Physiology & Behavior 129 (2014) 25–29

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Effects of inescapable versus escapable social stress in Syrian hamsters: The importance of stressor duration versus escapability

Katharine E. McCann [a,*], Corinne N. Bicknese [b], Alisa Norvelle [a], Kim L. Huhman [a]

[a] Neuroscience Institute, Center for Behavioral Neuroscience, Georgia State University, 161 Jesse Hill Junior Drive, Atlanta, GA 30303, USA
[b] University of Georgia Athens, GA 30602, USA

HIGHLIGHTS

- Controllability over a social stressor does not reduce its effects.
- A very brief defeat still results in significant social avoidance in hamsters.
- Conditioned defeat is a robust model of social stress-induced social avoidance.

ARTICLE INFO

Article history:
Received 25 August 2013
Received in revised form 13 January 2014
Accepted 19 February 2014
Available online 28 February 2014

Keywords:
Stressor controllability
Social avoidance
Conditioned defeat

ABSTRACT

Social avoidance is a common characteristic of many clinical psychopathologies and is often triggered by social stress. Our lab uses Syrian hamsters to model stress-induced social avoidance, and we have previously established that both inescapable and escapable social defeat result in increased social avoidance when compared with no-defeat controls. Our previous work suggested, however, that social avoidance was significantly greater after inescapable defeat. The goal of this study was to determine if this difference in behavior after the two types of defeat was due to experimental differences in the controllability (i.e., escapability) of the defeat or simply to differences in the overall duration of the defeat. In Experiment 1, we used a yoked design to hold constant the duration of defeat between escapable and inescapable defeat conditions. This design resulted in only a very brief social defeat, yet when comparing defeated animals with no-defeat controls, a significant increase in social avoidance was still observed. In Experiment 2, we also used the yoked design, but the escape task was made more difficult to ensure a longer defeat experience. Again, we observed no effect of controllability. Together, these data suggest that the ability to escape a social stressor does not reduce the impact of the stressful experience. These results emphasize that social stressors need not be prolonged or uncontrollable to produce marked effects on subsequent behavior.

1. Introduction

Social stress is a major risk factor for the development of psychopathologies such as mood and anxiety disorders [1–3]. Syrian hamsters are excellent subjects with which to study social stress because they readily exhibit high levels of territorial aggression towards an intruding conspecific, yet their agonistic interactions are highly ritualized and rarely result in physical injury [4]. Thus, with hamsters it is possible to effectively focus on the psychological effects of social stress rather than the physiological effects resulting from physical injury or trauma. Strikingly, after only one social defeat, Syrian hamsters subsequently abandon all territorial aggression and instead become highly submissive [5]. This drastic change in behavior, termed conditioned defeat, persists for up to one month in the majority of hamsters [4].

Our laboratory's standard method of producing conditioned defeat has been to expose hamsters to a 15 min inescapable defeat during which the animal is confined to the resident aggressor's home cage [6,7]. We have maintained that conditioned defeat is an ethologically relevant form of fear conditioning, but it is possible that the biological relevance of this phenomenon is limited somewhat by the fact that the animals are not able to escape from the aggressor. To determine if conditioned defeat is simply an epiphenomenon of the inescapable defeat experience, we previously examined whether conditioned defeat would also occur in animals subjected to a model of escapable social defeat [8]. While we demonstrated that animals experiencing an inescapable social defeat exhibited significantly more social avoidance than did either no-defeat controls or animals experiencing an escapable defeat, it is critical to note that the animals exposed to an escapable defeat also

* Corresponding author at: Neuroscience Institute Georgia State University 161 Jesse Hill Junior Drive Suite 832 Atlanta, GA 30303, USA. Tel.: +1 404 413 6337; fax: +1 404 413 5446.
E-mail addresses: kmccann3@gsu.edu (K.E. McCann), khuhman@gsu.edu (K.L. Huhman).

http://dx.doi.org/10.1016/j.physbeh.2014.02.039
0031-9384/

displayed significantly more social avoidance than did no-defeat controls. This study provided clear evidence that conditioned defeat is not merely an epiphenomenon of an inescapable defeat experience but also occurs after an escapable defeat. The question of whether inescapable defeat truly produces more social avoidance than does escapable defeat was left unanswered, however, because the animals in the escapable defeat group, in addition to having control in terms of being able to terminate the defeat, were also exposed to the resident aggressor for significantly less time than were animals in the inescapable defeat group.

Both the controllability and the duration of a stressor have been shown to influence the behavioral changes observed after a stressful experience. In rats, for example, the ability to control the termination of a tail shock decreases the behavioral reaction to later stressors, such that controllability purportedly acts as a stress buffer [9]. This effect of control is also observed in drug abuse studies wherein stressor controllability reduces the subsequent conditioned place preference for morphine [10]. Furthermore, the phenomenon of learned helplessness develops in rats only after exposure to uncontrollable, but not similar controllable, stressors (for a detailed review, see [11]). In humans, the subjective helplessness of a situation is correlated with perceived pain intensity, such that people who report higher feelings of helplessness during an electric skin stimulation test also report higher levels of pain [12]. Similarly, stressor duration also can alter stress responding and subsequent behavior. C57BL/6 mice exhibit social avoidance behavior after long-term but not after short-term social defeat [13], and antinociception is significantly greater in mice after 15 min of forced swim compared with 3 min [14]. Thus, the purpose of the current study was to determine whether the apparent difference in social avoidance previously observed between inescapable and escapable defeat was due to differences in the controllability or in the duration of the social stressor.

2. Material and methods

2.1. Animals

Adult male Syrian hamsters, approximately 12 weeks old and weighing between 120–140 g, were obtained from Charles River Laboratories (Wilmington, MA). All animals were singly housed upon arrival in polycarbonate cages (23 × 43 × 20 cm) with corncob bedding and cotton nesting material. Resident aggressors (RA) were larger hamsters, at least six months of age that had previously proven to quickly and reliably attack an intruding conspecific. Animals were maintained on a 14:10 h light/dark cycle and food and water were available ad libitum. Subjects were handled daily before the start of any manipulation to reduce the stress of experimenter handling. All behavioral manipulations were done in a dedicated hamster suite in the vivarium within the first 3 h after lights off. All procedures and protocols were approved by the Georgia State University Institutional Animal Care and Use Committee and were in accordance with the standards outlined in the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Experiment 1

Animals were randomly divided into 4 weight-matched behavioral groups: escapable defeat (n = 8); inescapable defeat (n = 8); novel cage no-defeat control (n = 8); home cage no-defeat control (n = 7). Defeated animals were divided into yoked pairs with one assigned to escapable defeat and the other to inescapable defeat. Defeats or novel cage exposure occurred on Day 1, and all animals were tested for social avoidance 24 h later (Day 2) as described below. Novel cage controls were also yoked to a defeat pair and were placed in a novel cage containing soiled bedding from a randomly assigned RA for the duration of the defeat to which they were yoked and were then returned to their home cage until testing. The plastic mesh box used to confine the RA during social avoidance testing on Day 2 was placed in the cage during all behavioral manipulations on Day 1. Home cage controls were brought to the testing suite but were left undisturbed in their home cage on Day 1. Animals were closely monitored during all defeat sessions to ensure no injury to either animal. All behavioral manipulations occurred under dim red illumination and were video recorded with a CCD camera for later analysis.

2.2.1. Escapable defeat

Escapable defeat followed the same protocol as described previously [8]. In brief, animals were placed into the home cage of a randomly assigned RA and were allowed to escape by jumping out of the cage. Each escapable defeat consisted of three trials separated by an intertrial interval of 3 min, during which the subject was returned to its home cage. Each trial was terminated when the subject successfully fled the RA's home cage. Latency to escape the RA's cage was recorded for each trial, and latencies were summed to obtain a total exposure time to the RA across all three trials. To account for variability in the time it took for the RA to attack the intruder during the first pairing, the latency to escape on the first trial was calculated from the time of the RA's first aggressive posture. Total exposure time after the first attack in Trial 1 was added to Trials 2 and 3 to obtain the yoked, total exposure time.

2.2.2. Inescapable defeat

Animals assigned to the inescapable defeat group were each yoked to an animal assigned to the escapable defeat group. Immediately after its partner concluded Trial 3 of the escapable defeat, the yoked subject was placed in a randomly assigned RA's cage, and a clear plastic lid was placed on top to prevent either animal from escaping during the defeat session. After the first agonistic behavior was produced by the RA, the subject in the inescapable defeat condition was left in the RA's cage for the yoked time calculated from its partner in the escapable condition.

2.3. Experiment 2

Because the duration of defeat was quite low in the first experiment and the associated defeat-induced behavioral responses were correspondingly modest, we designed Experiment 2 to re-examine the role of control and duration in a group of animals that were subject to a longer social defeat. We also altered the design slightly so that all of the subjects experienced three behavioral trials on Day 1. In Experiment 2, animals were randomly divided into 3 weight-matched behavioral groups: escapable defeat (n = 17); inescapable defeat (n = 17); novel cage no-defeat control (n = 17). Each animal in the inescapable and control group was yoked to an animal in the escapable group as in Experiment 1; however, instead of using the total time of exposure after first attack as the yoked time for the inescapable defeat group, each trial was yoked. This allowed both the inescapable group and the no-defeat control group to experience 3 separate trials and thus standardized the design among groups as much as possible. As in Experiment 1, the plastic mesh box used to enclose the RA during testing on Day 2 was in the cage during all defeats and novel cage exposures on Day 1.

2.3.1. Escapable defeat

Escapable defeat followed the same protocol as Experiment 1 except that each trial became increasingly harder to escape in order to ensure each escape was a result of the defeat itself and not in anticipation of the defeat. This also increased the duration of the defeat experience while still allowing control over the termination of each trial. In Trial 1 the plastic lid was left completely off the cage as it was in Experiment 1. In Trial 2 the lid covered half the cage, and in Trial 3 the lid covered three quarters of the cage. If the subject failed to escape during Trials 2 and 3 within 5 min, the lid was completely removed to allow easier escape. All trials were terminated after 10 min if the subject failed to escape. As in Experiment 1, the latency to escape on Trial 1 was calculated from the time of the first attack by the RA.

2.3.2. Inescapable defeat

In Experiment 2, animals in the inescapable group experienced 3 trials of defeat to more closely mimic the escapable defeat condition. Each trial was yoked, such that animals in the inescapable defeat group were placed in the RA's cage for the same amount of time as their escapable partner during Trials 1, 2 and 3. Subjects were placed back in their home cage during the 3-min intertrial interval.

2.3.3. Novel cage controls

Similar to animals in the inescapable defeat group, novel cage controls were placed in a novel cage with a handful of soiled RA bedding on 3 separate trials, each timed to match their escapable partner. No-defeat controls were also placed back in their home cages during the 3-min intertrial interval.

2.4. Social avoidance testing

Social avoidance testing on Day 2 for both Experiments 1 and 2 followed the protocol previously described by McCann and Huhman [8]. All subjects were tested with an unfamiliar RA for 5 min. We chose to use the caged-opponent method of testing, rather than a freely moving non-aggressive intruder [6,7], to mimic our original study comparing inescapable and escapable defeats. Unfamiliar RAs were chosen because we were not testing social recognition in this study and the no-defeat controls did not have any direct contact with an RA on Day 1, therefore, familiar RAs could not be used. RAs were confined to a small, plastic mesh box (13.5 × 13.5 × 7 cm) that was placed on one side of a novel arena. At the beginning of the testing period, subjects were placed in the far end of the arena facing away from the RA, and their movements about the cage were recorded throughout 5 min. All animals were returned to their home cage after testing. Time spent in the far half of the testing arena away from the confined RA was used to assess social avoidance and was compared across behavioral groups within each experiment. No-defeat controls served as a baseline for normal exploratory behavior about the cage. Overt submissive behavior (e.g., flees and risk assessments as defined previously [8]) and flank marking were also recorded and compared across groups within each experiment.

2.5. Statistical analysis

Independent t-tests were used when comparing two groups. When comparing 3 or more groups, a one-way ANOVA was completed using Fisher's Least Significant Difference for post-hoc analysis. Non-parametric tests (Kruskal–Wallis using Mann–Whitney U for post-hoc analysis) were completed when the variances in our behavioral data were not homogenous (Levene's Test $p < 0.05$). All mean comparisons were determined a priori. All data are shown as mean ± standard error of the mean.

Table 1
Latency to escape RA's cage in Trials 1, 2, and 3 of escapable defeat (mean in seconds ± S.E.M.) * significantly different than Trial 1 ($p < 0.05$).

	Trial 1	Trial 2	Trial 3
Experiment 1	106.50 ± 33.24	35.75 ± 12.04*	16.50 ± 9.77*
Experiment 2	100.18 ± 34.2	246.94 ± 30.93*	261.76 ± 35.32*

3. Results

3.1. Experiment 1

3.1.1. Duration of RA exposure during defeat training

The latency to escape the RA's cage during escapable defeat was significantly lower in Trials 2 and 3 compared with Trial 1 ($F_{(2,21)} = 11.59$, $p = 0.00$; Table 1). There was no difference in the latency to the first attack between escapable and inescapable defeats (escapable defeat 51.88 ± 11.06 s; inescapable defeat 77.00 ± 23.79 s; $t_{(14)} = -0.958$, $p = 0.354$) and therefore no difference in total exposure to the RA (escapable defeat 210.63 ± 44.64 s; inescapable defeat 235.75 ± 38.20 s; $t_{(14)} = -0.428$, $p = 0.675$). The average time of exposure after the first attack (yoked time) was 158.75 ± 41.82 s. The average duration of aggression of the RA towards the subject was not different between the two defeat groups (escapable defeat 80.27 ± 15.79 s; inescapable defeat 105.17 ± 22.11 s; $t(14) = 0.917$, $p = 0.375$).

3.1.2. Social avoidance testing

One subject in the novel cage control group had to be excluded from the analysis in Experiment 1 because the RA escaped the stimulus box during social avoidance testing (final n = 7 for this group). There were no statistically significant differences between the two no-defeat control groups in Experiment 1 (home cage control: 131.14 ± 18.07; novel cage control: 103.14 ± 11.35; $t_{(12)} = 1.312$, $p = 0.214$) and, therefore, these two groups were combined for final statistical analysis. Time spent in the far half of the arena during social avoidance testing was statistically similar across all groups (Kruskal–Wallis $p = 0.378$; Fig. 1). There were also no differences in number of risk assessments, flees, or flank marks (Table 2). There was an overall effect, however, of defeat when animals were collapsed across defeat type ($t_{(28)} = 2.129$, $p = 0.042$; Fig. 2).

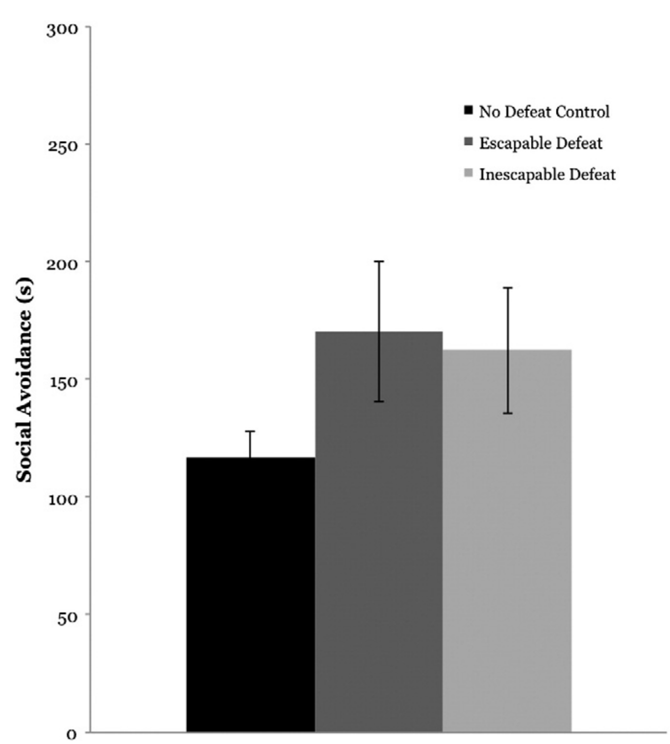

Fig. 1. Avoidance time (seconds) for Experiment 1. Time spent in the far half of the testing arena away from the caged opponent during social avoidance testing. There were no significant differences among groups ($p > 0.05$).

Table 2
Frequency of behavior observed during social avoidance testing (mean ± S.E.M.) *significantly greater than inescapable defeat and no defeat controls (p < 0.05).

	Risk assessments	Flights	Flank marking
Experiment 1			
Escapable defeat	1.50 ± 0.38	0.75 ± 0.37	0.38 ± 0.38
Inescapable defeat	3.00 ± 0.96	0.25 ± 0.16	0.00 ± 0.00
No defeat control	1.07 ± 0.40	0.00 ± 0.00	1.14 ± 0.65
Experiment 2			
Escapable defeat	2.06 ± 0.60	0.88 ± 0.28*	0.24 ± 0.14
Inescapable defeat	1.73 ± 0.46	0.20 ± 0.14	0.40 ± 0.34
No defeat control	1.00 ± 0.88	0.06 ± 0.06	2.00 ± 0.77

3.2. Experiment 2

3.2.1. Duration of RA exposure during defeat training

In order to increase the duration of exposure to the RA but also to maintain a level of escapability, escapable defeat trials became increasingly harder to escape in Experiment 2. Consequently, the latency to escape the RA's cage in Trials 2 and 3 in Experiment 2 was significantly higher than that in Trial 1 ($F_{(2,48)} = 7.093$, $p = 0.002$; Table 1). The average exposure to the RA after first attack in Experiment 2 was 608.88 ± 66.56 s. The amount of aggression was not different between the two defeat groups (escapable defeat 200.34 ± 33.77 s; inescapable defeat 170.4 ± 24.87 s; $t(30) = -0.698$, $p = 0.491$). Two animals in the inescapable defeat group in Experiment 2 were excluded from the study because they defeated their RAs during defeat training (final n = 15 for this group).

3.2.2. Social avoidance testing

Animals in both defeat groups avoided the caged opponent significantly more than did controls during social avoidance testing on Day 2 in Experiment 2 (Kruskal–Wallis p = 0.000; Fig. 3). Animals experiencing an escapable defeat also exhibited significantly more flees (Kruskal–Wallis p = 0.008; Table 2) from the caged opponent.

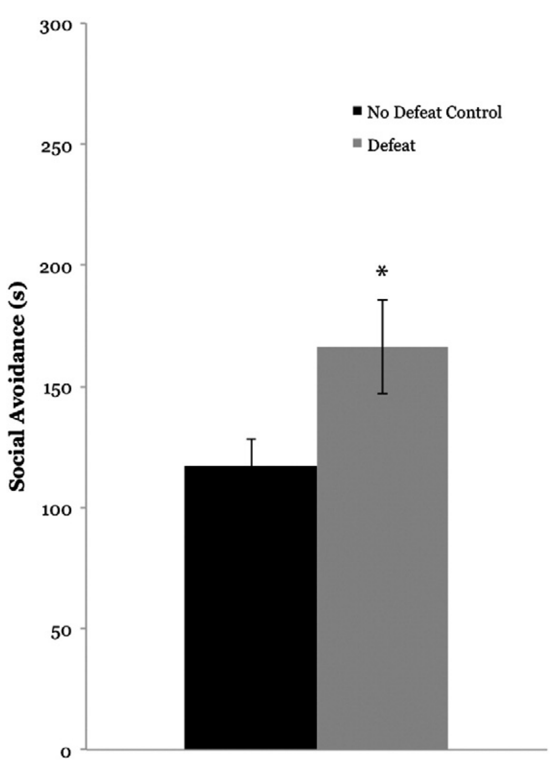

Fig. 2. Avoidance time (seconds) for Experiment 1. When defeat groups were collapsed, defeated animals avoided the RA significantly more than did no-defeat controls (* p < 0.05).

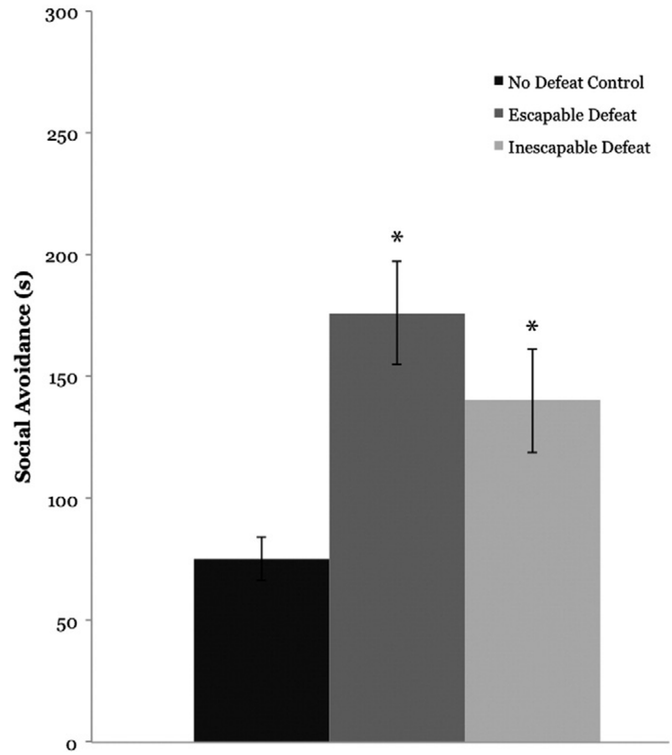

Fig. 3. Avoidance time (seconds) for Experiment 2. Defeated animals from both groups avoided significantly more than did no-defeat controls (* p < 0.05).

4. Discussion and conclusion

The yoked experimental design used in the current study allowed us to hold constant the duration of defeat in order to determine if controllability (i.e., escapability) or if duration was the primary factor contributing to the previously observed difference in social avoidance following escapable versus inescapable social defeat. The present results from both experiments demonstrate that having control over social defeat, in terms of being able to terminate the encounter by escaping from the cage of the resident aggressor, does not reduce the effect of defeat because animals in the escapable and inescapable defeat groups subsequently exhibited similar social avoidance.

It is perhaps surprising that having control over the termination of the social stressor did not reduce its impact. As mentioned above, having control over a stressor has generally been shown to reduce the detrimental effect of the stressful experience. There are several factors that may explain the differences in the findings. First, most studies investigating the effects of controllability have used non-social stressors, such as foot or tail shock (for review, see [15]). Thus, it is possible that social stressors, which are ethologically relevant, are simply more salient to the animals and that being able to terminate the encounter in no way diminishes its importance. Another important difference is that the defeated subjects are removed from the stressful environment and returned to their home cages during the inter-trial interval. In experiments examining escapable versus inescapable shock, animals are typically left in the context in which they are shocked until all trials are complete, thus prolonging and perhaps exacerbating the stressful experience. In addition, most studies examining the role of behavioral control use many trials in which the subject can control the termination of the stressor. For example, studies utilizing controllable shock usually incorporate 80–100 trials of the escapable stressor, slowly increasing the intensity of the shock over the course of the trials to maintain escape behavior [9,10]. The current study included only three, relatively brief trials of escapable defeat, perhaps precluding any effect of control. It is possible that escapable versus inescapable defeats experienced over many more trials or over several days or weeks might eventually generate differences in social avoidance based on controllability.

The results presented here suggest that a difference in the duration of the defeat experience is the primary factor leading to the previously observed differences in social avoidance after inescapable versus escapable defeat. In McCann and Huhman [8], the total exposure of subjects to the RA in the inescapable defeat group was an uninterrupted 15 min (900 s), whereas the escapable defeat condition resulted in only an average of 206 $\pm$ 43.85 s of total exposure to the RA separated across 3 trials. By contrast, the duration of defeat experience was held constant in this study, ultimately leading to similar levels of social avoidance behavior after inescapable and escapable social defeat. In Experiment 1, the escapable defeat followed the same protocol used previously [8], and the inescapable defeat was then yoked to the total duration of the escapable trials in order to mimic the 15 min, uninterrupted protocol used in our previous study. This resulted in very limited defeat (159 $\pm$ 42 s), because the hamsters quickly learned how to escape in Trials 2 and 3. Many studies examining stressor controllability will increase the difficulty of the task required to escape the stressor on subsequent trials to ensure that the escape is due to the stressor, itself, and is not produced in anticipation of the stressor [16–18]. In Experiment 2, we wanted to increase the duration of the overall defeat experience while still maintaining the differences in controllability; thus, we made it increasingly harder to escape on each subsequent trial. In addition, to equalize better the escapable and inescapable defeat experiences, we also yoked each trial so that all three groups (both defeat groups as well as no-defeat controls) experienced three separate trials. These procedural changes were effective in that the duration of exposure to the RA was longer in Experiment 2 than in Experiment 1 (average of 609 s of exposure versus 159 s, respectively), and both defeat groups in this experiment exhibited significantly more avoidance than did no-defeat controls. Notably, there were still no differences in social avoidance between the two defeat groups. Thus, it appears clear from the results of both Experiments 1 and 2 that the previously observed differences in behavior during social avoidance testing between the inescapable and escapable defeat groups was a result of the differential durations in aggressive behavior experienced by the two groups rather than the ability of one group to exercise control over the social stressor by escaping from the resident aggressor.

It is important to note that while there were no differences in social avoidance between the two defeat groups in Experiment 1, the extremely limited defeat experience (158.75 $\pm$ 41.82 s) still produced significant social avoidance in defeated animals when compared with no-defeat controls. These results provide evidence that social stressors need not be severe, uncontrollable, or prolonged to have a pronounced effect on subsequent behavior. In humans, stressors are frequently social in nature and can lead to the development of any number of clinical psychopathologies with which social avoidance is associated, including depression (for review, see [19]), anxiety [20], and posttraumatic stress disorder [21]. The stressors that can trigger the onset of social avoidance vary considerably in their perceived severity, and thus, it is significant that a seemingly mild social defeat in hamsters still resulted in significant social avoidance behavior. The present findings, in conjunction with our previous work, suggest that conditioned defeat is a particularly sensitive animal model for the social avoidance that is often observed in humans following social stress and that examination of this model is useful to expand our understanding of how additional environmental factors, such as the duration of or the ability to escape from a social stressor, contribute to stress-induced social avoidance.

Acknowledgments

Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Number R01MH062044 to KLH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

[1] Bjorkqvist K. Social defeat as a stressor in humans. Physiol Behav 2001;73:435–42.
[2] Lederbogen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, et al. City living and urban upbringing affect neural social stress processing in humans. Nature 2011;474:498–501.
[3] Wood AM, Boyce CJ, Moore SC, Brown GD. An evolutionary based social rank explanation of why low income predicts mental distress: a 17 year cohort study of 30,000 people. J Affect Disord 2012;136:882–8.
[4] Huhman KL, Solomon MB, Janicki M, Harmon AC, Lin SM, Israel JE, et al. Conditioned defeat in male and female Syrian hamsters. Horm Behav 2003;44:293–9.
[5] Potegal M, Huhman K, Moore T, Meyerhoff J. Conditioned defeat in the Syrian golden hamster (Mesocricetus auratus). Behav Neural Biol 1993;60:93–102.
[6] Cooper MA, Huhman KL. Blocking corticotropin-releasing factor-2 receptors, but not corticotropin-releasing factor-1 receptors or glucocorticoid feedback, disrupts the development of conditioned defeat. Physiol Behav 2010;101:527–32.
[7] Markham CM, Taylor SL, Huhman KL. Role of amygdala and hippocampus in the neural circuit subserving conditioned defeat in Syrian hamsters. Learn Mem 2010;17:109–16.
[8] McCann KE, Huhman KL. The effect of escapable versus inescapable social defeat on conditioned defeat and social recognition in Syrian hamsters. Physiol Behav 2012;105:493–7.
[9] Amat J, Aleksejev RM, Paul E, Watkins LR, Maier SF. Behavioral control over shock blocks behavioral and neurochemical effects of later social defeat. Neuroscience 2010;165:1031–8.
[10] Rozeske RR, Der-Avakian A, Watkins LR, Maier SF. Activation of the medial prefrontal cortex by escapable stress is necessary for protection against subsequent inescapable stress-induced potentiation of morphine conditioned place preference. Eur J Neurosci 2012;35:160–5.
[11] Maier SF, Watkins LR. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. Neurosci Biobehav Rev 2005;29:829–41.
[12] Muller MJ. Will it hurt less if I believe I can control it? Influence of actual and perceived control on perceived pain intensity in healthy male individuals: a randomized controlled study. J Behav Med 2012;35:529–37.
[13] Savignac HM, Finger BC, Pizzo RC, O'Leary OF, Dinan TG, Cryan JF. Increased sensitivity to the effects of chronic social defeat stress in an innately anxious mouse strain. Neuroscience 2011;192:524–36.
[14] Parikh D, Hamid A, Friedman TC, Nguyen K, Tseng A, Marquez P, et al. Stress-induced analgesia and endogenous opioid peptides: the importance of stress duration. Eur J Pharmacol 2011;650:563–7.
[15] Maier SF, Watkins LR. Role of the medial prefrontal cortex in coping and resilience. Brain Res 2010;1355:52–60.
[16] Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat Neurosci 2005;8:365–71.
[17] Helmreich DL, Watkins LR, Deak T, Maier SF, Akil H, Watson SJ. The effect of stressor controllability on stress-induced neuropeptide mRNA expression within the paraventricular nucleus of the hypothalamus. J Neuroendocrinol 1999;11:121–8.
[18] Rozeske RR, Der-Avakian A, Bland ST, Beckley JT, Watkins LR, Maier SF. The medial prefrontal cortex regulates the differential expression of morphine-conditioned place preference following a single exposure to controllable or uncontrollable stress. Neuropsychopharmacology 2009;34:834–43.
[19] Trew JL. Exploring the roles of approach and avoidance in depression: an integrative model. Clin Psychol Rev 2011;31:1156–68.
[20] Haller J, Bakos N. Stress-induced social avoidance: a new model of stress-induced anxiety? Physiol Behav 2002;77:327–32.
[21] Hofmann SG, Litz BT, Weathers FW. Social anxiety, depression, and PTSD in Vietnam veterans. J Anxiety Disord 2003;17:573–82.