The Medial and Lateral Entorhinal Cortex Both Contribute to Contextual and Item Recognition Memory: A Test of the Binding of Items and Context Model

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ABSTRACT: It has been suggested that the role of the hippocampus for episodic memory is to selectively bind together item and contextual information. One such model, the Binding of Items and Context (BIC) model, proposed that the perirhinal cortex provides item and the postrhinal/parahippocampal cortex provides context to the hippocampus via the medial (MEC) and lateral entorhinal cortices (LEC) to be bound into an episodic representation. This model proposes that item and context information are stored and processed independently and in parallel before hippocampal processing. To evaluate this model, the present experiment evaluated the role of the MEC and LEC for item and contextual novelty detection. The present results suggest that excitotoxic lesions to the LEC primarily disrupt item novelty detection, whereas lesions to the MEC primarily disrupt contextual novelty detection. These data provide a functional double dissociation between the MEC and LEC across item and contextual processing. Despite this dissociation, the present results suggest that item and contextual information are not represented independently before hippocampal processing. These data support the basic assumptions of the BIC model, but suggest that item and context information may interact in the entorhinal cortex. © **2013 Wiley Periodicals, Inc.**

KEY WORDS: medial entorhinal cortex; lateral entorhinal cortex; contextual discrimination; novelty detection; theoretical model

INTRODUCTION

It has proven difficult to develop animal models of episodic memory processing. At the heart of this issue are the difficulties in precisely defining the terms episodic and semantic for nonhumans without assuming that animals have a similar form of consciousness as is attributed to humans. It has been suggested that there are three fundamental elements that underlie episodic memory processes in animals: "what," "when," and "where" (Bierley et al., 1983; Rolls et al., 2002; Suzuki, 2003; Dere et al., 2005; Hunsaker and Kesner, 2008; Kesner and Hunsaker, 2010). Accordingly, all three of these elements must be simultaneously computed and bound into a single representation to perform a given task for it to specifically test episodic memory processes as opposed to nonepisodic memory processes (Morris, 2001).

Recently, a model for episodic recognition memory was proposed and extended by Eichenbaum et al. (Diana et al., 2007; Eichenbaum et al., 2007). This model, called the Binding of Items and Context (BIC) model, proposed that information pertaining to item identity (i.e., what) is generated primarily in the perirhinal cortex and information pertaining to the context wherein an item was experienced (i.e., where) is generated primarily in the postrhinal/parahippocampal cortex. The item and context information are transmitted through the lateral (LEC) and medial entorhinal cortices (MEC), respectively, and enter the hippocampus, at which point the item and the context are bound together into coherent episodes (i.e., "when" or "items in context"; cf., Ranganath, 2010). This model has proven influential as it has been demonstrated in functional magnetic resonance imaging studies that, at least at a rough level, processing of item and contextual information does appear to be segregated at the level of the perirhinal and parahippocampal cortices (Diana et al., 2007).

Furthermore, it has recently been demonstrated that at the level of single-cell recording, the MEC shows grid-like firing patterns that are proposed to underlie contextual representations when these firing patterns are transmitted to the hippocampus (Hafting et al., 2005; Rolls et al., 2006; Si and Treves, 2009; Rolls, 2010). This fits the BIC model predictions because the parahippocampal cortex (postrhinal cortex in rats) projects preferentially to the MEC, rather than the LEC. Importantly, even the portions of the MEC that do not show grid cells show firing patterns that are overwhelmingly spatial and contextual in nature (cf., Hafting et al., 2005; Hargreaves et al., 2005).

Interestingly, the firing patterns in the LEC of rats have been shown to be either relatively quiescent relative to the MEC or else to show an item-related firing pattern somewhat, but not entirely, independent to spatial context that is qualitatively similar to those observed in the perirhinal cortex (Hargreaves et al., 2005; Knierim, 2006; Knierim et al., 2006; Deshmukh et al., 2010, 2012; Deshmukh and Knierim, 2011; Yoganarasimha

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et al., 2011). Again, these reports support the BIC model because the perirhinal cortex preferentially projects to the LEC, as opposed to MEC, and thus firing correlates in the LEC should be driven more efficiently by item than spatial or contextual information. Similarly, it has been reported that MEC lesions in rats affect navigation, whereas LEC lesions primarily affect nonspatial information processing (Van Cauter et al., 2013).

Pharmacological inactivation experiments affecting the perforant path inputs from the MEC or LEC into the hippocampus show that the inputs to the hippocampus from the medial and lateral perforant path may not be functionally dissociable at the level of the hippocampus (Hunsaker et al., 2007). They found that although it appears the MEC and LEC show a bias toward processing context without item (for the MEC) or item without context (for the LEC), the two cannot be truly dissociated. Unfortunately, because of the nature of the inactivations and the experiments performed, this experiment was unable to determine if the pattern of results meant that the two perforant path inputs carried overlapping information or whether the hippocampus was combining the two inputs in a nonlinear manner that had not been previously anticipated. Interestingly, it has also been previously shown that the perirhinal cortex, but not LEC lesions result in lasting object recognition deficits (Kesner et al., 2001), suggesting that the entorhinal cortex integrates information from the other medial temporal lobe cortices rather than performing computations directly upon the incoming information itself.

To determine the role of the LEC and MEC for episodic recall and to evaluate the BIC model of episodic memory formation, rats that had received an axon sparing excitotoxic lesion to either the LEC or MEC were evaluated for their responses to item novelty, contextual novelty, or combined item and contextual novelty. To isolate the individual components of the BIC model, the item novelty task was designed such that the task did not require contextual cues to guide performance and the contextual novelty task did not require items to be processed to guide performance. As a control for general memory deficits, a condition in which both item and contextual novelty detection were concomitantly tested was included.

Rats with excitotoxic lesions to the LEC showed a profound deficit for item recognition memory, but also showed a mild deficit for contextual recognition memory. Rats with lesions to the MEC showed the opposing pattern, with a profound deficit for contextual recognition memory, but a mild deficit for item recognition memory. No rats showed any difficulty in performing the task when both the item and context were concomitantly changed. These data provide evidence for a double dissociation of MEC and LEC function, but still challenge some underlying assumptions of the BIC model.

MATERIALS AND METHODS

Rats

Sixteen 3-month-old male Long Evans rats from a commercial supplier (Simonsen Labs, Gilroy, CA) weighing 340–400 g at the beginning of the experiment served as subjects. All rats were kept on a 12 h light/dark cycle. All experimentation was carried out during the light portion of the light/dark cycle. Rats had ad libitum access to water and were reduced to 90% of their free-feeding weight before experimentation. All rat care and experimental protocols conformed to NIH and University of Utah IACUC approved protocols and an IACUC affiliated veterinarian assessed the health of all rats weekly. All rats were experimentally naïve at the onset of experimentation.

Experimental Apparatus

A white cheeseboard served as the testing apparatus for the experiment. The surface of the apparatus stood 65 cm above the floor, was 119 cm in diameter, and was 3.5 cm in thickness. One hundred seventy-seven food wells (2.5 cm in diameter and 1.5 cm in depth) were drilled into surface of the round board in evenly spaced parallel rows and columns, which were 5 cm apart. Either white or black poster board (22 cm high) surrounded the white cheeseboard, depending upon the experimental condition (see below). Velcro along the edge of the cheeseboard was used to attach the different poster boards to the cheeseboard. Two inserts cut out of plastic sheeting (i.e., shower curtain) to cover the holes in the cheeseboard were also used, one black and one white to match the walls and further differentiate the contexts. The poster board walls and colored floor were intended to provide for clearly distinct contexts based on previous work using hippocampal remapping as an index of rats' response to contextual changes, in particular, to changes of the color of the apparatus floor (cf., Anderson and Jeffery, 2003; Hayman et al., 2003; Jeffery and Anderson, 2003).

A black start box (24 cm long, 15 cm wide, and 17 cm high) was constructed to house the rat between trials. The black box was positioned on top of the round board perpendicular to the rows and parallel to the columns with the posterior edge of the box at the edge of the cheeseboard. The box had a hinged top for easily transferring rats into and out of the box. The front of the box had a guillotine door that could only be raised and lowered by the experimenter. The start box was used to transport the rat to the cheeseboard and as holding box during intersession intervals. The box was removed from the cheeseboard once the rat began to explore the apparatus.

Twelve objects were selected as "item" stimuli. The objects were chosen so as to be maximally visible against both a black and white background as well as to be texturally and visually unique. The objects ranged from 3 to 12 cm in diameter/width and 8 to 17 cm in height. The objects were placed in an equilateral triangle on the cheeseboard with 15 cm separating the vertices of the triangle from the edge of the cheeseboard. When objects on the board were replaced by novel objects, the location of the replaced object was standardized within each task. For the item novelty manipulation, the replaced object was the object on the right of the cheeseboard relative to the rat starting position. The object to the left was replaced in the item + context novelty condition (Fig. 1). No objects were replaced

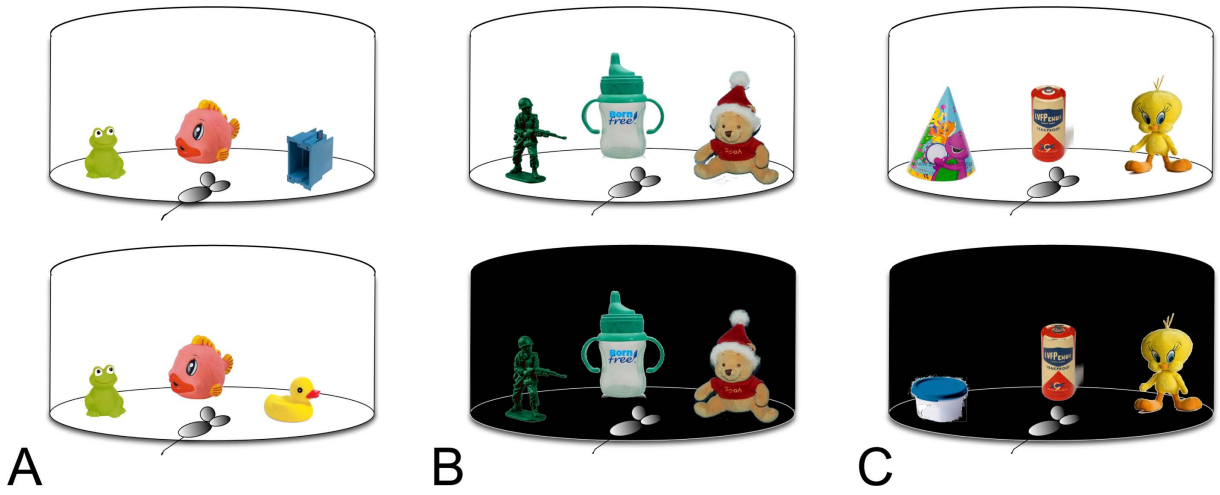

FIGURE 1. Item and contextual novelty detection tasks. A: Item novelty detection task. B: Contextual novelty detection task. C: Conjoint item + contextual novelty detection task. In all conditions, rats habituated to three objects in the original environment over 3- and 5-min exploration sessions before being transferred to one of the three experimental conditions and allowed to explore the objects for 5 min. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

during the contextual novelty condition. Preliminary experimentation demonstrated that there was no significant difference in rodent responses to item novelty in any of the three different locations.

Surgical Methods

Experimentally naïve rats were randomly assigned to a surgery group [vehicle lesion control $n = 6$ ($n = 3$ MEC control and $n = 3$ LEC control), MEC lesion $n = 5$, and LEC lesion $n = 5$]. Rats were anesthetized and maintained with isoflurane [2–4% (v/v) in 2 l/m medical air], given atropine sulfate (0.2 mg/kg i.m.), and placed in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). Lesions of the LEC were made by infusing 0.1 µl ibotenic acid (Ascent Scientific, Bristol, UK; 6 mg/ml phosphate buffer) at an infusion rate of 20 µl/h into each of the following coordinates: posterior from bregma 2.8 mm, lateral from the midline suture 6.4 mm, and ventral 8 mm from the dura mater; posterior 4.8 mm, lateral 6.5, and an injection was placed at both 7 and 8 mm ventral to the dura mater; and 6.8 mm posterior, 6.4 mm lateral, and 5.2 and 6.5 mm ventral to the dura. Excitotoxic lesions of the MEC were made using similar injections at the following coordinates: with the needle oriented 22° posteriorly, posterior from bregma 8.3 mm, lateral from the midline suture 4.8 mm, and ventral 7 mm from the dura mater; posterior 8.8 mm, lateral 6.2, and an injection was placed at both 7 and 8 mm ventral to the dura mater. In practice, MEC and LEC lesions made using these coordinates correspond well to those reported by Van Cauter et al. (2013) despite the difference in methodologies. After ibotenic acid infusion, the injection cannula remained in each site for at least 2 min to allow diffusion of the injected excitotoxin before retraction from the brain. Vehicle control lesions (LEC control $n = 3$ and MEC control $n = 3$) were made using the same coordinates and procedures; however, equivalent volumes of phosphate buffer vehicle were infused instead of ibotenic acid.

Following surgery, the incision was sutured, 1.5 ml of physiological saline was injected subcutaneously into each thigh, and the rats were allowed to recover on an isothermal pad at 37°C until they began to ambulate, at which point they were returned to their home cage. Animals received 150 g crushed food mixed with 20–30 g sucrose and were provided acetaminophen (200 mg/100 ml drinking water) in their drinking water as an analgesic for 3 days after surgery. In all cases, rats were eating and drinking within 6 h of recovery from anesthesia. All rats were allowed to recover for 10 days before beginning experimentation.

EXPERIMENTAL METHODS

Habituation

For 7 days before beginning experimentation after the surgical recovery period, rats were handled by an experimenter for 15 min daily and their weights were recorded. During preliminary testing, we found that including this handling procedure in the training protocol resulted in more consistent behavioral performance across rats.

Rats were given one 15-min session to habituate to each of the black and white contexts without the presence of the objects on separate days. The white context was the white cheeseboard with the white poster board walls and a white insert for the floor made from a white shower curtain. The black context was the cheeseboard with the floor covered by an insert black floor made from a black shower curtain and black poster board walls.

The order of the three paradigms presented to each rat was counterbalanced across rats beginning the day after habituation.

The objects presented to each rat were the same for all rats during a given task, but differed between tasks (cf., Fig. 1). This was done to facilitate comparisons across lesion groups. Seven days separated each testing session and all sessions were videotaped and scored offline by experimenters blinded to lesion group and animal identification.

Item Novelty Detection

Rats were placed on the cheeseboard with the white context and three objects. The rats were placed on the cheeseboard in the start box, which was removed immediately when the rats exited. The rat was allowed to explore the environment and the objects for 5 min, after which they were gently picked up and placed in the start box for a 3-min intersession interval. Thus, the rat was allowed to explore the objects for three 5-min sessions separated by 3-min intersession intervals in the start box. The intersession interval between the final habituation session and the test session was also 3 min.

After the third exploration session, one of the objects was replaced with a novel object (Fig. 1A) and the rat was returned to the environment and exploration of each of the objects was recorded, as was rearing behaviors directed toward the walls of the apparatus. Of particular interest was exploration of the object that had been changed.

Contextual Novelty Detection

Rats were placed on the cheeseboard with the white context and three objects. The rat was allowed to explore the environment and the objects for 5 min, after which they were gently picked up and placed in the start box for a 3-min intersession interval. Thus, the rat was allowed to explore the objects for three 5-min sessions separated by 3-min intersession intervals in the start box. The intersession interval between the final habituation session and the test session was also 3 min.

After the third exploration session, the objects remained the same, but the poster board was switched to black and the cheeseboard was covered with black plastic (Fig. 1B). The rat was returned to the environment and exploration of each of the objects was recorded, as was rearing behaviors directed toward the walls of the apparatus. Of particular interest was exploration of the object that was directly in front of the rat's starting position. This object was chosen as it was in a different relative location to the rat than the changed objects in the other two conditions that involved item changes. Rearing to the context was also of particular interest for the contextual novelty task as it has been shown that rearing is a valid measure of contextual novelty detection (Hunsaker et al., 2008).

Conjoint Item + Contextual Novelty Detection

Rats were placed on the cheeseboard with the white context and three objects. The rat was allowed to explore the environment and the objects for 5 min, after which they were gently picked up and placed in the start box for a 3-min intersession interval. Thus, the rat was allowed to explore the objects for three 5-min sessions separated by 3-min intersession intervals in the start box. The intersession interval between the final habituation session and the test session was also 3 min.

After the third exploration session, one of the objects was replaced with a novel object and the poster board was switched to black and the cheeseboard was covered with black plastic (Fig. 1C). The rat was returned to the environment and exploration of each of the three objects was recorded, as was rearing behaviors directed toward the walls of the apparatus. Of particular interest was exploration of the object that had been changed as well as rearing to the context as a measure of contextual novelty detection.

Histological Methods

After experimentation, all rats were deeply anesthetized with sodium pentobarbitol (1 ml at 70 mg/ml i.p.) and were intracardially perfused with phosphate-buffered saline for 5 min followed by 4% formalin in phosphate buffer for 2 min. The brains were extracted and stored for 72 h in a 30% (w/v) sucrose formalin solution. Forty-micrometer sections were using a cryostat through the hippocampus and the full caudal extent of the entorhinal cortices and mounted on gelatin-coated glass slides. After air drying for 3 days, the sections were Nissl stained with cresyl violet for microscopic visualization of the lesion.

Lesions were projected onto a flattened representation of the MEC and LEC after Dolorfo and Amaral (1998a,b) for quantification. Briefly, the procedure for making a straight-line unfolded map of the rat entorhinal cortex is as follows: (1) starting at the fundus of the rhinal sulcus, the pial surface of the MEC and LEC of each photomicrograph was divided into 250-μm-wide bins, each extending from the pial surface to the layer VI border with underlying white matter; (2) the degree of damage (no damage, minor damage, and major damage) in each bin was entered into a spreadsheet; and (3) the flat map was projected by straightening the cortical surface of each plot and stacking the straightened sections to produce a flattened representation of the surface of the MEC and LEC. The fundus of the rhinal sulcus was used to align the sections. Regions with minor and major damage were marked on each flattened map from the spreadsheet.

Dependent Measures and Statistical Analysis

Object exploration was defined as the rat having its nose within 1 cm of the object for greater than 0.5 s. The videotaped data were scored in duplicate by experimenters blinded to group identities of individual rats. These raters' scores did not systematically differ, and when there were differences between the scores, it was by 0.5 s, and the two scores were averaged before statistical analysis (intraclass correlation coefficient for agreement between raters = 0.93, $P < 0.001$). Similarly, rearing behaviors were recorded as a measure of contextual exploration as defined by Hunsaker et al. (2008). The rater's scores did not systematically differ for the rearing measure (intraclass coefficient for agreement = 0.90, $P < 0.005$).

The most common discrepancy was in determining if two subsequent rearing events were to be considered a single event or separated (i.e., did the forepaws make contact with the ground between apparent rearing events). Similar to the object exploration measure, the mean of the two scores was taken before statistical analysis.

General locomotor activity was also measured by overlaying a $3 \times 3 \times 3$ grid on the monitor used to score the object exploration and rearing. Whenever a rat crossed with all four paws into a new grid, it was recorded as a measure of locomotor activity. The identity of the grids (numbered 1–9) the rat entered was also recorded to verify that rats were not exploring only a small proportion of the maze (e.g., the left half or the top right quadrant only) and thus biasing their object and contextual exploration, but this was never the case. These data were recorded in duplicate by the same experimenters who recorded the other behavioral measures. There were no discrepancies between the two scores, and thus an intraclass correlation coefficient was not calculated. All three of these habituation measures were evaluated using a two-way repeated measures analysis of variance (ANOVA) with group (vehicle control, LEC lesion, and MEC lesion) as the between factor and habituation session (1, 2, and 3) as the repeated within-subject factor. The locomotor and object exploration measures during the test session were compared across groups using one-way ANOVA. For these analyses, task order was included as a covariate.

To quantify the response of the rats to the item or contextual changes, object exploration during the final 5-min habituation session was compared to the 5-min test session using the following ratio score: Object Exploration during Test Session/(Object Exploration during Test Session + Object Exploration during Habituation Session 3). The ratio value constrains the values between [0, 1], with 0.5 corresponding to identical exploration during the test as during the final habituation session. The same ratio was used for rearing behaviors. For this experiment, reaction to the item or contextual change was defined as a ratio value >0.5.

A similar ratio was computed for the sum total exploration of all three objects as well as selectively for the object that was changed in the tasks wherein an object was replaced and the ratio values showed a high correspondence with each other, and statistical analyses showed the same pattern of results using either ratio [the exact P values differed, but the general levels of significance (e.g., $P < 0.05$, $P < 0.01$, etc.) were the same under both conditions]. A look at the raw data confirmed that exploration of the selected object was responsible for any effects when all three objects were analyzed in the item and item + context conditions. For the item and item + context tasks, the ratio was made using the object that had been changed. For the contextual novelty change task, the ratio was made using the object that was at the apex of the triangle and straight from the rat's starting position (i.e., the left and right objects were assessed for the other two tasks so the remaining object was arbitrarily designated for the contextual change task as the object of interest). That being the case, the ratio values for the single objects that were replaced are reported here as they are most directly associated with the experimental hypotheses.

To verify specificity of object exploration during the test sessions, the percentage of the total exploration recorded that corresponded to each object was compared. For the item and item + context conditions, the percentage of total exploration time spent exploring the changed object was considered the dependent variable. For the contextual change task, the percentage of the total exploration spent exploring the object at the vertex of the triangle directly in front of the rat's starting point was considered the dependent variable. These objects were chosen as they were the objects used to generate the ratio values. Preferential exploration of objects of interest was determined by performing a one-tailed t-test against the null hypothesis of equal exploration of all objects (i.e., 33%). Failure to reject the null hypothesis was accepted as a confirmation of equal exploration of all objects.

Before further statistical analysis, it was verified that vehicle lesioned control rats showed a ratio score >0.5 by performing a one-tailed t-test against the null hypothesis that the ratio score $= 0.5$. Ratio values among groups were compared using one-way ANOVA within each task, and a two-way repeated measures ANOVA with groups as the between and task as the repeated within factor was performed with particular emphasis placed on the interaction term to compare the performance of each group across tasks.

Significant main effects and interactions were further characterized using Tukey–Kramer post hoc paired comparisons test and results were considered significant at $P < 0.05$. Significant effects are reported, as are all P values < 0.20. All other statistical results are stated as nonsignificant. All statistical analyses were performed in the R programming language (2.15.2; R Development Core Team, 2012) and data were plotted using DataGraph 3.1 (Visual Data Tools, Chapel Hill, NC). All P values were adjusted for false discovery rate to account for the number of statistical tests that were performed.

RESULTS

Histology

Figure 2 depicts the lesions to the MEC and LEC projected onto a flat maps after Dolorfo and Amaral (1998a,b) and Kerr et al. (2007). When quantified, for the MEC lesions, there was 58 ± 16 (SEM)% damage to the MEC with 8–9% damage to the LEC and no damage to the postrhinal cortex. There was no excitotoxin-induced damage along the needle track in all but one rat, which had very slight lesion (10–20 μm diameter ablation of layer II pyramidal neurons in the posterior parietal lobe where the needle was inserted). The superficial layers of the MEC where grid cells are commonly recorded (cf., Hafting et al., 2005) were spared in all cases. For the LEC lesions, there was $73\% \pm 11\%$ damage to the LEC and in all cases under 10% damage to the perirhinal cortex and 5–7% damage to the MEC. In two LEC rats, there was spread of drug up the needle

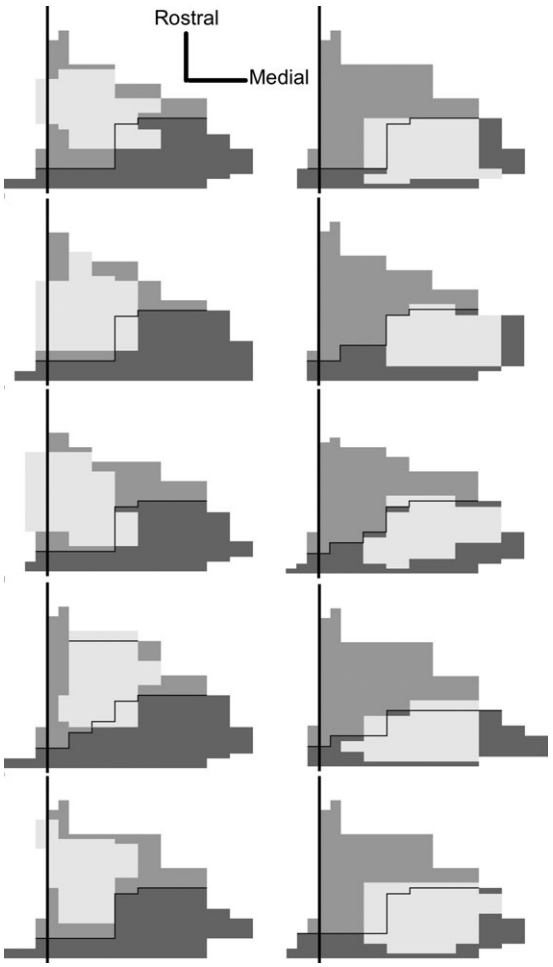

FIGURE 2. LEC and MEC lesions. Lesions result from each animal to either the LEC or the MEC projected onto flattened maps after Dolorfo and Amaral (1998a,b) and Kerr et al. (2007). The lesions in the present experiment resulted in MEC and LEC damage most likely affecting portions of the entorhinal cortex that project to the dorsal and intermediate hippocampus. Left plates: The lesions of the LEC resulted in damage primarily to the lateral and intermediate bands of the LEC and very little damage to the medial band. Right plates: The lesions of the MEC resulted in primarily damage to the intermediate band of the MEC with similar damage to the lateral and medial bands of the MEC. There is some damage in portions of the cortex projecting to the ventral hippocampus, slightly more for MEC than LEC lesions. Darkest gray = MEC; middle gray = LEC; and light gray = lesion extent. The black line corresponds to the fundus of the rhinal sulcus.

track, but the effects of this spread were subtle cell loss within 20–30 μm of the needle track in layer V of the mid-anterior portion of the parietal cortex. It was determined that the limited distribution of damage in these lesions was considered unlikely that the limited damage to these areas caused dysfunction to the brain regions affected (i.e., anterior or posterior parietal lobe). As can be seen in Figure 2, MEC and LEC lesions primarily affected the regions intended. Importantly, both lesions did clearly ablate portions of the entorhinal cortex that projects to the dorsal hippocampus (i.e., the lateral band; Kerr et al., 2007), which is thought to mediate performance for the present behavioral tasks. The MEC lesions, however, did extend into the medial band of the entorhinal cortex, and this affected entorhinal–ventral hippocampal projections to a larger degree than the LEC lesions did. In other words, the LEC lesions ablated almost the complete lateral and intermediate bands (cf., Kerr et al., 2007) of the entorhinal cortex with minor damage to the medial band. The MEC lesions ablated the intermediate band with both lateral and medial bands damaged similarly. Thus, there was differential damage to the medial and intermediate bands of the entorhinal cortices across the MEC and LEC lesions.

Behavioral Results

For all behavioral tasks, there were no between-group differences for locomotor activity during study or the test sessions and habituation curves were similar (all two-way repeated measures ANOVA $P_{adj} > 0.15$). This was reflected in similar level of grid crossings, object exploration times, and number of rearing events during the individual habituation sessions across groups (sessions 1–3 in all plates of Fig. 3). For all conditions, vehicle lesioned control animals showed object exploration and rearing ratio values >0.5 as verified by a *t*-test against the null hypothesis of a ratio value = 0.5 (lowest value for *t* statistic, $t(5) = 5.7$, $P_{adj} = 0.0012$). Ratio values for object exploration in each group are tabulated in Table 1 and ratio values for rearing are tabulated in Table 2.

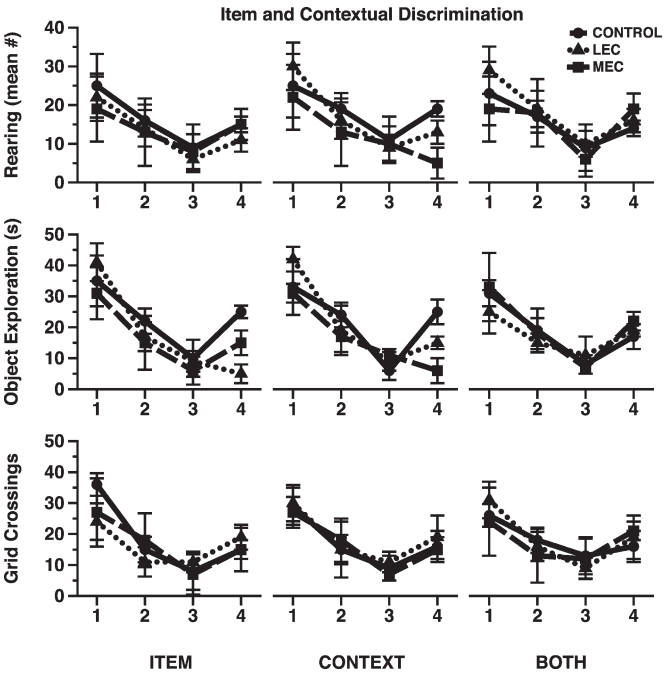

FIGURE 3. Habituation curves for locomotor behavior and object exploration. There were no differences observed among groups for habituation (sessions 1–3) for rearing (top), object exploration (middle), or locomotor (bottom) activity for any of the present behavioral tasks. Sessions 1–3 are connected by lines to demonstrate intact habituation curves. Session 4 corresponds to the test session and the differences among groups during test sessions are further characterized in Figure 4 and Tables 1 and 2.

TABLE 1.

Behavioral Results—Exploration

	Item	Context	Item + context
Control	0.68 ± 0.04	0.67 ± 0.04	0.67 ± 0.09
LEC	0.37 ± 0.02$^{**,\#}$	0.55 ± 0.01*	0.69 ± 0.06
MEC	0.57 ± 0.01*	0.30 ± 0.02$^{**,\#}$	0.70 ± 0.06

Object exploration ratio values for the item, context, and item + context novelty detection paradigms for all three experimental groups. Ratio values for both the LEC and MEC groups also significantly differed across all three paradigms, suggesting a performance gradient across tasks. The vehicle control group showed no statistical difference in ratio value across conditions.

$^{**}P_{adj} < 0.01$ vs. vehicle control,

$^{*}P_{adj} < 0.05$ vs. vehicle control,

$^{\#}P_{adj} < 0.05$ MEC vs. LEC based on Tukey–Kramer post hoc paired comparisons test.

Item Novelty Detection

Figure 4 shows group differences for object exploration after a novel object replaced a familiar object. To characterize these differences, one-way ANOVA was performed with groups (vehicle control, MEC lesioned, and LEC lesioned) as the between-group factor. There was a significant group effect for object exploration ($F(2,12) = 12.13$, $P_{adj} = 0.0013$). A subsequent Tukey–Kramer post hoc paired comparisons test revealed that the LEC group performed significantly more poorly than both vehicle control ($P_{adj} < 0.01$) and MEC ($P_{adj} < 0.05$) groups. There were no significant group differences for rearing measures. The object exploration data suggest a graded deficit for item novelty detection, with the LEC group showing the greatest impairments, followed by the MEC group showing an intermediate impairment compared to the vehicle control group.

Because the MEC group showed an intermediate level of performance relative to the control and LEC groups, we felt it was necessary to determine if the MEC group had a ratio value >0.5 by performing a one-tailed *t*-test against the null hypothesis of a ratio value = 0.5. This analysis suggested that the MEC rats, despite showing a deficit relative to control rats, were in fact able to detect item novelty ($t(4) = 2.91$, $P_{adj} = 0.04$).

Important to determining if this object exploration measure was primarily driven by heightened exploration of the novel object and not just general exploration of all objects, we compared the exploration of the rats in each group to the novel object compared to the unchanged objects during the test session. On an average, the vehicle control rats showed a marked increase in exploration to the novel object without a concomitant increase in exploration of the unchanged objects (i.e., increased exploration of the novel object with continued habituation to the unchanged objects—72.23% ± 8.23% of total exploration during the test was of the novel object). The MEC group showed the same pattern, but with a reduced overall increase in exploration of the novel object (57.93% ± 11.45% of total exploration was of the novel object). The LEC group, however, did not show a clear preference for the novel object relative to the unchanged objects (39.73% ± 9.91% of the total exploration was of the novel object). Statistically, the control and MEC groups showed a significant preference for the novel object, as verified by performing a two-tailed *t*-test against the null hypothesis of 33%, or equal exploration of all objects (control $t(5) = 8.10$, $P_{adj} = 0.0013$ and MEC $t(4) = 4.22$, $P_{adj} = 0.014$). The LEC group, however, did not show a significant preference for exploration of the novel object relative to the unchanged objects ($t(4) = 1.32$, $P_{adj} = 0.26$).

TABLE 2.

Behavioral Results—Rearing

	Item	Context	Item + context
Control	0.65 ± 0.07	0.64 ± 0.10	0.76 ± 0.03
LEC	0.64 ± 0.09	0.59 ± 0.03	0.61 ± 0.08
MEC	0.62 ± 0.11	0.33 ± 0.02$^{**,\#}$	0.63 ± 0.13

Ratio values for the item, context, and item + context novelty detection paradigms for all three experimental groups. The MEC group showed a significantly reduced ratio value for the context change task compared to the other conditions. The control and LEC groups showed no statistical differences in ratio value across conditions.

$^{**}P < 0.01$ vs. control,

$^{*}P < 0.05$ vs. control,

$^{\#}P < 0.05$ MEC vs. LEC based on Tukey HSD post hoc paired comparisons test.

Contextual Novelty Detection

Figure 4 shows group differences for object exploration after the context in which objects were presented was changed. To

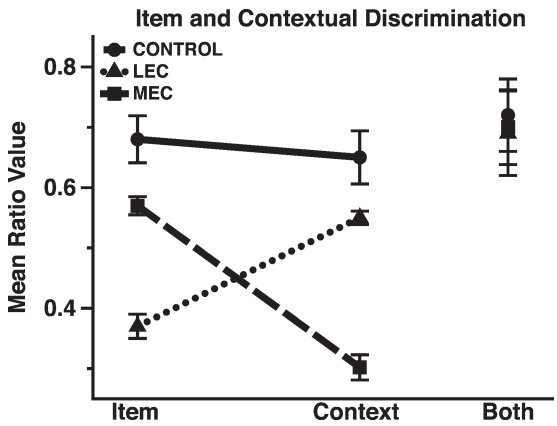

FIGURE 4. Interaction plot of MEC and LEC contributions to item and contextual discrimination. Behavioral results demonstrate that on the item novelty task the LEC rats performed more poorly than control and MEC rats. The MEC rats performed more poorly than the control rats, as well. On the contextual novelty task, the MEC rats performed more poorly than control and LEC rats. The LEC rats performed more poorly than the control rats, as well. No rats showed any deficits when both item and context were changed together. These data concurrently demonstrate a clear double dissociation of medial and lateral entorhinal cortex for item and contextual processing as well as suggest a graded involvement of both lateral and medial entorhinal cortex for item and contextual information processing.

characterize these differences, one-way ANOVA was performed with groups as the between-group factor. There was a significant group effect for object exploration ($F(2,12) = 18.31$, $P_{adj} < 0.0001$). The same pattern of deficits was observed in the ratio value derived from the rearing measure ($F(2,12) = 7.43$, $P_{adj} = 0.009$). Subsequent Tukey–Kramer post hoc paired comparisons test revealed that the MEC group performed significantly more poorly than both vehicle control (object exploration $P_{adj} < 0.001$; rearing $P_{adj} < 0.01$) and LEC (both object exploration and rearing measures $P_{adj} < 0.01$) groups. These data suggest a graded deficit for item novelty detection, with the MEC group showing the greatest impairments, followed by the LEC group.

Because the MEC group showed an intermediate level of performance relative to the control and MEC groups, we felt it was necessary to determine if the LEC group had a ratio value >0.5 by performing a one-tailed *t*-test against the null hypothesis of a ratio value = 0.5. This analysis suggested that the LEC rats, despite showing a deficit relative to control rats, were in fact able to detect contextual novelty (object exploration $t(4) = 3.11$, $P_{adj} = 0.03$; rearing $t(4) = 2.97$, $P_{adj} = 0.04$).

Important to determining if this was a contextual novelty-specific finding, we compared the exploration of the rats in each group to an arbitrarily chosen object that was used to calculate the ratio values compared to the other two objects during the test session. On an average, the vehicle control rats showed a marked increase in exploration to all objects without any particular preference for one object over another (i.e., equal exploration of all objects—36.01% ± 10.26% of total exploration during the test was of the object used to generate the ratio value). The MEC group showed the same pattern (32.00% ± 14.63% of total exploration was of the object used to generate the ratio value), as did the LEC group (35.41% ± 12.38% of the total exploration was of the object used to generate the ratio value). Statistically, no groups showed a significant preference for any of the objects, as confirmed by performing a two-tailed *t*-test against the null hypothesis of 33%, or equal exploration of all objects (control $t(5) = 1.22$, $P_{adj} = 0.29$; MEC $t(4) = 0.96$, $P_{adj} = 0.39$; LEC $t(4) = 1.50$, $P_{adj} = 0.21$).

Conjoint Item and Contextual Novelty Detection

Figure 4 shows group differences for object exploration after the familiar objects were placed in a novel context. To characterize these differences, one-way ANOVA was performed with groups as the between-group factor. There was not an effect for object exploration ($F(2,12) = 2.11$, $P_{adj} = 0.13$). There was also no effect for rearing measures ($F(2,12) = 1.87$, $P_{adj} > 0.20$). These data suggest that there were no deficits for novelty detection when both a novel item and a novel context are introduced for any of the rats.

Important to determining if the object exploration effect was driven by exploration of the novel object and no to all objects in general, we compared the exploration of the rats in each group to the novel object compared to the unchanged objects during the test session. On an average, the control rats showed a marked increase in exploration to the novel object without a concomitant increase in exploration of the unchanged objects (i.e., increased exploration of the novel object with continued habituation to the unchanged objects—69.93% ± 7.11% of total exploration during the test was of the novel object). The MEC group showed the same pattern (77.52% ± 9.46% of total exploration was of the novel object), as did the LEC group (74.99% ± 5.28% of the total exploration was of the novel object). Statistically, all groups showed a significant preference for the novel object, as verified by performing a two-tailed *t*-test against the null hypothesis of 33%, or equal exploration of all objects (control $t(5) = 9.86$, $P_{adj} = 0.0006$; MEC $t(4) = 7.83$, $P_{adj} = 0.00014$; and LEC $t(4) = 6.73$, $P_{adj} = 0.0025$).

Comparison of the Three Conditions

To elucidate any patterns in the above results, two-way repeated measures ANOVA was performed with groups as the between-group factor and task (item, context, or item + context) as the repeated within factor (Fig. 4). This analysis was carried out on the object exploration data rather than the rearing data as the item exploration measure was able to characterize effects for both item and contextual novelty, whereas rearing was only useful to identify deficits for contextual processing (Table 2; cf., Hunsaker et al., 2008). Task order was included as a covariate to account for any potential effects of experiment order on task performance. There was a significant group effect ($F(2,39) = 7.99$, $P_{adj} < 0.001$), a significant effect of task ($F(2,39) = 8.52$, $P_{adj} < 0.001$), and a significant group × task interaction ($F(4,39) = 5.13$, $P_{adj} < 0.003$). There was no contribution of task order to behavioral performance. A priori planned Tukey–Kramer post hoc paired comparisons test on the interaction term revealed that the LEC group showed a significantly greater impairment on the item change task than during the context change task ($P_{adj} < 0.01$) or the task wherein both item + context were manipulated ($P_{adj} < 0.001$). Furthermore, the MEC group showed greater impairments on the context change task than the item + context change task ($P_{adj} < 0.05$). The MEC group, however, showed a significantly greater impairment on the context change task than during the item change task ($P_{adj} < 0.01$) or the task wherein both item + context were manipulated ($P_{adj} < 0.001$). Furthermore, the MEC group showed greater impairments on the item change task than the item + context task ($P_{adj} < 0.05$; cf., Fig. 4 and Table 1 for a summary of these findings).

DISCUSSION

The data from the present experiment provide support for the BIC model, such that information entering the hippocampus via the LEC is critical for item recognition memory, as well as that information entering the hippocampus via the MEC is critical for contextual recognition (cf., Figs. 3 and 4,

Tables 1 and 2). However, these data do not provide unequivocal support to the BIC model in that there appears to be a graded contribution of the MEC and LEC to the opposing processes; that is, the LEC appears to play a minor role for contextual recognition and the MEC has a minor role for item recognition memory (cf., Fig. 4). One interpretation of these data is that the item and context information interact in some way at the level of the entorhinal cortex, albeit much less than at the level of the hippocampus.

Interestingly, despite these apparent deficits in item and contextual recognition memory, when both item and context are altered, no rats showed any difficulties in recognizing the conjoint item and contextual novelty as evaluated both by object exploration and rearing measures. We attribute this to the fact that despite the deficits relative to vehicle control rats, rats with LEC lesions did show preferential responding to changes in context, just not as robustly as control rats. Similarly, MEC lesioned rats showed preferential responses to item novelty, just not as robust as those seen in control rats. Neither lesion group showed impairments relative to control rats when both the item and context were changed.

Similarly, anatomical tracing experiments suggest that the parallel perirhinal—LEC—hippocampus and postrhinal/parahippocampal—MEC—hippocampus circuits are not nearly as segregated as often inferred in the behavioral literature. Despite wide acceptance of these circuits being parallel and not interacting before the level of the hippocampus (cf., literature reviews in Eichenbaum et al., 2007; Hunsaker et al., 2007), it has been repeatedly demonstrated in anatomical tracing experiments that the perirhinal cortex does in fact receive projections that may send contextual information from the postrhinal/parahippocampal cortex and send reciprocal projections that may send item information to the perirhinal/parahippocampal cortex. These reports also demonstrate similar patterns occur at the level of the MEC and LEC (cf., Amaral et al., 1987; Insausti et al., 1987a,b; Witter et al., 1989; Witter and Amaral, 1991; Suzuki and Amaral, 1994; Burwell et al., 1995, 1998, 2004a,b; Burwell and Amaral, 1998a,b; Dolorfo and Amaral, 1998a,b; Burwell, 2000, 2001; Agster and Burwell, 2009; Lavenex and Amaral, 2000; Burwell and Hafeman, 2003; Buckmaster et al., 2004; Chrobak and Amaral, 2007; Furtak et al., 2007; Burwell and Furtak, 2008; Insausti and Amaral, 2008). Additionally, Deshmukh and Knierim (2011) demonstrate clear spatial correlates of neural activity in the "non-spatial" LEC.

In fact, it appears from the anatomical data that there is a graded level of segregation across the postrhinal/parahippocampal and postrhinal cortex, with the postrhinal/parahippocampal processing mostly contextual/spatial information (Burwell and Hafeman, 2003) and perirhinal processing mostly item and sensory/perceptual information (Burwell et al., 1998), but both regions, to some degree, are involved in processing both contextual and item information. This lack of a cut and dried segregation is supported by experiments demonstrating that postrhinal cortex and perirhinal cortex lesions result in qualitatively similar deficits for contextual, elemental, and attentional processing (Bucci et al., 2000, 2002; Bucci and Burwell, 2004; Burwell et al., 2004a). Intriguingly, Furtak et al. (2012) recently demonstrated neurons within the postrhinal cortex perform functions akin to binding items in context in visual object discrimination tasks.

It has been suggested that the hippocampus may itself generate contextual information by combining object and place information (Rolls and Kesner, 2006), and previous research has shown that the dorsal dentate gyrus and dorsal CA3 subregions of hippocampus may play an important role for combining object and place information (Rolls and Kesner, 2006; Kesner, 2007a,b). On the basis of the hypothesis that the medial perforant path input into the dentate gyrus and CA3 mediates spatial information processing via NMDA receptor-dependent plasticity and the lateral perforant path input into the dentate gyrus mediates visual object information via μ-opioid receptor-dependent plasticity, the following experiment was conducted. Using a spatial novelty exploration paradigm originally developed by Poucet (1989), rats were tested for detection of a spatial change or detection of a novel visual object while under the influence of intrahippocampal infusions of AP5 (an NMDA antagonist) or naloxone (a μ-opiate antagonist) into the dentate gyrus or CA3.

Naloxone infusions into the dentate gyrus disrupted both novelty detection for spatial locations and visual objects, whereas AP5 infusions into the dentate gyrus disrupted only detection of novel spatial locations, but had no effect on detection of a novel object (Hunsaker et al., 2007). Infusions of both AP5 and naloxone into CA3 disrupted both novelty detection for spatial locations and objects.

These data were interpreted as suggestive that the dentate gyrus conjunctively encodes visual object and spatial information to provide for a representation of spatial context. They also showed that CA3 uses relational, associative encoding processes (i.e., arbitrary associations) to associate items and contextual information into a single entity. Furthermore, it has been shown that dentate gyrus lesions disrupt object recognition when a spatial context is available, but does not disrupt object recognition when there are no competing spatial stimuli (Dees and Kesner, unpublished observations; Dellu et al., 1997a,b; Mumby, 2001; Mumby et al., 2002a,b; O'Brien et al., 2006; Piterkin et al., 2008). Also, it has been shown that CA3 lesions disrupt object–place associations (Gilbert and Kesner, 2003), single trial arbitrary associations between objects and places (Kesner et al., 2008), and deficits in object–context recognition memory (Langston and Wood, 2010; Langston et al., 2010). Together, these data support the assumptions of the BIC model that in the hippocampus (particularly CA3), items and contexts are associated into single representations, or episodes (cf., Diana et al., 2007; Eichenbaum et al., 2007; Ranganath, 2010).

The present experiments were designed to directly examine the response of rats to item and contextual novelty, a process mediated by recognition memory (i.e., rats will respond to novelty if, and only if, they notice that there is a mismatch between the previous remembered episode and the current sensory/per-

ceptual inputs). Important to the study of episodic-like processing in rodents, the present behavioral paradigms emphasized the exploration of the objects in all conditions, even as a readout of contextual recognition memory. This outcome measure was chosen to directly evaluate the BIC model, that is, that the item information and context would not be bound into a single episodic memory until reaching the hippocampus.

The present experiments exploited this theory by accepting the assumption that an altered context would result in an altered episodic-like memory (different item + context binding), and rats would respond by exploring the items anew. Rearing was also included as an outcome measure for quantifying contextual exploration, but was unable to provide information concerning responses to item novelty, but did prove a sensitive measure for contextual novelty detection, as has been shown previously (Hunsaker et al., 2008).

The present data beg the question of what the effects of combined LEC and MEC lesions would be for the processing or recognition of item + context bindings. As stated above, Furtak et al. (2012) demonstrated that item and context (or object in space) bindings at the level of the postrhinal cortex and the perirhinal cortex have been proposed to process item information independent of hippocampal involvement. What makes this question interesting are reports that rats with full hippocampal ablations are able to perform certain elements of item + context tasks, but animals with pharmacological inactivations of the input pathways to the hippocampus show profound deficits (Lee et al., 2005; Hunsaker et al., 2007). These data suggest that the upstream cortices may be performing functions that may be passed to other brain regions to guide behavioral performance, whereas inactivations to the hippocampus deprive the system of this compensatory mechanism (cf., Hunsaker et al., 2007 for more on the logic of this argument). The present data suggest that either a combined perirhinal + postrhinal or MEC + LEC lesion would be catastrophic to item + context discrimination. Such experiments would provide the ultimate test of the BIC model by determining the relative roles of the entorhinal cortices and hippocampus for binding items and context.

What the present experiment was unable to elucidate was the precise role for the MEC and LEC for item and context recognition memory. Furthermore, the precise manner by which the hippocampus is able to either relationally or conjunctively bind item and contextual information remains elusive, even though some clues have been recently uncovered (Hunsaker et al., 2007). The implications of the present experiment are limited by the extent of the lesions to the entorhinal cortex. As there was a significant amount of entorhinal cortex sparing in both lesion conditions, the effects of each lesion in the present experiment may actually underestimate the contribution of the LEC and MEC to item and contextual processing. An additional limitation to the present experiment is the differential hippocampus projection targets of the areas lesioned in the LEC and MEC. The LEC lesions primarily resulted in damage to the lateral band of the entorhinal cortex, which projects to the dorsal aspect of the hippocampus, as well as the intermediate band with limited damage to the medial band that projects to the ventral hippocampus. The MEC lesions primarily damaged the intermediate band of the MEC with relatively similar damage to the lateral and medial bands of the MEC. This means that the MEC damage in theory may affect the intermediate hippocampus preferentially, whereas the LEC damage may affect the dorsal-intermediate hippocampus.

Similarly, future studies will be needed to determine if the projections from the entorhinal cortices to the dorsal or ventral hippocampus are more important for the performance of this task. This is important because the MEC lesions in this study affected ventral hippocampal projections slightly more than the LEC lesions did, based on the data from previous anatomical tracing experiments. Additionally, as the caudal most portion of the MEC where grid cells are commonly recorded from was not lesioned, the present experiment is unable to determine any specific role for grid cells as related to contextual processing. Despite these limitations, the present data provide compelling evidence for differential roles of the LEC and MEC in contextual and item novelty detection as would be predicted by the BIC model.

Despite the lack of a clear dissociation of item and contextual processing across the MEC and LEC, the present data do not warrant abandoning the BIC model. The present data disagree with the BIC model in that item and contextual information are not, as have been assumed, maintained independent to each other before reaching the hippocampus, but the fundamental premises that item and context recognition can be maintained independent of the hippocampus, at least under strictly controlled experimental conditions, are fully supported by the present results.

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REFERENCES

Agster K, Burwell RD. 2009. Cortical efferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. Hippocampus 19:1159–1186.

Amaral DG, Insausti R, Cowan WM. 1987. The entorhinal cortex of the monkey. I. Cytoarchitectonic organization. J Comp Neurol 264:326–355.

Anderson M, Jeffery KJ. 2003. Heterogeneous modulation of place cell firing by changes in context. J Neurosci 23:8827–8835.

Bierley R, Kesner RP, Novak J. 1983. Episodic long-term memory in the rat: Effects of hippocampal stimulation. Behav Neurosci 97:42–48.

Bucci D, Burwell RD. 2004. Deficits in attentional orienting following damage to the perirhinal or postrhinal cortices. Behav Neurosci 118:1117–1122.

Bucci D, Phillips R, Burwell RD. 2000. Contributions of postrhinal and perirhinal cortex to contextual information processing. Behav Neurosci 114:882–894.

Bucci D, Saddoris M, Burwell RD. 2002. Contextual fear discrimination is impaired by damage to the postrhinal or perirhinal cortex.

Behav Neurosci 116:479–488.
Buckmaster C, Eichenbaum H, Amaral DG, Suzuki WA, Rapp P. 2004. Entorhinal cortex lesions disrupt the relational organization of memory in monkeys. J Neurosci 24:9811–9825.
Burwell RD. 2000. The parahippocampal region: Corticocortical connectivity. Ann N Y Acad Sci 911:25–42.
Burwell RD. 2001. Borders and cytoarchitecture of the perirhinal and postrhinal cortices in the rat. J Comp Neurol 437:17–41.
Burwell RD, Amaral DG. 1998a. Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. J Comp Neurol 398:179–205.
Burwell RD, Amaral DG. 1998b. Perirhinal and postrhinal cortices of the rat: Interconnectivity and connections with the entorhinal cortex. J Comp Neurol 391:293–321.
Burwell RD, Furtak S. 2008. Recognition memory: Can you teach an old dogma new tricks? Neuron 59:523–525.
Burwell RD, Hafeman D. 2003. Positional firing properties of postrhinal cortex neurons. Neuroscience 119:577–588.
Burwell RD, Witter MP, Amaral DG. 1995. Perirhinal and postrhinal cortices of the rat: A review of the neuroanatomical literature and comparison with findings from the monkey brain. Hippocampus 5:390–408.
Burwell RD, Shapiro ML, O'Malley MT, Eichenbaum H. 1998. Positional firing properties of perirhinal cortex neurons. Neuroreport 9:3013–3018.
Burwell RD, Bucci D, Sanborn M, Jutras M. 2004a. Perirhinal and postrhinal contributions to remote memory for context. J Neurosci 24:11023–11028.
Burwell RD, Saddoris M, Bucci D, Wiig K. 2004b. Corticohippocampal contributions to spatial and contextual learning. J Neurosci 24:3826–3836.
Chrobak J, Amaral DG. 2007. Entorhinal cortex of the monkey. Vii. Intrinsic connections. J Comp Neurol 500:612–633.
Dellu F, Fauchey V, Le Moal M, Simon H. 1997a. Extension of a new two-trial memory task in the rat: Influence of environmental context on recognition processes. Neurobiol Learn Mem 67:112–120.
Dellu F, Mayo W, Vallee M, Le Moal M, Simon H. 1997b. Facilitation of cognitive performance in aged rats by past experience depends on the type of information processing involved: A combined cross-sectional and longitudinal study. Neurobiol Learn Mem 67:121–128.
Dere E, Huston J, De Souza Silva MA. 2005. Integrated memory for objects, places, and temporal order: Evidence for episodic-like memory in mice. Neurobiol Learn Mem 84:214–221.
Deshmukh S, Knierim JJ. 2011. Representation of non-spatial and spatial information in the lateral entorhinal cortex. Front Behav Neurosci 5:69.
Deshmukh S, Yoganarasimha D, Voicu H, Knierim JJ. 2010. Theta modulation in the medial and the lateral entorhinal cortices. J Neurophysiol 104:994–1006.
Deshmukh S, Johnson J, Knierim JJ. 2012. Perirhinal cortex represents nonspatial, but not spatial, information in rats foraging in the presence of objects: Comparison with lateral entorhinal cortex. Hippocampus 22:2045–2058.
Diana R, Yonelinas A, Ranganath C. 2007. Imaging recollection and familiarity in the medial temporal lobe: A three-component model. Trends Cogn Sci 11:379–386.
Dolorfo C, Amaral DG. 1998a. Entorhinal cortex of the rat: Organization of intrinsic connections. J Comp Neurol 398:49–82.
Dolorfo C, Amaral DG. 1998b. Entorhinal cortex of the rat: Topographic organization of the cells of origin of the perforant path projection to the dentate gyrus. J Comp Neurol 398:25–48.
Eichenbaum H, Yonelinas A, Ranganath C. 2007. The medial temporal lobe and recognition memory. Annu Rev Neurosci 30:123–152.
Furtak S, Wei S, Agster K, Burwell RD. 2007. Functional neuroanatomy of the parahippocampal region in the rat: The perirhinal and postrhinal cortices. Hippocampus 17:709–722.
Furtak S, Ahmed OJ, Burwell RD. 2012. Single neuron activity and theta modulation in postrhinal cortex during visual object discrimination. Neuron 76:976–988.
Gilbert PE, Kesner RP. 2003. Localization of function within the dorsal hippocampus: The role of the CA3 subregion in paired-associate learning. Behav Neurosci 117:1385–1394.
Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. Nature 436:801–806.
Hargreaves E, Rao G, Lee I, Knierim JJ. 2005. Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. Science 308:1792–1794.
Hayman R, Chakraborty S, Anderson M, Jeffery KJ. 2003. Context-specific acquisition of location discrimination by hippocampal place cells. Eur J Neurosci 18:2825–2834.
Hunsaker MR, Kesner RP. 2008. The attributes of episodic memory processing. In: Dere E, Easton A, Nadel L, Huston JP, editors. Handbook of Episodic Memory. Amsterdam: Elsevier. pp 57–80.
Hunsaker MR, Mooy GG, Swift JS, Kesner RP. 2007. Dissociations of the medial and lateral perforant path projections into dorsal dg, CA3, and CA1 for spatial and nonspatial (visual object) information processing. Behav Neurosci 121:742–750.
Hunsaker MR, Rosenberg JS, Kesner RP. 2008. The role of the dentate gyrus, CA3a,b, and CA3c for detecting spatial and environmental novelty. Hippocampus 18:1064–1073.
Insausti R, Amaral DG. 2008. Entorhinal cortex of the monkey. IV. Topographical and laminar organization of cortical afferents. J Comp Neurol 509:608–641.
Insausti R, Amaral DG, Cowan WM. 1987a. The entorhinal cortex of the monkey. Ii. Cortical afferents. J Comp Neurol 264:356–395.
Insausti R, Amaral DG, Cowan WM. 1987b. The entorhinal cortex of the monkey. Iii. Subcortical afferents. J Comp Neurol 264:396–408.
Jeffery KJ, Anderson M. 2003. Dissociation of the geometric and contextual influences on place cells. Hippocampus 13:868–872.
Kerr KM, Agster KL, Furtak SC, Burwell RD. 2007. Functional neuroanatomy of the parahippocampal region: The lateral and medial entorhinal areas. Hippocampus 17:697–708.
Kesner RP. 2007a. A behavioral analysis of dentate gyrus function. Prog Brain Res 163:567–576.
Kesner RP. 2007b. Behavioral functions of the ca3 subregion of the hippocampus. Learn Mem 14:771–781.
Kesner RP, Hunsaker MR. 2010. The temporal attributes of episodic memory. Behav Brain Res 215:299–309.
Kesner RP, Ravindranathan A, Jackson PA, Giles R, Chiba AA. 2001. A neural circuit analysis of visual recognition memory: Role of perirhinal, medial, and lateral entorhinal cortex. Learn Mem 8:87–95.
Kesner RP, Hunsaker MR, Warthen M. 2008. The CA3 subregion of the hippocampus is critical for episodic memory processing by means of relational encoding in rats. Behav Neurosci 122:1217–1225.
Knierim JJ. 2006. Neural representations of location outside the hippocampus. Learn Mem 13:405–415.
Knierim JJ, Lee I, Hargreaves E. 2006. Hippocampal place cells: Parallel input streams, subregional processing, and implications for episodic memory. Hippocampus 16:755–764.
Langston R, Wood E. 2010. Associative recognition and the hippocampus: Differential effects of hippocampal lesions on object-place, object-context and object-place-context memory. Hippocampus 20:1139–1153.
Langston R, Stevenson C, Wilson C, Saunders I, Wood E. 2010. The role of hippocampal subregions in memory for stimulus associations. Behav Brain Res 215:275–291.
Lavenex P, Amaral DG. 2000. Hippocampal-neocortical interaction: A hierarchy of associativity. Hippocampus 10:420–430.
Lee I, Hunsaker MR, Kesner RP. 2005. The role of hippocampal subregions in detecting spatial novelty. Behav Neurosci 119:145–153.

Morris RGM. 2001. Episodic-like memory in animals: Psychological criteria, neural mechanisms and the value of episodic-like tasks to investigate animal models of neurodegenerative disease. Philos Trans R Soc Lond B Biol Sci 356:1453–1465.

Mumby D. 2001. Perspectives on object-recognition memory following hippocampal damage: Lessons from studies in rats. Behav Brain Res 127:159–181.

Mumby D, Gaskin S, Glenn M, Schramek T, Lehmann H. 2002a. Hippocampal damage and exploratory preferences in rats: Memory for objects, places, and contexts. Learn Mem 9:49–57.

Mumby D, Glenn M, Nesbitt C, Kyriazis D. 2002b. Dissociation in retrograde memory for object discriminations and object recognition in rats with perirhinal cortex damage. Behav Brain Res 132:215–226.

O'Brien N, Lehmann H, Lecluse V, Mumby D. 2006. Enhanced context-dependency of object recognition in rats with hippocampal lesions. Behav Brain Res 170:156–162.

Piterkin P, Cole E, Cossette M, Gaskin S, Mumby D. 2008. A limited role for the hippocampus in the modulation of novel-object preference by contextual cues. Learn Mem 15:785–791.

Poucet B. 1989. Object exploration, habituation, and response to a spatial change in rats following septal or medial frontal cortical damage. Behav Neurosci 103:1009–1016.

R Development Core Team. 2012. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing.

Ranganath C. 2010. A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. Hippocampus 20:1263–1290.

Rolls ET. 2010. A computational theory of episodic memory formation in the hippocampus. Behav Brain Res 215:180–196.

Rolls ET, Kesner RP. 2006. A computational theory of hippocampal function, and empirical tests of the theory. Prog Neurobiol 79:1–48.

Rolls ET, Stringer SM, Trappenberg T. 2002. A unified model of spatial and episodic memory. Proc Biol Sci 269:1087–1093.

Rolls ET, Stringer SM, Elliot T. 2006. Entorhinal cortex grid cells can map to hippocampal place cells by competitive learning. Network 17:447–465.

Si B, Treves A. 2009. The role of competitive learning in the generation of dg fields from ec inputs. Cogn Neurodyn 3:177–187.

Suzuki WA. 2003. Declarative versus episodic: Two theories put to the test. Neuron 38:5–7.

Suzuki WA, Amaral DG. 1994. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. J Neurosci 14:1856–1877.

Van Cauter T, Camon J, Alvernhe A, Elduayen C, Sargolini F, Save E. 2012. Distinct roles of medial and lateral entorhinal cortex in spatial cognition. Cereb Cortex.

Witter MP, Amaral DG. 1991. Entorhinal cortex of the monkey. V. Projections to the dentate gyrus, hippocampus, and subicular complex. J Comp Neurol 307:437–459.

Witter MP, Van Hoesen GW, Amaral D. 1989. Topographical organization of the entorhinal projection to the dentate gyrus of the monkey. J Neurosci 9:216–228.

Yoganarasimha D, Rao G, Knierim JJ. 2011. Lateral entorhinal neurons are not spatially selective in cue-rich environments. Hippocampus 21:1363–1374.