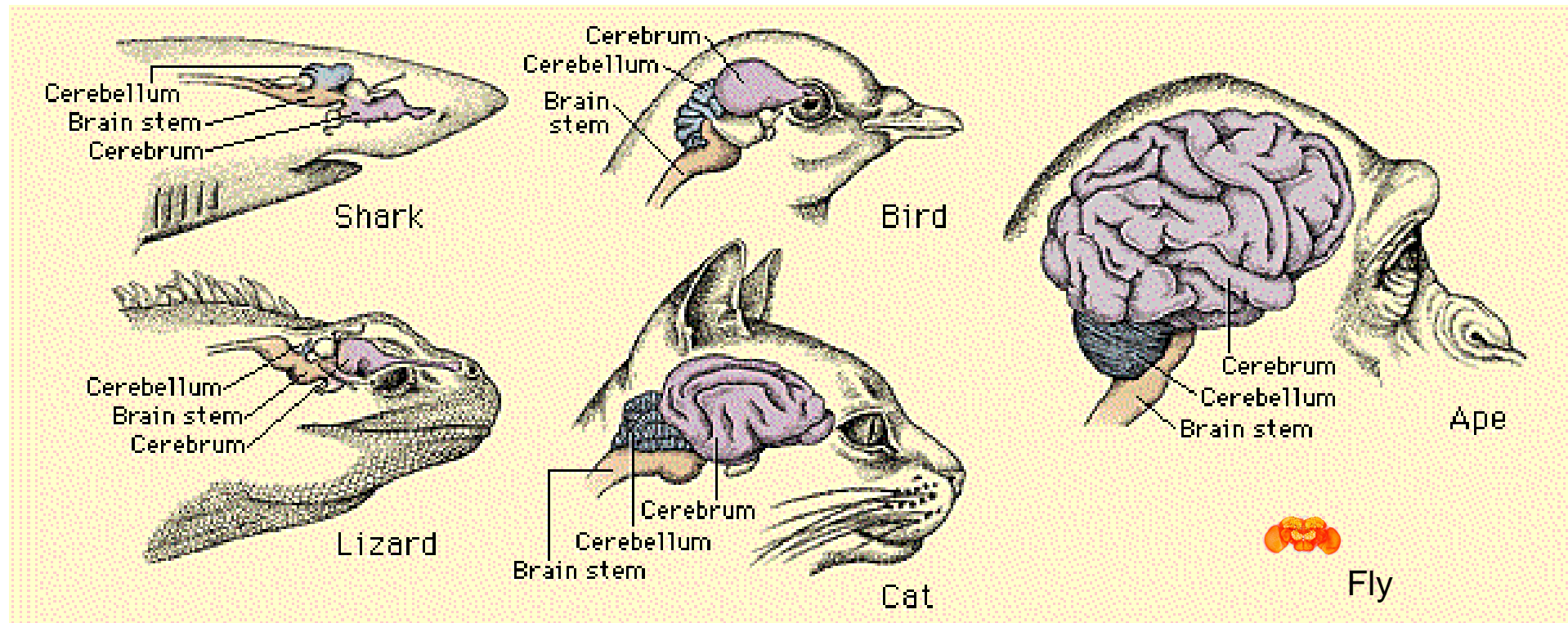


The impact of stress on the neurobiology of cognition

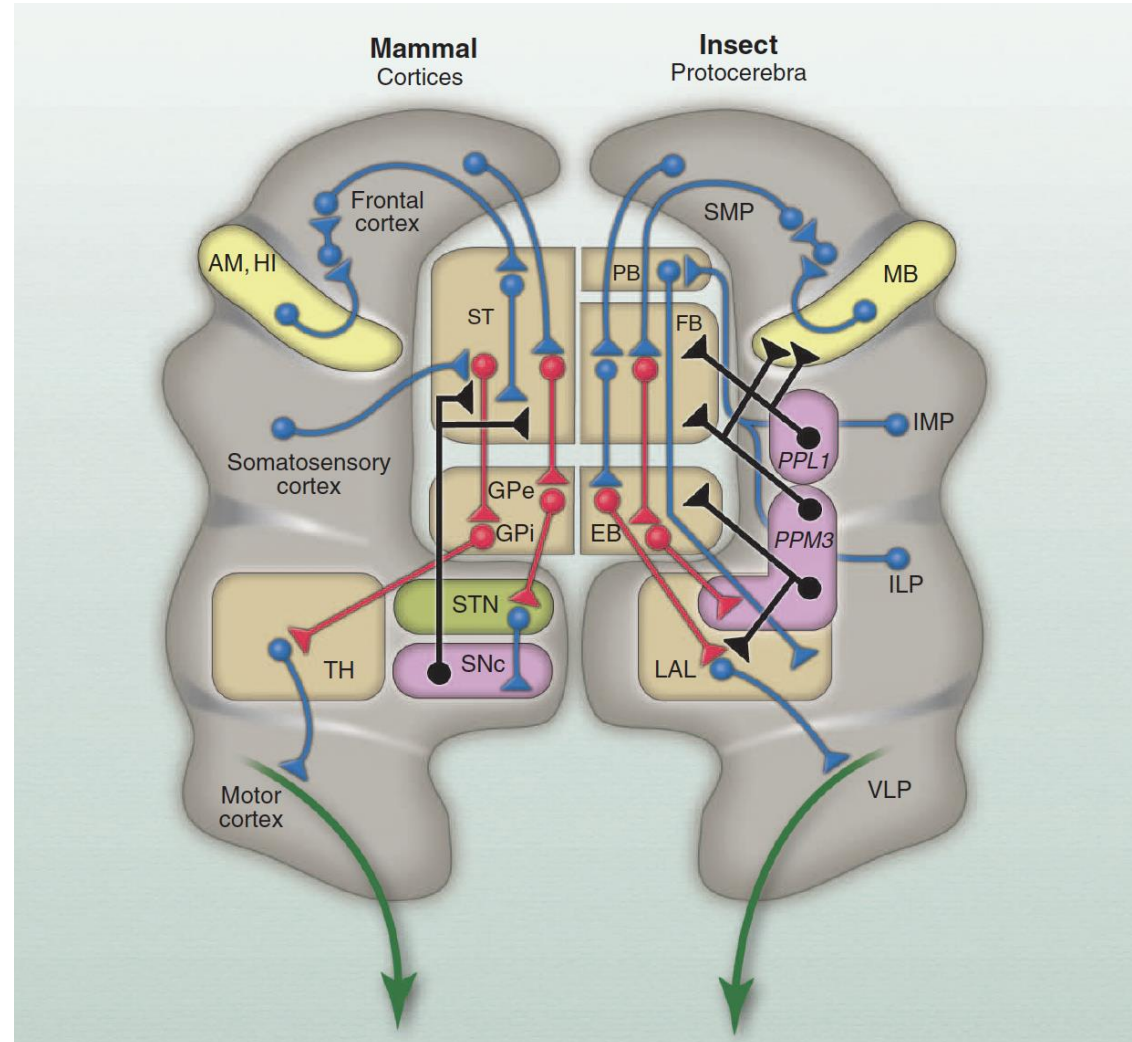
Dhruv Grover

Kavli Institute for Brain and Mind
University of California, San Diego

Relevance of *Drosophila* to cognitive function in humans



Deep functional homology between invertebrate and vertebrate brains

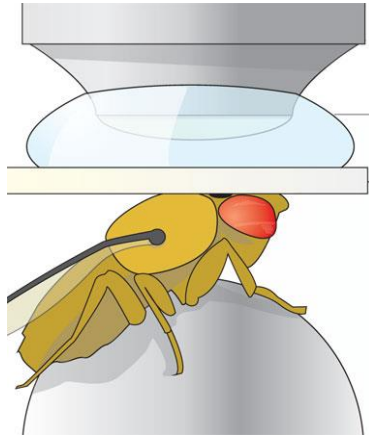


The kitchen sink model

Behavior



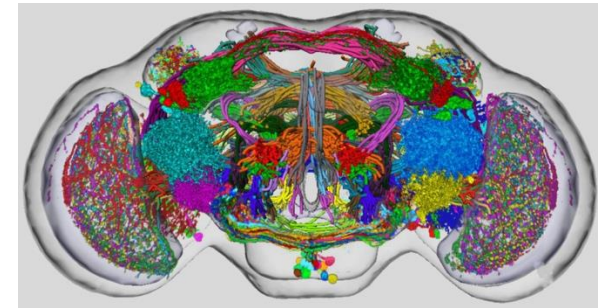
Physiology



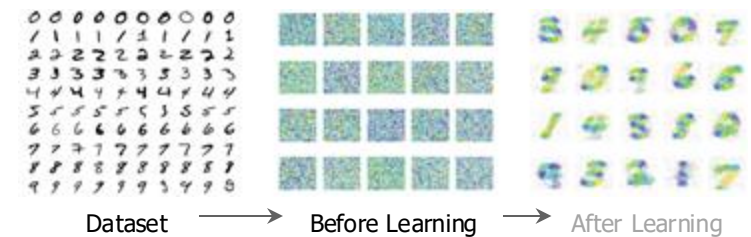
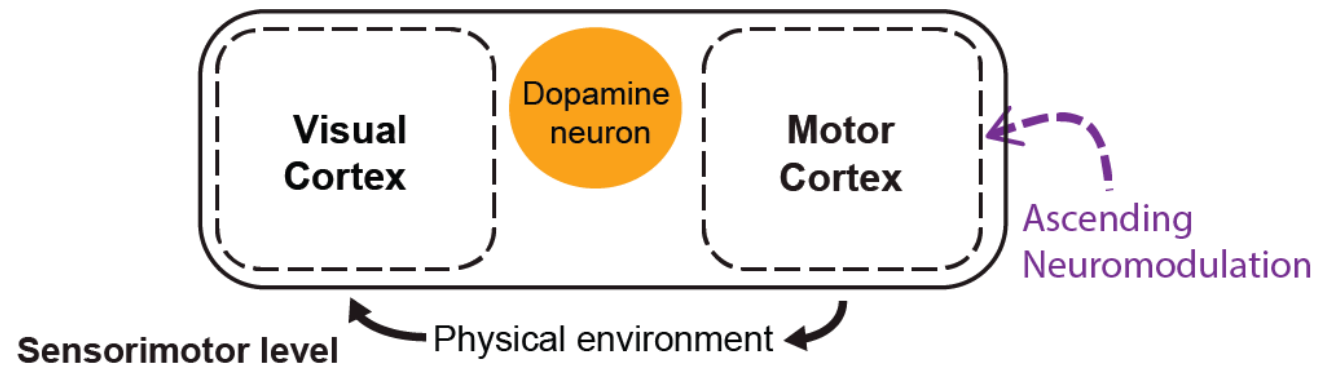
Biosensors



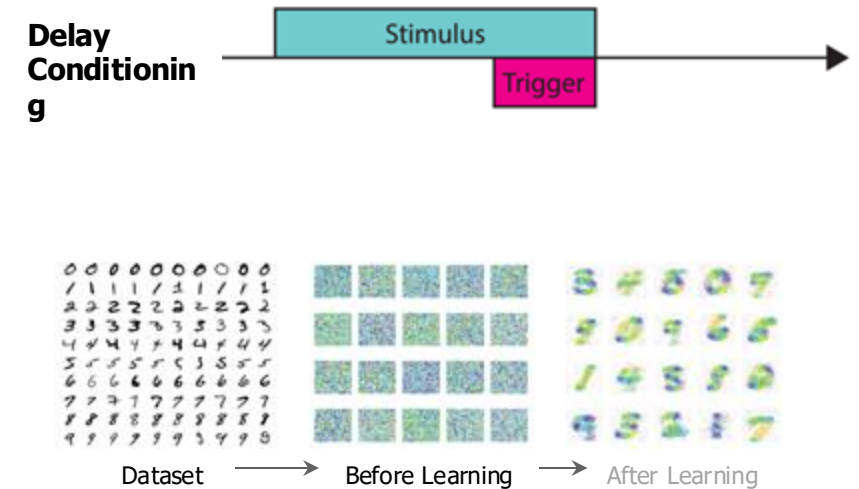
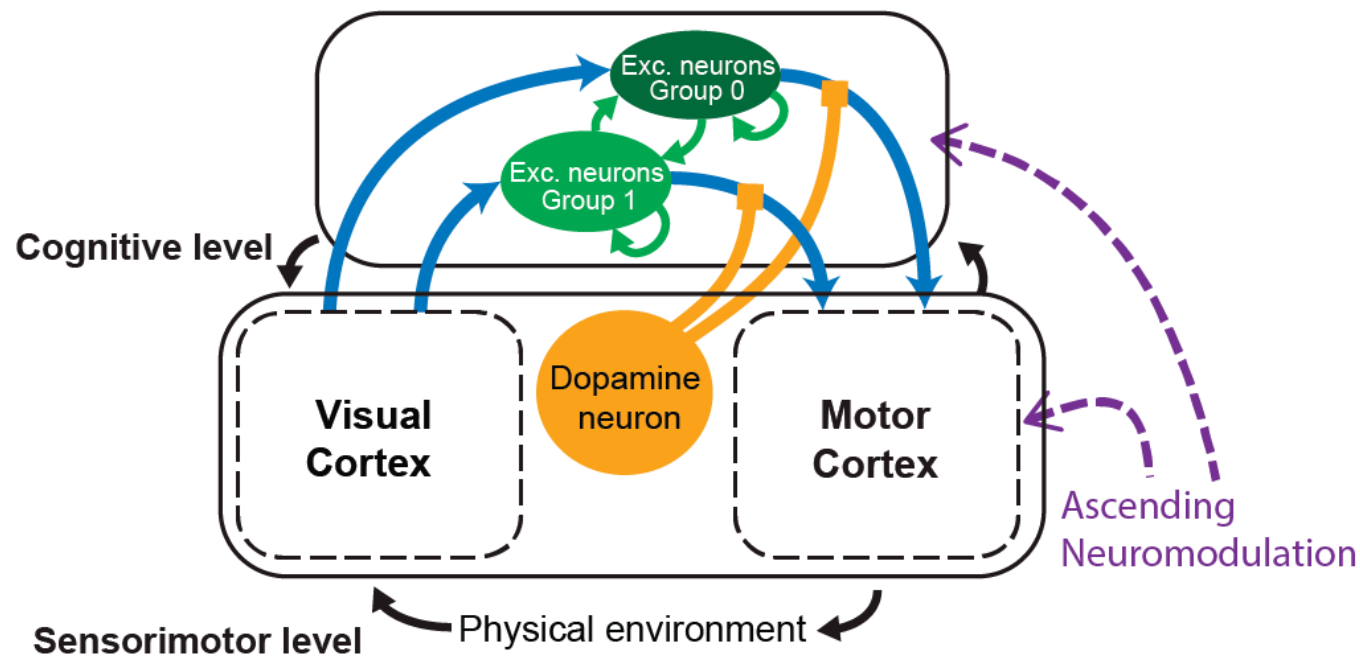
Connectomics



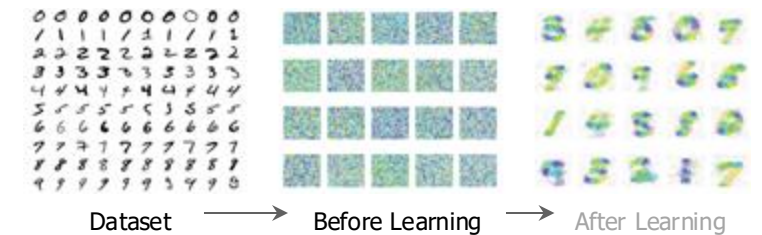
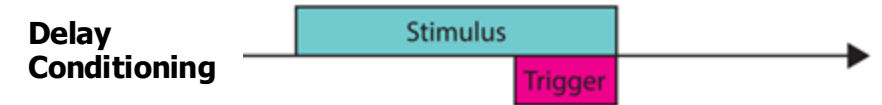
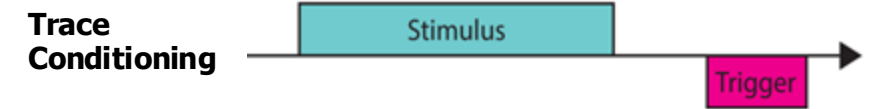
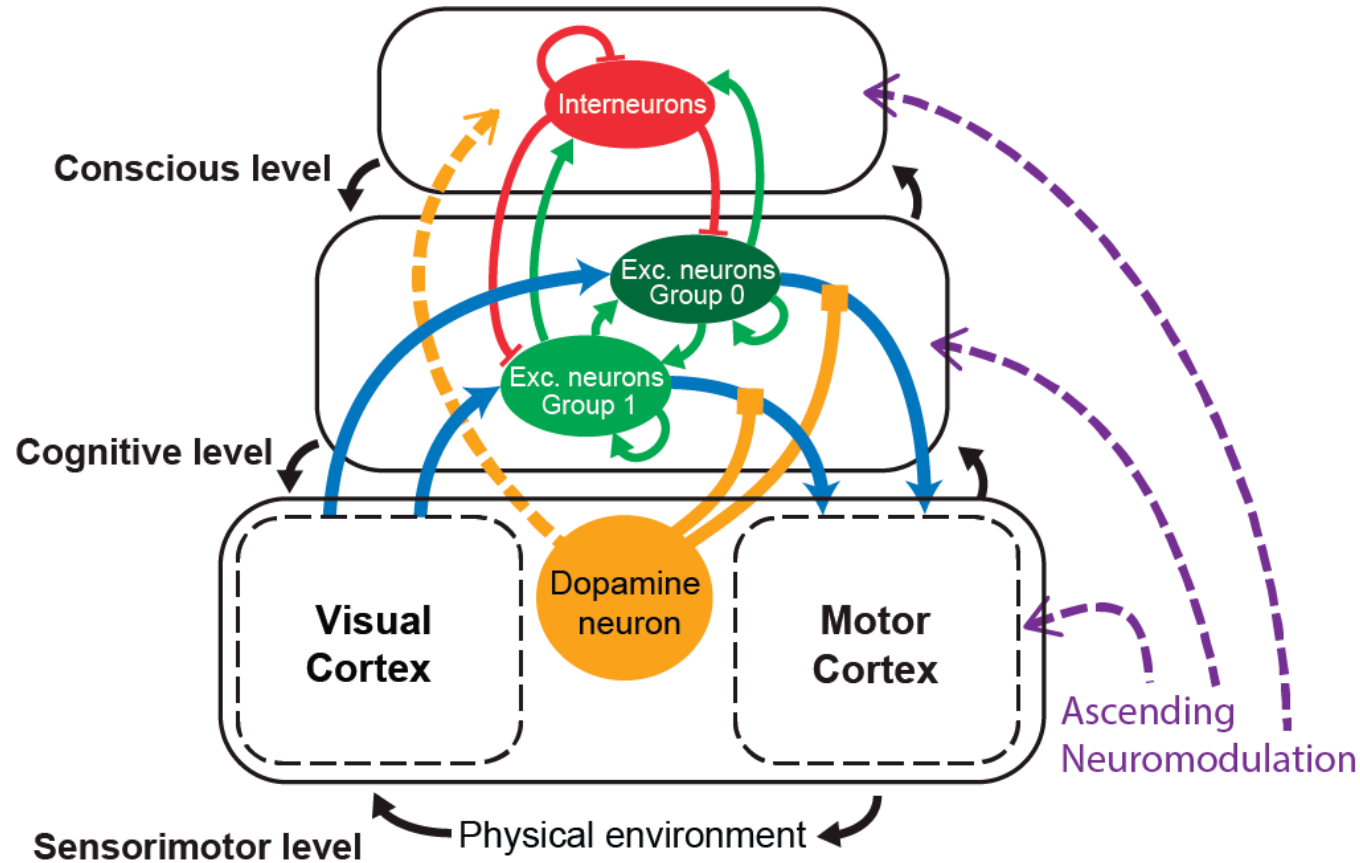
Multi-level computational model of cognitive abilities



Multi-level computational model of cognitive abilities

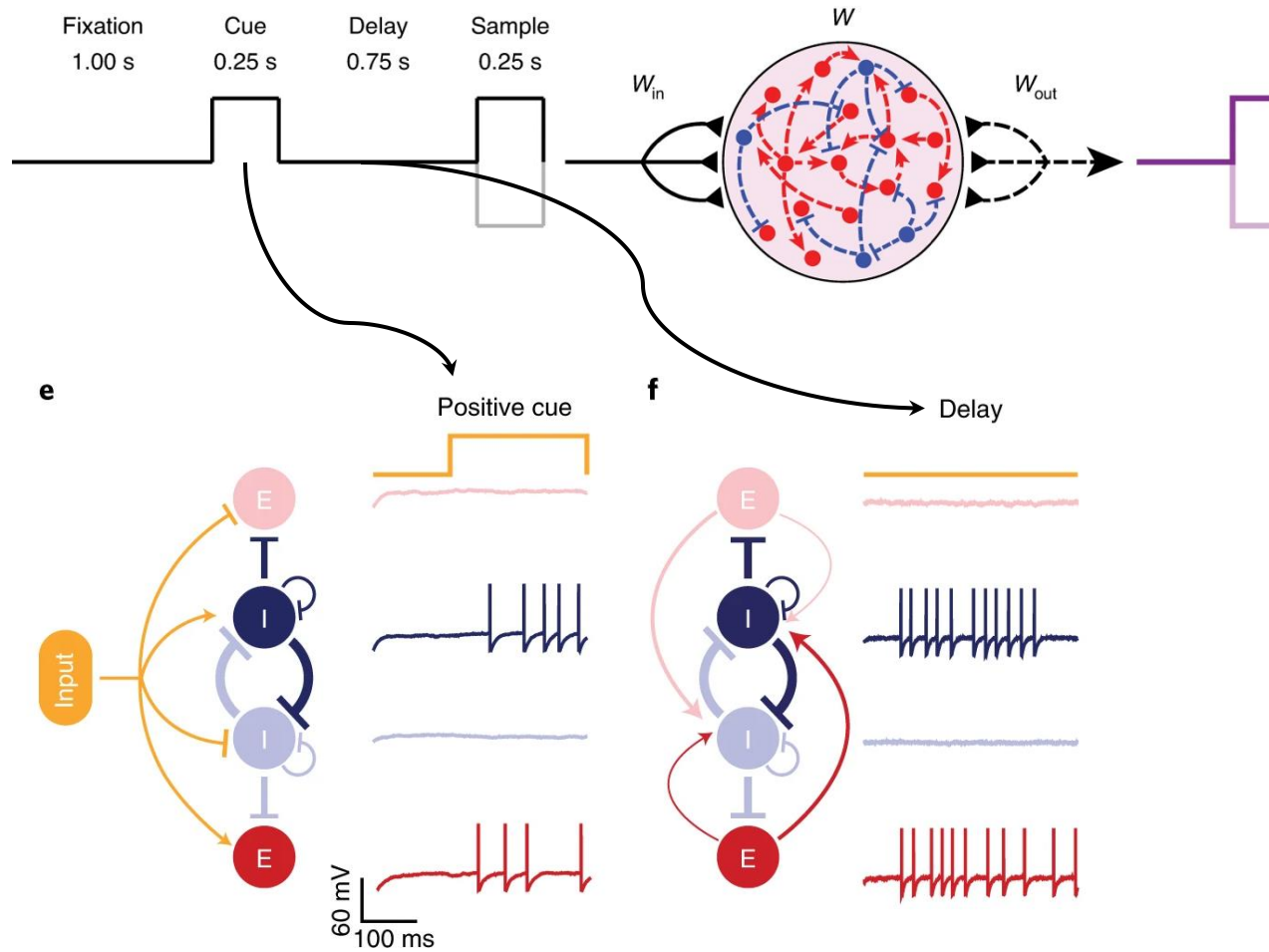


Multi-level computational model of cognitive abilities

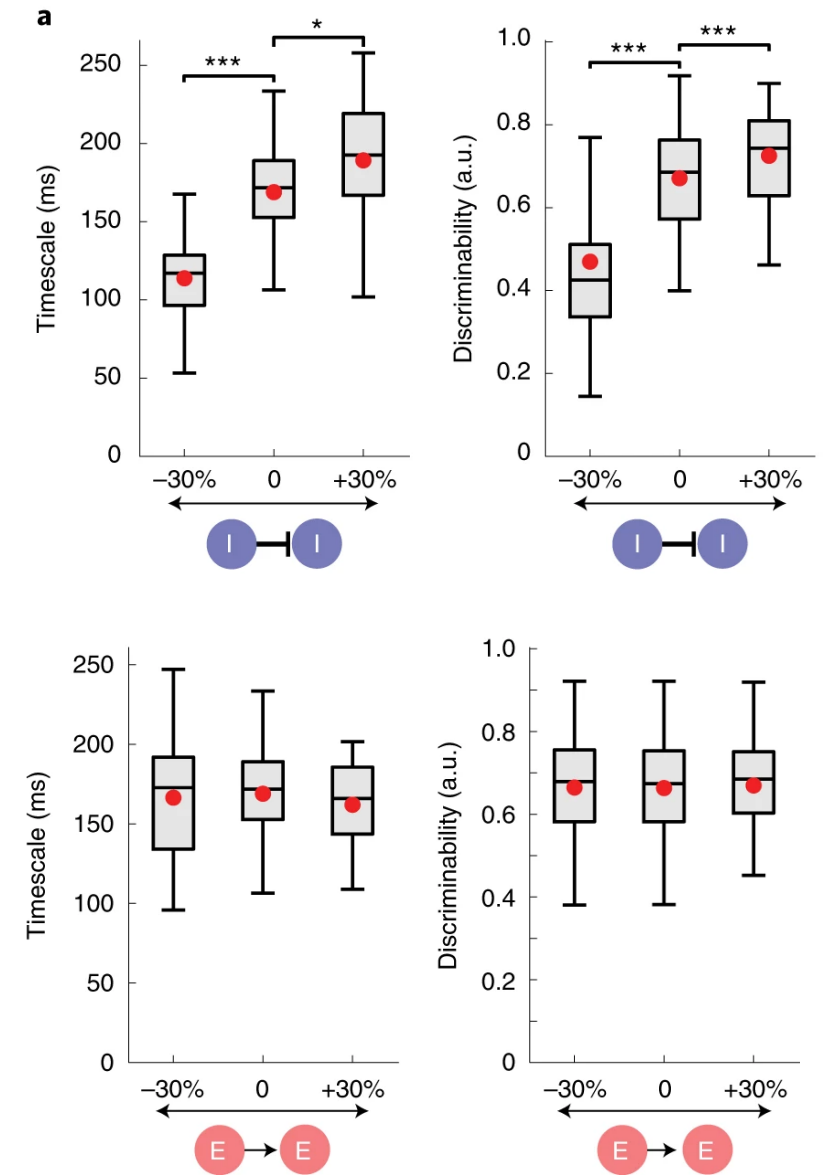


Strong inhibitory signaling underlies stable temporal dynamics and working memory in spiking neural networks

Robert Kim & Terrence J. Sejnowski



I -> I connectivity strength strongly mediates neuronal timescales and task performance



Trace conditioning as a test for *attention* and *working memory*

Trace but not delay fear conditioning requires attention and the anterior cingulate cortex

C. J. Han^{*†}, Colm M. O'Tuathaigh^{*}, Laurent van Trigt^{*}, Jennifer J. Quinn[‡], Michael S. Fanselow[‡], Raymond Mongeau^{*}, Christof Koch^{*§}, and David J. Anderson^{*¶}

The role of working memory and declarative memory in trace conditioning

David A. Connor, Thomas J. Gould  

Classical Conditioning and Brain Systems: The Role of Awareness

ROBERT E. CLARK AND LARRY R. SQUIRE

Conditioning, awareness, and the hippocampus

Kevin S. LaBar, John F. Disterhoft 

Working memory and fear conditioning

Ronald McKell Carter^{*†}, Constanze Hofstötter^{*‡}, Naotsugu Tsuchiya[§], and Christof Koch^{*§}

Bridging the interval: Theory and neurobiology of trace conditioning

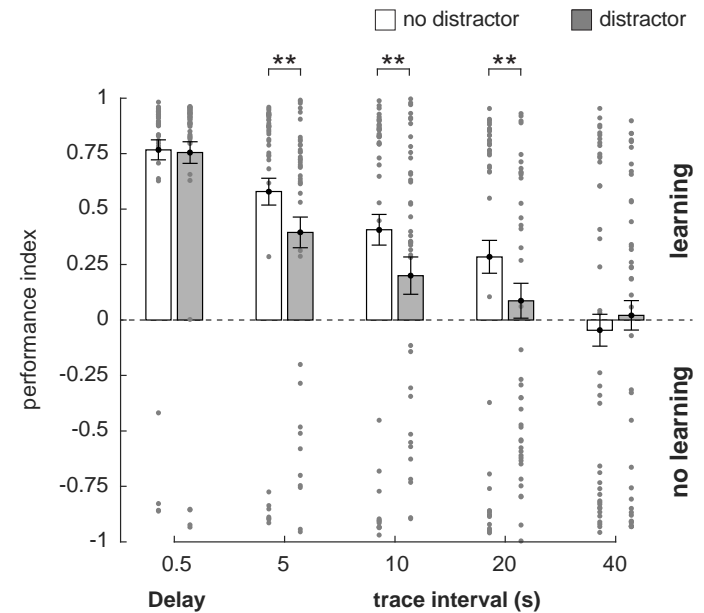
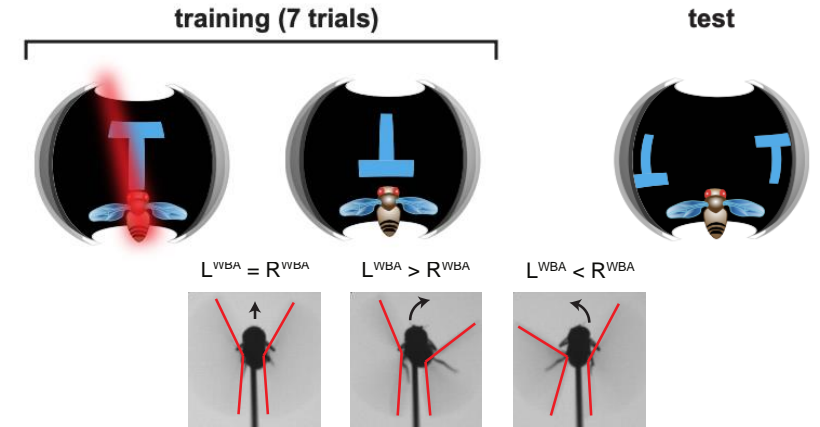
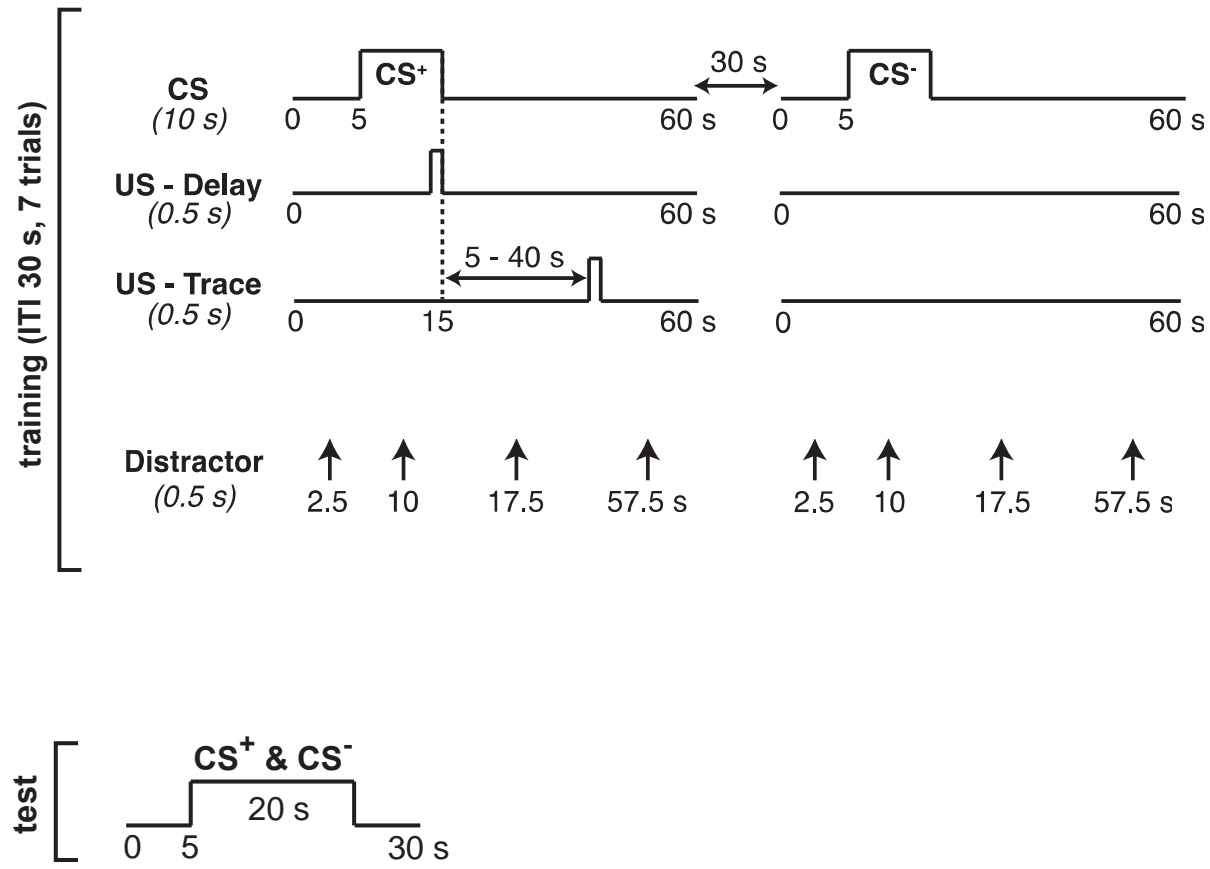
Jonathan D. Raybuck  , K. Matthew Lattal  

My Word

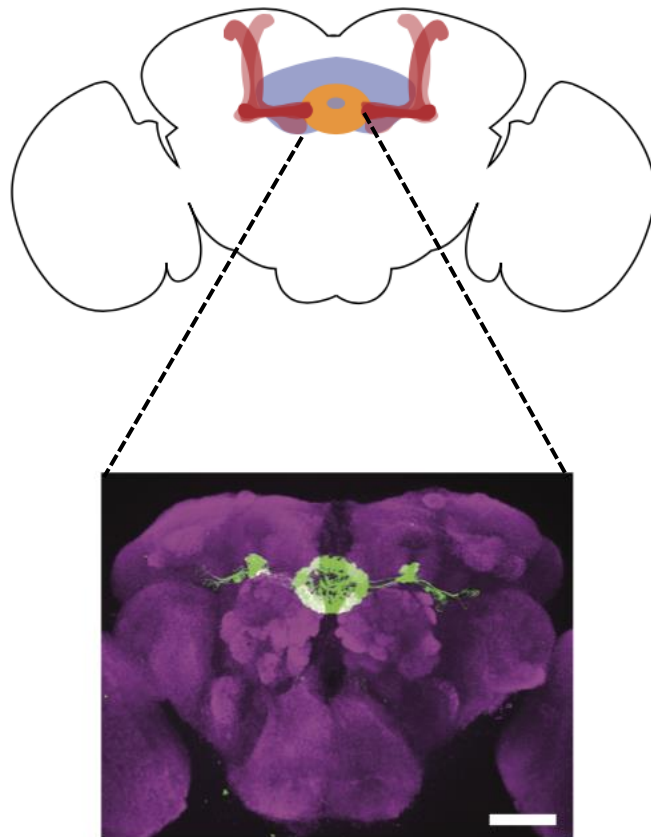
**Seeing
consciousness
through the lens of
memory**

Joseph E. LeDoux^{1,2,3,*}
and Hakwan Lau^{4,5}

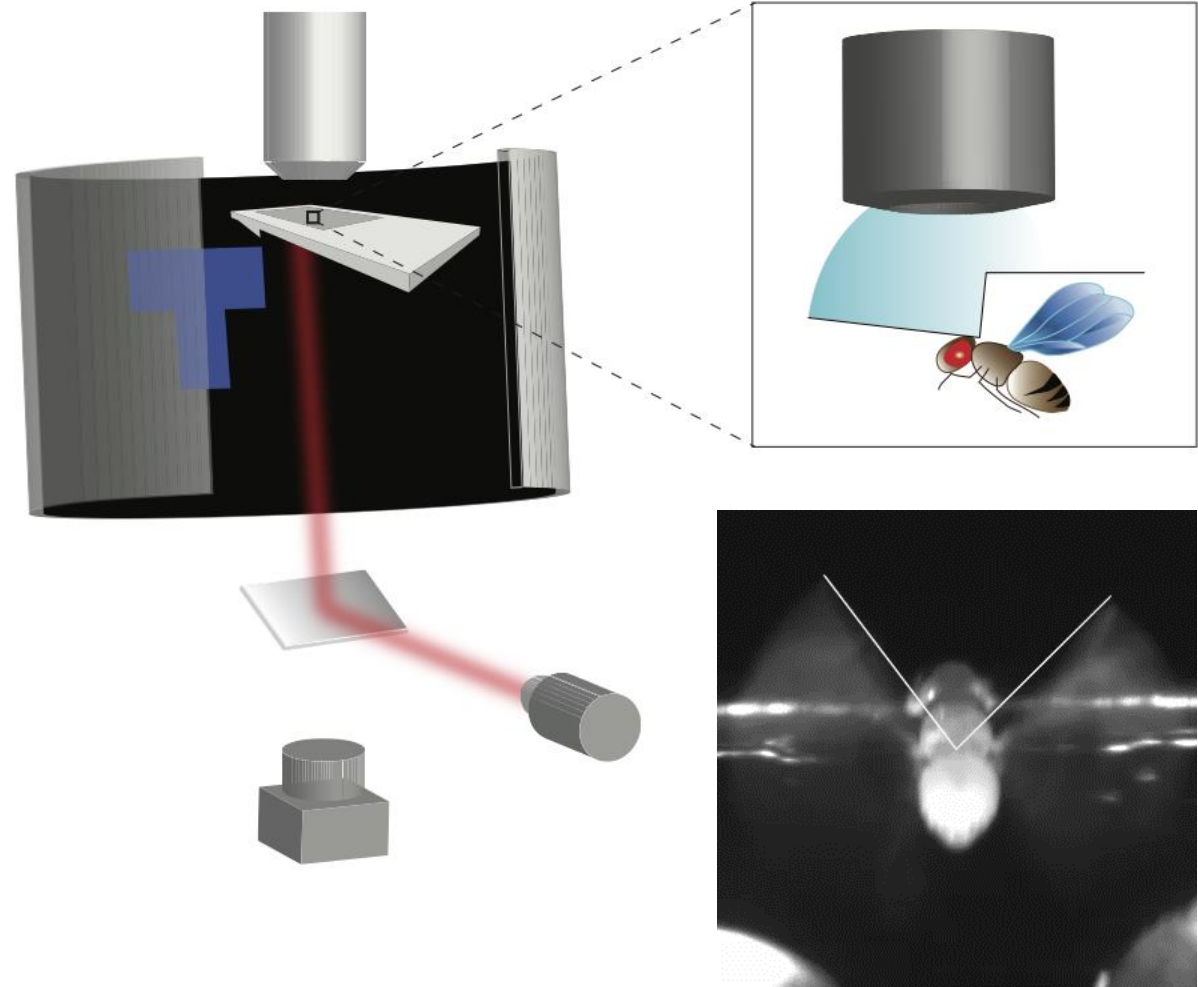
Drosophila can encode trace memories



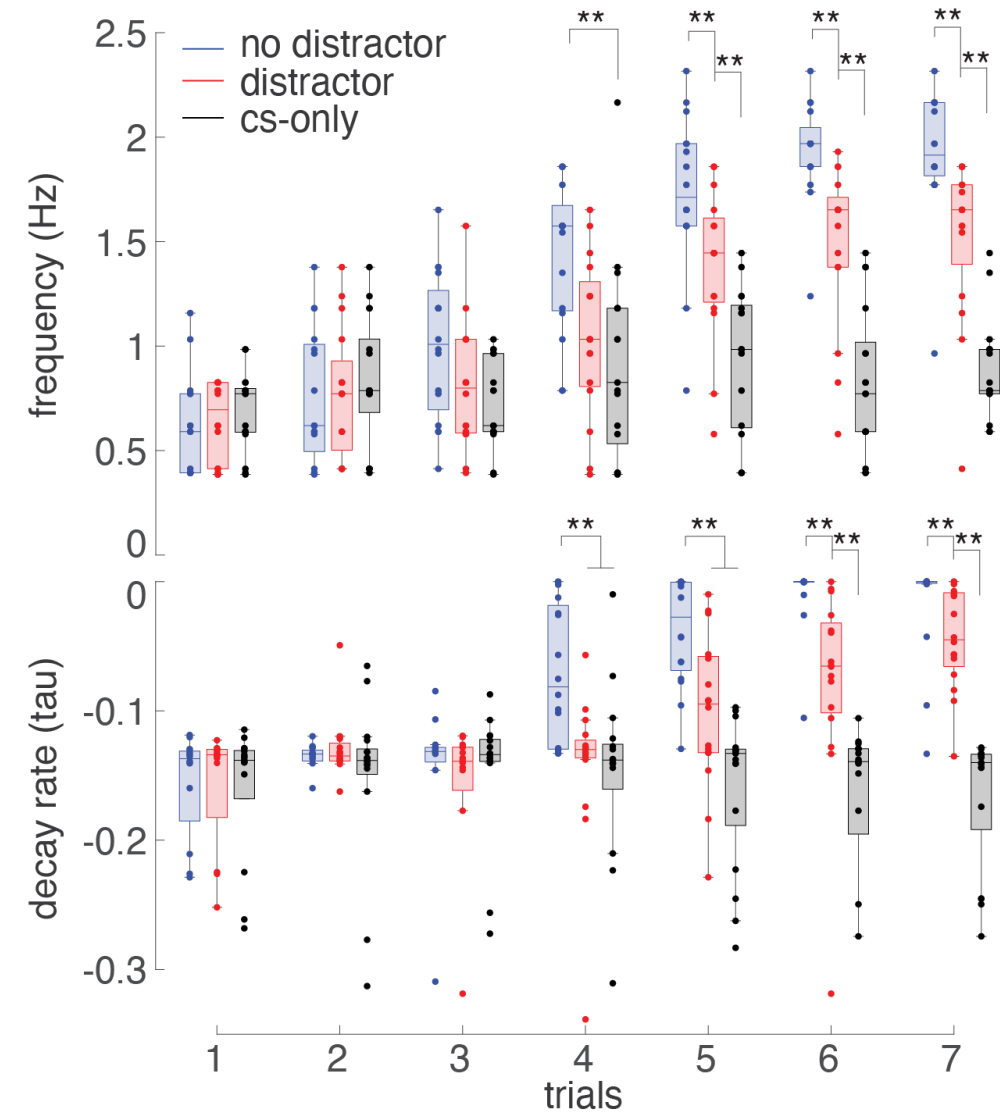
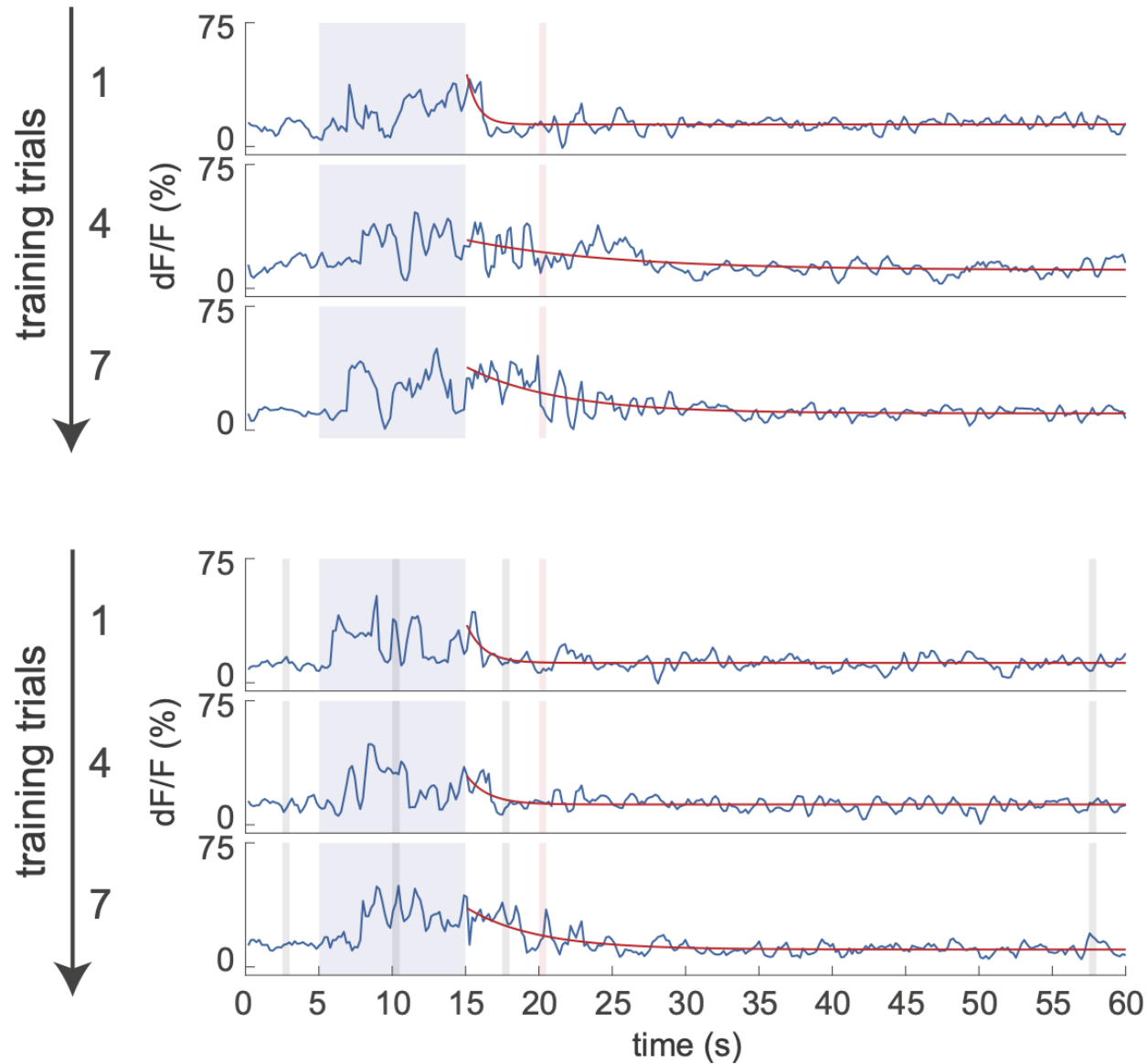
In vivo two-photon imaging of brain activity during trace conditioning



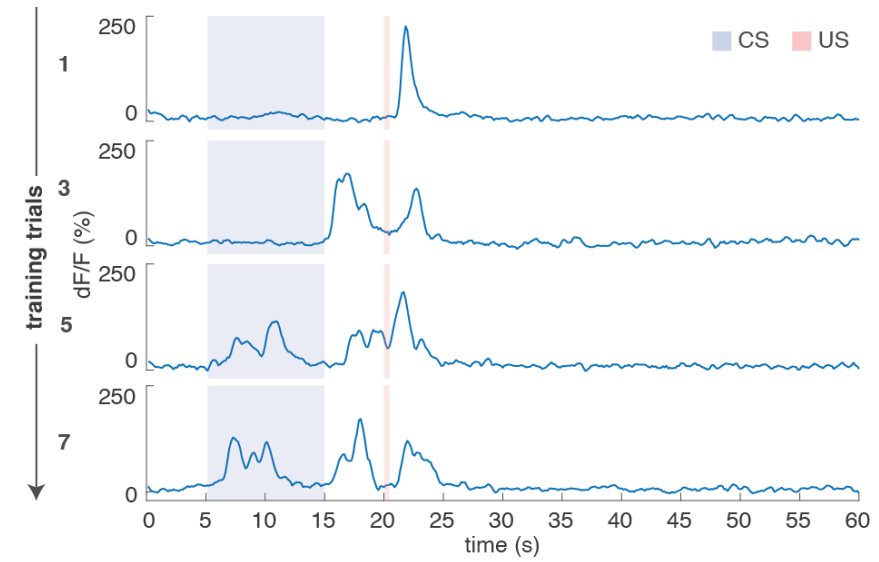
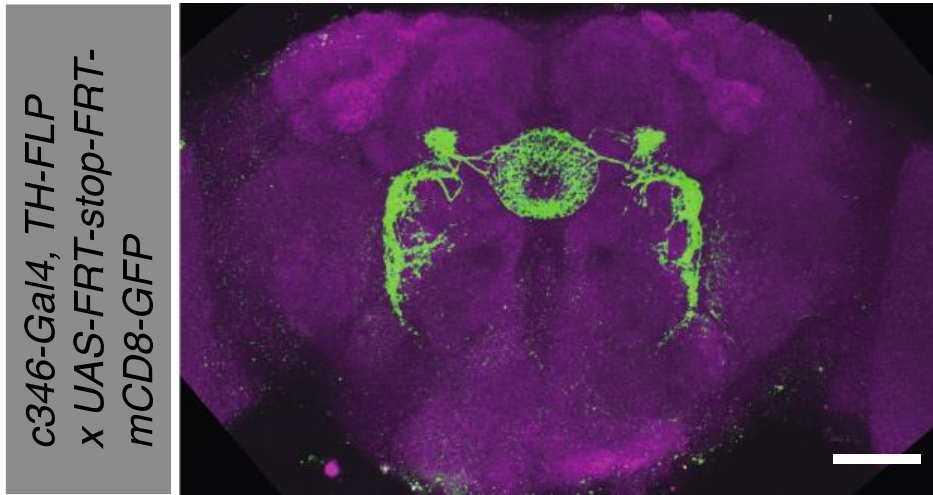
R2/R4m ring neurons of
the ellipsoid body



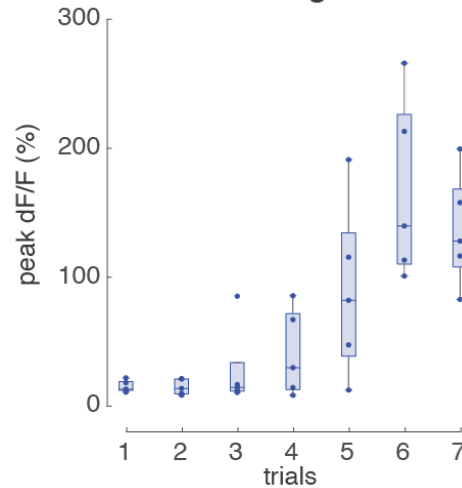
CS-driven Ellipsoid Body ring neurons exhibit sustained activity



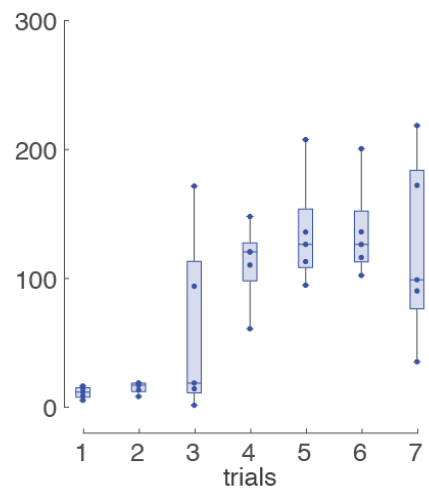
Dopamine encodes a prediction error-like activity



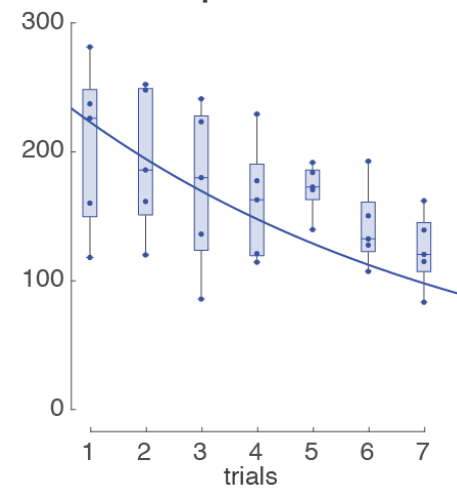
during CS



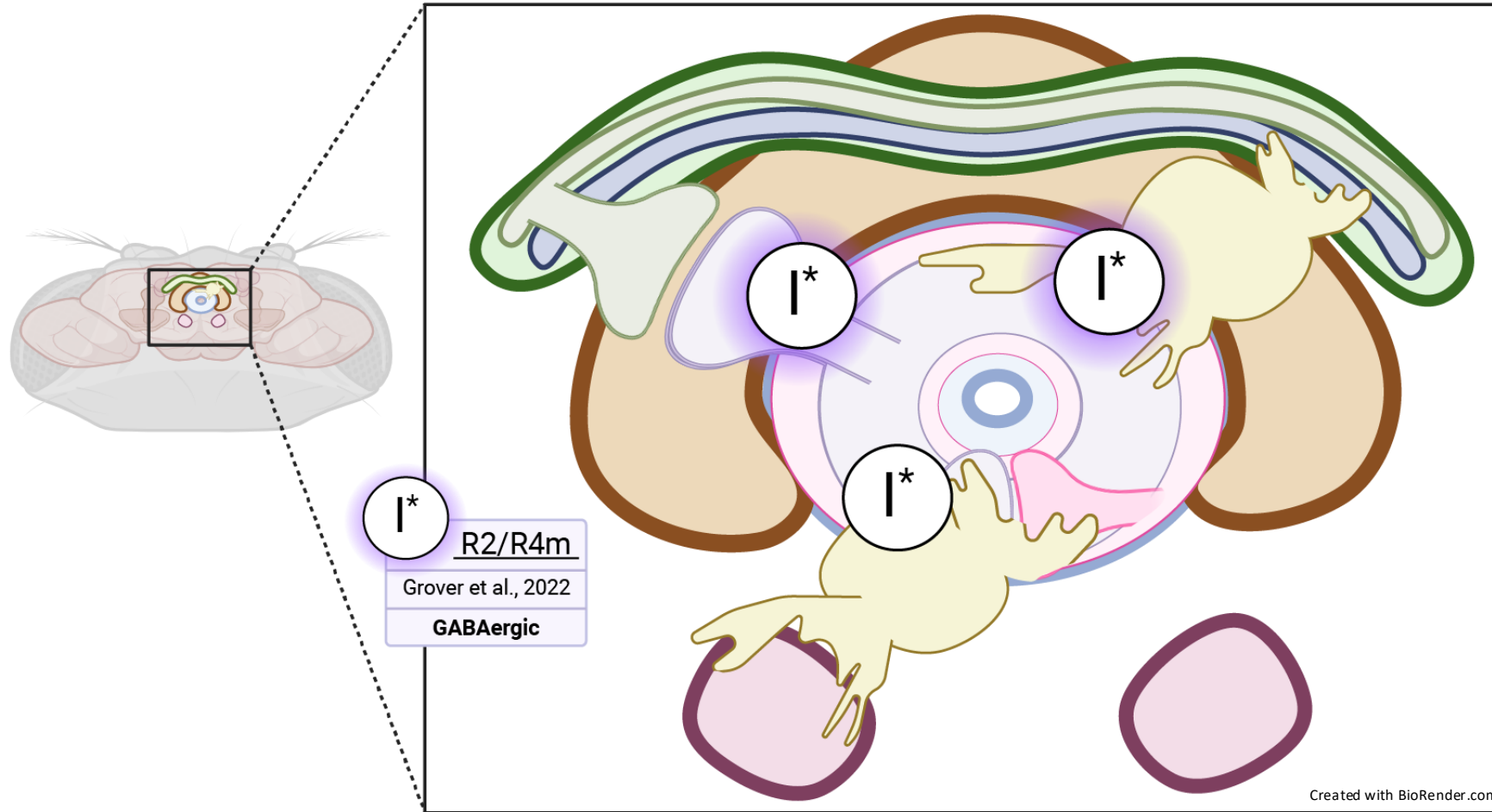
trace interval

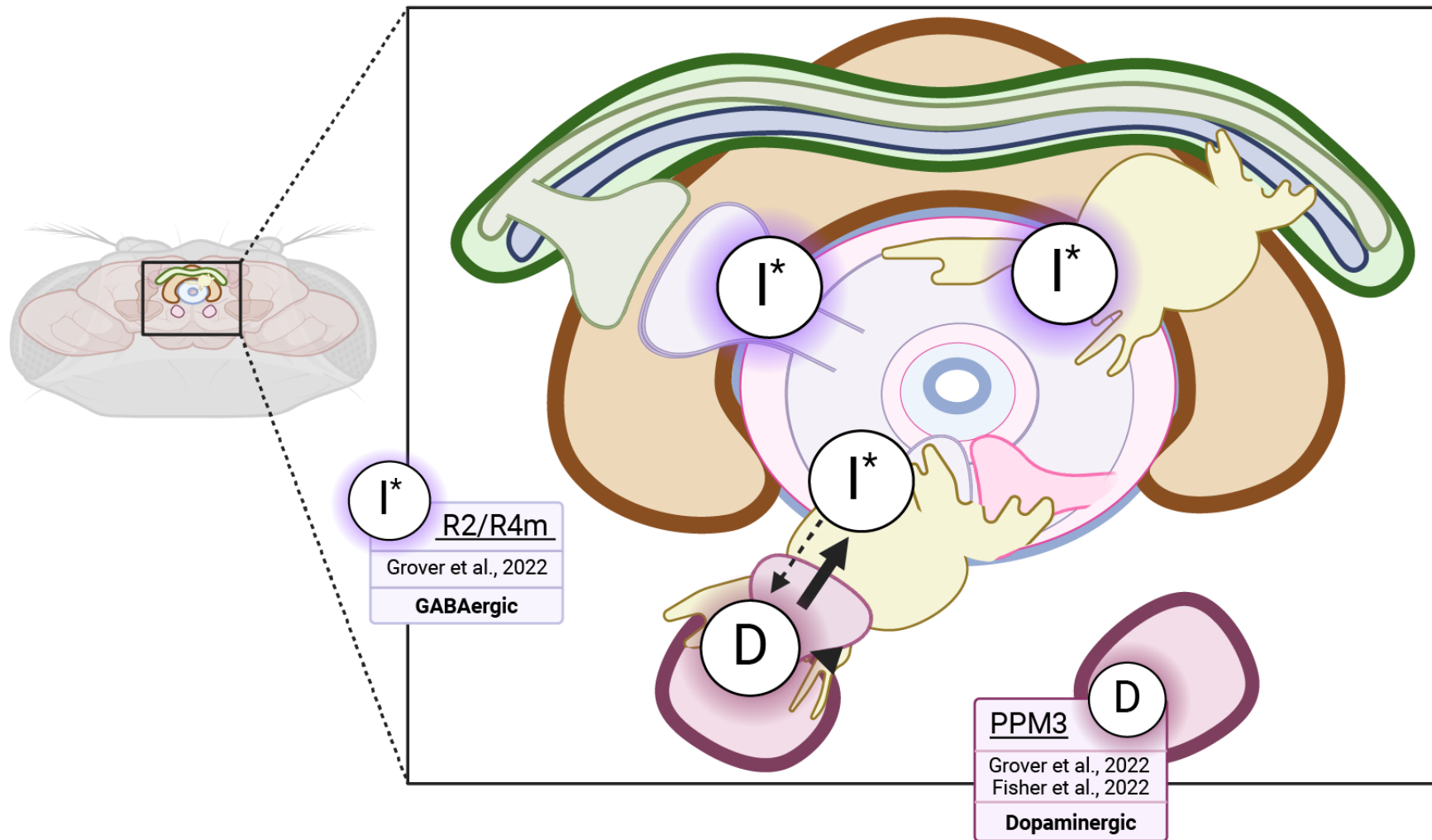


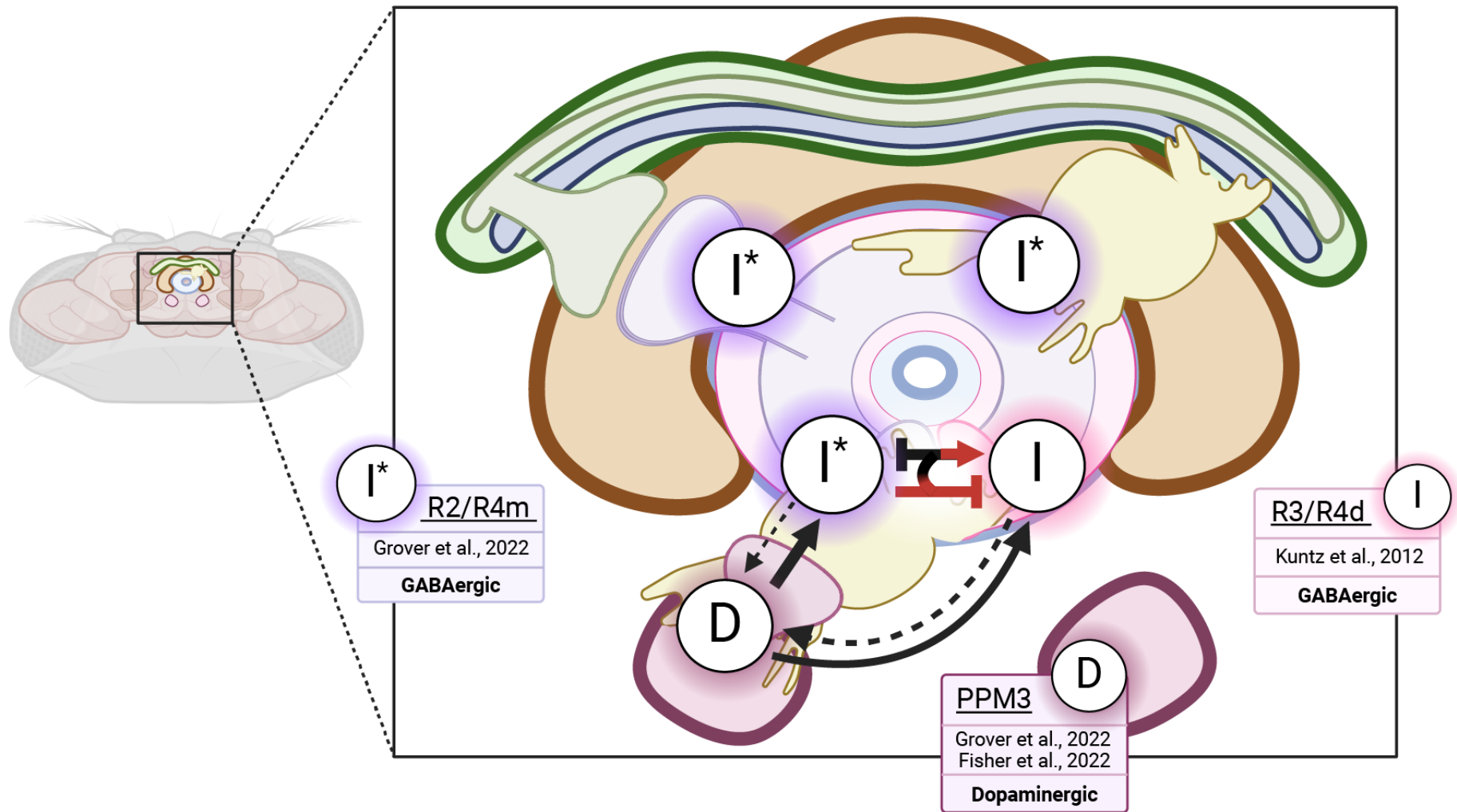
post US

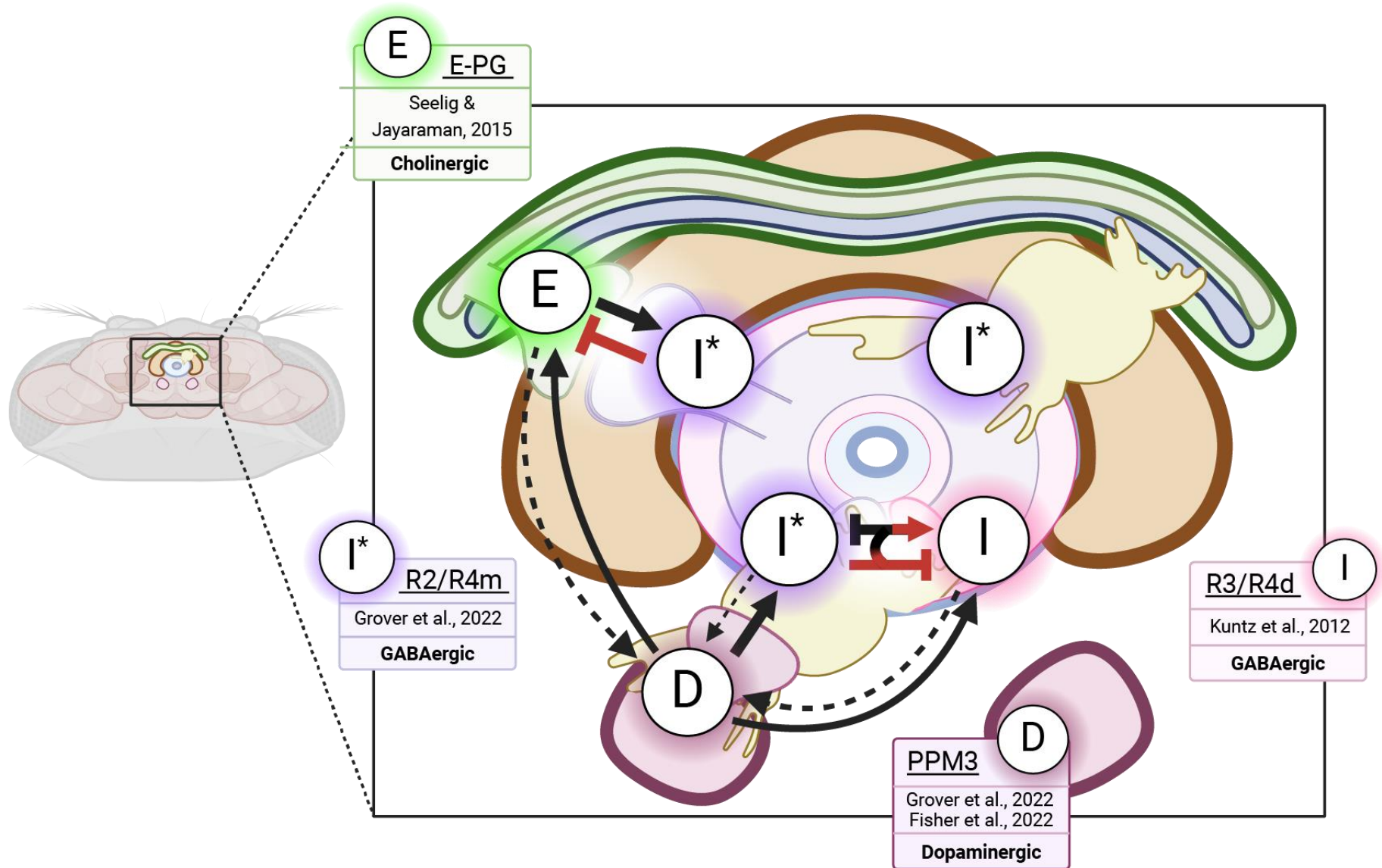


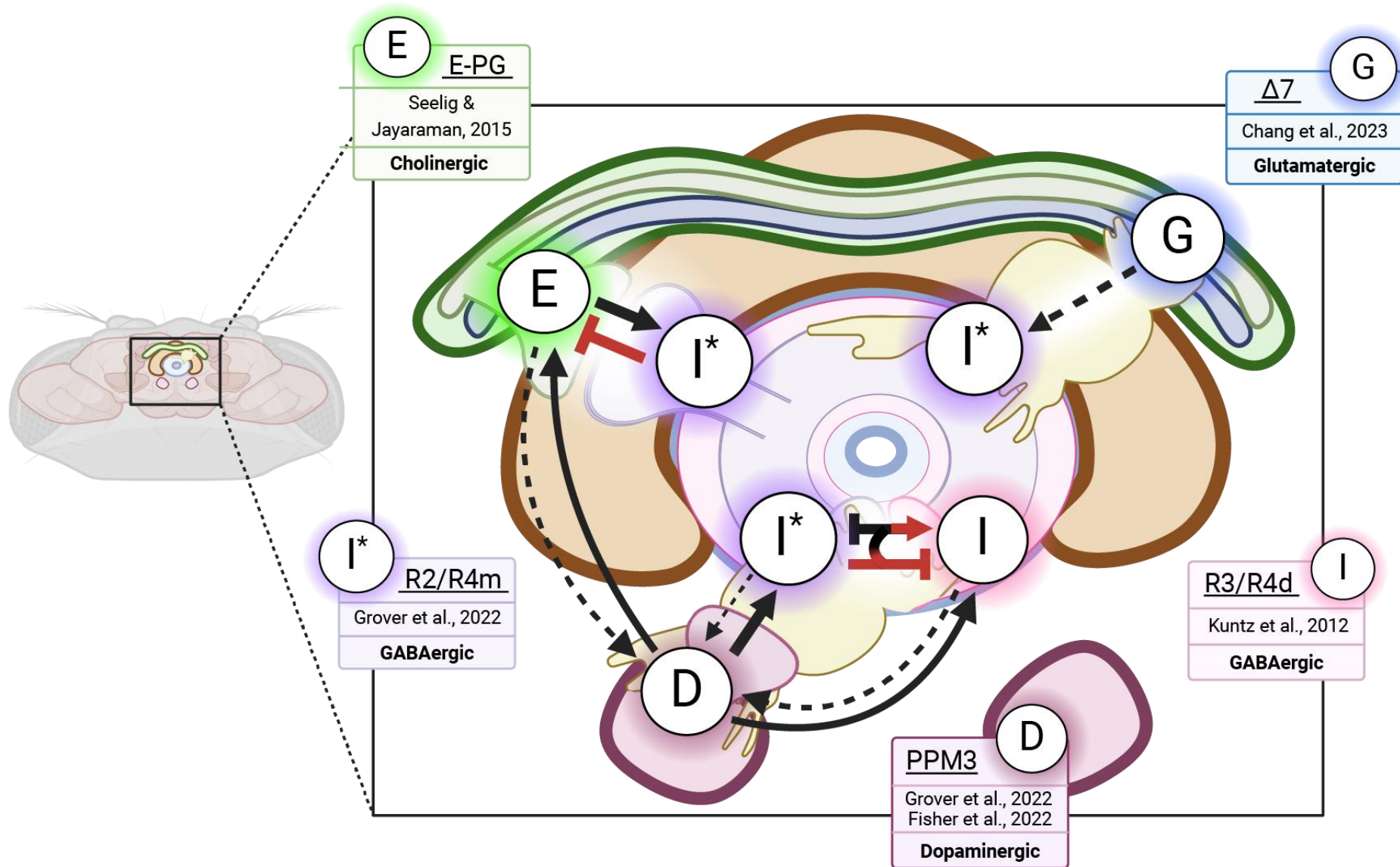
Insights from the fly connectome

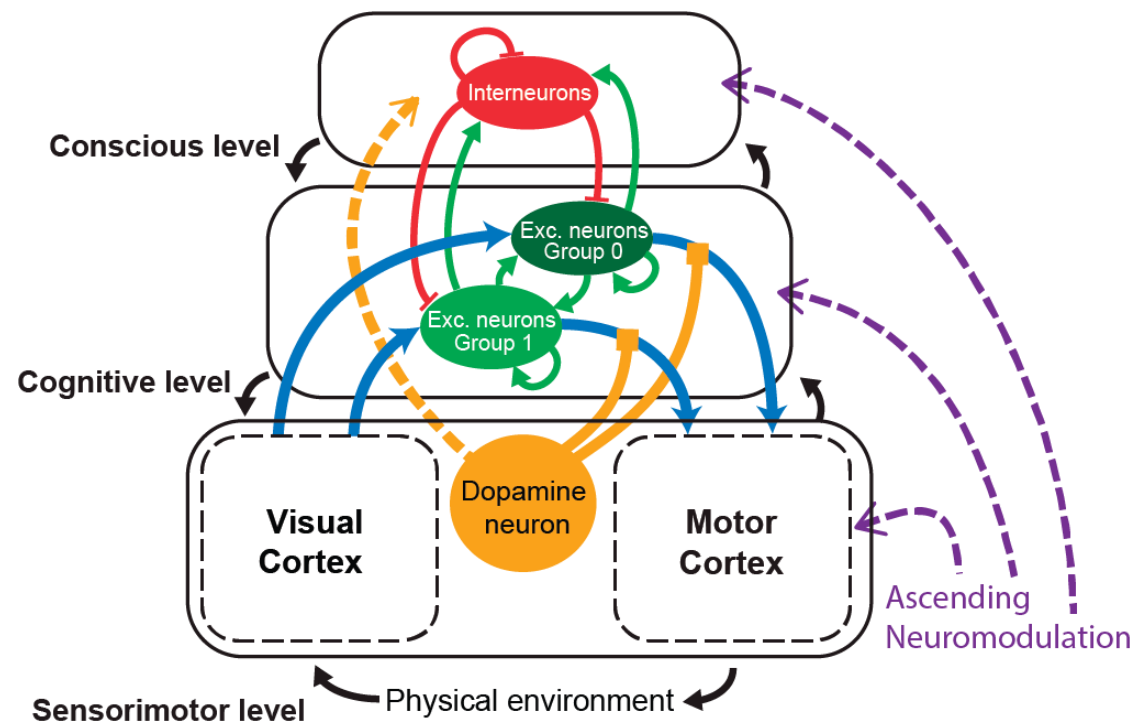
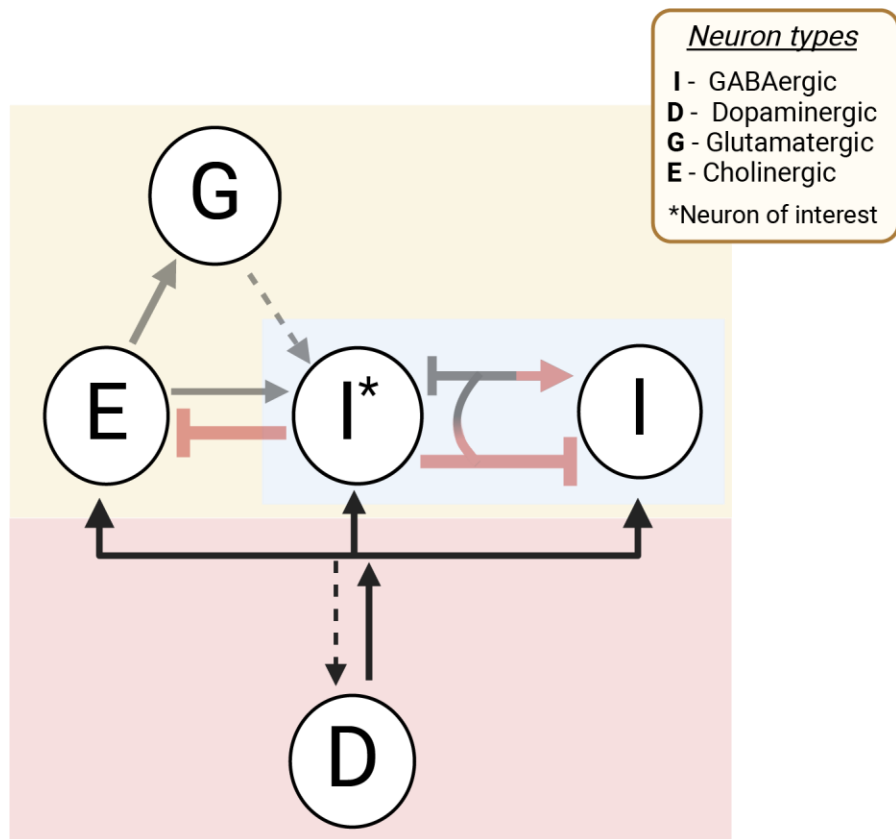






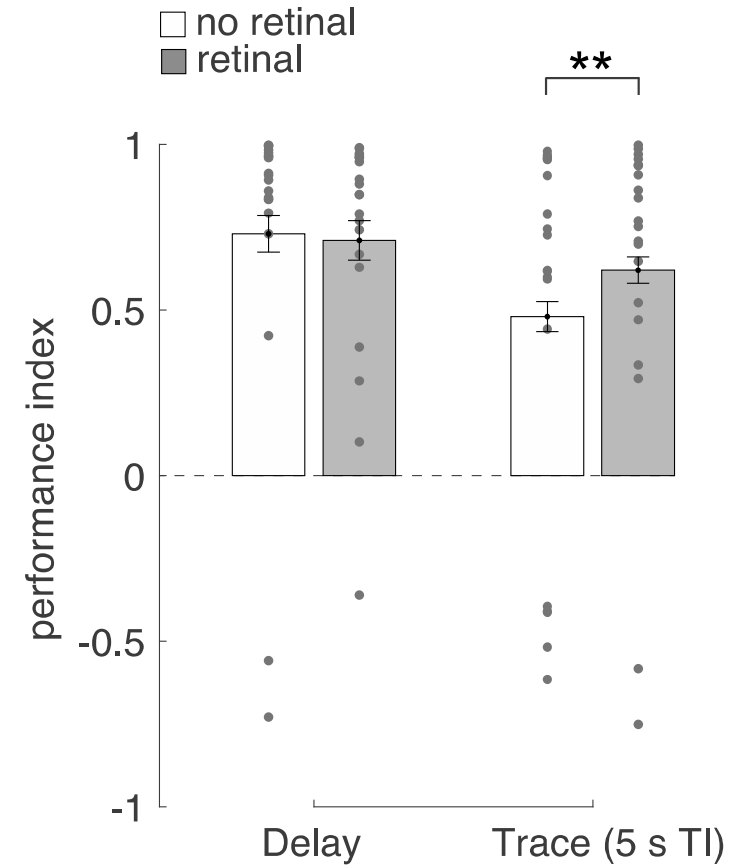
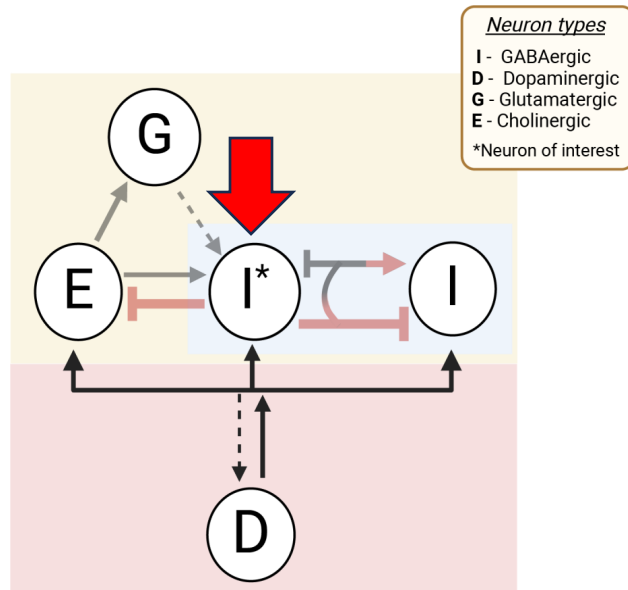




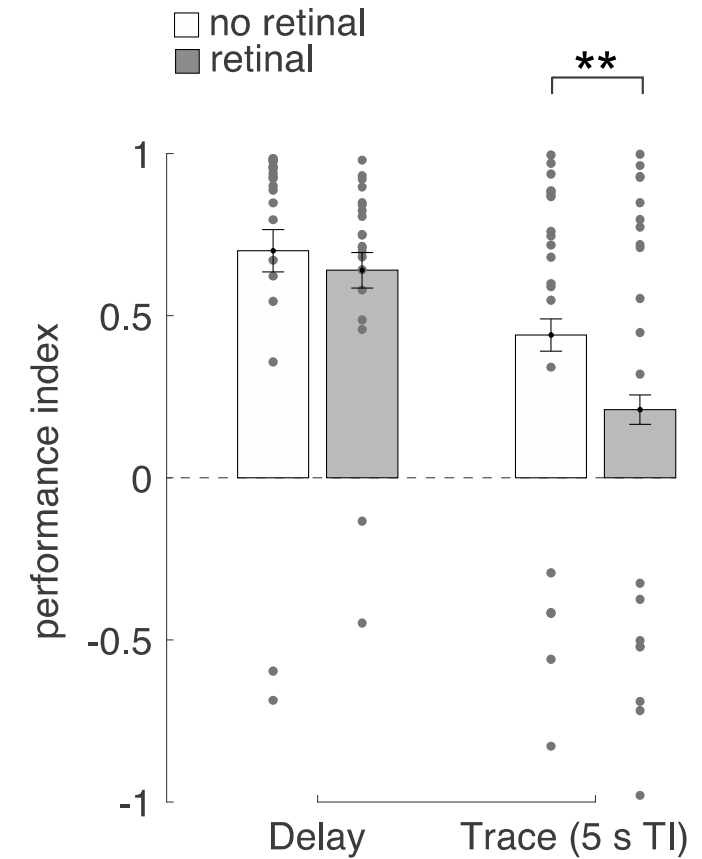
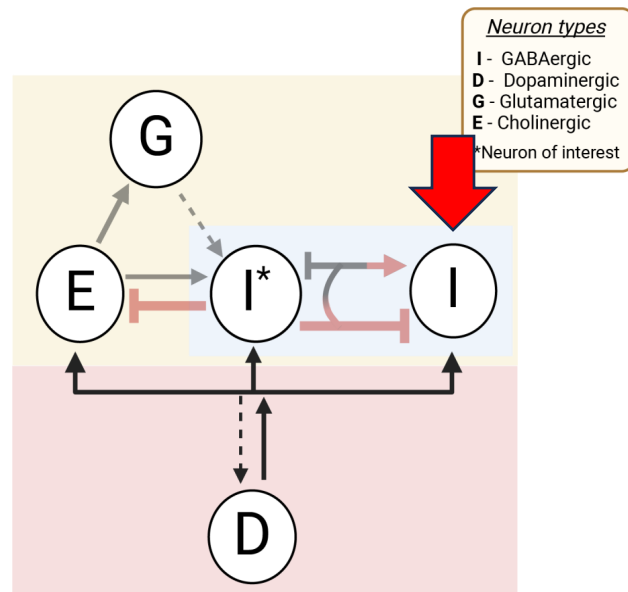


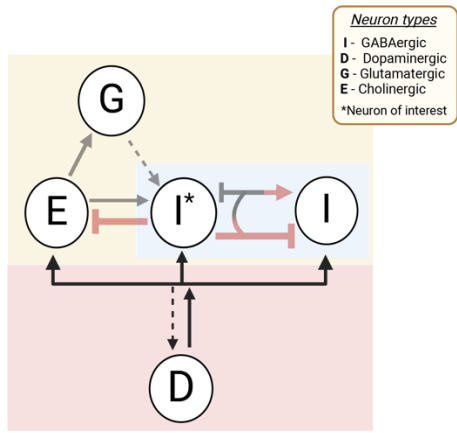
Volzhenin et al, PNAS, 2022

CsChrimson optogenetic activation of R2/R4m neurons during trace interval



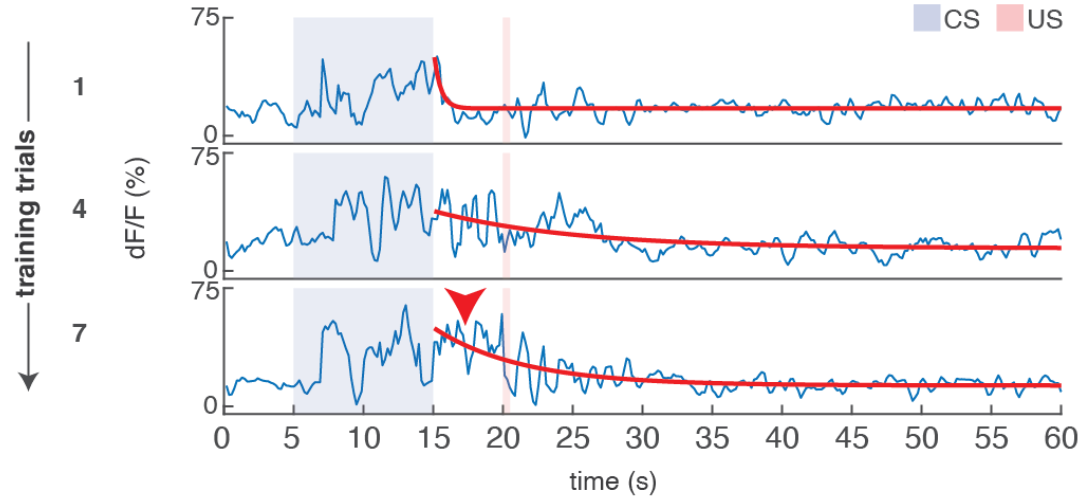
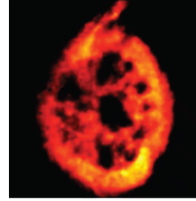
Optogenetic activation of R3/R4d neurons during trace interval



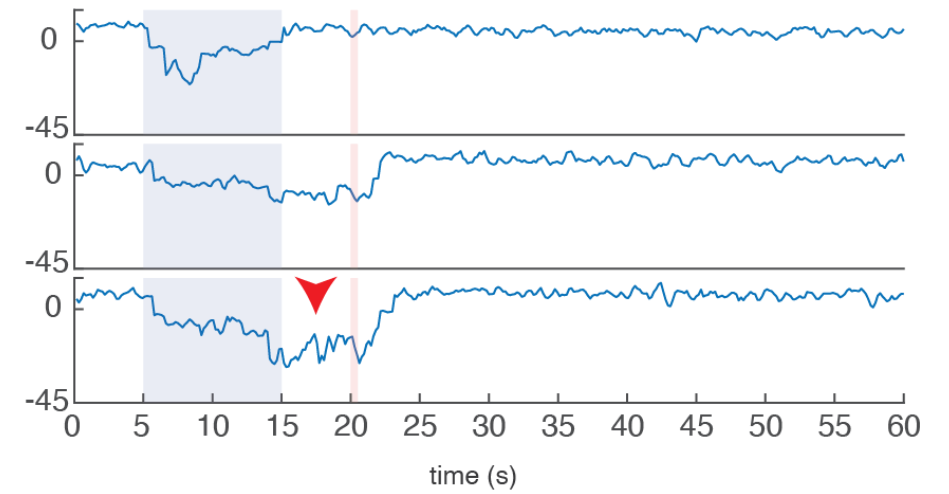
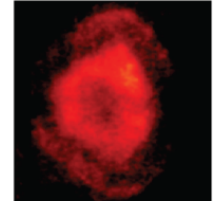


Inhibitory signaling key to persisting activity

R2/R4m
EB1>>GCaMP6f-tdTomato



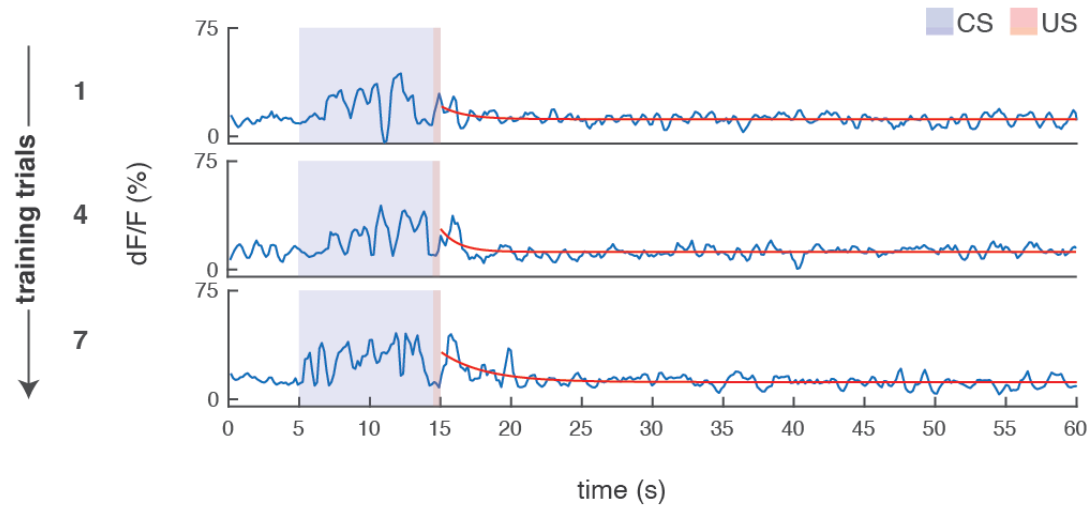
R3/R4d
c232>>GCaMP6f-tdTomato



Persisting activity not required for delay conditioning

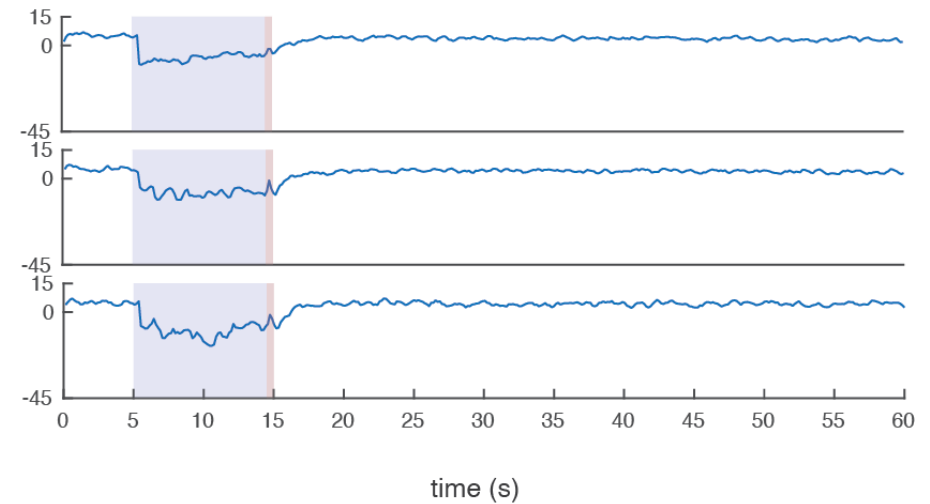
R2/R4m

EB1>>GCaMP6f-tdTomato

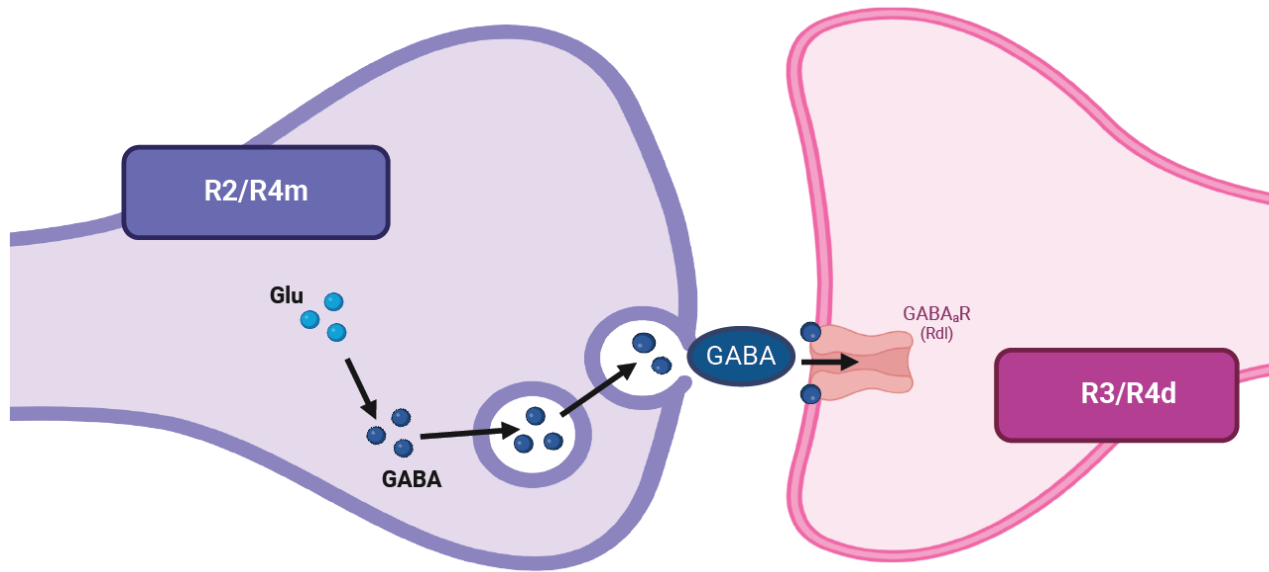


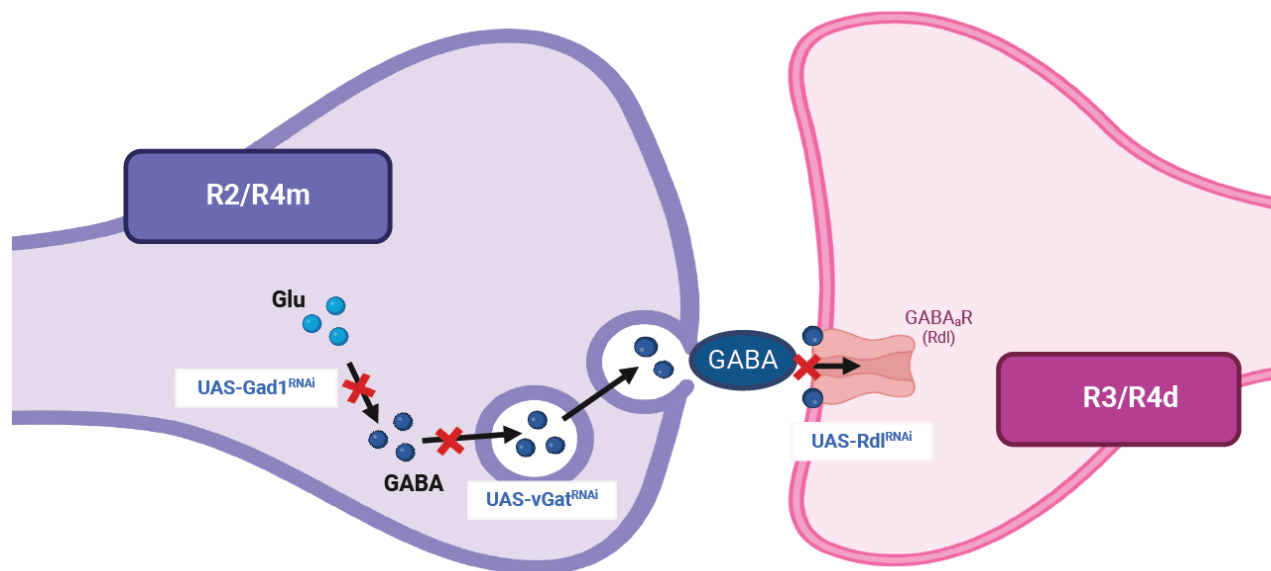
R3/R4d

c232>>GCaMP6f-tdTomato



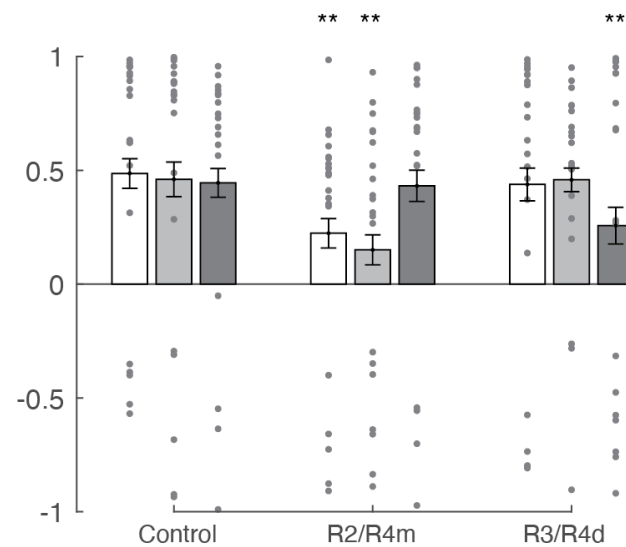
Cellular mechanisms of a non-coincidence detector in trace learning



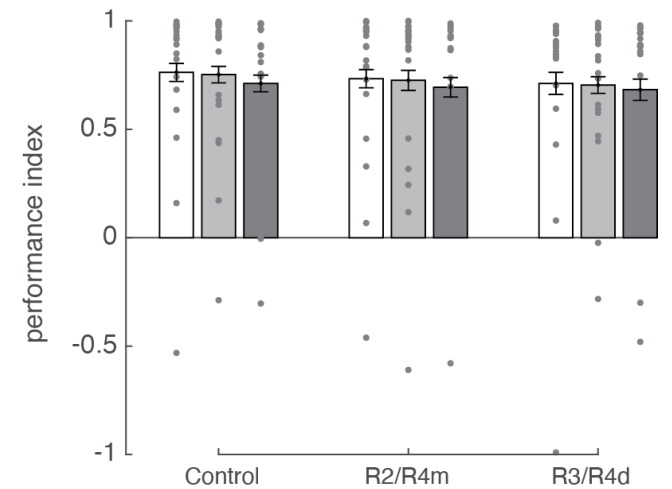


UAS-Gad1-RNAi
 UAS-vGat-RNAi
 UAS-Rdl-RNAi

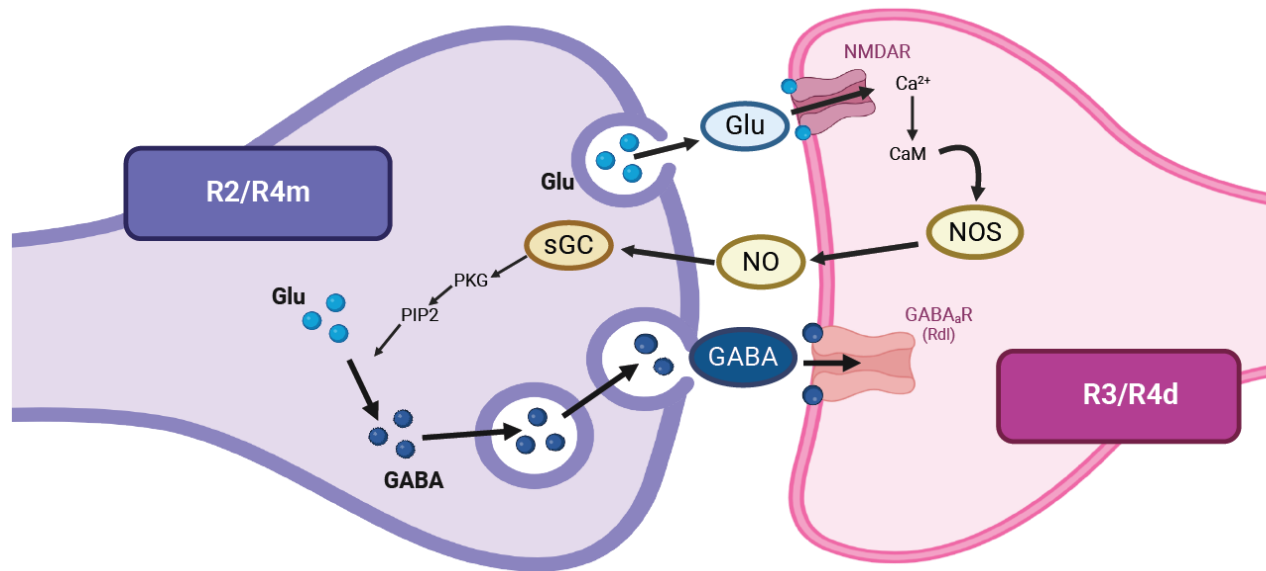
trace conditioning (5s trace interval)



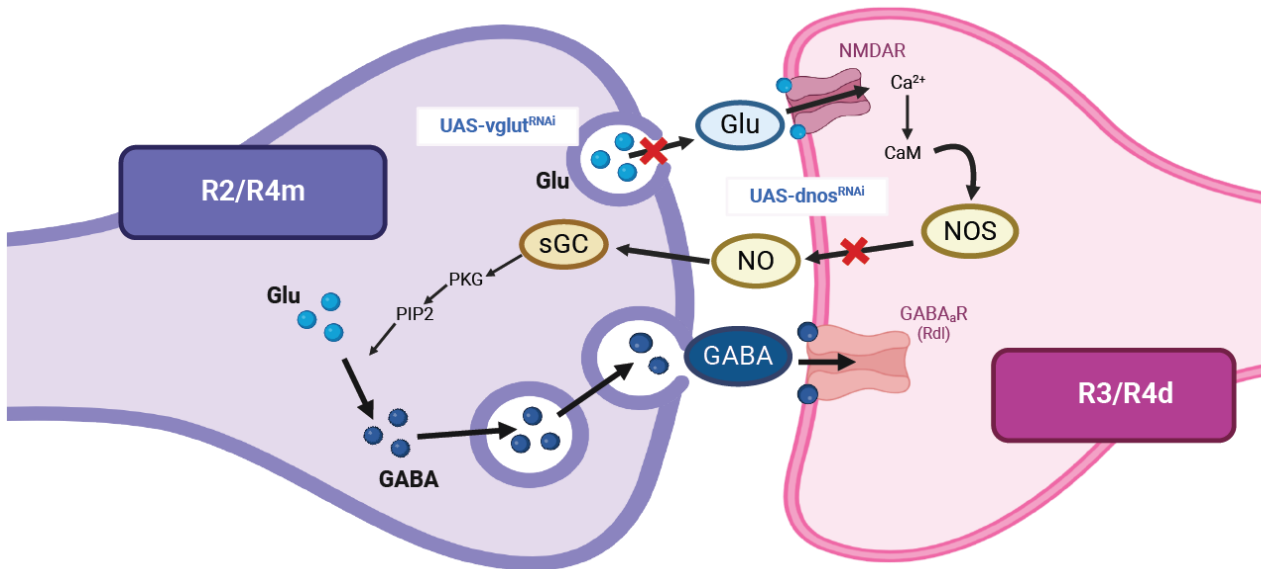
delay conditioning



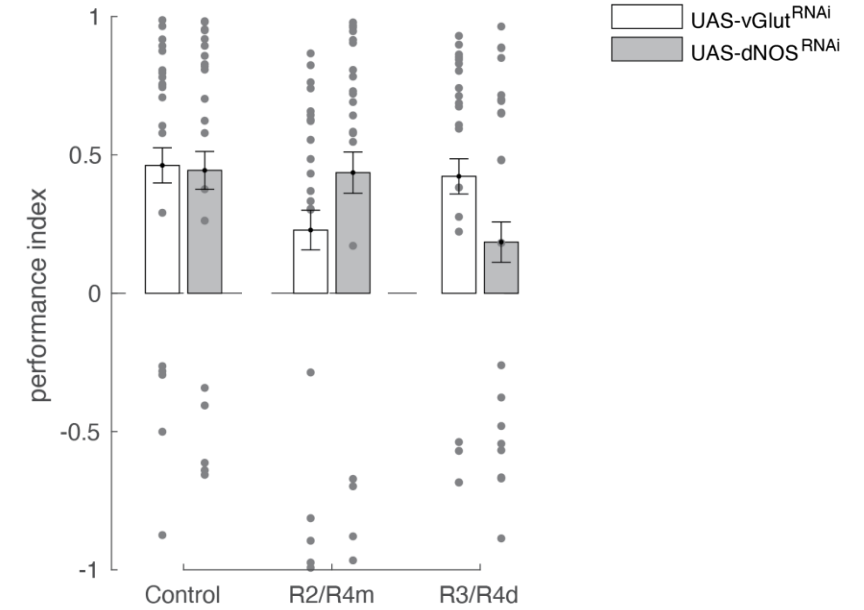
Co-transmission of Glu/NO/GABA pathway



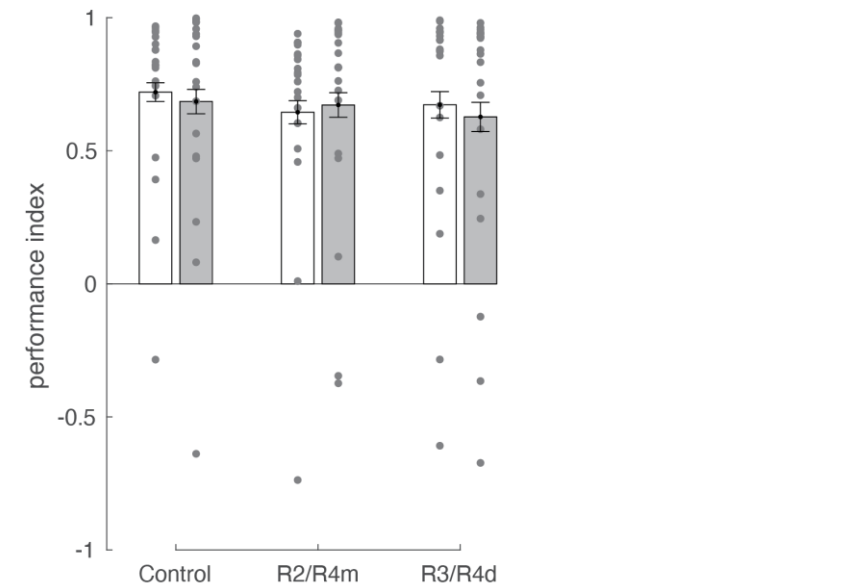
Role of NO-cGMP signaling in trace conditioning



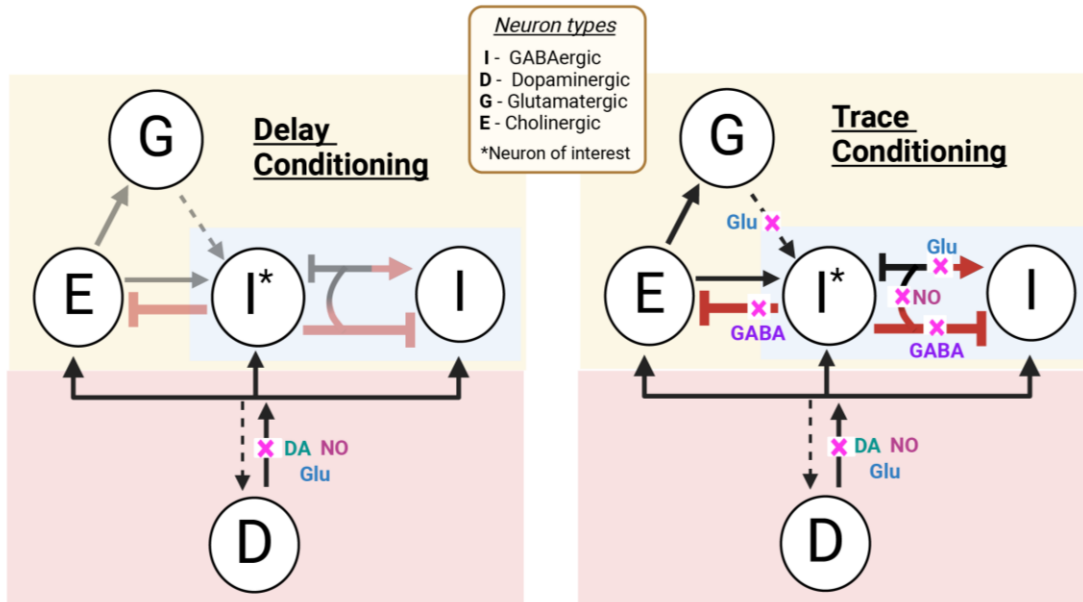
trace conditioning (5s trace interval)



delay conditioning

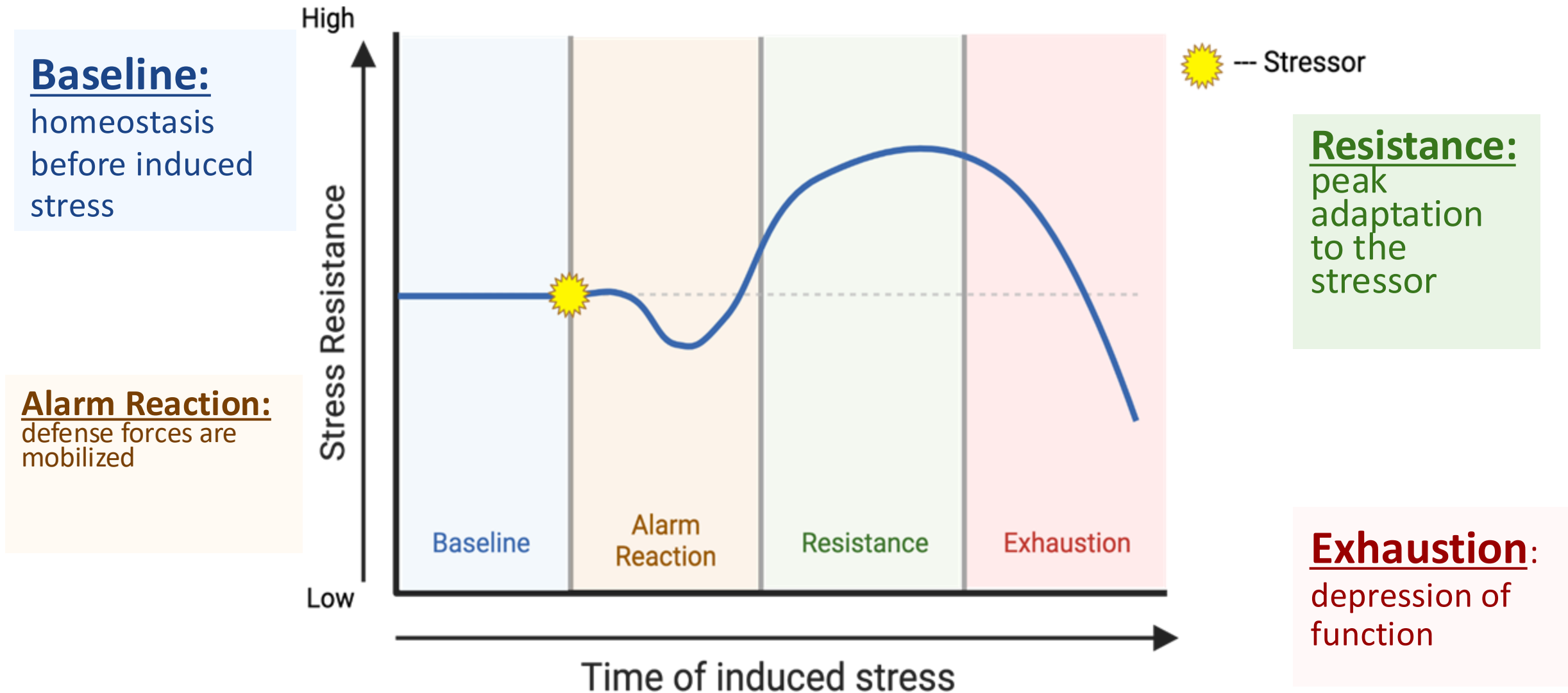


Ongoing work



- Fast GABA release vs. Glu/NO triggered GABA synthesis enables sustained activity
 - Does disrupting GABA signaling affect oscillatory activity (R2/R4m>>UAS-Gad1; UAS-GCaMP6f)?
- cAMP/cGMP convergence during GABA signaling drives neural oscillations
 - *In vivo* imaging of cAMP (UAS-cAMP_{Pr}) and cGMP (UAS-CUTie2) in R2/R4m (I*)

Coping with stress -- General adaptation syndrome



Chronic stress induces depressive-like state in *Drosophila*

A pair of dopamine neurons mediate chronic stress signals to induce learning deficit in *Drosophila melanogaster*

Jia Jia^{a,1}, Lei He^{a,1}, Junfei Yang^{a,1}, Yichun Shuai^b, Jingjing Yang^a, Yalan Wu^a, Xin Liu^a, Tianli Chen^a, Guaxiu Wang^a, Xingyu Wang^a, Xiaoxu Song^a, Zhaowen Ding^a, Yan Zhu^{c,d}, Li Zhang^e, Peng Chen^{e,2}, and Hongtao Qin^{a,2}

Serotonin modulates a depression-like state in *Drosophila* responsive to lithium treatment

Ariane-Saskia Ries¹, Tim Hermanns¹, Burkhard Poeck¹ & Roland Strauss¹

Stress affects dopaminergic signaling pathways in *Drosophila melanogaster*

WENDI S. NECKAMEYER, & JOSHUA S. WEINSTEIN

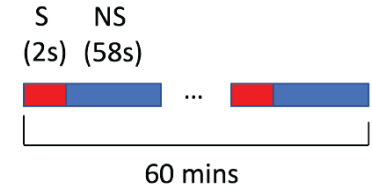
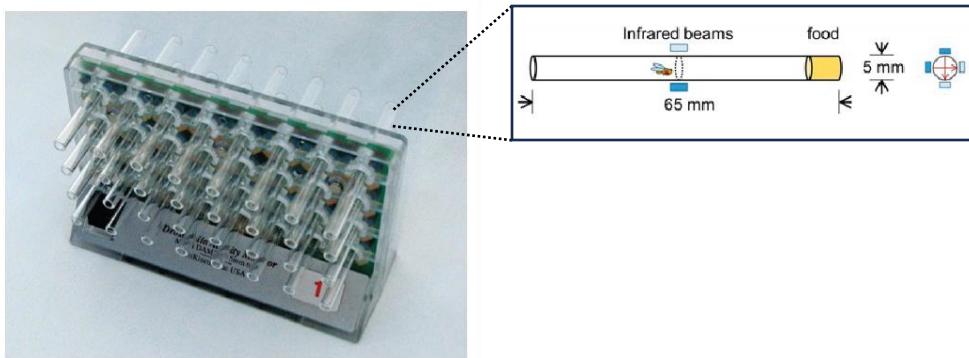
Chronic unpredictable mild stress-induced depressive-like behavior and dysregulation of brain levels of biogenic amines in *Drosophila melanogaster*

Stéfani Machado Araujo^a, Marcia Rósula Poetini^a, Vandrezza Cardoso Bortolotto^a, Shanda de Freitas Couto^{a, b}, Franciane Cabral Pinheiro^a, Luana Barreto Meichtry^a, Francielli Polet de Almeida^a, Elize Aparecida Santos Musachio^a, Mariane Trindade de Paula^a, Marina Prigol^{a, b}  

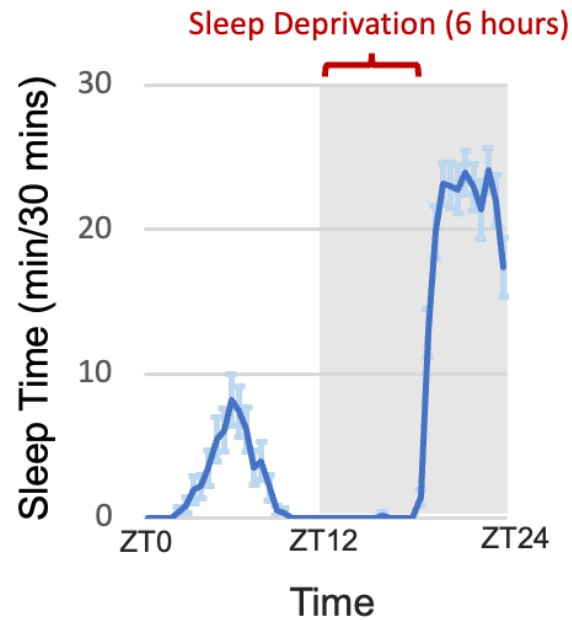
Octopamine mediates sugar relief from a chronic-stress-induced depression-like state in *Drosophila*

Tim Hermanns,¹ Sonja Graf-Boxhorn,¹ Burkhard Poeck,¹ and Roland Strauss^{1,2,*}

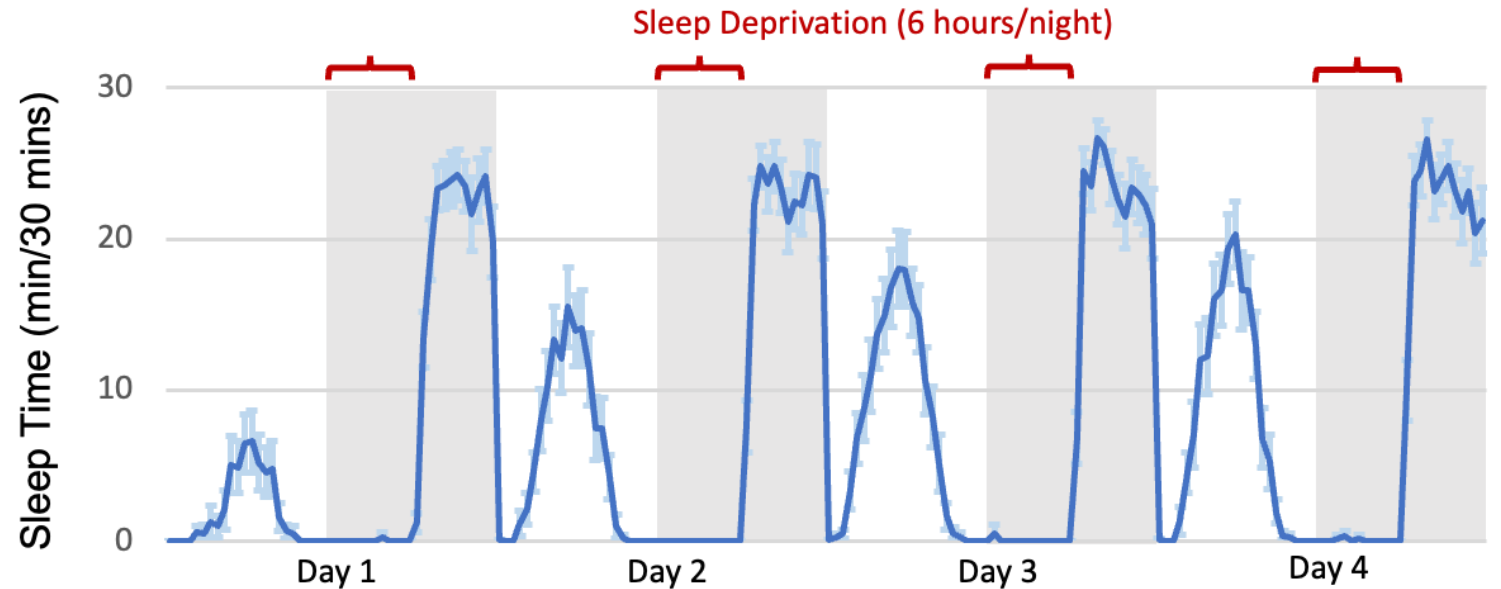
Sleep deprivation in *Drosophila*



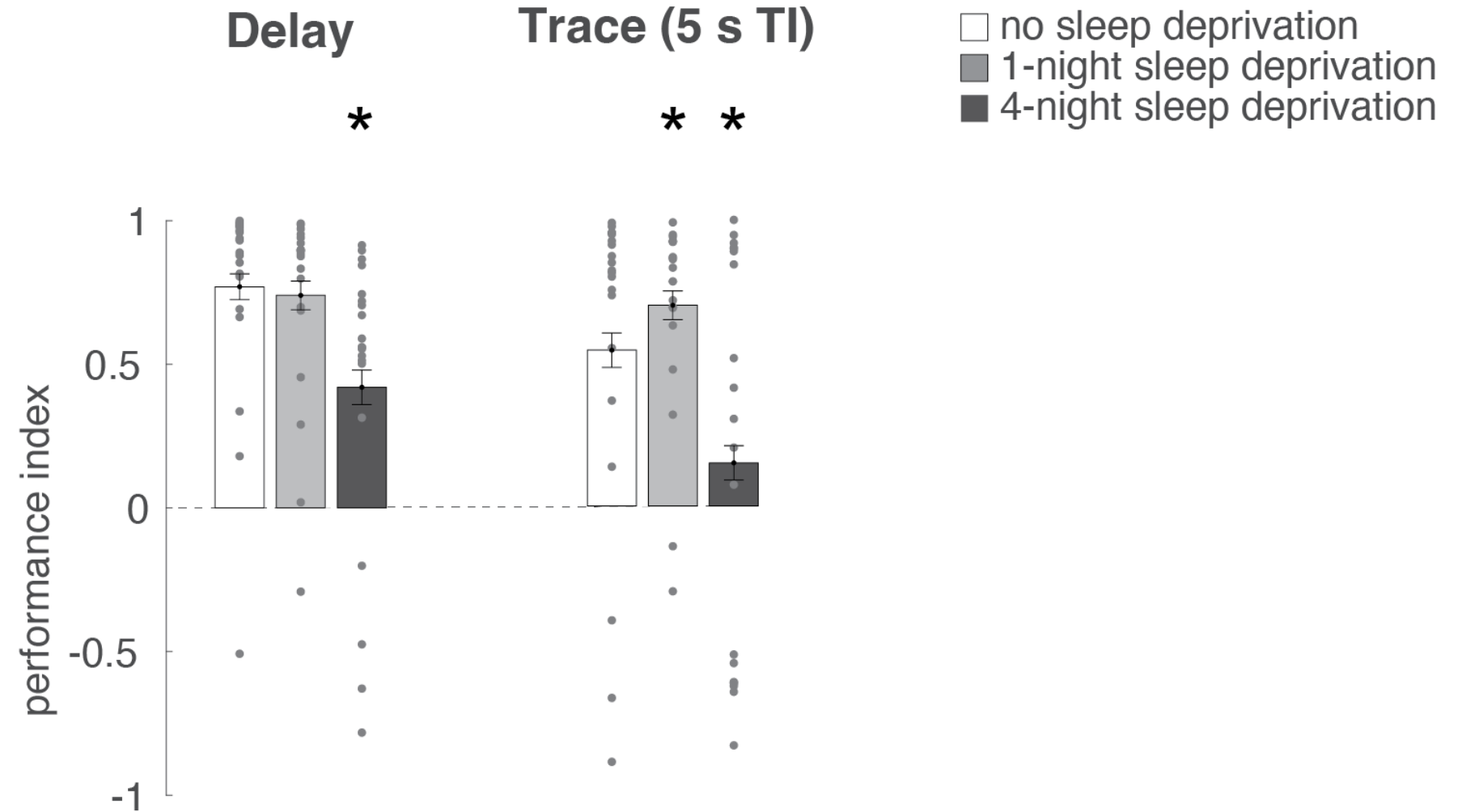
Short-term stress



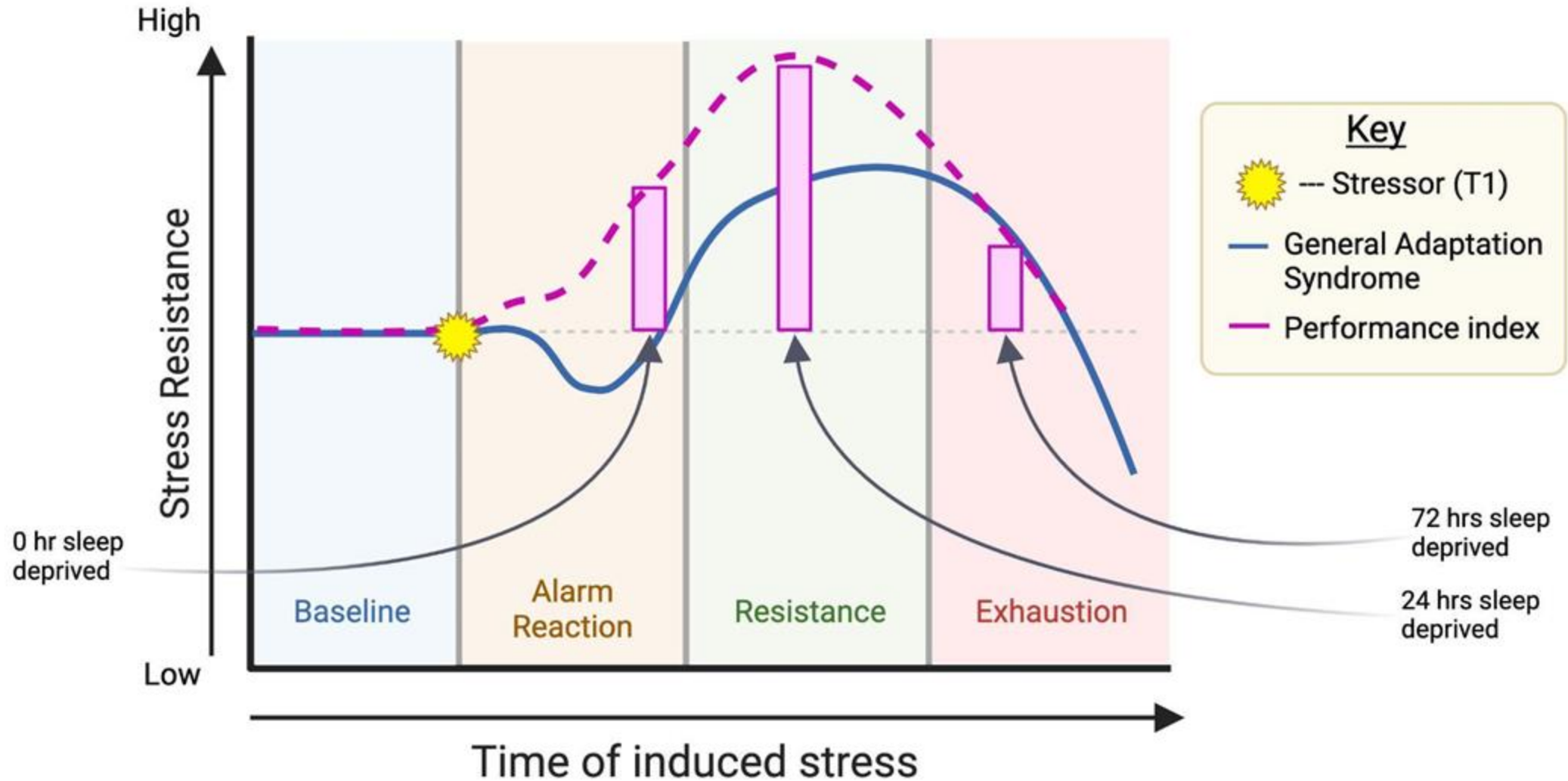
Long-term (chronic) stress



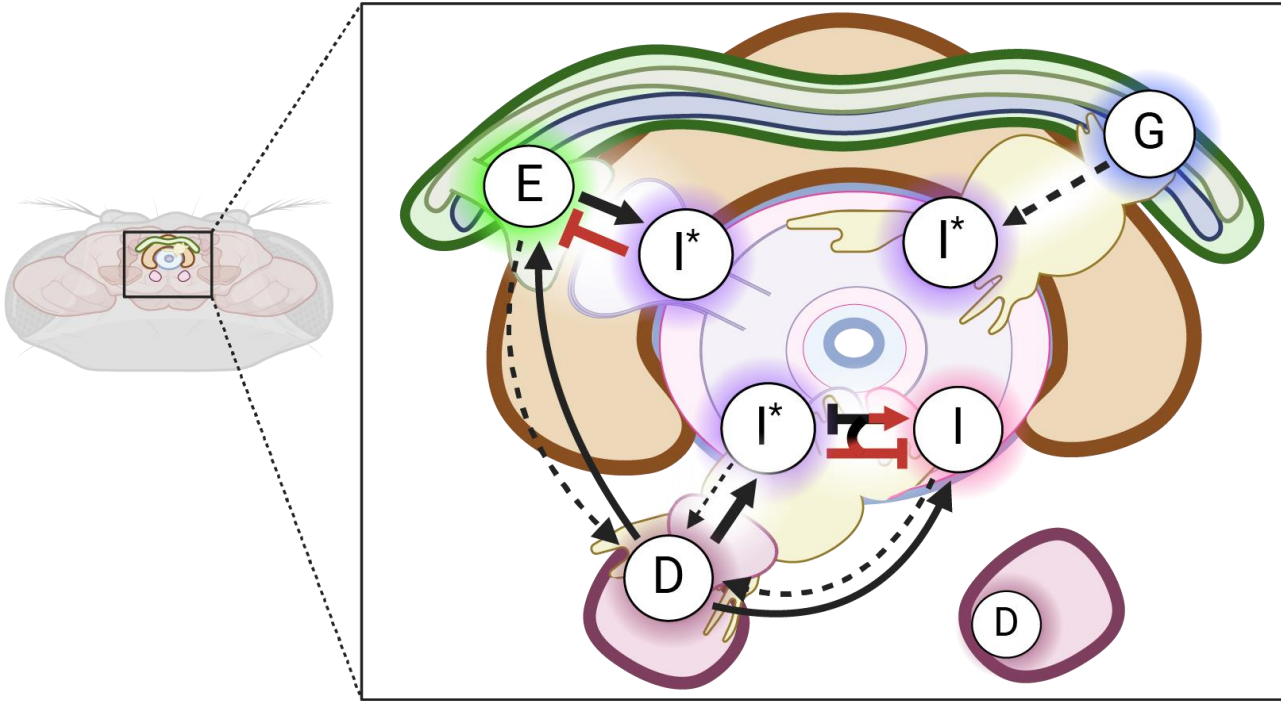
Flies exhibit resilience to short-term stress



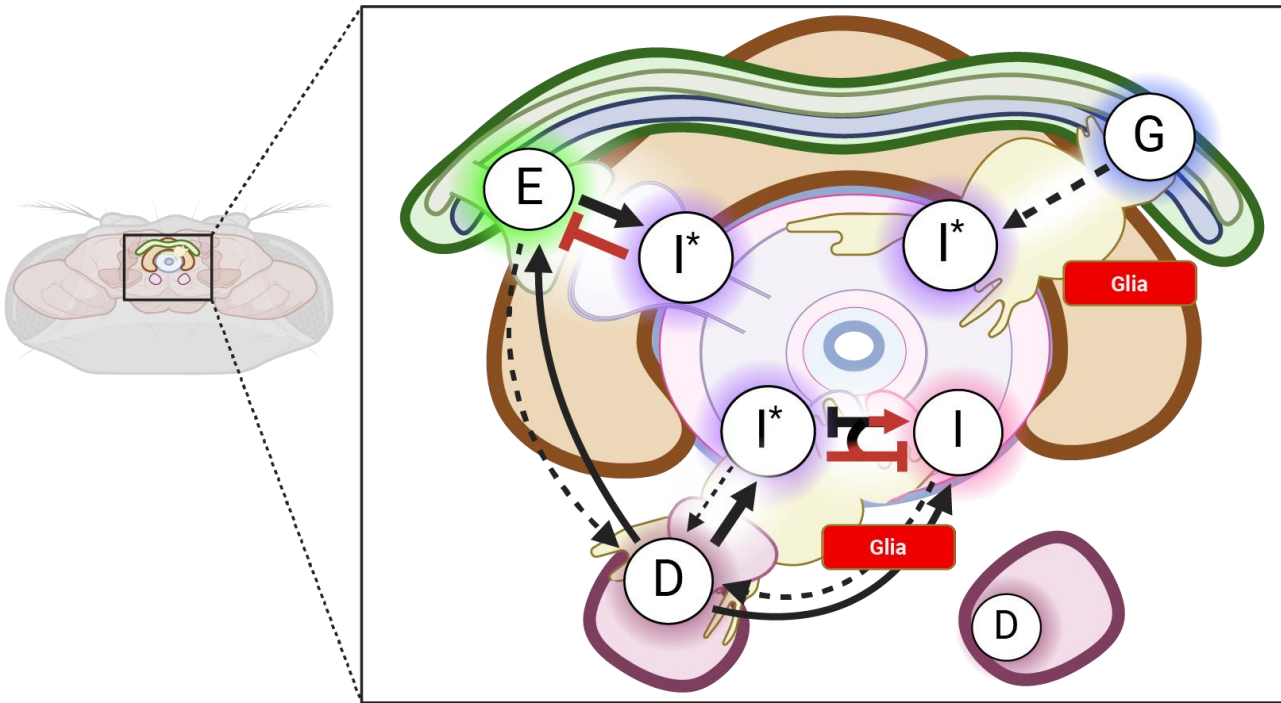
Good stress vs. bad stress



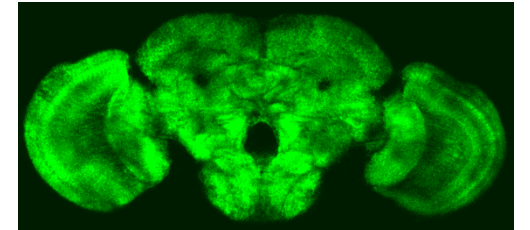
Next steps



Next steps



Astrocyte-like Glia



Ensheathing Glia

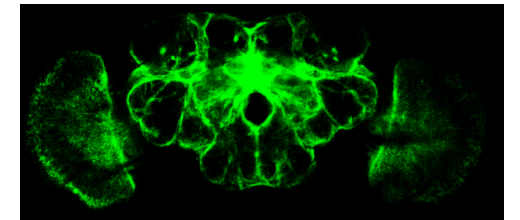
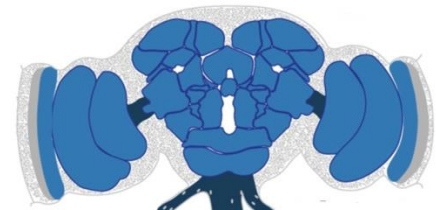
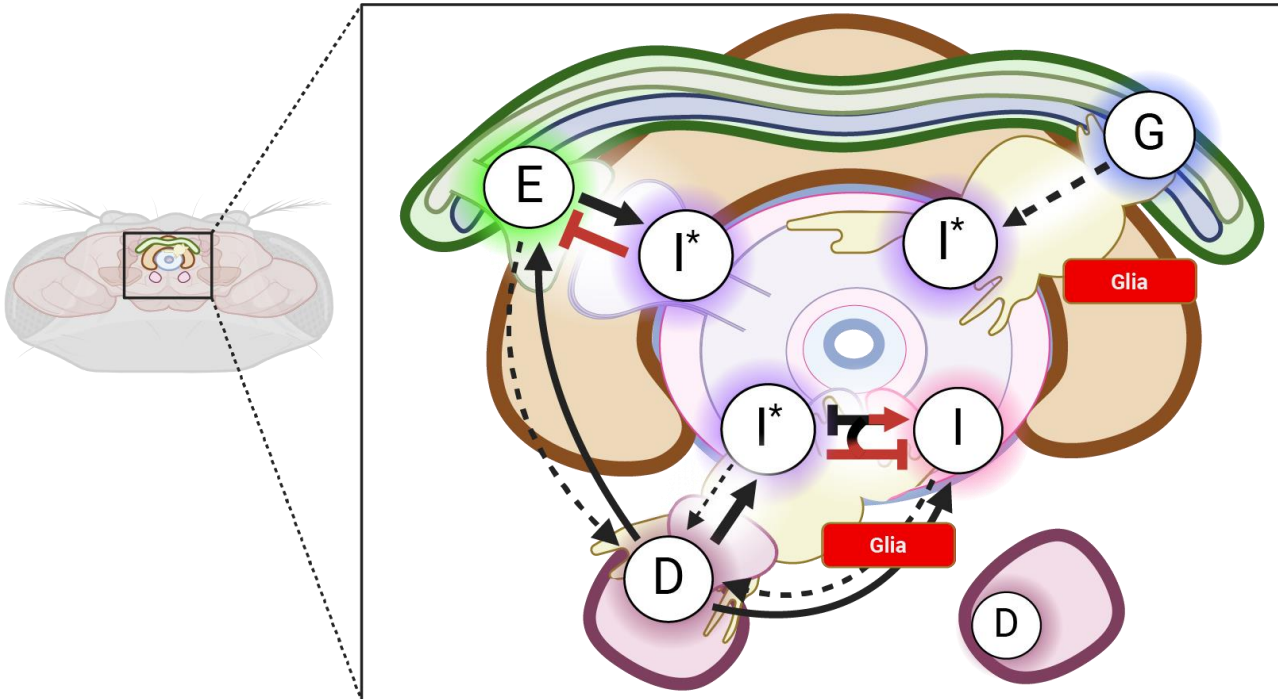


Image courtesy Jen-Yung Chen

Next steps



GCaMP7f	intracellular Ca²⁺ level
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Queen37c	intracellular ATP level
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mito-roGFP2-Orp1	intracellular ROS level
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cAMPr	cAMP level
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CUTie2	cGMP level
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FLII¹²Pglu-700μδ6	intracellular glucose level
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Thanks

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Marissa Heintschel

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Anirudh Sivarajan

Ralph Greenspan

Jean-Pierre Changeux

Jen-Yung Chen

Jiayun (Leon) Xie

Jinfang Li

Columbia

Rafael Yuste

Yuriy Shymkiv

Salk

Terry Sejnowski

Tatyana Sharpee

Mingchen Yao

AFOSR

Pat Bradshaw



The impact of stress on the neurobiology of cognition

Dhruv Grover, KIBM, UCSD



Objectives:

- (1) The role of sustained neural activity and inhibition to link temporally separated stimuli.
- (2) Molecular pathways governing energy homeostasis, memory storage and retrieval, and information processing.

Accomplishments:

Two journal papers under review during this grant period

Grover D, Greenspan RJ, Changeux J-P. Challenging conscious processing with the fly brain.

Heintschel M, Yao M, Sharpee TO, Grover, D. Inhibitory signaling drives neural persistence and working memory in *Drosophila*

Technical Approach:

Combination of virtual-reality behavior, genetic neural manipulations, and *in vivo* two photon brain imaging to reveal genes and neural circuits influencing working memory processing.

Volumetric whole brain *in vivo* imaging preparation to study long-range network interactions underlying cognition

Measurement of cAMP levels, synaptic plasticity and ATP at learning site.

Long-term chronic imaging in freely behaving flies to study effect of long-term stress on brain-wide neuromodulation.

DoD Benefit: Genes and neural circuits influencing higher cognitive functions in *Drosophila* will be relevant to human performance.

Visualizing long-term changes due to acute and chronic stress will provide valuable insights to improve cognitive performance in various contexts.

High-level cognitive learning circuitry in the fly can serve as a blueprint for developing energy and computationally optimized machine learning and AI algorithms.