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PERSPECTIVES

NEUROSCIENCE:
How Does the Brain Organize Memories?

Howard Eichenbaum

Cognitive neuroscientists agree that there are multiple forms of memory, each mediated by distinct brain pathways (1, 2). There is not such ready agreement, however, as to the critical distinctions among types of memory and the contributions of specific anatomical structures to each. On page 376 of this issue, Vargha-Khadem et al. (3) address both of these issues by analyzing the memory deficits in three individuals who had sustained brain lesions very early in life. Their results show that the hippocampus, a structure located within the medial temporal lobe of the brain and long associated with memory function (4), is critical for everyday episodic memory (our record of personal events), but is not necessary for semantic memory (our lifetime accumulation of universal factual knowledge). Although the hippocampus has been argued to function in episodic memory before (5), these new case studies offer a particularly impressive example that can be attributed to selective focal hippocampal damage early in life.

Striking as the findings are, they are also consistent with the possibility that both types of learning are impaired in these cases. Directly comparing new episodic and semantic learning in the laboratory turns out to be quite difficult, because normal subjects can take advantage of their episodic memory to recall new semantic material. This problem in separating performance of the two types of memory has led some to eschew the episodic-semantic distinction, focusing instead on amnesics' characteristic failure in conscious recollection of both events and facts. Such a deficit in so-called declarative memory is contrasted with fully spared acquisition of biases, skills, and habits expressed unconsciously through changes in performance speed or choice (6). Using this account, the seemingly selective deficit in these amnesics' memory for unique episodes, as well as their forgetting of a story or drawing, can be attributed to
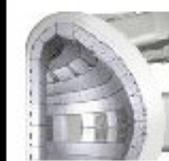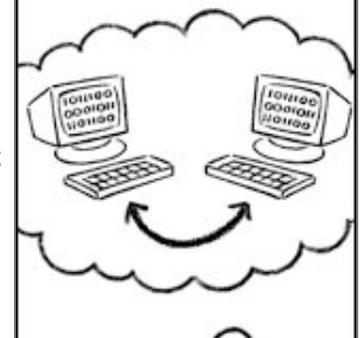
a partially compromised declarative capacity doing especially poorly on any type of complex material experienced only once.

Recognizing this interpretive stand-off, Vargha-Khadem *et al.* turned to nonconventional tests modeled after measures that in animals distinguish the memory functions of the hippocampus itself from that of the immediately surrounding parahippocampal cortical region (see the figure). Monkeys and rats with selective hippocampal damage do surprisingly well at stimulus recognition and stimulus association learning, but have severe deficits after parahippocampal damage ([7]). Likewise, the individuals with hippocampal lesions showed intact recognition memory in similar tests with words and faces, and even normal learning of verbal or face associations, as contrasted with the reports of more extensive impairment in these measures in a patient with identified damage in both the hippocampus and parahippocampal region ([4], [8]). Animals with selective hippocampal damage are impaired in memory for spatial location or spatial context ([9]), a deficit similar to that of the individuals described by Vargha-Khadem in associating an object with the place where it was seen, as well as a face with its voice. These parallels led Vargha-Khadem *et al.* to suggest an anatomically feasible model of complementary memory functions in which representations formed in the cerebral cortex are bound together into semantic associations by the parahippocampal region, and then further processed by the hippocampus to add the contextually rich episodic or spatial information (see the figure).
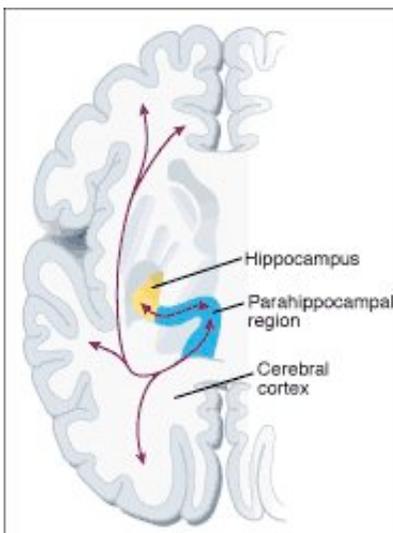
The human brain: wired for memory. Widespread regions of the cerebral cortex, the repositories of highly specific representations, are bidirectionally connected to the parahippocampal region. Interactions among these areas could underlie memories of some associations between cortical representations without hippocampal involvement. The parahippocampal region is then bidirectionally connected with the hippocampus, which can provide an additional influence on memory processing by the preceding areas.

More detailed neurobiological observations offer another perspective and a degree of reconciliation between the episodic and declarative accounts. One source of data

comes from neuropsychological studies showing that the hippocampal deficit observed in animals requires a deeper explanation than attribution to a (spatial) contextual factor (10). Thus, when animals with selective hippocampal damage acquire stimulus associations, they fail on novel queries in which the stimuli are only indirectly related through other stimulus elements (11). Drawing an even closer parallel with the human studies, animals with hippocampal damage seem to acquire a complex "semantic" structure involving an orderly hierarchy of stimuli. But the nature of their knowledge structure, or access to it, is abnormal in that these animals lack the flexibility of expression that supports inferences between stimulus elements that are only indirectly related within the hierarchy (12). A similar dissociation can be observed between their successful, albeit gradual, place learning contrasted with failure when challenged to navigate to the place by a novel route or when previous experiences can interfere with new place learning (13). Both rigidity of access and sensitivity to interference are hallmarks of human amnesics' difficulty in conscious recollection, suggesting a connection between hippocampal function in declarative memory and in flexibility of memory expression across species (5, 14).

Complementary evidence from studies on neural activity in the hippocampal area provides further clues about the distinct memory functions of the hippocampus and parahippocampal region. In a recent functional magnetic resonance imaging study, a part of the hippocampus was maximally activated when human subjects indirectly accessed the memory of a word cued by a picture of the corresponding object, whereas the parahippocampal region was maximally activated during simple differentiation and encoding of novel pictures for later recognition (15). Similarly, single-cell recordings in both rats and monkeys have shown that cortical areas, including those in the parahippocampal region, encode specific memory cues and can sustain and regenerate these item-specific representations (16). By contrast, the activity of hippocampal neurons reflects myriad combinations of items or abstract relations between stimuli, as observed in so-called place cells, whose activity reflects the position of a rat with respect to the configuration of spatial cues (17), and in cells whose activity reflects configurations of nonspatial cues and actions (18), including combinations of faces and gender or emotional expression in humans (19). In addition, a potentially telling property of hippocampal cells is their propensity to dramatically change representations, even across highly similar situations that vary only in the task contingencies or subtle variations in the stimuli (20). These findings have led to the suggestion that the hippocampus seeks to differentiate potentially ambiguous patterns and, at the same time, to capture the relevant contingencies in each of them.

These observations begin to fill in the mechanistic details of the model shown in the figure (21). Functionally specific cortical representations converge onto the parahippocampal region, which might support a binding of simultaneously experienced contiguities through feedback onto the cortex. When the items are in the same modality or are closely contiguous, this could lead to an overly rigid binding of the items, making them inaccessible when the elements are later separated (for example, we meet someone in a conference but can't recognize the person later on the street outside). The physiological data, as well as computational models (22), suggest that the hippocampus is suited to promote more flexible associations by recognizing relations among items and differentiating overlapping patterns (separating where one sees the person from the places and times of the events). This could contribute to the encoding of each unique episode, as well as relating the context-free information into semantic knowledge. The data from animals with amnesia, as well as computational modeling, indicate that the hippocampus may also

interleave patterns within the memory network so as to provide access to the whole knowledge structure from any point. Within this scheme, episodic and declarative memory are not alternative types of memory, but rather are two powerful benefits of the networking of cortical memories supported by the hippocampus.

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