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Memory systems 2018 – towards a new paradigm

J. Ferbinteanu

Dept, of Physiology and Pharmacology, Dept, of Neurology, SUNY Downstate Medical Center, 450 Clarkson Ave, Box 31, Brooklyn, NY 11203

Abstract

The multiple memory systems theory (MMS) postulates that the brain stores information based on the independent and parallel activity of a number of modules, each with distinct properties, dynamics, and neural basis. Much of the evidence for this theory comes from dissociation studies indicating that damage to restricted brain areas cause selective types of memory deficits. MMS has been the prevalent paradigm in memory research for more than thirty years, even as it has been adjusted several times to accommodate new data. However, recent empirical results indicating that the memory systems are not always dissociable constitute a challenge to fundamental tenets of the current theory because they suggest that representations formed by individual memory systems can contribute to more than one type of memory-driven behavioral strategy. This problem can be addressed by applying a dynamic network perspective to memory architecture. According to this view, memory networks can reconfigure or transiently couple in response to environmental demands. Within this context, the neural network underlying a specific memory system can act as an independent unit or as an integrated component of a higher order meta-network. This dynamic network model proposes a way in which empirical evidence that challenges the idea of distinct memory systems can be incorporated within a modular memory architecture. The model also provides a framework to account for the complex interactions among memory systems demonstrated at the behavioral level. Advances in the study of dynamic networks can generate new ideas to experimentally manipulate and control memory in basic or clinical research.

Keywords

memory systems; memory architecture; dorsal striatum; hippocampus; amygdala; spatial memory; spatial navigation; cue-response associations; affective memory; habits; cognitive memory; place learning; response learning; dynamic networks

Motto: ‘For I was afraid of memory; I knew that our memories and reminiscences are like icebergs. We see only the tips in passing, but the mass of land under water slips by unseen and inaccessible. We do not feel their immeasurable weight simply

Corresponding Author: Janina Ferbinteanu, Phone: 718-270-1796, janina.ferbinteanu@downstate.edu.

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because they lie submerged in time, as in water. But, if we carelessly find ourselves in their way, we shall run aground against our own past and be shipwrecked.'

Father Theoctist Nikolsky in Milorad Pavić-Dictionary of the Khazars

Introduction

In Pavić's *Dictionary of the Khazars*, the peculiar Father Theoctist Nikolsky is afraid of memory because the indelible imprints of the past on his mind can act as a self-directed palimpsest. The insight of the imaginary character in Pavić's book - that memory has eccentric properties - is scientifically accurate however and ironically, we gained it in this real world through a man struggling with the equally irregular but quintessentially opposite problem. On September 1, 1953 Henry Molaison, a young neurological patient at Hartford hospital in Connecticut, underwent bilateral surgical resection of medial temporal lobes to control epilepsy and woke up (almost) cured of epilepsy but with severe amnesia that lasted for the rest of his life. The 1957 case report on Molaison (or H.M., as he is best known) by William Scoville and Brenda Milner (Scoville & Milner, 1957) prompted hundreds of studies extending across many years that in turn led to the formulation of the multiple memory systems theory (MMS) of memory and the first model of memory architecture, the medial temporal lobe memory system (Squire & Zola-Morgan, 1991). According to this perspective, phenomenologically different types of memories result from the activity of distinct memory modules or systems, each with its own style of processing and properties. The memory deficits exhibited by H.M. and other patients with similar clinical profile are explained by damage to the medial temporal lobe, the neural basis of a system dedicated to memory for facts and events, also known as declarative memory. Other types of memories, collectively referred to by the portmanteau word of 'procedural' to convey the idea that they express through overt, non-verbal actions, are thought to be dependent on several other distinct memory systems. Memory modules are postulated to operate independently and in parallel, meaning that information flows through all of them at the same time while processing within a given module occurs autonomously (Schacter & Tulving, 1994; Squire & Zola-Morgan, 1991; White & McDonald, 2002; Squire & Zola-Morgan, 1988). It is significant for the subsequent discussion to keep in mind that the medial temporal lobe memory model and all the other models that followed encompass two distinct tenets. The most fundamental one states that memory is not unitary but modular; this idea has remained consistent across many years. The second tenet is the specific classification of memory systems, which has varied across authors; the 'medial temporal lobe/other systems' is one of several such classifications and it is currently the most accepted.

The idea that there are multiple memory systems has successfully organized memory research for many years to the present. The field has made good progress in several directions as for example in refining the definition of memory system, integrating the animal and human literature, and understanding the memory deficits associated with different types of brain damage. Nonetheless, the general principles of how distinct memory systems may combine to support behavior remains poorly understood. This is an aspect of fundamental importance because in natural settings organisms encounter complex situations during which

they need to engage different types of learning and need to use flexibly different memory-based behavioral strategies, shifting rapidly among them within the same behavioral episode if need be. These conditions are much different from lab experiments in which cognitive functions are teleologically targeted, typically by requesting animals to learn one thing at a time. New empirical data now suggest that the solid evidence resulting from the much simpler settings created in the lab may not be always valid for the messy experiences characteristic of real life situations.

These new data suggest that the empirical dissociations at the basis of the multiple memory systems theory are not valid in all circumstances, but rather depend on past experience; that memory networks are plastic to a larger extent than so far appreciated, and that what constitutes a memory module is a variable rather than a constant. Here, I provide a brief review of the origin and subsequent development of multiple memory systems theory, highlight several empirical findings that cannot be easily accommodated within the current view, and I propose a dynamic network model of memory systems which may provide a fruitful path for further development. The goal of this paper is not to provide a comprehensive review of the large body of literature pertaining to memory organization in the brain or an in-depth discussion of various aspects of the multiple taxonomies proposed in the memory field; such an endeavor would certainly occupy an entire book. Here, I rather aim to make the point that based on the selectivity of memory impairments that localized damage to brain circuits were found to have, the thinking in the field evolved from the perspective that memory is unitary and a general function of brain circuits, to the idea that memory is modular and resulting from the specialized activity of individual brain networks; currently, there are multiple accounts of this modularity and here I will present several of them. Against this background I will discuss several data sets that seem to challenge this conclusion; and I will suggest a way in which they can still be compatible with a modular organization of memory. The new data are intriguing because they indicate that core structures of memory modules, whose processing style is thought to determine the nature of the memories they support, can in certain circumstances support a quite different type of memory. Specifically, hippocampal activity, thought to support flexible representations, can become necessary to support behavior based on a rigid association between an individual stimulus and a motor response; and vice-versa, the lateral dorsal striatum activity, thought to support inflexible associations between individual stimuli and motor responses, can become necessary to spatial navigation, a behavior in which flexibility is key. According to the offered model, the neural networks underlying each memory module are intrinsically plastic at multiple temporal and spatial scales; as such, they respond to situational challenges by reconfiguring (as defined in the network neuroscience field, detailed below) and/or engaging in transient coordination among themselves to form temporary meta-networks. Depending on the situation, the large-scale network that guides behavior at a certain point could encompass the neural networks of more than one type of memory circuit, integrating the functions and processing styles of multiple memory circuits in a meta-system which should be understood not as a sum of its parts, but as a qualitatively new entity. This perspective would offer an adequate account for the fact that at times, otherwise self-sufficient memory systems are neither distinct nor operate independently and in parallel to support behavior. Second, the idea of a memory meta-system would also offer a conceptual framework for

investigating the mechanisms of complex interactions and transfer of information between memory networks. Third, allowing for the possibility that the representations of distinct memory circuits can not only combine as distinct elements, but be thoroughly integrated would open new roads in understanding the nature of mnemonic representations in the brain and the way they can lead to coherent behavior.

1. The theory of multiple memory systems

The idea that there are different types of memories originated before H.M.'s case, in the Tolman-Hull debate on multiple types of learning which took place at the beginning of twentieth century. At that time, Hull and Thorndike were supporters of the view that stimulus-response (S-R) associations were sufficient to generate adaptive behavior in rats by creating long S-R chains, each response bringing about the next stimulus (Thorndike, 1932; Hull, 1930). In contrast, Tolman argued that in addition to S-R representations which were the basis of inflexible chains of actions, animals also form flexible cognitive representations by learning stimulus-stimulus (S-S) associations (Tolman, 1948; Tolman, Ritchie, & Kalish, 1946). Tolman and his collaborators conclusively demonstrated their point by pitching one type of memory against the other in a series of ingeniously designed experiments. Tolman's experimental approach has been fruitfully used later to set the foundation for the memory systems theory (Box 1).

Ten years after Tolman's work cited above, evidence started to emerge that the neural bases of the different types of memories were also distinct. The surgical resection of medial temporal lobes in patient H.M. was followed by a profound amnesia, a loss of the ability to learn and remember factual information or autobiographical events (collectively referred to as *declarative memory]* Scoville & Milner, 1957; Penfield & Milner, 1958). The amnesia was both anterograde, for events occurring after the surgery, and temporally graded retrograde, meaning it affected events occurring during a finite number of years preceding the surgery. Despite the severity of his amnesia, H.M. could however learn motor skills, a finding confirmed in other patients with similar type of damage (Corkin, 1968; Milner, Corkin, &Teuber, 1968). Typically, these people reported no memories of a learning experience, but their performance nonetheless improved at normal rate in the motor skill tasks they were performing in the lab. Later research grouped motor skills memories and habits in a category known as *procedural memories*, characterized by gradual acquisition through repetition, expression in the absence of conscious recollection, and inflexibility (Reber, Knowlton, & Squire, 1996; Knowlton, Mangels, & Squire, 1996; Cohen & Squire, 1980; Bayley, Frascino, & Squire, 2005). Procedural memories were found to be dependent the neostriatum, a part of the basal ganglia (Heindel, Butters, & Salmon, 1988). Furthermore, other work reported that amnesics' actions would indicate memories of events with emotional valence combined with a thorough inability of consciously recollect these events (Nicolas, 1996) (Weiskrantz & Warrington, 1979).

Prompted by these findings, studies in animal models and clinical population provided examples of *double dissociations*, in which damage to brain area 1 affects behavior A but not B, while damage to brain area 2 has the opposite pattern of effects. This type of evidence constituted foundation for the idea that different neural networks support distinct types of

memories. Complementary to it was evidence provided by *disconnection* studies, in one of two distinct brain structures were lesioned, each in a different cerebral hemisphere; if followed by memory deficits at the behavioral level, then these data demonstrated that the two brain structure were supporting the same memory function (for an excellent summary of this type of work see Hunsaker & Kesner, 2018). Extensive work in animal models replicated results from the human studies and the literature converged in support of the idea that declarative memories, which involve the cognitive S-S flexible representations that Tolman was describing, depend on the medial temporal lobe (especially the hippocampus), while procedural memories, which involve S-R associations, depend on the neostriatum (lateral dorsal striatum in rats; Saint-Cyr, Taylor, & Lang, 1988; Packard, Hirsh, & White, 1989; Packard & McGaugh, 1992; Squire, 1992; Squire, Knowlton, & Musen, 1993; Squire & Zola-Morgan, 1991; Devan, McDonald, & White, 1999; Devan & White, 1999; Whishaw et al., 2007; Yin & Knowlton, 2004; Aggleton & Passingham, 1981; Aggleton, Neave, Nagle, & Sahgal, 1995; Ennaceur, Neave, & Aggleton, 1996; Gaffan, Bannerman, Warburton, & Aggleton, 2001; Burwell, Saddoris, Bucci, & Wiig, 2004; Wiig & Burwell, 1998; Bucci, Phillips, & Burwell, 2000; Cook & Kesner, 1988; Hunt, Kesner, & Evans, 1994; Kesner & Hardy, 1983; Kesner, Walser, & Winzenried, 1989).

Work with animal models permitted not only determining the functional role of different brain circuits, but also revealing the nature of neural activity in these networks. In 1971, it was found that the hippocampal principal neurons fire in spatially selective manner and these cells became known as *place cells* (O'Keefe & Dostrovsky, 1971). Several years later O'Keefe and Nadel gathered anatomical, neurophysiological, behavioral, and psychological data from both human and animal literature to combine Tolman's concept of cognitive map with Hebb's idea that neurons that 'fire together, wire together' to form processing units called 'cell assemblies' (Nadel & O'Keefe, 1974; O'Keefe & Nadel, 1978; Hebb, 1949). Aside of systematizing a large body of data that had looked until that time more like disparate facts, the remarkable accomplishment of this work was to essentially embed Tolman's cognitive map in the brain by describing how the spatially selective activity of hippocampal neurons may form a flexible representation of space that could guide behavior. This process *was* postulated to be the function of the hippocampus-based memory system called *locale* while in contrast, the *taxon* system was involved in generating inflexible routes. Furthermore, the authors proposed that the hippocampal cognitive map could provide the basis for the deep semantic structure of language. Thus, the cognitive map could expand its relevance from the spatial domain, to which the place cell recordings belonged, to the larger declarative domain, to which the neuropsychological literature spoke. Recent empirical findings suggest that this is indeed the case (Aronov, Nevers, & Tank, 2017).

A different brain structure, the amygdala, had been linked to emotional memories as early as the late 1930's, but the significance of this finding took longer to be fully acknowledged (Klüver & Bucy, 1938). More carefully controlled lesion and behavioral assessment procedures confirmed the emotional nature of amygdala's function and demonstrated that its lateral and central nuclei are involved in assigning value to individual stimuli which can predict positive or negative reinforcement (Weiskrantz, 1956; Jones & Mishkin, 1972; Aggleton & Passingham, 1981). Collectively, the experimental work on amygdala established that this structure was the neural basis of learning associations between a

stimulus and a reinforcer (S-Rf), a type of learning demonstrated by classical conditioning paradigms. The gist of these procedures is that the animal is not required to produce an overt motor response. Instead, it is passively presented with pairings between an initially neutral stimulus and a stimulus that naturally elicits a positive or negative affective response (unconditioned stimulus, US). For example, in fear conditioning an auditory tone is paired with mild electrical shock. After a number of such pairings, the formerly neutral stimulus starts to elicit the affective response by itself (fear in this case) and it becomes a conditioned stimulus, CS, while the learned fear response is known as conditioned response (CR; Zola-Morgan etal., 1991; Selden et al., 1991; Aggleton & Passingham, 1981). Experimental work conducted somewhat later demonstrated double dissociations between affective memories on one hand; and either declarative or procedural memories on the other hand (Bechara et al., 1995; Zola-Morgan etal., 1991; Selden etal., 1991; McDonald & Hong, 2004; McDonald & White, 1993; Phillips & LeDoux, 1992; Phillips & LeDoux, 1994).

In the course of investigating memory deficits in amnesics, research revealed yet a different type of memory spared in these patients that became known as *priming* (Tulving & Schacter, 1990; Schacter, 1992). The basic procedure in priming testing is to first present subjects once with a word or a picture (study phase) and then ask them at a later time to undergo a completion task (test phase), in which fragments are to be completed with whatever word or picture, respectively, comes first to mind. Normal people tend to produce the word or picture that they saw during the study phase, indicating memory for that information. Amnesic patients show the same phenomenon, although they could not recollect anything about the previous events (Warrington & Weiskrantz, 1968; Warrington & Weiskrantz, 1970; Warrington & Weiskrantz, 1974). Two subcategories of priming, repetition and semantic, have been introduced to distinguish between facilitation in processing of information after previous exposure to it in the perceptual vs. the cognitive domains; despite the fact that they are both referred to as ‘priming’, these two categories are considered distinct forms of memory and only repetition priming has been proposed to be a distinct category of learning, operating at the perceptual, pre-semantic level (Tulving & Schacter, 1990). More recently, Gupta and Cohen proposed that skill learning and repetition priming utilize the same unique underlying mechanisms that characterizes procedural learning in general (Gupta & Cohen, 2002).

The studies cited above strongly suggested that memory is not unitary but modular and that these modules operate independently of each other even as they might be active at the same time. Initially one, then two, then eventually six distinct memory systems were acknowledged in the *medial temporal lobe (MTL) model* of memory systems: declarative, comprised of episodic and semantic conscious remembering that can be reported verbally; affective; procedural (skills and habits); priming; classical conditioning involving skeletal responses (e.g., conditioning of nictitating membrane); and non-associative learning (habituation and sensitization), respectively (Squire & Zola-Morgan, 1988; Squire & Zola-Morgan, 1991; Squire, 2004). Each of these memory systems had a core neural structure whose processing style was reflected in the characteristics of the memory type it produced (Fig. 1A; Squire, 2004).

What is a memory system?—It would be tempting to think that once it became clear that different neural circuits supported different kinds of memories, the formal definition of the concept of memory system simply followed. This is not however true. It is difficult to pinpoint precisely when the concept emerged. In mid 1950's, the term referred to a neural circuit which enables the organism to acquire memories as for instance during a conditioning paradigm (Boycott & Young, 1955). A more complex definition offered that the memory system is a neural circuit able to store long term experiences that result in overt behaviors from which the organism later receives significant feedback (Young, 1965; Young, 1962). The memory process was postulated to have some degree of generalizability, allow correct reading of information from storage, involve motivation and reward, and guide behavioral choices. The memory mechanisms were conceived as comprising several components and operations. In this account, memory was still seen as unitary and S-R associations were invoked to explain the report on H.M. by Penfield and Milner (Penfield & Milner, 1958). However, as an ever-larger body of empirical data revealed that different types of memories were supported by distinct parts of the brain, the perspective in the memory field started to change and the idea that memory is modular gained traction (Milner, Pribram, & Broadbent, 1970; Warrington & Shallice, 1969; Kesner & Conner, 1972; McGaugh et al., 1972; Tulving, 1972; Hirsh, 1974). As mentioned above, O'Keefe and Nadel strongly promoted this perspective by describing two distinct systems, the *locale* and the *taxon* (O'Keefe & Nadel, 1978). This work promoted the articulation and fine-tuning of the theory in the subsequent years (Schacter, 1985; Squire & Zola-Morgan, 1988; Heindel et al., 1989; Squire et al., 1993; Squire & Zola-Morgan, 1991; Tulving & Schacter, 1990; Schacter, 1992; LeDoux, 1993). The most complete formal definition of the concept of memory system was provided by Schacter and Tulving (Schacter & Tulving, 1994) who postulated that a memory module had to satisfy a complex criterion comprising:

- task-transcending class-inclusion *selective* operations: a memory system supports many tasks of a particular class; this entire class of memory functions is affected when the memory system is changed; the class of memory functions is selective, meaning that it can be altered separately from other cognitive functions, including other classes of memory functions;
- properties and relations
  - rules of operation
  - kind of information
  - neural substrates
  - function
  - convergent dissociations: dissociations between task performances that different systems contribute to demonstrated in different populations and by using different techniques.

It is important to emphasize two aspects of this account that are often overlooked. First, neural basis is only one of the several criteria involved in defining a memory system – thus, a memory system should not be understood primarily as a distinct (local or extended) neural

network, it is more than that. Second and related, each type of memory is dependent on a distributed neural network, that encompasses multiple brain areas and some of these brain areas are shared among different memory systems (e.g., the entorhinal cortex provides information to both the hippocampus and amygdala, each of which are core structures of distinct memory systems).

The information processing styles of the hippocampus, striatum, and amygdala memory systems were described in detail in a later theoretical paper (White & McDonald, 2002). All learning situations are constituted of the same general elements: neutral cues (S) and reinforced cues (S*) which can elicit motor responses (R) or approach/escape responses typically elicited by a reinforcer (R*); central autonomic responses (r) that generate affective states (Sa); and memory modulation (M). Depending on the associations created among these elements by the core structures of each memory system, distinct types of representations are formed which in turn determine the function of the memory system (Fig. 1B). Similar work has described the representation formed by the cerebellar memory system (Thompson & Kim, 1996; Thompson, 2005). Critically, as postulated by the definition of memory system, the neurobiological basis of each system is considered to be not a brain area but a *brain network.* These networks have distinct cores - as for example hippocampus, striatum, or amygdala – which determine the style of information processing of the memory system, but some brain areas can be shared among memory systems as it is the case for instance with the entorhinal cortex, common to both amygdala and hippocampus memory modules.

From memory system to memory-based behavior—Each memory system receives sensory input, processes it, and generates output, forming a distinctive memory trace that can guide behavior (Fig. 1C, left). As mentioned above, the operational principle of memory systems was initially thought to be *independent parallelism.* The crucial evidence that led to this idea was provided by double dissociation experiments; there are also reports of triple dissociations which follow an analogous logic (e.g., McDonald & White, 1993; Kesner, Bolland, & Dakis, 1993). This type of evidence emerged from both human and animal models (Packard etal., 1989; Packard & McGaugh, 1992; McDonald & White, 1994; McDonald et al., 2010; Bechara et al., 1995; Knowlton et al., 1996). What rendered dissociations studies very convincing was the Tolmanian style of experimental design in which the sensory input, motor output, and motivation were maintained constant across testing conditions, the only varying factor being contingency. Because successful behavior required distinct types of representations, the results led to clear conclusions regarding the functional significance of activity in a given brain area.

If memory systems are concomitantly active and each system forms its distinct representation, how can behavior be guided by only one type of memory? White and collaborators proposed that during a learning experience, the activity within memory systems has different degrees of coherence (i.e., coordination) depending on the match between the requirements of the situation and the processing style of the network, determined in turn by the structure of that memory system’s core and the amount of exposure to the task. Thus, the structure of the memory network is ultimately reflected in its function. During states of high coherence, two phenomena are postulated take place. First,

plastic changes occur in the brain circuit, generating thus the memory trace. Second, the memory system with the most coherent activity exerts the highest influence on behavior (White & McDonald, 2002; White, 2009; White, Packard, & McDonald, 2013). There is ample empirical support for this hypothesis. The network architecture of each memory system is very different (for hippocampus, amygdala, and dorsal striatum see Amaral & Witter, 1995; Sah et al., 2003; Alexander & Crutcher, 1990; Voorn et al, 2004) and coherent activity in neural circuits has been involved in the formation of memory traces (Jutras & Buffalo, 2010; Tognoli & Kelso, 2014; Fell & Axmacher, 2011; Axmacher et al., 2006).

Interactions among memory systems—Even as memory systems operate independently and in parallel, they can also engage in competitive or cooperative interactions, Fig. 1C, right). Competition is revealed by findings that lesions of one memory system results in facilitation of learning based on a different memory system (White & McDonald, 1993; McDonald & White, 1995; Ferbinteanu & McDonald, 2001; Chai & White, 2004). Cooperation is shown when lesions of two memory systems are necessary to impair a given behavior, or when one memory system can eventually compensate for dysfunction in another memory system (McDonald & White, 1995; Voermans et al., 2004). These findings can be explained by the coherence hypothesis described above. Highly coherent activity in one memory network can cause (directly or indirectly) disorganization of activity in another memory network and the two memory systems engage in competitive interaction. It is also possible that two memory systems have activities with similar degree of coherence or promote coherence in each other's activity, in which case they will engage in cooperative interaction. In both these situations, each memory system continues to contribute to behavior in concordance with its function demonstrated though double dissociations studies.

Interactions among memory systems can take however more complicated forms and our current understanding of these processes remains poor (Kim & Baxter, 2001). This problem has been addressed a number of times in the literature (Poldrack & Packard, 2003; Poldrack & Rodriguez, 2004; Gruber & McDonald, 2012; McDonald & Hong, 2013; White et al., 2013; Ness & Calabrese, 2016), but we currently lack a comprehensive view of this process. Tolman mentioned brain damage, the constellation of cues in the environment, extent of training, and motivational/affective factors (Tolman, 1948); all these hypotheses were validated by later empirical work. The consequences of brain damage on memory started to be understood after H.M.'s case in 1957. Access to distal cues (White et al., 2013; White, 2009) and the cues' distinctiveness (McDonald & White, 1995; Gaskin, Chai, & White, 2005) are critically important in determining the contribution of memory systems to behavior. In a series of experiments based on Tolman's behavioral T-maze paradigm, Packard and collaborators demonstrated that while learning, rats initially use a hippocampus-based spatial strategy which gives way to a striatum-based response strategy after extensive training. Finally, the amygdala modulates both the hippocampus and striatum memory systems, but overall fear or stress tilt the balance in favor of the striatum-dependent habit type of behavior (Packard & McGaugh, 1996; Packard, Cahill, & McGaugh, 1994; Packard & Wingard, 2004; Goldfarb & Phelps, 2017; Packard & White, 1990; McDonald & White, 1995; White, 2004). Distraction favors automatic, striatum-dependent processes

(Jacoby, 1991). Attention, neurotransmitters, executive control through prefrontal cortex, and plasticity are also involved (Foerde, Knowlton, & Poldrack, 2006; McDonald & Hong, 2013; Poldrack & Rodriguez, 2004). From this evidence, important conclusions follow. First, neural activity forms a specific type of representation in each memory system, but that representation may or may not guide the behavior the organism ultimately displays (Hickok, 2009; Katz et al., 2016; see also Krakauer et al., 2017 for a general discussion). Hippocampal physiology provides a good illustration for this complex brain-mind relationship: the activity of the place cells can change dramatically without the hippocampus-dependent spatial behavior to be affected (Jeffery et al., 2003); and the spatial behavior can markedly deteriorate in the absence of modifications in place cells' activity (Robbe et al., 2006). Second, interactions between memory systems defy a simple explanation, as pointed out (Kim & Baxter, 2001).

The idea that memory is modular was accepted gradually—Establishing the selectivity and precise nature of memory deficits following damage to the hippocampus or the medial temporal lobe required much experimental work which lead to progressive improvements in behavioral testing and lesion techniques. This process took time, but it eventually resulted in the convergence of initially different results from animal and human studies. The discrepancies challenged the idea that the medial temporal lobe is the anatomical site of a brain system dedicated to declarative memory and the controversy went on for more than twenty years (Horel, 1978; Vanderwolf & Cain, 1994; Gaffan, 2001; Gaffan, 2002), only to resurface recently in the evolutionary model of memory systems (see below; Murray, Wise, & Graham, 2016). According to one of these views, memory is not the specific function of a localized brain circuit, but results from the act of information processing taking place in brain areas involved in perception (Gaffan, 2002). Notably, this particular perspective ignored the critical results of double and triple dissociations published in the rat literature and except a brief mention of habits, it also ignored any other type of memory except declarative. On the other hand, it has to be acknowledged that much empirical work produced discrepant results. Early experimental work in the memory field was based on techniques unable to produce sufficiently localized lesions in animal models; this situation changed only after the introduction of neurotoxins. In humans, patients come to the neurological clinic with brain damage extending across multiple, functionally heterogeneous brain areas and often involving white matter as well. Furthermore, different species have different types of innate abilities that are not part of memory per se, but impact the type of testing that can be devised (e.g., humans have language, animals do not; primates rely much on vision vs. rats rely on olfaction). Translating memory tasks across species so that they capture analogous mnemonic abilities cannot occur before an adequate understanding of memory and memory testing within species. A good example is episodic memory. Initially defined by Tulving as 'information about temporally dated episodes or events, and temporal-spatial relations among these events' that occurred in one's own past (Tulving, 1972), it was operationalized 26 years later as memory for *what, when*, and *where* to study *episodic-like* memory in scrub jays (Clayton & Dickinson, 1998). The two publications are separated by thousands of experiments and even today the presence of episodic memory in non-human animals remains a topic of debate. Taken together, these

factors generated a lot of debate in memory research but eventually, the consensus that memory is modular crystalized.

2. Further theoretical developments

Once formulated, the MMS theory organized memory research and has continued to do so until today. However, this dominance should not be understood monolithically. Prompted by accumulation of empirical data that raised problems for various aspects of the theory, several adjustments of the initial model have been formulated. While none of these proposals challenges the fundamental idea of modularity, each of them represent departures from the initial views and signal aspects that need to be incorporated in an account of memory.

Attribute model of memory—Following Schacter and Tulving (1994) definition of memory systems based on the kind of information represented, this model postulates the presence of event-based, knowledge-based, and rule-based memory systems, each constituted of a number of attributes (forms of memory): time, place, response, reward value, sensory perception, to which language is added in humans (Kesner, 2013; Kesner & Conner, 1972; Kesner, 1980; Kesner & DiMattia, 1987; Kesner, 2009). The event-based system deals with new and incoming information, which is egocentric oriented towards personally-experienced events (similar to episodic memory in MTL model) ; the knowledge-based system encompasses permanent representations stored in long-term memory, which relate to general knowledge about the world (similar to semantic memory in the MTL model); and the rule-based system integrates information from the event-based and knowledge-based systems through rules and strategies with the goal of subsequent action. The neural networks postulated as bases for these systems are complex and more widely distributed than in the MTL model, notably encompassing the prefrontal cortex as supporting much of the rule-based system and the time attribute in the knowledge-based memory system. Unlike the MTL model, the attribute model does not classify memories based on whether they are declarative vs. procedural, or conscious vs. unconscious. It also emphasizes the idea that each type of memory emerges from the integrated activity of extensive brain networks, which encompass multiple brain structures; thus, in this perspective, a memory system does not have a core structure that determines its characteristic style of information processing. The attribute model, which can only be sketched here, encompasses a large amount of empirical evidence and it is unique in that the core function of one of the postulated systems (the rule-based system) is working with already formed and stored representations to achieve a behavioral goal.

Knowledge (representational) systems—A problem that the memory systems theory has to address is the potential unlimited multiplication of the memory systems. For example, additional memory systems have been proposed based on the activity of different neural circuits (Goodman & Packard, 2017; Bratch et al., 2016). One proposed solution to this problem was to reserve the term ‘memory’ for the process of recollection while all stored information would be referred to as ‘knowledge’ (Nadel, 2008). Thus, rather than talking about memory systems, Nadel argues that one could talk about ‘knowledge systems’. According to this view, knowledge both supports behavior and constitutes the basis of memory, which results from a constructive process. Based on their content and processing

function, which determines the nature of the information processed, five different knowledge systems can be distinguished: what happened where and when, who was involved, how to act (procedural knowledge), and whether it was positive or negative (affective valence). As in the classical memory systems theory, the knowledge systems have distinct neurobiological basis, but they transcend the long- vs. short-term memory division and do not separate perception from memory (Nadel & Hardt, 2011). Empirical evidence supports this idea. Short- and long-term memories are not as distinct as it was initially thought (Ranganath & Blumenfeld, 2005; Craik & Lockhart, 1972) and perceptual mechanisms have been long implicated in priming, one form of memory (Schacter, 1992). The posterior parietal cortex, typically associated with perception and attention, also has a role in episodic memory while the prefrontal cortex, traditionally considered to have an executive function, represents sensory information (Sestieri, Shulman, & Corbetta, 2017; Ester, Sprague, & Serences, 2015). Perirhinal cortex in the medial temporal cortex may have both perceptual and memory functions (Baxter, 2009; but see Suzuki, 2009). Representational systems model is a reflection in the memory field of the changing in understanding of how information processing is organized in the brain in general. With it come an emphasis of the role of large brain networks rather than individual brain areas in memory, an explanation for why amnesic people retain remote memories, and a plausible account for why and how memories change across time (Nadel & Moscovitch, 1997; Moscovitch & Nadel, 1998; Moscovitch et al., 2016). This being said, it should be noted that in Schacter and Tulving's account, memory systems are not defined based on categories, processes, tasks, or neural networks, but rather on a complex combination of all these factors. If their definition of memory system is upheld, the number of memory systems remains in fact rather limited.

Processing modes model—This model proposed defining memory systems based on processing mode in order to eliminate the problem of dividing memory in explicit and implicit categories (Henke, 2010). The point is well taken. Explicit/implicit or declarative/procedural distinctions were based on human research and referred to the ability to state verbally the content of memories (Cohen & Squire, 1980; Squire, 1982). This classification has not been in fact included in the Schacter and Tulving definition of memory systems (Schacter & Tulving, 1994) and empirical work has eventually challenged it. Conscious and unconscious processing can be mixed in performing a particular task, as dual-process models have proposed (Jacoby, 1991; Yonelinas, 1999; Yonelinas, 2002; Taylor, Krakauer, & Ivry, 2014; Huberdeau, Krakauer, & Haith, 2015; Sun, Slusarz, & Terry, 2005), while the same core memory structure can support both explicit and implicit memory (Henke et al., 2003; Hannula et al, 2007; Hannula & Ranganath, 2009; Butters et al.,1985; Chun & Phelps, 1999). The model proposed three distinct memory systems in line with three distinct types of processing: rapid encoding of flexible associations, slow encoding of rigid associations, and rapid encoding of single items. The first type of processing, exemplified by episodic memory, is based on hippocampus and neocortex; the second, comprised of procedural memory, classical conditioning, and semantic memory, involves basal ganglia, cerebellum, and neocortex; and the third, encompassing familiarity and priming, involves parahippocampal gyrus and neocortex. The model is an attempt to solve a legitimate problem and a new classification system based on style of processing is logical enough, but in the end a glaring problem remains: the model does not seem to be able to accommodate

emotional memories. Aversive learning can be fast, as in fear conditioning and conditioned taste aversion where one training session (pairing of a tone or context with electrical shock; or a taste with LiCl) is sufficient for the animal to learn a fear response, while appetitive learning can be slow, as in conditioned place preference where normal animals need training across multiple days to show significant learning (White & McDonald, 1993). Beyond emotional memory however, the explicit/implicit distinction has not been in fact the criterion used to define the currently accepted memory systems, and animal research has generated a significant portion of the evidence leading to the theory, including double dissociation data. As Schacter and Tulving pointed out (Schacter & Tulving, 1994), the explicit/implicit dissociation refers to the phenomenological aspect that some memories can be consciously recollected while some cannot, but this in itself is not an indication of whether the memories result from the activity of one or more memory systems.

Expanded parallel model of memory systems—This model was formulated to address the fact that information acquired by one memory system can be utilized by a different memory system (White, 2004; White, 2009; White et al., 2013), which represent a different type of interaction among memory systems than competition or cooperation (Fig. 2, right). When rats are trained on a striatum-dependent S-R task, they can use the information acquired during learning to solve at a later point memory queries that target hippocampus-dependent and amygdala-dependent representations (McDonald, Ko, & Hong, 2002; McDonald, Foong, & Hong, 2004; McDonald et al., 2007; McDonald, Hong, & Devan, 2004). Similarly, in a class of behavioral paradigms called Pavlovian-instrumental transfer (PIT) animals are first trained in classical conditioning and then in instrumental conditioning, tasks dependent on the amygdala and the dorsal striatum memory systems, respectively. If the stimulus conditioned in the Pavlovian task is then presented in the operational chamber, the rats show increased rate of lever pressing, demonstrating that they transferred information acquired during classical conditioning. Underlying the transfer process is a link between the lateral amygdala and the dorso-lateral striatum (Corbit & Balleine, 2005; Corbit & Janak, 2007). In the examples cited above, one memory system ‘helps’ the other memory system. The opposite situation also exists, in which the activity of one memory system disrupts the function of another (Brown & Robertson, 2007). In all these examples, the evidence indicates transfer of information from one memory system to another, a process which cannot be explained if the only operational principle is independent parallelism.

To account for these findings, the expanded model emphasized that the core structures of the memory systems not only receive, but also send information back to the cortex, where the memory traces are thought to be stored in the long term (Fig. 2, dashed gray arrows). In situations that share sensory input and/or motor output, the cortical memory traces created by distinct memory systems end up sharing neural basis. Thus, the memory systems can communicate indirectly through a common cortical representation that acts like a transfer point, or ‘hub’ to provide the neural substrate through which information can be exchanged. It should be noted that ‘cortex’ in this context does not mean one specific brain area where all the memory systems may project, but is a generic term covering distributed cortical networks such as prefrontal, medial temporal, motor, and others (Groenewegen etal., 1990;

Dalley, Cardinal, & Robbins, 2004; Arruda-Carvalho & Clem, 2015; Padilla-Coreano et al., 2016; Rudebeck & Murray, 2014; Maren, Phan, & Liberzon, 2013; Tejeda & O'Donnell, 2014; McDonald & Mott, 2017; Hirai et al., 2012; Pitkanen et al., 2000; Ranganath & Ritchey, 2012; Gauthier & van Wassenhove, 2016; Cohen & Robertson, 2011; Hunnicutt et al., 2016). By allowing for communication between memory modules, the expanded model can also account for the multifaceted but unitary nature of remembering: we recollect facts or events, but at the same time we can also 'bring back' procedural or emotional elements of a past episode - all tied in a seamless experience. Such 'remembrances of things past' (as in the famous episode of Proust's description of how the taste of a madeleine triggers the recollection of events from his childhood) would certainly have the complex phenomenal quality that Tulving emphasized in his definition of episodic memory (Tulving, 1972; Tulving, 2002).

The expanded model explains the transfer-of-information data by adjusting the operational principle of the medial temporal lobe memory systems – clearly, memory modules do not operate independently and in parallel at all times if they can communicate information. The model also suggests questions of an even more fundamental nature: when can we talk of distinct memory modules? This issue will be discussed in detail under the dynamic network model of memory.

Heterarchic model of memory systems—The idea behind this model arose from the observation that hippocampal lesions produce smaller anterograde than retrograde effects (Lee, Zelinski, McDonald, & Sutherland, 2016). A heterarchy is a form of organization in which levels are not organized in supra- or subordinate relationships, as in a hierarchy, but circularly; this is achieved through cross-over connections among levels and the result is to yield nontransitive relations (McCulloch, 1945). In the context of this model, heterarchy is understood as the collection of core structures of distinct memory systems whose hierarchy is determined by their ability to influence activity in the res t of the brain and direct behavior. The hierarchy changes when one of these core structures is damaged. The hippocampus, which receives highly processed input from multiple sensory modalities and returns output to the same areas (a caveat here: the wide input/output is effected through the entorhinal cortex), is normally located at the top of this hierarchy. Based on the highly processed input it receives, the hippocampus generates conjunctive representations of environmental cues in the cortex. These representations are then integrated among several effector systems that can influence motor action (amygdala, frontal cortex, striatum, and cerebellum). Initially, the representations of the cue conjunctions are dependent of hippocampal reactivation, but with repeated experience of these conjunctions and the hippocampal-dependent activation of the cortical representations, associations are formed between cortex and other memory structures but the hippocampus. The new associations effect cross-over connections among memory structures (which is what confers heterarchic character to the architecture of memory) and enable hippocampal-independent retrieval of stored information after repeated exposure. When the hippocampus is damaged before the cross-over connections are fully implemented, memory is impaired; otherwise retrieval of the information can occur unimpeded. A prediction of this theory, validated empirically (Sparks, Lehmann, & Sutherland, 2011) is that memory impairment also occurs if the

hippocampus is inactive during the initial learning but then it comes back on line. The discrepancy between anterograde and retrograde amnesia is explained by the critical role the hippocampus plays in reinstating the distributed memory trace: retrograde amnesia is more devastating because the hippocampus is necessary to reinstate the memory trace. The model also accounts for overshadowing, a process whereby the hippocampus interferes with information acquisition and storage in other memory circuits: the conjunctive representations formed by the hippocampus use the same pathways to control motor output that other memory systems use for their own representations.

As with the expanded model of memory systems, this theory emphasizes the connections between the cortex and memory 'core' structures. Importantly, this model proposes that the hippocampal memory system's accesses to behavioral output is intrinsically linked to the output of the other memory systems and provides an account for how interactions among hippocampus and other memory systems may be effected. The idea of a memory architecture in which some memory circuits incorporate components of other memory circuits is taken to a full extent in the evolutionary accretion model which co-opts evolutionary biology to argue for a radically different memory architecture.

Evolutionary accretion model—This model constitutes the most articulated and thorough revision of the memory systems theory (Murray, Wise, & Graham, 2016). At the basis of the model are two premises: first, the various memory systems developed at different points in time during evolution, each new system conferring increased fitness to the environment; and second, the specialization of a cortical area is the representation it generates rather than a psychological process. From oldest to newest, seven different memory systems are listed: *reinforcement* (encompassing the basal ganglia-, amygdala-, and cerebellum-based memory circuits), to represent associations between stimuli, responses, and outcomes; *navigation*, for guiding journeys through the environment; *biased competition*, to mediate competition among and within already existing memory systems; *manual foraging*, for transforming visual information into metrics and modulating the value of actions in agreement with current needs; *feature*, with two sub-systems for attributes and metrics, respectively; *goal*, for reducing errors by combining representations of goals with representations of context, actions, and outcomes; and *social-subjective* for representing one's self and others (Fig.3). While still based on a modular concept of memory, this account differs significantly from the current view on the organization of memory in the brain. The memory systems are organized hierarchically in the sense that phylogenetically newer memory systems integrate representations generated by older memory systems through a process of *re-representation* - high-level abstraction of information represented at lower levels. Consequently, 'late' memory systems which produced more abstract representations are not built independently and from scratch, but rather are integrated with preexisting memory systems whose function they augment. Because of this organization, 'early' memory systems have a wider influence in memory processes. For example, the reinforcement system, evolutionarily oldest, is tied in the function of all other memory systems. According to this model, the dichotomy between explicit memories and habits does not make sense because both incorporate basal ganglia function. Explicit memory, unique to humans, is seen as resulting not from the function of a medial temporal memory system, but

from the interaction between navigation, feature, goal, and social-subjective memory systems. The brain areas currently included in the medial temporal lobe system (hippocampus plus entorhinal, perirhinal, and parahippocampal cortices) generate different types of representations (scene memory and perception; conjunctions of objects and goals; feature conjunctions; conjunctions of objects and locations, respectively) that are both mnemonic and perceptual in nature.

The idea that cognitive functions develop during evolution is not new (MacLean & Krai, 1973; MacLean, 1990; Sherry & Schacter, 1987). It has been fruitfully applied to basic affective processes (Panksepp, 2004; Panksepp et al., 2012) and to memory itself, although at a stage when the concept of memory system was not yet fully articulated (Sherry & Schacter, 1987). Compared to this earlier work, the evolutionary accretion model reflects recent advances in evolutionary biology and proposes a marked departure from the current view which describes a medial temporal lobe memory system dedicated to explicit memory and several other memory systems that support implicit memory (Fig. 1 A, Squire & Zola-Morgan, 1991). The account by Murray and colleagues does not include a discussion of operational principles of memory systems, but because evolutionarily newer memory modules are built ‘on top’ of the older ones, memory systems obviously cannot operate independently and in parallel only. Further theoretical implications of this model will be discussed below.

3. ‘Curious’ empirical data

What is the current status in memory research?—The current understanding of memory architecture is represented by the MMS theory initially formulated in the late 1980’s and early 1990’s, which postulates the existence of distinct memory systems or modules, each supported by an individual neural basis and characterized by a specific style of information processing resulting in a unique type of representation able to guide a particular type of behavioral strategy. More recent theoretical developments occurred in the areas of classification (attribute, medial temporal lobe, processing modes, and evolutionary accretion models), integration with perceptual brain functions (attribute and knowledge systems model), and interactions among memory systems (attribute, heterarchic and expanded models). Despite their differences, all models rest on the same fundamental view that memory is modular and are guided by the Schacter and Tulving (1994) definition of what constitutes a memory system. For example, the quite different taxonomies proposed by the medial temporal lobe and evolutionary accretion models originate in the perspectives the two models adopt: the former model looks at memory as parallel modules, each responsible for a distinct aspect of long term memory, whose end-products - the representations – are integrated to guide behavior, while the latter model sees memory as generated by the activity of a series of successive interlocked modules, a perspective that has been articulated earlier but not much pursued afterward (Lynch & Granger, 1994). Where the picture is much less clear is in the account of how memory systems work together to produce behavior. One line of evidence is constituted by the double dissociation data which support the idea that information processing in the memory systems occurs independently and in parallel meaning that in a given circumstance, multiple memory systems are concomitantly active but each of them processes information autonomously. A second line of evidence, compatible with the

first, indicates that in some circumstances more than one memory system is involved in behavioral performance, each system contributing some elements. Classical examples of such situations are active place learning on the 8-arm radial maze which involves both the hippocampus and dorso-lateral striatum when the arms are widely separated and the cues are not ambiguous (McDonald & White, 1995); and spatial conditioned place preference which requires amygdala activity but is impeded by the hippocampus (White & McDonald, 1993). Finally, there is yet another line of evidence which points towards more complex, non-linear types of interactions; those are not easily accommodated by the current framework (Kim & Baxter, 2001) and here is where questions start to appear.

Empirical data that raise questions—One such case is transfer-of-information type of data, which prompted the adjustment of the MMS theory in the form of the expanded model of memory systems. Other data remain however stubbornly challenging. One example in this category comes from contextual fear conditioning, in which shock delivery is paired with an individual stimulus such as an auditory tone in a specific environment. This paradigm involves both hippocampus and amygdala memory systems: the amygdala encodes the individual stimulus, while the hippocampus encodes the context (Selden et al., 1991; Phillips & LeDoux, 1992; Kim & Fanselow, 1992; Phillips & LeDoux, 1994), a pattern that remains valid if the conditioned stimulus is then extinguished and the fear response to the auditory tone becomes context specific (Hobin, Ji, & Maren, 2006; Ji & Maren, 2005). However, electrophysiological recordings show that both fear conditioning and direct stimulation of the amygdala change the hippocampal context representation (Moita et al., 2003; Moita et al., 2004; Wang et al., 2012; Kim et al., 2012); and that activity in the dorsal hippocampus is necessary for the amygdala neurons to show context-specific activity in response to the conditioned stimulus (Maren & Hobin, 2007). Thus, at least in some situations, there seems to be bidirectional communication between hippocampus and amygdala even as their contributions to behavioral output remains distinct. In this case, the challenge seems to point to the foundation of the current paradigm: how can a modular account of memory architecture accommodate a situation in which neural activities of two structures influence each other while the representations these activities form contribute to different aspects to behavior?

While this question continues to await answer, other data are emerging which pose similarly acute problems. As mentioned already, the idea of multiple memory systems is founded on the empirical finding of dissociations (Schacter, 1985; Schacter & Tulving, 1994; Eichenbaum, 2011, p. 223) which have been reported by many labs after using different species and behavioral tasks. However, in most of these studies groups of animals were trained in only one task at a time. The situation seems to be different when the animals concurrently learn two types of behavioral strategies. In one study, during the same individual training sessions rats learned to find food on a plus maze either by hippocampal-dependent spatial navigation or a striatal-dependent body turn strategy (Jacobson, Gruenbaum, & Markus, 2012). Any of the four arms could act as either start or goal arm and the illumination of the room acted as indicator for which of the two strategies the animals had to follow. Post-acquisition, dorsal hippocampal lesions resulted in impaired spatial navigation but dorso-lateral striatal lesions caused memory deficits in both tasks. In this

experiment ventral hippocampus remained intact. In a different experiment, using a similar plus shaped apparatus and concurrent training requiring spatial and response strategies (spatial navigation or cue-response), complete hippocampal or dorso-lateral striatum lesions each impaired performance in both tasks (Ferbinteanu, 2016). The classical double dissociation described in the literature was replicated when the animals learned only one of the two tasks at a time. Thus, even as hippocampus and dorsal striatum form different types of representations, their contribution to behavior depends on how information is initially acquired. This idea was further supported by the finding in the same experiment that past experience modulated not only retention, but also acquisition: learning the response task facilitated later acquisition of the spatial task, while learning the spatial task had the opposite effect on the response task (see also Ragozzino, Detrick, & Kesner, 1999). Unlike in transfer-of-information case, here a core structure of a memory system is co-opted to support an incongruent behavior (i.e., a behavior considered the hallmark of a different memory system). Furthermore, from previous electrophysiological recordings in the spatial navigation/cue-response paradigm (Ferbinteanu, Shirvalkar, & Shapiro, 2011) we know that hippocampal neurons show the same general patterns of activity when animals learn both tasks or only the spatial task, even as the hippocampal activity is modulated by the change in behavioral strategy. Thus, *what does the hippocampal representation, currently understood to support the cognitive map and a flexible behavior, contribute to a habit-type of behavior?* (An analogous problem stands for the activity of the dorso-lateral striatum neurons.) It is worth pausing for a moment to reflect on this problem: the data indicate that one type of mnemonic representation can support not only the ‘corresponding’ behavior (i.e, a S-S representation supports flexible spatial navigation in the case of the hippocampus), but also behaviors that are otherwise the hallmarks of incompatible types of representation.

Such data directly point to the issue of distinctiveness among memory modules because they challenge the type of evidence that led to the formulation of the multiple memory systems theory in the first place. If damage in a memory-related brain area has distinctive effects on memory only in certain circumstances, can we still talk about a modular architecture of memory and if so, how should we define these modules? Furthermore, what are the operational principles that can govern memory systems which are not always distinct? As discussed above, we know that memory systems interact in complex ways from behavioral studies, but currently we know neither the general principles of these interactions nor their neural mechanisms. Presently, these questions need answers.

4. Towards a new paradigm

Dynamic network model of memory: transient coupling of memory networks forms memory meta-systems—A way of moving forward from the dilemma described above is suggested by the developing field of network neuroscience, which aims to understand how large-scale neural networks implement cognitive functions (Bassett & Sporns, 2017). The basic idea of this approach is that the brain is a complex dynamic system, its networks and sub-networks having the ability to reconfigure so that they optimally combine functional segregation and integration. These network processes occur at multiple spatiotemporal scales and involve coordinated activity in widely distributed brain areas. Network neuroscience uses as analytical tool the graph theory, a branch of

mathematics studying systems formed by interacting elements. Graph analyses can be readily applied to brain networks because a neuron, a local circuit, or a brain area can be modeled as an element or *node*, and the anatomical or functional connections among neurons, local circuits, or brain areas can be modeled as *edges*. The graph is constituted by the nodes connected through edges, and its analysis can quantify important properties such as efficiency in transmitting information. The study of the nervous system from a graph perspective took off in the early 2000's, when it was shown that when analyzed from the graph perspective, the neural networks of the mammalian brain are structured to promote both integrated and segregated information processing (Sporns et al., 2004; Sporns & Kötter, 2004). Brain networks have a hierarchically modular structure, meaning that groups of highly interconnected nodes can operate as a unit but can also be one component in a hierarchically superior larger network. Activity in a given module can increase, decrease, or change pattern in a process known as dynamics-on-networks. Alternatively, a node can switch affiliation from one network to another or modules can fuse through a process known as dynamic-of-networks. These two processes can operate by themselves or together (Fig. 4A; Bassett & Sporns, 2017).

The critical aspect of the dynamic network perspective is that brain networks are not seen as static, but as evolving across time, depending on cognitive demand – the networks reconfigure. What this means is illustrated by a recently formulated model of cognitive control, the brain's ability to organize thoughts and actions to flexibly pursue goals (Fig. 4B). Like the architecture of memory, the architecture of cognitive control is thought to be modular, constituted of a frontoparietal network for adaptive control and a cingulo-opercular network for set maintenance. These networks can be distinguished though double dissociation and are thought to operate in parallel (Nomura et al., 2010; Dosenbach et al., 2008; Dosenbach et al., 2007). The current, 'static' theory in the field is that the cingulo-opercular network mediates competitive interaction between the fronto-parietal network and the default mode network (DMN), a neural system whose activity decreases during goal-oriented tasks (Bressler & Menon, 2010). In contrast, the proposed dynamic model posits that the fronto-parietal network can transiently couple with the cingulo-opercular network to form an *executive meta-system* operant during high working memory load; or with the default mode network to form an *integrative meta-system* operant during low working memory load (Cocchi et al., 2013). According to the model, the coupling between neural networks is determined by the task requirements and reorganizes the interaction among distinct neural systems.

New studies are starting to investigate the dynamics of neural networks during learning too (please see further below for descriptions of specific experiments; Wimmer et al., 2014; Gerraty et al., 2014; Jo & Lee, 2010; Fornito et al., 2012; Albouy et al., 2008; Watrous et al., 2013; Bassett et al., 2013), suggesting that as in the case of cognitive control, the neural bases of distinct memory systems could generate memory meta-systems which combine the functions of the subordinate memory systems (Fig. 4C). Thus, if circumstances require the use of only one type of behavioral strategy, then each memory system acts independently; if circumstances require the use of multiple behavioral strategy then the memory systems couple functionally and the memory trace will reflect this coupling. For example, successful behavior may be based on spatial navigation only. In this case, information processing

occurs in all memory systems, but the most coherent activity takes place in the hippocampal network and the end result is a stable cortical representation that can be later selectively reactivated through the hippocampus. Concomitant activity in the striatal memory system is insufficiently coherent to create a stable long-term representation, and consequently the striatal memory system is not involved during either acquisition or retrieval. An analogous reasoning stands for the striatal memory system if a stimulus-response strategy is required during learning. In each of these two cases learning results in distinct cortical representations involving the activity of only one memory system (red and blue rectangles) and each memory system's function can be revealed at the behavioral level through classical dissociation experiments. In other circumstances however, learning may involve behavior based on two types of strategies, spatial navigation and stimulus-response, involving both the hippocampus and the striatum. Each of these memory networks now forms its own coherent representation, and because the learning process occurs in the same environment and roughly at the same time, the two cortical representations (R1 and R2) involve a shared neural substrate. In this case, the striatal and hippocampal memory systems couple to form a meta-system whose activity results in an integrated representation of the two types of associations (stimulus-stimulus and stimulus-response). During remembering, the organism may engage in either spatial navigation, or stimulus-response, or switch between the two, but the two memory modules can no longer be dissociated as in the previous case because the system-specific representations are now welded together. Damage of either hippocampus or dorsal striatum will degrade the integrated representation and the animal will show impairment in both types of memory-based behavior. This hypothesis makes specific predictions regarding activity in the two core memory structures. When behavior is controlled by only one memory system, firing in the core memory areas such as hippocampus and dorso-lateral striatum should unfold independently of each other. However, when behavioral performance involves more than one memory system, activities of in the core memory structures may become intertwined. One instantiation of such a phenomenon would be if activity in one memory structure directly influenced patterns of activity in the other memory structure; interfering with the former would result in modifications of the latter. Another possible instantiation of the same phenomenon is synchronization of activity in the two memory structures through brain oscillations (DeCoteau et al., 2007).

The formation of a memory meta-systems could be achieved through multiple avenues. The discussion above focuses on the (neo)cortex as the avenue to connect memory systems, but subcortical structures may play a similar role (Fig. 4D). One example of such putative connecting area is nucleus accumbens, which has been implicated in linking actions to goals and is known to be connected to the hippocampus, amygdala, and prefrontal cortex (Voorn et al., 2004; Pennartz et al., 2009; Pennartz et al., 2011; Burton, Nakamura, & Roesch, 2015; Ito & Hayen, 2011; Goto & Grace, 2008; Ito, Robbins, Pennartz, & Everitt, 2008; Mulder, Hodenpijl, & Lopes da Silva, 1998). Other ways of achieving dynamic coupling between memory networks are direct projections between core structures of the memory systems as between hippocampus and amygdala (Pitkanen et al., 2000); various forms of coordinated oscillations across neural networks (Tognoli & Kelso, 2014; Remondes & Wilson, 2013; Lisman & Jensen, 2013; Bauer, Paz, & Pare, 2007; Burke et al., 2013; Jutras & Buffalo,

2010; Canolty & Knight, 2010; Tort et al., 2008; Khodagholy, Gelinas, & Buzsáki, 2017; Watrous et al., 2013; Gerraty et al., 2014); modulation by a different brain structure (amygdala vis-a-vis the hippocampal and striatal memory systems (Packard et al., 1994; Wingard & Packard, 2008); or neuromodulation (Gold, 2004; Poldrack & Rodriguez, 2004). A transient network may emerge based on one or several of the ways described above and it is important to note that direct anatomical connections are only one of the avenues through which coupling of memory networks can be achieved. The wide variety of ways whereby memory networks can achieve transient coupling may explain why general principles of interactions among memory systems are difficult to discern from empirical data.

Defining memory systems in a fluent network environment—Initially the term 'memory system' referred to a neural circuit that enables the organism to store information. The definition later expanded to encompass the three criteria of class-inclusion operations, properties and relations, and convergent dissociations (Schacter & Tulving, 1994) and in this form, it has organized a vast body of literature to this day. Can this definition still stand if neural networks are seen from the perspective of network neuroscience?

One possible answer is that there are really no memory systems, as it has indeed been suggested (Gaffan, 2002; Fuster, 2009). This is not the answer that I will propose here. Instead, I will argue that memory can be modular even if the modules do not operate as distinct units in all circumstances. This answer involves understanding how a memory system with an individually defined, static, neural circuit can function in a dynamic network context, where the topology and structure of neural networks undergo permanent change. Some have argued that '[m]odules of brain networks define communities of structurally and functionally related areas, but they do not represent or support discrete mental faculties' (Sporns, 2010, p. 195). Indeed, activity in discrete brain areas results in specific representations, not specific cognitive functions, but beyond this, distinct aspects of mental life result from activity in distinct brain networks – the lesions in H.M.'s brain, localized in the medial temporal lobe, produced strong declarative memory impairment but no language or sensori-motor deficits. The dilemma arises from the fact that the brain is constituted of a multitude of highly intricate neural networks. The study of these networks cannot occur without analytically breaking down the totality of these circuits (i.e., the brain) in subcomponents, each with different complexity, dynamics, and topology (see Fig. 2 in Wolff & Ölveczky, 2018). Modules at the cognitive level may not correspond directly to modules at the brain network level, but the two cannot be seen as completely independent either. Recent work is indeed starting to map cognitive systems, defined as collections of brain areas that support a cognitive function, onto brain networks (Mattar et al., 2015).

In network neuroscience, a module (also known as network community) is defined as a group of strongly interconnected nodes (neurons, groups of neurons, or entire brain areas). If the connections are anatomical, they describe a structural network. If the connections reflect the degree of coordination in activity among pairs of nodes, they describe a functional network. In either case, brain networks have hierarchically modular architecture (Chen et al., 2008; Meunier et al., 2009; Meunier, Lambiotte, & Bullmore, 2010; Sporns & Betzel, 2016) meaning that modules are nested in larger, more comprehensive modules. Such organization confers advantages such as facilitation of functional specialization, resilience in front of

damage, and stability (Variano, McCoy, & Lipson, 2004; Robinson et al., 2009; Meunier et al., 2010). Because the degree of activity coordination among nodes in a functional network varies in time, what qualifies as a module can also vary in time. Changes in network modules can be studied by using community detection algorithms applied to neural recordings across successive time windows (Garcia et al., 2018). For each time window, correlations in activity for each pair of nodes are computed. Every such correlation represents the weight of the connection (edge) between the corresponding nodes. The nodes and the edges that connect them define a neural network within which community detection algorithms identify putative modules. By aligning the resulting brain networks and their modules along the timeline one can investigate the dynamic of the functional connectivity of the network and the intra- or inter-modular changes that occur.

Multiple investigations have shown that modules in functional neural networks are dynamic, meaning that the strength of connections among nodes varies in time and individual nodes can even change allegiance to a network (Fig. 4A). One such study directly relevant to memory investigated how the functional architecture of neural networks changed during learning a motor skill (Bassett et al., 2013). The task required participants to use the five fingers of the right hand to produce a set of six different sequences of key presses, each sequence being 10 elements long. Two sets were practiced intensely, two moderately and two minimally. After the baseline session, training took place across 6 weeks in three two-week units, during which the subjects would practice home for two weeks and then be tested during an fMRI scan (3 test sessions). Learning was evaluated by measuring the time from the first to the last key press in a given sequence. Using the fMRI-generated time series, functional networks representing the coherence between 112 cortical and subcortical areas for each sequence were extracted. Modules were identified as groups of brain areas that exhibited similar BOLD time courses and their evolution in time revealed the dynamic of functional connectivity patterns as a function of cognitive processes. The results indicated a core-periphery type of organization (cf. Fornito, Zalesky, & Bullmore, 2016, pp. 179-194) in which the sensorimotor and visual cortex reconfigured little over time, while multimodal association areas formed a flexible periphery where brain areas frequently changed allegiance to a module. Extensive training was associated with decreased modularity (i.e, brain areas became less organized in functional groups), and better learning was associated with stronger distinction between core and periphery. Thus, the brain areas that were consistently active during the performance of the motor task at one point in time (a so-called geometrical core) remain so connected (i.e., in the same functional module) across learning, forming also a temporal core. In contrast, the brain areas that were less coherently activated (the geometric periphery) tended to be part of different functional modules across learning. This analysis suggests therefore that during learning, the neural networks involved have a more static core but also a dynamic periphery. The reconfiguration of the periphery may be related to the ability to integrate information. Supporting this idea, in a working memory task functional brain modularity decreased with when cognitive demand increased (Kitzbichler et al., 2011), indicating that brain networks can reconfigure fast to create what has been called a global neuronal workspace to facilitate transmission of information at long distance.

If the neural substrate supporting memory changes with learning, then can we still talk about a memory system with a distinct and static neural network as its basis? Stated at the general level, the question regards the relationship between static, localized and dynamic, distributed brain networks. Ciric and colleagues recently explored this issue (Ciric et al., 2017). The strategy of their analysis was to find a 'common denominator', a common 'elementary unit' between brain states, dynamic in nature, and brain networks, static in nature. Eighty nodes (cortical and subcortical brain areas) were assigned to six canonical functional networks (visual network; somatomotor network; dorsal attention network; cingulo-opercular/salience network; executive control network; and default mode network) by using a community detection algorithm. Each of these functional networks, which operated relatively independently of the rest of the cortex, was 'sliced' along the time line in spatially localized network connectivity (NC)-states, defined as recurring patterns of connectivity among the nodes of that given network. The NC-states were the elementary unit that linked brain networks and brain states and critically, the cluster of nodes belonging to an NC-state corresponded to structural subnetworks. In contrast to the canonical functional networks from which they were derived, the NC-states were not independent of the dynamics in the rest of the brain networks, but instead they were specific to whole-brain connectivity contexts, meaning that they were reflective of activity in large scale, distributed networks. For example, the default mode network (DMN) NC-states could be dissociated into medial temporal lobe (MTL), dorso-medial prefrontal cortex (dmPFC), and midline core (MC) subsystems, each a static and localized network. Distinct NC-states had distinct patterns of connectivity: in one NC-state (DMN2 in the notation of the authors) the connectivity of dmPFC subnetwork with other nodes in the DMN decreased while its connectivity to nodes in other networks, outside of the DMN, increased. At the same time, the nodes of MTL and MC sub-networks became highly cohesive. One may think of this phenomenon as MTL and MC sub-networks showing increased modularity while dmPFC demodularized. In a different NC-state, DMN3, MC sub-network was highly modular while dmPFC and MTL demodularized. Therefore, even as activity in DMN was relatively independent of activity in the rest of the cortex rendering DMN an autonomous functional entity, within DMN itself, the modularity of its three structural sub-networks varied across time.

A limitation of the analysis described above was that it utilized resting state data, meaning that the subjects did not engage in any cognitive tasks during the fMRI imaging. However, there is evidence that systems formed through functional coupling during resting state continue to exist during task performance (Mattar et al., 2015). Taken in the context of documented changes in neural networks during learning (Bassett et al., 2013) and by analogy with the proposed model of cognitive control mentioned in the beginning of this section (Cocchi et al., 2013), this work suggests how the static neural basis of a memory system can undergo the type of changes described by dynamic network neuroscience. In some situations, the neural networks associated with individual memory systems form strong individual modules and in this state, they can control a memory-based behavior exclusively or based on competitive/cooperative types of interactions with other memory systems. In such cases, memory systems operate independently and in parallel; and behavioral experiments reveal the classical dissociations that form the foundation of the multiple memory systems theory. In other situations, the neural networks specific of each memory

system can undergo demodularization by functionally coupling with brain areas belonging to other networks. This process results in integrated information processing within a heterogeneous memory meta-network whose sub-components have distinct activity patterns (e.g., place fields in hippocampal neurons, action-bracketing firing in striatal neurons, etc.). The memory systems now form a meta-system and can no longer be dissociated at the behavioral level. The transfer of information between memory systems (Fig. 2, lower right) marks the border between independent and integrated memory networks: information acquired by one distinct memory system can be utilized by a different memory system through the intermediate of a common brain network or area that can be part of either memory system across a longer period of time. In this case, the two memory systems remain distinguishable at both behavioral and neural network levels, but part of the memory trace formed by one of the systems is used by the other.

Thus, in the dynamic network model, the Schacter-Tulving definition of a memory system outlined above remains largely valid, although the neural substrate has to be understood as dynamic in the sense described above. Aside of explaining the new behavioral evidence that generated this inquiry (i.e., the absence of dissociations at behavioral level in certain circumstances), the network model also provides a solution for problems that prompted the theoretical adjustments in memory research mentioned above: it does not postulate short vs. long term or explicit vs. implicit memory categories; it does not separate perception from memory; it agrees with the idea that anterograde amnesia should be less severe than retrograde amnesia; it agrees with a hierarchical organization of memory modules; and it provides for the possibility of transfer of information between memory modules. Within the dynamic network framework, an evolutionary criterion does not exclude the medial temporal lobe memory system as in the evolutionary accretion theory. That brain areas may have emerged at different points in evolution does not preclude their potential functional coupling, particularly as brain oscillations are preserved across species (Buzsáki, Logothetis, & Singer, 2013). Indeed, one of the fundamental aspects of neural networks is that the activity of even widely distributed functionally specialized areas can become coordinated (Tognoli & Kelso, 2014). Second, as in the classical medial temporal lobe model and unlike in the evolutionary-accretion model, in the dynamic neural network model the amygdala-, striatum-, and cerebellum-dependent memory systems remain distinct because they form distinct types of representations which support fundamentally distinct classes of operations. Finally, the premise that memory networks can reconfigure excludes the possibility that these networks always operate independently and in parallel; as the empirical evidence cited above suggests it is rather the case that aside of independent parallelism, other operational principles guide the activity of the memory systems.

Brain and behavior: quo vadis?—The discussion above adds support for the idea that the complexity of investigating the neural basis of memory-guided behavior needs to be reevaluated (Krakauer et al., 2017; Wolff & Ölveczky, 2018). A direct implication of the behavioral data that question the distinctiveness and independent parallelism of function in memory systems is that the behavioral function of neural circuits is not set, but depends on past experience. The brain-behavior link, difficult to investigate since it crosses levels of organization, becomes that much more difficult to reveal when one has to additionally

consider that the neural network supporting the behavior can reconfigure. If memory networks are dynamic, so must be both the product of their activity and the link that leads from one to the other, a tenet amply supported by empirical data. Recollection is reconstructive rather than reproductive (Schacter, Norman, & Koutstaal, 1998), a fact often forgotten in many studies of memory mechanisms. Hippocampal recordings demonstrate that drastic changes in activity patterns can leave hippocampal-dependent behavior unaffected, while major perturbations of hippocampal-dependent behavior can occur in the absence of significant alterations of hippocampal activity (Jeffery et al., 2003; Robbe & Buzsaki, 2009). The hippocampus and amygdala neurons encode space and single stimuli, respectively. However, the neural activities within each structure (Moita et al., 2004; Moita et al., 2003; Sotres-Bayon et al., 2012; Maren & Hobin, 2007; Maren et al., 2013; McDonald & Mott, 2017; Peck, Lau, & Salzman, 2013) as well as the roles each of these areas plays in conditioning (Phillips & LeDoux, 1994; Hobin et al., 2006; Ji & Maren, 2005; Gaskin & White, 2013) are modulated by learning experience. Across widely different levels of organizational complexity, from *Aplysia* (Proekt, Brezina, & Weiss, 2004) to humans (Bassett et al., 2011; Mattar et al., 2015; Bertolero, Yeo, & D'Esposito, 2015; Bassett, Yang, Wymbs, & Grafton, 2015; Moussa et al., 2011), the behavioral significance of neural activity is not absolute, but depends on the preceding activity as networks change with learning. Finally, the neural basis of the same type of memory-driven behavior varies: compare results on place learning from White & McDonald (1993) and McDonald & White (1995) vs. Ferbinteanu (2016). Adding to the overall complexity of the problem, a behavior can be serendipitously affected by manipulations that do not in fact interfere with its generating processes (Otchy et al., 2015; Südhof, 2015). Thus, the explanatory power that the dynamic network perspective described above ads to the memory systems theory is associated with an increase in the stringency of the criteria operating while establishing a causal link between brain activity and memory. But unfortunately, there is no shortcut to knowledge.

5. Moving forward

In this article, I have argued that we are currently in front of a paradigmatic shift in memory research. Decades of work have led to the conclusion that memory results from the activities of multiple distinct modules, a perspective that has remained valid across the years even as multiple classifications of memory systems have emerged, the border between memory and perception/action has become more blurred, and the architecture of memory has been disputed. However, recent anomalous empirical data raise fundamental challenges to the idea that memory is modular. This problem can be solved if the neural bases of memory modules are understood not as static entities but as quasi-independent neural networks that can reconfigure in response or anticipation of environmental requirements. The new paradigm can not only accommodate all the data that prompted previous adjustments of the memory systems theory, but also provides a path towards building a systematic understanding of the principles governing the interactions among memory systems, a goal that has eluded us so far. This understanding is critical, because the lab conditions, where experiments are carefully designed to target specific types of memories, most likely do not universally apply to natural settings where different types of memories combine in fluid and complex manner to guide behavior. Empirical evidence enlists a multitude of factors involved in modulating memory functions, but currently we understand little about the general rules that organize

how the living organism deals with these factors, and even less about the underlying mechanisms. Last but not least, a network neuroscience-based approach to memory systems has not only descriptive but also predictive power, leading in turn to the development of means to control these systems, an ability with important direct applications for the clinic (Bassett & Sporns, 2017; Liu, Slotine, & Barabasi, 2011; Jia et al., 2013; Mattar et al., 2017; Khambhati et al., 2017). Working from the angle of large dynamic neural networks poses substantial challenges but it also opens the way for significant progress in the quest of understanding how memory emerges from brain activity.

The network model presented above continues to see memory as modular, but it regards memory modules as relative rather than absolute. Only the future can tell whether such a change in perspective may lead to significant progress, but Father Nikolsky's insights may be, once again, relevant: 'I sat down to transcribe the Life of St. Peter of Corishia, and when I reached the part about the days of the fast, instead of 5 I wrote 50 and gave the transcription to the young monk. He took it, singing, and read it that same evening; the next day, word spread through the gorge that the monk Longin had embarked upon a major fast…. On the fifty-first day, when they buried Longin at the Annunciation in the foothills, I decided never to take pen in hand again.'

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Memory is thought to have modular architecture
- The basis of this idea are dissociation data which reveal the functional specialization of distinct brain areas
- Recent work suggests that dissociations are not absolute, but depend on past history of the organism
- This challenge can be solved if modularity is understood from the perspective of network neuroscience
- Neural networks can reconfigure and/or couple functionally to form meta-networks with new functionality

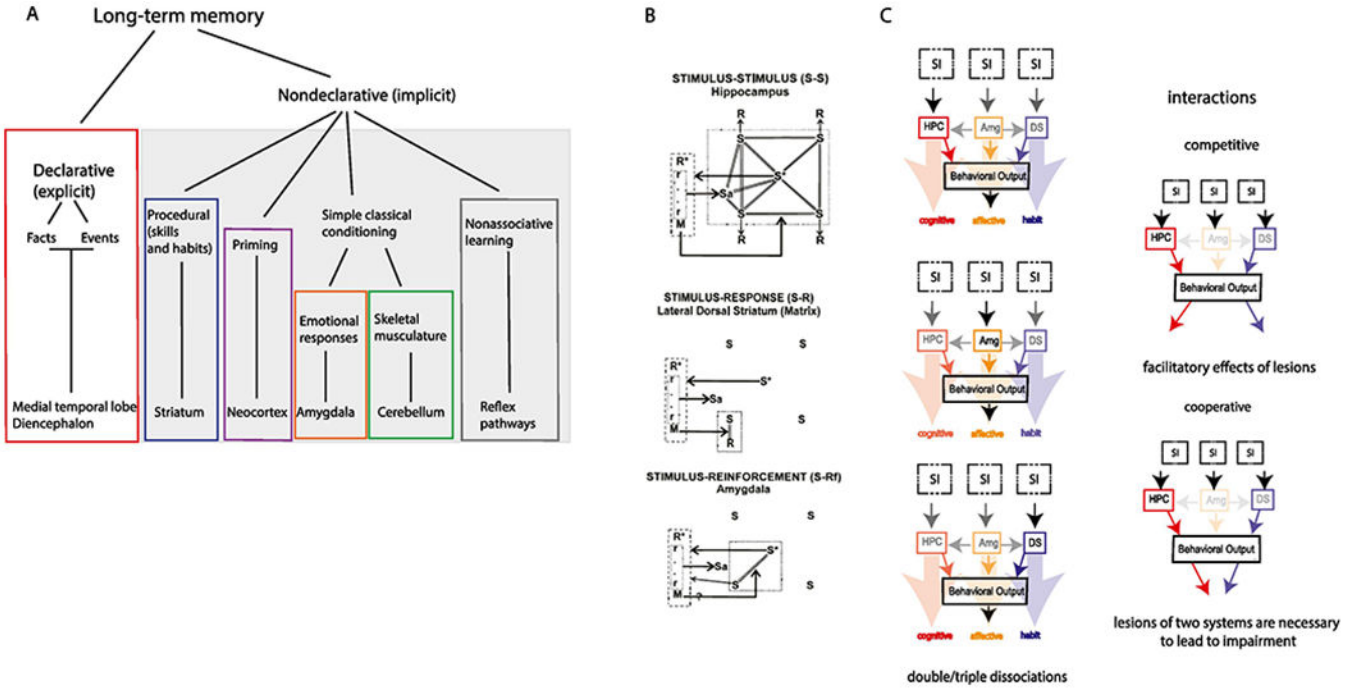

Figure 1. Medial temporal lobe memory systems model.

A. Currently accepted memory systems. Each memory module and its corresponding central brain structure is encased in a colored box. Long-term memory is postulated to be comprised of two large categories, declarative and procedural (gray area) or equivalently, explicit and implicit. This distinction originated in work with humans, in which remembering associated with conscious awareness is expressed verbally (declared) and remembering in the absence of conscious awareness is expressed though actions (procedures). As suggested by the diagram, in this model memory systems are envisioned to function independently and in parallel. Redrawn from Squire, 2004. **B.** Each memory system forms a distinct type of representation. **Top:** The hippocampal system stores complex stimulus-stimulus (S-S), stimulus-affective state (S-Sa) and stimulus-reinforcer (S-S*) associations (represented as the double lines). S* elicits various autonomic responses (r) which in turn generate Sa, also part of the hippocampal representation. The hippocampal representation can generate multiple responses (R), but does not include information about these responses. The S-S relationships can be modulated (M). **Middle:** The dorsal striatum system stores S-R associations that can be also modulated. **Bottom:** The amygdala memory system represents associations between S and the stimulus properties of S*; it does not include action representations. S* normally elicits r, R*, M, and Sa. After learning, the neutral stimulus (now a conditioned stimulus) leads to the same responses, now conditional responses. The types of responses in this case are limited to the ones normally elicited by S*. S=neutral stimulus; S*=stimulus with reinforcement value; Sa = affective state; r = autonomic response; R = response; R* = approach or escape response elicited by a reinforcer; M = modulatory response; double lines = associative bonds; dashed line rectangles = processes that take place within the corresponding system. Reproduced with permission from White and McDonald, 2002. **C left.** The operational principle of memory systems is considered to be independent and parallel processing of information: each of the three memory systems

receives sensory information, processes it in its specific way, and generates a representation that can be used to guide behavior: cognitive, affective, or habitual (black arrows). The independent and parallel processing principle is supported by double dissociations experiments in which interference with brain area 1 results in impairment in behavior A but not B, while interference with brain area 2 results in impairment in behavior B but not A. A triple dissociation among hippocampus, striatum, and amygdala memory systems has also been demonstrated (McDonald & White, 1993; Box 1). Aside of its memory function, amygdala has the ability to modulate the hippocampal and striatal memory systems (gray horizontal arrows). Any given situation generates information flow through all three memory systems, but the activity has different degrees of coherence in each memory network depending on the match between the processing style of the core memory network and the demand for a specific type of representation. Coherence is a prerequisite for the generation of a memory trace. The memory system with most coherent activity (represented here as the more intense color) has the greatest influence over behavior. **C right.** Memory systems can engage in competitive or cooperative interactions. Hippocampal and striatal memory systems are emphasized for clarity. Competitive interactions are demonstrated when interference with activity in system 1 facilitates behavior B, known to be dependent on system 2. Cooperative interactions are demonstrated when interference with activity in either system 1 or 2 does not impair the behavior, but interference with both systems does. HPC=hippocampus; Amg=amygdala; DS=dorsal striatum, SI=sensory information, MO = motor output.

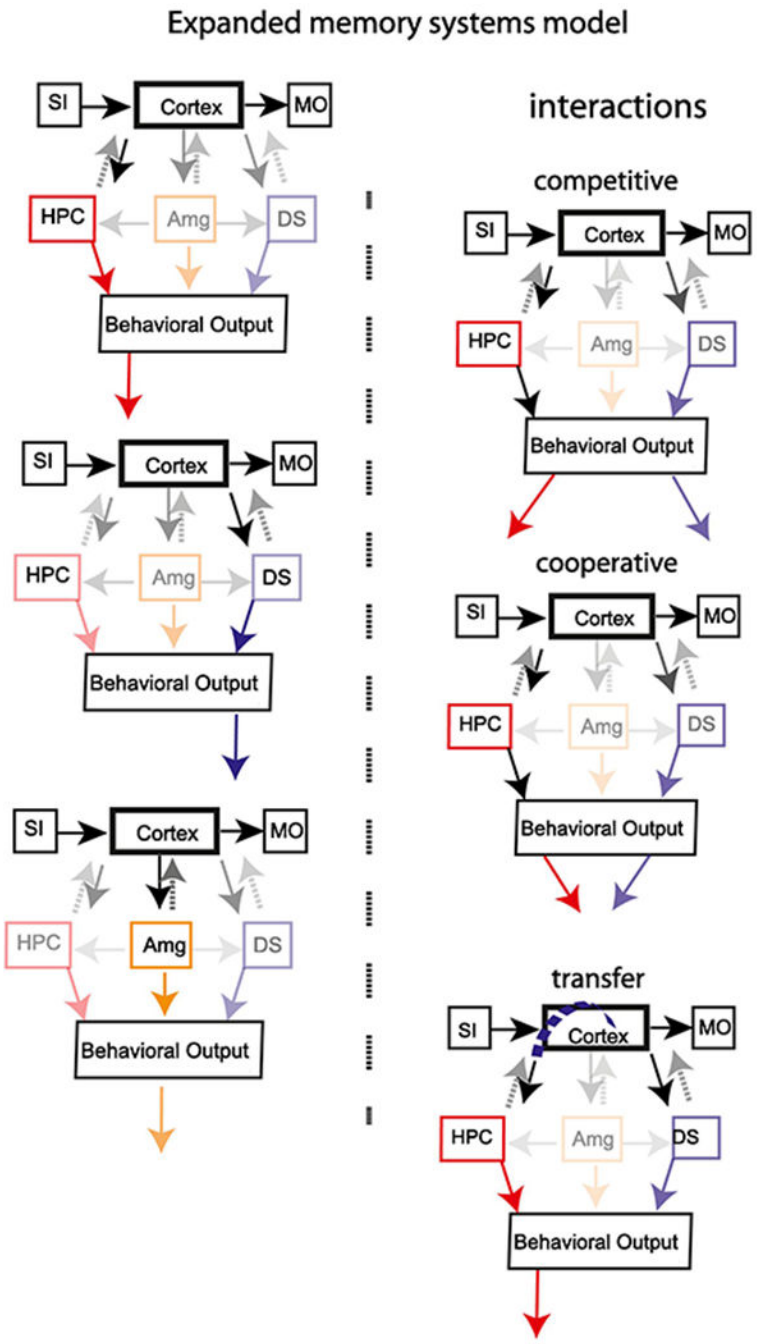

Figure 2. Expanded memory system model.

Memory systems can communicate at cortical level and allow for transfer of information from one memory system to another. The cortex sends sensory information to all memory systems, but it also receives back input after information has been processed (dashed gray arrows). These inputs are incorporated in a cortical representation that may be shared among distinct memory systems and act as a connection point though which information acquired by one memory system can be later utilized by a different memory system (blue dashed line). Note that in the transfer type of interaction, the core structure of the memory system

initially acquiring information *is not* involved in supporting the behavior dependent on the memory systems involved later. Hippocampal and striatal memory systems are emphasized for clarity. HPC=hippocampus; Amg=amygdala, DS=dorsal striatum, SI = sensory input, MO = motor output.

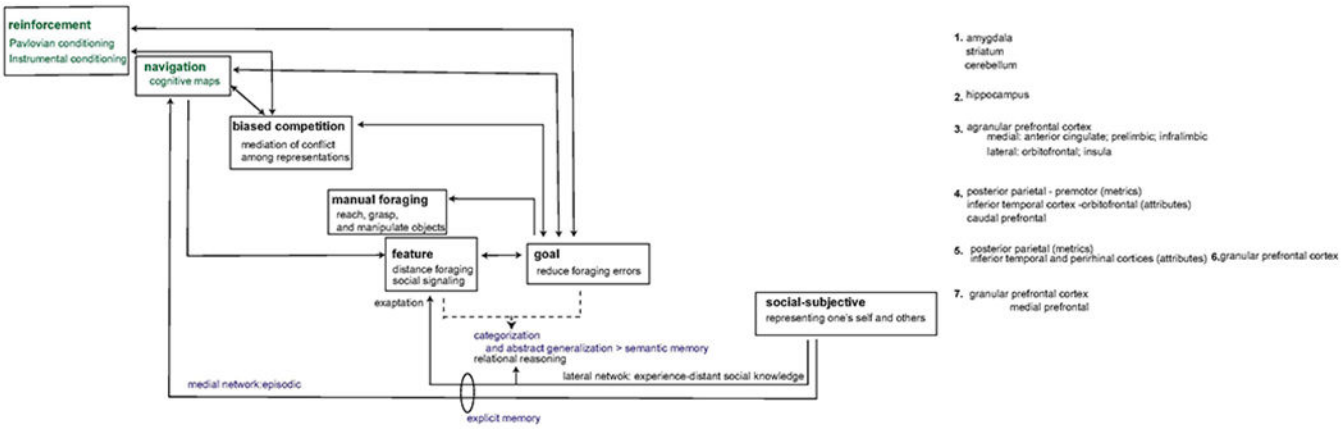

Figure 3. Evolutionary accretion model of memory systems.

The seven different memory systems postulated by the model (bold letters within boxes) are shown in the order of their development from the upper left to the lower right, with the function of each memory system indicated below and the core brain structures listed to the right. Memory systems common to medial temporal lobe and evolutionary models are shown in green fonts. The feature and goal memory systems appeared at the same time. The core neural structures of each memory system are listed to the right. Arrows indicate functional links between individual systems. In the evolutionary model, memory continues to be seen as modular, but its architecture is very different compared with the medial temporal lobe model (Fig. 1A): the amygdala-, striatum-, and cerebellum-based memory systems are grouped together under the reinforcement memory system; several new systems are newly defined; and priming and the medial temporal lobe are not acknowledged. Episodic and semantic memories (blue fonts) result from the combined activity of several distinct memory systems (social-subjective, goal, feature, and navigation). In the evolutionary model, memory systems are organized hierarchically, with older systems participating in the function of newer systems, and newer systems co-opting and modulating the function of older systems. Individual memory systems can operate at times independently and in parallel, but in general they work together in supporting memory-guided behavior.

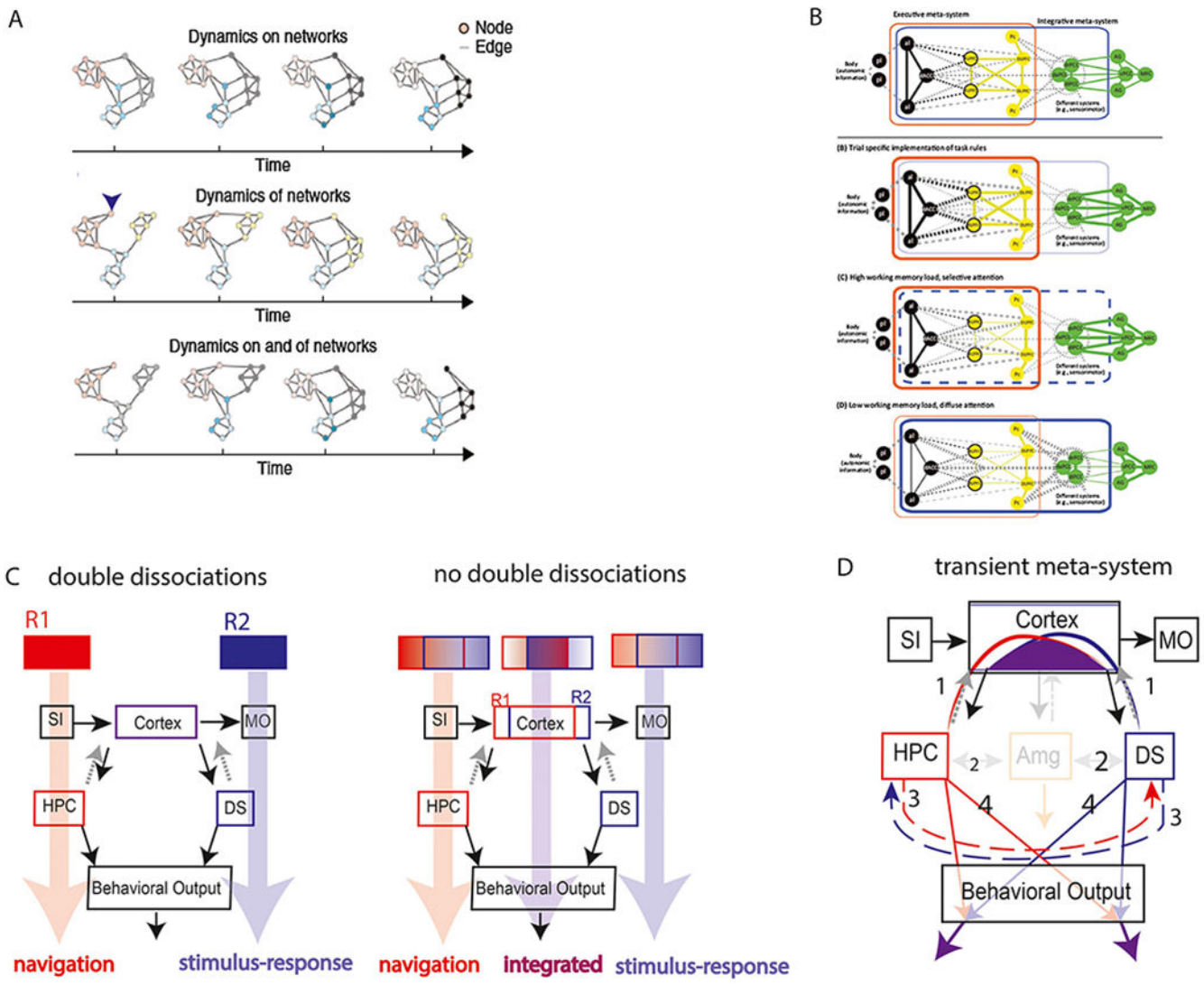

Figure 4. Model of transient coupling of memory networks.

A. Dynamics in neural networks. Each circle represents a node, which is an entity varying from a single neuron in a localized network to an entire brain area in a large-scale network. Top: activity in a network can increase (black), decrease (pink), or change (blue) over time in a process known as dynamics on networks. Middle: across time, networks can merge (blue and yellow) or a node (blue arrow) can change its functional connections so it shifts its allegiance to a network in a process known as dynamics of networks. Bottom: Dynamics on and of networks can combine leading to more complex reconfigurations. From Bassett and Sporns, 2017, reproduced with permission. **B**. Dynamic model of cognitive control. Each circle represents a brain area. Strongly connected areas are shown close together, weakly connected areas are shown far apart. Solid lines represent functional connections at rest, broken lines represent functional connections during a cognitive task. Three different large networks are color coded: fronto-parietal in yellow (dorsolateral prefrontal cortex, dorsal frontal cortex, inferior parietal lobe, intraparietal sulcus and precuneus), cigulo-opercular in black (anterior insula/frontal operculum, anterior prefrontal cortex, and dorsal anterior

cingulate), and default mode network (DMN) in green. The executive meta-system (in red) is formed by the coupling of the fronto-parietal and cingulo-opercular networks and implements adaptive control. The integrative meta-system (in blue) encompasses all three networks and accomplishes the coordination of activity to integrate sensory and autonomic information. The executive meta-system predominates when implementing task rules during individual trials is necessary. The integrative meta-system predominates when there is low working memory load and attention is diffuse. Both systems are active during tasks with high working memory load which requires focused attention. MFC=medial frontal cortex; AG= angular gyrus; vPCC = ventral posterior cingulate cortex; daPCC = anterior portion of the dorsal posterior cingulate cortex; dIPCC = left dorsal posterior cingulate cortex; drPCC = right dorsal posterior cingulate cortex; PC = parietal cortex; DLPFC = dorsolateral prefrontal cortex; RLPFC = rostrolateral prefrontal cortex; al = anterior insula; pi = posterior insula; dACC = dorsal anterior cingulate cortex. From Cocchi et al., 2013, reproduced with permission. C. For clarity, only the hippocampal (red) and striatal memory (blue) systems are emphasized here. Each memory system projects to the cortex forming its own representation of either S-S (red color) or S-R (blue color) associations. During a learning experience, the output of each memory system contributes to the cortical representation depending on the degree of coherence of activity in the neural network. **Left.** If the animal needs to learn using spatial navigation, the cortical representation R1 incorporates only hippocampal output, and the resulting memory trace is selectively hippocampal dependent. Similarly, if the animal has to learn an association between a stimulus and a motor response, the cortical representation R2 incorporates the output of the dorso-lateral striatum and the resulting memory trace is selectively striatal dependent. In this case, selective lesions of HPC or DSL lead to double dissociations. Damage in a memory system's core structure will result in impairments of the corresponding type of memory only. **Right.** If the learning experience involves both spatial navigation and stimulus-response associations, the cortical representation integrates input from hippocampal and dorso-lateral striatum and forms a *transient meta-system* by temporally coupling the neural networks belonging to the two memory systems. Depending on the type of memory-based strategy that is most useful at a later point, reactivation of this meta-system's representation can be stronger for the hippocampal component in which case the animal engages in spatial navigation, or is stronger for the striatal component and the animal engages in stimulus-response behavior. If the circumstances require both spatial navigation and stimulus-response memories, the reactivation of the hybrid memory trace leads to the display of both spatial navigation and stimulus-response behaviors. Damage in the core structure of either memory system will result in impairments in both types of memory-based behavioral strategies and the memory systems are no longer distinguishable. The spatial navigation and stimulus-response behaviors are overtly the same as in depicted to the left, *but their neural basis is different.* HPC = hippocampus; DS = dorsal striatum; SI = sensory input; MO = motor output. **D**. Memory systems can communicate at cortical and subcortical levels. Four different ways of interacting outside of the cortex are described, but the incorporation of all four in the hippocampal-striatal meta-system shown here is for illustration only; there is currently no clear understanding of the mechanisms underlying interactions among memory systems. The re-activation of the hybrid cortical memory trace (red and blue arches) is the same phenomenon as depicted in Fig. 4C, right. 1. One or more subcortical structures can provide

a path through which network coupling can be mediated. For example, hippocampus and amygdala outputs interact at the level of the nucleus accumbens. 2. Modulation either by a third structure or a neurotransmitter can change the coupling of memory networks. In this example, amygdala activation is known to increase the preference for a habit type of behavioral strategy (the effect is represented by the font size). 3. The core structure of two memory systems can interact through direct anatomical connections, as hippocampus and amygdala do. 4. Activity in one core structure of a memory system can interfere with the effect of the input a second core structure sends to a downstream area involved in behavioral output. HPC = hippocampus; DS = dorsal striatum; Amg = amygdala; SI = sensory input; MO = motor output.