



Where do harmful drinking urges come from?



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ARC

What is harmful drinking?

What makes it "harmful?"

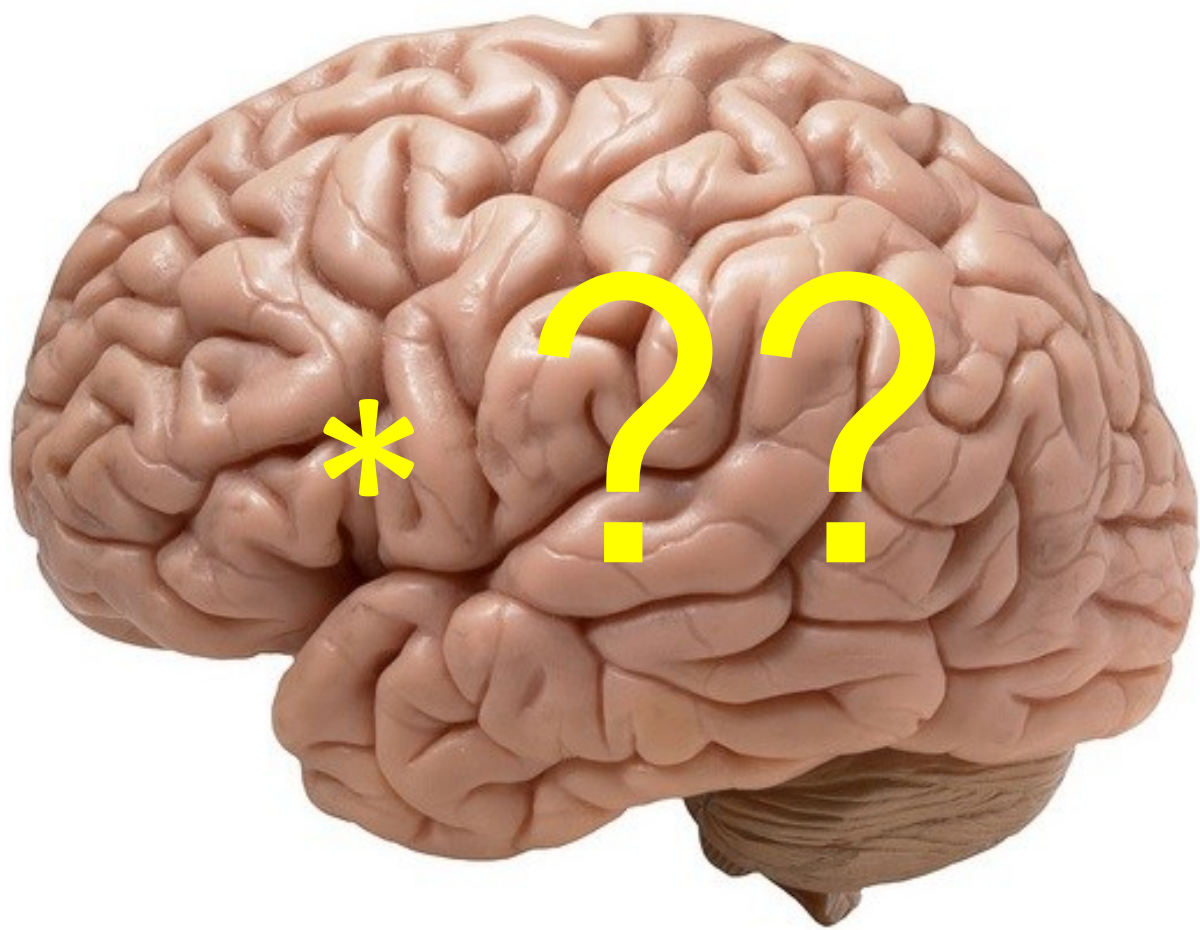
How much alcohol is "safe?"

What is harmful drinking?

What makes it "harmful?"

How much alcohol is "safe?"

**Apologize ahead of time for bringing up
uncomfortable observations**



Social alcohol drinking



Social alcohol drinking



Binge alcohol drinking



Moderate drinkers become binge drinkers

Binge drinking: 4-5 drinks in 2 hours

Binge alcohol drinking



Binge drinking: 4-5 drinks in 2 hours

Binge alcohol drinking



What is Binge Drinking?



4 DRINKS 
in  2 HOURS



5 DRINKS 
in  2 HOURS

The Cost of AUD (Alcohol Use Disorder)

>\$250 billion and ~90,000 preventable deaths in the US every year

**Health, Social, Family, Legal,
Economic, Domestic Violence,
Collisions while Driving**

The Cost of Binging

>\$250 billion and ~90,000 preventable deaths in the US every year

The Cost of Binging

>\$250 billion and ~90,000 preventable deaths in the US every year

The 1/7th of US adults that are binge drinkers

consume 3/4th of the cost



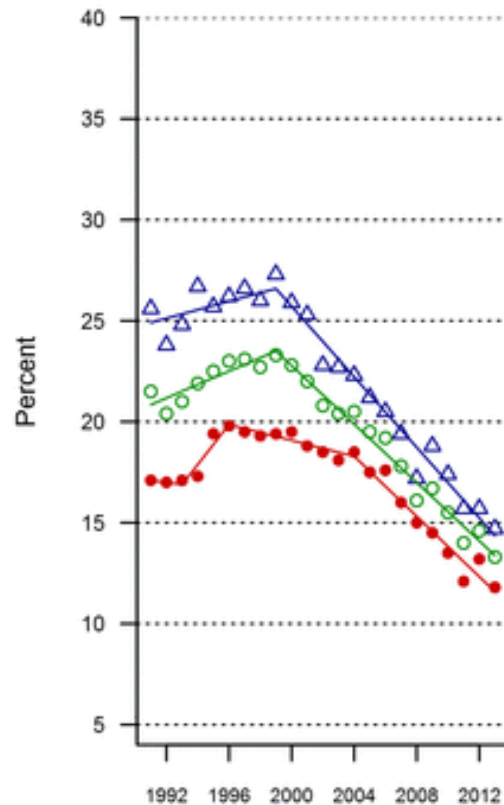
**Between 2002 and 2013, female
alcoholism increased by 84%**

National Institute on Alcohol Abuse and Alcoholism, 2017

<https://www.niaaa.nih.gov/>

Young people are drinking less

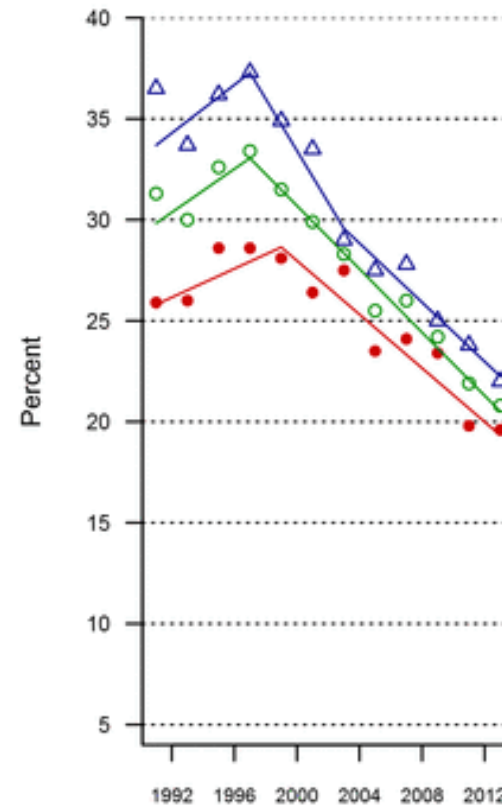
MTF: in the past 2 weeks/
among 8th, 10th, and 12th graders



1992

2012

YRBS: in the past 30 days/
among 9th–12th graders



1992

2012

Red: females
Blue: males

Binge drinking

Binge alcohol drinking



Compulsive alcohol drinking: Intake despite bad consequences

Binge alcohol drinking



Compulsive alcohol drinking

Pardon Me, Officer, While I Finish My Beer



Associated Press

Compulsive alcohol drinking: **Intake despite bad consequences**

Binge alcohol drinking



Compulsive alcohol drinking

Pardon Me, Officer, While I Finish My Beer



Bingers become compulsive drinkers

Compulsive alcohol drinking: Intake despite bad consequences

Binge alcohol drinking



Compulsive alcohol drinking

Pardon Me, Officer, While I Finish My Beer



moderate to high risk of harm

Bingers become compulsive drinkers

I know I shouldn't but I do it anyways

DSM-V: Addiction defined as "Choice to drink despite known cost"

Binge alcohol drinking



Compulsive alcohol drinking

Pardon Me, Officer, While I Finish My Beer



"Choice to drink despite cost" drives addiction

Binge alcohol drinking



Compulsive alcohol drinking

Pardon Me, Officer, While I Finish My Beer



"Choice to drink despite cost" allows addiction

Binge alcohol drinking



Compulsive alcohol drinking

Pardon Me, Officer, While I Finish My Beer



**How do we “put things out of our minds”
or “avert our eyes”**

**Where does "Choice to drink despite cost"
come from in the brain?**

Where does “Choice to drink despite cost” come from in the brain?

Can we use rats/mice to help identify
key addiction-driving

- (1) brain areas,
- (2) molecules, and
- (3) “psychological” mechanisms
(thoughts, mindstates)

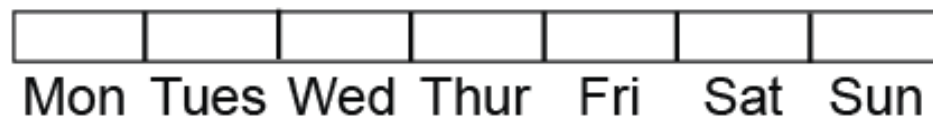
and Develop new therapies
(behavioral and drug-based)

Drinking alcohol from a bottle:



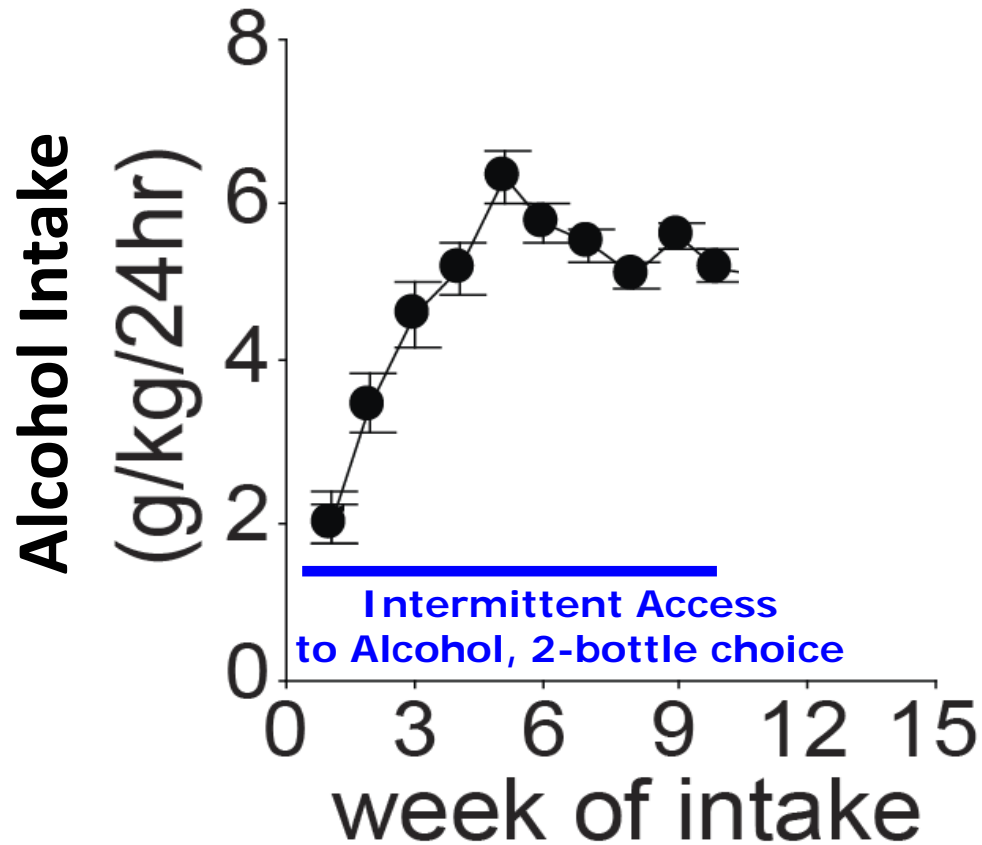


■ = 2-bottle choice for
20% alcohol or water

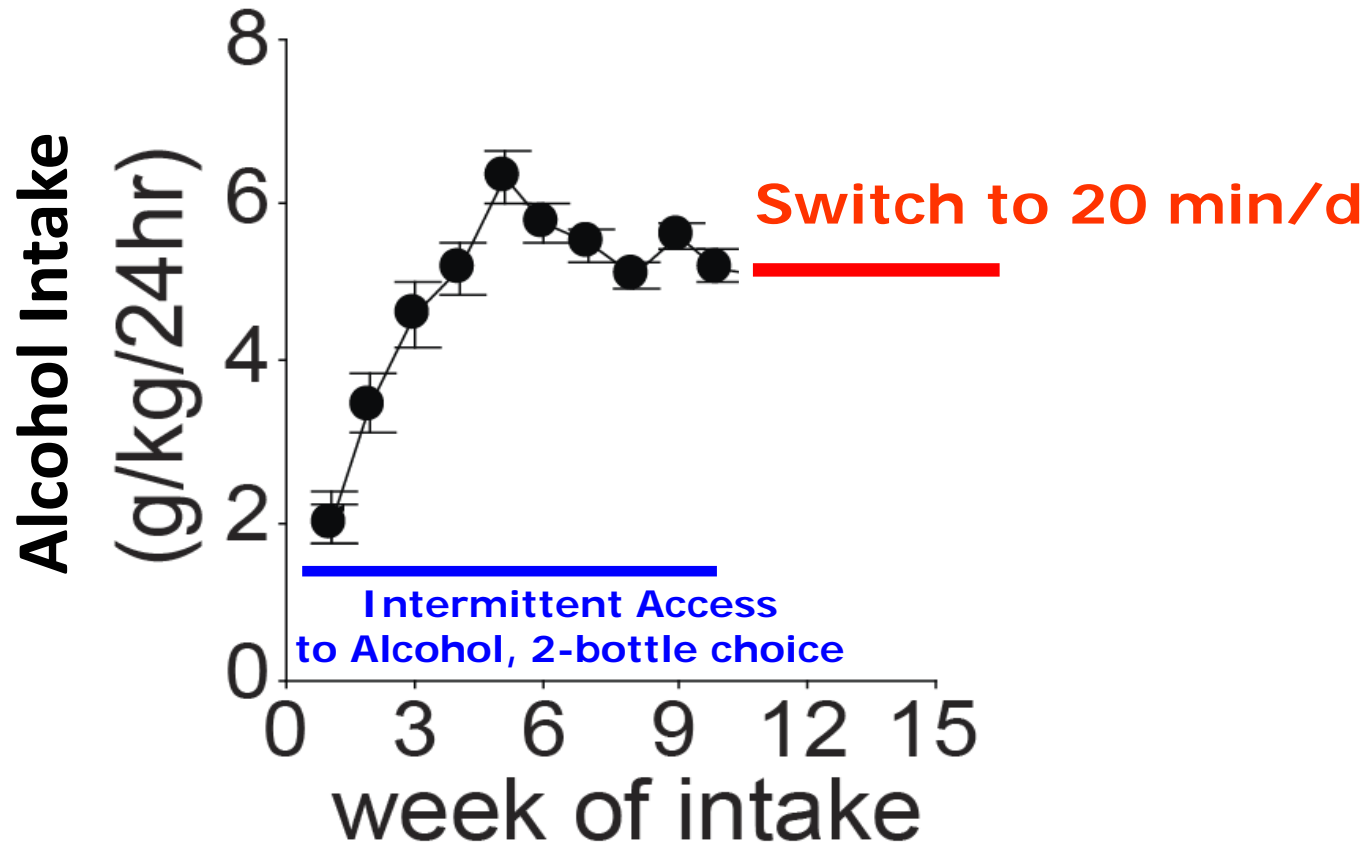


Monday afternoon to Tuesday afternoon

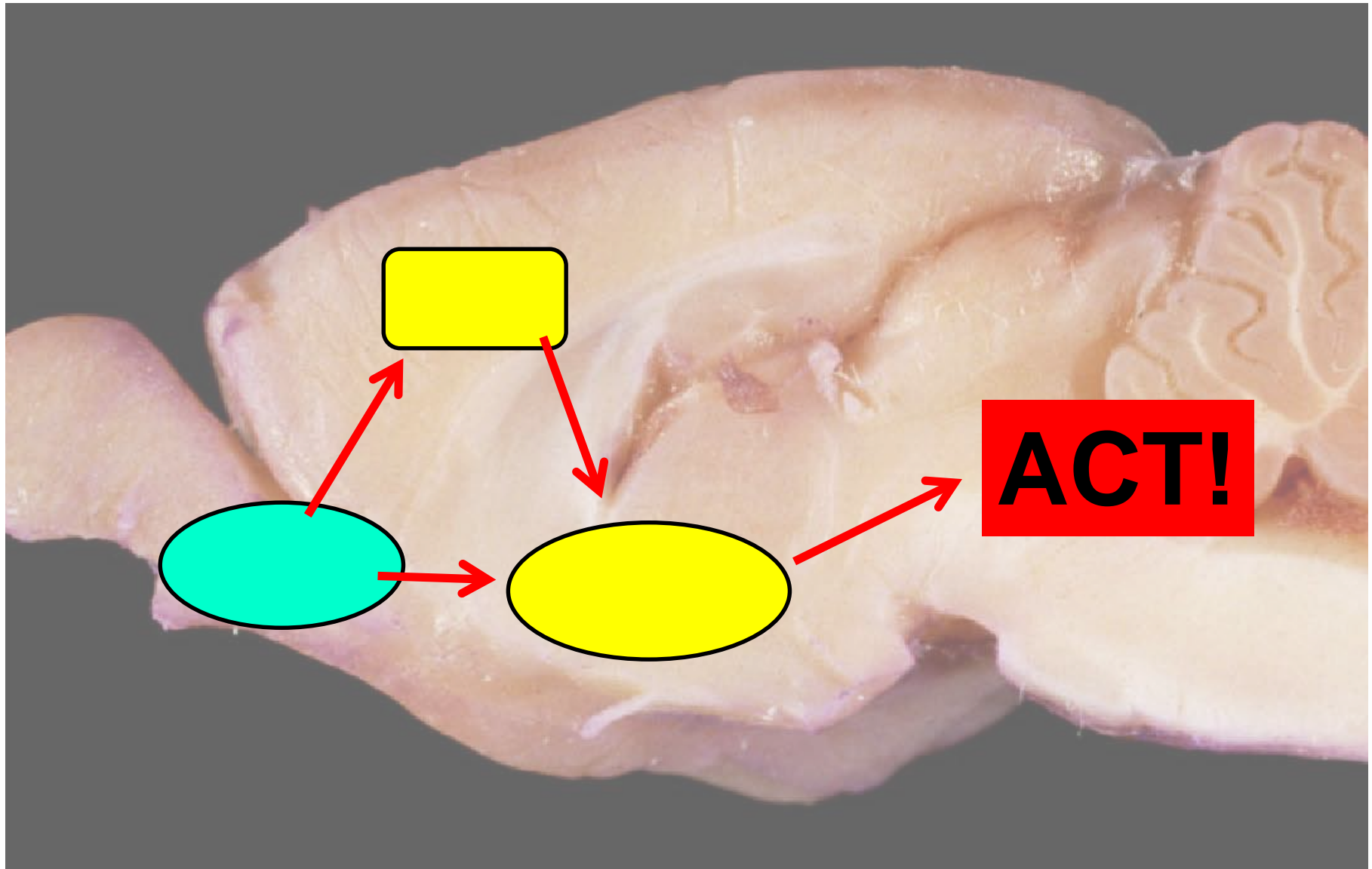
Alcohol Drinking Model



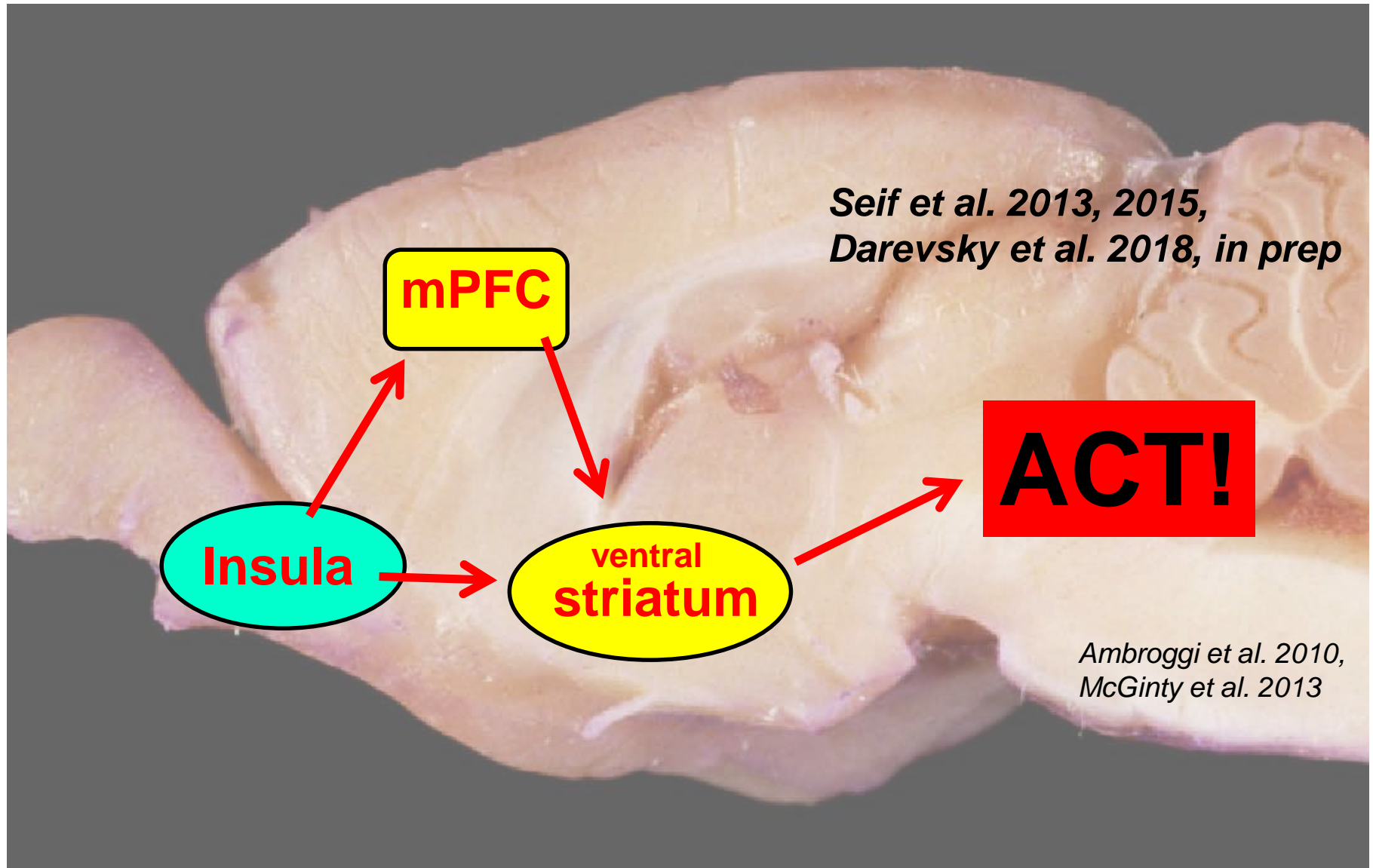
Alcohol Drinking Model



Brain Areas that mediate Compulsive Drives for Alcohol?



Brain Areas that mediate Compulsive Drives for Alcohol?



Brain Areas that mediate Compulsive Drives for Alcohol?

mPFC: medial prefrontal cortex

*Seif et al. 2013, 2015,
Darevsky et al. 2018, in prep*

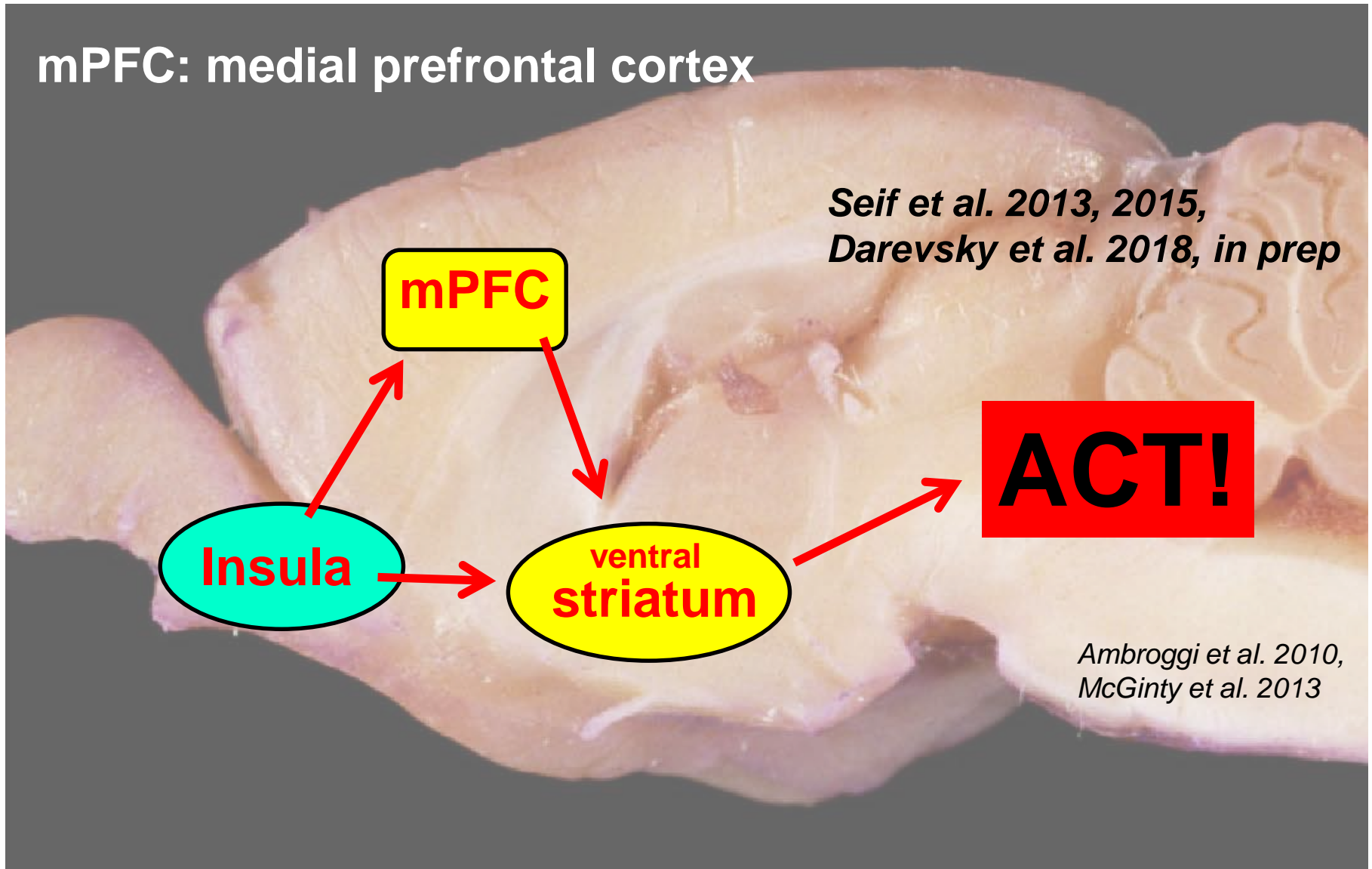
mPFC

Insula

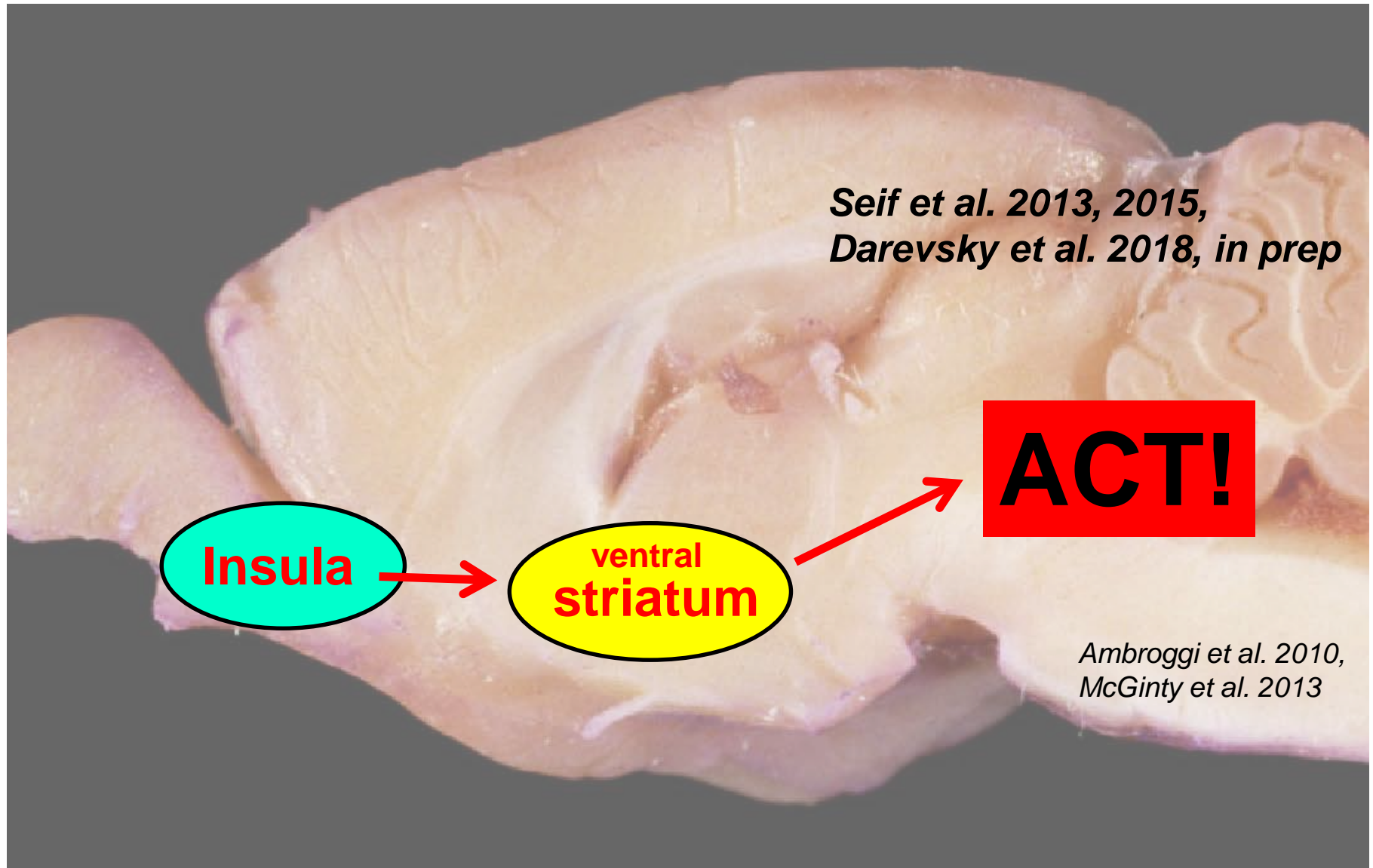
**ventral
striatum**

ACT!

*Ambroggi et al. 2010,
McGinty et al. 2013*



The "Insula Input" to Striatum



The "mPFC Input" to Striatum

mPFC: medial prefrontal cortex

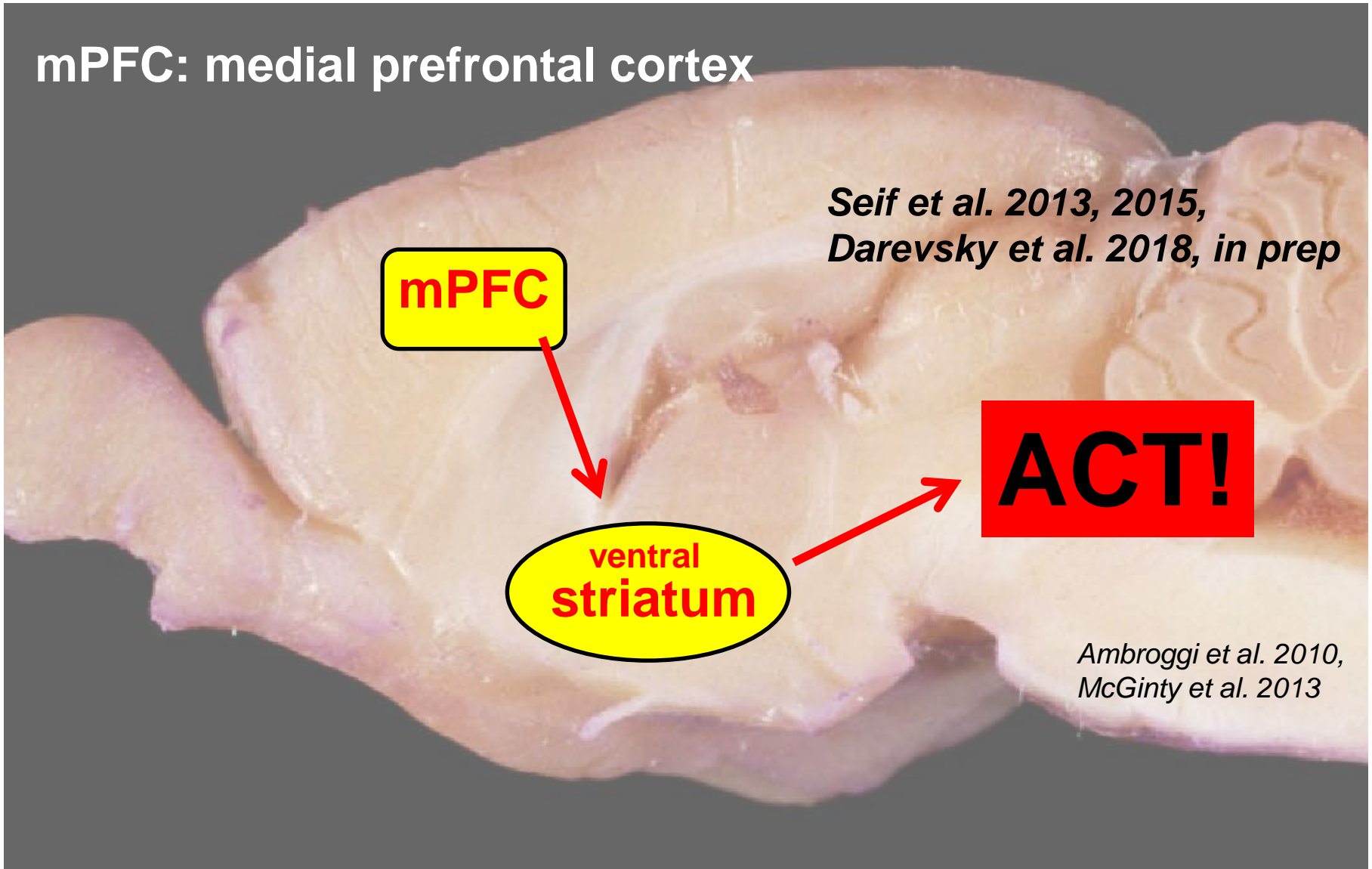
*Seif et al. 2013, 2015,
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mPFC

**ventral
striatum**

ACT!

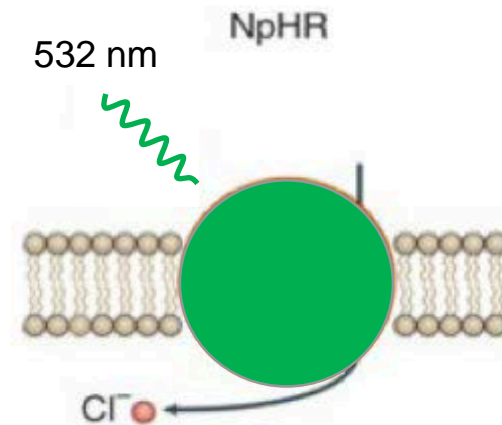
*Ambroggi et al. 2010,
McGinty et al. 2013*



Optogenetics

Tools to inhibit or activate specific connections in the brain

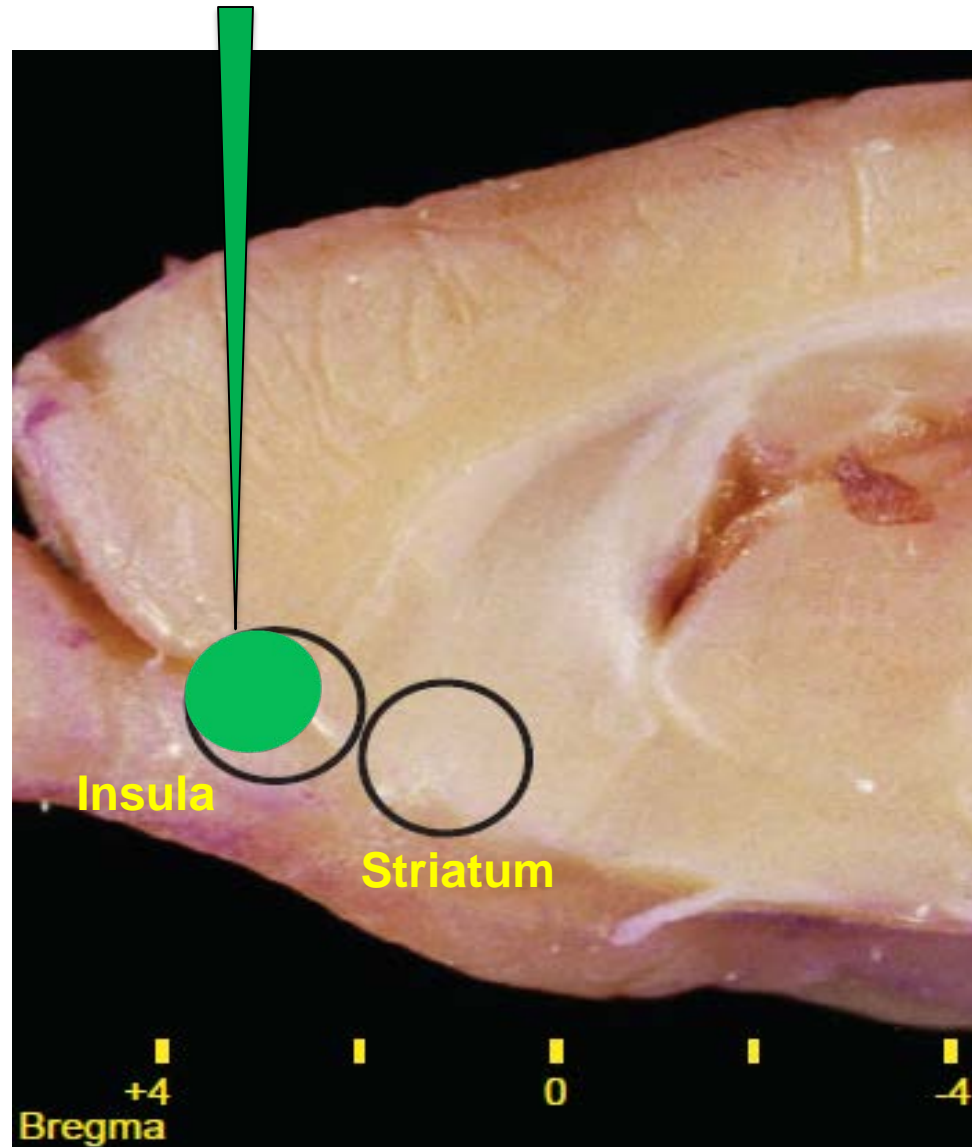
Halorhodopsin:
Light inhibits cells



Protein developed by bacteria
in sun-baked salt/mudflats (Death Valley)

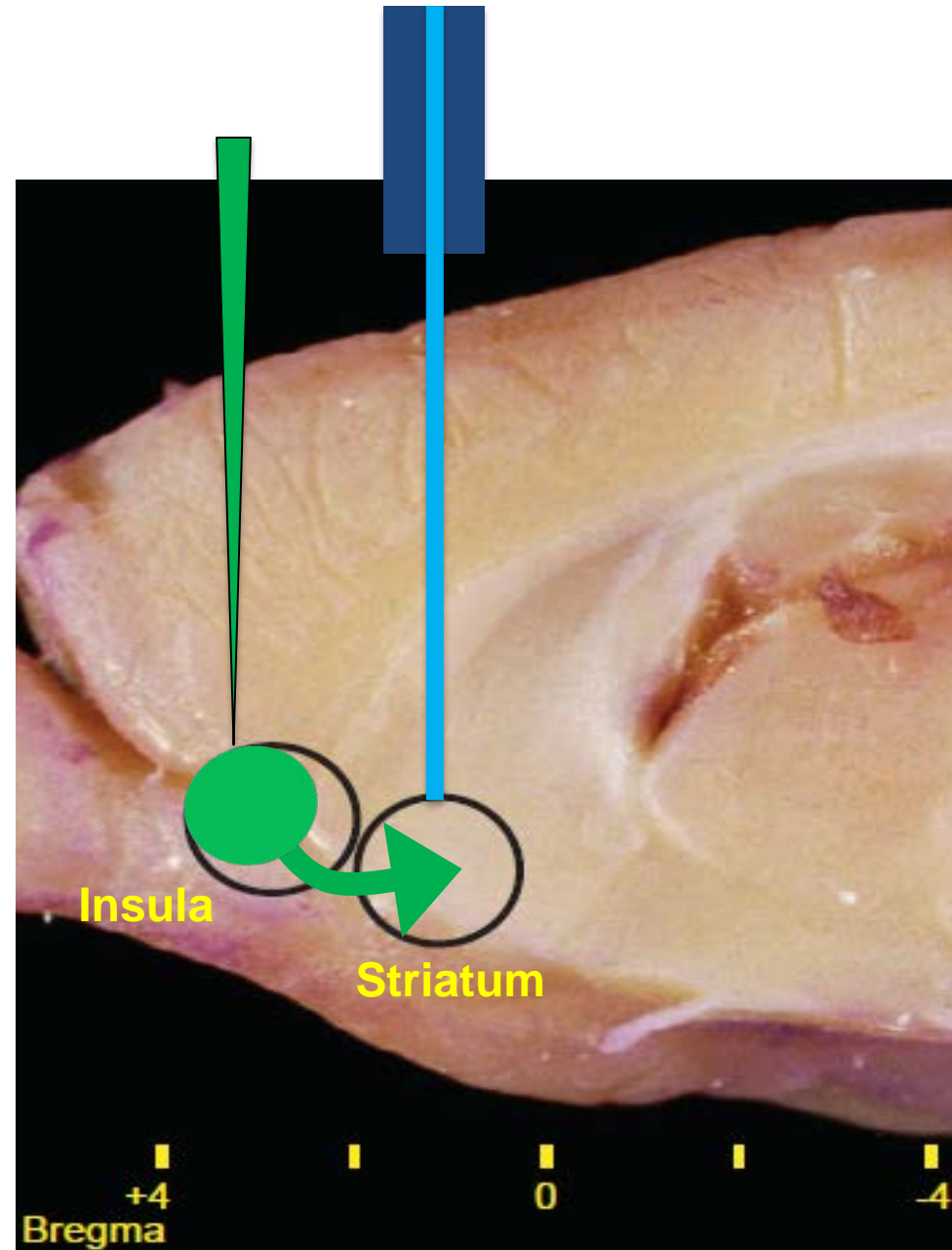
Absorb light, be less active
Survive in the sun better

Infect Insula
neurons with a
virus containing
the gene for
halorhodopsin

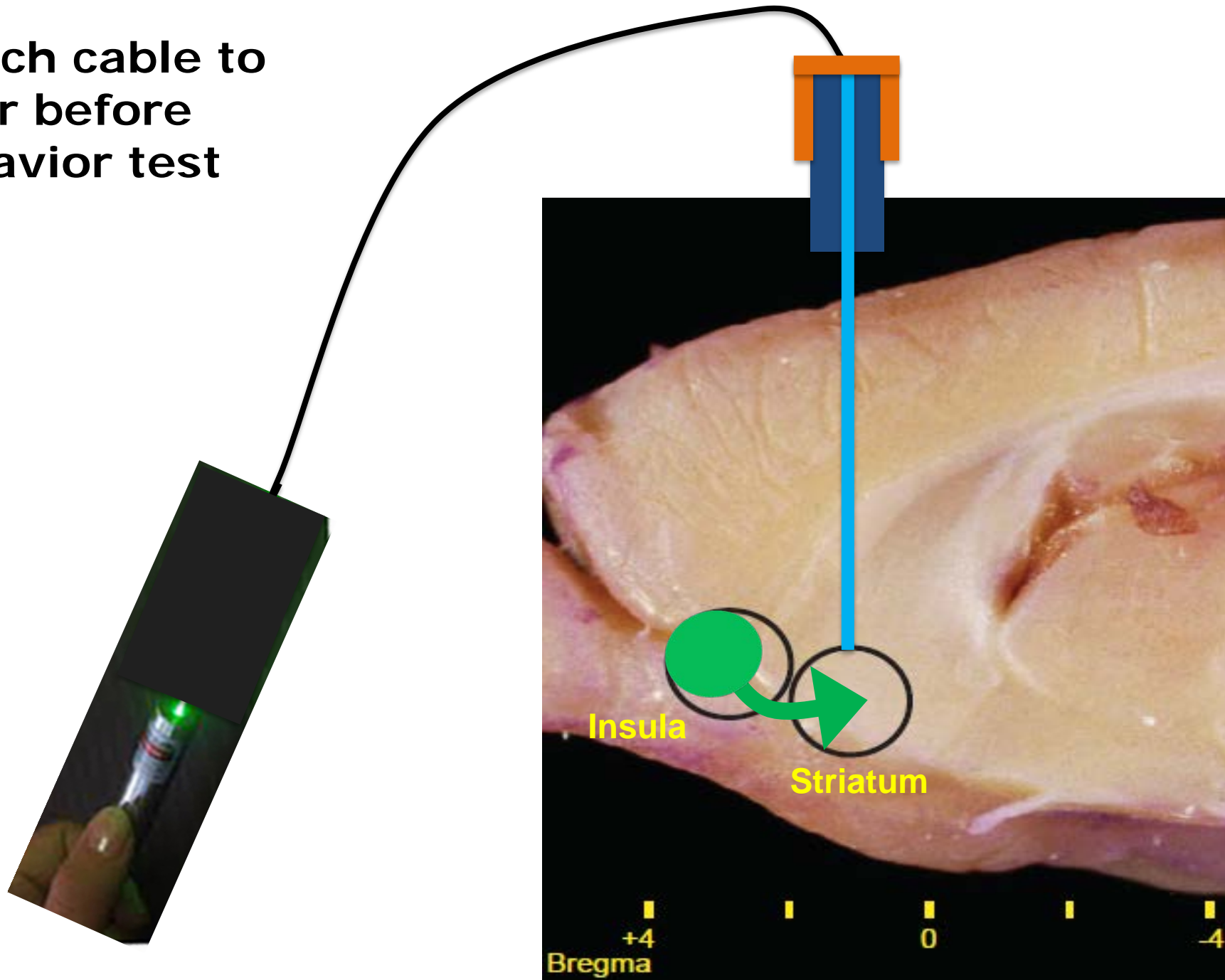


Infect Insula cells
with halorhodopsin

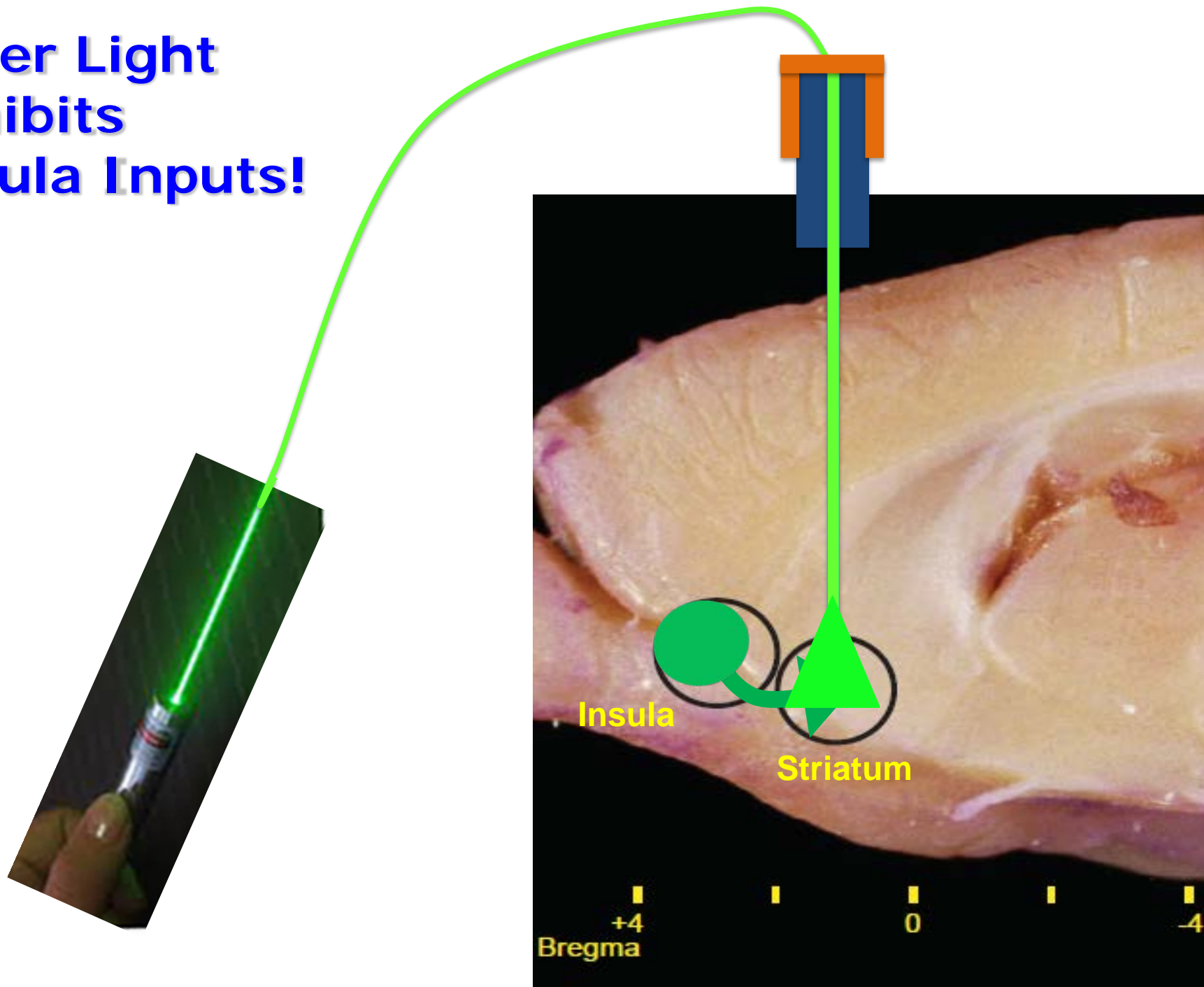
Target a fiber-optic
cable into the
Striatum



Attach cable to
laser before
behavior test

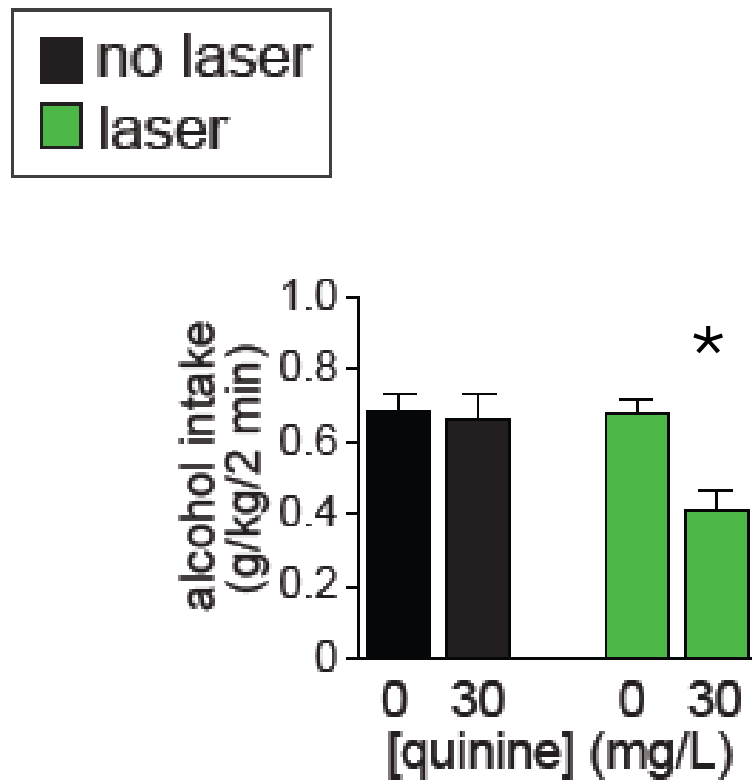


**Laser Light
Inhibits
Insula Inputs!**

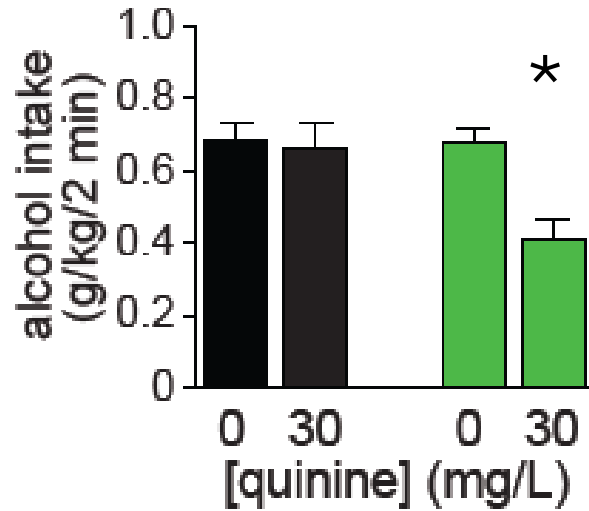


Needed for Compulsion-Like Alcohol Drinking

**Insula
input**

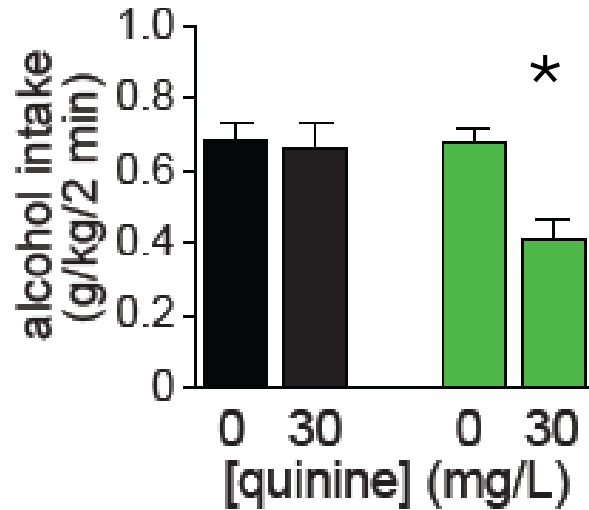


Alcohol Intake



Amount of challenge in alcohol:
0 no challenge, 30 tastes bad

Alcohol Intake



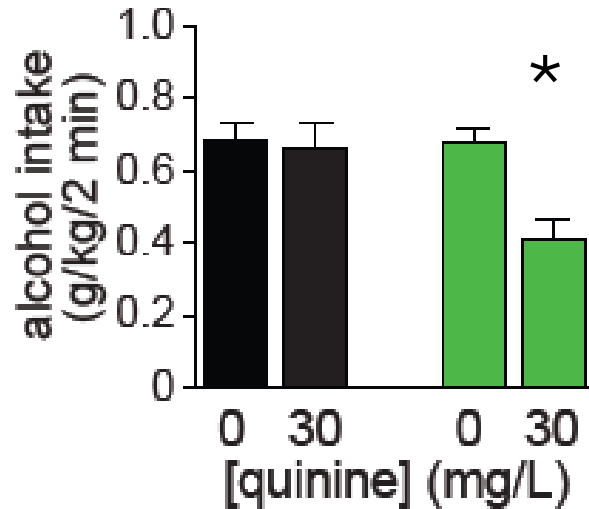
Laser light **turned on** or not

Amount of challenge in alcohol:
0 no challenge, 30 tastes bad

Insula input

Insula-Striatum Inputs
are **inhibited** or not

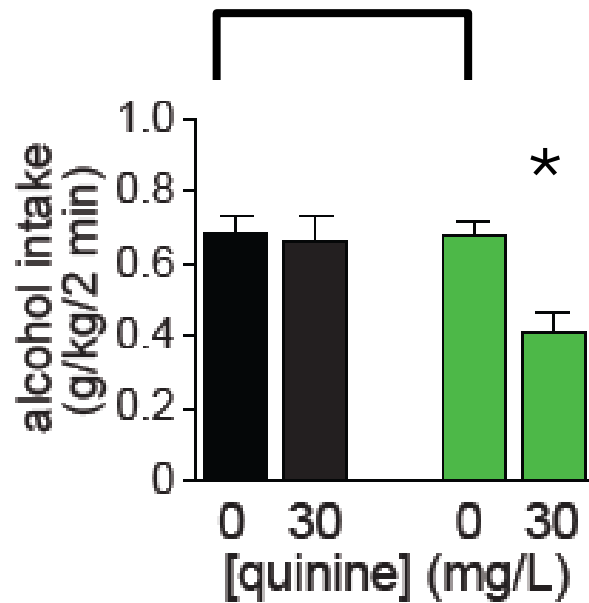
Alcohol Intake



Amount of challenge in alcohol:
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Alcohol Intake

Regular, Alcohol-Only Drinking

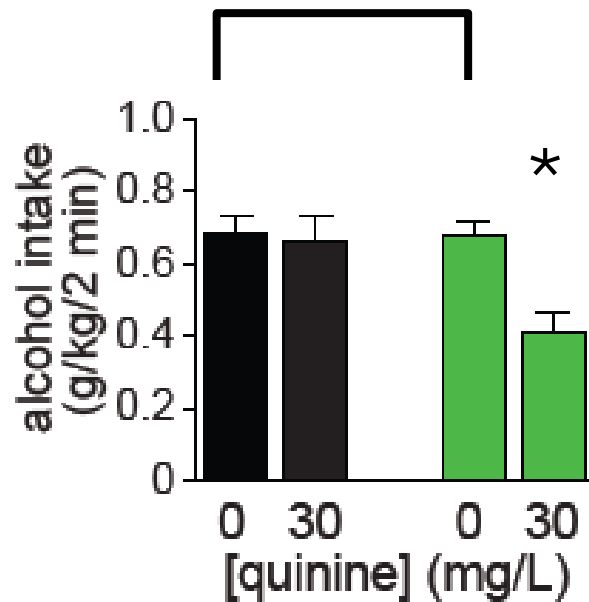


Amount of challenge in alcohol:
0 no challenge, 30 tastes bad

Alcohol Intake

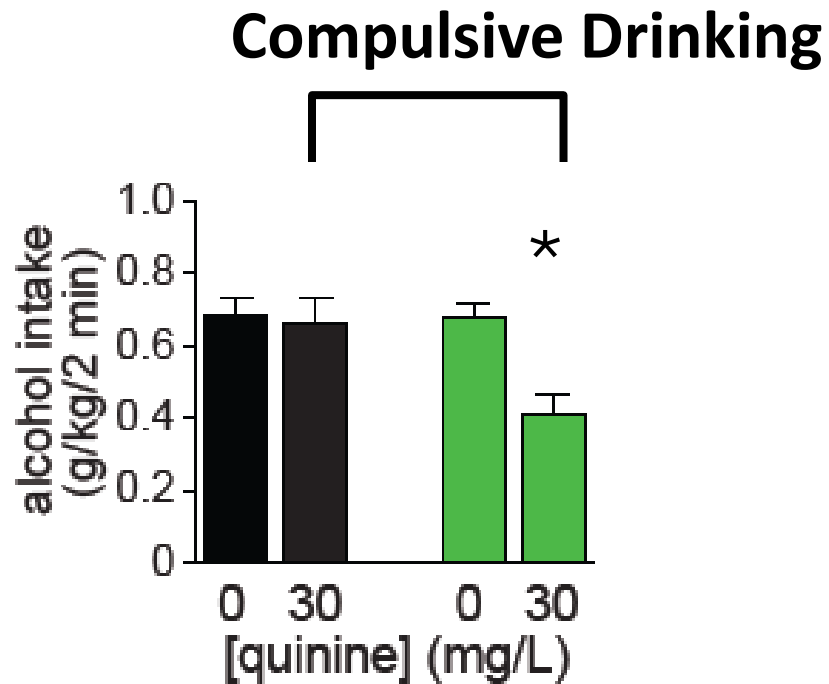
Regular, Alcohol-Only Drinking

NO CHANGE!!



Amount of challenge in alcohol:
0 no challenge, 30 tastes bad

Alcohol Intake

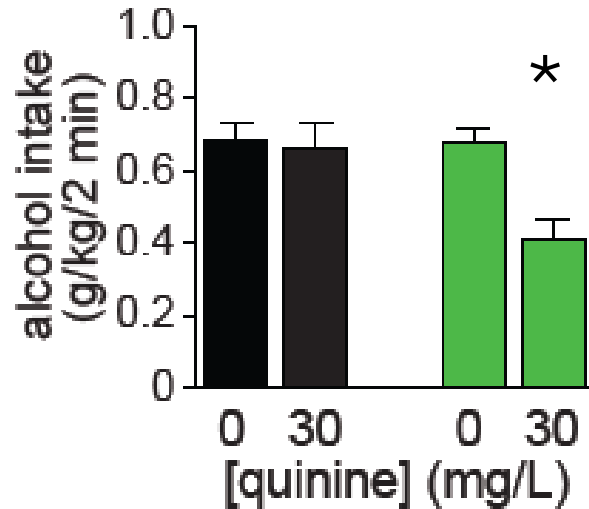
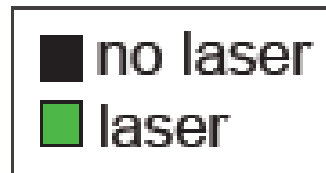


Reduced when Inhibit
Insula-Striatum inputs

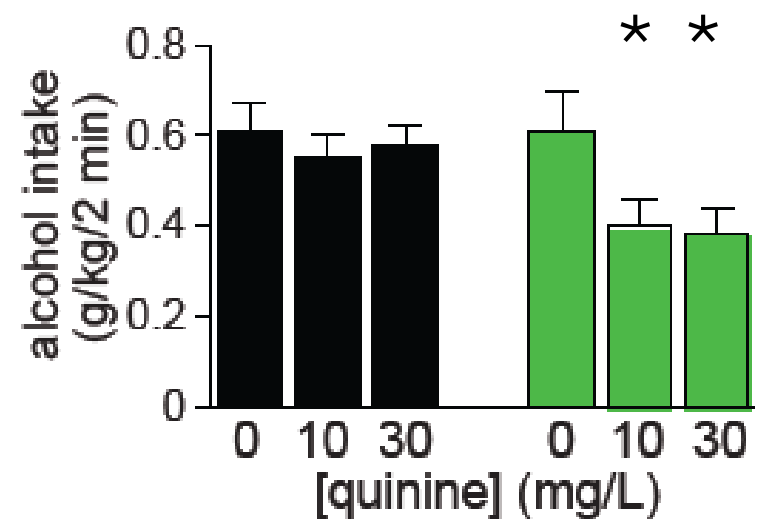
Amount of challenge in alcohol:
0 no challenge, 30 tastes bad

Needed for Compulsion-Like Alcohol Drinking

**Insula
input**



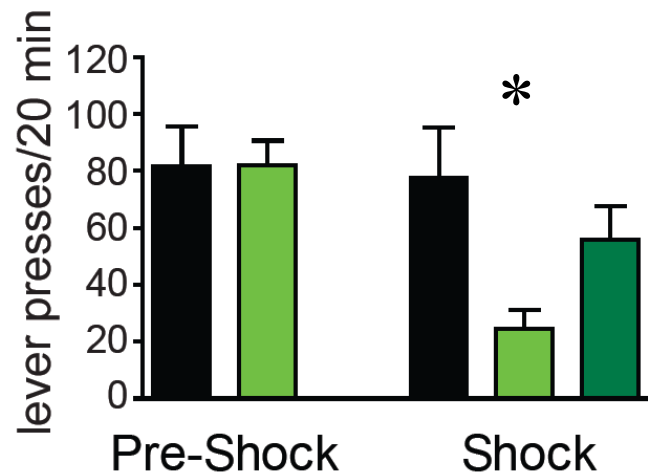
**mPFC
input**



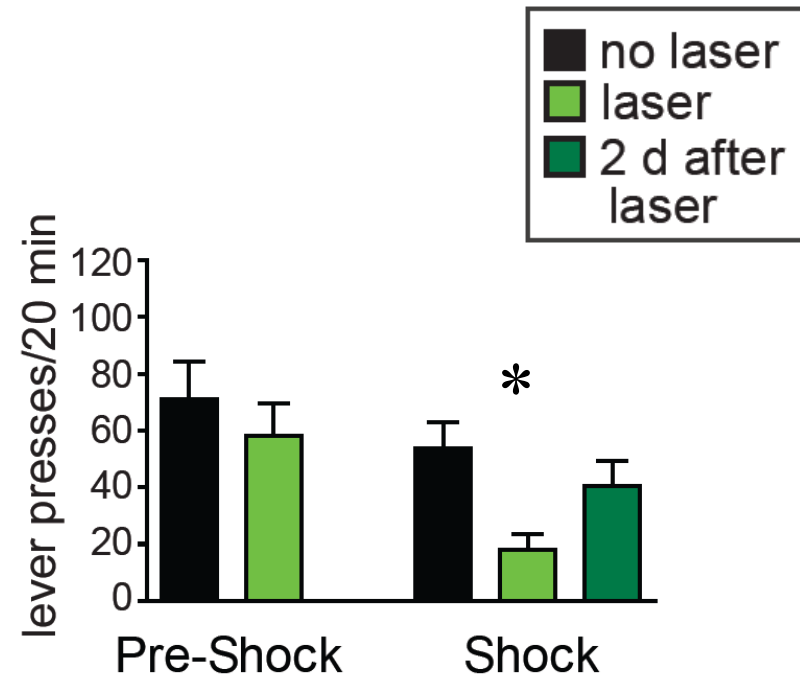
**What about for a different bad consequence?
(shock)**

Needed for Compulsion-Like Alcohol Drinking

**Insula
input**



**mPFC
input**



Both Inputs (Insula & mPFC) drive alcohol drinking that continues despite both types of badness (taste, shock)

A common mechanism
for consequence-resistant action?

Yay for Rats, but what about Humans?

Compulsion-like drinking in rodents

Keep drinking despite shock/bad taste

These consequences are more immediate

Is this like a human alcoholic?

Compulsion-like drinking in rodents

Keep drinking despite shock/bad taste

These consequences are more immediate

Is this like a human alcoholic?

No: Drink now, lose your job tomorrow

Yes: Treatment Seekers: negative consequences are more immediate

When they think about going in the bar, or
They look at beer glass

**Insula-mPFC-Striatum Circuit:
Compulsive Action for Alcohol
in Rats and Humans?**

Archival Report

Biological
Psychiatry:
CNI

2018

Neural Correlates of Compulsive Alcohol Seeking in Heavy Drinkers

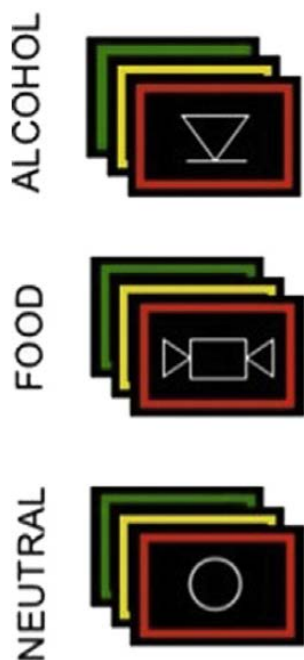
Erica N. Grodin, Lauren Sussman, Kelsey Sundby, Grace M. Brennan, Nancy Diazgranados, Markus Heilig, and Reza Momenan

Pressing for alcohol in the face of **shock**

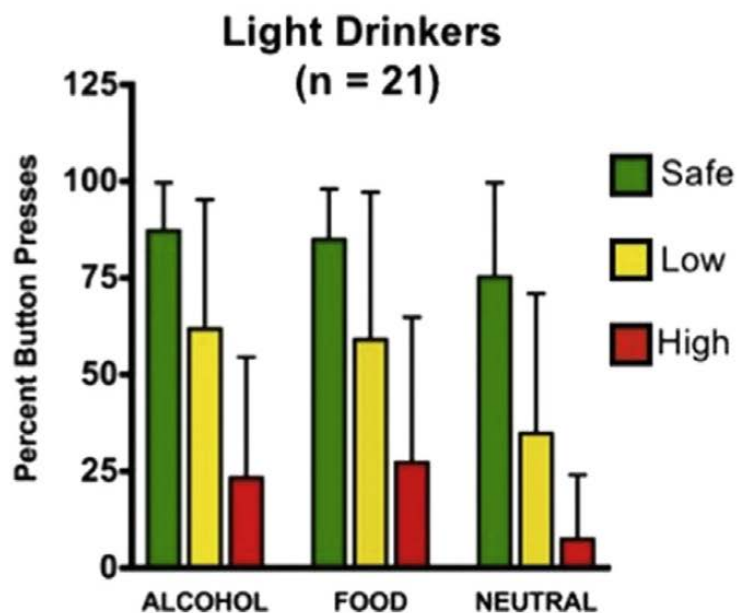
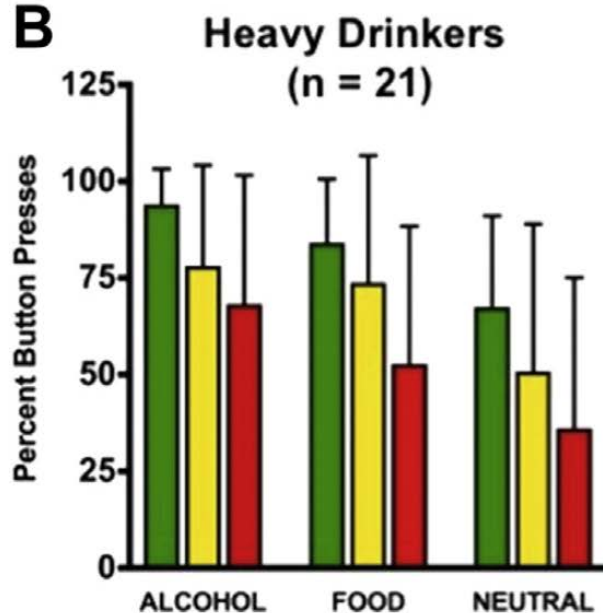


Lots of pressing when it is Safe (green bars)

A CUE

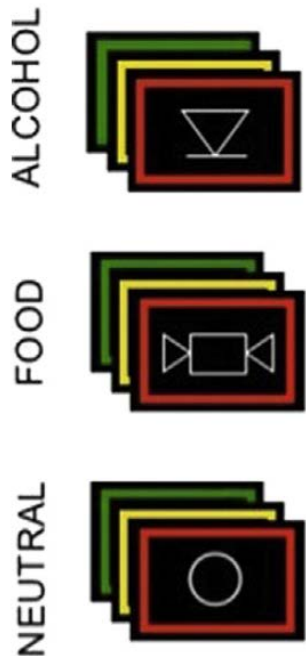


B

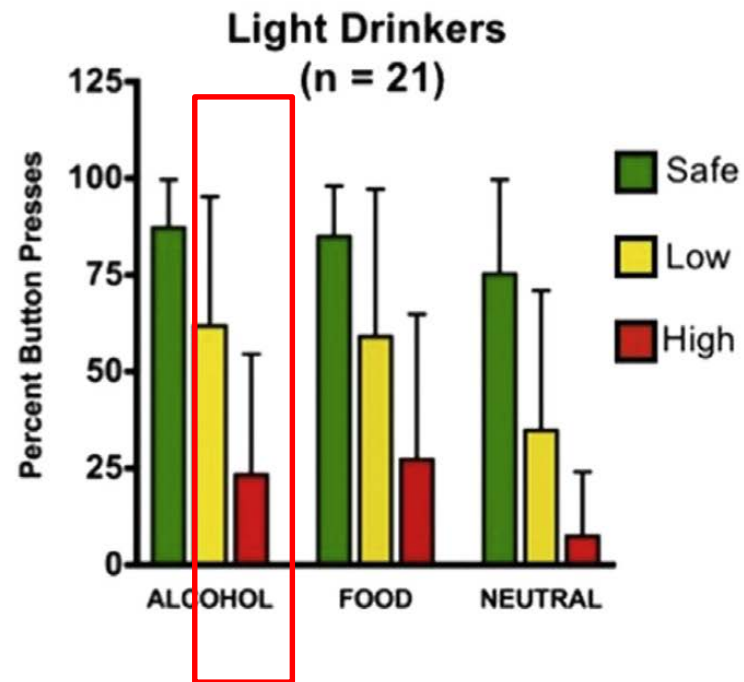
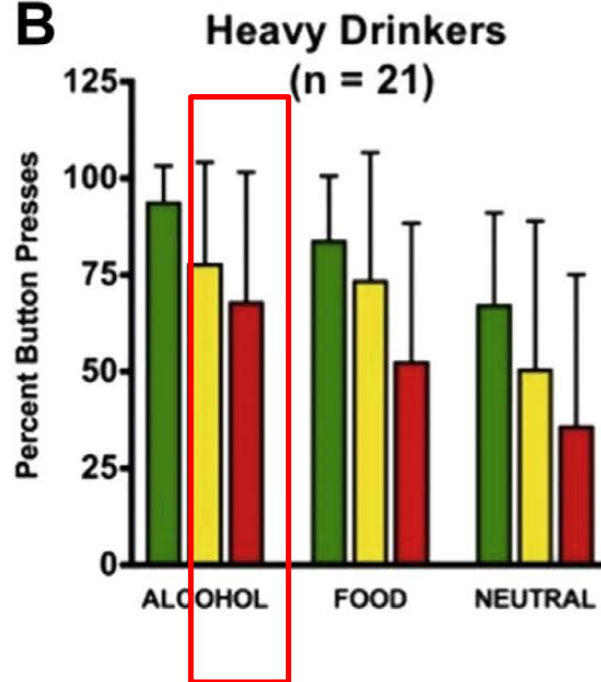


Heavy human drinkers: more willing to press for alcohol in the face of **threat**

A CUE



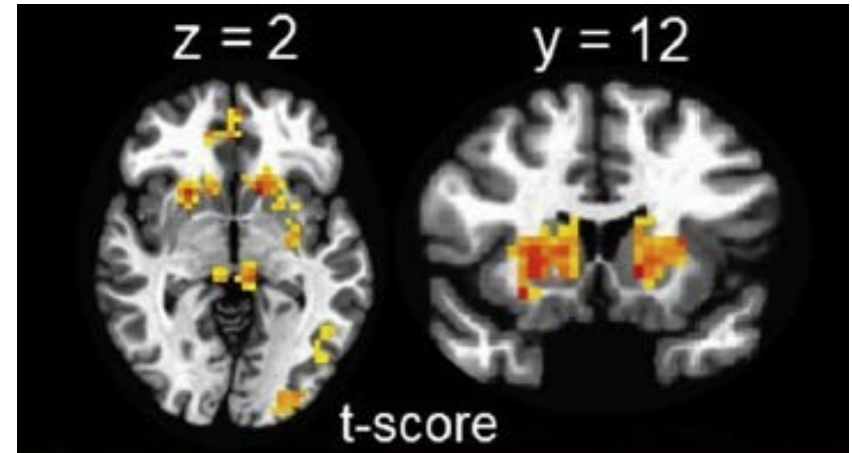
B



HEAVY DRINKERS:

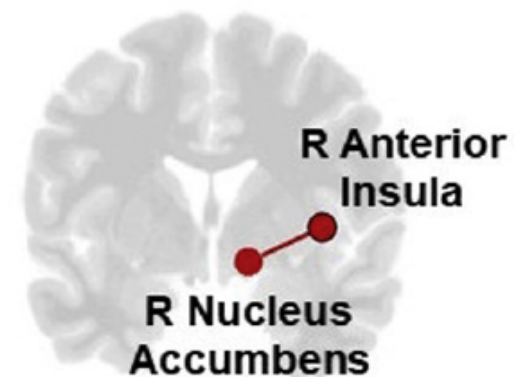
Insula/mPFC/Striatum

Alcohol response
despite bad
consequences



More Insula-Striatum connection correlates with

- more compulsive responding
- greater self-reported compulsivity



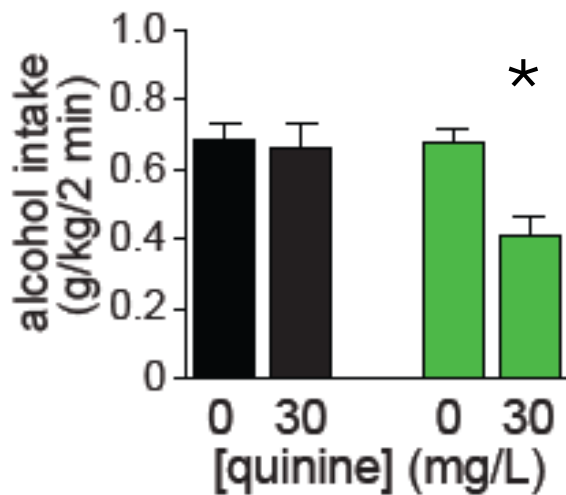
**Same Brain Circuit mediates
Compulsive Action for Alcohol
in Humans and Rats!**

Same Brain Circuit mediates Compulsive Action for Alcohol in Humans and Rats!

Why these regions? What are they “doing?”

Why do Insula-Striatum only regulate Compulsive Drinking?

Insula



Why do Insula-Striatum only regulate Compulsive Drinking?

Compulsive intake:

Automatic, habitual intake with actual challenge

Habitual intake:

Automatic, habitual intake

Why do Insula-Striatum only regulate Compulsive Drinking?

Compulsive intake:

Conflict Recruits Cortical Circuits

Habitual intake:

No Conflict, recruits more striatal,
less cortical areas

Why do Insula-Striatum only regulate Compulsive Drinking?

Compulsive intake:

Conflict Recruits Cortical Circuits

Habitual intake:

No Conflict, recruits more striatal,
less cortical areas

Compulsion: not giving in to “bad consequences”

**Cost of not drinking worse than
harms associated with drinking**

Why do Insula-Striatum only regulate Compulsive Drinking?

Compulsive intake:

Conflict Recruits Cortical Circuits

Habitual intake:

No Conflict, recruits more striatal,
less cortical areas

Different brain circuits drive your drinking
depending on your mindset
(conflict-ignoring or non-conflicted)

This can change from moment to moment

Why do Insula-Striatum only regulate Compulsive Drinking?

Compulsive intake:

Conflict Recruits Cortical Circuits

Habitual intake:

No Conflict, recruits more striatal,
less cortical areas

**Our therapies target “Moments of Crisis”
(at risk of relapsing)**

Why do Insula-Striatum only regulate Compulsive Drinking?

Compulsive intake:

Conflict Recruits Cortical Circuits

Habitual intake:

No Conflict, recruits more striatal,
less cortical areas

Our therapies target “Moments of Crisis”
(at risk of relapsing)

If one has no conflict,
then the therapy won't do anything

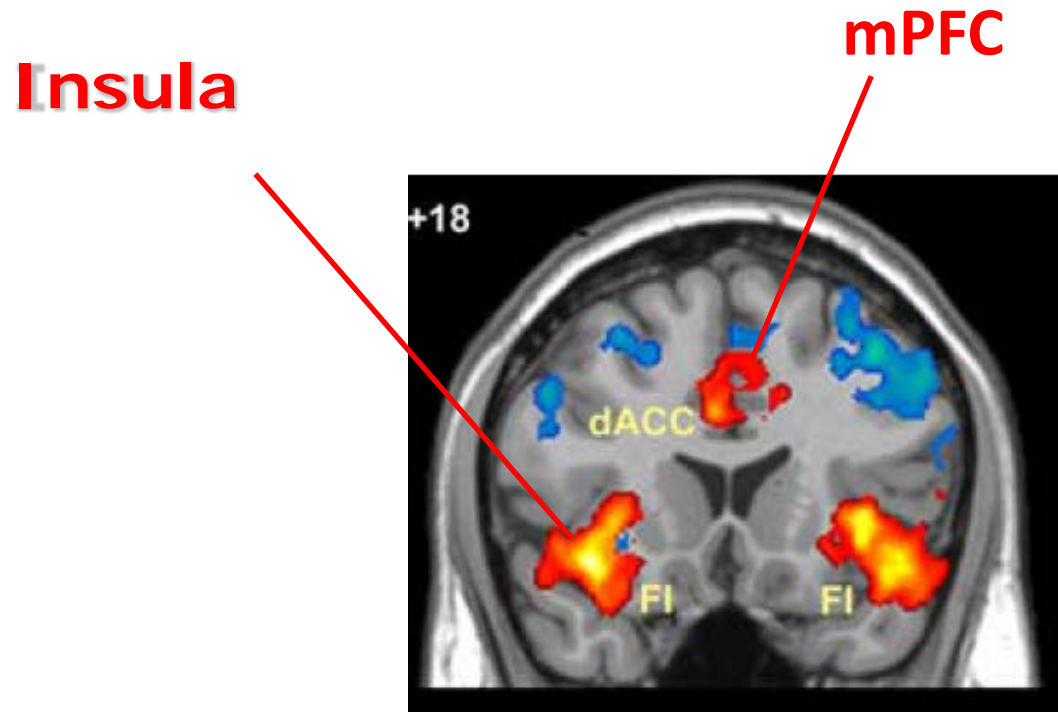
What does Insula "do normally?"

(Not there just to let us get addicted)

How to Deal with Challenges that get in the way of Reward

Challenges are Important!

The Salience Network mediates important events

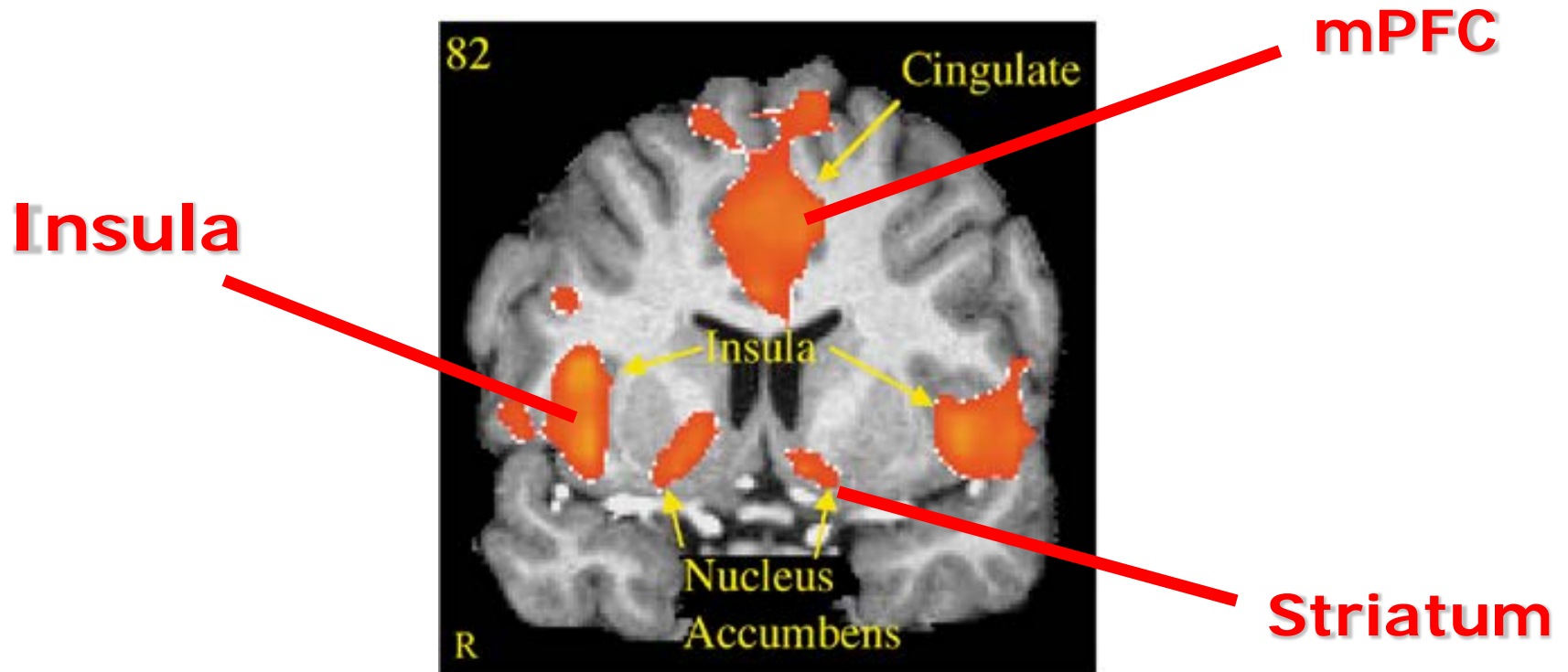


Short important things

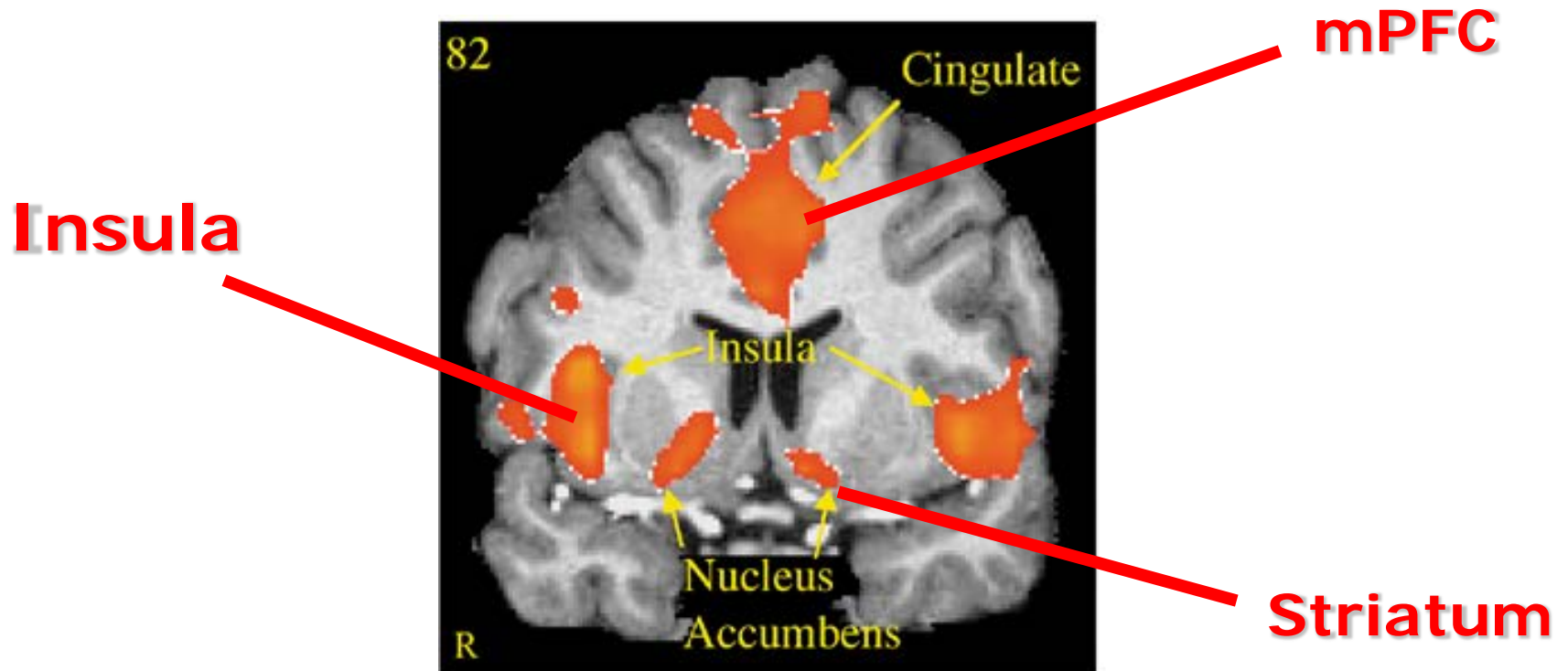
Alcohol cues promote drinking

Alcohol cues promote drinking

Insula activity PREDICTS
real-world intake and relapse



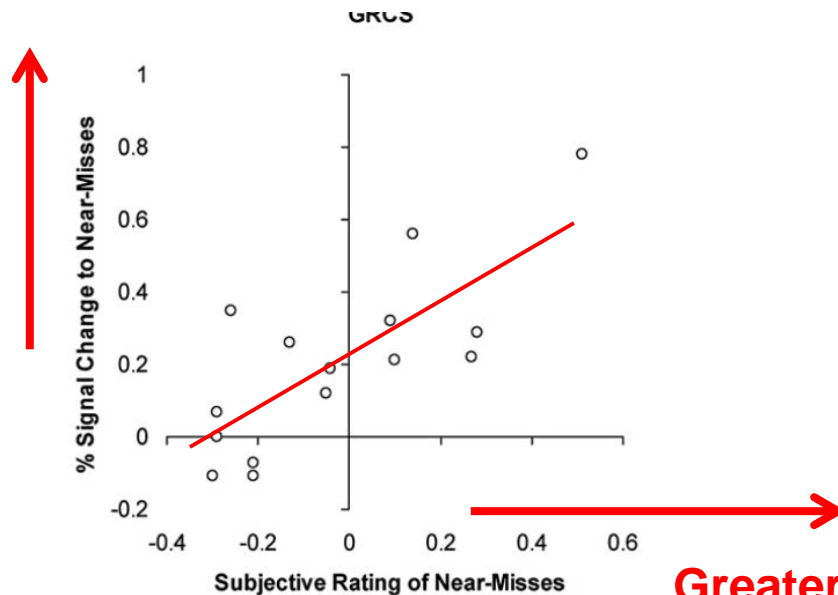
Alcohol cue “automatically captures attention”



If you gamble and "almost win"

Insula activation predicts the desire to gamble more

Greater Insula activity
for almost win



Gambling Near-Misses Enhance Motivation to Gamble and Recruit Win-Related Brain Circuitry

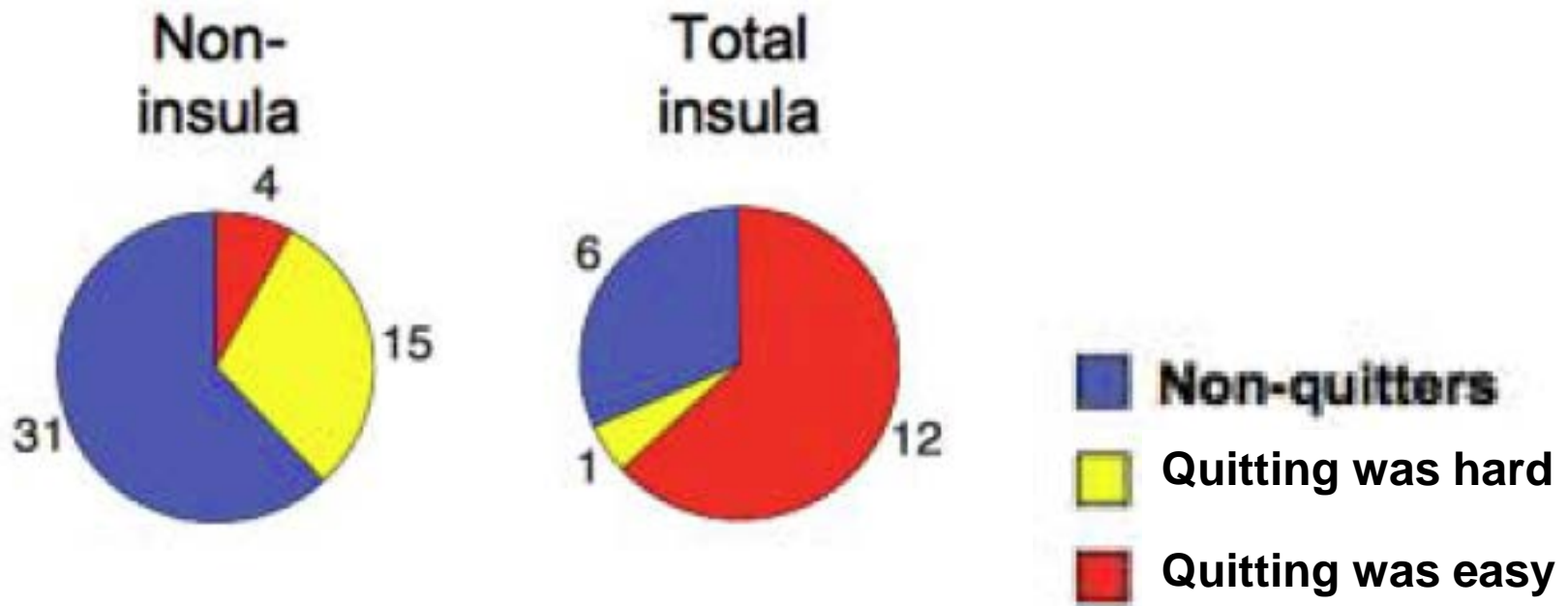
Luke Clark,^{1,*} Andrew J. Lawrence,¹ Frances Astley-Jones,¹ and Nicola Gray¹
¹Behavioural and Clinical Neuroscience Institute, Department of Experimental Psychology, University of Cambridge,
CB2 3EB Cambridge, UK
*Correspondence: lc260@cam.ac.uk
DOI 10.1016/j.neuron.2008.12.031

Luke 2011

Greater desire to keep gambling

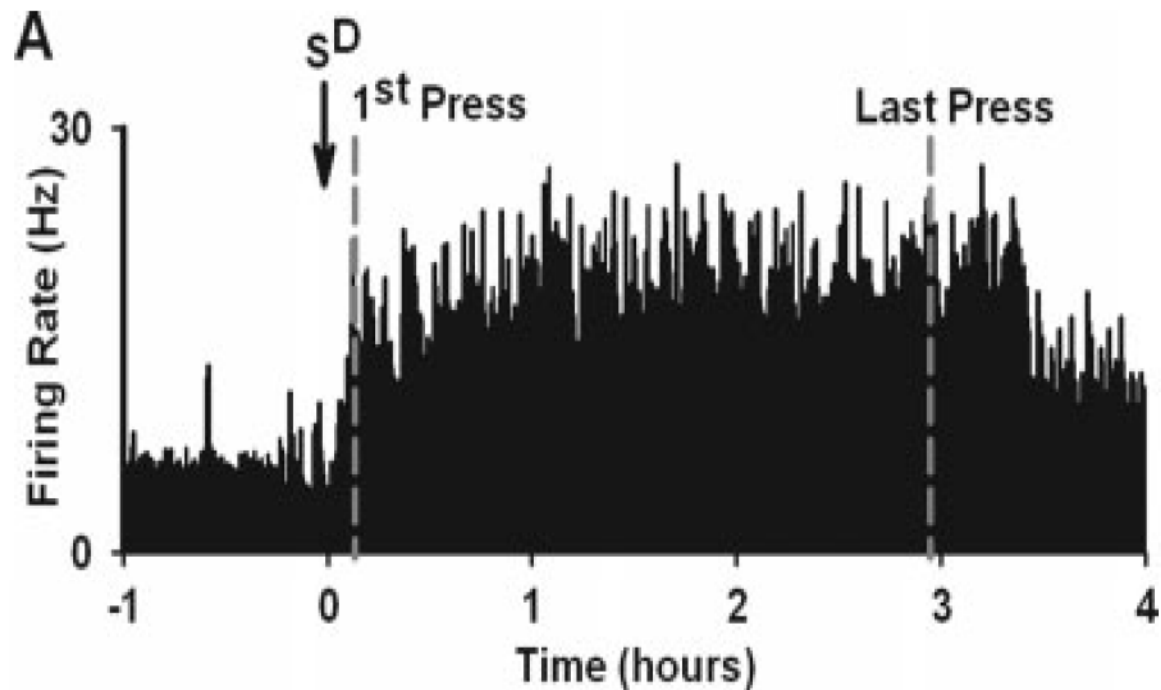
Partial Insula Stroke:

Give up smoking without effort



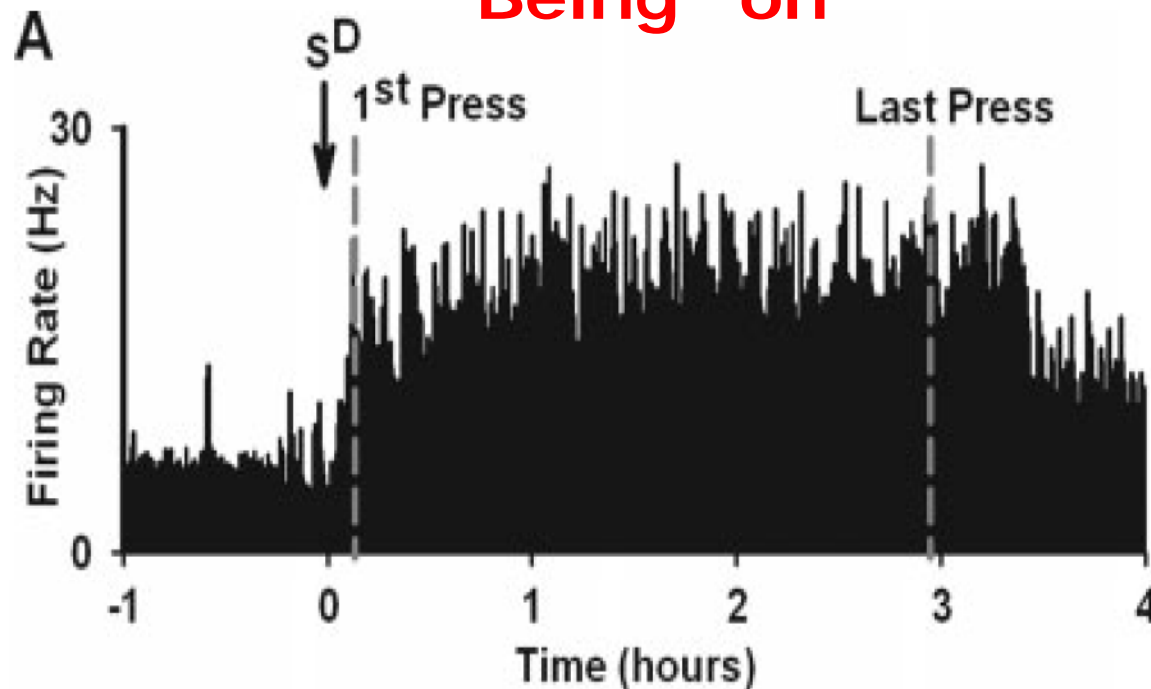
Long important things

Insula cells active for 3 hours (pressing a lever to get cocaine)



Insula cells active for 3 hours (pressing a lever to get cocaine)

Being "on"

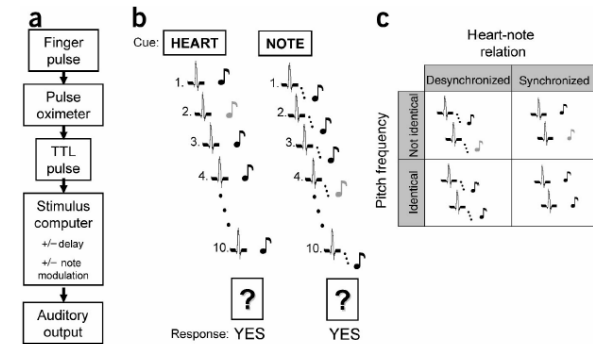


Insula key for anxiety:

- **Overvalue negative info**
- **Sustained attention**
- **Relief Seeking when bad feeling awakened**

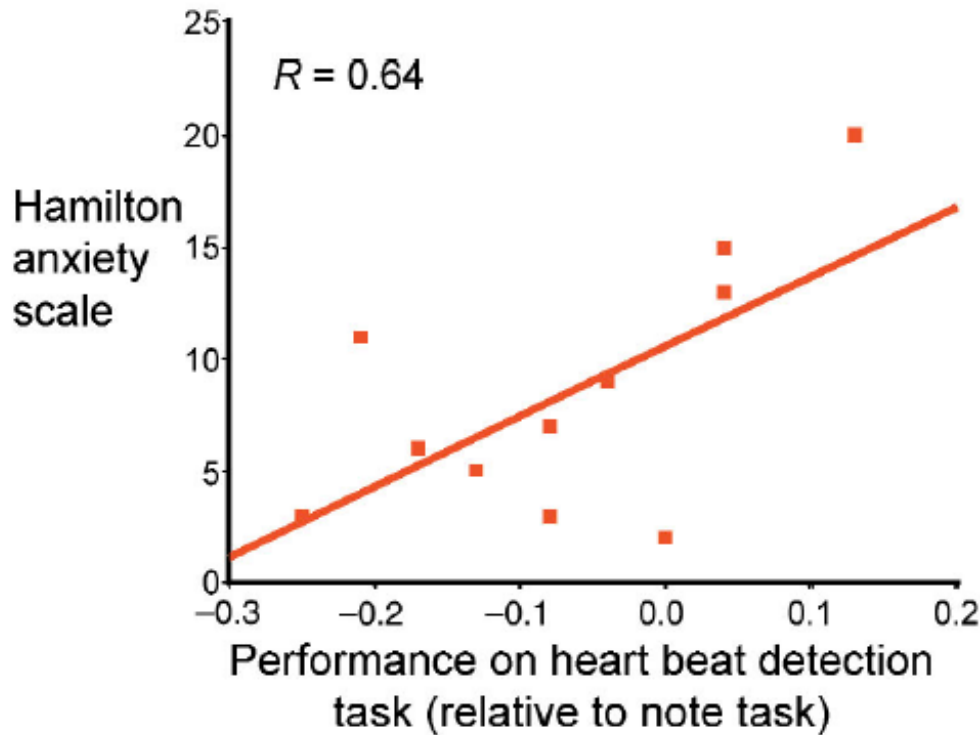
(subconscious and conscious levels)

A game: is my heart beat in time with music rhythm?

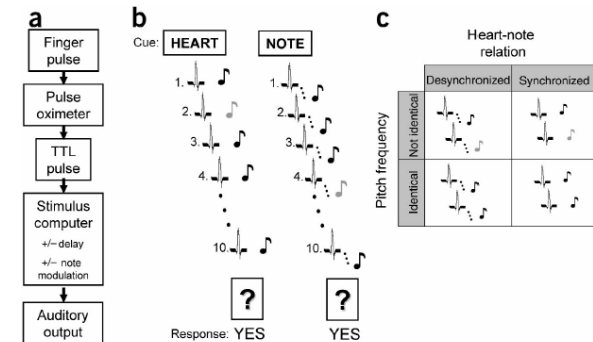


A game: is my heart beat in time with music rhythm?

More basal anxiety

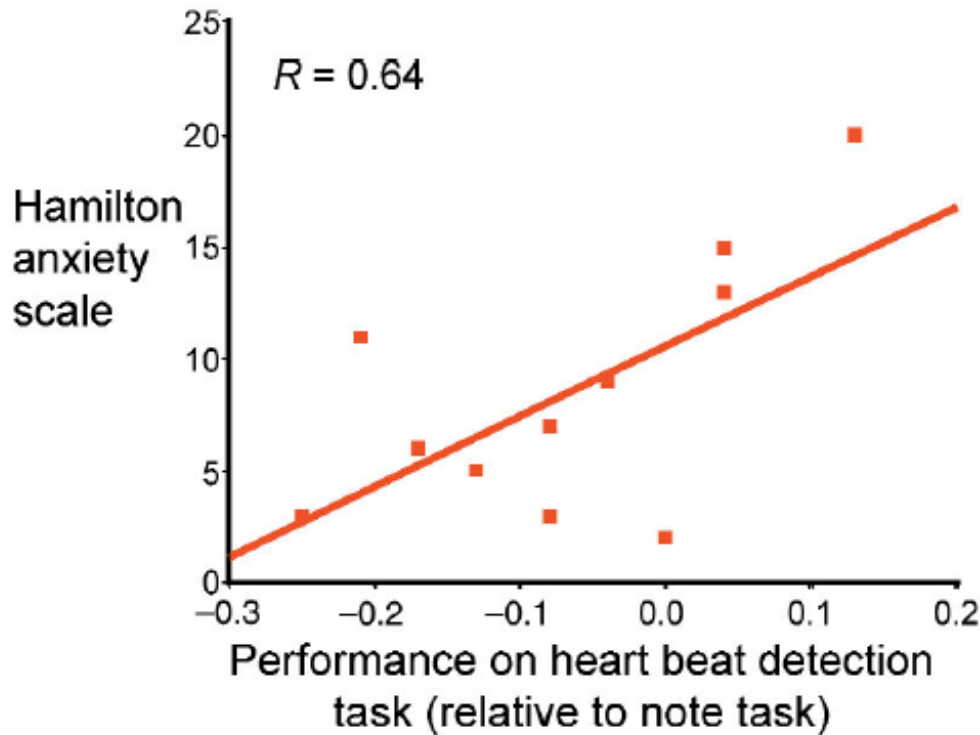


Better ability to feel body

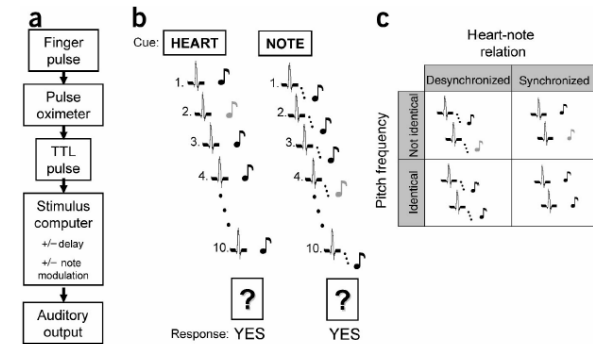


Awareness innately comes with some anxiety

More basal anxiety



Better ability to feel body



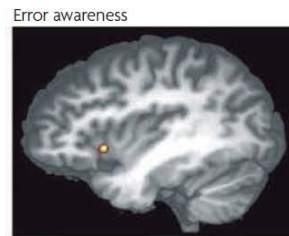
Insula

“Feeling of knowing”

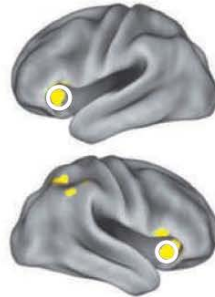
**Most singular sense
of Self in the moment**

**Moment of
recognizing**

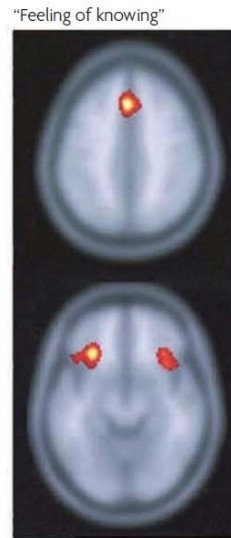
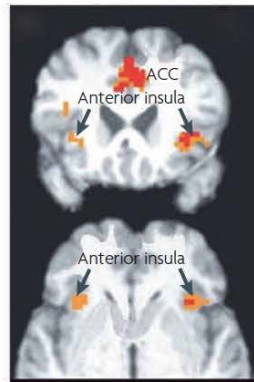
**Decision
making**



Moment of recognition



Decision making



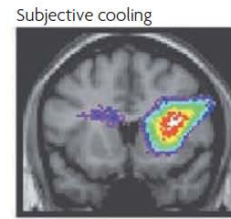
Inspection time



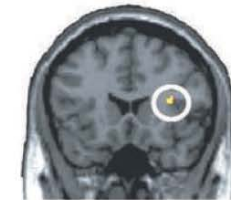
Time perception



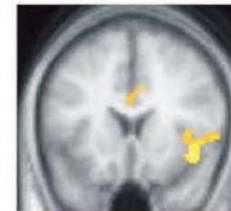
time perception



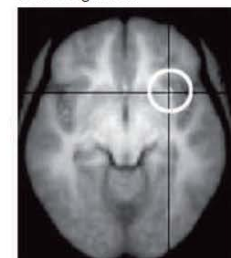
Heartbeat awareness



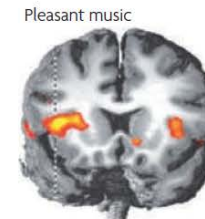
Learned pain ‘now’



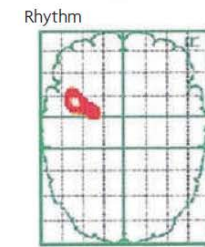
Self recognition



self-recognition



pleasant music

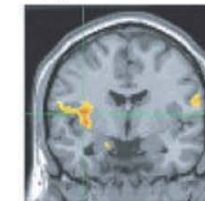


Maternal affiliation



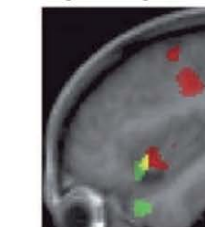
**maternal
affiliation**

Happy voices



happy voices

Seeing or making a smile



smile

Mindfulness as a therapy:

Likely effective because it reprograms
“fast reactivity to importance” memories

Both (1) being reactive, and (2) learning to be less
reactive, mediated through the Insula

Mindfulness as a therapy:

Likely effective because it reprograms
“fast reactivity to importance” memories

Both (1) being reactive, and (2) learning to be less
reactive, mediated through the Insula

The Insula is all about having awareness and using
awareness of importance to impact what happens

Insula: critical for important things

Balancing awareness and non-awareness
to help carry out importance-directed actions

This system regulates both
positive and negative situations

**Addiction takes over the system:
Alcohol becomes the most important thing**

What is harmful drinking?

Why do we call it "harmful?"

Binging

How much alcohol is harmful?

Thoughts/urges/cues which
“automatically” push one forward

What is harmful drinking?

Why do we call it “harmful?”

Binging

How much alcohol is harmful?

*I know I shouldn't do it
but I do it anyways*

Repeated practice in “giving in to urges”

Thoughts/urges/cues which
“automatically” push one forward

Costs:

- Organ Damage
- Harm to Others
And Self

What is harmful drinking?

Why do we call it “harmful?”

Binging

How much alcohol is harmful?

*I know I shouldn't do it
but I do it anyways*

Repeated practice in “giving in to urges”

Costs:

- Becomes “habitual”
- Pay less attention to negative info (*“it'll be fine” becomes habit*)
- Can't muster as much will to overcome (*gotten good at giving in*)

**How much alcohol is harmful?
(and is there a “healthy” level?)**

A lot of alcohol

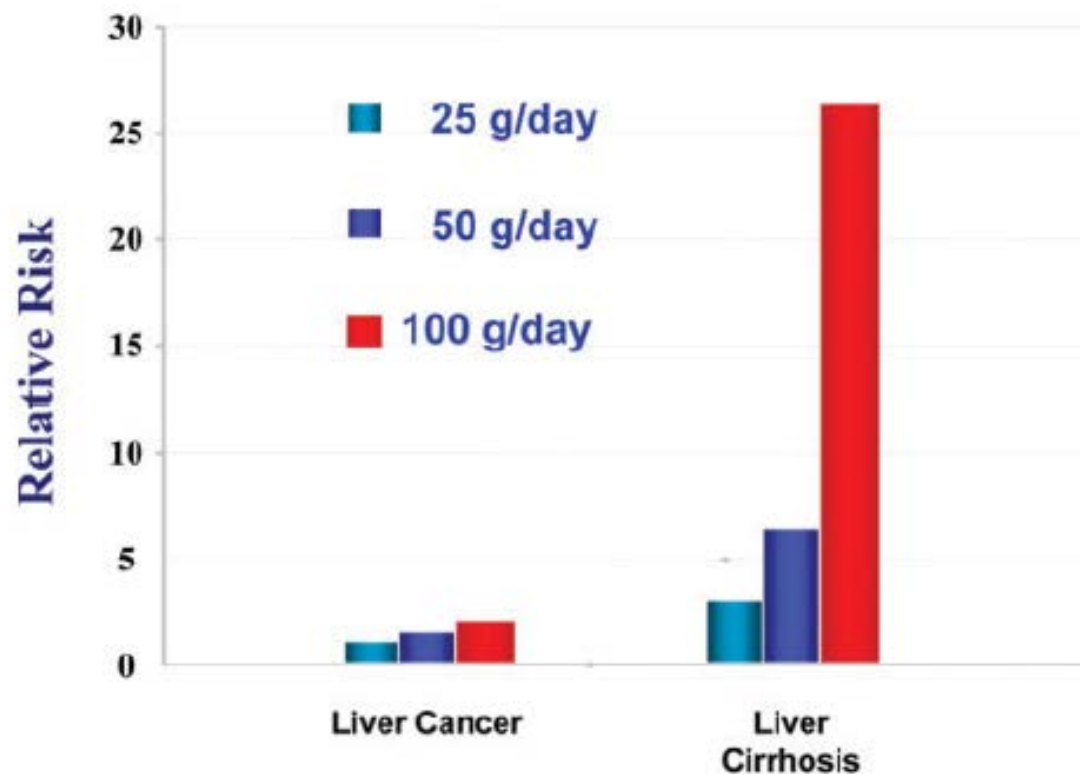
Risk is Proportional to Intake

Binge drinking is harmful at multiple levels (Health, Social, Family, Job, Legal Costs)

- Disease risk in multiple organs
- Injury to self and others
- Lost wages and productivity

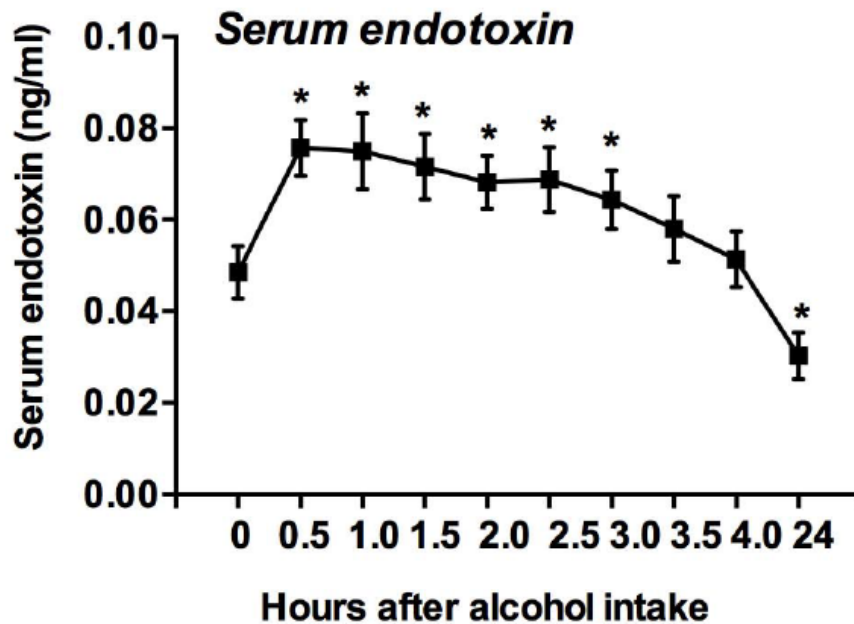


Excessive intake promotes liver disease



Binge-level alcohol increases leakage of bacterial factors from gut into blood

Bacterial toxins



Bacterial DNA



**Alcohol seen as such a toxin by the body:
Willing to turn it into
formaldehyde to get rid of it**

**ALDH2 mutation: ~560 million people with
alcohol “flush response”
Higher risk of many diseases**

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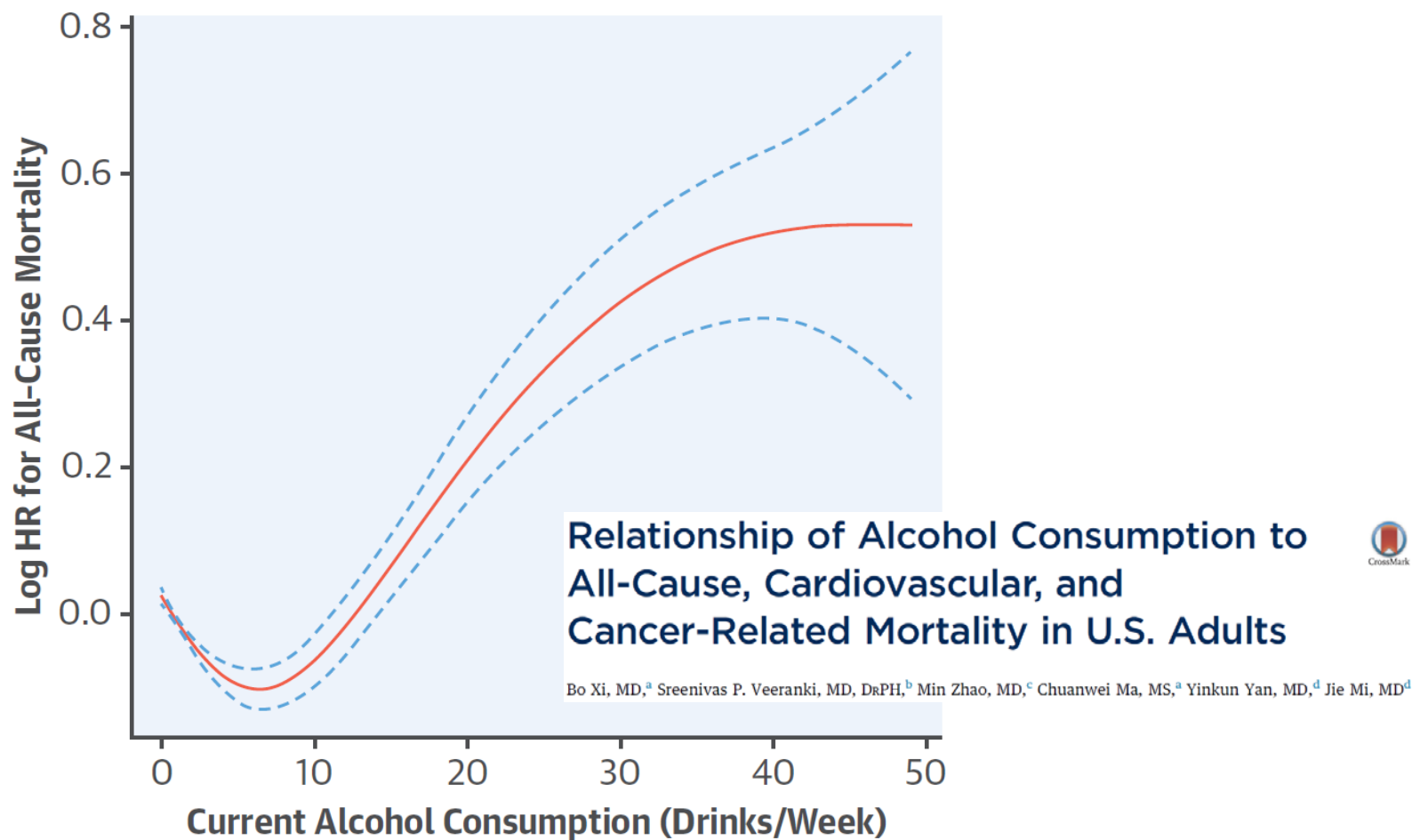
**ALDH2 mutation: ~560 million people with
alcohol “flush response”
Higher risk of many diseases**

But also

**Likely many adaptations for alcohol:
Earliest mammals like alcohol-living shrews
Even archebacteria have strong ALDH2**

Moderate alcohol

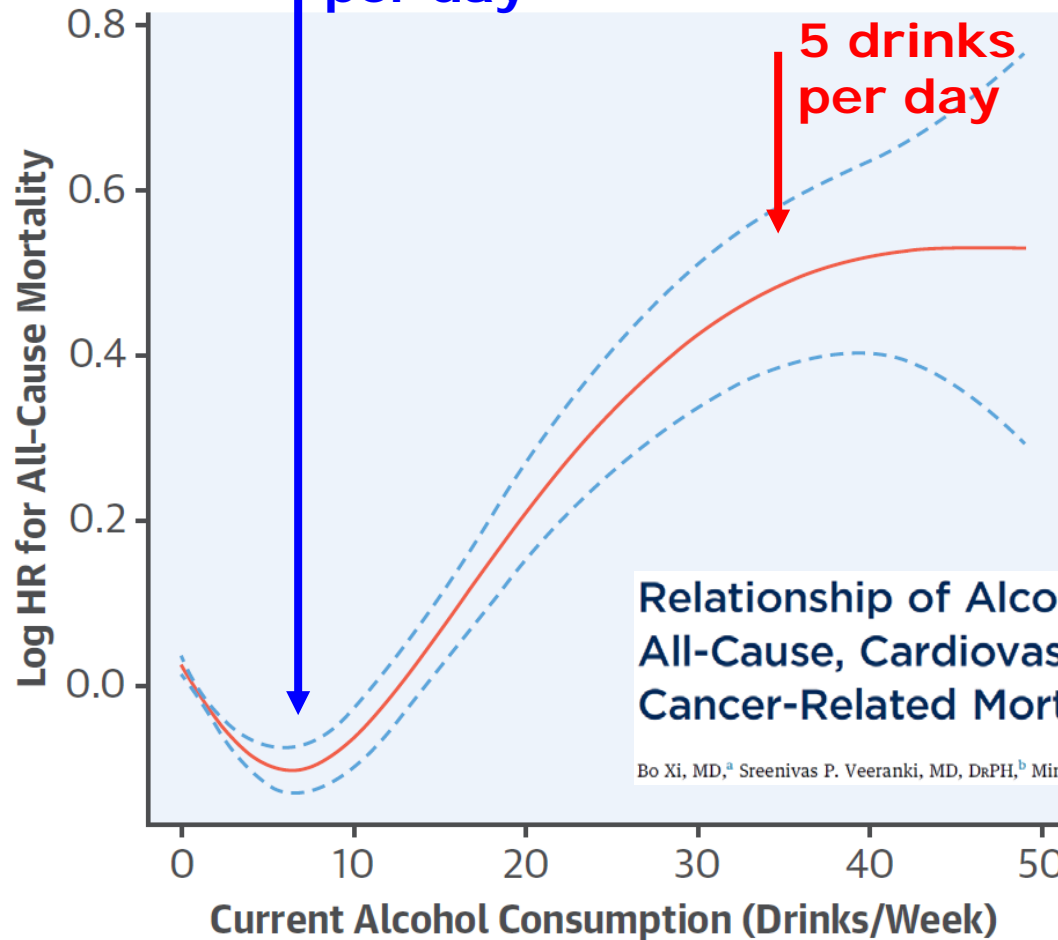
**Risk of
Harm**



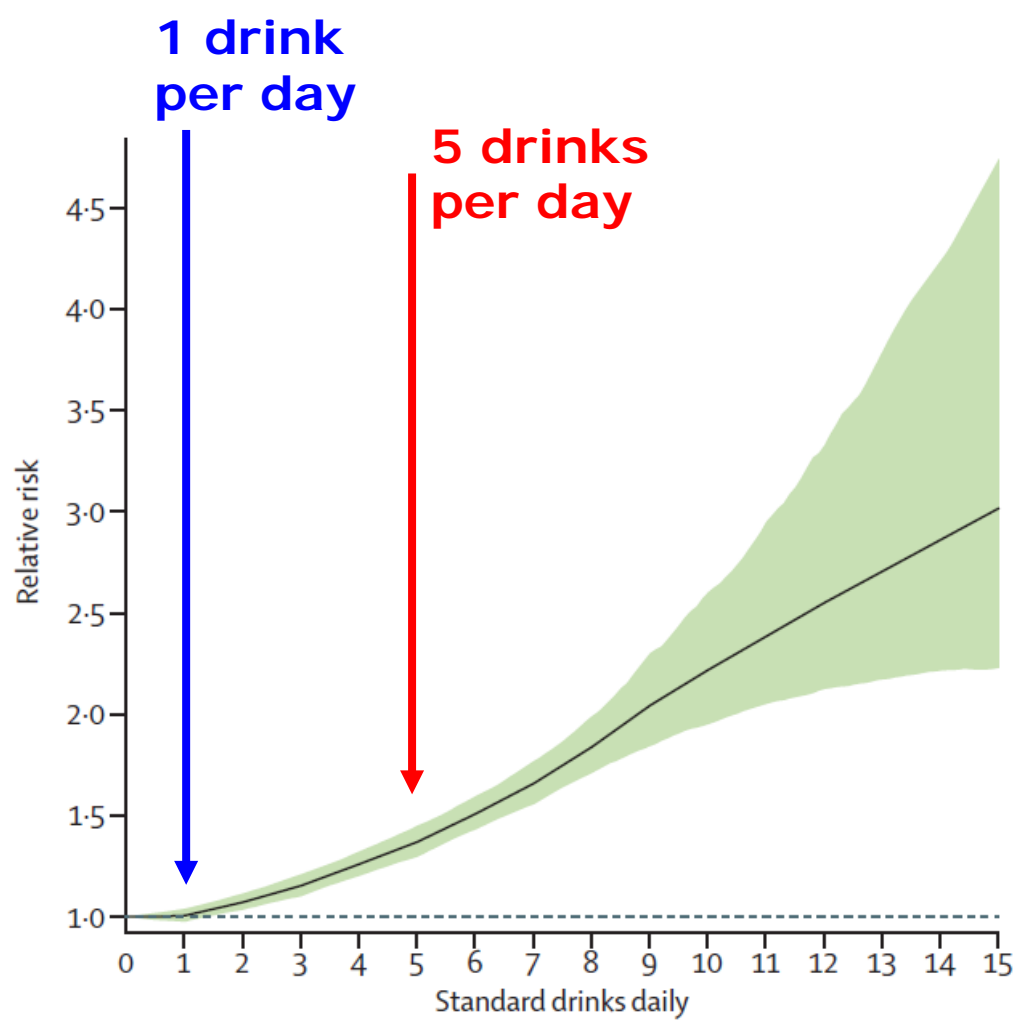
Possible benefit of

1 drink
per day

5 drinks
per day



Risk of Harm

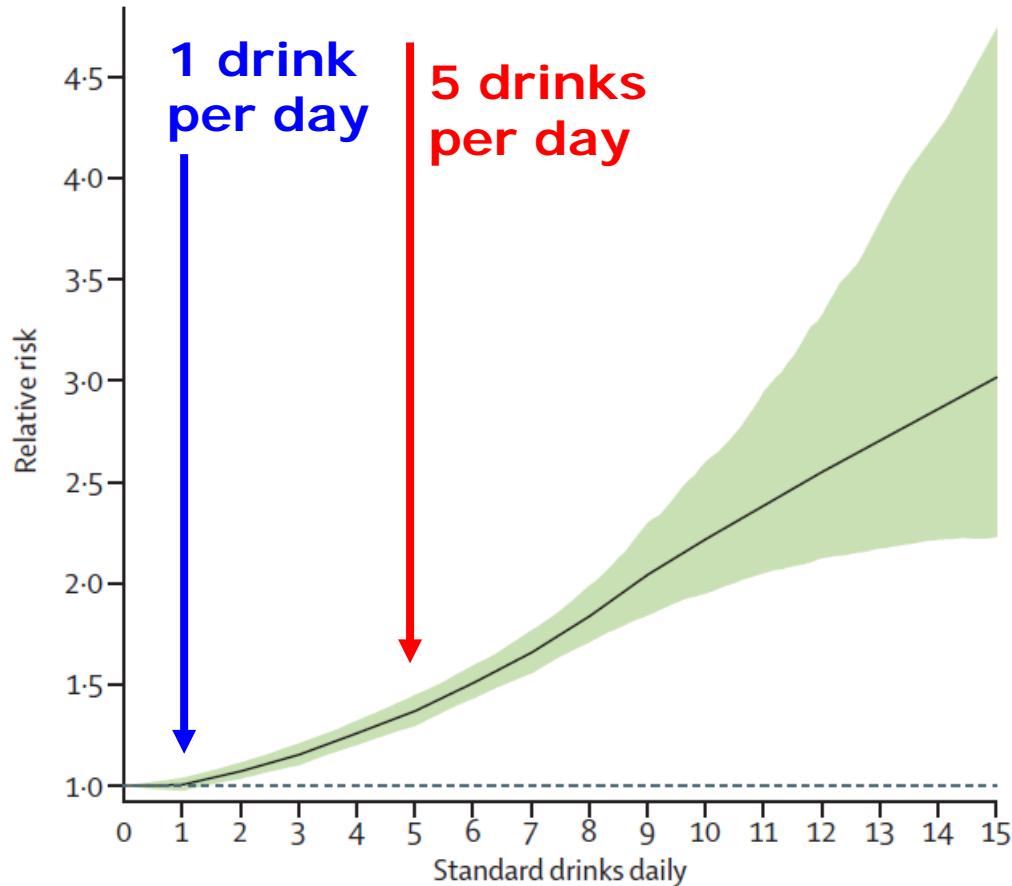


Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

Could Doctors Prescribe Alcohol?

Difference between studying people at the
Aggregate vs Individual Level

**Risk of
Harm**



Alcohol use and burden for 195 countries and territories,
1990–2016: a systematic analysis for the Global Burden of
Disease Study 2016

Drink Responsibly

Just Don't Binge



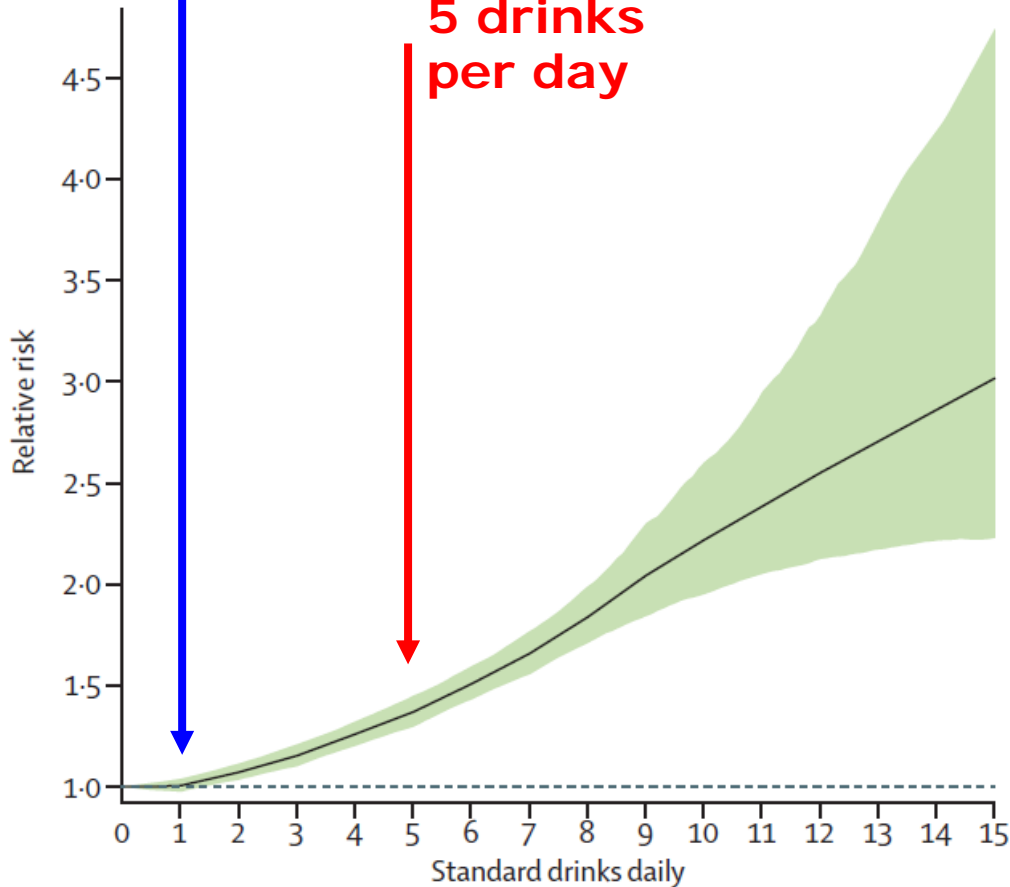
Drink Responsibly

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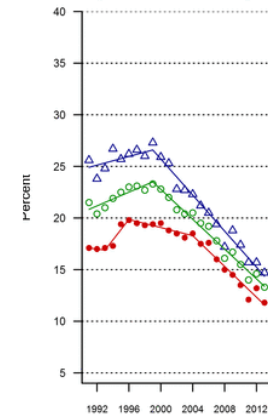
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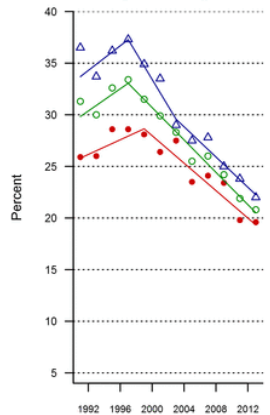
Risk of
Harm



MTF: in the past 2 weeks/
among 8th, 10th, and 12th graders



YRBS: in the past 30 days/
among 9th–12th graders



1992 to 2012