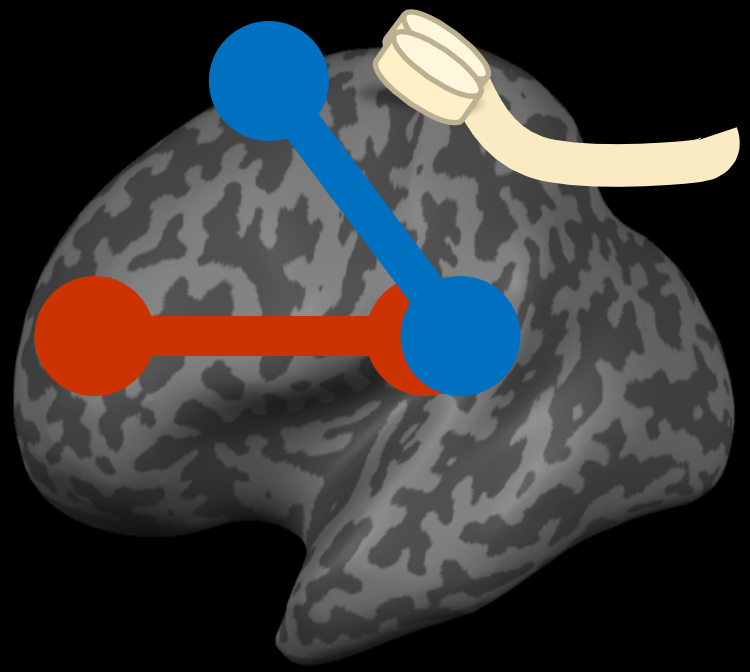
Transcranial Magnetic Stimulation - a new circuit-based strategy to decrease relapse among patients with drug and alcohol use?



Colleen A. Hanlon, Ph.D.

Professor, Clinical Neuromodulation Laboratory
Comprehensive Cancer Center
Wake Forest University School of Medicine

Disclosures:

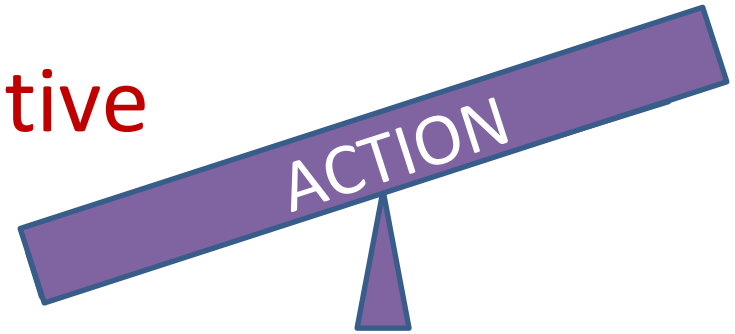
Research Funding was exclusively provided by grants from the National Institutes of Health.

Temptation of Adam, Tintoretto, 1551

Everyday modern struggles between

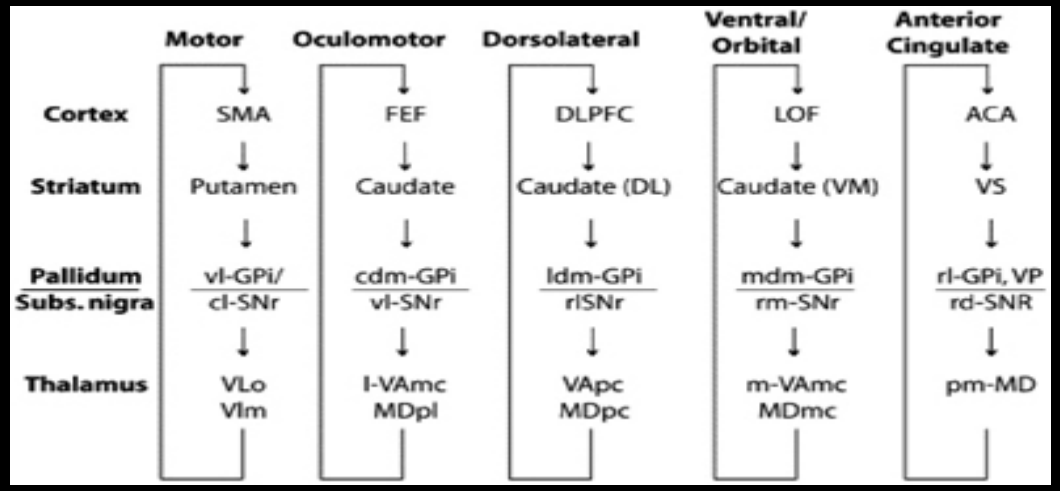
Cognitive Control

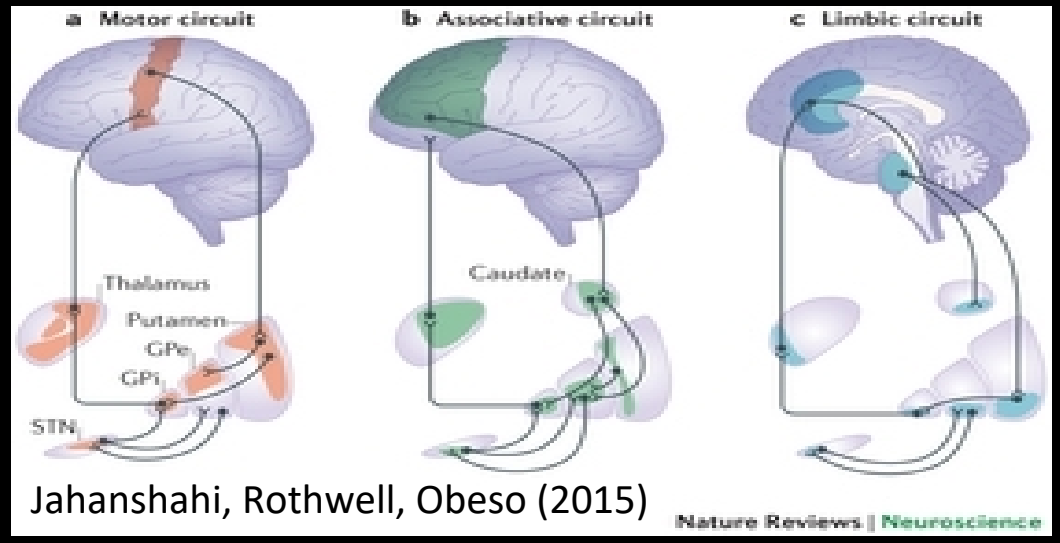
Appetitive Drive



Frontal-Striatal Circuits: Arousal, Control, Action

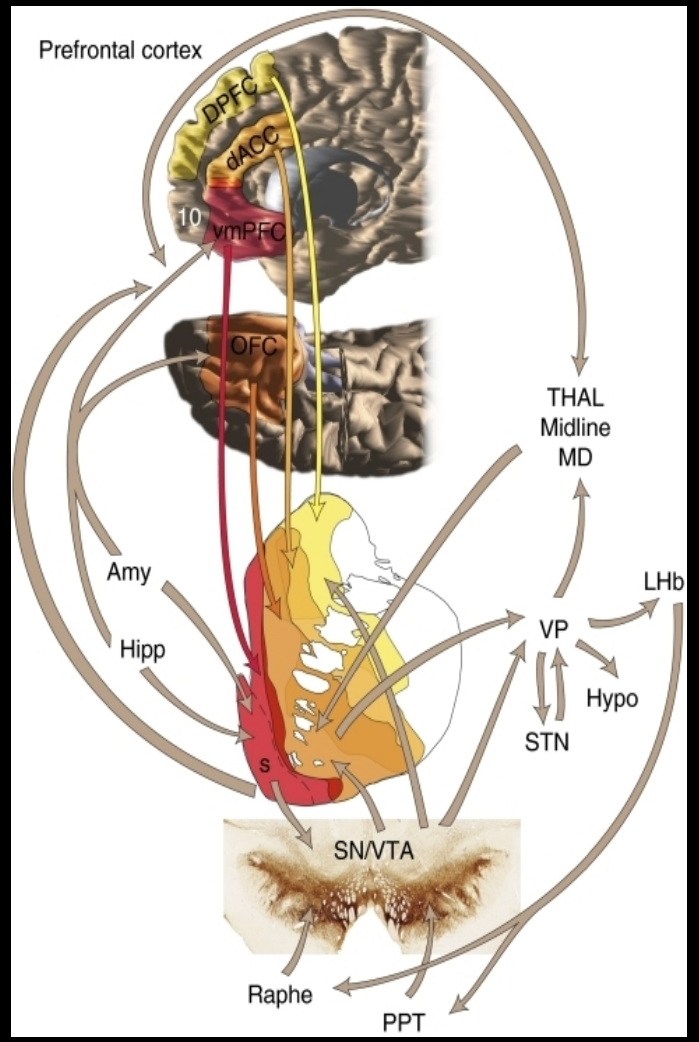
Alexander, DeLong, Strick
Ann. Rev. Neuro. 1986



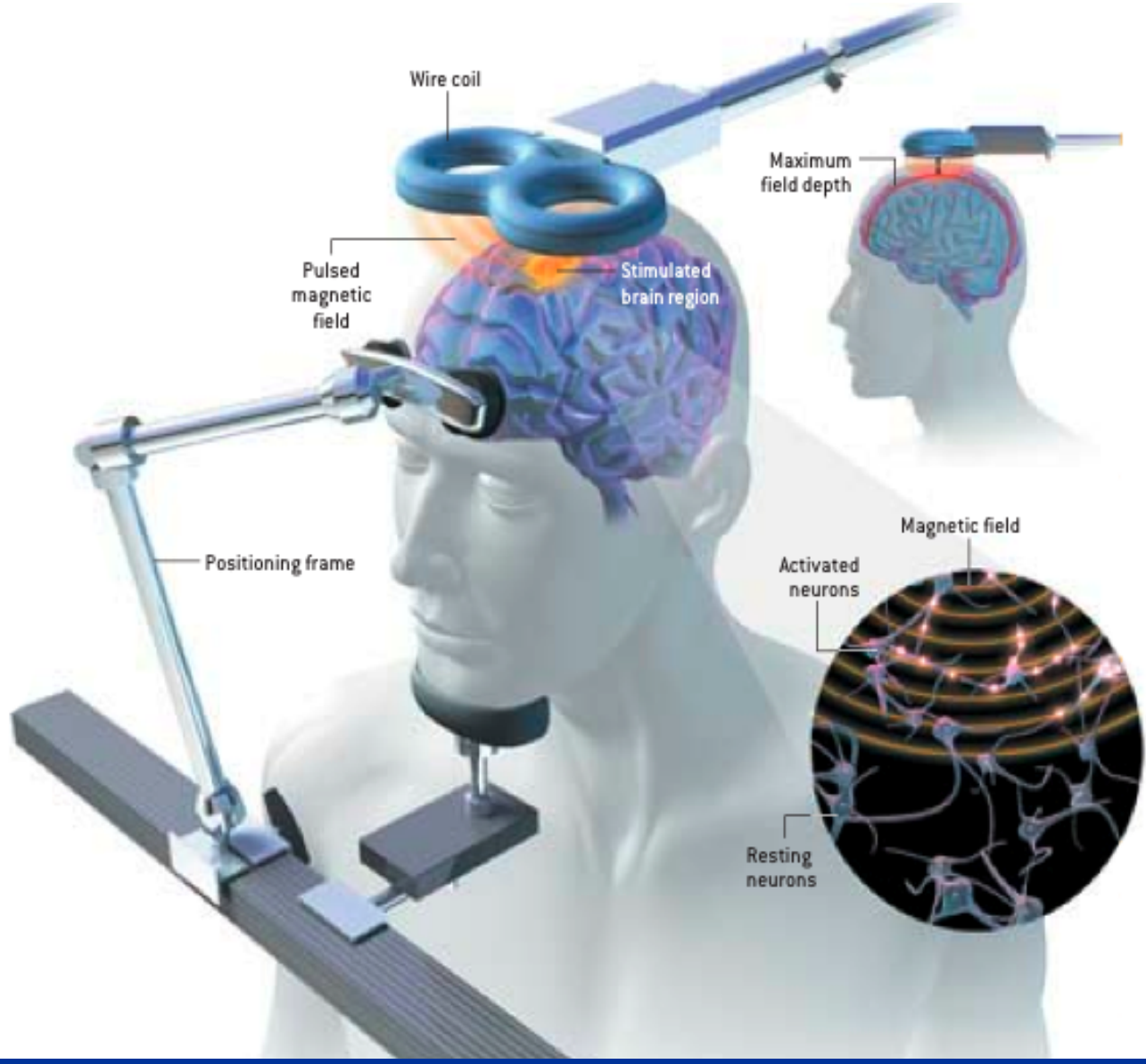


Jahanshahi, Rothwell, Obeso (2015)

Haber & Knutson,
Neuropsychopharm., 2010



What Is TMS?



"TMS can be rigorous, reliable, and sham-controlled"

George MS. *Sci Am*. 2003;289:66-73.

rTMS FDA-approved for depression – being widely adopted

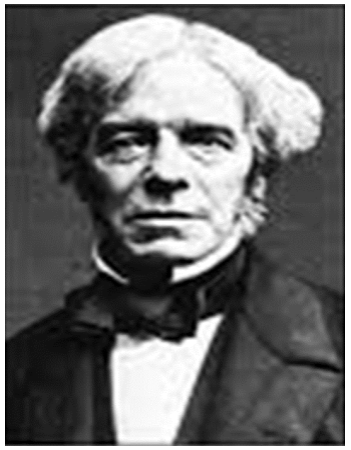
4 FDA approved devices, Medicare reimbursable, 500+ machines sold

Growing International enthusiasm (esp. Asia and South America)

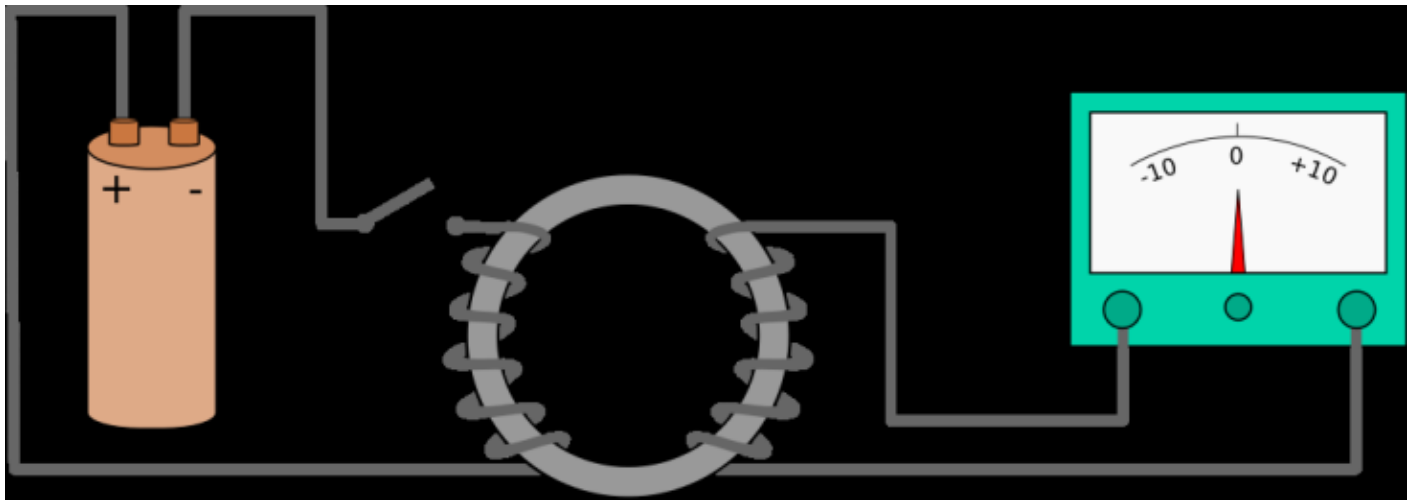
Clinical protocol for Depression:
10 Hz Left DLPFC,
3000 pulses/day (20 min)
5 days/week
6 weeks

Remission rate: 15-30% in double blinded phase, >30% in open label

Durability: 90% retention of response at 12 months



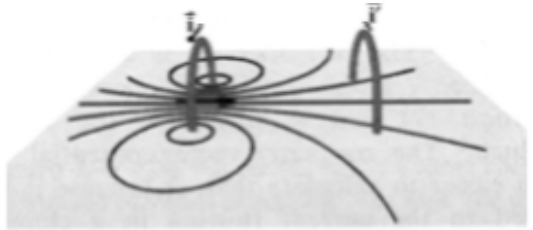
Physics of TMS



Faraday's law of inductance

(August 29, 1831)

A time-varying current (di/dt) in a wire loop will induce a
magnetic field



The magnetic field will induce an electromotive force in an adjacent conductor

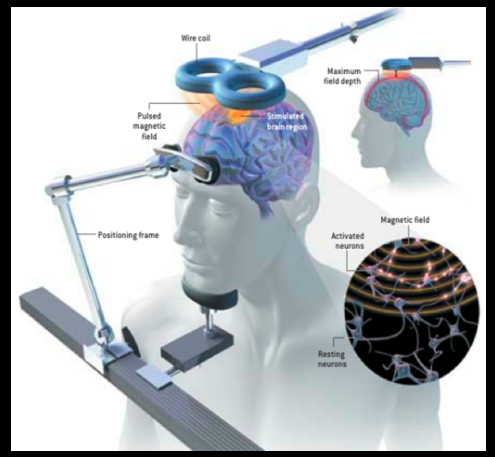
$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \qquad \mathcal{E} = -L\frac{di}{dt}$$

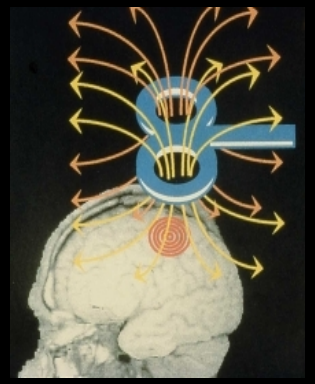
L = inductance

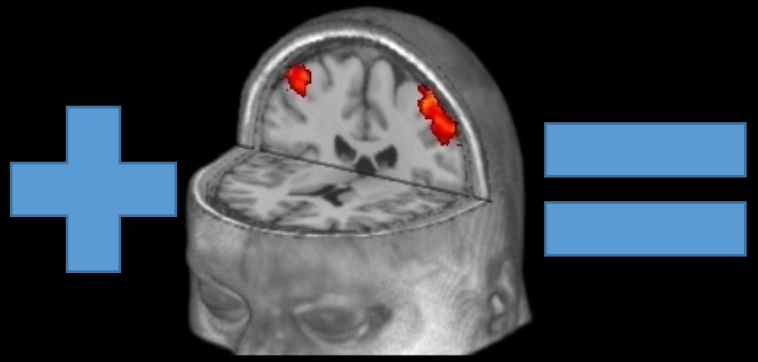
E = Electromotive force
L = inductance

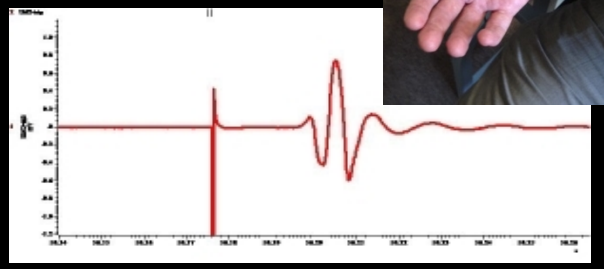
Physics of TMS

Mechanism of Action: Electromagnetic Induction



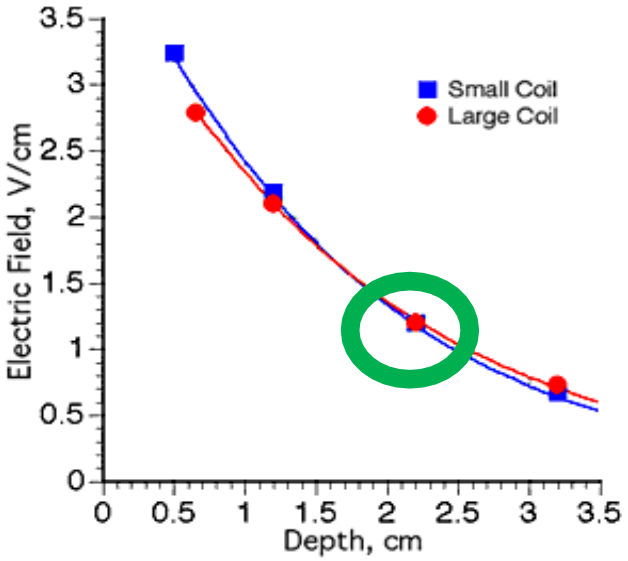


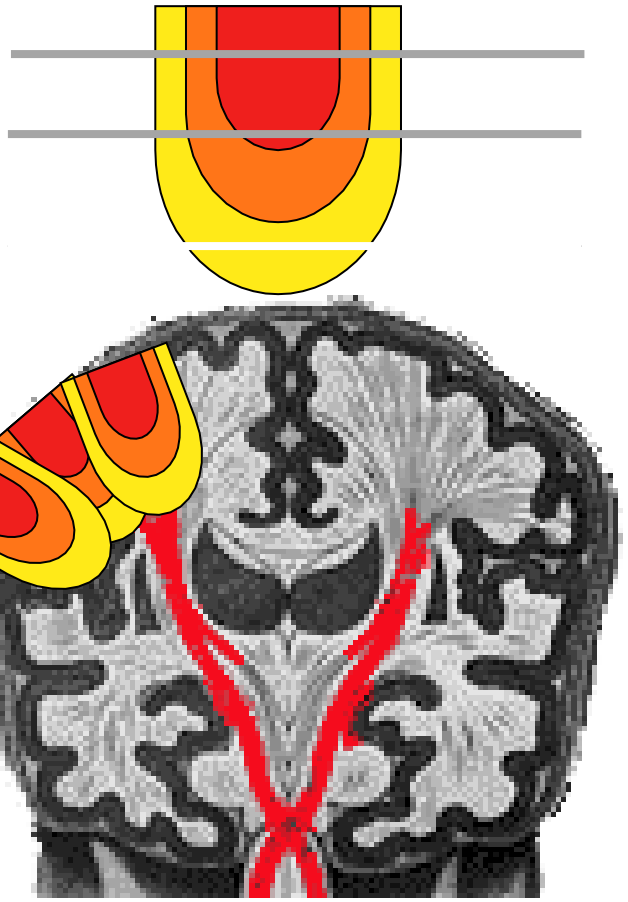




TMS Principles 1: Stimulation Breadth & Depth

Predicted by Maxwell's equations



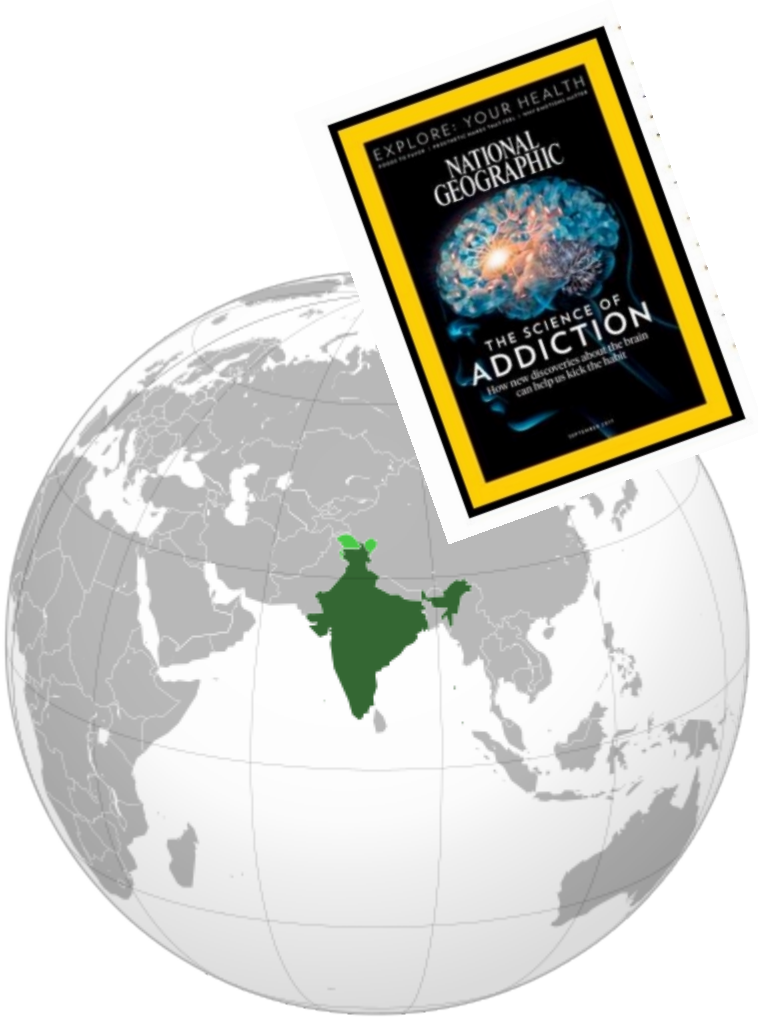


0.5 cm

1.5 cm

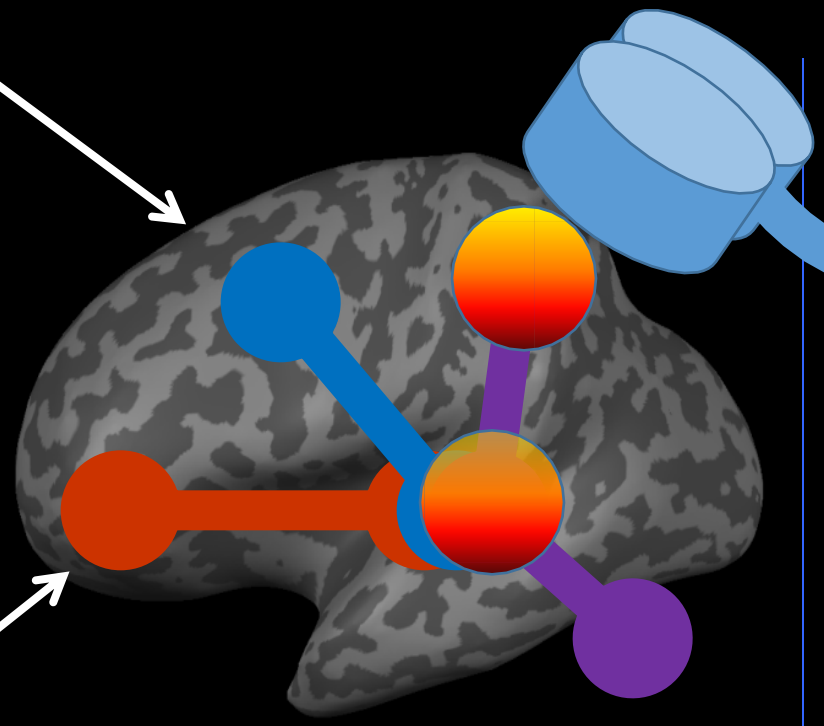
2.0 cm

1 V/cm = 20mm deep,
approx. 20mm wide



Hanlon, 2017. *Brain Stimulation.*

Principle 2: Transynaptic modulation



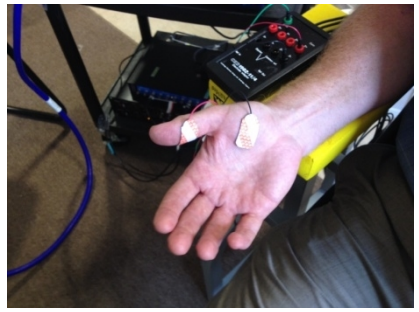
TMS ---> synaptic activity ~2cm under the coil

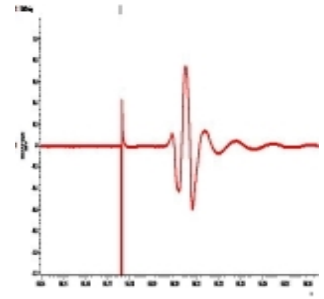
and monosynaptic striatal targets

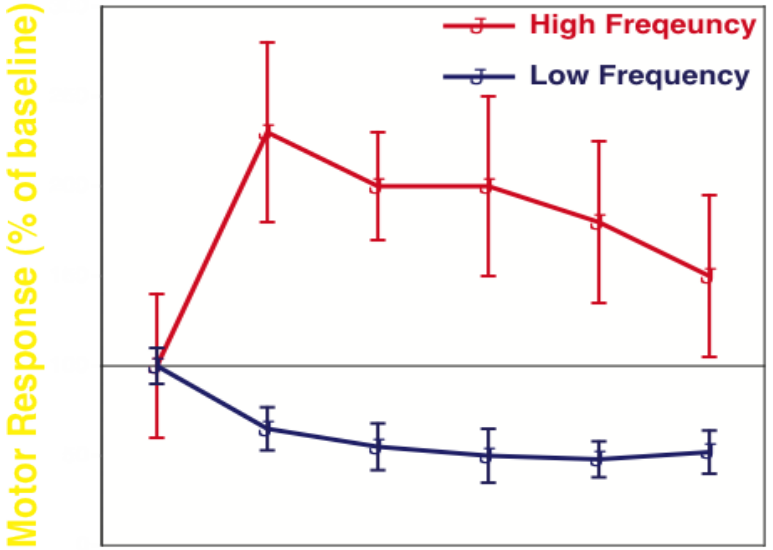
(Strafella, George, Etkin, Daskalakis, Lisanby, Pascual-Leone)

Principle 3: Behavioral and Brain effects are <u>frequency dependent</u>

Frequency dependent modulation of cortical targets		
High Frequency (10Hz) Intermittent Theta Burst	higher cortical excitability	Amplified neural response
Low Frequency (1Hz) Continuous Theta Burst	lower cortical excitability	Attenuated neural response





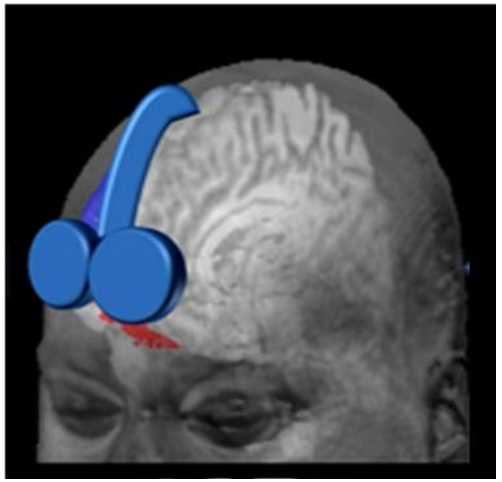


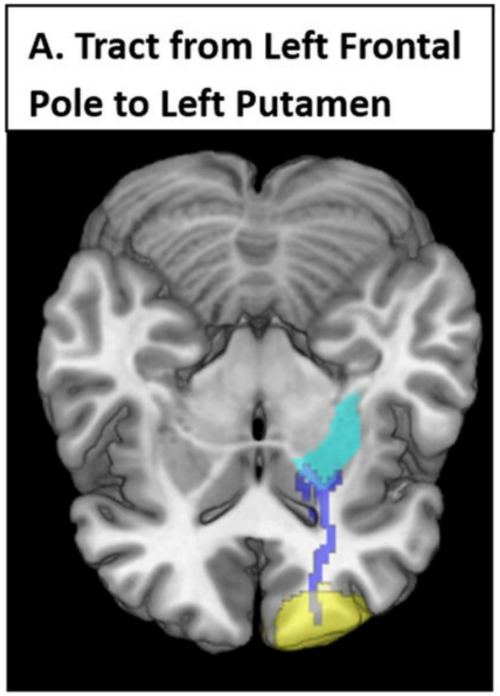
Principle 4: Signal propagation is dependent on structural integrity

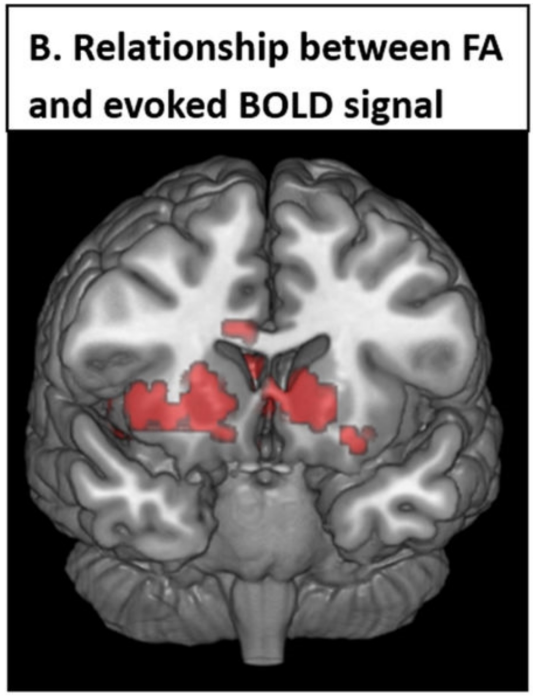
Tonisha Kearney -Ramos (Columbia Unv.)

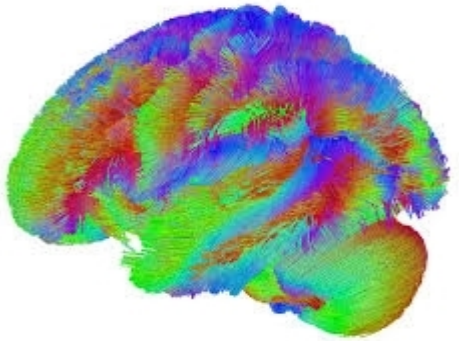
Daniel Lench, PhD (UMN)

Fiber tract integrity calculated between frontal pole and ROIS









Kearney-Ramos , Lench, et al 2018 Scientific Reports;
Hanlon et al 2019 Clinical Pharm & Therapeutics

Our Goal: Develop a TMS Based Strategy to Decrease Cue-reactivity

Where?

How Much?

Who?

"Individual Variability"

INFORMED DESIGN

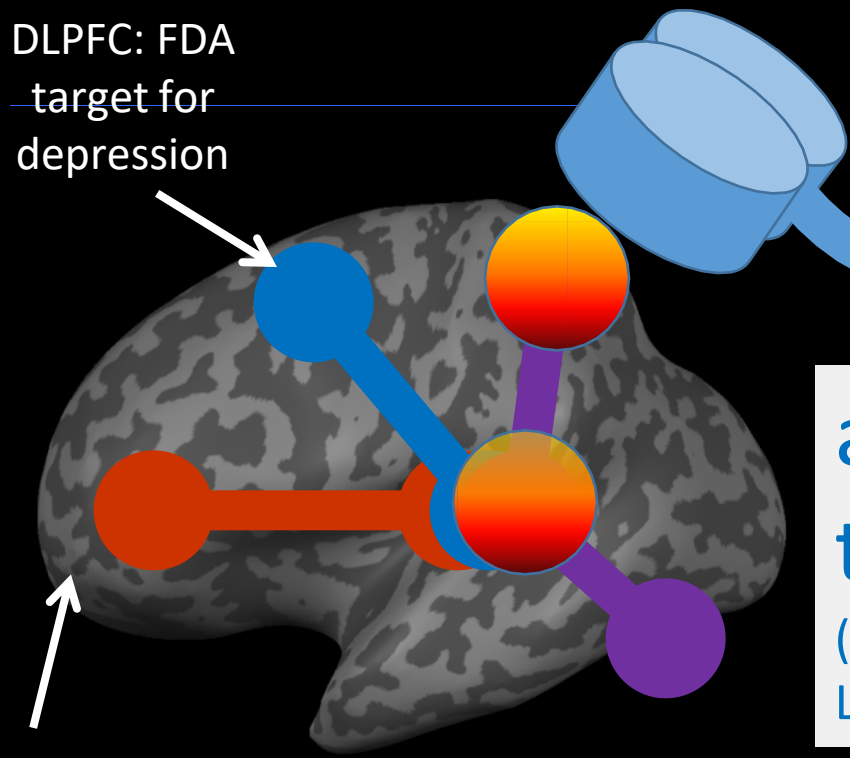
- TMS principle

*Insight from Preclinical Studies

*Insight from Clinical Research

Where?

Principle: Transcranial Magnetic stimulation can modulate frontal-striatal circuits



TMS ---> synaptic activity ~2cm under the coil

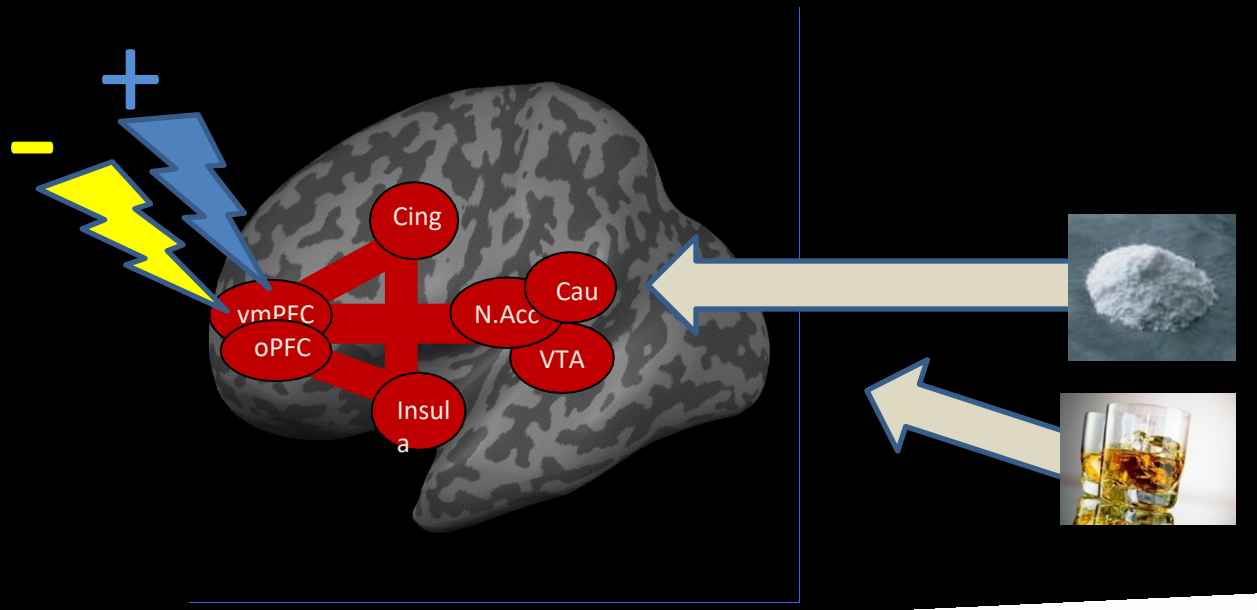
and monosynaptic striatal targets

(Strafella, George, Etkin, Daskalakis, Lisanby, Pascual-Leone)

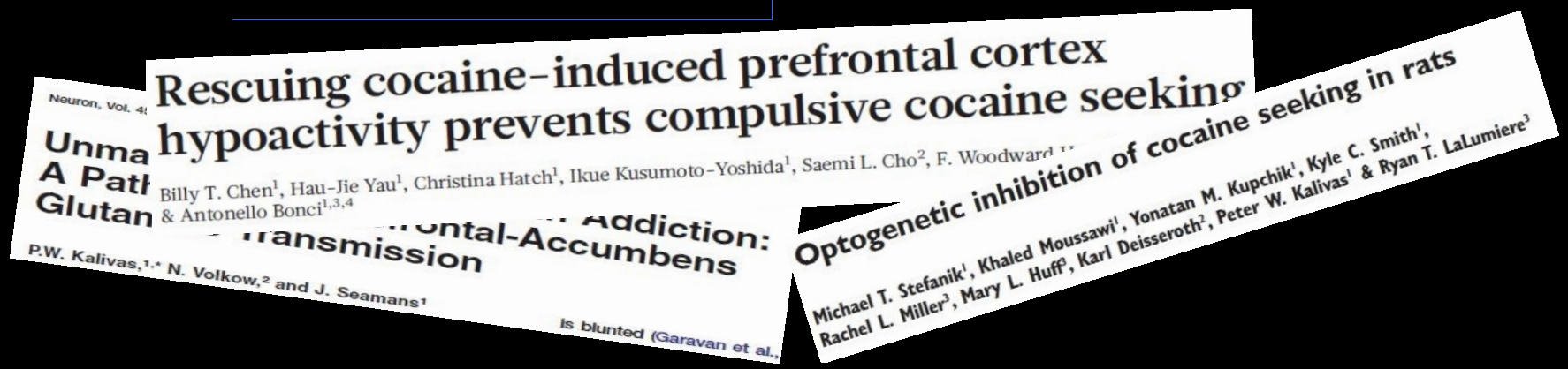
Where?

TARGET IDENTIFICATION:

Preclinical optogenetics demonstrates causal role of MPFC in drug-taking behavior



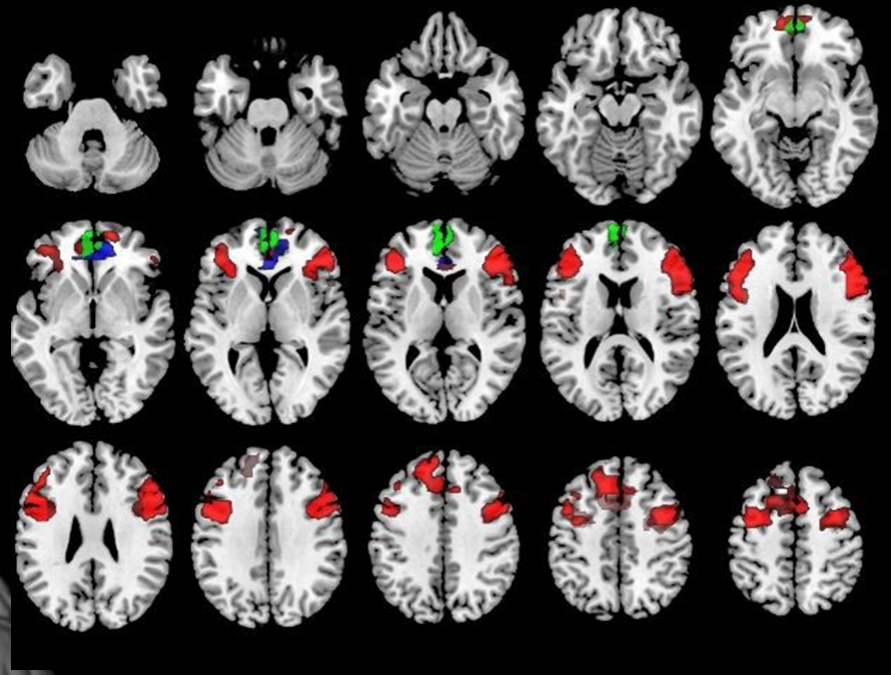
Chen et al 2013
Stefanik et al 2013
Seif et al 2013
Bass et al 2013
(and many others)



Where?

TARGET IDENTIFICATION:

Functional MRI demonstrates MPFC is transdiagnostic “hot spot” for drug cue-reactivity



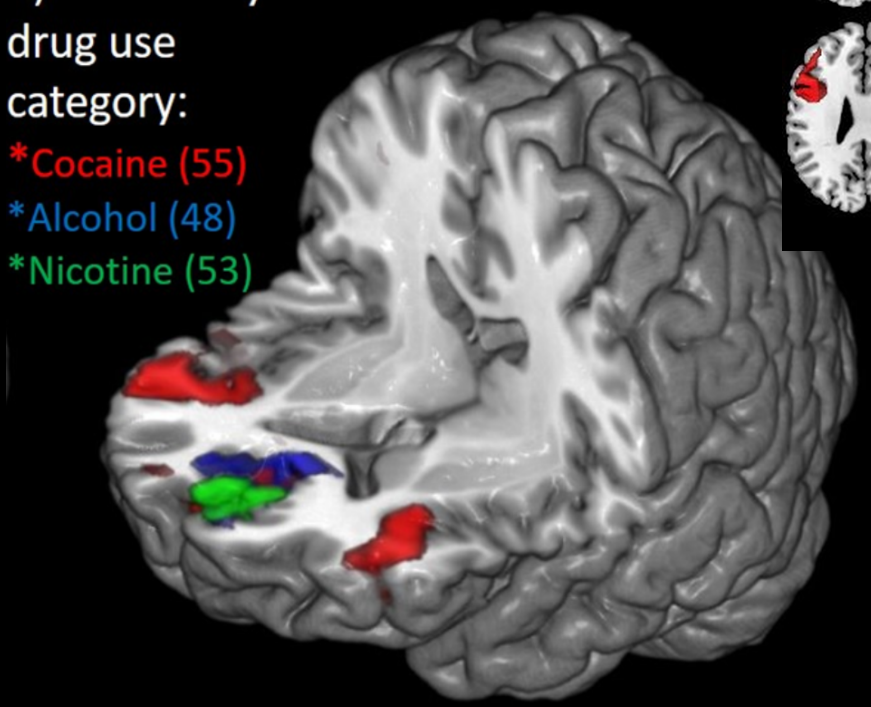
A) Aggregated data from all participants (n=156)

B) Divided by drug use category:

*Cocaine (55)

*Alcohol (48)

*Nicotine (53)

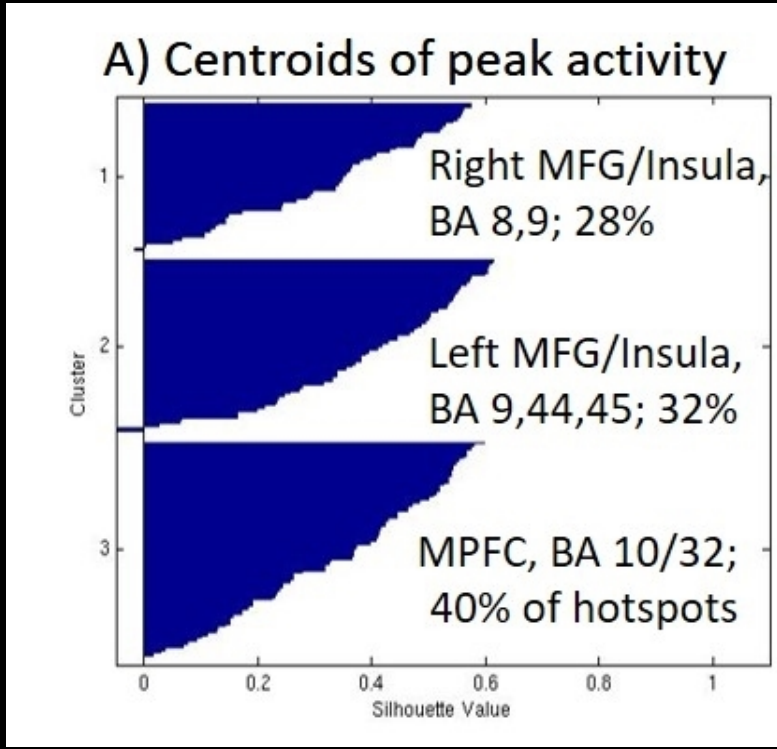


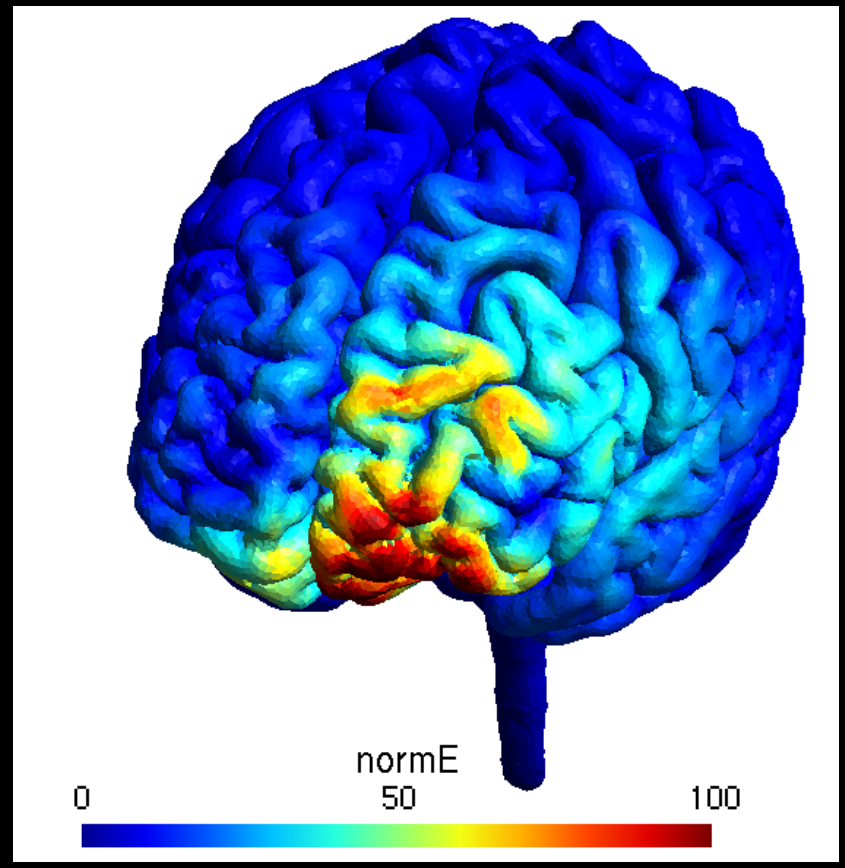
Hanlon et al, Translational Psychiatry, 2018

Where?

TARGET IDENTIFICATION:

The site most likely to directly effect cue-reactivity is the Frontal Pole (data from 156 individuals)

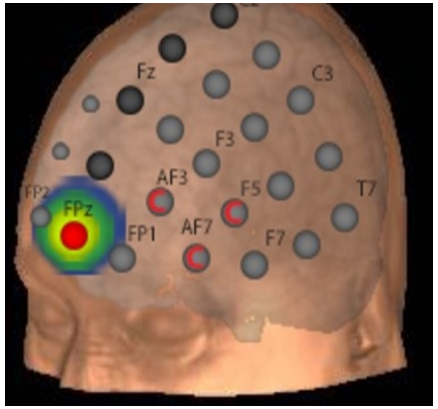




Electric Field Model (SimNIBS)

Hanlon et al, Translational Psychiatry, 2018

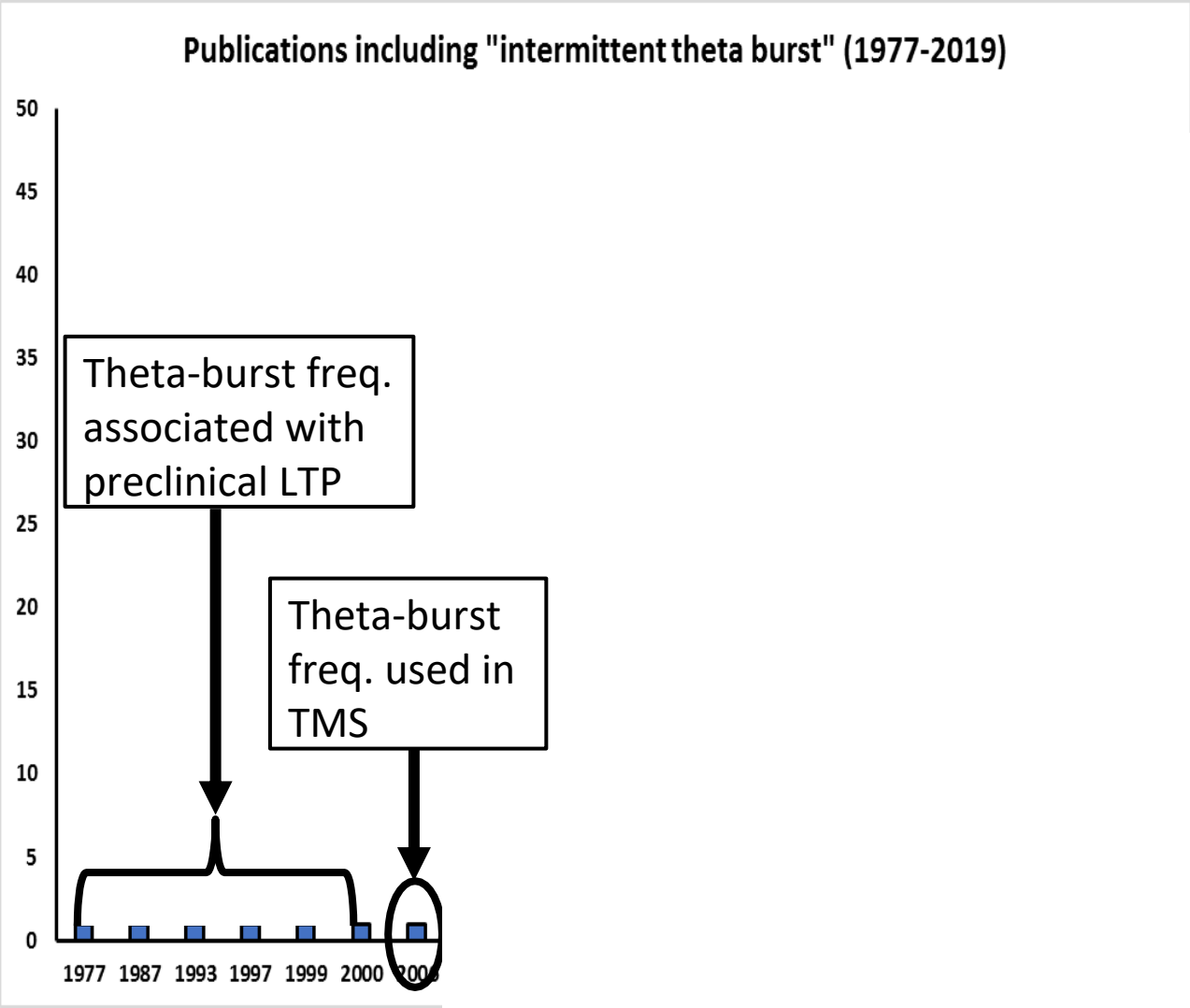
Where?

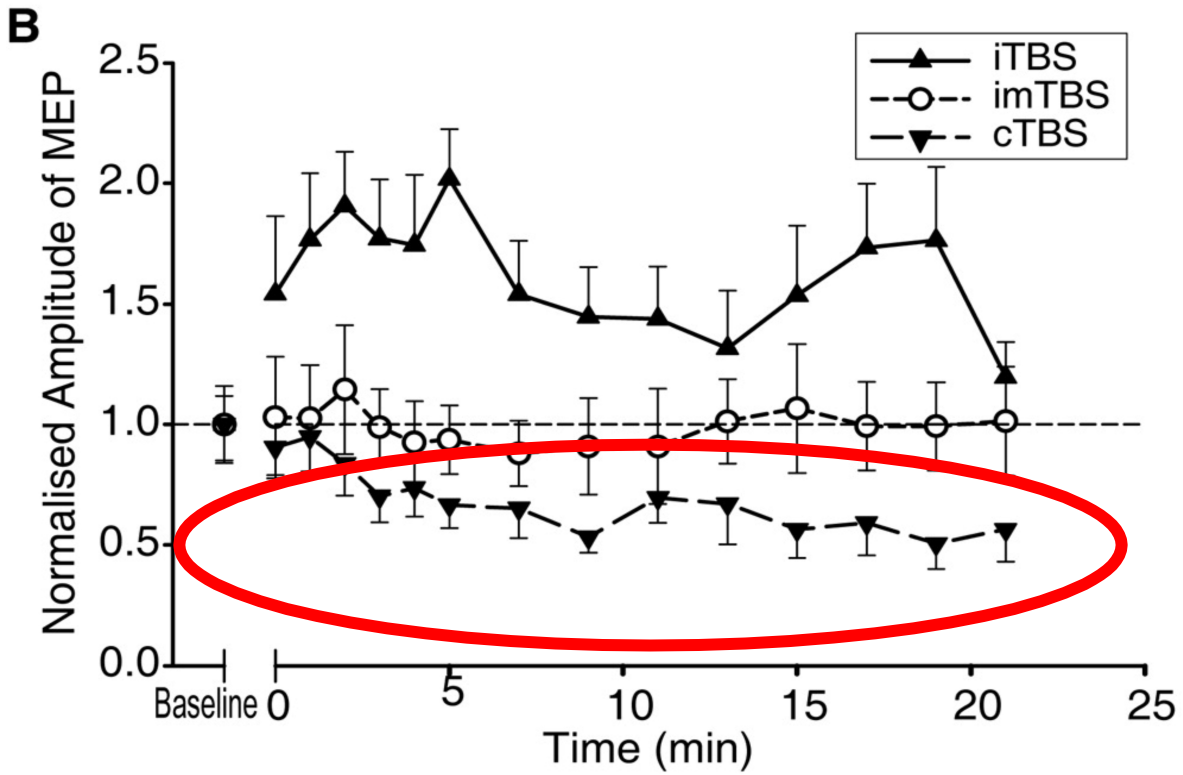


How Much?

Who?

Theta-burst popularized by Huang, Rothwell and colleagues 2005





Huang et al, 2005. *Neuron.*

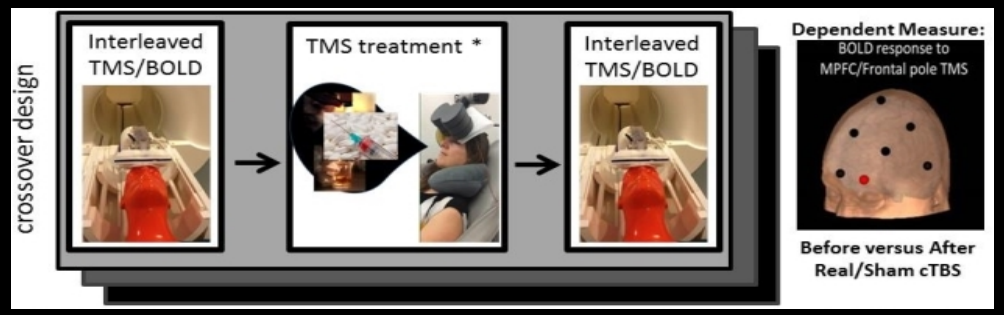
IMPORTANT METHODS ISSUE: TMS effects are amplified when paired with/primed by a task

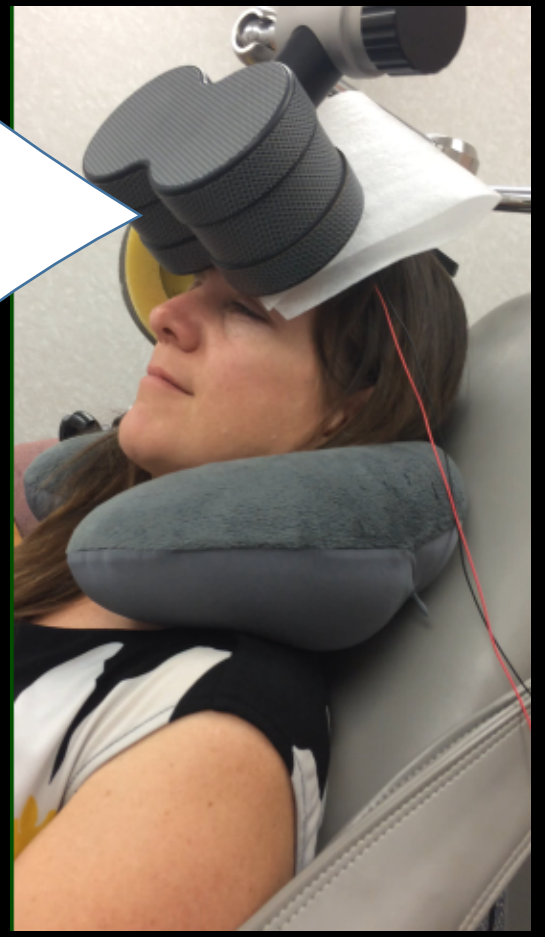
WHY SHOW CUES?

A PRIMED NEURAL CIRCUIT IS MORE PLASTIC THAN AN UNPRIMED CIRCUIT

Cue-exposure during TBS delivery

110% rMT (hand), cTBS
3600 pulses
(120 s ON, 60 s OFF, 120s ON)

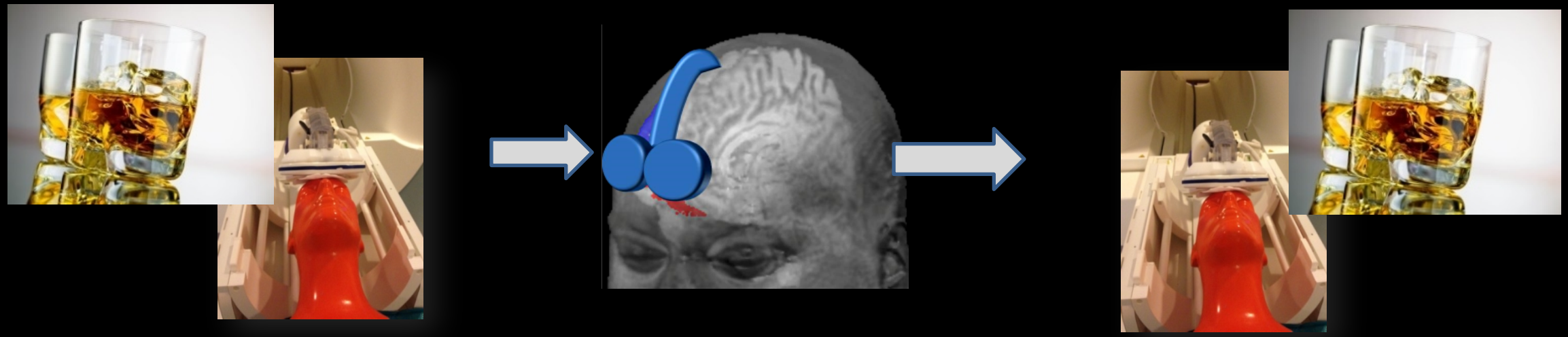




Hanlon et al 2017, Drug Alc. Dep.

FP/vMPFC Theta Burst Protocol

(designed based on brain-skull distance & total dose/ramp)



110% RMT, 3600 pulses

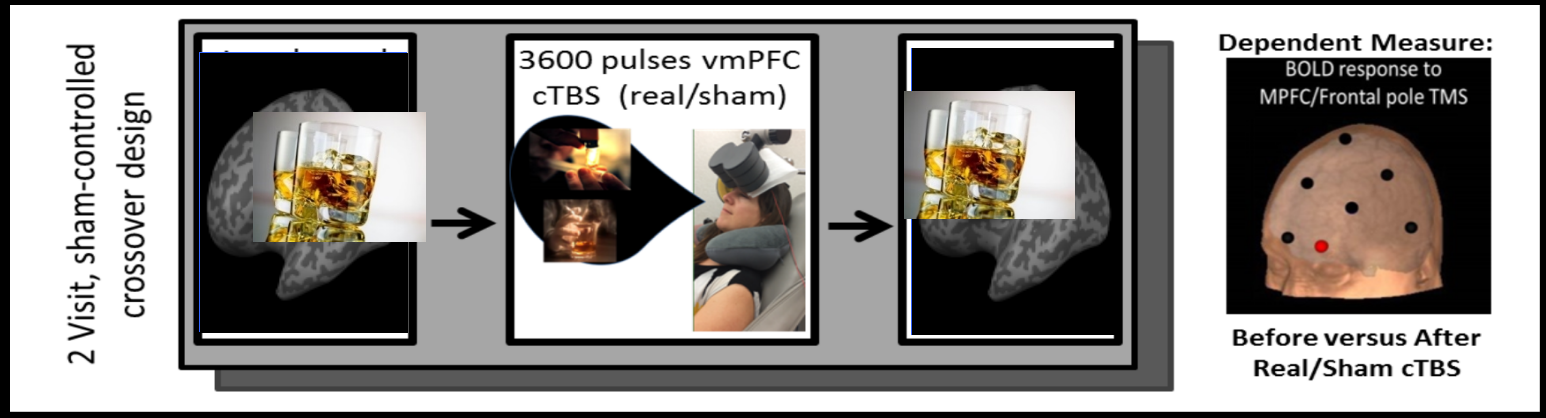
(2 trains: 1800pulses/train, 60s intertrain interval)

Active sham, 80-110% 15s ramp, Magpro Cool Sham coil

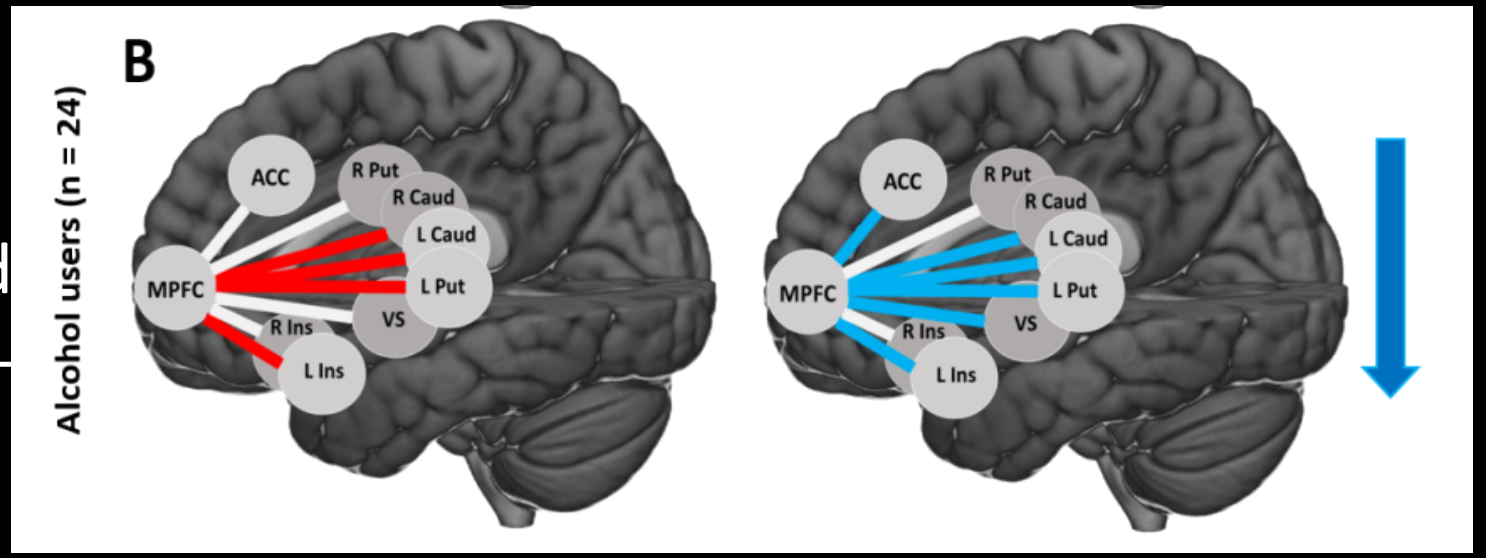
ENGAGEMENT- Can cTBS decrease alcohol cue-associated vmPFC-striatal activity in alcohol users?

Blinded, sham controlled study;

N=24 heavy alcohol users



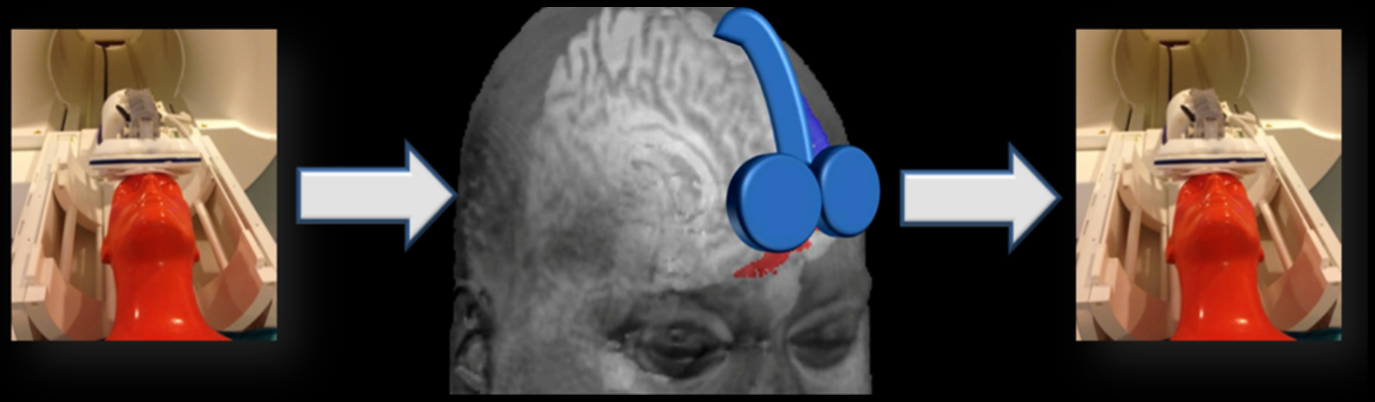
cTBS decreases MPFC-Striatal and MPFC- Insula Cue-reactivity



Kearney-Ramos et al, BioPsych:CNNI 2018

CLINICAL TRIAL: Can cTBS decrease alcohol relapse (via attenuation of cue reactivity)?

10 day (active) sham-controlled cohort study: Treatment-Engaged Cocaine Users/Alcohol Users



CBT Week 1

10 days, left vmPFC cTBS

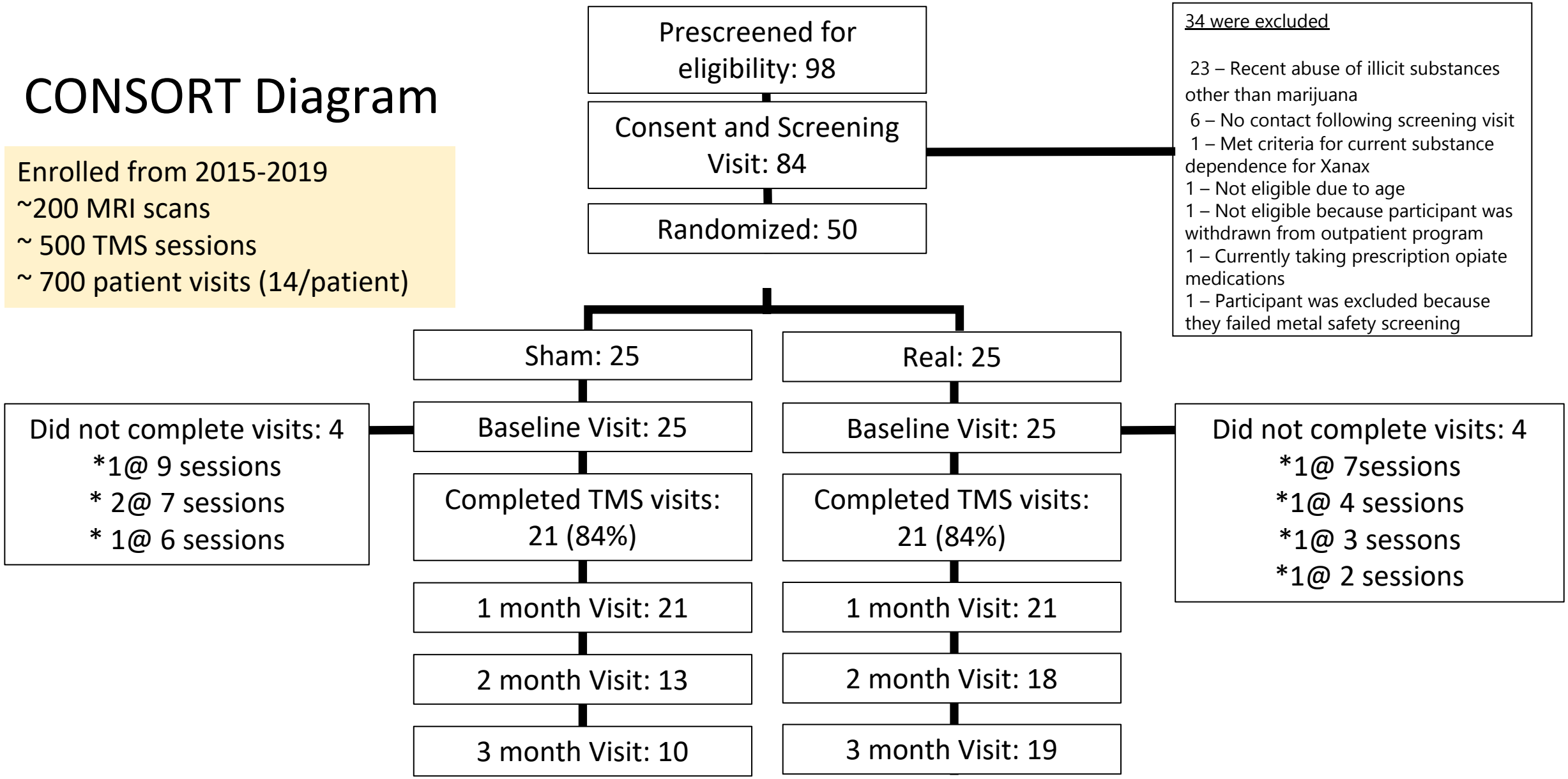
CBT Week 4

1m follow up

2m follow up

CONSORT Diagram

Enrolled from 2015-2019
~200 MRI scans
~ 500 TMS sessions
~ 700 patient visits (14/patient)



cTBS increases 3 month Sobriety

Demographics	TOTAL	Sham TMS	Real TMS
Participants	50	25	25
Men/Women	32/18	16/9	16/9
Age	46	46.2 (12.1)	45.8 (11.5)
Race (HHS catagories)		19W, 5B, 1As	22W, 1B, 1Na
% Cigarette Smoker	58	52	64
BDI	18.9	17.3 (9.7)	20.5 (13.3)
STAI-Trait	47.9	47.3 (14.6)	48.5 (14.2)
AUDIT	25.8	26.0 (5.6)	25.6 (5.8)
Age First Use:	16.4	16.9 (6.8)	15.9 (7.7)
Duration of Use:	28.2	27.7	28.7

"Patients that received Sham TMS were nearly half as likely to be sober as those that received Real TMS"

IMPORTANT CLINICAL TRIAL STATS:

% Sober in last month	
Baseline	
1 month	
2 month	
3 month	

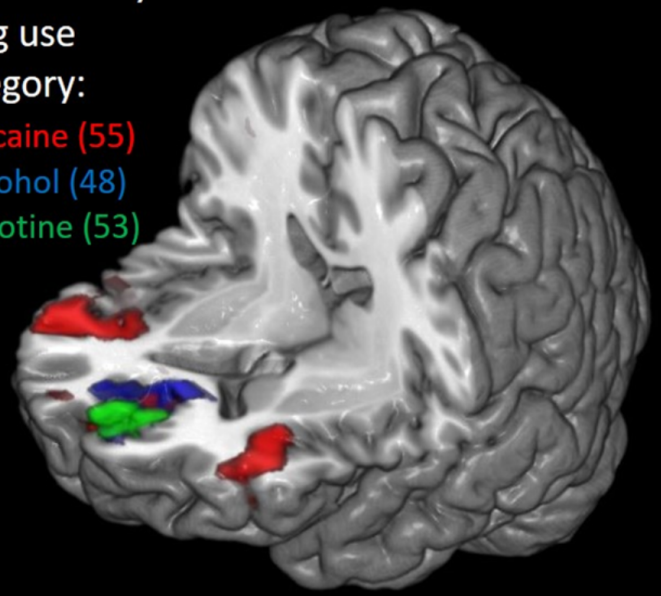
Individual Variability in Alcohol Cue Reactivity

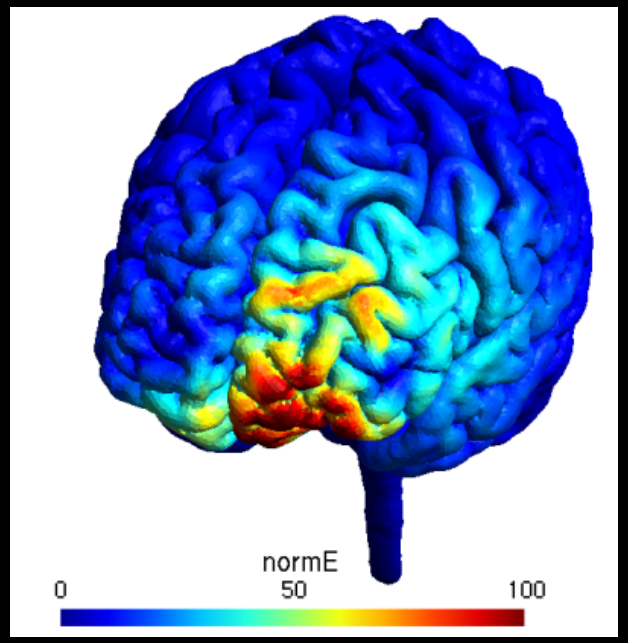
The Data-Based Foundation (Group-Averaged Data)

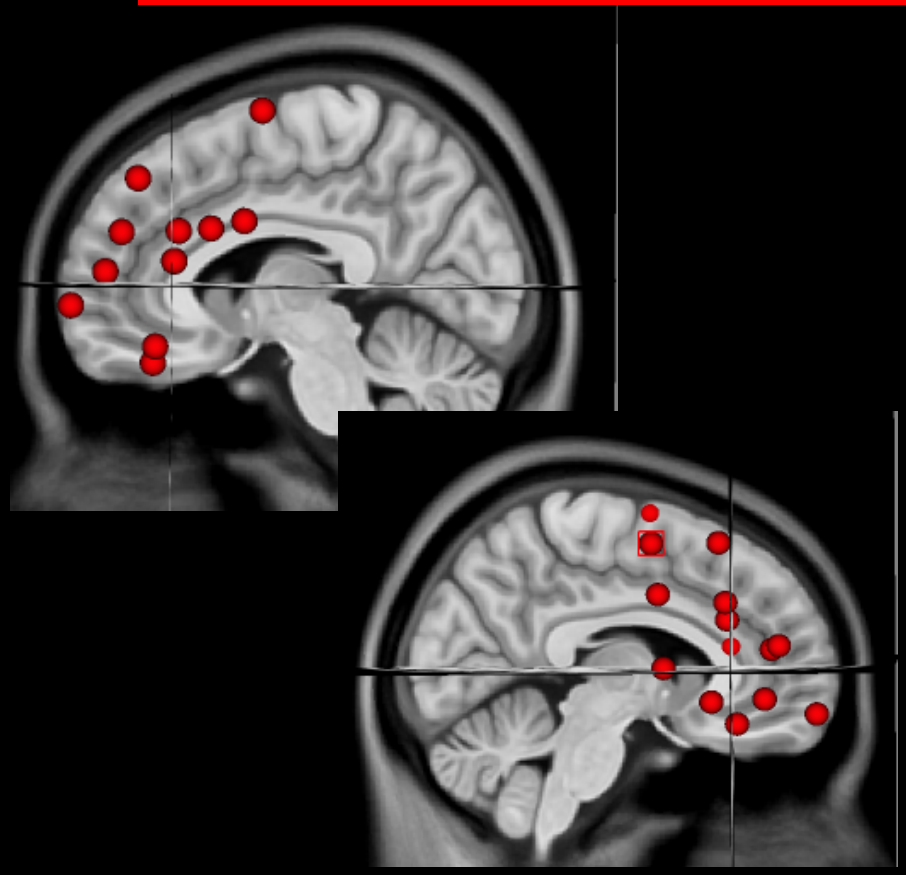
The Computational Model

The Messy Reality for Each Individual

B) Divided by drug use category:
*Cocaine (55)
*Alcohol (48)
*Nicotine (53)

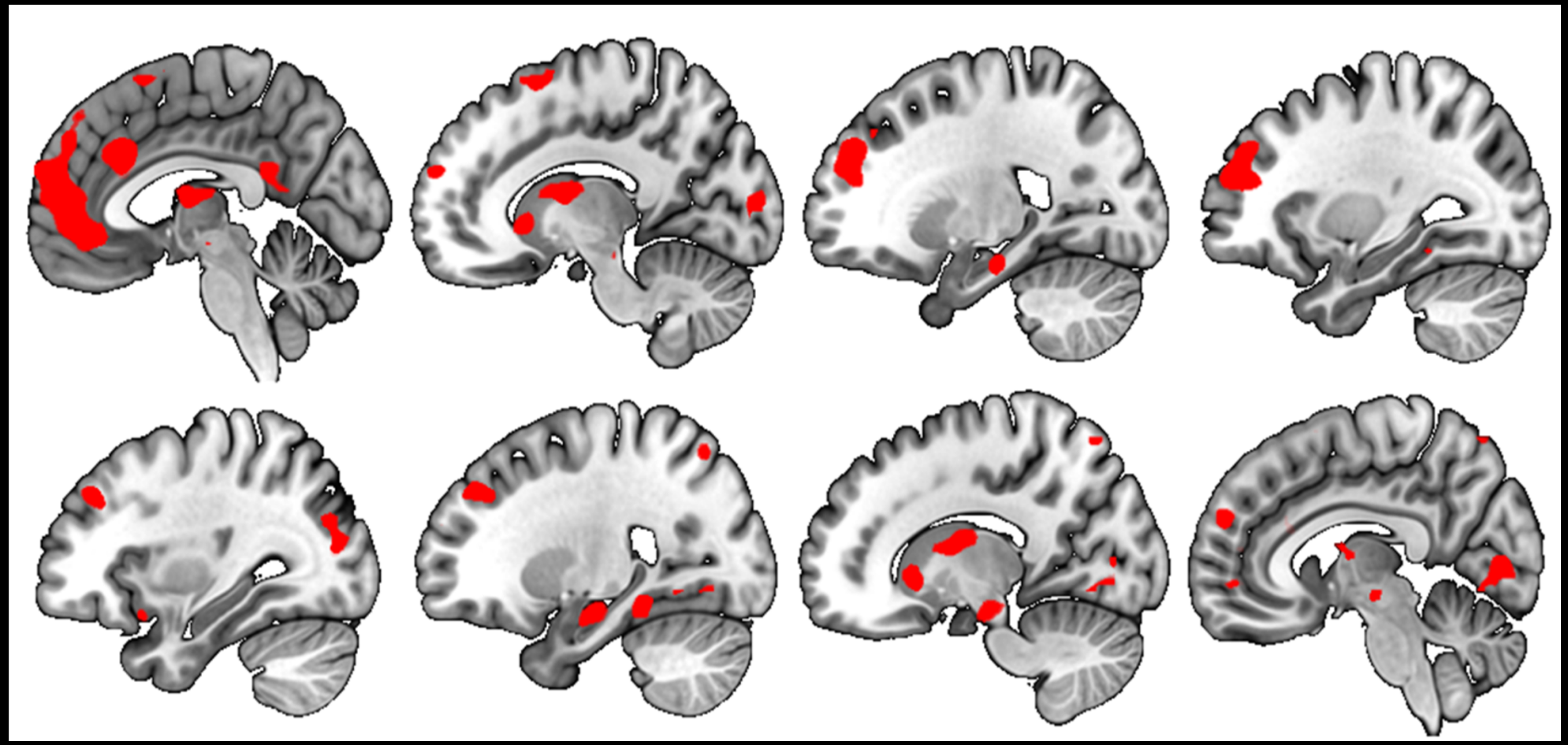






Average Alcohol Cue Reactivity (n=67)

Severe Moderate AUD At Risk Drinkers



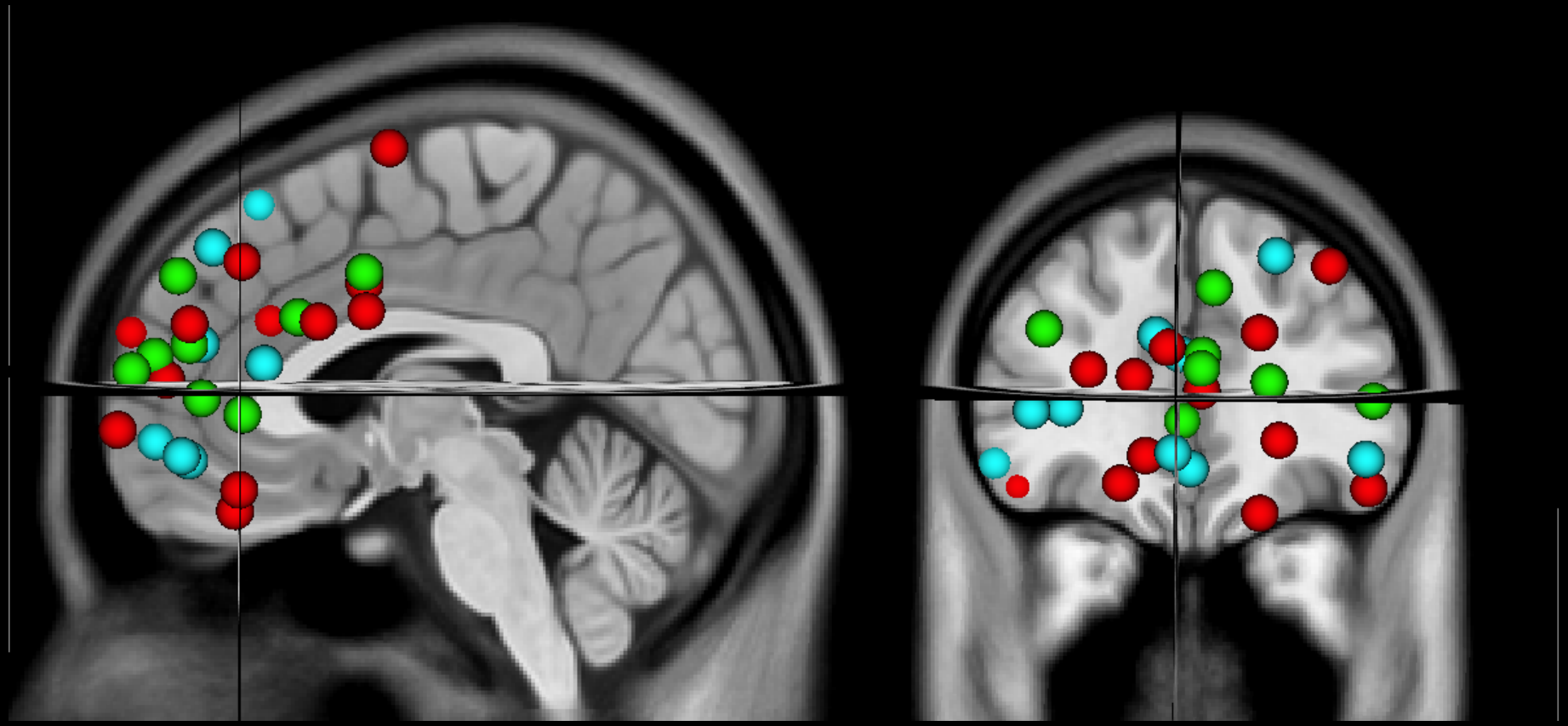
- Etoh > neutral cues
- thresholded at p=0.001, k>25.
- Strong activation in the PFC/ACC, visual cortex and striatum.

Individual Variability in Alcohol Cue Reactivity: Severe vs Moderate AUD vs At Risk Drinkers

The area of peak BOLD signal evoked by Alcohol versus Non-alcoholic beverage Cues

67 Individuals

AUDIT 20+ = Severe AUD
AUDIT 15-19 = Moderate AUD
AUDIT 8-14 = At Risk for AUD



Individual Variability in Alcohol Cue Reactivity

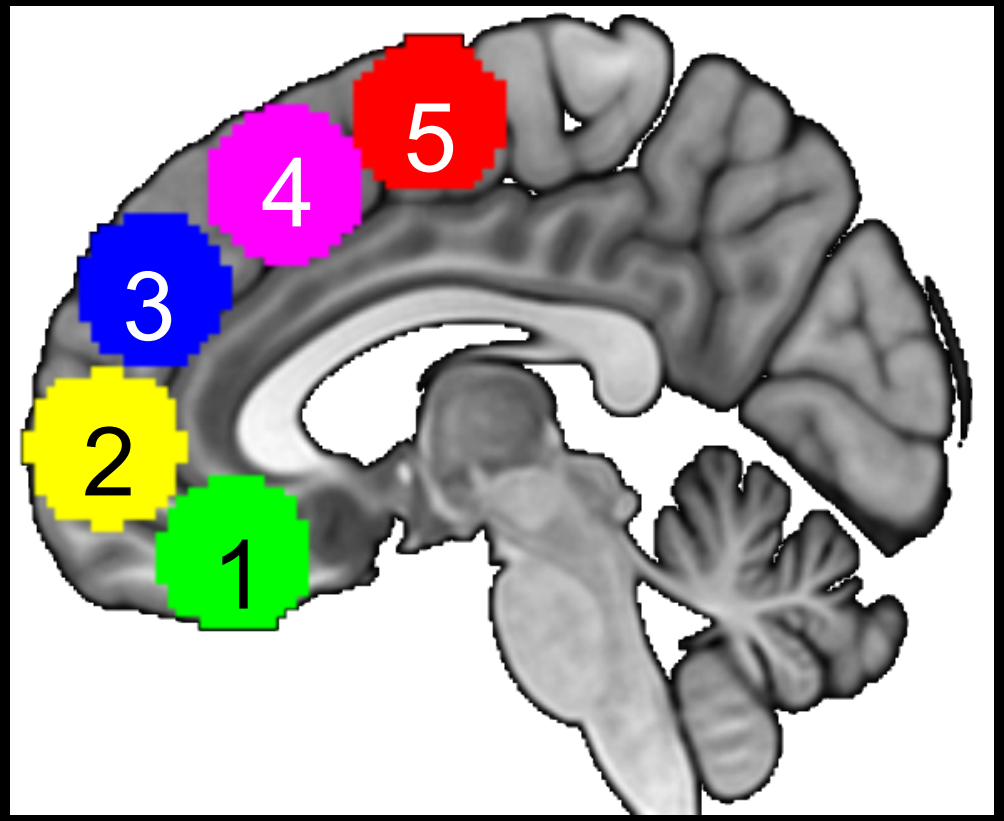
The area of peak BOLD signal evoked by Alcohol versus Non-alcoholic beverage Cues

67 Individuals

Individual Variability in Alcohol Cue Reactivity

The area of peak BOLD signal evoked by Alcohol versus Non-alcoholic beverage Cues

67 Indiviudals



OFC

vMPFC

dMPFC

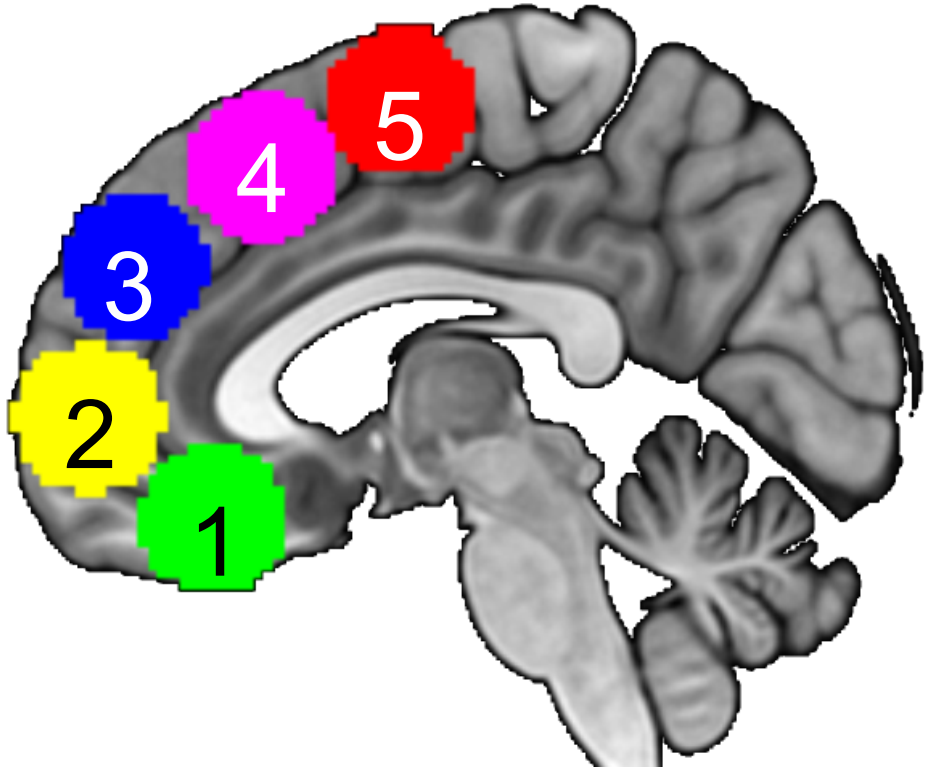
pre-SMA

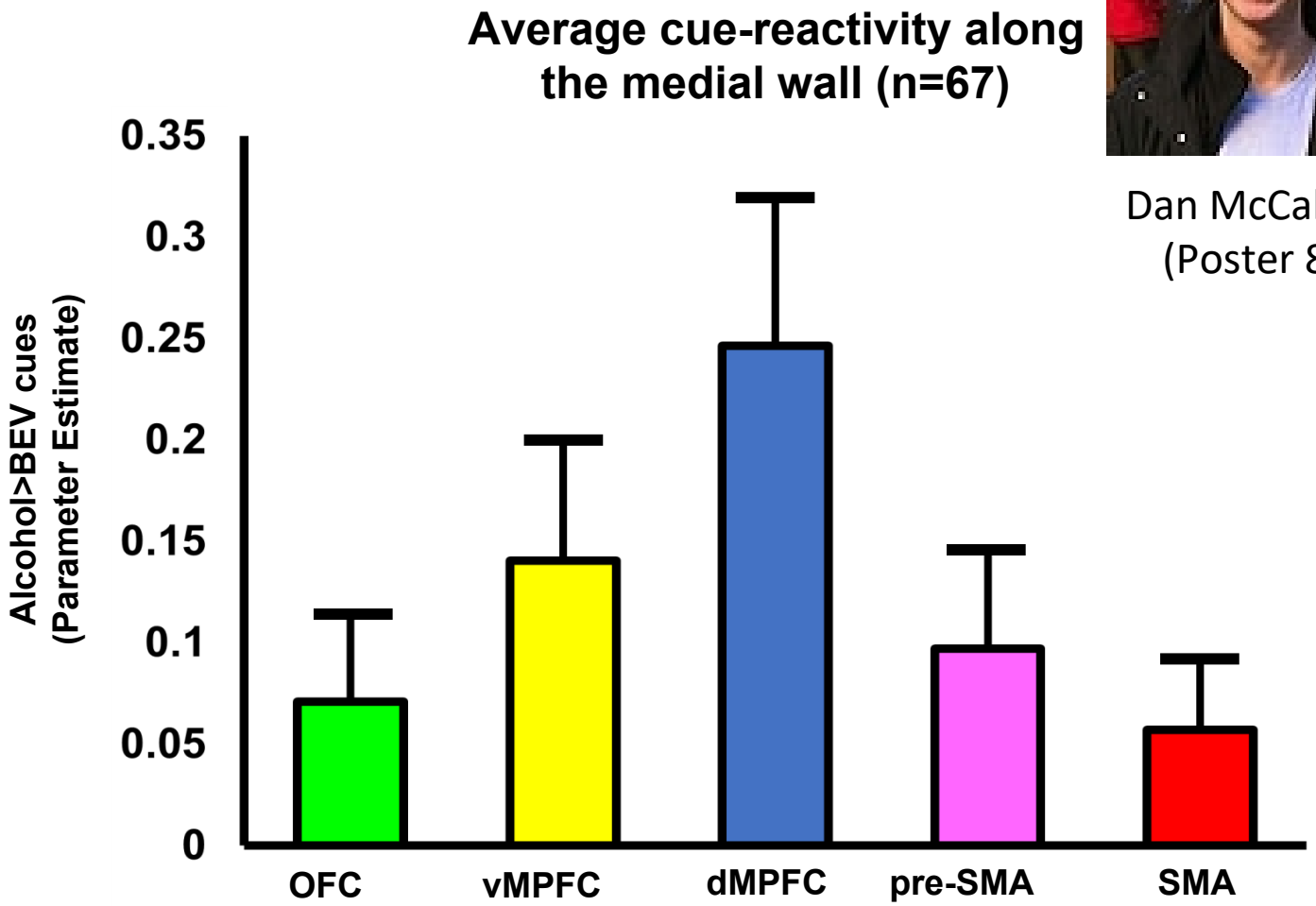
SMA

Dan McCalley
(Poster 8)

5, 15mm bilateral spherical ROIs.
Center of spheres 1, 4 and 5 matches the center of mass from pre-existing AAL ROIs.

Center of 2 and 3 were defined manually along the same X coordinate (same position along the medial wall)





F(3,330)=2.114, p=0.079

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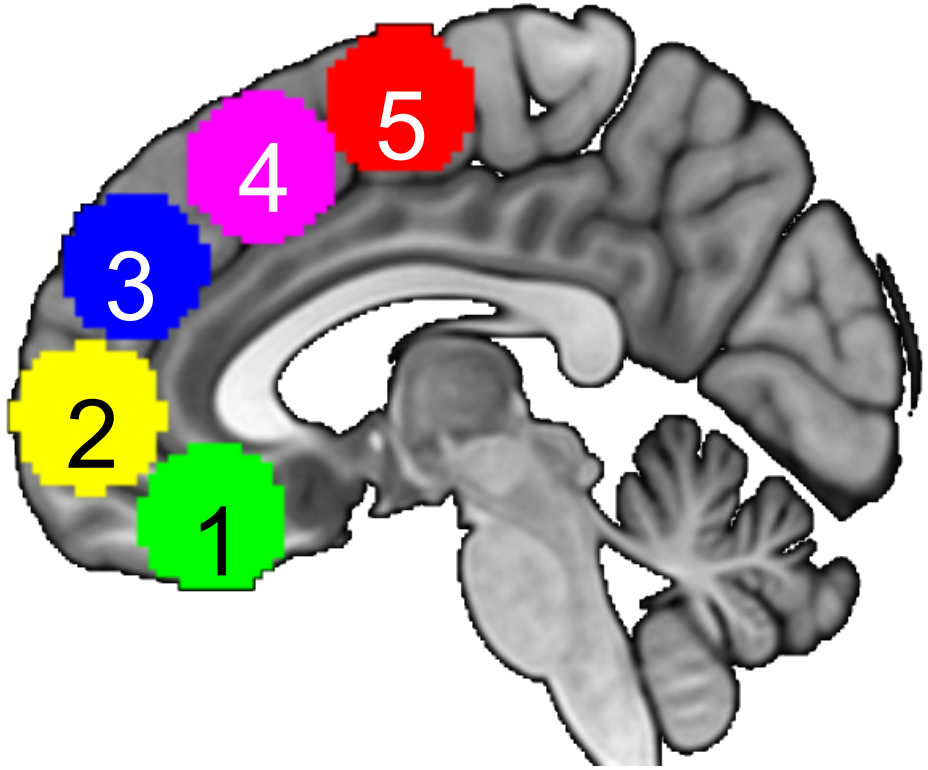
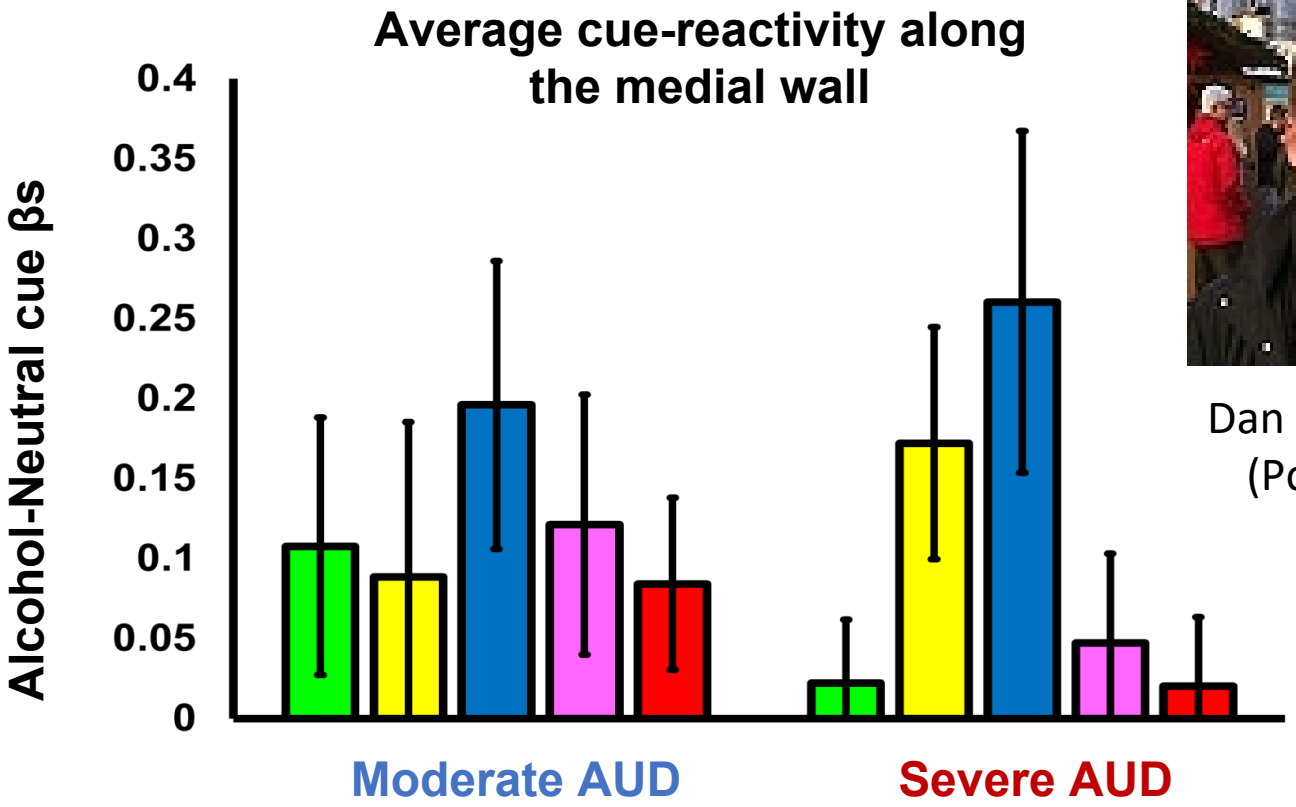
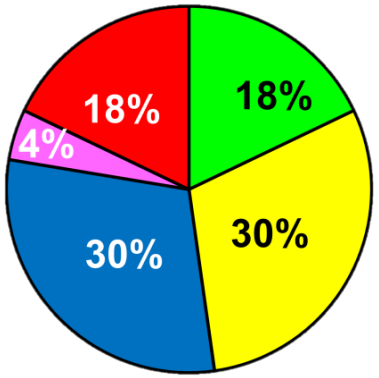
(Poster 8)

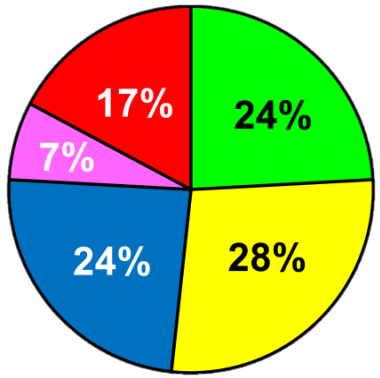




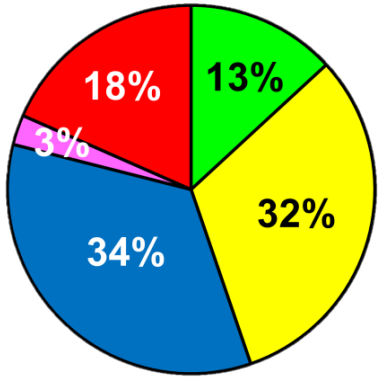
Dan McCalley
(Poster 8)



All
(n=67)



Moderate AUD
(n=29)

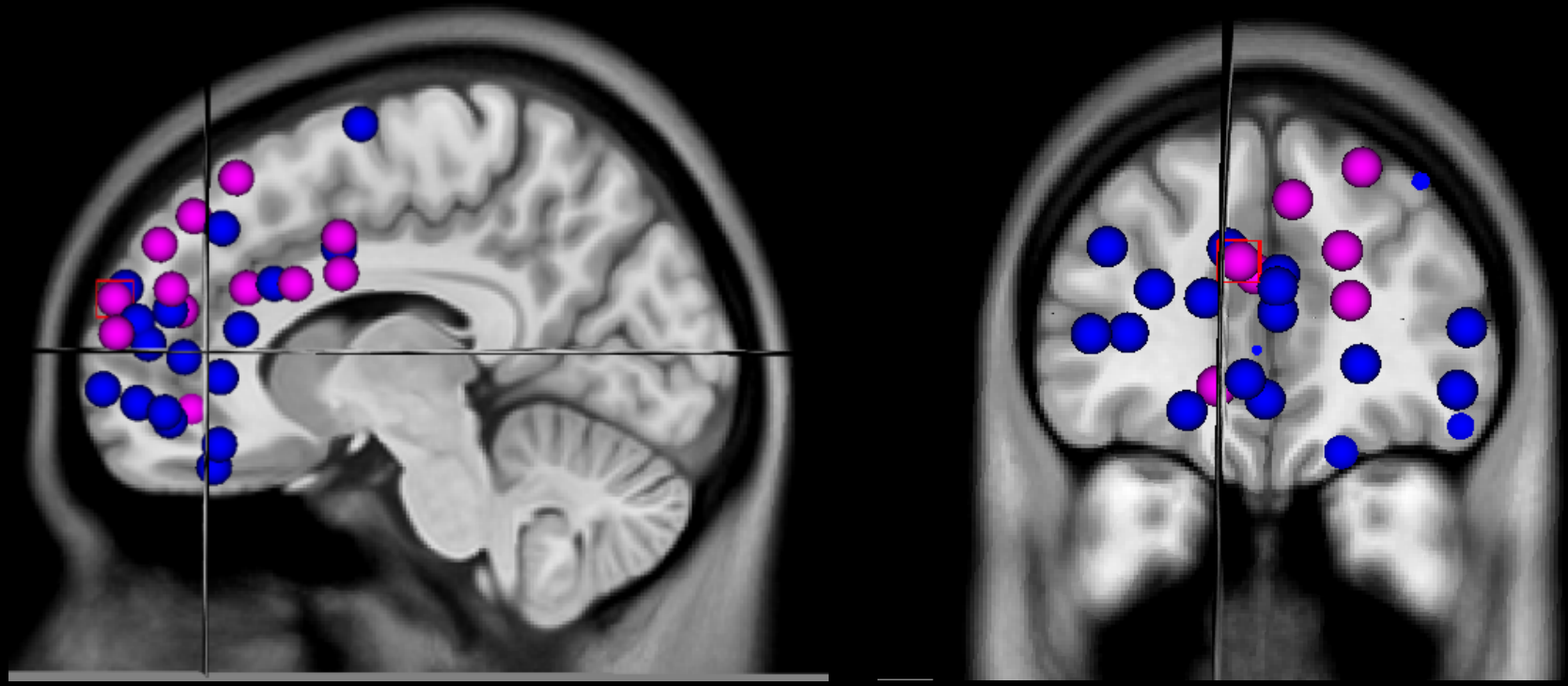


Severe AUD
(n=38)

Individual Variability in Alcohol Cue Reactivity: Men versus Women

The area of peak BOLD signal evoked by Alcohol versus Non-alcoholic beverage Cues

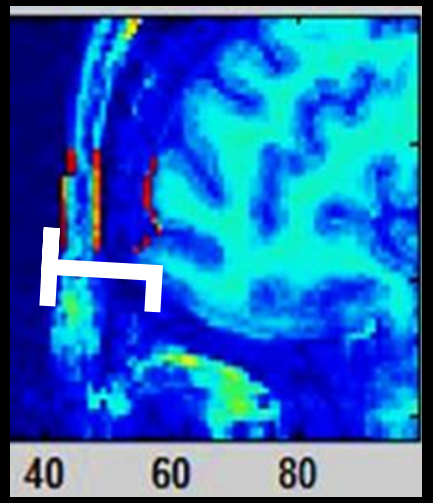
67 Individuals



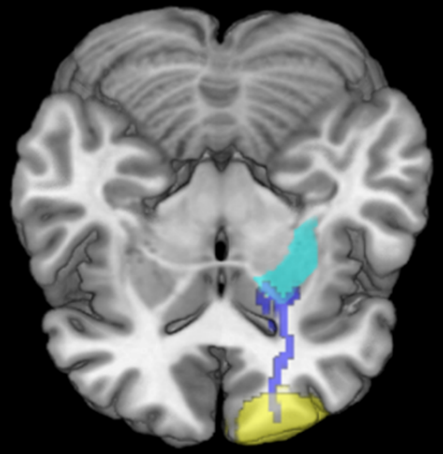
Individual Variability – Baseline striatal activity influences TMS-related change

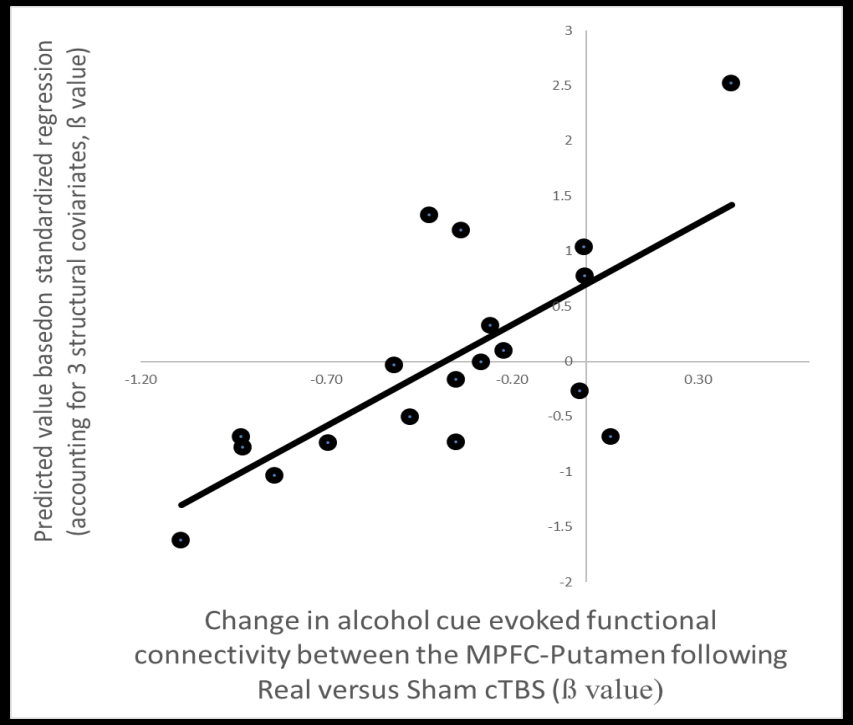
Measured aspects of neural architecture

Scalp to Cortex Distance



Gray matter volume at cortical target (yellow) and White Matter integrity to subcortical target (blue)





Hanlon et al. Clin Therap. 2019

TMS for Cue-reactivity: Logical progression of development 2013-2019

Step 1: Which **circuit should we choose?**
TARGET IDENTIFICATION **(2014, DAAD; 2016 Neuropsychopharm)**

Step 2: Can we "reach" the frontal pole/vmPFC? (2015, Neuropsychopharm; 2017, Brain Stimulation)

Step 3: Can we modulate it in healthy individuals? (2015, PlosOne; 2018 BrainStim)

Step 4: Can we induce transient change in this circuit TARGET ENGAGEMENT **(2017, DAAD; 2018, BioPsych:CNNI)**

Step 5: Can we induce sustainable LTP/LTDin this circuit TARGET CLINICAL TESTING **(unpublished, & in progress)**

Step 6: Tailoring treatment to our patients - impulsive versus compulsive choice….. REFINING TARGET IDENTIFICATION

Will the best TMS stimulation site for AUD be dependent on the Stage of Addiction/ Symptom Profile/ Biotype?

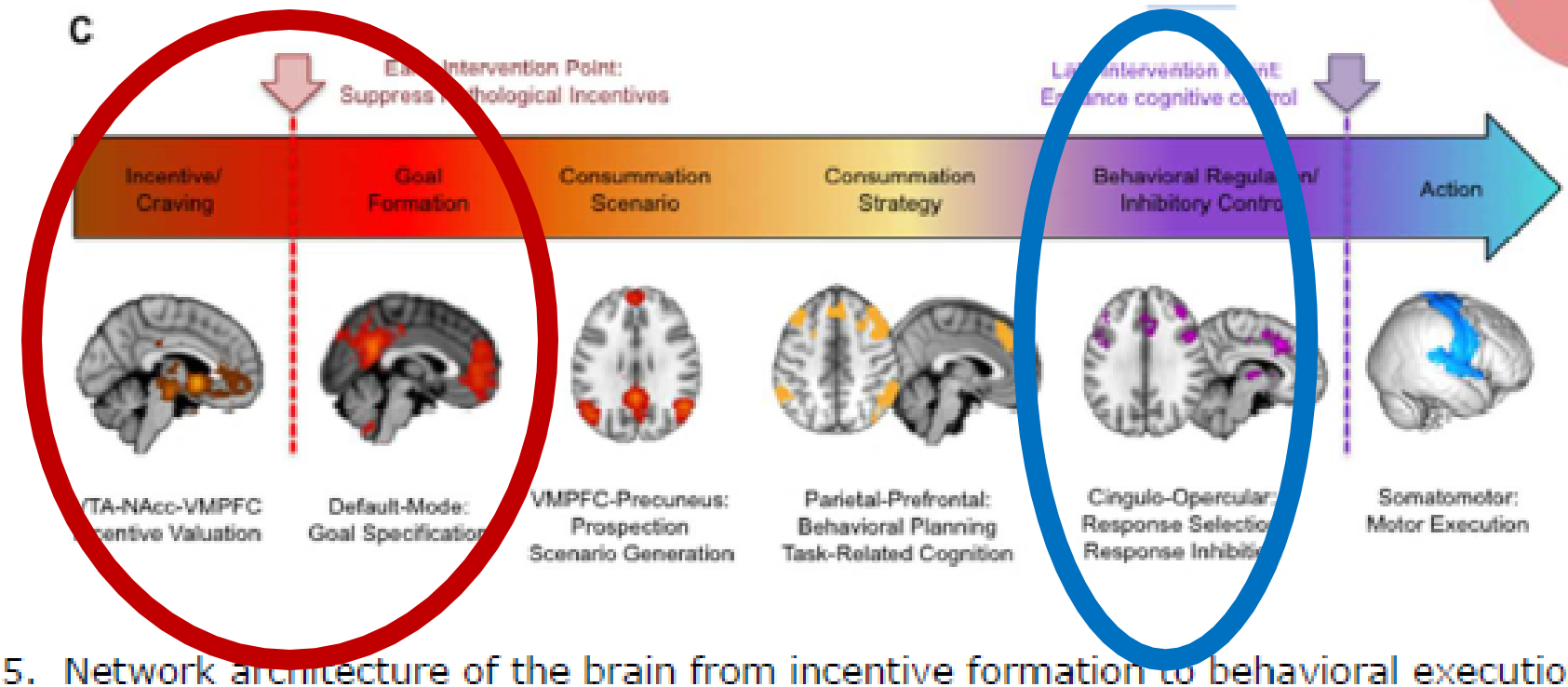


Figure 5. Network architecture of the brain from incentive formation to behavioral execution. A. The

Adapted from Powers et al 2011 – Included as Figure 5 in Dunlop, Hanlon, Downar, 2016

Acknowledgements

MUSC team

Daniel McCalley (POSTER 8!!)

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Kathleen T. Brady, MD PhD

Raymond Anton, MD

Howard Becker, PhD

Truman Brown, PhD

Elliot Stein, PhD

NIAAA National Institute on Alcohol Abuse and Alcoholism

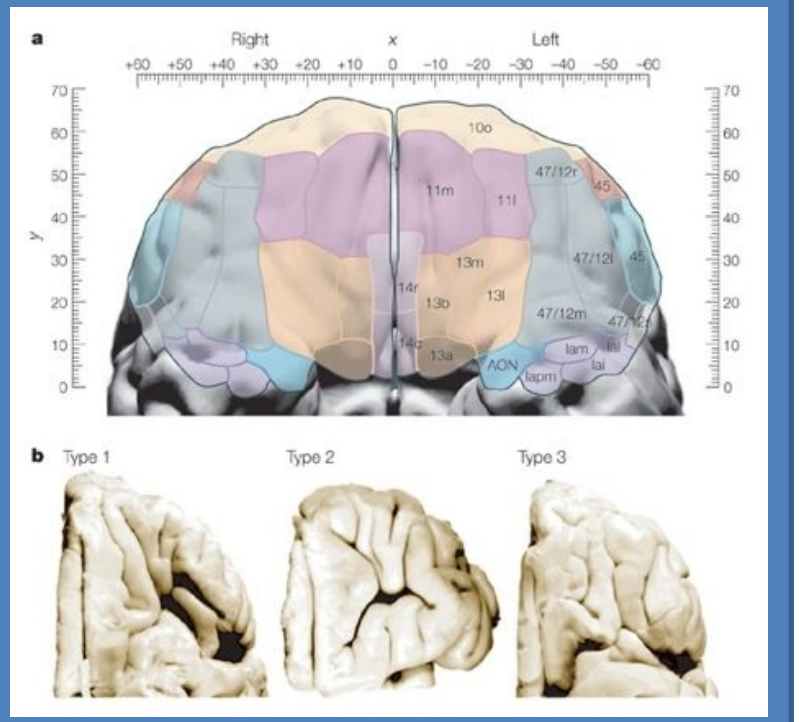
NIDA NATIONAL INSTITUTE ON DRUG ABUSE The Science of Drug Abuse & Addiction

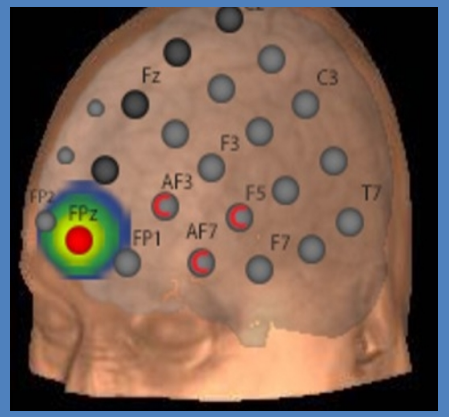
R01DA036617 (Hanlon), R21 DA 0412244 (Hanlon), P50 AA010761 (Becker), T32 007474 (Woodward), K05 AA017435 (Anton)

Postdoc & Engineer WANTED! Do you like Electricity? Can you code? Want to try humans? Contact me! @brainstimgrl

chanlon@wakehealth.edu

Are we stimulating the vMPFC or the OFC?

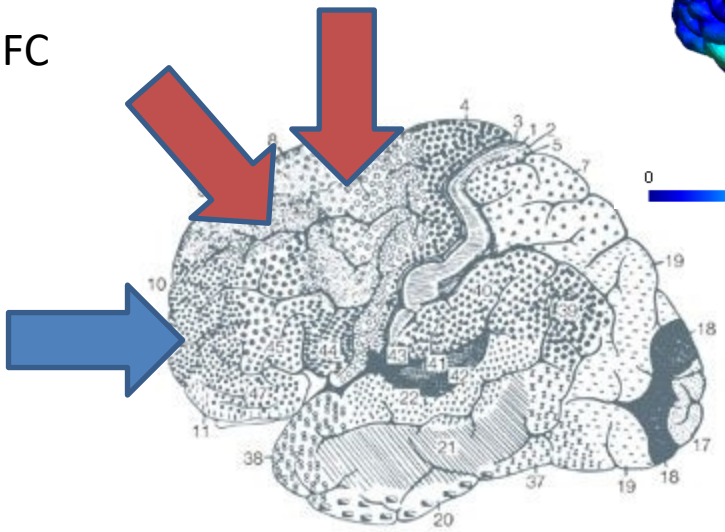


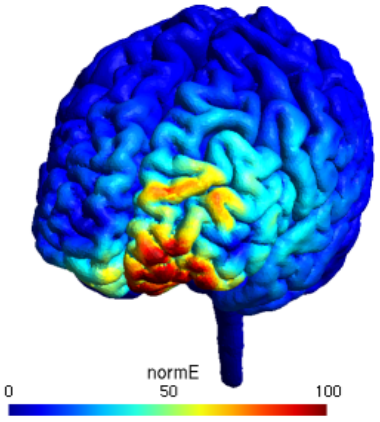


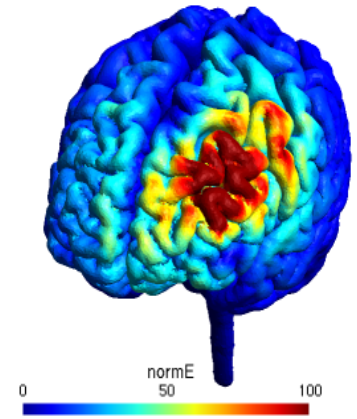
dmPFC/ACC- H7

dmPFC

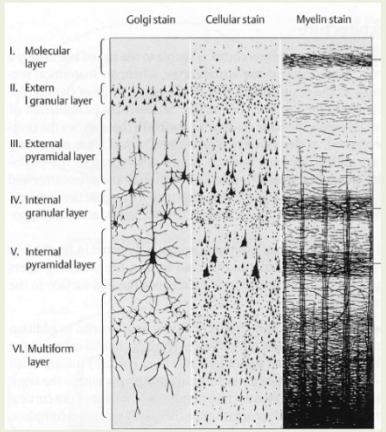
vmPFC/ frontal pole target

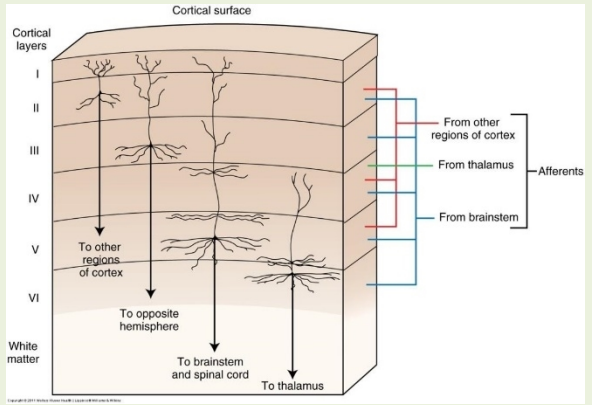






Cytoarchitectural Difference in Motor vs Prefrontal





Motor Cortex = Agranular (no layer 4)

PFC = Granular Cortex (dense layer 4, DM Thalamus inputs)

Baseline Alcohol Cue Reactivity in Clinical Trial:

Relapsers (2 month

Abstainers

The area of peak BOLD signal evoked by Alcohol versus Non-alcoholic beverage Cues

67 Individuals