Probing and Rescuing Dysfunctional Brain Circuits in Depression

Conor Liston, MD, PhD

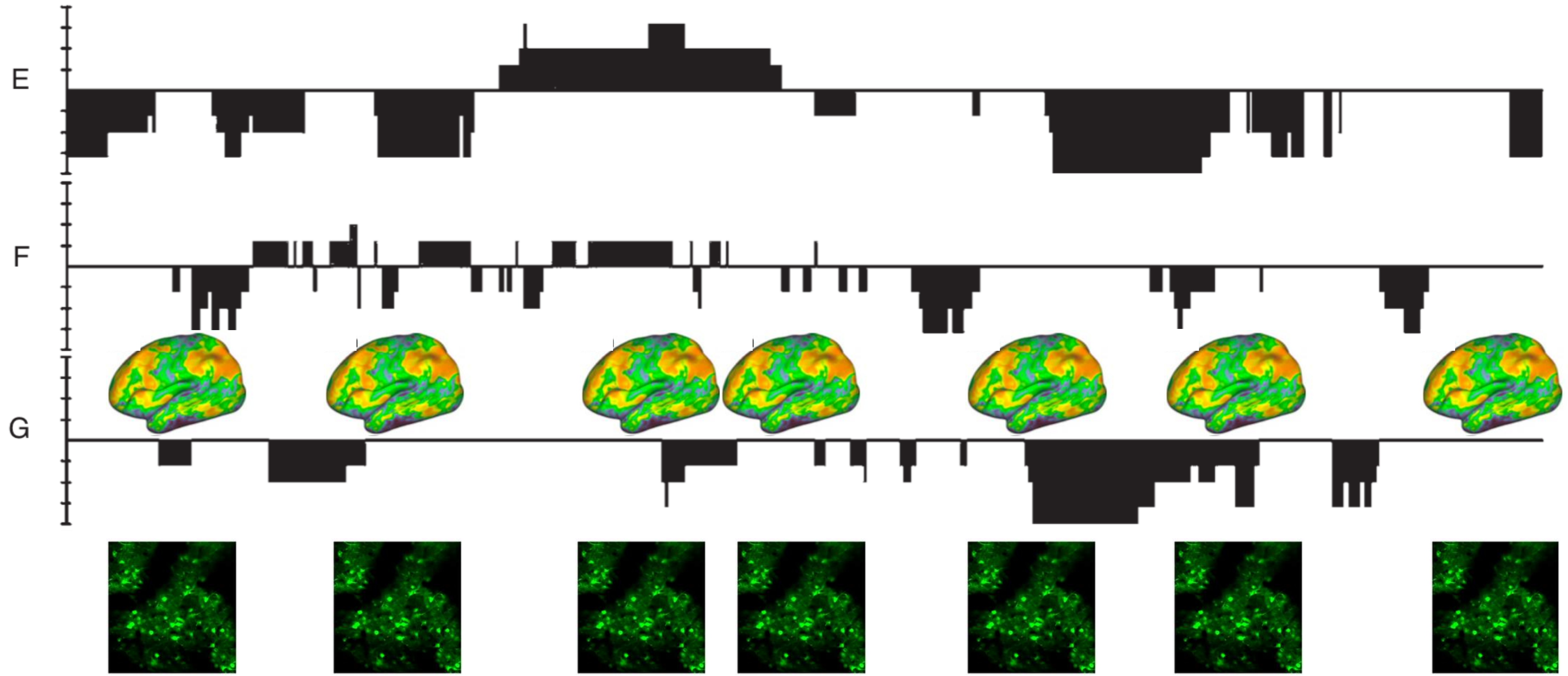
Professor of Neuroscience & Psychiatry

Director, Institute for Developmental Psychobiology

Research Director, Interventional Psychiatry Program

Weill Cornell Medicine

Depression is a fundamentally episodic psychiatric syndrome

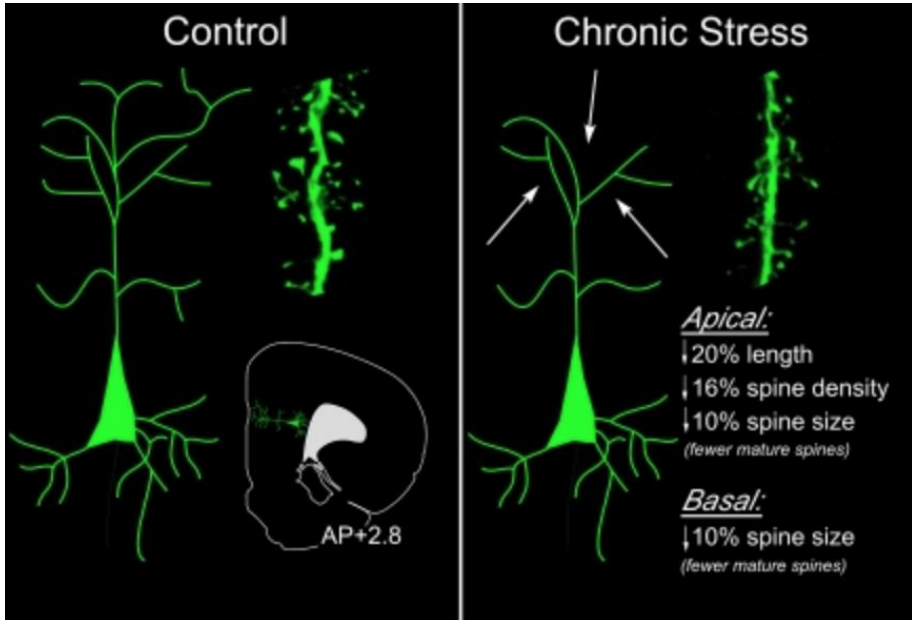


What are the mechanisms regulating mood state transitions?

Post et al., J Clin Psych, 2003

Prefrontal synaptic plasticity: a therapeutic target?

Chronic stress decreases postsynaptic spine density in prefrontal cortex



Radley, 2012

Antidepressant-dose ketamine increases prefrontal synapse formation

mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists

Nanxin Li, Boyoung Lee, Rong-Jian Liu, Mounira Banasr, Jason M. Dwyer, Masaaki Iwata, Xiao-Yuan Li, George Aghajanian, Ronald S. Duman*

LETTER

doi:10.1038/nature10130

NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses

Anita E. Autry[1], Megumi Adachi[1], Elena Nosyreva[2], Elisa S. Na[1], Maarten F. Los[1], Peng-fei Cheng[1], Ege T. Kavalali[2] & Lisa M. Monteggia[1]

ARTICLE

doi:10.1038/nature17998

NMDAR inhibition-independent antidepressant actions of ketamine metabolites

Antidepressant drugs act by directly binding to TRKB neurotrophin receptors

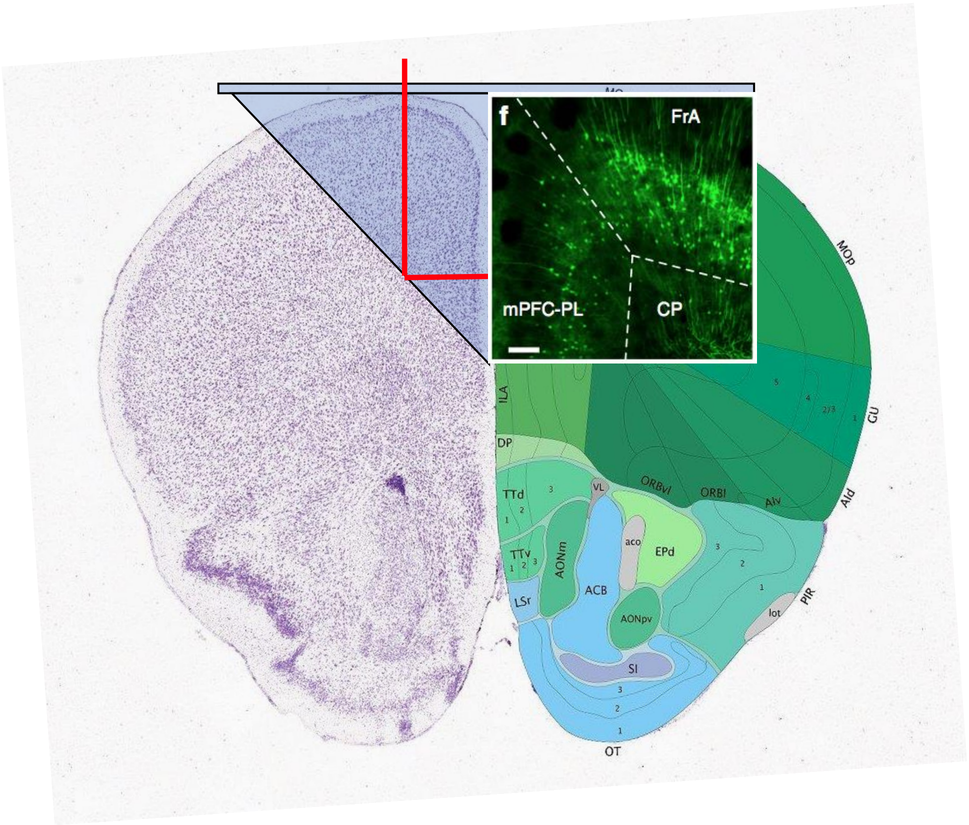
Authors

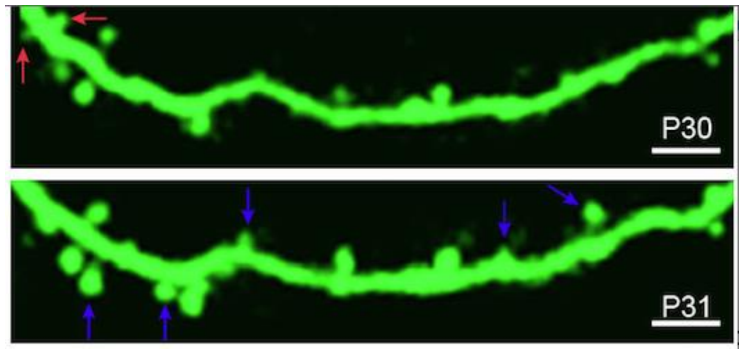
Plinio C. Casarotto, Mykhailo Girych, Senem M. Fred, ..., Mart Saarma, Ilpo Vattulainen, Eero Castrén

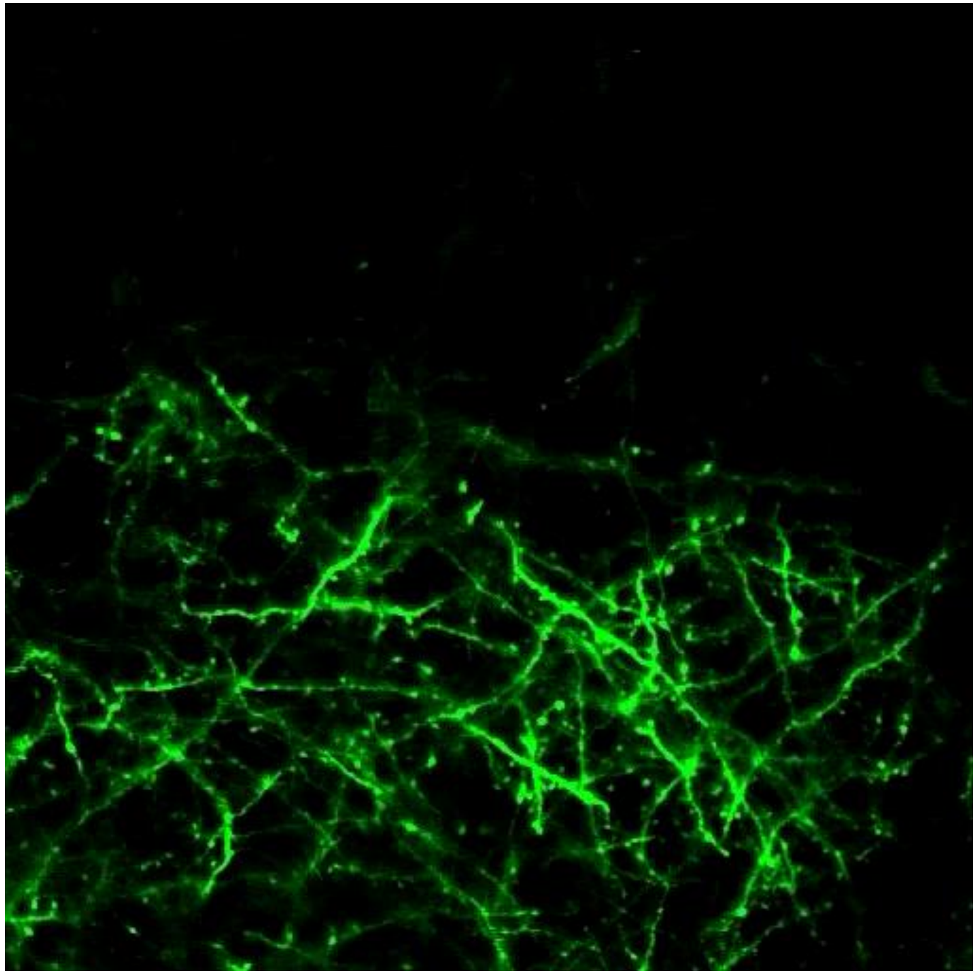
Cell

Li et al., Science 2010
Autry et al., Nature 2011
Zanos et al., Nature 2016
Casarotto et al., Cell, 2021

2-Photon Imaging of Prefrontal Cortical Microcircuits

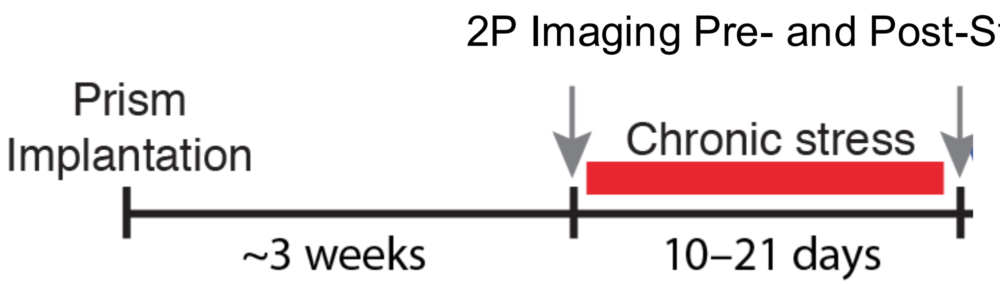


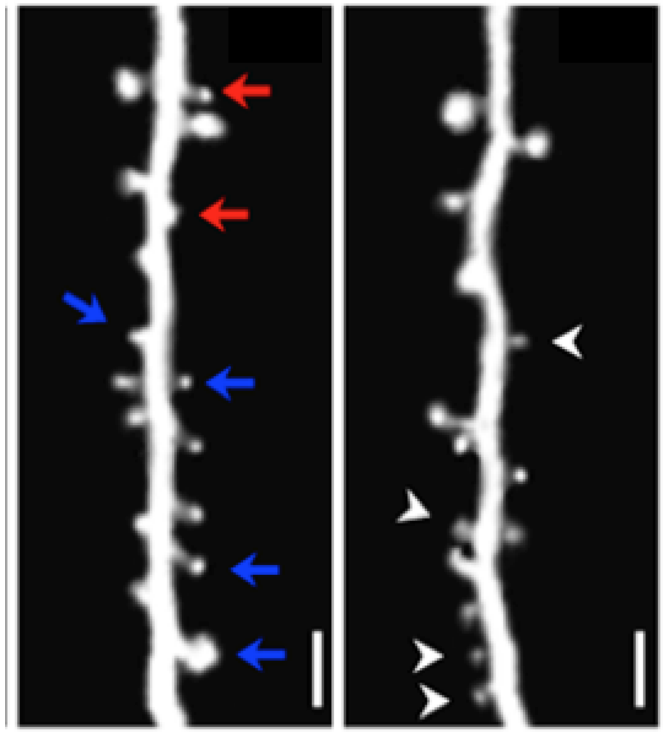


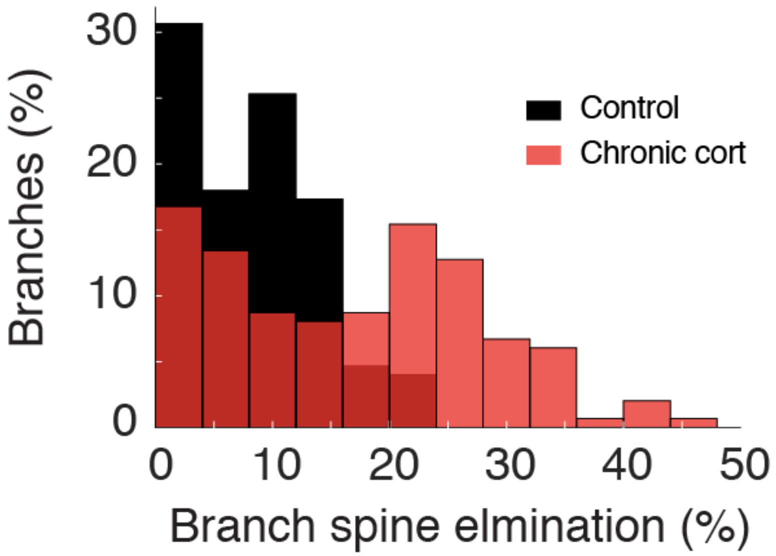


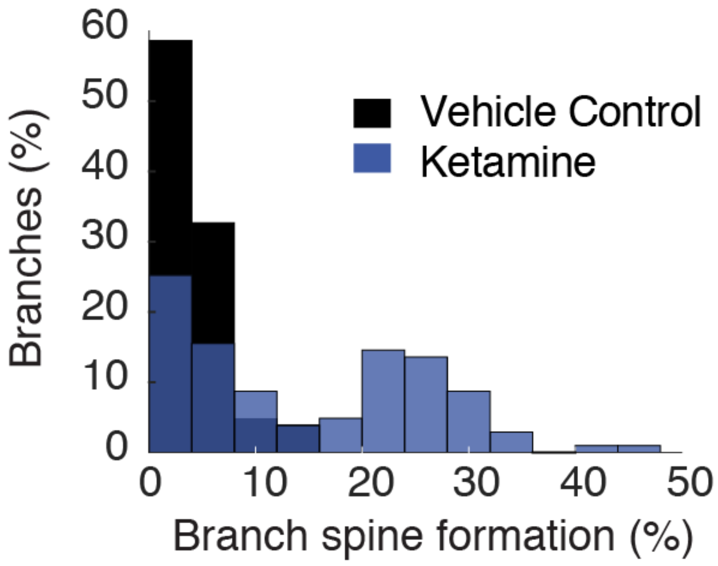
Pattwell et al., *Nature Comm.*, 2016

Chronic stress causes selective, branch-specific synapse loss





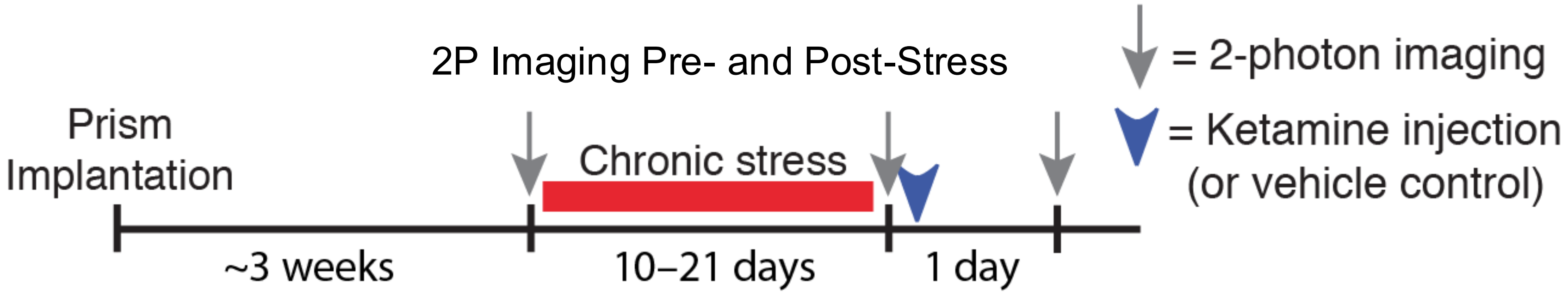


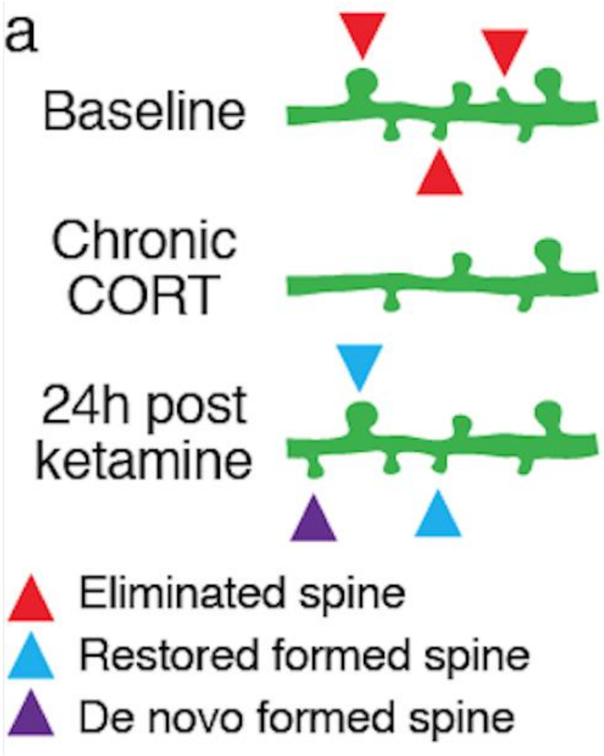


Adapted from Liston et al., PNAS, 2011

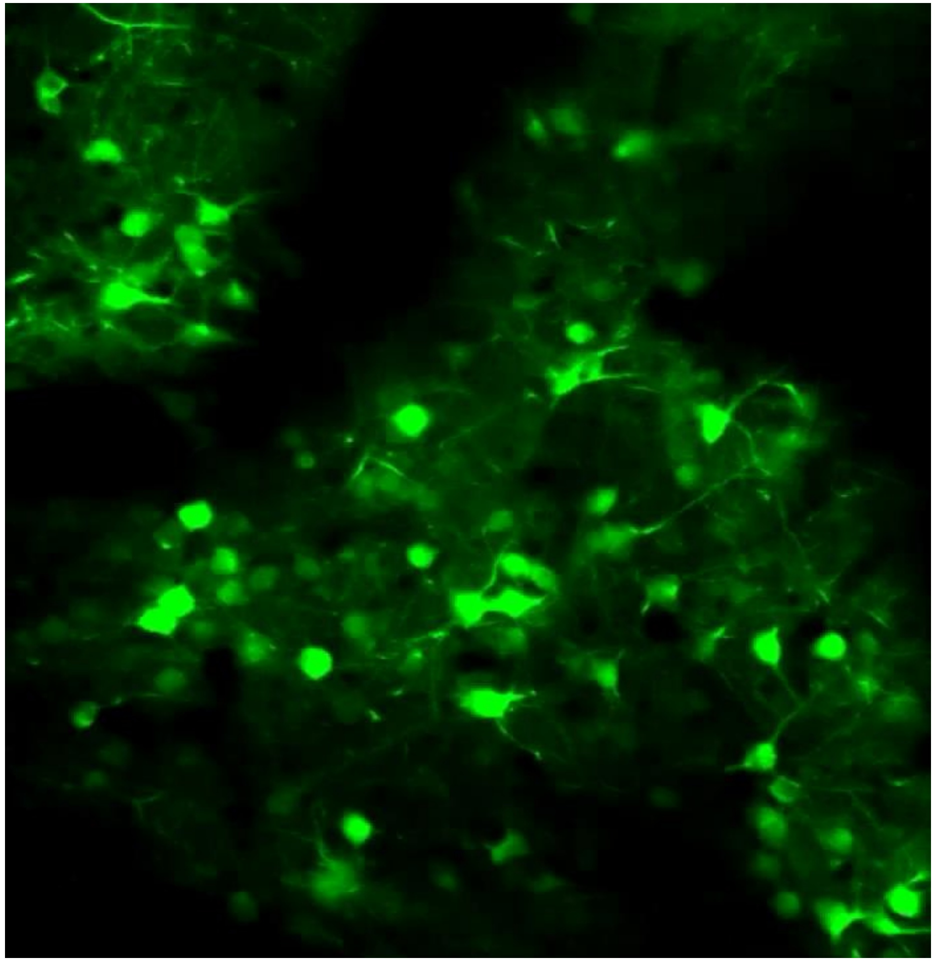
Moda, Murdock, Parekh et al., *Science,* 2019

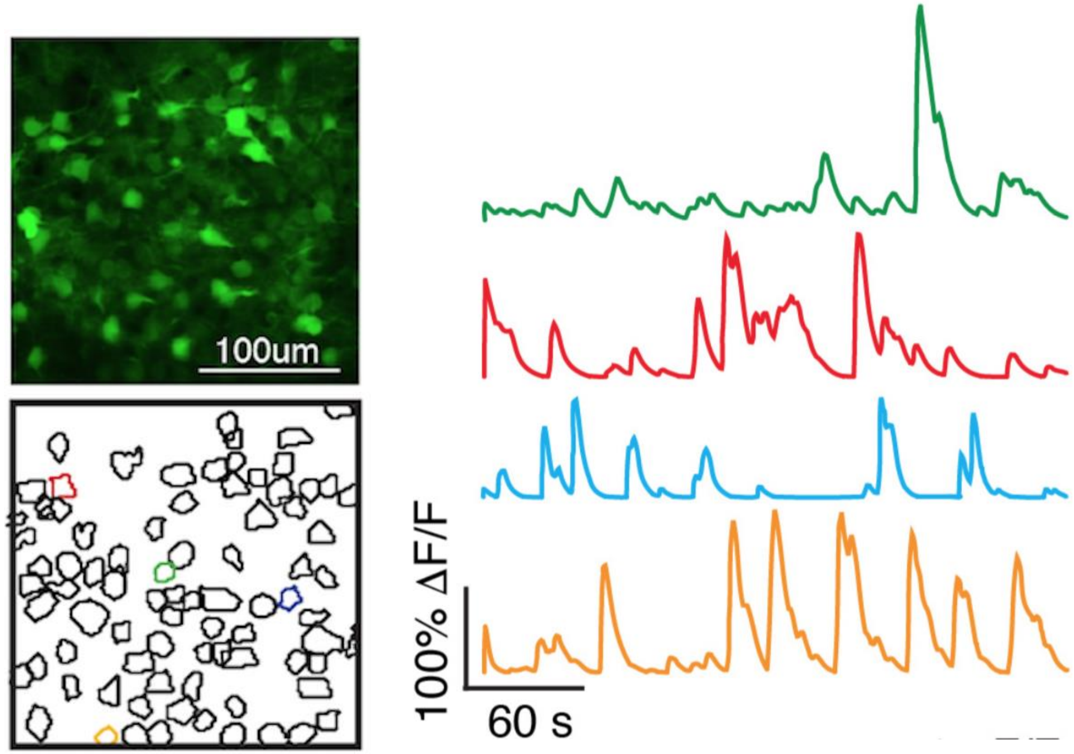
Rapid, targeted rescue of stress-related synapse pathology

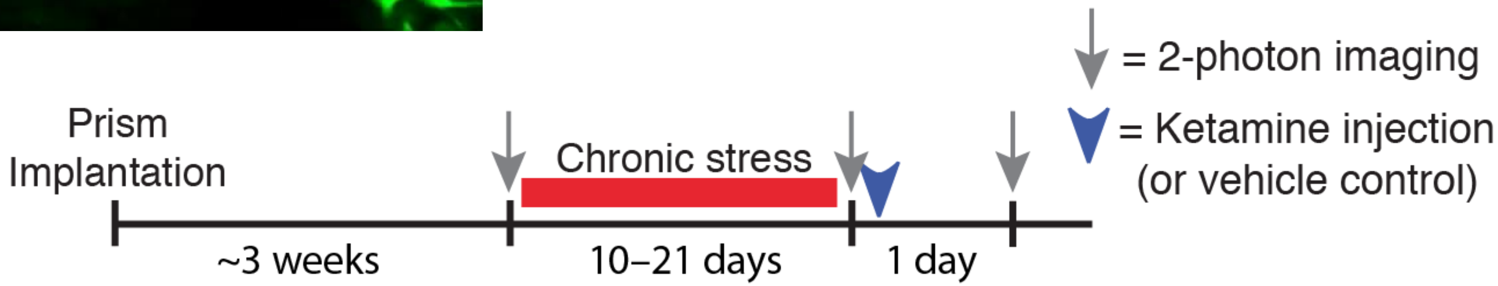




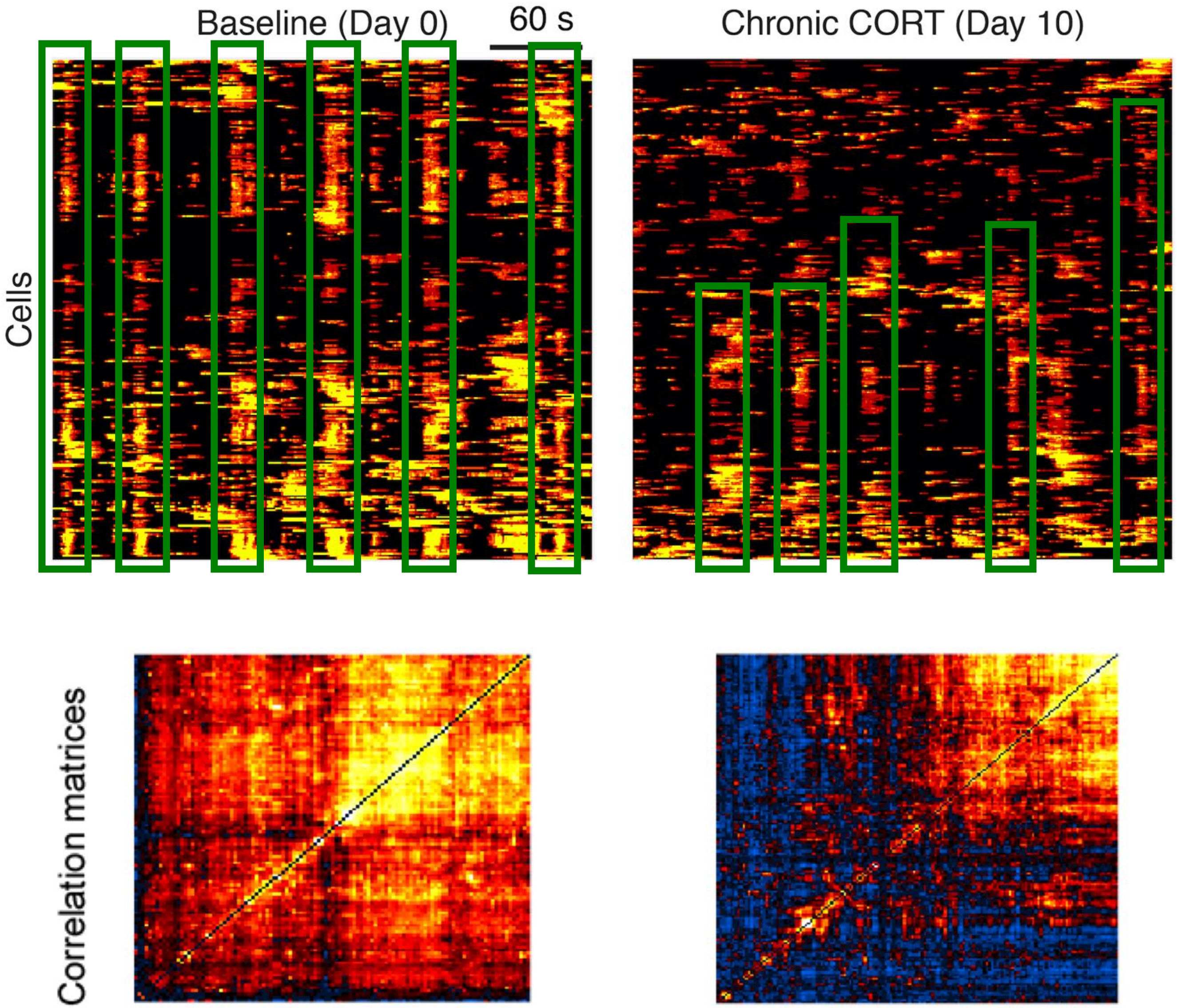
Stress-related synapse loss disrupts PFC circuit function







Stress-related synapse loss disrupts PFC circuit function



Chronic Stress and Ketamine Effects on mPFC Circuit Function and Behavior

1. Motivated escape behavior and response to threats
    - Moda-Sava et al., *Science*, 2019

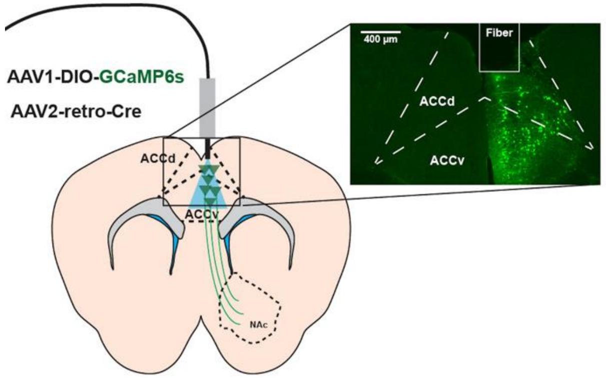
2. Extinction of conditioned fear learning
    - Chu et al., *Nature*, 2019

3. Cognitive flexibility and adaptive reward seeking
    - Spellman et al., *Cell*, 2021

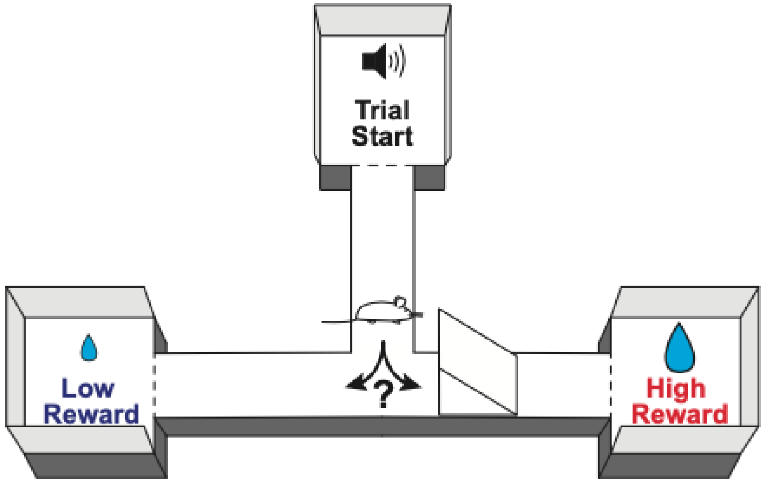
4. Social hierarchy perception and social interaction
    - Fetcho, Hall, Estrin et al., *Nature Communications,* 2023

5. Motivated reward-seeking behavior and effort-based decision making
    - Fetcho et al., *Neuron*, 2023

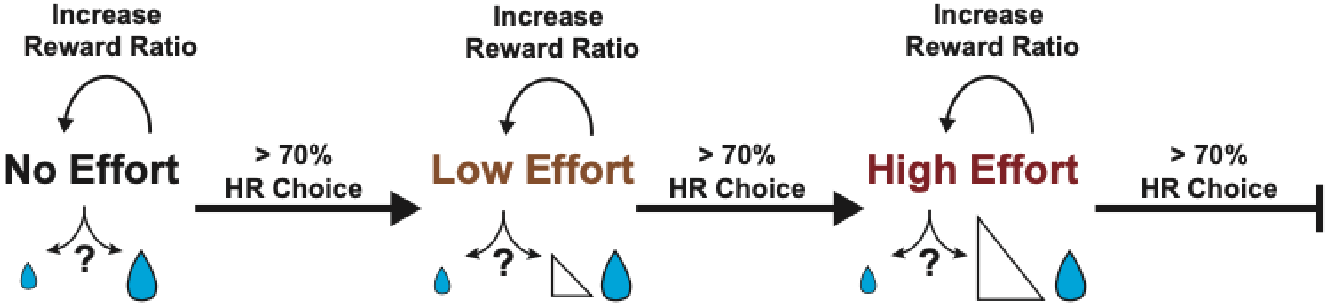
Automated High-Throughput Assessment of Effortful Reward-Seeking Behavior

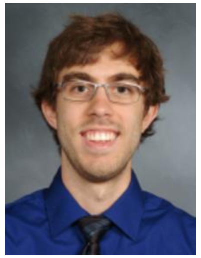


Accumbens-Projecting
Anterior Cingulate Cells



Devinsky et al., 1995
Jahanshahi & Frith, 1998
Walton et al., 2003
Kennerley et al., 2006
Rudebeck et al., 2006
Rushworth & Behrens et al., 2008
Pizzagalli et al., 2001
Zilverstand et al., 2018

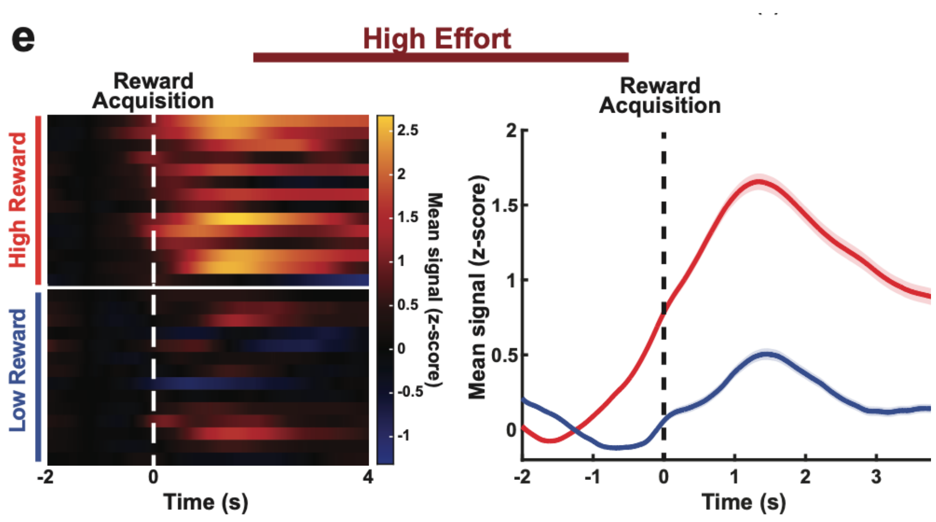


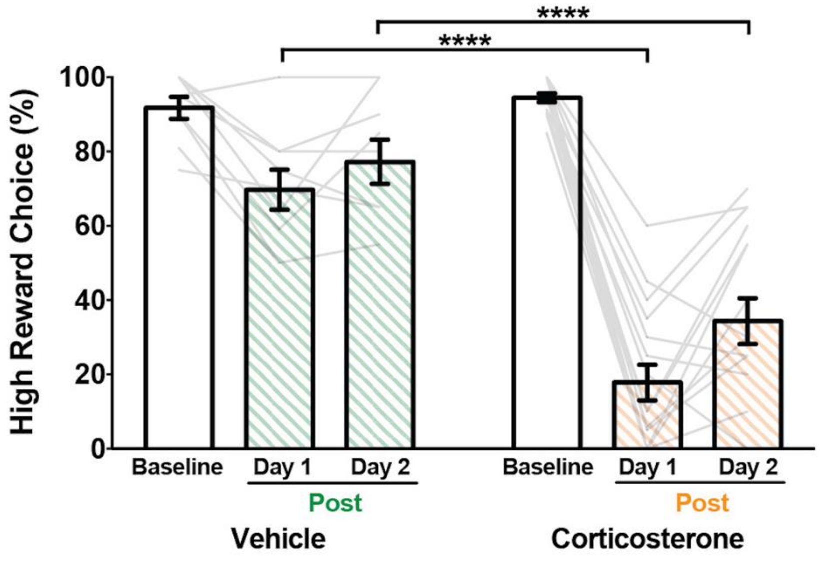


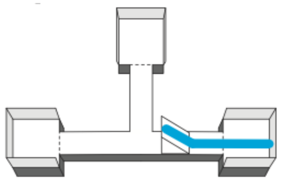
Rob Fetcho

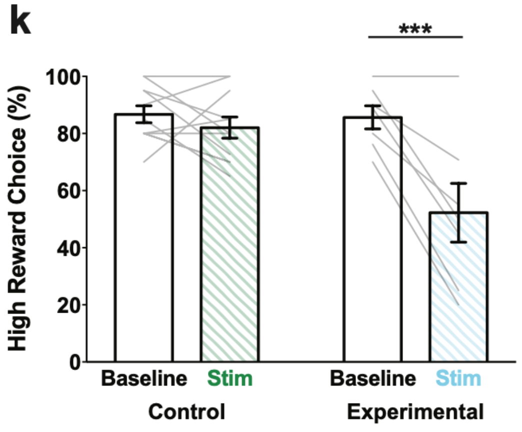
Fetcho et al., *Neuron,* 2023

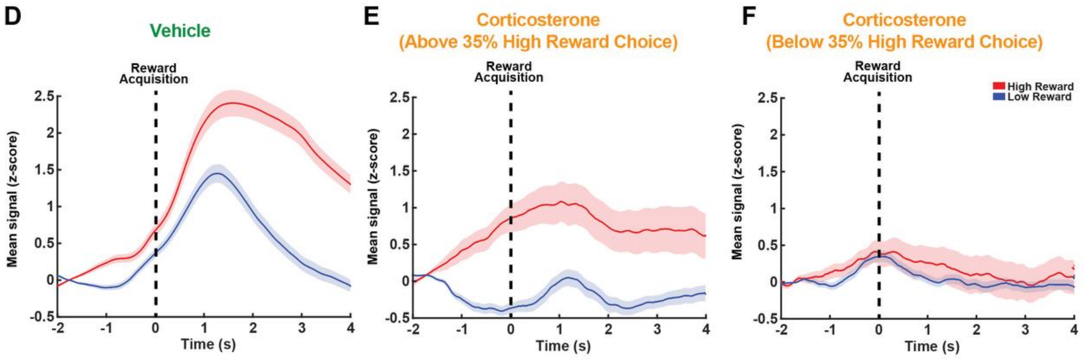
Accumbens-Projecting PFC Cells Support Effortful Reward Seeking Behavior







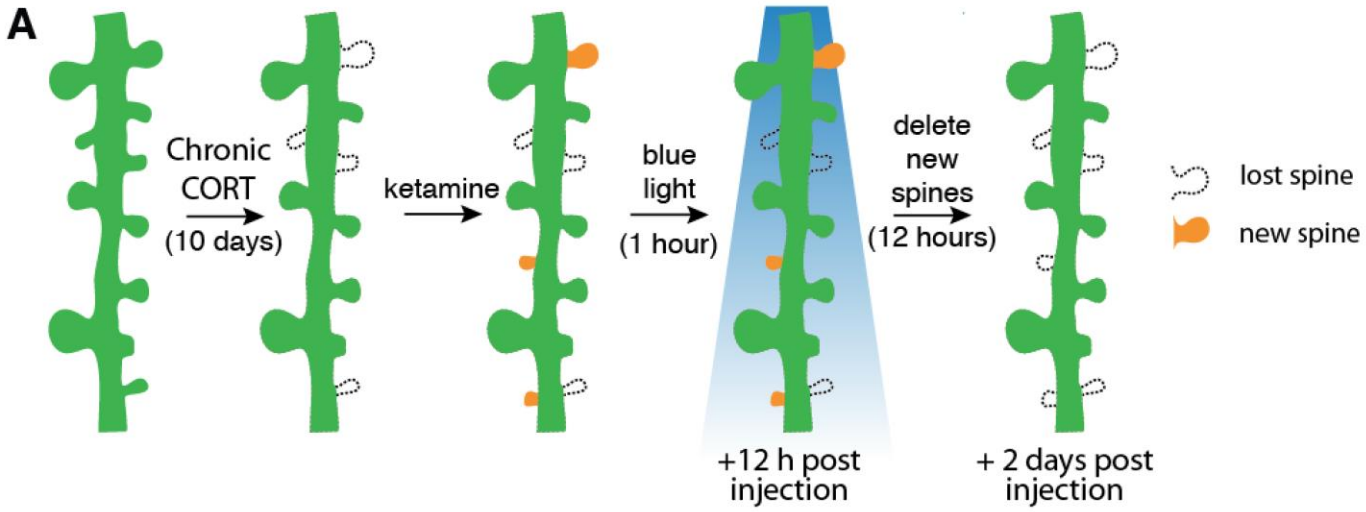


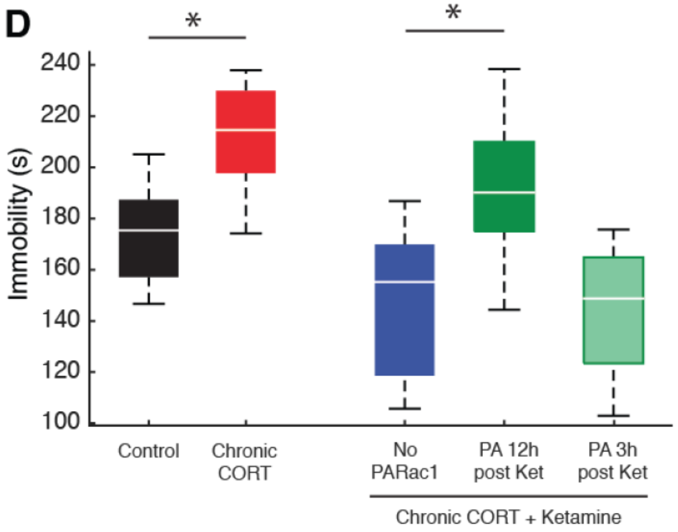


Chronic CORT disrupts effortful reward-seeking and suppresses ACC-NAc activity

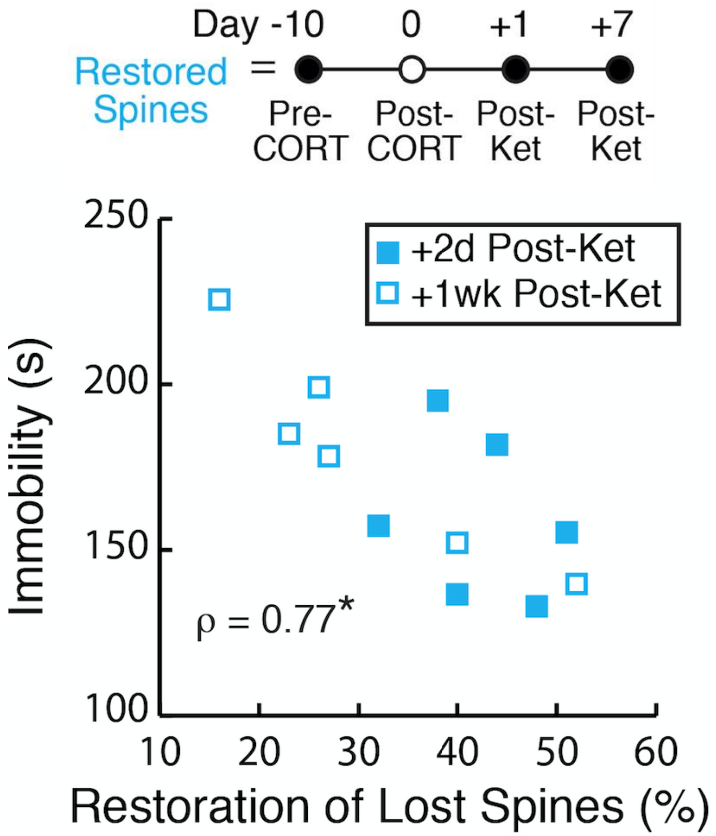
Fetcho et al., *Neuron,* 2023

Synaptogenesis is required for sustaining ketamine's antidepressant effects but not for initiating them



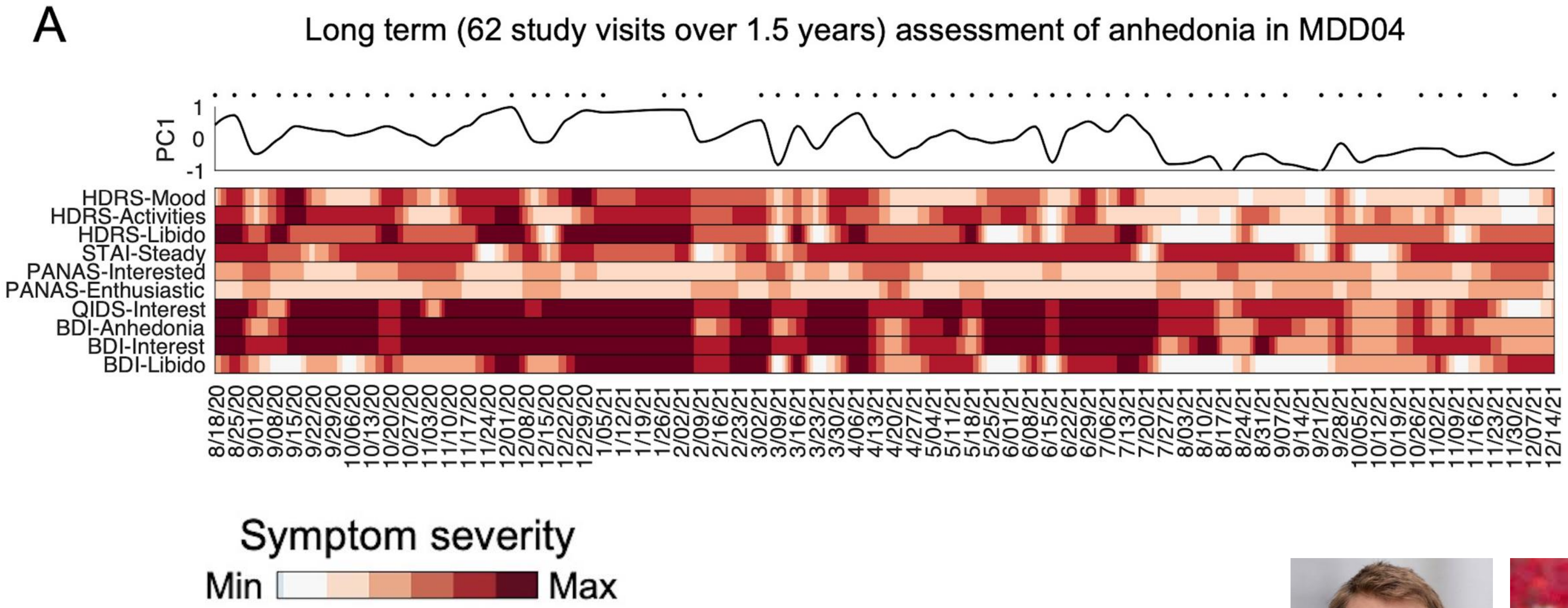


Deleting new synapses interferes with the maintenance of ketamine's antidepressant effects



Moda-Sava et al., *Science,* 2019

Longitudinal studies of mood state transitions within individual, densely sampled patients

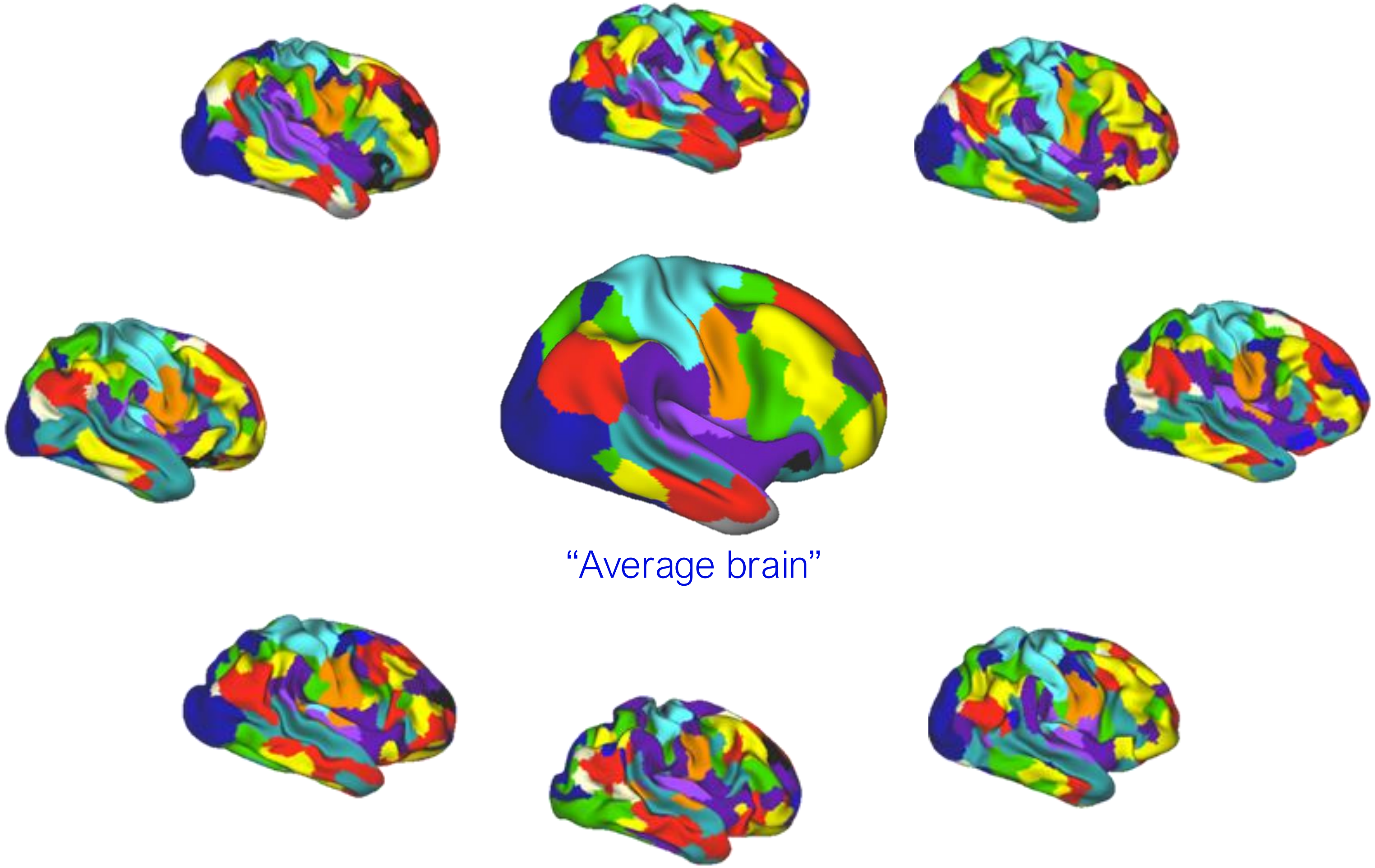



Immanuel Elbau


Chuck Lynch

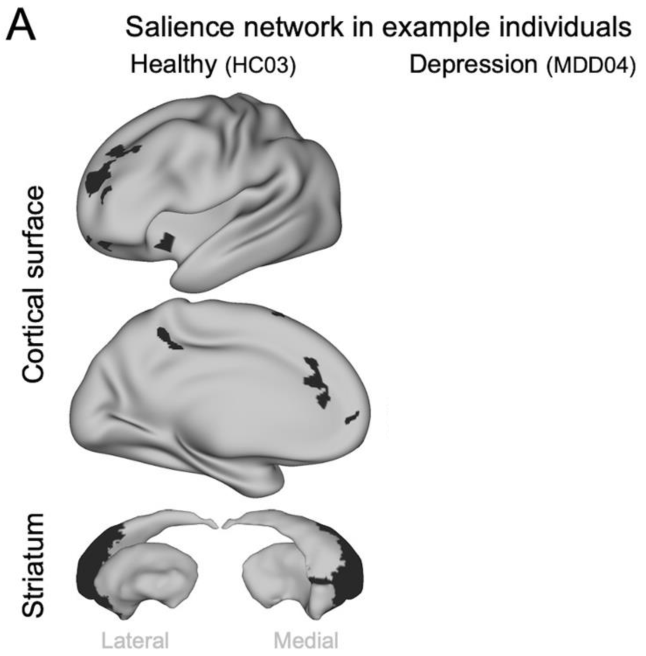
Lynch et al., *Nature,* 2024

Individualized Network Mapping in Depression



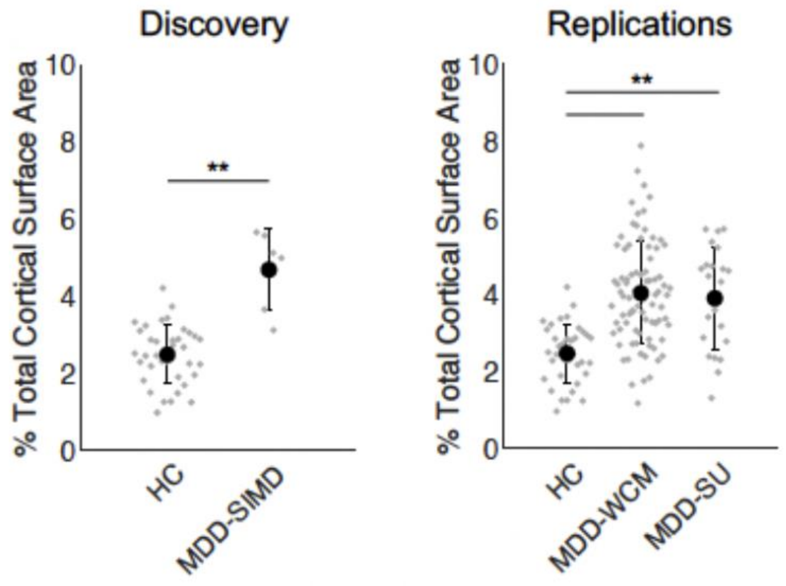
Braga & Buckner, *Neuron*, 2017
Gordon et al., *Neuron*, 2017
Gratton et al., *Neuron,* 2018

Abnormal salience network topology in highly recurrent depression



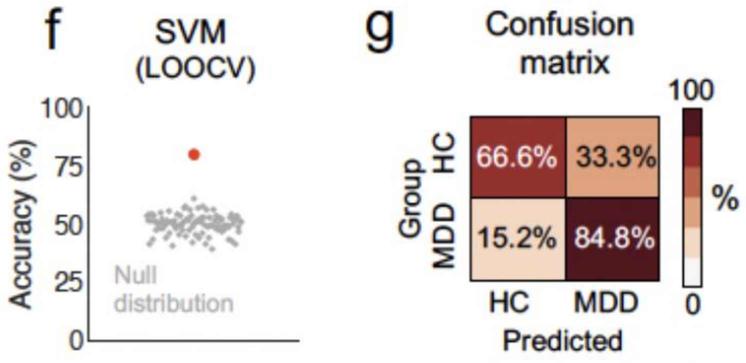
Healthy Depressed

Representative Individuals



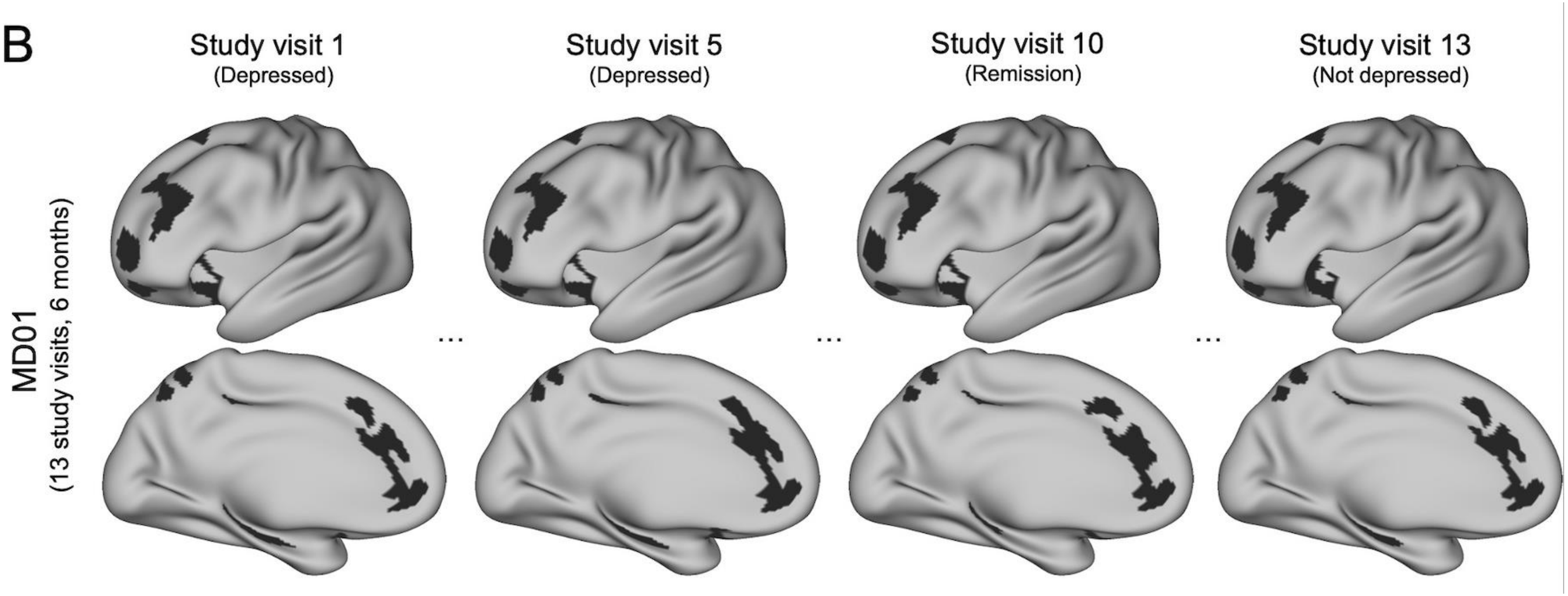
Effect Sizes: d = 1.16 – 1.97

Already replicated in other labs:
Vaghi et al., *Biorxiv*, 2025
Nahas et al., *PsyArXiv*, 2025



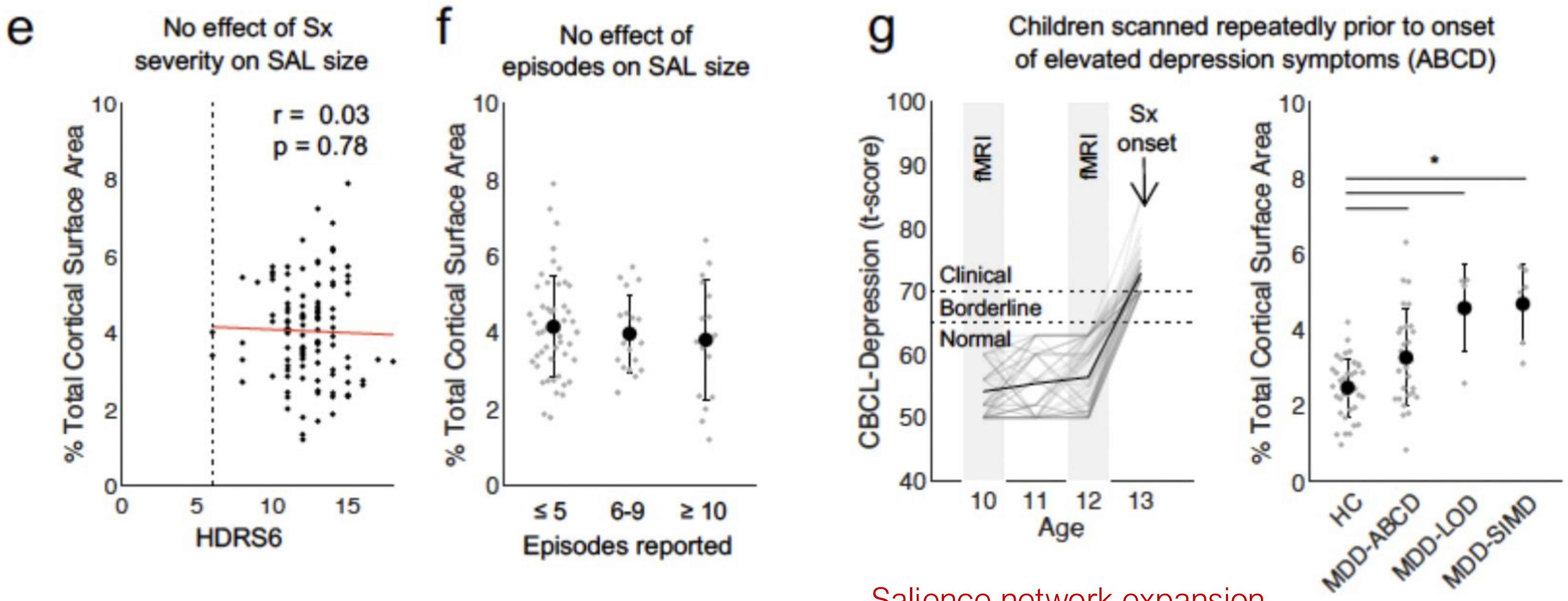
Lynch et al., *Nature*, 2024

Abnormal salience network topology is stable over time



- Salience network topological features are highly stable over time within individuals
- Unexpectedly, salience network does not vary with mood state

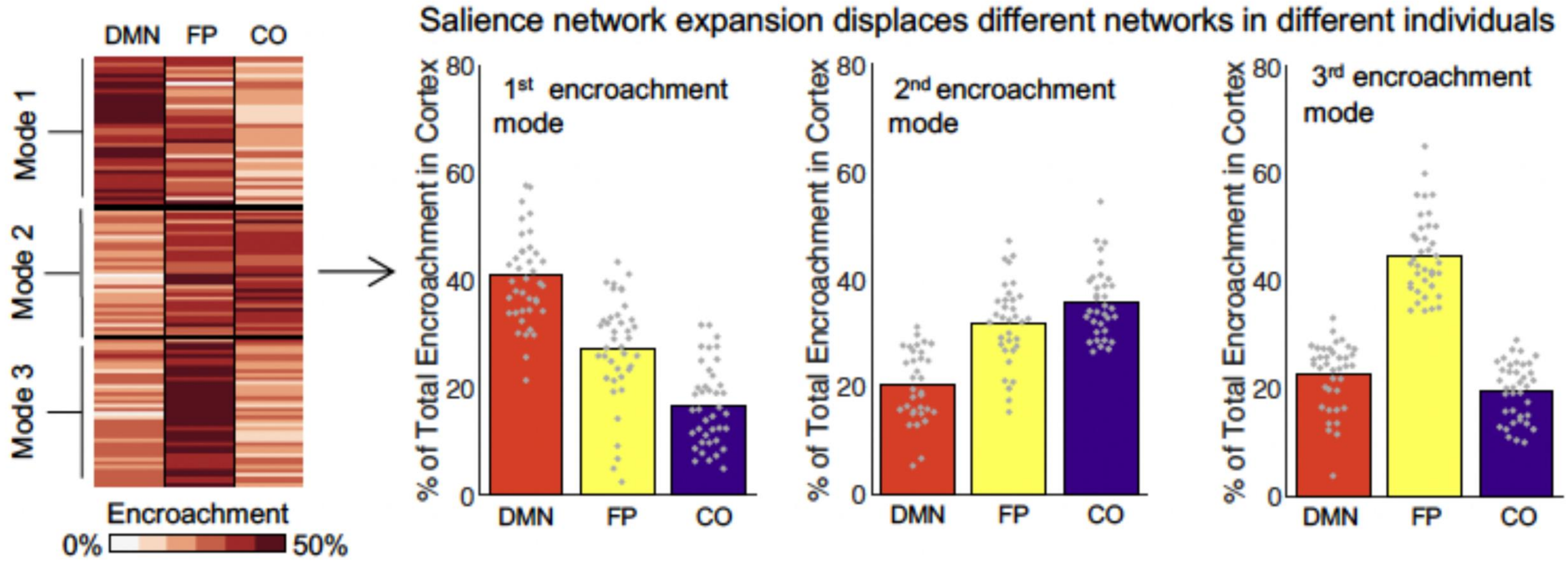
Salience Network Expansion:
A Stable Marker of Risk for Depression?



Salience network expansion is unrelated to current symptoms or number of past episodes

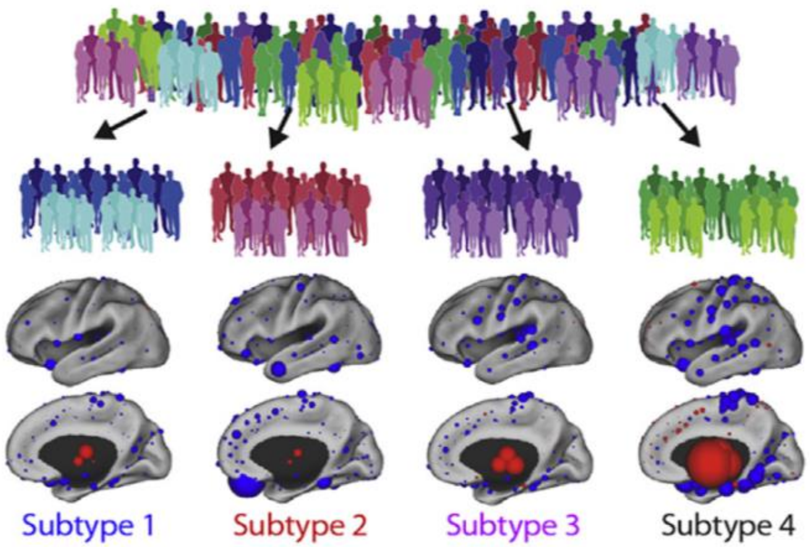
Salience network expansion emerges early in life

Three Subtypes of Network Expansion

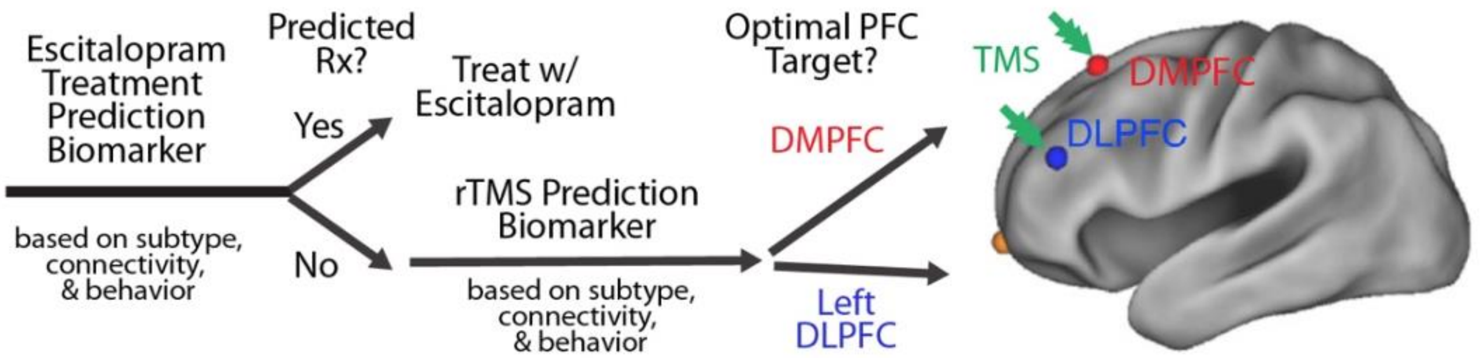


Lynch et al, *Nature*, 2024

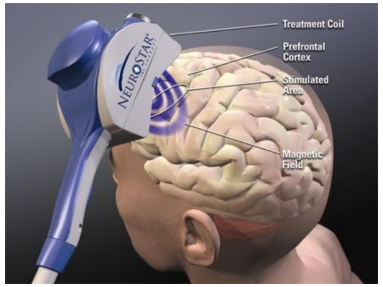
Leveraging Subtype Discovery to Enhance Treatment

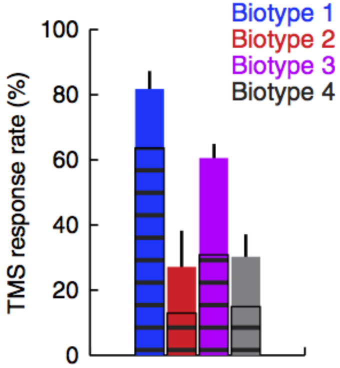


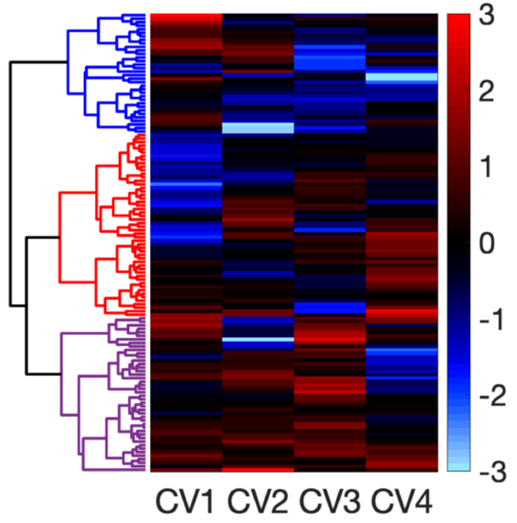
NCT#0401479, N=348 TRD pts
w/ Nolan Williams

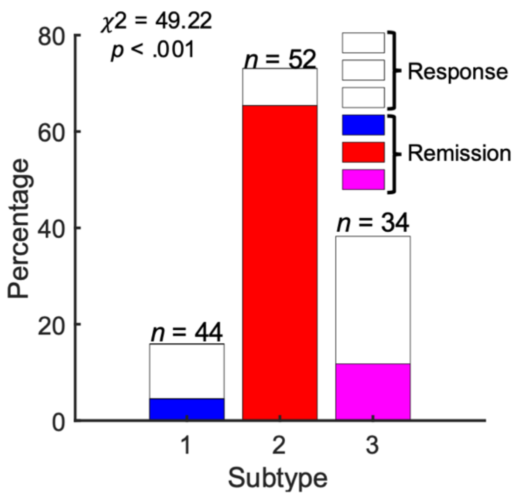


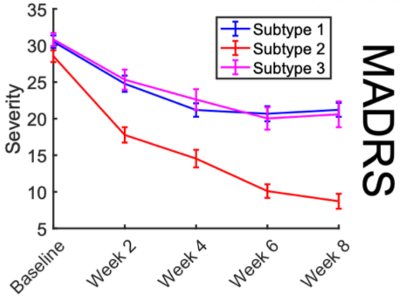
Subtypes of TMS Response
Drysdale et al., *Nature Medicine,* 2017
Dunlop et al., *Biol Psych,* 2014

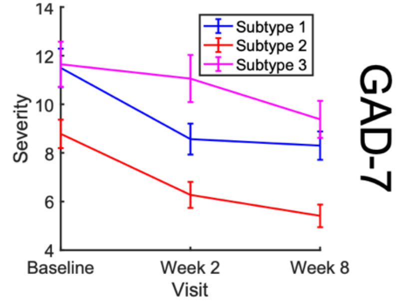






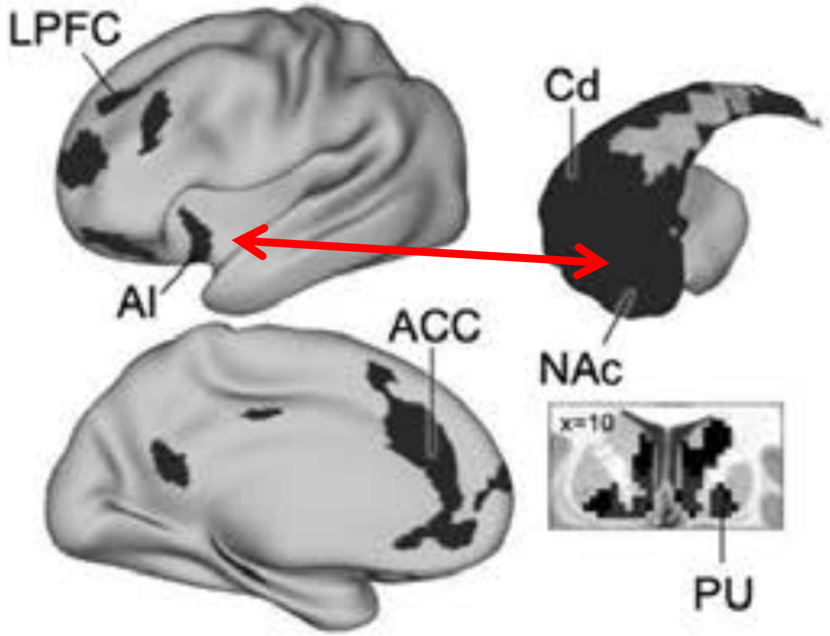


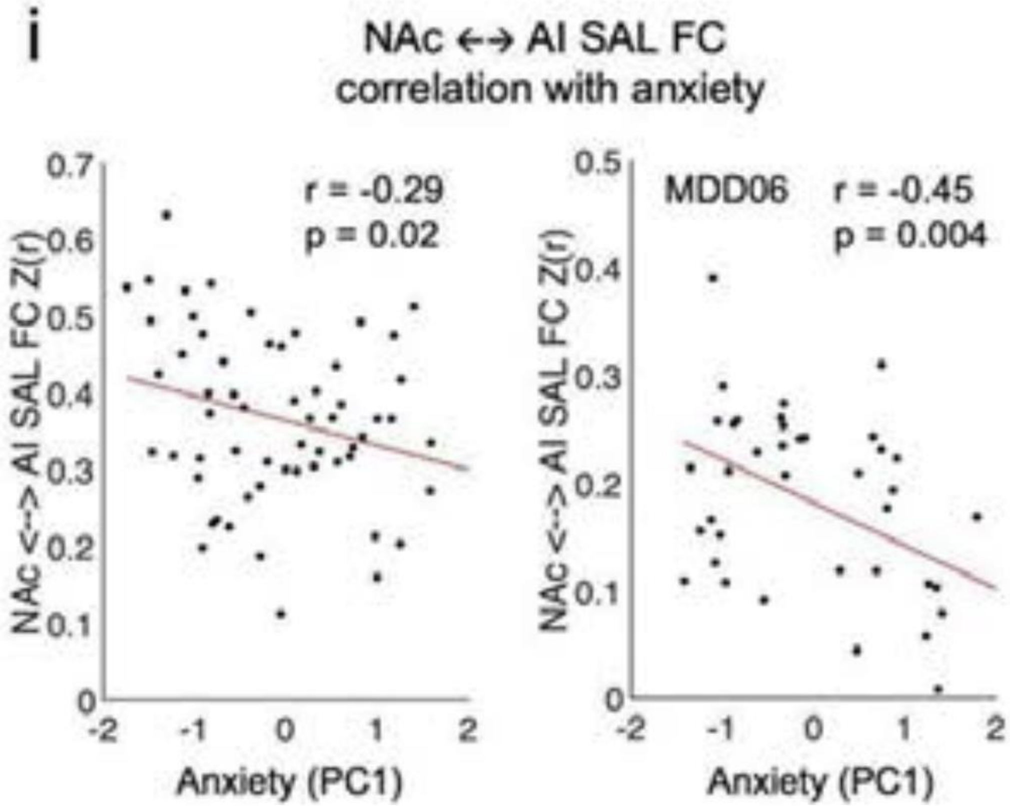




Subtypes of SSRI Response
Dunlop et al., *Nature Medicine,* in revision

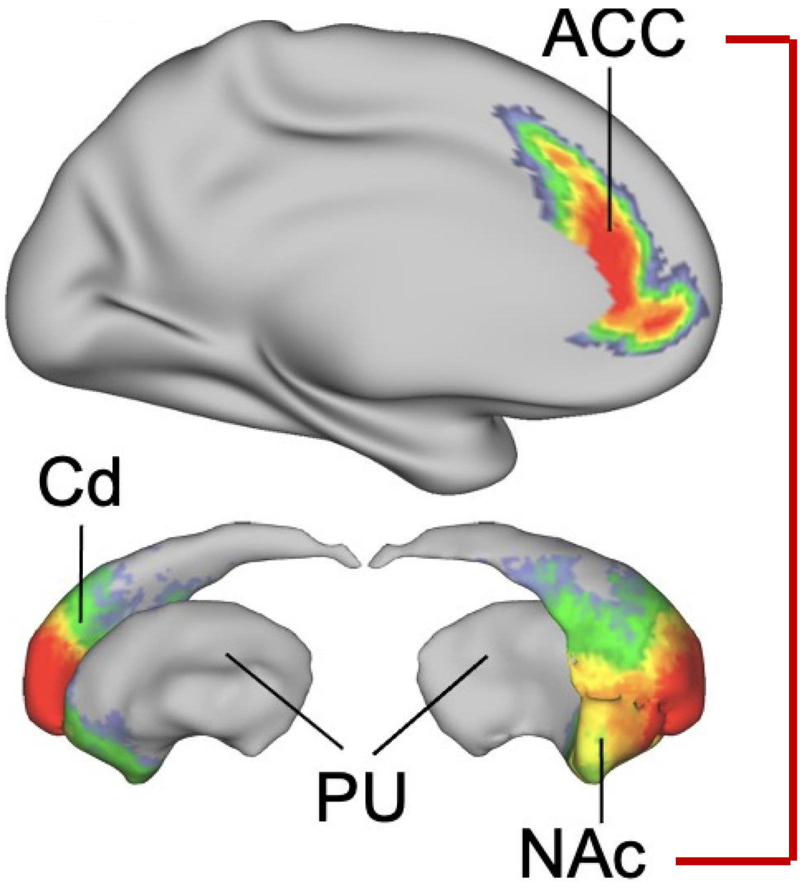
Fluctuations in Salience Network AIC-NAc Connectivity Predicts **Anxiety** within Individuals

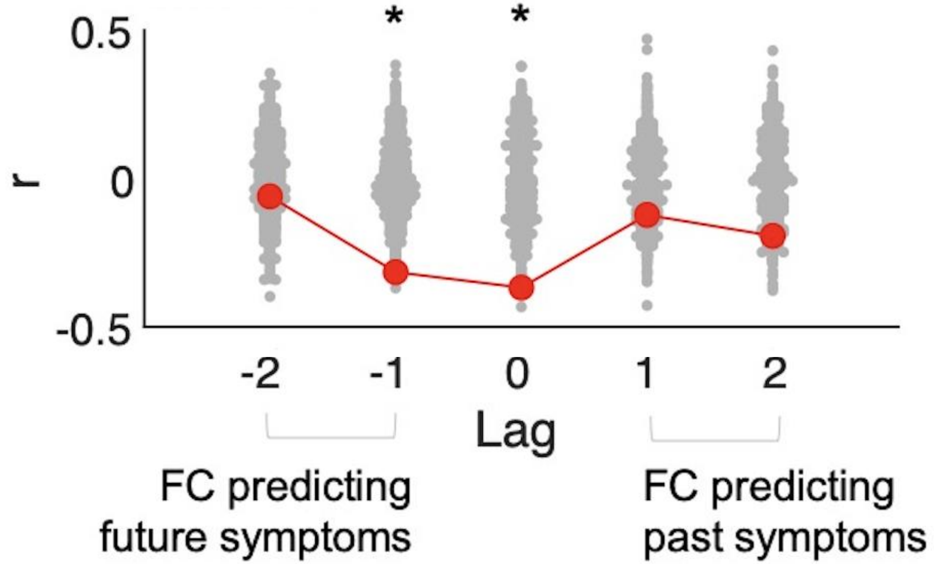




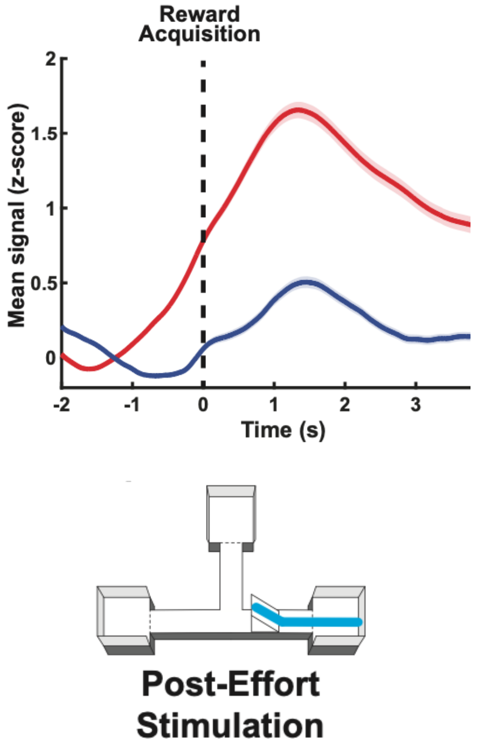
Lynch et al, *Nature*, 2024

Salience Network ACC-NAc Connectivity Predicts Future Emergence of Anhedonia within Individuals





Fetcho et al, *Neuron*, 2023

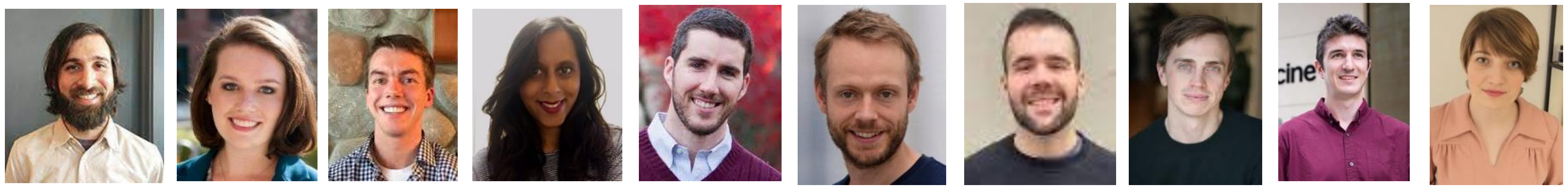


Lynch et al, *Nature*, 2024

Thank you!

Cornell Lab Members:

Amanda Buch
Megan Chang
Revathy Chottekalapanda
Katharine Dunlop
Andrew Drysdale
Immanuel Elbau
David Estrin
Rob Fetcho
Baila Hall
Ryota Hasegawa
Claire Ho
Ben Huang
Shane Johnson
Megan Johnson
Yuki Kageyama
Jesse Kaminsky
Samuel Kohtala
Alexandra Lenz
Chuck Lynch
Rachel Moda-Sava
Gabriela Manzano-Nieves
Mitchell Murdock
Rachel Mikofsky
Hermany Munguba
Parsa Nilchian
Puja Parekh
Grace Paquelet
Julius Pape
Chris Parkhurst
Rachel Rahn
Devin Rocks
Justin Rossi
Ashna Singh
Indira Summerville
Joseph Stujenske
Tim Spellman
Alex Talishinsky
KT Tsang
Danielle Wolk
Nakul Yadav



Josh Levitz, Rachel Moda-Sava, Mitchell Murdock, Puja Parekh, Chuck Lynch, Immanuel Elbau, Hermany Munguba, Shane Johnson, Devin Rocks, Laura Chalencon

Collaborators:

Cornell:
George Alexopoulos
David Artis
Marc Dubin
Faith Gunning
Logan Grosenick
Josh Levitz
Francis Lee
Jonathan Power
Lindsay Victoria
Ben Zebley

Stanford:
Corey Keller
Brian Kobilka
Karl Deisseroth
Evan O'Brien
Alan Schatzberg
Nolan Williams

Tokyo:
Haruo Kasai
Haruhiko Bito

UCLA: Scott Wilke, Laura DeNardo
Iowa: Aaron Boes
MSSM: Helen Mayberg, James Murrough
Yale: B.J. Casey
RU: Priya Rajasethupathy
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UCSD: Jeff Daskalakis

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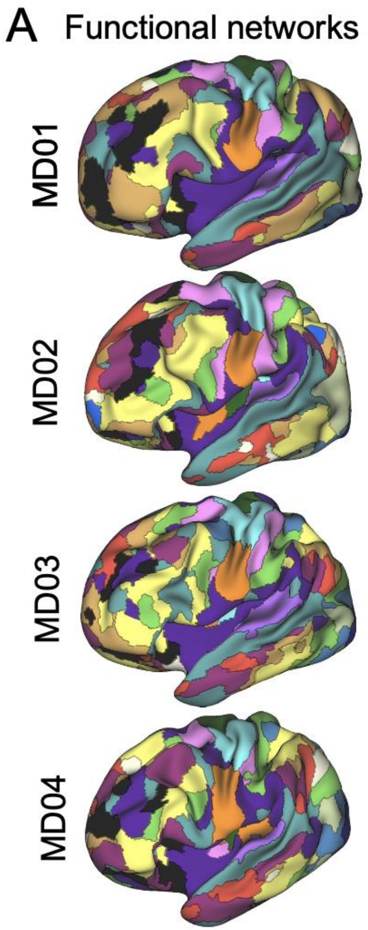
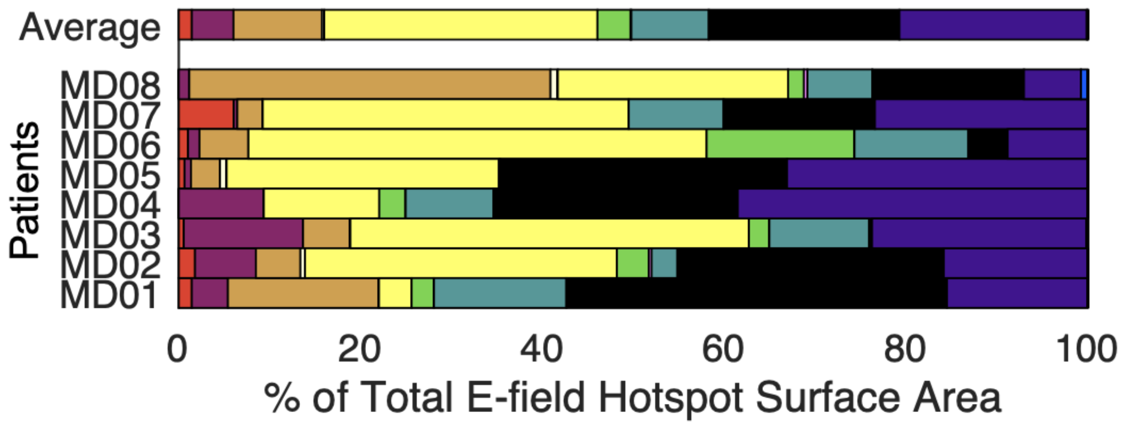
NIH The BRAIN Initiative
NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Rita Allen Foundation
FFOR the FOUNDATION for OCD RESEARCH
BRAIN & BEHAVIOR RESEARCH FOUNDATION
HOPE FOR DEPRESSION RESEARCH FOUNDATION

New Technology for Engaging Salience Network Dysfunction

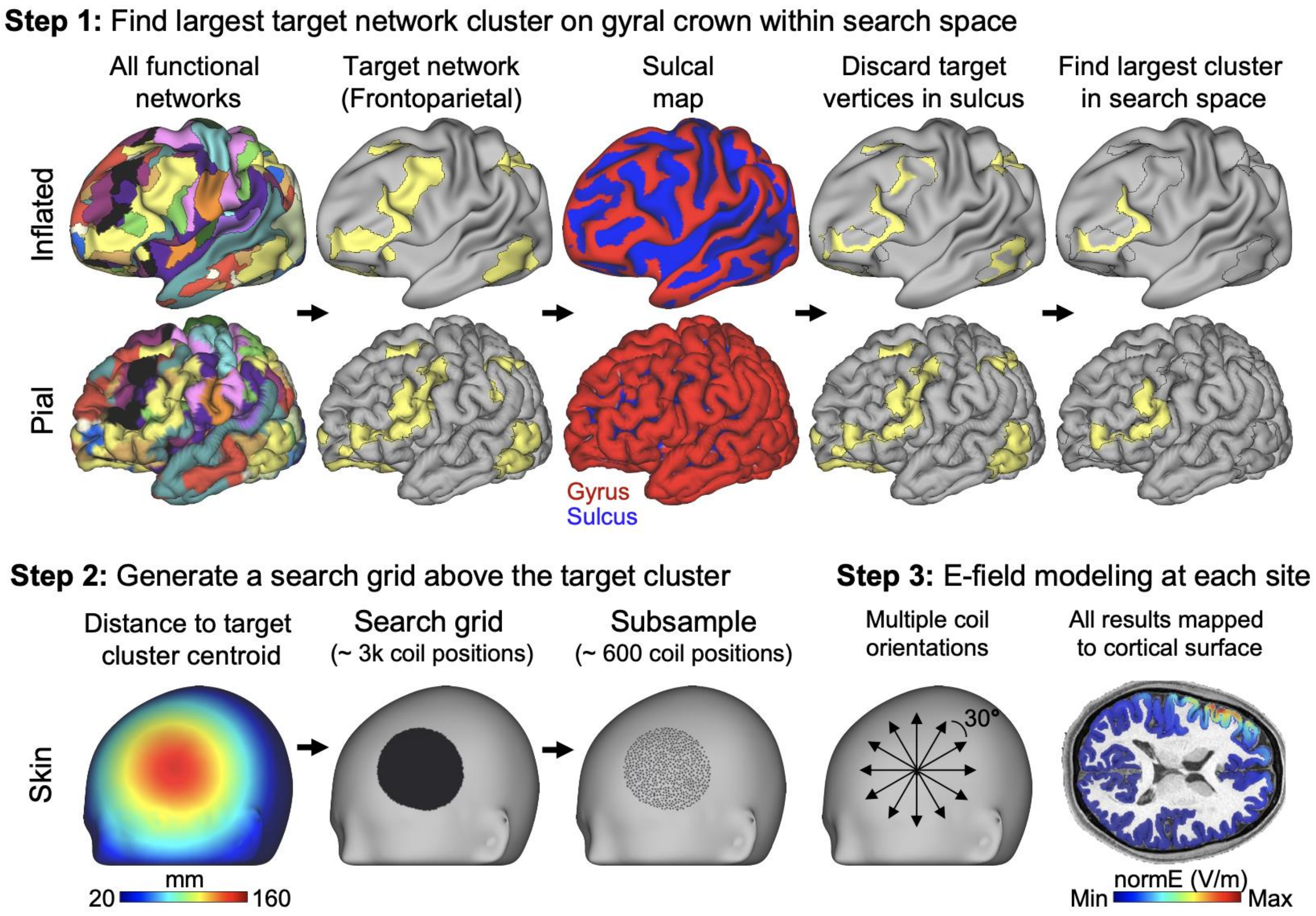


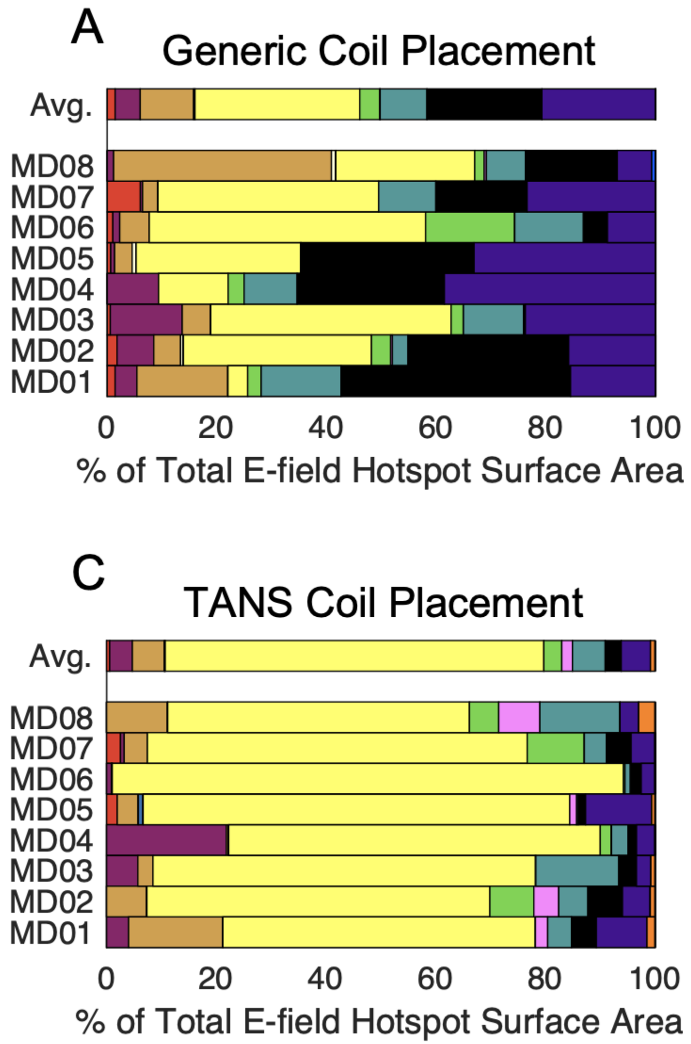


Default-Parietal
Default-Anterolateral
Default-Dorsolateral
Default-Retrosplenial
Frontoparietal
Dorsal Attention
Language
Salience
Cingulo-opercular

Lynch et al., *Neuron,* 2022
Lynch et al., *Nature,* 2024

New Technology for Engaging Salience Network Dysfunction





Lynch et al., *Neuron,* 2022
Lynch et al., *Nature,* 2024