Evaluating evidence from animal models of episodic memory

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Abstract

A fundamental question in comparative cognition concerns the ability to remember back in time to an earlier event or episode. This ability is referred to as episodic memory. Whether nonhumans can be used to model human episodic memory has engendered much interest and debate for over two decades. The central hypothesis of an animal model of episodic memory is that, at the moment of the memory assessment, the animal remembers back in time to a specific earlier event or episode. I describe (1) an approach for evaluating evidence of episodic memory in animal models, (2) what aspects of episodic memory are being modeled in animals, (3) what standards ought to be applied to a candidate model of episodic memory in nonhumans, (4) the first evidence of episodic memory in nonhumans, and (5) a brief overview of the diversity of approaches that are now available. The remainder of the article focuses on the development of a robust model of episodic memory in rats. Converging lines of evidence suggest that rats provide a good model for exploring episodic memory. This evidence includes studies that focus on (1) what-where-when memory, (2) source memory, (3) binding of episodic memories, (4) memory of multiple Items in context using episodic memory, (5) replay of episodic memories, (6), recollection, and (7) answering an unexpected question after incidental encoding. In each of these domains, I describe evidence for episodic memory in the absence of non-episodic judgments of familiarity. I end with some consideration of future directions.

Keywords: episodic memory, familiarity, animal models, what-where-when memory, source memory, binding, replay, recollection, hippocampus

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Overview

Whether nonhumans can be used to model human episodic memory has engendered much interest and debate (Crystal & Suddendorf, 2019; Gallistel, 1990). One challenge for evaluating evidence of episodic memory in nonhumans comes from the diversity of perspectives. In this article, I lay out an approach for evaluating evidence of episodic memory in animal models. I begin by noting what aspects of episodic memory are being modeled in animals. I then describe my perspective on what standards ought to be applied to a candidate model of episodic memory in nonhumans. I briefly described the first evidence of episodic memory in nonhumans and provide a brief overview of the diversity of approaches that are now available. The remainder of the article focuses on the development of a robust model in rats. Converging lines of evidence suggest that rats provide a good model for exploring episodic memory (Crystal, 2018, in press-a, in press-b). This evidence includes studies that focus on what-when-when memory, source memory, binding of episodic memories, memory of multiple items in context using episodic memory, replay of episodic memories, recollection, and answering an unexpected question after incidental encoding. I conclude with some consideration of future directions.

What aspects of episodic memory are being modeled in animals?

Tulving (Tulving, 1972, 1983) introduced a distinction between semantic and episodic memory. Semantic memory stores factual knowledge about the world. By contrast, episodic memory stores memories of specific personal events. A major challenge for validating an animal model of episodic memory is ruling out non-episodic hypotheses (Roberts et al., 2008).

Critically, episodic memory involves memory of a unique episode and is distinct from judgments of familiarity. Episodic memory involves remembering an event and the contextual details of the episode, whereas familiarity is the rather vague judgment that an item is known without remembering the contextual details (Henson et al., 1999; Hofer et al., 2007; Schmitter-Edgecombe & Anderson, 2007).

Tulving (Tulving, 1972, 1983) initially wrote that episodic memory consists of the spatial and temporal characteristics of an event. Subsequently, Tulving emphasized the conscious experience of episodic memory (Tulving, 1985; Tulving, 2001). Tulving's original definition of episodic memory is more tractable for investigations in animals because it focuses on the content of episodic memory, rather than focusing on the subjective experiences that may accompany episodic memory in people.

I use the terminology *animal model of episodic memory* to reflect that we do not expect all aspects of human episodic memory to be included in any one model; indeed, this review focuses on seven approaches to model episodic memory in rats because any single approach would be less compelling. I prefer this terminology over the more widely used term of "episodic-like memory" because our focus is on developing a model of specific aspects of human cognition. The focus on content of episodic memory has led to efforts to document that animals have memory of what happened, where you were, and when in time the event occurred. This has been referred to as what-where-when memory. As noted below, a number of approaches have been developed to document what-where-when memory in animals, only some of which provide strong evidence of episodic memory. However, there are other elements of episodic memory. Although many researchers have focused on what-where-when memory to document episodic memory in nonhumans, I argue that any approach that meets the standards of evidence described below provides strong evidence of episodic memory.

Standards of evidence

To convincingly claim that an animal relies on an episodic memory, it is necessary to show that relying on other aspects of memory are not sufficient to explain performance in the memory assessment. Thus, the case for episodic memory requires a demonstration that the animal is not using non-episodic memory. In a more formal formulation, we seek to compare the proposal that the animal is using a cluster of memory processes (e.g., working memory, semantic memory, associative memory, etc.) plus one other, namely episodic memory. This formulation needs to be compared to the same cluster of memory processes, with the notable absence of episodic memory. If the cluster that includes episodic memory —but not the smaller cluster— can explain the performance in a memory assessment, then the case for episodic memory is compelling. Because evidence is based on exclusion of alternative explanations, it is unlikely that any single demonstration is adequate. Instead, a stronger inference comes from converging lines of evidence using multiple approaches (Crystal, 2018). Any one approach likely has a set of strengths and weaknesses. If a diverse set of approaches each suggest episodic memory, then it is unlikely all of them are wrong in exactly the right way to falsely point to episodic memory, especially when rather different techniques are used across approaches.

I have argued that the *central hypothesis* of an animal model of episodic memory is that, at the moment of the memory assessment, the animal remembers back in time to a specific earlier event or episode (Crystal, 2013, 2016a, 2018, in press-a, in press-b). Non-episodic threats to a putative case of episodic memory are *pervasive*. The presentation of an event gives rise to a memory trace, and the ability to retrieve the trace decreases as a function of time; I refer to this class of explanation as *familiarity*. Because memory accuracy declines over time (Ricker et al., 2020), the age of memories provides a cue that may be used by an animal to solve a memory problem in the absence of episodic memory (Roberts et al., 2008). Notably, a number of claims of episodic memory are undermined by familiarity-based solutions to the memory problem.

I view the familiarity hypothesis as a general class of non-episodic memory. The selection of familiarity as a general class of non-episodic memory is not meant to take a theoretical stand about the varieties of non-episodic memory proposals. Indeed, I do not intend to make a commitment to the specific mechanisms that may support familiarity-based judgements. Indeed, to note that familiarity declines as a function of time is a general class of explanations that can encompass widely different theoretical views about memory retrieval. For example, theories of memory frequently assert that the probability of memory retrieval depends on the match between the context at encoding and retrieval (Tulving & Thomson, 1973). Notably, the retrieval context changes in small quantities as a function of time. According to this view, the probability of memory retrieval changes as a function of time, although interference from moment-to-moment changes in context, rather than time, is viewed as a causal variable (Howard & Kahana, 2002; Raaijmakers & Shiffrin, 1981; Sederberg et al., 2008). More broadly, memory failure occurs for a variety of reasons (Schacter, 2002), such as retrieval failure. The focus here on familiarity is not meant to preclude the importance of non-familiarity based contributions to remembering and forgetting.

In general, there are four strategies to deal with the problem of familiarity. First, it is important to identify familiarity-based explanations of putative episodic memory, thereby noting which cases provide only a weak claim for episodic memory; this provides a cautionary sign, but it does not solve the problem, unlike the three strategies described next. Second, if episodic memory and familiarity based explanations are confounded, it is possible to unconfound them to ask whether the animal had been using a familiarity or episodic-memory based solution to the memory problem. Third, it is possible to equate familiarity across conditions to document that successfully solving a memory problem is based on episodic memory in the absence of useful information from a familiarity cue; because familiarity is constant in this situation, differential familiarity cues are not available to provide an alternative solution to the memory problem. Fourth, it is possible to identify conditions in which familiarity and episodic-memory based solutions are dissociated (meaning that they make different predictions about behavior in at least some circumstances). Using these strategies (identify, unconfound, equate, dissociate) provides a guide for evaluating evidence for claims of episodic memory in nonhumans. Throughout this article, I will note which of the above approaches apply to putative evidence of episodic memory. Strong evidence for episodic memory comes from experiments in which familiarity is ruled out.

Initial evidence

Clayton and Dickinson (1998) provided the first evidence of what-where-when memory in non-humans. Food-storing scrub jays cached peanuts followed by worms on some trials. On other trials, they cached worms followed by peanuts. The birds retrieved the caches after a delay (i.e., a short or long retention interval). For some birds, the worms were decayed after the long retention interval, and for other birds they were replenished with fresh worms; peanuts never decayed, and, after the short retention interval, worms were always fresh. The birds learned to prefer the worm cache sites rather than the peanut sites when the worms were fresh, but reversed this preference when the worms were decayed. These data suggest that the jays are sensitive to what (food type), where (location in the tray), and when (time between caching and recovery). In other work, Clayton and colleagues showed that scrub jays are sensitive to decreases in the expected value of the to-be-recovered food item (e.g., degrading or satiating that food type) and to increases in the expected value (e.g., ripening it) (Clayton & Dickinson, 1998, 1999a, 1999b, 1999c; Clayton et al., 2001, 2003; de Kort et al., 2005).

The discrimination of what-where-when in scrub jays could be based on episodic memory of the caching event. An alternative explanation is that the birds are relying on judgments of the relative familiarity of caching peanuts and worms. Because familiarity declines as a function of time, memories will have a higher level of familiarity after a short delay than after a long delay. These observations focus on the identify strategy.

Diversity of evidence

Putative cases of episodic memory in nonhumans have been documented in many species. A number of early demonstrations of episodic memory did not adequately control familiarity. I will criticize my own early work to illustrate this problem. I will also describe other studies that do not adequately control familiarity.

We adapted Clayton's approach to ask if rats remember what, where, and when an earlier encoding event occurred. In our initial experiments (Babb & Crystal, 2005, 2006a, 2006b), rats foraged on an 8-arm radial maze as follows. In the study phase, the rats had access to a randomly selected set of 4 arms. One randomly selected arm in the study phase provided chocolate pellets, whereas all other arms in the maze provided standard rat-chow flavored pellets. Next, the rats waited during a retention interval that was either short or long. In the test phase (with all arms accessible), arms that were previously inaccessible in the study phase provided food. The replenishment of the distinctive location depended on the retention interval. After a long retention interval, the arm that previously provide chocolate replenished in the test phase with a second helping of chocolate. By contrast, after the short retention interval, the location that previously provided chocolate did not replenish. Chow locations never replenished. The rats revisited the chocolate location at a higher rate after the long retention interval, relative to the rate of revisits after the short retention interval. This study suggests that the rats learned that chocolate-locations replenish after the long, but not after the short, delay. These data suggest that the rats remembered what food they encountered on the maze (chow or chocolate), where they encountered these foods (arms of the maze), and when they had encountered the chocolate (short or long retention intervals). In a number of studies, we showed that the rats remember the specific flavor at each location, while avoiding revisits to chow locations. With multiple flavors at trial-unique locations, it is possible to devalue or degrade one flavor while leaving the other flavors unchanged. In such circumstances, the rats flexibly adjusted their subsequent visits to avoid locations that replenish devalued flavors while continuing to exploit other locations that provided valuable flavors (Babb & Crystal, 2006b). This finding suggests that rats have a detailed representation of the event and they flexibly adjust their behavior based on new information. Because we used short and long delays in the studies described above, it is not possible to preclude the possibility that the rats were relying on judgments of relative familiarity because an event, such as eating chocolate, is likely more familiar after a short delay than after a long delay. This observation focuses on the identify strategy.

Naqshbandi and colleagues (2007) replicated our study using a modification of our design. All test phases occurred at a constant time of day to control time of day at the test phase. Study phases occurred at different times of day (i.e., a short or long time before the test phase). The rats learned to discriminate what, where, and when. Naqshbandi et al. argued that the rats could not solve this discrimination by using time of day at test as a cue to adopt different search strategies (see also Babb & Crystal, 2006a). By contrast, the rats could encode time of day at the study phase and respond in the test phase based on the remembered time of the study. Alternatively, the rats could have used time of day at the study phase as a cue to encode (or fail to encode) the distinctively baited location; this encoding failure hypothesis can explain the observed revisit rates in the subsequent test phase (i.e., lower revisit rate after failing to encode). The use of short and long delays means that familiarity judgments cannot be precluded (identify strategy).

Roberts and colleagues (2008) were the first to *unconfound* episodic memory and familiarity in nonhumans. They pointed out that most studies of what-where-when confound time of day at study with how long ago the study phase occurred; how-long-ago is conceptually the same as the familiarity hypothesis described above. They designed an elegant series of experiments to unconfound these variables. Some trials started the study phase at a constant time of day (with test phases starting at varying times of day); other trials ended with the test phase at a constant time of day (with study phases starting at varying times of day). For some animals (referred to as the *when* group), the distinctive flavor replenished on the subset of trials with a consistent study phase time (thereby having inconsistent replenishment associated with each retention interval); for other animals (referred to as the *how-long-ago* group), the distinctive flavor replenished on the subset of trials with a consistent retention interval (thereby having inconsistent replenishment associated with the study phase time). The consistent mapping of how-long-ago (i.e., retention interval) onto replenishment would allow the animals to rely on judgements of the relative familiarity of the earlier event. The *how-long-ago* group learned the discrimination, but the *when* group did not. Roberts et al. concluded that rats are not sensitive to the time of day when they encounter a distinctive food item in the study phase, and rats are able to use the elapsed time or how long ago they found food to predict the replenishment of the distinctive flavor. Notably, they argue that the rats may remember only how much time has passed since an event occurred without remembering when food was encountered (Roberts et al., 2008). This work used the unconfound strategy.

In general, the failure to learn should be interpreted with caution. One strength of the approach used by Roberts et al. (2008) is that the failure to learn in the when group is contrasted with successful learning in the how-long-ago group, using similar methods. Nonetheless, an alternative explanation of these data is the hypothesis that when *both* when and how-long-ago information are available, rats rely on how-long-ago (or learn about it more rapidly). This hypothesis does not preclude the possibility that time of study may be encoded, which may require different experimental techniques to reveal (see *What-where-when: Evidence of episodic memory* section below).

A widely used approach to evaluating episodic memory in animals (Belblidia et al., 2015; de Souza Silva et al., 2015; Dere et al., 2005; Eacott & Norman, 2004; Hamilton et al., 2016; Kart-Teke et al., 2006) capitalizes on animals' natural tendency to explore novel situations. Novelty seeking is based on habituation. Habituation is typically defined as learning about a stimulus (Thompson & Spencer, 1966). A classic example involves the repeated presentation of a loud noise. Animals initially display a large startle response to the noise. The magnitude of the startle response declines when the same noise is presented repeatedly.

The preference for novel objects has been used to examine what-where-when memory (de Souza Silva et al., 2015; Dere et al., 2005; Eacott & Norman, 2004; Hamilton et al., 2016; Kart-Teke et al., 2006). Kart-Teke and colleagues presented objects in an open field, using a sequence of two presentations of objects followed by a test. Initially, four identical objects were placed in four of nine available locations; each identical object is referred to as an A object). Next, a new set of four identical objects was presented (referred to as four B objects); two of the B objects were presented in locations previously occupied by two of the A objects, whereas the other two B objects were in previously empty locations. In the test, two copies of an A object and two copies of a B object were presented, each in a familiar location (i.e., a location that was occupied in at least one previous sample phase). One of the A objects was presented in a location previously occupied by an A object (old familiar stationary object A), and one of the B objects was presented in a location previously occupied by a B object (recent familiar stationary object B). The other identical copies of the objects were placed in locations not previously occupied by that type of object in the previous sample (i.e., old familiar displaced object A was presented in a location previously occupied by a B object; the recent familiar displaced object B appeared in a location previously occupied by an A object). Note that the test permits an assessment of preference for object type (A vs. B), location (stationary vs. displaced), and temporal order (old vs. recent), which corresponds to what, where, and when. The rats spent more time exploring the stationary old familiar object relative to the stationary recent familiar object, suggesting that the rats remembered the objects and their order of presentation. The rats also spent more time exploring the displaced recent familiar object relative to the stationary recent familiar object. By contrast, the rats spent less time exploring the displaced old familiar object compared to the stationary old familiar object. These data suggest that rats are sensitive to the location of the objects (displaced vs. stationary). The rats preferred the displaced recent familiar object compared to stationary recent familiar object; they preferred the stationary old familiar relative to the displaced old familiar. The authors argue that the animals integrated what, where, and when.

Why does the animal explore the novel object-location combination? According to the episodic-memory proposal, the animal retrieves an episodic memory of the initial presentation of item and location; the item-location combinations are compared to the current options, namely two object-location combinations (only the location feature varies in the memory assessment), and spends more time in the location that does not match the retrieved object-location combination. Notice that familiarity is inherently embedded in the proposed episodic-memory explanation outlined above: one object-location is more familiar than the other, and the novelty preference is expressed by spending more time in the less familiar option. Because short and long delays were used in the study described above, it is not possible to preclude the possibility that the rats were relying on judgments of relative familiarity because an event (i.e., presentation of an object at a location is likely more familiar after a short delay than after a long delay). These observations focus on the identify strategy.

Development of a robust model in rats

We developed a model of episodic memory in rats that uses multiple, diverse techniques, each of which rules out non-episodic explanations of memory performance (Crystal, 2018, in press-a, in press-b). A strength of this literature includes the replication of episodic memory using varied techniques. Thus, we have sought to develop a number of approaches to document episodic memory in rats.

What-when-when: Evidence of episodic memory

Roberts et al (2008) showed that if rats are given a choice between using a how-long-ago cue and a when cue, the rats use the how-long-ago cue. Therefore, we sought to ask if rats can use a when cue in a circumstance in which using how-long-ago cues are uninformative in a what-where-when preparation (Zhou & Crystal, 2009). To this end, rats received a session in a radial maze in the morning or, on other days, in the afternoon (Figure 1A). Chocolate was always available at a randomly selected location during a study phase, and it replenished in the subsequent test phase depending on the time of day at which the event occurred. For some animals, chocolate replenished in the morning, whereas for other animals chocolate replenished in the afternoon. All other locations provided chow, and chow never replenished. Critically, the retention interval between study and test was always a few minutes. Therefore, the delay between encoding and memory assessment (i.e., the relative familiarity of the study event) did not provide any information to decode replenishment or nonreplenishment. By contrast, the time of day at which the session occurred provided a reliable cue for replenishment and nonreplenishment. If rats use episodic memory to remember what, where, and when, then they should revisit the chocolate location at a higher rate in replenishment than nonreplenishment conditions. By contrast, if rats rely on the relative familiarity of any aspect of the study phase, then rats should revisit the chocolate locations at equivalent rates in replenishment and nonreplenishment conditions. Our approach was to make familiarity uninformative for solving the memory problem. In our initial experiment, the rats revisited the chocolate location at a higher rate in the replenishment condition than in the nonreplenishment condition (Figure 2A) while avoiding revisits to chow locations. These data suggest that rats remember what, where, and when (i.e., the time of day at which the study event occurred) without using judgments of relative familiarity, consistent with the hypothesis that rats use episodic memory to remember what, where, and when. This study used the equate strategy.

Episodic memory is memory of an *earlier encoded event*. Therefore, to establish that the rats were using episodic memory, it is necessary to show that the rats remembered the time at which the *study event* occurred (*study time* hypothesis) rather than using information about the time of day at which the *memory assessment* occurred (*test time* hypothesis). Because the study and test phases occurred at a constant time of day (e.g., 7 am and 1 pm in morning and afternoon sessions, respectively), according to the test time hypothesis, rats may have been merely reactive to the time of the test phase (e.g., search for chocolate replenishment in the morning but not the afternoon). By contrast, according to the study time hypothesis, the rats are remembering back to the study phase, and they retrieve information about the time of day at which the study event occurred (in addition to information about location and flavor). Study time and test time were difficult to distinguish in the earlier experiment because the rats had been trained with a very short retention interval. Therefore, we dissociated study time and test time hypotheses by transferring the rats to a much longer retention interval (7 hours; Figure 1C), using the same rats (Zhou & Crystal, 2009). Now an early session occurred at the typical study-phase time (7 am) but the test phase occurred at a novel time of day (2 pm); similarly, a late session occurred at the typical study-phase time (1 pm) but the test phase occurred at a novel time of day (8 pm). Initially, the rats received a single early session and a single late session (counterbalance for order of presentation). According to the study time hypothesis, the rats should revisit the chocolate location in the replenishment condition at a higher rate than in the nonreplenishment condition. According to the test time hypothesis, performance should be disrupted (equal replenishment and nonreplenishment rates) in the transfer test because test phases occurred at times of day about which they have no information regarding replenishment (i.e., they had literally never been in the maze at those times of day). The rats revisited the chocolate location at a higher rate in replenishment than nonreplenishment conditions (Figure 2C-D), consistent with the study time hypothesis and episodic memory of the study episode (Zhou & Crystal, 2009). This study used the equate and dissociate strategies.

By using a 7-hour retention interval, the study-test sequences form early and late sessions overlapped in time (7 am to 2 pm in early sessions, and 1 pm to 8 pm in late sessions; Figure 1C); note that a *late* study phase (1 pm) occurred at an *earlier* time than an *early* test phase (2 pm). Therefore, in an additional experiment after extended training with early and late sessions, we provided a second dissociation of study time and test time hypotheses (Zhou & Crystal, 2009). In this experiment, we began with a study phase at the time of the *late* session

(1 pm) and a test phase that occurred at the time of a typical *early* session (2 pm; Figure 1D). Revisit rates to the chocolate location in the test phase could be based on the study time or the test time. The study time hypothesis predicts that they will revisit the chocolate location at the rate typical for a study phase (treating the session like a *late* session because the study phase occurred at the late study time). The test time hypothesis predicts that the rats will revisit the chocolate location at the rate typical for the test time (treating the session like an *early* session). We found that rats relied on the study time (Figure 2E), consistent with episodic memory of the study episode. This study used the equate and dissociate strategies.

In other experiments, we ruled out a number of alternative hypotheses. Because light onset is necessarily more recent (hence, more familiar) in the morning than in the afternoon, we sought to rule out this last remaining familiarity-based solution to the memory problem (Figure 1B). Thus, we showed that the rats used a circadian representation of time (Figure 2B), rather than timing an interval from light onset in the colony to the occurrence of the session (Zhou & Crystal, 2009). We also showed that rats did not fail to encode the chocolate location on nonreplenishment sessions (Zhou & Crystal, 2011). Overall, these experiments provide compelling evidence that rats use episodic memory to remember what, where, and when the study event occurred.

Source memory

Source memory is an aspect of episodic memory that encodes the source (i.e., origin) of information acquired in a previous event (Johnson et al., 1993; Mitchell & Johnson, 2009). Source memory refers to memories about the conditions under which information was acquired (Johnson et al., 1993; Mitchell & Johnson, 2009). For example, source memory is at work when I remember that I learned about some news on the radio vs. in the newspaper. Episodic memory typically involves source memory because those memories focus on the origin of representations (Johnson, 2005; McDuff et al., 2009). Notably, source memory allows us to differentiate one episodic memory from another because source memory includes features that were present when the memory was formed (Crystal & Smith, 2014; Johnson et al., 1993; Mitchell & Johnson, 2009).

To develop an animal model of source memory, we asked if rats could remember the origin (i.e., source) of how they came to acquire information about flavors and locations in a radial maze (Crystal & Alford, 2014; Crystal et al., 2013; Crystal & Smith, 2014; Smith et al., 2016). In our approach (Figure 3A), rats foraged for distinctive flavors of food that replenished or failed to replenish at its recently encountered location according to a source-information rule. Our strategy was to literally manipulate the source (i.e., origin) of information about eating chocolate pellets. The source memory of eating chocolate pellets was manipulated by the experimenter placing the rat at the food trough of an arm that dispensed chocolate (we refer to such an occasion as an *experimenter-generated* event). The rat encountered chocolate by walking on its own to a food trough on a different arm (we refer to such an occasion as a *self-generated* event). The self-generated and experimenter-generated arms were randomly selected on each trial and rats discovered chow-flavored pellets at two other randomly selected arms. Next, the rats received a brief retention interval. In the test phase, the rats discovered chow-flavored pellets at the previously inaccessible arms. The arm where the rat had discovered chocolate on its own now provided additional chocolate at the test (replenishment), whereas the arm where the rat was placed by the experimenter did not provide additional chocolate (nonreplenishment) in some experiments; in other experiments, the replenishment contingency was reversed. Chow-baited locations never replenished. Because only a single retention interval was used on each trial, the familiarity of encoded information (e.g., walking down runways, being place by an experimenter, chocolate, chow, etc.) was equated across replenishment and nonreplenishment locations. Thus, to identify the replenishment location, the rat needed to remember the source of chocolate (i.e., self-generated vs. experimenter-generated information). If rats use episodic memory to remember the source of information, they should revisit the replenishment location at a higher rate than the nonreplenishment location. If rats do not have source memory, then they should revisit replenishment and nonreplenishment locations at equivalent rates. In our experiment, rats revisited the replenishment location at a higher rate than at the nonreplenishment location (Figure 3B) while avoiding revisits to chow locations. These data are consistent with the hypothesis that rats remember the source of encoded information (Crystal & Alford, 2014; Crystal et al., 2013; Crystal & Smith, 2014). This study used the equate strategy.

To establish the generality of source memory, we used a number of variations (Crystal et al., 2013) on the basic approach outlined above. We also showed that rats retain source memory of a briefly encoded event for at least 7 days (Figure 3C). We found that forgetting functions dissociate source memory and general spatial memory; in source memory, there is *no* forgetting over the first two days, whereas in general spatial memory, *all* forgetting occurs in the initial 1-2 days. We ruled out a number of alternative hypotheses: that rats fail to encode the nonreplenishment location (Crystal & Alford, 2014); that rats are merely tracking reward value (Smith et al., 2017); and that rats are merely evaluating the contrast between rewards of different values (Dalecki et al., 2017).

In a further experiment, we showed that temporary inactivation of the hippocampus with lidocaine after encoding selectively eliminated source memory in a subsequent memory assessment. Thus, source memory in our model is dependent upon an intact hippocampus. The hippocampus is proposed to be a critical processing center in source memory (Davachi et al., 2003; Eichenbaum et al., 2007; Gold et al., 2006; Mitchell & Johnson, 2009; Weis et al., 2004) and, more broadly, in episodic memory (Corkin, 2002; Tulving & Markowitsch, 1998; Vargha-Khadem et al., 1997).

Binding of episodic memories

As noted above, source memory allows us to differentiate one episodic memory from another because source memories include features that were present when the memories were formed (Crystal & Smith, 2014; Johnson et al., 1993; Mitchell & Johnson, 2009). Notably, episodic memories of similar events can only be differentiated because each event is stored as a bound representation.

Thus, we used our source memory approach to test the hypothesis that rats remember episodic memories as bound representations (Crystal & Smith, 2014). The binding hypothesis proposes that the source memory for the event is stored with the remaining elements of the episodic event in an integrated manner. An alternative hypothesis proposes that memory consists of unconnected features, which we refer to as the unbound-feature hypothesis. Notably, binding episodic memory allows us to disambiguate similar episodes (i.e., episodes that share some, but not all, features) from one another.

We gave rats multiple features of an event to encode, namely what-where-source-context features: what (food flavor), where (maze location), source (self-generated or experimenter-generated food seeking), and context (spatial cues in the room where the event occurred). The first what-where-source encoding occurred in one room, followed immediately by a second what-where-source encoding in a second room. After a retention interval, one flavor replenished at the self-generated location but not at the experimenter-generated location independently in a memory assessment in each room; the order of room presentations was randomly selected each day. For comparison, we assessed memory for a single event (i.e., study and test in the same room). By increasing the memory load, we presented the rats with multiple overlapping features that can only be fully disambiguated by remembering that one study event occurred in one particular context (one room), whereas the other event occurred in a different context (another room; Figure 4).

Binding multiple events into separate episodic memories would allow a rat to disambiguate similar events. Bound representations of separate episodes predict successful performance with both memory loads. By contrast, the unbound-feature hypothesis predicts that retrieving information about two relatively similar events will produce interference between events if at least some of the features overlap (equal revisit rates to replenishment and non-replenishment locations; Figure 4).

The rats revisited the replenishing chocolate location in the memory assessment at a higher rate than the nonreplenishment chocolate location when we used a memory load of two rooms, at a level of proficiency similar to that observed when the memory load was one room (Figure 5A) (Crystal & Smith, 2014). Moreover, source-memory performance was resistant to interference from highly similar episodes (Figure 5B) and survived long retention intervals (1 week; Figure 5C) (Crystal & Smith, 2014). These studies suggest that multiple episodic memories are each structured as bound representations. These studies used the equate and dissociate strategy.

Items in context

Crystal and Smith (2014) showed that rats remember at least two items in episodic memory without suffering from interference. A key feature of episodic memory in people is our ability to replay a *stream* of events (e.g., the narrative of a movie) (Dede et al., 2016; Eichenbaum, 2000; Eichenbaum et al., 2007; Kurth-Nelson et al., 2016; Staresina et al., 2013; Tulving, 2002). In order to ask if rats replay episodic memories, we need to establish that they remember many events (described in this section) and that they represent the sequential order of trial-unique events from a recently presented list of events (described in *Replay of episodic memories* section below). The need to provide many trial-unique events in memory led us to develop an approach using odors because rats have excellent olfaction. In this work, we used a large pool of odors so that rats are not asked to choose an odor more than once per day. We use household spices and oils to infuse odors on plastic lids that can be placed on top of plastic containers where food may be presented.

As noted above, ruling out the use of familiarity is a pervasive problem because presentation of a stimulus always gives rise to a familiarity cue. Accordingly, we developed a technique to dissociate familiarity and episodic memory solutions to a memory problem (Panoz-Brown et al., 2016). We used a new-old recognition paradigm in which we rewarded new odors, whereas old (i.e., familiar) odors were not rewarded. We presented odors in each of two distinctive contexts (using arenas that differed in a number of features, such as size, pattern, extra-arena cues, etc.) in succession (Context A→B). Within a context, the locations of odors were randomly selected for each odor and provided no information about the correct choice. In the first context, the first odor of the day (e.g., basil) was presented alone and was rewarded. Next, pairs of odors were presented, one of which was new (i.e., it had not yet been presented, e.g., oregano) and was rewarded, and the other odor was old (e.g., presentation of basil) and was not rewarded. After 16 new odors were presented in the first context, the *same* set of new odors was presented in the second context (using a new random order). Items that were new to the second context were rewarded, despite the fact that they had previously been presented in the first context; old odors in the second context were not rewarded. This is a challenging memory problem because in the second context, all items had been presented earlier in the day, but they are considered new to the second context.

Initially, we presented all of the odors in each of two distinctive contexts in succession (Context A→B). According to the episodic memory hypothesis, the rats used episodic memory to remember the presentation of each item and the context in which it had been previously presented (Eichenbaum, 2007). Alternatively, according to a non-episodic memory hypothesis, the rats chose new odors by avoiding the familiar items (or equivalently by choosing odors based on memory trace strength or based on the age of memories). Because new odors are necessarily less familiar than old odors, the rats could attain high accuracy in the task by using familiarity.

To dissociate episodic memory from judgments of relative familiarity (Panoz-Brown et al., 2016), we unexpectedly transitioned between the contexts (e.g., context A→B→A).

Critically, we identified sequences of odor presentations that predict *above* chance performance for episodic memory and *below* chance performance for selecting the least familiar item (Figure 6A).

In most naturally occurring situations, familiarity cues and episodic memories are confounded. Thus, we identified sequences of odors that put familiarity cues and episodic memory in conflict (Figure 6A). Consider a particular pair of odors such as turmeric and coffee. Initially, we presented one item (turmeric) but not the other (coffee) in the first context. Next, both items were presented in the second context, importantly with turmeric followed by coffee. Finally, we focus on a memory assessment that occurred in the first context. In the memory assessment, the rats were given a choice between turmeric and coffee. Coffee is the correct choice based on item-in-context because it has not yet been presented in the first context; thus, coffee is rewarded when chosen in this test, and our measure of accuracy is the proportion of choices of the rewarded item. Note that, prior to the memory assessment, coffee was presented more recently than turmeric. Because coffee would be more familiar relative to turmeric in the memory assessment, an animal that relied on judgments of relative familiarity (i.e., follow the rule *avoid familiar items*) would choose the turmeric item. Choice of turmeric would result in accuracy *below* chance by our measure of accuracy (because turmeric has already been rewarded in this initial context). By contrast, an animal that relied on episodic memory of the items and the contexts in which the items were presented would choose coffee in the memory assessment, resulting in *above* chance accuracy. Notably, this memory assessment dissociates episodic memory (above chance) from familiarity (below chance). We restricted our analysis to items that dissociate familiarity and episodic memory using the pattern described above but with random odors that varied across trials (Panoz-Brown et al., 2016).

To test whether the rats were relying on item-in-context episodic memory or non-episodic judgments of familiarity, we examined the rats' accuracy in the initial memory assessments. The initial data were collected before the rats had the opportunity to learn from feedback provided by rewards in novel conditions. When the identity of items in context was put in conflict with familiarity cues, initial performance was above chance using 32 odors and context transitions that ranged from 2 (context A→B→A) to 3 (ABAB), 5 (ABABAB), and 15 (Figure 6B); to obtain 15 context transitions, we randomly selected which context would occur next on each of 32 trials. We recreated novel conditions with each new number of context transitions because it was not possible for the rat to anticipate a new transition between contexts. High accuracy in the novel conditions provides evidence that rats relied on episodic item-in-context memory rather than judgments of familiarity (Panoz-Brown et al., 2016). Item-in-context episodic memories are also intact after a long retention interval (context A→B→A→45 min delay→B), which is consistent with the hypothesis that episodic memory is a part of long term memory (Panoz-Brown et al., 2016).

The data from Panoz-Brown and colleagues (2016) suggest that rats remember many unique events using episodic memory. The rats remember at least 30 item-in-context events using episodic memory. These studies used a dissociate strategy. This work prompted us to ask if rats remember the sequential order of episodic memories.

Replay of episodic memories

Panoz-Brown and colleagues (2018) showed that rats remember at least 30 item-in-context events using episodic memory. In this section, I develop the case that rats remember the sequential order of episodic memories, an ability that would enable a rat to replay its episodic memories. We propose that rats represent multiple items in episodic memory and engage in memory replay, a process by which the rat searches its representational space in episodic memory to find items at particular points in the sequence (Panoz-Brown et al., 2018).

Episodic memories in people include the replay of the flow of past events in sequential order (Dede et al., 2016; Eichenbaum, 2000; Eichenbaum et al., 2007; Kurth-Nelson et al., 2016; Staresina et al., 2013; Tulving, 2002). Electrophysiological studies in animals suggest that rats replay the sequence of hippocampal place cells (Carr et al., 2011; Carr et al., 2012; Ego-Stengel & Wilson, 2010; Jadhav et al., 2012). However, these studies primarily use relatively inactive rats (e.g., sleeping, walking along a track without any behavioral choice points). Therefore, we developed a behavioral approach that gave rats opportunities to report, via their behavior, about a stream of events in sequential order using episodic memory.

In our approach, rats were presented with a list of odors (Figure 7A). The length of the list ranged from 5 to 12 items, one of which was randomly selected on each trial. The rat could not predict the length of the list until it ended. When a list ended, the rat was placed in one of two distinctive contexts, where two items from the list were presented as an assessment of memory. The correct item was rewarded. In one context, the second to the last item from the list was the correct choice. In the other context, the fourth from the last item was the correct choice. Because the list length was randomly selected for each list, it was *impossible* for the rat to identify the correct choices *before* the list ended; thus, when an odor was encoded in a list, it was not known that this item would subsequently be the correct or incorrect choice in the memory assessment. Locations of odors in arenas were randomly selected throughout the experiment and provided no information about the correct choice. Our strategy was to ask what could a rat with episodic replay do via its behavior. If the rat could replay the sequence of episodic memories, it would select the correct item in second and fourth last contexts. The rats passed a number of tests for episodic memory replay with accuracy above chance in both second and fourth last memory assessments (Figure 7C). In one test, we dissociated episodic memory replay from non-episodic memory alternatives (Figure 7B). As noted above, familiarity cues are pervasive; thus, we again developed a technique to dissociate familiarity and episodic memory solutions to the memory problem. According to the episodic memory replay hypothesis, rats represent multiple items in episodic memory and engage in memory replay, a process by which the rat searches its representational space in episodic memory to find information. Alternatively, we outlined a non-episodic memory solution. As noted above, when an item is presented, it gives rise to a memory trace whose probability of retrieval declines over time. Therefore, it is possible that the rats had learned to match the relative familiarity of memory traces in each memory assessment context. Accordingly, they could successfully choose the second last (relatively large trace) and the fourth last (smaller trace) items in the appropriate context; foils would have memory traces strengths above or below the levels of second and fourth last items, depending on its position in the list. For example, the rat could pick the item that matches the typical memory strength for the current context and avoid values above and below the typical level. Critically, using such a solution, the rat would choose the correct item but would not need to replay episodic memories to search the representational space in episodic memory for the second and fourth last items. To dissociate familiarity and episodic memory, we doubled the time between list items (Figure 7B), which impacts relative familiarity of items without impacting the sequential order of items. Importantly, in the memory assessment, the foil (i.e., the incorrect choice) was selected so that it had the typical memory strength of a correct item. The foil in the second last memory assessment was an attractive choice because it had occurred in the list at the delay typical of a second last item; thus, an animal that is relying on familiarity will choose the wrong item (below chance). In contrast, an animal that uses episodic memory replay will choose the second last item correctly (above chance) despite the unusually long delay since this particular second last item's appearance in the list. Similarly, in the fourth last context, the foil was an attractive choice because it had occurred in the list at the delay typical of a fourth last item. In both dissociation tests, we observed above chance accuracy (Figure 7C), which rules out judgments of familiarly (or equivalently memory trace strengths, the age of memories, and timing intervals from each event to the memory assessment) and supports the hypothesis that rats replay episodic memory. In other experiments, we showed that episodic replay is intact after at least a 1-hour retention interval and survives interference provided by memory of other odors (Figure 7C); these data are consistent with the hypothesis that episodic memory is a part of long term memory. Finally, we used DREADDs (Designer Receptor Exclusively Activated by Designer Drug) to document that temporary inhibition of hippocampal neurons impaired replay of episodic memories while sparing measures of hippocampal-independent memory (new-old recognition memory and an associative discrimination; Figure 7D) (Panoz-Brown et al., 2018). This work used a dissociate strategy.

Recollection and familiarity

Although people can detect information that corresponds to a previous episode (recognition), they also can retrieve memories in the absence of cues that prompt the retrieval (recollection). It is difficult to study recollection in nonhumans because it relies substantially on verbal reports in people. Arguably, all studies of memory in nonhumans investigate recognition. A small number of studies have sought to investigate recollection in nonhumans (Basile & Hampton, 2011; Eacott et al., 2005; Fortin et al., 2004). Because recollection is a fundamental property of human memory, the development of animal models of recollection is important.

How can we investigate recollection in the absence of language? One strategy focuses on the observation that recognition memory in people may be based on two independent mechanisms, episodic recollection of an earlier event and a sense of familiarity of a previously experienced stimulus. Signal detection theory has been used to distinguish recollection and familiarity because these two processes have different profiles. Receiver operating characteristic (ROC) curves plot the probability of a hit as a function of probability of a false alarm. Notably, the ROC can be decomposed into two underlying components. ROC curves have a curvilinear (i.e., bowed) shape, but they also have an asymmetrical shape. The combination of these two shapes produces an above zero y-intercept. The asymmetry suggests that a threshold is used for recollection whereas the curvilinear component suggests a graded strength of familiarity (Yonelinas, 2001; Yonelinas & Parks, 2007). An Alternative conceptualization was proposed by Wixted and colleagues (e.g., Wixted, 2007).

Fortin, Wright and Eichenbaum (Fortin et al., 2004) trained rats to dig for a piece of food that was buried in a cup of sand. They used a new-old odor recognition approach. In each trial, the rat was presented with a sequence of 10 cups, each with a trial-unique odor. Next, the rats waited 30 min. Finally, the rat was presented with 20 additional cups, half with new odors and half with the previously presented odors. Food was obtained by digging in the new-odor cups. If the odor was old, the rat was required to refrain from digging and approach a different cup at the back of the cage to get food. A hit is defined as correctly choosing a new item, and a false alarm is defined as incorrectly choosing an old item. ROC curves were estimated by manipulating the pay-off ratio (combination of reward magnitude and effort required to obtain the food) for correct new and old responses by varying the height of the test cup across sessions. ROC curves showed both asymmetrical and curvilinear components, suggesting that both recollection and familiarity processes contributed to performance. Next, some of the rats received a lesion to the hippocampus, and others received a sham control. ROC curves of sham rats continued to show both asymmetrical and curvilinear components. By contrast, ROC curves of rats with hippocampal lesions were fully symmetrical and curvilinear. Fortin and colleagues argued that the absence of the asymmetry suggests that damage to the hippocampus eliminated recollection, leaving performance based exclusively on familiarity. To evaluate recollection and familiarity, they algebraically removed the recollection component from the ROC of sham rats, which produced a ROC curve that superimposed on that of rats with hippocampal lesions. Control rats tested with a lengthened retention interval showed the recollection pattern in the apparent absence of familiarity. These data suggest that the hippocampus mediates recollection (Fortin et al., 2004). The loss of asymmetry (an index of recollection) combined with the retained curvilinearity (an index of familiarity) following damage to the hippocampus suggests that recollection and familiarity have distinct neural substrates. This work used a dissociation strategy.

Unexpected question after incidental encoding

Zentall developed a key insight about animal models of episodic memory. He noted that most approaches to investigating episodic memory in animals involve *training*, which naturally produces expectations. He argued that some data in episodic memory studies may occur using planned actions based on these expectations, without remembering back in time to the earlier event (Singer & Zentall, 2007; Zentall, 2005, 2006; Zentall et al., 2001; Zentall et al., 2008). Zentall and colleagues noted that when information is *explicitly* encoded for use in an *expected* memory test, explicitly encoded information may generate a planned action. When you encounter information that will be needed in the future, it is possible that the animal encodes this information and translates it into a planned action. When the opportunity to perform the action occurs, the animal, at that point, may merely execute the action without remembering back in time to the earlier event. In such a situation, the remembered action can occur successfully without retrieving an episodic memory. The focus on retrieving a memory of the earlier event is the *key element* that makes an animal model of episodic memory *episodic* according to the central hypothesis described above. Therefore, carrying forward information that is needed at a future test while not specifically retrieving a memory of the earlier episode is a major threat to an episodic memory hypothesis.

Zentall also outlined a solution to the problem of explicit encoding and expected tests of memory. He noted that *incidental encoding* and an *unexpected question* provide a powerful combination. To say that information is encoded incidentally is to note that it is not known that the information will be needed in the future. Because the test of memory is unexpected, it is impossible to predict the test at the time of encoding. Thus, when information is incidentally encoded and assessed in a subsequent unexpected test, it is impossible to transform information at encoding into a planned action to be used later. Zentall concluded that the only way to answer an unexpected test after incidental encoding is to retrieve an episodic memory of the incidentally encoded event. Zentall and colleagues (Singer & Zentall, 2007; Zentall, 2005, 2006; Zentall et al., 2001; Zentall et al., 2008) demonstrated that pigeons can answer an unexpected question after incidental encoding; Fugazza and Miklosi have recently demonstrated that dogs also can answer an unexpected question after incidental encoding (Crystal, 2016b; Fugazza et al., 2016; Fugazza et al., 2020).

We used Zentall's et al. (2001) approach to test the hypothesis that rats can answer an unexpected question after incidental encoding (Zhou et al., 2012). To this end, we embed two tasks in a radial maze (Figure 8A). In the first task, five of the arms in the maze were reserved for a foraging task. Initially, 3 randomly selected arms (from the set of 5 arms) were accessible and each provided 1 chow pellet. Next, all 5 of the arms were accessible, and food was available for visiting previously inaccessible arms. In the second task, three of the arms (in the shape of T) were reserved for a classification problem. In the T maze task, the rat began in the central hub. Next, it was forced to enter the stem of the T, which we refer to as a sample arm. When the rat broke the photobeam in the sample arm's food trough, several pellets were sometimes delivered (referred to as a food sample). On other occasions, the rat interrupted the photobeam but no pellets were provided (referred to as a no-food sample). Next, the 2 remaining doors of the T maze were opened, and the animal was permitted to choose between these arms. Left and right turns were rewarded contingent on the presence or absence of food in the sample arm (the rewarded turn was counterbalanced across rats). Thus, the animal needed to learn the rule that, for example, a left turn is rewarded after food, whereas a right turn is rewarded after no food.

The rats were trained in the foraging and T-maze tasks on separate days. To engineer an unexpected question after incidental encoding, we began with the foraging task and switched to the T maze task. In the *food probe*, the rats began with foraging as in the past, but we selected the top three arms (on the opposite side of the maze than the T maze sample arm). When the animal obtained food at each of the foraging arms, it was unexpectedly confronted (i.e., for the first time) with the opportunity to report that it had just had food or no food by presenting the rats with the choice arms from the T maze. If the rat retrieved a memory of the earlier foraging event, it would remember having had food and make a left/right turn accordingly. If the rat failed to retrieve a memory of the earlier foraging, it would choose randomly from the two available arms (which would also be expected if the rats treated the T-maze choice arms as opportunities to continue foraging). Notably, we conducted only a single food probe for each rat so that it could not learn from any feedback. The rats made the correct turn at a high rate (Figure 8B), similar to the baseline level of performance on the T maze task (Zhou et al., 2012).

We also gave rats a *non-food probe*. Again, the rats began foraging in the top 3 arms of the maze (opposite the T stem), but pellets were not dispensed in the arms on the non-food probe. This was a novel situation, as all of their previous experiences on foraging arms had provided food. Next, we confronted the rats with an opportunity to make left/right turns by presenting the T maze choice arms. Now, the rat should make the *opposite turn*, if it retrieved a memory of no-food. By contrast, if the rat failed to retrieve a memory of no-food, it would choose randomly between the available arms. We again observed that the rats made the correct turn at a high rate (Figure 8B), similar to the baseline level for the T maze task (Zhou et al., 2012). The non-food probe was conducted once per animal to preclude learning from feedback.

The food probe and non-food probe data suggest that rats are able to answer an unexpected question after incidental encoding. We tested this proposition in an additional experiment by asking if the ability to answer an unexpected question after incidental encoding is hippocampal dependent. As noted above, the hippocampus is a critical processing center for episodic memory (Eichenbaum, 2000, 2017; Eichenbaum et al., 2007; Nyberg et al., 1996). If answering an unexpected question after incidental encoding requires episodic memory, then temporary inactivation of the hippocampus should selectively impair the ability of rats to answer an *unexpected* question while sparing the ability to answer an *expected* question. To assess accuracy in answering an unexpected question, we used a no-food probe, as described above. To assess accuracy in answering an expected question, we designed a control procedure that combined elements of the T-maze task while equating other features of the no-food probe; we referred to this control condition as a rotation probe. As in the T-maze task (but unlike the no-food probe), the rotation probe presented a no-food sample followed immediately by the opportunity to turn left or right. Thus, the rotation probe can be solved by remembering a planned action without remembering the episode; because the rotation probe can be solved without remembering the episode, we expected that performance on the rotation probe will not be impaired by temporary inactivation of the hippocampus. To equate the control procedure with other aspects of the no-food probe, the rotation probe offered a no-food sample, and the sample was presented in the arm opposite to that used in training (i.e., rotated 180° with respect to the usual T-maze sample location); this rotation is equivalent to the average rotation in the no-food probe. Thus, the no-food and rotation probes varied the episodic-memory demands while equating rotation and the absence of food.

We surgically implanted cannulae bilaterally aimed at the hippocampus to temporarily inactive it with a microinjection of lidocaine. Accuracy was reestablished following surgery. Following infusion of lidocaine, accuracy in answering the unexpected question was significantly reduced relative to baseline (to the level expected by chance), whereas accuracy in answering the expected question was not impaired (Figure 8C). The selective reduction of accuracy on unexpected questions could be attributed to effects of lidocaine infusion because accuracy was not impaired relative to baseline by infusions of vehicle.

In summary, rats are able to answer an unexpected question after incidental encoding. The rats needed to retrieve an episodic memory of the incidentally encoded information (food vs. no-food) when unexpectedly confronted with the opportunity to report about this information (via left/right turns). This ability is hippocampal dependent. Overall, this provides strong evidence that rats are a good model for exploring episodic memory. Independent evidence that rats can answer an unexpected question after incidental encoding was recently reported (Sato, 2021) and implicates the retrosplenial cortex, which is a major output area of the hippocampus via the subiculum.

Future directions

Initial work on developing an animal model of episodic memory focused on successful demonstrations. This is important to establish the viability of the animal model. However, a more advanced state of the field points to identifying limitations of capacities (Crystal & Suddendorf, 2019). The notion here is that the work with nonhumans provides a model of human cognition. We do not expect that all details will be the same in human and nonhuman models. Thus, an avenue for future research focuses on identifying limits to the cognitive capacities established by the model.

I will offer an example of an effort to identify limits. Can episodic memory replay occur in forward and backward directions? This question is prompted from work on hippocampal replay (using electrophysiology in freely moving animals). The hippocampus has place cells that fire when the animal is in specific locations in the animal's environment (Moser et al., 2015). Notably, place cells fire at other times, in both forward and backward directions (referred to as hippocampal replay) (Carr et al., 2011; Carr et al., 2012; Ego-Stengel & Wilson, 2010; Jadhav et al., 2012). Studies of hippocampal replay tend to impose minimal behavioral demands on the animal (e.g., sometimes the animal is sleeping or walking along a track with no choice points). An example of a limitation would be the finding that rats can replay in one direction but not the opposing direction. More broadly, electrophysiological studies of rats engaged in an episodic memory replay task would help to establish the biological mechanisms of searching a representational space in episodic memory.

This article focuses on standards by which to examine the strength of evidence for claims about episodic memory in nonhumans. Why focus so heavily on this definitional question? One answer to this question emphasizes the application of animal models to better understand disorders of human memory. Episodic memory is profoundly impaired in Alzheimer's disease (Fodero-Tavoletti et al., 2009; Leube et al., 2008; Salmon & Bondi, 2009; Schwindt & Black, 2009; Storandt, 2008). Indeed, the loss of episodic memory is debilitating, and much of the societal burden of Alzheimer's disease stems from the loss of episodic memory. Thus, treatments that are effective at reducing or eliminating episodic memory impairments have the potential to improve quality of life of individuals with Alzheimer's disease and their families. The prospects of developing an animal model of episodic memory impairment requires that the model validly measures episodic memory. As noted above, not all approaches provide strong evidence of episodic memory in animals, so the design and the selection of tasks are important considerations.

Most animal models of Alzheimer's disease assess only general aspects of learning and memory (e.g., (O'Leary & Brown, 2008; Palop et al., 2003; Pennanen et al., 2006; Roberson et al., 2007; Stepanichev et al., 2006; Stepanichev et al., 2004; Timmer et al., 2008; Yates et al., 2008)), making the translational relevance to episodic memory impairments in Alzheimer's disease uncertain (Kimmelman & London, 2011). This is a significant problem because many models of Alzheimer's disease have appeared promising at early stages of preclinical testing, only to fail in subsequent clinical trials (Becker & Greig, 2010; Carlsson, 2008; Jacobson & Sabbagh, 2011; Mangialasche et al., 2010; Mullane & Williams, 2013; Schneider & Lahiri, 2009). At least 20 compounds have provided preliminary evidence for benefits in Alzheimer's preclinical studies and Phase II clinical trials, yet failed to succeed in Phase III trials, which occurs in 40-50% of tested compounds (Becker & Greig, 2008). Recent examples include drugs that failed for lack of efficacy in phase II and III trials (Bellus-Health, 2008; Elan, 2010; Feldman et al., 2010; Gold et al., 2010; Green et al., 2009; Salloway et al., 2009; Winblad et al., 2010). Although translational failure occurs for many reasons, we argue that even when all of these problems are remediated, it will be necessary to test interventions using preclinical models that assess episodic memory. Although the development of an animal model of episodic memory in Alzheimer’s disease is not sufficient, it is a *necessary* condition to prevent translational failure when testing Alzheimer’s disease therapeutics in the future.

A number of animal models of the genetic basis of Alzheimer’s disease have been developed. Most of this work uses mouse models, which is unfortunate given the limited behavioral repertoire of mice. Thus, researchers have used what is available for assessing a behavioral endpoint in mice (e.g., novel object recognition, Morris water maze). This work seeks to impact the types of cognitive impairments that occur in Alzheimer’s patients, including episodic memory, but it does not *measure* episodic memory. Translation from animals to humans would likely be improved by using a valid model of episodic memory. Advances in gene editing technologies have recently made it fast and relatively inexpensive to develop genetic models using rats. The combination of animal models of Alzheimer’s disease with animal models of episodic memory is potentially powerful. This work would develop along two lines. The first line of research would focus on documenting a selective decline in episodic memory using a rat model of Alzheimer’s disease. Here the definitional concerns developed in this article are needed to be convinced that the impairment is truly in episodic memory function. If the first line of research can be accomplished, this opens a second line of research, namely using the animal model of episodic-memory impairment in Alzheimer’s disease to investigate novel therapeutic approaches that specifically target episodic memory function. Currently, this type of selective targeting of episodic memory function is not possible in any animal model of Alzheimer’s disease.

I began this article by emphasizing that a fundamental question in comparative cognition concerns the ability to remember back in time to an earlier event or episode. I reviewed a number of approaches that have been used successfully with rats. The methods described above using rats can be used to investigate episodic memory in other animals (as has been done by a number of labs). The widespread application of valid models of episodic memory is an important tool for investigating the evolution of cognition (Crystal, in press-a).

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Figure captions

Figure 1

What-Where-When Episodic Memory in the Rat: Experimental Design

Note. Schematic representation of experimental design of Zhou and Crystal's (2009) study. **A.** Design of Experiment 1. First helpings (study phase; encoding) and second helpings (test phase; memory assessment) of food was presented either in the morning or afternoon, which was randomly selected for each session and counterbalanced across rats. Study and test phases show an example of the accessible arms, which were randomly selected for each rat in each session. Chocolate or chow flavored pellets were available at the distal end of four arms in the study phase (randomly selected). After a 2-min retention interval, the test phase provided chow-flavored pellets at locations that were previously blocked by closed doors. The figure shows chocolate replenished in the test phase conducted in the morning (7 a.m.) but not in the afternoon (1 p.m.), which occurred for a randomly selected half of the rats; these contingencies were reversed for the other rats (not shown). One session was conducted per day. **B.** Phase-shift design of Experiment 2. Performance in Experiment 1 could have been based on the time of day of sessions (morning vs. afternoon) or based on a judgment of how long ago light onset in the colony occurred (short vs. long delay; i.e., familiarity of light onset). Light onset occurred at midnight in Experiment 2, which was 6 hr earlier than in Experiment 1, and the session occurred in the morning in Experiment 2. The horizontal lines highlight the similarity of the 7-hr gap between light onset and sessions in probe (solid; Experiment 2) and training (dashed; Experiment 1) conditions. This design puts the predictions for time-of-day and familiarity cues in conflict; performance typical of the morning baseline is expected based on time of day whereas afternoon performance is expected based on familiarity. **C.** Transfer-test design of Experiment 3. Study phases occurred at the same time of day as in Experiment 1. Test phases occurred at novel times of day (7 hr later than usual). Thus, early and late sessions had study times (but not test times) that corresponded to those in Experiment 1. The initial two sessions in Experiment 3 were one replenishment and one non-replenishment condition, counterbalanced for order of presentation. An early or late session was randomly selected on subsequent days. More revisits to the chocolate location are expected in replenishment compared to non-replenishment conditions if the rats remembered the time of day at which the study episode occurred. Alternatively, revisit rates are expected to be equal in early and late sessions if the rats used the current time of day when the test phase occurred. Study and test phases were as in Experiment 1, except that they were separated by 7-hr delays (shown by horizontal brackets). **D.** Conflict-test design of Experiment 4. The study phase occurred at 1 p.m. and was followed by a test phase at 2 p.m. These times correspond, respectively, to the time of day at which a late-session study phase and early-session test phase occurred in Experiment 3, which put predictions for time of day at study and time of day at test in conflict. If rats remembered the time of day at which the study episode occurred, they would be expected to behave as in its late-session, test-phase baseline. Alternatively, if the rats used the current time of day at test, they would be expected to behave as in its early-session, test-phase baseline. **A-D.** Reproduced with permission from Zhou, W., & Crystal, J. D. (2009). Evidence for remembering when events occurred in a rodent model of episodic memory. *Proceedings of the*

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Figure 2

What-Where-When Episodic Memory in the Rat: Data

Note. Data from Zhou and Crystal's (2009) study. **A.** Rats preferentially revisited the chocolate location when it was about to replenish in Experiment 1 (see experimental design in Figure 1A). The probability of a revisit to the chocolate location in the first four choices of a test phase is plotted for replenishment and non-replenishment conditions. **B.** Rats used time of day, rather than information about remoteness, to adjust revisit rates in Experiment 2 (see Figure 1B). The figure shows the difference between observed and baseline revisit rates. For the bar labeled interval, the baseline is the probability of revisiting chocolate in the afternoon. The significant elevation above baseline shown in the figure documents that the rats did not use familiarity or an interval timing mechanism. For the bar labeled time of day, the baseline is the probability of revisiting chocolate in the morning. The absence of a significant elevation above baseline is consistent with the use of time of day. The horizontal line corresponds to the baseline rate of revisiting the chocolate location in Experiment 1. Positive difference scores correspond to evidence against the hypothesis shown on the horizontal axis. **C.** and **D.** Rats preferentially revisited the replenishing chocolate location when the study, but not the test, time of day was familiar in Experiment 3 (see Figure 1C). The probability of a revisit to the chocolate location in a test phase is shown for first replenishment and first non-replenishment sessions (**C**; initial) and for subsequent sessions (**D**; terminal). **E.** Rats remembered the time of day at which the study episode occurred in Experiment 4 (see Figure 1D). Rats treated the novel study-test sequence as a late-session test phase, documenting memory of the time of day at study rather than discriminating time of day at test. The figure shows the difference between observed and baseline revisit rates. For the bar labeled test time, the baseline was the probability of revisiting chocolate in the test phase of the early session in Experiment 3. The significant elevation above baseline documents that the rats did not use the time of day at test to adjust revisit rates. For the bar labeled study time, the baseline was the probability of revisiting chocolate in the test phase of the late session in Experiment 3. The absence of a significant elevation above baseline is consistent with memory of the time of day at study. The horizontal line corresponds to the baseline revisit rate to the chocolate location from Experiment 3 (terminal). Positive difference scores correspond to evidence against the hypothesis indicated on the horizontal axis. **A-E.** Error bars represent 1 SEM. **A**, **C**, and **D.** The probability expected by chance is 0.41. Repl = replenishment condition. Non-repl = non-replenishment condition. **A.** * P < 0.001 difference between conditions. **B.** * P < 0.05 different from baseline. **C** and **D.** * P < 0.05 and ** P < 0.0001 difference between conditions. **E.** * P < 0.001 different from baseline. Reproduced with permission from Zhou, W., & Crystal, J. D. (2009). Evidence for remembering when events occurred in a rodent model of episodic memory. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 9525-9529. ©2009 National Academy of Sciences, U.S.A.

Figure 3

Source Memory in the Rat

Note. **A.** Schematic of procedure. Two locations (randomly selected on each trial; shown in red or dark grey if printed in B&W) provide chocolate in the study phase – one is encountered when the rat navigates the maze (self-generated chocolate feeding), whereas the other is presented to the rat when the experimenter places the rat in front of the food source (experimenter-generated feeding; depicted by the hand icon). After a retention interval, the self-generated chocolate location replenishes (provides additional chocolate) whereas the experimenter-generated location does not replenish. Self-generated and experimenter-generated encounters with chocolate in study phases were presented in random order across sessions. Chow locations (shown in light grey) are encountered in study and test phases but do not replenish. **B-C.** Source memory is shown by a higher revisit rate to the replenishment than nonreplenishment chocolate location. **B.** Rats preferentially revisit the chocolate location when it is about to replenish. Accuracy in avoiding revisits to depleted chow-flavored locations was 0.85 ± 0.02. Error bars represent 1 SEM. * $p < 0.01$. **C.** Source memory and location memory are dissociated by different decline rates across retention intervals of up to 7 days. Source memory performance (indexed by more revisits to the replenishing chocolate location than to the non-replenishing chocolate location; left axis) is unaffected by retention-interval challenges of up to 2 days, whereas location memory (indexed by chow accuracy, right axis) completes its decline over this same time period. Source memory errors occur when the retention interval is 7 days. At this timepoint, rats revisit the non-replenish chocolate location at an elevated rate. These incorrect revisits are likely due to source memory failure because memory for the replenishing chocolate locations is intact at this time point. Rats encountered two chocolate locations per study phase, one self-generated and one experimenter-generated. Reproduced with permission from Crystal, J. D., Alford, W. T., Zhou, W., & Hohmann, A. G. (2013). Source memory in the rat. *Current Biology*, 23(5), 387-391. ©2013

Figure 4

Schematic of Unbound Features Hypothesis

Note. A proposed representation of unbound features. Poor performance is predicted because an unbound-feature representation does not segregate features according to the contexts in which the events occurred. Therefore, revisit rates in replenishment and non-replenishment chocolate locations are predicted to be equal according to the unbound feature hypothesis. Reproduced with permission from Crystal, J.D. & Smith, A.E. (2014). Binding of episodic memories in the rat. *Current Biology*, 24(24), 2957-2961. ©2014

Figure 5

Binding of Episodic Memory in the Rat

Note. Bound episodic memories function to disambiguate multiple, interleaved study episodes. Successful memory performance is shown by a higher revisit rate to replenishment than non-replenishment chocolate locations. Rats visited two chocolate locations per study phase, one self-generated and one experimenter-generated. Rats preferentially revisited the chocolate location when it was about to replenish; chow locations never replenished. **A.** The memory load was 1 (study and test in the same room) or 2 (study in one room, followed by study in a second room, followed by a test in each room) with a short (1-hour) retention interval between corresponding study and test phases; chocolate baiting in each room was randomly selected. **B.**

The memory load was 2, the retention interval was short, and the chocolate baiting was varied across three conditions: The *Random* condition used independent, random baiting in each room; the *Same* condition used the same orientation for replenishing and non-replenishing chocolate arms in both rooms; the *Different* condition reversed the orientation of replenishing and non-replenishing chocolate arms across the two rooms. **C.** The memory load was 1 or 2 with a long (1-week) retention interval. **A-C.** *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$. Error bars represent 1 SEM. The probability of a revisit to the chocolate location was calculated from the first five choices in test phases. RI = retention interval. (Adapted from: Crystal & Smith, *Current Biology*, 2014)

Figure 6

Rats Remember Items in Context using Episodic Memory

Note. Dissociating episodic item-in-context memory from familiarity cues. **A**. Yellow (light gray) and brown (or dark gray), respectively, are used to depict turmeric and coffee odors. Turmeric (light gray) is initially presented in Context A, and both turmeric and coffee (dark gray) are presented in Context B. Note that coffee was *not* presented in Context A, and turmeric occurred before coffee in Context B. Finally, the memory assessment is conducted in Context A, and the rats are confronted with a choice between turmeric and coffee. The correct choice, based on item in context, is coffee because it has not yet been presented in Context A. Coffee is rewarded when chosen in this test, and the proportion of choices of the rewarded item is the measure of accuracy. Importantly, prior to the memory assessment, coffee was presented more recently than turmeric. Consequently, in the memory assessment, turmeric is less familiar than coffee. Thus, an animal that relies on judgments of relative familiarity would choose the turmeric item in the memory assessment. By our measure of accuracy, this choice produces *below* chance accuracy. By contrast, an animal that relied on item-in-context memory would choose coffee in the memory assessment, which produces *above* chance accuracy. Notably, this memory assessment dissociates item-in-context memory (above chance) from judgments of relative familiarity (below chance). The presence of additional odors (not shown) is identified by "..." in the schematic. The schematic focuses on rewarded items (denoted by "√") by omitting comparison non-rewarded items prior to the memory assessment. Note that on other occasions (not shown) brown precedes yellow in Context B, accuracy is high (91%), but item-in-context episodic memory and familiarity judgments are not dissociated on these occasions. **B**. Accuracy in episodic memory assessment depicted in **A** is above chance, documenting episodic memory for multiple items in context (~30 items). Accuracy was equivalent (not shown) if an item was rewarded once or twice (JZS Bayes factor = 4.0). Error bars represent 1 SEM. Adapted from Panoz-Brown, D.E., Corbin, H.E., Dalecki, S.J., Gentry, M., Brotheridge, S., Sluka, C.M., Wu, J.-E., & Crystal, J.D. (2016). Rats remember items in context using episodic memory. *Current Biology*, 26(20), 2821-2826.

Figure 7

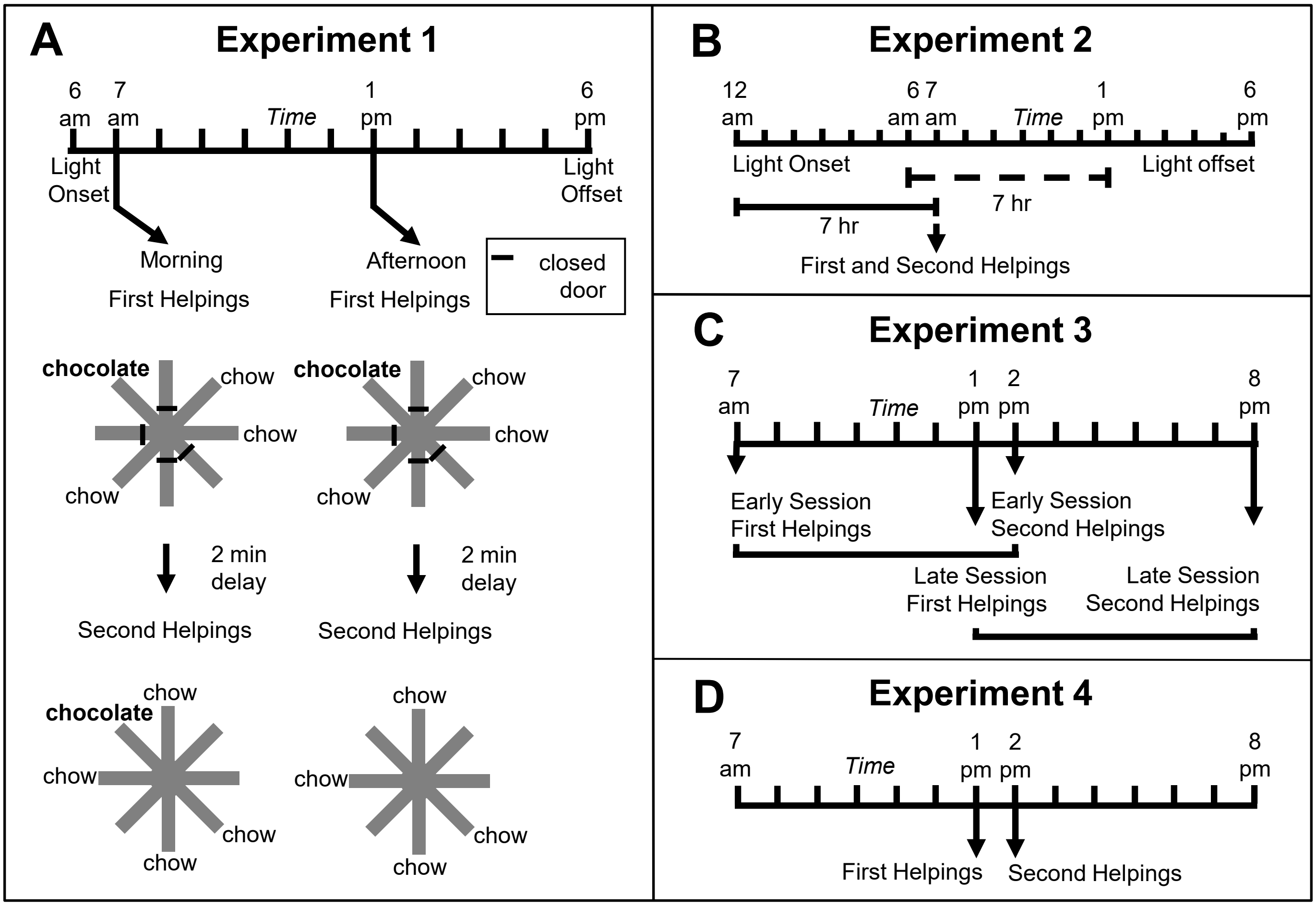
Replay of Episodic Memory in the Rat

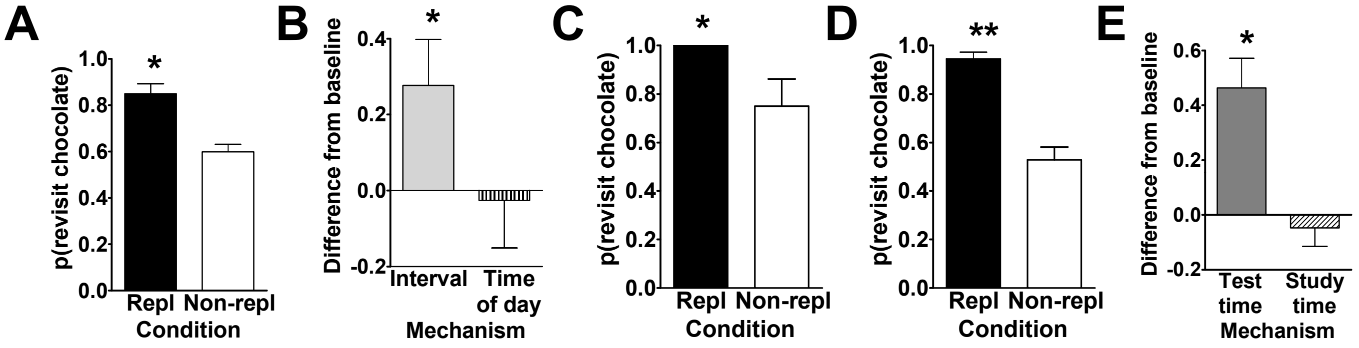
Note. Rats replay a stream of multiple episodic memories. **A.** A list of odors (▨, ▦, ◧, etc.) is presented in a distinctive context (▱). When the list ends, the rat is moved to one of two different contexts (▰, ⬭; randomly selected). In one context (▰), the second from the last item from the list is the correct choice (depicted by "√"); the foil is another item from the list. In the other context (⬭), the fourth from the last item is correct. The correct item is not known until the list ends because the list length is randomly selected on each trial. **B.** The presentation of an item gives rise to a memory trace whose probability of retrieval decreases with the passage of time (delays depicted by arrows at top of **A** and **B**). Thus, the correct choice in **A** could be based on judgments of relative familiarity (memory trace strength) of second and fourth last items (the time between second last item and memory assessment is shorter than between fourth last item and memory assessment). Familiarity and sequential information are dissociated in **B** by doubling the amount of time between list items. The foils in **B** were selected to pit the "correct" familiarity item vs. the "correct" sequential item. **C.** Rats chose the correct sequential item when familiarity and sequential information were dissociated (Exp 2). Similarly high accuracy was observed in training (Exp 1, depicted in **A**) and other conditions (Exp 3: long retention interval (60 min); replay was intact when other items were remembered after list encoding (Exp 4A: foils from list; Exp 4B: foils from intervening task). Our approach provides an animal model of episodic memory replay, a process by which the rat searches its representations in episodic memory in sequential order to find information. Error bars represent 1 SEM. Adapted from and reproduced with permission from Panoz-Brown, D., Iyer, V., Carey, L.M., Sluka, C.M., Rajic, G., Kestenman, J., Gentry, M., Brotheridge, S., Somekh, I., Corbin, H.E., Tucker, K.G., Almeida, B., Hex, S.B., Garcia, K.D., Hohmann, A.G., & Crystal, J.D. (2018). Replay of episodic memories in the rat. Current Biology, 28(10), 1628-1634.e1627. ©2018

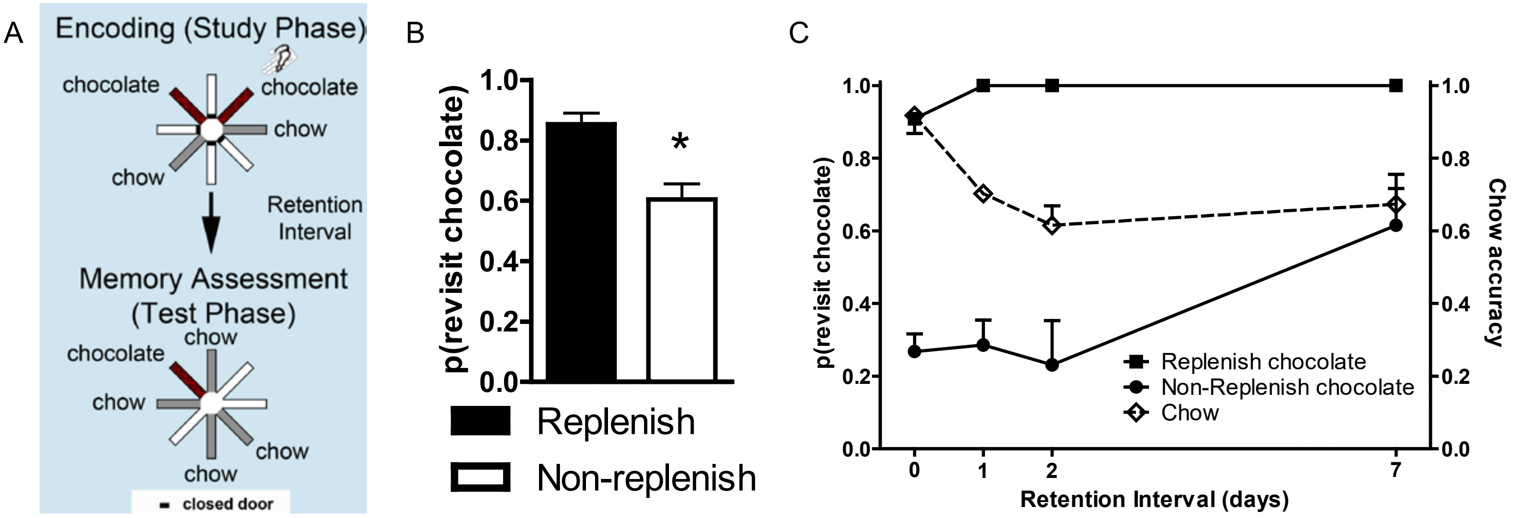
Figure 8

Rats Answer an Unexpected Question after Incidental Encoding using Episodic Memory

Note. **A.** Schematic of the radial maze with shading to illustrate assignment of arms to tasks. ***Baseline:*** The *T-maze task* used three arms (shown in black); the bottom-center black arm provided food (6 pellets) or no-food (zero pellet) samples and subsequent reward (6 pellets) was contingent on selecting left or right black arms, respectively (counterbalanced across rats). The *radial maze task* used the other five arms (shown in grey); one pellet was available at each of the five grey arms, but access was initially limited to three (randomly selected) arms followed by access to all five arms. Each rat received either 6 T-maze or 1 radial maze trial per day. ***Probes:*** Unexpected questions began with access to the top three (grey) arms (as could occur in a training radial-maze trial) with food (*food probe*) or without food (*no-food probe*), but continued with access to left and right (black) choice arms from the T-maze task (providing the opportunity to report whether the rat had food or not). All trials began with the rat in the central hub, and guillotine doors restricted access to selected arms. Rotation probes started with food or no-food in the top-center grey arm (i.e., rotated 180^o with respect to the sample location in corresponding baseline trials). All arms in the actual maze are white. **B.** Rats answered unexpected questions after incidentally encoding the presence or absence of food. Baseline data come from the first daily T-maze trial in the terminal 5 days before probe testing. Each rat was tested once in food and no-food probe conditions. Error bars represent 1 SEM. **C.** Temporary inactivation of the hippocampus before memory storage impaired accuracy on the unexpected question relative to baseline but did not interfere with answering the expected question. Accuracy was selectively reduced by lidocaine in the unexpected probe relative to baseline and other probes. Baseline data come from the first daily T-maze trial in the 5 sessions before and 5 sessions after surgery. Each rat was tested once in each probe condition with the order determined by a Latin Square design (a total of 4 conditions per rat, with one week separating each probe injection). Error bars represent 1 SEM. * $p < 0.01$ difference between the unexpected + lidocaine probe and baseline. (Adapted from: Zhou, Hohmann, & Crystal, *Current Biology*, 2012)


A
Experiment 1
6 am
7 am
Time
1 pm
6 pm
Light Onset
Light Offset
Morning First Helpings
Afternoon First Helpings
closed door
chocolate
chow
chow
chow
chocolate
chow
chow
chow
2 min delay
2 min delay
Second Helpings
Second Helpings
chow
chocolate
chow
chow
chow
chow
chow
chow
chow
B
Experiment 2
12 am
6 am
7 am
Time
1 pm
6 pm
Light Onset
Light offset
7 hr
7 hr
First and Second Helpings
C
Experiment 3
7 am
Time
1 pm
2 pm
8 pm
Early Session First Helpings
Early Session Second Helpings
Late Session First Helpings
Late Session Second Helpings
D
Experiment 4
7 am
Time
1 pm
2 pm
8 pm
First Helpings
Second Helpings


A
p(revisit chocolate)
1.0
0.8
0.6
0.4
0.2
0.0
*
Repl
Non-repl
Condition
B
Difference from baseline
0.4
0.2
0.0
-0.2
*
Interval
Time of day
Mechanism
C
p(revisit chocolate)
1.0
0.8
0.6
0.4
0.2
0.0
*
Repl
Non-repl
Condition
D
p(revisit chocolate)
1.0
0.8
0.6
0.4
0.2
0.0
**
Repl
Non-repl
Condition
E
Difference from baseline
0.6
0.4
0.2
0.0
-0.2
*
Test time
Study time
Mechanism


A
Encoding (Study Phase)
chocolate
chocolate
chow
chow
Retention Interval
Memory Assessment (Test Phase)
chow
chocolate
chow
chow
chow
▬ closed door
B
p(revisit chocolate)
1.0
0.8
0.6
0.4
0.2
0.0
*
Replenish
Non-replenish
C
p(revisit chocolate)
Chow accuracy
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
7
Retention Interval (days)
Replenish chocolate
Non-Replenish chocolate
Chow

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<th>Encoding in Room B</th>
</tr>
<tr>
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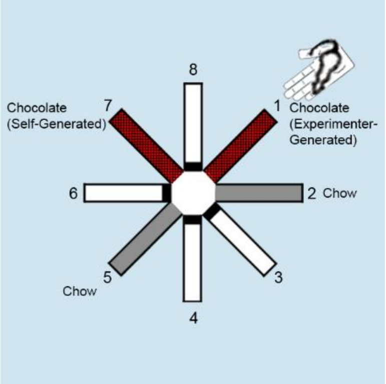

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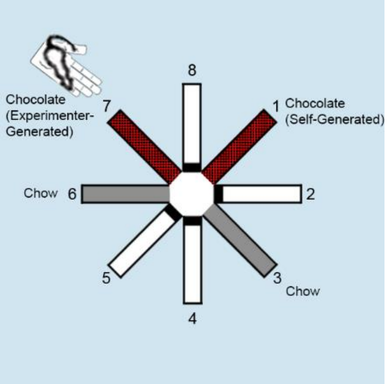
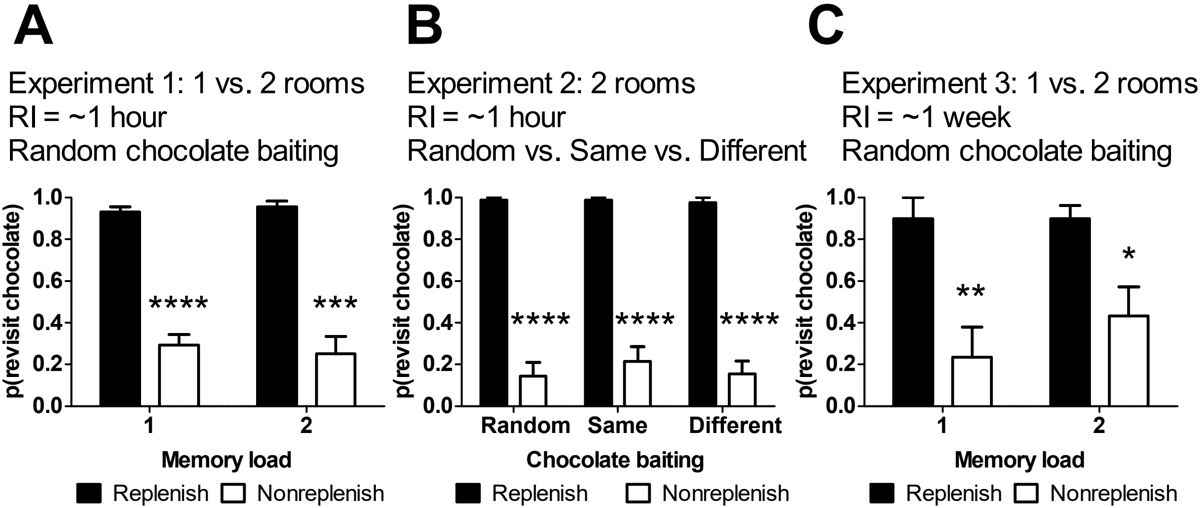


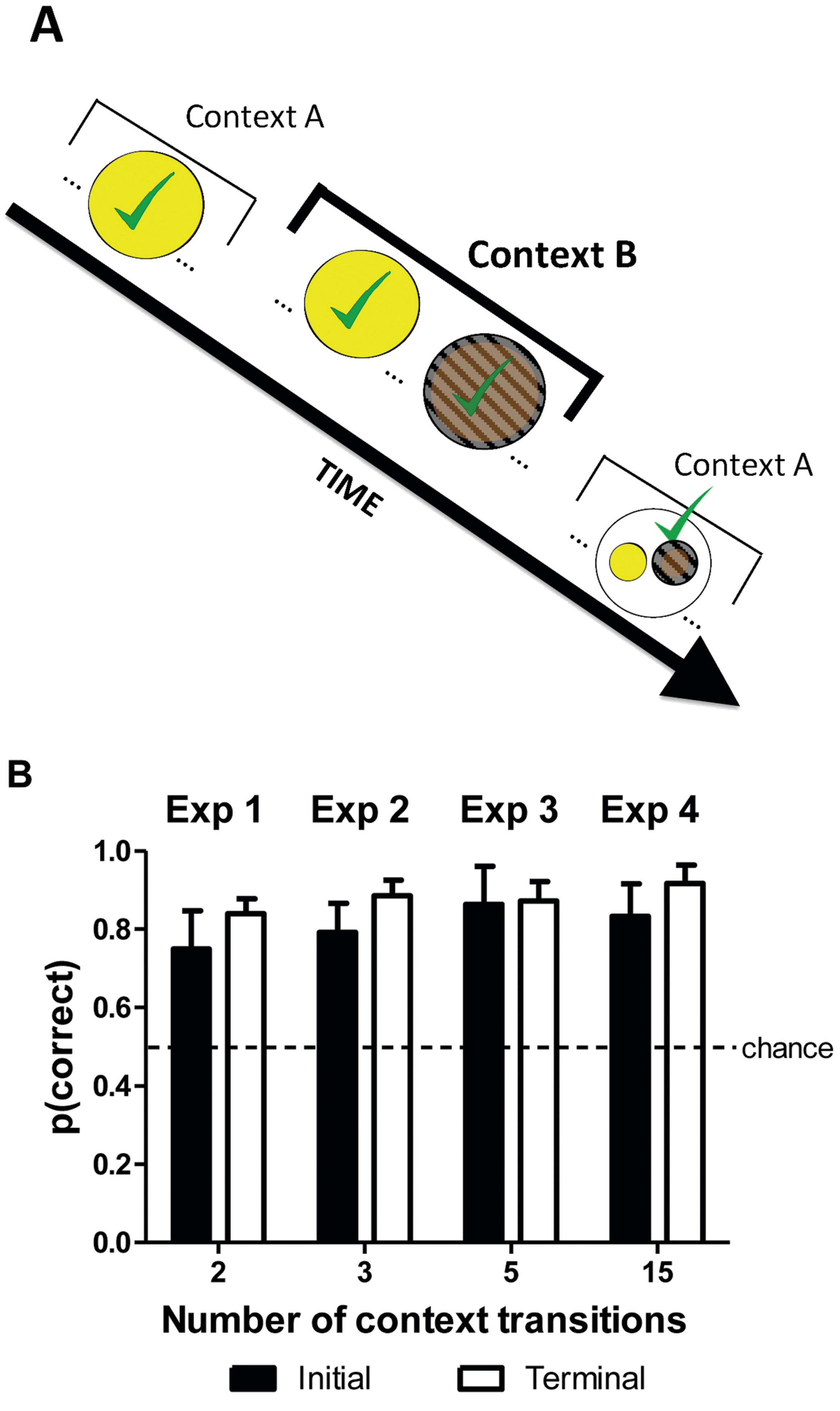
</td>
</tr>
<tr>
<th>Proposed Memory Representation (Unbound Features)</th>
<th>Tests in Rooms A and B</th>
</tr>
<tr>
<td>Room A
Room B
Chocolate-1
Chocolate-7
Self-generated-1
Self-generated-7
Experimenter-generated-1
Experimenter-generated-7
Chow-2
Chow-3
Chow-5
Chow-6</td>
<td>Very poor performance:
p(revisit replenish) =
p(revisit nonreplenish)</td>
</tr>
</table>

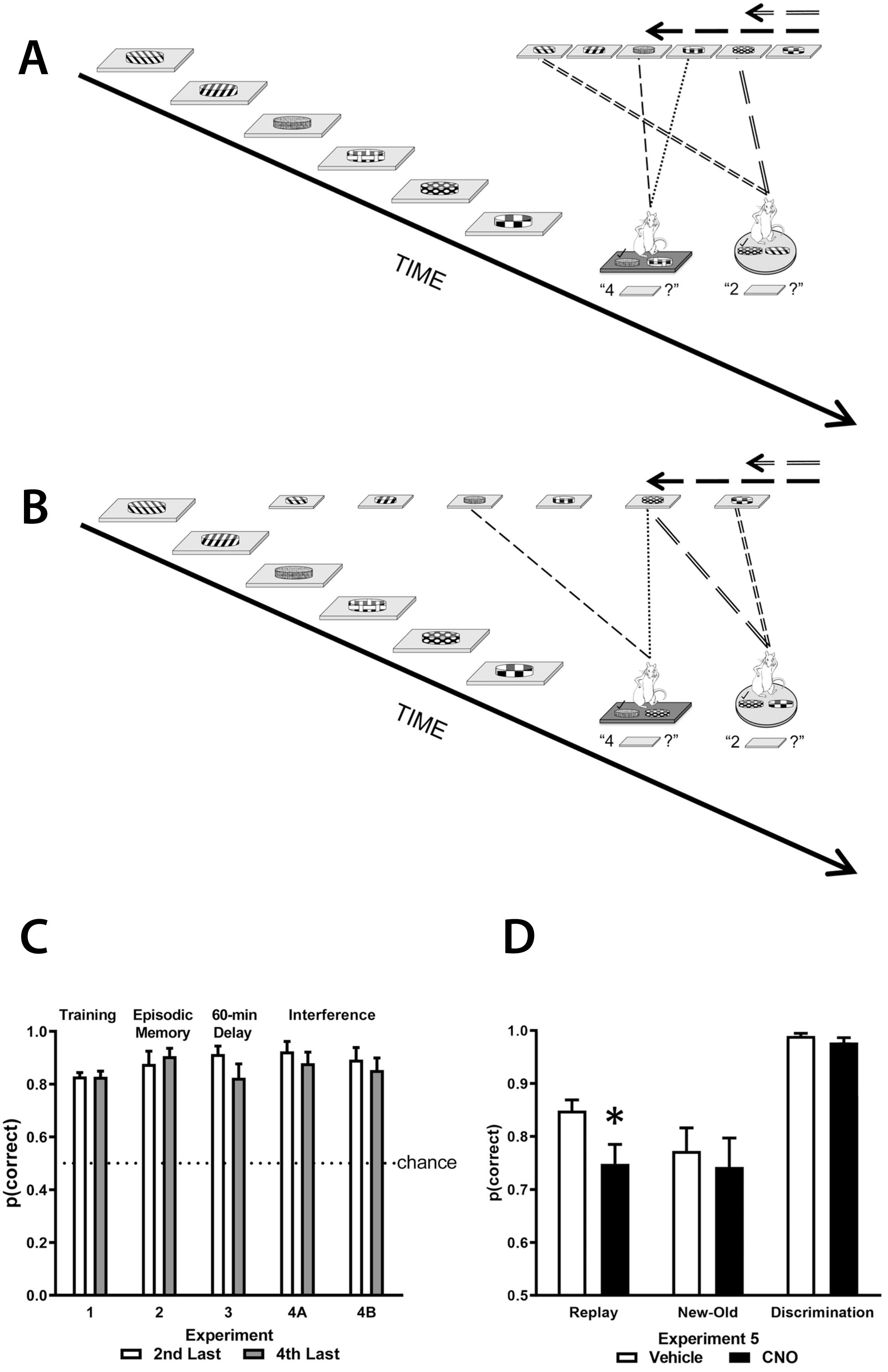


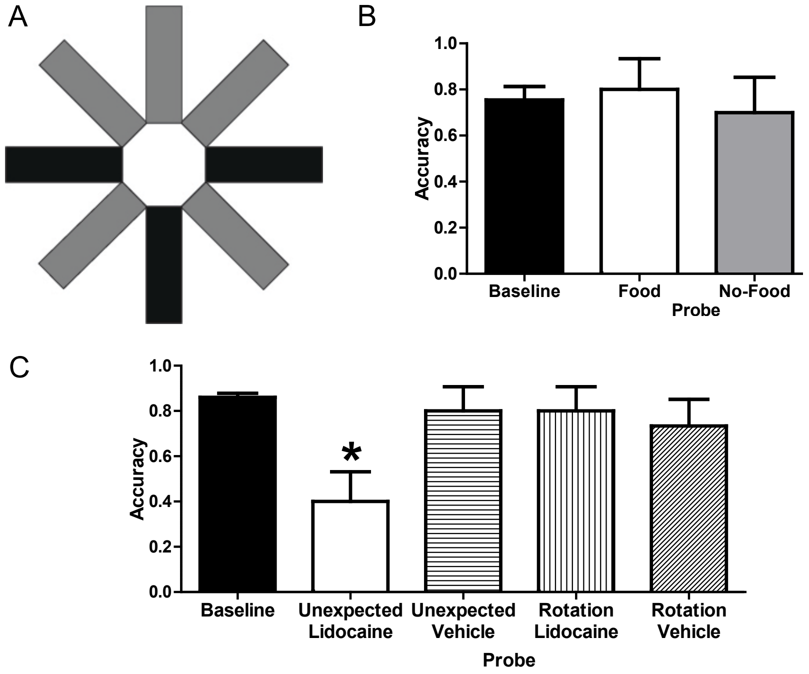
Experiment 1: 1 vs. 2 rooms
RI = ~1 hour
Random chocolate baiting

Experiment 2: 2 rooms
RI = ~1 hour
Random vs. Same vs. Different

Experiment 3: 1 vs. 2 rooms
RI = ~1 week
Random chocolate baiting


A
Context A
Context B
TIME
Context A
B
Exp 1
Exp 2
Exp 3
Exp 4
1.0
0.8
0.6
0.4
0.2
0.0
p(correct)
chance
2
3
5
15
Number of context transitions
Initial
Terminal


A
TIME
“4 ?”
“2 ?”
B
TIME
“4 ?”
“2 ?”
C
Training
Episodic Memory
60-min Delay
Interference
p(correct)
1.0
0.8
0.6
0.4
0.2
0.0
chance
1
2
3
4A
4B
Experiment
2nd Last
4th Last
D
1.0
0.9
0.8
0.7
0.6
0.5
p(correct)
*
Replay
New-Old
Discrimination
Experiment 5
Vehicle
CNO


A
B
1.0
0.8
0.6
0.4
0.2
0.0
Accuracy
Baseline
Food
No-Food
Probe
C
1.0
0.8
0.6
0.4
0.2
0.0
Accuracy
*
Baseline
Unexpected Lidocaine
Unexpected Vehicle
Rotation Lidocaine
Rotation Vehicle
Probe