Health disparities in addiction: Lessons from imaging and genetics, with implications for treatment

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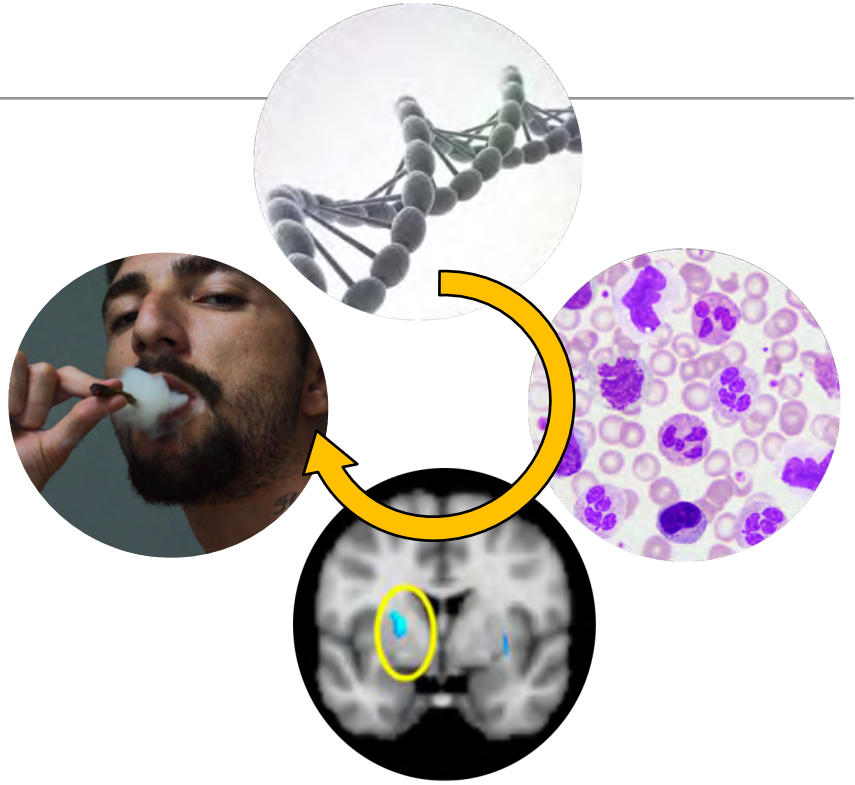
Penn Medicine

I have no conflicts of interest.

Overview

- **The tools we use**
  - Genetic variability
  - Protein expression
  - Neuroimaging
  - Behavior



- **Disparities in addiction**
  - Sex differences
  - Differences in brain and behavior
  - Implications for recovery

Addiction

- **Disease of the brain**
  - Motivation
  - Reward
  - Memory

  } Physical and chemical

- Chronic

- Continued use despite negative consequences

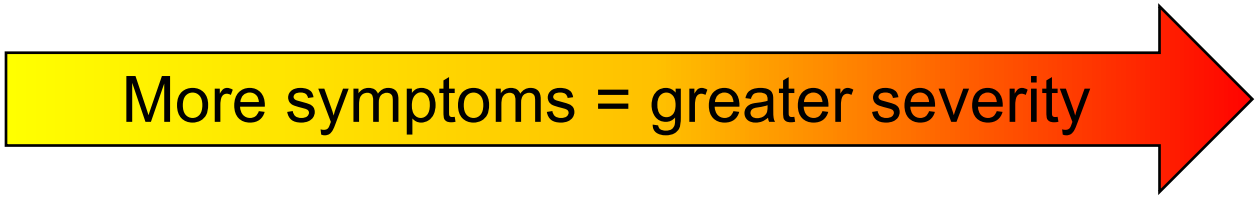
- Measured on a spectrum;
  more symptoms = increased severity

American Society of Addiction Medicine

Addiction Symptoms and Severity

- Failure to fulfill life obligations
- Giving up other activities
- Continued use despite negative consequences
  - Health
  - social
- Increased amount used, and time spent using
- Use in hazardous situations
- Tolerance
- Withdrawal
- Inability to control intake

- **Craving**

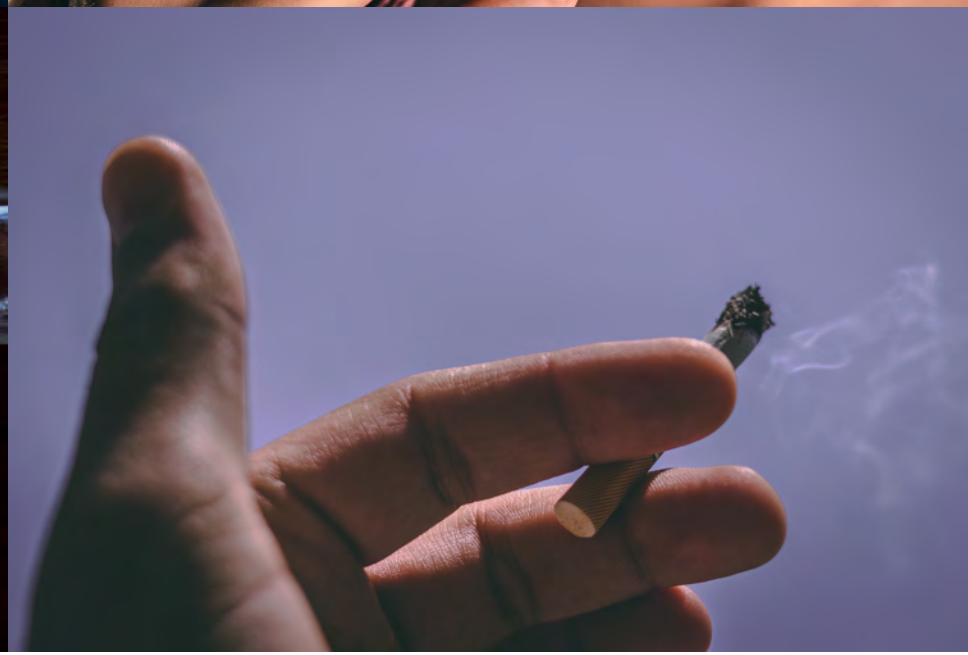


Cue-elicited Craving

- With repeated use, stimuli predict delivery of reward
- Over time, the brain begins to respond to the cue itself
- This triggers craving

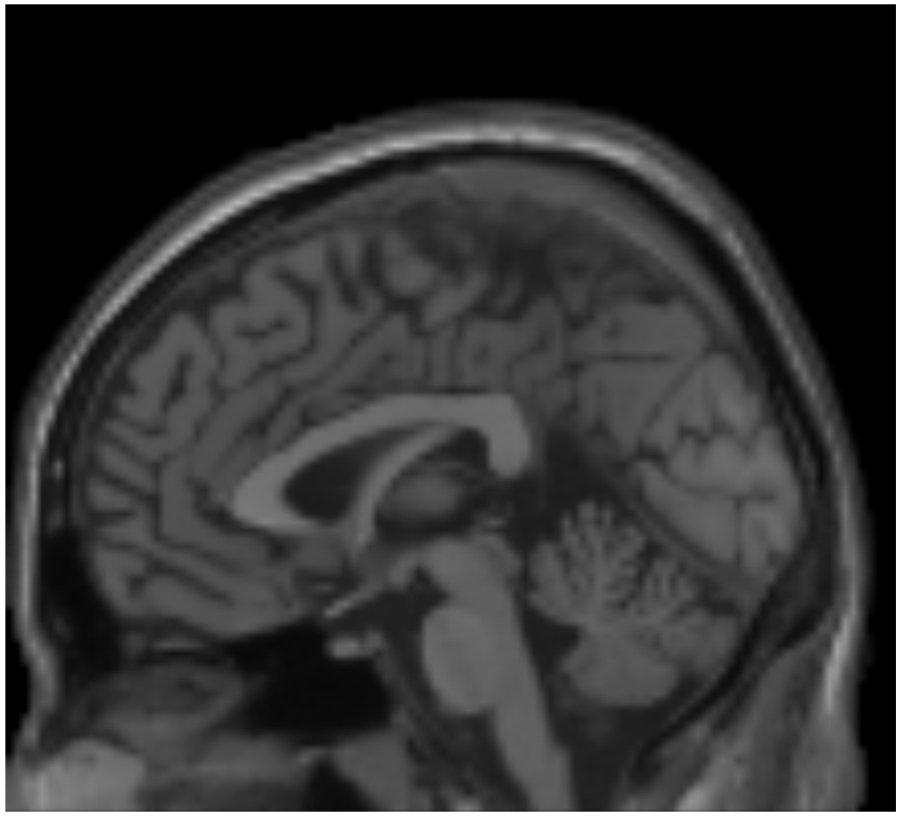
Cue +  Reward →  Neural Response

Cue-elicited Craving

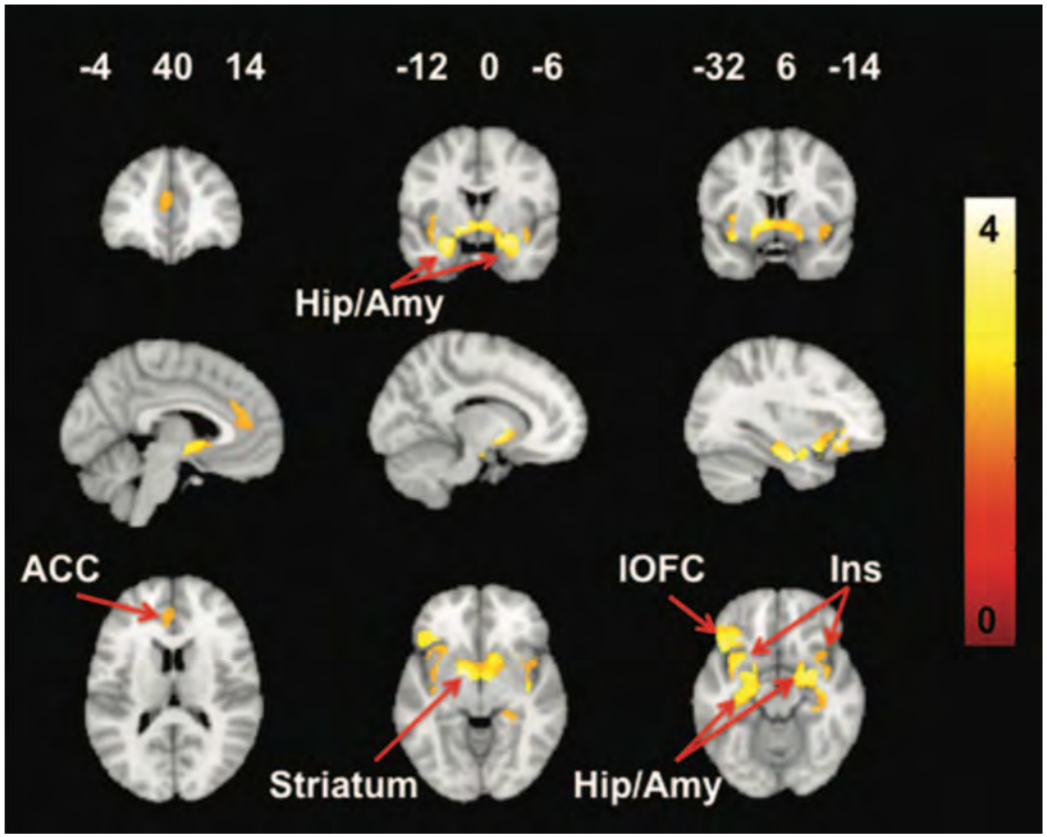


Neuroimaging

- **Structure**
- **Function**
  - Neural activity as a function of blood flow
  - Experimental paradigms specifically designed to responses to different stimuli

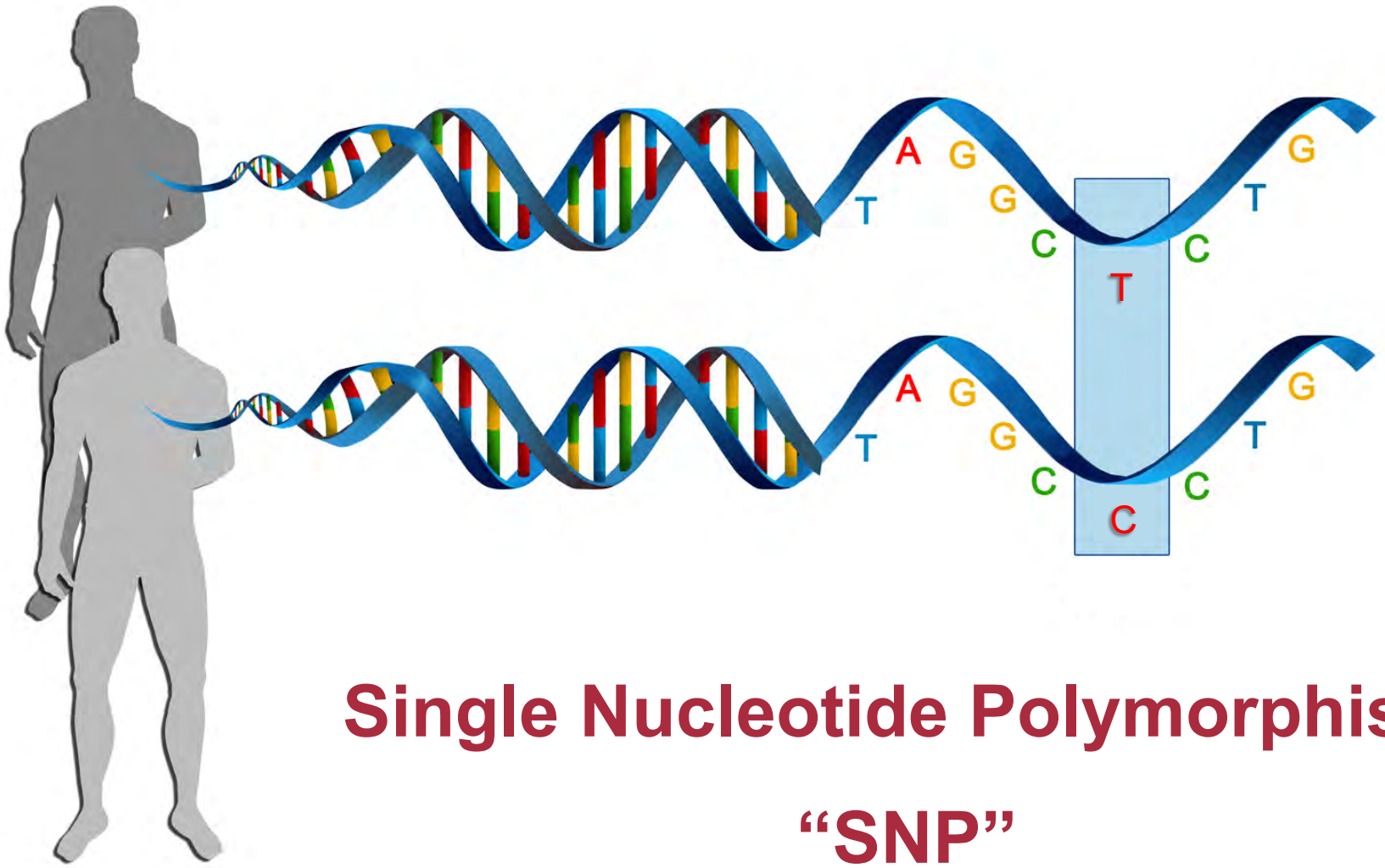


Neuroimaging: Cue paradigms



Wetherill et al. 2015

Genetic Variability

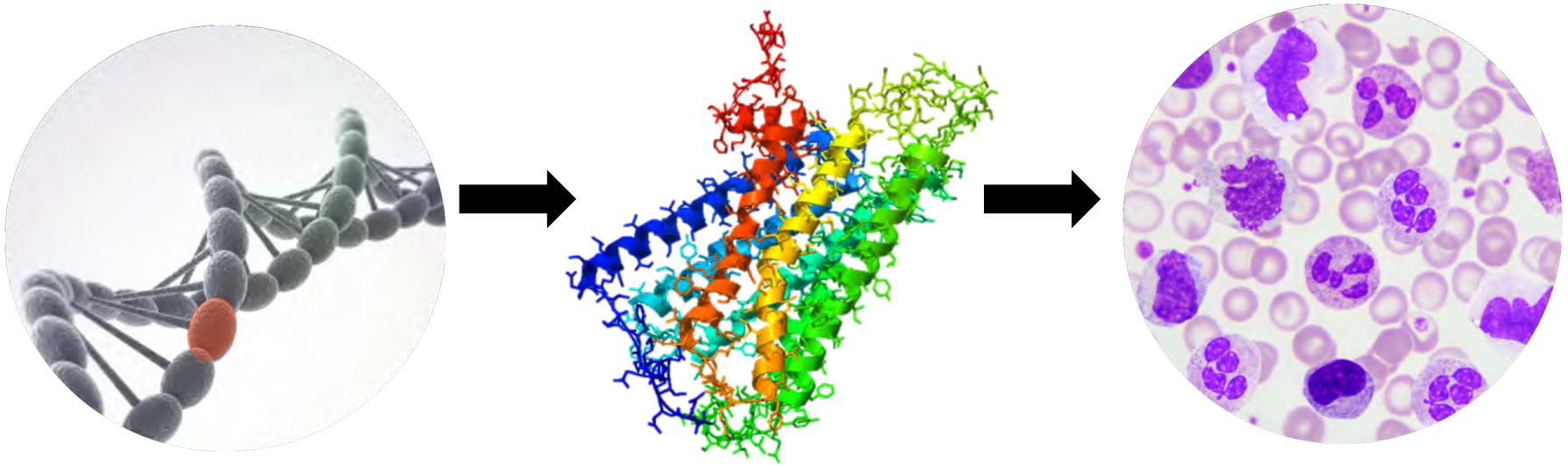


Single Nucleotide Polymorphism

"SNP"

Ducci and Goldman, 2012

Protein expression and Cell function



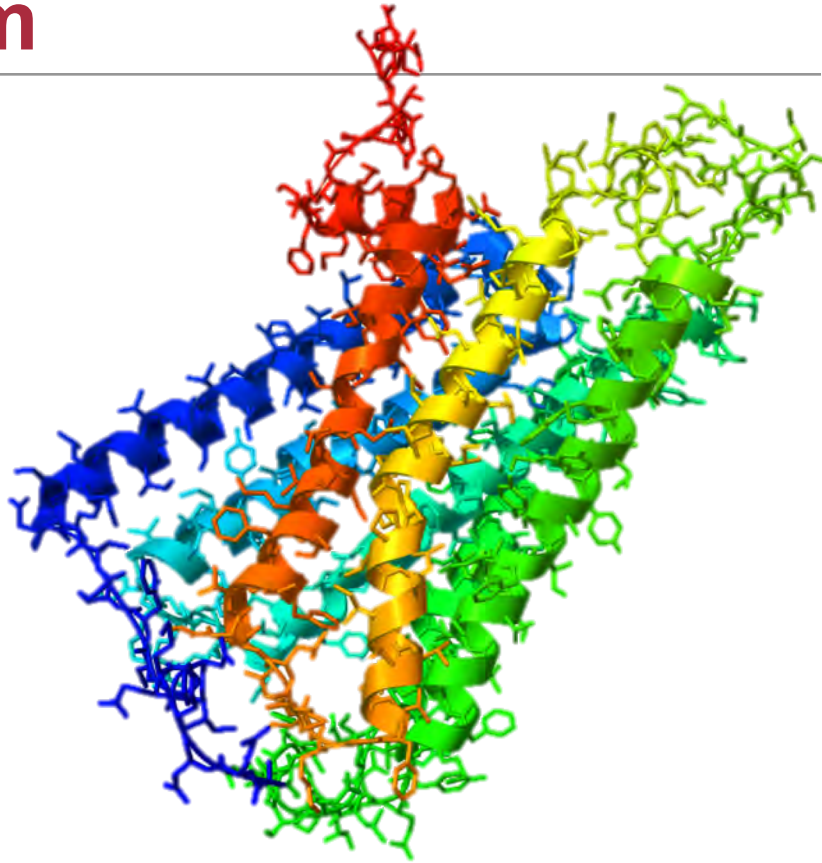
DNA

Proteins

Cells

Endocannabinoid System

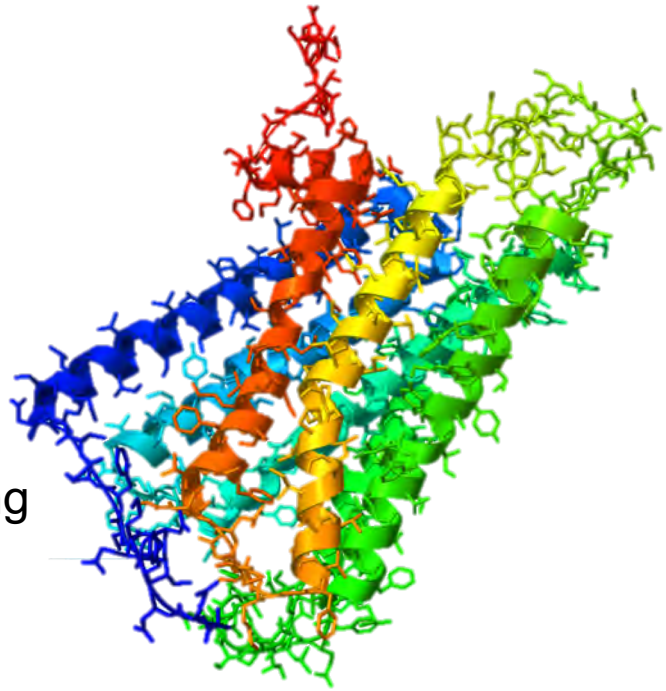
- **Neuromodulatory**
  - appetite
  - pain
  - mood
  - higher order cognitive functions
  - reward and motivation
- **CB1**
  - in the brain and the rest of the body
  - primary cannabinoid receptor in the brain



Agrawal et al., 2009; Lopez-Moreno et al., 2012

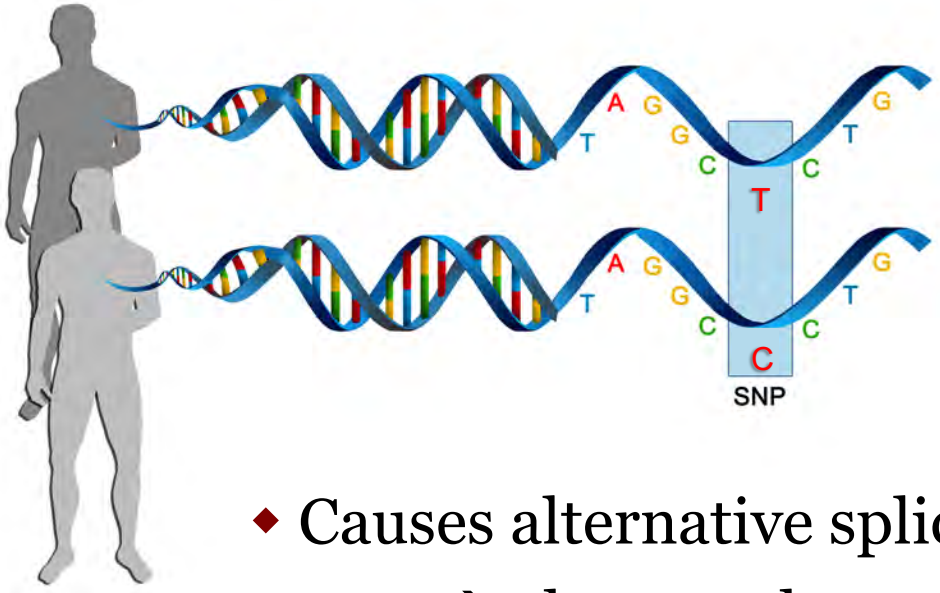
CB1 + Cannabis

- **THC (*trans*-Δ^9-tetrahydrocannabinol)**
  - Binds to CB1
  - Psychoactive
  - Activates reward circuitry and is therefore addicting
  - genetic variability in CB1 affects THC binding



Agrawal et al., 2009; Lopez-Moreno et al., 2012

Variability in the CB1 gene: rs2023239

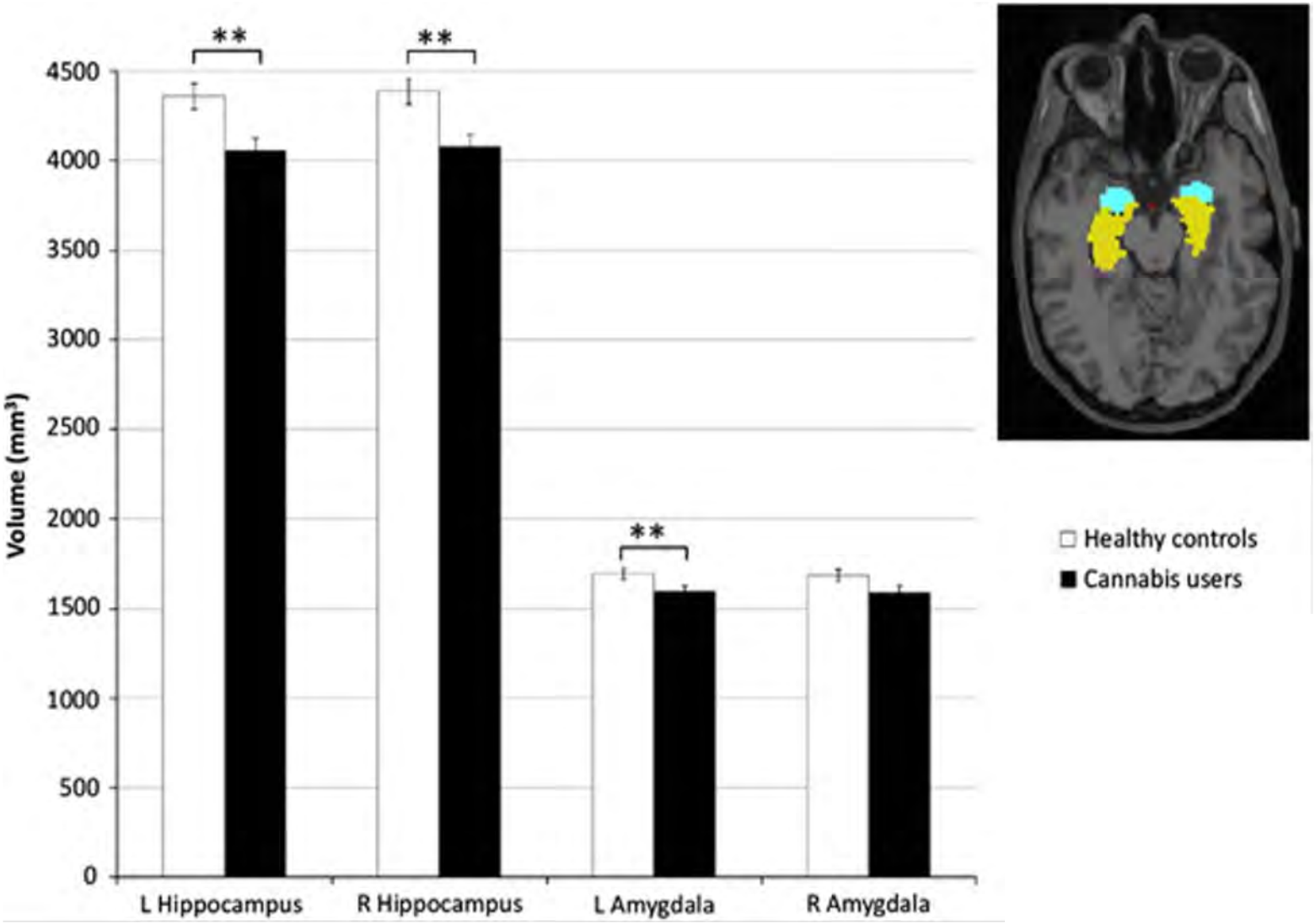


← The "risk" variant

- Causes alternative splicing of CB1 gene
  → changes the structure of CB1
  → changes the function of CB1 (ligand binding)
- Associated with
  - increased cannabis use disorder
  - increased craving for cannabis

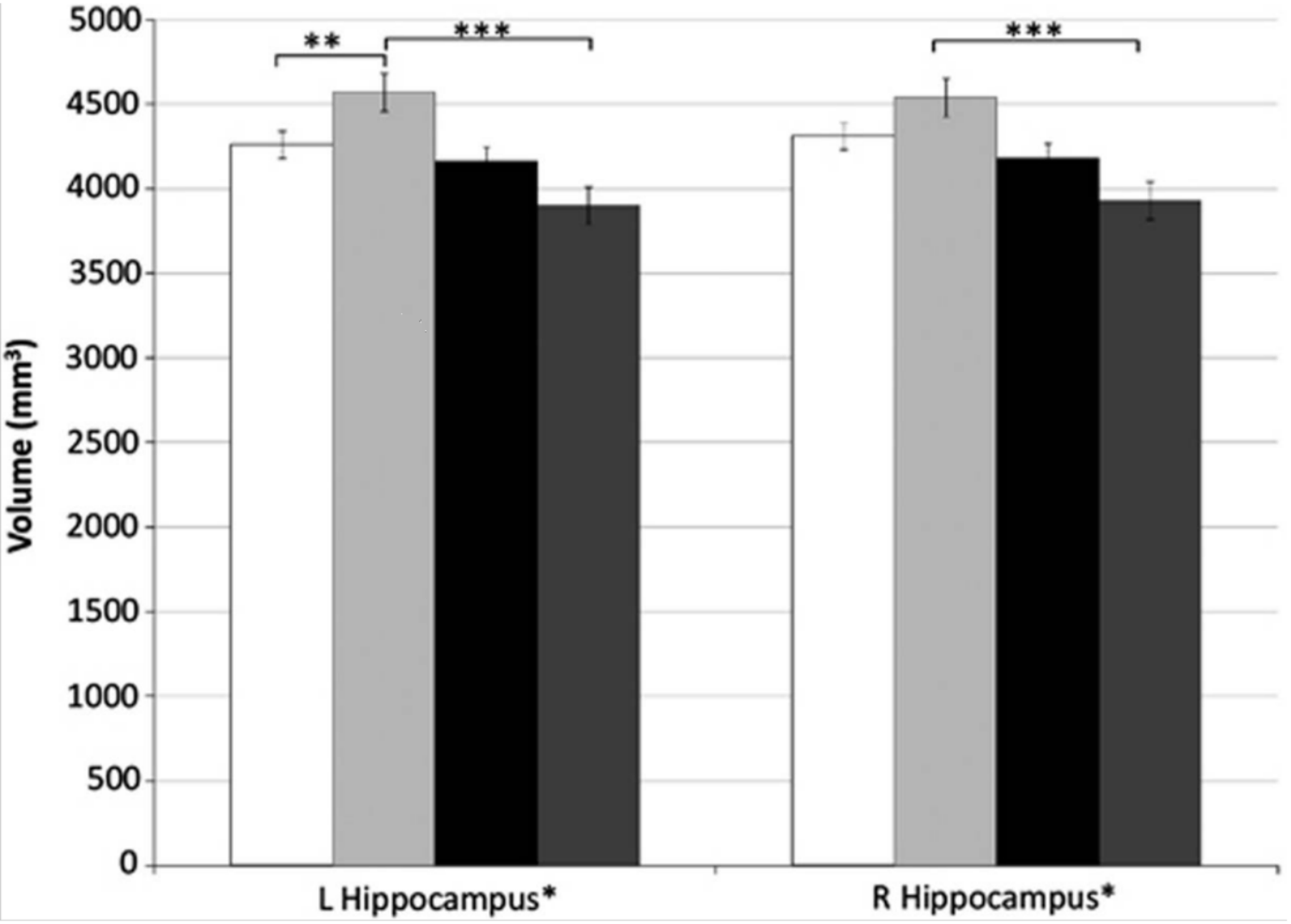
(Haughey et al., 2008, Schacht et al., 2009)

Cannabis use and brain volume



Schacht, Hutchision & Filbey, 2012

Rs2023239 and brain volume

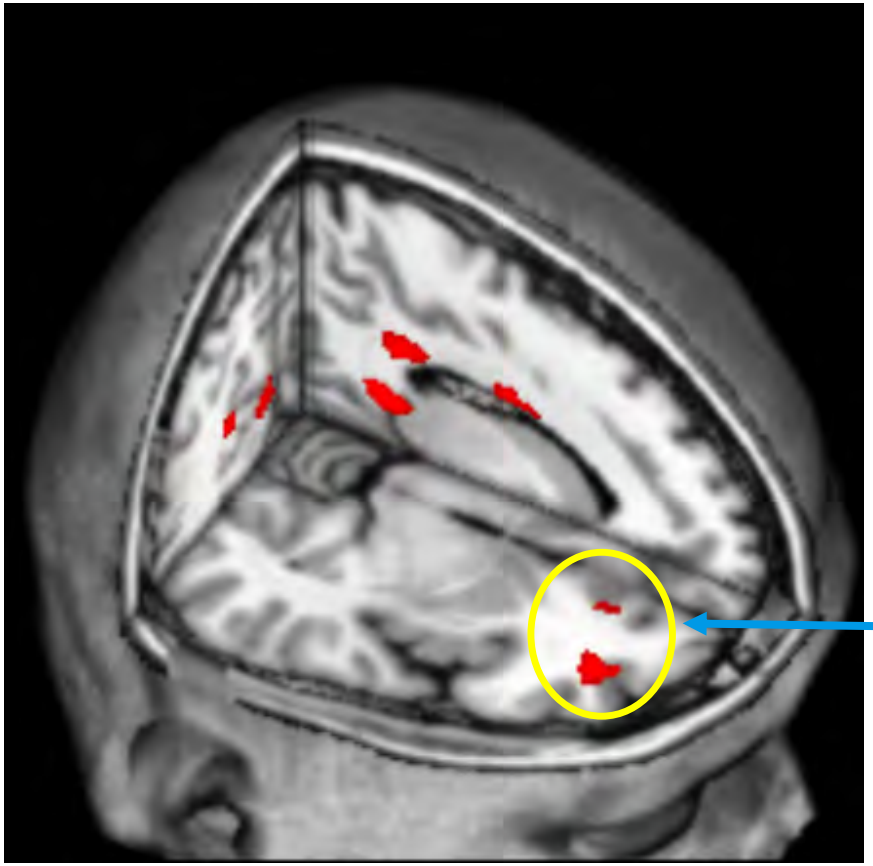


Controls
- without risk variant
- with risk variant

Cannabis users
- without risk variant
- with risk variant

Schacht, Hutchision & Filbey, 2012

Rs2023239 genotype is associated with brain's response to cues

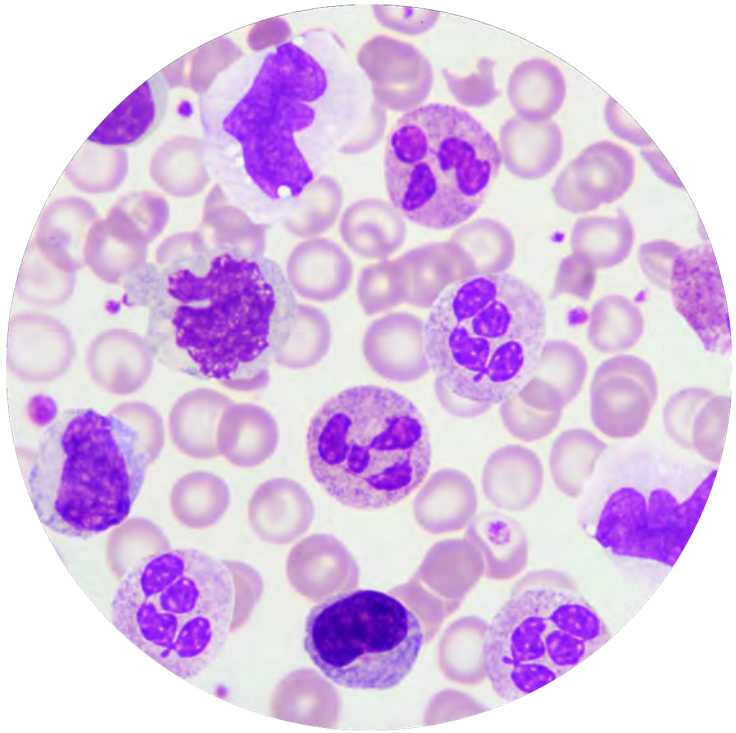


Risk allele carriers have greater activation in the orbitofrontal cortex than non carriers.

Filbey et al., *Neuropsychopharmacology*, 2010

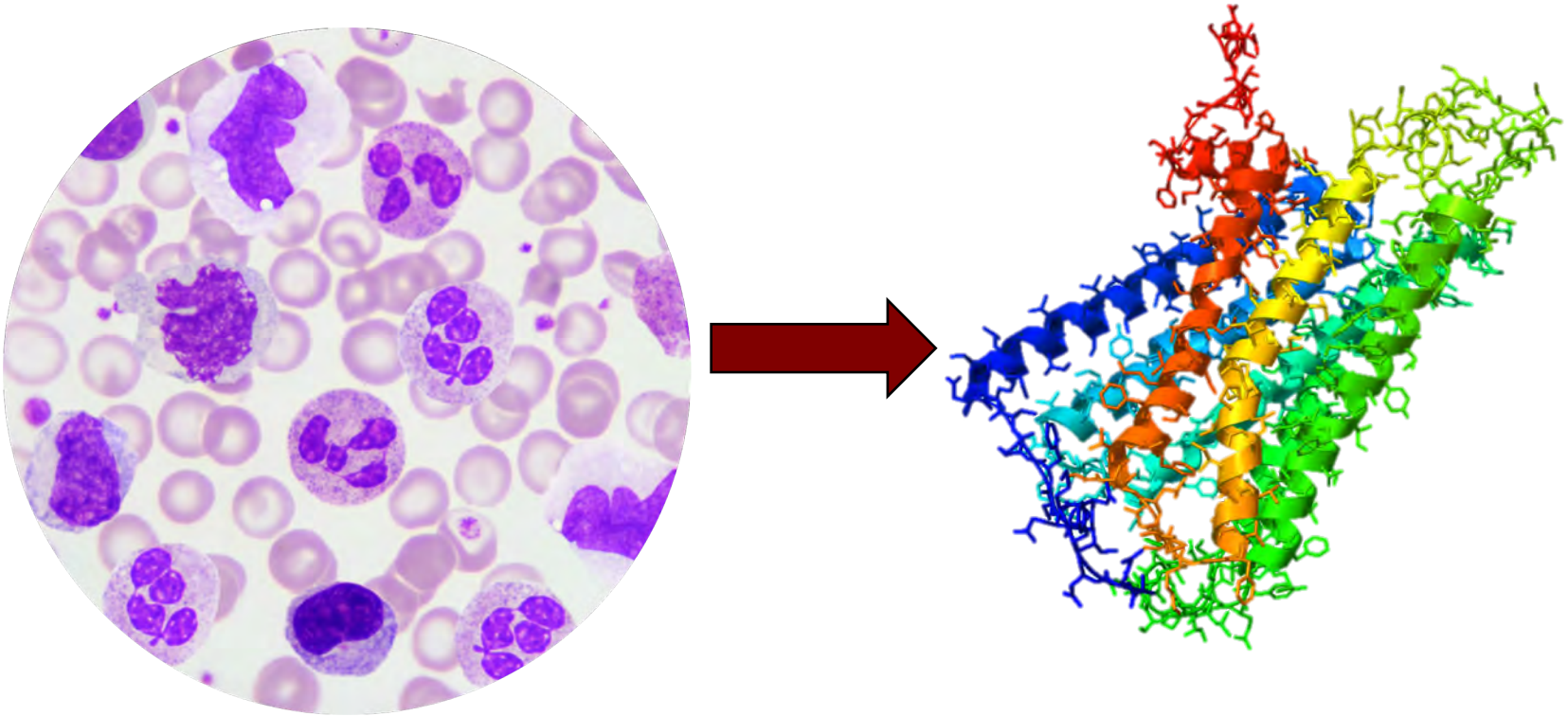
A biomarker for cannabis use disorder

- **What if rs2023239 has a measurable effect in a part of the body a little more accessible?**



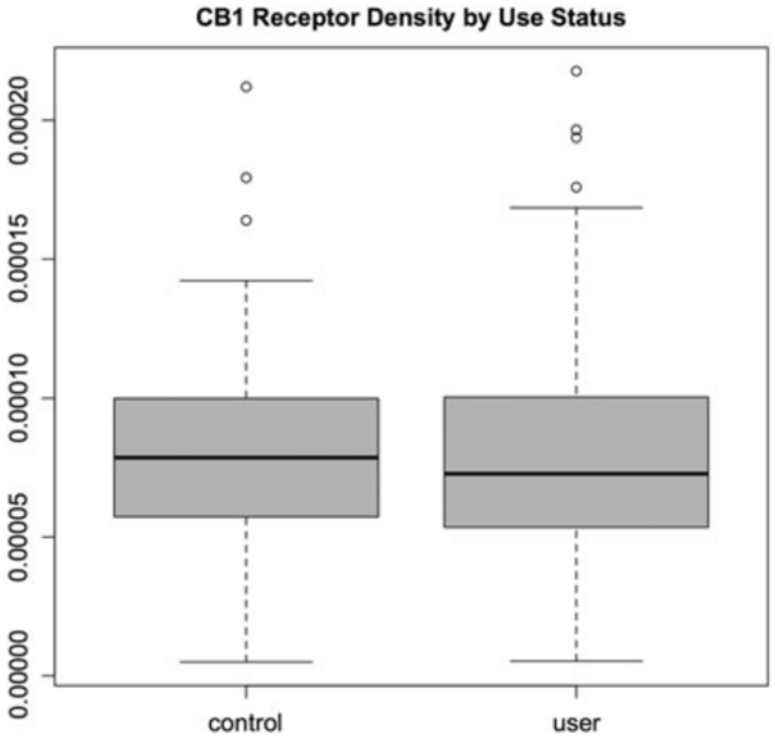
A biomarker for cannabis use disorder

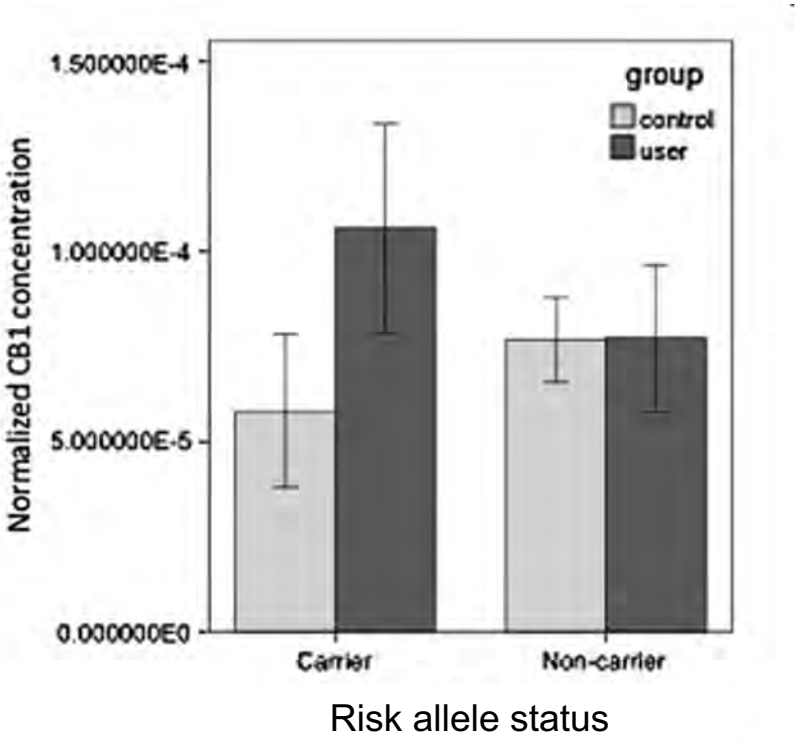
- Acquired blood samples from cannabis users (N=41) and healthy controls (N=26)
- Measured CB1 density in lymphocytes



Rs2023239 and CB1 receptor density

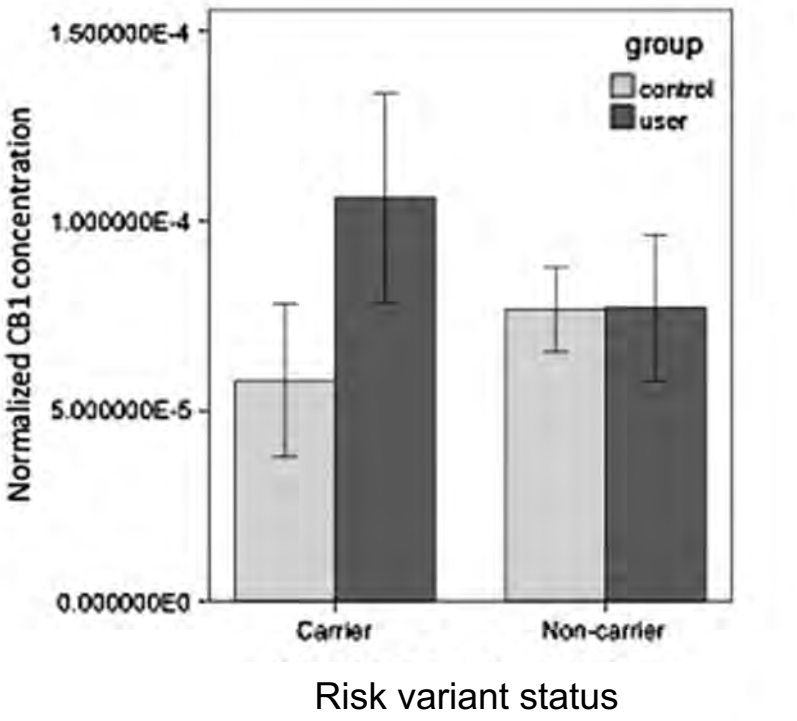
- **No difference between users and controls, until we look at the risk variant:**





Ketcherside, et al. 2017

A biomarker for cannabis use disorder



- **Cannabis users carrying the risk variant had more CB1 than nonusers and non-risk variant carriers.**
- **But the majority of the literature says CB1 in the brain goes *down* with heavy cannabis use**
- **Different post-translational regulatory mechanisms for different cells**
  - We're still figuring it out

Ketcherside, et al. 2017

Part II: Health Disparities in sex differences

Sex differences in research

- **Women are historically under-represented in research**
  - To protect women of childbearing potential
  - Hormonal variability considered a “complication”
- **The NIH did not have an official inclusion policy until 1993**
  - Overseen by the office of research on women’s health
- **We’re still catching up, especially when it comes to substance use disorders**
  - How do men and women respond differently to drugs?
  - Are they differently vulnerable to relapse?
  - Do some medications/treatments work better for one sex compared to the other?

https://orwh.od.nih.gov/toolkit/recruitment/history

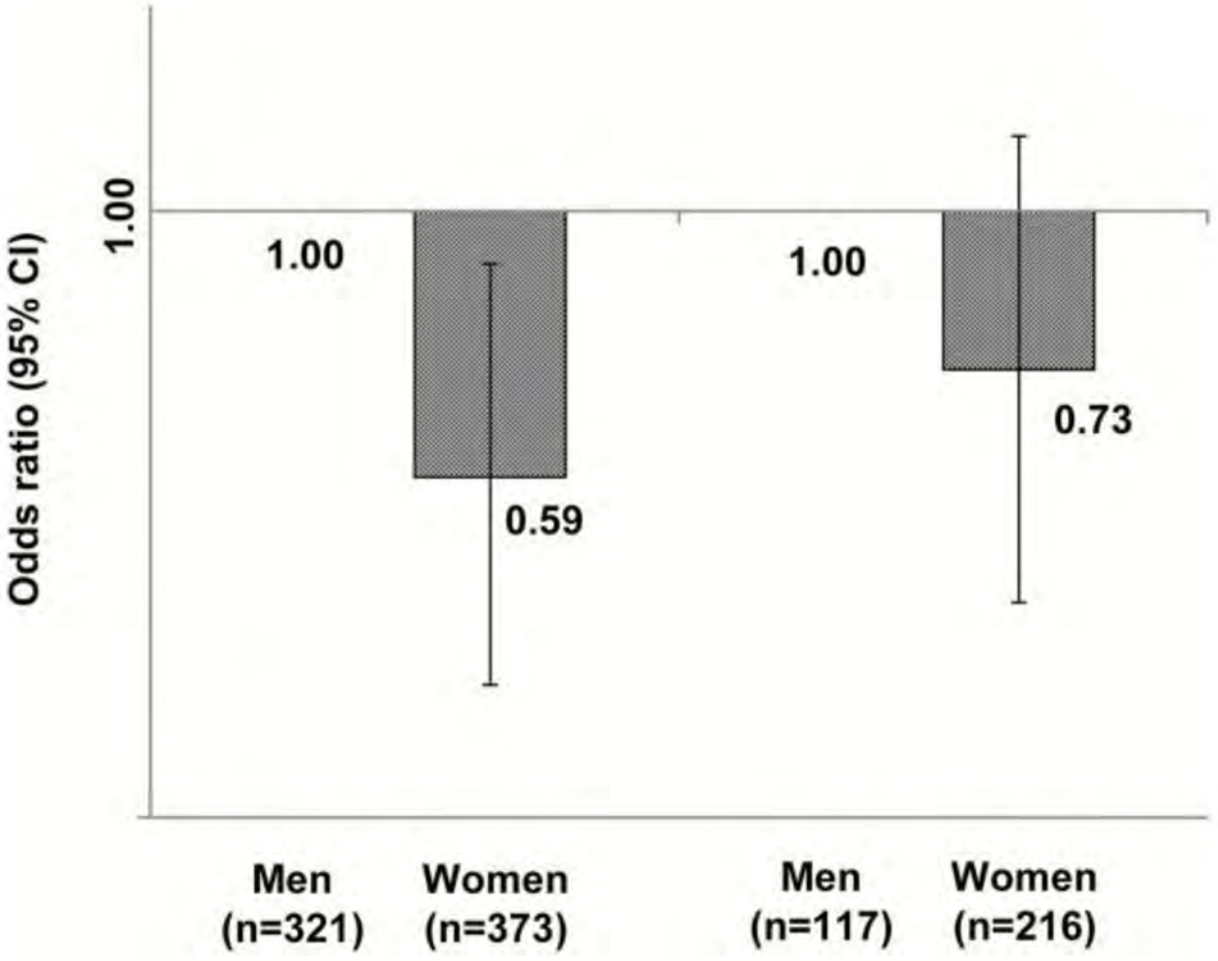
Sex differences in the health consequences of smoking

Compared to male smokers, female smokers:

- *have a 25% greater risk of coronary heart disease*
- are more likely to develop lung cancer
- have greater Chronic Obstructive Pulmonary Disease
- have additional reproductive health concerns

Huxley et al., 2011

Women have greater difficulty in quitting

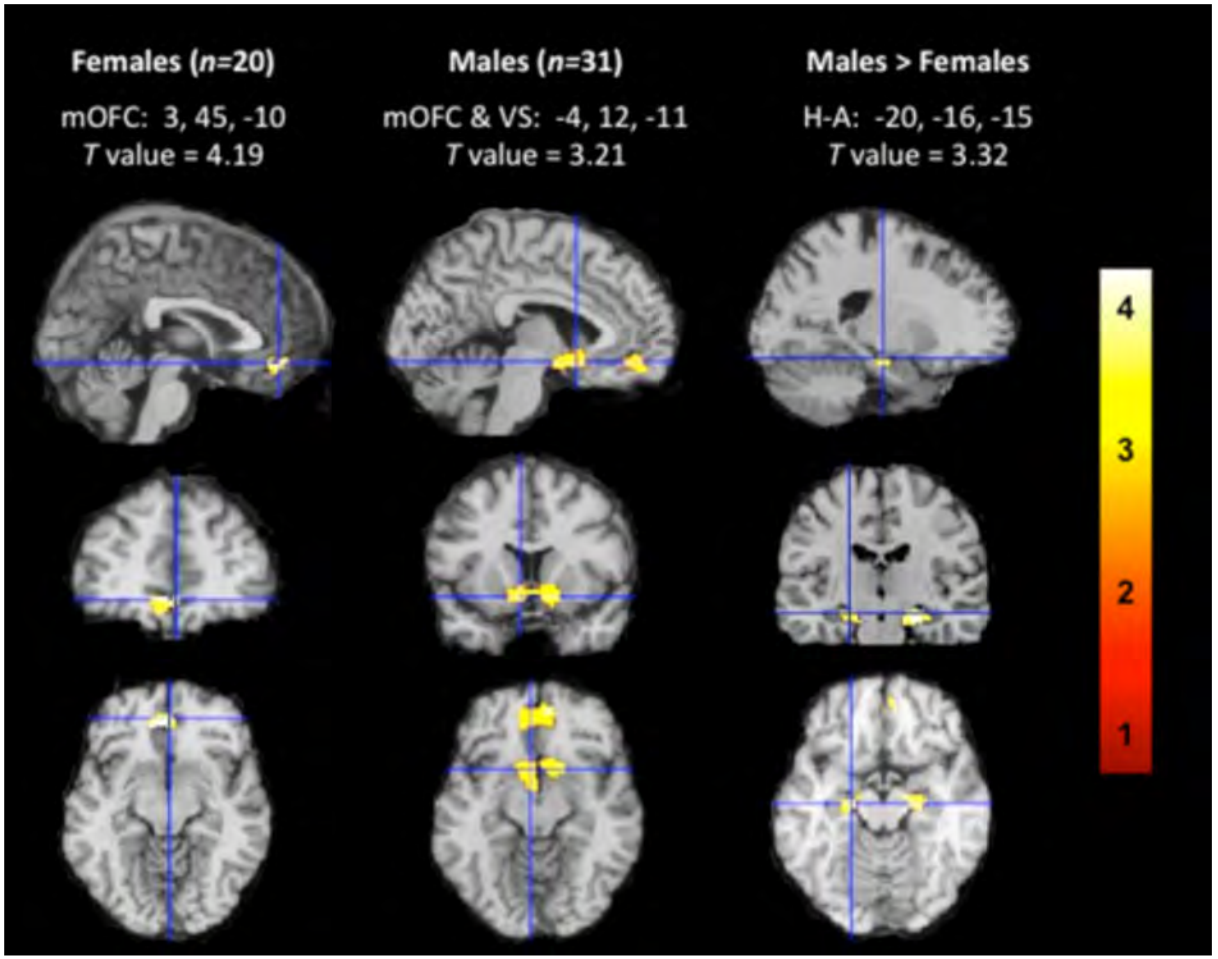


Smith et al. 2015

Why is it harder for women to quit?

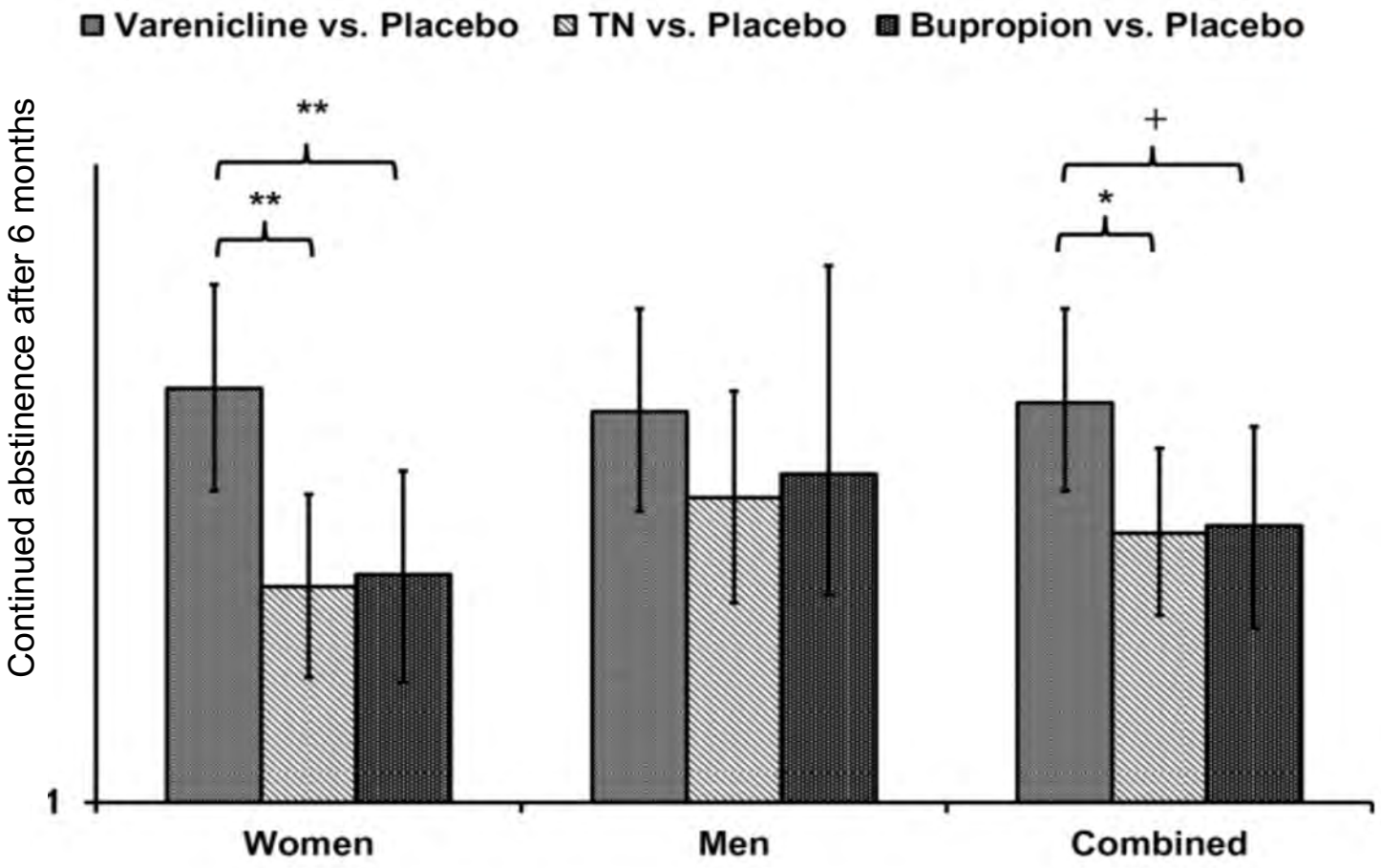
- **What is the mechanism?**

Sex differences in response to smoking cues



Wetherill et al. 2013

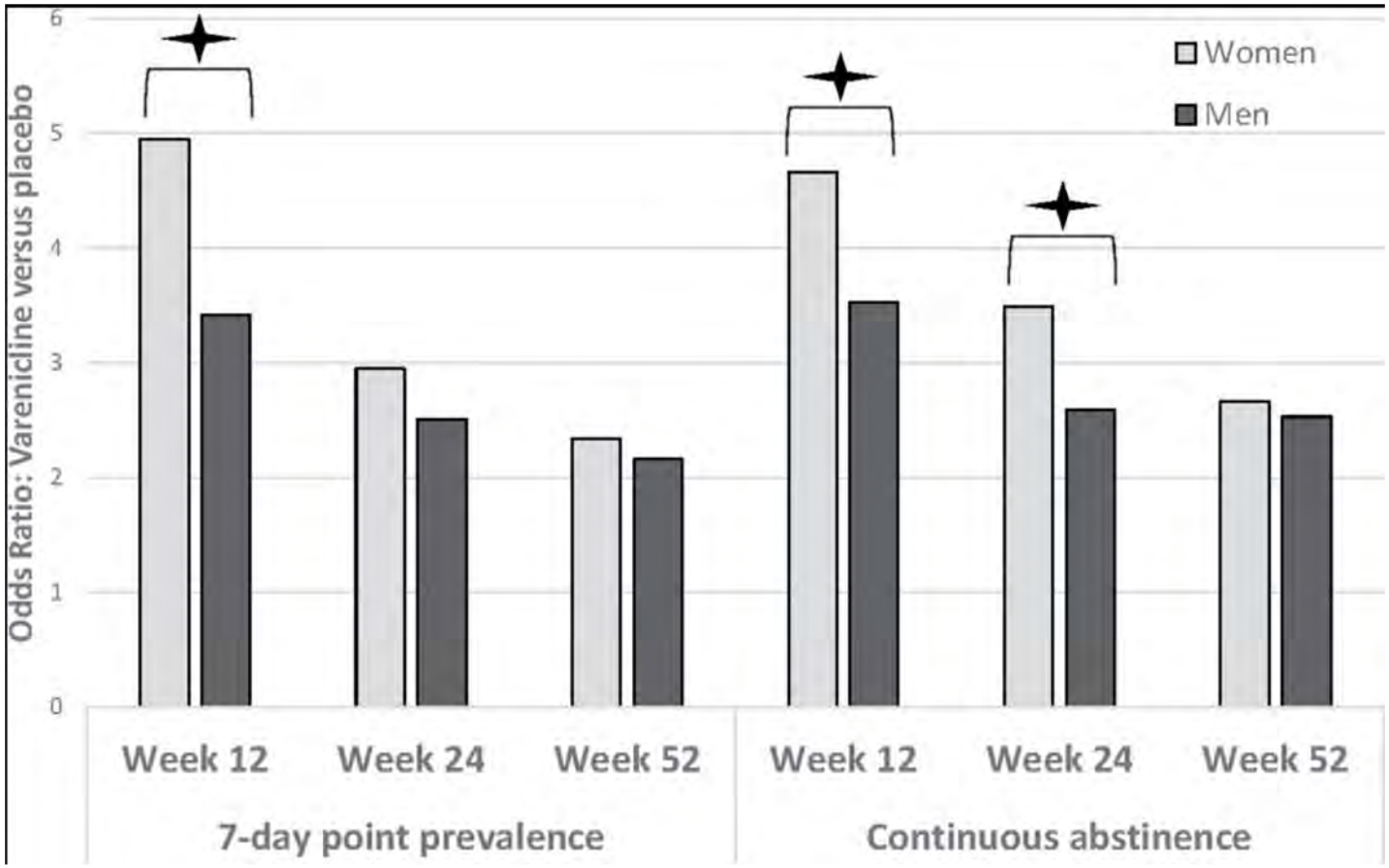
Women respond best to varenicline



- **Varenicline blocks the rewarding effects of cigarettes**
- **This decouples smoking from reward over time, devaluing the cues.**

Smith et al. 2015

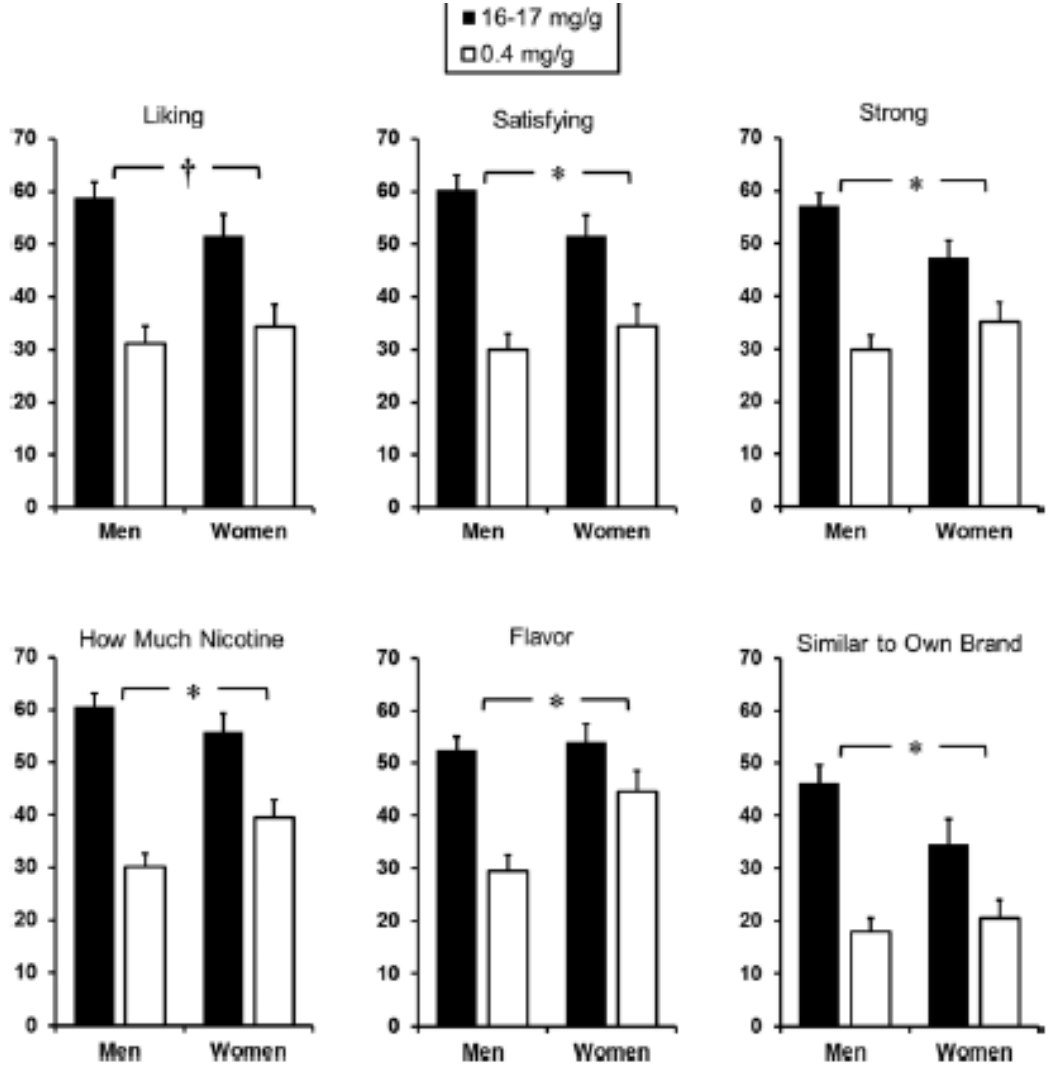
Women respond to varenicline better than men



McKee et al. 2015

Men respond to the pharmacological reward of nicotine

- **Men report greater reward from nicotine compared to women**
- **Women are less sensitive to nicotine dose**



Horizontal brackets indicate a dose by sex interaction * p<.05; † p<.10]

Perkins et al. 2018

Conclusions

- Neuroimaging + genetics allow us to understand the brain and behavior in non-invasive ways
- Combined with biology, we are getting better at characterizing addiction
- The biggest genetic difference is sex.
- We need to account for sex when treating substance use disorders

Conclusions: Sex differences in addiction

- **Men and women experience craving differently**

- **Treatment implications:**
  - Women are more cue-vulnerable to men and therefore respond better to varenicline

  - Men are susceptible to pharmacological withdrawal and thus respond better to nicotine replacement therapy

DeVito et al., 2014; Schiller et al., 2012; Sofuoglu et al., 2001

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All full references, as well as some full manuscripts presented today are available at www.arielketcherside.com.