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Research report

Single prolonged stress impairs social and object novelty recognition in rats

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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.

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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.

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 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 new-found 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

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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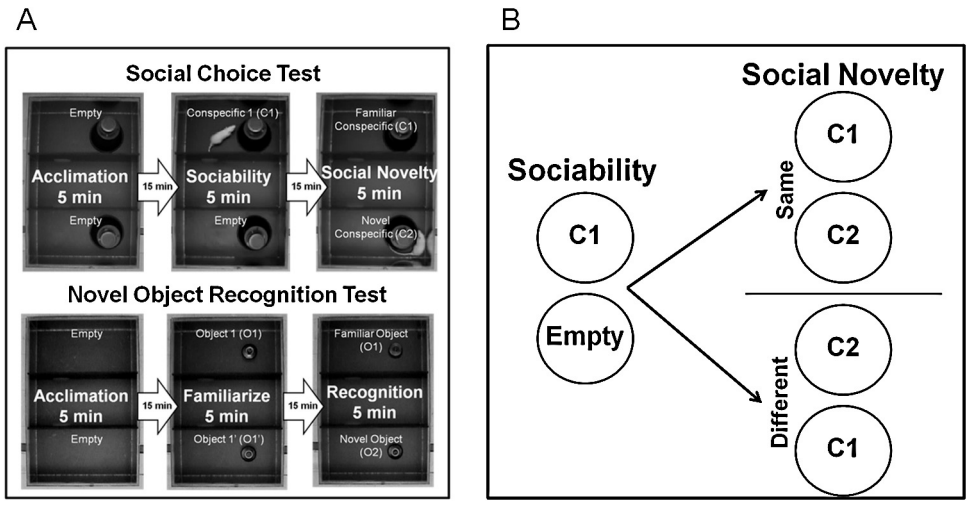

Fig. 1. Experimental design for social choice and novel object recognition tests. (A) Experimental testing design of social choice test (SCT; top) and novel object recognition test (NOR; bottom) within a 3-chamber box. (B) Counterbalancing design for SCT. The location of a familiar conspecific (C1) during a test for social novelty was either kept in the same or different position in relation to its position during the test for sociability.

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 days. 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 7 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 7 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 × 90 cm × 34 cm; chambers: 60 cm × 30 cm × 34 cm). Arched openings (10 cm × 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