



# **Understanding serotonergic regulation of motor functions**

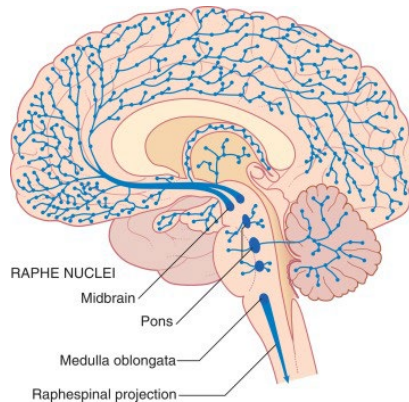
Yenah Bak

Department of Brain and Cognitive Sciences

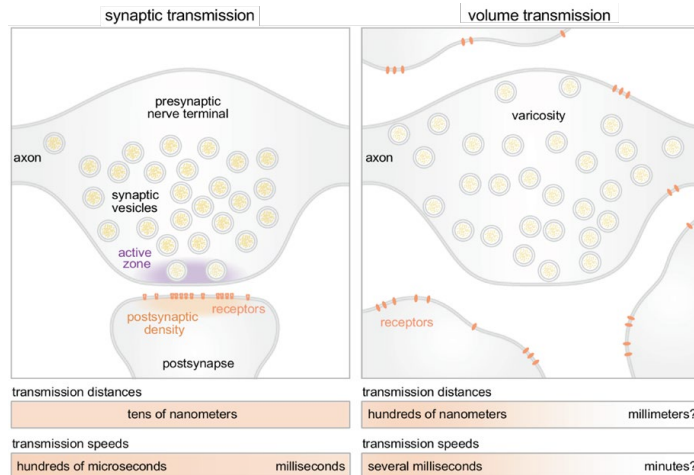
# Serotonergic system:

It is a complex system with brain-wide projection, multiple receptors, volume transmission that affects various functions.

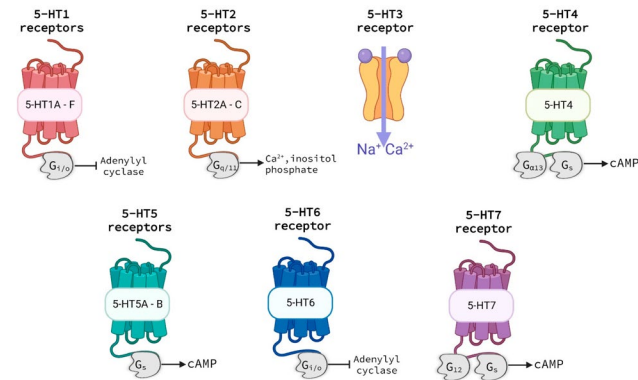
## Projections



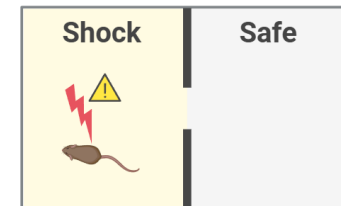
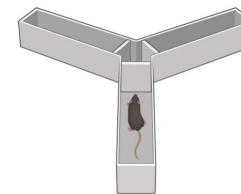
## Transmission



## Receptors

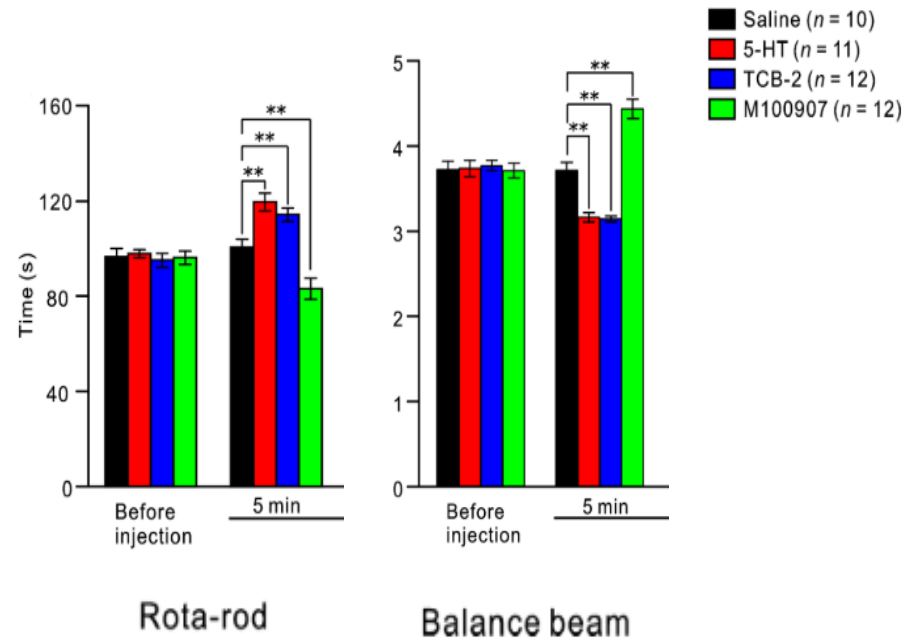
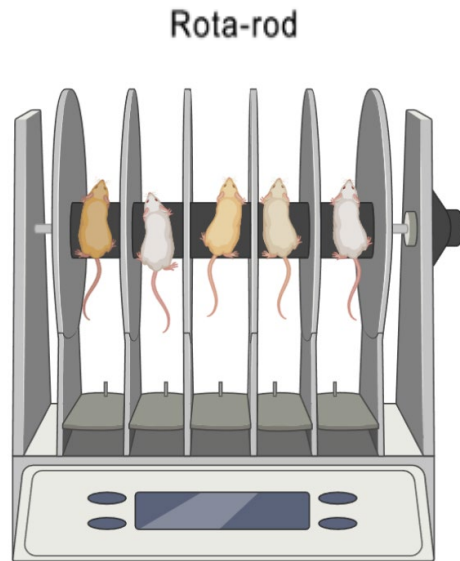


## Functions



# Serotonergic effect on Motor Control:

Serotonin (5-HT) regulates motor ability through Fastigial Nucleus (fDCN)

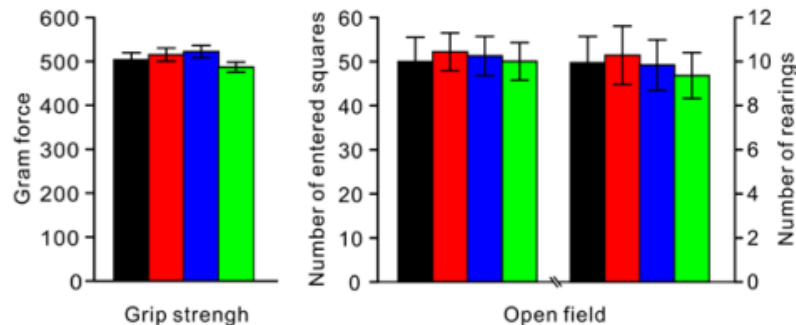
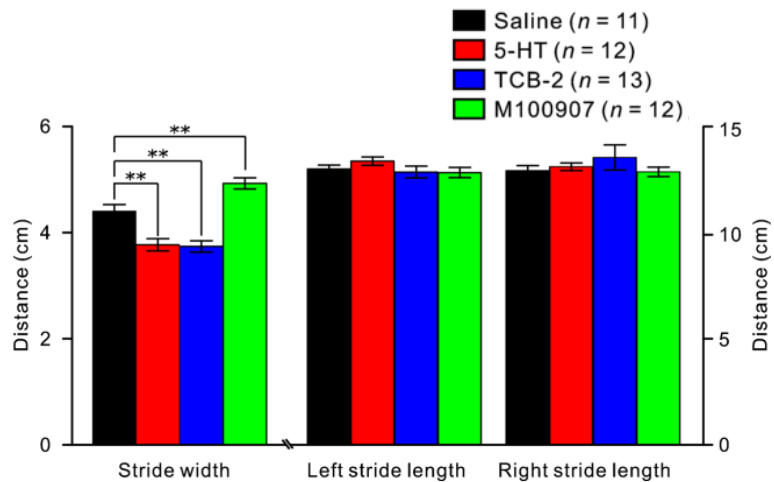
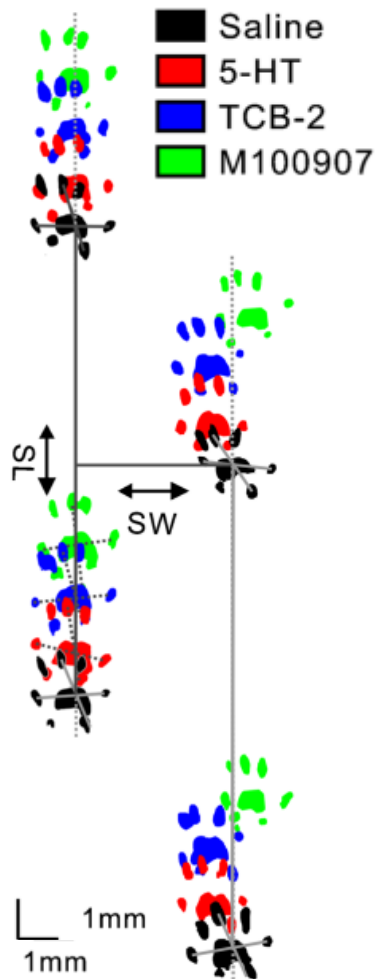


TCB-2: Serotonin 2A receptor Agonist

M100907: Serotonin 2A receptor Antagonist

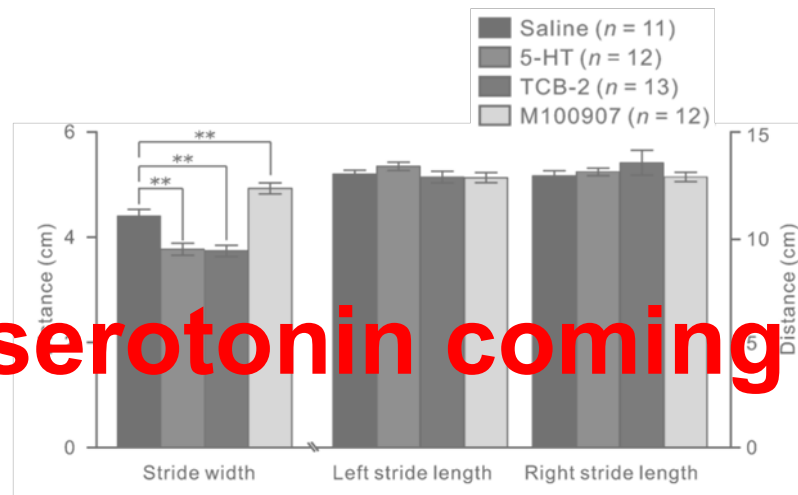
# Serotonergic effect on Motor Control:

Serotonin promotes motor performance, especially motor balance and coordination through 2a receptor  
in the cerebellar fastigial nucleus

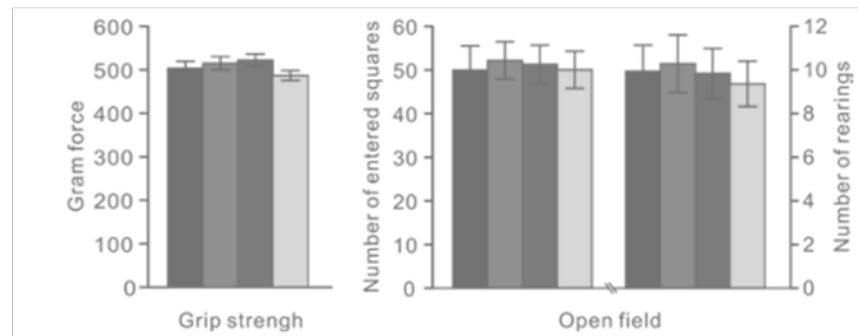


# Serotonergic effect on Motor Control:

Serotonin promotes motor performance, especially motor balance and coordination through 2a receptor in the cerebellar fastigial nucleus



Where is the serotonin coming from?

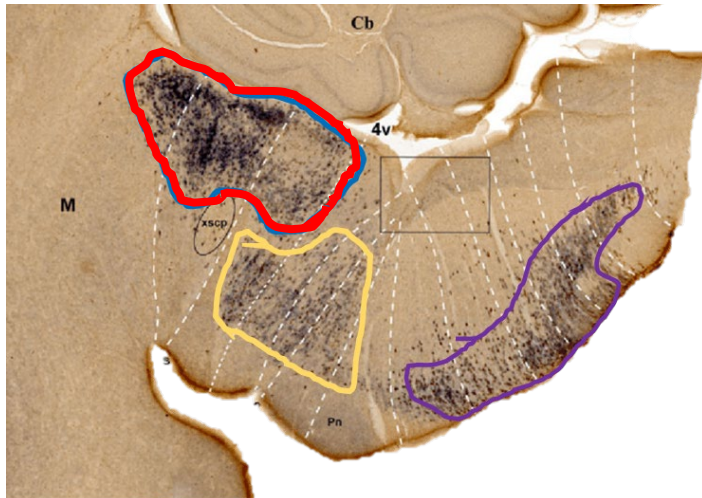


# Serotonergic effect on Motor Control:

Serotonergic neurons are primarily located in the raphe nuclei, including the dorsal raphe nucleus, median raphe nucleus, and caudal raphe nucleus

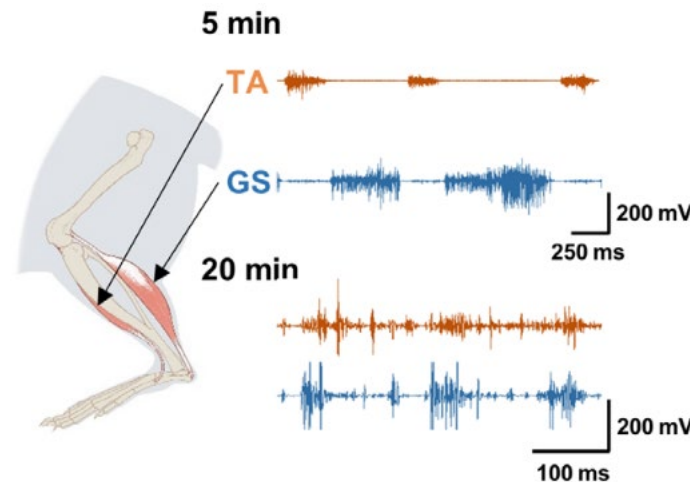
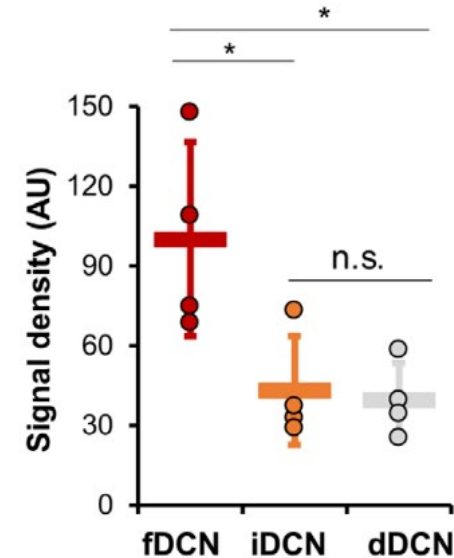
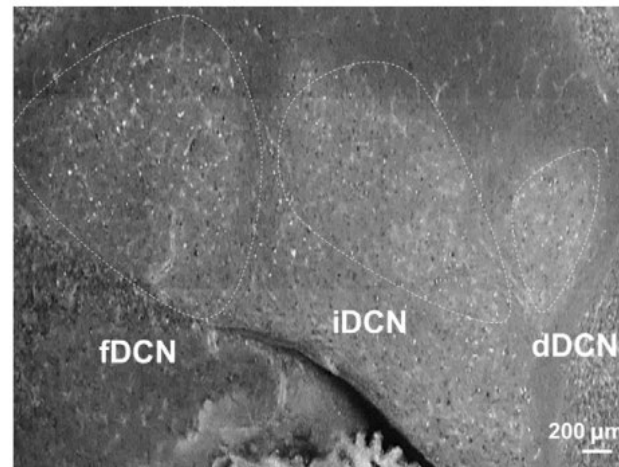
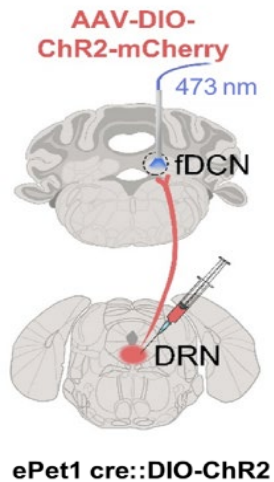
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Sagittal view of the raphe nucleus



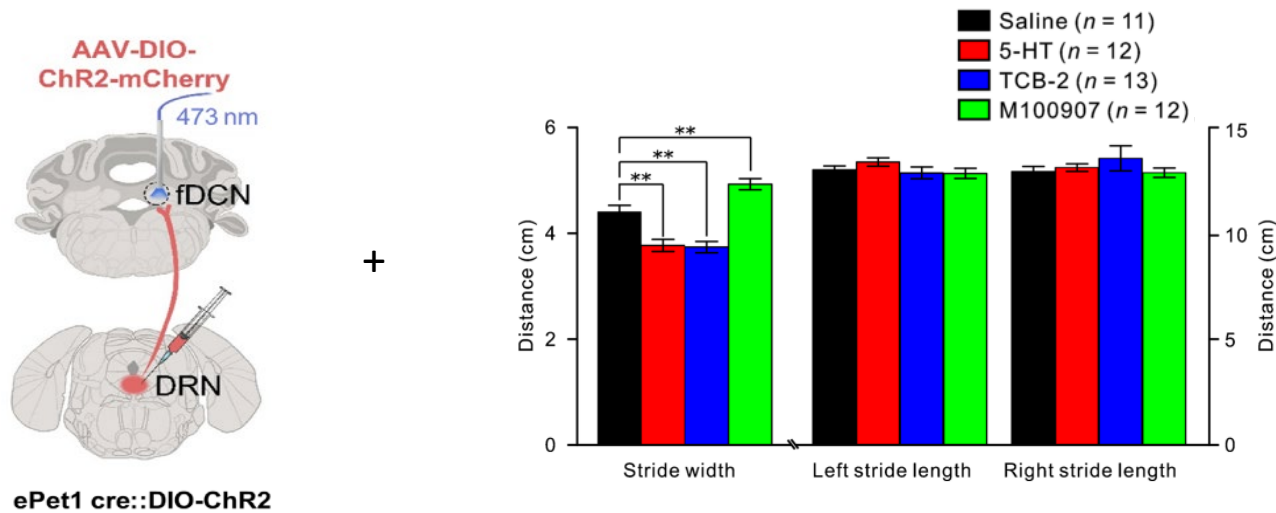
# Serotonergic effect on Motor Control:

Hyperexcitation of serotonergic neurons at fastigial nucleus induces motor disorder, dystonia



# Serotonergic effect on Motor Control:

Previous studies show DRN serotonergic neurons might regulate motor ability via fastigial nucleus



## Questions:

1. Could serotonin that regulates motor control from the DRN?
2. What information do these serotonergic neurons encode?





# Outline

## 1. Conducted Experiments

1. Circuit tracing and cell population
2. Chemogenetic study
3. Fiber photometry study

## 2. Future Experiments

### **Questions:**

1. Could serotonin that regulates motor control from the DRN?
2. What information do these serotonergic neurons encode?



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## 1. Conducted Experiments

1. Circuit tracing and cell population
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## 2. Future Experiments

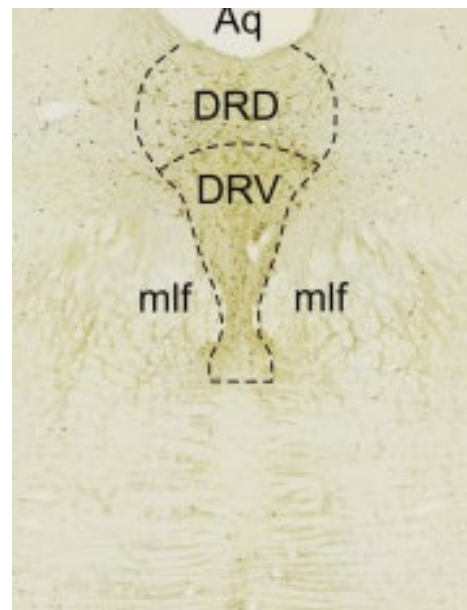
### **Questions:**

1. Could serotonin that regulates motor control from the DRN?
2. What information do these serotonergic neurons encode?

# 1. FN-projecting DRN population:

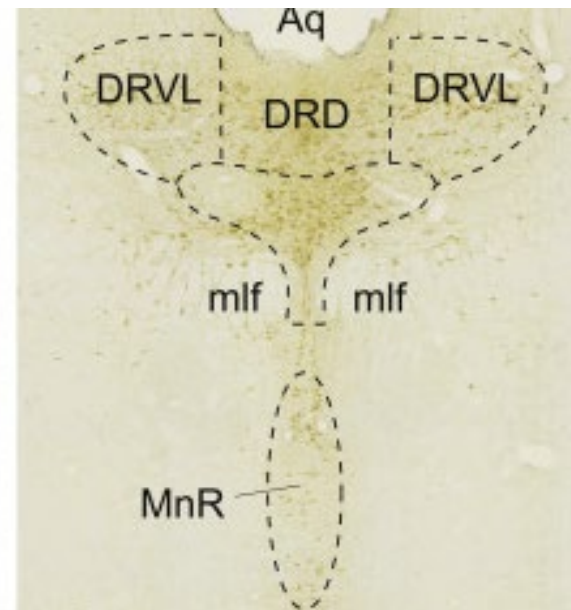
DRN can be divided into dorsal (DRD), ventral (DRV), and lateral (DRVL)

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AP:

-4.2

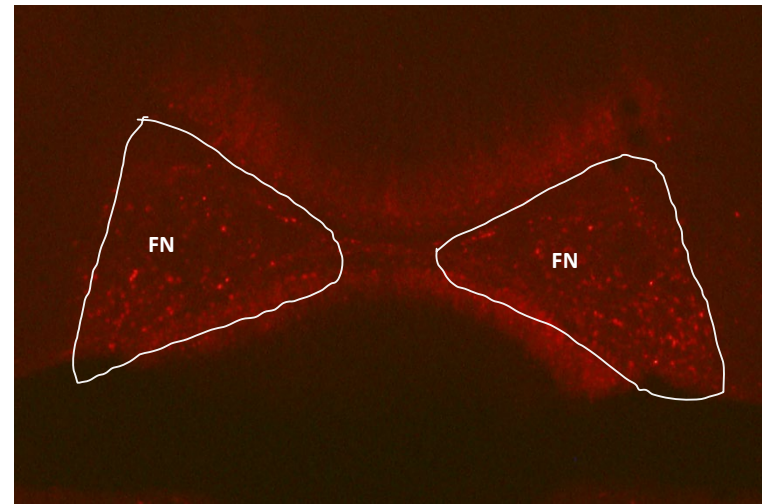
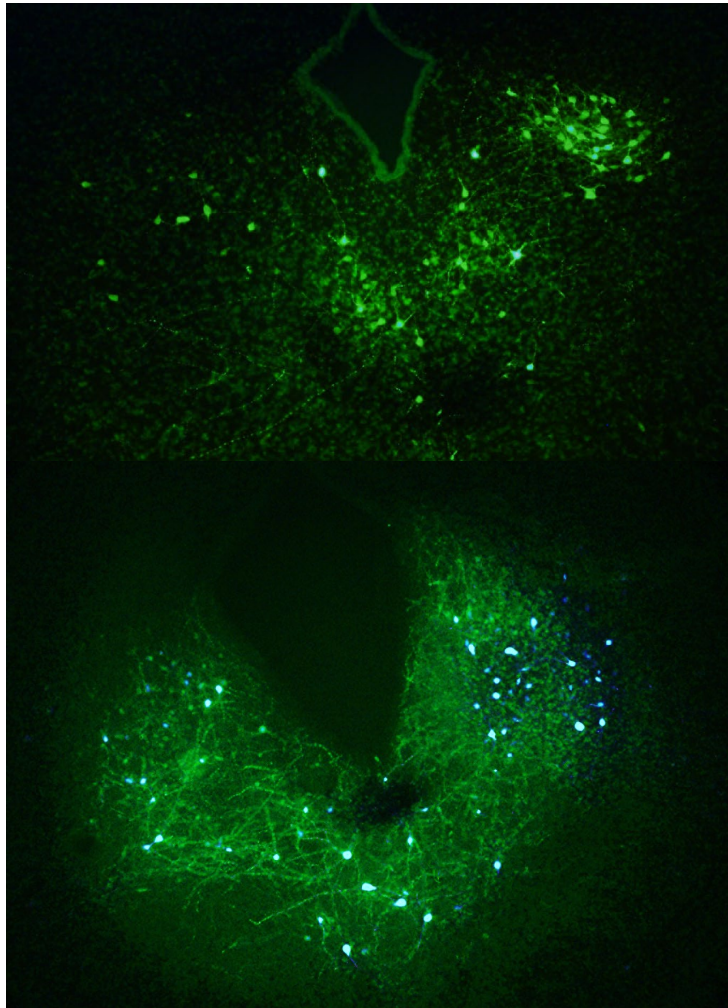


-4.6

# 1. FN-projecting DRN population:

Retrograde experiment showed neurons in the dorsal raphe nucleus project to the fastigial nucleus

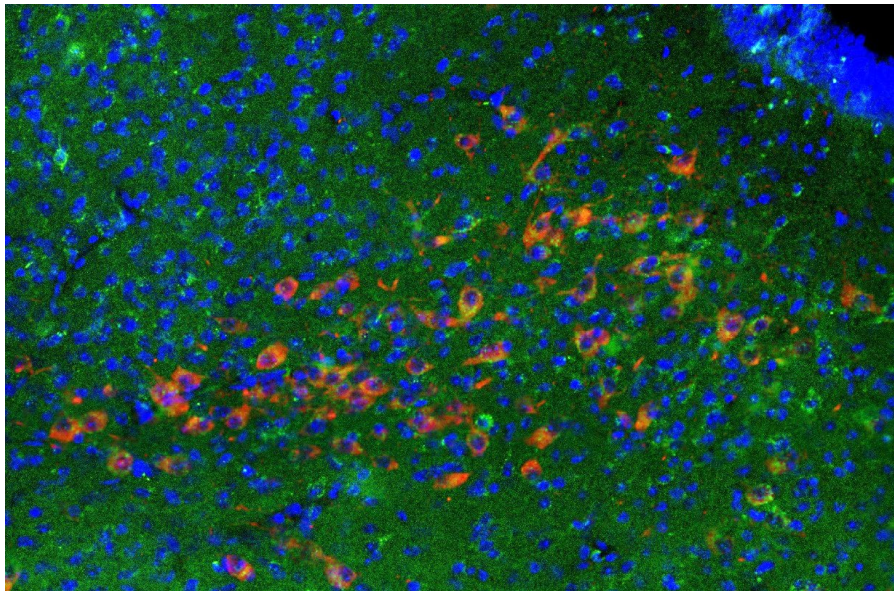
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# 1. FN-projecting DRN population:

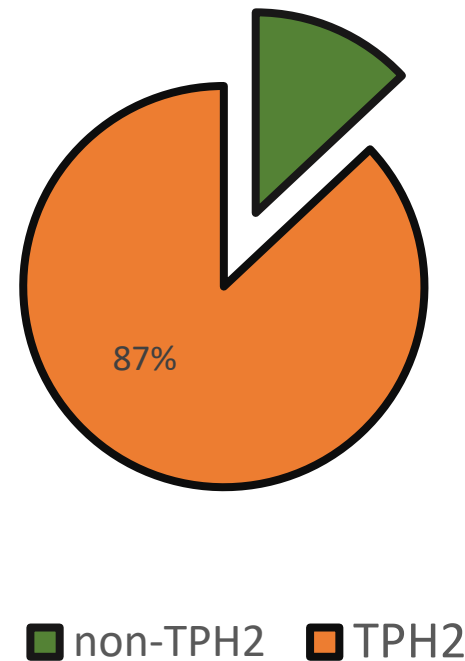
Anti-TPH2 staining showed majority of neurons projecting to the fastigial nucleus are serotonergic

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Retrogradely labelled

TPH2-positive



# Outline

## 1. Conducted Experiments

### 1. Circuit tracing and cell population

Result: Majority of dorsal DRN neurons projecting to the fastigial nucleus are serotonergic.

### 2. Chemogenetic study

### 3. Fiber photometry study

### 4. Electromyography study

## 2. Future Experiments

### **Questions:**

1. Could serotonin that regulates motor control from the DRN?
2. What information do these serotonergic neurons encode?

# Outline

## 1. Conducted Experiments

1. Circuit tracing and cell population
2. Chemogenetic study
3. Fiber photometry study
4. Electromyography study

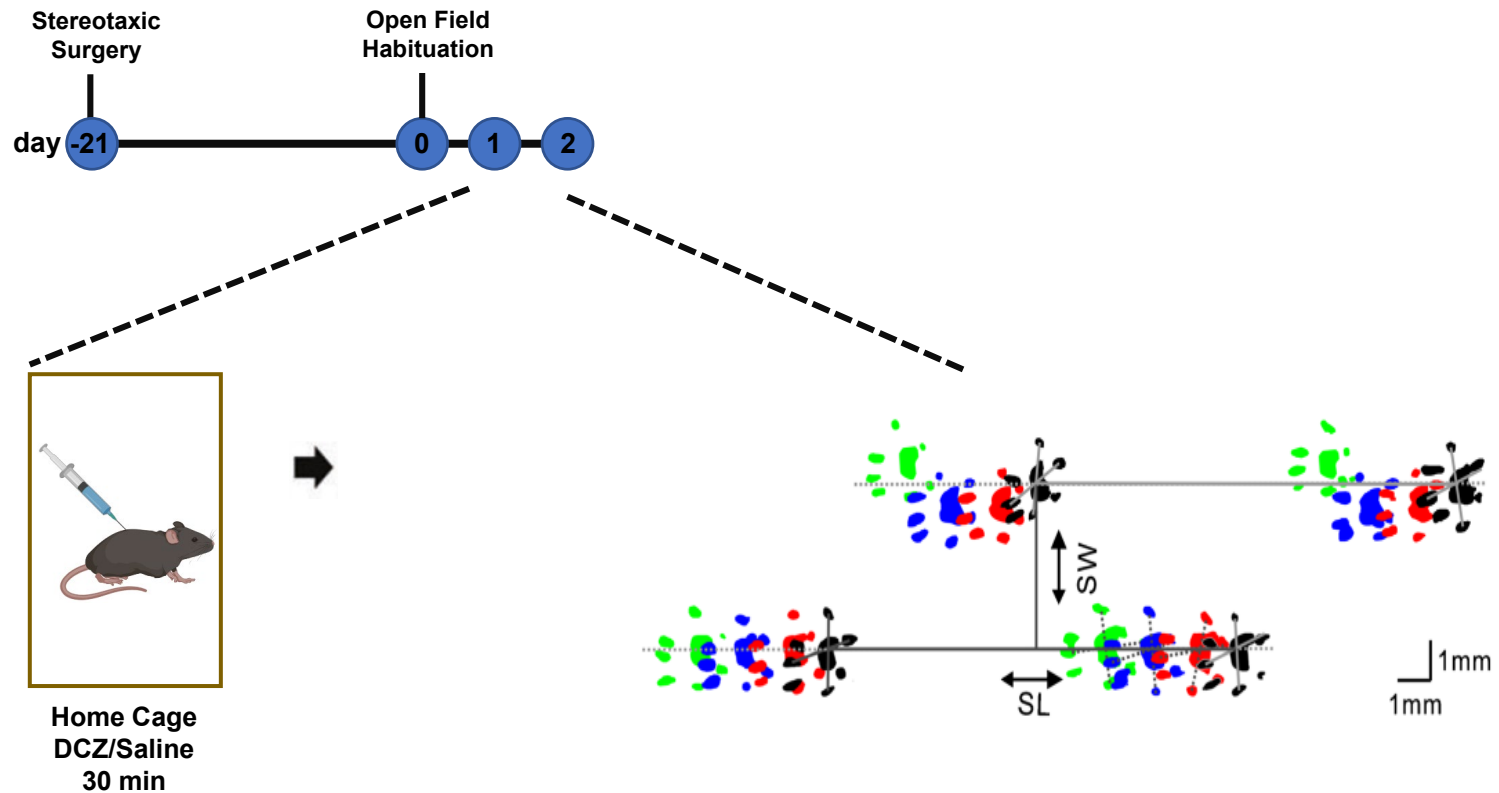
## 2. Future Experiments

### **Questions:**

1. Could serotonin that regulates motor control from the DRN?
2. What information do these serotonergic neurons encode?

## 2. DRN-FN Chemogenetic experiments:

Gait analysis were conducted during chemogenetic manipulation



DCZ: 0.2mg/kg in 0.9% saline;  
pre-experiment IP injection

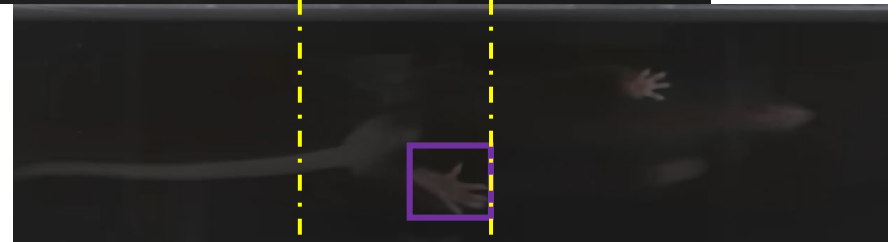
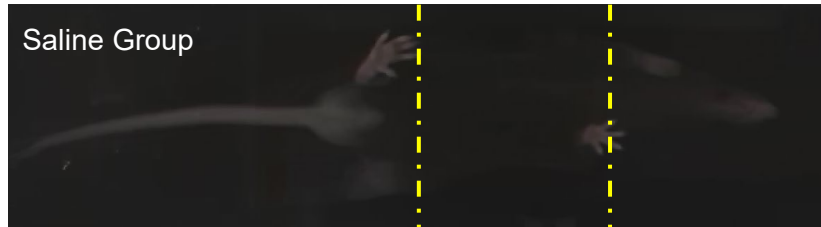
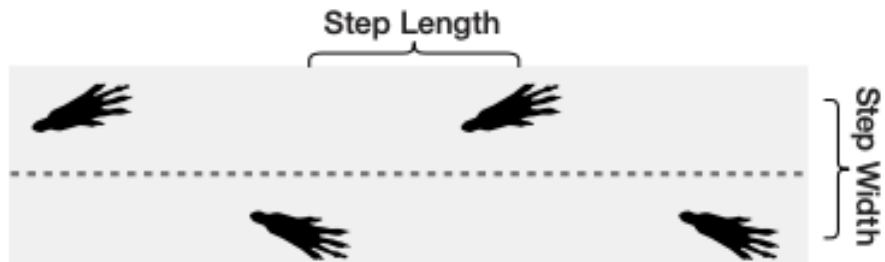


## 2. DRN-FN Chemogenetic experiments:

Catwalk: **Unilateral DRN (Right) excitation**

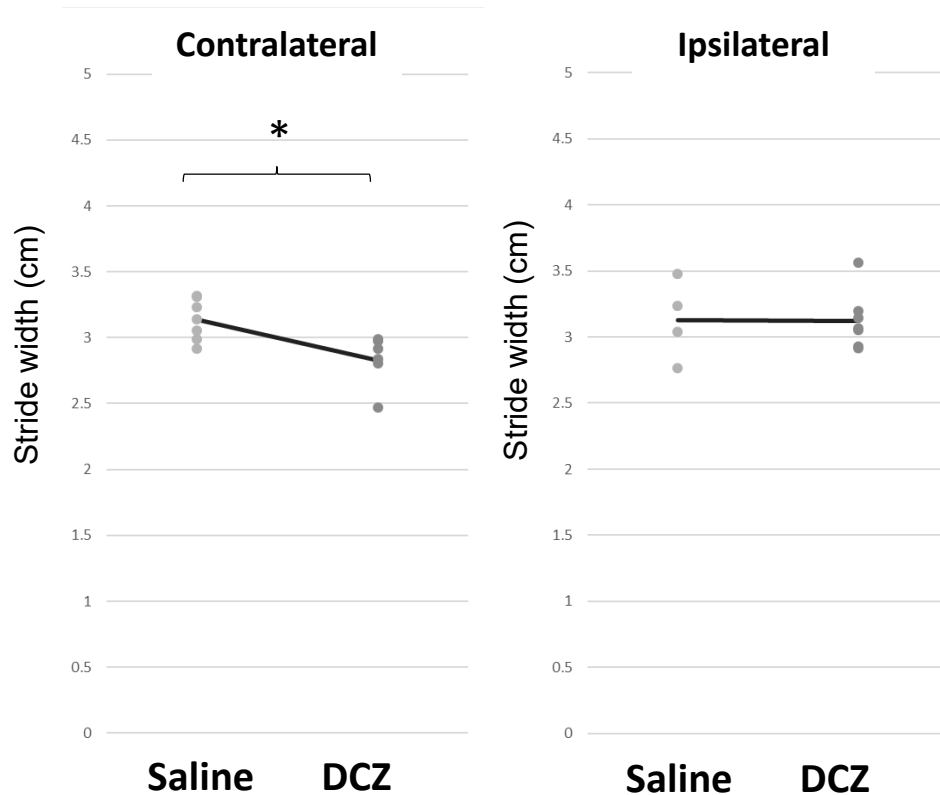
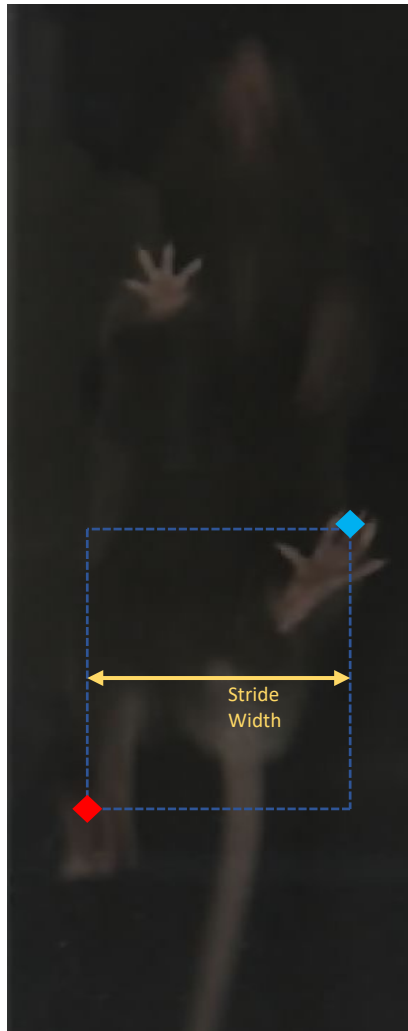
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### *Spatial Characteristics*



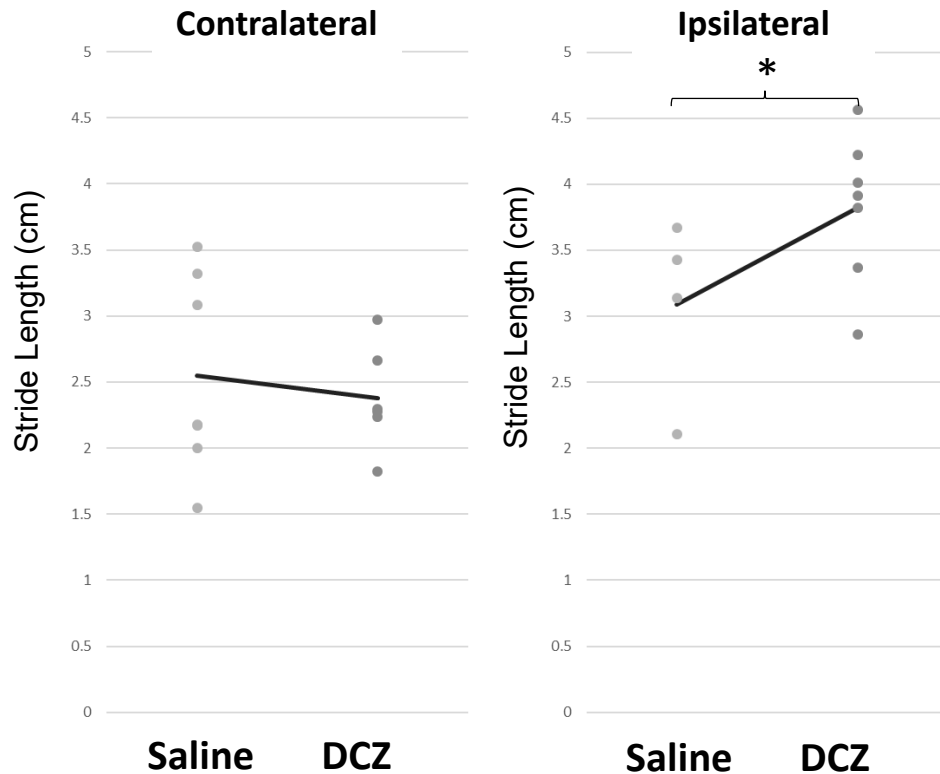
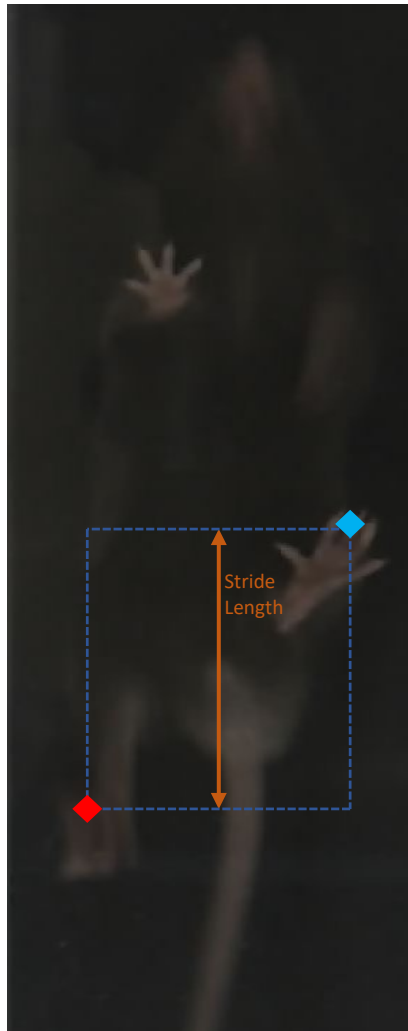
## 2. DRN-FN Chemogenetic experiments:

Unilateral DRN (Right) excitation induced narrower stride width on contralateral side



## 2. DRN-FN Chemogenetic experiments:

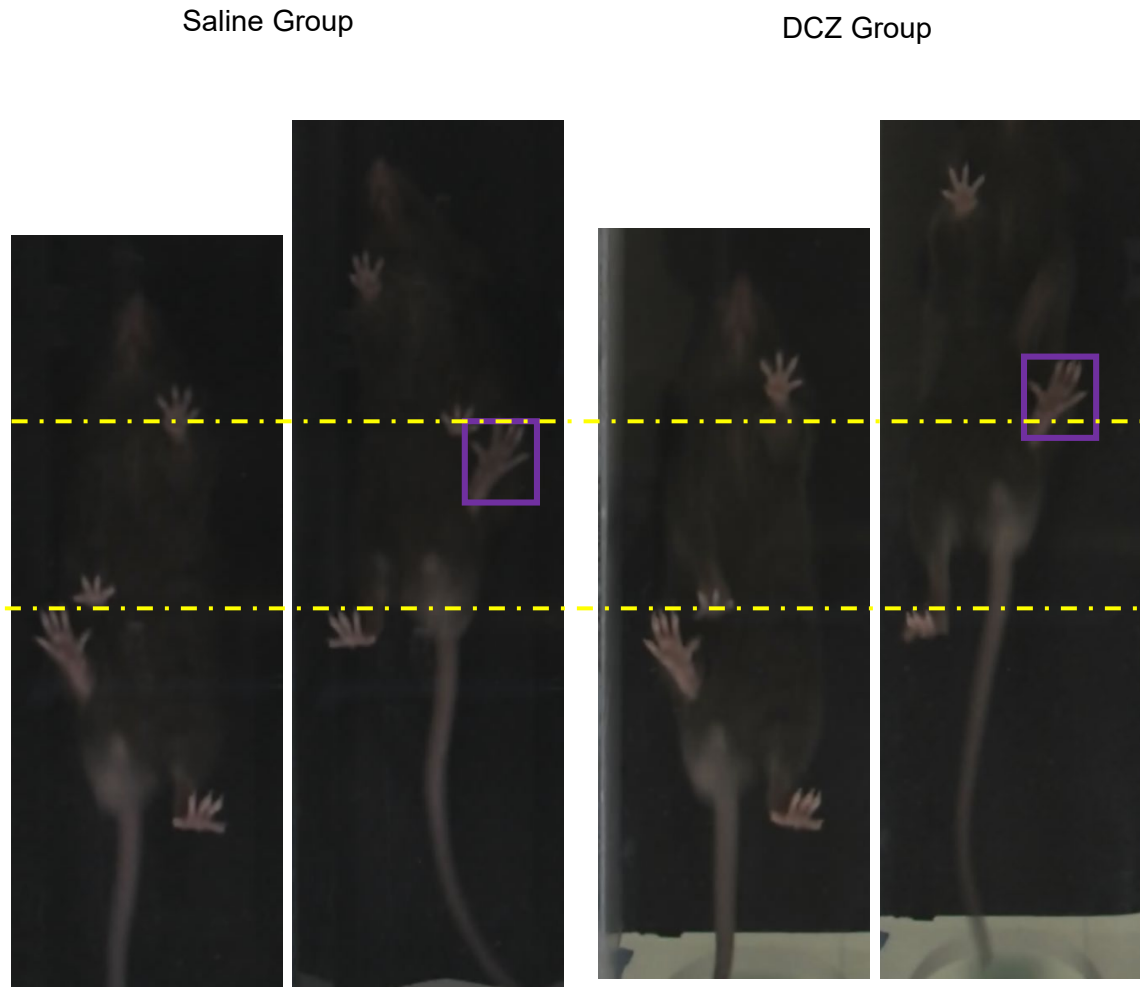
Unilateral DRN (Right) excitation induced longer stride length on ipsilateral side



## 2. DRN-FN Chemogenetic experiments:

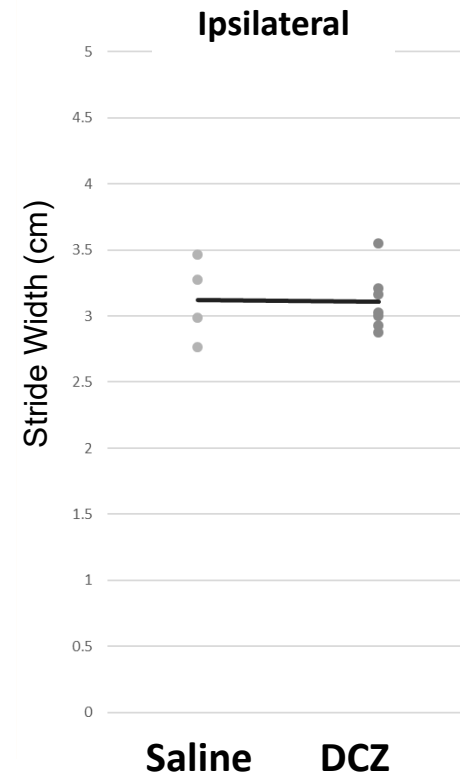
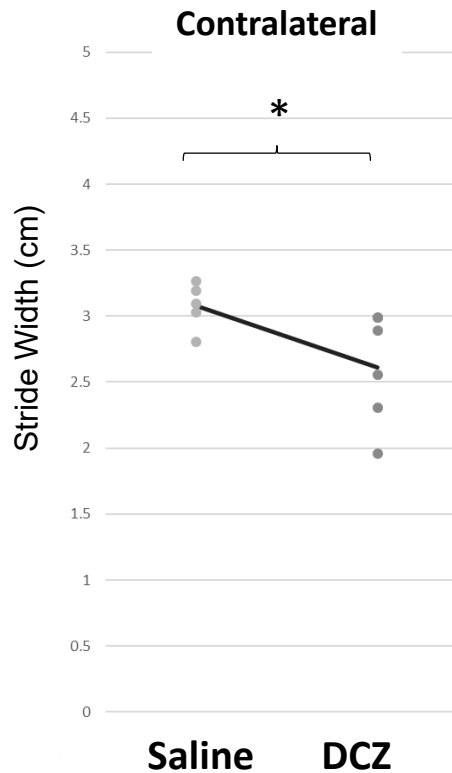
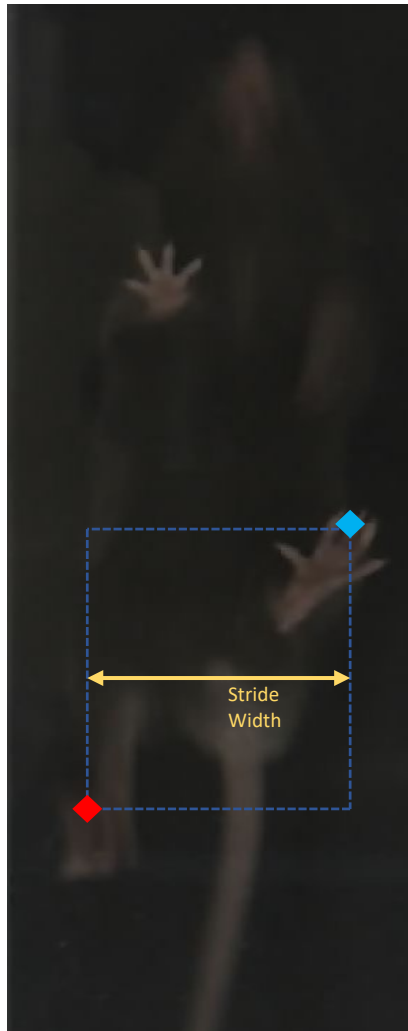
Unilateral FN excitation induced stride differences in the same pattern as DRN excitation

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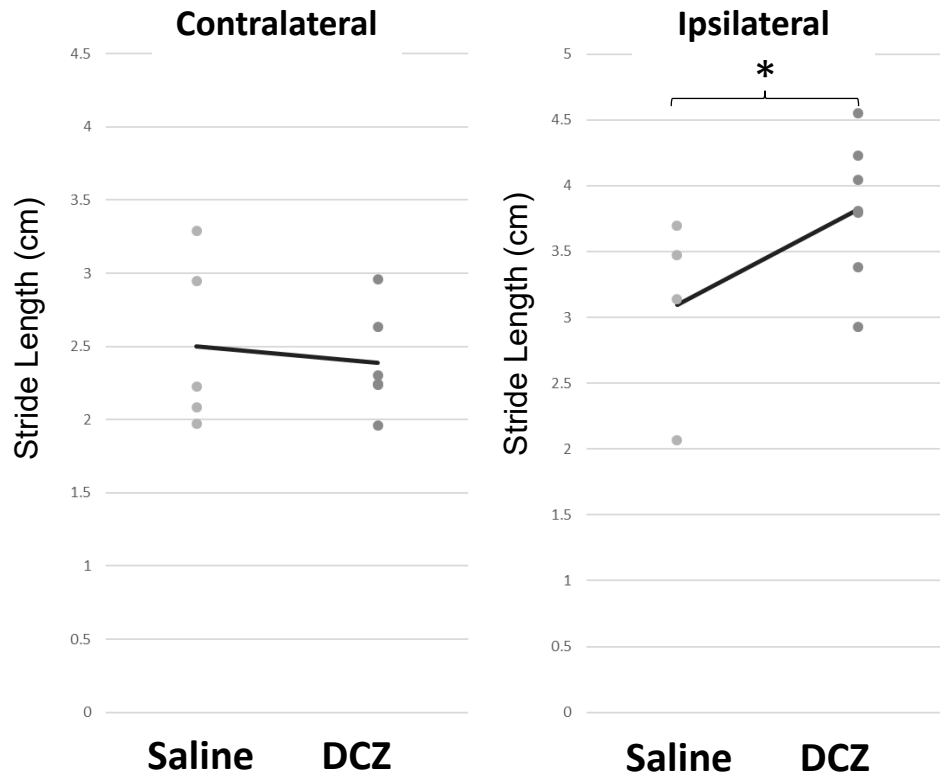
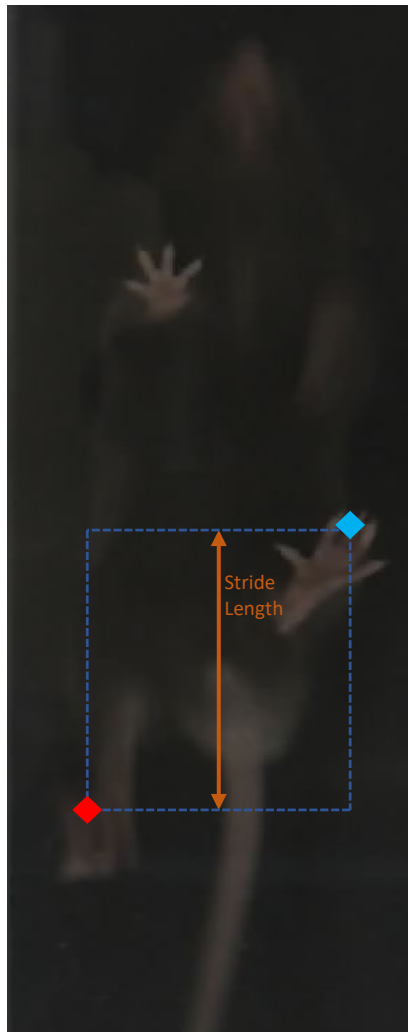
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## 2. DRN-FN Chemogenetic experiments:

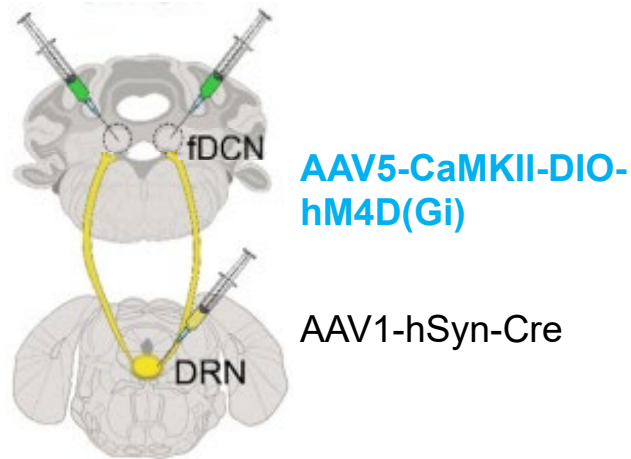
Unilateral FN (Right) excitation induced longer stride length on ipsilateral side



## 2. DRN-FN Chemogenetic experiments:

Bilateral inhibition of FN glutamatergic neurons results lagging of hindlimb but not different in gait pattern

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Saline Group

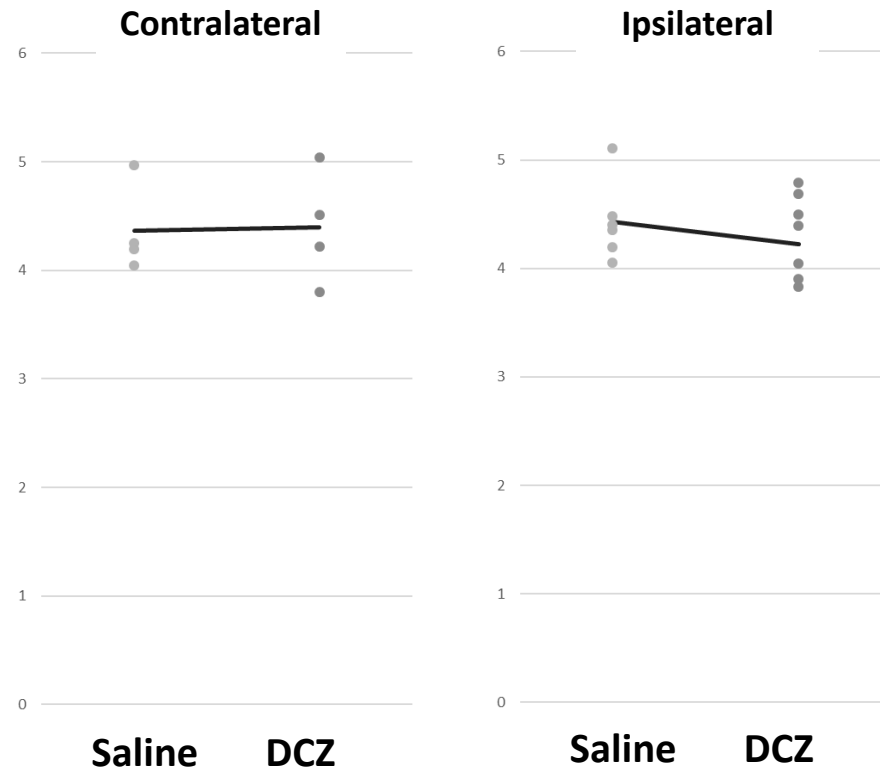
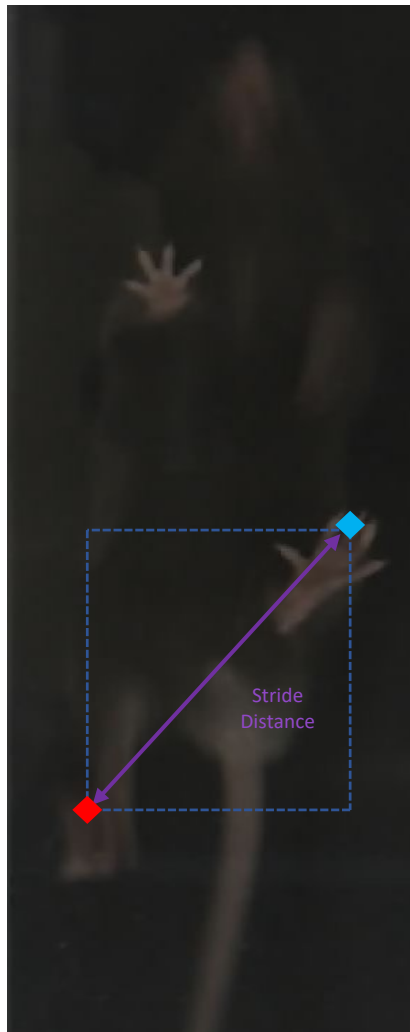


DCZ Group



## 2. DRN-FN Chemogenetic experiments:

Bilateral inhibition of FN glutamatergic neurons did not induce different in stride distance

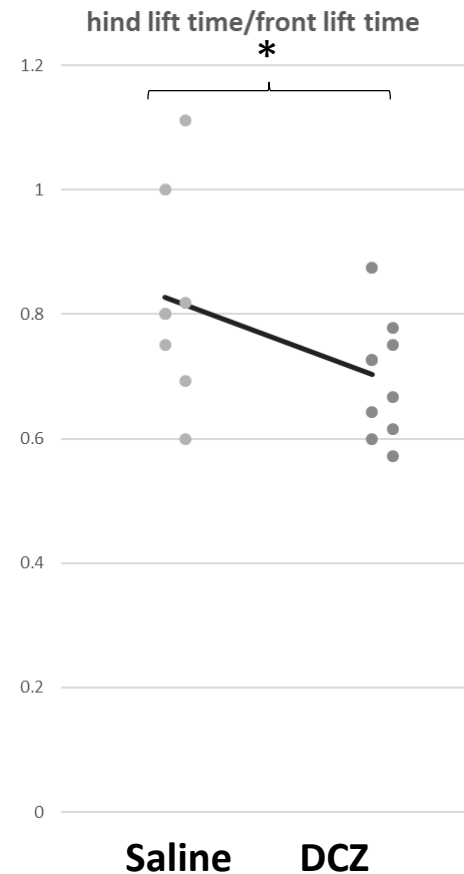




## 2. DRN-FN Chemogenetic experiments:

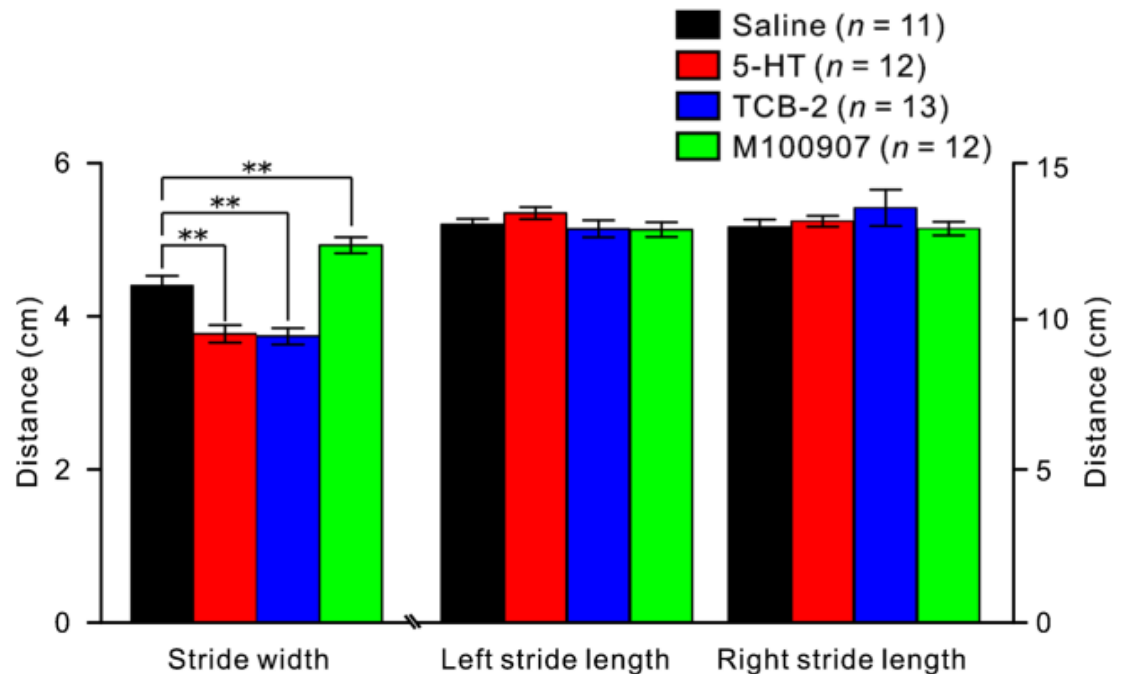
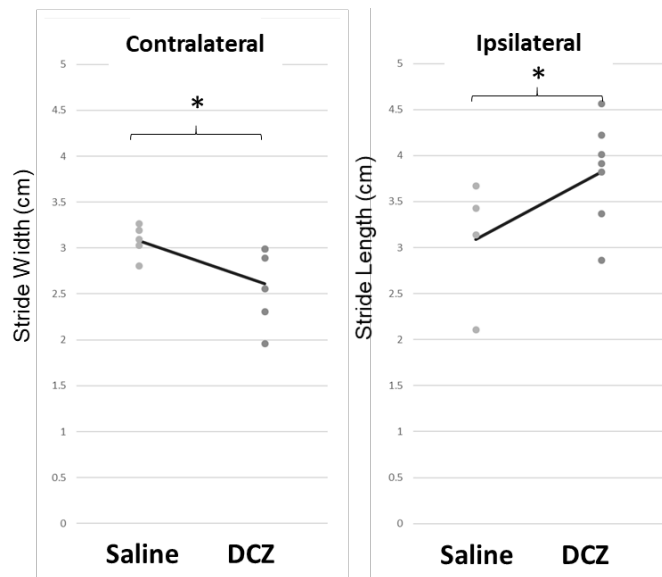
However, **FN glutamatergic neuron inhibition** decreased time that hindlimbs are lifted during strides

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## 2. DRN-FN Chemogenetic experiments:

DRN (Right) excitation showed similar patterns to decrease stride width as previously reported but not stride length





# Outline

## 1. Conducted Experiments

### 1. Circuit tracing and cell population

Result: Majority of dorsal DRN neurons projecting to the raphe nucleus are serotonergic.

### 2. Chemogenetic study

Result: DRN neurons projecting to the fastigial nucleus changes gait pattern.

### 3. Fiber photometry study

## 2. Future Experiments

### Questions:

1. Could serotonin that regulates motor control from the DRN? **Likely!**
2. What information do these serotonergic neurons encode?



# Outline

## 1. Conducted Experiments

1. Circuit tracing and cell population
2. Chemogenetic study
3. Fiber photometry study

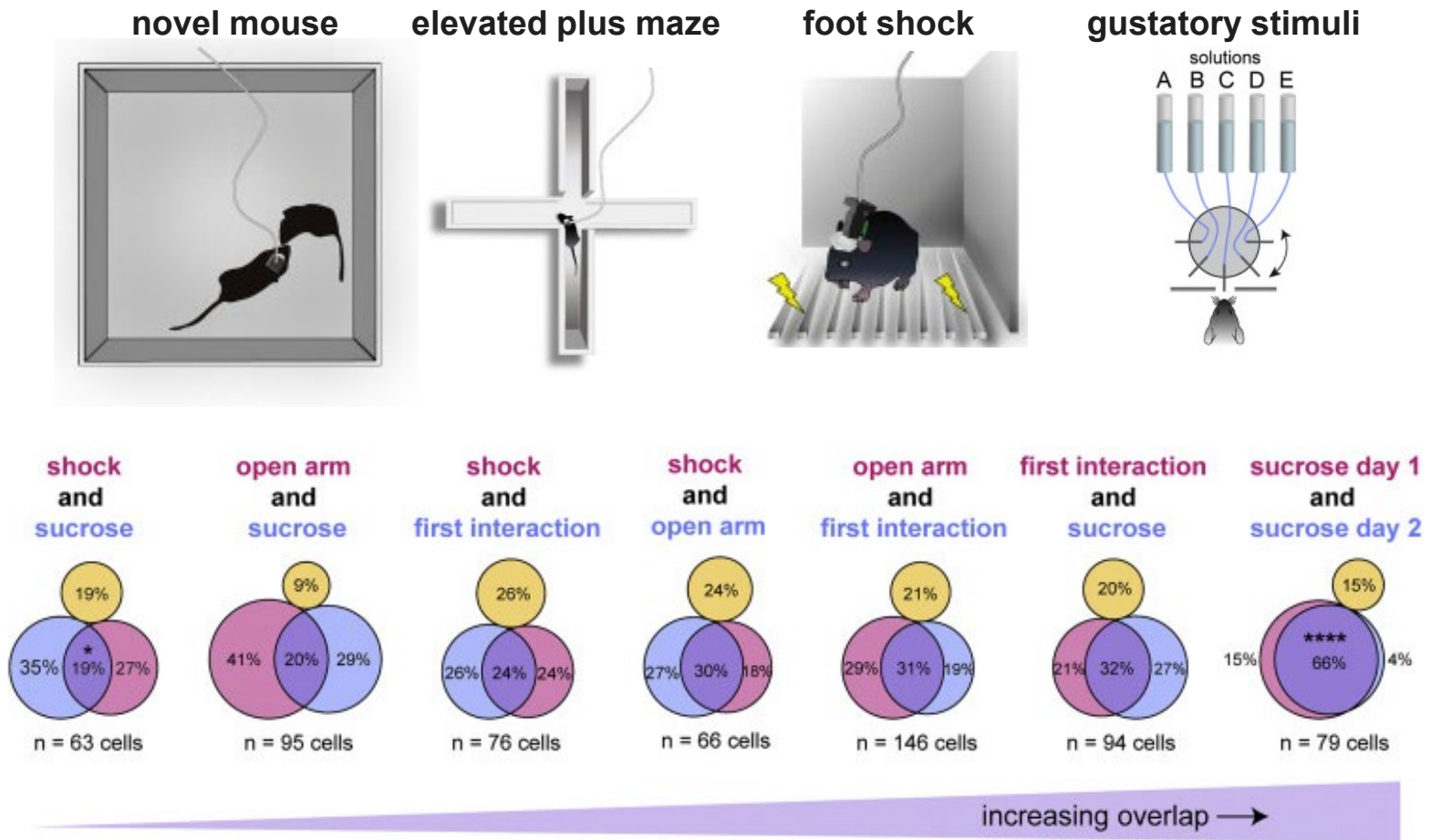
## 2. Future Experiments

### Questions:

1. Could serotonin that regulates motor control from the DRN? **Likely!**
2. What information do these serotonergic neurons encode?

# 3. Fiber photometry experiments:

Serotonergic neurons show heterogenous activities to different stimuli



### 3. Fiber photometry experiments:

Five different stimuli given during fiberphotometry recording

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**Juvenile interaction**



**Chow food interaction**



**Novel mouse interaction**



**Tail picking**



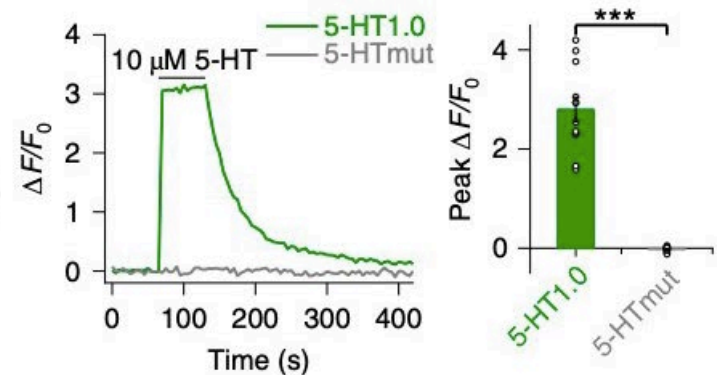
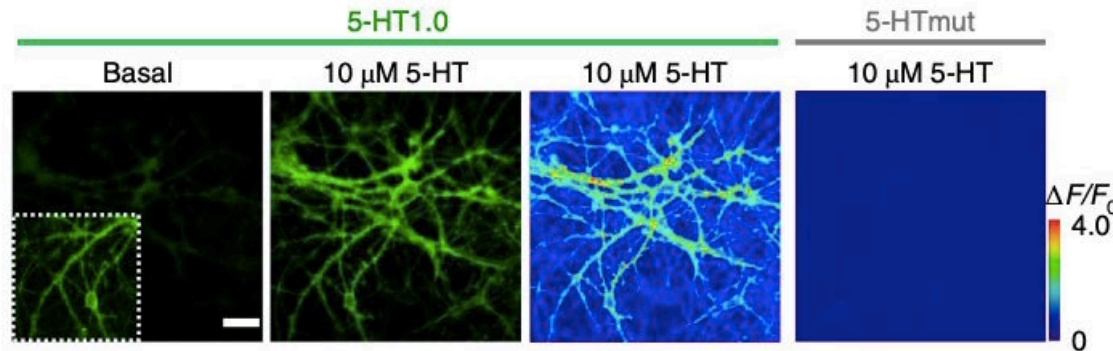
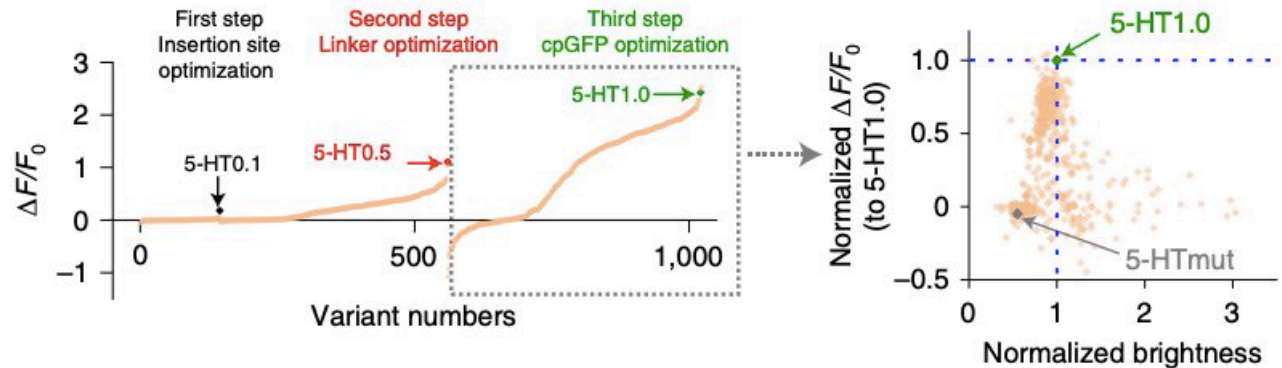
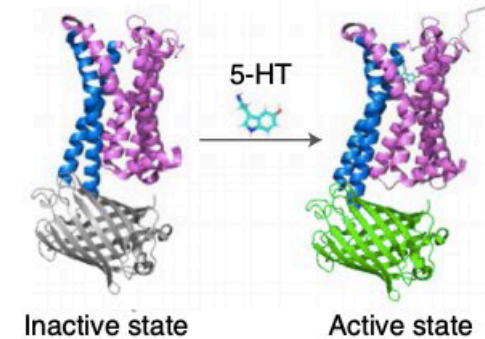
**Novel object interaction**



### 3. Fiber photometry experiments:

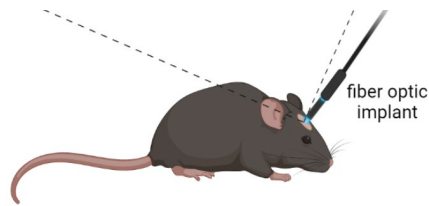
Use of GRAB 5-HT1.0 for alternative recording method due to low axon terminal expression of FN

HTR2C receptor

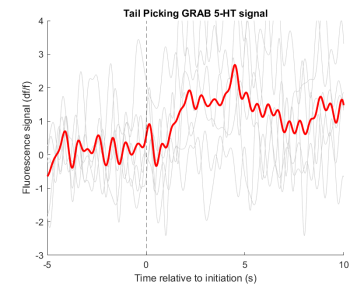
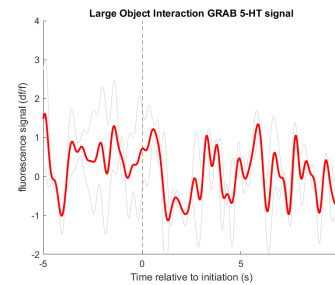
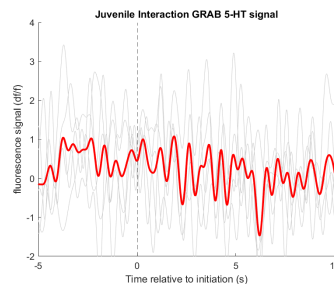
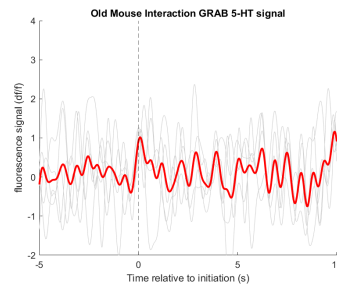
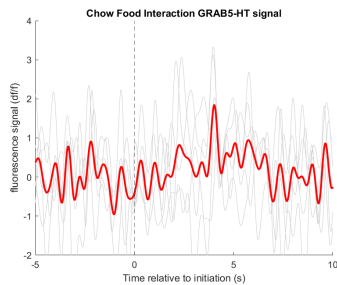
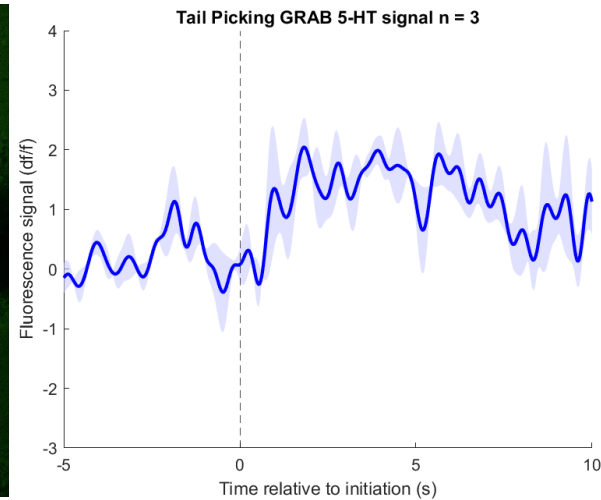
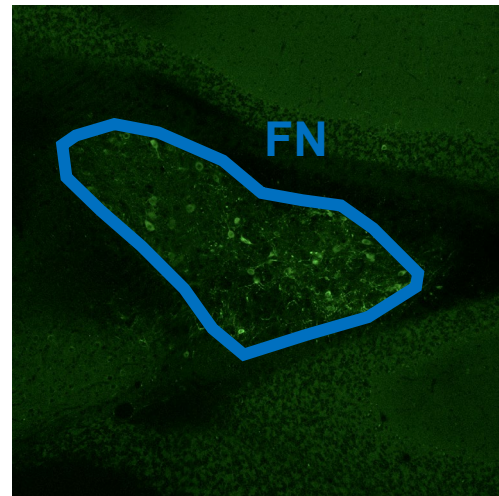


# 3. Fiber photometry experiments:

Use of GRAB 5-HT1.0 expressed on FN



GRAB soma recording  
from FN  
(B6J wt)

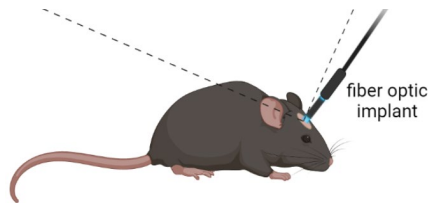




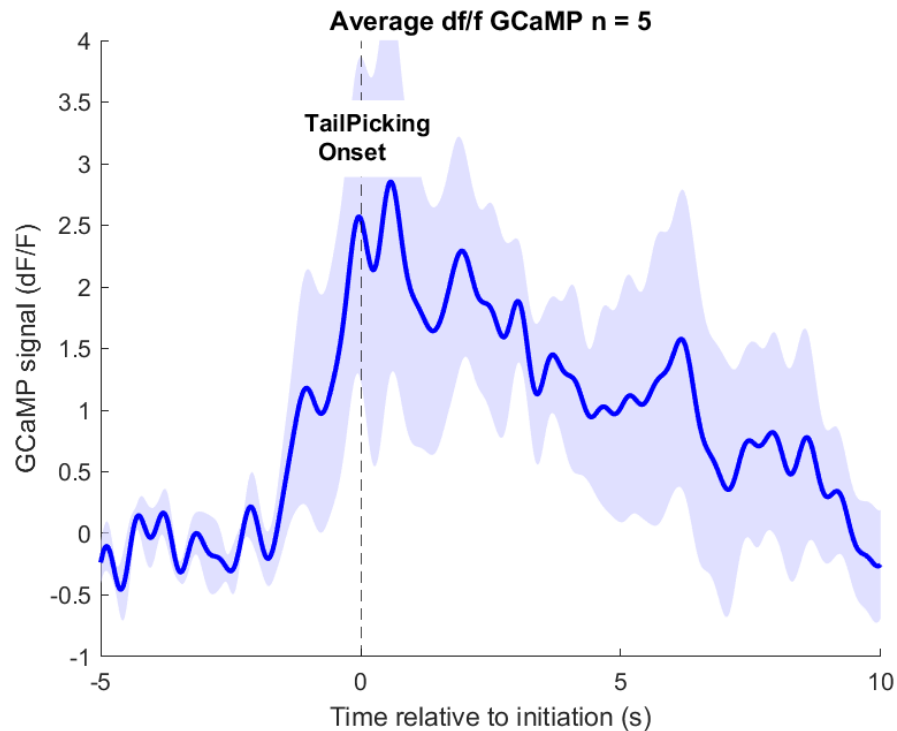
### 3. Fiber photometry experiments:

Soma recording from DRN by retrogradely expressing AAV9-DIO-GCaMP6s from Fastigial Nucleus

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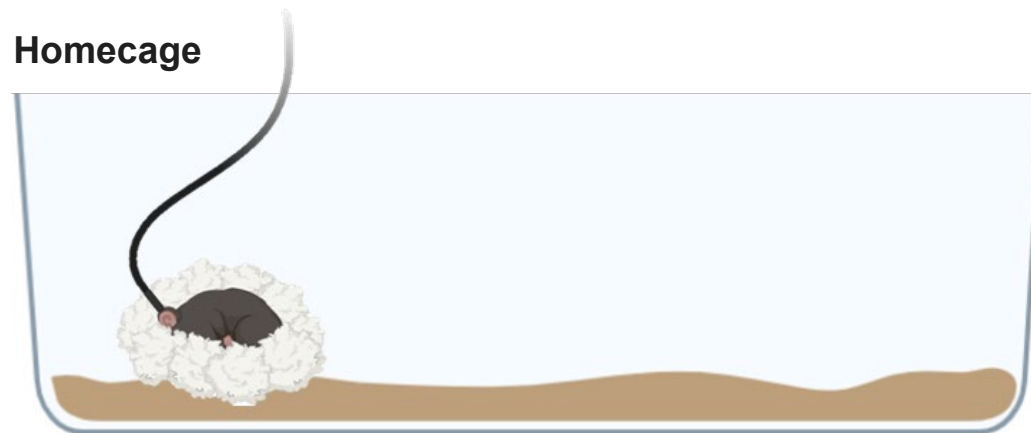
DRN neurons projecting to  
fastigial nucleus  
(B6J wt)



### 3. Fiber photometry experiments:

Serotonin activity was recording home cage to reduce human interference and measure more “natural” behaviors

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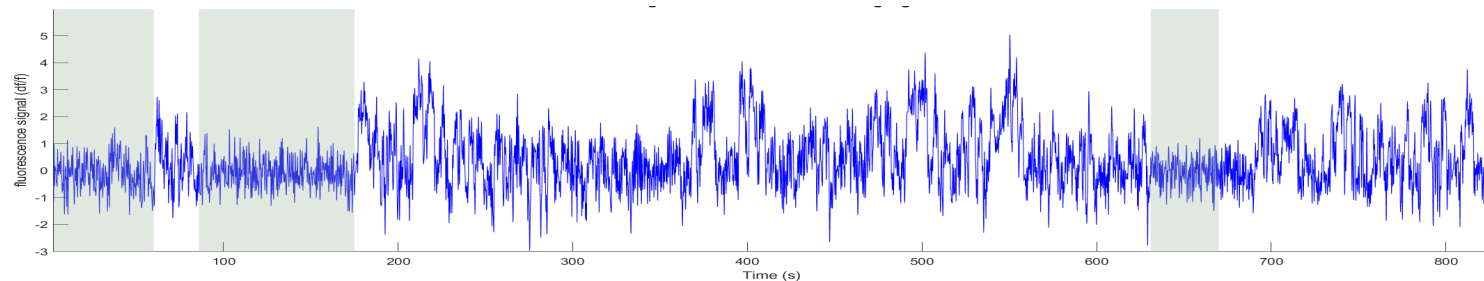
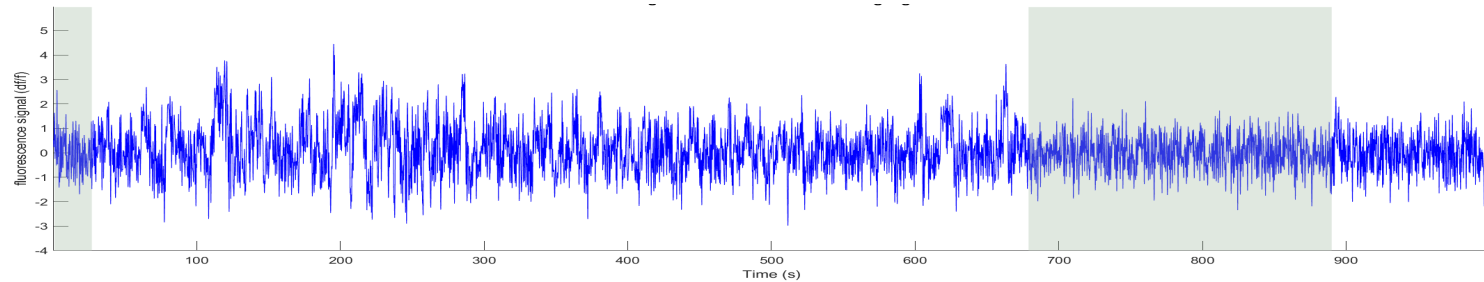
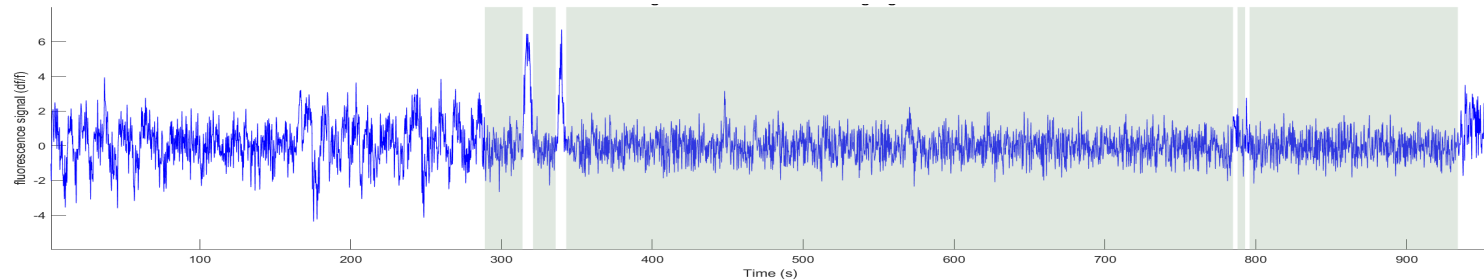
# 3. Fiber photometry experiments:

Serotonin levels decreased in the fastigial nucleus during sleep periods

Homecage



Sleeping periods in gray



# Outline

## 1. Conducted Experiments

1. Circuit tracing and cell population

2. Chemogenetic study

3. Fiber photometry study

Result: Serotonin released in fastigial nucleus at tail picking session might come from DRN neurons.

## 2. Future Experiments

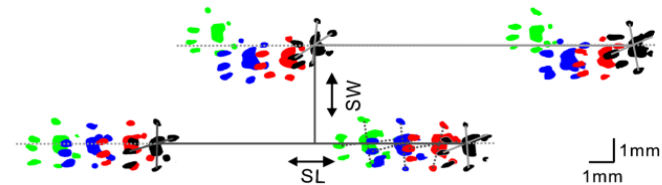
### Questions:

1. Could serotonin that regulates motor control from the DRN? Likely!
2. What information do these serotonergic neurons encode? Valence? 😊

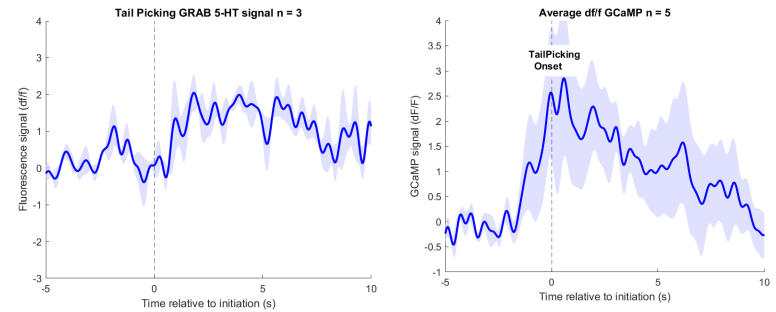
# Summary:

DRN neurons release serotonin to the fastigial nucleus for motor control during awake period and tail picking session

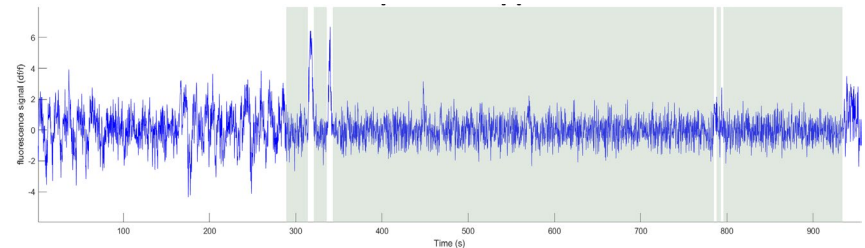
1. DRN activation regulates gait patterns in mice.



2. Serotonin release from the DRN increases in the fastigial nucleus at tail picking.



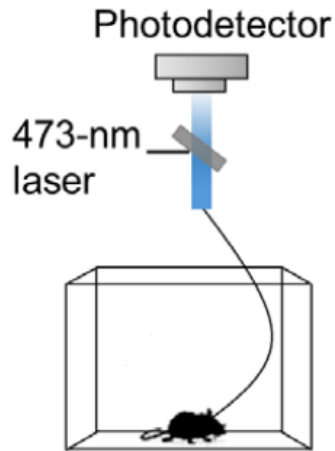
3. Serotonergic activities are silenced during sleep and increased when awake.



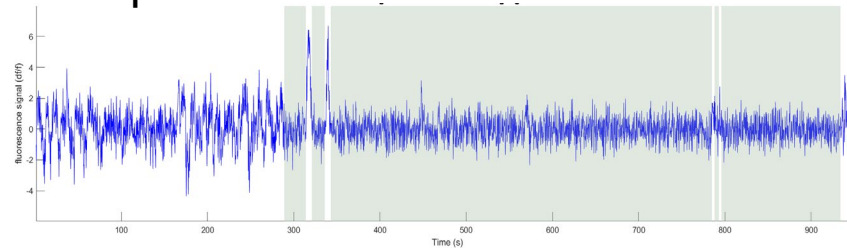
# Future plan:

Further recordings of serotonin activities at the fastigial nucleus are necessary to decipher the information encoded via serotonin for motor control

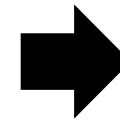
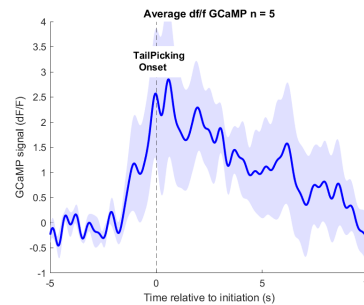
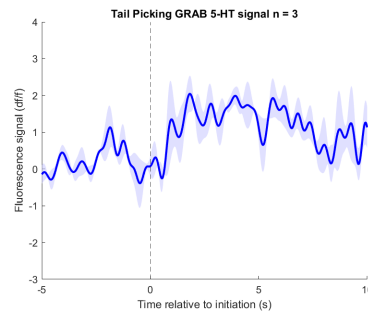
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Sleep < awake



awake < tail picking



Alert?

Arousal?

Threat?

? ? ? ? ? ?





# Acknowledgement

All BI Lab members



Professor  
Daesoo Kim

