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Imaging systems level consolidation of novel associate memories: A longitudinal neuroimaging study

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ABSTRACT

Previously, a standard theory of systems level memory consolidation was developed to describe how memory recall becomes independent of the medial temporal memory system. More recently, an extended consolidation theory was proposed that predicts seven changes in regional neural activity and inter-regional functional connectivity. Using longitudinal event-related functional magnetic resonance imaging of an associate memory task, we simultaneously tested all predictions and additionally tested for consolidation-related changes in recall of associate memories at a sub-trial temporal resolution, analyzing cue, delay and target periods of each trial separately. Results consistent with the theoretical predictions were observed though two inconsistent results were also obtained. In particular, while medial temporal recall related delay period activity decreased with consolidation as predicted, visual cue activity increased for consolidated memories. Though the extended theory of memory consolidation is largely supported by our study, these results suggest that the extended theory needs further refinement and the medial temporal memory system has multiple, temporally distinct roles in associate memory recall. Neuroimaging analysis at a sub-trial temporal resolution, as used here, may further clarify the role of the hippocampal complex in memory consolidation.

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Introduction

In 1953 a patient with intractable epilepsy, HM, underwent bilateral medial temporal lobe resection which removed much of the mesial surface of the temporal lobes including the majority of the hippocampi and hippocampal gyri (Scoville and Milner, 1957). As a consequence of the surgery HM, and patients with similar medial temporal damage, present with severe anteriograde amnesia for declarative memories as well as retrograde amnesia for declarative information acquired in the years prior to the surgery (Manns and Squire, 2001). However, information acquired earlier in life, including childhood autobiographical memory and lexical information such as the names of objects and meanings of words are relatively spared (Kensinger et al., 2001). Systems level consolidation theory suggests that the medial temporal lobes, and the hippocampal complex in particular, are necessary for the initial storage and recall of memories but that remote memories are eventually stored elsewhere in neocortex and may be recalled independently of the medial temporal lobe memory system (Squire et al., 1984; Zola-Morgan and Squire, 1990; Squire 1992; Squire and Alvarez, 1995; Squire and Bayley, 2007). To avoid interference between old and new memories, it has been suggested that a fast-learning hippocampal complex initially facilitates learning and recall with new memories slowly stabilized over time, possibly via subsequent recall and reconsolidation events or replay during rest and sleep (McClelland et al., 1995; Hoffman and McNaughton, 2002; Wilson, 2002). This stabilization process incorporates the memory into the slow-learning neocortical networks, which maintain existing knowledge (McClelland et al., 1995; Alverez and Squire, 1994). Though considerable debate continues regarding, for example, the necessity of the hippocampus for remote memories with autonoetic content (i.e. episodic memories), or the probability that some semantic memories can be acquired in spite of hippocampal damage, the major elements of the systems level consolidation of non-episodic memory has been well supported (Nadel and Moscovitch, 1997; Vargha-Khadem et al., 1997; Schmolck et al., 2002; Manns et al., 2003).

Additional lesion studies have identified temporally graded retrograde amnesia following lesions to several medial temporal structures including the hippocampus (CA fields and subiculum), entorhinal cortex, and perirhinal cortex (Cho et al., 1993; Bolhuis et

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al., 1994; Clark et al., 2002; Glenn et al., 2003). However, the effects of lesions to different areas appear to be temporally distinct, with, for example, memories remaining dependent on intact entorhinal cortex for a longer duration than on intact hippocampus (Izquierdo et al., 1997). Thus, while the hippocampus proper remains an important focus for consolidation studies, consolidation related effects occur throughout much of the medial temporal lobes.

Recently, Frankland and Bontempi (2005) proposed extensions to the standard theory of systems level consolidation based on extensive experimental evidence in animal models of memory. Their extended theory can be summarized by seven predictions regarding changes in regional activity and inter-regional functional connectivity within the brain (see Fig. 1 and Table 1). First, neural activity in the medial temporal memory region should be decreased during recall of consolidated remote relative to recent memories due to the decreased role of the hippocampus and related structures in consolidated memory recall. Second, neural activity in neocortical memory storage regions should increase during recall of consolidated remote relative to recent memories due to their increased role in storing the memory. Third, neural activity in prefrontal cortex should increase during recall of consolidated remote relative to recent memories due to its role in orchestrating memory retrieval and a possible role in suppressing medial temporal activity for consolidated memories (Laroche et al., 2000). Fourth, absolute magnitude of inter-regional functional connectivity (correlated neural activity) between prefrontal cortex and the medial temporal memory region should increase during recall of consolidated remote relative to recent memories due to the possible suppression (inhibition) of the hippocampus and related structures by the prefrontal cortex. Fifth, inter-regional functional connectivity between prefrontal cortex and neocortical memory storage regions should increase during recall of consolidated remote relative to recent memories due to the increased role of the prefrontal region in coordinating consolidated recall. Sixth, inter-regional functional connectivity between the medial temporal memory regions and neocortical memory storage regions should be decreased during recall of consolidated remote relative to recent memories due to the decreased role of the medial temporal memory regions in coordinating consolidated memory recall. And seventh, inter-regional functional connectivity within the neocortical storage regions should increase during recall of consolidated remote relative to recent memories due to the increased coordinated role of these regions in consolidated memory recall. While individually these predictions are based on experimental evidence mostly from animal models,

Table 1
Seven predictions of the extended theory of systems level consolidation.

	Systems level consolidation should lead to:
1	Decreased hippocampal activity
2	Increased neocortical (lateral temporal) activity
3	Increased prefrontal activity
4	Increased connectivity between prefrontal and hippocampal region (inhibitory)
5	Increased connectivity between prefrontal and lateral temporal regions (excitatory)
6	Decreased connectivity between hippocampal and lateral temporal regions
7	Increased connectivity within lateral temporal regions

neuroimaging studies of systems level consolidation related changes in humans have been less consistent regarding these predictions and have only recently begun to test all the predictions simultaneously.

Because of an important theoretical debate regarding systems level consolidation of non-semantic, purely episodic memories (c.f., Nadel and Moscovitch 1997), the primary focus of these consolidation studies has been the hippocampus proper. An alternative theory to the standard model, Multiple Trace Theory, agrees that the hippocampal complex is not necessary for consolidated semantic memories. However, Multiple Trace Theory posits that episodic memories with a strong autonoetic component are never consolidated to memory systems outside the hippocampus, regardless of their age. Several studies have now closely examined the relative activity in the hippocampal complex during recent versus remote recall and have yielded considerably mixed results with some studies showing greater hippocampal activity for remote memory recall (Haist et al., 2001; Niki and Luo, 2002; Maguire and Frith, 2003; Piefke et al., 2003; Douville et al., 2005), some studies showing greater hippocampal activity for recent memory recall (Gilboa et al., 2004; Piolino et al., 2004; Rekkas and Constable, 2005), and others showing little or no effect in the region (Maguire et al., 2001; Bernard et al., 2004; Steinvorth et al., 2006). Recent studies using experimentally induced memories which allow for greater control over age and strength of the memory trace have also yielded inconsistent results with reduced (Takashima et al., 2006), greater (Bosshardt et al., 2005), or equivalent (Stark and Squire, 2000) hippocampal complex activation during recall of more remote memories. However, several issues potentially confound the interpretation of many of these studies, including differences in familiarity between targets and foils, use of familiarity versus recall for response, use of blocked experimental designs, use of linguistic

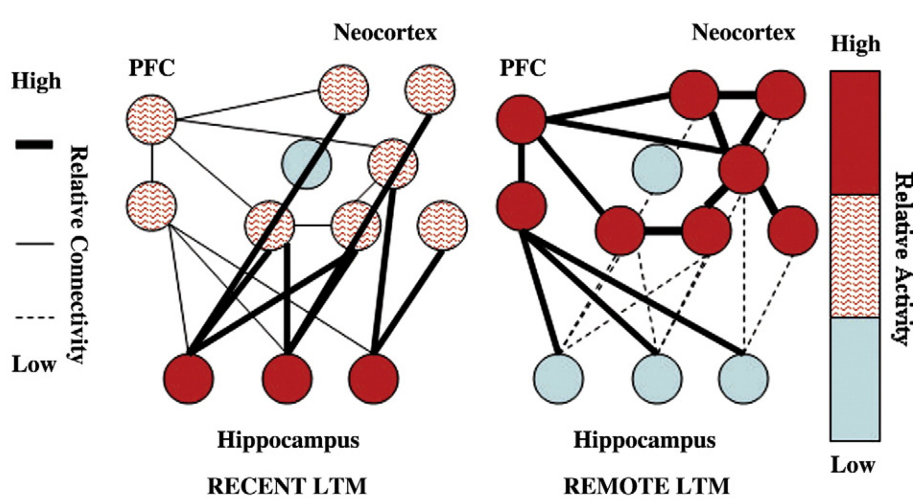

Fig. 1. Graphical depiction of the standard model of systems level memory consolidation. The figure, adapted from Frankland and Bontempi (2005), graphically depicts the seven changes in regional activity and inter-regional connectivity predicted by the standard theory. Node color indicates activity level with red indicating relatively greater activity. Connection line weight indicates strength of functional association with heavier lines indicating stronger functional connectivity.