The effects of cannabinoids on fear extinction recall and the underlying brain circuitry in humans

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Learning Objectives

• Understand fear extinction and how it is used to model exposure-based therapies.

• Understand the neural mechanisms underlying extinction learning and recall.

• Understand how the cannabinoid system is involved in extinction of fear memories.

• Discuss how the cannabinoid system may be a potential pharmacological target to enhance the learning during exposure sessions and what this may mean for advancements in treatment.

• Discuss the next steps in research with cannabinoids as a potential cognitive enhancer for extinction-based therapies.
Background

- Anxiety Disorders
  - Failure to appropriately inhibit or extinguish fear
  - Exposure-based therapy
Background

- Pavlovian Fear Extinction
  - Models underlying dysfunction in anxiety disorders

Background

- Pavlovian Fear Extinction
  - Basic neural circuitry that regulates fear extinction
    - Ventromedial prefrontal cortex [vmPFC] and hippocampus [HIPP]
    - Dysfunctional in anxiety disorders

vmPFC = cognition; fear extinction recall
HIPP = memory formation; fear extinction recall
AMYG = emotional learning and responding
‘Healthy’ Fear Extinction Recall

A. Conditioning
   - Day 1: Extinction Learning
   - Day 2: Recall

B. Conditioning vs. Extinction Recall
   - 8 CS+E, 8 CS+U
   - Amygdala
   - Hippocampus
   - vmPFC

Milad et al. (2007). Biological Psychiatry, 62: 446-454
PTSD and Impaired Fear Extinction Recall

• Deficient vmPFC-HPC during Extinction and Recall of Extinction Memory in PTSD
Background

• Pharmacological ‘Enhancers’ of Extinction Learning
  – Deletion of endocannabinoid CB1 receptors impairs extinction [Marsicano et al. 2002; Kamprath et al. 2006]
  – Extinction increases endocannabinoid levels (e.g. anandamide) [Marsicano et al. 2002]
  – Endocannabinoid-reuptake inhibitors facilitates extinction [Chhatwal et al. 2005]
  – Inhibition of endocannabinoid-degrading enzymes [e.g. FAAH] facilitates extinction [Gunduz-Cinar et al. 2012]

• However, the role of cannabinoids on the retention of extinction memory and its effect on the underlying neural circuits in humans is unknown.
Can cannabinoids facilitate fear extinction in humans?

Hypothesis: Pre-extinction administration of an acute dose of THC will facilitate extinction of conditioned fear responses compared to placebo (PBO) in humans.
Experimental Paradigm

Day 1
Fear Acquisition

Day 2
Extinction Learning
7.5 mg THC or PBO
120 min

Day 3
Extinction Memory Recall Test

8 x CS+E w/US
8 x CS+U w/US
15 x CS +E
15 x CS+U
15 x CS-
15 x CS +E
15 x CS-
20 x CS +E
20 x CS+U
20 x CS-

- Randomized, double-blind, placebo-controlled between-subjects design
- Acute pharmacological challenge of oral dronabinol [THC = 14] or placebo [PBO = 15] in healthy adult volunteers
Behavioral Results

THC does not affect within-session extinction learning to the CS+E

THC decreases SCRs to the CS+E compared to PBO
Participants that had received PBO during extinction learning exhibited spontaneous recovery of fear to a CS that was previously extinguished (CS+E), whereas THC attenuated spontaneous recovery of fear.

THC did not affect within-session extinction learning, but only influenced the ability to successfully recall extinction memory when compared to placebo, suggesting that THC affects the ability to maintain and/or successfully retrieve extinction memory.

Pre-extinction administration of THC facilitates extinction of conditioned fear in humans.

How does THC affect the underlying neural circuitry involved in fear extinction?
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Cannabinoid modulation of prefrontal–limbic activation during fear extinction learning and recall in humans

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Hypotheses

**Extinction Learning:**
- During early extinction the CS+E will elicit conditioned fear responses (e.g. SCRs), but with continued presentations of the CS+E in the absence of the US SCRs to the CS+E will diminish.
- THC will not affect extinction of SCRs to the CS+E (versus CS-).
- During early extinction learning there will be AMYG activation to the CS+E (versus CS-). THC will not affect AMYG reactivity to the CS+E.

**Extinction Recall:**
- Relative to PBO, THC will decrease SCRs to the CS that was previously extinguished (CS+E).
- Relative to PBO, THC will enhance regional activation in the vmPFC and HIPP to the CS+E (versus CS+U).
- Relative to PBO, THC will increase functional coupling between the vmPFC and HIPP to the CS+E.

Pre-extinction administration of THC enhances recall of fear extinction in healthy humans, which is mediated via increased activation and functional connectivity of the vmPFC and HIPP.
fMRI Experimental Paradigm

- Randomized, double-blind, placebo-controlled between-subjects design
- Acute pharmacological challenge of oral dronabinol [THC = 14] or placebo [PBO = 14] in healthy adult volunteers
- Functional data were processed and analyzed using SPM8
THC does not affect within-session extinction learning to the CS+E

Both groups demonstrated equivalent levels of extinction learning.
THC attenuates AMYG reactivity to the CS+E during early extinction.
Extinction Recall Results

No significant difference in SCR to the CS+E during extinction recall between PBO & THC

Both groups demonstrated successful extinction recall to the CS+E
THC increases regional activation in vmPFC & HIPP to the CS+E (>CS+U) during extinction recall
Functional Connectivity Analysis

- Functional connectivity was conducted with generalized psycho-physiological interaction (gPPI) analyses in SPM8.

THC increases functional coupling between the vmPFC and HIPP to the CS+E during extinction recall.

vmPFC ‘seed’

THC > PBO: CS+E > CS+U

x = -30

x = 30
Summary of fMRI Study

- THC did not affect within-session extinction learning, but did attenuate AMYG activation to the CS+E during early extinction.

- Both groups displayed significantly smaller SCRs to the CS+E compared to the CS+U during extinction recall; however, there was no significant difference between the THC and PBO groups.
  - THC may have reduced within group variability in extinction recall success

- THC increased regional activation within the vmPFC and the left HIPP and increased vmPFC-HIPP functional coupling to the CS+E (> CS+U) during extinction recall compared PBO.

⇒ Pre-extinction administration of THC modulates the underlying neural circuits involved in fear extinction in humans.
Conclusions & Future Directions

• Can cannabinoids facilitate fear extinction?
  – Maybe...
    • Conflicting behavioral results with the use of THC between our studies
      – Differential sensitivity to the effects of THC between individuals
      – ‘Floor Effect’
      – THC may not be effective in a non-clinical population (e.g. DCS studies)
      – Underpowered
      – SCR may not be sensitive to the effects of THC
      – Genetic influences**

Heitland et al. (2012). Translational Psychiatry, 2(e162)
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• Other cannabinoid compounds/targets
  – Cannabidiol (CBD) given before or after extinction learning in healthy volunteers has been shown to facilitate consolidation of extinction learning (Das et al 2013).
  – Endocannabinoid re-uptake/degradation inhibitors (FAAH inhibitor)
Conclusions & Future Directions

• How do cannabinoids affect the neural circuitry involved in fear extinction?
  – THC attenuates AMYG activation during extinction learning to the fear cue and increases vmPFC-HIPP activation and functional coupling during extinction recall.

• AMYG:
  – Activation of CB1 receptors on GABAergic interneurons with the AMYG, which decreases GABAergic transmission, thus leading to the potentiation of glutamaterigic “extinction” pathways; and/or
  – Activation of CB1 receptors on glutamaterigic neurons within the AMYG, which decrease glutamate transmission, thus leading to a de-potentiation of “fear” pathways

• vmPFC:
  – Activation of CB1 receptors in vmPFC induces neuronal plasticity, which increases top-down inhibition of fear-output neurons in the AMYG

• HIPP:
  – Activation of CB1 receptors in HIPP may support long-term extinction memory formation via enhanced glutamaterigic neurotransmission
Conclusions & Future Directions

• Can we ‘rescue’ behavioral and neural deficits in fear extinction recall in PTSD with an acute dose of THC?

• Prompt investigation of the cannabinoid system as a pharmacological target in exposure
  
  – What are the benefits?

  – What are the potential pitfalls/considerations?
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