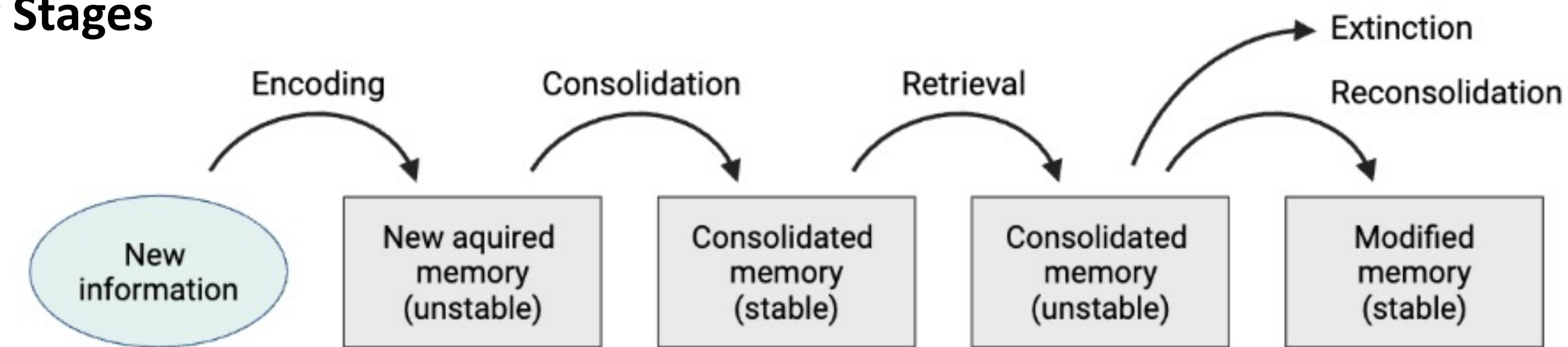


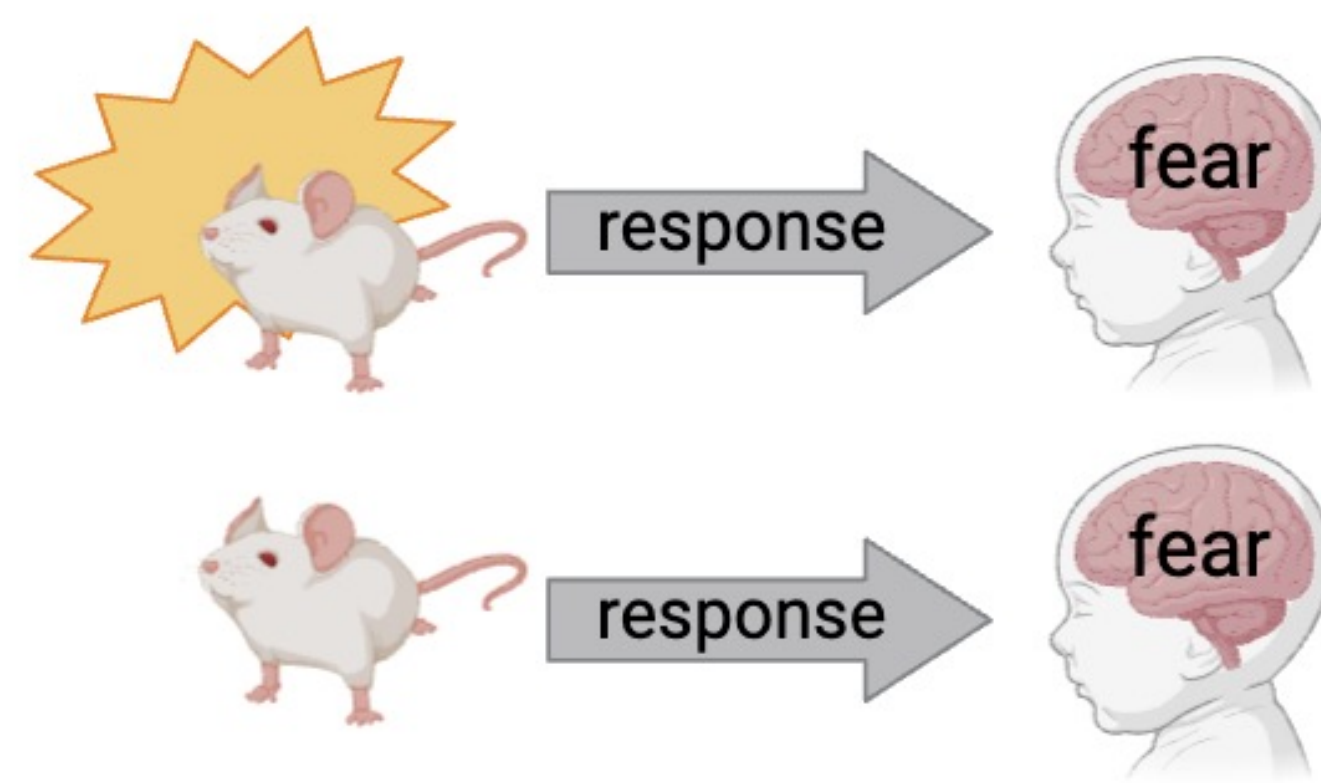
Background

A. Memory Stages



(A) **Memory:** fundamental cognitive process that uses past experiences to guide present and future behavior. (Zlotnik & Vansintjan, 2019).

B. Fear Conditioning – Little Albert Experiment

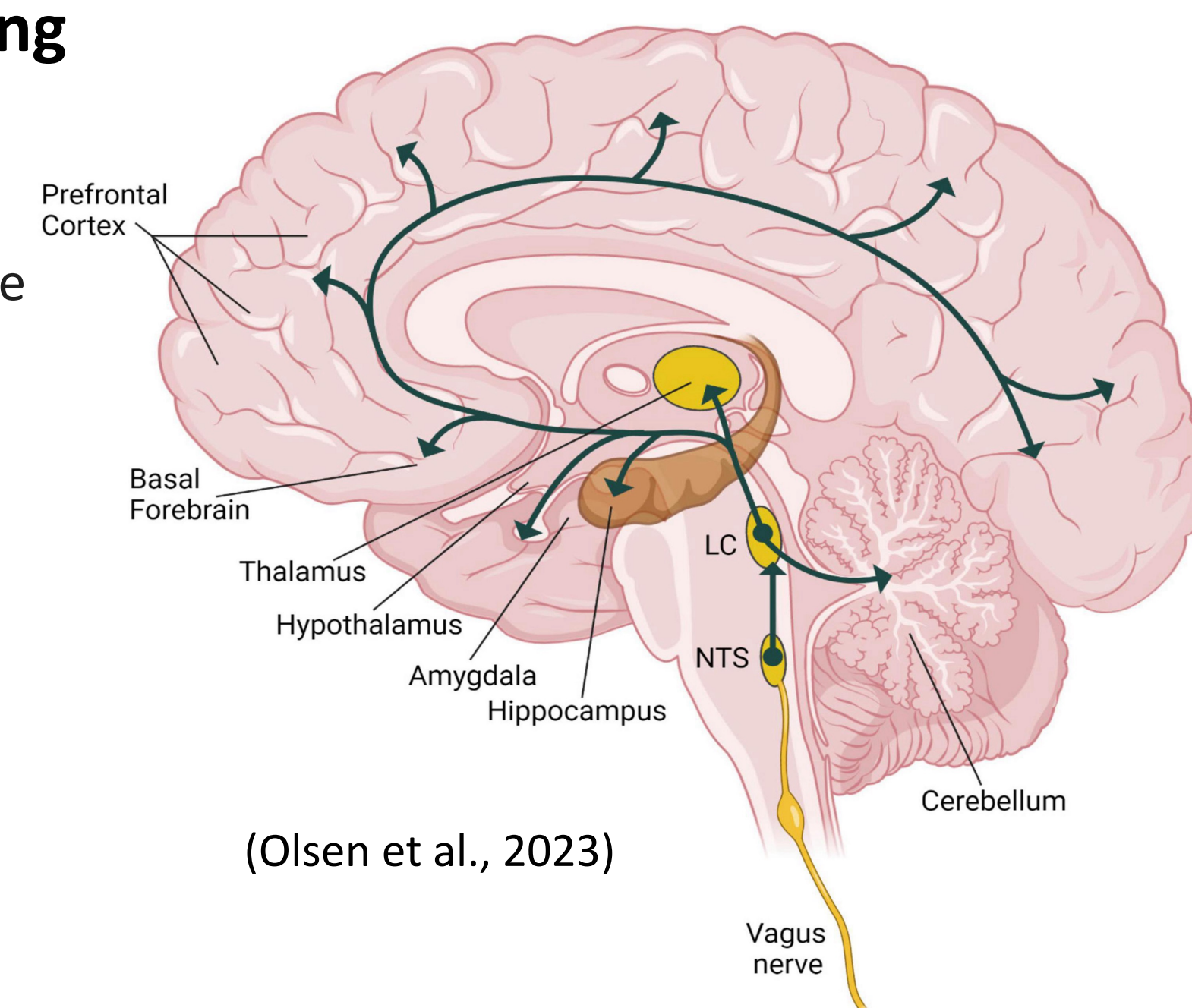


(B) **Fear conditioning:** learning process that pairs a neutral stimulus and aversive stimulus (Lee & Kaang, 2023).

Post-Traumatic Stress Disorder (PTSD): an anxiety disorder caused by a traumatic event (3.9% of global population). 40-60% of patient have a therapeutic effect under the current **exposure therapy** (Koenen et al., 2017; Bradley et al., 2025).

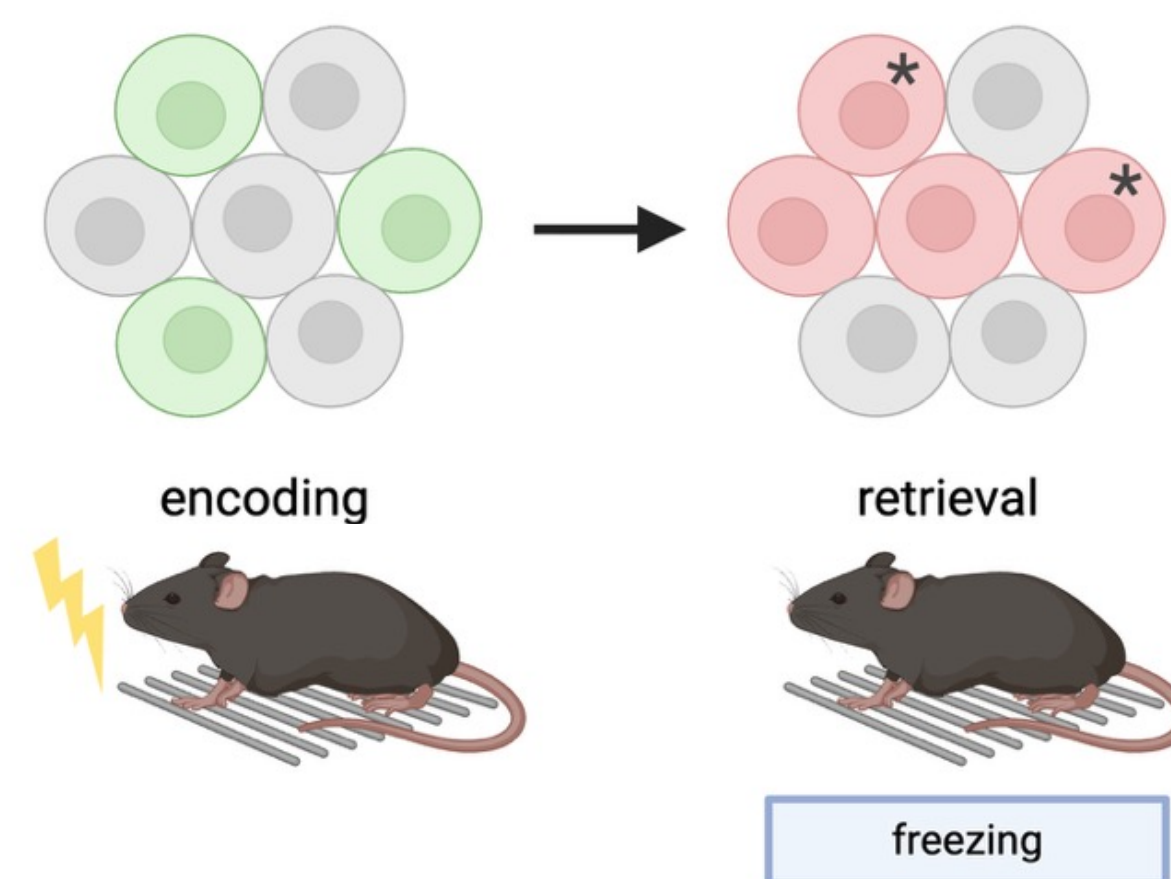
C. Brain Regions Related to Fear Conditioning

(C) **Amygdala:** emotional processing
Hippocampus: Memory processing
Locus Coeruleus (LC): arousal, attention, stress response
Vagus Nerve: connect brain stem to abdomen
VN stimulation: a neuromodulatory treatment for epilepsy, depression, and potentially PTSD



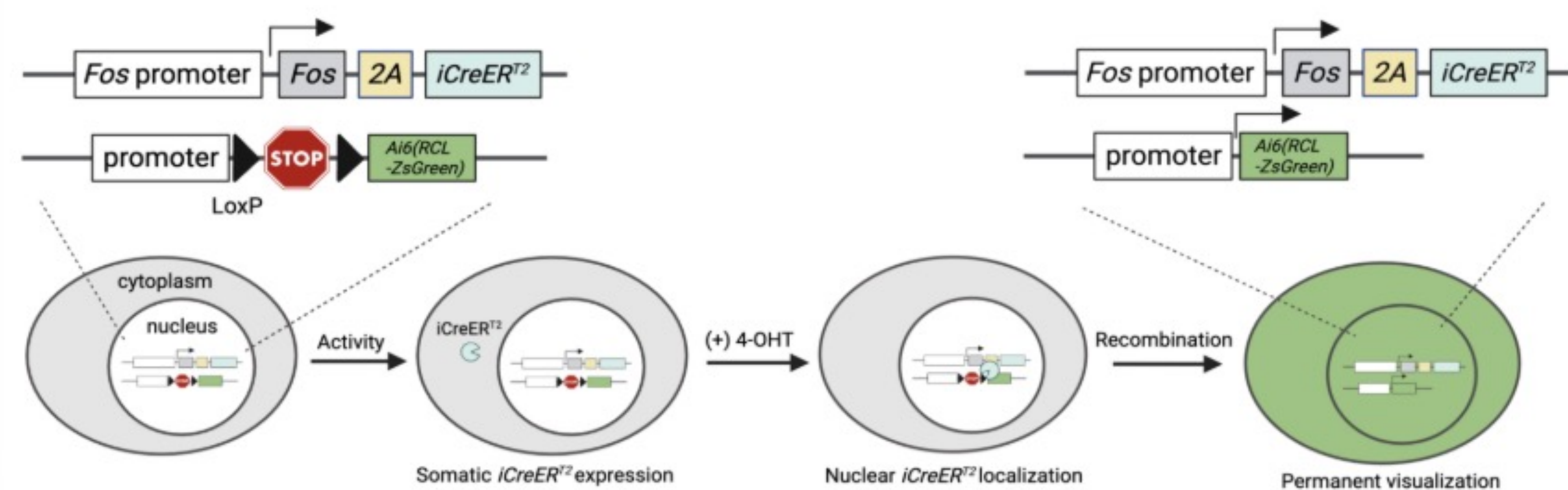
(Olsen et al., 2023)

D. Engrams



(D) **Engram:** neuronal population activated by learning and reactivated by retrieval. It undergoes chemical and physical changes. (Josselyn & Tonegawa, 2020)

Animal Models



Targeted Recombination in Active Populations: genetic approach for a permanent labeling of neurons with **tamoxifen** or **4-hydroxytamoxifen (4-OHT)** (DeNardo et al., 2019; Guenther et al., 2013).

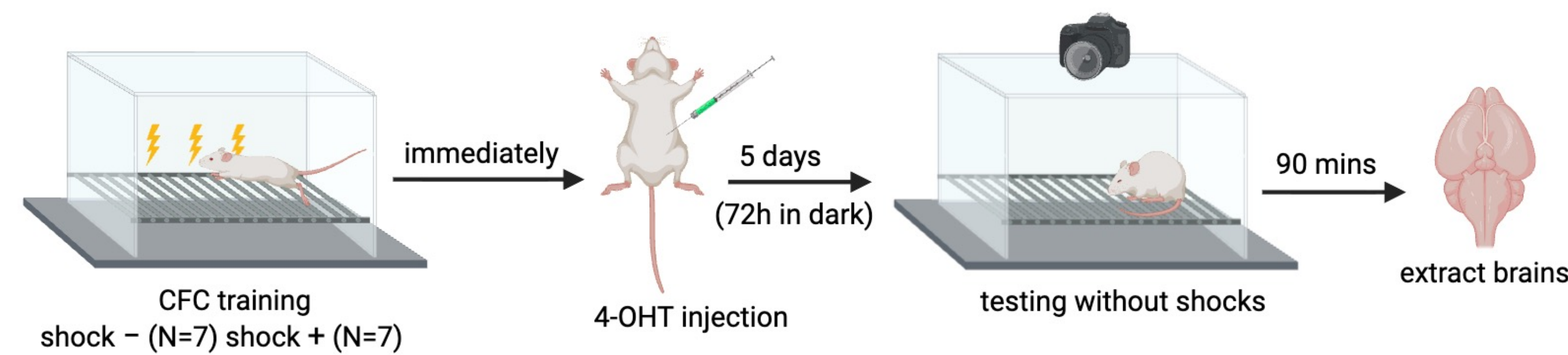
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Methods

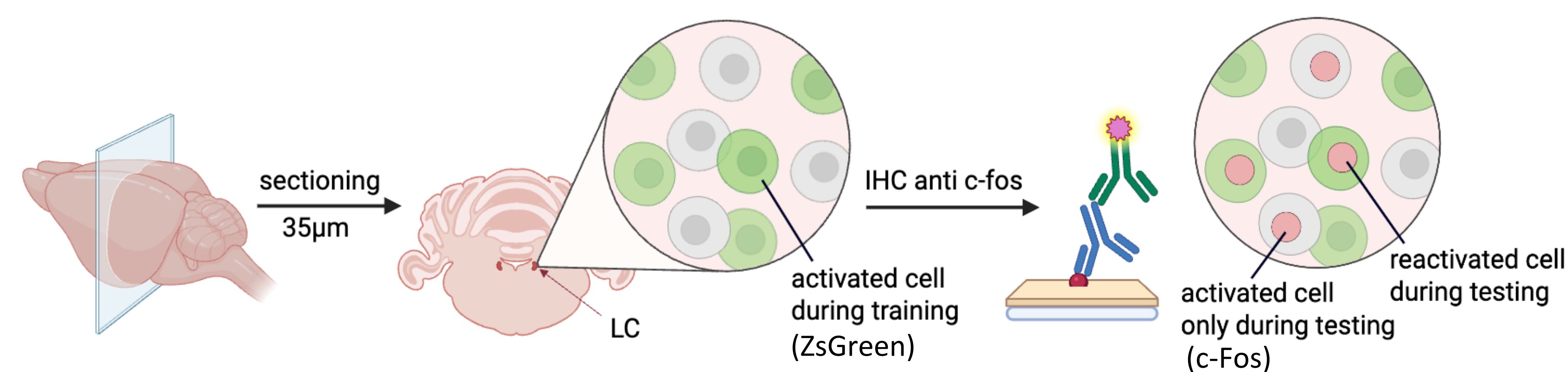
Question: Does the LC itself contain fear memory engrams?

A. Tagging of Activated Cells in Contextual Fear Conditioning



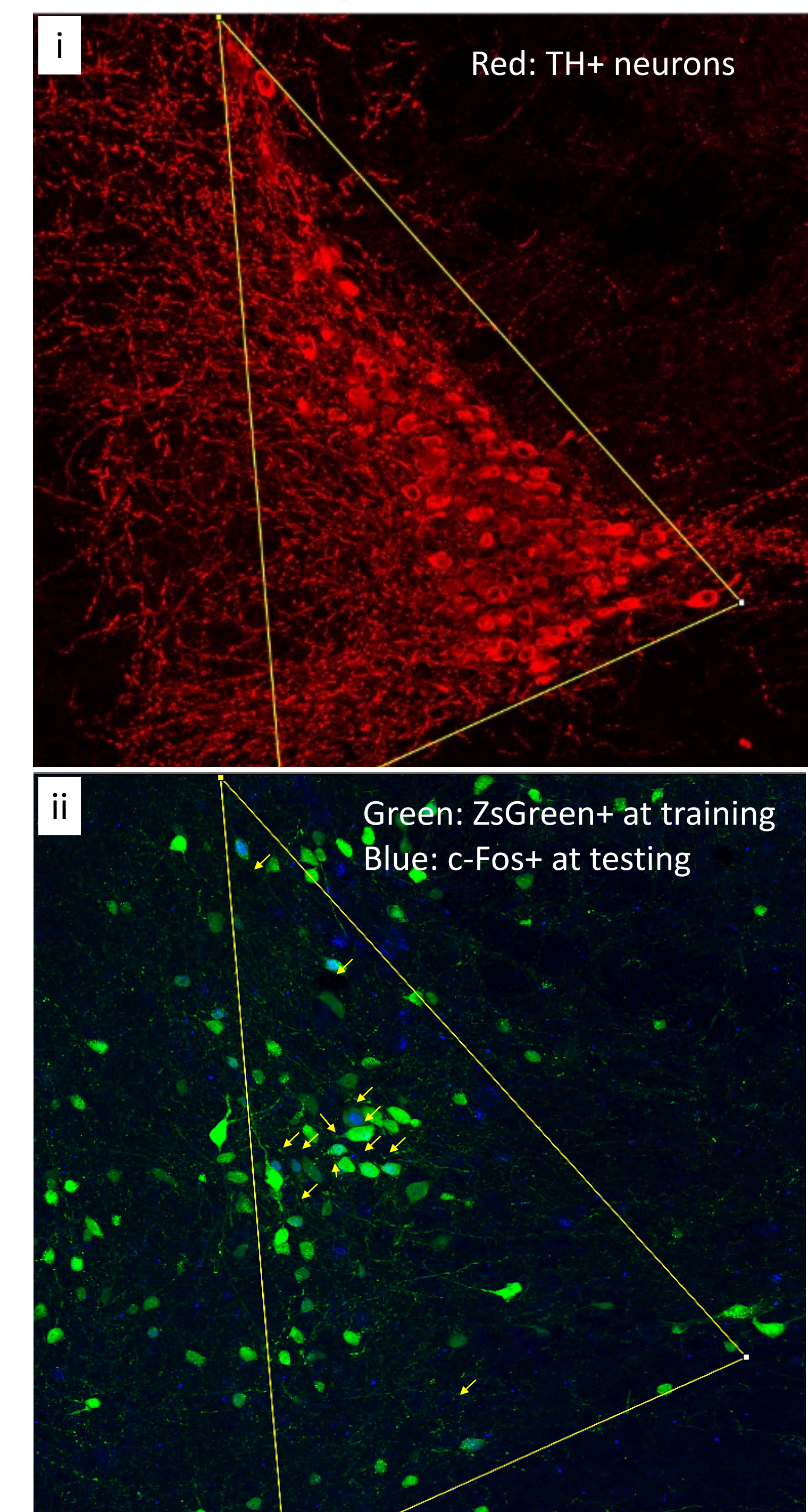
(A) TRAP 2 mice underwent training, 4-OHT was injected immediately to visualize the c-Fos activation with ZsGreen, and then testing occurred 5 days after conditioning.

B. Staining of Reactivated Cells with Immunohistochemistry (C-fos & TH)



(B) The brains sections were processed for TH and c-fos IHC.
 - **ZsGreen:** active neurons at training - **c-Fos:** active neurons at testing
 - **TH (tyrosine hydroxylase):** identification of Noradrenergic neurons in the LC

(ii) Yellow arrows: double-positive → **Engrams**
 # ZsGreen+ cells = 55,
 # double-positive cells = 12
 → reactivation (%) was 12/55*100 = 21.8%.



Results

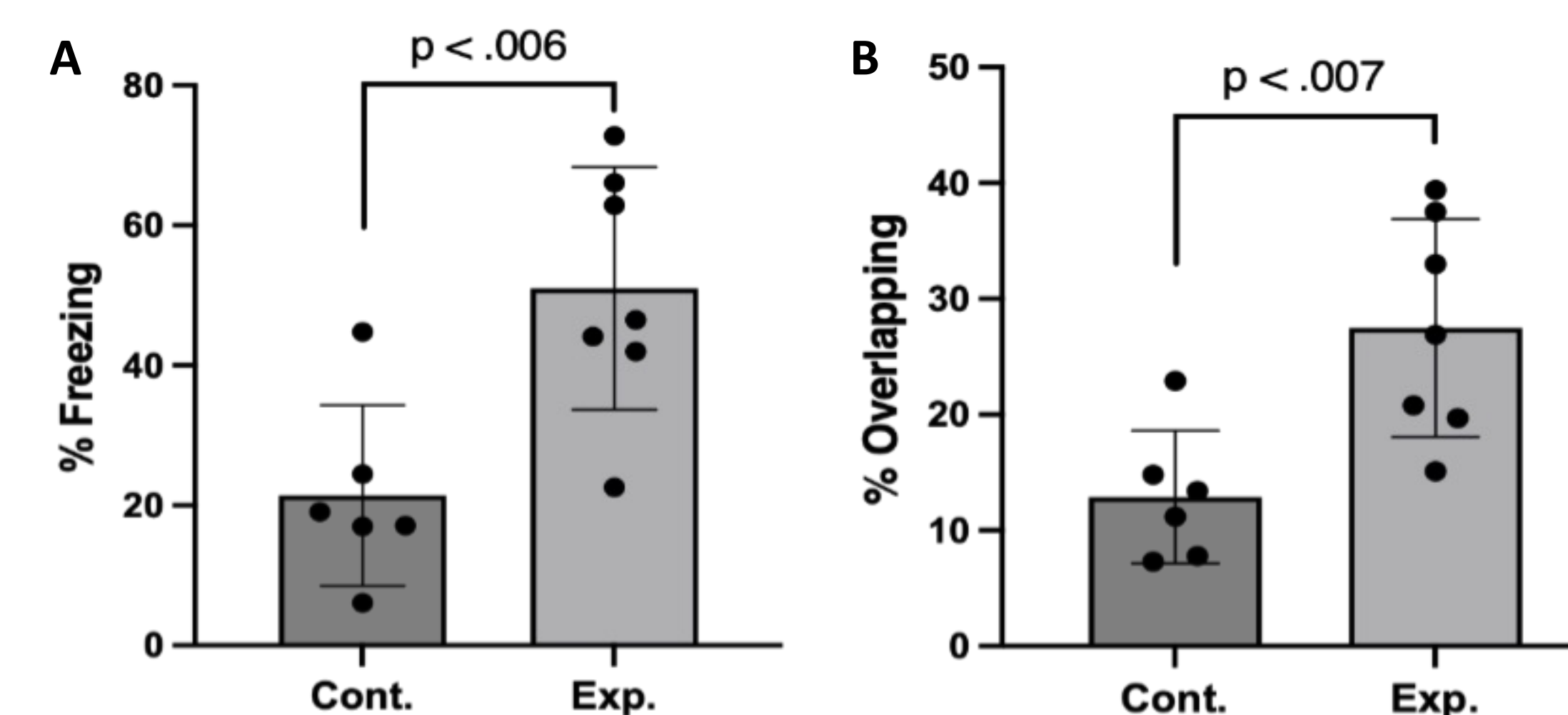
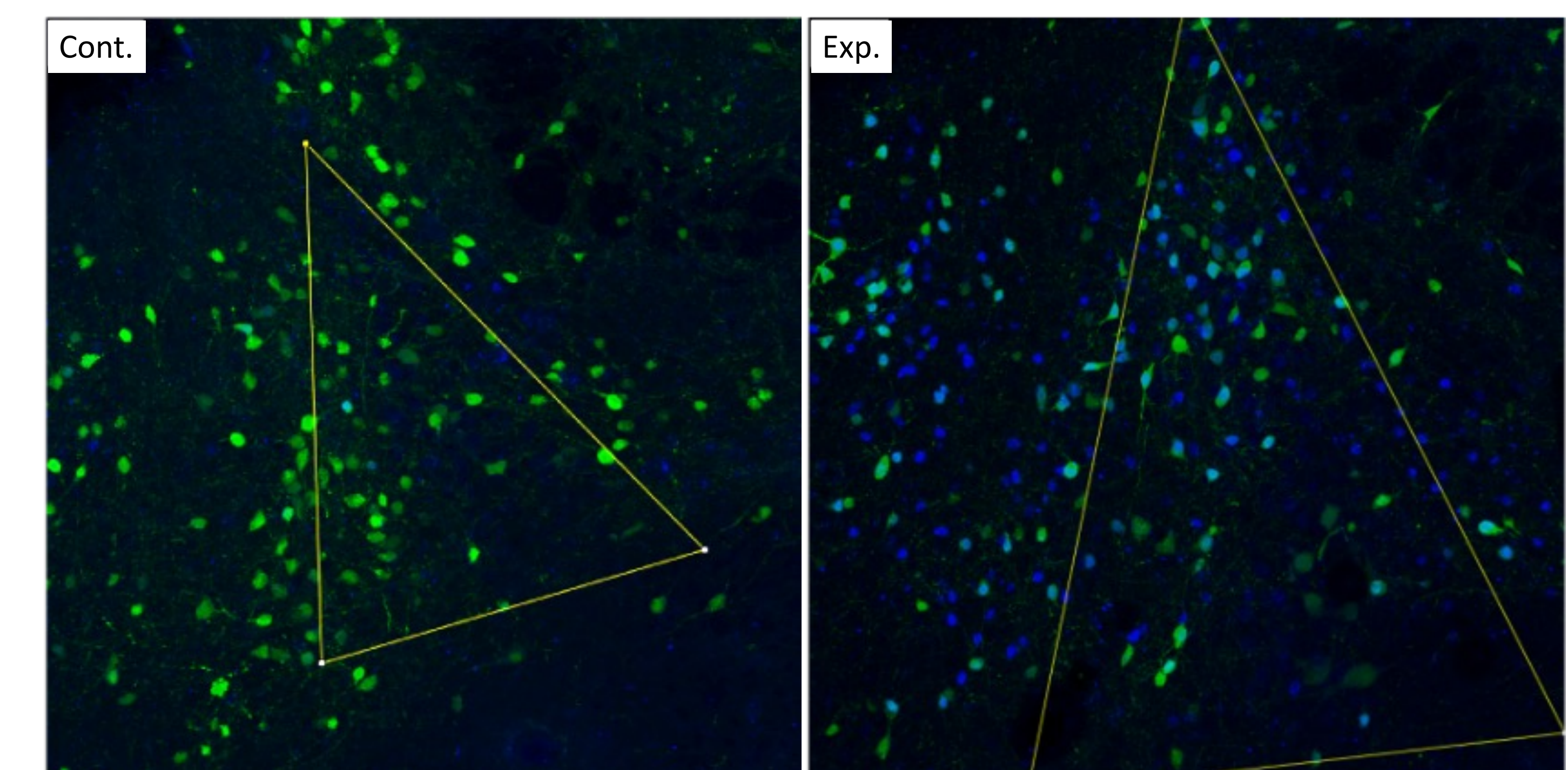


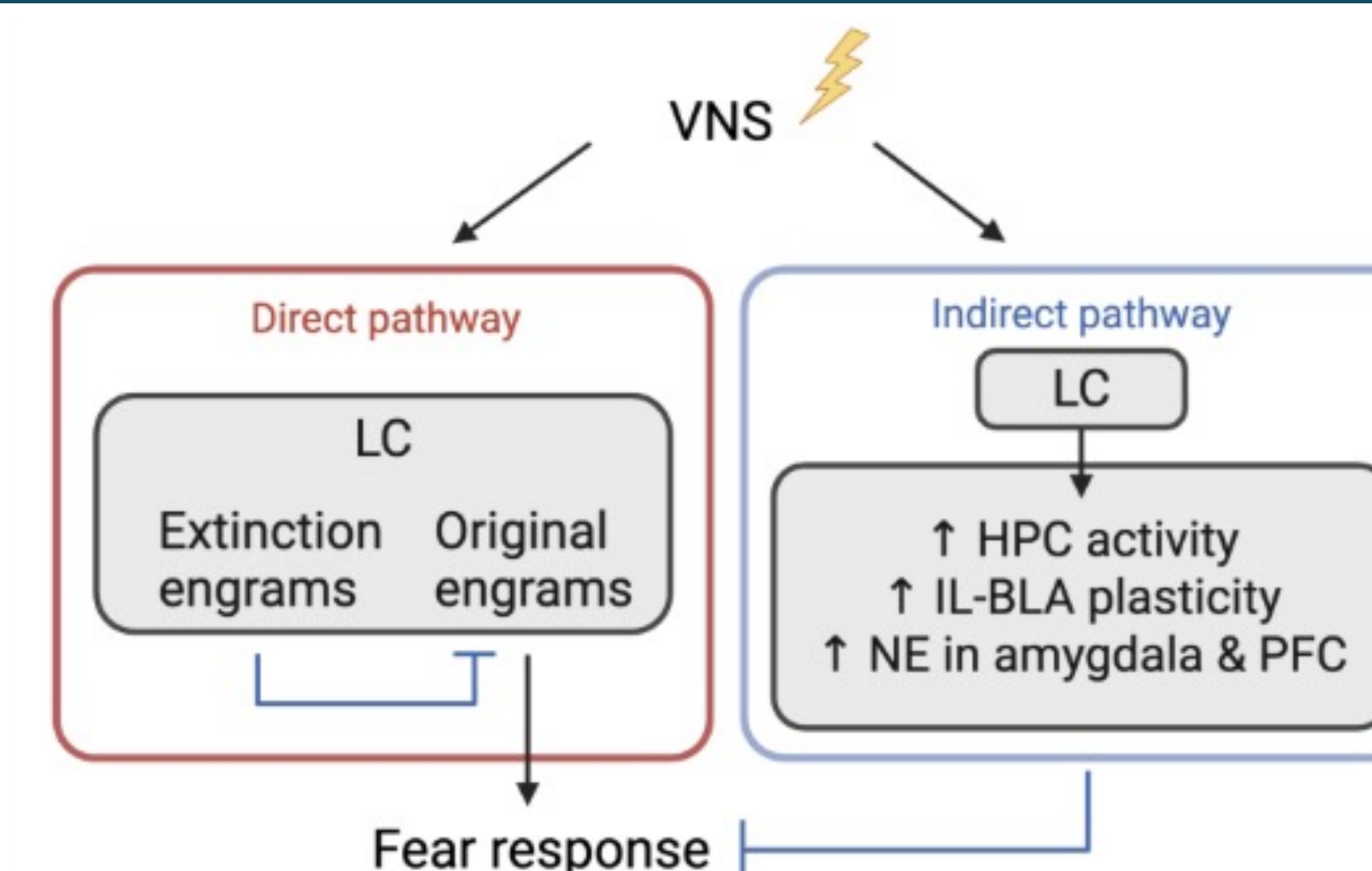
Figure 1. The experimental group exhibited (A) significantly higher freezing behavior ($p < 0.006$) and (B) significantly greater c-Fos+/ZsGreen+ double-positive cells ($p < 0.007$) than the control group.



Discussion

(A) **The LC contains engrams to store contextual fear memory**
 → the LC directly “**engage**” memory-storing networks

(B) Potentially exist “**extinction engrams**” in the LC
 → could **suppress** the fear response under VNS with indirect pathway



(C) Potential clinical strategies for PTSD
 - **Synchronizing VNS with exposure therapy** to strengthen extinction engrams
 - **Pharmacological regulation** of LC fear engrams
 - **Circuit-specific neuromodulation** targeting LC-higher-order brain engram networks

