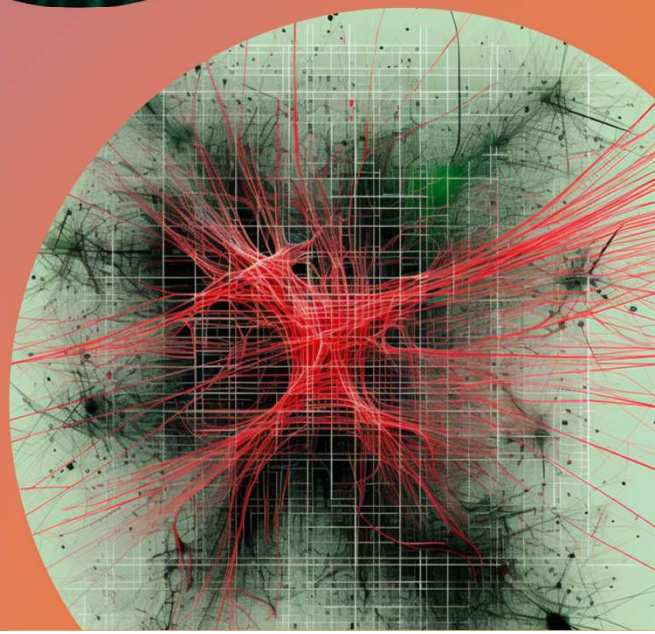
Cognitive Neuroscience of Psychedelics



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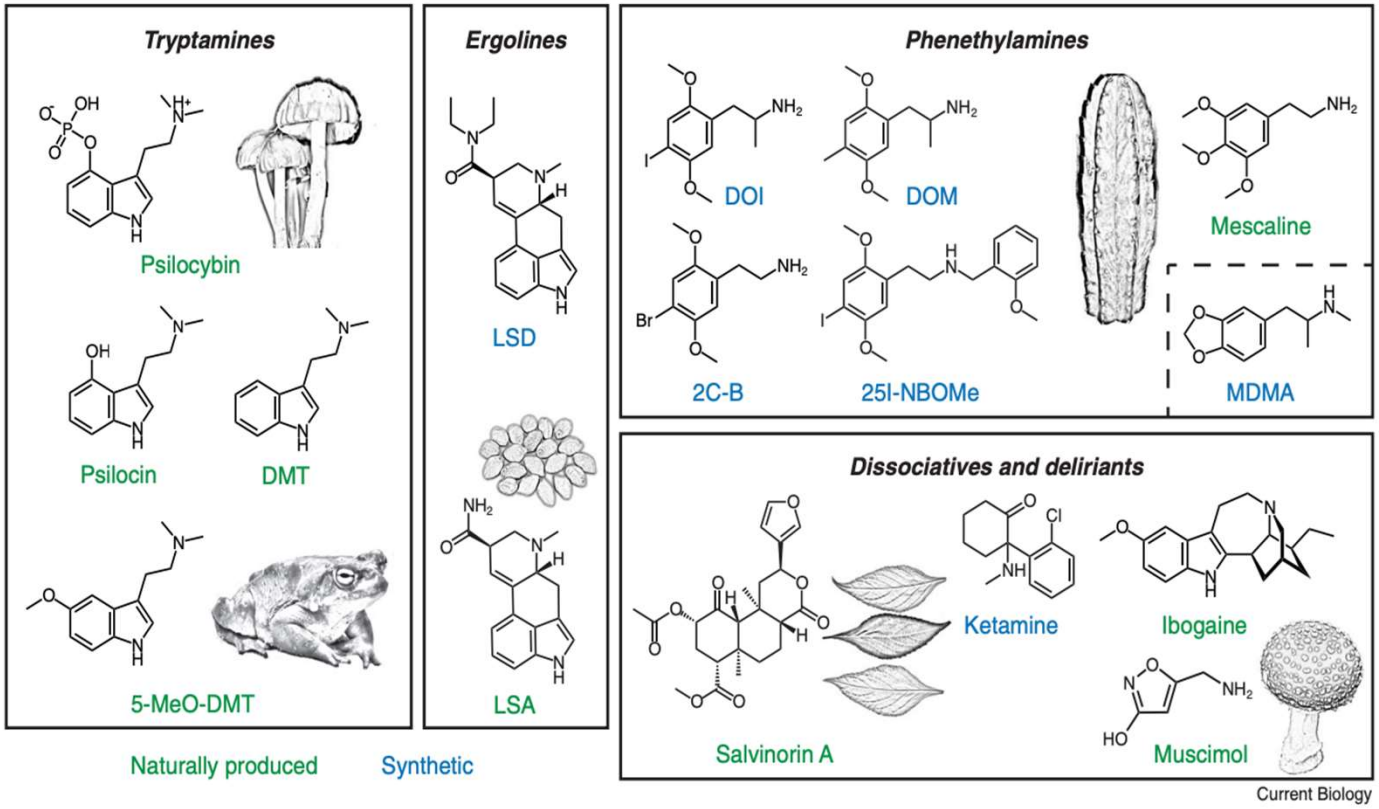
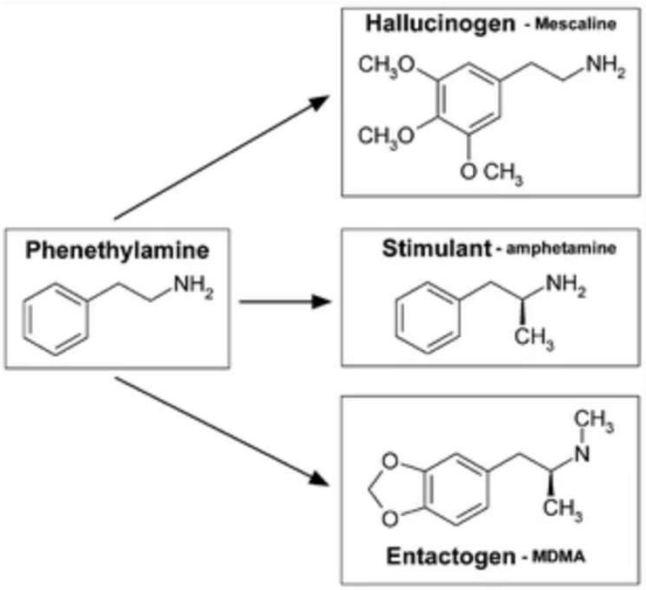
Disclosures

- Research Funding from Transcend Therapeutics and Freedom Biosciences
- Patent application related to psychedelics

Psychedelics and entactogens



Kelmendi, Kaye, Pittenger, Kwan



Fantegrossi et al, 2004

Hyperarousal

Mood

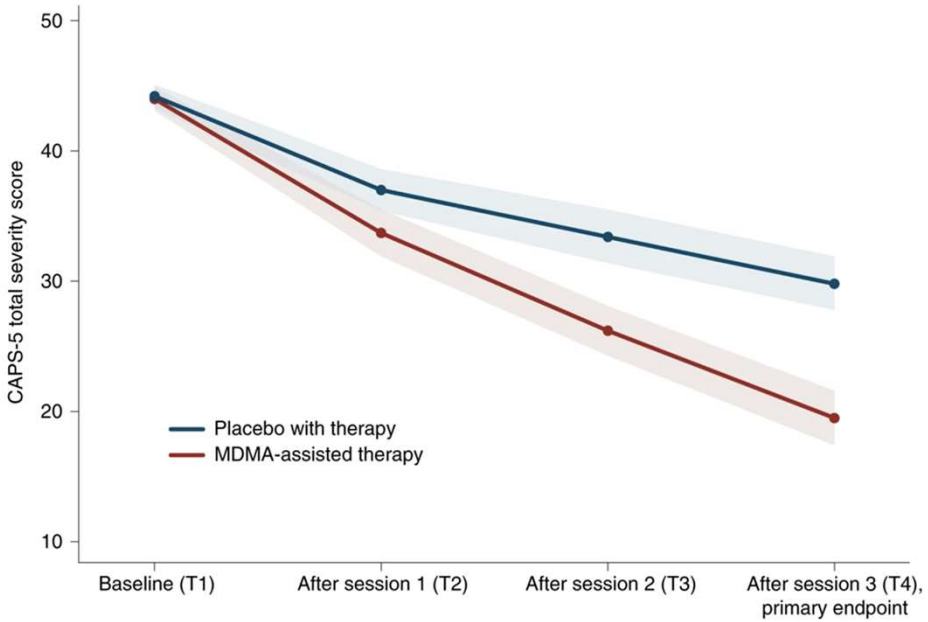
Re-experiencing

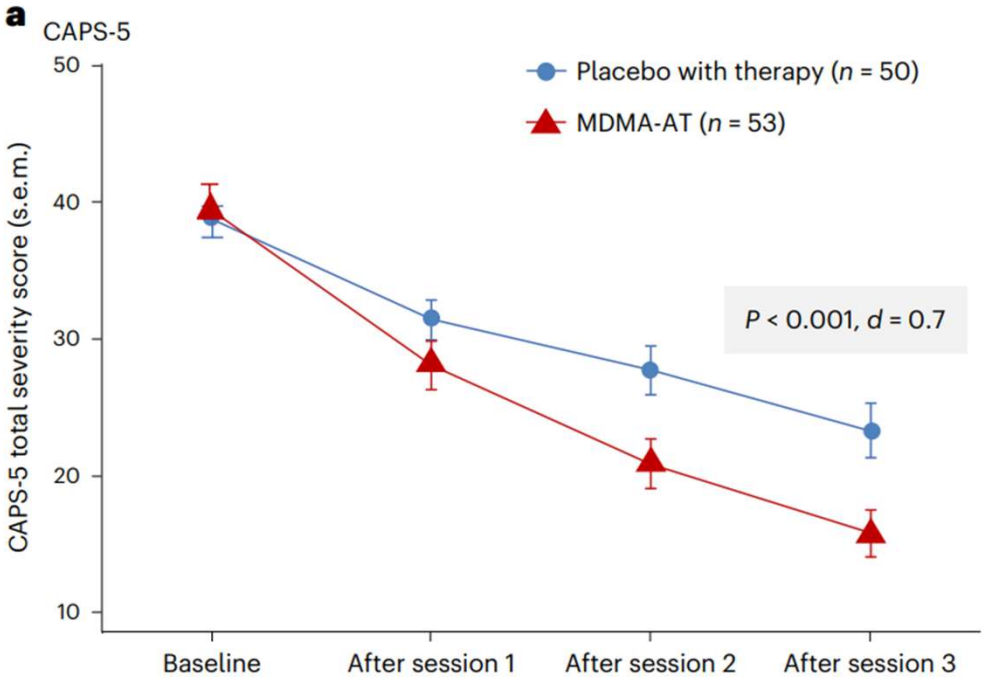
Subtypes of PTSD

Treatments

- SSRIs with moderate efficacy
- Evidence-based psychotherapy

MDMA was effective in Phase III clinical trials for PTSD





- SSRI effect size = 0.23 (Hoskins et al., 2015)
- MDMA effect size = 0.7-.91

- 67% of MDMA group vs 32% of placebo group no longer met criteria for PTSD

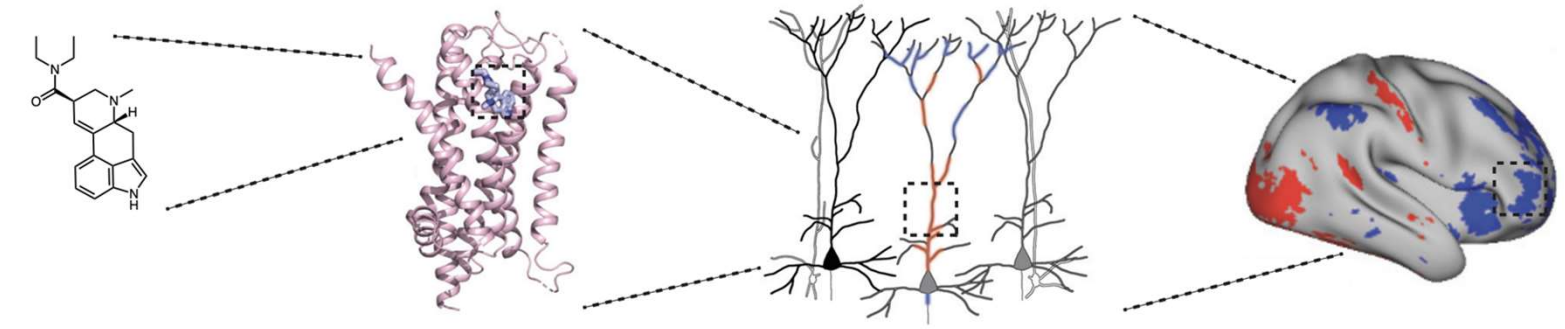
Mitchell et al 2021; 2023

Why we need psychedelic cognitive models

1. To understand and enhance therapeutic effects
2. To avoid iatrogenic harms
3. To convey understanding to patients
4. To refine conceptual understanding and define subsequent research questions

Why we need psychedelic neurobiology

- To develop improved psychedelic treatments and potential interactions
- Mechanism avoids the potential for expectancy bias
- To better assess emerging clinical evidence



Psychedelic

Molecular

Serotonin receptors
(5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, ...)

Signal transduction pathways

Cellular and circuit

Neural plasticity
(structural remodeling,
gene expression, ...)

Spiking activity dynamics

Network

Regional suppression
(default mode network)

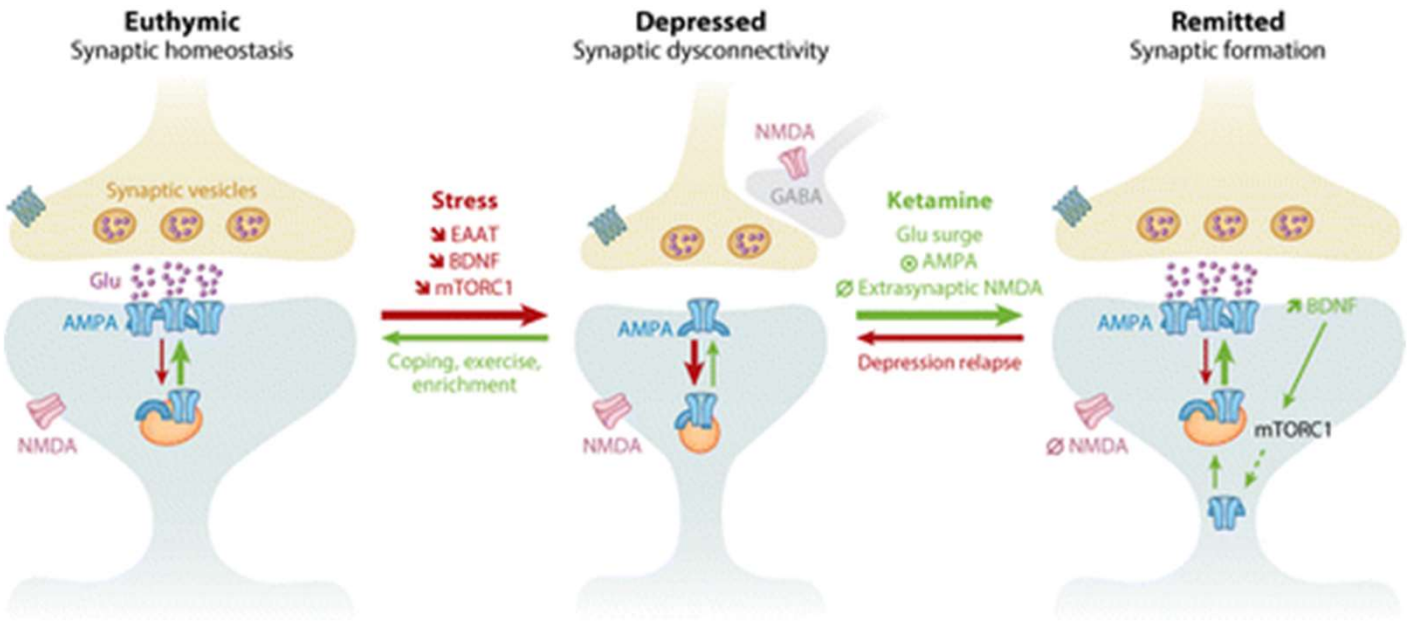
Functional connectivity

Key cognitive models of psychedelic drug effects

- Neuroplasticity
- Extinction of habits or traumatic associations
- Social connectedness
- Cognitive flexibility
- Experiential transformation

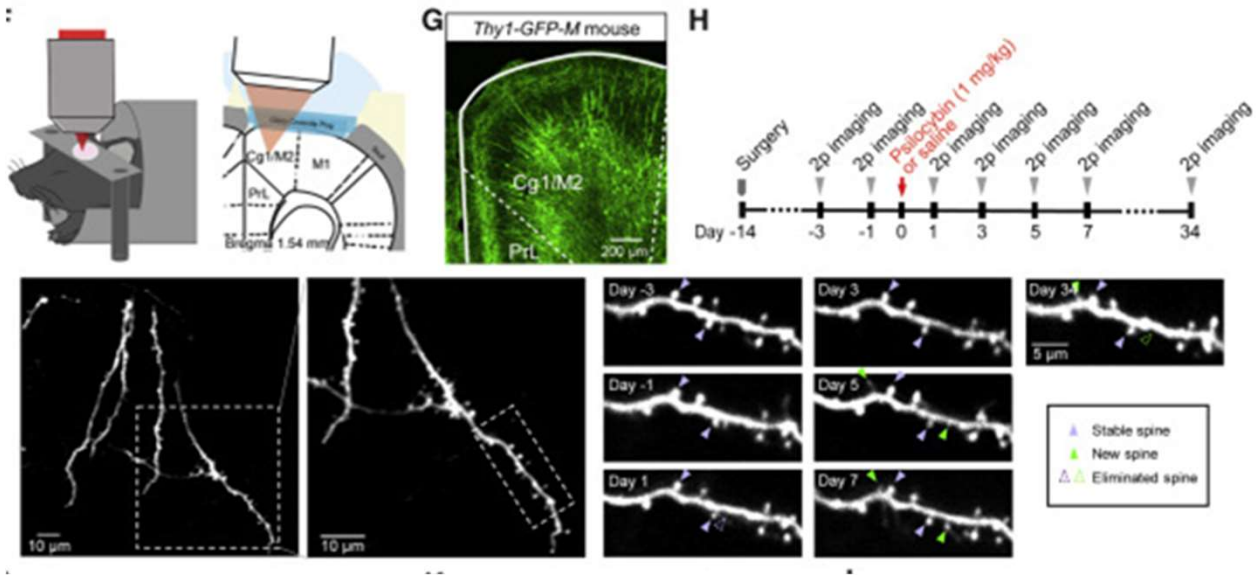
Goal: to develop understanding of these biological-cognitive models

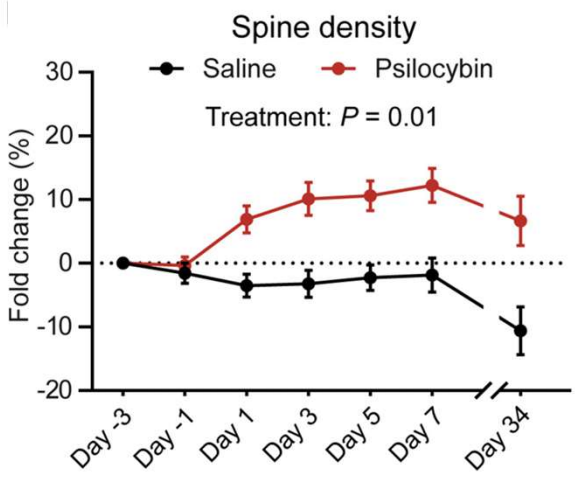
Neuroplasticity



Abdallah CG, et al. 2015.
Annu. Rev. Med. 66:509–23

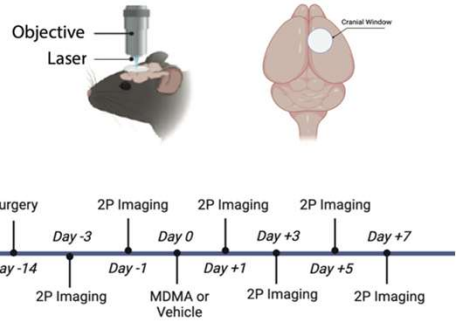
Psilocybin-induced structural plasticity

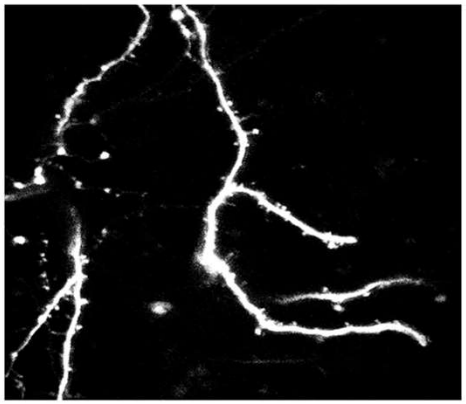


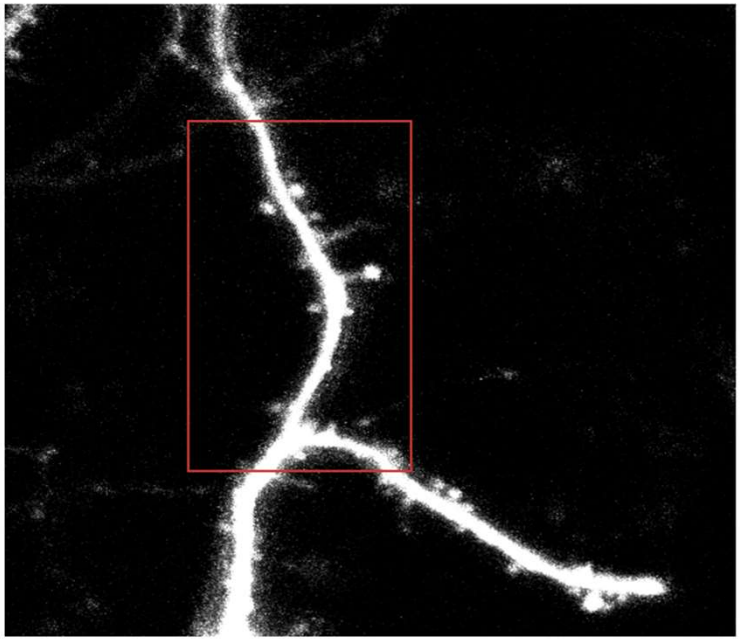


Shao et al 2021

Characterizing MDMA structural plasticity *in vivo*



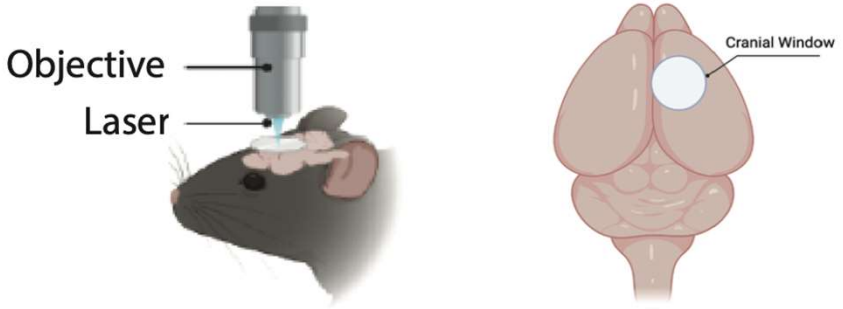


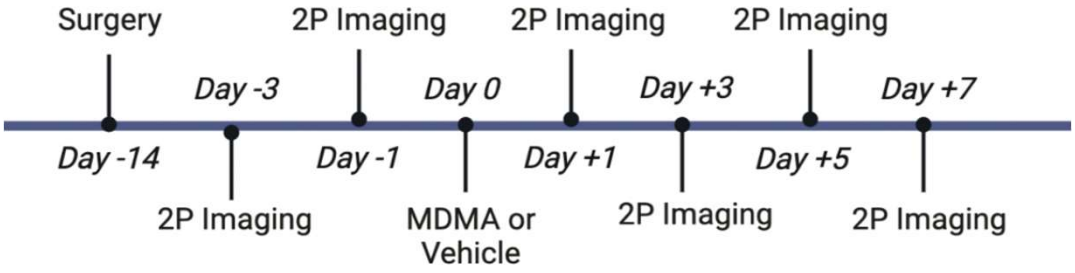


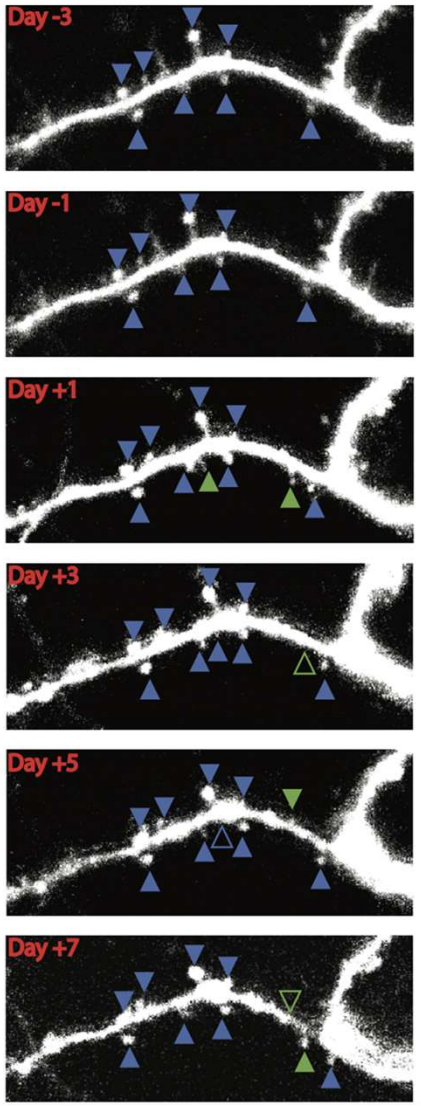
Sarah Jefferson

Patrick Wehrle

Jocelyne Rondeau

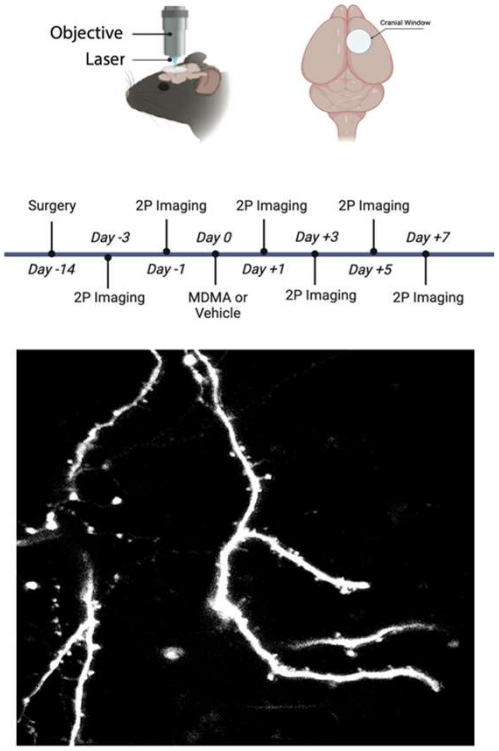


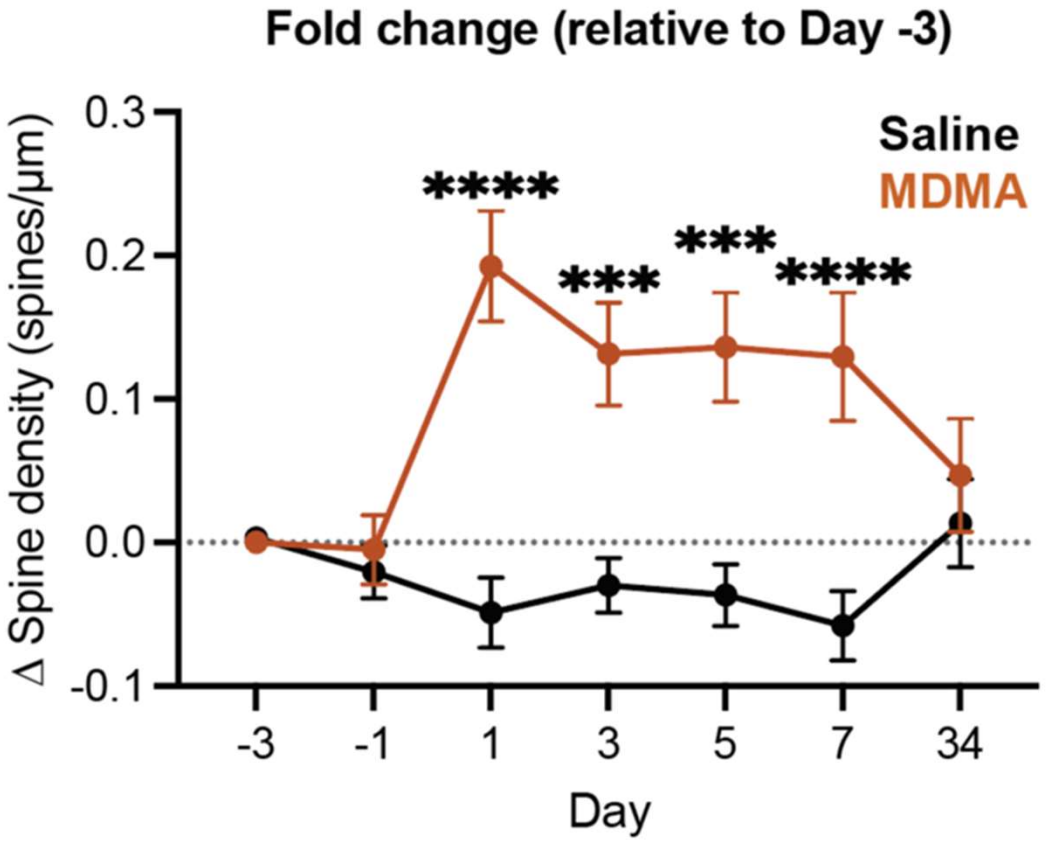


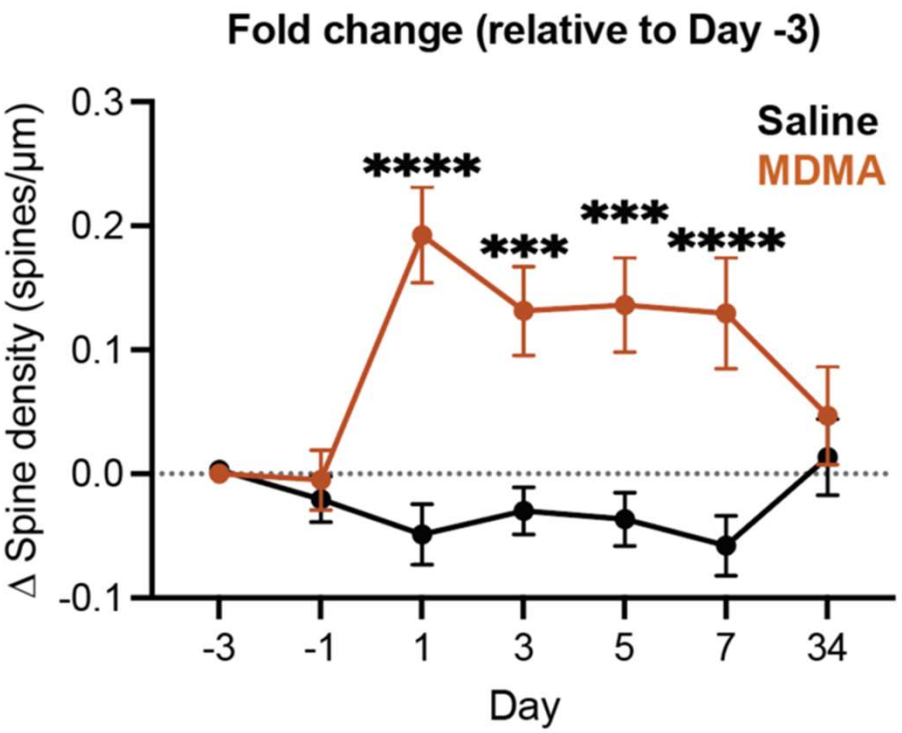


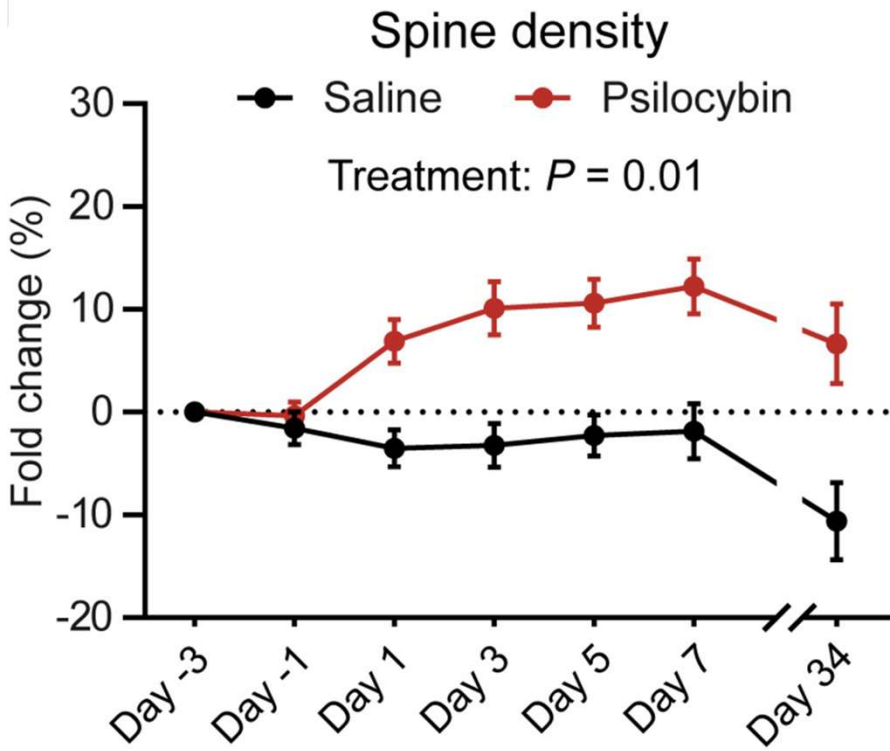
Tracking dendritic spines across days

MDMA induces structural plasticity in frontal cortex



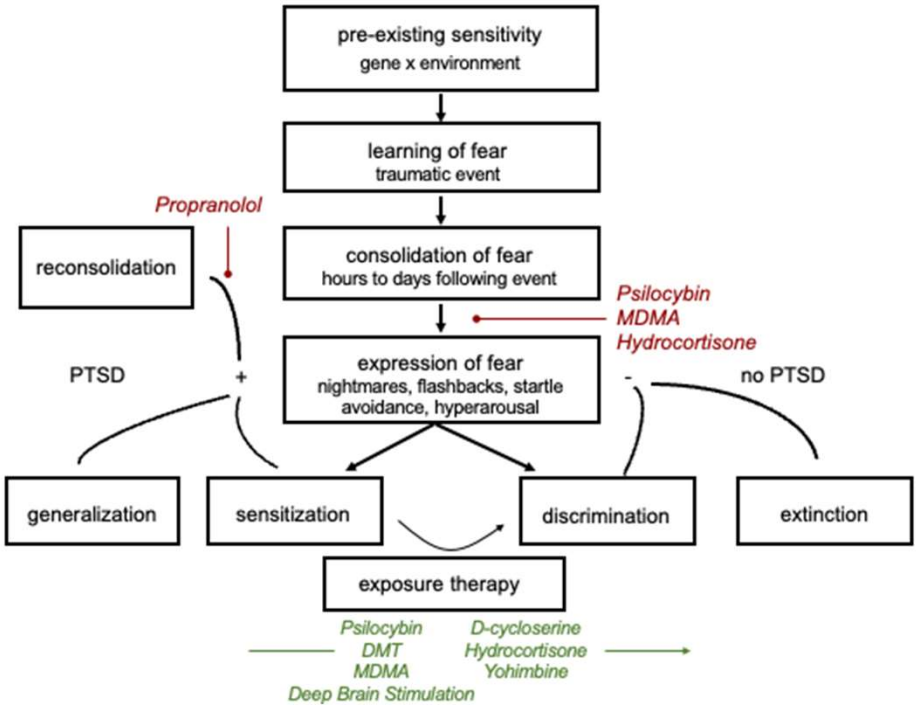






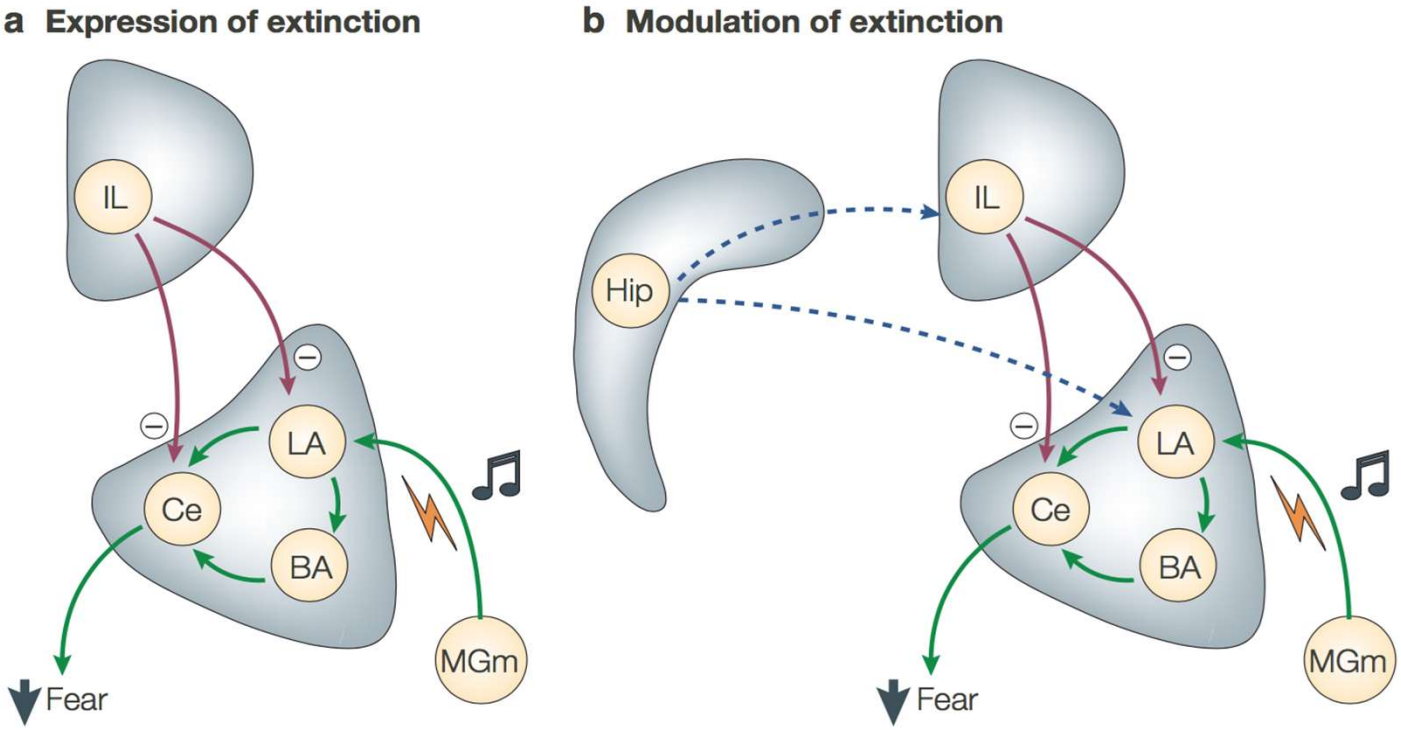
Shao et al 2021

Extinction of habits or traumatic associations



Kaye Jefferson Krystal (in press)

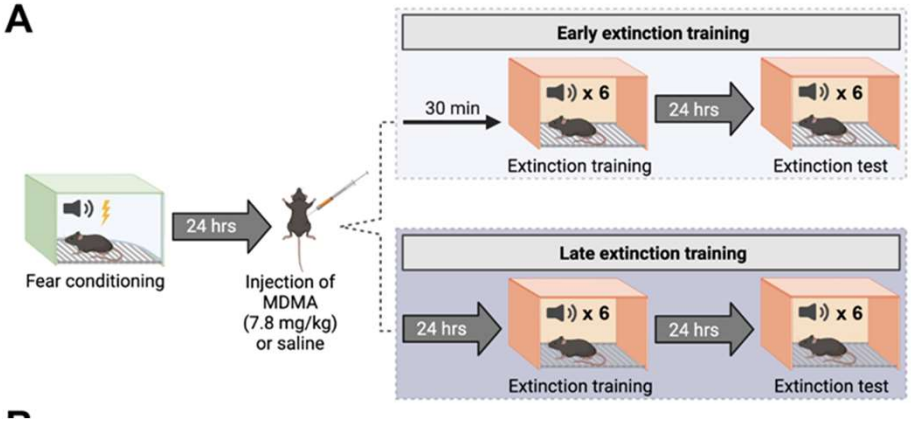
Extinction of habits or traumatic associations

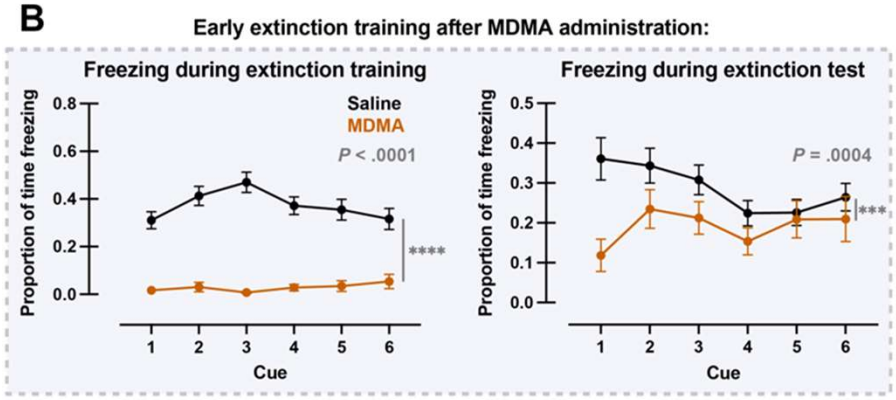


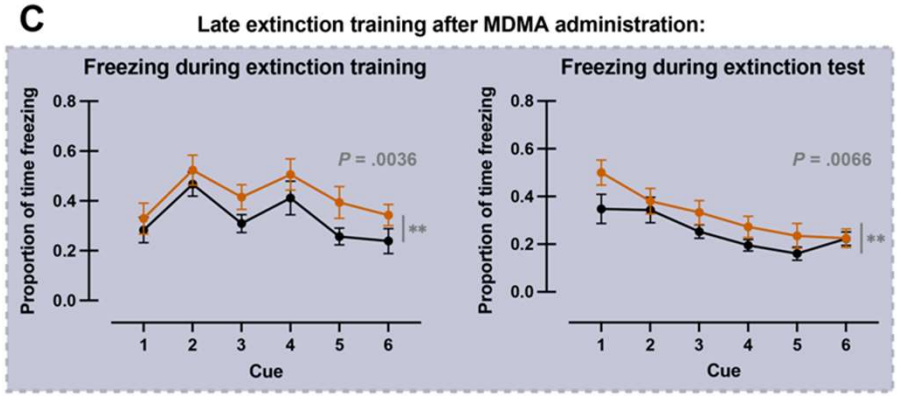
Maren and Quirk 2004

Extinction of habits or traumatic associations

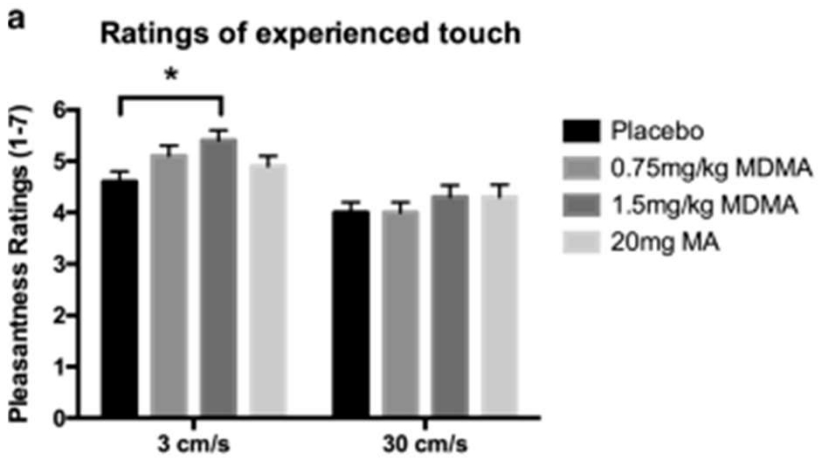
Axel Rosado

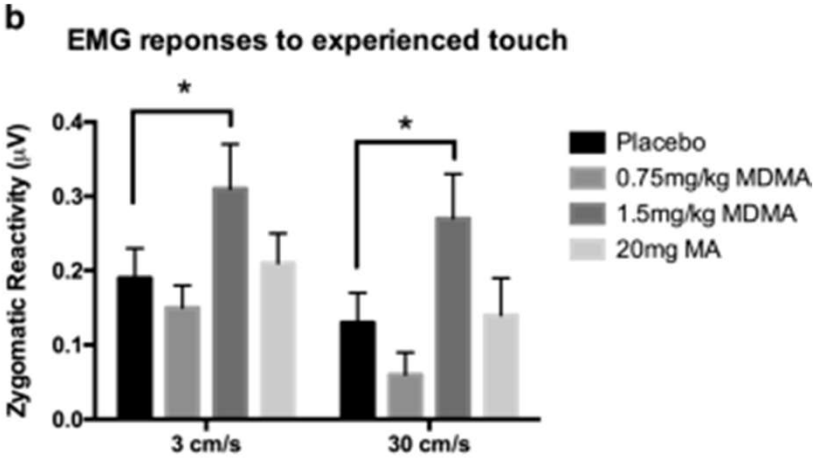


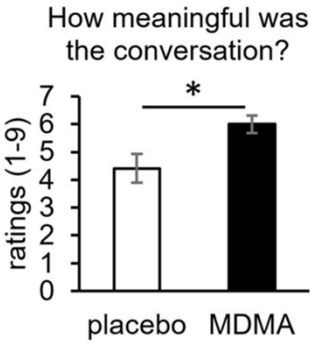


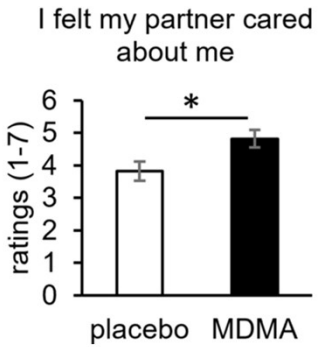


Social connectedness



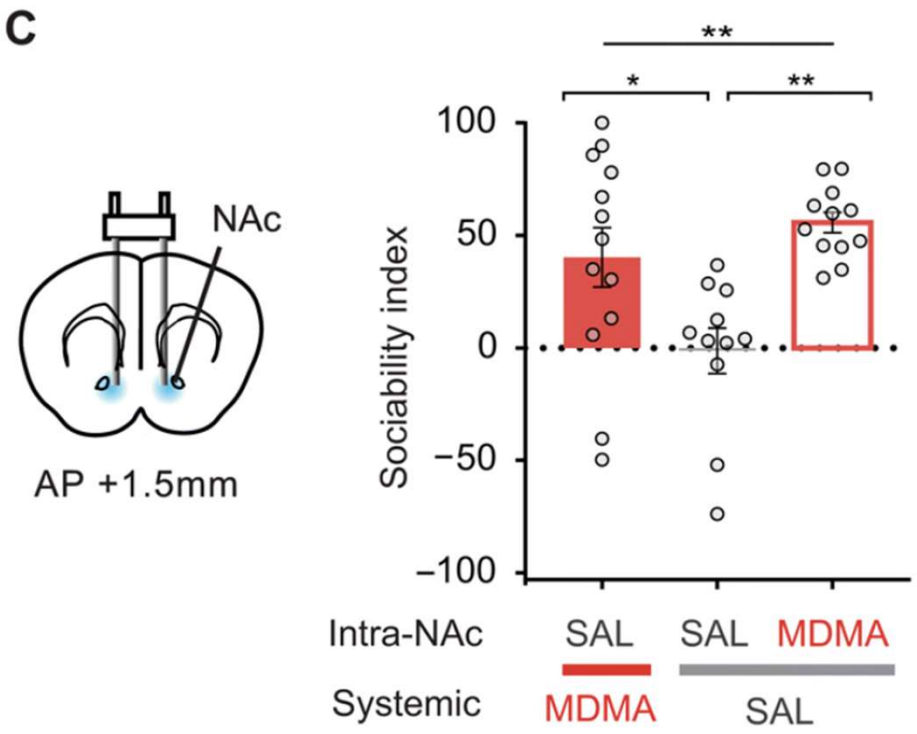






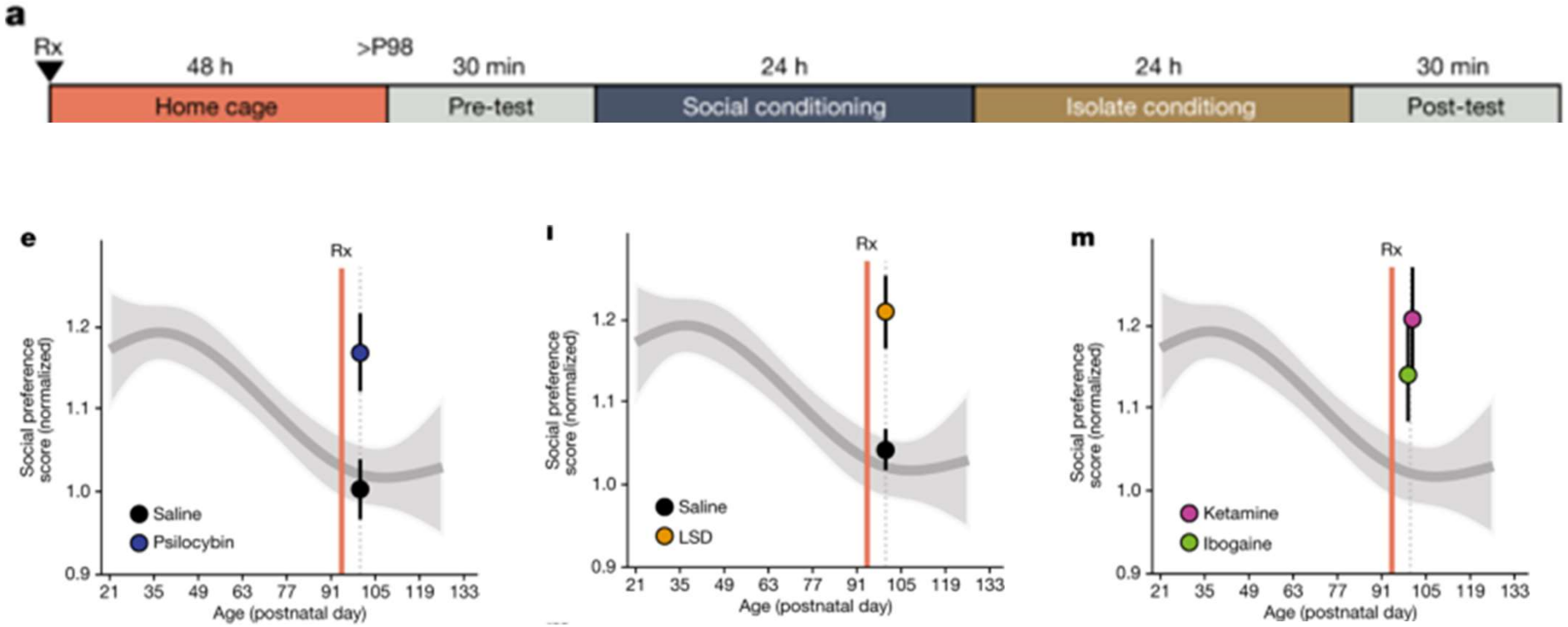
Bershad et al 2019; Molla et al 2023

Social connectedness



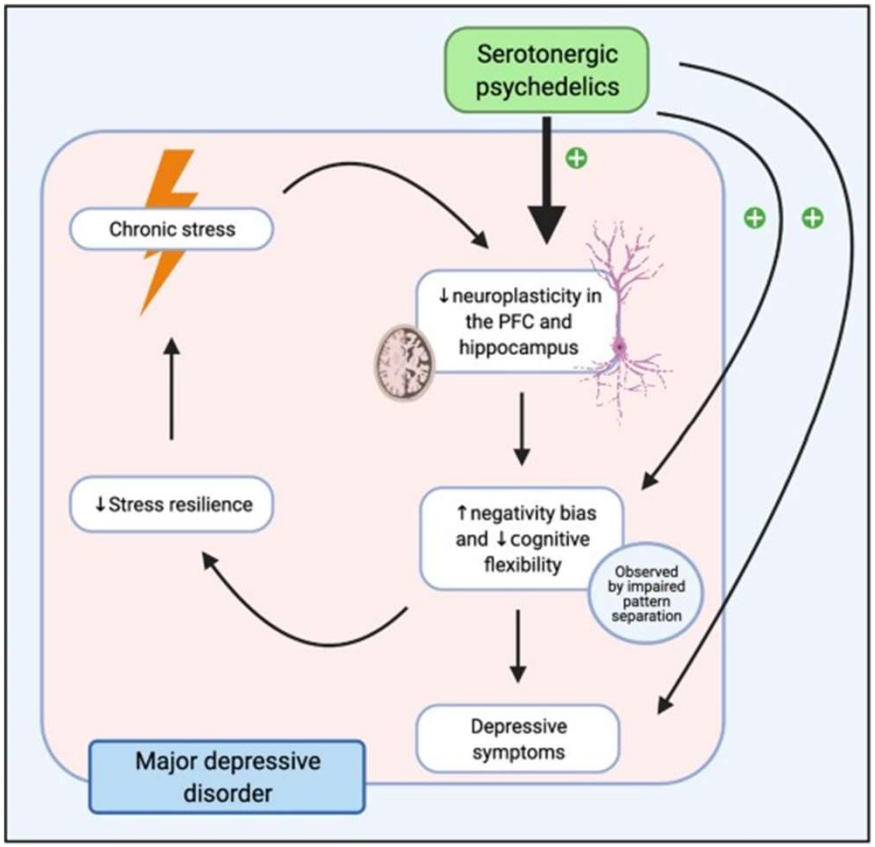
Heifets et al 2021

Social connectedness



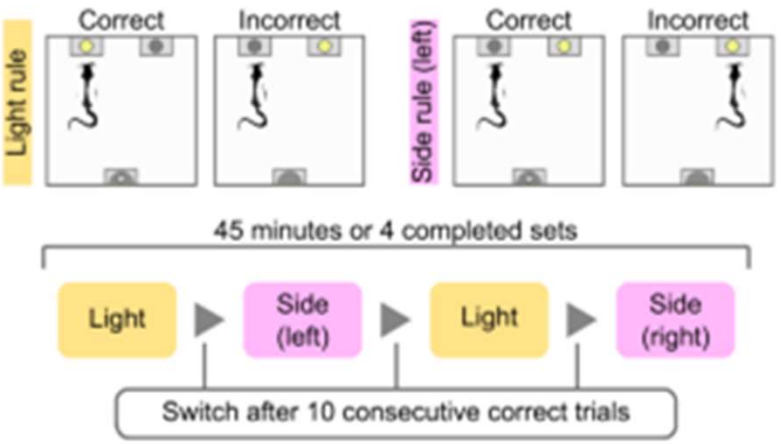
Nardou et al 2019; Nardou et al 2023

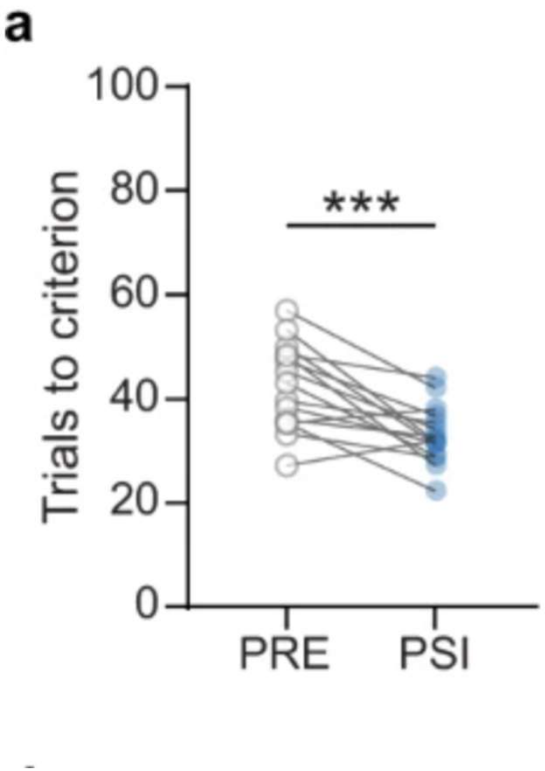
Cognitive flexibility

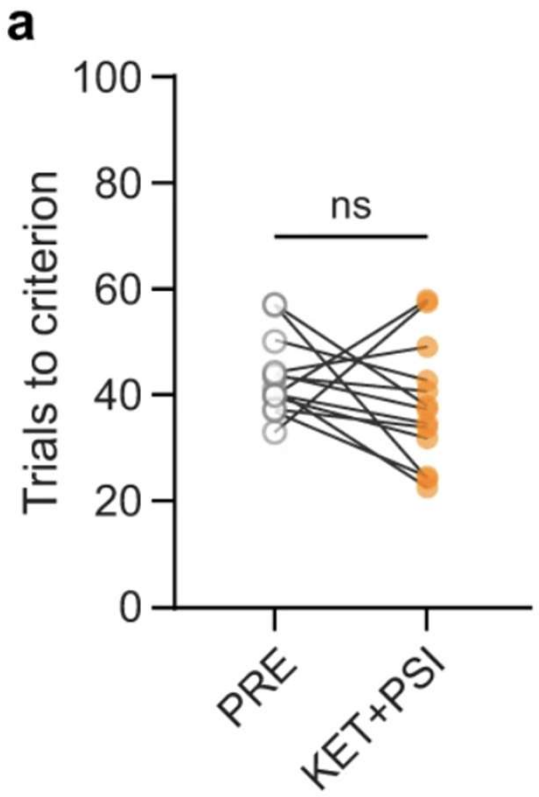


Magaraggia et al 2021

Cognitive flexibility

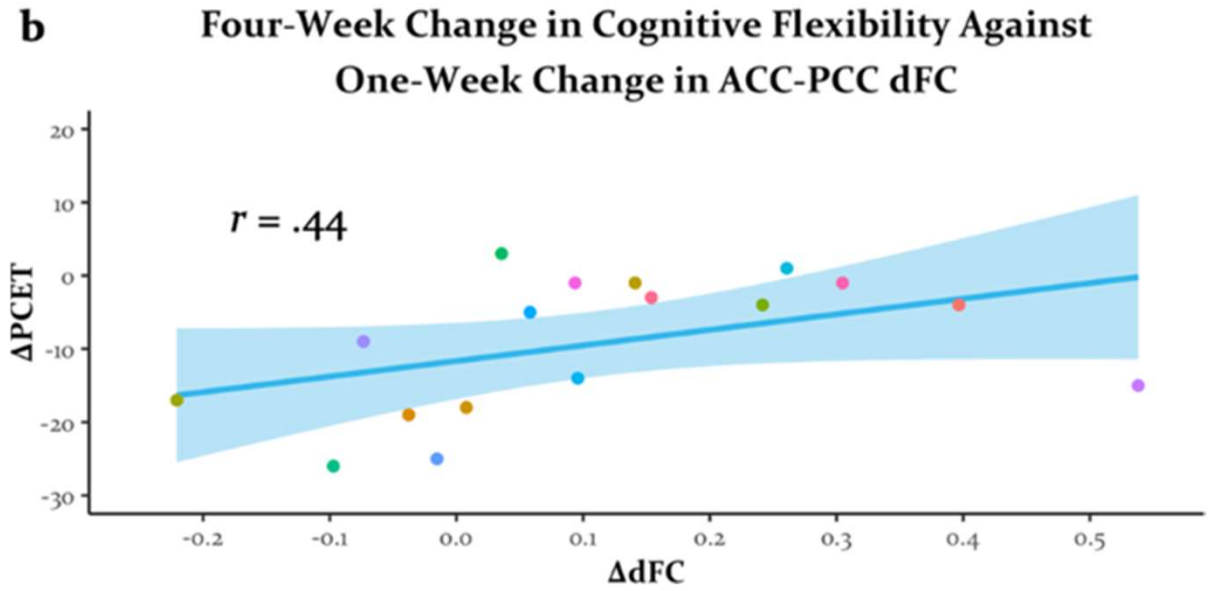






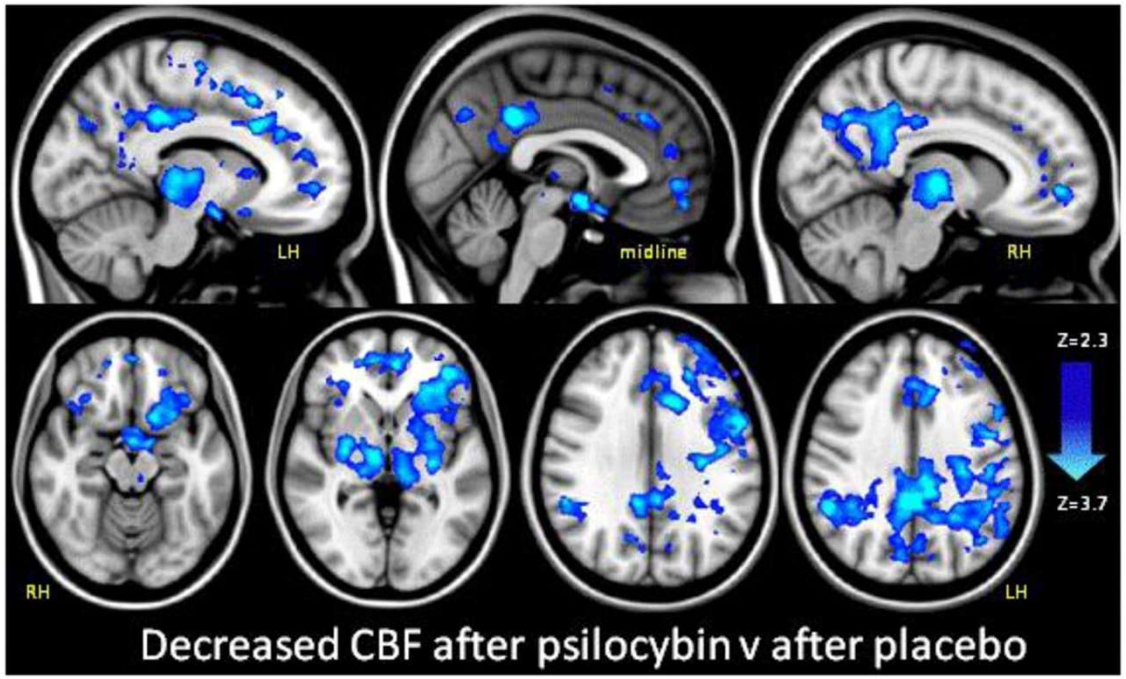
Torrado Pacheco et al

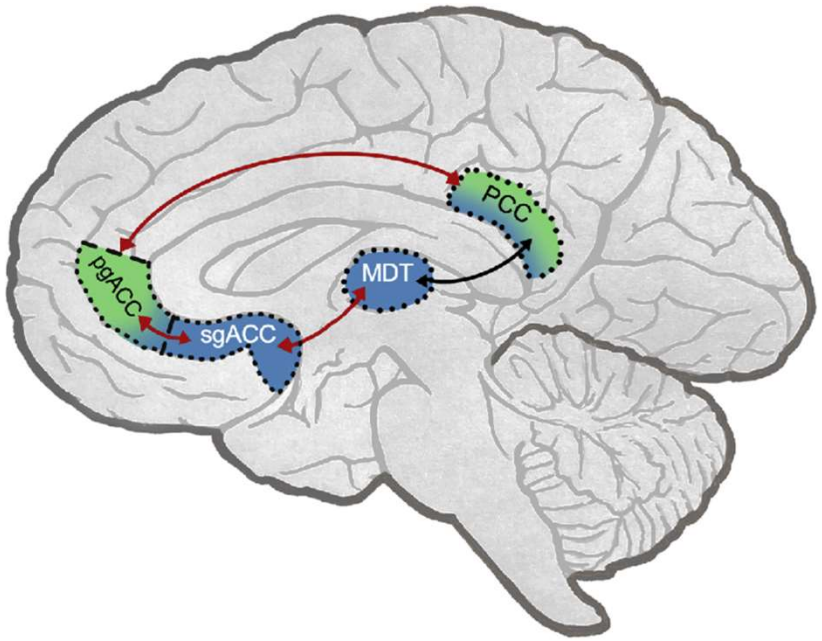
Cognitive flexibility



Doss et al 2021

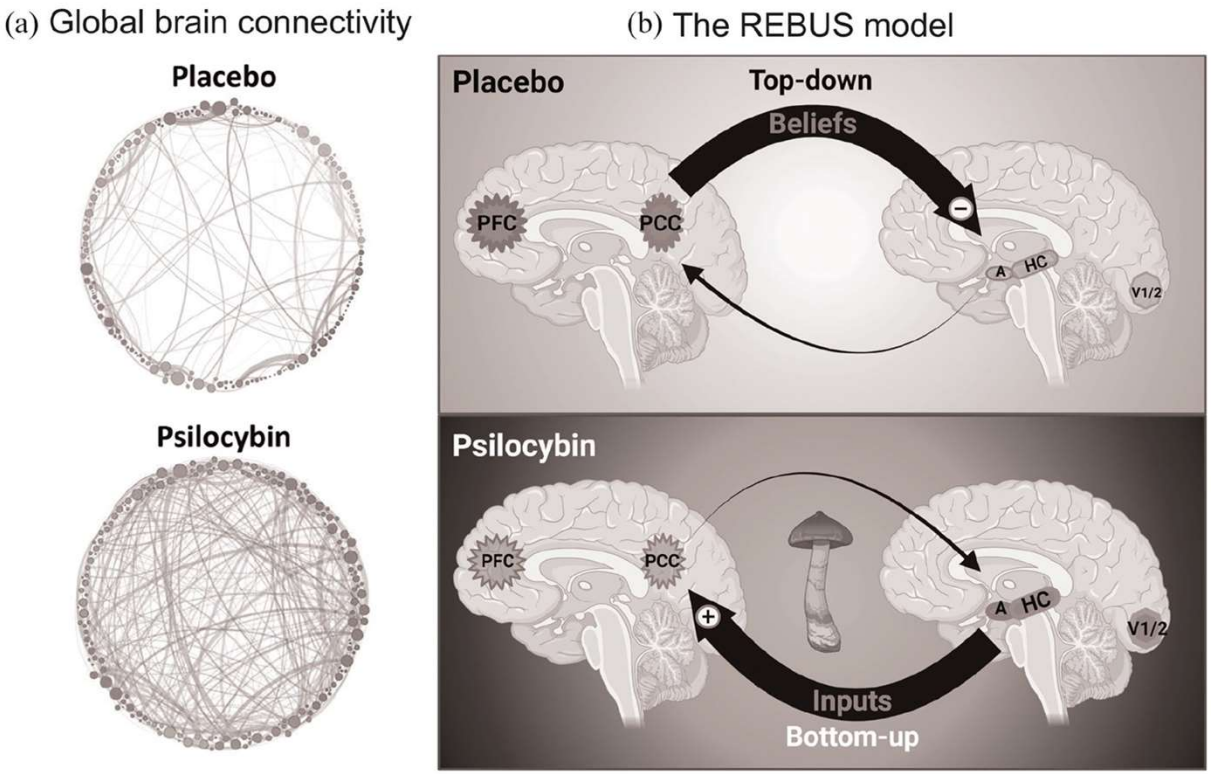
Experiential transformation





Carhart-Harris et al 2012; Alexander et al 2021

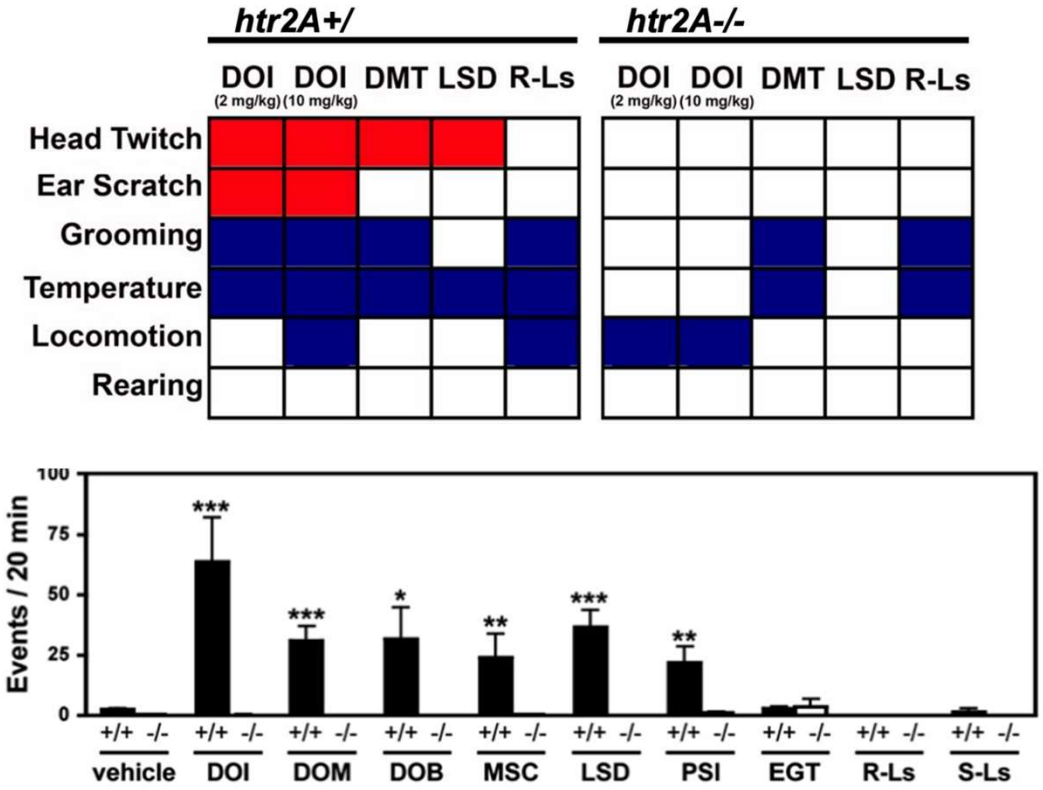
Experiential transformation



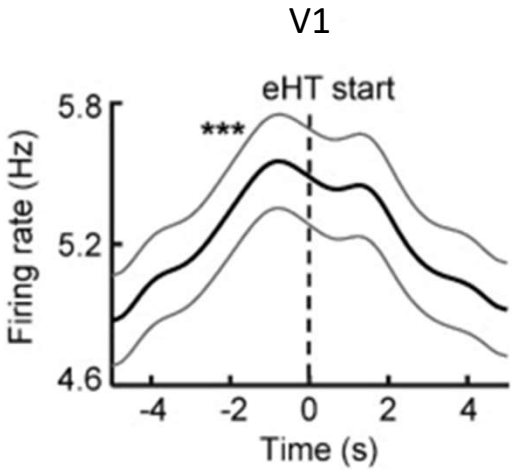
REBUS Model
- Relaxed beliefs under psychedelics

Carhart-Harris and Friston 2019; Smausz et al 2021

Experiential transformation



Gonzales-Maeso et al, 2007



Domenico et al, 2021

Summary

Psychedelic effects are mediated by **$5HT_{2A}$ receptors**

We discussed five conceptual models:

1. Plasticity – psychedelics cause growth of new dendritic spines in prefrontal cortex
2. Extinction Learning – psychedelics increase learning of competing memories or patterns of behavior
3. Social connectedness – psychedelics have powerful effects on social learning

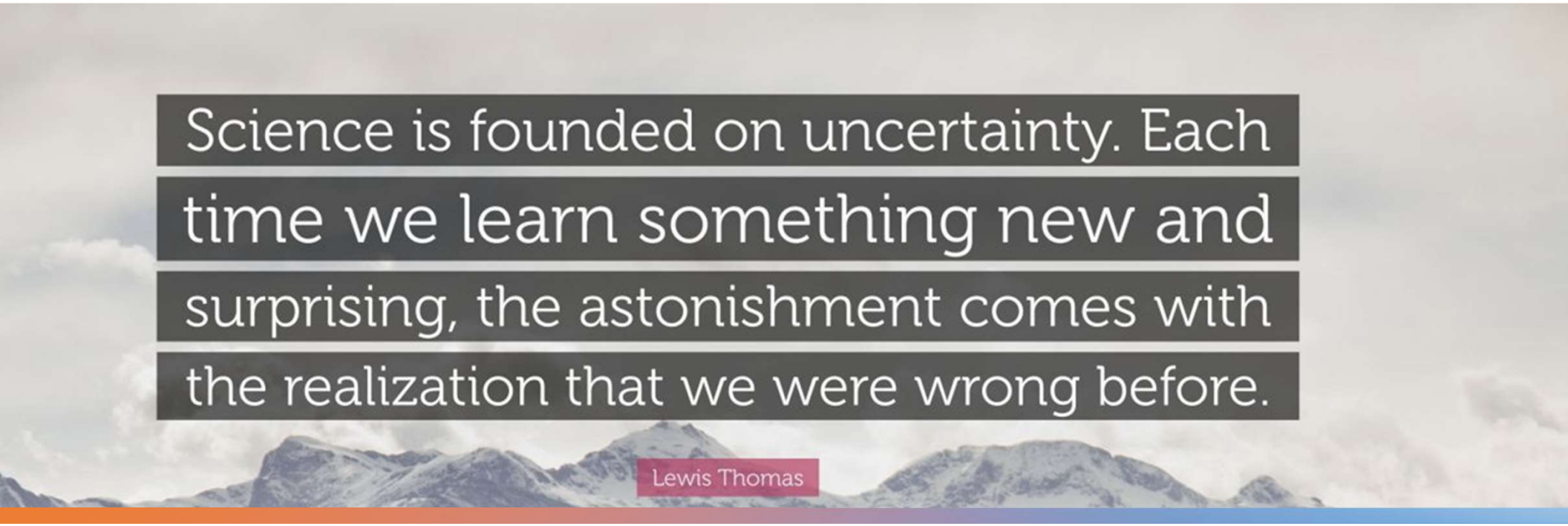
Summary

1. Plasticity – psychedelics cause growth of new dendritic spines in prefrontal cortex
2. Extinction Learning – psychedelics increase learning of competing memories or patterns of behavior
3. Social connectedness – psychedelics have powerful effects on social learning
4. Cognitive flexibility – psychedelics might enhance cognitive switching ability
5. Experiential – perhaps something intrinsic to the subjective experience is needed (relaxed beliefs, etc.)

These are very preliminary models!

•Questions for the field:

- What does a more precise circuit activation model look like?
- What are the time windows for plasticity and learning-related effects? Are these effects general or specific?
- Are experiences necessary for psychedelic treatments?
- Are entactogens and psychedelics really acting through similar mechanisms at all?



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