Where do harmful drinking urges come from?

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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
Moderate drinkers become binge drinkers
Binge drinking: 4-5 drinks in 2 hours
Binge drinking: 4-5 drinks in 2 hours

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

CDC, 2014
The Cost of Binging

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

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The Cost of Binging

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

The $1/7^{th}$ of US adults that are binge drinkers

consume $3/4^{th}$ 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

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

Red: females
Blue: males

Binge drinking
Compulsive alcohol drinking:
Intake despite bad consequences

Binge alcohol drinking

Compulsive alcohol drinking
Compulsive alcohol drinking: Intake despite bad consequences

Bingers become compulsive drinkers
Compulsive alcohol drinking:
Intake despite bad consequences

Binge alcohol drinking

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”
“Choice to drink despite cost” drives addiction

Binge alcohol drinking

Compulsive alcohol drinking
“Choice to drink despite cost” allows addiction

Binge alcohol drinking

Compulsive alcohol drinking
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

Wise, 1973, Simms et al., 2008; Hopf et al., 2010
Alcohol Drinking Model

Alcohol Intake (g/kg/24hr)

week of intake

Intermittent Access to Alcohol, 2-bottle choice
Intermittent Access to Alcohol, 2-bottle choice

Alcohol Drinking Model

Switch to 20 min/d
Brain Areas that mediate Compulsive Drives for Alcohol?
Brain Areas that mediate Compulsive Drives for Alcohol?

mPFC, Insula, striatum

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

mPFC

Insula

ventral striatum

ACT!

Ambroggi et al. 2010, McGinty et al. 2013
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

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

Ambroeggi et al. 2010, McGinty et al. 2013

Insula → ventral striatum → ACT!
The “mPFC Input” to Striatum

mPFC: medial prefrontal cortex

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

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

Stuber and Mason 2013
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

<table>
<thead>
<tr>
<th>No laser</th>
<th>Laser</th>
</tr>
</thead>
</table>

![Graph showing alcohol intake (g/kg/2 min) vs. quinine concentration (mg/L)]

- 0 mg/L: 0.7 g/kg/2 min (no laser), 0.6 g/kg/2 min (laser)
- 30 mg/L: 0.6 g/kg/2 min (no laser), 0.5 g/kg/2 min (laser)

* indicates statistical significance.
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
Alcohol Intake

Insula input

Insula-Striatum Inputs are inhibited or not

Amount of challenge in alcohol:
0 no challenge, 30 tastes bad
Regular, Alcohol-Only Drinking

Amount of challenge in alcohol:
0 no challenge, 30 tastes bad
Regular, Alcohol-Only Drinking

NO CHANGE!!

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

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

Seif et al., Nat Neurosci, 2013
What about for a different bad consequence? (shock)
Needed for Compulsion-Like Alcohol Drinking

**Insula input**

**mPFC input**

Seif et al., Nat Neurosci, 2013

![Graph showing lever presses for Pre-Shock and Shock conditions with and without laser input.](Image)
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

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

Red border: higher threat of shock, when pressing to get alcohol or other reward

Green border: Safe (no shock)

Grodin, Momenan et al., 2018
Lots of pressing when it is Safe (green bars)

Grodin, Momenan et al., 2018
Heavy human drinkers: more willing to press for alcohol in the face of threat

Grodin, Momenan et al., 2018
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

![Bar chart showing alcohol intake (g/kg/2 min) vs. [quinine] (mg/L) for 0 and 30 mg/L, with a significant difference indicated by an asterisk (*)]
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

*Tiffany and Conklin, 2000; Naqvi and Bechara, 2010*
Why do Insula-Striatum only regulate Compulsive Drinking?

Compulsive intake:
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Habitual intake:
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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?

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**Conflict** Recruits Cortical Circuits

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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

Seeley et al., 2007
Short important things
Alcohol cues promote drinking

Myrick 2004; Filbery 2008; Claus 2013
Alcohol cues promote drinking

Insula activity PREDICTS real-world intake and relapse

Myrick 2004; Filbery 2008; Claus 2013
Alcohol cue “automatically captures attention”

Myrick 2004; Filbery 2008; Claus 2013
If you gamble and "almost win"

Insula activation predicts the desire to gamble more

Greater Insula activity for almost win

Greater desire to keep gambling

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

Luke Clark, Andrew J. Lawrence, Frances Astley-Jones, and Nicola Gray

Department of Experimental Psychology, University of Cambridge, UK

Correspondence: luke.clark@cam.ac.uk


Luke 2011
Partial Insula Stroke:

Give up smoking without effort

Naqvi and Bechara 2007 Science
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”

Guillem et al., 2010
Insula key for anxiety:

• Overvalue negative info

• Sustained attention

• Relief Seeking when bad feeling awakened

(subconscious and conscious levels)

Paulus and Stein 2006
A game: is my heart beat in time with music rhythm?
A game: is my heart beat in time with music rhythm?

Better ability to feel body

Critchley et al., 2004
Awareness innately comes with some anxiety

More basal anxiety

Better ability to feel body

Critchley et al., 2004
Craig, 2009

Insula

Most singular sense of Self in the moment

“Feeling of knowing”

“Free won’t”

Moment of recognition

Decision making

Error awareness

Subjective cooling

Pleasant music

“Feeling of knowing”

Attention to heat pain

Rhythm

Maternal affiliation

Inspection time

Heartbeat awareness

Happy voices

learned pain ‘now’

Seeing or making a smile

Self recognition

smile

time perception

self-recognition

Craig, 2009
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?”

How much alcohol is harmful?

Binging
What is harmful drinking?

Why do we call it “harmful?”

How much alcohol is harmful?

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

Binging

I know I shouldn’t do it but I do it anyways

Repeated practice in “giving in to urges”
What is harmful drinking?

Why do we call it “harmful?”

How much alcohol is harmful?

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

I know I shouldn’t do it but I do it anyways

Repeated practice in “giving in to urges”

Costs:
- Organ Damage
- Harm to Others
- And Self

Binging

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

Binge drinking is defined as 4 or more alcoholic beverages per occasion for women or 5 or more drinks per occasion for men.

1 in 7 people binge drink
Excessive intake promotes liver disease

Zakhari & Li 2007
Binge-level alcohol increases leakage of bacterial factors from gut into blood

**Bacterial toxins**

**Bacterial DNA**

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_Bala et al. 2014_
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
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

But also

Likely many adaptations for alcohol:
Earliest mammals like alcohol-living shrews
Even archebacteria have strong ALDH2
Moderate alcohol
Risk of Harm

Relationship of Alcohol Consumption to All-Cause, Cardiovascular, and Cancer-Related Mortality in U.S. Adults

Bo Xi, MD, a Sreenivas P. Veeranki, MD, DrPH,b Min Zhao, MD,c Chuanwei Ma, MS,a Yinkun Yan, MD,d Jie Mi, MDd

Possible benefit of

1 drink per day

Risk of Harm

5 drinks per day

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1 drink per day

5 drinks per day

Risk of Harm

Could Doctors Prescribe Alcohol?
Difference between studying people at the Aggregate vs Individual Level

Risk of Harm

Drink Responsibly

1 drink per day

5 drinks per day

Risk of Harm

Drink Responsibly

Just Don’t Binge

Risk of Harm

1 drink per day

5 drinks per day

1992 to 2012