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ANIMAL MODELS OF SOURCE MEMORY

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Source memory is the aspect of episodic memory that encodes the origin (i.e., source) of information acquired in the past. Episodic memory (i.e., our memories for unique personal past events) typically involves source memory because those memories focus on the origin of previous events. Source memory is at work when, for example, someone tells a favorite joke to a person while avoiding retelling the joke to the friend who originally shared the joke. Importantly, source memory permits differentiation of one episodic memory from another because source memory includes features that were present when the different memories were formed. This article reviews recent efforts to develop an animal model of source memory using rats. Experiments are reviewed which suggest that source memory is dissociated from other forms of memory. The review highlights strengths and weaknesses of a number of animal models of episodic memory. Animal models of source memory may be used to probe the biological bases of memory. Moreover, these models can be combined with genetic models of Alzheimer's disease to evaluate pharmacotherapies that ultimately have the potential to improve memory.

Key words: source memory, episodic memory, animal model, retention interval, unexpected question, incidental encoding, Alzheimer's disease, aging, rat

Memory enables information to be stored and retrieved after seconds to years and is essential for daily life. Elements of episodic memory include memory for features of specific unique events, such as what happened, where it took place, and when in time the event occurred (i.e., what-where-when memory) (Nyberg et al., 1996; Tulving, 1972). Source memory is the aspect of episodic memory that encodes the origin (i.e., source) of information acquired in the past (Johnson, Hashtroudi, & Lindsay, 1993; K. J. Mitchell & Johnson, 2009). Source memory refers to memories about the conditions under which information was acquired (Johnson et al., 1993; Mitchell & Johnson, 2009). Episodic memory typically involves source memory because those memories focus on the origin of representations (Johnson, 2005; McDuff, Frankel, & Norman, 2009). Importantly, 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).

We recently developed an animal model of source memory using rats. This article reviews the development of the animal model of source memory. Next, we review research that suggests that source memory is dissociated from other forms of memory. Finally, other approaches that focus on animal models of episodic memory are reviewed to highlight strengths and weaknesses of approaches, including the source memory model.

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Source Memory in Rats

We documented that rats remember the source of encoded information (Crystal & Alford, 2014; Crystal, Alford, Zhou, & Hohmann, 2013; Crystal & Smith, 2014). In our approach, rats foraged for distinctive flavors of food that replenished or failed to replenish at its recently encountered location according to a source-information rule in a radial maze (Fig. 1); we literally manipulated the source (i.e., origin) of information about eating chocolate pellets. The source memory of eating chocolate pellets was manipulated by the experimenter by placing the rat at the food trough of an arm which dispensed chocolate (i.e., an experimenter-generated event), whereas the rat encountered chocolate on its own at a food trough on a different arm (i.e., a self-generated event); these arms were randomly selected and rats discovered chow-flavored pellets at two other randomly selected arms. After a retention interval, the rats discovered chow-flavored pellets at the other

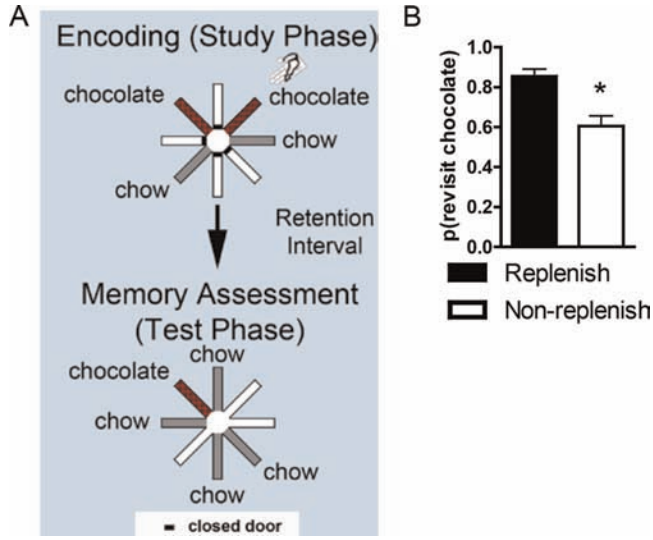

Fig. 1. Source memory is shown by a higher revisit rate to the replenishment than nonreplenishment chocolate location. **A**. Schematic of procedure. Two locations (randomly selected on each trial; shown in red or dark grey if printed in B&W) provide chocolate in the study phase—one is encountered when 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**. Rats ($n = 16$) 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. * $p < .01$. (Adapted from: Crystal, Alford, Zhou, & Hohmann, *Current Biology*, 2013)

four arms. The arm where the rat discovered chocolate on its own 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 (Fig. 1A); in other experiments, the replenishment contingency was reversed. Chow-baited locations never replenished. Thus, the rat needed to remember the source of chocolate (i.e., self-generated vs. experimenter-generated information). Rats revisited the replenishment location at a higher rate than the nonreplenishment location while avoiding revisits to chow locations (Fig. 1B). 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).

To establish the generality of source memory, we have used a number of variations (Crystal et al., 2013) on the basic approach outlined above. In one experiment, we reversed the replenishment contingency; rats that had initially been trained to return to locations with self-generated chocolate were subsequently trained to return to locations with experimenter-generated chocolate. In this experiment, we again observed a higher revisit rate to the replenishment location, now defined by the opposite set of encoded features.

In another experiment, we tested the hypothesis that rats relied on memorized cues (e.g., handling, flavor, specific locations, and replenishment) to solve the source memory task; according to this view, the rats have memorized a complete list of all combinations of cues that predict replenishment (i.e., they memorize the replenishment X encounter-contingencies for specific locations). Accordingly, when the rats perform well on the source memory task, it is because they have found a match between the currently presented cues and a "table-look-up" of previously presented cues and a memory of the corresponding correct choices (revisit the replenishment location and avoid revisits to the nonreplenishment location). If the rats relied on cues that

they had learned to use over repeated trials in the initial room, then the rats would be expected to fail to transfer to a novel room (i.e., when presented with an opportunity to encode a novel combination of cues). An alternative hypothesis is that the rats used source memory information flexibly based on the event that occurred at encoding; according to this latter view, the rats would be expected to transfer their source-memory performance to a novel room.

To this end, we deprived the rats of a critical piece of information: that is, the specific locations that they had learned about in the original training room. To test the memorization hypothesis, we conducted a transfer test to a novel room with different extramaze cues using rats that had been trained in another room. Critically, because the rats did not have an opportunity to memorize the replenishment X encounter contingencies at locations in the novel room, rats in the novel room could not rely on memorization when deprived of extramaze cues from the initial room used in training. Therefore, if rats had relied on memorization to solve the source memory task in earlier experiments, then in the novel room they would visit the chocolate location at equivalent rates in replenishment and nonreplenishment conditions (failure to transfer to the novel room). Alternatively, if the rats had learned a source-information rule, then in the novel room they would visit the chocolate location preferentially in the replenishment condition (i.e., successful transfer). We observed successful transfer when performance was assessed in a novel room (i.e., the rats preferentially revisited the chocolate location when it was about to replenish). The observation that rats could differentiate between self-generated and experimenter-generated encounters of food in a novel context is consistent with the hypothesis that rats monitor source information.

In a further experiment, we showed that temporary inactivation of the CA3 region of the hippocampus selectively eliminated source memory, suggesting that source memory is dependent upon an intact hippocampus. The hippocampus is posited to be a critical processing center in source memory (Davachi, Mitchell, & Wagner, 2003; Eichenbaum, Yonelinas, & Ranganath, 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).

To test the hypothesis that our behavioral task requires source memory, we asked whether it was similarly hippocampal-dependent. If our behavioral task requires source memory and that memory is hippocampal-dependent, then temporary inactivation of the hippocampus should impair the ability of rats to selectively revisit the replenishment chocolate location at a higher rate than the nonreplenishment chocolate location. The CA3 region of the hippocampus is postulated to mediate short-term elements of episodic memory (Hunsaker, Lee, & Kesner, 2008; Kesner, Hunsaker, & Warthen, 2008; Li & Chao, 2008; Zhou, Hohmann, & Crystal, 2012). Therefore, stainless-steel guide cannulae were implanted bilaterally above the CA3 region of the hippocampus to enable us to temporarily inactive this region using infusions of lidocaine. After surgery, we reestablished baseline source memory accuracy, demonstrating that surgical procedures alone did not disrupt performance. Next, to evaluate the impact of temporary inactivation of CA3, lidocaine or vehicle was infused before the encoding phase.

Although the rats revisited the replenishment chocolate location at a higher rate than the nonreplenishment chocolate location during baseline, this difference was eliminated after lidocaine infusion. By contrast, after vehicle infusions, rats revisited the replenishment chocolate location at a higher rate than the nonreplenishment location. General spatial memory (measured by accuracy in avoiding revisits to depleted chow-flavored locations) did not differ between lidocaine and vehicle conditions. These results suggest that temporary inactivation of the hippocampus eliminated source memory discrimination but not general spatial memory.

Dissociations of Memory

Source memory in our behavioral procedure is remarkably long lasting (Crystal & Alford, 2014; Crystal et al., 2013; Crystal & Smith, 2014). In our initial characterization of source memory, we discovered that source memory survives a retention-interval challenge of 7 days (see Fig. 2) (Crystal et al., 2013); note that the rats revisited the replenishment chocolate location

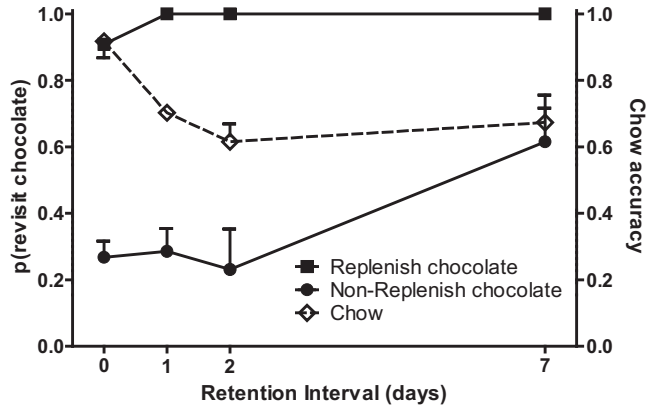

Fig. 2. Source memory and location memory are dissociated by different decay rates across retention intervals of up to 7 days. Source memory performance (indexed by more revisits to the replenishing chocolate location than to the nonreplenishing chocolate location; left axis) is unaffected by retention-interval challenges of up to 2 days, whereas location memory (indexed by chow accuracy, right axis) completes its decay over this same time period. Source memory errors occur when the retention interval challenge is 7 days. At this timepoint, rats revisit the nonreplenishing chocolate location. 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. (Adapted from: Crystal, Alford, Zhou, & Hohmann, *Current Biology*, 2013)

at a higher rate than they revisited the non-replenishment location.

We subsequently replicated the finding that source memory performance is intact after a 7-day retention interval (Crystal & Alford, 2014). We also examined performance after a retention interval of 14 days and found no evidence for source memory at that time point (Crystal & Alford, 2014). In a further study (Crystal & Smith, 2014), we selected a retention interval for each rat that degraded memory for spatial locations to a level not different from that expected by chance and verified intact source memory performance. At this time point (7 days, on average), source memory performance was intact; the two best-performing rats were tested with retention intervals of 11 days and showed intact source-memory performance. It is remarkable that item-specific information (self-generated encounter with chocolate at one arm and experimenter-generated chocolate at a different arm, randomly selected at each encoding opportunity) presented for a brief encoding opportunity is retained after delays between 1 and 2 weeks. The only other instance of item-specific information being retained for such long delays (i.e., 2 weeks) after a single presentation was reported in chimpanzees and orangutans (Martin-Ordas, Berntsen, & Call, 2013).

Memory systems can be dissociated by differential forgetting rates (Mitchell, 2006; Schacter & Tulving, 1994; Tulving, Schacter, & Stark, 1982). We have argued that source memory is dissociated from general spatial memory based on differential forgetting rates (Crystal & Alford, 2014; Crystal et al., 2013). We examined location memory (as indexed by accuracy in avoiding revisits to chow-depleted locations) using a wide range of delays between encoding and the memory assessment. In our experiments, general spatial memory decayed within 1-2 days (Crystal & Alford, 2014; Crystal et al., 2013; Crystal & Smith, 2014), which is similar to other reports for rats' spatial memory in standard radial maze experiments (Babb & Crystal, 2006a; Beatty & Shavalia, 1980b; Crystal & Babb, 2008). One way to highlight the dissociation is to note that general spatial memory decays markedly over the first 1-2 days of a retention interval, whereas there is no detectable decay in source memory over these retention intervals (see Fig. 2).

Although we have argued that differential forgetting functions dissociate memory systems, it is worth noting that the two tasks used different reward values. The source-memory task used multiple pellets of a preferred food flavor (chocolate), whereas the general-spatial-memory task provided access to a single

pellet of standard chow-flavored food at each location. Accordingly, enhanced performance in the source-memory task may stem from enhanced encoding/memory of a preferred reward, which we refer to as the reward-value hypothesis. We recently tested the reward-value hypothesis by comparing general-spatial memory accuracy using multiple chocolate or chow pellets at each location in a standard 8-arm radial maze task. Accordingly, the reward-value hypothesis predicts superior memory for high-valued rewards. We observed equivalent spatial memory accuracy for both flavors (Smith, Dalecki & Crystal, unpublished data). Moreover, a 24-hr retention interval produced an equivalent impairment in spatial-memory accuracy for both flavors (Smith, Dalecki, & Crystal, unpublished data). These data are inconsistent with the reward-value hypothesis and lend support to our interpretation of earlier data as documenting a dissociation of source memory and general spatial memory. Another possibility is that win–shift and win–stay strategies have differential forgetting curves. Further, it is possible that the comparison of two flavors produces improved memory (i.e., a contrast effect).

Binding

We used our source memory approach to test the hypothesis that rats remember episodic memories as bound (i.e., integrated) 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. According to an alternative hypothesis, memory consists only of unconnected features, which we refer to as the unbound-feature hypothesis; thus, the unbound-feature hypothesis proposes that source memory is one feature that is retrieved independently of the remaining features.

People remember an event as a coherent scene (Eichenbaum et al., 2007; Hasselmo & Eichenbaum, 2005; Staudigl & Hanslmayr, 2013; Tulving, 1983), which is thought to reflect binding of an integrated representation (Chalfonte & Johnson, 1996; Hannula & Ranganath, 2008; Newcombe, Balcomb, Ferrara, Hansen, & Koski, 2014; Staudigl & Hanslmayr, 2013). Binding functions to disambiguate similar episodes (i.e., episodes that share some, but not all, features) from one another. Previous research suggests that spatial memory in the rat is resistant to interference using a variety of interpolated events, including other spatial-memory tasks (Beatty & Shavalia, 1980a; Maki, Brokofsky, & Berg, 1979; Roberts, 1981). Therefore, we interpolated source memory information as an approach to test the binding hypothesis.

Rats were presented with the opportunity to encode multiple features of an event, including what-where-source-context features: *what* (food flavor), *where* (maze location), *source* (self-generated food seeking/running to the food site; or experimenter-generated food seeking/placement by the experimenter at the food site), and *context* (spatial cues in the room where the event occurred). The what-where-source encoding was provided in one room, followed immediately by a second what-where-source encoding in a second room. Next, the rat waited for the end of a retention interval delay. Finally, the trial continued with a memory assessment; during the memory assessment, one flavor replenished at the self-generated location but not at the experimenter-generated location independently in each room; the order of room presentations was counterbalanced across trials. For comparison, we assessed memory for one event by using our standard procedure in one context: 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, whereas the other event occurred in a different context. To produce potential interference, we used two identical radial mazes, with each arm pointing in the same orientation in two rooms that had similar geometric cues and a range of overlapping visual cues.

Although the precise mechanism by which rats may confuse events from two rooms is not known, a number of potential factors may contribute to making the two events similar, including: (1) orientation of the mazes, (2) global geometry of the rooms, (3) overlap of a subset of global landmarks in the room, and (4) baiting configurations of the mazes. Binding multiple events into separate episodic memories would allow a rat to disambiguate similar events (i.e., events with overlapping features). Thus, bound representations of separate episodes predict successful performance with both memory loads (higher revisit rate to the

replenishing than nonreplenishing chocolate location). By contrast, the unbound-feature hypothesis predicts that retrieving information about two relatively similar events is expected to produce interference between events if at least some of the features overlap. Thus, according to the unbound-feature hypothesis, it is not possible to fully disambiguate multiple interleaved episodes, and the probability of revisits would be predicted to be equal at replenishing and nonreplenishing chocolate locations.

The rats revisited the replenishing chocolate location in the memory assessment phase at a higher rate than the nonreplenishment chocolate location when we used a memory load of two rooms (Fig. 3A), at a level of proficiency similar to that observed when the memory load was one room (Crystal & Smith, 2014). We found that source-memory performance was resistant to interference from highly similar episodes (Fig. 3B) and survived long retention intervals (~1 week; Fig. 3C). These results suggest that multiple episodic memories are each structured as bound representations.

Animal Models

Any single animal model of memory is likely to be characterized by a pattern of strengths and weaknesses. Therefore, animal models of memory are strengthened by documenting multiple, converging lines of evidence (Crystal, 2009; Shettleworth, 1998). We have approached this problem by developing a number of animal models of episodic memory (Babb & Crystal, 2005, 2006a, 2006b; Crystal & Alford, 2014; Crystal et al., 2013; Crystal & Smith, 2014; Zhou & Crystal, 2009, 2011; Zhou et al., 2012). Below we highlight strengths and weaknesses of the source memory approach and describe other work that addresses the weaknesses.

One feature of source memory is its remarkable resistance to forgetting. We have documented (Crystal & Alford, 2014; Crystal et al., 2013; Crystal & Smith, 2014) memory of source information after retention intervals between 1 and 2 weeks, as described above, which is a notable level of performance for item-specific information. One line of evidence for resistance to interference comes from the ability to

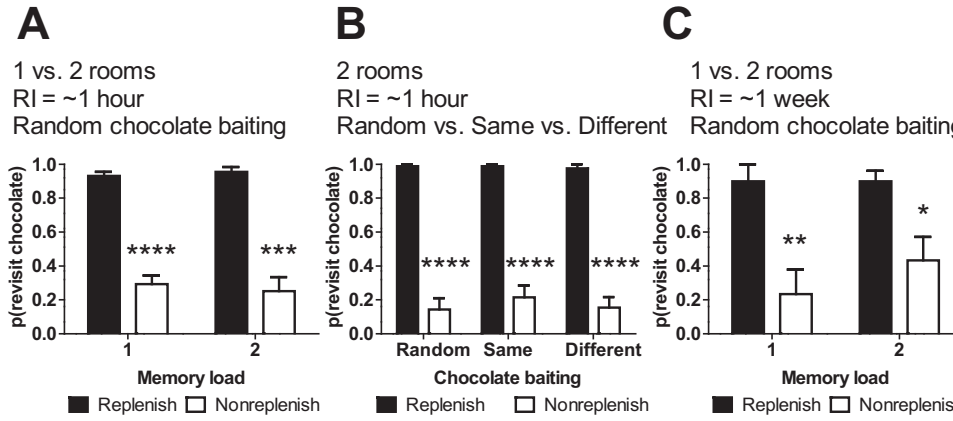

Fig. 3. Bound episodic memories function to disambiguate multiple, interleaved study episodes. Successful memory performance is shown by a higher revisit rate to replenishment than nonreplenishment chocolate locations. Rats visited two chocolate locations per study phase, one self-generated and one experimenter-generated. 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-hr) 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 random baiting in each room; the *Same* condition used the same orientation for replenishing and nonreplenishing chocolate arms in both rooms; the *Different* condition reversed the orientation of replenishing and nonreplenishing chocolate arms across the two rooms. (C) The memory load was 1 or 2 with a long (~1-week) retention interval. $n = 6$, 7, and 5 in (A), (B), and (C), respectively. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$, $^{****}p < .0001$. Data are mean with one 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)

disambiguate multiple, interleaved events, using a memory load of two events (Crystal & Smith, 2014). Nevertheless, there are also limitations to the source memory approach. Although we have increased the memory load from one to two events, it is logistically difficult to further increase the memory load. We used two computer-controlled radial mazes in two rooms, which limits our ability to evaluate the ability to interleave many more events. Other approaches have greater potential to substantially increase the memory load. For example, Fortin and colleagues (Fortin, Agster, & Eichenbaum, 2002; Fortin, Wright, & Eichenbaum, 2004) have examined the ability of rats to remember relatively long lists of odors. Branch and colleagues (Branch, Galizio, & Bruce, 2014) developed a method to assess what-where-when memory using many odors; one concern about this latter study is that it is not yet known if the rats remember location in each condition used in this approach.

One problem with many approaches to episodic memory in animals is that the training protocols generate expectations, which may lead to memory of a planned action (Singer & Zentall, 2007; Zentall, 2005, 2006; Zentall, Clement, Bhatt, & Allen, 2001). Zentall et al. (2001) have argued that when information is encoded for use in an expected test of retention, explicitly encoded information may be used to generate a planned action; thus, at the time of the test, the remembered action can occur successfully *without* remembering the earlier episode.

The central hypothesis of an animal model of episodic memory is that, at the moment of memory assessment, the animal remembers back in time to the event or episode; it is the focus on retrieving a memory of the earlier event that makes an animal model of episodic memory *episodic*. Thus, the ability to carry forward the information that is needed at a future test, while not specifically retrieving a memory of the earlier episode, is a serious threat to the episodic-memory hypothesis. Consequently, it is necessary to rule out the hypothesis that successful performance is based on a planned action generated when information was explicitly encoded, rather than a memory of the episode (Crystal, 2013; Singer & Zentall, 2007; Zentall et al., 2001; Zentall, Singer, & Stagner, 2008; Zhou & Crystal, 2011). Thus, it is possible that animals may have solved previous tests of episodic memory by using learned semantic rules without remembering the episode.

Formally, learned rules stored in semantic memory, a nonepisodic memory system devoted to storing generic facts (Tulving, 1993), could be used to generate a planned action. By contrast, when information is encoded incidentally, it is impossible to transform information into an action plan because the nature of the subsequent memory test is not yet known. Hence, accurate performance observed on an unexpected test after incidental encoding would suggest that this performance is based upon memory of the earlier episode (i.e., retrieval of an episodic memory) (Singer & Zentall, 2007; Zentall et al., 2001; Zentall et al., 2008; Zhou & Crystal, 2011).

We tested the hypothesis that rats can answer an unexpected question after incidental encoding (Zhou et al., 2012). In our approach, we enabled incidental encoding by embedding two different tasks within the same radial maze (Fig. 4A); a subset of arms were reserved for one task, and the other task used the remaining arms (shading appears in Fig. 4A to highlight allocation of specific arms to the two different tasks, but *all* arms in the actual maze were white).

In one task, the rats foraged for food (five-arm radial maze task) as in the standard eight-arm radial maze task (Olton & Samuelson, 1976), except only five arms were used (three arms were randomly selected from the set of five arms to be baited with a food pellet in the study phase; next, five arms were accessible and an additional pellet was baited at each of the two arms not yet visited during the daily trial); the five arms shown in grey in Figure 4A were reserved for the five-arm task. In the second task, the rats learned the "reporting" skill (T-maze task) that would be used later in the unexpected question task; the three arms shown in black in Figure 4A were reserved for the T-maze task. In the T-maze task, rats were rewarded for selecting a left/right turn after being presented with a sample of food or no-food, respectively; one arm was designated as the sample arm where the animals obtained a food (6-pellet) or no-food (0-pellet) sample after interrupting a photobeam in the sample arm; next the two choice arms were available, and additional food (6 pellets) could be obtained by a left or right turn (the rewarded turn was

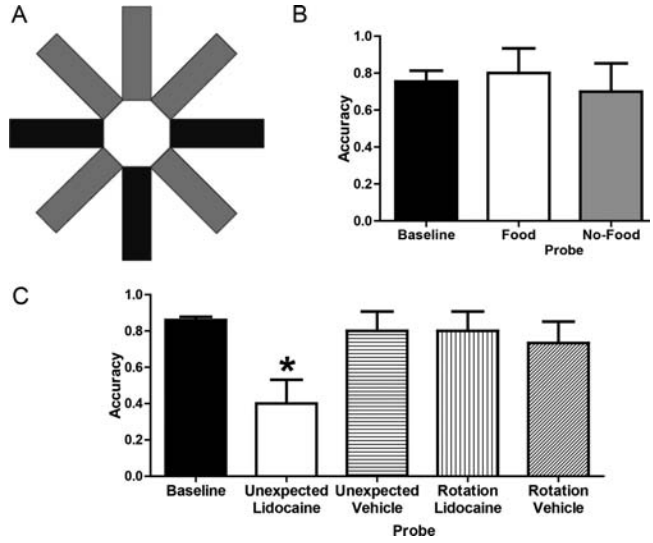

Fig. 4. **A**. Schematic of the radial maze with shading to illustrate assignment of arms to tasks. ***Baseline:*** The *T-maze task* used three arms (shown in black); the bottom-center black arm provided food (6 pellets) or no-food (zero pellet) samples and subsequent reward (6 pellets) was contingent 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 six T-maze or one 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° with respect to 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 ($n = 10$) was tested once in food and no-food probe conditions. Error bars represent 1 SEM. **C**. Temporary inactivation of CA3 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 five sessions before and five sessions after surgery. Each rat ($n = 15$) was tested once in each probe condition with the order determined by a Latin Square design (a total of four conditions per rat, with 1 week separating each probe injection). Error bars represent 1 SEM. $^{*}p < .01$ difference between the unexpected + lidocaine probe and baseline. (Adapted from: Zhou, Hohmann, & Crystal, *Current Biology*, 2012)

contingent on the identity of the sample food vs. no food and was counterbalanced across rats).

Terminal accuracy in the five-arm and T-maze tasks was 80%. To assess the ability of rats to answer an unexpected question, we allowed rats to forage for food in the five-arm radial maze task (using the three top arms show in Fig. 4A), thereby affording them the opportunity to incidentally encode either the presence (food probe) or the absence (no-food probe) of food. After the rat exited one of the top arms in Figure 4A, the rat was confronted with the opportunity to report in the T-maze task (via its left/right turn into an arm shown as black in Fig. 4A) whether it remembered encountering the presence or absence of food in the five-arm task; the uninterrupted transition from the five-arm task foraging to a T-maze choice phase was possible because the two tasks were embedded in the same radial maze.

A rat that incidentally encoded the availability of food would be able to successfully answer an unexpected question by retrieving a memory of the earlier episode. By contrast, a rat without episodic memory would be unable to answer an unexpected question after incidental encoding; hence, the probability of left and right turns should be equally likely in the absence of episodic memory. The rats answered the unexpected question with a level of accuracy similar to that observed in training (Fig. 4B).

To test the hypothesis that answering an unexpected question requires episodic memory,

we inquired whether it is hippocampal-dependent. 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 without impacting the ability to answer an expected question.

To assess accuracy in answering an unexpected question, we used a no-food probe. To assess accuracy in answering an expected question, we used a control procedure (rotation probe) that combined elements of the T-maze task while equating other features of the no-food 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, this control procedure can be solved by remembering a planned action without remembering the episode; because the rotation probe can be solved without remembering the episode, we expect 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, using the top-center arm shown in Fig. 4A); 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 absence of food.

Next, we surgically implanted cannulae bilaterally above the CA3 region of the hippocampus to temporarily inactivate this region with lidocaine. Accuracy was reestablished following surgical recovery, demonstrating that surgery did not disrupt performance. Following local infusion of lidocaine bilaterally into CA3, accuracy in answering the unexpected question was significantly reduced relative to baseline (Fig. 4C), whereas accuracy in answering the expected question was not impaired. 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 (Fig. 4C). Accuracy in answering an unexpected question was impaired by infusion of lidocaine relative to vehicle infusion.

Rats may report the availability of food using either of two strategies. The T-maze task can be solved by a response-mediated strategy in which the rat makes a turning response after sample presentation (e.g., food → turn left). An alternative way to solve the task is to use a spatially mediated strategy in which the rat navigates to a place on the maze after sample presentation (e.g., food → left side of maze). In T-maze training, these two strategies led to equivalent performance (i.e., they were confounded). By rotating the sample position in the probes, these two strategies were unconfounded, thereby dissociating response- and spatially mediated strategies. Indeed, it has previously been shown that response- and spatially mediated strategies are concurrently available and are mediated by different neural systems involving the hippocampus and dorsolateral striatum, respectively (De Leonibus et al., 2011; Packard, 1999, 2009; Packard & Knowlton, 2002; Packard & McGaugh, 1996; White & McDonald, 2002; Yin & Knowlton, 2004, 2006); with extended training, rats shift from a hippocampal-dependent spatial strategy to a striatal-dependent response strategy (De Leonibus, et al., 2011; Packard, 1999, 2009; Packard & Knowlton, 2002; Packard & McGaugh, 1996; White & McDonald, 2002; Yin & Knowlton, 2004, 2006).

Our data are consistent with the hypothesis that rats used a response-mediated strategy, as expected (De Leonibus, et al., 2011; Packard, 1999, 2009; Packard & Knowlton, 2002; Packard & McGaugh, 1996; White & McDonald, 2002; Yin & Knowlton, 2004, 2006). Performance on probes (excluding impaired performance in the unexpected question following lidocaine infusion) was significantly above chance with respect to a response-mediated strategy (0.77 ± 0.04, mean ± SEM); this level of performance is below chance performance with respect to a spatial strategy.

In summary, the suppressive effect of lidocaine on memory was selective for unexpected questions. Accuracy was significantly reduced in the unexpected- relative to expected-question conditions following lidocaine infusion. Importantly, impairment in answering the unexpected question was selective to inactivation of the hippocampus with lidocaine when an episodic memory needed to be retrieved.

It is noteworthy that the delay between encountering food or no food and subsequently

answering the unexpected question was quite short (12.0 ± 1.2 seconds; using probe data from Fig. 4B). Although it is likely that the delay could be increased using the unexpected-question approach, it is unlikely that discovering the presence or absence of food would be retained over long delays like those reported in the source memory approach.

Conclusions

This review highlights the feasibility of studying source memory in nonhumans. Animal models of source memory may be used to probe the biological bases of memory. Research of this type opens the door to combining a deep understanding of biological mechanisms with animal models of human cognition to advance translational research that may ultimately foster the development of therapeutic approaches to severe human memory disorders (Crystal, 2012; Crystal & Glanzman, 2013).

Source memory (and episodic memory, more broadly) is impaired in Alzheimer's disease and normal aging (Bäckman et al., 1999; Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Egerhazi, Berecz, Bartok, & Degrell, 2007; Kessels, Hobbel, & Postma, 2007; Le Moal et al., 1997; Liscic, Storandt, Cairns, & Morris, 2007; McDonald et al., 2006; Morcom & Friston, 2012; Nestor et al., 2007; Piolino, Desgranges, Benali, & Eustache, 2002). Therefore, a better understanding of normal and impaired episodic memory offers the potential to develop targeted pharmacological, molecular, and genetic treatments for cognitive decline that afflict normal and disordered aging (Anand, Gill, & Mahdi, 2014; Huang & Mucke, 2012; Karran, Mercken, & Strooper, 2011; Kim, Basak, & Holtzman, 2009; Liu, Kanekiyo, Xu, & Bu, 2013; Yu, Tan, & Hardy, 2014).

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