Circadian desynchronization disrupts information throughput in the prefrontal cortex

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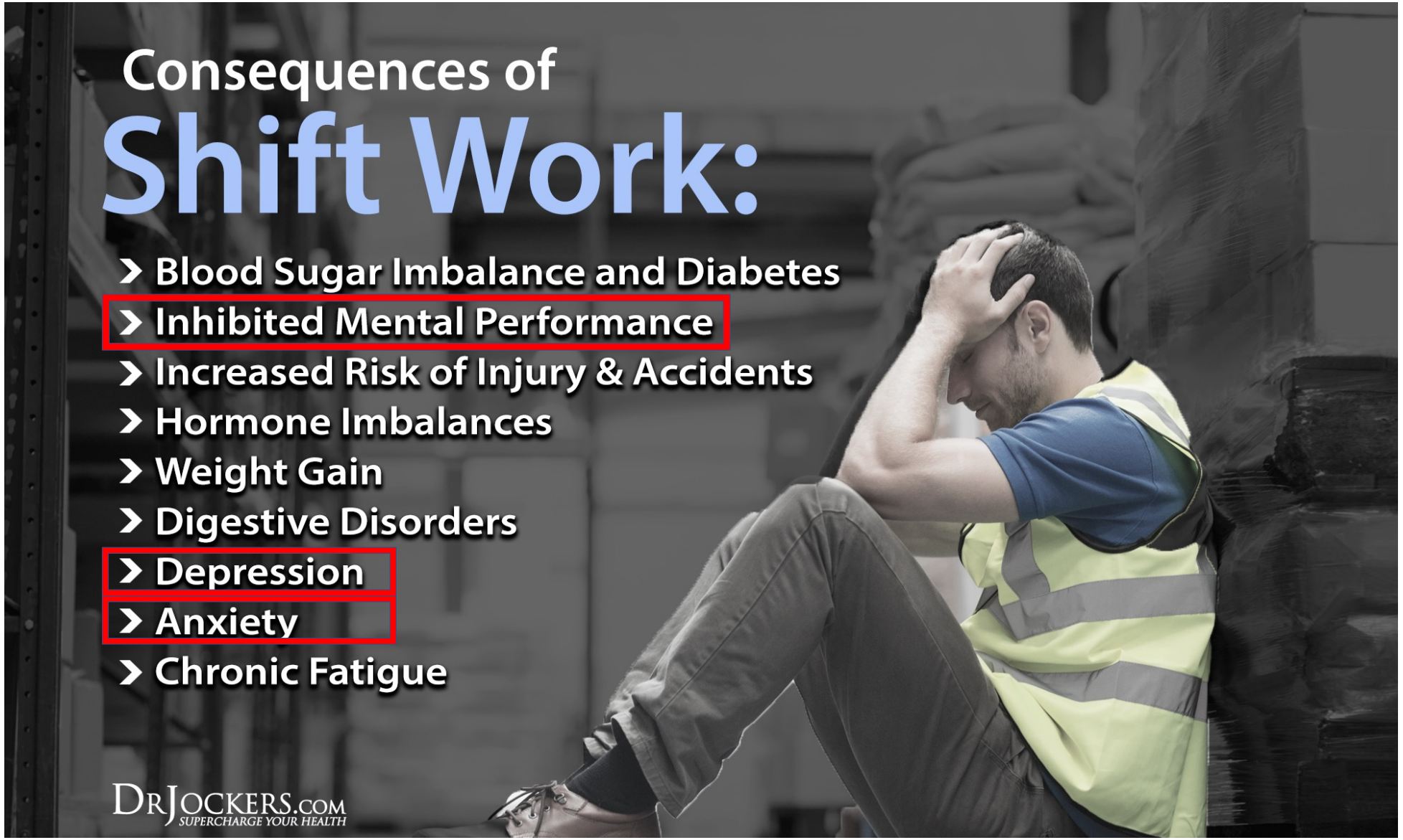
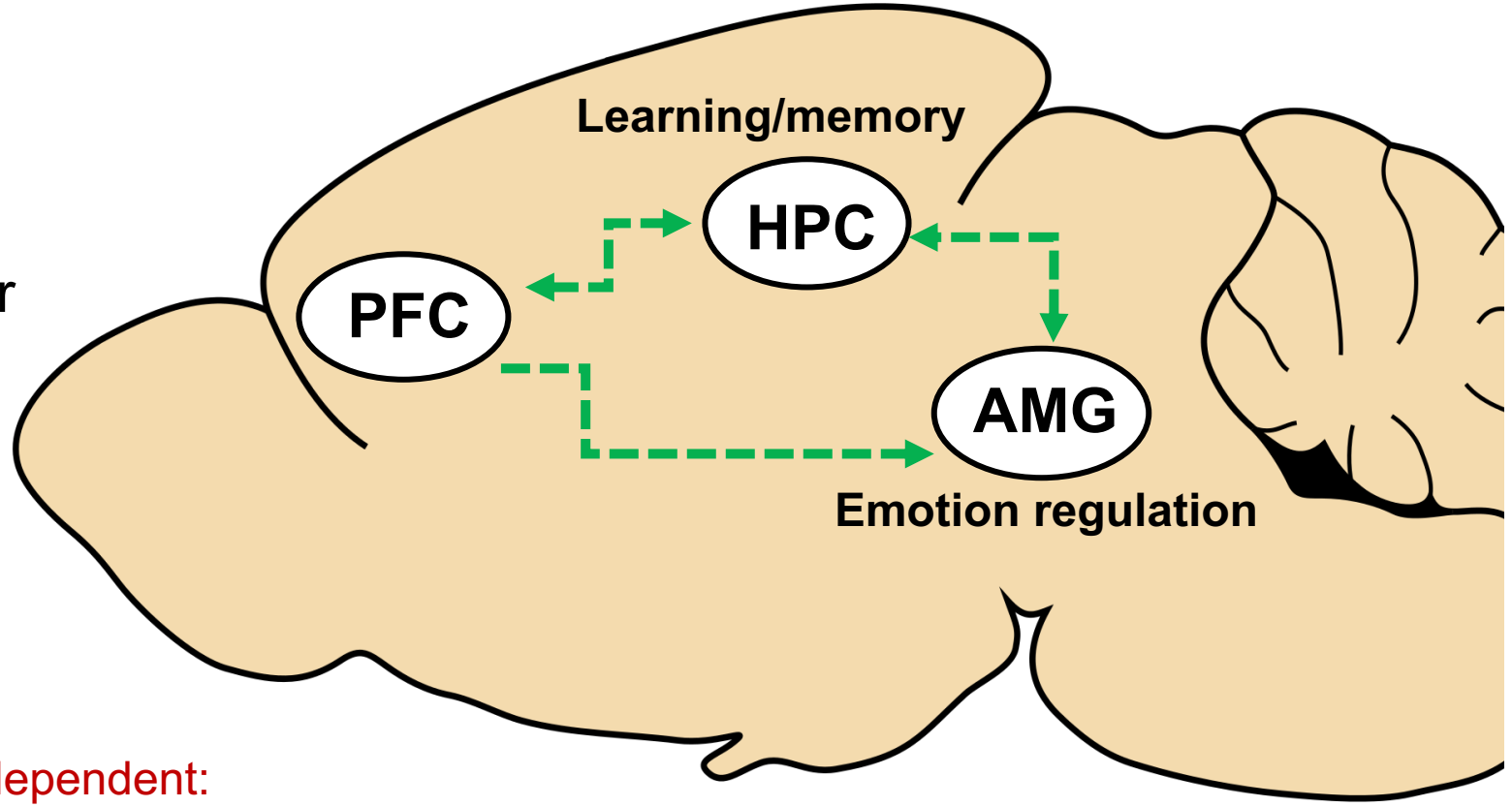
Sleep disruption, deprivation, and desynchronization leads to poor health outcomes



Medial Prefrontal Cortex (mPFC)

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

- Complex cognitive behavior
- Decision making
- Emotional responses



All these processes are time-of-day dependent:

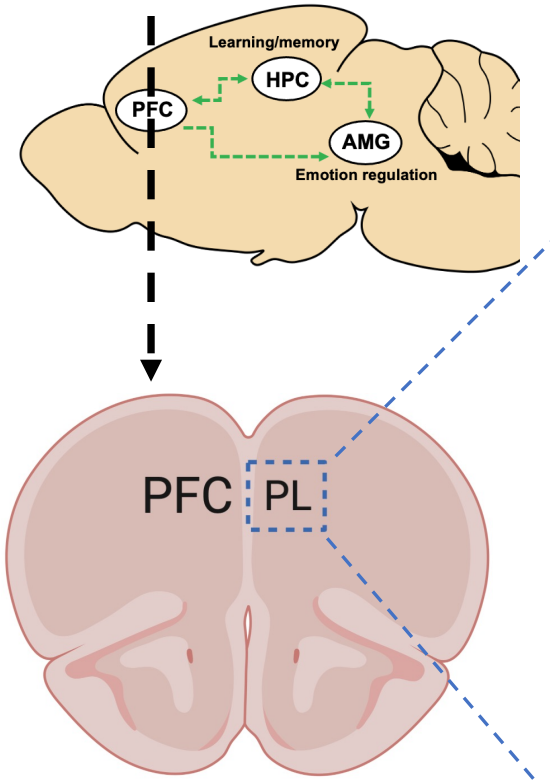
- Molecular
- Behavioral
- Neurophysiological?

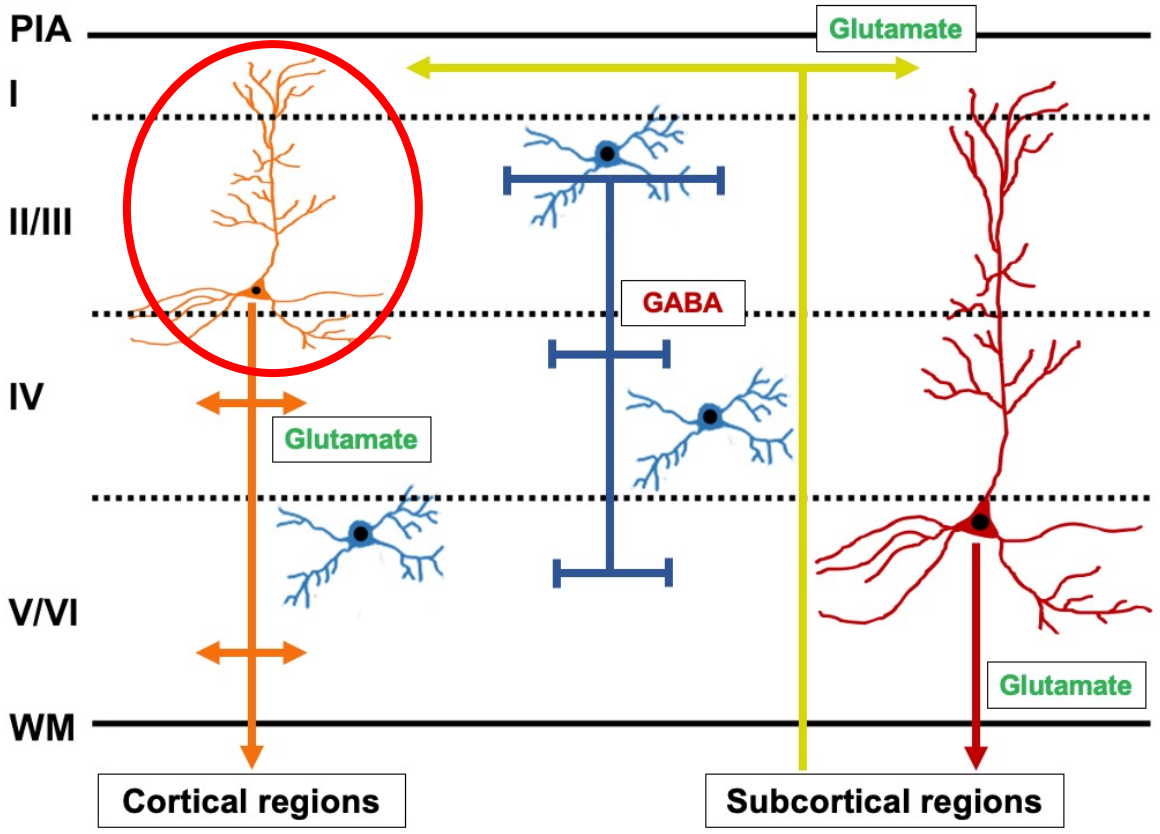
PFC – Prefrontal cortex
HPC – Hippocampus
AMG – Amygdala

Medial Prefrontal Cortex (mPFC)

Organized into distinct layers that include:

- Inhibitory (GABAergic) interneurons
- Excitatory (glutamatergic) *pyramidal* neurons





How the clock impacts synaptic inputs, cell endogenous properties, and information output from the PFC is *unknown*.

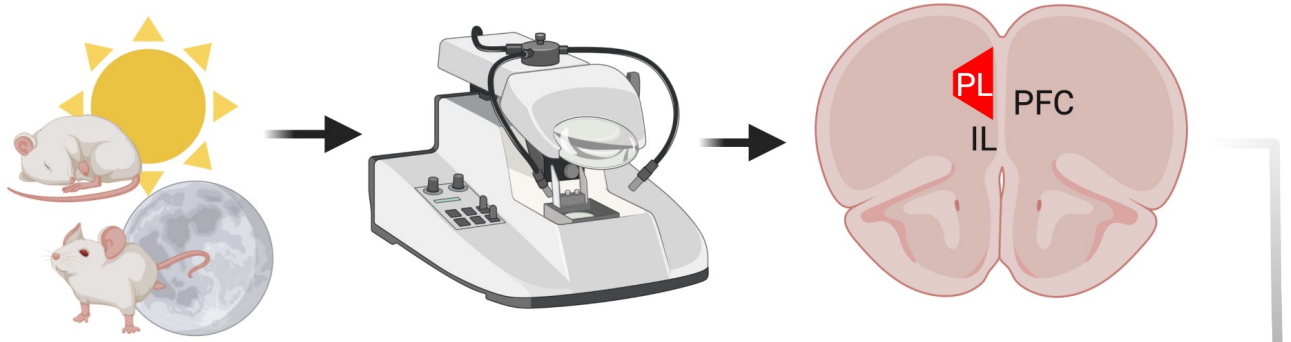
Two questions of focus:

1. How does time-of-day impact the fundamental *function* of PFC neurons?

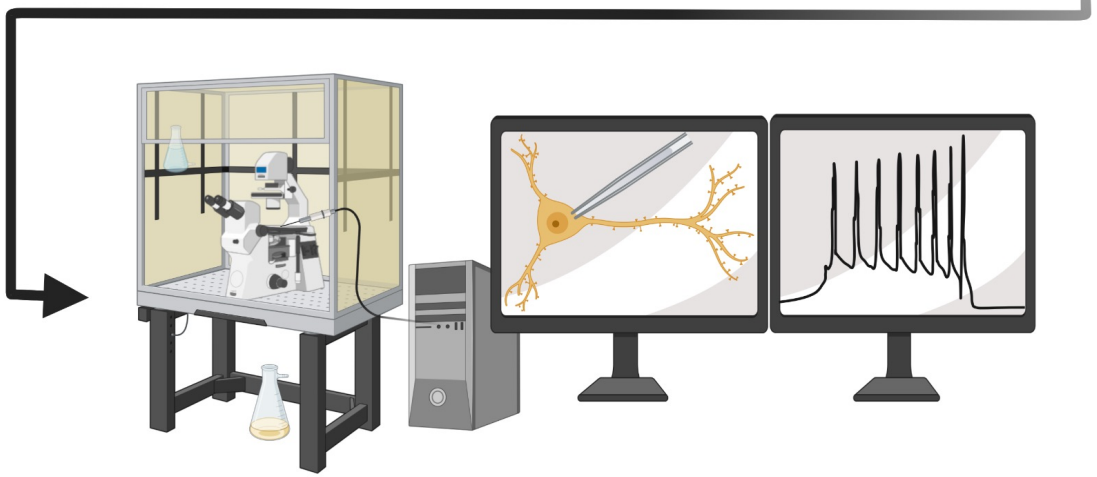
2. How does circadian disruption impact PFC neural *function*?

Electrophysiological Approach

- Collect *ex vivo* coronal brain slices at multiple Zeitgeber (ZT) times



- Measure changes in current and voltage of PFC neurons

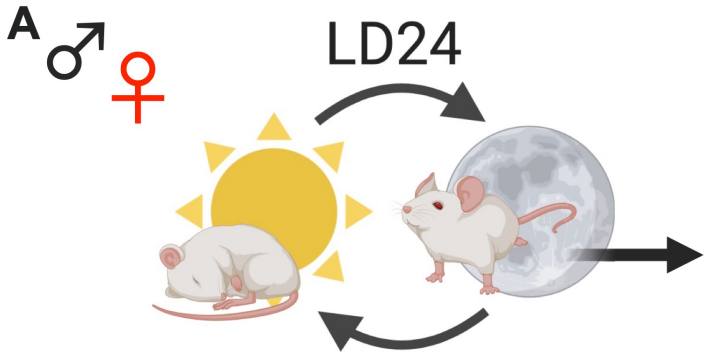


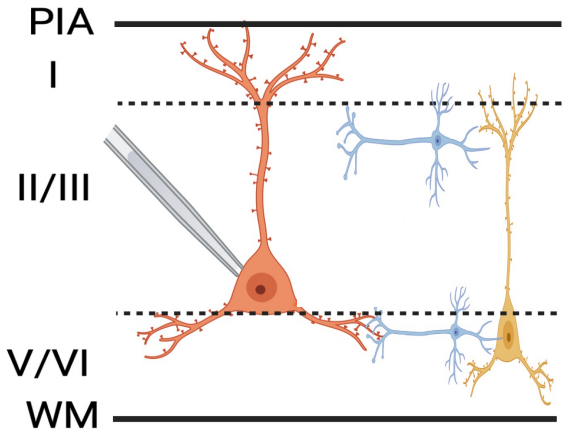
Chrobok L. et al., *J Physiol.* 2022
Fusilier AR. et al., *Neurobiol Dis.* 2021
Paul JR. et al., *Eur J Neurosci.* 2020
Chaudhury D. et al., *J Biol Rhythms.* 2005

Time-of-day impact on basal properties of mPFC pyramidal neurons

Design:

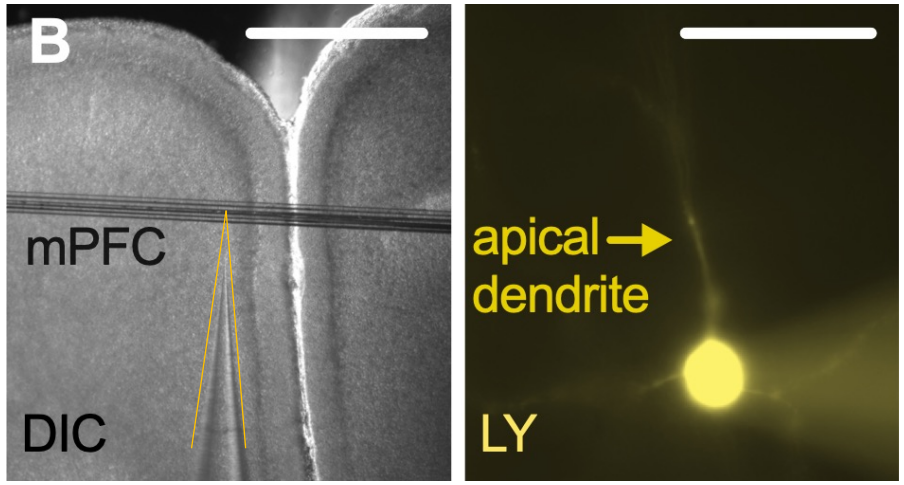
- Male and female mice
- Four 4h ZT bins





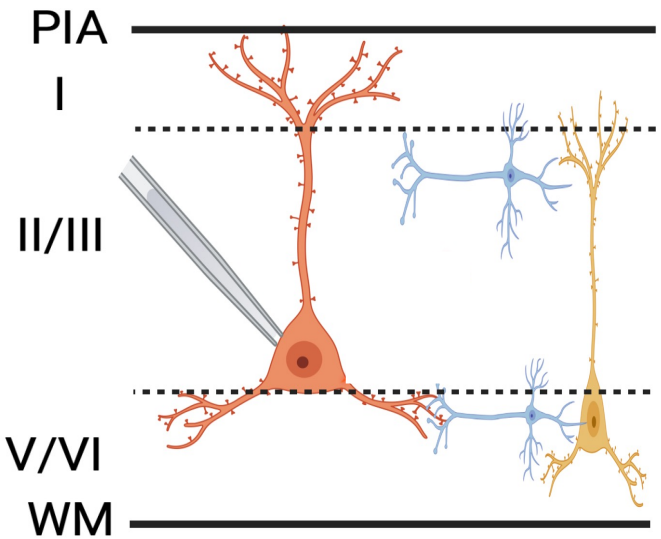
Measure membrane:

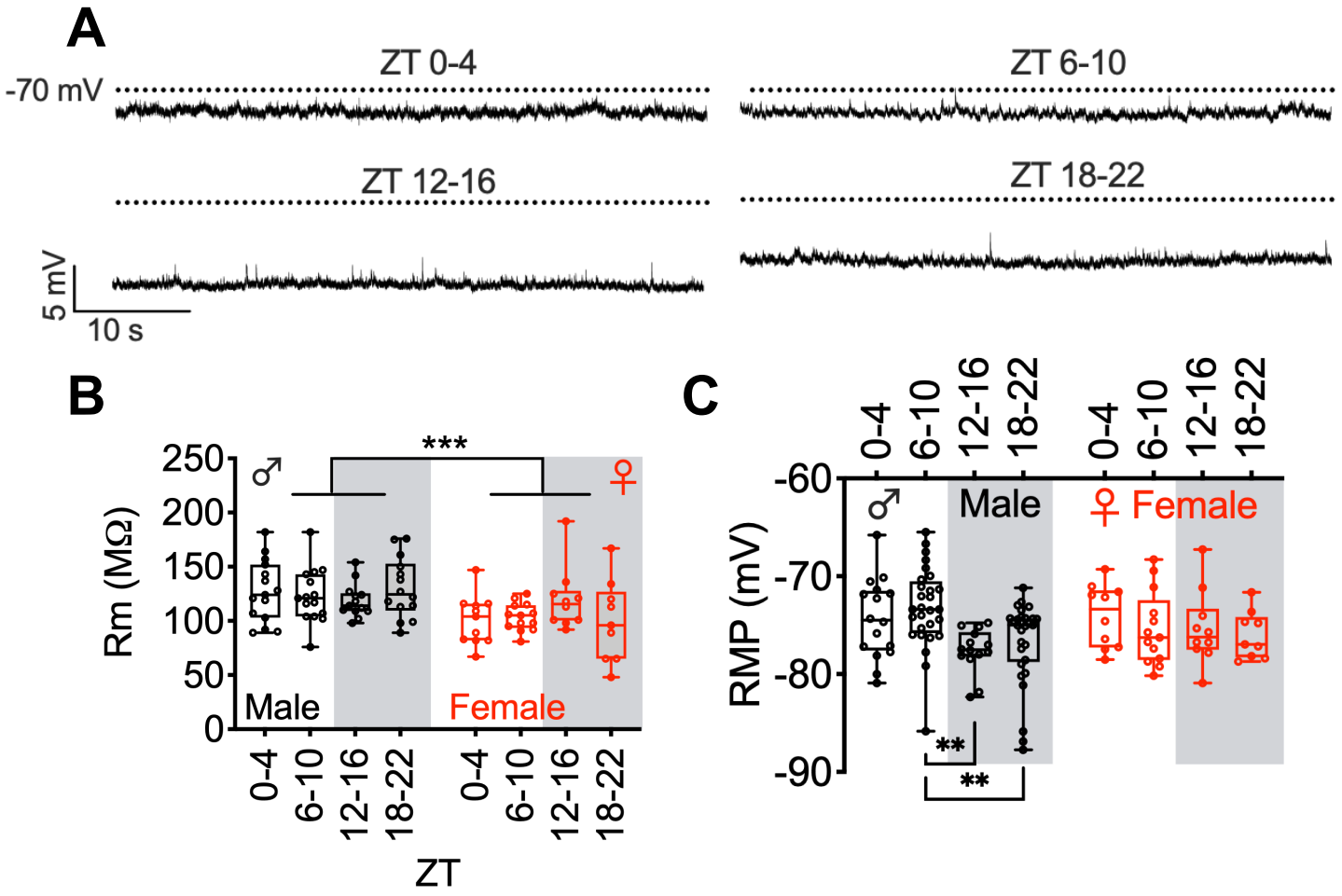
- Resistance
- Capacitance
- Resting potential



Time-of-day impact on basal properties of mPFC pyramidal neurons

- In males, neurons are more hyperpolarized (inhibited) during dark (active) period



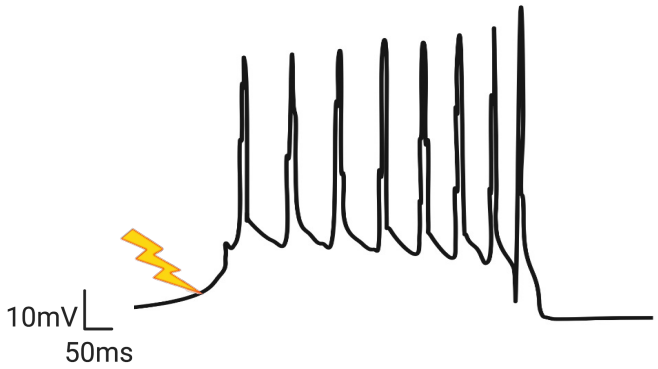


(*Unpublished*)

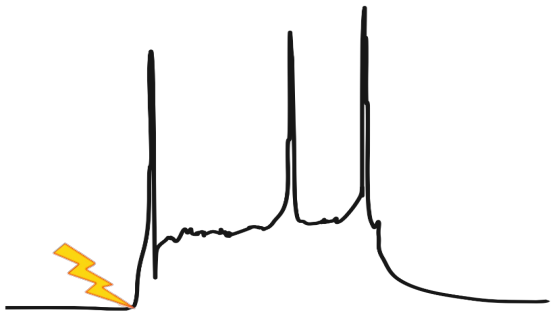
Information Throughput

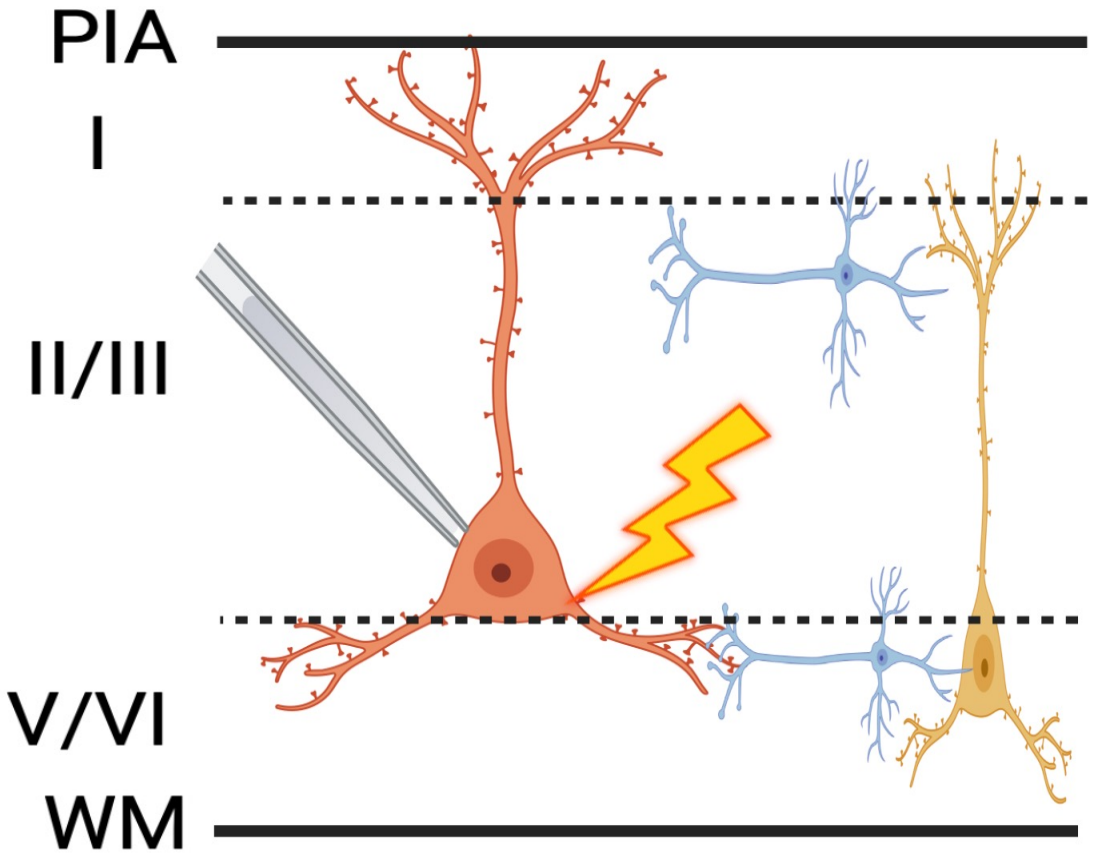
For equal input, is the resulting output:

Higher



Lower

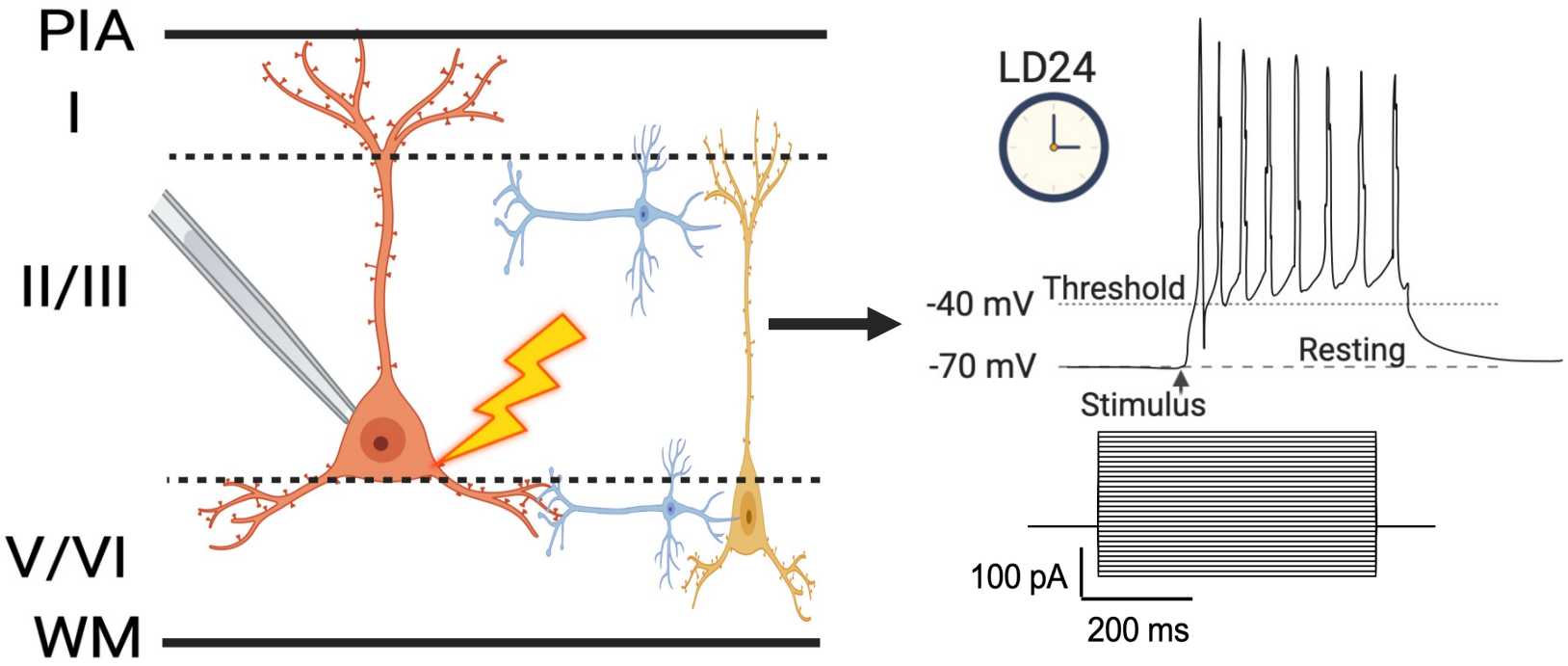




Time-of-day differences in action potential firing

Inject current as a stimulus and measure:

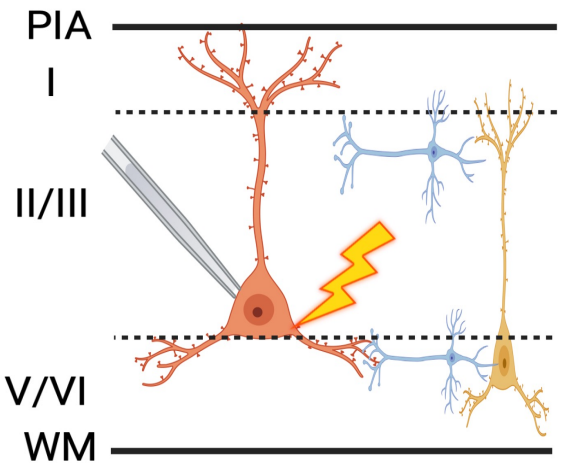
- Membrane potential
- Action potential threshold
- Firing frequency

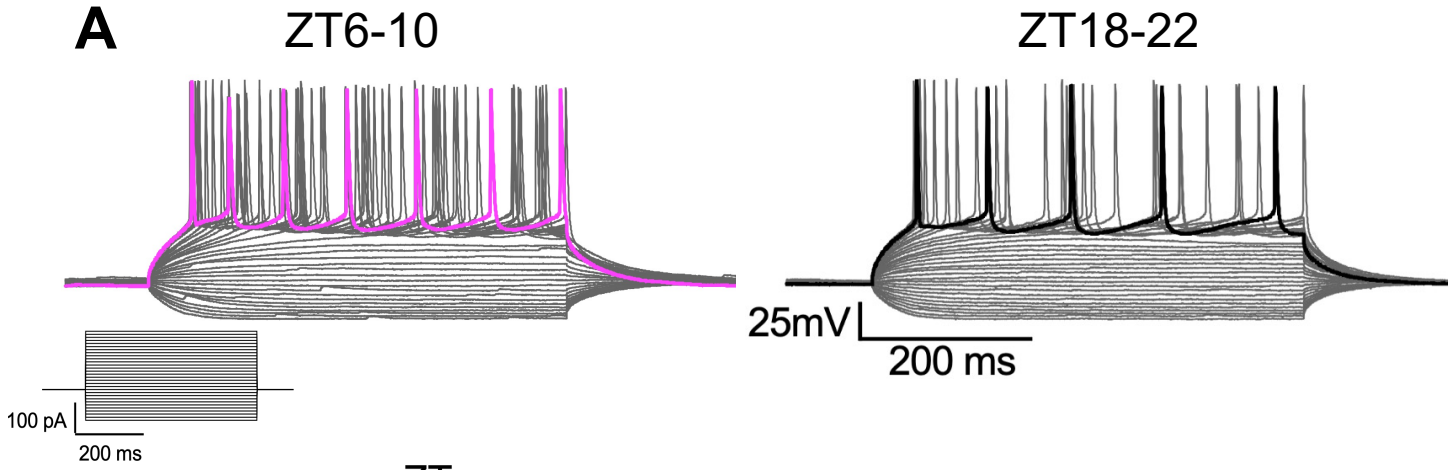


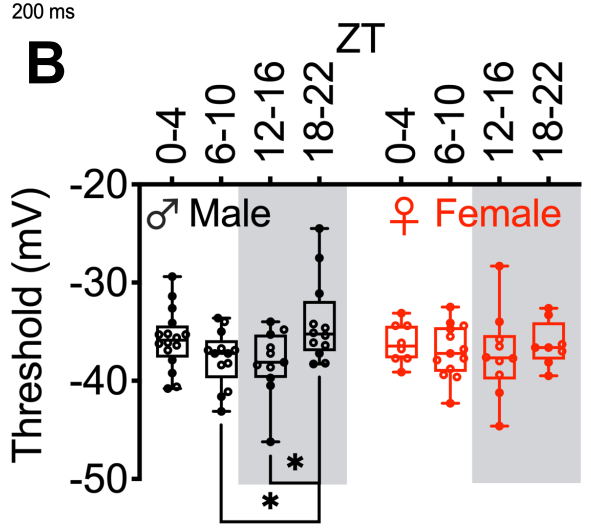
Time-of-day differences in action potential firing

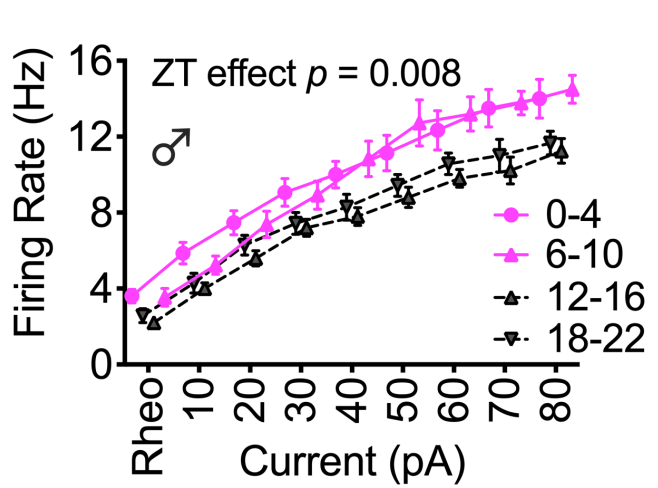
In males:

- Higher threshold for information throughput during dark (active) period
- Decreased firing frequency after threshold is met









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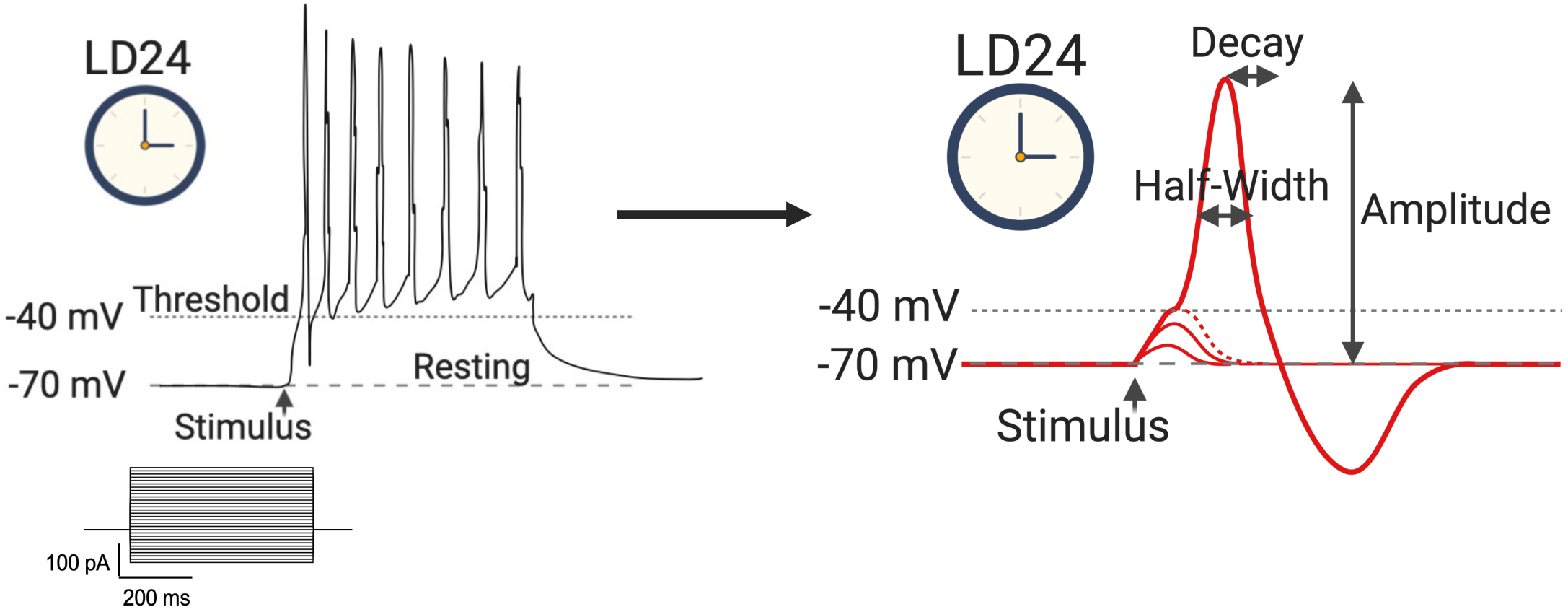
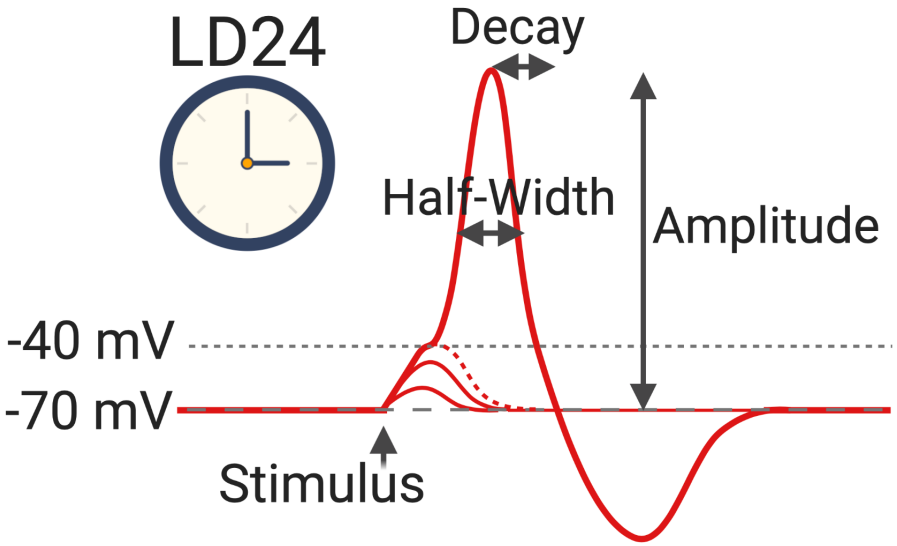
Time-of-day differences in action potential dynamics

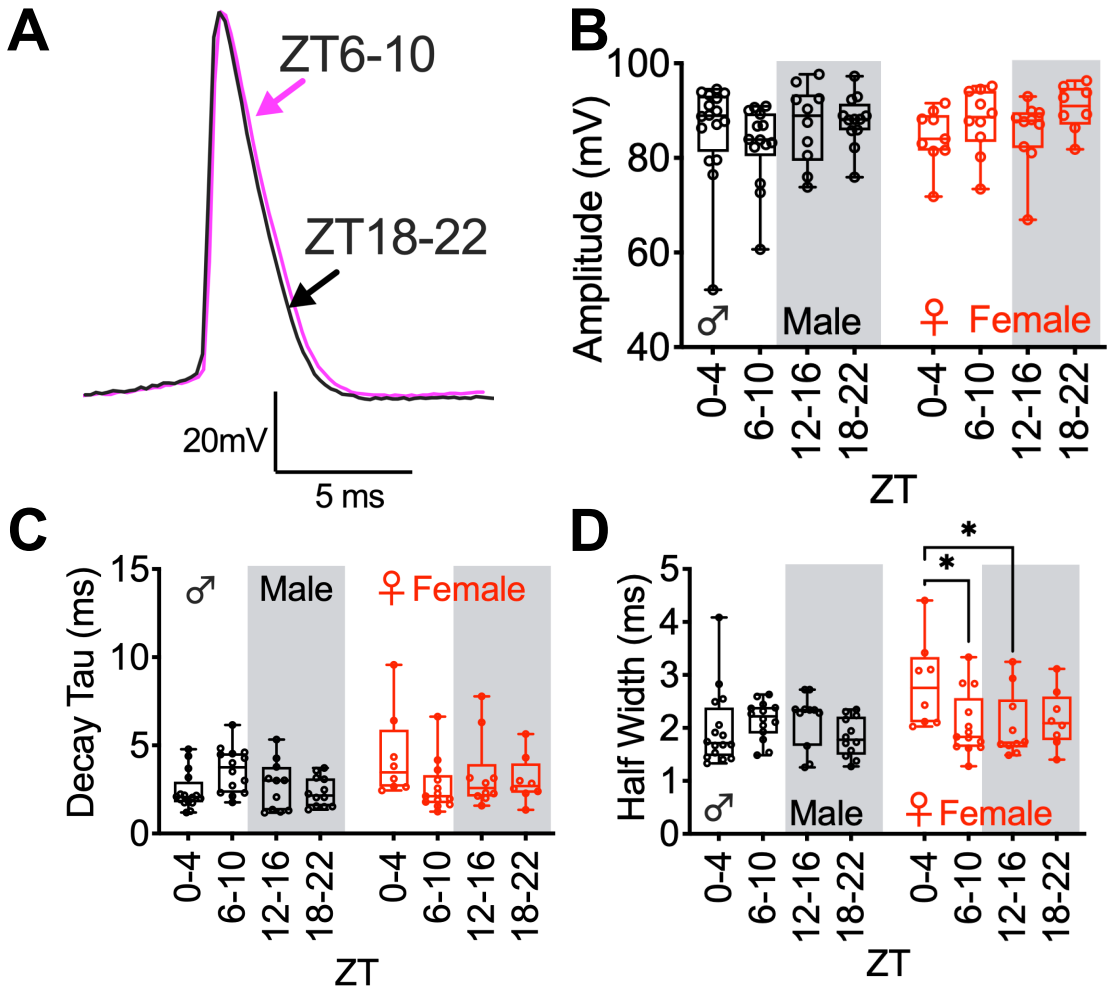
Insight into cell endogenous traits such as ion channel function



Time-of-day differences in action potential dynamics

Majority of action potential components are not time-of-day dependent





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Two questions of focus:

1. How does time-of-day impact the fundamental *function* of PFC neurons?

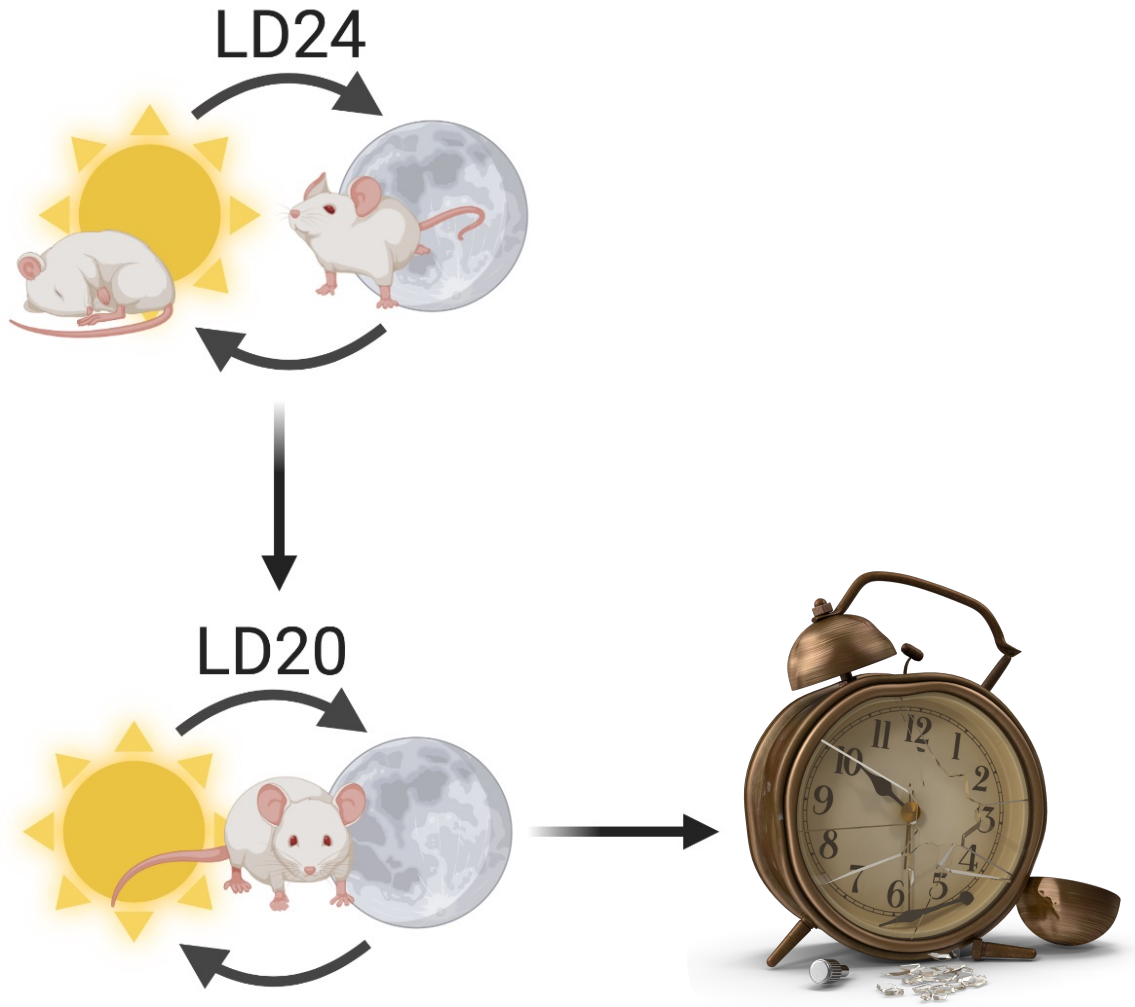
2. How does circadian disruption impact PFC neural *function*?

Environmental Circadian Desynchronization (ECD)

Control: Standard 12:12h light/dark (LD) cycle

ECD: Disruptive 10:10h LD cycle

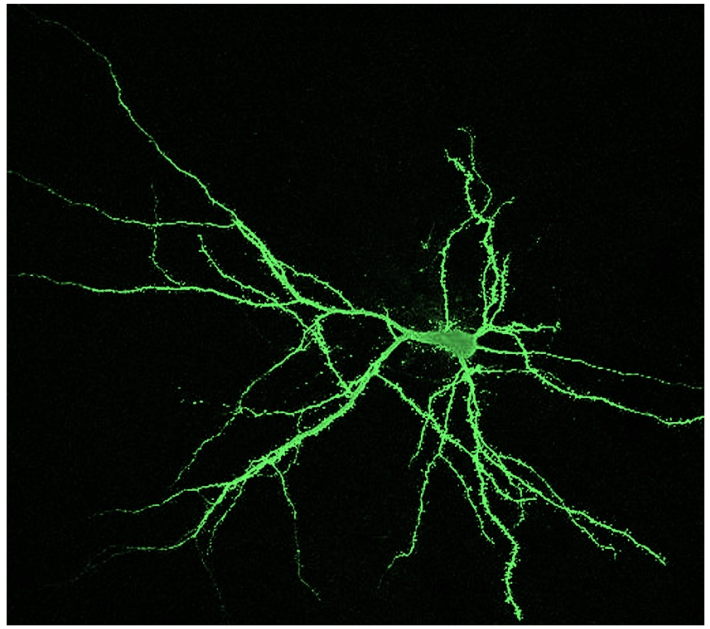
- Desynchronizes rhythms from normal 24h clock

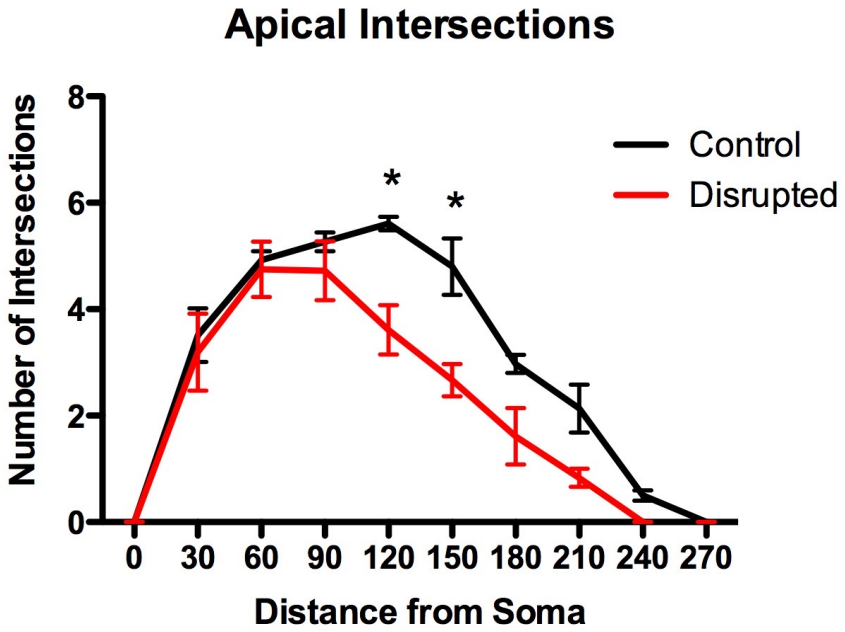


ECD changes PFC function and structure

Previously demonstrated effects of ECD:

- Mice display a constantly changing period and unstable entrainment
- Increased cognitive rigidity and increased errors
- Altered morphology of mPFC pyramidal neurons

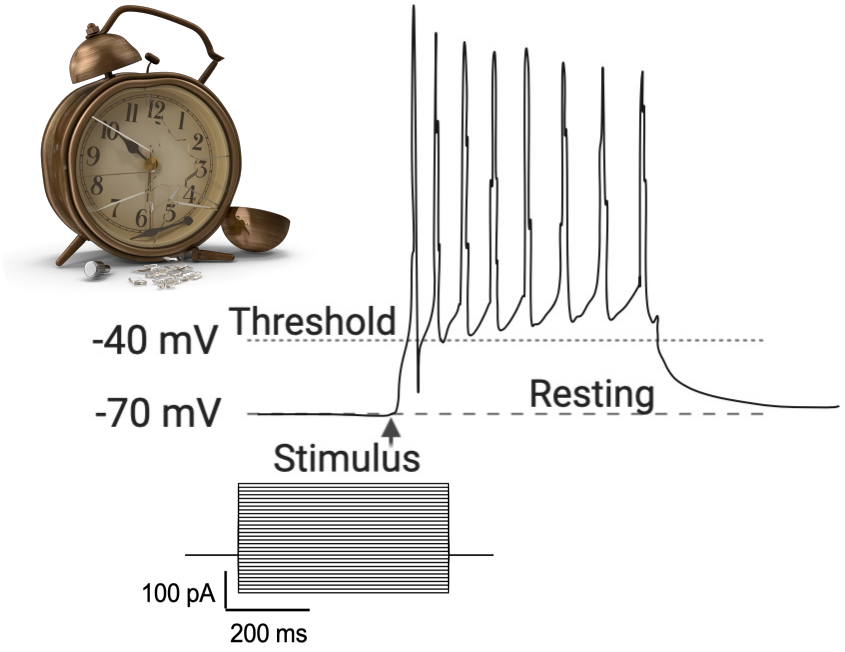


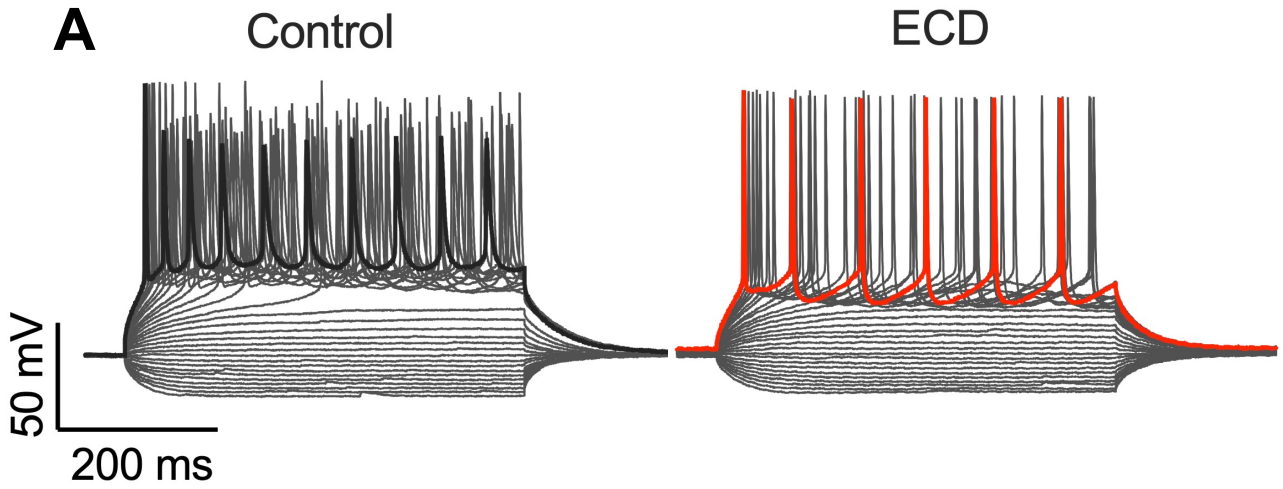


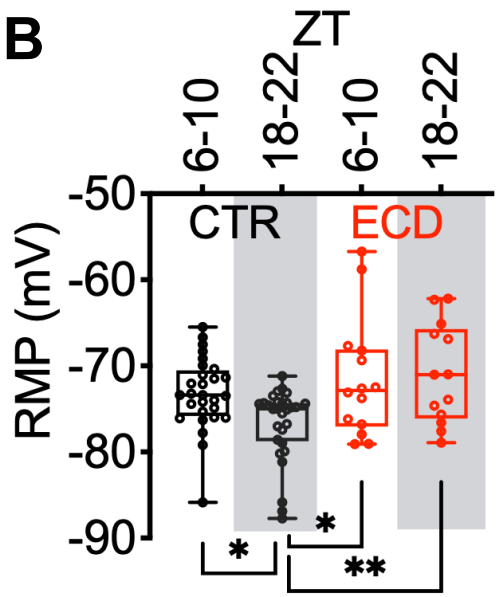
Karatsoreos, IN., et al. *PNAS* 2011

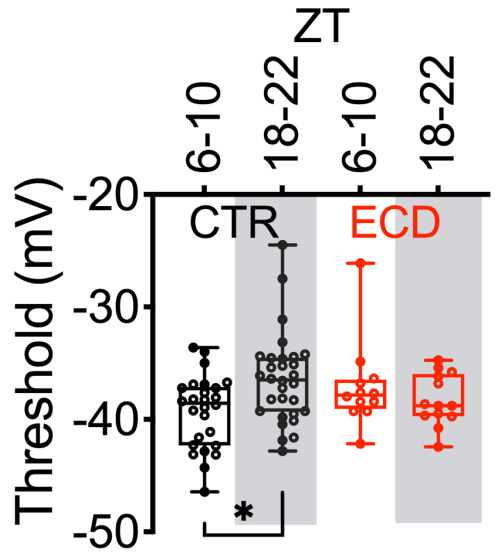
ECD may impact information filtering in PFC neurons

- ECD disrupts time-of-day changes in:
  - Resting membrane potential
  - Firing threshold









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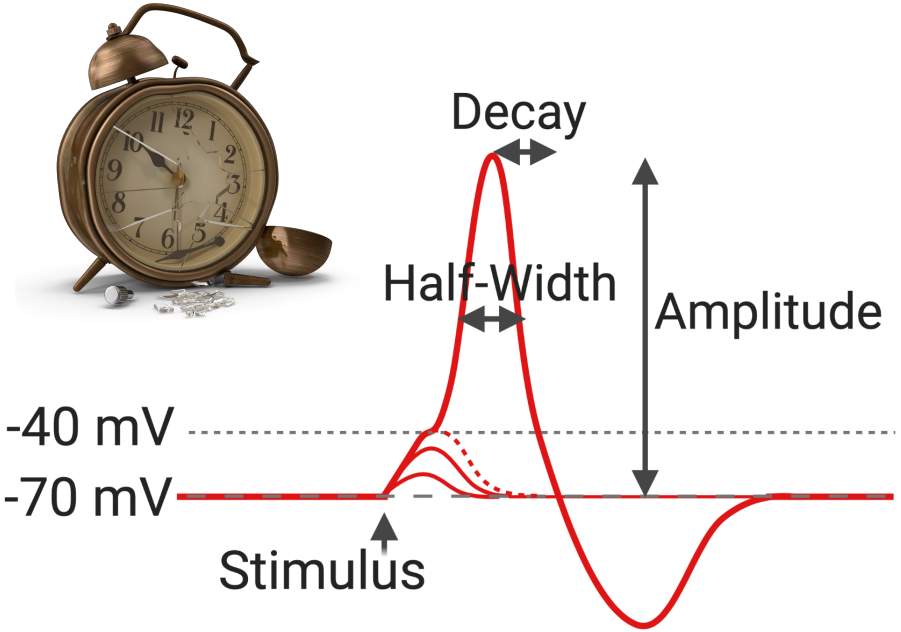
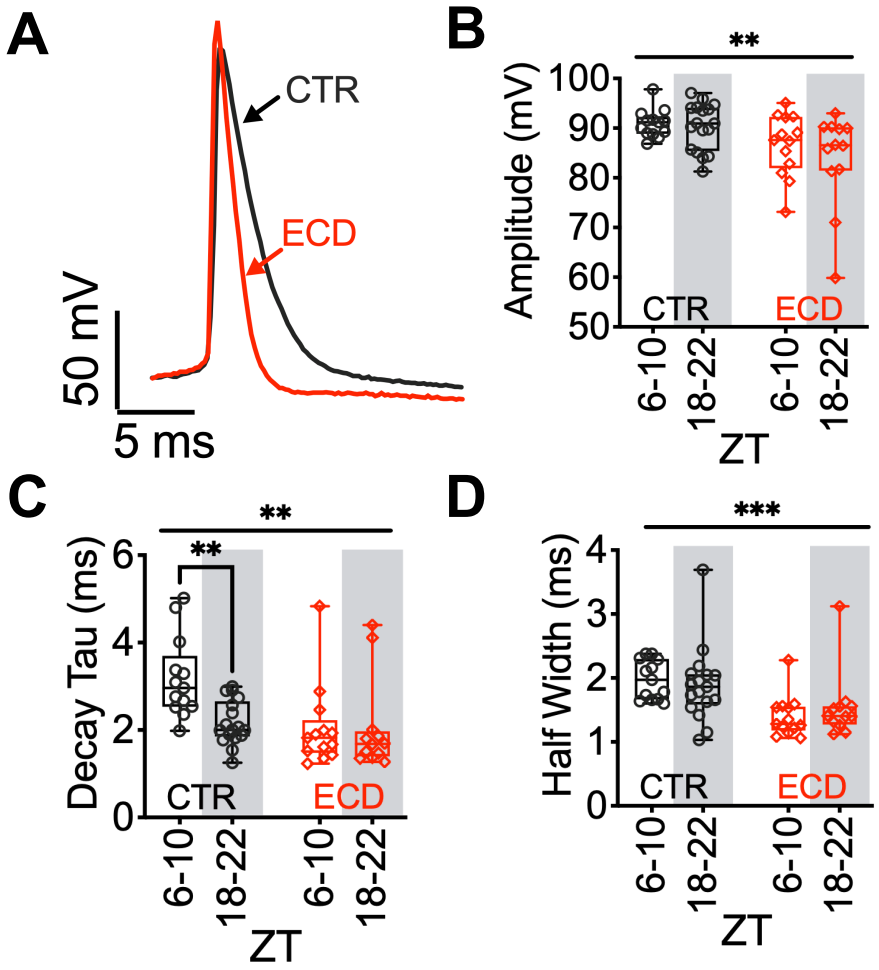
Impact of circadian desynchronization (ECD) on action potential dynamics

ECD alters multiple components of action potentials *independent* of time-of-day





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Summary

- Activity of prelimbic PFC neurons are regulated by time-of-day under entrained LD24 conditions
- Circadian desynchronization disrupts PFC cellular function independent of time-of-day
- There are distinct sex differences in the fundamental properties of PFC neurons, and in the influence of time-of-day

Future Directions

- Are time-of-day effects on PFC neurons dependent on the central or molecular clock?
- How does time-of-day impact inputs onto PFC neurons and other downstream brain regions?
- What is the mechanism by which ECD changes these functional properties?
- How do sex differences relate to overall circuit function and behaviors? Are the effects of ECD different in males vs. females?

Thank you!

Work Presented

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Jennifer Wang

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