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The Role of CA1 in the Acquisition of an Object–Trace–Odor Paired Associate Task

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This experiment was designed to determine whether adding a temporal component to an object–odor association task would recruit the hippocampus. The rats were given CA1, CA3, or control lesions prior to learning the object–trace–odor task. Rats were presented with an object for 10 s, after which the object was removed, followed by a 10-s trace period, followed by the presentation of an odor 50 cm away. If the odor and the object were paired, rats were to dig in the odor cup for a reward. If unpaired, rats were to refrain from digging. Rats that had CA1 lesions were unable to make the association, whereas rats that had CA3 lesions performed as well as controls. These results support the idea that the hippocampus is involved in forming arbitrary associations that do not necessarily involve space as long as they involve a temporal component.

Keywords: paired associate learning, CA1, CA3, objects, odors

Many computational models have proposed that the hippocampus mediates the formation of arbitrary associations (O'Reilly & McClelland, 1994; Rolls, 1996; Rolls & Treves, 1998). The models, however, do not specify what types of information may be associated by the hippocampus. Eichenbaum and Cohen (2001), O'Reilly and McClelland (1994), Rolls (1996), and Rolls and Treves (1998) have suggested that on the basis of the observation that cells within the hippocampus are activated by most types of sensory inputs—including visual, olfactory, auditory, vestibular, and somatosensory—the hippocampus represents both spatial and nonspatial information facilitating the processing of arbitrary associations. In contrast, Kesner, Lee, and Gilbert (2004) have suggested that the hippocampus may not be involved in forming all associations, but rather that the hippocampus only forms associations when a stimulus is associated with a spatial location or when a temporal component is present.

With respect to the importance of spatial information, it has been shown that rats or nonhuman primates with hippocampal damage display an object–place paired associate learning deficit (Gaffan, 1994; Gaffan & Harrison, 1989; Gilbert & Kesner, 2002; Sziklas, Lebel, & Petrides, 1998; Sziklas & Petrides, 1996). In addition, Gilbert and Kesner (2002) have shown that in addition to a deficit in object–place paired associate learning, hippocampal-lesioned rats are also impaired in odor–place paired associate learning; however, using the same paradigm, they are not impaired in learning an object–odor paired associate task. These data suggest that the hippocampus is clearly involved in paired associate learning when a stimulus is associated with a spatial location, but the hippocampus does not appear to be important when a spatial location is not a component of the paired associate task. Support for this idea comes from a number of studies demonstrating that the hippocampus is not involved in pattern associations that involve odor–odor (Bunsey & Eichenbaum, 1996; Li, Matsumoto, & Watanabe, 1999), odor–reward (Wood, Agster, Eichenbaum, & Wood, 2004), auditory–visual (Jarrard & Davidson, 1990), or object–object (Cho & Kesner, 1995; Murray, Gaffan, & Mishkin, 1993) associations.

With respect to the importance of temporal information, it has been shown that the hippocampus contributes to some forms of temporal associative learning. For example, using an instrumental learning paradigm, Mikulka and Freeman (1975) trained rats with hippocampal lesions to select the goal box opposite their initial preference in a Y maze following a 30-s delay. In one condition, choice of the goal box resulted in an immediate reinforcement, and in the other condition reinforcement was given after a 10-s delay. Compared with control groups, the rats with hippocampal lesions could learn the immediate but not the delay reinforcement condition. This result suggests that the temporal processing required to associate the correct spatial location with reward required the hippocampus. With a classical conditioning paradigm, lesions of the hippocampus in rabbits disrupted the acquisition of eyeblink trace conditioning. In trace conditioning, a short delay intervenes between the conditioned stimulus (CS) and the unconditioned stimulus (UCS). When, however, a UCS and CS overlap in time (delay conditioning), rabbits with hippocampal damage have typically performed as well as normals (Moyer, Deyo, & Disterhoft, 1990). Similar learning deficits in trace fear conditioning have been observed for rats with hippocampal lesions and for mice that lacked *N*-methyl-D-asparate (NMDA) receptors in the CA1 subregion of the hippocampus (Huerta, Sun, Wilson, & Tonegawa, 2000; McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998; Quinn, Oommen, Morrison, & Fanselow, 2002; Weiss,

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Bouwmeester, Power, & Disterhoft, 1999). However, there have been no deficits in a delay conditioning paradigm.

Given that the acquisition of an object–odor association is not dependent on the hippocampus, would adding a temporal component to an object–odor association task recruit the hippocampus? To answer this question, the first purpose of this study was to determine whether the hippocampus is important when a trace interval is interspersed between an object and an odor.

What subregions within the hippocampus support spatial and temporal paired associate learning? Recent studies have shown that rats with dorsal CA3 lesions show significant impairments in learning object–place associations. In contrast, rats with dorsal dentate gyrus and dorsal CA1 lesions learn the associations as readily as control rats. Similar results have been found for the odor–place paired associate task. Dorsal dentate gyrus and dorsal CA1 lesioned rats learn the task as quickly as controls, whereas dorsal CA3-lesioned rats show significant deficits comparable with rats with complete hippocampal lesions. Therefore, it appears that dorsal CA3, but not dorsal dentate gyrus or dorsal CA1, is involved in forming associations between objects or odors and spatial locations (Gilbert & Kesner, 2003).

On the basis of the idea that the hippocampus is important for temporal processing of information (Kesner, 1998), it is likely that the CA1 subregion of the hippocampus may play a role in influencing the formation of associations whenever a time component (trace) is introduced between any two stimuli than need to be associated. Support for this idea comes from studies based on a classical conditioning paradigm. Lesions of the hippocampus in rabbits or rats disrupt the acquisition of eyeblink trace conditioning but do not impair eyeblink delay conditioning (Moyer et al., 1990; Weiss et al., 1999). In a study that used trace fear conditioning, it was found that lesions of the dorsal or ventral CA1 subregion of the hippocampus did not disrupt the acquisition of trace fear conditioning, but only lesions of the ventral CA1 disrupted retention of trace fear conditioning (Jerman, Kesner, Lee, & Berman, 2005). Similar learning deficits in trace, but not delay, fear conditioning were observed for mice that lacked NMDA receptors in both dorsal and ventral CA1 subregions of the hippocampus (Huerta et al., 2000). In an interesting study, McEchron, Tseng, and Disterhoft (2003) recorded from single cells in the CA1 region of the hippocampus during and after trace heart rate (fear) conditioning using either a 10-s or 20-s trace interval. They reported that a significant number of cells showed maximal firing on CS-alone retention trials timed to the 10-s or 20-s trace after CS offset. These data support the idea that the maximal firing of the CA1 cells at the end of the trace interval might represent the process of chunking the duration of an event (trace interval) as separate from other events that occur in trace fear conditioning.

Thus, the second purpose of this study was to determine whether the CA1 or CA3 subregions of the hippocampus might be important if a time delay (trace) is introduced between an object and an odor. If CA3 processes both spatial and temporal information, then deficits should be found following dorsal CA3 lesions. If the introduction of time recruits the CA1 exclusively, then only dorsal CA1 lesions will result in a deficit. To test this idea, we examined rats with dorsal CA1, dorsal CA3, or control lesions during acquisition of a successive discrimination go/no-go task for paired associate learning of stimuli that were temporally discontiguous.

Method

Subjects

A total of 14 male Long–Evans rats (300–450 g) were used in this experiment and maintained on a 12-hr light–dark cycle. They were maintained at 300–450 g and handled 10 min a day until surgery. After surgery, the rats were fed once a day throughout the experiment and had access to water ad libitum. All experimentation was carried out during the light phase of the cycle. All surgical and experimental procedures conformed to the University of Utah Institute of Animal Care and Use Committee's guidelines.

Apparatus

The apparatus used in this experiment was a long box with a wooden floor that had painted black and red Plexiglas sides. It measured 107 cm long × 29.2 cm wide × 25.4 cm high. There were three doors located 15.25 cm apart that could be opened or closed. The first compartment represented the start box. The second compartment represented each of the two objects connected to each side of the second door. More specifically, one object was a hard plastic Garfield toy approximately 3 in. in height that was attached to the door by the feet so that the back of Garfield was exposed to the rat. The other object was a soft toy (yellow Winnie the Pooh with a red shirt) that was attached to the door by the back so that the front surface was not available to the rat. The third compartment represented the delay or trace area. The fourth compartment represented the testing area (61.25 cm long) and contained a small ring into which a sand cup could be placed approximately 50 cm away from the last door. Each of the sand cups that were used had approximately a 2.5-cm radius and was 8 cm deep. They were filled three fourths full with sand and mixed with odorants, including coarse ground coffee and generic talcum powder. These odors were chosen to be as different and salient as possible. Approximately 1 tablespoon of coffee and 3 tablespoons of talcum powder were mixed into sand cups to obtain a faint odor discernible to the experimenter. Froot Loops were submerged three fourths of a centimeter below the surface of the sand when a trial was rewarded. A schematic of the testing apparatus is shown in Figure 1.

Surgery

Rats were randomly assigned into three groups: vehicle injected controls ($n = 5$), dorsal CA3 ($n = 5$), and dorsal CA1 ($n = 4$) hippocampal lesions. Rats were deeply anesthetized with sodium pentobarbital (Nembutal, 65

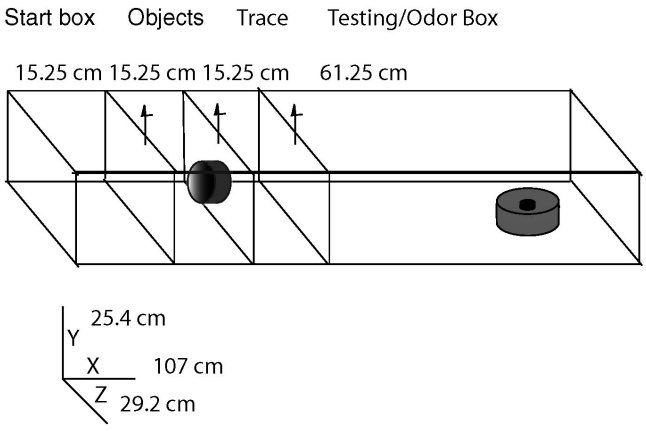

Figure 1. A schematic of the apparatus to test the acquisition of an object–trace–odor association.

mg/kg ip) and given atropine sulfate (0.54 mg/kg ip). To maintain body temperature at approximately 37 °C, we placed the rats on an isothermal heating pad throughout surgery. Burr holes (2 mm diameter) were drilled in the cranium, and dura was punctured to allow drug infusion. There were six injections of ibotenic acid or vehicle. Small burr holes were drilled on the skull for the following coordinates: CA1 lesion group: –3.6 mm posterior to bregma; 1.0 mm, 2.0 mm, and 3.0 mm lateral to midline; and 1.9 mm ventral from dura; CA3 lesion group: (a) 2.5 mm posterior to bregma, 2.6 mm lateral to midline, and 3.2 mm ventral from dura; (b) 3.3 mm posterior to bregma, 3.3 mm lateral to midline, and 3.2 mm ventral from dura; and (c) 4.1 mm posterior to bregma, 4.2 mm lateral to midline, and 3.1 mm ventral from dura. Neurotoxins were infused into different subregions of the dorsal hippocampus to produce axon-sparing, subregion-specific lesions. Ibotenic acid was used for both CA3 and CA1 lesions (Sigma–Aldrich, St. Louis, Missouri). For CA1 lesions, ibotenic acid (6 mg/mL; 0.10–0.15 μL/site for 3 sites per hemisphere; 0.07 μL/min) was slowly infused into pyramidal cell layers of the CA1 region to have both septotemporal and mediolateral spread in the dorsal CA1 region. For CA3 lesions, ibotenic acid (6 mg/mL) was injected into three different dorsal CA3 regions per hemisphere (0.10–0.20 μL/site for 3 sites per hemisphere; 0.07 μL/min). All injections were made with a 10-μL Hamilton syringe with a microinjection pump (Cole Parmer Instrument Company, Vernon Hill, Illinois). Vehicle solution (phosphate-buffered saline) was injected into the corresponding subregions to produce control lesions (n = 3 for CA1 and n = 2 for CA3). After suturing the rat, 1.5 mL saline was injected subcutaneously into each hip to induce urination and expel the anesthetic. For 3 days after the surgery, rats received Children's Tylenol (1–2 mg/mL) as an analgesic in their drinking water. Rats were given 1 week to recover from the surgery prior to experimentation.

Behavioral Procedure

After recovery from surgery, rats were handled by the experimenter and shaped to dig in unscented sand to receive a Froot Loop cereal reward over a 7-day period. Each rat was then trained on a successive discrimination go/no-go task to examine object–trace–odor paired associate learning. After shaping, rats were placed in the apparatus and trained on the task. The task consisted of pairing an object (A or B) with an odor (1 or 2) with a 10-s trace interval between the two stimuli. Correct pairings were A1 or B2 and were rewarded. Incorrect pairings were A2 or B1 and were not rewarded. Rats were trained to make the association between the object and the odor with a 10-s trace period interposed between the two.

Before beginning the experiment, the maze was wiped down with a damp sponge to remove any odor cues, and all the doors were closed. The rat was placed in the starting area and allowed to sit for 220 s to acclimatize to the maze. The first door was opened, and the rat was allowed to explore the object for 3 s. *Exploration* was defined as the rat's nose within 2 cm of the object and actively sniffing or pawing at the object. After the 3-s interval, the second door was opened, and the 10-s trace interval began. At the end of the 10-s interval, the third door was opened, and the rat was allowed to approach the odor cup. Latency was measured from opening the third door until the rat started digging in the sand. A latency of over 10 s was set as the criterion for a no-go. If the rat did not dig within 10 s, then the rat was removed from the testing compartment and returned to the start box. The box was wiped clean with a damp sponge. The intertrial interval was 20 s. There were 12 trials per day, with 6 go trials (A1 and B2) and 6 no-go trials (A2 and B1). The reward consisted of half a Froot Loop cereal submerged approximately three fourths centimeters deep in the sand. Go and no-go trials were randomly intermixed, but two identical trials were never run consecutively. Rats were tested 12 trials per day, 5 days a week for 6 weeks, for a total of 360 trials.

Histology

After experimentation, all rats were sacrificed with 1 mL sodium pentobarbital (70 mg/mL ip) and then intracardially perfused with 0.9% phosphate buffered saline (pH 6.0) for 2 min followed by 10% buffered formalin (pH 7.0) for another 5 min. The brains were stored for 72 hr at 4 °C in 30% sucrose formalin. Each brain was frozen and cut at 24 μm sections, and 11 slices (beginning at bregma −2.30 mm and ending at bregma −4.80 mm) were mounted on a glass slide, stained with cresyl violet, and examined for histological verification of the lesion placement.

The relative neurotoxic damage to cell layers in each of the two hippocampal subregions (CA1 and CA3) was measured with the computer software ImageJ 1.32j (Rasband, 1996). Sections collected from the dorsal hippocampus in each rat were used. Paxinos and Watson's (1986) stereotaxic atlas was used to mark the lesion placement across 11 slices beginning at bregma −2.30 mm and ending at bregma −4.80 mm. The lesions were measured and the percentage of damage for each subregion for each rat was computed. The CA2 region was included in measurements of CA3 for convenience because, in many respects, CA2 resembles a terminal portion of the CA3 region (Amaral & Witter, 1995).

Results

Histological Analysis

Ibotenic acid was used to produce lesions in pyramidal cells in CA1 or CA3. Ibotenic acid has been well known for its axon-sparing excitotoxicity (Jarrard, 1989). Because neither a CA1 nor a CA3-unique neurotoxin is currently available, we developed injection parameters suitable to induce subregion-specific lesions with ibotenic acid, which have produced fairly selective damage in either CA1 (Gilbert, Kesner, & Lee, 2001) or CA3 (Lee & Kesner, 2003). Although it is difficult to define the exact boundary that separates the dorsal from the ventral component of the hippocampus, the *dorsal region* is defined as the anterior 50% of the hippocampus (Moser & Moser, 1998). A quantitative analysis revealed that a CA1 lesion resulted in 95% damage to the dorsal CA1 with 5% damage to CA3 and 5% damage to dentate gyrus (DG), whereas a CA3 lesion resulted in 90% damage to CA3 with 4% damage to CA1 and 2% damage to DG. As shown in Figure 2A, ibotenic acid injections into CA1 produced almost complete degeneration of the pyramidal cells in CA1 while saving most of the pyramidal cells in CA3 and granule cells in DG. Ibotenic acid injected into CA3 eliminated most pyramidal cells in CA3 (see Figure 2B). Some damage in CA1 pyramidal cells close to CA2

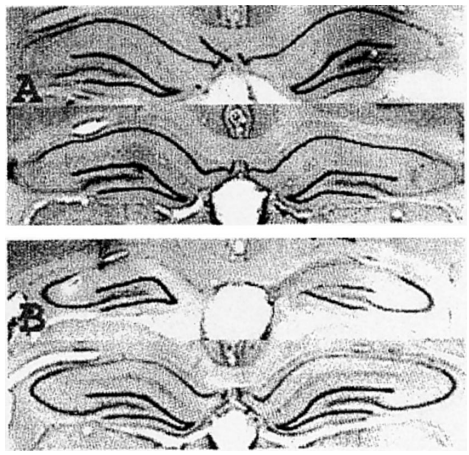

Figure 2. Photomicrographs (12.5 ×) of representative anterior and posterior sections of a CA3-lesioned (A) and a CA1-lesioned (B) rat.

were observed in some sections. The CA3 areas in the hilar zone were mostly spared because of technical difficulty in producing selective lesions in that region without affecting DG granule cells. The lesioned pyramidal cell layers were heavily infiltrated by glial cells, which provided an opportunity to identify intact pyramidal cells in most sections. On the basis of microscopic observation of cresyl-violet-stained sections, ibotenic acid lesions produced little damage, if any, in other extrahippocampal areas of the brain, including the entorhinal cortex and the subiculum. Also, it should be noted that on the basis of the use of Fluorojade to examine cell death 2 days following ibotenic acid lesions, there was no observable cell death outside the hippocampus (Rogers & Kesner, 2005).

Behavioral Analysis

The results of the experiment are shown in Figure 3. The results show that rats with CA3 lesions did not differ in the acquisition of the object–trace–odor task as compared with controls. In contrast, CA1-lesioned rats did not appear to learn this task at all. A two-way analysis of variance with groups as the between variable and blocks of trials as the within variable revealed a significant effect for groups, $F(2, 11) = 6.36$, $p = .015$; a significant blocks of trials effect, $F(5, 55) = 23.38$, $p = .0001$; and a significant interaction between groups and blocks of trials, $F(10, 55) = 4.14$, $p = .0003$. Subsequent Newman–Keuls tests on the main effect for groups revealed that the CA1 lesion group was significantly different ($ps < .05$) from CA3 or controls, but there were no significant differences between CA3 and controls. Subsequent Newman–Keuls tests for the Group × Block interaction revealed that there were no differences among controls, the CA3 group, or the CA1 group for the first three blocks of trials; however, for the last three blocks of trials, there was a significant difference between controls and CA3 in comparison with CA1 ($ps < .05$). Furthermore, there were no significant changes for the CA1 lesioned group across all blocks of trials.

Discussion

The results indicate that control rats learned this task as readily as an object–odor paired associate task without a trace (Gilbert & Kesner, 2002), so that when comparisons are made between object–odor and object–trace–odor paired associate learning, a lesion effect cannot be attributed to increased difficulty. The results also indicate that rats with dorsal CA1 lesions were impaired in learning the object–trace–odor task, whereas rats with dorsal CA3 lesions acquired the task as readily as controls. The deficit observed following dorsal CA1 lesions is consistent with the observation that lesions of the hippocampus in rabbits or rats disrupt the acquisition of eyeblink trace conditioning but do not impair eyeblink delay conditioning (Moyer et al., 1990; Weiss et al., 1999). Similar learning deficits in trace, but not delay, fear

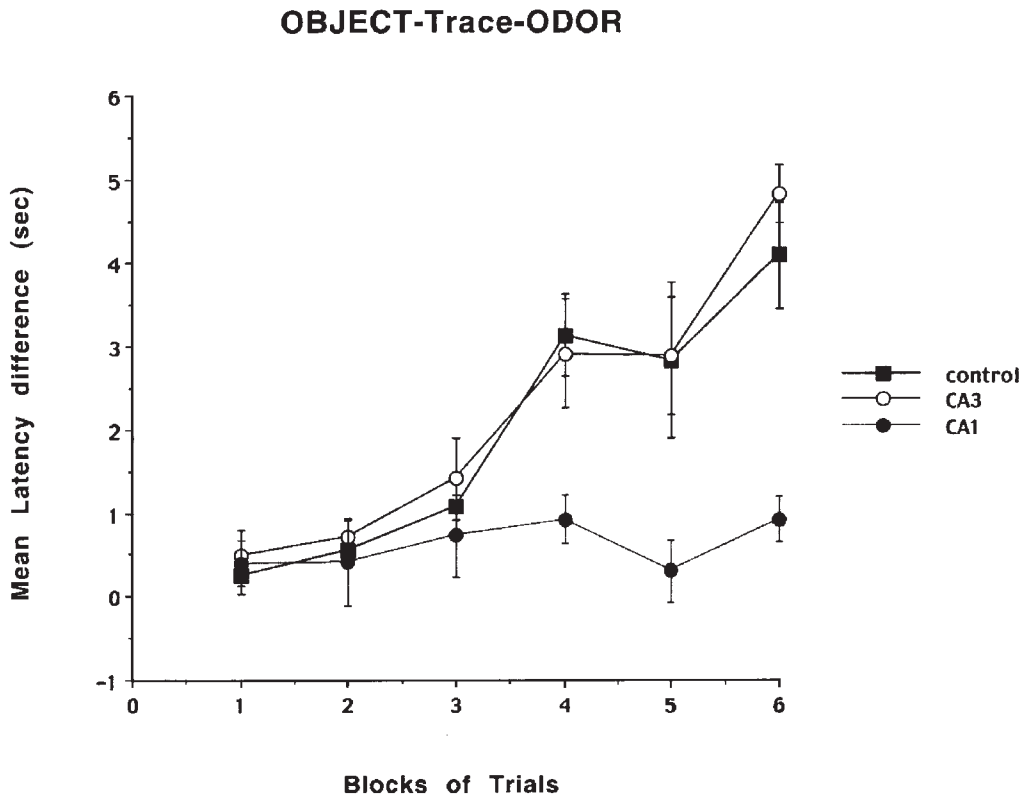

Figure 3. Mean latency differences (latency on mispaired trials minus latency on paired trials) as a function of blocks of trials (60 trials/block) for control, CA1-lesioned, and CA3-lesioned rats on acquisition of the object–trace–odor paired associate.

conditioning were observed for mice that lacked NMDA receptors in both dorsal and ventral CA1 subregions of the hippocampus (Huerta et al., 2000). In additional work, three rats were subjected to ibotenic acid induced ventral CA1 lesions. These rats learned the object–trace–odor task as readily as controls, suggesting that for this task the dorsal CA1, but not the ventral CA1, is critical in supporting the object–trace–odor association. The above mentioned data suggest that the dorsal CA1 region is directly involved in temporal processing. Further support for this idea comes from the findings that CA1 lesions disrupt a temporal pattern separation process based on memory for a sequence of spatial locations or odors (Gilbert et al., 2001; Kesner, 2005). Furthermore, CA1 lesions disrupt a temporal pattern completion process for a previously learned temporal sequence (Hoang & Kesner, 2005).

The CA1 region can also play an important role in plasticity associated with intermediate memory. Lee and Kesner (2002) manipulated the NMDA receptors in CA1 by injecting D,L-2-2-amino-5-phosphonovalerate (APV; a pharmacological blocker for the NMDA receptors) selectively into CA1 in a delayed nonmatching-to-place task using a mixed set of 10-s delay (short-term memory) and 5-min delay (intermediate-term memory) trials. The results indicated that relative to controls, the rats with APV injection into the CA1 displayed a sustained impairment for the 5-min, but not 10-s, delays. This suggests that NMDA dependent plasticity in the CA1 may be critical for intermediate, but not short-term, memory. In a follow-up study, the same results were obtained following a CA1 lesion (Lee & Kesner, 2003). One suggestion made by Rolls and Treves (1998) is that the CA1 region is directly involved in chunking information across time, generating specific units or duration of events based on specific order of occurrence of events in different epochs of time. In an interesting study, McEchron et al. (2003) supported this idea. They recorded from single cells in the CA1 region of the hippocampus during and after trace heart rate (fear) conditioning using either a 10-s or 20-s trace interval. They reported that a significant number of cells showed maximal firing on CS-alone retention trials timed to the 10-s or 20-s trace after CS offset. These data support the idea that the maximal firing of the CA1 cells at the end of the trace interval might represent the process of chunking the duration of an event (trace interval) as separate from other events that occur in trace fear conditioning.

Thus, in general, it appears that the CA1 region of the dorsal hippocampus is important in supporting a variety of arbitrary association where the stimuli can be spatial or nonspatial (i.e. object–odor, tone–shock) as long as there is a temporal interval interposed between the two stimuli. The recruitment of the dorsal CA1 is not dependent, however, on an increase in task difficulty. For the object–trace–odor paired associate paradigm and the object–odor paired associate paradigm, control rats were able to acquire the task in approximately the same number of trials and showed similar acquisition curves. This means that the object–trace–odor paradigm was not more difficult than the object–odor paradigm. Furthermore, the deficits cannot be due to difficulty in odor or visual object discrimination because it has been shown (Gilbert & Kesner, 2003) that these lesions do not disrupt odor–object discriminations.

The observation that there was no CA3 deficit in the object–trace–odor task implies that the CA3 region may not be involved in temporal processing for nonspatial information. Instead, it appears that the CA3 region is important for the processing of associations that involve a spatial component. Support for this idea comes from the findings that in object–place and odor–place paired associate tasks, there is a deficit in rats with CA3 lesion and no deficit in CA1 lesion rats (Gilbert & Kesner, 2003).

In conclusion, it appears that the hippocampus indeed is involved in supporting a large number of arbitrary associations, but CA3 requires the presence of a spatial component to facilitate the association, whereas CA1 requires the presence of a temporal component for any arbitrary association. These data further support subregional specificity of function within the hippocampus.

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