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Acute stress, but not corticosterone, facilitates acquisition of paired associates learning in rats using touchscreen-equipped operant conditioning chambers

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ABSTRACT

Acute stress influences learning and memory in humans and rodents, enhancing performance in some tasks while impairing it in others. Typically, subjects preferentially employ striatal-mediated stimulus-response strategies in spatial memory tasks following stress, making use of fewer hippocampal-based strategies which may be more cognitively demanding. Previous research demonstrated that the acquisition of rodent paired associates learning (PAL) relies primarily on the striatum, while task performance after extensive training is impaired by hippocampal disruption. Therefore, we sought to explore whether the acquisition of PAL, an operant conditioning task involving spatial stimuli, could be enhanced by acute stress. Male Long-Evans rats were trained to a predefined criterion in PAL and then subjected to either a single session of restraint stress (30 min) or injection of corticosterone (CORT; 3 mg/kg). Subsequent task performance was monitored for one week. We found that rats subjected to restraint stress, but not those rats injected with CORT, performed with higher accuracy and efficiency, when compared to untreated controls. These results suggest that while acute stress enhances the acquisition of PAL, CORT alone does not. This dissociation may be due to differences between these treatments and their ability to produce sufficient catecholamine release in the amygdala, a requirement for stress effects on memory.

1. Introduction

Stress is pervasive in society and is increasingly recognized as a cause of psychiatric and physical illness [1,2]. Acutely stressful experiences affect cognition, effects that may be relevant to brain disorders such as addiction, anxiety, and post-traumatic stress disorder (PTSD; reviewed by [3]). Impairments in spatial memory consolidation and recall are often found in people with these disorders [3]. Whereas chronic stress generally impairs aspects of hippocampal (HPC) dependent spatial memory in both humans (reviewed by Burgess et al. [4]) and rodents (reviewed by [5]), the effects of acute stress are not as consistent [6,7]. Although spatial memory recall is often similarly impaired following both acute and chronic stress [7,8], consolidation may be enhanced or impaired depending on factors such as the timing, arousal, or intensity of the stress [7,9].

The interaction between acute stress and spatial memory is influenced by the nature of the memory task used in assessment (see [10]). In rodent behaviour studies, acute stress promotes a shift from more cognitively demanding HPC-dependent strategies toward simpler, more procedural, stimulus-response (S-R) based strategies, which rely on the dorsal striatum (DSTR; [10–14]). These differences suggest a distinct mechanism by which stress hormones, primarily cortisol in humans and corticosterone (CORT) in rodents, interact with limbic and cortical structures essential for memory including the HPC, prefrontal cortex (PFC), DSTR, and amygdala [15–17].

Recent research has sought to improve the concordance between human studies and those which use animal models in stress and other fields. One method by which this has occurred is through use of analogous behavioural paradigms in both humans and rodents. One such task which has demonstrated similarities in cognition across species is paired associates learning (PAL; [18,40,19]). In humans, PAL is used clinically to detect mild cognitive impairment associated with HPC-mediated deficits in spatial associative memory in conditions such as Alzheimer's disease and schizophrenia [20,38]. A rodent version of PAL was recently developed in which visuospatial memory is assessed based on the ability to learn object-in-place associations [18]. In contrast to the human version, which is conducted in one session, the rodent version occurs over several weeks, with gradual improvement in learning

Abbreviations: PAL, Paired Associates Learning

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of the image-location pairings. Like human PAL, the rodent version is sensitive to HPC dysfunction and performance is impaired following lesions [21,22] and inactivations [22]. Furthermore, many psychoactive drugs, such as amphetamine, known to affect HPC-dependent spatial memory in humans impair retrieval and PAL performance when administered systemically or infused directly in the HPC [22–26].

However, while task performance in well-trained animals is impaired by manipulations of the HPC, acquisition of PAL is largely unaffected by pre-acquisition HPC lesions in mice [21,22] or by HPC catecholamine depletion in rats [27]. In contrast to later task performance, PAL acquisition may involve separate memory systems as lesions of the DSTR prevent PAL acquisition entirely [21].

To the best of our knowledge, no previous studies have explored the effects of stress on rodent PAL. Therefore, we first sought to determine the effect of acute stress on acquisition of this task. Previous evidence from rats and mice suggests a prominent role of DSTR-mediated memory in PAL acquisition, and we therefore hypothesized that both acute restraint stress (ARS) and CORT would facilitate this process. This was based on previous research suggesting that stress promotes preferential use of DSTR-mediated strategies rather than HPC-mediated strategies. Naïve adult male Long Evans rats were trained daily in 1 h sessions of PAL until reaching a predefined criterion early in task acquisition. The day immediately following, they were subjected to ARS (30 min), CORT (3.0 mg/kg), vehicle, or no manipulation and trained daily on PAL for an additional week.

2. Methods

2.1. Subjects

Adult male Long Evans rats (n = 58) were used for the ARS (n = 13), control (n = 13), CORT (n = 16), and vehicle groups (n = 16) (Charles River Laboratories, Kingston, NY, USA). Upon arrival at the facility, animals were pair housed and left undisturbed for 1 week with food and water *ad libitum* (Purina Rat Chow). Following facility acclimatization, animals were maintained at 90% of free feeding weight and singly housed to ensure the appropriate amount of food was consumed by each rat in the home cage after behavioural testing. Animals were housed in ventilated plastic home cages in a temperature and humidity-controlled vivarium with water available *ad libitum* except during testing. A 12:12 h lighting cycle was used with lights on at 7:00 a.m.. Animals were given environmental enrichment in their home cage in the form of a plastic tube throughout the experiment. Experiments were conducted from November 2016 to February 2017 for control and ARS animals, and from May 2017 to August 2017 for CORT and Vehicle animals. To control for normal circadian CORT rhythms, animals were trained at the same time daily. All experiments were conducted in accordance with the standards of the Canadian Council on Animal Care and the University of Saskatchewan Animal Research Ethics Board.

2.2. Training apparatus

Eight touchscreen-equipped operant conditioning chambers (Lafayette Instruments, Lafayette, IN, USA) were used for PAL (Fig. 1). Each chamber was contained within its own sound-attenuating box with a fan to provide background noise and air circulation. A live video feed of animal activity was maintained through a camera mounted within the box above the operant chamber. The chamber dimensions and layout were identical to those used previously (see Ref. [24]). A removable mask, interchangeable for different behavioural tasks, rested on the touchscreen and obscured the screen entirely except for areas where stimuli are presented, and response selection occurs. In PAL, the mask had three equally-sized rectangular response windows, arranged evenly across the mask. The windows are located above a spring-loaded response shelf that animals were required to press down to access the screen and make a selection.

2.3. Touchscreen habituation and pretraining

Habituation, pretraining, and training were conducted according to instructions and protocols established by Lafayette, and previous experiments conducted in our lab [24,25]. Animals advanced through training stages based on their individual performance and ability to meet intermediate criteria. Pretraining and training sessions occurred once daily, 6 days a week.

Animals were handled for at least 5 days before touchscreen habituation began. On the first day of habituation rats were brought from the vivarium to the touchscreen room and left undisturbed in their home cage for 1 h. They were given 5 reward pellets (Dustless Precision Pellets, 45 mg, Rodent Purified Diet; BioServ, NJ, USA) at the beginning of the habituation period. During this period, all equipment was on and the lights were dimmed to replicate the conditions used when training and testing. For all subsequent training days rats were left undisturbed for 30 min following transport to the touchscreen room.

Pretraining consisted of various intermediate and progressive steps to encourage rats to approach and nose-poke the display. It began with two 30 min chamber habituation sessions in which animals were left undisturbed in the chambers and given 5 reward pellets in the food port. Criterion was reached if all pellets were consumed within 30 min. Rats then began initial touch training in which one of the response windows was illuminated pseudorandomly. The window was illuminated for 30 s, or until touched. Three reward pellets were delivered if the rat correctly touched the illuminated window during this period and one pellet was delivered if the illuminated window was not touched. A 20 s intertrial period followed each trial. Criterion for initial touch was completion of 100 trials in 1 h. Must touch training was administered similarly, with animals receiving 1 reward pellet for correct touches only. The criterion for must touch training was 100 trials in 1 h. Must initiate training required the rat to nose-poke in the food port to initiate a trial before commencing as in the previous stage. Criterion for the must initiate phase was 100 trials in 1 h. The final stage of pretraining was the punish incorrect stage where rats were required to initiate each trial by nose-poking the food port as done previously, followed by selection of the pseudorandomly illuminated window. Correct touches to the illuminated window were rewarded with 1 food pellet, while incorrect touches were punished with illumination of the house lights and 5 s time out followed by a correction trial. During correction trials, the stimuli were repeatedly presented until a correct touch was made, triggering a food reward. A correct touch on a correction trial was recorded as a completed selection trial and followed by initiation of a new trial. The criterion for punish incorrect was 100 trials in 1 h, with greater than 80% correct, with accuracy calculated for the initial stimuli presentation only.

Rodent PAL requires the animal to differentiate between two different stimuli presented simultaneously in 2 of the 3 response windows pseudorandomly (Fig. 1; Fig. 2). Each stimulus (negative images of a flower, airplane, and spider) was correct only when paired with its respective location. The flower was always correct in the left position, the airplane in the centre position, and the spider in the right position. Correct responses were rewarded and punished in the manner previously described for punish incorrect training.

The current experiment included some adjustments to previous PAL experiments conducted in our lab. In Lins et al. [24], criteria of 100 trials, 80% accuracy for two consecutive days, and 90 trials, 80% accuracy, for 3 consecutive days were used for the punish incorrect stage and PAL task, respectively. In the present experiment, we lowered the criterions to 100 trials, 80% accuracy for one day, for punish incorrect, and to 65 selection trials, with 65% accuracy for one day in PAL. These criteria were selected based on pilot data (unpublished) in order to reduce the possibility of ceiling effects. Correction trials were not included in the count of selection trials completed and accuracy was calculated for the initial presentation of a stimulus pair only.