

Journal Club

Editor's Note: These short, critical reviews of recent papers in the Journal, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Short-Term Memory and the Human Hippocampus

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Review of Hannula and Ranganath (<http://www.jneurosci.org/cgi/content/full/28/1/116>)

Every undergraduate psychology student is taught that short-term memory, the ability to temporarily hold in mind information from the immediate past (e.g., a telephone number) involves different psychological processes and neural substrates from long-term memory (e.g., remembering what happened yesterday). This dichotomous account of memory is grounded on evidence of neuropsychological dissociations such as those shown by patients with damage to medial temporal lobe (MTL), who until now have been thought to exhibit impaired long-term memory but normal short-term memory (Squire, 1992). In recent years, however, this viewpoint has faced considerable challenges, given accumulating evidence suggesting that short-term memory and long-term memory, rather than being qualitatively distinct, may in fact share similar underlying neural mechanisms (for review, see Jonides et al., 2008).

A key recent observation is that patients with MTL damage perform poorly not only on long-term memory tasks, but also on short-term memory tasks that involve remembering novel information across brief intervals. Whereas the perirhinal cortex appears to support short-term memory for novel object information (Brown and Aggleton, 2001),

neuropsychological evidence suggests that the hippocampus is critical when associative information is involved (for review, see Jonides et al., 2008), in line with its proposed function as a relational binder in long-term memory (Cohen and Eichenbaum, 1993). For instance, in one recent study, patients with hippocampal amnesia were impaired at remembering the locations of novel objects, even across a delay of a few seconds (Jonides et al., 2008).

We know from neuropsychological evidence, therefore, that the hippocampus is critical to short-term memory for associative information. What is not clear from the neuropsychological data, however, is how the hippocampus supports this function. Hannula and Ranganath (2008) use functional magnetic resonance imaging (fMRI) to address this important issue by characterizing brain activity during each phase of a short-term associative memory task and by linking such neural activity to behavioral performance. Whereas a subsequent memory approach has been widely used to study long-term recognition memory, this has not been possible in previous short-term memory experiments because of the near-ceiling performance typically achieved by subjects. To circumvent this problem, the authors chose a relatively difficult task to ensure that sufficient numbers of correct and incorrect trials would be generated.

The paradigm used shares similarities with a task known to be hippocampal-dependent based on previous neuropsychological data (Hartley et al., 2007). Dur-

ing the sample phase of each trial, subjects viewed a novel scene consisting of four objects (out of a set of nine objects), each in one of nine possible locations in a 3×3 grid [Hannula and Ranganath (2008), their Fig. 1 (<http://www.jneurosci.org/cgi/content/full/28/1/116/F1>)]. To encourage use of a hippocampally mediated allocentric (or world-centered) strategy, rather than an egocentric (or viewer-centered) strategy thought to rely on parietal and prefrontal cortices, subjects were asked to form a mental image of the scene rotated 90° to the right of the original viewpoint. They were then required to maintain the rotated representation during the ensuing 11 s delay phase in anticipation of the test stimulus. During the test phase, subjects' memory for the positions of the objects was assessed. This was done by asking them to classify, by button press, the test stimulus according to whether it constituted (1) a "match" (i.e., the original scene rotated 90°); (2) "mismatch-position" (i.e., one object occupied a new location); (3) "mismatch-swap" (i.e., two objects had swapped locations). Performance in all conditions was significantly greater than a chance level of 33% correct responses: 78, 65, and 60% on match, mismatch-position and, mismatch-swap displays, respectively.

The authors first performed a subsequent memory analysis by contrasting correct trials with incorrect trials. This revealed that hippocampal activity during the sample phase predicted successful recognition judgments in the test phase [Hannula and Ranganath (2008), their Fig. 2 (<http://www.jneurosci.org/cgi/>

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content/full/28/1/116/F2)]. Critically, a subsequent memory correlation was also observed in the hippocampus during the test phase [Hannula and Ranganath (2008), their Fig. 3 (<http://www.jneurosci.org/cgi/content/full/28/1/116/F3>)]. This finding rules out an otherwise problematic explanation that greater neural activity during the sample phase predicts subsequent success not through the encoding of object-location associative information, but rather the objects (e.g., drums, birdbath) themselves. Indeed, a subsequent memory correlation was observed in the perirhinal cortex selectively during the sample phase, in line with proposals that this neural region is critical for the encoding of item-specific information.

Interestingly, there were no significant differences in hippocampal activity as a function of accuracy during the delay period. Although caution is advised in interpreting such a null finding, this result does suggest that persistent neural firing in the hippocampus does not occur during the delay period of short-term memory tasks, as is thought to occur in the entorhinal cortex. One possibility is that the hippocampus supports short-term memory for associative information through transient changes in synaptic efficacy, rather than active maintenance (Jonides et al., 2008). Alternatively, active maintenance may occur, but by a different mechanism not detectable by fMRI (e.g., involving theta/gamma oscillations).

These results suggest that the hippocampus plays an important role in the encoding and retrieval, but perhaps not the active maintenance, of novel associative information in short-term memory. But how does the hippocampus compute the novelty, or conversely familiarity, of the test stimulus such that a correct recognition judgment can be made? An influential theoretical proposal is that the hippocampus acts as a comparator (or match-mismatch detector), identifying discrepancies between previous predictions based on past experience and current sensory inputs (Norman and O'Reilly, 2003) (for review, see Kumaran and Maguire, 2007). One strategy for assessing the validity of this hypothesis is to characterize how hippocampal activity varies as a function of the novelty or familiarity of the test stimulus. Empirical evidence consistent with predictions arising from a comparator model was provided by a recent study using this approach (Kumaran and Maguire, 2006), with hippocampal activity observed specifically under conditions of match-

mismatch, and not in response to the mere presence of novelty per se.

Hannula and Ranganath (2008) adopted a similar approach to probe the nature of hippocampal novelty/familiarity signals, by including three types of test trials that varied according to their similarity to the sample stimulus. The authors used a region-of-interest analysis to demonstrate that hippocampal activation during correct trials was greatest in relation to match displays (compared with mismatch-position and mismatch-swap displays). Interestingly, when the novelty/familiarity of associative information is incidental to the task at hand (i.e., subjects are not required to make explicit recognition memory judgments), a qualitatively different pattern of findings has been observed with hippocampal activation maximal under conditions of mismatch rather than match (Kumaran and Maguire, 2006). Before turning to "interesting" explanations for this discrepancy, it is worth considering the influence of subjects' superior performance during match displays (compare mismatch displays) on the observed neural data. Although the authors carefully considered and discounted such an effect, without confidence rating data, it is difficult to entirely exclude the possibility that subjects may have been more confident in making (correct) match, as opposed to mismatch, judgments.

That said, the most likely explanation for the observed findings is that the amplitude of hippocampal responses to novel (or familiar) sensory inputs depends on the specific task being performed. As such, the findings observed by Hannula and Ranganath (2008) resemble the well known phenomenon of "match enhancement" observed in monkey inferotemporal/perirhinal cortex in relation to the arrival of an anticipated target stimulus that matches the current stimulus being held in mind (Miller and Desimone, 1994) [Hannula and Ranganath (2008), their Fig. 3 (<http://www.jneurosci.org/cgi/content/full/28/1/116/F3>)]. In contrast, during the automatic detection of novelty within the environment, increased neural activity in the hippocampus may reflect the relatively "pure" signature of a comparator mechanism, free from modulation by top-down influences (Kumaran and Maguire, 2006). An important avenue for future work, therefore, will be to explore the importance of reciprocal interactions between the hippocampus and prefrontal cortices that vary according to specific task requirements (e.g., explicit recognition memory task) and therefore

determine the amplitude of observed hippocampal novelty (or familiarity) signals.

To summarize, the study by Hannula and Ranganath (2008) nicely complements existing neuropsychological data concerning the importance of the hippocampus to short-term associative memory. Moreover, the evidence provided yields new insights into the nature of the hippocampal contribution to short-term memory, suggesting that it participates primarily in encoding and retrieval, but perhaps not active maintenance of associative information. One important direction for future research will be to develop and empirically test formal computational models of recognition memory [e.g., those described by Norman and O'Reilly (2003)] and automatic novelty processing using fMRI. Ideally, these models should include MTL components as well as task-specific modulatory interactions with higher regions (e.g., prefrontal cortex). In this way, it may be possible to achieve a precise understanding of how novelty and familiarity are computed in the MTL and how these signals are used by other brain regions to effect successful recognition memory judgments and to automatically detect novelty within our sensory environment.

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