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# Dissociating Space and Trace in Dorsal and Ventral Hippocampus

Jennifer Czerniawski, Taejib Yoon, and Tim Otto*

**ABSTRACT: Emerging evidence suggests that the hippocampus can be anatomically and functionally dissociated along its septotemporal axis into dorsal and ventral subregions. With respect to function, we have recently demonstrated that pre-training excitotoxic lesions of ventral, but not dorsal, hippocampus impair the acquisition of trace fear conditioning, whereas post-training lesions of either dorsal or ventral hippocampus impair the subsequent expression of trace fear conditioning (Yoon and Otto (2007) Neurobiol Learn Mem 87:464–475). In addition to trace fear conditioning, dorsal and ventral hippocampus appear to be differentially involved in a number of spatial memory tasks. The present study examined the effects of temporary inactivation of dorsal or ventral hippocampus on the acquisition and expression of trace fear conditioning and on performance of a spatial delayed reinforced alternation task. The findings demonstrate a double dissociation of dorsal and ventral hippocampal function: inactivation of ventral, but not dorsal, hippocampus attenuated the acquisition and expression of trace fear conditioning, whereas inactivation of dorsal, but not ventral, hippocampus dramatically impaired performance in the delayed reinforced alternation task. These data further support the notion that dorsal and ventral hippocampus contribute differentially to performance in a variety of paradigms. © 2008 Wiley-Liss, Inc.**

**KEY WORDS: trace fear conditioning; reinforced alternation; muscimol**

## INTRODUCTION

Converging evidence indicates that the hippocampus is involved in encoding and retrieving information in various spatial (O'Keefe and Nadel, 1978; Moser et al., 1993; Jung et al., 1994; Moser and Moser, 1998) and nonspatial (Eichenbaum et al., 1992; Eichenbaum, 1996; Hock and Bunsey, 1998; Kennedy and Shapiro, 2004; Otto and Poon, 2006; Parsons and Otto, 2008) memory tasks. Although it has been proposed that the different subregions of the hippocampus work together to support a unitary function of memory (Squire and Zola-Morgan, 1991), recent evidence suggests that there is an anatomical, and likely a functional, dissociation along its septotemporal axis (Moser and Moser, 1998; Bannerman et al., 1999; Richmond et al., 1999; Pitkanen et al., 2000).

Anatomically, the hippocampus can be divided into dorsal (DH) and ventral (VH) hippocampus, with the septal two-thirds comprising the dorsal subregion and the remaining one-third comprising the ventral subregion (Moser and Moser, 1998). These subregions differ with respect to neuronal organization and afferent and efferent connections. For example, the dorsal two-thirds of hippocampus receives visual, auditory, and somatosensory information originating in primary and secondary sensory cortices via medial entorhinal cortex (EC) (reviewed in Moser and Moser, 1998; Pitkanen et al., 2000). Conversely, VH, but not DH has direct reciprocal connections with the amygdala, particularly with the lateral, basal, accessory basal, central nuclei, and amygdalohippocampal area, as well as heavy connections with the hypothalamus (Pitkanen et al., 2000).

Consistent with these neuroanatomical differences, accumulating evidence suggests that there may be functional dissociations between DH and VH. Specifically, both neuropsychological (Moser et al., 1993; Moser and Moser, 1998; Mao and Robinson, 1998; Bannerman et al., 1999; Ferbinteanu and McDonald, 2001; Pothuizen et al., 2004) and electrophysiological (O'Keefe and Nadel, 1978; Jung et al., 1994) evidence suggests that DH, but not VH, plays a particularly prominent role in spatial learning. For example, lesions of DH have been known for years to result in robust deficits in a variety of forms of spatial learning (O'Keefe and Nadel, 1978; Eichenbaum, 1996). Moreover, the magnitude of impairment in spatial learning parallels the volume of DH damage (Moser et al., 1993). By contrast, lesions of VH have little or no effect on spatial learning (Moser et al., 1993; Richmond et al., 1999). The notion that spatial information is processed preferentially by DH is further supported by electrophysiological data indicating that a large proportion of principal cells in DH fire in a spatially-selective manner ("place cells"), whereas in the VH "place cells" are rarely encountered (Jung et al., 1994). By contrast, the VH appears to play a particularly prominent role in a variety of emotional and anxiety-related behaviors, including conditioned fear (Rogers et al., 2006; Yoon and Otto, 2007), neophagia, and other behavioral manifestations of anxiety (Bannerman et al., 2004; Trivedi and Coover, 2004). Collectively these data indicate that DH and VH may subserve functionally dissociable roles in memory that are consistent with their dissociable anatomical connections.

Given that these hippocampal subregions differ with respect to both anatomy and function, it is likely that they may also participate differentially in a variety of forms of learning, including Pavlovian fear conditioning. Data addressing this issue have been mixed. Specifically, while it is now widely accepted that the

**Department of Psychology, Rutgers University, New Brunswick, New Jersey**
Grant sponsor: National Science Foundation; Grant number: IBN0316247.
*Correspondence to: Tim Otto, Department of Psychology, Rutgers University, 152 Frelinghuysen Rd, Piscataway, NJ 08854, USA.
E-mail: totto@rci.rutgers.edu
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hippocampus is not critically involved in the acquisition of discrete CS-US associations in delay fear conditioning procedures (McEchron et al., 1998; Maren and Holt, 2004; Chowdhury et al., 2005; Burman et al., 2006), its role in trace fear conditioning is less clear. Although some studies suggest DH is important for the acquisition of trace fear conditioning (Fendt et al., 2005; Misane et al., 2005; Burman et al., 2006), others suggest that DH is instead critical for the expression of previously learned trace fear memories (Quinn et al., 2002; Yoon and Otto, 2007). Similarly, one recent study found that lesions of VH dramatically impair both the acquisition and expression of trace fear conditioning (Yoon and Otto, 2007), whereas another suggests that lesions of VH impair only the expression of trace fear conditioning 48 h after training (Rogers et al., 2006). These inconsistencies in the literature underscore the importance of systematically examining the potentially dissociable roles of both DH and VH in trace fear conditioning.

We have recently reported that pre-training excitotoxic lesions of VH, but not DH, resulted in a dramatic attenuation of both the acquisition and subsequent expression of auditory trace fear conditioning, whereas post-training lesions of either the VH or DH resulted in an attenuated freezing response during testing (Yoon and Otto, 2007). However, lesions are permanent and may result in excessive damage, potentially disrupting neighboring brain systems or pathways. To further characterize the potentially dissociable contributions of DH and VH to memory, the current study examined the effect of temporary inactivation of DH or VH, using the $GABA_A$ agonist muscimol, on the acquisition and subsequent expression of trace fear conditioning. In addition to trace fear conditioning, DH and VH appear to be differentially involved in a number of spatial memory tasks (Mao and Robinson, 1998; Bannerman et al., 1999; Richmond et al., 1999; Pothuizen et al., 2004). Therefore the present study also examined the effect of temporary inactivation of DH and VH on the performance of a delayed reinforced alternation task. Because lesions of the hippocampus have been shown to result in locomotor activity (Good and Honey, 1997), a final experiment examined whether muscimol affected basal levels of locomotion. Collectively, the data suggest that DH, but not VH, is critical to the performance of delayed reinforced alternation but not trace fear conditioning, whereas VH, but not DH, is critical to the acquisition and expression of trace fear conditioning but not spatial delayed reinforced alternation.

## MATERIALS AND METHODS

All procedures have been approved by Rutgers University's Institutional Animal Care and Use Committee.

### Subjects

One hundred thirty two naïve male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 250–300 g at the time of surgery served as subjects. All subjects were housed individually in plastic cages in a colony room with a 12 h light/dark cycle with lights on at 7 a.m. All behavioral testing occurred during the light cycle. Subjects had access to food and water ad libitum, except during the reinforced alternation task when they were maintained on a restricted diet to maintain 90% of free-feeding body weight. All subjects were handled for 2 min daily for 5 days before surgical procedures and behavioral training.

### Apparatus

Delayed reinforced alternation training was conducted in a T-maze made of black Plexiglas consisting of a central stem ($60(l) \times 16(w) \times 30(h)$ $cm^3$) with a start box ($15(l) \times 16(w) \times 30(h)$ $cm^3$) and two arms ($40(l) \times 16(w) \times 30(h)$ $cm^3$) situated at the distal end of the central stem. The central stem was separated from the start box by a sliding guillotine door. A sliding food tray ($5(l) \times 3.5(w) \times 1(h)$ cm) with a circular food dish (diameter 2.5 cm, 0.75 cm deep) was located at the end of each side arm for delivery of food reinforcers. The T-maze was located in a room lit by a single fixture (65 W) situated ~1 m from the distal end of the start box.

Auditory trace fear conditioning was conducted in a behavioral chamber ($30 \times 24 \times 27$ $cm^3$) enclosed in a sound-attenuating enclosure ($56 \times 41 \times 42$ $cm^3$). The floor of the chamber was composed of 16 stainless steel rods equally spaced by 1.9 cm which were connected to a shock generator (model H13–15, Coulbourn Instruments, Allentown, PA) designed to administer the footshock US (0.6 mA). Two of the opposing walls were composed of transparent Plexiglas and the other two were aluminum. When appropriate, a computer-generated tone (3.9 kHz, 80 dB) was presented through a speaker mounted 14 cm above the floor on the outside one of the aluminum chamber walls. A single light bulb (29 V, 0.04 A) was located 24.5 cm above the floor. A motion detector (model H24–61, Coulbourn Instruments, Allentown, PA) with Fresnel lens, dual element differential detector (13 nM infrared radiation), and 90-degree viewing angle was situated on top of the behavioral chamber and detected movement via a 3.8 cm hole drilled through the chamber ceiling where the sensor was located. Movement information was continuously sampled by the computer controlling all paradigmatic events during both training and testing sessions. A one-way glass window on the front door of the sound attenuating enclosure allowed an experimenter to observe and score the behavioral measure of freezing using a hand switch that was connected to the computer controlling all paradigmatic events. The training chamber was cleaned with a commercially available cage cleaner (Research Laboratories) between sessions.

The testing session for trace fear conditioning took place in a novel chamber located in a different experimental room. The testing chamber had the same dimensions and configuration as the training chamber but was differentiated from the training chamber in that the entire floor was covered with black Plexiglas and a black and white striped panel was attached to one of the opposing walls. As in the training chambers, the testing

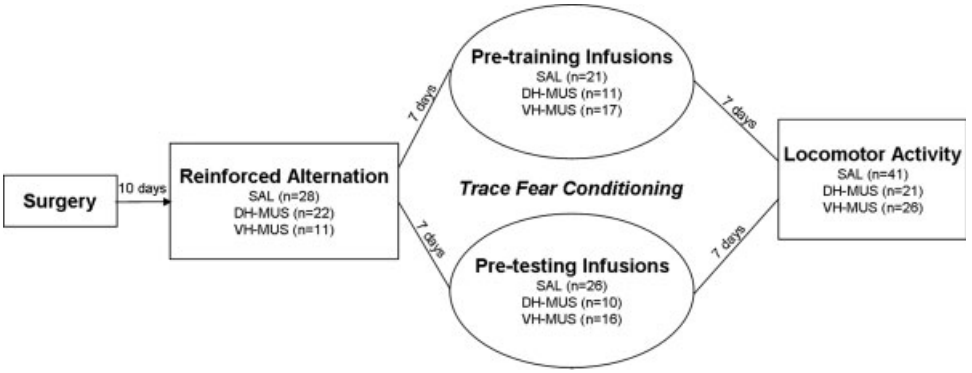


**FIGURE 1. Experimental design. Subject numbers reflect those included in analyses posthistology. A subset of subjects receiving muscimol ($n$ = 22) or saline ($n$ = 20) were trained in trace fear conditioning but not reinforced alternation. A separate group (not shown) received pre-testing infusions of muscimol ($n$ = 7) or saline ($n$ = 7) into DH 8 days after trace fear conditioning.**

chambers were equipped with a motion detector (model H24–61, Coulbourn Instruments, Allentown, PA), and a one-way glass window on the front door of the sound attenuating enclosure, and a hand switch to score freezing behavior. The testing chamber was cleaned with alcohol between sessions.

Locomotor activity was assessed 1 week after trace fear conditioning in an open-field chamber (85 × 85 × 30 $cm^3$) made of black Plexiglas. The floor of the chamber was divided into 36 squares (14 cm). The chamber was located in a room lit with a single fixture (65 W), and a video camera placed ∼1.5 m above the center of the chamber was used to record each session. An experimenter unaware of the experimental condition of each subject watched the video on a TV screen in a different room and manually recorded locomotor activity.

## Procedure

Surgical, training, and testing procedures are summarized in Figure 1.

## Surgery

After anesthetization with an i.p. administration of a ketamine (80 mg/kg)-xylazine (12 mg/kg) mixture, all subjects underwent aseptic stereotaxic surgery for cannula implantation. The subject's head was shaved, mounted in a stereotaxic apparatus (Kopf Instruments, Tujunga, CA), and cleaned with alcohol and Betadine. Subcutaneous injections of Marcaine (0.1 ml, 25%) in several locations below the scalp served as a local anesthetic and vasoconstrictor. The scalp was then incised and retracted. Six small burr holes were drilled into the skull. For subjects receiving muscimol or saline infusions into DH, guide cannulae (22-gauge, 11 mm, Plastics1, Roanake, VA) were implanted bilaterally into the DH (AP: −3.8 mm, ML: ± 2.5 mm from bregma; DV: −2.2 mm from dura). For subjects receiving muscimol or saline infusions into VH, guide cannulae (22-gauge, 11 mm, Plastics1, Roankae, VA) were implanted bilaterally into VH (AP: −5.2 mm, ML: ±5 mm from bregma; DV: −5.5 mm from dura). The cannulae were affixed with dental cement and anchored to the skull via four stainless steel screws. The incision was then closed with stainless steel surgical staples and obdurators were placed into the guide cannula. All animals were closely monitored during the 7 d postsurgical recovery period. Before behavioral testing, subjects were randomly assigned to the inactivation (muscimol) or control (saline) group.

## Infusions

Subjects received microinfusions of either physiological saline (0.9%) or muscimol dissolved in 0.1 M phosphate-buffered saline (1 μg/μl; Sigma, St Louis, MO, pH 7.4). The infusions were administered via insertion of an infusion cannula into the guide cannula targeted at the DH or VH. The infusion cannula protruded 1 mm beyond the tip of the guide cannula, and was connected via polyethylene tubing to a 10-μl Hamilton syringe mounted in an infusion pump (Harvard Apparatus). For animals receiving infusions into DH, a volume of 0.25 μl (0.25 μl/min) was infused bilaterally for a total volume of 0.5 μl. For animals receiving infusions into VH, a volume of 0.5 μl (0.25 μl/min) was infused bilaterally for a total volume of 1 μl. These volumes were selected based on pilot studies in which these volumes were found to be sufficient for behaviorally-evidenced inactivation without producing undesired side effects. The infusion cannula was left in position for 2 min following completion of infusion to allow for diffusion of the saline or muscimol. Subjects were then returned to their home cages for 30 min, and subsequently transferred to an experimental room to undergo behavioral testing.

## Delayed Reinforced Alternation

Following a 1-week postsurgical recovery period, animals were placed on a food deprivation schedule to maintain 90% free-feeding body weight. Once 90% of free feeding body weight was attained, subjects were pre-exposed to the T-maze during a single 20 min session. During pre-exposure, subjects were placed in the T-maze and allowed to explore freely and eat sucrose pellets (∼25) which were scattered throughout the T-maze and in the sliding food tray cups. After pre-exposure,

sucrose pellets were placed in each subject's home cage to further acclimate the subjects to the reinforcer.

Reinforced alternation training began 1 day following preexposure. Animals were trained in one reinforced alternation session per day, and each daily session consisted of 12 trials separated by a 30 s intertrial interval. For each trial, the subject was placed in the start box for 30 s, after which the guillotine door was raised permitting the subject to traverse the central stem and enter one of the two distal arms. Entering an arm was defined as all four paws crossing into the arm. Once a subject entered an arm, it was confined to that arm for 3 s. Sucrose pellets were placed in both sliding-tray food cups for every trial to eliminate odor as a cue, and were introduced into the arm on correct trials only. On the first trial, the animal received three sucrose pellets for entering either arm. On succeeding trials, the animal received sucrose pellet reinforcers for entering the arm opposite to the previously entered arm.

Because the first trial was a free choice trial, the percentage of correct trials for each session was calculated as: (number of correct alternations/total trials $-$ 1) $\times$ 100. Subjects were trained on consecutive days until they achieved at least 80% correct (9/11) on three consecutive days. One day after reaching criterion, animals were infused with either saline or muscimol into DH or VH 30 min prior to training in one reinforced alternation session. On the following day they were run in a final reinforced alternation session, without receiving any infusions. After completion of the reinforced alternation task, all subjects received food and water ad libitum.

## Auditory Trace Fear Conditioning

Trace fear conditioning was conducted 1 week after completion of delayed reinforced alternation. Although animals were infused with the same substance (saline or muscimol) as during reinforced alternation, they were randomly assigned to receive either pre-training or pre-testing infusions. For pre-training manipulations, subjects received infusions of either muscimol or saline into the DH or VH 30 min before conditioning. These subjects did not receive any microinfusions prior to the testing session 24 h later. For pre-testing manipulations, the rats underwent the trace fear conditioning training procedure without receiving any microinfusions. Then, either 24 h or 8 days after training they received microinfusions of saline or muscimol in the same manner as described earlier. Testing began 30 min after the completion of infusion.

Auditory trace fear conditioning took place in a single session consisting of 10 pairings of a tone (20 s, 3.9 kHz, 80 dB) and footshock (2 s, 0.6 mA), with a trace interval of 30 s between the offset of the tone and onset of the shock. The first tone was presented after a 4 min acclimation period and subsequent trials were separated by a 4 min intertrial interval (ITI). The behavioral response of freezing, defined as a rigid posture and lack of movement except that required for respiration, was recorded throughout the entire conditioning session by an observer blind to the subjects' condition; immobility was also recorded continuously by the automated motion detector. These measures were subsequently transformed into the percentage of time spent freezing or immobile for each minute of the training session.

The testing session for trace fear conditioning was conducted in a novel chamber 24 h after conditioning in one session consisting of six trials. A separate experiment examined pre-testing inactivation of only DH 8 days following training. In all cases, the procedure was the same as during conditioning except that footshock was not presented. As during conditioning, behavioral measures of freezing and immobility were recorded throughout the entire testing session.

## Locomotor Activity

To examine whether muscimol infusions affected basal levels of activity, locomotion was assessed in an open field in three sessions over three consecutive days, 1 week after trace conditioning. At the start of each session subjects were placed in a corner of the open chamber, and they were then allowed to explore freely for 10 min. Each session was recorded by a video camera placed $\sim$1.5 m above the open field and scored by an observer who watched the video on a TV screen in another room. The experimenter, who was unaware of the experimental condition of the subjects, recorded both ambulations, defined as the crossing of all four legs from one square to another, and rearing, defined as lifting the two front legs off the floor. On the second day of locomotor activity testing, subjects received microinfusions of either saline or muscimol (each subject received the same solution that was administered before the reinforced alternation task and trace conditioning) 30 min before being placed in the open chamber; no infusions occurred on the first or third day of locomotor activity testing.

## Histology

Following completion of all behavioral testing, animals were administered a sublethal dose of sodium pentobarbital (100 mg/kg, i.p.) and perfused transcardially with 0.9% saline followed by buffered 10% formalin. The brain was removed and placed in a 10% formalin-30% sucrose solution for at least 3 days. The brain was then frozen and sliced into coronal sections with a thickness of 50 μm using a cryostat. Every other slice throughout the DH or VH was mounted on gelled glass microscope slides and subsequently stained with cresyl violet and coverslipped. An observer blind to the subject's condition verified cannula placement throughout the DH or VH. Subjects with inaccurate cannula placement or extensive damage were excluded from data analysis.

## Statistical Analysis

Data for all experiments were analyzed using two-way repeated measures analyses of variance (ANOVAs). An $\alpha$ level of 0.05 was used for all statistical analyses. Post hoc comparisons, where necessary, were conducted using Student-Newman-Keul's (SNK) post hoc test.

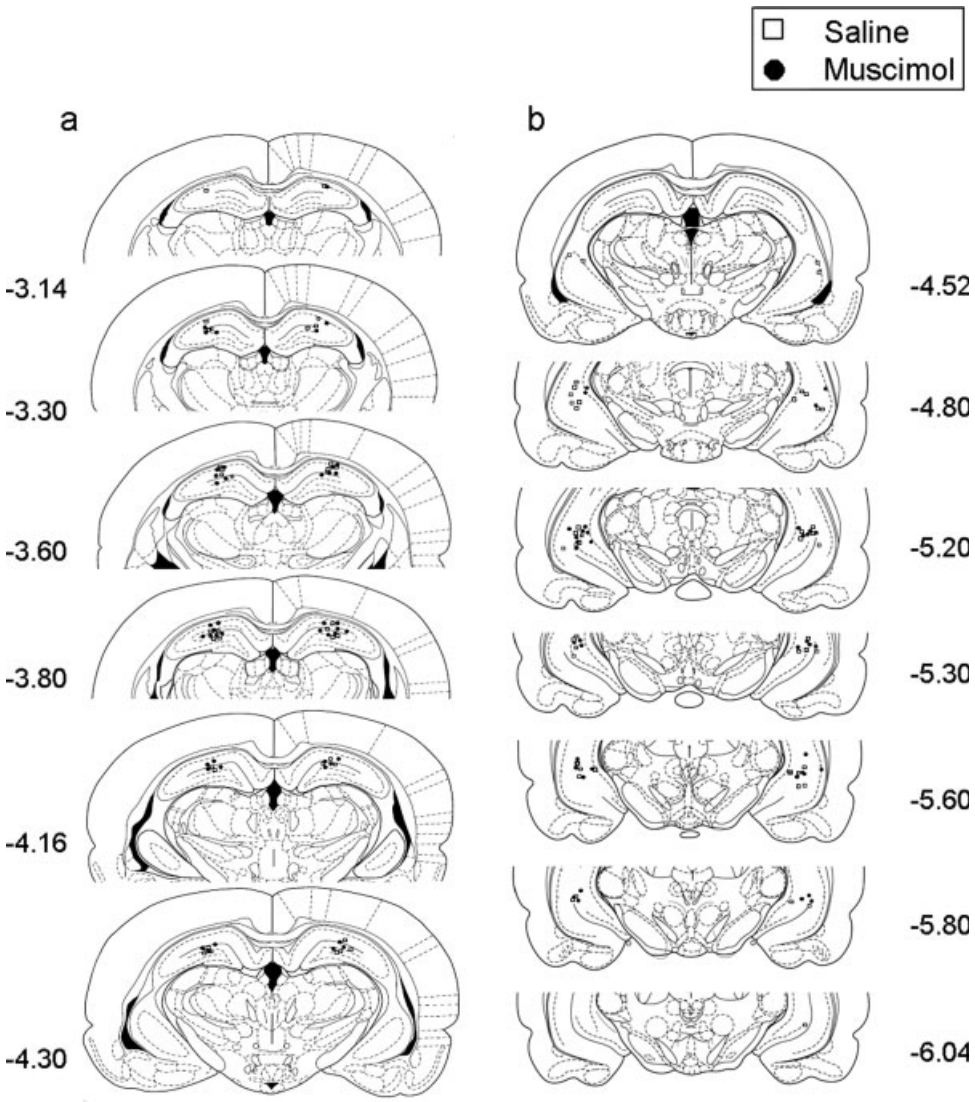


**FIGURE 2. Schematic representation of cannula placement in coronal sections of (a) DH or (b) VH.**

## RESULTS

### Cannula Placement

Following histological verification, 10 animals with cannulae targeted at DH and 7 animals with cannulae targeted at VH were excluded from statistical analyses because of improper cannula placement and/or extensive damage. Figure 2 illustrates cannula placements for all subjects.

### The Effect of Inactivation of Dorsal or Ventral Hippocampus on Delayed Reinforced Alternation

There was no significant difference in reinforced alternation between animals receiving saline into DH ($n = 17$) or VH ($n = 11$), ($F(1,28) = 0.062$, $P = 0.8$). Data from all subjects receiving saline were therefore combined into a single saline control group (SAL, $n = 28$). After exclusion of subjects with inaccurately placed cannulae, 22 subjects received infusions of muscimol into DH (DH-MUS) and 11 subjects received infusions of muscimol into VH (VH-MUS).

Mean (±standard error of mean (SEM)) percentage of correct alternations exhibited by animals receiving infusions into DH or VH is shown in Figure 3. Temporary inactivation of DH but not VH dramatically impaired performance in the delayed reinforced alternation task. A two-way analysis of variance (ANOVA) with test day as the within-subjects factor and infusion condition as the between-subjects factor revealed significant main effects of infusion condition ($F(2,59) = 22.9$, $P < 0.0001$) and test day ($F(4,185) = 69.9$, $P < 0.0001$), and a significant interaction between test day and infusion condition ($F(4,185) = 37.6$, $P < 0.0001$). Subsequent post hoc analyses (SNK) revealed that group DH-MUS differed significantly

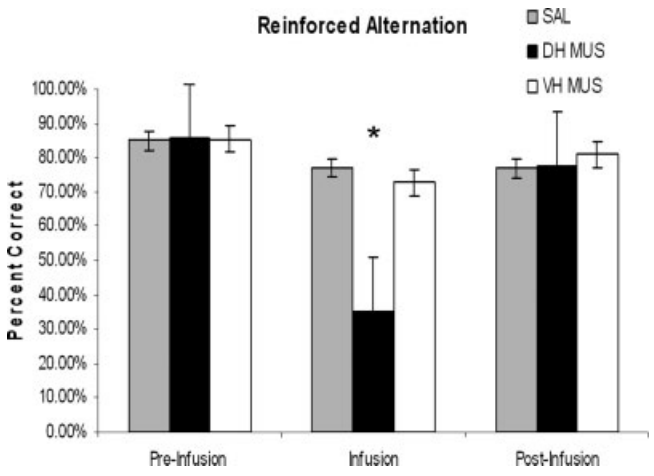


**FIGURE 3. Mean (±SEM) percentage of correct alternations for groups receiving infusions of muscimol or saline into DH or VH. Temporary inactivation of DH ($n$ = 22) dramatically impaired reinforced alternation performance on the day of infusion only ($P < 0.05$). There was no difference between subjects that received temporary inactivation of VH ($n$ = 11) and control subjects ($n$ = 28).**

from both the SAL and VH-MUS groups on the day of infusion. No other pairwise comparisons reached statistical significance.

## The Effect of Pre-Training Inactivation of Dorsal or Ventral Hippocampus on Auditory Trace Fear Conditioning

One week following completion of the reinforced delayed alternation task, a subset of the subjects received infusions of saline or muscimol prior to the acquisition of trace fear conditioning. Eleven subjects received pre-training infusions of muscimol into DH (DH-MUS), 17 subjects received pre-training infusions of muscimol into VH (VH-MUS), and 21 subjects received infusions of saline into DH or VH (SAL). A subset of animals with cannulae targeted at VH (muscimol, $n$ = 12; saline, $n$ = 9) were trained in trace fear conditioning but not in the reinforced alternation task. Since there were no significant differences during trace fear conditioning or testing between subjects that were trained in reinforced alternation and those that were not, data from these subjects were combined into either a VH muscimol or VH saline group. Because there was a significant positive correlation between freezing and immobility ($r$ = 0.75; $P < 0.05$ for subjects that received saline; $r$ = 0.79, $P < 0.05$ for subjects that received muscimol), only immobility data are presented in order to maintain objectivity.

### *Acquisition of trace fear conditioning*

The effect of muscimol or saline infusions on the acquisition of trace fear conditioning is illustrated in Figures 4a–c. The mean (±SEM) percentage of immobility expressed by the different infusion groups during the 4 min ITIs is shown in Figure 4a. Inactivation of VH significantly attenuated the level of immobility across trials. A two-way ANOVA revealed a significant main effect for infusion condition ($F$(2,46) = 23.04, $P < 0.001$), a significant main effect for trial ($F$(18,489) = 63.23, $P < 0.001$), and a significant interaction between infusion condition and trial ($F$(18,489) = 4.47, $P < 0.001$). Subsequent post hoc analyses (SNK) revealed that the group VH-MUS exhibited significantly lower levels of immobility than both DH-MUS and SAL groups during trials 2–10 with the exception of trial 4. There were no significant differences found between the DH-MUS and SAL groups on any trial, or between all three groups during the first trial.

The mean (±SEM) percentage of immobility expressed by the different infusion groups during the 20 s auditory CS presentations is shown in Figure 4b. A two-way ANOVA revealed a significant main effect for infusion condition ($F$(2,46) = 13.73, $P < 0.001$), a significant main effect for trial ($F$(18,489) = 18.67, $P < 0.001$), and a significant interaction between infusion condition and trial ($F$(18,489) = 1.89, $P$ = 0.015). Subsequent post hoc analyses (SNK) revealed that the VH-MUS group exhibited significantly lower levels of immobility than both the DH-MUS and SAL groups during trials 2, 3, 4, and 6, but not during trials 1, 5, 7, 8, 9, and 10. There were no significant differences between the DH-MUS and SAL groups on any trial.

The mean (±SEM) percentage of immobility expressed by the different infusion groups during the 30 s trace intervals is shown in Figure 4c. Inactivation of VH significantly attenuated the level of immobility across trials. A two-way ANOVA revealed a significant main effect for infusion condition ($F$(2,46) = 22.71, $P < 0.001$), a significant main effect for trial ($F$(18,489) = 28.38, $P < 0.001$), and a significant interaction between infusion condition and trial ($F$(18,489) = 2.10, $P$ = 0.005). Subsequent post hoc analyses (SNK) revealed that group VH-MUS had significantly lower levels of immobility than both DH-MUS and SAL groups during trials 2, 3, 4, 5, 6, 7, and 10. There was a significant difference between groups DH-MUS and VH-MUS during trials 8 and 9, but neither differed from SAL. There were no differences between any groups on trial 1, nor were any differences between groups DH-MUS and SAL for any trial.

### *Expression of trace fear conditioning during testing*

Data from only the first three trials of the testing session were used for statistical analysis, as they were least likely to be affected by extinction learning. The mean (±SEM) percentage of immobility exhibited by the different infusion groups during the 4 min ITIs is shown in Figure 4d. Temporary inactivation of VH, but not DH, significantly attenuated the level of immobility across trials. A two-way ANOVA revealed a significant main effect for infusion condition ($F$(2,46) = 13.85, $P < 0.001$), a significant main effect for trial ($F$(4,143) = 49.44, $P < 0.001$), and a significant interaction between infusion condition and trial ($F$(4,143) = 4.70, $P$ = 0.001). Subsequent post hoc analyses (SNK) revealed that group VH-MUS had signifi-

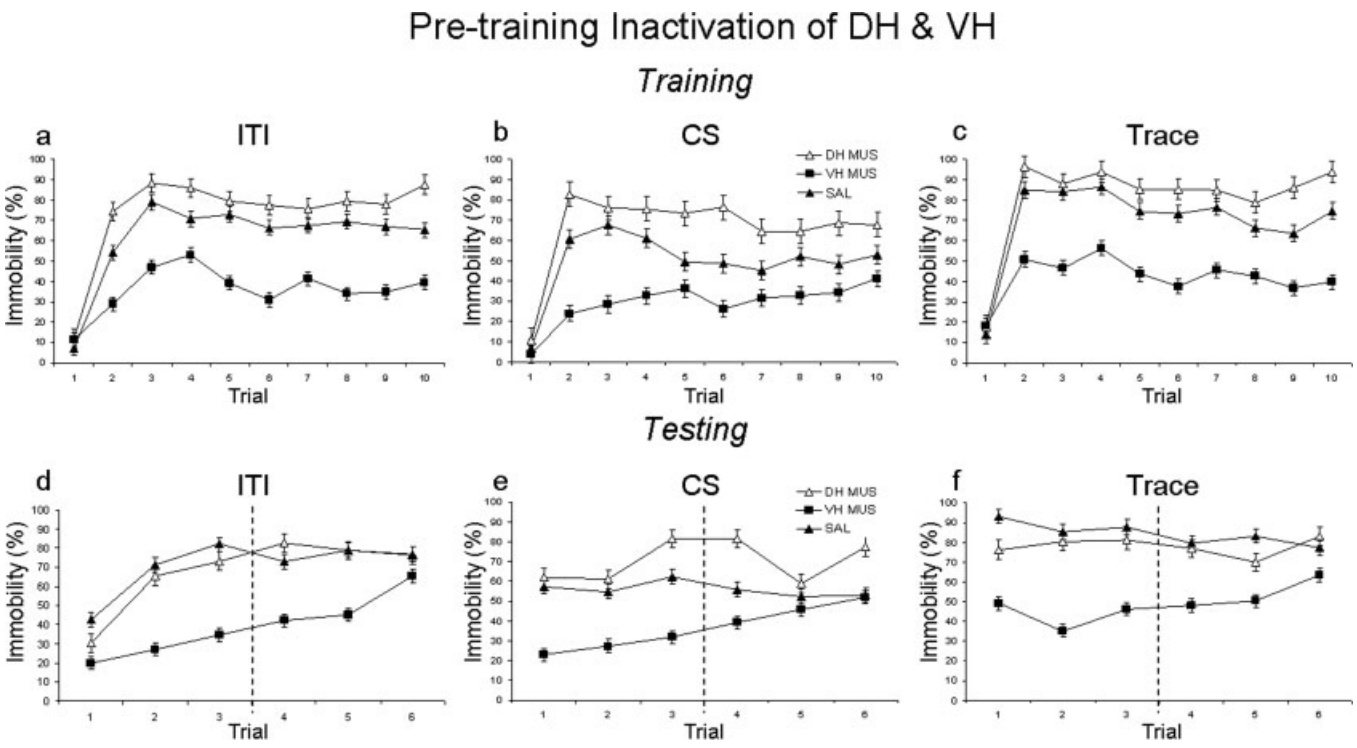


**FIGURE 4. Mean (±SEM) percentage immobility during trace fear conditioning and testing exhibited by different groups that received bilateral pre-training infusions of muscimol or saline into VH or DH. SNK post hoc analyses revealed that subjects that received temporary inactivation of VH ($n$ = 17) exhibited significantly less immobility across trials than subjects that received temporary inactivation of DH ($n$ = 11) or SAL ($n$ = 21) during the (a) 4 min ITIs, (b) 20 s tone presentations, and (c) 30 s trace intervals of the conditioning session and during the (d) 4 min ITIs, (e) 20 s tone presentations, and (f) 30 s trace intervals of the testing session ($P < 0.05$). No differences were observed between the DH and SAL groups during the conditioning or testing session. For the testing session, only the data from the first 3 trials were used for statistical analyses.**

cantly lower levels of immobility than the SAL and DH-MUS groups during trials 2 and 3, but not during trial 1. There were no significant differences between the DH-MUS and SAL groups during the ITIs on any trial.

The mean (±SEM) percentage of immobility exhibited by the different infusion groups during the 20 s auditory CS presentations is shown in Figure 4e. Temporary inactivation of VH but not DH significantly attenuated the level of immobility across trials. A two-way ANOVA revealed a significant main effect for infusion condition ($F$ (2,46) = 14.10, $P < 0.001$), a significant main effect for trial ($F$(4,143) = 4.14, $P$ = 0.018), but failed to reveal a significant interaction between infusion condition and trial ($F$(4,143) = 0.731, $P$ = 0.57). Subsequent post hoc analyses (SNK) revealed that group VH-MUS had significantly lower levels of immobility than groups DH-MUS and SAL during the first three trials. There were no significant differences between the DH-MUS and SAL groups during the CS presentation on any trial.

The mean (±SEM) percentage of immobility exhibited by the different infusion groups during the 30 s trace intervals is shown in Figure 4f. Temporary inactivation of VH but not DH significantly attenuated the level of immobility across trials. A two-way ANOVA with infusion condition as the between subjects factor and trial as the within subjects factor revealed a significant main effect for infusion condition ($F$(2,46) = 15.51, $P < 0.001$) but failed to reveal a significant effect for trial, ($F$(4,143) = 1.51, $P$ = 0.22) or a significant interaction between infusion condition and trial ($F$(4,143) = 1.10, $P$ = 0.36). Subsequent post hoc analyses (SNK) revealed that group VH-MUS had significantly lower levels of immobility than both DH-MUS and SAL groups during the first three trials. There were no significant differences between the DH and SAL groups during the trace interval on any trial.

## The Effect of Pre-Testing Inactivation of Dorsal or Ventral Hippocampus on Auditory Trace Fear Conditioning

To assess the effect of inactivation of DH or VH on the expression or maintenance of trace fear conditioning, animals were initially trained in the trace fear conditioning paradigm without receiving any infusions. Then either 24 h or 8 days following training, they received infusions of muscimol or saline 30 min prior to the testing session. A subset of animals with cannulae targeted at VH (muscimol, $n$ = 10; saline, $n$ = 11) was trained in trace fear conditioning but not in the

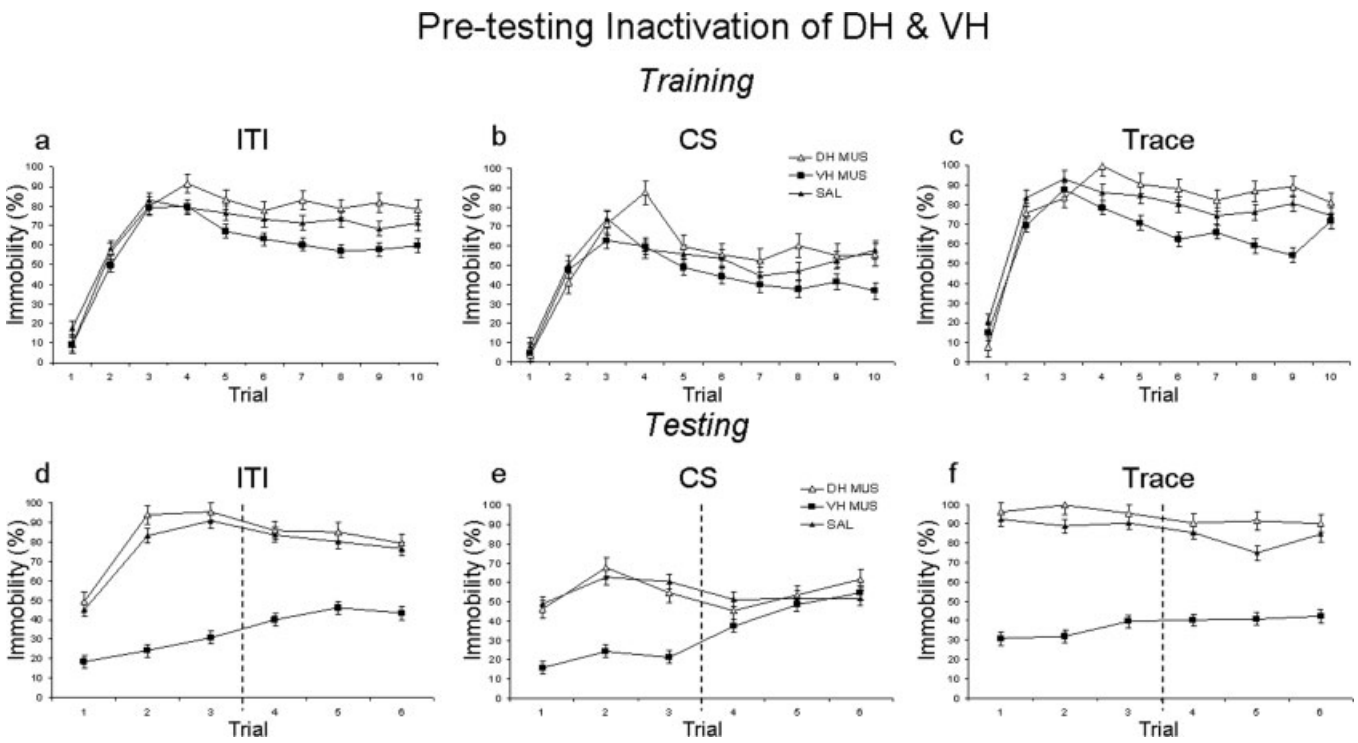


**FIGURE 5. Mean (±SEM) percentage immobility during trace fear conditioning and testing exhibited by different groups that received bilateral pre-testing infusions of muscimol or saline into VH or DH. For conditioning, there were no significant differences between groups in the level of immobility exhibited across trials during the (a) 4 min ITIs, (b) 20 s tone presentations, or (c) 30 s trace intervals. SNK post hoc analyses revealed subjects that received temporary inactivation of VH exhibited significantly less immobility across trials than subjects that received temporary inactivation of DH or saline during the (d) 4 min ITIs, (e) 20 s tone presentations, and (f) 30 s trace intervals ($P < 0.05$). No differences were observed between the DH muscimol group and controls. For the testing session, only the data from the first three trials were used for statistical analyses.**

delayed reinforced alternation task. Since there were no significant differences during trace fear conditioning or testing between subjects that were trained in reinforced alternation and those that were not, data from these subjects were combined into either a VH muscimol or VH saline group. In addition, there were no statistical differences between animals receiving saline infusions into DH or VH, and thus they were combined into a single saline group (SAL, $n = 26$). A total of 10 subjects received muscimol infusions into DH (DH-MUS) and 16 subjects received muscimol infusions into VH (VH-MUS). There was a strong and significant positive correlation between freezing and immobility ($r = 0.9$; $P < 0.01$ for subjects that received saline; $r = 0.95$, $P < 0.01$ for subjects that received muscimol). Thus, only immobility data are presented in order to maintain objectivity.

## *Acquisition of trace fear conditioning*

In view of the fact that no infusions were administered before the conditioning session, group differences in acquisition were neither expected nor found for subjects receiving pre-testing inactivation 24 h or 8 days after training. The mean (±SEM) percentage of immobility during conditioning exhibited by the different infusion groups that received pre-testing inactivation 24 h after conditioning is shown in Figures 5a–c.

## *Expression of trace fear conditioning during testing 24 h after training*

Data from only the first three trials of the testing session were used for statistical analysis, as they were least likely to be affected by extinction. The mean (±SEM) percentage of immobility exhibited by the different infusion groups during the 4 min ITIs is shown in Figure 5d. Temporary inactivation of VH but not DH significantly attenuated the level of immobility across trials. A two-way ANOVA revealed a significant main effect of infusion condition ($F(2,49) = 65.2$, $P < 0.001$), a significant main effect of trial ($F(4,155) = 81.3$, $P < 0.001$), and a significant interaction between infusion condition and trial ($F(4,155) = 10.9$, $P < 0.001$). Subsequent post hoc analyses (SNK) revealed that the VH-MUS group exhibited significantly lower levels of immobility than both the SAL and DH-MUS groups during the first three trials ($P < 0.05$). There were no significant differences found between the DH-MUS and SAL groups during the ITI on any trial.

The mean (±SEM) percentage of immobility exhibited by the different infusion groups during the 20 s auditory CS presentations is shown in Figure 5e. Temporary inactivation of VH but not DH significantly attenuated the level of immobility across trials of the testing session. A two-way ANOVA revealed a significant main effect for both infusion condition

($F(2,49) = 12.2$, $P < 0.001$) and trial ($F(4,155) = 6.3$, $P = 0.003$), but failed to reveal a significant interaction between infusion condition and trial, $F(4,155) = 0.55$, $P = 0.69$). Subsequent post hoc analyses (SNK) revealed that group VH-MUS had significantly lower levels of immobility than both the DH-MUS and SAL groups during the first three trials. There were no significant differences between the DH-MUS and SAL groups during the CS presentation on any trial.

The mean (±SEM) percentage of immobility exhibited by the different infusion groups during the 30 s trace intervals is shown in Figure 5f. Temporary inactivation of VH nut not DH significantly attenuated the level of immobility across trials. A two-way ANOVA revealed a significant main effect of infusion condition ($F(2,49) = 103.46$, $P < 0.001$), but failed to reveal a significant effect of trial ($F(4,155) = 0.57$, $P = 0.57$) or a significant interaction between infusion condition and trial ($F(4,155) = 1.43$, $P = 0.23$). Subsequent post hoc analyses (SNK) revealed that the VH-MUS group exhibited significantly lower levels of immobility than both the DH-MUS and SAL groups during the first three trials. There were no significant differences between the DH-MUS and SAL groups during the trace interval on any trial.

### *Expression of trace fear conditioning during testing 8 days after training*

Our laboratory has recently reported that lesions of DH 24 h after training severely impaired the expression of trace fear conditioning 8 days following acquisition (Yoon and Otto, 2007). Because the pre-testing infusion of muscimol into DH did not replicate the effects of DH post-training lesions observed previously, we examined the effect of inactivation of DH only. The training-testing interval of 8 days was chosen to be consistent with the training-testing interval utilized by Yoon and Otto (2007). Data from only the first three trials of the testing session were used for statistical analysis, as they were least likely to be affected by extinction. Seven subjects received muscimol infusions and seven subjects received saline infusions into DH. There were no group differences between subjects receiving muscimol or saline infusions into DH during the ITI ($F(1,12) = 0.61$, $P = 0.45$), CS presentation ($F(1,12) = 2.41$, $P = 0.15$) or the trace interval ($F(1,12) = 1.96$, $P = 0.18$) on any trial.

## Locomotor Activity

Locomotor activity was assessed 1 week after trace fear conditioning in an open field during three consecutive days (i.e., Pre, Infusion, Post). With the exception of six saline and seven VH muscimol animals that were excluded due to postsurgical complications, all subjects were tested for locomotor activity, regardless of whether they received pre-training or pre-testing infusions of muscimol or saline. There were no statistically significant differences in ambulation or rearing between animals receiving saline infusions into DH or VH, therefore the data from these animals were combined, resulting in 41 subjects who received saline into DH or VH (SAL), 26 subjects who received inactivation of VH (VH-MUS), and 21 subjects who received inactivation of DH (DH-MUS).

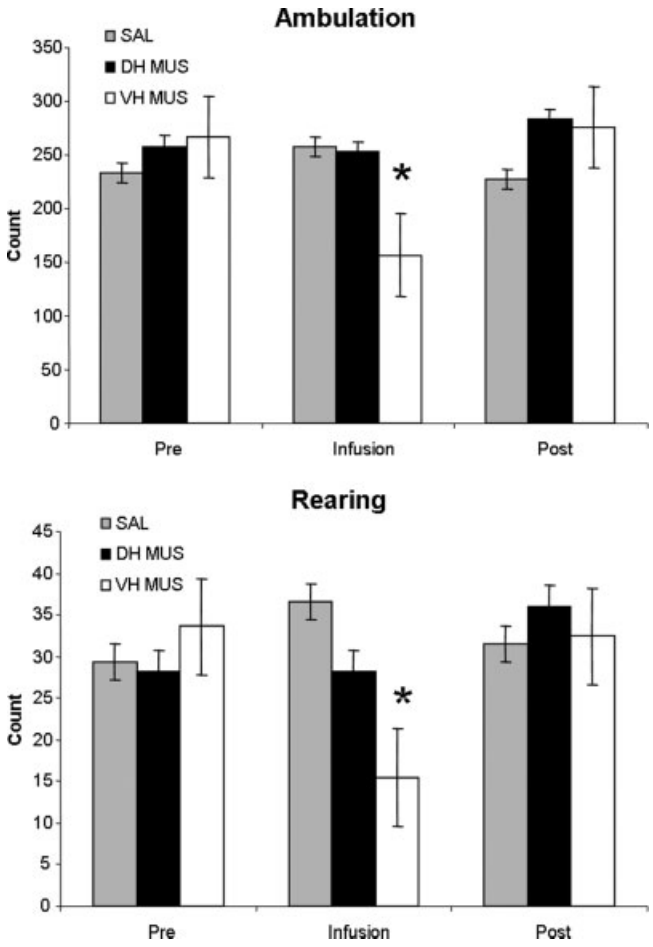


**FIGURE 6. Mean (±SEM) number of (a) ambulation and (b) rearing counts during locomotor activity assessment. Muscimol infusions into VH but not DH resulted in a reduction of both ambulation of rearing.**

The mean (±SEM) number of ambulation counts exhibited by different infusion groups is illustrated in Figure 6a. Muscimol infusions of VH, but not DH, resulted in hypoactivity. A two-way ANOVA revealed a main effect for day ($F(2,260) = 7.67$, $P = 0.0,006$) and a significant interaction between condition and day ($F(2,260) = 12.06$, $P < 0.0,001$), but failed to reveal a main effect for condition ($F(2,84) = 1.17$, $P = 0.13$). Subsequent post hoc analyses (SNK) revealed a significant difference between group VH-MUS and groups DH-MUS and SAL on the day of infusion only. There was no difference in ambulation between the DH-MUS and SAL groups.

The mean (±SEM) number of rearing counts exhibited by different infusion groups is illustrated in Figure 6b. Muscimol infusions of VH, but not DH, resulted in a reduced amount of rearing. A two-way ANOVA revealed a main effect for day ($F(2,260) = 6.28$, $P = 0.0023$) and a significant interaction between condition and day ($F(2,260) = 11.11$, $P < 0.0001$), but failed to reveal a main effect for condition ($F(2,84) = 1.43$, $P = 0.245$). Subsequent post hoc analyses revealed a

significant difference between group VH-MUS and both DH-MUS and SAL groups on the day of infusion only. There was no difference in rearing between the DH-MUS and SAL groups.

## DISCUSSION

The present data suggest that DH, but not VH plays a critical role in performance of the delayed alternation task. Conversely, VH, but not DH is critically involved in both the acquisition and maintenance of trace fear conditioning. This double dissociation of dorsal and ventral hippocampal function is discussed more fully below.

### Pre-Training Inactivation of Dorsal, but not Ventral, Hippocampus Impairs Performance of Delayed Reinforced Alternation

Temporary inactivation of DH but not VH dramatically impaired performance in the delayed reinforced alternation task. This finding is consistent with a growing body of data demonstrating that DH is importantly involved in spatial learning and/or working memory (Moser et al., 1993; Mao and Robinson, 1998; Bannerman et al., 1999; Richmond et al., 1999; Pothuizen et al., 2004). However, it is important to note that rats can use either a place or a response strategy to learn and perform this T-maze task (see Gold, 2004 for review). Therefore, while it seems likely that the observed deficits in reinforced alternation are due to the critical role of DH in spatial learning, they may alternatively reflect a role for the DH in response learning. It should also be noted that, regardless of whether a place or response strategy was used, there is a strong working memory demand inherent in delayed reinforced alternation tasks. Specifically, in order to correctly alternate on each trial, subjects must remember over the 30 s ITI either the particular arm that was entered or the response that was executed. Consistent with the data presented here and prior data demonstrating a role of DH in working memory (Olton and Papas, 1979; Olton and Feustle, 1981), inactivation of DH but not VH impairs delayed nonmatching-to-position performance (Mao and Robinson, 1998) and an operant delayed alternation task (Maruki et al., 2001). In addition, lesions of DH but not VH disrupt spatial reference and working memory in a radial arm maze task (Pothuizen et al., 2004). Collectively, these studies suggest DH may contribute to both spatial and nonspatial working memory tasks moreso than does VH.

### Pre-Training Inactivation of Ventral, but not Dorsal, Hippocampus Impairs the Acquisition of Trace Fear Conditioning

Pre-training inactivation of VH, but not DH attenuated the acquisition and subsequent expression of trace fear conditioning. These findings are consistent with previous findings from our laboratory suggesting that pre-training excitotoxic lesions of VH impaired the acquisition and subsequent expression of trace fear conditioning while pre-training lesions of DH did not (Yoon and Otto, 2007). The fact that both excitotoxic lesions and temporary inactivation of these hippocampal subareas produced consistent behavioral effects in the same paradigm provides consistent and reliable evidence of an important role for VH, but not DH, in the acquisition of trace fear conditioning.

Consistent with the data reported here and by Yoon and Otto (2007), Rogers et al. (2006) found that pre-training lesions of ventral, but not dorsal, CA1 disrupted the acquisition or subsequent expression of trace fear conditioning. However, unlike in the present study, Rogers et al. (2006) found that pre-training lesions of VH attenuated freezing only during subsequent testing 48 h after conditioning, not during the acquisition of trace fear conditioning itself. It is important to note that there were methodological differences between these studies that may account for this apparent discrepancy, including differing trace intervals (10 s in Rogers et al. (2006); 30 s in the present study and in Yoon and Otto (2007)) and the specific areas within VH that were involved (CA1 subfield only in Rogers et al. (2006); CA1, CA3, and dentate gyrus (DG) in Yoon and Otto (2007)). Given that muscimol in the concentrations and volumes used here likely spread up to 2 mm from the infusion site (Martin, 1991; Edeline et al., 2002), it is likely that ventral CA1, CA3, and DG were inactivated in the present study. Therefore, it is possible that the subtle differences between the findings of Rogers et al. (2006) and the present study are due to the inactivation of CA3 or DG in addition to area CA1.

In contrast to the present study and the findings of Rogers et al. (2006) and Yoon and Otto (2007), both electrolytic (Burman et al., 2006) and excitotoxic (Fendt et al., 2005) lesions of DH have been reported to impair the acquisition of trace but not delay fear conditioning in a fear-potentiated startle paradigm. The inconsistency between studies measuring fear-potentiated startle and the aforementioned studies measuring freezing suggest that the DH may serve a dissimilar role in the expression of these responses during fear conditioning. However, in addition to measuring different responses, there were other methodological differences between each of these studies and the present study that may explain the apparent inconsistencies. The trace interval in the present study and Yoon and Otto (2007) was 30 s, whereas it was 10 s in the studies by Burman et al. (2006) and Fendt et al. (2005). In addition, the electrolytic lesions in Burman et al. (2006) were considerably more likely to have damaged fibers of passage than the excitotoxic lesions used in both Yoon and Otto (2007) and Rogers et al. (2006). Furthermore, in the studies reported by both Burman et al. (2006) and Fendt et al. (2005), acquisition was conducted over several days, while in the present study and Yoon and Otto (2007), acquisition was conducted in a single session. These inconsistencies suggest that the potential role of DH in trace fear conditioning is complex and perhaps paradigm specific.

Our finding that both pre-training inactivation of DH had no effect on the acquisition of trace fear conditioning is inconsistent with several studies examining the effect of NMDA receptor antagonism. Specifically, dorsal hippocampal NMDA receptor blockade by APV has been shown to dramatically impair the acquisition of auditory trace fear conditioning in both rats and mice (Quinn et al., 2005; Misane et al., 2005; Wanisch et al., 2005). Collectively, these data suggest that, if intact, the hippocampus participates in learning CS-US associations in trace fear conditioning, but if absent, other brain areas compensate for the lack of hippocampal processing. Moreover, these data raise the intriguing possibility that in the presence of APV the "intact" (i.e., unlesioned) DH may participate in CS-US processing via uncompromised AMPA receptors, but cannot support the plastic mechanisms required for the acquisition of associations between those stimuli. This notion is consistent with that proposed by Wiltgen and Fanselow (2003) to account for the differential effects of NMDA receptor antagonism and DH lesions on contextual conditioning.

## Pre-Testing Inactivation of Ventral, but not Dorsal, Hippocampus Impairs the Expression of Trace Fear Conditioning

Pre-testing inactivation of VH dramatically attenuated the expression of trace fear conditioning, where as pre-testing inactivation of DH had no effect. These data are consistent with prior data suggesting that post-training lesions of VH impair the expression of trace fear conditioning (Burman et al., 2006; Yoon and Otto, 2007). Collectively, these data suggest that VH is critically important for the expression, maintenance, or retrieval of the CS-US associations in trace fear conditioning. It may be argued that this VH involvement in fear conditioning may not be exclusive to trace fear conditioning, but rather may extend to delay fear conditioning as well (Bast et al., 2001; Maren and Holt 2004). Specifically, pre-training temporary inactivation of VH has been reported to result in a mild, but statistically significant attenuation in the acquisition of delay fear conditioning (Maren and Holt, 2004). However, in the same study, pre-testing inactivation of VH had no effect. Moreover, pre-testing lesions of VH have been reported to attenuate the expression of delay fear conditioning (Maren and Holt, 2004), but it is important to note that these lesions included extensive damage to the ventral subiculum, medial EC, ventral DG, CA1, and CA3. Therefore, while the VH may contribute in some potentially noncritical way to the acquisition and expression of delay fear conditioning, it seems to be particularly important to the acquisition and expression of trace fear conditioning.

Although no other study to our knowledge has utilized temporary inactivation to examine the role of DH in this task, Quinn et al. (2002) observed that post-training lesions of DH impaired the expression of trace fear conditioning. Similarly, and in contrast to the present data, previous data from our laboratory suggest that post-training lesions of DH attenuate the subsequent expression of trace fear conditioning (Yoon and Otto, 2007). Although the parameters of the conditioning and testing sessions were the same in both studies, it is important to note that lesions cause extensive and permanent damage, while inactivation is more selective and temporary. Therefore, it is possible that post-training lesions of DH impair the expression of trace fear conditioning because they permanently disrupt connections between DH and VH. Another important consideration is the training-testing interval, which was 8 days in Yoon and Otto (2007). However, in the present study inactivation of DH either 24 h or 8 days after training had no effect on the expression of trace fear conditioning, suggesting that the differing effects of temporary inactivation and lesions are not due to a difference in the training–testing interval. Finally, it is possible that inactivating a larger area within DH might replicate the effects of lesions.

During testing, the level of baseline immobility for groups SAL and DH-MUS during the first ITI (prior to the first presentation of tone) was significantly higher than for group VH-MUS. This suggests that there may have been some level of generalization between the conditioning and testing contexts for animals in groups SAL and DH-MUS, and in turn that the levels of fear elicited by subsequent ITIs, the CS, or the trace interval are confounded with different levels of baseline fear. However, two lines of evidence suggest that these effects are not likely due to a baseline shift. First, fear responses among animals with inactivation of VH were not elevated during trial 2–3 relative to those during trial 1 for any of the periods examined. Second, previous studies in our laboratory (Cousens and Otto, 1998; Herzog and Otto, 1999, 2002; Otto and Poon, 2006) have reported levels of conditioned fear (~80% freezing) that are similar to those of the SAL and DH-MUS groups in the present study, but in the absence of significant levels of baseline fear. These data suggest that while it is possible that animals with saline or muscimol infusions into DH may have exhibited some level of context generalization, the conditioned fear responses reported here are not importantly confounded by differentially enhanced levels of baseline fear.

## Inactivation of Ventral, but not Dorsal, Hippocampus Induces Hypoactivity

Lesions of the hippocampus have been shown to result in locomotor hyperactivity (Good and Honey, 1997). This is a key concern as hyperactivity may interact with the measured response of immobility. In the present study, animals who had received inactivation of either DH or VH were not hyperactive, as measured by ambulation counts in the open field. Instead, while muscimol infusions of DH had no effect on ambulation or rearing, muscimol infusions of VH reduced both ambulation and rearing. This hypoactivity is in direct contrast with the attenuation of immobility (i.e., more activity) observed during trace fear conditioning. Therefore, the observed deficits in the present study are likely due to a deficit in the acquisition and maintenance of learned associations, not to a performance deficit induced by muscimol.

## SUMMARY AND CONCLUSIONS

The present studies provide evidence for a double dissociation in DH and VH function: inactivation of DH, but not VH, dramatically impaired performance of delayed reinforced alternation, while in the same subjects inactivation of VH, but not DH, severely attenuated both the acquisition and subsequent expression of trace fear conditioning. Although this dissociation may reflect a differential role of these areas in processing spatial vs. temporal information, there are a number of alternative explanations that need to be considered. For example, the observed dissociation may reflect a differential role for these areas in tasks that are appetitively-motivated vs. aversively motivated, or in tasks that have a strong working memory component vs. those that do not. The extent to which these issues contribute to the pattern of findings reported here remains to be explored.

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