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Replay of incidentally encoded episodic memories in the rat

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Highlights

- We remember info even though it was seemingly unimportant when it was encountered
- Remembering a stream of events from the past is a key aspect of remembering
- Rats replay incidentally encoded info in an unexpected test of episodic memory
- We document a critical aspect of human episodic memory in a nonhuman animal

eTOC

Sheridan et al. show that rats encode multiple pieces of putatively unimportant information and later replayed a stream episodic memories when that information was needed to solve an unexpected problem. They conclude that the cognitive building blocks needed to replay a stream of episodic memories is quite old in the evolutionary timescale.

Summary

Although events are not always known to be important when they occur, people can remember details about such incidentally encoded information using episodic memory. Importantly, when information is explicitly encoded for use in an expected test of retention (as in most assessments in animals), it is possible that it is used to generate a *planned action*[1-3]; thus, the remembered action can occur *without remembering the earlier episode*. By contrast, when a test is unexpected, transforming information into an action plan is unlikely because the importance of the information and the nature of the test are not yet known. Thus, accurate performance in an unexpected test after incidental encoding documents episodic memory[1-8]. Here, we present evidence that rats replay episodic memories of incidentally encoded information in an unexpected assessment of memory. In one task[9], rats reported the third last item in an explicitly encoded list of trial-unique odors. In a second task[10], rats foraged in a radial maze in the absence of odors. On a *critical test*, rats foraged in the radial maze, but *scented lids* covered the food. Next, memory of the third last odor was assessed. All participating rats correctly answered the unexpected question. These results suggest that rats encode multiple pieces of putatively unimportant information, and later they replayed a stream of episodic memories when that information was needed to solve an unexpected problem. We propose that rats replay episodic memories of incidentally encoded information, which documents a critical aspect of human episodic memory in a nonhuman animal.

Results and Discussion

In many situations, we can remember events that happened to us in the past even though the information was seemingly unimportant at the time we encountered it (e.g., what interesting activities did you do last weekend?). The ability to remember a stream of events that occurred in the past is a key aspect of remembering[11-13]. An important feature of this type of remembering is that we often did not know that the information surrounding the event would be called upon later to be remembered. This type of remembering consists of incidental encoding (the information was not known to be important enough to explicitly encode into memory) followed by an unexpected assessment of memory[1-3]. Moreover, the sequence of events is often critical to understanding the remembered scenario (e.g., the order of events in a hit-and-run accident). Accordingly, vivid episodic memories in people have been characterized as the replay of unique events in sequential order[11-13]. Neurophysiological studies of place cells in the hippocampus of rats have documented the sequential reactivation of neuronal coding for where events occurred (transient, brief, high-frequency network oscillations, described as sharp wave ripple complexes, or SWRs;), a phenomenon known as *hippocampal replay*[14-20]. Previously we provided behavioral evidence that rats remember multiple unique events in episodic memory[9,21,22] and proposed that rats search the content of episodic memory to find items that occurred in a particular ordinal position within a list of items[9], a phenomenon that we call *replay of episodic memory*[1,9]. Although we use the terminology replay of episodic memory in rats and have shown that such searching of episodic memory is hippocampal dependent[9], we do not claim that SWRs of hippocampal replay are involved in searching episodic memory. Notably,

although there are some suggestions that hippocampal replay may be implicated in memory[23-27], neurophysiological evidence that hippocampal replay involves actively searching memory to guide future behavior is currently lacking[23,28,29].

A notable feature of our work is that it measures behavior that was not specifically made in response to a previously trained scenario. Most approaches to modeling episodic memory in nonhumans involve some degree of training. Because the animal receives multiple rounds of related experiences, it may detect that newly encountered information is important (warranting explicit encoding into memory, which may be subserved by forming a prospective memory[30-35]). Moreover, it may anticipate that this information will be needed in a later assessment of memory. Such approaches are akin to studying for an upcoming test. Notably, when we study for a test, we often retain the to-be-studied information without remembering the details of the study episode. Furthermore, explicitly studying for an expected test of memory is unlike naturally occurring situations such as remembering innocuous activities that recently occurred.

Consequently, an important feature of our work is that it rules out non-episodic solutions to our findings. Training animals to explicitly encode and report information in expected assessments of memory raises the possibility that non-episodic memory solutions, in the absence of episodic memory, may be used to solve the memory problem. If at the time of encoding information, an animal can anticipate that the presented information is relevant to a future test of memory, then the animal could use a non-episodic memory trace to preselect a planned action. At the time of the test, the animal may use the planned action without remembering back in to time to retrieve an episodic memory. The possibility just described is a major threat to the episodic-

memory central hypothesis that an animal remembers back in time to a specific earlier event or episode[1-3]. By contrast, when information is incidentally encoded and assessed in a subsequent unexpected test, transforming information at encoding into a planned future action is unlikely. You cannot plan a future action when you do not know that the information is important and you do not know the nature of the unexpected test of memory.

We prepared to assess incidental encoding by first training rats in two separate tasks (Figure 1A-B). In one task, rats were trained to identify items that were the third to last item in a recently presented list[9] (Figure 1A). In our approach, rats were presented with a list of trial-unique odors and later were rewarded for selecting items that were previously encountered in a distinct ordinal position from the end of the list. Rats were tested in two distinctive arenas with “food holes” covered by scented opaque lids in training (STAR Methods). Each list consisted of 4-11 trial-unique odors in a distinctive encoding context (referred to as the “list encoding”). Notably, because the length of the list was unpredictable, the rat could not predict when the list would end until the rat was moved to a different context. Immediately following the list presentation, the rat was presented with a memory assessment. In the distinctive memory assessment context, the rat was confronted with two odors from the list (referred to as the “list memory assessment”). The correct odor was the third to last item in the list, and the incorrect odor was from a different ordinal position in the list. The rat was rewarded for selecting the third to last item in the list. Because the rats received training in this task, it may involve explicit encoding of information for the purpose of answering an expected question.

In the second task, rats foraged for food in an eight-arm radial maze[10] (Figure 1B). Food was available at the end of each runway, covered by *unscented* plastic lids. Initial foraging was restricted to four accessible baited arms (referred to as the "study phase"). Next, all eight arms were accessible (referred to as the "test phase"), and food was only available in arms that had not yet been visited. Accurate performance in the test phase was documented by visits to baited locations while avoiding the locations that were already depleted of food (STAR Methods). When a rat forages in a study phase, it likely expects the continuation of foraging in the test phase. Moreover, it is well established that rats remember maze locations with respect to the global geometry of the room [36-39], which may consist of visited and/or not-yet-visited locations[30,31].

Our approach to provide an opportunity for incidental encoding is to allow rats in a critical test to forage in the radial maze with scented lids unexpectedly covering food cups, followed by a memory assessment for odors encountered in the maze. However, a non-episodic memory solution available to the rats comes from stimulus generalization (i.e., treating odors in the new condition like they did in the earlier trained condition). To address this issue, we conducted a control condition to give the rats an opportunity to generalize to a novel context. The objective of our control condition is to determine if rats generalize or fail to generalize in a novel context. If the rats fail to generalize in the control condition, then it is unlikely that they generalized in the novel situation in our critical test. In our control condition (Figure 1C, STAR Methods), the rats received a list of odors in the usual list encoding context (List 1), followed by a list of odors in a novel context (List 2; another arena with distinctive features), followed by a memory assessment with a choice between the third last odor in List 1 and the third last

odor in List 2. If rats automatically encode odors for the purpose of an upcoming test (stimulus generalization), then the rats would choose the odor from List 2 (literally the third last odor). In contrast, if the rats do not automatically encode odors for the purpose of an upcoming test (failure of stimulus generalization), then the rats would be expected to choose the odor from List 1 (which occurred in the arena that corresponds to the original list encoding task). We note that this latter option is unlikely if rats automatically encode odors for the purpose of taking a future test of memory using stimulus generalization because the actual third last item occurred in List 2. Our data indicate that 100% of rats tested in the control condition selected the odor from List 1 and 0% selected the odor from List 2 (Figure 2, binomial test, $n=7$, $p < 0.01$). Accuracy with respect to stimulus generalization was disrupted (0% relative to the baseline performance of 91%, dashed line in Figure 2), documenting a failure of generalization. The failure to document the use of automatic encoding of odors for the purpose of an upcoming test in the control condition makes it unlikely that automatic encoding of odors occurred in the critical test.

To generate incidental encoding, we allowed rats to forage in the radial maze, but *scented lids* covered the food cups *on a single occasion* (Figure 1D). Next, instead of being placed back into the radial maze for a test phase, the rats were immediately and unexpectedly confronted with a list memory assessment (the opportunity to report the third to last odor from the radial maze) also *on a single occasion* (STAR Methods). Prior to this test, the rats never encountered scented lids while foraging in the radial maze, and they were never presented with a list memory assessment after foraging in the radial maze; thus, the rats could not know that the odors in the radial maze were

important or that they would be asked about the maze odors in the future; moreover, the scented lids in the radial maze are incidental to foraging for food[40]. A rat that can replay incidentally encoded episodic memories would be able to successfully answer the unexpected question by searching memory of the sequence of odors encountered in the maze. By contrast, a rat without the ability to replay incidentally encoded episodic memories would be unable to answer an unexpected question after incidental encoding (producing chance accuracy, 0.5).

When rats were asked to identify the ordinal position of items from the list (STAR Methods), rats selected the third to last item at a high level of accuracy above chance (Figure 3. List training, $t(8) = 23.8$, $p < 0.001$). When rats encountered odors while foraging on the radial maze and their memory for the order of encountered odors was immediately assessed, all participating rats correctly answered the unexpected question (Figure 3. Radial maze test; binomial test, $n=9$, $p < 0.01$). Notably, the data for the critical test in Figure 3 come from a single test conducted with each rat; thus, the data were obtained *before the opportunity for new learning*. These results are consistent with the hypothesis that rats can replay a stream of unique events that were not known to be important when the events were encountered and report this information when unexpectedly asked to search episodic memories.

We present six lines of evidence that collectively provide a compelling case for replay of incidentally encoded episodic memories in the rat: First, during initial training, rats never encountered scented lids while foraging in the radial maze. Second, displacing lids and eating are incidental to efficient navigation in the radial maze[40]. In addition, the list memory assessment after foraging in the radial maze is a novel

situation. Third, if incidental encoding followed by an unexpected question can be answered without the use of episodic memory, then hippocampal inactivation would equivalently affect unexpected and “expected” tests, which is contrary to our published data using unexpected and expected questions[3]. Fourth, we provide data using only a single critical list memory assessment for each participating rat (data were obtained before the opportunity for new learning). Fifth, four lines of evidence suggest that it is unlikely that rats relied on working memory in the absence of episodic memory to solve the list task[9] (Table S5 and STAR Methods). Finally, in a complimentary experiment (STAR Methods), we show that the ability to answer an unexpected question after incidental encoding is retained under a modest delay, which is consistent with the view that episodic memory is an aspect of long-term memory[41]. After conducting the primary experiment above (with a 0-minute delay between the end of the list and the memory assessment), we increased the delay to 15 minutes (STAR Methods). When rats encountered odors while foraging on the radial maze and their memory for the order of encountered odors was assessed after a 15-minute delay, all participating rats correctly answered the unexpected question (Figure 4; binomial test, $n=8$, $p < 0.01$). Moreover, our data cannot be explained by the ability of the rats to detect the presence of food pellets under scented lids because we placed an equal number of pellets below correct and incorrect lids in all memory assessments (STAR Methods).

It is unlikely that stimulus generalization explains our data. If rats automatically encoded odors for the purpose of taking an upcoming test of memory, then rats in the control condition would have selected the third last item from List 2, which is contrary to our data (Figure 2). The failure to document the use of automatic encoding of odors for

the purpose of an upcoming test in the control condition makes it unlikely that automatic encoding of odors occurred in the critical test. The control condition is a conservative test of generalization because the two arenas used in the control condition are more similar to each other than are the radial maze and list encoding arena; in any case, rats readily discriminate these arenas and maze based on our earlier studies which used these pieces of equipment[9,22,42].

Why did the rats in the control condition not demonstrate incidental encoding of the novel second list? We propose that the rat interpreted the list memory assessment context in the control condition as "what scented lid was in the third last position in the *list training context?*" We designed the control condition to pit explicit encoding of an initial list in the trained list-encoding context against stimulus generalization in a novel context. We arranged for the list encoding context of List 1 to correspond to the list memory assessment context based on earlier training, whereas the novel context had never been paired with the list memory assessment context. In this situation, the prepotent response to choose with respect to the trained encoding context triggers retrieval of information presented in the trained list encoding context (List 1). Our proposal is consistent with our earlier work that showed that list memory is resistant to retroactive interference[9]. We hypothesize that incidental encoding may have occurred in the control condition, but the List 1 choice was selected because the List 1 encoding context provided the strongest match to the memory assessment context. We offer this proposal as a hypothesis to be explored in future research. By contrast, a different situation occurred in the critical test. In the critical test, because only a single list encoding context was used and both odors appeared in the list, a prepotent response

would not influence selection of an odor. In this situation, the rats selected the best choice from the available options (a third last item is better than a non-third last item) despite the lack of the trained list encoding context.

We randomly sampled without replacement each day from a large pool of 67 odors to select odors for use in lists in training, control, and 0- and 15-min test conditions. Although it is unlikely that a specific sequence of odors in the radial maze was previously presented to the rat in earlier training, the familiarity of specific odors may increase the likelihood that it generalizes from training to test conditions. However, if familiarity of specific odors or other factors led rats to generalize, rats would have selected the List 2 odor in the control condition, which is contrary to our data (Figure 2). Nonetheless, future studies would benefit from using non-overlapping sets of odors in training and testing conditions to reduce the likelihood that a familiar odor promotes generalization. In addition, given the high accuracy on 0- and 15-min tests after experiencing non-odorized lids in radial maze training, future studies may explicitly train animals to ignore odors during radial maze training to determine if rats also remember when encountered odors are known to be irrelevant rather than unexpected. Additional future directions may focus on introducing proactive interference during training, for example, by repeating odor locations within a trial, repeating odor types within sessions, or varying the size of the odor pool[43,44].

We observed a modest increase in accuracy in the radial maze test relative to prior training in Figure 3; the small increase in Figure 4 may have been limited by training accuracy that had reached a near ceiling level of performance. A variety of factors may explain the increase in accuracy in the radial maze, including novelty[45] of scented lids,

the active selection of the order of odors in the radial maze[46,47], and a release from proactive interference[44,48].

We propose that rats incidentally encode multiple pieces of putatively unimportant information, and later they replayed a stream of episodic memories when that information was needed to solve an unexpected problem. Our findings suggest that the cognitive building blocks needed to replay a stream of episodic memories is quite old in the evolutionary timescale, which suggests that replay of episodic memories predates, for example, the emergence of language. It is often assumed that key aspects of human cognition are unlikely to be profitably modeled in non-primates (e.g., [49-52]). The only way to test this hypothesis is to explore cognitive processes in non-primates. We have modeled a number of key of aspects of human cognition in rats, including for example: what-where-when memory[53], source memory[54], binding of episodic memories[21], retrieval practice[55], and prospective memory[56]. Together with evidence that rats replay incidentally encoded episodic memories, our approach supports the view that rats may be used to model fundamental aspects of human memory.

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Author contributions

Conceptualization, J.D.C. and C.S.; Methodology, J.D.C., C.S., and D.P.B.; Formal Analysis, C.S.; Investigation, C.S., S.L., M.K., C.A., R.L., B.T., J.S., A.W., and T.H.; Data Curation, C.S.; Writing – Original Draft, C.S. and J.D.C.; Writing – Review & Editing, C.S. and J.D.C.; Visualization, C.S.; Supervision, C.S., D.P.B., and J.D.C.; Project Administration, C.S. and J.D.C.; Funding Acquisition, J.D.C.

Declaration of interests

The authors declare no competing interests.

Figure Legends

Figure 1. Replay of episodic memories after incidental encoding in an unexpected assessment of memory.

Rats are presented with a list of trial-unique odors and trained to pick items that occupied the third last position from the end of the list (**A**). Separately, rats forage for food (encountered below unscented lids on a radial maze), (**B**). In a control condition (**C**), rats are presented with a list of odors in the usual list encoding context (List 1) and in a novel context (List 2), followed by a memory assessment with a choice between the third last items from Lists 1 and 2. On a critical test (**D**), rats forage on the radial maze but encounter food below scented lids. Next, rats are prompted to replay episodic memories to identify the third last odor encoded during foraging. Scented lids in the

radial maze provide a novel condition, never experienced in earlier training, and are incidental to foraging (*incidental encoding*). A list memory assessment after foraging is a novel situation (*unexpected test*).

Figure 2. Rats are sensitive to the contextual features in list presentation.

In list training (last six sessions of list training prior to the control condition test, left bar), rats were asked to identify the ordinal position of items from a list of odors presented in the usual list encoding context. In the control condition, the rats received a list in the usual list encoding context (List 1) followed by a second list in a novel encoding context (List 2), and finally a memory assessment with a choice between the third last items from Lists 1 and 2. In the control condition (on a single occasion, two right bars), all rats selected the odor that was from List 1 rather than from List 2, despite the List 2 item literally being the third last odor. The dashed line depicts the expected level of List 2 performance based on stimulus generalization (extrapolated from left bar). Chance = 0.5. The error bar represents 1 SEM. See Table S1 and S5.

* Difference between List 2 and list training, $t(6)=65.1$, $p<0.001$.

Figure 3. Rats replay incidentally encoded episodic memories.

In list training (last six sessions of list training prior to the critical test, left bar), rats were asked to identify the ordinal position of items from a list of odors. In the critical test (on a single occasion, Radial maze test, right bar), rats encountered odors while foraging in the radial maze and their memory for the order of encountered odors was immediately assessed. Chance = 0.5. The error bar represents 1 SEM. See Tables S2-S5.

* Difference between conditions, $t(8)=8.5$, $p<0.001$.

Figure 4. Rats replay incidentally encoded episodic memories after a retention interval challenge of 15 minutes.

In a complimentary experiment, a 15-minute delay was inserted between memory encoding and memory assessment. In list training (last six sessions of list training prior to the critical test, left bar), rats were asked to identify the ordinal position of items from a list of odors. In the critical test (on a single occasion, Radial maze test, right bar), rats encountered odors while foraging in the radial maze and their memory for the order of encountered odors was assessed after a 15-minute delay. Chance = 0.5. The error bar represents 1 SEM. See Tables S3, S5, and S6.

STAR METHODS

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources are available upon request from the lead contact, Jonathon D. Crystal (jcrystal@indiana.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Data from each rat are provided in supplemental information (Tables S1-S6). All data reported in this paper will be shared by the lead contact upon request. This paper does not report original code. Any additional information required to analyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Fifteen male Sprague-Dawley rats were obtained from Envigo (Indianapolis, IN; 75 days old and weighed an average of 261 g at the beginning of the experiment). Rats were housed individually and maintained on a 12:12 light/dark cycle, with light onset at 7:30 a.m. and offset at 7:30 p.m. Water was available *ad libitum*, except during testing sessions. The rats received 45-mg chocolate and chow pellets (F0229 and F0164, respectively; Bio-Serv, Frenchtown, NJ) during experimental sessions. Daily rations consisted of pellets consumed during experimental sessions and Teklad Global 18% Protein Rodent Diet (Tekland Diets, Madison, WI), adjusted to maintain 15 g of food per day. All procedures followed the Guide for Care of Use of Laboratory Animals and were approved by the Bloomington Institutional Animal Care and Use Committee at Indiana University. All rats completed list training. The primary experiment was completed by 9 rats, and the complementary experiment was completed by 8 rats. At about the time that the above rats completed these experiments, the remaining 6 rats completed list training, at which point their testing ended. List memory performance for each rat in Figures 3 and 4 is shown in Tables S2 and S6, respectively. Terminal performance in list training for the remaining 6 rats is shown in Table S4. Baseline performance in study-test radial maze training is shown in Table S3. After all other procedures were completed, the control condition was conducted with 7 rats that had served in the

primary experiment (2 rats from the primary experiment were not available due to health issues); data from the control condition is shown in Table S1.

METHOD DETAILS

Apparatus

Three open-field arenas constructed from acrylic plexiglass served as distinctive contexts for list encoding and memory assessment. All arenas contained “food holes” that were used for the placement of scented lids. Each food hole was circular (5 cm diameter, 2.5 cm depth), which allowed a cup to be firmly snapped into place so that the cup lay flush with the floor and could be covered with a lid placed loosely on top. The arena used for list encoding was circular, with a 46-cm diameter floor, and a transparent 30-cm high wall. The floor pattern in the encoding arena consisted of 3 concentric circles, with the inner, middle, and outer circles that were black, white, and black, respectively. The inside of the arena consisted of 8 equidistant food holes positioned along the walls. The black arena that was used for the third to last memory assessment was square (61-cm length, 61-cm width, and 30-cm height) and had 12 equidistant food holes arranged along the perimeter of the walls. The arena used for the control condition was gray and triangular (walls measured 51-cm length and 30-cm height) and had 9 equidistant food holes arranged along the perimeter of the walls. The radial maze (modified components from Lafayette Instruments) consisted of 8 arms (each 75 cm length) and a central hub (33 cm diameter). The arms and hub were surrounded with clear, plexiglass approximately 20 cm high and the arms were covered with a clear plexiglass lid that contained air holes. The ends of each arm contained a 5 cm food hole, inlayed in the floor, which allowed a cup to be firmly snapped into place so that the

cup lay flush with the floor and could be covered with a lid placed loosely on top. Guillotine doors, made of clear plexiglass, separated the hub from each of the arms and could be individually raised using pneumatic cylinders via remote control. The open-field arenas and the radial maze were cleaned with 2% chlorhexidine solution after each animal completed its daily session.

False-bottom cups

To ensure that the rats could not use the odor of the chocolate reward to select the correct lid, false-bottom cups were used in all memory assessments. Each memory assessment contained two cups: one for the correct item and another for the incorrect item. The metal grates (44.5 mm diameter, 179 holes, < 1 mm thick) were placed in the plastic cups at an angle above the pellet(s). The correct choice cup contained two chocolate pellets, separated by the thin metal grate (i.e., one chocolate pellet was placed below the metal grate, and the other pellet was placed above the grate). The incorrect choice cup contained two chocolate pellets placed below the metal grate, with no pellets placed above. The angle at which the metal grates were placed in the plastic cups resulted in the two chocolate pellets being approximately at the same level (i.e., height). The metal grates were fabricated to securely fit into the plastic cups, ensuring the rat could not remove the grate. At the end of each session, false-bottom cups were cleaned with 2% chlorhexidine solution. New false-bottom cups were prepared each day.

Stimuli

Odors were presented with opaque plastic lids that were odorized by storing them in sealed plastic containers. Plastic containers were filled with 90 ml of an oil odorant or approximately 150 ml of a dry spice powder odorant, and lids were odorized for at least 2 weeks before being presented to the rats. A metal grating was used in each container to separate the lids and the odorants in order to prevent direct contact. Odorants were refreshed approximately every 2 months in order to maintain scent potency and consistency. Odorants included: allspice, amaretto oil, anise, apple, apricot, banana, bay, black walnut, blackberry, blueberry oil, butterscotch oil, caraway seed, carob powder, celery seed, champagne, cheddar, cherry oil, chicory root, cilantro, cinnamon, clove, coconut, coffee oil, coriander, cumin, dill weed, fenugreek seed, garlic powder, hazelnut, hickory smoke, honey oil, horseradish, Indian curry, Irish cream oil, lavender, lemon zest, maple, marjoram, menthol-eucalyptus, Mexican oregano, mustard seed, nutmeg, onion powder, peach oil, pecan oil, pineapple oil, pistachio, pumpkin, raspberry, rosemary leaf, root beer, sage leaf, sesame oil, spearmint, spinach powder, strawberry oil, sumac, summer savory, sweet basil, tarragon, thyme, tomato, turmeric, wasabi, watermelon oil, white willow bark, Worcestershire. All stimuli used as odors were purchased from The Great American Spice Company (Rockford, MI).

General Methods

One session was conducted each day, 5-7 days per week. During each session, the rat was removed from its home cage and placed in a holding cage, where it also resided during inter-trial intervals. Holding cages were the same as cages used in vivarium housing, except bedding, food, and water were not present. The behavioral testing room contained two to three open-field arenas, the 8-arm radial maze, and a platform for the

holding cage. Arenas and the radial maze were elevated approximately 85 cm above the floor. During sessions, the default position for the experimenter was located in the middle of the two open-field arenas, approximately 1-m from the center of the arenas. For each trial, the experimenter removed the rat from the holding cage and placed the rat in the designated arena positioned with head pointed away from experimenter. Next, the experimenter returned to the default position where he/she remained with hands at his/her sides until the rat displaced the lid of the designated odor. The experimenter then removed the rat from the arena and returned it to the holding cage. When odors were presented multiple times during a session, new lids were used to prevent the rat from relying on scent marking. The following variables were randomized each session: the length of the lists, the odors used (sampled without replacement), and location of the odor lids. Individual rats advanced to subsequent phases of the procedure when it met a training criterion as outlined below, which allowed us to tailor advancement to the learning abilities of individual rats.

Preliminary training

Before odors were introduced, rats were trained to search the arenas and displace unscented lids from food holes to obtain food rewards.

Initial list training

Because learning the rules in our approach may be difficult for the rats, we used a training approach to optimize learning, as described in Panoz-Brown et al. [9] To this end, we implemented training strategies that provided the rat with immediate feedback, allowed the rat to continue each trial until it displaced the lid to the correct item, and

used a large reward for an initial correct choice. Since timely feedback promotes learning, we utilized a strategy that provided the rat with immediate feedback to facilitate acquisition of the third to last rule. To ensure that the rats could not track the odor of the chocolate reward, false-bottom cups were utilized during all memory assessments. Each memory assessment contained two false bottom cups: one for the correct item and another for the incorrect item. The incorrect item cup contained two chocolate pellets, both placed below a metal grate. The cup for the correct item contained two chocolate pellets, separated by a metal grate (i.e., one chocolate pellet was below the metal grate, and the other pellet was above the grate). Having one pellet above the grate provided immediate access to the reward after lid displacement, thereby minimizing the delay between the response and the delivery of the food reward. To further optimize learning, we provided the rat with feedback in every trial by allowing the rat to continue each trial if the initial response was incorrect. To this end, if the rat's initial lid displacement was to an incorrect item, the trial continued until lid displacement of the correct item occurred (the second choice was not included in calculations of accuracy). Because our approach baited the cups of correct items and allowed the rat to continue in each trial following an initial incorrect choice, it is possible for the rat to choose randomly and still obtain many food rewards. Thus, in order to incentivize learning while implementing features described above, we provided the rat with a large reward following a correct first choice. Specifically, a correct first response was rewarded with five additional pellets. To this end, immediately following the rat's initial correct lid displacement, the experimenter delivered additional food pellets to the cup; the experimenter did not initiate delivery of the additional food reward until after the rat's

initial correct response had occurred. The large reward was not delivered if the initial choice was incorrect.

Sessions consisted of approximately 5 trial-unique lists and corresponding memory assessments. At this stage, each list consisted of 4-8 trial-unique odors. Lists were presented to the rat in a distinctive encoding context, one item at a time; the number of items in the list was randomly selected for each trial. Each list item presentation consisted of a single cup and odorized lid placed at a randomly determined location and baited with a single chow pellet. The rat was removed from the holding cage and placed in the list encoding context facing away from the experimenter. A response was defined as the vertical or horizontal displacement of the lid from the cup. The rat remained in the encoding context until it displaced the lid and consumed the food reward. Immediately after the rat displaced the lid, it was removed from the arena and returned to the holding cage. This procedure continued until all items in the list were presented.

Immediately after completing each list presentation, the rat was moved to a distinctive context for the memory assessment. Memory assessments consisted of a choice between two odors presented in the list; one odor was from the third to last ordinal position in the list (the correct choice) and was baited with a single accessible chocolate pellet, whereas the other odor was not baited with an accessible pellet and was from another randomly selected ordinal position in the list (incorrect choice, foil odor). A correct choice was defined as the first lid displacement for the third to last list item, whereas an incorrect response was defined as the first lid displacement for an odor from the different ordinal position. Approximately 13 sessions were conducted in initial list training.

Baseline list training

The procedure used in baseline list training was the same as described above in initial list training, except that the list ranged from 4-11 odors. Sessions consisted of approximately 4 trial-unique lists and corresponding memory assessment. Training continued for each rat until performance in the memory assessment met the following criterion: Mean accuracy observed in the third to last memory assessment was at least 75% in the last 6 consecutive sessions. Rats that completed the primary experiment (n=9) required approximately 46 sessions to complete the criterion.

Radial maze pre-training

In radial maze pre-training, each of the 8 arms was baited with 3 chow pellets along each arm, 1 chow pellet in each cup and 4 chow pellets in the central hub. The rat was placed in the hub and, following a 30-second delay, all 8 doors were opened. The rat was allowed to explore the maze until all pellets were consumed, or 30 minutes elapsed, whichever occurred first. Approximately 11 sessions of radial maze pre-training were conducted (1 trial per session).

Radial maze 8-arm training

In radial maze 8-arm training, each food cup was baited with 1 chow pellet, and an unscented plastic lid was placed over the cup. The rat was then placed in the central hub for 30 seconds, after which all 8 doors were opened. The rat was allowed to navigate the maze until all 8 pellets were consumed or 15 minutes elapsed, whichever occurred first. A visit to an arm was recorded if the rat placed all four paws in the arm, even if it did not displace the lid and obtain the food reward. Rats advanced to the next

phase when accuracy was at least 70% in the last four sessions. Approximately 12 8-arm sessions were conducted (1 trial per session).

Radial maze study-test training

In study-test training, each food cup was baited with 1 chow pellet, which was covered by an unscented plastic lid. In the study (i.e., encoding) phase, 4 doors (randomly selected on each session for each rat) were opened. The rat was allowed to navigate the maze until all 4 pellets were consumed or 15 minutes elapsed, whichever occurred first. The rat was then removed, placed back into the holding cage, and the arms of the radial maze were cleaned. For the test (i.e., assessment) phase, all 8 doors were opened; at this stage, food was only available at the 4 arms not visited in the study phase. Visits were scored as described above. The number of baited arms entered in the first four choices of the test phase (expressed as a proportion of four arms) was the dependent measure. This version of the radial maze procedure is a standard assessment of spatial working memory[10,57,58]. Rats advanced to the next phase when accuracy was at least 70% in the last four sessions. Approximately 17 sessions were conducted in study-test training (1 trial per session).

Alternation of list training and radial-maze training

List training and study-test radial-maze training alternated across blocks of days. On any given day, only one task was scheduled to occur (list or radial maze, but not both). The number of consecutive days of list and radial maze was decreased across successive alternations. During this period before the critical test described below, the number of the consecutive days of training was increased if the animal showed any

signs of poor performance (e.g., below baseline criterion described above). Consequently, advancement to the critical test was preceded by a run of days (6 list, 2 radial maze, 4 list) with high accuracy in both list and radial maze tasks. The above precautions were used to ensure that high accuracy would be expected on the next day given the lack of any disruption in performance in the run up to the critical test. Approximately 62 sessions were conducted.

Critical test

On a single occasion, the rat received a novel presentation of a radial maze study phase with four randomly selected scented lids placed on top of the food cups at the end of four accessible runways. In all other respects, the procedure was identical to a study phase in the radial maze described above. Next, the rat was immediately transferred to the memory assessment context. The odors in the memory assessment context consisted of the third to last odor from the radial maze (which was designated as the correct choice) and a foil randomly selected from the other odors presented in the radial maze (which was designated as the incorrect choice). The rat was rewarded for choosing the third to last item encountered in the radial maze. In the unexpected memory assessment of the critical test, the two odors were placed at equal distances (randomly selected from 6 of 12 food holes) away from the rat's head to eliminate any bias to select an item nearest to the rat's head.

Complementary Experiment with a 15-minute Retention Interval

List training with a 15-minute retention interval

After completing the critical test, rats were given list training (as described in baseline list training above) for approximately 43 sessions (the memory assessment began immediately after completion of the list of odors ended, as described above). Next, the rats were introduced to list training with a retention interval between the list presentation and the memory assessment. The procedure was the same as described in baseline list training, except that (i) sessions consisted of 2 trials and (ii) after the end of the list presentation a delay occurred before the start of the memory assessment. During the retention interval the rat was placed in the holding cage and remained in the testing room. The retention interval was increased across successive sessions as follows: 1-, 5-, and 15-minutes (for approximately 2, 2, and 12 sessions, respectively).

Radial maze study-test training with a 15-minute retention interval

The sessions were the same as the radial maze study-test training described above, except that there was a 15-minute retention interval between the study phase and the test phase. The rat was placed in the holding cage and remained in the testing room during the retention interval. Approximately 12 sessions were conducted.

Alternation of list training with a 15-minute retention interval and radial-maze training with a 15-minute retention interval

List training with a 15-minute retention interval and study-test radial-maze training with a 15-minute retention interval alternated across blocks of days. On any given day, only one task occurred (list or radial maze, but not both). The number of consecutive days of list training was decreased across successive alternations. Prior to the critical test described below, the number of the consecutive days was increased if the animal

showed any signs of poor performance (e.g., below baseline criterion described above). Consequently, advancement to the critical test was preceded by a run of days (6 list, 2 radial maze, 4 list) with high accuracy in both list and radial maze. The above precautions were used to ensure that high accuracy would be expected on the next day given the lack of any disruption in performance in the run up to the critical test. Approximately 32 sessions were conducted.

Critical Test with 15-minute Delay

On a single occasion, the rat received a novel presentation of a radial maze study phase with four randomly selected scented lids placed on top of the food cups at the end of four accessible runways. In all other respects, the procedure was identical to a study phase in the radial maze described above. Next, the rat received a 15-minute retention interval in its holding cage, and it was then transferred to the memory assessment context. The odors in the memory assessment context consisted of the third to last odor from the radial maze (which was designated as the correct choice) and a foil randomly selected from the other odors presented in the radial maze (which was designated as the incorrect choice). The rat was rewarded for choosing the third to last item encountered in the radial maze. In the unexpected memory assessment of the critical test, the two odors were placed at equal distances (randomly selected from 6 of 12 food holes) away from the rat's head to eliminate any bias to select an item nearest to the rat's head.

Control condition

Although data from the control condition (Figure 2) is presented before other data in the main text, the control condition was conducted after all other procedures described above were completed. Rats continued to receive baseline list training as described above for approximately 2 months. The last six sessions of baseline list training were followed by the control condition. In the control condition, a single session began with the presentation of a list of odors as in baseline list training (List 1). Next, a list of four odors was presented in a novel triangular arena (List 2); in all other respects the presentation of the list in the triangular arena was identical to baseline list training, except that a novel arena was used. Finally, a list memory assessment was conducted in the memory assessment context as in baseline list training, except that the two odors used in the memory assessment were the third last odor from List 1 and the third last odor from List 2. Prior to the presentation of List 2, the rats had not been exposed to the triangular arena. Although rats did not show signs of disruption when presented with odors in the novel arena (e.g., they approached lids, displaced lids, ate food, made a choice in subsequent memory assessment etc.), it is possible that novelty impaired odor tracking despite foraging normally to all overt appearances. Future studies would benefit from parametrically varying the degree of novelty to test this hypothesis. A single session using the control condition was conducted. Because the sample size is small, we did not counterbalance the assignment of trained and novel contexts to first and second lists. By presenting a list in the trained context before a novel list, our goal was to pit the predictions of resistance to interference against stimulus generalization. Allocating half of the animals to a condition that does not pit these hypotheses against

each other (novel followed by trained contexts) would make it impossible to attain a significant binomial test in the remaining animals given our sample size.

Evaluation of potential bias based on foil ordinal position

Because the foil was randomly selected from values 1, 2, 4, 5, 6, 7, 8, 9, 10, and 11 in list training, values above 3 were more likely to appear as the foil than values below 3. By the end of the experiments (Figure 4 left bar), performance was very high, which precludes substantially different levels of performance across different trial types. In the primary experiment, to explore the use of the potential cue that relatively old items were more likely to be the foil, we compared accuracy on the subset of trials that were just below (1 and 2) and just above (4 and 5) the third position using data from Figure 3 (left bar). We did not find evidence for a bias in favor selecting positions above the third position ($t(8)=1.4, p=.2$).

Assessment of non-episodic memory resources

Four lines of evidence suggest that it is unlikely that rats relied on working memory in the absence of episodic memory to solve the list task[9] (see Table S5).Retaining the last items in memory would require rapid updating as each new item is presented, which would require working memory resources. First, because a defining feature of working memory is that such memory is short lived[59,60], high accuracy after long retention interval delays (Figure 4 and Panoz-Brown et al. [9]) is not consistent with working memory. Second, a fundamental feature of long-term episodic memory (that is not supported by working memory) is resistance to interference from new information. Our earlier work[9] and the control condition (Figure 2) documented resistance to interference.

Third, another dominant feature of working memory is that performance is susceptible to manipulations of memory load[61-63]. Our earlier work[9] manipulated memory load but found equivalent performance, which does not support the use of working memory resources. Fourth, because the hippocampus is a critical structure for processing episodic memory, we used the chemogenetic technique DREADDs to inhibit neurons in the dorsal hippocampus. The selective and reversible impairment of list memory performance following suppression of hippocampal neurons, while sparing other aspects of memory (a working memory assay of new-old odor recognition memory and a conditioning assay of +/- odor discrimination), suggests that list memory performance relies on episodic memory.

QUANTIFICATION AND STATISTICAL ANALYSIS

Quantification was represented by the mean value and the standard error of the mean for each condition. Baseline training performance was compared to chance (0.5) by a one-tailed t-test. List training and radial maze test were compared with a two-tailed, within-subjects t-test. Data from a single critical test was evaluated using a binomial distribution (n=7 in Figure 2, n=9 in Figure 3, n=8 in Figure 4; chance=0.5). Alpha was set at 0.05.

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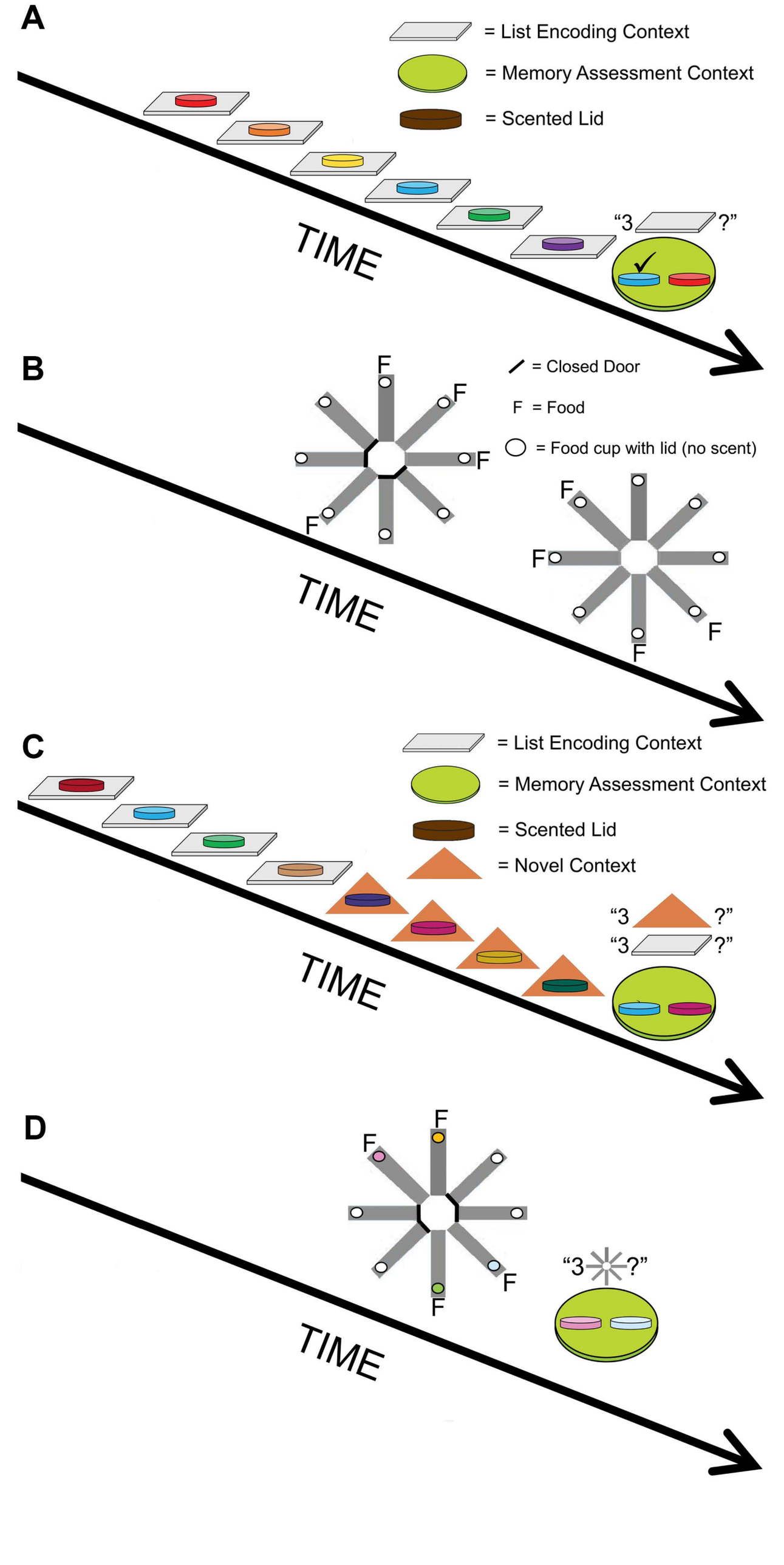
A
= List Encoding Context
= Memory Assessment Context
= Scented Lid
TIME
"3 ?"
B
= Closed Door
F = Food
= Food cup with lid (no scent)
F
F
F
F
F
F
F
TIME
C
= List Encoding Context
= Memory Assessment Context
= Scented Lid
= Novel Context
"3 ?"
"3 ?"
TIME
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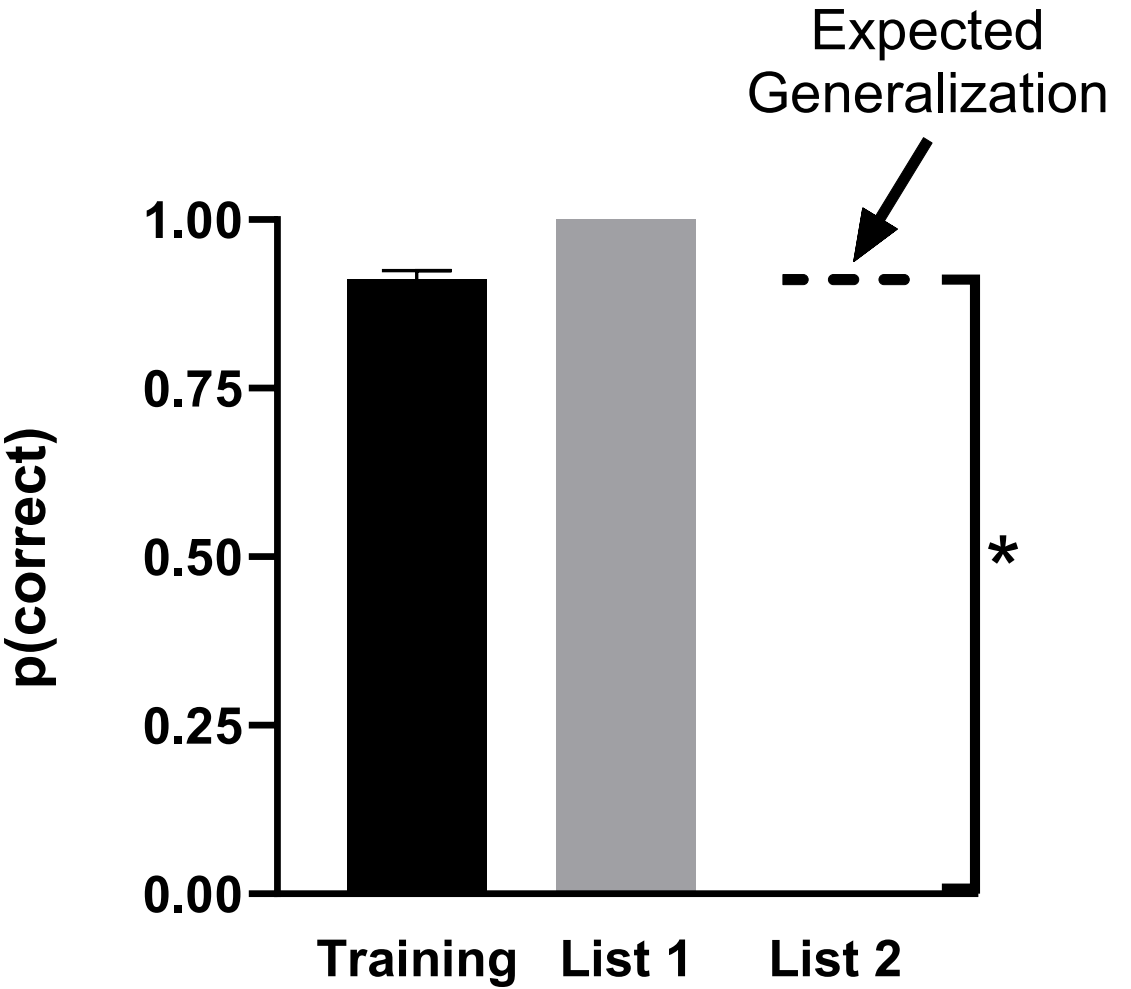
"3 ?"
TIME


Expected
Generalization
1.00
0.75
0.50
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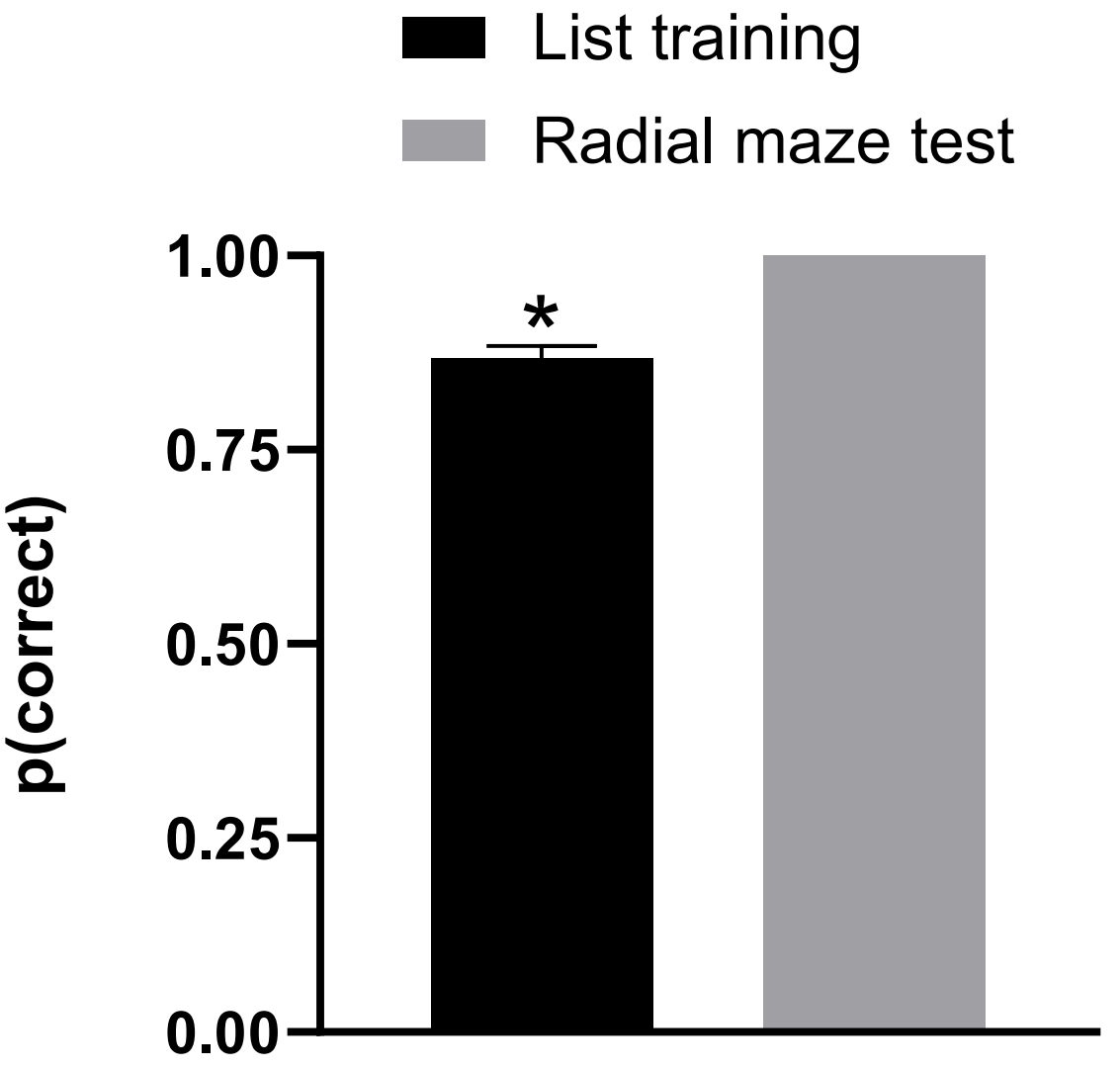
0.00
p(correct)
*
Training
List 1
List 2


List training
Radial maze test
1.00
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p(correct)
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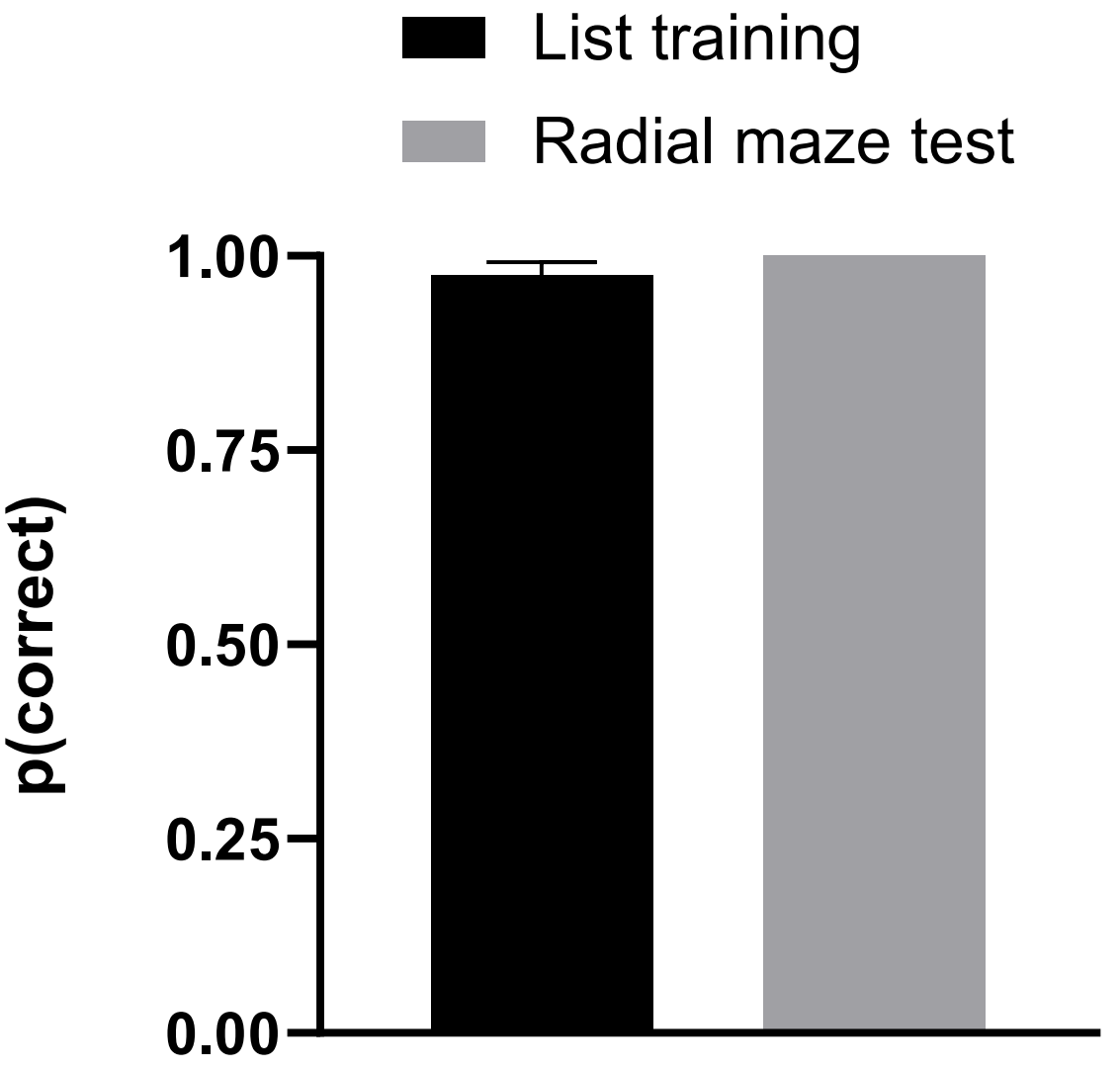
List training
Radial maze test
1.00
0.75
0.50
0.25
0.00
p(correct)

Subject number	p(correct | List), 0-minute retention interval		
	Baseline list training	List 1	List 2
NZ-04	0.958	1	0
NZ-06	0.870	1	0
NZ-08	0.913	1	0
NZ-10	0.957	1	0
NZ-12	0.870	1	0
NZ-14	0.900	1	0
NZ-15	0.909	1	0
Mean ± SEM	**0.911 ± 0.014**	**1 ± 0**	**0 ± 0**

Table S1. Performance of individual rats in the control condition, corresponding to data presented in Figure 2.
If presentation of an odor automatically triggers a habit to explicitly encode the odor into memory, then rats would be expected to choose the item from the most recently presented list (List 2, literally the third last odor). All of the rats tested choose the item from List 1, which is unlikely if rats automatically encode odors for the purpose of taking a future test of memory using stimulus generalization.

Subject number	p(correct), 0-minute retention interval	
	Baseline list training	Critical test
NZ-04	0.897	1
NZ-05	0.889	1
NZ-06	0.913	1
NZ-08	0.852	1
NZ-10	0.900	1
NZ-12	0.923	1
NZ-13	0.815	1
NZ-14	0.793	1
NZ-15	0.833	1
Mean ± SEM	**0.868 ± 0.015**	**1 ± 0**

Table S2. Performance of individual rats in the primary experiment, corresponding to data presented in Figure 3.
The expected level of accuracy (chance) is 0.5.

Subject number	p(correct) in radial maze test phase	
	0-minute retention interval	15-minute retention interval
NZ-04	0.875	0.813
NZ-05	0.750	0.875
NZ-06	0.875	NA
NZ-08	0.938	0.688
NZ-10	0.813	0.750
NZ-12	0.813	0.938
NZ-13	0.750	0.688
NZ-14	0.813	0.688
NZ-15	0.875	0.813
Mean ± SEM	**0.833 ± 0.021**	**0.789 ± 0.035**

Table S3. Performance of individual rats at the end of study-test radial maze training. Related to Figures 3 and 4.
The expected level of accuracy[S1] (chance) is 0.45. NA indicates that the rat was not tested in this condition. Data are from the last 4 days in radial maze before the critical test.

Subject number	p(correct), 0-minute retention interval
	Baseline list training
NZ-01	0.800
NZ-02	0.750
NZ-03	0.792
NZ-07	0.760
NZ-09	0.773
NZ-11	0.762
Mean ± SEM	**0.773 ± 0.008**

Table S4. Performance of individual rats that completed list training at about the time that other rats completed primary and complementary experiments. Related to Figure 3.
The expected level of accuracy (chance) is 0.5. Individuals listed in this table did not receive additional training leading up to the critical test and control condition and thus did not receive the critical test and control condition.

Property	Data	Episodic memory	Working memory
Memory intact after long retention interval	Figure 4 (15 min) in main text and Figure 2A (60 min) in our previous work[S2]	✓	X
Memory resistant to interference	Figure 2 in main text and Figure 2A in our previous work[S2]	✓	X
Equivalent memory performance under varying memory load demands	Figures 2A and S2 in our previous work[S2]	✓	X
Dependent on the hippocampus	Figures 2B, 3, 4, and S1 in our previous work[S2]	✓	X

Table S5. Properties observed in data are consistent with episodic memory but not with working memory. Related to Figures 2 and 4.
Episodic memory is an aspect of long-term memory, is resistant to retroactive interference, and is hippocampal dependent. A dominant feature of working memory is that performance is susceptible to manipulations of memory load. Check mark denotes verified prediction. X indicates the absence of the property, contrary to data.

Subject number	p(correct), 15-minute retention interval	
	Baseline list training	Critical test
NZ-04	1	1
NZ-05	1	1
NZ-08	1	1
NZ-10	0.917	1
NZ-12	1	1
NZ-13	1	1
NZ-14	1	1
NZ-15	0.889	1
Mean ± SEM	**0.976 ± 0.016**	**1 ± 0**

Table S6. Performance of individual rats in the complementary experiment, corresponding to data presented in Figure 4.
The expected level of accuracy (chance) is 0.5.

Supplemental References

1. Olton, D.S., and Samuelson, R.J. (1976). Remembrance of places passed: Spatial memory in rats. J. Exp. Psychol. Anim. Behav. Process. *2*, 97-116.
2. Panoz-Brown, D., Iyer, V., Carey, L.M., Sluka, C.M., Rajic, G., Kestenman, J., Gentry, M., Brotheridge, S., Somekh, I., Corbin, H.E., et al. (2018). Replay of episodic memories in the rat. Curr. Biol. *28*, 1628-1634.e1627. https://doi.org/10.1016/j.cub.2018.04.006.