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RESEARCH ARTICLE

The hippocampus is critical for value-based decisions guided by dissociative inference

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Abstract

The hippocampus supports flexible decision-making through memory integration: bridging across episodes and inferring associations between stimuli that were never presented together ('associative inference'). A pre-requisite for memory integration is flexible representations of the relationships between stimuli within episodes (AB) but also of the constituent units (A,B). Here we investigated whether the hippocampus is required for parsing experienced episodes into their constituents to infer their re-combined within-episode associations ('dissociative inference'). In three experiments male rats were trained on an appetitive conditioning task using compound auditory stimuli (AB+, BA+, CD–, DC–). At test either the compound or individual stimuli were presented as well as new stimuli. Rats with hippocampal lesions acquired and retained the compound discriminations as well as controls. Single constituent stimuli (A, B, C, D) were presented for the first time at test, so the only value with which they could be associated was the one from the compound to which they belonged. Controls inferred constituent tones' corresponding values while hippocampal rats did not, treating them as merely familiar stimuli with no associated value. This finding held whether compound training occurred before or after hippocampal lesions, suggesting that hippocampus-dependent inferential processes more likely occur at retrieval. The findings extend recent discoveries about the role of the hippocampus in intrinsic value representation, demonstrating hippocampal contributions to allocating value from primary rewards to individual stimuli. Importantly, we discovered that dissociative inferences serve to restructure or reparse patterns of directly acquired associations when animals are faced with environmental changes and need to extract relevant information from a multiplex memory. The hippocampus is critical for this fundamental flexible use of associations.

KEYWORDS

inference, lesion, rodent, value learning

1 | INTRODUCTION

The hippocampus is involved in inferential processing by virtue of the relational representations it forms (D'Angelo, Rosenbaum, & Ryan, 2016; Dusek & Eichenbaum, 1997; Frank, Rudy, & O'Reilly, 2003; Greene, Gross, Elsinger, & Rao, 2006; Schlichting, Zeithamova, & Preston, 2014). For example, animals with hippocampal lesions are impaired on tests of associative inference in which a relationship is formed between two stimuli that have never been co-presented (e.g., AC) because of their previously overlapping association with a third stimulus (e.g., AB, BC). The hippocampus is critical for this kind of memory integration across discrete events. Using similar paradigms, a novel role for the hippocampus was also identified in value based inferential decision-making (Gilboa, Sekeres, Moscovitch, & Winocur, 2014; Wimmer & Shohamy, 2012). We showed that while the hippocampus was not required for first-order conditioning (e.g., A+, B–) in which conditioned stimuli co-occur with primary rewards, it was critical for second-order conditioning (SOC). During SOC neutral stimuli gain positive or negative value (e.g., C+) by being associated with first-order conditioned stimuli (e.g., –A+C) without the direct presence of a primary reward. Hippocampal lesions specifically prevented the acquisition of SOC associations and the retrieval of previously acquired

SOC preferences (Gilboa et al., 2014), presumably because the hippocampus is needed to bridge over these separate events. Similarly, in humans the hippocampus was found to be active during transfer of value from a conditioned stimulus to its previous associates during sensory pre-conditioning (Wimmer & Shohamy, 2012), thereby relating current value to previous overlapping experiences.

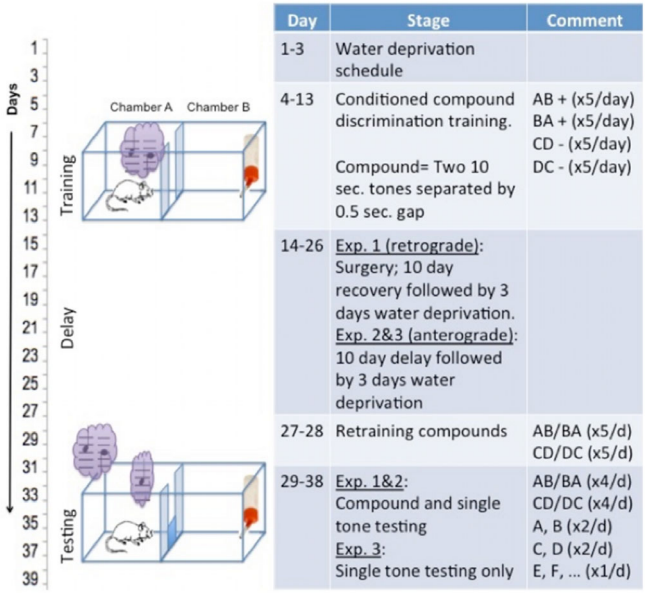
When multiple constituent elements are co-presented in the same event, the units of information can be combined online into a configural or compound unit that signals reward in an associative process of "chunking" (Wickelgren, 1979). Compound conditioning studies typically train subjects alternately on the compound and constituent stimuli often explicitly differentiating the compound and its components (e.g., positive patterning: A–, B–, AB+) (Kehoe & Macrae, 2002). In such tasks the hippocampus is implicated (a) in the process whereby configural units (AB+) acquire associative strength and (b) in discriminating between configural units and their constituent elements, particularly when the latter are of different valence (A–, B–) (Honey, Iordanova, & Good, 2014; Rudy & Sutherland, 1995; Ito & Lee, 2016). Configural learning, or chunking, reflects the brain's capacity to represent and use information in flexible ways, an important feature that depends on the hippocampus's role in creating new relationships (e.g., associative inference).

Building on our finding that, in SOC, the hippocampus is required for inferring value across events (Gilboa et al., 2014), our goal here was to investigate whether it is required for a different type of inferential processing of value. We ask whether the hippocampus is necessary for generalizing value from compound stimuli to their constituents, when there is no need to bridge across events (as in associative inference) or to resolve conflicting information (as in configural learning). On the basis of our previous results we predicted that the hippocampus would not be necessary for discriminating the value of compound stimuli, but that assigning value to the individual constituents would require hippocampal inferential processing. Unlike associative inference, in which new associations or value are inferred for stimuli across different events, generalization in this case would entail a process we call "dissociative inference": allocation of value to individual stimuli that co-occur during the same event and in the direct presence of the primary reward.

2 | MATERIALS AND METHODS

We developed a dissociative inference paradigm in which distinctly different combinations of auditory stimuli (e.g., Tone 1 + Tone 2 [CS^+] or Tone 3 + Tone 4 [CS^-] must be discriminated in order to obtain water reward. During testing, the animals' responses to the compound stimuli, the component stimuli presented individually, as well as novel stimuli, are assessed. In three experiments, processing patterns of normal rats and rats with hippocampal lesions are compared in anterograde and retrograde tests of learning and memory, as outlined below (Figure 1).

Training and testing were conducted in a 2-chamber (A and B) enclosure (57 × 27 × 27 cm), separated by clear Plexiglas with a central opening as previously described (Gilboa et al., 2014). Chamber-A was constructed of opaque Plexiglas; Chamber-B had clear Plexiglas



Day	Stage	Comment
1-3	Water deprivation schedule	
4-13	Conditioned compound discrimination training. Compound= Two 10 sec. tones separated by 0.5 sec. gap	AB + (x5/day) BA + (x5/day) CD - (x5/day) DC - (x5/day)
14-26	Exp. 1 (retrograde): Surgery; 10 day recovery followed by 3 days water deprivation. Exp. 2&3 (anterograde): 10 day delay followed by 3 days water deprivation	
27-28	Retraining compounds	AB/BA (x5/d) CD/DC (x5/d)
29-38	Exp. 1&2: Compound and single tone testing Exp. 3: Single tone testing only	AB/BA (x4/d) CD/DC (x4/d) A, B (x2/d) C, D (x2/d) E, F, ... (x1/d)

FIGURE 1 Schematic of the experimental timeline and the different conditions across the three experiments [Color figure can be viewed at wileyonlinelibrary.com]

walls. During testing, an 8-cm high barrier separates the two chambers to make approach to the water somewhat challenging such that rats will only approach when confident of the valence associated with a stimulus (Eichenbaum, Fortin, Sauvage, Robitsek, & Farovik, 2010; Fortin, Wright, & Eichenbaum, 2004; Gilboa et al., 2014). A water bottle was attached to the back of Chamber-B. Three days before the beginning of the experiment, rats were placed on a water-deprivation schedule in which they were allowed access to water for 1 hr over each 24-hr period.

All three experiments involved three stages: compound conditioning (either before or after surgery), re-training of compound discrimination (always after surgery), and testing (either mixed compound and single tones or only single tones in experiment 3).

This study was carried out in strict accordance with the guidelines of the Canadian Council on Animal Care and the research protocol was approved by the Trent University Animal Care Committee.

2.1 | Experiment 1: Retrograde training compound and single tone testing

In experiment 1, we tested whether having acquired a compound discrimination, the hippocampus is needed to infer reward value for the compounds' constituent stimuli. To this end, rats were trained pre-operatively on the compound discrimination over 10 days and post-operatively tested on discrimination of both compound and constituent stimuli.

2.1.1 | Subjects

Seventeen male Long-Evans rats, 5 months old at the beginning of the experiment, served as subjects for experiment 1. After compound conditioning training, 8 rats were randomly assigned to the Hippocampal lesion group and 9 rats to the Sham-surgery control group. All rats successfully completed post-surgical testing.

2.1.2 | Stimuli

Two, 2-tone combinations served as either CS+ or CS−. Combination 1 consisted of a 4 kHz 80 db and a 14 kHz 60 db tone. Combination 2 consisted of a 3 kHz 100 db and 10 kHz 75 db tones. The tones were each 10 s long, and were separated by a 500 ms gap. Each tone appeared first within its compound half the time such that CS+ could be AB or BA and CS− could be CD or DC. Pair combinations randomly served as CS+ for half the rats and CS− for the other half. In addition, 40 different tone combinations (4–14 kHz, 50–100 db, sine or saw-tooth) served as novel tones during testing. Each new tone or tone combination only appeared once during testing. Tones were presented using a speaker affixed to the top of the apparatus and tone delivery was controlled by a computer.

2.1.3 | Procedure

Pre-surgical training (10 days)

Rats received conditioned discrimination training for 10 days. On each day, 10 CS+ (5 AB and 5 BA) and 10 CS− (5 CD and 5 DC) compound tones were presented in random order in Chamber A. CS+ signaled the presence of water in Chamber B; CS− signaled no water, and the passage between chambers was opened as soon as the compound tone ended. The tones were counterbalanced so that, for half the rats one compound pair was positive and the other negative; the reverse applied for the other half. On all trials, the latency to reach the water was measured. On CS+ trials, if the rat contacted the spout within 30 s, it was allowed to drink for 20 s, then placed in a holding cage to await the next trial. If the rat failed to reach the water within 30 s, it was removed from the test box and placed in the holding cage to await the next trial. On CS− trials, the rat was removed from the chamber when it made contact with the water spout or when 30 s had elapsed. Once trained, rats from both groups approached the water spout within 3–4 s on average for CS+ trials and over 7 s on average for CS− trials.

About 24–48 hr after training, half the rats underwent hippocampal lesion surgery and half underwent sham surgery (see details below). Rats were then allowed the remaining of the 10 days to recover before being placed on the 3-day water deprivation schedule in preparation for the next stage.

Post-surgical reminder (2 days)

Training procedures were identical except rats were only re-trained for 2 days. Water was available only on CS+ trials, unlike the testing stage (see below) when water was always available.

Post-surgical testing (10 days)

Water was available during all testing trials. Rats were placed individually in Chamber-A and, on each trial rats were presented with either compound CS+ (AB or BA), compound CS− (CD or DC), novel compounds (EF, GH, FE, HG etc.) or single tones that could be inferred as positive (A, B) or negative (C, D). The rat's latency to cross over to Chamber B and contact the spout to obtain water was measured. On each of 10 testing days, 16 testing trials were conducted in random order: 2× (AB, BA, CD, DC), 1× (EF, GH, FE, HG), 1× (A, B, C, D). If the rat crossed over to Chamber-B within 40 s it was allowed to drink for 20 s, then placed in a holding cage to await the next trial. If the rat failed to reach the water within 40 s, it was removed from the test box and placed in a holding cage to await the next trial (see Figure 1 for experimental timeline).

2.2 | Experiment 2: Anterograde training compound and single tone testing

In experiment 2, we tested whether the hippocampus was needed for acquisition of the compound tones. Compound conditioning studies typically employ visual–auditory compound stimuli that can appear simultaneously, whereas our stimuli were both auditory, comprised of 10 s tones separated by 0.5 s which could be challenging for hippocampus-lesioned rats. Surgery was performed 2 weeks prior to the beginning of compound conditioning training. A delay of 10 days was introduced between training and the introduction of water deprivation 3 days before re-training, in order to match the delay in experiment 1.

2.2.1 | Subjects

Twenty male Long-Evans rats, 5 months old at the beginning of the experiment, served as subjects for experiment 2. Ten rats received hippocampal lesions, and 10 received sham surgery. All rats completed post-surgical testing.

Stimuli were identical to those used in experiment 1.

Procedure was the same as experiment 1, with the exception that surgery was performed 2 weeks prior to training (Figure 1).

2.3 | Experiment 3: Anterograde training with only single tone testing

In experiment 2, the initial acquisition of the compound discrimination during training and re-training performance was slower for the sham surgery control rats compared with hippocampal surgery rats. Because of this unexpected finding we replicated the training procedure from experiment 2.

We also wanted to compare latencies for single previously presented constituent tones with latencies for new single tones to better understand the relationship between inferential processes and value allocation. We suspected that testing conditions involving old compounds, new compounds, and old and new individual tones were too complex. In the present experiment, therefore, we tested rats only on constituent tones and novel single tones. This allowed us to investigate familiarity effects for the constituent stimuli independent of inferred value.

2.3.1 | Subjects

Twenty male Long-Evans rats, 5 months old at the beginning of the experiment, served as subjects for experiment 3. Nine rats received hippocampal lesions, and 11 received sham surgery. Nineteen rats successfully completed post-surgical testing (8 hippocampal and 11 sham surgery). One hippocampal lesioned rat was removed from the experiment because from the very first day of training it completely ignored the tones and ran directly to the water spout as soon as the door was opened.

2.3.2 | Stimuli

Training stimuli were identical to those used in experiments 1 and 2. In addition, 40 different single tones (4–14 kHz, 50–100 db, sine or sawtooth) served as novel tones during testing. Each new tone only appeared once during testing.

2.3.3 | Procedure

Post-surgical training and re-training were the same as experiment 2.

Post-surgical testing (10 days)

Water was available during all testing trials. Rats were placed individually in Chamber-A and, on each trial rats were presented with either single tones that could be inferred as positive (A, B) or negative (C, D) or with new single tones (E, F, G, H…). The rat's latency to cross over to Chamber B and contact the spout to obtain water was measured. On each of 10 testing days, 8 testing trials were conducted in random order: 1× (A, B, C, D), 1× (E, F, G, H). If the rat crossed over to Chamber-B within 40 s it was allowed to drink for 20 s, then placed in a holding cage to await the next trial. If the rat failed to reach the water within 40 s, it was removed from the test box and placed in a holding cage to await the next trial.

2.4 | Surgery methods

During surgery, rats were maintained on oxygen and isoflurane respiratory anesthetic, and their internal temperature was regulated using a homoeothermic warming pad unit (Harvard Apparatus). The procedure for making hippocampal lesions was identical to that routinely practiced in our lab (Gilboa et al., 2014; Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005). A small incision (2 cm) was made in the scalp along the midline of the skull. Using a small dental burr, 8 holes were drilled through the skull directly above the hippocampus in each hemisphere. Hippocampal lesions were produced by 10 intra-cranial micro-injections of a solution containing the neurotoxin, NMDA (5 mg/μl PBS per site, Sigma Aldrich) into each hemisphere. The stereotaxic injection coordinates were based on the Paxinos and Watson (1998) atlas and calculated from a level skull surface with respect to bregma: −3.1 mm posterior (p), ±1 mm lateral (l), and −3.6 mm ventral (v); −3.1 (p), ±2 (l), −3.6 (v); −4.1 (p), ±2 (l), −4 (v); −4.1 (p), ±3.5 (l), −4 (v); −5 (p), ±3, (l), −4.1 (v); −5 (p), ±5.2 (l), −5 (v); −5 (p), ±5.2 (l), −7.3 (v); −5.8 (p), ±4.4 (L), −4.4 (v); −5.8 (p), ±5.1 (l); −6.2 (v); −5.8 (p), ±5.1 (l), −7.5 (v). The solution was infused at a rate of 0.4 μl/min through 30-gauge stainless steel cannulae for 38 s, using a 10-μl syringe attached to a motorized infusion pump (Harvard Apparatus). The last two ventral hippocampal sites were injected for 2 min each. The cannula remained in place for 2 min after each infusion to allow NMDA diffusion away from the cannula tip prior to removal. In the sham surgery (control) procedure, scalp incision and burr holes were identical to the lesioned animals' with the exception that there was no penetration of brain tissue. To facilitate recovery from surgery, all rats were given IP injections of diazepam (10 mg/kg). All rats were allowed at least 10 days to recover from surgery prior to resuming the experiment.

2.5 | Histology methods

Following testing, rats were deeply anesthetized with sodium pentobarbital (65 mg/kg) via intraperitoneal injection. Brains were intracardially perfused using phosphate-buffered saline (PBS), followed by a 10% formal saline solution. The fixed brains were removed from the skull and stored in 10% formal saline at 4 °C for 72 hr, then transferred to a 30% sucrose and PBS solution for 72 hr prior to sectioning. Brains were coronally sectioned at 40 μm using a cryostat. Every 5th section was mounted on a glass slide, and stained using cresyl violet. Slides were dried overnight, and coverslipped using Permount mounting medium.

Brains were photographed at 2× magnification using an EVOS XL Core (Life Technologies) microscope and digital camera and digitally stitched together. Every second section corresponding to Figures 28–44 in Paxinos and Watson's rat brain atlas (Paxinos & Watson, 1998) was used to measure the area of surviving hippocampal tissue in each brain (9 sections per brain). Hippocampal lesions were scored using ImageJ (NIH, https://imagej.nih.gov/ij/). For each section, surviving hippocampal tissue was traced, and the traced area was measured. Measurements were obtained separately for dorsal and ventral regions of the left and right hippocampus in each section to identify any unilateral lesions, or lesions restricted to the dorsal planes. Measurements for surviving tissue were then combined to generate a final area of intact hippocampal tissue per brain.

Control measurements were obtained by tracing the hippocampus from a subset of sham-operated brains to generate control values for the hippocampal subregions in the dorsal and ventral planes of the left and right hippocampi in every second section corresponding to Figures 28–44 in the rat brain atlas. For each lesioned brain section, the area of surviving tissue was divided by the total hippocampal area in the corresponding control section and multiplied by 100 to obtain the percentage of surviving tissue. That value was subtracted from 100 to report the percent of lesioned tissue.

2.5.1 | Statistical analysis

All three experiments were mixed design. For the training stage, valence (positive, negative) and testing day (1–10) served as within-subject factors, and prospective or retrospective surgery type (hippocampus, sham) served as between subjects factor. For post-surgical re-training valence and testing day (1 and 2) served as within-subject factors, and surgery type as between subject factor. For the testing stage, because water was always available, we collapsed the data over the first 7 days of testing, consistent with our previous studies (Gilboa et al., 2014); the full ranges of data for the 10 testing days for experiments 1–3 are provided in the Supporting Information Figures S2–S6. In the first two experiments, valence (positive, negative) and tone type (single, compound) served as within subject factors, and surgery type as the between subject factor. An additional ANOVA looking only at compound tones and adding new tones as a third level for the valence factor was also performed in experiments 1 and 2. In experiment 3, valence (positive, negative, new) served as within-subject factor, and surgery type as between subject factor. Greenhouse–Geisser corrections were used for analyses where the data did not meet the assumption of sphericity, and significant interactions were followed

up with individual *t*-tests. Because censored trials were treated as maximum latency there was potential for normality violation. We, therefore, conducted Jarque-Bera normality tests for all training and testing conditions. Most censored trials occurred during initial training; despite this the test did not reject the null hypothesis of normality on any of them (all *p*'s > .2). In experiment 1 single tone CS+ significantly deviated from normality (JB = 11.373, $p < .01$) and single tone CS- was subthreshold (JB = 4.747, $p = .09$). For that condition we supplemented the parametric tests with nonparametric statistical tests that confirmed the findings. Spearman correlations were used to investigate possible relationships between lesion size and latency to run.

3 | RESULTS

3.1 | Experiment 1: Retrograde training with compound and single tone testing

3.1.1 | Pre-surgical training (10 days)

Rats were trained on basic Pavlovian appetitive discrimination using tone pairs as CS+ (AB/BA) or CS− (CD/DC). Repeated measures ANOVA with valence (CS+, CS−) and training day (day 1 to day 10) as within-subject factors, and subsequent group (HPC, SHAM) assignment as between subject factor revealed that the assumption of sphericity was violated and Greenhouse–Geisser correction was applied. There was a significant effect of training day ($F[3.05, 61.84] = 77.18$, $p < .001$, $\eta^2_p = 0.83$), reflecting shorter latencies over time, a significant effect of valence ($F[1, 61.84] = 48.73$, $p < .001$, $\eta^2_p = 0.74$), reflecting longer latencies for CS− tone pairs, and a significant time by valence interaction ($F[4.12, 61.84] = 5.62$, $p < .001$, $\eta^2_p = 0.26$), reflecting the gradual acquisition of the discrimination. No other interaction was significant, and there was no group difference in overall latency to reach the waterspout.

3.1.2 | Post-surgical re-training (2 days)

Ten days after surgery, rats were placed back on the water deprivation schedule for 3 days. To ascertain whether the compound discrimination was retained despite the time and surgery, rats were retrained for 2 days on the compound discrimination task. There was a marginal effect of training day ($F[1,15] = 4.094$, $p = .06$, $\eta^2_p = 0.21$) reflecting somewhat longer latencies on the first day and a significant effect of valence ($F[1,15] = 100.02$, $p < .001$, $\eta^2_p = 0.87$) reflecting longer latencies for CS− tone pairs, and no time by valence interaction ($F[1,15] = 0.17$, $p = .69$, $\eta^2 = 0.01$). Importantly, despite the surgery, there was no group difference ($F[1,15] = 0.37$, $p = .55$, $\eta^2 = 0.02$) with both HPC and sham lesioned groups displaying comparable latencies in all conditions (Figure 2). Therefore, regardless of the type of surgery, the groups maintained their discrimination of value of the compound stimuli.

3.1.3 | Testing (7 days)

As in our previous studies (Gilboa et al., 2014), during testing water was always available. We therefore collapsed across the first 7 days of testing before subjects learned this new rule and stopped differentially responding.

There was a significant effect of tone type (compound vs. single: $F[1,15] = 76.79$, $p < .001$, $\eta^2_p = 0.84$) reflecting overall longer latencies for single compared with compound tones, with a significant tone type by valence interaction ($F[1,15] = 28.20$, $p < .001$, $\eta^2_p = 0.65$), and a marginal tone type by group interaction ($F[1,15] = 4.16$, $p = .06$, $\eta^2_p = 0.22$). There was a significant effect of valence ($F[1,15] = 70.74$, $p < .001$, $\eta^2_p = 0.83$) reflecting overall longer latencies for negative compared with positive tones, and a significant valence by group interaction ($F[1,15] = 18.09$, $p < .001$, $\eta^2_p = 0.55$). Last, there was a significant 3-way interaction of tone type by valence by group ($F[1,15] = 7.02$, $p = .018$, $\eta^2_p = 0.32$), as both groups showed similar differential latencies responding to valence in the compound condition, but only the sham group showed shorter latencies for CS+ in the single (constituent) tone condition (Figure 3).

Because single tone stimuli violated the assumption of normality, we also conducted nonparametric tests. Confirming the parametric tests, in Hippocampal rats, Friedman test showed significant overall difference ($\chi^2_{[3]} = 16.2$, $p < .001$) across the 4 conditions (CS+/−, compound/constituent tones). Follow up Wilcoxon rank tests showed that in all 8 hippocampal rats compound CS+ had shorter latencies than compound CS−, constituent CS+ and constituent CS− (all $Z = -2.52$, $p = .012$). Compound CS− had longer latencies than constituent CS+ in 6/8 rats ($Z = -2.1$, $p = .036$) and also longer latencies than constituent CS− in 6/8 rats, which was marginally significant ($Z = -1.82$, $p = .069$). Importantly, rank order of constituent CS+ and CS− was equally distributed (4/4) and did not differ significantly ($Z = -1.12$, $p = .263$). For sham operated rats the overall Friedman test was also significant

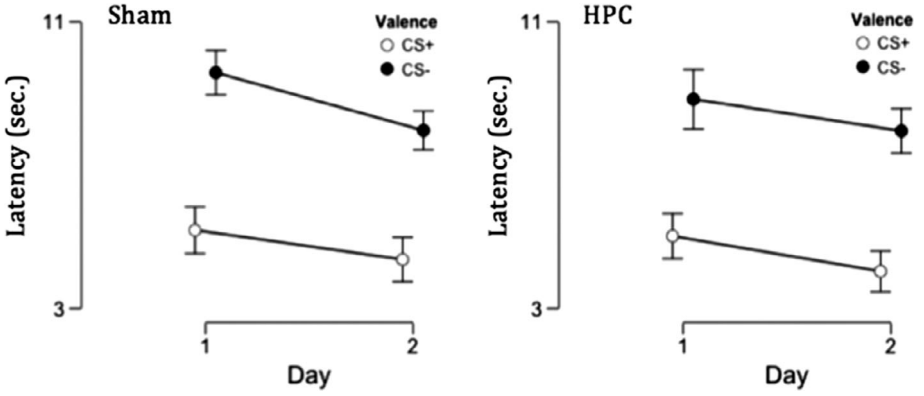


FIGURE 2 Re-training of retrograde compound conditioning

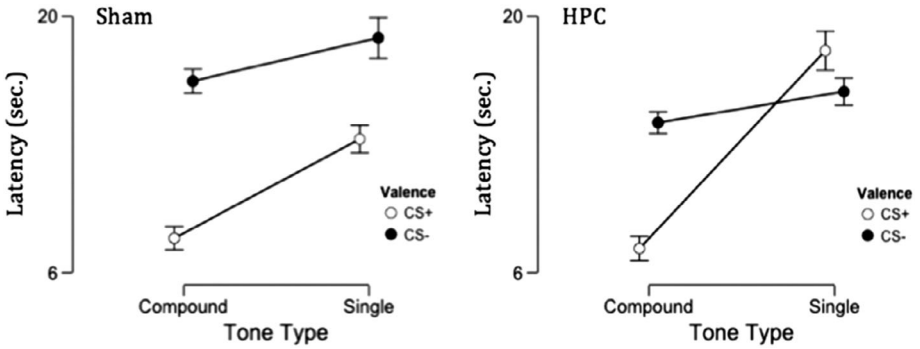


FIGURE 3 Testing of retrograde compound and single items averaged over 7 days

($\chi^2_{[3]}$ = 21.93, p < .001). Follow up Wilcoxon rank tests showed that in all 9 rats latencies for compound CS+ were shorter than those for compound CS−, constituent CS+ and constituent CS− (all Z = −2.66, p = .008). Contrary to the hippocampal rats, however, constituent CS+ also had shorter latencies in 8/9 rats, compared with those of the compound CS− (Z = −2.43; p = .015) and constituent CS− (Z = −2.54; p = .011). Compound and constituent CS− did not significantly differ from each other (Z = −1.34, p = .17).

Because new tones were only presented as compound stimuli, a separate analysis was performed for all compound tones, correcting for sphericity violation (Mauchly's W = 0.622, p = .036) using Greenhouse–Geisser correction (Figure 4). There was a significant effect of valence (F[1.45, 21.77] = 121.92, p < .001, η^2_p = 0.89), no group effect (F[1,15] = 0.06, p = .81, η^2_p = 0.004) and a marginal valence by group effect (F[1.45, 21.77] = 3.37, p < .07, η^2_p = 0.18). None of the post-hoc between group tests was significant for the different tone types; CS− was marginal for longer latencies of shams and the marginal interaction is probably a combination of that with somewhat shorter latencies for shams for New tones.

3.2 | Experiment 2: Anterograde training with compound and single tone testing

3.2.1 | Post-surgical training (10 days)

Following recovery from surgery, rats were trained on the discrimination using tone pairs as above. Repeated measures ANOVA with valence and training day as within-subject factors and group as between subject factor revealed that the assumption of sphericity was violated and Greenhouse–Geisser correction was applied. There was a significant effect of training day (F[3.99, 92.72] = 37.29, p < .001, η^2_p = 0.64) reflecting shorter latencies over time, and a significant effect of valence (F[1, 92.72] = 33.62, p < .001, η^2_p = 0.57) reflecting longer latencies for CS− tone pairs, and a significant time by valence interaction (F[5.15, 92.72] = 5.73, p < .001, η^2_p = 0.19) reflecting the gradual acquisition of the discrimination (Figure 5). There was also a marginal valence by group interaction (F[1, 92.72] = 4.25, p = .054, η^2_p = 0.06) because the hippocampal rats tended to acquire the discrimination a little earlier (starting day 5) than the sham surgery rats (starting day 7). No other interaction was significant and there was no group difference in overall latency.

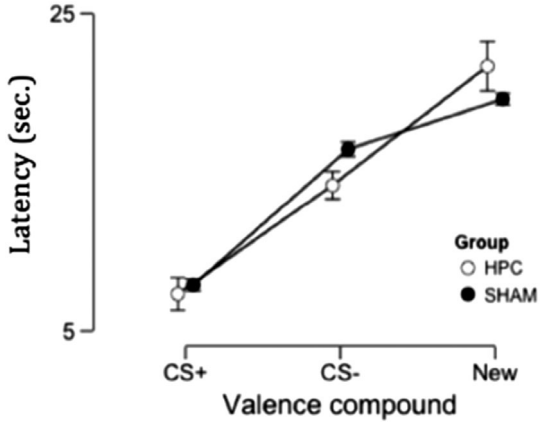


FIGURE 4 Testing of retrograde trained and new compound stimuli averaged over 7 days

3.2.2 | Re-training (2 days)

After 10 days of ad lib water access, rats were put back on a water deprivation schedule for 3 days and then received 2 days of reminder training (Figure 6). There was a main effect of valence (F[1,18] = 87.74, p < .001, η^2_p = 0.83) and a significant 3-way interaction of valence by day by group (F[1,18] = 5.82, p < .05, η^2_p = 0.24), as well as a significant group difference (F[1,18] = 15.68, p < .001, η^2_p = 0.47). The latter reflected the sham group being slower and showing a smaller latency difference between CS+ and CS− on day 1, but equivalent difference on day 2.

3.2.3 | Testing (7 days)

Testing data were collapsed across the first week of testing as above. There was a significant effect of tone type (compound vs. single: F[1,18] = 15.671, p < .001, η^2_p = 0.465) reflecting overall longer latencies for single compared with compound tones, but unlike the retrograde data there was no significant tone type by valence or tone type by group interaction (Figure 7). There was a significant effect of valence (F[1,18] = 20.89, p < .001, η^2_p = 0.54), reflecting overall longer latencies for negative compared with positive tones, but unlike the retrograde data there was no valence by group interaction or 3-way interaction of tone type by valence by group. There was no overall significant group difference in latency.

We next compared compound positive, negative, and new tones correcting for sphericity violation (Mauchly's W = 0.559, p = .007) using Greenhouse–Geisser correction. There was a significant effect

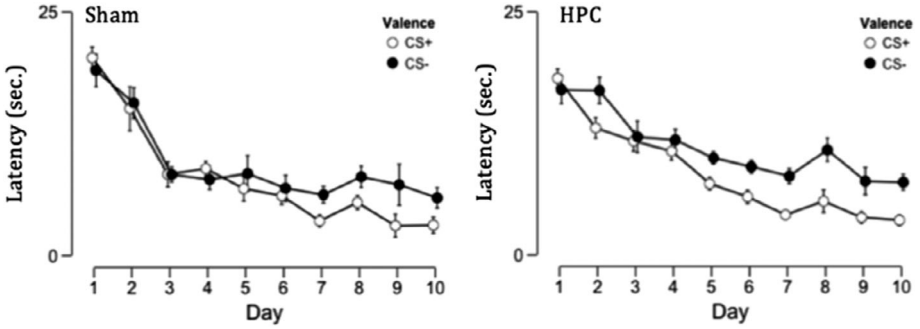


FIGURE 5 Latencies in response to CS+ (open circles) and CS− (full circles) over 10 training days for sham surgery rats (left) and hippocampal rats (right)

of valence (F[1.39, 24.98] = 42.60, p < .001, η^2_p = 0.70), with no group effect or valence by group interaction (Figure 8).

Because, counter-intuitively, the initial acquisition of the compound stimuli and the re-training phase revealed marginally impaired learning and significant forgetting in the sham surgery rats compared with the hippocampal rats, we decided to replicate this study. Additionally, in experiment 3, we tested only single tones to allow better measures of generalization through dissociative inference and to introduce new single tones, as opposed to new compound tones.

3.3 | Experiment 3: Anterograde training with single tone testing only

3.3.1 | Post-surgical training (10 days)

Following recovery from surgery rats were trained on discrimination using tone pairs as above (Figure 9). Repeated measures ANOVA with valence and training day as within-subject factors and group as between subject factor revealed a significant effect of training day (F[9, 153] = 57.60, p < .001, η^2_p = 0.77) reflecting shorter latencies over time, a significant effect of valence (F[1, 17] = 89.58, p < .001, η^2_p = 0.84) reflecting longer latencies for CS- tone pairs and a significant time by valence interaction (F[9, 153] = 10.38, p < .001, η^2_p = 0.38) reflecting the gradual acquisition of the discrimination. There was a marginal valence by group interaction (F[1, 17] = 3.65, p = .07, η^2_p = 0.18), but this time sham surgery rats exhibited slightly better discrimination learning than hippocampal rats. There was no group difference in overall latency.

3.3.2 | Re-training (2 days)

After 10 days of ad lib water access, rats were put back on a water deprivation schedule for 3 days and then received 2 days of reminder training (Figure 10). There was a main effect of valence (F[1,17] = 45.18, p < .001, η^2_p = 0.72) reflecting shorter latencies for CS+, and a significant effect of day (F[1,17] = 8.94, p < .05, η^2_p = 0.33) reflecting shorter latencies on day 2. Importantly, unlike experiment 2, there were no group differences or any significant interactions during re-training.

3.3.3 | Testing (7 days)

Testing data were collapsed across the first week of testing as above but only single tones were tested. There was a significant effect of tone valence (F[2,34] = 16.07, p < .001, η^2_p = 0.49) reflecting overall shorter latencies for CS+ compared with both CS− and new tones, and no difference between the latter two (Figure 11). There was no significant group difference (F[1,17] = 1.46; p = .24, η^2_p = 0.08). There was a significant interaction between valence and group (F[2,34] = 11.35, p < .001, η^2_p = 0.40) reflecting significantly shorter latencies for sham surgery rats on CS+ (t[17] = 3.75; p = .002, d = 1.74) and for new tones (t[17] = 2.19; p = .04, d = 1.02), and non-significant longer latencies for CS− (t[17] = −1.51, p = .14, d = −0.7). Interestingly, while hippocampal rats showed similar latencies to CS+ and CS− (t[7] = −0.139, p = .89, d = −0.05), they demonstrated a familiarity effect in that the latencies to CS+ and CS− were both shorter than the latency in response to the new tones (t[7] = 2.64, p = .03, d = 0.93 and t[7] = 3.38, p = .01, d = 1.19, respectively) suggesting they recognized the individual tones but not their associated

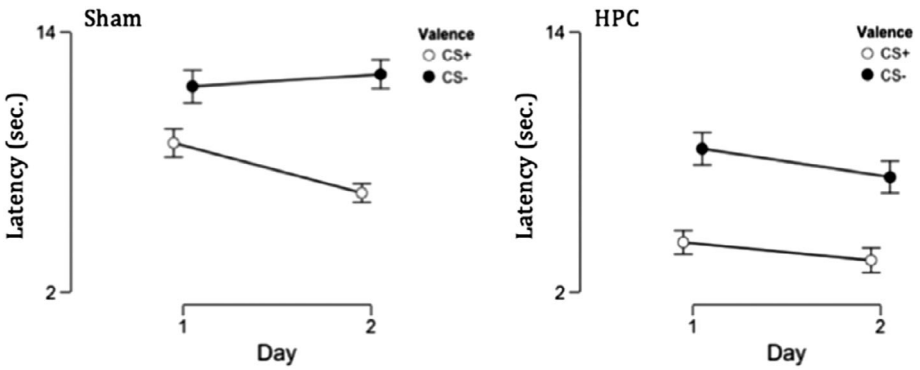


FIGURE 6 Re-training of anterograde compound conditioning

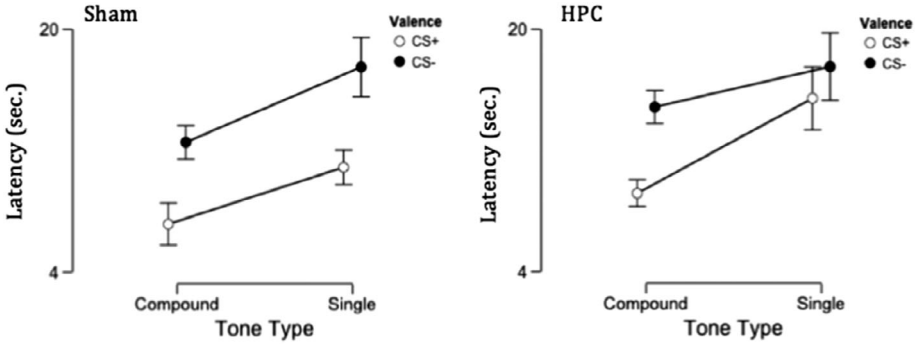


FIGURE 7 Testing of anterograde compound and single items averaged over 7 days

value. By contrast, sham surgery rats had shorter latencies for CS+ compared with both CS− and new tones (t[10] = −5.53, p < .001, d = −1.67 and t[10] = −4.58, p = .001, d = −1.38, respectively) but longer latencies for CS− compared with new tones (t[10] = 3.21, p = .009; d = −0.97) suggesting they were responding to inferred value rather than familiarity.

Lastly, because testing was conducted over 10 days, there was a concern that differences in rates of extinction could account for the findings. To test whether there were differential extinction rates across conditions in hippocampal rats, we conducted repeated-measures ANOVA with group as between subject factor and valence (CS+, CS−, New) and day (1–10) as within subject factors (Figure 12). In addition to the valence and valence by group effects reported above, there was also a day effect (F[9,153] = 42.12, p < .001, η^2_p = 0.71) reflecting the overall decrease in response rates, but importantly there were no significant day by group, or day by group by valence interactions (all p's > .2). We also calculated the individual latency slopes for each rat for each condition and conducted a 2 × 3 repeated measures ANOVA with group as between subject and slope (CS+, CS−, New) as within subject factors. There was an overall slope effect (F[2,34] = 12.4, p < .001, η^2_p = 0.42) and overall group difference in slope (F[1,17] = 9.64, p < .01, η^2_p = 0.36) but importantly no group by slope interaction that could account for the differences reported above (p > .2). The slope difference reflected steeper slopes for CS+ and New tones compared with CS− (p_{tukey} = .003 and p_{tukey} < .001, respectively) and the group difference reflected the fact that control rats had flatter slopes (p_{tukey} = .006), equally across conditions, suggesting less extinction, but no differential extinction, across groups.

3.3.4 | Lesion size and lesion-behavior correlations

There were three groups of rats with hippocampal lesions across the three experiments (N = 26; Figures 13 and 14). On average, 74.02% (SD = 17.48, range: 37.6–97%) of the total hippocampus was damaged, with lesions being more extensive in the dorsal (M = 83.35%; SD = 17.44, range: 43.2–100%) than ventral (M = 58.32%, SD = 23.45; range: 22.4–92.10%) hippocampus (t[25] = 6.57, p < .001; d = 1.29). The three groups did not differ in overall lesion size (F[2,23] = 2.16, p = .14, η^2_p = 0.16), or dorsal lesion size (F[2,23] = 0.58, p = .57, η^2_p = 0.05), but did significantly differ in size of the ventral lesion (F[2,23] = 3.63, p = .04, η^2_p = 0.24). This difference occurred because the group in experiment 3 had significantly larger ventral lesions than the corresponding group in experiment 2 (mean difference = 27% [SE = 10.11], t = 2.67, p_{tukey} = .03), with no other significant between group differences.

Despite the considerable variance in size of hippocampal lesions, there were no correlations between behavior and lesion size, even when all three groups were collapsed together and the valence effect (difference between CS+ and CS−) for single tone testing was used to calculate the correlation. This suggests that even relatively small hippocampal lesions impair the ability to infer value for individual stimuli that comprise a compound stimulus.

3.4 | Additional analysis: Extinction of compound versus constituent stimuli in sham surgery rats

One reviewer turned our attention to the similarity between our task and tests of pattern completion. We agree that the results could also be interpreted within this framework (see more in the Discussion section). One way in which the pattern completion and our interpretations differ concerns what is being retrieved during testing when constituent stimuli serve as retrieval cues. By the pattern completion account, animals complete the compound (BA) in order to retrieve the value for that compound (+ve or −ve). By the dissociative inference account, animals with intact hippocampus associate the part cue itself with value, without need to refer back to the compound from which it is derived. In aversive conditioning, tests of extinction have previously been used to examine similar questions in high-order conditioning. Animals continue to respond to a second order conditioned stimulus (SO) even when responses to the first order CS had been extinguished,

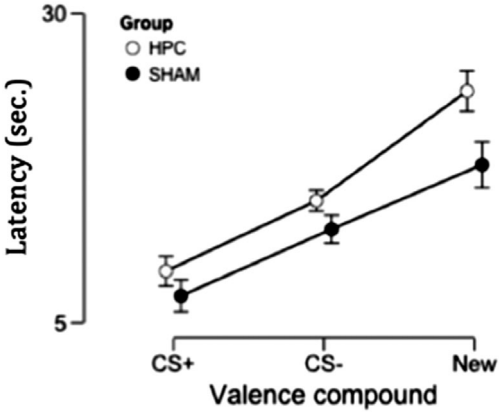


FIGURE 8 Testing of anterograde trained and new compound stimuli averaged over 7 days

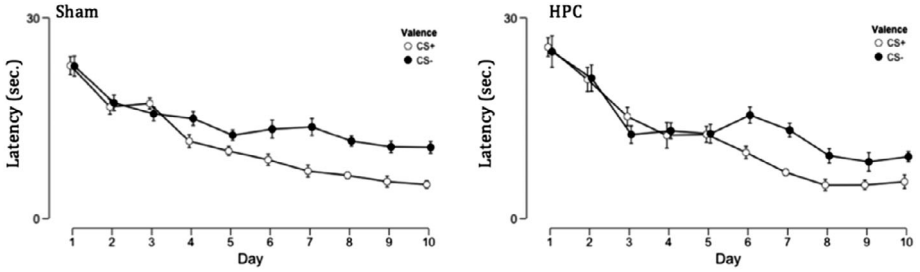


FIGURE 9 Latencies in response to CS+ (open circles) and CS− (full circles) over 10 training days for sham surgery rats (left) and hippocampal rats (right)

suggesting independent SO-value associations (Gewirtz & Davis, 2000). In our study, examining decrease in response latencies to CS− could provide a clue as to the representational similarity between compound and constituent stimuli. If response to constituent items reflects retrieval of the compound (pattern completion), then response latency slopes across testing days should be similar. By contrast, if constituent stimuli are independently associated with value (dissociative inference), slopes might differ.

We tested slopes for compound CS−, constituent CS− and new tones with repeated measures ANOVA, using the intercepts as covariates, in the 19 control rats from experiments 1 and 2 (Figure 15). Contrary to pattern completion predictions and more in line with dissociative inference, slopes were significantly different (F [2,30] = 3.67; p = .037 η^2_p = 0.197) because constituent items had steeper slopes than both compound (p_{tukey} < .001) and New (p_{tukey} = .012) and because compound items had a flatter slope than new tones (p_{tukey} = .006). These results suggest constituent CS− tones were differently represented, or differently retrieved, from both compound CS− and new tones, which is inconsistent with a pattern completion view and consistent with the dissociative inference predictions. This finding does not completely rule out the possibility that pattern completion contributes to performance on our task.

4 | DISCUSSION

This study investigated the role of the hippocampus in direct acquisition of value for compound stimuli and in the subsequent inference of value for their constituents during classical appetitive conditioning. Rats with hippocampal damage normally acquired and retained discriminations between compound stimuli that signaled reward and those that signaled absence of reward. Compared with controls, however, rats with hippocampal lesions were impaired at dissociative inference—the ability to infer the value of the constituents of the compound stimuli whose value they had learned. These findings held whether the compound discriminations were acquired before or after hippocampal lesions. The findings have important implications for understanding the role of the hippocampus in inferential processing, in demonstrating its core role in representation of value and decision-making, and in suggesting that these functions primarily occur during information retrieval.

4.1 | Dissociative inference and the hippocampus

Environments consist of complex combinations of stimuli and events that may signal reward or punishment. There are, however, countless possible combinations of stimuli that could predict significant events and only a limited number of experiences. Inferential processes are necessary, therefore, in order to abstract information and generalize from limited experiences (Tenenbaum, Kemp, Griffiths, & Goodman, 2011). The hippocampus is known to support inference and generalization through memory integration (associative inference); here we report the novel finding that it is also critical for supporting inferences and generalization through parsing of constituents of memory representations, or dissociative inference (see below).

In our task, constituent stimuli always appeared with the same value as the compound, but did not appear as individual stimuli during training, so animals had to infer their associated value. We found that the hippocampus was not required for reinstating learned complex associations (experiments 1–3) and is also not required for identifying constituents of prior experiences as familiar (experiment 3). It was required, however, for inferring the associative value of simple (untrained) constituents that could be derived from the more complex experiences. Inferential processes support memory flexibility for rapidly correcting erroneous expectations (e.g., that certain events need to co-occur for certain outcomes to ensue). Selecting what might be

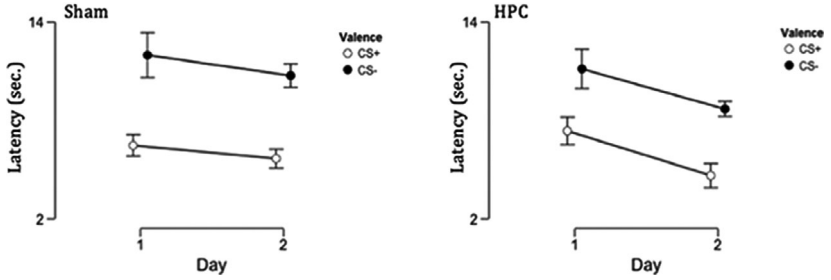


FIGURE 10 Re-training of anterograde compound conditioning

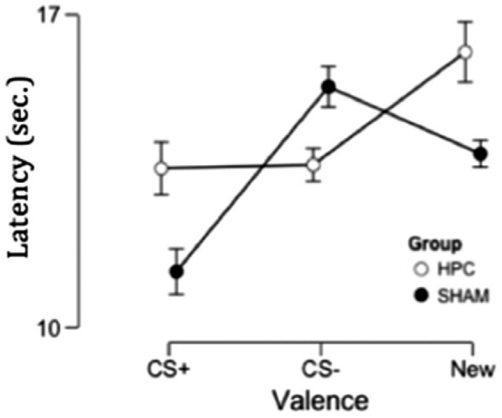


FIGURE 11 Testing of anterograde trained and new single tones averaged over 7 days

biologically relevant information from rich experiences may be of limited value if the organism cannot restructure the pattern of associations in the face of an evolving reality, a function critically supported by the hippocampus.

The hippocampus supports flexible re-combination of the elements of prior experiences to infer relationships among stimuli in order to respond adaptively to changing task demands. This direct inference is distinct from (indirect) associative inference. In situations requiring associative inference, the hippocampus promotes the integration of elements that were experienced previously in separate, but related, events (Eichenbaum & Fortin, 2009; Preston & Eichenbaum, 2013). The present results show that the hippocampus is also crucial for a related, but distinct phenomenon, which we call "dissociative inference." The converse of associative inference, dissociative inference entails direct extraction of novel information from a multiplex single experience, by parsing an integrated or configural representation of that experience into its distinct components and assigning value to each.

The hippocampus's crucial involvement in the flexible use of information is also reflected in tasks that require pattern separation, the ability to differentiate similar and potentially interfering experiences (Bakker, Kirwan, Miller, & Stark, 2008; Leutgeb, Leutgeb, Moser, & Moser, 2007) and pattern completion, the ability to reinstate a previously formed memory on the basis of partial cues (Baker et al., 2016; Bakker et al., 2008; Gold & Kesner, 2005; Nakazawa et al., 2002). Pattern completion could serve as an alternate explanation to the present results, if rats reinstated the compound representation in order to respond to the constituents' inferred value. Our examination of extinction gradients, however, suggests that the results are more consistent with the interpretation that constituents and their values are represented independently (Figure 15). Clearly, to be conclusive, more experiments are needed.

Other examples of flexible use of information include acquired equivalence (Coutureau et al., 2002; Myers et al., 2003; Winocur & Salzen, 1968) and transitive inference (D'Angelo et al., 2016; Dusek & Eichenbaum, 1997; Ryan et al., 2016) where relationships are derived between disparate stimuli that were not previously presented together. These cognitive processes, dissociative inference among them, differ in substantive ways from one another, including whether they are more likely to occur at encoding or retrieval, but they are similar to the extent that they require inferential processing and the re-organization of information. Moreover, they serve to highlight the diverse role of the hippocampus in leveraging an organism's limited set of experiences into a broad range of potential associations that allow for the prediction of future events and guiding behavior.

4.2 | Relationship to configural learning and to other forms of generalization

Rats with hippocampal damage normally acquired and maintained compound representations comprised of constituent tones that were separated by 500 ms. This finding is inconsistent with models suggesting the hippocampus is critical for configural learning (Rudy & Sutherland, 1995), while it is consistent with other studies showing intact learning of compounds under conditions of reduced competition between the compounds and their constituents (Gallagher & Holland, 1992; Han, Gallagher, & Holland, 1998; Whishaw & Tomie, 1991). In fact, such findings led Rudy and Sutherland (1995) to revise their position and propose that the hippocampus is not critical for learning all kind of compound stimuli. Instead they proposed that during encoding of compound stimuli, cortical units that represent the conjunctive co-occurrence (AB), as well as cortical units that represent the constituent elements (A and B), are activated. The hippocampus is critical for decreasing the similarity between the representation of the AB compound and that of its constituent cues by selectively enhancing the salience of the conjunctive cortical units in addition to intensifying the associative strength acquired by the configural units (Rudy & Sutherland, 1995). Our findings, however, are inconsistent also with this revised version of configural learning because the task

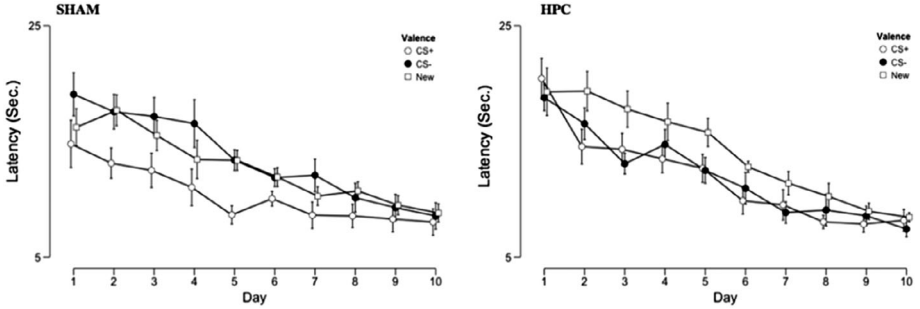


FIGURE 12 Latencies in response to CS+ (open circles) and CS− (full circles) over 10 testing days for sham surgery rats (left) and hippocampal rats (right)

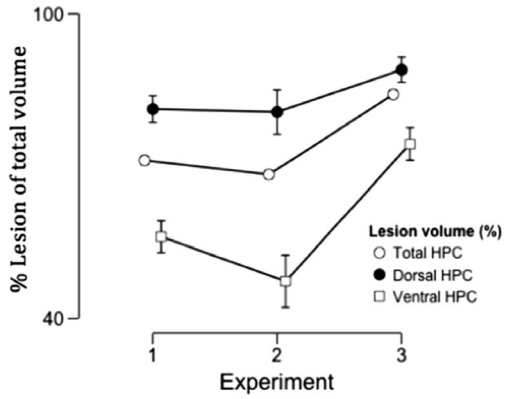


FIGURE 13 Percent lesion to the hippocampus across the three experiments

requires increasing, rather than decreasing, the similarity between the compound and its constituents. By this view, in our study, hippocampal lesions should have slowed the acquisition of compounds because the associative strength of the configural units should have decreased, leading to overgeneralization to the constituents because the similarity between configural and constituent units should have increased. In fact, the reverse pattern emerged. A likely explanation of this reversal is that in our task, and contrary to many configural memory tasks, the constituents never appeared on their own, and there was no competition between configural and constituent associative values that required animals to demonstrate differential configural and item knowledge (Ito & Lee, 2016; Rudy & Sutherland, 1995).

Similar to configural learning tasks, and in contrast to our finding with dissociative inference, hippocampal lesions can also lead to enhanced perceptual generalization, the kind of generalization captured by varying stimulus perceptual characteristics. Hippocampal lesions have long been known to increase perceptual generalization in the auditory (tone frequency; Solomon & Moore, 1975) and visual (light intensity; Wild & Blampied, 1972) domains. Contrary to the failure to generalize valued to the compound stimulus' constituents, generalized stimulus characteristics acquire stronger association with the US, presumably because they are not overshadowed by the original CS–US association (Schmajuk and DiCarlo, 1992). Similar effects have widely been described in humans (Lissek et al., 2014; Laufer et al., 2016). These findings suggest that inference-based (associative or dissociative) generalization is qualitatively different from perceptual generalization, and is likely more akin to human conceptual generalization.

4.3 | Value allocation occurs at retrieval

The process of restructuring existing associations could occur at encoding, during consolidation, or at retrieval (Gilboa & Marlatte, 2017; Hebscher & Gilboa, 2016; Schlichting, Mumford, & Preston, 2015; Zeithamova, Schlichting, & Preston, 2012) For example, during acquisition animals might encode AB+, BA+, A+, and B+. Alternatively, it could be that during offline replay and consolidation different constituents are independently stored to allow later retrieval either in combination or on their own. Finally, generalization may occur only during retrieval when animals are cued with constituent stimuli and need to decide about its reward value. Our data are most consistent with the latter possibility, although the other options cannot be ruled out. In experiment 1, animals with intact hippocampi learned the discrimination and had sufficient time before surgery to consolidate these associations, but were unable to infer the value of the constituent tones after hippocampal lesions. Coupled with the evidence that lesioned rats identified constituents as familiar regardless of their reward value (Figure 11), the results are consistent with a retrieval-based inferential process wherein the hippocampus is critical for reassessing the associative

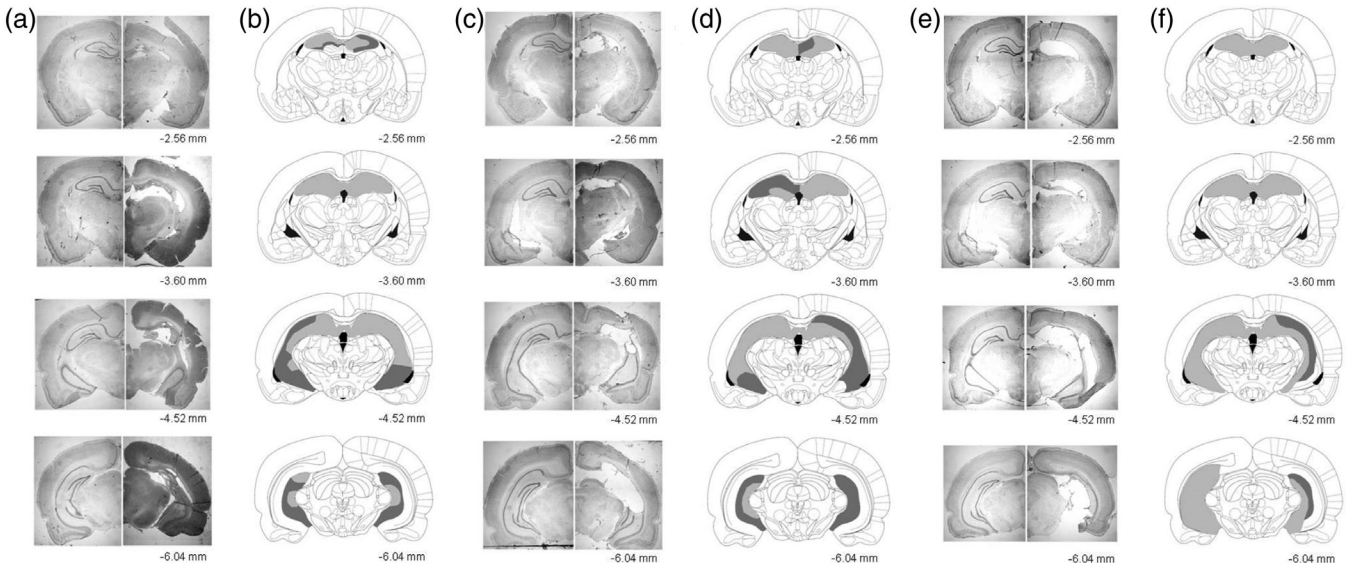


FIGURE 14 Extent of hippocampal lesions. Representative hippocampal lesions (right hemisphere) and sham-operated control (left hemisphere) brain sections for experiments 1 (panel a), 2 (panel c), and 3 (panel e). Minimum (light gray) and maximum (dark gray + light gray) hippocampal lesion throughout the hippocampus in experiments 1 (panel b), 2 (panel d), and 3 (panel f). Anterior to posterior stereotaxic coordinates of the coronal sections are relative to bregma

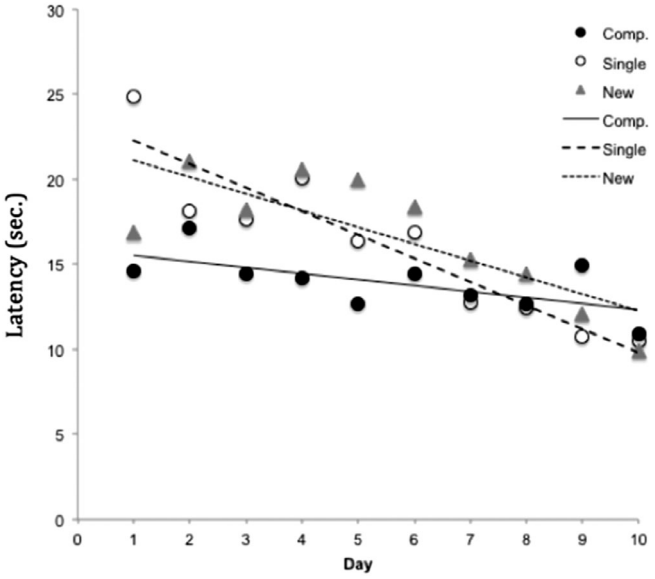


FIGURE 15 Mean response latencies of sham surgery rats across testing days for CS– compound and single (constituent) tones and new tones in experiments 1 and 2 demonstrating differential extinction slopes

structure of prior experiences and reparsing stimulus-value associations to support subsequent decision-making.

There are competing views about the memory mechanism of hippocampal inferential processing. Retrieval-based models similar to the one described here argue that pattern-separation is maintained for overlapping associative representations and related episodes are recombined during retrieval (Carpenter & Schacter, 2017; Kumaran & McClelland, 2012). However, other studies suggest that the hippocampus contributes to inferential generalization at all stages of memory formation (Gilboa & Marlatte, 2017; Zeithamova et al., 2012). For example, human neuroimaging studies revealed increased representational similarity between constituent items that never co-occurred (A and C) in anterior hippocampus as participants were encoding the overlapping pairs (AB and BC) from which they were drawn (Schlichting et al., 2015). This finding is consistent with models of changes in associative weights of individual elements that occur during learning to support later inference (Frank et al., 2003). Others have demonstrated that post-encoding offline processing facilitates generalization processes (Ellenbogen, Hu, Payne, Titone, & Walker, 2007; Werchan & Gomez, 2013) and that this facilitation may relate to hippocampal coupling with cortical regions (Schlichting et al., 2015). Rodent evidence is also consistent with hippocampal contributions to inference through multiple mechanisms (Devito, Kanter, & Eichenbaum, 2010; Dusek & Eichenbaum, 1997). While our retrograde training data from experiment 1 are more consistent with a retrieval-based model, it could be that the hippocampus also contributes to dissociative inference through other mechanisms. In experiments 2 and 3 it could be that animals with hippocampal damage use alternative nonhippocampal dependent strategies to learn the compound stimuli (e.g., Graf & Schacter, 1989; Kent & Brown, 2012; Merhav, Karni, & Gilboa, 2015; Ryan, Moses, Barense, & Rosenbaum, 2013) that can support similar behavior to that of controls, but not the extraction of dissociated associations. Experiments in which the hippocampus is temporarily inactivated during acquisition and reinstated during retrieval could distinguish the different mechanistic accounts.

4.4 | Role in core value representation

The present results also extend recent discoveries in humans (Wimmer & Shohamy, 2012) and animals (Gilboa et al., 2014) that suggest the hippocampus represents intrinsic value by forming flexible, associations between stimuli and primary reinforcement whose value can be transferred to form new associations (Palombo, Keane, & Verfaellie, 2015). The hippocampus has long been known to critically support relationships extrinsic to primary reinforcement. It does so in contextual fear conditioning in which constellations of background stimuli modulate fear responses and in tests that require bridging long temporal gaps between stimuli as occurs in trace conditioning (Maren, Phan, & Liberzon, 2013). Recently, it was found that the hippocampus is also important for transferring value from a CS to previously associated stimuli in sensory preconditioning (Wimmer & Shohamy, 2012) or to new stimuli that are not directly associated with reward in second order conditioning (Gilboa et al., 2014). In both cases hippocampal processing is required to add reward value to a stimulus through an indirect association. Here we found that the hippocampus may be needed for value representation even when stimuli and primary rewards are directly associated, but the stimuli are part of a complex event.

5 | CONCLUSION

Hippocampal involvement in decision-making is typically attributed to its ability to bridge information across different experiences via associative inference or transverse patterning. Here we describe a novel fundamental function of the hippocampus: dissociative inference, the ability to extract the value of single elements (e.g., A or B) from values associated with multielement events (AB). By generalizing value through dissociative inference the hippocampus helps form flexible models of possible future outcomes that transcend the specifics of previous experiences. These findings have important implications for understanding the role of the hippocampus in inferential processing, by demonstrating its core role in representing value and decision-making, and in suggesting that processes underlying dissociative inference occur at retrieval.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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