Chapter 9.1. Amnesic Syndrome

[In: Handbook of Human Memory: Foundations and Applications]

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Abstract

Clinical studies of patients with amnesia have inspired decades of research, contributing to the characterization of distinct forms of memory. At the same time, it has become clear that amnesia can result from lesions of a number of brain regions – including but not limited to the medial temporal lobes – that form an integrated neural network subserving memory.

In the first part of this chapter, we characterize the amnesic syndrome, including its anatomic correlates and associated pattern of functional impairment. In the domain of anterograde memory, we examine how amnesia impacts the ability to acquire new episodic memories as well as new semantic memories, with an emphasis on the contribution of distinct processes to patients' performance. In the domain of retrograde memory, we discuss the scope of impairment with regard to the distinction between episodic and semantic memory. The status of implicit memory in amnesia is also briefly reviewed, followed by consideration of impairments in domains other than long-term memory, including perception, short-term memory, and episodic simulation.

In the second part of the chapter, we discuss the most common neurological etiologies of amnesia, with consideration of the pattern of memory impairment and associated neuropathology. These include stroke, hypoxic-ischemic brain injury, encephalitis, Korsakoff's syndrome, and transient global amnesia. For etiologies typically associated with lesions outside or beyond the medial temporal lobe, additional neurocognitive deficits are considered that may be superimposed on the classic presentation of the amnesic syndrome.

Chapter 9.1. Amnesic Syndrome

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The amnesic syndrome is characterized by profound memory deficits in the context of otherwise relatively preserved cognitive function. It entails severe anterograde amnesia (i.e., difficulty remembering events and facts encountered after onset of a neurological condition) and a variable level of retrograde amnesia (i.e., impaired memory for events and facts acquired prior to the neurological event). Memory loss is usually global, affecting all types of information (verbal and nonverbal) in all modalities (visual, auditory).

The impact of amnesia is pervasive, with patients requiring support and supervision for completing instrumental activities of daily living such as managing their finances, medications, or appointments. Individuals with amnesia may feel as if constantly tuning in to the middle of a movie and having to make sense of it. Patient H.M., who at age 27 underwent bilateral surgical removal of the medial temporal lobes (MTL) to treat intractable epilepsy (Scoville & Milner, 1957), described it as “waking from a dream”. H.M. was observed to use people’s accents to guess their place of origin, or the weather to infer the current season (Milner, Corkin, & Teuber, 1968, p. 217). Although patients can engage appropriately in the moment, they may repeat the same question within a few minutes of a conversation taking place, and may not recognize individuals they met since becoming amnesic, even after repeated and extended encounters with them. Unlike portrayed in some movies, patients with an amnesic syndrome usually do not lose the sense of who they are, and their memory for remote events is at least relatively preserved compared to their profound anterograde amnesia.

Amnesia must be differentiated from more common forms of memory problems, for example those associated with age-related cognitive decline or with depression and anxiety. In those cases, memory problems are generally related to reduced learning efficiency, decreased processing speed, and diminished ability to ignore irrelevant information rather than forgetting per se (e.g., Harada, Natelson Love, & Triebel, 2013; Kizilbash, Vanderploeg, & Curtiss, 2002). The amnesic syndrome must also be distinguished from memory difficulties associated with executive dysfunction following disruption of frontal-subcortical circuits, for example resulting from traumatic brain injury (see Chapter 9.6. on "A Review of the Consequences of Moderate-to-Severe Traumatic Brain Injury on Various Memory Processes") or white matter changes due to vascular disease. These difficulties pertain to the top-down control of memory processes, and present as a less severe impairment, marked by susceptibility to interference and intrusions across sources and contexts (Preston & Eichenbaum, 2013). Further, although severe memory impairments are the hallmark deficit of early stage neurodegenerative disorders such as Alzheimer's disease (e.g., Tierney et al., 1996), these memory deficits are typically accompanied by impairment in multiple neurocognitive domains.

This chapter focuses on amnesia related to non-neurodegenerative neurological etiologies. Psychogenic forms of amnesia without direct brain basis occur in the context of psychiatric disorders, but are not discussed here [for review, see Staniloiu and Markowitsch, 2014 and Harrison et al. 2017]. We first briefly consider the neuroanatomic correlates of amnesia. The functional syndrome of amnesia is then characterized, detailing patterns of neurocognitive deficits and areas of preserved function. In this section we focus primarily on the effect of MTL lesions, as MTL amnesia has been studied most extensively. In the final section, the neurological etiologies associated with

the amnesic syndrome are examined, with consideration of associated neuropathology. For etiologies typically associated with lesions outside or beyond the MTL, additional neurocognitive deficits that may color the amnesic syndrome are discussed.

I. Anatomic Correlates of Amnesia

Reviewing the effects of MTL resections in H.M. and a number of other cases, Scoville and Milner (1957) concluded that only resections extending posteriorly into the hippocampus resulted in amnesia. Moreover, the severity of amnesia appeared to be linked to the extent of MTL resection. These findings set the stage for subsequent evidence from animal and human studies (Mishkin, 1978; Squire & Zola-Morgan, 1991) demonstrating the importance of the hippocampus as well as other MTL structures in memory. At the same time, evidence of amnesia in the context of Wernicke-Korsakoff syndrome (Victor, Adams, & Collins, 1971) and thalamic stroke (Teuber, Milner, & Vaughan, 1968) provided evidence for a critical role of the diencephalon in memory. Significant memory impairment was also reported with lesions of the major white matter tracts connecting the hippocampus and diencephalon, i.e., the fornix (Grafman, Salazar, Weingartner, Vance, & Ludlow, 1985; Heilman & Sypert, 1977) and the mammillary-thalamic tract (Von Cramon, Hebel, & Schuri, 1985).

Taken together, these findings have highlighted the critical role of an extended hippocampal network in memory. This circuitry, originally described by Papez (1937), proceeds from the hippocampus (subiculum) to the mammillary bodies (via the fornix), anterior thalamic nuclei (via the mamillary-thalamic tract), cingulate gyrus (via the cingulum bundle and internal capsule), parahippocampal cortex (via the cingulum bundle), and back to the hippocampus (Figure 1). Recent revisions have suggested a system of hippocampal-diencephalic-cingulate interconnections that is more complex, for

example including direct routes connecting the hippocampus to the cingulate cortex (through the retrosplenial cortex) or to the anterior thalamic nuclei (Bubb, Kinnavane, & Aggleton, 2017). Amnesic syndromes may result from disconnection at any level of the memory network, as discussed in more detail below.

Lesions of the basal forebrain also can result in amnesia (Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985), suggesting that in addition to the MTL and diencephalon, the basal forebrain plays a critical role in memory. This structure is thought to provide modulatory inputs via diffuse cholinergic connections that reach across the entire hippocampal system (Aggleton, 2014).

Postmortem neuropathological analysis of cases with human amnesia has demonstrated that damage limited to selective portions of the hippocampal formation, such as the CA1 subfield, may be sufficient to produce enduring moderately severe memory impairment (Rempel-Clower, Zola, Squire, & Amaral, 1996; Zola-Morgan, Squire, & Amaral, 1986). With the advent of high resolution MRI, additional cases of amnesia have been described with lesions limited to other specific hippocampal subfields (Baker et al., 2016; Miller et al., 2017). Interpretative caution should be exercised, however, as focal hippocampal damage may lead to broader structural (Henson et al., 2016) and functional abnormalities (Hayes, Salat, & Verfaellie, 2012; Henson et al., 2016; Reed et al., 1999) in other parts of the extended hippocampal system.

II. The Functional Syndrome of Amnesia

Much of the initial description of the amnesic syndrome comes from detailed investigations of H.M. (Corkin, 1984), which demonstrated that severe amnesia can exist as an isolated impairment in the context of preserved intelligence, language and

abstraction, and perception. Moreover, H.M.'s ability to encode and retain information in the very short term, i.e., with minimal delay and in the absence of distraction, appeared intact (e.g., he could repeat six digits forwards and five backwards). Even more strikingly, it became apparent that he could learn and retain new perceptual-motor skills over longer periods of time (Milner et al., 1968). These findings led to the understanding that memory is not unitary, and that declarative memory, specifically, depends on the integrity of the MTL. Subsequent studies of amnesic cases that allowed for more precise lesion localization, in combination with functional neuroimaging research in normal individuals, have led to a more nuanced view, suggesting that damage to the hippocampus proper and surrounding MTL cortices may yield distinct patterns of impairment. In turn, a better understanding of the processes mediated by these regions has guided examination of patients' performance in domains beyond long-term memory that may depend on these same processes.

II.1. Anterograde Amnesia

Anterograde amnesia, or the inability to form new long-term memories, i.e., memories that persist beyond delay and distraction, is the hallmark deficit of the amnesic syndrome. The impairment is evident in the difficulty forming new memories of events (episodic memory), as well as acquiring facts and concepts (semantic memory).

II.1.a. Acquisition of Episodic Information

Findings in H.M. suggested that the impairment in new learning in amnesia is evident across a variety of tasks and affects all types of materials (Corkin, 1984; Milner et al., 1968). More recent work, however, has qualified both of these premises. In a review of recognition memory in human amnesia, Aggleton & Shaw (1996) found that

patients with selective lesions to the hippocampus (or its diencephalic projections) had relatively preserved forced-choice item recognition in the context of impaired cued and free recall, whereas patients with more extensive lesions had marked deficits in both types of tasks. These findings were interpreted with reference to dual process models of recognition (Jacoby & Dallas, 1981; Yonelinas, 1994), which distinguish between recollection (the ability to retrieve specific contextual details) and a sense of familiarity (the feeling of immediate knowing without connection to a specific context). Namely, it was suggested that the hippocampus is critical for recollection – a process necessary for recall, whereas other MTL regions, particularly perirhinal cortex, can support familiarity-based recognition (Brown & Aggleton, 2001; Yonelinas, 2005).

Although recognition typically involves both recollection and familiarity, recognition memory tasks vary greatly in their relative dependence on these two processes. For instance, familiarity is particularly useful on forced-choice recognition tests, where assessment of the relative difference in familiarity between a target and its corresponding foil is sufficient to support accurate performance. By contrast, in a yes/no recognition task with highly similar targets and foils, familiarity is a poor diagnostic, and memory for the list context becomes crucial (Norman and O'Reilly, 2003). Accordingly, the performance of patients with hippocampal lesions would be expected to vary depending on the nature of the recognition task and its relative dependence on recollection versus familiarity.

Using methods designed to distinguish the contribution of recollection and familiarity within a single task, additional patients were subsequently described with selective impairment in recollection following lesions to the hippocampus (Aggleton et al., 2005) or extended hippocampal circuit, including atrophy of the fornix and/or

mammillary bodies (Vann, Tsivilis, et al., 2009) and anterior thalamic lesions (Carlesimo, Lombardi, Caltagirone, & Barban, 2015). Yet, other studies reported impairments in recollection and familiarity with lesions limited to the hippocampus (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Wais, Wixted, Hopkins, & Squire, 2006). These discrepant findings likely reflect differences among amnesic patients, but the nature of these differences remains poorly understood. It should be noted, however, that contradictory findings have similarly been obtained in studies of pre-surgery epileptic patients in whom electrophysiological activity was directly measured from the hippocampus (Merkow, Burke, & Kahana, 2015; Staresina et al., 2016) as well as in neuroimaging studies of healthy individuals (e.g., Rugg et al. 2012; Smith, Wixted, & Squire, 2011). This suggests that other factors, including the nature of the stimuli and exact test demands, also require further consideration.

One argument against the anatomical dissociation between recollection and familiarity in the MTL has been that recognition tests are typically easier than recall tasks, and thus less sensitive to more restricted damage of the hippocampus only (Wixted & Squire, 2010). Compelling evidence against this argument, however, comes from a report of the reverse dissociation in a patient who underwent a rare resection of the left anterior temporal lobe including the perirhinal cortex but sparing the hippocampus: That patient showed impaired familiarity but intact recollection (Bowles et al., 2007, 2010).

Other studies have suggested that the status of recognition memory following hippocampal lesions may depend on the nature of the to-be-learned information. Evidence suggests that recognition memory for faces is consistently spared following restricted hippocampal lesions (e.g., Aly, Knight, & Yonelinas, 2010; Bird & Burgess, 2008; Cipolotti et al., 2006; Smith, Jeneson, et al., 2014). By contrast, studies of

recognition memory for other types of stimuli, and especially verbal materials, have yielded more mixed results, with either intact (Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Turriziani, Serra, Fadda, Caltagirone, & Carlesimo, 2008) or impaired (Bird & Burgess, 2008; Cipolotti et al., 2006) recognition. These mixed findings nonetheless can be accommodated by the dual process framework, on the assumption that there is commonly a significant contribution of recollection to recognition memory. In other words, the impairment in recognition of verbal materials may be due to the fact that successful performance requires assessing the source of familiarity (i.e., judging whether an item's familiarity is due to its presentation in the experimental context rather than to another non-experimental source). Recognition memory for novel faces, in contrast, may be preserved, as the use of novel faces obviates the need to disambiguate the source of familiarity considering their uniqueness.

Recollection by nature depends upon successful binding of the elements of experience, and as such, associative memory tasks can be particularly sensitive tests of recollection. Consistent with this observation, amnesic patients with extensive MTL lesions tend to display disproportionate impairment in associative compared to single item recognition (Giovanello, Verfaellie, & Keane, 2003; Kan, Giovanello, Schnyer, Makris, & Verfaellie, 2007) and in patients with restricted hippocampal lesions who show intact item recognition, associative recognition nonetheless is impaired (Mayes et al., 2004; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004). Interestingly, patients with selective hippocampal lesions tend to show deficits that are more pronounced for the association of stimuli across domains (e.g., visual and auditory) compared to within-domain (e.g., visual and visual) – (e.g., Borders, Aly, Parks, & Yonelinas, 2017; Mayes et al., 2004; but see Turriziani, Fadda, Caltagirone, & Carlesimo, 2004). This may reflect

the larger contribution of familiarity to within- compared to cross-domain recognition. Notably, Quamme, Yonelinas, & Norman (2007) showed that when two unrelated words are encoded as a novel compound with specific meaning (e.g., "cloud-lawn" defined as a "a yard used for sky-gazing"), familiarity processes were more likely to be recruited, and patients with selective hippocampal lesion displayed improved associative recognition under these conditions. The creation of such unitized representations may account for the relative preservation of within-domain associative recognition.

More broadly, the anterograde memory deficits discussed here can be understood within the context of an anatomical model of the MTL that places the hippocampus at the top of the processing hierarchy (see Figure 2). "What" information from the ventral visual stream culminates in the perirhinal cortex, allowing for the integration of object features into complex object representations that can support familiarity. "Where" information from the dorsal stream culminates in parahippocampal cortex, supporting representation of the spatial and broader situational context in which items are presented (Aminoff, Kveraga, & Bar, 2013; Diana, Yonelinas, & Ranganath, 2007). Representations from the perirhinal and parahippocampal cortices are then relayed to the hippocampus via the lateral and medial entorhinal cortex, respectively, enabling further information refinement and integration into episodic memory representations. These complex hippocampal representations, which encompass both the separate features of an event and their relations within a spatial and temporal context, are necessary to support recollection.

II.1.b. Acquisition of New Semantic Information

Semantic memory refers to knowledge that is not tied to a particular context (Tulving, 1972). Its neurobiological substrate includes modality-specific representations

and supramodal representations that increase in abstraction with gradual convergence of multiple perceptual streams in the temporal lobe and inferior parietal lobe (Binder & Desai, 2011; Patterson, Nestor, & Rogers, 2007).

A main process by which new semantic knowledge is acquired consists of an episodic-to-semantic progression, by which new information, through repetition or rehearsal, is gradually transformed and integrated into existing knowledge structures (Squire & Zola, 1998; Winocur & Moscovitch, 2011). The learning of new semantic knowledge therefore is impaired in the amnesic syndrome, with severity correlating with extent of MTL damage. Amnesic patients with extensive MTL damage show severely impaired learning of new public events, famous faces, and vocabulary that gained popularity post-onset of amnesia (Bayley & Squire, 2005; Verfaellie, Koseff, & Alexander, 2000); patients with restricted hippocampal lesions are also impaired, but may show some evidence of new learning, particularly on tasks that can be mediated by familiarity. For example, Patient P.S., who suffered hippocampal injury secondary to anoxia at age 40, displayed severe difficulties recalling vocabulary and famous faces that entered the culture after onset of amnesia, but demonstrated intact word recognition and fame judgment (Verfaellie et al., 2000).

More striking evidence for semantic learning comes from children with developmental amnesia who sustained hippocampal lesions during the neonatal period. Despite pronounced impairment in the ability to recall day-to-day events, these children develop normal vocabulary and acquire a level of academic knowledge comparable to their peers (Vargha-Khadem et al., 1997). At the same time, within a laboratory setting, their learning is slow, and usually requires many more exposures to the information before reaching a level of recall similar to that of matched controls (Elward & Vargha-

Khadem, 2018). These findings are consistent with the notion that the hippocampal memory system is critical for efficient learning of new semantic information. In addition, they demonstrate that, absent hippocampal contribution, a cortically mediated memory system may support the gradual acquisition of new factual knowledge. The available evidence suggests that perirhinal cortex may support this learning through a sense of familiarity with new concepts and facts in both adult and developmental amnesia (Aggleton & Brown, 1999), but the potential for plasticity and reorganization in children is likely responsible for their overall higher capacity for semantic learning.

Although any semantic learning in amnesic patients typically requires repeated exposure to information, work by Gilboa and colleagues (Merhav, Karni, & Gilboa, 2014; Sharon, Moscovitch, & Gilboa, 2011) recently has raised the intriguing possibility that patients may be able to acquire novel arbitrary associations through a form of incidental learning whereby participants infer the name of a novel object by disjunctive reasoning. This form of learning is termed “fast mapping”, a process thought to underlie the rapid acquisition of vocabulary in children. However, subsequent failures to replicate these results have cast doubt on whether such learning can happen in the absence of a functioning hippocampus (Cooper, Greve, & Henson, 2018; Smith, Urgolites, Hopkins, & Squire, 2014; Warren & Duff, 2014). Further work establishing the boundary conditions of fast mapping learning in amnesia is needed (Gilboa, 2019).

II.2. Retrograde Amnesia

Difficulty retrieving memories that were formed prior to the onset of amnesia constitutes an important feature of the amnesic syndrome. There has been particular theoretical interest in elucidating the extent and severity of remote memory deficits following MTL lesions, as such information speaks to whether the hippocampus plays a

temporary or permanent role in the recovery of memory. In addressing this question, the distinction between the retrieval of autobiographical events (episodic memory) and knowledge of concepts and facts (semantic memory) is essential.

II.2.a. Retrieval of Premorbid Episodic Memories

The first formal assessment of premorbid episodic memory in H.M. suggested that he was impaired in recollecting events up to 11 years predating his surgery, but had well-formed memories for earlier events (Sagar, Cohen, Corkin, & Growdon, 1985). Subsequent studies of MTL amnesia documented a similar pattern of temporally graded retrograde amnesia, whereby more recent memories are disrupted more than older ones (for review, see Squire & Wixted, 2011). These findings were taken as evidence for the standard systems consolidation view (see Chapter 6.7 on "Systems Consolidation"), which suggests that episodic memories over time become independent of the hippocampus due to a process of reorganization (Squire & Alvarez, 1995). By this view, the hippocampus is critical for the initial binding of informational elements that are processed in disparate neocortical areas into coherent memories. With repeated reactivation of these hippocampal-neocortical interactions, a neocortical network is strengthened, which alone becomes sufficient to maintain and retrieve the memory trace. Although some patients were described who have extensive, ungraded memory loss, this was ascribed to lesions extending beyond the MTL to involve neocortical storage sites such as the lateral temporal lobe (e.g., Cermak & O'Connor, 1983; McCarthy & Warrington, 1992) or frontal sites important for strategic retrieval (Bayley, Gold, Hopkins, & Squire, 2005).

Re-examination of the evidence, however, brought to light that the findings in patients with MTL lesions were not as supportive of standard systems consolidation

theory as initially had appeared, as retrograde amnesia can extend several decades or even be lifelong (for review, see Winocur & Moscovitch, 2011). This evidence led to the development of multiple trace theory (Nadel & Moscovitch, 1997; see Chapter 6.8 on "Multiple Trace Theory"), which postulates that the retrieval of highly detailed context-specific memories always involves the hippocampus, no matter the age of the memory. Building on this view, trace transformation theory was subsequently advanced, which proposes that some memories are transformed with time and experience from highly detailed context-specific memories to schematic representations that retain the gist of the event. It is the latter semanticized memories that become independent of the hippocampus (Winocur & Moscovitch, 2011).

A criticism leveled against some studies favoring consolidation theory (for review, see Lah & Miller, 2008) is that, in reporting intact retrieval of very remote memories, these studies may not have captured the essence of episodic recollection, namely the ability to vividly re-experience the details of an event. To address this concern, Levine and colleagues (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002) developed an approach that quantifies different types of episodic details that may unfold in a person's mind when recounting memories. Using this method, Rosenbaum et al. (2008) demonstrated an inverse association between the extent of hippocampal damage and the ability to retrieve episodic detail in four patients with MTL lesions. Using the same approach, however, another study found no impairment in episodic recollection of childhood to middle-age memories in patients with hippocampal lesion (Kirwan, Bayley, Galvan, & Squire, 2008). Thus, the two-decade controversy regarding consolidation theory versus multiple trace/transformation theory continues. Although differences in methods of testing and scoring autobiographical memory may account for some

discrepancies (Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012), other inconsistencies remain. These may reflect limitations in the precision of lesion identification and in understanding the impact of focal lesions on the broader disruption of relevant networks.

II.2.b. Retrieval of Premorbid Semantic Knowledge

Semantic memory encompasses general facts about the world such as public events, vocabulary, and culturally shared concepts (general semantic knowledge), and personal knowledge about one's life including autobiographical facts, personal traits and roles, and personal beliefs (personal semantic knowledge). Like episodic memory, personal semantic memory is grounded in personal memories, yet is devoid of contextual details and, like general semantic memory, represents commonalities abstracted across experiences (Renoult, Davidson, Palombo, Moscovitch, & Levine, 2012).

General Semantic Memory. Studies of remote memory for facts, public events and personalities typically show intact to mildly impaired performance in patients with lesions largely limited to the hippocampus, with a temporal gradient spanning at most 10 years (for review, see Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006). This evidence suggests that the hippocampus plays a time-limited role in semantic knowledge, a point on which systems consolidation theory and multiple trace theory agree. There are some reports of patients with a more extensive gradient (e.g., Cipolotti et al., 2001), but this may reflect the fact that normal individuals are able to use episodic recollection to enhance their memory for public information (Westmacott, Black, Freedman, & Moscovitch, 2004). Contrasting with the temporally limited semantic loss associated with restricted hippocampal lesions, more profound and temporally extensive semantic memory impairment has consistently been reported with damage extending to other

cortical areas, especially the anterolateral temporal cortex (Reed & Squire, 1998; Schmolck, Kensinger, Corkin, & Squire, 2002). This finding is in keeping with the established role of this region in the long-term storage of semantic representations (Binder & Desai, 2011; Patterson et al., 2007).

The above findings suggest that the hippocampus plays a time-limited role in the retrieval of semantic memories – memories that are characteristically schematic or gist-like. However, an interesting exception arises when semantic memory requires access to fine-grained memory representations. For example, whereas MTL patients can recount the main thematic elements of semantic narratives such as fairy tales, their memory for story details is impaired (Verfaellie, Bousquet, & Keane, 2014). A similar dissociation between preserved gist memory and impaired detail memory has been observed with regard to remote spatial memory. Assessing an amnesic patient with extensive hippocampal damage on knowledge of his familiar neighborhood, Rosenbaum et al. (2000) demonstrated that he retained information about major landmarks, routes, and distances sufficient to allow for navigation, but was unable to specify location details (see also Herdman, Calarco, Moscovitch, Hirshhorn, & Rosenbaum, 2015; Maguire, Nannery, & Spiers, 2006; Teng & Squire, 1999). These findings suggest that even within the domain of semantic knowledge, the preservation of detailed information may remain hippocampally dependent.

Personal Semantic Memory. Reviewing the findings on personal semantic memory in patients with MTL lesions, we observed that highly conceptual and abstract knowledge, such as personal traits and roles, was preserved following MTL lesions, whereas retrieval of autobiographical facts was commonly impaired (Grilli & Verfaellie, 2014). We postulated that this might reflect the fact that autobiographical facts often

remain associated with spatial-temporal and perceptual details (i.e., are experience-near), and thus depend on the MTL for retrieval. In a subsequent study in which patients were asked to generate "I am…" open-response narratives, autobiographical facts were coded as being experience-near (e.g., "I have a dog with black hair") versus experience-far (e.g., I am a psychologist"). Patients with MTL lesions generated fewer experience-near personal facts than controls but did not differ from controls in generating experience-far personal facts (Grilli & Verfaellie, 2016). Patients with lesions extending to the anterolateral temporal cortex were impaired in retrieving both experience-near and experience-far facts. Thus, although experience-far personal facts are specific to each individual, after consolidation, storage and retrieval of such information may depend on the same neocortical regions involved in general semantic memory.

II.3. Implicit Memory

In contrast to the striking impairments in explicit memory, patients with amnesia show intact performance in a number of forms of memory that do not depend on intentional retrieval, often classified together as non-declarative (Squire, 1992) or implicit memory (Schacter, 1987). This form of learning may reflect a universal principle of brain plasticity, whereby experience leads to adaptive changes in the neural circuits responsible for task performance (Reber, 2013). Here, we briefly describe evidence pertaining to procedural learning and repetition priming and discuss boundary conditions of MTL independence.

Procedural learning. Procedural learning refers to the process by which, through repeated practice, a series of simple movements can be executed without effort as a unitary sequence (for review, see Doyon, Gabitov, Vahdat, Lungu, & Boutin, 2018). Intact motor sequence learning in patients with MTL lesions was initially reported in a

mirror tracing study with patient H.M. (Milner, 1962), and subsequently extended to other tasks such as rotary pursuit (Brooks & Baddeley, 1976; Tranel, Damasio, Damasio, & Brandt, 1994) and serial reaction time (Nissen & Bullemer, 1987), as well as to a number of skills relevant to activities of daily living (Cavaco, Anderson, Allen, Castro-Caldas, & Damasio, 2004). Interestingly, when motor learning depends on higher-order sequence representations, amnesic patients perform worse than controls (Curran, 1997), consistent with their difficulty extracting statistical regularities across experiences (Schapiro, Gregory, Landau, McCloskey, & Turk-Browne, 2014). We also recently showed that the sleep-dependent improvement in motor sequence learning observed in normal individuals is absent in MTL patients, suggesting that the hippocampus may play a causal role in the consolidation of tasks that do not depend on the MTL for initial acquisition (Schapiro et al., 2019).

Repetition Priming. Repetition priming refers to facilitation in identifying or classifying a stimulus following prior encounter with the same or a related stimulus (Tulving & Schacter, 1990). For example, a picture of a bicycle will be identified more quickly after earlier exposure to that same picture (perceptual priming) or the word "transportation" (conceptual priming). In addition to item-specific priming, studies have examined associative priming, i.e. priming of the specific link between different informational elements.

Amnesic patients show intact performance on a variety of tasks that measure priming for single items, reflecting intact perceptual and conceptual priming (Moscovitch, Goshen-Gottstein, & Vriezen, 1994; Verfaellie & Keane, 2002). Given the critical role of the hippocampus in relational processing, an important question has been the status of associative priming in amnesia. Here, evidence has been mixed, with some

studies reporting impaired priming for the relation among elements in a visual scene (Ryan, Althoff, Whitlow, & Cohen, 2000) or in a spatial array (Chun & Phelps, 1999), but another demonstrating intact priming when lesions are limited to the hippocampus (Manns & Squire, 2001). Similarly, within the verbal domain, performance varies across tasks (for review, see Verfaellie & Keane, 2002). We have postulated that a critical distinction may be between associations that involve binding across distinct processing modules (e.g., visual form and spatial location) and those that involve binding within-module (e.g., two visual word forms or two conceptual representations), with only the former impaired in amnesic patients.

II.4. Beyond Long-Term Memory

Although impairments in acquiring new long-term episodic and semantic memories are undoubtedly the most salient clinical feature of the amnesic syndrome, work over the last two decades has revealed deficits in a number of other cognitive domains, including short-term memory, perception, and episodic simulation.

II.4.a. Short-Term Memory

Patients with MTL lesions typically show intact performance when asked to retain simple stimuli such as digits, tones, words, or single-dot locations for a short delay (e.g., Baddeley & Warrington, 1970; Cave & Squire, 1992; Milner et al., 1968; Wickelgren, 1968). However, a different pattern occurs in tasks that require the maintenance of relational information. Initial evidence came from a study of short-term memory requiring subjects to remember three objects in distinct locations for delays of 1-8 seconds. Patients with MTL lesions, including patients with lesions limited to the hippocampus, demonstrated intact recognition of objects and locations tested in isolation,

but impaired recognition of object-location combinations, even after a 1 second delay (Olson, Page, Moore, Chatterjee, & Verfaellie, 2006). Similar impairments have since been reported for associations between items and colors (Olson, Moore, Stark, & Chatterjee, 2006), temporal sequences (Mayes et al., 2001), relations among items in a scene (Hannula, Tranel, & Cohen, 2006), and face-scene pairings (Hannula et al., 2006).

It has been argued that tasks involving associations are more difficult than those involving individual features, and are therefore more likely to exceed short-term memory capacity. By this view, the impairment in amnesia reflects the recruitment of long-term memory in healthy participants (Jeneson & Squire, 2011). In support of this hypothesis, several studies have demonstrated intact short-term associative memory in amnesic patients under conditions of lower load and shorter delays, but impaired performance at higher load and longer delays (Jeneson, Mauldin, & Squire, 2010). Yet, other studies (Pertzov et al., 2013; Warren, Duff, Cohen, & Tranel, 2015; Watson, Voss, Warren, Tranel, & Cohen, 2013) have demonstrated impairments under conditions of low load (2 or 3 items) and short delays (4 seconds or less). In an attempt to reconcile these findings, Yonelinas (2013) postulated that hippocampal damage may specifically disrupt short-term memory for bindings that require high precision. Supporting this view, recent studies of MTL patients have demonstrated impaired short-term memory for color-location (Goodrich & Yonelinas, 2016), object-location (Koen, Borders, Petzold, & Yonelinas, 2017), and object-color binding (Koen et al., 2017) in conditions that require high precision but not low precision, findings that cannot be accounted for by differences in task difficulty across conditions.

Whereas circumscribed hippocampal lesions yield impairments in associative short-term memory tasks, patients with lesions extending to perirhinal cortex display

additional impairments in short term memory for nonverbalizable stimuli such as visual patterns (Sidman, Stoddard, & Mohr, 1968), fractals (Holdstock, Gutnikov, Gaffan, & Mayes, 2000), and unfamiliar faces (Olson, Moore, et al., 2006; Race, LaRocque, Keane, & Verfaellie, 2013). These findings suggest that the MTL specialization evident in long-term memory, whereby the hippocampus is critical for relational (between-item) binding and the perirhinal cortex for configural (within-item) binding, extends to short-term memory as well.

II.4.b. Perception

Although visual perception of simple features such as color or size is preserved in amnesia, subtle perceptual deficits are apparent in tasks that require the discrimination or identification of complex visual stimuli (for review, see Lee, Yeung, & Barense, 2012). Moreover, as for short-term memory deficits, there is evidence for functional specialization within the MTL. For example, in a visual discrimination task consisting of stimuli that were blended to create different levels of feature overlap, patients with lesions circumscribed to the hippocampus showed impaired discrimination of scenes but not of faces or objects, when there was high feature overlap among stimuli, whereas patients with more extensive MTL lesions performed poorly for all three categories (Lee, Bussey, et al., 2005). Similar findings were obtained in a task requiring identification of the odd stimulus among a set of scenes, faces, or objects presented from different viewpoints (Lee, Buckley, et al., 2005).

It has been argued that the impairment of amnesic patients in complex visual perception tasks is due to the fact that performance can make demands on short-term memory and/or can be facilitated by long-term learning. Consistent with this notion, both in discrimination tasks (Kim et al., 2011; Shrager, Gold, Hopkins, & Squire, 2006) and

oddity tasks (Knutson, Hopkins, & Squire, 2012) in which care was taken to eliminate memory contributions, the performance of patients with MTL lesions has been shown to be intact. Nonetheless, impairments have been observed in other tasks that pose no obvious memory demands, such as judging the structural integrity of individual scenes (McCormick, Rosenthal, Miller, & Maguire, 2017; but see Rungratsameetaweemana & Squire, 2018) or three-dimensional objects (Lee & Rudebeck, 2010; but see Urgolites, Levy, Hopkins, & Squire, 2018). Consistent with the high-precision account outlined above, it has been suggested that only some aspects of perception are impaired, namely those that require the processing of relations among multiple features (Aly, Ranganath, & Yonelinas, 2013). Yet, the boundary conditions of perceptual deficits following MTL lesions remain to be fully elucidated (Hannula, Ryan, & Warren, 2017).

II.4.c. Episodic Simulation

Paralleling their impairment in retrieving past events, amnesic patients have difficulty imaging hypothetical and future events (for reviews, see Addis & Schacter, 2012; Verfaellie, Race, & Keane, 2012). For instance, when asked to imagine "standing in the main hall of a museum containing many exhibits" or "winning the lottery" twenty years in the future, amnesic patients provide descriptions that lack vividness and spatial coherence and are impoverished in detail (Hassabis, Kumaran, Vann, & Maguire, 2007; Race, Keane, & Verfaellie, 2011; Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009). These impairments are not simply due to demands associated with creating a coherent verbal narrative, as patients perform normally when asked to create narratives about pictures of real-life settings (Keven, Kurczek, Rosenbaum, & Craver, 2018; Race et al., 2011). Directly comparing amnesic patients' ability to construct past and future scenarios, Race et al. (2011) found that the number of details across conditions was

strongly correlated, suggesting that episodic remembering and simulation rely on similar underlying processes. The existence of a close link between remembering and thinking about the future may also explain why no future thinking impairments were found in MTL patients with intact retrieval of remote past events (Squire et al., 2010).

When thinking about future events, contents are retrieved from long-term memory, which form the building blocks for a potential scenario. These elements are then flexibly recombined to create a novel coherent simulation (Schacter, 2012; Schacter, Addis, & Buckner, 2007). Interestingly, even when demands on memory retrieval are minimized, amnesic patients have difficulty forming coherent novel events. Romero and Moscovitch (2012) provided patients with the objects (e.g., "bird", "mailbox", "grass") and setting (e.g., "yard") that form the core of an event or scene and asked them to create a novel event by relating the elements to one another in the provided setting. Patients made fewer inter-item relations than controls, an impairment that became more apparent as the number of objects provided increased. These findings suggest that impaired hippocampal binding processes also impact event simulation.

Another critical process involved in the construction of detailed mental scenarios, whether past or future, is scene construction, as scenes provide the spatial scaffold in which an event can unfold (Hassabis & Maguire, 2007). Compelling evidence that amnesic patients have an impairment in scene construction comes from the finding that they fail to show boundary extension – the normal tendency to extrapolate beyond the borders of a scene to form an extended mental representation (Mullally, Intraub, & Maguire, 2012; but see Kim, Dede, Hopkins, & Squire, 2015). Whether scene construction represents the fundamental mechanism underlying patients' impaired autobiographical memory and prospection (Maguire & Mullally, 2013) or is just one

expression of a more general impairment in relational processing is a matter of ongoing debate (Roberts, Schacter, & Addis, 2017).

The ability to vividly imagine a hypothetical or future event is adaptive in that it allows one to pre-experience an outcome, whether pertaining to oneself or to another person. It is therefore not surprising that patients with hippocampal damage perform poorly on a number of tasks that involve episodic simulation such as open-ended problem solving (Sheldon, McAndrews, & Moscovitch, 2011), empathy (Beadle, Tranel, Cohen, & Duff, 2013), and future-oriented decision making (Palombo, Keane, & Verfaellie, 2015). By contrast, patients perform normally on future-oriented tasks when performance can be supported by reasoning and semantic (rather than episodic) processing (Craver, Kwan, Steindam, & Rosenbaum, 2014; Palombo, Keane, & Verfaellie, 2016).

III. Neurological Conditions Associated with Amnesia

The amnesic syndrome may result from of a number of etiologies that disrupt the extended hippocampal memory network. Because the memory circuit becomes diffuse beyond the hippocampus, with a complex system of interconnections and parallel bypassing projections, damage to brain areas other than the hippocampus often result in only partial disruption of the memory network, and thus in less severe memory difficulties (Bubb et al., 2017). With involvement of regions beyond the hippocampus, the syndrome is also likely to be less “pure” and can be accompanied by cognitive deficits in domains other than memory. The neurological conditions most commonly leading to amnesia are reviewed here, with consideration of the pattern of memory impairment as well as any accompanying cognitive deficits.

III.1. Stroke

A stroke occurs when a blood vessel that carries energy supplies to the brain is either occluded (ischemic) or ruptures (hemorrhagic). Ischemic strokes lead to cell death within minutes due to deprivation of oxygen and nutrients. Hemorrhagic strokes cause cell damage through swelling, pressure, and toxicity, related to the collection of blood in brain tissues. Because a stroke can occur in a wide variety of locations, it constitutes the only etiology that can affect the entire memory circuitry, and its study has been helpful for identifying the points of convergence of the network (for review, see Lim & Alexander, 2009).

III.1.1. Medial Temporal Lobe Lesions

Bilateral posterior cerebral artery (PCA) infarction is a well-documented cause of amnesia (Benson, Marsden, & Meadows, 1974; Victor, Angevine, Mancall, & Fisher, 1961). The PCA represents a main source of blood supply for the MTL, especially perfusing posterior and inferior areas, including the posterior hippocampus and parahippocampal gyrus. The PCA territory is susceptible to bilateral infarction as both left and right arteries arise from one common (basilar) artery. Memory deficits resulting from bilateral PCA infarction are consistent with a classic amnesic syndrome, including prominent anterograde amnesia, variable retrograde amnesia extending to many years prior to the stroke, and relatively preserved working memory and intelligence (Benson et al., 1974; Schnider, Regard, & Landis, 1994; Victor et al., 1961).

Unilateral left PCA infarction can yield a transient amnesic syndrome, lasting a few weeks to a year, with long-term residual memory deficits restricted to the verbal domain (De Renzi, Zambolin, & Crisi, 1987; Ott & Saver, 1993; Von Cramon, Hebel, & Schuri, 1988). Right PCA infarction does not tend to produce full blown amnesia (Von

Cramon et al., 1988), but deficits have been reported in visual and spatial memory, for example involving learning the location of objects (Luzzi, Pucci, Di Bella, & Piccirilli, 2000). This functional lateralization is consistent with findings from neuroimaging studies and unilateral temporal lobectomy patients, demonstrating relative specialization of the left hippocampus for verbal memory (Frisk & Milner, 1990; Powell et al., 2005), and right hippocampus for visuospatial memory (Burgess, Maguire, & O'Keefe, 2002; Smith & Milner, 1981).

The PCA territory supplies a large area of the temporal lobe, and a number of cognitive and perceptual deficits may accompany amnesia secondary to PCA infarction, including visual field defects, alexia, anomia, color agnosia, constructional apraxia, topographical disorientation, prosopagnosia, and cortical blindness (Benson et al., 1974). These associated perceptual and language deficits can complicate assessment of verbal and visuospatial memory abilities.

The anterior and superior portions of the MTL, including the anterior hippocampus and amygdala, are supplied by the anterior choroidal artery (AchA), which originates 2-5 mm distal to the posterior communicating artery. The AchA may be subject to infarction but also to bleed by ruptured aneurysm or traumatic tearing (Yu, Xu, Zhao, & Yu, 2018). Amnesia resulting from isolated stroke of the AchA territory has been reported in a handful of patients (Amarenco et al., 1988; Ott & Saver, 1993).

III.1.2. Thalamic Lesions

Significant memory difficulties have been associated with strokes to the medial and anterior portions of the thalamus (Gold & Squire, 2006; Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Von Cramon et al., 1985), regions that are supplied by a complex network of small arteries, including the tuberothalamic, paramedian, and

anterior choroidal arteries. The structure of these vascular connections tends to vary widely across individuals (Schmahmann, 2003). This variability, added to a tight packing of numerous nuclei in a small space, has rendered difficult identifying the contribution of specific nuclei to memory functions. Further, because the thalamus acts as a relay for perceptual and frontal processing, a complex array of cognitive deficits often associated with thalamic strokes may contribute to decreased memory performance. These include attention and executive dysfunction (Carlesimo, Lombardi, & Caltagirone, 2011; Van der Werf, Witter, Uylings, & Jolles, 2000), transcortical aphasia, hemispatial neglect, and visuospatial processing difficulties (Bogousslavsky, Regli, & Assal, 1986).

The memory disturbances resulting from thalamic stroke have traditionally been classified together under the term “diencephalic amnesia”, implying a consistent constellation of symptoms. Recent reviews, however, have highlighted the need to better distinguish between thalamic lesions that cause an amnesic syndrome and those that cause memory deficits related to executive dysfunction (Carlesimo et al., 2011; Van der Werf et al., 2000). An amnesic syndrome similar to that resulting from hippocampal lesions occurs in the context of rostral thalamic strokes that damage the anterior thalamic nuclei or the mammillary-thalamic tract, which connects the hippocampus to the anterior thalamic nuclei. By contrast, milder memory disturbances associated with executive dysfunction occur with damage to other thalamic areas, including the medial dorsal nucleus, midline nuclei, and intralaminar nuclei (Danet et al., 2015; Van der Werf et al., 2003). Damage to the dorsomedial thalamic nuclei has also been associated with impaired familiarity-based processes (reviewed in Carlesimo et al., 2011). These findings are consistent with two proposed independent MTL-thalamic circuits, one subserving recollection through connections between the hippocampus, mammillary bodies, and

anterior thalamic nucleus, and the other subserving familiarity through perirhinal cortex-medial dorsal thalamus nucleus connections (Aggleton & Brown, 1999; but see Cipolotti et al., 2008).

III.1.3. Basal Forebrain Lesions

The most common vascular etiology of basal forebrain lesions is ruptured aneurysm of the anterior communicating artery (ACoA). In particular, lesions of the septal nuclei and diagonal band of Broca – the main sources of cholinergic projections to the hippocampus – have been associated with severe memory impairment (Alexander & Freedman, 1984; Damasio et al., 1985). Additional disruption of frontal-subcortical networks is often observed due to hemorrhage-induced swelling, pressure, and blood toxicity.

In the acute phase after surgical repair of the aneurysm, patients typically present with a severe confusional state, followed by apathy, confabulation, and denial of illness (Alexander & Freedman, 1984). Over the weeks to months that follow, confusion tends to clear, but memory impairments, colored by the presence of executive disturbance, become apparent. These impairments include inefficient learning (Diamond, DeLuca, & Kelley, 1997), disproportionate deficits in recall (Hanley, Davies, Downes, & Mayes, 1994; Volpe & Hirst, 1983) and contextual memory (Damasio et al., 1985; Parkin, Leng, Stanhope, & Smith, 1988), as well as retrograde amnesia that is generally less severe than in MTL lesions (O'Connor & Lafleche, 2004). These impairments all tend to improve in parallel with recovery of executive functioning (D'Esposito, Alexander, Fischer, McGlinchey-Berroth, & O'Connor, 1996). Also closely linked to executive function is confabulation, which involves statements or actions that reflect unintentional distortions of memory (Gilboa & Verfaellie, 2010). Confabulations can range from intrusions of past

experiences (“I am at the hospital for hip replacement surgery”) to completely fantastical statements (“I am at the hospital because I am serving meals to patients”) (Stuss, Alexander, Lieberman, & Levine, 1978).

III.1.4. Retrosplenial Lesions

Lesions restricted to the retrosplenial cortex, albeit rare, may occur following ischemic or hemorrhagic stroke in the region of the splenium of the corpus callosum (for review, see Maguire, 2001). Consistent with disruption of the extended hippocampal circuit, retrosplenial damage can produce a classic amnesic syndrome (Valenstein et al., 1987; Vann, Aggleton, & Maguire, 2009). Deficits in spatial navigation affecting both new and familiar environments are a hallmark impairment of retrosplenial damage. The restrosplenial cortex is thought to play an important role in memory by integrating various spatial perspectives (for review, see Mitchell, Czajkowski, Zhang, Jeffery, & Nelson, 2018), allowing translation between allocentric (or viewpoint-independent) representations mediated by the MTL and egocentric (or viewpoint-dependent) representations mediated by the parietal cortex (Burgess, 2008). In line with this notion, retrosplenial cortex is engaged when information from the visual environment needs to be retrieved from memory to orient oneself in space (see chapter 3.3. “Memory for Space”). This may also explain its role in the retrieval of autobiographical memories, as such memories similarly require referencing oneself within a spatial context and updating of spatial representations as events are recalled. Whereas a full amnesic syndrome typically occurs following bilateral or unilateral left lesions, spatial disorientation is the primary symptom associated with unilateral right lesions (Maguire, 2001).

III.2. Hypoxic-Ischemic Brain Injury

Hypoxic-ischemic brain injury results from shortage of oxygen and nutrients to the brain, due to hypoxia (deprivation from oxygen), ischemia (decreased blood perfusion), cytotoxicity (blocked binding of oxygen to hemoglobin), or their combination (Busl & Greer, 2010). The most common causes of hypoxic-ischemic brain injury are cardiac arrest, respiratory failure, incomplete suffocation (e.g., near-drowning, near-hanging), and carbon monoxide poisoning. Cell damage, in this context, results from a cascade of biochemical events, including influx of calcium into the cells, edema, release of excitatory neurotransmitters, excitotoxicity, and the formation of unstable free oxygen radicals. Brain structures particularly vulnerable to hypoxic-ischemic injury are those with high metabolic demands, such as the hippocampus, cerebellum, and basal ganglia, as well as gray and white matter located at the fringes of arterial perfusion territories (Busl & Greer, 2010). Upon initial presentation, hypoxic-ischemic brain injury may involve disorders of consciousness (coma, vegetative state), seizures, motor disturbances, and a variable range of cognitive and behavioral changes (Anderson & Arciniegas, 2010). Following a period of recovery, some patients are left with severe memory deficits.

One of the first well-documented cases of isolated amnesia following hypoxic-ischemic injury is that of R.B., a 52-year-old male patient who developed amnesia following heart surgery complication and subsequent ischemic event (Zola-Morgan et al., 1986). R.B. presented with moderate anterograde amnesia for verbal and non-verbal material in the context of very mild retrograde amnesia and otherwise intact cognitive abilities. Post-mortem histological examination revealed bilateral lesions restricted to the CA1 subfield of the hippocampus. A subsequent autopsy study of three cases confirmed that circumscribed CA1 lesions are sufficient to produce anterograde amnesia (Rempel-

Clower et al., 1996). Extensive temporally graded retrograde amnesia spanning 15 years or more was also reported in this study, with severity of both anterograde and retrograde deficits correlated with hippocampal lesion size, extending beyond CA1. Severe anterograde and retrograde amnesia were also seen in a 67-year-old retired seaman who had suffered repeated ischemic events accompanied by seizures, with bilateral damage restricted to the CA1 and CA2 subfields of the hippocampus (Kartsounis, Rudge, & Stevens, 1995). In that case, retrograde amnesia extended several decades without suggestion of a clear temporal gradient.

Hippocampal amnesia has traditionally been regarded as the prototypical presentation of hypoxic-ischemic injury, possibly because of the focus in the literature on anoxic patients with restricted hippocampal damage. Yet, this presentation is rare. Focal hippocampal damage occurs primarily in the context of slow or stepwise hypoxic (e.g., carbon monoxide) or excitotoxic (e.g., seizures) injury, but more extensive damage is the norm following sudden, global, and complete shortage of oxygen, such as in cardiac arrest (Lim, Alexander, LaFleche, Schnyer, & Verfaellie, 2004; Markowitsch, Weber-Luxemburger, Ewald, Kessler, & Heiss, 1997). The basal ganglia, thalamus, and watershed areas of neocortex tend to be damaged more frequently than the hippocampus, leading to executive dysfunction, changes in behavior or personality (e.g., emotional lability, irritability, apathy, or child-like behaviors), and visuoperceptual deficits (Caine & Watson, 2000), as well as subtle motor difficulties (Lim et al., 2004). In studies examining the cognitive consequences of cardiac arrest in clinical settings, patients almost always display a dysexecutive syndrome, whereas about half also demonstrate severe memory impairments (Lim et al., 2004; Peskine, Picq, & Pradat-Diehl, 2004).

Developmental Amnesia. Hypoxic-ischemic episodes during the neonatal period are the primary etiology of developmental amnesia. Patients with developmental amnesia achieve normal developmental milestones, including language and vocabulary acquisition, and attain average intellectual abilities, but show severely compromised development of episodic memory (Elward & Vargha-Khadem, 2018). The episodic memory impairment is characterized by markedly impaired recall and relatively spared recognition (Adlam, Malloy, Mishkin, & Vargha-Khadem, 2009), consistent with preservation of familiarity (Bindschaedler, Peter-Favre, Maeder, Hirsbrunner, & Clarke, 2011; Brandt, Gardiner, Vargha-Khadem, Baddeley, & Mishkin, 2009). As described earlier, especially striking in these patients is the impressive capacity for acquiring semantic knowledge, but subtle impairment in the structure of semantic knowledge may be present (Blumenthal et al., 2017).

The pattern of memory impairment seen in developmental amnesia was initially attributed to selective lesions in the hippocampus (Vargha-Khadem et al., 1997), although additional abnormalities in the putamen, thalamus and retrosplenial cortex were also observed (Vargha-Khadem et al., 2003). More recent evidence has revealed that other parts of the extended hippocampal system, in particular the mammillary bodies and anterior thalamus, are also commonly involved (Dzieciol et al., 2017). Notably, abnormal prenatal development of the extended hippocampal system with complete absence of mammillary bodies has recently been described as a possibly distinct origin of developmental amnesia (Rosenbaum et al., 2014).

Compared to adult-onset amnesia, patients with developmental amnesia can be quite high functioning, relying on their semantic memory to keep up with their affairs, news items, and new discoveries (Elward & Vargha-Khadem, 2018). They also tend to

produce reasonable responses to questions about specific episodes, thus giving the impression of intact memory (e.g., Brandt et al. 2006). For example, Elward & Vargha-Khadem related the case of Jon, who had bilateral hippocampal atrophy following neonatal hypoxia-ischemia, and would visit their lab regularly. On one occasion, the elevator was broken, and Jon had to climb the equivalent of 14 floors of stairs. Upon questioning, Jon had forgotten the event and, relying on semantic memory, recounted taking the elevator as usual, "because [he] always does" (pp.23).

III.3. Encephalitis

Encephalitis is an inflammation of the brain parenchyma resulting in neurological dysfunction. Herpes simplex encephalitis and encephalitis secondary to autoimmune disease both can lead to dense amnesia.

III.3.1. Herpes Simplex Encephalitis

Brain infection by the herpes simplex virus is rare, but occurs when the virus, which tends to lay dormant in the trigeminal ganglia, is reactivated and transmitted to the brain (for review, see Bradshaw & Venkatesan, 2016). In the acute stage, patients may experience fever, rapid-onset headaches, lethargy, confusion, aphasia, seizures, focal neurological signs, and in some cases coma (Kennedy & Chaudhuri, 2002). Outcomes are poor in the absence of antiviral therapy, with mortality exceeding 70% and most survivors being left with disabling impairments. However, antiviral treatment has markedly improved these outcomes (Hokkanen & Launes, 2007).

Neural damage following herpes simplex encephalopathy centers on the medial temporal lobes, but often extends to the anterolateral and inferior temporal cortices, orbitofrontal cortex, and insula (Colchester et al., 2001; Damasio & Van Hoesen, 1985;

Kapur et al., 1994). Memory difficulties constitute the most commonly reported deficit, and because of the relative preservation of frontal brain regions, patients often display insight into their difficulties. Alterations in mood and personality, and difficulties with verbal semantic and visuoperceptual abilities, however, can also occur (Hokkanen et al., 1996).

Anterograde amnesia in herpes simplex encephalitis can be profound, with the pattern of impairment depending on the extent of neural damage within and beyond the MTL. For example, patient S.S, who suffered a severe episode of herpes simplex encephalitis, initially presented with one-month coma, aphasia, and hemiparesis. Although his speech and motor problems resolved, he was left with a complete inability to remember events that occurred following his illness (Cermak & O'Connor, 1983). He also had a striking inability to acquire new semantic knowledge, despite repeated exposure through newspaper and television programs (Verfaellie et al., 2000). Contrasting with S.S., patient R.F.R. demonstrated acquisition of some new word meanings in a 16-year follow-up, as well as some, although more limited, knowledge of new celebrities (McCarthy, Kopelman, & Warrington, 2005). This variability might be attributed to the sparing of the left lateral temporal lobe in R.F.R compared to S.S., presumably allowing for direct, albeit inefficient, cortical learning of new semantic representations. With improved treatment, unilateral lesions are now more commonly reported (Chow et al., 2015). As expected, right temporal damage disproportionately affects nonverbal memory (Eslinger, Damasio, Damasio, & Butters, 1993) and left temporal damage disproportionately affects verbal memory (Tranel, Damasio, & Damasio, 2000).

Retrograde amnesia is typically also very extensive (Cermak & O'Connor, 1983), with the pattern of deficits depending on laterality. Notably, disproportionate right lateralized damage has been associated with complete inability to recount any past personal events, including from childhood. Personal factual information (e.g., remembering the name of a first grade teacher) tends to be relatively better preserved, but with answers often stereotyped and unelaborated (McCarthy et al., 2005; O'Connor, Butters, Miliotis, Eslinger, & Cermak, 1992). By contrast, patients with disproportionate left lateralized damage, extending into the left anterior inferotemporal cortex, display impaired semantic memory (i.e., impaired knowledge of the name, meaning, and attributes of words and pictures) in the context of otherwise preserved language and perceptual abilities (De Renzi et al., 1987). In rare cases, category-specific impairments have been reported, for example with differential deficits for concrete versus abstract concepts or for animate versus inanimate objects (for review, see McKenna & Warrington, 2000).

III.3.2. Autoimmune Encephalitis

Autoimmune encephalitis is an inflammation of the brain caused by the development of antibodies by the immune system against proteins implicated in neurotransmission. This reaction may sometimes signal the presence of an underlying tumor in another part of the body (paraneoplastic encephalitis). In recent years, a number of studies have focused on the leucine-rich glioma inactivated (LGI1) antibody subtype as a cause of amnesia. This subtype is often categorized under the family of voltage-gated potassium channels (VGKCs)-complex antibodies (for review, see Leypoldt, Armangue, & Dalmau, 2015). In the acute phase, patients with anti-LGI1 encephalitis present with memory deficits, confusion, frequent seizures, and sleep disruption. Without timely and

aggressive immunotherapy, patients may be left with lesions that selectively affect the hippocampus. One study suggested that the disease specifically targets the CA3 hippocampal subfield, with extent of CA3 atrophy predicting severity of episodic memory impairment (Miller et al., 2017), but another study reported damage also extending to other hippocampal subfields (Finke et al., 2017). Considering the homogeneity of lesions to the hippocampus, patients with anti-LGI1 may provide an important assay of hippocampal function. In a study assessing seven patients (Lad, Mullally, Houston, Kelly, & Griffiths, 2019), significant anterograde amnesia was reported for verbal and visual material, with recognition relatively preserved compared to recall, consistent with sparing of familiarity processes. Retrograde amnesia was significant for recall of episodic events, with half of the participants demonstrating equal impairment across all life periods, and the other half showing a temporally graded trend (also see Chan, Henley, Rossor, & Warrington, 2007). Personal semantic memory, by contrast, was intact across all time periods for all patients. The authors postulated that intact semantic knowledge of childhood might support early autobiographical memory in those patients who demonstrated an episodic memory temporal gradient.

III.4. Korsakoff Syndrome

Korsakoff syndrome is a chronic disorder subsequent to incomplete resolution of Wernicke's encephalopathy, caused by thiamine deficiency (Arts, Walvoort, & Kessels, 2017; Kopelman, 1995). It is most commonly seen in individuals with a history of severe alcohol abuse, reflecting a combination of poor nutritional habits and malabsorption of thiamine in the intestine due to alcohol-induced damage of the intestinal tract. However, non-alcoholic etiologies associated with thiamine deficiency have also been described (Scalzo, Bowden, Ambrose, Whelan, & Cook, 2015).

The acute phase of Wernicke encephalopathy is characterized by a confusional state, oculomotor problems, and ataxia (Caine, Halliday, Kril, & Harper, 1997). Prompt thiamine replacement therapy is critical to prevent the occurrence of fatal midbrain hemorrhages and leads to clearing of the confusional state. However, if treatment is delayed, patients may present with irreversible amnesia, marking the onset of the chronic Korsakoff stage of the syndrome. Persistent changes in personality, including apathy, flat affect, and decreased insight, are also common (Arts et al., 2017).

The main pathology of Wernicke-Korsakoff syndrome consists of punctate lesions in the area of the aquaduct, third ventricle, and fourth ventricle, areas known to be especially sensitive to thiamine deficiency, often with concomitant frontal atrophy (Victor, Adams, & Collins, 1989). The exact neural substrate of the amnesia associated with Korsakoff syndrome has been a matter of much debate; lesions of the dorsomedial thalamic nuclei, anterior thalamic nuclei, and mammillary bodies each have been postulated to be critical (for review, see Kopelman, 2015). An autopsy study of the brains of individuals who had Wernicke encephalopathy in the context of alcohol dependence found that neuronal loss in the anterior thalamic nuclei differentiates Korsakoff patients from those without amnesia, whereas degeneration in the dorsomedial thalamus and mammillary bodies is common to both groups (Harding, Halliday, Caine, & Kril, 2000).

The central symptom of Korsakoff syndrome is an inability to acquire new verbal and nonverbal information (Fama, Pitel, & Sullivan, 2012). Even in the face of extensive repetition, patients have difficulty learning new information and they forget information to which they were exposed just minutes before. Susceptibility to interference is a core feature of the amnesic presentation, and may reflect both failure to fully encode information and competition from irrelevant information at the time of retrieval

(Verfaellie, 2003). Also characteristic are disproportionate impairments in contextual memory. Even when patients are provided additional exposure to boost their item memory, memory for the temporal sequence in which information is presented, and less consistently its spatial context, remains impaired (Kessels & Kopelman, 2012). It is likely that frontal executive deficits influence the amnesic presentation.

Korsakoff patients also suffer from severe retrograde amnesia in a temporally-graded pattern, with memories of childhood and early adulthood relatively better preserved. Notably, this gradient is extensive and tends to affect equally memory for personal events (Rensen et al., 2017) and memory for personal and public semantic information (for review, see Race & Verfaellie, 2012). Faulty memory retrieval and memory monitoring processes are thought to be an important mechanism underlying patients' retrograde amnesia, and consistent with this notion, patients often perform better on recognition tasks than on recall tasks. Yet, how to account for the presence of such an extensive temporal gradient has been less clear. It was initially proposed that the graded pattern might be due to the development of a progressive anterograde amnesia during the alcoholic premorbid period (Albert, Butters, & Brandt, 1981; Cohen & Squire, 1981), which might be superimposed on a strategic retrieval deficit that affects memories regardless of their age. However, this proposal was refuted by the case study of a respected scientist, who had written an autobiography in the several years just prior to Wernicke encephalopathy onset. This patient also displayed a temporally graded loss of information drawn from his autobiography – information that clearly had been encoded adequately (Butters & Cermak, 1986). An alternative possibility is that a retrieval deficit alone can lead to a graded pattern of impairment. Namely, recent memories may be more

susceptible to retrieval failure than remote ones, given that they have been rehearsed less frequently (Race & Verfaellie, 2012).

Another clinical feature of Korsakoff syndrome is confabulation. Whereas spontaneous confabulation is mostly seen in the acute Wernicke's phase, provoked confabulation (i.e., confabulation in the context of a challenge to memory) is commonly seen in the chronic phase. Such confabulatory responses have also been linked to controlled aspects of memory retrieval, although results remain inconclusive (Borsutzky, Fujiwara, Brand, & Markowitsch, 2008; Kessels, Kortrijk, Wester, & Nys, 2008).

III.5. Transient Global Amnesia

Transient global amnesia (TGA) is defined by the sudden onset of anterograde and retrograde amnesia lasting up to 24 hours (for review, see Bartsch & Butler, 2013). It is almost always preceded by a period of intense emotional or bodily stress (Bartsch et al., 2006; Erkelens & Snoek, 2010). In general, patients with TGA display little insight into their deficits but may exhibit some anxiety and perplexity, asking self-orientation questions such as "Where are we? What day is it?" Headache, nausea, or dizziness are also relatively common accompanying complaints (Hodges & Warlow, 1990). A number of etiologies of TGA have been proposed including ischemia, migraine-related mechanisms, and epileptic phenomena.

The pattern of memory deficits displayed during TGA is similar to hippocampal amnesia (Bartsch & Butler, 2013). It is characterized by severe anterograde amnesia, with information retained for a few seconds but rapidly lost with distraction (Bartsch et al., 2010; Jäger, Bäzner, Kliegel, Szabo, & Hennerici, 2009). The deficit has been shown to affect recollection, with sparing of familiarity-based processes (Jäger, Szabo, et al., 2009). A moderately severe retrograde amnesia for autobiographical events is also

apparent during TGA, with striking impairment of recent memories, but also affecting memories of events that occurred up to 30 to 40 years prior, albeit less severely (Bartsch, Dohring, Rohr, Jansen, & Deuschl, 2011). Anterograde memory typically recovers gradually over the course of a week, with complete long-term recovery. Retrograde amnesia tends to recover even more quickly, but patterns of recovery vary across patients (Jäger, Bäzner, et al., 2009).

Recent high-resolution MRI studies using diffusion-weighed or T2 sequences have revealed small lesions restricted to the CA1 subfield of the hippocampus that become apparent 24 to 72 hours after the episode (Bartsch et al., 2006; Scheel, Malkowsky, Klingebiel, Schreiber, & Bohner, 2012). These lesions usually disappear within 14 days, with no long-term sequelae (Bartsch & Deuschl, 2010). Metabolic or cytotoxic stress, to which CA1 cells are selectively vulnerable, constitutes the leading hypothesis of TGA pathophysiology, but the exact mechanisms remain unclear (for review, see Spiegel et al., 2017).

Conclusions

The study of patients with amnesia has proven fertile ground for elucidating the role of specific brain regions in normal and disordered memory. Although distinct etiologies can be associated with varying neuropsychological profiles, a core amnesic syndrome is shared among them that can be traced to disruption of the extended hippocampal system. This system comprises the hippocampus, mammillary bodies, anterior thalamic nuclei, cingulate gyrus, retrosplenial and parahippocampal cortices, and key white matter tracts that connect these regions, including the fornix, mammillothalamic tract, and cingulum bundle.

The hallmark of amnesia is an inability to form new long-term memories, whether reflecting specific events (episodic memory) or novel facts or concepts (semantic memory). Nonetheless, limited acquisition of semantic knowledge may be possible via inefficient neural routes involving direct cortical learning or a perirhinally mediated sense of familiarity. Regardless of etiology, retrograde amnesia is also present, which most strikingly compromises the retrieval of premorbid episodic memories. The retrieval of premorbid semantic memories is more variably affected, with temporally limited impairment following hippocampal lesions, and more extensive impairment with involvement of neocortical storage sites, in particular anterolateral temporal cortex.

The pattern of cognitive deficits associated with the amnesic syndrome has been refined over the past decade, with recent research uncovering impairments in domains other than long-term memory, including perception, short-term memory, and simulation of hypothetical or future events. The question has been raised whether these impairments are secondary to a fundamental deficit in long-term memory or reflect a more basic core function that is shared between long-term memory and these other domains. Although impairments in the construction of simulated events could reflect failure to access appropriate long-term memory representations, such failure alone does not account for impairments when relevant building blocks are provided. Furthermore, impairments in perception and short-term memory cannot easily be understood in terms of demands on long-term learning. Rather, this array of deficits points to a core binding mechanism that enables the construction of associative representations that are hierarchically organized within the MTL, and that are critical both for memory and for other cognitive functions. As demands on complex and precise binding increase, deficits beyond the domain of long-term memory become apparent in amnesia.

With the advent of advanced neuroimaging, it has become possible to identify patients with lesions to discrete hippocampal subfields. Evaluation of such patients using behavioral paradigms with well-specified cognitive demands has only recently begun, but yields the exciting prospect of testing hypotheses – derived from functional neuroimaging studies – about the necessity of these regions for specific neural computations. In the same vein, neuroimaging studies have postulated distinct roles for the anterior and posterior hippocampus (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Sheldon & Levine, 2016), a distinction that remains to be explored in human amnesia studies.

Despite advances on a number of fronts, there remain discordant findings in the literature that still await resolution. Although some contradictory findings may be due to differences in behavioral paradigms and scoring methods, another potential explanation lies in lesion variability among amnesic patients. In addition to the need to better characterize focal lesions, it will be important to consider the impact of such lesions at a network level, as functional disruption of remote regions may be key to understanding individual differences in observed patterns of impairment.

Studies of patients with amnesia have been instrumental in developing theoretical models of memory. Such models, in turn, have inspired new assessment techniques in the clinic, including tests of procedural learning (Heindel, Salmon, Shults, Walicke, & Butters, 1989), measures of short-term memory that tax relational processing (Blackwell et al., 2004), and assessment of autobiographical memory (Irish et al., 2011), to name just a few. By comparison, less progress has been made in the application of memory theory to the development of treatment strategies for patients with severe memory disorders. This translational agenda poses both challenge and opportunity for students of amnesia in the years ahead.

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Figures

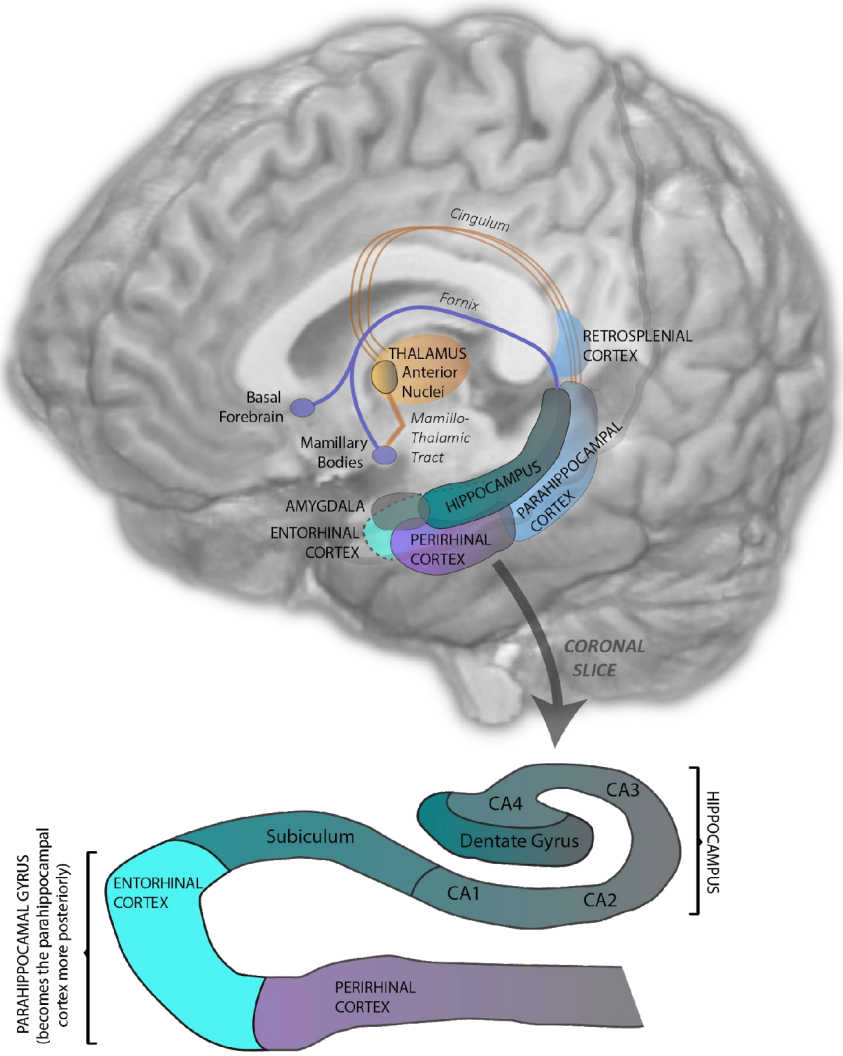

Figure 1: The Extended Hippocampal Network (originally "Papez circuit"). The circuit proceeds from the subiculum of the hippocampus to the mammillary bodies (via the fornix), anterior thalamic nuclei (via the mamillary-thalamic tract), cingulate gyrus (via the cingulum bundle and internal capsule), parahippocampal cortex (via the cingulum bundle), and back to the hippocampus. A more complex system of hippocampal-diencephalic-cingulate interconnections provides direct connections from the hippocampus to the cingulate cortex and anterior thalamic nuclei – this system is not represented here for clarity. An anterior coronal slice of the hippocampus and parahippocampal gyrus is also depicted, with hippocampal subfields. The parahippocampal gyrus is composed of the entorhinal cortex and perirhinal cortex anteriorly, but becomes the parahippocampal cortex more posteriorly.

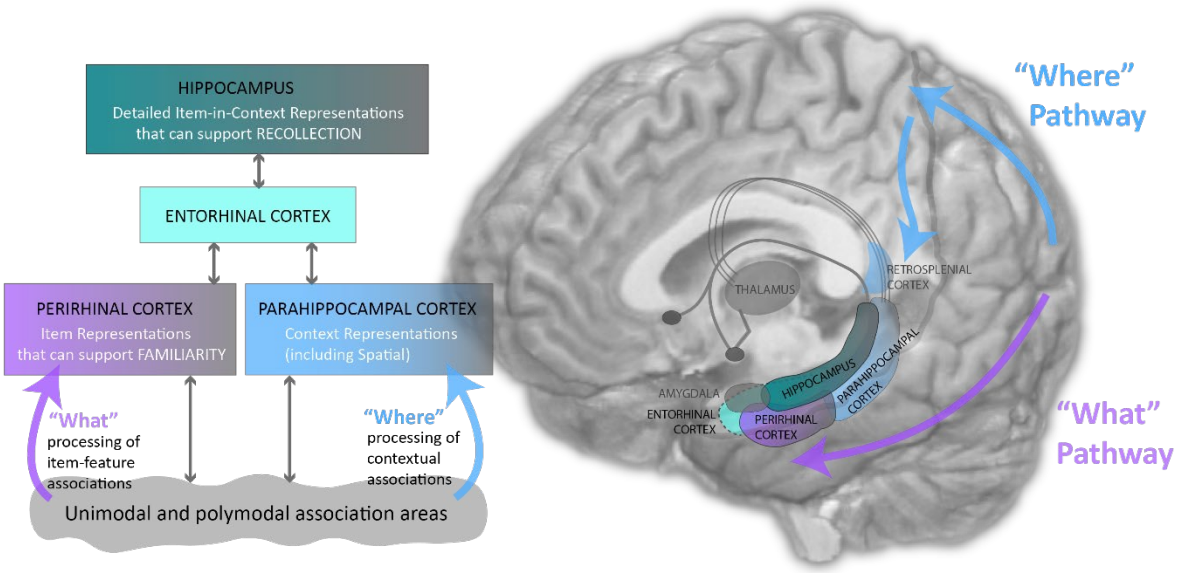

Figure 2: Functional division of the Medial Temporal Lobe (MTL) after Diana, Yonelinas, & Ranganath (2007). The hippocampus is at the top of the hierarchy of information processing, receiving "What" information from the ventral stream that culminates in the perirhinal cortex (item representations that can support familiarity), and "Where" information from the dorsal stream that culminates in the parahippocampal cortex (context representations). The hippocampus integrates information from both streams into memory representations that encompass item-in-context information, necessary for recollection.