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Research report

Dorsal, ventral, and complete excitotoxic lesions of the hippocampus in rats failed to impair appetitive trace conditioning

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Abstract

Three experiments examined appetitive trace and delay conditioning of the licking response (LR). In Experiment 1, normal rats were trained in trace conditioning using different trace intervals (2, 4, or 8 s) and in delay conditioning (i.e., with a 0-s trace) in order to determine an appropriate trace interval for the following lesion experiments. Only the rats trained with a 2-s trace interval ultimately reached the same level of learning as rats trained in delay conditioning. In Experiments 2A and 2B, the performance of rats with dorsal, ventral, and complete excitotoxic hippocampal lesions was compared to that of sham-operated rats in LR conditioning with a 2-s trace. In Experiment 2B, the performance of rats in trace LR conditioning was also compared to that of rats tested in the delay paradigm. In both experiments, acquisition did not differ in lesioned and sham-operated rats and, in Experiment 2B, it was faster in the delay than in the trace paradigm. These results contrast with those showing that aversive trace conditioning is impaired after hippocampal damage. Experiment 3 examined whether the differential effects of hippocampal lesions on aversive and appetitive trace conditioning could be related to a parametric difference, that is, the relative durations of the conditional stimulus and of the trace interval. Again, hippocampal damage failed to produce a learning impairment. It is suggested that the procedure of aversive, but not of appetitive, trace conditioning is context-specific and that an intact hippocampus is required only in these situations.

Keywords: Hippocampus; Lesion; Rats; Trace conditioning; Appetitive; Licking response; Water restriction; Pavlovian conditioning

1. Introduction

One approach to the study of the neural mechanisms underlying associative learning and memory is Pavlovian, or classical, conditioning. In this paradigm, the conditional stimulus (CS) and the unconditional stimulus (US) can be linked by different temporal relationships. In delay conditioning, the CS and the US are temporally contiguous: the CS begins before the US and lasts at least until the onset of the US. In trace conditioning, the two stimuli are not contiguous: a trace interval separates the offset of the CS from the onset of the US. Numerous experiments indicate that damage to the hippocampus does not interfere, in the delay paradigm, with the acquisition of the conditioned response (CR) [7,39,40]. By contrast, complete hippocampal lesions impair acquisition of the CR in trace conditioning [7,23,39] or when learning is especially difficult, for example in delay conditioning with a very long interstimulus interval (ISI) [7]. A deficit was also observed in trace conditioning after either dorsal [24,36,37] or ventral [36] lesions of the hippocampus, although in some experiments an effect of ventral lesions was found only in extinction and not in acquisition [32]. All of the aforementioned experiments used aversive conditioning of either the fear or the eyeblink response.

Experiments on appetitive delay conditioning generally corroborated findings from aversive delay conditioning. When a food-US is preceded by a visual CS or by an auditory CS, the acquisition of appetitive CRs is usually not impaired in rats with either complete or dorsal hippocampal lesions [9,14,18], although a deficit has been reported in rats after dorsal lesions when the CS was a localized cue [9]. Only a few experiments examined appetitive trace conditioning in animals with a dysfunctional hippocampus. It was investigated in rabbits using jaw

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movements as the CR. The results indicated that disruption of hippocampal functioning by central cholinergic blockade or by medial septal inactivation retarded the acquisition of the CR in water-deprived rabbits when a 450-ms trace interval separated the tone-CS from the water-US [3,4,33]. Although these results were consistent with those in aversive trace conditioning, none of the injections were made into the hippocampus and thus, activity in this structure was only partially and indirectly disturbed. Furthermore, the deleterious effect of central cholinergic blockade was not specific to trace conditioning and also retarded aversive delay conditioning [35]. No published experiment has examined appetitive trace conditioning in animals after either dorsal, ventral, or complete lesions to the hippocampus.

In the following experiments, we used an appetitive Pavlovian paradigm, the conditioning of the licking response (LR) which was initially developed by Baker and Mackintosh [5] to study a variety of phenomena such as inhibitory conditioning, CS preexposure (also called latent inhibition), US pre-exposure, and learned irrelevance. In conditioning of the LR, water-deprived rats are exposed to pairings of a tone-CS and a water-US. The rat learns to approach and lick the drinking tube (i.e., the CR) during the tone before the water-US is available. This paradigm is similar to Holland's Pavlovian appetitive situation [14,15] where a visual or auditory CS is paired with a food-US and the CR is the time that rats spent during the CS with their noses in the food cup. In both cases, the CR includes two components: an approach and a consummatory response (licking or eating) which is similar to the unconditioned response (UR). Like avoidance conditioning, both appetitive paradigms also involve an instrumental and a Pavlovian contingency [30]. In LR conditioning or Holland's appetitive situation, the US is not delivered directly to the animal as it is in Pavlovian conditioning of reflexes (e.g., salivary and eyeblink reflexes, jaw movement, freezing). The rat must approach the vicinity of the drinking tube to have access to the US. This approach response is acquired and maintained by an instrumental contingency of positive reinforcement between the appropriate behavior, the approach of the drinking tube, and its consequence, the delivery of the water reinforcement [13,22]. However, in LR conditioning, the tone-CS, which is neutral at the beginning of learning, acquires its appetitive value and its capacity to elicit the consummatory CR through a Pavlovian association with the US. Like in any other classical conditioning, the presentation of the water-US is independent of the animal's behavior: the water is delivered only if preceded and/or accompanied by the tone-CS and whether or not the rat licked the drinking tube during the tone.

Because there are no available data on trace conditioning of the LR, we had first to determine an appropriate trace interval, which is a trace that would eventually produce a level of learning similar to delay conditioning but at a slower rate. Therefore, in Experiment 1, normal rats were trained on LR trace conditioning with one of three trace intervals or on delay conditioning and the performances of the four groups were compared. In Experiments 2A and 2B, one of those trace intervals was selected to examine whether *N*-methyl-D-aspartate (NMDA) dorsal, ventral, or complete hippocampal lesions disrupt LR trace conditioning. Experiment 2B also tested whether trace conditioning of the LR was distinct from conditioning of the same response in a delay paradigm. In Experiment 3, we compared the performance of rats with complete lesion of the hippocampus with that of sham-operated rats in a similar learning paradigm but where the CS length was shortened to investigate the possibility that there was some form of contiguity between the CS and the US in the procedure used in Experiments 2A and 2B.

2. General materials and methods

2.1. Subjects

The experiments used 127 Long-Evans male rats (Charles River, St-Constant, Canada). Subjects were housed individually and maintained on a 12-h:12-h light-dark cycle (light at 7:00 a.m.). All behavioral testing was conducted during the light phase. The research received approval from the Comité de protection des animaux de l'Université Laval, which is responsible for the application and enforcement of the rule of the Canadian Council on Animal Care.

2.2. Surgery

In Experiments 2A, 2B, and 3 which involved surgeries, general anaesthesia was induced and maintained by isoflurane (1.0–2.5%) mixed with oxygen. The ears and scalp were locally anesthetized by injections of Marcaine (7.5 mg/ml; 0.2 ml sc). Rats were placed in the stereotaxic apparatus (Kopf Instruments, Tujunga, CA) and the scalp was incised to reveal the skull. With bregma and

Table 1
Stereotaxic Coordinates and Injection Volumes of NMDA

AP	ML	DV	Volume (μl)
Dorsal hippocampal lesion			
−2.9	±1.1	−3.8	0.08
−3.2	±2.3	−3.7	0.06
−3.9	±1.9	−3.7	0.10
−4.1	±3.3	−3.7	0.08
Ventral hippocampal lesion			
−5.0	±5.0	−7.5	0.10
−5.0	±5.0	−5.5	0.04
−5.0	±5.0	−4.6	0.04
−5.6	±4.7	−5.5	0.04
−5.6	±5.1	−6.0	0.04
−5.6	±5.1	−5.2	0.05
−5.6	±5.1	−4.9	0.05
Complete hippocampal lesion			
−2.9	±1.1	−3.8	0.07
−3.2	±2.3	−3.7	0.06
−3.9	±1.9	−3.7	0.06
−4.1	±3.3	−3.7	0.06
−5.0	±4.0	−3.8	0.05
−5.0	±5.0	−7.4	0.09
−5.0	±5.0	−4.6	0.05
−5.6	±4.2	−4.3	0.04
−5.7	±5.1	−6.0	0.04
−5.7	±5.1	−5.3	0.05
−5.7	±5.1	−5.0	0.05

Note: All coordinates are given in millimetres and are relative to bregma. NMDA = *N*-methyl-D-aspartate acid; AP = anteroposterior; ML = mediolateral; DV = dorsoventral.