ROLE OF DOPAMINE IN CIRCADIAN ENTRAINMENT TO REWARD

Proof-of-principle study using in-vivo electrophysiology in the SCN of mice

Aarti Purohit
UVA Department of Biology
Lowe College Science Scholar

DOPAMINE

- Neurotransmitter in the brain
- Several dopamine systems in brain
- Major role in reward-motivated behavior

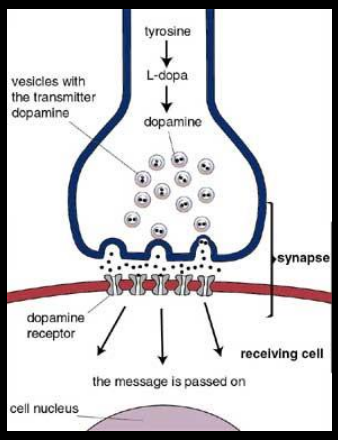
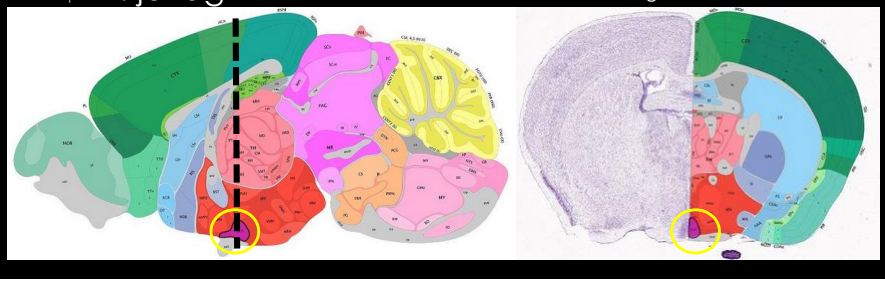


Image from:
http://www.cs.stedwards.edu/

SUPRACHIASMATIC NUCLEUS (SCN)

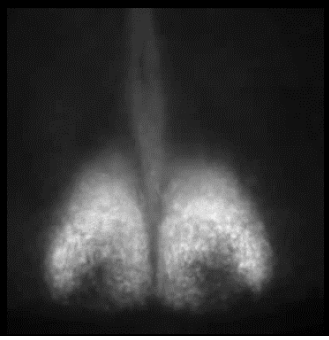
- Master biological clock & circadian rhythms
- Rhythms are endogenous but regulated by environmental cues
- Photic vs. non-photic input
  - Ex: jetlag

Images from: Allen Brain Atlas



CENTRAL PREMISE

- Premise 1: SCN has receptors for dopamine (D1R)
- Premise 2: SCN neurons should have light/dark rhythmicity



Video from: Welsh DK, Takahashi JS, Kay SA. 2010. Suprachiasmatic nucleus: cell autonomy and network properties. *Annu. Rev. Physiol.* 72:551–77

TECHNIQUE 1: "DREADDs"

- "**D**esigner **R**eceptor **E**xclusively **A**ctivated by **D**esigner **D**rugs"
  - Example of "designer drug": clozapine-N-oxide (CNO)
- Cre recombinase used to target DREADD receptors to ONLY neurons that express D1R receptors

TECHNIQUE 2: RECORDING IMPLANTS

- Records action potentials from single cells
- Freely behaving mice
- Long-term recordings

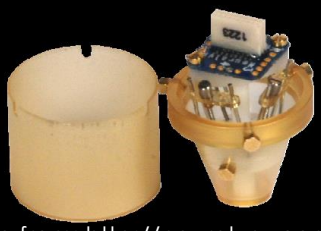


Image from: http://neuralynx.com

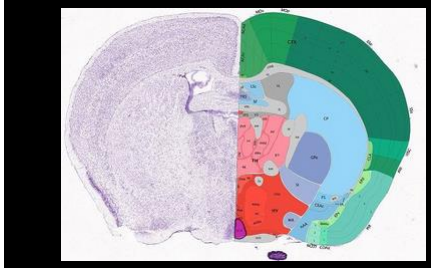
Image from: Anikeeva, P. *et al*. Optetrode: a multichannel readout for optogenetic control in freely moving mice. *Nature Neurosci.* **15**, 163–170 (2012).

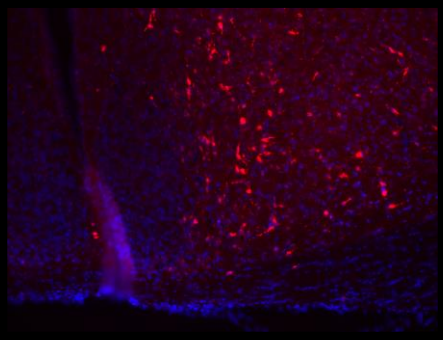
EXPERIMENTAL DESIGN

- Step 1: surgically implant 4 mice with electrodes targeted at the SCN
- Step 2: entrain mice to 12 hr light: 12 hr dark cycle
- Step 3: Activate dopamine system and monitor SCN activity
  - day & night
  - before & after injecting CNO: 30 min wait time

RESULTS

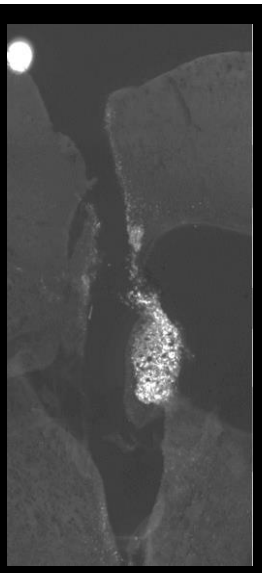
- 4 mice injected; 1 headstage had wiring issues
- Several units had day/night rhythmicity as well as CNO responsiveness
- Interesting action potential shapes recorded





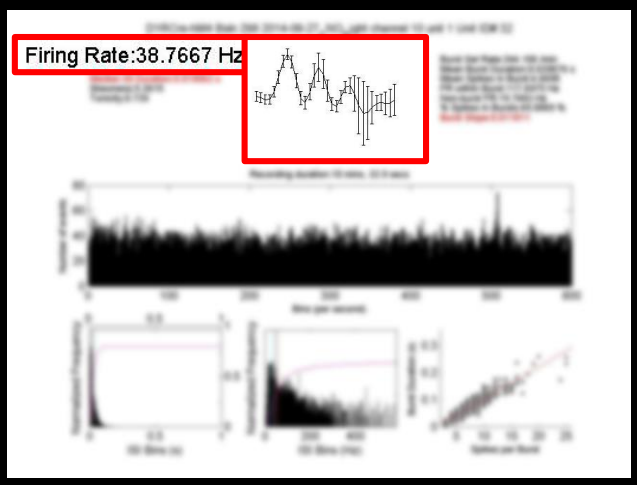
Mouse 0298

Mouse 0351



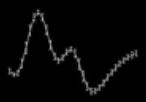
Mouse 0353

DATA ANALYSIS



From Matlab: computational software

EXAMPLE: CELL #11



June 9
Baseline Day
Firing Rate:
5.94 Hz

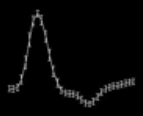
June 9
Baseline Night
Firing Rate:
10.39 Hz

June 10
Baseline Day
Firing Rate:
6.98 Hz

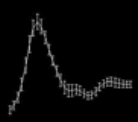
June 10
CNO Day
Firing Rate:
3.34 Hz

EXAMPLE: CELL #28

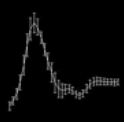
June 16
Baseline Day
Firing Rate:
0.49 Hz



June 16
Baseline Night
Firing Rate:
0.62 Hz



June 17
Baseline Day
Firing Rate:
0.43 Hz



June 17
CNO Day
Firing Rate:
0.19 Hz

SIGNIFICANCE

- Interesting action potential shape of SCN neurons
  - Very fast recovery period?
- Proof of principle study successful: neuronal activity can be controlled
- Next steps:
  - repeat experiment with more mice and proper targeting
  - Induce dopamine production in brain (ex. leptin/ghrelin) and monitor SCN activity

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