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Repeated social defeat stress enhances the anxiogenic effect of bright light on operant reward-seeking behavior in rats

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Abstract

Repeated stress can trigger episodes of depression, along with symptoms of anhedonia and anxiety. Although often modeled separately, anxiogenic factors potently modulate hedonic, or appetitive, behavior. While repeated stress can increase anxiety and decrease appetitive behavior, it is not clear whether repeated stress can influence the impact of anxiogenic factors on appetitive behavior. This study tests whether repeated stress shifts behavior in a task that measures anxiogenic-appetitive balance. To test this, adult male rats were trained to lever press for sucrose pellet reward, and the effect of anxiogenic bright light on this behavior was measured. The impact of the bright light anxiogenic stimulus on lever pressing was compared between groups exposed to either daily repeated social defeat stress or control handling. We found that repeated stress reduced exploration in the open field and decreased social interaction, but had minimal effect on baseline lever pressing for reward. Repeated stress substantially enhanced the effect of anxiogenic bright light on lever pressing. This effect was greater two days after the last stress exposure, and began to diminish within two weeks. These data demonstrate that the anxiogenic and anhedonic features induced by repeated stress can be separately measured, and that the impact of anxiogenic stimuli can be greatly enhanced after repeated stress, even in the face of appetitive drive. The data also demonstrate that some apparent anhedonic-like effects of repeated stress can be due to increased sensitivity to anxiogenic stimuli, and may reflect an imbalance in an appetitive approach-withdrawal continuum.

Keywords

social defeat; repeated stress; sucrose; appetitive; anxiety; light

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1. Introduction

Two major symptoms of depression are anhedonia and anxiety. These symptoms are sometimes viewed as two components of a tripartite model of depression [1] or expressions of abnormalities along an appetitive approach-withdrawal continuum [2] that has become unbalanced [3]. However, anhedonic and anxiety symptom expression is variable across patients with major depression. Understanding the balance between anxiogenic and appetitive stimuli, and their imbalance in depression, may provide hints about the source of symptom variability in patients, and ways to selectively target depressive symptoms. A balance between approach and withdrawal can be modeled in studies that pit anxiogenic stimuli against appetitive stimuli, and often demonstrate that anxiogenic stimuli can suppress appetitive behaviors. This is commonly observed in tests of novelty-suppressed feeding and drinking [4], conditioned suppression [5] and a range of conflict tests [6, 7].

Repeated stress is a common trigger for depression. Repeated stress can induce symptoms of anxiety and anhedonia in humans [8–12] and in rodent models [13–17]. Stress may cause an imbalance between the response to appetitive and anxiogenic stimuli that is similar to depression. While much is known about how anxiety influences appetitive behavior, little is known about whether stress shifts this balance. Previous studies demonstrate that stress further suppresses drinking in a punished drinking Vogel conflict test [18], and further suppresses feeding in a novel environment [19–21], consistent with a shift in favor of anxiety. However, in previous studies a confounding deprivation state is often imposed on the rat to induce consummatory behavior. In addition, both the appetitive and anxiogenic components are sensitive to stress in those tasks, making it difficult to parse the influence of stress on anxiety and appetitive drive. This study will test whether repeated stress shifts the balance towards anxiety-like behavior when appetitive and anxiogenic conditions are overlaid, using an operant appetitive task that is less sensitive to the effects of acute or repeated stress (leverpressing for sucrose; [22–25]), and does not rely on induction of a deprivation state.

In these experiments, the effects of repeated social defeat on the balance between anxiety-like and appetitive behavior was measured. Bright light is an unconditioned anxiogenic stimulus [26–31] that can suppress appetitive behavior [32]. The interaction between anxiety and appetitive behavior was measured as the effects of bright light on conditioned operant lever pressing for a sucrose pellet. This was compared between adult rats that underwent repeated social defeat or control handling.

2. Materials and Methods

All studies had prior approval of the Rosalind Franklin University Institutional Animal Care and Use Committee, and complied with the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011). Care was taken to minimize animal distress and reduce the number of animals used.

2.1 Animals

Male Sprague-Dawley rats (Harlan Laboratories, Madison, Wisconsin) were used for these studies. Rats arrived at the Rosalind Franklin University vivarium at 53–58 days postnatal. The rats were provided water and food (Rodent Diet 2020× pelleted feed, Harlan Teklad) ad libitum. The housing rooms were set to a 12 h/12 h reverse light–dark cycle. Temperature was maintained between 64 and 79 F and the humidity was maintained between 30 and 70%. Rats were housed 2–3 per cage (polycarbonate solid bottom, 43.2 × 21.5 × 20.3 height, in cm), and were habituated to the facility for 1–2 weeks. Rats were handled daily for three days prior to initiation of training. All experiments were performed during the dark phase of the light-dark cycle.

2.2 Appetitive Conditioning

2.2.1 Apparatus—Conditioning was performed in an operant chamber (Med Associates, ENV-001, St. Albans, VT). The chamber was enclosed within a sound-attenuating cabinet (Med Associates). Each cabinet was affixed with an IR-sensitive digital camera (Fire-i, Unibrain, San Ramon, CA), infrared lighting, and dim white house lighting (20 lux). There was a fan in each cabinet that provided airflow and ~60 dB of ambient noise. The chamber was also fitted with 2 levers, one designated as the active lever and the other designated as the inactive lever, a cue light placed proximal to the levers, and a food receptacle where sucrose pellets were delivered.

2.2.2 Appetitive Conditioning Procedure—Rats were taken from their home cages and individually transferred by transport cages to the procedure room, where rats were placed in the operant chamber. After each session, rats were returned to their home cage. Each rat was habituated to the operant chamber for 2 sessions (one/day) before training. During these 2 sessions, sucrose pellets (45 mg) were placed in both the food receptacle and on the active lever to facilitate subsequent learning. After two habituation sessions, appetitive conditioning sessions began. Each appetitive conditioning session was 30 minutes in length. Sucrose pellets were remotely delivered when the rat neared the active lever, in order to facilitate differentiation between the active and inactive lever. When the rat pressed the active lever, the cue light (green, 2.5 cm diameter, 1 sec) was triggered immediately and a sucrose pellet was delivered 1 second after the cue light (Fixed ratio schedule (FR) 1). Manual delivery of pellets ceased by the third training session, as rats displayed preference for the active levers by this session. By the fourth day of training, and throughout the remainder of the entire experiment, rats consumed all delivered pellets. The number of presses on active and inactive levers was recorded for each session. All rats were required to meet a minimum criterion of 35 active lever presses by their final session in order to move onto the next phase of the experiment. This criterion was attained between 7 to 9 days. One day after criteria was reached, rats were tested at a FR 4 schedule for 30 minutes.

2.3 Treatment groups: Social defeat and control

There were two treatment groups: social defeat stress and control. These groups were further divided into two subgroups: rats tested after 2 days (n=8 rats/group, and a second cohort of n=8 rats/group for experiments with no anxiogenic light; see below, 2.6 Suppression of

Appetitive Behavior by Anxiety) and rats tested after 2 weeks (14–17 days; n=14 rats/group) for a total of 60 rats. This does not include 3 rats that were excluded because they did not reach lever pressing criteria. The number of rats was based on the expected effect size from other studies. Rats were matched for number of lever presses on the day that criteria was reached, and then randomly assigned into control or social defeat treatment group. Beginning one day after rats were tested at the FR 4 schedule, the rats were exposed to social defeat or control handling once/day for 5 consecutive days (Fig 1A). Social defeat began by transporting rats to a procedure room, and placing an "intruder" (male Sprague-Dawley rat) into the home cage of a "resident" (male retired breeder Long Evans rat, Harlan Laboratories). The two rats were allowed to be in physical contact with each other for a maximum period of 15 minutes. They were separated when one of the following conditions was met: submission of the intruder, 15 minutes with no submission, 10 attacks with no submission, 5 minutes without any attack, or any attack that wounded a rat. The intruder rat was separated using a wire mesh cage placed over the animal and it remained in the residents' cage for an additional 15 minutes to permit unrestricted visual, auditory, and olfactory contact without any further physical attacks. Intruder rats were rotated through different resident rats each day. Control handling comprised of placement of rats into a transport cage for 20 minutes. At the end of each session, rats were returned to their home cage. Experimental rats remained in their home cage for 2 days or 14–17 days before subsequent behavioral testing. After this interval, rats were tested in the open field, social interaction, operant lever pressing for sucrose pellets, and suppression of sucrose seeking by anxiogenic stimulus (Fig 1A). Over the course of these experiments, rats were weighed daily and their body condition was assessed.

2.4 Open Field

Rats were individually placed in an open field (61 × 89 cm) in a room with dim white light (20–25 lux; 5 min) and dim red light. Video was captured with an IR-sensitive camera (Fire-I, Unibrain). The field was divided into 16 boxes (15.2×14.8 cm) during analysis. The central area was defined as the middle four boxes. Exploration in the open field was quantified as the amount of time the rat was in the central area of the field (AnyMaze software, Stoelting Co., Wood Dale, IL).

2.5 Social Interaction

One day after the open field test, a novel rat was placed in the open field, and the test rat was placed in the same open field (5 minutes, same conditions as above). The novel rats had a body weight within 50 g of the test rats, and had previously been exposed to this open field for at least 10 minutes. As above, video was captured with an IRsensitive camera (Fire-I, Unibrain). The video was used by trained raters to measure the number of rat interactions and the total amount of time in contact. The raters showed >85% concordance in their tabulations before data was compiled. The trained rater manually tabulated the number of times the test rat approached and interacted with the other rat (defined as exploration of novel rat with nose) during video replay, and used a digital stopwatch to quantify the total time of interaction during a separate video replay.

2.6 Suppression of Appetitive Behavior by Anxiety

Rats were individually placed in the operant chamber for a period of 15 minutes, divided into three 5-minute phases. Rats could lever press freely to obtain sucrose pellets (FR 4) during all three phases. During the first 5-minute phase (OFF_1), lighting conditions were the same as light during training (20 lux). During the second 5-minute phase (ON), an anxiogenic bright light (200 lux) was illuminated in the cabinet. For the final 5-minute phase (OFF_2), the bright light was turned off and normal light conditions (20 lux) were restored. Active and inactive lever presses were recorded for each 5-minute session. The raw number of lever presses were used for analysis of the effects of light or stress. To compare effects of light and stress between the 2 day and 2 week delay testing conditions, the effect of light on the number of lever presses in control and stress groups was compared: [(OFF_1- ON) + (OFF_1 - (OFF_2)]/2. In a separate group of rats, the light remained off during all three phases of the session (N=8 rats/group).

2.7 Data Acquisition and Analysis

All data was video recorded using AnyMaze software. Detection thresholds for rat tracking were set based upon >95% convergence with a manual rater. Data analysis was performed using GraphPad Prism software (La Jolla, CA). Significance was set at $p < 0.05$. Data was tested for homogeneity of variance (Bartlett's test) and distribution normality (Kolmgorov and Smirnov test). If data passed these tests, parametric statistical approaches were used. When two factors were compared, a two-way ANOVA was used. Significant main effects and interactions were followed by post hoc Holm- Sidak tests, when appropriate. For one factor planned comparisons, two-tailed unpaired t-tests were used to compare groups. Raw values were used for most analyses. Where noted, the effect size was compared (defined as $[X_{stress} - \bar{X}_{control}]$, where X_{stress} = the values from individual rats from the stress group, and $\bar{X}_{control}$ = the average value of the control group).

3. Results

3.1 Social defeat effectively produces anxiety-like behavior

Separate groups of rats were tested 2 days or 2 weeks after the final stress or control session. Similar to previous studies, repeated social defeat reduced open field exploration (Fig 1B; time in center area; two-way ANOVA, main effect of stress p=0.006, F(1,40)=8.473) when tested 2 days (n=8 rats/group, p<0.05, post hoc Holm-Sidak) but not 2 weeks after the final stress (n=14 rats/group; p>0.05, post hoc Holm-Sidak). There was no effect of stress on total distance traveled (Fig 1B; two-way ANOVA, main effect of stress p=0.380, F(1,40)=0.788). Social defeat also reduced social interaction time (Fig 1C; two-way ANOVA, main effect of stress p=0.0004, F(1,40)=14.900) when tested 2 days (n=8/group; p<0.05, post hoc Holm-Sidak) or 2 weeks after the final stress (n=14/group; p<0.05, post hoc Holm-Sidak). Repeated stress did not significantly decrease the total number of contacts (Fig 1C; two-way ANOVA, main effect of stress p=0.821, F(1,40)=0.005), although there was a significant effect of stress on the duration of each social contact (Fig 1C; two-way ANOVA, main effect of stress p=0.002, F(1,40)=10.870). These data are consistent with increased anxiety-like behavior after social defeat, and a diminishment of the effects of social defeat stress on open field exploration over 2 weeks [effect of stress on center time, 2 day (−13.5 ± 3.2 s)

compared to 2 week (−4.4 ± 2.6 s), two-tailed unpaired t-test, p=0.040, t=2.201, df=20], but persistent effects of stress on social interaction over two weeks [effect of stress on time of interaction, 2 day (−13.4 ± 2.8 s) compared to 2 week (−12.9 ± 1.09 s), two-tailed unpaired t-test, p=0.860, t=0.178, df=20]. In addition, these data provide confirmatory evidence for effectiveness of this stress model.

3.2 Anxiogenic light decreases active lever presses in socially defeated animals

Only rats that displayed acquisition of lever pressing for sucrose to criteria were included in analysis. Rats were matched for number of lever presses on the day that criteria was reached, and then randomly assigned into control or stress treatment group. This matching was effective, as there was no significant difference between groups on active lever presses (Fig 2A; two-way ANOVA, main effect of group p=0.569, F(7,381)=0.326) or inactive lever presses (Fig 2A; two-way ANOVA, main effect of group p=0.232, F(1,381)=1.327) across acquisition. Rats displayed a significant increase of active lever-pressing across training (two-way ANOVA, main effect of session p<0.0001, F(1,381)=46.210), reflective of acquisition of this operant behavior.

Two days—When tested at 2 days after the final stress or control session, significant differences in lever-pressing behavior emerged. Anxiogenic light significantly reduced lever pressing compared to the no-light condition (Fig 2B; two-way RMANOVA, light × phase interaction p=0.048 F(2,28)=3.391). This verifies the effectiveness of bright light in reducing appetitive behavior under these conditions. This effect of light was evident in control and stress groups (Fig 3A, left; two-way repeated measures ANOVA, main effect of light p<0.0001, F(2,28)=81.100). However, there was a significant effect of stress that depended on the phase of testing (two-way repeated measures ANOVA, stress × phase interaction p=0.0005, F(2,28)=10.100). There was no effect of stress on lever pressing during the initial lights-off phase (p>0.05, post hoc Holm-Sidak, control compared to stress during first 5 minutes (OFF_1)), however, the effect of bright light (during lights-on phase (ON)) was significantly greater in social defeat rats (p<0.05, post hoc Holm-Sidak, control compared to stress during second 5 minutes). Furthermore, the bright light caused longer-lasting effects in the stress group, so that even when the light was turned back off, lever pressing did not return to the same level as control rats (Fig 3A, left; p<0.05, post hoc Holm-Sidak, control compared to stress during third 5 minutes (OFF_2)). This led to a significant difference in the total number of sucrose pellets delivered during the session (Fig 3A, right; two-tailed unpaired t-test, p=0.043, t=2.226, df=14). This difference is not simply due to differences in satiety, as stress did not influence lever pressing when comparing equivalent 5-minute phases with no bright light in a different group of rats subjected to the same experimental design (Fig 2C, left; two-way repeated measures ANOVA, main effect of stress p=0.837, F(1,14)=0.044, n=8 rats/group), and there was no significant effect of stress on the total number of sucrose pellets delivered during the testing session (Fig 2C, right; two-tailed unpaired t-test, p=0.843, t=0.202, df=14).

Two weeks—When tested at two weeks after the final stress or control session in a separate group of rats, bright light still significantly decreased lever pressing (Fig 3B; two-way repeated measures ANOVA, main effect of light p<0.0001, F(2,52)=19.500).

Furthermore, the effect of bright light was significantly greater in social defeat rats ($p<0.05$, post hoc Holm-Sidak, control compared to stress during second 5 minutes (ON)). However, when the light was turned back off, the stress group recovered to lever-pressing levels equivalent to controls (Fig 3B, left; $p<0.05$, post hoc Holm-Sidak, control compared to stress during third 5 minutes (OFF_2)), and stress did not lead to a significant difference in the total number of sucrose pellets delivered during the session (Fig 3B, right; two-tailed unpaired t-test, $p=0.407$, $t=0.842$, $df=26$). Furthermore, when comparing the effect of bright light on lever pressing between 2 days and 2 weeks, there was a main effect of stress (Fig 3C, left; two-way ANOVA, main effect of stress $p=0.009$, $F(1,40)=7.46$, stress × time interaction $p=0.042$, $F(1,40)=4.417$). Stress had a greater impact when measured after 2 days compared to 2 weeks (Fig 3C, right; two-tailed unpaired t-test, $p=0.039$, $t=2.211$, $df=20$).

4. Discussion

The present study demonstrated that repeated social defeat stress shifted the balance between approach and withdrawal behavior. Anxiogenic bright light suppressed leverpressing for a reward. Stress enhanced this suppressive effect of anxiogenic bright light. This effect of stress was not explained by reduced basal reward seeking behavior, because stress had minimal effect on lever pressing to obtain a reward when the bright light was not present. Instead, the effects of stress are most likely due to enhanced impact of anxiogenic stimuli on reward-seeking. In support of this, repeated social defeat stress was anxiogenic, decreasing exploration in the open field and decreasing social interaction. In addition, the effects of stress on the interaction between appetitive and anxiogenic stimuli lasted at least 2 weeks after the final stress exposure, mirroring some of the enhanced anxiety behavior in the social interaction test.

Previous studies demonstrated that repeated stress suppresses unconditioned approach of appetitive stimuli, such as food and sucrose. This is often interpreted as anhedonia-like behavior. However, in many studies, a confounding deprivation state is introduced by food or water restriction. Furthermore, in many studies that measure appetitive approach, there is a component of anxiety-like behavior that must be overcome by the rodent [33–38]. This anxiety component is sensitive to stress [39–45] and may produce apparent decreased reward seeking by increasing anxiety-like withdrawal behavior. However, stress has less impact on simple conditioned appetitive behaviors [22–25], as further affirmed in the current study. Because this conditioned appetitive behavior is not strongly impacted by stress, it provides an opportunity to measure the effect of stress on the interaction between anxiogenic and appetitive stimuli. The appetitive component (lever pressing) was separately measureable, not significantly altered by stress, and sensitive to anxiogenic stimuli. We found that this sensitivity to anxiogenic bright light was selectively enhanced by repeated stress.

In the current study, repeated stress had minimal influence on basic characteristics of lever-pressing for sucrose pellets, consistent with previous studies [22, 23, 46] (but see [47]). This could be interpreted as minimal effect of stress on reward processing per se. Repeated stress often shifts choice in sucrose preference test and consumption of appetitive foods under certain situations, such as limited access to the palatable substance [48–51]. However,

neither acute nor repeated stress strongly influences consumption of freely available palatable food, with some evidence of repeated stress increasing consumption [52–54]. One possible interpretation is that stress has a more selective suppressive effect on appetitive behavior when there are conflicting or opposing components. In fact, acute stress can reduce lever pressing for reward in such circumstances. For instance, acute stress reduces preference for larger yet costlier rewards [24], and reduces reward-related responding if the effort requirement is very demanding (e.g. >FR50; [55]). Stress can also enhance the motivational effects of downward shifts in reward magnitude on reward-seeking [56] and the effects of reward devaluation via satiety manipulations. [57]. These effects of stress appear to modify the perception of the value of an appetitive stimulus, particularly when there is some change in its relative value. This may be reflected by negative cognitive bias in patients with depression [58–60]. Similarly, an anxiogenic stimulus can devalue a co-occurring appetitive stimulus, and increased anxiogenicity after stress may further devalue the appetitive stimulus. In several animal studies where anxiogenic, appetitive, or ambiguous stimuli are presented after repeated stress, animals tend to make choices guided by avoidance of anxiogenic stimuli instead of appetitive stimuli [61–63] or "pessimistic" choice of a lesser reward [64, 65].

Activation of the ventral striatum is closely associated with reward processing in humans and rodents, while activation of the amygdala and extended amygdala is associated with anxiety. A wide range of neural structures is sensitive to acute and repeated stress. Acute stress or repeated stress can lead to reduced ventral striatal processing of reward and reward-related cues in humans [66–72]. Similarly, depression is also associated with reduced activation of the ventral striatum in response to rewards and cues associated with rewards [68, 73]. Aversive stimuli reduce the response of striatal regions to appetitive stimuli [74]. On the other hand, acute aversive or anxiogenic stimuli recruit the amygdala and extended amygdala [75–79]. Extended amygdala circuitry may be recruited into modifying behavior more readily when a prolonged anxiogenic state is induced [80, 81], after a history of stress exposure [81–89], and in patients with depression [90–93]. The increased activity of the amygdala and associated increases in anxiety may, in turn, modify activity of the ventral striatum and appetitive behavior. In rodents, the impact of nucleus accumbens manipulation on appetitive function can be strongly modified by anxiogenic environments [94]. Lever pressing for cued delivery of a reward relies on a pathway from the basolateral amygdala to the ventral striatum [95, 96], and anxiogenic influences of bright light are mediated by the bed nucleus of the stria terminalis (BNST) portion of the extended amygdala [97]. There is evidence for a direct pathway from the BNST to the ventral striatum [98–101], and ventral tegmental area [102, 103]. In addition, the BNST can modulate NAc-mediated motivated behaviors [104–109]. Thus, increased sensitivity of extended amygdala circuitry to anxiogenic stimuli that occurs following repeated stress may lead to a greater ability of this system to suppress ongoing reward seeking behaviors that are mediated, in part, by the NAc. As such, the shift in reward-seeking behavior observed after repeated stress in the current study may reflect imbalance in the recruitment of the NAc and amygdala during these behaviors.

The expression of anxiety and anhedonic symptoms varies across patients with major depression, and can vary across time. An understanding of the factors that differentially

impact these symptoms, and how they interact, may lead to insight into factors that contribute to symptom variability. In addition, better understanding of these factors may aid in the development of more selective therapeutics to target different depressive symptomology.

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Abbreviations

ANOVA	analysis of variance
FR	fixed ratio
OF	open field
SI	social interaction

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Highlights

- Anxiogenic bright light decreases lever-pressing for reward
- Stress increases anxiety-like behavior
- Stress increases the effect of anxiogenic light on lever-pressing for reward

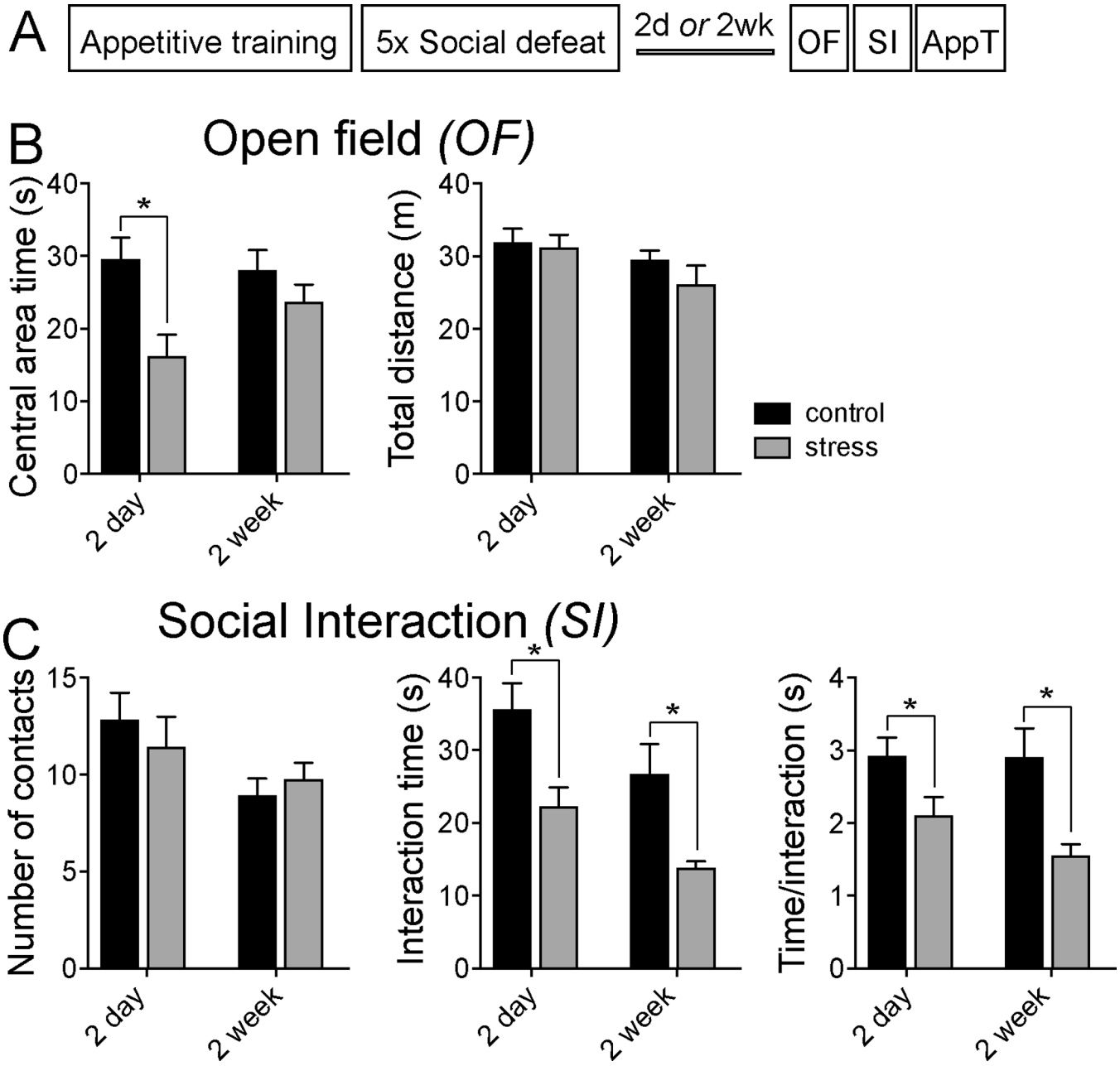

Figure 1. Repeated social defeat increases anxiety-like behavior

A) Schematic of the experimental timeline. One day after completion of appetitive training, rats were subjected to daily social defeat or control procedures for 5 consecutive days. Beginning after 2 days or 2 weeks, rat behavior was measured in the open field test (OF), social interaction test (SI), and appetitive test (AppT). B) Rats that were exposed to social defeat displayed decreased exploration in the center of the open field when measured at 2 days but not 2 weeks (left), with no significant difference in total distance traveled (right). C) While there was no significant effect of social defeat on the number of social interactions (left), there was a significant decrease in the total time of social interaction (middle) and the duration of social contacts (right). * $p<0.05$ in post hoc Holm-Sidak after two-way ANOVA.

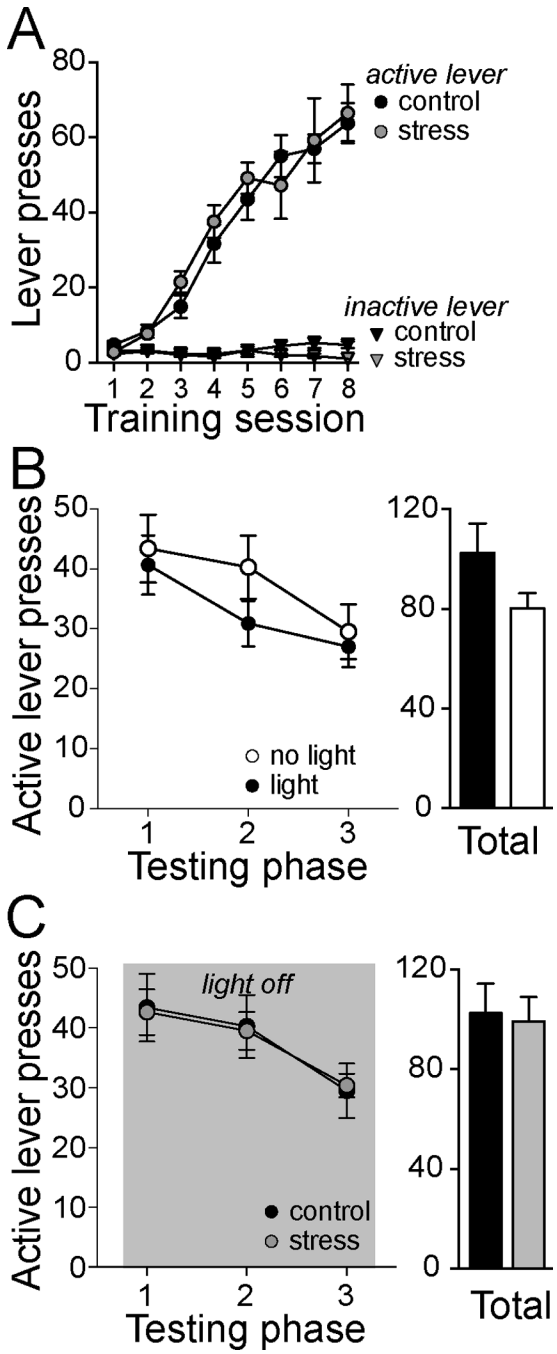

Figure 2. Repeated social defeat does not impact appetitive lever-pressing

A) Rats were trained in an appetitive conditioning task to lever press for sucrose, were matched for lever-pressing and then randomly assigned to control or stress groups. Indicative of the effectiveness of the matching, there was no significant difference between these groups in the number of active or inactive lever presses before control or stress procedures. B) Presentation of a bright light suppressed lever-pressing in the control group, compared to the no-light condition. The total number of active lever presses during the three 5-minute segments of appetitive testing was not significantly different (right). C) In a

separate group of rats, there was no significant difference in lever-pressing between control and stress groups on the number of active lever presses in 5-minute segments (Testing phase) when measured after control or stress procedures (left). There was no significant difference between control and stress groups in the total number of active lever presses of the three 5-minute segments of appetitive testing (right).

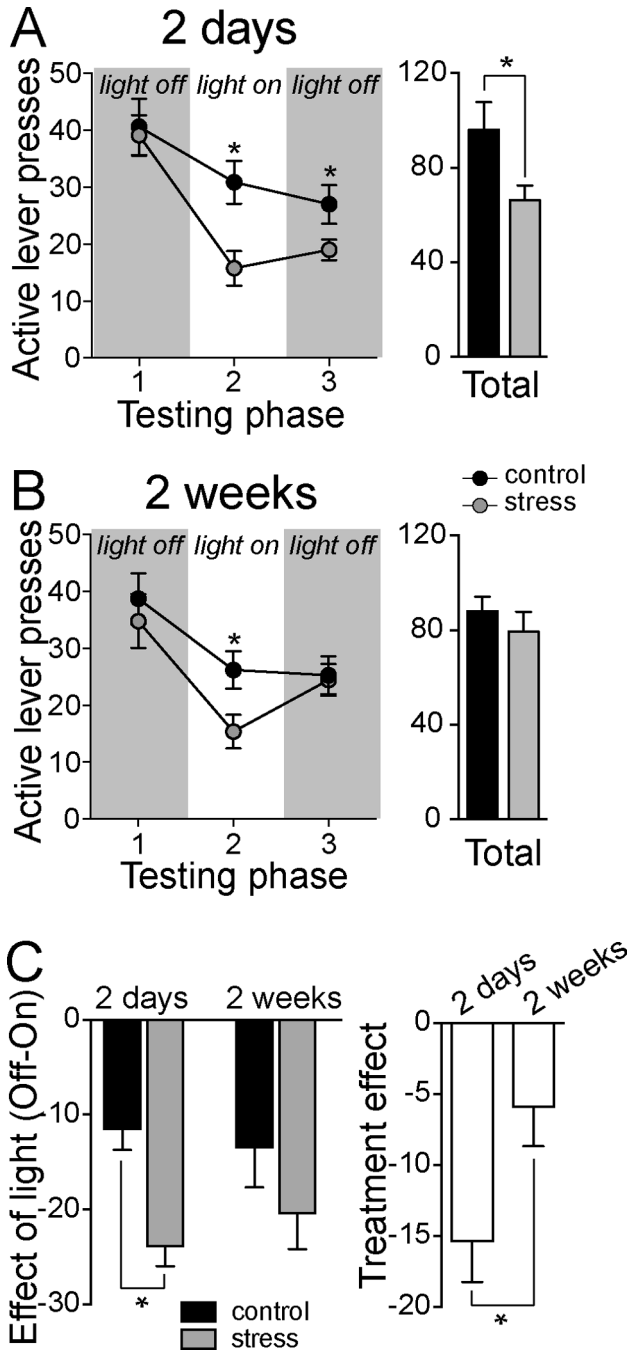

Figure 3. Repeated social defeat increases the effect of anxiogenic bright light on appetitive lever-pressing

Rats were exposed to a testing session with 5-minute offon- off segments of bright light. A) Bright light presented during appetitive testing suppressed lever pressing when tested after 2 days. The effect of bright light was greater in rats that were exposed to repeated stress and this effect lasted longer than the duration of the light (left, *p<0.05 in post hoc Holm-Sidak after two-way ANOVA). This led to a decrease in the total number of active lever presses during this appetitive testing session in rats that were exposed to repeated stress (right). B) Bright light presented during appetitive testing suppressed lever pressing when tested after 2

weeks. The effect of bright light was greater in rats that were exposed to repeated stress, but did not last longer than the duration of the light (left, *$p<0.05$ in post hoc Holm-Sidak after two-way ANOVA). There was no significant difference in the total number of active lever presses during this appetitive testing session between control and stress groups (right). C) To directly compare the effects of stress when tested after 2 days or 2 weeks, the effect of bright light was subtracted from baseline (see Methods, 2.7 Data Acquisition and Analysis) and compared across time. Stress significantly enhanced the effect of anxiogenic light on active lever pressing (left), and this effect was greater when measured after 2 days compared to 2 weeks.