Papers of our interests that published on *Cell&Nature&Science* from 2019 to 2021

2021 Jun.24th

12:00-12:40 Sun Mengshi

12:40-13:05 Jin Sihui

13:05-13:30 Su Xiangbin

Part I. Overview of those selected papers

-Sun Ms

nature

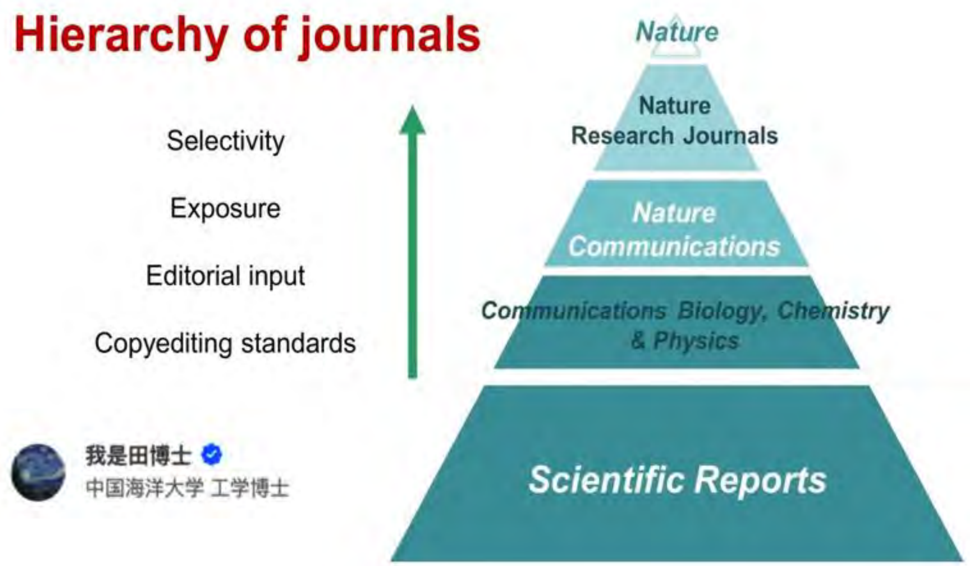
Macmillan Publishers

A weekly international journal publishing in all fields of science and technology.

The first issue of Nature was published on 4 November 1869.
Founder: Alexander Macmillan

2 year Impact Factor - 42.779
5 year Impact Factor - 46.488

Article:
they do not normally exceed 5 pages
3-4 modest display items (figures and tables)
2000-2500 words (summary paragraph plus body text).



Science AAAS

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

Science is a weekly, peer-reviewed journal that publishes significant original scientific research, plus reviews and analyses of current research and science policy.
It was first published in 1880.

Publication	2-year Impact Factor[1]	5-year Impact Factor[1]
Science	41.845	44.372

AAAS, an international nonprofit scientific association established in 1849, publishes: Science, Science Advances, Science Immunology, Science Robotics, Science Signaling and Science Translational Medicine.

Science

Research Articles: present a major advance. up to ~4500 words and ~5 printed pages. Up to six figures or tables.
Science also accepts a few Research Articles for online presentation. These can be up to 8000 words.

Reports: present important new research results of broad significance. up to ~2500 words, ~3 printed pages, four figures or tables and 30 references.

Reviews: up to~6000 words and 4-6 figures or tables, 100 references

Cell

CellPress
Science that inspires

Cell journal was established in 1974 and is published twice monthly by Cell Press.

Cell publishes findings of unusual significance in any area of life science.

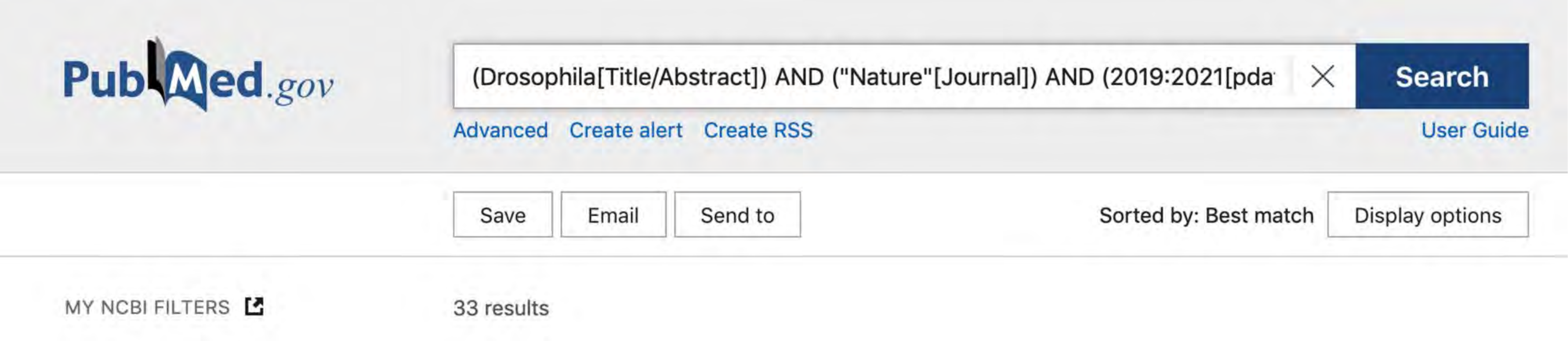
Cell article types

Research journals	Impact factor (JIF)	5-year IF
Cell	38.637	38.620

Research | Resource | Theory | Matters Arising | Preview | Review

Research articles present conceptual advances of unusual significance regarding **a biological question of wide interest.** The total character count of an article must be under 45,000* and no more than seven figures and/or tables.

Cell
Cancer Cell
Cell Chemical Biology
Cell Genomics
Cell Host & Microbe
Cell Metabolism
Cell Reports
Cell Reports Medicine
Cell Reports Methods
Cell Reports Physical Science
Cell Stem Cell
Cell Systems
Chem
Chem Catalysis
Current Biology
Developmental Cell
Heliyon
Immunity
iScience
Joule
Matter
Med
Molecular Cell
Neuron
One Earth
Patterns
STAR Protocols
Structure



Search: "Drosophila"[Title/Abstract] AND "Nature"[Journal] AND 2019/01/01:2021/12/31[Date - Publication]

Selected:
Nature: 15/33
Science: 3/17
Cell: 4/20

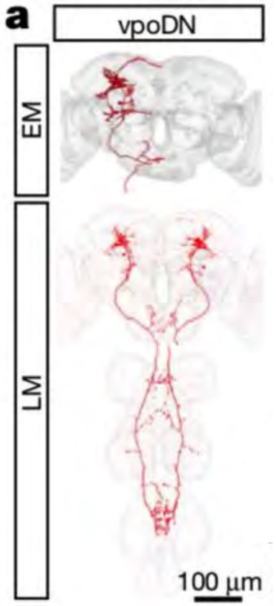
Article

Neural circuit mechanisms of sexual receptivity in *Drosophila* females

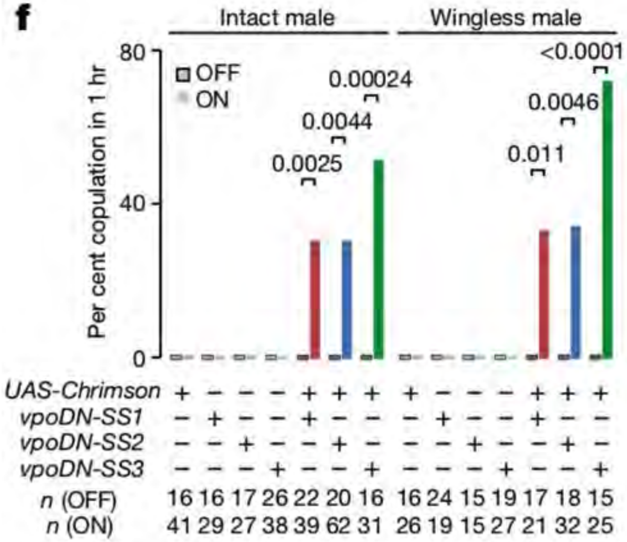
https://doi.org/10.1038/s41586-020-2972-7
Received: 13 January 2020

Kaiyu Wang[1,3], Fei Wang[1,3], Nora Forknall[1], Tansy Yang[1], Christopher Patrick[1], Ruchi Parekh[1] & Barry J. Dickson[1,2]✉

1. Screened 234 lines (labelled fru+ or dsx+ neurons) and found vpoDN supplementary

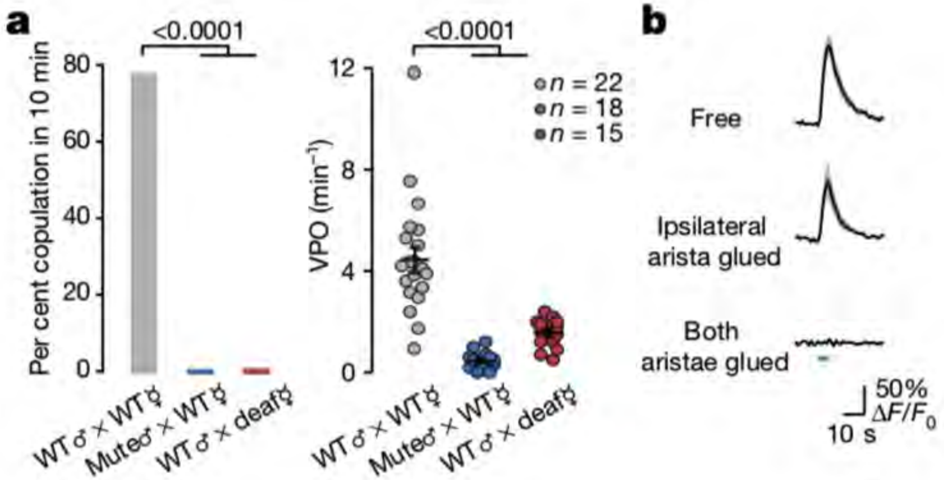


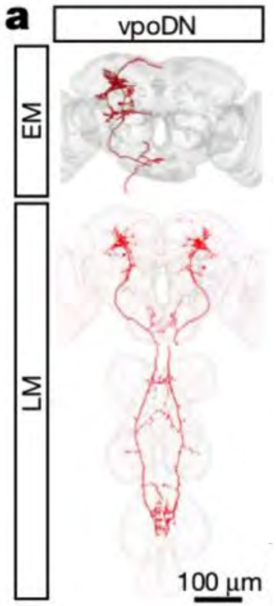
2. Manipulation of vpoDN activity. mated female (internal states) and wingless male (external cues): locate the position of vpoDN in receptivity circuity



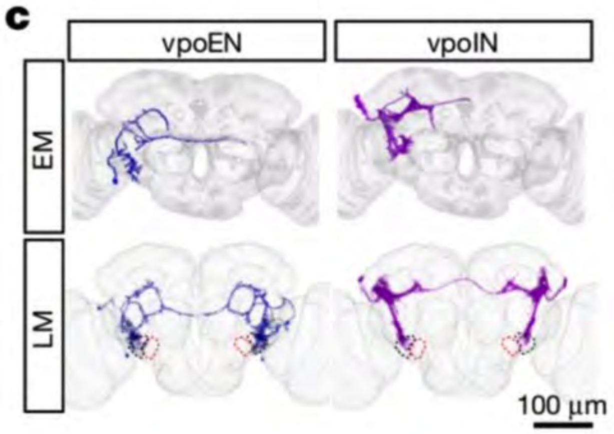
3. vpoDNs respond to courtship songs but do not have direct projections to AMMC region.

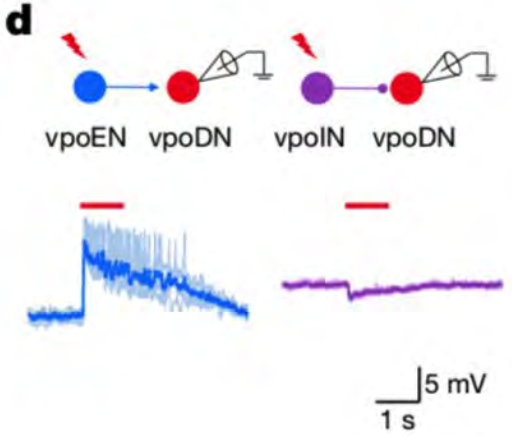
vpoDN





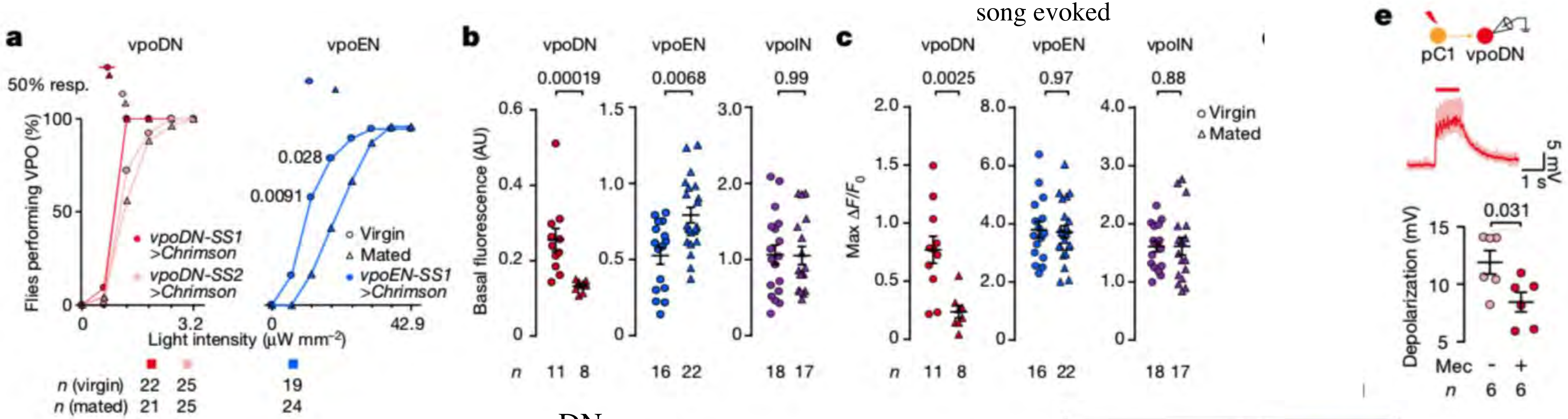
4. Search for the interneurons by electron microscopy volume of a full adult female brain.



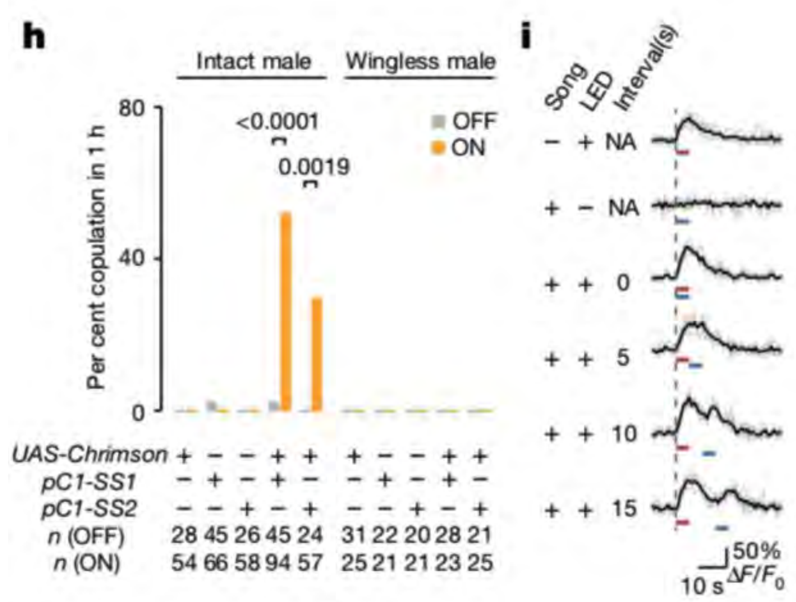


5. Discover the relationship between pC1 (internal mating status) and vpoDN

song evoked

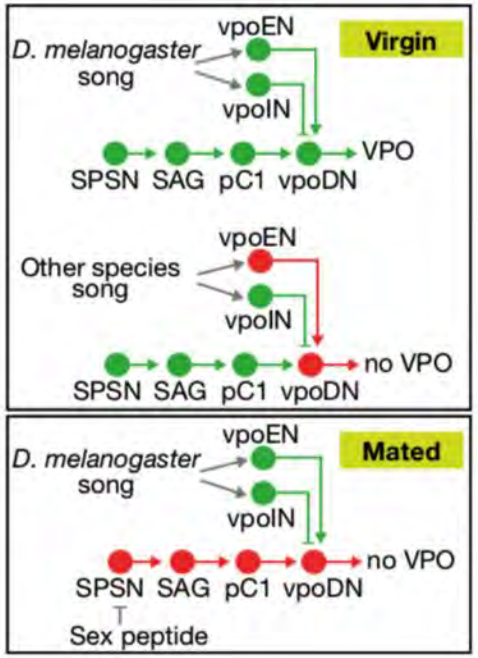


vpoDN



photoactivation (red)

song playback (blue)



Article

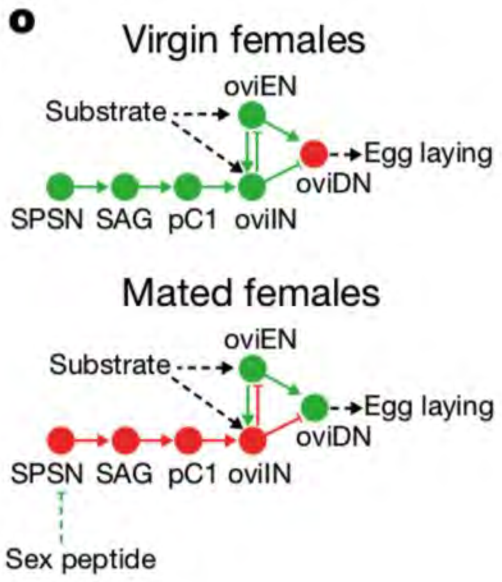
Neural circuitry linking mating and egg laying in *Drosophila* females

https://doi.org/10.1038/s41586-020-2055-9

Received: 15 May 2019

Accepted: 13 January 2020

Fei Wang[1,4], Kaiyu Wang[1,4], Nora Forknall[1], Christopher Patrick[1], Tansy Yang[1], Ruchi Parekh[1], Davi Bock[1,3] & Barry J. Dickson[1,2] ✉



LETTER

https://doi.org/10.1038/s41586-019-1571-y

Daytime colour preference in *Drosophila* depends on the circadian clock and TRP channels

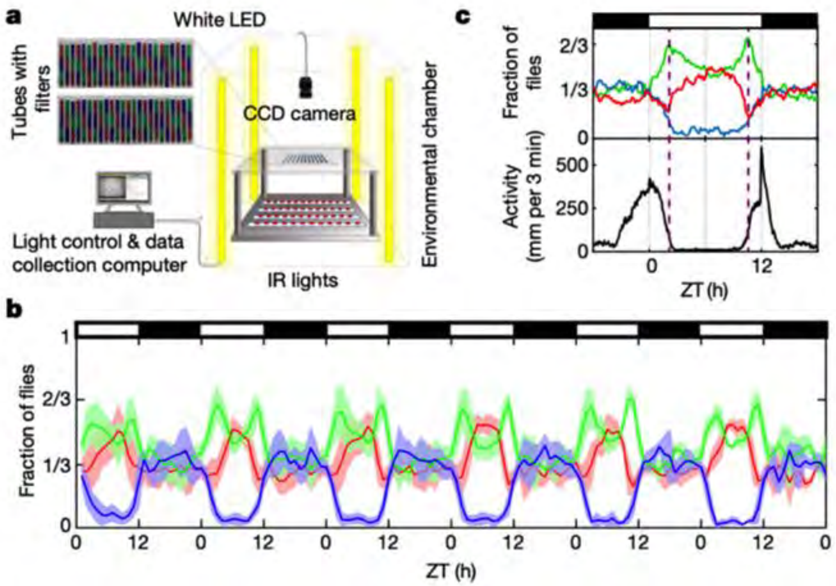
Stanislav Lazopulo[1], Andrey Lazopulo[1], James D. Baker[2] & Sheyum Syed[1]*

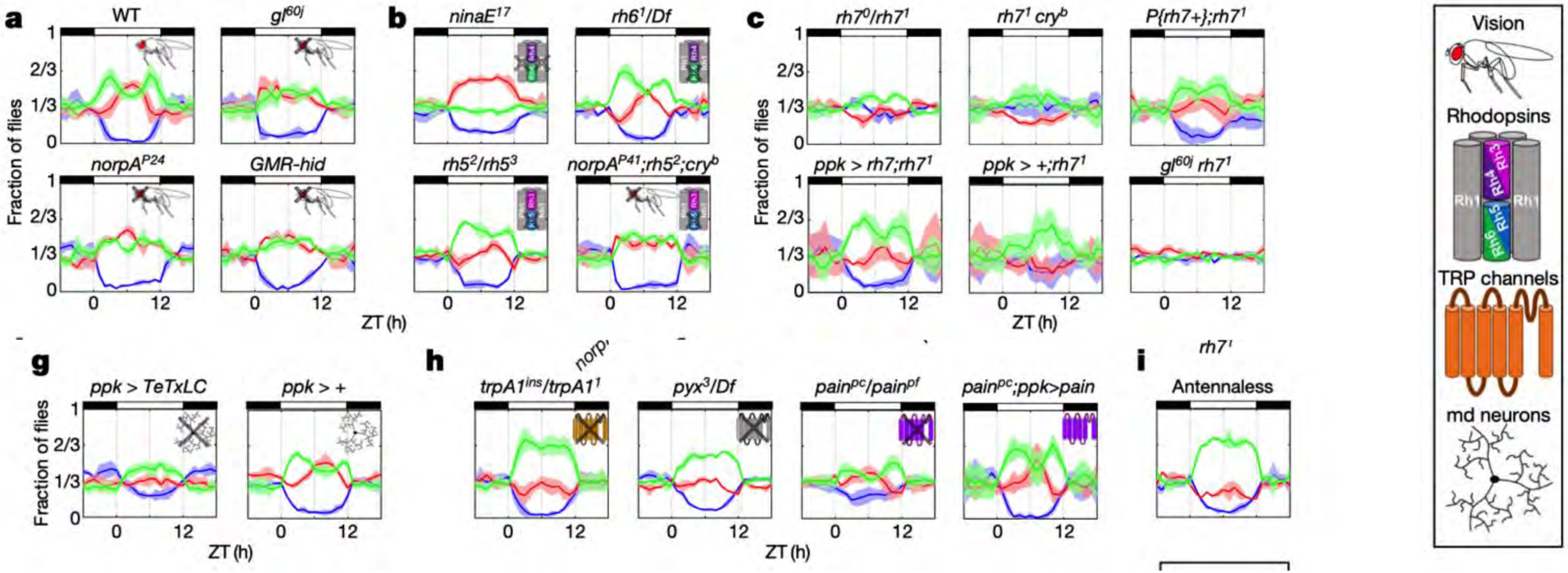
108 | NATURE | VOL 574 | 3 OCTOBER 2019

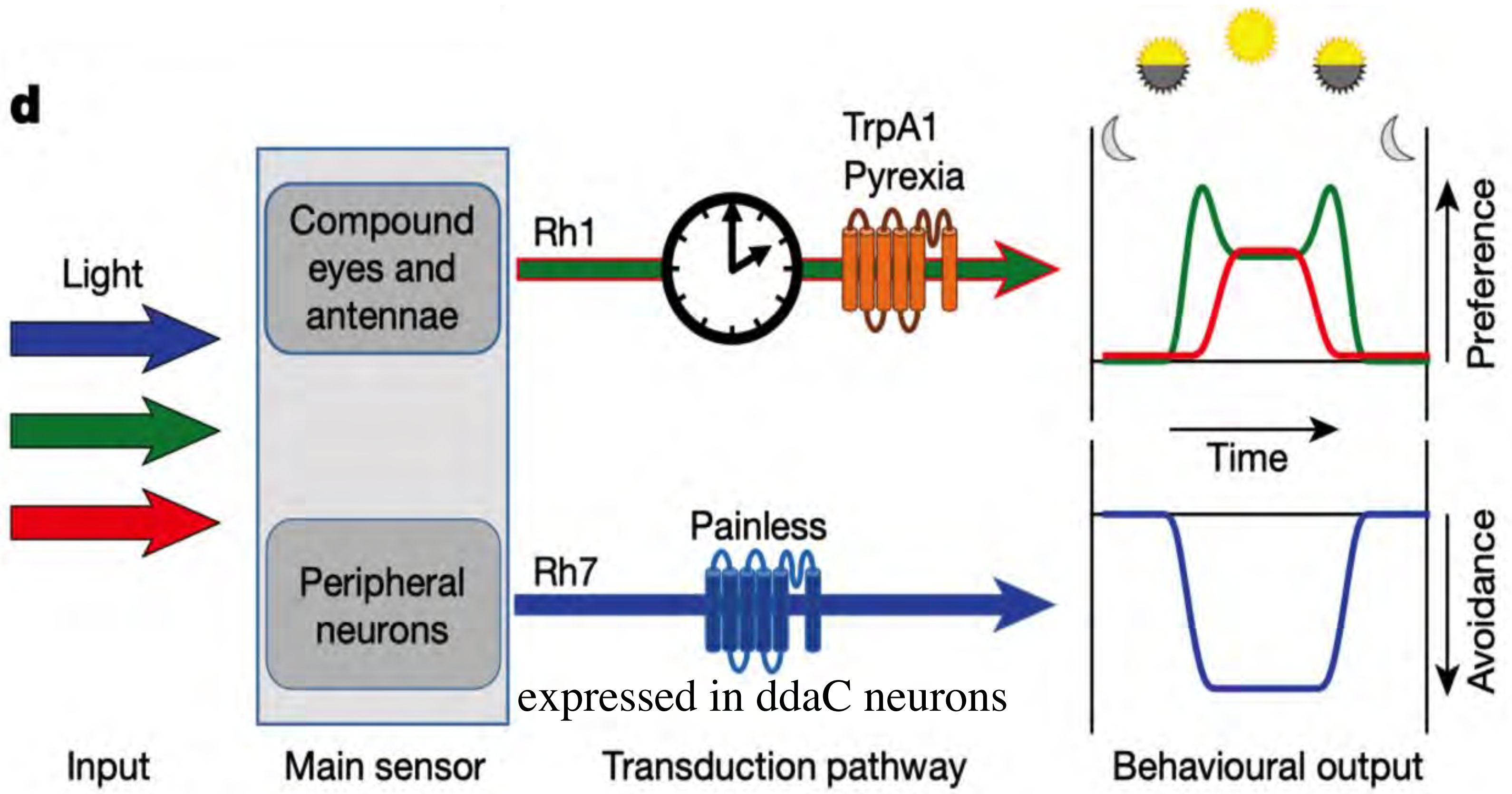
> **Articles** are original reports whose conclusions represent a substantial advance in understanding of an important problem and have immediate, far-reaching implications.
>
> **Letters** are short reports of original research focused on an outstanding finding whose importance means that it will be of interest to scientists in other fields.

Source: http://blogs.nature.com/nautilus/2009/12/difference_between_nature_arti.html

Phenotype: Flies exhibit a systematic change in color preference during day.





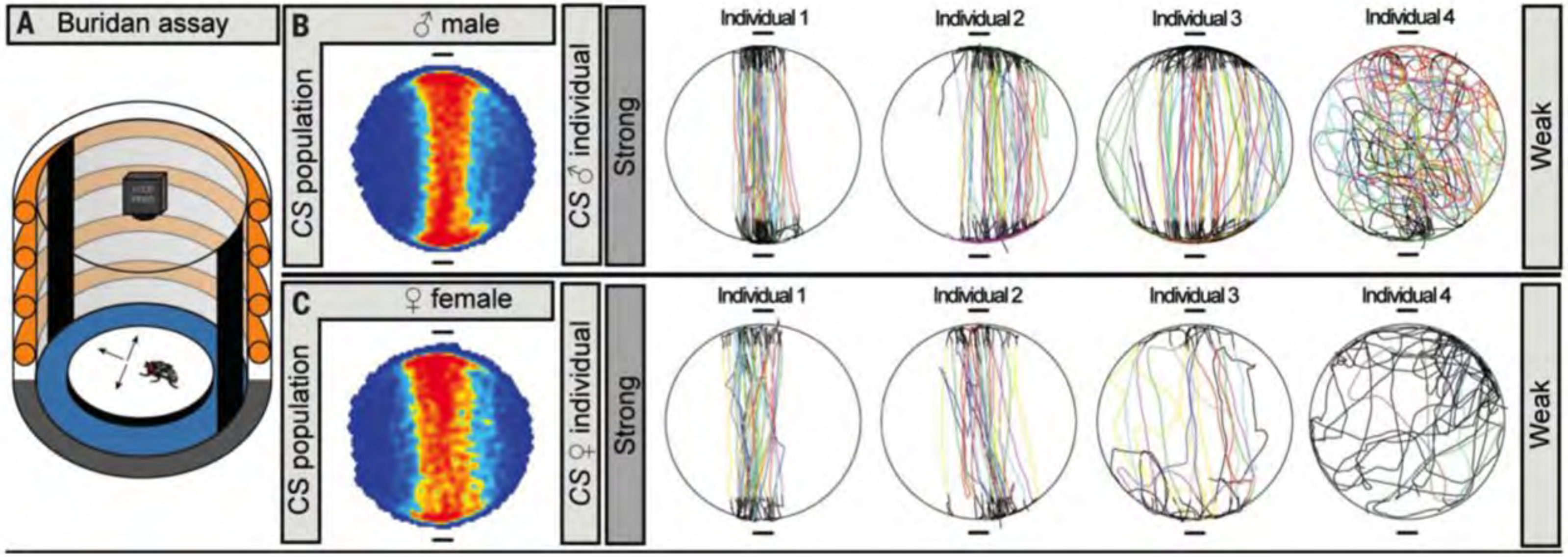


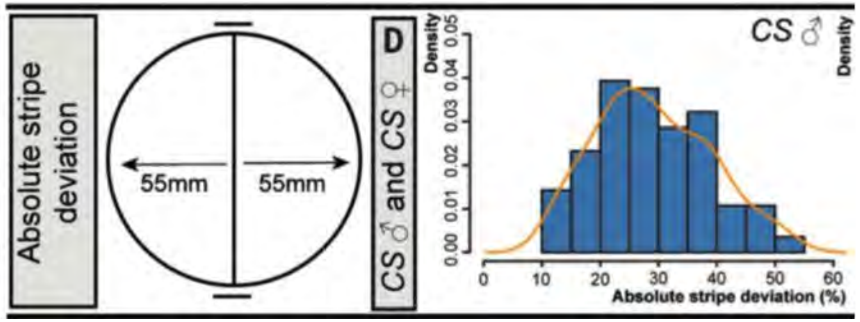
TrpA1 and Pyx sense both temperature and light.

NEURODEVELOPMENT

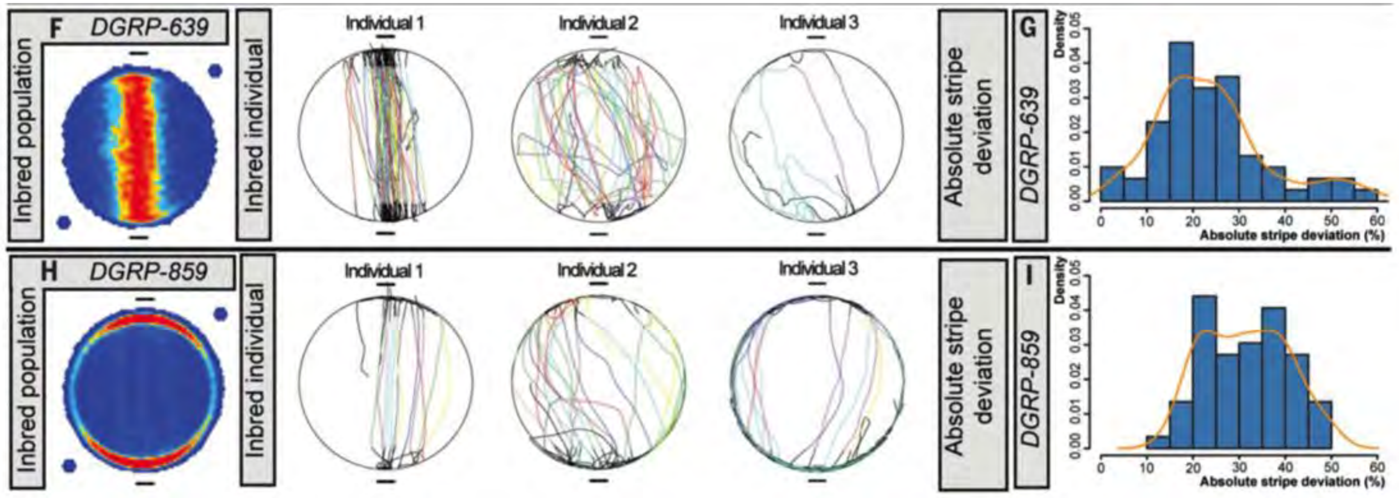
A neurodevelopmental origin of behavioral individuality in the *Drosophila* visual system

Gerit Arne Linneweber[1,2,3], Maheva Andriatsilavo[1,2,3], Suchetana Bias Dutta[1,2,3], Mercedes Bengochea[1], Liz Hellbruegge[2,3], Guangda Liu[4,5], Radoslaw K. Ejsmont[1]*, Andrew D. Straw[6], Mathias Wernet[2], Peter Robin Hiesinger[2,3], Bassem A. Hassan[1,2,3]†



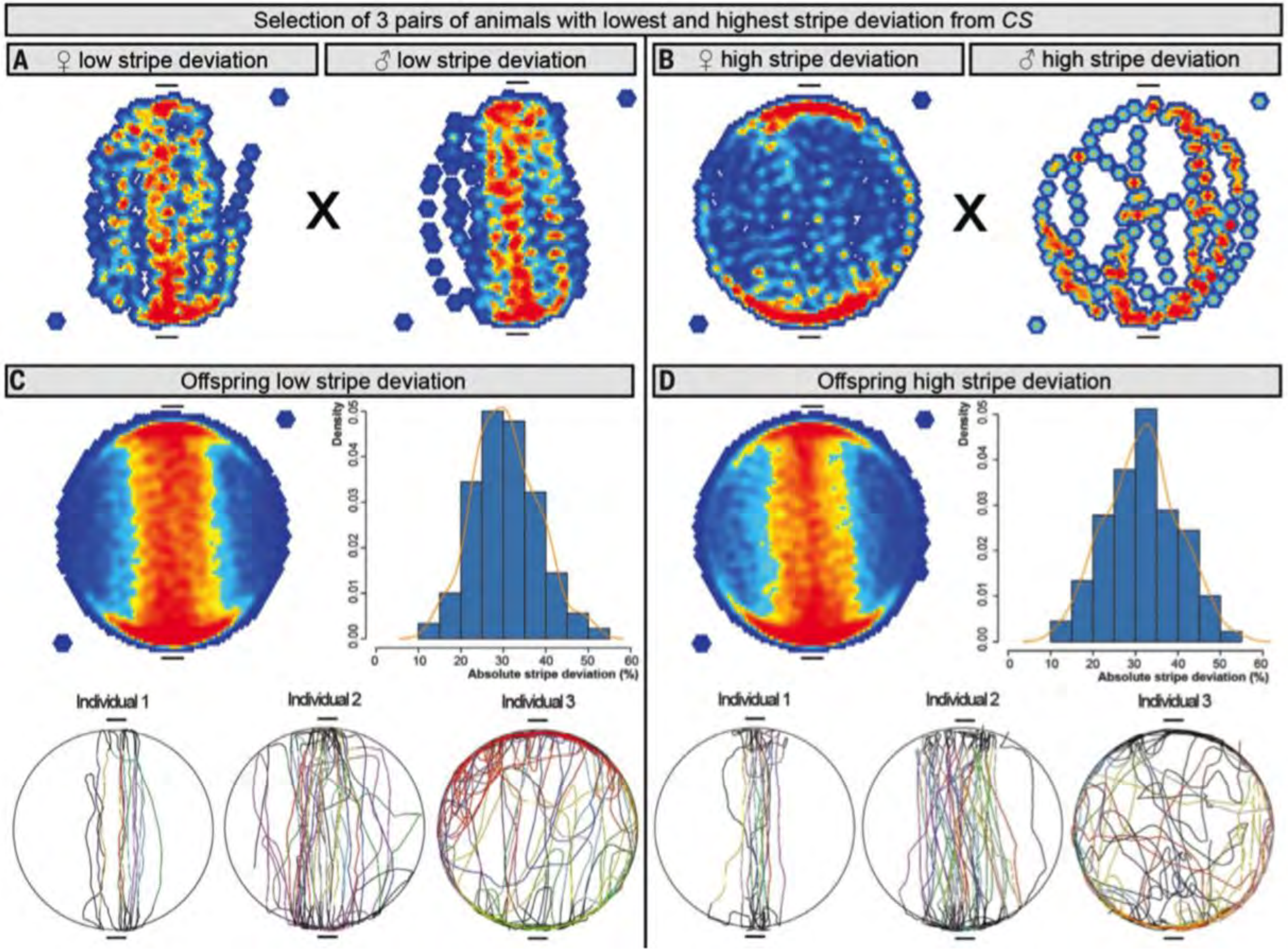


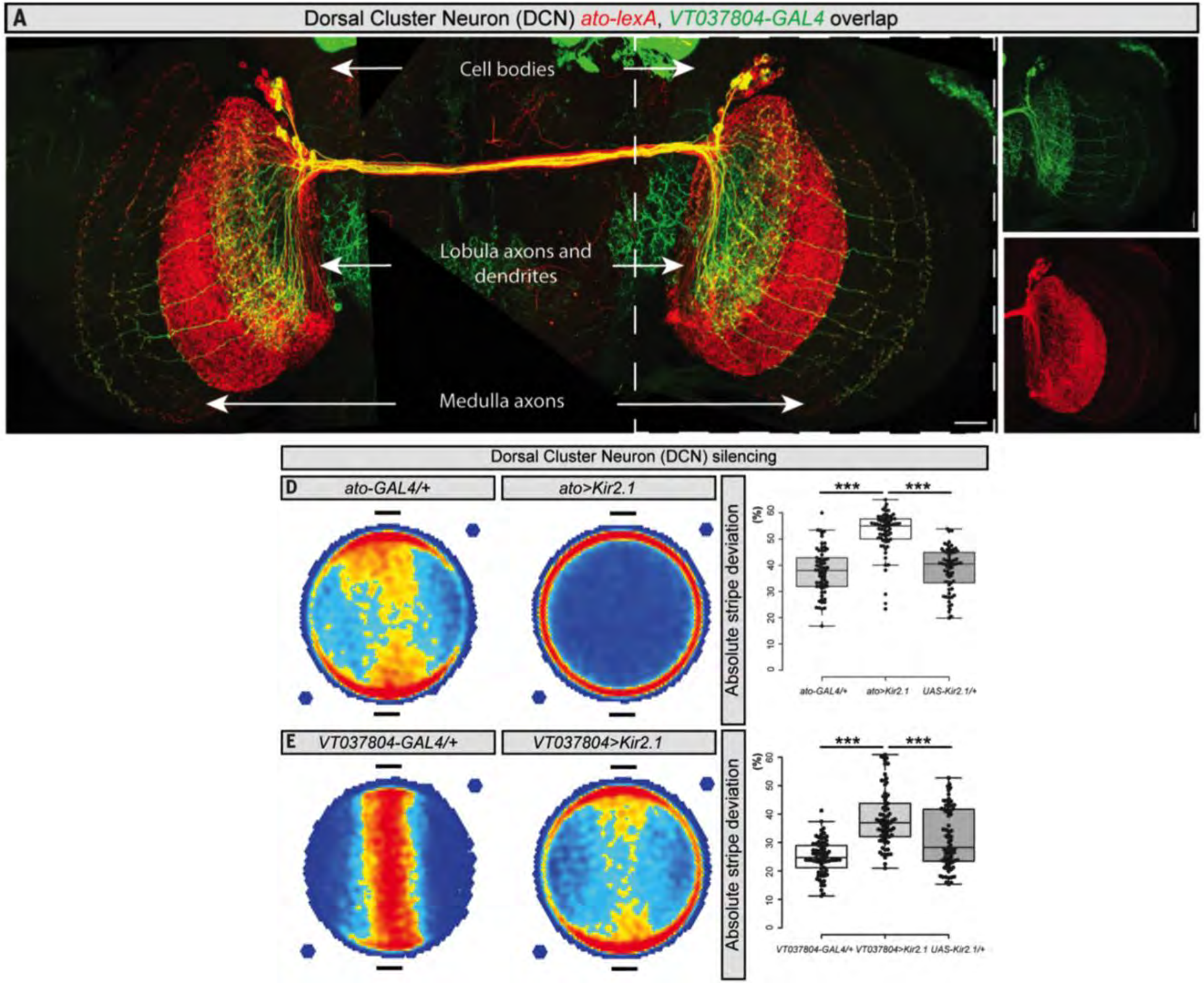
1. Object orientation variability is independent of genetic diversity.



The Drosophila Genetic Reference Panel (DGRP) is a population consisting of more than 200 inbred lines derived from the Raleigh, USA population.

2. Individual object orientation responses are nonheritable.

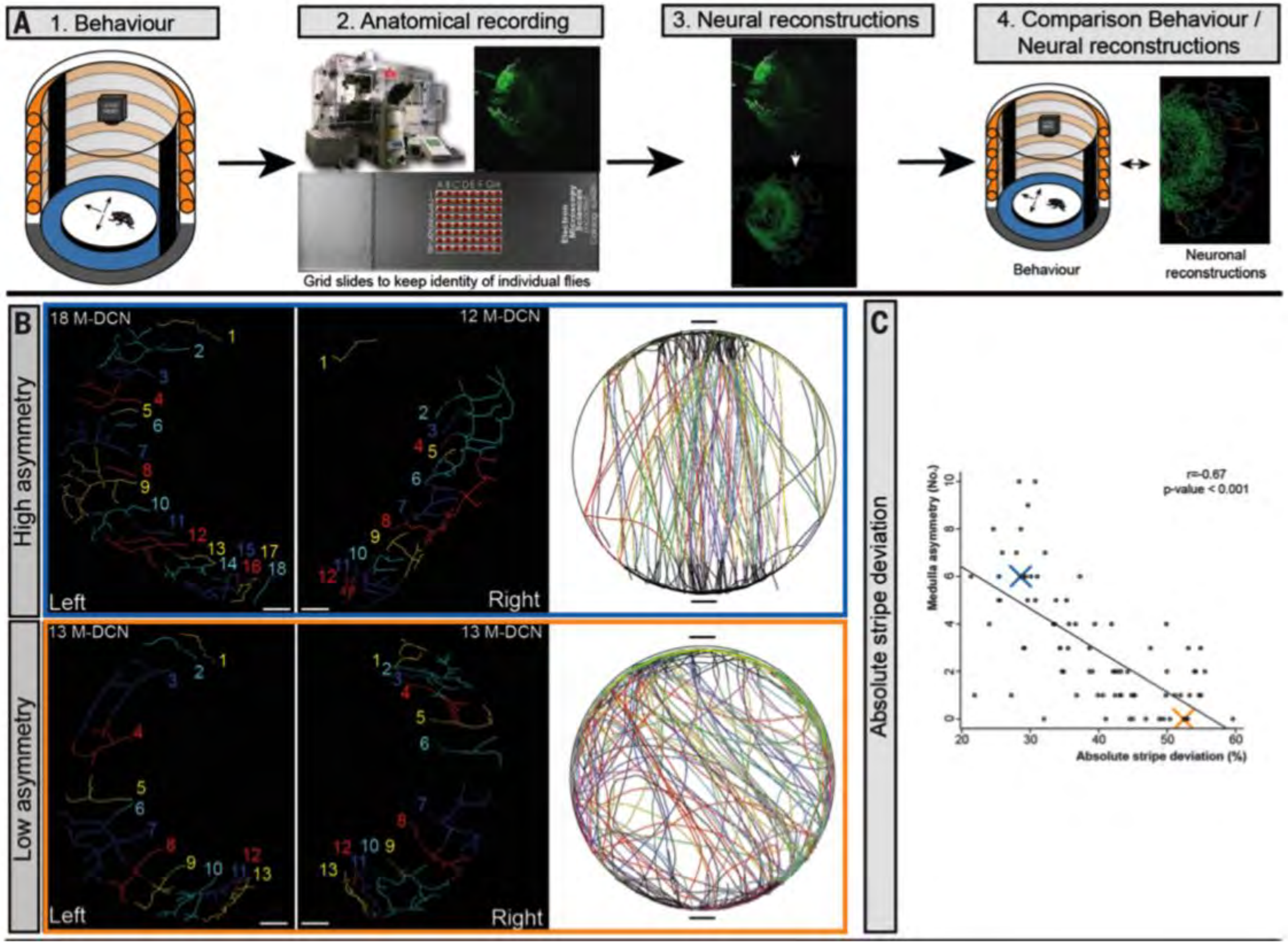




Green: M-DCNs Red: DCNs

The number of DCNs varied from 22 to 68 cells and 6 to 23 M-DCNs.

3. DCN asymmetry determines object orientation in individuals



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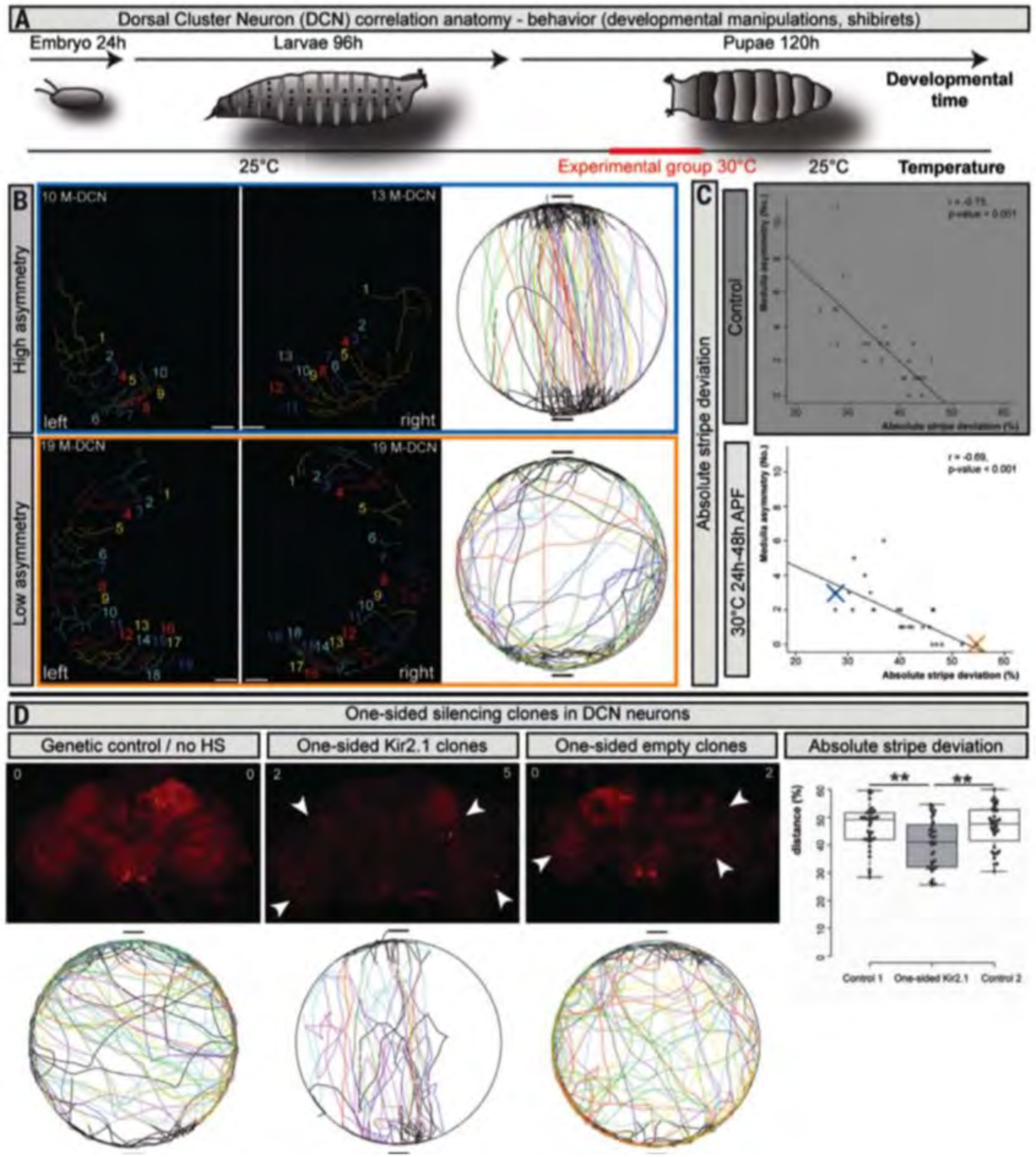
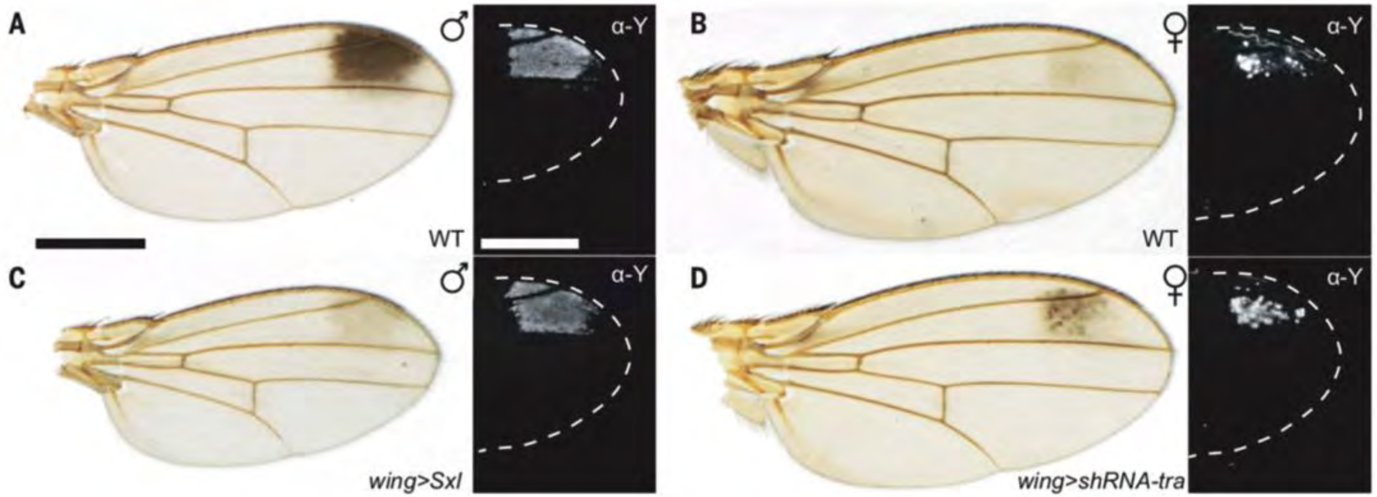


SEXUAL DIMORPHISM

Transvection regulates the sex-biased expression of a fly X-linked gene

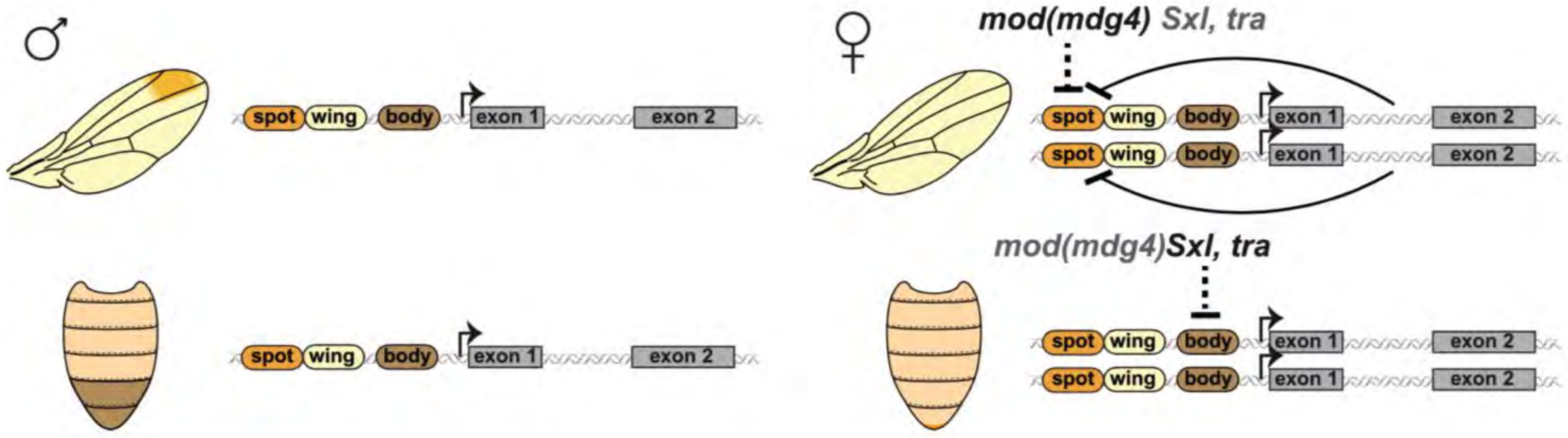
Charalampos Chrysovalantis Galouzis and Benjamin Prud'homme*

1. Yellow sex-biased pattern in the D. biarmipes wing is independent of the sex determination hierarchy.



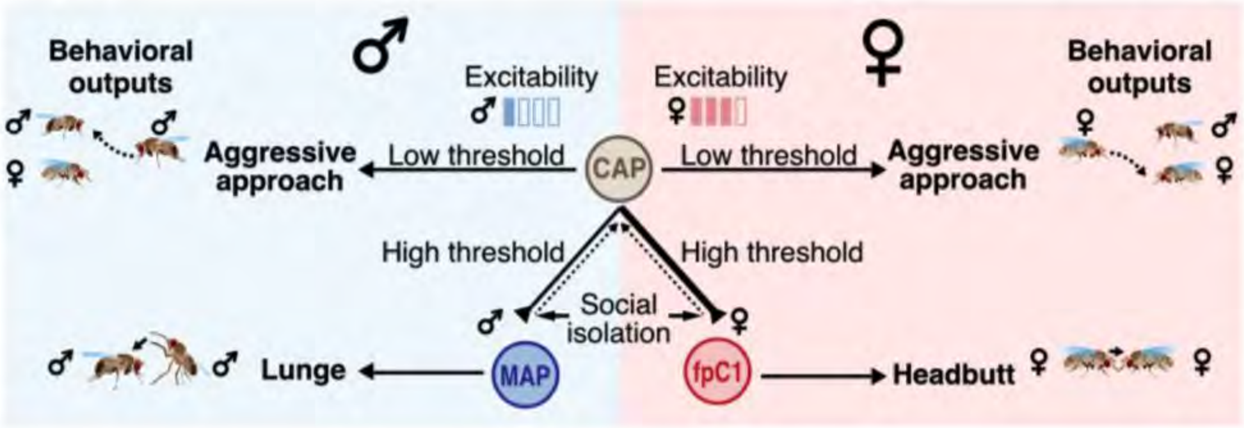
2. Sexually dimorphic regulation of y requires functional homolog interaction

3. Regulatory model of y sexually dimorphic expression in the wing and posterior abdomen of *D. biarmipes*.



Cell

A circuit logic for sexually shared and dimorphic aggressive behaviors in *Drosophila*



Authors

Hui Chiu, Eric D. Hoopfer, Maeve L. Coughlan, Hania J. Pavlou, Stephen F. Goodwin, David J. Anderson

Highlights

- Sexually dimorphic attack is controlled by sexually dimorphic neurons in *Drosophila*
- Shared cells that control aggressive approach activate the dimorphic attack neurons
- The transition from approach to attack occurs at a higher threshold than approach
- Isolation enhances shared → dimorphic functional connectivity to promote aggression

Article

Dopamine-based mechanism for transient forgetting

https://doi.org/10.1038/s41586-020-03154-y

Received: 3 April 2020

Accepted: 9 December 2020

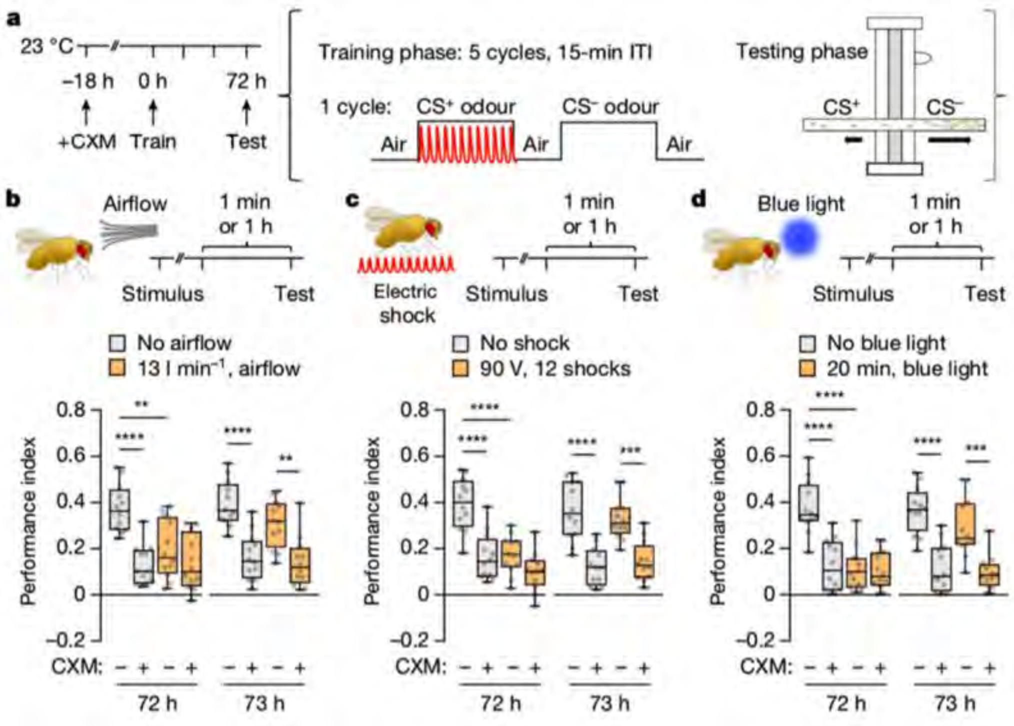
Published online: 20 January 2021

Check for updates

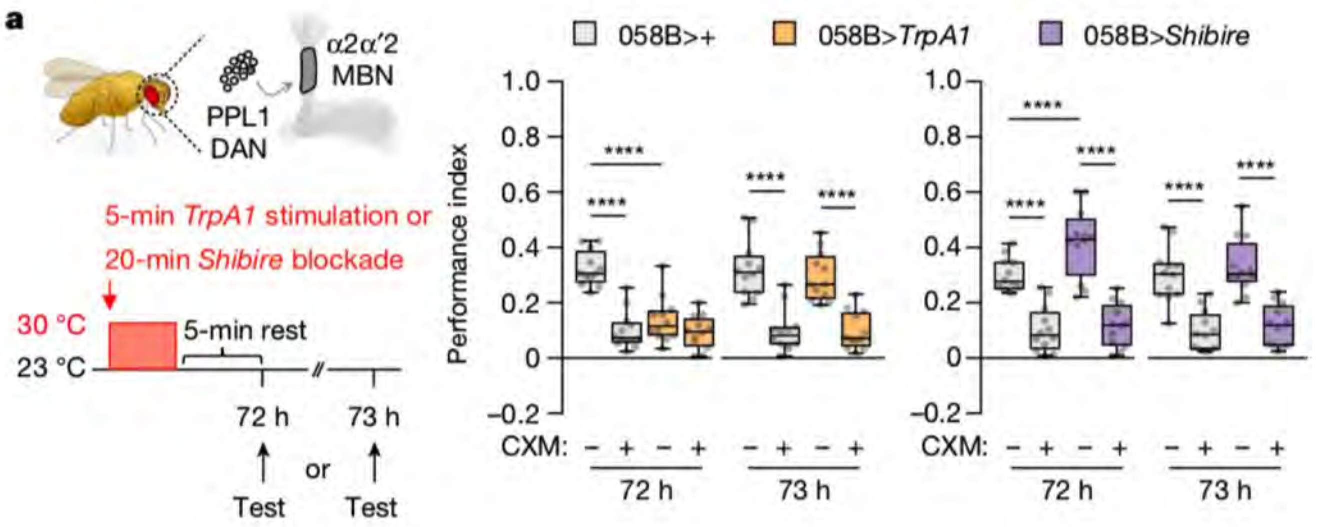
John Martin Sabandal[1], Jacob A. Berry[1] & Ronald L. Davis[1]✉

1. 记忆的过程分为形成（formation），巩固（consolidation）和提取（retrieval）。遗忘则分为内源性长期遗忘（intrinsic forgetting）和瞬时遗忘（transient forgetting）。
2. 确立瞬时遗忘表型：外界刺激会导致瞬时遗忘，影响记忆的提取但是不影响记忆本身
3. 确定参与瞬时遗忘的脑区-PPL1-α2α′2 MBN和 DA 受体 DAMB
4. 生理水平上确定瞬时遗忘并不会影响记忆形成：检测 cellular memory traces

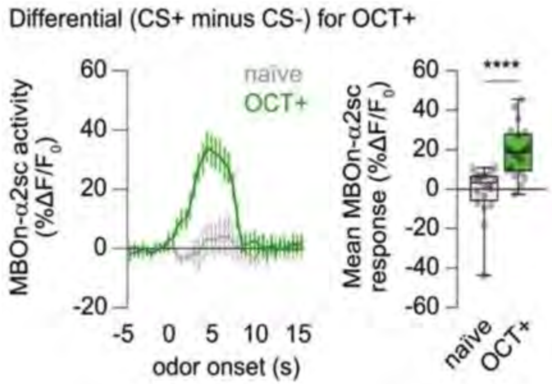
1. 表型

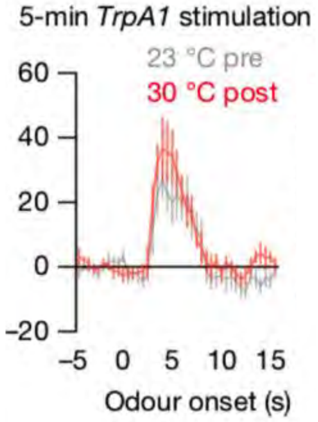


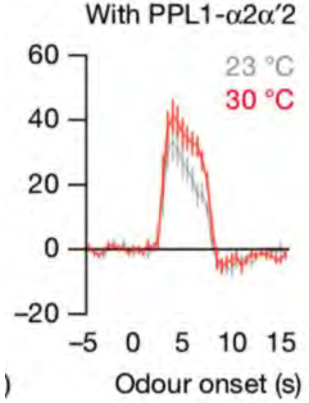
2. 确定脑区及 DAMB

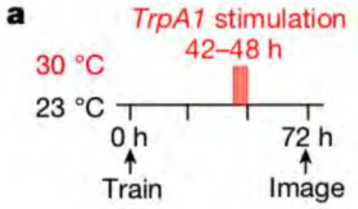


3. Cellular memory trace detected by GCAMP









Article

Coupling of activity, metabolism and behaviour across the *Drosophila* brain

https://doi.org/10.1038/s41586-021-03497-0

Received: 11 March 2020

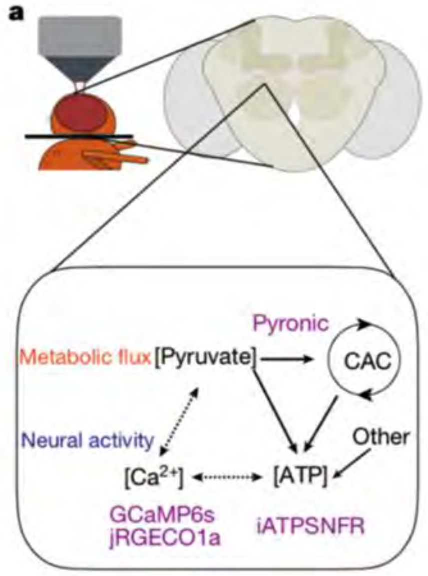
Accepted: 26 March 2021

Published online: 28 April 2021

Check for updates

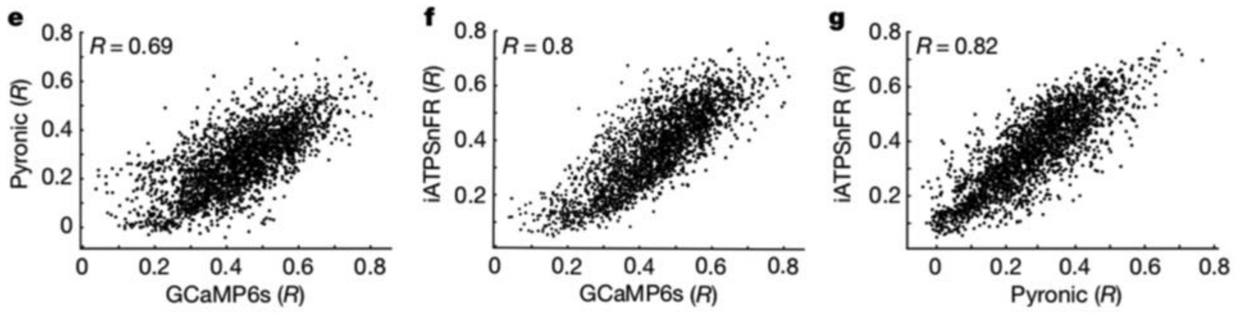
Kevin Mann[1,3], Stephane Deny[2,3], Surya Ganguli[1,2]✉ & Thomas R. Clandinin[1]✉

1. 同时观察神经元代谢和放电情况，证明神经元的能量变化和钙信号发放高度相关。



Pyronic: a sensor of changes in intracellular pyruvate concentration

iATPSnFR: a sensor of changes in ATP concentration



2. 光遗传激活特定神经元，即使是转瞬即逝的神经元电活动也会引起快速持续的能量变化。
3.即使是微小的行为也会引起巨大的电活动和能量代谢。

Article

Astrocytes close a motor circuit critical period

https://doi.org/10.1038/s41586-021-03441-2

Received: 21 July 2020

Accepted: 10 March 2021

Published online: 7 April 2021

Check for updates

Sarah D. Ackerman[1]✉, Nelson A. Perez-Catalan[1,3], Marc R. Freeman[2] & Chris Q. Doe[1]✉

1. Critical period: 神经元重塑中的一个重要时期，这个时期中神经环路的组装受神经元的活性修饰。过长的 critical period 会影响神经系统的发育。
2. 星型胶纸细胞对终止果蝇的运动神经元的critical period，有重要作用。
3. 神经元层面astrocyte– motor neuron signaling pathways 和其中的分子层面Neuroligin– Neurexin signaling.

Article

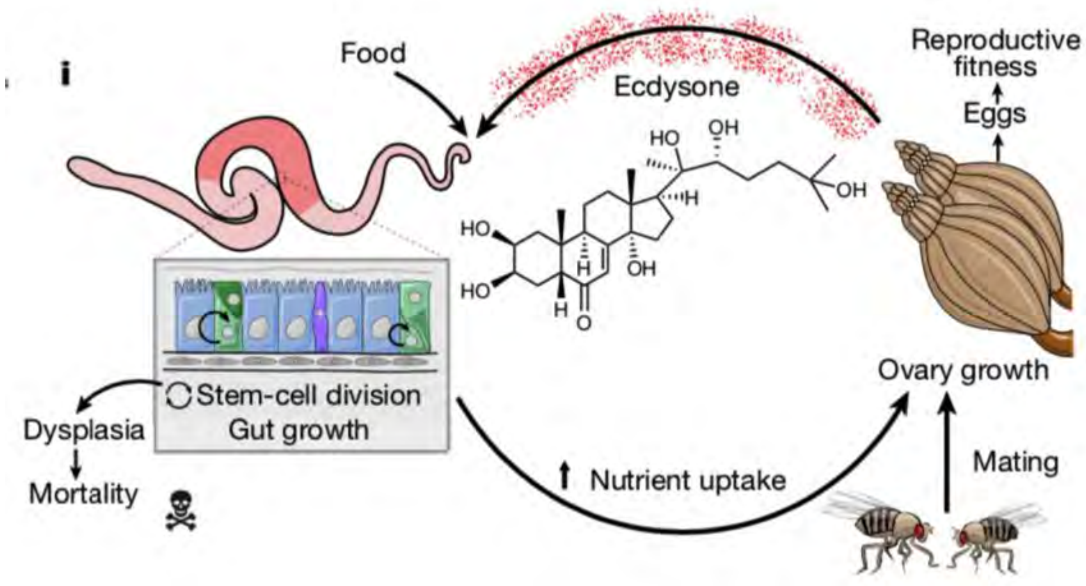
Fitness trade-offs incurred by ovary-to-gut steroid signalling in *Drosophila*

https://doi.org/10.1038/s41586-020-2462-y

Received: 7 September 2018

Accepted: 15 April 2020

Sara Mahmoud H. Ahmed[1,2,3], Julieta A. Maldera[1,2], Damir Krunic[1], Gabriela O. Paiva-Silva[4], Clothilde Pénalva[5], Aurelio A. Teleman[1,3]✉ & Bruce A. Edgar[1,2,5]✉



1. 果蝇肠道干细胞(Intestinal stem cells, ISCs)在雌性中比雄性更容易增殖, 在 mated 的雌蝇中比对 virgin 雌蝇分裂更多。
2. 交配之后雌性果蝇中的卵巢会产生20HE，证明了 ISCs 的增值由 20HE 调控。
3. 卵巢产生的20HE会刺激肠道尺寸的改变使得雌果蝇生殖能力适应性最大化，但同时会使得雌果蝇对肠道发育异常和肿瘤更加敏感。

CLIMATE RESPONSES

Predicting temperature mortality and selection in natural *Drosophila* populations

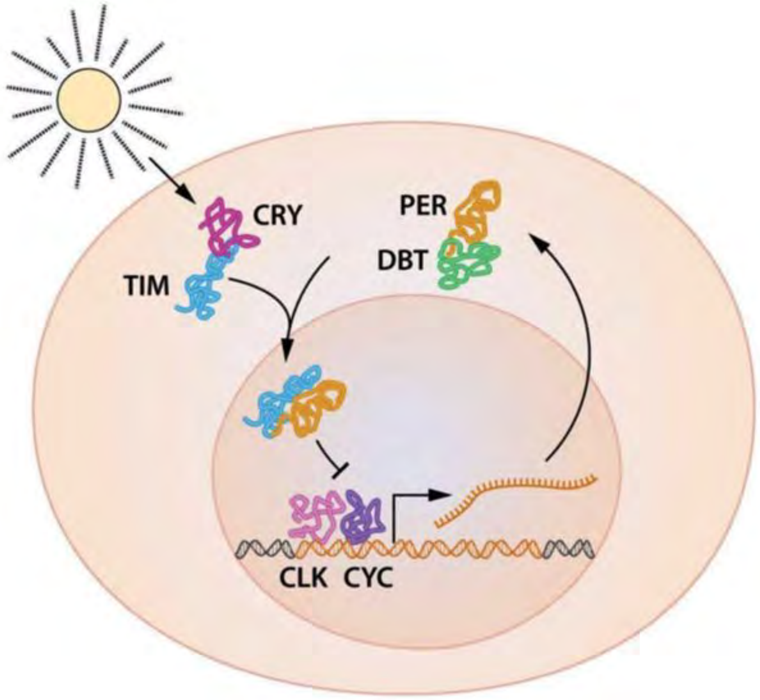
Enrico L. Rezende[1*], Francisco Bozinovic[1], András Szilágyi[2,3], Mauro Santos[3,4]

Average and extreme temperatures will increase in the near future, but how such shifts will affect mortality in natural populations is still unclear. We used a dynamic model to predict mortality under variable temperatures on the basis of heat tolerance laboratory measurements. Theoretical lethal temperatures for 11 *Drosophila* species under different warming conditions were virtually indistinguishable from empirical results. For *Drosophila* in the field, daily mortality predicted from ambient temperature records accumulate over weeks or months, consistent with observed seasonal fluctuations and population collapse in nature. Our model quantifies temperature-induced mortality in nature, which is crucial to study the effects of global warming on natural populations, and analyses highlight that critical temperatures are unreliable predictors of mortality.

PART 2:
An update on sleep behavior in drosophila

——Why are these articles accepted by CNS?

Speaker：JSH



Sleep → Circadian system

Sleep → Homeostasis

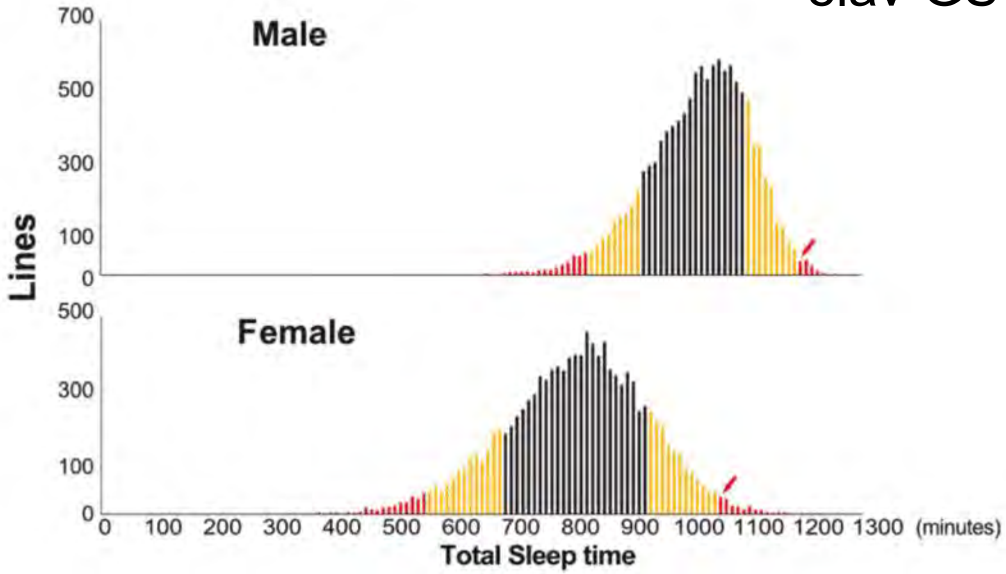
↓

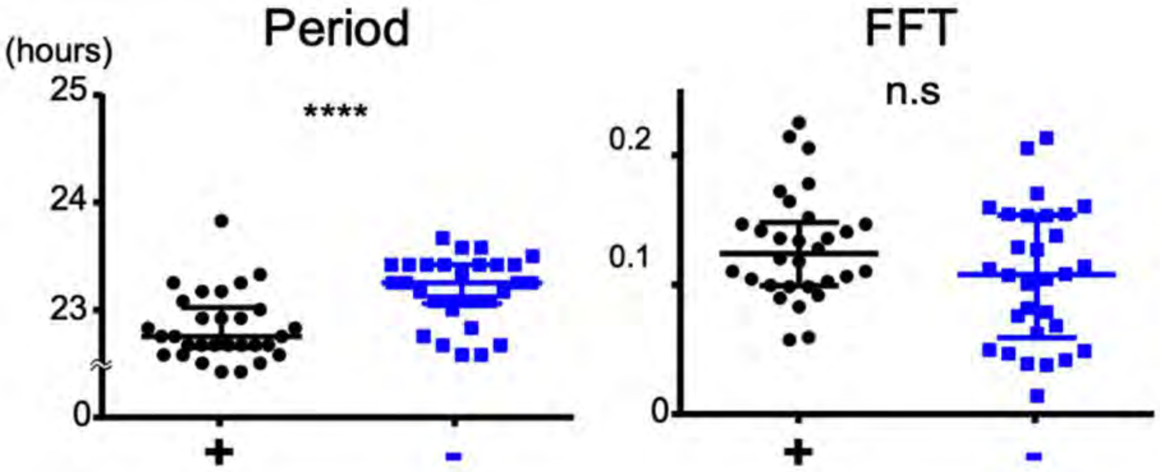
"how and why the drive to sleep is generated? "

Meet Nemuri, the Gene That Puts Flies to Sleep and Helps Them Fight Infection

A team of researchers looked at 8,015 genes and found one that made the insects super-sleepers

elav-GS



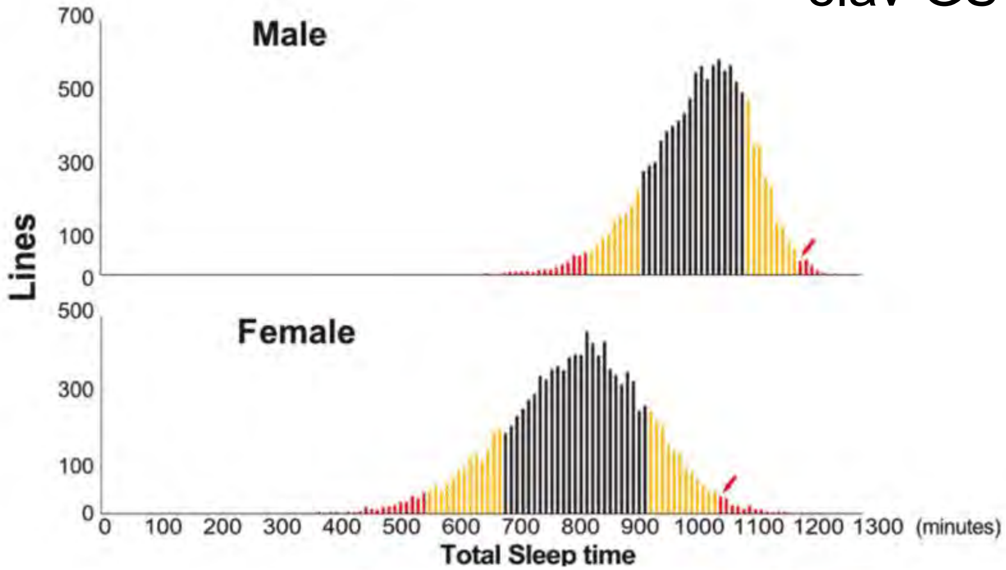


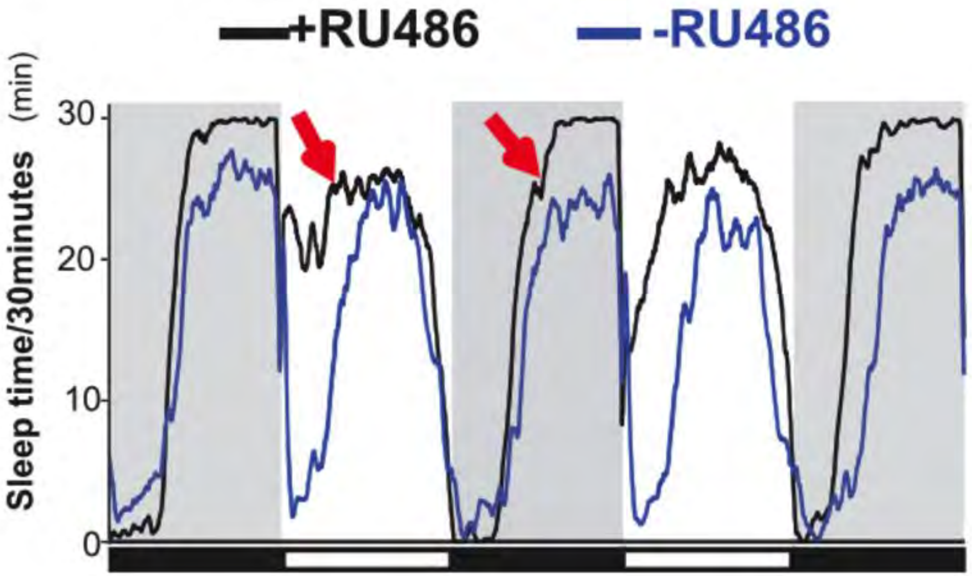
Toda et al., Science, 2019

Meet Nemuri, the Gene That Puts Flies to Sleep and Helps Them Fight Infection

A team of researchers looked at 8,015 genes and found one that made the insects super-sleepers

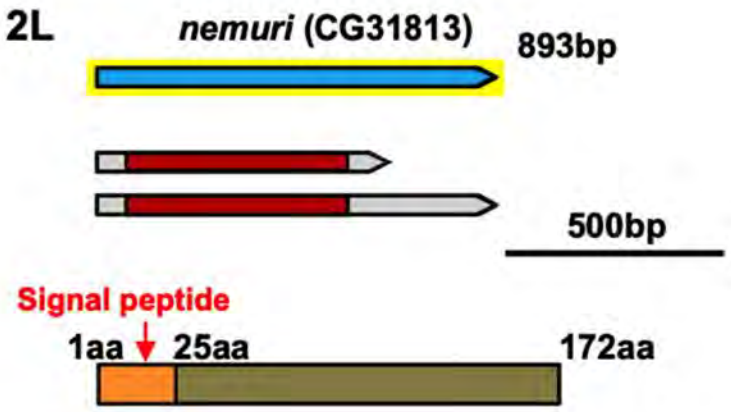
elav-GS



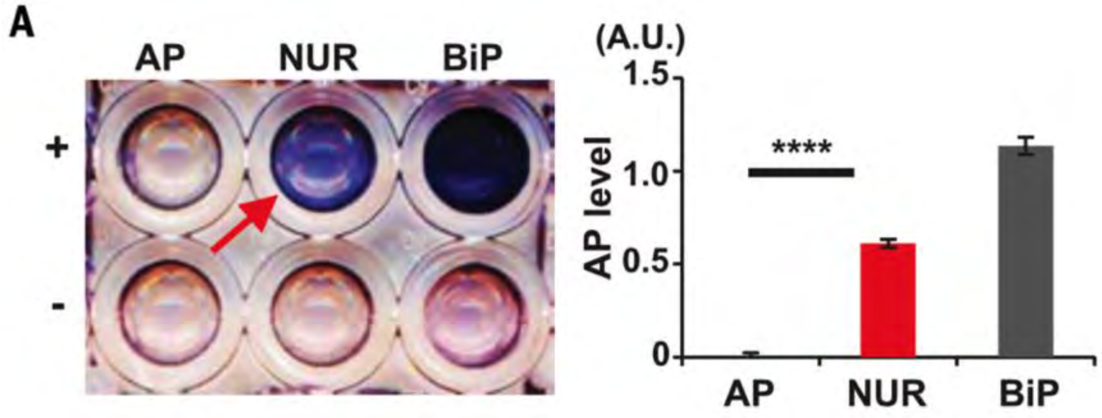


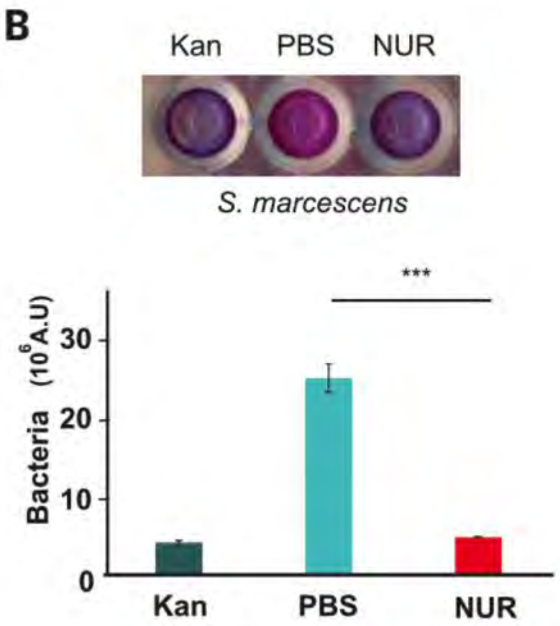
Toda et al., Science, 2019

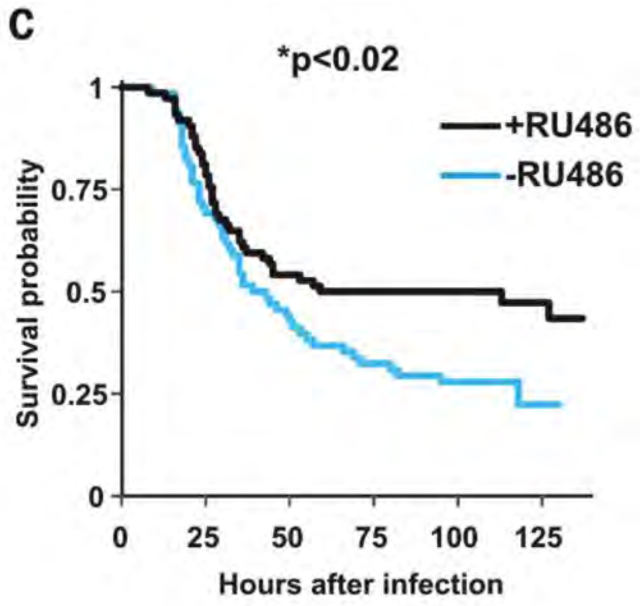
NUR as a secreted sleep-inducing molecule has antimicrobial activity



- N-terminal signal peptide
- ORF— arginines and glycines
- no transmembrane region



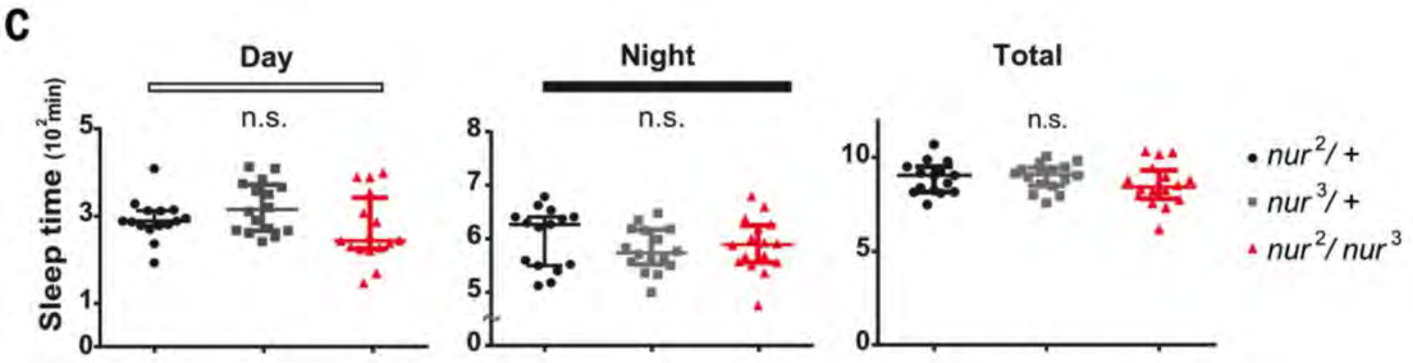




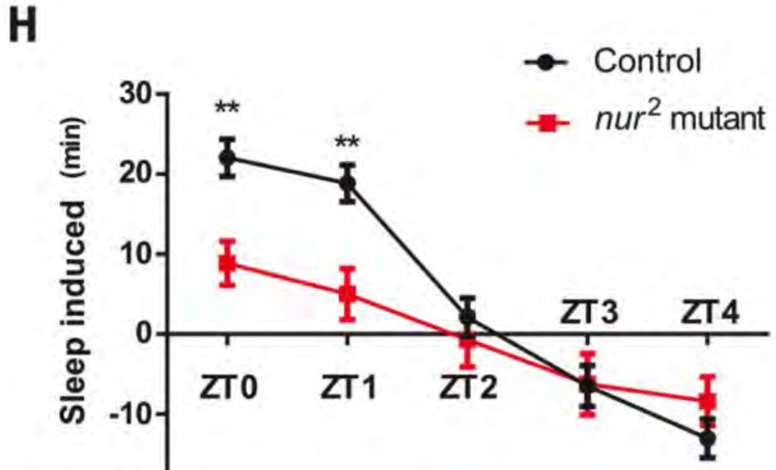
Toda et al., Science, 2019

Requirement of nur for sleep depth and for acute sleep induction after infection

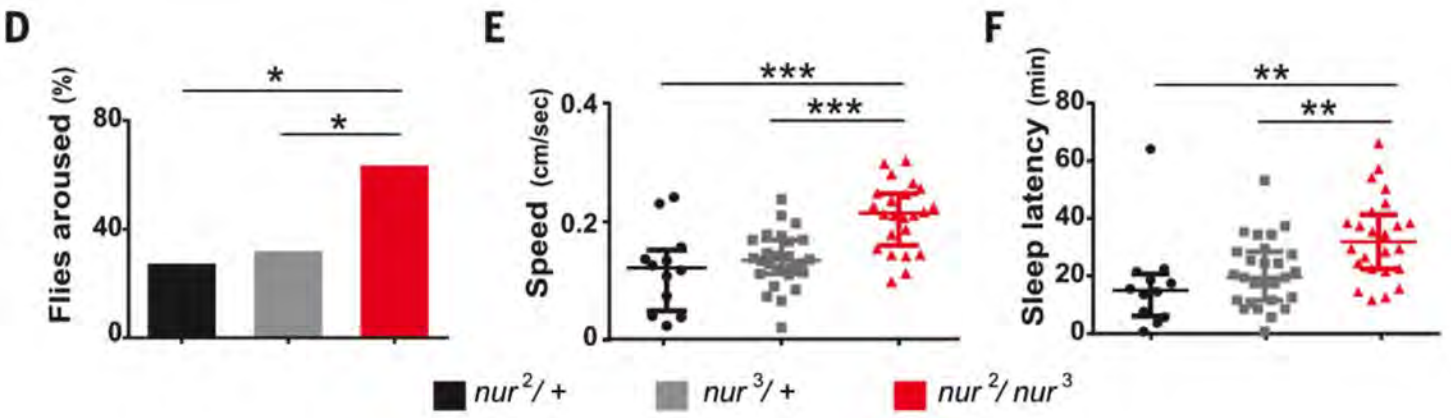
Common situation:



Bacterial infection:



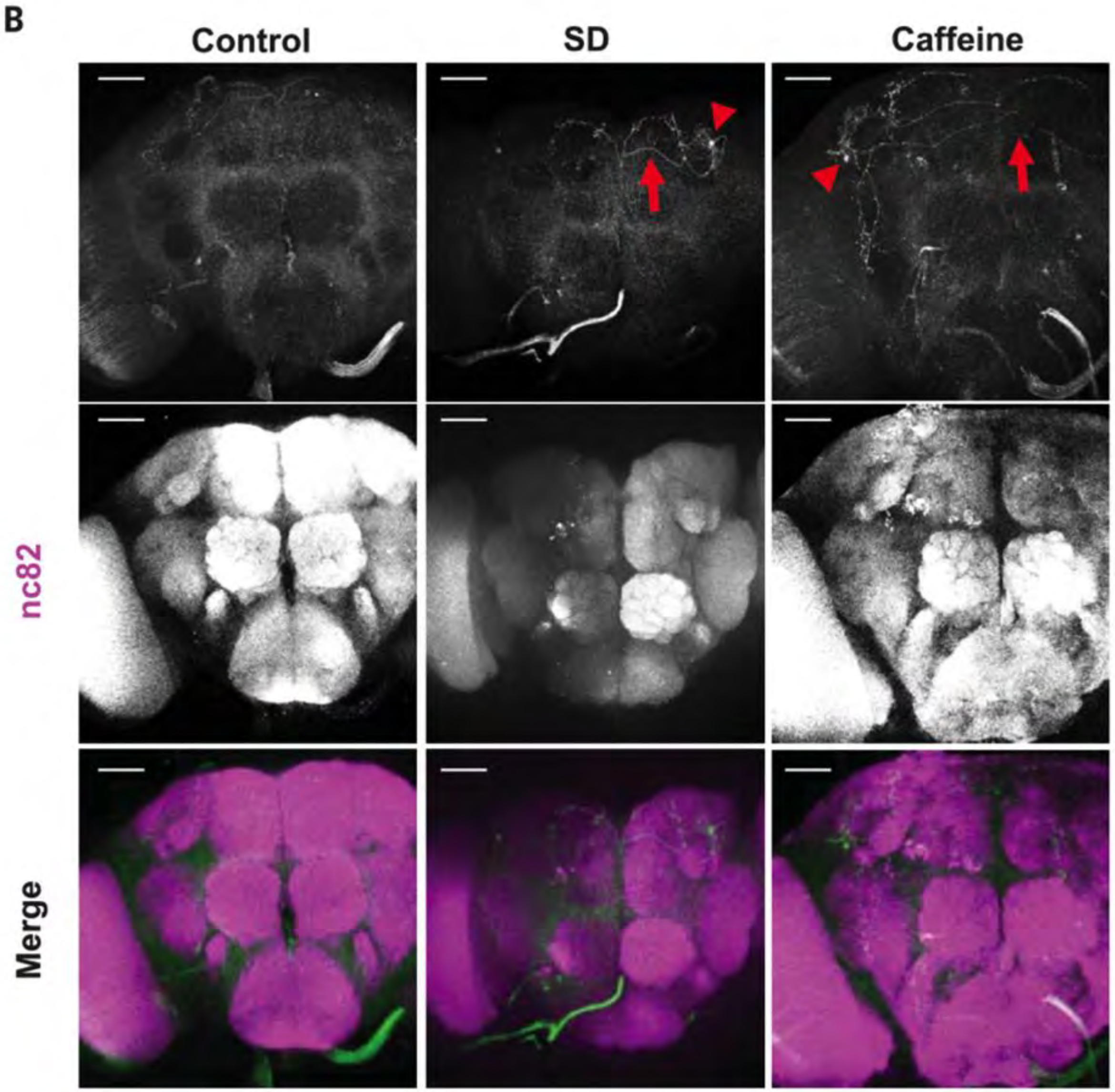
Mechanical stimulus:



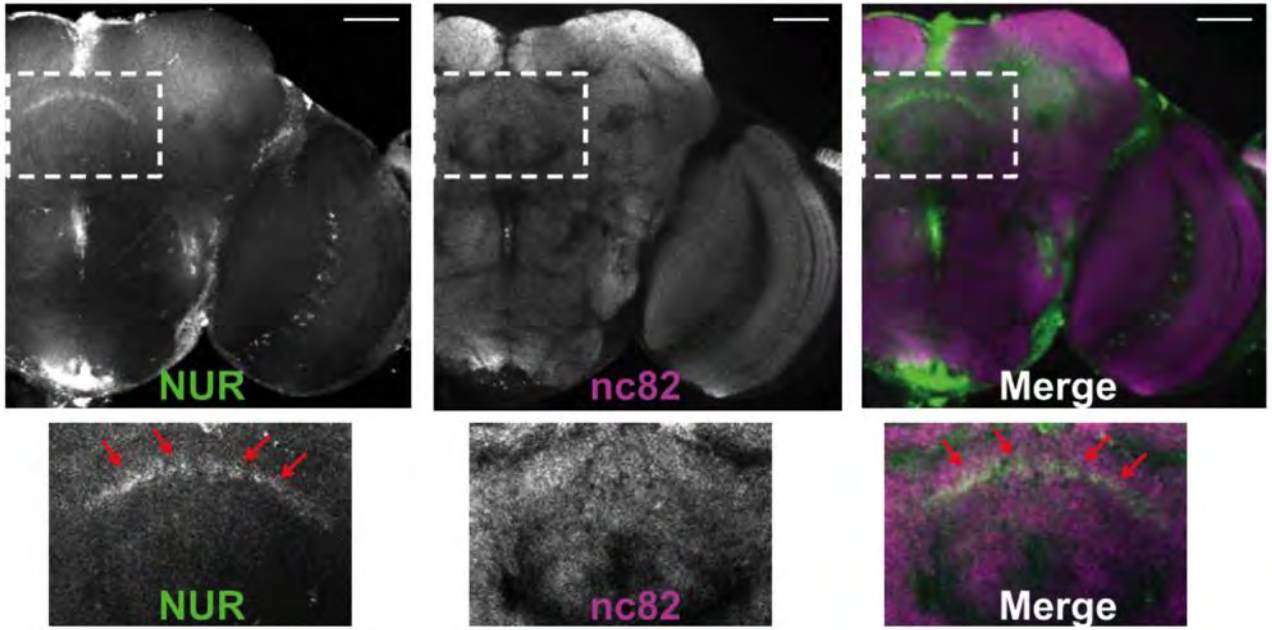
"immune function and sleep-inducing property"

Toda et al., Science, 2019

Nur^{Gal4} flies expressed GFP signals only after the flies were sleep-deprived



Nur-Gal4 / UAS-CD4::tdGFP



Toda et al., Science, 2019

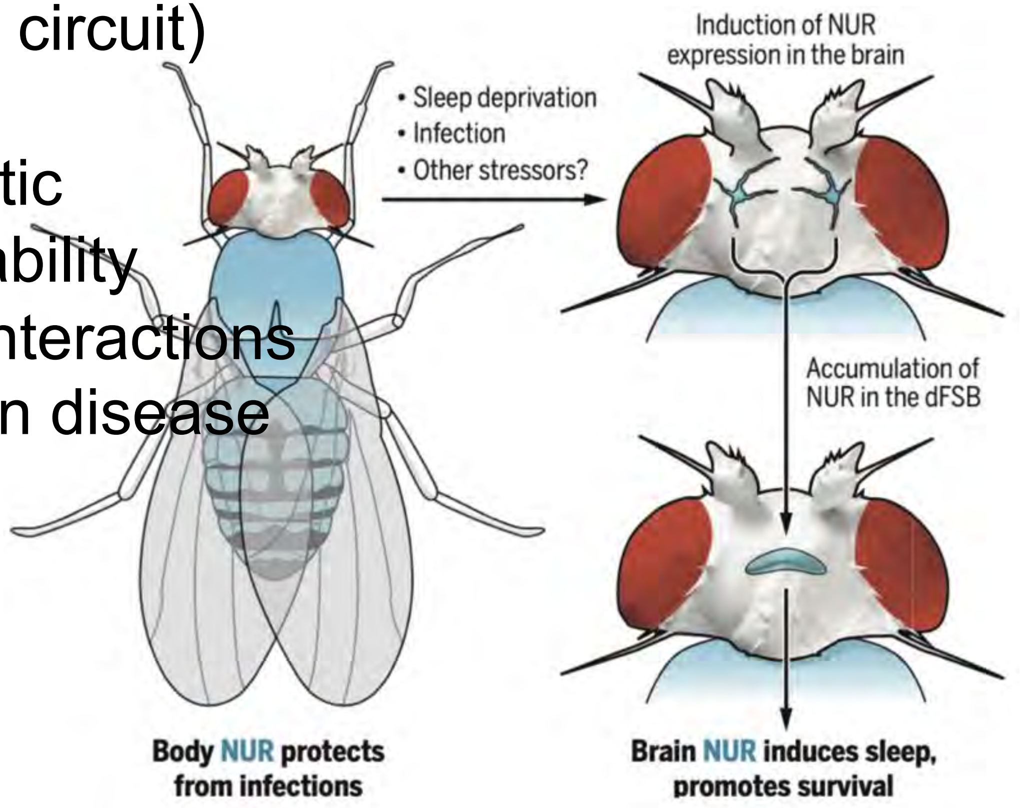
Summary:

1.Interesting standpoint: “Feeling sleepy when you are sick”
— — A protein puts flies to sleep and fights infection

2.Basic work: 12198 *Drosophila* lines screening (involved 8015 *Drosophila* genes)
Nur expression was induced in only a single neuron per brain hemisphere(a small and highly specialized neuronal circuit)

3.NUR— a molecule that provides a clear mechanistic link between increased sleep and increased survivability
AMPs—more than 100 in human implications for interactions between sleep and immunity during human disease

Stress-induced sleep (SIS)

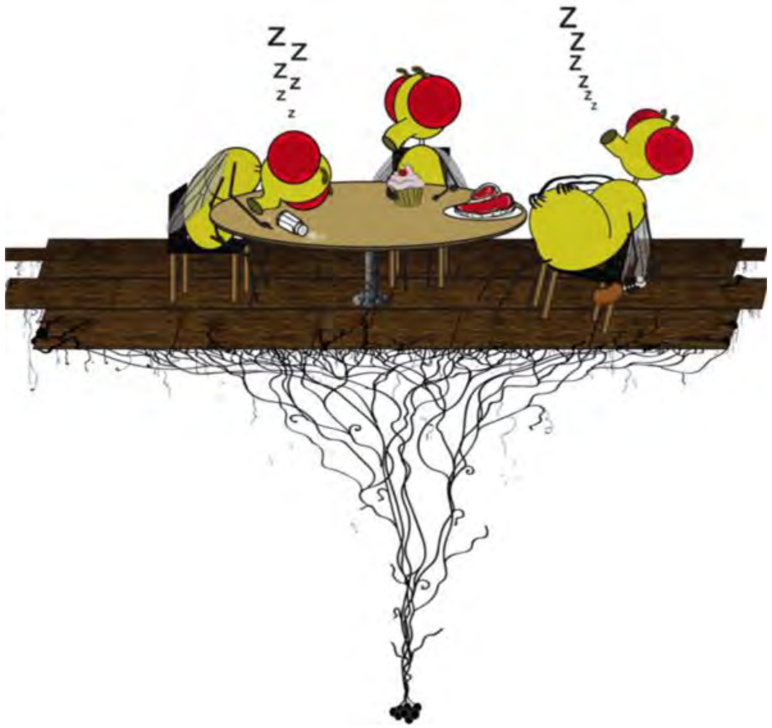


Article | Published: 02 December 2020

Availability of food determines the need for sleep in memory consolidation

Nitin S. Chouhan, Leslie C. Griffith, Paula Haynes & Amita Sehgal

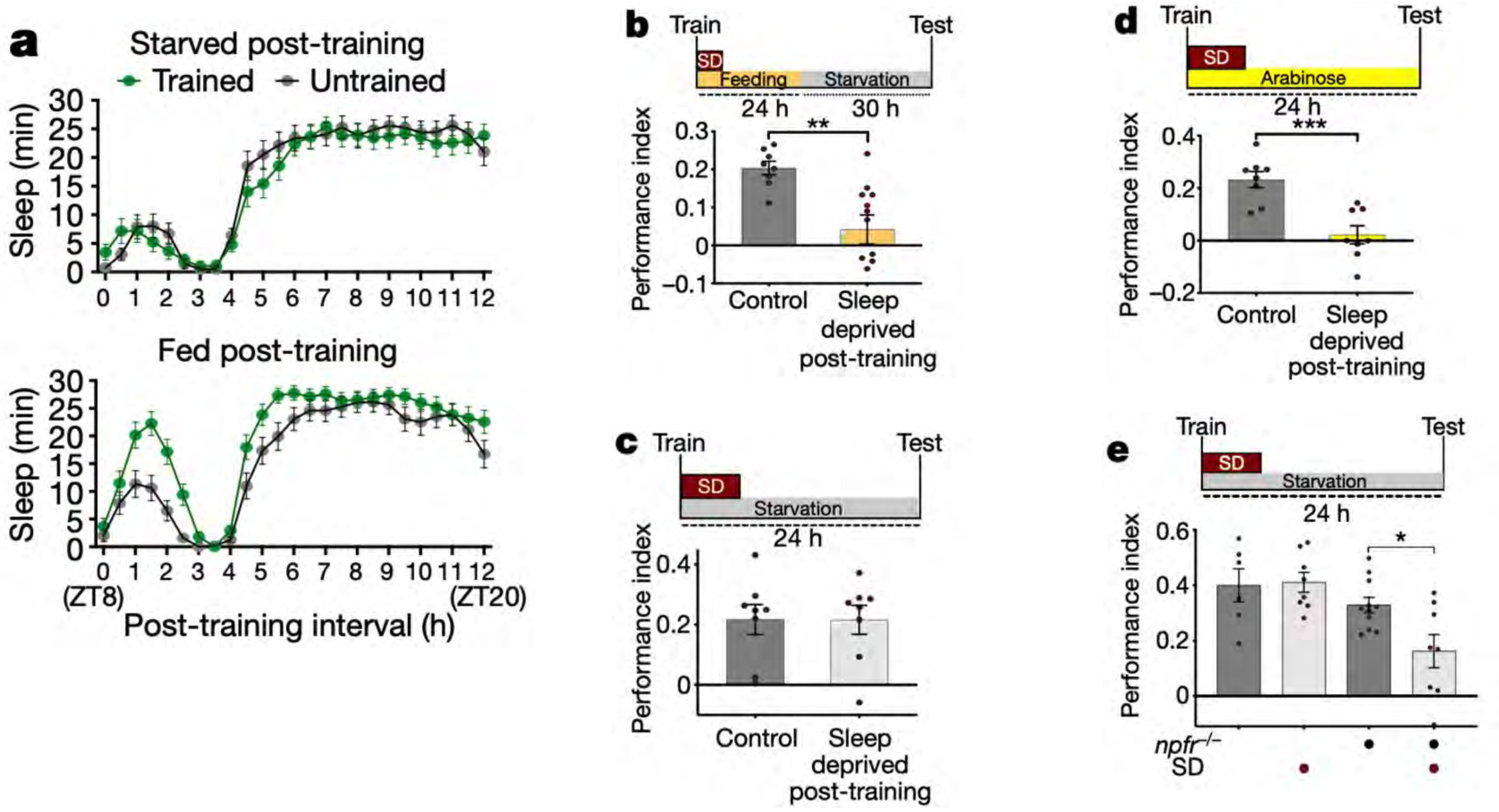
Nature **589**, 582–585 (2021) | Cite this article



Feeding — sleep-dependent — α′/β′ ap neurons → appetitive long-term memory

Hunger — sleep-independent — α′/β′ m neurons → appetitive long-term memory

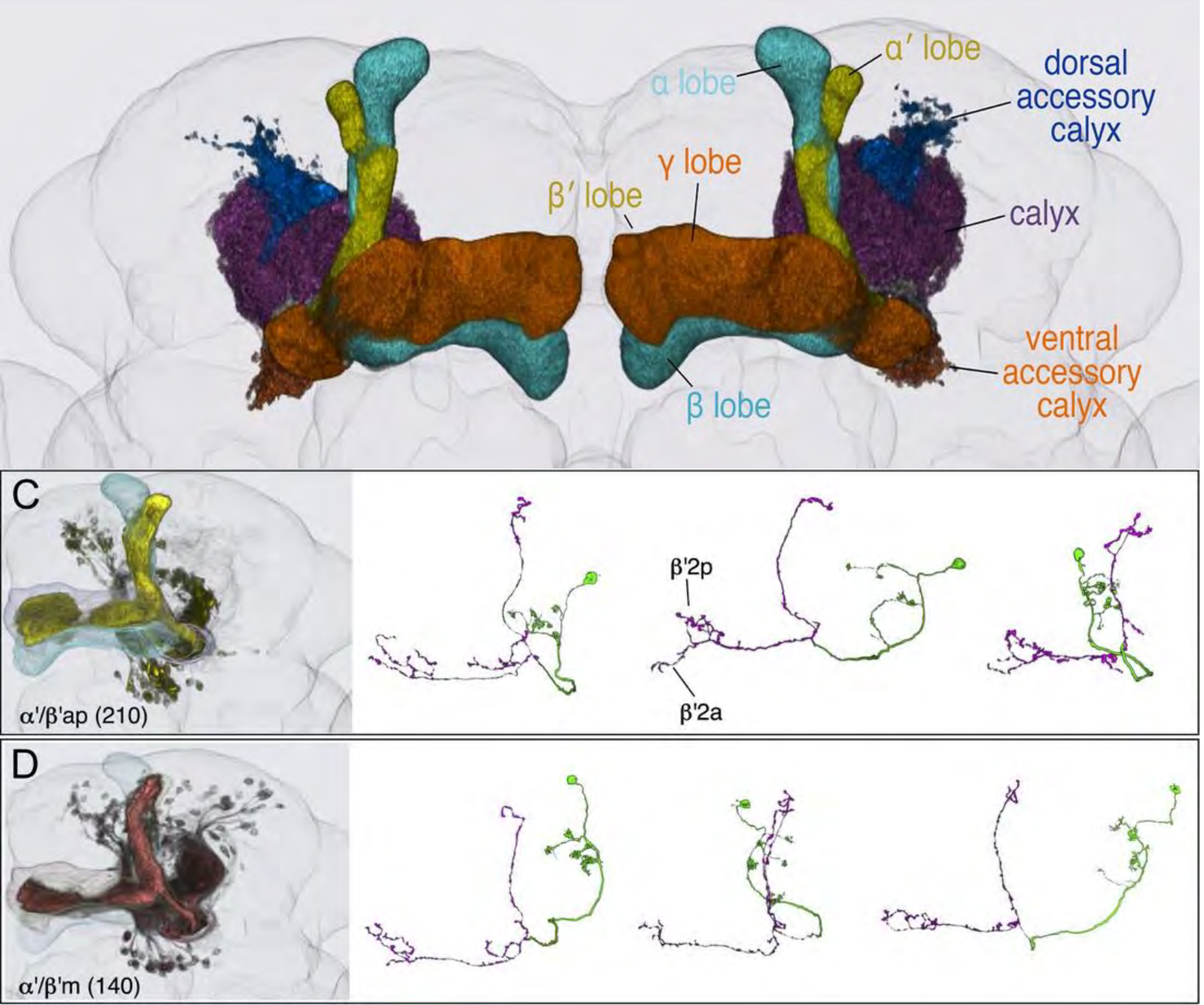
Flies fed post-training require sleep for memory consolidation



Chouhan N.S et al., Neuron, 2021

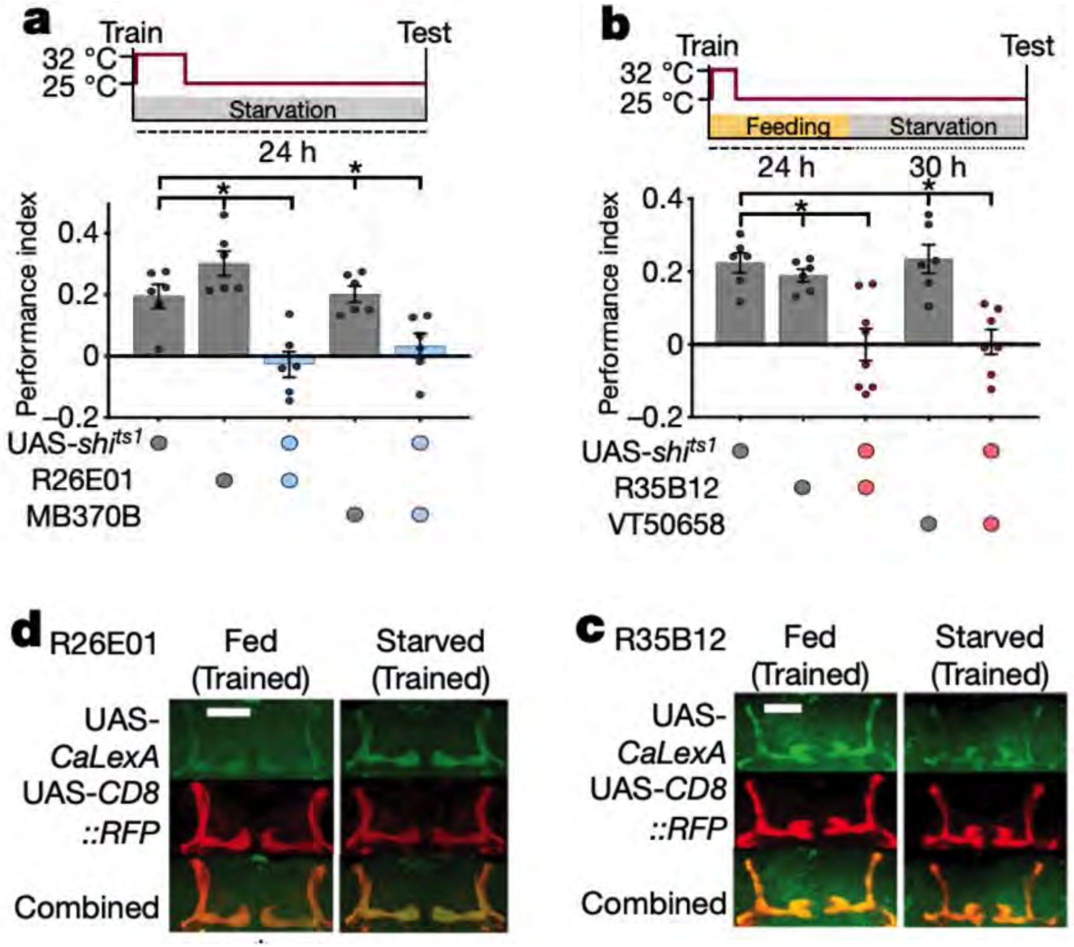
Distinct α′/β′ subsets mediate sleep-dependent and sleep-independent memory

α′/β′ lobes are particularly important for appetitive memory



α′/β′m neuron

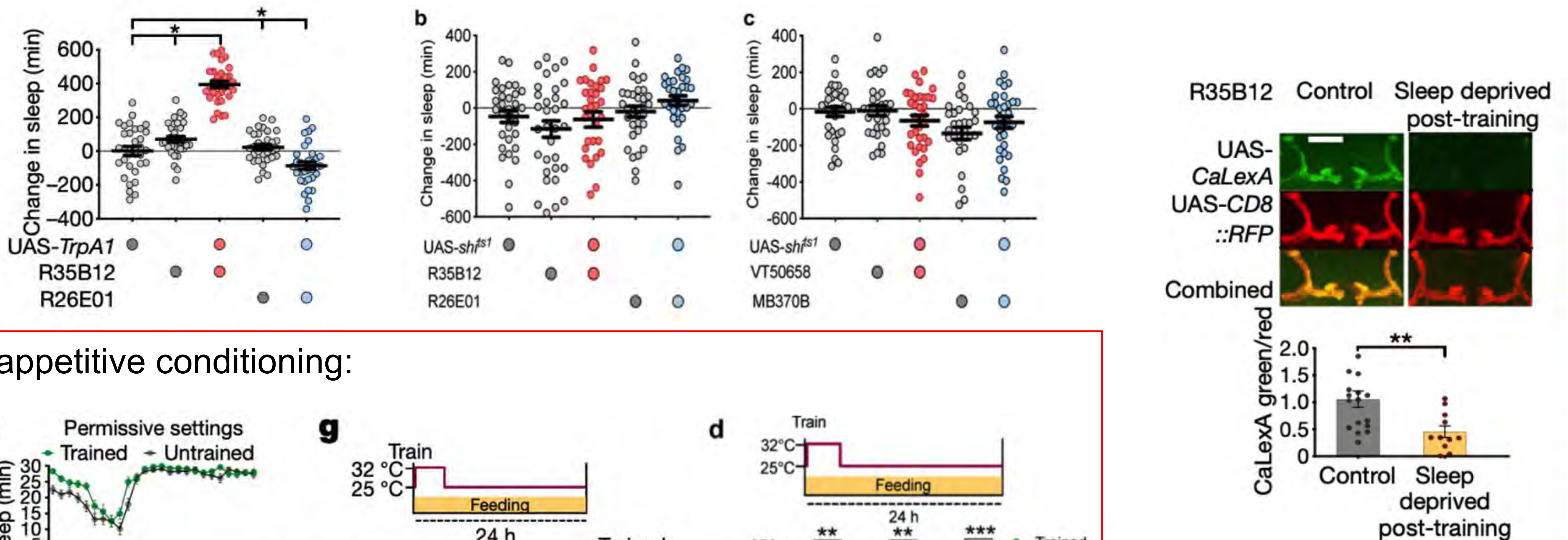
α′/β′ap neuron



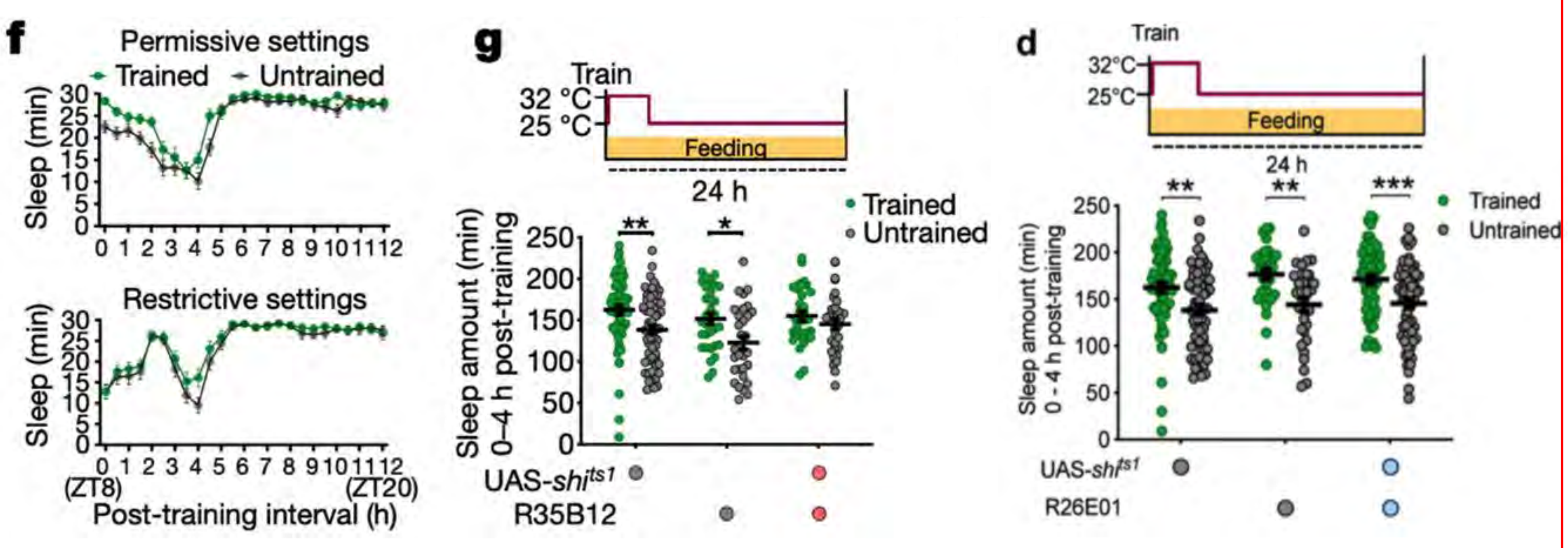
Chouhan N.S et al., Neuron, 2021

Yoshinori Aso et al., elife, 2014

α′/β′ap activity is required for the post-training sleep increase



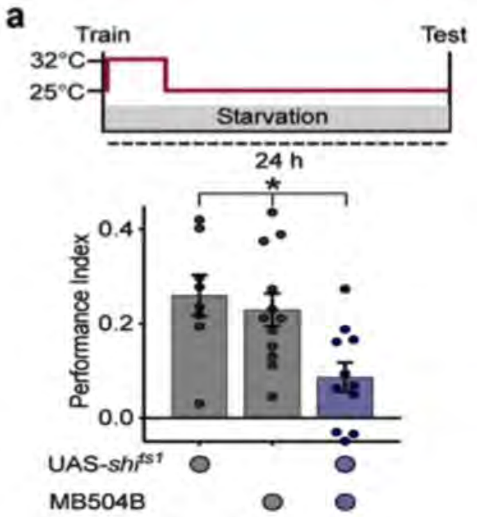
appetitive conditioning:

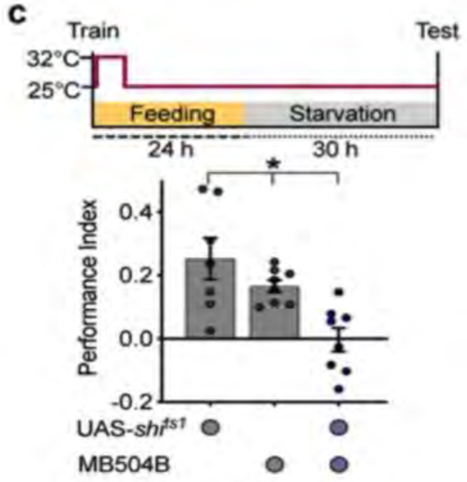


Chouhan N.S et al., Neuron, 2021

Feeding drives different DANs and MBONs for appetitive memory formation

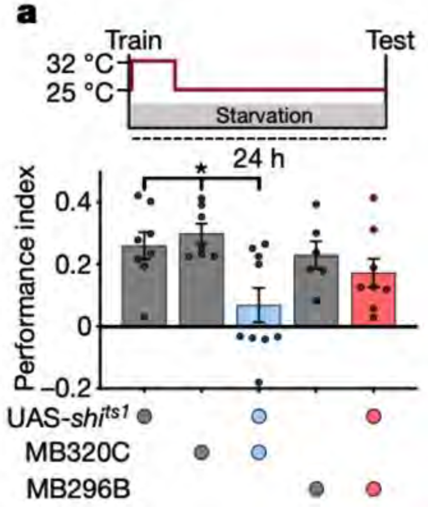
MB504B: multiple PPL1 DANs

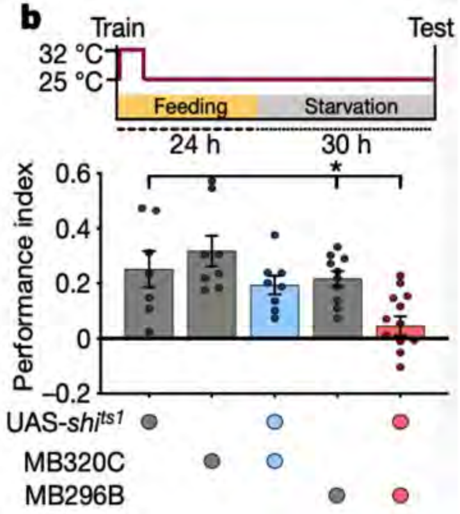




MB320C: MB-MP1 DANs

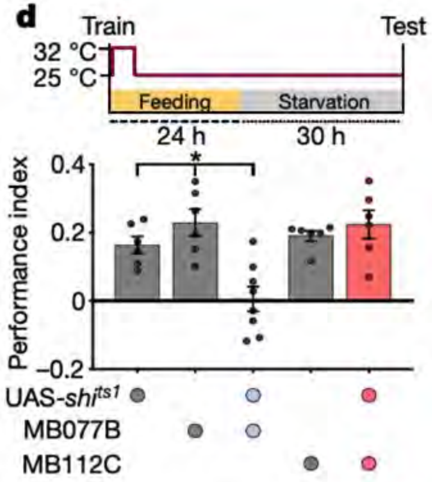
MB296B: MB-MV1 DANs

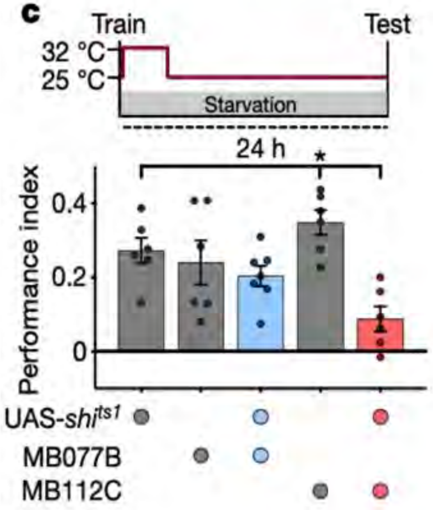




MB112C: MBON-γ1pedc neurons

MB077B: MBON-γ2α′1 neurons





Chouhan N.S et al., Neuron, 2021

Summary:

1. Behavioural plasticity is critical for adaptation in varying environments

Common view: Sleep is required for the consolidation of long-term memory
(accumulation of catabolic waste products / energy demands)

Appetitive memory: starved flies can still consolidate memory related to food
(survival)

In rats and humans, sleep is specifically required for hippocampus-dependent memory.

2. A feeding/hunger-dependent adaptive switch/ The recruitment of distinct neural circuit mechanisms

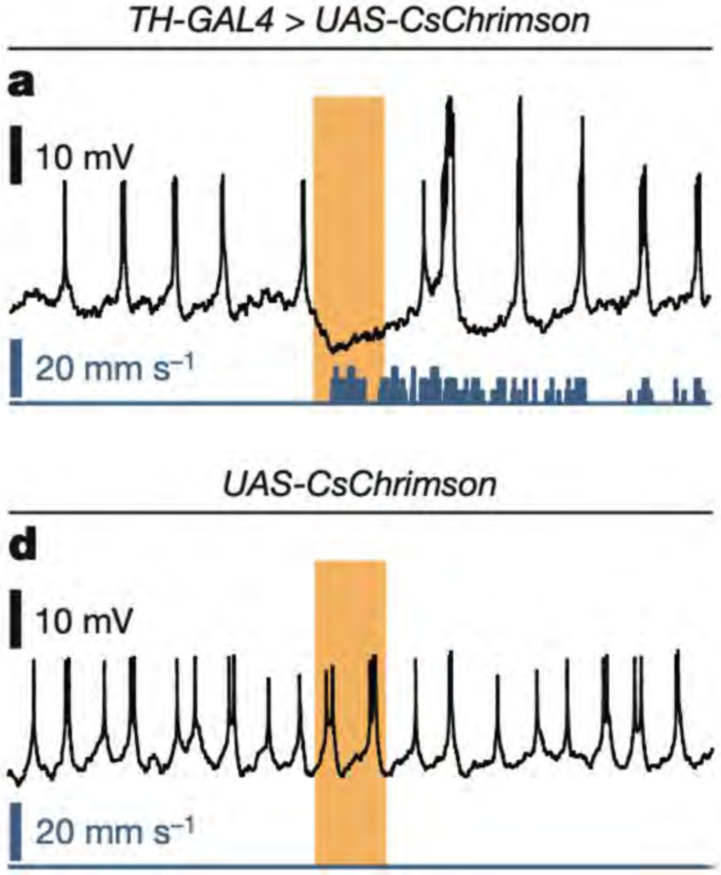
sweet taste/NPF   anterior– posterior α'/β' neurons/medial α'/β' neurons

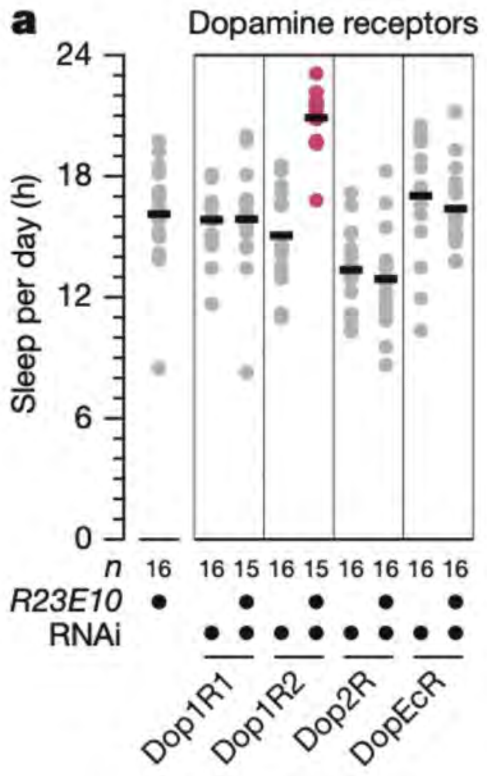
Gero Miesenböck

'We study two neural integrators: those that accumulate evidence during decision-making, and those that accumulate sleep pressure during waking.'

“a homeostatic sleep switch”

“homeostatic sleep control: switching sleep-promoting neurons (dFB nuerons)between active and quiescent states”

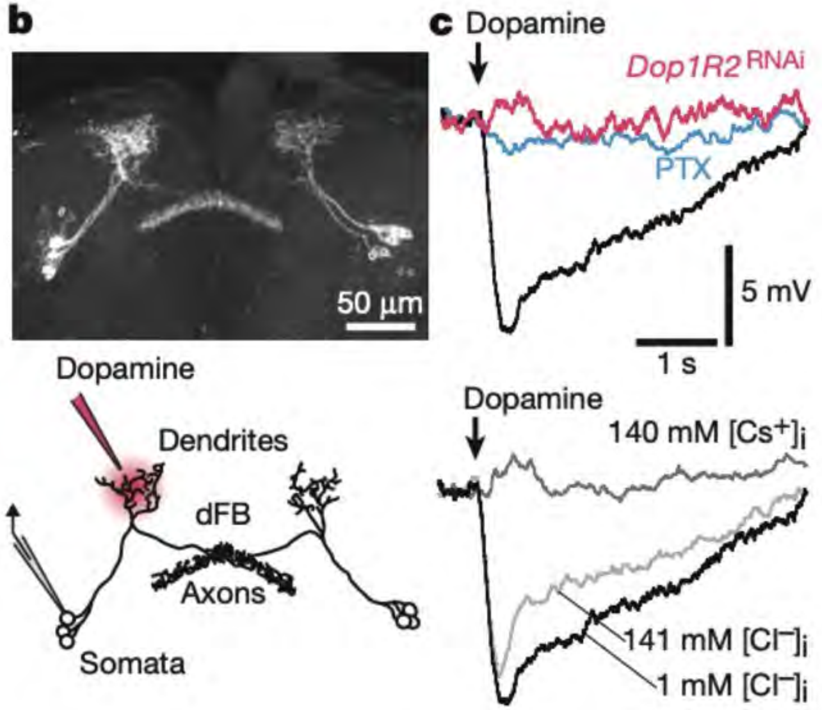


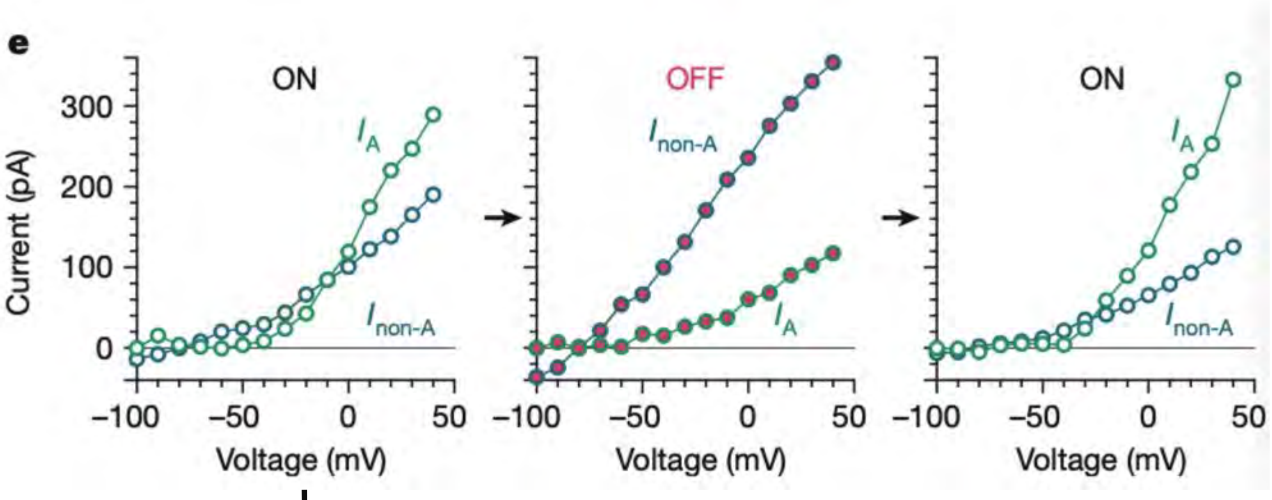


Dopamine inhibits dFB neurons via Dop1R2 and promotes awakening.

Pimentel D et al., Nature. 2016

potassium conductances mediate the bulk of dopaminergic inhibition





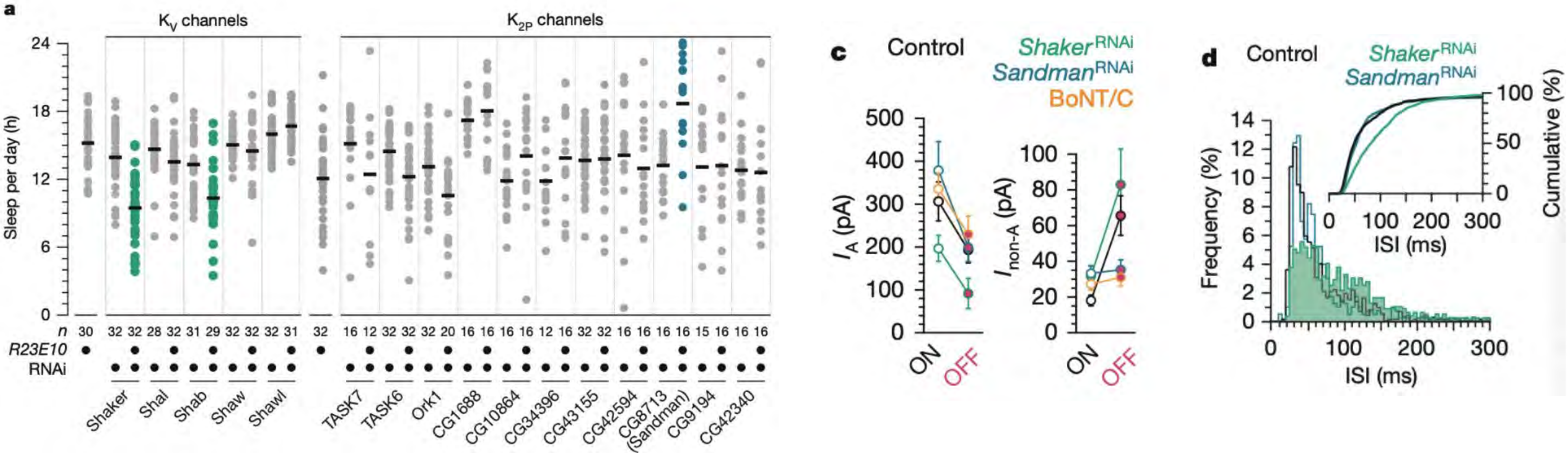
voltage-dependent A-type currents: Shaker

voltage-independent non-A-type currents: Sandman

- Dop1R2 knock out
- PTX: the $G_{i/o}$ family inactivation
- Caesium: the pores of inward-rectifier channels
- elevated intracellular chloride

Pimentel D et al., Nature. 2016

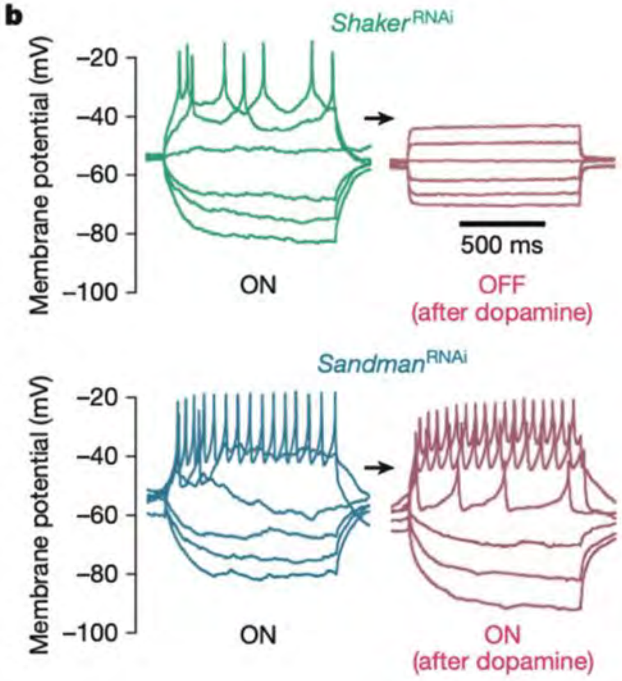
Shaker and Sandman have opposing effects on sleep



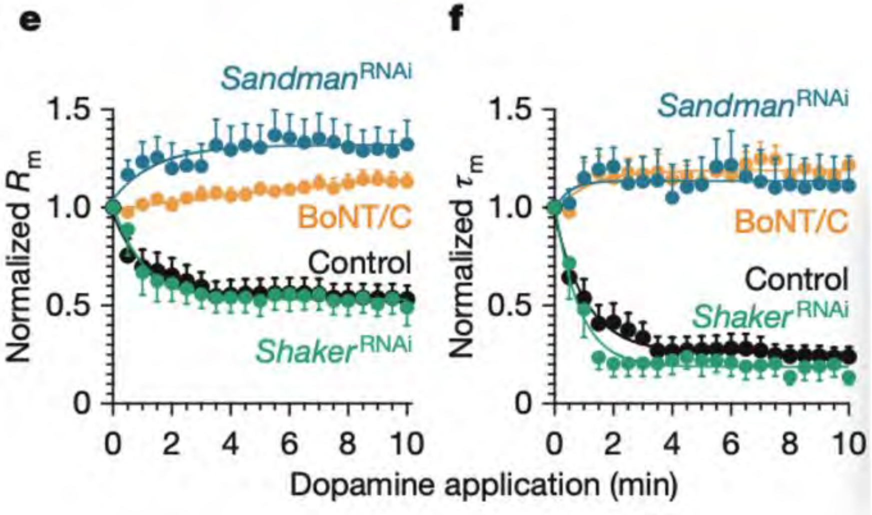
Pimentel D et al., Nature. 2016

Summary:

The leak channel Sandman imposes silence during waking, whereas increased A-type currents through Shaker support tonic firing during sleep.



transient dopamine responses



sustained dopamine responses

Pimentel D et al., Nature. 2016

> Nature. 2019 Apr;568(7751):230-234. doi: 10.1038/s41586-019-1034-5. Epub 2019 Mar 20.

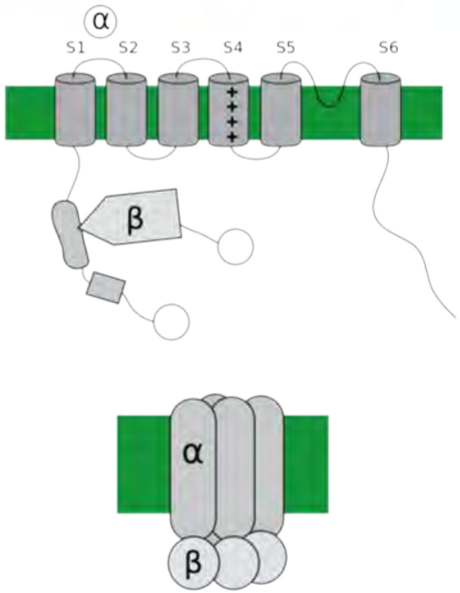
A potassium channel β-subunit couples mitochondrial electron transport to sleep

Anissa Kempf [1], Seoho M Song [1], Clifford B Talbot [1], Gero Miesenböck [2]

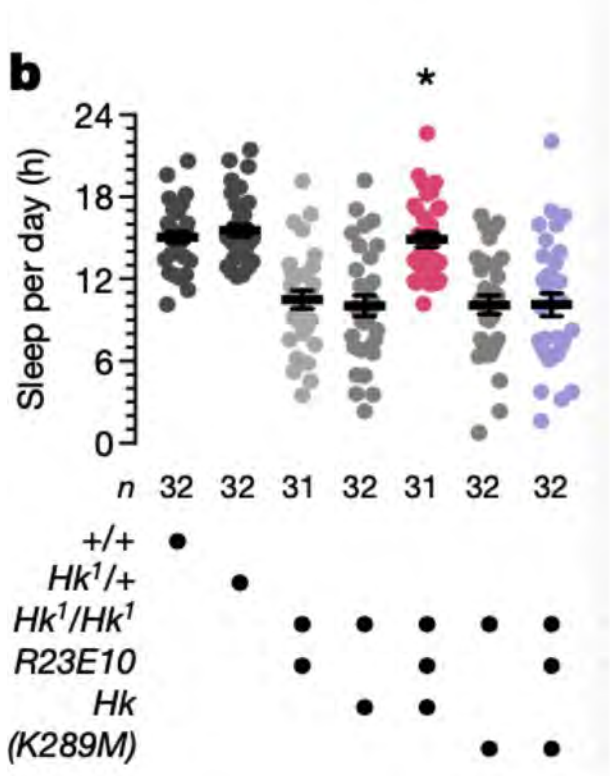
Affiliations + expand

PMID: 30894743 PMCID: PMC6522370 DOI: 10.1038/s41586-019-1034-5

Free PMC article



Shaker potassium channel
a β-subunit: Hyperkinetic



redox

sleep

Kempf A et al., Nature. 2019

- The sleep-regulatory role of Hyperkinetic is tied to its ability to sense changes in cellular redox state, which are therefore expected to accompany changes in sleep pressure.

- Perturbing the redox chemistry of dFB neurons should have consequences for sleep.

  1. manipulation of mitochondrial electron transport
  2. chronic interference with antioxidant enzymes
  3. acute optogenetic induction of singlet oxygen formation

- It identifies a biophysical mechanism for coupling redox chemistry and sleep.

energy metabolism **oxidative stress** **sleep**

Summary:

1.Cutting-edge research needs effective technical support.

optogenetics   electrophysiological

2. More detailed neural circuitry studies on sleep homeostasis

biophysical changes in a small population of neuron

3. A special point of view: Shaker/Sandman potassium channel   ON/OFF

4.Energy metabolism, oxidative stress, and sleep are mechanistically connected.

—three processes implicated independently in lifespan, ageing, and degenerative disease

5. For human, some potential sleep-regulatory drugs would be invented for insomnia induce by doxidative stress.

Hello *D.mel*

Part III. Dissect papers about feeding and food intake

Why were these papers accepted by CNS？

Speaker: Su Xb

Irene Miguel-Aliaga and publications from her lab

Article

An intestinal zinc sensor regulates food intake and developmental growth

https://doi.org/10.1038/s41586-020-2111-5
Received: 17 May 2019
Accepted: 18 February 2020
Published online: 18 March 2020
Check for updates

Siamak Redhai[1,2,10], Clare Pilgrim[1,2,10], Pedro Gaspar[1,2], Lena van Giesen[3], Tatiana Lopes[1,2], Olena Riabinina[1,2,9], Théodore Grenier[4], Alexandra Milona[1], Bhavna Chanana[1,2], Jacob B. Swadling[1,2], Yi-Fang Wang[1], Farah Dahalan[5,6], Michaela Yuan[7], Michaela Wilsch-Brauninger[7], Wei-hsiang Lin[8], Nathan Dennison[5], Paolo Capriotti[5], Mara K. N. Lawniczak[6], Richard A. Baines[8], Tobias Warnecke[1,2], Nikolai Windbichler[5], Francois Leulier[4], Nicholas W. Bellono[3] & Irene Miguel-Aliaga[1,2,11]

In cells, organs and whole organisms, nutrient sensing is key to maintaining homeostasis and adapting to a fluctuating environment[1]. In many animals, nutrient sensors are found within the enteroendocrine cells of the digestive system; however, less is known about nutrient sensing in their cellular siblings, the absorptive enterocytes[1]. Here we use a genetic screen in *Drosophila melanogaster* to identify Hodor, an ionotropic receptor in enterocytes that sustains larval development, particularly in nutrient-scarce conditions. Experiments in *Xenopus* oocytes and flies indicate that Hodor is a pH-sensitive, zinc-gated chloride channel that mediates a previously unrecognized dietary preference for zinc. Hodor controls systemic growth from a subset of enterocytes—interstitial cells—by promoting food intake and insulin/IGF signalling. Although Hodor sustains gut luminal acidity and restrains microbial loads, its effect on systemic growth results from the modulation of Tor signalling and lysosomal homeostasis within interstitial cells. Hodor-like genes are insect-specific, and may represent targets for the control of disease vectors. Indeed, CRISPR–Cas9 genome editing revealed that the single *hodor* orthologue in *Anopheles gambiae* is an essential gene. Our findings highlight the need to consider the instructive contributions of metals—and, more generally, micronutrients—to energy homeostasis.

To investigate nutrient sensing in enterocytes, we selected 111 putative nutrient sensors in *D. melanogaster* on the basis of their intestinal expression and their predicted structure or function (Extended Data Fig. 1a, Supplementary Information). Using two enterocyte-specific driver lines, we downregulated their expression in midgut enterocytes throughout development under two dietary conditions, nutrient-rich and nutrient-poor; we reasoned that dysregulation of nutrient-sensing mechanisms may increase or reduce the normal period of larval growth, and might do so in a diet-dependent manner (Extended Data Fig. 1b–d). Enterocyte-specific knockdown of the gene *CG11340*, also referred to as *pHCl-2*[2], resulted in developmental delay. This delay was exacerbated, and was accompanied by significantly reduced larval viability, under nutrient-poor conditions (Fig. 1a, Extended Data Figs. 1h, 2b); these phenotypes were confirmed using a second *RNAi* transgene and a new *CG11340* mutant (Fig. 1b, c, Extended Data Fig. 1e–i). In the tradition of naming *Drosophila* genes according to their loss-of-function phenotype, we have named *CG11340* '*hodor*'—an acronym for '*hold on, don't rush*', in reference to the developmental delay.

A transcriptional reporter revealed that Hodor was expressed in the intestine[1]. A new antibody (Extended Data Fig. 2a, b) revealed that Hodor expression was confined to enterocytes in two midgut portions that are known to store metals: the copper cell region and the iron cell region (Fig. 1d–h). Within the copper cell region, Hodor was expressed only in so-called interstitial cells (Fig. 1e, f, g). *hodor-Gal4* was also present in the interstitial cells of the copper cell region; however, in our experimental conditions and in contrast to published results, it was not detected in the iron cell region[1] (Fig. 1e, Extended Data Fig. 2d). Apart from the intestine, Hodor was found only in principal cells of the excretory Malpighian tubules[2,3] (Fig. 1d, e). To identify the cells from which Hodor controls systemic growth, we conducted region- or cell-type-specific downregulation and rescue experiments (Extended Data Figs. 1b, 2d–g). Only fly lines in which *hodor* was downregulated in interstitial cells showed slowed larval development (Fig. 1a, i–k, Extended Data Figs. 1j, 2c–h). This developmental delay persisted when *hodor* knockdown was induced post-embryonically during larval growth (Fig. 1l), and was rescued only in fly lines in which *hodor* expression was

[1]MRC London Institute of Medical Sciences, London, UK. [2]Institute of Clinical Sciences, Faculty of Medicine, Imperial College London, London, UK. [3]Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA, USA. [4]Institut de Génomique Fonctionnelle de Lyon (IGFL), Université de Lyon, ENS de Lyon, CNRS UMR 5242, Lyon, France. [5]Department of Life Sciences, Imperial College London, London, UK. [6]Malaria Programme, Wellcome Sanger Institute, Cambridge, UK. [7]Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany. [8]Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [9]Present address: Department of Biosciences, Durham University, Durham, UK. [10]These authors contributed equally: Siamak Redhai, Clare Pilgrim. [11]e-mail: i.miguel-aliaga@imperial.ac.uk

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Enteric neurons increase maternal food intake during reproduction

Dafni Hadjieconomou[1,2], George King[1,2], Pedro Gaspar[1,2], Alessandro Mineo[1,2], Laura Blackie[1,2], Tomotsune Ameku[1,2], Chris Studd[1,2], Alex de Mendoza[3,4,5], Fengqiu Diao[6], Benjamin H. White[6], Andre E.X. Brown[1,2], Pierre-Yves Plaçais[7], Thomas Préat[7], Irene Miguel-Aliaga[1,2]

[1]MRC London Institute of Medical Sciences, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK

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[5]Queen Mary University of London, School of Biological and Chemical Sciences, Mile End Road, E1 4NS, London, UK

[6]Laboratory of Molecular Biology, National Institute of Mental Health, National Institutes of Health, Bethesda, United States

[7]Genes and Dynamics of Memory Systems, Brain Plasticity Unit, CNRS, ESPCI Paris, PSL Research University, 10 rue Vauquelin, 75005 Paris, France

Abstract

Reproduction induces increased food intake across females of many animal species[1–4], providing a physiologically relevant paradigm for exploration of appetite regulation. Parsing enteric neuronal diversity in *Drosophila*, we identify a key role for gut-innervating neurons with sex- and reproductive state-specific activity in sustaining the increased food intake of mothers during reproduction. Steroid and enteroendocrine hormones functionally remodel these neurons, leading

Author contribution statement
D.H. and I.M.-A. designed and conceived the study. D.H. and G.K. performed most experiments and analysed data. P.G. conducted crop enlargement, feeding and fecundity experiments, developed ways to quantify crop enlargement and analysed data. A.M. conducted some immunohistochemistry and fecundity experiments. L.B. conducted immunohistochemistry experiments and acquired and analysed feeding/crop enlargement videos. T.A. conducted some immunohistochemistry and RT-qPCR experiments. C.S. assisted with fecundity experiments, fly husbandry and video recordings. A.d M. performed phylogenetic analyses. F.D. and B.H.W. contributed the *Ms*^{TGEM}*-Gal4* mutant/driver line. A.B. provided the mathematical model. P-Y.P. and T.P. hosted and trained D.H. to perform *in vivo* brain calcium imaging experiments, P-Y.P performed calcium imaging experiments and analysed these data. I.M-A. wrote the manuscript, with contributions from D.H.

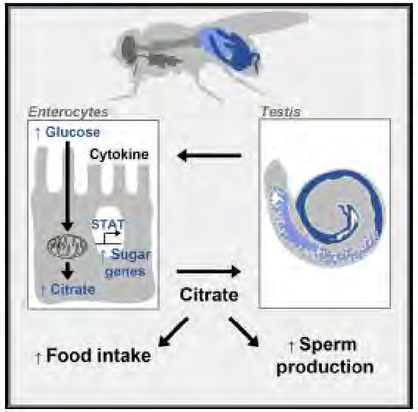
Competing interests
The authors declare no competing interests.

Cell

Article

Sex Differences in Intestinal Carbohydrate Metabolism Promote Food Intake and Sperm Maturation

Graphical Abstract



Authors

Bruno Hudry, Eva de Goeij, Alessandro Mineo, ..., Pierre-Yves Plaçais, Thomas Preat, Irene Miguel-Aliaga

Correspondence

Bruno.Hudry@unice.fr (B.H.), i.miguel-aliaga@imperial.ac.uk (I.M.-A.)

In Brief

Inter-organ communication couples diet with gamete production. The male gonad promotes sex differences in carbohydrate metabolism within an adjacent intestinal portion via JAK-STAT signalling. In response to this gonadal signal, gut-derived citrate controls food intake and sperm maturation.

Highlights

- Intestinal carbohydrate metabolism is male-biased and region-specific
- Testes masculinize gut sugar handling by promoting enterocyte JAK-STAT signaling
- The male intestine secretes citrate to the adjacent testes
- Gut-derived citrate promotes food intake and sperm maturation

Hudry et al., 2019, Cell 178, 901–918
August 8, 2019 © 2019 Medical Research Council on behalf of UKRI and Imperial College London. Published by Elsevier Inc.
https://doi.org/10.1016/j.cell.2019.07.029

CellPress

Miguel-Aliaga Lab

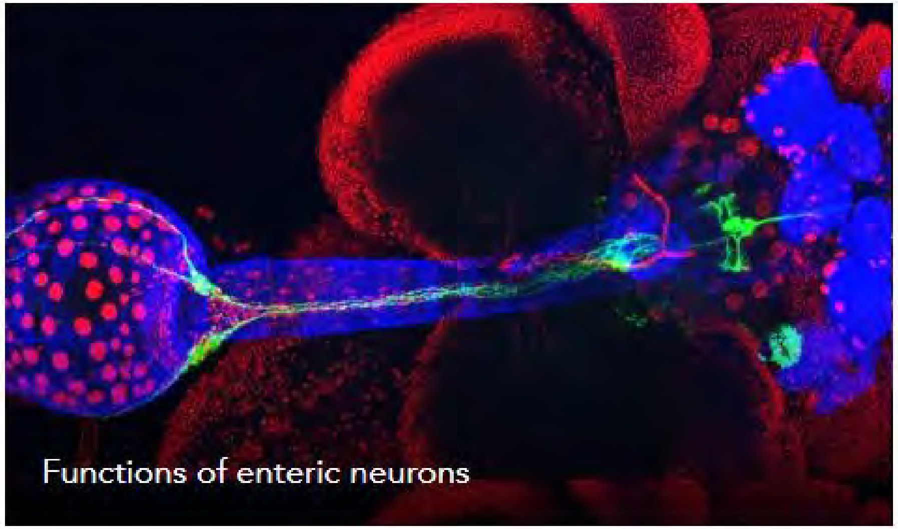
Gut Signalling and Metabolism

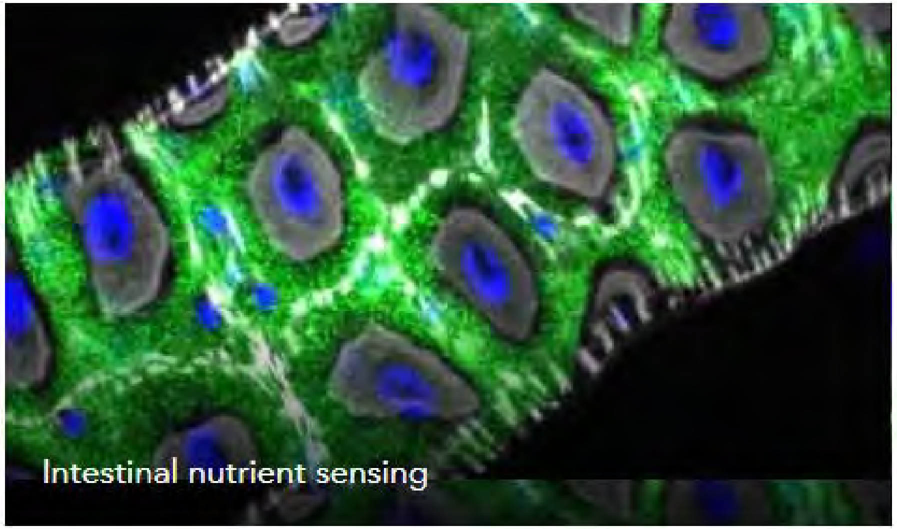
Irene Miguel-Aliaga
Imperial College London

We are interested in the plasticity of adult organs.

Current projects

Our ongoing work is exploring these questions:





An intestinal zinc sensor regulates food intake and developmental growth

Article

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In cells, organs and whole organisms, nutrient sensing is key to maintaining homeostasis and adapting to a fluctuating environment[1]. In many animals, nutrient sensors are found within the enteroendocrine cells of the digestive system; however, less is known about nutrient sensing in their cellular siblings, the absorptive enterocytes[1]. Here we use a genetic screen in *Drosophila melanogaster* to identify Hodor, an ionotropic receptor in enterocytes that sustains larval development, particularly in nutrient-scarce conditions. Experiments in *Xenopus* oocytes and flies indicate that Hodor is a pH-sensitive, zinc-gated chloride channel that mediates a previously unrecognized dietary preference for zinc. Hodor controls systemic growth from a subset of enterocytes—interstitial cells—by promoting food intake and insulin/IGF signalling. Although Hodor sustains gut luminal acidity and restrains microbial loads, its effect on systemic growth results from the modulation of Tor signalling and lysosomal homeostasis within interstitial cells. Hodor-like genes are insect-specific, and may represent targets for the control of disease vectors. Indeed, CRISPR–Cas9 genome editing revealed that the single *hodor* orthologue in *Anopheles gambiae* is an essential gene. Our findings highlight the need to consider the instructive contributions of metals—and, more generally, micronutrients—to energy homeostasis.

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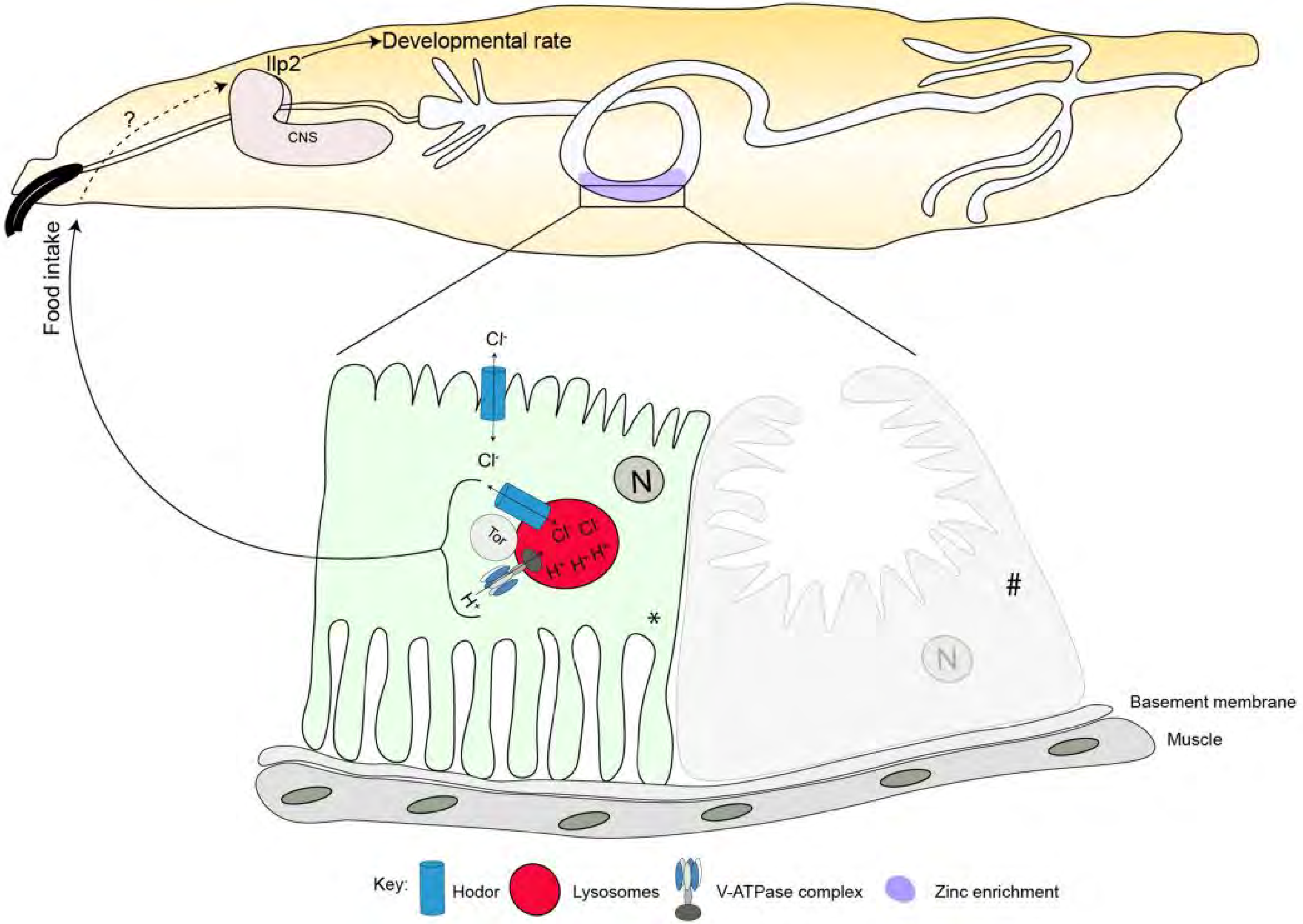
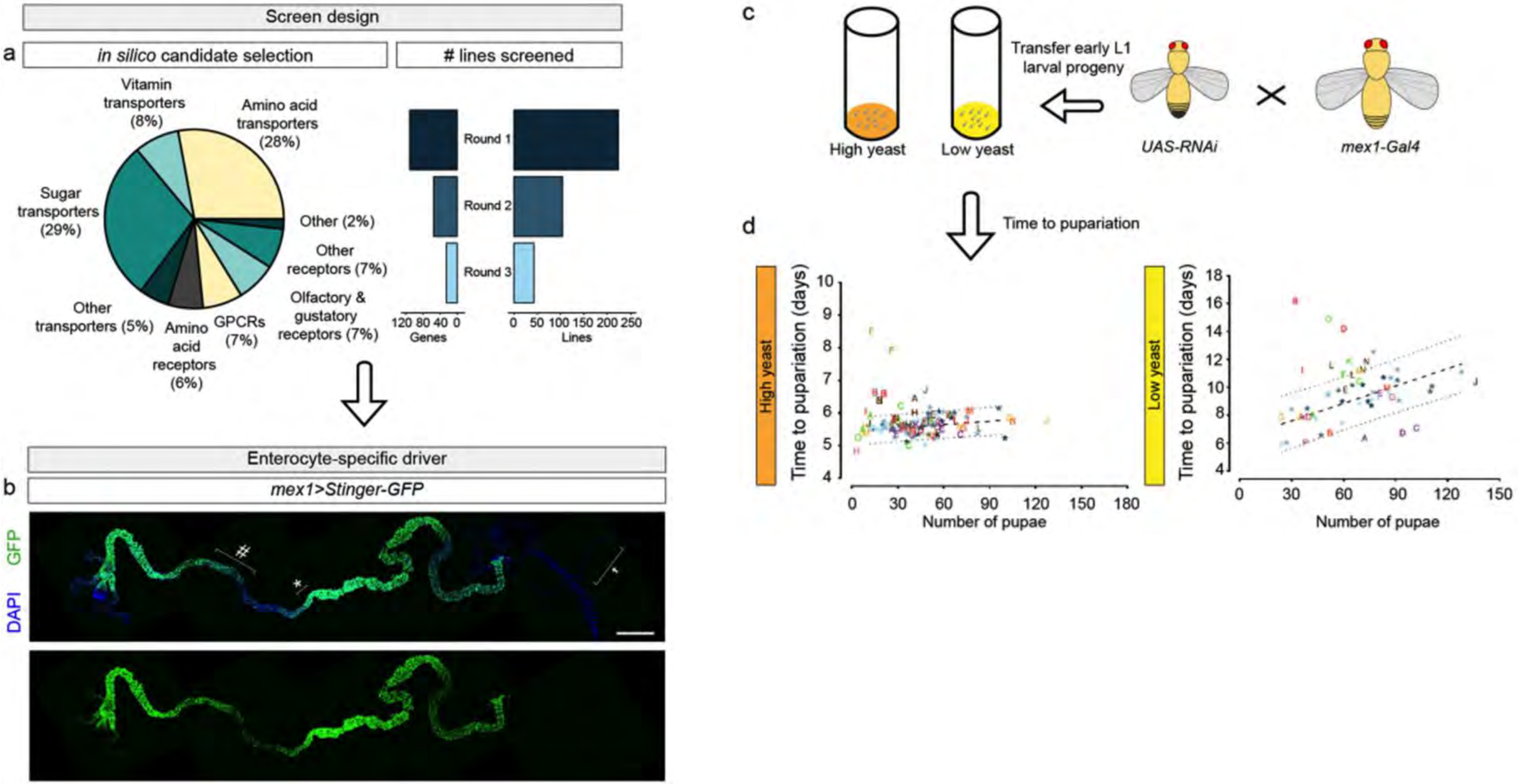
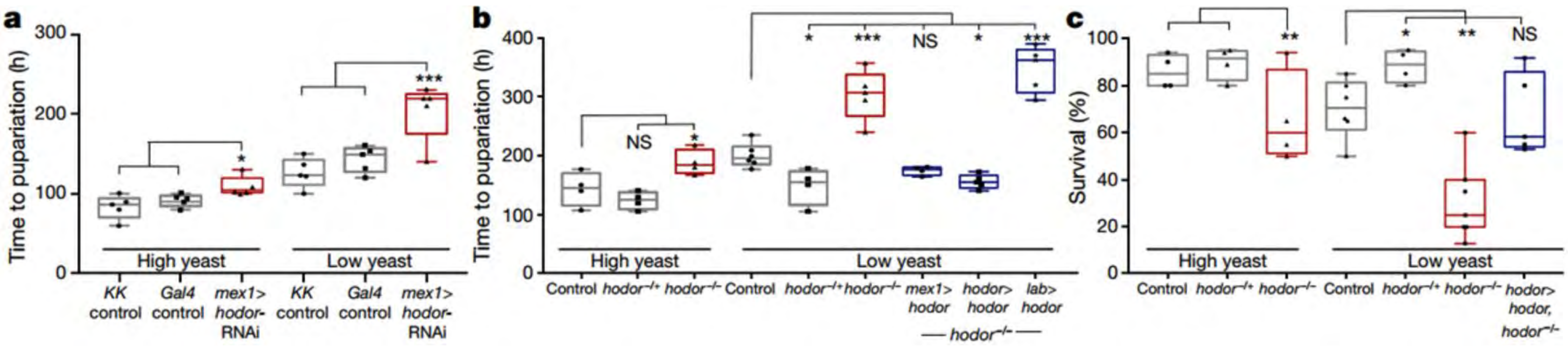


Design of enterocyte-specific RNAi-screen

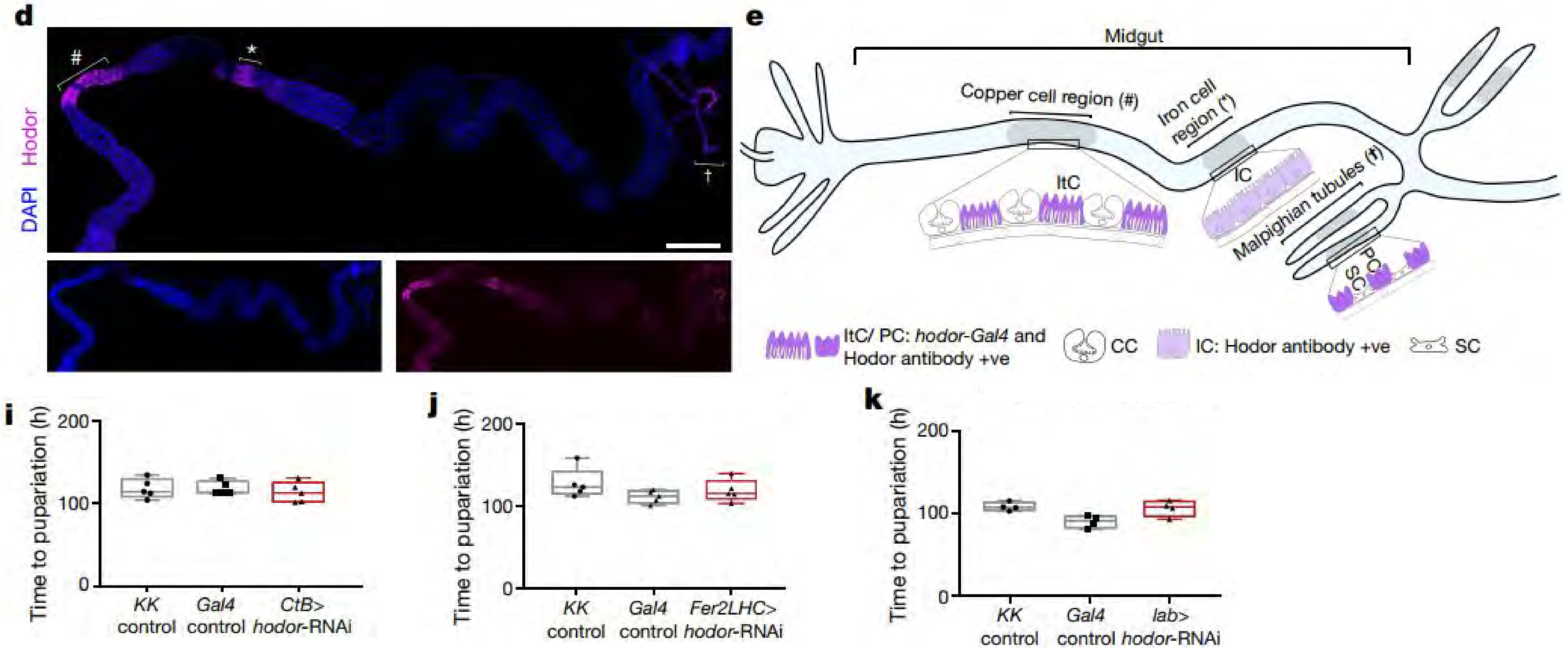


Intestinal Hodor sustains larval growth



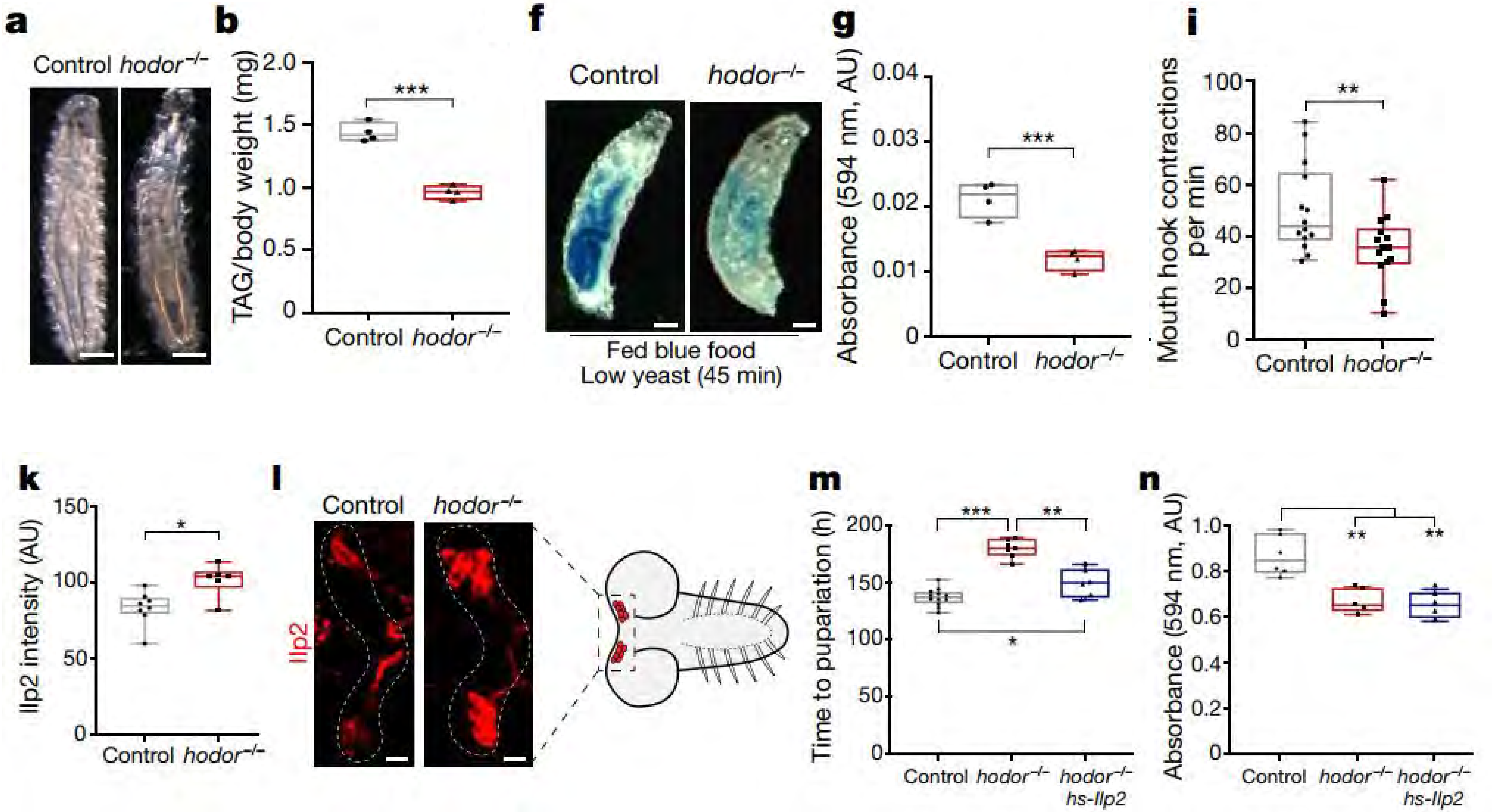
hodor—an acronym for ‘hold on, don’t rush’, in reference to the developmental delay

Hodor expression was confined to enterocytes in two midgut portions

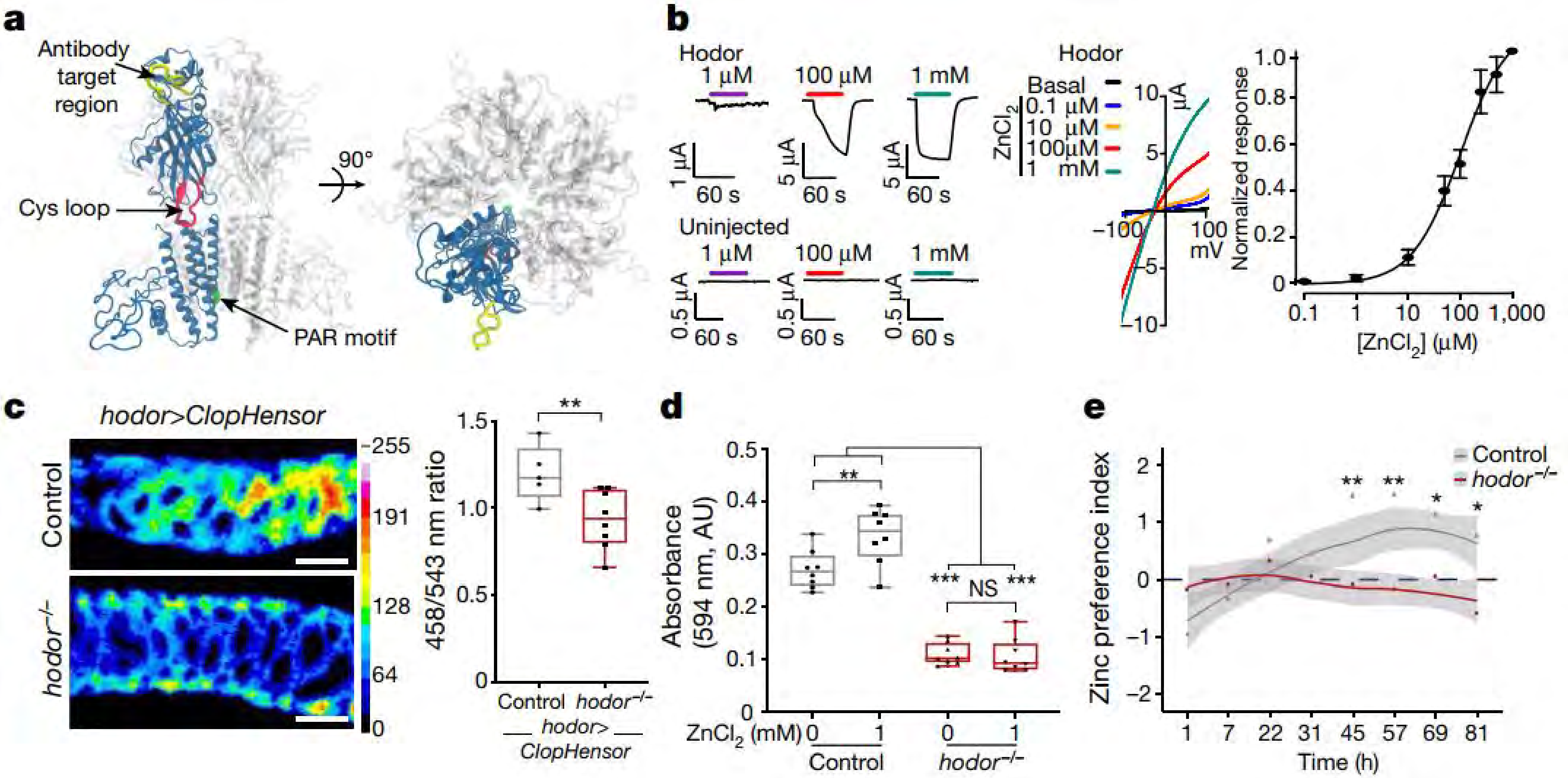


principal cells (using CtB-Gal4)
iron cells (using Fer2LCH-Gal4)
copper cells (using lab-Gal4)

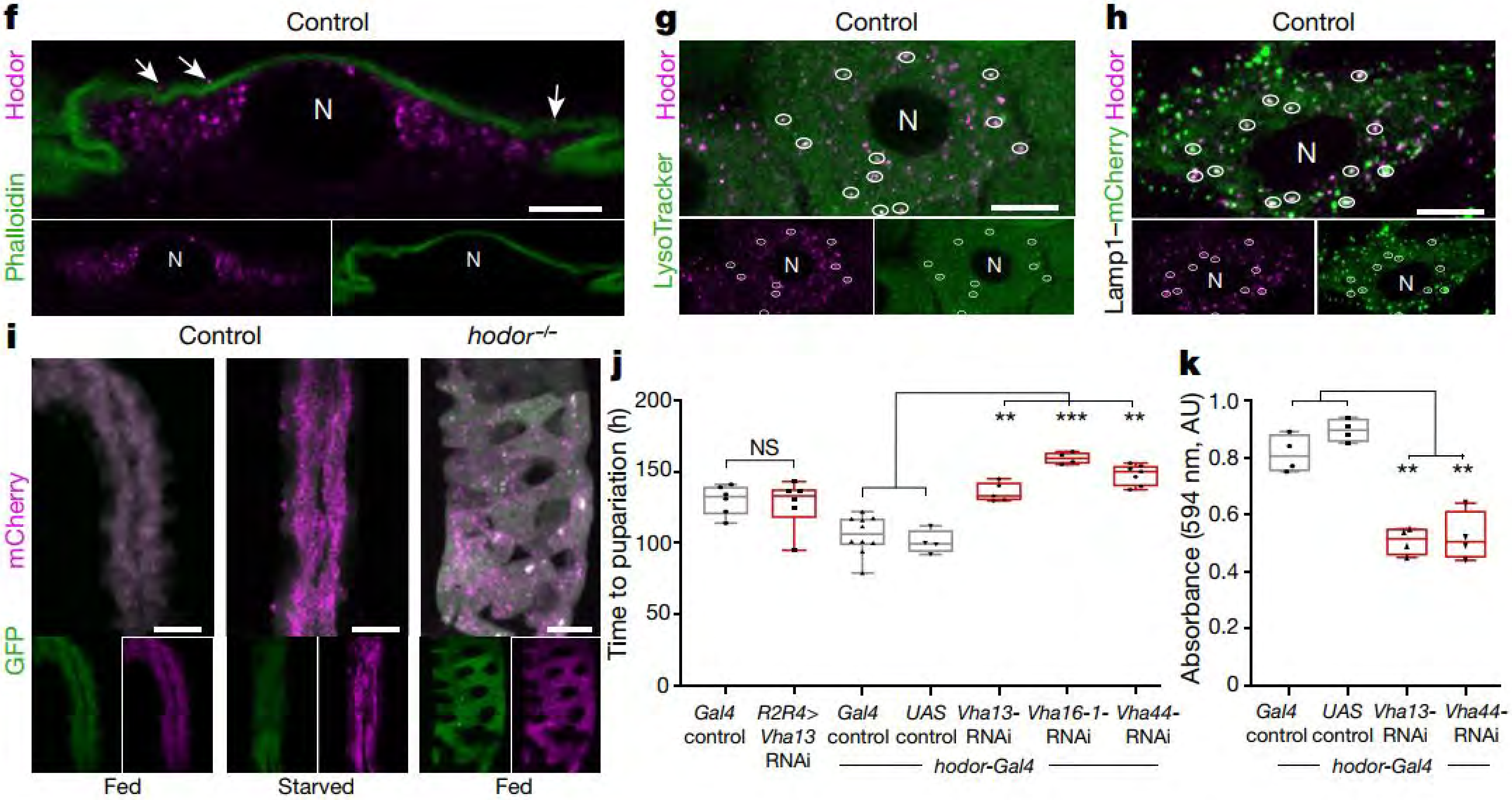
Hodor controls larval growth by promoting food intake and systemic insulin signalling



Hodor is a zinc-gated chloride channel



Cellular roles of a zinc-gated chloride channel



An intestinal zinc sensor regulates food intake and developmental growth

Article

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Siamak Redhai[1,2,10], Clare Pilgrim[1,2,10], Pedro Gaspar[1,2], Lena van Giesen[3], Tatiana Lopes[1,2], Olena Riabinina[1,2,9], Théodore Grenier[4], Alexandra Milona[1], Bhavna Chanana[1,2], Jacob B. Swadling[1,2], Yi-Fang Wang[1], Farah Dahalan[5,6], Michaela Yuan[7], Michaela Wilsch-Brauninger[7], Wei-hsiang Lin[8], Nathan Dennison[5], Paolo Capriotti[5], Mara K. N. Lawniczak[6], Richard A. Baines[8], Tobias Warnecke[1,2], Nikolai Windbichler[5], Francois Leulier[4], Nicholas W. Bellono[3] & Irene Miguel-Aliaga[1,2]✉

In cells, organs and whole organisms, nutrient sensing is key to maintaining homeostasis and adapting to a fluctuating environment[1]. In many animals, nutrient sensors are found within the enteroendocrine cells of the digestive system; however, less is known about nutrient sensing in their cellular siblings, the absorptive enterocytes[1]. Here we use a genetic screen in *Drosophila melanogaster* to identify Hodor, an ionotropic receptor in enterocytes that sustains larval development, particularly in nutrient-scarce conditions. Experiments in *Xenopus* oocytes and flies indicate that Hodor is a pH-sensitive, zinc-gated chloride channel that mediates a previously unrecognized dietary preference for zinc. Hodor controls systemic growth from a subset of enterocytes—interstitial cells—by promoting food intake and insulin/IGF signalling. Although Hodor sustains gut luminal acidity and restrains microbial loads, its effect on systemic growth results from the modulation of Tor signalling and lysosomal homeostasis within interstitial cells. Hodor-like genes are insect-specific, and may represent targets for the control of disease vectors. Indeed, CRISPR–Cas9 genome editing revealed that the single *hodor* orthologue in *Anopheles gambiae* is an essential gene. Our findings highlight the need to consider the instructive contributions of metals—and, more generally, micronutrients—to energy homeostasis.

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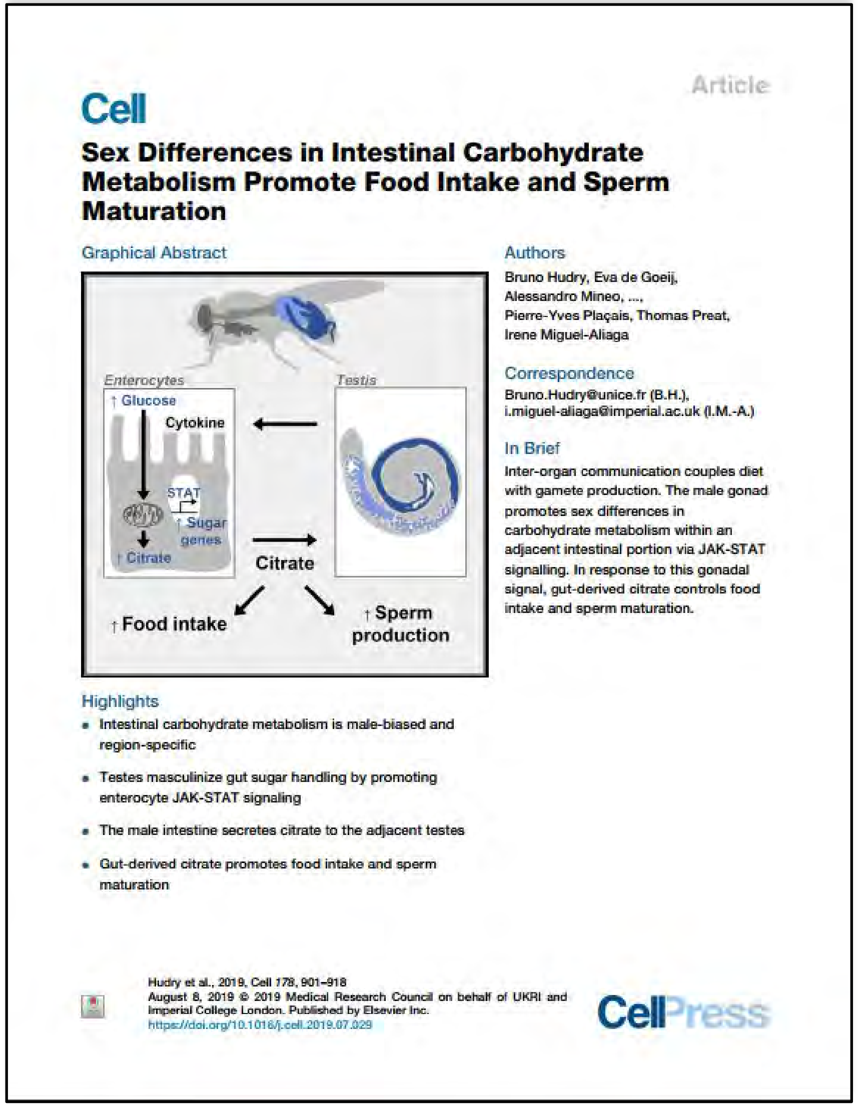
hodor—an acronym for 'hold on, don't rush', in reference to the developmental delay.

Review:

该文章发现了位于果蝇消化道内一类新的用于感知锌离子的氯通道蛋白-Hodor。并阐述了其在幼虫摄食调节和发育中的重要作用。这一发现也证实了金属离子在个体和细胞水平上对代谢的调控作用。

在动物的消化系统中，多数消化道的功能是和营养物质的分解与吸收联系起来的。在过去的研究中，人们通常认为营养物质的吸收是由一部分肠上皮细胞完成，感知是由一部分肠道内分泌细胞完成。而在该研究中揭示了果蝇肠上皮细胞也可以借助金属离子感受蛋白发挥感知功能，颠覆了认知。

Sex Differences in Intestinal Carbohydrate Metabolism Promote Food Intake and Sperm Maturation



Cell

Article

Sex Differences in Intestinal Carbohydrate Metabolism Promote Food Intake and Sperm Maturation

Graphical Abstract

Authors

Bruno Hudry, Eva de Goeij, Alessandro Mineo, ..., Pierre-Yves Plaçais, Thomas Preat, Irene Miguel-Aliaga

Correspondence

Bruno.Hudry@unice.fr (B.H.), i.miguel-aliaga@imperial.ac.uk (I.M.-A.)

In Brief

Inter-organ communication couples diet with gamete production. The male gonad promotes sex differences in carbohydrate metabolism within an adjacent intestinal portion via JAK-STAT signalling. In response to this gonadal signal, gut-derived citrate controls food intake and sperm maturation.

Highlights

- Intestinal carbohydrate metabolism is male-biased and region-specific
- Testes masculinize gut sugar handling by promoting enterocyte JAK-STAT signaling
- The male intestine secretes citrate to the adjacent testes
- Gut-derived citrate promotes food intake and sperm maturation

Hudry et al., 2019, Cell 178, 901–918
August 8, 2019
https://doi.org/10.1016/j.cell.2019.07.029

CellPress

How gut derived signals contribute to sex differences in whole-body physiology?

Highlight

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- The male intestine secretes citrate to the adjacent testes
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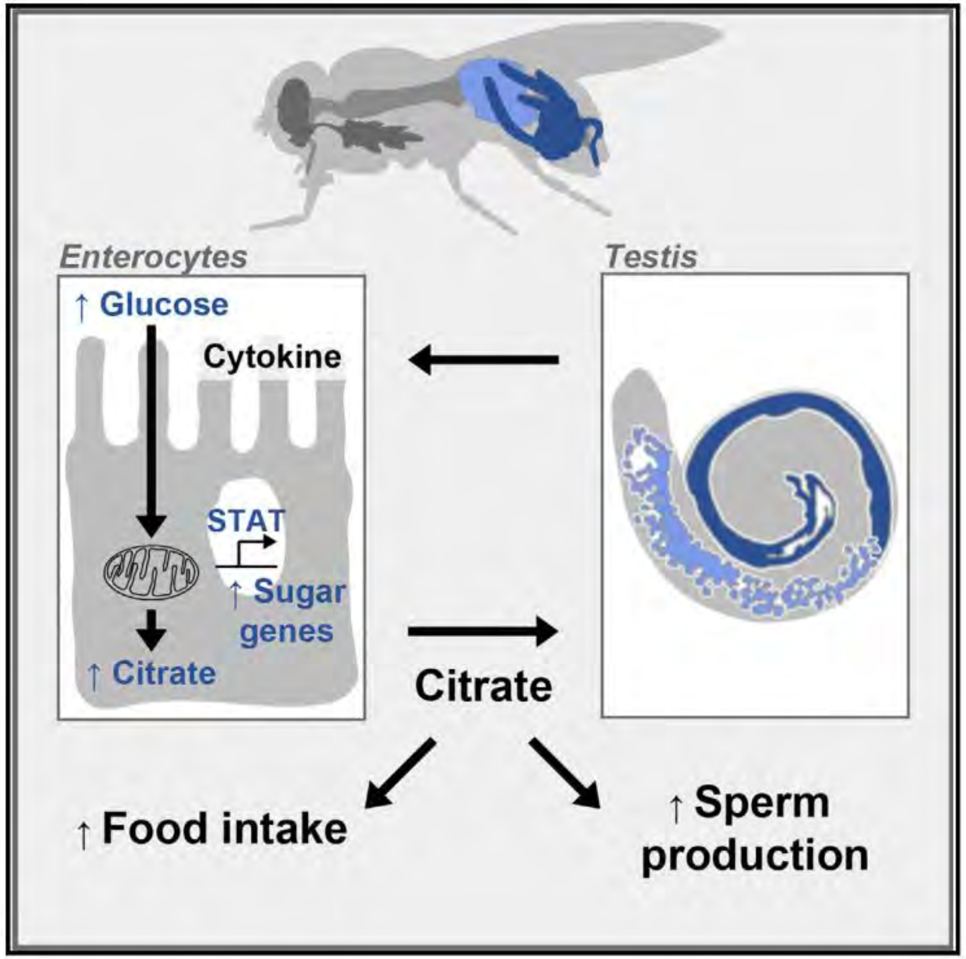

Review:

该工作发现了男性性腺和邻近肠道区域之间的双向交流。这种交流影响肠道和睾丸的功能，是由细胞信号和代谢物柠檬酸介导的。

揭示了雄性生殖腺-肠道轴耦合饮食和精子生产，说明了跨器官的代谢通信在生理学上的重要性。柠檬酸在器官间通讯的指导作用可能比之前认识到的更重要。

Enteric neurons increase maternal food intake during reproduction

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Enteric neurons increase maternal food intake during reproduction

Dafni Hadjieconomou[1,2], George King[1,2], Pedro Gaspar[1,2], Alessandro Mineo[1,2], Laura Blackie[1,2], Tomotsune Ameku[1,2], Chris Studd[1,2], Alex de Mendoza[3,4,5], Fengqiu Diao[6], Benjamin H. White[6], Andre E.X. Brown[1,2], Pierre-Yves Plaçais[7], Thomas Préat[7], Irene Miguel-Aliaga[1,2]

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Abstract

Reproduction induces increased food intake across females of many animal species[1–4], providing a physiologically relevant paradigm for exploration of appetite regulation. Parsing enteric neuronal diversity in *Drosophila*, we identify a key role for gut-innervating neurons with sex- and reproductive state-specific activity in sustaining the increased food intake of mothers during reproduction. Steroid and enteroendocrine hormones functionally remodel these neurons, leading

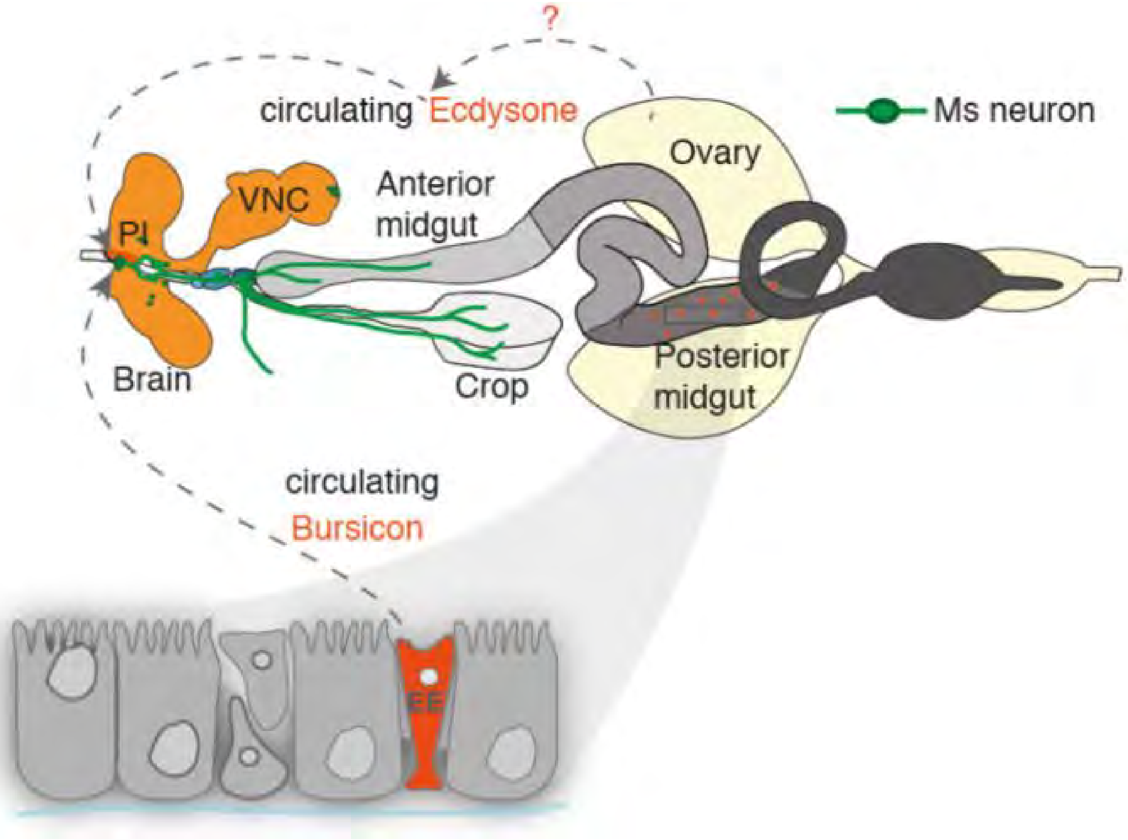
Author contribution statement

D.H. and I.M.-A. designed and conceived the study. D.H. and G.K. performed most experiments and analysed data. P.G. conducted crop enlargement, feeding and fecundity experiments, developed ways to quantify crop enlargement and analysed data. A.M. conducted some immunohistochemistry and fecundity experiments. L.B. conducted immunohistochemistry experiments and acquired and analysed feeding/crop enlargement videos. T.A. conducted some immunohistochemistry and RT-qPCR experiments. C.S. assisted with fecundity experiments, fly husbandry and video recordings. A.d M. performed phylogenetic analyses. F.D. and B.H.W. contributed the Ms^{TGEM}-*Gal4* mutant/driver line. A.B. provided the mathematical model. P-Y.P. and T.P. hosted and trained D.H. to perform *in vivo* brain calcium imaging experiments, P-Y.P performed calcium imaging experiments and analysed these data. I.M-A. wrote the manuscript, with contributions from D.H.

Competing interests

The authors declare no competing interests.

Why do pregnant women eat more？



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Competing interests

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Why do pregnant women eat more？

Review:

该研究利用虽然简单但生理上复杂的果蝇肠道，确定了具有性别和生殖状态特定活性的肠道神经元在维持母亲生殖期间增加的食物摄入量方面的关键作用。

该发现提供了一种新的机制来获得维持妊娠的正能量平衡。同时该发现为研究营养平衡、器官重塑与体内代谢稳态提供了新的机制。这些机制可能最终被用来抑制食欲和/或体重增加。

A glucose-sensing neuron pair regulates insulin and glucagon in *Drosophila*

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Nature. Author manuscript; available in PMC 2020 April 23.

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Nature. 2019 October ; 574(7779): 559–564. doi:10.1038/s41586-019-1675-4.

A glucose-sensing neuron pair regulates insulin and glucagon in *Drosophila*

Yangkyun Oh[2], Jason Sih-Yu Lai[2,§], Holly J. Mills[2,§], Hediye Erdjument-Bromage[2], Benno Giammarinaro[2,§], Khalil Saadipour[2], Justin G. Wang[2,§], Farhan Abu[2,§], Thomas A. Neubert[2], Greg S. B. Suh[1,2,*]

[1]Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea

[2]Skirball Institute of Biomolecular Medicine, Department of Cell Biology, Neuroscience Institute, New York University School of Medicine, 540 First Avenue, New York, NY, USA

Summary

Although glucose-sensing neurons were discovered more than 50 years ago, the physiological role of glucose sensing in metazoans remains unclear. Here, we identify a pair of glucose-sensing neurons (dubbed *CN* neurons) in the *Drosophila* brain with bifurcating axons whereby one axon branch projects to insulin-producing cells (IPCs) to trigger the release of *Drosophila* insulin-like peptide 2 (dilp2), and the other one extends to adipokinetic hormone (AKH)–producing cells to inhibit the secretion of AKH, fly's analog of glucagon. These axonal branches undergo synaptic remodeling in response to changes in their internal energy status. Silencing of *CN* neurons largely disabled IPCs' response to glucose and dilp2 secretion, and disinhibited AKH secretion in corpora cardiaca (CC), and caused hyperglycemia, a hallmark feature of diabetes mellitus. We propose that *CN* neurons maintain glucose homeostasis by promoting the secretion of dilp2 and suppressing the release of AKH when hemolymph glucose levels are high.

Glucose-sensing neurons respond to glucose or its metabolite that act as a signaling cue to regulate their neuronal activity. According to the glucostatic hypothesis proposed in 1953,

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Author contributions

Y.O. performed nearly all immunohistochemistry, calcium imaging, behavior testing, hemolymph glycemia measurement, statistical analyses, and figure design. J.S.L., H.J.M., and B.G. carried out a Gal4 screen using the two-choice assay. H.E.B and T.A.N conducted mass spectrometry to measure the dilp2 and AKH levels in hemolymph. K.S performed dot blot assay to measure the dilp2 and AKH levels in hemolymph. J.G.W. performed feeding assay and assisted in measuring hemolymph glycemia. F.A. assisted CaLexA experiment. G.S.B.S. supervised the project and provided intellectual support. Y.O. and G.S.B.S. wrote the manuscript with inputs from other authors.

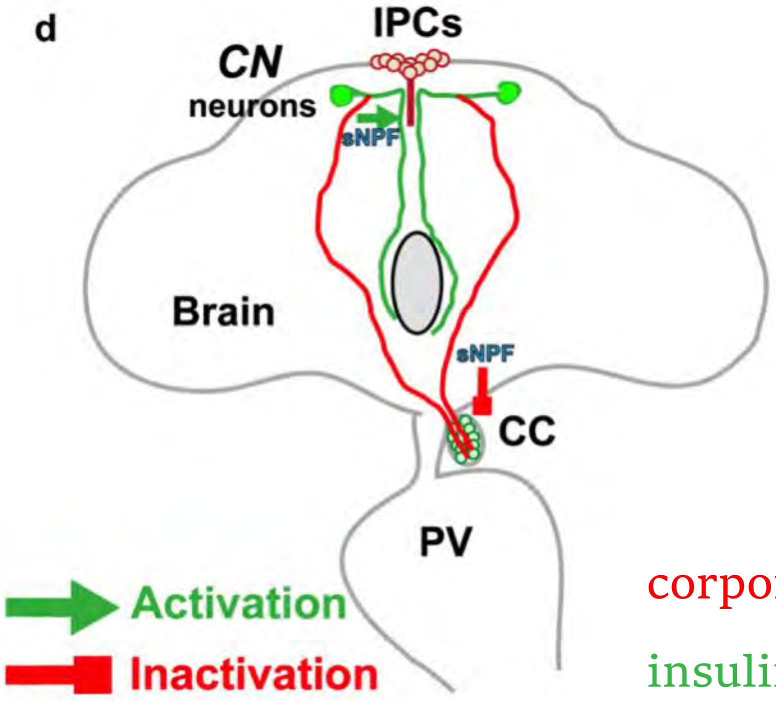
Competing interests

The authors declare no competing interests.

Data availability

Raw mass spectrometry files have been deposited in the MassIVE database (https://massive.ucsd.edu/ProteoSAFe/static/massive.jsp), with MassIVE accession ID: MSV000083796. All other raw data are available from the corresponding author on reasonable request.

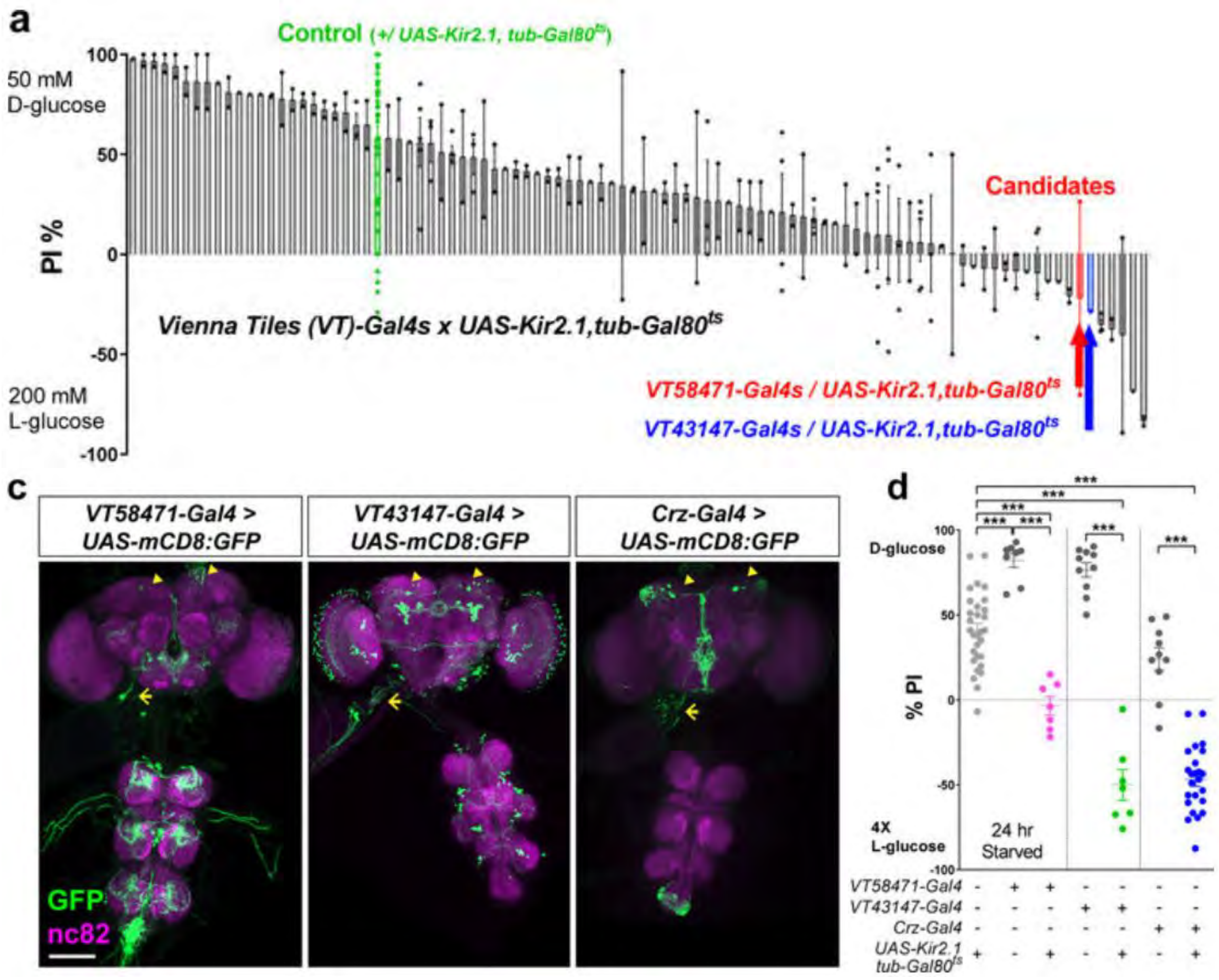
We report herein the discovery of a pair of glucose-excited neurons in the *Drosophila* brain that maintain glucose homeostasis by coordinating the activity of the two key hormones involved in that process: insulin and glucagon.



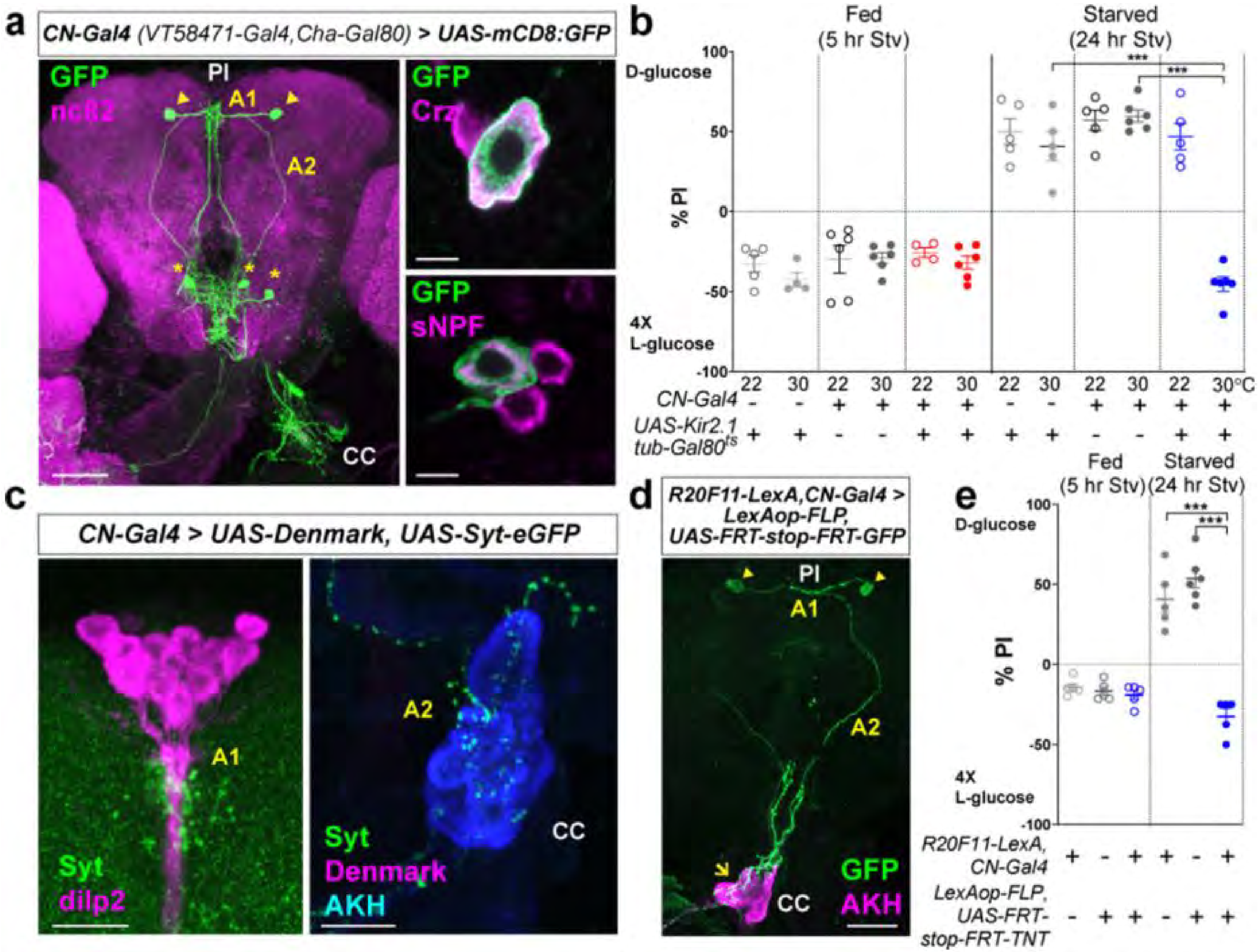
corpora cardiaca (CC)

insulin-producing cells (IPCs)

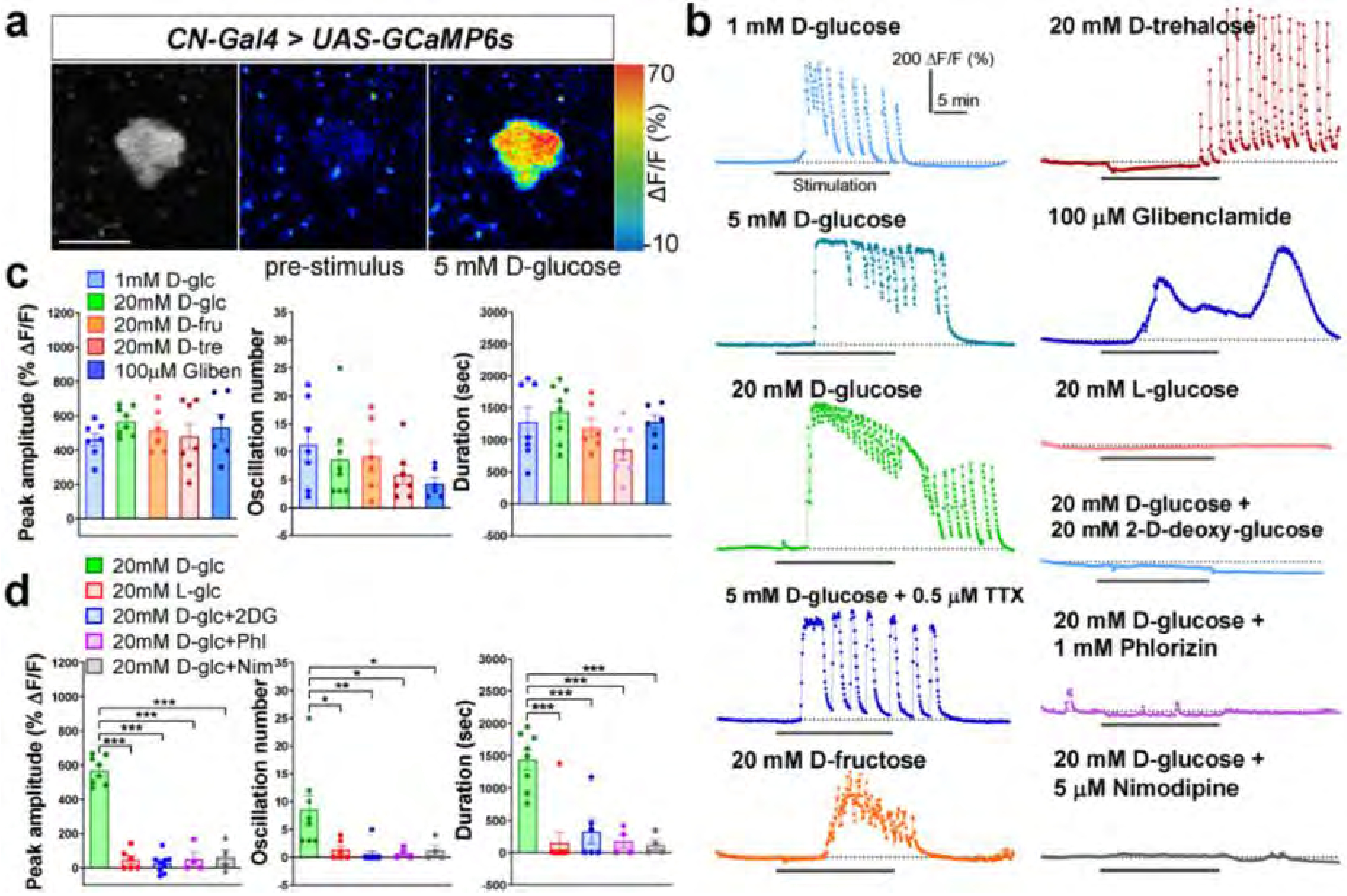
Identification of neurons that are required for the starvation-induced nutrient selection



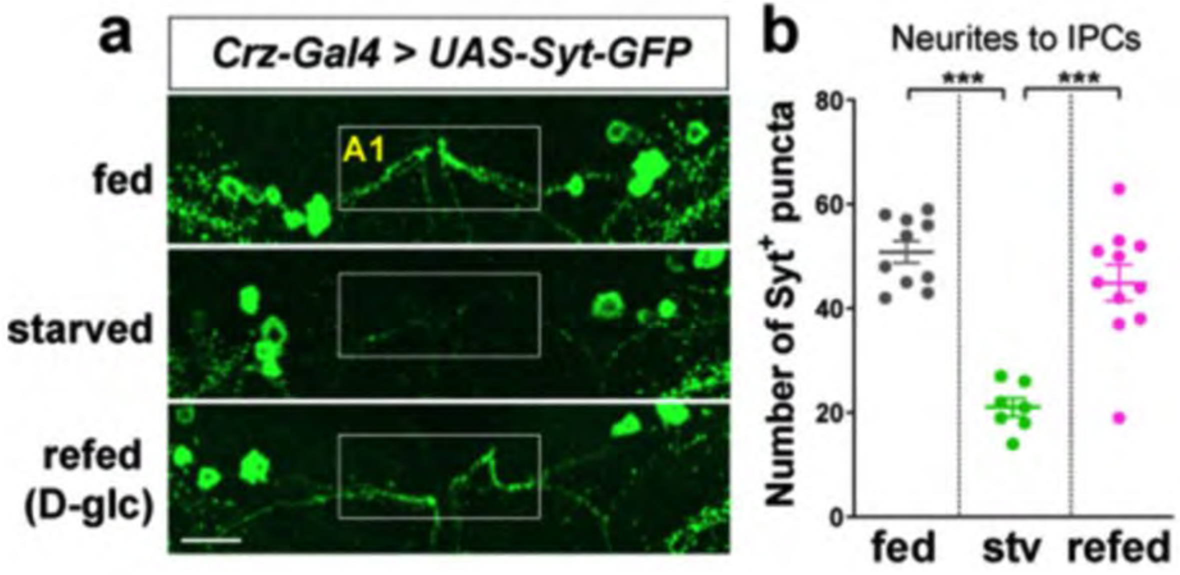
A pair of glucose-sensing neurons in the brain, CN neurons, show a unique projection pattern

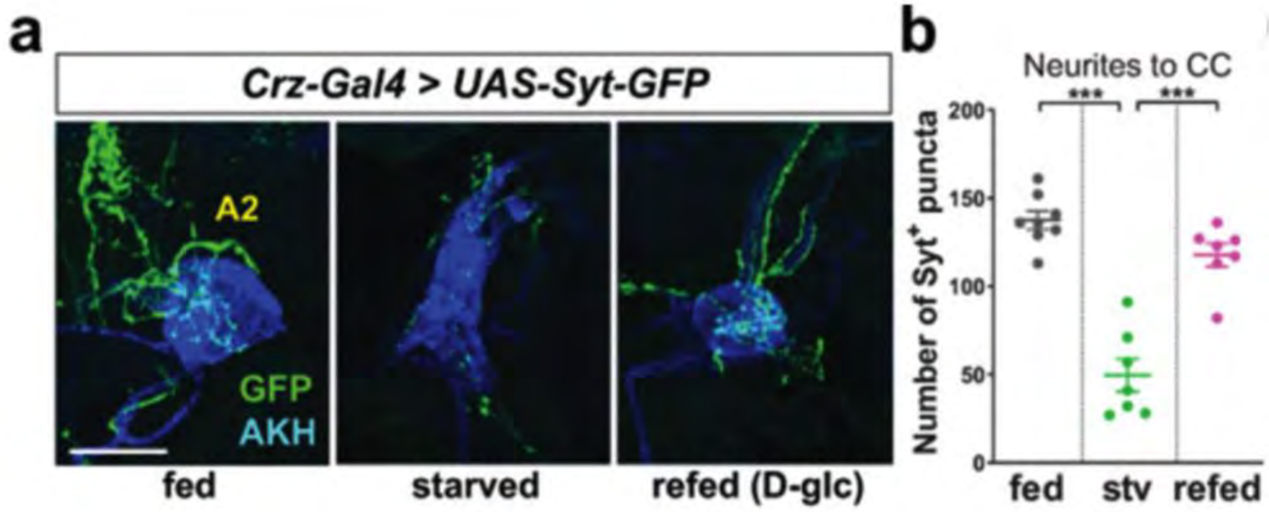


CN neurons are activated by nutritive sugars, but not by nonnutritive sugars

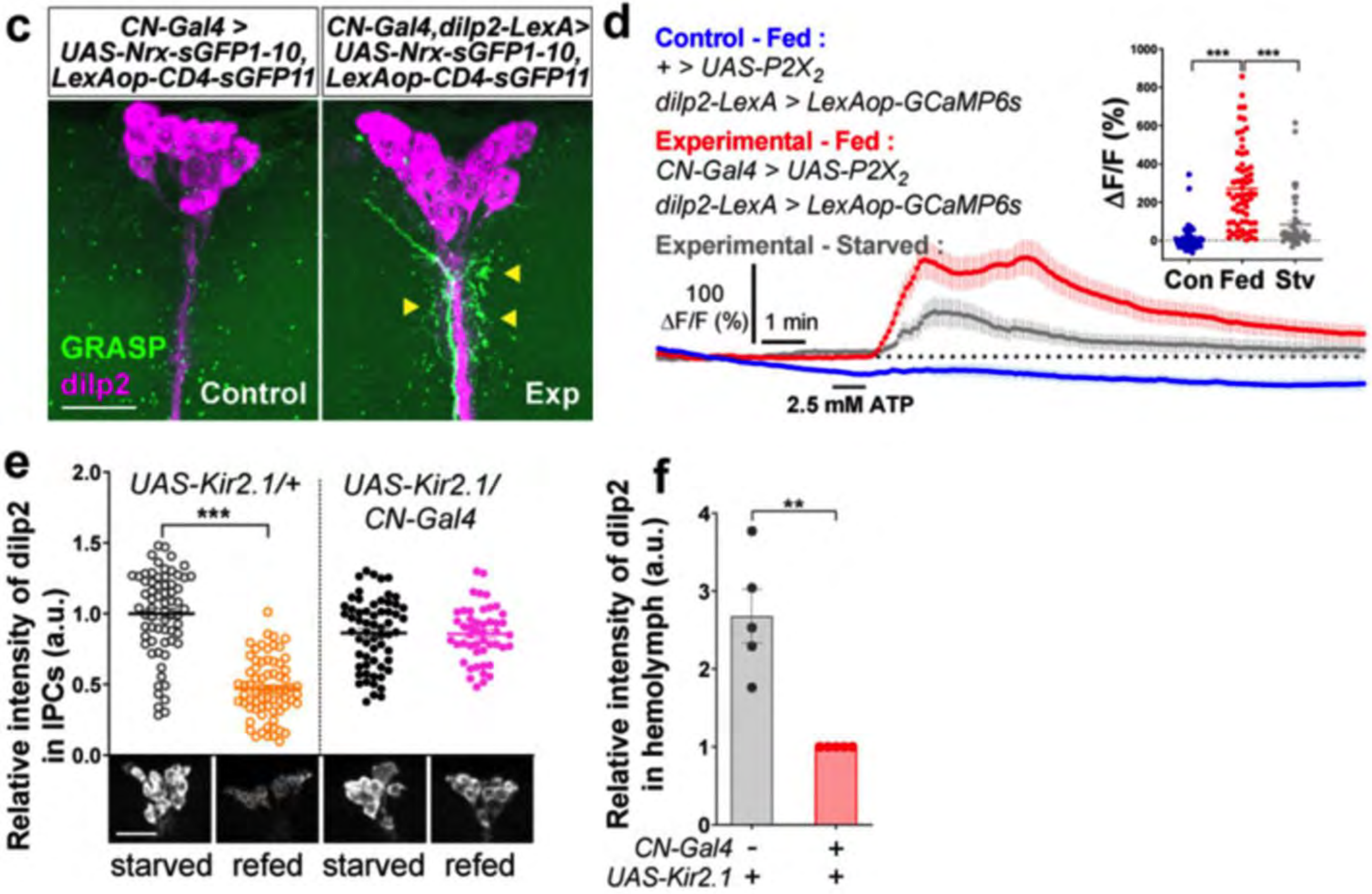


Nutrient-dependent plasticity occurs in axon 1 and axon 2 of the *CN* neurons

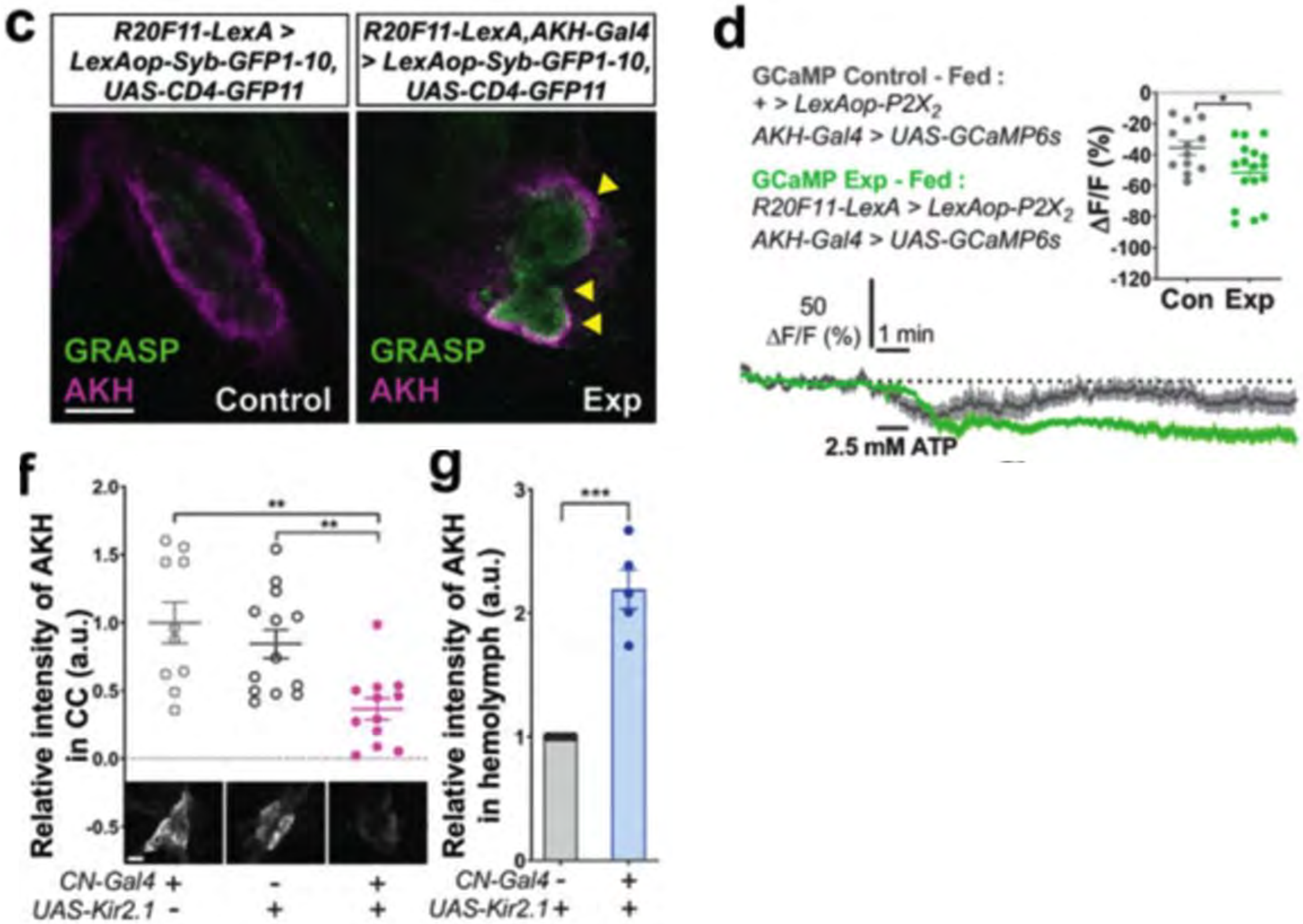




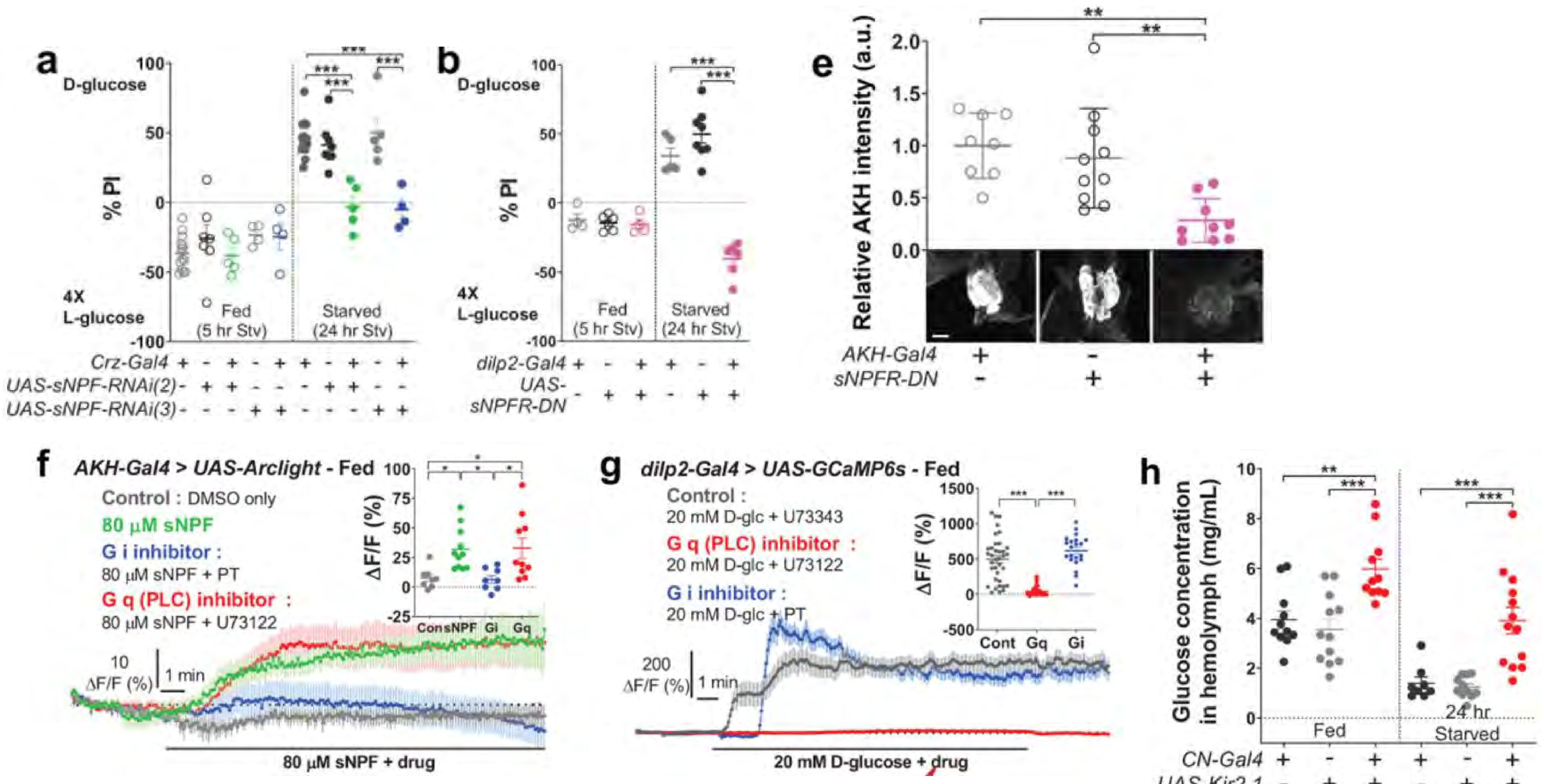
IPCs' activity and dilp2 secretion require an excitatory signal from *CN* neurons



AKH retention in AKH-producing cells requires an inhibitory signal from *CN* neurons



sNPF is the functional neurotransmitter of *CN* neurons



A glucose-sensing neuron pair regulates insulin and glucagon in *Drosophila*

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A glucose-sensing neuron pair regulates insulin and glucagon in *Drosophila*

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Summary

Although glucose-sensing neurons were discovered more than 50 years ago, the physiological role of glucose sensing in metazoans remains unclear. Here, we identify a pair of glucose-sensing neurons (dubbed *CN* neurons) in the *Drosophila* brain with bifurcating axons whereby one axon branch projects to insulin-producing cells (IPCs) to trigger the release of *Drosophila* insulin-like peptide 2 (dilp2), and the other one extends to adipokinetic hormone (AKH)–producing cells to inhibit the secretion of AKH, fly's analog of glucagon. These axonal branches undergo synaptic remodeling in response to changes in their internal energy status. Silencing of *CN* neurons largely disabled IPCs' response to glucose and dilp2 secretion, and disinhibited AKH secretion in corpora cardiaca (CC), and caused hyperglycemia, a hallmark feature of diabetes mellitus. We propose that *CN* neurons maintain glucose homeostasis by promoting the secretion of dilp2 and suppressing the release of AKH when hemolymph glucose levels are high.

Glucose-sensing neurons respond to glucose or its metabolite that act as a signaling cue to regulate their neuronal activity. According to the glucostatic hypothesis proposed in 1953,

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Author contributions
Y.O. performed nearly all immunohistochemistry, calcium imaging, behavior testing, hemolymph glycemia measurement, statistical analyses, and figure design. J.S.L., H.J.M., and B.G. carried out a Gal4 screen using the two-choice assay. H.E.B and T.A.N conducted mass spectrometry to measure the dilp2 and AKH levels in hemolymph. K.S performed dot blot assay to measure the dilp2 and AKH levels in hemolymph. J.G.W. performed feeding assay and assisted in measuring hemolymph glycemia. F.A. assisted CaLexA experiment. G.S.B.S. supervised the project and provided intellectual support. Y.O. and G.S.B.S. wrote the manuscript with inputs from other authors.

Competing interests
The authors declare no competing interests.

Data availability
Raw mass spectrometry files have been deposited in the MassIVE database (https://massive.ucsd.edu/ProteoSAFe/static/massive.jsp), with MassIVE accession ID: MSV000083796. All other raw data are available from the corresponding author on reasonable request.

Review:

本研究发现了位于果蝇大脑背外侧的一对葡萄糖感觉CN神经元，可以通过平衡体内产生胰岛素和胰高血糖素的细胞来维持葡萄糖稳态。它们的协调是在葡萄糖感觉神经元的直接控制下进行的。这种来自于单个细胞的营养依赖的可塑性变化，使得一些相反行为的精准调控成为了可能。

Thanks！