

Effect of paradoxical sleep deprivation and stress on passive avoidance behavior

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Abstract

Previous studies have shown that several types of stress can induce memory impairment. However, the memory effects of paradoxical sleep deprivation (PSD), a stressor in itself, are unclear. We therefore compared passive avoidance behavior of rats undergoing PSD and PSD stress yoked-control (PSC) using the “reversed flowerpot method.” When rats were kept isolated on a PSC platform for 24 h immediately after criterion training, retention trials showed impaired aversive memory storage. When delayed for 24 h after criterion training, PSC stress did not disrupt retention performance. In rats subjected to PSD, either immediately or 24 h after criterion training, there was no disruption of aversive memory consolidation. These results suggest that, during stress, paradoxical sleep plays a role in erasing aversive memory traces, in line with the theory that we “dream in order to forget.”

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1. Introduction

Exposure to acute or chronic stress influences cognitive function such as memory, problem solving and thought processes [1–3]. It has been shown that stress can modulate memory both in a positive and in a negative way, depending on the specific characteristics of the stressor, the individual differences and the type of learning that is being measured. It has been shown that mild stress may improve cognitive function, most likely mediated by low levels of stress hormones, while severe or chronic stress disrupt cognitive function through high levels of stress hormones [4,5]. However, the memory effects of sleep deprivation, a psychological as well as a physiological stress, are unclear because it also induces cognitive effects independent of stress [6–8].

Electroencephalographic (EEG) recordings have shown several stages of sleep, each characterized by distinctive

brain-wave frequencies. Broadly, sleep can be divided into paradoxical sleep or rapid eye movement sleep (REM sleep) and non-REM sleep. Paradoxical sleep, which makes up ~20% of sleep time in adult humans, is interspersed with non-REM sleep every 30–40 min throughout the night. It is during paradoxical sleep that dreams are experienced. Paradoxical sleep is characterized by typical low-amplitude, relatively fast rhythms on EEG recordings, termed cortical EEG desynchronization, similar to those during waking state, as well as by ocular saccades. In this stage, physiological parameters, such as heart rate, breathing rhythm and blood pressure, also resemble those in the waking state. However, muscle tone decreases to the point of paralysis.

Paradoxical sleep deprivation (PSD), by itself or as a consequence of the technique to induce it, is a stressor and influences a number of physiological mechanisms, such as food intake, thermoregulation, immune function and modulation of serotonergic, dopaminergic and cholinergic activity [9–14]. In addition, PSD also has effects on cognitive function not directly related to stress. In contrast to the clear physiological effects of PSD, however, its effects on cognitive function still remain unclear. It has

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been suggested that information acquired during wakefulness may be reprocessed “off-line” during the following paradoxical sleep in human and animals [7,15–17]. Paradoxical sleep increases have been observed following acquisition of information in behavioral tasks and following exposure to enriched environments [18–23]. A number of studies have suggested that PSD impairs memory consolidation in an eight-arm radial maze, in Morris water maze and in other mazes [23–25]. On the other hand, there is also evidence to suggest PSD has no effect on or even facilitates memory consolidation in many memory tasks [21,26–33]. These studies used a variety of behavioral models, ages and strain of animals and intervals between stress and behavioral tests.

The aim of the present study was to reevaluate the effect of PSD and stress on memory. The usual technique studying the effect of PSD on memory function is the “reversed flowerpot method,” which includes keeping the animals on a small platform (PSD platform) for PSD or a larger platform as yoked-control [34]. Thus, stress was similar in the two groups [35], but one group was allowed paradoxical sleep whereas the other group was not. In our protocol, the platform was wet, adding to the stress level of the rats. Because the effect of stress is time dependent, rats were submitted to the corresponding treatment either immediately after the last trials or after a 24-h interval. A step-through criterion task [36] was used to assess learning and memory. Unlike previous studies, the rats we used were ~1 year old (middle-aged) because, at this age, the subjects are more sensitive to the effect of stress on sleep, neurotransmitters release and other changes than young subjects [37,38].

2. Materials and methods

2.1. Subjects

Male and female Wistar rats of 13 months of age (300–400 g body weight) were used. They were housed five or six per group in large plastic cages (48 × 36 × 20 cm) with food and water available ad libitum. The male and female rats were kept in separated cages. The animals were maintained on a 12-h light/dark cycle (lights on from 07:00 to 19:00 h). Animals were exposed to the experimenter and the home cage environment for 1 week before the experiment started. Behavior testing was performed between 08:30 and 12:00 h. The experiments were conducted following the guidelines for the National Care and Use of Animals approved by the National Animal Research Authority.

2.2. Apparatus: reversed flowerpot for sleep deprivation

A plastic container (30 cm in diameter and 45 cm in height) had a wooden PSD platform (5 cm in diameter, 1 cm above the water) mounted in the center and was filled with

15 cm deep water. Because the PSD platform is narrow and paradoxical sleep is accompanied by muscle relaxation, the rat would fall into the water or get part of its body wet at the beginning of paradoxical sleep.

PSD stress yoked-controls (PSC) were kept in similar containers, except that the wooden platform was larger (15 cm in diameter), allowing the animal paradoxical sleep without dropping into the water. Platforms were moist, as the wood would absorb water.

2.3. Behavioral apparatus and method

Experimental sessions were conducted using a GEMINI Active and Passive Avoidance System (San Diego Instruments, USA), which has two compartments and was connected to a computer. Each animal was handled by the experimenter daily for 1 week before the experiment and was accustomed to the behavioral apparatus for 2–3 min the day before the training session.

A step-through “Trials to Criterion” procedure was used in the training session on the first day (D1). The animal was given a foot shock (0.8 mA, 3 s) whenever it entered the dark compartment. The training session ended after the animal stayed in the bright compartment for more than 300 s. After training, the rats were placed onto the PSD platform or the large platform immediately or 24 h later or were brought back to their cages. It was observed that almost every PSD rat fell into the water at least once during the period on the platform. Therefore, animals on the large platform were pushed into the water once by the experimenter, at least 2 h after being placed on the large platform, to experience comparable stress as PSD animals.

All animals were tested for retention on 4 (D4), 7 (D7), 14 (D14) or 49 (D49) days after the learning trials. No electric shock was applied when rats entered the dark compartment during the retention test. Animals were directly brought back to their home cages after they entered the dark compartment within 300 s or if they stayed in the bright compartment for 300 s.

Thus, the experimental groups (Fig. 1) were as follows: Group A: “Dry” control group (dry-control, $n = 10$), animals were brought back to their cages after they were trained to criterion on D1. Group B: Immediate posttraining PSD group (PSD-0, $n = 10$), animals were deprived of paradoxical sleep for 24 h on a PSD platform immediately after they were trained to criterion. They were brought back to their cages when PSD was completed on D2. Group C: Immediate posttraining PSC group (PSC-0, $n = 10$), animals were placed on a large platform for 24 h immediately after they were trained. On D2, they were brought back to their cages. Group D: 24-h delayed posttraining PSD group (PSD-24, $n = 9$), animals stayed in their cages for 24 h after they were trained. On D2, they were subjected to 24 h of PSD, after which they were taken back to their cages on D3. Group E: 24-h delayed posttraining PSC group (PSC-24, $n = 10$), animals stayed in their cages for 24 h after they were trained. On D2, they were

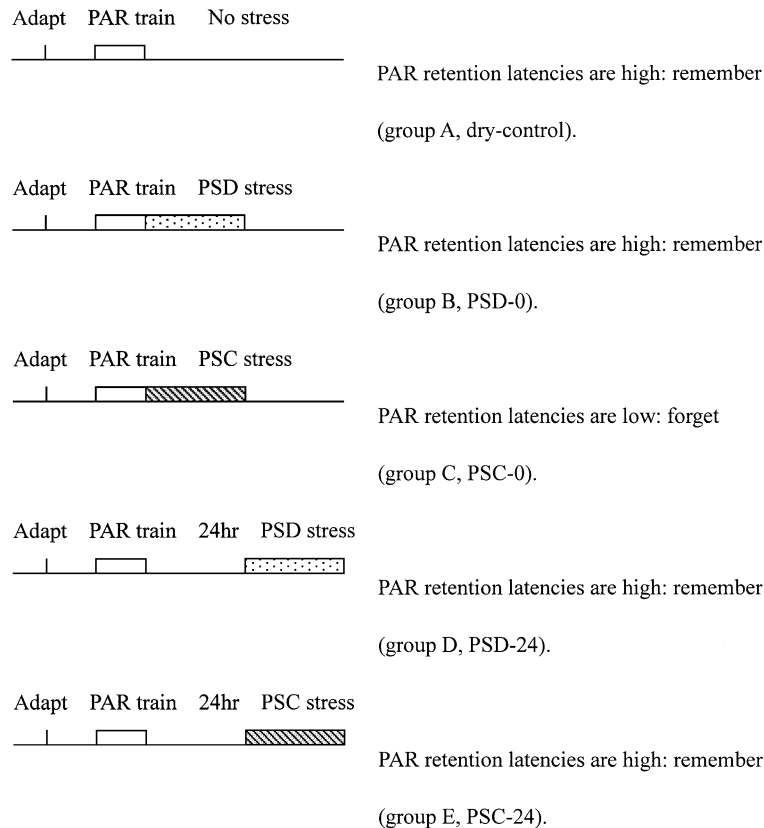


Fig. 1. Group A: dry-control animals; Group B: immediate posttraining PSD animals (PSD-0); Group C: immediate posttraining large platform-stressed animals (PSC-0); Group D: 24-h delayed posttraining PSD animals (PSD-24); Group E: 24-h delayed large platform-stressed animals (PSC-24). PAR: passive avoidance response.

placed onto a large platform for 24 h and were taken back to their cages on D3.

2.4. Analysis of data

The statistical package Systat 9 was used. Differences between treatment groups were assessed by analysis of variance (ANOVA). We compared each treatment group with the dry-controls in an ANOVA including Group and Day (Session) as main factors. Thus, we report main effects of Group and Time after learning (Day, Session) and interactions where they were found. Between-group comparisons were done with Fisher's Least Significant Difference Test (LSD).

3. Results

Performance of Group C (immediate posttraining PSC group, PSC-0) was lower than that of Group A (dry-controls). ANOVA on the time course of changes in latency revealed a significant overall reduction in this group [$F(1,18) = 5.32, P = .033$], whereas none of the other groups showed such a difference with controls (Figs. 1 and 2). Thus, immediate posttraining large platform stress (Group C, PSC-0) caused a reduction in test latencies, but im-

mediate posttraining PSD (Group B, PSD-0) did not. After a 24-h delay, neither stress nor PSD caused changes in performance latency (Fig. 2).

Four days after the stress or PSD, retention performances for Group B (immediate posttraining PSD animals, PSD-0), Group C (immediate posttraining large platform stress, PSC-0) and Group D (24-h delayed PSD animals, PSD-24) tended to be lower compared with those for Group A (dry-control animals), although this difference failed to reach statistical significance. When retention tests were conducted again 7, 14, 21 or 49 days after the stress, the performances for the two PSD groups returned to levels seen in the dry-control group (Fig. 2A). In contrast, at 7 and 14 days, but not at 21 and 49 days after the stress, latencies in Group C (immediate stress, PSC-0) remained reduced compared with the other groups (Fig. 2A). ANOVA showed significant overall differences between groups on D7 and D14 [$F(4,44) = 2.98, P = .029$ and $F(4,44) = 2.66, P = .045$]. Post hoc comparison with Fisher's LSD showed a significantly lower latency in the Group C versus controls on D7 ($P = .046$) and D14 ($P = .003$).

Also, when the proportion of animals reaching criterion in the retest was taken as the variable tested (Fig. 2B), Group C showed significant deficits on D7 [$F(1,18) = 6.08, P = .024$] and D14 [$F(1,18) = 6.82, P = .018$] after stress.

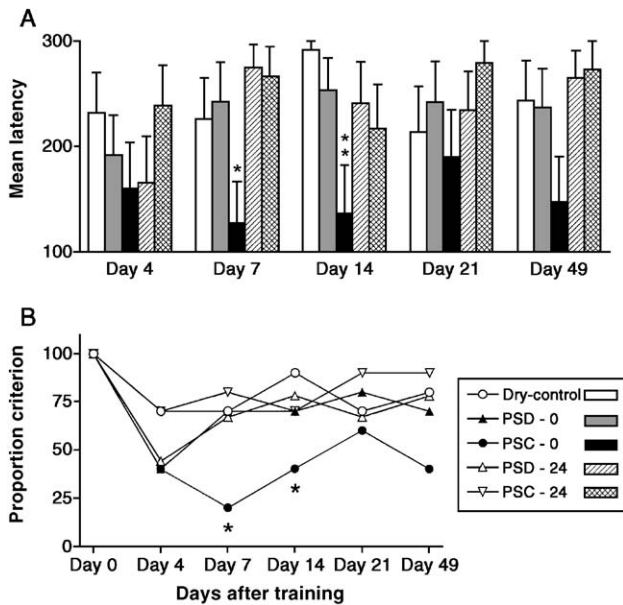


Fig. 2. The effect of immediate or delayed platform yoked-control stress or PSD on retention latencies in a step-through paradigm. Group A are Dry-controls, trained on D1, then returned to their cages; Group B (PSD-0) are immediate posttraining PSD animals subjected to PSD platform stress and PSD for 24 h immediately after training; Group C (PSC-0) are immediate posttraining large platform-stressed animals subjected to stress for 24 h immediately after training; Group D (PSD-24) are 24-h delayed posttraining PSD animals subjected to PSD platform stress and PSD after a 24-h delay after training; Group E (PSC-24) are 24-h delayed large platform-stressed animals subjected to stress after a 24-h delay after training. Data are expressed as means \pm S.E.M. (Panel A) latency to enter the dark compartment on days 4, 7, 14, 21 and 49 after the training session. Panel B shows the proportion of rats reaching the 300 s criterion in the retest. * $P < .05$, ** $P < .01$ for difference in retention performance of Group C versus Group A on D7 and D14.

There was no significant difference between groups in the amount of foot shocks that animals received because all rats learned to stay in the bright compartment for more than 300 s after they were shocked one to three times during the training session. Most rats reached criterion after one or two shock trials. There was no difference in retest performance between the fast learners who reached the learning criterion only after one shock and the slow learners who needed more foot shocks to reach the criterion (up to three times). Similarly, there was no difference in training and retention performance between male rats and female rats (data not shown).

4. Discussion

In our present study, PSD was induced by keeping middle-aged rats on a PSD platform (“reversed flowerpot method”), whereas non-PSD controls were kept on a larger platform. Both groups were expected to experience similar levels of stress, the effect of which on memory consolidation was measured in a step-through paradigm. Our present

study found that a posttraining stress on the larger platforms, allowing rats paradoxical sleep, significantly impaired memory consolidation, as measured by retention trials on D7 and D14. In contrast, when the animals were subjected to posttraining stress on the PSD platform, accompanied by PSD, no memory impairments were observed (Fig. 2).

Our results are consistent with those of Smith et al. who found that PSD following the training session enhanced the avoidance performance after a 7-day retention interval, while this effect was not obtained when animals were kept on larger platforms [32]. Also, other studies have shown effects of stress on memory consolidation [39,40]. In our study, the extent of stress was more severe, as the rats were kept on wet platforms and each fell into water at least once. Moreover, the animals were middle aged, which has been shown to be associated with increased sensitivity to stress [37]. They may show increased vulnerability of sleep to stress hormones, possibly resulting in impairments in the quality of sleep during periods of stress [37]. Despite these methodological differences, in our study, PSD animals showed no lasting disruptions of memory consolidation, which supports the assumption of Vertes and Eastman [28] that paradoxical sleep serves no role in the processing or consolidation of memory. A number of reports have shown that PSD has no or even facilitative effect on consolidation or acquisition of memory on a variety of tasks in animals [21,26–33]. Although it is also widely acknowledged that depriving animals of paradoxical sleep pretraining or post-training impairs acquisition and consolidation of memory [30,41,42], many of the PSD techniques include various forms of stress, including isolation, wetness, confinement, movement restraint and frustration, which may have been responsible for the disruption of memory. Further, in humans, it is unclear whether paradoxical sleep contributes to memory consolidation. Numerous studies were conducted in patients using antidepressant drugs or with pontine lesions who severely lack paradoxical sleep but show no impairment of memory [43,44].

In the present study, 4 days after stress, both PSD groups also tended to show reduced latencies. We previously found that retention latencies for PSD animals were significantly decreased compared with the dry-control group when the retention test was conducted immediately following PSD treatment (unpublished results). These memory deficits may not be specific to PSD but rather a more general effect of physical stress leading to locomotor hyperactivity. In the step-through paradigm, this may have led to reduced latency scores. This effect diminishes after a certain period of time in our present experiments shown by the recovered latencies on D7 and D14 compared with that on D4. Thus, the effect of PSD-associated stress on memory was small and temporary, partly due to the physically debilitating effects of PSD, which may withdraw as time goes on.

In contrast to the short-lasting effect of PSD on memory, immediate posttraining large platform stress caused a

significant and long-lasting disruption of memory consolidation. Clearly, the difference between these groups lies in the paradoxical sleep that large platform-stressed animals had during the stress period, as opposed to the PSD platform-stressed animals. This would indicate that paradoxical sleep plays a role in forgetting of the aversive information obtained during the learning trials. The influence of loss of nonparadoxical sleep cannot be fully rejected because the PSD animals may also have lost some nonparadoxical sleep during PSD by this method. However, PSD is likely to be the main contributor to this process because the “reversed flowerpot method” tends to deprive animals mostly of paradoxical sleep while allowing most other stages of sleep.

Dry-control animals did not show any impairment in memory even though they had paradoxical sleep after the training. The distinction between PSC and dry-control groups was that PSC animals had paradoxical sleep while experiencing the stress of staying on the platform, whereas dry-control animals had paradoxical sleep in their home cages without being exposed to any stress. Thus, it would suggest that particularly under stress paradoxical sleep may facilitate forgetting.

Studies have suggested a paradoxical sleep rebound after stress. For example, immobilization stress caused paradoxical sleep rebound in the following sleep period [45,46]. Moreover, increased paradoxical sleep also appeared in PSD animals after the treatment of PSD. However, because the performances for the large and PSD platform-stressed animals were evidently different, we suggest that paradoxical sleep rebound contributed little to memory process in our present experiment.

When rats were subjected to PSD or the large platform stress 24 h after training, no impairments were detected in either group, which was consistent with reports from other groups [39,40]. Memory information is obviously consolidated in a short period following the training; thus, the late stress had no influence upon memory consolidation.

In conclusion, disruption of memory consolidation was observed in rats subjected to a platform stress that allowed the animals to experience paradoxical sleep immediately after training. In contrast, rats subjected to platform stress and PSD showed a good performance. The difference between these two groups was paradoxical sleep, suggesting that this sleep stage, rather than stress of the isolation, moist environment procedure, might facilitate loss of the aversive memory of the learning procedure (Fig. 1). The inability to recall aversive information might be related to memory-erasing processes associated with paradoxical sleep, which may fragment memory traces and cause reverse learning. Because this is seen in PSC animals but not in dry-controls, this mechanism appears particularly operative under stress. These results suggest that, during stress, paradoxical sleep plays a role in erasing aversive memory traces, in line with the theory that “we dream in order to forget” [47,48].

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