

From metabolism to mental health: The role of timekeeping in neural development and function

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Amherst **BE REVOLUTIONARY™**

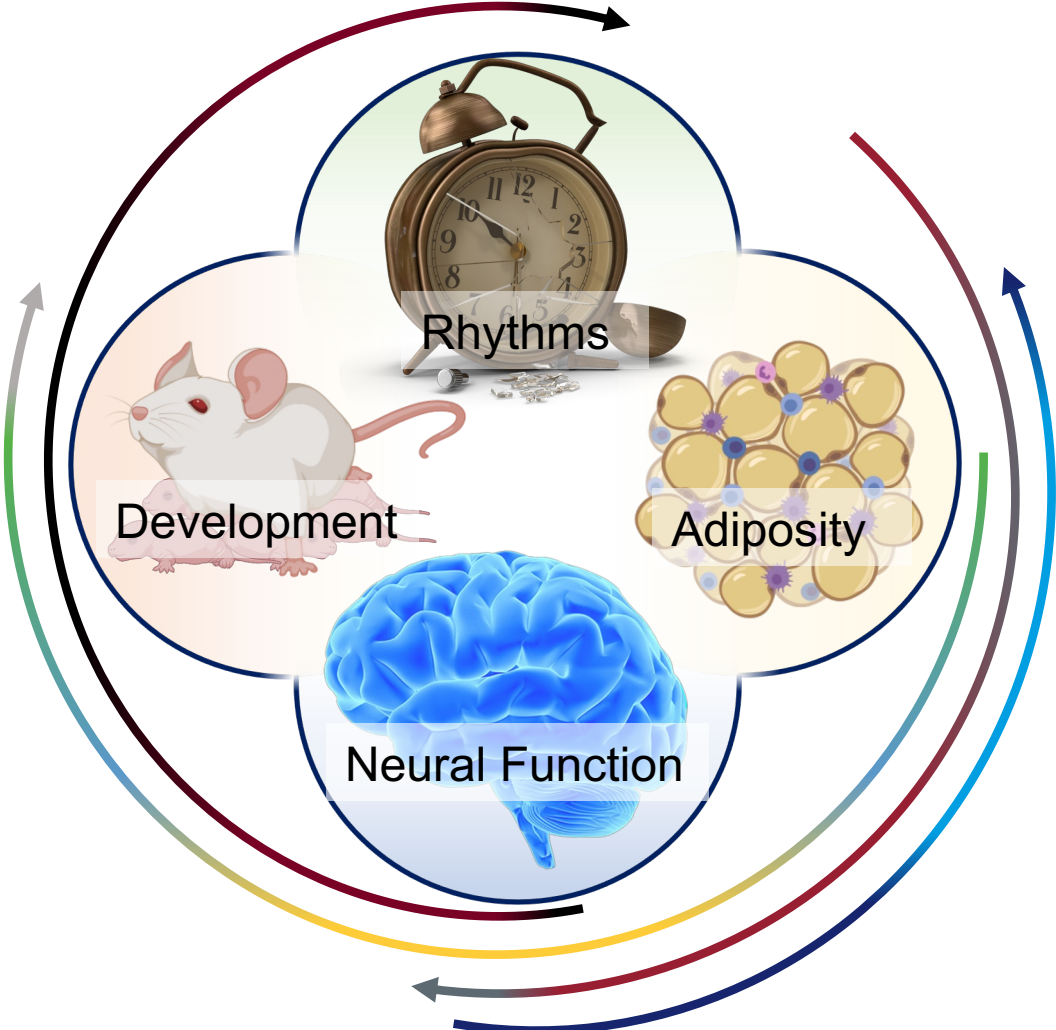
Overarching question: How do changes in environmental stimuli, such as nutritional state and daily rhythms, impact the development of brain-body physiology?

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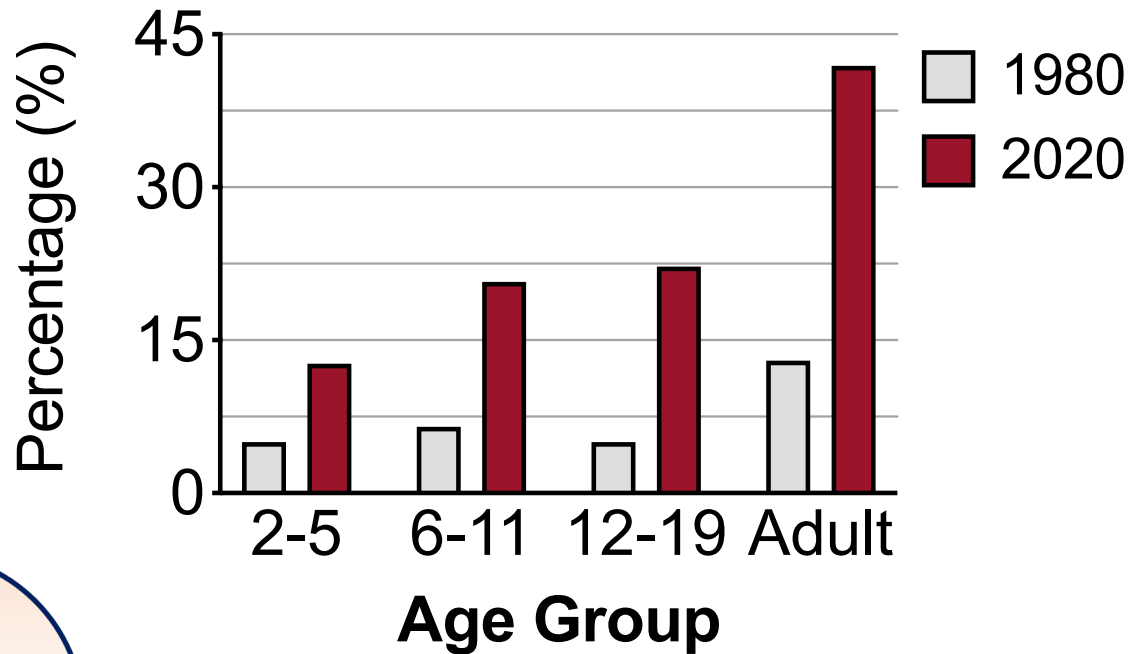


WASHINGTON STATE
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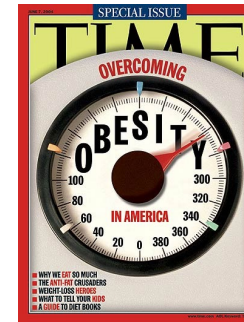


Childhood obesity is a growing worldwide problem

U.S. Obesity Rates over 40 Years

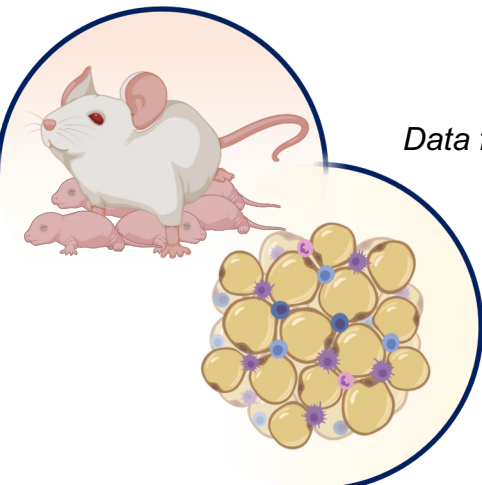


Data from Center of Disease Control: www.cdc.gov



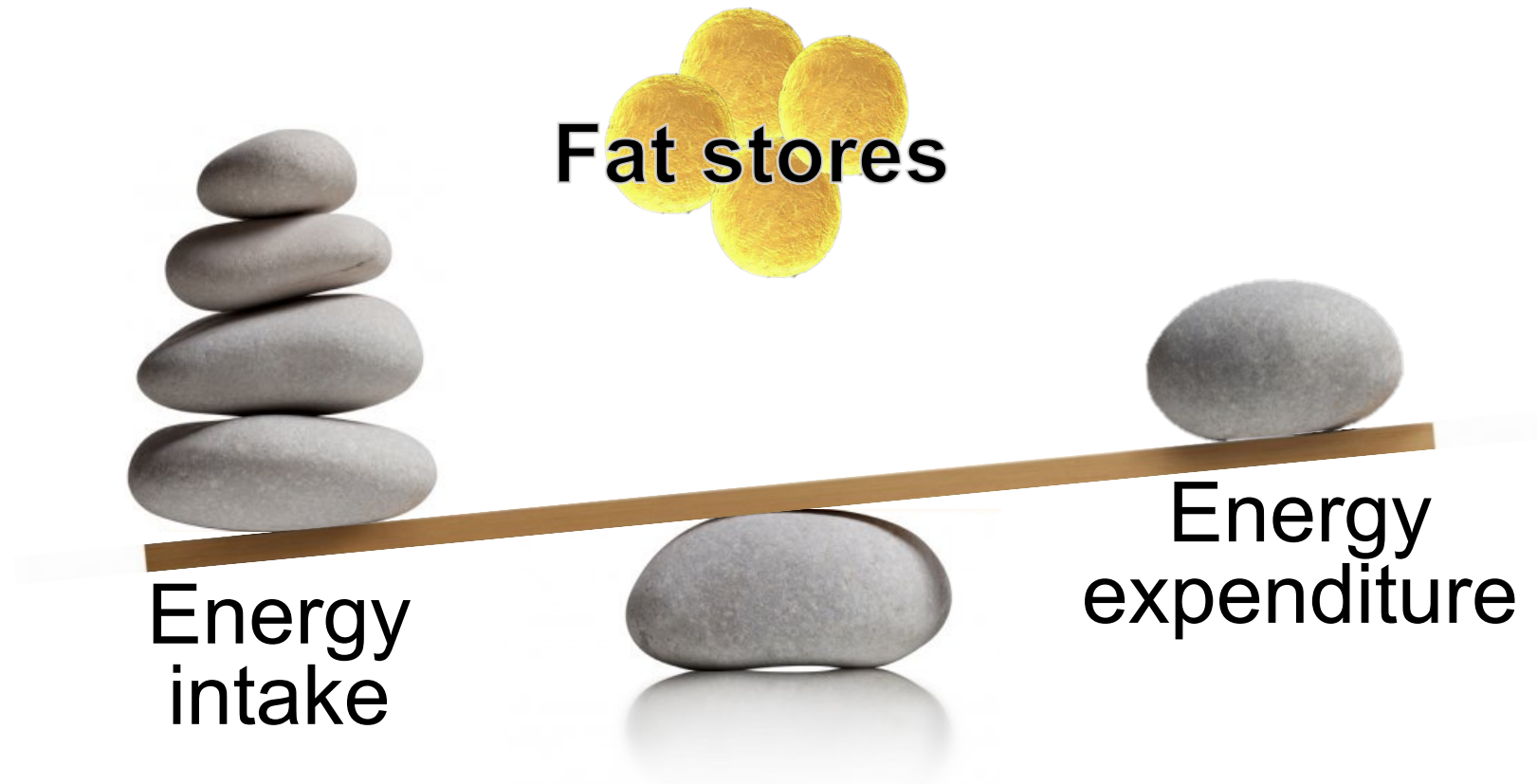
Increases risk for:

- Adulthood obesity
- Diabetes
- Psychiatric disorders
- Sleep disorders

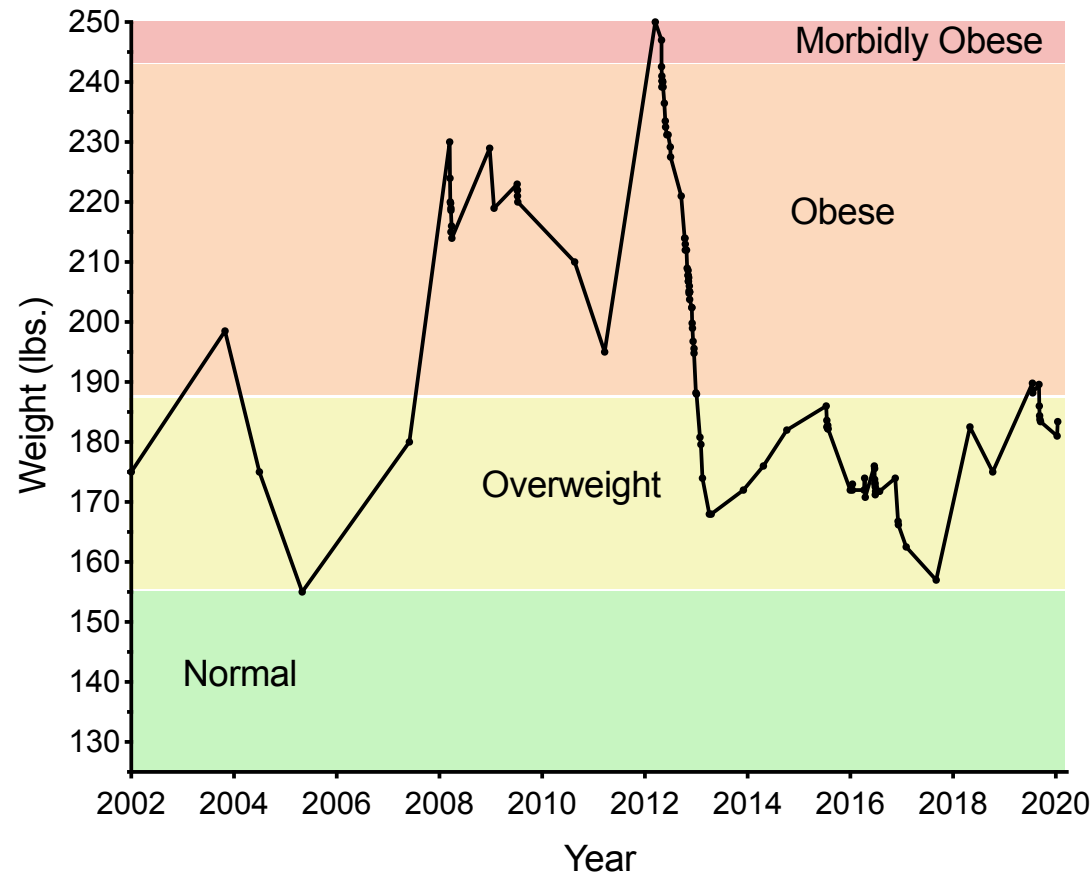


What causes obesity?

Long-term positive energy balance



“It’s easy- exercise and eat right.”

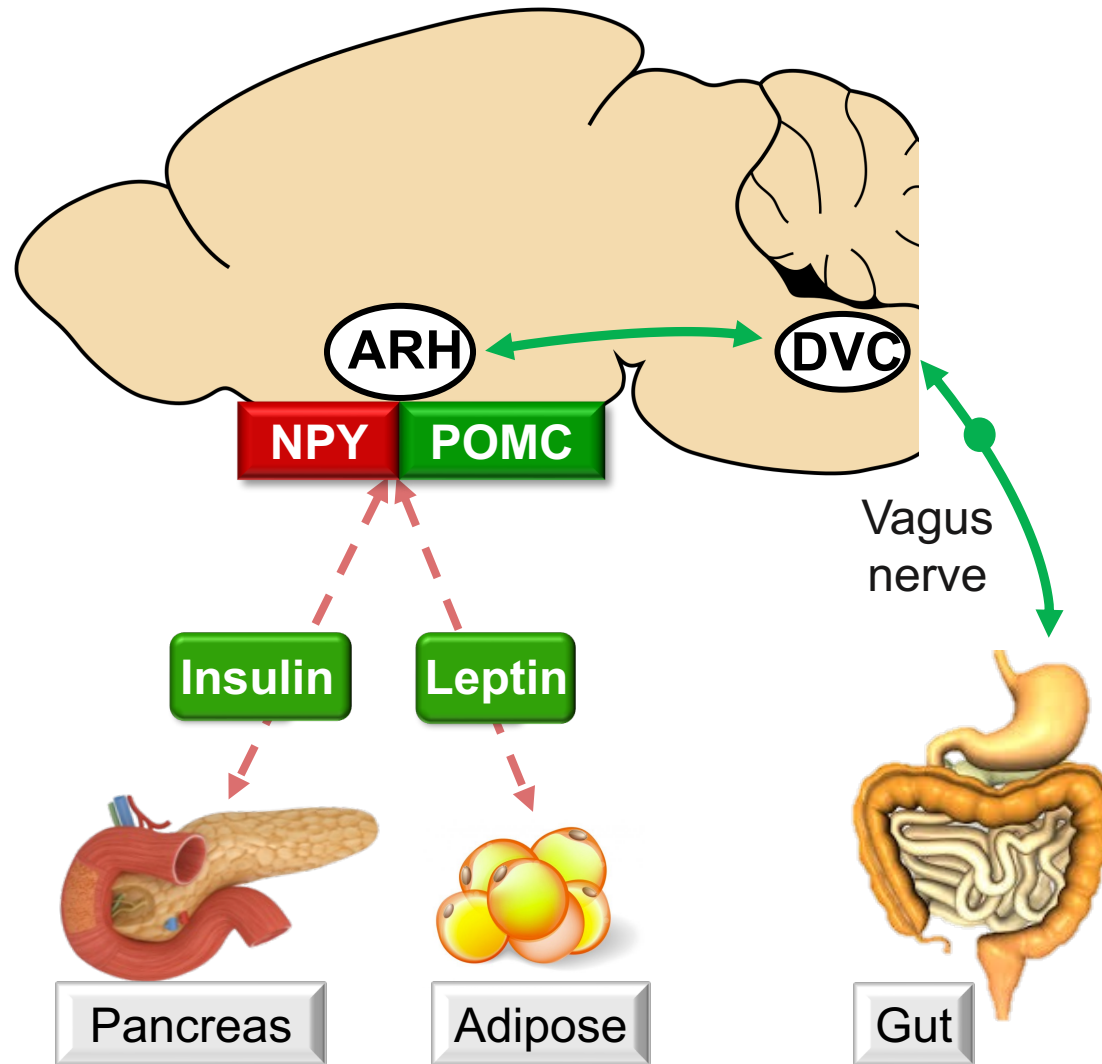


Short nucleotide polymorphisms (SNPs)

- Rs1121980 (C;T) – 1.67 higher risk
- Rs17817449(G;T) – 1.3x higher risk
- Rs5746059(A;G) – 4.6% higher fat mass
- Rs12970134(A;G) – **Melanocortin receptor 4 gene variant**

It’s a complex physiological process!

Brain-body interactions regulate energy metabolism



Neuropeptide Y (NPY)
Orexigenic

(↑ Food intake)

- Ghrelin
- **NPY**
- Orexin
- Low glucose

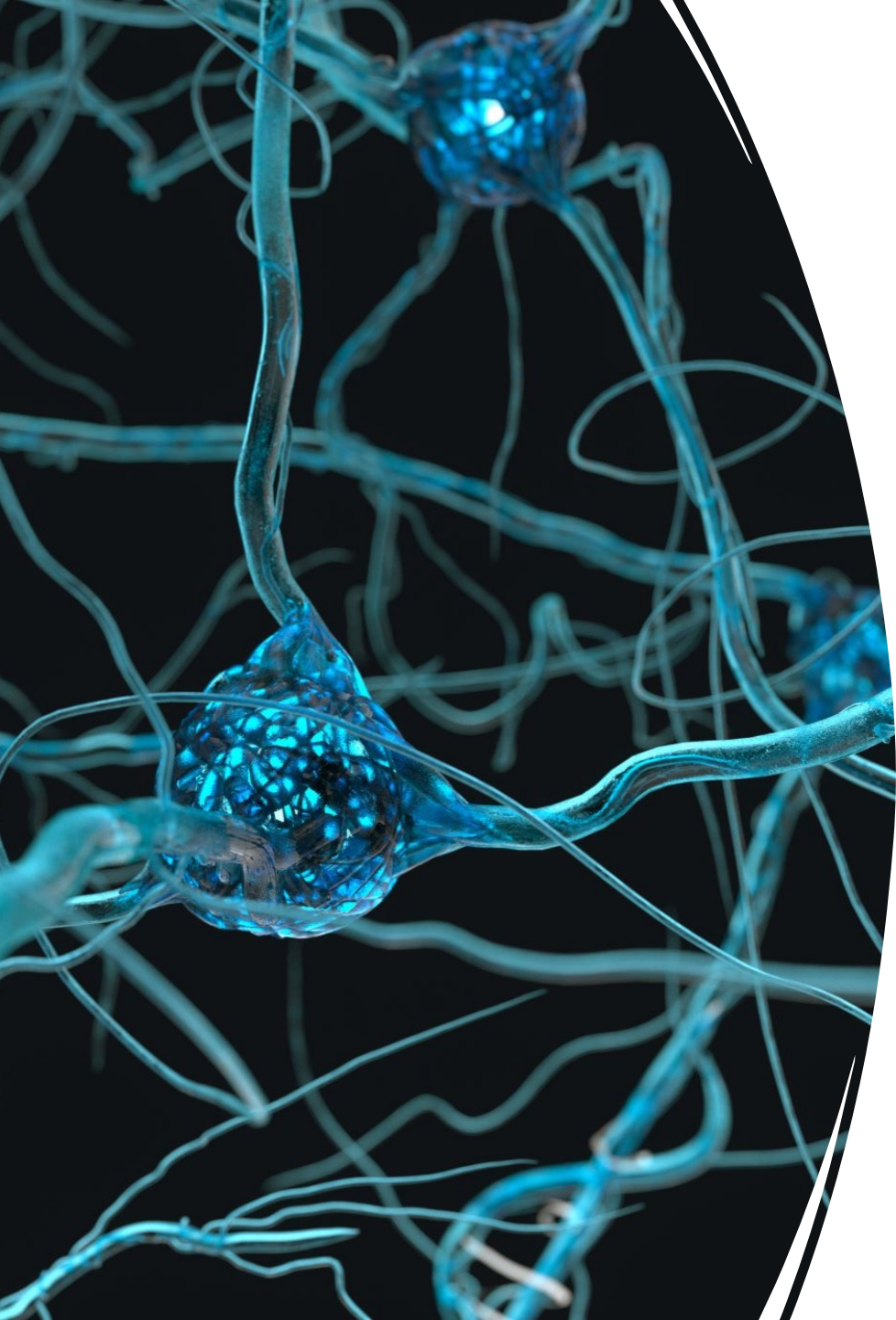
Proopiomelanocortin (POMC)
Anorexigenic

(↓ Food intake)

- CCK
- **Leptin**
- Serotonin
- α MSH (MC4R)

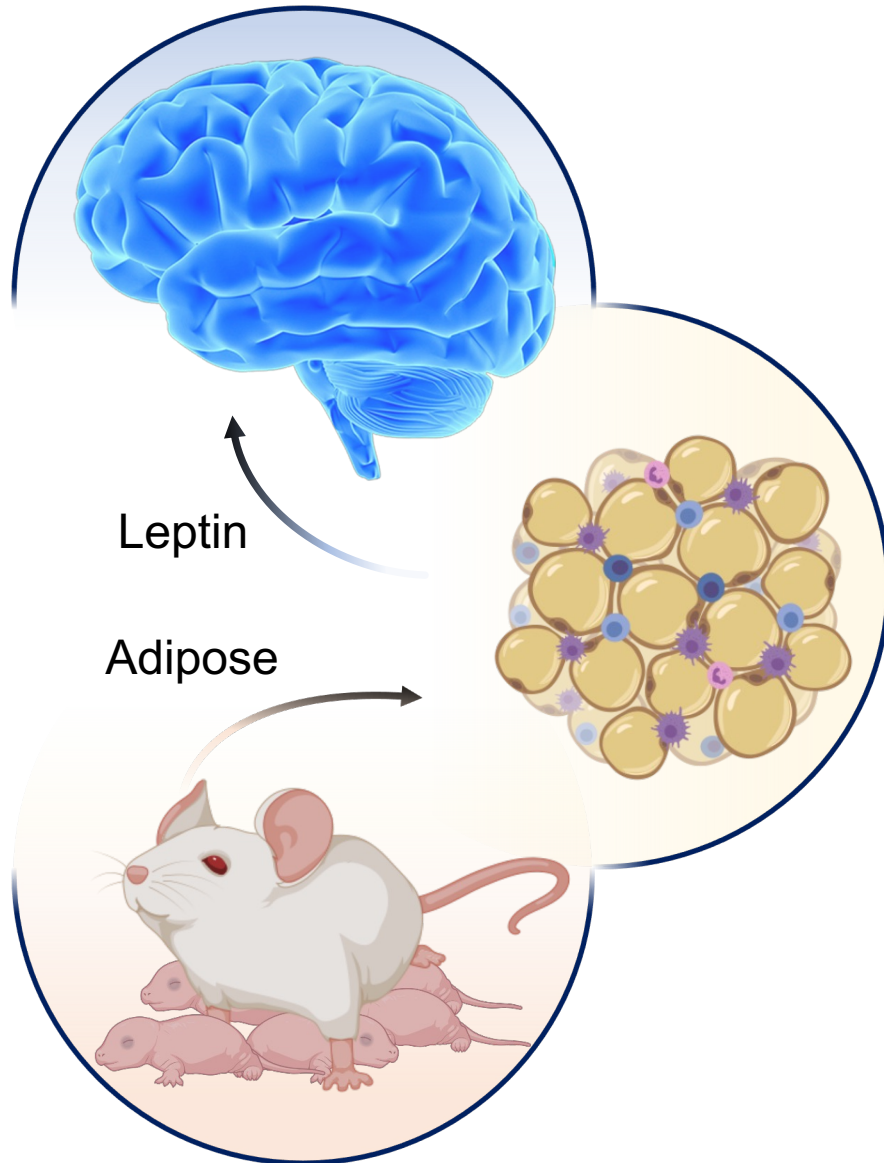
Primary central circuits

- DVC** Dorsal vagal complex
- ARH** Arcuate nucleus



Overview

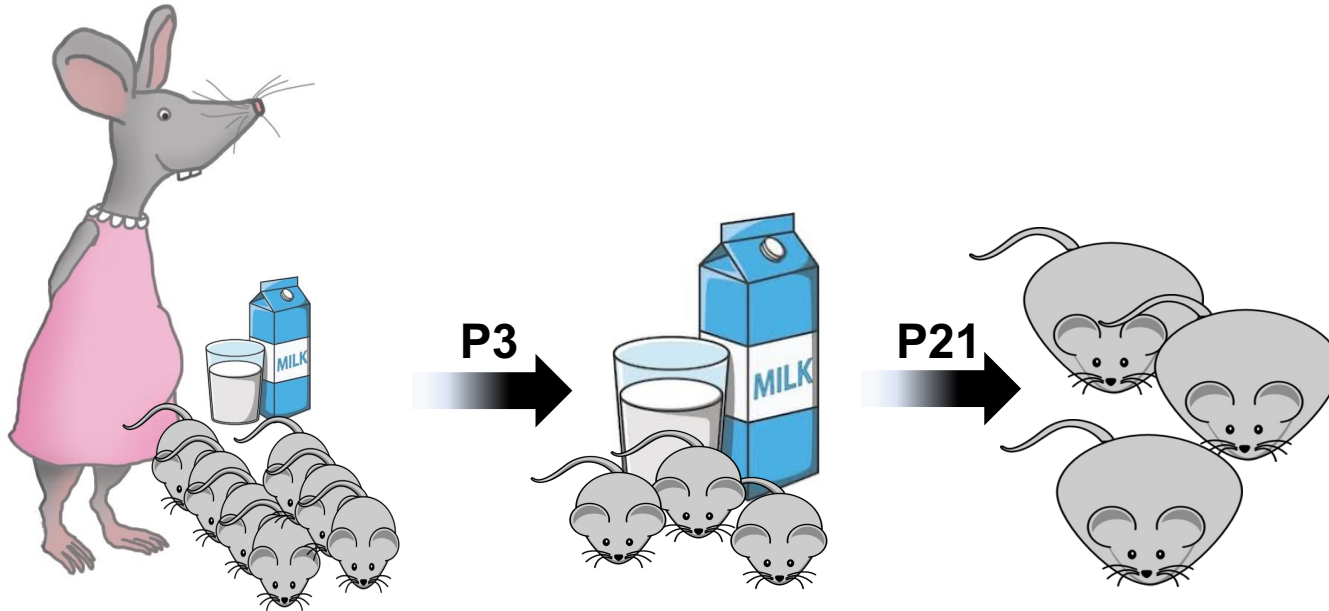
- I. How does developmental overnutrition impact brain-body physiology?
- II. How do daily rhythms impact metabolic and neural function?
- III. Where do we go from here?



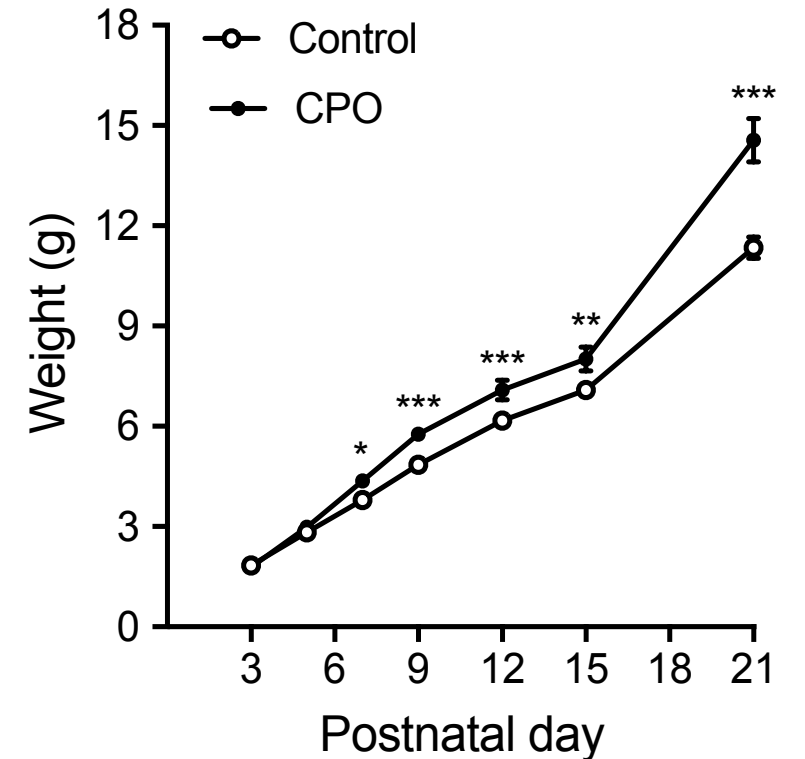
Part I

- I. How does developmental overnutrition impact brain-body physiology?
- II. How do daily rhythms impact metabolic function?
- III. Where do we go from here?

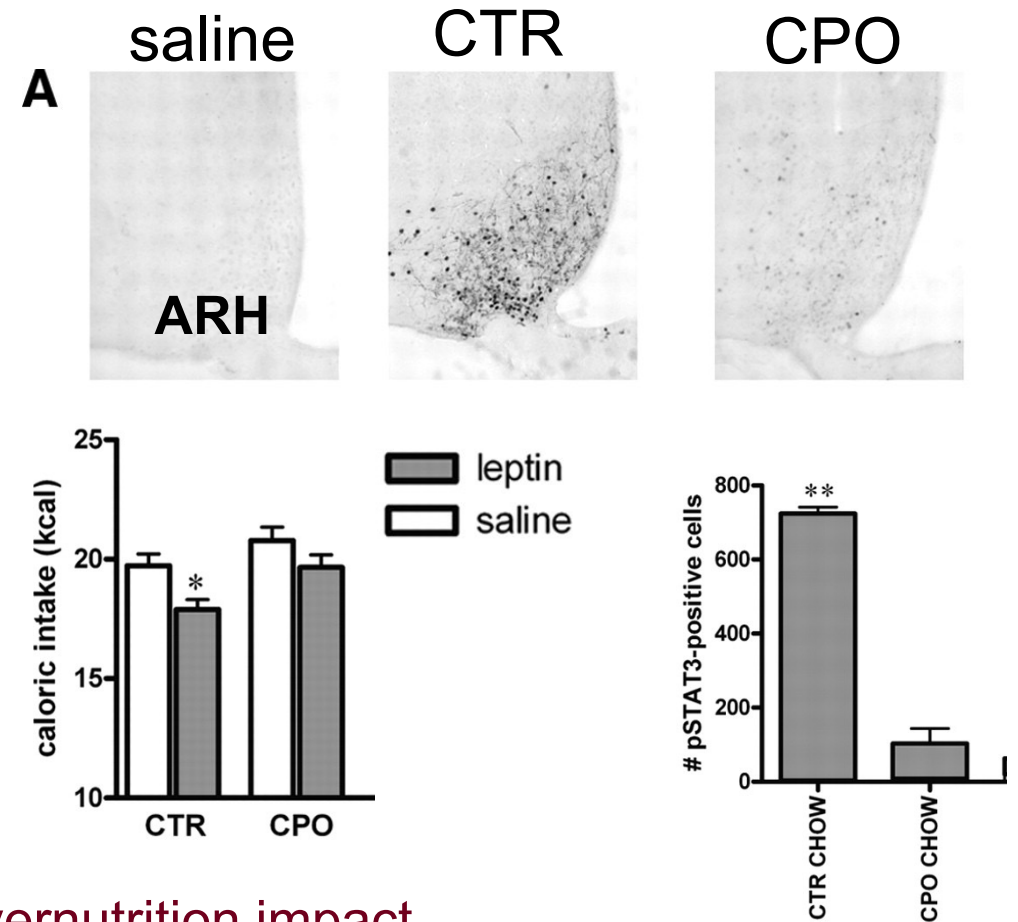
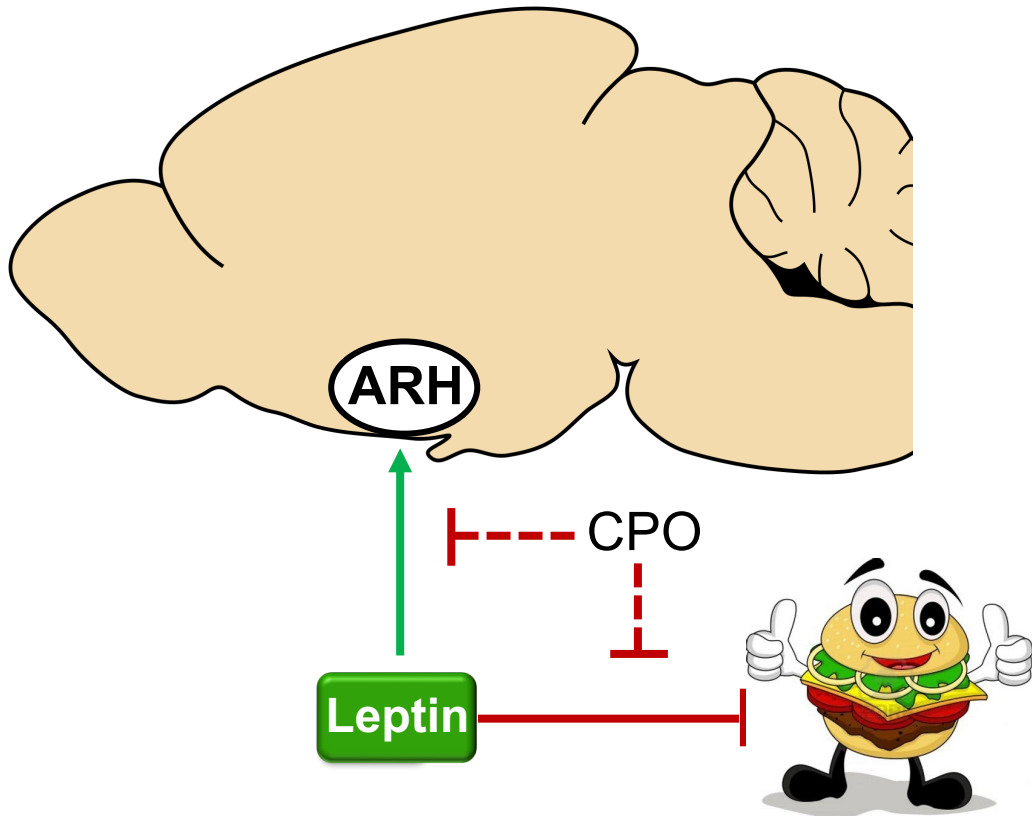
Chronic postnatal overnutrition (CPO) leads to sustained weight gain



NOT a high-fat or high-sugar diet

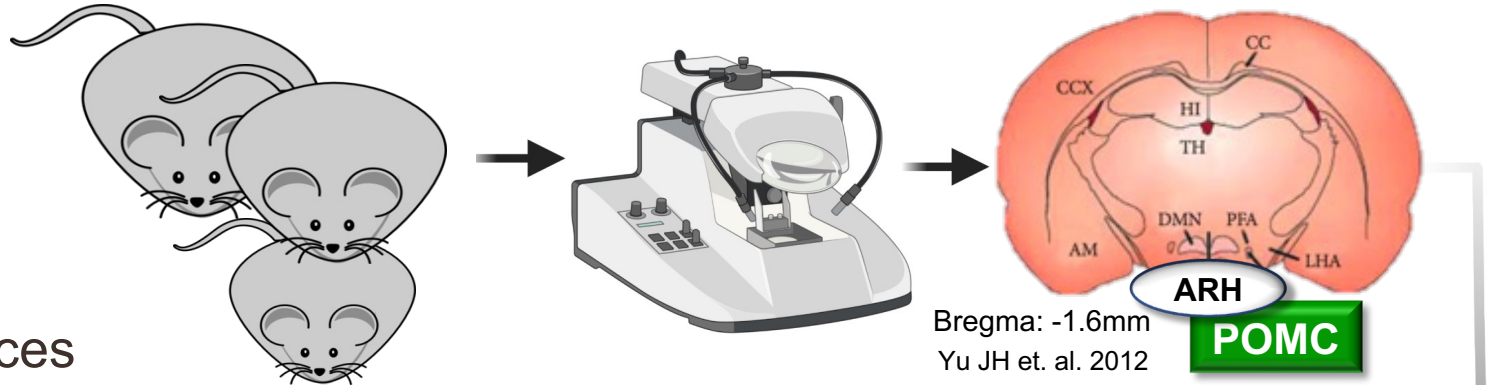


Chronic postnatal overnutrition (CPO) leads to leptin resistance

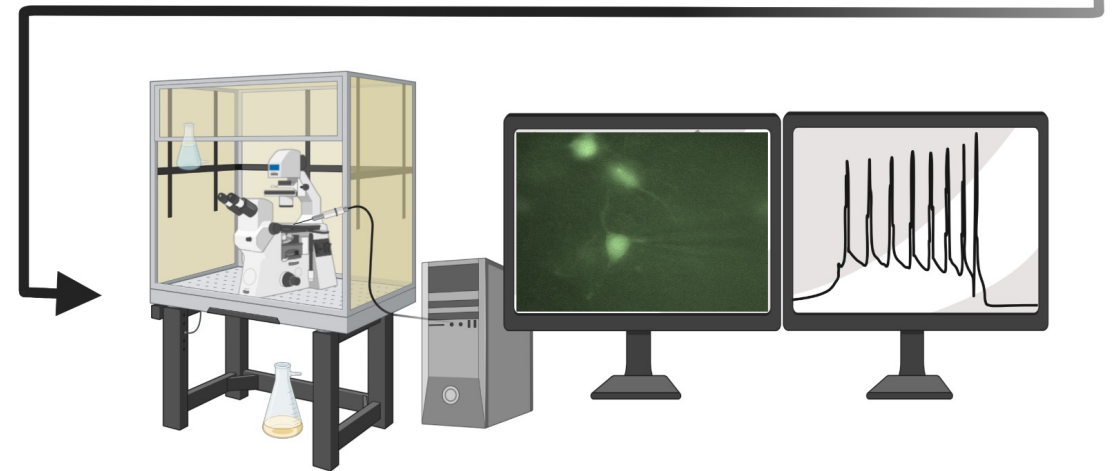


How does developmental overnutrition impact leptin signaling onto **ARH-POMC** neurons?

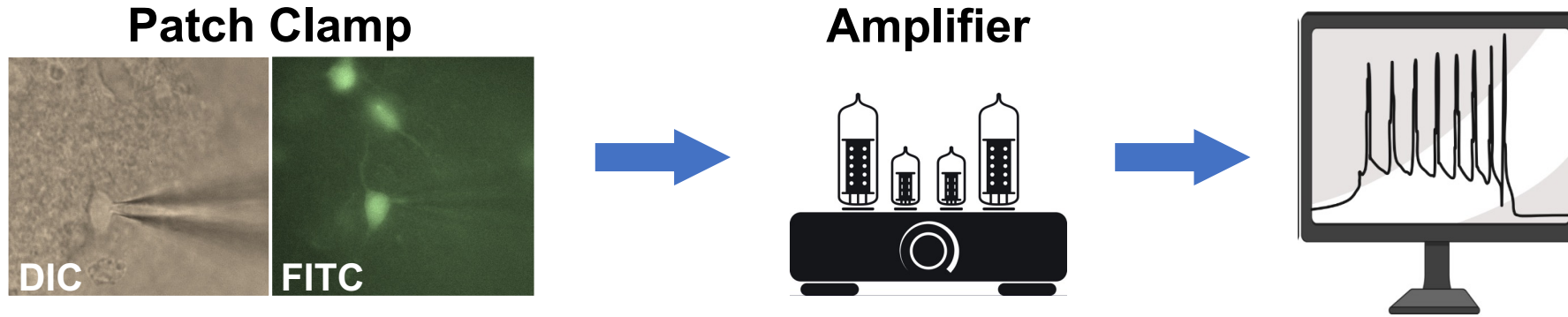
Electrophysiological Approach



- Collect *ex vivos* coronal brain slices from CPO mice
- Transgenic POMC-GFP mice
- Measure changes in current and voltage of ARH-POMC neurons

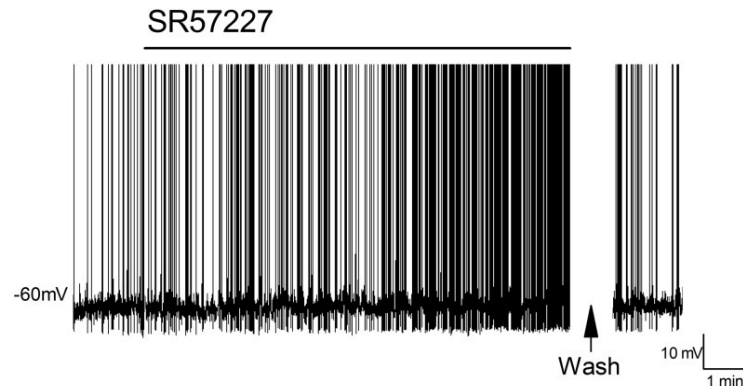


Electrophysiological Approach



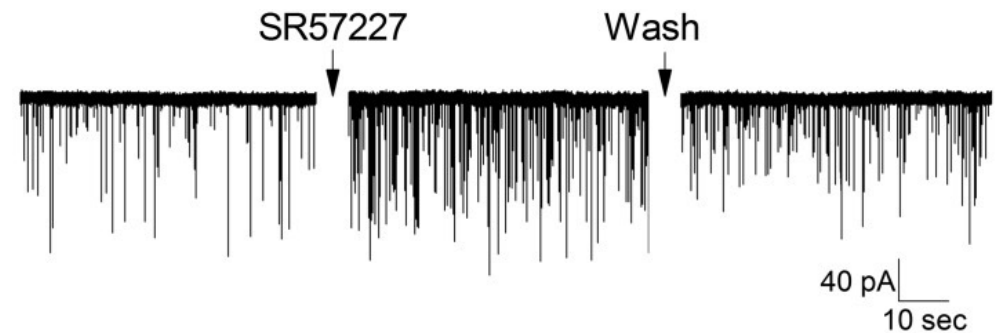
Neuronal activity (current clamp)

- Membrane potential (mV)
- Action potential frequency (Hz)



Synaptic function (voltage clamp)

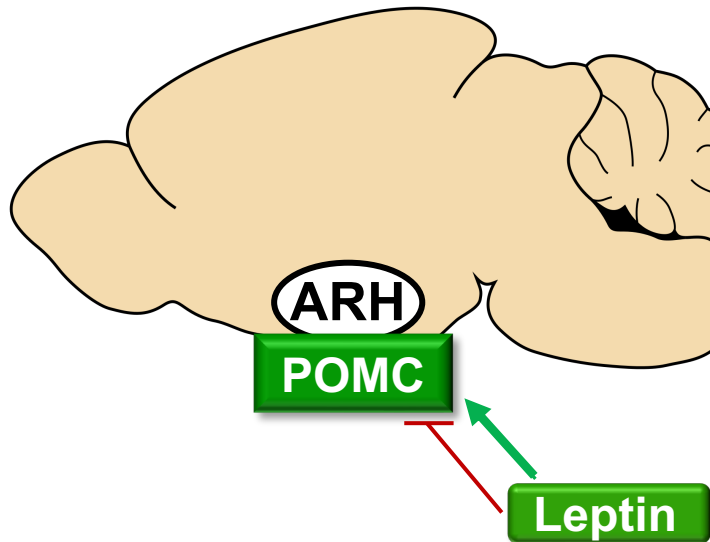
- Frequency (Hz)
- Amplitude (pA)



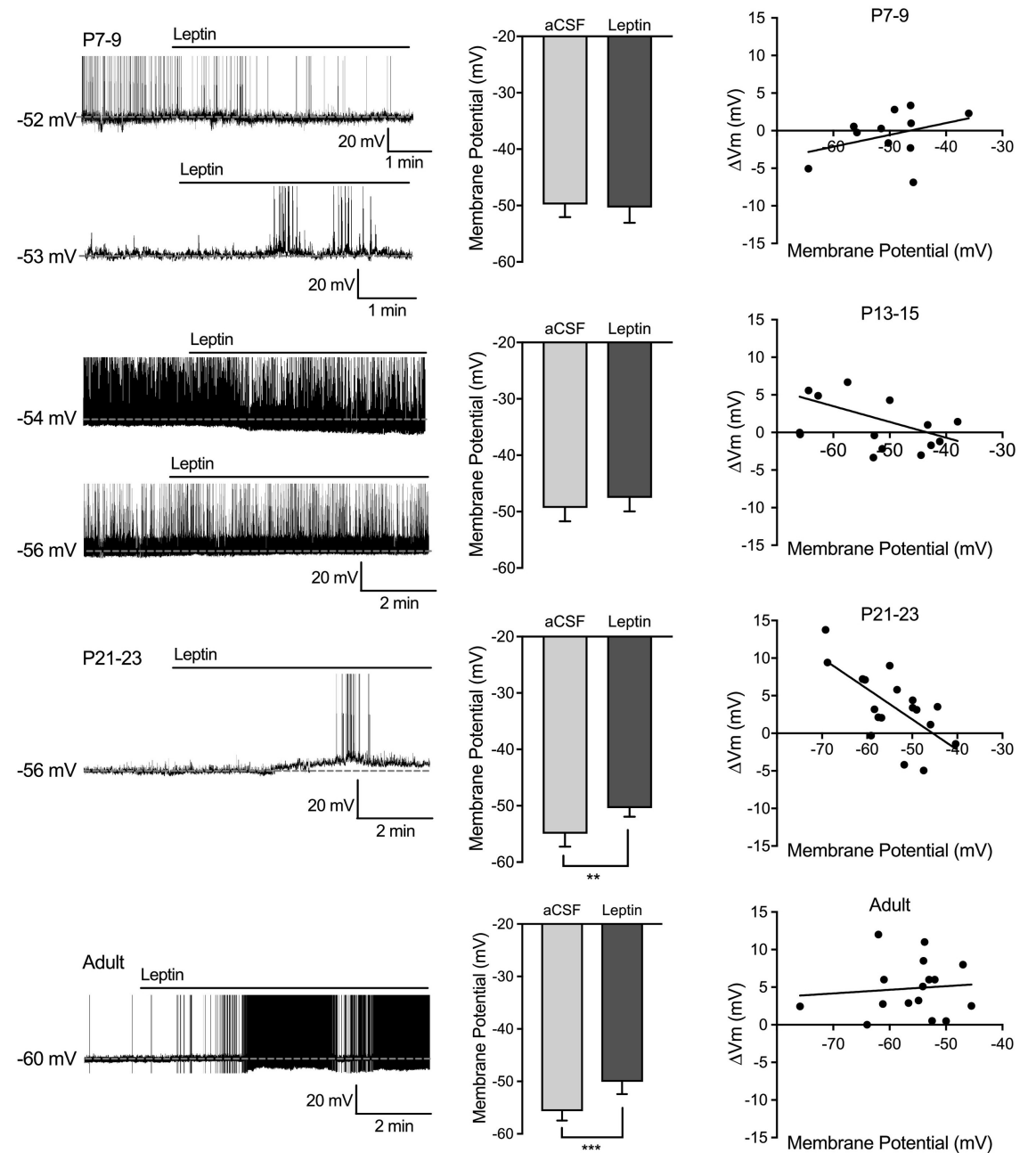
(Roberts et. al., JNeuro 2012)

Leptin excitation of ARH-POMC neurons increases throughout development

- Low and variable leptin responses first two weeks of life
- Consistent and strong leptin responses in adulthood



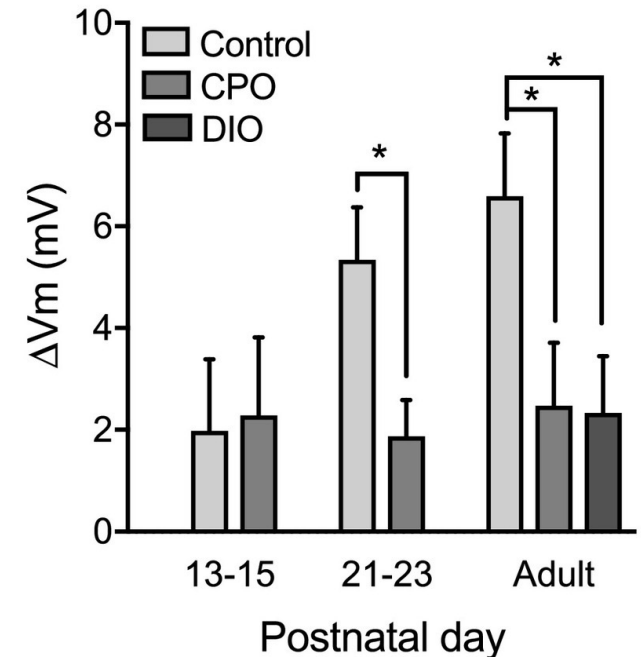
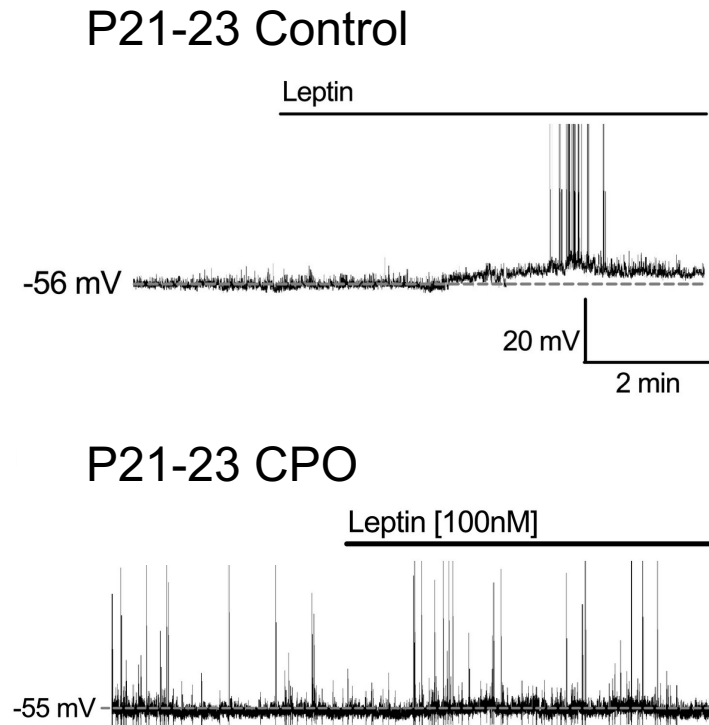
How do CPO mice respond to leptin?



(Roberts et al., Behav & Phys 2019)

CPO leads to leptin resistance in ARH-POMC neurons

- CPO reduces leptin net effect on membrane potential by > 50%
- This effect remains into adulthood
- Mimics effect of diet-induced obesity (DIO)
- Mice are on a **standard diet!**

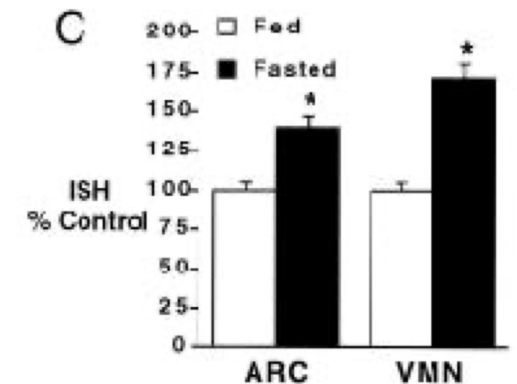
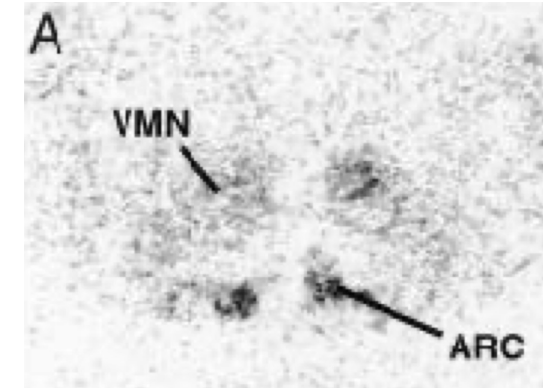
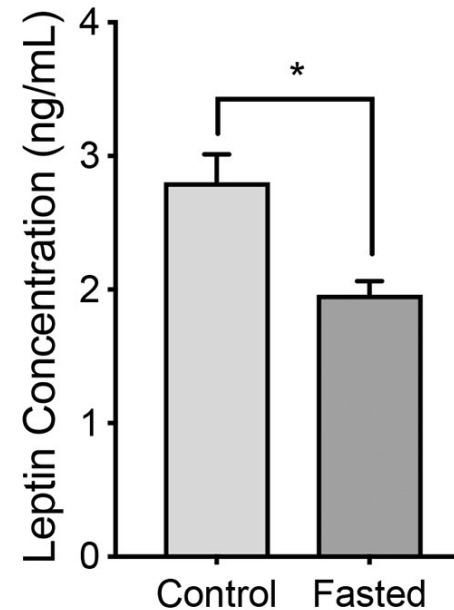


Can we rescue leptin signaling in ARH-POMC neurons?

(Roberts et al., Behav & Phys 2019)

Does an overnight fast rescue leptin signaling?

- Fasting decreases circulating leptin
- Fasting increases leptin receptor expression in the ARH

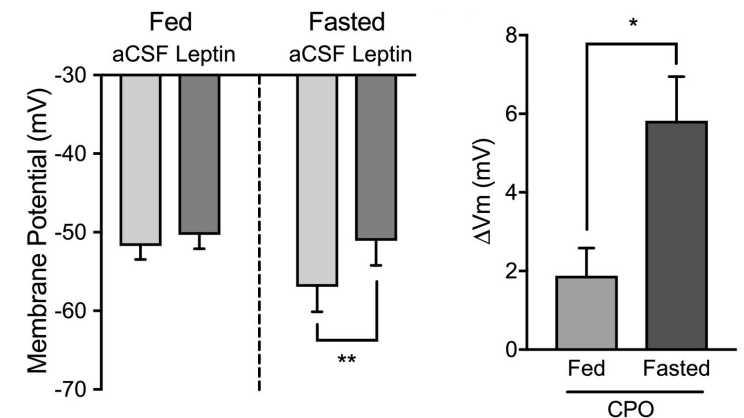
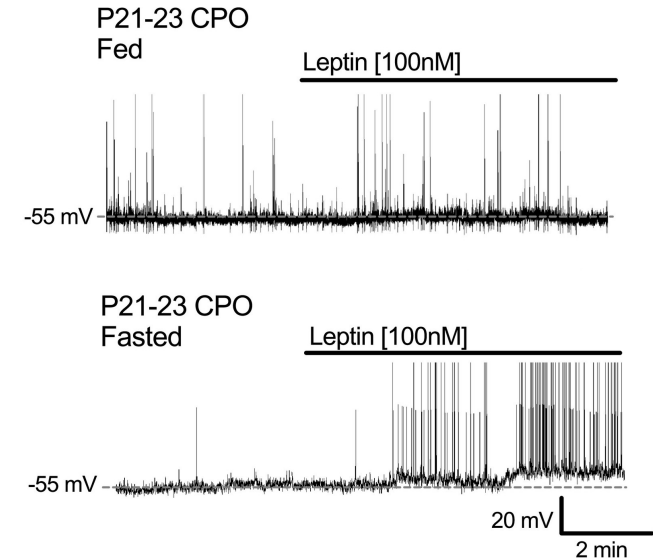


Baskin et. al., *Diabetes* 1998

(Roberts et. al., *Behav & Phys* 2019)

An overnight fast rescues leptin signaling onto ARH-POMC neurons

- Mice weaned at P21
- Fasted overnight (~12-14hr)
- Recorded from ARH-POMC neurons
- Fed CPO mice were leptin resistant
- Fasting rescued leptin signaling

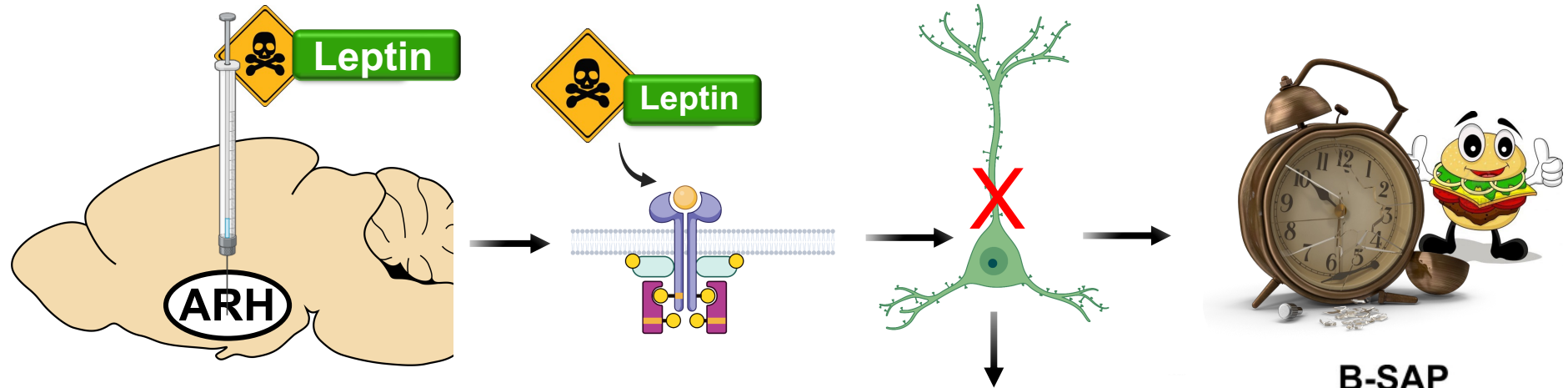


Is meal-timing misaligned in CPO mice?



(Roberts et. al., Behav & Phys 2019)

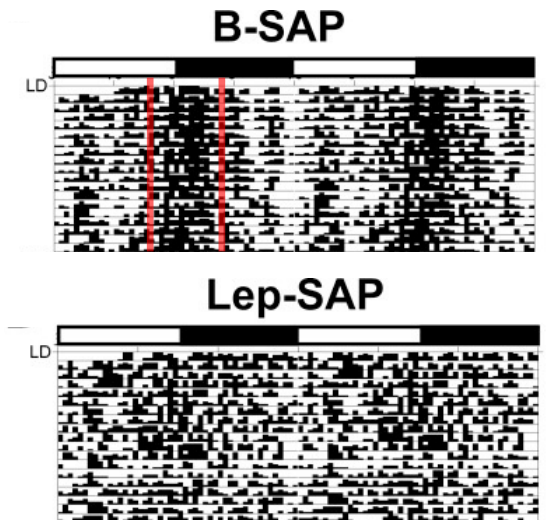
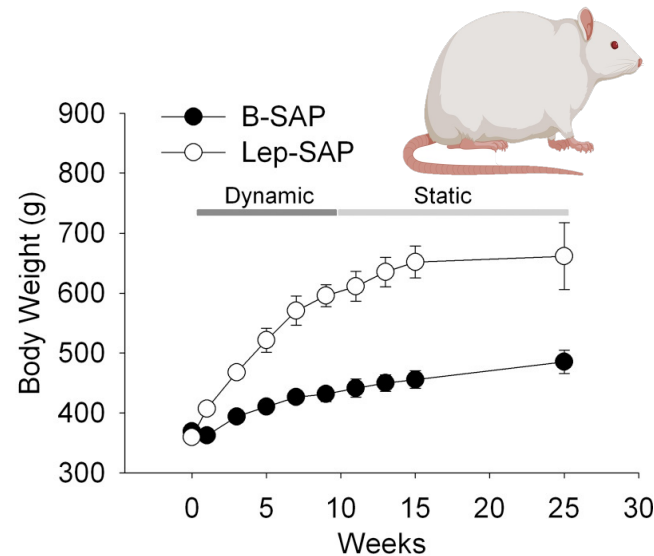
Leptin sensitive neurons in ARH contribute to endogenous feeding rhythms



If CPO induces leptin resistance, how does CPO impact endogenous rhythms?

Can fasting realign rhythms?

The neurophysiology is *unknown*



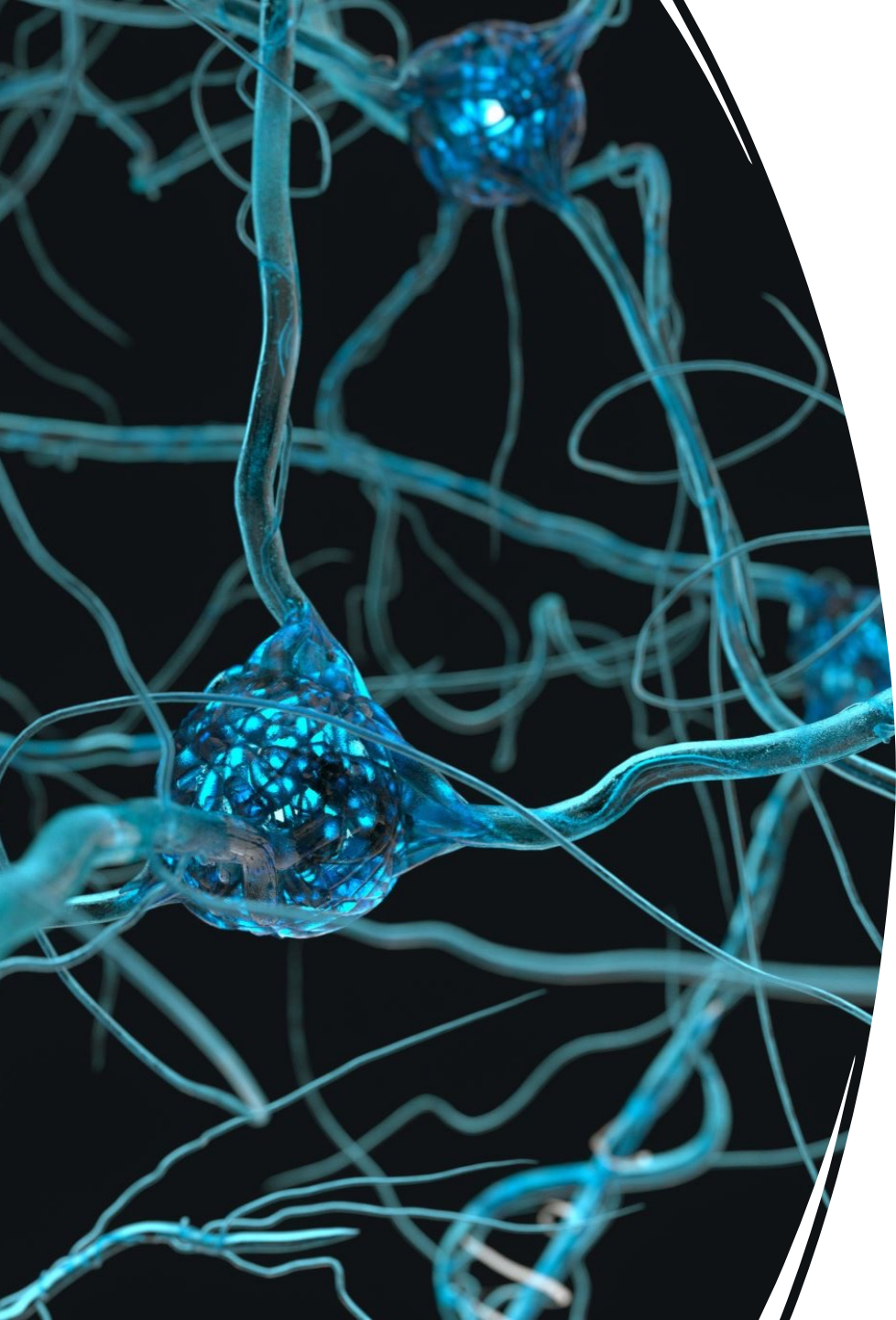
(Li AJ, Roberts et. al., AJP2012)

Are fasting diets a potential therapeutic strategy?

- Come in many forms
- Literature is highly conflicted

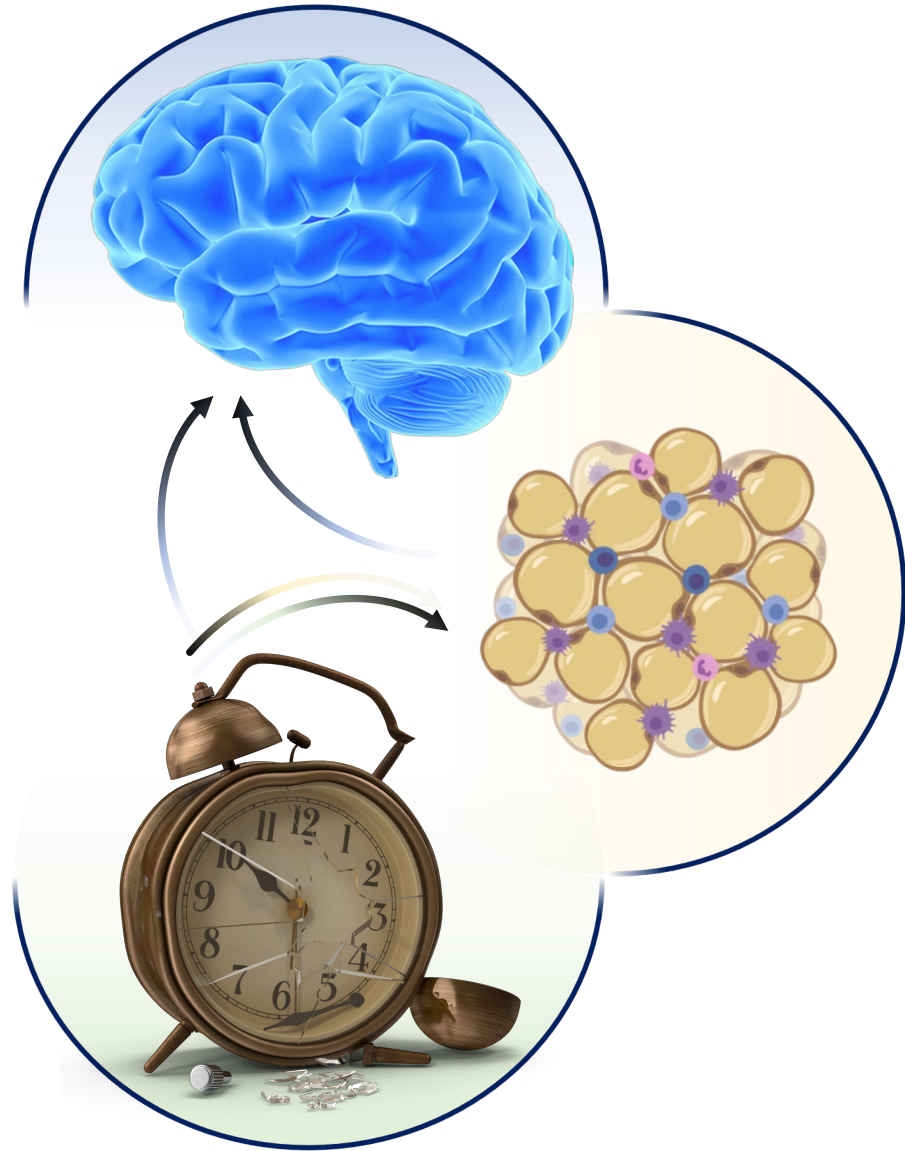
Underlying neurophysiology is *unknown*





Part I: Summary

- I. Developmental overnutrition has lifelong consequences
- I. CPO leads to leptin resistance in ARH-POMC neurons
- II. Fasting rescues leptin signaling in ARH-POMC neurons
- III. Leptin and feeding rhythms are intertwined



Part II

- I. How does developmental overnutrition impact brain-body physiology?
- II. How do daily rhythms impact metabolic function?
- III. Where do we go from here?

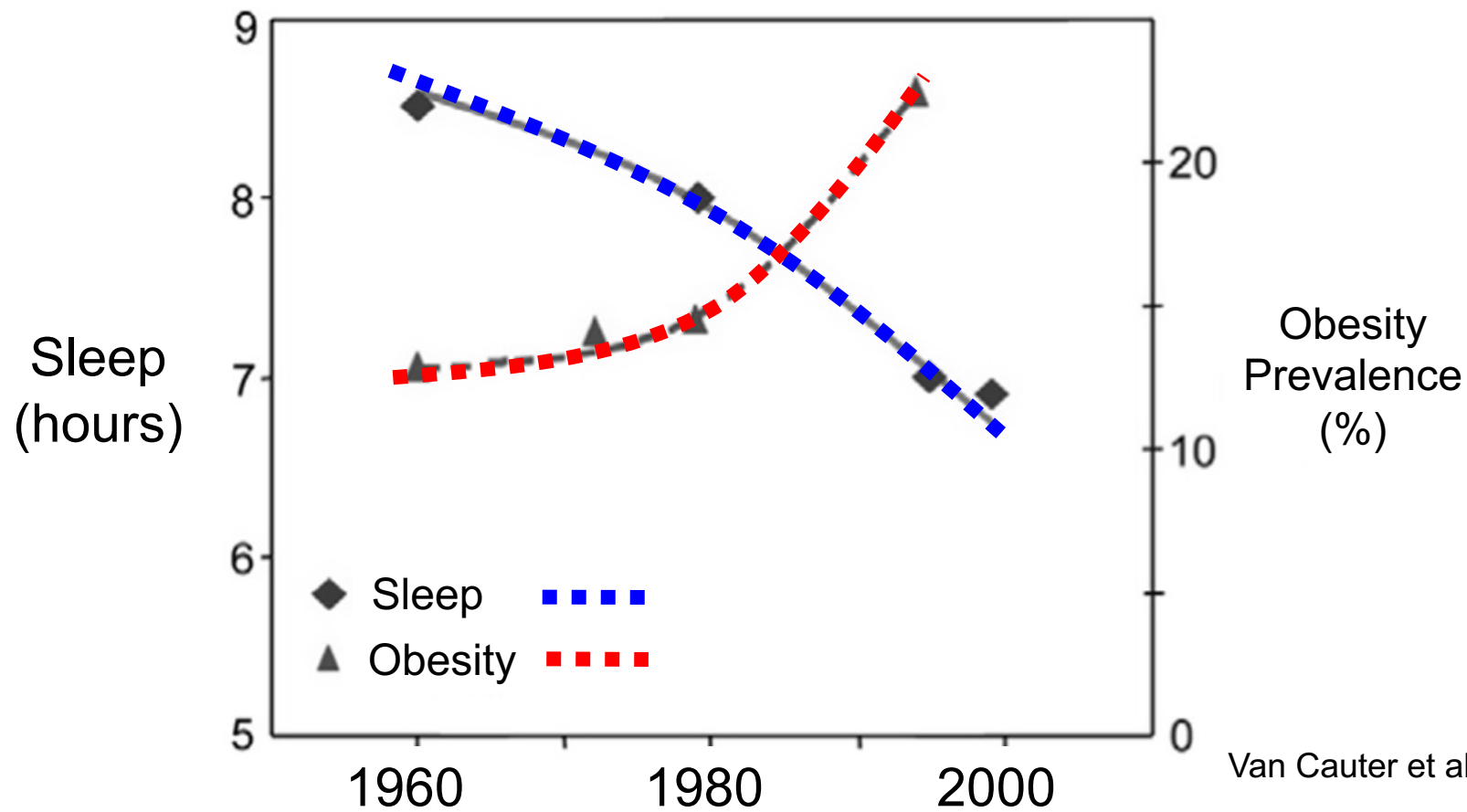
Sleep disruption leads to poor health outcomes

Consequences of **Shift Work:**

- Blood Sugar Imbalance and Diabetes
- Inhibited Mental Performance
- Increased Risk of Injury & Accidents
- Hormone Imbalances
- Weight Gain
- Digestive Disorders
- Depression
- Anxiety
- Chronic Fatigue

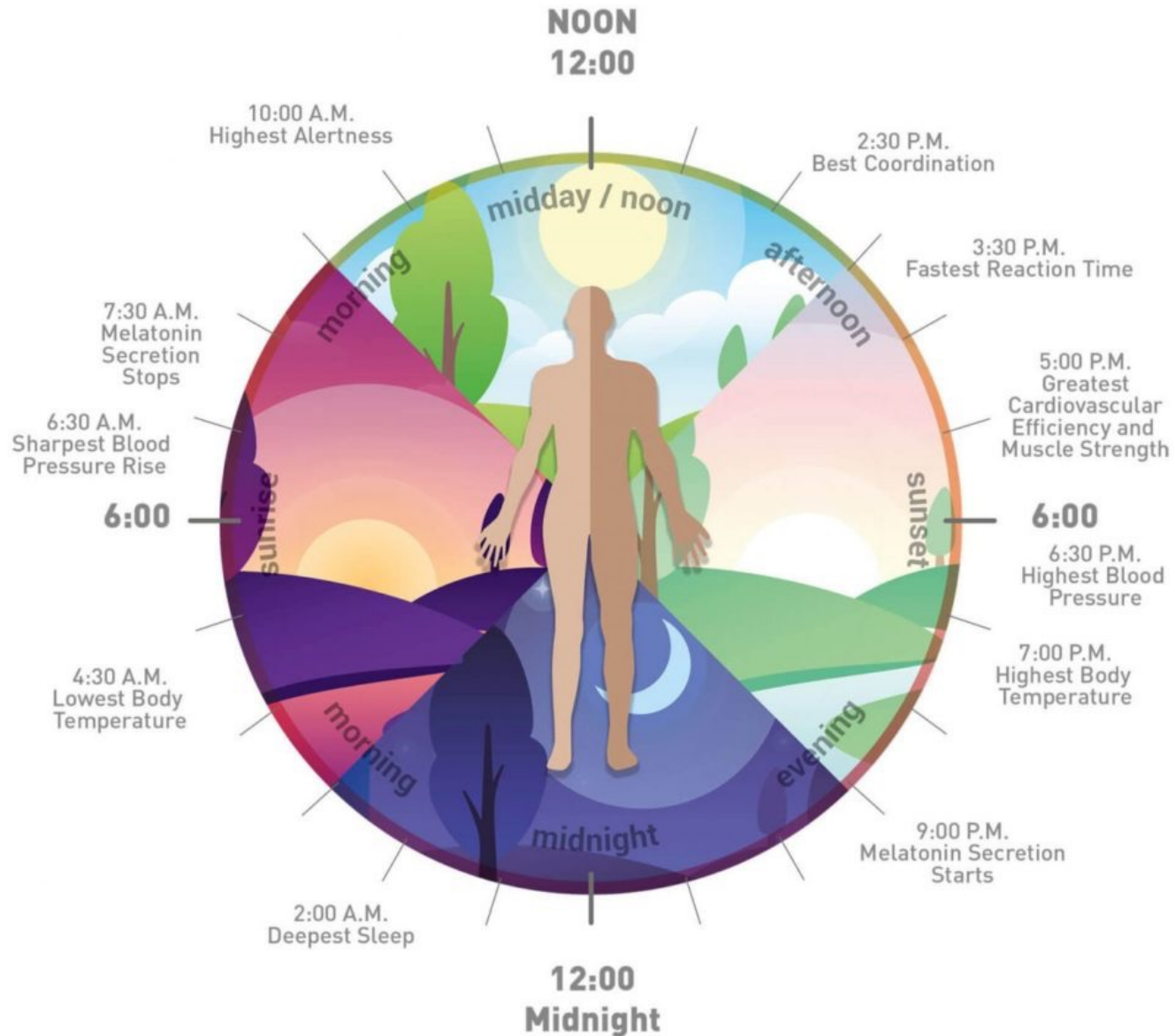


Obesity and Sleep: Correlation vs. Causation



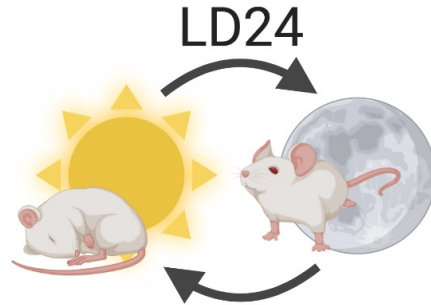
Van Cauter et al., 2008, *Sleep Medicine*

Circadian (daily) rhythms

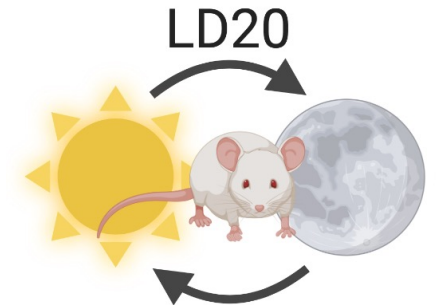


Environmental Circadian Desynchronization (ECD)

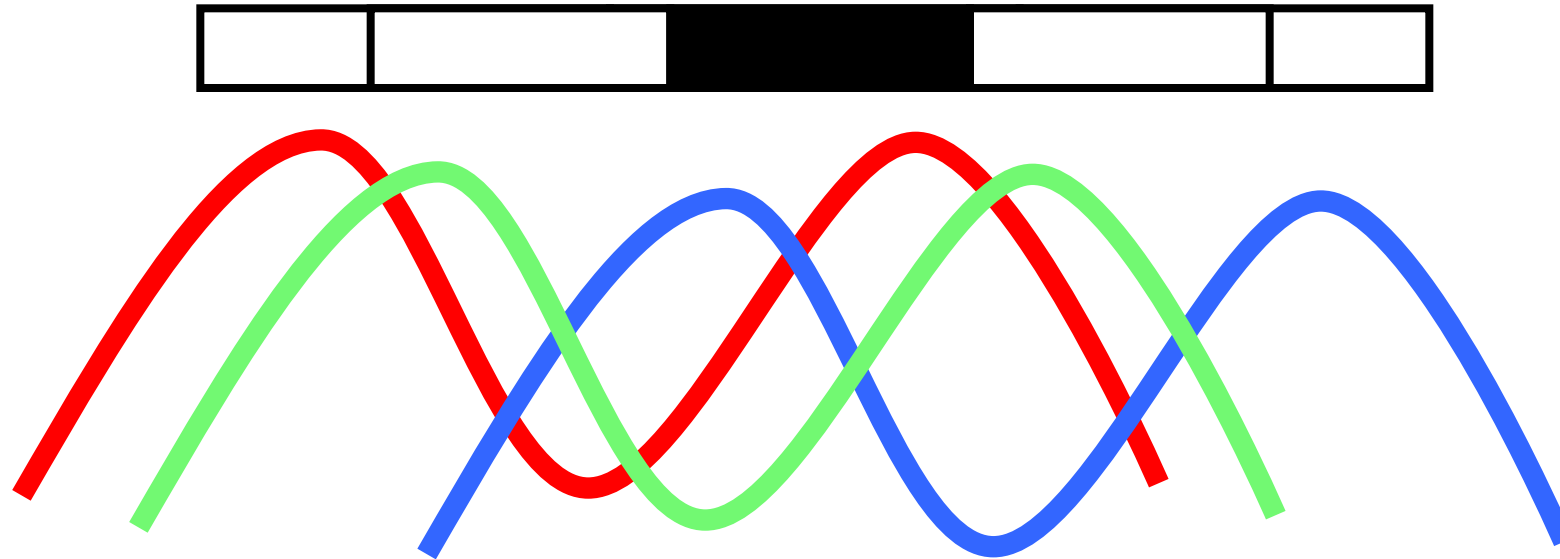
Control
12:12h LD cycle



ECD
10:10h LD cycle

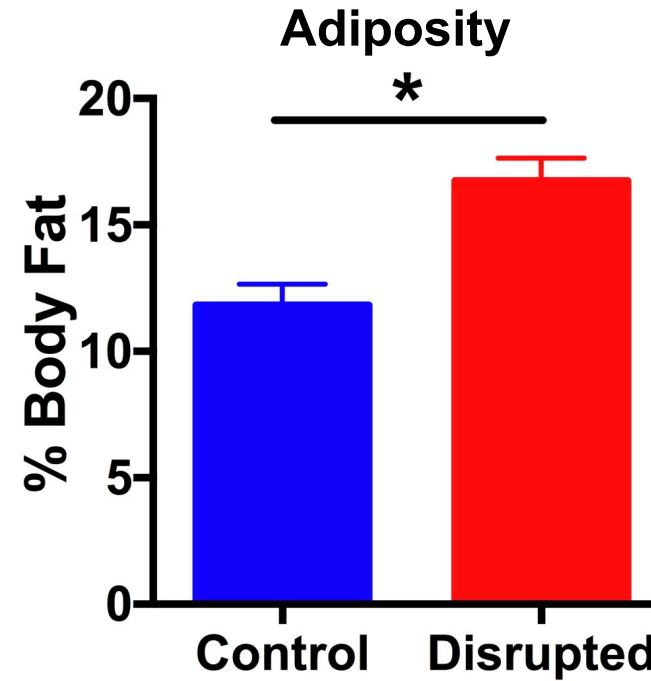
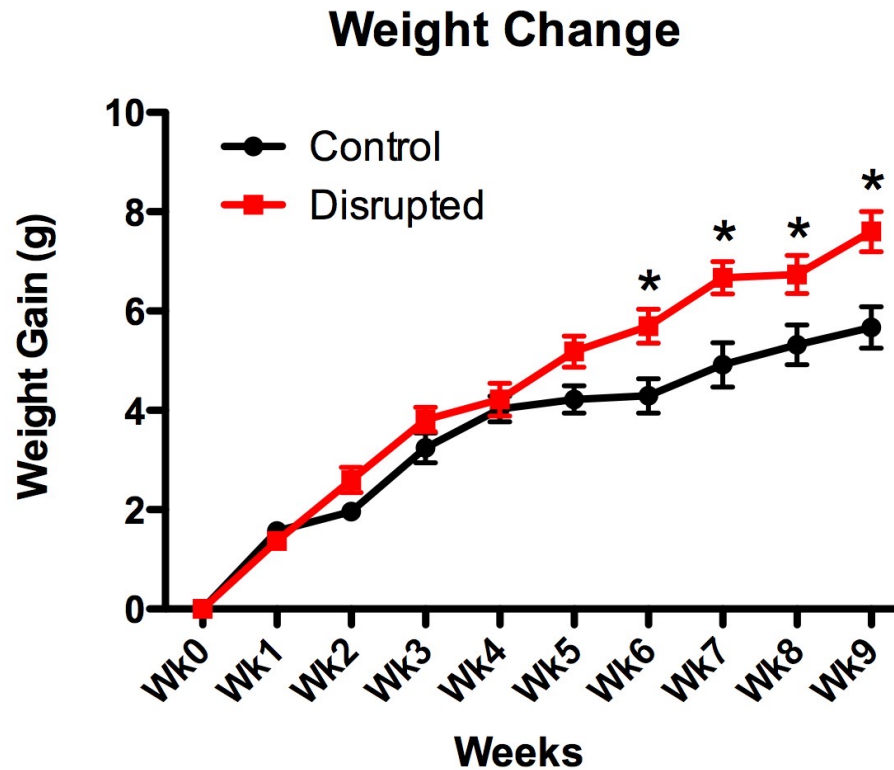


Environmental Circadian Desynchronization (ECD)

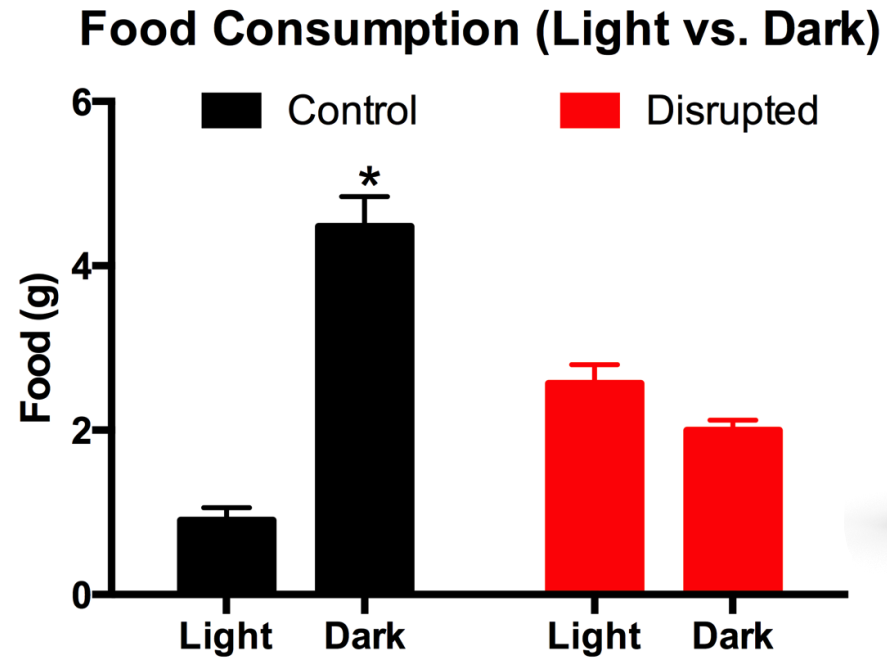


Compressing the light-dark cycle

ECD Increases weight and adiposity



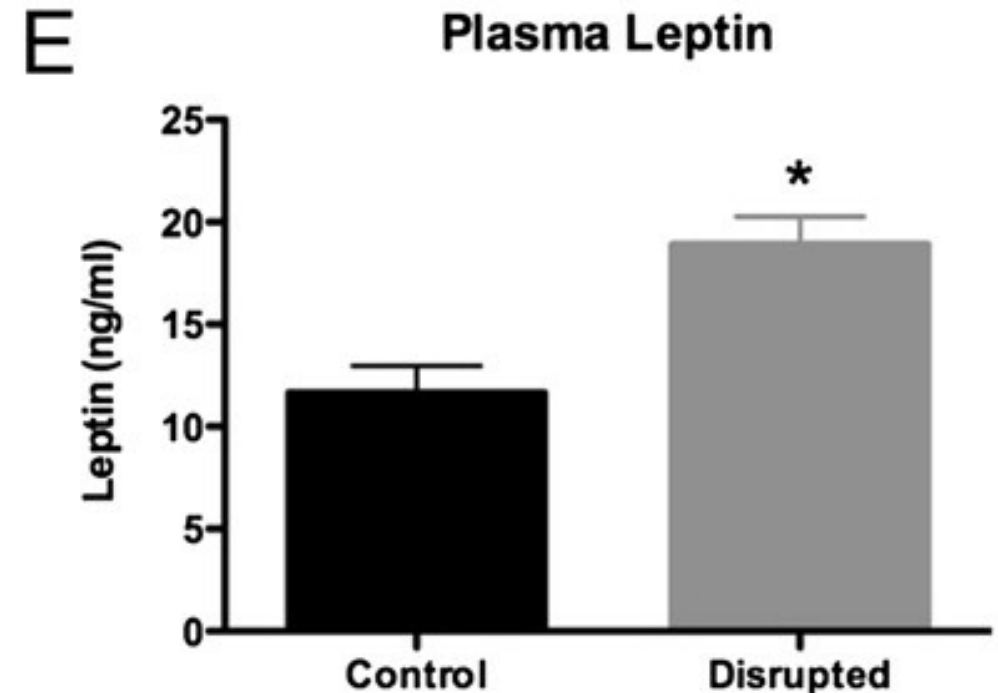
ECD Mice don't eat more... Just at the wrong time.



Circadian Disruption: Metabolic Stress?

Environmental CD increases:

- Insulin
- Triglycerides
- plasma leptin
- Cognitive rigidity



Karatsoreos et al., 2011, *PNAS*

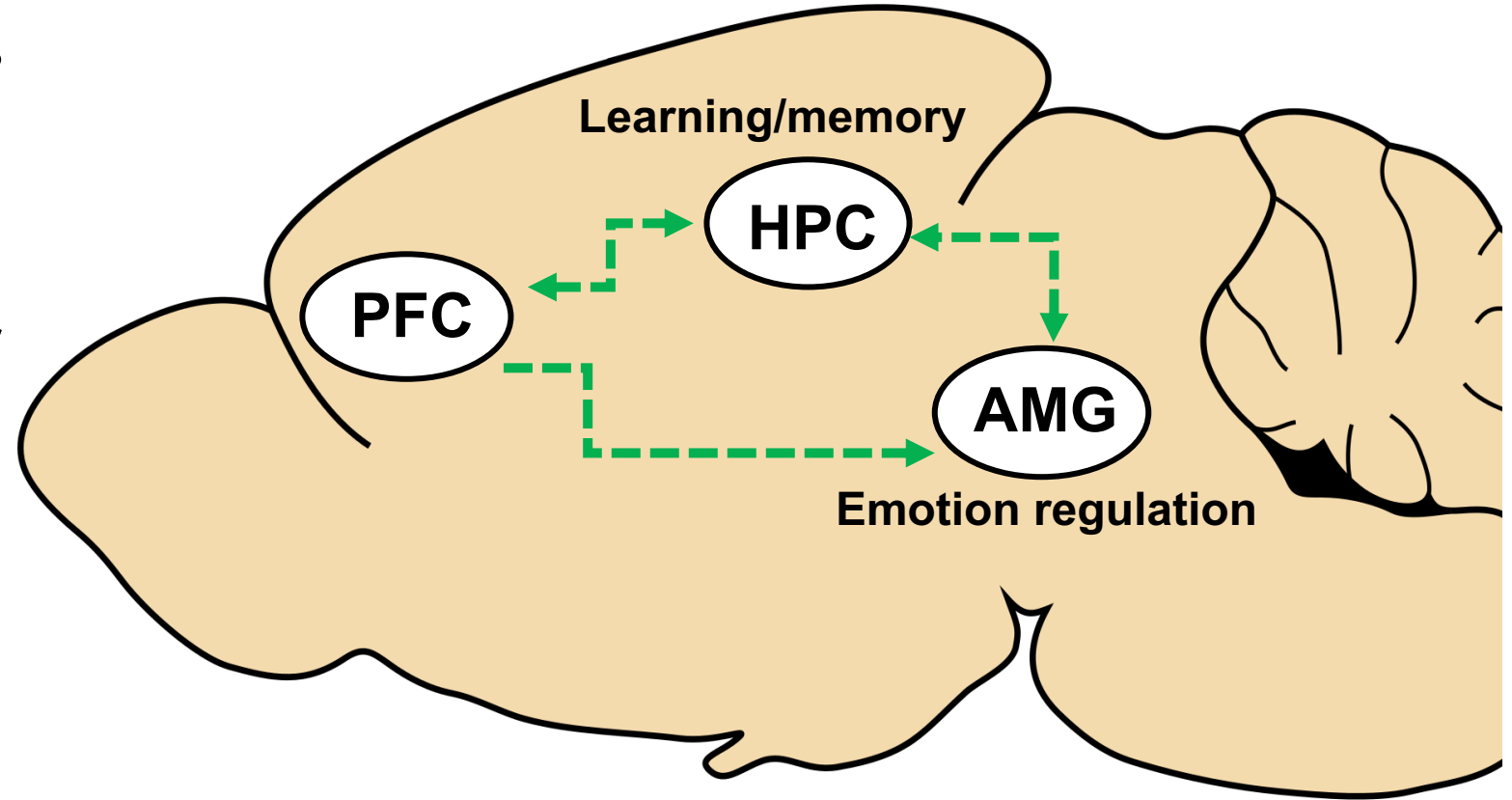
How does circadian disruption impact neural *function*?



Medial Prefrontal Cortex (mPFC)

Part of a circuit that modulates many other brain regions and behaviors:

- Complex cognitive behavior
- Decision making
- Emotional responses

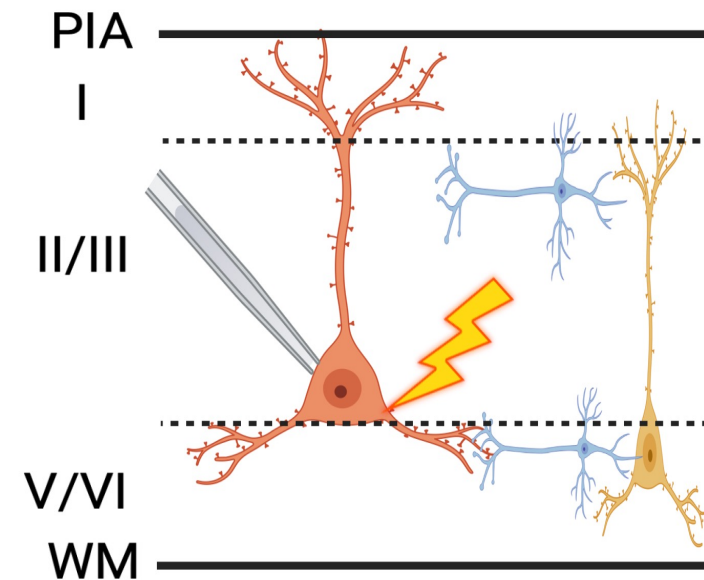
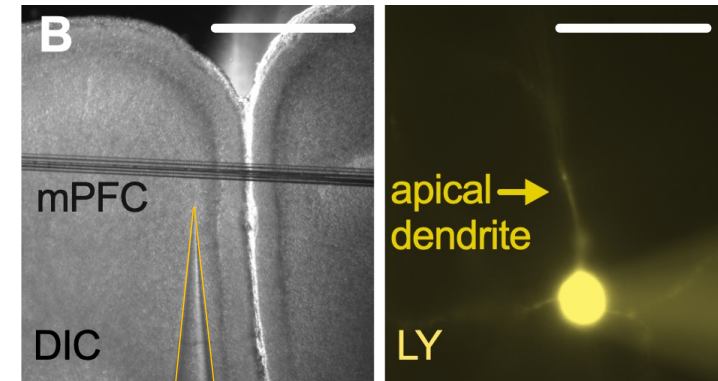
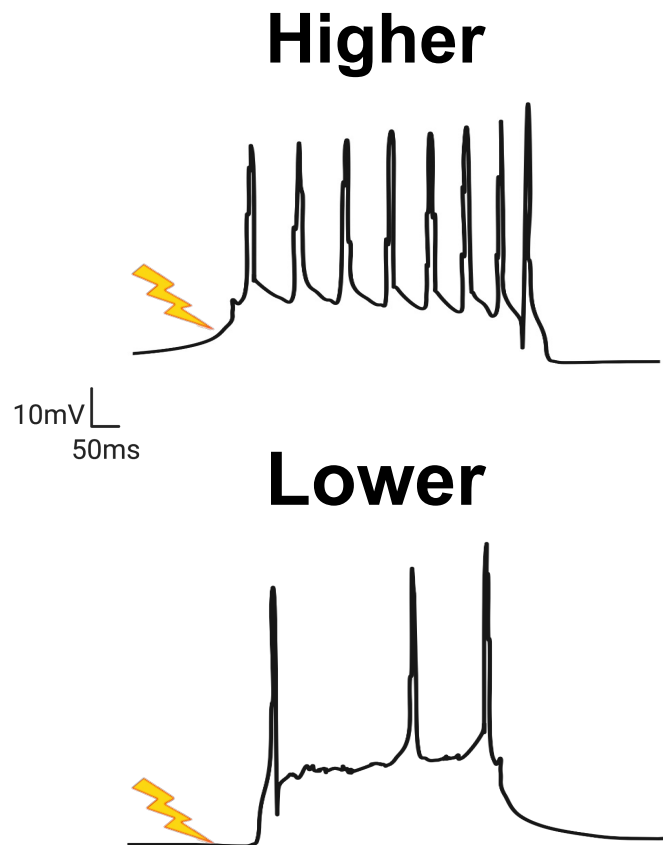


How does ECD impact information processing in the PFC?

PFC – Prefrontal cortex
HPC – Hippocampus
AMG – Amygdala

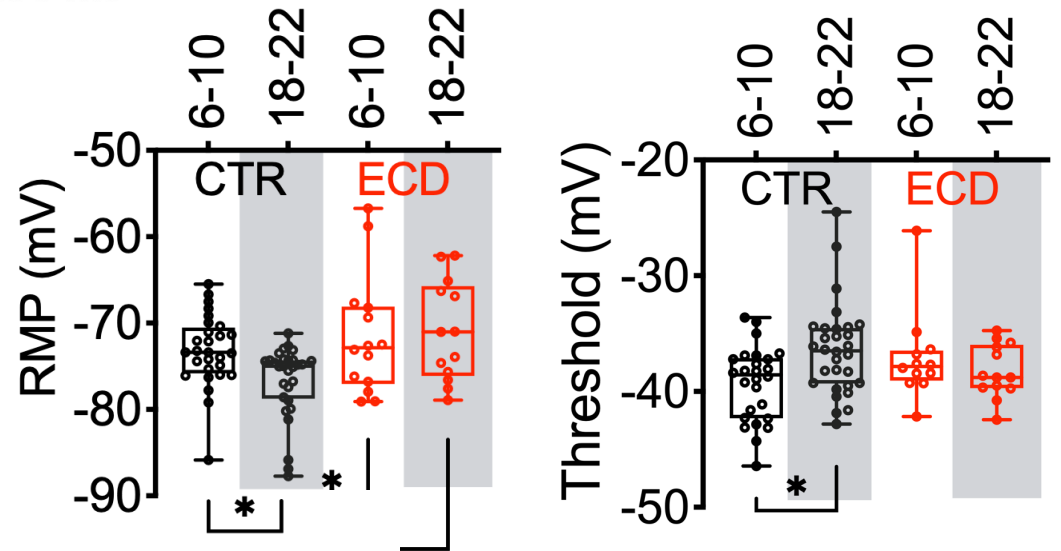
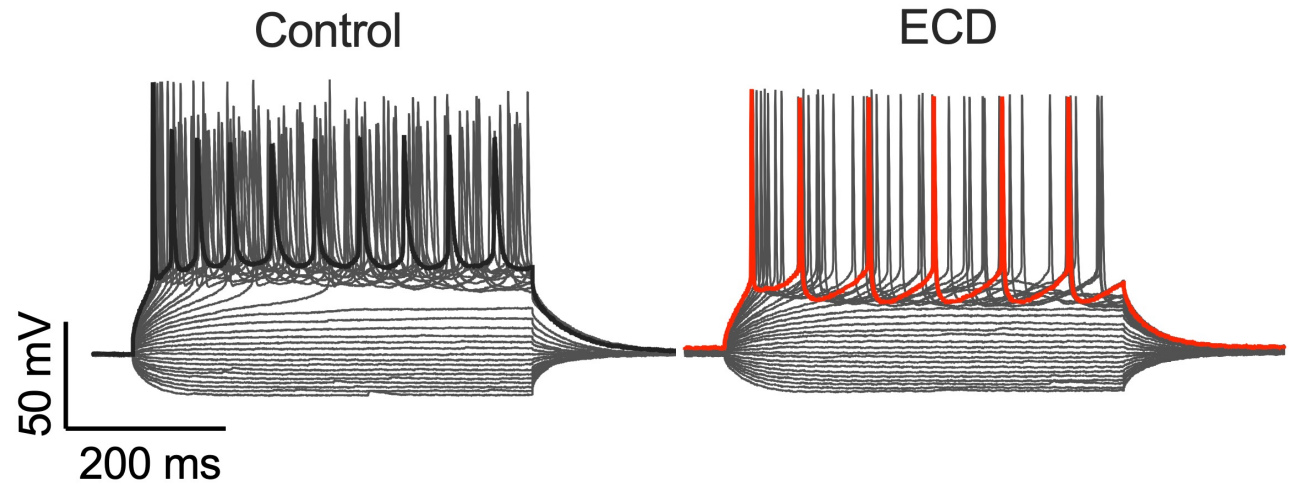
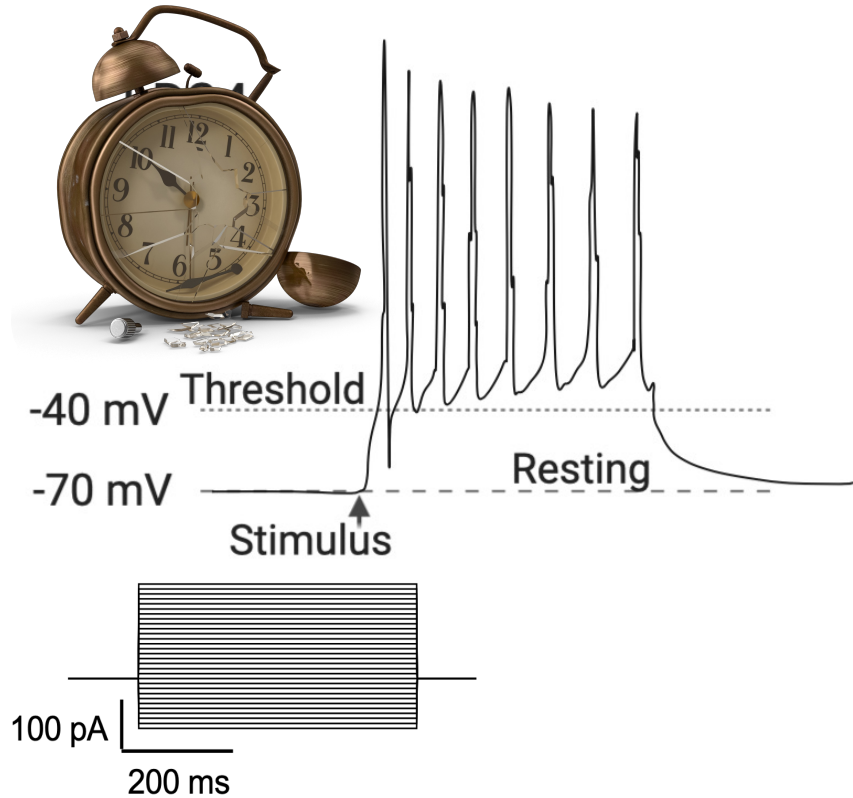
Information Throughput

For equal input, is the resulting output:



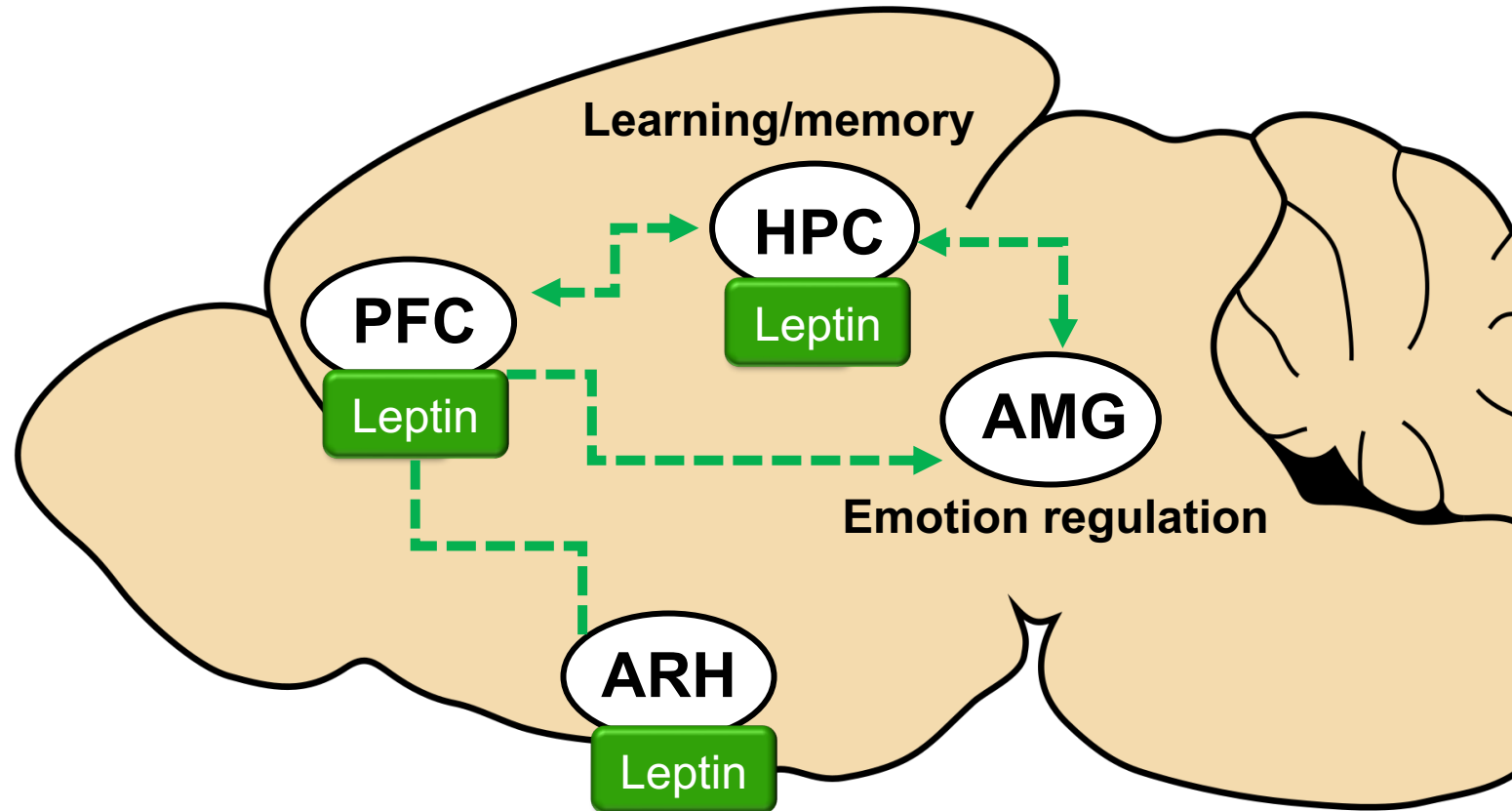
(Roberts & Karatsoreos; PNAS *Under review*)

ECD may impact information filtering in PFC neurons

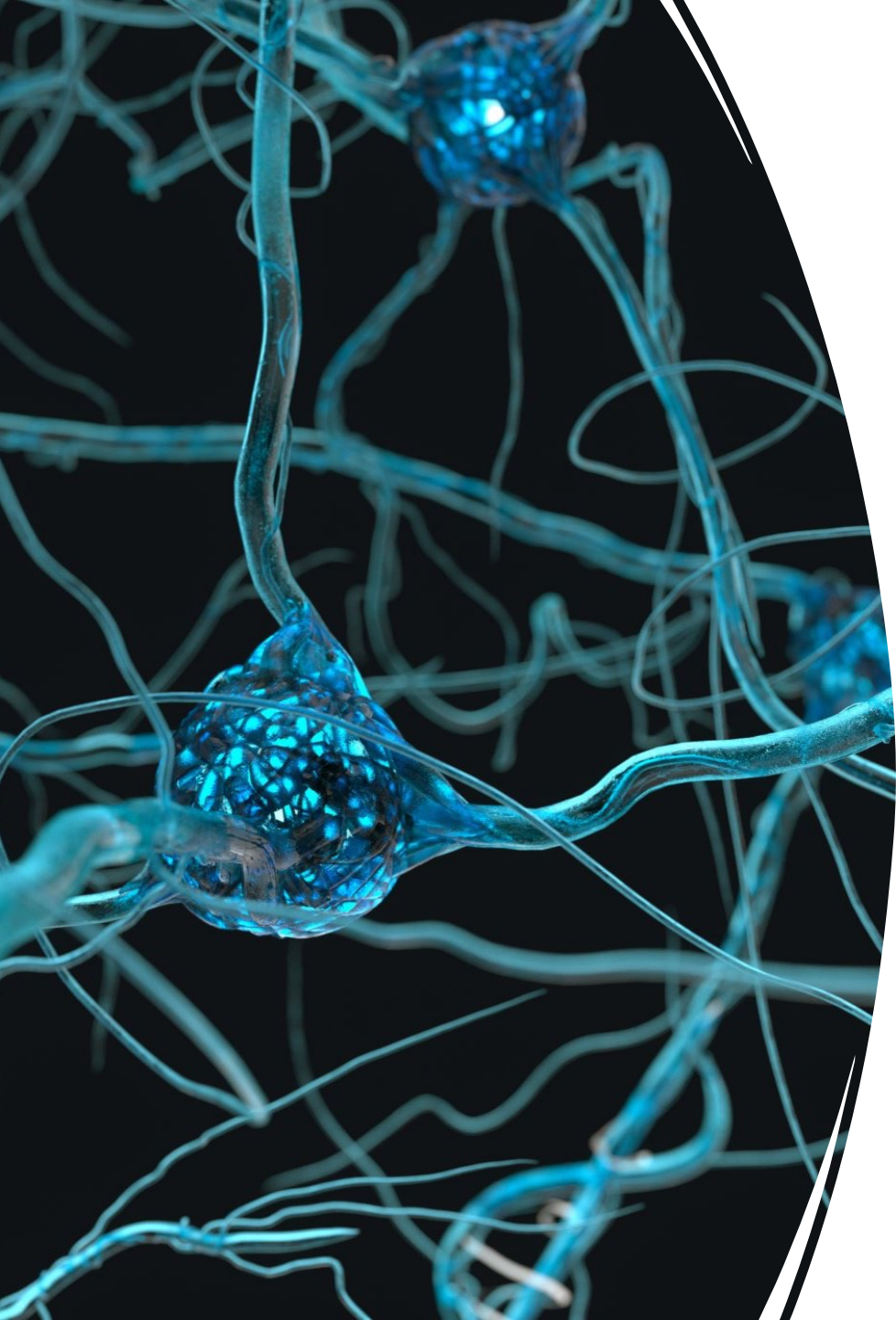


(Roberts & Karatsoreos; PNAS *Under review*)

Medial Prefrontal Cortex (mPFC)

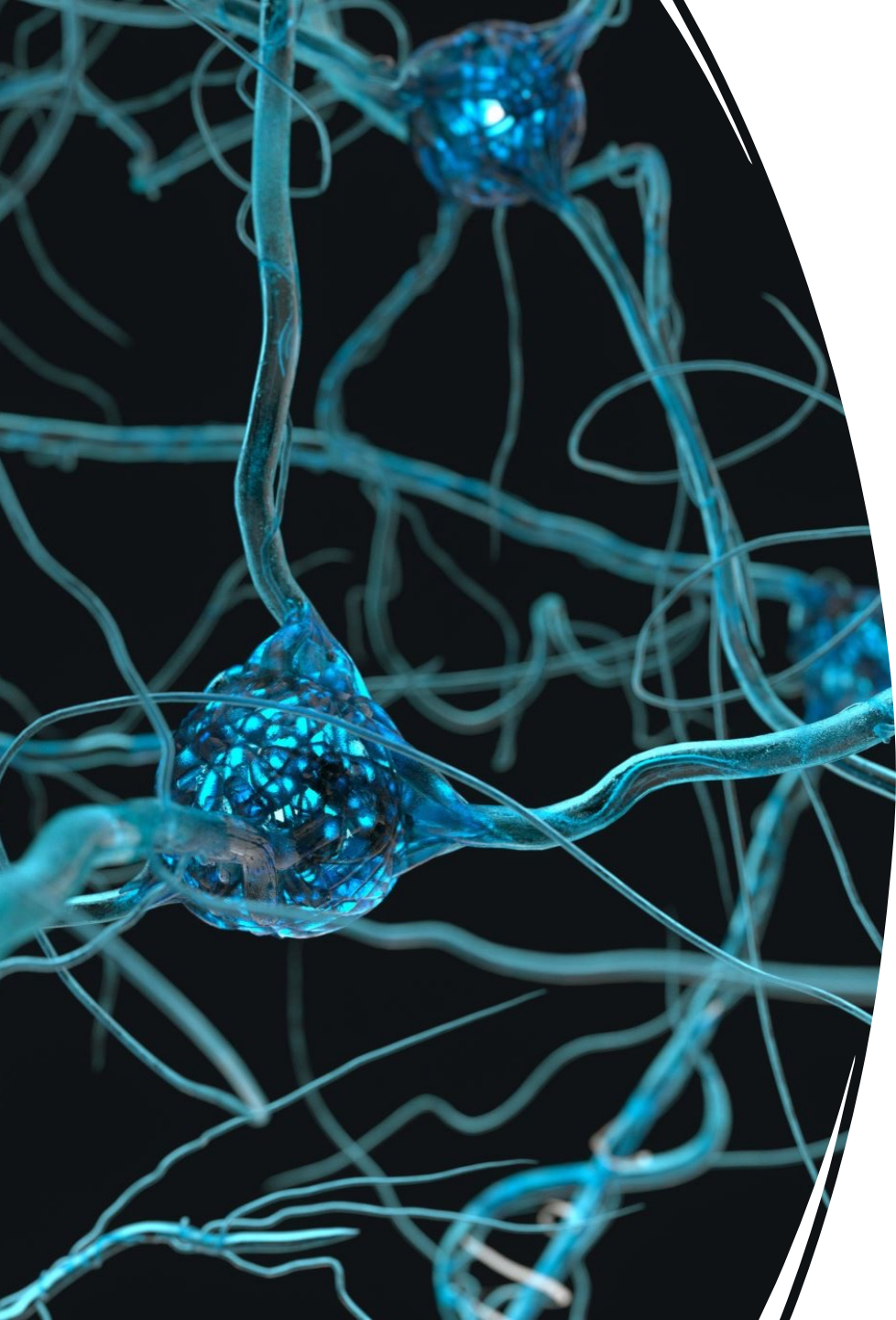


HPC – Hippocampus
AMG – Amygdala



Part II: Summary

- ECD disrupts rhythms in metabolic and cognitive function
- ECD alters information throughput in the PFC



Part III

- I. How does developmental overnutrition impact brain-body physiology?
- II. How do daily rhythms impact metabolic function?
- III. Where do we go from here?

Future Directions



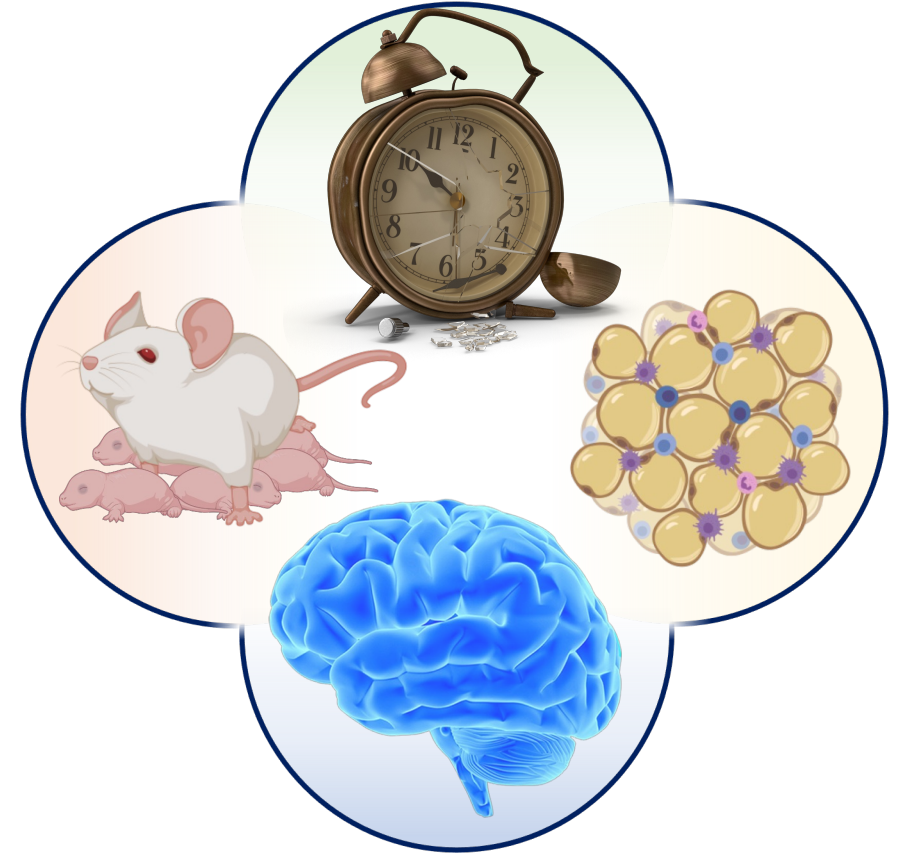
How does CPO impact daily rhythms in ARH-NPY neurons?



How does CPO impact leptin signaling in ARH-NPY neurons?



Does CPO alter rhythms in metabolic behavior?



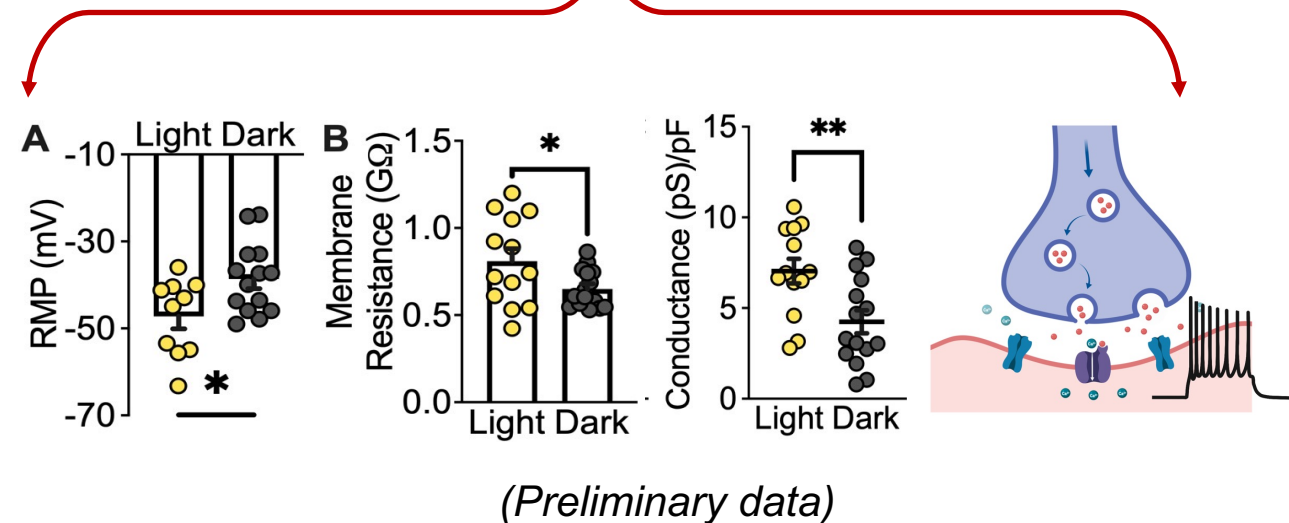
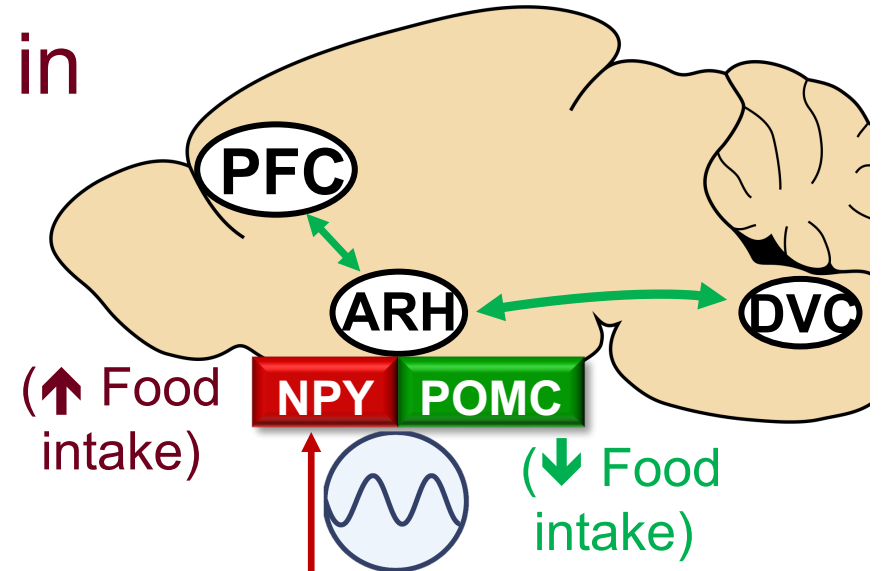
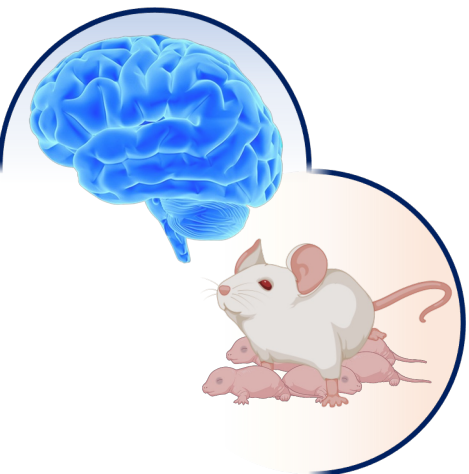
How does CPO impact daily rhythms in ARH-NPY neurons?

Basal physiological properties of ARH-NPY neurons

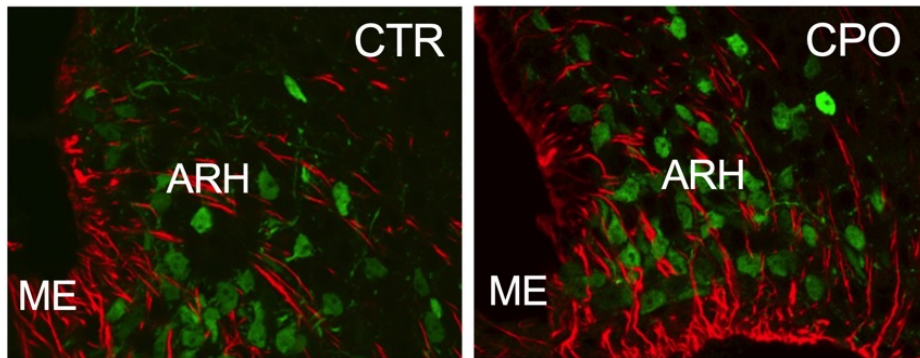
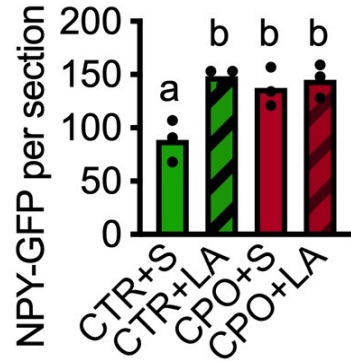
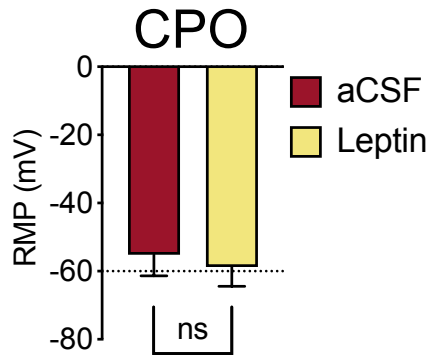
- Action potential dynamics
- Current-voltage relationship

Synaptic function in ARH-NPY neurons

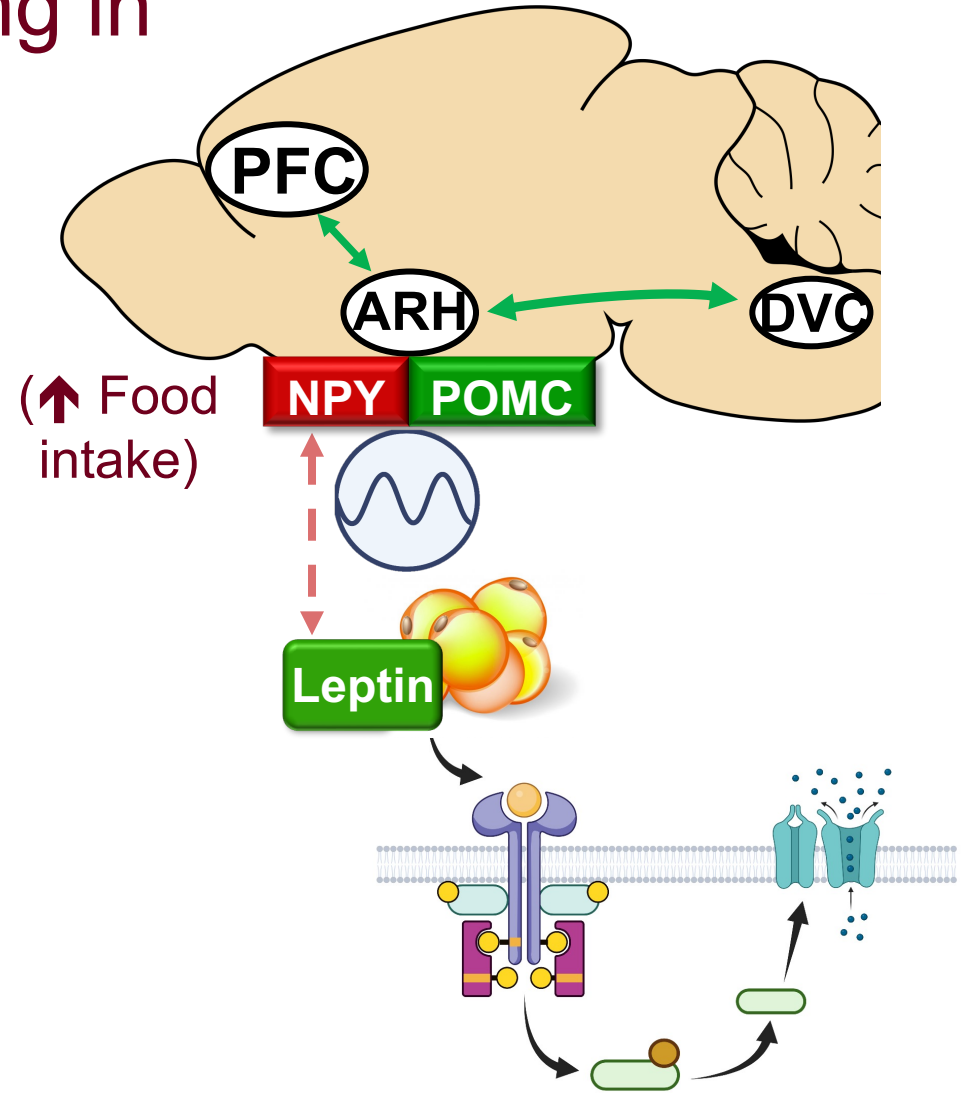
- GABA (inhibitory)
- Glutamate (excitatory)



How does CPO impact leptin signaling in ARH neurons?



(Preliminary data)

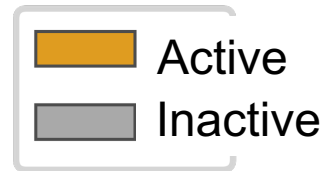
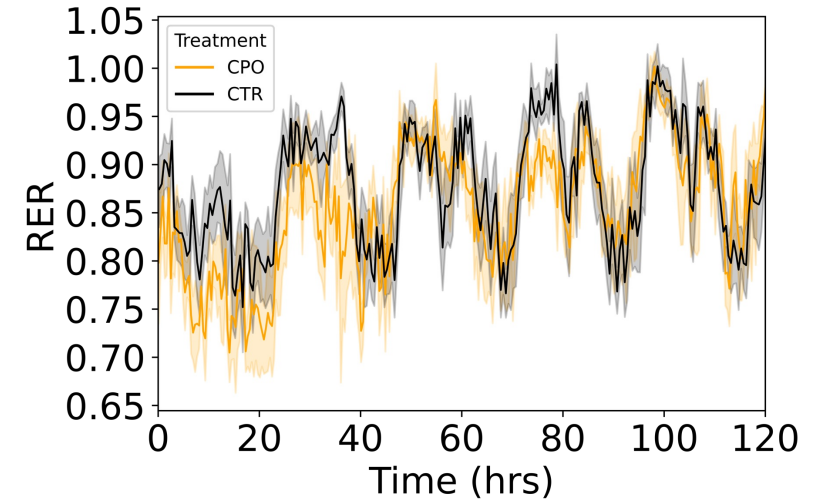
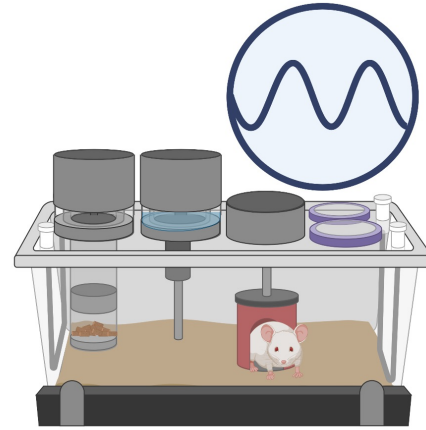


What is the *mechanism*?

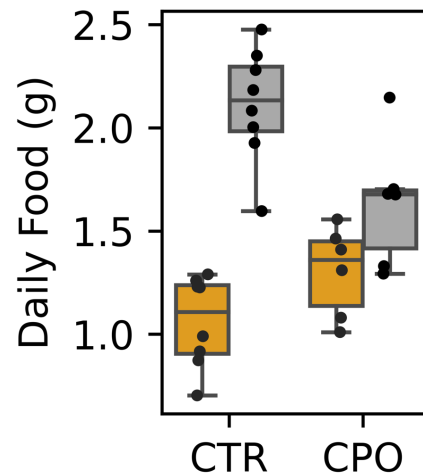
Does CPO alter rhythms in metabolic behavior?

Metabolic phenotyping by measuring changes in daily:

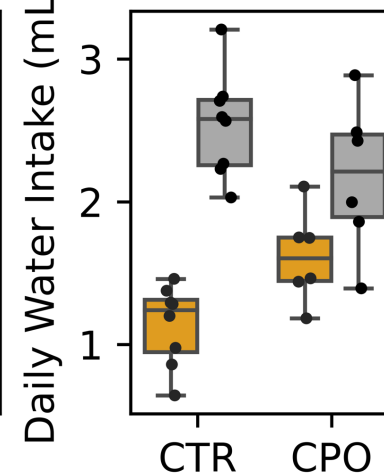
- Metabolic rate
- Food intake
- Water intake
- Locomotor activity



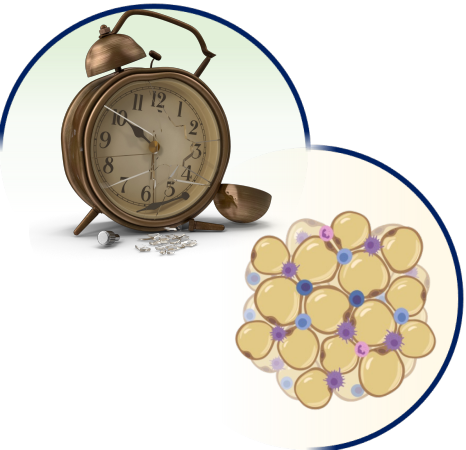
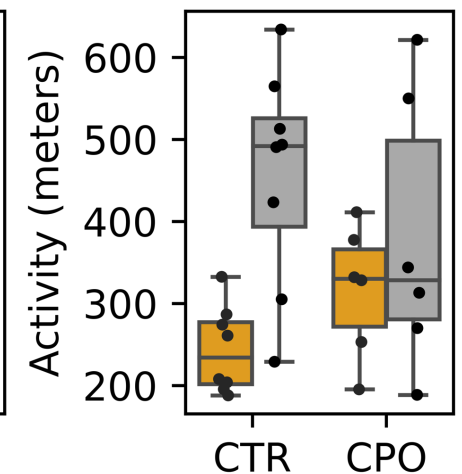
CT p= 0.0001
Group p=0.063
CT*Group p= 0.0153



CT p= 0.0
Group p= 0.6742
CT*Group p= 0.0203



CT p= 0.0008
Group p= 0.9779
CT*Group p= 0.0499

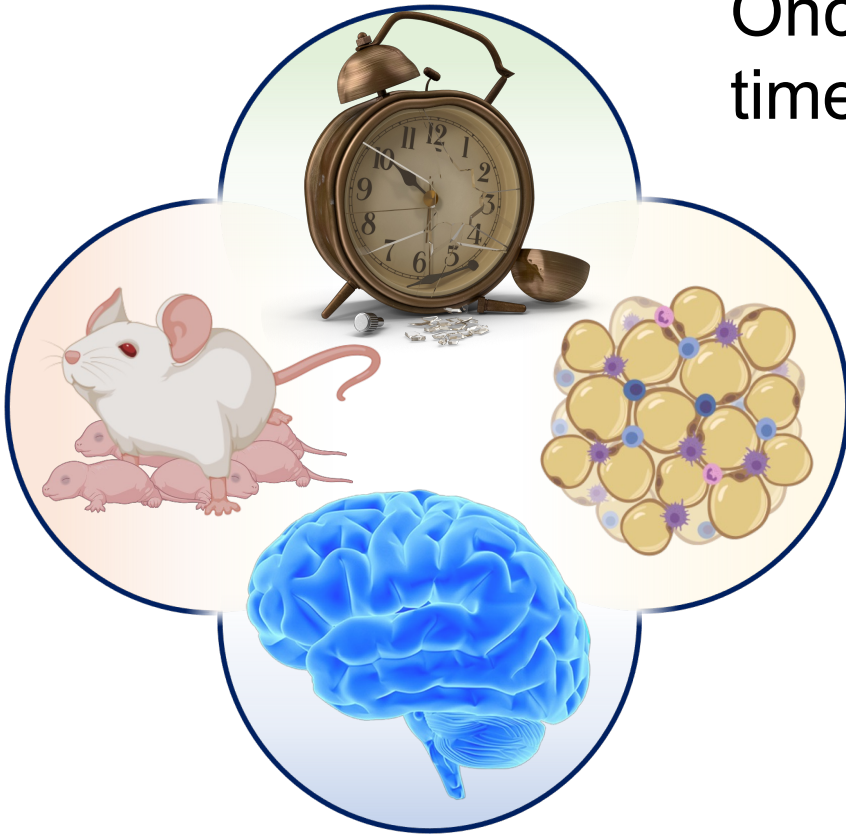


(Preliminary data)

Part III: Summary

Once we understand the underlying physiology of *how* time of day and overnutrition interact, we can *then*:

- Identify optimal meal timing
- Potential therapeutic targets
- Personalize timing of medications



Thank you

University of
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UNIVERSITY



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Ilia Karatsoreos Lab

Jennifer Wang
Brennan Falcy
Gregory Pearson
Said Akli
Giancarlo Denaroso
Nathan Santos

Suzy Appleyard Lab

Ranji Cui
Stephen Page
Huan Zhao
Mingyan Zhu

Sue Ritter Lab

Than Huston
Thu Dinh
Michael Wiater

Paul Kievit Lab

Camdin Bennett
Melissa Kirigiti
Sarah Lindsley
Julie Carroll

Trainees

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Questions?