



An Anxiety Profile of Stress Enhanced Fear Learning, a Rodent Model of Post-traumatic Stress Disorder

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Introduction:

Post-traumatic stress disorder (PTSD) is an anxiety disorder that is growing in prevalence and is becoming an increasingly important social issue not only for veterans and their families but also to civilian populations exposed to violence and survivors of natural disasters [1]. PTSD is precipitated by exposure to a traumatic event and is characterized by psychological and physiological symptoms that interfere with everyday functioning [2]. Patients with PTSD are more likely to acquire new phobias and show behavioral symptoms such as hyper-vigilance, anxiety, and increased startle responding.

Stress-enhanced Fear Learning (SEFL) is a rodent model of PTSD that examines how normally adaptive fear learning becomes maladaptive. SEFL uses an electric foot-shock procedure in rats to simulate a traumatic event. After experiencing this acute stressor animals show disproportionately enhanced learning of a new fear after experiencing milder aversive events.

The SEFL procedure generates several of the behavioral symptoms characteristic of PTSD, one of which is an increased susceptibility to the acquisition of new fears[3], resistance to extinction[4]and pharmacological resistance[3,5]. The goal of these experiments was to extend the SEFL phenotype by characterizing behavior in anxiety-related and anxiety-like behaviors. Using three different test procedures we examined animals that were previously exposed to the SEFL-inducing stress procedure.

Experiment 1: Open Field (anxiety and defensive behavior)

In this modified open-field procedure designed to assess anxiety and defensive response [6], both exploratory activity and reaction to changes in illumination were quantified after pre-exposure to the 15-shock stressor (or 0-shock control) in the SEFL procedure. The open field test consisted of three phases: 1) four minutes of dark, 2) four minutes of light and 3) four minutes of dark. Locomotion, defined as the number of crossovers during the 12-minute test. The transient increase in locomotion between changes in illumination, or activity response, is an exploratory response to stimulus change. This activity response between dark to light (phase 1 to phase 2) [(minute 5 crossover count)-(minute 4 crossover count)] and light to dark light (phase 2 to 3) [(minute 9 crossover count)-(minute 8 crossover count)] was also determined.

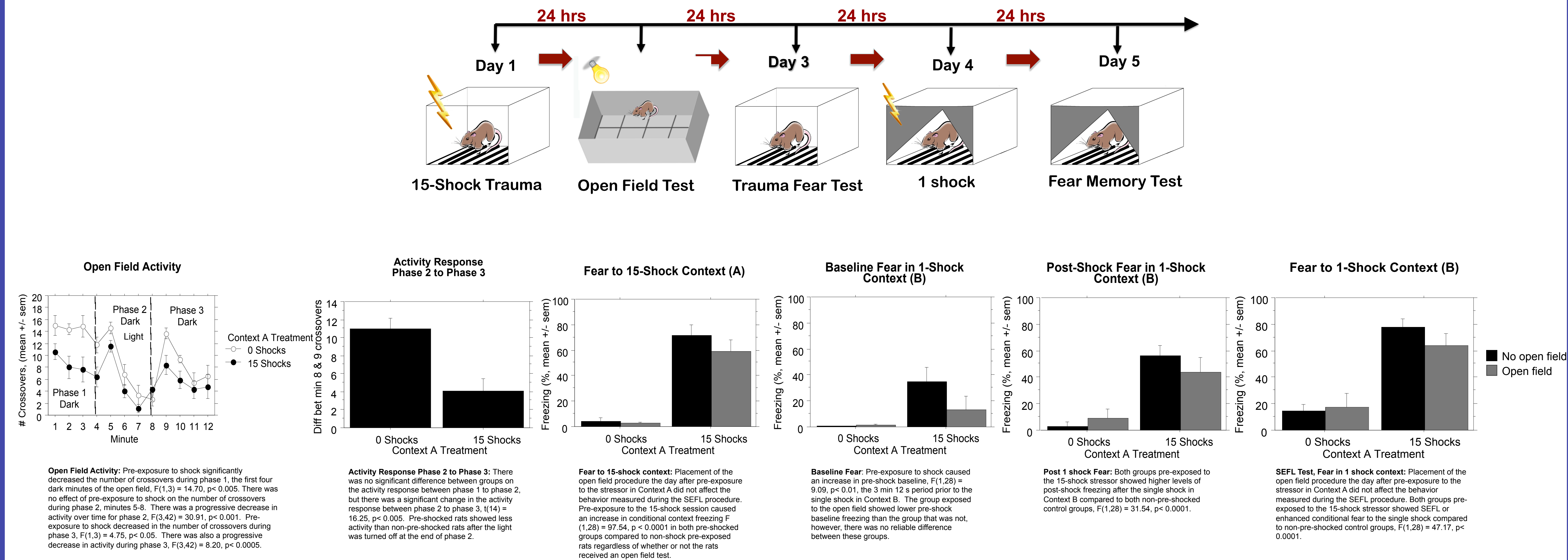
Experiment 2: Aversive Noise (hyper-vigilance and increased startle)

Previously, we found that subsequent to traumatic-stress animals showed enhanced fear learning to a novel context in which they were given a single reminder shock. In this experiment we attempted to extend these findings by using a noxious noise stimulus in place of the single shock, and determine how prior traumatic-stress may alter response to stimuli not of the same perceptual category as the initial stressors. Animals were pre-exposed to 15 (1 mA) unsignaled foot-shocks (or 0-shock control) in the SEFL procedure. On the following day all animals were tested in a novel context; animals were given 3 minutes to explore the context before exposure to a burst of three pulses of 100 dB white noise. Pre-noise and post-noise freezing was measured; changes in reactivity during the noise burst were also measured. Twenty-four hours later, all animals were tested in the novel context and fear memory was assessed.

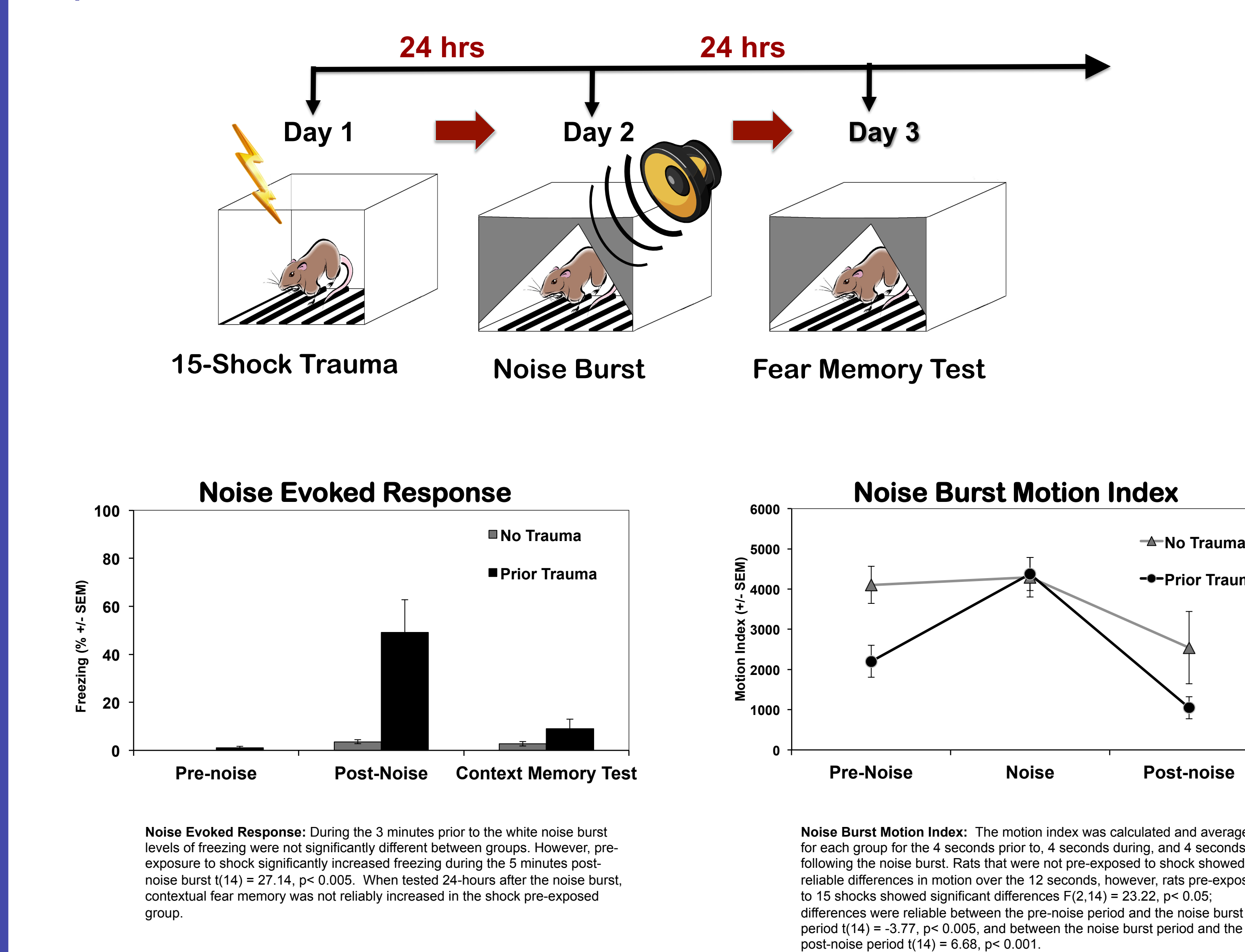
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2. American Psychiatric Association., *Diagnostic criteria from DSM-IV-TR2000*, Washington, D.C.: American Psychiatric Association. xii, 370 p.
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Experiment 1: Open Field



Experiment 2: Aversive Noise



Discussion:

Open Field:

- Pre-exposure to the 15-shock stressor reduced exploration during both light phases (1 and 3) as measured by the number of crossovers.
- Both shocked and non-shocked rats showed an increase in activity at the onset of the light replicating previous findings with this task.
- A reduced activity response was observed in pre-shocked rats during the transition from dark phase 2 to light phase 3.
- During the dark to light change pre-shocked rats show less responsiveness and willingness to explore during the light to dark stimulus change compared to the non-pre-shocked rats.
- Modifying the SEFL procedure to include the open field test on Day 2 did not affect the conditional fear measured in each context.
- Both shock pre-exposed groups showed SEFL in Context B and increased post-shock freezing after the single shock while both non-shock-pre-exposed groups showed an appropriate level of fear in response to cues associated with the single shock.
- These data suggest that pre-exposure to the 15-shock stressor is associated with measures of increased generalized anxiety, reduced exploration of a novel environment and decreased reactivity to changes in light stimulation.

Aversive Noise:

- Baseline fear response in the novel context were comparably low during the baseline 3 minute period.
- During the 5 minutes post-noise the animals that had received traumatic-stress showed a reliably elevated freezing response compared to their non-shocked counterparts.
- The results from the fear memory test in the novel context revealed no reliable differences in freezing levels between the pre-shocked SEFL group and controls.
- Although the noise burst was not capable of conditioning fear, rats that were pre-exposed to the 15-shock stressor showed hyper-responsive fear following the noise suggesting a potentiation of startle responding and hyper-vigilance.

Summary:

- The SEFL procedure not only produces enhanced fear learning it also produces an anxiety-like phenotype. This further supports the use of the SEFL procedure as a model of PTSD.