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Research report

Role of hippocampus in polymodal-cue guided tasks in rats

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ABSTRACT

To examine how signals from different sensory modalities are integrated to generate an appropriate goal-oriented behavior, we trained rats in an eight-arm radial maze to visit a cue arm provided with intramaze cues from different sensory modalities, i.e. visual, tactile and auditory, in order to obtain a reward. When the same rats were then examined on test trials in which the cue arm contained one of the stimuli that the animals were trained with (i.e. light, sound or rough sheet), they showed a significant impairment with respect to the performance on the polymodal-cue task. The contribution of the dorsal hippocampus to the acquisition and retention of polymodal-cue guided task was also examined. We found that rats with dorsal hippocampal lesions before training showed a significant deficit in the acquisition of polymodal-cue oriented task that improved with overtraining. The selective lesion of the dorsal hippocampus after training disrupted memory retention, but the animals' performance improved following retraining of the polymodal task. All hippocampal lesioned rats displayed an impaired performance on the unimodal test. These findings suggest that the dorsal hippocampus contributes to the processing of multimodal sensory information for the associative memory formation and consolidation.

1. Introduction

The distinction between elemental and configural models is a central issue in associative learning theory about how the hippocampus contributes to learning and memory (Harris, 2006; Iordanova et al., 2011; Pearce and Bouton, 2001; Rudy and Sutherland, 1989). According to the elemental theories, stimuli are processed separately, independent of whether they have been presented alone or compounded with other stimuli, meaning that the associative strength of a compound is equal to the algebraic sum of the associative strength of its components (Rescorla and Wagner, 1972). The configural theories assume that conditioning with a compound results in a unitary representation of the compound as a configuration entering into an association with the reinforcement (Pearce, 2002). Interestingly, patients and animals with damage to the hippocampus are unable to solve a novel associative learning task whose solution required the acquisition of specific combinations of elements i.e. configuration, rather than single elements (Rudy and Sutherland, 1989; Schmajuk and DiCarlo, 1992). Negative patterning is a well-known discrimination task that has been proposed for comparing elemental and configural theories in animal models (Rescorla, 1972; Whitlow and Wagner, 1972). To solve the problem, animals have to learn to respond to two single reinforced stimuli (A+, B+) but not to their combination, which is non-reinforced (AB-). By using this paradigm, Rudy and Sutherland (1989) demonstrated that rats with hippocampal lesions behaved similarly to their controls in the presence of a single stimulus, but were unable to generate the appropriate response when the two cues were associated. However, these results are in contrast with those reported by other authors who found little or even no effect of the hippocampal lesion on the acquisition of a configural associative task (Davidson et al., 1993; Gallagher and Holland, 1992; Whishaw and Tomie, 1991).

Nevertheless, the hippocampus is considered a critical brain area where spatial and non-spatial information can be integrated into a unified event representation (Eichenbaum et al., 1999; Moser et al., 2008). Indeed, during new memory formation the hippocampus forms connections between sensory stimuli that can be stored and recalled later (Cohen and Eichenbaum, 1993; Gluck et al., 2005; O'Reilly and Rudy, 2001). To better understand how multiple stimuli combine to produce an appropriate behavior during associative learning, we developed a multisensory apparatus that allows us to measure the navigational behavior along with the precisely controlled presentation of visual, auditory and tactile stimuli. For this purpose, rats were trained in an eight-arm radial maze to visit a cue arm provided with intramaze cues from different sensory modalities, i.e. light, sound and rough sheet, in order to obtain a reward. At the end of the training, the same rats were examined on test trials in which the cue arm contained one

Abbreviations: DH, dorsal hippocampus; pre-DH lesion, pre-training dorsal hippocampus lesion; post-DH lesion, post-training dorsal hippocampus lesion

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of the stimuli, that the animals were trained with, to determine whether the animal's performance was primarily controlled by the sum of the elements presented, as a compound stimulus, or by one specific sensory element of the compound.

Since most of the highly processed information from the sensory cortices enters the hippocampus mainly through its dorsal section (Fanselow and Dong, 2010; Strange et al., 2014), we next determined the role played by dorsal hippocampus during acquisition and retention of the polymodal associative task. For this purpose, we examined the behavioral effects of discrete electrolytic lesions of the dorsal hippocampus, before and after training of the polymodal cue-guided task.

2. Results

2.1. Histology

A schematic representation of the extent of the electrolytic lesion of the dorsal hippocampus is shown in Fig. 1. The electrolytic lesions appeared to be complete within the targeted region with no damage to the surrounding tissue. The sham groups did not show any damage to any brain region.

2.2. Effect of the dorsal hippocampal lesion on acquisition

2.2.1. Polymodal associative task

Dorsal hippocampal (pre-DH; n=8) and sham (n=8) lesioned rats were trained on the polymodal-cue guided task in the eight-arm radial maze (Fig. 2). During the polymodal training, each rat was required to visit the cue arm containing the visual (light), auditory (sound) and tactile (rough sheet) stimuli to obtain a reward. The position of the cue arm changed for each trial. Initially, both pre-DH and sham animals reached the cue arm taking random routes. However, the sham group learned the task more rapidly than the pre-DH group. As shown in Fig. 3, sham and pre-DH animals achieved the learning criterion after 18 and 25 daily sessions of training, respectively. A two-way ANOVA (lesion group x session) of the mean percentage of correct choices for the first 18 sessions indicated a significant difference between the sham and pre-DH groups [$F(1, 14)=61.8$, $p<0.01$] and revealed also an effect of sessions [$F(17, 238)=17.69$, $p<0.01$] and group x session interaction [$F(17, 238)=2.4$, $p<0.01$]. The two-way ANOVA (lesion group x session) of the mean errors for the first 18 sessions showed a significant difference between groups [$F(1, 14)=33.44$, $p<0.01$] and sessions, [$F(17, 238)=4.20$, $p<0.01$] but no significant lesion group x session interaction [$F(17, 238)=1.15$, $p=$n.s.]. Concerning the latency, the effects of lesion group [$F(1, 14)=50.2$, $p<0.01$] and session [$F(17, 238)=10.5$, $p<0.01$] were significant for the first 18 sessions as was the session x lesion group interaction [$F(17, 238)=2$, $p<0.05$].

2.2.2. Unimodal associative test

One day after the animals completed the polymodal-cue training, each animal was tested on the unimodal-cue task in which the cue arm was signaled by one of the three stimuli at a time, i.e. light, sound or rough sheet. As shown in Fig. 4, both sham and pre-DH rats were impaired irrespective of which unimodal cue was used. The mean percentage of correct choices scored in the unimodal-cue task with light, sound and rough sheet was 37.5 ($\pm$5.1), 37.5 ($\pm$6.3) and 61.1 ($\pm$5.9), respectively, in the sham group vs 43.0 ($\pm$6.4), 22.2 ($\pm$5.9) and 52.7 ($\pm$3.5), respectively, in the pre-DH group.

A two-way ANOVA (group $\times$ session) was used to compare the mean errors in the unimodal-cue sessions with those scored in the last session of training with the polymodal cues by sham and pre-DH animals (Fig. 4A). This revealed a significant effect of session [$F(3, 42)=20.58$, $p<0.01$] but no significant effect of lesion group [$F(1, 14)=0.13$, $p=$n.s.] and lesion group x session interaction [$F(3, 42)=1.29$, $p=$n.s.]. Tukey HSD test indicated that the performance with the unimodal cues was significantly different from to that observed in the polymodal-cue task ($p<0.01$). A three way ANOVA of the errors scored across the trials with the unimodal cues (lesion group x cue x trials) showed a significant effect of unimodal cue [$F(2, 32)=16.9$, $p<0.01$], but no significant effect of lesion [$F(1, 32)=0.07$, $p=$n.s.] and trial [$F(8, 256)=0.43$, $p=$n.s.]. In addition, the lesion group x cue interaction was significant [$F(2, 32)=4.7$, $p<0.05$], whereas there was no significant difference for group x trial [$F(8, 256)=2.8$,

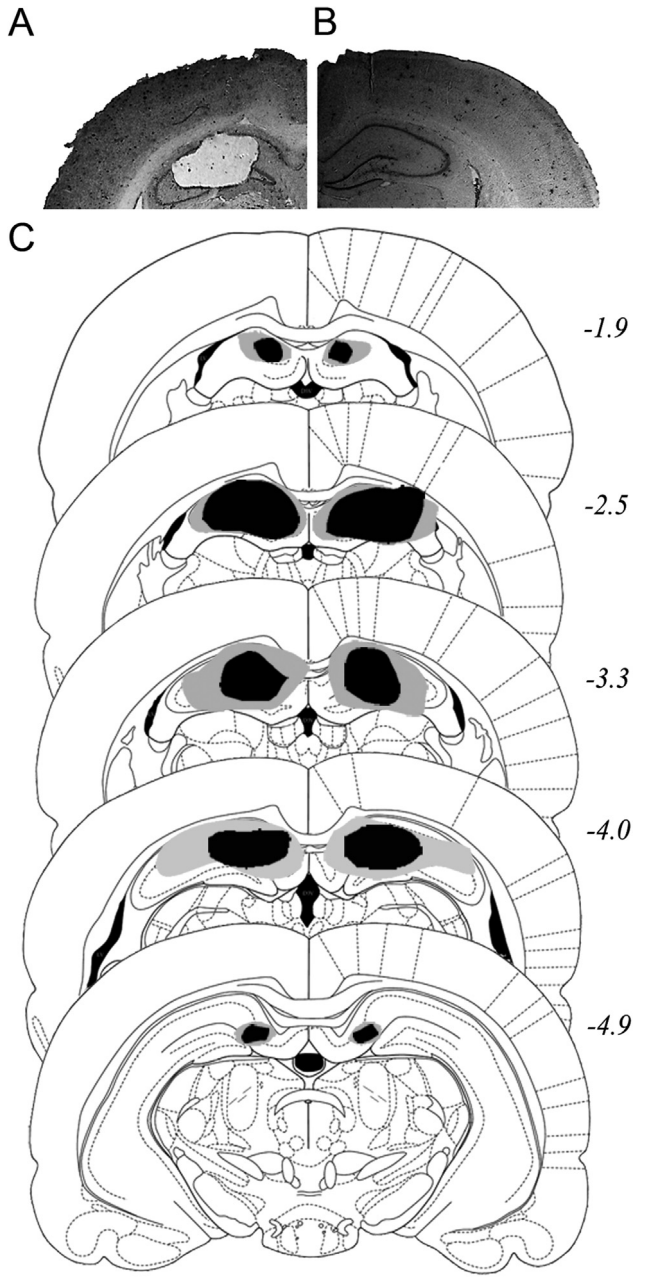

Fig. 1. : **Histological evaluation of the electrolytic dorsal hippocampal lesion.** Photomicrographs of representative coronal brain sections stained with cresyl violet from animals with a bilateral lesion of dorsal hippocampus (A) and sham surgery (B). (C) Histological reconstruction of representative electrolytic lesions of the dorsal hippocampus. The gray area represents the extent of the largest lesion, and the black area represents the extent of the smallest lesion. The coronal sections were taken from Paxinos and Watson (2007).