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Research report

Post-training re-exposure to fear conditioned stimuli enhances memory consolidation and biases rats toward the use of dorsolateral striatum-dependent response learning

Kah-Chung Leong, Jarid Goodman, Mark G. Packard*

Department of Psychology & Institute for Neuroscience, Texas A&M University, College Station, TX 77843-4235, United States

HIGHLIGHTS

- Anxiety by exposure to *unconditioned* stimuli enhances the use of response learning.
- Re-exposure to fear *conditioned* stimuli biased rats towards response learning.
- Re-exposure to fear *conditioned* stimuli enhanced consolidation of response learning.

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ABSTRACT

In a dual-solution task that can be acquired using either hippocampus-dependent "place" or dorsolateral striatum-dependent "response" learning, emotional arousal induced by *unconditioned* stimuli (e.g. anxiogenic drug injections or predator odor exposure) biases rats toward response learning. In the present experiments emotionally-arousing *conditioned* stimuli were used to modulate the relative use of multiple memory systems. In Experiment 1, adult male Long-Evans rats initially received three standard fear-conditioning trials in which a tone (2 kHz, 75 dB) was paired with a brief electrical shock (1 mA, 2 s). On day 2, the rats were trained in a dual-solution plus-maze task to swim from the same start arm (South) to a hidden escape platform always located in the same goal arm (East). Immediately following training, rats received post-training re-exposure to the fear-conditioned stimuli (i.e. tone and context) without shock. On day 3, the relative use of place or response learning was assessed on a probe trial in which rats were started from the opposite start arm (North). Post-training re-exposure to fear-conditioned stimuli produced preferential use of a response strategy. In Experiment 2, different rats received fear conditioning and were then trained in a single-solution task that *required* the use of response learning. Immediately following training, rats received post-training re-exposure to the fear-conditioned stimuli without shock. Re-exposure to fear-conditioned stimuli enhanced memory consolidation in the response learning task. Thus, re-exposure to fear-*conditioned* stimuli biases rats toward the use of dorsolateral striatum-dependent response learning and enhances memory consolidation of response learning.

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Numerous neurobehavioral studies provide evidence supporting a multiple systems approach to the organization of mammalian memory. According to this view, relatively independent neural systems mediate different types of memory (for reviews see [1–4]). For instance, evidence from brain lesion experiments employing dissociation methodology indicates that the hippocampus and dorsolateral striatum differentially mediate "cognitive" and "stimulus–response habit" memory, respectively (e.g. [5–8]).

Although brain lesion studies have been instrumental in dissociating the neural bases of multiple memory systems, additional studies have investigated the various factors that modulate the *relative* use of memory systems in the intact brain (for review see [9]). One prominent memory modulatory factor is robust emotional arousal (e.g. stress and/or anxiety). In a dual-solution plus-maze task that may be solved adequately using either hippocampus-dependent "place" learning or dorsolateral striatum-dependent "response" learning, injection of anxiogenic drugs pre-training [10], post-training [11], or pre-retrieval [12] produces a bias toward the use of response learning. In addition, in a single-solution plus-maze task that *requires* the use of response learning, post-training

* Corresponding author. Tel.: +1 979 845 9504; fax: +1 979 845 4727.
E-mail address: markpackard@tamu.edu (M.G. Packard).

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administration of an anxiogenic drug [11] or exposure to predator odor [13] enhances memory consolidation.

Whereas these previous studies have primarily used exposure to *unconditioned* stimuli (e.g. anxiogenic drug injection or predator odor exposure) to modulate the relative use of multiple memory systems, relatively few studies have investigated the potential memory modulatory effects of exposure to *conditioned* emotional stimuli [14–16]. Therefore, in Experiment 1 we examined the effect of post-training re-exposure to fear-conditioned stimuli on the relative use of "place" and "response" learning in a dual-solution plus-maze. Rats were first exposed to a standard fear-conditioning paradigm, which involved repeated tone-foot shock pairings. On the following day the rats were trained in a dual-solution water plus-maze task to swim from the same start arm (South) to a hidden escape platform that was always located in the same goal arm (East). This dual-solution plus-maze task can be adequately acquired using either hippocampus-dependent "place" or dorsolateral striatum-dependent "response" learning. Immediately post-training, rats were re-exposed to the previously fear-conditioned stimuli (i.e. tone and context) without shock. On the following day, rats received a probe trial in the plus-maze that allowed for an assessment of the relative use of place or response learning. On the probe trial, rats that swam to the spatial location in which the platform was located during training were designated place learners, whereas rats that made the body turn response reinforced during training were designated response learners.

In Experiment 2 we examined the effect of post-training re-exposure to fear-conditioned stimuli on memory consolidation in a dorsolateral striatum-dependent plus-maze task that *requires* the use of response learning. Different groups of rats received fear-conditioning as in Experiment 1 and on subsequent days received training in a single-solution plus-maze task. In this task, rats were started from varying start arms (North, South) and trained to always make the same body turn response (turn right) at the maze choice point. Immediately post-training, rats were re-exposed to the previously fear-conditioned stimuli without shock to examine the effect of stimuli exposure on memory consolidation of response learning.

1. General methods

1.1. Subjects

Subjects ($n = 43$) were experimentally naïve adult male Harlan Long-Evans rats (275–375 g). Rats were individually housed in a climate-controlled vivarium on a 12-h light:12-h dark cycle, with lights on from 7:00 a.m. to 7:00 p.m. All experiments were conducted during the light phase of the cycle. All animals received food and water *ad libitum*. Each rat was handled daily for 3 min for 5 days prior to the beginning of behavioral testing.

1.2. Apparatus

The water plus-maze used was identical to the apparatus described in our previous studies [13,17]. A clear Plexiglas plus-maze (43 cm height, arm-width of 27 cm, and arm-length of 60 cm) was inserted in a black circular water maze (180 cm diameter, 45 cm height). The water maze was filled to a water level of approximately 21 cm, and water temperature was maintained at 25 °C. A clear Plexiglas escape platform (15 cm × 14 cm × 20 cm) was submerged 1 cm below water level inside the plus-maze at the end of the designated goal arm, which varied depending on the specific training protocol. The arm opposite to the start arm was blocked by a piece of clear Plexiglas so that the animals were trained in a T-maze configuration. The maze was located in a room containing several extra-maze cues.

1.3. Fear conditioning

The fear conditioning chamber (San Diego Instruments) was located in a moderately lit and isolated room. The chamber was constructed of aluminum (walls) and Plexiglas (hinged ceiling). The floor of the chamber consisted of 19 staggered stainless steel rods (4-mm diameter), spaced 1.5 cm apart. The rods were wired to a computer-controlled shock generator for delivery of foot shock. Auditory tone (2 kHz, 75 dB, 20 s) was supplied by a speaker located directly above the chamber.

1.4. Behavioral procedures

1.4.1. Fear conditioning

Fear-conditioning procedures were adapted from previous studies examining conditioned stimulus-mediated memory modulation [14]. Rats were removed from the home cage and transported to the fear conditioning chamber. Rats remained in the chamber for a duration of 7 min. During the first 3 min ("Pre-Shock" period) no tones or shocks were presented. At the start of the 4th minute a tone was presented (2 kHz, 75 dB) for 20 s. During the final 2 s of the tone presentation, a footshock (1 mA) was administered through the floor rods and co-terminated with the tone. The tone-shock pairings occurred two additional times with a 1 min interval between tone presentations. In sum, each rat received three tone-shock pairings. Following the last tone-shock pairing rats remained in the chamber for an additional 1 min. "Tone alone" control animals received presentations of the tone but without shock. After the rat was removed following conditioning the rod floor, walls, and catch pan underneath the floor of the chamber were cleaned with 70% alcohol. Following conditioning rats were returned to their home cages.

1.4.2. Experiment 1: dual-solution water plus-maze task

The day following fear conditioning, rats ($n = 42$) were trained in the dual-solution water plus-maze task. Rats received training for 1 day (6 trials). The start arm and goal arm remained fixed throughout training. For each trial, animals were placed into the start-arm of the maze (i.e. south arm) facing the maze wall and were given 60 s to swim to a hidden escape platform located in the goal-arm (i.e. east arm). If the rat made an initial full-body turn into the correct arm (i.e. the east arm), a trial was scored as correct. If the rat made a full-body turn into the incorrect arm (i.e. the west arm), a trial was scored as incorrect. If the rat did not find the platform within the allotted 60 s, the experimenter manually guided the rat to the platform. After reaching the platform, rats remained there for 10 s before being removed and placed in an adjacent opaque holding container for a 30 s inter-trial interval. Following the sixth and final training trial, rats were immediately transported to the fear conditioning chamber and received post-training tone (CS) presentations in a manner similar to the initial conditioning phase, except without the shocks. Following tone presentations rats were returned to their home cages.

Aside from the tone-alone control group, the present experiment included two additional control groups. One group of animals that had originally received tone-shock pairings during fear conditioning was not given re-exposure to the fear CS (i.e. tone and chamber) after maze training. Immediately after training, these animals were returned to their home cages (i.e. tone-shock with no re-exposure). Another control group that had received tone-shock pairings during fear conditioning was only given post-training re-exposure to the fear CS 3 h after maze training (i.e. tone-shock with delayed re-exposure). This group was added to rule out potential proactive effects of fear CS re-exposure on learning strategy.

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