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Single prolonged stress impairs social and object novelty recognition in rats

Andrew L. Eagle, Chris J. Fitzpatrick^{*}, and Shane A. Perrine

Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI

Abstract

Posttraumatic stress disorder (PTSD) results from exposure to a traumatic event and manifests as re-experiencing, arousal, avoidance, and negative cognition/mood symptoms. Avoidant symptoms, as well as the newly defined negative cognitions/mood, are a serious complication leading to diminished interest in once important or positive activities, such as social interaction; however, the basis of these symptoms remains poorly understood. PTSD patients also exhibit impaired object and social recognition, which may underlie the avoidance and symptoms of negative cognition, such as social estrangement or diminished interest in activities. Previous studies have demonstrated that single prolonged stress (SPS), models PTSD phenotypes, including impairments in learning and memory. Therefore, it was hypothesized that SPS would impair social and object recognition memory. Male Sprague Dawley rats were exposed to SPS then tested in the social choice test (SCT) or novel object recognition test (NOR). These tests measure recognition of novelty over familiarity, a natural preference of rodents. Results show that SPS impaired preference for both social and object novelty. In addition, SPS impairment in social recognition may be caused by impaired behavioral flexibility, or an inability to shift behavior during the SCT. These results demonstrate that traumatic stress can impair social and object recognition memory, which may underlie certain avoidant symptoms or negative cognition in PTSD and be related to impaired behavioral flexibility.

Keywords

single prolonged stress; posttraumatic stress disorder; behavioral flexibility; avoidance; negative cognition; social choice; novel object recognition

1. Introduction

Posttraumatic stress disorder (PTSD) is triggered by a trauma and develops into a serious mental health problem in particularly vulnerable individuals. It presents with symptoms of chronic re-experiencing of the trauma memory, arousal, avoidance, and the newly defined negative cognition/mood [1]. Previously considered symptoms of avoidance, estrangement from others and markedly diminished interest in important or positive activities are now

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Corresponding Author: Shane A. Perrine, 2353 Scott Hall, 540 E Canfield, Detroit, MI 48201, sperrine@med.wayne.edu, [Office] 313-577-9989.

^{*}This author is currently affiliated with the Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI.

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considered symptoms of negative cognition and mood.. Avoidant symptoms include loss of interest in once important or positive activities, such as hobbies and social relationships. Despite a newfound appreciation for the cognitive aspect of these two symptoms, the basis of avoidant symptoms and negative cognition remains unknown. These symptoms may be related to impaired recognition and/or decreased preference for social stimuli. In particular, PTSD impairs recognition memory for objects [2] and social-related stimuli (e.g., emotions in narratives and faces) [3, 4] which may underlie avoidant symptoms and negative cognition.

In order to better understand the neural substrates and phenomena of PTSD-induced alterations in recognition memory/novelty preference processes, such as social and object recognition, it is necessary to develop animal models that exhibit a similar trauma-induced phenotype. Although current animal models demonstrate that stress impairs object recognition memory in rodents [5, 6], no animal model of traumatic stress recapitulates both impaired social and object recognition, which present in PTSD and may be equally important to the development of avoidance symptoms or negative cognition. Single prolonged stress (SPS) is a rodent model of traumatic stress exposure that models key phenotypes of PTSD [7, 8]. SPS also produces impairments in learning and memory, such as hippocampal long-term potentiation [9], contextual fear conditioning [10–12] and the Morris water maze [9, 13]. In addition, a modified SPS paradigm (e.g., enhanced SPS in mice, which includes an additional footshock stressor) also produces object recognition impairments [14]. Therefore, we hypothesized that SPS would impair social and object recognition memory.

In order to determine this, SPS-treated rats and controls were tested in the social choice test (SCT), which measures preference for social novelty and for novel object recognition (NOR), which measures preference for object novelty. Both tests are ideal for measuring recognition memory, because rats naturally prefer to investigate novel social stimuli and objects. In addition, the SCT minimizes the stressful effects of social interaction. Minimizing social interaction was important for the current study to avoid situations of social defeat, which can be a significant stressor to both rodents [15] and humans [16].

2. Methods

Guidelines described in the Guide for the Care and Use of Laboratory Animals 8th edition [17] were adhered to and prior to any testing all experimental procedures were approved by the Institutional Animal Care and Use Committee at Wayne State University. Wayne State University maintains facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. Upon arrival to the facility rats were housed in the vivarium for at least 4 days before experimentation. Rats were pair-housed, weighed, and briefly handled daily throughout the study.

2.1. Subjects

Male Sprague-Dawley experimental rats (N=48; Crl:CD; Charles River Laboratories, Portage, MI) weighing approximately 225 – 250 g upon arrival were pair housed before and during experimentation in standard polycarbonate home cages. Conspecific rats used for SCT (n = 4) were ordered separately and maintained in pair housing in a separate room of the vivarium. Experimental rats were never exposed to the conspecifics at any time prior to the SCT. Rats were allowed food and water *ad libitum* in their home cages and housed on a 12 h light/dark cycle (7:00–19:00). Temperature (~24°C) and humidity (35–40%) were controlled in the vivarium and behavioral testing laboratory.

2.2. Single prolonged stress (SPS)

Half ($n = 22$) of the experimental rats were exposed to the SPS procedure as previously described [18–20]. Briefly, SPS rats were restrained for 2 h followed by a 20 min group forced swim ($n = 6$ –8 per swim). Afterward, SPS rats were allowed a 15 min recuperation period and then exposed to diethyl ether until unconscious. Rats were then returned to the vivarium and housed undisturbed for 7 d. The other half of the rats served as controls. They were handled during the SPS procedure and then transported back to the vivarium and housed undisturbed until testing began seven days later. Conspecifics were handled daily and at separate times than the experimental rats.

2.3. Social choice test (SCT)

One group of experimental rats ($n = 12$ control; $n = 12$ SPS) was tested in the SCT for sociability and social novelty preference. This test was conducted using a previously established behavioral paradigm for social discrimination [21] and autism-like sociability and social novelty preference impairments in mice [22], which uses wire mesh to eliminate tactile social interaction. Briefly, the SCT measures preference for social novelty in rats. After familiarization to a conspecific, which doubles as a test for sociability, rats are exposed to the familiar conspecific in addition to a novel one. Testing began seven days after exposure to the traumatic stressors. Rats were tested in a 3-chamber box (Fig. 1A, Formtech Plastics, Oak Park, MI) for habituation and social testing trials. Each chamber consisted of Plexiglas with a matte black floor and walls (outer: 60 cm x 90 cm x 34 cm; chambers: 60 cm x 30 cm x 34 cm). Arched openings (10 cm x 12 cm) located on the inner dividing walls and offset from the center of the box allowed access among chambers so that rats were able to freely explore each outer chamber via the middle chamber. Within the distant end of each of the outer chambers in relation to the arched openings, a metal mesh basket was placed upside down. Both of the outer chambers contained an empty basket, while the middle chamber was devoid of any objects.

Experimental rats were first habituated to the testing chamber for 15 min. Rats were placed into the far end of the middle chamber in relation to the arched openings and behavior was recorded. Twenty-four hours after habituation, SCT testing began. Testing consisted of 3 consecutive trials: acclimation, sociability, and social novelty. Each trial lasted for 5 min with 15 min between each trial. Experimental rats were placed back into their home cages between trials. During the acclimation trial, experimental rats were allowed to freely explore all 3 chambers. During the sociability trials, a conspecific (C1) was placed under one of the mesh baskets, while the other remained empty. During the social novelty trials, C1 was kept in one of the baskets and a novel conspecific (C2) was placed in the empty basket. The placement of C1 was counterbalanced for previous location in the social novelty preference trials, so that for half of the experimental rats C1 remained in the same location as the sociability trials and for the other half C1 was placed in the other chamber. Conspecifics were habituated to being under the metal mesh basket in the 3-chamber box prior to experimentation.

Behavioral flexibility in the SCT was also examined. C1 location in the social novelty trial was counterbalanced to its previous location in the sociability trial, so that for half of the experimental rats ($n = 6$ control; $n = 6$ SPS) C1 location remained the same during the social novelty trial and for the other half C1 location was placed in the previously empty chamber (Fig. 1B). Experimental rat behavior for all testing was recorded with a digital CCD camera that was connected to a PC computer installed with an automated tracking software package (Ethovision XT8, Noldus, Inc., Leesburg, VA).

2.4. Novel object recognition test (NOR)

A separate group of experimental rats ($n = 10$ control; $n = 10$ SPS) were tested for NOR. NOR testing used experimental procedures similar to SCT. Testing began seven days after exposure to the traumatic stressors within the same 3-chamber box (Fig. 1A; no baskets were used for novel object testing). Rats were first allowed to habituate to the empty 3-chamber box for 15 min. Twenty-four hours after habituation, novel object testing began. Novel object testing consisted of 3 trials: acclimation, object familiarization, and object recognition. During the object familiarization and recognition trials, but not acclimation trial, objects were placed at the distal end of each outer chamber in relation to the arched openings. Objects consisted of clear or green dissimilar glass goblets turned upside down. Trial length and duration between trials were the same as social testing. During acclimation, experimental rats were allowed to freely explore all 3 chambers devoid of objects. During object familiarization, 2 similar objects (e.g. both clear glass goblets; O1 & O1') were placed into the two outer chambers, one in each chamber. Rats were assessed for initial object bias of one similar object over another and rats were removed if they exceeded a preference index score greater than 0.6, which equates to spending 80% or more of the time with one object. This was done to eliminate any bias that may affect object recognition. Four rats ($n = 2/\text{group}$) exceeded the criterion during the object familiarization and were subsequently removed from the study. During object recognition, one of the objects (O1) was replaced with a dissimilar object (e.g., 1 clear glass goblet and 1 green glass goblet; O2) and then behavior was recorded using automated tracking software while rats were freely exploring. Behavioral flexibility was not assessed in the object recognition task, since two similar objects were used during the object familiarization trial.

2.8. Statistical Analysis

For behavioral testing, activity and exploration were recorded. Activity was measured as the distance moved (cm). Exploration was measured as the duration time spent (s) of the center point of the experimental rat in each chamber and preference index score. Preference index was calculated based on the time spent in each chamber as:

$$p(\text{Pref}) = (\text{Novel}^d X - \text{Familiar}^d X) / (\text{Novel}^d X + \text{Familiar}^d X)$$

where $p(\text{Pref})$ = proportion of preference for the novel stimulus (object or conspecific rat), d is the duration in seconds in the associated chamber, and X is the associated chamber containing either novel or familiar object/conspecific.

Two-way mixed-design ANOVAs were conducted on time spent in chamber with SPS group as the between-subjects factor and chamber as the repeated factor. In the case of a significant ANOVA, Fisher's LSD post-hoc tests were conducted. Independent samples t -tests were conducted on the preference index scores and distance moved for each test trial in the SCT. Independent samples t -tests are justified for the SCT considering the marked difference between each testing trial. Separate two-way mixed-design ANOVA was conducted on the effects of SPS group and testing trial on index scores and distance moved for the NOR task. Separate two-way mixed-design ANOVAs were conducted for each SPS group with counterbalancing as the between-subjects factor and chamber as the repeated factor. Confidence intervals were set at 95% ($p < .05$). The data are expressed as the mean $\pm$ standard error of the mean.

3. Results

3.1. Single prolonged stress impairs social novelty preference, but not sociability

Experimental rats were tested in the SCT for sociability and social novelty preference. In the sociability test, a two-way ANOVA revealed a significant increase in time spent in the chamber containing a conspecific (C1) compared to the chamber containing an empty basket [Fig. 2A; $F(1, 22) = 69.06, p < .001$]. No differences were observed between SPS and controls in time spent with C1 ($p > .05$). In the social novelty test, two-way ANOVA revealed an interaction of group and chamber on time spent in chamber that trended towards significance [Fig. 2B; $F(1, 22) = 3.93, p = .060$]. Post hoc comparison revealed that controls spent more time with a novel conspecific (C2) than the now familiar conspecific (C1) ($p = .009$). SPS-exposed rats, on the other hand, spent an equal amount of time with both C1 and C2 ($p > .05$). Preference index scores were also examined using Student's t-tests for each SCT trial (Fig. 2C). Independent samples t-test revealed no differences in preference during the test for sociability between control and SPS groups ($p > .05$); however, in the test for social novelty, t-test revealed a significant decrease in preference index in SPS-exposed rats compared to controls [$t(22) = 2.45, p = .023$]. These findings demonstrated that SPS did not impair sociability; however, SPS decreased preference for a novel conspecific relative to a familiar conspecific. Deficits in conspecific recognition appeared to be independent of locomotor activity, because there were no differences between controls and SPS-exposed rats in distance moved during either of the test trials (Fig. 2D; $p > .05$).

3.2. Single prolonged stress impairs behavioral flexibility in the SCT

Experimental rats from the SCT were counterbalanced as previously described to determine behavioral flexibility. Two-way ANOVA revealed that controls, regardless of whether C1 location was the same or different, always preferred the chamber containing the C2 [Fig. 3A; $F(1, 10) = 14.71, p = .003$]. On the other hand, SPS-exposed rats spent more time in the chamber that was previously associated with C1 during the test for sociability, regardless of the location of C1 during social novelty testing. Two-way ANOVA revealed a significant interaction of counterbalancing group and chamber and time spent in chamber in SPS-exposed rats [Fig. 3B; $F(1, 20) = 7.48, p = .013$]. SPS rats spent more time with C1 when the location was the same, which trended towards significance (Fig. 3B; $p = .075$), and spent more time with C2 when location of C1 was different, which also trended towards significance ($p = .060$). Thus, while control rats readily explored a novel conspecific (C2) compared to a familiar conspecific (C1), SPS rats spent more time in the location previously associated with a conspecific (C1) during the sociability trial.

3.3. Single prolonged stress impairs object recognition

To determine whether the recognition impairment in social novelty was specific to social stimuli, NOR was also assessed in a separate group of rats. During the object familiarization trial, no differences were observed between the time spent with one object (O1) over a similar object (O1'), and no differences were observed between control and SPS groups (Fig. 4A; $p > .05$ for all ANOVA effects). When a novel object (O2) was introduced during the object recognition trial, results from the two-way ANOVA revealed a significant effect of object (familiar or novel) [Fig. 4B; $F(1, 28) = 5.05, p = .033$]; however, the interaction only trended towards significance [$F(1, 28) = 3.80, p = .061$]. Control rats spent more time with the novel object (O2) than a familiar one (O1) (Fig. 4B; $p = .014$), illustrating successful object recognition; however, SPS rats spent an equal amount of time with both O1 and O2 ($p > .05$), indicating a lack of object recognition. Preference index scores were also examined within each trial for both groups (Fig. 4C). Two-way ANOVA revealed an interaction that trended towards significance [$F(1, 14) = 3.90, p = .068$]. Controls demonstrated increased preference for the novel object during the object recognition trial

compared to the object familiarization trial ($p = .037$), whereas SPS preference index scores remained the same across both trials ($p > .05$). Controls appeared to have higher preference scores during the object recognition phase than SPS, which trended towards significance ($p = .097$). The SPS-induced decrease in NOR was not due to changes in locomotor activity, because no differences were observed between control and SPS in distance moved in either trial (Fig. 4D; $p > .05$).

4. Discussion

In the current study, we demonstrated that traumatic stress exposure impairs both social and object recognition using the SCT and NOR tests. Specifically, SPS impaired preference for social and object novelty (the social preference trial in SCT and the object recognition trial in NOR, respectively) without impairing investigation of an initially novel conspecific (sociability trial in the SCT) or object (object familiarization trial in the NOR). In addition, SPS did not affect locomotor activity. This selective impairment may be related to the inherent differences between sensation-seeking and novelty-seeking behaviors. Initial studies of these behaviors measured novelty-induced locomotion and place preference in rats to novel environments. These studies demonstrated that exploration of an inescapable novel environment with no choice promotes sensation-seeking behavior (i.e., increased exploration of the environment; [23]) whereas free choice to explore a familiar or novel environment promotes novelty-seeking behavior (i.e., increased exploration of the novel versus familiar environment; [24]). In our study, investigation of one conspecific or two similar objects would represent sensation-seeking behavior, because free choice between two different, discrete stimuli was eliminated. On the other hand, investigation of familiar or novel conspecifics and objects would represent novelty-seeking behavior, because free choice was provided. It is important to note that novelty-seeking behavior under free choice conditions requires recall and recognition of familiarity versus novelty. Therefore, our results suggest that SPS selectively attenuates social and object novelty-seeking, which requires recognition memory, while sparing sensation-seeking, which does not. In addition, locomotion behavior (i.e., exploratory behavior) was similarly unaffected by SPS, in line with our previous findings that locomotor activity is not affected by SPS [19].

It should be noted that a possible limitation of this model is that the impairment in recognition memory may be caused by a decrease in preference for novelty. Richman and Frueh [25] demonstrated that novelty-seeking behavior is increased in PTSD patients. These findings, however, are not necessarily in contradiction with our results. Clinical measures of novelty-seeking often focus on trait personality and do not often assess novelty preference behaviors [25–27], specifically those that require intact learning/memory processes. Novelty-seeking in the SCT and NOR tests, however, require intact recognition memory, which is known to be impaired in PTSD [2–4]. There also exists considerable individual variation in personality types (e.g., externalizing versus internalizing; [28]), ability to discriminate cues [29], and novelty-seeking behavior [26] in PTSD patients, suggesting the existence of subgroups of PTSD patients. Furthermore, PTSD patients show hyperarousal and increased activation in neural fear circuits to novel, potentially threatening stimuli [30, 31]. Future studies are therefore needed to better understand how individual variation in rodent behavior may model different traits and symptoms in subgroups of PTSD patients.

SPS also tended to impair behavioral flexibility in the social preference trial of the SCT. In other words, controls spent more time in the chamber containing a novel conspecific, regardless of its location relative to the test for sociability, whereas SPS-treated rats tended to spend more time with the chamber of their first social encounter during the sociability trial of the SCT. These results agree with reports that stress impairs behavioral flexibility in rodents [32, 33] and that PTSD patients exhibit impaired behavioral flexibility [34, 35],

which is related to PTSD symptom severity [36]. Furthermore, the ability to discriminate cues in PTSD predicts the response to the antidepressant, duloxetine [29]. Although most studies of behavioral flexibility investigate spatial [37] or operant [38] learning, behavioral flexibility is relevant for any behavior (e.g., non-spatial and social) that involves adaptive choice and discrimination. Adaptively choosing between approach of familiar and novel stimuli therefore may constitute a form of behavioral flexibility that is affected by traumatic stress.

5. Conclusions

Recognition impairments are poorly understood in PTSD; however, PTSD-induced impairments in social and object recognition may underlie avoidant symptoms, such as loss of interest in important or positive activities, or negative cognition/mood. Preclinical and clinical research is necessary to further determine the role of traumatic stress exposure on recognition memory. We demonstrated that traumatic stress in rats impairs social and object recognition memory and/or novelty preference. In addition, our results suggest that the stress-induced impairment in recognition may be related to impaired behavioral flexibility. Taken together, our study provides a foundation for future investigations into the neural substrates and molecular mechanisms underlying the stress-induced impairment in recognition memory and/or novelty preference.

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Abbreviations

PTSD	posttraumatic stress disorder
SPS	single prolonged stress
SCT	social choice test
NOR	novel object recognition test
C	conspecific
O	object

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Research Highlights

- Avoidance symptoms and negative cognition in posttraumatic stress disorder (PTSD) are poorly understood.
- Single prolonged stress (SPS) in rodents models characteristics of PTSD.
- SPS impairs object and social novelty, which may be due to behavioral inflexibility.
- Impaired recognition of familiarity and novelty may underlie avoidance symptoms and negative cognition.

Figure 1. Experimental design for social choice and novel object recognition tests

(A) Experimental testing design of social choice test (SCT; top) and novel object recognition test (NOR; bottom) within a 3-chamber box. (B) Counterbalancing design for SCT. The location of a familiar conspecific (C1) during a test for social novelty was either kept in the same or different position in relation to its position during the test for sociability.

Figure 2. SPS impairs social novelty preference, but not sociability

(A) Control and SPS rats ($n=12/\text{group}$) spent significantly more time in the chamber with a conspecific (C1) than an empty basket in a test for sociability. No differences were observed between groups in time spent with C1. (B) Control rats spent significantly more time with a novel conspecific (C2) than a familiar conspecific (C1) in a test for social novelty preference, while SPS rats spent equal amount of time with both C1 and C2. (C) Preference index scores were not different between groups during test for sociability; however, SPS significantly decreased preference scores compared to controls during test for social novelty. (D) SPS did not have an effect on distance moved, as a measure of locomotor activity, during either trial of the SCT. * $p < 0.05$, ** $p < 0.01$, *** $p < .001$

Figure 3. SPS impairs behavioral flexibility in a test for social novelty

(A) Regardless of whether a familiar conspecific (C1) was kept the same from the sociability to social novelty tests ($n = 6$) or different ($n = 6$), control rats spent significantly more time with a novel conspecific (C2). (B) When C1 location was the same ($n = 6$), SPS rats spent more time with C1 but not to the level of significance. When C1 location was different ($n=6$), SPS rats spent more time with C2 but not to the level of significance. Overall these data suggest that control rats are able to alter their behavior but SPS exposed rats show behavioral inflexibility. ** $p < .01$, # $p < .10$

Figure 4. SPS impairs novel object recognition

(A) Neither control nor SPS rats ($n=8/\text{group}$) spent more time with one familiar object (O1) over a similar object (O1') during object familiarization. Furthermore, no differences were observed between control and SPS groups in time spent with O1. (B) Control rats spent significantly more time with a novel object (O2) than a familiar object (O1) during object recognition, while SPS rats spent equal amount of time with both O1 and O2. (C) Preference index scores were significantly increased in control rats during the NOR test compared to the object familiarization trial, and were decreased by SPS in the object recognition trial but not to the level of significance. Preference scores for SPS rats remained unchanged from object familiarization to object recognition trials. (D) SPS did not have an effect on distance moved, as a measure of locomotor activity, during either trial relative to control treated rats. * $p < .05$, # $p < .10$