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

Morris Moscovitch, PhD

University Professor

Departmet of Psychology, University of Toronto, Toronto, Ontario, Canada

Rotman Research Institute, Baycrest, Toronto, Ontario, Canada

momos@psych.utoronto.ca

Asaf Gilboa, PhD

Associate Professor

Department of Psychology, University of Toronto, Toronto, Ontario, Canada

Rotman Research Institute, Baycrest, Toronto, Ontario, Canada

agilboa@research.baycrest.org

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 structures) 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 suggest 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.

Introduction

What is the relation between consolidation and cognition? Surprisingly, many theories of consolidation, particularly those concerned primarily with non-human behaviour, but not

confined to them, view systems consolidation as a physiological process, with little or no consideration of its potential cognitive correlates. By this view, systems consolidation is mediated by the hippocampus, through hippocampal-neocortical interactions, and comes into play automatically only after all the heavy cognitive work is completed (see Craik, 2020; Tonegawa et al, 2015). As early as 1904, Burnham argued against this view of consolidation, noting that consolidation "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." He does not indicate, however, how psychological and physiological processes are related to one another.

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 the memory dynamics that have been dubbed *'systems consolidation'*. We argue that neural changes cannot be understood without reference to psychological properties, and that classical notions of systems consolidation, and its contemporary varaints, may be hindering research efforts for understanding memory dynamics. In doing so we consider various models or theories of memory consolidation which we classify into three types: 1. Standard (Classical) Consolidation Theory which views systems consolidation as a uni-directional process in which declarative memories, initially mediated by the hippocampus, become independent of it as memories are consolidated in neocortex but without a change in their psychological representation. 2. Hybrid Theories that acknowledge the continuing involvement of the hippocampus in representing detailed, episodic memories in perpetuity but also posit that the hippocampus is always necessary for consolidating information in neocortical (extra-hippocampal) structures, with those memories ultimately existing independently of the hippocampus. Here, neocortical consolidation is still a uni-directional

process, and the nature of the psychological representations that distinguish hippocampal from extra-hippocampal memories are left unspecified. Included in these theories, as well as those listed in 3, is the idea that some system consolidation processes are evident in the hippocampus, with changes in neural representation along the anterior-posterior axis, and among the hippocampal subfields. 3. Dynamic systems re-organization theories that posit that interactions within the hippocampus, and between the hippocampus and neocortex (extra-hippocampal structures) are bi- (multi) directional from the moment of acquisition and throughout a memory's lifetime, with the correspondence between psychological and neural representations being an essential aspect of these theories. As the term *systems consolidation* implies a uni-directional process of memory stabilization, we, as proponents of this third view, recommend that it be replaced by the term *interactive systems re-organization* to reflect the dynamic, interactive and multi-directional nature of memory processes and mechanisms.

History and nomenclature

The term *consolidation* 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). 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; Russell, 1948; 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.

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 (repeated, sequential firing) of interconnected neurons which were activated by co-occurring aspects of an experience. Reactivating the cell assembly by stimulating only 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 or synaptic consolidation is a relatively rapid process, lasting on the order of minutes to hours. Disrupting the process of synaptic consolidation leads to memory loss; however, contrary to older notions, even apparently 'stable' memories can become labile again and susceptible to disruption - consolidation may never end (Dudai, 2012)..

Cell assemblies that represent memory are now construed as memory *engrams*, a term coined by Semon (Semon, 1904/1921; Schacter et al., 1978) to refer to the lasting physical changes that accompany an event or experience. He distinguished it from *ecphory*, the process by which retrieval cues interact with engrams to yield memories (Josselyn et al., 2017; Josselyn & Tonegawa, 2020;). The engram provides the initial, dormant substrate that makes memory

possible, but a memory does not exist until ecphory has occurred (Moscovitch, 2012). Like Bartlett (1932; 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 to dynamic systems re-organization). 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 engrams represent vary depending on the neurons forming the engram and their projections. These disturbed engrams, and their precursors, constitute the beginning of *memory systems* and ultimately would also lead to ideas about *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 (about three years in one of their patients, HM) with more remote memories being preserved (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.

Milner's findings, and subsequent research with other amnesic patients (Moscovitch, 1982, 1995, 2012; Squire, 2009), laid the groundwork for our knowledge of *systems consolidation* which is typically far more prolonged than cellular consolidation, beginning within hours, but 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 some cases, cease to depend on structures, such as the hippocampus, that subserved their acquisition.

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 pointers to the distributed neocortical representations of the engram (Teyler & Rudy, 2007; Teyler & DiScenna, 1986; Mosovitch, 1995). 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, possibly through replay of the hippocampal-neocotical ensemble (Wilson & McNauhton, 1994; Buzsaki, 2019), 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; Frankland and Bontempi, 2005)

Early Challenges to SCT

Since its inception following Milner's reports, 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 (Hardt et al., 2009; Miller & Matzel, 2006; Nader & Hardt, 2009; Sara, 2000a, 2000b; 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. 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's (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. 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? Finally, some rodent models argued that some longer (days) retrograde gradients in fact reflect cellular consolidation (Rudy & Sutherland, 2008); moreover, several tasks that are used to demonstrate hippocampal dependence through retrograde gradient experiments, can be performed normally when trained with hippocampal damage (anterograde memory) which is inconsistent with SCT (Sutherland et al., 2010).

More Recent Challenges to SCT

SCT continued to dominate the field despite 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, 2004b, 2005b; 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 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 (Kandel et al., 2014; Moscovitch et al., 2016; Sekeres et al., 2018a; 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 relives the event by reinstating the context in which it occurred (Suddendorf & Corballis, 1997, 2007; Tulving, 1985, 2001, 2002; See chapter 5. 5 by Yonelinas, Ramey & Riddell, 2022 and chapter 2.1 by Ranganath, 2022). 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, By comparison, *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., 2018a; Winocur & Moscovitch, 2011; Winocur et al., 2010).

To account for the extensive retrograde amnesia for episodic memory (context-specific in rodents), and relatively preserved semantic (context-general) memory, Nadel and Moscovitch (1997) proposed that the MTL, and hippocampus in particular, is needed for the retention and retrieval of episodic memories in perpetuity. Because there was 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 obligatorily encodes all information in conscious awareness, whether externally presented or internally generated (Moscovitch, 1992, 1995, 2008).

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, 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 as assumed by SCT.

Having a plausible, alternative theoretical framework to SCT led to a burgeoning of studies and theories 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., 2018a).

 New evidence emerged that was consistent, for the most part, with MTT, greatly enabled by the development of more sensitive measures which targeted those aspects of memory which were at the heart of the debate between SCT and MTT: episodic vs. semantic contributions to remote memories for autobiographical and public events (Kopelman et al., 1989; Kopelman & Marsh, 2018; Levine et al., 2002; Piolino et al., 2003, 2009; Renoult et al, 2020), and schematic vs. fine detail to spatial memories (Herdman et al., 2015; Hirshhorn et al., 2012a, 2012b; Rosenbaum et al., 2000, 2001, 2005b). 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., 2018a; Winocur & 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 (Gilboa et al., 2005; 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., 2018a; 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 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.

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). Although this claim has been disputed (Rosenbaum et al., 2008, 2009), the critique does not apply to studies of patients with damage restricted to hippocampal subfields or output pathways (see above, this section), or to work on animal models where location of lesions or disruption is controlled.

Another objection is that 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) unless they are provided with appropriate guidance. Here, too, the objection does not hold water, as temporally extensive deficits in episodic memory are observed even in studies using recognition (Gilboa et al., 2006a) or 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; see chapter 5.12 by levine, Fan, Simpson & Sokolowki, 2021).

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). 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., 2018a). 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; see chapter 5.12 by Levine et al, 2022).

To date, almost 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. The same pattern of results was observed even when participants narrate memories in the scanner. Gilmore et al. (2021) found that a decline in posterior hippocampal activation with time from memories acquired the same day to ten years earlier, was associated with a comparable decline in functional connectivity between the hippocampus and neocortical regions implicated in memory (see section of Hippocampal Neocortical Interacctions). Consistent with MTT, the decline in activation was accompanied by a decline in internal, episodic details from recent to remote memories.

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., 2001 see reviews in Cabeza & St. Jacques, 2007; Svoboda et al., 2006) to the most recent (see reviews in Sekeres et al., 2018a; 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; see chapter 2.1 by Ranganath, 2022). 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 & Mayes, 2008), multimodal integration (Bonnici et al., 2016), or the processes needed to retrieve (Fletcher, 1998a, 1998b) and monitor episodic memories (e.g. vmPFC; Gilboa et al., 2006b, Moscovitch et al., 2016).

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, depending on the type, 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

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. 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 or rest (Wilson & McNaughton, 1994) (Dinkelmann & Born, 2010; Dudai et al., 2015; Kim et al., 2019). With its focus on the hippocampus, MTT 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 MTT was proposed 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 & Mullally, 2013; Robin & Moscovitch, 2017; Sekeres et al., 2018a; 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, 2012b; 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: Contrary to MTT, 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 titled, "Trace Transformation Theory (TTT): Details, gist, schema, and semantics".

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

Trace Transformation Theory (TTT; Winocur et al., 2007, 2010; Winocur & Moscovitch, 2011; Sekeres et al., 2018a) builds on MTT's foundations but extends its scope to deal with some of MTT's limitations. In its most recent version (Robin & Moscovitch, 2017; Sekeres et al., 2018a), 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; see chapter 7.2 by Varga, Morton & Preston, 2022). *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).

Three basic principles underlie TTT.

1. The hippocampus retains its function in representing detailed, episodic memories (context-specific memories in rodents) as long as they exist, whether they are memories of the past or of episodic simulations of future or imagined events (Addis et al. 2007b; Addis & Schacter, 2012; Addis, 2020; Hassabis et al., 2007; Maguire & Hassabis, 2011; Maguire & Mullally, 2013;

Moscovitch et al., 2016; Viard et al., 2012). The hippocampus does not relinquish this representational function to other structures over time.

2. Systems consolidation is not a unidirectional time-dependent process, but a dynamic multi-directional process in which different forms of memory can co-exist and interact with one another. (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 the form of the memory that is expressed.

3. Each of these psychological 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 even before an event occurs, and thus diverges from the idea that the hippocampus is the gateway to systems consolidation (Gilboa & Moscovitch, 2021). As such, systems consolidation is not the mere relinquishing of hippocampal involvement to the neocortex over time, (in fact, for truly episodic 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, and continues throughout life. Consequently, we believe the term *memory systems re-organization*, rather than systems consolidation, best describes this process neural-psychological process.

The evidence we present accords with a more general principle termed *neural-psychological representation correspondence (NPRC),* namely that each type of representation is mediated by its corresponding structure and vice-versa (Gilboa & Moscovtich, 2021). If episodic memory is mediated by the hippocampus, this relationship should hold regardless of whether the memory

occurred recently or long ago. Conversely, if there is a change in the mediating structure, such as sometimes occurs as memories age, there should also be a corresponding change in the nature of the psychological representation.

Thus, 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 (Gilboa & Moscovitch, 2021; Sekeres et al., 2018a; 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., 2018a), according to NPRC (Gilboa & Moscovitch, 2021).

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 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, 2018a; Squire et al., 1984; Winocur & Moscovitch, 2011). In accord with NPRC, TTT posits that the nature of the transformed memory determines how it will be represented neuraly; 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, 2021)[1].

Systems consolidation in humans: recent evidence

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.

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, and how interactions between the structures are

implicated in the formation, and expression, of episodic memories and schemas.

Time and experience dependent changes in memory representations mediated by the

hippocampus and mPFC: Univarite, fMRI analyses

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[1] Consideration of the full implication of the NPRC principle, and the evidence that semantic and schematic memory traces are created at the time of encoding (Hebscher et al., 2019b), led Gilboa and Moscovitch (2021) 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 consistent with this view.

Using fMRI during encoding and retrieval of memories of the video clips from St-Laurent et al. (2009), Sekeres et al. (2018b) found that at encoding and immediate retrieval, when memory for both central (gist) 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, 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. Also, providing a reminder before test (a blurred small section of a screen shot of the clip which lacks significance on its own), 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 both delay conditions. The reverse held for the hippocampus at encoding and at a week's delay. 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, respectively, to mPFC activation, (Bonasia, thesis; see below in relation to SLIMM model in the section on Theories of Schema).

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, suggesting that only a fraction of hippocampal cells are needed to code memory over extended delays (Ziv et al, 2013).

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, especially pronounced in older compared to younger adults, was 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, but see Söderlund et al., 2012). For memories that remain detailed and context specific over time, both univariate and multivariate analyses (see sections on Multivariate fMRI analysis) 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: retrieving coarse, large scale information about spatial location of remote memories (e.g. venue of wedding) is associated with anterior hippocampal activation, whereas retrieving fine-grained information (seating arrangement) is associated with posterior hippocampal activation (Evensmoen et al., 2013, 2015), and involvement of CA2/CA3/DG subfields whose volume is related to memory precision (Bakker et al., 2008; Yassa et al., 2011) of personal events (Hebscher et al., 2018) or video clips (Chadwick et al., 2014). Thus, damage restricted to CA3 leads to autobiographical memory loss for episodic details, but not semantics, across almost a lifetime (Miller et al., 2020).

Similar results are obtained in neuroimaging studies that employ more traditional laboratory-based stimuli, such as paired associates. Equating performance across all intervals from 20 minutes to 30 days, Du et al., (2019) found that hippocampal activation remained stable across all intervals for associative (relational) memory. By comparison, hippocampal activation declined for item memory, as activation in peri-rhinal cortex and vmPFC increased. Likewise, Viskontas et al. (2009a) found that as recollection of pairs of pictures declined from ten minutes to 10 days, so did hippocampal activity. 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 multivariate pattern analysis (MVPA) and representational similarity, provide an opportunity to relate representations at the neural level to those at the psychological level over time. Bonnici et al. (2012) and Bonnici and Maguire (2017) used MVPA (Chadwick et al., 2010) to track and classify vivid (detailed, context-specific) autobiographical memories over a two year period, and compared them to ten-year old memories. They found that their neural representations remained stable over two years in the 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 at ten. As the memories were of different events, they likely differed from one another in both peripheral and central details. Thus, what distinguished one memory from another may have differed across regions, with posterior hippocampus being sensitive to peripheral details, and mPFC to central details.

Bird and his colleagues (Bird et al., 2015; Oedekoven et al., 2017) used memory for video clips and representational similarity analyses to examine neural reinstatement effects between encoding, and retrieval a day and a week later. They found reinstatement effects that predicted memory performance at 7 days in the posterior left hippocampus and in structures in posterior midline cortex, such as the precuneus and posterior cingulate.

In an EEG study, Larzabal et al. (2020) tested participants' memory of frames from clips they viewed hours, one day and three weeks earlier. Using MVPA of the EEG signal to classify new and old items, they, too, found reinstatement effects that correlated with recollection even at the longest delay which emerged from the same neural processes as at encoding, indicating that that the engram created at acquisition was still viable weeks later.

Applying representational similarity analysis to associative memories, Ritchey et al. (2015 see Univariate fMRI section), 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.

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 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.

By focusing on changes in psychological and neural representations, we should not lose sight of the fact that different aspects of memory, details, gist and schema, can co-exist with one another. Though co-existing, one representation may be dominant and the other dormant or silent, but capable of reasserting dominance, when revived by a reminder (Sekeres et al, 2020) or when promoted by task requirements or retrieval orientation (Rudoy et al., 2009; Aizpurua & Koutsaal,

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2015) (see below for similar effects in rodents in the <u>Systems consolidation in non-human animals: Recent evidence section</u>).

Hippocampal-neocortical interactions: functional connectivity and cross-regional coupling of neural oscillations

As the hippocampus does not act alone, according to TTT, interactions between the hippocampus and neocortex should be maintained even for remote memories as long as they retain their episodic nature, with a decline in such interactions as memories lose their episodic signature. This general pattern, with some variations, has been observed across different indices of interaction including measures of functional connectivity in fMRI studies, and cross-regional coupling of neural oscillations in electrophysiological studies. Functional connectivity between HPC and neocortex was evident during retrieval of autobiographical memory at a single, remote time point (McCormick et al., 2015; Addis et al., 2007a), cross-sectionally at recent and remote time points (Soderland et al, 2012), and longitudinally (Sheldon and Levine, 2013), and of memories acquired in the laboratory (Dolcos et al., 2004; Gais et al., 2007; but see Sterpenich et al., 2009; Cowan et al., 2020). The strucutres to which the hippocampus is functionally connected, and whether it is its anterior or posterior portion, depends on a variety of factors including whether memory is being constructed (aHPC to vmPFC) or elaborated (pHPC to posterior neocortex; McCormick et al., 2015), whether the memory is emotional (aHPC – amygdala; Dolcos et al., 2004), and whether the memory is incongruent with existing schemas (pHPC-mPFC-lingual gyrus, Bonasia et al., 2018).

Recording brain activity with magnetoencephalography (MEG) as participants listened to recordings of 2-7 month old memories (episodic) or a passage from a geograpgy text (semantic), Fuentemilla et al. (2014) identified a peak of theta power within a left MTL region of interest

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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.

In a more recent MEG study which sampled autobiographical memories over a ten-year interval, McCormick et al. (2020), 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. Moreover, using effective connectivity analysis, they showed that mPFC drove HPC activity throughout the entire retrieval phase, consistent with our working-with-memory model (Moscovitch, 1992, Moscovitch & Winocur, 1992).

Other investigators, however, found that under some conditions, HPC activity precedes that of mPFC in retrieving autobiographical memories (Treder et al, submitted). 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 autobiographical 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.

Effects of HPC damage or disruption

According to TTT, HPC damage or disruption by TMS should lead to corresponding declines in HPC-neocortical interactions and in recent and remote episodic memory. Thus, following unilateral MTL lesions or epilepsy, hippocampal-mPFC-posterior neocortical connectivity is disrupted and replaced by mPFC-neocortical connectivity (Addis et al., 2007a; McCormick et al., 2018b) accompanied by declines in episodic memory. Likewise, the difference in gamma synchrony between episodic and semantic memory was not found in a person with severely deficient autobiographical memory (Fuentemilla et al, 2018). Their finding is consistent with Hebscher et al.'s (2019a) observation that applying continuous theta burst stimulation to the precuneus disrupts theta and gamma synchrony between MTL and precuneus in healthy people which leads to a reduction in their episodic autobiographical memory, likely influenced by slowed frontally-distributed activity on MEG early during the construction phase of autobiographical retrieval (Hebscher et al., 2020). Damage to higher-order visual cortex (Greenberg et al., 2005; Ogden, 1993; Rubin & Greenberg, 1998) has similar detrimental effects on episodic memory presumably because of the role visual imagery plays in episodic memory (Greenberg & Knowlton, 2014; Shallice et al., 1994).

Argyropoulos et al. (2019) found that damage to the hippocampus in patients with autoimmune limbic encephalitis, even if confined only to CA3 (Miller et al., 2020), had remote episodic memory loss extended across the entire lifetime. Like others before them (Winocur et al., 2009; Lehmann et al., 2007; reviewed in Sutherland et al, 2019 Sekeres et al., 2018a), they found that the extent of remote memory loss was not directly related the volume of the HPC but, in Argyropoulos et al.'s (2020) study, to volume loss in the thalamus (see also Kopelman, 1999; Kopelman & Marsh, 2018), a region that is becoming increasingly implicated in co-ordinating

activity between mPFC and hippocampus (Varela et al., 2014; Vertes et al., 2007; and in expression of hippocampal engrams in remote memory via CA3 (Vetere et al., 2021). 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).

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 et al., 2007; Eichenbaum et al., 2007; Cooper & Ritchey, 2020; Ritchey & Cooper, 2020). According to TTT, the nature of episodic memory deficits should vary depending on which subfield, or which region along the long axis, was most implicated (Poppenk et al., 2013, Dimsdale-Zucker et al., 2018), as suggested by functional neuroimaging studies on consolidation in normal people (see univariate and multivariate fMRI sections, Bonnici et al., 2013: Bonnici & Maguire 2017 Tompary & Davachi 2017, 2020; Dandolo & Schwabe 2018; and Audrain & McAndrews, 2020).

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

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(Gilboa et al., 2006b; Gilboa & Marlatte, 2017; Moscovitch, 1992). Patients with vmPFC lesions are significantly impaired during processing of schemas (Ghosh et al., 2014), schema-related memory (Stolk et al., 2015; Spalding et al., 2015) and factual semantics (Kan et al., 2009; Hebscher et al., 2016; Hebscher & Gilboa., 2016; O'connor & Lafleche, 2004). On tests of autobiographical memory, however, 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), but not if it is absent (Bertossi et al., 2016).

These different outcomes are to be expected if schemas or scripts serve as scaffolds to support retrieval of episodic details during memory construction (McCormick et al., 2018a; Robin and Moscovitch, 2017). Generation of scripts of familiar everyday activities (e.g. going to a doctor or restaurant), however, is impaired in patients with mPFC lesions (Burgess & Shallice, 1996; Godbout & Doyon, 1995; Godbout et al., 2004; Grafman, 1989; Grafman et al., 1993; Shallice & Cooper, 2012; Sirigu et al., 1995, 1996), as is generation of well-known fairy tales (Gilboa et al, 2006a). 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, performance, consistent with Bonasia et al's (2018) observation in healthy people that that schema- incongruent errors in recalling video clips are negatively related to mPFC activation.

When combined with damage to adjacent orbito-frontal cortex, which control decision responses, faulty monitoring resulting from mPFC damage leads to *confabulation*, a disorder in which participants, without intention to deceive, produce episodic and semantic memories that are patently false and inconsistent with other knowledge (Gilboa & Moscovitch, 2017; Moscovitch, 1989; Schnider, 2008; Moscovitch & Melo, 1997; Gilboa et al., 2006a; Gilboa & Marlatte, 2017; Dalla Barba & La Corte, 2013; Schnider et al., 2017).

INTERACTIONS AMONG MEMORY SYSTEMS

One of the guiding principles of TTT is that 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; Gilboa & Moscovitch, 2021). We now examine how this principle plays out in the formation of schemas and episodic memory, and illustrate how they are interwoven as a result.

 mPFC and hippocampus in formation of schemas

Our working definition of schemas is that they are representations of what is common across a series of events (see chapter 7.2 by Varga et al, 2022). The mPFC is implicated in mediating these representations. One approach to study schema formation, therefore, has been to present items with overlapping_content (e.g., A-B, B-C) and trace their neural and psychological representation during acquisition and retention. Using this approach, Preston and colleagues found that encoding of overlapping information is associated with increased activation in vmPFC, which is related to inference of AC pairs, and functional coupling between vmPFC and hippocampus (Zeithamova & Preston, 2010; Zeithamova et al., 2012; Schlichting et al., 2015; Schlichting & Preston, 2015), which is predictive of subsequent successful inference (inferring A-C). As expected, damage to vmPFC leads to impaired associative inference despite relatively preserved premise pairs learning (Spalding et al., 2015, suggesting vmPFC is needed for integrating new information with retrieved prior knowledge.

In variations of this paradigm, but with the focus on memory of the studied items, several studies have shown greater representational similarity among items with shared content than without shared content. Evident at acquisition, this similarity, as revealed also by MVPA, increased with

time in mPFC (Ritchey et al., 2015; Tompary & Davachi, 2017; Audrain & McAndrews, 2020; Cowan et al., 2020), leading to reduced associative memory and recollection. Similar representational shifts were also observed in the hippocampus, though why such shifts were found in the aHPC in some studies, and pHPC in others, is unclear.

Using a learning approach, Sommer (2017) trained participants on ten different spatial arrays of object-location paired associates, in a human analogue of Tse et al's (2007) rodent study. Participants were followed over 9 months of intensive training with changes to neural representations tracked over the first two days and again at 3 and 6 months. As schemas developed for the over-trained spatially-associated pairs, there was shift in activation from the HPC to vmPFC, and later to vlPFC, the latter being part of a semantic memory network (e.g. Binder et al., 2009; Binder & Desai, 2011). 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. They, too, identified increased activity over time in vmPFC, as well as involvement of angular gyrus and high-level associative visual areas in posterior cingulate. 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 neocortical regions (Yazar et al., 2017).

Together, these studies suggest that episodic memory and schemas are formed at acquisition, coexist and interact with one another via the hippocampus and mPFC, respectively. In

accordance with TTT, changes in the relative contribution of one or the other, are reflected in representational shifts at the neural and psychological level.

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 interact with environment and stored knowledge to interpret the world and help form memory representations (Ghosh & Gilboa, 2014; Gilboa & Marlatte, 2017; see chapter 7.2 by Varga et al, 2022). To date, however, almost all research on schemas, and memory in general, 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 an event 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 schema is *instantiated* to interact with the environment. To test the idea of schema reinstatement, they had participants decide whether face stimuli depicted people with whom they were personally familiar, or judge the schema membership of exemplars (viz. Does "lion" belong to the schema visiting a zoo?; Giuliano, et al., 2021). In both cases, they found that that prior to stimulus onset, there is a period of theta coherence desynchronization between medial prefrontal areas, inferotemporal and lateral temporal cortices, which is reduced in patients with vmPFC damage, especially in those with clinical histories of spontaneous confabulation. Similar post-stimulus oscillatory patterns, but in the alpha and beta frequency bands, were interpreted as evidence of schema instantiation (Giuliano et al., 2021).

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 (Fernández et al., 1999; Liu et al., 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) which show that neurons that are more excitable prior to encoding are more likely to be recruited to form part of the subsequent, consolidated 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.

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 (consolidation) 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., 2016 Paller et al., 2021; Staresina et al., 2013; Tambini & Davachi, 2019), and that are modulated by prior knowledge (Liu et al, 2017). 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.

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 observed even at the most remote time tested.

Episodic, semantic and schematic memory are intertwined

The foregoing suggests that the hippocampus, in interaction with neocortex and other structures, binds into a memory trace or engram, co-activated neurons that reepresent all conscious aspects of an experience, that include schemas, semantics, and perceptual and emotional details (Gilboa & Moscovitch, 2021; Moscovitch, 1992, Moscovitch & Winocur, 1992),. This idea is captured in a recent review on episodic and semantic memory, in which Renoult et al (2019), following 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)." Here, we review briefly only those studies that are relevant for systems consolidation.

Performance on classical semantic memory tests, such a category fluency (generating animal names), is impaired in patients with medial temporal damage (Newcombe, 1969; Gleissner & Elger, 2001; Greenberg et al., 2009; Ryan et al., 2008), presumably because their deficient episodic memory prevents them from using it (e.g.memory of a visit to the zoo) to help them identify exemplars of the category. Likewise, MTL damage or degeneration, accompanied by episodic memory loss, is associated with deficits in naming, reading and recognizing famous people, places and well-known public events, which also ostensibly part of semantic memory, but that have personal significance (Westmacott et al., 2001; Westmacott and Moscovitch,

2003;Wesmacott et al., 2004; Petrican et al., 2010). 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). Waidergoren et al. (2012) also 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'). Consistent with this idea, 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). Conversely, performance on many such tests can be relatively preserved in people with semantic dementia and lateral and infero-temporal damage, as long as their episodic memory is not severly affected (Westmacott et al., 2001; Moss et al., 2003; Maguire et al, 2010; Hodges & Graham, 1998; Graham et al., 1999).

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 a hippocampally-mediated episodic component that contributes to performance. Although the age of the memory was not examined systematically in all these studies, in those where it was, the deficits extended for decades (Westmacott et al., 2004), indicating that it is likely that the type of information sampled drew on memories accumulated over a lifetime.

Evidence from fMRI and single untit rcordings is consistent with the lesions studies. Hippocampal activation is observed during exemplar generation in semantic fluency (Ryan et al., 2009), especially for items generated late in the sequence (Sheldon et al., 2016) and for famous faces encountered in the remote past (Trinkler et al., 2009; Liu et al., 2017). Likewise, single

units in the hippocampus, dubbed "concept cells", 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 (Quiroga et al., 2005; Quiroga, 2012, 2019) suggested that these cells code semantic representations that "constitute the building blocks for declarative memory functions" (Quiroga, 2012, p.592). As the large majority of these cells respond to items with which the person is personally familiar (Viskontas et al., 2009b), 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., 2018a; Renoult et al., 2019).

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. 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 (Moscovitch, 1989, 1992; Moscovitch & Winocur, 2002; Gilboa et al., 2006b; Gilboa & Moscovitch, 2017).

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, 2013. Some cases show deficits in remote, but not recent, autobiographical memory, (Graham & Hodges, 1997; Maguire et al., 2010), whereas others show impoverished autobiographical memory across the lifespan (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 mediated by the hippocampus more easily without the intervention of semantics, whereas verbal stimuli always depend on semantic mediation via inferior and lateral temporal cortex (Irish & Piguet, 2013).

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 without cuing, their recent and remote memory for autobiographical events is impaired; with it, it 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; Irish & Van Kesteren, 2018; Irish & Vatansever, 2020; 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 is mediated by different structures.

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 (see chapter 5.5 by Yonelinas, Ramey & Riddell, 2022). 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 (see below section on Systems consolidation in non-human animals). 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.

Results concerning activation along the long axis of the hippocampus and their functional connectivity are more variable: Some 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 while others show the opposite. Studies on the role of 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

pattern also observed in rodents (see below section on Systems consolidation in non-human animals).

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, 2004 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 & Moscovitch, 2017; Sekeres et al., 2018a). Accordingly, whereas damage to the hippocampus will impair context-specific, episodic memories, and leave schematic and semantic memories relatively spared, damage to mPFC and anterior temporal lobe

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will not only affect schematic and semantic memory, respectively, but will also affect encoding and retrieval of episodic memory under many circumstances.

Systems consolidation in non-human animals: Recent evidence

Findings and conclusions from human studies on the role of the hippocampus and neocortex in systems consolidation are remarkably consistent with those from studies on non-human animals. Because animal studies can exert a level of control and neurobiological interventions not afforded to human studies, some vexing issues in human studies, such as the nature of engrams and the interactions of one region with another at different points in time, can be addressed more clearly in animal studies. By complementing one another, studies on humans and animals produce converging evidence that advances our knowledge of systems consolidation.

We summarize the evidence from animal studies on systems consolidation, and refer the interested reader to Moscovitch & Gilboa (2021) for a more extensive treatment. Before proceeding, we remind the reader that we consider detailed, context-specific and context general memory in animals to be the homologues of episodic and non-episodic memory in humans. At the anatomical level, the ventral and dorsal hippocampus in rodents are the homologues of anterior and posterior hippocampus in humans.

The hippocampus is necessary for retention and retrieval of recent and remote context specific memory

Early lesion studies on systems consolidation in animals showed a temporally-graded memory loss following hippocampal damage, such that recent, but not remote memories, were affected. The most commonly used paradigm to study systems consolidation in rodents is contextual fear conditioning (Kim and Fanselow, 1992) in which 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. Consitent with predictions from SCT, initial tests showed that hippocampal lesions led to memory loss at short (within a day) but not at long (days or weeks) delays following acquisition. Similar results were obtained with other paradigms that were amenable to context manipulations (for review see Winocur et al., 2010). The preserved remote memories were mediated by extra-hippocampal neocortical structures, particularly the medial prefrontal cortex (mPFC), which included the anterior cingulate cortex (ACC), as lesioning or disrupting them led to remote memory loss (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.

Working within the framework of TTT, Winocur and his colleagues (2010; Sekeres et al, 2018a) and others (Wiltgen & Silva, 2007; Wiltgen et al., 2010) challenged this interpretation. By testing animals in the same or different context from acquisition, they showed that different memories mediated performance at the two time points: context specific at recent time points (freesing only in the same context), and context-general at remote ones (freezing in both contexts) as memory for the specific context declined. Damage to the mPFC had the opposite effect (Jasnow et al., 2017. In accord with NPRC, the neural representation reflected its psychological counterpart.

Studies on hippocampal and neocortical activation using immediate early gene expression, and optogenetics, provide converging evidence to support these conclusions. Sekeres et al. (2018b) and Wiltgen et al. (2010), found greater activation of the hippocampus than of neocortex at short delays, when the memory was context-specifc, than at long delays, when the memory was

context-general. The reverse patern held for the neorcotex. Differences between hippocampal and neocortical activation was an index of context-specificity (Wiltgen et al., 2010).

Such representational shifts, from context-specific to gist-like memories, are also observed within the hippocampus, with some reseearchers noting that activation of engram cells in DG diminishes with time as it increases in CA3 over 30 days (Tayler et al., 2013; Guo et al., 2018). Others, however, attributed a decline in specificity to diminished CA3 contribution, with CA1, and related neocortical regions, contributing to context-general memory at recent and remote time-points one month (Cullen et al., 2015; Jasnow et al., 2017) and 6-12 months later (Lux et al., 2016; Atucha et al., 2021).

Systems consolidation is not a unidirectional, but a dynamic, multi-directional process, in which different forms of memory can co-exist and interact with one another.

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 & Hardt, 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). In accord with TTT, Winocur et al. (2009) showed that these changes in neural representation are accompanied by corresponding changes in functional/psychological representation. Once revived, the previously context-general, hippocampally-independent memory reverted to being a context-specific and hippocampally dependent (Finnie et al, 2018).

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, or elimination of competing structures, to be activated sufficiently to be expressed in behaviour. This interpretation is supported by evidence that c-Fos expression in the dorsal hippocampus remains greater in the training than novel context, even at remote time point, and by evidence that hippocampal, context specific memories can be revived by optogenetic stimulation 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). Also, removing the influence of mPFC (schema) and CA1 (gist), eliminates the context general memory at both delays, enabling the context-specific memory to be revealed (Cullen et al., 2015; Lux et al., 2016), whreas anhancing or diminishing DG influences on CA3 increases or decreases context specificity at long delays (Guo et al., 2018).

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; Guskjolen et al., 2018), at which point it may come to dominate behaviour.

As these examples illustrate, context specific and context general memories can co-exist from acquisition to retrieval at recent or remote time points. Dynamic interactions among the structures mediating the memories determine which type of memory is expressed in behaviour and which is dormant/silent or masked (Moscovitch, 2012) according to principles of TTT and NPRC.

Schemas and context-specific memories (episodes): Their acquisition and utilization

Studies of memory allocation found that neurons that are most excitable prior to the occurrence of an event are recruited to form the engram of that event suggesting that memory formation effectively begins before an event can be encoded (Josselyn & Frakland, 2018) . Successful memory retrieval depends on reactivating these engrams (see Sadeh et al, 2019, above for humans). Although such processes have been observed for acquisition of emotional, associative and spatial memory, it is not known whether they also apply to schemas. Using trace CS-US conditioning, and recording from mPFC neurons, Takehara-Nishiuchi et al (2020) found that a subset of them showed elevated responses to the pairing within a minute, which generalized to a CS that was not used in training. Evidence that context-general memories can be formed rapidly at encoding, suggest that similar allocation processes may apply to them.

Other mPFC engrams, though formed rapidly, seem to take longer to become functionally viable. Kitamura et al. (2017) identified such mPFC engrams which initially were "silent", becoming viable only at two weeks when hippocampal engrams gradually receded and memory generalized. Removng competition from hippocampal engrams by deactivating them earlier led to accelerated mPFC engagement and contextual generalization (De Sousa et al., 2019). This finding suggests that viability of mPFC engrams may depend as much on eliminating competition with hippocampal engrams, as on a prolonged consolidation process. The rapid generalization of memories that are cortically dependent is consistent with the NPRC principle (Gilboa & Moscovitch, 2021) 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).

Having been formed, how do schemas influence acquisition and retention of new memories? In a series of studies, Tse and colleagues (2007, 2011; Wang et al., 2012, cf. Hasan et al., 2019) trained rats over several weeks to form a schema consisting of eight flavour-place associations in an "event arena". The establishment of such mPFC schemas was critically dependent on the hippocampus (Hasan et al., 2019). Once established, however, this schema accelerates the consolidation of new flavour-place associations from the hippocampus to mPFC. 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. Winocur et al. gave rats extensive experience living in a complex maze, resembling a village, open to its surroundings. Once the village schema was established, they lesioned the hippocampus. Rats with hippocampal lesions learned to navigate from start boxes towards goal locations in the village as quickly as controls, and much more quickly than rats with hippocampal lesions who had no prior knowledge (experience) of the village. The way they navigated, however, indicated that rats with intact hippocampi represented the village differently from rats with lesions, as predicted by TTT. When the most direct route to the goal was blocked, intact rats 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) and Farovik et al. (2015) used neural similarity analytic approaches, akin to representational similarity analytic methods used in human imaging studies,

to show that the nature of schematic representations within the rodent hippocampus and orbitofrontal cortex differ from one another. When new items are learned within previous spatial contexts, hippocampal 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. By contrast, orbitofrontal neural representational similarity reflects a hierarchy driven by stimulus reward value.

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, mediated by the hippocampus.

What is clear from these studies 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.

Theories of Memory Consolidation

A crucial question that we did not address directly in reviewing the evidence is: What are the psychological processes that underlie memory transformation, leaving it to others to deal with

the neurobiological processes? 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., 2019); by extraction of statistical regularities among events (McClelland et al., 1995; Schapiro et al., 2017b); 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., 2007b; 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 crucial tenet 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 from acquisition, to retention, to retreival, and are usually bi-(multi)directional between the hippocampus, neocortex, and other structures, SCT and its derivatives posit 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 or both, but either challenge crucial aspects of these 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.

Complementary Learning Systems

Perhaps the most influential computational model of systems consolidation, *Complementary Learning Systems* (CLS; McClelland et al., 1995; Norman, 2010) stipulates that memories must be encoded rapidly in the hippocampus before they can be integrated slowly into neocortical representations in order to prevent 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, during sleep and wakefulness, induces gradual changes in neocortical semantic/schematic networks so that the new memory traces can be integrated with them and become independent of the hippocampus.

CLS computationally simulates systems consolidation according to the principles that govern SCT. CLS's weaknesses, however, are also those that bedevil SCT. The neocortical system into which episodic memories are integrated is a semantic network or knowledge structure that is not suited for supporting context-specific information that is the hallmark of episodic memory. Episodic memories are effectively lost in that model; only semantics or schemas remain. Even if we concede that the neocortical system can support episodic memories, damage to the hippocampus should leave them unscathed. Yet the evidence we reviewed indicates that hippocampal damage impairs even remote episodic memories.

To counter the challenge that some neocortical memories are acquired rapidly (Tse et al., 2007; Sharon et al., 2011; 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. Such a process may be 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) mediated by peri-rhinal and anterolaeral temporal cortex, without benefit of the hippocampus (Atir-Sharon et al., 2015; Merhav et al., 2014, 2015; Sharon et al., 2011; Hebscher et al, 2019b). Contrary to CLS, however,inconsistent memories, may never be fully integrated into neocortex (Bonasia et al., 2018; van Kesteren et al., 2012) yet remain viable, and dependent on the hippocampus, for an extended time. Moreover, neocortical learning mediated by mPFC and not related to prior knowledge can also be rapid, occurs concurrently with learning in the hippocampus, and sometimes is necessary to support the rapid acquisition of hippocampally-based memories (Takehara-Nishiuchi, 2020; Jasnow et al, 2017; Tompary & Davachi, 2017; 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.

Complementary Memory Systems

By assigning complementary roles to the hippocampus and neocortex, Takehara-Nishiuchi's model resemblesCLS, but unlike it, she focuses on the crucial involvement of the mPFC in the formation of episodic memory and schemas. She presents evidence from behavioural, lesion, electrophysiological and molecular studies showing that mPFC, like the hippocampus, is

implicated in the encoding of new experiences (Lesburgueres et al., 2011; 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.

Schema theories and their influence on memory formation and long-term retention

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; chapter 7.2, by Varga et al, 2022). Schema theories work with a loose definition of schemas, often using the term interchangeably with general knowledge, context general information, and semantics. Although Gilboa and Marlatte (2017) took care to specify what distinguishes schemas from other types of prior knowledge,

most studie on schemas rely on much looser definitions, effectively treating schemas as any type of prior knowledge that is declarative but not episodic.

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, This framework relies heavily on neural substrates, rather than psychological representation, 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. When congruence is high SLIMM predicts rapid neocortical learning that is independent of the hippocampus, and may even lead to hippocampal inhibition by mPFC which, in turn, leads to suppression of memory for event details that are unrelated or incongruent with the active schema. 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. 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).

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 by (Greve et al., 2019) with the additional finding that incongruency influences memory at encoding whereas congruency also exert its effects post-encoding (but see Wynn et al., 2020). Findings by Bonasia et al. (2018) suggests that similar relationships may hold for remote memories.

By contrast, that vmPFC inhibits MTL during encoding of congruent events has only rarely been demonstrated (van Kesteren et al., 2012). More troubling for SLIMM is that several studies have reported increased coordination between vmPFC and HPC during encoding of schema-congruent information (e.g. Liu et al., 2017 Sommer, 2017), and Bonasia et al. (2018) found equivalent MTL activation for the two types at encoding.

These latter findings are consistent with alternative theories of schema related learning that posit that schema formation relies on the HPC (Tse et al, 2007; Wang et al, 2010), and that 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). Functionally, Preston and Eichenbam's 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, promoting integration or assimilation of new incompatible information into existing memory networks. Thus, 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.

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. From the point of view of TTT and the evidence adduced to support it, none of the models note whether memories integrated into schemas retain or lose their episodic signature.

Interference models

In comparison to schema models, interference models are very sensitive to changes in representation. 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 (but see Sutherland et al's, 2020). Like MTT/TTT, Yassa and Reagh (2013) 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 leading to competitive interference among them. In neocortex, only those elements that overlap are retained, enabling the slow formation of semantic memories or schemas, as proposed by CLS and MTT. 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.

It is not always the case, however, that remote memories contain more illusory details than recent ones. Whereas memory quantity and episodic richness declines with retention interval, accuracy often remains high, sometimes on the order of 90%, 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.

Contextual Binding Theory uses the effects of contextual drift, which is the change over time in environmental, cognitive, and emotional context, and their corresponding neural representations to account for systems consolidation (Folkerts et al., 2018; Howard & Kahana, 2002; Long & Kahana, 2019 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 (see, also, Chapter 5.11 by Manning, 2021).

By their own admission, Yonelinas et al. (2019) note that Contextual Binding Theory shares most of its core assumptions with MTT/TTT, acknowledging the pivotal role that context plays in accounting for episodic memory and forgetting. Unlike MTT/TTT, however, Contextual Binding Theory says little about the role of schemas and the interactions between mPFC and hippocampus in their acquisition, maintenance and instantiation. These, it should be

acknowledged, all play 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.

Sleep has acquired a prominent role in research on memory (Dudai et al, 2015), 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 section on Interactions between memory systems). Studies on targeted memory activation during sleep in humans (Berkers et al., 2018; Hu et al., 2020; Lewis & Bendor, 2019; Paller et al., 2021; Rudoy et al., 2009) and on sharp wave ripples which accompany memory replay in rodents (Buzsáki, 2015) and likely in humans (Norman et al., 2017, 2019; Vaz et al., 2019, 2020) suggest that it is more replay, than absence of interference, that is crucial. Eliminating sharp wave ripples during sleep leads to memory loss (Buzsáki, 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).

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 and related

theories, 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. In most cases that have been examined closely,

the two have been shown to differ from one another (see section on Multivariate analyses and

memory representations in system consolidation). In the few studies that have used the multiple learning episodes to bolster memory representation in non-hippocampal sites as (Frankland et al., 2006; Lehmann et al., 2009) it may be the case that the extended learning afforded the rat the opportunity to become acquainted with non-configural features (Rudy & Sutherland, 1989) that distinguish one learning environment from another, and whose association with shock does not depend on the hippocampus (Hardt & Nadel, 2018). 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 (2011; Sutherland et al, 2019) 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. MTT/TTT concedes this point. Mindful of findings in humans (Viskontas et al, 2000) and rodents (Winocur et al, 2010) on lesion size, this claim has been dropped in more recent formulations of TTT (Winocur & Moscovitch, 2011; Sekeres et al., 2018a). Instead, noting the burgeioning literature on specialization along the long axis, the function of hippocampal subfields, and connectivity with each other and with extra-hippocampal structures reviewed above on recent and remote memory (Ferguson et al., 2019; Barry et al., 2020), we now consider 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.

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. 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. We know from studies in humans, however, that re-studying the same material

has very different effects than retrieval practice behaviourally (Karpicke & Roediger, 2008; Roediger & Butler, 2011; Roediger & Karpicke, 2006, 2018).and neurally, on the hippocampus, mPFC (Wing et al., 2013; Brodt, et al., 2016, 2018) and parietal cortex (Gais et al., 2007) 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 et al. (2019), 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., 2017a). 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/memory re-organization (Nadel et al., 2000).

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. Barry and Maguire (2019a, 2019b), however, take Yassa and Reagh's (2013) recontextualization proposal to its extreme, arguing 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. 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).

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 (Ziv et al, 2013; Pavlowsky et al., 2017; Hsieh et al., 2017; Attardo et al, 2018).

As noted earlier, studies on reconsolidation, (see section on System Consolidation is not unidirectional) and retrieval through optegenetic stimulation or strong environmental cues (Guskjolen et al., 2018; personal communication) of memories forgotten as a result of neurogenesis, suggests that these hippocampal mediated memories were not lost but merely inaccessible. Likewise, degraded 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). 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 (2019a; 2019b) model than that from rodents. As Alba and Hasher (1983 noted in their review, evidence is lacking for a radical reconstructive view of memory that relies on schemas. 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). Note that even the distorted, schema-driven memories of Bartlett's famous War of the Ghosts story retained details specific to its origins.

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), monitoring its output, and initiating the process anew if the output is found wanting (Moscovitch, 1989, 1992; Moscovitch & Winocur, 1992). 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).

Let us relate an anecdote that indicates how resilient context-specific memories are, and how unlikely they are merely to be reconstructed. A few years ago, one of us (M.M.) took his ten-year old grandson to a Raptors' basketball game. During a security check, M.M. was told he could not bring his yellow Swiss-army pen-knife into the arena. Instead of having them confiscate it, M.M. hid it inside the bumper of a car that was displayed in the lobby. At the end of the game, after we left the arena, M.M. went to retrieve his 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 bumper of a car is not a typical hiding place for a knife. With these thoughts in mind, M.M. asked his now 14-year old grandson, if he remembered what happened when he took him to the Raptors' game. He remembered, without prompting, that M.M. was stopped at security because he had a pen-knife.

When M.M. asked him the colour, he said, "Yellow?" M.M. asked if he remembered what M.M. did with it, and he immediately replied that M.M. hid it under a car's bumper in the lobby. M.M. asked him if he had thought of this event since then, and he replied he had not.

Conclusion

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 survived scrutiny and determine which open up avenues of discovery and which lead to dead ends. In the meantime, the principles enunciated at the beginning of the paper (pp 18-20) can serve as a foundation for a new theory of systems consolidation

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