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Evidence That the Rat Hippocampus Has Contrasting Roles in Object Recognition Memory and Object Recency Memory

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Adult rats with extensive, bilateral neurotoxic lesions of the hippocampus showed normal forgetting curves for object recognition memory, yet were impaired on closely related tests of object recency memory. The present findings point to specific mechanisms for temporal order information (recency) that are dependent on the hippocampus and do not involve object recognition memory. The object recognition tests measured rats exploring simultaneously presented objects, one novel and the other familiar. Task difficulty was varied by altering the retention delays after presentation of the familiar object, so creating a forgetting curve. Hippocampal lesions had no apparent effect, despite using an apparatus (bow-tie maze) where it was possible to give lists of objects that might be expected to increase stimulus interference. In contrast, the same hippocampal lesions impaired the normal preference for an older (less recent) familiar object over a more recent, familiar object. A correlation was found between the loss of septal hippocampal tissue and this impairment in recency memory. The dissociation in the present study between recognition memory (spared) and recency memory (impaired) was unusually compelling, because it was possible to test the same objects for both forms of memory within the same session and within the same apparatus. The object recency deficit is of additional interest as it provides an example of a nonspatial memory deficit following hippocampal damage.

Keywords: hippocampus, perirhinal cortex, rat, recency memory, recognition memory

There is continued debate over whether the hippocampus has an obligatory role in overseeing the mnemonic contributions of parahippocampal areas such as the perirhinal cortex (Squire & Zola–Morgan, 1991; Squire, Wixted, & Clark, 2007; Wixted & Squire, 2011) or whether parahippocampal areas support independent forms of memory (Aggleton & Brown, 1999, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007). This debate has centered on recognition memory as the perirhinal cortex is known to be important for this form of memory (Brown & Aggleton, 2001; Murray, 1996; Winters, Saksida, & Bussey, 2008), raising the question of whether the hippocampus is of comparable importance. Determining the contributions of the hippocampus for recognition memory also has broader implications for distinguishing models of recognition memory (Mandler, 1980; Yonelinas, 2002).

These issues can be examined in rats where it is possible to make hippocampal lesions that spare parahippocampal areas. Initial studies of recognition memory, which used reinforced delayed matching-to-sample or delayed nonmatching-to-sample tasks, often found no apparent hippocampal lesion deficit (Aggleton, Hunt, & Rawlins, 1986; Mumby, 2001; Mumby, Wood, & Pinel, 1992; but see Clark, West, Zola, & Squire, 2001). A limitation was that these tasks involved relatively short retention delays. This limitation was removed by the introduction of the spontaneous object recognition task (Ennaceur & Delacour, 1988), which has the added benefit that it does not require an initial phase of rule learning. While many subsequent studies using the spontaneous object recognition task reported no apparent hippocampal lesion effect on spontaneous object recognition, even after long retention delays (e.g., Barker, Bird, Alexander, & Warburton, 2007; Barker & Warburton, 2011b; Forwood, Winters, & Bussey, 2005; Mumby, 2001; Mumby, Tremblay, Lecluse & Lehman, 2005; Winters, Forwood, Cowell, Saksida, & Bussey, 2004), other studies found deficits (e.g., Clark, Zola, & Squire, 2000; Broadbent, Squire, & Clark, 2004, Broadbent, Gaskin, Squire, & Clark, 2010; Gaskin et al., 2010). One possibility is that these different results arise from attributes of the spontaneous object recognition task.

It has been noted that spontaneous object recognition is typically run in a large arena, often providing a wealth of spatial cues both from the apparatus itself and the test room (Forwood et al., 2005; Gaskin et al., 2010; Winters et al., 2008). It is also known that rats will spontaneously associate object–location and object–context information (Save, Poucet, Foreman, & Buhot, 1992; Dix & Aggleton, 1999), and that this learning often involves the hippocampus (Barker & Warburton, 2011b; Ennaceur, Neave, & Aggleton, 1997; Mumby, Gaskin, Glenn, Schramek, & Lehman, 2002; Piterkin, Cole, Cossette, Gaskin, & Mumby, 2008; Save et al., 1992). Such associative information might make individual objects easier to discriminate and so indirectly aid recognition. Another issue is that hippocampal lesions can cause hyperactivity (Davidson & Jarrard, 2004; Gray & McNaughton, 1983) and so potentially disrupt exploration. Indeed, changes in exploration levels have been linked to hippocampal lesion deficits for spontaneous object recognition (Ainge et al., 2006). Finally, quantifying

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object exploration in the spontaneous object recognition task is problematic as all experiments have to assume that only behavior in the immediate vicinity of an object (e.g., <1 cm) constitutes exploration, even though it has been shown that objects can be visually inspected from further away (Winters & Reid, 2010).

The present study reexamined the impact of hippocampal lesions on object recognition memory but took advantage of the unique features of the bow-tie maze (Albasser et al., 2010). In this apparatus (see Figure 1) two triangular arenas are joined by a short alleyway, with a door to control access to either arena. This arrangement ensures that rats can shuttle between test arenas so that multiple recognition trials can be given within a single session, during which the rat is not handled. As the test objects are placed in enclosed, restricted arenas with high opaque walls it is difficult for the rat to see beyond the apparatus. Furthermore, the test objects are also located close to each other and reappear at different ends of the apparatus. These features should help to negate the use of spatial and contextual information to aid object discrimination. In addition, because the animal shuttles back and forth across the apparatus for food reward, the rats' exploration patterns are partly under experimenter control. Also, because the rat typically faces away from the test objects when it is not retrieving food or exploring objects there may be less opportunity for object sampling from a distance, that is, active exploration that is not formally measured.

The ability to give rats multiple, continuous trials in the bow-tie maze (Albasser et al., 2010) makes it possible to increase interstimulus interference within a session. By having multiple trials it is also possible to test object recognition and object recency for the same objects within the same session, the latter form of memory being more consistently linked to hippocampal function (Barker et al., 2007; Barker & Warburton, 2011b; Brown, Warburton, & Aggleton, 2010; Charles, Gaffan, & Buckley, 2004; Fortin, Agster, & Eichenbaum, 2002). For these reasons, Experiment 1 examined the importance of the hippocampus for object recognition memory in the bow-tie maze across varying retention intervals, that is, to compile a forgetting curve. Experiment 2 examined recency judgments using a design with two key elements. First, the retention intervals required to solve the recency task overlapped with those assessed for object recognition in Experiment 1. Second, the objects to be discriminated for recency judgments had previously been tested for recognition during the sample phase of the same session. In this way, the selectivity of any recency memory deficit could be determined.

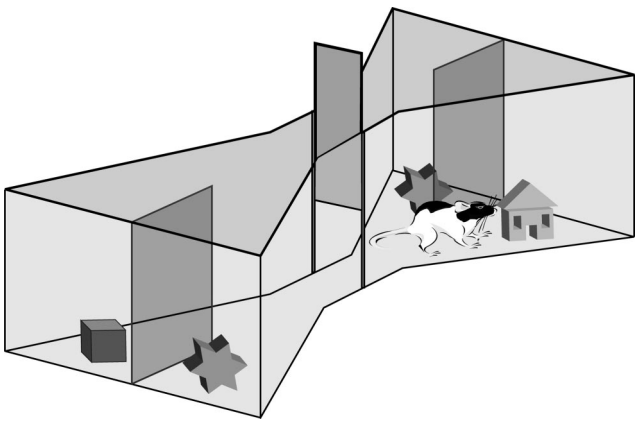

Figure 1. Schematic of the bow-tie maze. A sliding door separates the two ends of the maze in which two objects are placed.

Materials and Methods

Animals

The experiments used 26 male rats (*Rattus norvegicus*) of the Lister Hooded strain (Harlan, Bicester, UK). The rats were housed in pairs under diurnal conditions (14:10-hr light–dark cycle). Water was provided ad libitum throughout the study. Sixteen rats received bilateral ibotenic acid lesions of the hippocampus (Group HPC) and 10 rats received sham operations (Group Control). A week before the beginning of the experiments, animals were food deprived to no lower than 85% of their free-feeding body weights. All experiments were performed in accordance with the UK Animals (Scientific Procedures) Act, 1986, and associated guidelines. Prior to the experiments described below, the rats had been trained on an appetitive trace conditioning task in an operant chamber (Lin et al., unpublished data). This task involved two different trace intervals.

Surgery and Histology

The surgical procedure was closely modeled on that described by Iordanova, Burnett, Good, Aggleton, and Honey (2009). To summarize, rats were first anesthetized with isoflurane and then placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA). Once the scalp had been incised and the bone overlying the area of neocortex directly above the hippocampus removed, a 2-μl Hamilton syringe mounted on the stereotaxic frame was used to infuse ibotenic acid into the hippocampus. The ibotenic acid (Biosearch Technologies, San Rafael, CA) was dissolved in phosphate-buffered saline (pH 7.4) to provide a solution with a concentration of 63 mM. Injections, each of 0.05–0.10 μl, were made at 28 sites with a KD Scientific electronic pump (Model 5000; Boston, MA) at a rate of 0.05 μl/min. The coordinates for each injection site have been published previously (Iordanova et al., 2009). After each injection, the needle was left in position for 2 min to allow diffusion of the ibotenic acid and to limit the spread of the drug into overlying cortical areas. Sham-operated rats received an identical treatment with the exception that the dura was repeatedly perforated with a 25-gauge Microlance3 needle (Becton Dickinson, Drogheda, Ireland) and no fluid was infused. At the completion of the study all rats were perfused intracardially, and coronal brain sections cut (40 μm) and stained (Nissl) as described elsewhere (Iordanova et al., 2009).

Apparatus

For all experiments, rats were tested in a bow-tie-shaped maze made with steel walls and a wooden floor (see Albasser et al., 2010). The maze was 120 cm long, 50 cm wide, and 50 cm high. Each end of the apparatus formed a triangular arena, the apices of which were joined by a narrow corridor (12 cm wide). An opaque sliding door set in the middle of the corridor could be raised by the experimenter. The far wall of each triangular arena contained two

recessed food wells, 3.5 cm in diameter and 2 cm deep. The food wells were separated by a short, opaque dividing wall that protruded 15 cm from the middle of the end wall. The purpose of this central dividing wall was to ensure that when a rat was close to one object it could not see the other object, although it could readily walk around the wall to access the other object. These food wells were covered by objects in the experiment proper.

Objects

The experiments used numerous junk objects, each differing in shape, texture, size, and color. Every object was large enough to cover a food well, but light enough to be displaced. Any object with an obvious scent was excluded. Sufficient objects ensured that no object was repeated across experiments. All objects had multiple, identical copies, so that different copies of the same object were always used when an object was repeated within a session. All objects were cleaned with alcohol wipes after each session.

Habituation and Pretraining

All rats were habituated to the maze so that after seven pretraining sessions they would run from one side of the maze to the other and displace an object covering a food well in order to reach food rewards (For fuller description, see Albasser et al., 2010). Four pairs of objects were used during pretraining, but these objects were not used in any of the following experiments.

General Protocol—Object Recognition

Each session contained multiple trials, and during each trial the animal could freely explore two objects, typically one novel the other familiar (see Table 1). To start each session, a rat was placed on one side of the maze (Trial 0; Table 1, Standard object recognition), where a single object (object A) covered a food well that contained a single sucrose pellet (45 mg; Noyes Purified Rodent Diet, Lancaster, NH). The rat remained in that part of the maze (with object A) for 1 min. The central sliding door was then raised and the rat ran to the opposite side of the maze. There, the rat had a free choice between object A, now familiar, and novel object B (Trial 1; Table 1). Again each object was free to explore for a maximum of 1 min (see Table 1) before the start of Trial 2 (familiar object B vs. novel object C). Animals received multiple trials (up to 24 in a session, see Table 1). Both the familiar and the novel objects always covered a single 45-mg sucrose pellet, which the rat pushed aside to retrieve. This baiting procedure, which ensured that the objects were approached, did not affect the validity of the recognition test, as this relied on the differential exploration of the objects. The placement of objects (including novel objects) varied from left to right according to a pseudorandom schedule. For all experiments, the order of the particular objects used in the test was reversed for half of the rats. This counterbalancing ensured that the novel object in any given pair is reversed; for example for half of the rats in the trial that paired together the following two objects, a toy and a cup, the cup was the novel object. For the remaining rats, the toy was the novel object.

Table 1
Sequences of Object Presentation Used for the Three Object Recognition Memory Studies (Experiments 1A-C) and the Object Recency Study (Experiment 2)

A. Retention delays of 1–24 min (Exp 1A)

Trials	object	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
		—	A	B	C	D	E	F	G	H	I	J	K	L	N	O	P	Q	R	S	T	U	V	W	X	Y
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**												

B. Retention delays of 1 h or 2 h (Exp 1B-C)

Trials	object	0	1	2	3	4	5	6	7	8	9	10		11	12	13	14	15	16	17	18	19	20
		—	A	B	C	D	E	F	G	H	I	J	1 h or 2 h Delay	A	B	C	D	E	F	G	H	I	J
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**		**L**	**M**	**N**	**O**	**P**	**Q**	**R**	**S**	**T**	**U**

C. Recency (Exp 2)

Trials	object	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
		—	A	B	C	D	E	F	G	H	20 min delay	—	J	K	L	N	O	P	Q	60 min delay	J	K	L	M	N	O	P	Q
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**		**J**	**K**	**L**	**M**	**N**	**O**	**P**	**Q**	**R**		**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**

Note. Each trial has two objects, each depicted by a letter. The exception is Trial 0, which allows the initial object to become familiar. Novel objects are indicated in bold type. For object recognition, a delay of 1 min (Experiment 1A), or a delay of either 1 h or 2 h (Experiment 1B) was placed mid-way through the testing protocol. Every trial consists of one novel object and one familiar object, although the length of time between initial exposure to an object and its subsequent use as a "familiar" object varied with the conditions. Object recency (C) consisted of two blocks of sample stimuli, 20 min apart, followed by a test phase 60 min later in which an object from the first block was always paired with an object from the second block.

Experiment 1—Retention Delay Protocol

Experiment 1A—Retention Delays of 1–24 Min

Rats received one session of 24 trials, of which the first 12 trials matched the general protocol described above, that is, 1-min trials each with two different objects, one of which was novel, while the other was familiar (as it had also been present on the previous trial). Trial 12 was followed by a "blank" trial of 1-min duration, in which the rat ran to the other side of the maze to get the food rewards, but no objects were present. On Trial 13, the delay phase began. For Trials 13–24, a novel object was always presented with a familiar object that had been used during Trials 1–12 (see Table 1A). The objects made familiar from Trials 1–12 were repeated in the reverse order for delay testing; for example, if A was presented in Trial 1, then the copy of A was the last familiar object used in the delay phase, that is, Trial 24. In this way, the retention interval, or lag, increased from 2 to 24 min across trials, an increase of 2 min per trial from Trials 13–24.

Experiments 1B and 1C—Retention Delays of 1 Hr and 2 Hr

Two separate delay experiments (1 hr and 2 hr) were performed. Each experiment consisted of two phases (see Table 1B). First, animals were tested on the standard object recognition task with a retention delay <1 min for 10 trials (as described above). At the end of this phase, the rats were placed back in their home cage for 1 hr (Experiment 1B). This delay phase was followed with 10 further trials. On each trial (11–20), a novel object was presented along with an object that had been presented during the standard object recognition phase (Trials 1–10). After a minimum of 3 days, all rats were tested with new objects in exactly the same way except that the retention delay between the two phases was increased to 2 hr (Experiment 1C).

Experiment 2—Recency Protocol

The experiment consisted of three phases, each of eight trials (see Table 1C). In Phase 1, animals were run in the standard object recognition phase (SOR1) using nine different objects over eight trials (List A). At the end of this phase, animals were placed back in their home cage for 20 min. In Phase 2, the animals were returned to the bow-tie maze and tested for eight trials, again on the standard object recognition protocol (SOR2) but using a new set of nine different objects (List B). Phase 2 was followed by a further retention delay of 60 min. In Phase 3, the animals were now tested on the recency task in which each trial (eight in total, 60 s each) contained one object from List A and one object from List B. As a consequence, the time from the first object in List A to the start of recency testing was 96 min (see Table 1). The expectation was that normal rats would prefer objects from List A, that is, spend less time with the object from List B that had been explored more recently.

Analysis of Behavior

Animals were video recorded throughout training. Object exploration was defined as directing the nose at a distance <1 cm from the object, with the vibrissae moving, and/or touching it with the nose or the paws. Object exploration was not scored when animals sat on the object, when rats used the object to rear upward with the nose of the rat facing the ceiling, or when chewing the object. The duration of exploration was determined by holding down a key pad on a computer during the bursts of exploration recorded on video. For tests of object recognition, two performance indices were calculated, D1 and D2 (Ennaceur & Delacour, 1988). Index D1 is the duration of exploration time devoted to the novel object minus the exploration time devoted to the familiar object. Thus, the "cumulative D1" is the sum of the D1 scores across each trial. The second measure (D2) also uses the difference in exploration times (i.e., D1), but then divides D1 by the total duration of exploration given to both the novel and familiar objects. Thereby, the D2 index, which can vary between $+1$ and -1, better compensates for individual changes in amounts of exploration. A positive D2 index shows a preference for novel objects while a D2 of 0 corresponds to no preference, that is, chance. The "updated D2" scores corresponds to the D2 ratio recalculated after each trial of a block of trials. For this updating the cumulative D1 score was divided by total exploration. The indices D1 and D2 were also used to examine recency performance.

Data Analysis

In all experiments, the rats received multiple trials. These trial data were then combined to help reduce variance. The final results are based on these grouped trial data.

Experiment 1A (short retention delays). The test trials (Trials 13–24) were grouped into three blocks, each of four trials (Trials 13–16, Trials 17–20, Trials 21–24). The mean retention interval for a recognition trial in each block was 5 min (Trials 13–16), 13 min (Trials 17–20), and 21 min (Trials 21–24). A further block of data (retention <1 min) came from the 12 initial trials (their D1 scores divided by 3). The two surgical groups were compared in a mixed analysis of variance (ANOVA; within-subjects factor = retention interval; between-subjects factor = surgical group) for both D1 (cumulative for each block of four trials) and D2 (updated for each block of four trials).

Experiments 1B and 1C (long retention delays). The analysis was as for Experiment 1A except that the longer retention delays were either 1 hr or 2 hr. For each rat, the cumulative D1 score and the updated D2 score were first calculated. One-sample *t*-tests (one-tailed) examined whether recognition performance by individual groups was above chance.

Composite forgetting curve. Object recognition data were available for retention delays of 1 min, 5 min, 13 min, 21 min (blocked data from Experiment 1A), 60 min, and 120 min (Experiments 1B, 1C). The updated D2 score from each delay condition was plotted to provide a forgetting curve (The D1 index was not used as the number of trials differed across the various delay conditions, and the D2 index better compensates for any individual activity levels).

Experiment 2 (recency judgments). The first set of analyses compared the recency scores of the two groups using a *t*-test (D1 then D2). The next step was to determine whether the two groups differed on the initial object recognition phase (SOR1, SOR2, <1 min delay). This second analysis involved a mixed ANOVA (within-subjects factor = SOR1, SOR2; between-subjects factor =

surgical group). Finally, a direct comparison was made between recognition and recency by comparing the mean performance across the two sample phases (SOR1 + SOR2) with performance in the object recency test (mixed ANOVA). One-sample *t*-tests (one-tailed) again examined whether performance by individual groups was above chance.

Results

Histology

Figure 2 depicts a series of coronal sections of the brain (adapted from Paxinos & Watson, 2005), showing the case with the largest overall lesion (in gray) and the case with the smallest lesion (in black). To estimate the extent of hippocampal damage all lesions were plotted onto six equally spaced, coronal sections (Bregma −2.28, −3.12, −3.96, −4.80, −5.64, −6.48) from Paxinos and Watson (2005). All 16 rats in the HPC group had extensive bilateral lesions. Assessments of total hippocampal tissue loss gave a mean of 81.9% (range 64.5% – 92.3%) with a median of 85.4%.

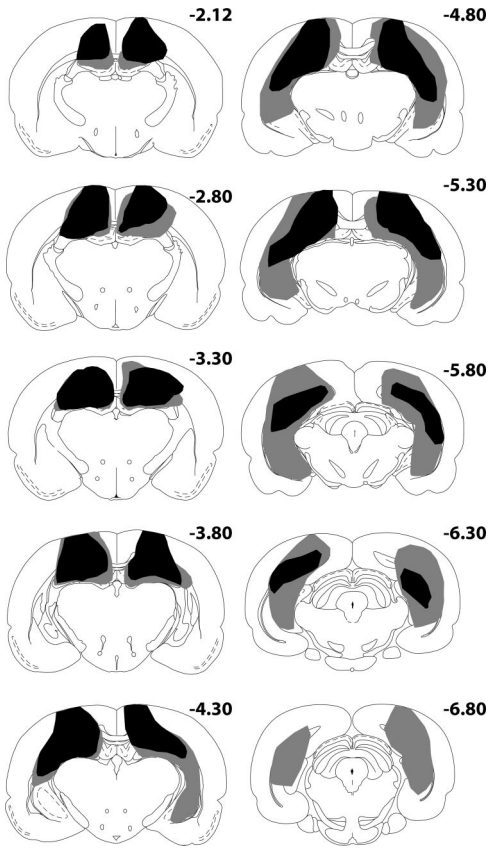

Figure 2. Series of ten coronal sections showing the extent of the lesions in the two HPC cases with the largest (gray) and smallest (black) amount of tissue loss. The sections are from Paxinos and Watson (1997), and the numbers refer to the level of the section behind bregma. *The Rat Brain in Stereotaxic Coordinates* (4th ed.), pp. 28, 31, 33, 35, 41, 43, 45, 47, 357, and 359 by G. Paxinos & C. Watson, 1997, New York, NY: Academic Press. Copyright 1997 by Elsevier Academic Press. Adapted with permission.

Of these 16 rats, 12 had a total hippocampal tissue loss of >75% (see Broadbent et al., 2004).

The tissue loss in the dorsal (septal) hippocampus was particularly extensive (dentate gyrus, CA1–4), with 14 cases having >75% tissue loss. [For this analysis the border between dorsal and ventral hippocampus was arbitrarily placed at −5.5 below bregma (Paxinos & Watson, 2005)]. The only septal area that consistently showed some tissue sparing was the most medial part of the septal hippocampus. As a consequence, the medial blade of the dentate gyrus (or part of the medial blade) was partially spared at the most rostral parts of the dorsal hippocampus in some hemispheres. There were occasionally remnants of the immediately adjacent CA3 at the septal extreme of the hippocampus. The lesions were a little more variable in the ventral hippocampus, such that only seven rats had tissue loss >75% (mean 67%). The lesions typically involved most of the CA1 and CA3 subfields in the ventral hippocampus, though remnants of the ventral dentate gyrus were typically present. The perirhinal cortex was consistently spared.

Estimates of tissue loss in the subicular cortices (subiculum, parasubiculum, presubiculum, and postsubiculum) gave a mean of 32.6% (range 12.2% – 57.3%) and a median of 33.5%.

The dorsal subiculum was extensively damaged in all cases, and in six cases the region was removed completely in both hemispheres. The ventral subiculum was partially damaged in both hemispheres in all cases. The postsubiculum was consistently affected, with extensive loss of that part of the postsubiculum adjacent to the dorsal subiculum in five cases. There was, however, sparing of the postsubiculum at the most caudal level of the hippocampus.

Reflecting the extent of the tissue loss in the dorsal hippocampus, there was additional loss of parts of the overlying cortex in all cases. This damage typically included parts of the motor cortex, lateral dysgranular retrosplenial cortex, and parietal cortex (above dorsal CA1), often extending caudally to reach visual areas. While this extrahippocampal damage was greater than intended, it only partially affected the sites mentioned above, that is, there was considerable sparing in each of these areas.

Experiment 1—Retention Delay

Experiment 1A (short retention delays). Object recognition memory over four delays (1, 5, 13, and 21 min) was compared. As is evident from Figure 3 (upper), there was no significant lesion effect on the various short retention delays (D2: $F < 1$; D1: $F < 1$) and no significant retention delay effect (D2: $F_{(3,72)} = 1.37$, $p = .26$; D1: $F < 1$). Likewise no Group × Delay interaction was found (D2: $F < 1$; D1: $F < 1$). Further analyses that used the data from across the session showed that both groups successfully discriminated the novel from familiar objects, one-sample *t*-test, controls, D2 $t_{(9)} = 9.74$, $p < .001$; D1 $t_{(9)} = 7.70$, $p < .001$: HPC, D2 $t_{(15)} = 14.7$, $p < .001$; D1 $t_{(15)} = 7.83$, $p < .001$. Finally, there was no evidence that overall exploration rates (Figure 3 upper) were affected by the surgery ($F < 1$), or the various delays ($F < 1$), and there was no Group × Delay interaction ($F < 1$) for total exploration times. Attention was also given to the exploration time for the very first object in the session (Object A, Trial 0, see Table 1), as this provides the clearest measure of exploration levels as it is unaffected by competition with another object. No evidence was

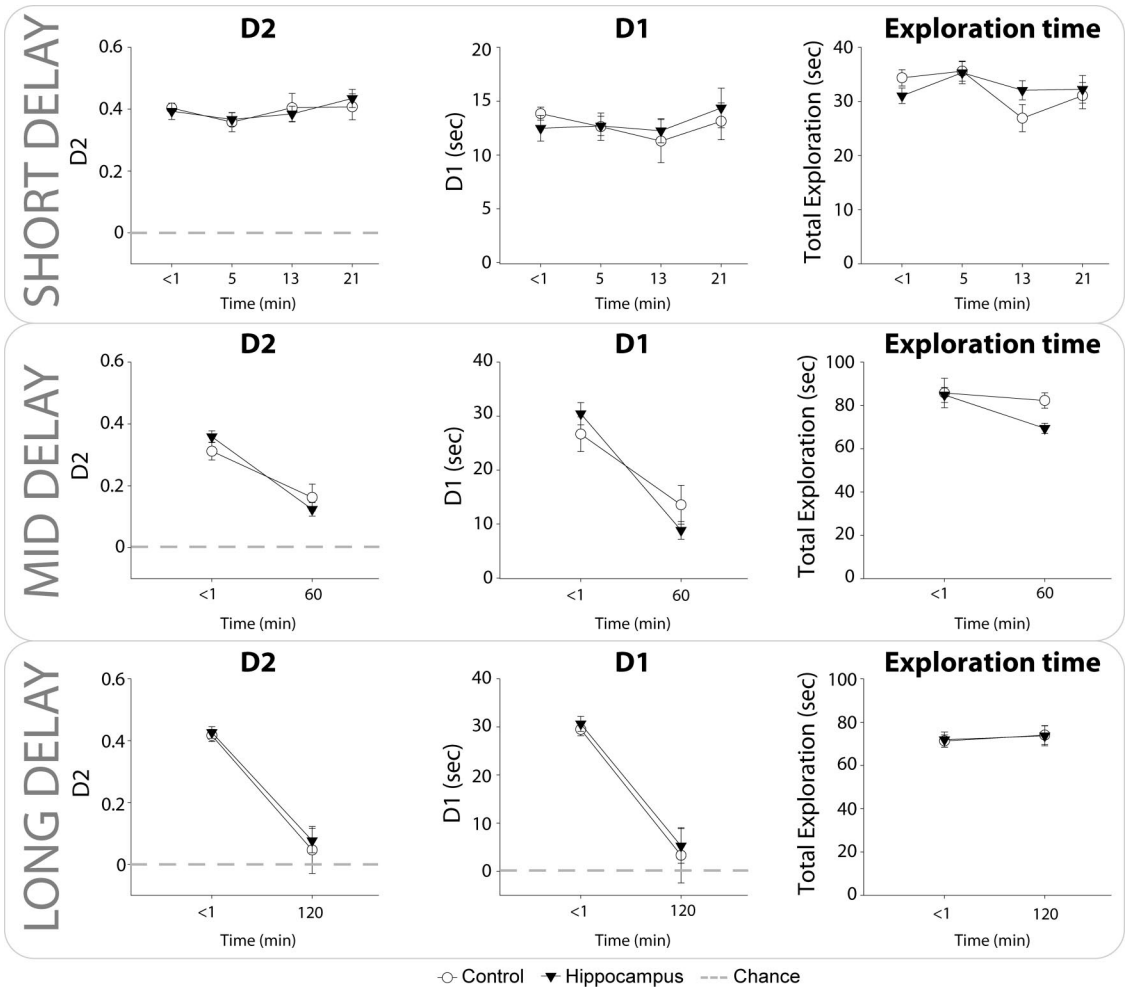

Figure 3. Object recognition: Graphs showing the performance of rats with hippocampal lesions (black square) and their controls (open circle) on the three separate tests of object recognition memory. The upper graphs (short delay) show recognition performance (mean D2 and D1 scores, ±1 standard error [SE]) across the four sets of time intervals in Experiment 1A (blocked in sets of 4 trials). The mid level (mid delay) shows mean D2 and D1 (1 SE) scores for the 1 min and 60 min retention intervals in Experiment 1B. The bottom level (long delay) shows mean D2 and D1 scores (1 SE) for the 1 min and 120 min retention intervals in Experiment 1C. Chance levels are shown by the dashed line. Total object exploration times are depicted on the right.

found of a group difference on Trial 0 (means, controls = 12.4s, HPC = 13.7 s).

Experiment 1B (mid-length retention delays). Object recognition memory was compared over 1 min and 60 min. As shown by Figure 3 (mid delay), neither D1 nor D2 provided evidence of a hippocampal lesion effect (D2: $F < 1$; D1: $F < 1$). There was, however, a decrease in performance from 1 min to 60 min, Figure 2 mid delay: D2, $F_{(1,24)} = 56.95$, $p < .001$; D1, $F_{(1,24)} = 59.63$, $p < .001$. The Group × Delay interaction was not significant, and although it suggested a possible group difference, D2: $F_{(1,24)} = 2.81$, $p = .11$; D1: $F_{(1,24)} = 3.58$, $p = .071$, there was no evidence that the two groups differed at either time interval. Subsequent analysis showed that both groups performed above chance after a retention delay of 60 min; that is, both groups spent more times exploring novel objects as compared with the familiar objects, one-sample *t*-test, controls, D2 $t_{(9)} = 3.75$, $p = .003$; D1 $t_{(9)} = 3.77$, $p = .002$: HPC, D2, $t_{(15)} = 5.72$, $p < .001$; D1 $t_{(15)} = 5.41$, $p < .001$.

Levels of overall exploration (Figure 3 mid delay) did not differ between the control and HPC rats, $F_{(1,24)} = 2.14$, $p = .16$, and again there was no difference on Trial 0 (means, controls = 9.7 s, HPC = 9.4 s). There was, however, a significant delay effect for total exploration, $F_{(1,24)} = 8.78$, $p = .007$, and a borderline Group × Delay interaction, $F_{(1,24)} = 3.48$, $p = .075$. Analysis of the simple effects revealed no significant difference between the two groups at 1min ($F < 1$), but that controls spent more time exploring both novel and familiar objects after a retention delay of 60 min, $F_{(1,48)} = 5.01$, $p = .028$. For this reason, the results using the recognition index D2 are probably the more meaningful as this index partially compensates for rates of exploration.

Experiment 1C (long retention delays). As shown in Figure 3 (long delay), there does not appear to any lesion effect when rats

were tested at 1-min or 120-min delays. No significant lesion effect was found (D2: $F < 1$; D1: $F < 1$), but performance fell on increasing the retention delay from 1 min to 120 min, D2: $F_{(1,24)} = 79.31$, $p < .001$; D1: $F_{(1,24)} = 55.13$, $p < .001$. There was no Group × Delay interaction (D2: $F < 1$; D1: $F < 1$). Further analysis revealed that the recognition scores after a retention delay of 120 min of the control group were not significantly above chance while those scores of the HPC group were either above chance or at borderline levels, one-sample *t*-test, controls, D2 $t < 1$; D1, $t < 1$: HPC, D2 $t_{(15)} = 1.94$, $p = .036$; D1 $t_{(15)} = 1.46$, $p = .08$. Finally, total exploration time did not distinguish the two groups ($F < 1$), and there was no effect of delay ($F < 1$) [see Figure 3, long delay]. Likewise, there were no lesion effects on the exploration levels for Trial 0 (means, controls = 8.2 s, HPC = 8.0 s).

Composite Forgetting Curve (Experiments 1)

The D2 scores for object recognition were calculated for retention delays of 1, 5, 13, 21, 60, and 120 min (see Figure 4). Overall, there was no significant group effect (D2: $F < 1$) although, as expected, there was a very clear effect of delay, that is, recognition performance decreased as the retention delay increased [D2: $F_{(5,120)} = 41.19$, $p < .001$]. Further analyses showed that both groups discriminated the novel object from an object that had been explored up to 60 min earlier, one-sample *t*-test, D2, controls $t_{(9)} = 3.75$, $p = .003$; HPC $t_{(15)} = 5.67$, $p < .001$. While the control group did not differ from chance after the longer retention delay of 120 min (D2 controls $t < 1$), the hippocampal lesion group remained narrowly above chance, HPC $t_{(15)} = 1.94$, $p = .036$. It is likely that the latter significant result reflected the larger number of animals in Group HPC. Finally, no group by delay interaction was found (D2: $F < 1$). The total exploration times for the six retention delays also did not differ between the two groups ($F < 1$).

Experiment 2 (recency judgments). The mean performance scores from the recency phase are depicted in Figure 5. The sham rats had superior scores to those of the HPC group for both D2, $t_{(24)} = 2.86$, $p = .009$, and for D1, $t_{(24)} = 2.51$, $p = .019$. Using one-sample *t*-tests (one-tailed) it was found that the sham recency scores were significantly above chance, D2: $t_{(9)} = 5.49$, $p < .001$; D1: $t_{(9)} = 4.11$, $p = .002$, while those of the HPC group narrowly failed to differ from chance, D2: $t_{(15)} = 1.39$, $p = .093$; D1: $t_{(15)} = 1.68$, $p = .057$. There were no group differences in total amounts of object exploration during the recency phase ($t < 1$, Figure 4).

The next step was to see if both sets of rats could recognize the objects used in the two sample phases (SOR1, SOR2) that were initially given to familiarize the objects to be used for recency judgments (see Figure 5). This was possible because each object used in SOR1 and SOR2 was also tested for object recognition (1-min delay) as part of the familiarization procedure. There was no apparent difference between the scores for SOR1 and SOR2 (D2: $F < 1$; D1: $F < 1$), no group effect (HPC vs. sham, D2: $F < 1$; D1: $F < 1$) and no Group × Recognition test interaction (D2: $F < 1$; D1: $F < 1$). Overall exploration levels did not distinguish the two groups ($F < 1$).

The final analysis compared performance on object recognition (data from SOR1 and SOR2 combined – mean D2 or mean D1) with the recency performance from the same session (D2). Recency performance was lower than object recognition, D2: $F_{(1,24)} = 39.44$, $p < .001$; D1: $F_{(1,24)} = 51.50$, $p < .001$, and overall the HPC group were outperformed by the sham rats, D2: $F_{(1,24)} = 11.10$, $p = .003$; D1: $F_{(1,24)} = 7.14$, $p = .012$. The borderline interaction, D2: $F_{(1,24)} = 4.24$, $p = .051$; D1: $F_{(1,24)} = 2.71$, $p = .113$, suggests that the HPC rats had a greater fall in performance on the recency task. Subsequent analyses of simple effects revealed that both groups had similar discrimination scores during the SOR phases (D2 and D1: $F < 1$), but that shams had a greater discrimination scores in the recency phase, D2: $F_{(1,48)} = 13.14$, $p < .001$; D1: $F_{(1,48)} = 8.28$, $p = .003$.

Recency memory: Hippocampal lesion size correlations. In view of the recency deficits, the correlations (Spearman) between recency memory (D2) and lesion volume (septal hippocampus and total hippocampus) were examined. Septal hippocampal volumes correlated significantly with the D2 scores ($\rho = -0.532$, $p = .035$, two-tailed), whereas total hippocampal volume narrowly failed to reach significance ($\rho = -0.476$, $p = .062$). In both cases, the greater the lesion, the poorer the recency memory.

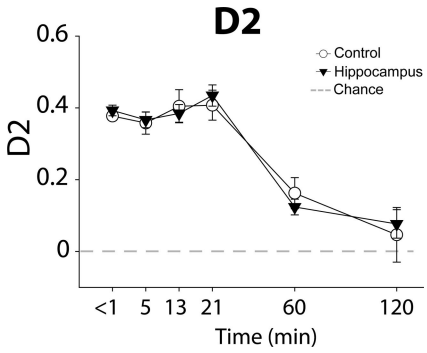

Figure 4. Object recognition forgetting curve: Graphs showing composite object recognition memory performance of rats with hippocampal lesions (black square) and their controls (open circle) across the various retention intervals used in Experiments 1 and 2. Results are just presented for the D2 index. The bars show 1 SE. Chance levels are shown by the dashed line.

Discussion

Rats with extensive cytotoxic lesions of the hippocampus were tested in the bow-tie maze for object recognition memory. There was no evidence that hippocampal damage impaired object recognition memory even though the rats were tested across retention intervals (1 min to 120 min) sufficient to capture a full range of performance levels. This null result is strengthened by the fact that each rat received many individual trials, far more than given in conventional spontaneous object recognition memory tasks. The results considerably extend a previous report, which noted that hippocampal lesions do not disrupt object recognition in the bow-tie maze when tested with short (1 min) retention delays (Albasser et al., 2010). Despite their intact object recognition performance, the same rats with hippocampal lesions were impaired at discriminating between two familiar objects that differed in their relative recency. The extent of this recency deficit was correlated with the extent of tissue loss in the dorsal (septal) hippocampus. This recency discrimination deficit did not appear to be due to the abnormally rapid forgetting of the two familiar test objects (so they

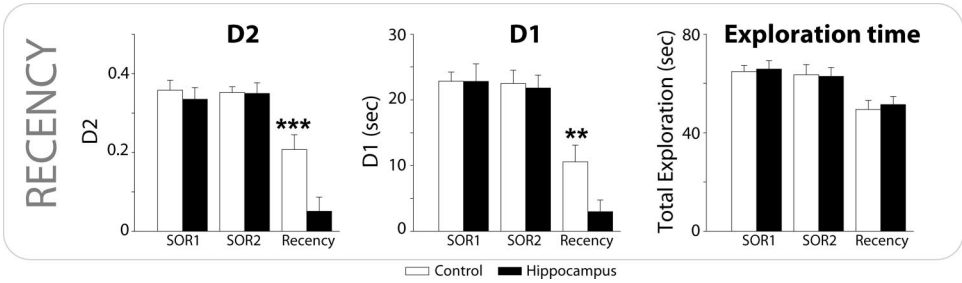

Figure 5. Object recency: Bar charts showing the mean performance of rats with hippocampal lesions (black) and their controls (white) on recency discrimination performance. Only the control group performed above chance ($^{**}p < 0.005$, $^{***}p < 0.001$). In addition, recognition performance is given for the two blocks of stimulus familiarization (SOR1 and SOR2) that included object recognition (retention delay <1 min). Results are given for both the D1 and D2 indices. The bars show 1 SE.

could not be discriminated by temporal order), as the rats with hippocampal lesions could successfully recognize objects after retention delays that overlapped with those for recency. Likewise, there was no evidence that the recency deficit was due to a failure to encode information about the individual objects as these same objects had also been used to test recognition memory in the same session as the recency tests. Finally, it seems unlikely that the recency deficit reflected a sensitivity to increased interstimulus interference as both Experiment 2 (recency) and Experiment 1A (recognition) involved the same number of object pairings per session. Consequently, the findings strongly indicate that hippocampal lesions in rats can spare recognition memory yet impair recency memory, so signaling qualitative differences between these two forms of memory. This recency deficit provides an example of a nonspatial memory impairment following hippocampal damage.

Numerous previous studies have described the effects of hippocampal lesions on object recognition memory using a variety of protocols (for reviews see Mumby, 2001; Steckler, Drinkenburg, Sahgal, & Aggleton, 1998; Winters et al., 2008). While many experiments have found no hippocampal lesion deficit, this is not always the case. One potential factor that can be ruled out is the length of the retention delay, as rats with hippocampal lesions can perform at normal levels after extended retention delays of a day or more (Forwood et al., 2005; Mumby et al., 2005). Likewise, the present study increased task difficulty by having multiple objects within a list to learn, but again there was no lesion deficit, despite the presumed increase in stimulus interference. Of critical importance, the various conditions assessed a wide range of performance levels (see Figure 4). Other factors that might explain the variation in hippocampal lesion effects include: i) the unintended contribution of spatial or contextual information to the recognition task that may aid or hinder novelty discrimination (Dix & Aggleton, 1999; Gaskin et al., 2010; Mumby et al., 2002; Shaw & Aggleton, 1993; Winters et al., 2008); ii) the indirect consequences of changes in activity and exploration patterns following hippocampal damage (Ainge et al., 2006); and iii) the completeness of the hippocampal lesions (Broadbent et al., 2004; Ainge et al., 2006).

Taking this final factor (lesion size) first, there is some evidence that the loss of at least 75% of the total hippocampus might be required for robust recognition memory deficits (Broadbent et al., 2004; but see Ainge et al., 2006). In fact, the hippocampal lesions in the present study were extensive giving a median of 85.4% tissue loss (12 of the 16 rats had over 75% total tissue loss). The study by Broadbent et al. (2004) made the further qualification that object recognition deficits were only found when the dorsal hippocampal damage exceeded 75% and the ventral hippocampal damage exceeded 50%. Thirteen of the HPC rats fitted these criteria. Separate analyses (not reported) examined the object recognition scores of these 13 rats, but again found no evidence of lesion-induced deficits. Likewise, other studies involving particularly extensive hippocampal lesions have also reported intact spontaneous object recognition (e.g., Langston & Wood, 2010; Mumby et al., 2002; O'Brien, Lehmann, Lecluse, & Mumby, 2006; Winters et al., 2004).

The bow-tie maze used in the present study, in common with the Y maze used by some other groups (Forwood et al., 2005; Winters et al., 2004, 2008), was designed to reduce the influence of extramaze spatial influences upon performance. In other related studies, opaque curtains or bare test-room walls (e.g., Ainge et al., 2006; Barker & Warburton, 2011a,b) have helped to obscure spatial and contextual cues. In these particular studies, hippocampal lesions were not associated with a specific object recognition deficit. It is intriguing that one study reported that rats with hippocampal lesions show enhanced context dependency of object recognition (O'Brien et al., 2006), that is, that the hippocampus may help to recognize repeats of the same object even though it occurs in different contexts. Given these considerations, it is perhaps unfortunate that many spontaneous object recognition studies do not explicitly state whether the rat could see distinctive room cues beyond the test arena, making it difficult to assess this potential factor.

An additional concern stems from the well-known finding that hippocampal lesions can cause hyperactivity (Davidson & Jarrard, 2004; Gray & McNaughton, 1983), and so potentially disrupt normal patterns of exploration. In fact, most studies report normal exploration times during the initial object familiarization stage for rats with hippocampal lesions (e.g., Barker & Warburton, 2011a; Broadbent et al., 2004; Forwood et al., 2005; Gaskin et al., 2010; O'Brien et al., 2006; Winters et al., 2004). Meanwhile, some studies have found that hippocampal lesions can retard initial object exploration (Ainge et al., 2006; Clark, Zola, & Squire, 2000), while others have reported enhanced object exploration (Broadbent et al., 2010). With these activity issues in mind, it is

relevant that the rats with hippocampal lesions in the present study typically showed normal overall levels of object exploration, along with normal exploration levels on the first sample trial. It is also possible that the reward contingencies in the bow-tie maze task (each object covered a reward), combined with the requirement for the rats to shuttle back and forth across the apparatus, made it easier to distinguish exploratory from nonexploratory behavior (as rats would turn their backs on the objects for much of each sample period prior to shuttling across the maze when the central door opened). Even so, in the present study there remains the issue of potential object sampling when the rats first push the objects to find the food rewards underneath.

The second phase of the experiment examined recency discriminations, as reflected by the rat's spontaneous preference for that familiar object sampled furthest ago in time. Direct evidence that rats can acquire temporal order information comes from their ability to learn concurrent, sequential order discriminations (Aggleton, Amin, Jenkins, Pearce, & Robinson, 2011; Fortin et al., 2002; Murphy, Mondragon, Murphy, & Fouquet, 2004). Spontaneous tests of object recency are, however, not so rigorous and could arguably be solved by comparing the different trace strengths associated with individual items (older items would typically have weaker trace strengths). Such a mechanism would presumably be based on item recognition information. Indeed, electrophysiological recordings in both monkey and rat rhinal cortex reveal some neurons whose response to the second presentation of an initially novel visual stimulus depends upon the time elapsed since the first presentation (Fahy, Riches, & Brown, 1993; Xiang & Brown, 1998; Zhu, Brown, & Aggleton, 1995). Population "forgetting curves" could be constructed for the decline in the mean response reduction between initial and subsequent presentations, and so these kinds of response changes across time could provide a potential basis for recency discriminations based on trace strength (Fahy et al., 1993; Xiang & Brown, 1998). It is, therefore, notable that previous studies have found that permanent or temporary lesions in sites such as the prefrontal cortex and medial dorsal thalamus can impair object recency discriminations but spare object recognition memory (Barker et al., 2007; Barker & Warburton, 2011a; Hannesson, Howland, & Philips, 2004; Warburton & Brown, 2010; Cross, Aggleton, Brown, & Warburton, 2012). Likewise, the current findings clearly point to a particular role for the hippocampus in temporal order analysis (see also Barker & Warburton, 2011b; Charles et al., 2004; Fortin et al., 2002; Warburton & Brown, 2010) given the dissociation with object recognition. Such findings strongly indicate that the preference by rats to explore the less recent of two objects is not simply because that item has largely been forgotten, and so is treated as if novel. One explanation is that the more recent object is less likely to have altered its properties over the intervening period, and so greater attention is given to the older object. A more formal explanation is provided by the SOP (Sometimes Opponent Process) model (Wagner, 1981) whereby a novel event is initially in a primary "active" state but then moves to a secondary state. This refractory state means that the more recent stimulus receives less exploration in comparison to an older stimulus. Indeed, there is evidence that hippocampal lesions lead to a greater tendency to resample recently explored contextual cues, reflecting a possible change in the balance between habituation and sensitization to stimuli (Honey, Marshall, McGregor, Futter, & Good, 2007; see also Marshall, McGregor, Good, & Honey, 2004).

While the present study examined object recency, some studies with rats have focused on the serial order of olfactory cues and reached the same conclusion, that is, that temporal order information and familiarity information can be dissociated, and that the former depends on the hippocampus (Agster, Fortin, & Eichenbaum, 2002; Fortin et al., 2002). Other related studies have examined serial effects on simple visual stimuli (Marshall et al., 2004). More recently, these same dissociations concerning the hippocampus have been extended to studies of mouse odor memory (DeVito & Eichenbaum, 2011). The generality of these results is further underlined by clinical studies of both temporal lobe and diencephalic amnesia that have again found dissociations between recognition memory and recency memory (Huppert & Piercy, 1978; Sagar, Gabrielle, Sullivan, & Corkin, 1990; Shaw & Aggleton, 1995), findings further supported by studies of monkeys (Charles et al., 2004). It is hard not to conclude that these are distinct mnemonic processes given their reliance on different neural substrates. Indeed, a possible specific mechanism for recency judgments is suggested by those neurons in the hippocampus, as well as those in perirhinal and adjacent cortex, that distinguish match from mismatch trials in delayed matching tasks with small stimulus sets (e.g., Gross, Rochamiranda, & Bender, 1972; Otto & Eichenbaum, 1992; Riches, Wilson, & Brown, 1991). Given that the stimuli in these matching tests are all highly familiar, the response differences are likely to rely on either differences in recency or contextual (e.g., trial information) factors.

As stated in the Introduction, the questions addressed in the present study are relevant to the debate over competing models of medial temporal lobe memory systems. The findings do not accord with the view that the hippocampus has a vital role in overseeing all contributions of the perirhinal cortex to declarative memory (Squire & Zola Morgan, 1991; Squire et al., 2007; Wixted & Squire, 2011). Rather, the findings point to an independent role for extrahippocampal areas, such as the perirhinal cortex, in supporting recognition memory (Brown & Aggleton, 2001; Murray, 1996; Murray & Mishkin, 1998), despite the dense interconnections between these two areas (Aggleton, 2012). This is not to say that these dense interconnections are not important for memory. Indeed, object recency may well rely on perirhinal–hippocampal connections. Not only do hippocampal lesions disrupt object recency judgments but so do perirhinal cortex lesions (Barker et al., 2007; Hannesson et al., 2004), and evidence is accumulating that these regions function together, along with the prefrontal cortex, to support temporal order memory (Barker & Warburton, 2011; Warburton & Brown, 2010). At the same time, the existence of highly effective mechanisms for recognition memory that do not require the hippocampus underlines how aspects of recognition memory appear to be independent from episodic or episodic-like memory.

References

Aggleton, J. P. (2012). Multiple anatomical systems embedded within the primate medial temporal lobe: Implications for hippocampal function. *Neuroscience and Biobehavioral Reviews,* in press.

Aggleton, J. P., Amin, E., Jenkins, T. A., Pearce, J. M., & Robinson, J. (2011). Lesions in the anterior thalamic nuclei of rats do not disrupt acquisition of stimulus sequence learning. *The Quarterly Journal of*

Experimental Psychology, 64, 65–73. doi:10.1080/17470218.2010.495407

Aggleton, J. P., & Brown, M. W. (1999). Episodic memory, amnesia and the hippocampal–anterior thalamic axis. *Behavioural and Brain Sciences, 22,* 425–444. doi:10.1017/S0140525X99002034

Aggleton, J. P., & Brown, M. W. (2006). Interleaving brain systems for episodic and recognition memory. *Trends in Cognitive Sciences, 10,* 455–463. doi:10.1016/j.tics.2006.08.003

Aggleton, J. P., Hunt, P. R., & Rawlins, J. N. P. (1986). The effects of hippocampal lesions upon spatial and nonspatial tests of working memory. *Behavioural Brain Research, 19,* 133–146. doi:10.1016/0166-4328(86)90011-2

Agster, K. L., Fortin, N. J., & Eichenbaum, H. (2002). The hippocampus and disambiguation of overlapping sequences. *Journal of Neuroscience, 22,* 5760–5768.

Ainge, J. A., Heron–Maxwell, C., Theofilas, P., Wright, P., de Hoz, L., & Wood, E. R. (2006). The role of the hippocampus in object recognition in rats: Examination of the influence of task parameters and lesion size. *Behavioural Brain Research, 167,* 183–195. doi:10.1016/j.bbr.2005.09.005

Albasser, M. M., Chapman, R. J., Amin, E., Iordanova, M. D., Vann, S. D., & Aggleton, J. P. (2010). New behavioral protocols used to extend our knowledge of rodent object recognition memory. *Learning & Memory, 17,* 407–419. doi:10.1101/lm.1879610

Barker, G. R. I., Bird, F., Alexander, V., & Warburton, E. C. (2007). Recognition memory for objects, places, and temporal order: A disconnection analysis of the role of the medial prefrontal cortex and perirhinal cortex. *The Journal of Neuroscience, 27,* 2948–2957. doi:10.1523/JNEUROSCI.5289-06.2007

Barker, G. R. I., & Warburton, E. C. (2011a). Evaluating the neural basis of temporal order memory for visual stimuli. *European Journal of Neuroscience, 33,* 705–716. doi:10.1111/j.1460-9568.2010.07555.x

Barker, G. R. I., & Warburton, E. C. (2011b). When is the hippocampus involved in recognition memory? *The Journal of Neuroscience, 31,* 10721–10731. doi:10.1523/JNEUROSCI.6413-10.2011

Broadbent, N. J., Gaskin, S., Squire, L. R., & Clark, R. E. (2010). Object recognition memory and the rodent hippocampus. *Learning & Memory, 17,* 5–11. doi:10.1101/lm.1650110

Broadbent, N. J., Squire, L. R., & Clark, R. E. (2004). Spatial memory, recognition memory, and the hippocampus. *Proceedings of the National Academy of Sciences, 101,* 14515–14520. doi:10.1073/pnas.0406344101

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience, 2,* 51–61. doi:10.1038/35049064

Brown, M. W., Warburton, E. C., & Aggleton, J. P. (2010). Recognition memory: Material, processes, and substrates. *Hippocampus, 20,* 1228–1244. doi:10.1002/hipo.20858

Charles, D. P., Gaffan, D., & Buckley, M. J. (2004). Impaired recency judgements and intact novelty judgments after fornix transection in monkeys. *The Journal of Neuroscience, 24,* 2037–2044. doi:10.1523/JNEUROSCI.3796-03.2004

Clark, R. E., West, A. N., Zola, S. M., & Squire, L. R. (2001). Rats with lesions of the hippocampus are impaired on the delayed nonmatching-to-sample task. *Hippocampus, 11,* 176–186. doi:10.1002/hipo.1035

Clark, R. E., Zola, S. M., & Squire, L. R. (2000). Impaired recognition memory in rats after damage to the hippocampus. *The Journal of Neuroscience, 20,* 8853–8860.

Cross, L., Aggleton, J. P., Brown, M. W., & Warburton, E. C. (2012). The medial dorsal thalamic nucleus and the medial prefrontal cortex of the rat function together to support associative but not item recognition. *Cerebral Cortex*. [manuscript under reviewReview of General Psychology

Davidson, T. L., & Jarrard, L. E. (2004). The hippocampus and inhibitory learning: A "Gray" area? *Neuroscience and Biobehavioral Reviews, 28,* 261–271. doi:10.1016/j.neubiorev.2004.02.001

DeVito, L. M., & Eichenbaum, H. (2011). Memory for the order of events in specific sequences: Contributions of the hippocampus and medial prefrontal cortex. *The Journal of Neuroscience, 31,* 3169–3175. doi:10.1523/JNEUROSCI.4202-10.2011

Dix, S. L., & Aggleton, J. P. (1999). Extending the spontaneous preference test of recognition: Evidence of object–location and object–context recognition. *Behavioural Brain Research, 99,* 191–200. doi:10.1016/S0166-4328(98)00079-5

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience, 30,* 123–152. doi:10.1146/annurev.neuro.30.051606.094328

Ennaceur, A., & Delacour, J. (1988). A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. *Behavioural Brain Research, 31,* 47–59. doi:10.1016/0166-4328(88)90157-X

Ennaceur, A., Neave, N. J., & Aggleton, J. P. (1997). Spontaneous object recognition and object location memory in rats: The effects of lesions in the cingulate cortices, the medial prefrontal cortex, the cingulum bundle and the fornix. *Experimental Brain Research, 113,* 509–519. doi:10.1007/PL00005603

Fahy, F. L., Riches, I. P., & Brown, M. W. (1993). Neuronal activity related to visual recognition memory: Long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. *Experimental Brain Research, 96,* 457–472. doi:10.1007/BF00234113

Fortin, N. J., Agster, K. L., & Eichenbaum, H. B. (2002). Critical role of the hippocampus in memory for sequences of events. *Nature Neuroscience, 5,* 458–462.

Forwood, S. E., Winters, B. D., & Bussey, T. J. (2005). Hippocampal lesions that abolish spatial maze performance spare object recognition memory at delays of up to 48 hours. *Hippocampus, 15,* 347–355. doi:10.1002/hipo.20059

Gaskin, S., Tardif, M., Cole, E., Piterkin, P., Kayello, L., & Mumby, D. G. (2010). Object familiarization and novel-object preference in rats. *Behavioural Processes, 83,* 61–71. doi:10.1016/j.beproc.2009.10.003

Gray, J. A., & McNaughton, N. (1983). Comparison between the behavioural effects of septal and hippocampal lesions: A review. *Neuroscience and Biobehavioral Reviews, 7,* 119–188. doi:10.1016/0149-7634(83)90014-3

Gross, C. G., Rochamiranda, C. E., & Bender, D. B. (1972). Visual properties of neurons in inferotemporal cortex of the macaque. *Journal of Neurophysiology, 35,* 96–111.

Hannesson, D. K., Howland, J. G., & Phillips, A. G. (2004). Interaction between perirhinal and medial prefrontal cortex is required for temporal order but not recognition memory for objects in rats. *Journal of Neuroscience, 24,* 4596–4604. doi:10.1523/JNEUROSCI.5517-03.2004

Honey, R. C., Marshall, V. J., McGregor, A., Futter, J., & Good, M. (2007). Revisiting places passed: Sensitization of exploratory activity in rats with hippocampal lesions. *Quarterly Journal of Experimental Psychology, 60,* 625–634. doi:10.1080/17470210601155252

Huppert, F. A., & Piercy, M. (1978). The role of trace strength in recency and frequency judgments by amnesic and control subjects. *The Quarterly Journal of Experimental Psychology, 30,* 347–354. doi:10.1080/14640747808400681

Iordanova, M. D., Burnett, D., Good, M., Aggleton, J. P., & Honey, R. C. (2009). The role of the hippocampus in mnemonic integration and retrieval: Complementary evidence from lesion and inactivation studies. *European Journal of Neuroscience, 30,* 2177–2189. doi:10.1111/j.1460-9568.2009.07010.x

Lin, T. E., & Honey, R. C. (2010). Dissociable roles of the hippocampus in trace conditioning and the conditioning of traces: Evidence from a novel appetitive procedure. Unpublished raw data.

Langston, R. F., & Wood, E. R. (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. doi:10.1002/hipo.20714

Mandler, G. (1980). Recognizing: The judgment of previous occurrence. *Psychological Review, 87,* 252–271. doi:10.1037/0033-295X.87.3.252

Marshall, V. J., McGregor, A., Good, M., & Honey, R. C. (2004). Hippocampal lesions modulate both associative and nonassociative priming. *Behavioral Neuroscience, 118,* 377–382. doi:10.1037/0735-7044.118.2.377

Mumby, D. G. (2001). Perspective on object-recognition memory following hippocampal damage: Lessons from studies in rats. *Behavioural Brain Research, 127,* 159–181. doi:10.1016/S0166-4328(01)00367-9

Mumby, D. G., Gaskin, S., Glenn, M. J., Schramek, T. E., & Lehman, H. (2002). Hippocampal damage and exploratory preferences in rats: Memory for objects, places, and contexts. *Learning & Memory, 9,* 49–57. doi:10.1101/lm.41302

Mumby, D. G., Tremblay, A., Lecluse, V., & Lehman, H. (2005). Hippocampal damage and anterograde object-recognition in rats after long retention delays. *Hippocampus, 15,* 1050–1056. doi:10.1002/hipo.20122

Mumby, D. G., Wood, E. R., & Pinel, J. P. J. (1992). Object recognition memory is only mildly impaired by lesions of the hippocampus and amygdala. *Psychobiology, 20,* 18–27.

Murphy, R. A., Mondragon, E., Murphy, V. A., & Fouquet, N. (2004). Serial order conditional stimuli as a discriminative cue for Pavlovian conditioning. *Behavioural Processes, 67,* 303–311. doi:10.1016/j.beproc.2004.05.003

Murray, E. A. (1996). What have ablation studies told us about the neural substrates of stimulus memory? *Seminars in the Neurosciences, 8,* 13–22. doi:10.1006/smns.1996.0003

Murray, E. A., & Mishkin, M. (1998). Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *The Journal of Neuroscience, 18,* 6568–6582.

O'Brien, N., Lehmann, H., Lecluse, V., & Mumby, D. G. (2006). Enhanced context-dependency of object recognition in rats with hippocampal lesions. *Behavioural Brain Research, 170,* 156–162. doi:10.1016/j.bbr.2006.02.008

Otto, T., & Eichenbaum, H. (1992). Complementary roles of the orbital prefrontal cortex and the perirhinal–entorhinal cortices in an odor-guided delayed-nonmatching-to-sample task. *Behavioral Neuroscience, 106,* 762–775. doi:10.1037/0735-7044.106.5.762

Paxinos, G., & Watson, C. (1997). *The rat brain in stereotaxic coordinates* (4th ed.) New York, NY: Elsevier.

Piterkin, P., Cole, E., Cossette, M.-P., Gaskin, S., & Mumby, D. G. (2008). A limited role for the hippocampus in the modulation of novel-object preference by contextual cues. *Learning & Memory, 15,* 785–791. doi:10.1101/lm.1035508

Riches, I. P., Wilson, F. A. W., & Brown, M. W. (1991). The effects of visual stimulation and memory on neurons of the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of primates. *Journal of Neuroscience, 11,* 1763–1779.

Sagar, H. J., Gabrielle, J. D. E., Sullivan, E. V., & Corkin, S. (1990). Recency and frequency discrimination in the amnesic patient H. M. *Brain, 113,* 581–602. doi:10.1093/brain/113.3.581

Save, E., Poucet, B., Foreman, N., & Buhot, N. (1992). Object exploration and reactions to spatial and non-spatial changes in hooded rats following damage to parietal cortex or hippocampal formation. *Behavioral Neuroscience, 106,* 447–456. doi:10.1037/0735-7044.106.3.447

Shaw, C., & Aggleton, J. P. (1993). The effects of fornix and medial prefrontal lesions on delayed nonmatching-to-sample by rats. *Behavioural Brain Research, 54,* 91–102. doi:10.1016/0166-4328(93)90051-Q

Shaw, C., & Aggleton, J. P. (1995). Evidence for the independence of recognition and recency memory in amnesic subjects. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior, 31,* 57–71.

Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: A new perspective. *Nature Reviews Neuroscience, 8,* 872–883. doi:10.1038/nrn2154

Squire, L. R., & Zola–Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253,* 1380–1386. doi:10.1126/science.1896849

Steckler, T., Drinkenburg, W. H. I. M., Sahgal, A., & Aggleton, J. P. (1998). Recognition memory in rats: II neuroanatomical substrates. *Progress in Neurobiology, 54,* 313–332. doi:10.1016/S0301-0082(97)00061-0

Wagner, A. R. (1981). SOP: A model of automatic memory processing in animal behavior. In N. E. Spear, & R. R. Miller (Eds.), *Information processing in animals: Memory mechanisms* (pp. 5–47). Hillsdale, NJ: Erlbaum.

Warburton, E. C., & Brown, M. W. (2010). Findings from animals concerning when interactions between perirhinal cortex, hippocampus and medial prefrontal cortex are necessary for recognition memory. *Neuropsychologia, 48,* 2262–2272. doi:10.1016/j.neuropsychologia.2009.12.022

Winters, B. D., Forwood, S. E., Cowell, R., Saksida, L. M., & Bussey, T. J. (2004). Double dissociation between the effects of peri-postrhinal cortex and hippocampal lesions on tests of object recognition and spatial memory: Heterogeneity of function within the temporal lobe. *The Journal of Neuroscience, 24,* 5901–5908. doi:10.1523/JNEUROSCI.1346-04.2004

Winters, B. D., & Reid, J. M. (2010). A distributed cortical representation underlies crossmodal object recognition in rats. *The Journal of Neuroscience, 30,* 6253–6261. doi:10.1523/JNEUROSCI.6073-09.2010

Winters, B. D., Saksida, L. M., & Bussey, T. J. (2008). Object recognition memory: Neurobiological mechanisms of encoding, consolidation and retrieval. *Neuroscience and Biobehavioral Reviews, 32,* 1055–1070. doi:10.1016/j.neubiorev.2008.04.004

Wixted, J. T., & Squire, L. R. (2011). The medial temporal lobe and the attributes of memory. *Trends in Cognitive Sciences, 15,* 210–217. doi:10.1016/j.tics.2011.03.005

Xiang, J. Z., & Brown, M. W. (1998). Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology, 37,* 657–676. doi:10.1016/S0028-3908(98)00030-6

Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *Journal of Memory and Language, 46,* 441–517. doi:10.1006/jmla.2002.2864

Zhu, X. O., Brown, M. W., & Aggleton, J. P. (1995). Neuronal signalling of information important to visual recognition memory in rat rhinal and neighbouring cortices. *European Journal of Neuroscience, 7,* 753–765. doi:10.1111/j.1460-9568.1995.tb00679.x

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