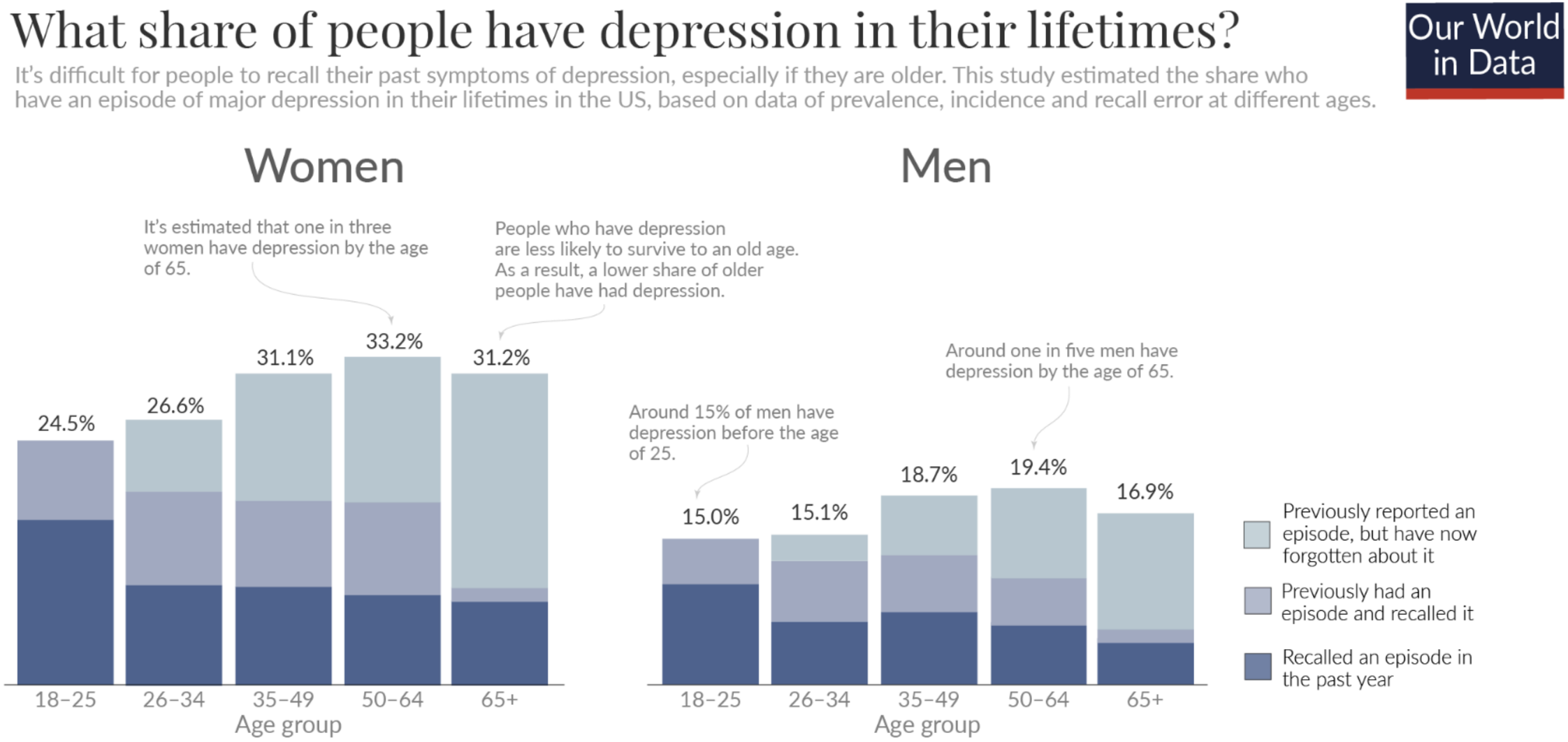
Psychedelics as Immune Modulators of Brain Plasticity in Stress-Related Disorders

The Gene Lay Institute of Immunology & Inflammation
The Ann Romney Center for Neurologic Diseases
Brigham & Women's Hospital
Harvard Medical School

Michael A. Wheeler, PhD

Depression is an epidemic

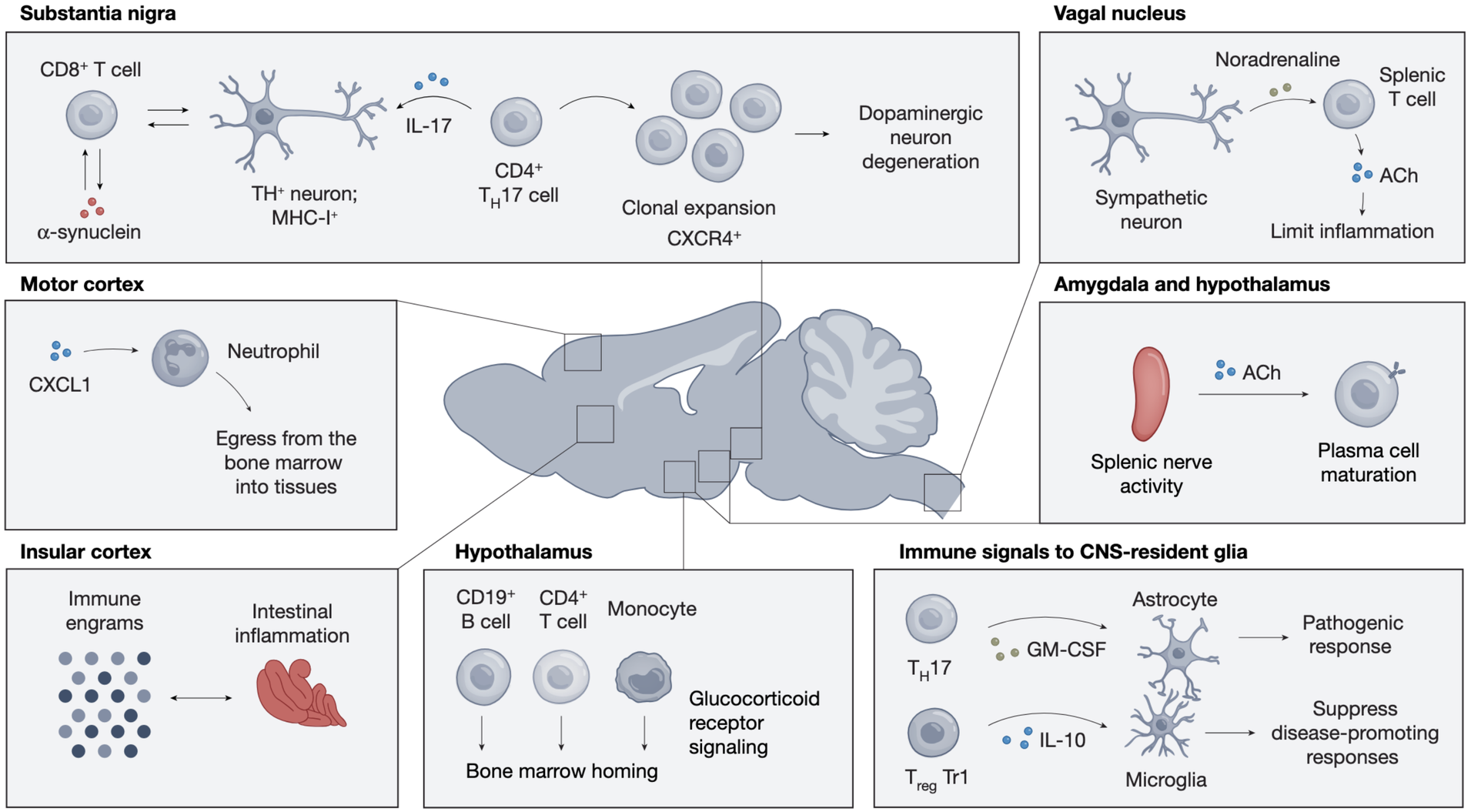


Source: Tam et al. (2020) U.S. Simulation of Lifetime Major Depressive Episode Prevalence and Recall Error. *American Journal of Preventive Medicine.*

OurWorldinData.org – Research and data to make progress against the world's largest problems.

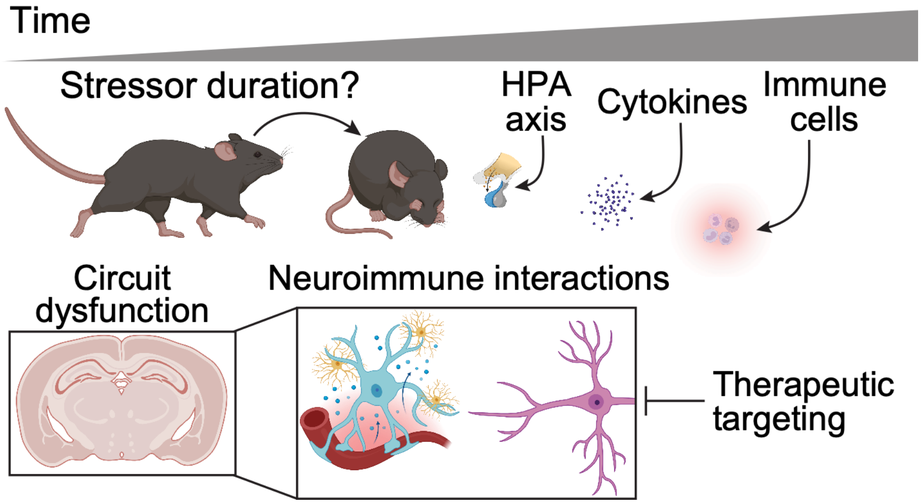
The brain is a mucosal tissue

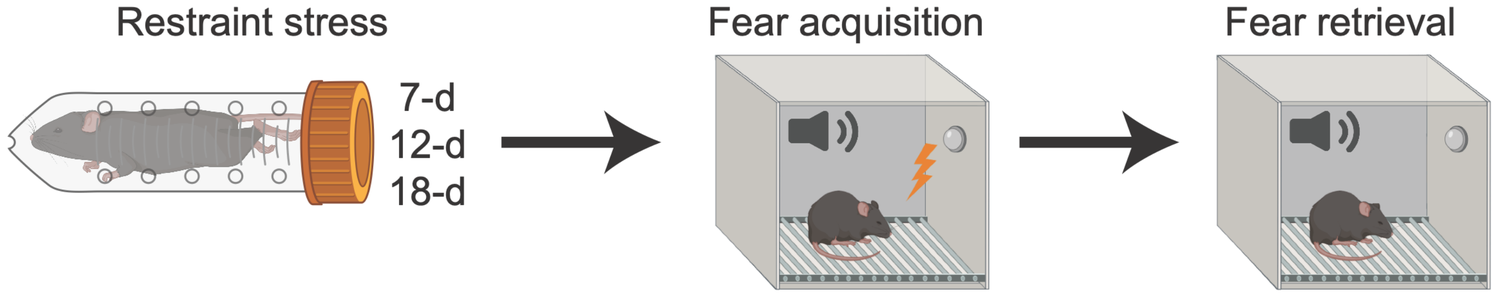
…that happens to control behavior



Wheeler & Quintana, *Nature* 2025

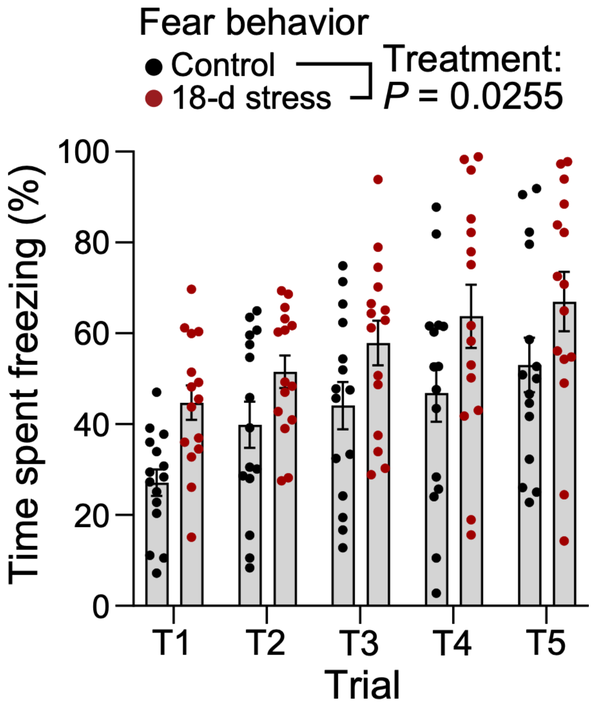
Can we link behavior and immunity?

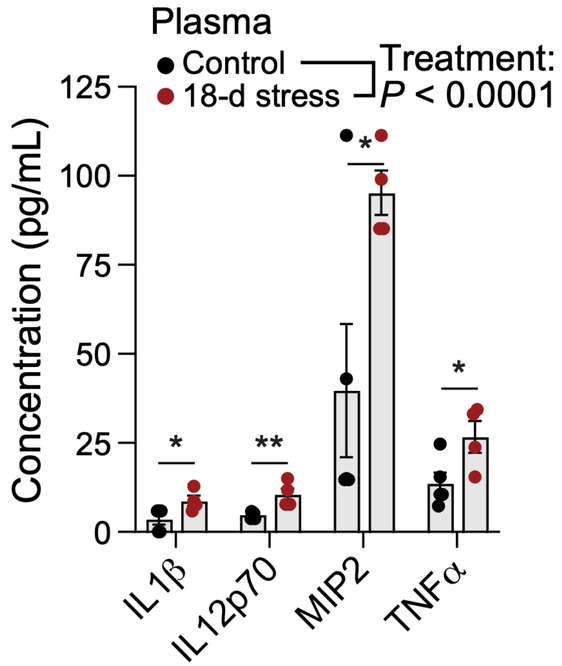


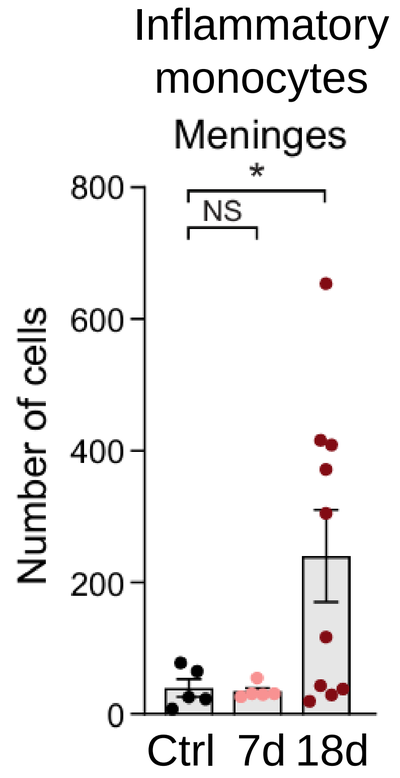


Lizzie Chung
(now MSTP, UCSF)

Jinsu Lee, PhD

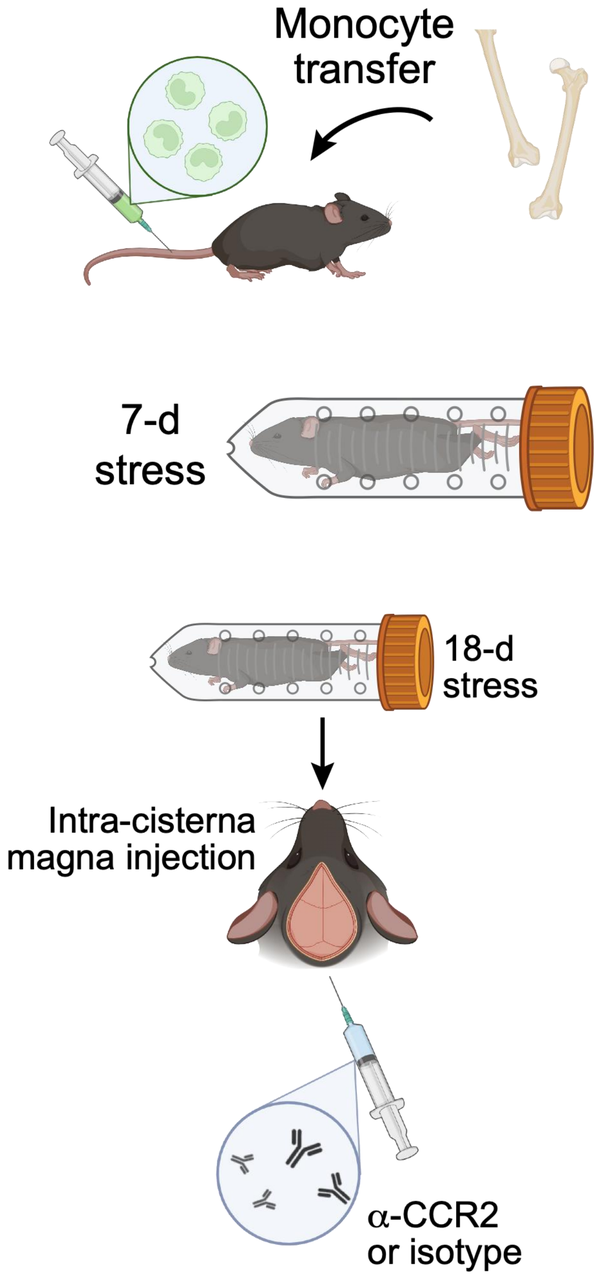


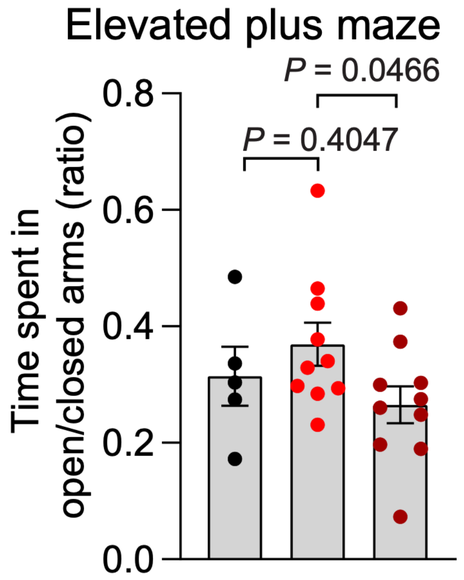


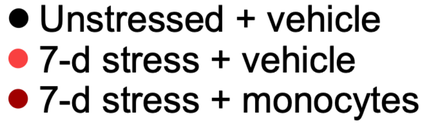


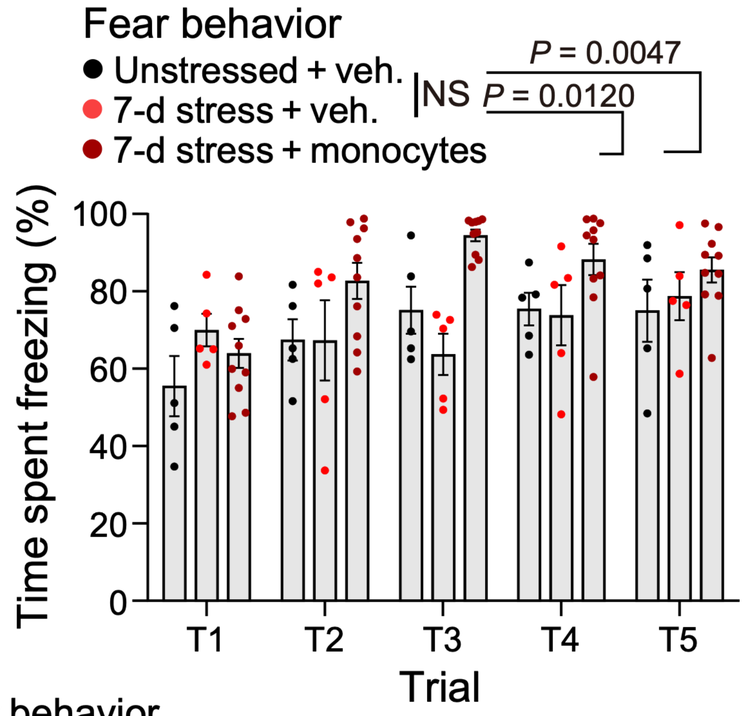
*Chung, *Lee et al., *Nature* 2025

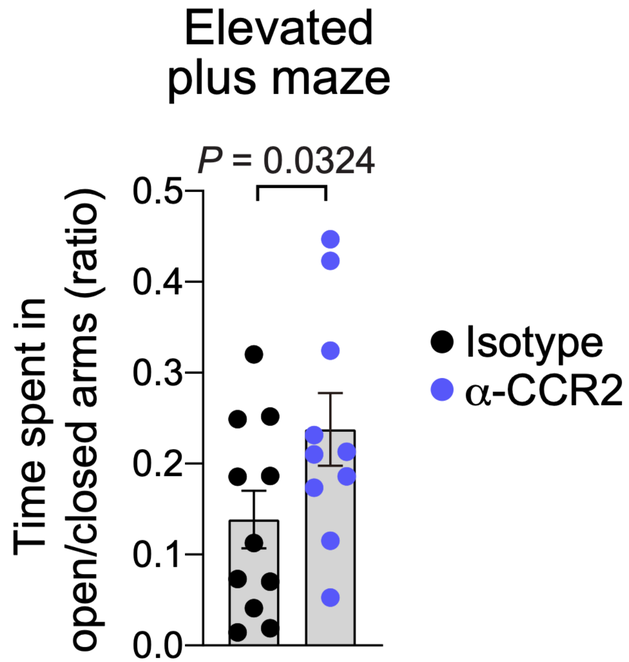
Pro-inflammatory monocytes drive fear behavior

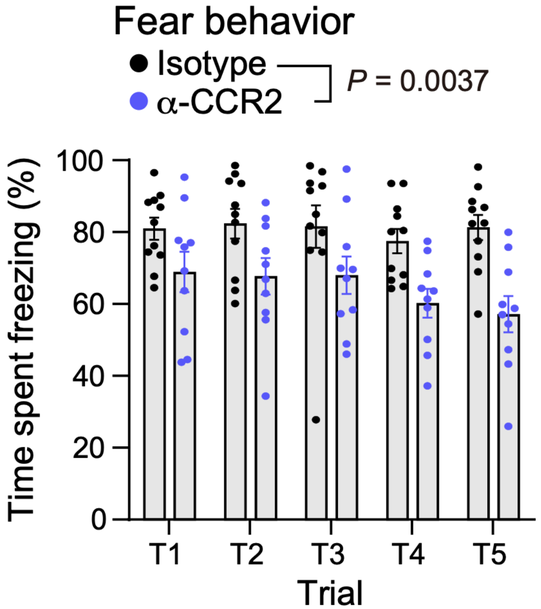






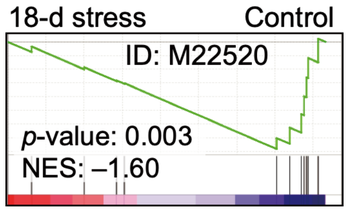




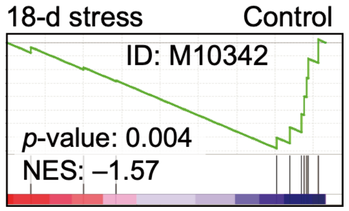


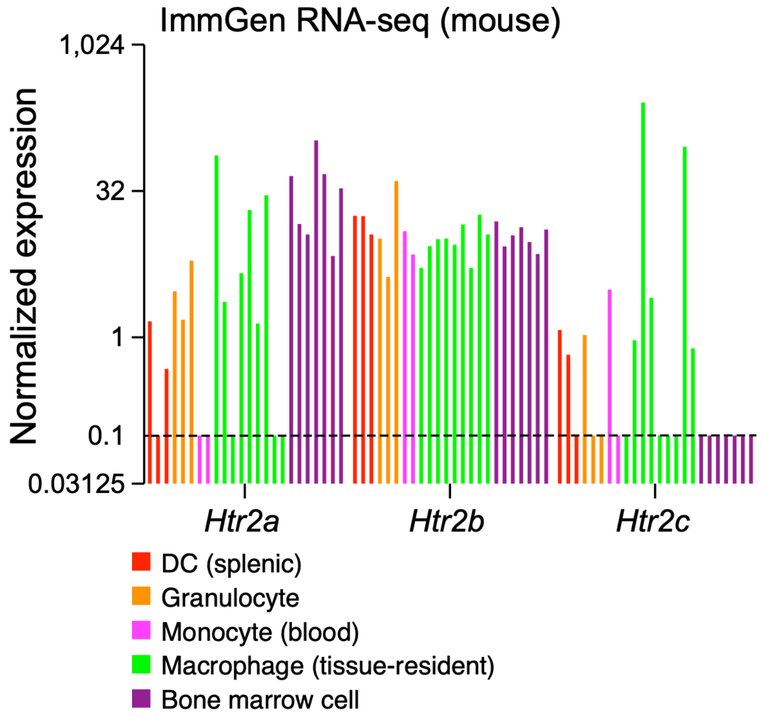
Psychedelics reverse fear behavior and monocyte recruitment

GOBP: Serotonin receptor signaling pathway



GOMF: G-protein coupled serotonin receptor activity



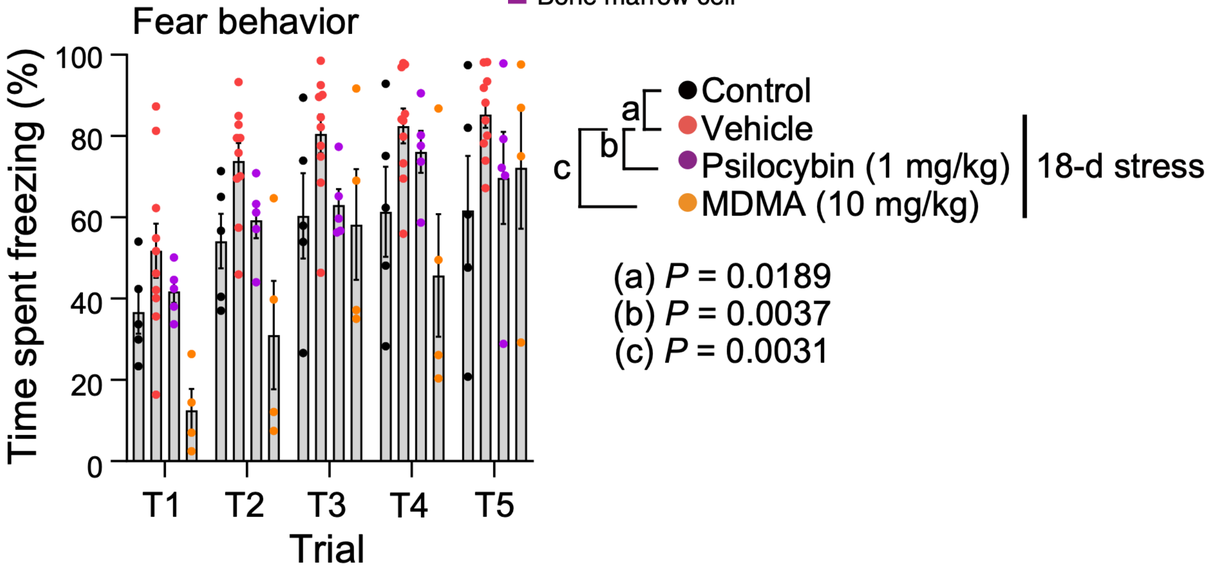


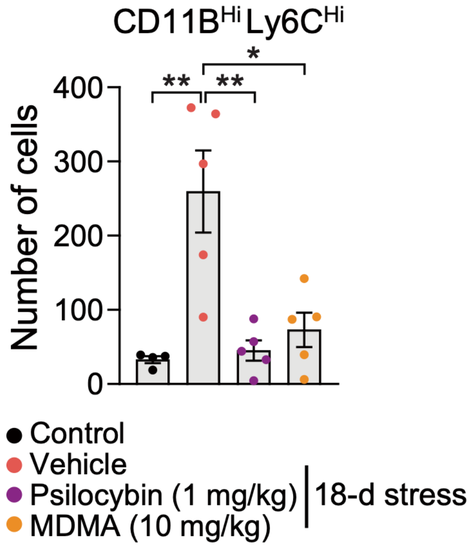
The NEW ENGLAND JOURNAL of MEDICINE

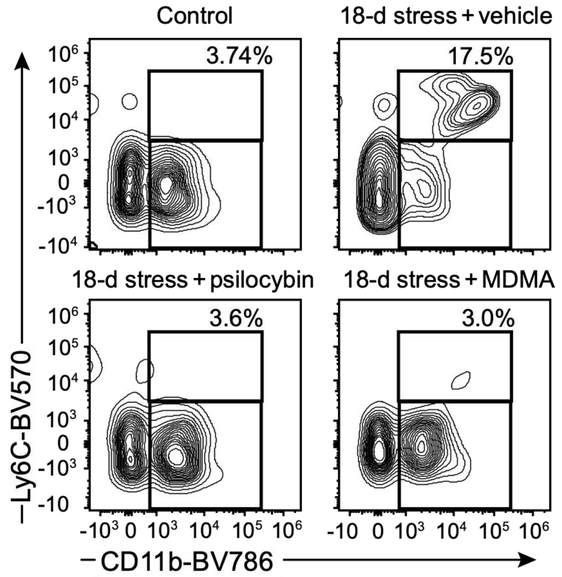
ORIGINAL ARTICLE

Trial of Psilocybin versus Escitalopram for Depression

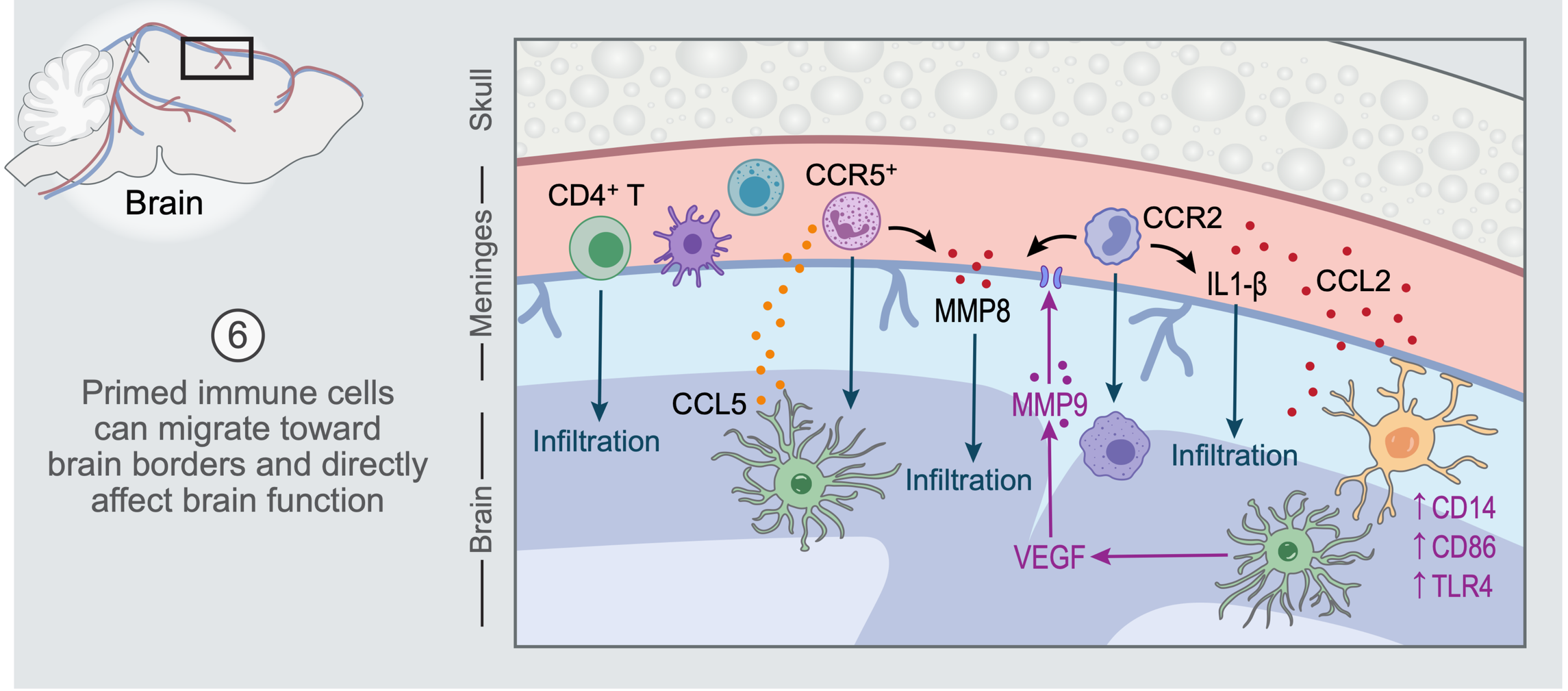
Robin Carhart-Harris, Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy., Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc., Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc., David Erritzoe, M.D., and David J. Nutt, M.D.



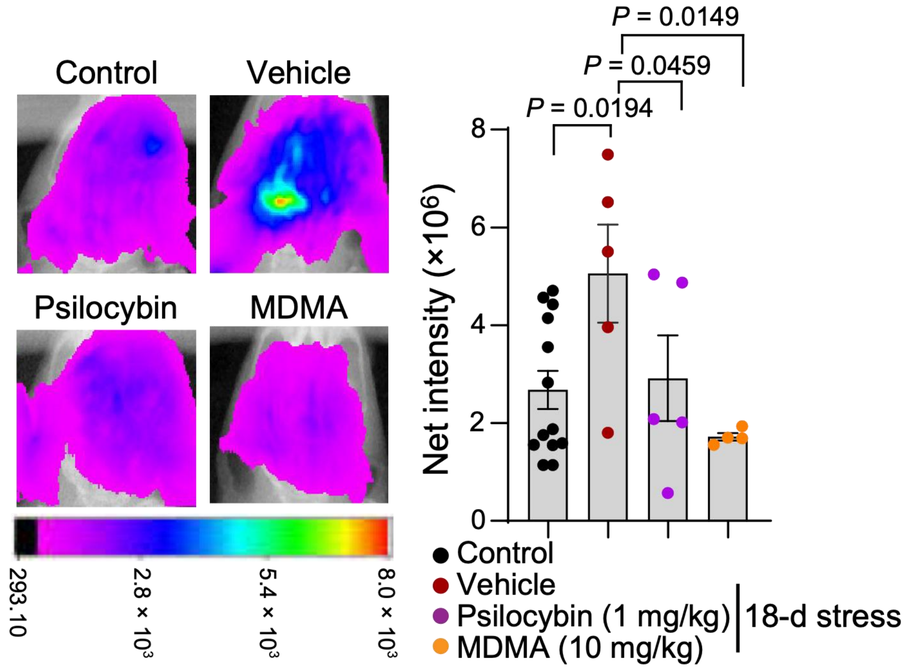


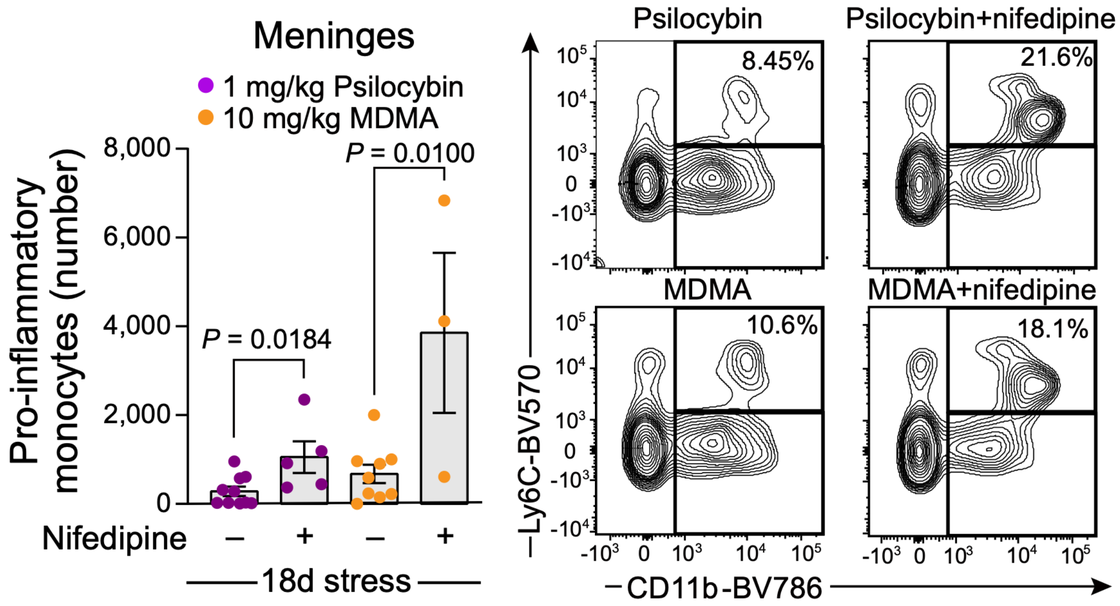


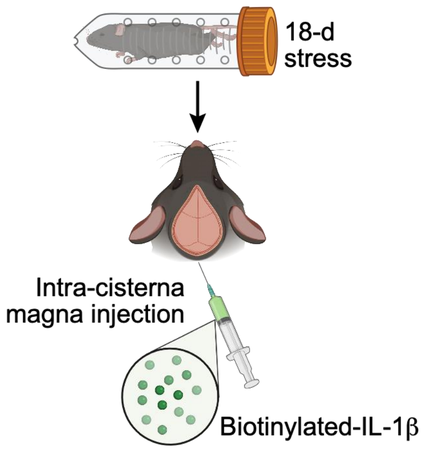
Stress dysregulates the blood-brain barrier

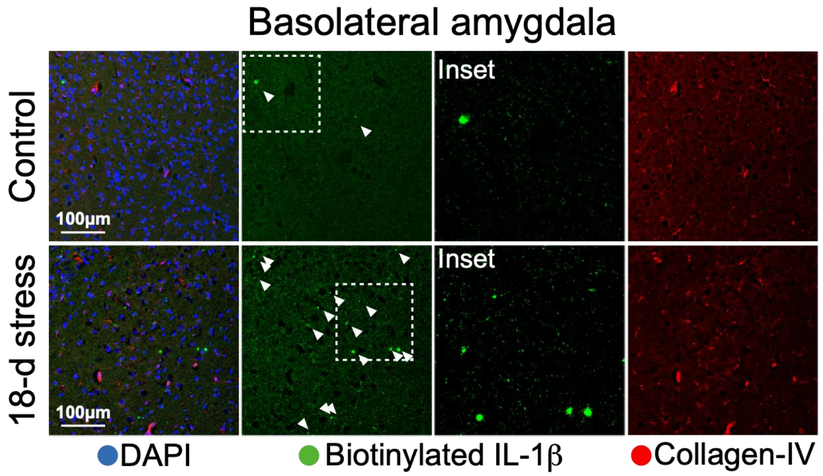


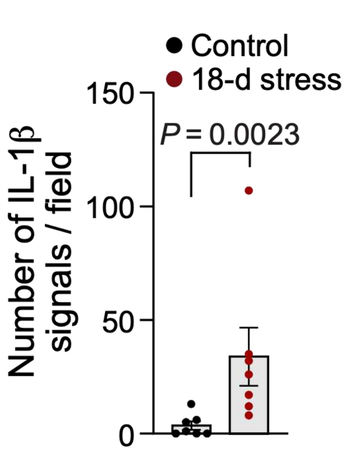
Psychedelics influence meninges-brain signals

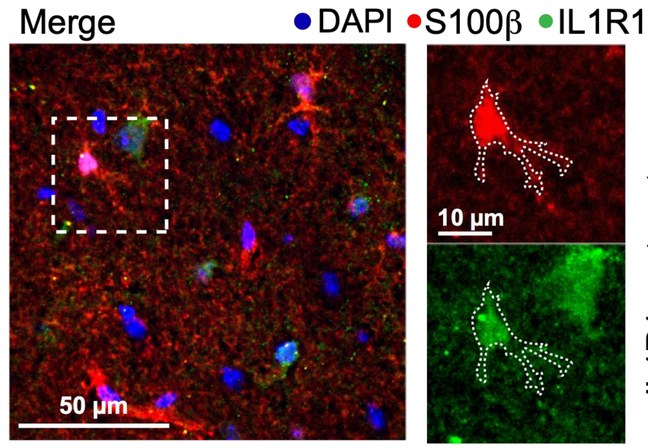


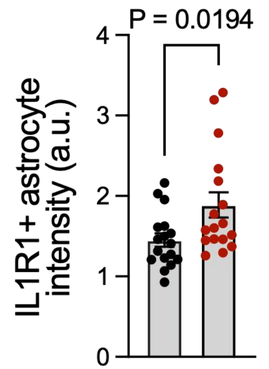




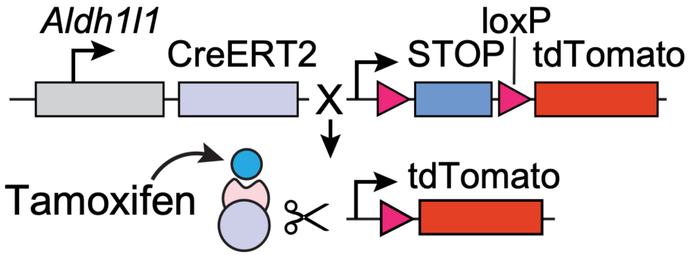




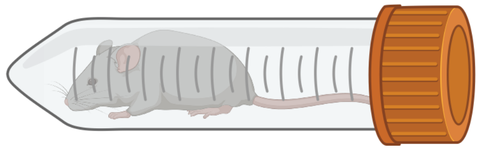


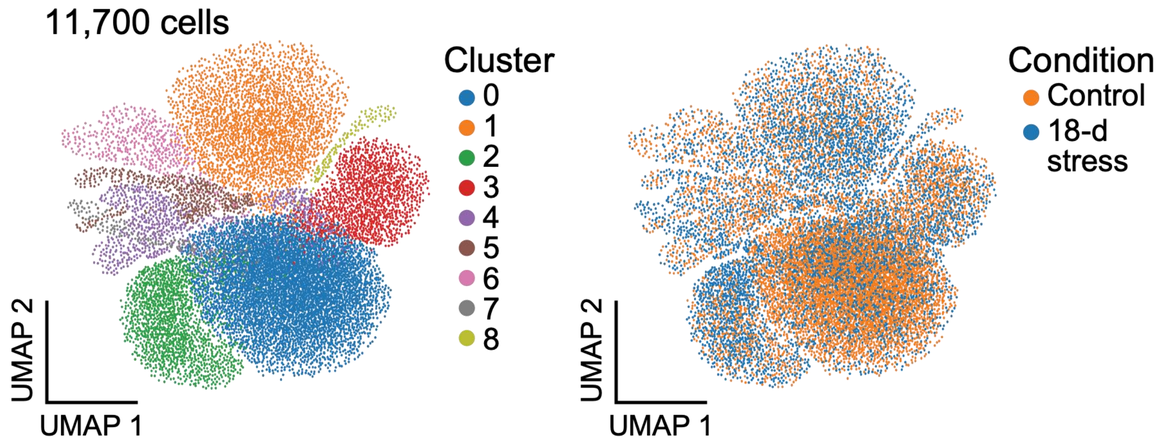


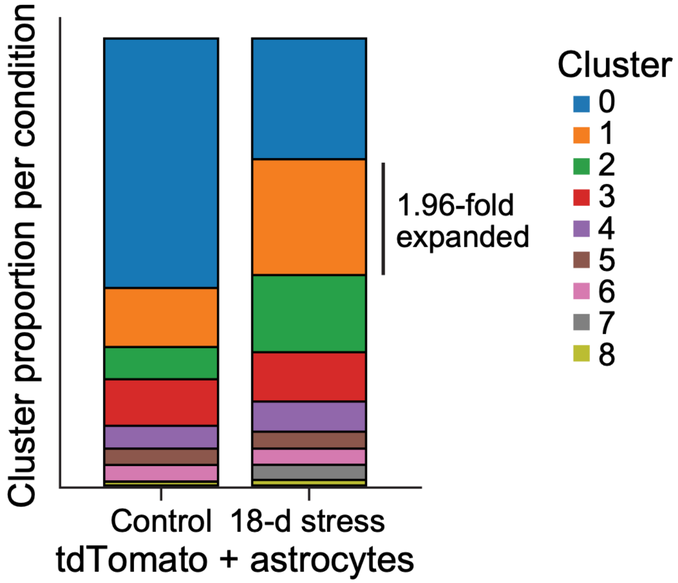
Stress impairs astrocyte EGFR signaling

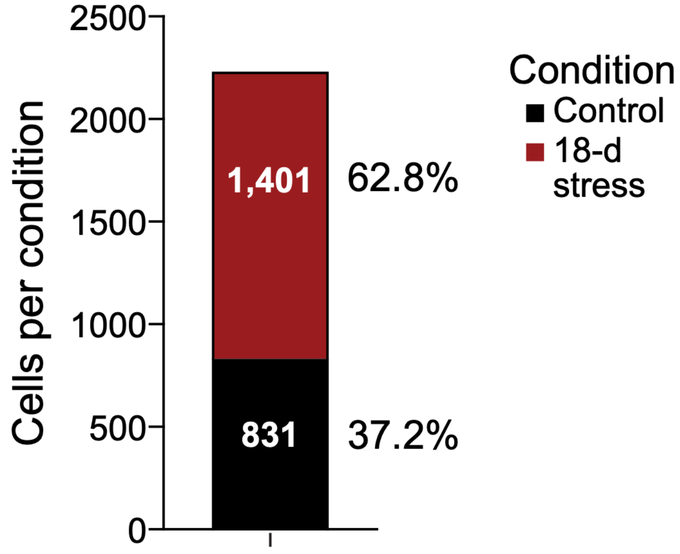


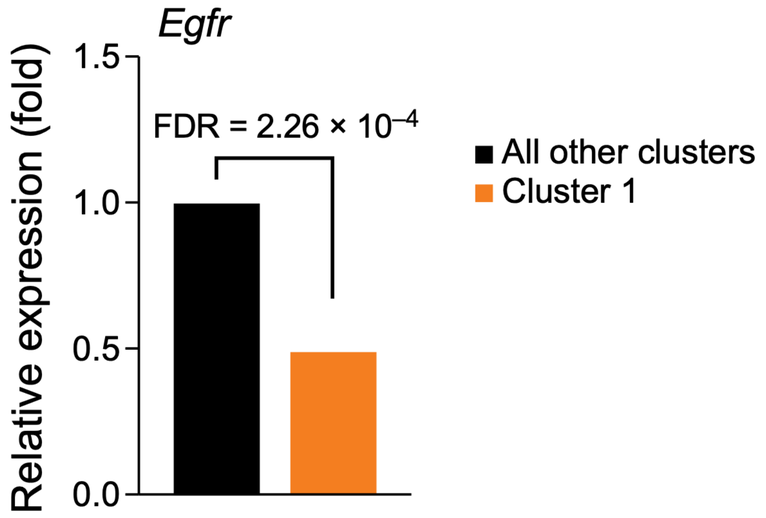
Chronic restraint stress



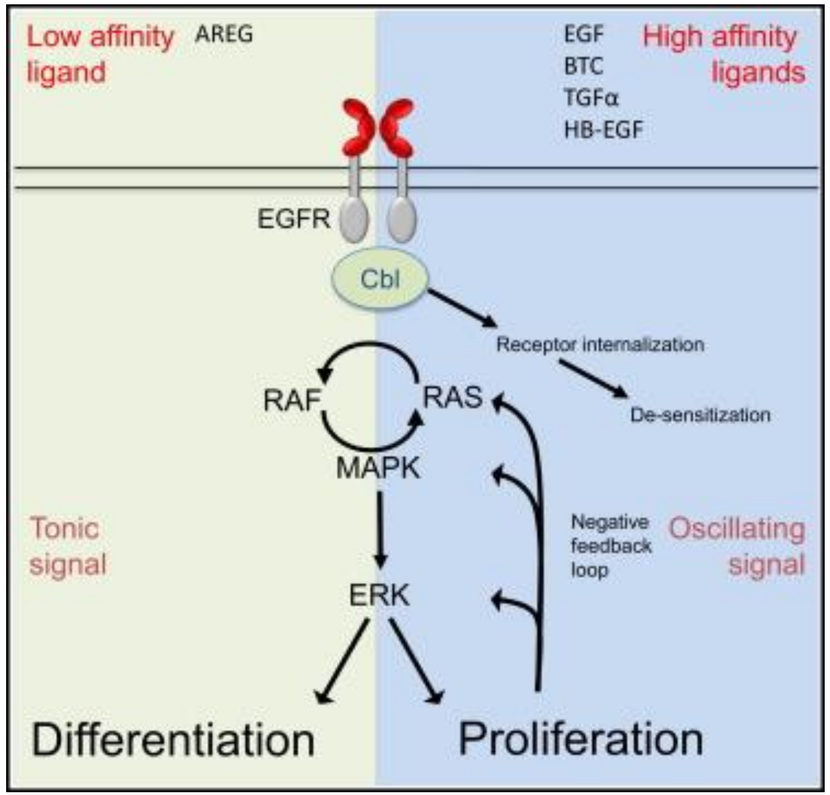




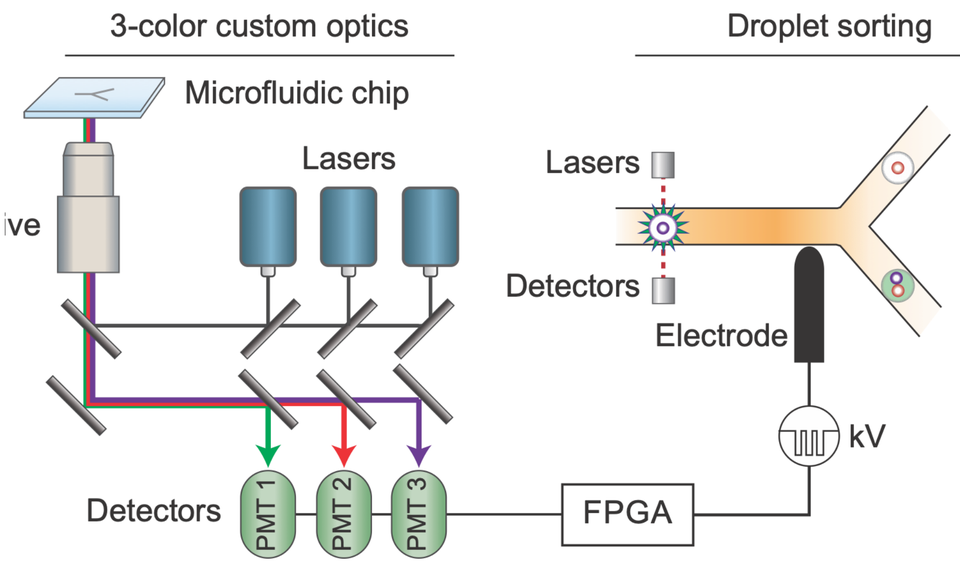


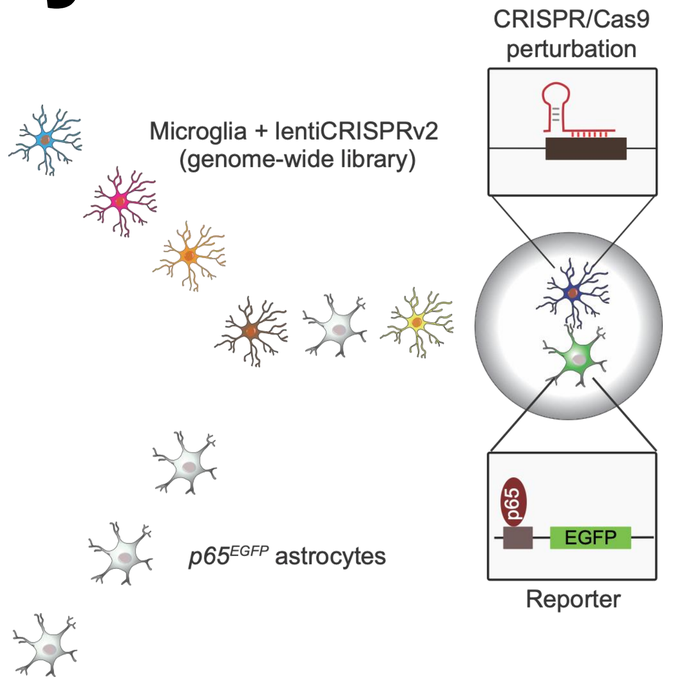


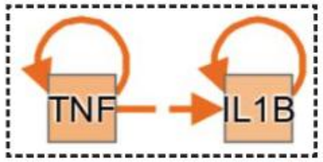
EGFR+ astrocytes limit NF-κB activity



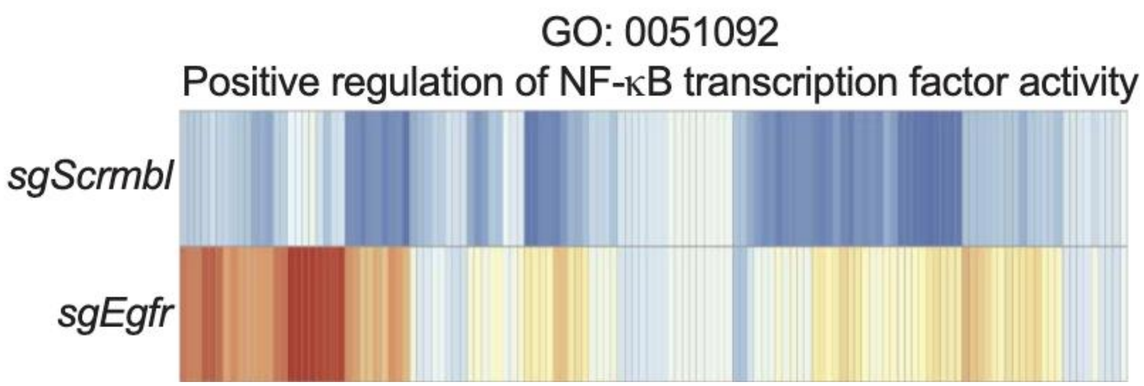
Zaiss et al., *Immunity* 2015





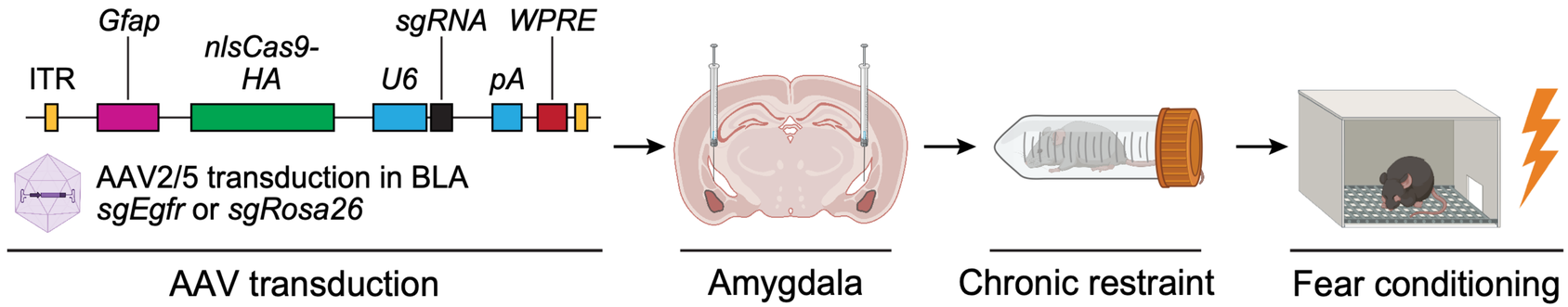


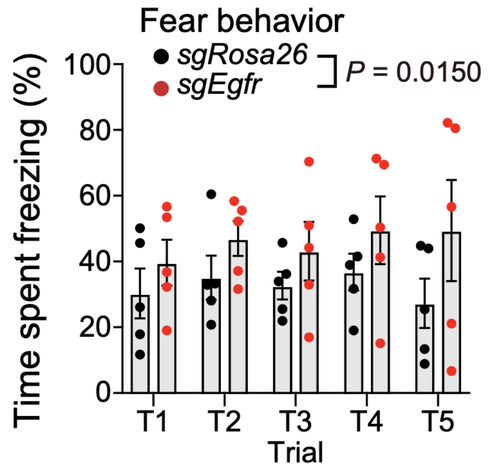
Tnf: $P = 0.00174$, z-score = 0.694
Il1b: $P = 0.0213$, z-score = 0.615

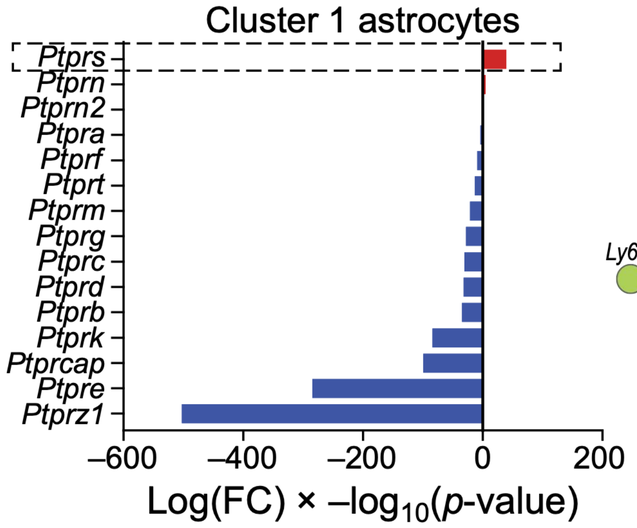


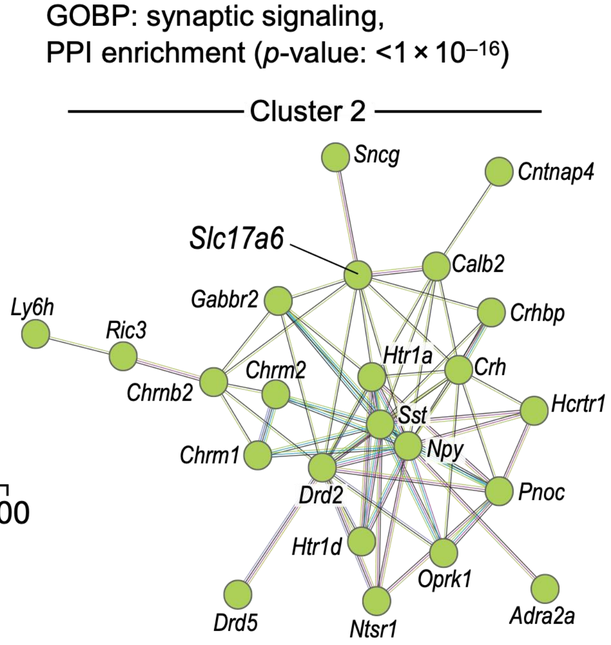
Wheeler et al., *Science* 2023

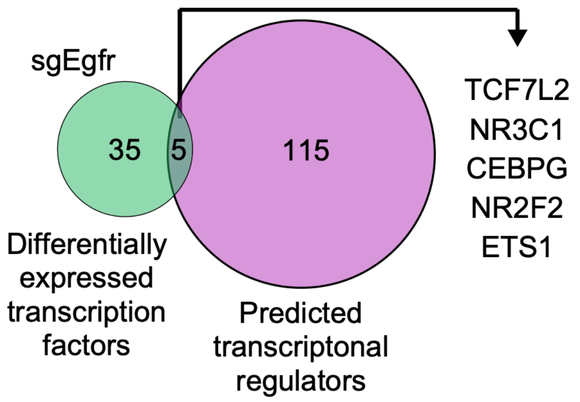
EGFR+ amygdala astrocytes limit fear expression

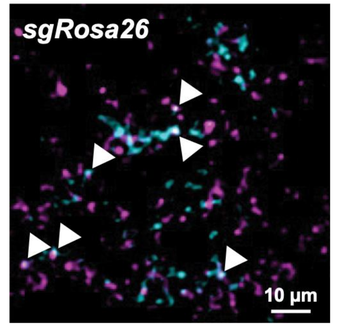


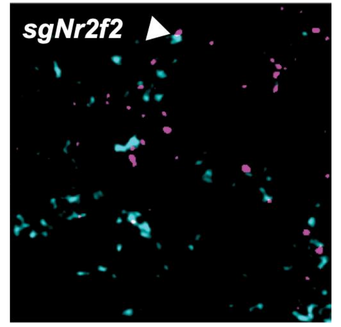


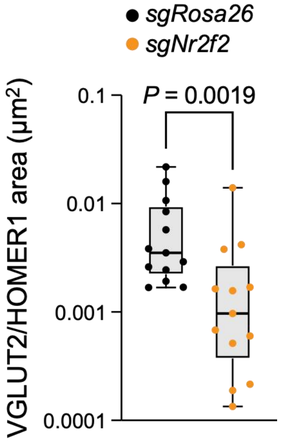




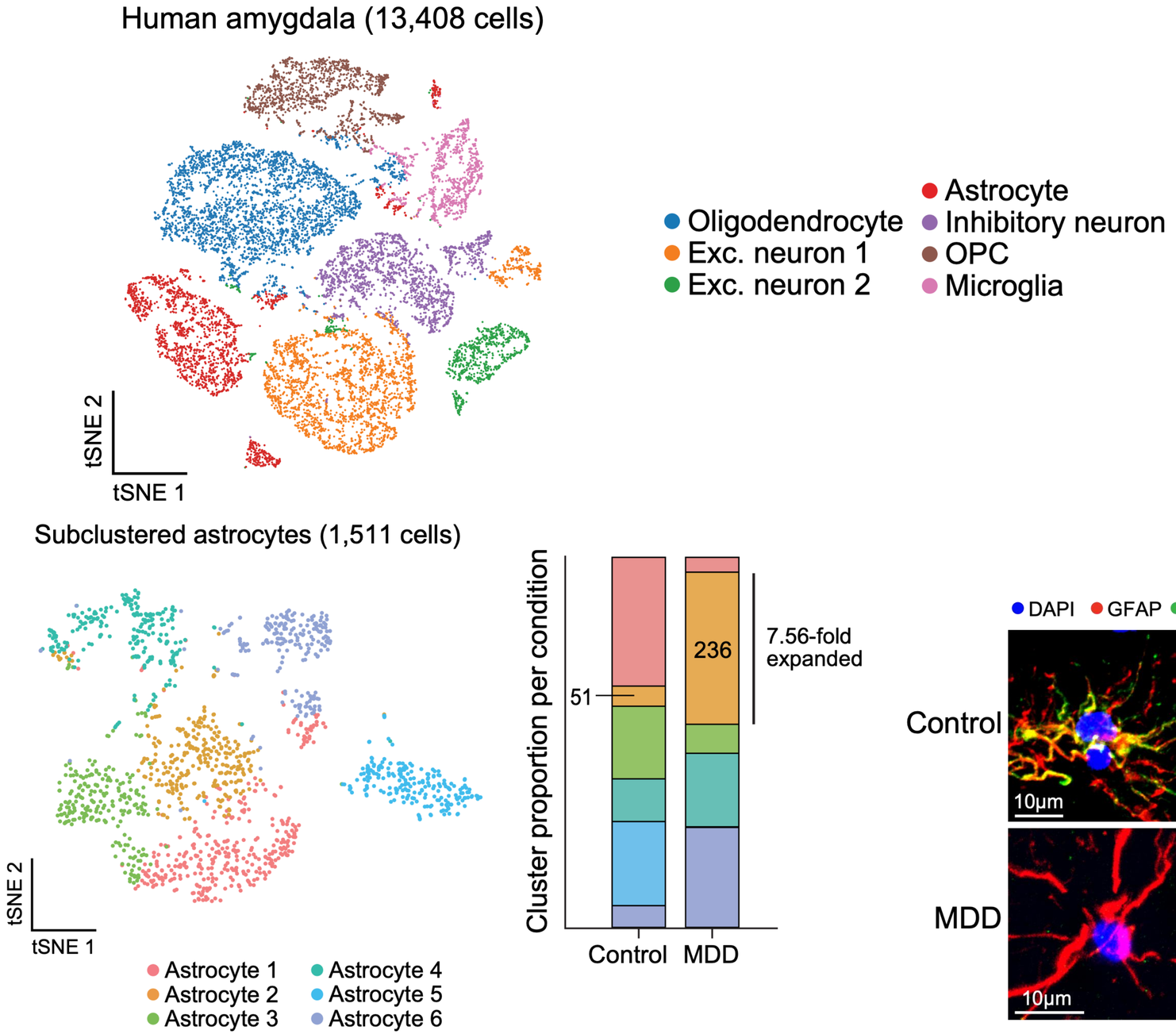




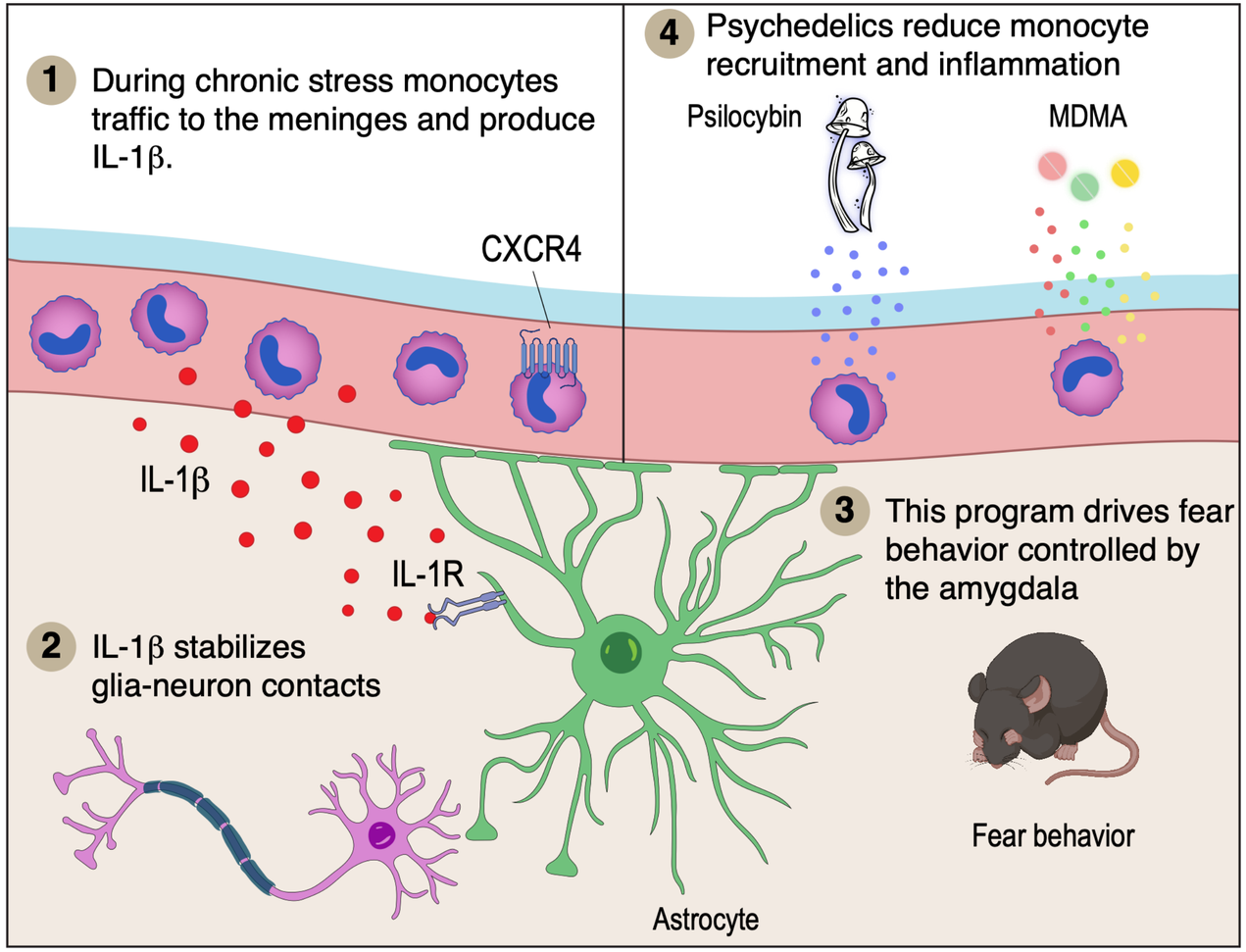




Decreased EGFR expression in MDD amygdala astrocytes



Summary



1. Chronic stress induces immune cell redistribution to the meninges which act on amygdala via permeable BBB

2. Inflammatory signals induce astrocyte-neuron communication that drives fear behavior

3. Psychedelics (MDMA, psilocybin) reverse meningeal monocyte accumulation and fear behavior

Acknowledgments

Wheeler lab
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Josh Choi, PhD
Weibke Weiss

Isaac Chiu (HMS) & lab
Georgia Gunner, PhD
Liwen Deng, PhD

NIH NeuroBioBank (human samples)

Leslie Gaffney (illustrations)

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