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Differential contributions of dorsal vs. ventral hippocampus to auditory trace fear conditioning

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Abstract

The effect of excitotoxic lesions of dorsal vs. ventral hippocampus on the acquisition and expression of auditory trace fear conditioning was examined in two studies. In Experiment 1, animals received excitotoxic lesions of either the dorsal or ventral hippocampus or sham surgeries one week prior to conditioning, and were tested 24 h later. In Experiment 2, animals received excitotoxic lesions of either the dorsal or ventral hippocampus or sham surgeries 24 h after training, and were tested one week after surgery. Both pre- and post-training lesions of ventral hippocampus impaired the acquisition and expression, respectively, of auditory trace fear conditioning. Pre-training lesions of dorsal hippocampus had no effect on the acquisition of trace fear conditioning, while post-training lesions of dorsal hippocampus dramatically impaired expression during subsequent testing. Although in some cases animals with lesions of ventral hippocampus exhibited locomotor hyperactivity, it is unlikely that the pattern of observed deficits can be attributed to this effect. Collectively these data suggest that the dorsal and ventral hippocampus may contribute differentially to the mnemonic processes underlying fear trace conditioning.

Keywords: Trace conditioning; Dorsal hippocampus; Ventral hippocampus; Fear conditioning; Learning; Memory; Pavlovian conditioning; Rat

1. Introduction

Converging lines of evidence suggest that different regions within the hippocampus can play functionally distinct roles in memory (Moser & Moser, 1998; Richmond et al., 1999). Specifically, findings from recent studies indicate that the hippocampus is a heterogeneous structure, with both anatomical (Burwell & Amaral, 1998; Pitkanen, Pikkarainen, Nurminen, & Ylinen, 2000; Risold & Swanson, 1996) and functional (Bannerman et al., 1999; Maren & Holt, 2004; Richmond et al., 1999; Rogers, Hunsaker, & Kesner, 2006) dissociations along its septotemporal axis, supporting the view that the dorsal and ventral hippocampus may be involved in discrete processes that separately mediate some forms of memory (Moser & Moser, 1998).

The results of a number of studies suggest that the hippocampus plays a particularly prominent role in some forms of trace conditioning, a Pavlovian conditioning paradigm in which the offset of the conditioned stimulus (CS) precedes the onset of the unconditioned stimulus (US). Specifically, hippocampal damage has been shown to impair performance in both trace eyeblink (Moyer, Deyo, & Disterhoft, 1990; Solomon, Schaaf, Thompson, & Weisz, 1986) and trace fear conditioning (Chowdhury, Quinn, & Fanselow, 2005; McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998; Quinn, Oommen, Morrison, & Fanselow, 2002) paradigms. With respect to trace fear conditioning, acquisition of hippocampal-dependent CS–US associations necessarily relies on interactions between the hippocampus and the amygdala, a structure known to be critically involved in both the acquisition and expression of fear conditioning in general (LeDoux, 2000). Anatomically, the ventral, but not the dorsal, hippocampus makes direct connections to the amygdala

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(Pitkanen et al., 2000). Specifically, the CA1 region within the ventral hippocampus projects to the basal, accessory basal, and amygdalohippocampal transition area of the amygdala (Canteras & Swanson, 1992; Pitkanen et al., 2000), while the dorsal hippocampus projects to the amygdala only via the ventral hippocampus (Pitkanen et al., 2000). These anatomical considerations suggest that trace fear conditioning may depend more on the ventral hippocampus than on the dorsal hippocampus. However, although prior studies have examined the effect of either complete aspirative hippocampal lesions prior to conditioning (McEchron et al., 1998), or post-conditioning excitotoxic lesions of the dorsal hippocampus (Chowdhury et al., 2005; Quinn et al., 2002) only one study to date has systematically examined the effects of pre-training, excitotoxic lesions of dorsal vs. ventral hippocampus on the acquisition of trace fear conditioning (Rogers et al., 2006); the results of this study indicate that neither dorsal nor ventral hippocampal lesions affected the acquisition of trace fear conditioning, while ventral damage alone impaired the retention of trace fear conditioning over a 48 h retention interval. These data are consistent with the notion that the dorsal and ventral subfields may participate differentially in some aspects of trace fear conditioning.

The goal of the present experiments was to further explore the extent to which the dorsal and ventral hippocampus are differentially involved in trace fear conditioning to a discrete auditory CS. Specifically, separate experiments examined the effects of pre-training and post-training excitotoxic lesions of the dorsal or ventral hippocampal subfields on the acquisition and expression of CS–US associations. Because hippocampal lesions often produce hyperactivity, a behavior in competition with the freezing response used to assess conditioning, lesion-induced hyperactivity was also examined. Collectively, the data suggest that while lesions of the ventral, but not dorsal, hippocampus dramatically impair the acquisition of auditory trace fear conditioning, both ventral and dorsal hippocampal lesions after training impair the expression of trace conditioning during testing. This pattern of deficits is not likely to be due to lesion-induced hyperactivity.

2. General methods

Methods common to both experiments are described in detail below. All procedures have been approved by Rutgers University's Institutional Animal Care and Use Committee.

2.1. Subjects

Sixty-nine naive male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing between 225 and 275 g at the time of surgery were used as subjects. All subjects were housed individually in hanging metal wire mesh cages in a colony on a 12-hr light/dark cycle with lights on at 7 a.m. All behavioral procedures occurred during the light cycle. Subjects were provided with ad libitum access to food and water. Subjects were handled for 3 min daily for 5 days prior to surgical procedures and behavioral training.

2.2. Apparatus

2.2.1. Fear conditioning and testing chambers

Auditory trace fear conditioning was conducted in two identical behavioral chambers (30 × 24 × 27 cm) from BRS/LVE (Beltsville, MD). Each chamber was enclosed within an aluminum sound-attenuating enclosure (56 × 41 × 42 cm). A pair of opposing walls and the ceiling of the conditioning chamber were made of transparent Plexiglas; another pair of opposing walls were made of aluminum. The floor of the chamber consisted of 16 stainless steel rods (5 mm in diameter), equally spaced from each other by 1.9 cm. These rods were connected to a shock generator (model H13-15, Coulbourn Instruments, Allentown, PA), and served to deliver the scrambled footshock US. A tray filled with sawdust was placed under the grid floor. Each chamber was equipped with a computer-activated tone generator (3.9 kHz, 80 dB) and speaker mounted 14 cm above the floor outside one of the aluminum walls. A single light bulb (28 V, 0.04 A) was situated 10.5 cm above where the tone generator was mounted.

An infrared motion detector with fresnel lens, dual element differential detector (13 nM infrared radiation), and 90-deg viewing angle (model H24-61, Coulbourn Instruments, Allentown, PA) was mounted on the ceiling of each chamber. Relative changes in detected energy produced by movement provided a continuous output for the entire duration of that movement or consecutive movements with an inter-event interval of less than 400 ms. This output was directed to the computer that also controlled all paradigmatic events, which sampled the detector at 1 Hz and recorded both movement and immobility throughout the entire session.

Testing (either 24 h or 8 days following conditioning) was conducted in a separate chamber located in a different experimental room. The testing chambers had the same configuration as those used for conditioning except that the floor of the testing chamber was covered with black Plexiglas, and the transparent Plexiglas walls were modified with alternating black and white stripes in order to provide the testing chamber with different visual cues from the conditioning chambers. As during conditioning, movement and immobility were recorded throughout the entire session.

2.2.2. Open-field chamber

Locomotor activity was measured in a walled square chamber (85 × 85 × 30 cm) made of black Plexiglas. White lines on the floor divided the chamber floor into thirty-six 14 cm squares. The chamber was placed on a table (73 cm high) in the center of a novel room relative to those used for conditioning and testing. The room was lit with a light fixture (65 W) placed 90 cm above the center of the chamber. An experimenter unaware of the experimental condition of the animal was seated approximately 1 m from the open-field chamber and manually recorded locomotor activity.

2.3. Procedure

2.3.1. Surgery

Subjects were treated with atropine (0.4 mg/kg, ip) before surgery to suppress respiratory secretion. Subjects were then anesthetized with sodium pentobarbital (50 mg/kg, ip). The subject's head was shaved and mounted in a stereotaxic frame (Kopf Instruments, Tujunga, CA). The shaved area was cleaned with 20% Nolvasan solution and the local anesthetic bupivicaine (0.1 ml, 0.25%) was injected at several locations below the scalp. The scalp was then incised and retracted, and six small burr holes (three per hemisphere) were drilled into the skull over the intended lesion sites. Lesions were produced by infusions of NMDA (20 μg/μl; Sigma, St. Louis, MO), dissolved in 0.1 M phosphate-buffered saline (pH 7.4). The NMDA was loaded in a 10-μl Hamilton syringe that was mounted on a microinjector (Kopf), which was, in turn, attached to a standard stereotaxic arm (Kopf). Infusion of NMDA was performed over 4 min (0.05 μl/min, 0.2 μl per site) at three sites per hemisphere in the dorsal hippocampus (AP: −2.8, ML: ±1.6, DV: −3.3; AP: −4.2, ML ±2.6, DV: −3.0; AP: −5.3, ML: ±4.0, DV: −3.3), or in the ventral hippocampus (AP: −4.4, ML: ±4.6, DV: −6.4; AP: −5.2, ML: ±4.6, DV: −6.5; AP −5.6, ML: ±4.6, DV: −6.0 mm). All DV coordinates were relative to dura. After infusion at each site, the syringe was left in position for 5 min to allow for drug diffusion. On completion of all of the infusions, the incision was closed