EFFECTS OF REPEATED INTERMITTENT EPISODES OF SOCIAL STRESS ON THE ACQUISITION AND EXTINCTION OF A REWARD-SEEKING TASK

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INTRODUCTION

Social stress is a strong determinant of drug abuse (1), yet how and when stressful experiences make us more vulnerable to develop drug addiction is not fully understood. Intermittent social defeat stress increases drug self-administration and behavioral sensitization to psychostimulants weeks after the last stress episode (2), which suggests time-dependent neuronal adaptations in the brain reward system (3).

This study investigates whether repeated intermittent social stress changes reward-seeking behavior on the days in between stress episodes (Experiment 1) or weeks after the last stressful episode (Experiment 2). We also assessed anxiety-like behavior in the Elevated Plus Maze (EPM).

METHODS

Experimental procedure. Thirty-two male Long Evans rats (3-4 months of age) were food restricted (85% body weight) to perform two different experiments (Figure 1, Top). Experiment 1. Animals (n= 8, Control; n= 8, Stress) were trained in the Discriminative Stimulus reward-seeking task (DS Task, see below) (4) and then submitted to intermittent social defeat stress (Figure 1, bottom). Animals performed the DS Task on the days in between social stress episodes. Experiment 2. Animals (n=8, Control; n= 8, Stress) were submitted to intermittent social defeat stress and 4 weeks later trained in the DS Task to evaluate the acquisition and extinction of the task.

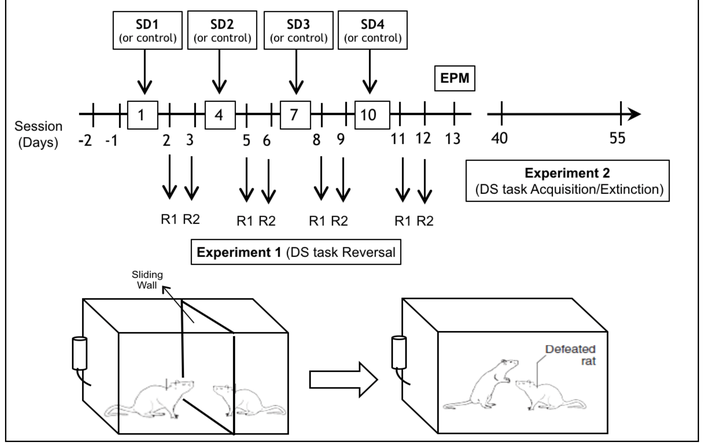
Intermittent social defeat stress. The rats assigned to the social stress group underwent 4 sessions of social stress via the resident/intruder paradigm (2), each separated by 3 days (Figures 1, top and bottom). The intruder rats were placed in the resident's cage (H x L x W: 45×61×61 cm) separated by a divider wall for 10 min, allowing sensory exposure, but no physical interaction. Next, the divider wall was removed, allowing the rats to interact. The interaction was stopped when either 6 attacks were witnessed, the intruder was in supine position for 5 s, or 5 min had elapsed. At that point, the divider wall was reinserted, and the intruder remained in the cage for 10 min. Control rats were moved to a different room for the same amount of time and handled for 5 min.

Discriminative Stimulus reward-seeking Task (DS Task).

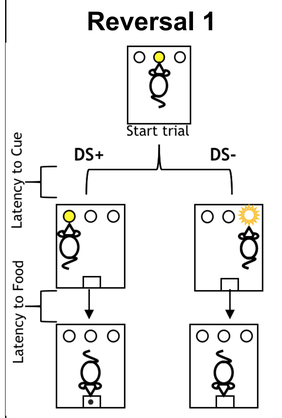
Experiment 1 (Figure 2). Rats were trained in the DS Task until criterion (< 35% DS- responses) and tested on the days in between social stress sessions. Rats started every trial by poking in the lit center hole. One second later the right or the left hole was illuminated (DS+, fixed light) and rats were required to poke to earn a sugar pellet. Nose pokes in the other hole (DS-, intermittent light) had no consequences (no pellet was delivered). Reward contingencies were reversed (Fixed light= no pellet; intermittent light= pellet) after every episode of social stress to test flexibility to stimulus discrimination. Number of nose pokes in the DS+ and DS- as well as the latencies to cue-response and food trough were recorded. Experiment 2 (Figure 3). Four weeks after the last social stress session (SD4), rats were trained in the DS Task. During the acquisition period, rats were rewarded with a food pellet for responding to a fixed light cue (DS+), but not to an intermittent light cue (DS-). Once the rats reached criterion (< 25% DS- responses), they were trained in the extinction protocol, in which responses to neither cue was rewarded. Number of nose pokes in the DS+ and DS- were recorded. The Elevated Plus Maze (EPM) was performed 4 days after the last social stress session. Rats were placed on the EPM apparatus for 5 minutes. The amount of time spent in both the open and closed arms, along with the number of crosses from one arm to another, were recorded.

Data analysis. Two-way ANOVAs with repeated measures were performed to analyze performance in the DS task. Independent Student *t* test was used to analyze EPM results.

1. Intermittent social stress protocol

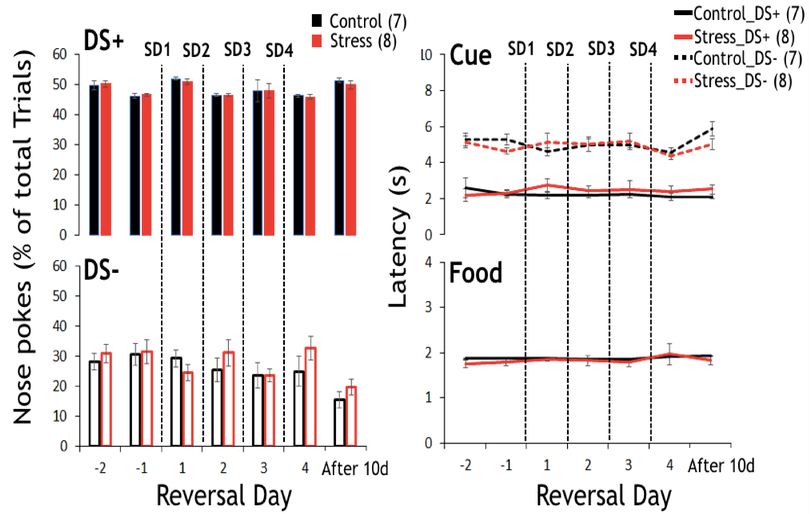


2. Social stress does not change reward-seeking performance on the days in between stress episodes (Experiment 1).

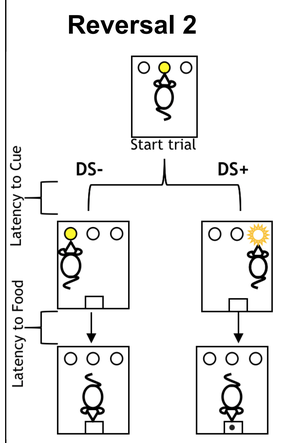


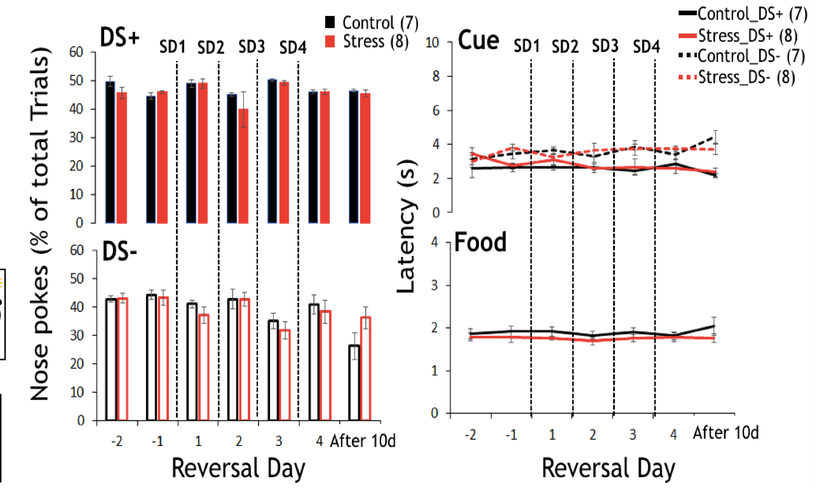
Number of Trials

	Control	Stress
-2	99 ± 11	103 ± 8
-1	102 ± 4	101 ± 4
1	108 ± 4	99 ± 5
2	106 ± 2	101 ± 4
3	105 ± 5	85 ± 13
4	101 ± 3	96 ± 3
after 10 d.	106 ± 4	100 ± 3



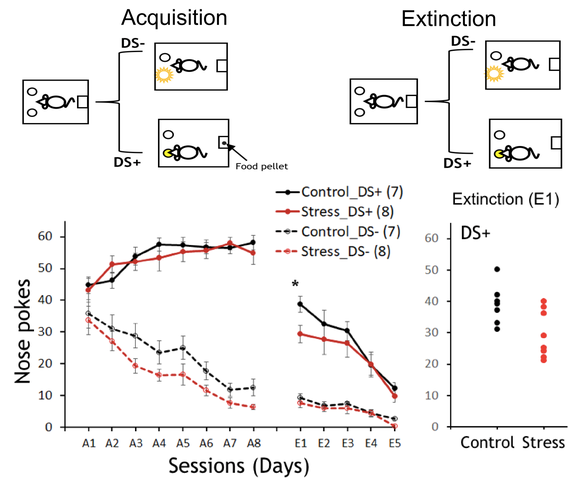
Left. Number of nose pokes in response to DS+ (top) and DS– (bottom) (50 trials each) on the days in between social stress episodes (SD1-4) as well as 10 days after the last stress episode (SD4), when reward contingencies were reversed to the original protocol (Reversal 1).
Right. Latency to respond to DS+ and DS- (top) and to the food trough (bottom) on the days in between social stress episodes (SD1-4) as well as 10 days after the last stress episode (SD4).





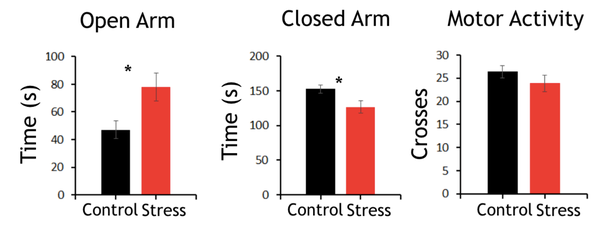
Left. Number of nose pokes in response to DS+ (top) and DS– (bottom) (50 trials each) on the days in between social stress episodes (SD1-4) as well as 10 days after the last stress episode (SD4), when reward contingencies were reversed to a new protocol (Reversal 2).
Right. Latency to respond to DS+ and DS- (top) and to the food trough (bottom) on the days in between social stress episodes (SD1-4) as well as 10 days after the last stress episode (SD4).

3. Social stress facilitates the extinction of reward-seeking in the long-term (Experiment 2).



Left. Number of nose pokes in response to DS+ and DS– during the acquisition (A1-8) and extinction (E1-5) of the DS Task.
Right. DS+ responses during the first extinction session (E1) (each dot represents one animal).

4. Social stress changes performance in the elevated plus maze.



SUMMARY AND CONCLUSIONS

1/ Intermittent social stress did not change DS Task performance on the days in between social stress episodes when reward contingencies were reversed (Experiment 1). These results suggest that intermittent social stress does not alter reward-seeking behavior in the short-term.

2/ Intermittent social stress changed extinction learning four weeks after the last social stress episode (Experiment 2). Stressed animals responded less times than controls to the DS+ during the first day of extinction learning. These results suggest that intermittent social stress alters reward-seeking behavior in the long-term.

3/ In the EPM, social stress animals spent more time than controls in the open arms, which could indicate an increased risk-taking behavior.

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4. D.E. Moorman and G. Aston-Jones (2015) Prefrontal neurons encode context-based response execution and inhibition in reward seeking and extinction. PNAS 112: 9472-9477.

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