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Stress enhances return-based behaviors in Wistar rats during spatial navigation without altering spatial performance: Improvement or deficit?

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HIGHLIGHTS

- Spatial performance was not affected by repeated stress in the MWT.
- Spatial performance was not affected by repeated stress in the ZT.
- Search strategy on memory days in the ZT was significantly affected by stress.
- Search strategy on learning days in the ZT was not affected by stress.

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ABSTRACT

Stress is frequently reported to be deleterious to spatial learning and memory. However, there are many instances in which spatial performance is not affected by stress. This discrepancy observed across different studies, in addition to the animals' strain and gender, may be caused by the type of the task employed to assess stress-related behavioral changes. The present experiments set out to investigate the effects of repeated restraint stress (3 h/21 days) on spatial performance within the two wet-land (Morris water task; MWT) and dry-land (the ziggurat task; ZT) tasks for spatial learning and memory in adult male Wistar rats. All rats were tested before and after stress treatment. Stressed rats gained less weight than controls. Stress also enhanced circulating corticosterone (CORT). We did not observe a deleterious effect of stress on spatial learning and memory in either of the tasks: both groups successfully performed the wet- and dry-land tasks across all spatial testing days, indicating intact spatial cognition in control and stress rats. However, daily restraint stress for 21 days significantly caused enhancement in rats' memory-dependent returns during the goal-directed investigation in the ZT. The number of returns on learning days was not affected by repeated restraint stress. Return-based spatial investigation induced by stress only on memory days in the dry-land task, not only emphasize on the task-dependent nature of stress-related alterations, it may reveal one of the silent, but arguably deleterious effects of stress on spatial memory in Wistar rats.

1. Introduction

An increased body of evidence suggest that spatial performance is exquisitely sensitive to psychological stress [9,13,30,33,43]. Stress can produce enhancement [11,26], impairment [31,40], or no effect on spatial learning and memory [2,54]. Therefore, although differences in stress effects observed across different studies may be attributed to sex differences, animal strain, type of stressor, disparity in task demands, and duration of stress [1,31,38,56], the nature of stress-induced cognitive alterations and their alternative behavioral reflections are still a matter of further investigation.

Since several cognitive components are engaged in spatial performance, different tasks in animal studies reflect different functional competencies. For instance, it has previously been reported that rats and mice show different spatial performance in the wet- and dry-land tasks [23,55] indicating that (1) the procedural demands for spatial

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assessment may reveal alternative aspects of spatial performance, and (2) the observed differences in spatial performance does not necessarily display differences in spatial abilities. Task difficulty, training and testing procedures and the level of motivation during spatial navigation are shown to be the most important sources of the task-dependent differences reported by different investigations [7]. Notably, studies on the type of tasks employed to examine stress-induced spatial alterations in rats provide additional insights into the contributing task parameters. Considering the nature of aversively versus appetitively motivated tasks [4], for example, it is commonly believed that the repeated stress outcome in aversively motivated tasks (e.g. Morris water task; MWT) may be very different than revealed by the appetitive paradigms (e.g. the ziggurat task; ZT). These findings, in general, support the notion that interactions between repeated stress and task-specific procedures may influence the spatial learning and memory in an extremely dynamic labile or even different manner.

Challenges on the effects of psychological stress on spatial cognition processes do not seem to be solely restricted to the procedural parameters. Strain differences may also play a key role in the diversity of the stress-induced spatial changes [21,31]. Because of differences in stress sensitivity, it seems that individual rat strains have unique profiles in response to stress.

The principal goal of the present study is to evaluate the effects of repeated stress on spatial performance in Wistar rats using the MWT [34] and the ZT [10], two sensitive wet- and dry-land arenas developed to measure spatial learning and memory. Two experiments were conducted to investigate whether previous psychological stress influences spatial performance in the wet- and dry-land environments. The pattern of the return-based spatial investigation or the act of going and coming back shown by rats during the goal-directed navigation after stress was specifically examined in the ZT.

2. Material and methods

2.1. Subjects

Forty-three adult (3–4 months old) male, Wistar rats weighing 220–303 g, were used. The animals were housed in pairs under a 12:12 h light/dark cycle with light starting at 07:30 h and the room temperature set at 22 °C. All testing and training was conducted during the light phase of the cycle at the same time of day. The animals received water ad libitum and were weighed daily throughout the experiments. Daily weight measures were obtained for four time points: (1) training and habituation phase, 8 days, (2) pre-stress spatial testing, 6 days, (3) during stress, 21 days, and (4) post-stress spatial testing, 6 days. Each rat was also handled, approximately 2–3 min for five consecutive days prior to any experimental manipulation. All procedures were approved by the local Ethical Committee and were performed at the Avicenna Institute of Neuroscience (AIN).

2.2. Experimental procedures and data collection

2.2.1. Experiment 1: Repeated restraint stress and spatial performance in Morris water task (MWT)

2.2.1.1. Blood samples. Twenty-one rats (control, $N = 10$; stress, $N = 11$) in this experiment underwent blood sampling. Blood samples were taken the day prior to restraint stress (pre-stress). Blood sample were also taken after stress on the tenth day (acute time point) and twenty-first day (chronic time point) of treatment. All samples were collected in the morning hours (11:00–11:30 am). Rats were placed in a restraint tube and blood samples were obtained by tail notch with a scalpel blade [5]. Pre-stress blood was collected from all rats within the first 1–2 min of being placed in the tube to ensure circulating corticosterone (CORT) levels did not have the chance to significantly increase in response to the brief stress of the procedure. Acute and chronic time blood samples were collected using the same procedure. The same sampling procedure was applied to stress rats on the two time points while they were still in the tubes. All blood samples (0.4–0.6 mL) placed in heparinized tubes were then transferred to centrifuge tubes and plasma was obtained by centrifugation at 8000 rpm for 8 min. The plasma samples were stored at −20 °C until analyzed for CORT concentration.

2.2.1.2. Repeated restraint stress. For restraint stress, animals in the stress group were maintained in custom-made transparent Plexiglas tubes (8 cm inner diameter) of adjustable length, from 8:00 am to 11:00 am for 21 consecutive days. All stress rats were stressed simultaneously in a quiet room with approximately 100 cm distance between restraint tubes [9,13]. The tubes allowed the complete restraint of the animals while at the same time allowing them to breathe through perforated ends of the tube. The tubes maintained the animals in a standing position without compression of the body. Rats were also manually vibrated for 5–10 s in every 15 min of stress phase in order to prevent the habituation effect of the given stress. Control animals were transported to a room near the stress room but remained undisturbed in their home cages during the stress duration. All animals including controls received equal amounts of handling daily throughout the experiments. Both control and stress groups were then tested in the MWT to determine the functional effects of restraint stress on their spatial cognition.

2.2.1.3. Morris water task (MWT). The moving hidden platform version of the Morris water task (MWT, [34]) was employed to assess spatial learning and memory. The training and testing procedures were previously published in detail [9,13]. Briefly, animals were taught to escape from the water (21 ± 1 °C) by climbing onto the hidden platform. Each trial began with the rat being placed in the pool at one of the four cardinal compass positions around the perimeter of the pool according to a pseudo-random sequence. The maximum duration of each swim trial was 60 s. Animals in this experiment were tested in six trials per day for 6 consecutive days of training before and after stress. In this version of the task, the hidden platform is moved to a new location every second day. In other words, the platform remains in the same location for two consecutive days. Because the location of the hidden platform was different every 2 days, all odd days were called “different-platform” or *learning* days, and even days were called “same-platform” or *memory* days. The movements of the animals were recorded and analyzed by an image-computerized tracking system (HVS Image, UK).

2.2.2. Experiment 2: Repeated restraint stress and spatial performance in the ziggurat task (ZT)

Twenty-two rats (control, $N = 10$; stress, $N = 12$) were used in this experiment. Animals were food-restricted prior to baseline training and testing in the ZT, and maintained at about 90% of their initial body weight throughout the experiment. To maintain body weight, rats were given an additional amount of food in their home cage at least 3–4 h after completion of the behavioral training and testing. Because animals were housed in pairs, they were weighed daily throughout the experiment in order to monitor their food consumption.

2.2.2.1. Blood samples. Blood sample procedures used in the present experiment were identical to those described in Experiment 1.

2.2.2.2. Repeated restraint stress. The stress procedure used was identical to those described in Experiment 1. Following the 21-day (3 h/day) restraint stress, and in order to assess spatial learning performance of the animals, all groups were tested in the standard version of the ZT.

2.2.2.3. Ziggurat task (ZT). All procedures for ZT testing were the same as that previously reported by [12]. Briefly, all animals were food-restricted one week prior to habituation sessions and spatial testing. Rats also spent 4 days to habituate to the ZT environment. After habituation, the testing sessions were conducted over 6 trials per day for 6