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Review article

Heterarchic reinstatement of long-term memory: A concept on hippocampal amnesia in rodent memory research

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ABSTRACT

Evidence from clinical and animal research highlights the role of the hippocampus in long-term memory (LTM). Decades of experimental work have produced numerous theoretical accounts of the hippocampus in LTM, and each suggests that hippocampal disruption produces amnesia for specific categories of memory. These accounts also imply that hippocampal disruption before or soon after a learning episode should have equivalent amnestic effects. Recent evidence from lesion and inactivation experiments in rodents illustrates that hippocampal disruption after a learning episode causes memory impairment in a wider range of memory tasks than if the same disruption occurs before learning. Although this finding supports that multiple circuits can acquire and retrieve similar information, it also suggests they do not do so independently. In addition, damage after learning produces amnesia for simple elements of a task as well as complex, conjunctive features. Here we develop an explanation for why anterograde and retrograde hippocampal effects differ. This explanation, the heterarchic reinstatement view, also generates novel predictions.

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1. The hippocampus and LTM

LTM is the ability to recall information long after a learning episode. The period of recall can last hours, days, years, or an entire lifetime. Evidence from clinical research and experimental work with non-human animals emphasizes the role of the hippocampus in LTM. A key finding supporting this conclusion is that damage to the hippocampus causes retrograde amnesia (RA), that is, the inability to recall information from a learning episode that preceded the damage, in addition to an inability to form new long-term memories (anterograde amnesia, AA; Gilboa et al., 2006; Scoville and Milner, 1957; Steinvorth et al., 2005; Sutherland et al., 2010; Squire, 1992). Early on it was also shown that certain types of LTM were not affected by hippocampal damage. Some memories were lost and subjects were unable to acquire certain types of new memories, while other types of memory and abilities remained intact (Scoville and Milner, 1957; Zola-Morgan et al., 1986). Despite the early recognition of these facts, no consensus on their explanation has emerged. In the present discussion, our goal is not to present

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a comprehensive theory of the hippocampus in LTM, but rather is much more limited. We examine anomalous experimental results on amnesia and their conceptual implications for a modern view of how memory is organized in the brain.

Several theories have been developed to explain memory impairments following hippocampal disruption. Popular models highlight the role of the hippocampus in spatial (Morris et al., 1982; O'Keefe and Nadel, 1978; Sutherland et al., 1983, 1982), temporal (Eichenbaum, 2014; Davachi and DuBrow, 2015), episodic (Nadel and Moscovitch, 1997; Steinvorth et al., 2005; Squire and Zola, 1998), and more generally, relational and configural memory (Cohen and Eichenbaum, 1993; Eichenbaum et al., 1988; Rudy and Sutherland, 1995; Sutherland et al., 1989; Sutherland and Rudy, 1989; Wickelgren, 1979). Although contemporary views differ in their categorization of hippocampal function, they collectively posit two hypotheses: 1) hippocampal disruption will cause memory impairments in a specific range of memory tests; 2) hippocampal disruption before or soon after learning should elicit similar impairments.

The idea that memory should be equally affected if the hippocampus is disrupted before or soon after learning is consistent with the general notion that different brain areas are required for different types of memory (Gold, 2003; Hirsh, 1974; McDonald and Hong, 2013; McDonald and White, 1993; Packard et al., 1989; Packard and White, 1991; Scoville and Milner, 1957; Squire, 1992; White and McDonald, 2002), and that each system stores information more or less independently and in parallel (Gulbrandsen et al., 2013; Packard and White, 1991; Sutherland et al., 2010; White and McDonald, 2002). These types of memory might include that for objects, locations, actions, visual and auditory stimuli, odours, and various outcomes. The segregation of memory functions to different brain areas is a basic tenet of a class of theories that are termed Multiple Memory Systems Theories (MMST; Squire, 1992; White and McDonald, 2002). Indeed, a large body of empirical work details the role of the hippocampus in spatial, temporal, relational, and episodic memory (Schiller et al., 2015). For example, hippocampal damage or inactivation impairs the ability of animals to acquire spatial (Morris et al., 1982; Sutherland et al., 1982; Sutherland et al., 1983), temporal (Fortin et al., 2002), and relational or configural associations (Eichenbaum et al., 1988; Sutherland and McDonald, 1990; Sutherland et al., 1989). The same damage or inactivation made before or during a learning episode does not impair other types of memory, including non-spatial, non-temporal, and elemental features of an episode (Alvarado and Rudy, 1995; Bangasser et al., 2006; Solomon et al., 1986; Sutherland and McDonald, 1990). *Prime facie*, these findings support contemporary views of hippocampal function. However, damage or inactivation of a brain area prior to a learning episode does not necessarily reveal whether that region is normally involved in learning and memory as a result of the episode. Rather, these approaches demonstrate which functions can be supported by other brain networks. Nonetheless, popular theories on the hippocampus in LTM suggest that its disruption prior to or after learning should result in similar memory deficits. Each popular view of the hippocampus in LTM, including the Standard Model of Systems Consolidation (SMSC; Squire, 1992), Multiple Trace Theory (MTT; Nadel and Moscovitch, 1997), Transformation Theory (Winocur et al., 2013), Indexing Theory (Teyler and DiScenna, 1986), Relational Memory Theory (Cohen and Eichenbaum, 1993), Configural Association Theory (Rudy and Sutherland, 1995; Sutherland and Rudy, 1989), Spatial Mapping Theory (O'Keefe and Nadel, 1978), and the Multiple Memory Systems Theory (Squire, 1992; White and McDonald, 2002) assume that different brain areas are involved in different types of memory. Each popular model suggests that hippocampal damage would specifically impair mnemonic processes to which it uniquely contributes.

Table 1
The table illustrates findings within and across studies that demonstrate RA but not AA for several types of memory. Examples have been limited to reports of complete hippocampal damage or inactivation (>70%) resulting in RA but not AA. As we discuss, these findings are anomalous in the context of modern theories on the hippocampus in LTM. Some conflicting results exist with hippocampal lesions on object memory (see Broadbent et al., 2004, 2010). The reason for these differences between reports is unknown, and we suggest merits further investigation (see Section 7).

Task	AA	RA	Reference
Context	No	Yes	Sparks et al. (2011b)
Context	No	Yes	Wiltgen et al. (2006)
Context	–	Yes	Broadbent and Clark (2013)
Context	–	Yes	Lehmann et al. (2007a,b,c)
Context	–	Yes	Sparks et al. (2011a)
Context	–	Yes	Sparks et al. (2013)
Context	–	Yes	Wang et al. (2009)
Context	–	Yes	Sutherland et al. (2008)
Home base	No	Yes	Travis et al. (2010)
Home base	No	–	Lehmann et al. (2007a,b,c)
Light	No	Yes	Lehmann et al. (2010)
Object	–	Yes	Sutherland et al. (2001)
Object	No	–	Morris et al. (1986)
Object	No	Yes	Gaskin et al. (2003)
Object	No	Yes	Broadbent et al. (2007)
Picture	No	Yes	Driscoll et al. (2005)
Picture	No	Yes	Epp et al. (2008)
Tone	No	–	Bangasser et al. (2006)
Tone	–	Yes	Sutherland et al. (2008)
Tone	–	Yes	Broadbent and Clark (2013)

Contrary to this basic tenet of popular theories, many investigators have reported that hippocampal disruption before and after learning in rodents do not produce equivalent amnestic effects. Hippocampal damage or inactivation prior to a learning episode causes AA for spatial, temporal, and relational memory, while its disruption after learning results in RA for a much wider range of memory types. This includes RA for spatial and non-spatial, temporal and non-temporal, elemental, and relational types of memory. This outcome is not likely due to non-specific effects of lesion or acute inactivation, since both types of disruption result in similar experimental outcomes (Otchy et al., 2015; Table 1). Evidence for the differential effects of hippocampal damage or inactivation on AA and RA are described almost uniquely in rodent literature. As a result, the evidence we discuss is restricted primarily to rodent memory research.

Table 1 illustrates examples wherein complete (>70%) hippocampal damage or inactivation has resulted in RA but not AA for numerous memory types, including context fear, tone fear, light fear, picture memory, object recognition, and home base memory. Although an exhaustive list of examples may be greater than Table 1 demonstrates, including tasks such as paired associate learning (Kim et al., 2015), and earlier reports of context and tone fear conditioning (Frankland et al., 1998; Maren et al., 1997), we have restricted Table 1 to cases wherein hippocampal damage or inactivation is extensive (>70%). Several studies have revealed that the extent of RA soon after learning correlates with hippocampal damage (Epp et al., 2008; Lehmann et al., 2007a,b,c; Sutherland et al., 2008). Therefore, outcomes of studies with incomplete (<70%) or unreported amounts of hippocampal damage or temporary inactivation should be interpreted carefully (Sutherland et al., 2010).

The prediction that hippocampal disruption introduced before or soon after learning should result in similar, specific deficits in memory is at odds with the experimental outcomes in Table 1. Instances wherein hippocampal disruption causes RA but not AA for a given type of memory are anomalies in the context of popular theories of the hippocampus in LTM. As Table 1 illustrates, this phenomenon has been observed in a variety of rodent memory tasks, and has been previously explained by a concept termed, "hippocampal overshadowing" (Driscoll et al., 2005; Fanselow, 2009;