



# PRDM2: an epigenetic mediator of alcohol addiction and anxiety

**Kanat Chanthongdee**

# Outline

## 1) Background

- My inspiration
- A previous work about alcohol addiction and PRDM2

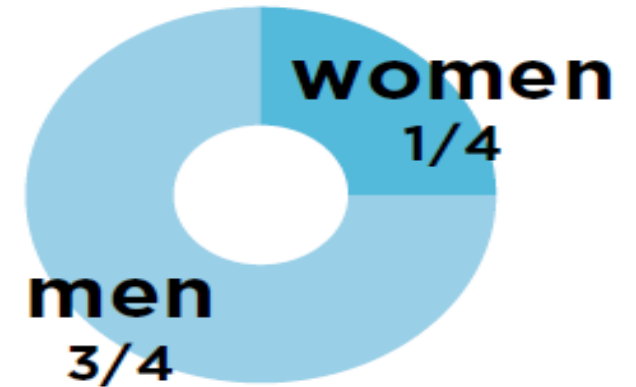
## 2) PRDM2 and its role in fear memory

## 3) PRDM2 and its role in comorbid anxiety disorder

## 4) My upcoming PhD plan

# 3 million deaths every year

6 deaths every minute from harmful use of alcohol



**100%** of alcohol use disorders



**18%** of suicides



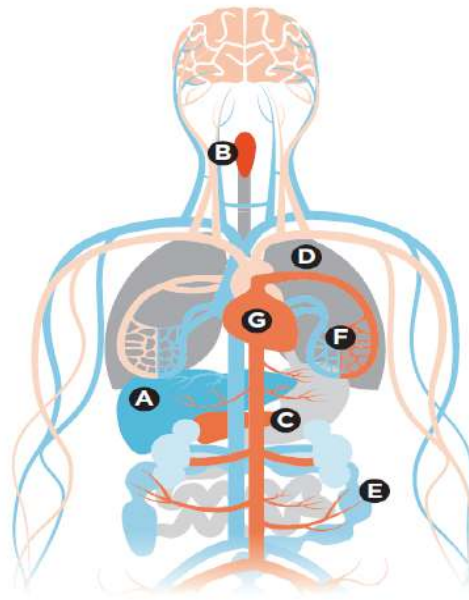
**18%** of interpersonal violence



**27%** of traffic injuries

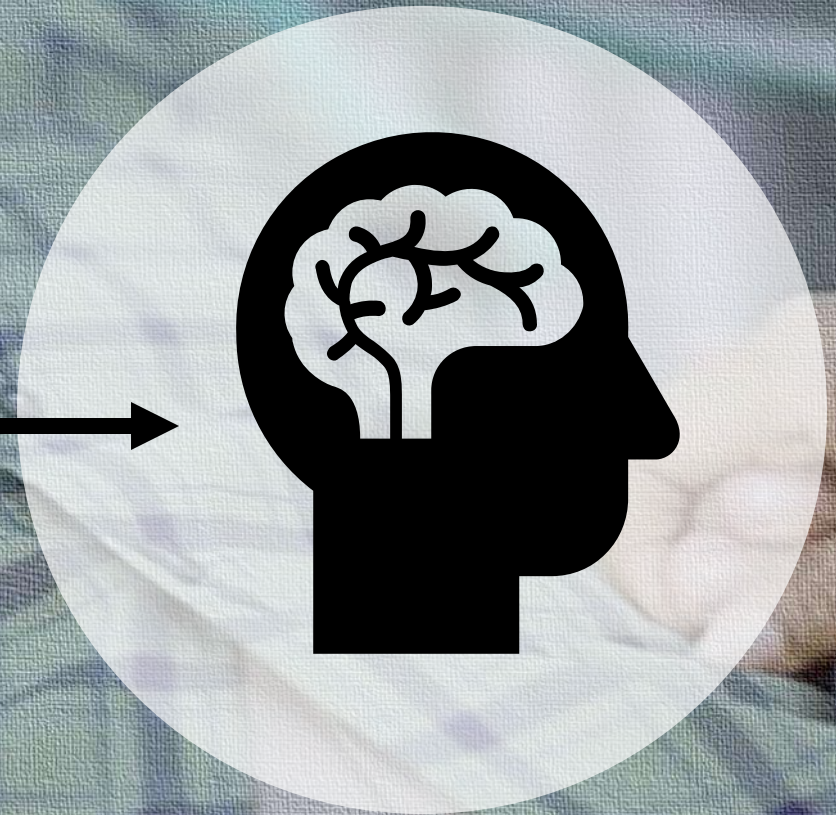


**13%** of epilepsy



- A 48%** of liver cirrhosis
- B 26%** of mouth cancers
- C 26%** of pancreatitis
- D 20%** of tuberculosis
- E 11%** of colorectal cancer
- F 5%** of breast cancer
- G 7%** of hypertensive heart disease





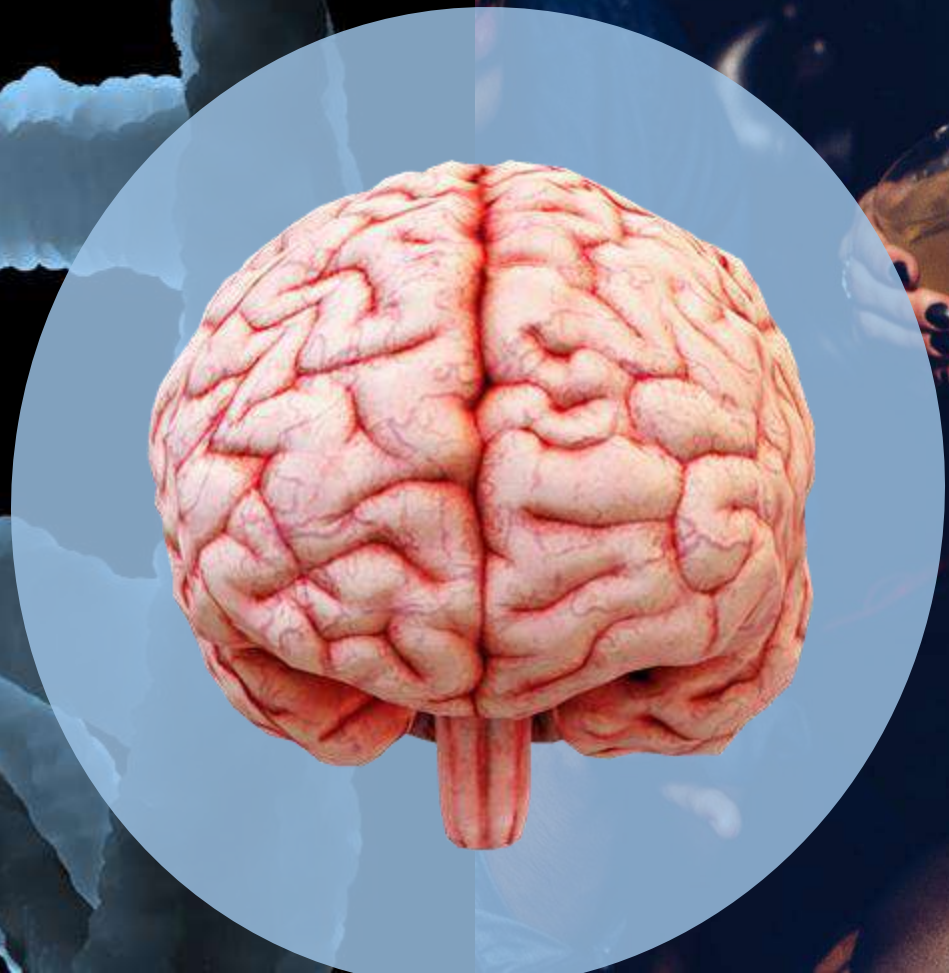
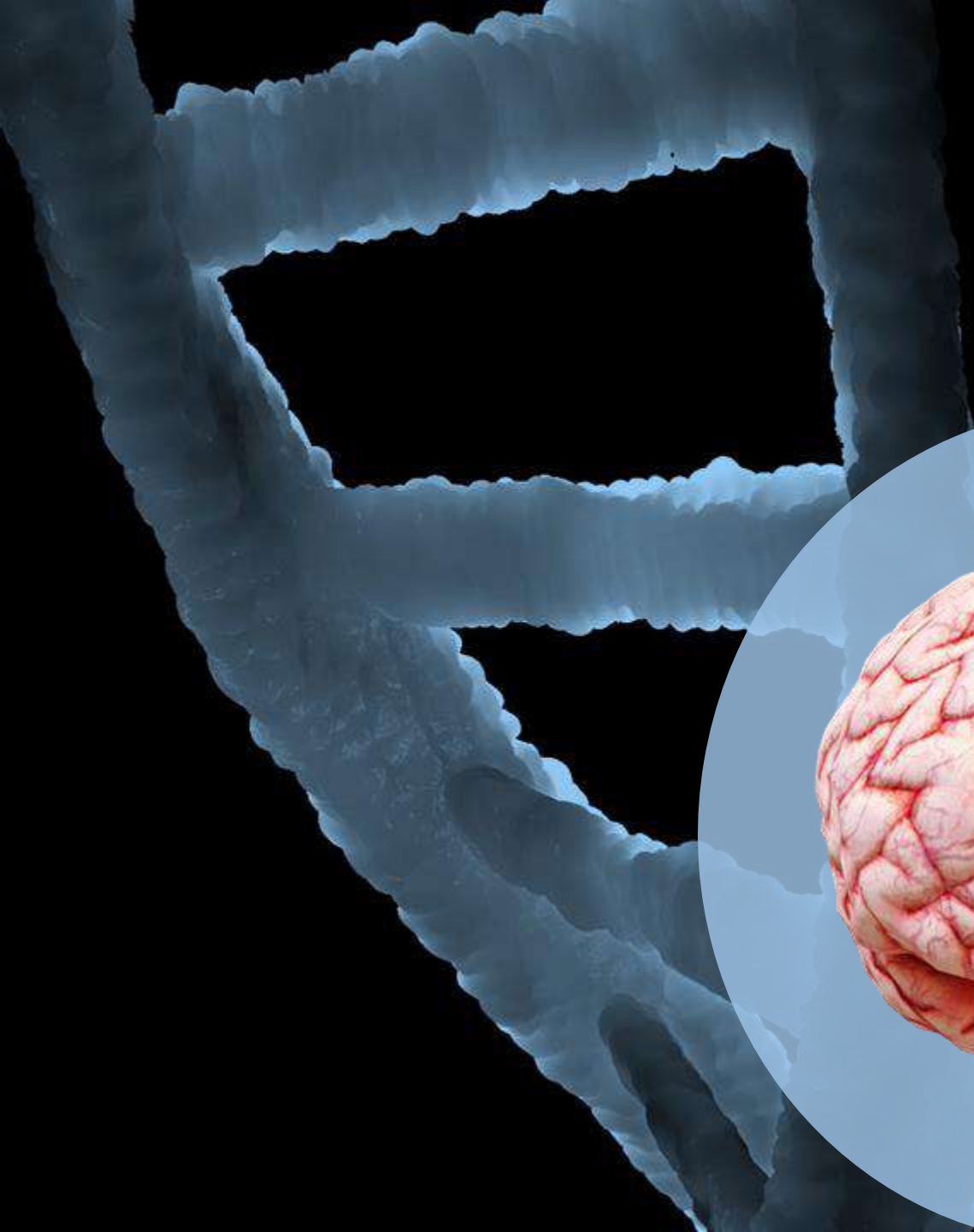


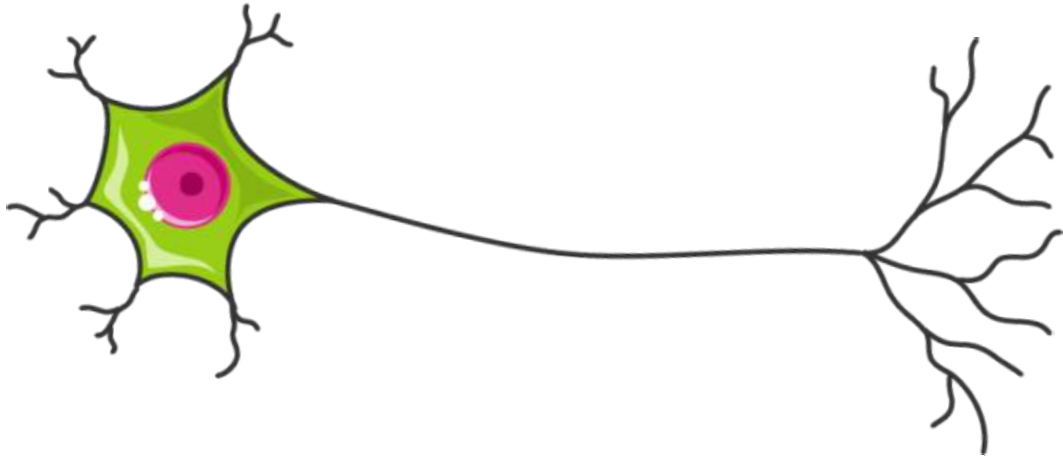
**CSAN**

**Center for Social and  
Affective Neuroscience**

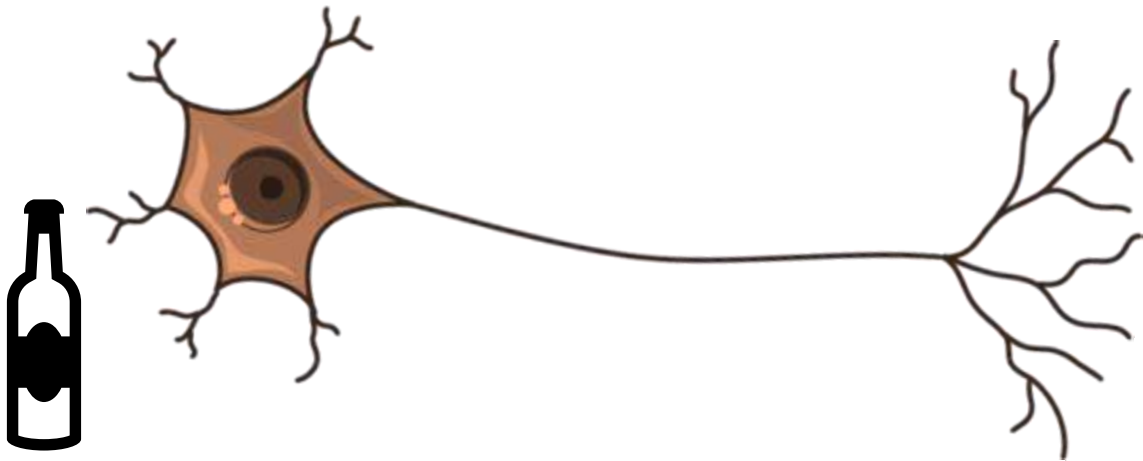
**li.u**  
LINKÖPINGS UNIVERSITET



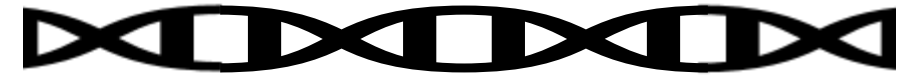
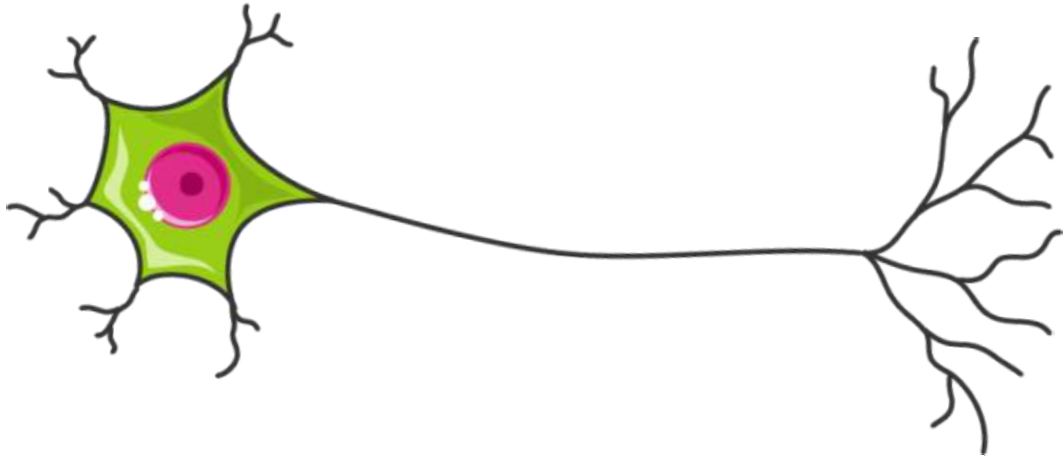




An apple a day keeps the doctor away.

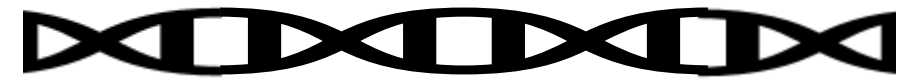
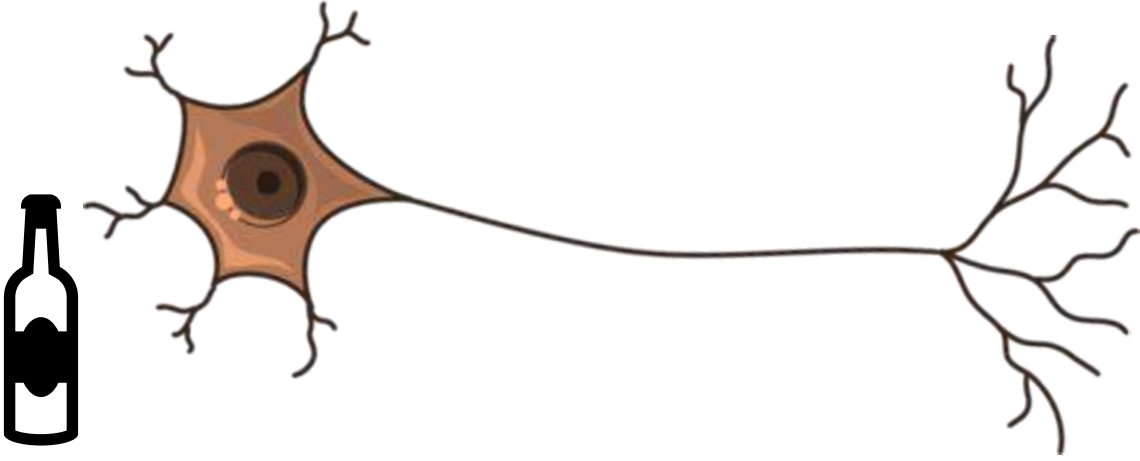


A shot of spirits a day keeps the stress away!



An apple shot of spirits a day keeps the stress doctor away

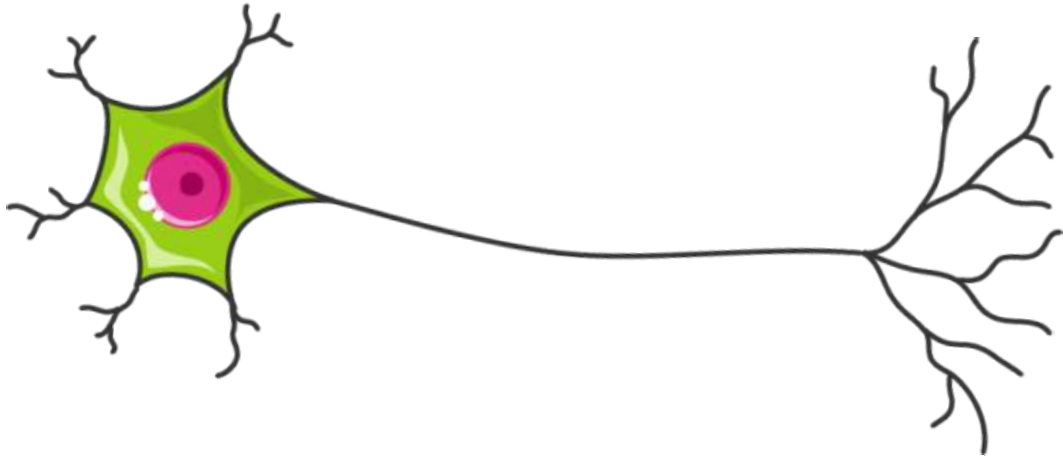
**An apple a day keeps the doctor away.**



An apple shot of spirits a day keeps the stress doctor away

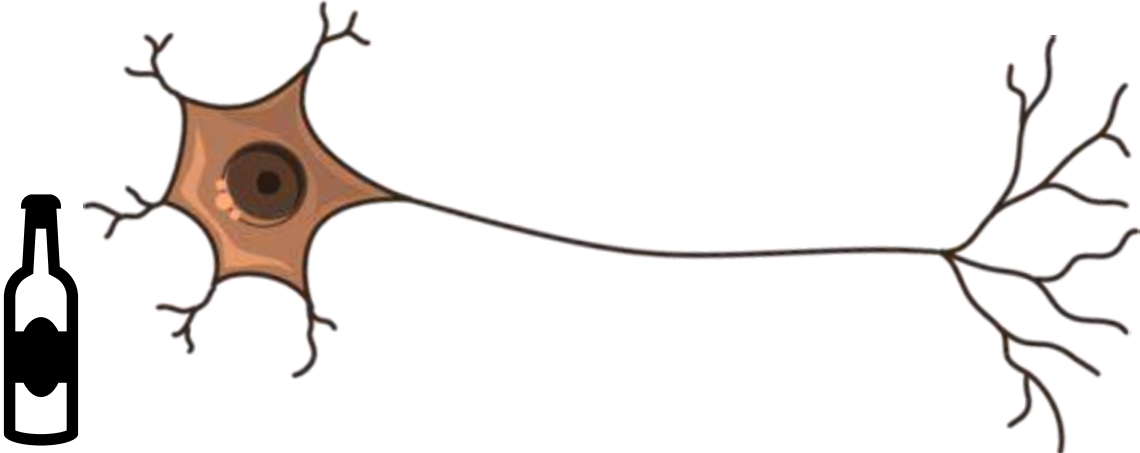
**A shot of spirits a day keeps the stress away!**





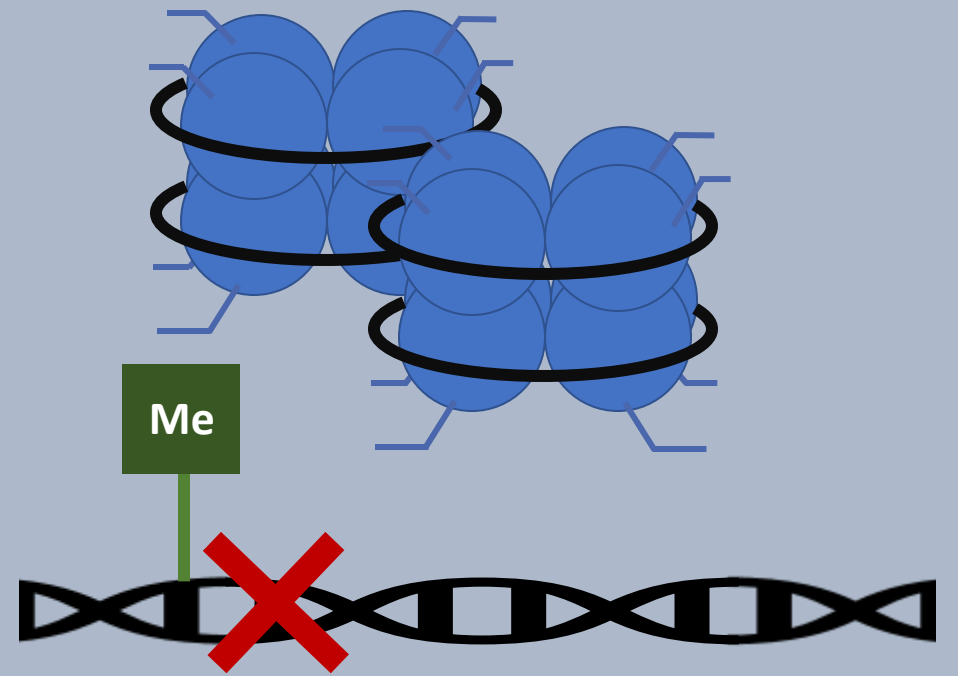
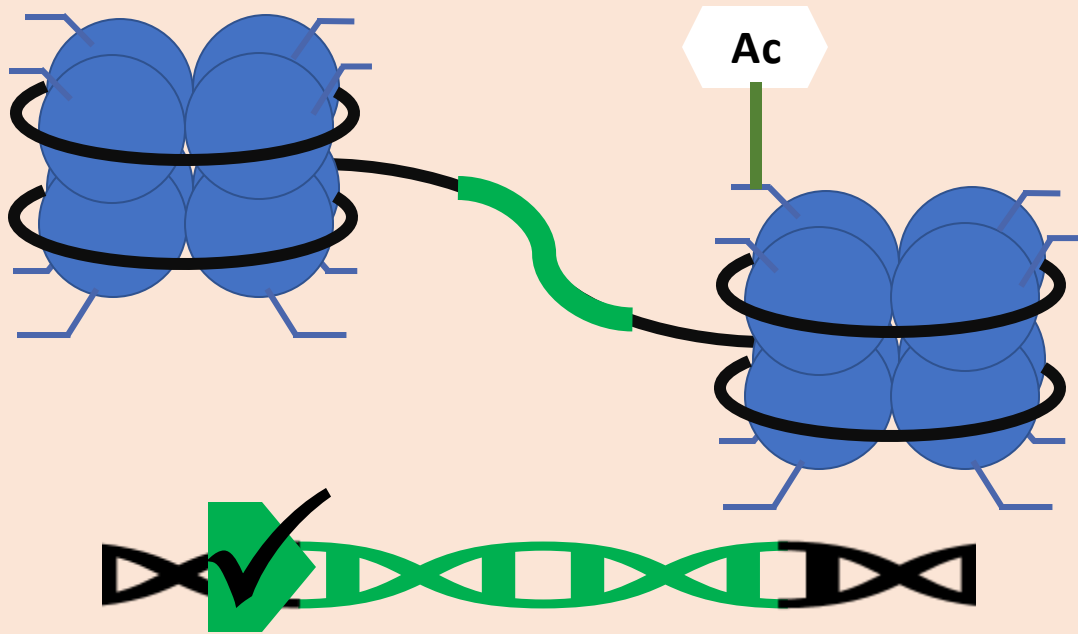
  
An apple ~~shot of spirits~~ a day  
keeps the ~~stress~~ doctor away

**An apple a day keeps the doctor away.**

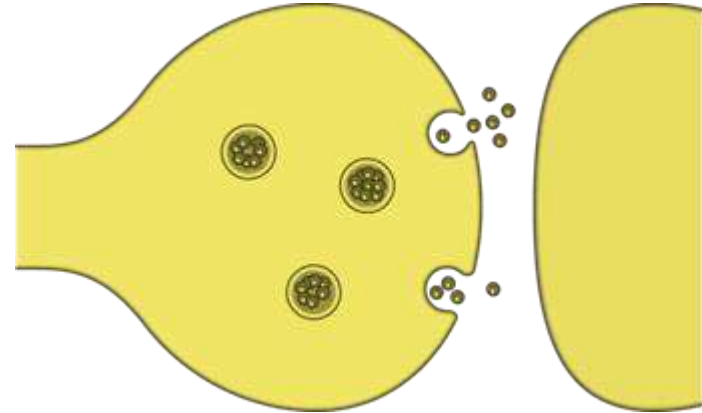
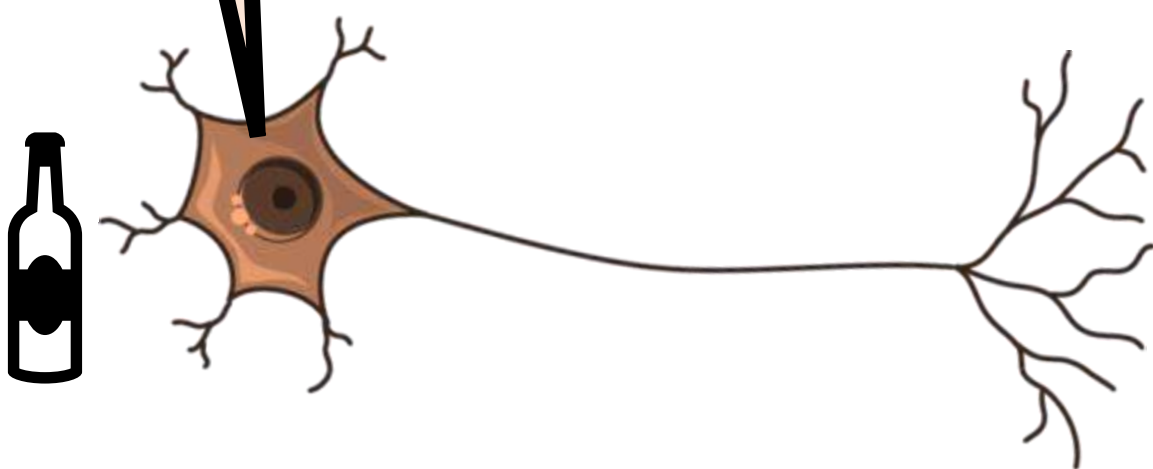


  
~~An apple~~ shot of spirits a day  
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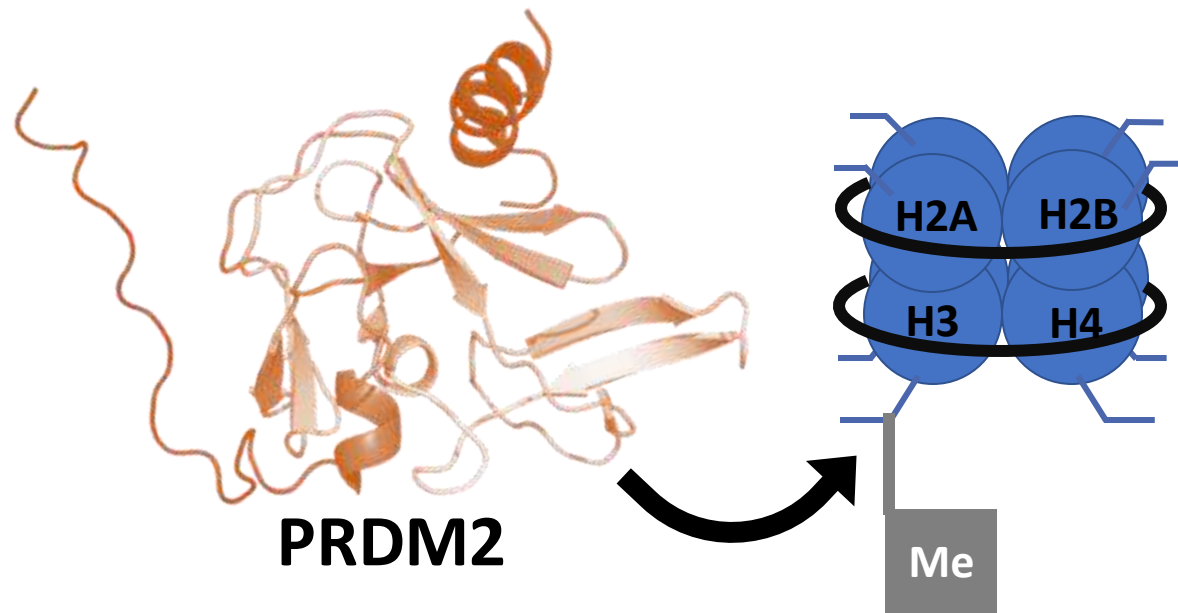
**A shot of spirits a day keeps the stress away!**



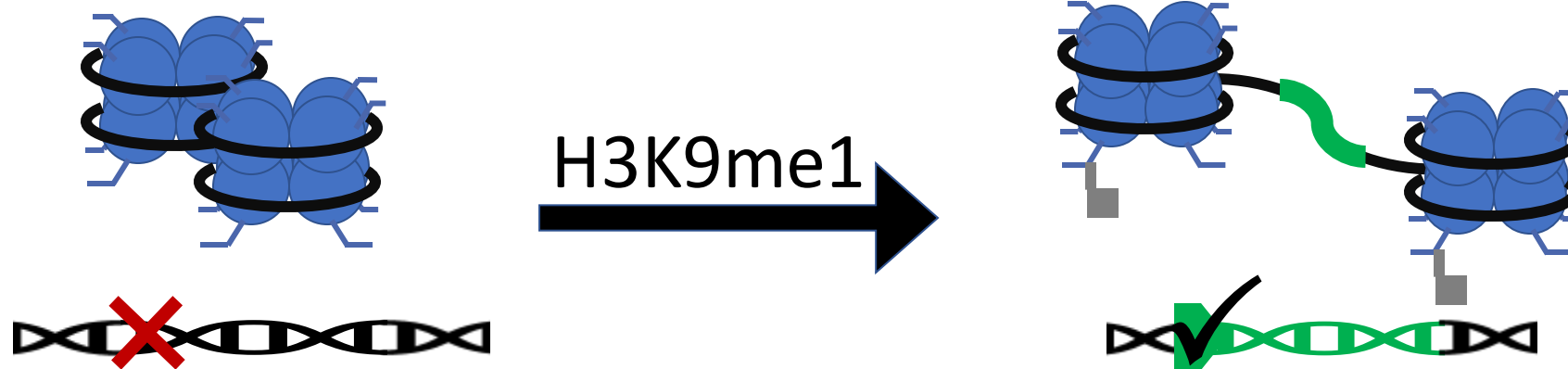
# EPIGENETICS



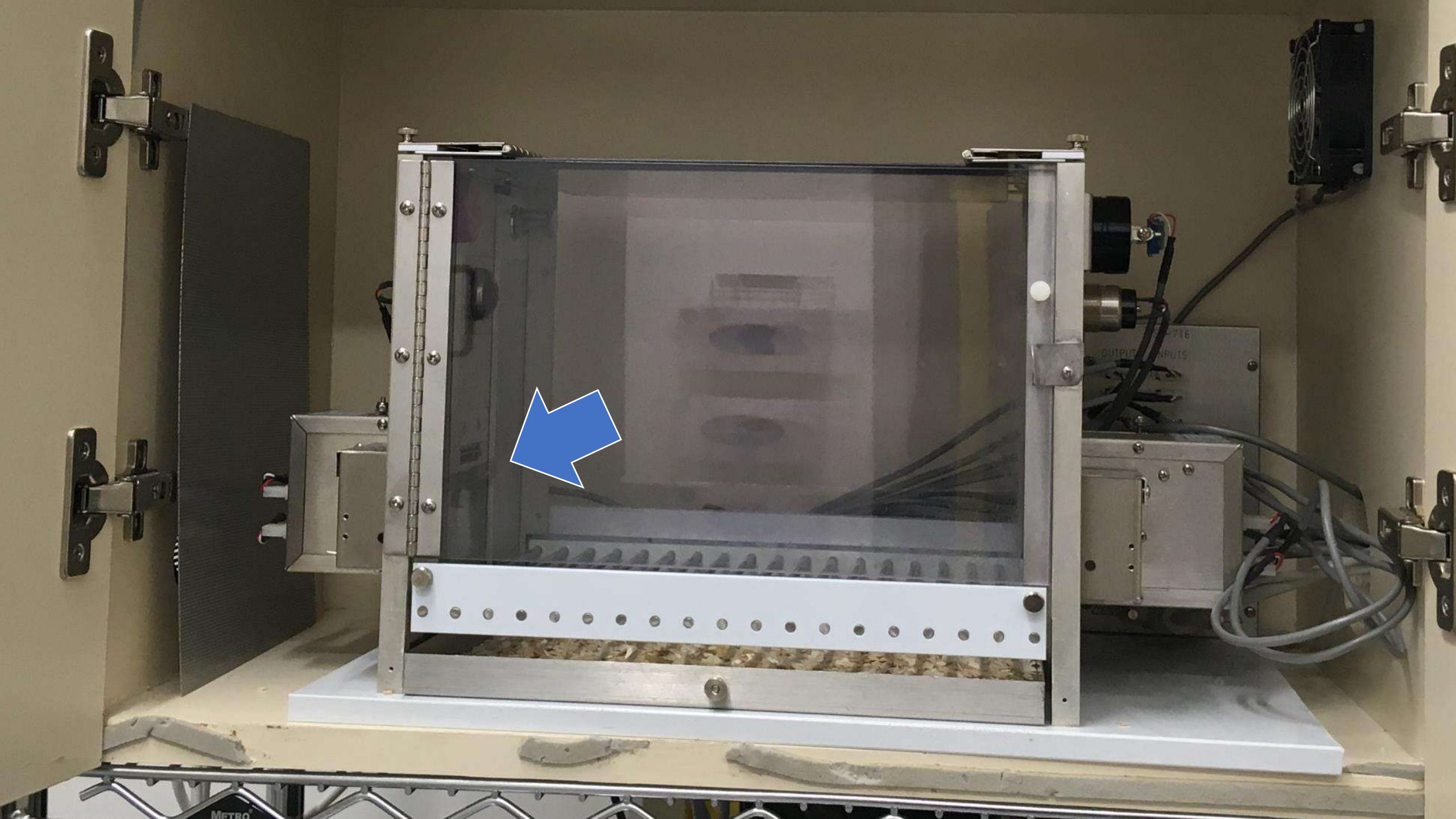
# Histone methyltransferase PR domain containing 2 (PRDM2)



- Highly expressed in the prelimbic (PL) region
- Down-regulated in post-dependent rat
- Facilitate a methylation at lysine 9 of histone 3 (H3K9me1)

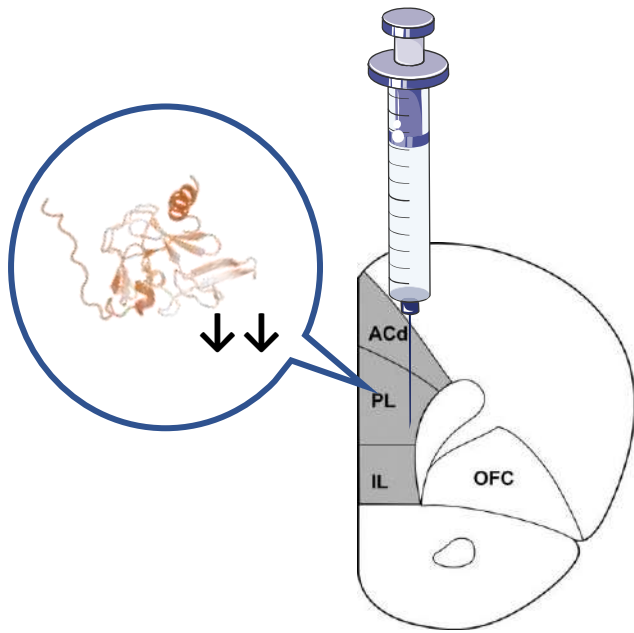


H3K9me1 promotes gene expressions involved in synaptic transmission at the PL

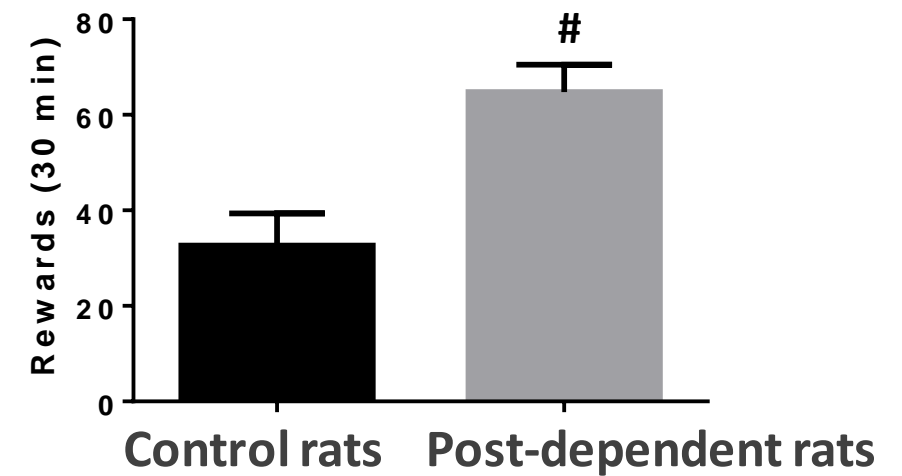
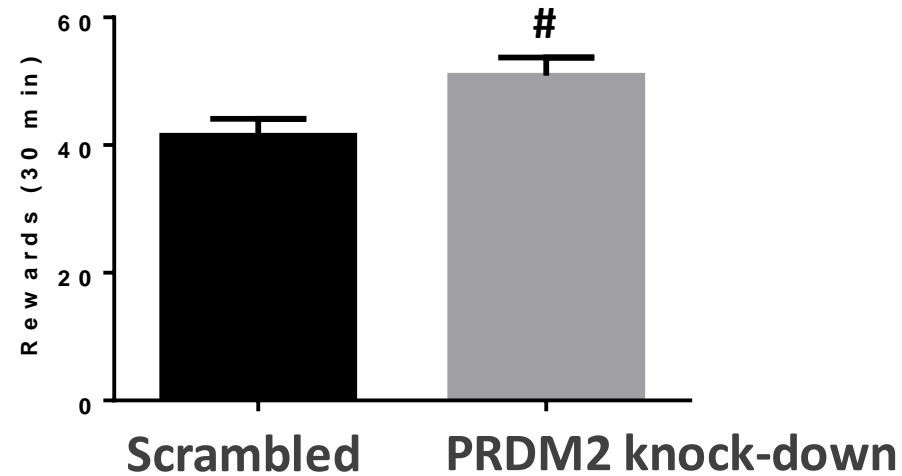
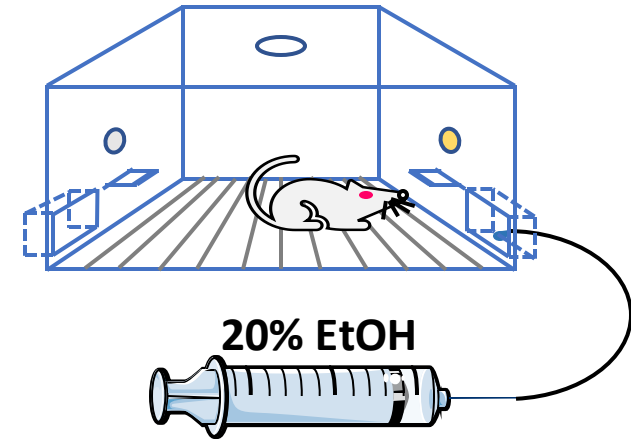


# PRDM2 plays a role in the escalation of alcohol intake

Viral-mediated  
PRDM2 knock-down

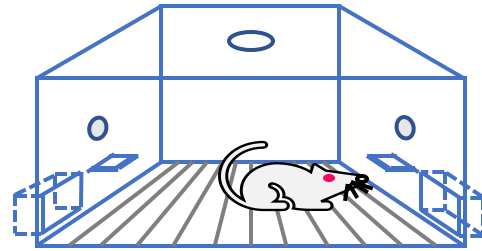


Alcohol self-administration



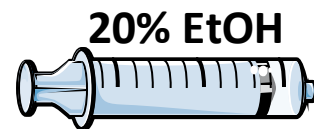
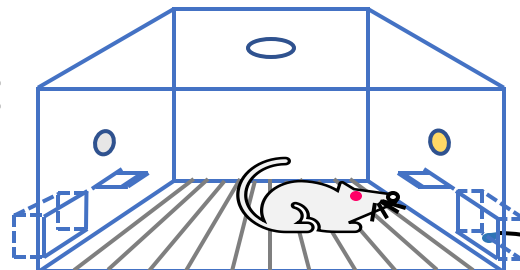
# PRDM2 plays a role in stress-induced relapse

Extinction

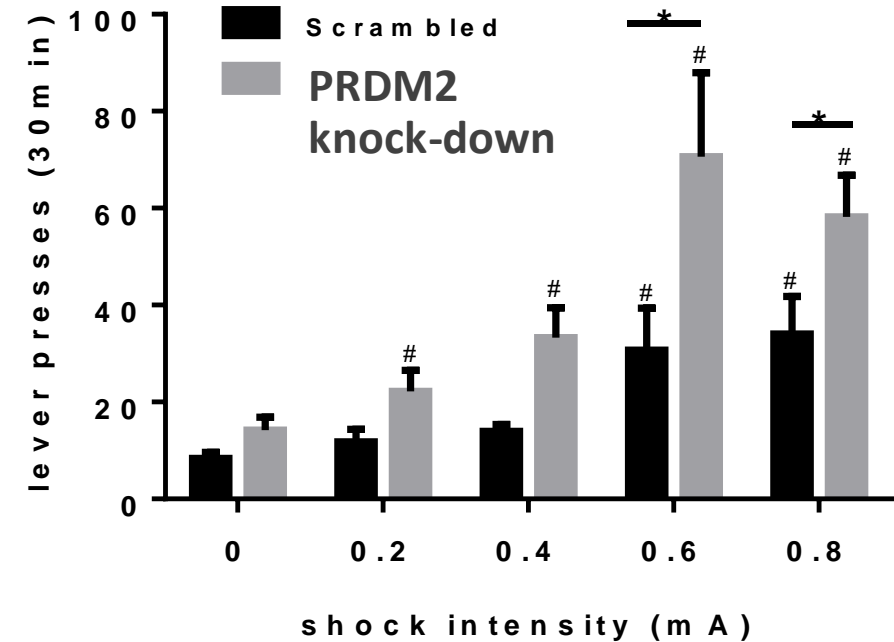


+

15 min unpredictable  
footshock THEN  
alcohol reinstatement



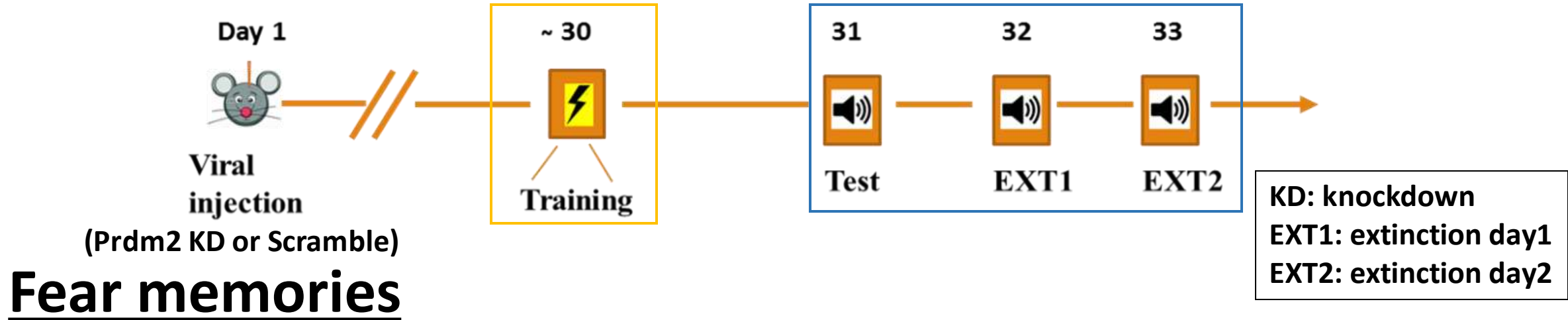
Stress-induced reinstatement







Mean +/- SEM, n=9-10/gr, \*: p < 0.05 ; Barbier et al., 2016

## 2) PRDM2 and its role in fear memory

# Does PRDM2 play any role in fear memories?

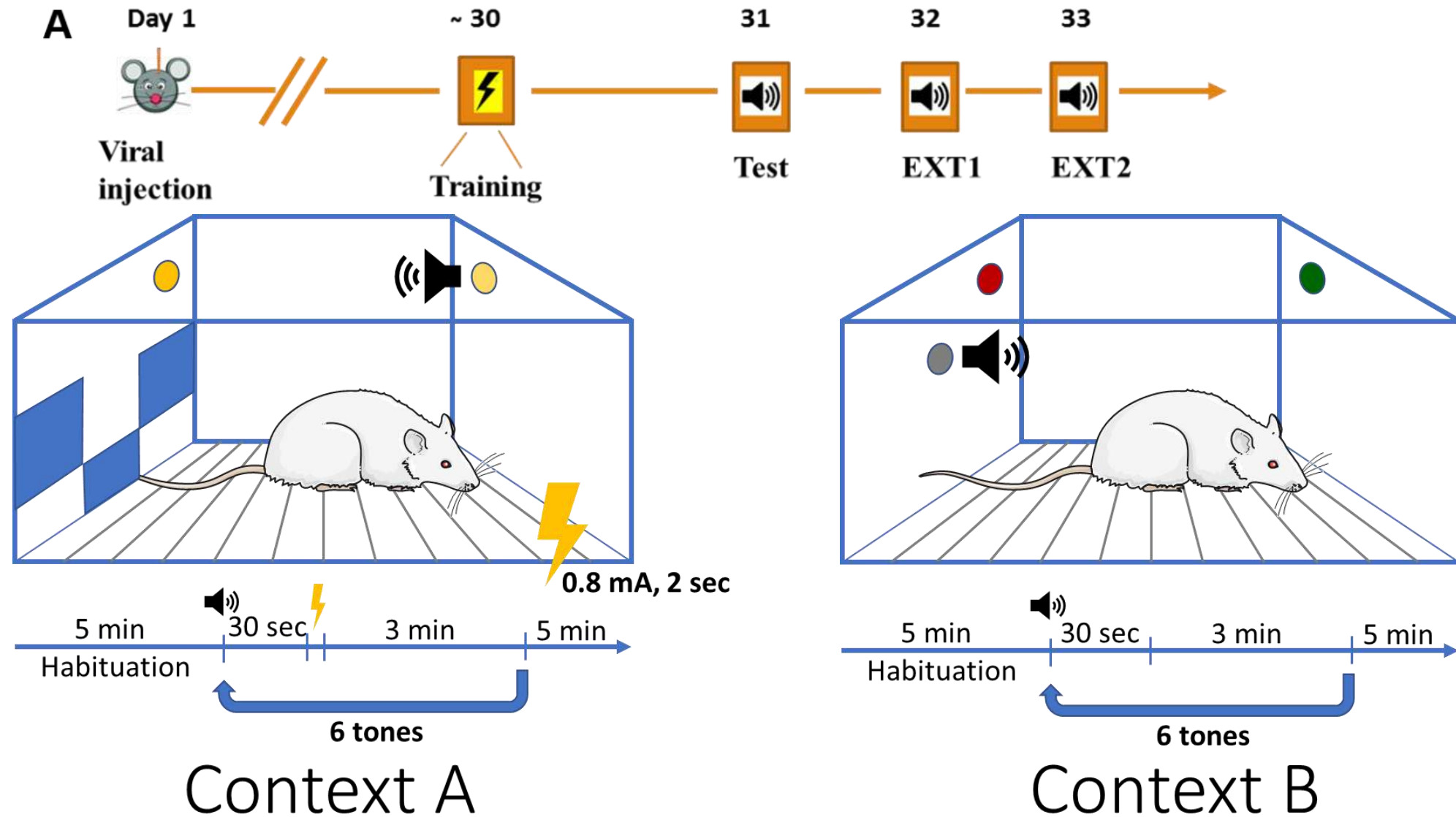


## Fear memories

- |                  |                                      |                                                                                                                                                                                                                                                             |
|------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Acquisition   | • “Fear conditioning”                |    |
| 2. Consolidation | • Repeated cycle of conditioning     |                                                                                                                                                                                                                                                             |
| 3. Expression    | • Innate response => <b>Freezing</b> |                                                                                                                                                                                                                                                             |
| 4. Extinction    | • Rate of extinction                 |                                                                                                                                                                                                                                                             |
| 5. Recall        | • Overgeneralization                 |                                                                                                                                                                        |



# Method: Fear conditioning and fear expression (training) (test)

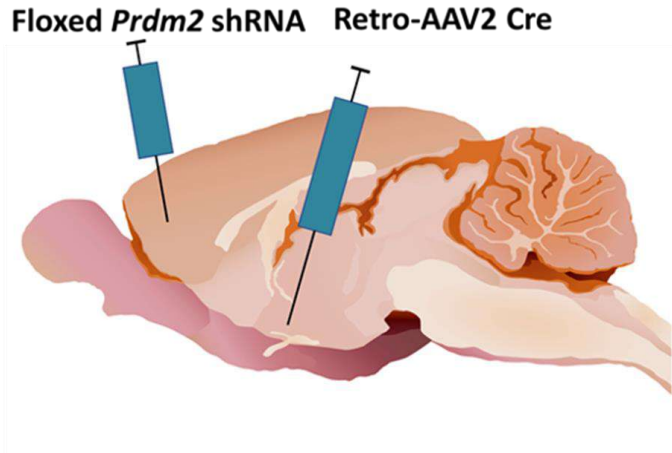


PRDM2 KD increased fear expression but had no effect on the acquisition nor the rate of extinction



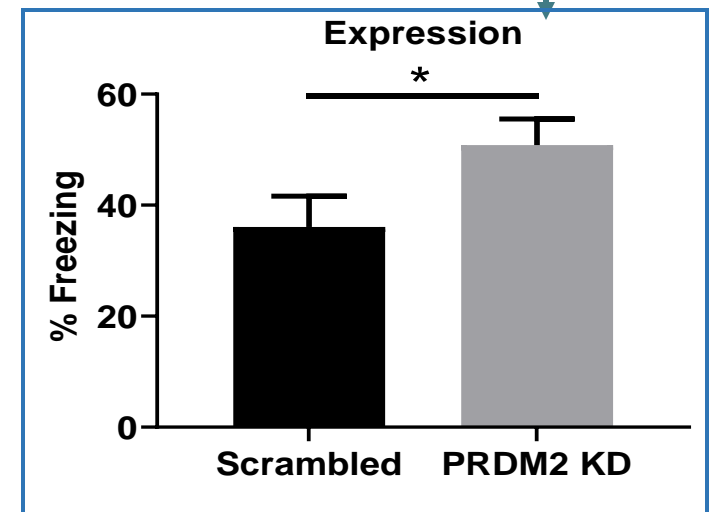
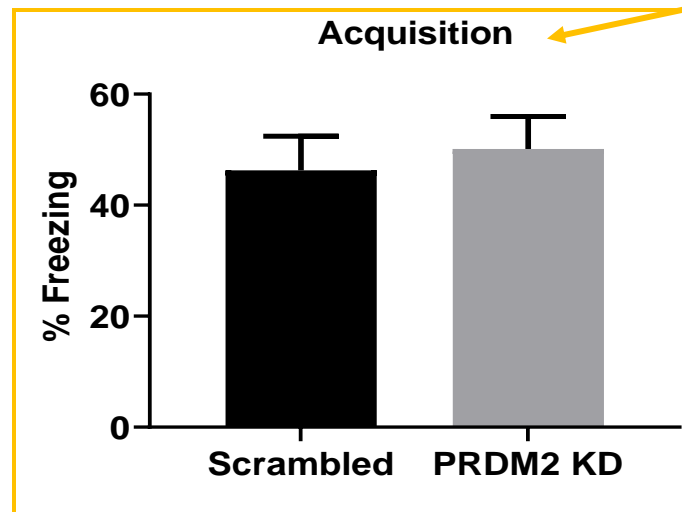
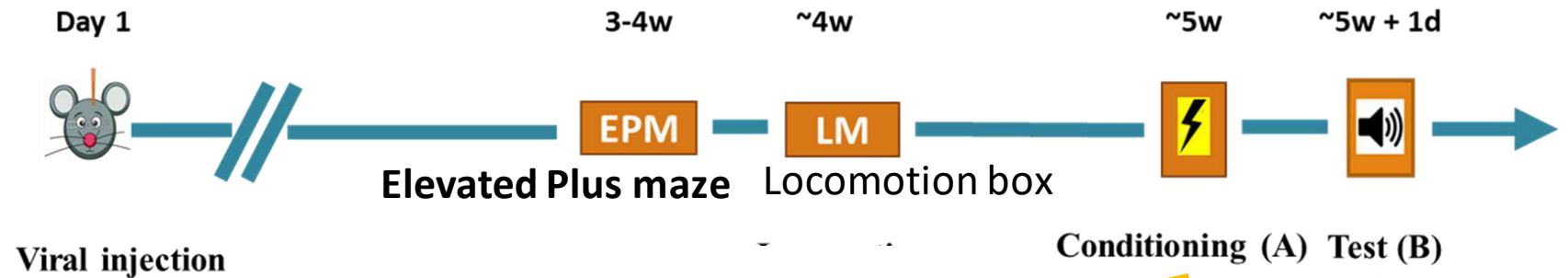
%Freezing = % time spent freezing during the tone, Mean +/- SEM \*: p<0.05, n = 20/group

# KD of Prdm2 in PL->BLA neural projection results in higher fear memory expression



PL → BLA

shRNA: short-hairpin RNA  
 Floxed: flanked by loxP  
 Retro-AAV: retrograde adeno-associated virus  
 KD: knockdown  
 PL: prelimbic  
 BLA: basolateral amygdala



%Freezing = % time spent freezing during the tone, Mean +/- SEM \*: p<0.05, n = 20/group

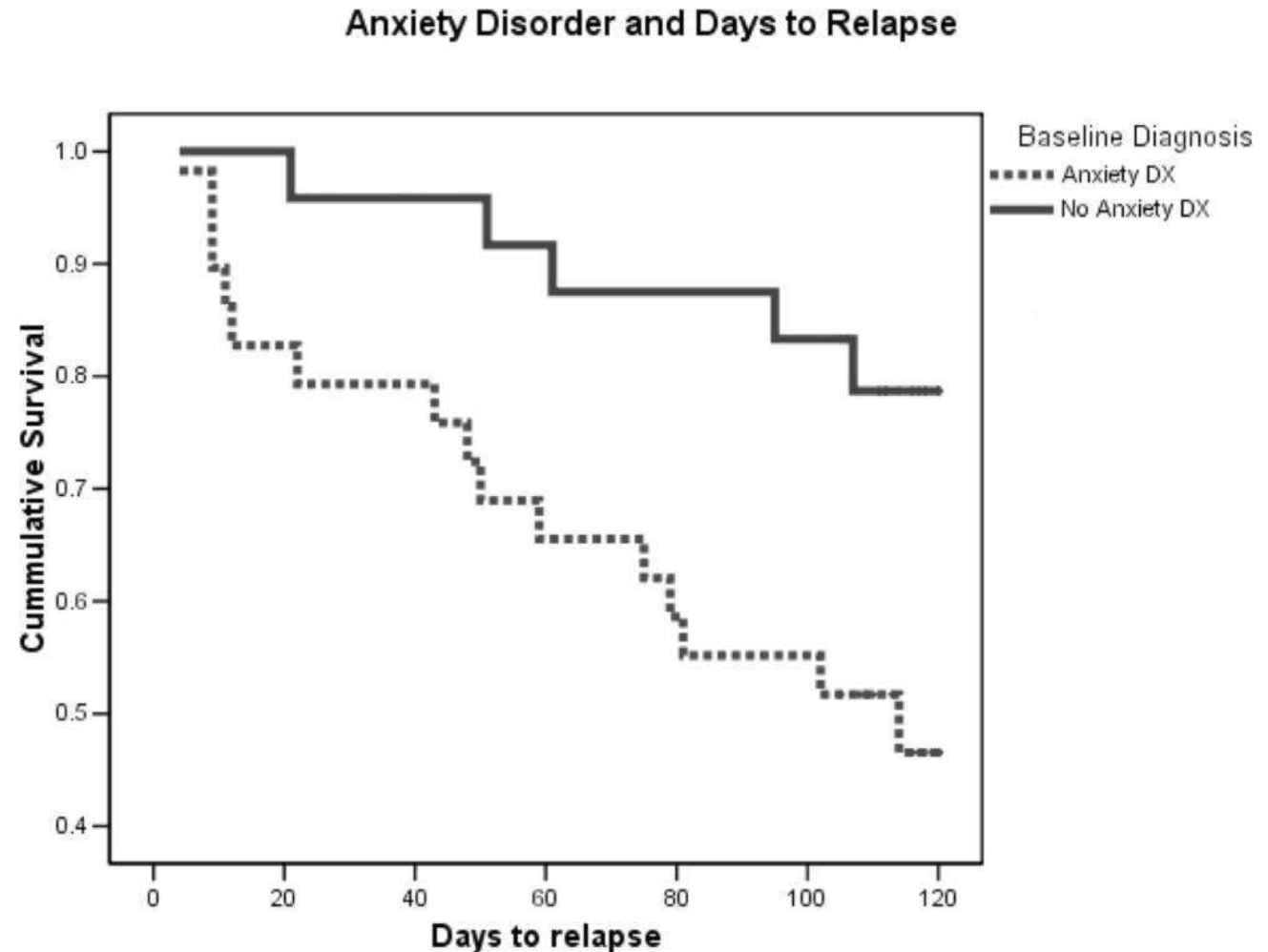


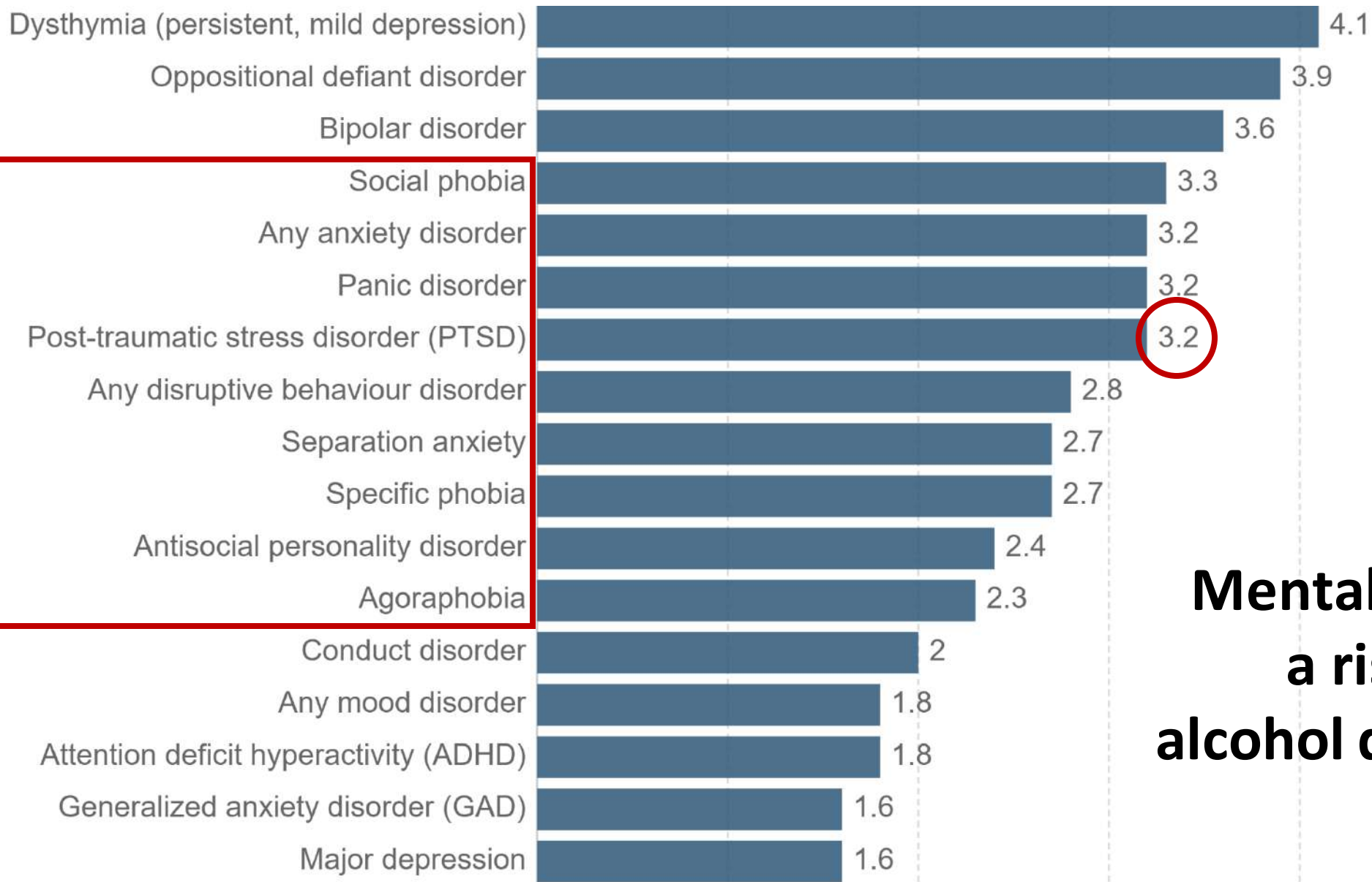
### 3) PRDM2

and its role in comorbid anxiety disorder

# Stress-related/ Anxiety disorders comorbid with alcohol use disorder

- ➔ Faster transition from regular drinking to alcohol dependence
- ➔ Treatment difficulties
- ➔ Poor prognoses
- ➔ High relapse rate



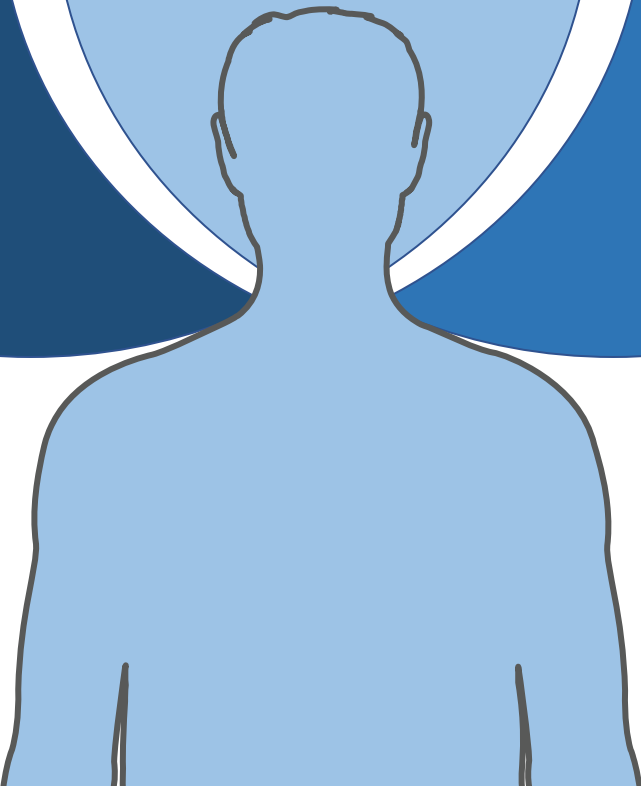
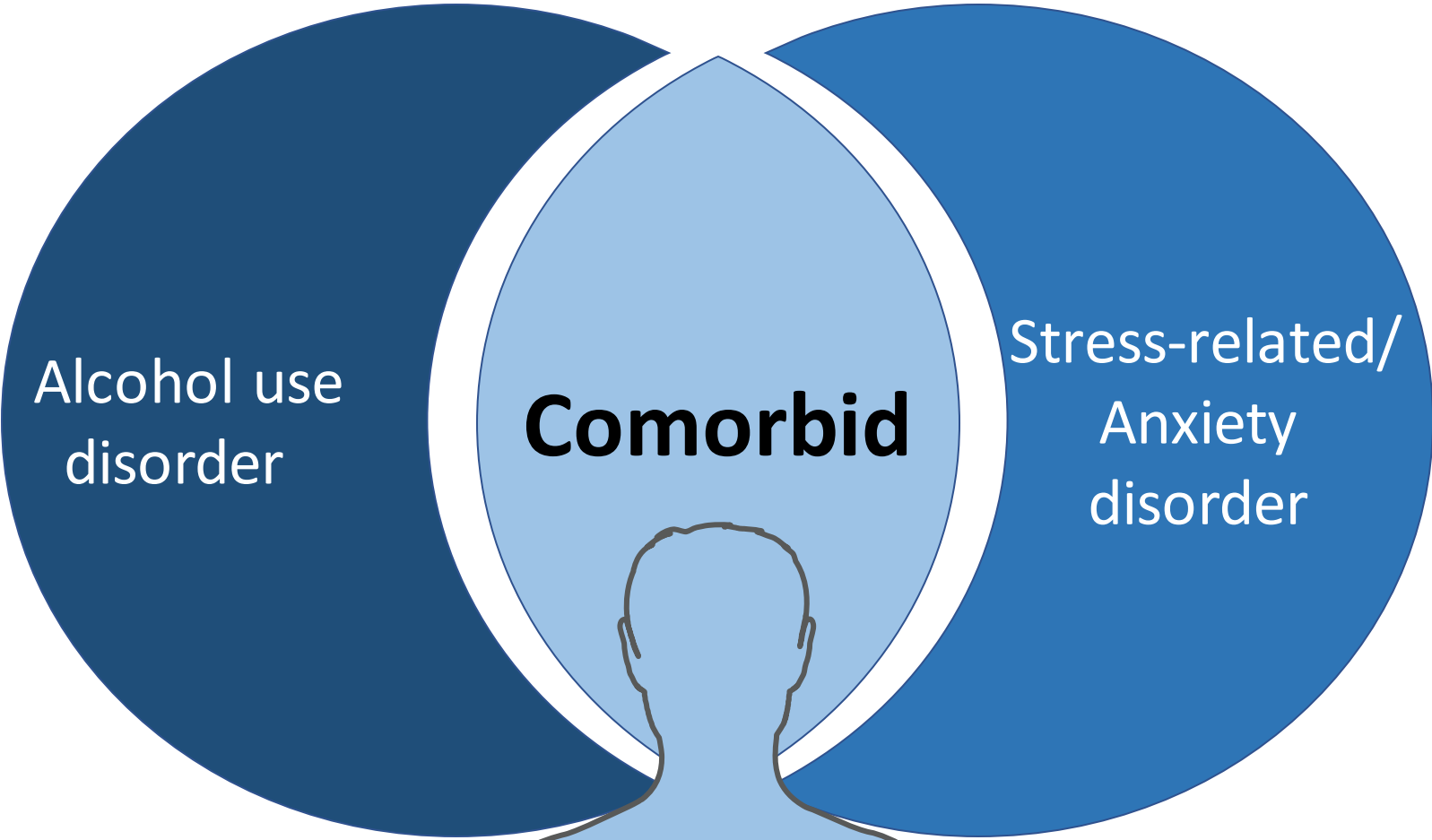


Graph from  
Our World  
in Data

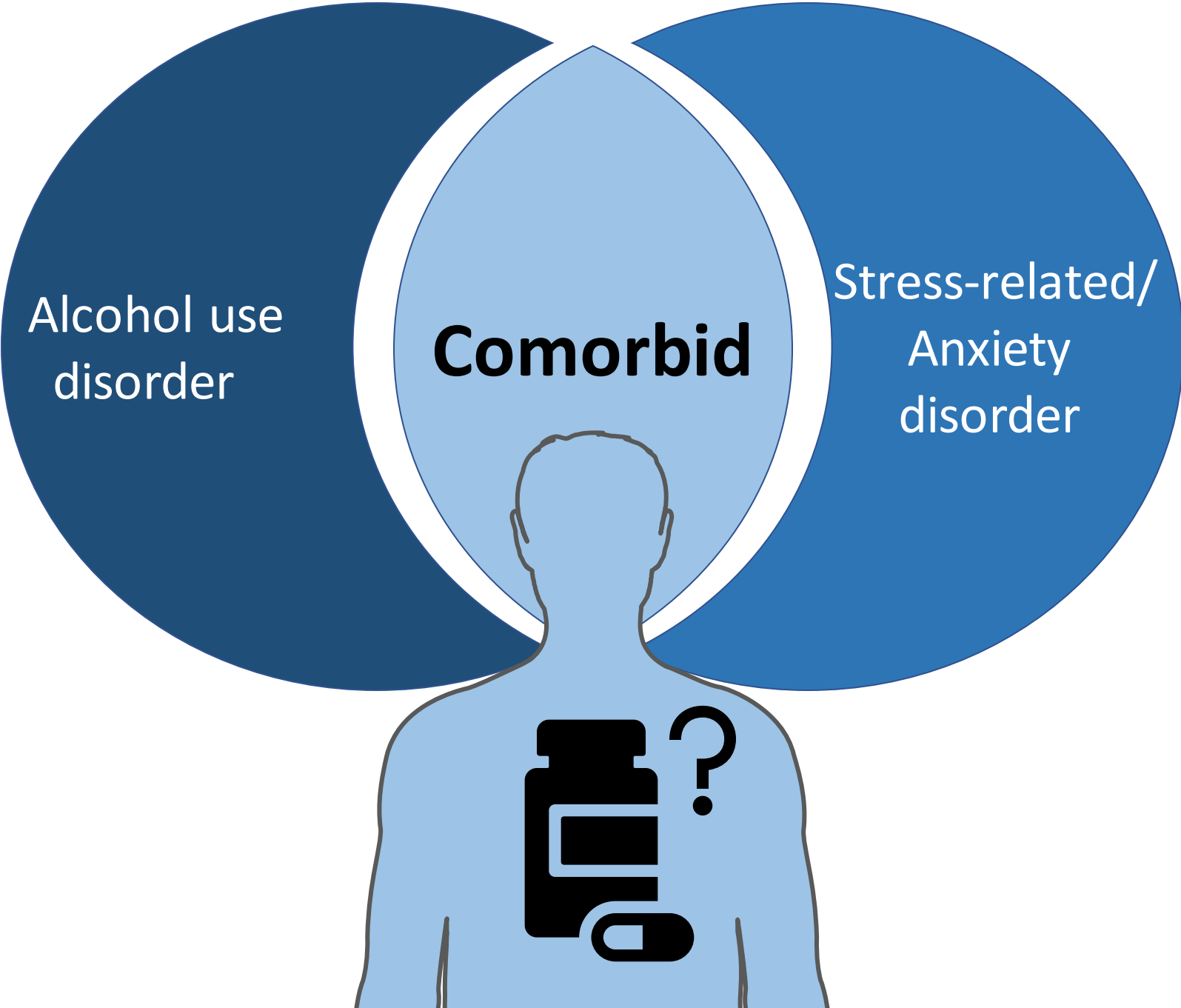
## Mental illnesses as a risk factor for alcohol dependency or abuse

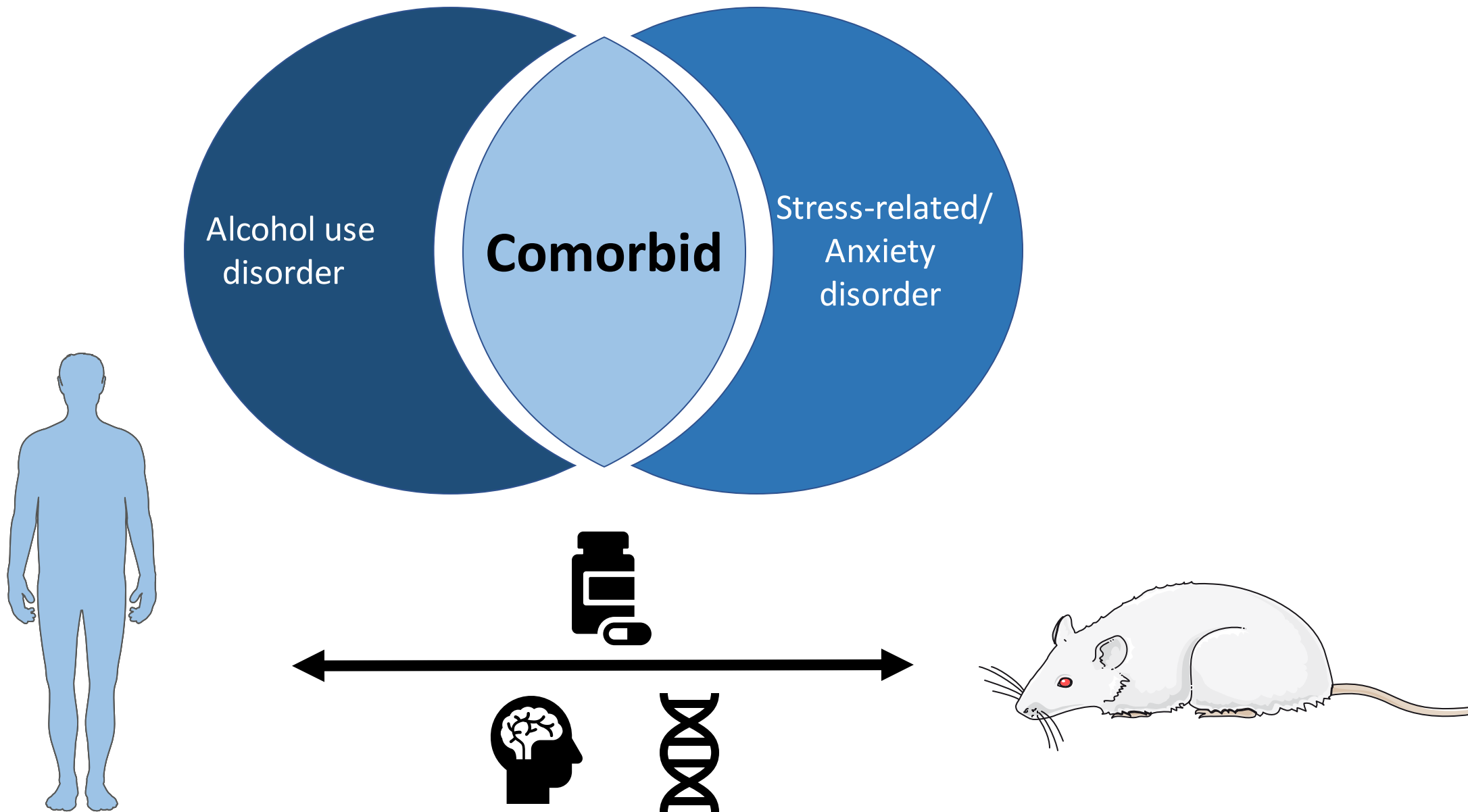
Odds ratio: 0 1 2 3 4 5 6

Swedsen et al. 2010

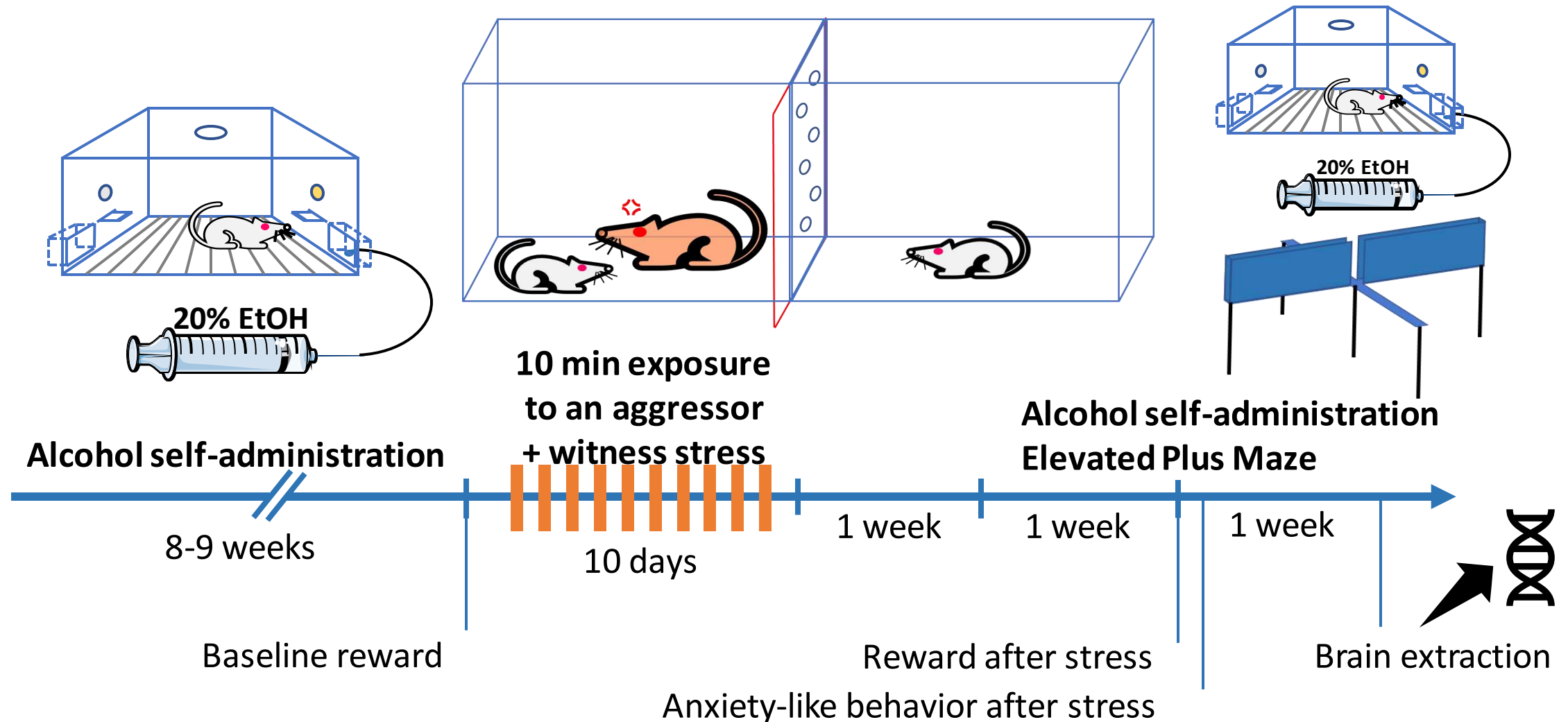








# Molecular mechanisms underlying individual differences in susceptibility and resilience to social defeat- and witness stress in rats



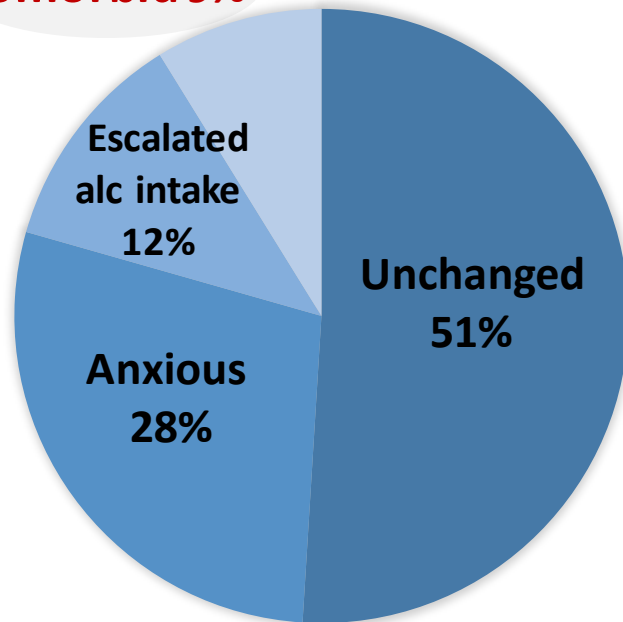


# Cluster analysis reveals individual differences

n=42

CONTROL (CTL)

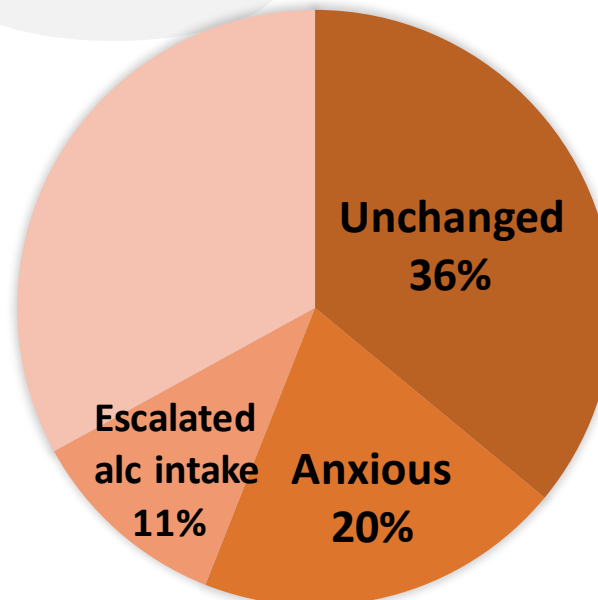
Comorbid 9%



n=45

SOCIAL DEFEAT STRESS (SDS)

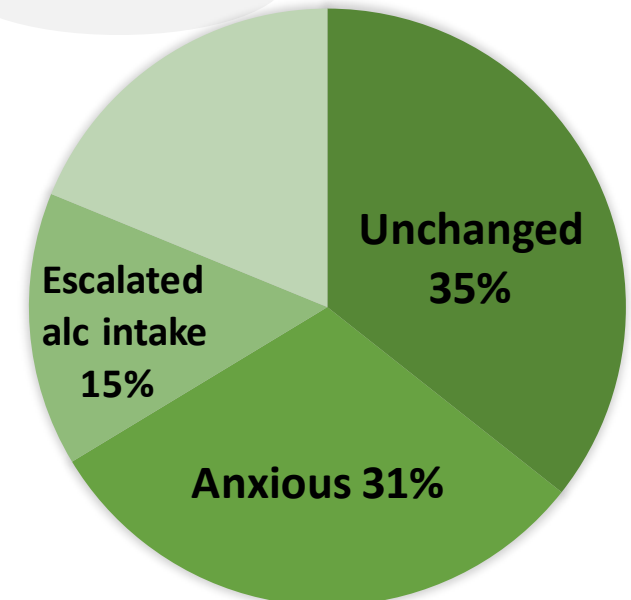
Comorbid 33%



n=47

WITNESS STRESS (WS)

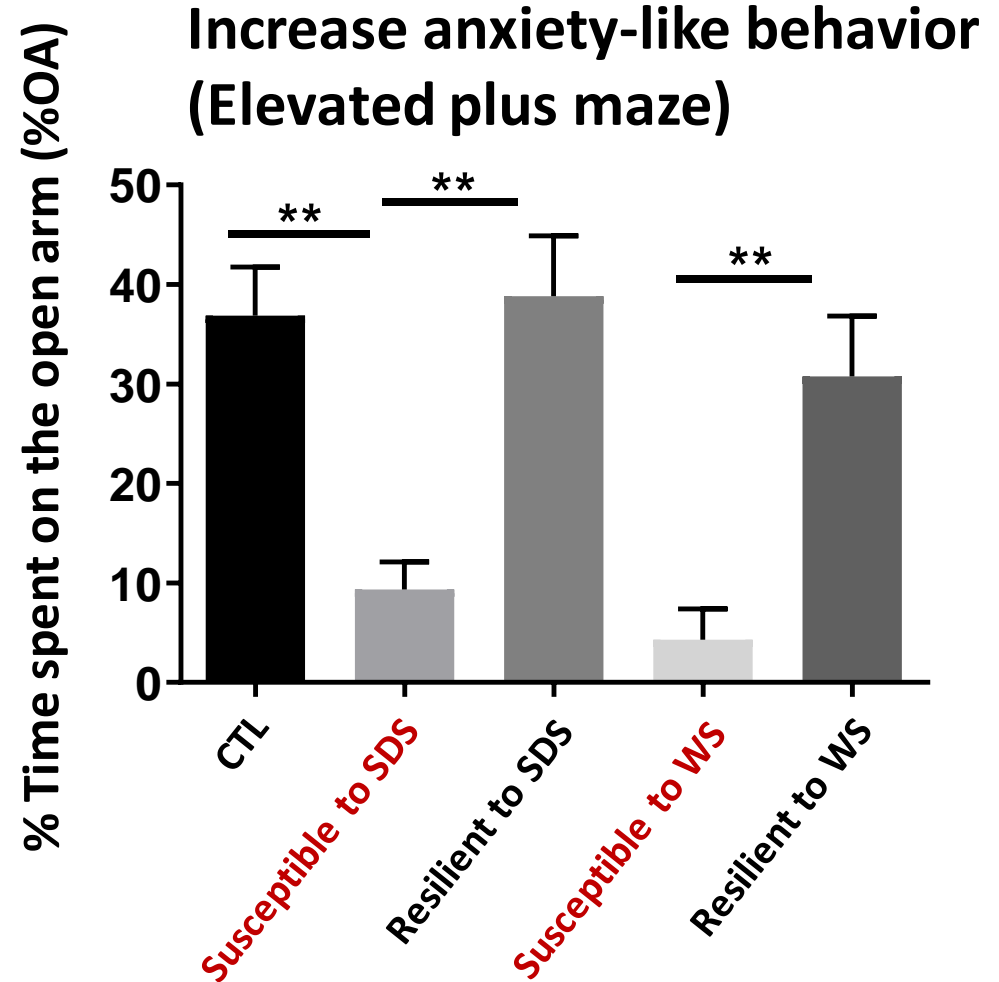
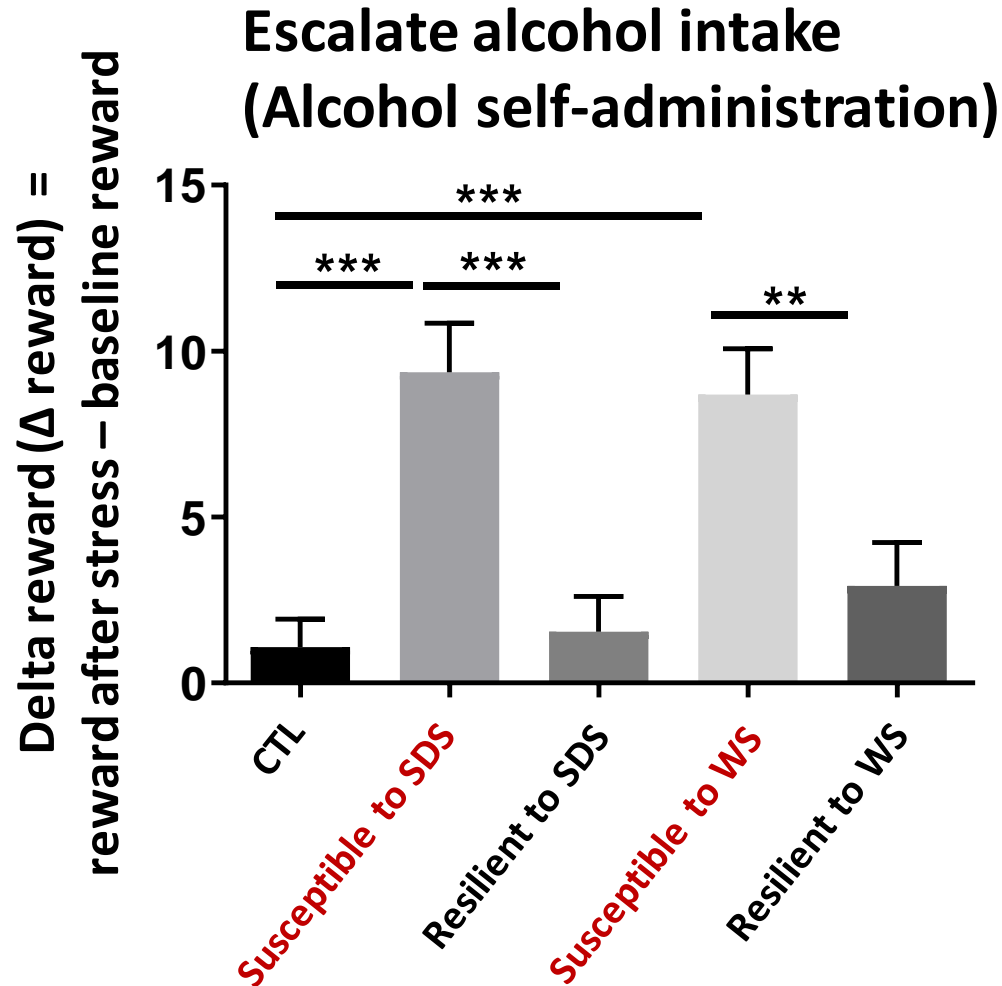
Comorbid 19%



*Susceptible  
to the stress*

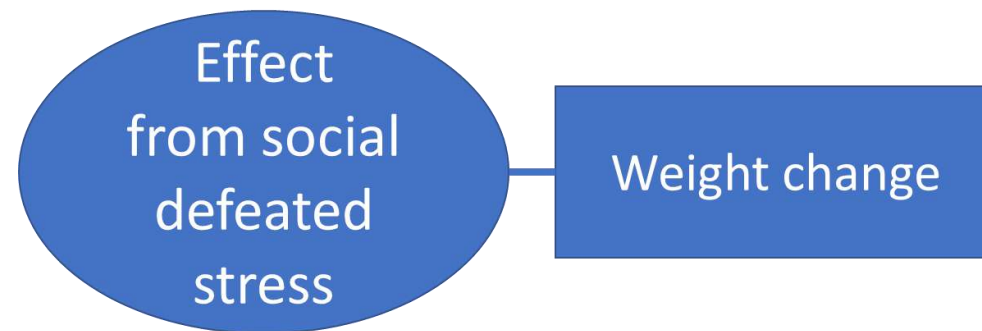
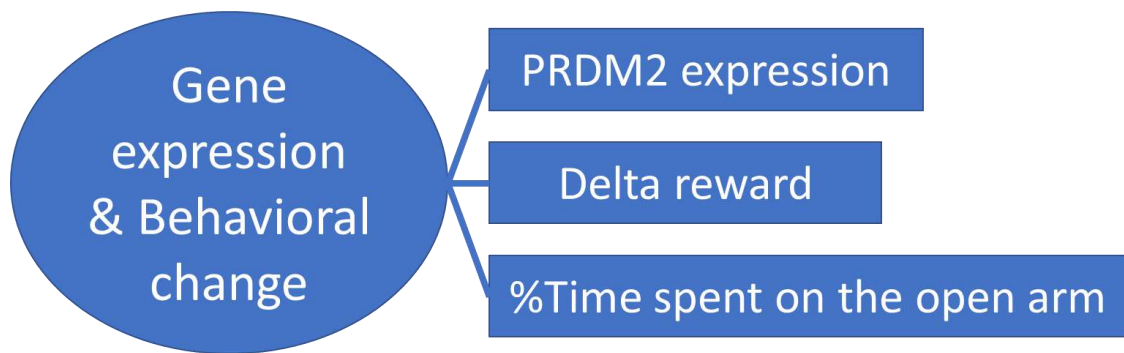
*Resilient  
to the stress*

# Behavioral changes after stress

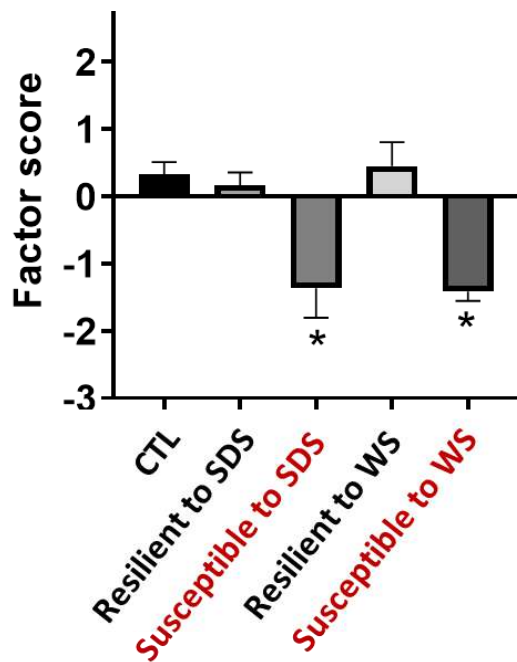


Data were shown as mean +/- SEM

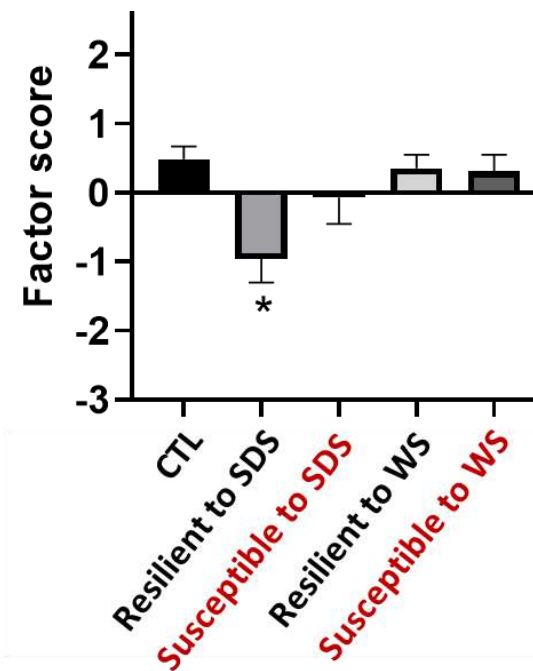
# Preliminary factor analysis from the social defeat stress data



account for ~42% of the total variance



account for ~26% of the total variance

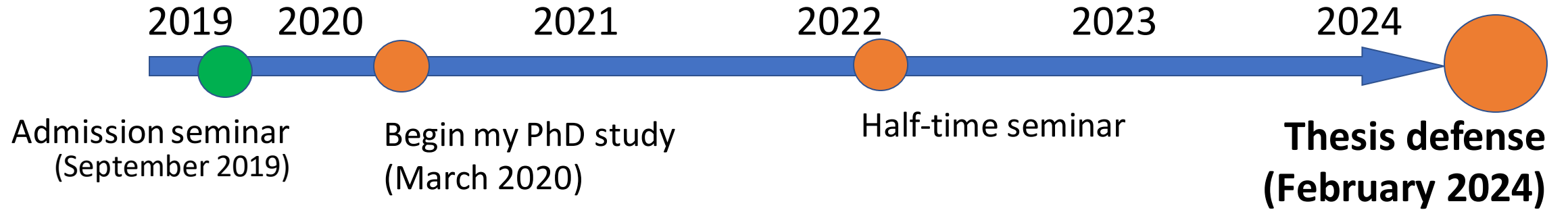


# Take home message

- *Prdm2* is a histone methyltransferase which is highly expressed in the prelimbic (PL) of human and rat
- Knockdown of *Prdm2* in the PL enhances the expression of fear memory and increase alcohol consumption, particularly in stress-induced reinstatement
- Decrease *Prdm2* expression has been associated with susceptibility to develop comorbid traits in social defeat- and witness stress rat model



# My timeline



# Plan of my PhD study

- **To identify susceptible & resilient molecular factors among different traits**
  - RNA extraction
  - Targeted transcriptomic analysis
- **To explore the causal role of the identified genes**
  - Stereotaxis surgery
  - Pharmacological intervention
  - Chemogenetic tools
- **To assess functional downstream targets in neural projections**
  - Viral-mediated gene manipulation
  - RNA in situ hybridization (RNAscope<sup>®</sup>) and immunohistochemistry
  - Dynamic calcium imaging

# Acknowledgements



**ii.u**



True success is not in the learning, but  
in its application to the benefit of mankind



M. Srinivasan

