Neural Circuitry Underlying the Regulation of Conditioned Fear and Its Relation to Extinction

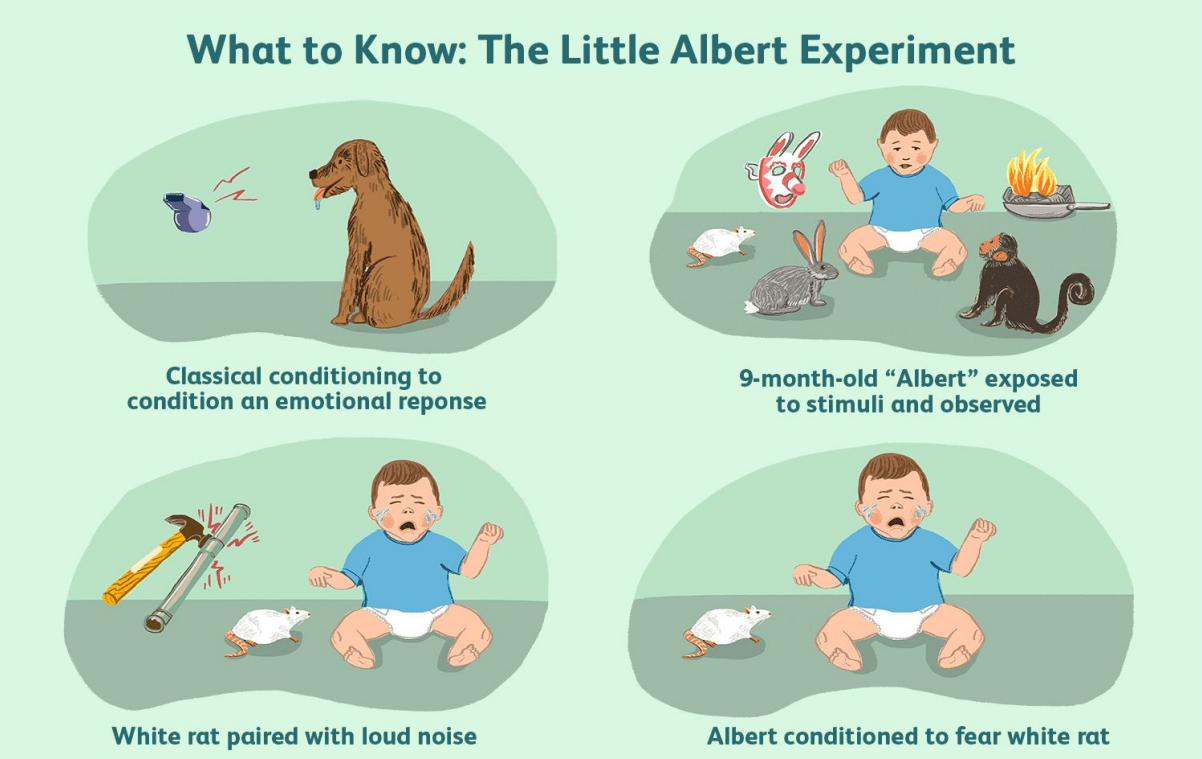
Delgado M. R., Nearing K. I., LeDoux, J. E. & Elizabeth A. P. (2008)

2020.07.13

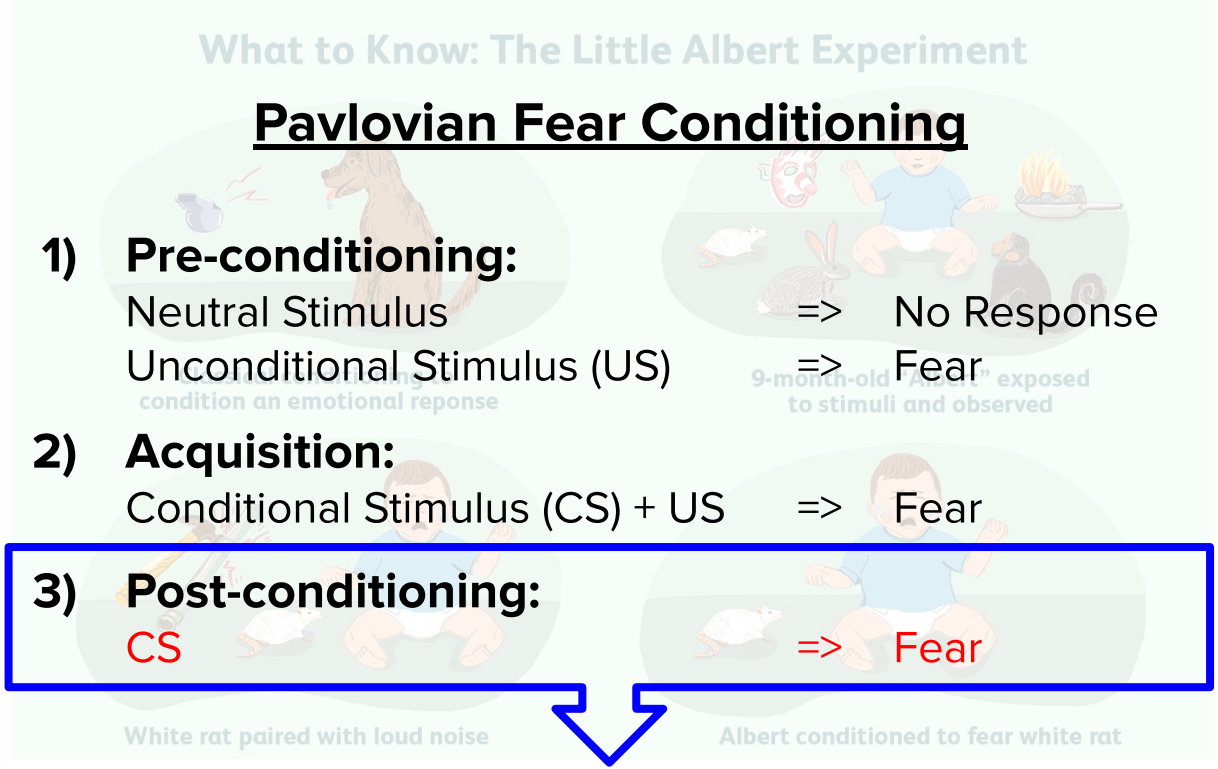
Computational Clinical Science Lab

Jihyun Hur

Fear Conditioning



Fear Conditioning



Pavlovian Fear Conditioning

1) **Pre-conditioning:**
   - Neutral Stimulus => No Response
   - Unconditional Stimulus (US) => Fear
2) **Acquisition:**
   - Conditional Stimulus (CS) + US => Fear
3) **Post-conditioning:**
   - CS => Fear

Anxiety disorders (Specific phobias)

Extinction versus Emotion Regulation

Extinction: by no reinforcement on CS

1. Acquisition

   CS + US => Fear

   CS => Fear

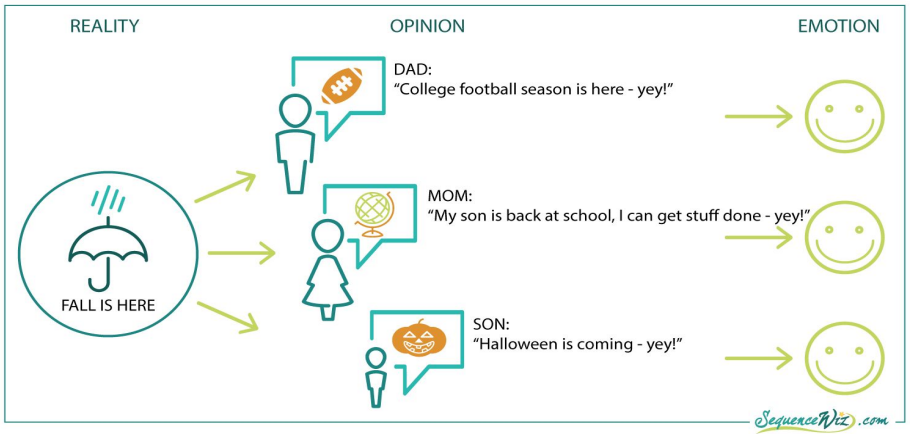
2. Fear extinction-ing

   CS + (US X)

3. Post-extinction

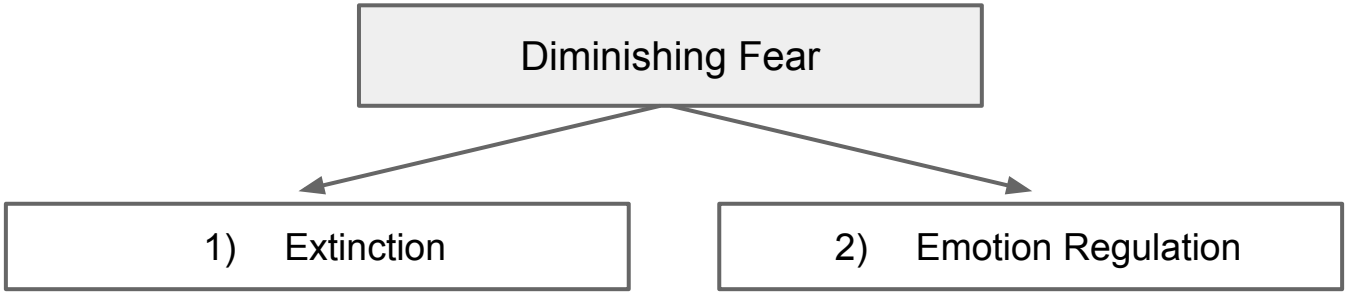
   CS => No Fear

Emotion Regulation: cognitive function



https://sequencewiz.org/2017/09/20/change-emotional-responses-pratipaksha-bhavana-reappraisal/

Diminishing Fear



Diminishing Fear

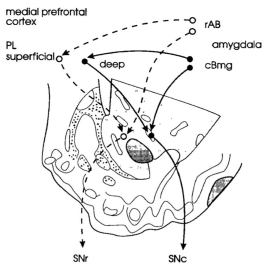
Diminishing Fear

1) Extinction

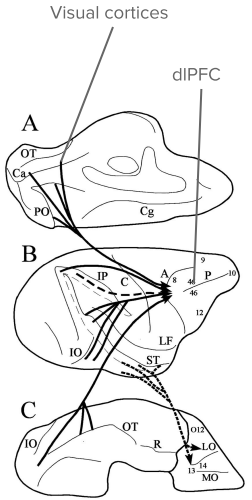
- Across species (e.g. rodents, humans)
- Ventral medial prefrontal cortex (vmPFC) ↑
- Amygdala ↓

2) Emotion Regulation

- Unique to humans
- Dorsolateral prefrontal cortex (dlPFC) ↑
- Amygdala ↓
  - Not interconnected

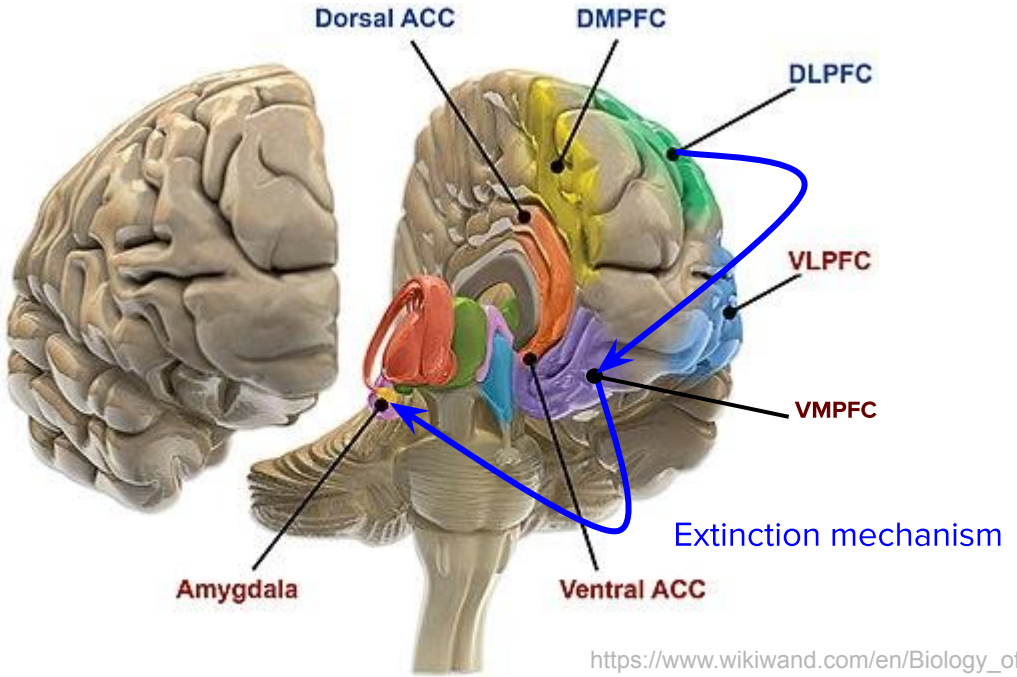


Groenewegen et al. (1997)



Barbas (2000)

Neural Correlates of Emotion Regulation



https://www.wikiwand.com/en/Biology_of_bipolar_disorder

dlPFC - vmPFC Connections + Extinction (EXT) Mechanism = Emotional Regulation (ER)

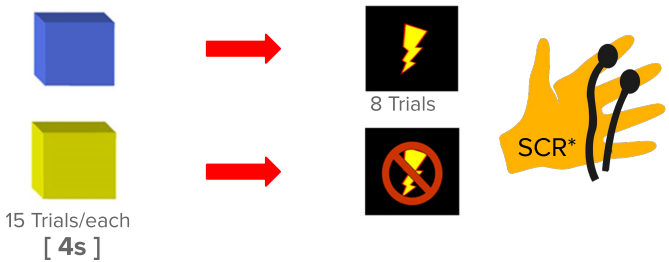
(mediator) (overlap)

Method (1)

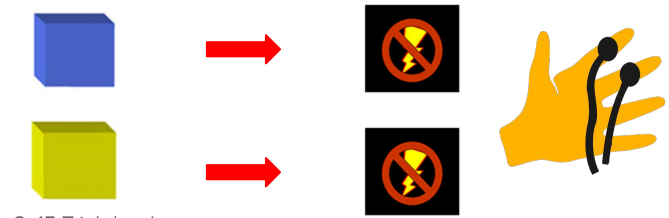
Partial Reinforcement Paradigms

EXT Paradigm (Phelps et al., 2004)

Acquisition

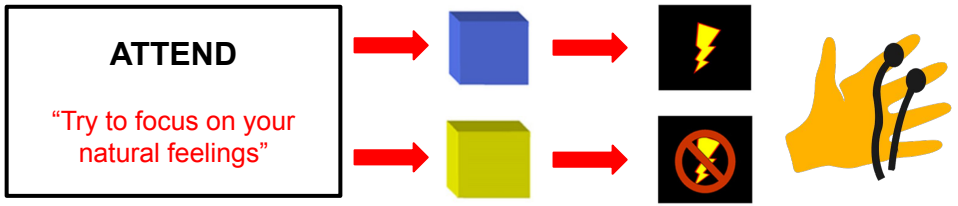


Day 1 & 2 (Extinction; Day 2 after 24 hrs)

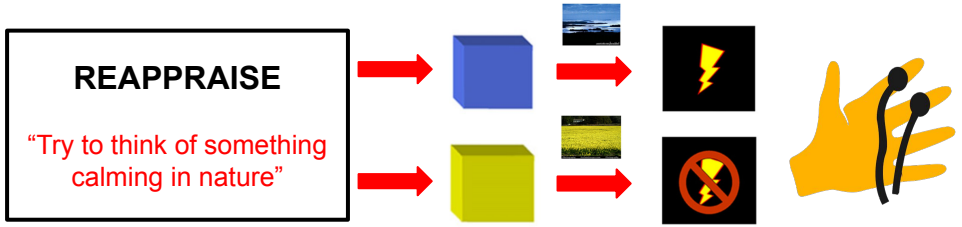


ER Paradigm (Delgado et al., 2008)

Attend



Regulate



SCR*: Skin Conductance Response

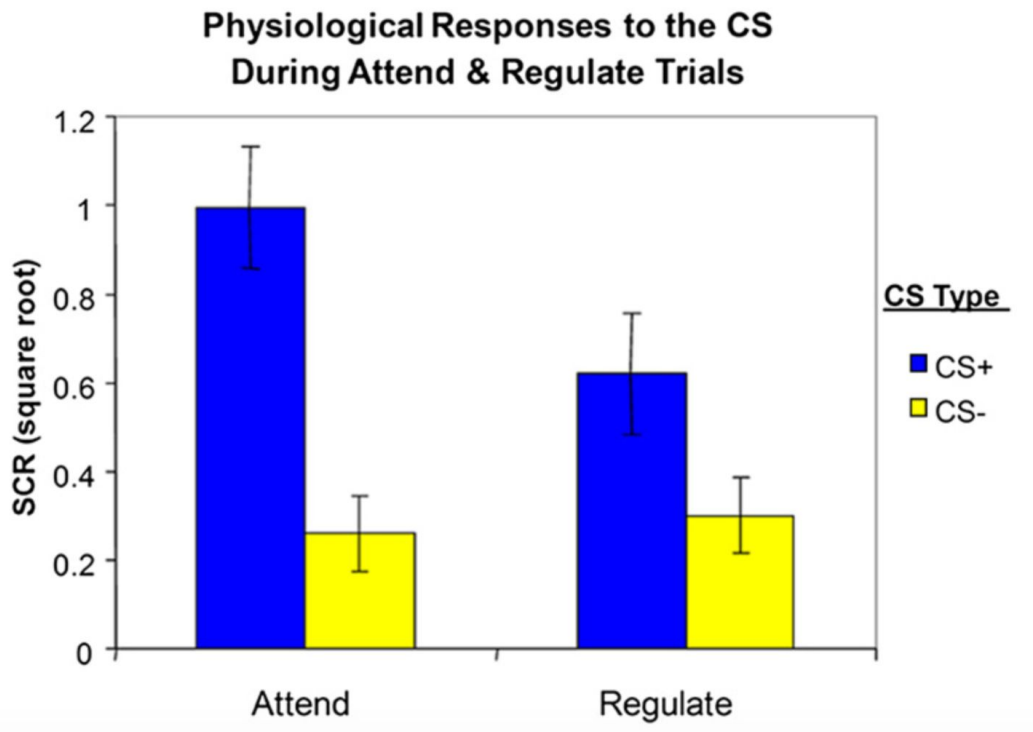
Method (2)

Participants, Neuroimaging & Analysis

		EXT	ER
Participant	Number	11 (5 males)	12 (6 males)
	Age	18-25	23.29
fMRI	Voxel size	3 x 3 x 3mm	
Analysis	SCR	**1) Repeated ANOVA** **2) Two-tailed paired t-test**	
	fMRI	**3) ROI specific analysis,** **4) Exploratory connectivity analysis**	

Result (1)

Physiological Results - ER



Repeated ANOVA Results

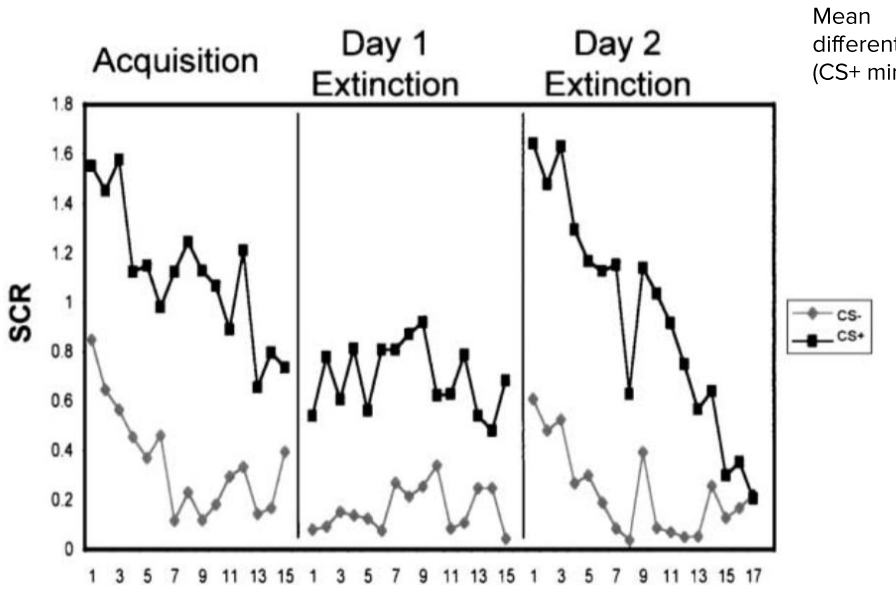
1. Higher SCR in Attend than Regulate
2. Higher SCR in CS+ than CS-
3. Difference in SCR within Attend is higher than that within Regulate

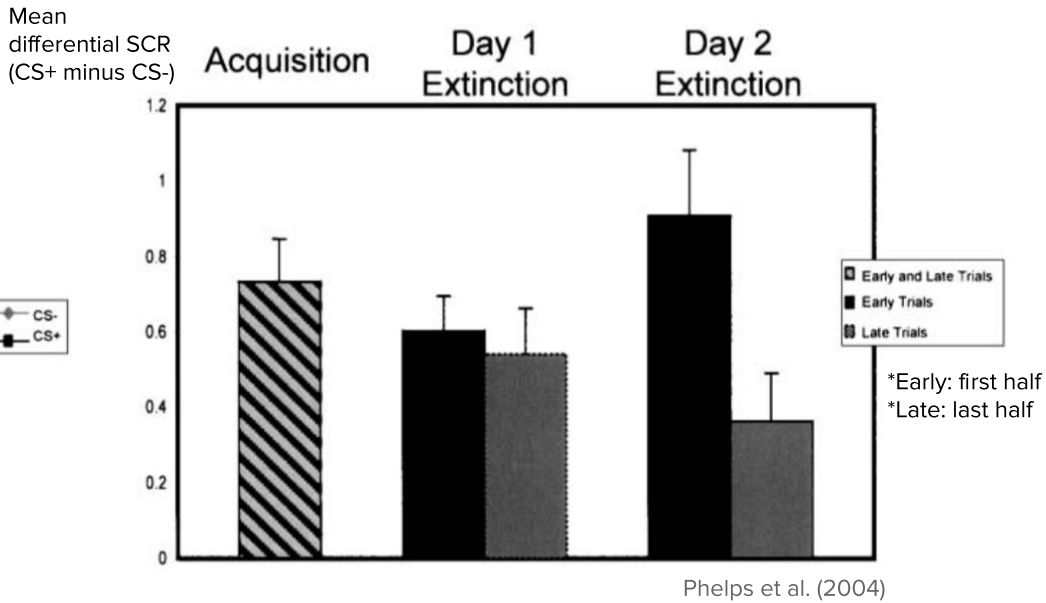
Paired t-test

: Greater SCR difference in Attend than SCR difference in Regulate

Result (2)

Physiological Results - EXT





Phelps et al. (2004)

1. Higher SCR for CS+ than CS- during acquisition, day 1 and day 2
2. Differential SCR during late day 1 is marginally less than during acquisition
3. Differential SCR during late day 2 is significantly less than during early day 2 and acquisition

Result (3)

Neuroimaging Results

1. Select *a priori* ROIs based on Extinction study (Phelps et al., 2004)

    a. Left dlPFC (middle frontal gyrus)
    b. vmPFC (subgenual anterior cingulate)
    c. Amygdala

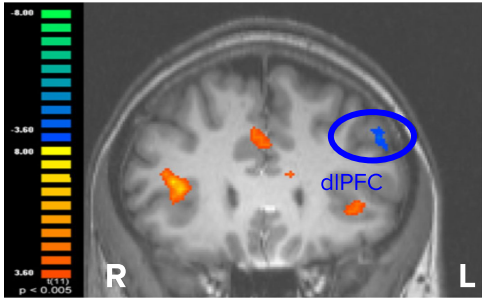
2. ROI Specific analysis

    a. Choose a peak activation voxel in each region
    b. Calculate mean beta weights across participants
    c. Apply it to all predictors (Attend CS+, Attend CS-, Regulate CS+, Regulate CS-)

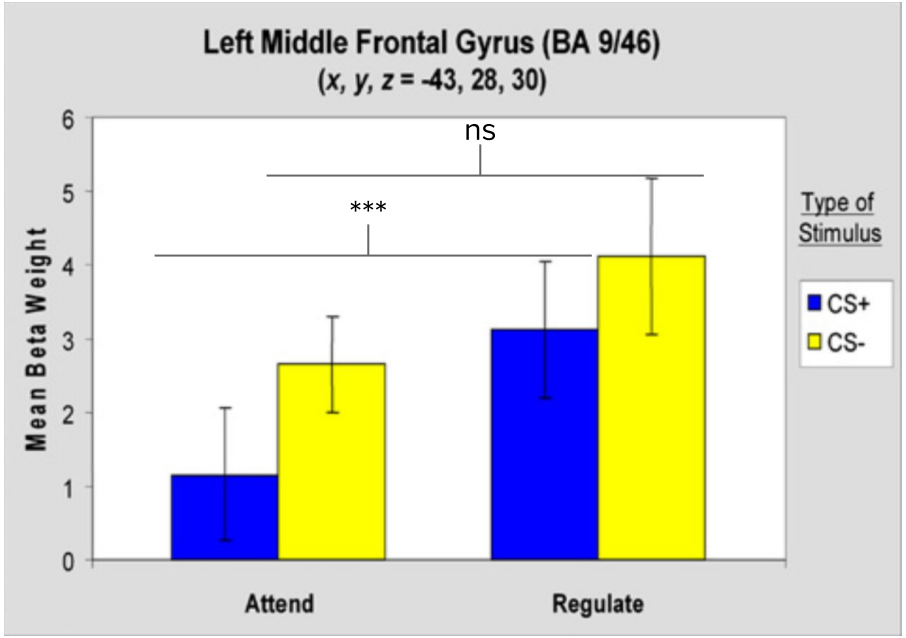
Result (4)

Neuroimaging Results - ER

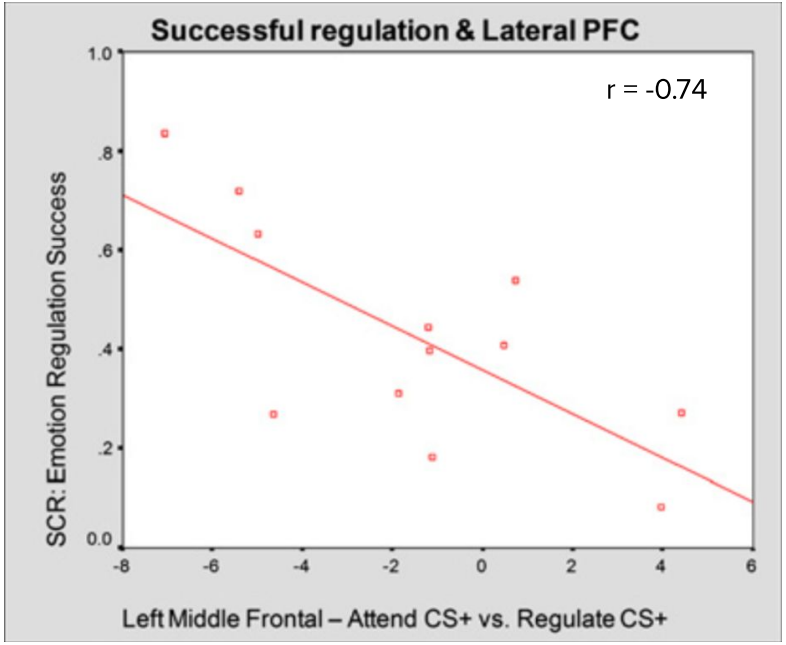
Finding 1. opposite pattern in PFC ROIs and the amygdala (dlPFC)



Contrast: Attend CS+ vs. Regulate CS+



***: $p < 0.05$



*Mean SCR for Attend CS+ Trials - Regulate CS+ Trials

Result (5)

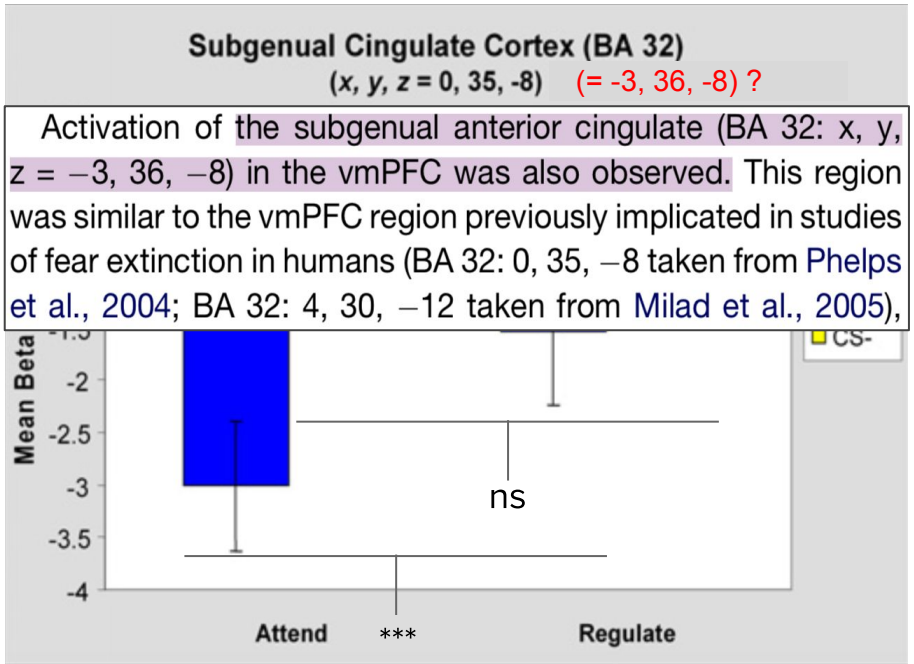
Neuroimaging Results - ER

Finding 1. opposite pattern in PFC ROIs and the amygdala (vmPFC)

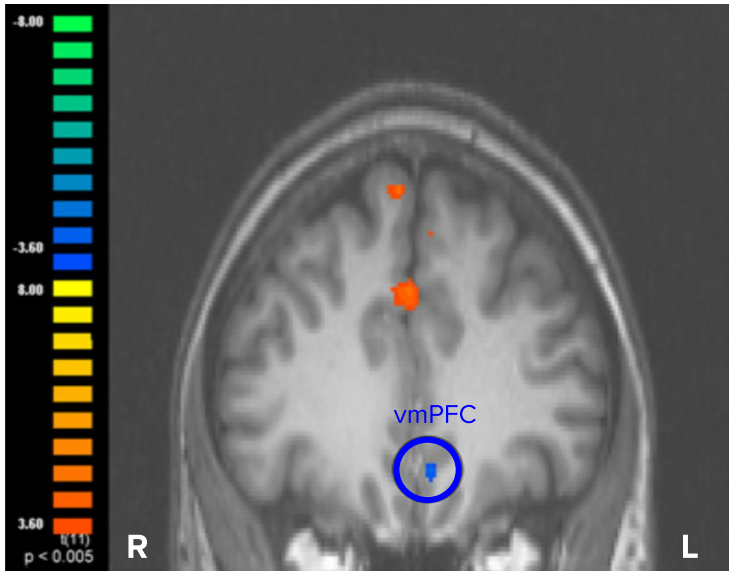
Subgenual Cingulate Cortex (BA 32)

(*x*, *y*, *z* = 0, 35, -8) (= -3, 36, -8) ?

Activation of the subgenual anterior cingulate (BA 32: x, y, z = −3, 36, −8) in the vmPFC was also observed. This region was similar to the vmPFC region previously implicated in studies of fear extinction in humans (BA 32: 0, 35, −8 taken from Phelps et al., 2004; BA 32: 4, 30, −12 taken from Milad et al., 2005),



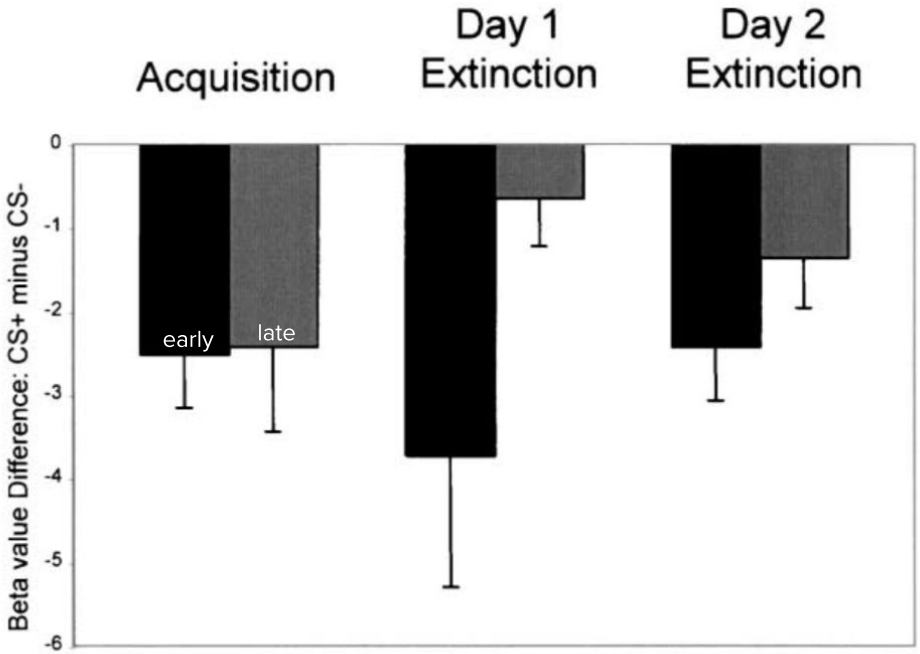
***: p < 0.05



Contrast: Attend CS+ vs. Regulate CS+

Result (6)

Neuroimaging Results - EXT



Phelps et al. (2004)

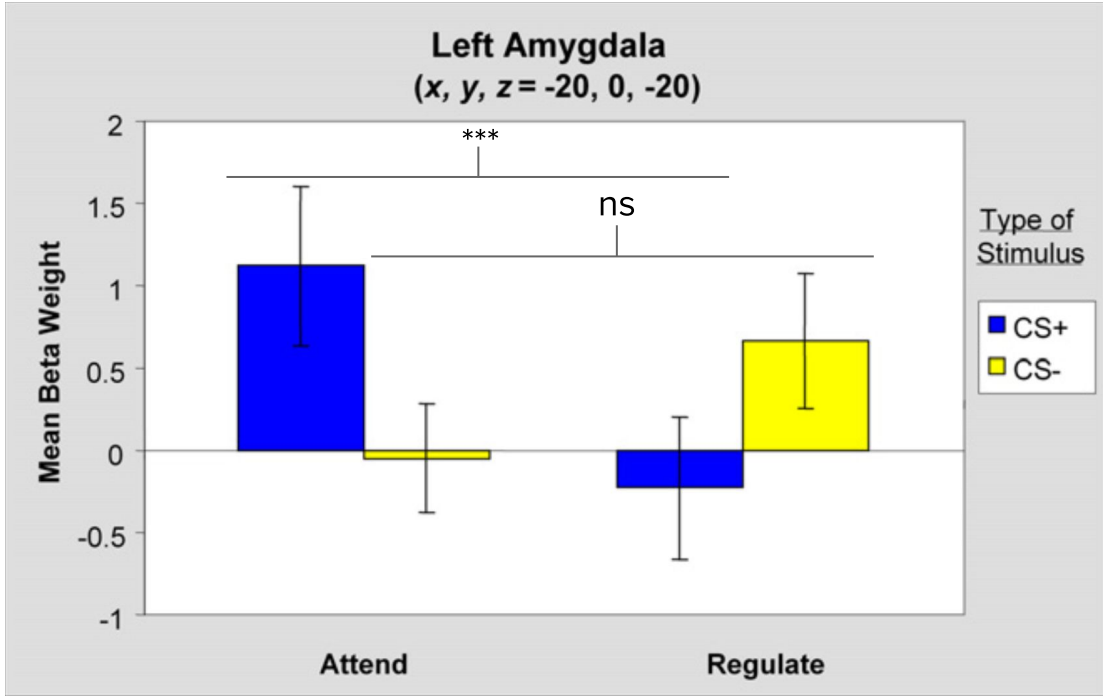
Figure 4. Subgenual Anterior Cingulate Activation and Correlation with SCR

(A) Mean differential β values (CS^+ minus CS^-) for the subgenual anterior cingulate ROI during early and late acquisition, day 1 extinction, and day 2 extinction. Error bars represent standard error.

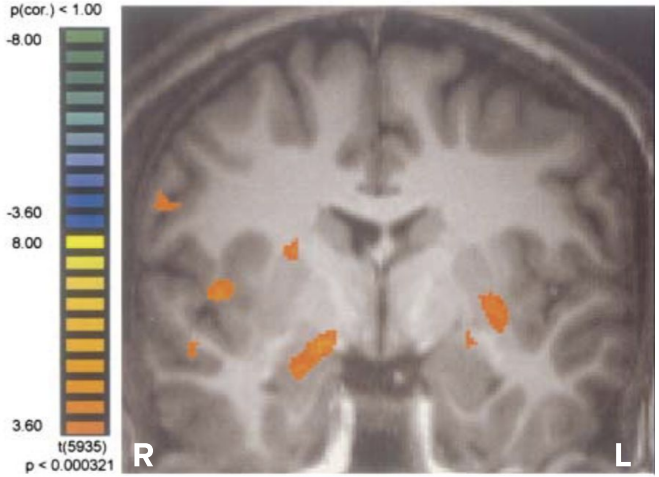
Result (7)

Neuroimaging Results - ER

Finding 1. opposite pattern in PFC ROIs and the amygdala (amygdala)



***: p < 0.05



Contrast: CS+ Acquisition - CS+ Day 1 Extinction

Phelps et al. (2004)

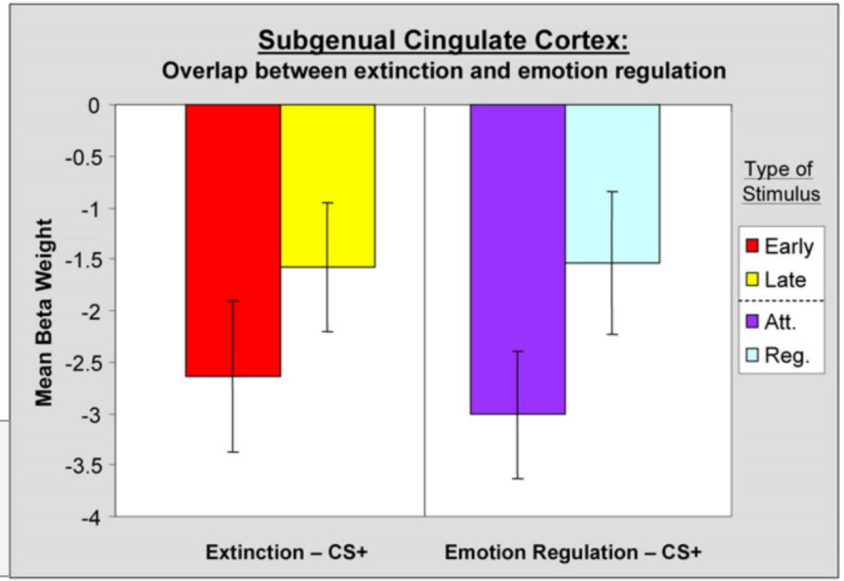
Result (8)

Neuroimaging Results - ER

Finding 2. Using the ROIs identified in EXT, similar pattern in vmPFC activation observed in ER

Voxel **(BA 32: 0, 35, -8)** in vmPFC from ER Paradigm

- Attend CS+ minus Regulate CS+***:
  - [t(11) = -2.40, p < 0.04]
- Attend CS- minus Regulate CS-:
  - [t(11) = 0.28, p = n.s.]



Left Panel: Day 2 Extinction, (BA 32: 0, 35, -8)
(Phelps et al., 2004)

Right Panel: (BA 32: -3, 36, -8)

Take-away: the decrease in vmPFC to the CS+ was attenuated during extinction learning and a cognitive regulation strategy.

Result (9)

Neuroimaging Results - ER

Finding 3. Using the ROIs identified in EXT, similar pattern amygdala activation observed in ER

Voxel **(15, -3, -13)** in amygdala from ER Paradigm

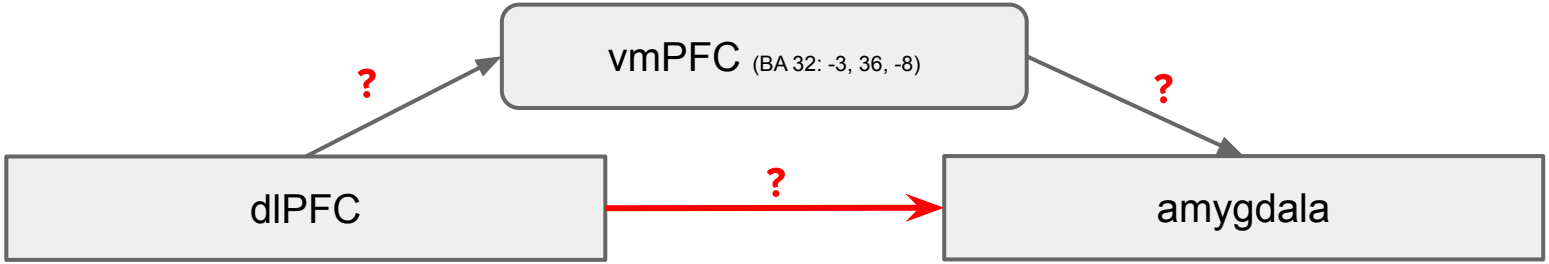
- Attend CS+ minus Regulate CS+***:
  - [t(11) = 2.54, p < 0.03]
- Attend CS- minus Regulate CS-:
  - [t(11) = 0.82, p = n.s.]

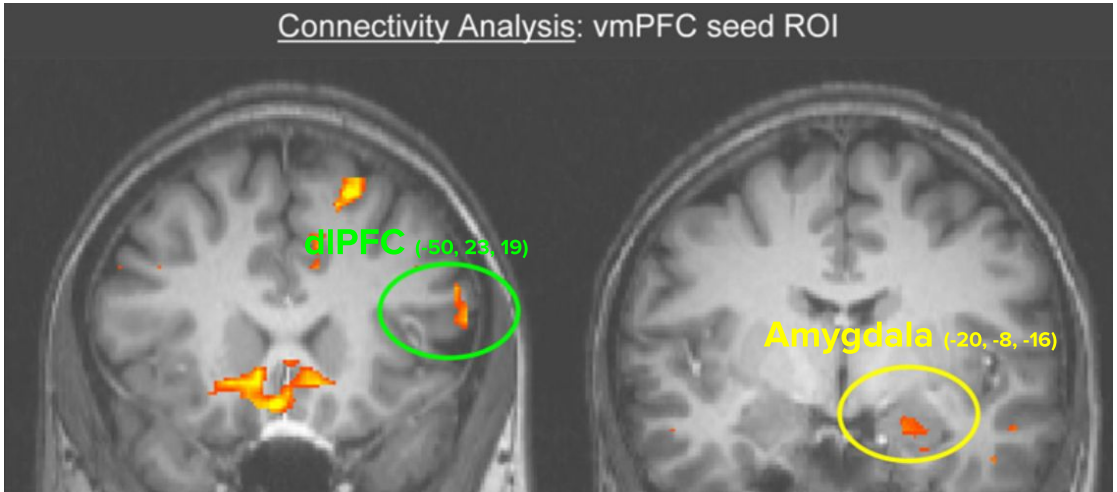
*No significant BOLD activation during EXT in left amygdala ROI defined in ER (-20, 0, -20)

Result (10)

Neuroimaging Results - ER

Finding 3. Exploratory Connectivity Analysis: vmPFC as seed ROI, correlation with the amygdala and dlPFC





Discussion & Limitation

Discussion

1. Examined the overlap in the neural correlates underlying EXT and ER

2. Used an imagery strategy for ER, which is similar to traditional cognitive behavioral therapies
3. Replicated other ER studies that the vmPFC ROI identified in this study is similar to theirs

Limitation

1. Different interpretation is possible on the imagery strategy: simple distraction?

2. More explanation is needed to understand the laterality of the amygdala activation

Thank you for your listening!