

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)



2020.04.13

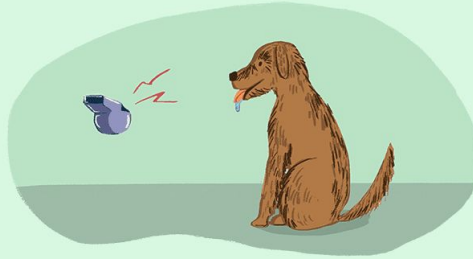
Computational Clinical Science Lab

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Fear Conditioning

What to Know: The Little Albert Experiment



Classical conditioning to condition an emotional response



9-month-old "Albert" exposed to stimuli and observed



White rat paired with loud noise



Albert conditioned to fear white rat

Fear Conditioning

What to Know: The Little Albert Experiment

Pavlovian Fear Conditioning

1) **Pre-conditioning:**

Neutral Stimulus

Unconditional Stimulus (US)

condition an emotional response

=> No Response

=> Fear

9-month-old "Albert" exposed to stimuli and observed

2) **Acquisition:**

Conditional Stimulus (CS) + US

=> Fear

3) **Post-conditioning:**

CS

=> Fear

White rat paired with loud noise

Albert conditioned to fear white rat

Anxiety disorders (Specific phobias)

Extinction versus Emotion Regulation

Extinction: by no reinforcement on CS

Emotion Regulation: cognitive function

1. Acquisition

CS + US => **Fear**

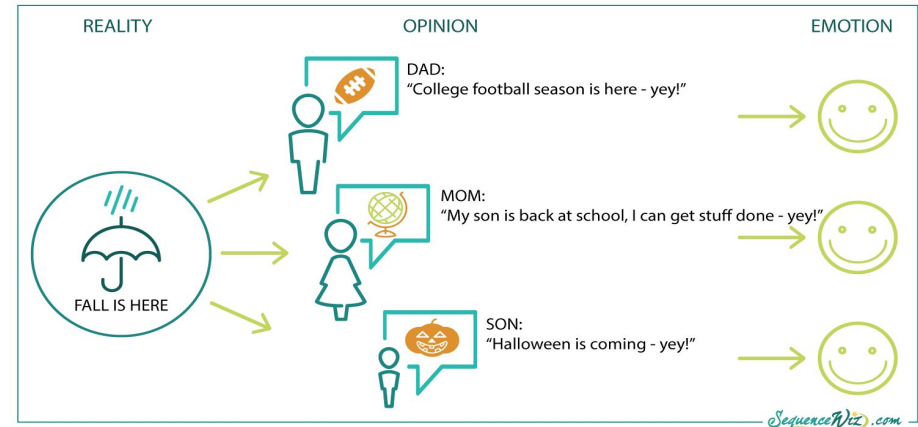
CS => **Fear**

2. Fear extinction-ing

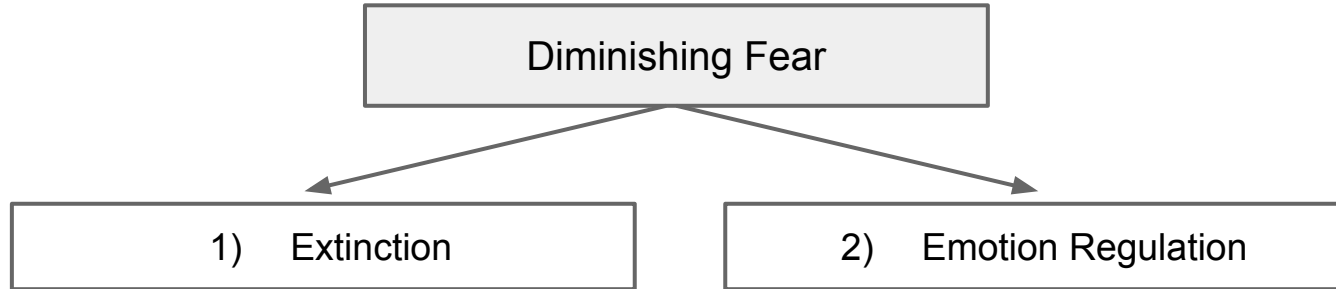
CS + (US X)

3. Post-extinction

CS => **No Fear**



Diminishing Fear



Diminishing Fear

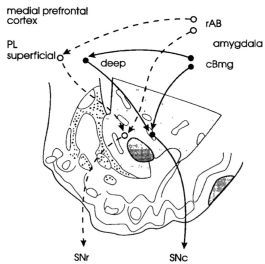
Diminishing Fear

1) Extinction

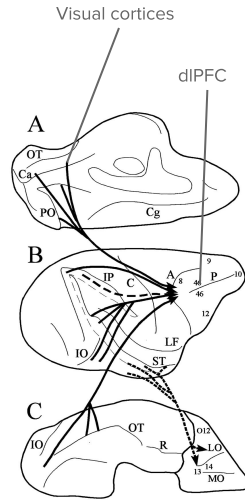
- Across species (e.g. rodents, humans)
- Ventral medial prefrontal cortex (vmPFC) ↑
- Amygdala ↓

2) Emotion Regulation

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

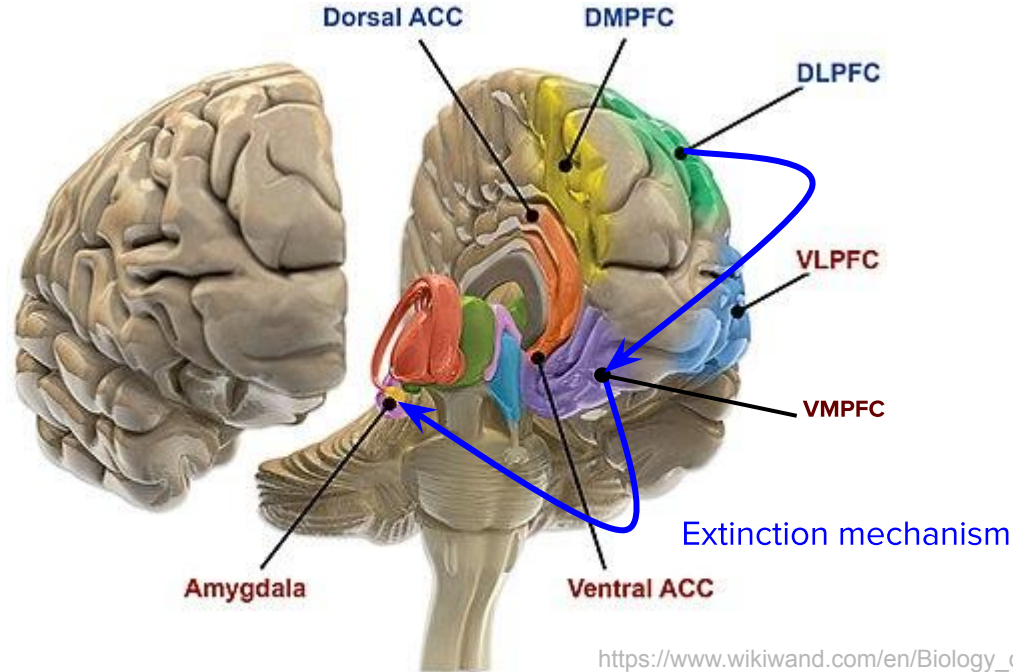


Groenewegen et al. (1997)



Barbas (2000)

Neural Correlates of Emotion Regulation



dIPFC - **vmPFC** Connections + **Extinction (EXT) Mechanism** = Emotional Regulation (ER)
(mediator) (overlap)

Method (1)

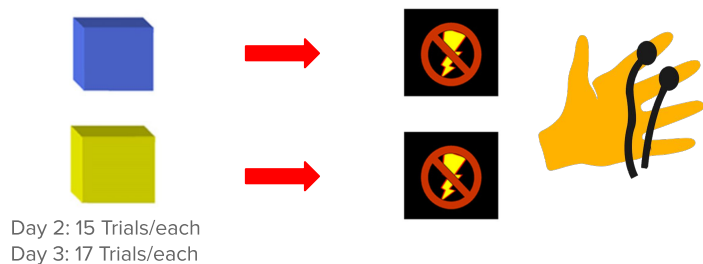
Partial Reinforcement Paradigms

EXT Paradigm (Phelps et al., 2004)

Acquisition

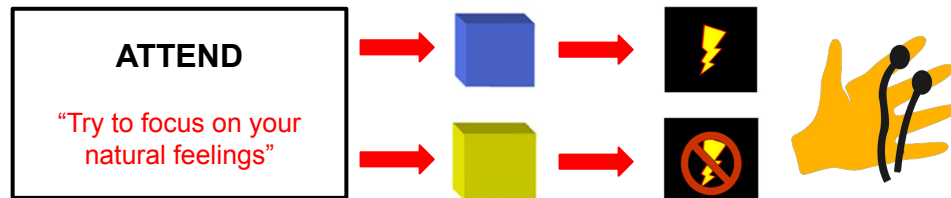


Day 1 & 2 (Extinction; Day 2 after 24 hrs)

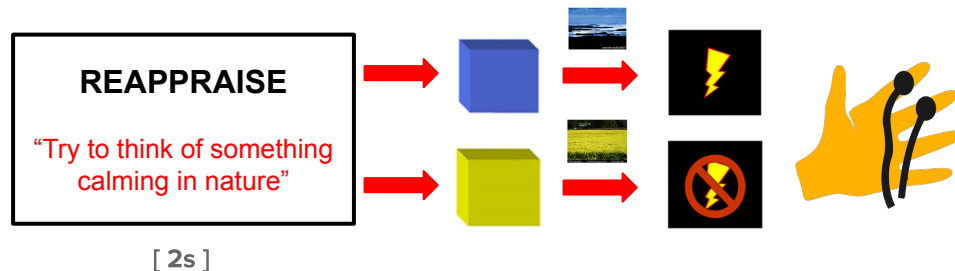


ER Paradigm (Delgado et al., 2008)

Attend



Regulate



SCR*: Skin Conductance Response

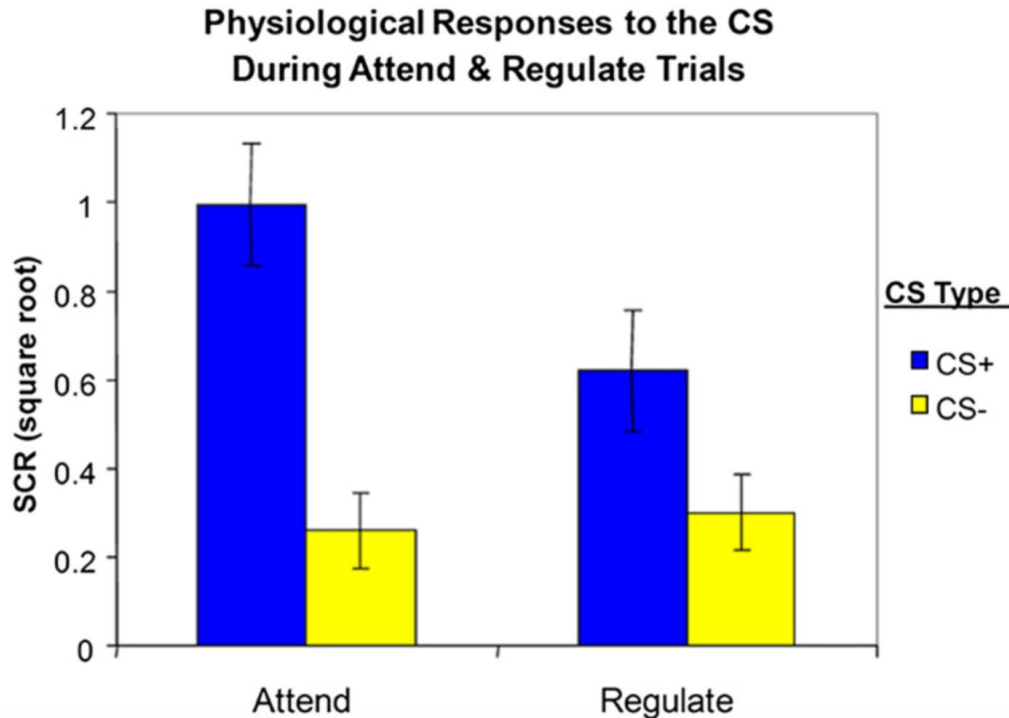
Method (2)

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

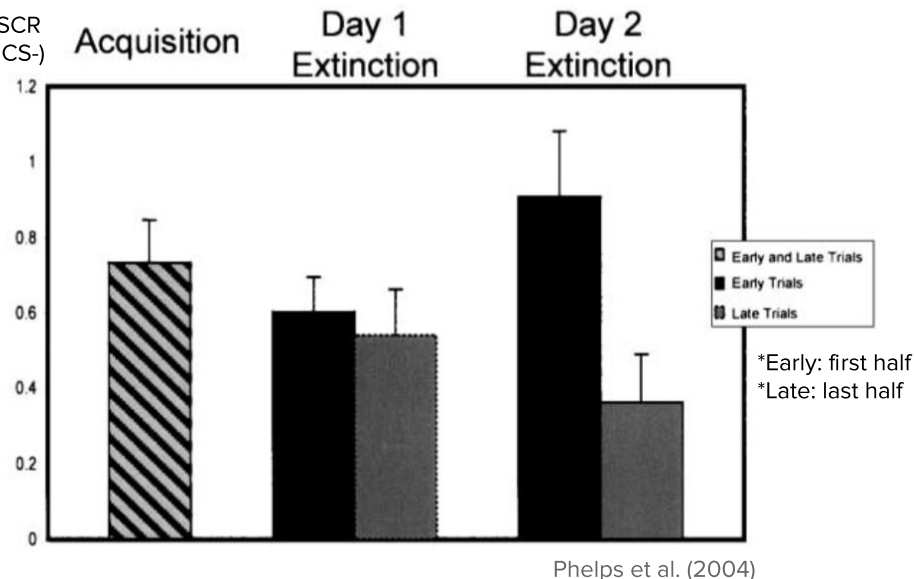
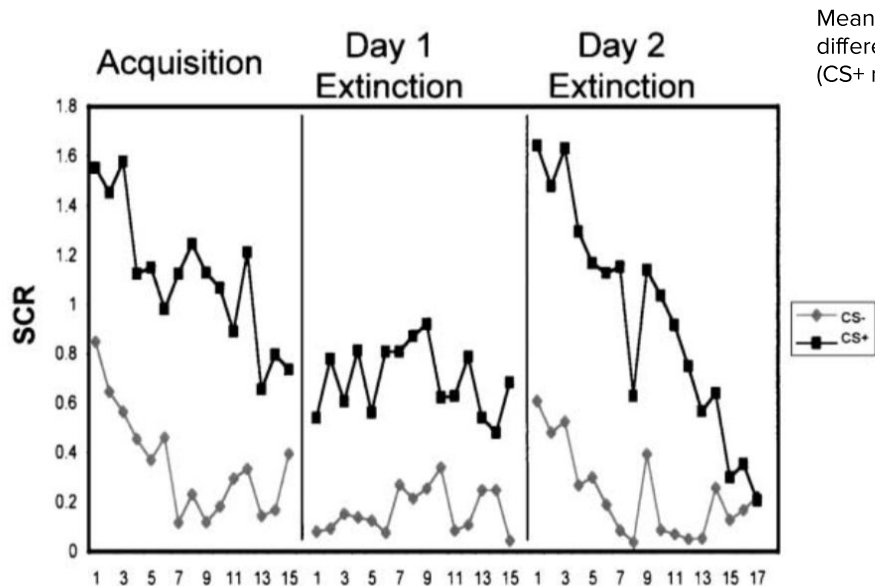
1. Higher SCR in Attend than Regulate
2. Higher SCR in CS+ than CS-
3. Difference in SCR within Attend is higher than that within Regulate

Paired t-test

: Greater SCR difference in Attend than
SCR difference in Regulate

Result (2)

Physiological Results - EXT



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

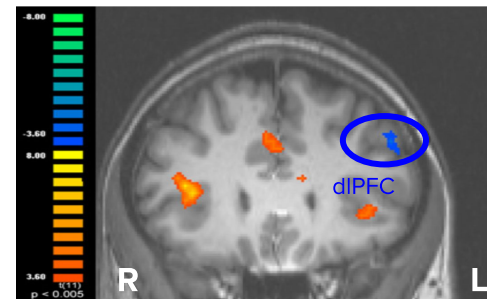
2. ROI Specific analysis

- 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-)

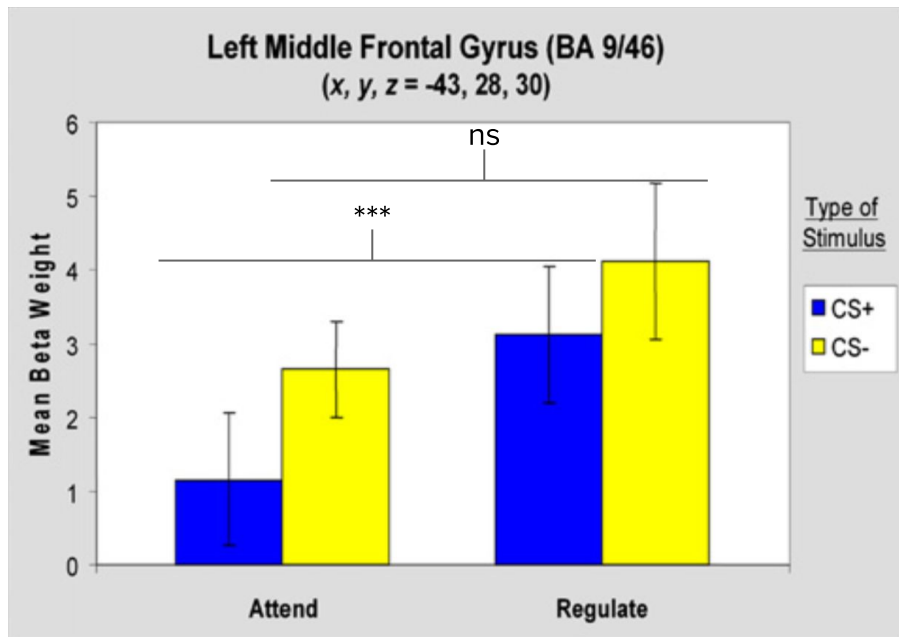
Result (4)

Neuroimaging Results - ER

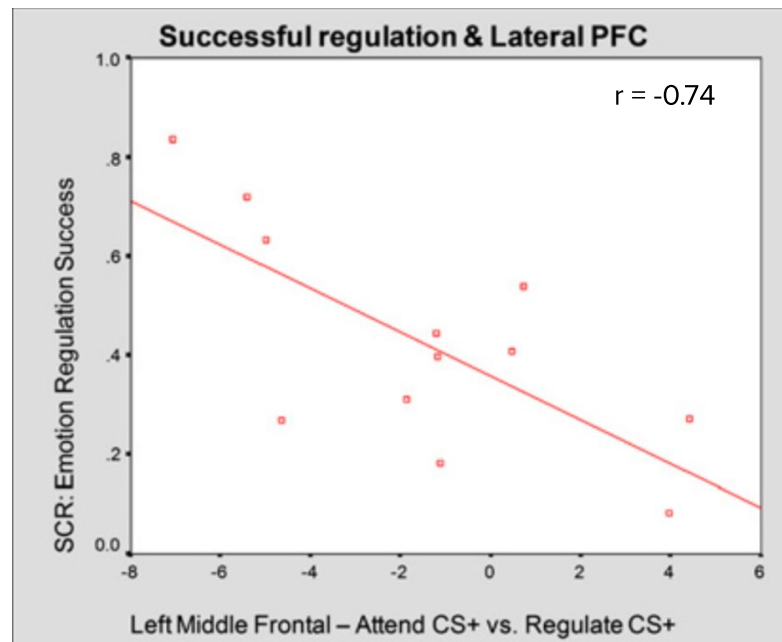
Finding 1. opposite pattern in PFC ROIs and the amygdala (dIPFC)



Contrast: Attend CS+ vs. Regulate CS+



***. $p < 0.05$

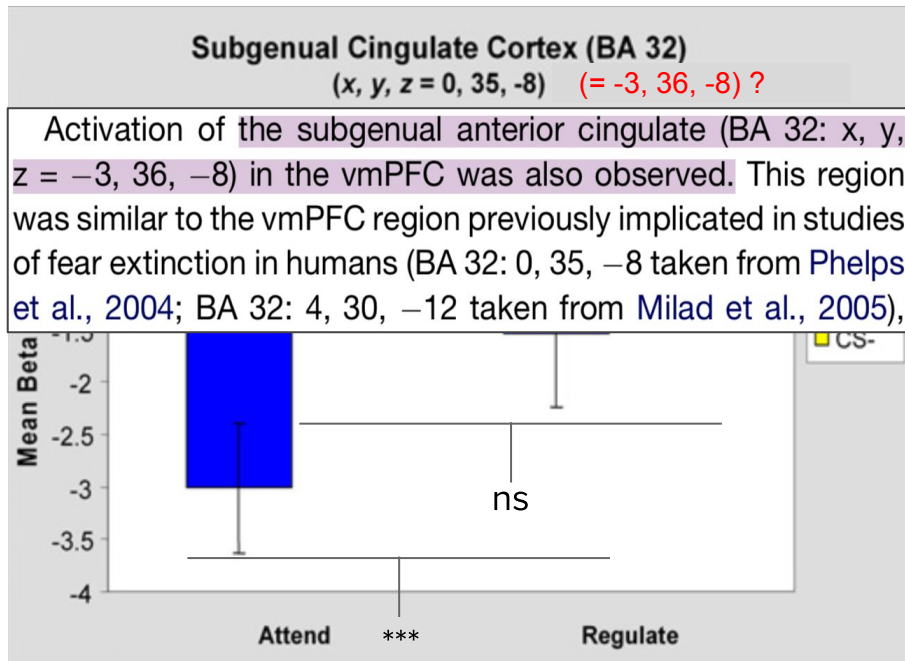


*Mean SCR for Attend CS+ Trials - Regulate CS+ Trials

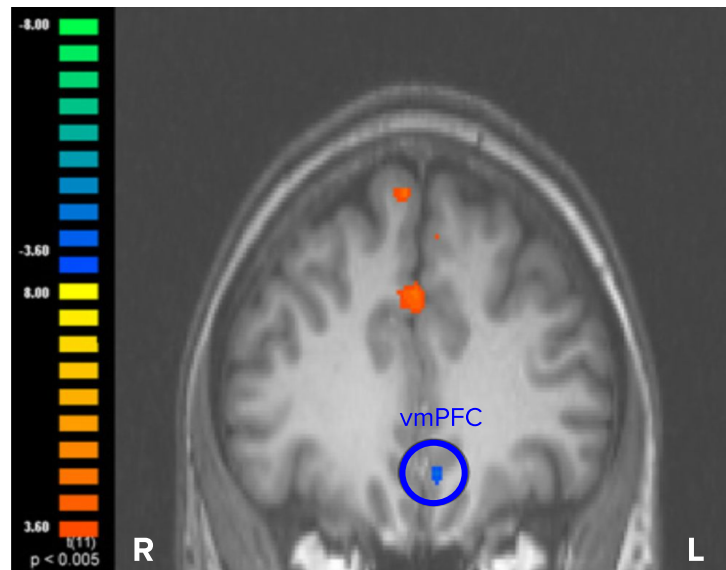
Result (5)

Neuroimaging Results - ER

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



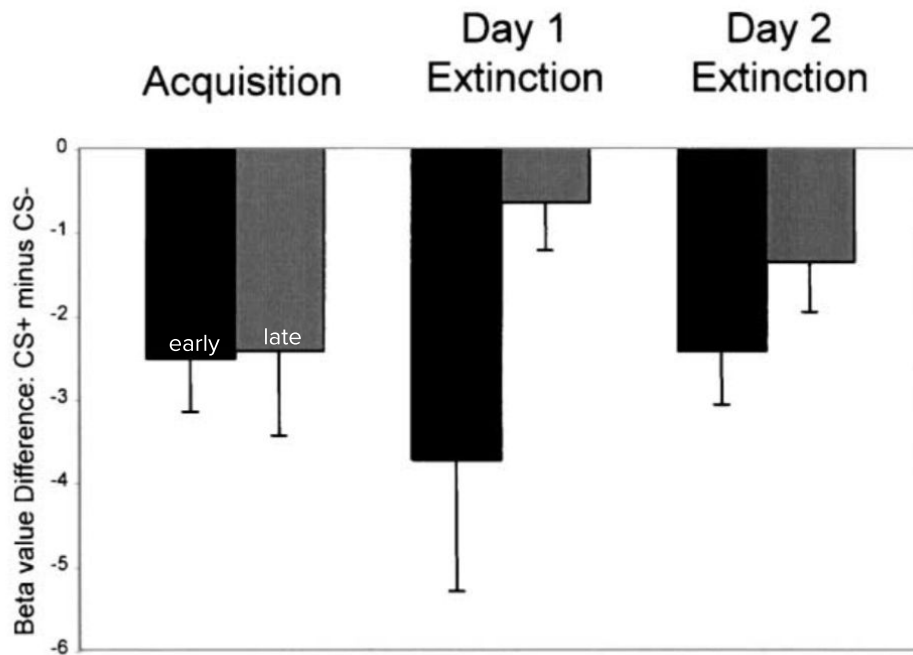
***: p < 0.05



Contrast: Attend CS+ vs. Regulate CS+

Result (6)

Neuroimaging Results - EXT



Phelps et al. (2004)

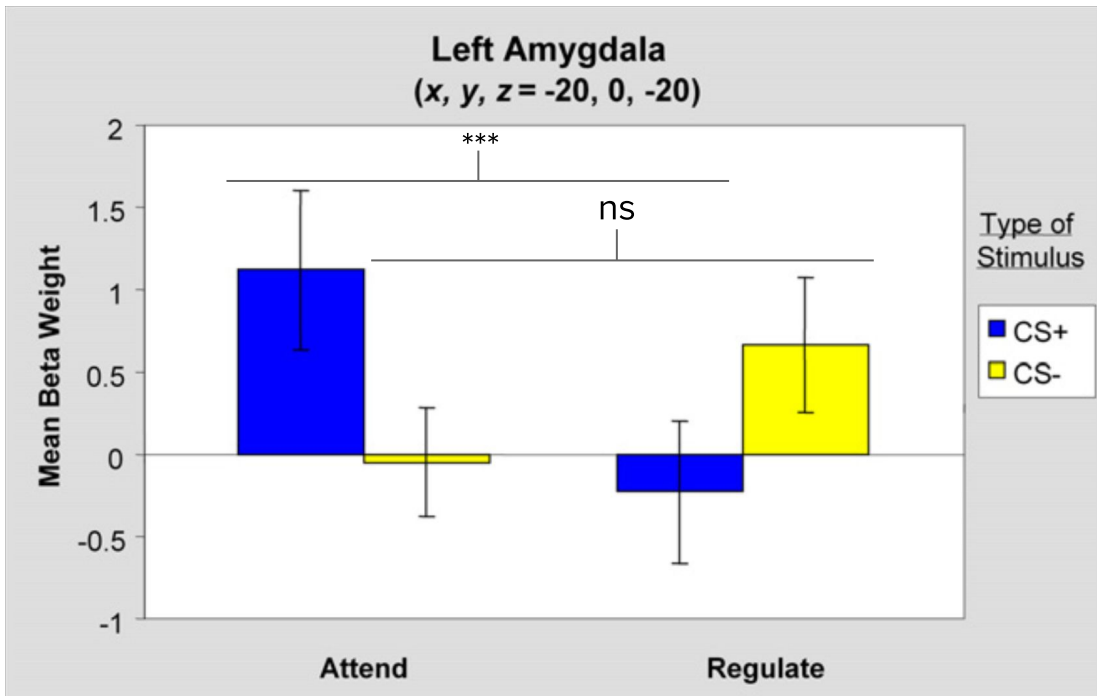
Figure 4. Subgenual Anterior Cingulate Activation and Correlation with SCR

(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.

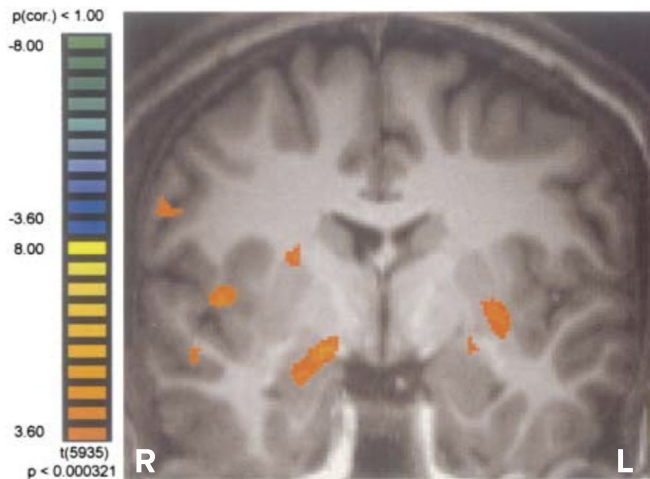
Result (7)

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

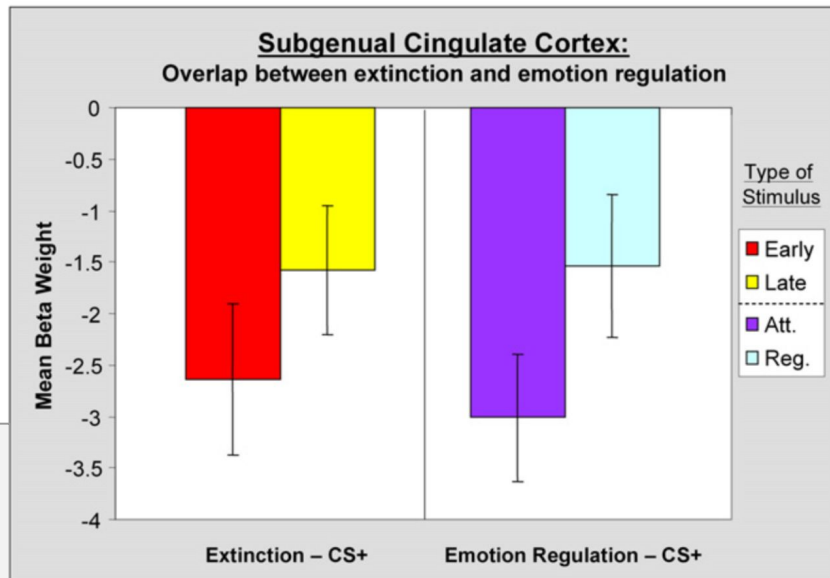
Finding 2. Using the ROIs identified in EXT, similar pattern in vmPFC activation observed in ER

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

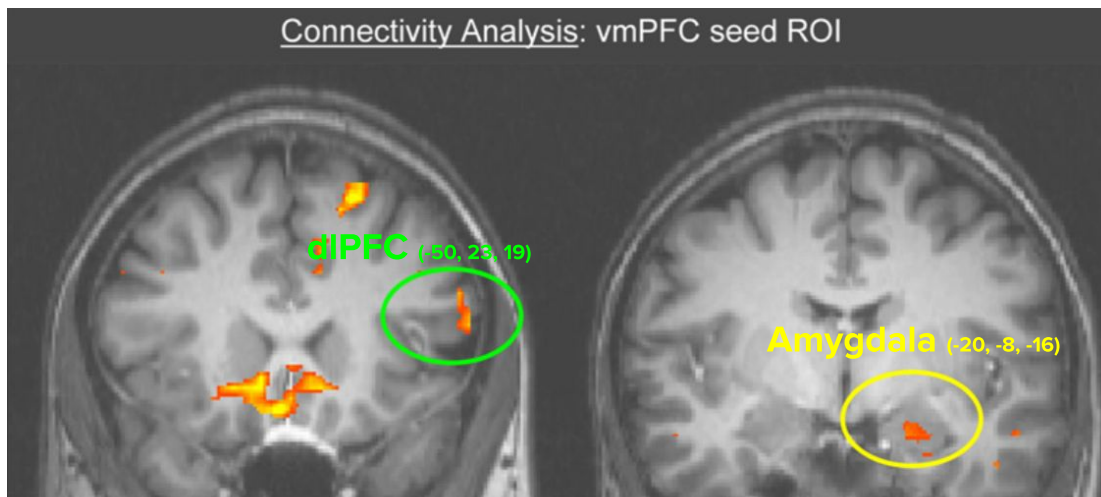
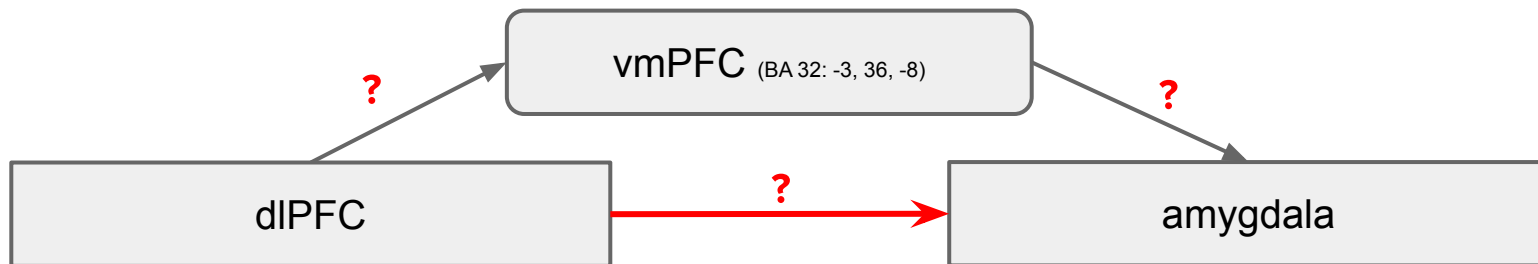
- Attend CS+ minus Regulate CS+***:
 - [t(11) = 2.54, p < 0.03]
- Attend CS- minus Regulate CS-:
 - [t(11) = 0.82, p = n.s.]

*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 dIPFC



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!

