The Relationship Between Cholinergic and Noradrenergic Activity and Behavioral State

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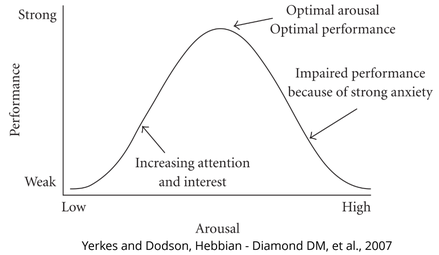
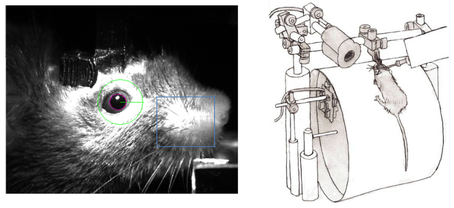
Background

- Moment-to-moment fluctuations in brain-state and arousal ultimately influence an animal's ability to perform and engage in different perceptual or cognitive behavioral tasks.



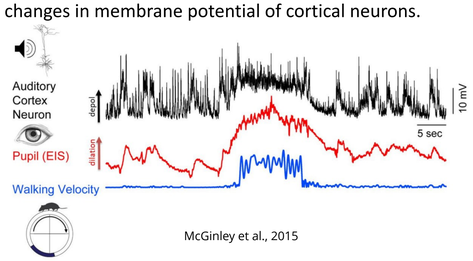
Yerkes and Dodson, Hebbian - Diamond DM, et al., 2007

- External behavioral motifs allow for a careful analysis of the relationship between neural circuitry and behavior.



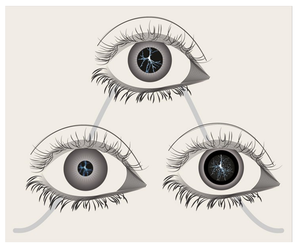
McGinley et al., 2015

- The activity of these behavioral variables is highly correlated with changes in membrane potential of cortical neurons.



McGinley et al., 2015

- Using observable behavioral motifs, such as pupil diameter, walk velocity, whisker and snout movement, and grooming, we are given accurate and reliable, external metrics of variability of brain state and arousal.

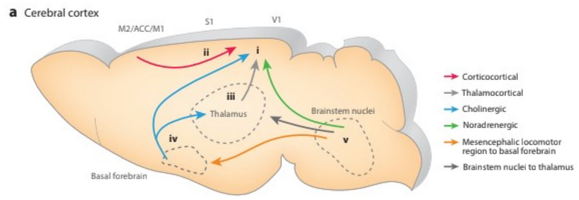


Objectives

My project will investigate this relationship between cholinergic and noradrenergic activity and behavioral state in three ways:

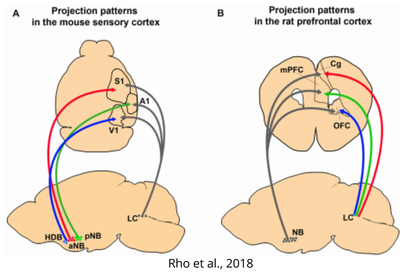
1) **Confirm the relationship between neuromodulatory activity and arousal while also including whisker pad motion and tail motion in our analyses**
2) **Determine whether changes in neuromodulatory activity precede or follow the onset of behavioral events**
3) **Determine whether ACh and NA neuromodulation is specific to particular regions within the brain or if there is widespread synchrony of neuromodulatory systems across the brain during fluctuating arousal states**

- Rapid variation in behavioral state is, in part, influenced by various neuromodulatory systems within the brain.



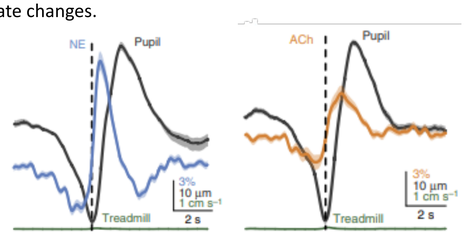
McCormick et al., 2020

- Cholinergic and noradrenergic neurons produce and release the neurotranmitters acetylcholine (ACh) and noradrenaline (NA), respectively.



Rho et al., 2018

- Neuromodulatory activity is linked to arousal state and behavioral state changes.

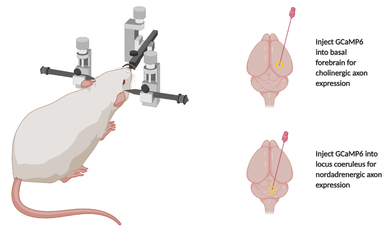


Reimer et al., 2016

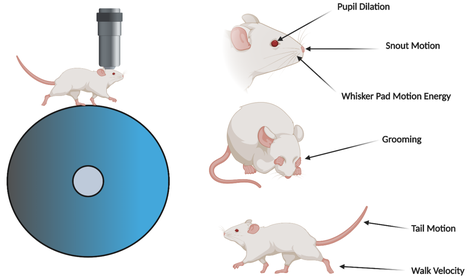
Methods

DBH^{cre} and ChAT^{cre} mice are injected with GCaMP6 virus in the locus coeruleus and the basal forebrain, respectively.

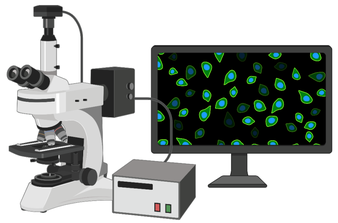
- Introduction of this fluorescent calcium indicator allows for a visualization of cholinergic or noradrenergic axon activity.



- Simultaneous 2-Photon axon imaging and behavioral data acquisition allows us to directly compare axonal activity to behavioral state.

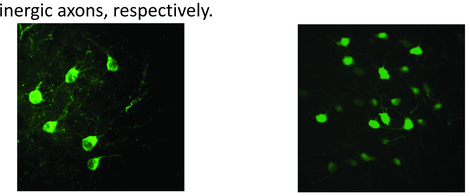


- Histological verification of injection sites confirms that we are recording from either cholinergic or noradrenergic axons.

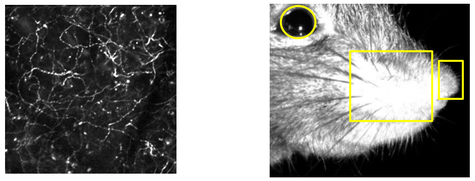


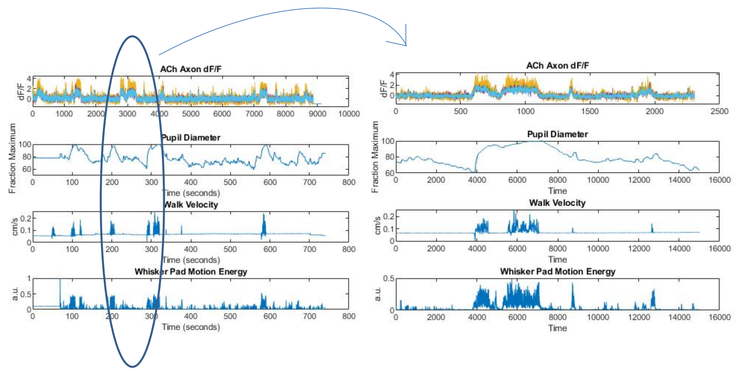
Preliminary Data

- Histological verification of injections into the locus coeruleus (left) and basal forebrain (right) confirm imaging of noradrenergic or cholinergic axons, respectively.



- Changes in cholinergic and noradrenergic axonal fluorescence reflect changes in behavioral state.





Future Directions

Analyze temporally how neuromodulatory activity is related to the onset of behavioral events

- Does ACh or NA activity predict the onset of behavioral motifs?

Determine whether ACh and NA activity is localized to particular regions of the brain or if there is synchronous, widespread neuromodulation across multiple cortical regions

- Is the neuromodulation of multiple cortical regions temporally related?

References

- Diamond et al. *Neural Plast* **2007**, 60803 (2007).
- McCormick et al. *Annu. Rev. Neurosci.* **43**, (2020).
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- Reimer et al. *Nat Commun* **7**, 13289 (2016).
- Rho et al. *Front. Neural Circuits* **12**, 47 (2018).

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