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COMMENTARY

Who's the Fairest of Them All? Role of the Human Hippocampus in the Relational Organization of Memory

Peter R. Rapp*

A central property of memory is that it provides access to information outside the setting in which it was acquired, allowing us to benefit from past experience when challenged with new circumstances. By one account, the hippocampus represents ongoing experience according to the salient relationships among events, establishing precisely the sort of organization that could enable linking temporally distinct items in memory. Recent efforts to evaluate this proposal have taken advantage of transitive inference procedures originally adopted to study cognitive development in children. In generic form, the task involves an initial phase of explicit instruction about associations between items presented in pairs, followed by critical tests asking subjects to infer the relationship between stimuli that are related only indirectly, by virtue of their shared association with one or more intervening items. Having learned that Sue is darker than Bill but fairer than Helen, for example, normal individuals have little difficulty determining who is fairest of all, despite the lack of any direct comparison between Bill and Helen during training. Studies using analogous, nonverbal assessments have demonstrated similar abilities in birds, rats, and monkeys. Moreover, experimental damage involving the cortical or subcortical connections of the hippocampus severely impairs transitive inference performance, without substantially affecting acquisition during initial training (Dusek and Eichenbaum, 1997). Together these findings suggest that the ability to generalize and draw inferences from memory is conserved, and that this capacity requires the integrity of the hippocampus. As the song says, however, it ain't necessarily so.

Behavioral scientists recognized years ago that multiple computational mechanisms can account for apparent inferential responding observed in animals, without reference to memory for the associations among items (e.g., von Fersen et al., 1991). The procedures used in these experiments typically involve training on a series of overlapping, conditional discriminations, following the general form that stimulus A is rewarded when paired with B, but B is rewarded when presented with C. The aim, then, is to establish an implied, symbolic hierarchy of the form A>B>C; an organization that can be surveyed under novel conditions, when A is paired with C. Another possibility, however, is that each stimulus might effectively accrue a distinct reward value over the course of training, and that choices on the critical test trials are guided by a nontransitive solution, on the basis of knowledge about the individual items. Although disrupting hippocampal function consistently impairs transitive inference performance, some investigators have suggested that these alternate accounts call into question the specific nature of the deficit observed (Frank et al., 2003; Van Elzakker et al, 2003). More importantly perhaps, while the effects of experimental brain damage are clearly informative, what has been lacking is converging evidence from other methodologies, demonstrating that the intact hippocampus normally participates in information processing supporting transitive inference.

Two independent reports in this volume of *Hippocampus* address these issues (see Heckers et al., 2004; Preston et al., 2004). Both used functional magnetic resonance imaging (fMRI) to examine regional brain activation while young adults performed nonverbal variants of a transitive inference task. In one case, subjects learned relatively long series of overlapping associations using complex visual patterns as discriminative stimuli, with the learning of nonoverlapping associations as a control (Heckers et al., 2004). A somewhat different protocol was adopted in the other study and involved instruction on overlapping face-house paired associates as a background for examining subsequent transitive inference abilities, with direct learning of face-face pairs as a control (Preston et al., 2004). Despite these procedural differences, the main findings were in close agreement across investigations. Behavioral observations confirmed that, after learning a series of visual paired associates with overlapping elements, subjects accurately judged the relationship between items presented in novel combinations, on the basis of memory for their overlapping association with intervening stimuli (i.e., they made transitive inferences). Remarkably, the corresponding imaging data revealed that a region of the anterior hippocampus was the only area examined that exhibited significantly greater activation during transitive judgments relative to control conditions, such as recognition tests involving previously learned stimulus pairs. Although it might be supposed that this effect reflects hippocam-

Kastor Neurobiology of Aging Laboratories, Fishberg Research Center for Neurobiology, Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, New York
*Correspondence to: Peter R. Rapp, Kastor Neurobiology of Aging Laboratories, Mount Sinai School of Medicine, Box 1639, One Gustave Levy Place, New York, NY 10029-6574. E-mail: peter.rapp@mssm.edu
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pal activation associated with encoding the novel combination of familiar items, direct training on novel pairs failed to replicate the effect.

In addition to documenting that the hippocampus is normally engaged when we navigate memory flexibly to derive inferences or generalizations from past events, the findings also suggest that other components of the medial temporal lobe system make a qualitatively different contribution. In both studies, recognition of previously learned stimuli lead to activation outside the area of the hippocampus engaged by transitive inference judgments, in the parahippocampal cortex. Consistent with other findings (e.g., Davachi et al., 2003), these results suggest that whereas the parahippocampal region critically participates in the representation of experienced items, the relational organization of declarative memory may depend selectively on the hippocampus. Many questions remain, of course, and it will be important to determine what other operating characteristics might be central to the role of the hippocampus. Nonetheless, the findings reported by Heckers et al. (2004) and Preston et al. (2004) represent a significant advance toward defining the structure and organization of memory in the medial temporal lobe. The evidence encourages the view that this system mediates a common set of information processing functions across species, and accordingly, that research in animal models can profitably illuminate the fundamental mechanisms of declarative and episodic memory.

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