

Neuromodulation for Addiction

Emerging Insights and Approaches

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Ausaf A. Bari MD PhD FAANS
Associate Professor and Vice Chair
Director, Functional Neurosurgery Program
UCLA Department of Neurosurgery

Disclosures

NIH UH3 NS113661

Deep Brain Stimulation of the Subgenual Cingulate Cortex for the Treatment of Medically Refractory Chronic Low Back Pain
Principle Investigator

NIH 1UG1EY032039

Visuomotor Prosthetic for Paralysis
Co-PI

NIH UH3 NS107673

Responsive Neurostimulation for Post-traumatic Stress Disorder
Co-Investigator

NIH #1K01DA060327 (JR)

Speaker and Consultant for Medtronic

Speaker and Consultant for RebrAln

Advisory Board: Nervonik

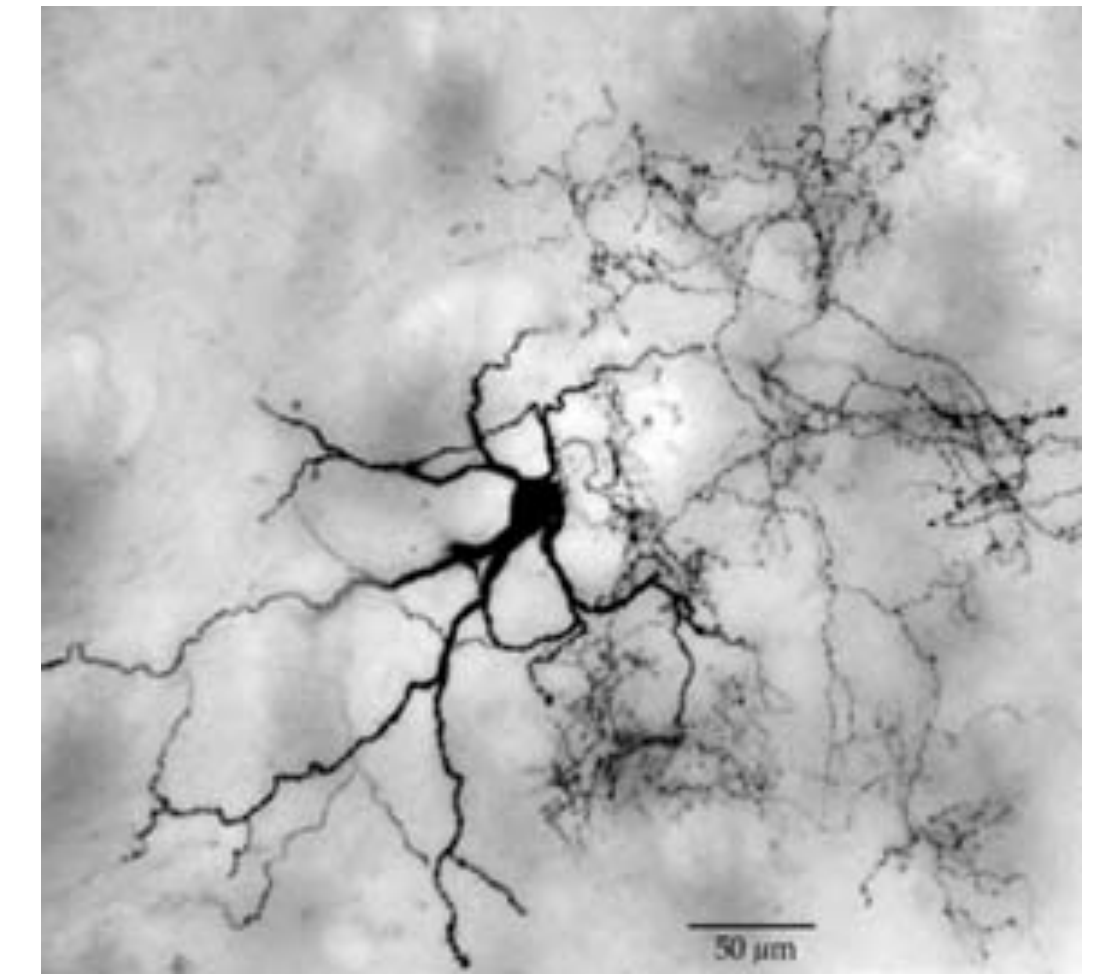
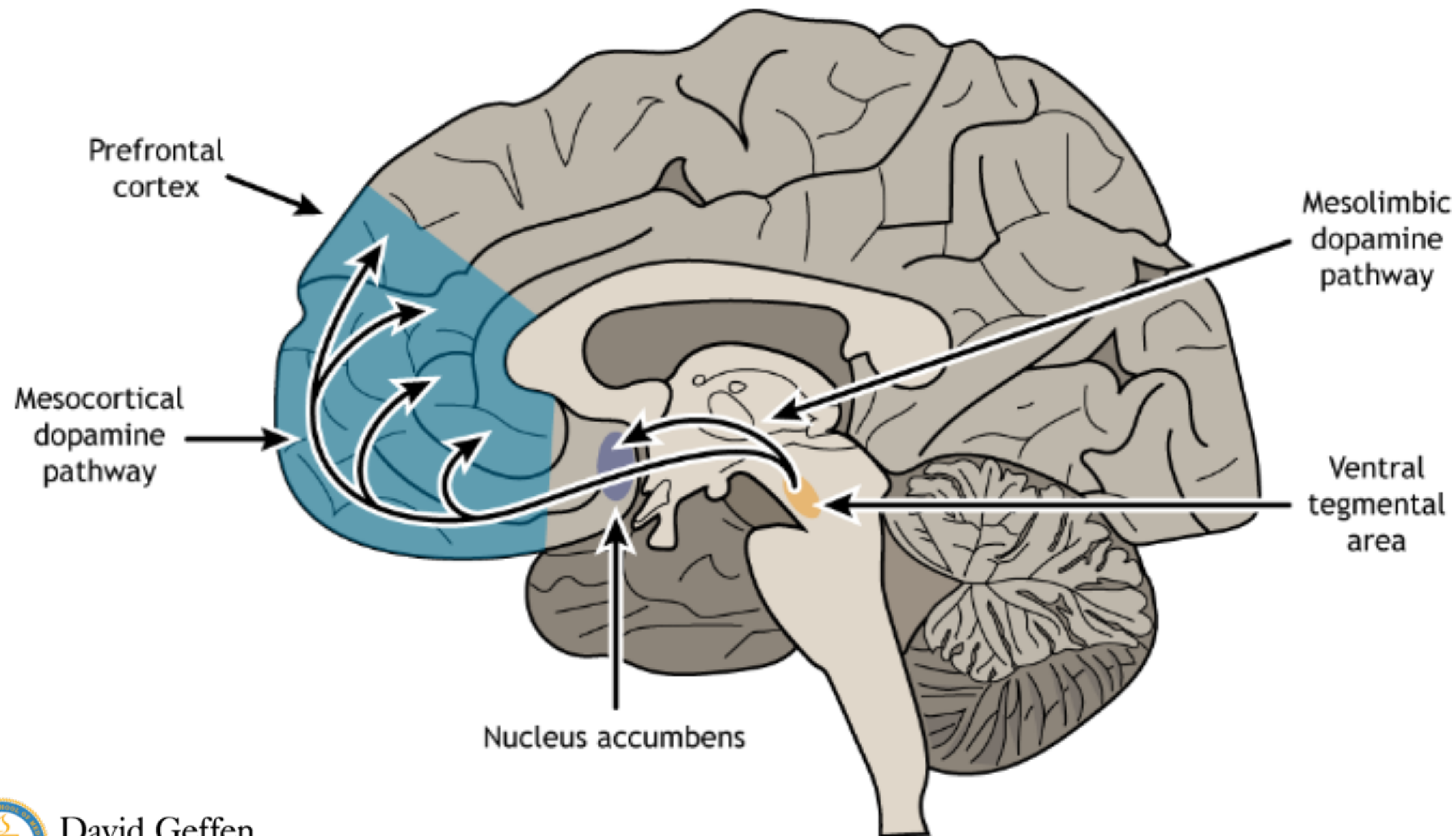
Speaker and Advisory Board: Insightec

Fellowship Funding: Boston Scientific, Medtronic, Abbott

Demographics of Addiction

- Worldwide, in 2020 alone, 284 million individuals abused drugs
- Alcohol and nicotine alone are responsible for the highest number of deaths.
- In the past century, Nicotine has claimed the lives of about 100 million people
- 1.1 billion smokers worldwide and half expected to die due to nicotine addiction
- Now, emergence of a new behavioral addiction: social media and short-form video abuse/dependence

Dopamine - Accumbens Theory



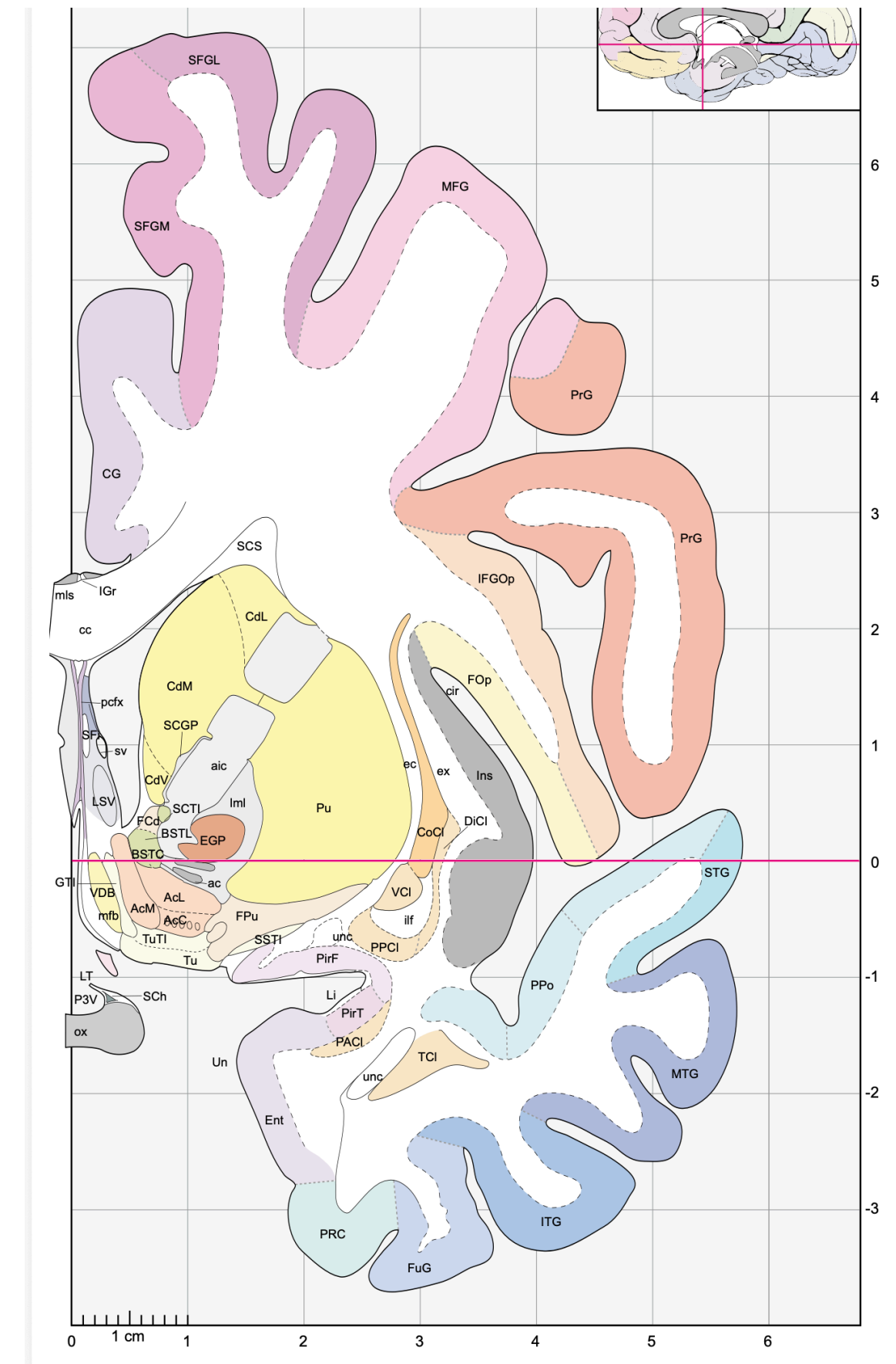
History of Lesions

- Leucotomy, Hypothalamotomy (Germany, Sweden, Russia, 1960s)
- Cingulotomy (Russia 1999-2002) 30% remission heroin users
- Nucleus accumbens ablation (China 2000-2004) 60% reduction in opioid relapse and 5 year abstinence

A Move Toward Stimulation

DBS Targets

- Nucleus Accumbens/Ventral Striatum/ALIC
- Bed Nucleus of the Stria Terminalis
- Anterior Cingulate Cortex
- Subthalamic Nucleus
- Addictions Explicitly Targeted to Date: **Alcohol (legal)**, **Cocaine**, **Methamphetamine**, **Opioids (Rx)** and **Nicotine (legal)**



What's wrong with the current approaches?

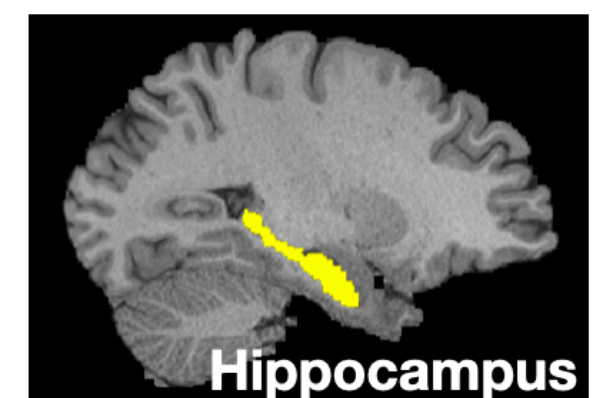
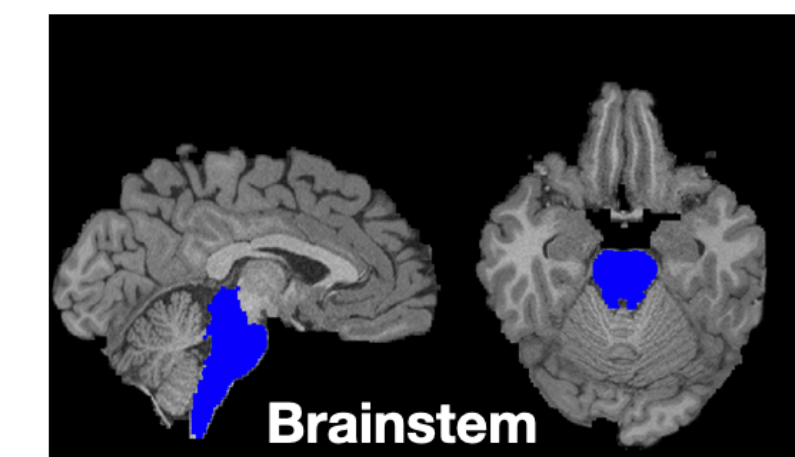
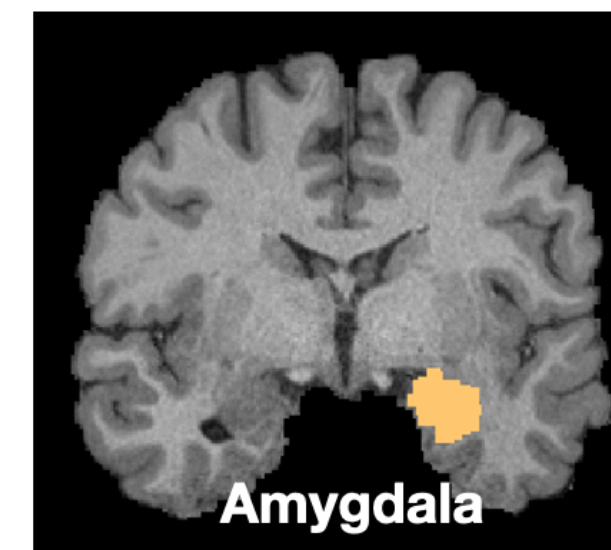
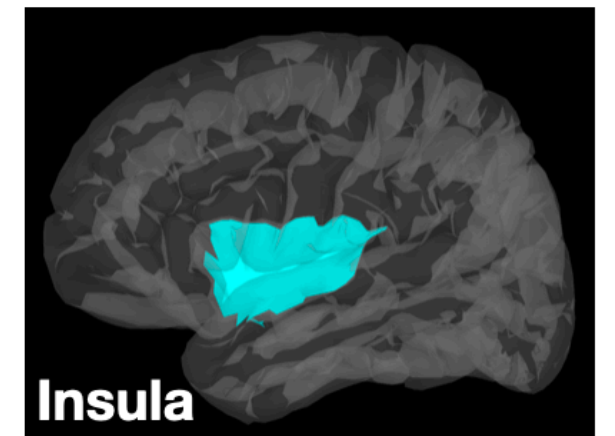
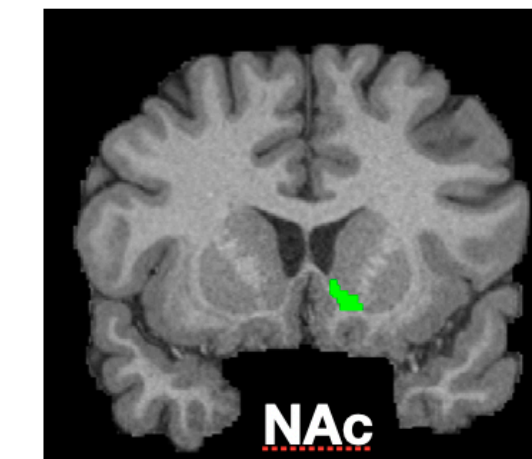
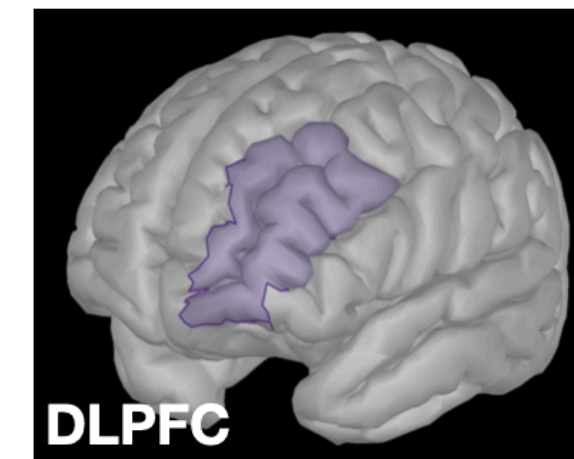
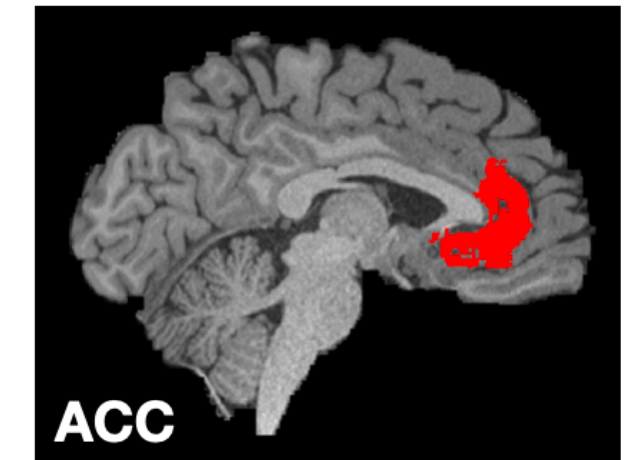
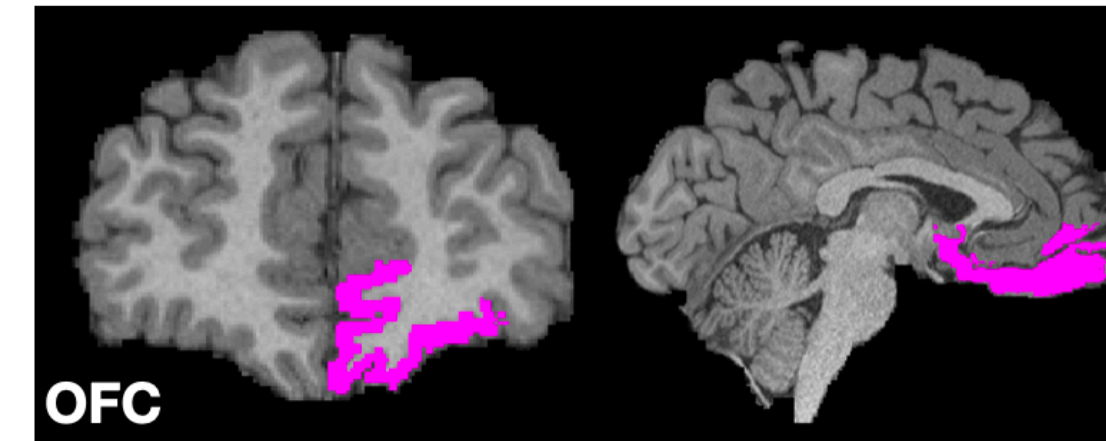
- Relapse rates remain high (70%)
- Therapy is not individualized
- Biomarkers not well characterized
- Theoretical basis is outdated

Incentive Sensitization Theory

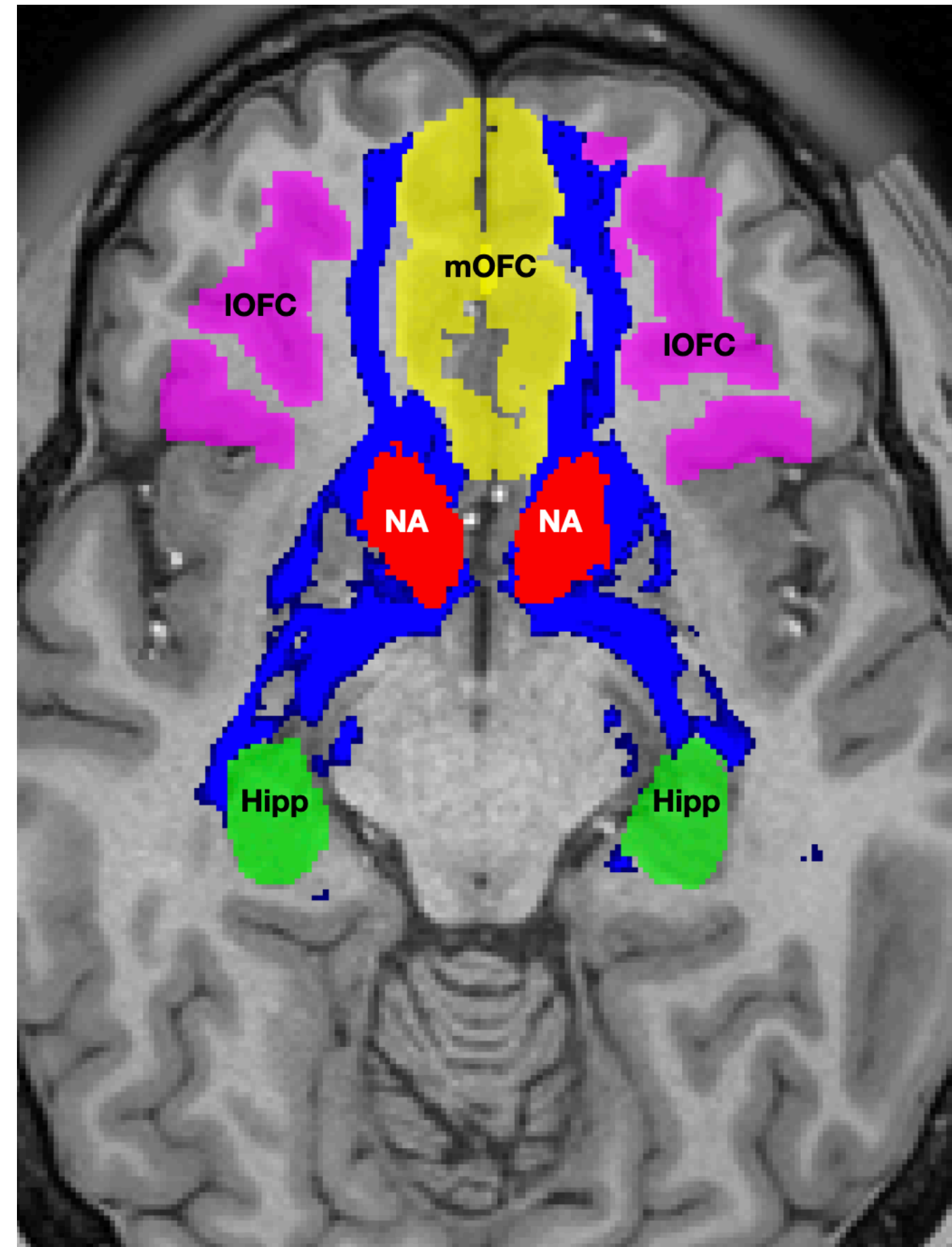
- **Wanting** vs. **Liking**
- Wanting is the desire to obtain drug reward (CRAVING)
- Liking is the hedonic/pleasure response during reward *consumption*
- Tightly coupled but distinct processes with distinct brain circuits
- The nucleus accumbens *is not* the pleasure center but rather involved in working towards acquisition of rewards (one node in a broader addiction circuit)

The Broader Reward Circuit

- **Orbitofrontal Cortex:** encodes reward values and may play a greater role in the hedonic response to reward consumption: *LIKING*
- **Anterior Cingulate:** Error encoding, cognitive control
- **Nucleus accumbens:** Reward motivation, effort
- **Amygdala:** Reward associations, emotional salience
- **Hippocampus:** Contextual, Craving, Memory of Pleasure



NAc-Hippocampus-OFC Circuit

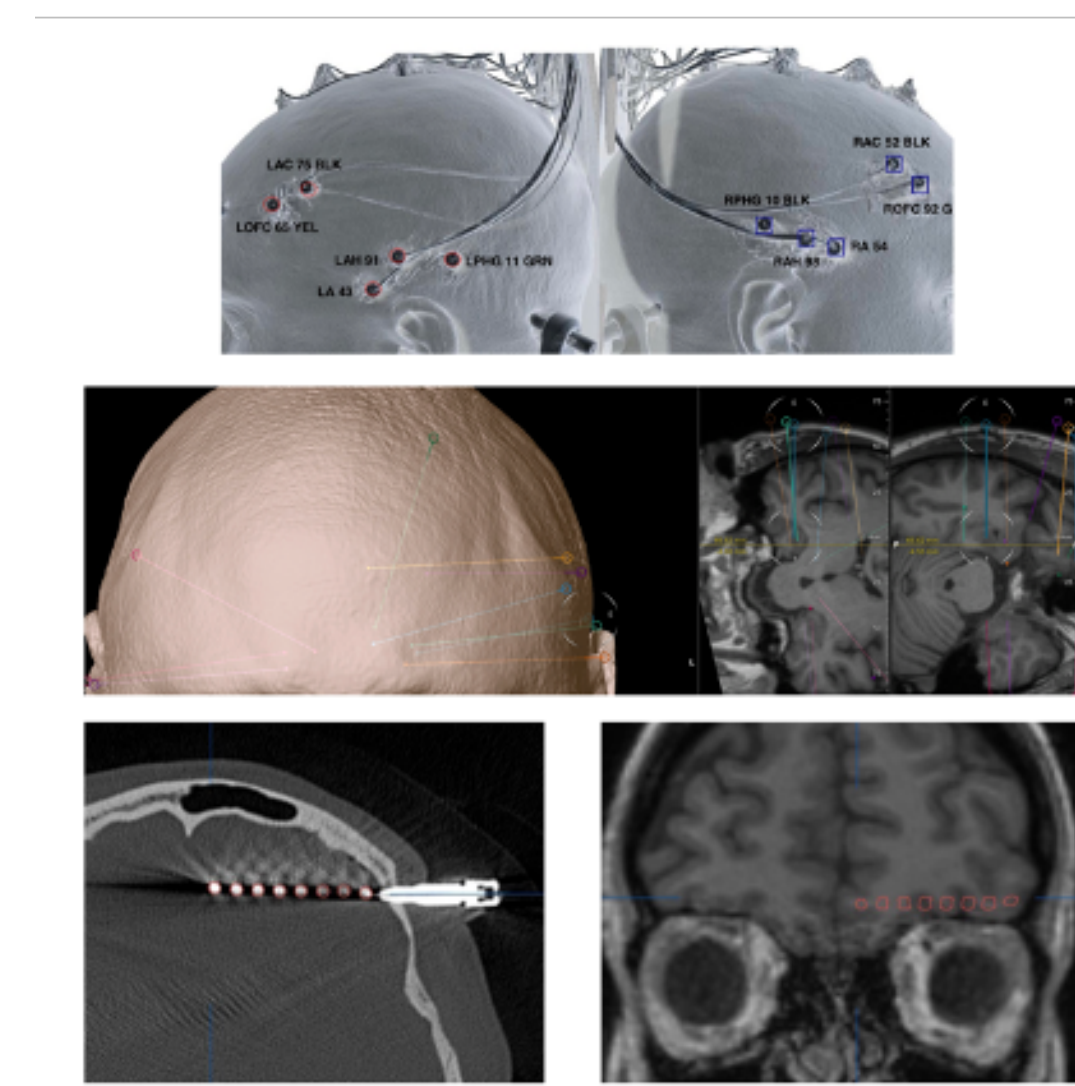
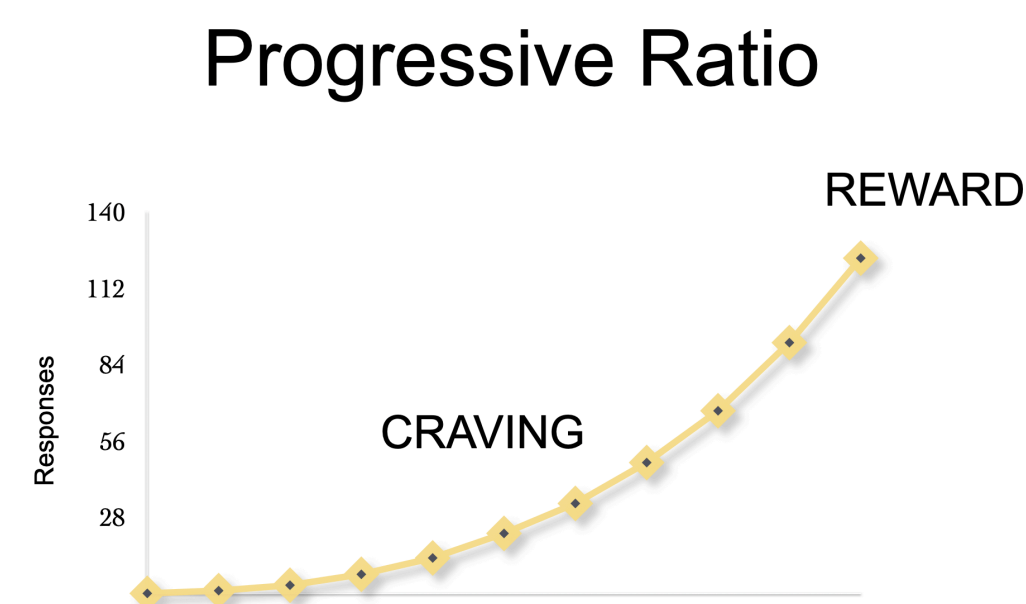
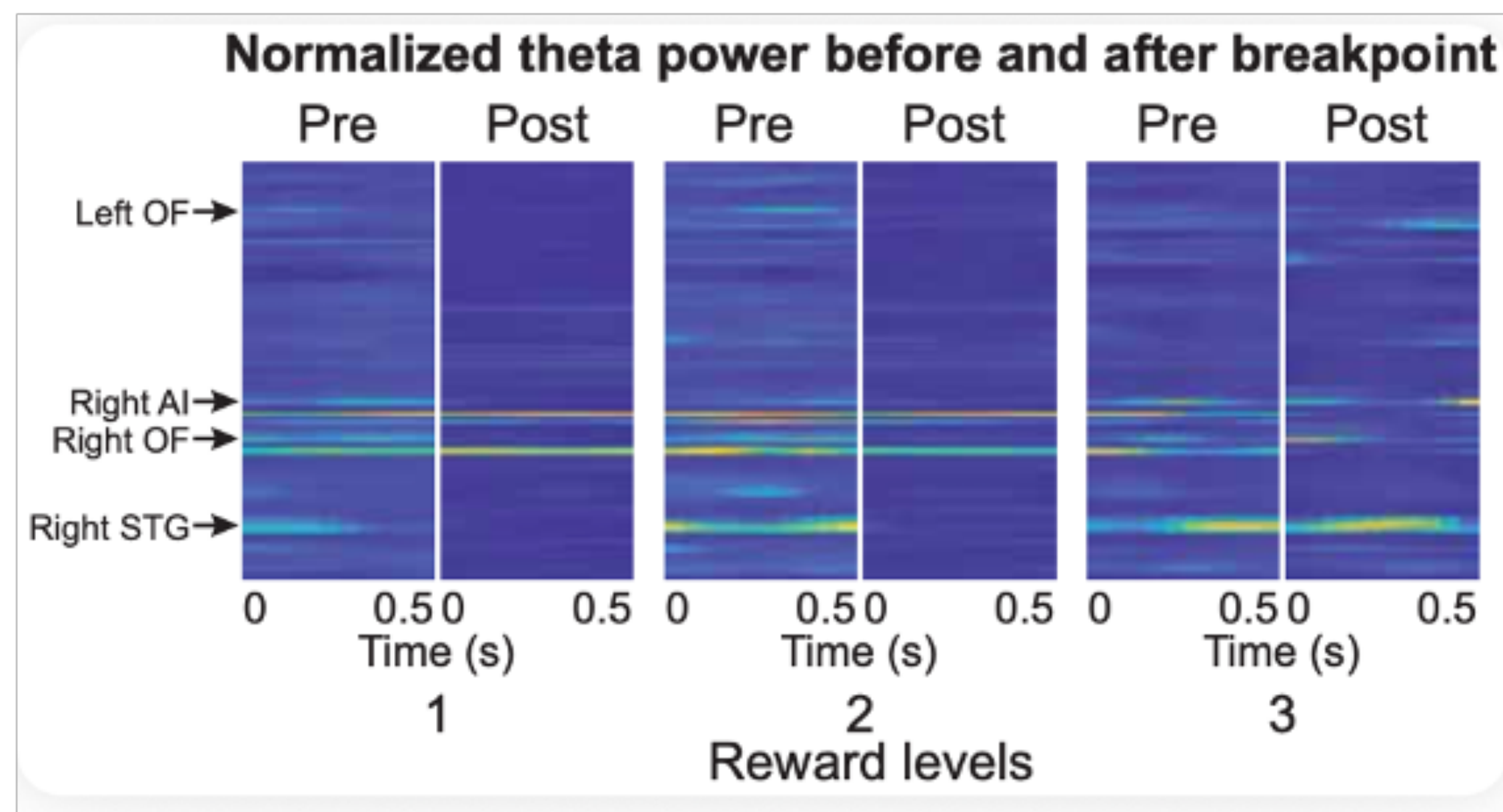


- Probabilistic Tractography Demonstrating Individualized Connectivity
- Significant connectivity between the NAc, Hippocampus and OFC

Orbitofrontal Cortical Dynamics in Reward

Electrophysiological Data from SEEG Subjects

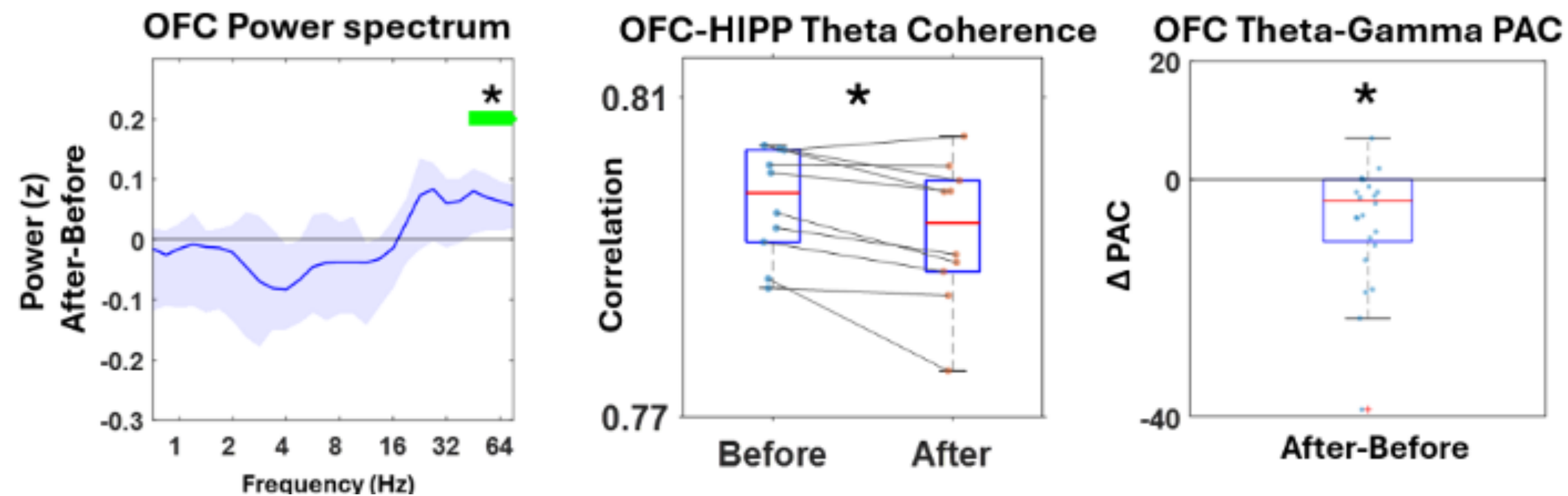
- SEEG electrodes in patients with epilepsy responding for monetary reward



- We observed increases in **OFC theta power** associated with reward acquisition as opposed to the craving phase

Opioids and the OFC

SEEG Data with Opioid Administration



- Acute effects of opioid administration
- Opioids Decreased OFC-hippocampus theta coherence
- Opioids Increased OFC theta-gamma PAC

Nicotine Addiction

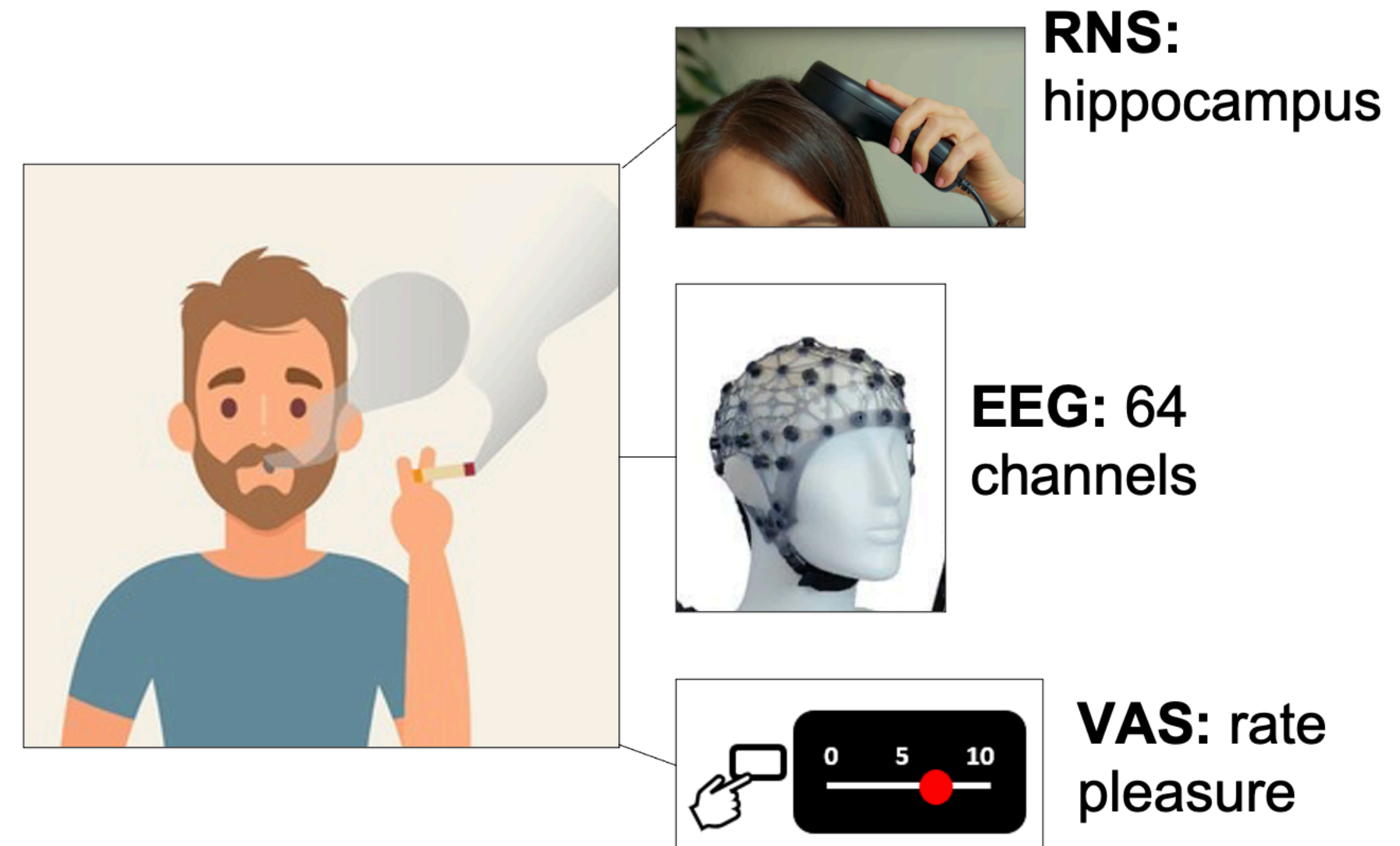


- More people in the US addicted to nicotine than to any other drug.
- Smoking increases the risk for serious health problems and death.
- Quitting is notoriously HARD
-and it is LEGAL.

In vivo hippocampal recordings during cigarette smoking

RNS Recordings During Cigarette Smoking

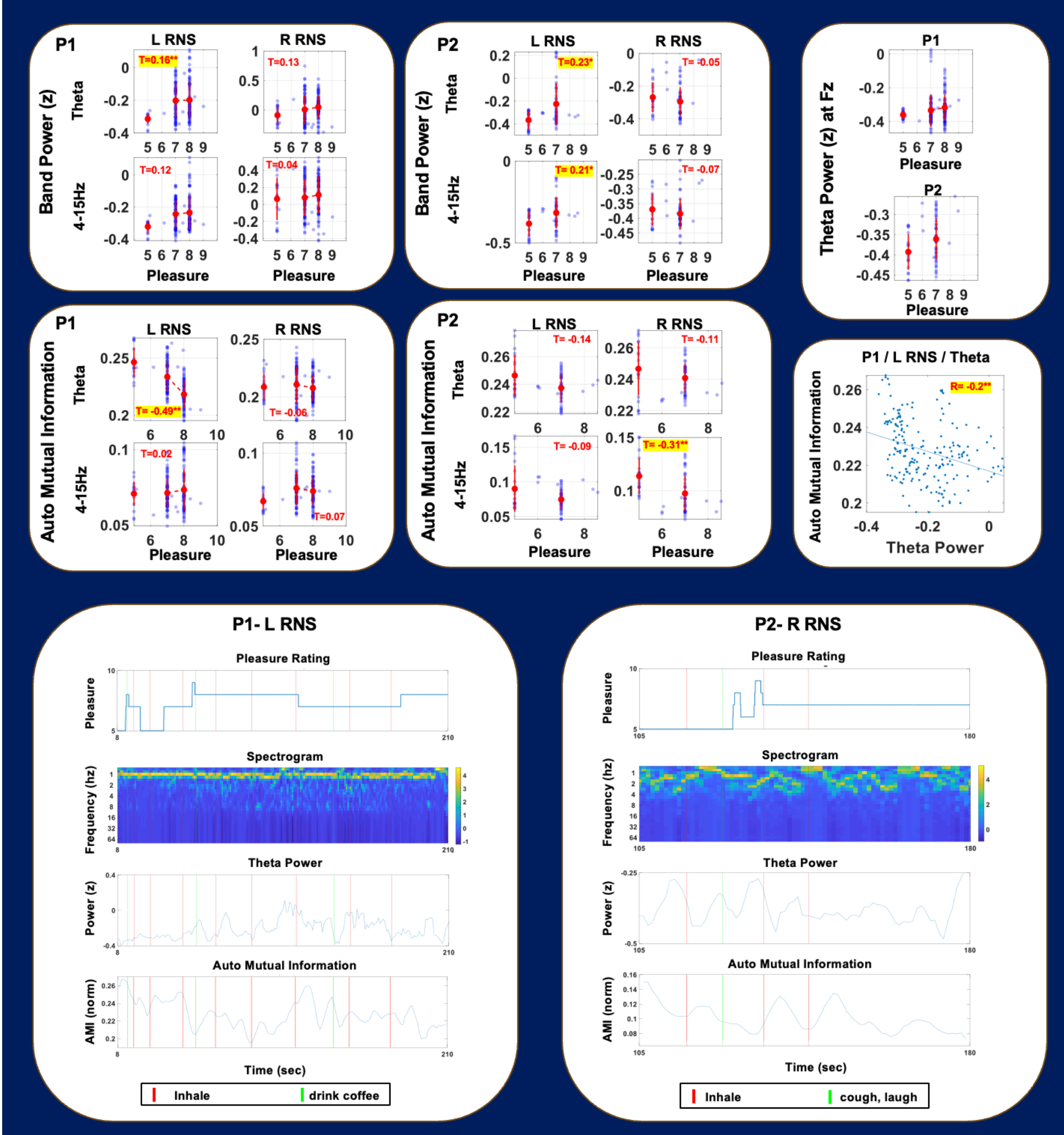
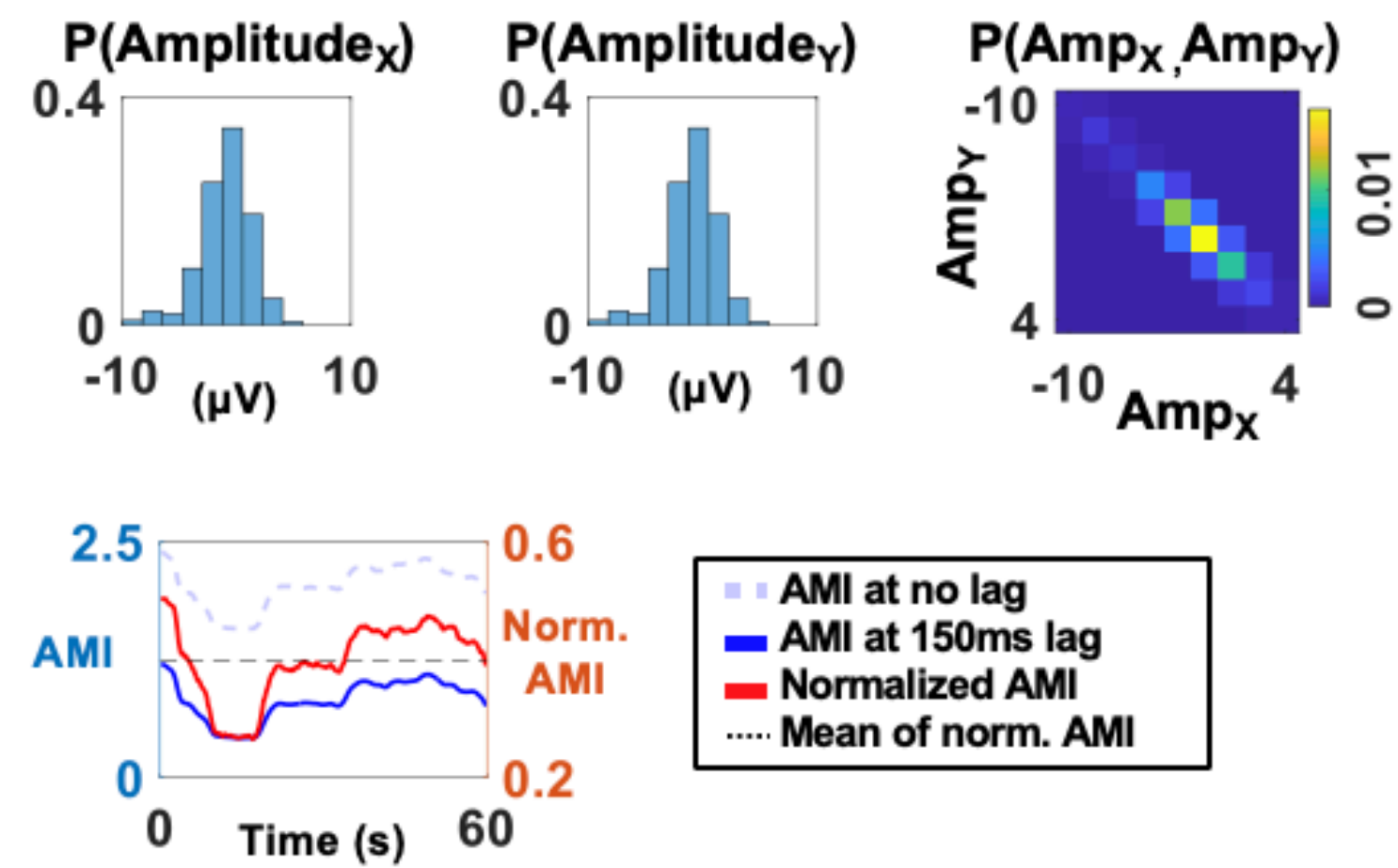
- Objective: To characterize dynamic theta-band oscillatory activity in the hippocampal–entorhinal region and prefrontal cortex during nicotine use.
- 2 patients with Neuropace RNS implants who are regular nicotine users
- Protocol: Patients naturalistically smoked/vaped and rated their pleasure on a VAS pleasure scale
- Recordings: RNS, 64 channel EEG, VAS scale
- Theta (4-8Hz) and theta/alpha (4-15Hz) activity were analyzed during nicotine use.



Nicotine Pleasure is Characterized by Increased Theta in the Hippocampus

- Theta oscillatory power increased as participants' pleasure increased in both patents left RNS site and EEG recordings from the PFC.
- Theta signal became more regular (quantified by AMI) **as pleasure increased.**

Auto mutual information (AMI)



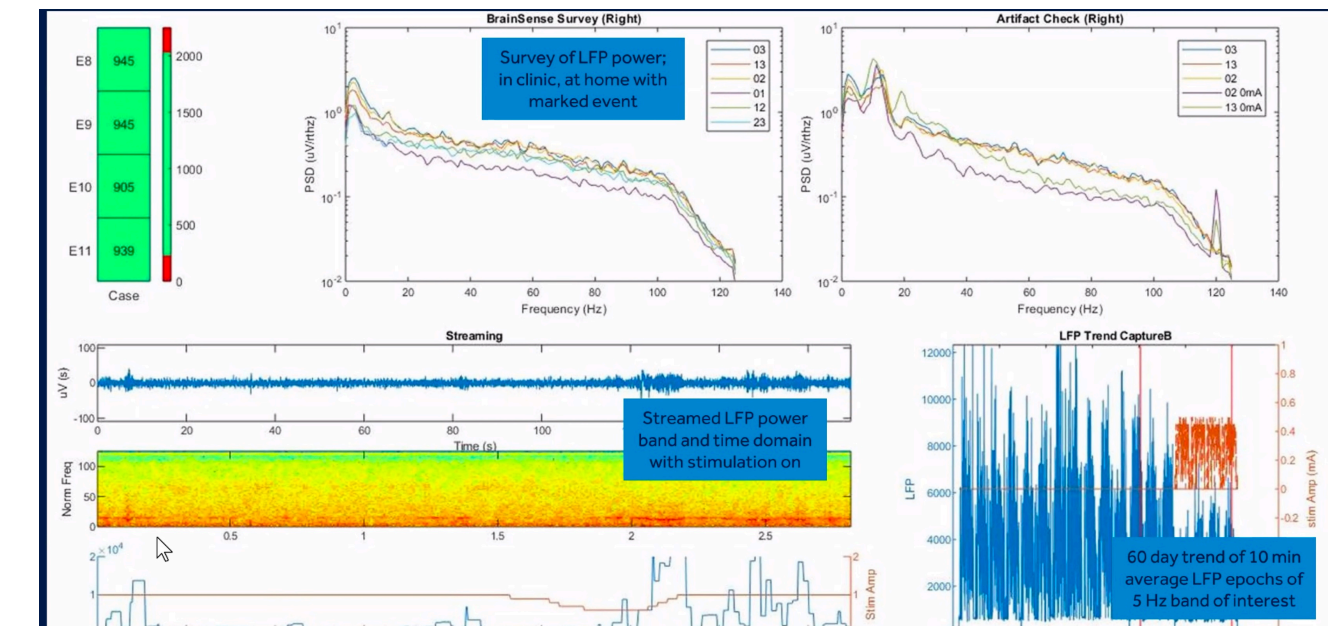
This research was funded by NIH #1K01DA060327 grant (JR)

Potential Biomarker for Addiction

- Theta coherence between the OFC and hippocampus
- OFC theta-gamma PAC
- Current experiments underway to ascertain the role of the NAc within this paradigm.
- Use of fMRI/DTI to identify addiction specific hotspots within the OFC

Future Approaches to Neuromodulation for Addiction

- Development of neuronal biomarkers associated with craving and pleasure
- Multi-target approach: Hippocampal-NAC-OFC circuit
- Closed-loop devices: RNS and sensing DBS.
- RE-emerging role of LESIONS using FUS/SRS.



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Andrew Vivas
Jingwen Yao

Post-docs

Jihye Ryu
Mahmoud Omidbeigi

Project Scientist

Evie Tsolaki

Lab Assistant

Meski Tolossa

Students

Jacob Alderete
Jay Gill
Nick Kelhofer
Lisette Torres
Michael Ward
Matthew Zilberman

