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Research article

# Witnessing traumatic events and post-traumatic stress disorder: Insights from an animal model

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## HIGHLIGHTS

- Witnessing trauma causes behavioral deficits
- Post-trauma witnessing deficits last at least up to 6 weeks
- Auditory and olfactory stresses alone are not enough to cause PTSD-like phenotype

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## ABSTRACT

It is becoming increasingly recognized that post-traumatic stress disorder (PTSD) can be acquired vicariously from witnessing traumatic events. Recently, we published an animal model called the "Trauma witness model" (TWM) which mimics PTSD-like symptoms in rats from witnessing daily traumatic events (social defeat of cage mate) [14]. Our TWM does not result in any physical injury. This is a major procedural advantage over the typical intruder paradigm in which it is difficult to delineate the inflammatory response of tissue injury and the response elicited from emotional distress. Using TWM paradigm, we examined behavioral and cognitive effects in rats [14] however, the long-term persistence of PTSD-like symptoms or a time-course of these events (anxiety and depression-like behaviors and cognitive deficits) and the contribution of olfactory and auditory stress vs visual reinforcement were not examined. This study demonstrates that some of the features of PTSD-like symptoms in rats are reversible after a significant time lapse of the witnessing of traumatic events. We also have established that witnessing is critical to the PTSD-like phenotype and cannot be acquired solely due to auditory or olfactory stresses.



## 1. Introduction

Approximately 40% of the North American population is exposed to at least one traumatic event during their lifetime [10]. Exposure to traumatic events may be short-lived (e.g., a car accident) or sustained and repeated (e.g., sexual abuse). Several studies have reported strong association between experiencing of traumatic events and developing post-traumatic disorder (PTSD) [14,19]. While the link between experiencing traumatic events and PTSD seems well established, the impact of witnessing traumatic events and acquiring PTSD is not clear. This is alarming as approximately 25% to 30% of individuals who witness a traumatic event may also develop PTSD and other forms of mental disorders including depression [20]. Approximately half of the individuals who develop PTSD continue to suffer from its effects several years later [10]. Recently, we published an animal model called the "Trauma witness model" (TWM) which mimics majority of PTSD-like symptoms in rats from witnessing daily traumatic events (social defeat of cage mate) [14]. Using TWM paradigm, we examined behavioral and cognitive effects in rats [14] however, the long-term persistence of PTSD-like symptoms (anxiety and depression-like behaviors and cognitive deficits) and the contribution of olfactory and auditory stress vs visual reinforcement were not examined.

Several studies have reported that PTSD-like behaviors last at least 3–4 weeks after experiencing traumatic events [1,21] and that olfactory or auditory stress alone cause cognitive and behavioral impairments in animals [16,17]. Limited information is however available regarding the witnessing aspects of trauma and persistence of PTSD-like behaviors [19]. Recently, Warren et al. had reported that deficits in social avoidance and sucrose preference

*Abbreviations:* LE, Long Evans; SD, Sprague Dawley; TWM, trauma witness model; LD, light-dark test; OFT, open field test; EPM, elevated plus maze; RAWM, radial arm water maze; FST, forced swim test.

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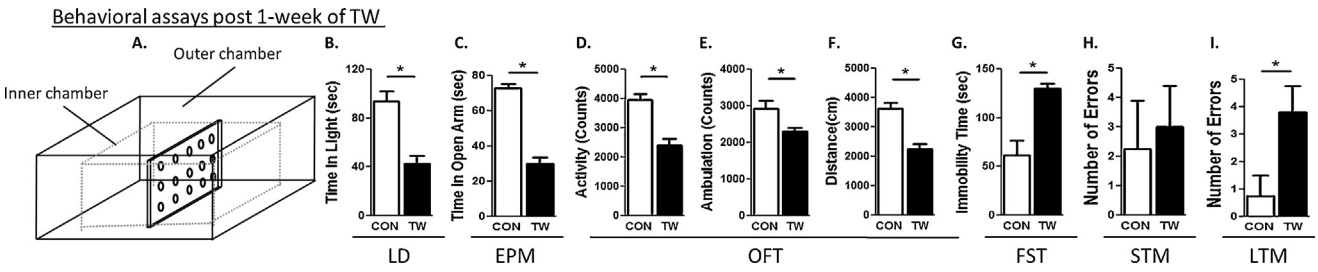


**Fig. 1.** Examination of anxiety and depression-like behaviors and cognitive deficits 1 week after TWM: A schematic representation of the TWM apparatus (A). Light-dark test (B), elevated plus maze test (C). The open-field test determined total (D), ambulatory (E) activities and distance travelled (F). Forced swim test (G) were conducted. Short-term (H) and long-term memory (I) tests were conducted in all rats. (*) significantly different from control rats, $p < 0.05$. Bars represent means ± SEM, $n = 10$ rats/group.

are salient 1 month after emotional stress of witnessing traumatic events, perhaps indicating that neuronal adaptations underlying these behavioral effects build over time, in the absence of continued stress [7,9,19]. In the present study, we have addressed the question of whether the behavioral and cognitive deficits seen in our TWM model are long-lasting or a result of acute stress reaction due to witnessing traumatic events.

## 2. Methods and materials

### 2.1. Animals

Male Sprague Dawley (SD) rats (225–250 g) were used as controls or intruders, and male Long-Evans (LE) retired breeders (400–500 g) served as residents (Charles River, Wilmington, MA). Rats were singly housed with a 12 h light, 12 h dark cycle (lights on at 0700 h) in a climate-controlled room with ad libitum food and water. All experiments were conducted in accordance with the NIH guidelines using approved protocols from the University of Houston Animal Care Committee.

### 2.2. Selection of aggressors

Successful application of chronic social defeat stress to SD rats was dependent on appropriate selection of LE rats with consistent levels of aggressive behaviors, as determined from the 3-d screening process as published by us [12,13].

### 2.3. Trauma witness model (TWM)

The social defeat model used in the present study was modified from the resident-intruder model originally developed by Miczek [11]. As we previously published [14], this paradigm consisted of 7 encounters, carried out for 7 consecutive days, with an aggressive male Long Evans (LE) rat. Each intruder (Sprague Dawley) was defeated by 7 different resident LE rats [4,6]. After defeat, a plexiglass partition with holes was placed in the cage to avoid direct physical contact between the LE and intruder. This partition allowed visual, auditory, and olfactory interactions for the remainder of the 30 min session (Fig. 1A). Social defeat was observed by the SD rat present outside the cage, initiating a freezing response. Two more bouts of social defeat were performed with 5 min separation, in order to reinforce the visual stress in the TW rat. Controls were placed behind a wire partition in a novel cage and another SD rat present outside the cage for 30 min daily. TW and SD rats were housed in separate cages after each social defeat exposure. Behavioral assessments were performed at 1, 2, 6 and 8 weeks post trauma witness. The experiments were conducted three times (experiment 1: $n = 4$ rats/group, experiment 2: $n = 8$ rats/group, experiment 3: $n = 10$ rats/group).

*Auditory Stress*: A Sprague-Dawley male rat (intruder rat) was put into the home cage of a large male LE rat (resident rat) resulting in social defeat of the intruder. During this process occasional vocalization sounds were made by the intruder. Brief sounds were also made when the intruder hit the walls of the central enclosure in an effort to escape attacks and avoid defeat. These sounds were audible to the cage mate (another small Sprague-Dawley male rat) of the intruder rat. The cage mate could hear the noise but not see the defeat process as the central enclosure was covered with opaque black paper (Fig. 5).

*Olfactory Stress*: Small Sprague-Dawley rat was allowed to smell but not see the LE rat. This was done either by placing the LE rats in a blacked-out central enclosure, or by putting LE fur and urine inside the enclosure. No social defeat was done (Fig. 5).

### 2.4. Anxiety-like behavior tests

First, open-field test was conducted followed by light-dark (LD) and elevated-plus maze (EPM) tests as published [15,18].

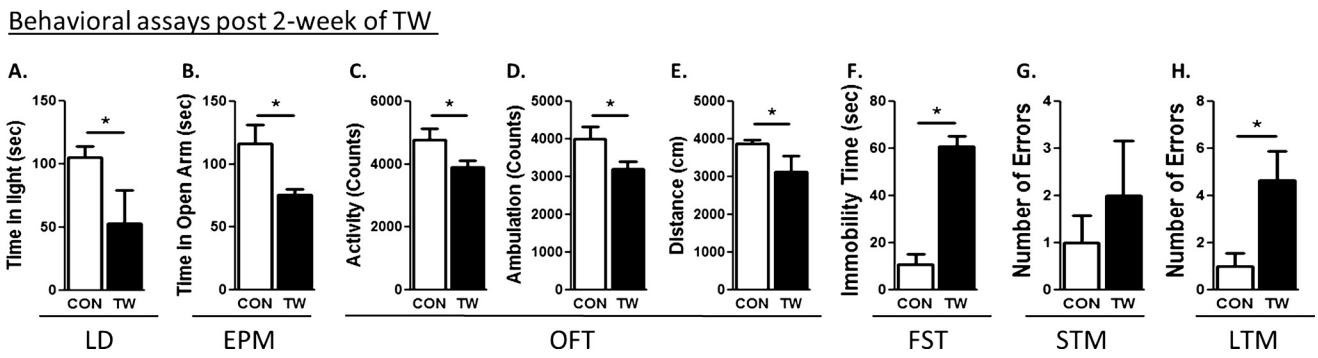


**Fig. 2.** Examination of anxiety and depression-like behaviors and cognitive deficits 2 week after TWM: light-dark test (A), elevated plus maze test (B). The open-field test determined total (C), ambulatory (D) activities and distance travelled (E). Forced swim test (F) were conducted. Short-term (G) and long-term memory (H) tests were conducted in all rats. (*) significantly different from control rats, $p < 0.05$. Bars represent means ± SEM, $n = 10$ rats/group.