Optogenetic Activation of Substantia Nigra Neurons Projecting to the Dorsal Lateral Striatum during Fear Extinction Reduces Fear Renewal

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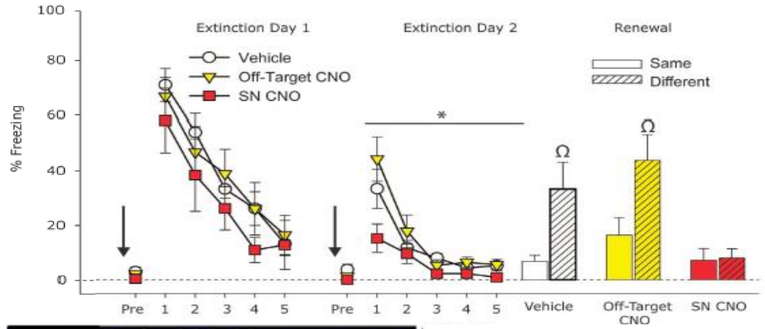
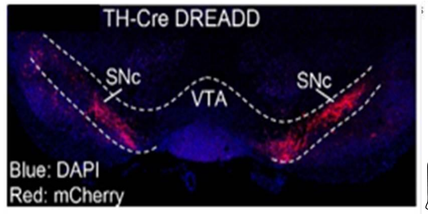
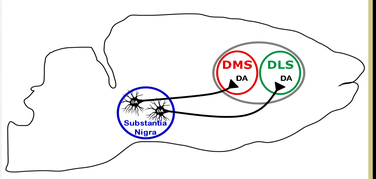
Background

- Fear extinction represents new learning that a previously fear-conditioned stimulus is no longer associated with a predicted aversive event
- One limitation of fear extinction memory is that fear often returns even after successful extinction. Fear renewal is a return of fear in a context different from where fear extinction was learned
- Identification of novel strategies to prevent fear renewal is of utmost importance to mental health
- We have observed that DREADD-induced activation of substantia nigra dopamine neurons during fear extinction enhances fear extinction learning and blocks fear renewal (Bouchet et al. NPP, 2018)
- The majority of DA neurons in the SN project to the dorsal striatum, and injection of a D1 receptor agonist into the dorsal striatum partially mimicked the effects of DREADD (Bouchet et al. NPP, 2018)



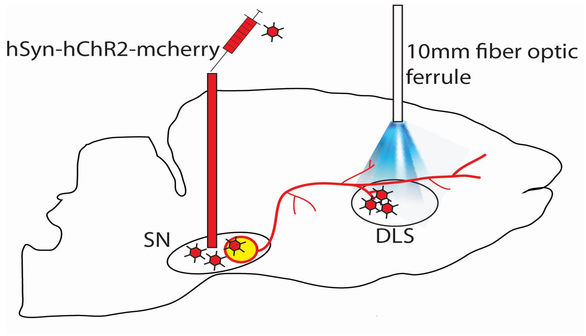




- One limitation of our prior observations is that we failed to target specific subregions of the dorsal striatum which may play independent roles in fear extinction learning and renewal
- The neural circuit between the substantia nigra (SN) and dorsal lateral striatum (DLS) is important for habit formation. Facilitating the use of a habit learning strategy during fear extinction learning could help prevent renewal by freeing the memory from contextual modulation
- Here, we will take advantage of modern techniques to optogenetically activate dopaminergic terminals originating from the SN projecting to the DLS during fear extinction to determine if activating this pathway during extinction can reduce fear renewal

Hypothesis

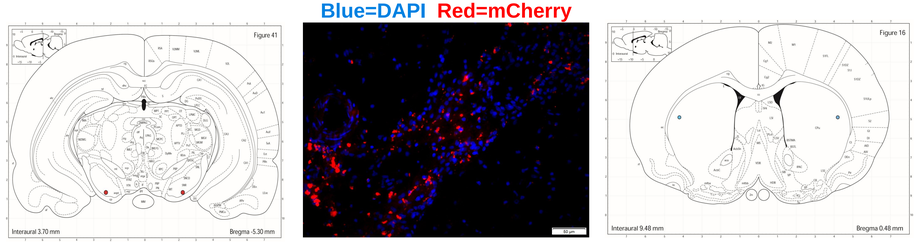
Optogenetic activation of substantia nigra terminals in the dorsal lateral striatum during fear extinction learning will reduce fear renewal



- h-syn (Human synapsin) targets all neurons
- ChR2 virus codes for a light-sensitive sodium channel (channel rhodopsin)
- When exposed to light of the appropriate wavelength (473nm), the light-sensitive ion channels open causing depolarization of the neuron

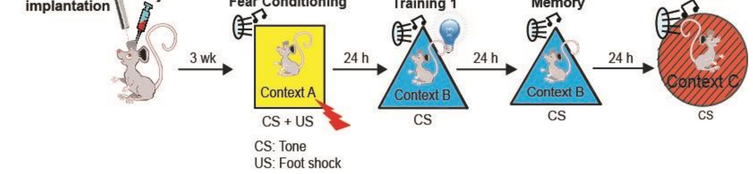
Methods

Blue=DAPI Red=mCherry

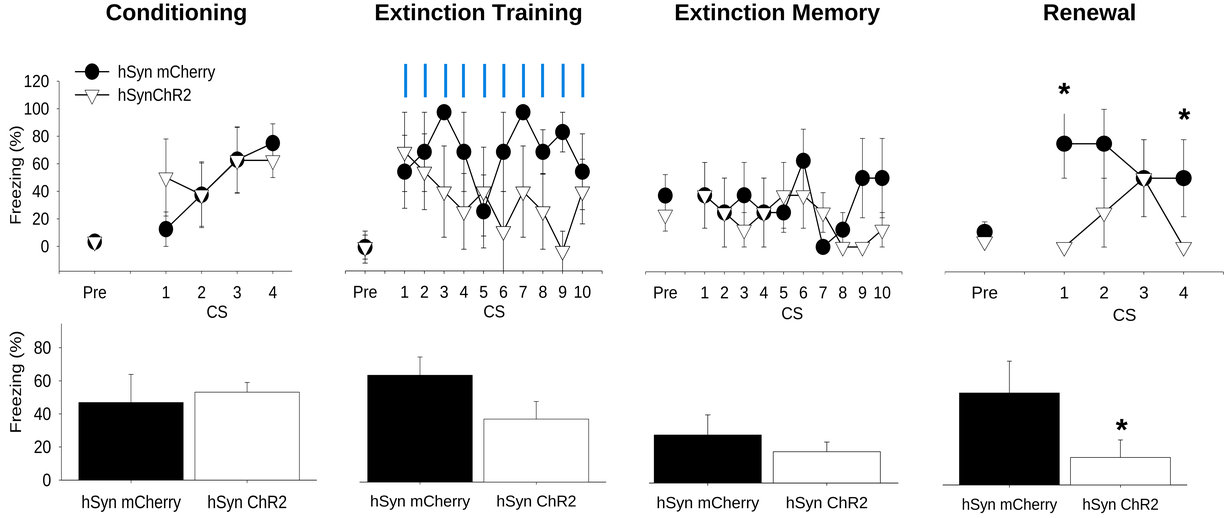


- Bilateral AAV-hSyn-mCherry (control) or Chr2-hSyn-mChery injected into the SN
- **A/P: -5.4; M/L:±2.3; D/V:-8.8**
- Bilateral 10mm ceramic fiber optic ferrules (THOR LABS) implanted into the DLS
- **A/P:+.05; M/L:±4.2; D/V:-4.9**

Experimental Timeline



Results



Conclusions

- Activation of SN terminals in the DLS during fear extinction reduces fear renewal without impacting fear extinction memory
- These data suggest that dopamine in the DLS can free fear extinction memory from its contextual modulation
- Dopamine in the DLS could be a novel target for preventing the relapse of fear after extinction

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