

The Functional and Structural Neuroanatomy of Systems Consolidation for Autobiographical and Semantic Memory

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Abstract It is well established that patients with memory impairment have more difficulty retrieving memories from the recent past relative to the remote past and that damage to the medial temporal lobe (MTL) plays a key role in this pattern of impairment. The precise role of the MTL and how it may interact with other brain regions remains an area of active research. We investigated the role of structures in a memory network that supports remembering. Our chapter focuses on two types of memory: episodic memory and semantic memory. Findings from studies of patients with brain damage and neuroimaging studies in patients and healthy individuals were considered together to identify the functional and structural neuroanatomy of past remembrance.

Keywords Retrograde amnesia · Autobiographical memory · Semantic memory · Connectivity · Neuroimaging · Lesion · Patient

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1 Introduction

Memory-impaired patients can more easily remember facts and events (declarative memory) formed long before the onset of amnesia compared to those formed more recently (Ribot 1881). This pattern of impaired recent memory and spared remote memory is known as temporally graded retrograde amnesia (TGRA) and this observation has led to the concept of systems consolidation. The idea is that gradual changes occur in the brain systems that support memory retrieval resulting in memories that are more robust to disruption as time passes after learning. In addition, patients exhibiting TGRA often exhibit impairment forming new memories (anterograde amnesia). This pattern of behavior is now thought to occur after damage to structures in the medial temporal lobe (MTL, i.e., the hippocampus and parahippocampal gyrus, which is composed of the perirhinal cortex, entorhinal cortex, and parahippocampal cortex) as well as to the medial diencephalon (McClelland et al. 1995; Kopelman and Bright 2012; Squire 1992). Nevertheless, the precise role of these structures for memory retrieval and how they may interact with other regions of the brain remains a point of controversy.

Although there is agreement that the MTL, and in particular the hippocampus, is always needed for the formation of new declarative memories, it is less clear whether the MTL is always needed to remember information from the past. Declarative memory concerns two types of information: semantic and episodic; and theoretical ideas differ with respect to the function of the MTL for each type of information. Semantic memories are fact-like, divorced from their encoding context, and strongly associated with each other. By contrast, episodic memories are experiential, intrinsically tied to their encoding context, and not strongly associated with each other (Tulving 1983).

Despite these differences, semantic and episodic memory interact substantially to facilitate remembering of autobiographical events. Indeed, the scoring systems used by researchers to evaluate autobiographical memories include separate categories for semantic autobiographical information and episodic autobiographical information. One idea is that semantic information may interact with episodic information

at retrieval through an interactive and constructive process. This process results in the retrieved material being consciously registered in the mind of the rememberer (Semon and Simon 1921; Tulving 1983; Bartlett 1932). An implication of this idea is that episodic memories may never be retrieved without semantic information to guide retrieval, and thus, remembered information does not directly represent either semantic or episodic memory but is the result of their interaction at the moment of remembering. Accordingly, to understand fully the nature of systems consolidation for semantic and episodic memory, it is necessary to identify the brain regions important for semantic memory, episodic memory, and the integrative process that links them during remembering. In addition, it will be important to determine how the brain areas involved in these processes and the connections between them change over time.

There are three main theories that have attempted to explain systems consolidation of semantic and episodic information. One theory posits that all kinds of declarative memory (semantic and episodic) become independent of the hippocampus as time passes after learning (standard consolidation theory (SCT); McClelland et al. 1995; Squire and Alvarez 1995). This feat is accomplished by gradual changes in connectivity within the neocortex (Marr 1971). Eventually, connections representing a particular memory in the neocortex are sufficiently well formed that the hippocampus is no longer needed for retrieval.

Another idea is that the episodic component of autobiographical memories is always dependent on the hippocampus (multiple trace theory and transformation hypothesis, Nadel and Moscovitch 1997; Winocur et al. 2010). According to this idea, each retrieval of an episodic memory results in the encoding of a copy of the memory within the hippocampus. With increasing numbers of copies, episodic memories become more robust to disruption over time. In parallel, gradual changes in connectivity within the neocortex affect the integration of new information into semantic memory. Unlike SCT, the transformation hypothesis holds that episodic information is transformed into semantic information as it is incorporated into the neocortex, leaving truly episodic information permanently dependent on the hippocampus. By contrast, semantic memories are thought to eventually become independent of the hippocampus.

Finally, another idea is that the hippocampus is not directly involved in memory encoding and storage at all, but is instead responsible for the construction of atemporal spatial scenes in which the details of memories may be organized (Mullally et al. 2012). According to this view, the organization of information into coherent scenes is critical for the retrieval of episodic information regardless of memory age. The theory is agnostic with respect to semantic information.

Thus, with respect to semantic information, all three theories accommodate the idea that retrieval becomes independent of the hippocampus as time passes after learning. With respect to episodic information, these theories may be summarized as follows: SCT, the hippocampus is important for encoding and time-limited storage; transformation hypothesis, the hippocampus is important for both encoding and storage irrespective of memory age; and spatial view, the hippocampus is

important for representing spatial information, a process needed during encoding and retrieval irrespective of memory age. All three theories lack detailed specification of the interactions that may exist between the MTL and other brain areas.

This review primarily considers evidence concerning the process by which autobiographical memories undergo systems consolidation. Beginning with autobiographical memory will facilitate later discussion of semantic memory, episodic memory, and the interaction between them. Our approach is to integrate findings from studies of memory-impaired patients together with findings from neuroimaging studies in order to identify the brain regions relevant for systems consolidation. Accordingly, we begin with studies of autobiographical memory in patients with circumscribed brain damage to several regions, including the MTL, which make up an autobiographical memory network. Next, we turn to neuroimaging studies of autobiographical memory where it is possible to consider how activity and connectivity in these regions changes as memories age in healthy individuals and patients. Finally, we briefly consider evidence from studies of semantic memory and compare it to autobiographical memory. We conclude that the autobiographical memory network may be thought of as two overlapping subnetworks, each responsible for the consolidation of a different type of information (semantic or episodic), and each intrinsically tied to the other by their interaction during retrieval and their mutual dependence on the MTL for the encoding of new information.

2 Autobiographical Memory

2.1 Autobiographical Memory in Memory-Impaired Patients

Studies of memory-impaired patients support the idea that memories become more invulnerable to disruption over time. Although this phenotype had been noted for some time (Ribot 1881), the study of the biological dissociation between recent and remote memory storage came to prominence when Scoville and Milner (1957) reported on the effects of bilateral MTL resection in the famous patient HM. In their initial description, HM's memories for his childhood were described as "vivid and intact" (pg. 14), yet he exhibited a profound deficit in his ability to encode new information. In addition, HM lost the ability to recall information learned within the three years prior to his surgery (e.g., the death of a favorite uncle). Although these reports of HM were suggestive of TGRA, they were based on clinical report rather than quantitative study.

For the early quantitative tests of autobiographical memory, individuals were invited to recall memories from throughout their lives when prompted with concrete nouns (e.g., Tell me a memory from your life that comes to mind when I say, "Tree")(e.g., Tell me a memory from your life that comes to mind when I say

“Tree”; Crovitz and Schiffman 1974). In these studies, the data are the approximate dates of the memories produced by participants. Using this technique, Sagar et al. (1985) found that (unlike controls) HM recalled all of his memories from a time when he was younger than 17 years old (11 years before his surgery). Similarly, this bias toward retrieval of distant memories as opposed to recent memories was also observed for other etiologies that cause memory impairment (i.e., bilateral electroconvulsive therapy, Korsakoff’s syndrome, damage to the medial diencephalon, and hypoxia; Zola-Morgan et al. 1983; Beatty et al. 1987). By contrast, this effect was not observed for other etiologies, such as patients with focal brain damage outside the MTL, Parkinson’s disease, Alzheimer’s disease, and unilateral electroconvulsive therapy (Sagar et al. 1985; Zola-Morgan et al. 1983). These results suggest two ideas. First, they demonstrate that different etiologies may impact retrograde memory in different ways. Second, they provide evidence for systems consolidation in that recent memories were less accessible than remote memories.

Yet, these early studies did not assess the quality of memory. Therefore, these studies could not differentiate between competing views about the fate of truly episodic memories after brain injury or disease. In order to address this issue, researchers measured the quality of memories by counting the number of episodic versus semantic details produced during narrative recollection. In addition, methods were developed to rate the quality of episodic memories holistically through the use of standardized rubrics that seek to evaluate the specificity of memories to time and place, the coherence of narratives, and the richness of imagery.

With increased attention to memory quality came an increased incidence of conflicting reports regarding the status of episodic memory retrieval in patients. Results were largely dichotomous. Patients could either recall richly detailed autobiographical memories from their remote past, or they could recall nothing at all of their remote past. For example, Wilson and Baddeley (1988) reported on a patient (KJ) who suffered from postmeningitic amnesia and was unimpaired at remembering richly detailed episodes from his past. By contrast, Tulving (1985) reported on a patient (KC) who suffered from amnesia pursuant to a closed head motorcycle injury and who exhibited severe impairment remembering any of his past or imagining his future.

Reports of spared or impaired retrieval of remote episodic memories have continued to appear to this day and Lah and Miller (2008) have exhaustively reviewed this literature that encompassed 53 single case studies and 10 group studies. They found that 83 % of studies reported some deficit in autobiographical memory. Of the subset of studies that examined the status of autobiographical memory across different time periods, 46 % found TGRA and 54 % found dense and ungraded retrograde amnesia (RA). These percentages changed very little when we added in the 14 additional studies that were published since Lah and Miller’s report (Philippi et al. 2015; Witt et al. 2015; Baird and Samson 2014; St-Laurent et al. 2011; Herfurth et al. 2010; Kurczek et al. 2015; Rosenbaum et al. 2008; Squire et al. 2010; Race et al. 2011; Irish et al. 2011; Thaiss and Petrides 2008; St-Laurent et al. 2014; Kirwan et al. 2008; St-Laurent et al. 2009).

Next, we explore three factors to determine if they can help explain the conflicting results across different patients. First, there may be differences in the procedures used to elicit memories. Second, there may be differences in the way that memories are evaluated. Third, there may be differences in the location and extent of brain damage in different patients.

First, differences in the methods used to elicit memories might explain discordant findings. To elicit memories, participants are typically given a memory prompt. There are many variations on this procedure where some studies provide support by asking specific questions for more detail, whereas others do not. If differences in the methods used to elicit memory were the cause of the discordant findings, then the findings should become concordant if the same method were used. However, this is not the case. For example, the autobiographical memory interview is a standardized tool for assessing episodic memory ability (Kopelman et al. 1989). Using the AMI, patients were reported to have intact autobiographical memory (Bright et al. 2006; Bayley et al. 2003, 2005; Stefanacci et al. 2000) or impaired autobiographical memory (e.g., Philippi et al. 2015; Cipolotti et al. 2001). Thus, one finds considerable variability in the ability to remember the past even when the same method was used.

A second possibility is that individual differences in scoring could have contributed to the different results across studies. For example, if a research group was liberal in their scoring methods then a ceiling effect would occur and both patients and controls would appear to have a similar capacity to retrieve autobiographical memories. This difficulty would be exacerbated when using measures that are coarse, when the range of scores is small, and when scoring relies on interpretation of somewhat ambiguous scoring instructions like evaluating whether memories are “specific in time and place” (pg. 732, Kopelman et al. 1989). However, when the same patients were tested using both coarse and fine-grained rating systems the severity of amnesia was the same (e.g., Hassabis et al. 2007; Bayley et al. 2005; Kirwan et al. 2008). In addition, when the same patients were scored by different laboratories where scorers were blind to group membership the results were the same (Dede et al., under review). Finally, ratings of data sets from different patient groups (e.g., patients with lesions limited to the MTL and patients with lesions to the MTL and lateral temporal cortex, Bright et al. 2006) carried out by a single laboratory would be expected to be similar. This is also not the case.

Third, there is the possibility that anatomical differences between patients may be the cause of the different results across studies. Indeed, it has long been recognized that patients of different etiologies have different RA profiles (e.g., Lidz 1942). Lah and Miller (2008) investigated how the location of anatomical damage affected the probability of observing TGRA by examining the findings from 11 patients or groups of patients with damage limited to the MTL and where memory had been tested for both recent and remote events. Ninety percent of these studies found evidence for TGRA and this percentage increases to 92 % when findings from similar studies published since their report (Squire et al. 2010; Kirwan et al. 2008) are also considered. By contrast, when lesions were not limited to the MTL

or when anatomy was not reported, fewer than half of the studies reported TGRA. This result underscores two important points. First, it indicates that obtaining detailed anatomical information from memory-impaired patients is a useful way to clarify the role of damaged areas. Second, the weight of evidence from studies where lesions were restricted to the hippocampus or MTL indicates that these regions are not necessary for the retrieval of truly episodic, remote autobiographical memories.

2.2 Possible Semanticization of Episodic Memories

Although the above findings from the study of patients with memory impairment support the idea that the MTL is not necessary for either the storage or retrieval of remote episodic memories, some have questioned whether the episodic content of these memories may ever be independent of the MTL (e.g., Winocur and Moscovitch 2011). According to the transformation hypothesis, semanticization is a necessary consequence of systems consolidation. The idea is that memories transform into semantic scripts as they become independent of the hippocampus. By this view, the experience of mental time travel that accompanies normal autobiographical memory is lost after hippocampal damage. If this is the case, then two predictions can be made: (1) when patients with hippocampal damage are instructed to recollect very detailed memories and fine-grained measures are used, a deficit should be revealed; and (2) when analysis is limited to only those memories that qualify as truly episodic, any deficit observed in patients with MTL damage should be magnified, because they should have no such memories. Neither of these predictions were confirmed.

To test the first prediction, two studies used the same method to assess whether patients could produce very detailed (non-semanticized) memories using scoring methods designed to capture the rich details that accompany autobiographical memories (Kirwan et al. 2008; Rosenbaum et al. 2008). Curiously, these two studies found opposing results: Kirwan et al.: patients were intact relative to controls, Rosenbaum et al.: patients were impaired relative to controls. The key to this puzzle, as reviewed earlier, pertains to whether or not the patients under study had damage limited to the MTL. With the exception of one patient with additional damage to the basal ganglia, the patients examined by Kirwan et al. (2008) had no damage beyond the MTL. By contrast, each patient examined by Rosenbaum et al. (2008) had volume reductions below the 95 % confidence intervals of controls in at least four regions outside of the MTL. In fact, regions outside the MTL best predicted performance for these patients. Specifically, using the data provided in Rosenbaum et al. (2008; Figs. 4 and 5), we used regional volume reductions to predict performance. Performance was best predicted by the volumes of right posterior temporal cortex, left posterior cingulate cortex, and the interaction between the volumes of these two regions ($R_{\text{adj}}^2 = 0.99$).

To test the second prediction, Kopelman and Bright (2012) reanalyzed the data from their earlier study (Bright et al. 2006) to exclude all but the most episodic and specific memories. Although they had originally reported that MTL patients exhibited weak remote memory, the reanalysis revealed that patients' remote memories were as strong as controls. If the episodic component of memories depended on the hippocampus then the opposite pattern of results would have occurred. That is, the patients' deficit should have increased because none of their memories would have been episodic or specific.

Taken together, these studies suggest that when damage is limited to the MTL, patients exhibit highly detailed memories of the past, their memories are indistinguishable from controls, and their memories are not semanticized (according to the most sensitive tests that exist).

2.3 The Autobiographical Memory Network

The above discussion used evidence from patients with focal brain damage to consider the role of the hippocampus and MTL alone in retrieving autobiographical memories. However, among neuroimaging studies of autobiographical memory, there is now broad agreement that memory retrieval is associated with activity in a network of brain regions (Fig. 1). The network is predominantly left lateralized and is composed of the hippocampus, parahippocampal gyrus, middle temporal gyrus, retrosplenial/posterior cingulate cortex, the temporoparietal junction (angular

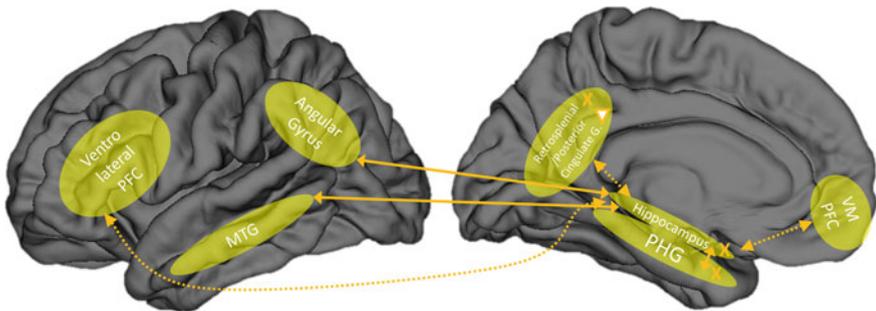


Fig. 1 The autobiographical memory network and memory consolidation. Regions in the autobiographical memory network are shown in yellow (cerebellum not shown). Yellow Xs indicate regions where damage is associated with temporally-graded retrograde amnesia. Yellow triangles indicate regions where brain activity decreases as memories age. Yellow arrows indicate that functional connectivity between the regions is associated with autobiographical memory retrieval. Dashed yellow arrows indicate functional connectivity that changes as memories age. The left image shows lateral surface of the brain and the right image shows the medial surface of the brain. The hippocampus is not visible on the surface of the brain, so it is depicted near the parahippocampal gyrus (PHG). PFC prefrontal cortex, MTG middle temporal gyrus, VM PFC ventromedial PFC, G. gyrus

gyrus), ventromedial prefrontal cortex (PFC), ventrolateral PFC, and the cerebellum (Svoboda et al. 2006; Cabeza and St Jacques 2007; Maguire 2001).

2.4 Effects of Lesions in the Autobiographical Memory Network Beyond the MTL

The patient literature reviewed thus far indicates that the hippocampus is not necessary for the retrieval of remote autobiographical memories. This implies that the information must be stored elsewhere. One prediction is that if the location of autobiographical memory storage outside the hippocampus were to be damaged, then focal RA should result. Focal RA is defined as RA without anterograde amnesia. Reports of focal RA are rare, and it is debated whether or not the phenomenon even exists (for review, see Kopelman 2000). Candidate structures for autobiographical memory storage may include those in the autobiographical memory network. In this section, we will examine the effects of focal damage to three of these regions: lateral temporal cortex, retrosplenial cortex, and medial PFC.

The lateral temporal cortex has long been implicated as a storage site for autobiographical memory. In Penfield's (1938) famous electrical stimulation studies in epilepsy patients, direct stimulation of lateral temporal cortex would sometimes produce vivid recollection-like mental experiences in the patients. Although the terms episodic and semantic were not in use at the time, Penfield's descriptions suggest that these recollections were episodic because the recollections included rich perceptual elements.

Patients with damage to both lateral temporal cortex and MTL exhibit a severe and ungraded RA for both episodic and semantic information (e.g., Bayley et al. 2005; Bright et al. 2006). However, when damage includes lateral temporal cortex alone, episodic memory is relatively spared and semantic memory is impaired (Hodges et al. 1992; Kapur et al. 1994; Irish et al. 2012; Hart and Gordon 1990). Somewhat confusingly, patients with damage thought to be limited to lateral temporal cortex have also been observed with dense RA for autobiographical events (O'Connor et al. 1992; Kapur et al. 1992). One potential difficulty is that damage limited to the lateral temporal cortex may result from several etiologies that are associated with variable patterns of damage. The examples cited here include patients who suffered from trauma (e.g., Kapur et al. 1992), encephalitis (e.g., O'Connor et al. 1992), and semantic dementia (e.g., Irish et al. 2012). These etiologies are all associated with the potential for widespread damage to multiple locations. In addition, the degree and precise location of damage within lateral temporal cortex itself is likely variable between patients. Thus, it may be that patients who exhibit dense RA for autobiographical events have damage that more completely encompasses the critical storage areas in lateral temporal cortex or that extends beyond lateral temporal cortex. To resolve this issue more research will be necessary where the location and extent of damage are measured.

Setting aside specific anatomical considerations, the dynamic interaction between semantic and episodic memory is important when considering the data from patients with damage to lateral temporal cortex. Under Tulving's (1983) conceptualization of semantic and episodic memory, episodic memories cannot be retrieved without a suitable semantic cue, and it has been suggested that semantic information may play a pivotal role in organizing episodic information during retrieval (Irish and Piguet 2013). Thus, the finding that patients with damage to lateral temporal cortex may sometimes exhibit a broad RA for both semantic and episodic information may not represent a true loss of episodic information. Rather, such deficits may be caused by a loss of the semantic information needed to cue episodic information. Indeed, Penfield (1938) found that removal of the very tissue he had stimulated to produce a specific recollection did not destroy the recollection, indicating that the stimulated tissue was not the site of storage. If this is the case, then more consideration of the methods used to cue memories may elucidate further the nature of deficits after lateral temporal lobe damage.

Another region in the autobiographical memory network that has been associated with memory deficits is retrosplenial cortex. Gainotti et al. (1998) found that a patient with a surgical lesion limited to retrosplenial cortex exhibited TGRA that extended approximately 10 years into the past for autobiographical events. Importantly, Gainotti et al. established that the hippocampus (which is adjacent to the retrosplenial cortex) was not damaged. Similar results were reported for a patient with retrosplenial damage following hemorrhage of an arteriovenous malformation (Valenstein et al. 1987). The close proximity of the retrosplenial cortex and the hippocampus makes it difficult to interpret findings from patients whose damage may encompass both regions (Heilman and Sybert 1977; Vann et al. 2009). In addition to TGRA, Gainotti et al. reported that the patient exhibited anterograde amnesia for visual stimuli, but not verbal stimuli. Other reports confirm a specific role for retrosplenial cortex in the episodic aspects of memory (for review see Miller et al. 2014). This modality-specific effect is strikingly different from the global anterograde amnesia exhibited by patients with hippocampal damage. Thus, the retrosplenial cortex appears to play a role in the consolidation of episodic memory and in encoding of new visual memories.

Finally, the medial PFC is part of the autobiographical memory network, but damage to this region does not consistently result in RA (for review, see Nieuwenhuis and Takashima 2011). Instead, medial PFC lesions are associated with confabulation (Schnider 2008), loss of impulse control (e.g., the famous patient Phineas Gage; Harlow 1868), and decreased self-related processing (Philippi et al. 2012). Given these results, it may be that the medial PFC is consistently activated during autobiographical memory retrieval because of the self-referential nature of autobiographical remembering rather than because of any specific role in memory encoding or storage.

Taken together the evidence reviewed here suggests that neither lateral temporal cortex, retrosplenial cortex, nor medial PFC acts as the ultimate site of episodic memory storage. Combined lesions to both MTL and lateral temporal cortex result

in dense RA. However, lesions limited to either region alone do not result in dense RA, and it may be that these regions are involved in the dynamic process of remembering rather than in storage. Specifically, semantic information represented in lateral temporal cortex may be necessary for cueing episodic retrieval. Finally, damage to medial PFC results in a wide range of executive impairments, but it does not result in a dense RA.

Although the review provided in this section is not exhaustive, it is important to consider what phenotype would be expected if one of these regions were the ultimate storage site of episodic memory. Such a phenotype would be clear and severe. The idea is not to say that the regions of the autobiographical memory network reviewed here play no role in the long-term storage of episodic information. Rather, our point is that damage to these regions does not result in a clear and severe RA for episodic information, suggesting that the primary site of storage must be elsewhere.

Perhaps one reason there is such difficulty locating the site of autobiographical memory storage is that the contents of memory are distributed throughout the cortex (for an early formulation of this idea, see Lashley 1950). Thus, memories for particular events are represented as connections between the regions that store the elements of content, rather than located in a single storage site. Based on the patient studies reviewed above, hippocampus and retrosplenial cortex likely act as important hubs for these connections during and shortly after encoding. With time, these connections are not needed for retrieval. One possibility is that as time passes after learning, connections between content elements in cortex may be retrieved via cortico-thalamo-cortical loops. Direct cortico-cortical connection is unlikely as it would be difficult to form new long-range connections. If this is true, then damage to this circuit should impair remote memory but not recent memory. Indeed, a patient with damage limited to the medial thalamus (patient JG) exhibited this pattern of RA (Miller et al. 2001, 2003). Moreover, the importance of interactions between MTL and anterior thalamus during memory encoding has been recognized for some time, and damage to anterior thalamus can result in anterograde amnesia (for review see Aggleton and Brown 1999). More investigation into the roles of different nuclei of the thalamus in anterograde and retrograde memory would illuminate this idea.

2.5 Neuroimaging Studies of Autobiographical Memory

Considering the patient literature reviewed above, two predictions can be made in turning to neuroimaging studies of autobiographical memory. First, the involvement of hippocampus and retrosplenial cortex in remembering should decrease with memory age. Second, the role of lateral temporal cortex might increase with memory age, but this finding may reflect this region's role in semantic memory. Although these predictions are relatively straightforward, the findings from

neuroimaging studies do not consistently support these predictions, with the exception of retrosplenial cortex.

For neuroimaging studies of autobiographical memory, participants are asked to retrieve autobiographical memories in the scanner. Either before or after scanning, participants are typically asked to provide narrative descriptions of the memories retrieved during scanning. Scoring of these narratives is used to relate neuroimaging data to aspects of memory quality. Even though there is agreement across studies that a specific set of regions is active during memory retrieval (i.e., the autobiographical memory network; Svoboda et al. 2006; Cabeza and St Jacques 2007; Maguire 2001), there is no consensus whether activity in these regions changes as a function of memory age.

Among the 14 studies that have examined activity as a function of memory age, no brain regions exhibited consistent increases or decreases in activity. In fact, the most common finding for these regions was to exhibit no change in activity with memory age, with the exception being posterior cingulate/retrosplenial cortex. Although the hippocampus exhibited changes with memory age in 7 studies, these changes had no consistent direction (Addis et al. 2004; Gilboa et al. 2004; Maguire and Frith 2003; Piefke et al. 2003; Piolino et al. 2004; Rekkas and Constable 2005; Soderlund et al. 2012).

The story is more consistent for the posterior cingulate/retrosplenial cortex. Most studies (7 out of the 12 that examined activity outside of the MTL) reported that activity changed with memory age and all the studies reported higher activity for recent than for remote memory. It is also worth mentioning that, although only 4 studies detected activity in parahippocampal gyrus that changed with memory age (Niki and Luo 2002; Rekkas and Constable 2005; Soderlund et al. 2012; Tsukiura et al. 2002), all but one of these studies found that activity was higher for recent memory than for remote memory.

In summary, the consistent reduction of activity in retrosplenial cortex with memory age is in accord with findings from memory-impaired patients suggesting that this area is more involved in remembering recent memories than remote memories. By contrast, the mixed results for the hippocampus are at odds with findings from patient studies. Further, throughout the rest of the autobiographical network activity does not appear to change with memory age. These results suggest two possibilities. First, although hippocampus and other areas of the autobiographical network remain active for old memories, these regions may not be necessary for remembering. Another possibility is that methodological difficulties may have contributed to the lack of temporal gradients in many areas of the autobiographical network.

Next, we discuss whether three factors could have contributed to the mixed pattern of results across the 14 studies, focusing on the hippocampus. None of the factors appear to explain why these studies fail to detect temporally graded activity. Nevertheless, future studies will benefit from avoiding these difficulties as novel procedures and analysis techniques are brought to bear on this issue. Indeed, carefully designed studies that incorporate new neuroimaging methods are

beginning to shed light on the ways in which the functional roles of brain regions may change with memory age, even as overall activity remains stable (see Novel neuroimaging approaches, below).

2.6 *Complicating Factors in Neuroimaging Studies of Autobiographical Memory*

One methodological concern for autobiographical studies is that remote memories tend to be less vivid, less detailed, and less emotional than recent memories (e.g., Addis et al. 2004; Gilboa et al. 2004; Maguire and Frith 2003). Thus, when one observes differences in brain activity between recent and remote memories, it is difficult to know whether these differences reflect memory age or differences in other qualities that change with memory age. For example, Addis et al. (2004) found that bilateral hippocampal activity was higher for recent memory than for remote memory. However, when the number of details and emotionality were covaried out, only the right hippocampus continued to respond according to memory age.

If differences in memory quality were driving differences in hippocampal activity, one would expect that most of the extant studies should also have identified the hippocampus; this is not the case. Further, one would also expect that the studies that did not detect differential activity would be the same ones that did not report differences in recent and remote memory quality. This is not the case. Taken together, these results suggest that hippocampal activity during episodic memory retrieval does not reliably reflect memory age or memory quality. To clarify the interpretation of memory consolidation studies it will be important for each study to ensure that recent and remote memories are similar in terms of quality before carrying out comparisons for brain activity (e.g., Addis et al. 2004; Gilboa et al. 2004; Bonnici et al. 2012). A good practice is to ensure that memories are similar according to the qualities that are considered central to episodic remembering (i.e., vividness, a sense of mental time travel, and specificity to time and place) and then carry out neuroimaging analyses.

Another methodological concern is how incidental encoding during memory retrieval may affect retrieval-related brain activity. In memory retrieval experiments, the events of the experiment are also encoded into memory. Consequently, subtle differences in activity for recent and remote memory retrieval may be overshadowed by encoding-related activity (Reas and Brewer 2013; Okado and Stark 2003; Buckner et al. 2001; Stark and Squire 2000). Future studies that measure incidental encoding will help disentangle these processes.

A third methodological concern regards the common practice of conducting a pre-scan interview to identify the memories to query during scanning. At first glance, it might appear that this practice would reduce the likelihood of identifying differential activation for recent and remote time periods because memories from

both time periods were retrieved recently. However, this is not the case. In fact, the majority of studies that used pre-scan interviews detected differential hippocampal activity for recent and remote memories (even though there was no consistent pattern to the differences). Moreover, hippocampal findings from studies that did not use a pre-scan interview were just as mixed. Thus, even though brain activity can change as a function of the number of recent memory retrievals (Rekkas and Constable 2006; Nadel et al. 2007; Svoboda and Levine 2009), it does not appear that retrieving memories prior to scanning is problematic when detecting activity related to memory age, at least where hippocampus is concerned.

2.7 Novel Neuroimaging Approaches to the Study of Autobiographical Memory Consolidation

The neuroimaging studies discussed above all examined the amplitude of evoked activity for memories as a function of memory age. Alternative ways to investigate how brain signals relate to memory consolidation do not require statistical differences between the evoked neural amplitudes for conditions of interest. For example, some techniques detect correlations between activity in different regions of the brain regardless of the mean amplitude (e.g., connectivity analyses) and other techniques detect patterns of activity across voxels regardless of the mean amplitude of activity (e.g., multi-voxel pattern analysis, MVPA; Norman et al. 2006; Haynes and Rees 2006). Next, we explore findings using these methods as well as studies that have used prospective designs to study autobiographical memory age over shorter timescales (e.g., days to months).

Only one study has examined connectivity as a function of memory age (see below). Instead, most work has examined how connectivity changes according to other factors, such as the stages of retrieval or the quality of memory. For example, within the autobiographical network, St Jacques et al. (2011) found that a subset of regions centered around the MTL (i.e., MTL, posterior cingulate/retrosplenial cortex, tempoparietal junction, and ventromedial PFC) exhibited high interconnectivity during both construction and elaboration stages of autobiographical retrieval. When memories were more easily retrieved, this MTL subnetwork influenced activity in another subnetwork centered around dorsomedial PFC (i.e., dorsomedial and ventrolateral PFC, middle temporal gyrus, tempoparietal junction, and posterior cingulate). Finally, greater connectivity between these two subnetworks during the elaboration stage of retrieval was associated with higher ratings of reliving.

Within its subnetwork, the MTL was more strongly connected with posterior cingulate and ventromedial PFC during autobiographical relative to semantic retrieval (Fuentemilla et al. 2014; Muscatell et al. 2010). Similarly, data collected while participants were at rest revealed that stronger connectivity between MTL and

posterior cingulate was associated with more episodic detail production in a subsequent test of autobiographical memory (Sheldon et al. 2016). In addition, findings from complimentary techniques with better temporal resolution, such as magnetoencephalography and intracranial recordings, support the idea that connectivity and coherence between MTL and medial parietal cortex are important for autobiographical retrieval, particularly when memories are associated with visual imagery (Foster et al. 2013; Fuentemilla et al. 2014).

Considering the central role of the MTL in the autobiographical memory network in healthy subjects, it is of interest to examine how damage to the MTL affects connectivity within the network. Maguire et al. (2001) identified similarities and differences in the autobiographical memory network between healthy individuals and an adult patient (Jon) with perinatal injury to the hippocampus. First, Jon had bilateral activations, whereas controls had predominantly left lateralized activations. Second, the most highly connected region of the autobiographical network was the retrosplenial cortex for Jon, but was the hippocampus for controls. A later study examined functional connectivity during rest in a group of three patients of mixed etiology with damage to the MTL (Hayes et al. 2012). They found that retrosplenial connectivity with ventromedial PFC, posterior cingulate, and posterior inferior parietal lobule was higher in the patients relative to controls. By contrast, connectivity between retrosplenial cortex and MTL was lower in patients relative to controls. These findings have been replicated with individuals who have temporal lobe epilepsy (Addis et al. 2007). These results indicate that the brain is capable of compensating for the loss of the hippocampus within the autobiographical memory network and that retrosplenial cortex and medial PFC appear to be important for this compensation. In addition, the fact that activation of the network is more or less intact following hippocampal damage suggests that although the hippocampus may play a role in normal autobiographical remembering, this role is not critical.

One study has examined connectivity for memories that differ according to memory age. Soderlund et al. (2012) used a within-subject test to identify how hippocampal activity and connectivity changed for memories ranging from 1 week to 10 years old. Although they did not detect differences in hippocampal activity as a function of memory age, they did detect differences in hippocampal connectivity. Specifically, hippocampal activity was positively correlated with activity in anterior cingulate, posterior cingulate, anteromedial PFC, and the precuneus for recent memories (1 week, 1 month, and 1 year old), but not for remote memories (10 years old). By contrast, hippocampal activity was negatively correlated with activity in superior temporal gyrus, ventrolateral PFC, and cuneus for remote memories (but not for recent memories). Thus, hippocampal activity was positively associated a set of midline regions for recent memory, but not for remote memory. At the same time, hippocampal activity was negatively associated with set of more lateral regions for remote memory, but not for recent memory. This study illustrates the idea that there can be dissociations between measures of evoked activity and

measures of connectivity. Connectivity studies represent fertile ground for detecting how the brain distinguishes between recent and remote memory.

MVPA assesses whether the pattern of activity in a set of voxels carries information capable of differentiating between two or more conditions of interest. Using this technique, Bonnici et al. (2012) demonstrated that regions of the autobiographical memory network could distinguish between 10 individual recent memories (2 weeks old) and it could also distinguish between 10 individual remote memories (10 years old). Specifically, temporal pole and ventromedial PFC contained more information about remote than recent memories. By contrast, MTL (i.e., the hippocampus, entorhinal cortex, and parahippocampal cortex) contained the same amount of information about recent and remote memories. Finally, they observed that voxels in posterior hippocampus (particularly subregions CA3 and dentate gyrus; Bonnici et al. 2013) contained more information about remote than recent memories while voxels in anterior hippocampus contained the same amount of information for recent and remote memories. This study supports the idea that cortical areas become more important for memory storage over time. In addition, it demonstrates the new types of questions that can be posed with MVPA.

In terms of study design, recent studies have employed prospective designs to study autobiographical memory. The benefit of prospective designs is that one has control over the time periods tested and the strength of memory. Although these studies typically measure memory age across short time scales (e.g., days, week, and months) they can detect the autobiographical memory network (Levine et al. 2004; Sheldon and Levine 2013). For example, in a heroic study by Sheldon and Levine (2013), participants recorded narratives soon after significant events in their lives in the 2 years preceding scanning. During scanning, audio clips of these narratives were replayed for recent memories (mean = 31 days old) or remote memories (mean = 565 days old). The authors found that, although evoked activity was no different for recent and remote memories, connectivity of anterior hippocampus differed according to memory age. Hippocampal connectivity with medial parietal regions (posterior cingulate and precuneus) was higher for recent versus remote memories, whereas hippocampal connectivity with PFC and superior temporal gyrus was higher for remote versus recent memories.

Another recent study relied on obtaining photographs of participant's autobiographical events by having them wear a camera (i.e., SenseCam) that took photos about every 30 s. Brain activity was different for the photos when tested 36 h versus 5 months after the photos were obtained. Specifically, activity in hippocampus, parahippocampal gyrus, and ventromedial PFC was higher for recent than for remote memories (Milton et al. 2011). However, according to MVPA analysis of whole-brain activity in response to SenseCam photos that were 1 versus 3 weeks old, there was insufficient information contained in brain activity to distinguish between these conditions (Rissman et al. 2016). Nevertheless, brain activity could distinguish between traditional categories of memory such as hits versus correct rejections or recollection versus familiarity judgments.

2.8 *Autobiographical Memory: Conclusions*

When memory-impaired patients have damage restricted to the MTL they exhibit TGRA and anterograde amnesia, suggesting that the MTL plays a permanent role in forming new memories and time-limited role in memory retrieval for autobiographical information. For these patients, recent memories are more vulnerable to disruption than remote memories, and remote memories are as detailed as memories from healthy individuals. Thus, the content of autobiographical memory does not reside exclusively in the MTL.

Candidate structures for memory storage might include the large network of regions revealed by neuroimaging studies of autobiographical memory. In patient studies, damage to either the hippocampus or the retrosplenial cortex causes TGRA, but there is no single area where loss results in dense RA for the lifetime. Instead, damage to other regions in the network is associated with impairments in components or features of autobiographical memory. For example, the loss of semantic memory results from lateral temporal cortex damage and the loss of self-referential thinking results from medial PFC damage. Finally, when damage compromises many regions in the network (e.g., patients KC, HC, PH, and GT), ungraded and dense deficits occur. Thus, even if the damaged areas are not involved in memory storage per se, extensive damage to the autobiographical memory network compromises memory retrieval regardless of the age of memory.

The findings from patients suggest that the regions of the autobiographical memory network are primarily associated with retrieval processes rather than memory storage. If this is the case, then so long as the retrieval processes are similar for recent and remote memory, brain activity should be similar for these conditions within the network. Neuroimaging studies of recent and remote memory confirm this idea, as brain activity in the autobiographical memory network does not correspond to the age of memory. An exception to this finding is retrosplenial cortex, which consistently exhibits higher activity for recent memories than remote memories. The hippocampus also exhibits changes in activity with memory age, but there is no consistent direction of change across studies. Activity changes in the hippocampus and other regions may be related to factors that differ across the individual studies such as the quality of memory or the extent of incidental encoding.

Connectivity within the autobiographical memory network changes according to the stage of retrieval (e.g., memory search vs. memory elaboration) and according to features of autobiographical memory (e.g., ease of retrieval, amount of reliving, visual imagery). In particular, connectivity between midline structures (e.g., MTL, retrosplenial and medial parietal cortex, and ventromedial PFC) is associated with features that are characteristic of episodic retrieval. Little is known about how connectivity changes with memory age. The one study that examined brain activity and brain connectivity as memories age indicates that connectivity between the

MTL and these same midline structures changed with memory age. Finally, memory consolidation was more readily detected as changes in connectivity between regions than as changes in activity in individual regions.

3 Semantic Memory

3.1 *Semantic Memory in Memory-Impaired Patients*

Semantic memory is not tied to any particular encoding context or event, and can be retrieved without interaction with episodic memory. Semantic memory is often assessed by asking participants to demonstrate everyday knowledge (e.g., word meanings, object names, and historical and cultural facts). Such tests draw on retrograde memory, often learned long before testing.

Memory-impaired patients of different etiologies have exhibited both spared and impaired semantic memory. For example, patient RFR exhibited a severe loss of autobiographical memory following encephalitis, but he was relatively unimpaired when asked to provide meanings of words, identify famous names, and rate the familiarity of famous faces (Warrington and McCarthy 1988). By contrast, other patients exhibited pure loss of word meanings without any apparent loss of other functions (Hart and Gordon 1990).

As with autobiographical memory, the locus and extent of brain damage is an important factor in the study of semantic memory impairment. For example, patient RFR had damage that encompassed all of right temporal lobe and left MTL, but left lateral temporal lobe was spared (McCarthy et al. 2005). By contrast, the patients who had impaired knowledge of word meanings had damage limited to left lateral temporal lobe (Hart and Gordon 1990). This pattern extends beyond these examples, and memory-impaired patients whose damage included MTL but spared left lateral temporal cortex consistently exhibit relatively intact retrograde semantic memory (Bayley et al. 2006; Kapur and Brooks 1999; Manns et al. 2003; but see Klooster and Duff 2015). Memory-impaired patients whose damage included left lateral temporal cortex consistently exhibited impaired retrograde semantic memory (Bayley et al. 2005; Gilboa et al. 2005; Bright et al. 2006; Hodges et al. 1992; Barbeau et al. 2012; Gardini et al. 2013; Smith 2014; Levy et al. 2004). These findings indicate that the MTL is not necessary for storage of semantic memory, but that areas within lateral temporal cortex are necessary.

Although the MTL is not necessary for storing semantic memory, it is needed for encoding new semantic memories. For example, patient RFR was retested 14 years after the initial test described above (McCarthy et al. 2005) and he continued to demonstrate intact semantic retrograde memory. By contrast, on a test of words that had entered the lexicon since his injury, RFR was severely impaired. Several other studies have confirmed that the MTL is critical for the encoding of new semantic

memories (e.g., Shimamura and Squire 1987), suggesting that MTL damage does not impact maintenance of information encoded before the onset of amnesia.

Thus, as with autobiographical memory, semantic memory relies on the MTL for encoding but retrieval eventually becomes independent of the MTL over time. Unlike autobiographical memory, lateral temporal cortex becomes increasingly important over time as new experiences are transformed into semantic knowledge. Studies examining the extent of RA after damage to the MTL indicate that the hippocampus remains important for the retrieval of semantic information for several years after memory encoding, and that the parahippocampal gyrus remains important for several more years (up to several decades) (Smith et al. 2013; Bayley et al. 2006).

3.2 Neuroimaging Studies of Semantic Memory Consolidation

The functional neuroanatomy of semantic memory has been less well characterized than autobiographical memory. Most studies have investigated brain activity associated with viewing famous faces or names. These studies identified some of the same regions as those involved in the core autobiographical memory network, such as the MTL, lateral temporal cortex, medial and lateral parietal cortex, and PFC (Denkova et al. 2006; Seidenberg et al. 2009; Woodard et al. 2010). In fact, a semantic memory network has been identified by a meta-analysis of 120 neuroimaging studies of semantic memory processing (Binder et al. 2009) and the network overlaps substantially with the autobiographical memory network (Fig. 2).

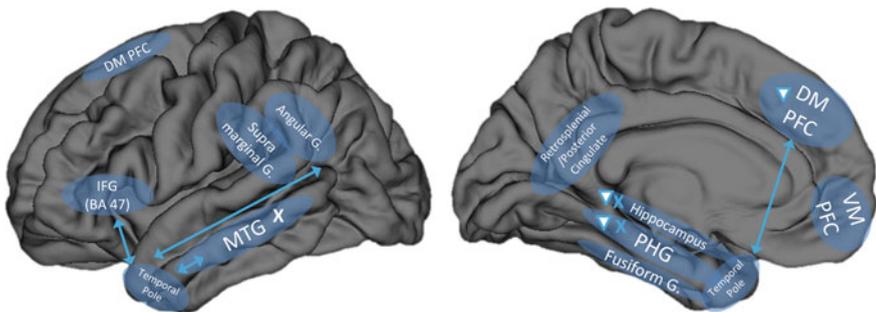


Fig. 2 The semantic memory network and memory consolidation. Regions in the semantic memory network are shown in blue. Blue Xs indicate regions where damage is associated with temporally graded retrograde amnesia and a white X indicates dense, ungraded retrograde amnesia. Blue triangles indicate regions where brain activity decreases as memories age. Blue arrows indicate that functional connectivity between the regions is associated with semantic memory and processing. The left image shows lateral surface of the brain and the right image shows the medial surface of the brain. The hippocampus is not visible on the surface of the brain, so it is depicted near the parahippocampal gyrus (PHG). PFC prefrontal cortex, IFG inferior frontal gyrus, MTG middle temporal gyrus, VM PFC ventromedial PFC, DM PFC dorsomedial PFC, G. gyrus; BA Brodmann area

In addition to the regions that are shared between the networks [(parahippocampal gyrus, middle temporal gyrus, posterior cingulate/retrosplenial cortex, angular gyrus, inferior frontal gyrus (BA 47), and ventromedial PFC (BA 9,10)], the semantic network also includes dorsomedial PFC (BA 8), supramarginal gyrus (just anterior to the angular gyrus), fusiform gyrus, and temporal pole (Visser et al. 2010).

One idea is that the regions that are common to both networks support the semantic memory component of autobiographical memory. Alternatively, these regions may support cognitive operations that are common for both autobiographical memory and semantic memory such as selecting relevant information from memory stores. Notably absent from this network is the hippocampus, though the studies examined by the meta-analysis examined semantic information learned long ago (e.g., information about word meanings).

Seven studies have examined semantic memory as a function of memory age (two of these studies used the same dataset for MTL analyses, Douville et al. 2005; and non-MTL analysis, Woodard et al. 2007; these two publications are considered one study here). Half of these 6 studies identified activity in the MTL that changed with memory age and all these studies found that activity was higher for recent memories than for remote memories (entorhinal cortex, Haist et al. 2001; hippocampus and parahippocampal gyrus, Douville et al. 2005; hippocampus and entorhinal cortex, Smith and Squire 2009).

Looking outside the MTL for evidence supporting semantic memory consolidation, only two of the six studies identified regions where activity changed with memory age (Smith and Squire 2009; Woodard et al. 2007). For both studies, the activity in dorsomedial PFC (middle frontal gyrus, BA 8) decreased with memory age. In addition, activity in middle temporal gyrus decreased with memory age when participants were asked to recognize famous names (Woodard et al. 2007), but increased with memory age when they identified news events (Smith and Squire 2009).

More work is needed to identify the non-MTL regions that support semantic memory consolidation. Most of the extant studies identified no regions outside the MTL, but the study that identified many regions outside the MTL (Smith and Squire 2009) differed from the other studies. It examined memory age for many items across many time periods instead of for relatively few items across few time periods. Specifically, Smith and Squire (2009) examined 160 news events that occurred 1–30 years prior to scanning separated into 7 time periods. By contrast, the other studies either examined few time periods (one recent time period and one remote time period) or queried few items (as few as 24).

No studies have examined how connectivity changes during semantic memory consolidation. Nevertheless, functional connectivity studies of semantic memory and processing indicate that connectivity associated with the temporal pole is important for semantic retrieval. For example, Maguire et al. (2000) determined that connectivity between temporal pole and middle temporal gyrus was stronger for semantic memory than for autobiographical memory. Using scanning procedures designed to capture signal in the temporal pole, Jackson et al. (2016) found that semantic retrieval was associated with connectivity between temporal pole and

middle temporal gyrus. Further, the temporal pole was also connected to dorso-medial PFC, and temporo-parietal junction during semantic memory judgments.

3.3 Prospective Studies of Memory Consolidation Across Short Time Scales

The time scales investigated with prospective designs are much shorter than retrospective designs, i.e., ranging from hours to months. The benefit of prospective designs is that one has control over variables such as the time periods tested and the strength of memory. Prospective studies have not examined semantic memory *per se*, because true semantic memory is thought to form as regularities are extracted across many separate episodic experiences. Instead, prospective studies have examined laboratory-based memory that is typically devoid of the rich, contextual information associated with episodic memory. Thus, we discuss these studies in the semantic memory section because they are distinct from the type of memory normally considered to be episodic memory (i.e., studies of autobiographical memory).

The findings for the hippocampus are mixed across many of the prospective studies, with some studies reporting decreasing hippocampal activity with memory age (Takashima et al. 2006, 2009; Smith et al. 2010; Yamashita et al. 2009), and some studies reporting the opposite pattern (Bosshardt et al. 2005a; Suchan et al. 2008). Other studies found both patterns or no effect memory age (Stark and Squire 2000; Bosshardt et al. 2005b; Janzen et al. 2008; Vilberg and Davachi 2013; Takashima et al. 2007).

A shortcoming of most prospective studies, and a possible explanation for the mixed findings, is that many of these studies have examined only two time periods: recent and remote. In a study that examined 4 time periods across three months (Takashima et al. 2006), there was a steep reduction in hippocampal activity and a parallel increase in ventromedial PFC activity with most of the changes occurring in the first day after learning. Studies that demonstrate systematic differences across multiple time periods should be considered more reliable than studies that find a difference across just two time periods.

Changes in functional connectivity as memories age from hours to weeks have also been observed across many studies and the findings are consistent with the ideas of systems consolidation. Specifically, connectivity between hippocampus and cortex decreased with memory age (Takashima et al. 2006, 2009; Smith et al. 2010), whereas connectivity between cortical regions increased with memory age (Nieuwenhuis et al. 2012; Takashima et al. 2007, 2009; Smith et al. 2010). These findings indicate that changes in connectivity can occur over timeframes as short as days and weeks, but more effort is needed to identify cortical regions that demonstrate a consistent pattern of changes with memory age.

Perhaps the most striking aspect of prospective studies is that the neural reorganization appears to occur over a short time scale (hours to months). By contrast,

TGRA in memory-impaired patients extends over several years. It is possible that the neural changes observed in the days and weeks after learning are the first reflection of a process that takes years to complete. In this case, changes in brain activity and functional connectivity are observed over a short time frame, whereas changes in anatomical connectivity (i.e., the strengthening of connections between the brain regions that contain the contents of memory) take years to form.

Another important observation about the short time frame examined by prospective studies is that this time frame is in good agreement with the findings from the animal literature (Bontempi et al. 1999; Maviel et al. 2004; Frankland et al. 2004). In animal studies of memory consolidation, memory retrieval typically becomes independent of the hippocampus within a few weeks after learning. Thus, the prospective method may provide a way to begin to connect the human and animal literatures.

Prospective studies also allow the assessment of the neural changes associated with factors known to improve memory consolidation (i.e., to attenuate forgetting). For example, study episodes that are spaced over time (spaced learning) reliably create longer lasting memories. By contrast, study episodes that follow each other closely (massed learning) are less effective. Several studies have investigated neural differences between memories studied in a spaced versus massed fashion. Vilberg and Davachi (2013) found that word-picture associations studied in a spaced fashion were more likely to be remembered if activity in the hippocampus and perirhinal cortex was correlated during encoding. By contrast, the correlation between activity in these regions was not important for remembering associations that were learned in a massed fashion, suggesting that connectivity between brain regions supports the improved memory consolidation observed after spaced learning. Takashima et al. (2007) contrasted brain activity during retrieval for face-locations associations learned via massed versus spaced learning. They found that activity in precuneus, temporal pole, temporoparietal junction, middle temporal gyrus, and ventromedial PFC were higher for associations learned in a spaced versus massed fashion, even though memory performance was similar for the two conditions. Furthermore, connectivity between fusiform face area (an area associated with face processing and face memory) and precuneus was higher for associations learned in a spaced versus massed fashion.

3.4 Semantic Memory: Conclusions

Damage limited to the MTL consistently causes anterograde amnesia and TGRA for semantic information. In agreement with these findings, the hippocampus is not a part of the semantic memory network identified by studies of remote semantic memory (e.g., word knowledge). By contrast, the hippocampus is readily identified by neuroimaging studies examining recently learned semantic information (e.g., famous faces, news events), and in these studies MTL activity decreases with memory age. Taken together, these findings are consistent with the idea that the

hippocampus plays a permanent role in encoding new semantic memory, but plays a time-limited role in semantic memory retrieval.

The semantic memory network overlaps substantially with the autobiographical memory network including 7 of the same regions (hippocampus, parahippocampal gyrus, middle temporal gyrus, retrosplenial cortex/posterior cingulate cortex, angular gyrus, ventromedial PFC, and ventrolateral PFC). In addition, the semantic network includes four additional regions (dorsomedial PFC, supramarginal gyrus, fusiform gyrus, temporopolar cortex) and the network excludes one region (cerebellum). Although little work has examined how activity in this network changes with the age of memory, it appears that activity in the MTL and dorsomedial PFC consistently decreases with memory age.

Most regions in the network did not exhibit changes in activity with memory age. This finding may indicate that these regions are always involved in semantic memory retrieval. For example, damage to lateral temporal cortex causes severe and ungraded RA, suggesting that this region may store the long-term representation of semantic information. Indeed, semantic memory and semantic processing are both associated with increased connectivity of the temporal pole. It will be important to identify which connections are important for semantic memory consolidation.

There has been an explosion of recent work examining memory consolidation over shorter timescales (days, weeks, and months), when systems consolidation is observed in animals. In humans, the neural changes that emerge within the days and weeks after learning may be the first signs of systems consolidation that takes years to complete.

4 Conclusions

In this section, we compare and contrast memory consolidation for autobiographical memory and semantic memory, identifying three main points that reflect the findings from patient studies and neuroimaging studies.

First, the autobiographical network (Svoboda et al. 2006; Cabeza and St Jacques 2007; Maguire 2001) overlaps substantially with the semantic network (Binder and Desai 2011; Binder et al. 2009). It is perhaps unsurprising that these networks overlap because autobiographical memory requires retrieval of both episodic and semantic components. Indeed, TGRA for both semantic and episodic information is observed after damage limited to MTL. One idea is that there may be a common network for all declarative memory retrieval (Burianova et al. 2010; Burianova and Grady 2007), whereby episodic and semantic retrieval are not distinguished by whether or not regions are active. Instead, episodic and semantic retrieval may be better differentiated by the relative degree of activity and connectivity between regions of the network (Maguire et al. 2000; Heisz et al. 2014).

Although this common memory network was identified by studies of memory retrieval, it is also identified when individuals simply rest quietly (default mode network; Andrews-Hanna et al. 2010, 2014), suggesting that the memory retrieval

network may play a role in other cognitive operations. Specifically, the network is active when individuals imagine the future (Addis et al. 2009) or think about events from different perspectives (theory of mind; Spreng and Grady 2010). These findings suggest that the cognitive resources brought to bear during autobiographical and semantic remembering represent a number of subprocesses that interact in different ways depending on the specific task at hand (Addis et al. 2009). Certain regions within the network operate as common connection points across cognitive operations. For example, posterior cingulate and anteromedial PFC may be particularly important because they were the most highly interconnected of all the regions (Andrews-Hanna et al. 2014).

Second, even though semantic and episodic memory are contained within larger one network, focal damage to each of two regions is associated with amnesia for one type of memory but not for the other. Specifically, damage limited to lateral temporal cortex is associated with ungraded RA only for semantic memory, whereas damage limited to retrosplenial cortex is associated with TGRA only for episodic memory. Interestingly, there is no single region within the memory network where damage results in ungraded RA for autobiographical events. By contrast, multiple regions must be damaged for all autobiographical memories to become inaccessible.

Changes in regional brain activity with memory age also distinguish the two types of memory. For autobiographical memory, most studies detected regions outside the MTL where activity changed with memory age, even though the only consistent change was reduction of activity over time in posterior cingulate/retrosplenial cortex. For semantic memory, only a small minority of studies detected regions outside the MTL where activity changed according to memory age. Thus, the cortical regions in the network must be more sensitive to autobiographical memory age than to semantic memory age.

Changes related to memory age within the MTL also differentiate semantic from episodic memory. Specifically, the MTL consistently exhibits less activity for remote semantic memories than for recent ones, but this consistent pattern is not observed for autobiographical memory. On its own, the observation that the MTL is active during remote autobiographical retrieval suggests that the MTL might play a permanent role in retrieving episodic content. However, patients with damage limited to the MTL do not exhibit deficits in remote autobiographical retrieval. Taken together, it is likely the case that although MTL activity sometimes occurs during both recent and remote memory retrieval, it is only necessary for retrieval of recent memories.

One possibility is that, as time passes after learning, episodic memories form multiple, redundant traces supported by different regions of the network making them stronger and more invulnerable to disruption. Analysis of brain connectivity in patients with hippocampal lesions supports the idea that traces stored outside the MTL can support successful autobiographical memory when the MTL is damaged. In accordance with this idea, rodent studies investigating the acute versus chronic effects of hippocampal lesions on remote memory retrieval suggest that the hippocampus may be the default structure that supports memory retrieval, but that

other structures can take over this role when the hippocampus is not available (Goshen et al. 2011).

Finally, the memory network is primarily important for supporting memory retrieval rather than for storing the content of memory. Neuroimaging in healthy participants and studies of patients with focal lesions to cortical areas suggest that the content of memory is stored throughout cortex, primarily in secondary sensory cortex and association cortex. For example, Gallant and colleagues (Huth et al. 2016, 2012) have identified that information about semantic meaning is stored throughout cortex. Specific regions of cortex appear to specialize in semantic meaning related to different concepts, such as animate versus inanimate or man-made versus natural. Moreover, patients with focal damage to sensory and association cortex often exhibit RA for specific components of memory, such as amnesia for the colors but not the content of memory or amnesia for animate but not inanimate objects (for review, see Squire and Wixted 2011).

In summary, the results reviewed here tend to agree with SCT (McClelland et al. 1995; Squire and Alvarez 1995). When a memory is created, new connections are formed between cortical regions (e.g., sensory and association cortices), and regions in a memory network initially support these connections. Some regions in the network have a time-limited role in storing the memory trace (e.g., the hippocampus, retrosplenial cortex, and dorsomedial PFC), but others have a permanent role (e.g., lateral temporal cortex for semantic memory). As time passes after learning, connections between cortical storage areas become stronger, making the memory less vulnerable to disruption.

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