The Neural Correlates of Aversive to Appetitive Counterconditioning

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1.) Introduction

- Fear extinction is not unlearning, and extinguished behaviors can re-emerge through spontaneous recovery, contextual renewal or fear reinstatement.
- Previous studies in rodents have shown that pairing reward with fear extinction training reduces the return of fear that normally follows extinction training (Correia et al, 2016).
- A within-subjects study in humans found that reward enhanced explicit episodic memory of extinction and reduced conditioned fear renewal relative to standard extinction (Keller et al, 2019).
- Despite the fact that a lot is known on the neural correlates of fear extinction, very little is known on the neurobiology counterconditioning (CC) in the brain.
- **Research goal:** using fMRI in humans, investigate if reward reduces fear more effectively than standard extinction and determine the correlates of counterconditioning, in comparison to extinction.

2.) Methods

N=25

Task: three session Pavlovian fear conditioning design

In scanner sessions

Implicit fear

Skin Conductance Response (SCR)

Explicit fear

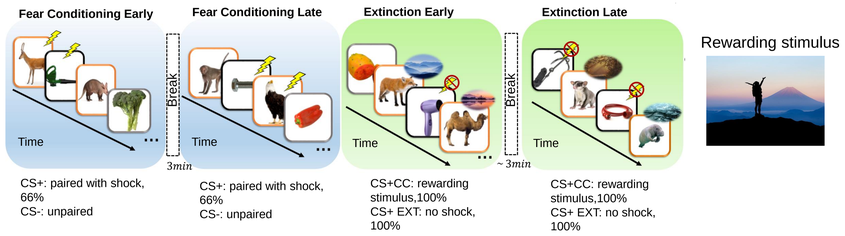
2 Alternative forced choice task

Do you expect to receive a shock following this picture?

Yes | No

Episodic memory

Day 1: Fear Conditioning and Extinction/Counterconditioning



CS+: paired with shock, 66%
CS-: unpaired

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CS-: unpaired

CS+CC: rewarding stimulus,100%
CS+ EXT: no shock, 100%

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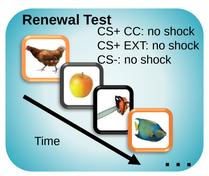
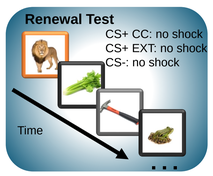
CS+ EXT: no shock, 100%

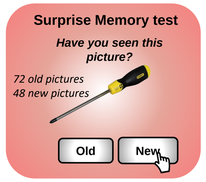
Day 2 and ~ 1 month later: Fear Renewal Test and Episodic Memory

24 hours later



1 month later





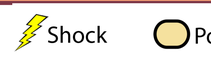
Stimulus material: 144 basic-level exemplars of animals and tools and food (72 each). Animals and tools as CS+, food as CS- (6 s duration). CS+ CC and CS+ EXT, counterbalanced (animals and tools). **CS+CC**: fear conditioned exemplars that were paired with a rewarding stimulus in lieu of shock during extinction. **CS+EXT**: fear conditioned exemplars that were paired with no shock during extinction. **CS-**: unpaired category.

fMRI acquisition: Scanning was completed using the Siemens Vida 3T MRI scanner. Functional data were acquired with a 64-channel head-coil. Functional image resolution was 2.5mm isotropic voxels (TR = 1s).

GLM analysis: Analysis of the preprocessed data included GLMs with separate regressors for each stimulus presented (CS+CC, CS+EXT and CS-) during fear acquisition, fear extinction, and fear renewal 24 hours later and 1 month later.

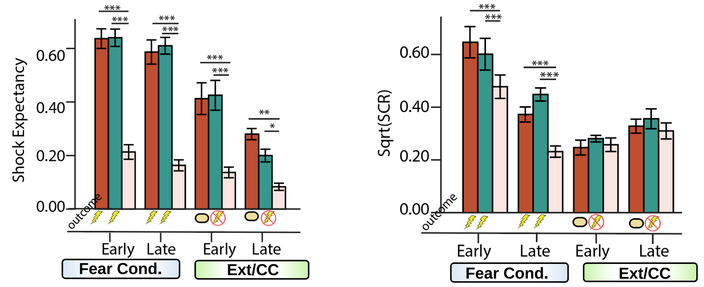
3.) Behavioral Results

**** P < .001*
*** P < .01*
** P < .05*
ns = not significant



CS+CC | CS+EXT | CS-

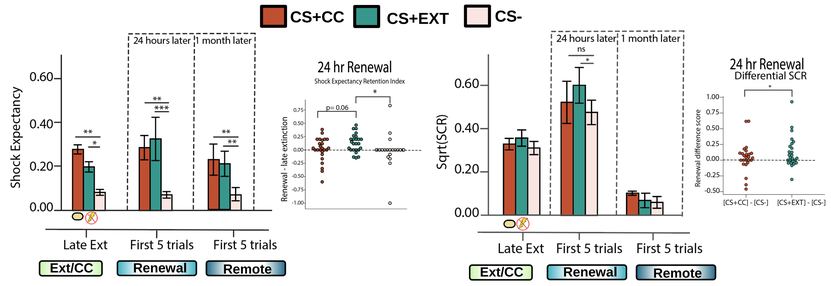
Fear Acquisition and Fear Extinction



Take home: Mean shock expectancy ratings, and SCRs of CS+ vs. CS- during fear conditioning confirmed **successful acquisition and extinction of fear.**

Fear Renewal: 24 hrs and ~1 month later

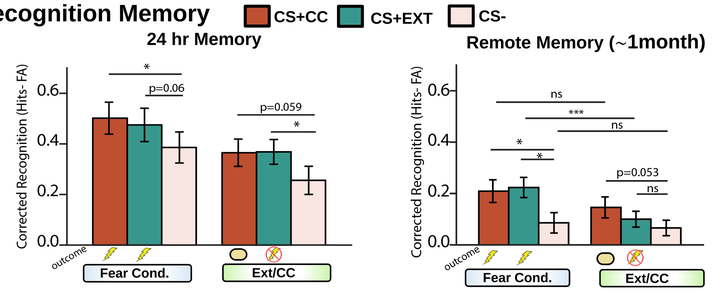
CS+CC | CS+EXT | CS-



Take home: 24 hrs later, implicit (SCR) and explicit (shock expectancy) **fear renewal was reduced for CC stimuli** in comparison to EXT. 1 month later there was no fear renewal to any stimuli.

Recognition Memory

CS+CC | CS+EXT | CS-



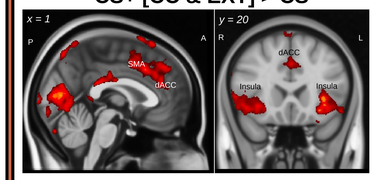
- **Take home for 24 hr memory:** there is **selective enhancement of memory for CS+ items** during fear conditioning, replicating previous findings.
- **Take home for remote memory: reward mitigated the drop in memory** from fear conditioning to extinction.

4.) Whole-brain fMRI Results

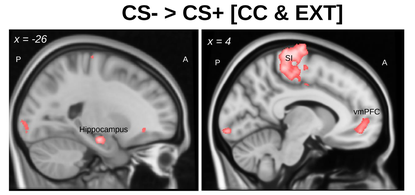
Single-Group Average (One-Sample T-Tests); Threshold p<0.001, uncorrected

Fear Acquisition

CS+ [CC & EXT] > CS-



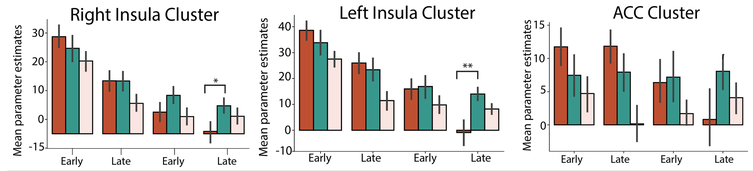
CS- > CS+ [CC & EXT]



Take home: Threat conditioning [CS+ > CS-] and the inverse contrast [CS- > CS+] revealed activity in regions which are consistently implicated in fMRI studies of human conditioning (Sehlmeyer et al., 2009; Mechias et al., 2010; Fullana et al., 2016).

Regions involved in threat acquisition (CS+>CS-)

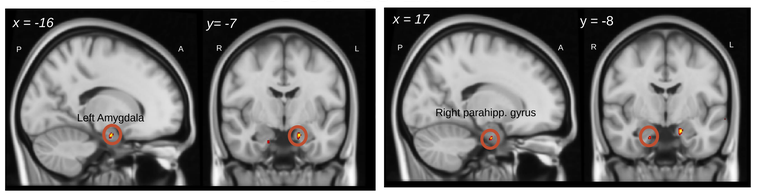
CC cope | EXT cope | CS- cope



Take home: A parameter estimate analysis using cluster regions active during fear conditioning revealed lower activity for CC items in comparison to EXT items, during late extinction.

Fear Renewal-24 hours later

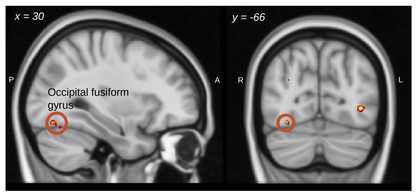
CS+CC > CS+EXT



Take home: During fear renewal, a contrast of novel stimuli from the **CC category – EXT category** revealed activity in the **amygdala** and **parahippocampal gyrus**.

Fear Renewal-1 month later

CS+CC > CS+EXT



Take home: One month later, stimuli from **counterconditioning** category activated the **left fusiform gyrus** significantly more than stimuli from the standard extinction category.

4.) Conclusion

- **Behavior**: Counterconditioning reduced the return of fear more effectively than standard extinction.
- **Episodic Memory**: Reward mitigated the drop in memory from fear conditioning to extinction at a long term memory test.
- **fMRI**: fMRI results reveal that compared to standard extinction, rewarded extinction mitigates the involvement of brain areas traditionally involved in threat acquisition, and activates the amygdala, parahippocampal gyrus and occipital fusiform gyrus during renewal, areas implicated in extinction recall.

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