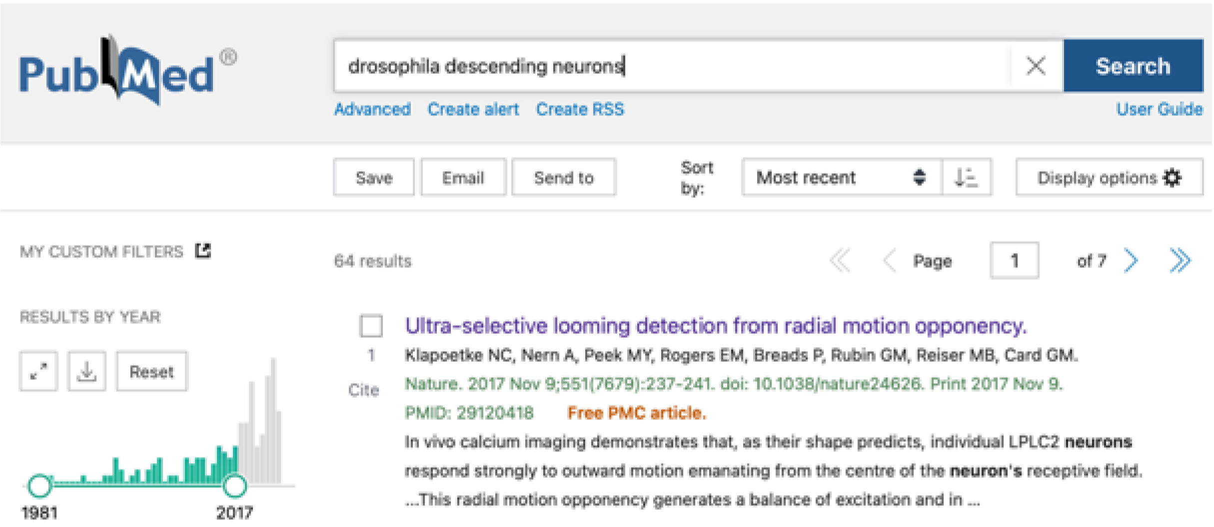
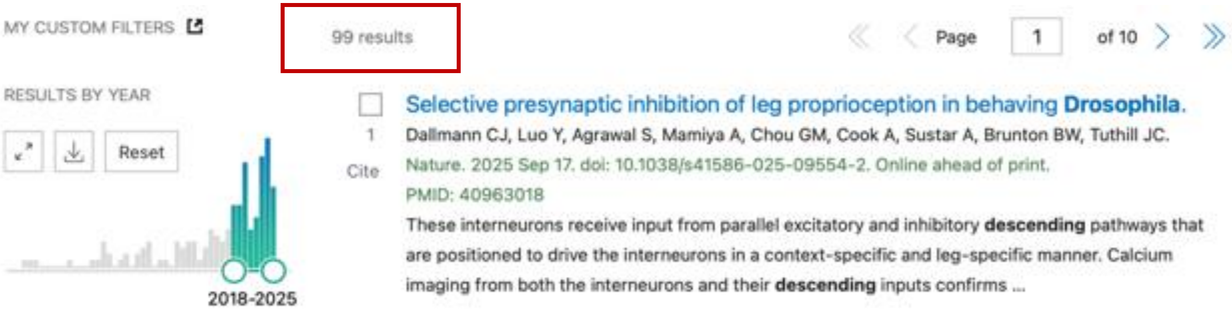
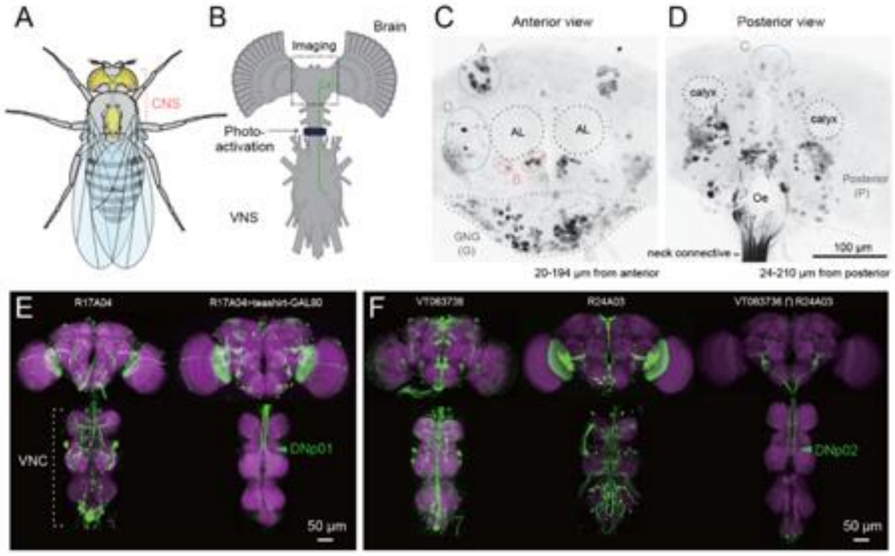
Command and Control: The role of descending neurons in *Drosophila* behaviors

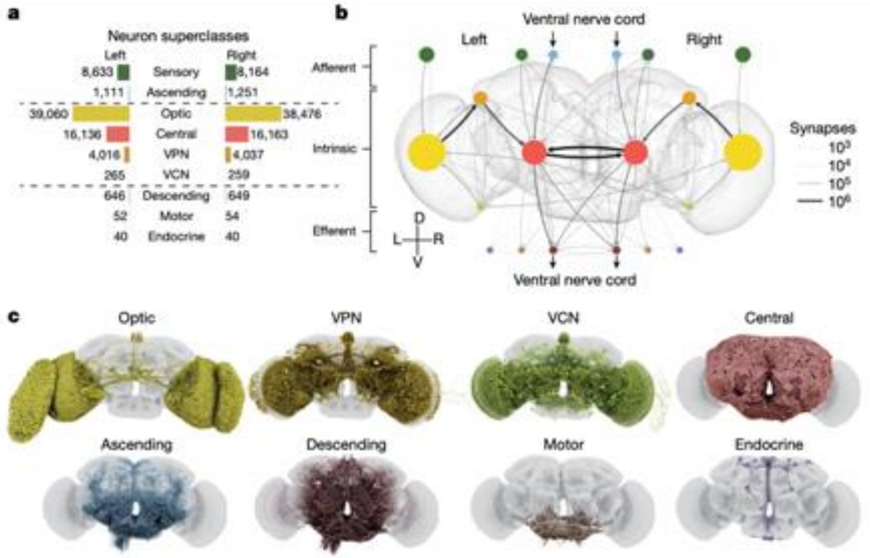
JSH / CDL / LZJ

2025/09/25

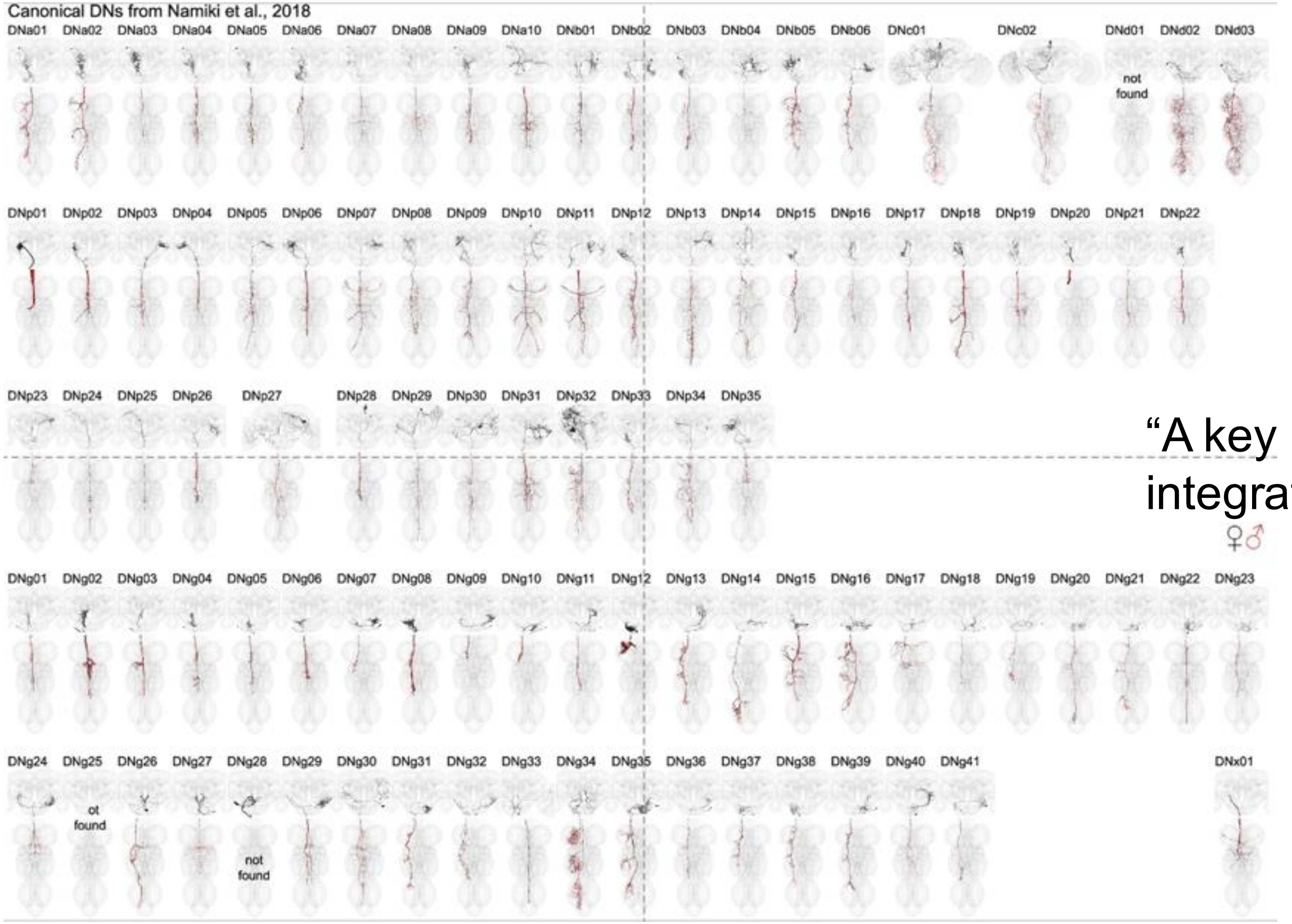








Namiki S, et al., eLife. 2018
Dorkenwald S, et al. Nature. 2024



“A key bridge between sensory integration and motor execution”

Stürner T; Nature; 2025

1. Structure and organization of DNs —— CDL

2. Functional logic of DNs in behavioral control —— JSH

3. Orchestrating complex behavioral sequences —— LZJ

Structure and organization of descending neurons

Reporter-CDL

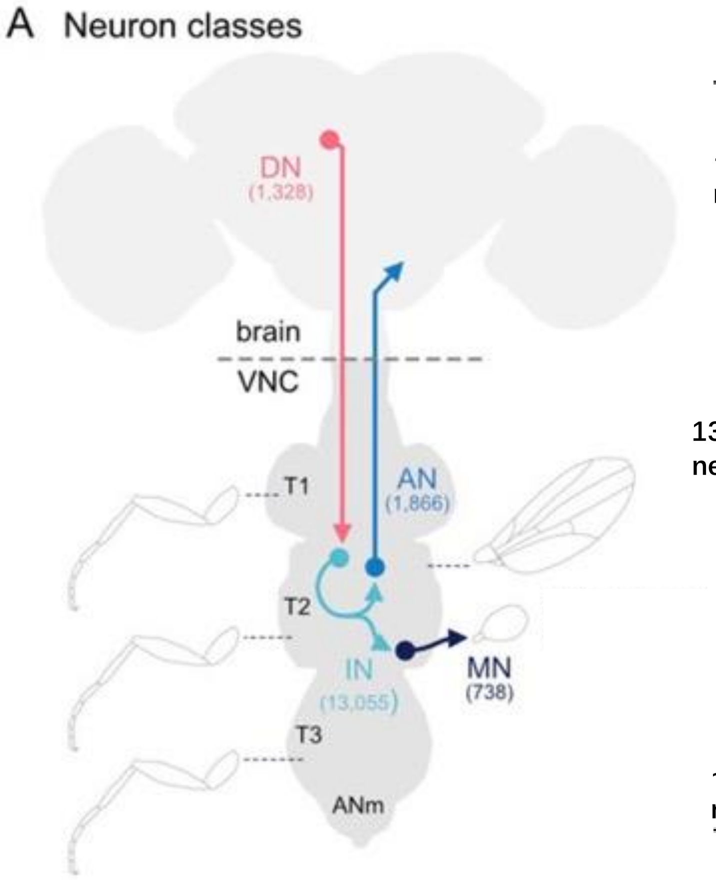
2025/9/25

- What is the definition of descending neurons?

We operationally define a DN as a neuron that: (1) connects brain and VNC with an axon through the neck connective and (2) has its cell body in the brain."

—— **Namiki, S., et al. (2018). *eLife*.**

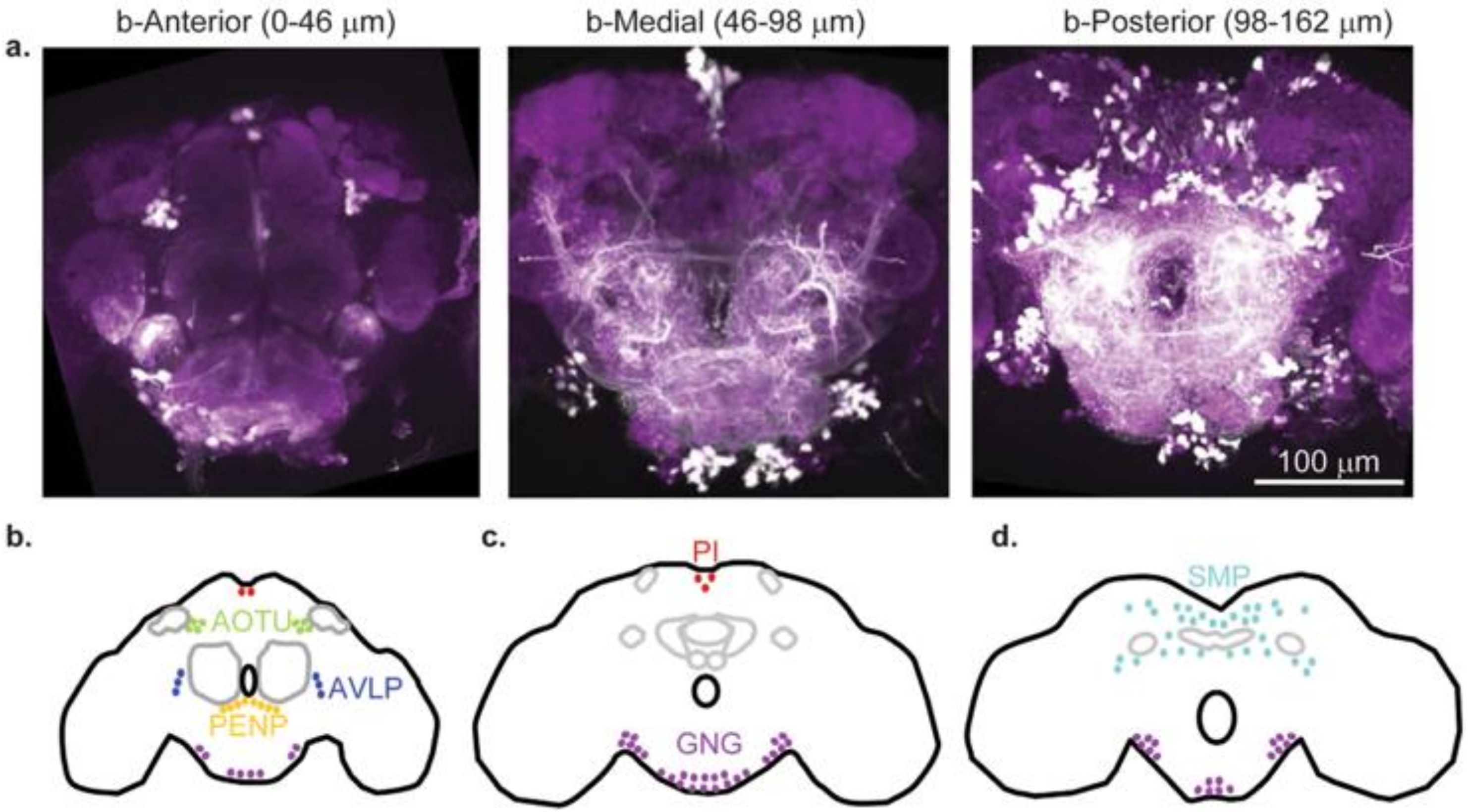
The Core Problem: An Information Bottleneck



~130000 neurons

1328 neurons

~22000 neurons



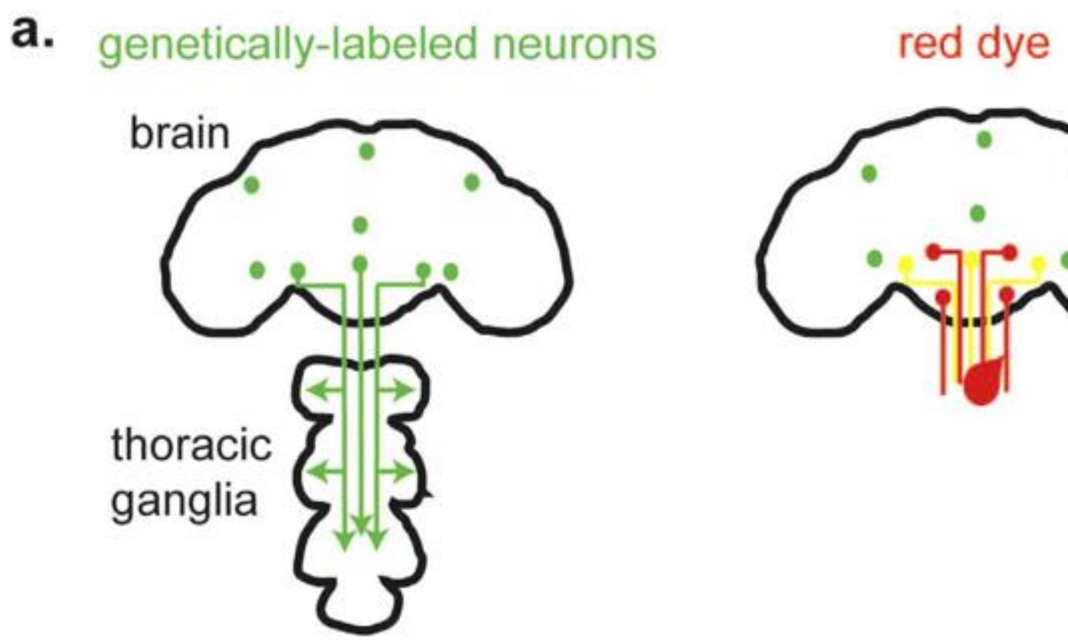
Cheong et al. (2024) *eLife*

Hsu & Bhandawat (2016) *Scientific Reports*

How do we map the 'hardware blueprint' of DNs?

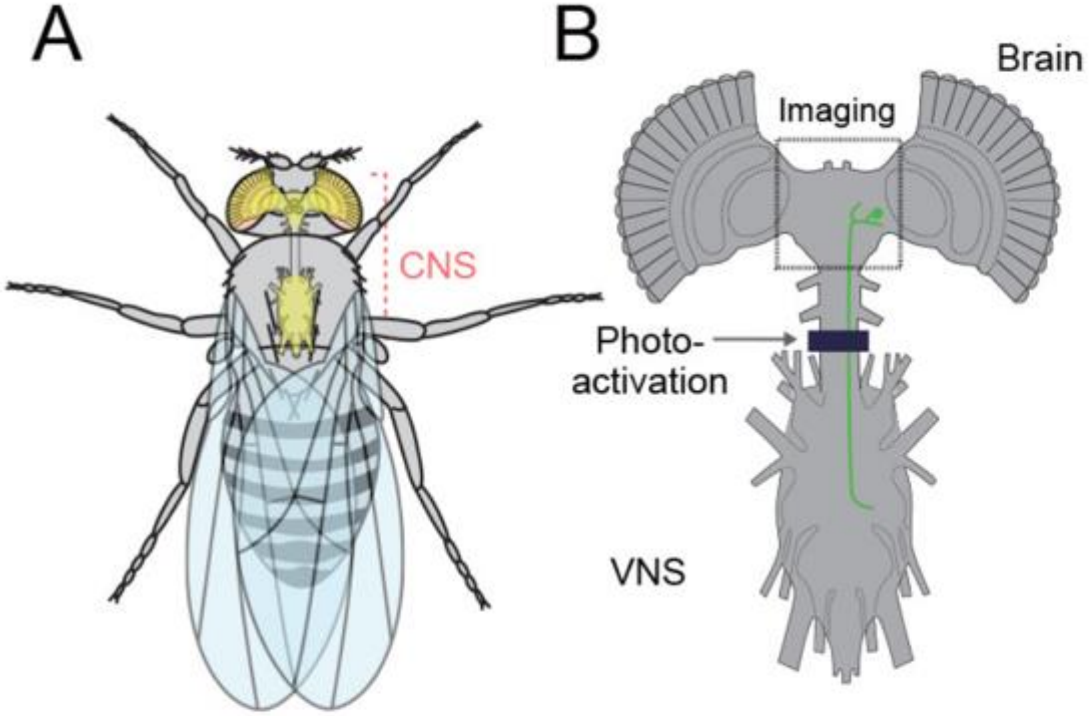
What core 'design principles' does this blueprint reveal?

Method 1: Macro-Tracing



Dye backfilling

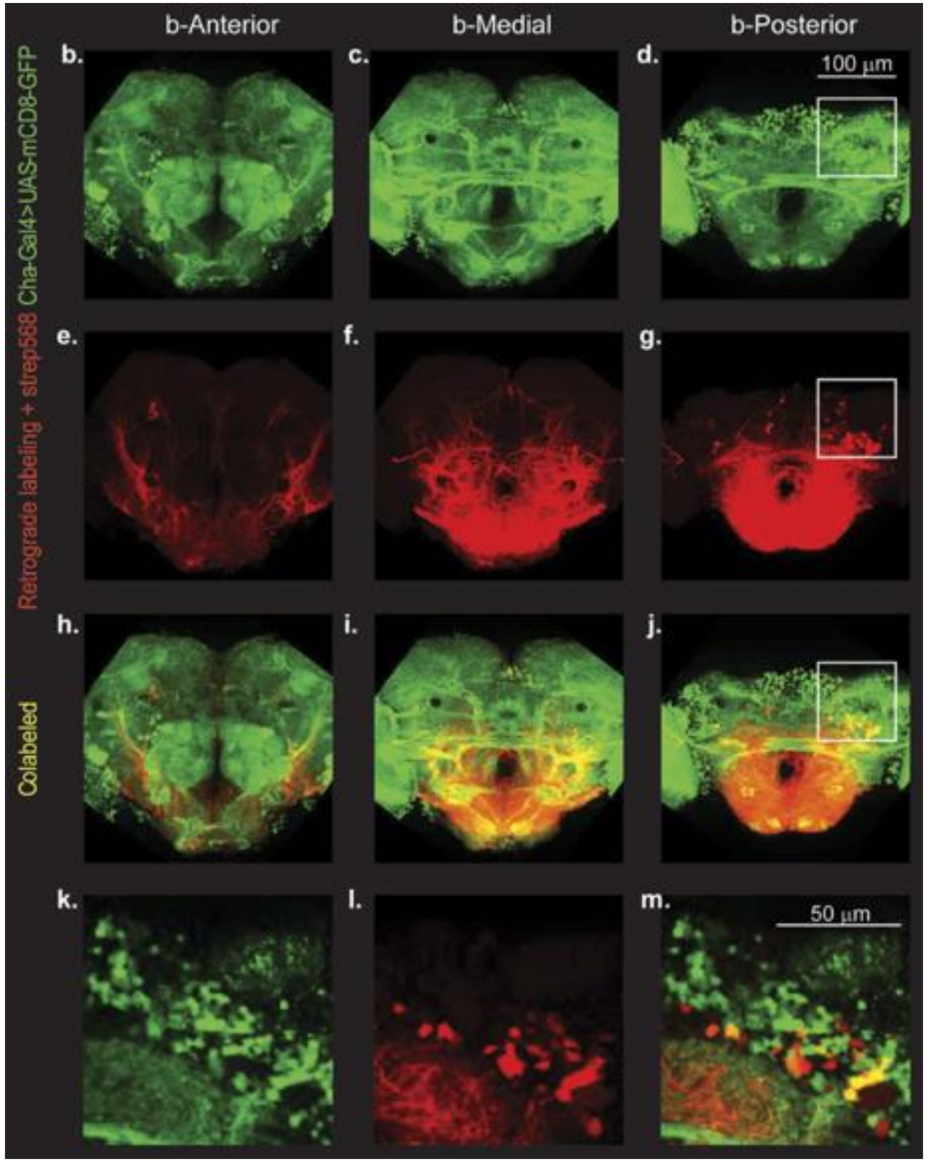
Hsu & Bhandawat (2016) *Scientific Reports*



Photoactivation

Namiki et al. (2018) *eLife*

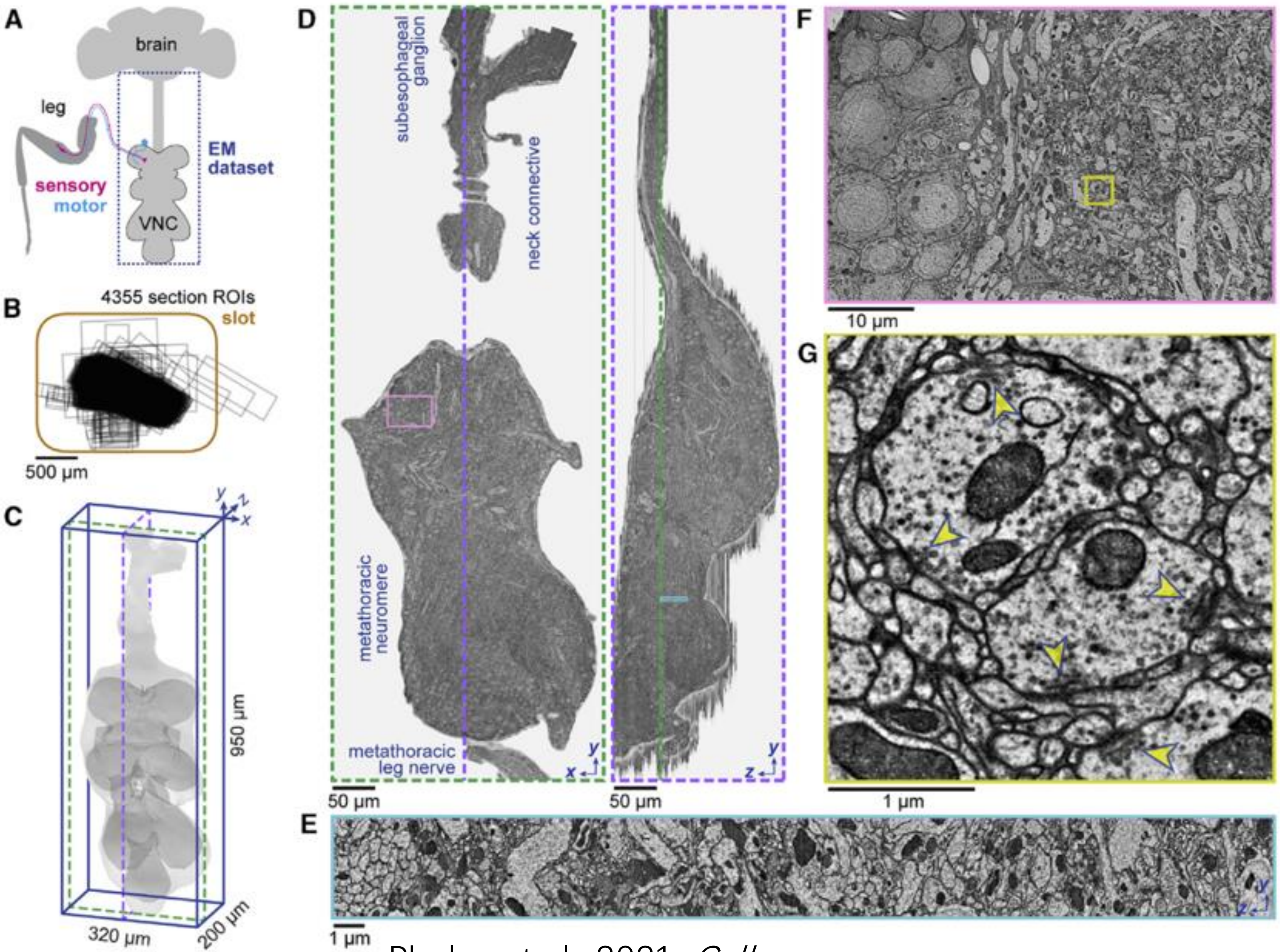
Method 2: Genetic & Chemical ID for a DNs



Hsu & Bhandawat (2016) *Scientific Reports*

- Double-labeling experiments combine genetic markers for specific neuron types (green) with anatomical tracing of all DNs (red).
- The colocalized (yellow) cells are thereby identified as DNs with a specific chemical identity.

Method 3: EM Connectomics to 'Draw the Complete Blueprint'

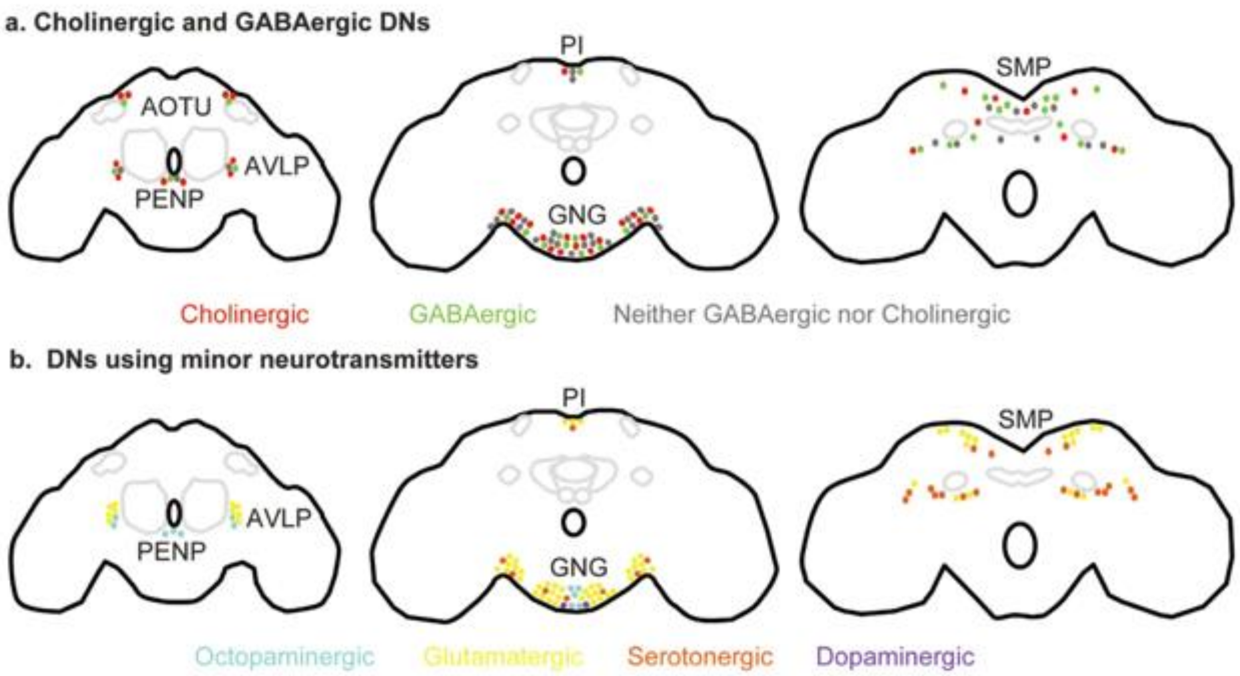


Phelps et al., 2021. *Cell*

Summary of Methods: From Macro to Micro

方法	优点	缺点 (导致计数差异的原因)	计数结果
染料填充法	经典、直接，能标记所有物理上穿过颈部的轴突	特异性不足，会把颈部运动神经元等非VNC目标神经元也算进去，导致“多算”。	~1100
荧光蛋白法	遗传学标记，更“干净”	启动子覆盖不全，无法在所有DNs中表达荧光蛋白，导致“漏算”。	~700
电镜连接组学	金标准，可追踪每一个神经元	工作量巨大	1328

Design Principle 1: A Balanced Chemical System

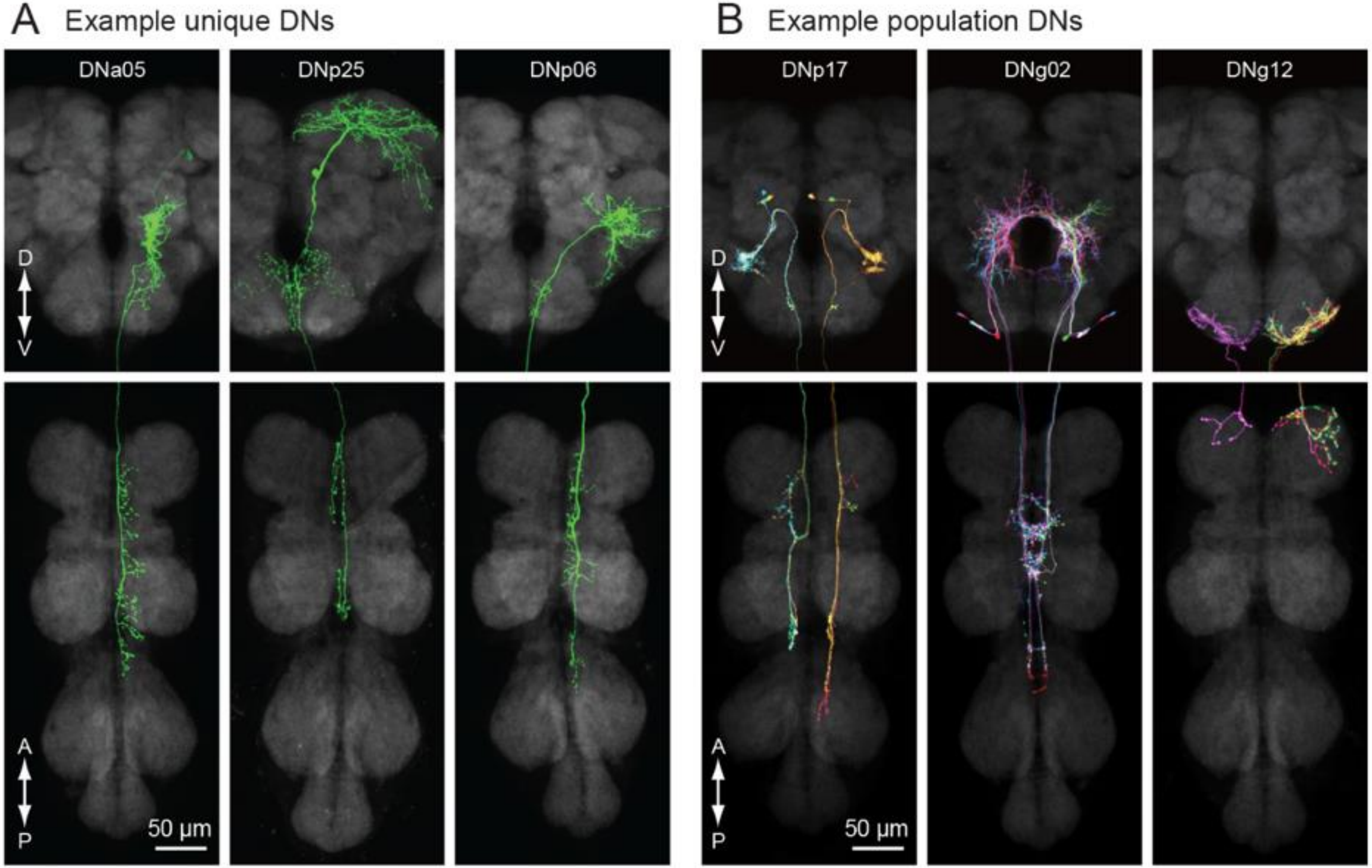


Neurotransmitter	Labeled using	Percent
Acetylcholine	Cha-Gal4 > GFP (neurons expressing choline acetyltransferase)	38
GABA	GABA antibody	37
Glutamate	VGlut-Gal4 > UAS-mCD8-GFP (neurons expressing vesicular glutamate transporter)	6*
Serotonin	Ddc-Gal4 > UAS-mCD8-GFP (neurons expressing dopamine decarboxylase)	3*
Octopamine	Tdc2-Gal4 > UAS-mCD8-GFP (neurons expressing tyramine decarboxylase)	1*
Dopamine	TH antibody	0.2*
Total		85

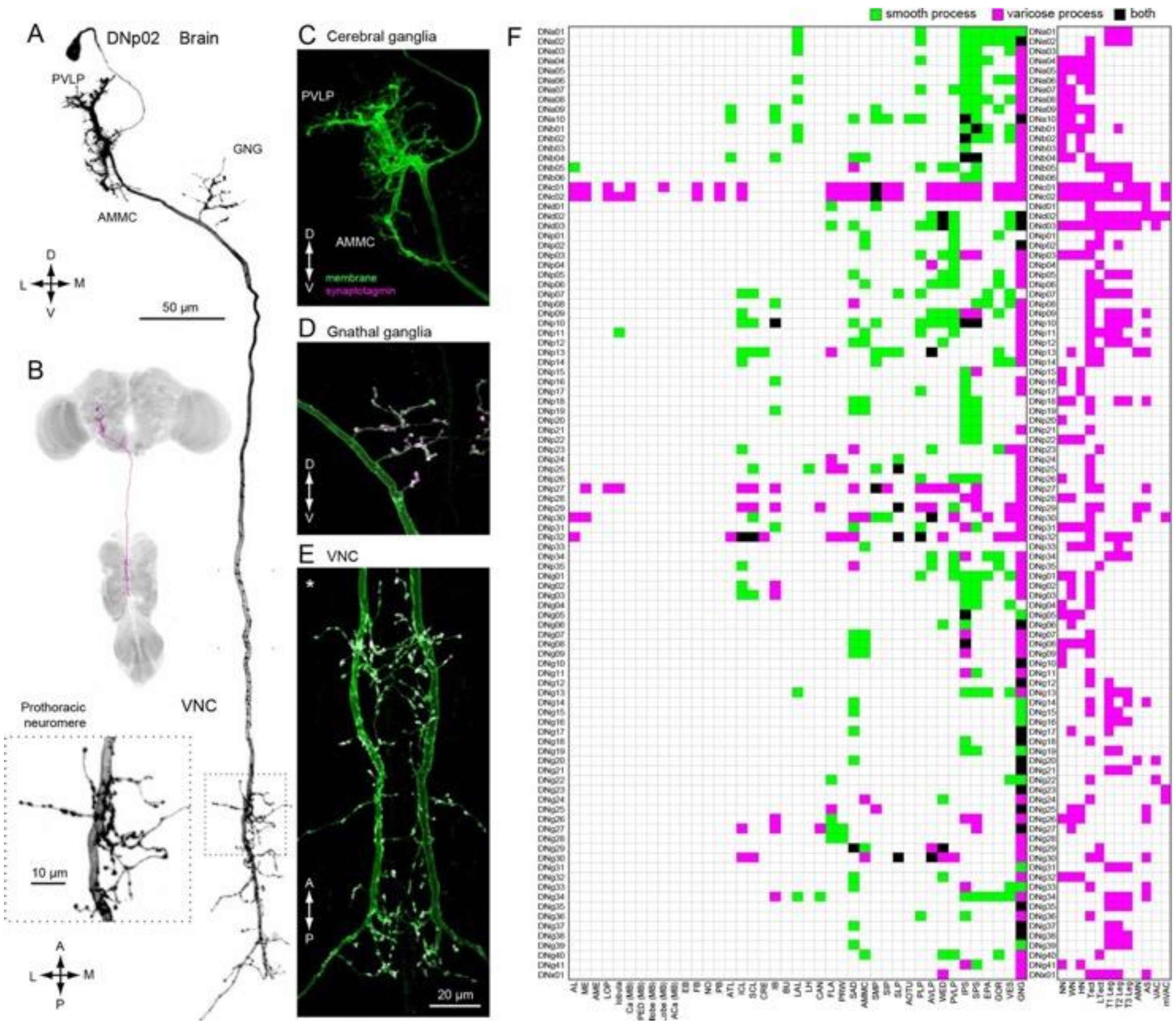
The fly's descending system is balanced between excitatory (cholinergic, ~38%) and inhibitory (GABAergic, ~37%) neurons.

Hsu & Bhandawat (2016) *Scientific Reports*

Design Principle 2: Two Morphological 'Philosophies'

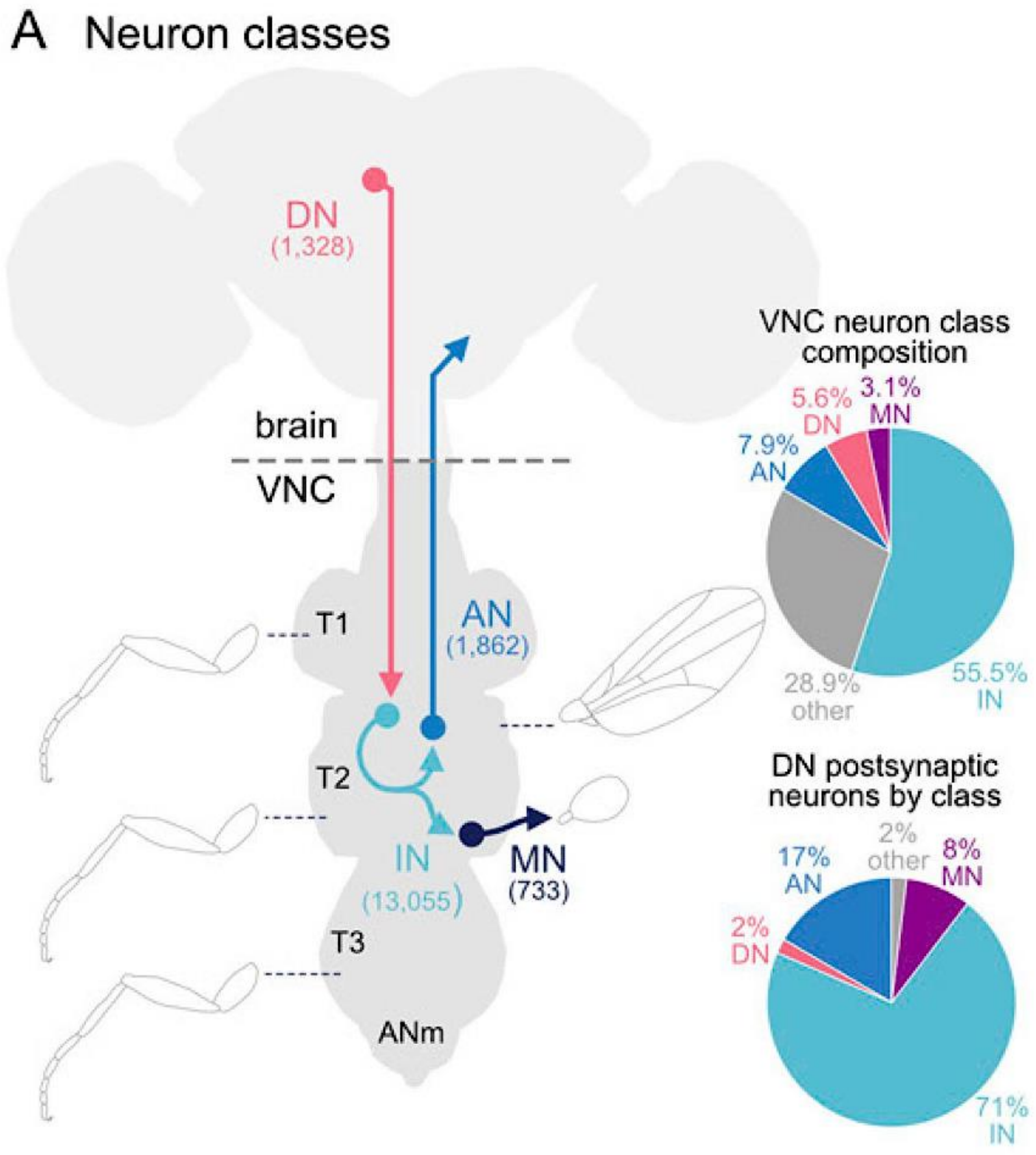


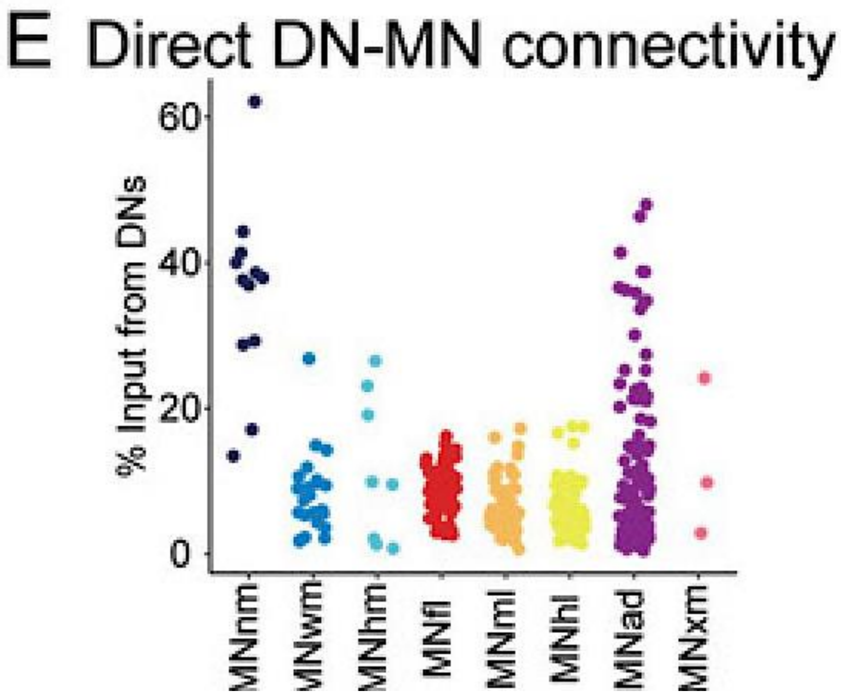
Namiki et al. (2018) *eLife*



Namiki et al. (2018) *eLife*

Most DN inputs are in the brain and outputs (magenta) are in the VNC

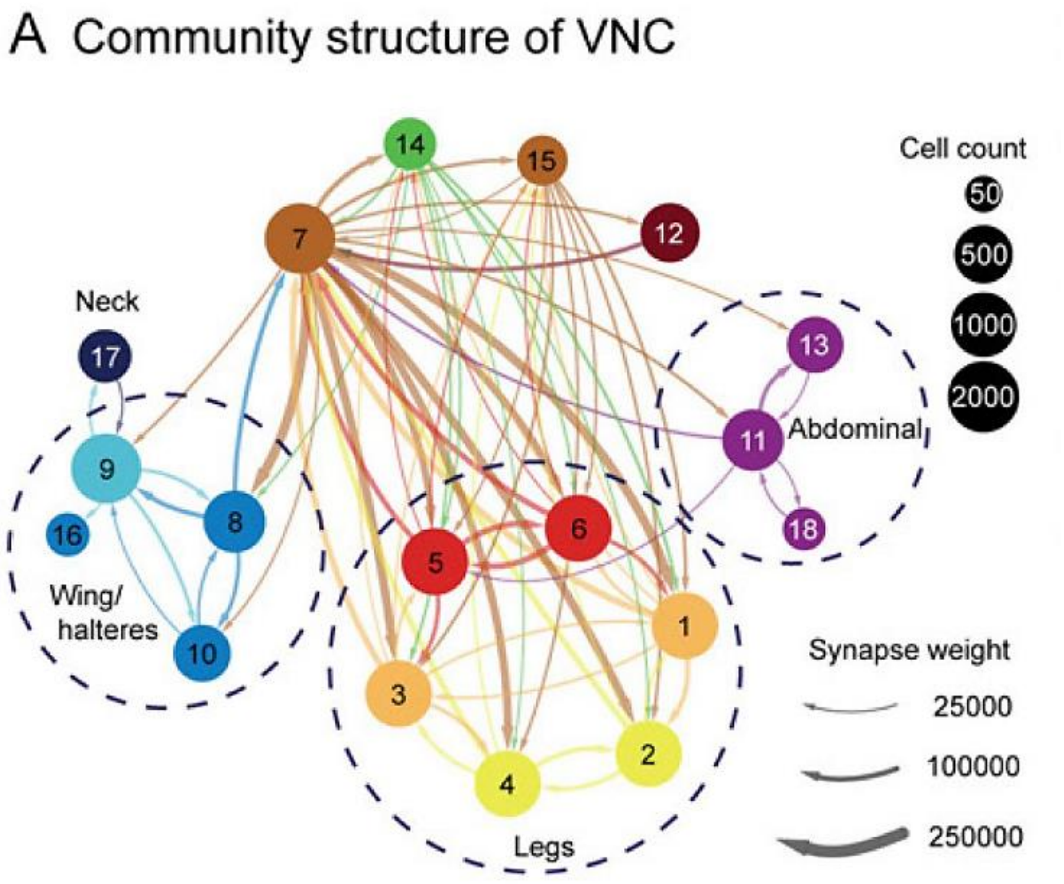




- **MNnm**: neck muscle -> **颈部肌肉**的运动神经元。
- **MNwm**: wing muscle -> **翅膀肌肉**的运动神经元。
- **MNhm**: haltere muscle -> **平衡棒肌肉**的运动神经元。
- **MNfl**: front leg -> **前足**的运动神经元。
- **MNml**: middle leg -> **中足**的运动神经元。
- **MNhl**: hind leg -> **后足**的运动神经元。

Cheong et al. (2024) *eLife*

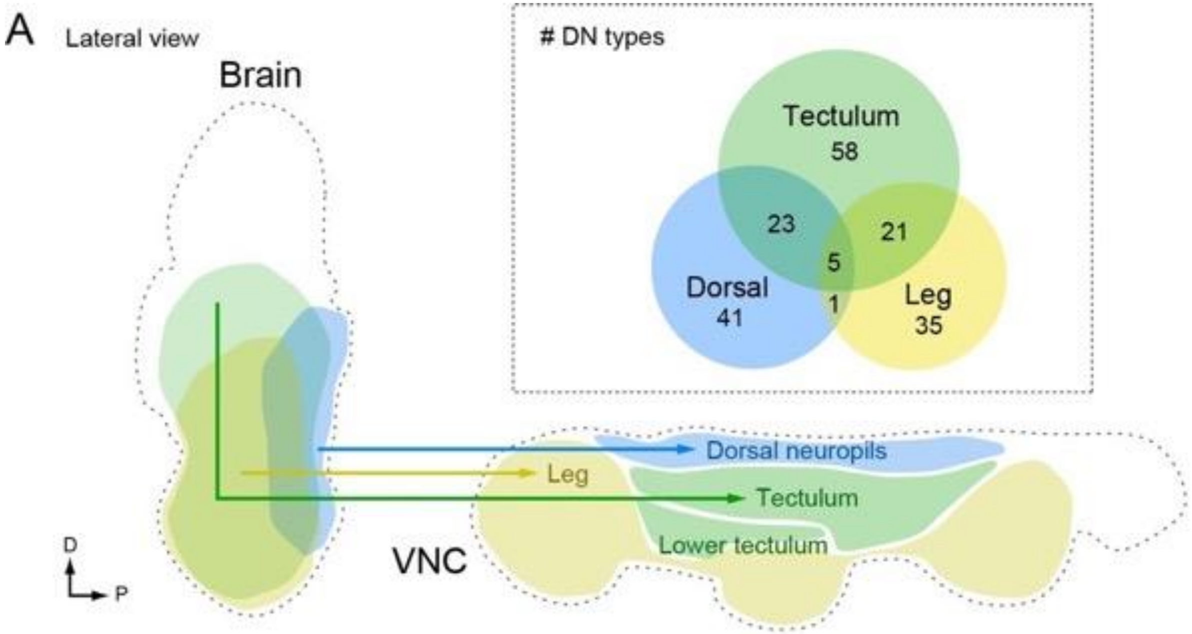
Wiring Rule 2: Indirect Control via Premotor Circuits



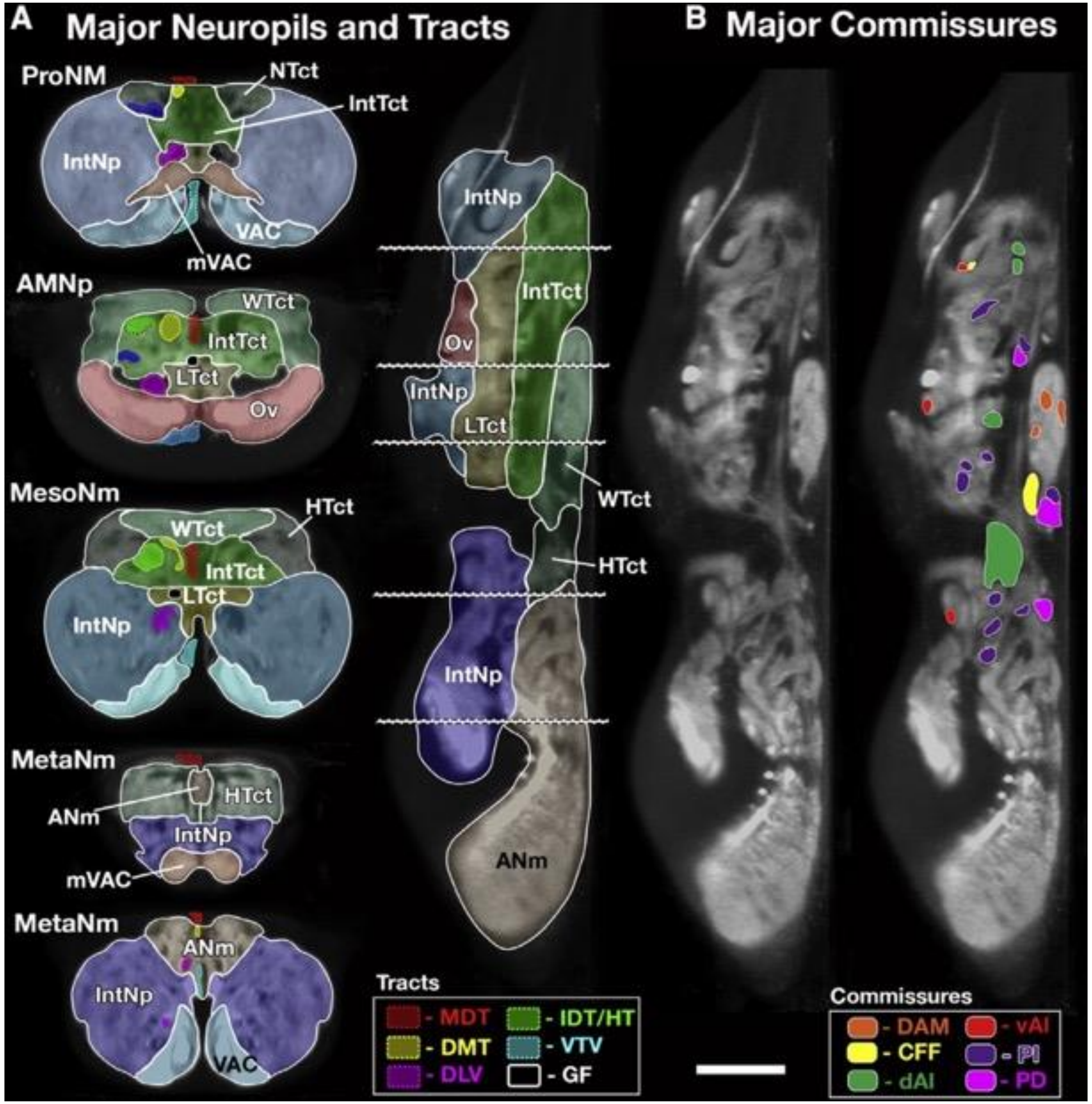
Cheong et al. (2024) *eLife*

Connectomics data reveals that DNs rarely connect directly to motor neurons (MNs).
The majority of their outputs (~71%) target a large population of intrinsic premotor interneurons (INs).

Wiring Rule 3: Functional Partitioning into Three Major Pathways

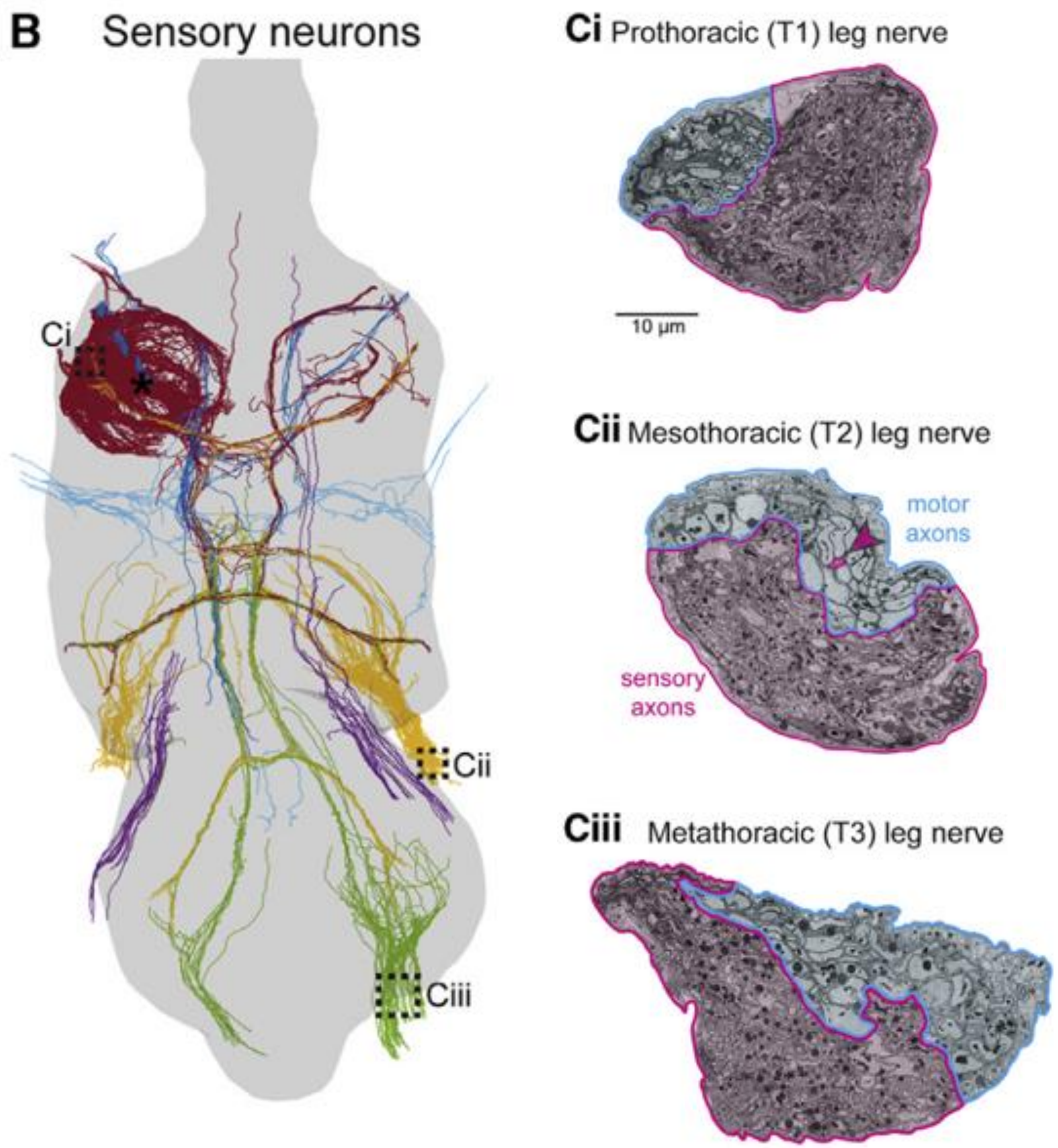


Namiki et al. (2018) *eLife*



Court et al., 2020. *Neuron*

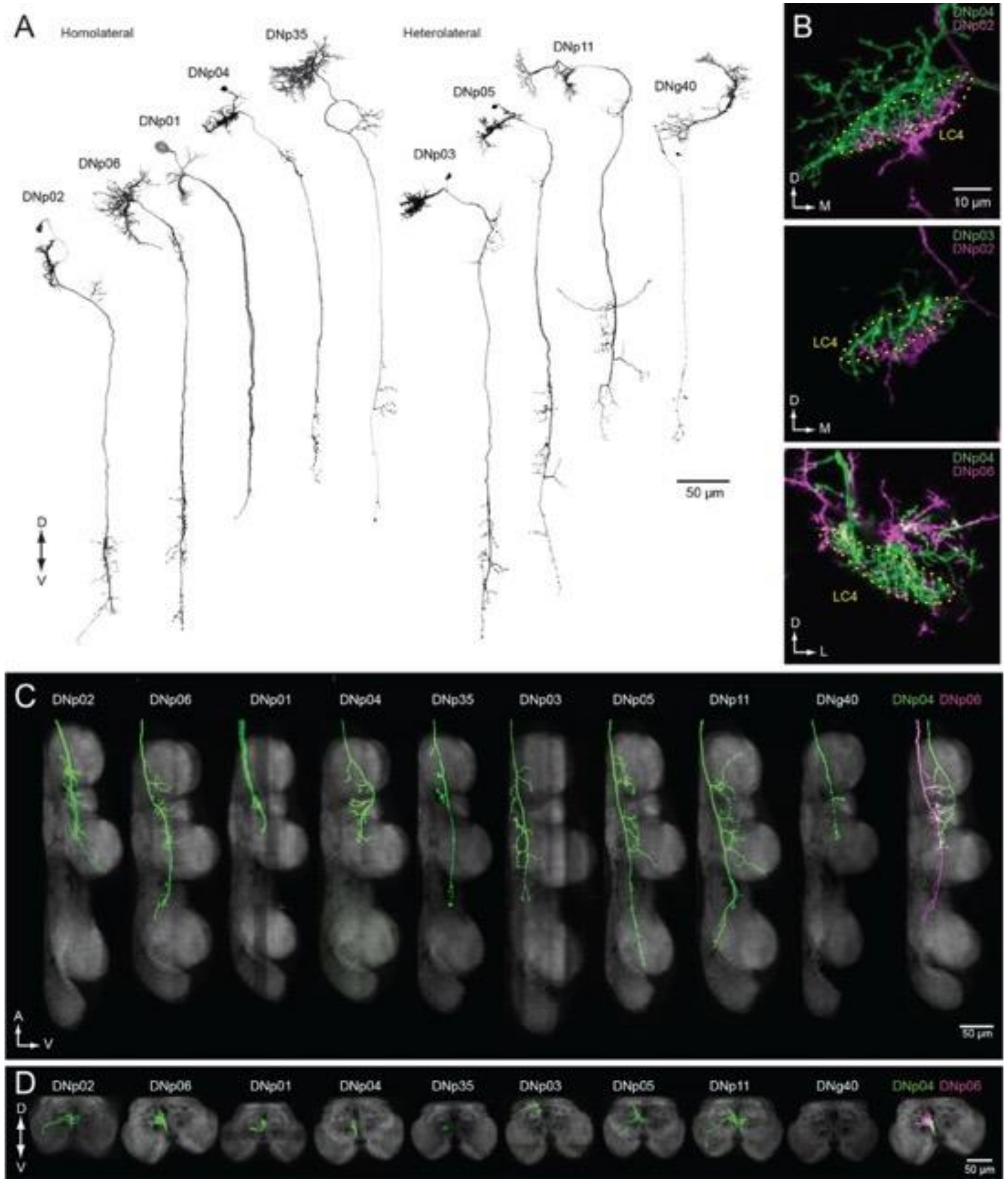
Principle in Action: Functional Segregation in Peripheral Nerves



The principle of functional segregation extends to the periphery. Within a single leg nerve, motor axons (output, blue) and sensory axons (input, magenta) are bundled into separate domains.

Phelps et al., 2021. *Cell*

Case Study: How a Visual Threat is Channeled to Different Actions



- A single visual input representing a threat (from the LC4 glomerulus) is distributed to multiple, distinct DNs.
- These DNs project to different motor pathways, allowing the same sensory cue to trigger different behaviors.

Namiki et al. (2018) *eLife*

Summary : An Efficient, Flexible, and Modular Hardware System

- **Efficient** Information Transfer
  - The DN system is a significant "information bottleneck," conveying **highly integrated,** high-level commands from the brain to the VNC.
- **Flexible** Dual-Design
  - The system employs two design philosophies: "**command-like**" neurons for triggering rapid, all-or-none behaviors, and "**population-type**" neurons for graded, fine-tuned control.
- Complex **Indirect** Control
  - DNs rarely synapse directly onto motor neurons. Instead, they primarily exert control through a vast network of premotor interneurons, allowing for immense computational flexibility.
- Clear **Modular** Wiring
  - The system is **highly modular**, organized into three major, functionally segregated pathways for flight (dorsal), leg-based actions (ventral), and coordination (intermediate).

Functional logic of DNs in behavioral control

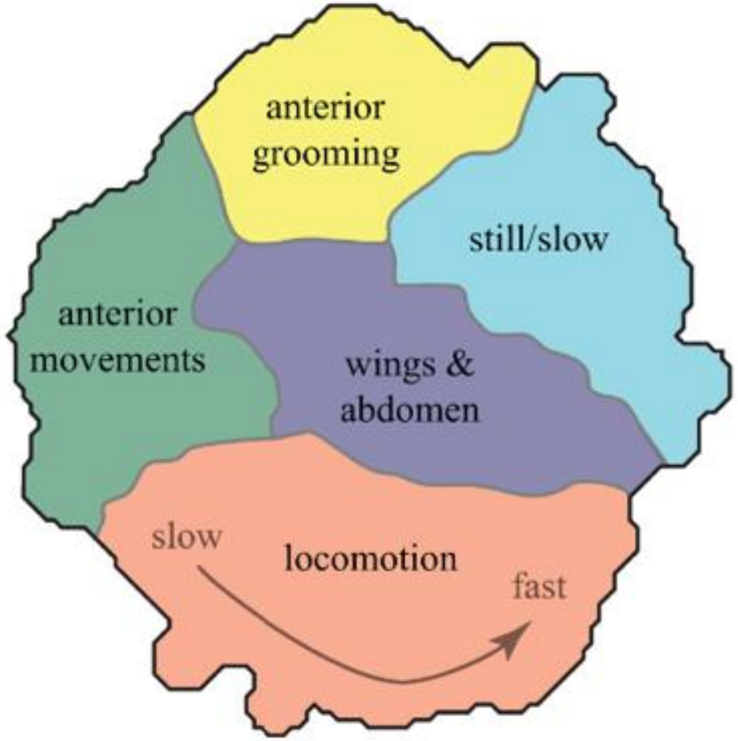
Q1: Which specific descending neurons (DNs) have been proven to possess specific functions?

Q2: Do specific DNs trigger a single stereotyped behavior?

Q3: How do DNs achieve flexible switching of behavioral control strategies?

By JSH

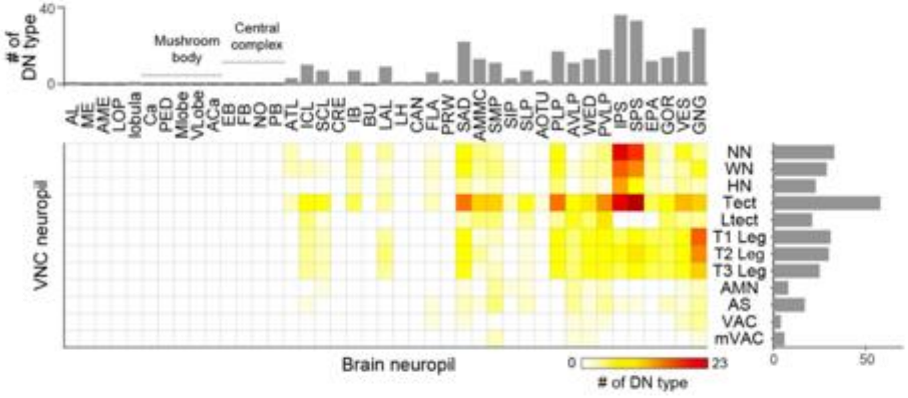
Structure & Function: Mapping descending neurons with split-Gal4

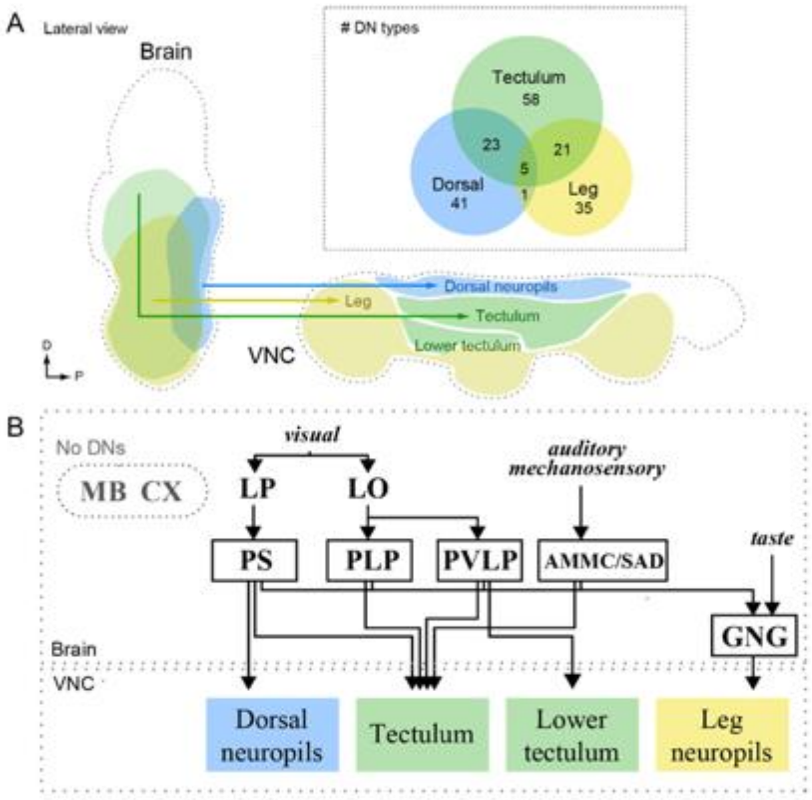


1. Most DNs drove stereotyped behaviors
2. Functional redundancy
3. State-dependent

Cande J et al. eLife. 2018

Namiki S et al. eLife 2018





Professor Barry Dickson

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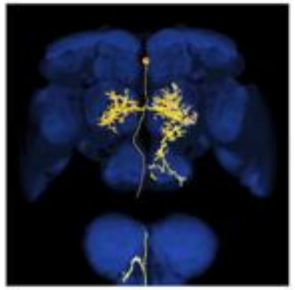
View researcher profile



Professor Barry Dickson: Neural circuits and behaviour

The Dickson laboratory investigates the neural circuits that control walking in the fruit fly, *Drosophila melanogaster*. The goal is to understand how local circuits in the nerve cord produce rhythmic motor patterns, how these patterns are co-ordinated across each leg joint and all six legs, and how descending signals from the brain modulate these operations to alter the fly's direction, speed and gait.

Find out more

Michael H. Dickinson

Esther M. and Abe M. Zarem Professor of Bioengineering and Aeronautics; Executive Officer for Biology and Biological Engineering

Sc.B., Brown University, 1984; Ph.D., University of Washington, 1989. Visiting Associate, Caltech, 2001-02; Professor, 2002-03; Zarem Professor, 2003-; Executive Officer, 2020-.

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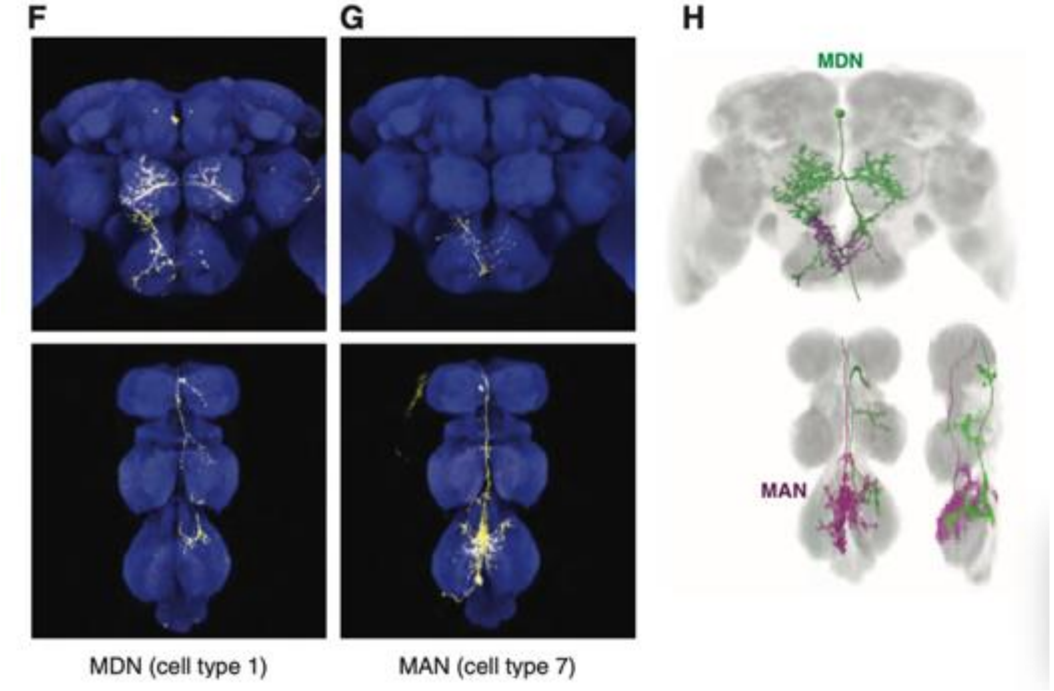
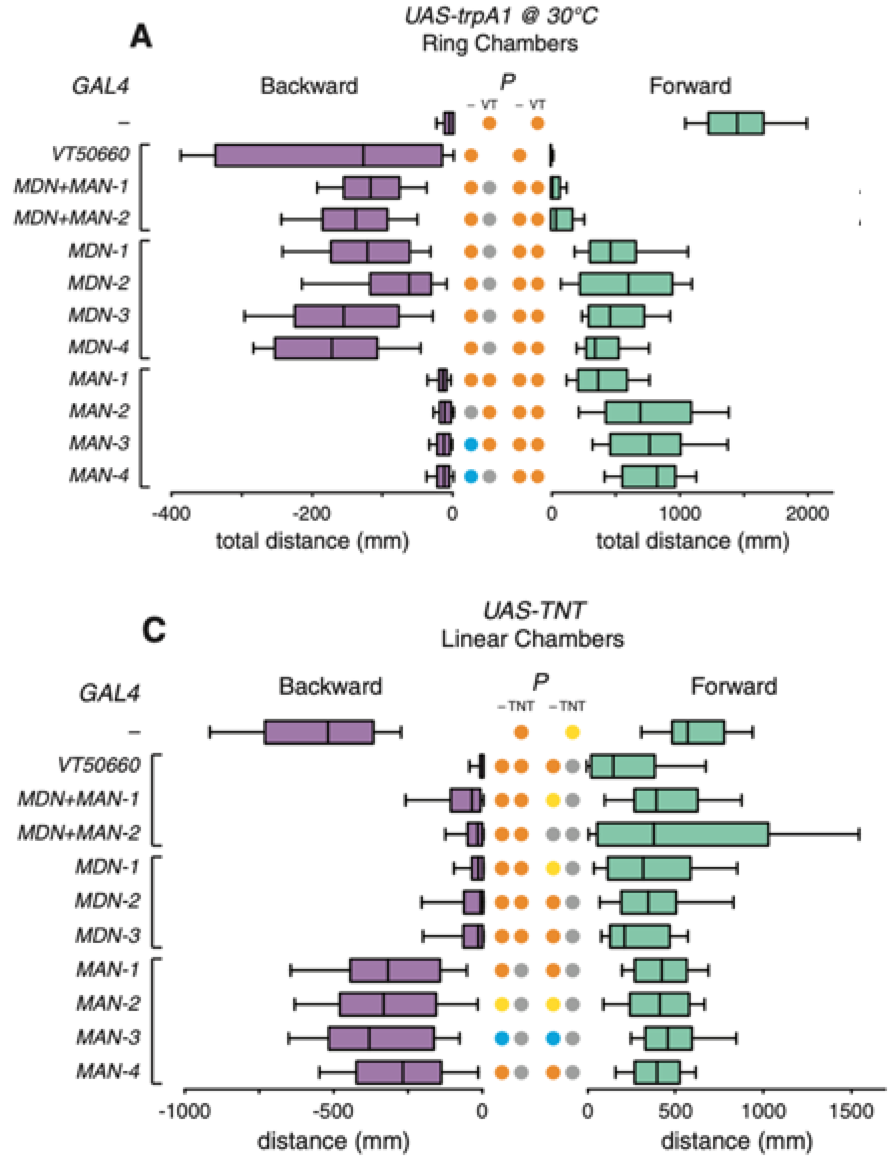
Profile | Publicat

Research Summary
Neurophysiology, Decision, Behavior

Profile
Complex and intellectually challenging problems can be so commonplace that they escape our attention. The research in my lab focuses on one such everyday phenomenon - the motion of a fly through the air. While the buzz of fly wings is more likely to elicit a sense of annoyance than wonder, insect flight behavior links a series of fundamental processes within both the physical and biological sciences: neuronal signaling within brains, the dynamics of unsteady fluid flow, the structural mechanics of composite materials, and the behavior of complex nonlinear systems. The aim of my research is to elucidate the means by which flies accomplish their aerodynamic feats. A rigorous mechanistic description of flight requires an integration of biology, engineering, fluid mechanics, and control theory. The long term goal, however, is not simply to understand the material basis of insect flight, but to develop its study into a model that can provide insight to the behavior and robustness of complex systems in general. Students and post-docs fascinated with any aspects of insect flight behavior, physiology, or evolution are invited to join my laboratory. What is more important than an interest in insect flight, however, is a love of complexity and a commitment to interdisciplinary approaches.

Command-like DNs: The role of MDN in backward walking



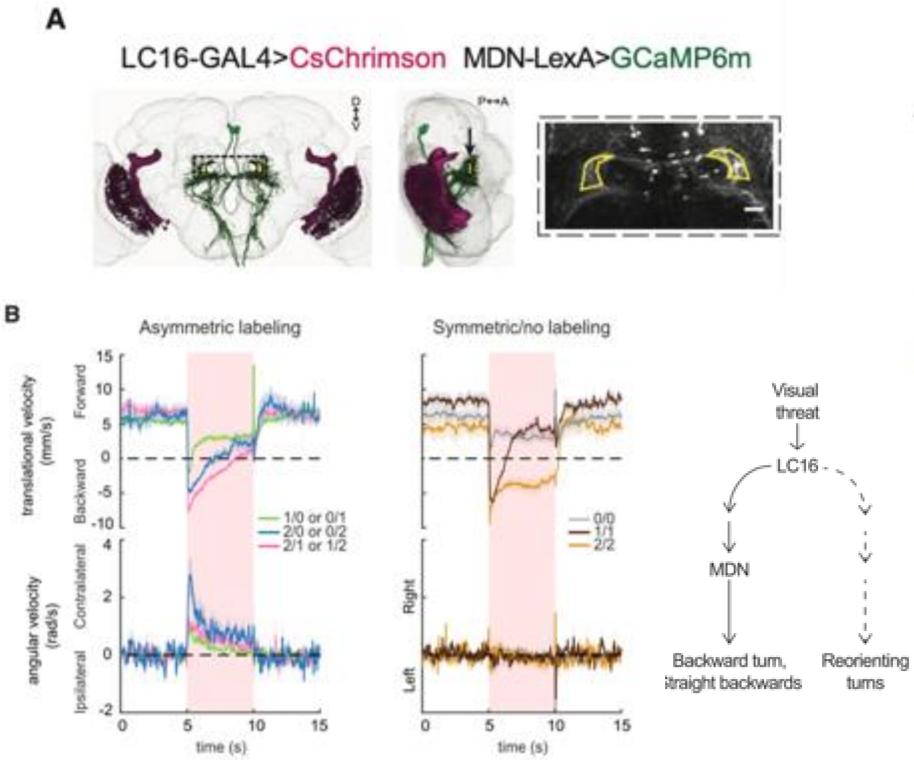


Bidaye S.S, et al. Science. 2014

Mapping neural inputs to the MDN command-like neuron

visual inputs

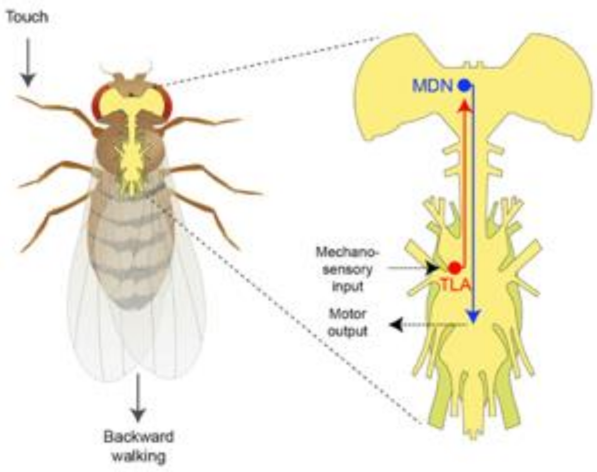
LC16 ⟶ MDN neurons



Sen R, et al. Current Biology. 2017

mechanosensory inputs

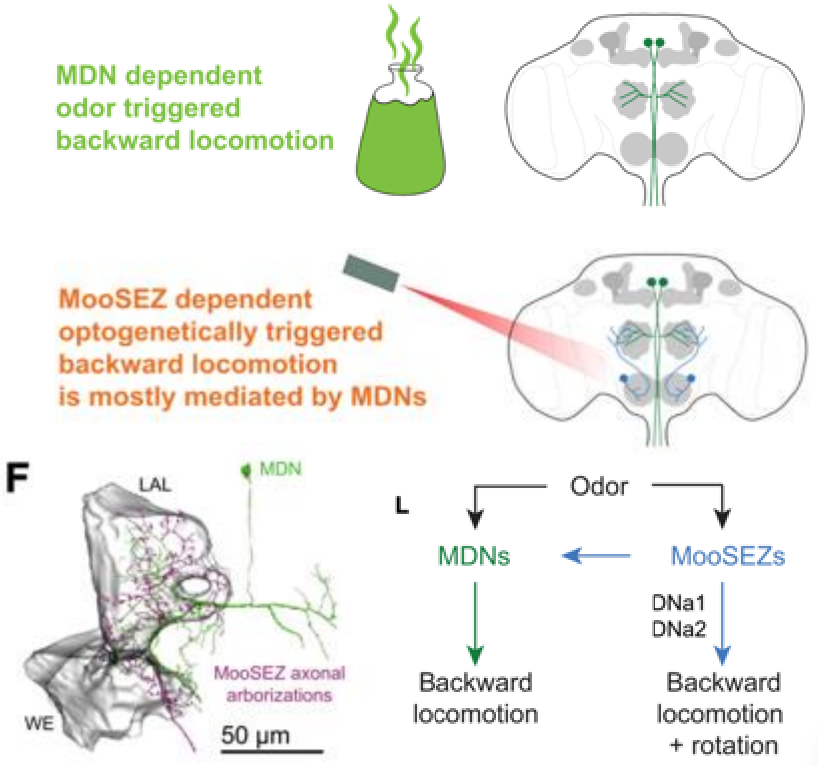
TLA neurons ⟶ MDN neurons



Sen R, et al. Current Biology. 2019

olfactory inputs

MooSEZ ⟶ MDN neurons

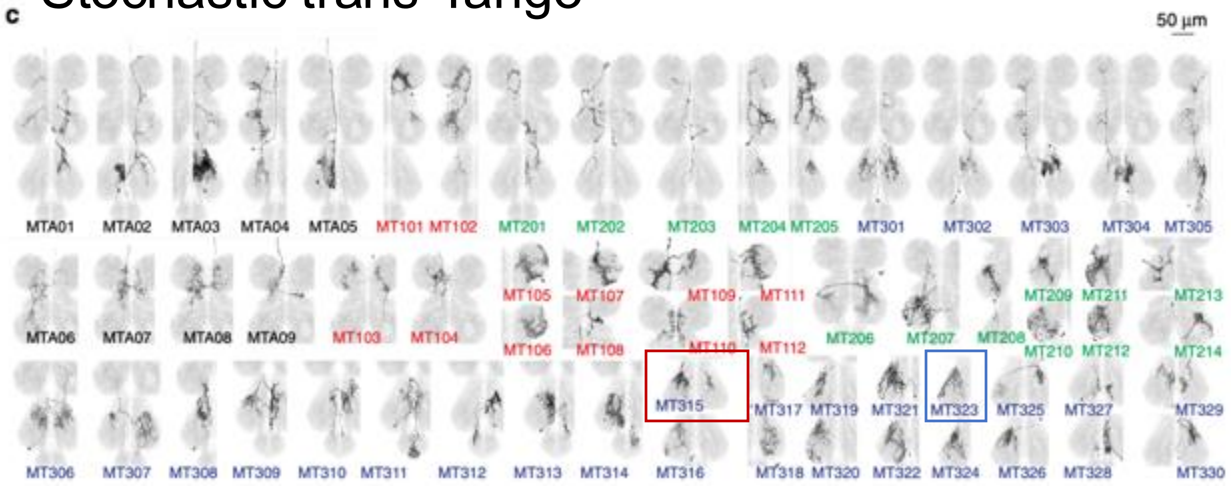


Israel S, et al. Current Biology. 2022

The command-like MDNs serves as a critical hub, integrating multiple sensory information to drive a stereotypic behavior (backward walking).

Functional Characterization of MDN-Targeted Neuronal Circuits in VNC

Stochastic trans-Tango



MDN trans-Tango-positive cells

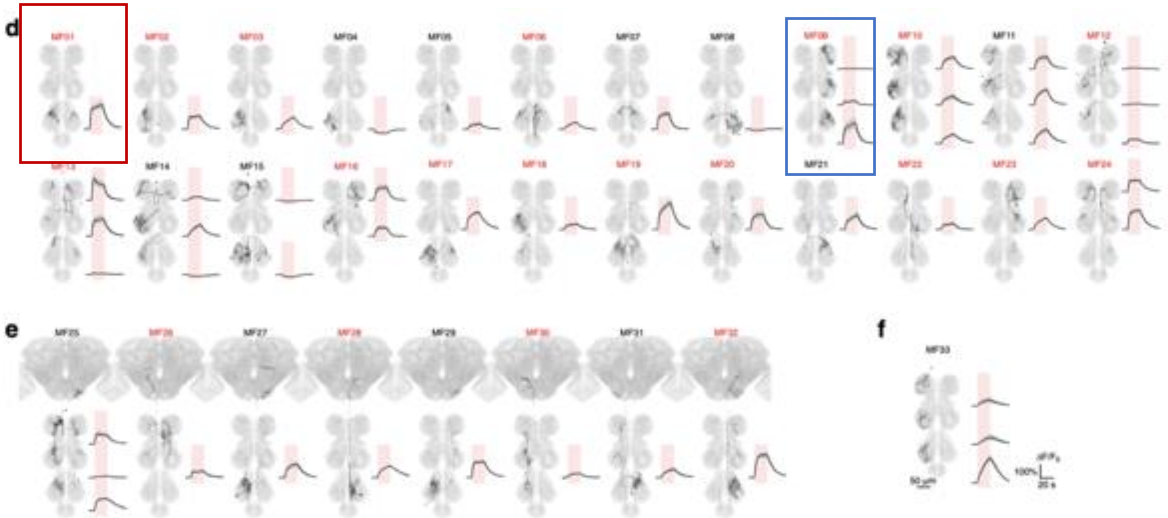
distinct ascending neurons and 56 interneurons

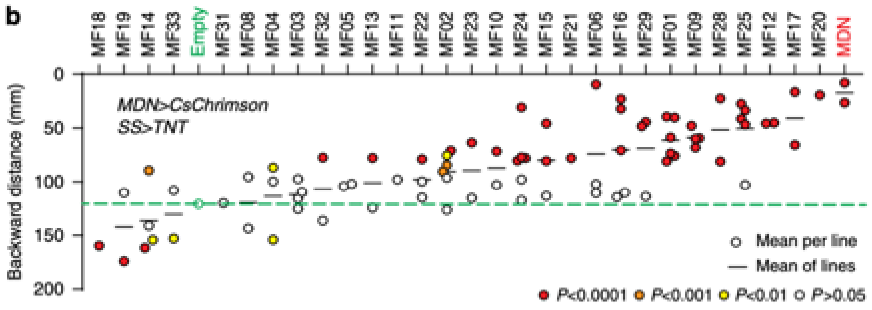
LBL40 neurons

LUL130 neurons

Feng K, et al. Nature communication. 2020

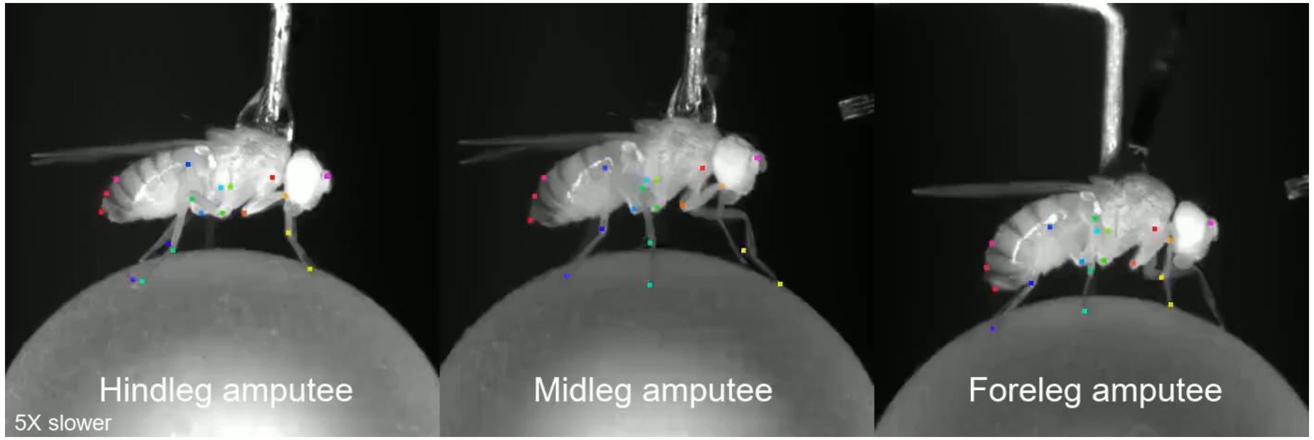
GCaMP6s imaging



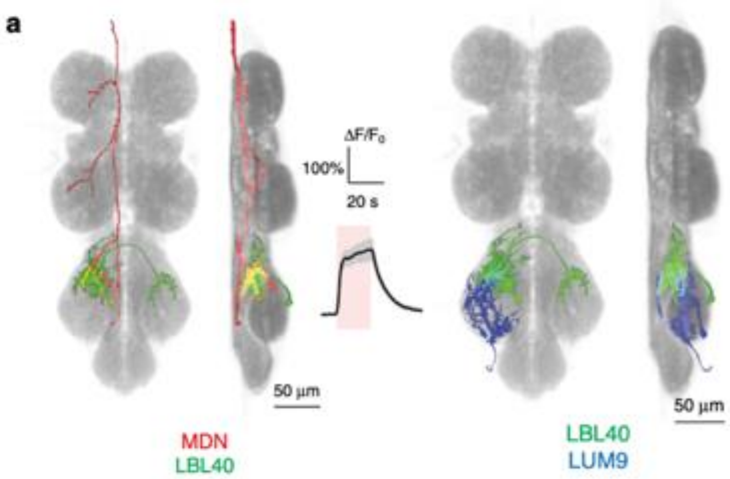


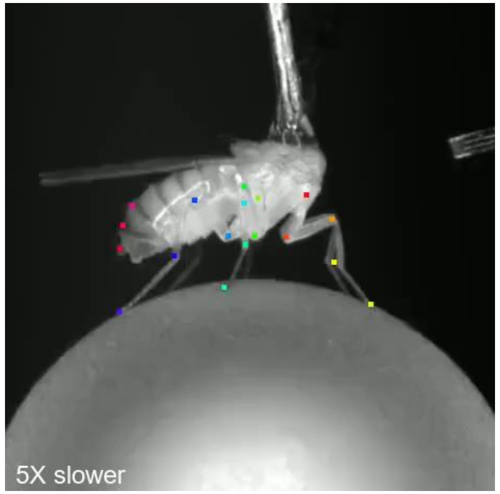
MDN functional cells (33)

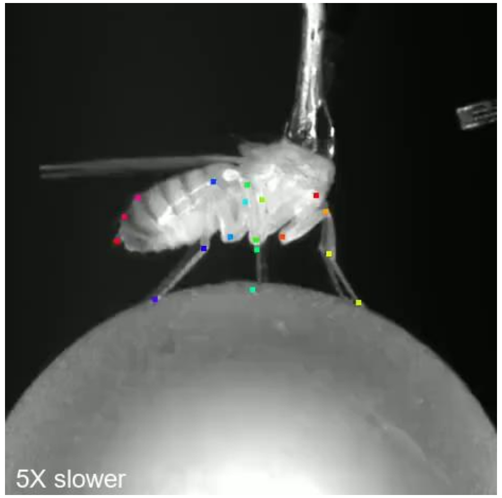
MDN control motor circuit dynamics in a distributed and localized manner

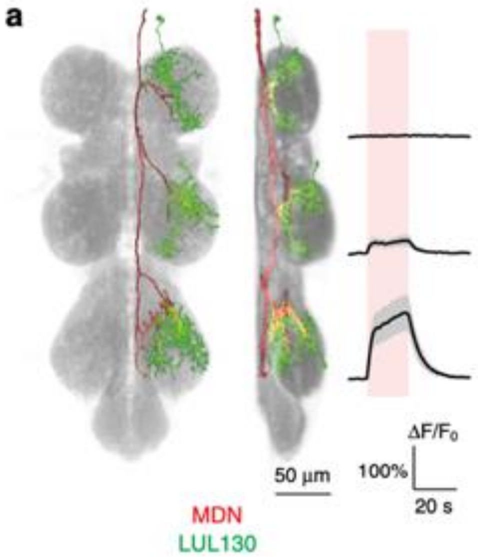


LBL40 → the power stroke (tibia flexion) during the stance phase;
LUL130 → the initiation of the swing phase (leg lifting)



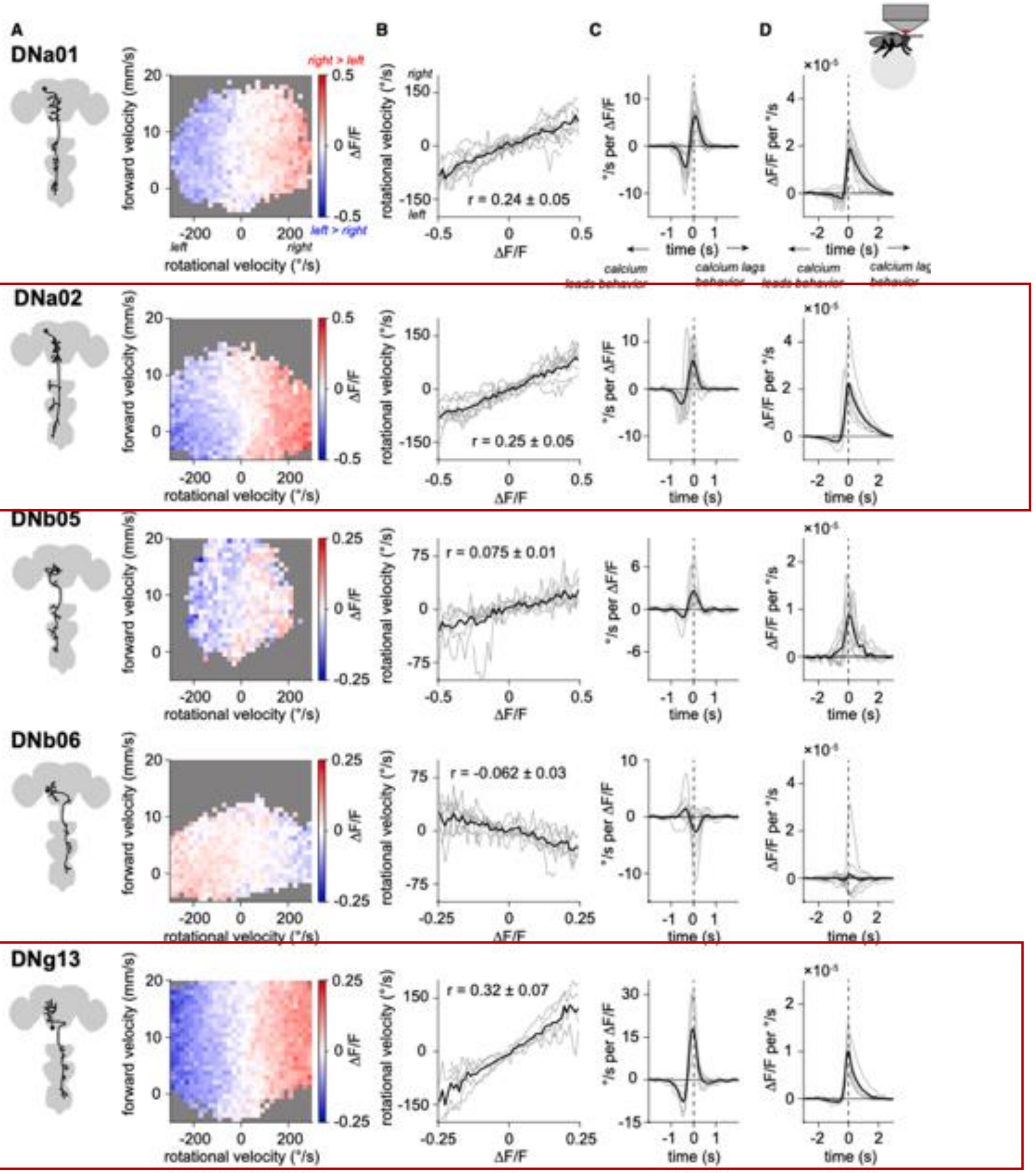


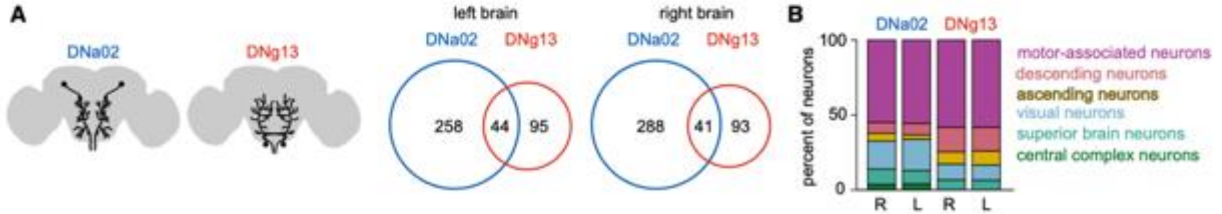




Feng K, et al. Nature communication. 2020

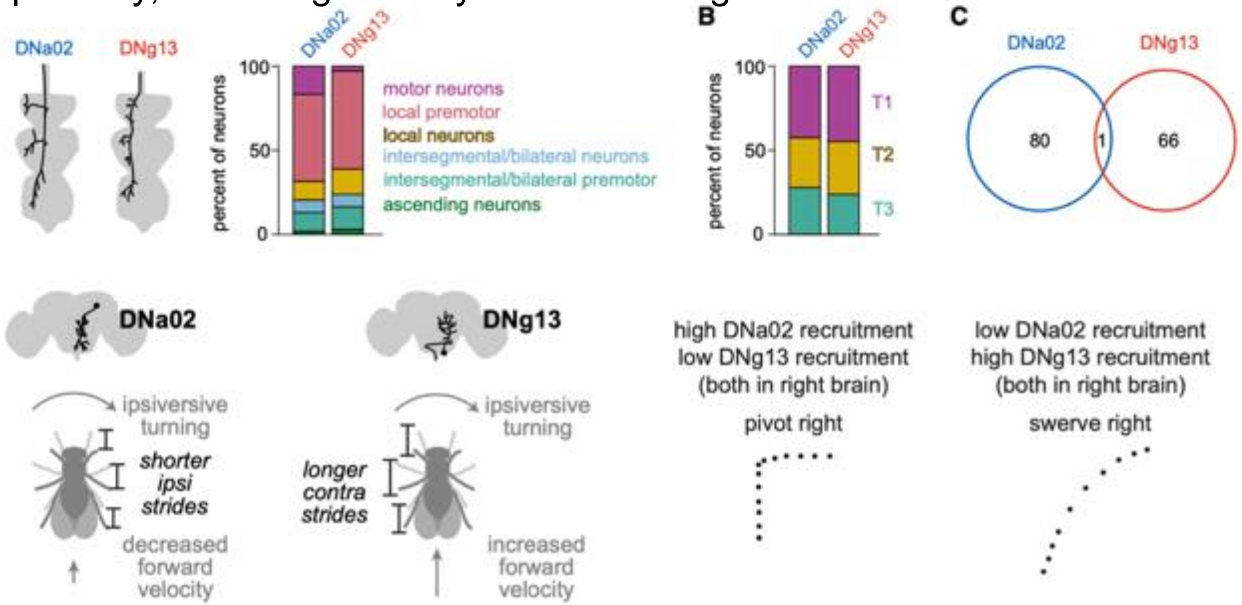
Command-like DNs mediate steering maneuvers in walking *Drosophila*





DNa02: Receives direct input from the central complex (CX), mediating goal-directed steering.

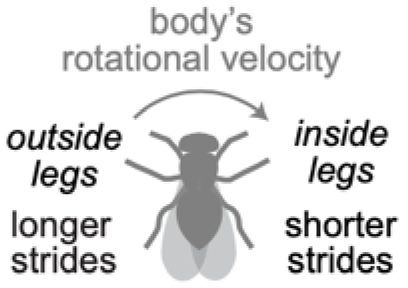
DNg13: it primarily receives input from the visual pathway and the olfactory pathway, mediating sensory-driven steering.

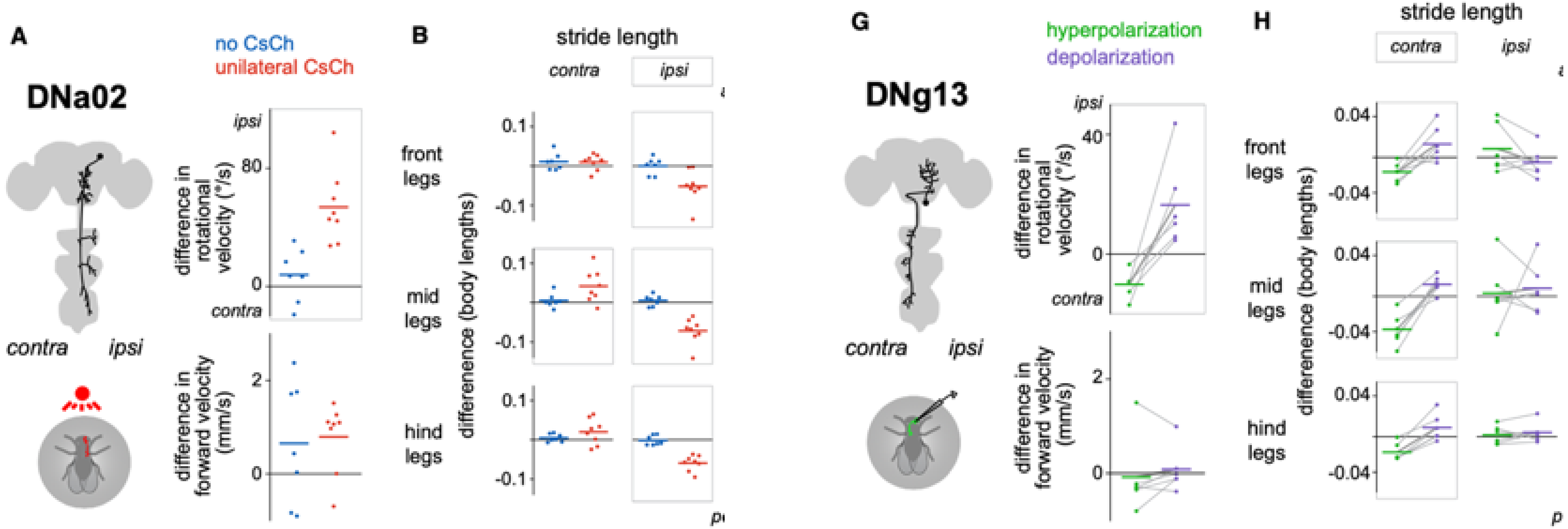


DNa02 and **DNg13** are completely independent DNs to achieve functional specialization

Yang H.H et al. Cell. 2024

DNa02 and DNg13 modulate distinct leg gestures for steering

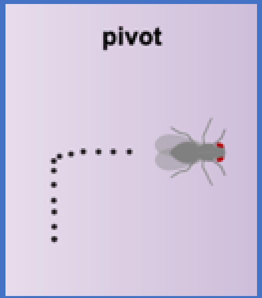


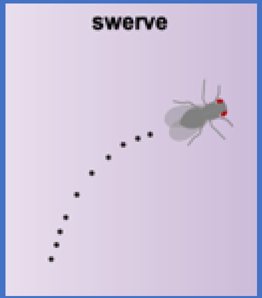


"**non-overlapping inputs + complementary outputs**"

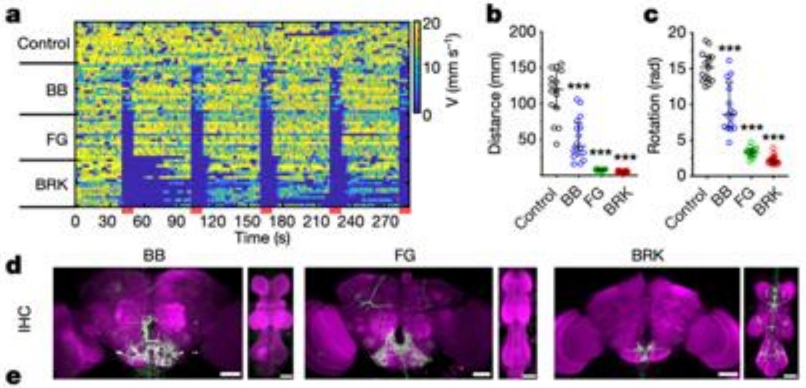
•DNa02: input from CC / ipsilateral descending projections / inhibitory outputs
• achieving small-radius turns by shortening the stride length of the inner legs and reducing forward velocity.

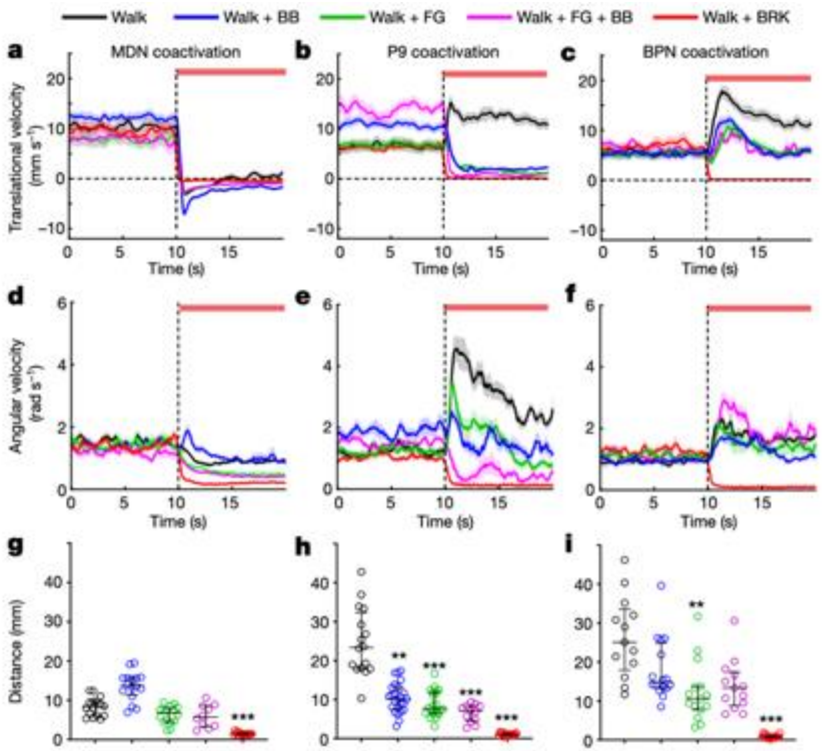
•**DNg13**: visual input / contralateral descending projections / excitatory outputs achieving smooth large-radius turns by lengthening the stride length of the outer legs and maintaining or even increasing forward velocity.

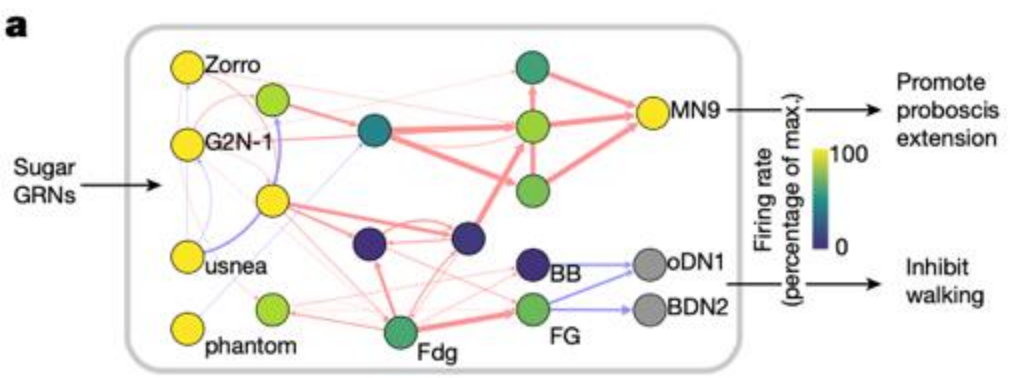


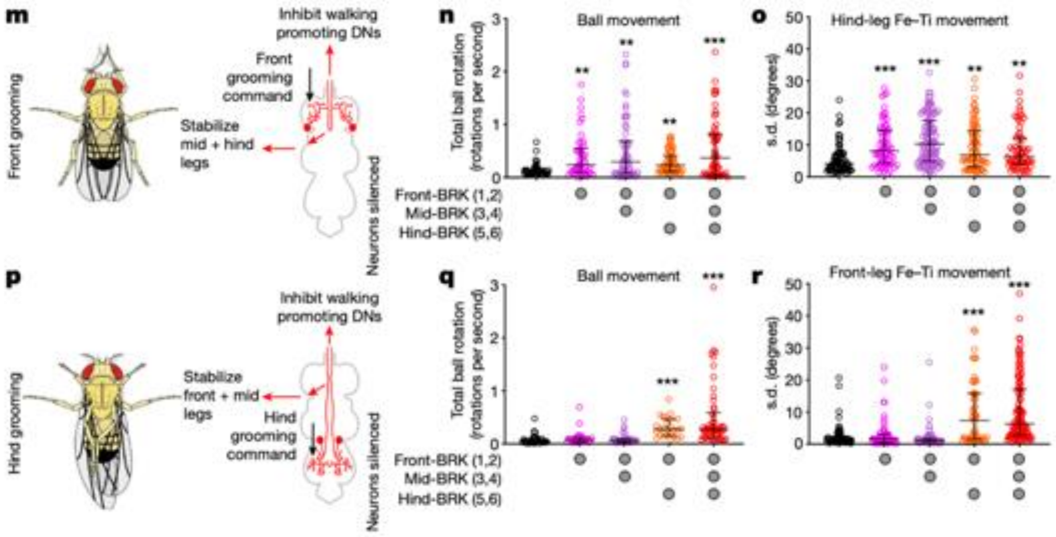


BB, FG, and BRK DNs mediate context-specific halting in Drosophila

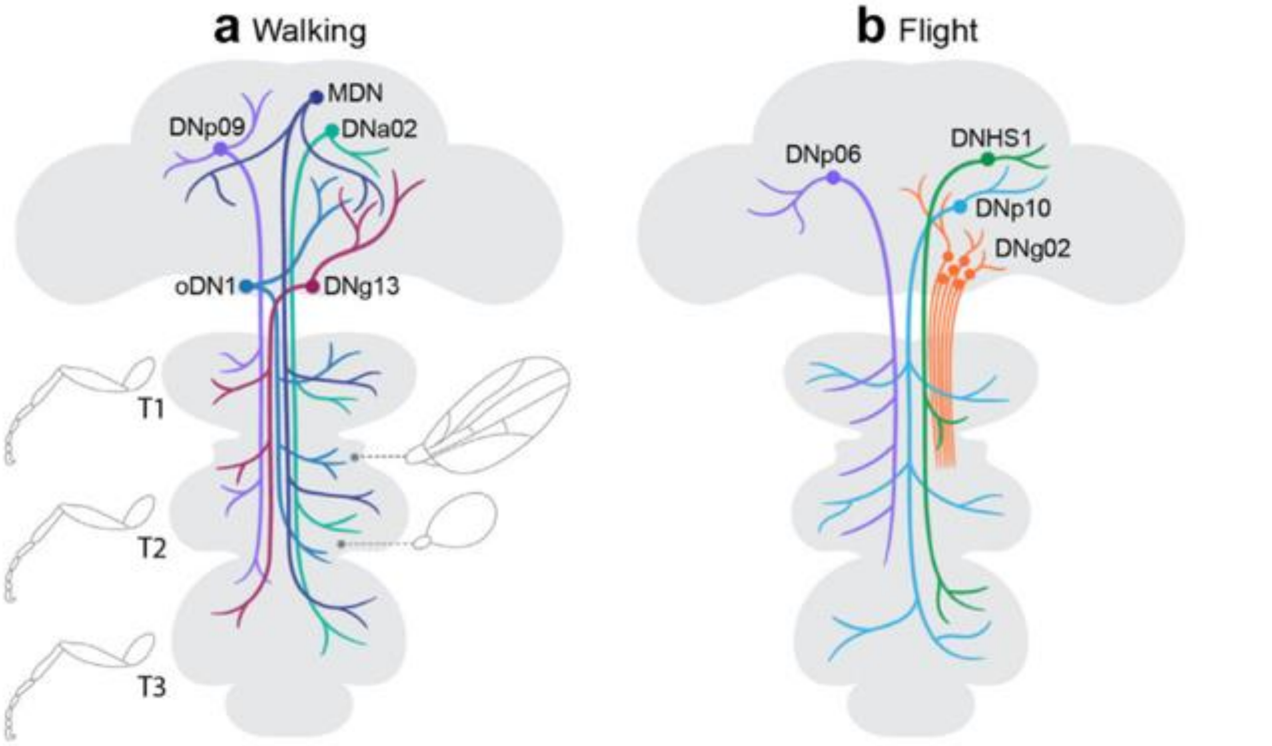








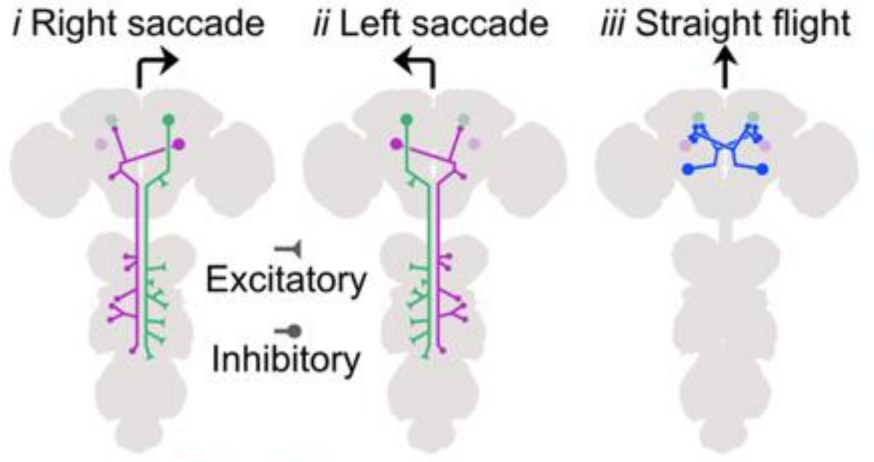
Sapkal N et al. Nature. 2024



MDN – backward walking
oDN1 – bolt forward walking
DNa02 / DNg13 – steering
DNp09 – freeze or forward walk with ipsilateral turns during courtship

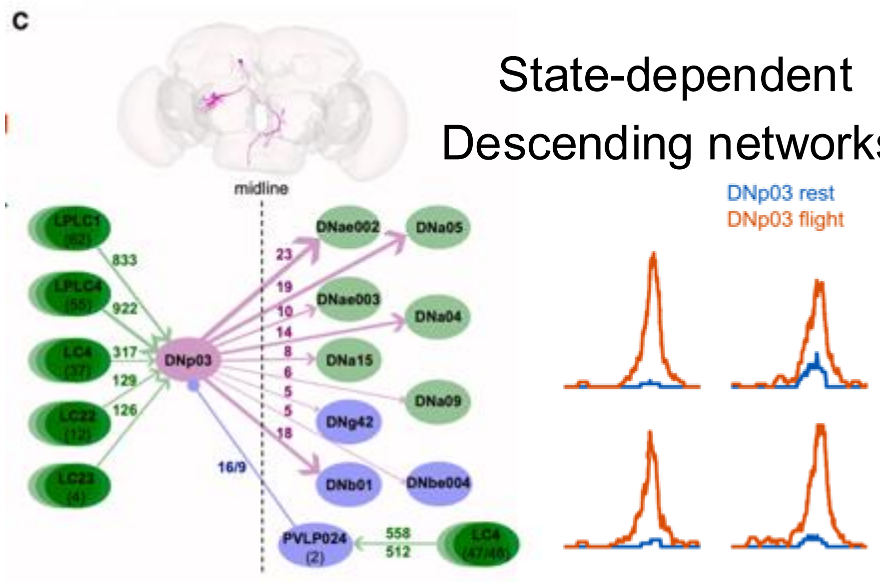
DNHS1 (DNp15) – looming
DNp06 – evasive turns
DNg02 – steering
DNp10 – landing initiation

“Flip-flop”



Excitatory DNae014 + Inhibitory DNb01 generate saccades | Inhibitory VES041 suppresses saccades

State-dependent Descending networks

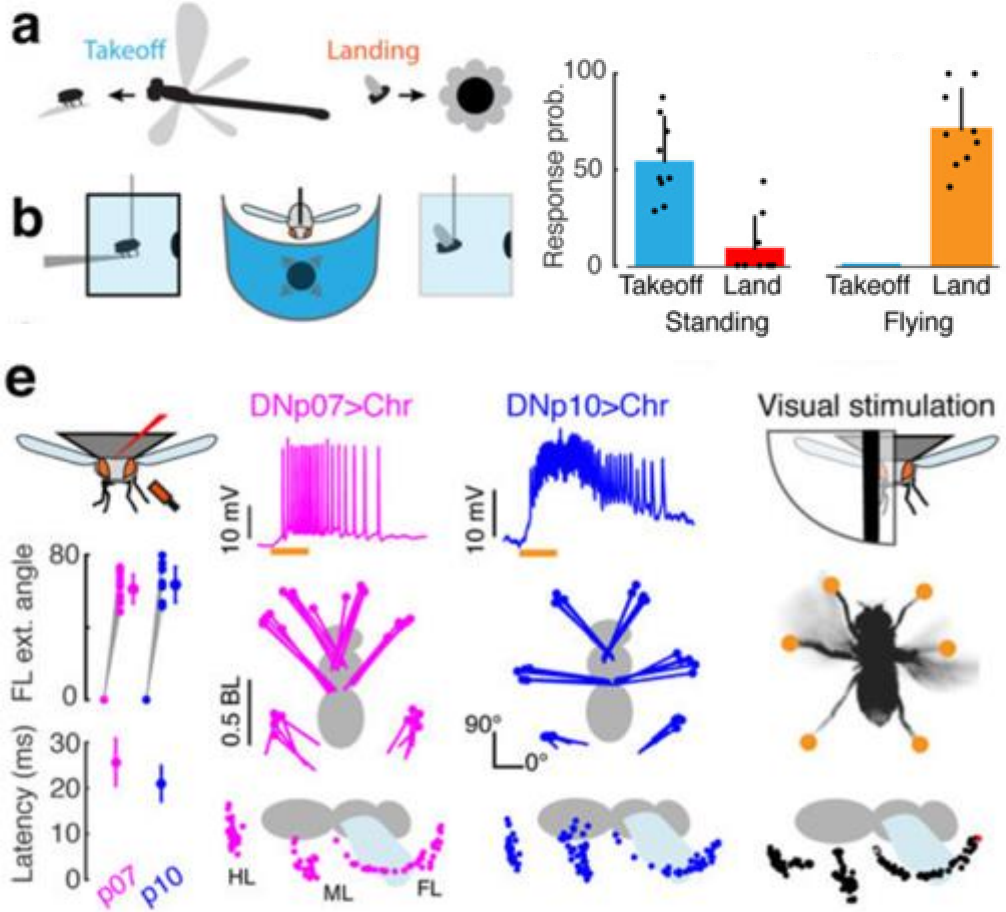


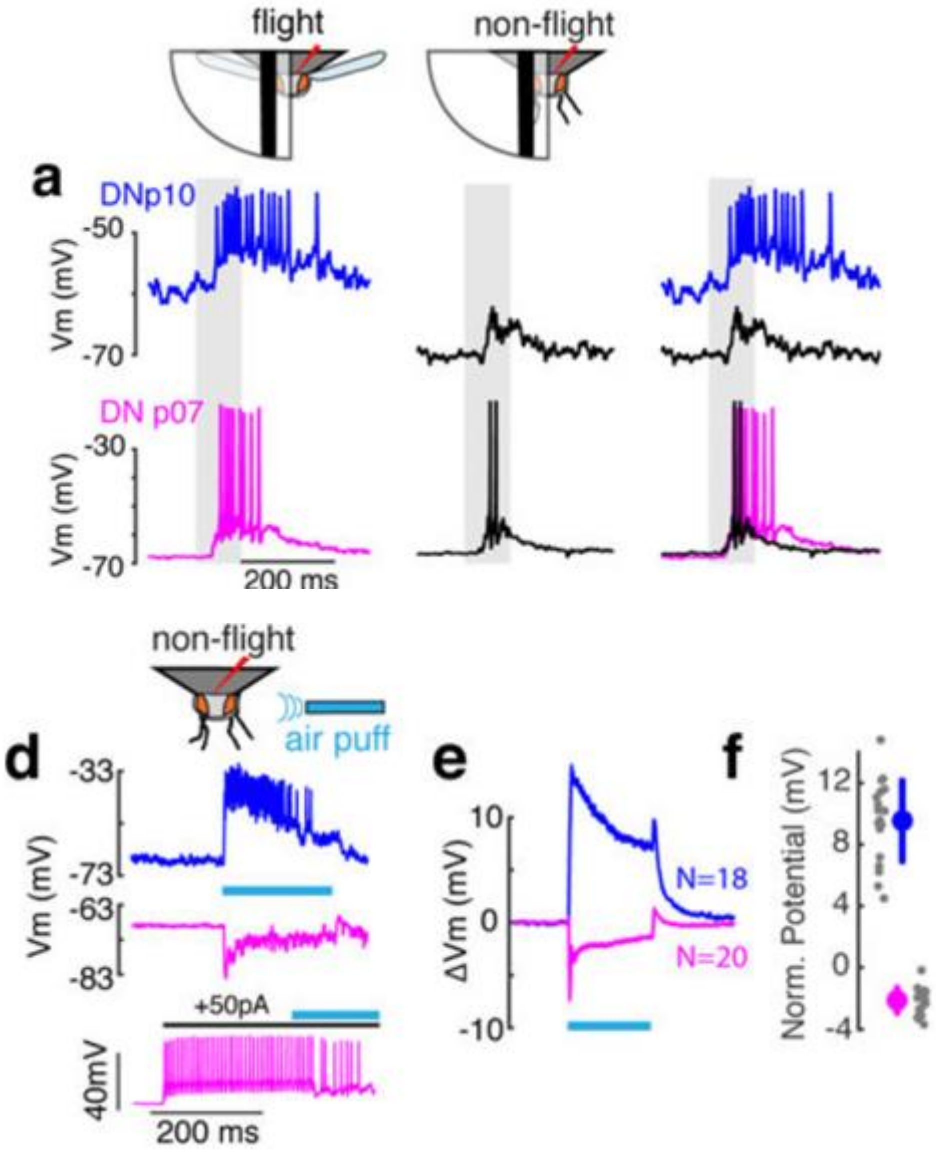
Simpson H.J. Curr Opin Neurobiol. 2024

Ros G.I. et al., Current Biology. 2024

Buchsbaum E and Schnell B. Current Biology. 2025

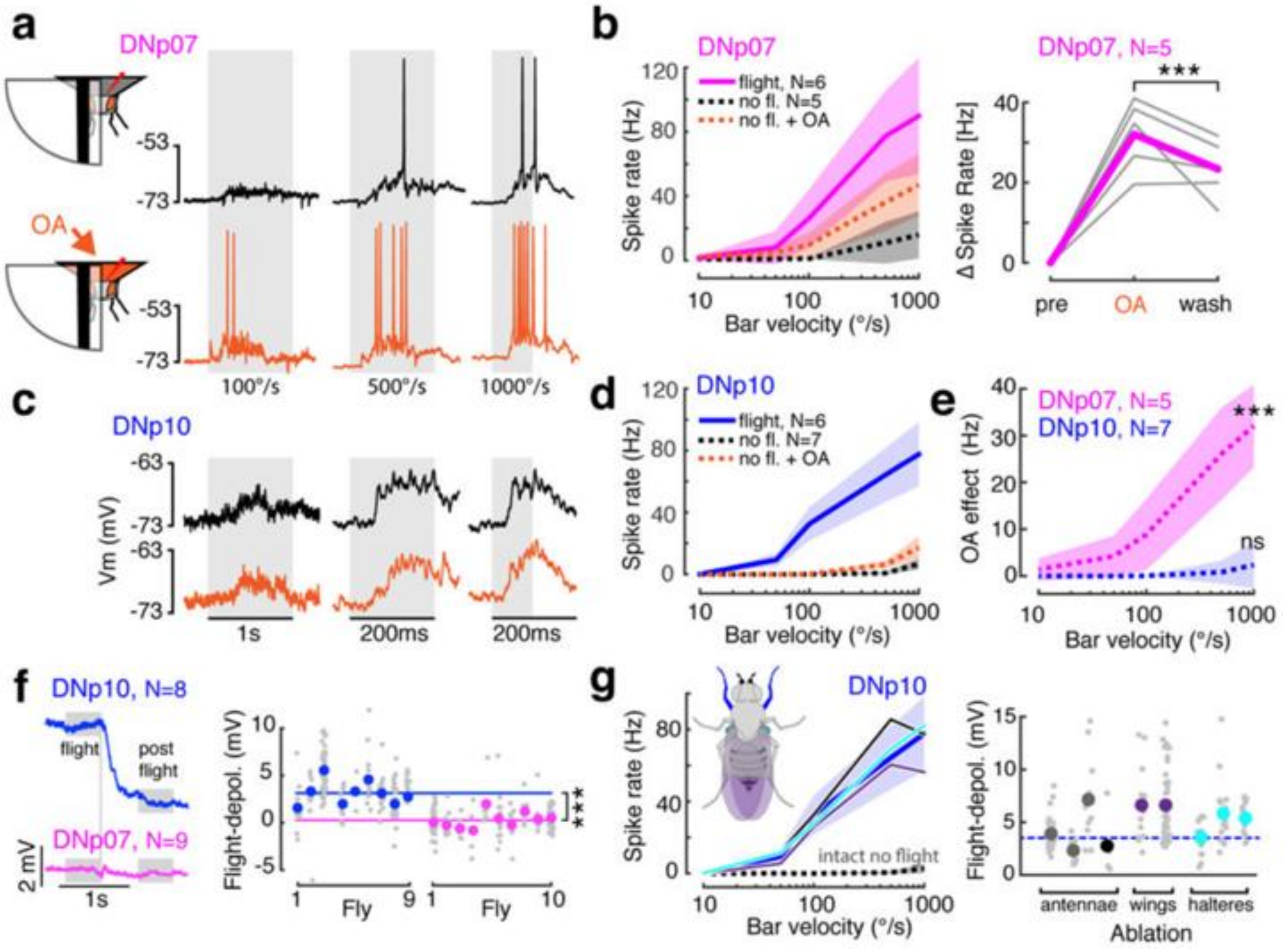
Landing command neurons exhibit flight-gated, visual-specific activity





Ache M.J, et al. Nat Neurosci. 2020

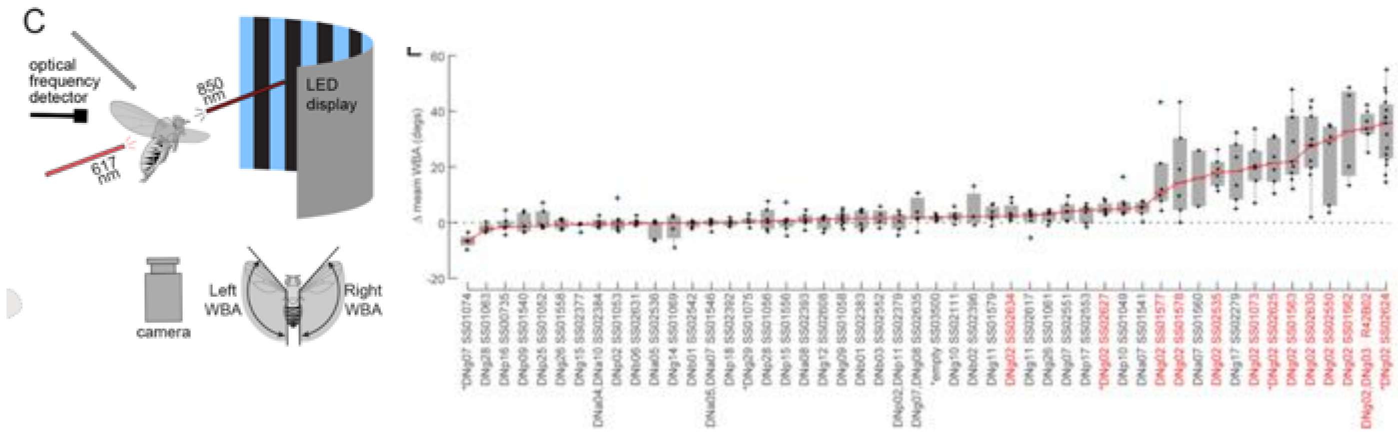
Distinct gating mechanisms for landing descending neurons

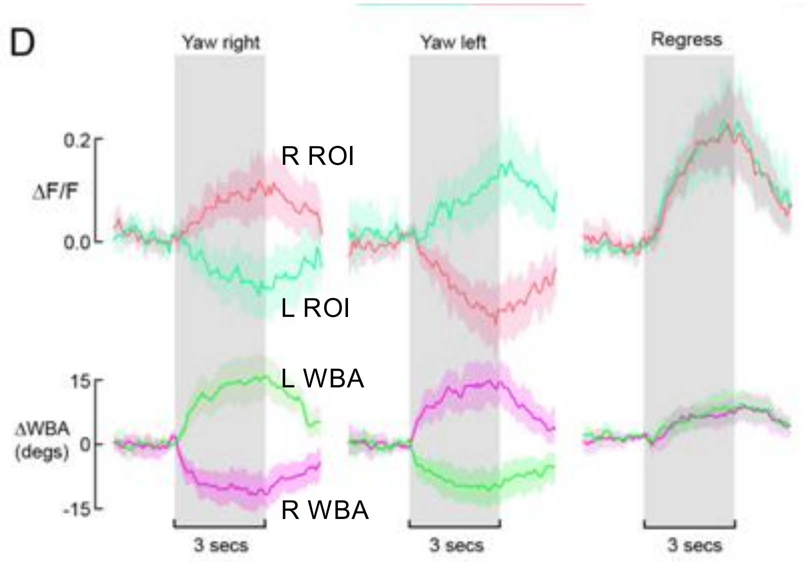


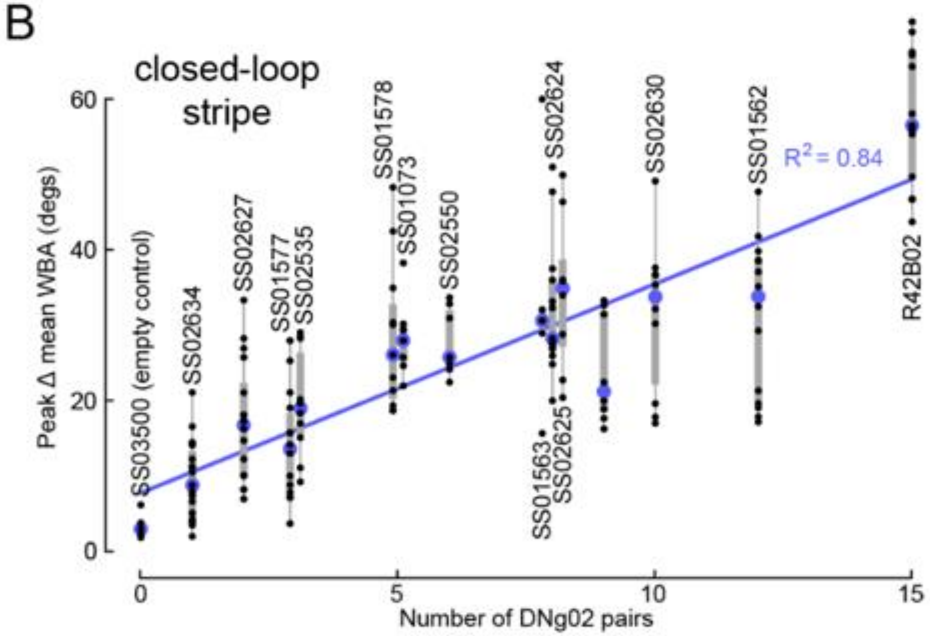
Ache M.J, et al. Nat Neurosci. 2020

Octopaminergic modulation for DNp07 and flight motor circuit feedback for DNp10

Population coding of wingbeat amplitude by DNg02 descending neurons



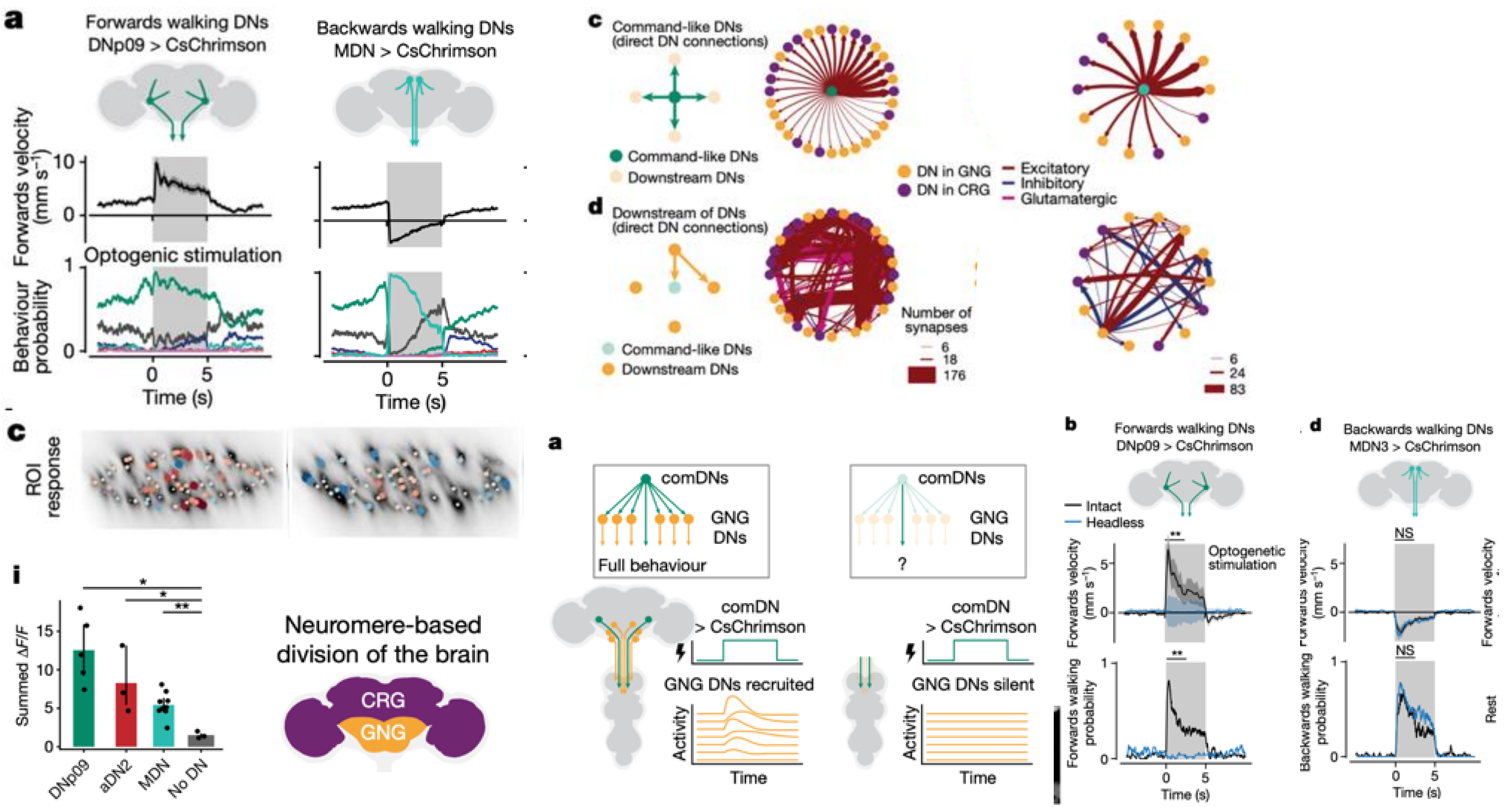




Left and right DNg02 neurons can act independently to regulate wingbeat amplitude

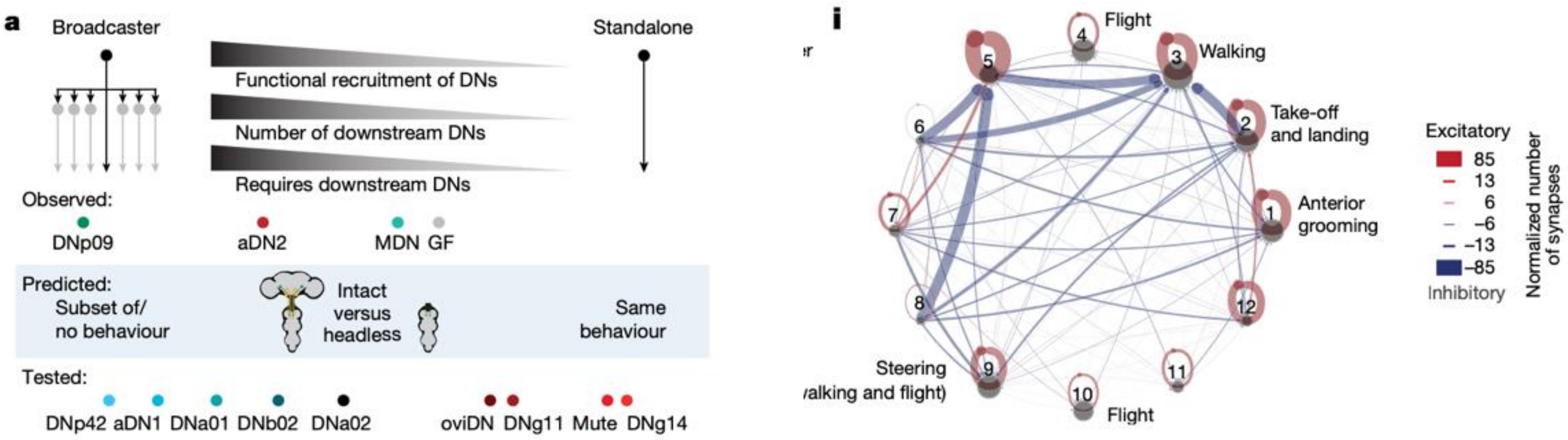
Namiki S, et al. Current Biology. 2022

ComDNs recruit additional downstream DN populations



Braun J. Nature. 2024

Network connectivity predicts the necessity for downstream DNs to drive behavior



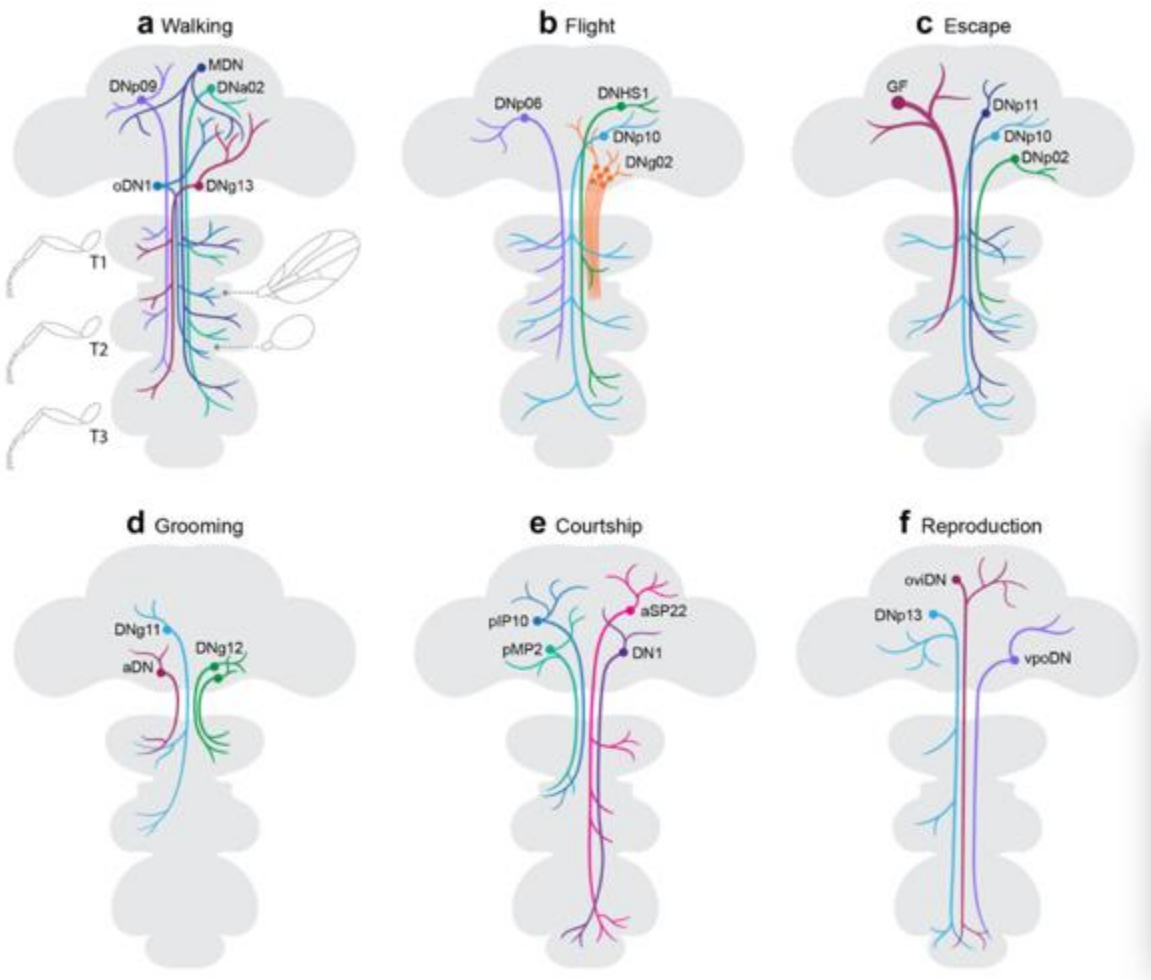
Braun J. Nature. 2024

Take-home message

1. Specific Drosophila descending neurons (DNs) control distinct behaviors: MDN (backward walking), DNa02/DNg13 (steering), BB/FG/BRK (context-specific halting), and DNp10 (landing initiation).

2. Most DNs elicit single stereotyped behaviors (e.g., MDN solely drives backward walking), though functional redundancy exists among some DN populations to ensure behavioral robustness.

3. DNs achieve precise and context-adaptive behavioral control via specialized “input-output” modes, state-dependent gating, and hierarchical recruitment of downstream DNs.



Article https://doi.org/10.1038/s41467-024-54694-0

Synaptic connectome of the *Drosophila* circadian clock

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Nils Reinhard[1,4], Ayumi Fukuda[2,4], Giulia Manoli[1], Emilia Derksen[1], Aika Saito[2], Gabriel Möller[1], Manabu Sekiguchi[2], Dirk Rieger[1], Charlotte Helfrich-Förster[1], Taishi Yoshii[2] & Meet Zandawala[1,3]

Current Biology Article

Regulation of pre-dawn arousal in *Drosophila* by a pair of trissinergic descending neurons of the visual and circadian networks

Highlights

- DNp27 neurons integrate circadian and visual signals

Authors

Ruihan Jiang, Yue Tian, Xin Yuan, Fang Guo

Sex difference: DN1 for male aggression; aIPg for female aggression

Evolutionary conservation:

pIP10 for courtship song in *D. melanogaster* and *D. yakuba*

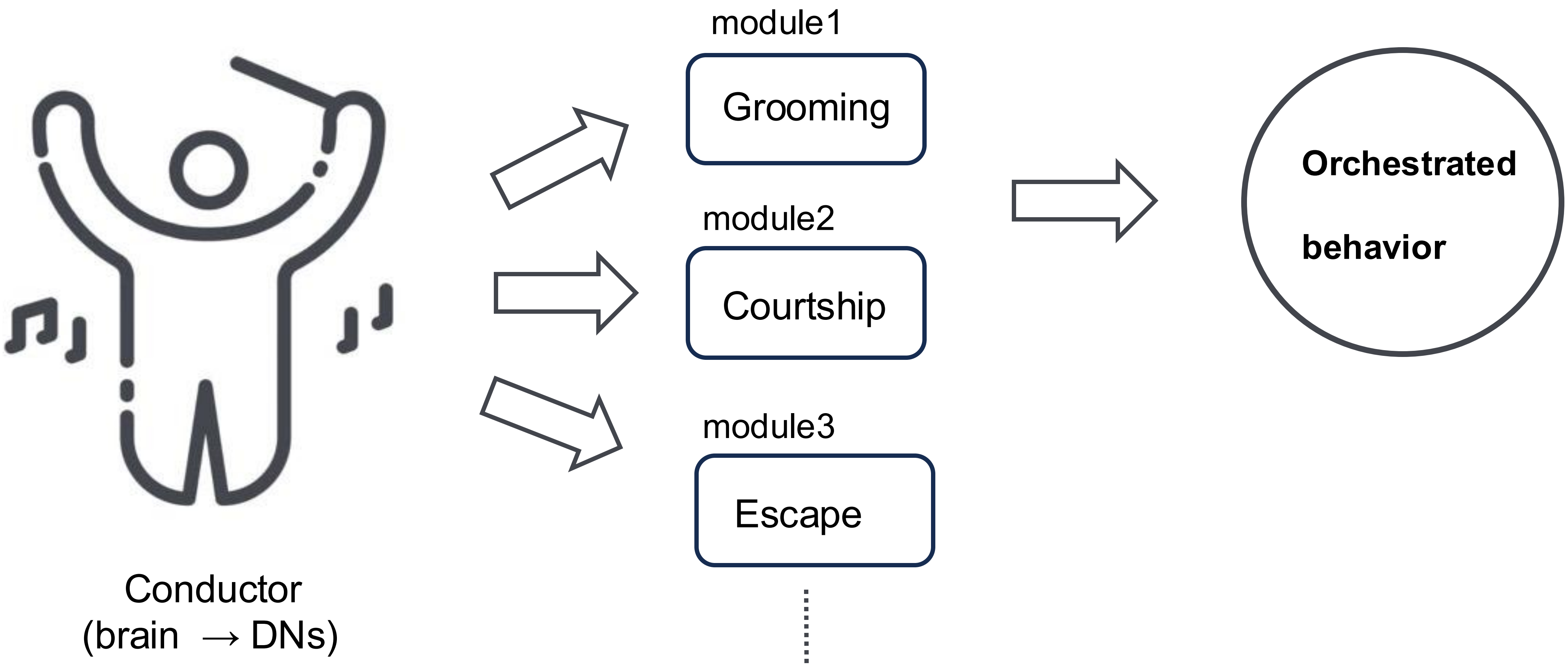
DNp13 and oviDN in *D. melanogaster* and *D. mojavensis*

Orchestrating complex behavioral sequences

2025-09-25

Joshua Liang

How do descending neurons orchestrate complex behavioral sequences?



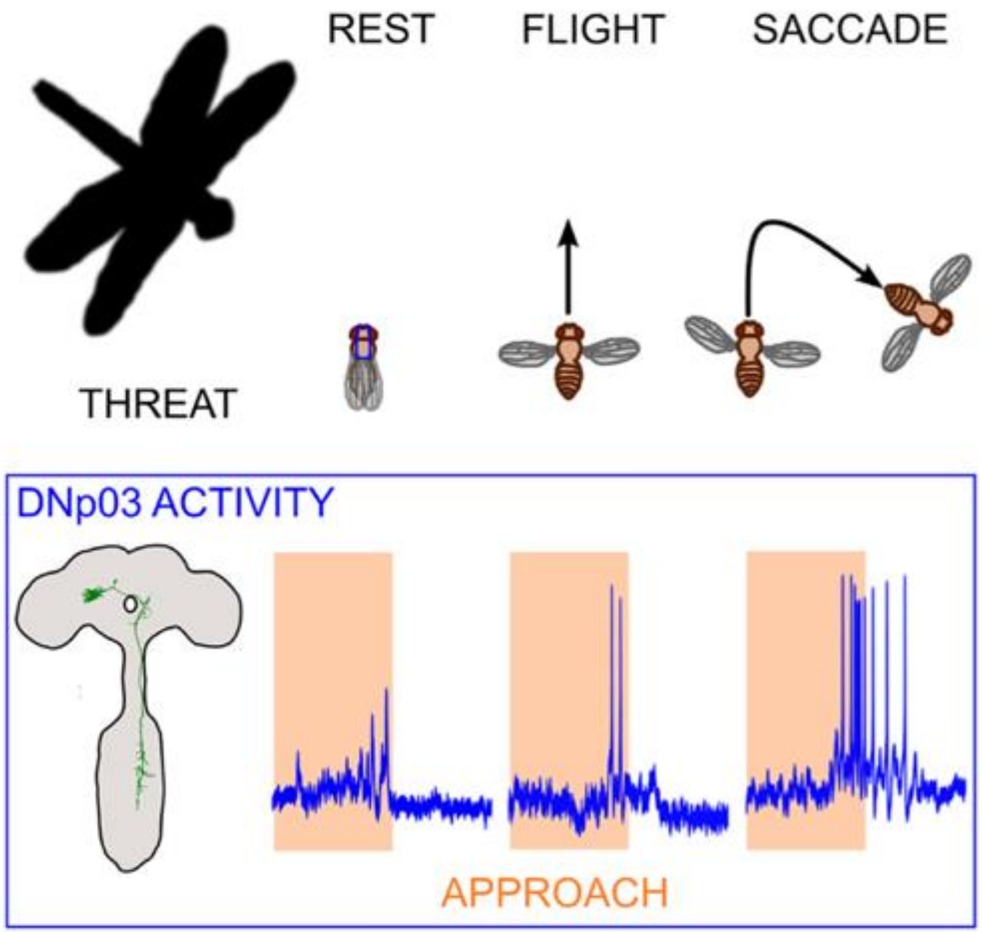
How do descending neurons orchestrate complex behavioral sequences?

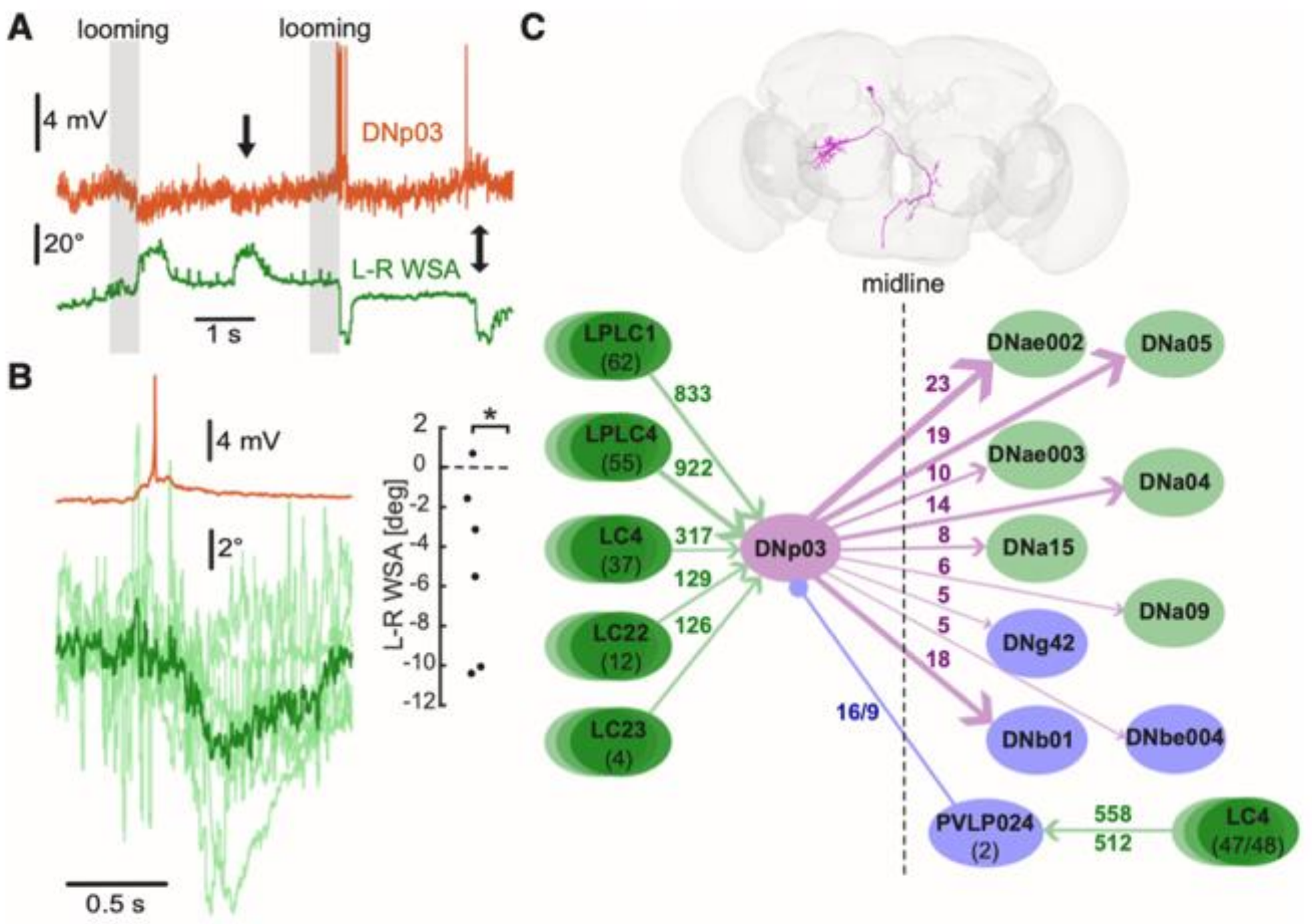
1. **How are complex behaviors divided into modular units and coordinated into orderly sequences?**

2. **How do descending neurons control timing, gain, and integrate internal states to shape actions?**

3. **Are these organizing principles unique to insects, or conserved across species?**

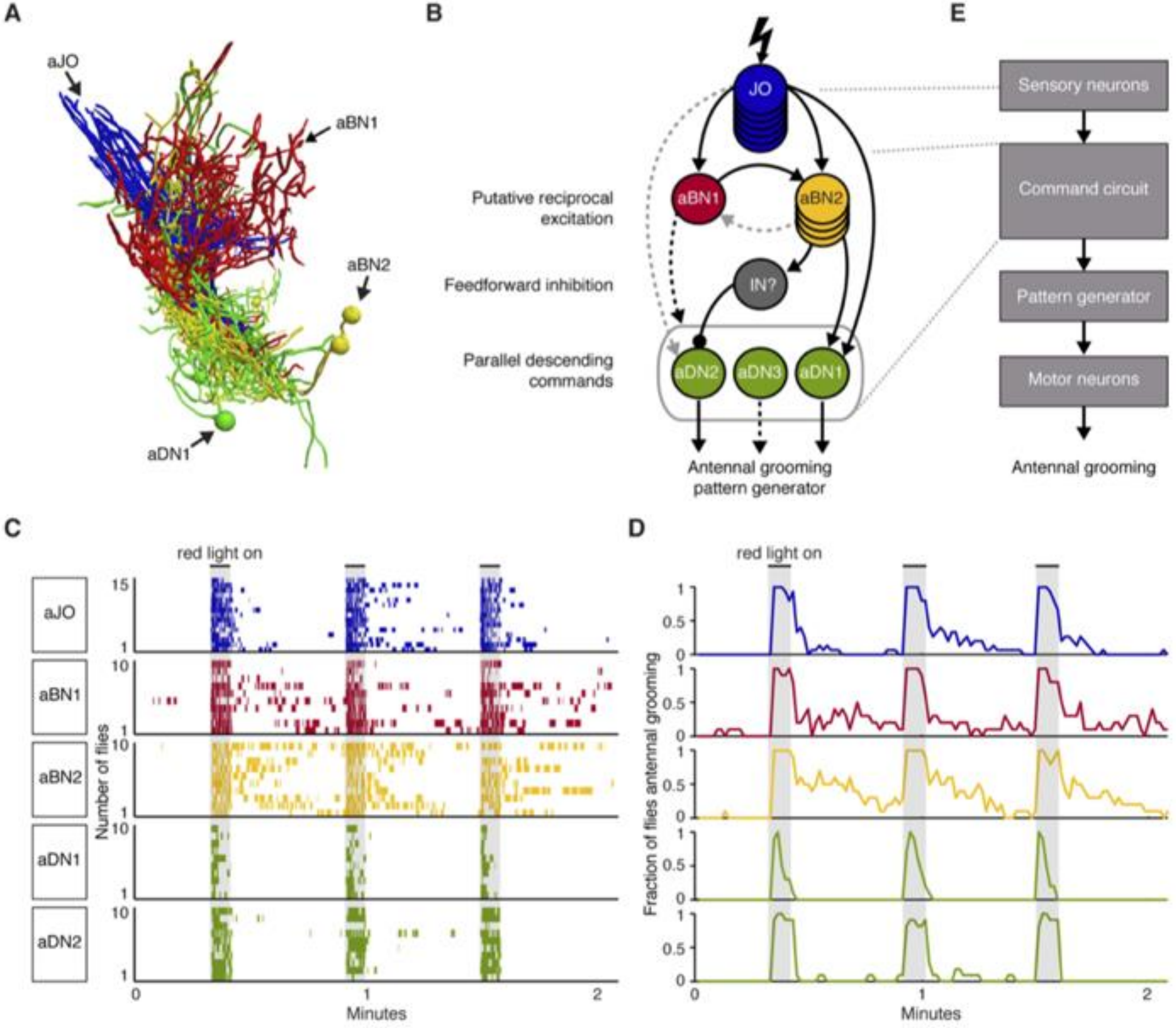
A descending neuron (DNp03) transforms visual input into escape behavior





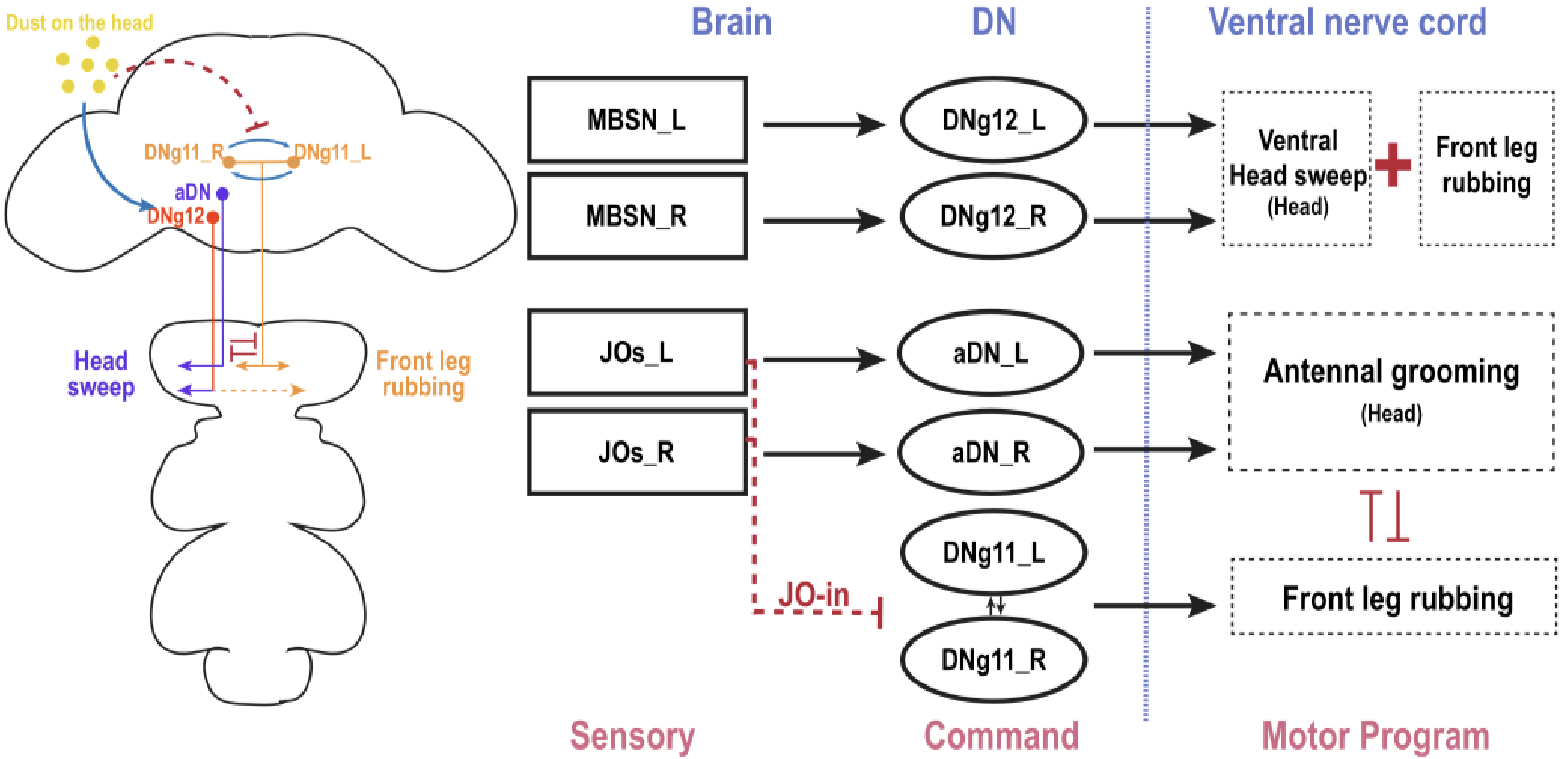
Buchsbaum E et al., *Curr Biol*. 2025

Module-based control and suppression hierarchy in grooming



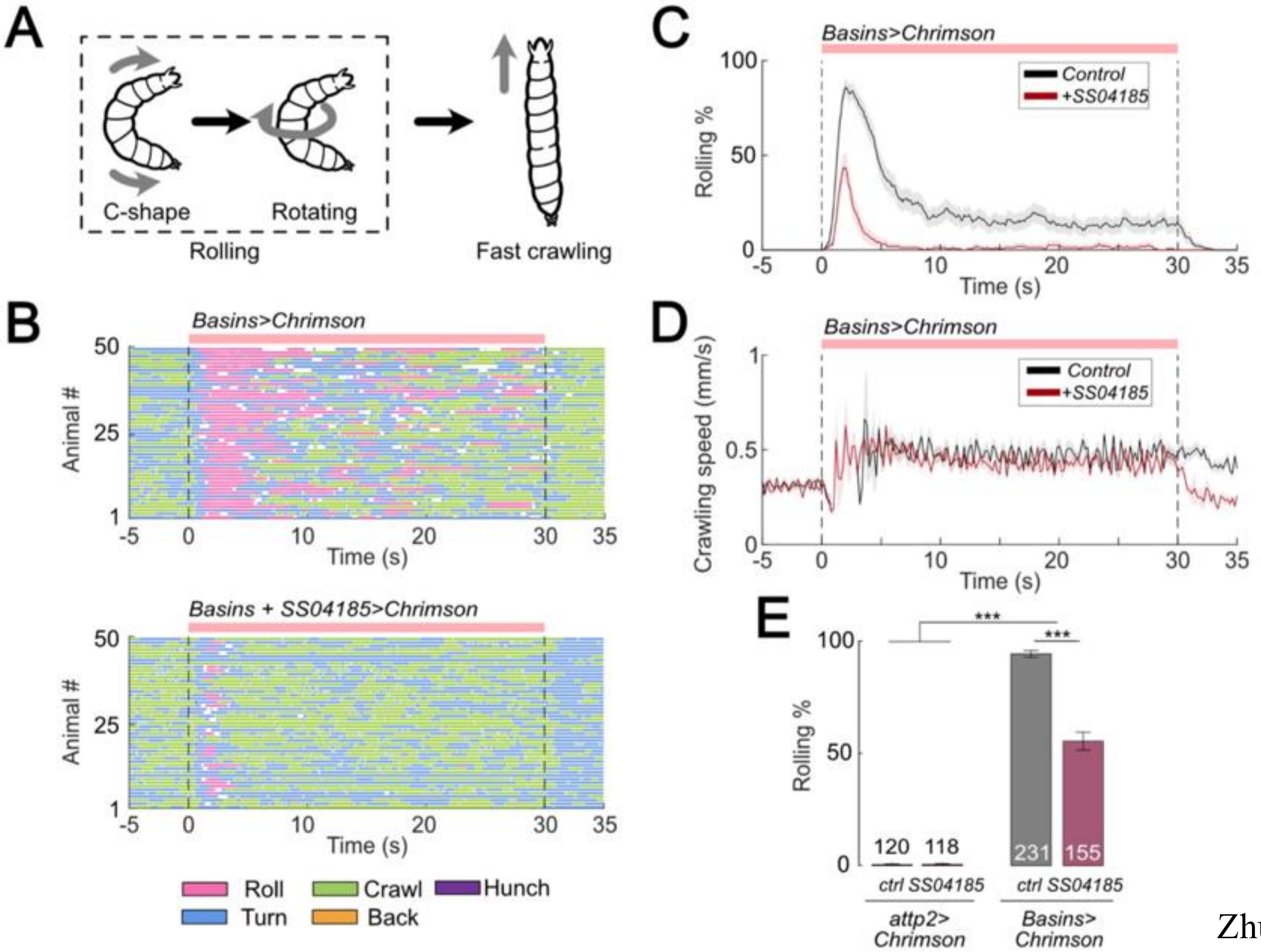
Hampel S et al., *Elife.* 2015

Coordination of grooming modules by multiple descending neurons

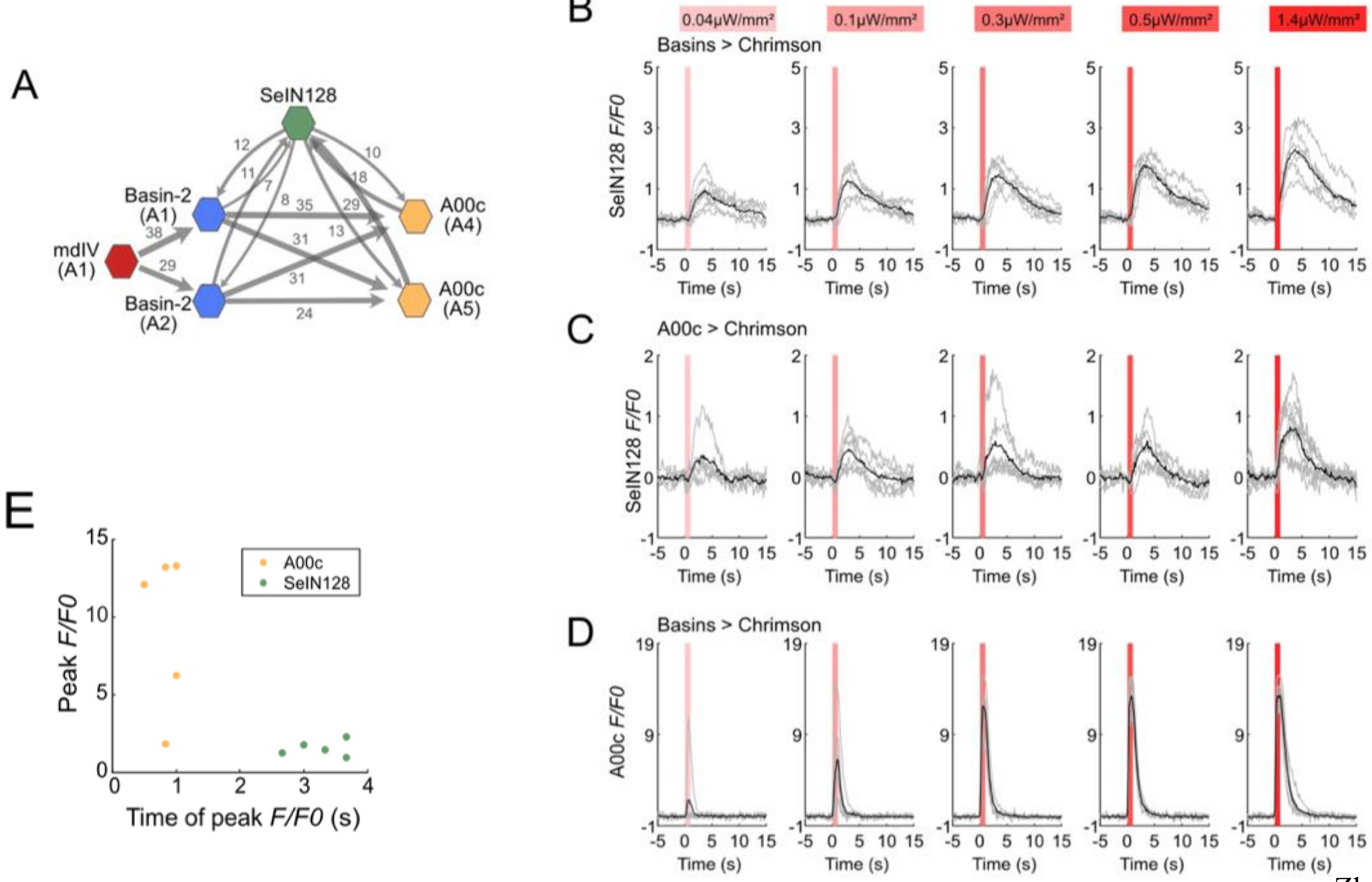


Guo L et al., *Curr Biol.* 2022

Descending control of when to act: timing of escape sequences

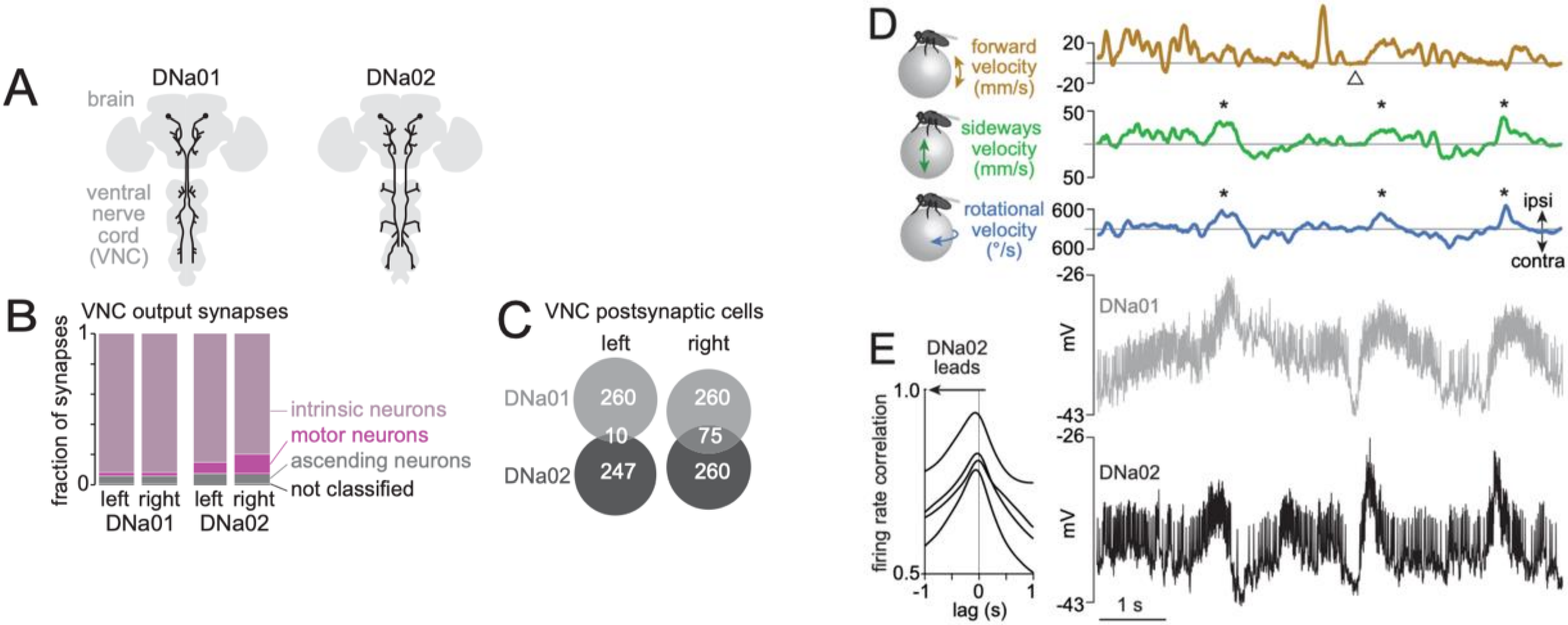


Zhu J et al., *Elife*. 2024

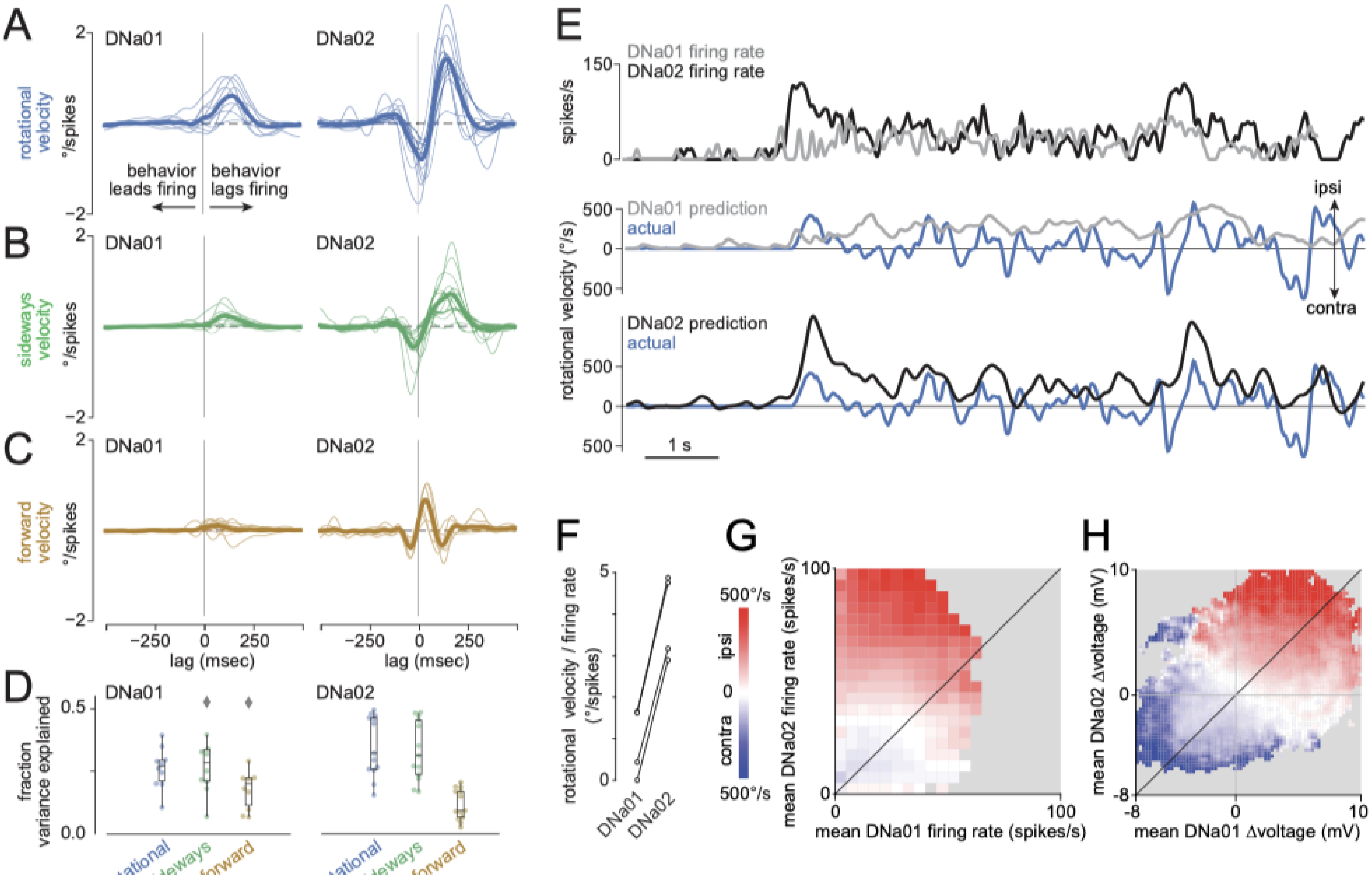


Zhu J et al., *Elife*. 2024

Descending control of steering: low- vs. high-gain pathways

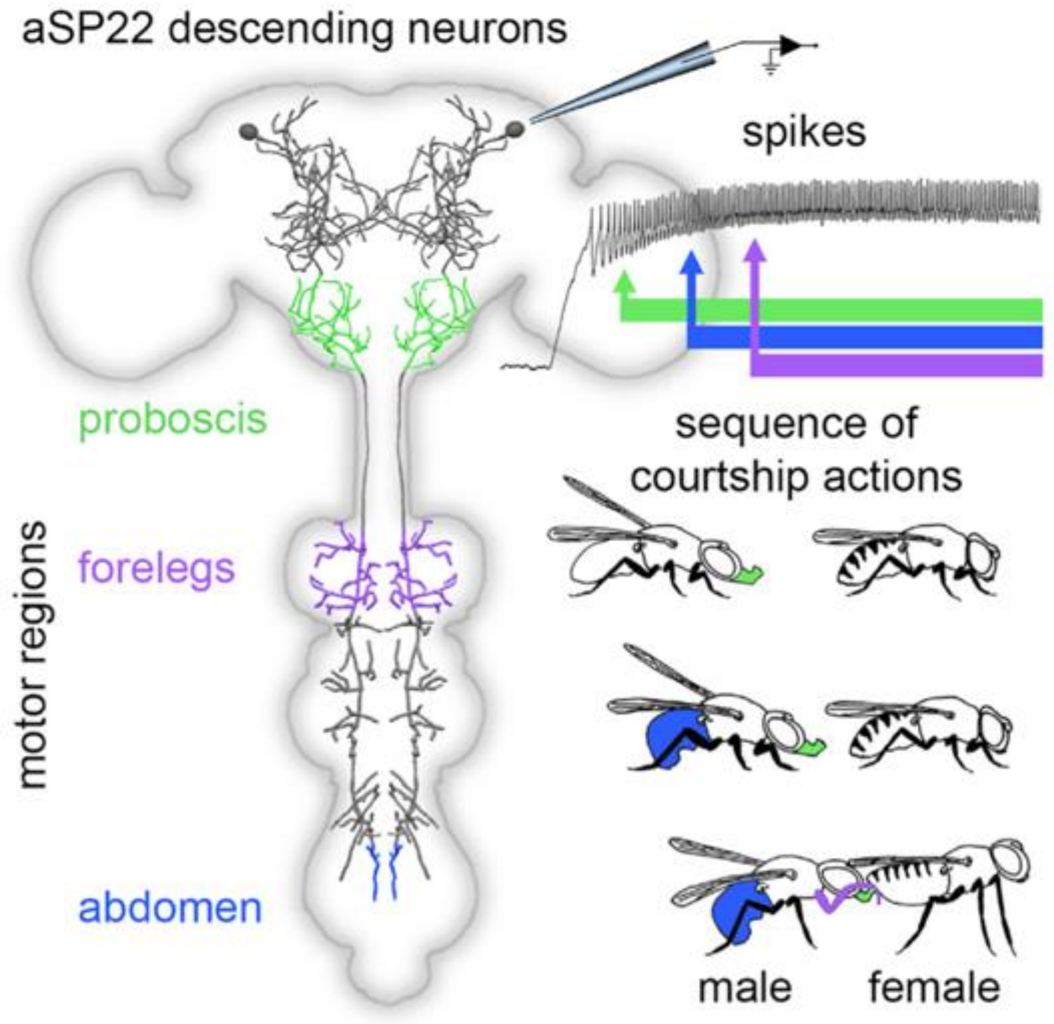


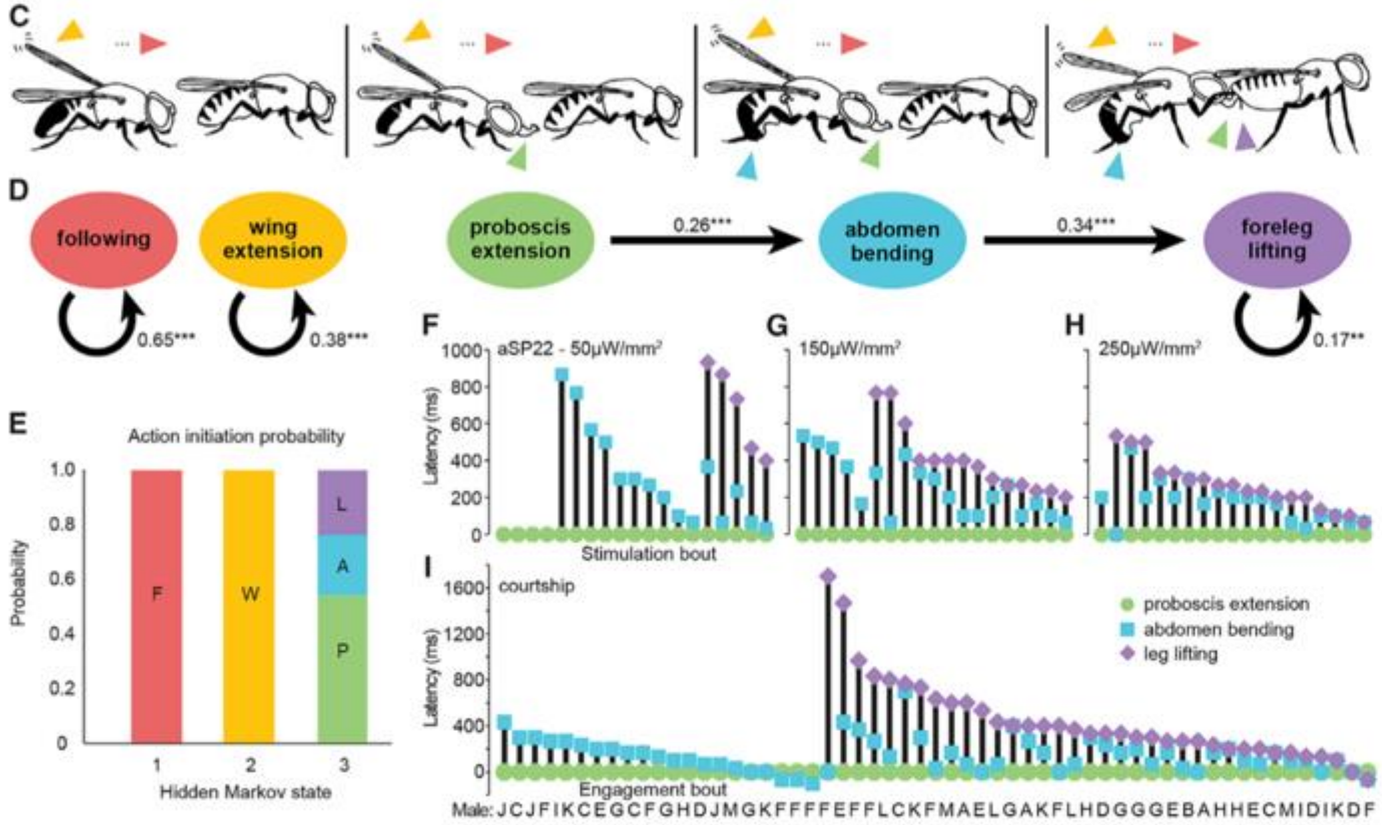
Rayshubskiy A et al., *Elife*. 2025



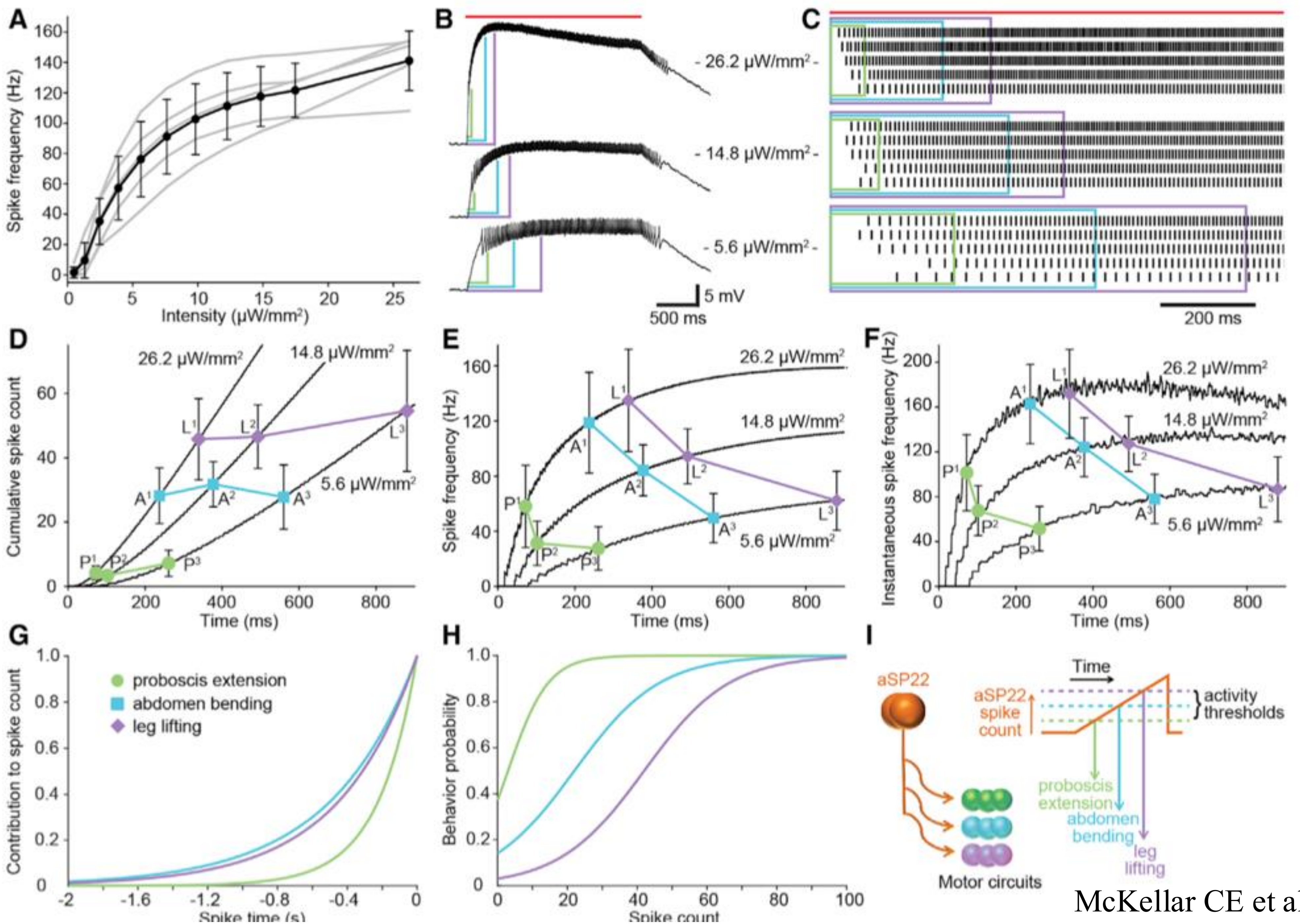
Rayshubskiy A et al., *Elife*. 2025

Threshold-based ordering of courtship sequences



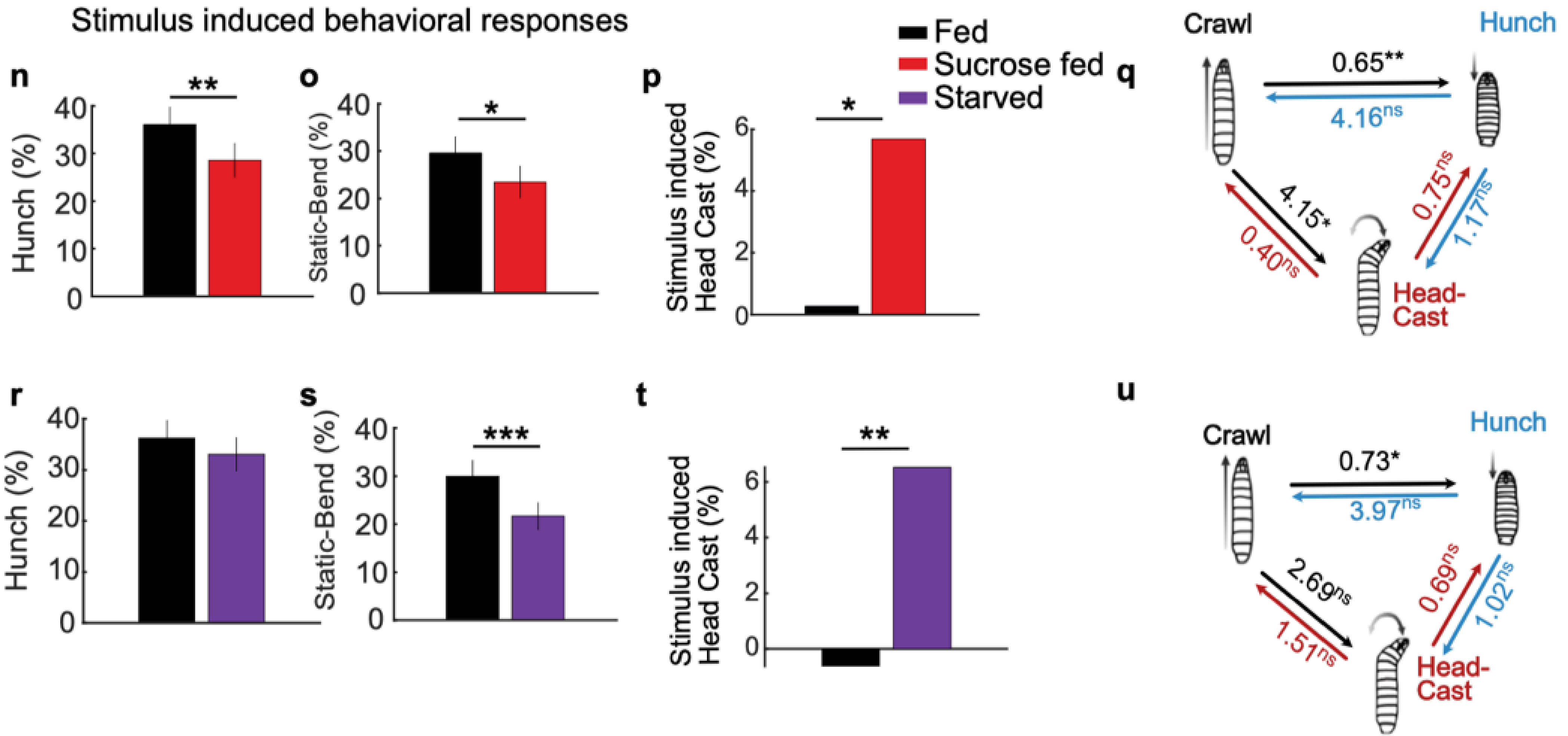


McKellar CE et al., *Curr Biol*. 2019

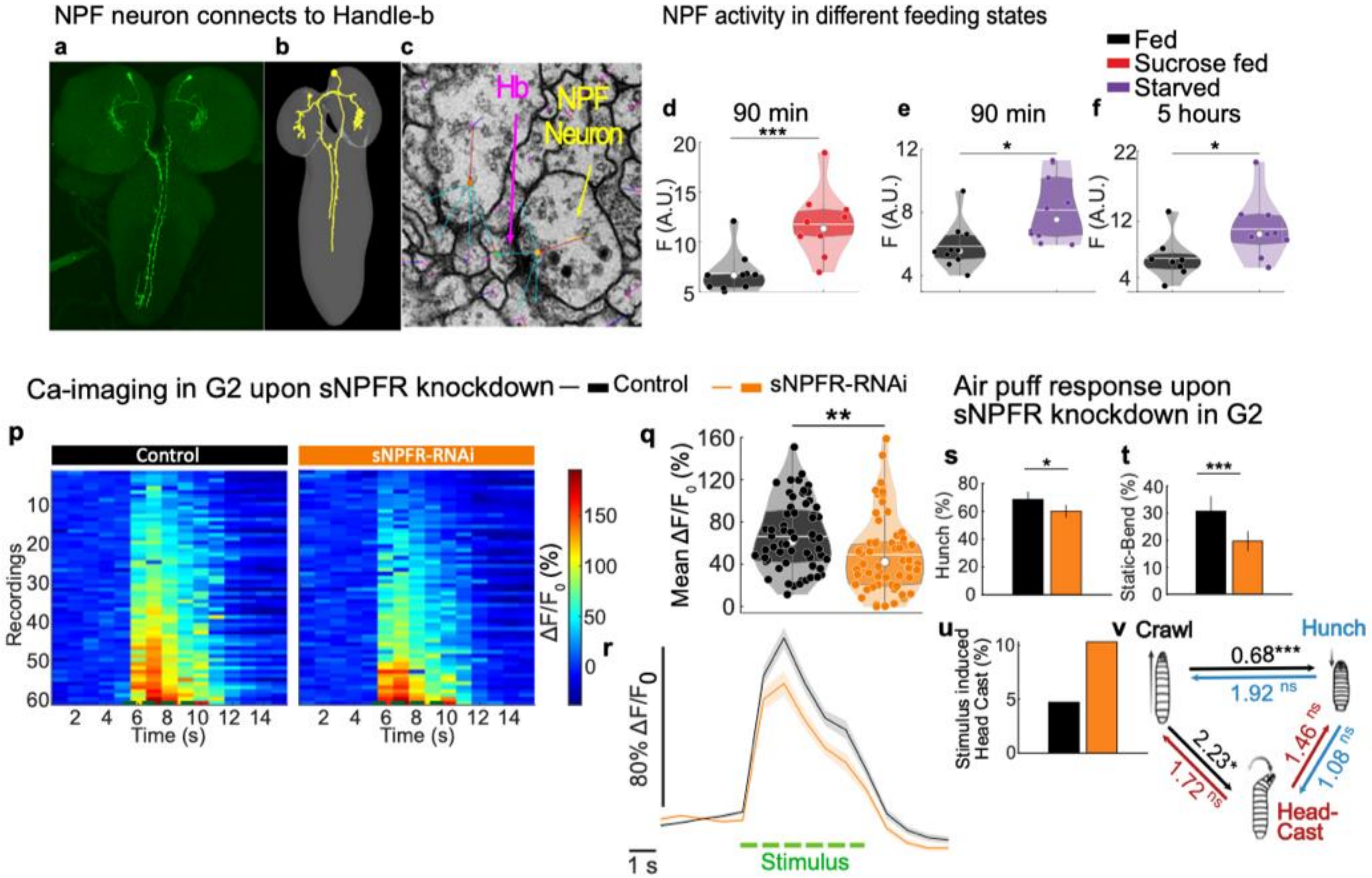


McKellar CE et al., *Curr Biol*. 2019

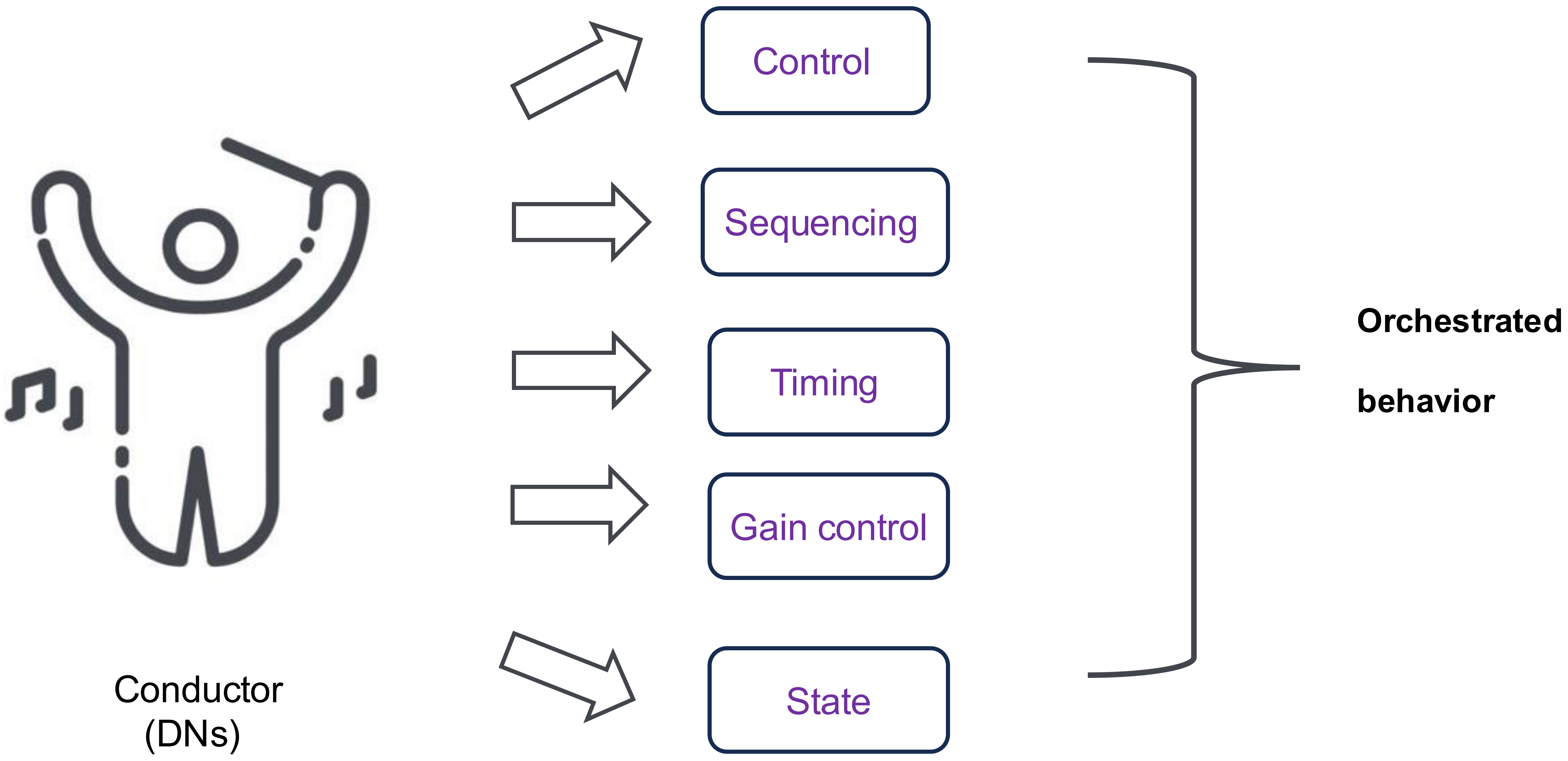
Feeding state biases sensorimotor decisions



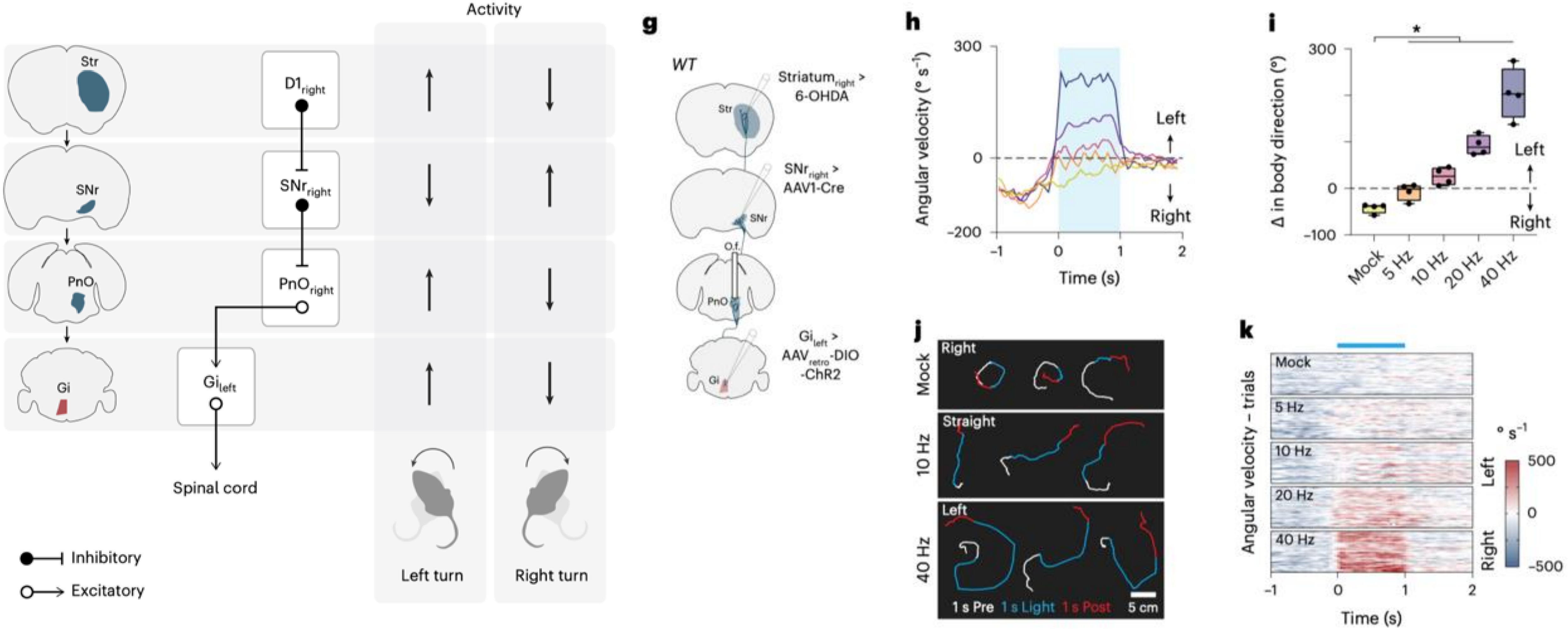
de Tredern E et al., *Nat Commun*. 2025



de Tredern E et al., *Nat Commun*. 2025

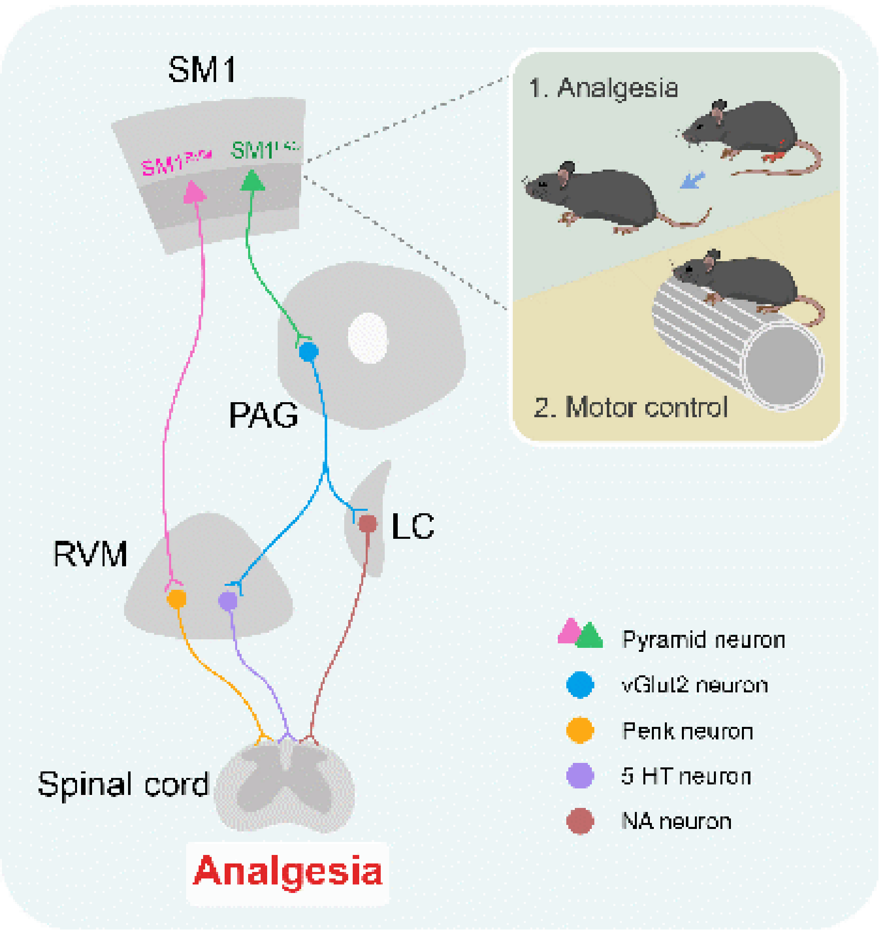

Control
Sequencing
Timing
Gain control
State
Orchestrated behavior
Conductor (DNs)

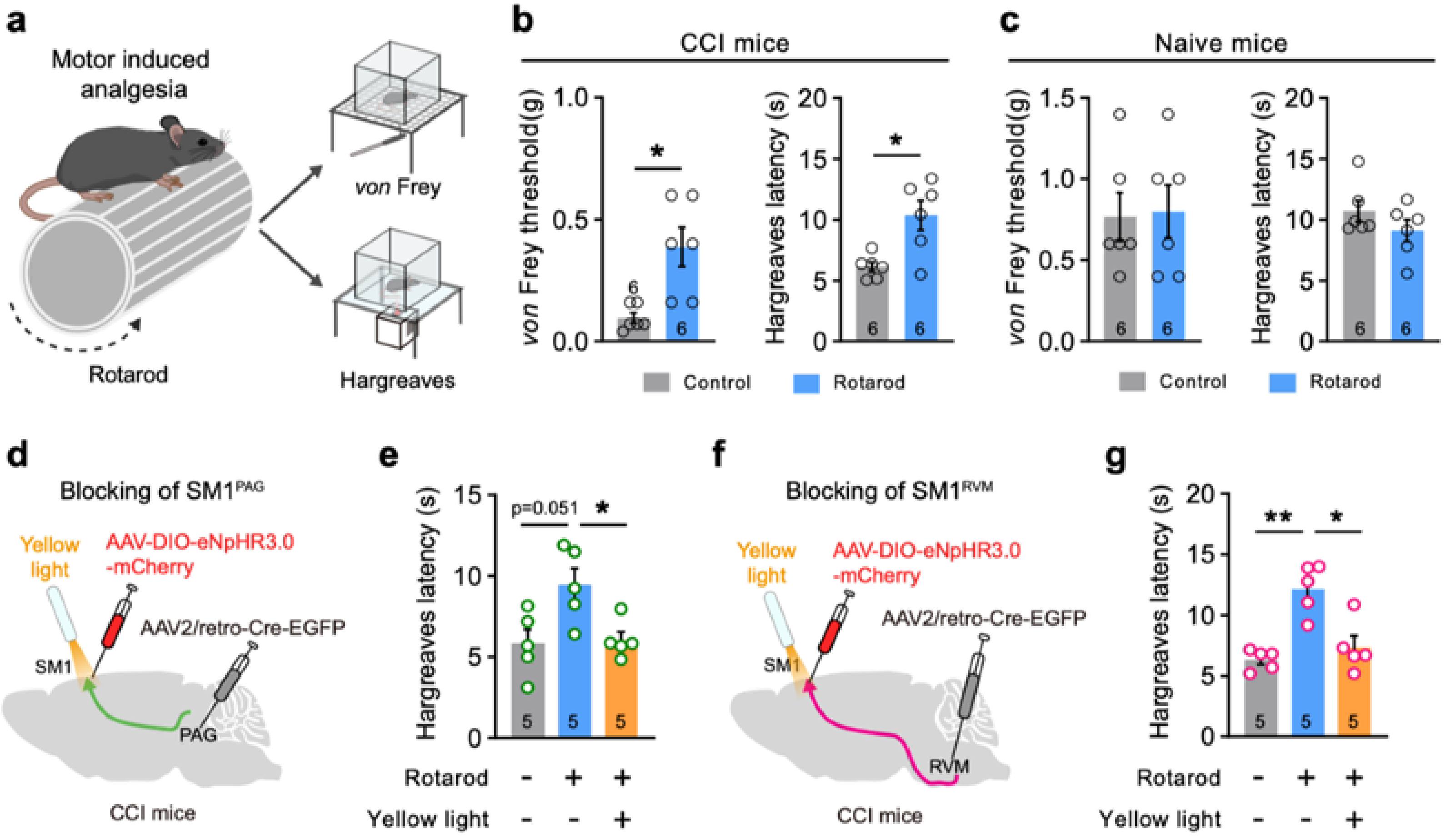
Basal ganglia–spinal cord descending pathway orchestrates locomotor gait asymmetries



Cregg JM et al., *Nat Neurosci*. 2024

Descending control in mammals: integrating motor and analgesia





Wang GH et al., *Nat Commun*. 2025

Take-home message

- **Modular control:** Descending neurons can trigger and coordinate action modules, ensuring orderly behavioral sequences.

- **Integration across dimensions:** DNs orchestrate not only sequence and timing, but also gain control and internal state modulation.

- **Conserved principle:** From insects to mammals, descending pathways act as "conductors" that integrate sensory inputs, motor outputs, and internal states to generate flexible and adaptive behaviors.

Thank you!