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Episodic Memory and the Hippocampus: It's About Time

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Abstract

Several recent studies have sought to develop animal models of episodic memory, the capacity to recollect unique personal experiences. However, these studies have not yet provided unambiguous evidence that this capacity is based on recollection of the learning episodes. A recent study that examined memory for the ordering of events within unique experiences, and demonstrated a critical and selective role for the hippocampus, suggests a new and promising model for neurobiological analyses of episodic memory.

Keywords

episodic memory; recognition; sequence learning; olfactory memory; animal memory

Episodic memory refers to the capacity to mentally reexperience a previous occasion in one's life. Examples include your ability to recall things you saw on the way to work this morning and the events of a meeting with a colleague last week. The notion of episodic memory as a special capacity for the recollection of specific personal experiences has received increasing support since its original conception by Tulving in 1972. Furthermore, research on amnesia and functional brain imaging point to the hippocampus as a brain structure in the temporal lobe that is critical to episodic memory (Tulving, 2002). Investigators have recently explored episodic memory in animals in an effort to identify the role of the hippocampus, but

this work, although necessary for a full characterization of the basis of episodic memory, has been challenged by the view that animals do not in fact possess a capacity for episodic memory (Griffiths, Dickinson, & Clayton, 1999, Morris, 2001; Tulving, 2002). Here we consider the difficulties in validating two characteristics of episodic memory that are featured prominently in current experimental studies on humans and animals. Then we focus on a third characteristic that may be more fruitfully employed.

AWARENESS OF THE PAST

Tulving's (2002) current formulation of episodic memory emphasizes the conscious awareness of prior experience, the capacity to mentally travel back in time and relive experiences. This capacity has been operationalized in the distinction between *remembering* a specific personal experience as opposed to *knowing* a concept or a fact. In experiments in which this distinction is employed, subjects are asked whether they explicitly remember the experience when something was learned, or rather just know that something happened without recalling the episode in which the information was obtained. For example, in studies of verbal list learning, subjects are asked whether they remember hearing particular words on a list in the setting of the ongoing experiment, or just know that those words were on the list.

The remember-know distinction has been quite useful in investigating how a variety of psychological variables and neurological conditions affect memory (Baddeley, Conway, & Aggleton, 2002). However, in these studies there is no independent validation of the subjective experience of remembering—one simply has to take the subject's word for it that the experience was actually remembered. Can one believe subjects when they say, "remember"? Experiments on false memory weigh in on this issue, and indicate that human subjects often claim to remember events that did not actually occur. For example, in a study of list memory, a subject might sense a rare word as highly familiar, and be convinced that it must have been experienced in that day's training session.

Even more problematic is that it is impossible to directly assess awareness of a prior experience in animals, making this characteristic of episodic memory useless in comparative and neurobiological studies with animals. Are there other properties of episodic memory that could be applied in both humans and animals?

"WHAT, WHEN, AND WHERE"

Investigators who have sought to develop animal models of episodic memory have avoided the issue of awareness, and instead have relied on another feature of episodic memory emphasized in Tulving's (1972) original formulation. This feature focuses on episodic memory as oriented to the time and place of the experience, and distinguishes episodic memory from semantic memory, which involves factual information organized by a conceptual structure that is timeless and not bound to the place or situation in which learning occurred. This distinction has been operationalized in experiments that determine the ability of animals to remember when and where a specific event occurred.

For example, Olton and his colleagues (Olton, Becker, & Handlemann, 1979) distinguished a form of memory for the occurrence of unique experiences. He argued strongly that temporal organization is paramount for this kind of memory and that its units are events or episodes (Olton, 1984). In an elegant series of studies, Olton employed a maze composed of up to 17 arms, each extending radially from a central platform. At the outset of each test session, every arm was baited, then the rat was allowed to forage for the rewards. Rats could readily remember visits to many particular arms of the maze, as shown by visiting each arm only once in the session (reviewed in Olton et al., 1979).

Memory for unique events has also been examined using recognition memory tests, such as the widely used delayed nonmatch-to-sample task (Gaffan, 1974; Mishkin & Delacour, 1976). In this task, initially a novel object is presented as a sample stimulus. Then, following a delay, this sample is presented along with a novel stimulus, and the subject must select the novel stimulus (i.e., the nonmatch to the sample). This protocol has been viewed as a test of memory for the sample episode. Indeed, in both the radial-maze task and the delayed nonmatch-to-sample task, episodic memory could support performance. However, in both cases, there is an alternative strategy—choices could instead be guided by the greater familiarity of the more recently experienced stimulus or stimuli (Griffiths et al., 1999). Thus, animals might simply avoid maze arms (in the radial maze) or a sample object (in delayed nonmatch to sample) that evoke a strong sense of familiarity, without explicit recall of the earlier experience with those items.

Recently, Clayton and Dickinson (1998) addressed this concern in a clever experiment that explored the natural caching behavior of scrub jays. Initially the birds

cached both worms and peanuts in an array of locations. Ordinarily scrub jays prefer worms over peanuts, and if recovery was allowed within a few hours after caching, the jays recovered worms first. However, if several days elapsed between caching and recovery, the jays recovered the peanuts first, because the worms had degraded and were no longer palatable. Thus, scrub jays were capable of selecting either type of food depending on the time since caching, leading Clayton and Dickinson to conclude the jays remembered what had been cached, as well as where and when each item was cached. Because the stimuli were equally familiar at the time of test, the birds could not choose on the basis of differential familiarity, unlike in maze and delayed nonmatching tests.

However, in this situation, the jays might have used an alternative strategy that does not require memory for when the caching occurred. They could have taken advantage of the fact that memory traces fade as time passes, and food selection could have been guided by signals about the trace strengths of the caching memories. Thus, the jays may have learned to prefer worms when their memory for the caching memory was very strong, but not when the memory was somewhat weaker, although still sufficiently strong to identify items and places.

A second challenge in the use of "what, when, and where" tasks to study episodic memory regards a potential confound with spatial cognition. There is a large body of studies showing severe deficits in spatial learning and memory following hippocampal damage (O'Keefe & Nadel, 1978). A prevalent interpretation of these findings is that the hippocampus is required for spatial cognition and memory. Accordingly, if animals with hippocampal damage show a deficit in performance on a "what, when, and where" task, this deficit can readily be interpreted as secondary to an impairment in spatial cognition. That is, if an animal cannot perceive or remember space, one can hardly expect the animal to locate temporally tagged events. Unfortunately, this potential confound calls into question the usefulness of investigating episodic memory with any task that requires remembering a location (see Morris, 2001).

SEQUENCES OF EVENTS

So far, we have focused on two features of episodic memory that have been emphasized explicitly by Tulving, and are prominent in experimental studies on humans and animals. A third distinction is that episodic memory is organized as sequences of events that unfold over time and space. Thus, a rich episodic memory contains not only a particular item or items that one is attempting to recall, but also the experience of preceding and following events. Tulving (1972) featured temporal coding as the primary organizational structure of episodic memory, distinguishing it from the conceptual and timeless organization of semantic memory. In addition, recent computational models of episodic memory have focused on neural circuits in the hippocampus that could encode the flow of events and retrieve event sequences upon demand (Lisman, 1999; Wallenstein, Eichenbaum, & Hasselmo, 1998). Note that semantic memory and the simpler capacities to use familiarity, recency, and memory-trace strength do not rely on memory for sequences of events. Thus, a consideration of memory for the sequential order of events in unique experiences, a capacity that can be tested in animals, may provide a fruitful avenue for neurobiological explorations of episodic memory.

MEMORY FOR A UNIQUE SEQUENCE OF EVENTS

We developed a behavioral protocol that assesses memory for episodes composed of unique sequences of olfactory stimuli (Fortin, Agster, & Eichenbaum, 2002; see also Kesner, Gilbert, & Barua, 2002). Furthermore, we directly compared memory for the sequential order of odor events with memory for the prior occurrence of the odors independent of memory for their ordering.

On each trial, a rat was presented with a series of five odors, selected randomly from a large pool of common household scents. Memory for each series was subsequently probed using a choice test in which the animal was presented with two odors and reinforced for selecting the one that had appeared earlier in the series. For example, the rat might have been initially presented with odors A then B then C then D then E. Following the delay, two nonadjacent odors (e.g., B and D) were presented, and the animal would be rewarded for selecting the odor that had appeared earlier (in this case, B). The choice tests assessed memory for different separations (lags) in the initial sequences. Because any pair of nonadjacent odors might be presented on a test trial, the animal had to remember the entire sequence in order to perform well throughout the testing session.

After the rats had learned how to perform this task, they were operated on, receiving either a selective lesion of the hippocampus or the same surgical procedure but without the lesion. In postoperative testing, the control rats, who had undergone the sham surgery, performed well on test trials at all lags, whereas the animals with hippocampal lesions performed at near-chance levels. Notably, performance was dependent on the lag,

indicating that order judgments were easier the more widely separated the items. Nevertheless, rats with hippocampal damage were impaired at all lags. Indeed, their performance was not significantly better than that expected by chance at any lag except the greatest one.

After completion of the sequential-order tests, the same rats were tested on their ability to recognize the odors presented in the series. On each trial, a series of five odors was presented in a format identical to that used in the sequential-order task. Then recognition was tested by presenting the animal with one of the odors from the series and another odor that was not in the series. Reinforcement was given for selecting the odor not presented in the series. The test trials assessed recognition of odors presented at all five possible positions in the initial series.

Both control rats and rats with selective hippocampal damage learned the task rapidly, and there was no overall difference between the groups in their rate of learning. Subsequent analyses of performance on the test trials showed that rats with hippocampal lesions performed as well as normal rats in recognizing odors from all series positions. Furthermore, in both groups, recognition scores were consistently superior for odors that appeared later in the series, suggesting some forgetting of items that had to be remembered for a longer period and through more intervening items. The variation in performance across different positions in recognition test trials and across lags in sequential-order test trials allowed us to match performance on subsets of the two kinds of tests on which control animals performed equally well. On these matched test trials, animals with hippocampal damage were impaired selectively in remembering the order of events and not in recognition.

A potential confound in any study that employs time as a critical dimension in episodic memory is that memories obtained at different times are likely to differ in the strength of their memory traces, because these traces degrade over time. To what extent could normal animals have used differences in the relative strengths of memory traces for the odors to judge their sequential order? The observation of a temporal gradient in recognition performance by normal animals suggests that memories were in fact stronger for the more recently presented items in each sequence. These differences in trace strength may have provided sufficient signals for the animals to judge the order of the odors' presentation. However, the temporal gradient in their recognition performance indicated that rats with hippocampal damage had normal access to the differences in trace strengths for the odors, and yet did not perform above chance on any sequential-order trials except those involving items with the furthest separation (and even then their performance was deficient relative to the control rats). These considerations strongly suggest that normal rats also did not utilize the relative strengths of memories for the sequential-order task, and instead based their judgments directly on remembering the odor sequences.

CONCLUSIONS

The experiment just described avoided some of the problems in previous efforts to examine other features of episodic memory, such as awareness of past events and memory for what happened when and where, and captured another defining feature of episodic memory, specifically, that episodic memories unfold over time. Furthermore, the findings reveal a critical role for the hippocampus in memory for the order of items in a unique episode, but not for simple recognition of the individual items that compose the episode. These observations confirm models of hippocampal circuits that record and recall sequences of events, and provide an experimental protocol in which the neurobiological mechanisms for episodic memory may be studied. Further behavioral analyses in humans and animals must demonstrate the general applicability of defining episodic memory as the ability to remember the orderliness of a unique sequence of events. Furthermore, to provide a comprehensive understanding of episodic memory, it will eventually be necessary to extend this model to account for the full experience of conscious recollection and for the contribution of episodic memory to the accumulation of knowledge that becomes unbound to the episode in which it was acquired (semantic memory).

Recommended Reading

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Ovarian Steroids and Cognitive Function

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Abstract

The ovarian steroids, estrogen and progesterone, not only govern reproductive events in mammalian females but also influence an array of other processes. Of particular clinical interest is the potential of ovarian steroids to facilitate storage of new memories and to protect neurons from various threats. Research during the past decade confirms that estrogen and progesterone influence the biochemical, electrical, and structural properties of neurons in brain regions that subserve learning and memory. These mechanisms form the biological foundations for the complex effects of ovarian steroids on cognitive functions in various species, including humans. Despite significant progress in our understanding of the roles of hormonal factors in cognitive function and neuronal survival, the value of hormone replacement as a treatment and deterrent for cognitive impairments associated with age, disease, and injury remains uncertain as we enter the new century.

Keywords

Alzheimer's disease; estrogen; memory; menopause; neuroprotection

As the principal steroid hormones secreted by the ovaries, estrogen and progesterone control many processes necessary for successful reproduction in mammalian females. These actions include regulating pituitary hormone secretion, stimulating the uterine endometrium, maintaining gestation, promoting mammary function, and, in some species, activating mating and maternal behaviors. Estrogen and progesterone also affect physiology and behavior not typically considered to be reproductive in nature. These actions range from altering body temperature to inducing motor activity to affecting cognitive functions. Because many of these effects may be related to reproduction only indirectly and often are weaker in magnitude than the direct effects on reproduction, their significance to the survival of females continues to be debated by scientists.

During the previous decade, investigations into the putative effects of estrogen on learning and memory were motivated by several interrelated findings. First, various laboratories demonstrated that estrogen, sometimes in combination with progesterone, can alter neurochemical profiles in brain regions that subserve learning and memory, including the basal forebrain, the hippocampus, and the cerebral cortex (Luine, 1985). Second, the structure of hippocampal neurons and their connections were found to fluctuate with circulating levels of estrogen and progesterone in female rats (Woolley, Gould, Frankfurt, & McEwen, 1990). Third, epidemiological studies indicated that