

REVIEW ARTICLE

The Ensemble That Plays Together, Stays Together

Lila Davachi

It has long been known that the medial temporal lobe is crucial for the formation and retrieval of episodic memories. This region includes the hippocampal formation (the hippocampus proper and subiculum) and the underlying entorhinal, perirhinal, and parahippocampal cortices, all of which receive a unique complement of cortical inputs. How best to characterize the precise roles of these different brain regions and their interactions is of central concern in understanding the medial temporal lobe contributions to episodic memory.

Using functional magnetic resonance imaging (fMRI) to assess brain activity while subjects performed an episodic retrieval task, Giovanello et al. (2004) have contributed two important pieces to this puzzle. First, their findings show that the hippocampal formation is differentially recruited when subjects are asked to make memory decisions about the conjunctive relationship (in this case, the co-occurrence) of two stimuli compared to decisions about each stimulus independently. Second, their data demonstrate that the extent to which the hippocampus is activated also depends critically on whether the two stimuli were actually previously paired. In this study, subjects encoded a series of word pairs by forming sentences that contained the two words. At retrieval, subjects were asked to engage in two different tasks: an “Item” task that asked subjects to report whether the two test words had been previously presented and an “Associative” task that asked subjects to report whether the two items had been previously presented together. Giovanello and colleagues collected fMRI data during this retrieval phase, demonstrating that the hippocampus shows greater BOLD signal increase when subjects performed the Associative task compared with the Item task. Furthermore, greater BOLD increase within the Associative task was seen to “intact” word pairs (i.e., test words were paired during the study phase) compared to both “rearranged” (i.e., both test words were presented during the study phase but paired with a different word) and to novel word pairs.

The implications of these findings are twofold. First, they add to a growing literature demonstrating the involvement of the hippocampus in conjunctive processing (i.e., making decisions about conjunctions between stimuli) above and beyond item processing (i.e., making decisions about individual stimuli). More specifically, these findings underscore the hypothesis that the role of the hippocampus in episodic memory is in the creation of an ensemble of activity that is a filtered representation of all activity in the cortical and subcortical mantle during the moment to moment processing of

events. In this way, each singular hippocampal representation might, in essence, act as a mirror reflection of all other activity in the brain and it is through this process that multiple elements of an episode might get bound into a single, conjunctive representation (Norman and O'Reilly, 2003). Second, these results demonstrate not only that the hippocampus is preferentially engaged during conjunctive processing, but also that activity in the hippocampus signals when previously associated stimuli appear together again or are “intact.” Taken together, these findings suggest that hippocampal processes can be modulated by our attentional orientation or goals and is further sensitive to the external environment, namely the repetition of the co-occurrence of conjunctions between stimuli (i.e., a “match”). Intriguingly, it might be the case that the hippocampus can signal an external “match” in the environment regardless of where or how our attention is being focused.

Greater engagement of the hippocampal formation during the Associative orienting task complements results from single cell recordings in rats and monkeys demonstrating that hippocampal neurons primarily code for the associations between stimuli and not for individual stimuli (Brown and Aggleton, 2001; Wirth et al., 2003). This is in contrast to the neighboring perirhinal cortex where, instead, neurons have been shown to code for the familiarity or recency of individual items (Brown and Aggleton, 2001). Extending these findings from animal models, a growing number of neuroimaging studies have now shown that the human hippocampus is more active during encoding when attention is oriented towards conjunctions of stimuli rather than to each individual stimulus (Davachi and Wagner, 2002; Henke et al., 1997). Importantly, the magnitude of hippocampal activation during conjunctive encoding has been shown to affect memory formation as many of these studies have demonstrated correlations between hippocampal activation during encoding and later conjunctive memory as measured by recall, paired associate recognition or source recollection (Sperling et al., 2001; Strange et al., 2002; Davachi et al., 2003; Jackson and Schacter, 2004; Ranganath et al., 2004). Of these studies, a small number have also provided evidence for a dissociation between hippocampal and perirhinal encoding processes. Namely, it has been shown that hippocampal and perirhinal cortical engagement can be modulated differentially by task demands to attend either to the conjunc-

Department of Brain and Cognitive Science, Massachusetts Institute of Technology, Cambridge, Massachusetts.

Correspondence to: Lila Davachi, Department of Psychology, New York University, New York, NY 10003. E-mail: lila.davachi@nyu.edu
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tions between stimuli or to the individual stimuli (Davachi and Wagner, 2002). Furthermore, within the same encoding task, the magnitude of activation in the hippocampus and perirhinal cortex during encoding has been shown to correlate, respectively, with either later conjunctive memory (i.e., source recollection) or item memory (i.e., item recognition or familiarity) (Davachi et al., 2003; Ranganath et al., 2004). Taken together, this growing literature provides support for a distinction between hippocampal and perirhinal encoding processes such that the hippocampus might support the rapid, conjunctive learning necessary to bind a variety of elements (e.g., sensory, affective, cognitive) into a cohesive episode while perirhinal learning processes might support later item recognition irrespective of associated contextual elements.

What do we know about the hippocampus and other medial temporal lobe structures during retrieval? First, if the hippocampal representation formed during encoding is to aid in later retrieval of conjunctive information, then one would expect hippocampal responses at retrieval to reflect a repetition of conjunctions of items (Brown and Aggleton, 2001; Miller and Desimone, 1993). Second, within the context of this retrieval task, subjects encountered two stimuli and were asked to assess whether the stimuli had co-occurred during encoding. Thus, in order to perform the retrieval task, subjects were, in essence, being asked to again orient to the conjunctive relationship between the two stimuli, just as they had been instructed to do in the study phase. Giovanello's findings provide new evidence that hippocampal responses are, indeed, greater during Associative compared to Item memory decisions. Complementing this finding are recent data that show increased hippocampal activation during retrieval when subjects correctly identify the "source" of a presented item (Cansino et al., 2002; Dobbins et al., 2003) and when they claim that they "remember" having encountered the item because they can recollect details about its prior encounter compared to when they simply "know" they had encountered an item without being able to bring back details of the event (Eldridge et al., 2000). In other words, these retrieval patterns mirror those seen at encoding by demonstrating that the hippocampus exhibits an increase in activation when subjects are successful at recovering conjunctive information.

Perhaps the most intriguing finding from the Giovanello study is that the greatest hippocampal activation was seen when pairs were presented "intact" compared to when they were "rearranged." If hippocampal activation is merely reflective of attention to, or success at, retrieving conjunctive information, one would expect a similar level of activation for all conditions in the Associative recognition task. In other words, one could argue that since only correct trials are used in the analysis, subjects are attending to conjunctions for all conditions within the Associative task and are likely successfully retrieving conjunctive information for both the intact and rearranged conditions. However, Giovanello and colleagues report that there is also a BOLD signal advantage for "intact" pairs compared to "rearranged" pairs, suggesting that the hippocampus signals that an environmental stimulus conjunction "matches" one that was previously presented. As noted by the authors, their data are

ambiguous as to whether the fundamental dimension for engaging the hippocampus is attentional orientation (i.e., Associative or Item tasks) or the stimulus condition (i.e., "intact" or "rearranged" pairs). The critical question, then, is how would the hippocampus respond to "intact" pairs presented during the Item orienting task (a condition not included in the present study)? Would the hippocampus again show robust activation? That is, just as task independent response suppression for repeated objects has been described in the perirhinal cortex (Brown and Aggleton, 2001), does the hippocampus signal the presence of a stimulus configuration "match" regardless of whether the assessment of that match is task relevant? Furthermore, does the hippocampus signal a configurational match even if subjects are unaware of the match? Initial evidence from the implicit learning literature has recently explored the latter question. For example, recent data from amnesic patients show that they are impaired in implicit contextual and relational learning tasks (Chun and Phelps, 1999; Ryan et al., 2000). However, these patients have damage extending beyond the hippocampus proper, and it is under dispute whether patients with selective hippocampal damage will show the same deficit (Manns and Squire, 2001). To this end, interestingly, a couple of recent neuroimaging studies have demonstrated engagement of the medial temporal lobe during implicit learning even in the absence of awareness (Henke et al., 2003; Schendan et al., 2003). Thus, although the critical attentional and stimulus configurational factors that engage the hippocampus and other cortical structures remain to be specified, neuropsychological and neuroimaging studies are beginning to provide some leverage. In this manner, further research should help clarify the extent to which perirhinal and hippocampal processes (as well as entorhinal and parahippocampal cortical) are functionally independent or representative of functional gradients within the medial temporal lobe. Giovanello et al. (2004) have provided important additional information regarding the conditions under which the hippocampus is maximally engaged and, ultimately, to our understanding of how the medial temporal lobe contributes to memory.

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