# Vagus nerve stimulation enhances longevity of conditioned fear extinction

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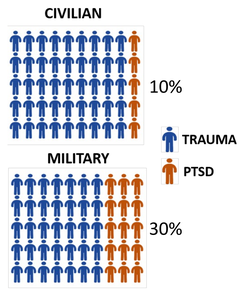
## Introduction

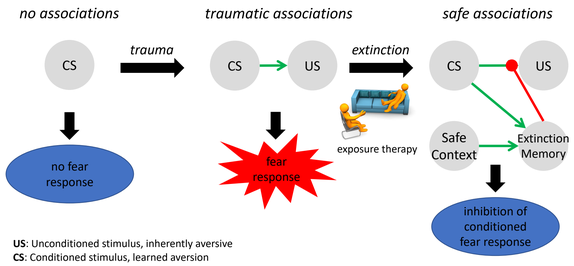
### *Post-traumatic stress disorder*

| DSM-5 Symptoms | | |
|---|---|---|
| | **Intrusion** *Vivid, distressing memories of trauma* | **Avoidance** *of trauma-related thoughts, feelings, and stimuli* |
| | **Hyperarousal** *Irritability, hypervigilance, startle response, etc.* | **Cognition & Mood** *Comorbidities: depression, substance abuse* |




### *Exposure-Based Therapy & Extinction*

- Standard of care
- Goal: Extinguish conditioned emotional response
- Limitations:
  - Dropout
  - Generalization
  - Relapse

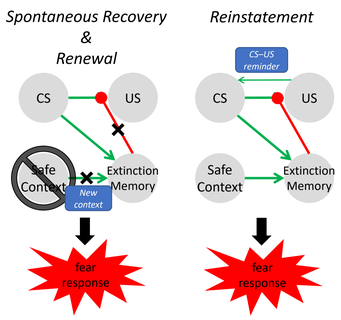



### *Relapse of Fear: Mechanisms*

**(1) Spontaneous Recovery** (passage of time)
- Change in temporal/interoceptive context

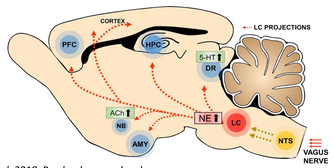
**(2) Renewal** (CS in novel context)
- Change in spatial context

**(3) Reinstatement** (eg, stress)
- Reminder of US




### *Vagus Nerve Stimulation (VNS)*

- Enhances extinction learning
- Recruits activity of brain regions involved in fear learning

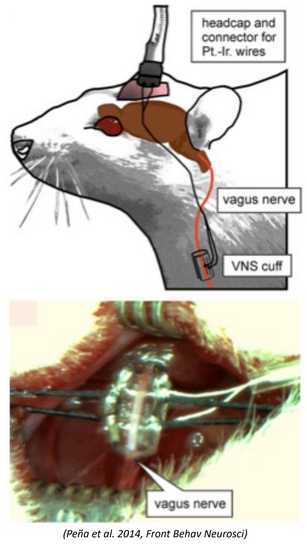



(Noble et al. 2018, Psychopharmacology)

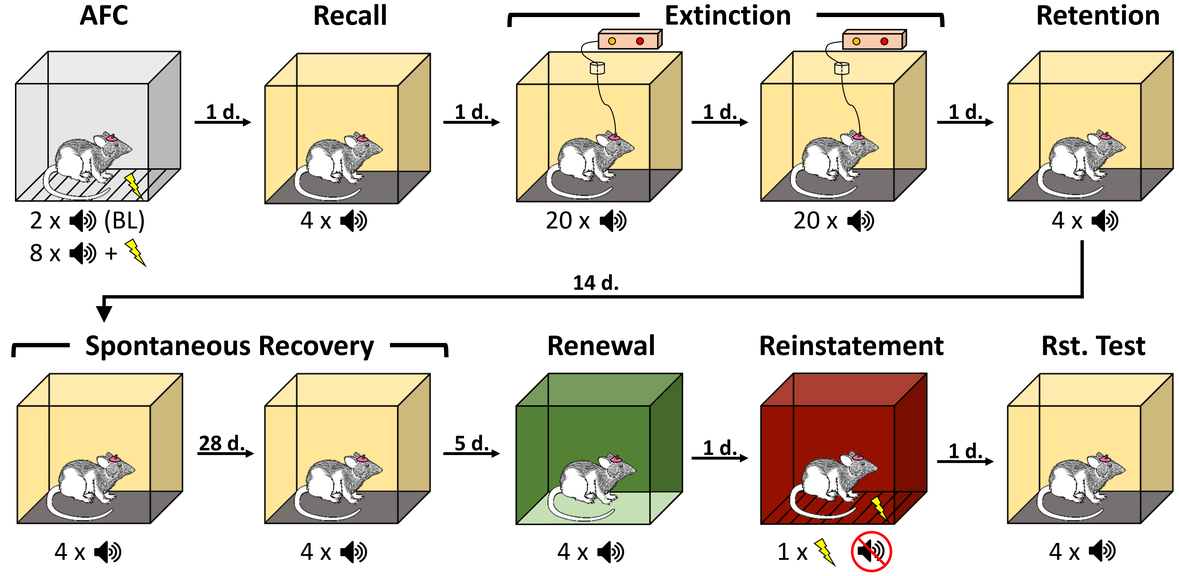
***Does VNS leverage fear learning pathways for extinction?***

**Hypotheses:** VNS will
(1) Increase speed of extinction
(2) Protect against fear relapse

## Methods

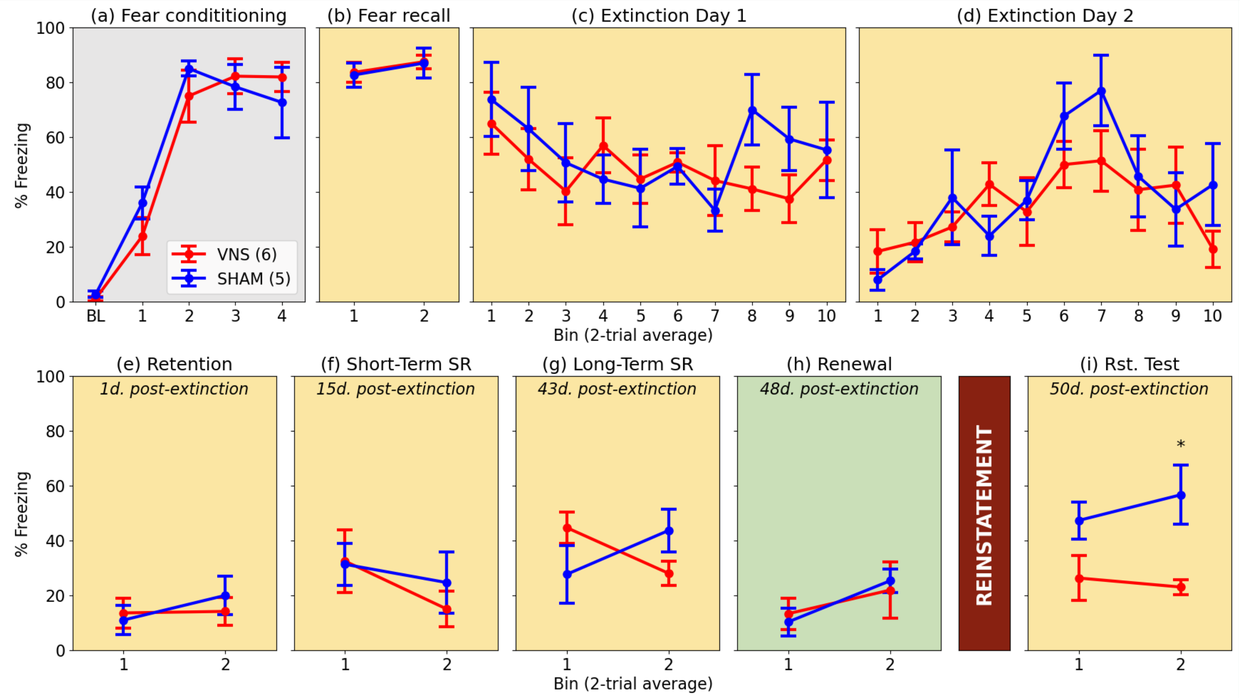



(Peña et al. 2014, Front Behav Neurosci)




## Results

- No difference between groups in extinction (c,d)
- Both groups achieve full remission of conditioned fear (e)
- No VNS improvement for
  - Short-term spontaneous recovery (f)
  - Long-term spontaneous recovery (g)
  - Renewal (h)
- **VNS prevented reinstatement (i)**




## Methods

- **Animals**: Adult male and female Long-Evans rats.
- **VNS Surgery:** Custom-made cuffs implanted around left vagus nerve and tunneled under skin to a headcap mount.
- **Auditory fear conditioning (AFC):** 2 baseline (BL) trials; then 8 CS+US
  - CS: 9kHz tone (75dB/30s)
  - US: footshock coterminating with CS (0.8mA/1s)
- **Extinction:** 2 days of 20 CS-only extinction trials (extended extinction, EE) with VNS or sham stimulation.
- **Contexts:** 4 contexts were used across tests, indicated by cage color.
- **VNS Parameters:** 4, evenly-spaced, 2s, 0.8mA VNS trains in each 30s trial.

## Discussion

*Conclusions*
- VNS protects extinction memory against reinstatement
- **Supports a distinct mechanism for VNS-enhanced extinction**
  - Enhance function of typical circuits, or recruit additional circuits (eg, fear learning circuits)?

*Future work*
- Replication with more animals (n=11, planned n>20)
- Mechanisms of VNS-enhanced learning (eg, with optogenetics)
- VNS amelioration of other PTSD symptoms (eg, avoidance, hyperarousal)
- Stronger fear (eg, Single Prolonged Stress model of PTSD)

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