscher et al., 2019b).

Reminders and reconsolidation: the revival of dormant context-specific memory (silent engrams)

The co-existence of context-specific and context-general memories, the dynamic interplay between them, and the central role of functional-neural correspondence is brought into relief by studies on re-consolidation (Nader & Hart, 2009, Nadel & Sederberg, *in press*, current volume). Reconsolidation is a phenomenon in which a memory that had become independent of the hippocampus over time becomes dependent on it once again after the organism is re-exposed to

the training context prior to testing at a remote time point (28 days). Studies on re-consolidation focused primarily on changes in neural representation, from hippocampus (or amygdala) to neocortex, and back again, and operated on the assumption that the same memory was implicated at all stages. Winocur et al. (2009) successfully challenged this assumption by showing, in accord with TTT, that changes in neural representation are accompanied by corresponding changes in functional/psychological representation (contra premise 11). By testing the rat either in the training or novel context, they showed that as long as the memory was dependent on the hippocampus, whether after training or after the reminder at re-consolidation, it was context-specific, whereas the memory that was independent of the hippocampus following systems consolidation was context general. Once the context-specific memory was revived, hippocampal lesions once again led to memory loss (contra premise 8). Recent work by Finnie et al. (2018) suggests that consolidation and reconsolidation not only engage distinct neural circuits but also different, plasticity-dependent receptor mechanisms when learning occurs in the context of existing knowledge as compared.

For the reminder to be successful, the original context-specific engram must have been dormant (Moscovitch, 2012) or "silent" (Kitamura et al., 2017), awaiting the proper cue to be activated and expressed in behaviour. This interpretation was supported by Sekeres et al. (2018b) who showed that c-Fos expression at the remote time point was greater in the dorsal hippocampus in the training context than in the novel context, whether or not there was a reminder, though overall activation was greater in the latter condition. c-Fos expression in mPFC, however, was always insensitive to context, consistent with its role of supporting context-general memory.

At a remote time point, the default condition is a context-general memory mediated by the mPFC, though it may be supported in its function by connections to the hippocampus (Einarsson

et al., 2015; Goshen et al., 2011; Jasnow et al., 2017). The context-specific hippocampal representation (engram) remains silent, unless activated naturally by specific cues (reminder), or artificially by optogenetic stimulation (Kitamura et al., 2017), at which point it may come to dominate behaviour.

Schemas: Their acquisition and utilization in systems consolidation

While evidence from animal studies is accumulating regarding context-rich and gist memory for specific events, much less is known about schematic memory and its acquisition in animals. This is partly the case because of the difficulty in designing paradigms and executing experiments that mimic extraction of statistical regularities across multiple events and construction of large-scale knowledge systems which are at the heart of schema representations (Gilboa & Marlatte, 2017). Perhaps the most direct test of the dynamic nature of integration and adaptation of knowledge across multiple episodes comes from a study that used a modified version of the Morris Water Maze with mice (Richards et al., 2014). In that paradigm, the exact location of the platform varied across trials, being drawn randomly from a spatial distribution. Search patterns more accurately matched the pattern of location distribution 30 days after training, compared to 1 day after training. Moreover, there was evidence that this delay-dependent process of extraction of statistical commonalities across events (schematization) was dependent on mPFC coding that was only expressed at long delays. The slowly evolving operation of the schema was reflected by a delay-dependent increased sensitivity to new locations that conflicted with the overall schema, a sensitivity which was abolished by pharmacogenic inhibition of mPFC, but only at 30 days and not at 1 day. Importantly, and consistent with the idea that consolidation is more than simply a linear process of selection of details to retain, the bias towards schematic information at 30 days was not a result of simple memory degradation leading to reduced precision. Instead, mice

preferentially responded according to the most recent platform locations in the short delay test but the most probable platform location in the long delay, consistent with the idea of different types of representations associated with each memory type.

Most other studies that have examined schemas and memory in rodents did not focus on the acquisition of schemas themselves but rather on the influence of prior knowledge on acquisition of new memories (Winocur et al., 2005; Tse et al., 2007, 2011; Wang et al., 2012; Hasan et al., 2019). These studies have demonstrated that well-established knowledge dynamically interacts with novel information and accelerates the ability of cortical traces to express memory independently of the hippocampus (Tse et al., 2007, 2011; Hasan et al., 2019). Nonetheless, these studies can provide some insight into the representational and neurobiological aspects of schema memories.

In a series of studies, Tse and colleagues (2007, 2011; Wang et al., 2012, cf. Hasan et al., 2019) used a modified flavour-place paired associates (PAs) task to study the influence of a pre-existing spatial schema on new learning. Rats were exhaustively trained over several weeks on an "event arena" consisting of a set of eight flavour-place association within it that could be accessed from different directions. Note that the operationalization of a schema in this case is different from the one used by Richards et al (2014; see also schema theories, below). Schemas in this paradigm are not generalized knowledge structures extracted from statistical regularities across multiple varying experiences; instead, they are specific and constant associative elements or units, learned by the rats, likely along with generalized information about task rules. The establishment of schematic memories of this kind over weeks of training was critically dependent on the hippocampus, as reflected by the fact that when hippocampal function was temporarily blocked mid-way through acquisition, so did improvement on the task (Hasan et al.,

2019). The effect was fully reversible once hippocampal function was restored. Acquisition of spatial schemas was associated with increased myelinization in mPFC mediated by proliferation of oligodendrocytes progenitor cells and oligodendrogenesis, differentiation, and maturation; conversely, induced demyelination of the ACC impaired spatial schema learning. Schema acquisition was also associated with neurophysiological mechanisms such as increases in theta band power, spike-field coherence and phase locking (Hasan et al., 2019) that have also been identified in the human literature (Gilboa & Moscovitch, 2017).

The Tse et al. (2007) study was highly influential, drawing the neurobiological community's attention to the role of schemas in memory. It should be noted, however, that the above studies provide no information as to the type of memory that is assimilated to schemas and represented by the mPFC, although it is assumed by the authors that it resembles the memory that was initially dependent on the hippocampus. An earlier study by Winocur et al. (2005) suggests otherwise, namely, that the hippocampal and extra-hippocampal memories assimilated to schemas are fundamentally different (contra premise 8). Winocur et al. gave rats extensive experience living in a complex maze, resembling a village, and open to its surroundings. After such an experience, they introduced learning trials in which rats had to navigate from one of four start locations to a goal in one of the four corners of the maze where they would be rewarded. Having had this extensive experience with the village, rats with hippocampal lesions learned to navigate towards the goal as quickly as controls, and much more quickly than rats with hippocampal lesions who had no prior knowledge (experience) of the village. Moreover, the experienced rats with hippocampal lesions performed comparably to controls on a blocked routes task, which often is used as an assay of cognitive map representations (Tolman, 1948). Had they relied, as did Tse et al. (2007), only on errors and trials to criterion as a measure of learning,

Winocur et al. would have concluded that experienced rats with hippocampal lesions and controls had comparable representations. By examining how they navigated the mazes, however, Winocur et al. (2009) concluded that their representations of the maze were different. When the most direct route to the goal was blocked, controls took another short-cut to it, as would be expected if they based their navigation on a cognitive map (Tolman, 1948; O'Keefe & Nadel, 1978). Rats with hippocampal lesions, on the other hand, took a circuitous route, often hugging the perimeter of the maze until they came to their goal, suggesting that they may have used distal, environmental landmark cues to identify it rather than a flexible cognitive map.

McKenzie et al. (2013, 2014) used neural similarity analytic approaches, akin to representational similarity analytic methods used in human imaging studies (see below), to probe the nature of schematic representations within the rodent hippocampus. Their definition of a schema is quite broad; it entails any knowledge structure that systematically organizes relational networks of multiple overlapping memories. The function of rapid assimilation of additional related memories into the knowledge structure is an inherent property of schemas by this definition. To model overlapping, but distinct, representations, rats learned to associate rewarded and unrewarded objects with locations, but reward contingencies for the same objects were context dependent, and no single location within a context predicted reward. Representational similarity analysis of hippocampal neural firing revealed a hierarchical structure. At the top of the hierarchy were context-sensitive activity patterns which were anti-correlated, consistent with a function of pattern separation. Objects' position, valance and identity, were showing increasing similarity (overlapping) patterns at lower levels of the hierarchy (McKenzie et al., 2014). When new items are learned within previous contexts, neurons immediately display the position, valance, identity hierarchy in their representation, providing a mechanism by which hippocampal

schemas support rapid integration of new knowledge based on context. Using the same paradigm and analytic approach, Farovik et al. (2015) demonstrated that unlike hippocampal neuronal ensembles, orbitofrontal neural representational similarity reflects a hierarchy driven by stimulus reward value. They propose that orbitorfrontal cortex supports schema-based learning by linking context-specific rules associated with their expected reward value suggesting that different networks are involved in acquiring rule-based memory schemas depending on whether a given schema is "context-based" or "value-based".

There is much more to learn about how schemas are represented at a functional and neural level, how they contribute to memory acquisition mediated by the hippocampus, and how hippocampally mediated memories are assimilated into schemas mediated by mPFC. What is clear, however, is that the mPFC, and possibly other structures, do not simply replace the hippocampus as a node that activates the same neocortically represented engrams as did the hippocampus. Memories mediated by mPFC are different from those mediated by the hippocampus in the variety of ways outlined above.

Summary

The reviewed studies suggest that recent, hippocampally dependent memory are not comparable to the remote memory that is mediated by extra-hippocampal structures, such as mPFC. Rather, they are fundamentally different, with one being context-specific and the other context-general. The mPFC cannot act as a substitute for the hippocampus, as only the latter can activate context-specific memories (contra premise 11). By contrast, representations mediated by the mPFC are related to schemas, rather than context specific episodic memories. Last, evidence of reconsolidation undermines the premise that memories are stable once consolidation is complete. Indeed, as Dudai (2012) stated, there is no end to consolidation, or put another way, given the

proper conditions, memories become unstable and prone to loss by hippocampal damage or change throughout their lifetime, needing to be re-consolidated if they are to be preserved. In short, consistent with MTT and TTT, it is the nature of the memory, not time, that determines its neural representation in the hippocampus and neocortex, as stipulated by the NPRC hypothesis. The same holds for studies in humans, to which we now turn.

Systems consolidation in humans: recent evidence

Because the literature on humans is more attuned than that on non-humans to the nature of the psychological representations of memory and its corresponding neural correlates, our review of the evidence on humans is more extensive. We begin by reviewing the most recent evidence of differences in how memories are represented by the hippocampus and neocortex, particularly the mPFC. We first consider evidence from univariate analyses of fMRI data, and then from multivariate analyses, particularly representational similarity analyses, to argue consistently with our NRPC hypothesis, that it is the nature of the memory, rather than its age, that determines its neural representation. We next show that different representations of the same event can co-exist in hippocampus and neocortex, as stated in our principles at the beginning of the paper. Because the representation of a memory is not confined to a single structure, we turn to the literature on functional connectivity and neural oscillations to show that the full representation of a memory depends on interactions between the hippocampus and neocortex, that themselves change along with the nature of the memory. Last, we examine how damage to HPC and mPFC alters the nature of memory representations.

Time and experience dependent changes in memory representations mediated by the hippocampus and mPFC: Univarite, fMRI analyses

The close correspondence between rodent and human studies on systems consolidation is illustrated nicely by Sekeres et al. (2018b, 2020) who conducted homologous, functional neuroimaging studies on humans and IEG studies on rodents (see above). Using fMRI during encoding and retrieval of memories of the video clips from St-Laurent et al. (2009), Sekeres et al. (2018b) tracked memory transformation and its neural correlates over time in neurologically-intact people. Retrieval was tested by cued recall in the scanner immediately after viewing the clips and then a week later. They found that at encoding and immediate retrieval, when memory for both central and peripheral details was high, posterior and anterior regions of the hippocampus were activated as was the mPFC. At a week's delay, when memory for peripheral details was reduced disproportionately compared to central details, activation was diminished in posterior hippocampus, remained stable in anterior hippocampus, and increased in mPFC, as participants' memory came to rely more on gist and schemas. If, however, memory remained vivid and detailed even after a week, activation remained high in posterior hippocampus, but increased somewhat in mPFC, suggesting that even detailed memories mediated by the hippocampus rely on schematic support from the mPFC once they age, paralleling the pattern of results obtained in rodents using IEG (see above). Also, as in rodents, providing a reminder before test (here in the form of a blurred small section of a screen shot of the clip which lacks meaning) increased the probability of successful recall. The reminder shortened the temporal onset of peak mPFC activation so that it preceded the peak anterior hippocampus activation which also was enhanced by the reminder (Sekeres et al., 2021).

To examine the role of schemas more closely in memory transformation, Bonasia et al. (2018), using Sekeres et al.'s (2018b) data, found that clips which conformed to typical scenarios (schema-congruent) engaged the mPFC more than schema incongruent clips, at encoding and at

all delay conditions. The reverse held for the hippocampus at encoding and at a week's delay. In fact, at a week, no hippocampal activation was observed for congruent clips suggesting that recall relied primarily on the mPFC. Importantly, mPFC activation was related to the type of errors people made in 1-week delayed recall, such that schema congruent and incongruent errors were positively and negatively related to mPFC activation, respectively (Bonasia, thesis).

Using much longer (27 min) narrative clips, Furman et al. (2012) showed that memory for them decreased between three hours to three months, but like Sekeres et al., they found stable anterior hippocampal activity on tests of recall, but markedly reduced hippocampal activation on recognition, presumably because the recollection component of recognition declines with time. Nonetheless, remote recognition memory that captured the "crux of the event" or its gist, was significantly correlated with residual hippocampal activation, in line with findings by Ziv et al. (2013) in rodents that only a fraction of hippocampal place cells are need to code place accurately over extended delays.

Turning from video clips to autobiographical memory, Soderlund et al. (2012), in a cross-sectional study, had participants retrieve detailed memories in the scanner that ranged in age from one week to ten years. Overall, they found bilateral hippocampal activity regardless of memory age, but with anterior-posterior differences. Activity in the anterior hippocampus increased from one week to a year, and then declined, whereas it remained stable in the posterior hippocampus.

Tracking vivid (detailed, context-specific) memories over a two year period, and comparing them to ten-year old memories, Bonnici et al. (2012) and Bonnici and Maguire (2017) used MVPA (Chadwick et al., 2010) to classify these memories. They found that as these memories aged over two years, their neural representations remained stable in anterior hippocampus, but

became more distinguishable from one another in mPFC and posterior hippocampus, particularly in the CA3 and DG subfields (Bonnici et al., 2013), reaching the same levels at two years as those at ten years. What distinguished one memory from another, however, may be different across regions as the memories were of different events. Consequently, they likely differed from one another in terms of both peripheral and central details. It is possible that peripheral details determined differences in posterior hippocampus, and central details in mPFC, as they are more closely related to schemas.

In a meta-analysis of studies on autobiographical memory in young and older adults, Viard et al. (2007) found that retrieval cues associated with the gist of the event activated the anterior hippocampus regardless of memory age. This effect that was especially pronounced in older compared to younger adults, consistent with older adults' greater reliance on gist as their detailed, episodic memories declined with age (Levine et al., 2002).

Thus, patterns similar to those observed for narrative video clips were evident in cross-sectional and longitudinal studies of autobiographical memories whose age extends from days to years. If memories are allowed to take their natural course and decline with time since acquisition, univariate analyses of the level of activation with time, yields increases in mPFC activity, relative stability in anterior hippocampus and declines in posterior hippocampus (see Boccia et al., 2019). For memories that remain detailed and context specific over time, both univariate and multivariate analyses (see below) show increases in mPFC, with variable activity in anterior and posterior hippocampus. According to TTT, these findings suggest that schemas mediated by the mPFC become increasingly important over time in retention and retrieval of episodic memories, even those that remain detailed and context specific. Variations in anterior and posterior

hippocampal involvement may depend on the extent to which gist and details contribute to retrieval.

Studies that target coarse or fine-grained detail at retrieval are consistent with this interpretation. In addition to Sekeres et al. (2018a), Evensmoen and his colleagues (Evensmoen et al., 2013, 2015) showed that retrieving coarse, large scale information about spatial location of remote memories (e.g. the venue of a wedding) is associated with anterior hippocampal activation, whereas retrieving fine-grained information (who was sitting next to you at the wedding dinner) is associated with posterior hippocampal activation. Likewise, CA3/DG activation in Bonnici et al. (2013) may be indicative of detailed, pattern separation that orthogonalizes overlapping information among memories and reduces interference (Bakker et al., 2008; Yassa et al., 2011). Individual differences in CA2/CA3 volumes predict the ease with which subjects retrieve detailed personal memories when cued with a personal location, consistent with the idea of efficient cue-related pattern completion (Hebscher et al., 2018). CA3 size is predictive of the precision of recall of short clips with overlapping information (Chadwick et al., 2014). Accordingly, damage restricted to this subfield leads to autobiographical memory loss for episodic details across the lifetime, with the exception of childhood when performance in controls is also low (Miller et al., 2020). Semantic memory, however, was unaffected.

Though the time scale is usually only on the order of days or at most weeks, neuroimaging studies that employ more traditional laboratory-based stimuli, such as paired associates, which afford a greater measure of control, yield the same pattern of results observed for stimuli that have a narrative structure. Du et al. (2018) had participants study pairs of words and tested them in the scanner at intervals ranging from 20 minutes to 30 days after study. Because changes in neural activation are often confounded by changes in memory accuracy, they equated

performance as much as possible at all intervals. Because relational memory underlying associations is believed to be mediated by the hippocampus, its activation remained stable across all intervals. By comparison, hippocampal activation declined for item memory, as activation in peri-rhinal cortex and vmPFC increased. These results are consistent with the interpretation that as recollection for item memory declines from short to long delays, so does hippocampal activation, and performance comes to rely on extra-hippocampal structures.

Confirmatory evidence comes from Viskontas et al. (2009a) who has participants make recollection and familiarity judgements to pairs of pictures that they had studied either ten minutes or seven days earlier. As recollection declined, so did hippocampal activity, particularly in the subiculum over the week interval. Ritchey et al. (2015) found similar evidence regarding recollection of items studied in different contexts and tested immediately or after a day. Although recollection declined over the interval, insofar as items were recollected, recollection-related activity remained steady in the anterior hippocampus, but declined in posterior hippocampus.

Multivariate analyses and memory representations in system consolidation

Multivariate analyses, particularly MVAP and representational similarity, provide an opportunity to relate representations at the neural level to those at the psychological level over time. Tracking vivid (detailed, context-specific) autobiographical memories over a two year period, and comparing them to ten-year old memories, Bonnici et al. (2012) and Bonnici and Maguire (2017) used MVPA (Chadwick et al., 2010) to classify these memories. They found that as these memories aged over two years, their neural representations remained stable in anterior hippocampus, but became more distinguishable from one another in mPFC and posterior hippocampus, particularly in the CA3 and DG subfields (Bonnici et al., 2013), reaching the same

levels at two years as those at ten years. What distinguished one memory from another, however, may be different across regions as the memories were of different events. Consequently, they likely differed from one another in terms of both peripheral and central details. It is possible that peripheral details determined differences in posterior hippocampus, and central details in mPFC, as they are more closely related to schemas.

Multivariate pattern analysis has also been applied to memories of short video clips. Bird and his colleagues (Bird et al., 2105; Oedekoven et al., 2017) had participants study video clips and tested their memory for the very same clips after a day and after a week. They used representational similarity analyses to examine neural reinstatement effects between clips at encoding, and at first and second test. Their results revealed reinstatement effects at 7 days in the posterior left hippocampus and structures in posterior midline cortex, such as the precuneus and posterior cingulate, that predicted memory performance.

In an EEG study, Larzabal et al. (2020) also used video clips but tested participants' remember/know judgements of frames from those clips at delays of hours, one day and three weeks. Using MVPA of the EEG signal to classify new and old items, they, too, found sustained patterns indicative of reinstatement effects that correlated with recollection. Although the sustained patterns faded over time, they were evident even at the longest delay and emerged from the same neural processes as the earlier effects, indicating that that the engram created at acquisition was still viable weeks later, reminiscent of sparse engram effects observed by Furman et al. (2012) in humans and Ziv et al. (2013) in rodents (see above).

That the reinstatement effect was evident across many regions of the recollection or retrieval network suggests that the nodes that comprise the network should be functionally connected to

one another both at acquisition and at retrieval. Studies of functional connectivity on system consolidation, though few in number, bore this out.

Using associative memories acquired in the laboratory and representational similarity analysis, Ritchey et al. (2015 see above), found that that context-related similarity in the anterior hippocampus was predictive of associative memory performance at a day's delay, a finding consistent with gist representation in the anterior hippocampus (see also Gutchess & Schacter, 2012). The same pattern was observed for other regions, including the mPFC, that are part of the recollection network, though in this particular design it was not possible to distinguish between schema and gist. By contrast, no such representational similarity across context was observed in the posterior hippocampus probably because its representations are context-specific rather than gist-like or schematic (See below for evidence on associations from single unit recordings, De Falco et al., 2016).

In picture-picture paired associate paradigm, Tompary and Davachi (2017) tested for recognition immediately and at a week's delay. They found that it was only at a week that greater representational similarity emerged between items that were paired with a common picture (overlapping) as compared to those that were paired with different pictures. Seen most prominently in in mPFC and posterior hippocampus, this similarity was inversely related to recognition accuracy which emphasized detail specificity, suggesting that performance came to rely more on gist-like representations. Likewise, Dandolo & Schwabe (2018), using single pictures as targets and lures from the same category (e.g. different pictures of a tractor), found that over the course of a month, targets became progressively more difficult to distinguish from lures indicative of increasing reliance on gist-like representations in memory over time. These

psychological changes were accompanied by increases in neural similarity between related lures compared to unrelated items, particularly in the anterior hippocampus, consistent with TTT.

Summary: Consistent with TTT, these studies in humans, as those in rodents, show that memory transformation is accompanied by a corresponding change in its neural correlate. As detailed (recollective) memory becomes impoverished and reliance on gist and schema increases, activation of the posterior hippocampus declines accompanied by increases in mPFC and sometimes in aHPC. These different aspects of memory, however, can co-exist with one another, and the regions that mediate them interact with one another. Though co-existing, one representation is dominant and the other may be dormant or silent, but capable of reasserting dominance, when revived by a reminder or when promoted by task requirements or retrieval orientation. For example, manipulating gist vs. detailed retrieval orientation influences the quality of subsequently retrieved autobiographical memories (Rudoy et al. 2009) and can offset age-related deficits in retrieval of episodic details (Aizpurua & Koutsaal, 2016). Similarly, provision of reminders can revive detail retrieval, as is the case for hippocampally mediated context specific memory at remote time-points in both humans (Sekeres et al., 2020) and rodents (Winocur et al., 2007; see review in Jasnow et al., 2017). Reminders can reactivate dormant or silent, presumably, hippocampal engrams via the mPFC, and change performance from being dependent on context-general memories to context-specific ones, a process, we noted, can be mimicked by direct optogenetic activation of silent hippocampal engrams (Guskjolen et al., 2019).

Functional connectivity and hippocampal-neocortical interactions

Given the interaction between the hippocampus and neocortex that we noted in the previous section, studies of functional connectivity between them should illuminate the status of the

relation between them during systems consolidation. Cross-sectional, functional connectivity studies of autobiographical memories have examined memories over long time courses. The pattern of findings resemble those obtained from longitudinal studies on memories acquired in the laboratory (see below). Using fMRI and prospectively collected audio recordings of recent (1.5 months) and remote (1 year) memories in health young adults, Sheldon and Levine (2013) found early, co-activation of the anterior hippocampus with posterior neocortex for vivid memories, whether they were recent or remote. For less vivid memories, there was later co-activation of the hippocampus that included both posterior neocortical and frontal regions, with more sustained hippocampal activation throughout the retrieval period for recent memories. They interpreted the difference in the time course and pattern of activation between vivid and less vivid memories, particularly with recruitment of frontal structures for the latter, as consistent with the idea that retrieval of less vivid memories was more indirect, requiring the recruitment of frontal structures to guide search, which required more time (Moscovitch, 1992).

Similarly, in examining autobiographical memories that were 1 week, 1 month, 1 year and 10 years old, Soderlund et al. (2012) found that the hippocampus was active bilaterally for all memories, particularly for those that are vivid, with anterior hippocampal activity increasing up to a year, and decreasing afterwards, with no change in posterior activity. The pattern of functional connectivity varied with memory age: for memories one year or younger, the hippocampus was functionally connected to midline posterior and frontal structures, whereas for 10 year old memories, there was an initial negative correlation of hippocampal activation with frontal and parietal structures, followed by a positive co-activation with the anterior cingulate.

As we noted earlier, McCormick et al. (2015) found greater functional connectivity between the mPFC and anterior hippocampus during the construction phase of autobiographical memory

retrieval followed by greater connectivity between the hippocampus and posterior neocortex during the elaboration phase, consistent with earlier reports by Conway (2009; Conway & Pleydell-Pierce, 2000; Conway, Pleydell-Pierce, Whitecross & Sharpe, 2003) when tracking EEG power. By comparison, in patients with right hippocampal excisions and impoverished autobiographical memory, this pattern of hippocampal-mPFC connectivity is disrupted and replaced by mPFC-neocortical connectivity (Addis et al., 2007a; McCormick et al., 2018), which is not adequate for reactivating the detailed perceptual representations that constitute rich episodic memories.

Using naturalistic stimuli that resemble autobiographical events, such as video clips, Oedekoven et al. (2017) found that functional connectivity between the hippocampus and posterior midline cortical structures predicted how detailed participants' memory was for the clips when tested shortly afterwards. Damage to the hippocampus should lead to a reduction in functional connectivity of these regions at both encoding and retrieval, leading to memory loss. This prediction was confirmed in a patient with amnesia resulting from a stroke to the right and possibly left thalamus, associated with grey matter reduction in the hippocampus, though the patient did not show a reduction in activation.

Although Oedekoven et al. (2017) did not examine changes in functional connectivity with delay, Bonasia et al. (2018), who also examined memory for video clips, found changes in functional connectivity that were modulated by the relation of the clips to typical schema of the events that were depicted. Using mPFC and Medial Temporal (posterior hippocampus/parahippocampal) seeds, they found that increasing congruence of the clip with the schema was a associated with connectivity of the mPFC to frontal, occipital and parietal structures at immediate testing, and with a different set of regions, but in the same structures, at

7-day delay. Functional connectivity of the MTL, on the other hand, was associated with increasing incongruence of the clips, with connectivity to mPFC and occipital cortex at immediate test, and with only the lingual gyrus at 7 days. Combined with evidence of changes in activation of these structures across the seven days, these results are consistent with TTT and the SLIMM model (van Kesteren et al., 2012; see 'theories of schema' section for discussion) that retrieval of schema-congruent information increasingly recruits mPFC and its associated structures with time, whereas retrieval of schema-incongruent information continues to rely on MTL, and its connectivity to posterior neocortex across time.

Using more laboratory typical discrete stimuli, such as emotional and neutral pictures, Dolcos et al. (2004) examined recollection of remote, emotional memory over the course of a year. Immediately after study, there was greater anterior hippocampal and amygdala activation for emotional memory and but greater posterior hippocampal activation for neutral memory, consistent with evidence of neuroanatomical connectivity between the anterior hippocampus and the amygdala which is implicated in processing emotion. A year later, they found similar engagement of the hippocampus and amygdala for memories that were recollected, as compared to those that were merely familiar, as well as a significant correlation between activity in the hippocampus, particularly its anterior portion, with that of the amygdala. Though memory performance declined in the interval, the results indicated relatively preserved hippocampal and amygdala involvement across time for recollection, consistent with MTT/TTT.

By contrast, Sterpenich et al. (2009) found that sleep after study promotes recollection of emotional memories when tested at 3 days and again at 6 moths. Unlike Dolcos et al., however, they found that hippocampal activation and functional connectivity with mPFC that was present for recollection of emotional memories at 3 days was no longer evident at 6 months. Instead,

they observed mPFC activation and functional connectivity with amygdala, precuneus and occipital cortex. It is not clear why their results differ from those of Dolcos et al with regard to hippocampal activation during recollection, though it is important to note that it is one of the few in which that relation is absent. Gais et al. (2007) also showed loss of HPC activity, but they studied related words and participants hardly remembered anything at 6 months. Insofar as they remembered something, it could have been gist, rather than contextual details, but evidence bearing on this interpretation was not available.

Ezzyat et al. (2018) used a combination of MVPA and functional connectivity analyses to examine memory differentiation and its effect on performance in a word-object associative memory task that was distributed across two days or studied in one day. The extent to which participants' associative memory benefitted from distributed study when tested a week later was related to differentiation of activity patterns in mPFC which, in turn, were influenced by functional connectivity of the mPFC and hippocampus.

Similar influences were reported by Cowan et al. (2020) who found that sleep spindle activity was related to differential connectivity of the hippocampal long axis during relearning of associates studied the previous day: posterior hippocampal-posteromedial connectivity for scene word-pairs, and anterior hippocampal-mPFC connectivity for object-word pairs. The latter also determined the representational similarity in mPFC for associative memories, consistent with the idea that objects engage conceptual representations associated with anterior hippocampal networks (Reagh & Ranganath, 2018; Sheldon & Levine, 2018; Sheldon et al., 2019).

Neural oscillations and cross-regional coupling

Neural oscillation and cross-regional coupling of oscillatory activity may control or orchestrate interactions among structures that underlie their functional connectivity at retrieval and that contribute to memory transformation. Thus, using the same prospective audio-visual recordings as Sheldon & Levine (2013), Fuentemilla et al. (2014) presented participants with audios of their 2-7 month old memories, and of passages of readings from a book on geography (semantic memory) while recording brain activity with magnetoencephalography (MEG).They identified a peak of theta power within a left MTL region of interest that was selectively phase-synchronized with theta oscillations on precuneus (posterior neocortex)and mPFC, more so for episodic than for semantic memory. In a subsequent study, Fuentemilla et al. (2018) found that large scale gamma synchrony, which reflects integration of neural activity within and across brain regions, was greater in the episodic, than the semantic, condition. This difference in gamma synchrony between episodic and semantic memory was not found, however, in a person with severely deficient autobiographical memory. These findings are consistent with Hebscher et al.'s (2019a) observation that disrupting theta and gamma synchrony between MTL and precuneus in healthy people, by applying continuous theta burst stimulation to the precuneus, led to a reduction in their episodic autobiographical memory.

No differences between recent and remote autobiographical memories were reported in any of the above oscillatory studies, although such differences were evident in some of their fMRI analogues. One possibility is that changes in memory representations were evident in the fMRI studies, or because spatial resolution was better in the fMRI studies so that such changes could be detected more easily.

In a more recent MEG study which sampled autobiographical memories over a ten-year interval, McCormick et al. (2020), (see below) showed that the greatest changes in broadband power

spectra occurred in the mPFC and left HPC with mPFC activity leading that of the hippocampus in all but the most recent memories.

Co-existence of mPFC and hippocampally mediated representations of recent and remote memories, and their interaction

Different distinct, yet active, representations of the same event can co-exist in the mPFC and hippocampus and interact with one another from encoding onwards (Jasnow et al., 2017; Sutherland et al., 2019; Takehara-Nishiuchi, 2020). As noted at the beginning, the PFC is a "working-with-memory" (Moscovitch, 1992, 1994; Moscovitch & Winocur, 1992) structure that interacts with the hippocampus at encoding and retrieval. Schemas, represented in mPFC, can influence encoding (Gilboa et al., 2017). At retrieval, higher order, schematic/ conceptual information may be used to initiate and guide search to activate context-specific hippocampal representations, and serve as templates against which output from the hippocampus can be compared and monitored to ensure that it is consistent with the goals of the task and the to-be-remembered target (Gilboa & Marlatte, 2017; Moscovitch, 1992; Moscovitch & Winocur, 2002; Shallice & Burgess, 1996; Shallice & Cooper, 2011).

Functional neuroimaging studies are instructive in this regard. McCormick et al. (2015) asked healthy people in a scanner to retrieve context-specific autobiographical memories that were at least two years old in response to broad cues, such as "first kiss". These cues are likely to instantiate schemas and initiate search for a particular memory whose content can then be richly elaborated. They found that during the initial memory construction phase, mPFC interacted closely with aHPC bilaterally, presumably to yield the gist of the memory. In the subsequent

elaboration phase, there was a shift in functional connectivity from mPFC and aHPC to pHPC and posterior neocortex which supports the perceptual representations that constitute the detailed episodic memory.

McCormick et al. (2020) adapted this paradigm for MEG so that they could track more precisely the temporal dynamics of retrieval of recent (less than a month) and more remote (4 months to 5 years) autobiographical memories. Source analyses of broadband power spectra showed that mPFC and left HPC had the greatest changes. Except for the most recent memories, activity in mPFC began about 120 msec after onset of retrieval and preceded that of the left HPC by about 65 msec. Moreover, using effective connectivity analysis, they showed that mPFC drove HPC activity throughout the entire retrieval phase, consistent with our working-with-memory model.

Also using MEG, Hebscher et al. (2020) observed that inhibiting the precuneus with TMS led to slowed frontally-distributed activity early during the construction phase of autobiographical retrieval, consistent with disruption of frontally-mediated access to personal memories. These findings are also consistent with observations by Sekeres et al. (2020) in their reminder experiment (see above), though the temporal precision was much lower in that study.

Other investigators, however, found that under some conditions, HPC activity precedes that of mPFC in retrieving autobiographical memories. Applying a novel deterministic tractography protocol to diffusion-weighted magnetic resonance imaging (dMRI) of the fornix, Williams et al. (2020) found that retrieval of episodic details of past events (and construction of possible future events) in response to cue words (Crovitz & Schiffman, 1974) was correlated with the size of the pre-commissural fornix whose fibres project only unidirectionally from hippocampus to mPFC.

William et al.'s findings temper the conclusions drawn by McCormick et al. and suggest that more work needs to be done to determine the conditions under which one or the other scenario applies. With regard to systems consolidation, however, TTT's assertion remains: remote, detailed episodic memories depend on continued hippocampal-neocortical interactions.

A feature of many of these studies is that both the hippocampus and neocortical structures, particularly the mPFC, are implicated, making it difficult to determine what the contribution of each is to the psychological representation of the retrieved memory. The rule of thumb we adopt is that reduction of functional connectivity with the hippocampus implies a transformation from detail rich, context-specific memory, to a more schematic, context-general representation. To avoid the reverse inference that this statement implies, it is necessary that studies examining changes in functional connectivity should also provide psychological evidence about the nature of the memory, and the processes and information used to recover them. Another is to examine the effects of HPC and vmPFC lesions on the functional and effective connectivity, and their relation to psychological memory representations.

Hippocampal-neocortical interactions, and effects on memory, following damage to the hippocampus

Damage to hippocampus should alter the functional and effective connectivity between mPFC, HPC and posterior neocortex. Confirming previous findings by Addis et al. (2007a) and complementing those of St-Laurent et al. (2016), McCormick et al (2018b) found that functional connectivity between mPFC, hippocampus and posterior neocortex differed in patients with left unilateral temporal lobectomy from the pattern they observed in controls (McCormick et al., 2015). In patients, unlike in controls, mPFC activation was related to activation in lateral temporal cortices in the construction phase, and to visual perceptual cortices in the during the

elaboration phase. Despite mPFC's functional connectivity to posterior neocortex, episodic memory in these patients was impoverished, suggesting that without hippocampal involvement, mPFC could not recruit the pattern of neocortical perceptual activity necessary to form a detailed, rich memory. Likewise, damage to higher-order visual cortex (Greenberg et al., 2005; Ogden, 1993; Rubin & Greenberg, 1998; or temporarily disabling part of it (precuneus) with TMS (Hebscher et al., 2019a; 2020) also leads to episodic memory loss, presumably because of the role visual imagery plays in episodic memory (Greenberg & Knowlton, 2014; Shallice et al, 1994).

Argyropoulos et al. (2020) found that damage to the hippocampus in patients with autoimmune limbic encephalitis also was accompanied by reduced volume in anterolateral thalamus and entorhinal cortex, structures that are part of the extended hippocampal system. These patients had extensive remote autobiographical memory loss as determined by their performance on AMI (Kopelman et al., 1989). Like others before them (Winocur et al., 2009; Lehmann, Lacanilao & Sutherland, 2007; ,reviewed in Sutherland & Lehmann, 2020; Sekeres et al., 2018a), they found that the extent of remote memory loss was not directly related the volume of the HPC. Instead, they found that it was mediated almost wholly by the correlated volume loss in the thalamus (see also Kopelman, 1999; Kopelman & Marsh, 2018), a point to which we will return later in the paper.

The interpretation of the above study needs to be considered in light of Miller et al.'s (2020) finding in a group of patients with similar aetiology whose damage was confined to the CA 3 subfield. Compared to healthy controls, remote episodic memory loss extended across the entire lifetime except for childhood when control performance had also declined. Remote episodic memory performance was related to CA3 volume when both groups were combined, but not in

each group alone. Using graph theoretical analyses of resting state activity, they found that remote memory loss was related to loss of global integration between the hippocampus and the necorotical regions that comprised the medial temporal component of the default mode network (Andrews-Hanna et al., 2010; Bellana et al., 2017). These areas included the left and right parahippocampal cortex, left retrosplenial cortex left and right hippocampal formation and ventromedial prefrontal cortex.

When taken together with the effects of damage to CA1 (Bartsch et al., 2011) and DG (Kwan et al., 2015), the evidence suggests that damage to any of the hippocampal subfields can lead to temporally extensive retrograde amnesia, and deficient future thinking, respectively, as might be expected of an integrated system. The extent of episodic memory loss is not related to hippocampal damage in isolation, but to its ability to recruit neocortical and diencephalic representations, consistent with the idea that the engram or memory trace consists of a bound ensemble of hippocampal-neocortical-diencepahlic neurons (Diana, Yonelinas & Ranganath, 2007; Eichenbaum, Yonelinas & Ranganath, 2007; Cooper & Ritchey, 2020; Ritchey & Cooper, 2020). According to TTT, which aspects of episodic memory are affected, whether gist or details, may depend not only on whether the anterior or posterior aspects of long axis are most implicated, but also which subfield. It is informative to know that CA3 and DG, important for pattern completion and separation, respectively, and that support detailed memories, are over-represented in posterior hippocampus. By comparison, CA1, implicated in memory integration, is over-represented in anterior hippocampus which supports gist or common context (Poppenk et al., 2013, Dimsdale-Zucker et al., 2018). The nature of autobiographical memory should vary depending on which subfield was most implicated. At the moment, no pertinent evidence is available.

Consistent with this proposal, representation similarity analysis revealed that that in CA1 objects sharing a common context were represented more similarly to one another than objects sharing different contexts, whereas in CA23DG objects sharing the same contexts were differentiated from one another (Dimsdale-Zucker et al., 2018). It would be informative for theories of memory consolidation to know how these representations change over time. Studies by Tompary and Davachi (2017, 2020), and Dandolo and Schwabe (2018) suggest that representational similarity among items that share common elements increases in the mPFC and hippocampus, but little is known about the subfields that are implicated (but see Bonnici et al., 2013 for autobiographical memory).

Effects of damage to the mPFC: Differential effects on schemas and episodic memory

Unlike damage to the medial temporal lobe, damage to mPFC is associated with impaired schema representations which support perception at encoding and, at retrieval, help initiate and guide search, and monitor memories to ensure they are appropriate to the goals of the task (Gilboa et al., 2006b; Gilboa & Marlatte, 2017; Moscovitch, 1992). Patients with vmPFC lesions can show some impairments on tests of factual semantics (Kan et al., 2010; Hebscher et al., 2016; Hebscher & Gilboa., 2016; O'connor & Lafleche, 2004) and are significantly impaired during processing of schemas (Ghosh et al., 2014) and schema-related memory (Stolk et al., 2015; Spalding et al., 2015). When combined with damage to adjacent orbito-frontal cortex, which control decision responses, faulty monitoring leads to confabulation, a disorder in which participants, without intention to deceive, produce memories that are patently false and inconsistent with other knowledge (Gilboa & Moscovitch, 2017; Moscovitch, 1989; Schnider, 2008). They affect recent and remote memories equally, and can also affect personal and semantic memory (Moscovitch & Melo, 1997; Gilboa et al., 2006; Gilboa & Marlatte, 2017)

though not as reliably (Dalla Barba & La Corte, 2013; Schnider et al., 2017). Given proper cuing and guidance, people with mPFC damage, like rodents, should have impaired schematic, context-general memory or poor generalization, with relatively preserved detailed, context-specific memories. To a large extent that is what is observed.

This outcome is especially noteworthy in the DRM paradigm in which participants are given a list of schema-related or semantically-related words to remember (Rodediger & McDemott, 1995). In addition to recalling and recognizing words from the list, healthy controls also incorrectly produce or select critical lures which are words that did not appear on the list but are highly related to them and the schema. Having impoverished schema representations, mPFC patients produce and select fewer critical lures than controls, suggesting that the incorrect intrusions and endorsement of critical lures is dependent on schema-related processing in mPFC (Melo et al., 2000; Warren et al., 2014). This interpretation is consistent with Bonasia et al.'s (2018) observation that schema-congruent errors in recalling remote events from video clips is positively related to mPFC activation, whereas incongruent errors are negatively related to it.

Performance on tests of autobiographical memory indicate that although retrieval of schemas and memories is impaired in patients with PFC damage, memory for details and temporal order can equal, or even surpass, that of controls if proper cuing and guidance is provided (Kurczek et al., 2015; Thaiss & Petrides, 2008). Kurczek et al. found that once memory for an autobiographical event that was relatively remote was recovered using Crovitz and Schiffman's (1974) word-cue technique, participants with mPFC damage could describe one moment from that event in as much detail as controls. By contrast, scripts of familiar everyday activities (e.g. going to a doctor or restaurant) is impaired in patients with mPFC lesions (Burgess & Shallice, 1995; Godbout & Doyon, 1995; Godbout et al., 2004; Grafman, 1989; Grafman et al., 1993; Shallice & Cooper,

2011; Sirigu et al., 1995, 1996). Although they can produce the major elements of the script, they have difficulty with minor and trivial elements, generating fewer of them, and then they do so haphazardly, rather than in the proper temporal order. Likewise, Gilboa et al. (2006a) found that patients with mPFC lesions had difficulty in generating well-known fairy tales. Compared to controls, they made more idiosyncratic errors that were unrelated to the fairy tale's schema and were willing to endorse such schema-incongruent items on a recognition test.

Deficient schema representation and instantiation may also account for those conditions in which memory for episodic details of autobiographical events is impaired in mPFC patients. In a study similar to Kurczek et al.'s (2015), Bertossi et al. (2016) had people retrieve autobiographical memories in response to cue words. Instead of asking them to describe only a moment from the event, as Kurzcek et al did, Berotssi et al. asked participants to recount the entire event. If schemas or scripts serve as scaffolds to support retrieval of episodic details during memory construction, as McCormick et al. (2015, 2020) and Robin and Moscovitch (2017) suggest, then mPFC patients should produce fewer details than controls in this condition, as indeed was the case. Here, too, more specific cuing, rather than the general cuing they employed, may have increased their retrieval of episodic and temporal details, as Levine (2004) and Thaiss and Petrides (2008) found in other AM studies (see McCormick et al., 2018a, for review).

mPFC and hippocampus in formation of schemas

The renewed interest of cognitive neuroscientists and neurobiologists in the contributions of schemas and prior knowledge to new learning has produced a significant body of knowledge, but understanding of the formation or representation of schemas themselves still lags behind. This asymmetry exists, in part, because of the inherent challenges associated with investigating the acquisition of extensive systems of knowledge that typically take years to form. Nonetheless, as

in the animal research, there is a small number of studies that have addressed this question using either longitudinal designs that extensively trained participants on experimental stimuli (Sommer, 2017; van Buuren, et al., 2014) or taught participants premise information that was later used to interpret or encode new incoming information (Schlichting & Frankland, 2017; Schlichting & Preston, 2014, 2015; Van der Linden et al., 2017; Wagner et al., 2015).

Adapting Tse et al.'s (2007) rodent paradigm to humans, Sommer (2017) trained participants on ten different spatial arrays of object-location paired associates. Importantly, not all locations were initially occupied by objects, which allowed for later introduction of new information into existing knowledge. Participants were followed up over 9 months of intensive training of the premise paired associates, with changes to neural representations tracked over the first two days and again at 3 and 6 months. The first night of training was associated with a shift in activation such that hippocampal activation was reduced whereas vmPFC activity increased, consistent with the predictions of TTT and some of the studies described so far. Surprisingly, however, as training continued, vmPFC activity was no longer evident. Instead, over-trained paired-associates activated ventrolateral prefrontal cortex, anterior temporal lobes and angular gyrus. This network of structures is reminiscent of areas that are typically associated with semantic memory representations (e.g. Binder et al., 2009; Binder & Desai, 2011) and these patterns may reflect a transition of representations from schematic/gist that still hold some information about learning context to abstract semantic knowledge, devoid of context.

Wagner et al. (2015) used a learning task akin to the weather prediction task, to investigate the manner in which rule-based schemas are represented over two days of training. Similar to the findings during the first two days of Sommer's study, they identified increased activity over time in vmPFC, as well as posterior cingulate and high-level associative visual areas. Using MVPA

these authors also suggested an important role for the angular gyrus as a convergence zone for low-level perceptual features and high-level decision rules that consisted as the schema in this paradigm. The angular gyrus was also identified by van der Linden et al. (2017) as an important site for integration of new information into existing schemas. As predicted by TTT, this process was paralleled with disengagement of posterior hippocampal activity and loss of detail from memory, suggesting that angulr gyrus could serve as an important trans-modal hub of schematic representations in posterior cortical regions.

In a series of imaging and lesion studies, Preston and colleagues have explored the neural substrates of associative inference and memory integration, as a model of how prior knowledge, or schemas, supports new learning (Zeithamova & Preston, 2010; Zeithamova et al., 2012; Schlichting et al., 2015; Schlichting & Preston, 2015). In these studies, the role of mPFC-hippocampal interactions in the inference of relationships between stimuli based on the overlap between discrete episodes (e.g. inferring A-C after being exposed to the pairs AB and BC). Encoding of the overlapping information is associated with increased activation in vmPFC and functional coupling between vmPFC and hippocampus (Zeithamova & Preston, 2010; Zeithamova et al., 2012; Schlichting & Preston, 2015), and is predictive of subsequent successful inference. Inference itself of the AC pairs is also associated with increased vmPFC activation (Zeithamova & Preston, 2010). These findings are consistent with observations that patients with damage to vmPFC are impaired on associative inference despite relatively preserved premise pairs learning (Spalding et al., 2018) suggesting vmPFC is needed for integrating new information with retrieved prior knowledge. All these studies, however, only tested people shortly after acquisition. To understand the role of mPFC in system consolidation more fully, it is important to determine how such information is retained and applied at remote intervals.

mPFC and Hippocampus in formation of episodic memories: pre-stimulus and post-encoding effects on consolidation

Having been formed, when do schemas begin to influence memory? As noted at the beginning of the chapter, schemas are adaptable associative networks of knowledge (frameworks) extracted over multiple similar experiences. They interact with environment and stored knowledge to interpret the world and help form memory representations (Ghosh & Gilboa, 2014; Gilboa & Marlatte, 2017). To date, however, almost all research on schemas are concerned with psychological processes and neural mechanisms that occur after a stimulus is presented or an event occurs. If schemas operate as we conjecture, schemas should already be operating before the event occurs to guide perception and extract or convey meaning.

With these ideas in mind, Gilboa & Moscovitch (2017) proposed that the relevant schema for the situation is *reinstated* in vmPFC prior to stimulus onset to prepare individuals for the type of information that they are likely to encounter, and then the instantiated schema is *instantiated* to interact with the environment. To test the idea of schema instantiation, they had participants decide whether face stimuli depicted people with whom they were personally familiar. They found that that prior to stimulus onset, there is a period theta coherence desynchronization between medial prefrontal areas, inferotemporal and lateral temporal cortices which are correlated with modulation of the face N170 in inferotemporal corex and response accuracy. Importantly, these oscillatory coherence patterns, and performance, were significantly reduced in patients with vmPFC damage, especially in those with clinical histories of spontaneous confabulation.

Using a different paradigm that tests schema membership of words (viz. Does “lion” belong to the schema visiting a zoo?), Giuliano, Bonasia, Moscovitch & Gilboa (2021) replicated their

findings about schema reinstatement, namely, theta and alpha desynchrony between vmPFC and the posterior parietal cortex, that was absent in patients with damage to the subcallosal vmPFC that is related to confabulation. Similar oscillatory patterns in the post-stimulus time frame, but in the alpha and beta frequency bands, were interpreted as evidence of post-stimulus schema instantiation.

The schema-associated pre-stimulus effects may part of a class of other pre-stimulus effects that have been reported in the literature, namely, that pre-stimulus activation patterns measured by both EEG and fMRI predict subsequent memory for the upcoming stimuli (Fernandez et al., 1999; Liu et al., Rugg, 2021; Otten et al., 2006; Park & Rugg, 2009; Sweeney-Reed et al., 2016). These, in turn, may be related to more general *memory allocation* effects reported in rodents (Silva et al., 2009; Josselyn & Frankland, 2018). Studies of memory allocation in rodents show that excitable neurons that are more excitable prior to encoding are more likely to be recruited to form part of the subsequent memory trace. Using multivoxel pattern analysis in humans, Sadeh et al., (2019) reported a human analogue of the allocation effect, showing that the overlap of voxel patterns during pre-encoding rest and encoding in the hippocampus and related structures predicts subsequent memory for items presented at encoding (contra premise 4).

In Sadeh et al's study, the items were unrelated to one another nor were they related to some overarching concept or event. It is intriguing to consider whether schema reactivation exerts its effect by modulating these memory allocation effects.

As with pre-stimulus effects, investigators have also reported post-encoding or post-learning reactivation effects in the hippocampus and other structures, either during sleep or rest, that predict subsequent memory in rodents (Silva et al., 2009; Sutherland & McNaughton, 2000; Wilson & McNaughton, 1994) and humans (de Voogd et al., 2016; Dudai et al., 2015; Gruber et

al., 2016; Hermans et al., 2017; Paller et al., 2021; Staresina et al., 2013; Tambini & Davachi, 2019). It is noteworthy that not only changes in HPC activity alone, but also in its functional connectivity with other structures, correlated with subsequent memory, suggesting that they reflect early memory consolidation processes.

As with pre-stimulus effects, the question arises whether prior knowledge can modulate these the effects observed during post-encoding rest. Liu et al. (2017) addressed this question by having participants associate houses with either familiar or unfamiliar faces. The found that familiarity (prior knowledge) led to increased functional connectivity between the hippocampus and fusiform face area, and the vmPFC. Moreover, increases in functional connectivity between the HPC and fusiform face area, and between the anterior temporal lobe and posterior neocortex, predicted subsequent memory only for the face-house associations, but not for the items themselves. The latter finding is consistent with the idea that Process Specific Assemblies (Cabeza & Moscovitch, 2013) of which the hippocampus is a part typically support recollection-related processes but not familiarity.

There are no studies to date, however, that relate these pre-stimulus effects to awake post-encoding reinstatement effects, and the latter to remote memory. Specifically, are the pre-stimulus neurons that were activated, or subset of them, also re-activated post-encoding, and does the latter set also support representations of detailed, remote memories? There is no definitive answer, but Larzabal et al.'s (2020) study tracking memory to reinstatement effects suggests that it is possible that similar neural populations are implicated at all time points. Using MVPA of the EEG signal to video clips, they found that although the signal faded over time, sustained patterns indicative of reinstatement effects were

Interim summary

These complex patterns of activation, revealed by univariate and multivariate fMRI studies, and by studies of functional connectivity and neural oscillations underscore the complexity of memory transformation processes that underlie systems consolidation. In addition to being influenced by memory age, hippocampal-neocortical activation and interaction are also modulated by vividness, perceptual richness (details), congruency with prior knowledge, central or peripheral elements of the event, and recollection and familiarity. Despite the variety of findings across different methodologies, there are some notable regularities. Memory representations that are vivid and perceptually-detailed are associated with hippocampal activation, and hippocampal-neocortical connectivity whether measured by fMRI or frequency oscillations, regardless of memory age. This pattern in humans is consistent with that observed in rodents. These patterns are likely initiated even before the stimulus is presented (memory allocation effect) and may be related to post-encoding reinstatement effects during wakefulness and sleep. Damage to the hippocampus, or disruption of its function, leads to reduced hippocampal involvement associated with loss or reduction of rich episodic memories. Conversely, loss of rich episodic memories is associated with diminished hippocampal involvement and increased involvement of the mPFC. Activating the mPFC, however, does not restore the rich, episodic memory representation that is dependent on the hippocampus. These findings, consistent with TTT, violate the premises of comparability (Premise 8) and substitution (Premise 9) associated with SCT. As well, studies of human analogues of reconsolidation (memory reconstruction) undermine the premise of unidirectionaly (Premise 10) and post-consolidation memory stability (Premise 11).

Results concerning activation along the long axis of the hippocampus and their functional connectivity are more variable. Although some studies are consistent with our prediction that as

memories are transformed with time, the posterior hippocampus is more implicated in perceptually detailed representations and the anterior, with gist, others seem not to conform to this pattern. The few studies on the role of each of the subfields in system consolidation suggest that the DG/CA2/3 subfields are implicated more in representing detailed context-specific memory and the CA1 subfields in representing gist. A recent review by Brunec et al. (2020) on representational similarity along the long axis of the hippocampus noted that increases or decreases in similarity across the long-axis are not fixed but are modulated flexibly by task goals that emphasize extraction of generalities or reinstatement of specific experiences. No doubt, these factors will also determine the nature of memory transformations and how regions of the long axis are implicated in systems consolidation.

Memory retrieval depends on the co-activation of various structures. Whereas hippocampal involvement serves as a marker for retrieval of episodic memory, whether context-specific or gist-like, the same is not true for mPFC and anterior temporal lobes as markers, respectively, of retrieval of schematic or semantic context-general memory. Often, these structures are implicated even when context-specific, episodic memories are retrieved suggesting the following: (1) that they contribute to general functions, such as search and monitoring, that aid retrieval of episodic memory (Moscovitch, 1992; Gilboa, 2005; Gilboa & Marlatte, 2017; Gilboa & Moscovitch, 2017); (2) that schematic or semantic information can be part of the fabric of episodic memory (Renoult et al., 2012, 2019); and/or (3) that each type of memory representation can co-exist with the others, the extent to which one is dominant or interacts with the other being determined by a variety of factors, much like those that influence the involvement of different regions along the long axis of the hippocampus (Winocur & Moscovitch, 2011; Robin et al., 2017; Sekeres et al., 2018). Accordingly, whereas damage to the

hippocampus will impair context-specific, episodic memories, and leave schematic and semantic memories relatively spared (but see below), damage to mPFC and anterior temporal lobe will not only affect schematic and semantic memory, respectively, but will also affect encoding and retrieval of episodic memory under many circumstances (see above). In the next section we examine the interaction of all of these types of memory to gain a more nuanced purchase on systems consolidation.

Episodic, semantic and schematic memory are intertwined

In a recent review on episodic and semantic memory, Renoult et al (2019), following an earlier review by Greenberg and Verfaeillie (2010), concluded that "Current behavioural, neuropsychological and neuroimaging data are compatible with the idea that episodic and semantic memory are inextricably intertwined, yet retain a measure of distinctiveness, despite the fact that their neural correlates demonstrate considerable overlap (pp. 1041)." Although I am an author on that paper, I believe that "inextricably" may be too strong a term, since there are conditions in which episodic and semantic components of the very same memory can be identified, consistent with NPRC hypothesis. Here, we review briefly only those studies that are relevant for systems consolidation.

It had long been known that damage to the temporal lobes led to deficits in semantic fluency which reflect a lifetime of acquired knowledge (Newcombe, 1967). Until relatively recently, however, these deficits had been attributed to damage to the lateral surface. Studies initiated by Gleissner and Elger (2001), however, showed that the loss was related to medial temporal damage which included the hippocampus. Following these seminal observations, investigators found that after generating the initial items in response to a category name, such as animals, participants resorted to episodic memory, such as memories of visiting a zoo, to generate the

remainder (Greenberg et al., 2009; Ryan et al., 2008), particularly if the category has a spatial or autobiographical component that afforded such a strategy (Sheldon & Moscovitch, 2012). Having deficient episodic memories, patients with medial temporal lobe lesions were impaired on the semantic fluency task but not on letter fluency for which such episodic strategies are ineffective (Troyer et al., 1998; Troyer, 2000). fMRI evidence is consistent with the lesions studies: Hippocampal activation is observed during exemplar generation in semantic fluency (Ryan et al., 2009), particularly for items generated late in the sequence (Sheldon et al., 2016). Moreover, the anterior and posterior hippocampus are differentially implicated, with the anterior hippocampus being activated more on autobiographical fluency tests (tell me all the movies you saw) and the posterior on fluency tests that have a spatial component (tell me all the items in a kitchen).

The relevance of these studies for systems consolidation is that although the task is ostensibly semantic, and should be mediated by extra-hippocampal structures, such as anterior temporal or inferior frontal cortex, there is none-the-less a hippocampally-mediated episodic component. Although the age of the memory was not examined systematically in these studies, it is likely that the type of information sampled drew on memories accumulated over a lifetime.

A study of semantic memory in a person with semantic dementia caused by antero-lateral temporal atrophy speaks directly to this point. Such individuals have difficulty reading words, including those denoting famous places or people, but these difficulties are ameliorated if they have had a personal experience associated with the word or face, even if that experience occurred decades ago (Westmacott et al., 2001). Building on this finding, Westmacott and Moscovitch (2003) discovered that even in healthy individuals, reading names aloud, and making lexical, fame and recognition decisions, is better for names that have some personal significance, an

advantage that is lost in people with medial temporal lobe damage caused by trauma or degeneration (Alzheimer's Disease) (Westmacott et al., 2004). Focal damage to prefrontal cortex, on the other hand, did not influence performance. Similarly, Waidergoren et al. (2012) found that the hippocampus was needed during recognition of semantic facts when these facts require the retrieval of semantic information that is not intrinsic to the concept ('semantic context'). This occurred independently of any personal experiences participants may have had with the information. Consistent with the idea that the hippocampus is important for knowledge of extrinsic semantic features, a patient with hippocampal developmental amnesia was shown to be impaired on generation of extrinsic but not intrinsic semantic features of object concepts (Blumenthal et al., 2017)

The involvement of the hippocampus in representing famous people and places encountered in the remote past is supported by evidence from single-unit recordings from the hippocampus in humans (Quiroga et al., 2005; Quiroga, 2012, 2019). Dubbed "concept cells", they respond to specific people, places and objects (or stimuli associated with them) regardless of modality or of transposition and variation within a modality as long as the entity is identifiable (e.g. different views or different pictures of the same person). Quiroga and his collaborators suggested that these cells code semantic representations that "constitute the building blocks for declarative memory functions" (Quiroga, 2012, p.592) It is important to note, however, that the large majority of these cells respond to items with which the person is personally familiar (Viskontas, Quiroga, & Fried, 2009b) in keeping with Westmacott et al.'s observations. Indeed, they may more properly be called "experiential or episodic cells" that link a specific entity to an experience of which the entity was a part (Sekeres et al., 2018; Renoult et al., 2019).

Memory for public events, a task that is ostensibly semantic, may also draw on both semantic and episodic representation, and their neural substrates. Petrican et al. (2010) asked older and younger participants were to make recollection and familiarity judgements to public events that spanned fifty years. In all participants, recollection responses declined proportionately more than familiarity responses over time, a decline that was significantly more pronounced for adults between 74-85 years old. That this disproportionate decline in older adults may have been related to their failing hippocampus was supported by the performance of two patients, one with medial temporal lesions, whose recollection was disproportionately impaired relative to familiarity. Recollection, however, was preserved in another patient without such lesions.

As with memory for public events, memory for semantic narratives, such as Bible stories and fairy tales, is impoverished in people with medial temporal lobe lesions (Verfaellie et al., 2014), particularly if they have a scene construction aspect to them (Lynch et al., 2020).

On the other side of the ledger, we already noted how on tests of autobiographical memory and of memory for narratives, such as video clips, detailed episodic components are intertwined with gist and schematic components (Levine et al., 2002). Damage to the hippocampus affects the episodic component no matter how old the memory. As noted in the previous Section, damage to the vmPFC, however, produces more variable results depending on the demands of the task, in part because schemas may be needed to guide memory search and to monitor its output, particularly if retrieval is strategic or indirect (Moscovitch, 1989, 1992). Likewise, as noted earlier, both the vmPFC and hippocampus are likely to be activated, and functionally connected to one another, when detailed episodic memories are retrieved. When episodic memory is impoverished, however, hippocampal involvement, typically is diminished or absent (see also review by McCormick et al., 2018a).

There are fewer studies on the contribution of the antero-lateral, inferior temporal and inferior frontal cortex, central regions in the semantic network, on tests of episodic memory (Renoult et al., 2019). The best evidence comes from studies of individuals with semantic dementia whose antero-lateral temporal cortex has degenerated (Viard et al., 2013; Irish & Piguet, 2019). Very early in the disease, when their semantic deficits are mild, performance on autobiographical tests of memory can be within the normal range no matter how old the memory is (Moss et al., 2003). As the dementia progresses, however, and hippocampal function declines, memory for recent events, say within the past month, can be preserved whereas more remote memories are impaired (Graham & Hodges, 1997; Maguire et al., 2010). These findings suggest that the hippocampus can be accessed directly by information/cues pertaining to recent memories, but indirectly via sematic networks for more remote memories (Moscovitch & Nadel, 1999), in keeping with evidence from EEG on the temporal dynamics of EEG oscillations for recent and remote memories (see above – McCormick et al., 2015; Maguire et al., 2020). These contrast with other reports of impoverished autobiographical memory across the lifespan in semantic dementia (Irish & Piguet, 2013). A possible source of the difference between the two sets of findings are the stimuli used to cue memory. Pictorial stimuli may access recent, perceptually-preserved memories more easily without the intervention of semantics, whereas verbal stimuli always depend on semantic mediation (Irish & Piguet, 2013).

Although our focus has been on the hippocampus and mPFC, other regions of the autobiographical/recollection network related to semantics are also implicated in retrieval of recent and remote autobiographical memories (Renoult et al., 2019). Examining patients with lateral, focal frontal lesions, Levine (2004) found that when properly cued, their recent and remote memory for autobiographical events is preserved. In patients with the behavioural

variant of fronto-temporal dementia, however, autobiographical memory decline was related to degeneration of lateral and medial frontal regions (Liu et al., 2020; for excellent reviews on recent and remote memory, and future thinking in dementia, see Irish & Van Kesteren, 2018; Irish & Vatansever, 2020 and short summary by her in Renoult et al., 2019).

The findings reviewed in this section underscore the complexity of understanding systems consolidation. We have now gone beyond the idea that a memory is mediated by one structure or another (HPC vs neocortex) depending on memory age, as SCT predicts, or even that dividing memories into semantic and episodic is sufficient, as the early versions of MTT suggested. Instead, consistent with TTT and NPRC, what is crucial in identifying the structures that mediate memory in systems consolidation is understanding how memories are represented, leaving open the possibility that the expression of some (all?) memories consist of different, integrated, but separable components, each of which are mediated by different structures.

Theories of Memory Consolidation

So far, we focused on comparing SCT and MTT/TTT because the major differences between them are clear, and help delineate the issues that are at stake in developing theories of memory consolidation. Although they differ with respect to most of the premises underlying SCT (see above), the major difference concerns the correspondence between representation at the psychological level with that at the neural level. According to SCT, episodic memories retain their episodic nature even with a change in neural representation as they become independent of the hippocampus and are consolidated in neocortex. By contrast, MTT/TTT posits that a change in neural representation, from hippocampus to neocortex, is accompanied by a corresponding change in psychological representation, so that episodic memories are transformed from detailed,

context-specific memories to gist-like, semantic or schematic memories. As long as they retain their episodic representation they continue to be dependent on the hippocampus.

A crucial question that was not addressed directly is how is transformation achieved. To repeat what we stated earlier, the different representations related to an event are encoded into memory concurrently, and can be considered as different aspects of the experienced event which interact dynamically with one another. Time and experience can transform the initial representations in a variety of ways (Winocur & Moscovitch, 2011): by decay (Barry & Maguire, 2019a; Hardt et al., 2013; Sadeh et al., 2014, 2016) or interference (Frankland et al., 2019; Richards & Frankland, 2017; Yassa & Reagh, 2013; Yonelinas et al., 2017); by regularization via extraction of statistical regularities among events (McClelland et al., 1995; Schapiro et al., 2017 b); by assimilation into pre-existing knowledge structures (Bartlett, 1932; semantics: McClelland et al., 1995; McClelland, 2013; schemas: Gilboa & Marlatte, 2017; Tse et al., 2007, 2011; van Kesteren et al., 2012; Wang & Morris, 2010); by updating via reconsolidation (Nadel & Sederberg, *in press*, this volume); by reconstruction influenced by past knowledge as well as by current goals and motivation (Schacter et al., 2012b); by episodic simulation and imagination (Addis et al., 2007; Addis, 2018); and by errors at retrieval (Bridge & Paller, 2012). None of these is mutually-exclusive and, potentially, all can co-occur and influence one another.

MTT/TTT is agnostic as to which and how many of these transformations underlie the changes in psychological and neural representations observed in systems consolidation. Its main point is that whichever psychological representation is expressed as a result of the transformation process, it is accompanied by co-activation of its corresponding neural structure, and vice-versa. In comparison to MTT/TTT which considers that these transformations can occur at any point during systems consolidation, and are usually bi-(multi)directional between the hippocampus,

neocortex, and other structures, SCT posits that these transformations are unidirectional and occur only before memories have become independent of the hippocampus and been consolidated in neocortex (Squire et al., 1984).

Current theories of systems consolidation have elements in common with SCT or MTT/TTT, but either challenge crucial aspects of the theories or complement them in important ways, or both. We highlight these differences as we believe they point to the direction that future research on systems consolidation will take.

Distributed Reinstatement Theory and Memory Manifold Theory (Sutherland & Lehmann).

Like TTT, Distributed Reinstatement Theory holds that memories are represented concurrently in hippocampus and non-hippocampal regions, but with the added premise that the representation is stronger in the hippocampus than in non-hippocampal networks, enabling the hippocampal representation to overshadow the others. As in TTT, damage to the hippocampus leads to temporally extensive and ungraded retrograde amnesia, with the size of the lesion determining the severity of the memory loss, but not its extent as MTT predicted (Sutherland & Lehmann, 2011; Sutherland et al 2019). With repetition of learning episodes, the non-hippocampal representations are strengthened and, contrary to MTT/TTT, but consistent with SCT, can store context-specific memories that resemble those of the hippocampus (Sutherland et al., 2010; Sutherland & Lehmann, 2011; Sutherland et al., 2020). Most recently, Sutherland et al. (2020) proposed an updated version of their theory which they called Memory Manifold Theory to account for the effects of repetition, pattern processing in the hippocampus, amount of damage and state matching, essentially a measure of the reinstatement of the neural activity patterns at encoding,

The evidence suggests that neocortical (non-hippocampal) memories may indeed be weaker initially than those mediated by the hippocampus (Kitamura et al., 2017) although there is not universal agreement on this point (Takehara-Nishiuchi, 2020). More contentious, from MTT/TTT's point of view, is the idea that the representation of hippocampal and non-hippocampal memories resemble one another. As we have argued in this chapter, in most cases that have been examined closely, the two have been shown to differ from one another. There are a few studies, however, that have used the multiple learning episodes to bolster memory representation in non-hippocampal sites as Lehmann et al. (2009) have done using contextual fear conditioning in rats (see also Frankland et al., 2006). Although rats with hippocampal lesions froze more in the learning context than in a novel context, it may be the case that the extended learning afforded the rat the opportunity to become acquainted with non-configural features (Rudy & Sutherland, 1989), such as the colour and pattern of the walls and floor, that distinguished the two contexts, and whose association with shock does not depend on the hippocampus. This critique, leveled by Hardt and Nadel (2018) on Kitamura's study, applies here, and to Frankland et al.'s (2006) study, too. Unless further tests show that functionally equivalent representations are formed in the two cases, the issue remains unresolved.

More telling is Sutherland and Lehmann's critique of a major tenet of MTT, namely, that the severity and extent of retrograde amnesia for episodic memory should vary with the size of the lesion in the hippocampus. According to Nadel and Moscovitch (1997), this occurs because each memory retrieval results in a newly-encoded hippocampal memory trace that retains elements of the initial trace in addition to representations of the context in which the retrieval occurs. As such, according to MTT, older memories, having more opportunity for retrieval, are associated with more traces distributed through more of the hippocampus. This predicted increase should

also be reflected in the greater number of HPC neurons mediating remote as compared to recent memories, as measured electrophysiologically, by calcium imaging and by immediate early genes (IEGs). Although some IEG studies report results in the predicted direction (e.g. Sekeres et al., 2018b, Sutherland et al., 2020), in all other cases the predicted increase is not observed (Sutherland et al., 2020).

We concede this point. MTT was initially based on evidence from the few available studies in humans at the time which suggested that the greater the size of medial temporal lesions (not confined to the hippocampus), the greater the extent of RA. Our own first study to test this prediction disconfirmed it, as temporally extensive RA was found regardless of the extent of hippocampal damage or sclerosis in humans (Viskontas et al., 2000). Our studies on rodents also showed extensive RA regardless of lesion size (Winocur et al., 2009). Previous and subsequent studies in humans and rodents are consistent with these observations (see above; Winocur et al., 2010). Mindful of these findings, the claim that the extent of RA depends on the size of hippocampal lesions has been dropped in more recent formulations of TTT (Winocur & Moscovitch, 2011; Sekeres et al., 2018).

Sekeres et al (2018a) suggested that our gain in knowledge of the functional neuroanatomy of the hippocampus, particularly specialization along the long axis, the function of hippocampal subfields, and connectivity with each other and with extra-hippocampal structures (Brunec et al., in preparation) makes it unlikely that there is a simple relation between the size of the hippocampal lesion and its effects on memory. Even small lesions in some structures, such as the CA1 or CA3 subfields (Argyropoulos et al., 2020; Bartsch et al., 2011; Miller et al., 2020), or subiculum (Ferguson et al., 2018) may lead to severe and extended retrograde amnesia for episodic memories, indicating that the structures affected may be more of a determining factor

than the size of the lesion (see also Barry, Clark & Maguire, 2020, on relation of subfield volume to remote autobiographical memory). The fact that episodic memories are so multifaceted, drawing on widely distributed information, makes it likely that damage to any part of the extended hippocampal system will lead to some episodic memory loss, with the severity and type of loss being related to the nodes in the system that are affected and their connections. The same can be said for evidence from electrophysiology, calcium imaging and IEG. These considerations need to be incorporated into as much into Memory Manifold Theory as into MTT/TTT.

The central question, however, is whether the hippocampal neurons retain their contextual specificity as MTT/TTT predicts, and that extra-hippocampal neurons are less context-specific. Here, much of the evidence reviewed by Sutherland et al. (2020) is consistent with MTT/TTT, although in many cases stringent tests of context specificity are lacking. For example, Sutherland et al (2020) report studies in which multiple learning episodes prevent memory loss after hippocampal lesions or enable the acquisition of contextual memories without a hippocampus. Without knowing the nature of the functional representation of these memories, it is difficult to know whether such evidence supports or refutes MTT/TTT (discussion above on schemas). We know from studies in humans, however, that retrieval practice has very different effects behaviourally and neurally than re-studying the same material (Karpicke & Roediger, 2008; Roediger & Butler, 2011; Roediger & Karpicke, 2006, 2018). Comparing retrieval practice with re-studying, some investigators observed that the former is associated with an increase in hippocampal activation and in connectivity between the hippocampus and neocortical structures that include the mPFC (Wing et al., 2013). Other investigators, however, have found no change or decline in hippocampal activation with retrieval across sessions separated by two days (Brodt, et al., 2016, 2018). There was, however, an increase in mPFC activation within a single day's

session (Gais et al., 2007). Representational similarity analyses showed retrieval practice led to a slow increase in both semantic and episodic aspects of memory, but primarily in parietal cortex, a region known to code for both types of information (Bellana et al., 2017; Binder et al., 2009; Binder & Desai, 2011; Vilberg & Rugg, 2008) and to be linked both to the hippocampus and frontal cortex. Most interestingly, retrieval practice promotes the semanticization of episodic memories (Lifanov, et al., 2020) suggesting increased reliance on extra-hippocampal structures, particularly following sleep (Brodt & Gais, 2020; Himmer et al., 2019).

Thus, the effects of multiple retrievals on psychological and neural representations are more complex than Sutherland and Lehmann claim, and that Nadel and Moscovitch (1997) foresaw. They lead not only to stabilization of episodic memory but, contrary to Sutherland and Lehmann, to formation of non-episodic representations in neocortex. The literature on the effects of replay, or involuntary retrieval, during sleep in humans and rodents is no less complex (see Diekelman & Born, 2010; Dudai et al., 2015 for reviews). Although there is a consensus that sleep benefits systems consolidation, there is less agreement as to which structures are affected, and whether the memory benefit pertains only to semantic or schematic aspects of studied episodes (Lewis & Durrant, 2011) or to context-specific (episodic) aspects (Aly & Moscovitch, 2010; Dudai et al., 2015; Yonelinas et al., 2019) or both (Schapiro et al., 2017). Although MTT may have been incorrect in proposing that repeated retrievals lead to formation of multiple traces in the hippocampus, it was correct in recognizing that such retrievals have a profound effect on systems consolidation (Nadel, Samsonovich, Ryan, & Moscovitch, 2000). Judging from the current literature, the type of effects are likely to be consistent with the basic views of MTT/TTT, namely, that both episodic and non-episodic aspects of memory, along with their neural

substrates, can be affected, the degree to which one or the other occurs being determined by a variety of factors including repetition and retrieval practice.

According to TTT these different representations related to an episode can be encoded into memory concurrently, can co-exist with one another in memory, and can interact dynamically with each other, supporting one another in some instances, competing in others, and, in still other instances, transforming one into the other and back again. The variants that are expressed are determined by a variety of factors, including the age of the memory and the demands of the task. In this regard, TTT resembles Memory Manifold Theory. The important point, according to TTT and the NPRC hypothesis, is that whichever variant is expressed is accompanied by co-activation of its corresponding neural structure, and vice-versa.

Complementary Memory Systems

Takehara-Nishiuchi (2020) has proposed a *Complementary Memory Systems* model that is compatible with the interactive aspects of TTT, and the concurrent encoding aspects of TTT and Distributed Reinstatement Theory. The model focuses on the relation between hippocampus and neocortex, and particularly the mPFC, at encoding, emphasising the different information encoded in these structures. She draws attention to the crucial involvement of the mPFC in the formation of episodic memory traces. Beginning with lesion studies by Lesburgueres et al. (2011), she presents evidence from behavioural, electrophysiological and molecular studies showing that mPFC, like the hippocampus, is implicated in the encoding of new experiences (see also Jasnow et al., 2017), but the type of information that is encoded and their ensuing representations differ between the two structures. Whereas the hippocampus captures moment-to-moment changes in the temporal, spatial and perceptual aspects of the event, leading to context-specific representations of it, the mPFC captures similarity among inputs (and likely also

with stored representations) and integrates them over time, enabling it to capture the central content of the event, its underlying schema. In short, consistent with TTT, the hippocampus and mPFC form complementary memory representations from the outset, one for context-specific representations and one for schemas, raising the possibility that the mPFC exerts top-down modulation of the hippocampus, enabling more "selective, perhaps more intelligent, encoding of new information (abstract, p1)." In all likelihood, schema-guided modulation by the mPFC operates at various levels, including early perceptual ones, to determine the type of information that is delivered to the hippocampus (Gilboa & Marlatte, 2017; Gilboa & Moscovitch, 2017; Moscovitch, 1992; Moscovitch & Winocur, 1992, 2002). The model, however, has little to say about systems consolidation after encoding.

Complementary Learning Systems

By assigning complementary roles to the hippocampus and neocortex, Takehara-Nishiuchi's model resembles the influential *Complementary Learning Systems* (CLS) model proposed by McClelland et al. (1995; see also Norman, 2010), but differs from it in fundamental ways. The most important of these is that McCLelland et al's model stipulates that memories must first be encoded in the hippocampus before they can be integrated into neocortical representations. The reason for that is that rapid encoding of novel information into neocortical memory representation can lead to catastrophic interference with old memories, and loss of the newly-acquired memory (McCloskey & Cohen, 1989). By contrast to the neocrotex, the hippocampus is suited to rapid acquisition and retention of new information. Through repeated interactions with neocortex over prolonged intervals, hippocampal replay of these memory traces induces gradual changes in neocortical semantic/schematic networks so that they can integrate the new memory traces, which become independent of the hippocampus.

On the surface, it would seem that by using computational modeling, McClelland et al.'s CLS model simulates systems consolidation according to the principles that govern SCT. Its strength is that it provides a computationally precise formulation of how episodic memories are consolidated into neocortex. Examined more closely, however, CLS stipulates how hippocampal representations can be transformed into neocortical representations. In that sense, it also resembles TTT.

The CLS model's weaknesses, however, are also those that bedevil SCT. The neocortical system into which episodic memories are integrated is, by the model's own admission, a semantic network or knowledge structure that does not support the kind of context-specific information that is the hallmark of episodic memory. Episodic memories are effectively lost in that model; only semantics or schemas remain. Moreover, according to the model, even if we concede that the neocortical system, somehow can support episodic memories, damage to the hippocampus should leave them unscathed. Yet as the evidence we reviewed suggests, hippocampal damage impairs episodic memory no matter how long ago the memory was acquired.

Another challenge to the CLS Model came from studies by Tse et al (2007; 2011; Wang & Morris, 2010) who found that newly-formed odour-spatial associations by rodents become rapidly independent of the hippocampus, and rely instead on neocortex, if the rodents had previously formed schemas representing odour-spatial relations. Integration of newly-formed memories into neocortex need not be as slow as the CLS Model predicted. To counter this challenge, McClelland (2013; Kumaran et al., 2016) showed that CLS can accommodate such rapid, neocortical learning if the new episodic memory is consistent with pre-existing schemas. It is only inconsistent episodic memories that need to be integrated more slowly into neocortex. Even leaving aside the question of whether the integrated representation is truly episodic, the

model runs into the problem that inconsistent memories may never be fully integrated into neocortex (Bonasia et al., 2018; van Kesteren et al., 2012) yet remain viable for an extended time, and like all episodic memories worthy of the name, continue to rely on the hippocampus.

There is now good evidence that neocortical learning can also be rapid. Some of this evidence is reviewed by Takehara-Nishiuchi and summarized above. Contrary to CLS, not only do neocortical changes occur concurrently with those in the hippocampus, but they are necessary to support the rapid acquisition of hippocampally-based memories. In addition, neocortical learning, likely mediated by the peri-rhinal cortex and anterolaeral temporal cortex, is implicated in fast-mapping (Carey & Bartlett,1978), a procedure whereby single (or very few) presentations of novel material, is integrated into semantic networks (Coutanche & Thompson-Schill, 2015) without benefit of the hippocampus (Atir-Sharon et al., 2015; Merhav et al., 2014, 2015; Sharon et al., 2011). Although the effectiveness of fast-mapping in adults is disputed (Cooper et al., 2019; Greve et al., 2014; Smith et al., 2014) some of the discrepancies may be related to variations across individuals and items (Coutanche & Koch, 2017).

Last, there is evidence that long-lasting priming effects, and other forms of non-declarative learning, depend on rapidly-formed neorcortical changes independently of the hippocampus (for review, see Hebscher et al., 2019b). Thus, while providing a good computational account of how some aspects of hippocampally mediated episodic memory are transformed with time and repetition into neocortically-mediated semantic memories, the CLS Model is not fully successful in accounting for various other aspects of systems consolidation.

Interference models

The *Competitive Trace Theory* (Yassa & Reagh, 2013) and the *Contextual Binding Theory* (Yonelinas et al., 2019) are both based on the idea that context specific information bound by the hippocampus at encoding is lost over time due to interference from related material, resulting in reduced hippocampal, and increased neocortical, representation. Although the two theories have much in common with one another, and draw on aspects of SCT and MTT/TTT, there are some important differences between the interference theories, and between both theories and SCT and MTT.

The Competitive Trace Theory borrows from MTT/TTT the idea that many older memories are associated with more repeated retrievals than recent memories which leads to more neural representations in the hippocampus and neocortex (see above for Sutherland et al's, 2020, critique of this idea). Like MTT/TTT, Yassa and Reagh assume that each reactivation of a memory during retrieval occurs in a new context, and leads to encoding of those elements of the old memory that are retained along with the novel context. They refer to this as a process of re-contextualization. Pattern separation allows for distinct representations of each of version in the hippocampus, whereas in neocortex, the versions overlap. Instead of treating these multiple encodings as beneficial for retention of episodic memories, Yassa & Reagh treat them as detrimental, leading to competitive interference among them. In neocortex, only those elements that overlap are retained, leading to the slow formation of semantic memories or schemas, as proposed by CLS. As a result, veridical episodic details are available only for recent memories. Older memories are either decontextualized versions of the original represented in neocortex, or are re-contextualized versions of the original which depend on the hippocampus but are fraught with illusory details that increase with memory age.

Although there is no disputing that recent events are remembered better than remote ones, it is not always the case that remote memories contain more illusory details than recent ones. Here it is important to distinguish between memory quantity and memory accuracy. Whereas memory quantity and episodic richness declines with retention interval, accuracy often remains high, sometimes on the order of 90% correct, even for intervals lasting years (Diamond et al., 2020; Evans & Fisher, 2011; Goldsmith et al., 2005), consistent with MTT/TTT. Likewise, the literature on the effects of repeated retrievals or retrieval practice on memory does not always (or even often) lead to competitive interference and memory decline. Instead, again consistent with MTT/TTT, retrieval practice typically leads to improved memory, both with respect to its episodic and semantic components when compared both to memories that have not been retrieved or to those that have been re-studied (see above).

Like its counterpart, *Contextual Binding Theory* also assumes that the hippocampus binds item and contextual information into a memory trace, and that interference from other memories leads to decontextualization, making memories less dependent on the hippocampus and more on extra-hippocampal structures (Yonelinas et al., 2018). Whereas the Competitive Trace Theory focuses on the effec ts that re-contextualization during retrieval has on memory traces represented in the hippocampus and neocortex, Contextual Binding Theory also deals with the effects of contextual drift, which is the change over time in environmental, cognitive, and emotional context, and their corresponding neural representations (Folkerts et al., 2018; Howard & Kahana, 2002; Long & Kahana, 2018; Manning et al., 2011). Because retrieval of episodic memories depends on reinstating the encoding context at retrieval, contextual drift is a contributing factor to interference, facilitation and temporal organization in memory.

By their own admission, Yonelinas et al. note that Contextual Binding Theory shares most of its core assumptions with MTT/TTT, including the roles assigned to the hippocampus and neocortex in retrieving contextually rich and decontextualized memories, respectively, whether recent or remote, and the effects of multiple retrievals on memory and its neural substrate. As such, both acknowledge the pivotal role that context plays in accounting for episodic memory and forgetting. Contextual Binding Theory, however, provides a more varied account of the role of context on memory and forgetting, with additional predictions about manipulations such as interference and sleep. These, it should be acknowledged, all paly out over relatively short intervals, from minutes to days, and not over the longer intervals, extending to years or decades that are observed in human studies of systems consolidation. Moreover, unlike MTT/TTT, Contextual Binding Theory says little about the role of schemas and the interactions between mPFC and hippocampus in their acquisition, maintenance and instantiation.

Sleep has acquired a prominent role in research on memory, but the primary one assigned to it by Contextual Binding Theory is one of experiential quiescence, providing an interval free of interference during which memories can be consolidated. Considering the changed neural context between wakefulness and sleep, one would assume that contextual drift would be high and lead to increased, rather than decreased, forgetting as a result of sleep. That aside, it is also not clear whether it is the period of quiescence that accounts for reduced forgetting during sleep rather than wakefulness, or whether it is the replay during sleep of hippocampal memory traces that accounts for sleep's benefits (see above). Studies on targeted memory activation during sleep in humans (Berkers et al., 2018; Hu, Cheng, Chu & Paller, 2020; Lewis & Bendor, 2019; Paller et al., 2021; Rudoy et al., 2009) and on sharp wave ripples which accompany memory replay in rodents (Buszaki, 2015) and likely in humans (Norman et al., 2017, 2019; Vaz et al.,

2019, 2020) suggest that it is more the replay, than absence of interference, that is important, perhaps by reinstating the neural context from encoding. Eliminating sharp wave ripples during sleep leads to memory loss (Buszaki, 2015) even though, on the face of it, this manipulation does not increase interference. Last, in addition to studies reporting preservation of context-specific memories with sleep, there are also many studies showing that sleep leads to decontextualization of memory and the promotion of semantic and schematic representations (Lewis & Durrant, 2011), contrary to the predictions of Contextual Binding Theory. Specifying the conditions under which sleep helps preserve context-specific memories and those in which it promotes decontextualized memories would contribute greatly to our understanding of systems consolidation from which all theories would benefit (Dudai et al., 2015; Paller et al., 2021).

Scene and Event Construction and Reconstruction Theory

All previous theories assume that some episodic representation of the originally acquired memory has been retained over extended intervals, some lasting years or decades. Even Competitive Trace Theory which posited that only recent memories were veridical, with remote memories being recontextualized versions of the original, still assumed that the memory was not wholly illusory, with some aspects of the original being retained, a view consistent with Bartlett (1932). Barry and Maguire (2019a,b), however, take Yassa and Reagh's recontextualization proposal to its extreme. Their bold and provocative proposal states that all but recent memories are recontextualized around a schematic core associated with the original memory. Citing evidence of instability of hippocampal place cells and synaptic processes, such as rapid loss of dendritic spines (Attardo et al., 2015), and the interference produced by life-long neurogenesis (Richards & Frankland, 2017), Barry and Maguire argue that the hippocampus lacks the neurobiological mechanisms needed to sustain detailed, context-specific memories over long

intervals, siding in this regards with proponents of SCT. All that remains are gist of episodes or schemas mediated by extra-hippocampal structures, particularly the mPFC. To account for ostensible evidence of detailed, context specific (episodic) remote memories, some of it emanating from their own laboratory, Barry and Maguire propose that cues at retrieval activate appropriate schemas of events mediated by the mPFC which in turn guides the hippocampus to construct scenes that serve as scaffolds for binding event content on the fly. The process, essentially, is no different from the one engaged in episodic simulation of fictitious or imagined events. Damage to the hippocampus disrupts this on-line process and leads to impoverished memories, whether recent or remote, an argument resembling one that proponents of SCT used to account for impaired, remote memory of rodents on various spatial tasks (Clark et al., 2005).

In responding to their proposal, Moscovitch and Nadel (2019), while acknowledging the instability of hippocampal processes, suggest that such instability is not sufficient to discount the hippocampus as a viable substrate for long-term memory retention. They note that instability is also evident in neocortex, suggesting that may be a general characteristic of the brain, and possibly the entire organism. Moreover, in cortex, stabilizing spines is not always necessary for learning to persist (Clark et al., 2018). More importantly, Moscovitch and Nadel note that instability at the neuronal level does not translate into instability at the behavioural/psychological level. Considering that the engram consists of at least tens of thousands of cells (Josselyn & Tonegawa, 2020; Quiroga, 2012, 2019), retention of a proportion of them, properly configured, may be sufficient to support context-specific memories and, in the case of neurogenesis, to recruit novel neurons into their orbit. Thus, Ziv et al. (2013) showed although only 15% or so of cells retain their membership in a given hippocampal ‘map’ across days, the network can still faithfully represent the environment for at least 30 days. Plasticity in the CA3-CA1 pathway and

good retention on a place task went together, and could last at least a month (Pavlowsky et al., 2017). Finally, a direct link between long-lasting spatial memory and specific cellular correlates in the hippocampus has been reported by Hsieh et al. (2017). Whatever the fate of individual spines, Attardo et al. (2018) have now shown that notwithstanding the rapid turnover of structural elements, the hippocampus can establish and even sharpen a long-lasting representation, consistent with Ziv et al.'s work on place cells.

As noted earlier, studies on reconsolidation provide further evidence in favor of long-lasting, though sometimes inaccessible, hippocampal traces (see above). For example, Winocur et al. (2009) showed that when context fear memories were reactivated, the recovered memories, and the cues/reminders that elicit them, were specific to the original context rather than generalized to other, schematically similar, contexts. Barry and Maguire (2019b) argue that this evidence is also consistent with their point of view. When confronted with the "old" context as a reminder, scene construction processes mediated by the hippocampus, and guided by mPFC event schemas, bind it into a new memory trace, leading to greater freezing in the "old" than "novel" context at test. They do not, however, consider the evidence that is inconsistent with their point of view. When rodents were exposed to the "novel" context as a reminder, they froze equally to the "old" and "novel" context, rather than showing preferential freezing to the novel context, as Barry and Maguire's model would predict.

With respect to interference from neurogenesis, evidence from optogenetic studies suggest that hippocampally-mediated traces can be reactivated to overcome the interference suggesting that they are not lost, but merely inaccessible (Guskjolen et al., 2018). Strong environmental cues can have similar effects (Guskjolen, personal communication). Likewise, though the connectivity between EC Layer II and DG may be degraded with time (due to neurogenesis), remote engram

cells in CA1 (Goode et al., 2020; Tanaka et al., 2018; Tanaka & McHugh, 2018) can be activated through the direct projections from EC. Moreover, recent evidence suggests that neurogenesis also simultaneously acts to stabilize and protect the remaining memories from degradation (Guo et al., 2018). These findings are consistent with recent work showing that active neurochemical processes are implicated in the loss of hippocampally-mediated processes over time, and the consequent decline in context-specific but not generalized memories (Guo et al., 2018; Hardt & Nadel, 2018). Interrupting this process, prevents the decline of context-specific memory. Conversely, optogenetic suppression of engram cells leads to memory loss even at long delays, attesting to the longevity and viability of hippocampal traces (Cullen et al., 2015; Einarsson et al., 2015; Goshen et al., 2011). Cellular mechanisms that could support such long-term retention have been demonstrated in the hippocampus (Migues et al., 2016). In sum, there is little evidence from animal research to support the view that the flux observed in hippocampus renders it incapable of forming and sustaining long-lasting representations within networks of its neurons.

The evidence from humans is no more supportive of Barry and Maguire's model than that from rodents. As Alba and Hasher (1984) noted in their review, evidence is lacking for a radical reconstructive view of memory that relies on schemas. Their conclusion, however, were based primarily, but not exclusively, on studies that tested retention over relatively short intervals. More recent studies, however, have examined memory over much longer intervals, lasting weeks to years. As we noted earlier, although many memories are forgotten, accuracy, and even precision, can be maintained if participants are free to report only those memories about which they are certain, rather than being forced to report or recognize memories about which they are uncertain (Diamond et al., 2020; Evans & Fisher, 2011; Goldsmith et al., 2005). What changes

with time is the grain of reported memories. For the most part, older memories are coarser, tending towards gist. Crucially, even at very long intervals some fine-grained memories are retained, and even the coarser gist-like memories retain some of the specificity peculiar to the described event. The grain at which memories are reported is under the participants' strategic control.

We agree with Barry and Maguire that retrieval is an iterative process in which the mPFC may be necessary for implementing the appropriate search strategy by directing hippocampal processes (McCormick et al., 2018a, 2020), and monitoring its output (Moscovitch, 1989, 1992; Moscovitch & Winocur, 1992), and initiating the process anew if the output is found wanting. The retention of accurate event-specific information, particularly if it schema-inconsistent, depends on the hippocampus (Bonasia et al., 2018; Gilboa & Marlatte, 2017; van Kesteren et al., 2012). Note that the distorted, schema-driven memories of Bartlett's famous War of the Ghosts story retained details specific to its origins.

Before concluding, let me relate an anecdote that indicates how resilient context-specific memories are, and how unlikely they are merely to be reconstructed. A few years ago, I took my ten-year old grandson to a Raptors' basketball game. During a security check, I was told I could not bring my yellow Swiss-army pen-knife into the arena. Instead of having them confiscate it, I hid it inside the fender of a car that was displayed in the lobby. At the end of the game, after we left the arena, I went to retrieve my knife, but it was gone.

This event had nothing to do with the schema of going to a basketball game, the penknife did not have the prototypical red colour of Swiss army knives, and the fender of a car is not a typical hiding place for a knife. With these thoughts in mind, I asked my now 14-year old grandson, if he remembered what happened when I took him to the Raptors' game. He remembered, without

prompting, that I was stopped at security because I had a pen-knife. When I asked him the colour, he said, "Yellow?" I asked if he remembered what I did with it, and he immediately replied that I hid it under a car in the lobby. I asked him if he had thought of this event since then, and he replied he had not.

T*heories of schemas and their influence on memory formation and long-term retention*

Schemas have figured prominently in theories of memory, beginning with Bartlett's work in the early part of the 20th century (summarized in Bartlett, 1932) and in subsequent studies to the present (see reviews by Alba & Hasher, 1983; Schacter et al., 2012). Prior knowledge (Burnham, 1904) and schemas in particular have also played a central role in theories of systems consolidation in humans beginning with Squire et al. (1984) and extending to the present (see Gilboa & Marlatte, 2017 for review). Tse, Morris's and colleagues work on schemas (Tse et al., 2007, 2011; Wang & Morris, 2010) was instrumental into introducing schemas to neurobiological research on systems consolidation). Our review of systems consolidation reflects these developments. Indeed, many of the theories reviewed in this section refer to the effects of schemas on consolidation or the formation of schemas in the course of systems consolidation. They all, however, work with a loose definition of schemas, often using the term interchangeably with general knowledge, context general information, and semantics. We, too, adopted a working definition of schemas that distinguish them from other types of knowledge. Here, however, we wish to provide a more precise characterization of schemas and consider their role in two prominent theories that we have not received much attention in this chapter.

Ghosh and Gilboa (2014) have discussed at length the potential challenges to research progress of having very different definitions of the same term, a discussion that is beyond the scope of the present chapter. Regardless of schema definition, however, most models place the medial

prefrontal cortex (mPFC) and hippocampus and the interaction between them at the center of schema-related memory processes, as has been evident throughout this chapter. The specific roles of vmPFC and HPC in schema processing and the kinds of interactions between them differ, sometimes considerably, among models.

Ghosh and Gilboa (2014) conducted an extensive review of the use of the term schema in psychology over the past few decades and advanced a definition of schemas based on their characteristic features. They proposed that schemas (i) entail an associative network structure, (ii) are extracted over multiple similar experiences, (iii) lack specific unit detail, (iv) are adaptable such that they both modify incoming information and are modified by it, (v) often contain action scripts and (vi) have a hierarchical organization. It is the combination of these features that distinguish schemas from other types of prior knowledge which may share some features with schemas, but also differ on at least one of these characteristics. For example, like schemas, categorical knowledge is extracted over multiple events and experiences and forms an associative network structure, but categories do not entail action scripts, are less adaptable and have specific unit detail (i.e. defining features such as birds lay eggs). Neuropsychological and neurobiological models of schema sometimes differ significantly in their definition of schema, and consequently also with respect to the underlying neuroanatomical and neurofunctional mechanisms. In line with previous studies, Gilboa et al. (2006a, 2010) proposed that vmPFC supports coordinated activation of schema representations in the posterior neocortex prior to stumulus presentation, a process termed call “schema reinstatement” and that its activity is associated with monitoring the relevance of incoming information or memories to the context-relevant activated schema, a process termed “schema instantiation” (Gilboa & Moscovitch, 2017; Giuliano, Bonasia, Moscovitch & Gilboa, 2021).

van Kesteren et al. (2012) proposed a theoretical framework, dubbed *schema-linked interactions between medial prefrontal and medial temporal lobes* (SLIMM), to account for the influences of schemas and novelty on new learning,. As suggested by the name, this framework relies heavily on neural substrates to define schemas. By this view, a schema is a collection of neocortical nodes that are mutually reinforcing and that when co-activated influence processing of new information. Encoding of novel information is driven by the extent to which it is congruent or incongruent with the schema represented by the activated network. It is suggested that vmPFC supports the detection of 'resonance' between incoming information and the currently active schema. These ideas are similar to models that suggest the vmPFC biases context-relevant posterior cortical representations and detects the 'goodness of fit' between incoming information and these activated templates (Gilboa, 2004; 2010; Gilboa & Moscovitch, 2017; Hebscher & Gilboa, 2016; Moscovitch & Winocur, 2002). When there is high resonance, SLIMM predicts neocortical learning that is independent of the hippocampus and under particularly strong resonance it predicts that vmPFC even inhibits hippocampal function. Hippocampal inhibition, in turn, leads to suppression of memory for event details that are unrelated or incongruent with the active schema. Only schema-congruent information gets rapidly integrated into existing cortical knowledge networks. By contrast, incongruous events produce a strong prediction error, which in turn triggers the medial temporal lobe and the HPC to support representations of event information including the main event details and the context in which they occur. Prediction-error driven memory for context serves to retain potentially important information by separating it from existing knowledge, and that information could later be gradually integrated into the active schema should it prove to have future predictive value (see McClelland et al., 1995; McClelland, 2013; Kumaran et al., 2016, for comparable ideas in CLS).

The formal definition of schema provided by the SLIMM model is rather vague and overextended and could equally apply to any form of prior neural representation, including narratives, conceptual categories, event gists, scripts and statistical regularities, as is the case in much of the empirical and theoretical literature we reviewed on systems consolidation. Even motor plans and habits are a collection of cortico-subcortical nodes that are coactivated and mutually reinforcing that influence how one processes and responds to new information. Implicitly, however, by virtue of the types of experimental tasks and everyday examples that these authors consider as representative of schemas, their definition broadly aligns with that of Ghosh and Gilboa (2014).

Some of the interesting predictions that arise from the SLIMM model have received support while others still await empirical evidence. For example, because both extreme incongruency and extreme congruency enhance memory, SLIMM predicts a U-shaped relationship between congruency and memory performance, with mid-range levels of congruency associated with worse memory. This was recently demonstrated in an elegant set of studies, along with findings that incongruency influences memory at encoding whereas congruency may also exert its effects post-encoding (Greve et al., 2019). Findings by Bonasia et al. (2018) suggests that similar relationships may hold for remote memories. By contrast, the prediction that vmPFC should exert inhibition over MTL function during encoding of congruent events has only rarely been demonstrated (van Kesteren et al., 2012) awaits further empirical support. In fact, several studies have reported increased coordination between vmPFC and HPC during encoding of schema-congruent information (e.g. Liu et al., 2016; Sommer, 2017), and Bonasia et al. (2018) found equivalent MTL activation for schema congruent and incongruent clips at encoding. These latter findings are consistent with alternative theories of schema related learning that posit schemas are

formed in and by the HPC and the vmPFC's role in the process is one of control and context-sensitive conflict resolution (Eichenbaum, 2017; McKenzie et al., 2014; Preston & Eichenbaum, 2013).

Preston and Eichenbaum's (2013) place the HPC at the center of schema formation and representation, but their definition of schema is similar to that proposed by SLIMM in that it derives from the neural network properties of prior knowledge. Schema by this view is any network of overlapping representations that support mnemonic functions including integration, network adaptation, inferences, and generalization. Functionally, this model suggests that mPFC signals events or occurrences that are inconsistent with prior knowledge and consequently mPFC-hippocampal interactions facilitate the retrieval of potentially relevant information for conflict resolution. These processes allow for the integration or assimilation of new incompatible information into existing memory networks. As such, it diverges from the van Kesteren et al.'s (2012) suggestion that mPFC-hjppocampal interactions support separation (rather than integration) of new associations and existing knowledge. Like the SLIMM model, the definition of schema is underspecified, but can be inferred from the experimental tasks used by these authors. Unlike studies inspired by the SLIMM model, many of the tasks these authors use entail learning arbitrary premise information to a criterion, and subsequently encountering new information that needs to be processed with relation to the premise memories (e.g. McKenzie et al., 2014; Schlichting et al., 2015; Zeithamova et al., 2012). The SLIMM and Preston and Eichenbaum models make opposite predictions with respect to the impact of mPFC-hippocampal interaction on learning of new information in the context of prior knowledge. Testing these predictions against each other, however, is complicated by their underspecified definitions of

schemas as associative networks and by including their influence on new learning as part of the definition.

In addition, what is left unspecified by these models, but is evident in some of the other schema-related theories we discussed, is how memories change with time and experience. Even assuming that these theories can account for memory acquisition, it is not clear how they account for changes in memory representation at the psychological and neural level with time, so as to provide viable models of systems consolidation.

Interim summary

We have reviewed a number of theories of systems consolidation, and found each able to account for some, but not all, of the evidence on systems consolidation. Given the magnitude and complexity of the evidence we reviewed, that is to be expected. Having an all encompassing theory of systems consolidation is almost tantamount to having a unified theory of memory. We are not there yet. What remains to be done is to test the predictions of each theory that survive scrutiny to determine which ones open up new avenues of discovery and which ones lead to dead ends. In the meantime, the three principles enunciated at the beginning of the paper can serve as a foundation for a new theory of systems consolidation

Conclusion: Where do we stand now?

We began the paper with three quotations, two of which stake out a position (Burnham, 1904; Squire et al., 1984), and one of which poses a question (Craik, 2020). Burnham advocated for an approach to memory consolidation that gives equal consideration to neurobiological and psychological factors. Squire et al extended Burnham's view of consolidation by drawing on a scientific literature that considers memory to be a dynamic process," which changes over time

through reorganization and assimilation to pre-existing memories". Importantly, they considered these events to operate in the pre-consolidation phase when memories were still dependent on the medial temporal lobe. We adopted their general views on memory, but modified it in the following ways: 1. These dynamic processes continue to operate for the lifetime of a memory, well after memories have traditionally thought to be consolidated, and begin exerting an influence even before any memories are formed. 2. We provide a neurobiological and systems neuroscience foundation for the dynamic memory approach by drawing on a literature that only emerged in the years following Squire et al's publication 3. We do not endorse the claim that the MTLs, and particularly the hippocampus's role in memory is time-limited and marks the end of the systems consolidation process. Instead, following MTT/TTT, we argue that the hippocampus mediates detailed, context-specific memories in perpetuity, relinquishing their hold only if the memory has been transformed so that it loses details and context-specificity, and assumes a form that is more in tune with the representational capacities of extra-hippocampal structures. Moreover, systems consolidation itself is a dynamic process that continues "without end" (Dudai, 2012).

Based on these changes we proposed three principles which guide our empirical and theoretical investigations and summarize them here.

1. The hippocampus retains its function in representing truly episodic memories and does not relinquish it to other structures over time. Whether the memory is recent or remote does not matter.

2. Systems consolidation is not a unidirectional time-dependent process. Memories are always in flux, and throughout their "lives" there are potentially multiple interactive forms of event representations (Winocur & Moscovitch, 2011; Sekeres et al., 2017, 2018), and which ones are

expressed depend on a multitude of factors, including memory age, task demands, and pre- and post-encoding experiences (Tompary, Zhu & Davachi, 2020).

3. Each of these psychological forms of representations is supported by distinct neurobiological substrates and processes, and their interactions drive memory dynamics (Robin & Moscovitch, 2017; Sekeres et al., 2018; Winocur & Moscovitch, 2011).

These principles, in turn, are in accord with more general principles which we repeat here: functional-neural isomorphism which states that "representations that differ from one another must necessarily be mediated by different structures (collections of neurons), and representations mediated by different structures must necessarily differ in some fundamental way from one another (Moscovitch et al., 2016, pp. 109 ." Its corollary is that there is neural-psychological representation correspondence, namely that each type of representation is mediated by its corresponding structure and vice-versa (Gilboa & Moscovtich, submitted). If episodic memory is mediated by the hippocampus, this relationship should hold regardless of whether the memory occurred recently or long ago. Conversely, these principles suggest that if there is a change in the mediating structure, such as often occurs as memories age, there should also be a change in the nature of the psychological representation.

With these principles in mind, we offer our current view of systems consolidation according to MTT/TTT.

1. *Memory formation.*The groundwork for consolidation of episodic memories is laid in the pre-encoding phase when neurons made excitable by dynamic neural events and by psychological processes, such as schema reinstatement and attention, are preferentially recruited to respond to the events that occur at encoding. These neurons, along with

> additional ones made excitable by the events and experiences that occur at encoding, are bound by the hippocampus into an engram or memory trace. Thus, the engram consists of an ensemble of neurons distributed throughout the neocortex (and possibly subcortex) that are bound by the hippocampus, and represent the totality of the experienced event, including its perceptual aspects, its meaning, its relation to whatever prior knowledge informed its apprehension, and the consciousness that accompanied it (Moscovitch, 1995).

Here we may have a rejoinder to Craik's assertion that "consolidation [is] a process with no cognitive correlates as far as I can tell that presumably proceeds automatically after the cognitive processes associated with depth and elaboration." The cognitive correlate is the apprehension of a cohesive representation of the *totality* of the experienced event. Depth and elaboration of particular stimuli capture only an aspect of the encoded experience. They are embedded within an overarching context – the totality of the episode – which is absent without the hippocampus, and which is a precondition for recollecting the items even though they were processed deeply and elaborated.

According to this view, all aspects of the experienced event, from its perceptual detail to its overarching meaning are available at the time of encoding, their accessibility being determined by various factors. For example, when asked to describe a birthday party shortly after it occurred, one may provide a detailed description of the venue and the cake, the gist of what happened, or a mere schematic description, "it was like any other birthday party – cake, singing, and presents." Each of these aspects of the event is mediated by different neural structures: vmPFC for schemas and posterior neocortex for details, linked, respectively, by the anterior and posterior hippocampus, the former coding preferentially for gist, possibly by its CA1 subfield, and the

latter for details and specificity, possibly by DG/CA3 subfields. This view is not contradictory to the view that schemas develop with experience and possibly with time, but is complementary to it.

2. *Memory retention and transformation.* Time and experience, beginning with post-encoding processes at rest or sleep, either reinforce the episodic memory or transform it so that one or other aspects of the encoded event are represented in memory and expressed in behaviour. To what extent, and for how long, these different aspects of one's memory of an event remain dependent on the hippocampus has yet to be determined, with the possibility that some aspects may become independent of the hippocampus at different rates. For example, one may lose the details or even gist of an event, such as a movie one saw, yet retain a memory of the emotion associated with the event, that is whether one liked it or not. Insofar as the memory retains its episodic character, the hippocampus will be implicated no matter how long ago the memory was formed; as the episodic nature of the memory declines or its expression is reduced, hippocampal involvement will be diminished correspondingly.

Memory transformation can be accomplished in a variety of ways: decay, interference, assimilation to schemas, reconsolidation, updating, reorganization, reconstruction, formation of schemas and semantics by extracting regularities among events and concepts, among others. The neural mechanisms underlying these processes are still poorly understood, but it is already clear that there are differences among them, and that they have different implications for theories of systems consolidation. MTT/TTT is agnostic with regard to how memories are transformed as long the processes and mechanisms honour the basic principles enunciated earlier.

3. *Neural assemblies and networks.* The hippocampus does not act alone, but interacts with structures that comprise a process specific assembly (Cabeza & Moscovitch, 2013) or a larger network whose activities it coordinates or integrates to form a rich, episodic representation. These larger neural substrates are evident in studies examining functional connectivity, neural oscillations, and eCOG, as well as in studies using multivariate analyses to determine the nature of memory representations. As with univariate and multivariate analyses confined to the hippocampus, changes in the larger networks with time and experience reflect corresponding changes in memory representation from episodic to more gist-like, or semantic or schematic, and back again, if proper conditions prevail. Similar effects are observed in rodents where neurobiological techniques, such as optogenetics and IEG are applied. The temporal dynamics of these HPC-neocortical, and is some cases subcortical, interactions are just beginning to be investigated. There already is evidence of differences in directionality among these structures, but competing interpretations as to why the hippocampus is leading in some conditions, and the mPFC, and other regions, in others.
4. *Intertwining of memory kinds*. Episodic, semantic and schematic aspects of memories typically are intertwined yet retain a measure of distinctiveness that allow one to identify a behavioural and neural signature characteristic of each type. Thus, narratives of episodes have semantic and schematic components imbedded in them, and ostensibly semantic memories, such recognizing names of famous people or generating exemplars of semantic categories, may have episodic components that influence performance.

The modern concept of systems consolidation arose to explain the retention of remote memories in the face of severe anterograde amnesia following medial temporal lobe damage. SCT was

proposed to account for this fundamental finding by postulating that memories initially mediated by the hippocampus become (systems) consolidated in neocortex and no longer need the hippocampus for retention or retrieval. Based on the evidence we reviewed, not only does this premise not survive scrutiny, but neither do any of the remaining ten premise on which SCT is based, except for two (premise 1 & 2) and possibly three (premise 5) others. To fill the theoretical vacuum, other theories and models have been proposed, MTT/TTT among them.

The concept of systems consolidation and SCT were instrumental in promoting research on the neural basis of memory change across time and experience. In this regard, they both have been extremely successful. Given the variety, complexity and longevity of the psychological processes and neural mechanisms that this research has uncovered, the concept of systems consolidation, so closely linked to SCT, may have outlived its usefulness. Perhaps Sutherland and Lehmann (2020) are correct in arguing that the only consolidation process is synaptic (or intracellular, Gallistel, 2021), which underlies all changes in memory, whether recent or remote. What we have called systems consolidation is nothing more than the changes memories undergo at both the pyshcological and neural level over a lifetime. Although the dawn of scientific memory research began with the publication of a forgetting curve measured over 48 hours (Ebbinghaus, 1885), the vast majority of memory research confines its observation to the first hour or two – we study memory's birth, but not the long life that follows. We hope that the research we've reviewed will encourage others to venture beyond memory infancy and follow it along its life's course.

Having begun with a quote, we end with one. "The selective retention and retrieval of detailed, remote memories can be supported by long-lasting hippocampal traces which may operate in conjunction with reconstructive processes guided by schematic, vmPFC [and other cortical]

representations. How these two distinct representations interact in any particular recollection, and how they influence each other over longer durations remain questions for future research… Our own view is that memory altering processes such as [neurogenesis, reconsolidation], sleep, [recontextualization, interference, assimilation, regularization, and distortion]playing out in … vmPFC and hippocampus ,[and other brain regions] *sculpt remote memories* by strengthening some, transforming and hence updating others, and eliminating the rest. (Moscovitch & Nadel, 2019, pp 634)" .

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