# How Brain Circuits Function in Health and Disease: Understanding Brain-wide Current Flow

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Department of Neuroscience, Mt Sinai, New York, USA

**Brain & Behavior Foundation 'Meet the Scientist' Webinar, Feb 9, 2021**

Icahn School of Medicine at Mount Sinai

RAJAN LAB
Brain Research & AI in NY

# Colleagues & Key Collaborators

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Eugene Carter
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Yosif Zaki
Claire Sun

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Christopher Harvey
Sofie Soares
Charlotte Arlt

Icahn School of Medicine at Mount Sinai

Peter Rudebeck
Megan Young

Juri Minxha
Ueli Rutishauser

# Funding sources

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

Young Investigator Award

JSMF

Understanding Human Cognition Scholar Award

ALFRED P. SLOAN FOUNDATION 1934

Research Fellowship

NSF

FOUNDATIONS Award

NIH National Institutes of Health

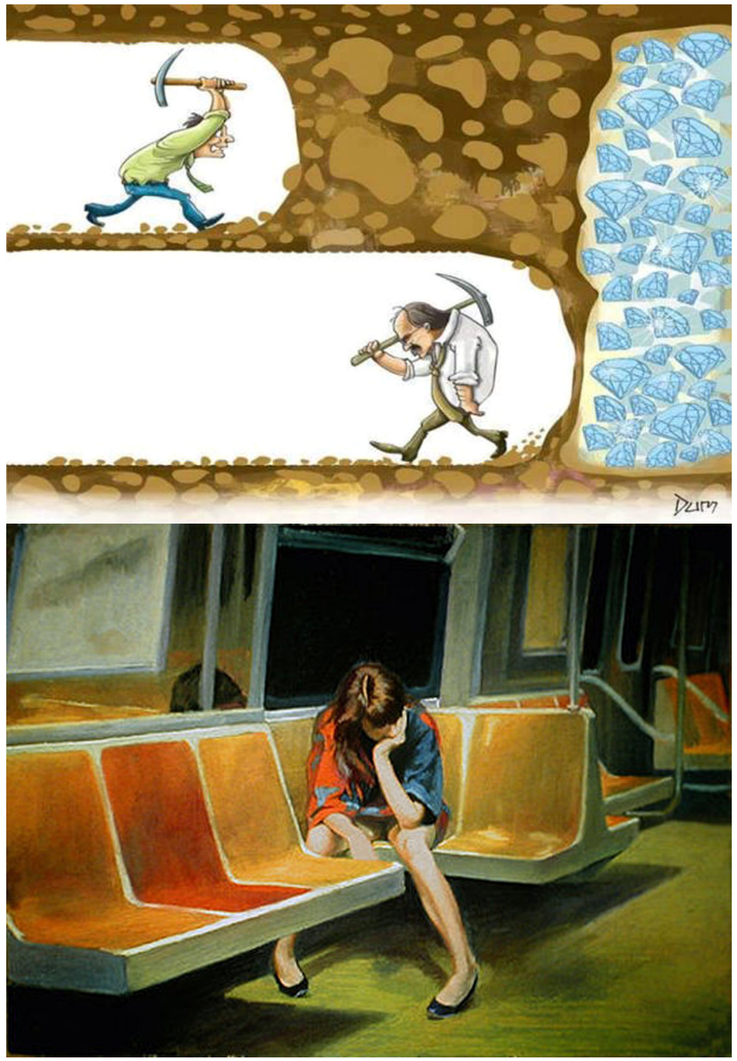
NIBIB

BRAIN Initiative R01CB028166-01

Di Sabato Foundation Award

Dyal Foundation Award

# Behaviors involve evaluating whether actions are worth the effort

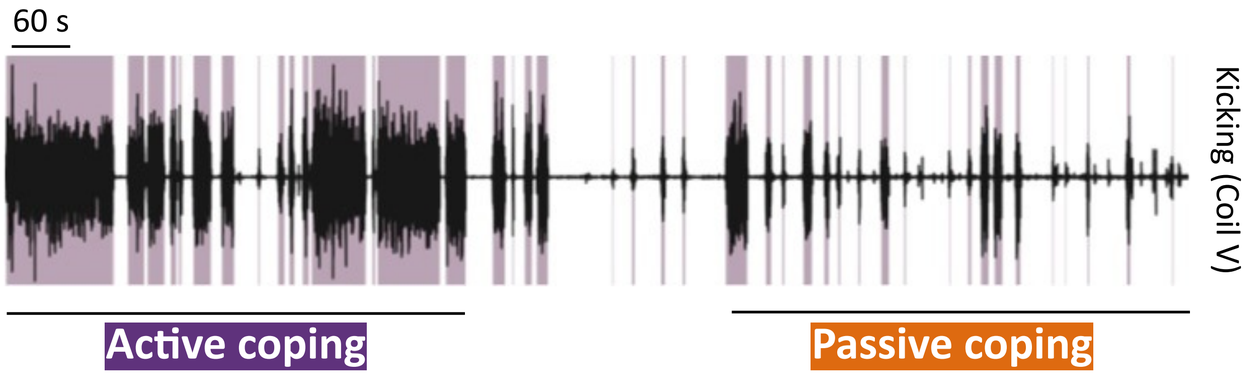


**Hopelessness** “Q Train” Nigel Van Wieck, 1990

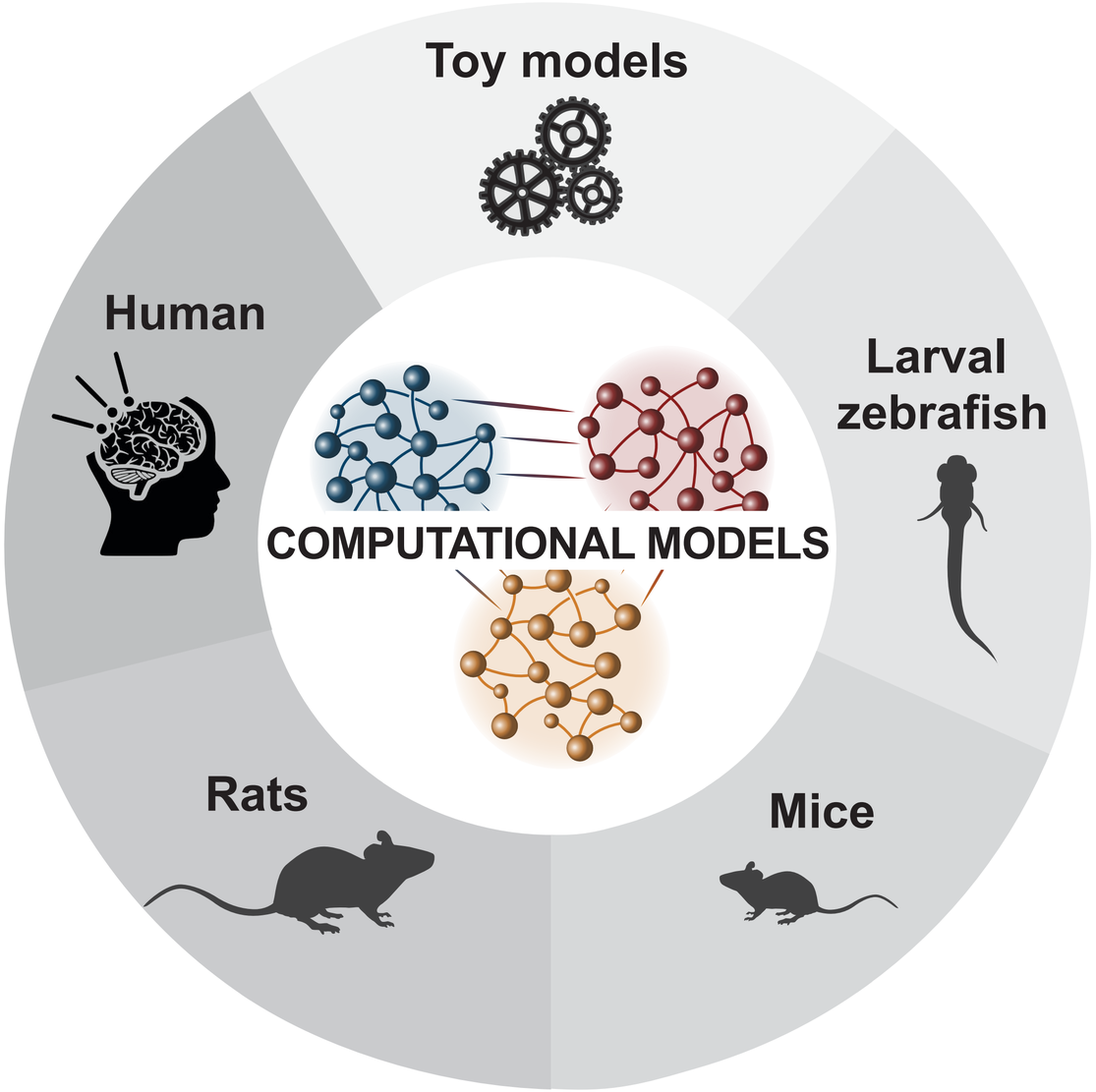
# Hopelessness is seen in many experimental settings involving persistent stress

## Forced swim paradigm

## Behavioral response to adversity



# Are any circuit mechanisms conserved (+ where they diverge)?




## My approach is to build <u>Neural Networks</u>

1. constrained **directly** by experimental data, and
2. analyze them using **new methods** and similar ones as those used on data
3. infer circuit mechanisms inaccessible from measurements


<u>Neural dynamics-level RNNs:</u> *Perich & **Rajan**, CoNEUR, 2020; Andalman, … , **Rajan**, and Deisseroth, Cell, 2019; **Rajan**, Harvey and Tank, Neuron, 2016*

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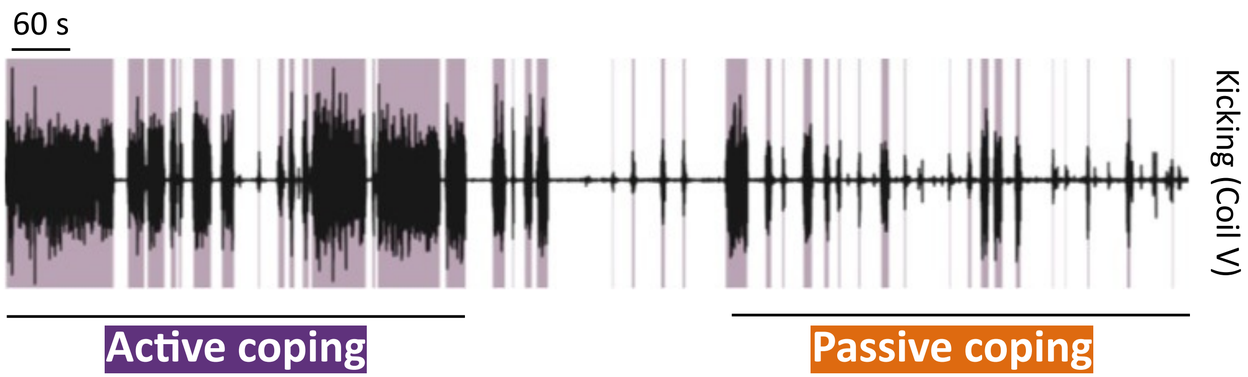
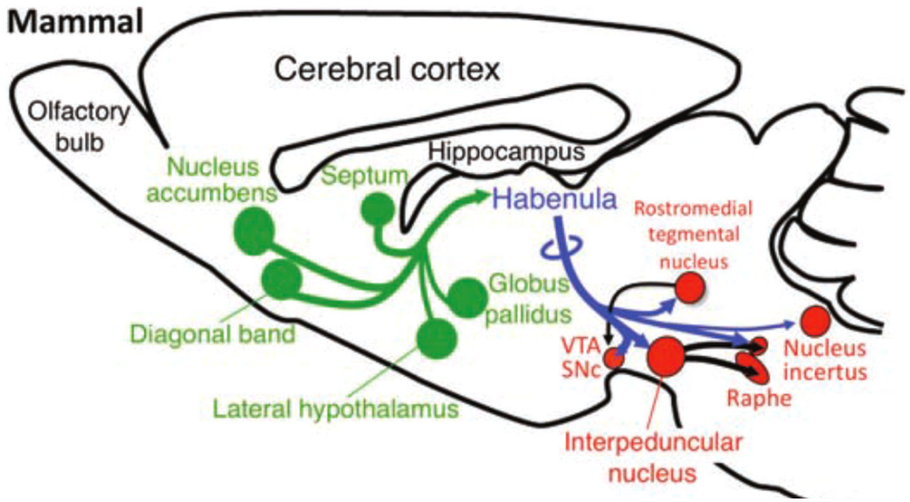


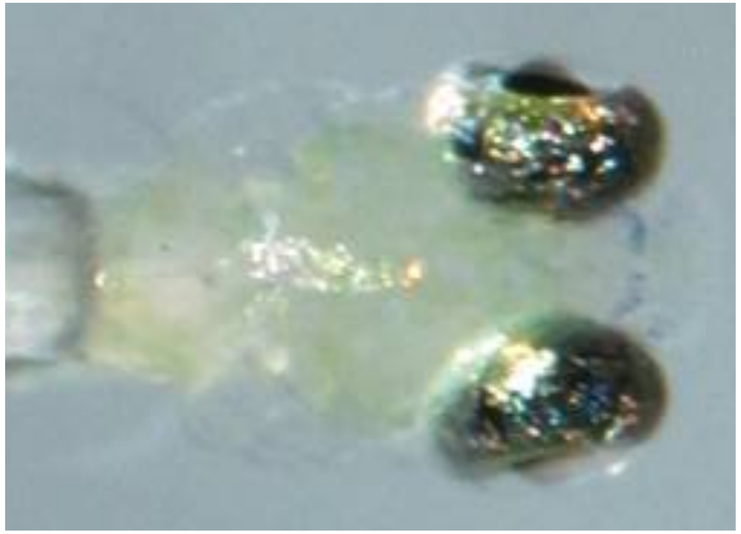

## Mouse neurobiology in passive coping and similar states

***mPFC***: Warden et al., 2012; Hamani et al., 2010; Maier and Watkins, 2010
***Septum***: Singewald et al. 2010; Anthony et al., 2014
***NAc***: Shabel et al., 2012; Stephenson-Jones et al., 2016
***PAG***: Bandler et al., 2000
***Hypothalamus***: Wang et al. 2015
***DRN Raphe***: Roche et al., 2003; Yang et al., 2008
***VTA***: Stamatakis et al., 2012; Tye et al., 2013
***Habenula***: Li et al. 2011; Li et al. 2013; Shumake et al., 2004; Dolman et al., 2016

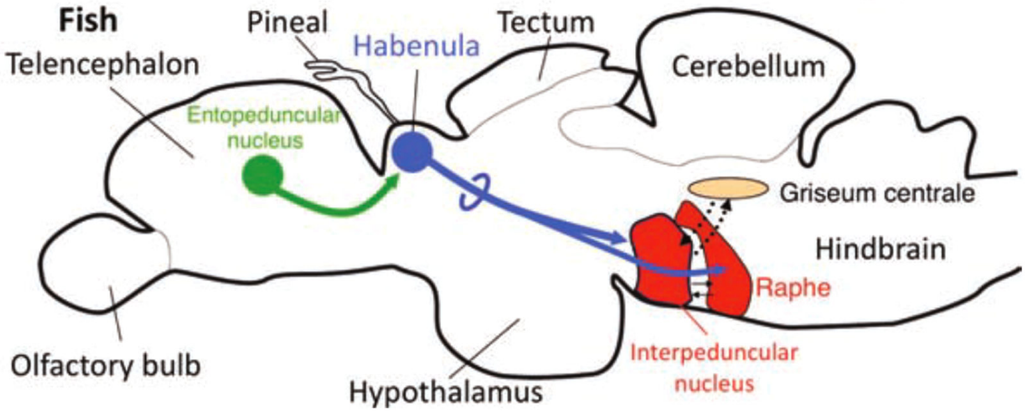


# Extract mechanisms and principles from smaller brains with more access…

## Larval Zebrafish



## Larval zebrafish neurobiology

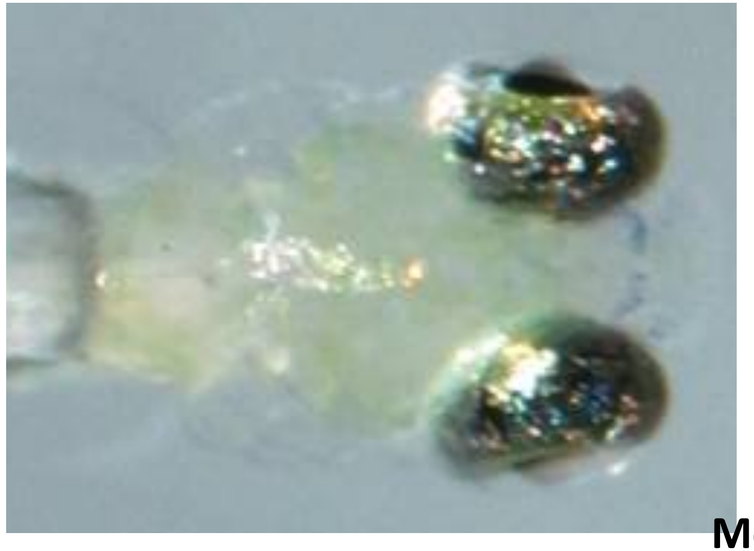



McLean and Fetcho, 2004; Hikosaka, 2010; Amo et al., 2010; Okamoto et al., 2012; Lovett-Baron et al., 2017

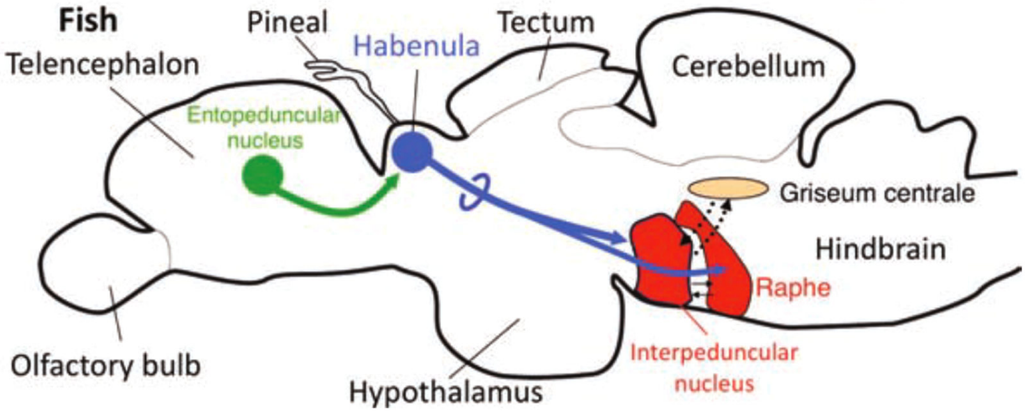
*Andalman, … , **Rajan**, and Deisseroth, Cell, 2019*
All zebrafish data courtesy Deisseroth lab, Stanford

# … scale the approach to larger brains to look for similar or divergent mechanisms

**Larval Zebrafish**



**Homologies with mammalian system**

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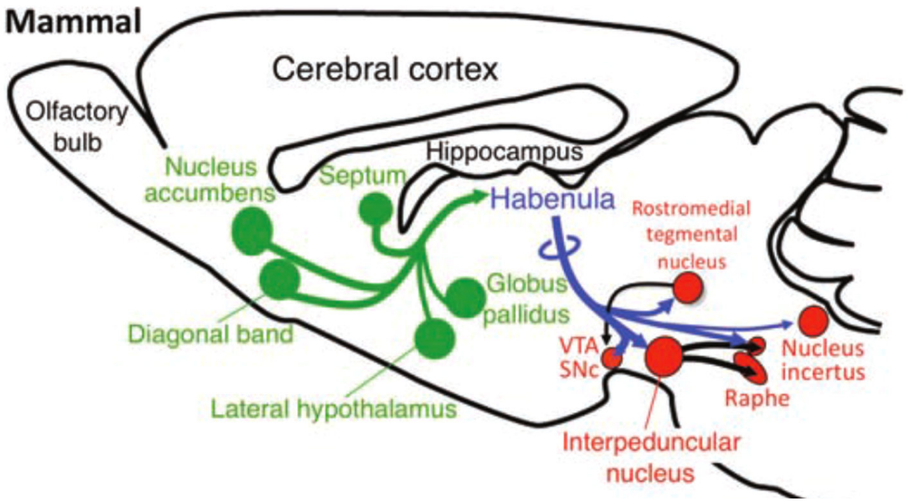


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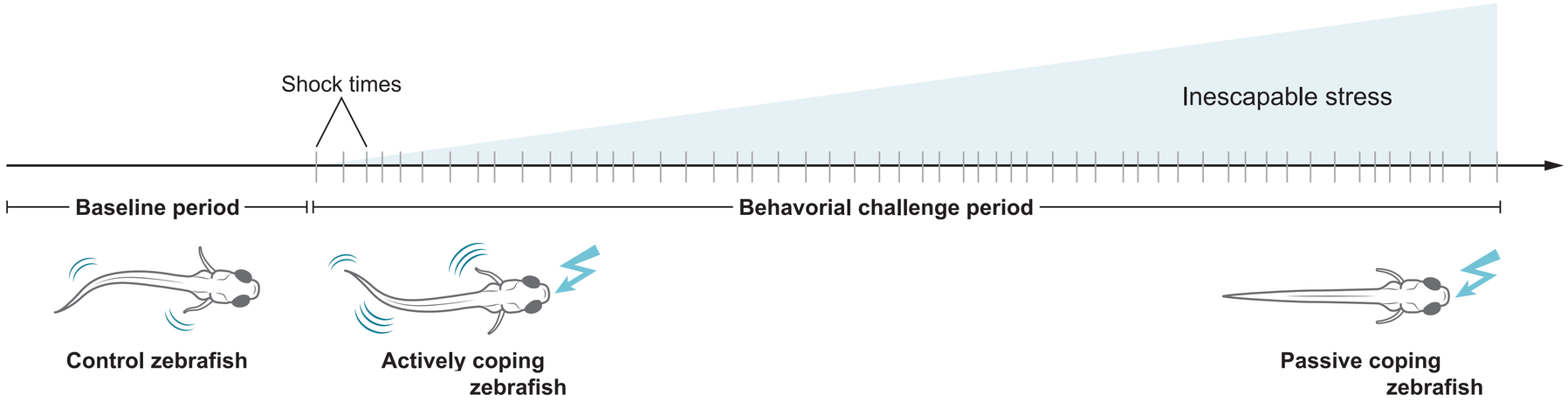
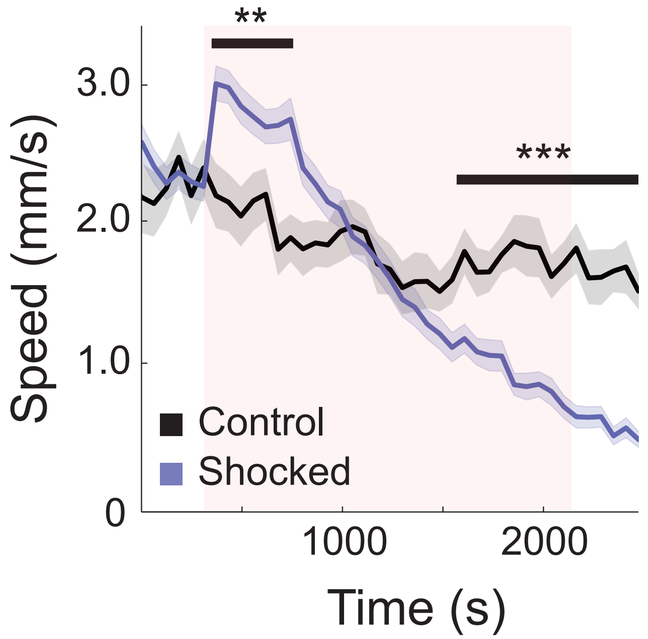
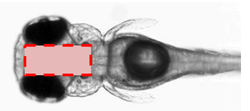
# Tracking of behavior + neural activity brain-wide at cellular resolution

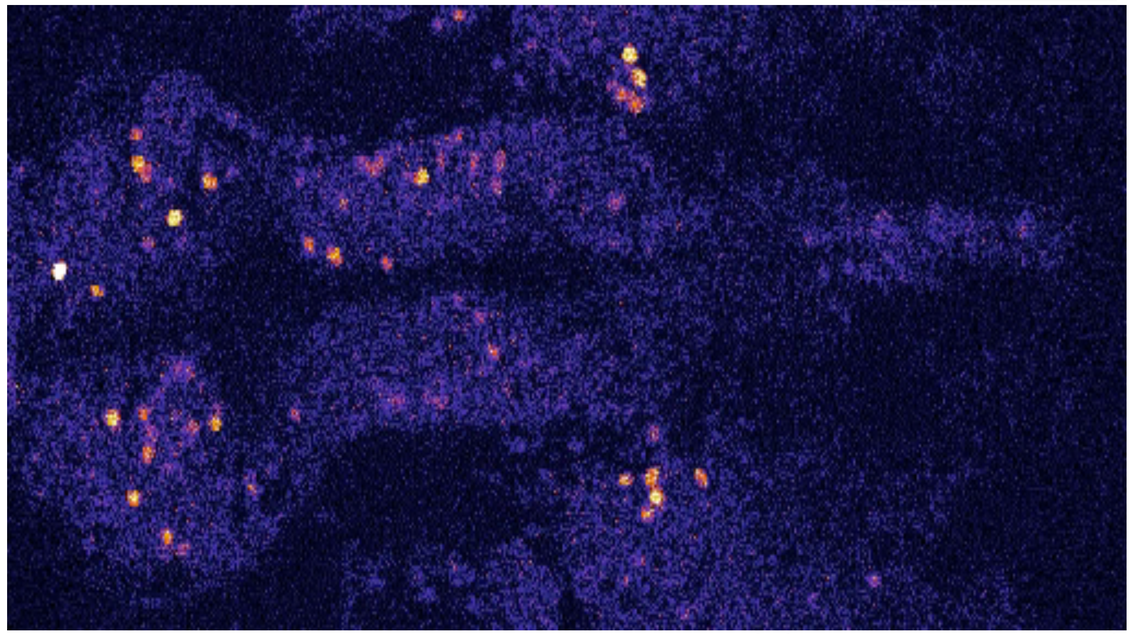



## Tail-whip velocity over time




## Cellular-resolution multi-region imaging





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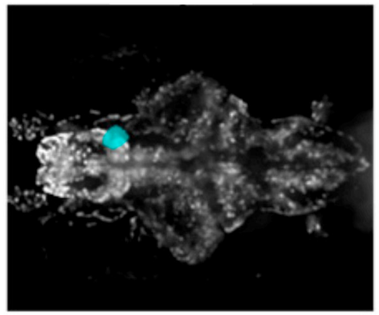
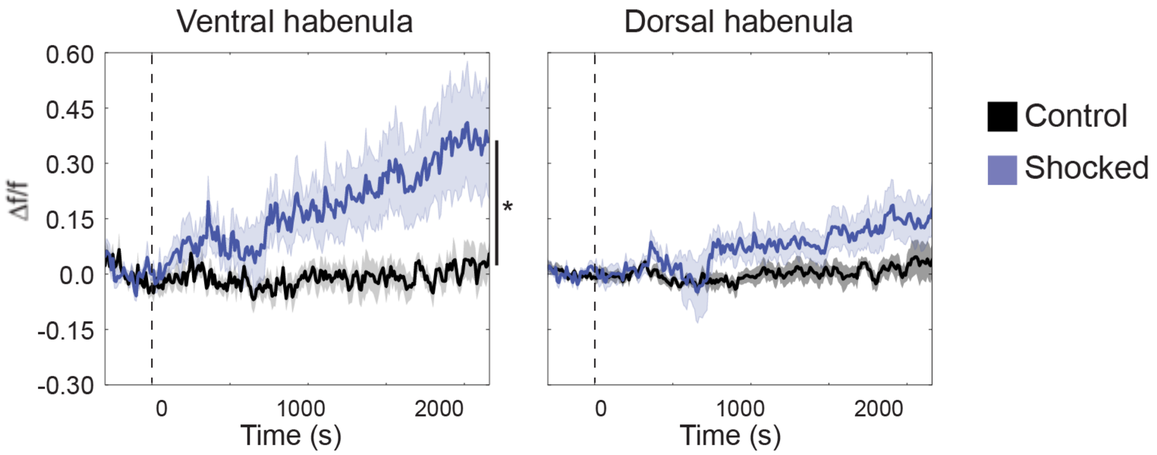
# Main neural findings (population activity) from data

## 1. Steady increase in habenula (Hb) activation



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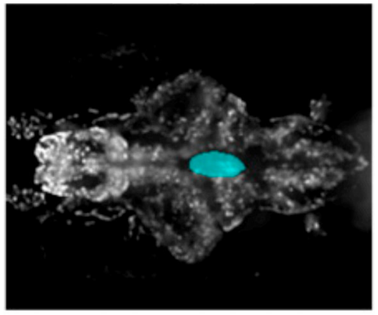

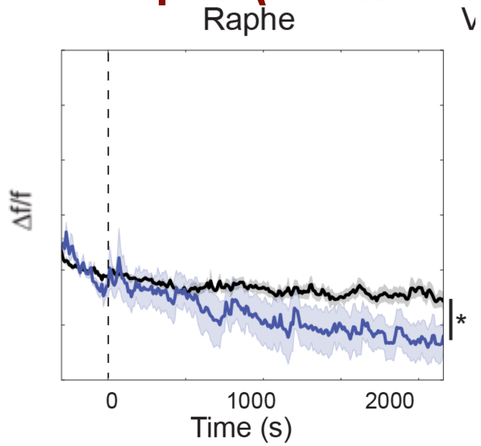


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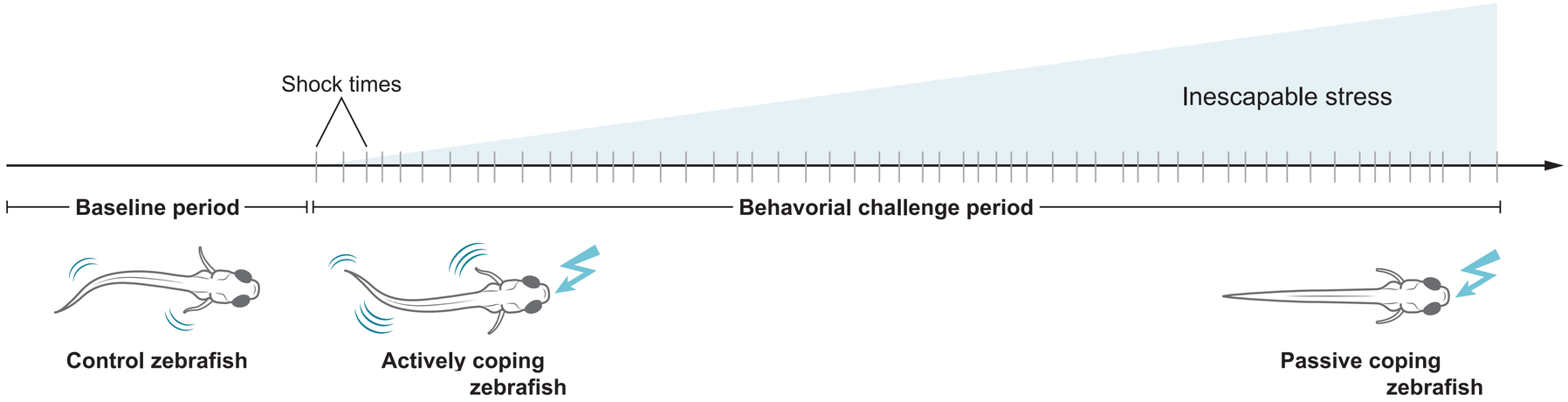


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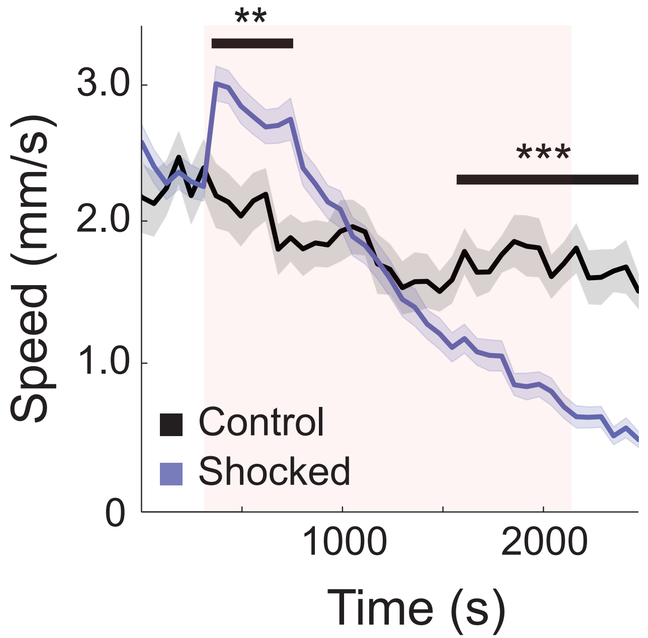


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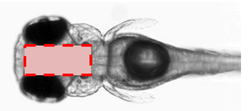

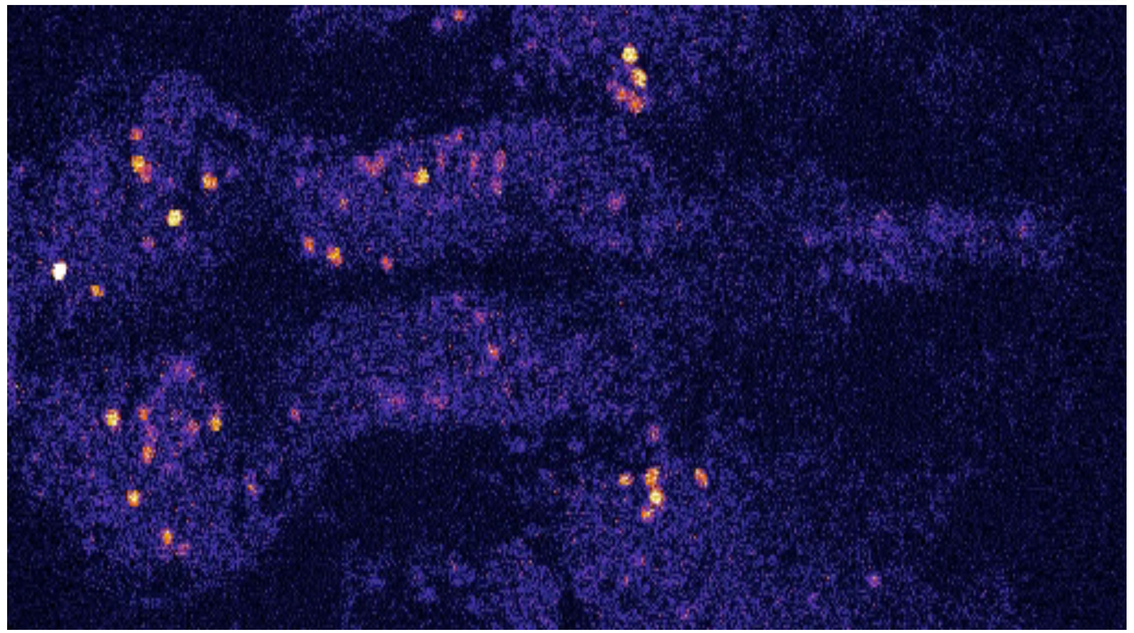

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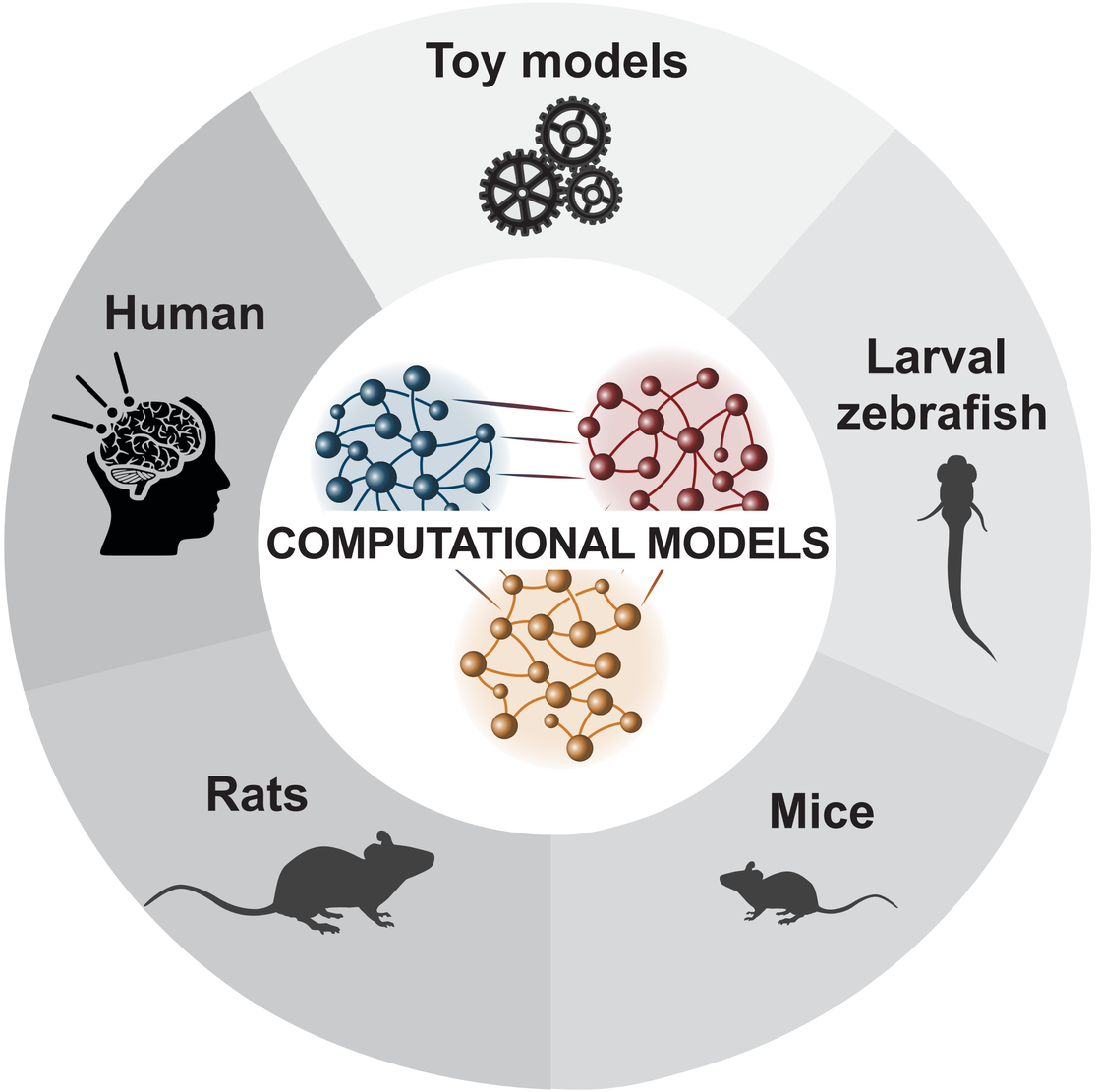
## Question: *What brain-wide mechanism mediates active- to passive coping in zebrafish?*

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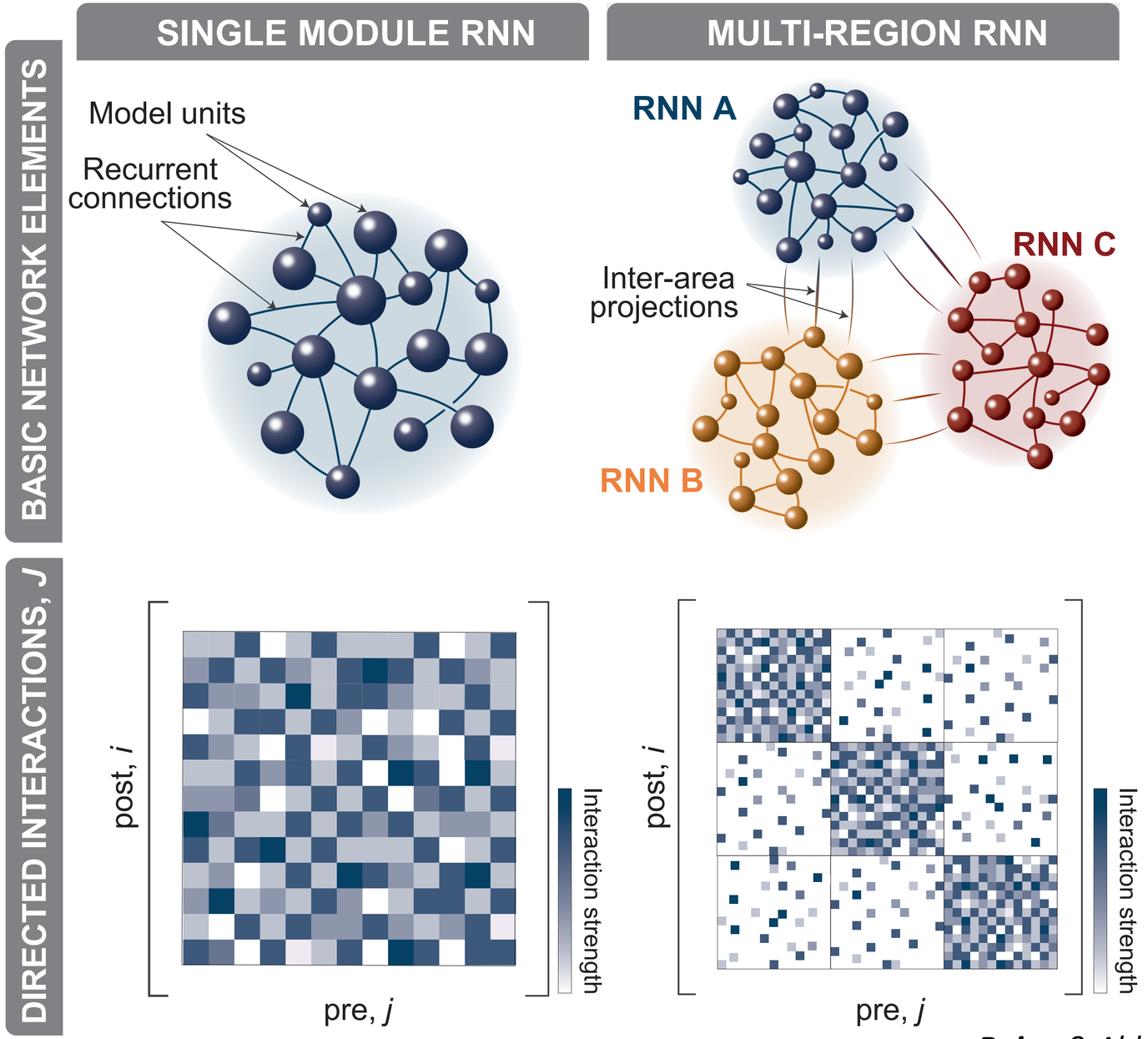
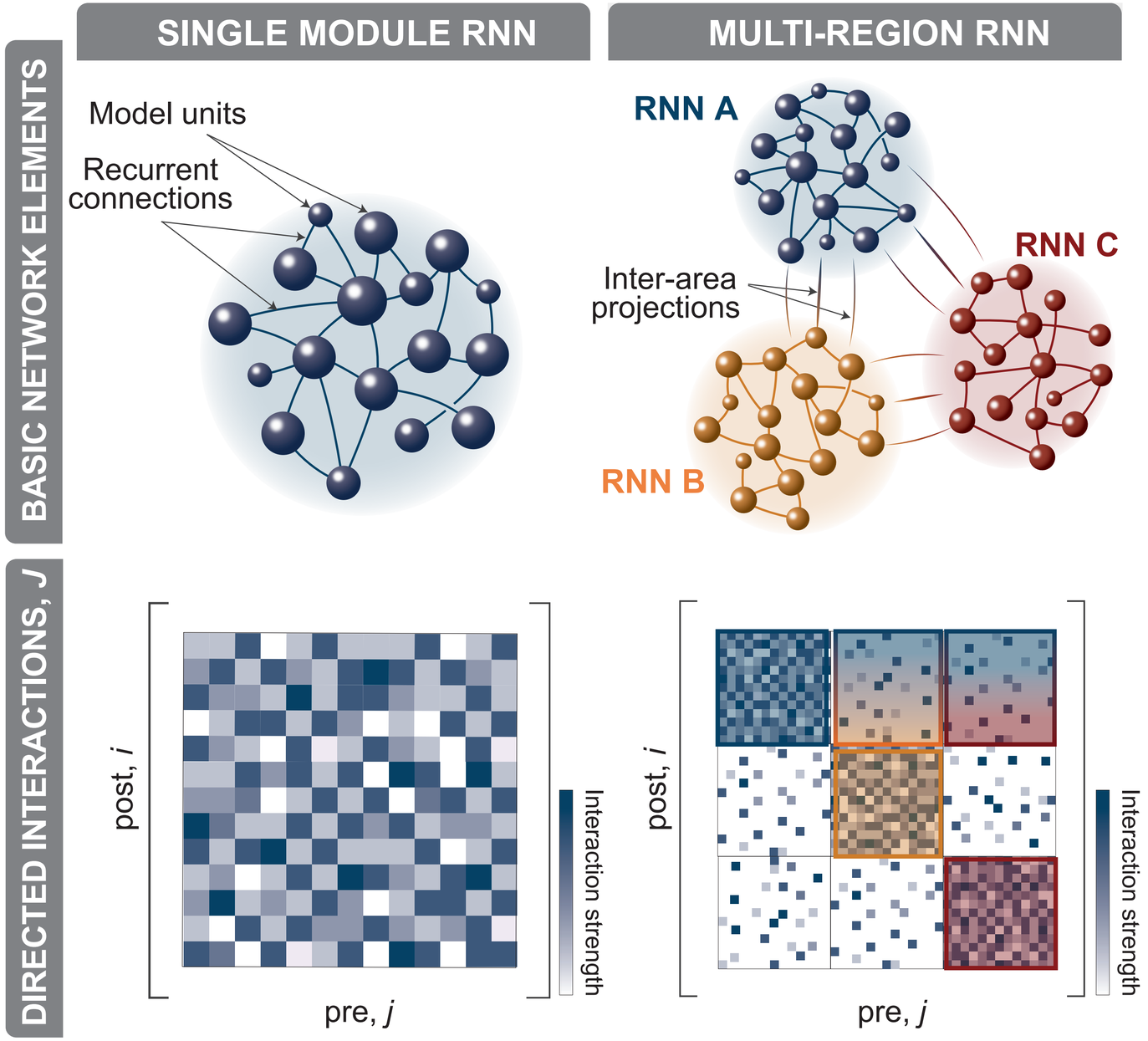
# 1. From single region- to multi-region Recurrent Neural Networks (RNNs)

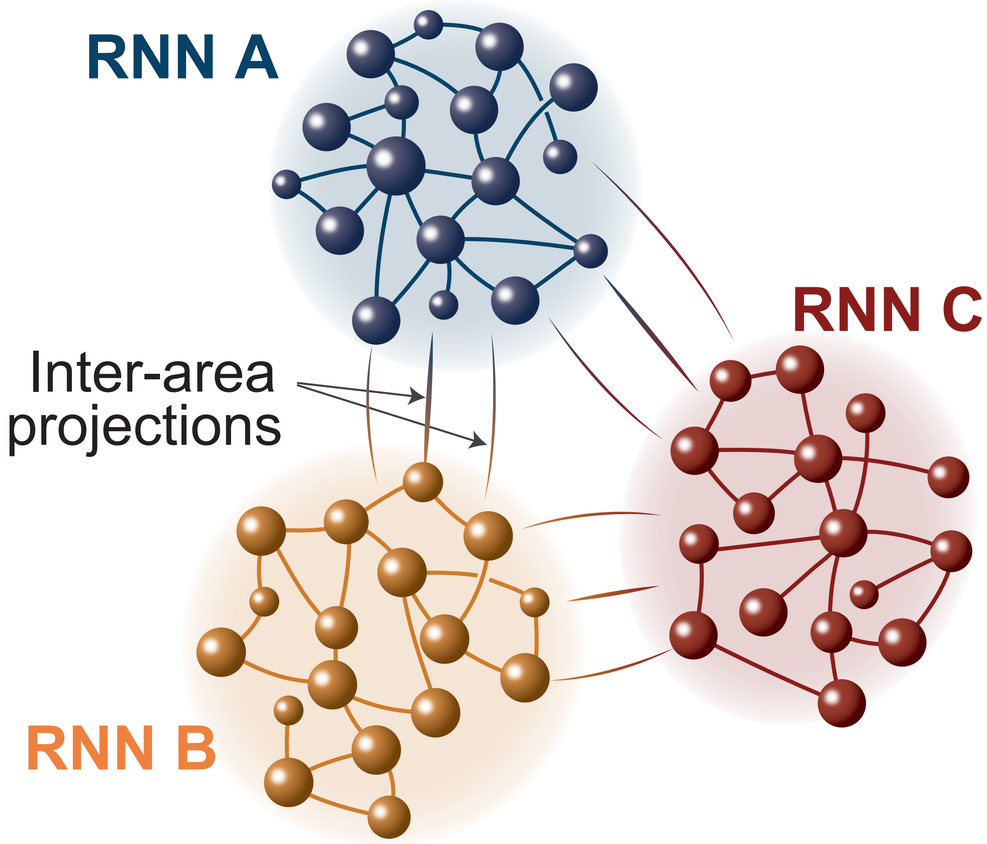



***Rajan*** *& Abbott, with Sompolinsky, 2010a–c, 11*

# Multi-region RNNs capture both *within & inter-area* interactions



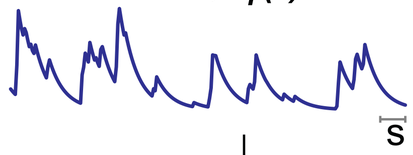
# 2. Train activity of model units to match neural data directly




**Learning algorithm**
**Recursive least squares (RLS)**

activity of unit $i$, $z_i(t)$

target derived from $Ca^{2+}$ data, $f_i(t)$




learning error = $z_i(t) - f_i(t)$

update for matrix $\Delta J_{ij}(t)$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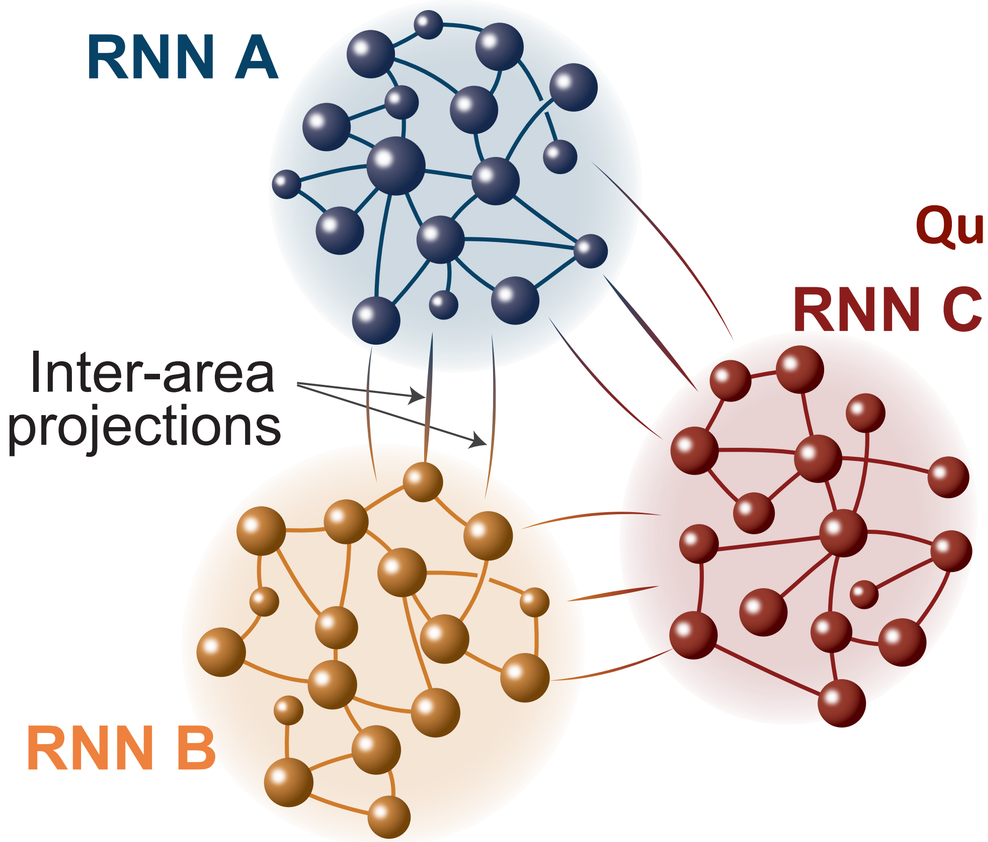
# What we gain from multi-region RNNs constrained directly by data




**Quantities inaccessible from measurements alone!**

1. Multi-region RNN model that produces realistic neural dynamics
2. Inference of consistent brain-wide "directed interactions" ✓
3. Currents due to recurrence ***within*** and ***between*** areas ✓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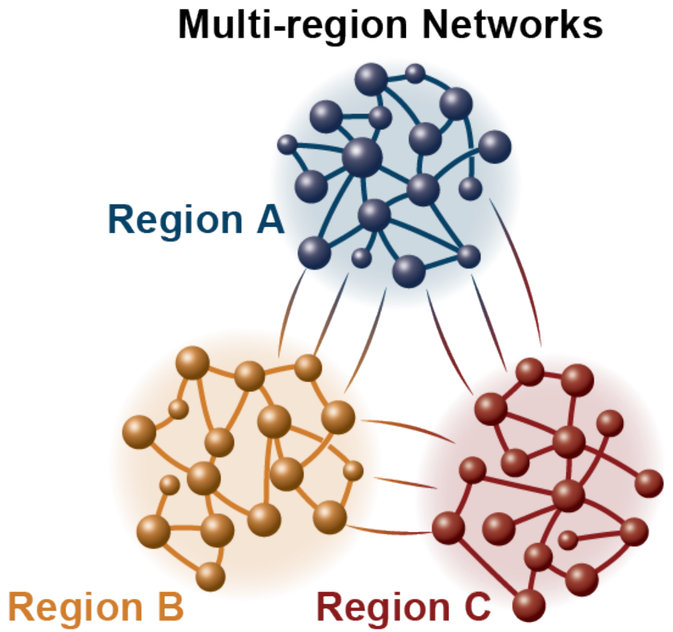
# Current-Based Decomposition of Population Activity (CURBD)




Activations similar to data

Directed Interactions matrix

*Dot product*

Currents due to recurrent interactions

# Question: *Is there a "cortex" in the zebrafish responsible for shutting down movement?*

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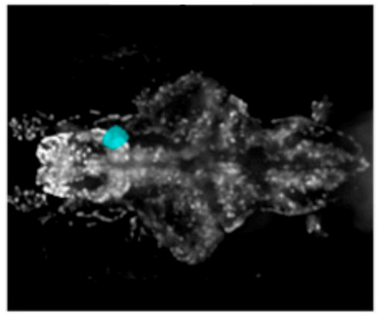

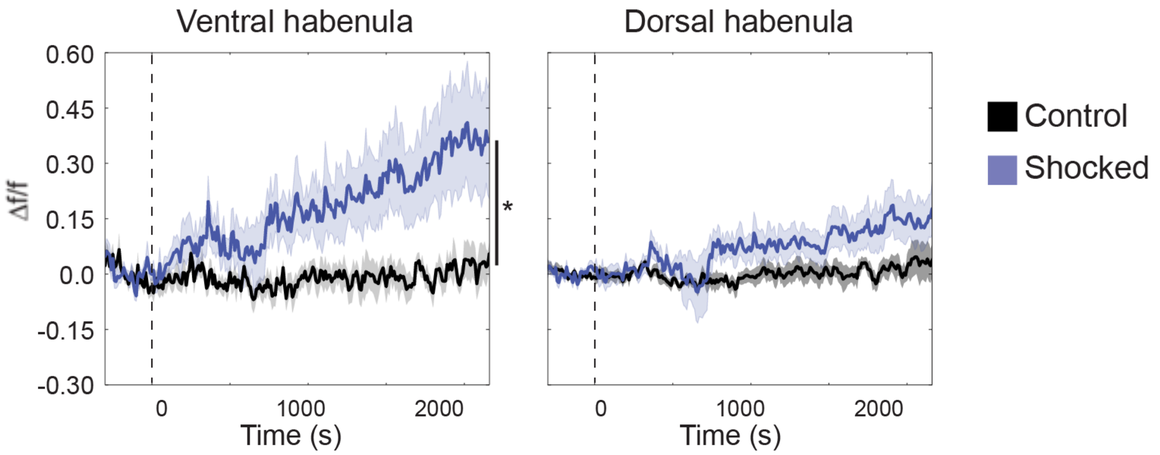


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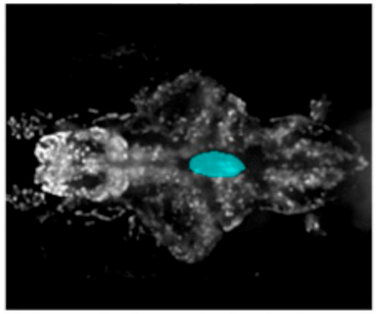
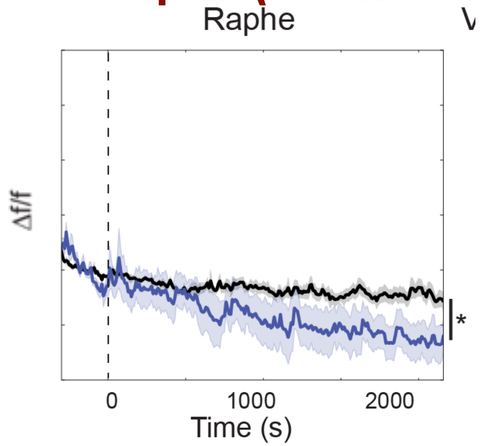
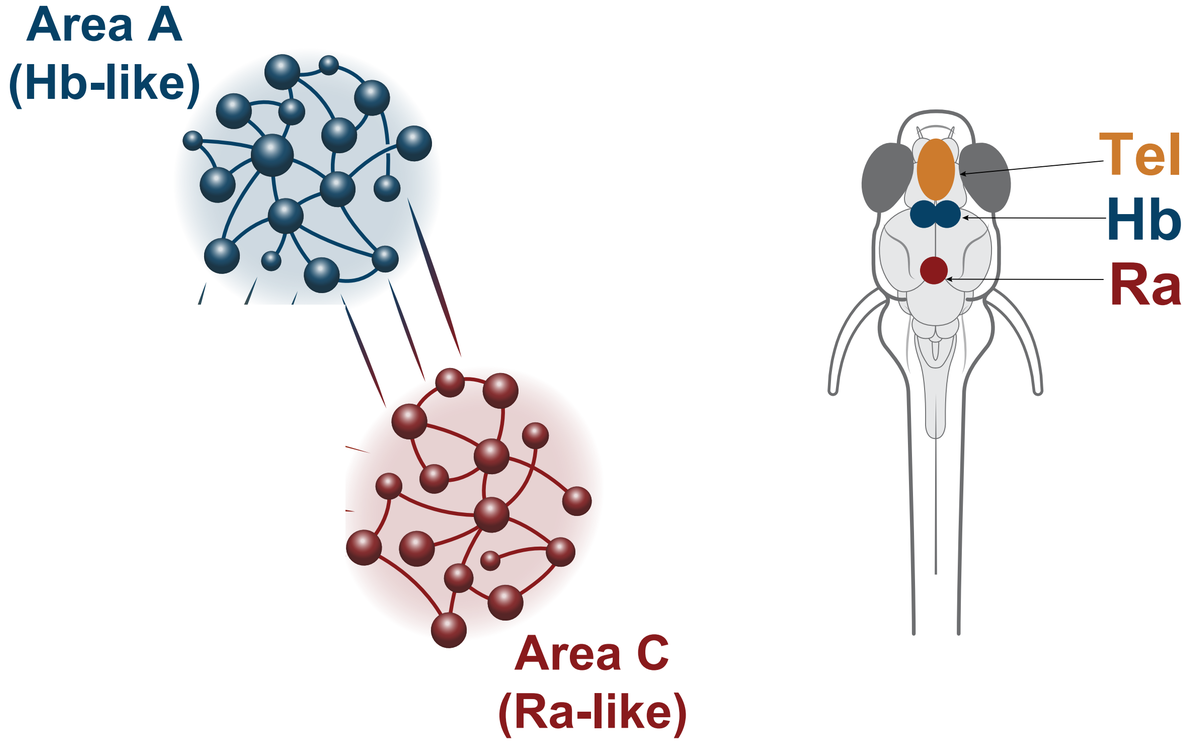


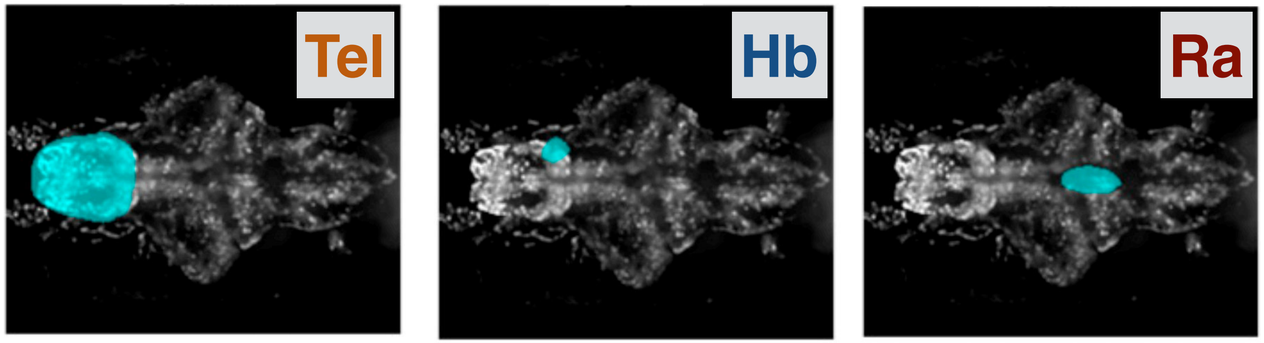



*Andalman, … , **Rajan**, and Deisseroth, 2019*

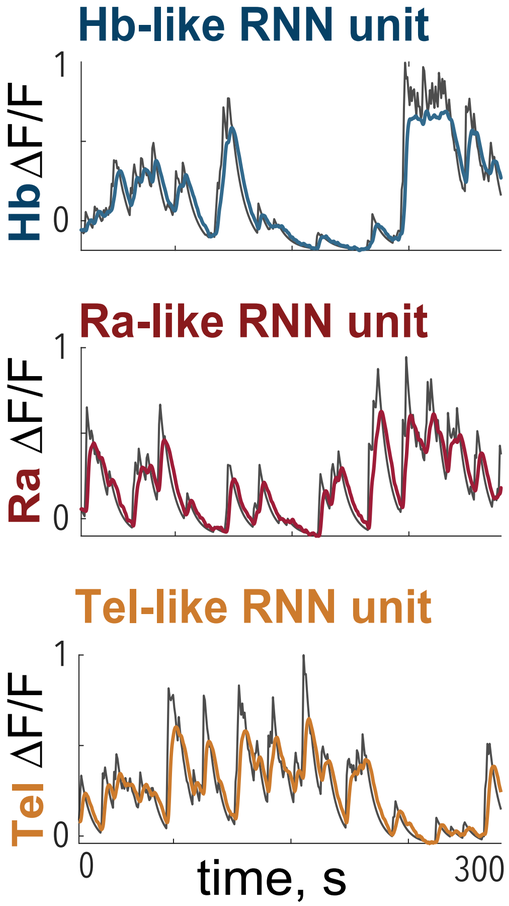
# Three-region RNN model of the neural dynamics in the larval zebrafish

## MULTI-REGION RNN OF LARVAL ZEBRAFISH

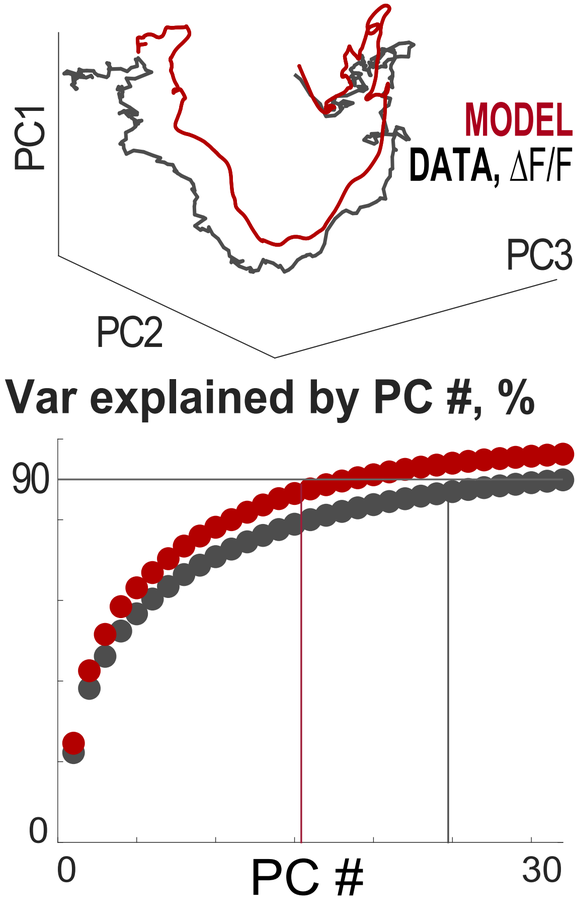



## NEURAL ACTIVITY




## STATE SPACE ANALYSIS



# Looking at currents from the *same* or *different areas* using CURBD

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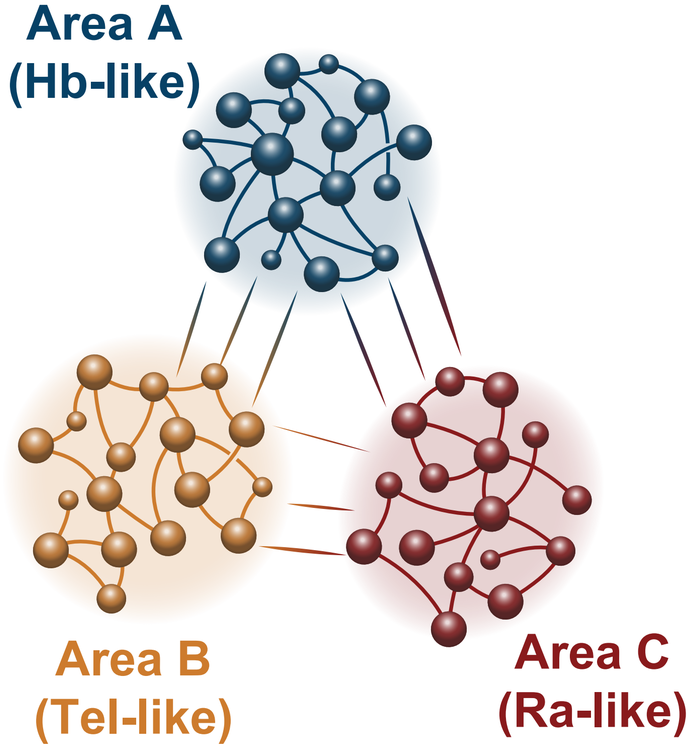
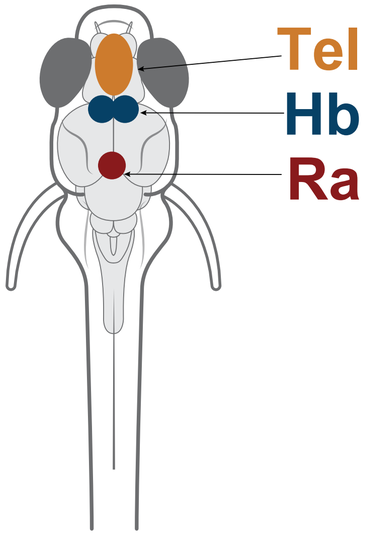
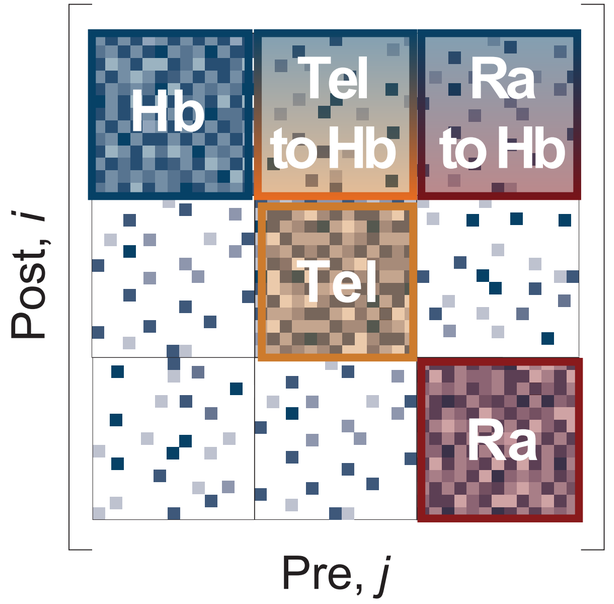
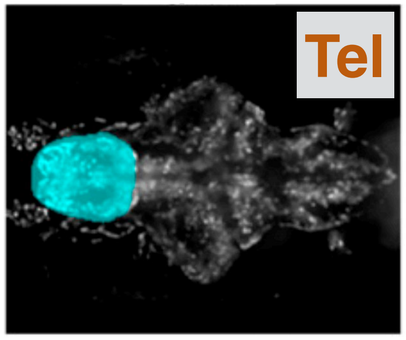
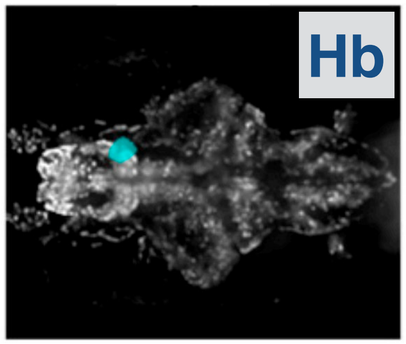
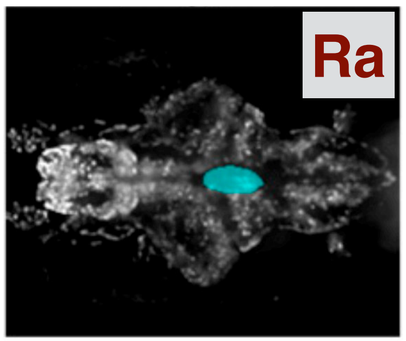



Directed Interactions

●

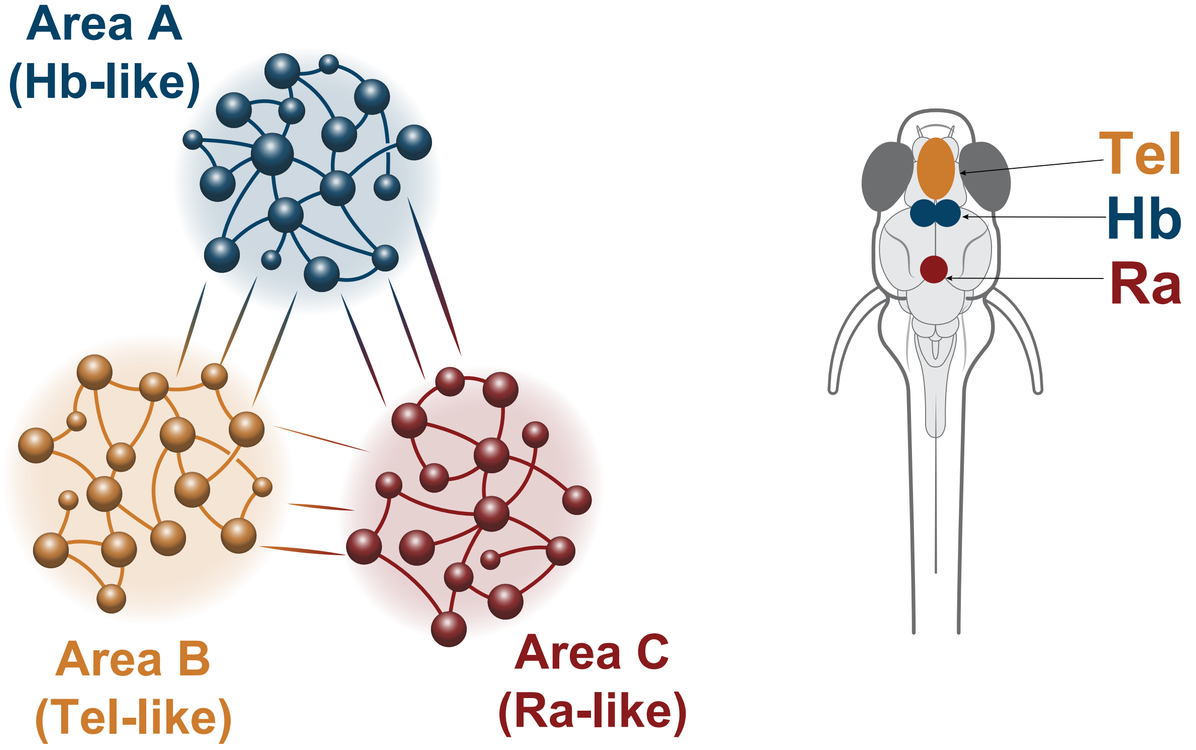
Activity similar to data

*Dot product*

**Currents due to recurrent interactions**

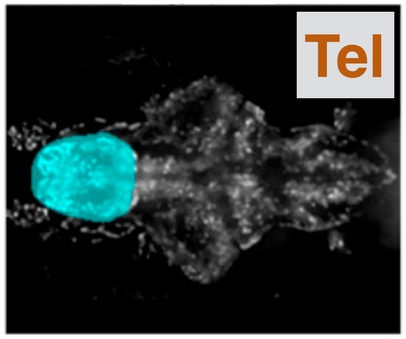
# Currents due to recurrent inputs into the Habenula

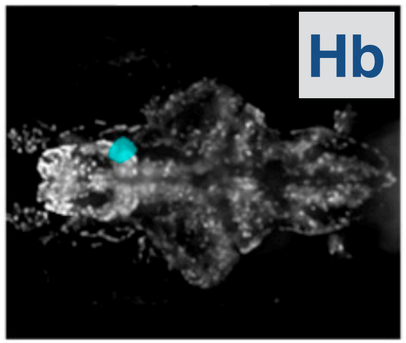
## MULTI-REGION RNN OF LARVAL ZEBRAFISH

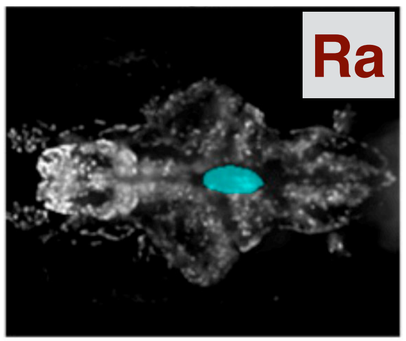




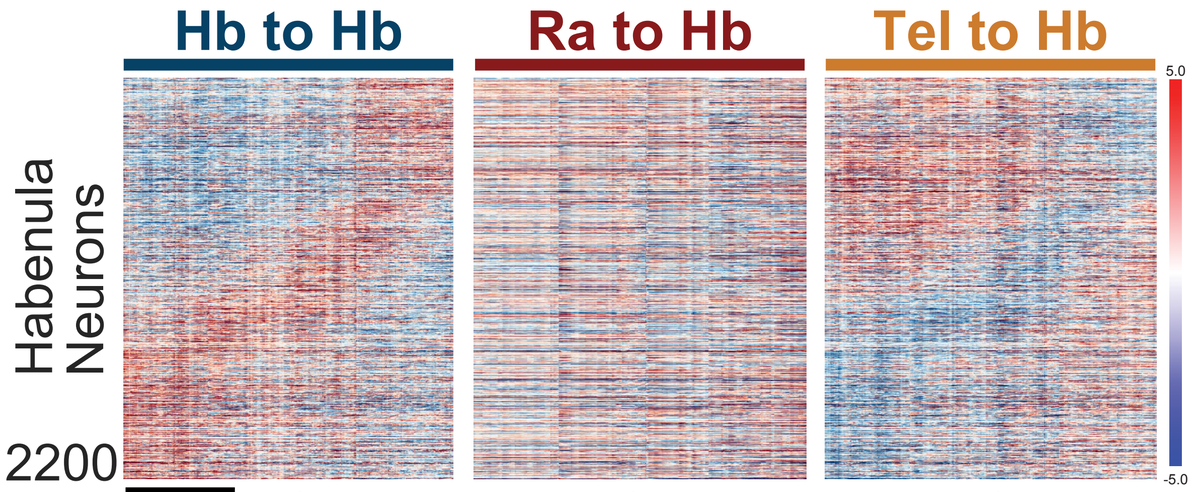





## DEMIXED SOURCE CURRENTS INTO Hb



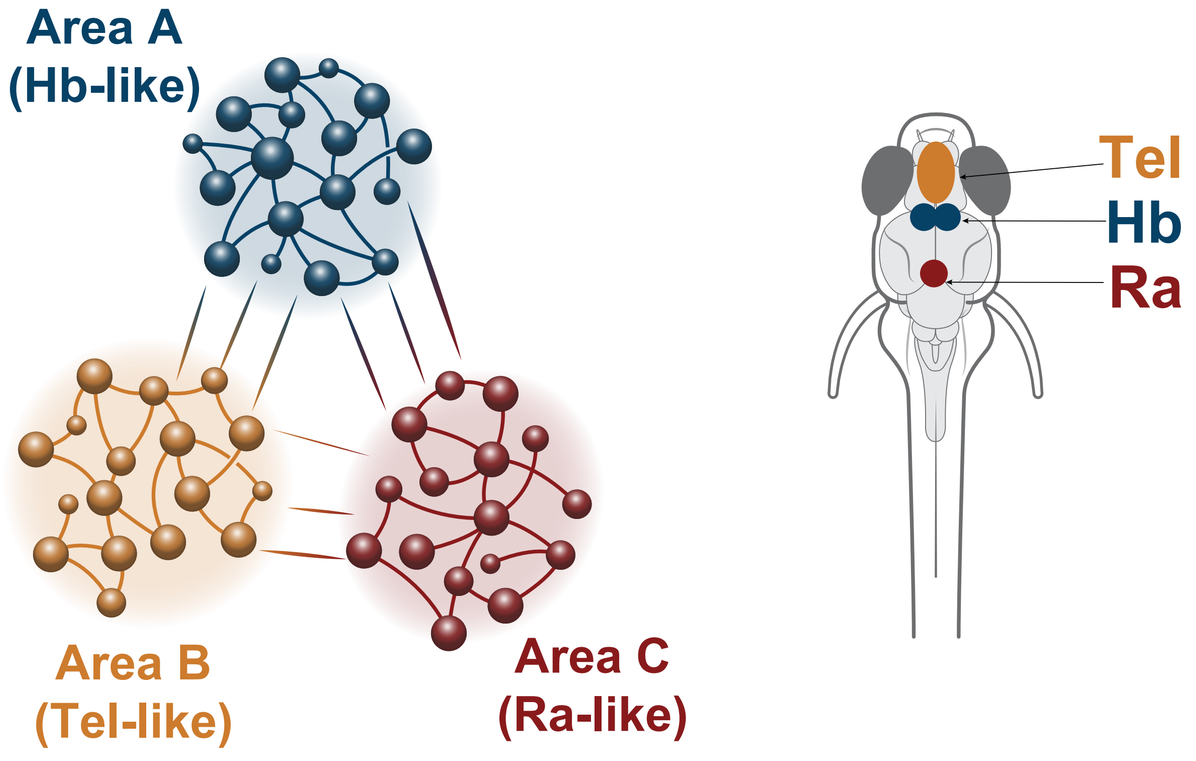

**Within area current**
(Hb activity . Hb-Hb DIs)

**Inter-area current**
(Hb activity . Ra-Hb DIs)

**Inter-area current**
(Hb activity . Tel-Hb DIs)

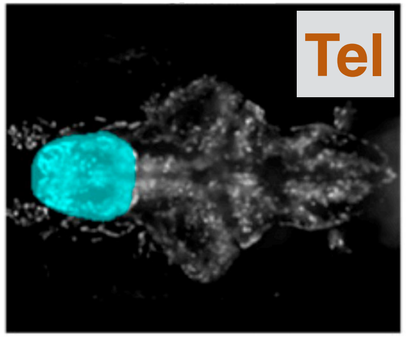
# Currents due to recurrent inputs into the Habenula add up to the measured output

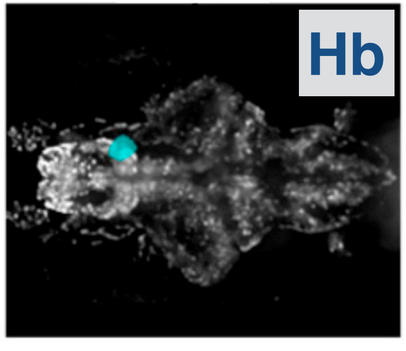
## MULTI-REGION RNN OF LARVAL ZEBRAFISH

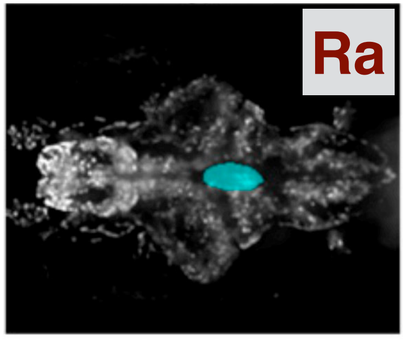




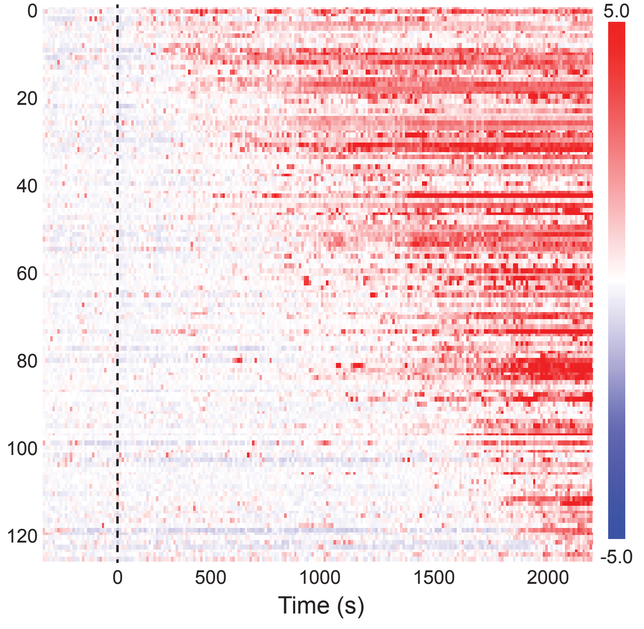




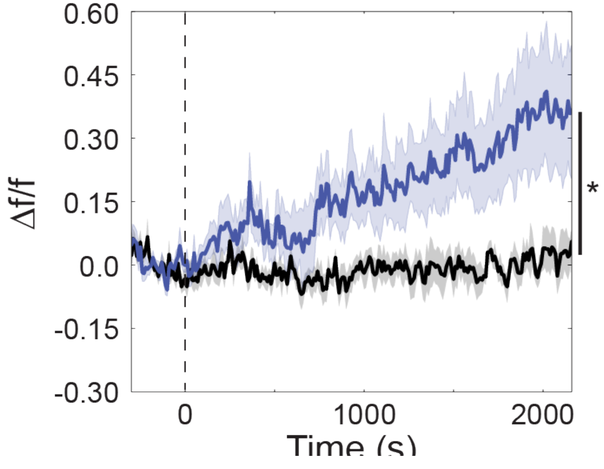




## 1. Activity in Habenula

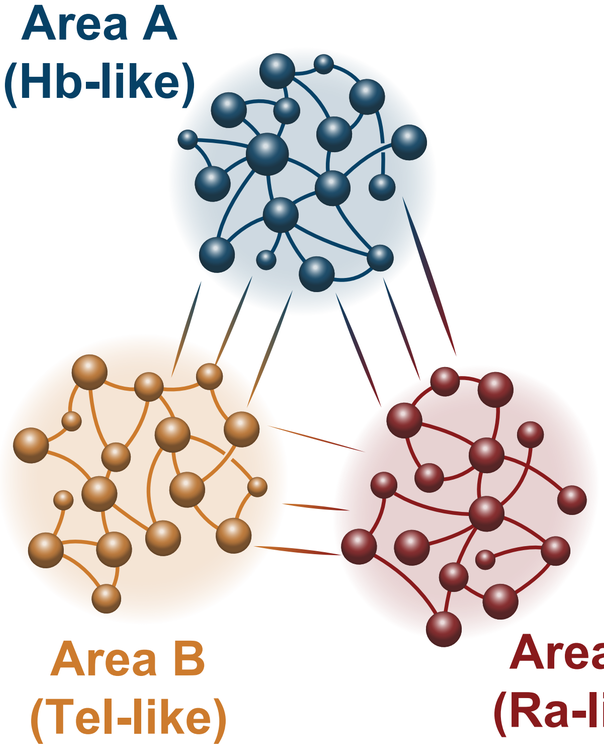


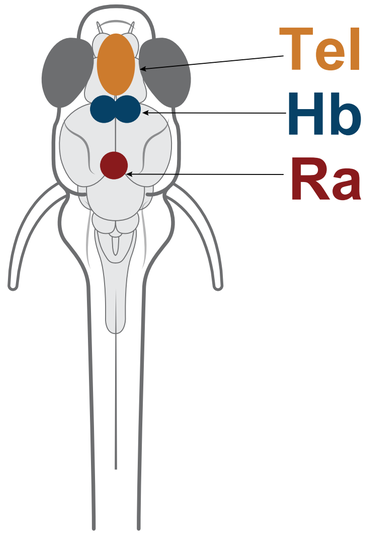

## 2. Average population activity

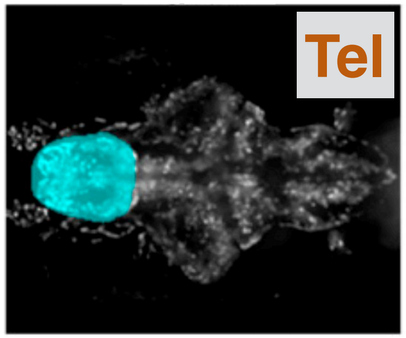


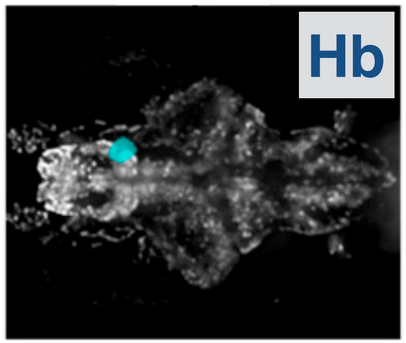
# State space view of how the three source currents evolve…

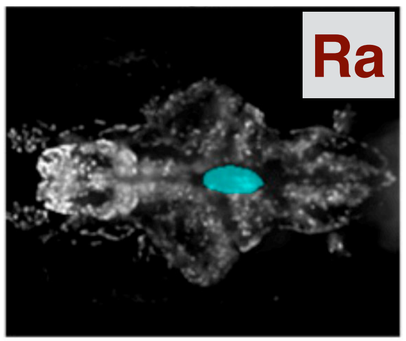
## MULTI-REGION RNN OF LARVAL ZEBRAFISH



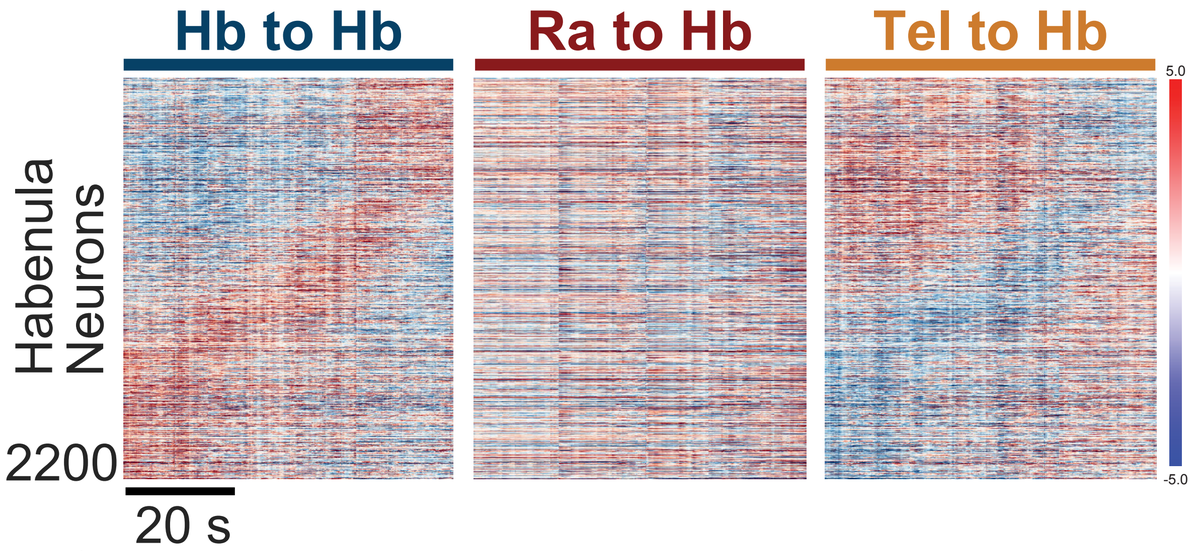



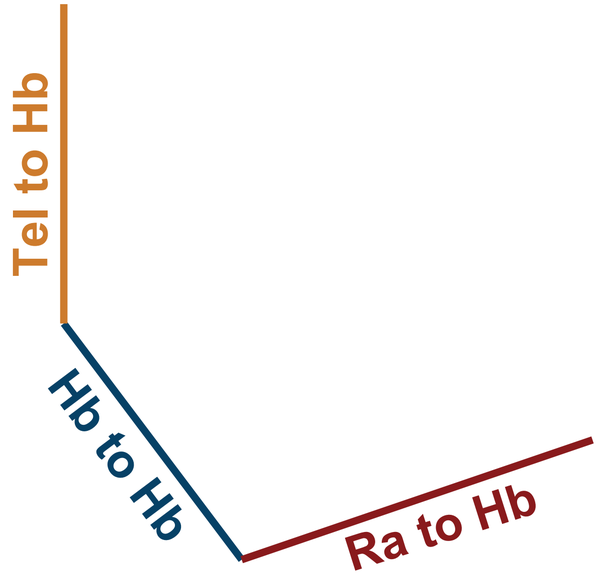



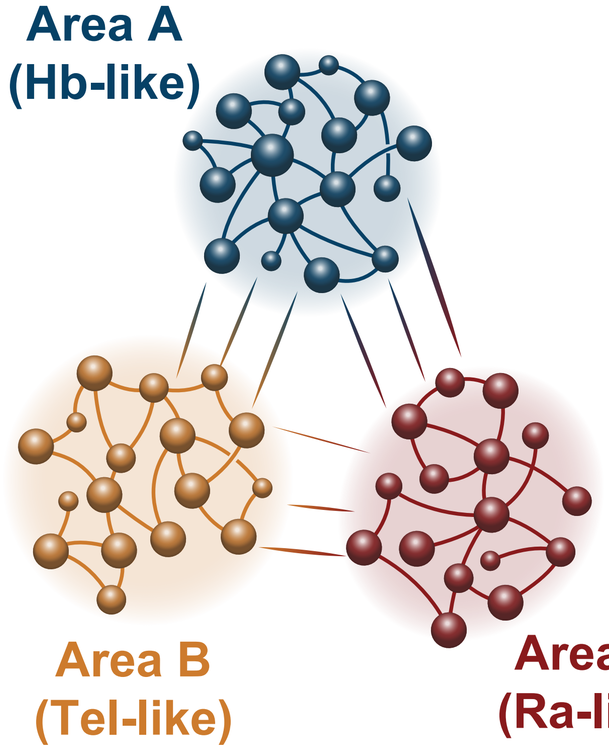

## DEMIXED SOURCE CURRENTS INTO Hb

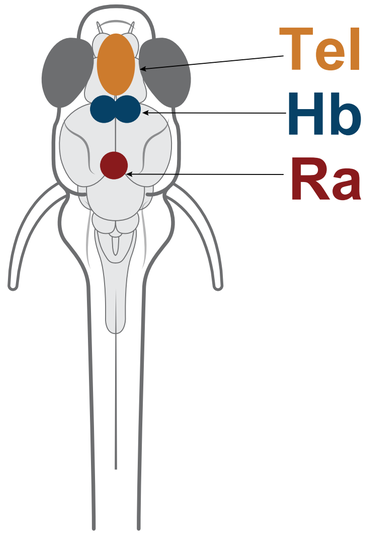


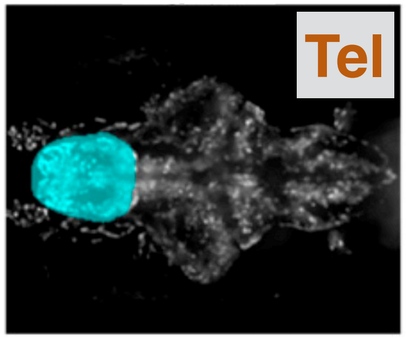



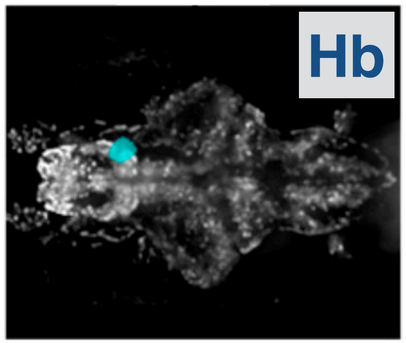
# … reveals surprising inter-area effects, *e.g., timing of inter-area currents*

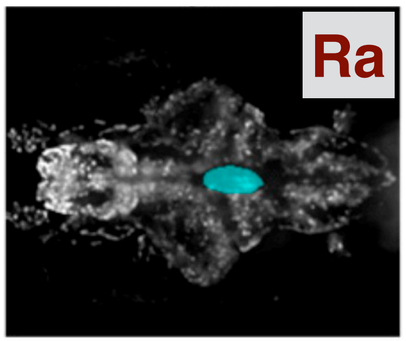
## MULTI-REGION RNN OF LARVAL ZEBRAFISH



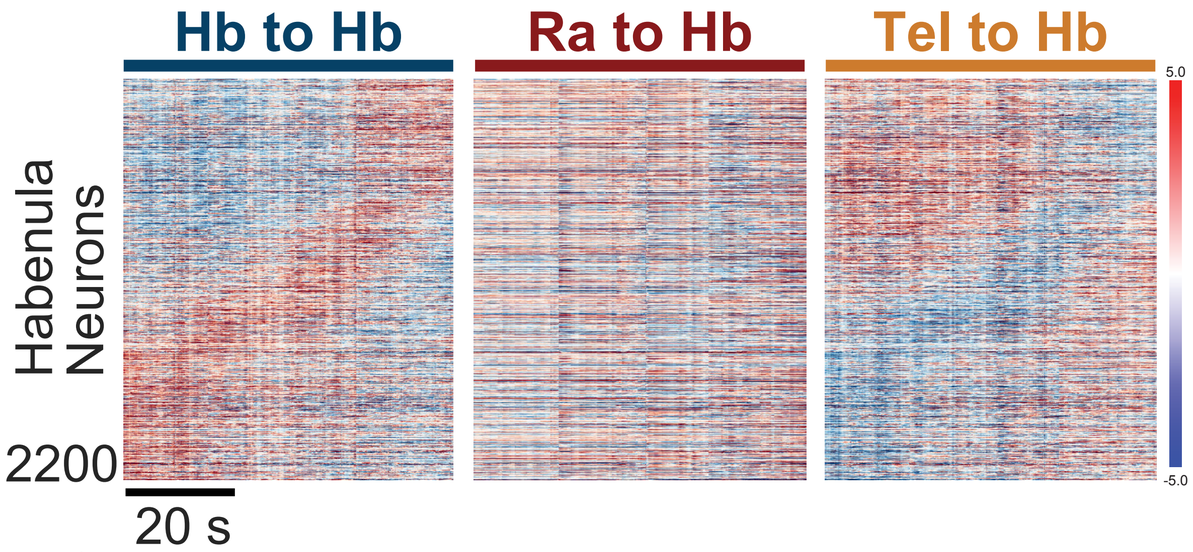



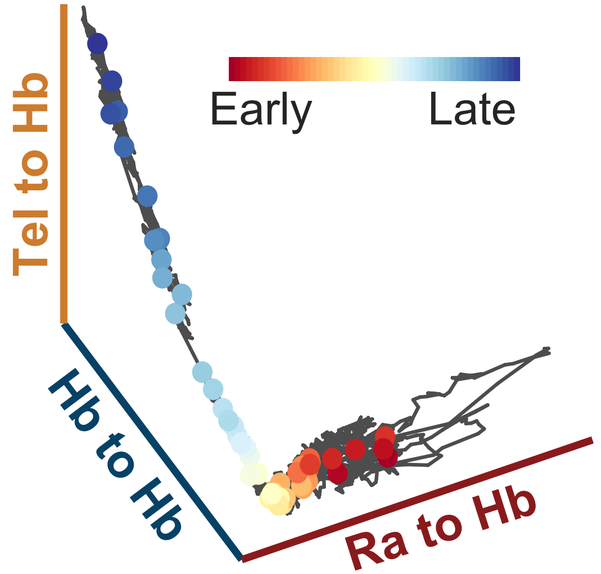



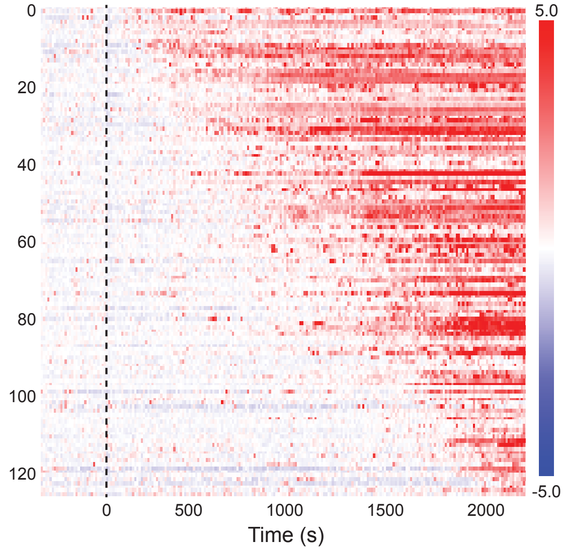

## DEMIXED SOURCE CURRENTS INTO Hb



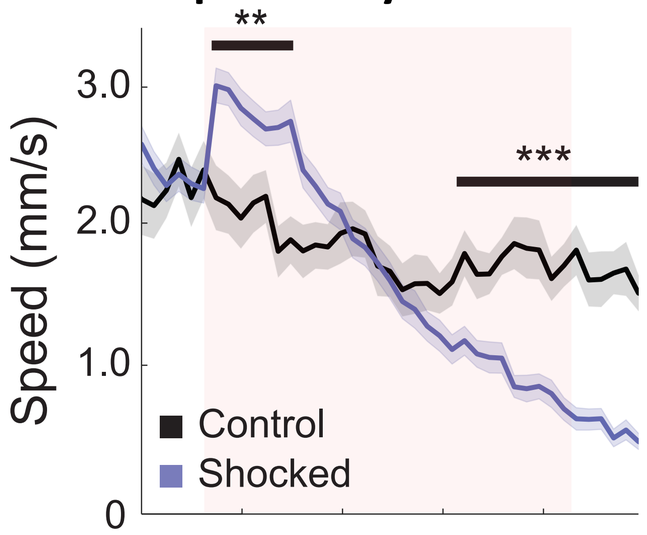



# Inter-area effects from CURBD is a powerful alternative to traditional p.o.v.

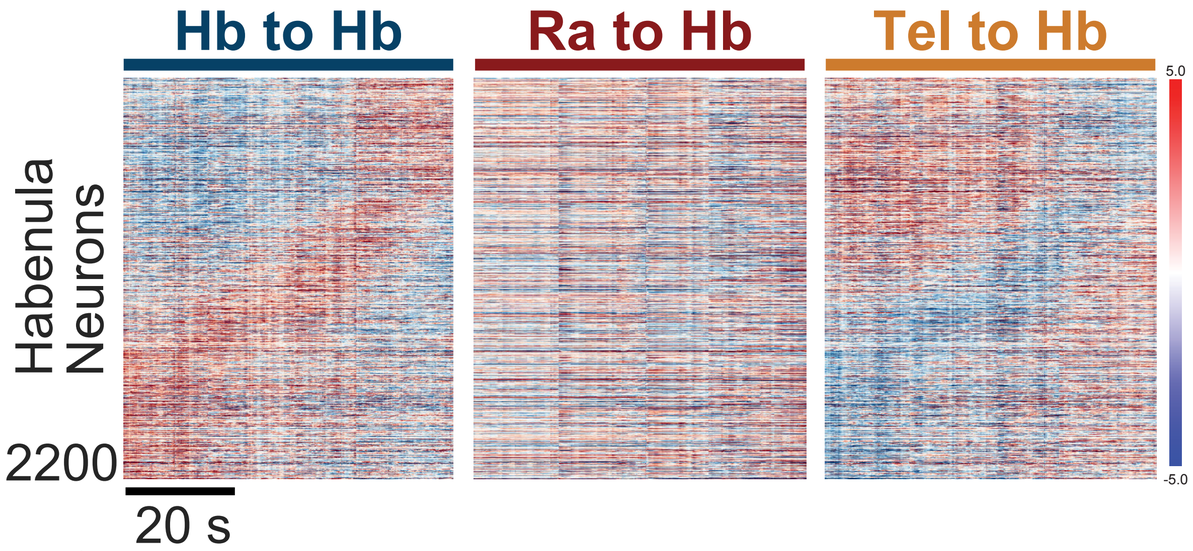
## 1. Activity in Habenula



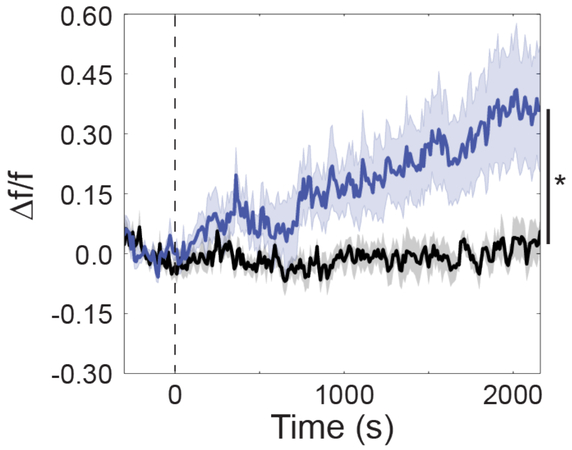

## Tail-whip velocity over time

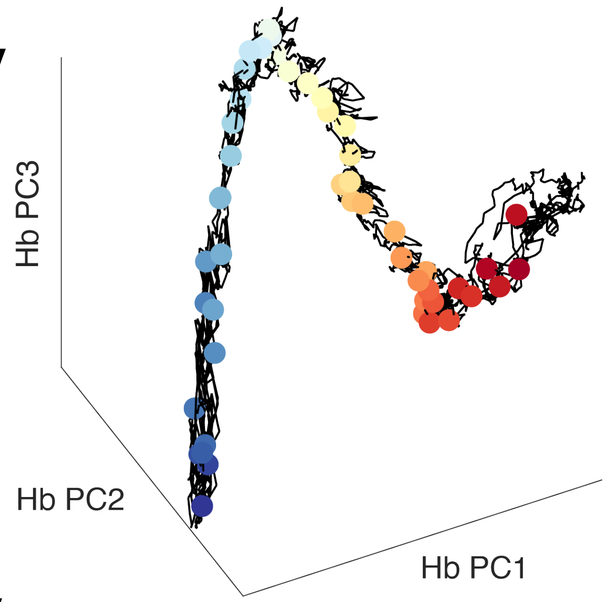


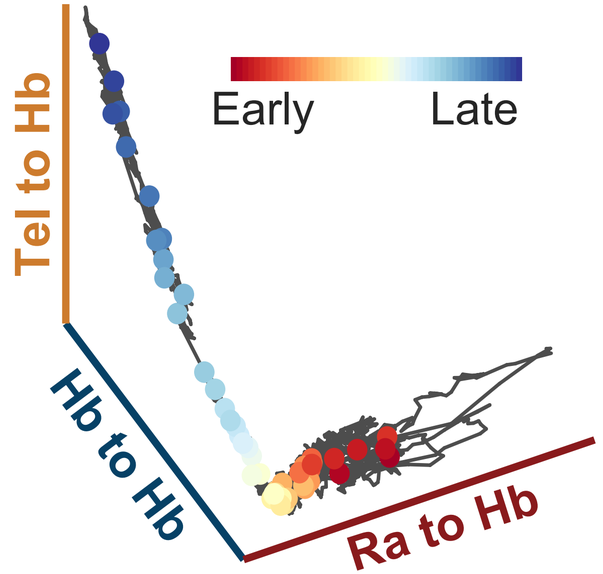

## DEMIXED SOURCE CURRENTS INTO Hb




## 2. Average population activity



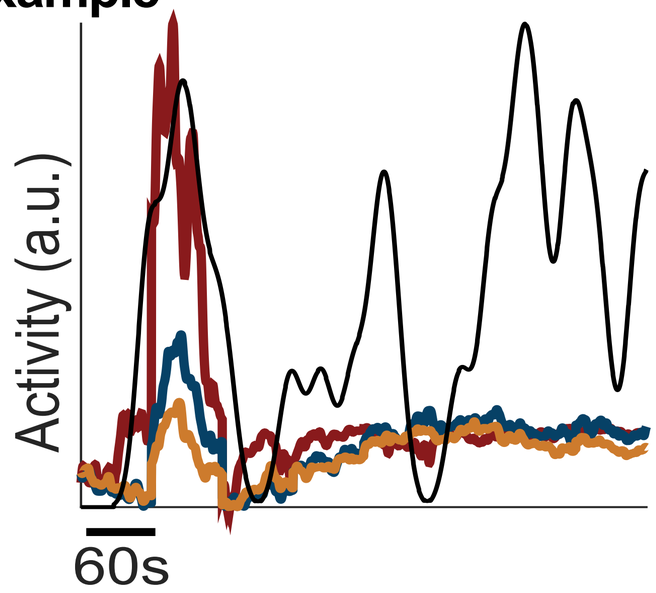



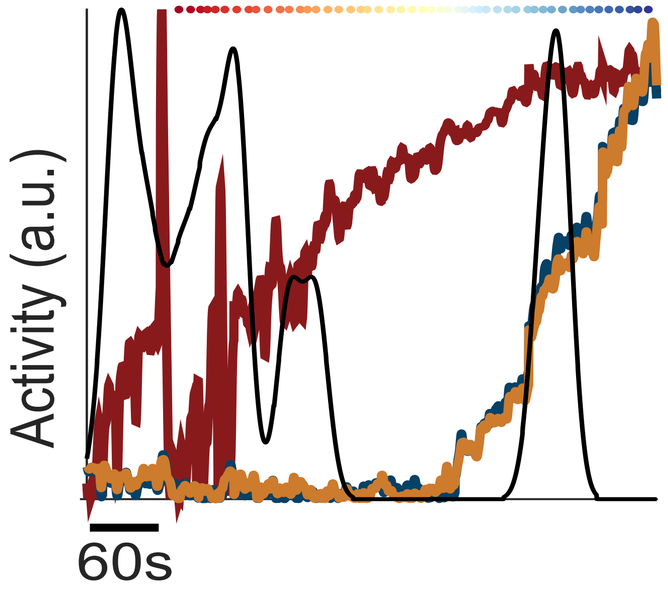

## 3. Traditional state space view

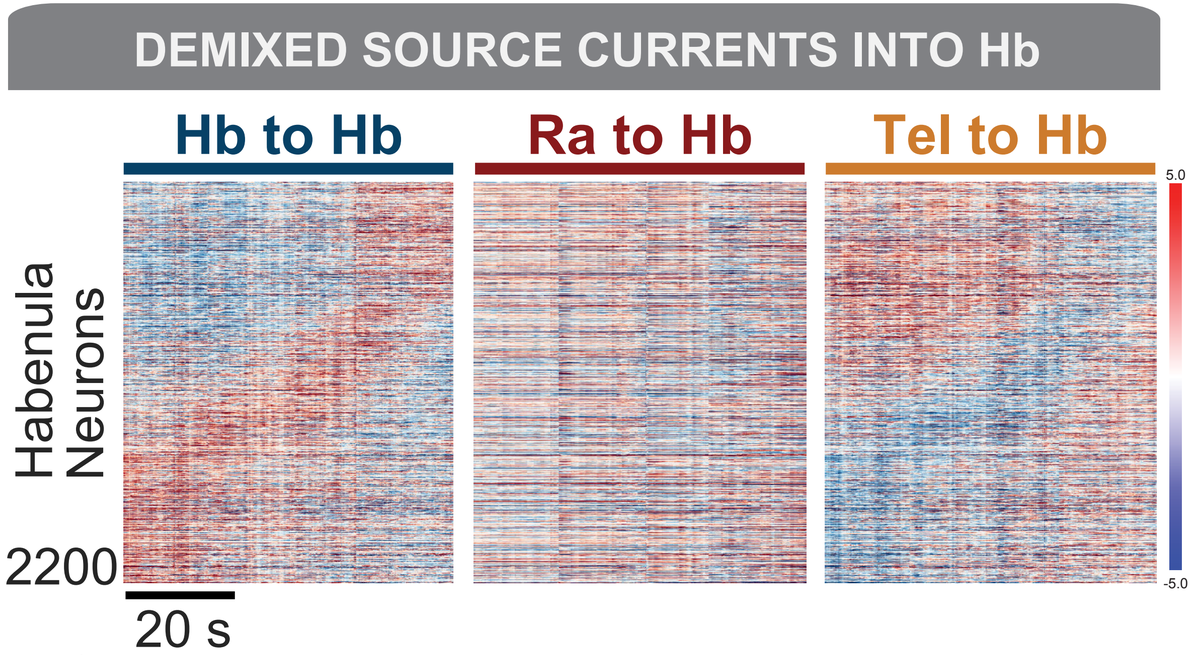
# Input currents behave differently in control v shocked fish

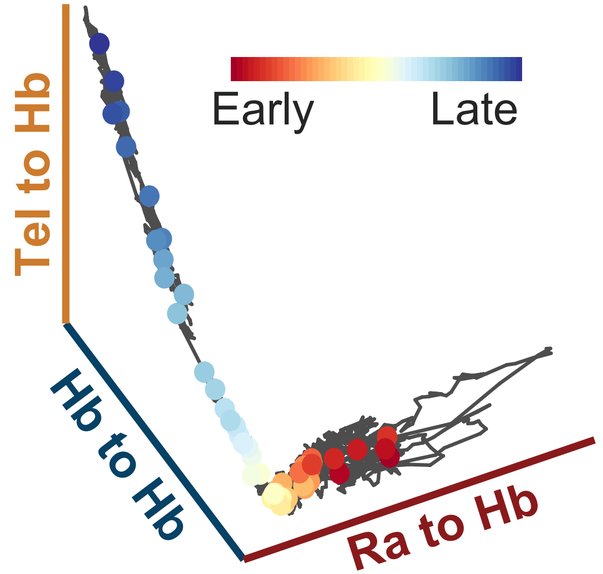
**Control fish, example**




**Shocked fish, example**

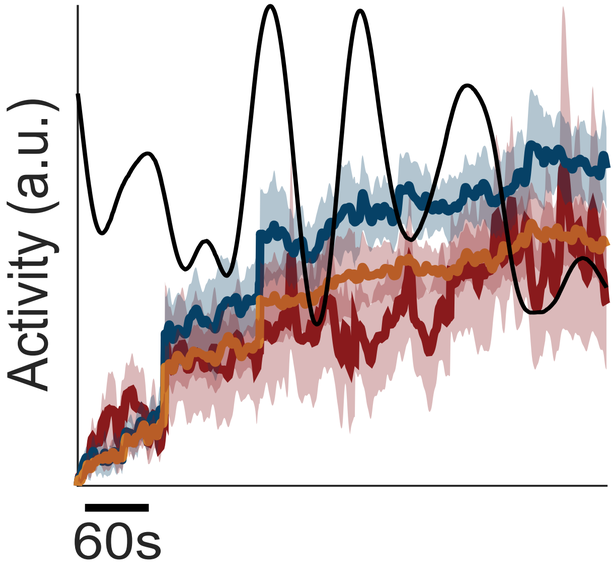


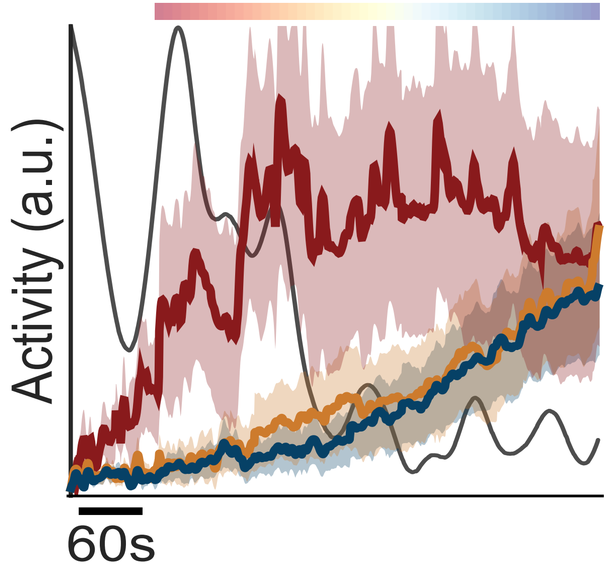



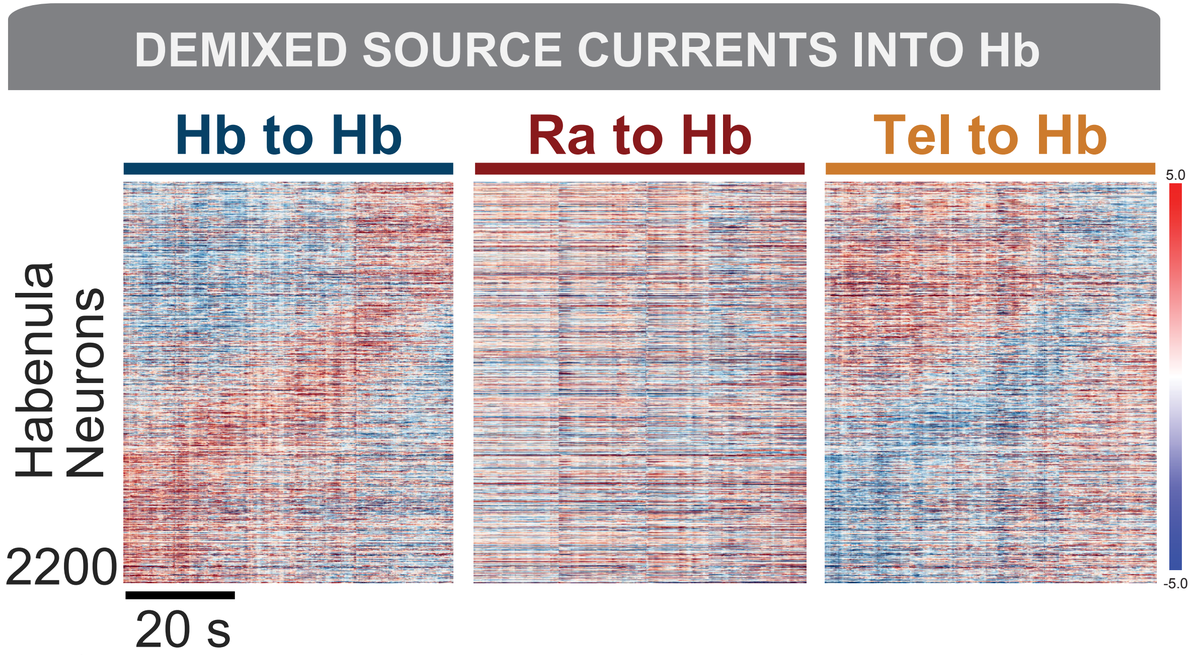
# Input currents behave differently across multiple control v shocked fish

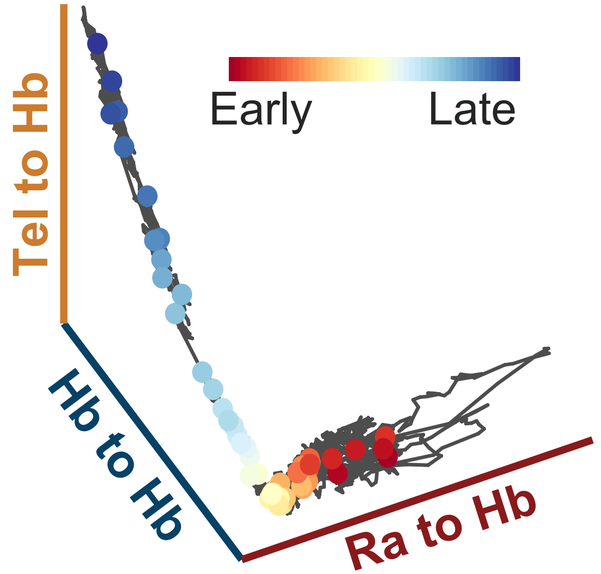
**Control fish, averaged over 5 individuals**




**Shocked fish, averaged over 5 individuals**

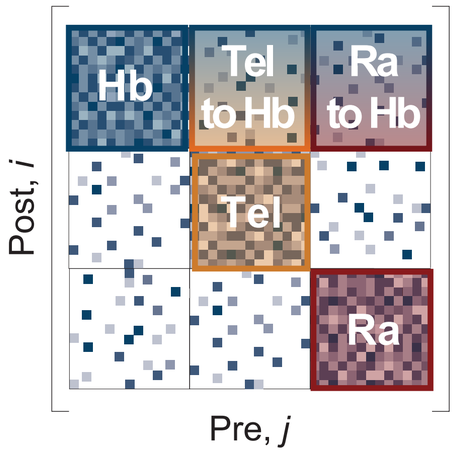


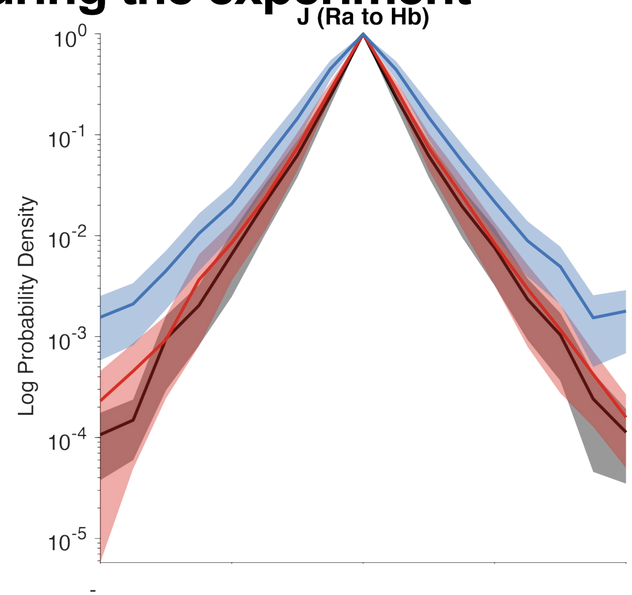



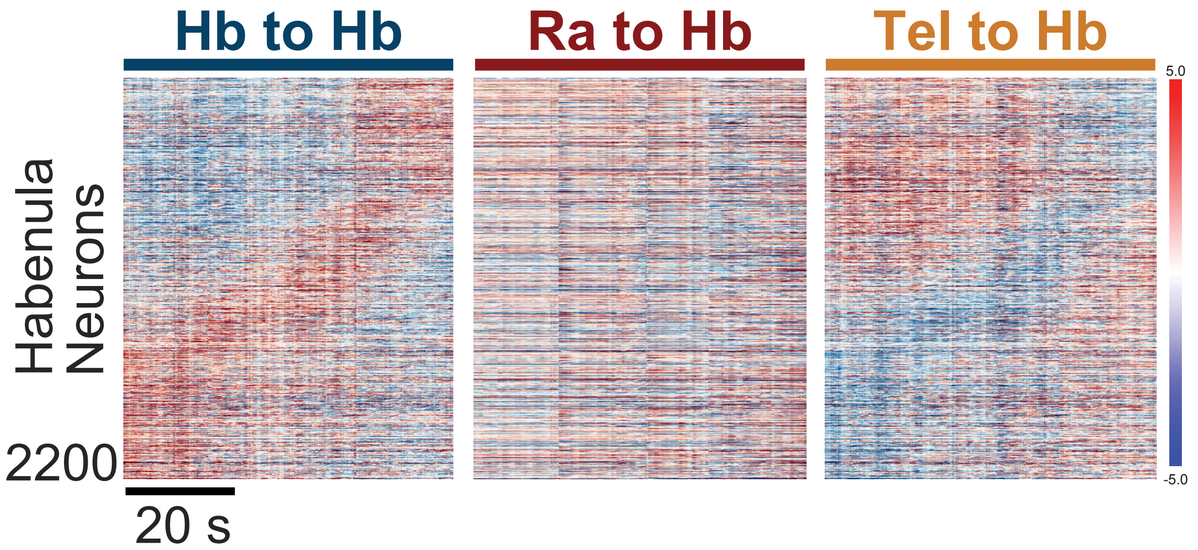
# Slow passivity may be driven via DI changes; early changes in active coping, currents driven

## DI changes during the experiment

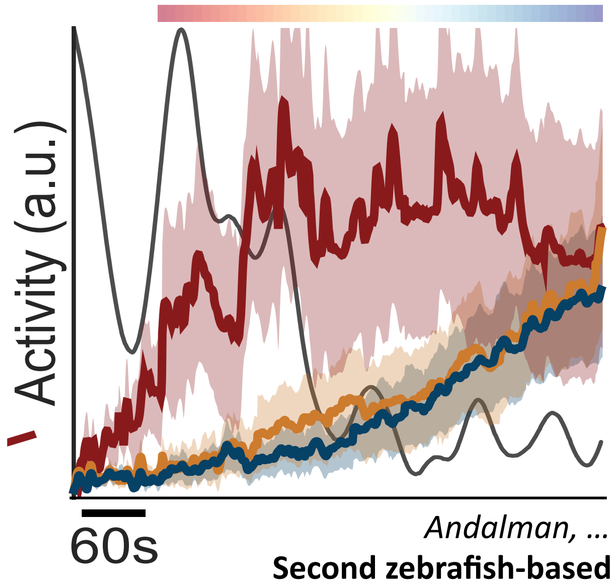


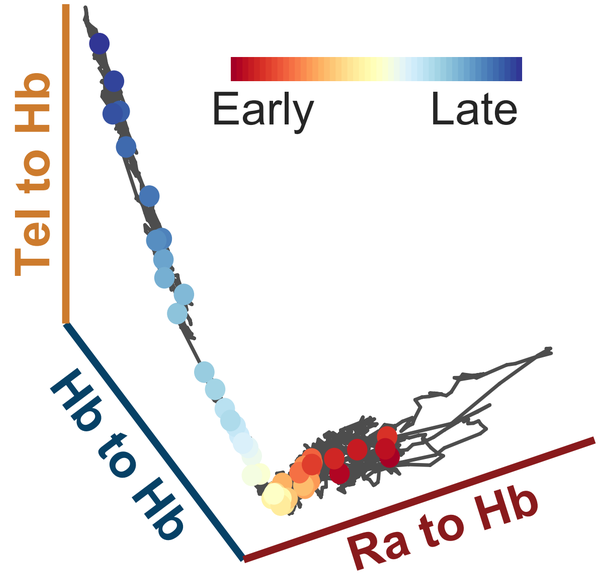




## DEMIXED SOURCE CURRENTS INTO Hb




## Shocked fish, averaged over 5 individuals

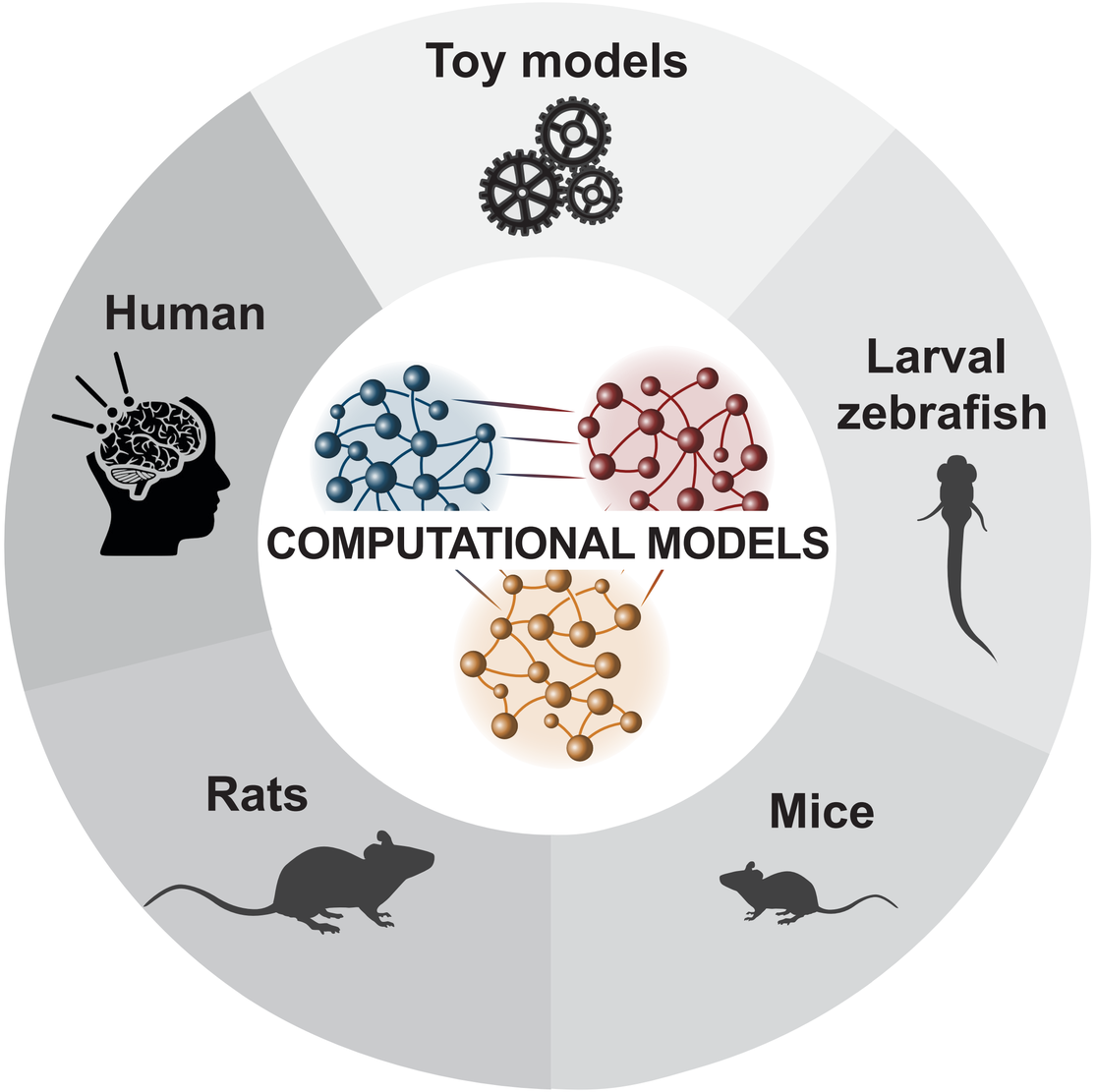



*Andalman, … , **Rajan**, and Deisseroth, 2019*

**Second zebrafish-based RNN manuscript in prep, watch bioRxiv**

## Question: *What brain-wide mechanism mediates active- to passive coping in zebrafish?*




## My approach is to build <u>Neural Networks</u>

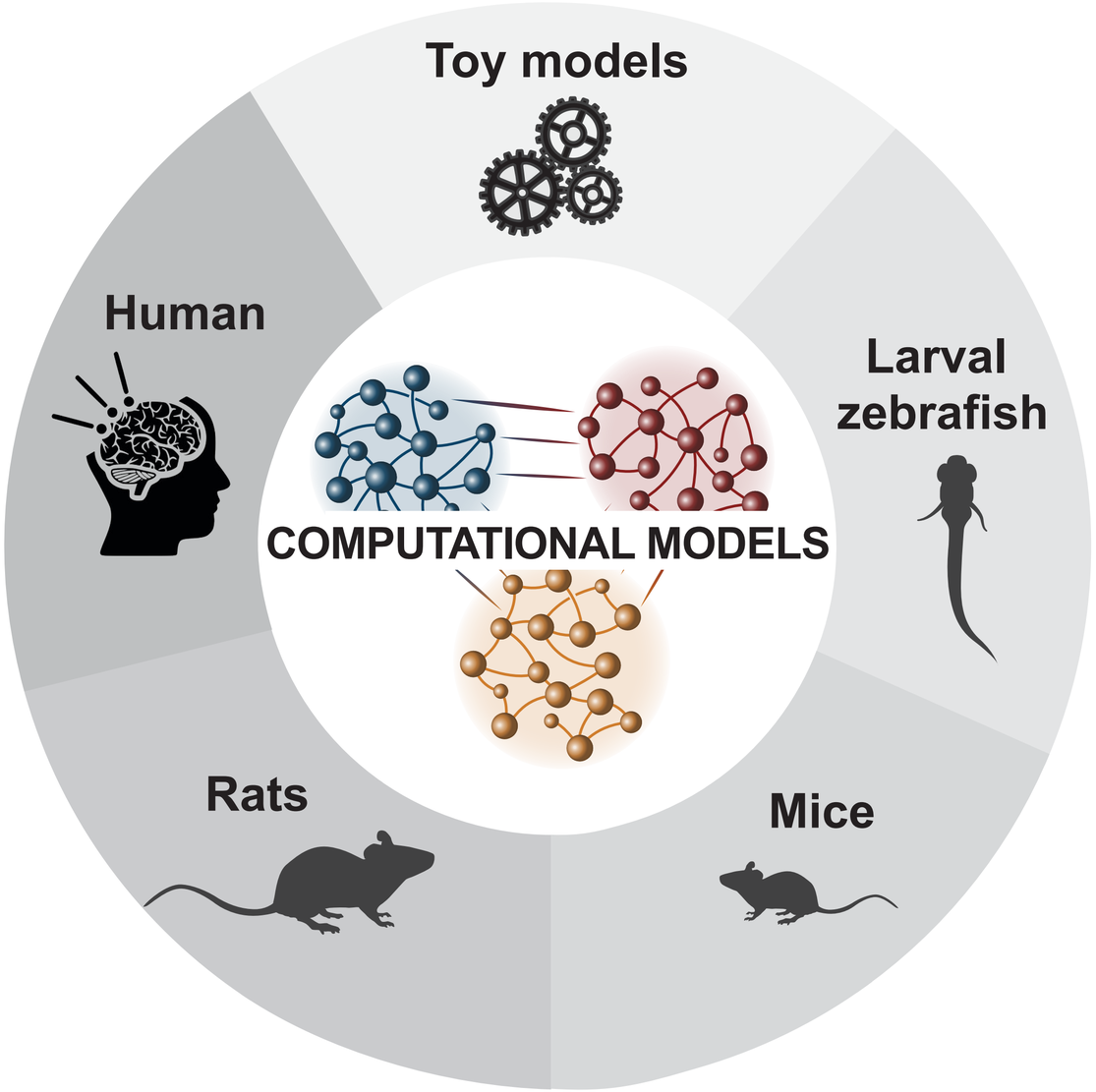
1. constrained **directly** by experimental data, and
2. analyze them using **new methods** and similar ones as those used on data
3. infer circuit mechanisms inaccessible from measurements


<u>Neural dynamics-level RNNs:</u> *Perich & **Rajan**, CoNEUR, 2020; Andalman, … , **Rajan**, and Deisseroth, Cell, 2019; **Rajan**, Harvey and Tank, Neuron, 2016*

<u>Behavior-level RNNs:</u> *Yang, Cole, **Rajan**, COBEHA, 2019; Insanally,…,**Rajan** et al, eLife, 2019; Pinto, **Rajan** et al, Neuron, 2019*

<u>In Prep & Review:</u> *Perich,…, Deisseroth & **Rajan**, BioRxiv, 2020; Young, …, **Rajan** & Rudebeck, BioRxiv, 2020; Benster, …,**Rajan*** & Deisseroth*, in preparation*

# Brain-wide mechanisms mediating active- to passive coping transition in zebrafish




## Our results from multi-region RNNs and CURBD:

1. Hb interactions ramp with persistent, inescapable adversity. Feedback interactions from Ra to Hb change. ***(2019 Cell paper)***
2. Roles of Ra and Tel projections into Hb, some driven by fast changes to the current manifold and some by slower structural changes. ***(what I told you today)***


Neural dynamics-level RNNs: *Perich & **Rajan**, CoNEUR, 2020; Andalman, … , **Rajan**, and Deisseroth, Cell, 2019; **Rajan**, Harvey and Tank, Neuron, 2016*

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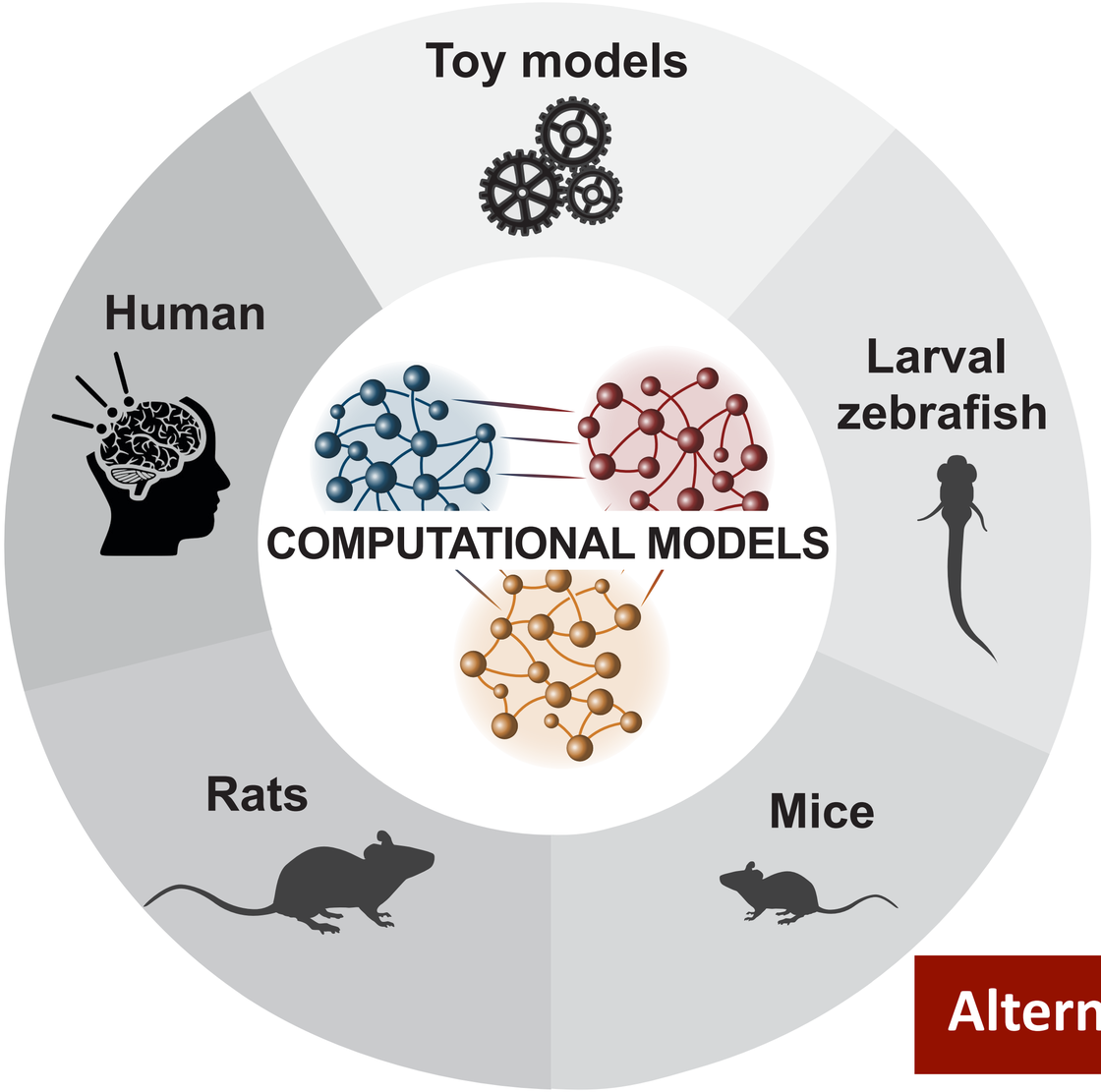
In Prep & Review: *Perich,…, Deisseroth & **Rajan**, BioRxiv, 2020; Young, …, **Rajan** & Rudebeck, BioRxiv, 2020; Benster, …,**Rajan*** & Deisseroth*, in preparation*

# Are any circuit mechanisms conserved (+ where they diverge)?




## Advantages of computational models

1. Multi-region RNN models generating neural dynamics consistent with data from active-to passive coping experiments
2. Inference of consistent Directed Interaction matrices, which
   - reflect both ***within*** and ***inter-area*** connectivity, and
   - correlate with behavioral state change
3. CURBD inferred currents suggest distinct time scales: ***early and slower effects***.

**Alternative to traditional functional connectivity**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***Thank you!***

# Funding sources

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

Young Investigator Award

JSMF

Understanding Human Cognition Scholar Award

ALFRED P. SLOAN FOUNDATION 1934

Research Fellowship

NSF

FOUNDATIONS Award

NIH National Institutes of Health

NIBIB

BRAIN Initiative R01CB028166-01

Di Sabato Foundation Award

Dyal Foundation Award

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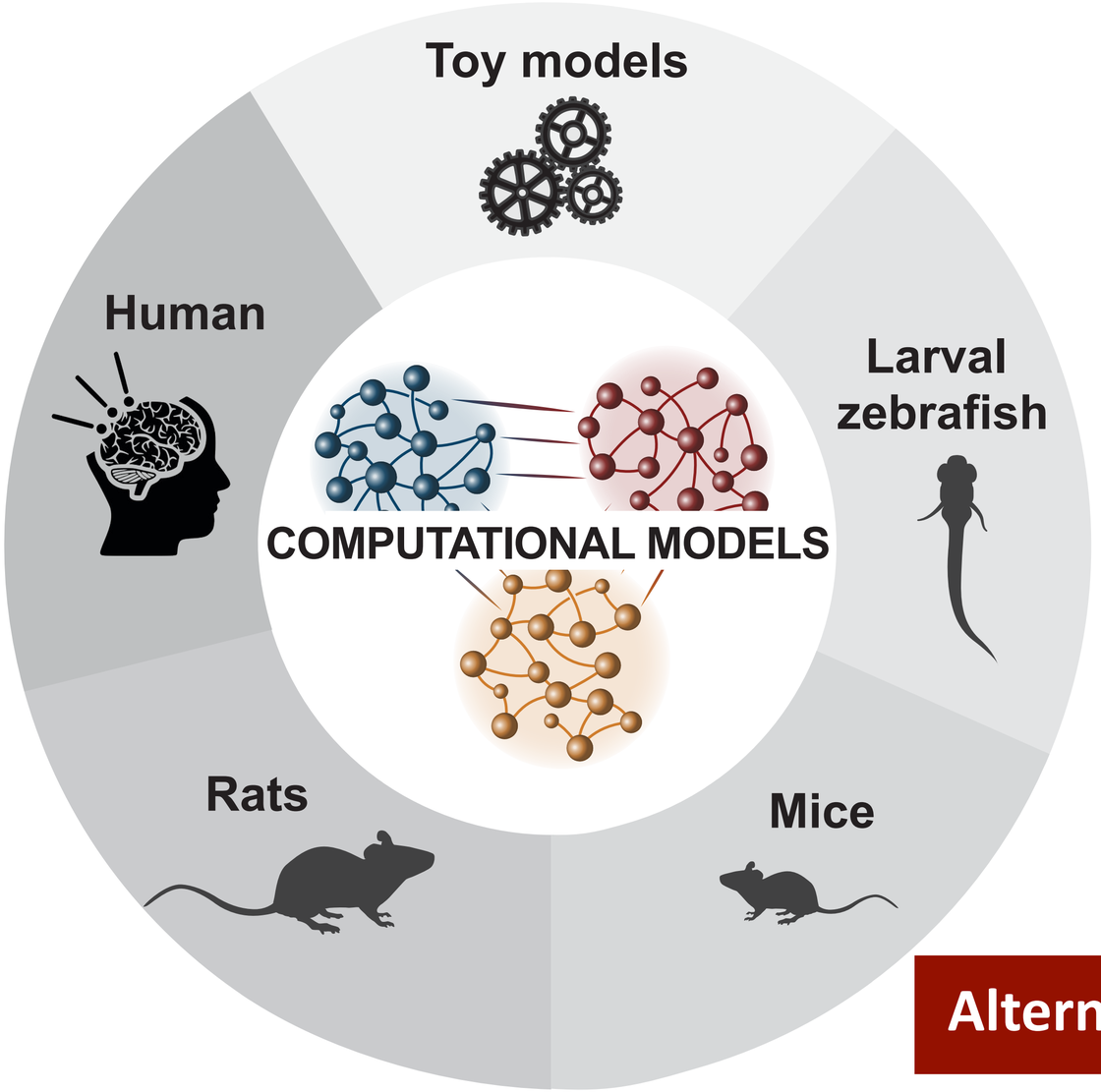


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