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Hippocampal Lesion Effects on Occasion Setting by Contextual and Discrete Stimuli

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Abstract

Three experiments examined the role of the dorsal hippocampus (dHIPP) in occasion setting with diffuse contextual and discrete light stimuli serving as occasion setters in classical fear conditioning with rats. Both sham-operated and dHIPP-lesioned animals readily learned a L→T+, T− serial feature positive discrimination in which a light (L) "set the occasion" for reinforcement of a tone (T+). dHIPP-lesioned animals were deficient, however, in acquiring a similar discrimination in which different contexts (A and B) served as occasion setters, i.e., A(T+) and B(T−). The lesioned animals also failed to discriminate between a context in which a tone had been partially reinforced and a context in which no conditioning had taken place, whereas sham-operated animals froze more to the tone in the conditioned context than in the novel context. Collectively, the data indicate that the dorsal hippocampus is important in processing information about the signaling value of contextual, but not discrete, stimuli.

Keywords

rat; cognition; reinforcement; fear; discrimination

Introduction

Memories are typically separated into declarative (or explicit) memory and non-declarative (or implicit) memory systems based on information content and neuroanatomical substrates (Cohen, Eichenbaum, Deacedo, & Corkin, 1985; Schacter, 1987; Scoville and Milner, 1957; Tulving, 1972; van Strien, Cappaert, & Witter, 2009). Declarative memories depend on the medial temporal lobe structures (such as the hippocampus and surrounding cortical areas) and are thought to comprise relatively complex information (e.g., facts and events), whereas non-declarative memories are thought to be independent of the medial temporal lobe structures and involve simple information (e.g., classical conditioning). However, in a classic study, Richard F. Thompson and colleagues (Berger, Alger, & Thompson, 1976) have demonstrated that the hippocampus is engaged even during simple classical or Pavlovian conditioning and in some cases is required (Solomon, Vander Schaaf, Thompson, & Weisz, 1986). In this special issue of *Neurobiology of Learning and Memory*

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commemorating Richard F. Thompson's 50+ years of memory research, we present a study demonstrating the necessity of the hippocampus in Pavlovian conditioning.

In a typical Pavlovian conditioning procedure, a conditioned stimulus (CS) is contingently paired with an unconditioned stimulus (US) and comes to elicit a conditioned response (CR). While the CS is most often a discrete stimulus such as a tone or a light, it has long been recognized that the context in which conditioning occurs may itself act as a CS and form an association with the US, and thereby come to control a CR (e.g., Hull, 1943; Pavlov, 1927). Most modern theories of Pavlovian conditioning consider context-US associations to be analogous to discrete CS-US associations both in the mechanisms by which they are formed and in the response-eliciting properties that they confer (e.g., Mackintosh, 1975; Pearce & Hall, 1980; Rescorla & Wagner, 1972). Context-US associations have proven to be useful theoretically in accounting for certain challenging observations, such as the "reinstatement" of responding to an extinguished CS by unsignalled US presentations (Rescorla & Heth, 1975; see Bouton & King, 1983) and the importance of CS-US contingency in determining the amount of associative strength that accrues to a CS (see Rescorla & Wagner, 1972).

Nevertheless, several investigators have challenged the simple conditioning view of context as insufficient to account for some of the more interesting effects of context, such as the context-dependence of various conditioning phenomena (e.g., extinction; for reviews see Bouton, 2004; Ji & Maren, 2007). An alternative approach holds that context may serve a modulatory or hierarchical function, in addition to directly controlling a CR, by virtue of its association with the US. Thus, a context may modulate the formation and retrieval of associations between discrete CSs and USs that are paired in its presence (e.g.,; Baeyens et al., 2005; Bouton, 1993, 2004; Hirsh, 1974, 1980; Miller & Schachtman, 1985; Nadel & Willner, 1980; Spear, 1973) in a manner that is relatively independent of any context-US associations that may be assumed to exist (Bouton, 1984; Bouton & King, 1986; Bouton & Swartzentruber, 1986; Swartzentruber, 1991).

This modulatory function of context is reminiscent of the "occasion setting" function of discrete cues trained as features in certain conditional discriminations, such as the serial feature-positive (FP) discrimination (Baeyens et al., 2005; Holland, 1983; Ross & Holland, 1981). In this discrimination a target CS, X, is reinforced when preceded by a feature stimulus, A, and nonreinforced when presented in isolation (i.e., A→X+, X−). In contrast to the simultaneous FP discrimination (in which A and X are presented as a simultaneous compound), which is solved on the basis of direct associations formed between A and the US, the serial FP discrimination (in which A and X are separated by a temporal gap) appears to be solved on the basis of a "gating" or "occasion setting" function carried by A, which acts on an association between X and the US (Holland, 1983, 1992). In other words, A does not directly control a response, but instead modulates or "sets the occasion" (Skinner, 1938) for responding to X.

The apparent correspondence between the modulatory function of contextual stimuli and discrete occasion setters is interesting from a biological perspective. Many current theories of learning and memory assume that the hippocampus (particularly the dorsal region) is important in processing information about contextual-spatial, but not discrete, cues. Considerable evidence supports this assumption. For example, dorsal hippocampal lesions have been found to interfere with the acquisition (Ammassari-Teule, Passino, Restivo, & de Marsanich, 2000; Chen, Kim, Thompson, & Tonegawa, 1996; Kim, Rison, & Fanselow, 1993; Maren & Fanselow, 1997; Paylor, Tracy, Wehner, & Rudy, 1994; Phillips & LeDoux, 1992, [1995]; Rudy, 1993; Stiedl, Misane, Spiess, & Ogren, 2000; but see Maren, Aharonov, & Fanselow 1997; Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998; Cho, Friedman

and Silva, 1999; Wiltgen, Sanders, Anagnostaras, Sage, & Fanselow, 2006) and retention (Anagnostaras, Maren, & Fanselow, 1999; Frankland et al., 1998; Kim & Fanselow, 1992; Maren et., 1997; Sutherland, O'Brien, & Lehmann, 2008; Wiltgen et al., 2006) of contextual fear conditioning while having relatively no effect on tone fear conditioning (but see complete and ventral hippocampal lesion effects on auditory trace and delay fear conditioning by McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998 and Richmond et al., 1999, respectively). However, much of the available data concerns the effect of hippocampal lesions on simple conditioning of context–that is, on the formation and retention of context-US associations. The issue of whether the hippocampus is similarly necessary for higher-order, occasion setting functions of context has not been extensively investigated, and the data that do exist are far from unequivocal.

Several studies have indicated that the hippocampus is not necessary for occasion setting by discrete cues (Davidson & Jarrard, 1989; Jarrard & Davidson, 1990, 1991; but see Ross, Orr, Holland, & Berger, 1984), although others have reported certain patterns of impairments (Holland, Lamoureux, Han, & Gallagher, 1999) and enhancements (Han, Gallagher, & Holland, 1998) in the learning of conditional discriminations by hippocampally lesioned animals. If occasion setting by contextual and discrete stimuli are subserved by similar (i.e., extra-hippocampal) brain systems, it is possible that contextual occasion setting may be unaffected by hippocampal lesions despite the apparent importance of the hippocampus for simple conditioning of context. Alternatively, contextual information–which is necessarily complex and multimodal–may by its very nature require higher-order, hippocampal processing, implying that the occasion setting function of context, like the formation of context-US associations, should be vulnerable to the impairing effect of hippocampal lesions.

While no study to date, to our knowledge, has directly compared the effect of dorsal hippocampal lesions on occasion setting by discrete and contextual cues, a few authors have examined the hippocampal dependence of certain conditional contextual discriminations that are similar to those sometimes used in the examinations of occasion setting with explicit stimuli. For example, a biconditional contextual discrimination (in which a target stimulus, X, is reinforced in context A but nonreinforced in context B, whereas a second target, Y, is reinforced in context B but nonreinforced in context A; i.e., A[X+], B[X−], A[Y−], B[Y+]) has been the subject of several studies that have, nevertheless, produced contrasting results: some authors (Hall, Purves, & Bonardi, 1996; McDonald et al., 1997) have reported that hippocampally lesioned animals are able to solve the discrimination as well as controls, and others (Good & Honey, 1991) have found substantial impairments. Other studies have examined the context specificity of conditioning (often taken to reflect an occasion setting or retrieval function of context; see Bouton, 1993, 2004) under various circumstances and, again, failed to agree as to whether hippocampally lesioned animals are lacking in contextual control of responding (e.g., Good, de Hoz, & Morris, 1998; Good & Honey, 1991; Holt & Maren, 1999; Honey & Good, 1993; Penick & Solomon, 1991) or are not different from control animals (e.g., Hall et al., 1996; McDonald et al., 1997; Wilson, Brooks, & Bouton, 1995).

The present series of experiments were designed to examine the question of the dorsal hippocampal dependence of occasion setting by contextual and discrete cues more directly (schematically summarized in Table 1). Experiment 1 first established the hippocampal dependence of contextual occasion setting by determining the effect of dorsal hippocampal (dHIPP) lesions on contingent contextual modulation of responding. It may be argued that, while contingent contextual modulation requires the intact hippocampus, incidental contextual modulation does not (e.g., Frankland et al., 1998;Young, Bohenek, & Fanselow, 1994). Even though this possibility is unresolved, given the unfavorable outcome of certain

studies designed specifically to bear on the question of the hippocampal dependence of incidental and contingent contextual conditioning (Good et al., 1998;Phillips & LeDoux, 1994), Experiment 2 was designed to further examine the dHIPP role in incidental contextual modulation. Experiment 3 then compared the effect of dHIPP lesions on occasion setting by contextual and discrete stimuli. This experiment examined the performance of a discrete FP discrimination (in which a light set the occasion for responding to a tone) in the context in which the discrimination was trained and in a novel context. This design permits, for the first time, a within--subjects comparison of the effect of dHIPP lesions on contextual and discrete occasion setting. It may thus represent the most powerful test to date of the (often cited but ill-supported) notion that all types of occasion setting are hippocampus-dependent.

Materials and Methods

Animals

Animals were experimentally naive male Long-Evans rats (250–300 g) were individually housed in standard plastic cages in a climate-controlled vivarium with ad libitum access to food and water. Animals were maintained on a 12-hr light:dark cycle (lights on at 7AM). All test procedures were conducted during the light phase of the cycle and completed at Yale University, New Haven, CT (J.J.K.'s former laboratory).

Surgery

The rats were anesthetized with ketamine HC1 (30 mg/kg) and xylazine (2.5 mg/kg) and placed in a stereotaxic apparatus. A stainless steel insect pin (#00), insulated with epoxy except for 0.5 mm at the tip, was lowered into the dorsal hippocampus (coordinates: 2.8 mm posterior to bregma, ± 2.0 mm lateral to midline, and 4.0 mm ventral to the surface of the skull). Lesions were produced in 30 animals by passing 1.5 mA anodal current for 15 sec (Grass Instruments, West Warwick, RI). Thirty control animals were treated identically except that no current was passed to create a lesion. Animals were adapted to handling and transportation procedures each day during a 7 day postoperative recovery period.

Apparatus

Training and testing took place in two modular operant test chambers (both 27 cm width × 28 cm length × 30.5 cm height) equipped with a speaker module (Coulbourn Instruments, Allentown, PA), located in an acoustic isolation room. The floor of each chamber was composed of 16 stainless steel bars (4.5 mm diameter) spaced 17.5 mm center-to-center and wired to a Coulbourn Precision Regulated Animal Shocker. The grid floor and base pan were washed thoroughly with tap water and completely dried prior to conditioning and testing.

Procedure

Experiment 1—Conditioning took place over ten consecutive days. On Day 1 and subsequent odd days, the rats (n = 20) were placed into Context B (denoted safe context), which was comprised of the following features: the side walls of the modular operant chamber were aluminum, while the front and back walls were clear Plexiglas covered with black and white checkered wallpaper; the tone and light modules were on the right side wall; the overhead light in the acoustic isolation room was off; the grid floor was covered by a Plexiglas plate scattered with sawdust; and the chamber walls were wiped with 20% ethanol. In the safe context the animals were exposed to ten presentations of a 15-s tone (2 KHz, 80 dB), which were separated by a 3-min inter-trial interval (ITI). On Day 2 and subsequent even days of training, the rats were placed into Context A (denoted shock context) which

was comprised of the following features: all four walls of the modular operant chamber were clear Plexiglas; the tone and light modules were on the left side wall; the overhead light in the acoustic isolation room was on; the grid floor was exposed; and the chamber walls were wiped with 5% ammonium hydroxide. In the shock context the animals were exposed to ten presentations of the same 15-sec tone, which now overlapped and coterminated with a 1-sec footshock (0.5 mA). The ITI was 3 minutes. Upon completion of each day's training session, the rats were returned to their home cages.

Three days after the completion of training, a test was conducted in the safe context (Context B) in which freezing in the presence of the tone was assessed. The test consisted of a 1-min baseline period followed by 8 minutes of continuous tone. Three days subsequent to this test, a second, identical test was conducted in the shock context (Context A). This order of testing (i.e., a test in the safe context followed by a test in the shock context) was chosen because it provides the most sensitive measure of conditioned tone fear in the safe context.

Experiment 2—The animals were trained similarly to those of Experiment 1, except that conditioning was conducted in a single training context (which corresponded to Context A, the shock context, of Experiment 1). Conditioning took place over ten consecutive days. On Day 1 and subsequent odd days, the rats (n = 20) experienced the "safe" paradigm: they were exposed to ten presentations of a 15-s tone, which were separated by a 3-min ITI. On Day 2 and subsequent even days of training, the rats experienced the "shock" paradigm: they were exposed to ten presentations of the same 15-s tone, which now overlapped and co-terminated with a 1-sec (0.5 mA) footshock. The ITI was 3 minutes. Upon completion of each day's training session, the rats were returned to their home cages.

Three days after the completion of training, a test was conducted in a novel context (which corresponded to Context B, the safe context, of Experiment 1) in which freezing in the presence of the tone was assessed. The test consisted of a 1-min baseline period followed by 8 minutes of continuous tone. Three days subsequent to this test, a second, identical test was conducted in the conditioning context (Context A).

Experiment 3—Conditioning was conducted in a single training context (which corresponded to Context A, the shock context, of Experiment 1) and took place over ten consecutive days. On Day 1 and subsequent odd days, the rats (n = 40) experienced the safe paradigm: they were exposed to ten presentations of a 15-s tone, which were separated by a 3-min ITI. On Day 2 and subsequent even days of training, the rats experienced the shock paradigm: they were exposed to ten presentations of a 15-s light (occasion setter), immediately followed by a 15-s tone, which overlapped and co-terminated with a 1-s footshock. The ITI was 3 minutes. Upon completion of each day's training session, the rats were returned to their home cages.

Three days after the completion of training, a test was conducted in either a novel context (for half of the animals of each group; the novel context corresponded to Context B, the safe context, of Experiment 1) or the training context (for the remaining animals of each group) in which freezing in the presence of the tone was assessed. The test consisted of a 1-min baseline period, followed by a 15-s light, followed by 8 minutes of continuous tone. Three days subsequent to this light-tone test, a second test was conducted in the same context, and consisted of a 1-min baseline period followed by 8 minutes of continuous tone. Three days after this tone test, a third test was given in the same context, and consisted of a 1-min baseline period followed by 8 minutes of continuous light.

Behavioral Data Collection

The experimental events were controlled, and the data collected, by an IBM-PC computer equipped with the Coulbourn LabLinc Habitest Universal Linc System. A 24-cell infrared activity monitor, which detects movement in the x, y, and z axes of the animal's emitted infrared (1300 nm) body heat image, was mounted on the top of each chamber and used to assess freezing behavior (cf., Lee & Kim, 1998). In brief, the total time of inactivity exhibited by each animal was measured using a computer program, and freezing was defined as inactivity lasting ≥ 3 sec. Any period of inactivity lasting less than 3 sec was recorded as general activity. (Freezing scores obtained via infrared monitoring and observer time sampling methods [cf., Kim, DeCola, Landeira-Fernandez, & Fanselow, 1991] have been consistently and robustly correlated.)

Histology

At the completion of behavioral testing, the animals were overdosed with ketamine HC1 and xylazine and perfused intracardially with 0.9% saline followed by 10% buffered formalin. The brains were removed and stored in 10% formalin for at least 2 weeks before slicing. Coronal sections (60 μm) were taken through the extent of the lesion, mounted on gelatinized slides, and stained with Prussian blue and cresyl violet dyes. The histological reconstruction of the lesions was assessed by an observer who was blind to the behavioral data.

Data Analysis

Freezing data were analyzed using repeated-measures multivariate analysis of variance (ANOVA), with the between-subjects factor group (sham vs. lesion), and within-subjects factors minute, context (shock vs. safe; training vs. novel) and test (tone, light, light-tone). The level of statistical significance was $p < 0.05$.

Results

Histological Results

Figure 1 presents a reconstruction of the minimum and maximum extent of the damage in animals from all three experiments with lesions of the dHIPP. Hippocampal damage was found mainly in medial portions of the dorsal hippocampal formation (areas CA1 and dentate gyrus), but there were also small amounts of damage to the overlying cortex.

Behavioral Results

Experiment 1—Experiment 1 used an analogue of the serial FP discrimination in which a context, rather than a discrete feature, set the occasion for responding to a target cue: A(X+), B(X−). Figure 2 depicts the mean percent freezing exhibited by both groups of animals during 1 minute of baseline and 8 minutes of continuous tone in the tests in the safe and shock contexts. No group or context differences were apparent in baseline freezing (largest $F = 1.61$; all p values > 0.05). The groups did, however, perform differently during the 8 minutes of continuous tone. An ANOVA revealed significant main effects of context ($F_{(1,18)} = 20.41$, $p < 0.01$) and minute ($F_{(7,126)} = 5.77$, $p < 0.01$), a significant context × group interaction ($F_{(1,18)} = 10.69$, $p < 0.01$) and a significant context × minute interaction ($F_{(7,126)} = 6.08$, $p < 0.01$). No other main effects or interactions were significant (all F values < 1). The significant context × group interaction demonstrates that the discrimination between the contexts was not equally evident in the lesion and sham groups. Tests of simple main effects (using the error term appropriate to each comparison; Howell, 1997) revealed that the sham-operated animals froze reliably more to the tone in the shock context than in the safe context

($F_{(1,9)} = 24.22$, $p < 0.01$), whereas the dHIPP-lesioned animals did not freeze differentially to the tone in the two contexts ($F_{(1,9)} = 1.04$, $p > 0.05$).

Experiment 2—Two animals died following surgery and one was excluded from further data analyses because of an inaccurate lesion placement, leaving 9 animals in the lesion group and 8 in the sham group.

Figure 3 presents the mean percent freezing exhibited by both groups of animals during 1 minute of baseline and 8 minutes of continuous tone in the tests in the training and novel contexts. The sham-operated animals exhibited robust freezing during the baseline period in the training context but not in the novel context, whereas the dHIPP-lesioned animals exhibited little baseline freezing in either context. Similarly, the sham-operated animals exhibited considerably more freezing to the tone in the training context than in the novel context, while the dHIPP-lesioned animals froze indiscriminately to the tone in the two contexts.

An ANOVA was used to compare baseline freezing across groups and contexts. There was a significant main effect of group ($F_{(1,15)} = 6.67$, $p < 0.05$), and of context ($F_{(1,15)} = 19.08$, $p < 0.01$), and a significant group × context interaction ($F_{(1,15)} = 6.64$, $p < 0.05$). Tests of simple main effects revealed that both groups froze more in the trained context than in the novel context (*Fs* = 11.22 and 17.19 for sham and lesion groups, respectively; all p values < 0.05), but that the sham group froze reliably more than the lesion group in the trained context ($F_{(1,16)} = 6.86$, $p < 0.05$), and not in the novel context ($F_{(1,16)} = 2.01$, $p > 0.05$). Overall, however, very little freezing was observed in either group and in either context during the baseline period.

An ANOVA was used to assess freezing during the 8-minute tone test with group, context, and minute as factors. There were significant main effects of context ($F_{(1,15)} = 33.09$, $p < 0.01$), minute ($F_{(7,105)} = 24.78$, $p < 0.01$), and group ($F_{(1,15)} = 14.06$, $p < 0.01$), and a significant context × group interaction ($F_{(1,15)} = 23.82$, $p < 0.01$). No other interactions were significant (largest $F = 2.01$; all p values > 0.05). The context × group interaction suggests that the discrimination between the two contexts was not equal in the two groups. Tests of simple main effects revealed that the sham-operated animals froze significantly more to the tone in the trained context than in the novel context ($F_{(1,7)} = 37.95$, $p < 0.01$), while the dHIPP-lesioned animals did not respond differentially to the tone in the two contexts ($F_{(1,8)} < 1$).

Experiment 3—Experiment 3 compared the effect of dHIPP-lesions on occasion setting by contextual and discrete cues. Since lesions of the dorsal hippocampus impair contextual occasion setting (Experiments 1 and 2), these same lesions should also impair occasion setting by discrete cues if it is true that the two forms of modulation share a similar neural basis.

Two animals died following surgery and one was excluded from the further data analyses because of an inaccurate lesion placement, leaving 19 animals in the lesion group (9 tested in the novel context and 10 tested in the trained context) and 18 animals in the sham group (9 tested in each context).

Panel A of Figure 4 presents the mean percent freezing exhibited during 1 minute of baseline, 15 seconds of light, and 8 minutes of continuous tone or light in the light-tone, tone, and light tests for those animals tested in the novel context. These data were analyzed using multiple ANOVAs comparing group performance during the baseline period, the light feature, and the tests of freezing to the tone, the light, and the tone that followed the light

feature. An ANOVA with group and test as factors assessed freezing during the baseline periods preceding the tone, light, and light-tone tests. There were no main effects of group and test, and no group × test interaction (all F values < 1). Similarly, a one-way ANOVA comparing group performance during the 15-s light feature revealed no group difference (F < 1). The data from the tone, light, and light-tone tests were analyzed using an ANOVA with group, test, and minute as factors. There were significant main effects of test ($F_{(2,34)}$ = 17.39, p < 0.01) and minute ($F_{(7,119)}$ = 4.71, p < 0.01), and a significant test × minute interaction ($F_{(14,238)}$ = 4.04, p < 0.01). No other main effects or interactions reached significance (all F values < 1). Tests of simple main effects revealed that the animals generally froze more in the light-tone test than in the light test ($F_{(1,18)}$ = 17.83, p < 0.01), or the tone test ($F_{(1,18)}$ = 19.60, p < 0.01), and that they also froze more in the light test than in the tone test, ($F_{(1,18)}$ = 6.61, p < 0.05).

Panel B of Figure 4 presents the data from the analogous tests conducted in the trained context. Analysis of the baseline freezing revealed a significant main effect of group ($F_{(1,16)}$ = 15.08, p < 0.01), but no main effect of test ($F_{(2,32)}$ = 2.97, p > 0.05), or group × test interaction (F < 1). There was no main effect of group during the 15-s light feature ($F_{(1,17)}$ = 3.14, p > 0.05). During the tone, light, and tone preceded by light tests, there were significant main effects of group ($F_{(1,16)}$ = 11.65, p < 0.01), of test ($F_{(2,32)}$ = 38.66, p < 0.01), and of minute ($F_{(7,112)}$ = 4.93, p < 0.01). There were significant interactions between group and test ($F_{(2,32)}$ = 4.20, p < 0.05), group and minute ($F_{(7,112)}$ = 2.20, p < 0.05), and test and minute ($F_{(14,224)}$ = 7.46, p < 0.01), and a significant group × minute × test interaction ($F_{(14,224)}$ = 3.68, p < 0.01). Tests of simple main effects revealed that the animals generally froze more in the light-tone test than in the light test ($F_{(1,17)}$ = 31.94, p < 0.01), or the tone test ($F_{(1,17)}$ = 38.44, p < 0.01), whereas there was no difference in freezing between the tone and light tests, ($F_{(1,17)}$ = 3.40, p > 0.05). Comparisons of the groups' performance in each test confirmed that the groups did not differ in the tone test ($F_{(1,17)}$ < 1), but that the sham-operated animals did freeze more in the light test ($F_{(1,17)}$ = 8.37, p < 0.05), and the light-tone test ($F_{(1,17)}$ = 7.51, p < 0.05), than did the dHIPP-lesioned animals.

Discussion

The present series of experiments had two objectives: first, to determine whether contextual occasion setting, like other forms of contextual conditioning, is hippocampus-dependent; and second, to compare the effect of dorsal hippocampal lesions on occasion setting by discrete and contextual cues. Animals with dHIPP-lesions were found to be impaired in learning a discrimination in which contextual modulation is necessary for appropriate performance (Experiment 1), and in expressing any degree of contextual specificity of responding, a measure of "incidental" contextual modulation (Experiment 2). dHIPP-lesioned animals were not impaired, however, in learning a serial FP discrimination in which a light set the occasion for responding to a tone, although again they were lacking in contextual modulation of performance (Experiment 3). Collectively, these data indicate that the dorsal hippocampus is important in processing information about the signaling value of contextual, but not discrete, stimuli.

These findings join a large body of evidence implicating the hippocampus in the processing of contextual information for certain conditioning phenomena (e.g., Penick & Solomon, 1991), whether that information is relevant to simple conditioning of context (i.e., the formation of context-US associations) or higher-order contextual conditioning (i.e., contextual occasion setting; see Holland & Bouton, 1999, but see also Rudy, 2009). Nevertheless, this conclusion has not been universally accepted (Benoit, Davidson, & Chan, 1999; Good & Honey, 1997; McNish, Gewirtz, & Davis, 1997); particularly with respect to the hippocampal-dependence of contextual occasion setting, there are a number of studies

that suggest otherwise. For example, among the studies that have examined the effect of hippocampal lesions on the solution of a biconditional contextual discrimination, only one of them (Good & Honey, 1991) reported an impairment, while others (Good et al., 1998; Hall et al., 1996; McDonald et al., 1997) did not. This type of discrimination is quite similar to the contextual analogue of the FP discrimination that we examined in Experiment 1 because it consists of two concurrent contextual FP discriminations, arranged such that each of the contexts signals reinforcement of one target and nonreinforcement of the other.

Given our finding that the solution of the contextual FP discrimination is devastated by dorsal hippocampal lesions, it is not at all clear why the apparently more complex contextual biconditional discrimination should be spared. Studies that make use of other measures of contextual modulation, such as the context specificity of responding, have also reported conflicting findings (Fox & Holland, 1998; Good & Honey, 1991; Good et al., 1998; Hall & Honey, 1989; Hall et al., 1996; Holt & Maren, 1999; Honey & Good, 1993; Penick & Solomon, 1991; McDonald et al., 1997; Wilson et al., 1995). There are sometimes clear procedural differences that might account for the discrepancies, such as the use of aversive versus appetitive conditioning procedures (compare, e.g., Fox & Holland, 1998; Wilson et al., 1995), the method used to create and/or the ultimate extent of the hippocampal lesions (compare, e.g., Good & Honey, 1991; Good et al., 1998), or the use of different training and/or testing protocols (compare, e.g., Good & Honey, 1991; Hall et al., 1996). Different outcomes are, perhaps, to be expected with differences in lesion type and/or experimental design. However, differences among studies that are identical in all respects except for the choice of an appetitive or aversive paradigm are puzzling.

In fact, these types of differences have also been notable in studies examining the hippocampal-dependence of simple contextual conditioning, and are the source of much of the controversy surrounding the claim that the formation of context-US associations requires the intact hippocampus. With appetitive conditioning procedures, the contextual conditioning, which occurs when the unsignaled US is repeatedly presented within a context, is seldom disrupted by hippocampal lesions (Fox & Holland, 1998; Good & Honey, 1991; Honey & Good, 1993); whereas with aversive fear conditioning procedures, the contextual conditioning produces mixed results (Chen et al., 1996; Kim et al., 1993; Maren, Aharonov & Fanselow, 1997; McNish et al., 1997; Wiltgen et al., 2006), which have been postulated as a compensatory conditioning to ‘elements’ of context in the absence of the hippocampus (Gonzalez, Quinn, & Fanselow, 2003; Rudy, Huff, & Matus-Amat, 2004). Some have suggested that appetitive USs might be less readily associated with contextual stimuli than are aversive USs (Fox & Holland, 1998). However, there are inconsistencies even among studies using similar conditioning paradigms. One might appeal to lesion type and extent as at least partially accounting for the discrepant results of these studies. Two appetitive conditioning studies that reported no impairment used neurotoxic lesions (Good et al., 1998; McDonald et al., 1997), whereas the one that found a deficit used electrolytic lesions (Good & Honey, 1991). However, a third study finding no impairment also used electrolytic lesions (Hall et al., 1996), and almost exactly replicated the experimental design used by Good and Honey (1991). In this instance, then, the impact of an argument based on procedural details is considerably lessened.

Our finding that the solution of a discrete, serial FP discrimination is not affected by dorsal hippocampal lesions also joins a literature that is marked by inconsistencies. In the first study to consider the effect of hippocampal lesions on occasion setting, Ross, Orr, Holland, and Berger (1984) reported that aspiration lesions of the hippocampal formation prevented the acquisition and eliminated the retention of a serial FP discrimination. However, subsequent work using neurotoxic hippocampal lesions failed to replicate the impairment in either acquisition (Jarrard & Davidson, 1990) or retention (Davidson & Jarrard, 1989).

Moreover, when the performance of groups of rats with aspiration and neurotoxic lesions was directly compared, the aspiration-lesioned group was found to be impaired but the neurotoxic-lesioned group was not (Jarrard & Davidson, 1991), leading to the conclusion that occasion setting is subserved by extra-hippocampal structures that are damaged with aspiration but not neurotoxic lesions. More recently, the question of the hippocampal-dependence of simple occasion setting has again been raised in light of findings that the learning of serial FP or feature-negative (FN) discriminations may, under some circumstances, be either enhanced (Han et al., 1998) or impaired (Holland et al., 1999) by neurotoxic lesions of the hippocampus proper. It is worth noting that the observed enhancements occurred in situations in which the inter-trial interval (ITI) was relatively short (30 or 60 seconds), unlike the 3 minute ITI used in our Experiment 3, and that the impairments were primarily observed in the learning of a FN discrimination, which the present study did not consider. Thus, our finding that the learning of a discrete serial FP discrimination is not affected by hippocampal lesions is consistent with the bulk of the data collected to date.

Studies that use contextual FP discrimination have provided perhaps the strongest evidence to date for an occasion setting function of context distinct from simple contextual conditioning. For example, Bouton and Swartzentruber (1986) demonstrated that the solution of the contextual FP discrimination is not readily explainable by appeal to simple context-US associations. Using a conditioned suppression paradigm, these authors found that response suppression in the presence of the target was reliably greater in the reinforced context (A), and reliably smaller in the nonreinforced context (B), than in a novel context (C), indicating that both contexts modulated responding. However, subsequent tests of conditioned excitation and inhibition failed to reveal any simple associative tendencies held by either context. Moreover, extended nonreinforced exposure to context A after discrimination training had little impact on subsequent discrimination performance, strongly suggesting that the occasion setting ability of a context is largely independent of its simple associative value.

An alternative interpretation of the outcome of Experiment 1 is possible, considering the mechanisms by which contexts may come to act as occasion setters. It is commonly held that, in order for a discrete cue to become an occasion setter, two criteria must be met: first, an appropriate temporal and/or salience relationship must exist between feature and target (see, e.g., Holland, 1986, 1989), and second, an “informational” relationship must be established in which the target cue is uniquely reinforced or nonreinforced in the presence of the feature (see Swartzentruber, 1995, for a review). The second criterion is most easily and effectively met through the use of a discrimination procedure in which, for example, the target is reinforced in the presence of the feature but nonreinforced in its absence (i.e., the FP discrimination). However, there is evidence that discrimination training is not necessary for a feature cue to become an occasion setter (Bonardi, 1992; Hall & Mondragon, 1998; Wagner & Brandon, 2000). All that is needed, by these accounts, is that the feature signals the reinforcement (or nonreinforcement, as the case may be) of the target stimulus (see Bonardi, 2007; Bonardi & Jennings, 2009). That the establishment of contextual occasion setting may similarly not require discrimination training is suggested by the contextual specificity of certain types of conditioning (e.g., latent inhibition; see, e.g., Hall & Honey, 1989) in which discrimination training is not involved (Hall & Mondragon, 1998).

Frohardt, Guarraci, and Bouton (2000) examined the hippocampal role in renewal effect and used the context as the occasion setter. Their finding indicated the complete hippocampal lesions do not disrupt the renewal effect. One might argue that this finding conflicts with the present results from Experiment 1. In addition to the difference in the extent of the lesions in the hippocampus, the renewal effect in their study was tested after several extinction

sessions. However, our contextual occasion setting was tested during the extinction phase. In fact, like similar freezing responses for the hippocampal group between the safe and shock contexts in our experiment, the performance of hippocampus-lesioned group in the Frohardt et al. study (2000) showed comparable suppression ratio of bar-pressing for the novel and trained contexts throughout the extinction trials.

The novel context test in Experiment 2 was conducted on an odd day that corresponds to the safe paradigm of the ten days of training; the trained context test was done on an even day for shock paradigm of training. Therefore, one might argue that control rats learned the 'safe-shock' alternating training contingency and used the previous session type as an occasion setter. However, this is unlikely in that the same training schedule was used in Experiment 3 and the control group showed robust freezing (sham-light-tone) on the odd day.

An important finding from the discrete, serial FP discrimination study (Experiment 3) is that, even though a single explicit CS is regarded to be a more difficult indicator to be conditioned for serial FP discrimination than simple contextual CS, the dHIPP-lesioned group successfully exhibited freezing during light-tone presentations in the novel context. Therefore, the impairment of occasion-setting in the trained context isn't likely due to the disrupted role of the dorsal hippocampus in solving difficult (or complex) associative learning. In addition, the possibility that the light worked as a simple excitor rather than the occasion setter prior to tone is also unlikely because the separate presentation of light by itself didn't increase the level of freezing.

On a theoretical level, the findings of the present study indicate that the dorsal hippocampus is not primarily involved in the representation of conditional (Hirsh, 1974, 1980) or configural (Gluck & Myers, 1993; Rudy, 2009; Sutherland & Rudy, 1989) relations among stimuli, at least not in the simple manner assumed by most early theories. If this were the case, then one would expect that the learning of both the discrete FP discrimination and its contextual analogue would be impaired by dHIPP lesions. However, the deficit that we observed was selective to the contextual discrimination.

Other theories have assumed that the processing of information relevant to discrete and contextual cues occurs in different areas of the hippocampal formation (Myers, Gluck, & Granger, 1995; Zackheim, Myers, & Gluck, 1998), or that hippocampal lesions may be expected to have quite different effects on the learning of discrete and contextual conditional discriminations as a function of the qualitatively different temporal encoding demanded by discrete (phasic) and contextual (tonic) cues (Schmajuk & Buhusi, 1997). Our data are consistent with either possibility. As Han et al. (1998) have noted, it seems clear that quantitative, real-time models such as these are necessary to capture the complexity of hippocampal lesion effects on various conditioning phenomena, as simpler models have not been able to do so with similar accuracy.

In summary, although the functions of the hippocampus in classical conditioning remain incompletely characterized, the extensive amount of research to date and the continued pursuit of clarity in this topic are acknowledgements to the significance of Richard F. Thompson and his colleagues' pioneering work.

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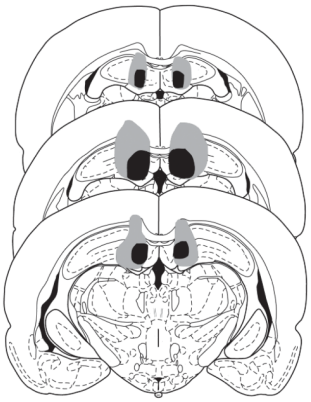

Figure 1.
Minimum (black) and maximum (gray) extent of dorsal hippocampal lesions in animals from Experiments 1–3. The lesions were reconstructed on successive coronal sections (−2.30, −3.60, and −4.16 mm bregma) from Paxinos and Watson (1997). Reprinted with permission from Elsevier ©1997.

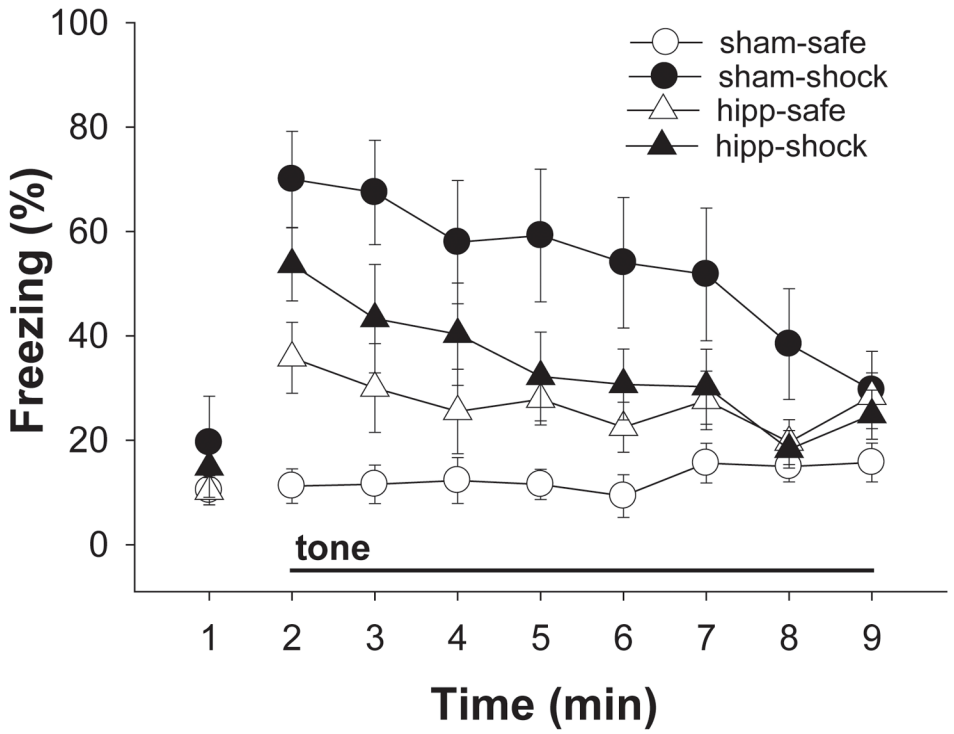

Figure 2.
Mean percent freezing (±SEM) during 1 minute of baseline measurement and 8 minutes of continuous tone in the “safe” and “shock” contexts of Experiment 1.

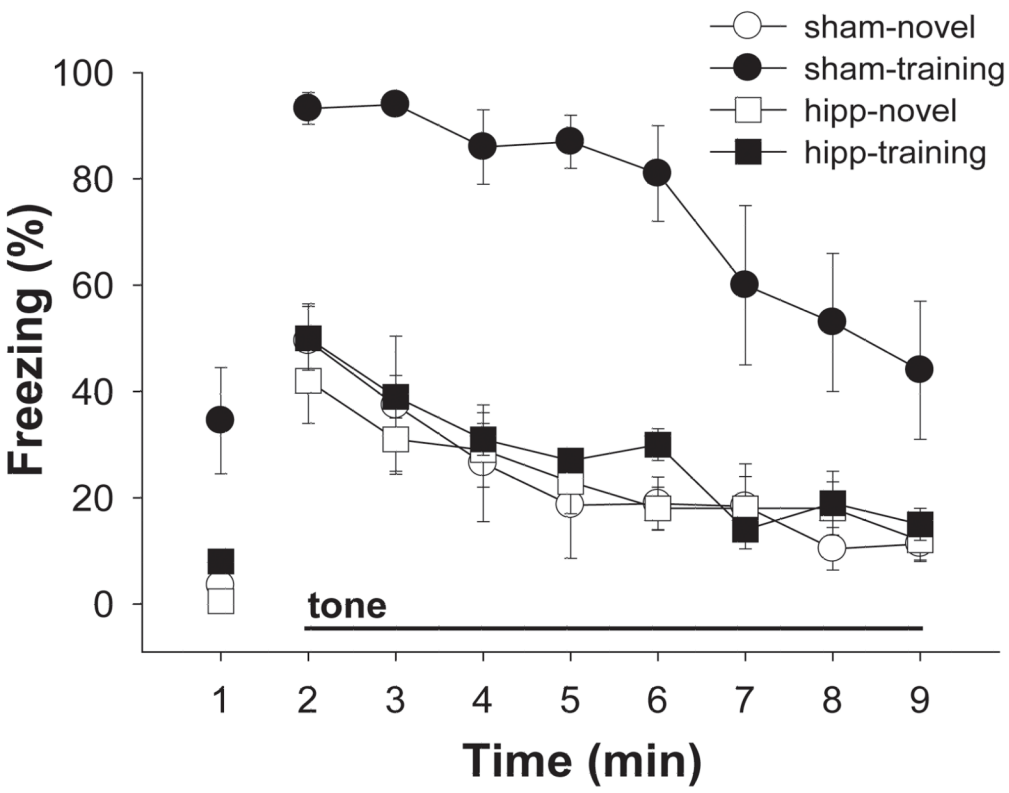

Figure 3.
Mean percent freezing (±SEM) during 1 minute of baseline measurement and 8 minutes of continuous tone in the training and novel contexts of Experiment 2.

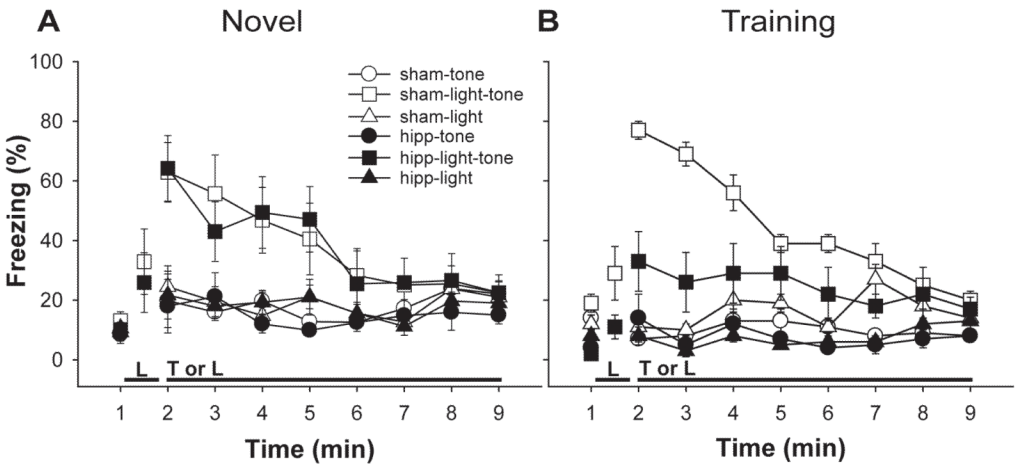

Figure 4.

Panel A. Mean percent freezing (±SEM) during the tone, light, and light-tone tests of Experiment 3, in animals tested in the novel context. Panel B. Mean percent freezing (±SEM) during the tone, light, and light-tone tests of Experiment 3, in animals tested in the training context.

Table 1

Design of Experiments 1–3

	Training		Test	
Experiment	**Context A**	**Context B**	**Context A**	**Context B**
1	T+	T−	T	T
2	T+, T−		T	T
3	L→ T+, T−		L→T, T, L	L→T, T, L

Note. T and L refer to tone and light CSs. + and − indicate reinforced and nonreinforced trials.