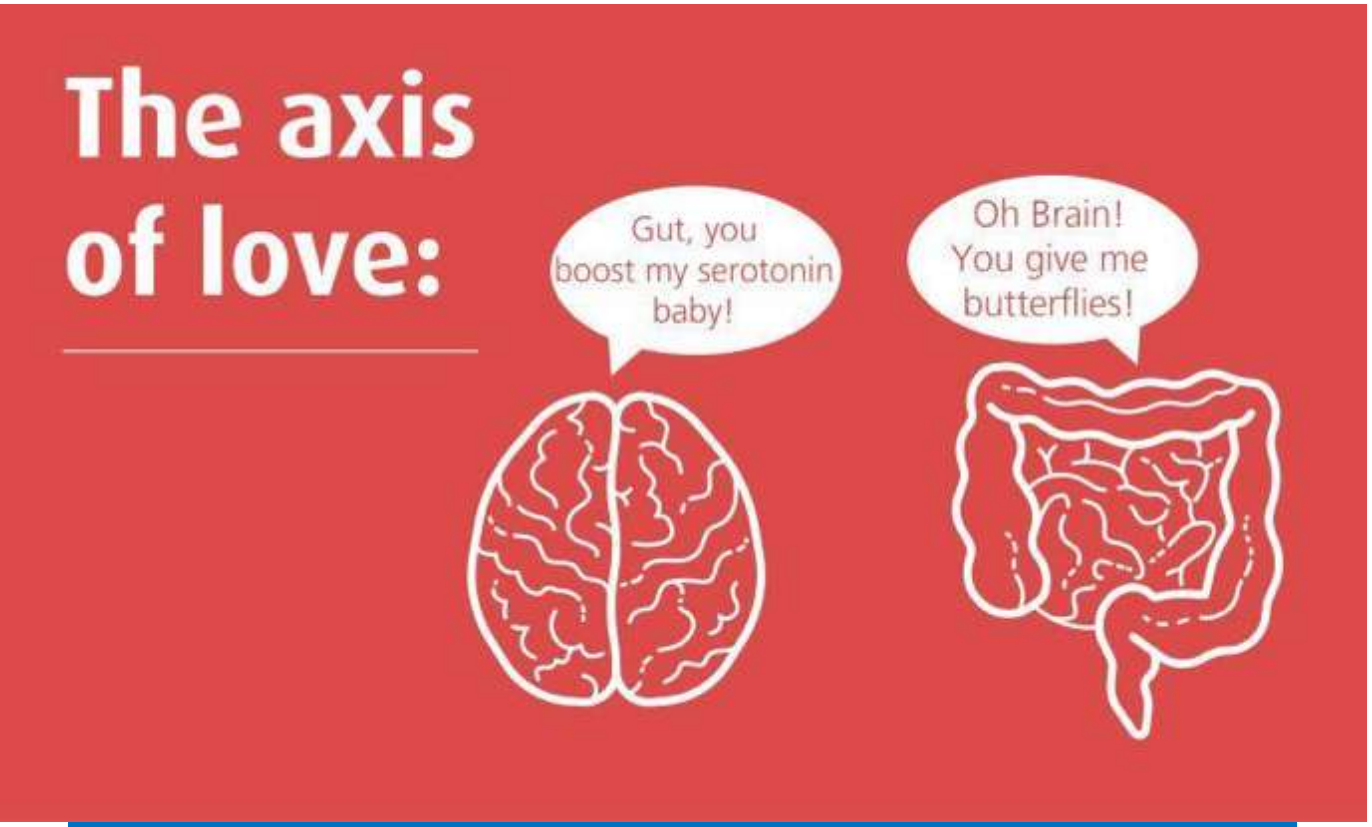


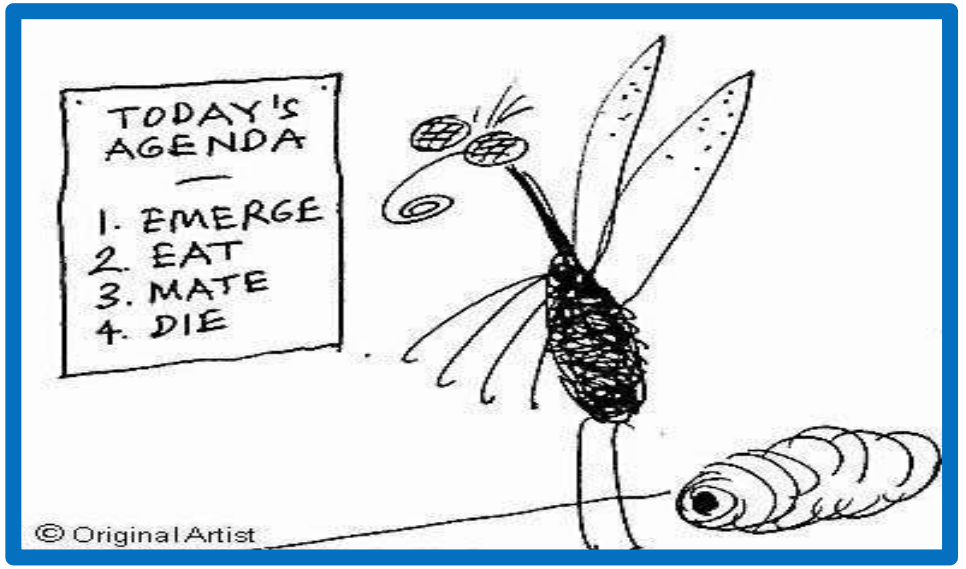
FOLLOW YOUR GUT

The bidirectional communication between brain and gut

2020-07-30

Content

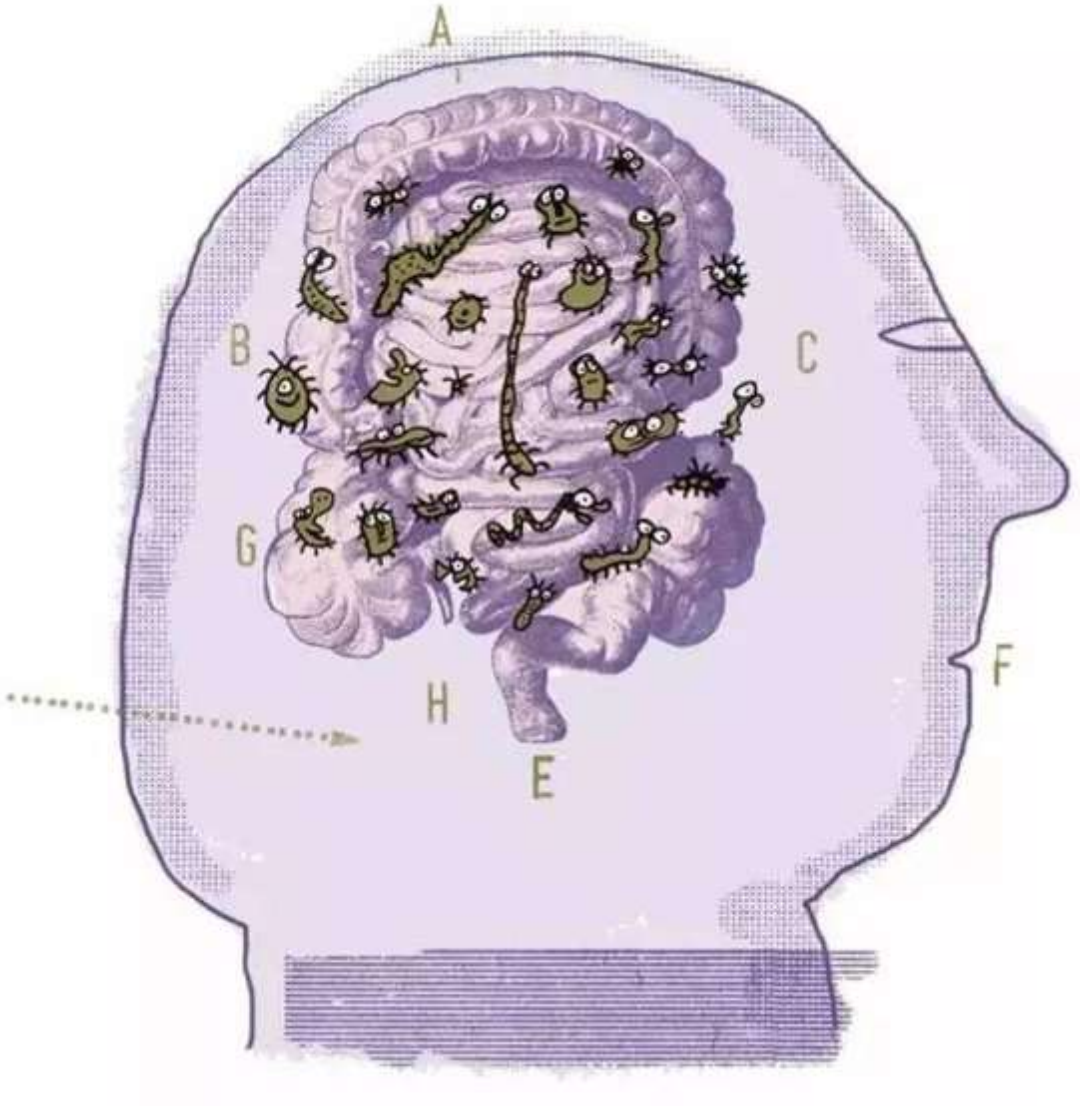
- The signal mechanism regulating Gut-Brain Axis
- The Gut-Brain regulation of behavior in mice
- Physiological function in Drosophila through Gut-Brain communication



Gut: The Second Brain

Gut-brain peptide

Nervous system



appetite

social

depression

aging

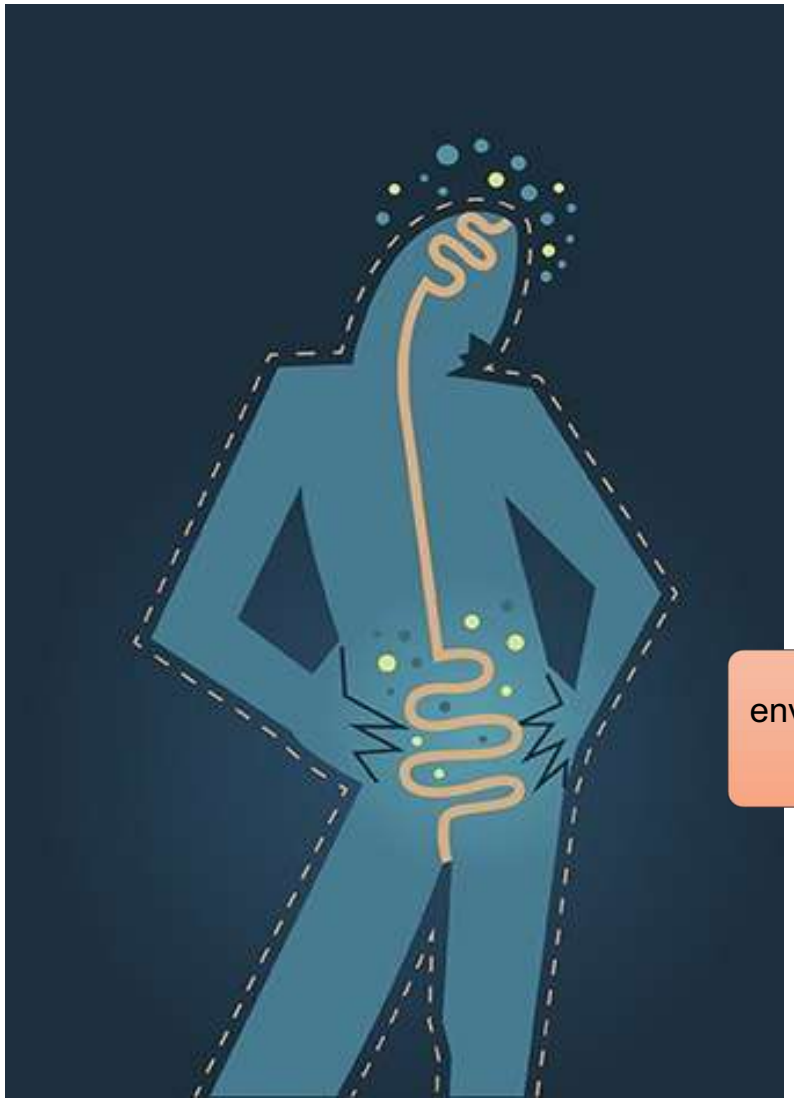
mice

The signal mechanism regulating Gut-Brain Axis

Germ-free mice

- ✓ germfree caesarean section
- ✓ germfree breeding technology
- ✓ fecal microbiota transplantation
- ✓ taking probiotics

Part 1



Top-down regulation:

- sympathetic nerve/ vagus nerve
- hypothalamic-pituitary-adrenal axis （ HPA axis ）
- neurotrophic factors

environmental stimulus → emotion → central nervous system → top-down effect → gut microbiota

brain → gut

Published in final edited form as:
Nature. 2016 July 21; 535(7612): 440–443. doi:10.1038/nature18644.

Glial cell-derived neuroregulators control type 3 innate lymphoid cells and gut defence

Sales Ibiza[#1], **Bethania García-Cassani**[#1], **Hélder Ribeiro**[1], **Tânia Carvalho**[1], **Luís Almeida**[1], **Rute Marques**[2,†], **Ana M. Misic**[3,‡], **Casey Bartow-McKenney**[3], **Denise M. Larson**[4], **William J. Pavan**[4], **Gérard Eberl**[2], **Elizabeth A. Grice**[3], and **Henrique Veiga-Fernandes**[1,5]

[1]Instituto de Medicina Molecular, Faculdade de Medicina de Lisboa, Av. Prof. Egas Moniz, Edifício Egas Moniz, 1649-028 Lisboa, Portugal

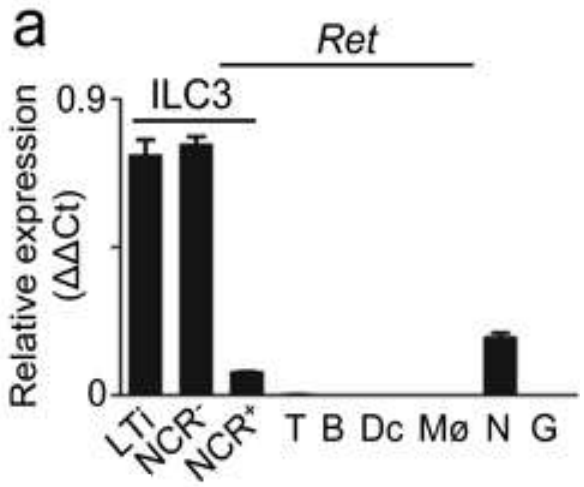
[2]Microenvironment and Immunity Unit, Institut Pasteur, 25 Rue du Docteur Roux, 75724 Paris, France

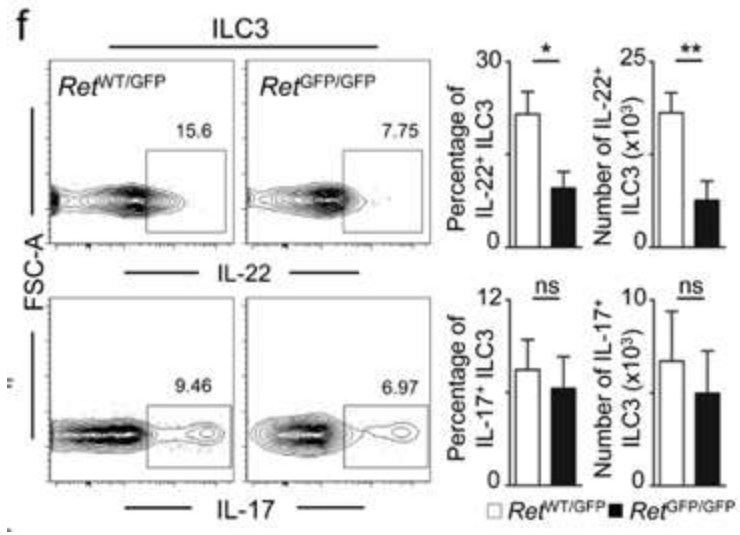
[3]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, 421 Curie Blvd, 1007 Biomedical Research Building, Philadelphia, PA 19104, US

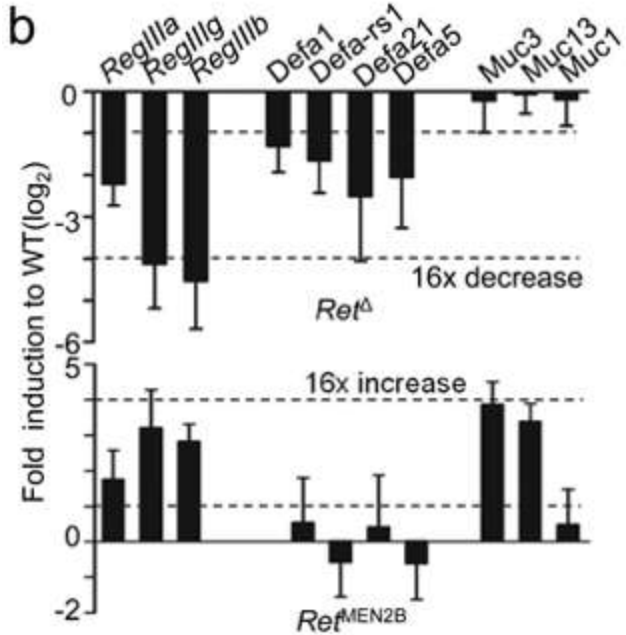
[4]Genetic Disease Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, US

[5]Champalimaud Research. Champalimaud Centre for the Unknown. 1400-038 Lisbon, Portugal

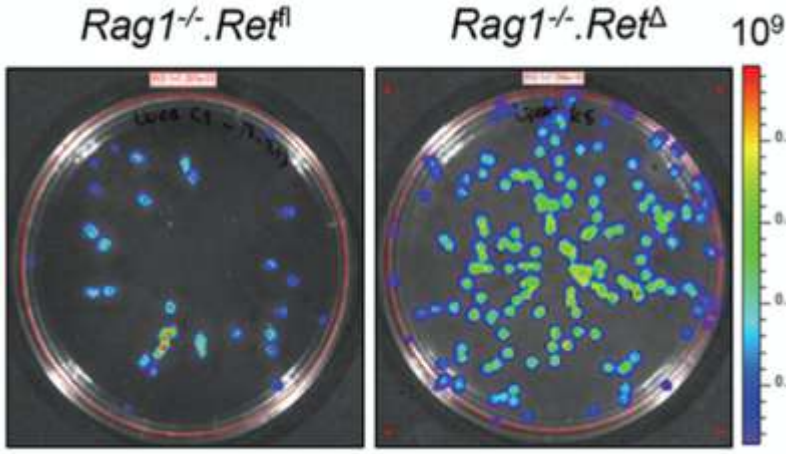
RET signals control innate IL-22 and regulate gut defense and homeostasis

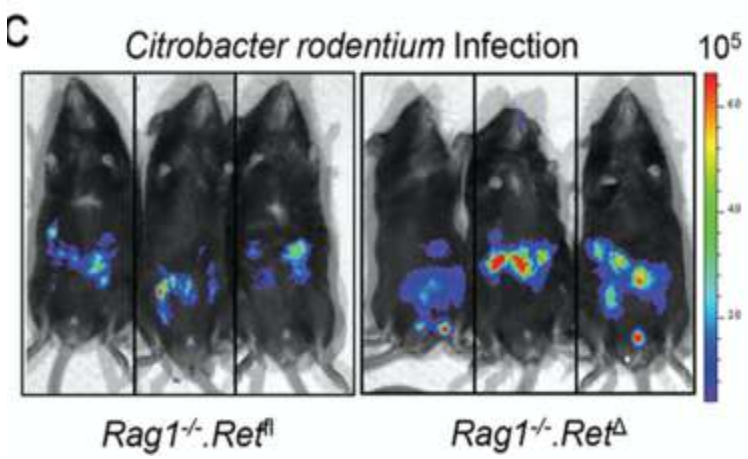


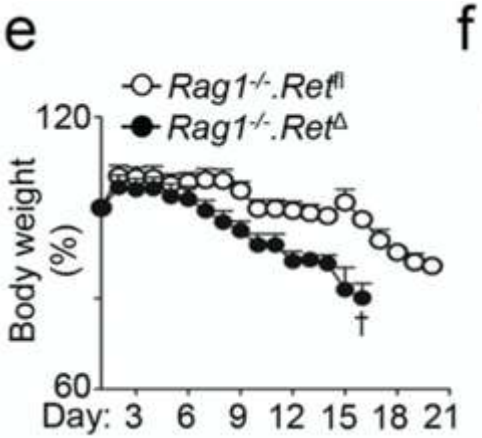


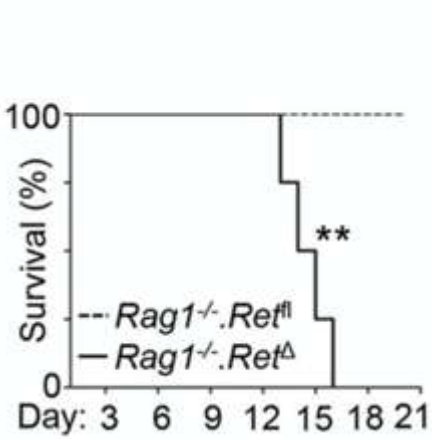


epithelial reactivity and repair genes



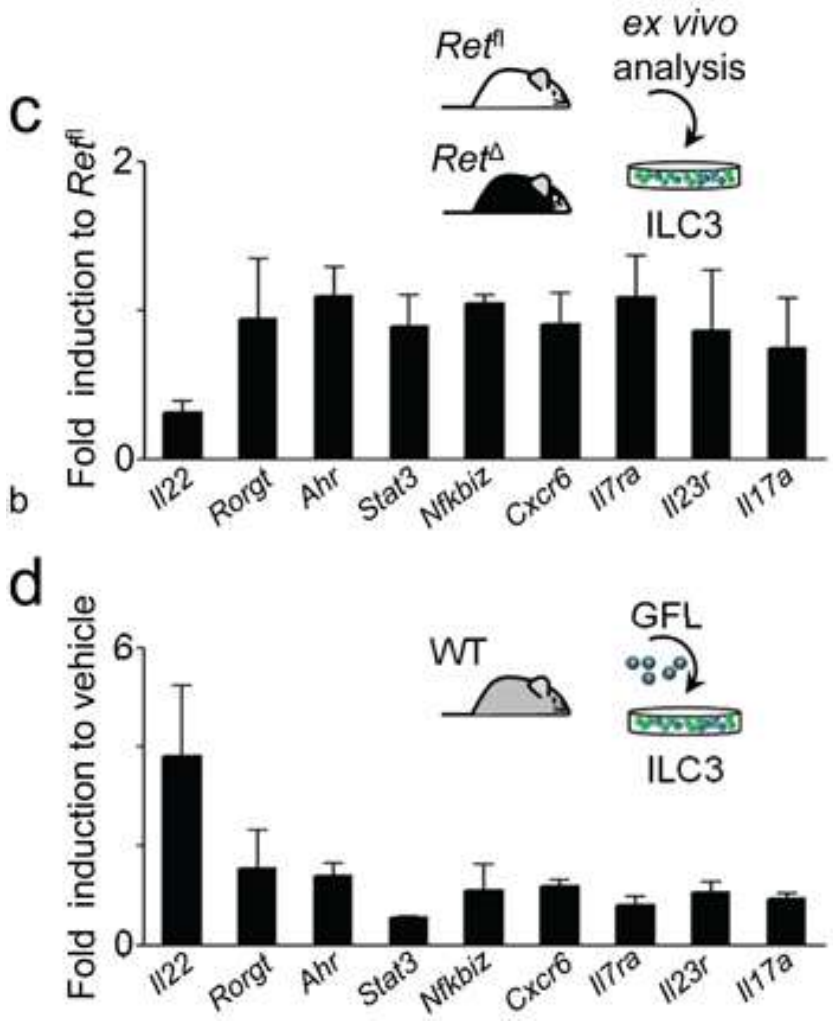


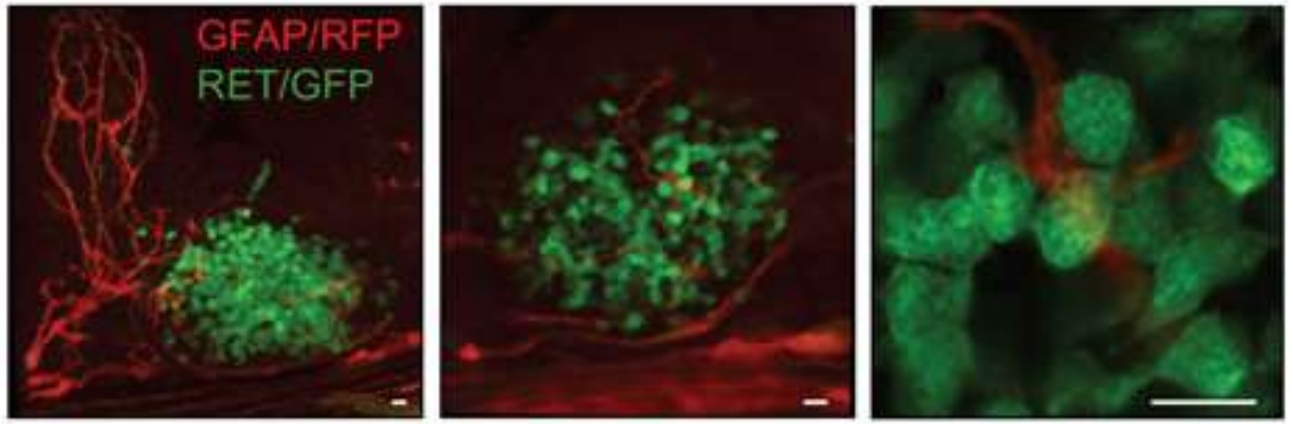


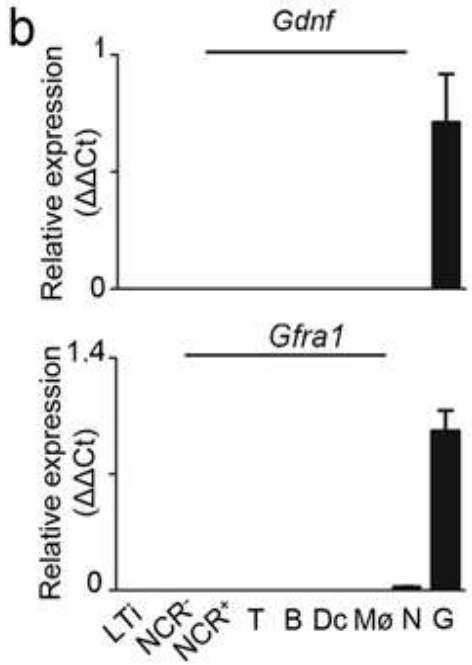


Ibiza s, et al. Nature.2016

Glial cells set GFL expression and innate IL-22







Ibiza s, et al. Nature.2016

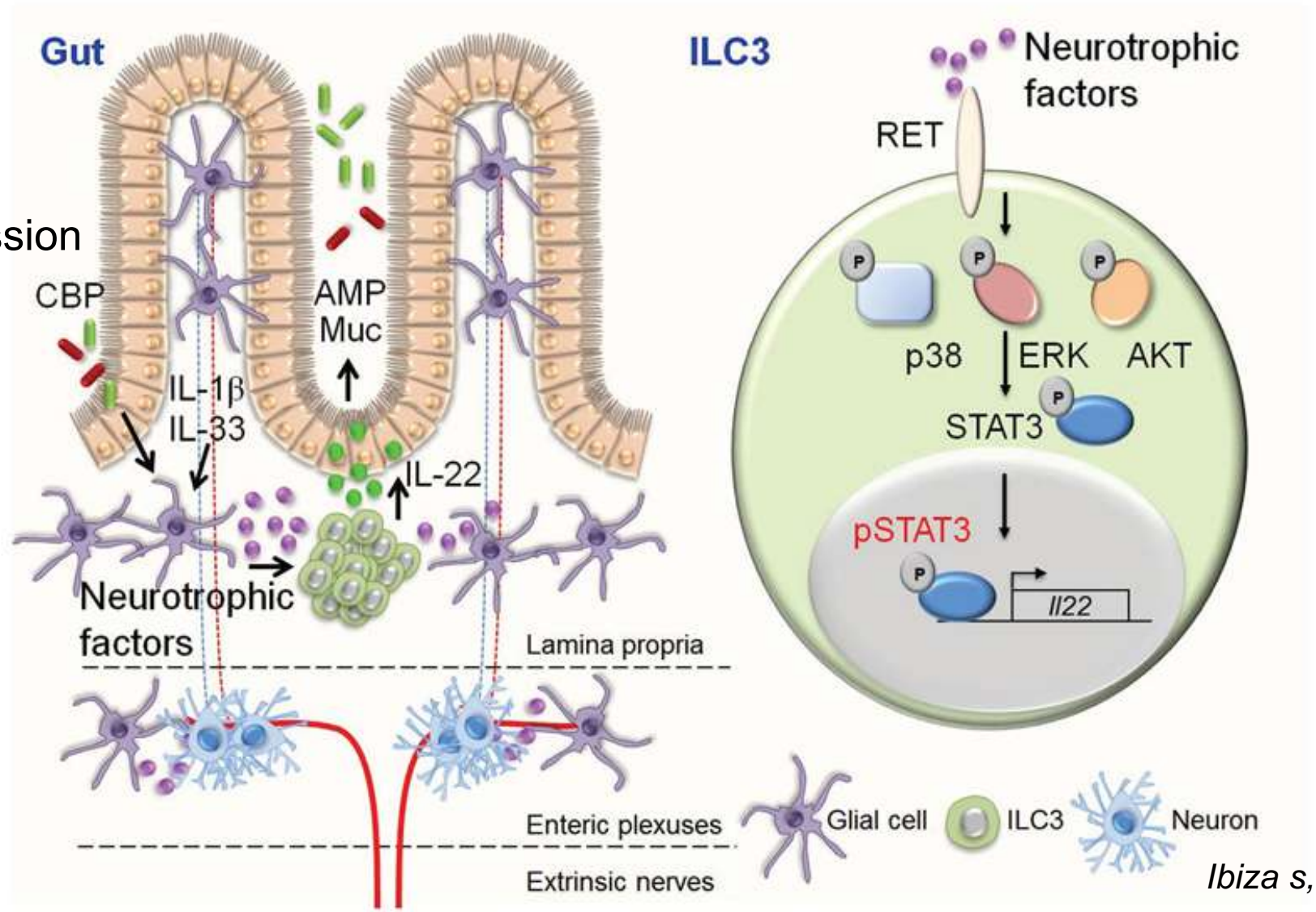
summary

A novel glial-ILC3-epithelial cell unit orchestrated by neurotrophic factors

reactivity gene expression

GDNF family

alarmin

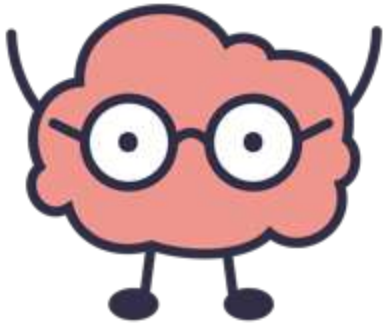


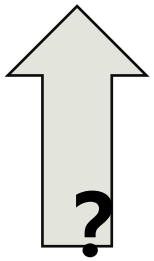
Ibiza s, et al. Nature.2016

Part 2

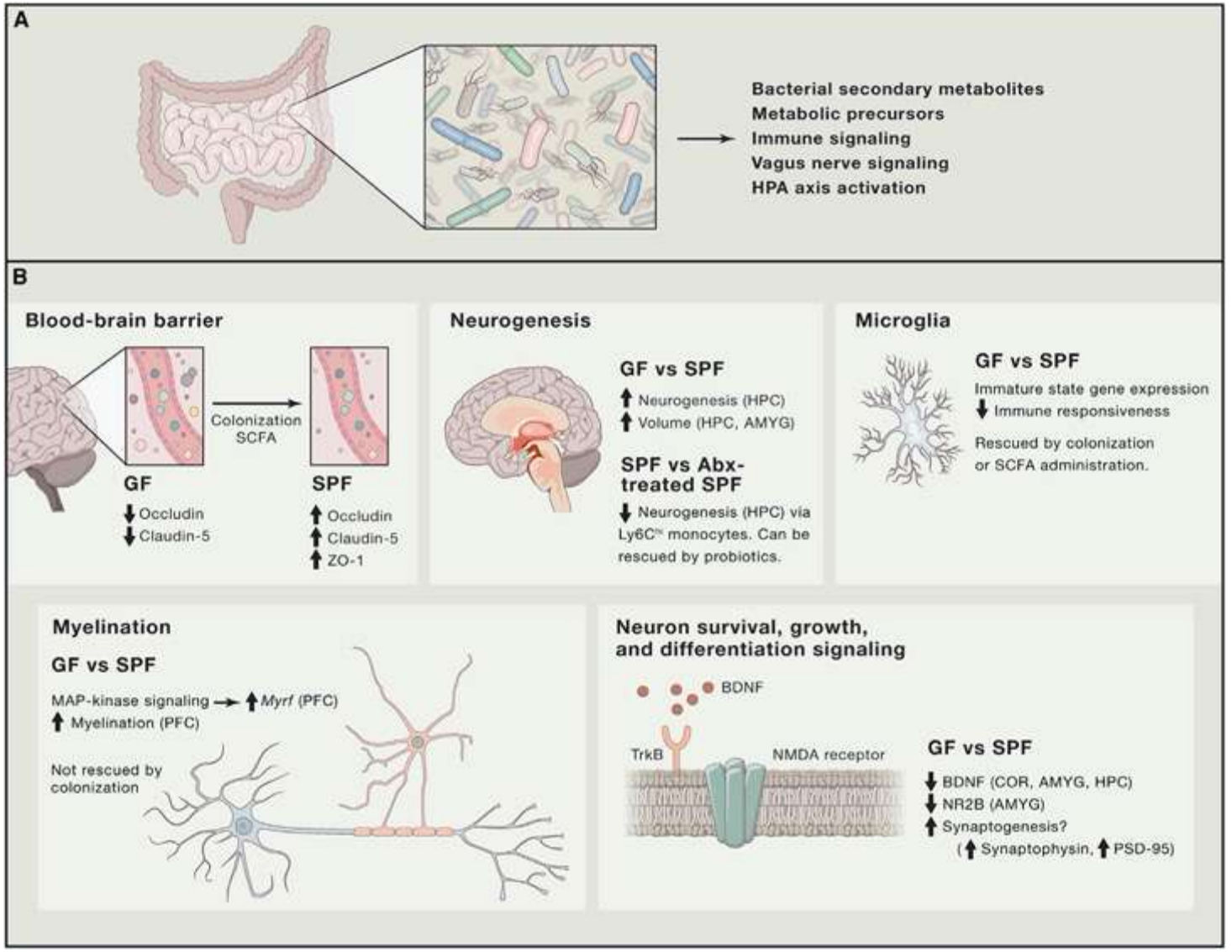
Down-top regulation

brain





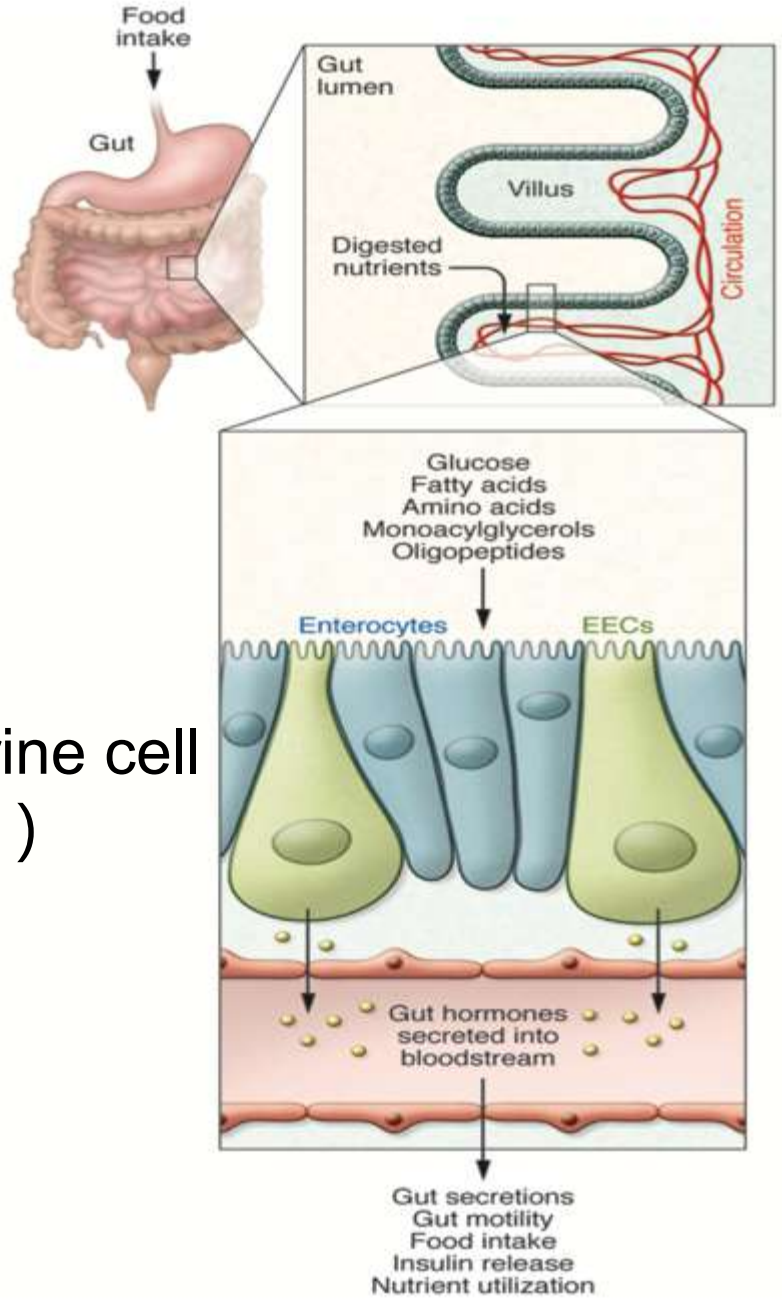
gut



Sharon G, et al. Cell. 2016

Part 2.1

enteroendocrine cell
(EEC)

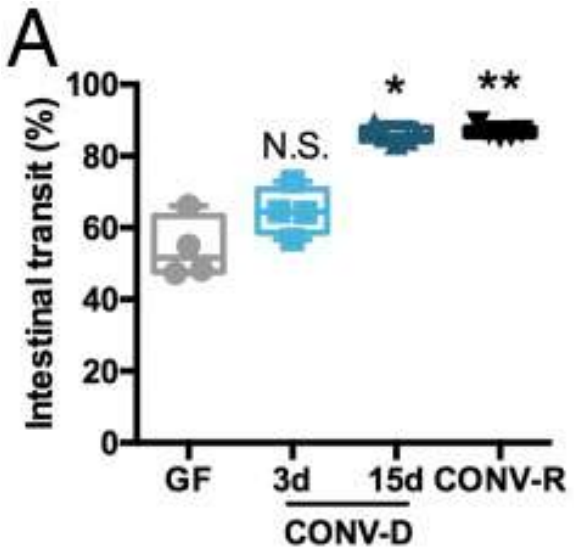


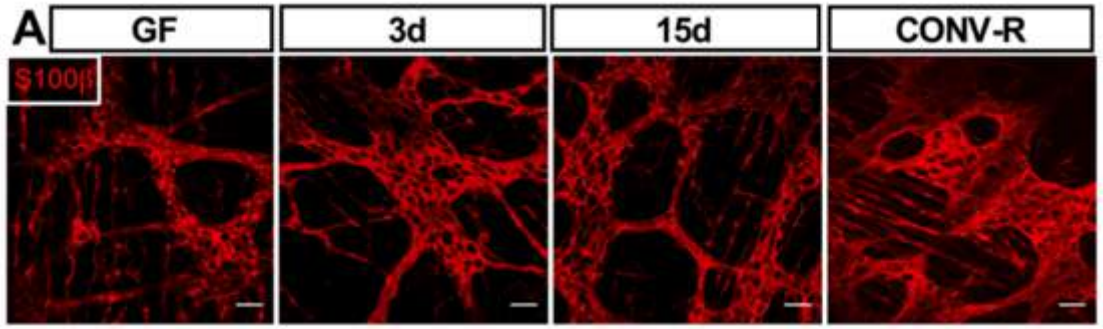
Gut hormones：

cholecystokinin (CCK)
glucagon-like peptide 1 (GLP1)
glucose-dependent insulinotropic peptide (GIP)
peptide YY (PYY)
somatostatin
ghrelin
serotonin (5-hydroxytryptamine [5-HT])
…

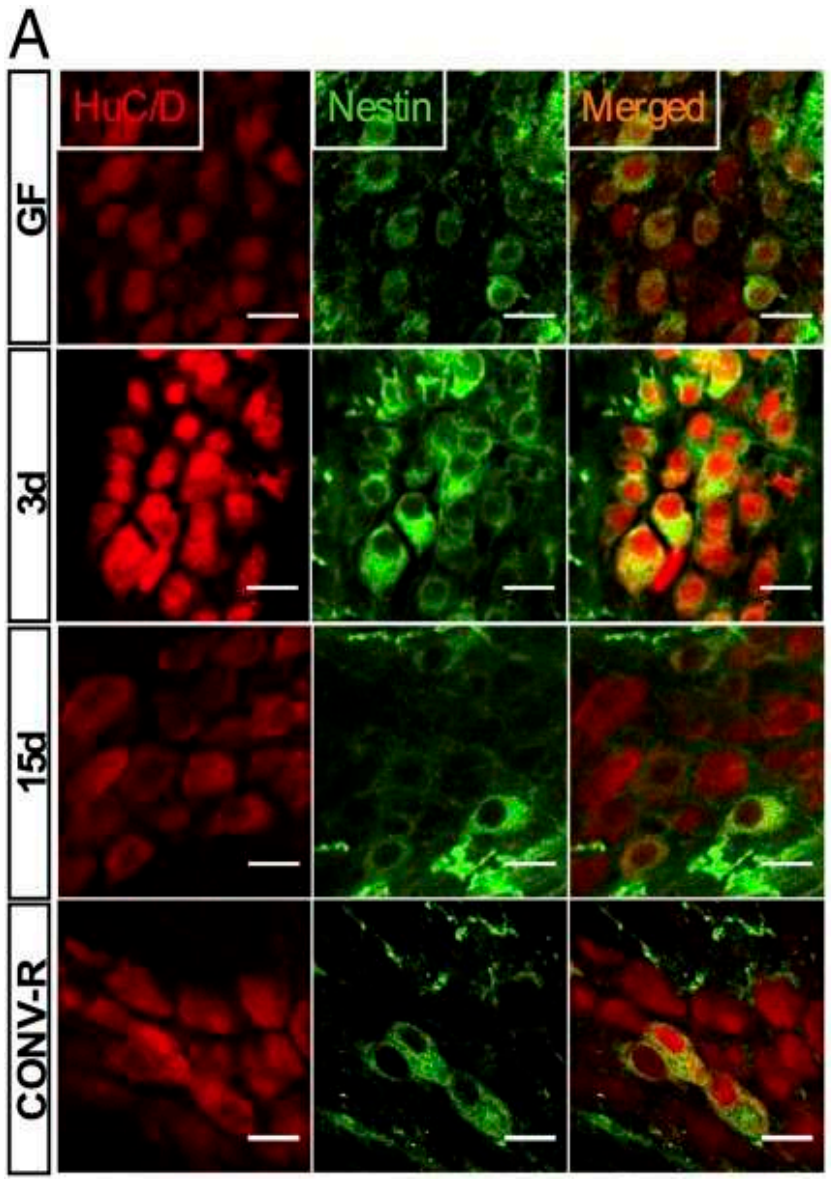
Psichas A and Reimann F, J Clin Invest. 2015

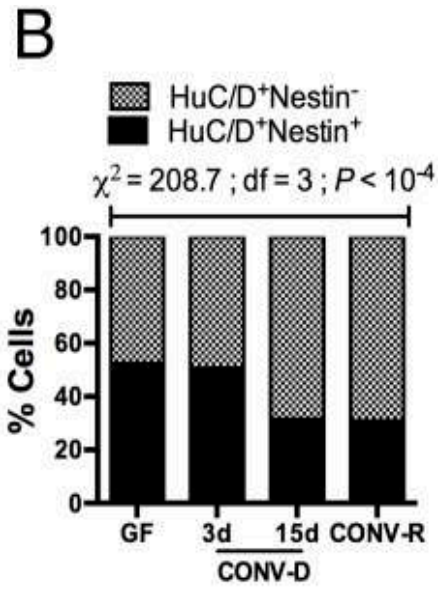
Colonization of GF mice with a gut microbiota induces maturation of neuronal precursors





the enteric glial network



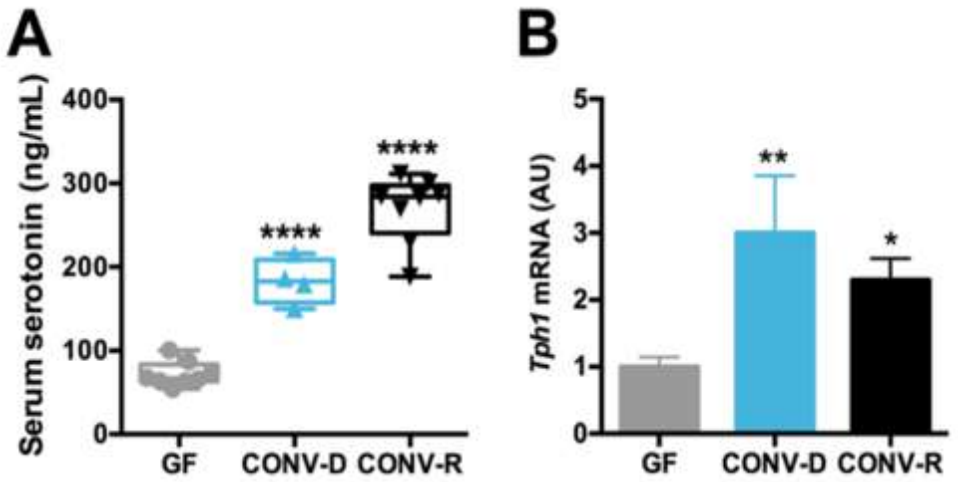


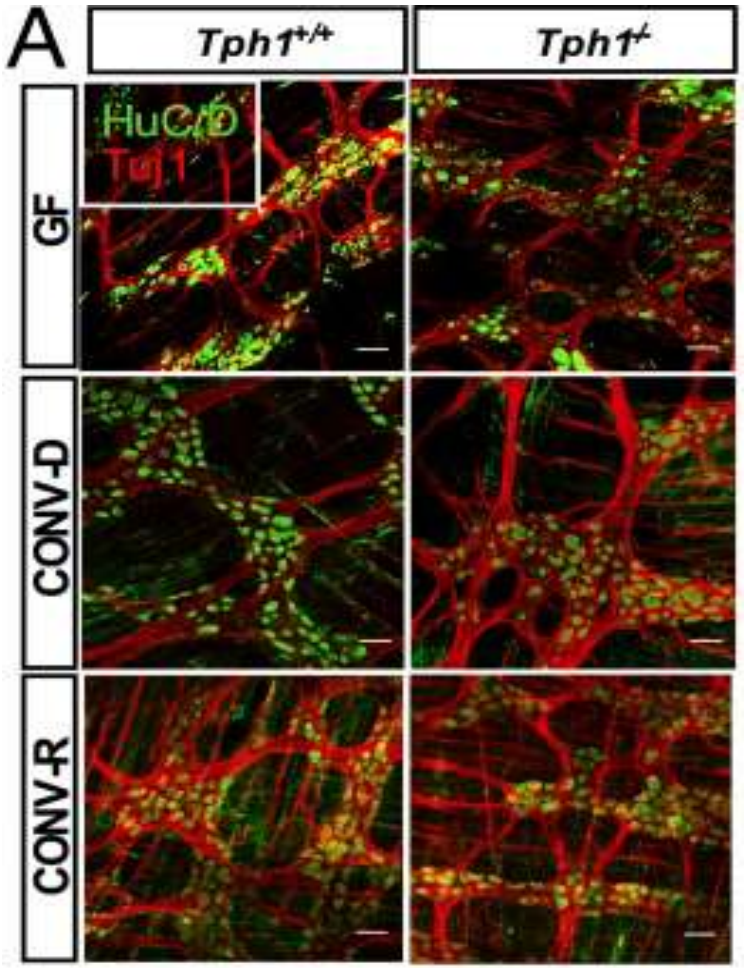
Nestin: a cytoskeletal protein that is expressed by a variety of neural stem cells ,

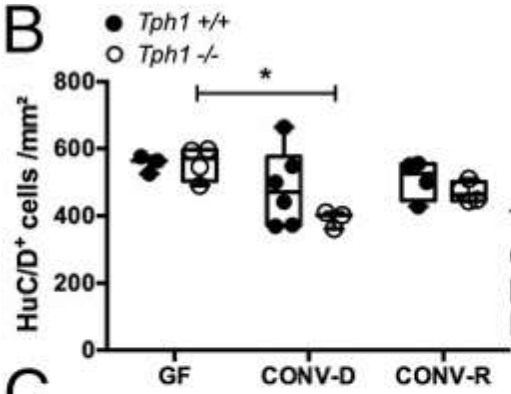
coexpression of Nestin and HuC/D: a signature of neuronal plasticity in the adult ENS

Vadder FD et al. PNAS.2018

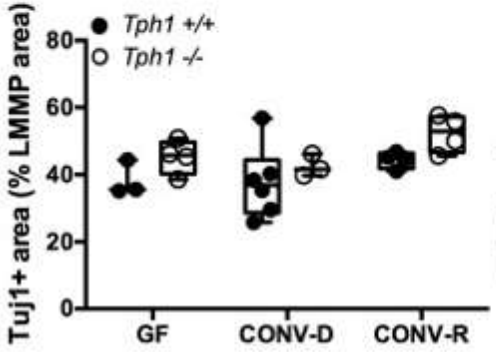
microbiota-induced release of mucosal 5-HT is neuroprotective for the ENS







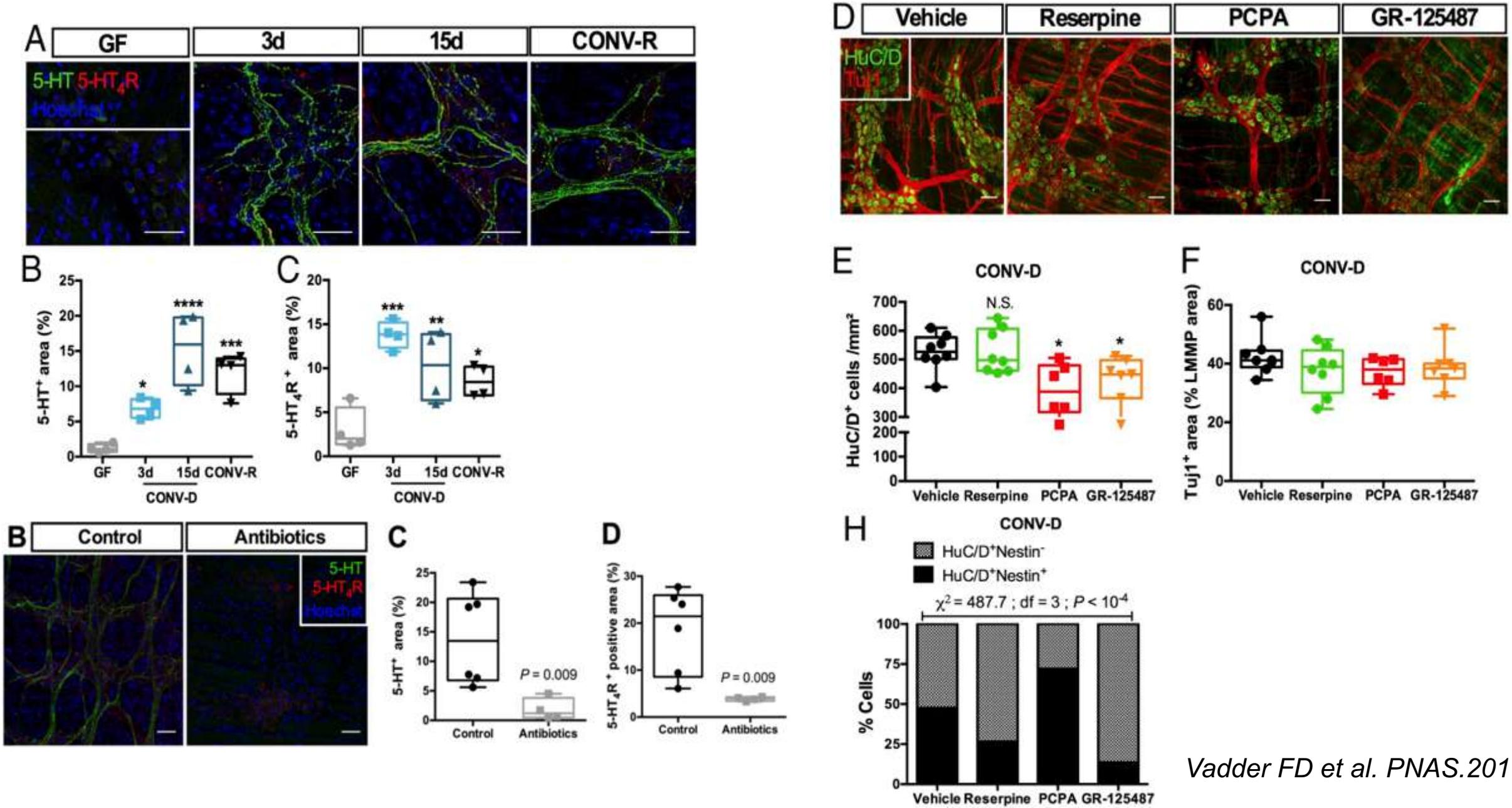
Two-way ANOVA
Genotype: *NS*
Microbiota: $P < 0.05$
Interaction: *NS*



Two-way ANOVA
Genotype: $P < 0.05$
Microbiota: *NS*
Interaction: *NS*

Vadder FD et al. PNAS.2018

The gut microbiota regulates neuronal 5-HT release

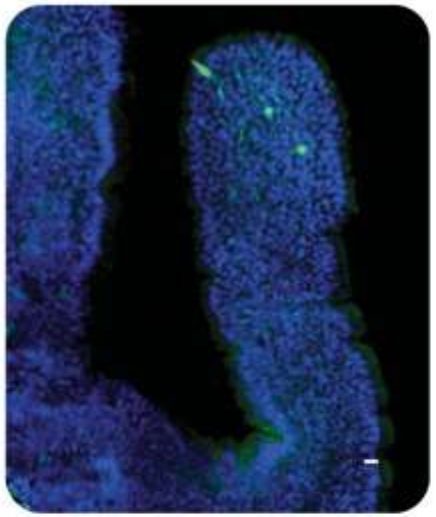


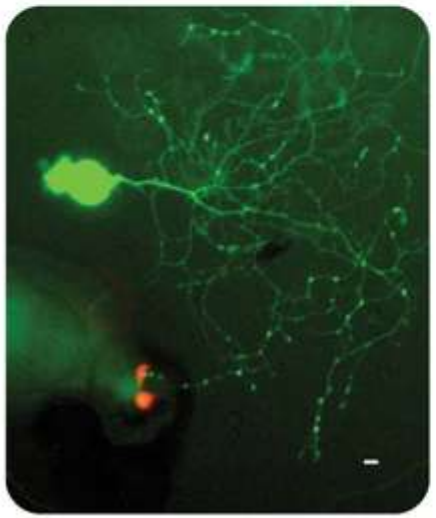
Vadder FD et al. PNAS.2018

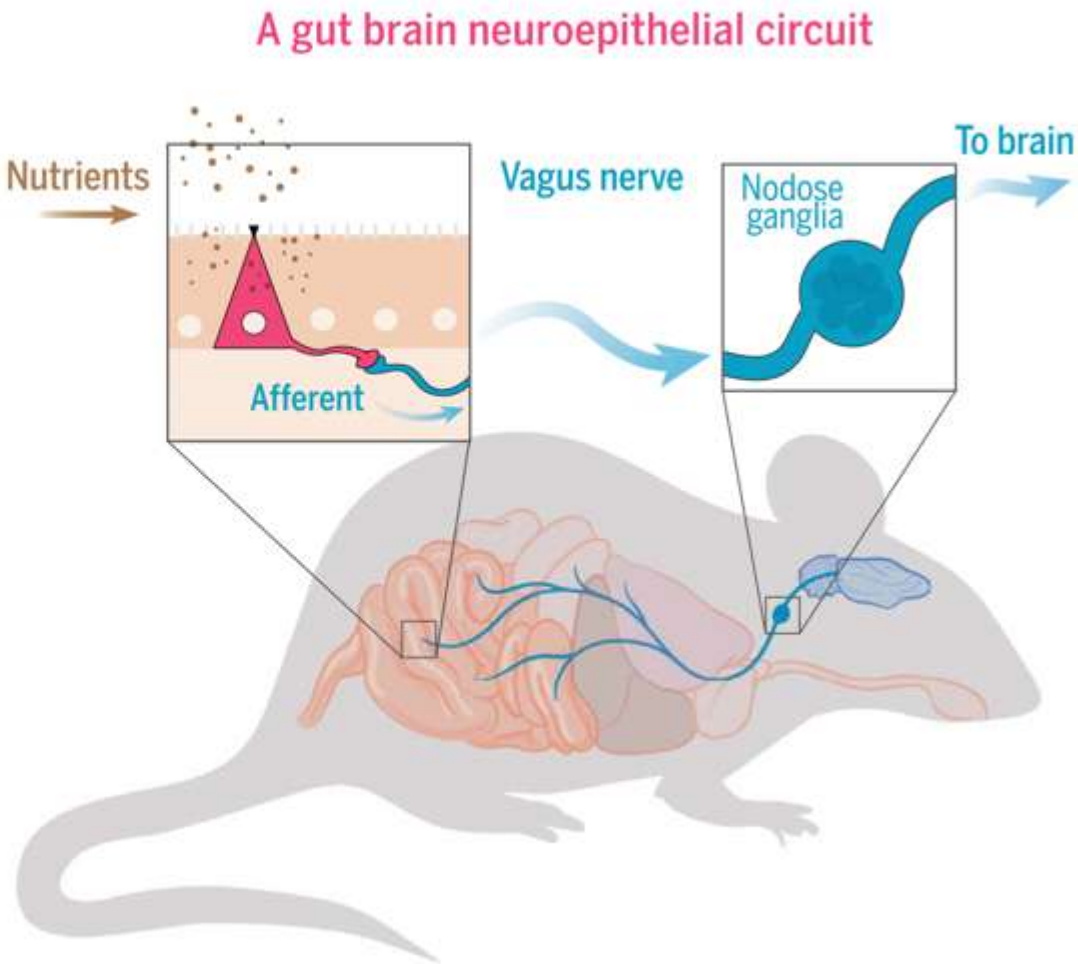
summary

- 90% of the body’s serotonin (5-hydroxytryptamine, 5-HT) is produced by enterochromaffin (EC) cells.
- The gut microbiota stimulates neuronal and mucosal 5-HT in GF mice leads to differentiation and maturation of enteric neurons.
- GABA、BNDF、dopamine、adrenaline

Part 2.2

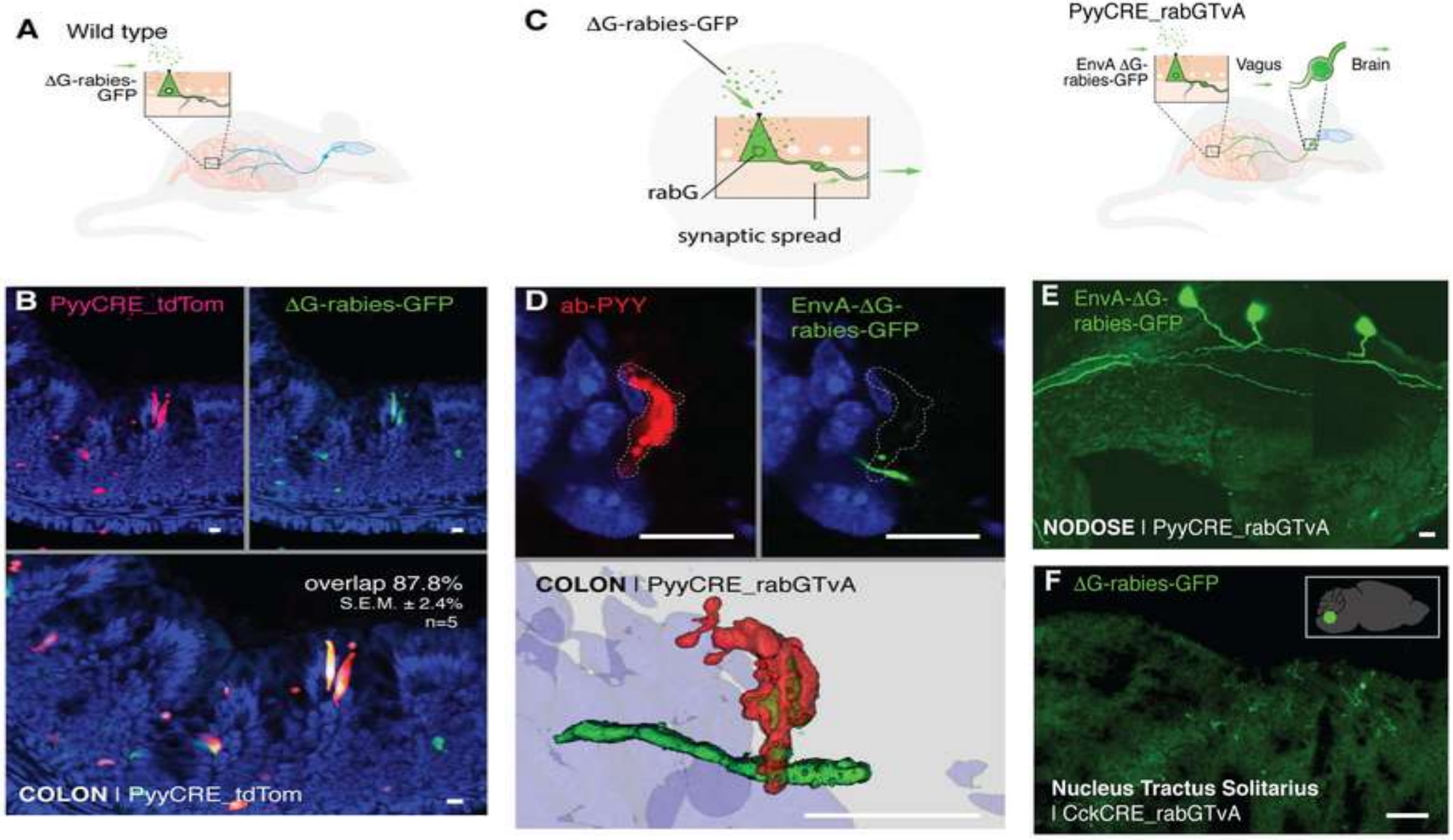




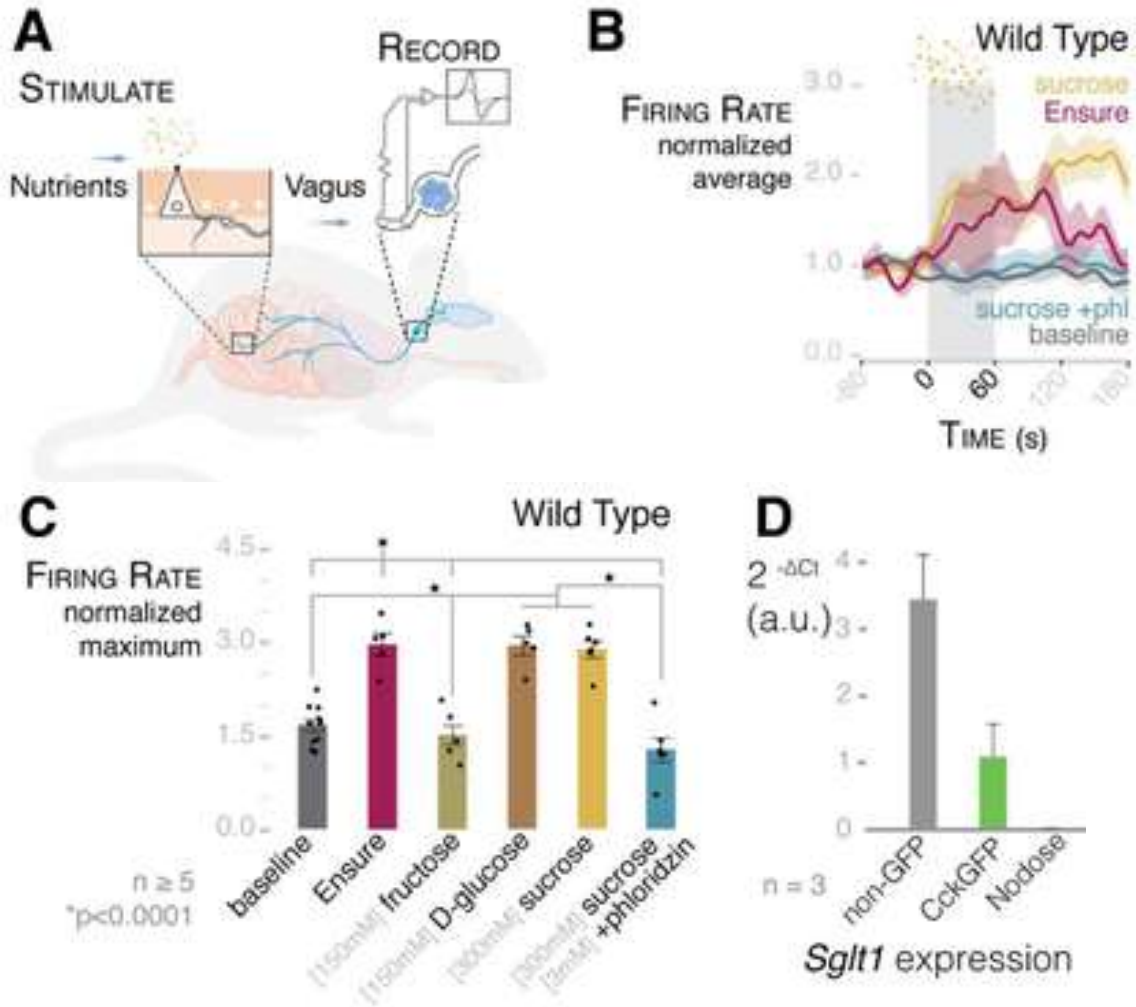


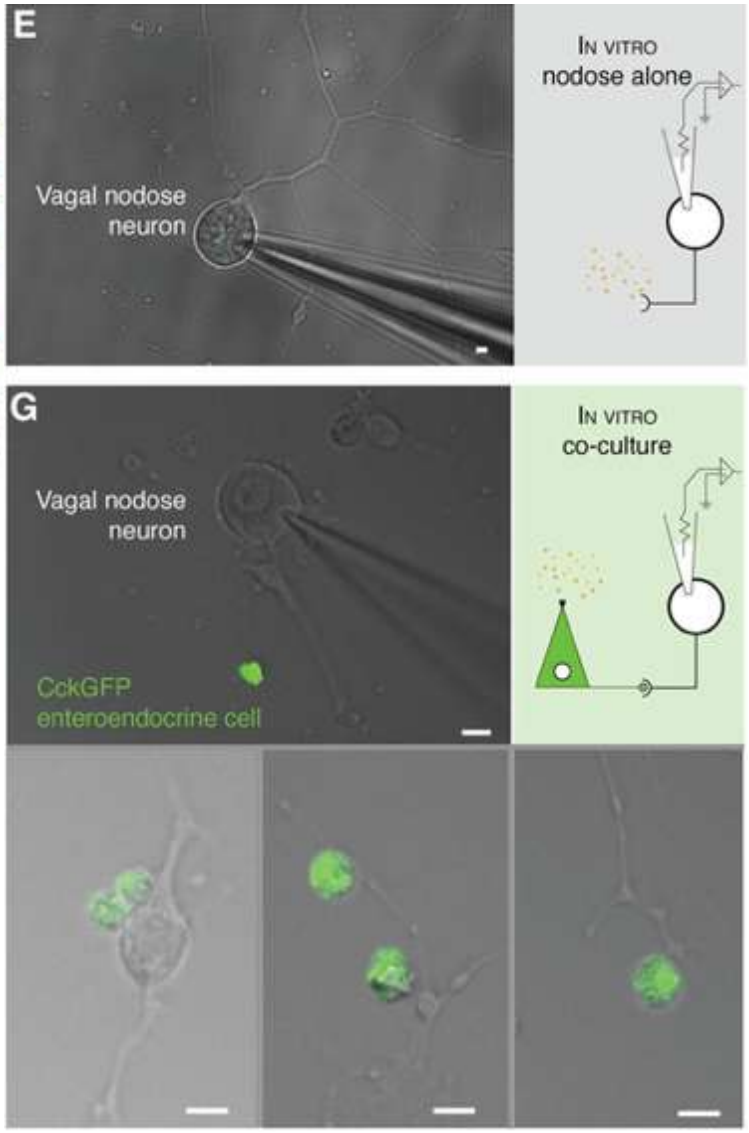
Kaelberer et al., Science.2018

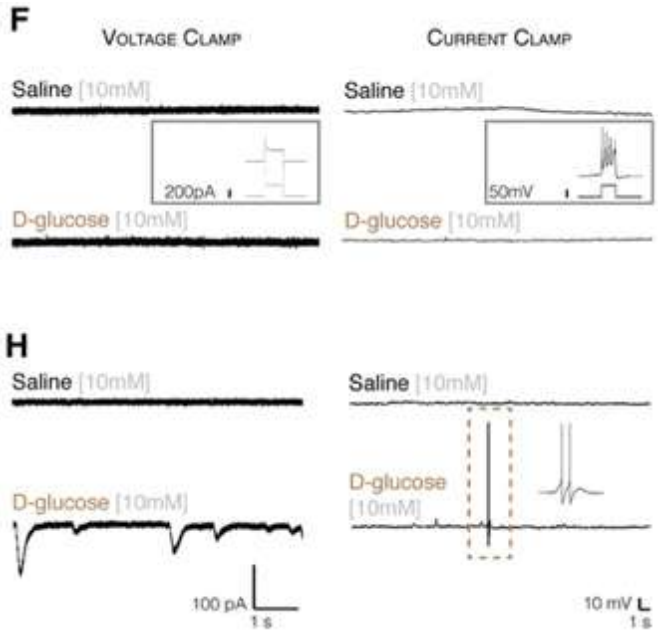
Enteroendocrine cells of the colon synapses with vagal nodose neurons



Enteroendocrine cells transduce glucose stimuli onto vagal neurons



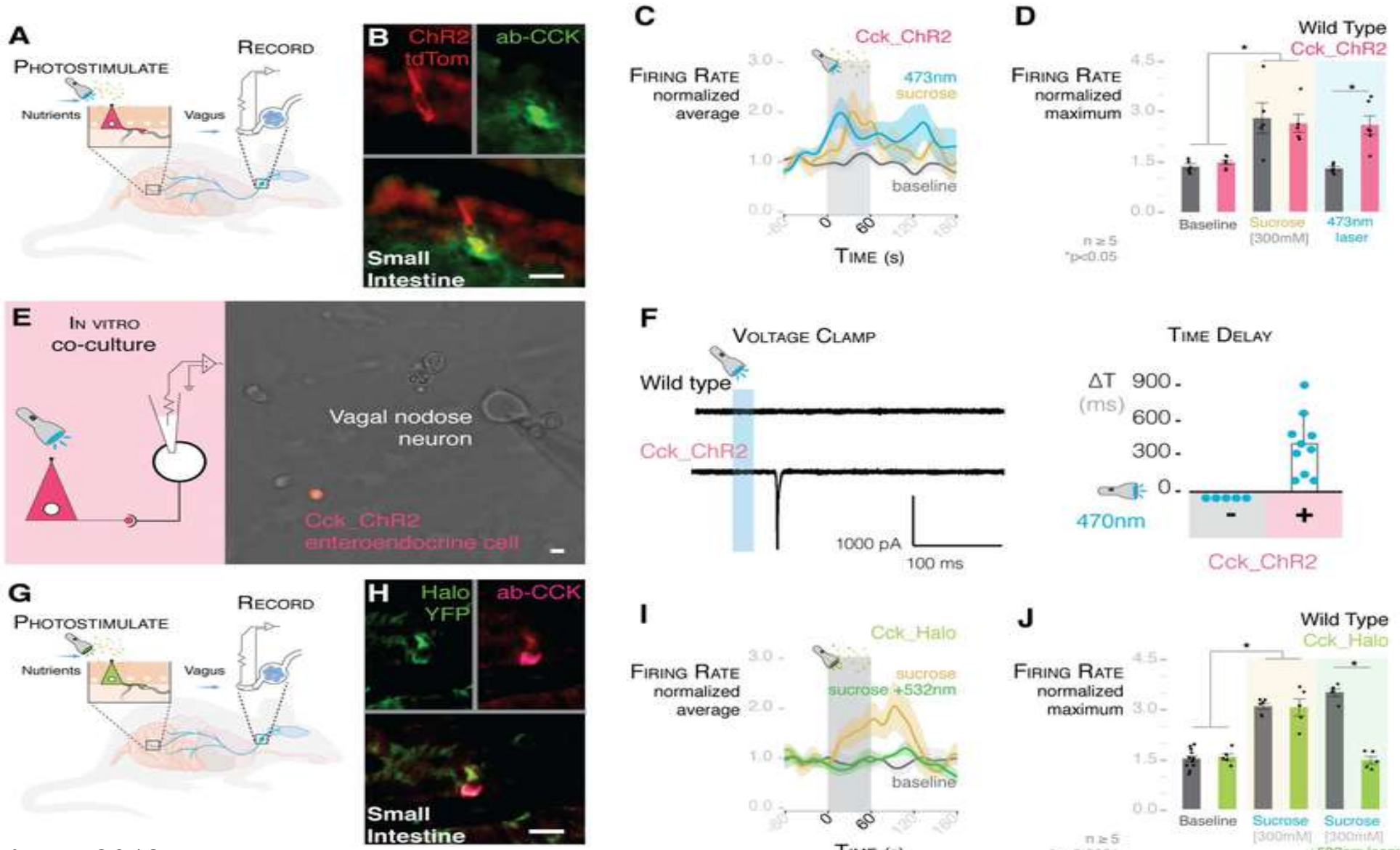




electrogenic glucose transporter SGLT1

Kaelberer et al., Science.2018

Enteroendocrine cells transduce a stimulus onto vagal neurons within milliseconds



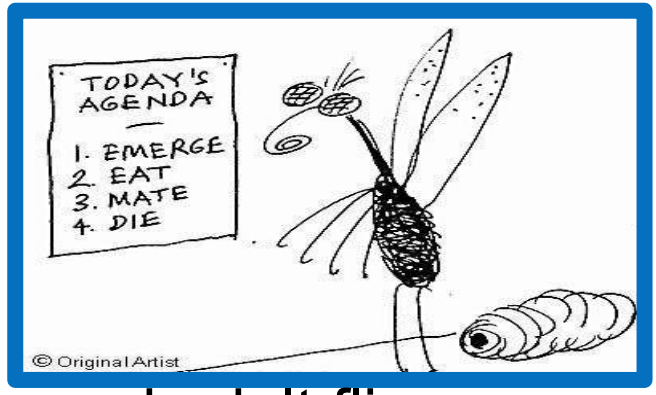
Kaelberer et al., Science.2018

summary

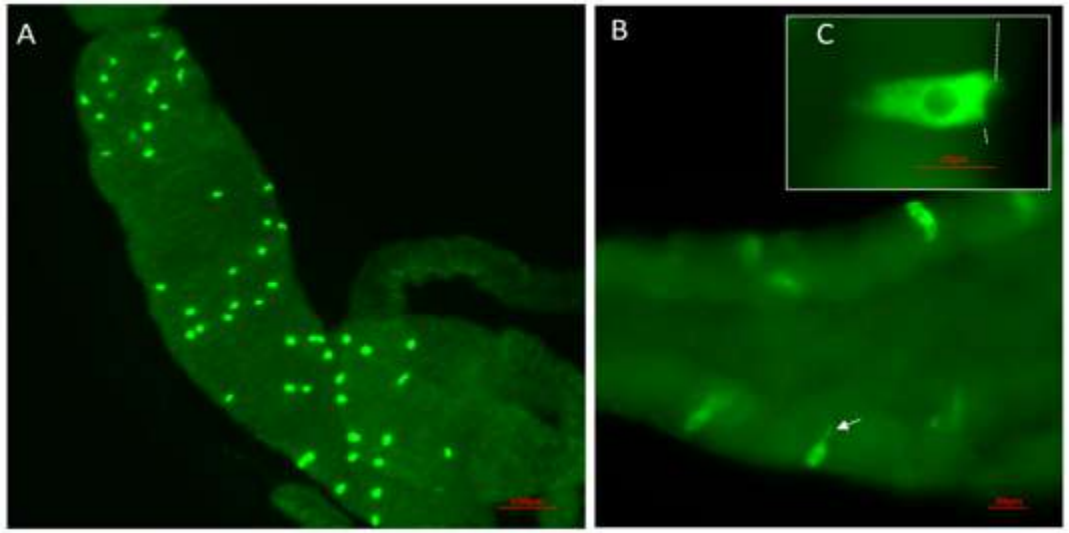
- Enteroendocrine cells synapse with vagal nodose neurons. This neuroepithelial circuit connects the intestinal lumen with the brainstem in one synapse.

- Enteroendocrine cells elicited excitatory postsynaptic potentials in connected nodose neurons within milliseconds.

Part 3

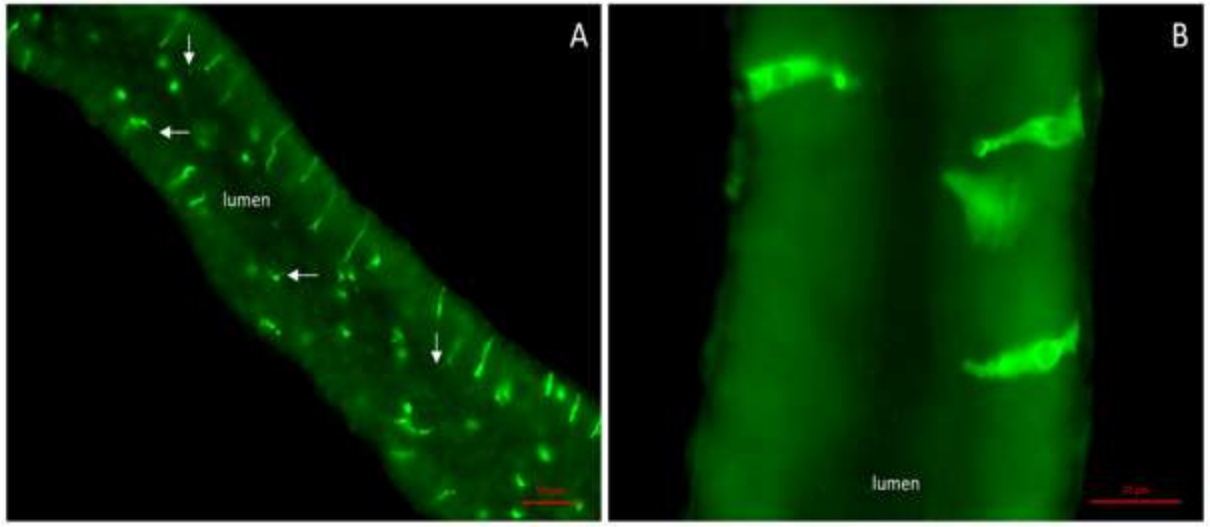


CCHamide-2 is localized in endocrine cells of the midgut of larvae and adult flies



(third instar larvae)

triangular appearance

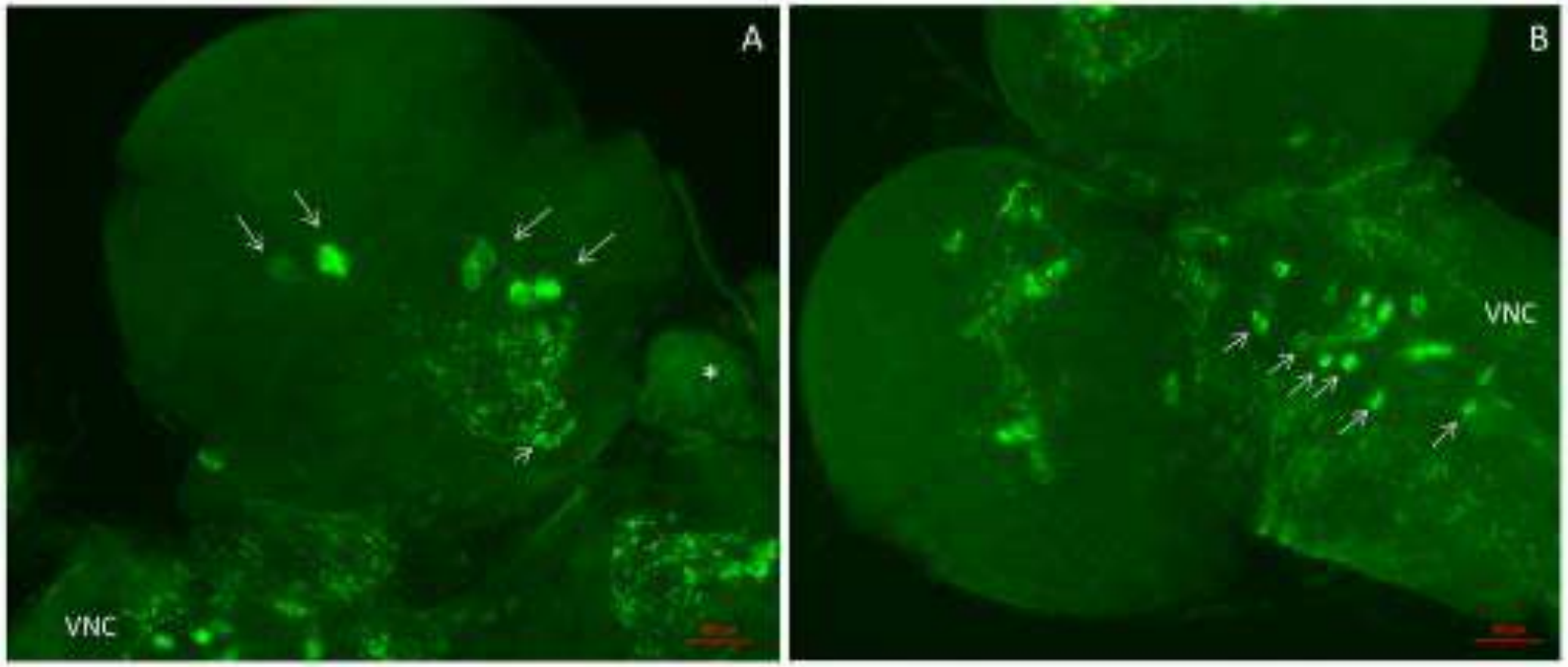


(adult flies)

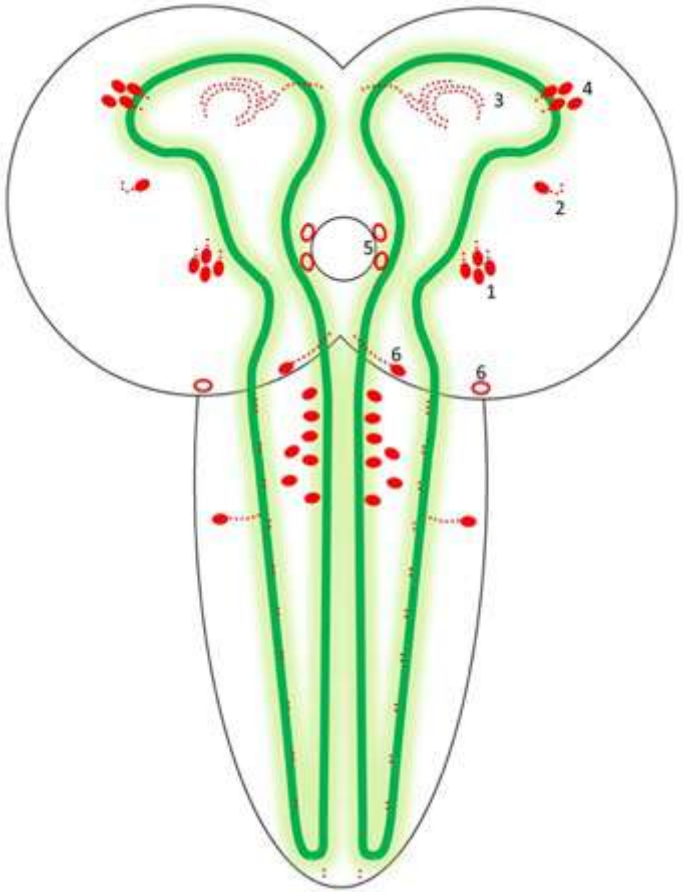
a small “knob”

Li SZ, et al. PLoS ONE.2013

CCHamide-2 is also produced in the larval central nervous system (CNS)



CCHamide2 immunostaining wasn’t found in the brain of adult flies.

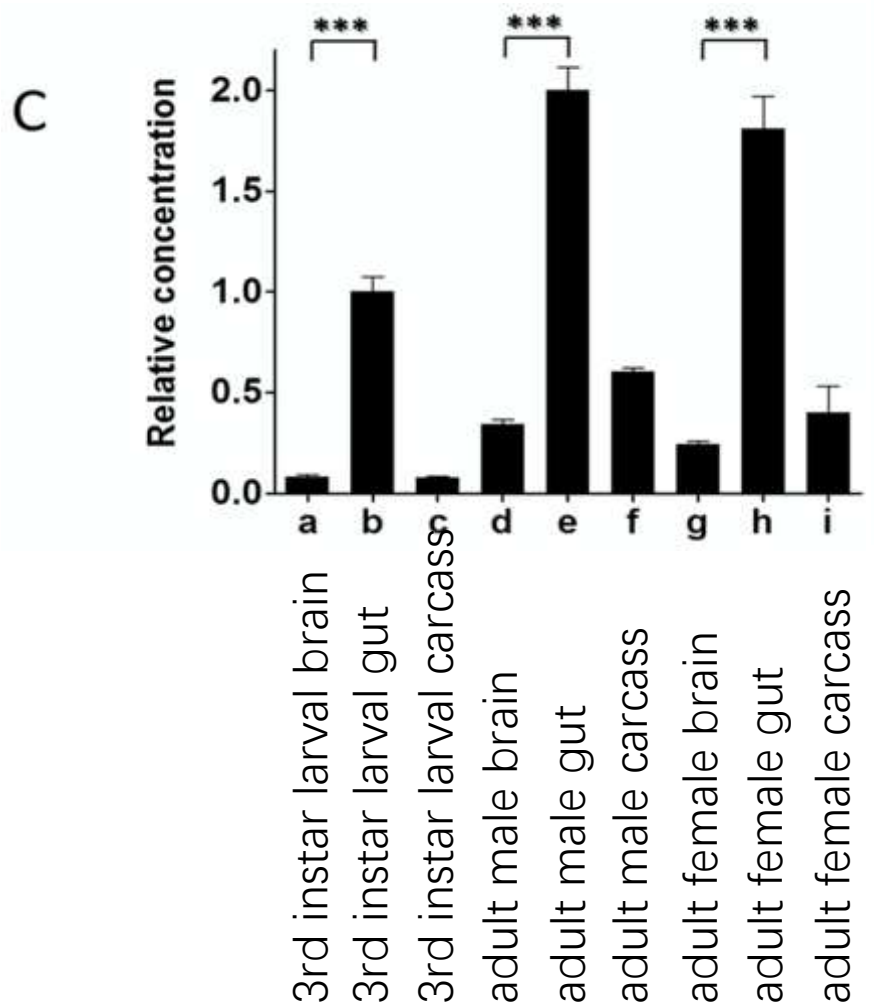


double-labeling

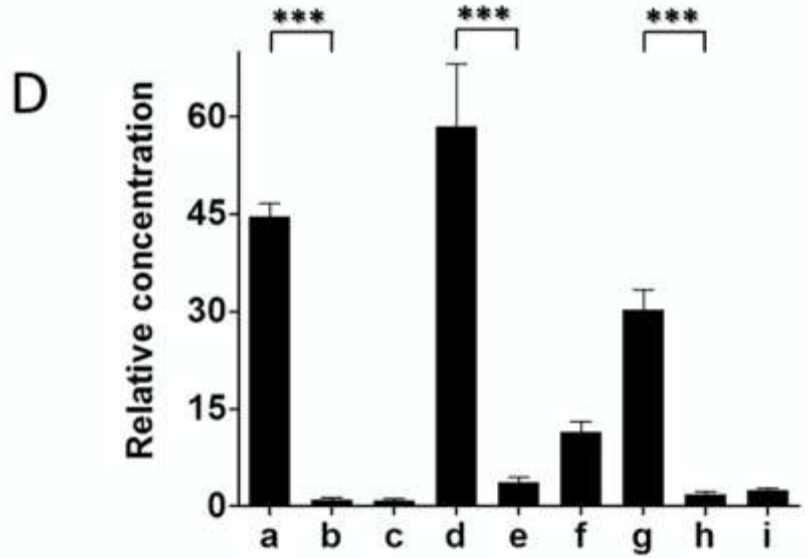
Li SZ, et al. PLoS ONE.2013

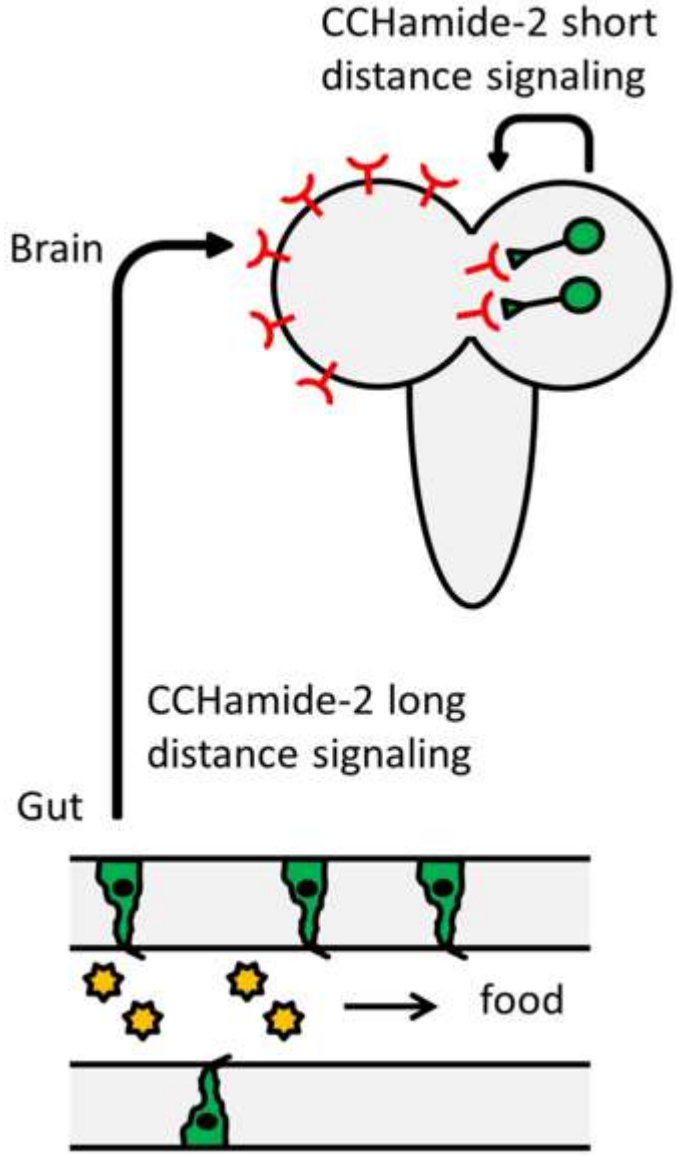
There is high expression of the CCHamide-2 gene in the gut

CCHamide-2 gene (CG14375)



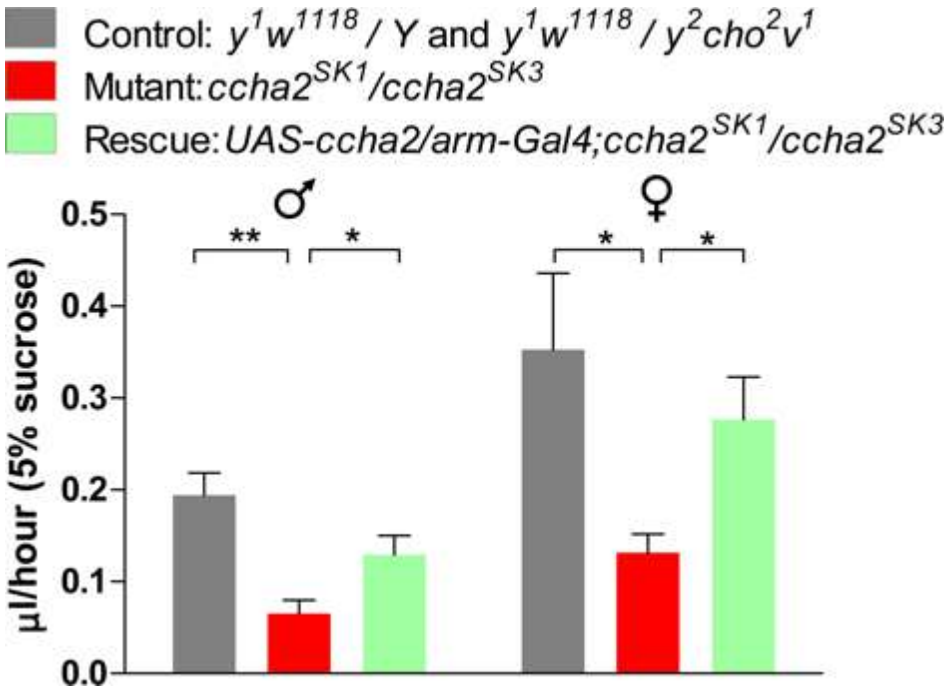
CCHamide-2 receptor gene (CG30106)

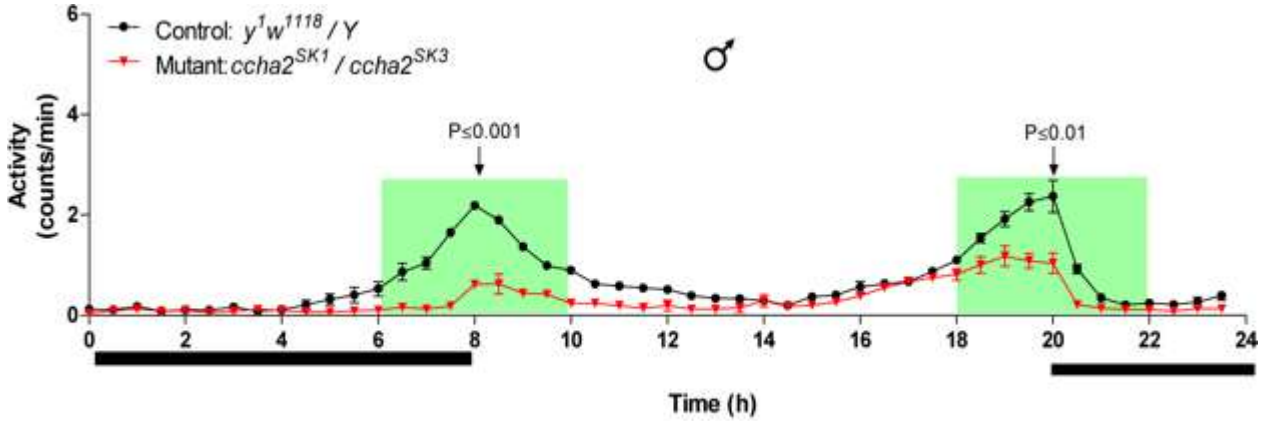


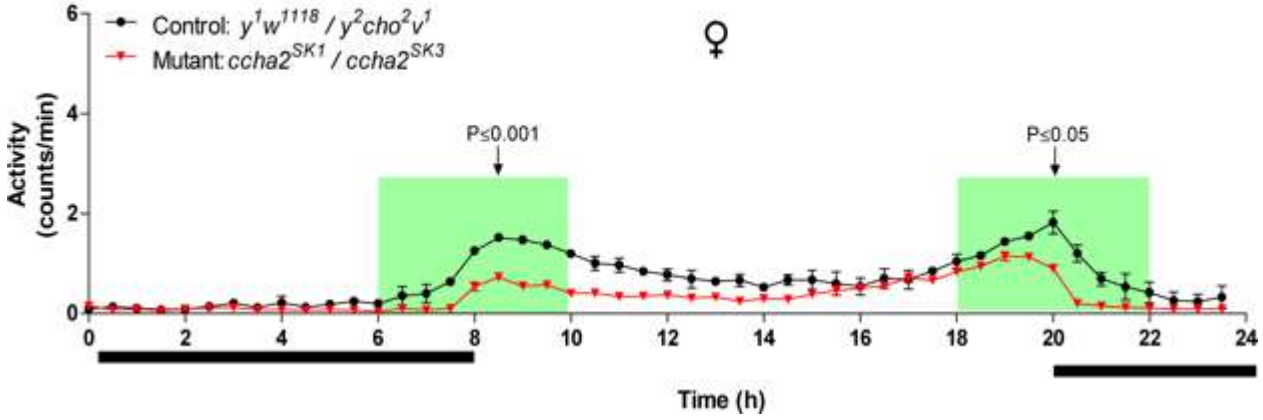


Li SZ, et al. PLoS ONE.2013

CCHamide-2 stimulates locomotion related to feeding in adult flies

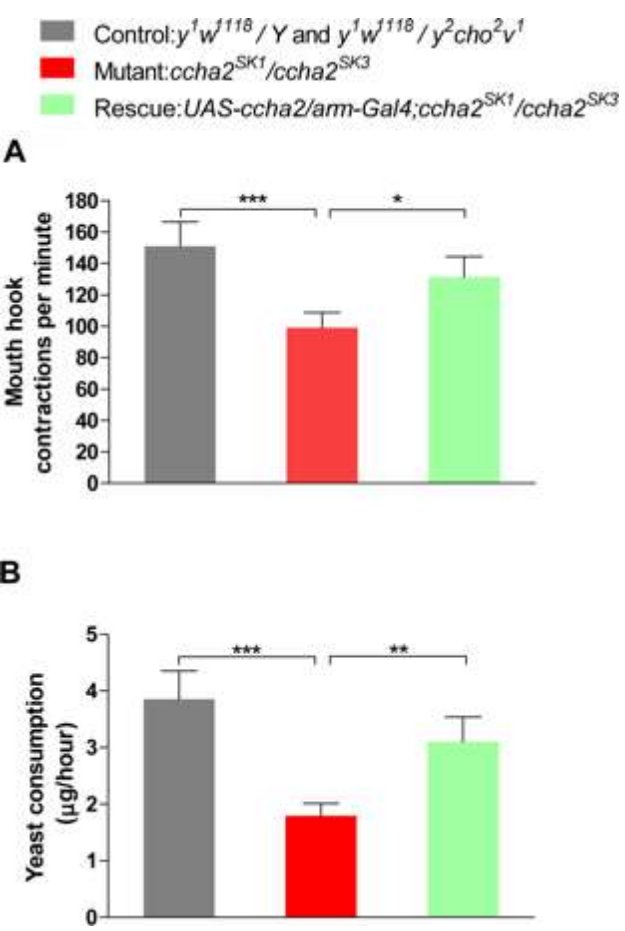




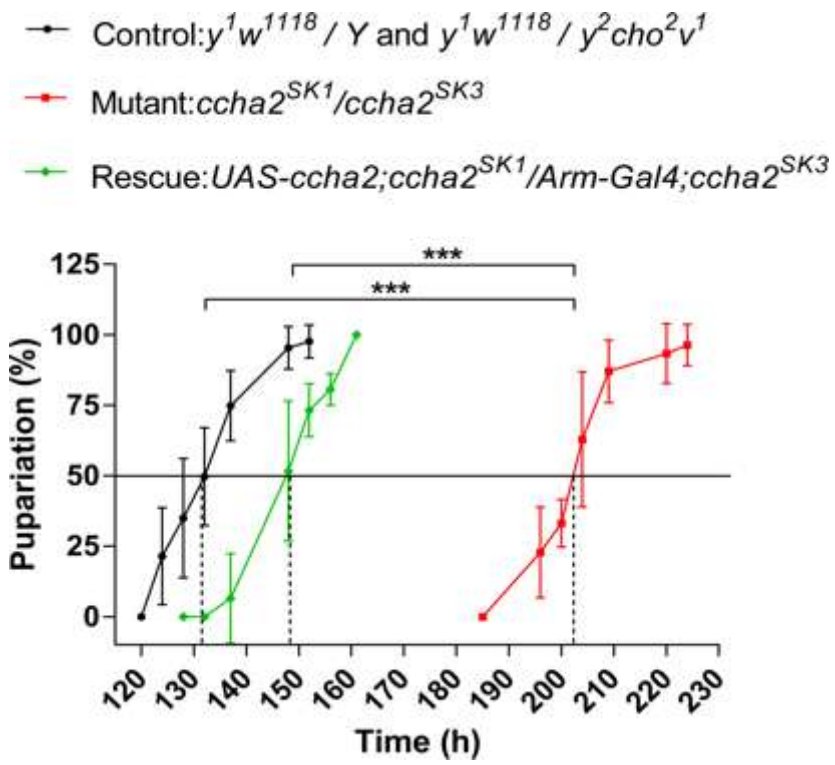


Ren GR, et al. PLoS ONE.2015

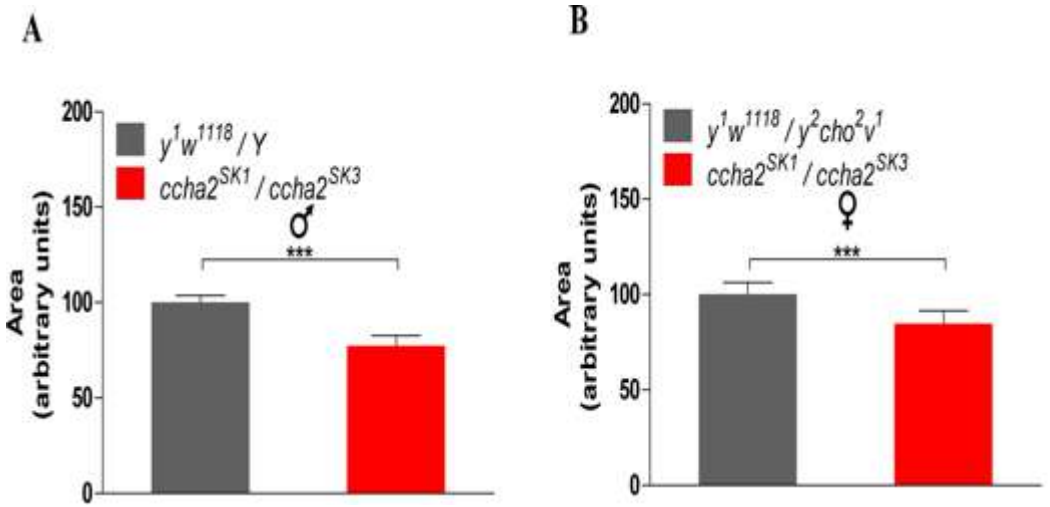
CCHamide-2 stimulates larval development



Larval feeding



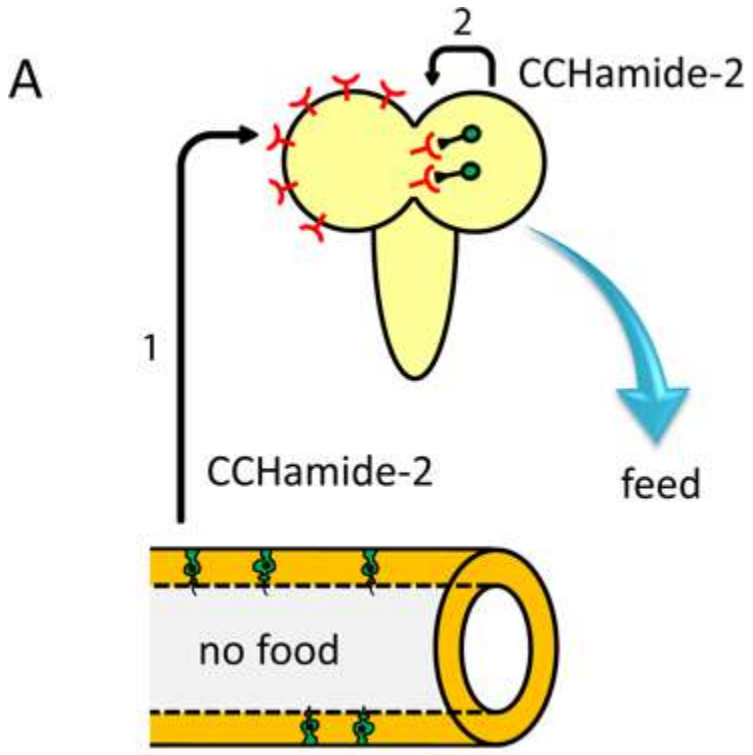
Pupariation time

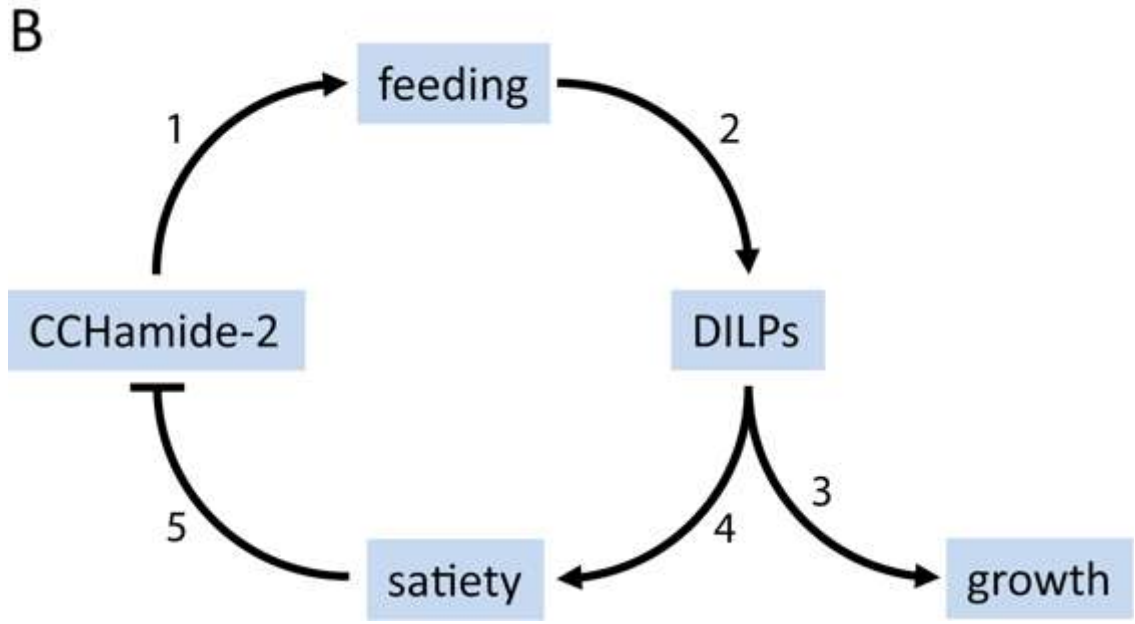


Wing size

Ren GR, et al. PLoS ONE.2015

summary





CCHamide-2 is an orexigenic brain-gut peptide in *Drosophila*

Ren GR, et al. PLoS ONE.2015

Neuron
Article

CellPress

Nutrient Sensor in the Brain Directs the Action of the Brain-Gut Axis in *Drosophila*

Monica Dus,[1,3] Jason Sih-Yu Lai,[1] Keith M. Gunapala,[1] Soohong Min,[1] Timothy D. Tayler,[2] Anne C. Hergarden,[2] Eliot Geraud,[1] Christina M. Joseph,[1] and Greg S.B. Suh[1,*]
[1]Department of Cell Biology, Skirball Institute of Biomolecular Medicine, New York University School of Medicine, 540 First Avenue, New York, NY 10016, USA
[2]Division of Biology 156-29, California Institute of Technology, 1200 E. California Boulevard, Pasadena, CA 91125, USA
[3]Present address: Department of Molecular, Cellular, and Developmental Biology, The University of Michigan, 830 North University Avenue, Ann Arbor, MI 48109, USA
*Correspondence: greg.suh@med.nyu.edu
http://dx.doi.org/10.1016/j.neuron.2015.05.032

a sweeter yet nonnutritive sugar

(L-glucose or D-arabinose)

sated

or

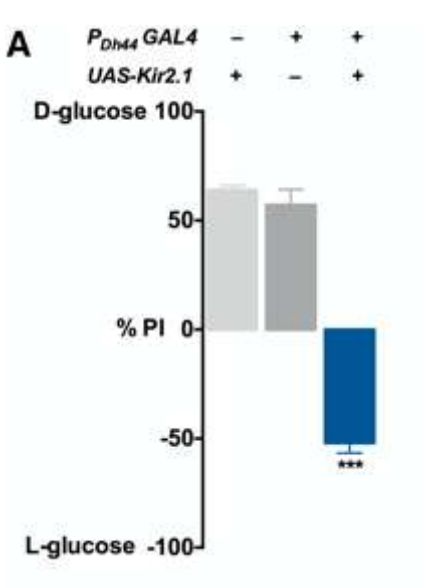
a nutritive sugar

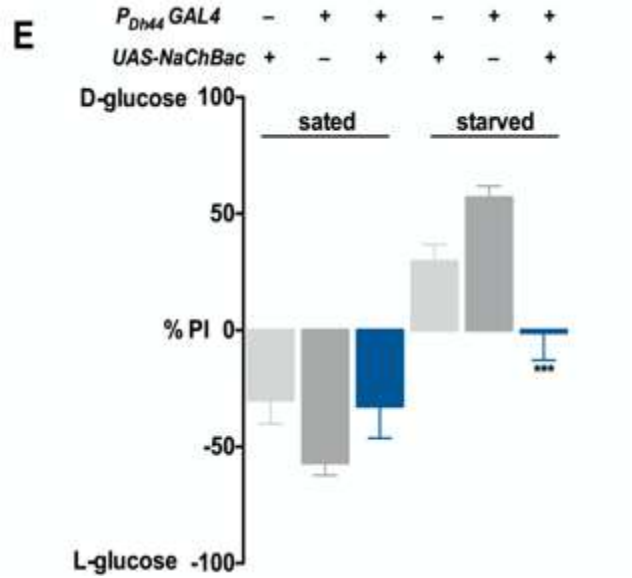
(D-glucose, D-trehalose, D-fructose, or sorbitol)

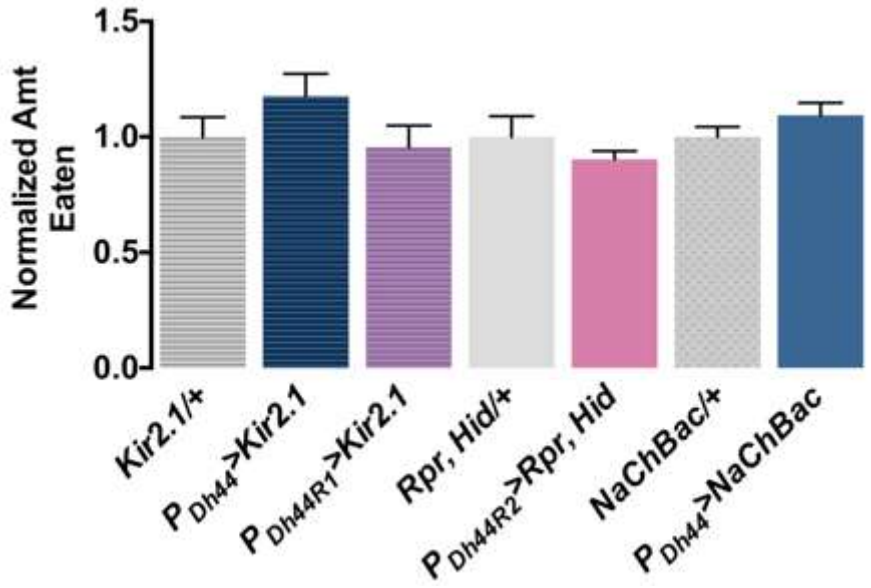
or

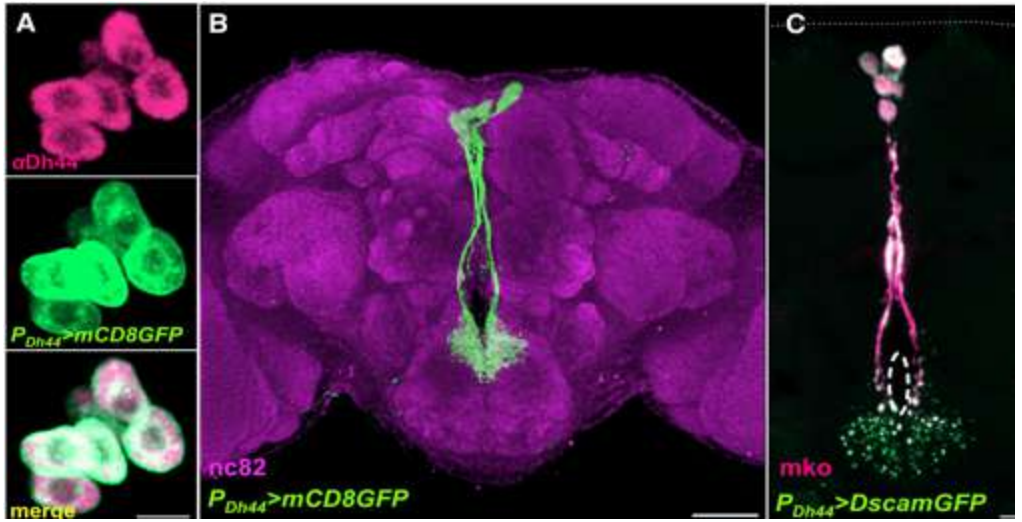
starved

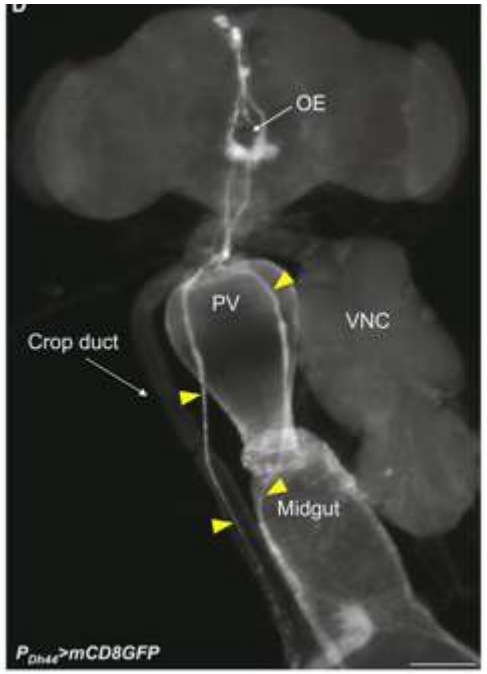
Dh44 neurons mediates the selection of nutritive sugars independent of taste input







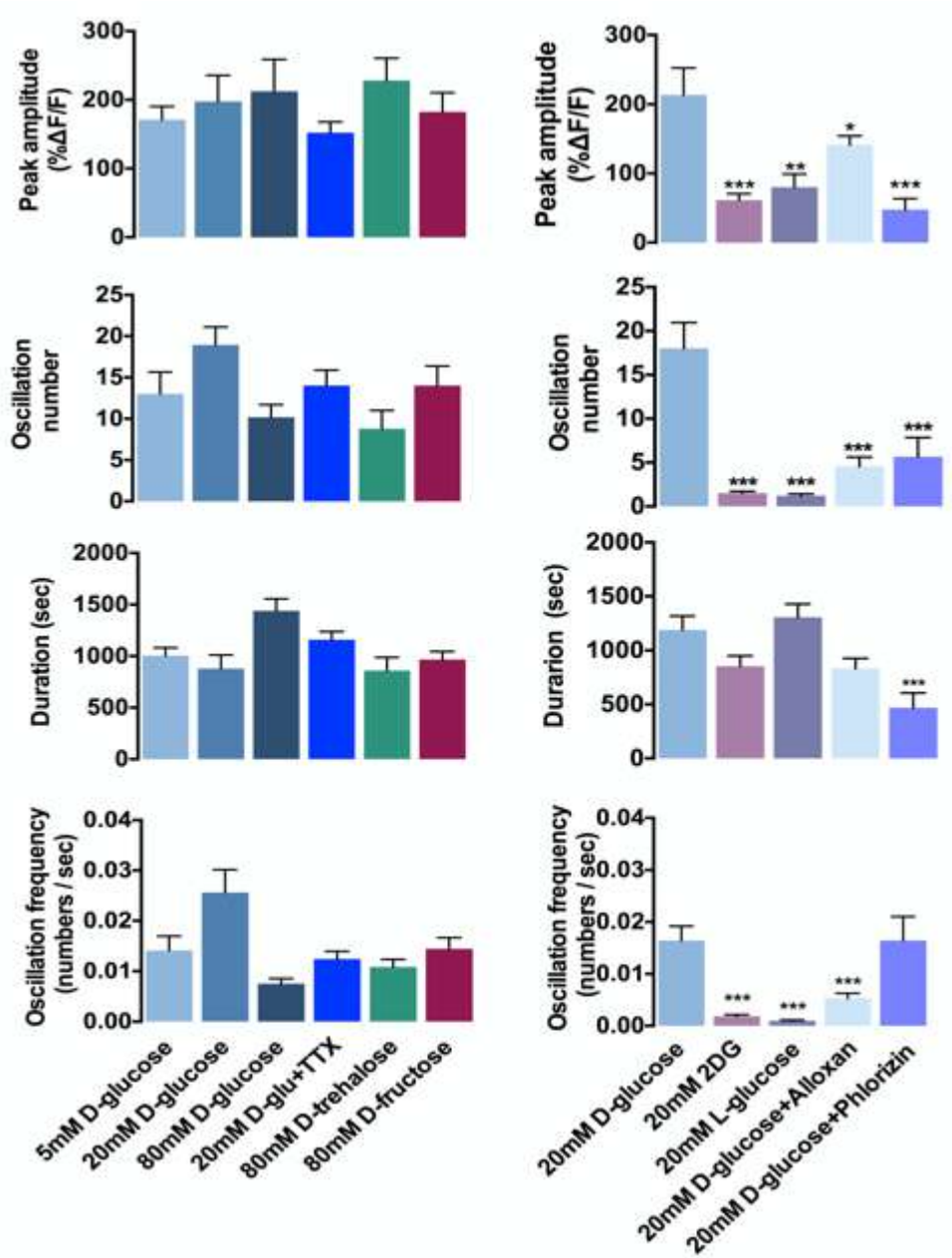


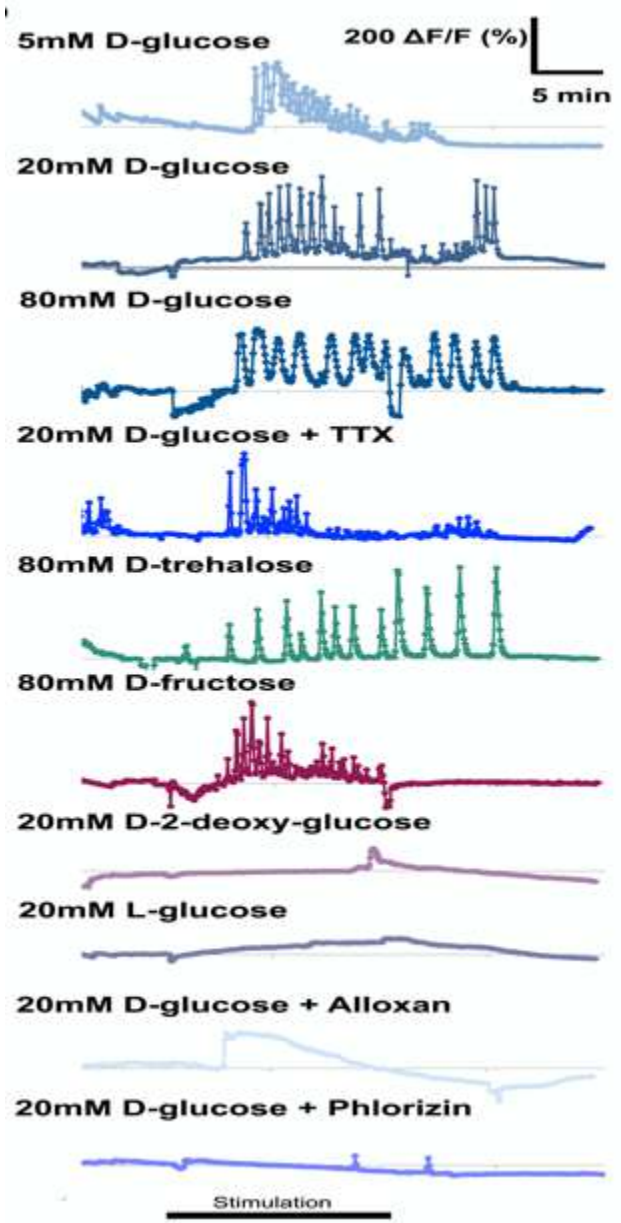


Dus M, et al. Neuron. 2015

Dh44 neurons are activated by nutritive sugars and not by nonnutritive sugars

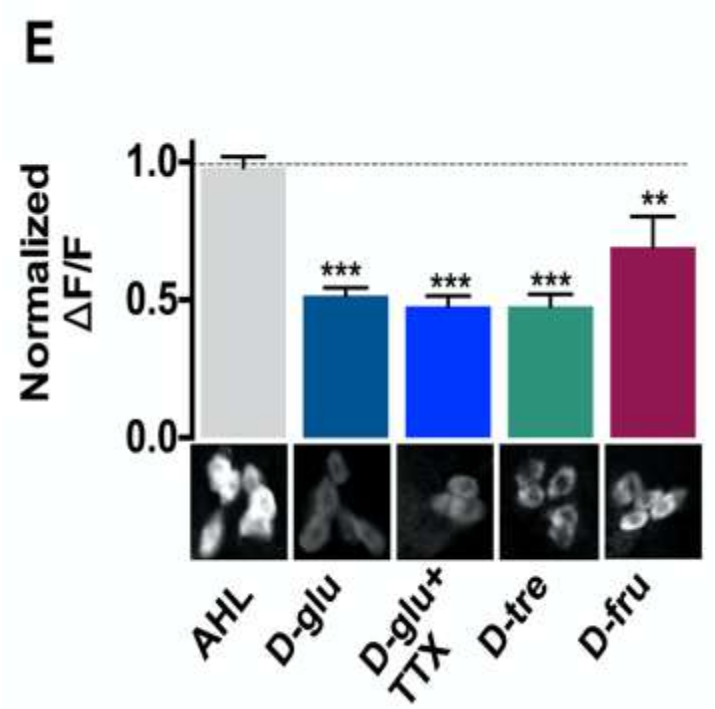
Calcium oscillations are a characteristic of neurosecretory cells and occur when these cells are secreting neuropeptides.

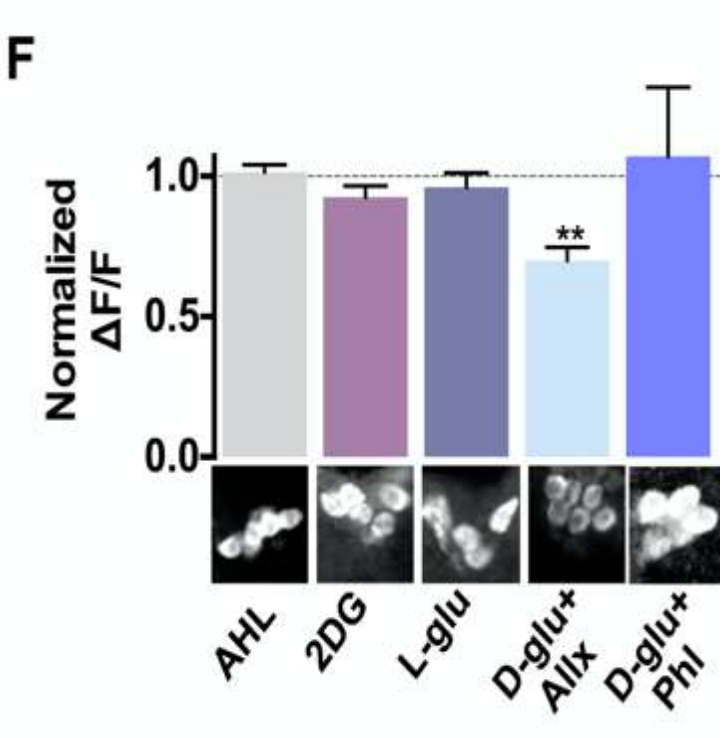




Dus M, et al. Neuron. 2015

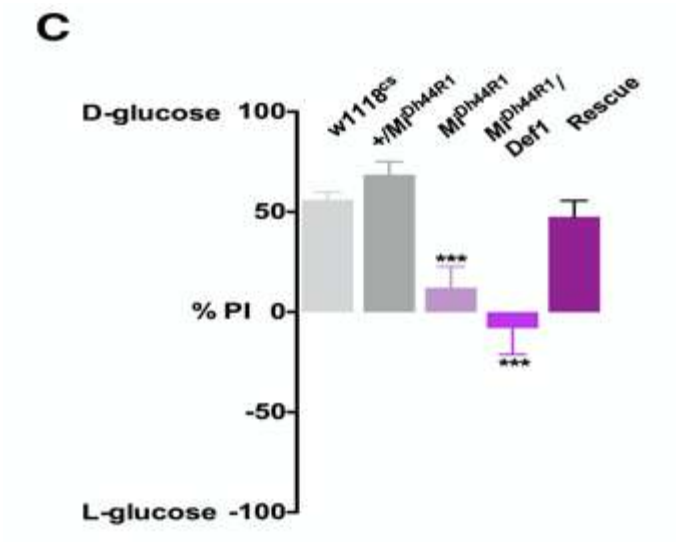
Sugar-induced activation promotes the release of Dh44 neuropeptide

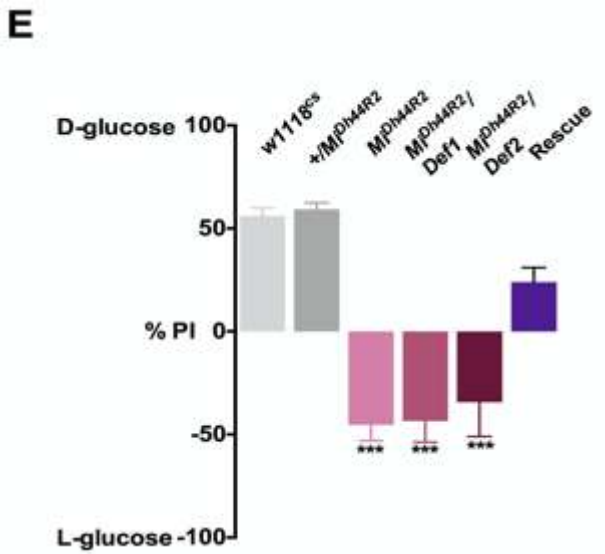




Dus M, et al. Neuron. 2015

Dh44 R1 and *Dh44 R2* receptors are required for the selection of nutritive sugar

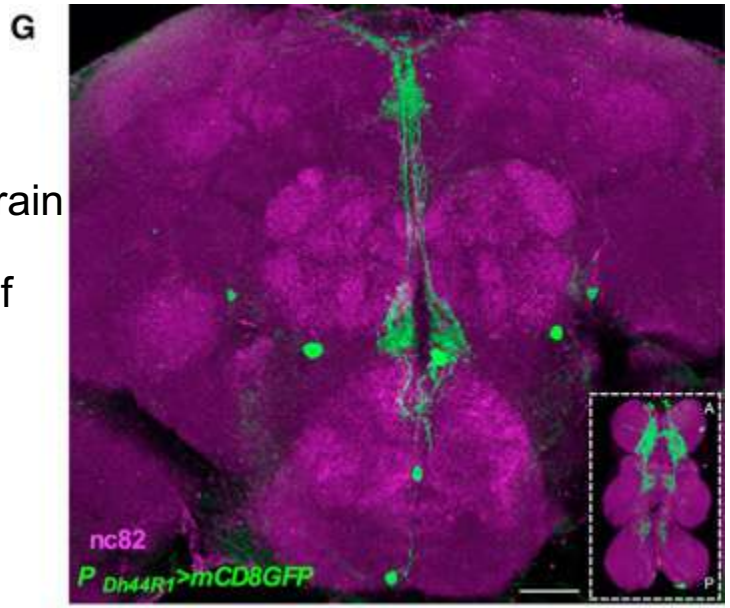


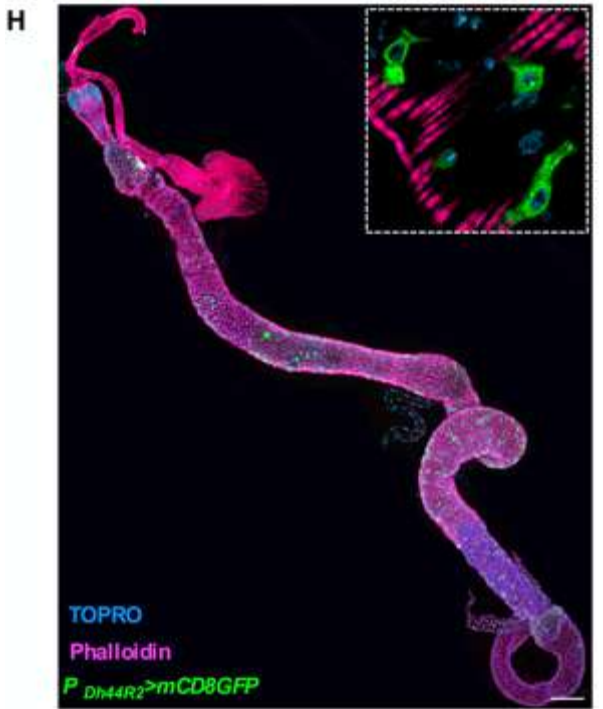


P_{Dh44R1}-GAL4 line

ten cells in the fly brain

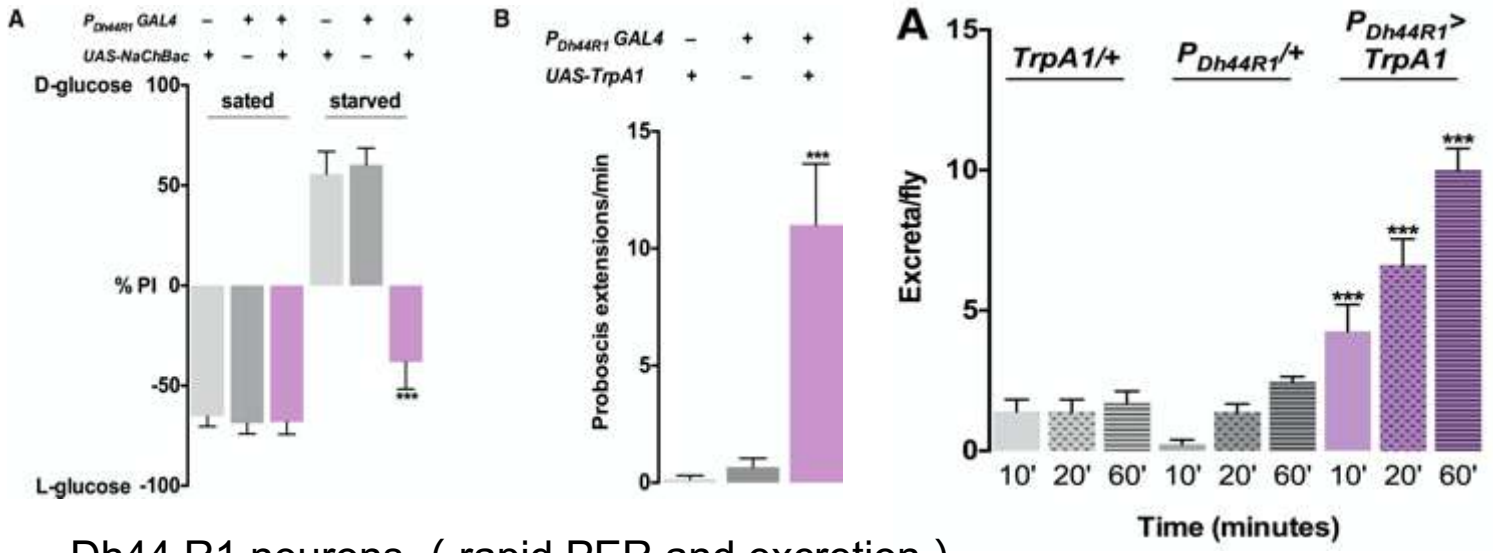
three to four pairs of cells in the VNC



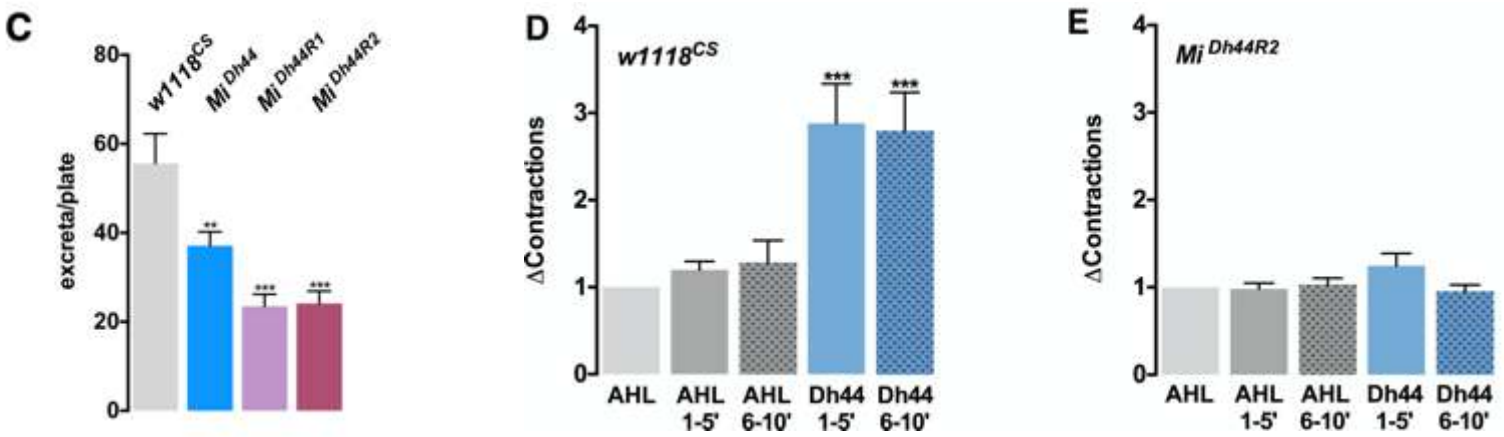


Dus M, et al. Neuron. 2015

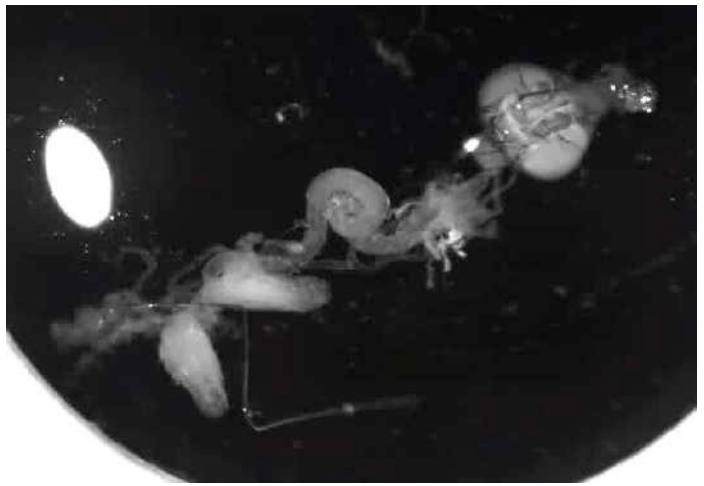
The Dh44 system regulates rapid PER, excretion and gut motility



Dh44 R1 neurons (rapid PER and excretion)

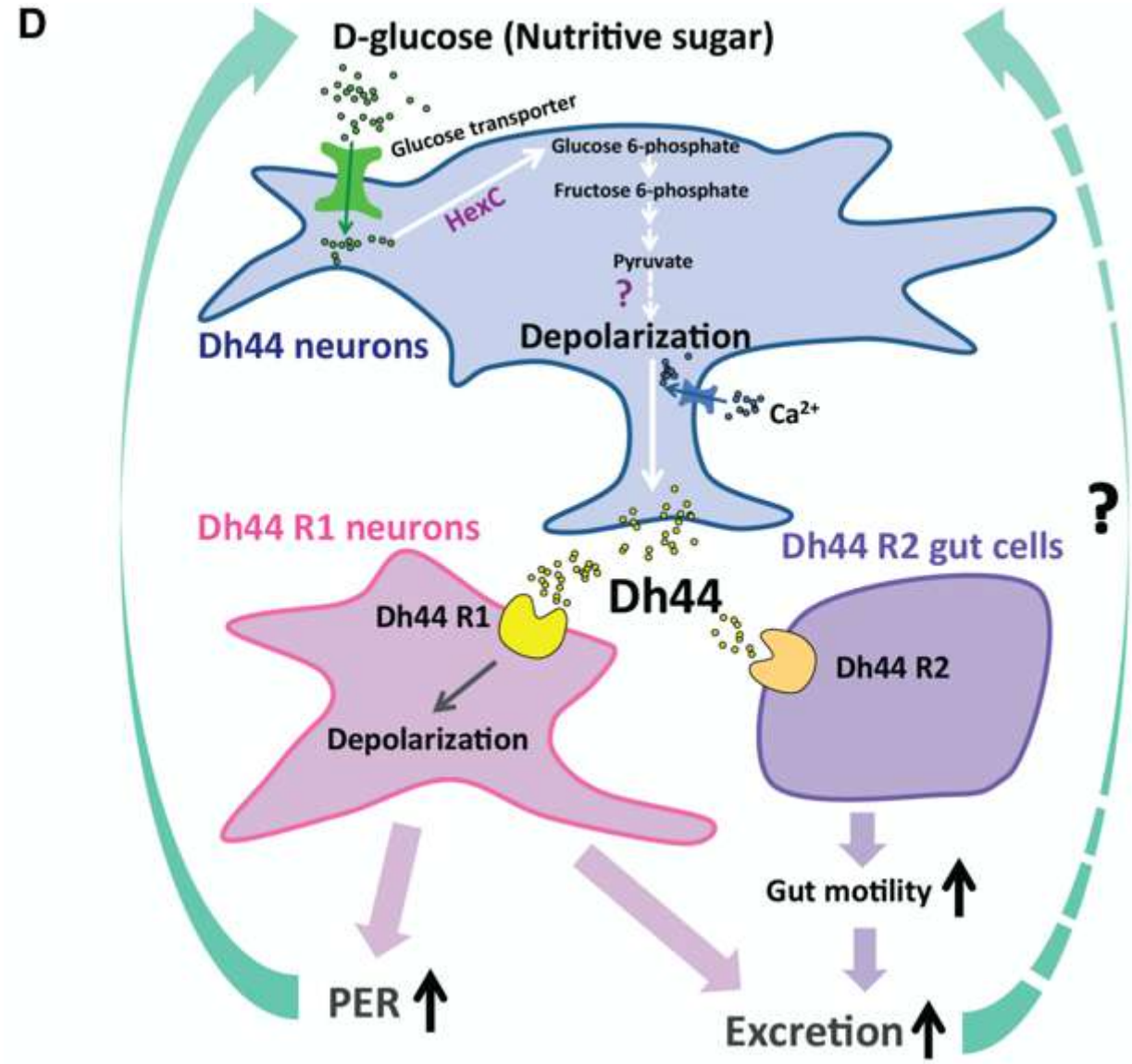


Dh44 R2 neurons (gut motility and excretion)



Dus M, et al. Neuron. 2015

summary



Dus M, et al. Neuron. 2015

References

Sharon G, Sampson TR, Geschwind DH, et al. The Central Nervous System and the Gut Microbiome. Cell.2016,167:915-932.

Vadder FD, Grasset E, et al. Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks. PNAS.2018 ;115(25):6458-6463.

Psichas A, Reimann F and Gribble F.M. Gut chemosensing mechanisms .J Clin Invest. 2015;125(3):908-917

Kaelberer MM et al., A gut-brain neural circuit for nutrient sensory transduction. Science 2018;361(6408):eaat5236.

Ibiza S et al., Glial cell-derived neuroregulators control type 3 innate lymphoid cells and gut defence .Nature. 2016 July 21; 535(7612): 440–443.

Li S, Torre-Muruzabal T, Søgaard KC, Ren GR, Hauser F, et al. (2013) Expression Patterns of the Drosophila Neuropeptide CCHamide-2 and Its Receptor May Suggest Hormonal Signaling from the Gut to the Brain. PLoS ONE 8(10): e76131. doi:10.1371/journal.pone.0076131

Ren GR, Hauser F, Rewitz KF, Kondo S, Engelbrecht AF, Didriksen AK, et al. (2015) CCHamide-2 Is an Orexigenic Brain-Gut Peptide in Drosophila. PLoS ONE 10(7): e0133017. doi:10.1371/journal.pone.0133017

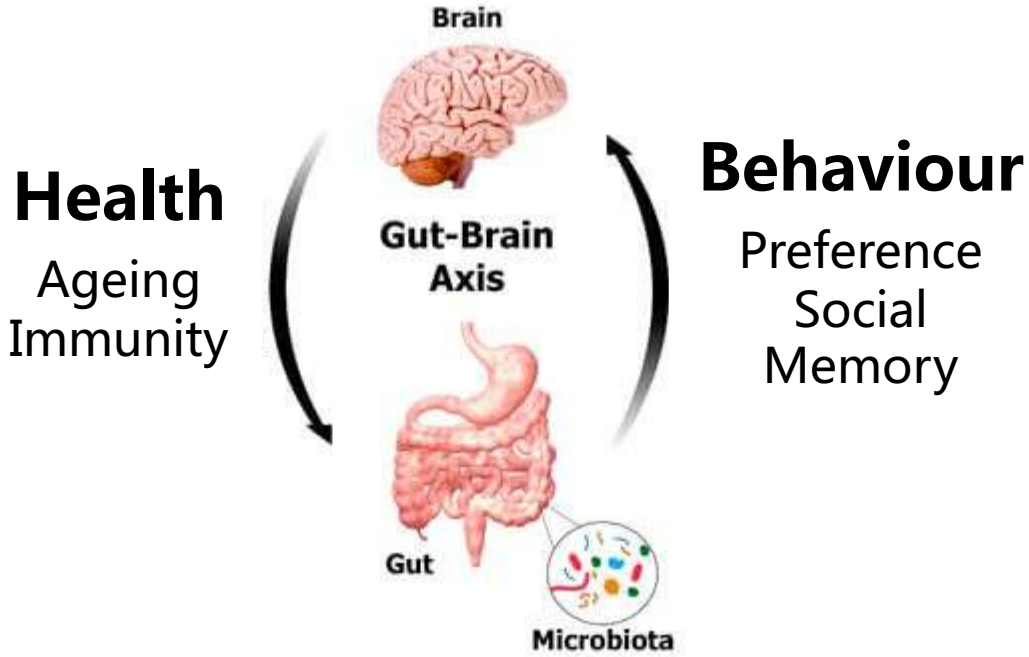
Dus M, Gunapala KM, et al. Nutrient Sensor in the Brain Directs the Action of the Brain-Gut Axis in Drosophila.Neuron.2015 Jul 1;87(1):139-51.

The Gut-Brain regulation of behaviour in mice

Ma Mingze

2020.07.30

The influence of gut-brain axis signals on individuals



www.cliniconthegreen.com

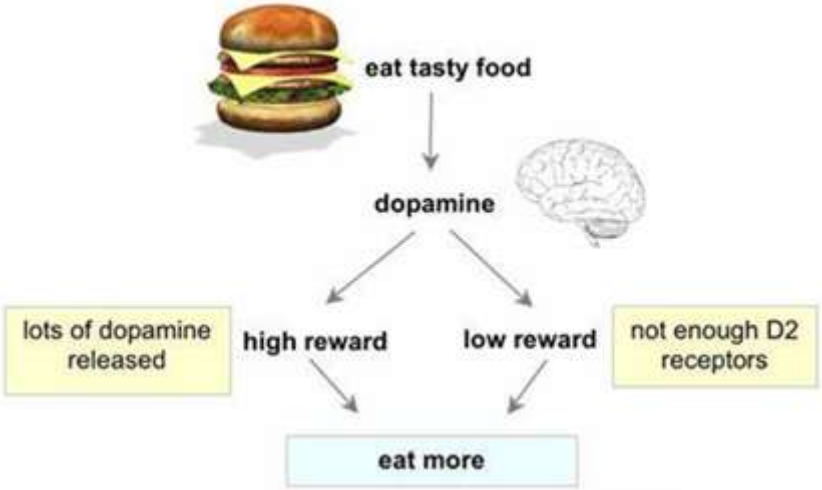
Preference

Article

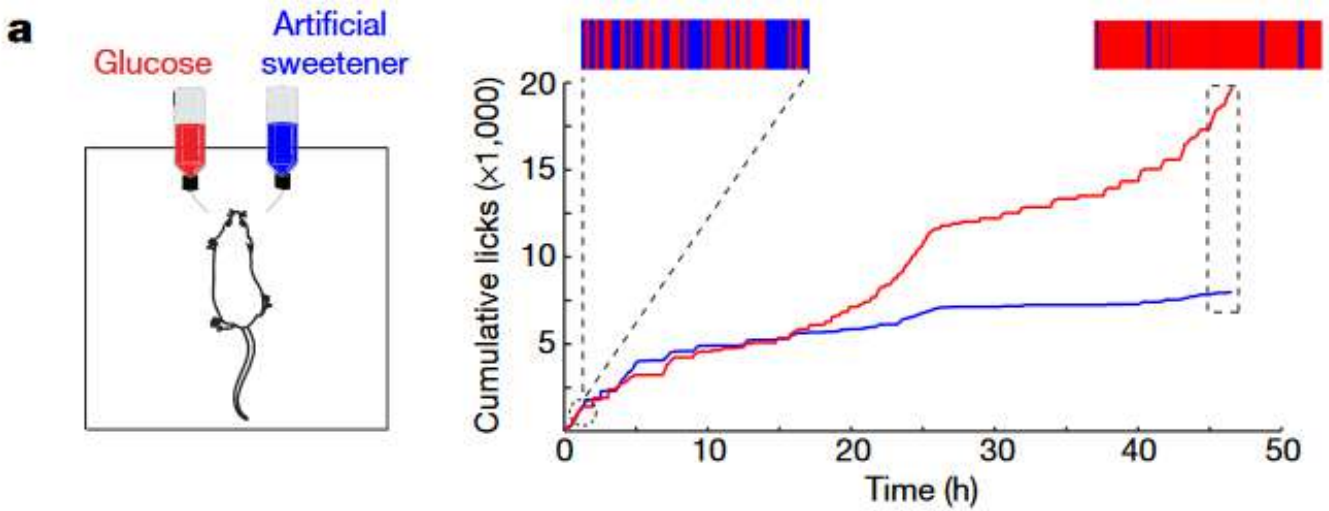
The gut–brain axis mediates sugar preference

https://doi.org/10.1038/s41586-020-2199-7
Received: 12 April 2019
Accepted: 21 February 2020
Published online: 15 April 2020
Check for updates

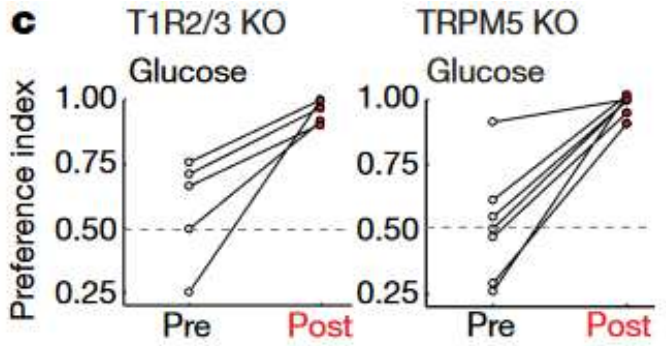
Hwei-Ee Tan[1,2,4], Alexander C. Sisti[1,3,4], Hao Jin[1,3], Martin Vignovich[1,3], Miguel Villavicencio[1,3], Katherine S. Tsang[1,3], Yossef Goffer[2] & Charles S. Zuker[1,3]



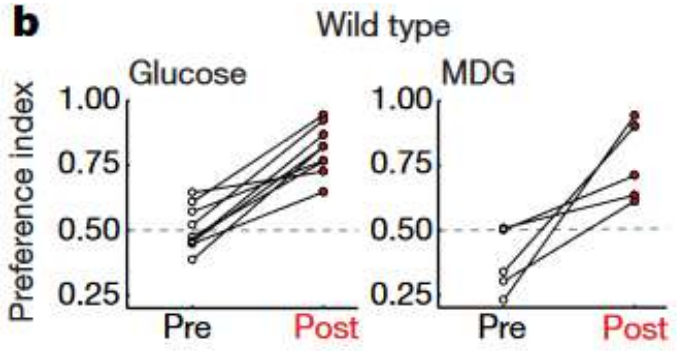
Taste-independent sugar preference



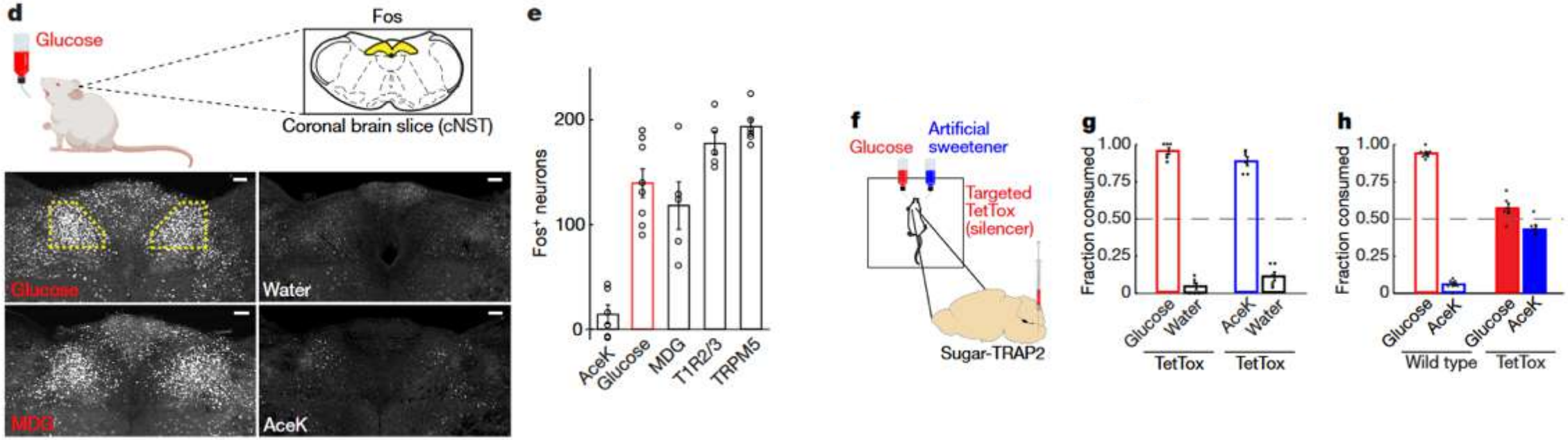
taste



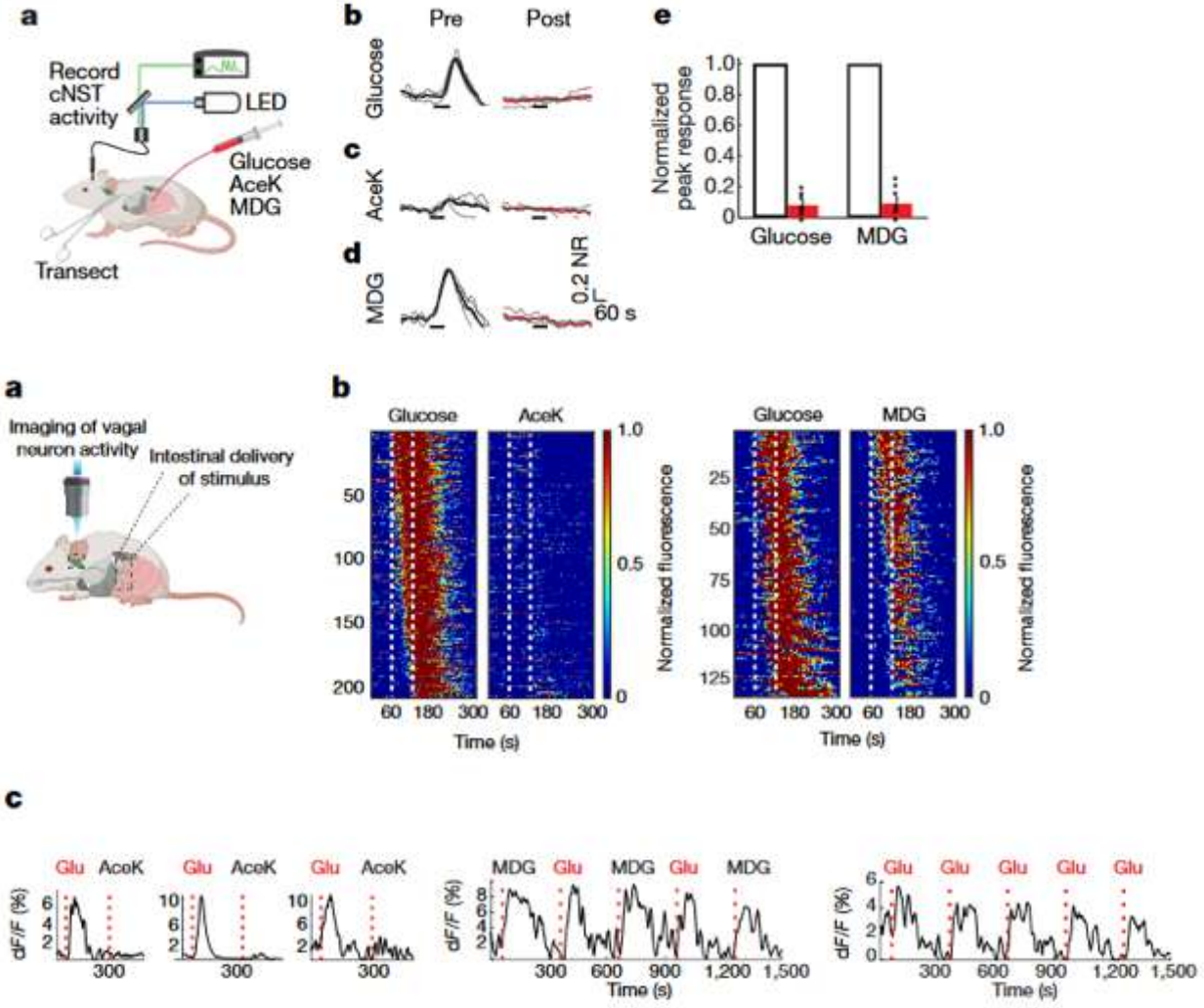
energy



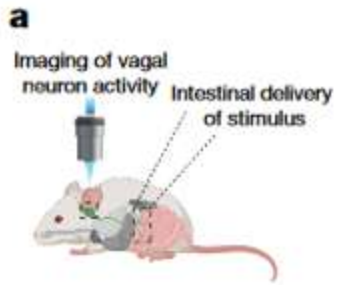
Neurons in the cNST mediate sugar preference

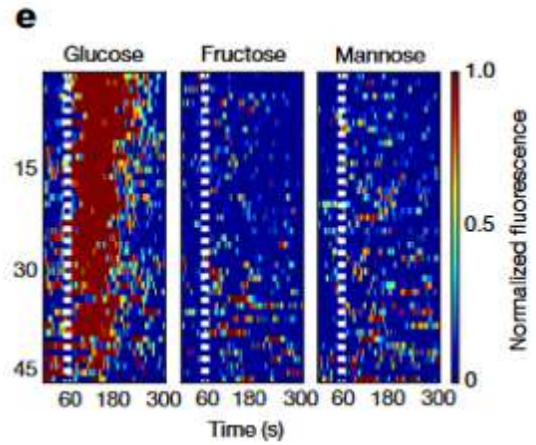


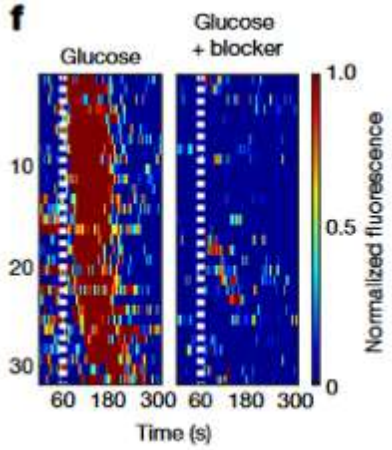
Vagal neuron participates in signal transmission in the intestinal-brain axis

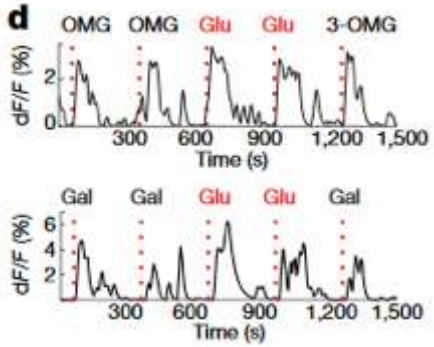


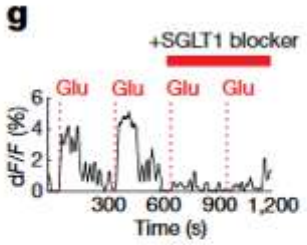
SGLT1 transduces gut–brain sugar signals



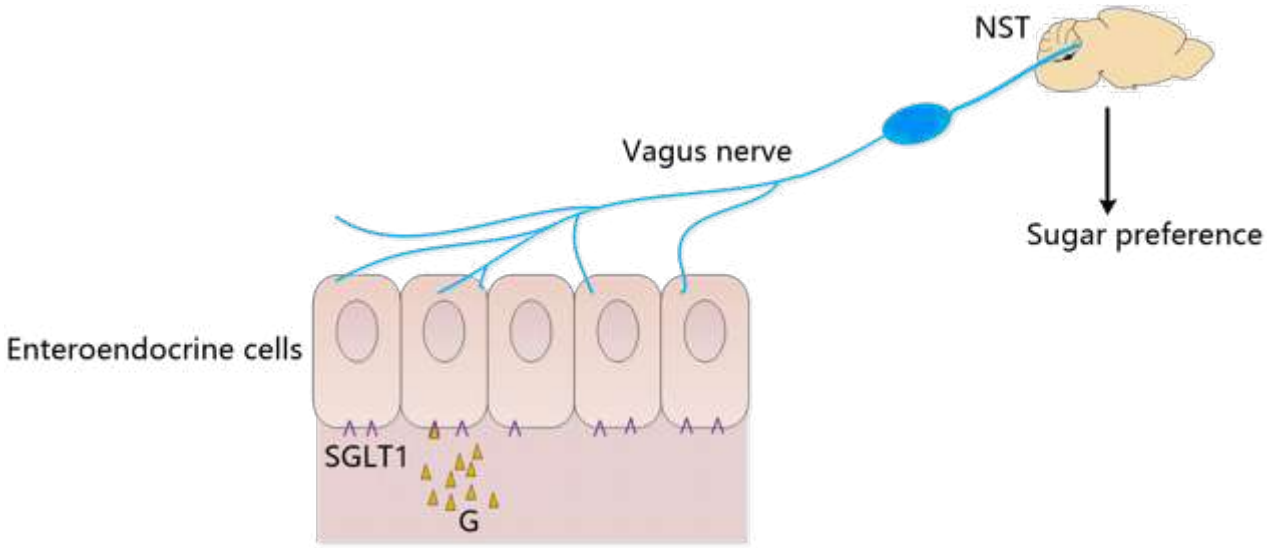


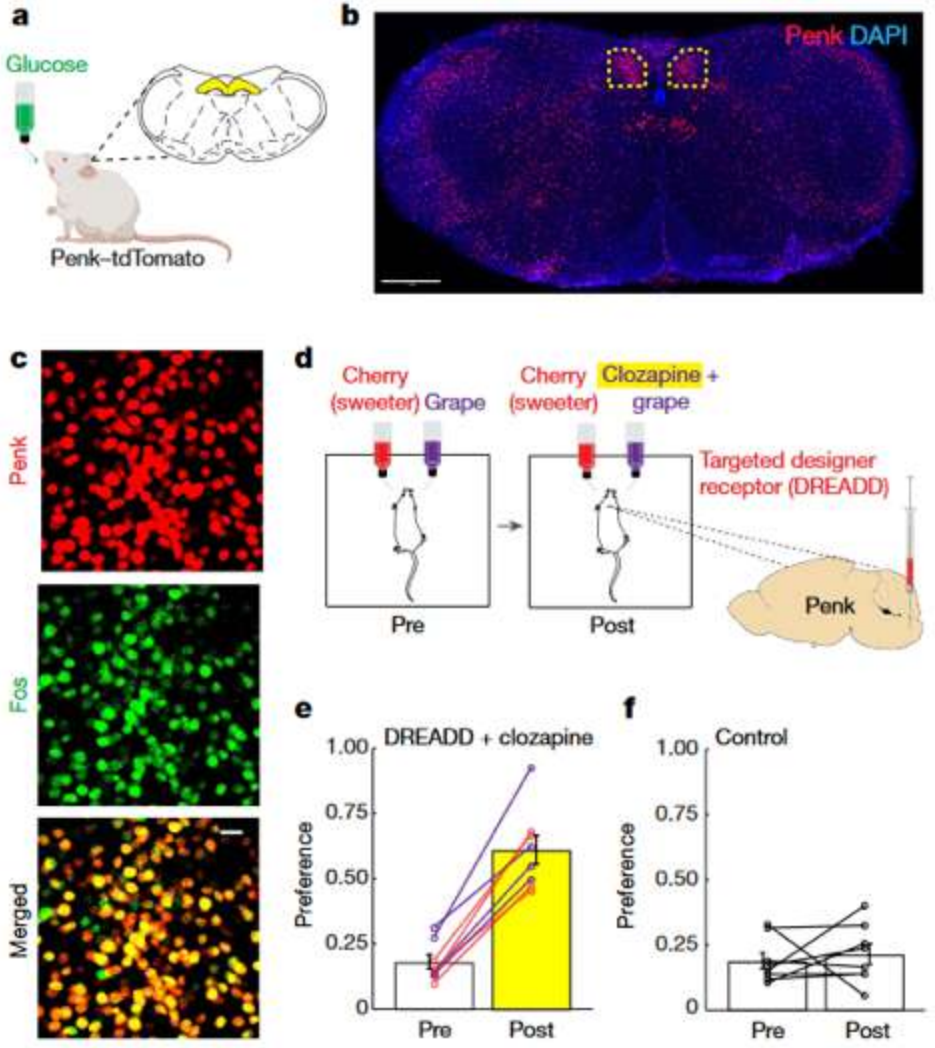






NST is sufficient for development of sugar-preference





Social

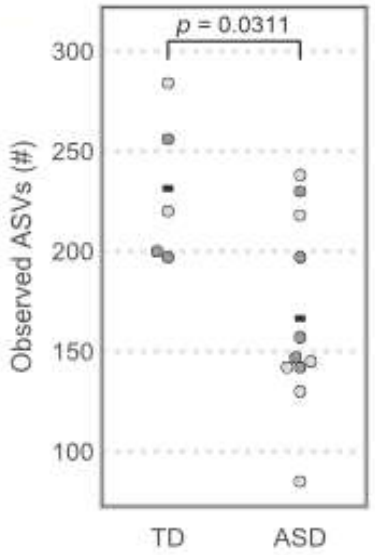
14.415 > Neuron. 2019 Jan 16;101(2):246-259.e6. doi: 10.1016/j.neuron.2018.11.018. Epub 2018 Dec 3.

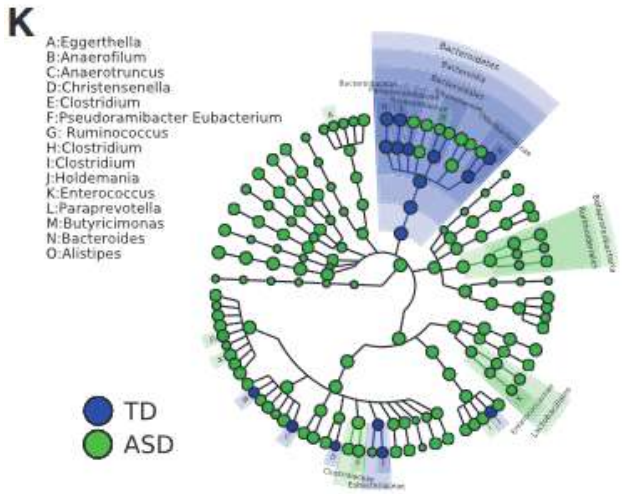
Mechanisms Underlying Microbial-Mediated Changes in Social Behavior in Mouse Models of Autism Spectrum Disorder

Martina Sgritta [1], Sean W Dooling [2], Shelly A Buffington [1], Eric N Momin [3], Michael B Francis [1], Robert A Britton [4], Mauro Costa-Mattioli [5]

Affiliations + expand

PMID: 30522820 PMCID: PMC6645363 DOI: 10.1016/j.neuron.2018.11.018

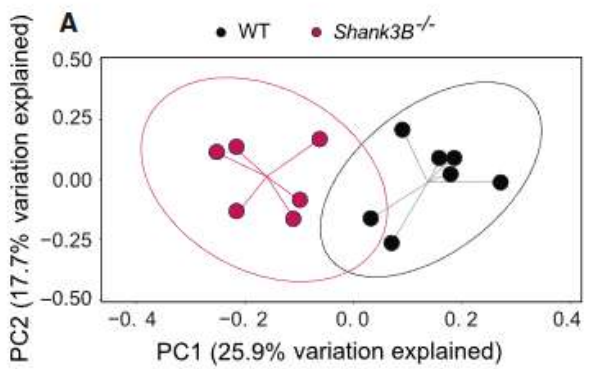


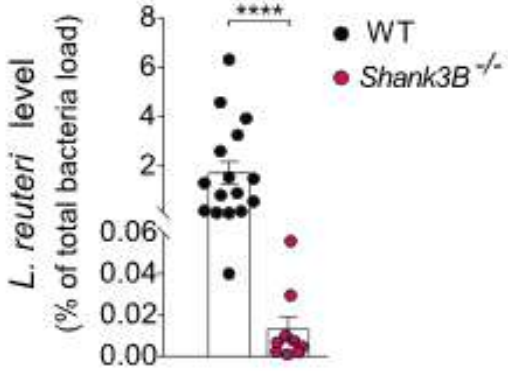


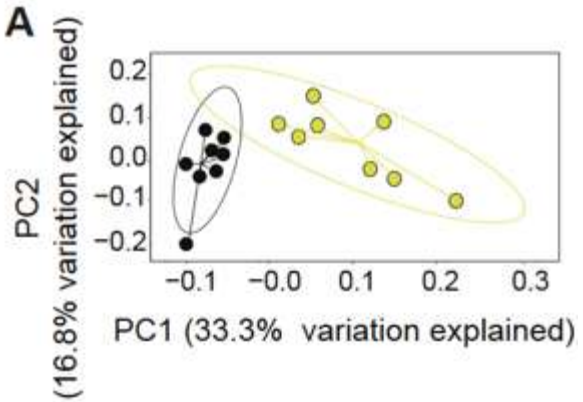
Microbes change →ASD or ASD → Microbes change ?

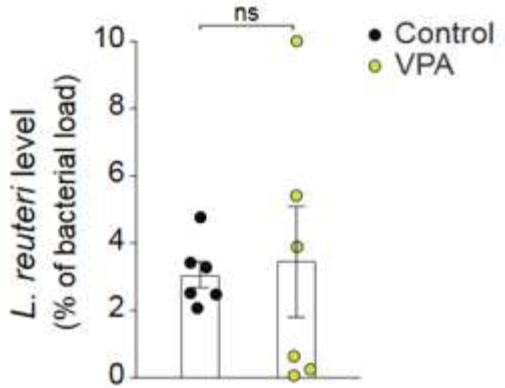
Sharon G, et al., *Cell*, 2019.

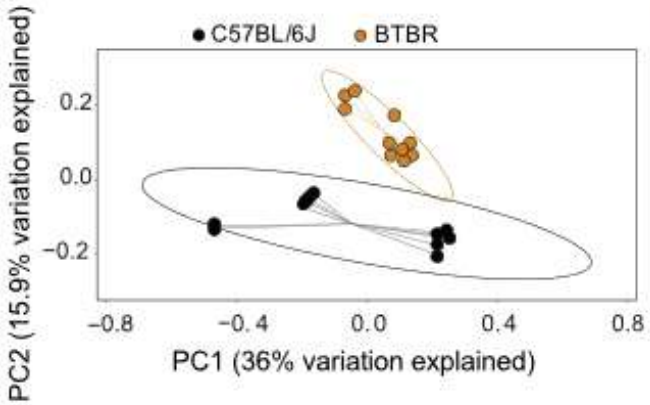
Lower L. *reuteri* in the intestine of ASD model mice

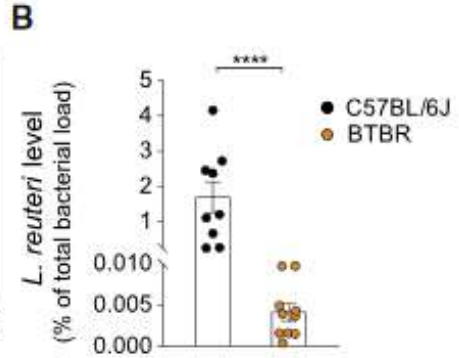






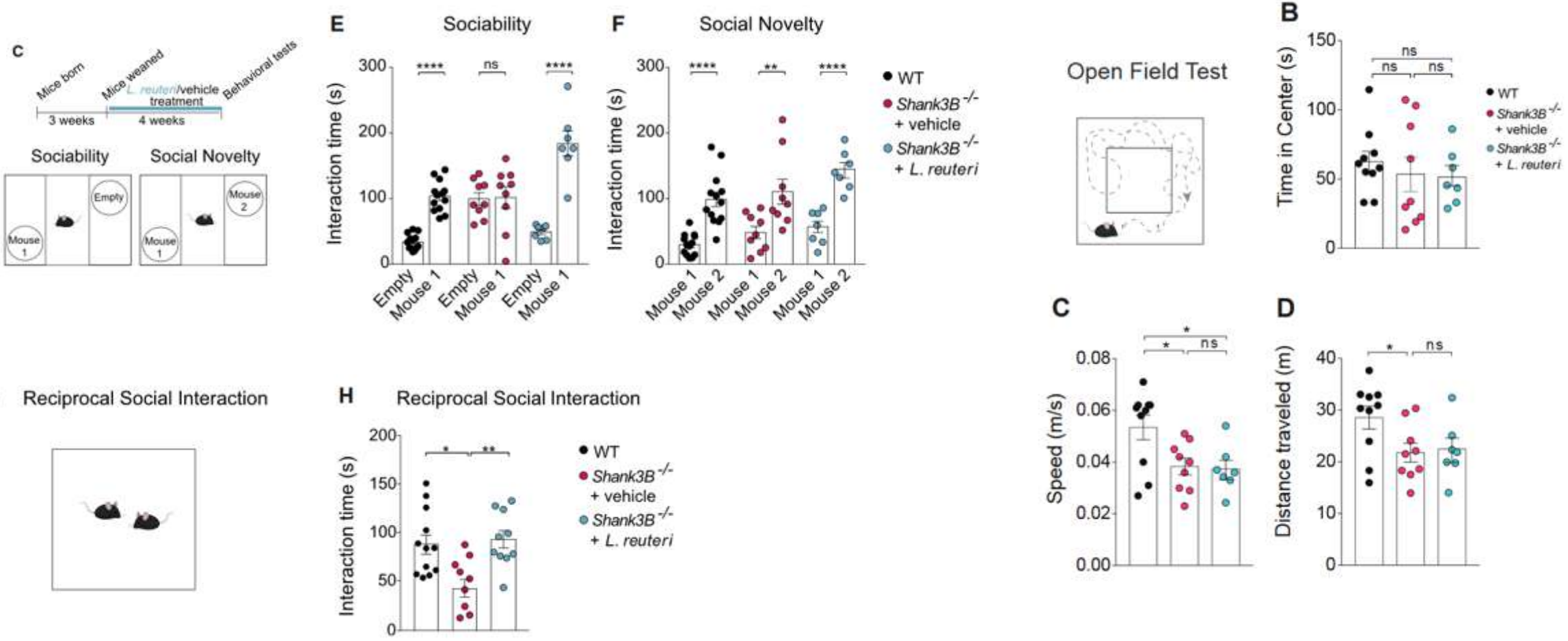




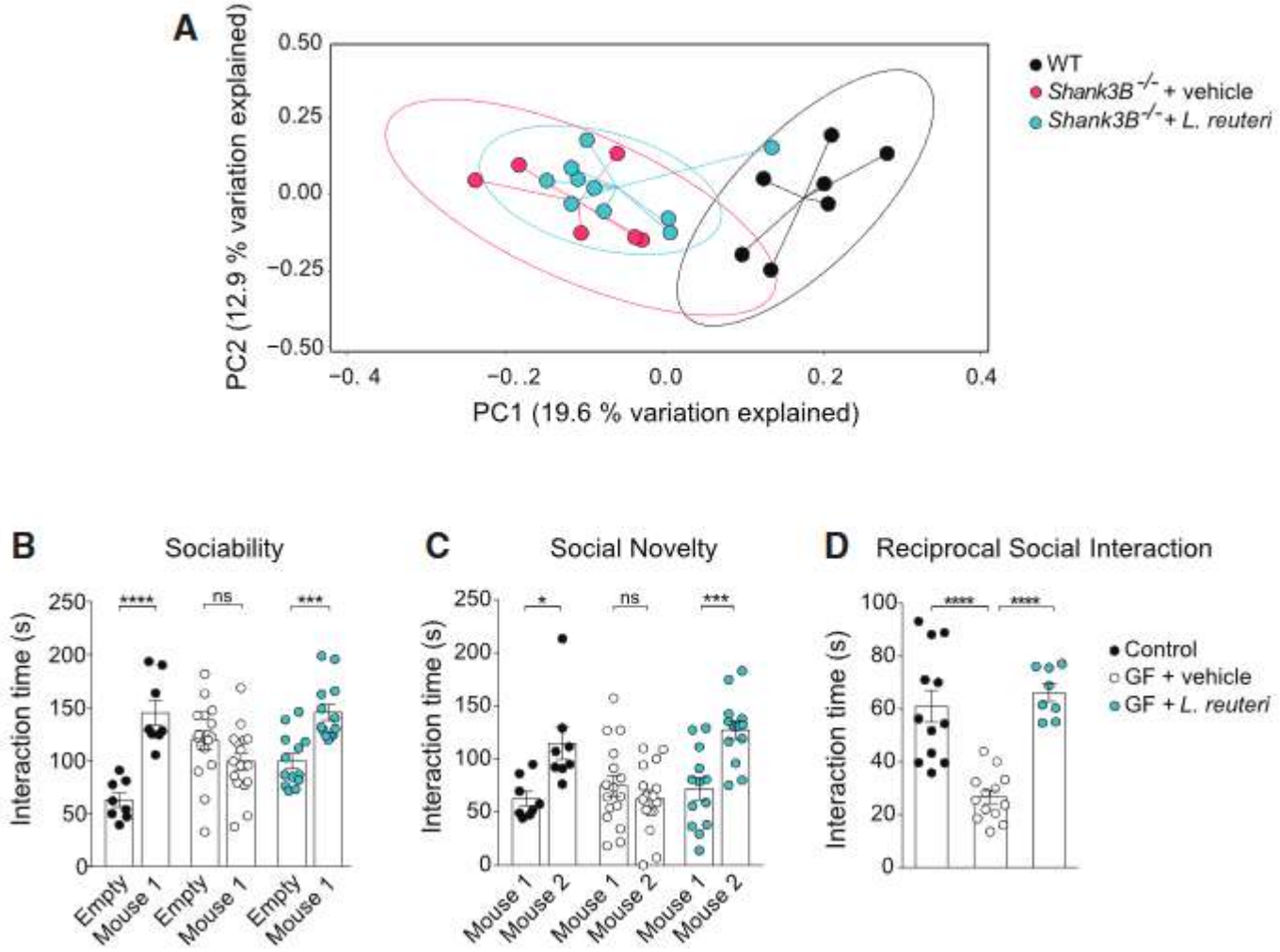


GF mice

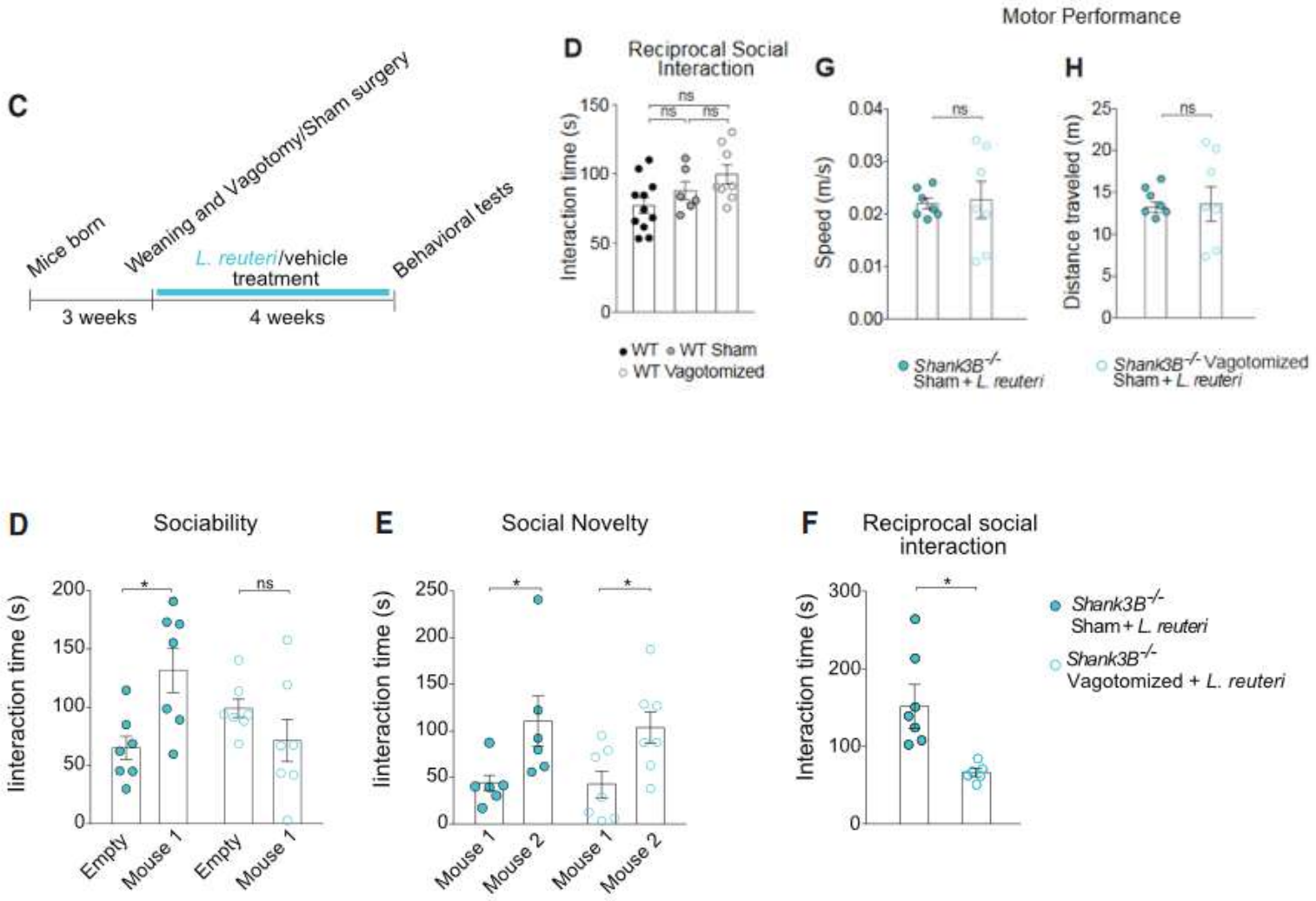
Treatment with L. *reuteri* can rescues social deficits of Shank3B$^{-/-}$ mice



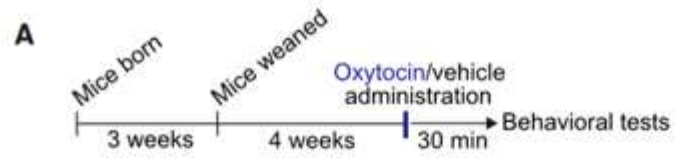
L. *reuteri* can rescue social deficits without relying on other microbes

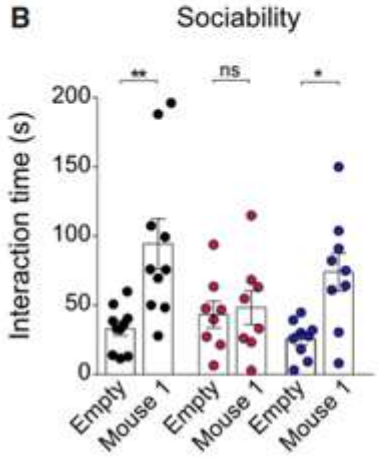


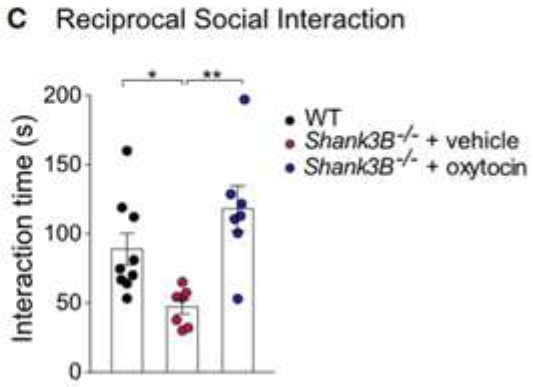
Vagus nerve is required for the relevant gut-microbiota-brain communication



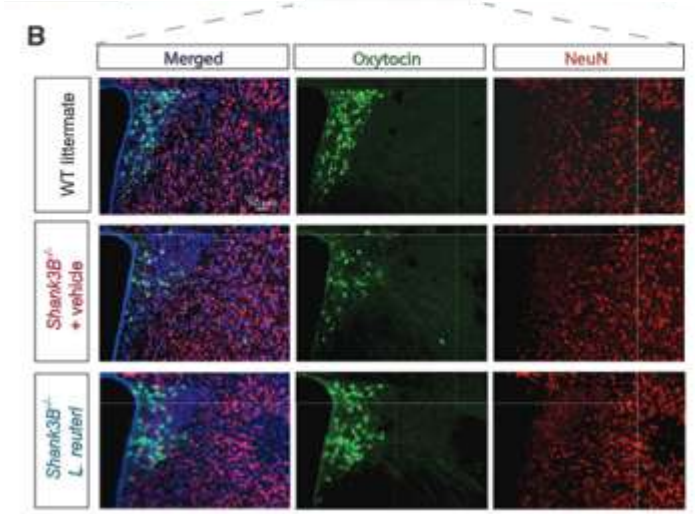
L. *reuteri* can increase the number of oxytocin+ neurons in the PVN

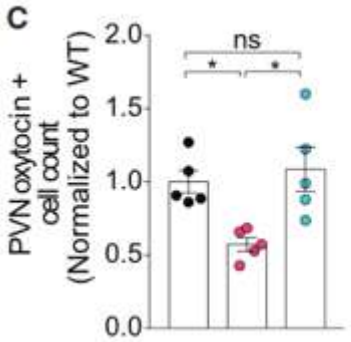


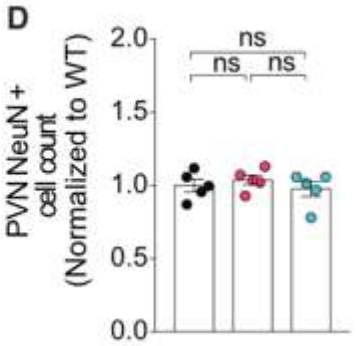


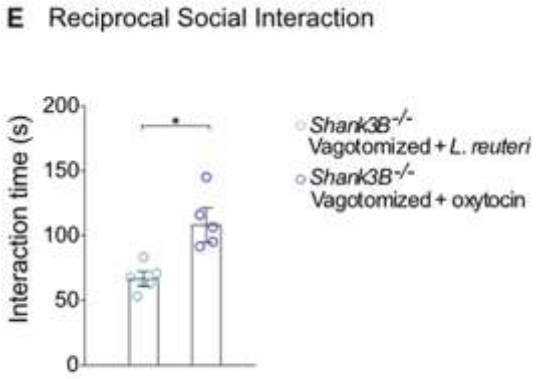


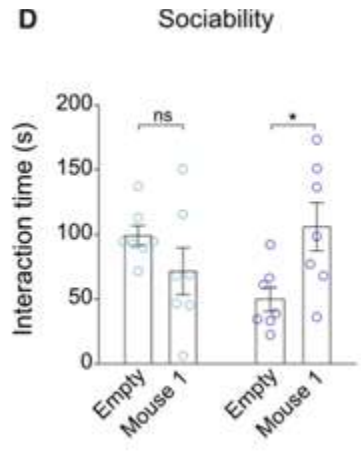
PVN



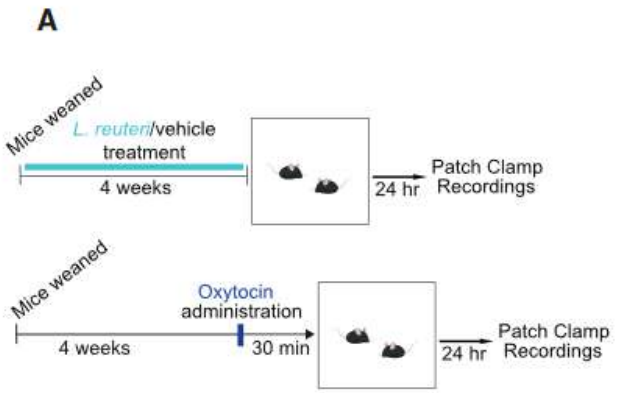


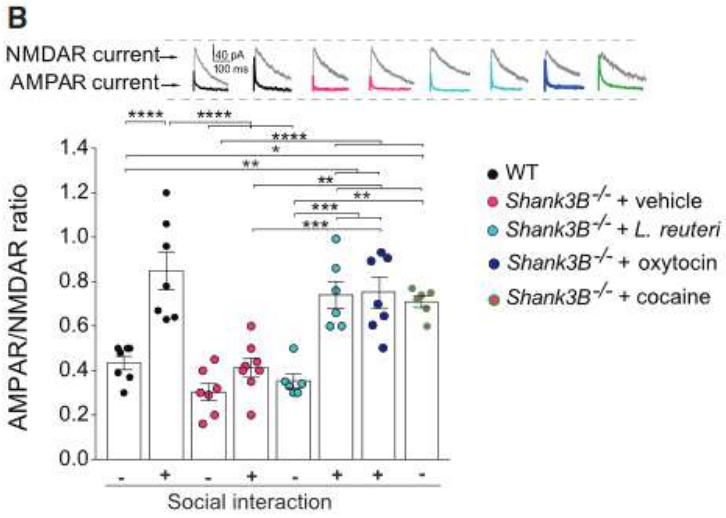


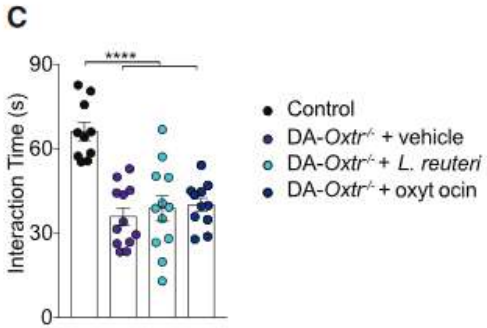


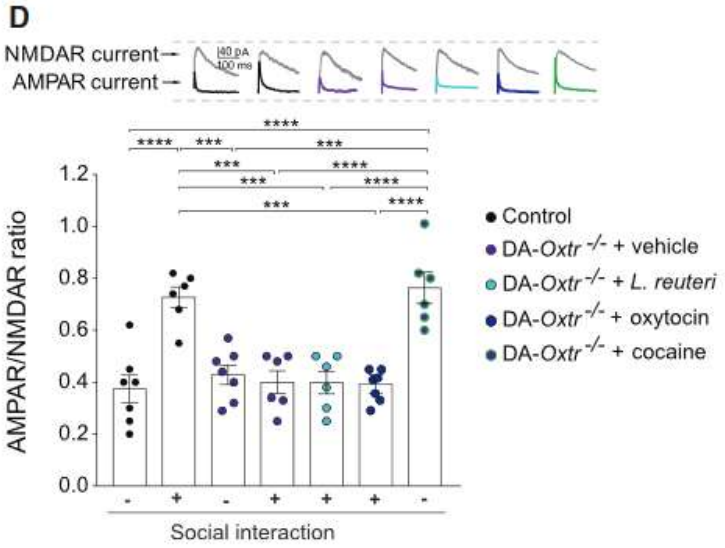


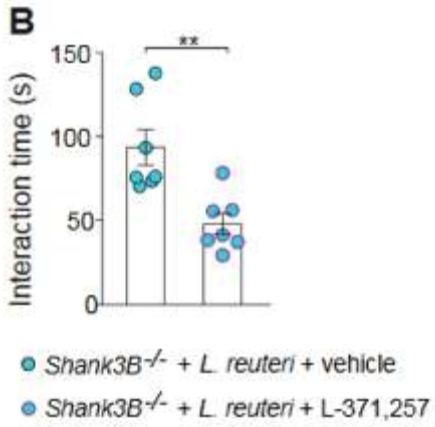
L. *reuteri* increases the basal strength of excitatory synapses of DA neurons through oxytocin



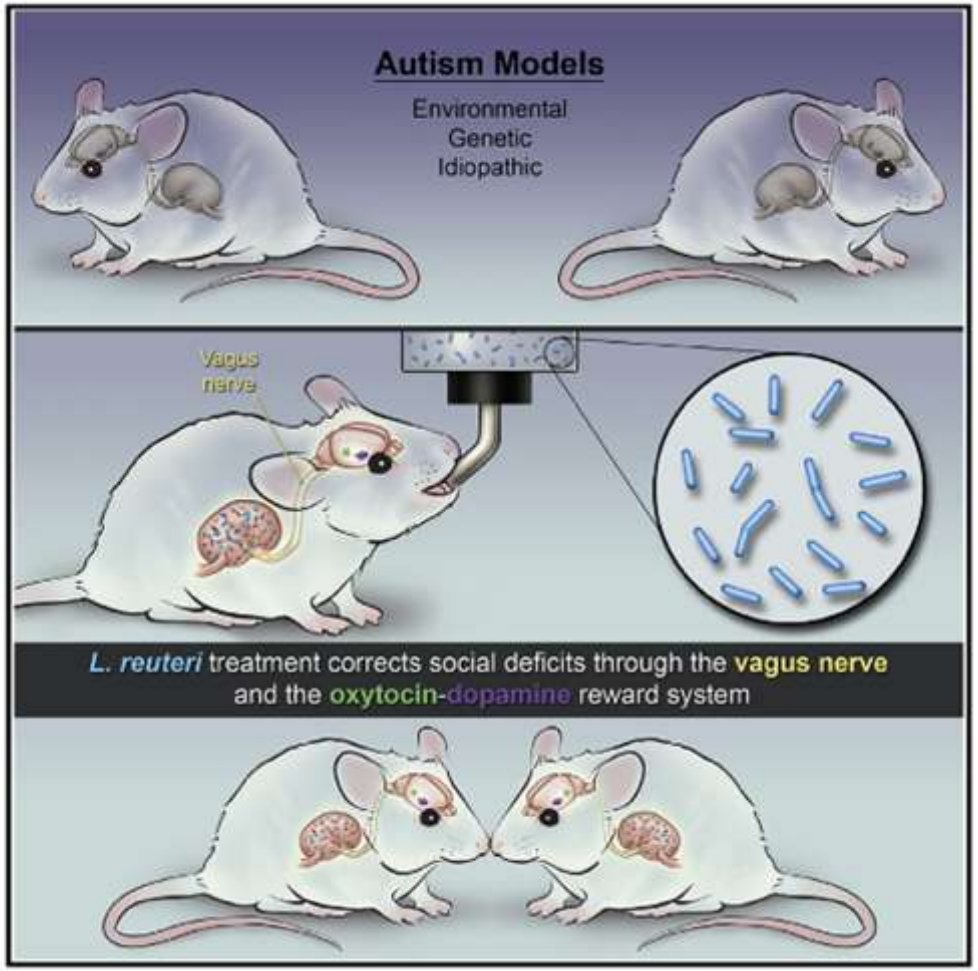








Microbial-mediated neural circuits for relieving ASD symptoms



Microbes change →ASD

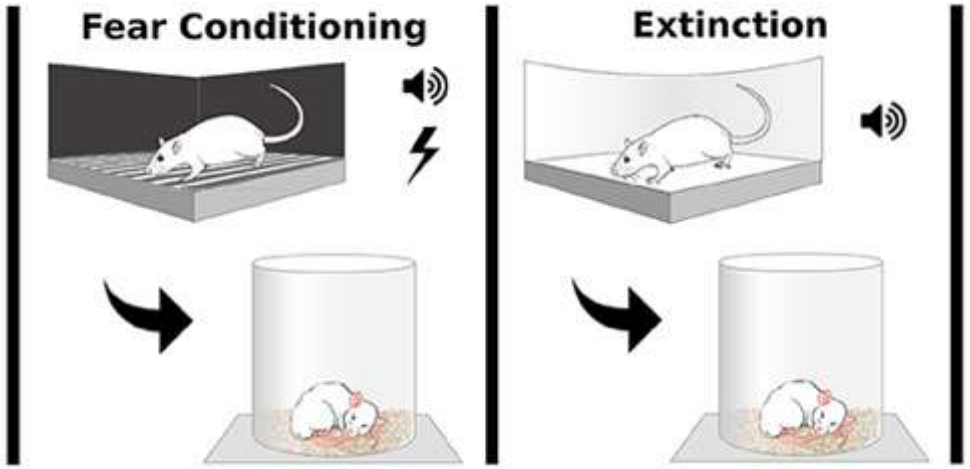
Learning and memory

Article

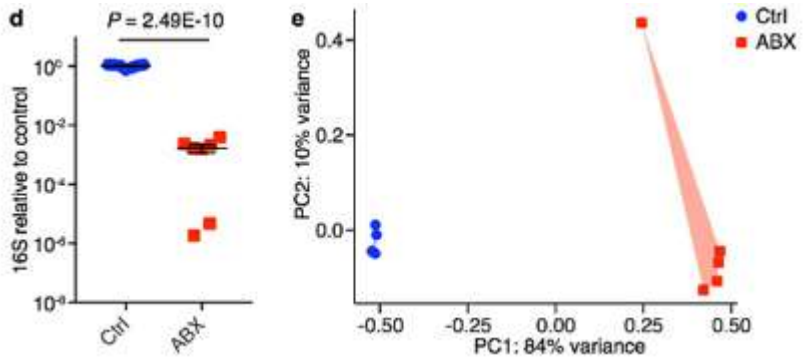
The microbiota regulate neuronal function and fear extinction learning

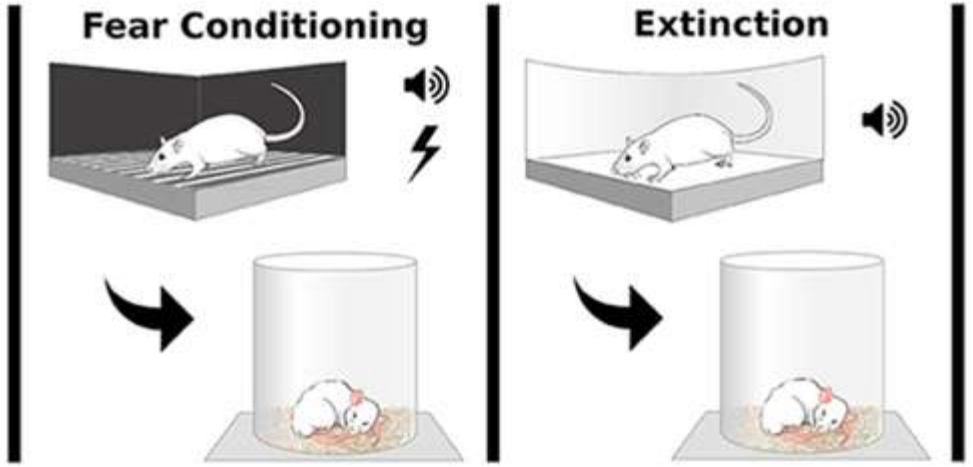
https://doi.org/10.1038/s41586-019-1644-y
Received: 23 August 2018
Accepted: 5 September 2019
Published online: 23 October 2019

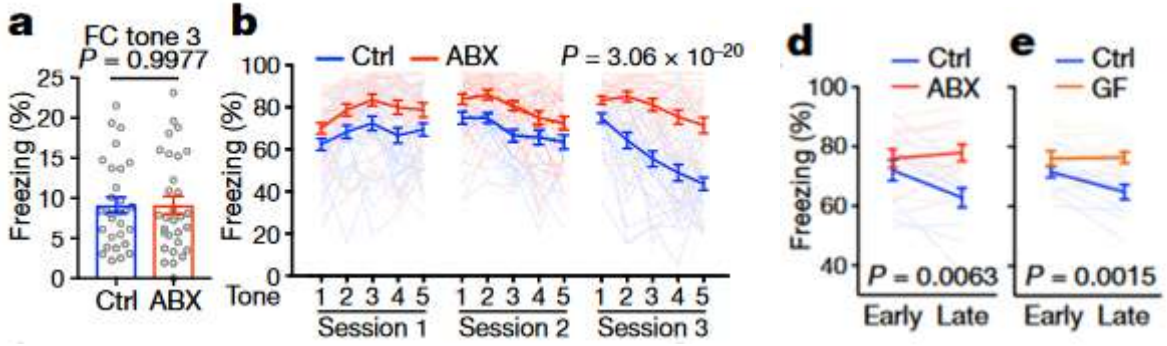
Coco Chu[1], Mitchell H. Murdock[2,3,4], Deqiang Jing[2,4,5], Tae Hyung Won[6], Hattie Chung[7], Adam M. Kressel[6,8,10], Tea Tsaava[8], Meghan E. Addorisio[8], Gregory G. Putzel[1], Lei Zhou[1], Nicholas J. Bessman[1], Ruirong Yang[2,4,5], Saya Moriyama[1], Christopher N. Parkhurst[1], Anfei Li[2,4], Heidi C. Meyer[9], Fei Teng[1], Sangeeta S. Chavan[6,8,11], Kevin J. Tracey[6,8,11], Aviv Regev[2,12], Frank C. Schroeder[6], Francis S. Lee[2,4,5], Conor Liston[2,3,4]* & David Artis[1,13]*

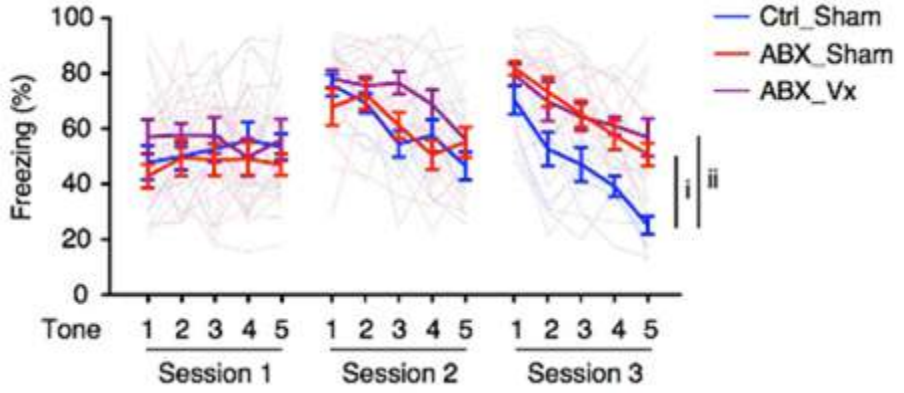


Lack of microbiota impairs extinction learning

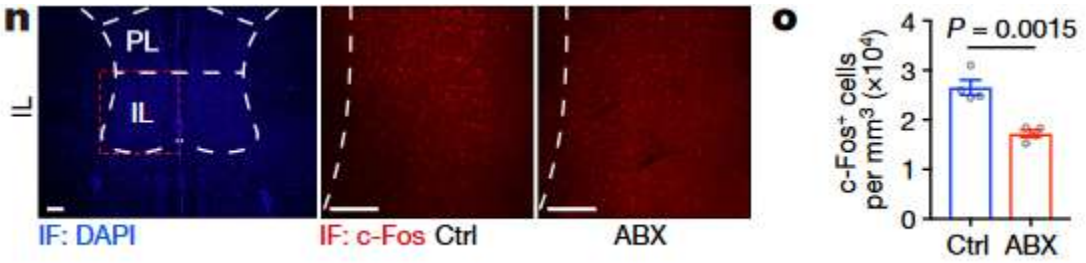


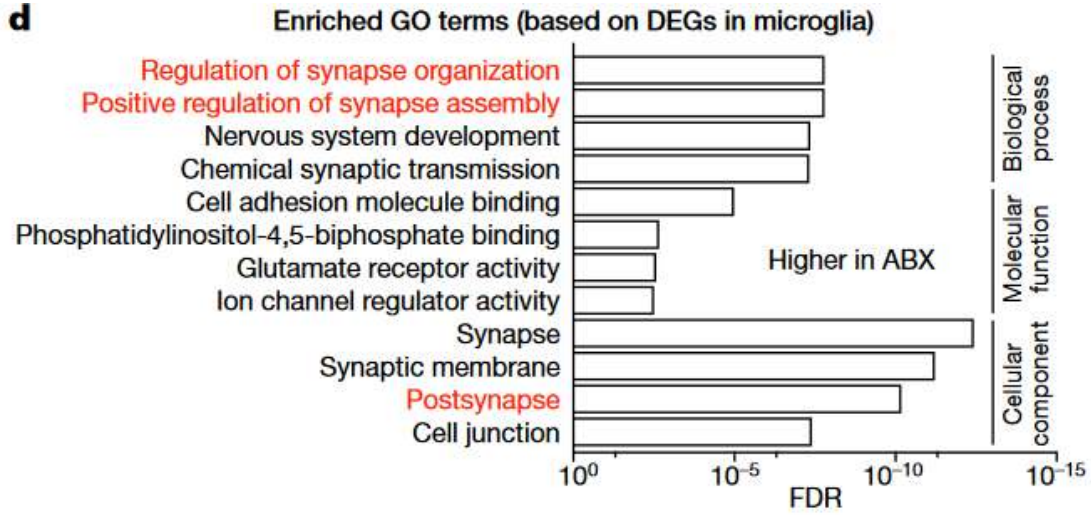


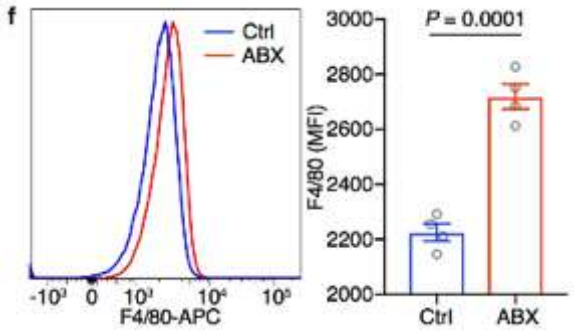


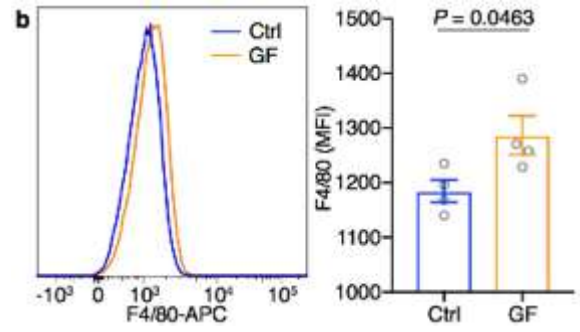


Neuronal and glial changes in microbes-lacking mice

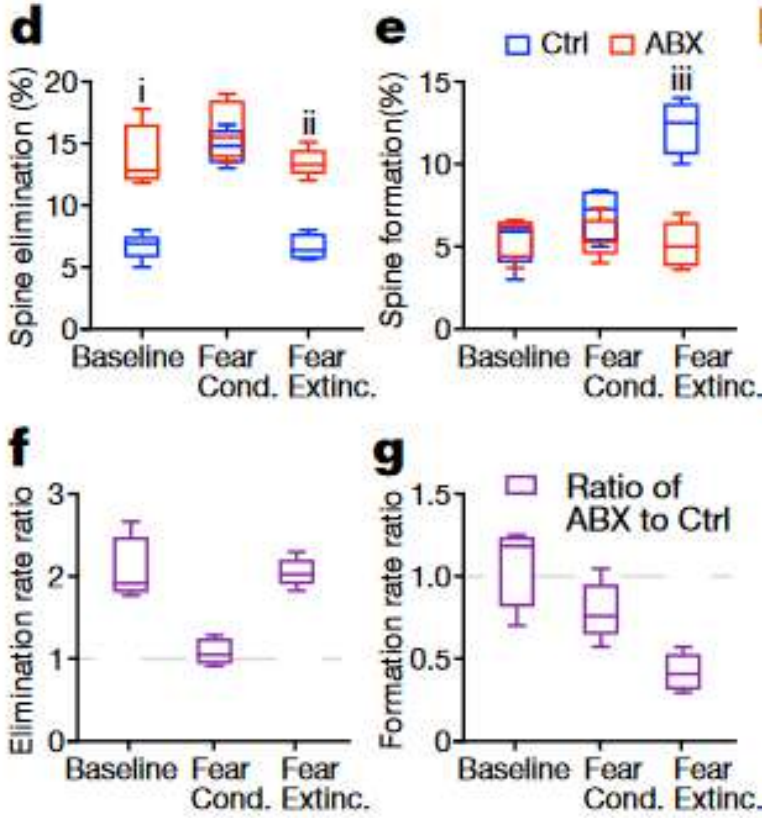


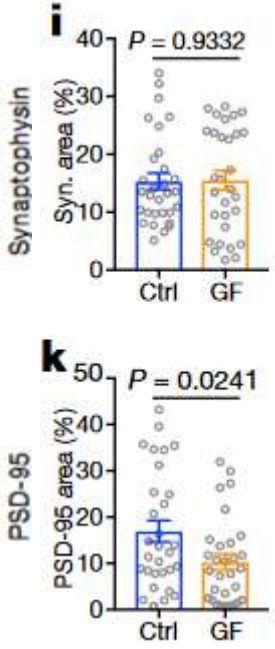


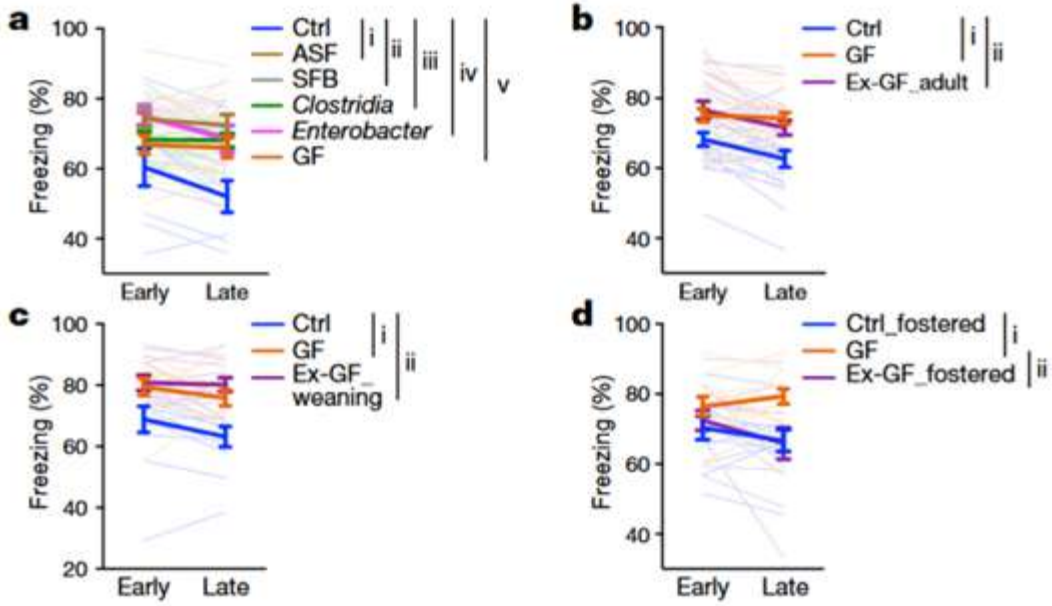




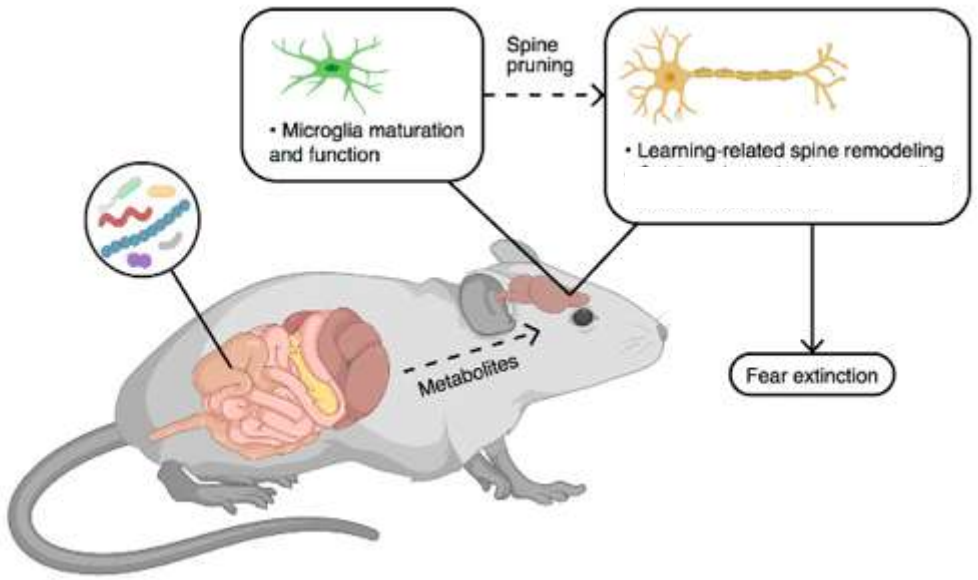
Defective extinction-learning-related dendritic spine formation before weaning

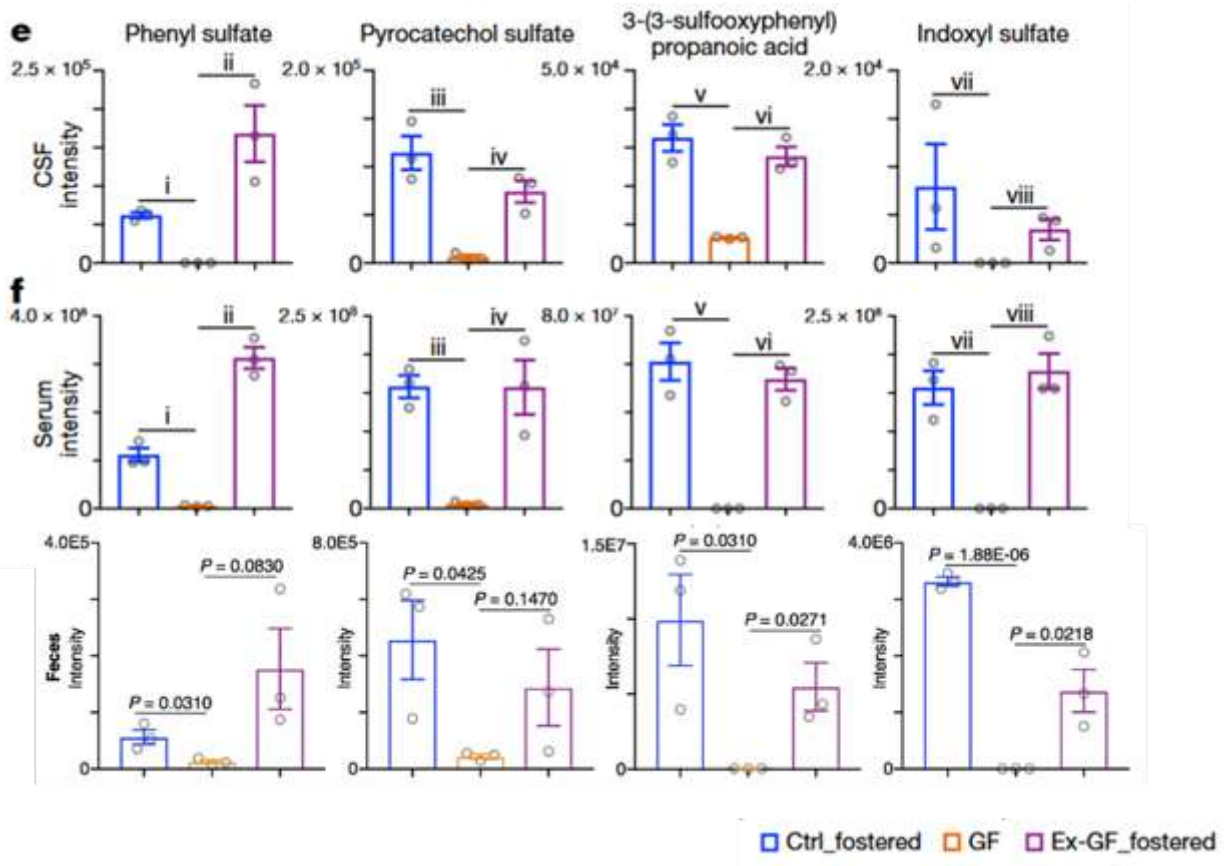




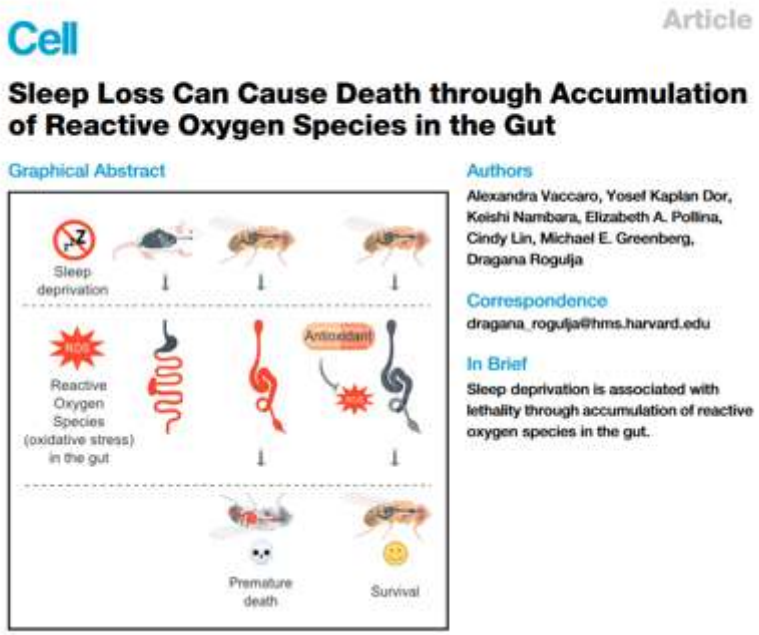


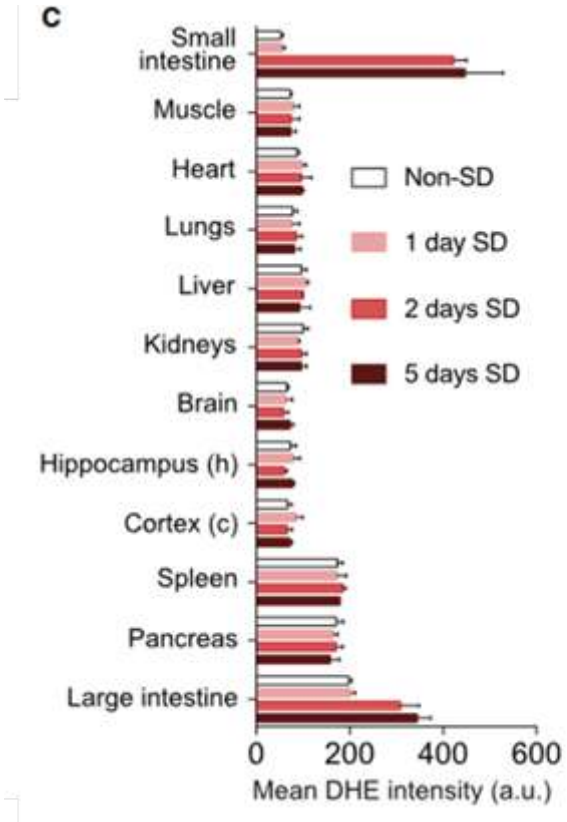
Gut microbes change behavior by regulating metabolism

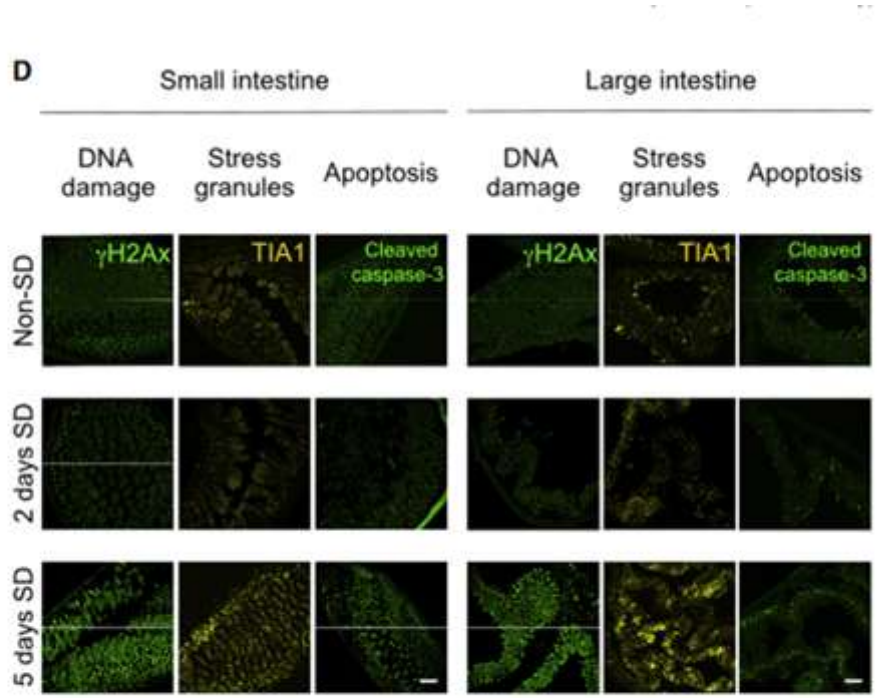




Oxidative stress







Melatonin rescues intestinal inflammation and cell damage caused by sleep loss

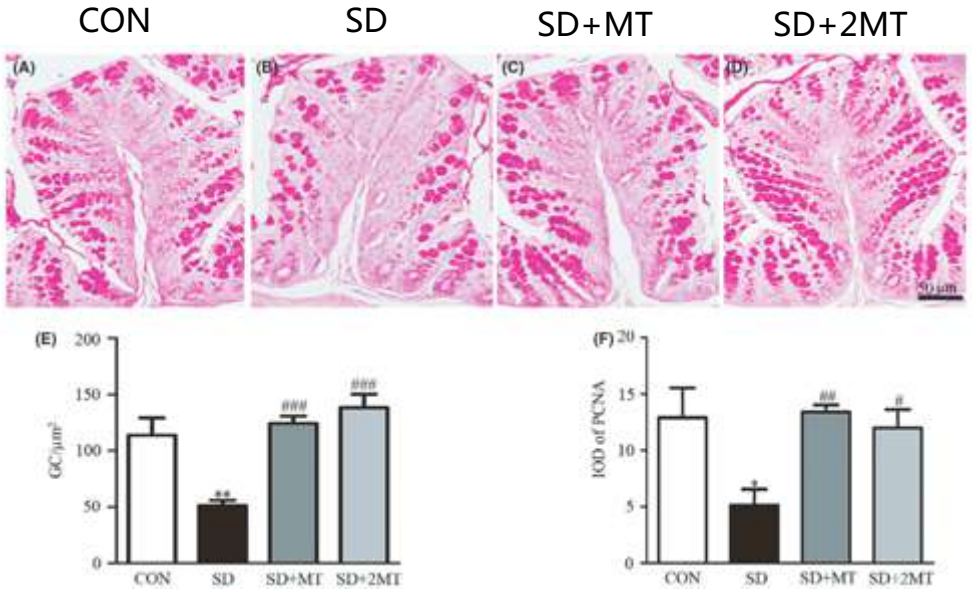
Received: 15 November 2018 | Revised: 20 March 2019 | Accepted: 21 March 2019
DOI: 10.1111/jpi.12574

ORIGINAL ARTICLE

Journal of Pineal Research WILEY

Role of melatonin in sleep deprivation-induced intestinal barrier dysfunction in mice

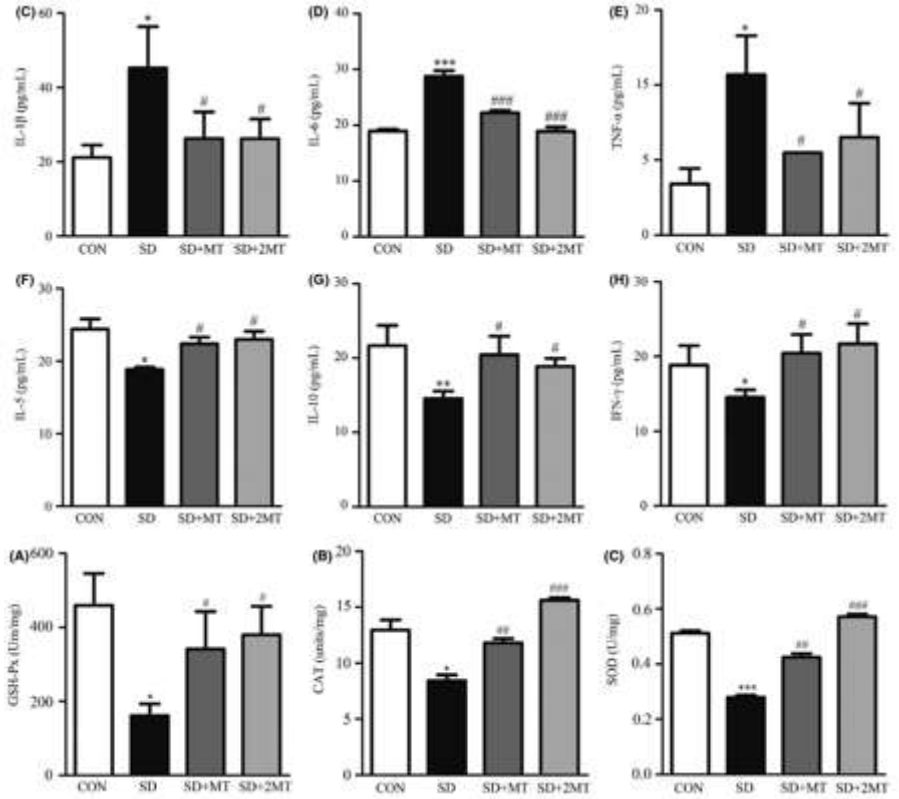
Ting Gao[1] | Zixu Wang[1] | Yulan Dong[1] | Jing Cao[1] | Rutao Lin[1] | Xintong Wang[1] | Zhengquan Yu[2] | Yaoxing Chen[1]



Proinflammatory

Antiinflammatory

Antioxidation



Take home messages

- The gut-brain axis can regulate animal health and some behaviors
- The signal communication in the gut-brain axis is not only through the vagus nerve, but also through circulatory system

References

Tan HE, Sisti AC, Jin H, et al. The gut-brain axis mediates sugar preference. *Nature*. 2020;580(7804):511-516. doi:10.1038/s41586-020-2199-7

Sgritta M, Dooling SW, Buffington SA, et al. Mechanisms Underlying Microbial-Mediated Changes in Social Behavior in Mouse Models of Autism Spectrum Disorder. *Neuron*. 2019;101(2):246-259.e6. doi:10.1016/j.neuron.2018.11.018

Chu C, Murdock MH, Jing D, et al. The microbiota regulate neuronal function and fear extinction learning. *Nature*. 2019;574(7779):543-548. doi:10.1038/s41586-019-1644-y

Totty MS, Chesney LA, Geist PA and Datta S (2017) Sleep-Dependent Oscillatory Synchronization: A Role in Fear Memory Consolidation. *Front. Neural Circuits* 11:49. doi: 10.3389/fncir.2017.00049

Alexandra Vaccaro, Yosef Kaplan Dor, Keishi Nambara, Elizabeth A. Pollina, Cindy Lin, Michael E. Greenberg, Dragana Rogulja. Sleep Loss Can Cause Death through Accumulation of Reactive Oxygen Species in the Gut. *Cell*, 2020; DOI: 10.1016/j.cell.2020.04.049

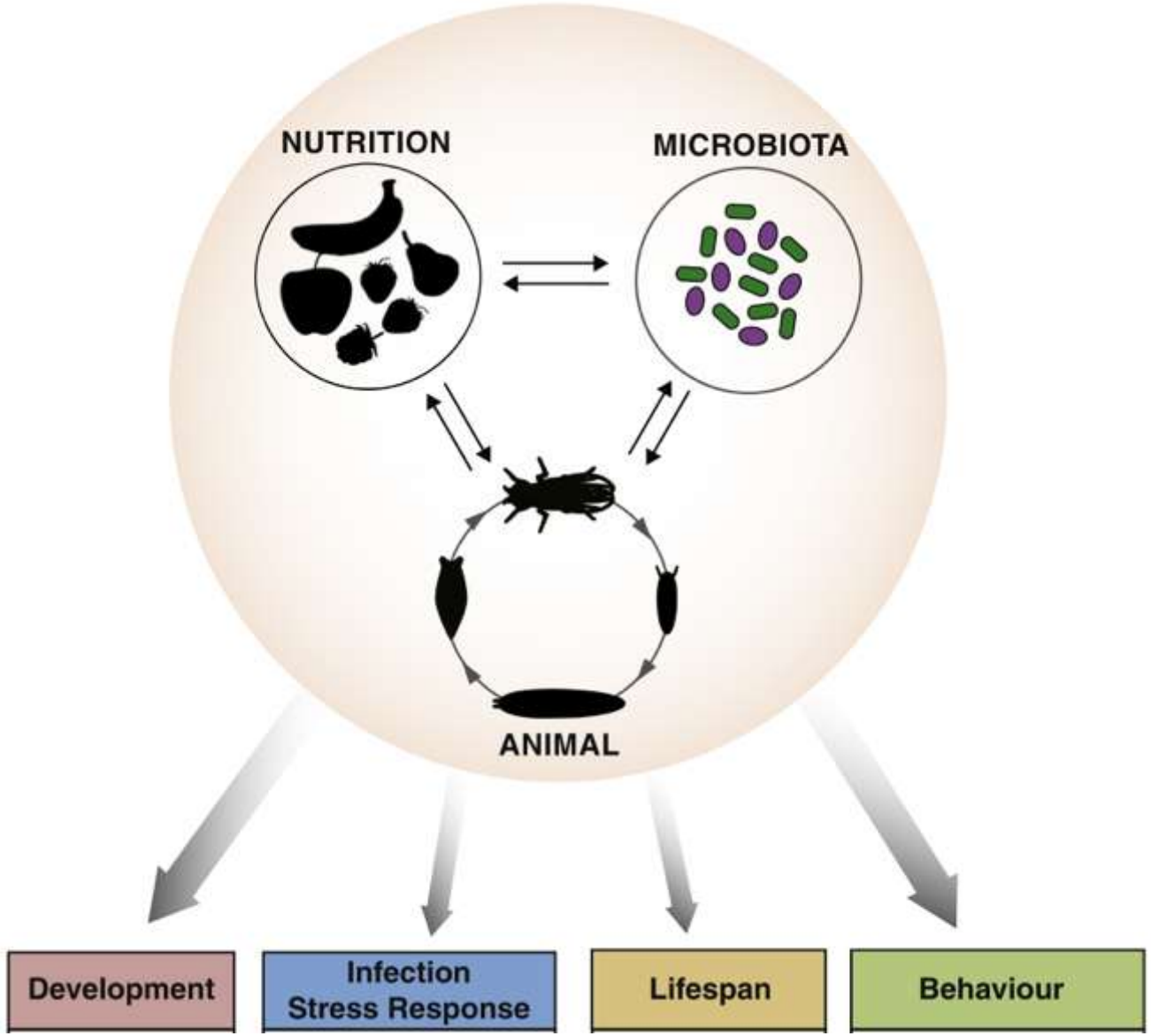
Sharon G, Cruz NJ, Kang DW, et al. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. *Cell*. 2019;177(6):1600-1618.e17. doi:10.1016/j.cell.2019.05.004

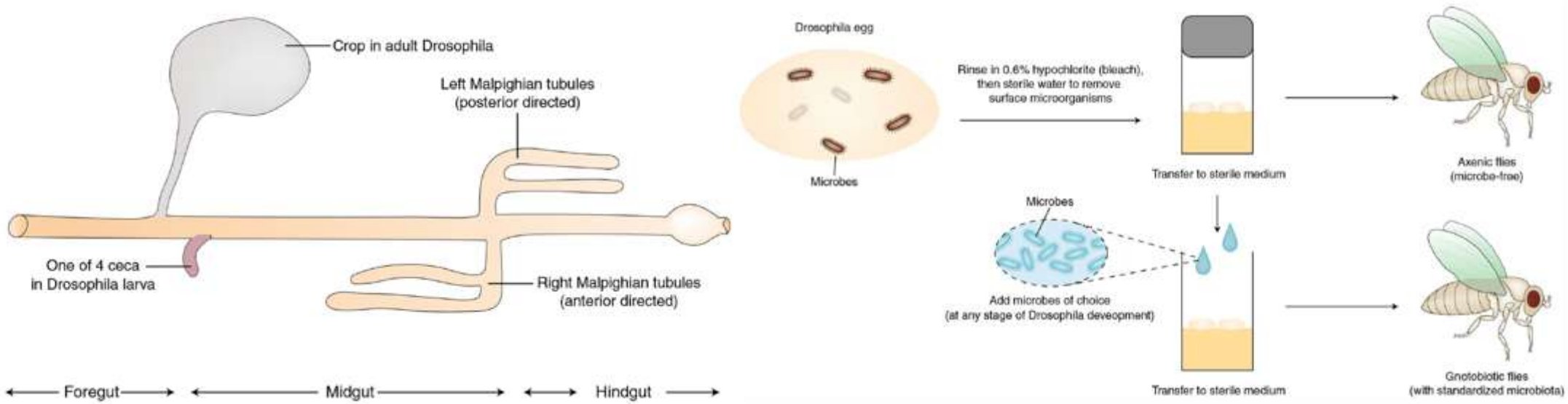
Gao T, Wang Z, Dong Y, et al. Role of melatonin in sleep deprivation-induced intestinal barrier dysfunction in mice. *J Pineal Res.* 2019;67(1):e12574. doi:10.1111/jpi.12574

PART III:

Physiological function in Drosophila through Gut-Brain communication

Wang Lin
2020.7.30


NUTRITION
MICROBIOTA
ANIMAL
Development
Infection
Stress Response
Lifespan
Behaviour



The major commensals in the Drosophila intestine:
Acetobacter pomorum, Acetobacter tropicalis, Lactobacillus brevis, Lactobacillus plantarum

Section 1: The microbiome and Physiological characteristics of hosts

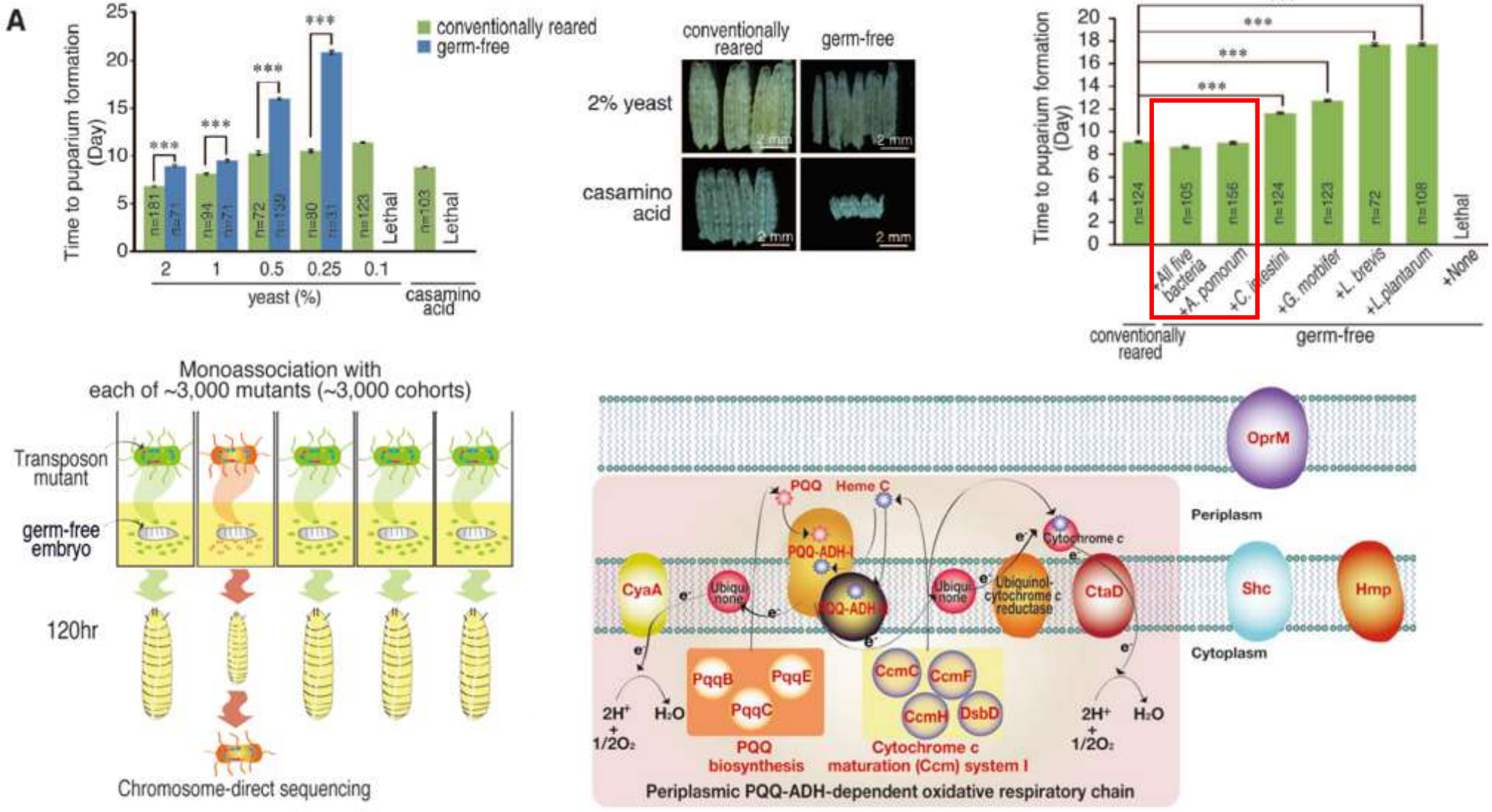
Science
AAAS

Drosophila Microbiome Modulates Host Developmental and Metabolic Homeostasis via Insulin Signaling

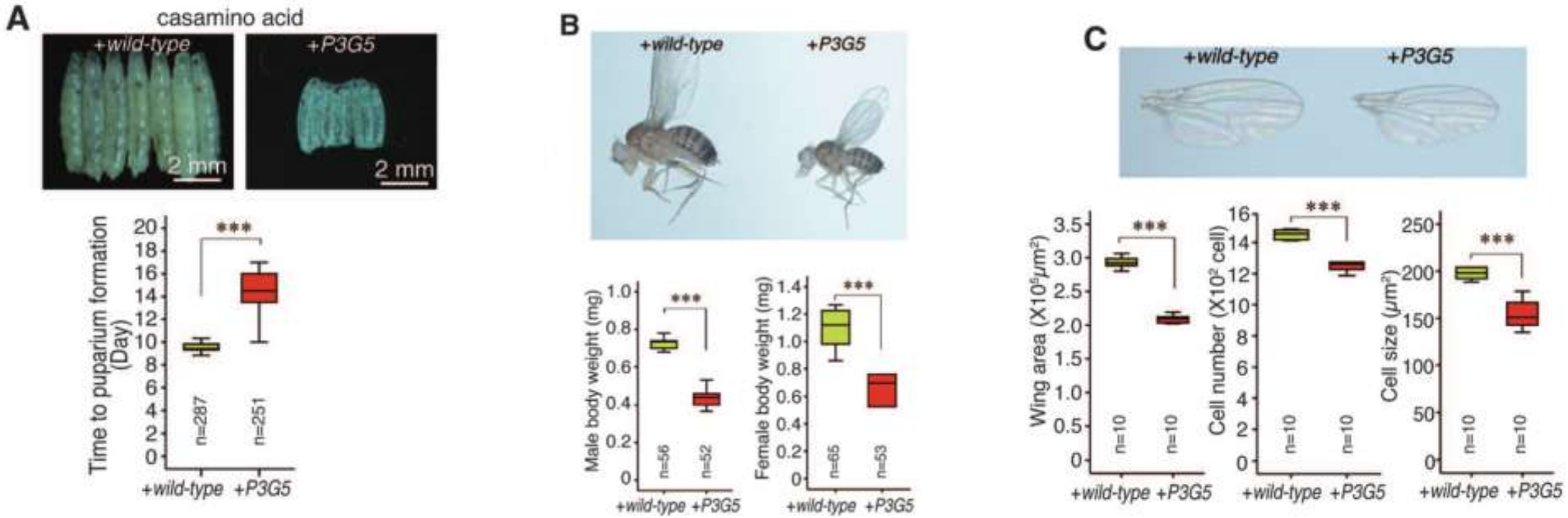
Seung Chul Shin *et al.*

Science **334**, 670 (2011);
DOI: 10.1126/science.1212782

- Genome-wide screening of the Acetobacter genes essential for host growth.



- Commensal PQQ-ADH activity is required for controlling developmental rate, body size

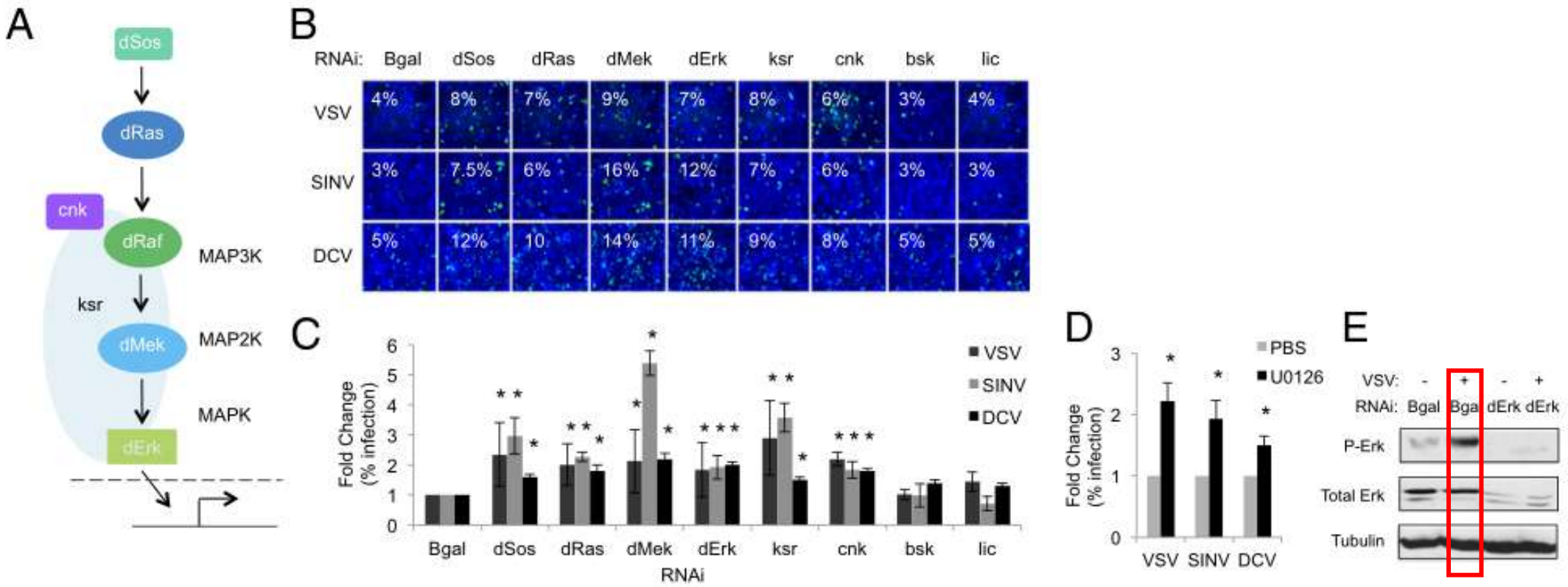


Cell Host & Microbe
Article

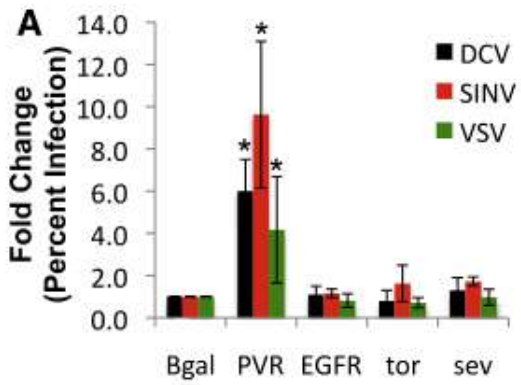
Microbiota-Dependent Priming of Antiviral Intestinal Immunity in *Drosophila*

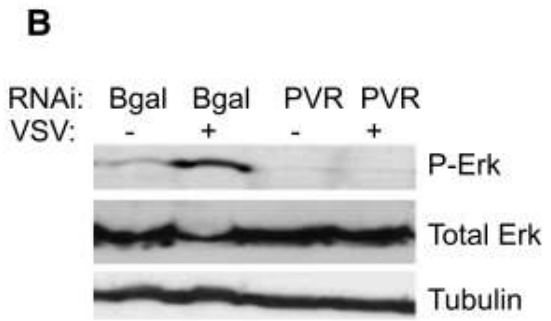
Christine L. Sansone,[1] Jonathan Cohen,[1] Ari Yasunaga,[1] Jie Xu,[1] Greg Osborn,[1] Harry Subramanian,[1] Beth Gold,[1] Nicolas Buchon,[2] and Sara Cherry[1,*]
[1]Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA
[2]Department of Entomology, Cornell University, Ithaca, NY 14853, USA
*Correspondence: cherrys@mail.med.upenn.edu
http://dx.doi.org/10.1016/j.chom.2015.10.010

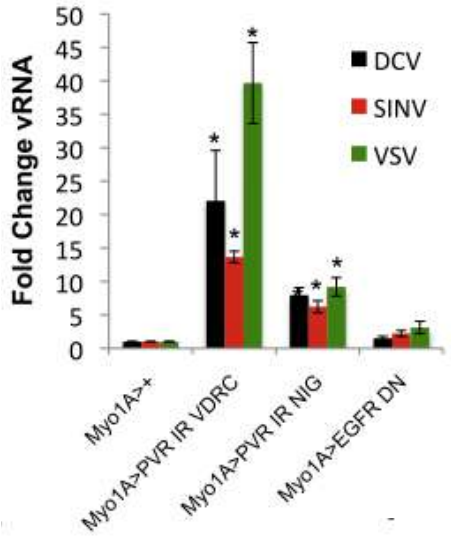
- The ERK pathway is broadly activated by and restricts viral infections in Drosophila cells.

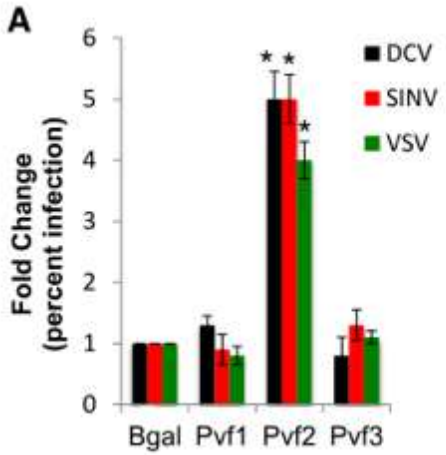


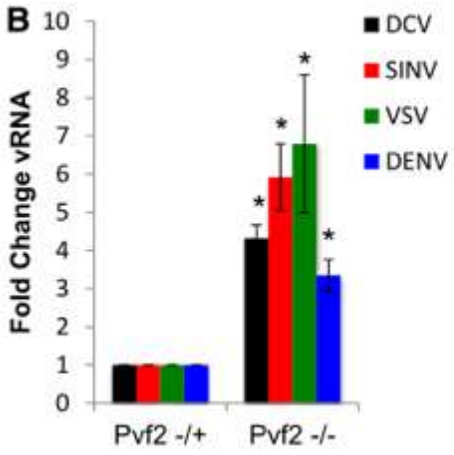
- PVR and Pvf2 are Required for Antiviral Defense

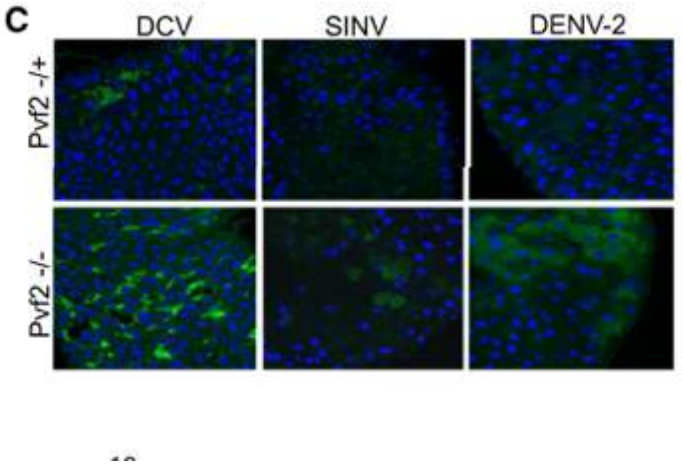


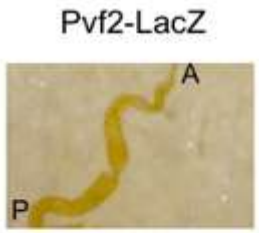


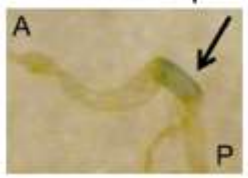




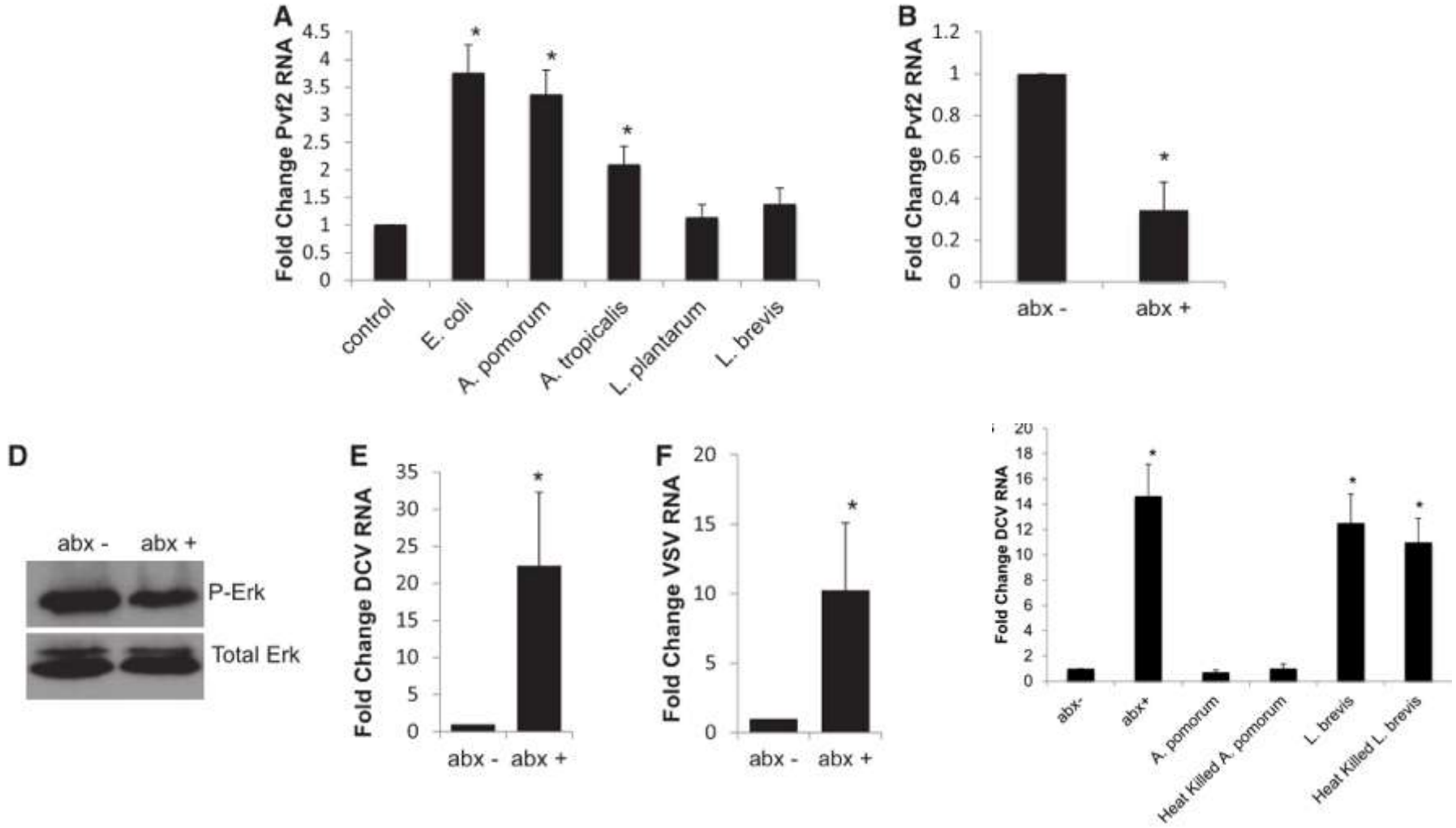


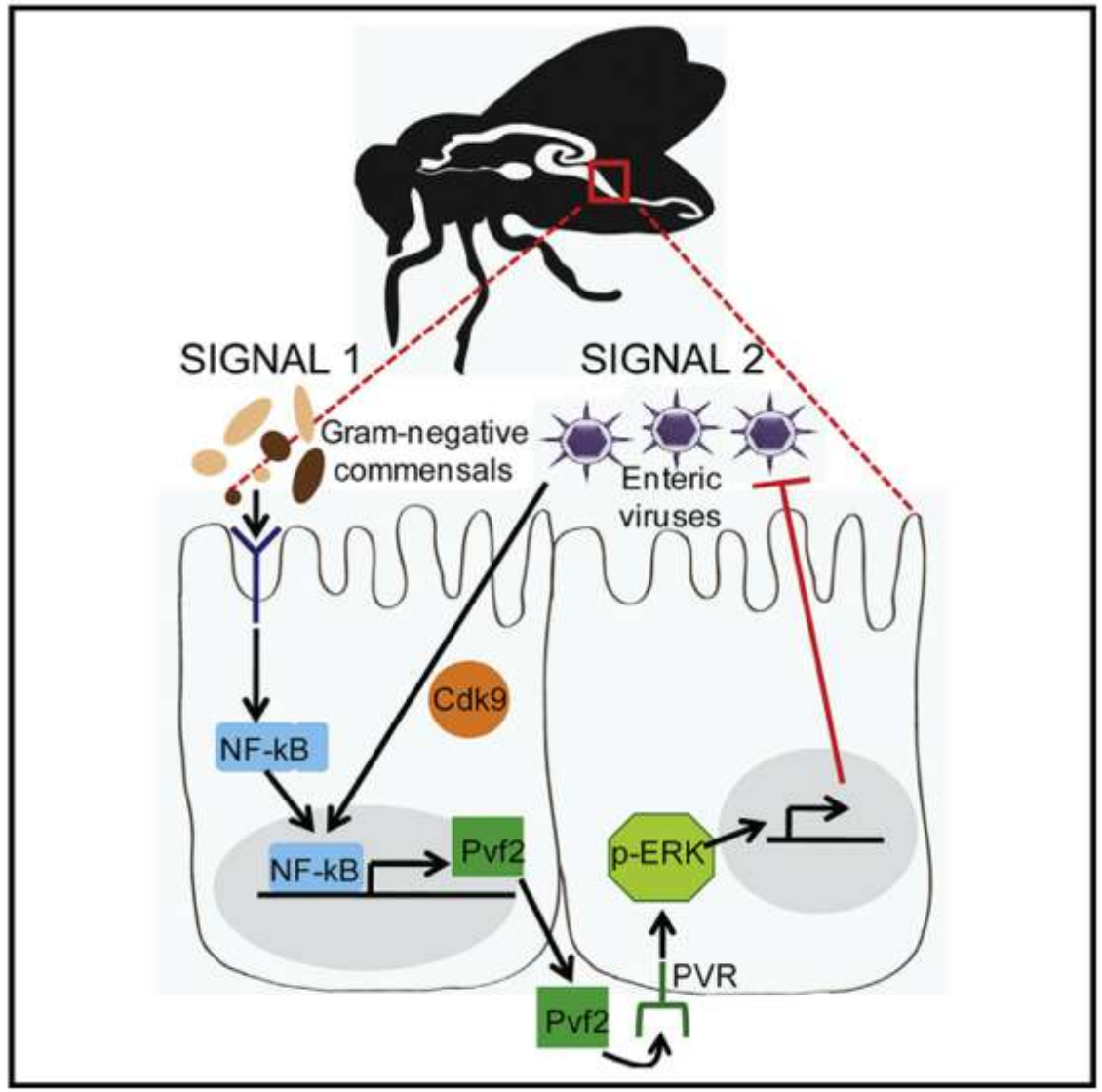






- The Microbiota Regulates Pvf2 Expression and Antiviral Defense



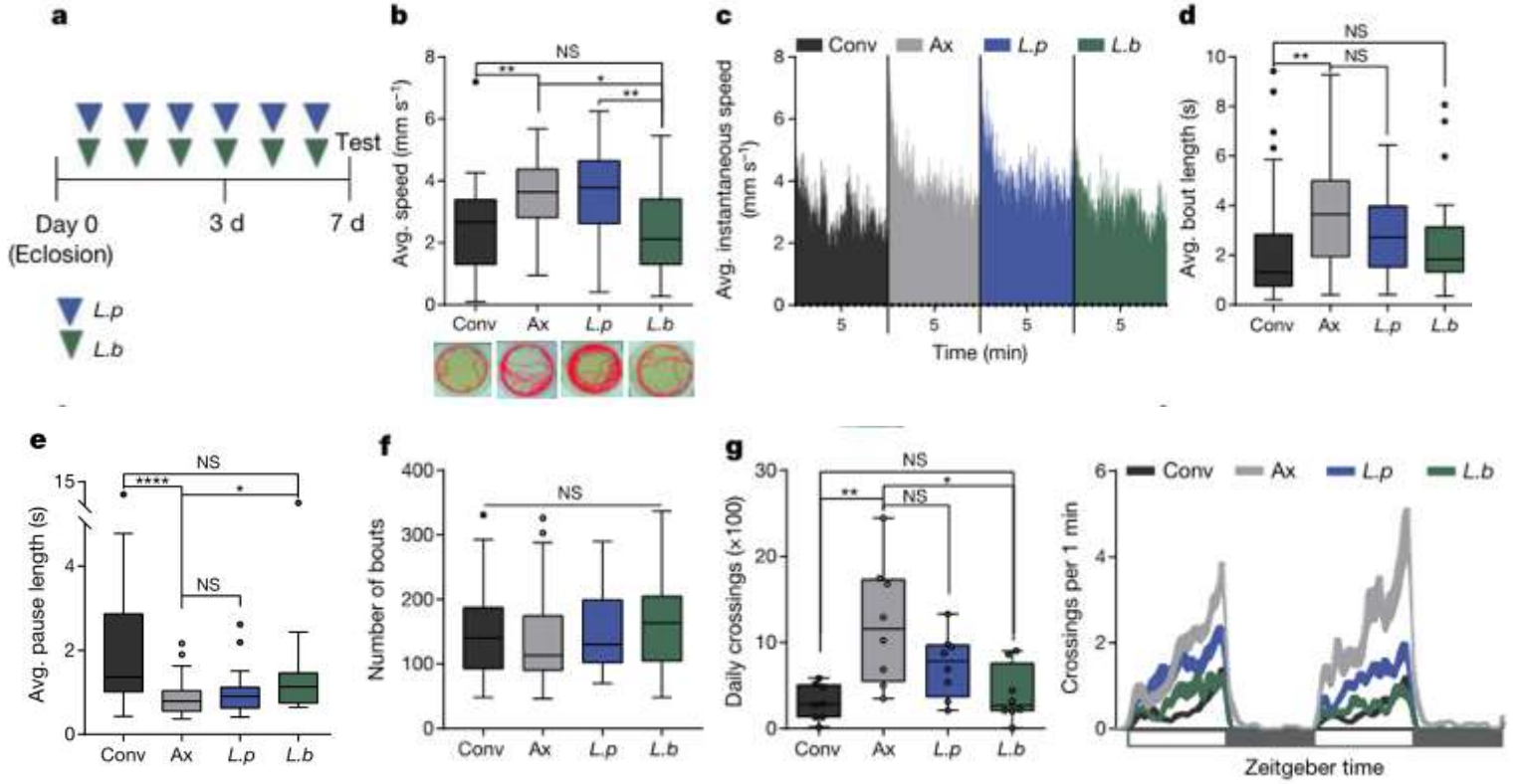

SIGNAL 1
SIGNAL 2
Gram-negative commensals
Enteric viruses
Cdk9
NF-kB
NF-kB
Pvf2
p-ERK
PVR
Pvf2

Section 2: The microbiome and behavior

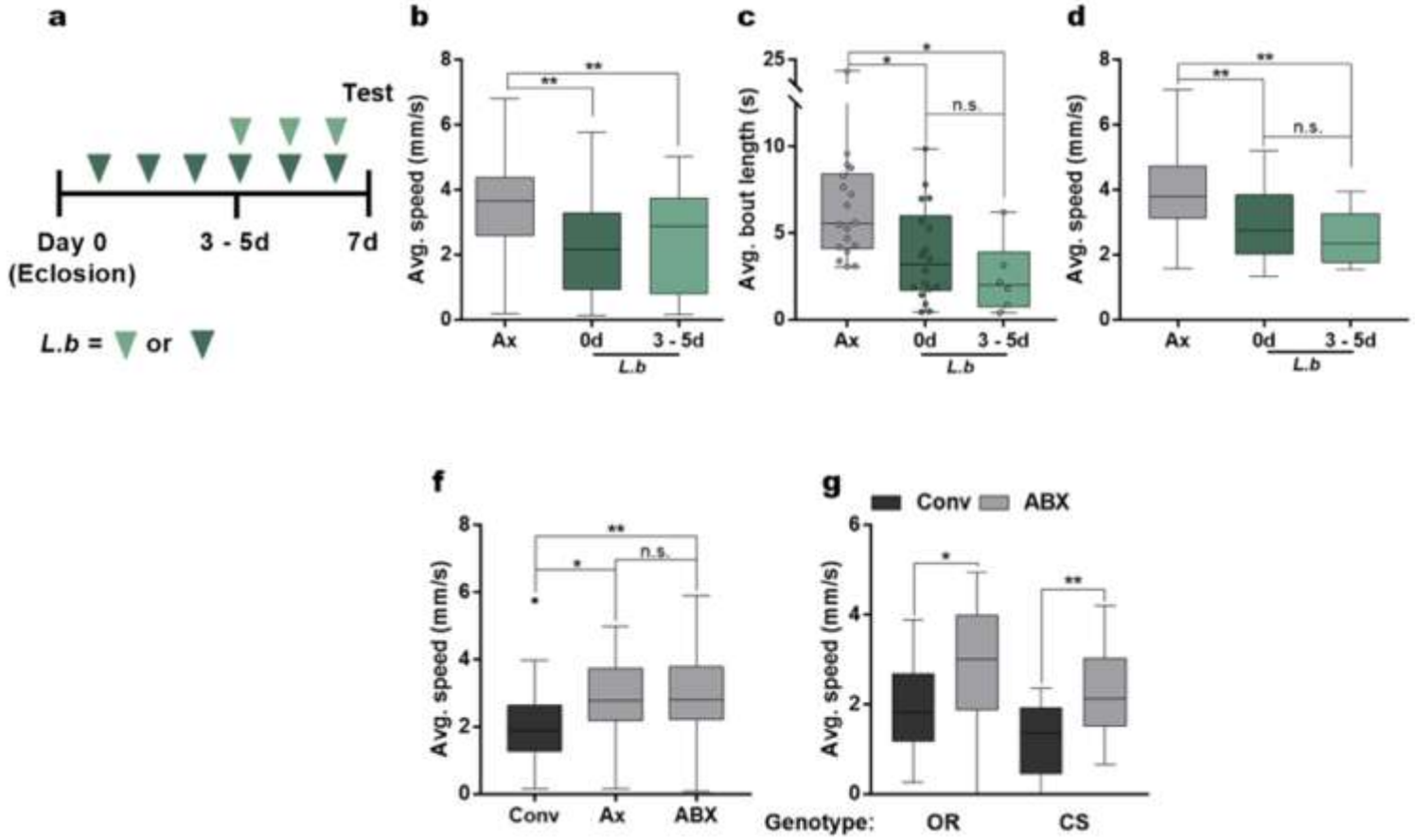
A gut microbial factor modulates locomotor behaviour in *Drosophila*

Catherine E. Schretter[1]*, Jost Vielmetter[2], Imre Bartos[3], Zsuzsa Marka[3], Szabolcs Marka[3], Sulabha Argade[4] & Sarkis K. Mazmanian[1]*

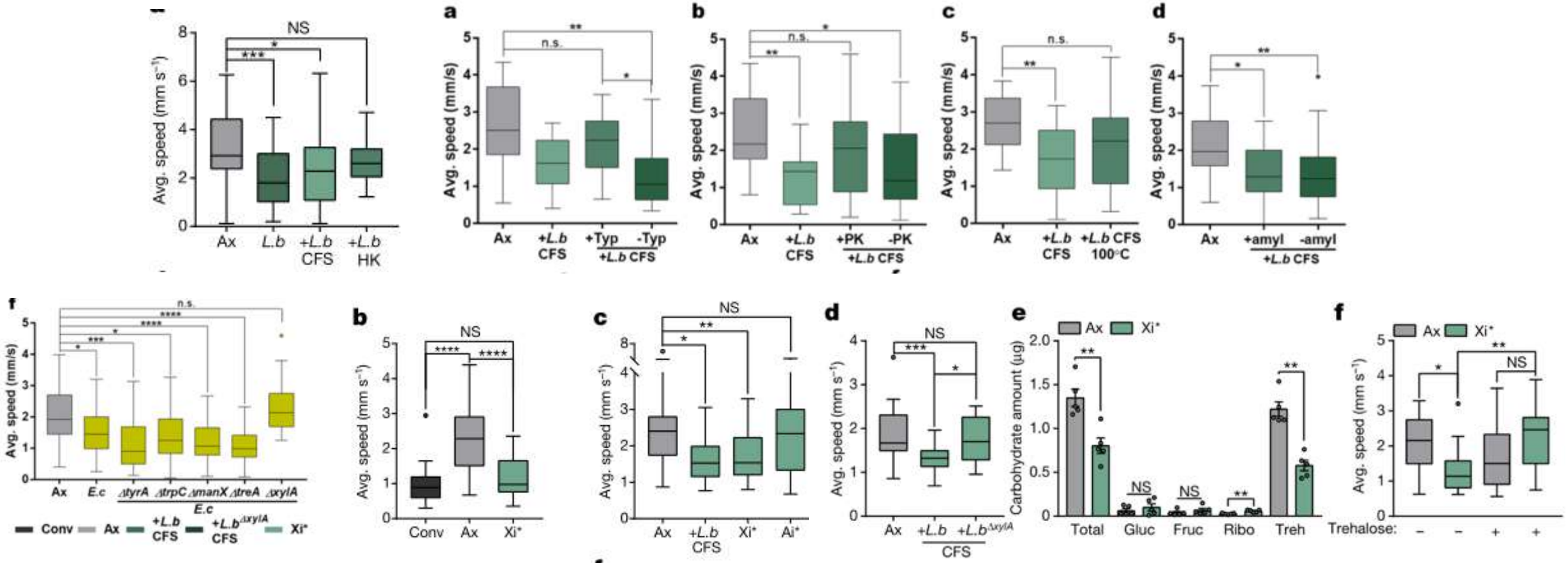
- Select gut bacteria modulate locomotor behavior in flies



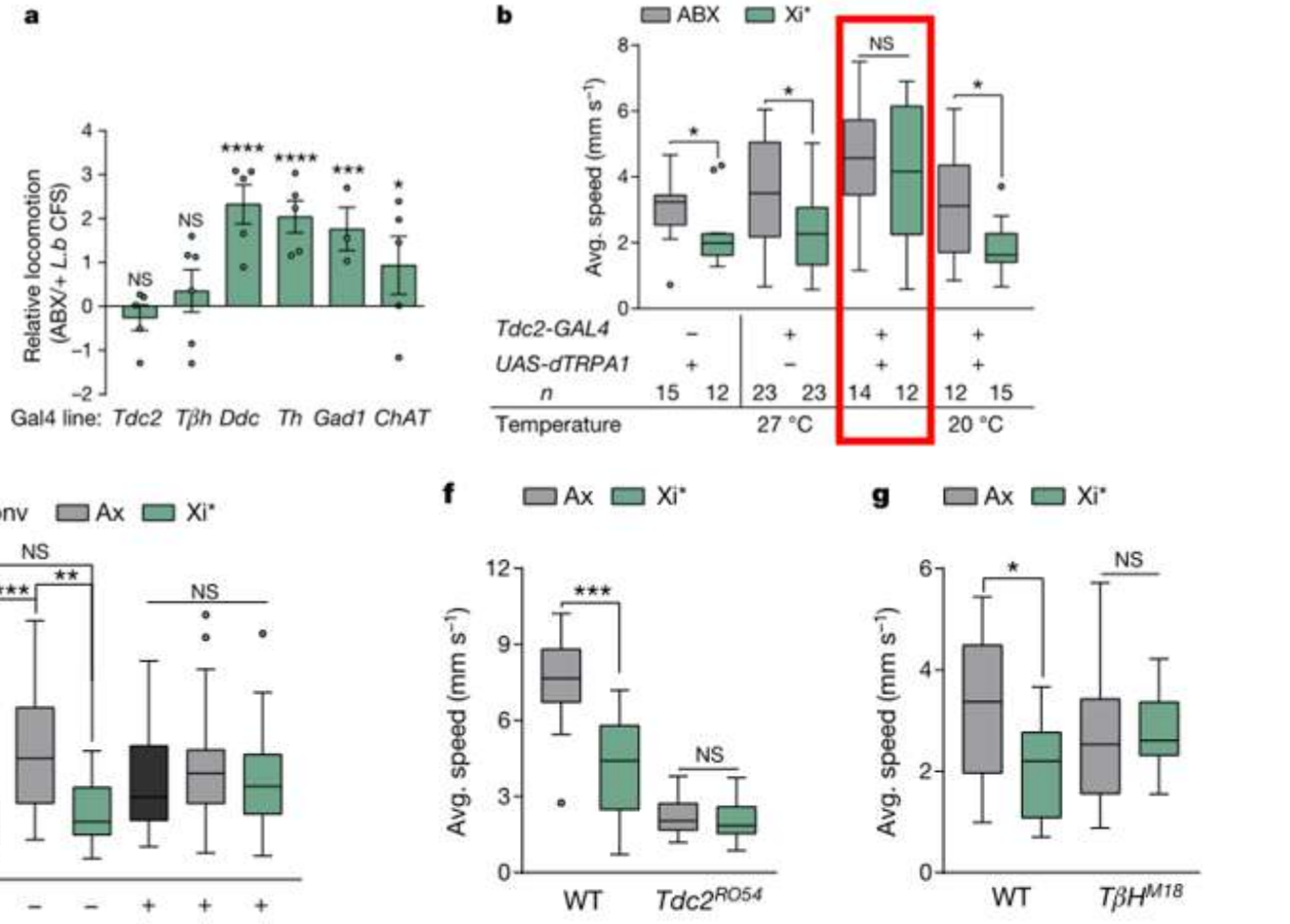
- Post-eclosion microbial signals decrease host locomotion

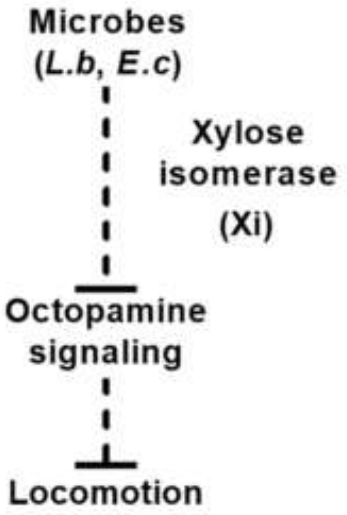


- Xylose isomerase from *L. brevis* alters host locomotion



- Octopamine mediates Xi-induced changes in locomotion.





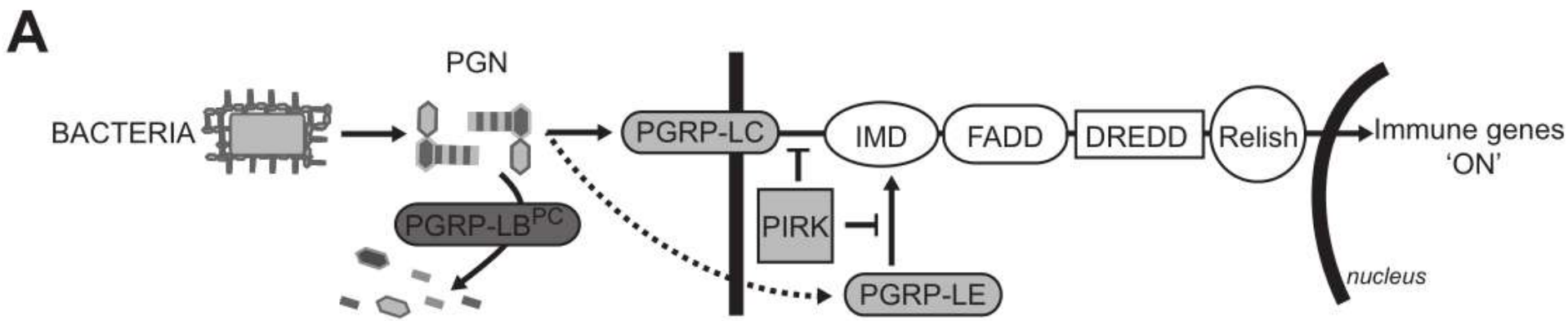
eLIFE elifesciences.org

RESEARCH ARTICLE

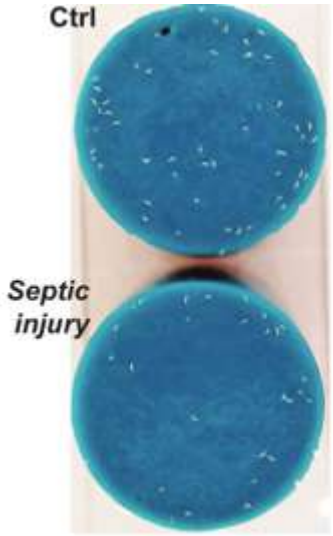
Peptidoglycan sensing by octopaminergic neurons modulates *Drosophila* oviposition

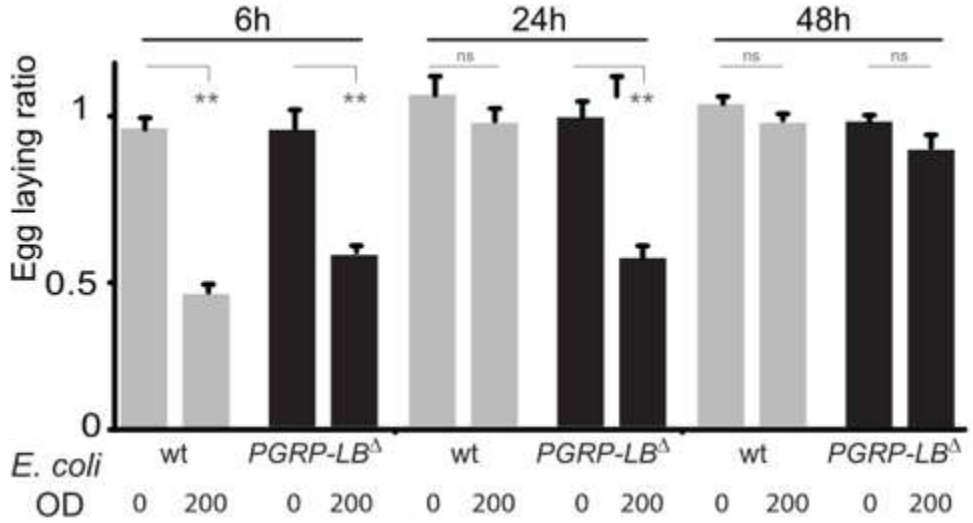
C Leopold Kurz†, Bernard Charroux†, Delphine Chaduli, Annelise Viallat-Lieutaud, Julien Royet*

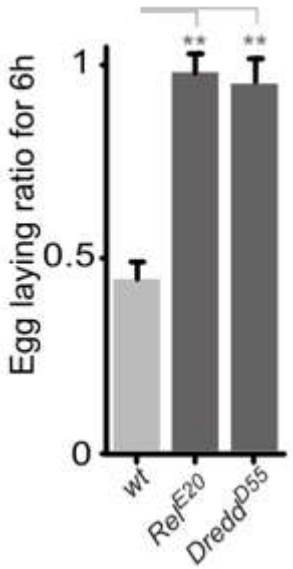
Aix-Marseille Université, Centre National de la Recherche Scientifique, UMR 7288, Institut de Biologie du Développement de Marseille, Marseille Cedex, France



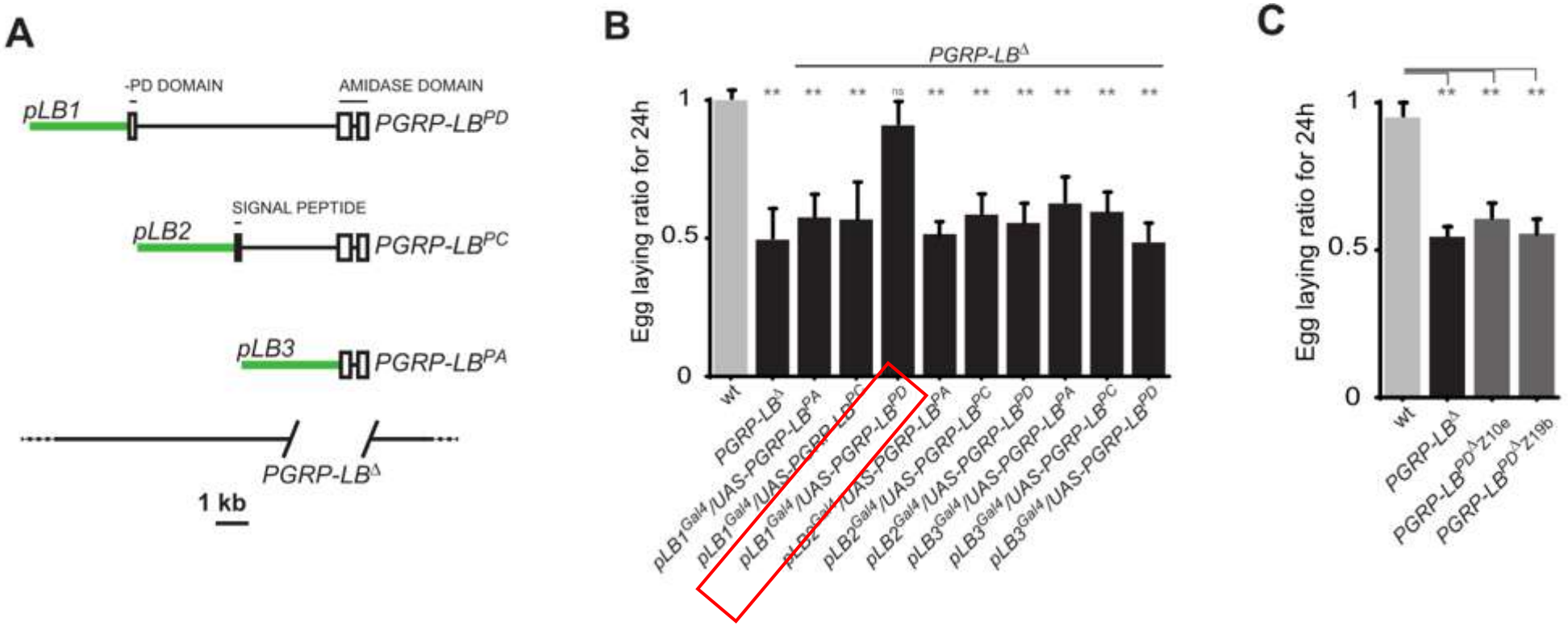
- PGN-mediated NF-kB pathway activation decreases female oviposition.



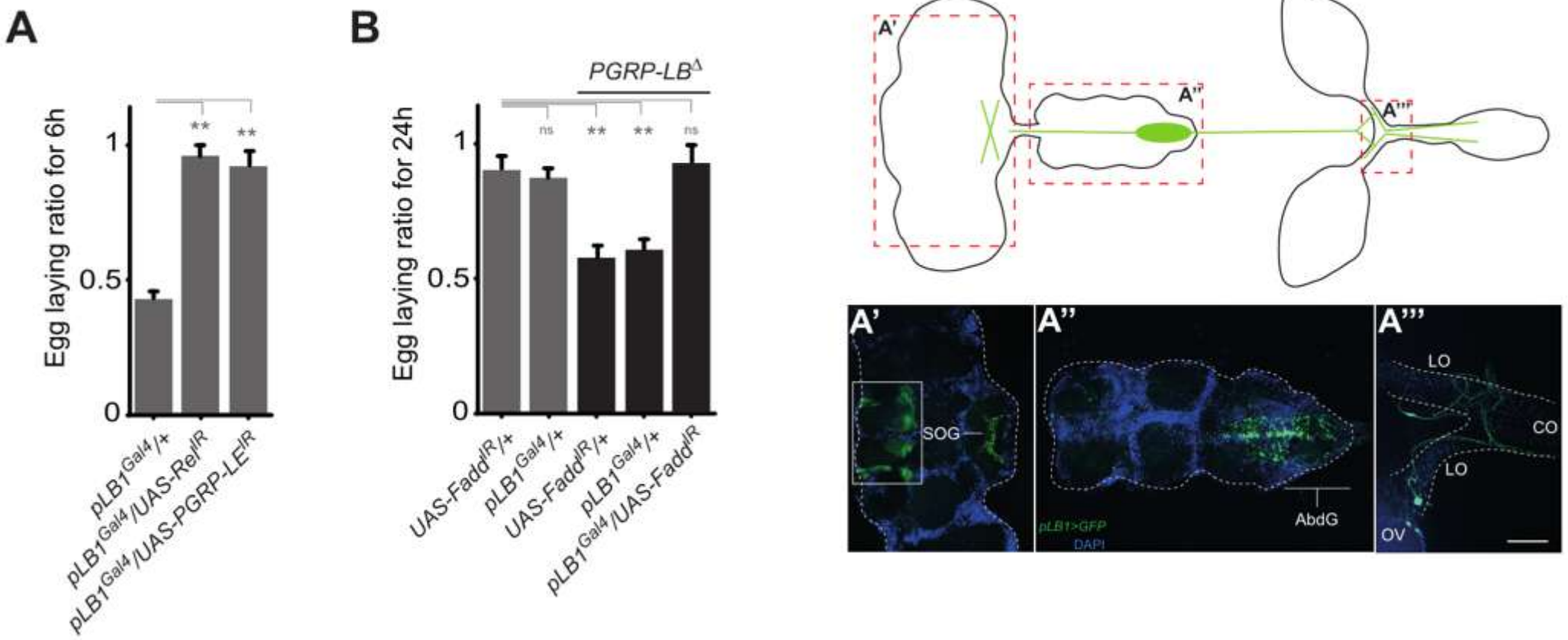


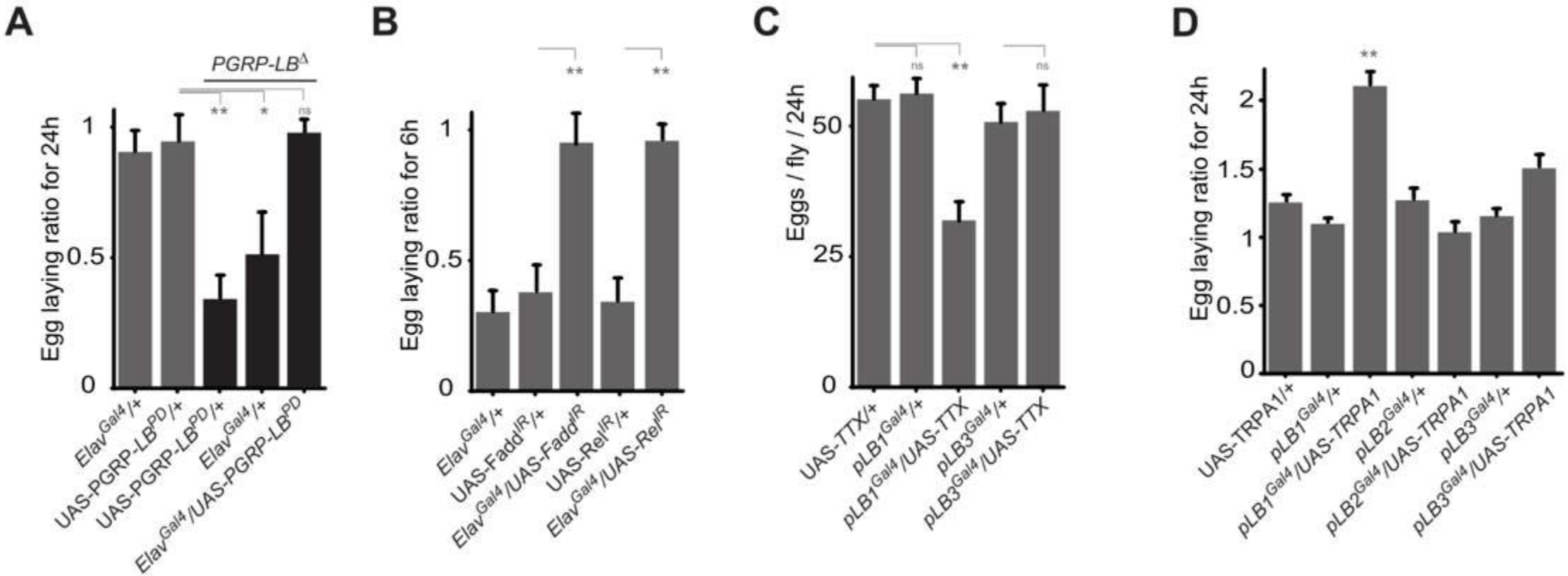


- One specific PGRP-LB isoform controls oviposition

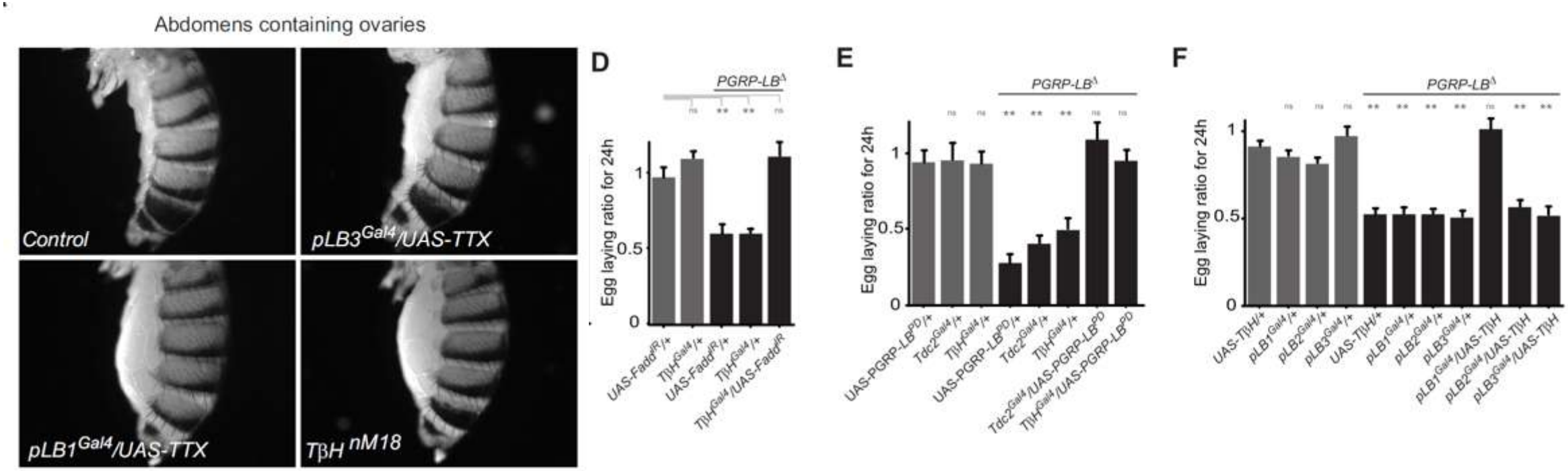


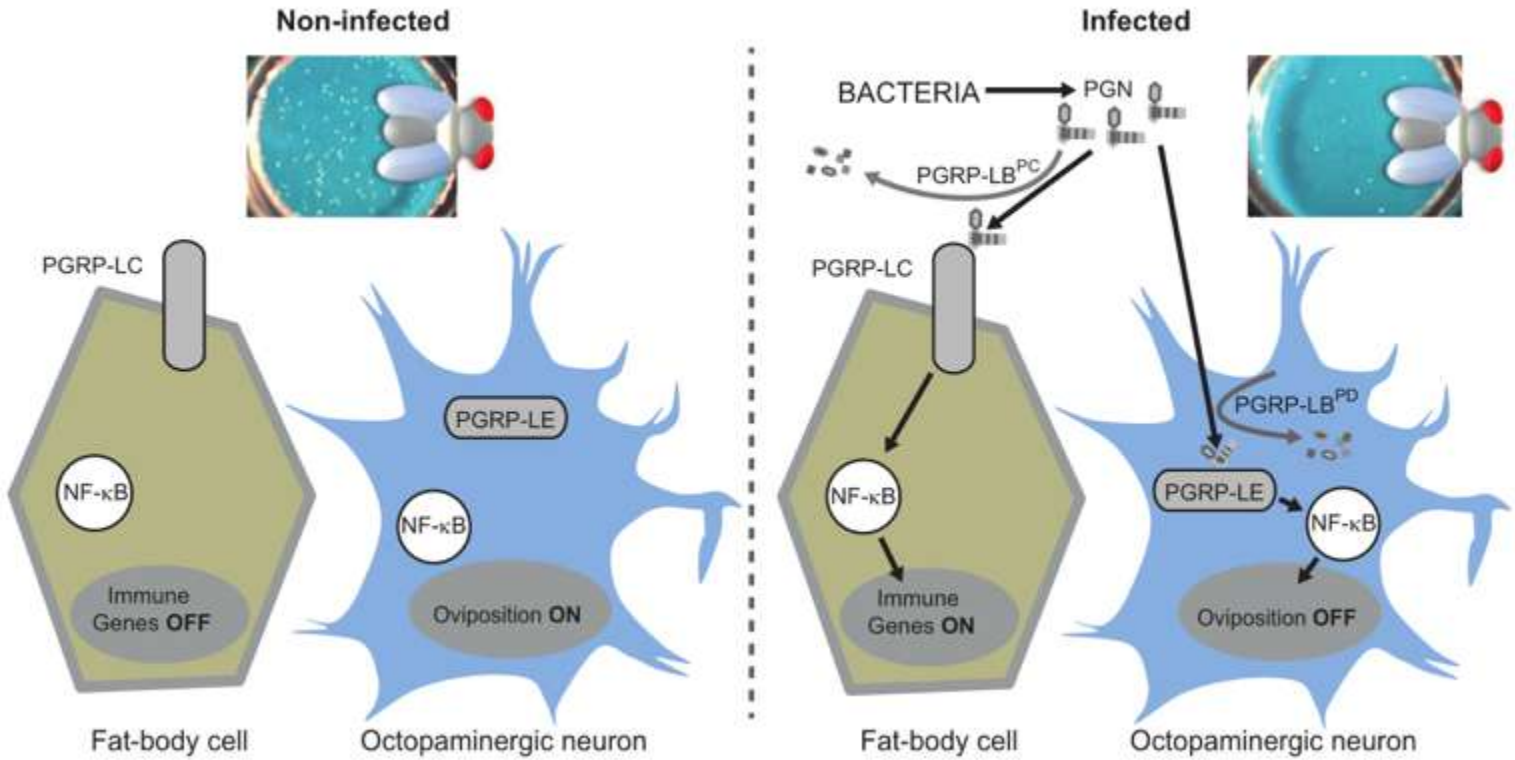
- NF-κB acts in neurons to regulate infection-dependent egg laying




A
PGRP-LB^Δ
**
*
ns
Egg laying ratio for 24h
1
0.5
0
Elav^Gal4/+
UAS-PGRP-LB^PD/+
UAS-PGRP-LB^PD/+
Elav^Gal4/+
Elav^Gal4/UAS-PGRP-LB^PD
B
**
**
Egg laying ratio for 6h
1
0.5
0
Elav^Gal4/+
UAS-Fadd^IR/+
Elav^Gal4/UAS-Fadd^IR
UAS-Rel^IR/+
Elav^Gal4/UAS-Rel^IR
C
ns
**
ns
Eggs / fly / 24h
50
25
0
UAS-TTX/+
pLB1^Gal4/+
pLB1^Gal4/UAS-TTX
pLB3^Gal4/+
pLB3^Gal4/UAS-TTX
D
**
Egg laying ratio for 24h
2
1.5
1
0.5
0
UAS-TRPA1/+
pLB1^Gal4/+
pLB1^Gal4/UAS-TRPA1
pLB2^Gal4/+
pLB2^Gal4/UAS-TRPA1
pLB3^Gal4/+
pLB3^Gal4/UAS-TRPA1

- Bacteria modulate egg-laying behavior via the octopamine pathway.



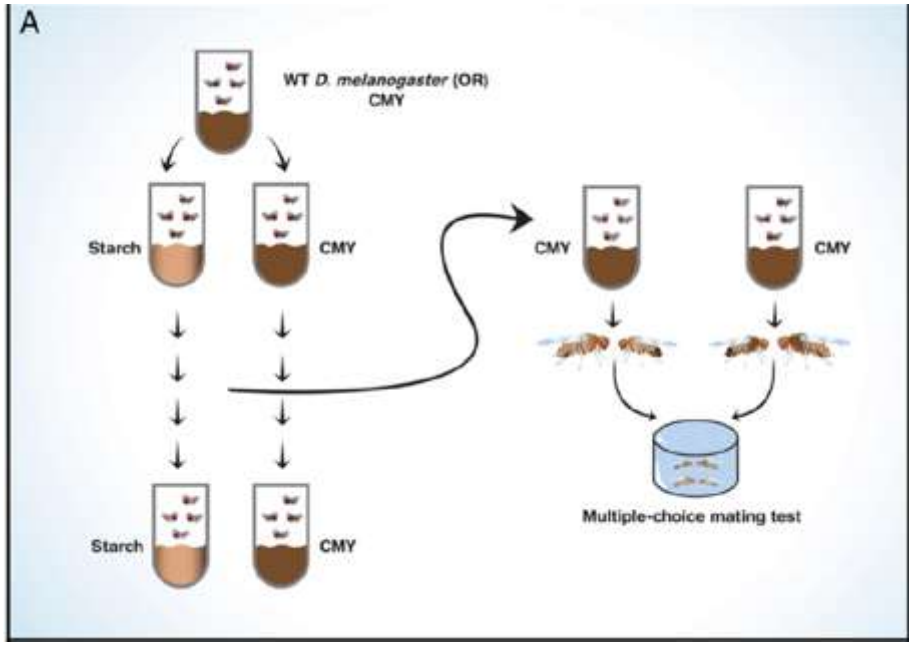

Non-infected
PGRP-LC
NF-κB
Immune
Genes OFF
PGRP-LE
NF-κB
Oviposition ON
Fat-body cell
Octopaminergic neuron
Infected
BACTERIA
PGN
PGRP-LB^PC
PGRP-LC
NF-κB
Immune
Genes ON
PGRP-LB^PD
PGRP-LE
NF-κB
Oviposition OFF
Fat-body cell
Octopaminergic neuron

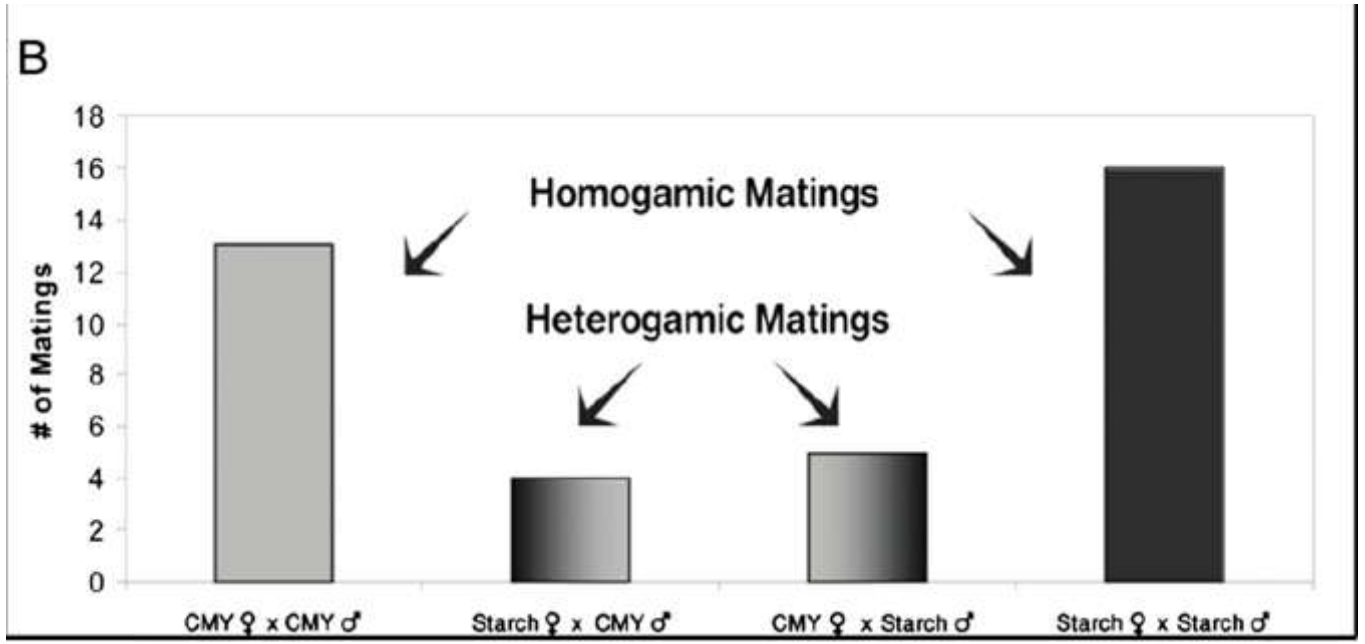
Commensal bacteria play a role in mating preference of *Drosophila melanogaster*

Gil Sharon[a], Daniel Segal[a], John M. Ringo[b], Abraham Hefetz[c], Ilana Zilber-Rosenberg[d], and Eugene Rosenberg[a,1]

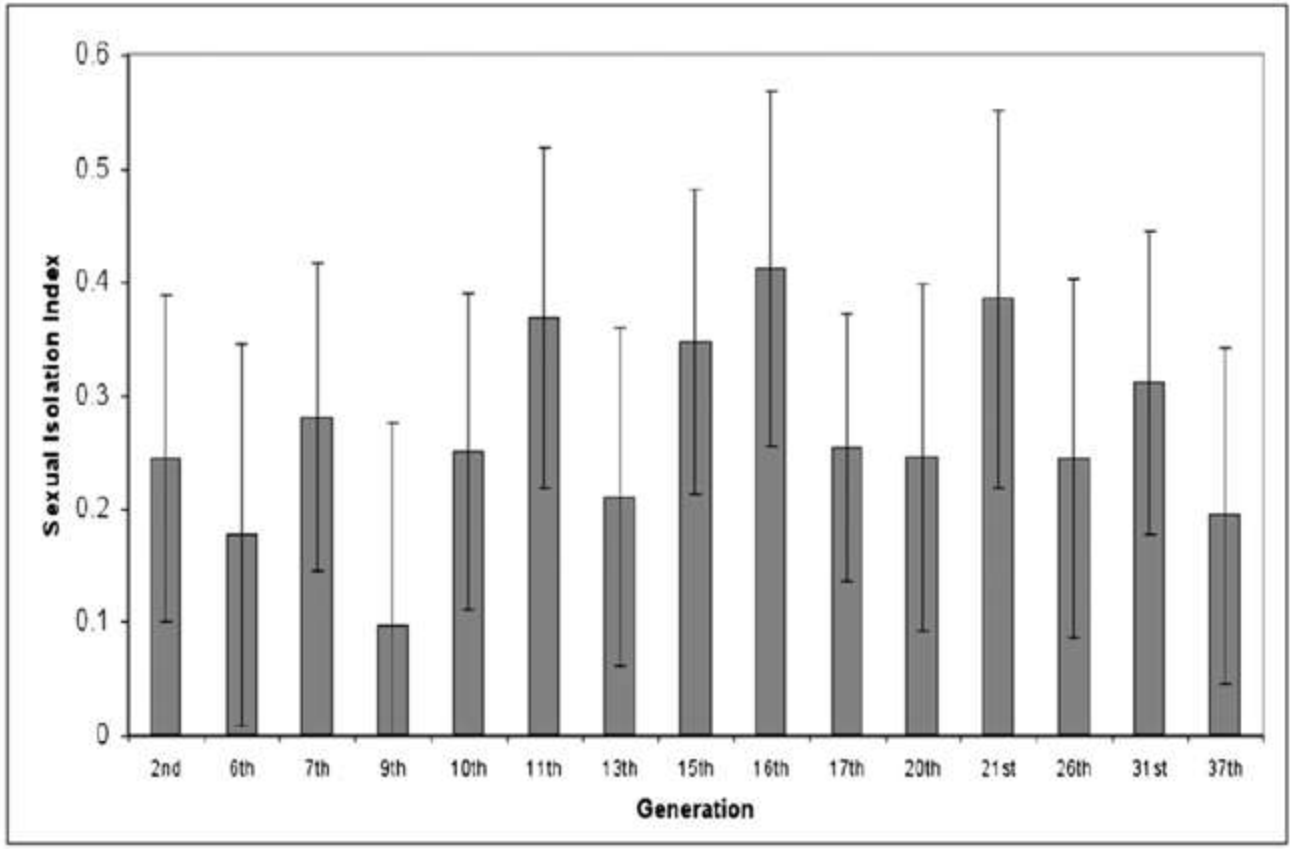
[a]Department of Molecular Microbiology and Biotechnology, Tel Aviv University, Tel Aviv 69978, Israel; [b]School of Biology and Ecology, University of Maine, Orono, ME 04469; [c]Department of Zoology, Tel Aviv University, Tel Aviv 69978, Israel; and [d]18 Rachavat Ilan St., Givat Shmuel 51905, Israel

Edited by R. John Collier, Harvard Medical School, Boston, MA, and approved September 28, 2010 (received for review July 12, 2010)





- Mating preference tests of D. melanogaster after growth for different numbers of generations on either starch or CMY medium.



$$SII = \frac{homogamic\ matings - heterogamic\ matings}{n(total\ matings)} \qquad [1]$$

Table 1. The role of bacteria in diet-induced mating preference of *D. melanogaster*

Experiment	Fly treatment*	Matings	SII, mean ± SEM	*P* value†
1	Starch-grown × CMY-grown	18	0.27 ± 0.02	<0.0001
2	Experiment 1 after antibiotics	10	0.01 ± 0.03	0.4483
3	Experiment 2 after infection with homologous bacteria‡	4	0.22 ± 0.03	0.0024
4	Experiment 3 with *Lactobacillus* replacing homologous bacteria in starch-bred flies	4	0.16 ± 0.06	0.0392
5	Experiment 3 with *Lactobacillus plantarum* replacing homologous bacteria in starch-bred flies	5	0.19 ± 0.05	0.0004
6	Infection control (no added bacteria)	4	−0.04 ± 0.08	0.4052

*After all treatments, the flies were grown for one generation in CMY medium before performing the mating preference test.
†*P* value of the normal approximation to the binomial test. $P < 0.05$ was considered to indicate significant mating preference.
‡Antibiotic-treated starch- and CMY-grown flies were infected with bacteria isolated from their respective growth medium (before antibiotic treatment).

Table 2. Bacterial communities in *D. melanogaster* grown on CMY or starch

Closest match (accession no.)	Identity, %	Representation in clone library, %*	
		CMY†	Starch‡
Acetobacter pomorum strain EW816 (EU096229.1)	89.81	1.49	—
Acetobacter pomorum strain EW816 (EU096229.1)	93.99	1.49	—
Acetobacter pomorum strain EW816 (EU096229.1)	94.00	1.49	—
Acetobacter pomorum strain EW816 (EU096229.1)	100.00	14.93	—
Bacillus firmus strain XJSL2-8 (GQ903397.1)	100.00	11.94	—
Enterococcus faecalis strain 3–12 (GU177628.1)	100.00	1.49	—
Lactobacillus plantarum strain IMAU:10272 (GU138600.1)	100.00	2.99	26.09
Low G+C Gram-positive bacterium T135 (AB116139.1)	99.44	5.97	—
Weissella paramesenteroides strain CTSPL5 (EU855224.1)	97.24	1.49	—
Weissella paramesenteroides strain CTSPL5 (EU855224.1)	99.64	4.48	—
Wolbachia endosymbiont of *Drosophila melanogaster* (AB360385.1)	100.00	47.77	73.91

16S rRNA gene analysis was performed on files (third generation) grown on CMY medium for one generation before mating preference tests.
*Sequences with ≥99% identity were clustered by DOTUR (9).
†Based on 64 clones.
‡Based on 23 clones.

Table 3. Major differences in CH profiles of CMY and starch bred flies

			Mean CH per fly ± SEM, ng			
			No antibiotic treatment		Treated with antibiotics	
Peak name	Retention time (min)	Identified compound[a]	CMY (n = 3)	Starch (n = 2)	CMY (n = 3)	Starch (n = 3)
Females						
F16	17.92	7-Tricosene	44.7 ± 10.1	22.6 ± 0.5	25.8 ± 2.3	16.2 ± 0.8
F24	21.08	7-Pentacosene	37.1 ± 7.7	11.1 ± 2.3	20.3 ± 2.5	10.5 ± 0.8
FF12	23.77	7,11-Heptacosadiene	117.4 ± 21.8	172.0 ± 5.6	50.6 ± 8.1	59.4 ± 8.8
F40	26.54	2-Methyloctacosane	87.2 ± 2.5	136.2 ± 4.3	34.2 ± 4.3	49.0 ± 6.1
Males						
M12	16.4	Cis-vaccenyl acetate	9.9 ± 6.2	51.6 ± 7.8	16.2 ± 5.7	32.4 ± 14.0
M16	17.92	7-Tricosene	259.1 ± 59	495.4 ± 39.9	181.2 ± 15.8	415.0 ± 10.5
M24	21.08	7-Pentacosene	146 ± 29.8	61.5 ± 8.4	93.1 ± 3.5	69.7 ± 4.8

[a]Based on the GC CH profiles of *D. melanogaster* (12) and on GC-MS analyses.

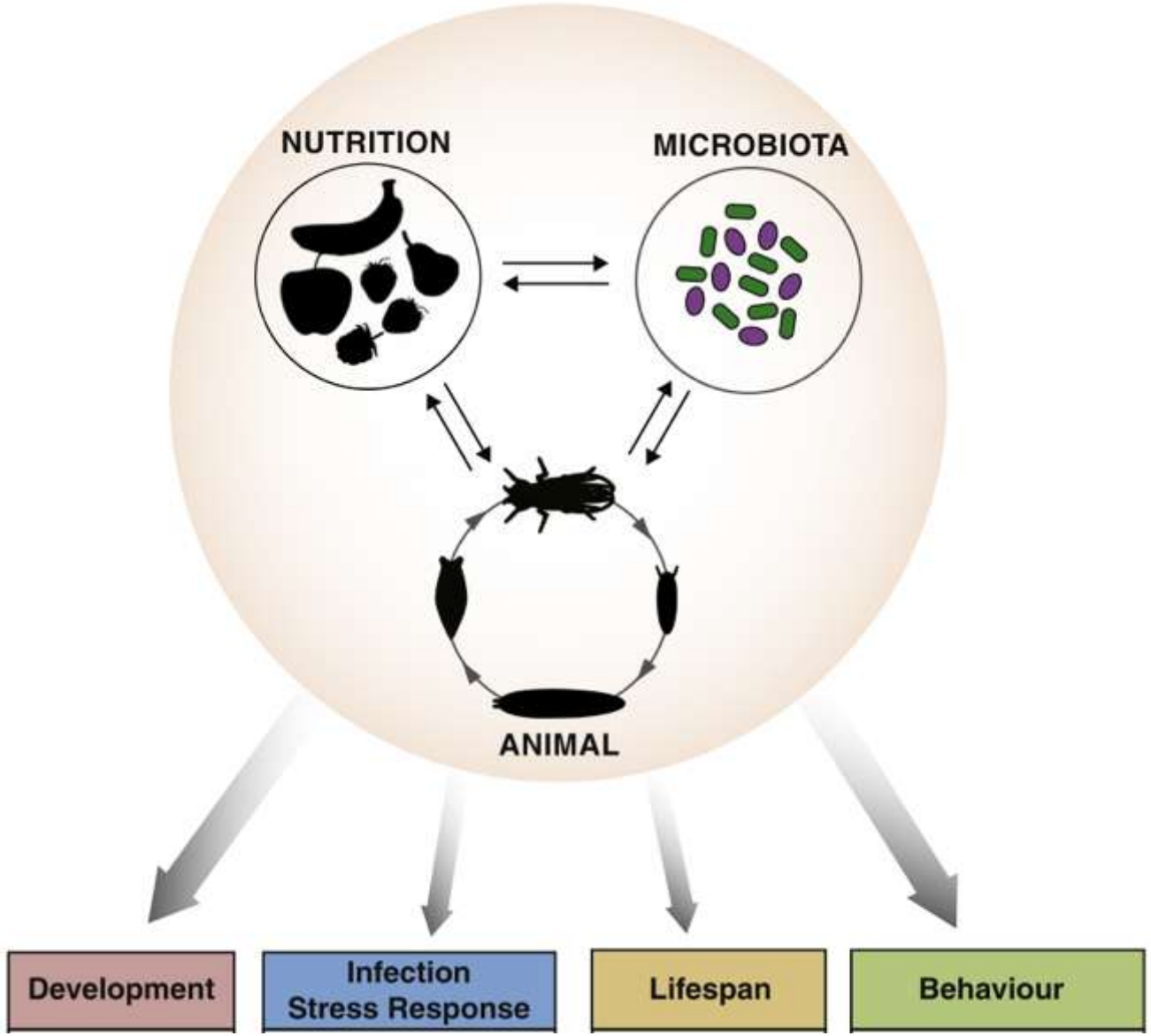
Reference:

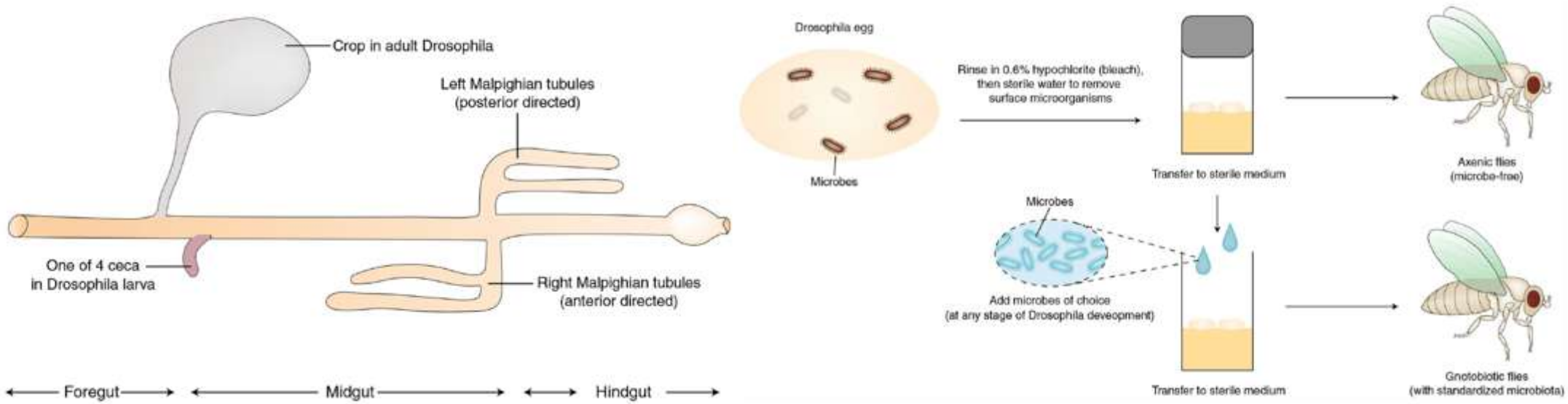
- Martino M , Ma D , Leulier F . Microbial influence on Drosophila biology[J]. Current Opinion in Microbiology, 2017, 38:165.
- Shin S C , Kim S H , You H , et al. Drosophila Microbiome Modulates Host Developmental and Metabolic Homeostasis via Insulin Signaling[J]. ence, 2011, 334(6056):670-674.
- Xu J , Hopkins K , Sabin L , et al. ERK signaling couples nutrient status to antiviral defense in the insect gut[J]. Proceedings of the National Academy of Sciences, 2013, 110(37):15025-15030.
- Xu, Jie, Osbom, et al. Microbiota-Dependent Priming of Antiviral Intestinal Immunity in Drosophila[J]. Cell Host & Microbe, 2015.
- Douglas, Angela E . The Drosophila model for microbiome research[J]. Lab Anim, 2018, 47(6):157-164.
- Sharon G , Segal D , Ringo J M , et al. Commensal bacteria play a role in mating preference of Drosophila melanogaster (vol 107, pg 20051, 2010)[J]. Proceedings of the National Academy of ences, 2013, 110(12):4853-4853.
- Catherine, E, Schretter, et al. A gut microbial factor modulates locomotor behaviour in Drosophila.[J]. Nature, 2018.

PART III:

Physiological function in Drosophila through Gut-Brain communication

Wang Lin
2020.7.30


NUTRITION
MICROBIOTA
ANIMAL
Development
Infection
Stress Response
Lifespan
Behaviour



The major commensals in the Drosophila intestine:
Acetobacter pomorum, Acetobacter tropicalis, Lactobacillus brevis, Lactobacillus plantarum

Section 1: The microbiome and Physiological characteristics of hosts

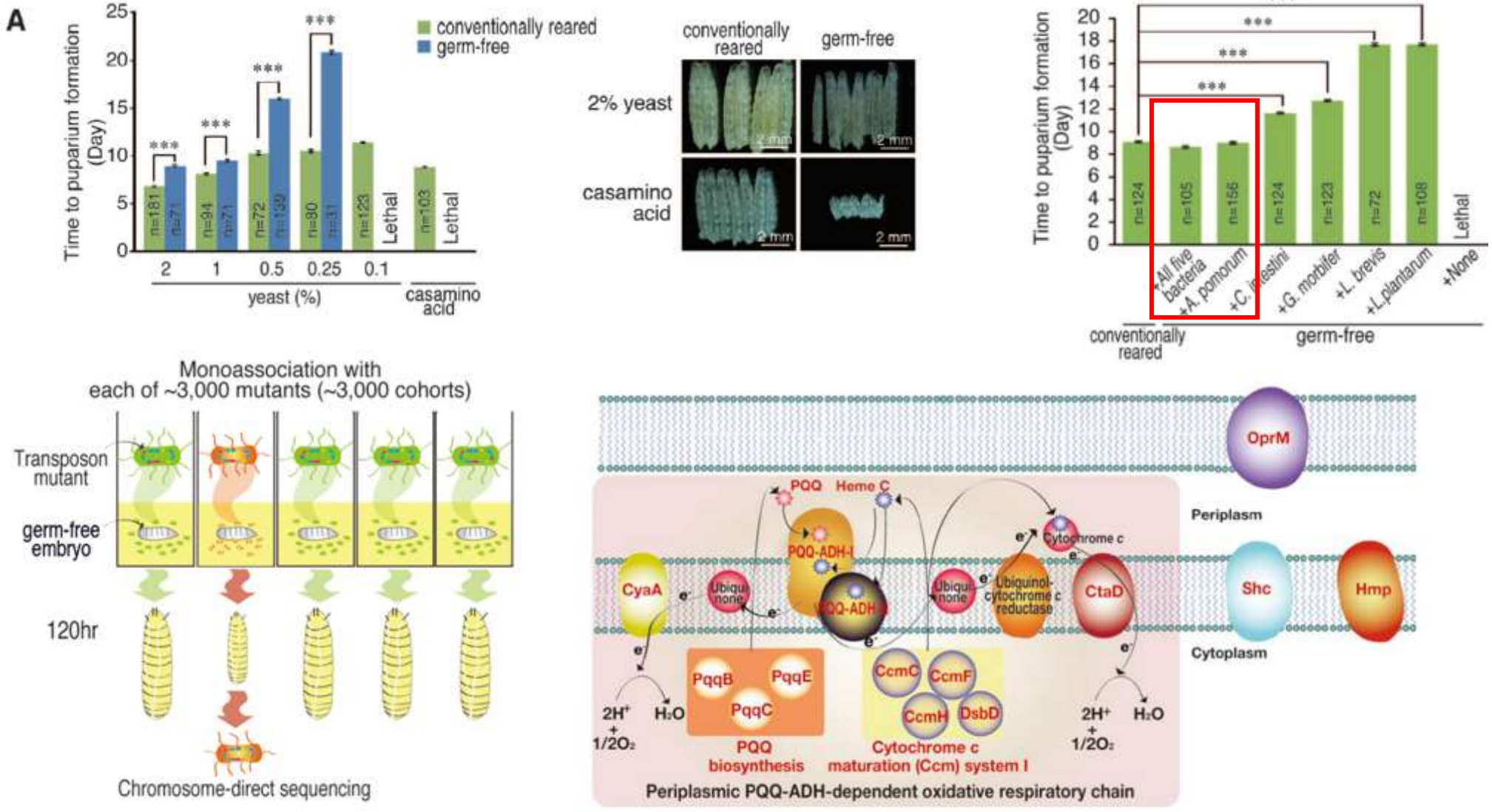
Science
AAAS

Drosophila Microbiome Modulates Host Developmental and Metabolic Homeostasis via Insulin Signaling

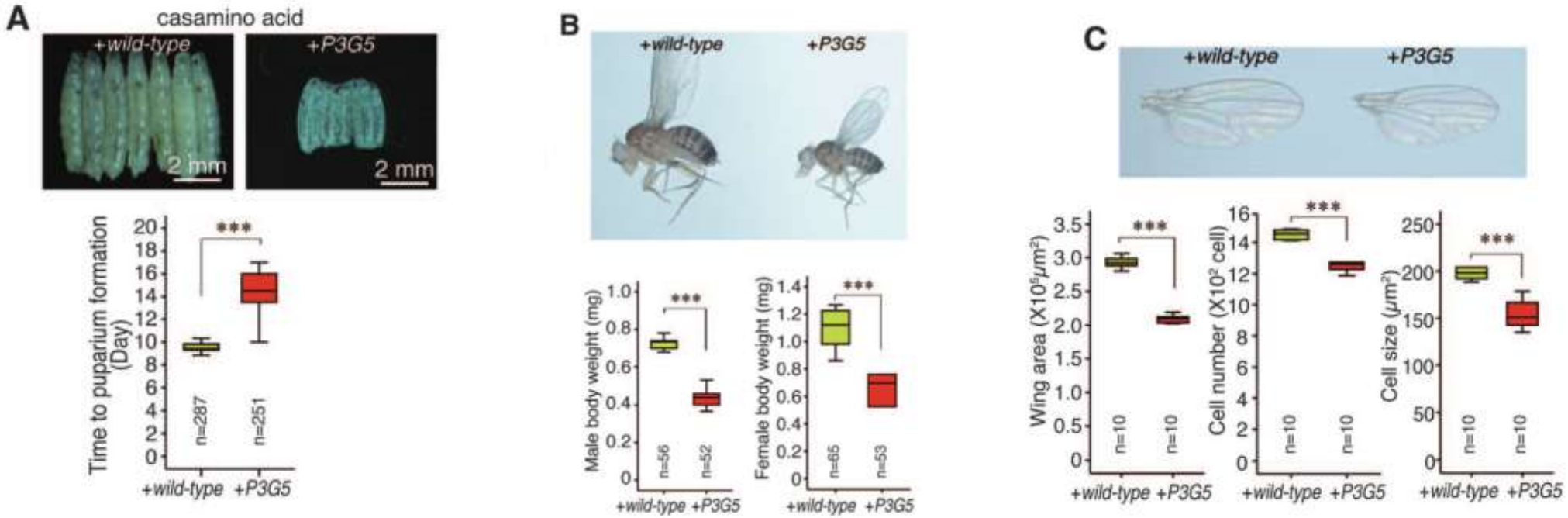
Seung Chul Shin *et al.*

Science **334**, 670 (2011);
DOI: 10.1126/science.1212782

- Genome-wide screening of the Acetobacter genes essential for host growth.



- Commensal PQQ-ADH activity is required for controlling developmental rate, body size

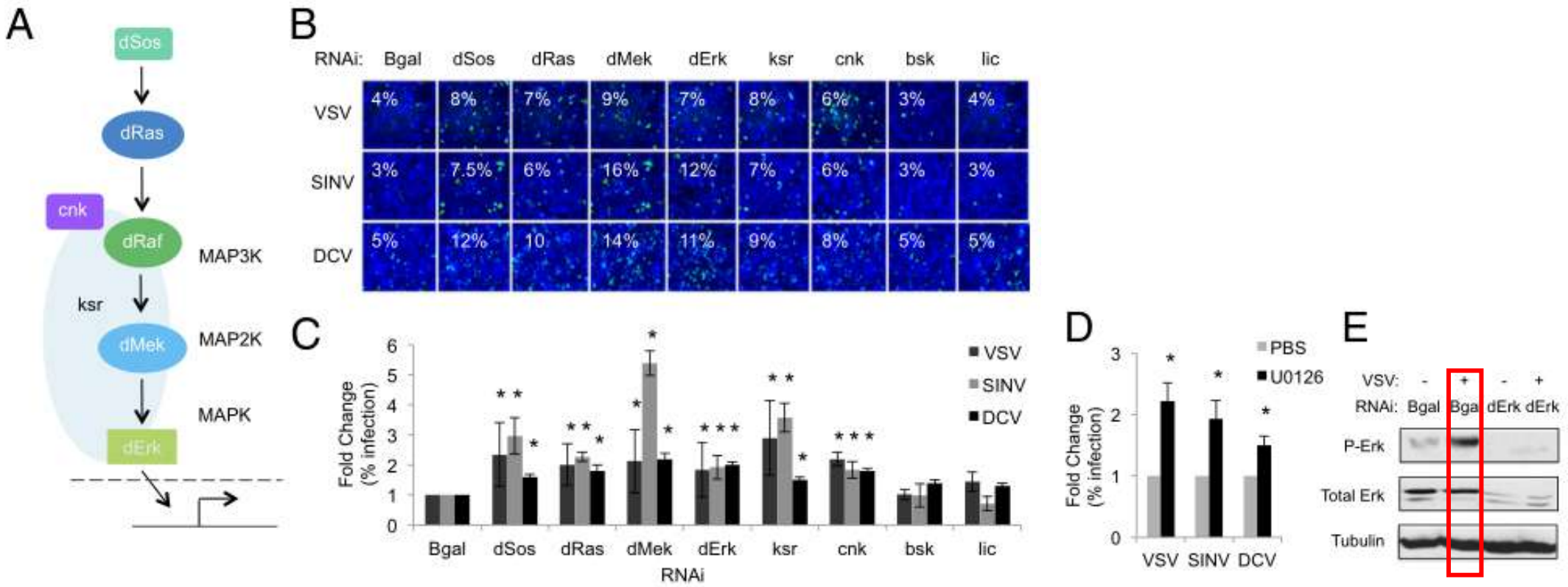


Cell Host & Microbe
Article

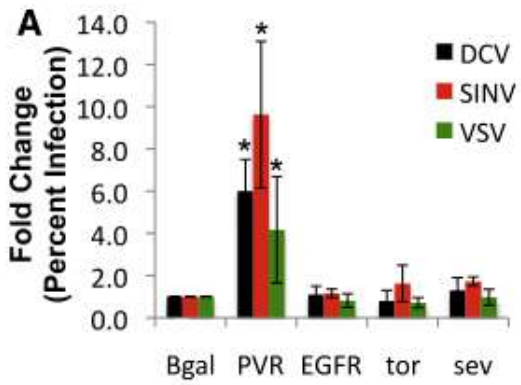
Microbiota-Dependent Priming of Antiviral Intestinal Immunity in *Drosophila*

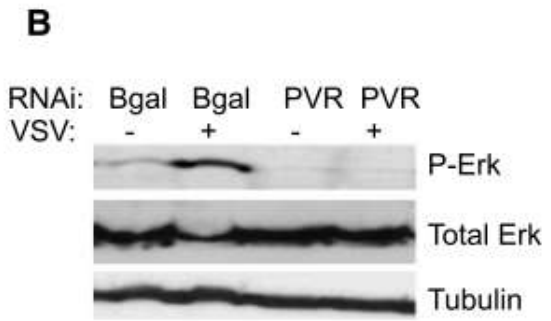
Christine L. Sansone,[1] Jonathan Cohen,[1] Ari Yasunaga,[1] Jie Xu,[1] Greg Osborn,[1] Harry Subramanian,[1] Beth Gold,[1] Nicolas Buchon,[2] and Sara Cherry[1,*]
[1]Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA
[2]Department of Entomology, Cornell University, Ithaca, NY 14853, USA
*Correspondence: cherrys@mail.med.upenn.edu
http://dx.doi.org/10.1016/j.chom.2015.10.010

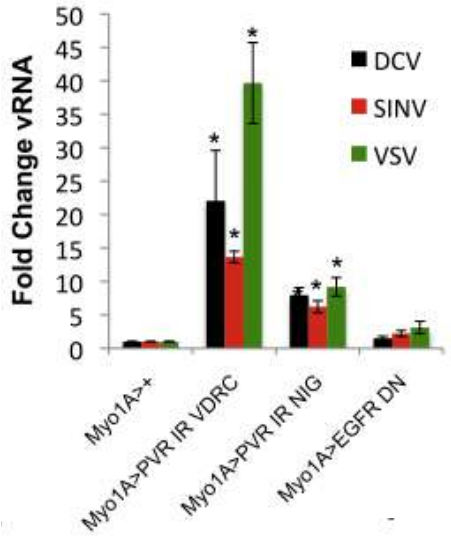
- The ERK pathway is broadly activated by and restricts viral infections in Drosophila cells.

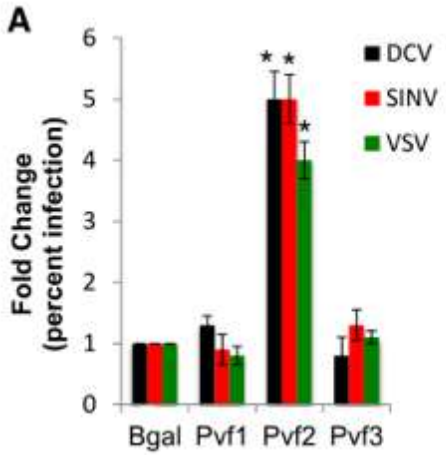


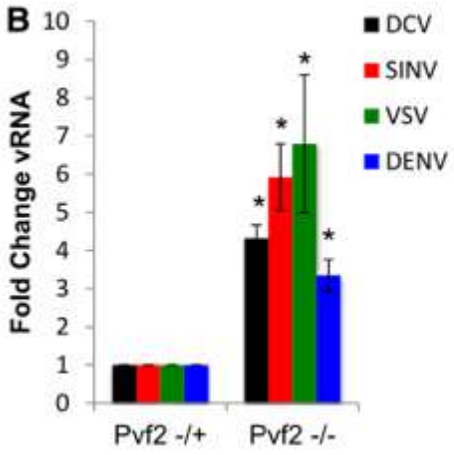
- PVR and Pvf2 are Required for Antiviral Defense

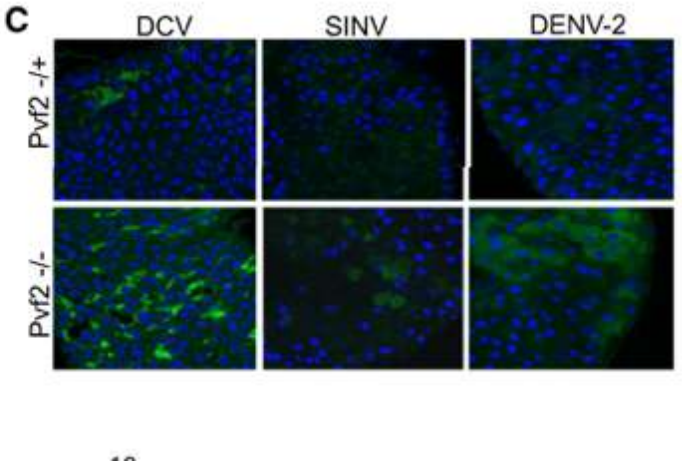


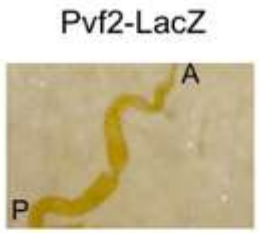


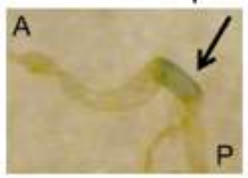




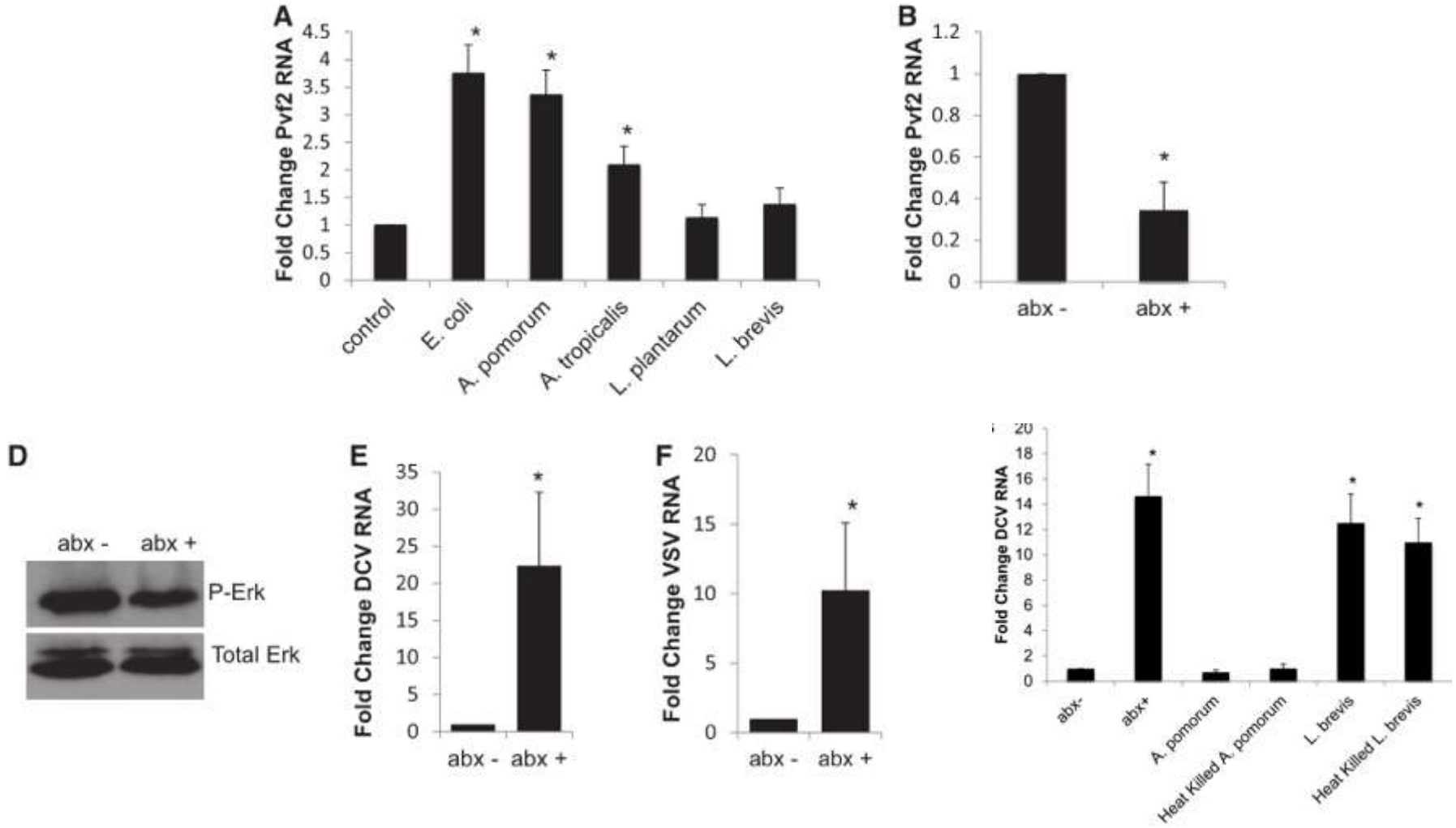


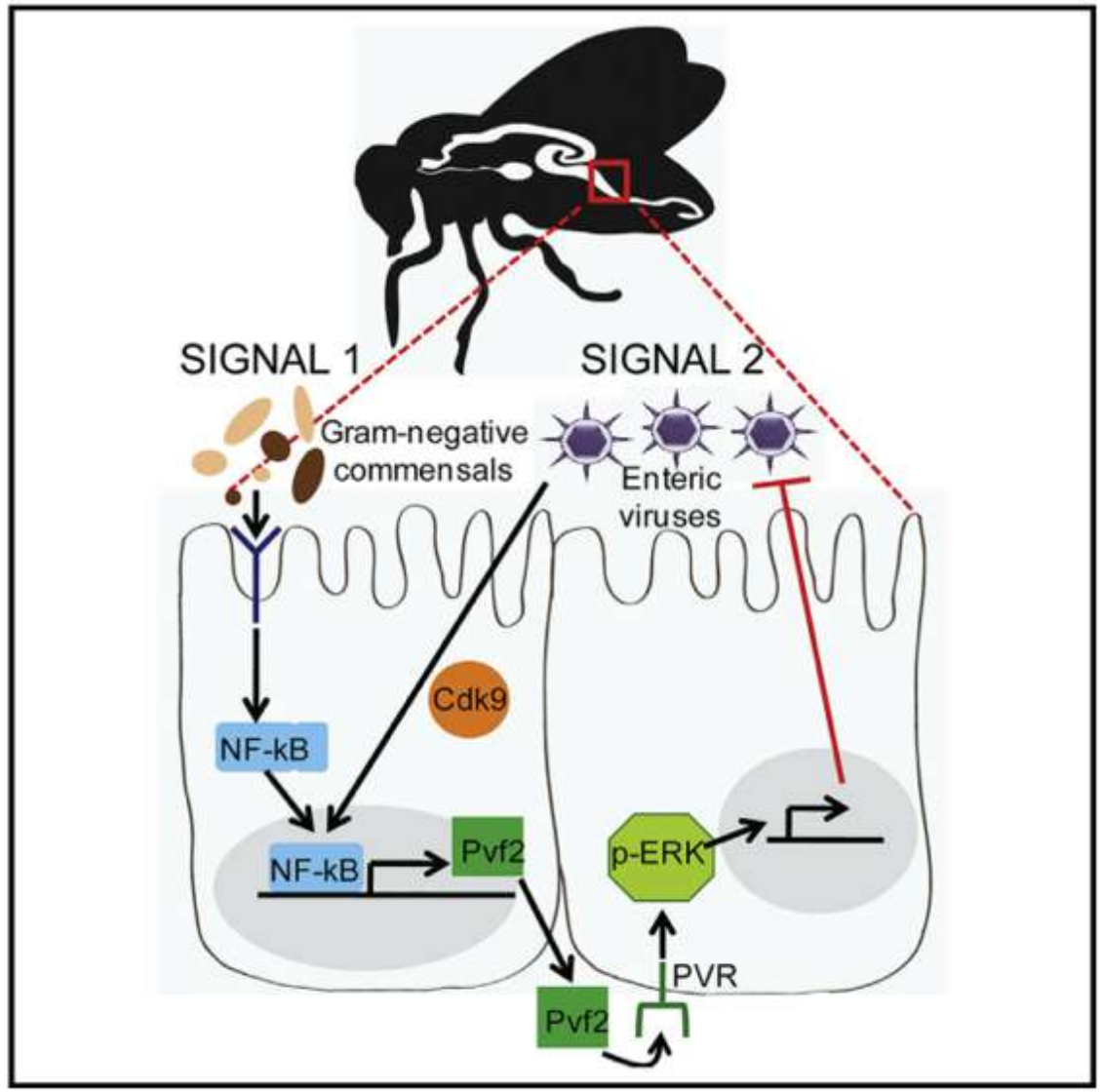






- The Microbiota Regulates Pvf2 Expression and Antiviral Defense



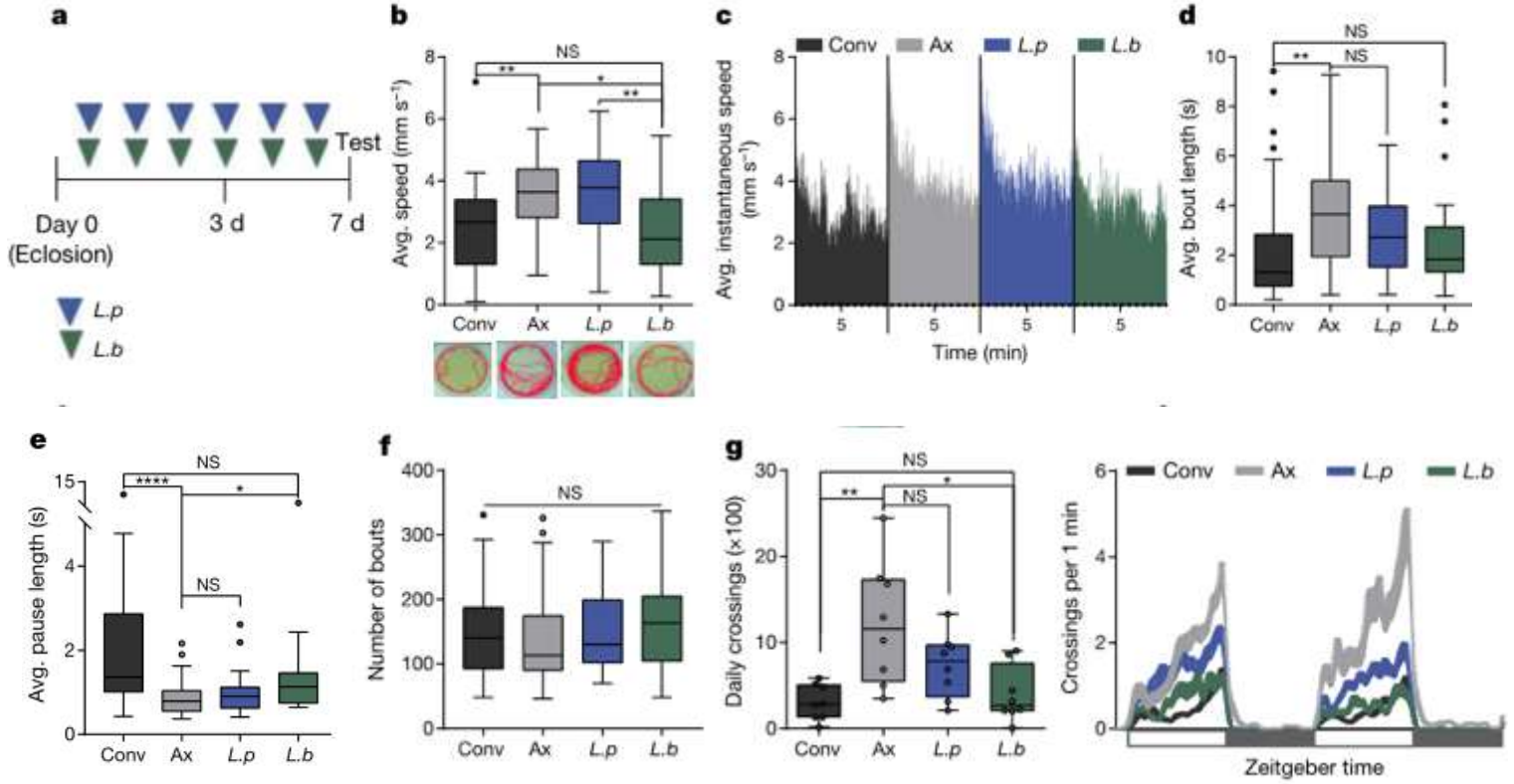

SIGNAL 1
SIGNAL 2
Gram-negative commensals
Enteric viruses
Cdk9
NF-kB
NF-kB
Pvf2
p-ERK
PVR
Pvf2

Section 2: The microbiome and behavior

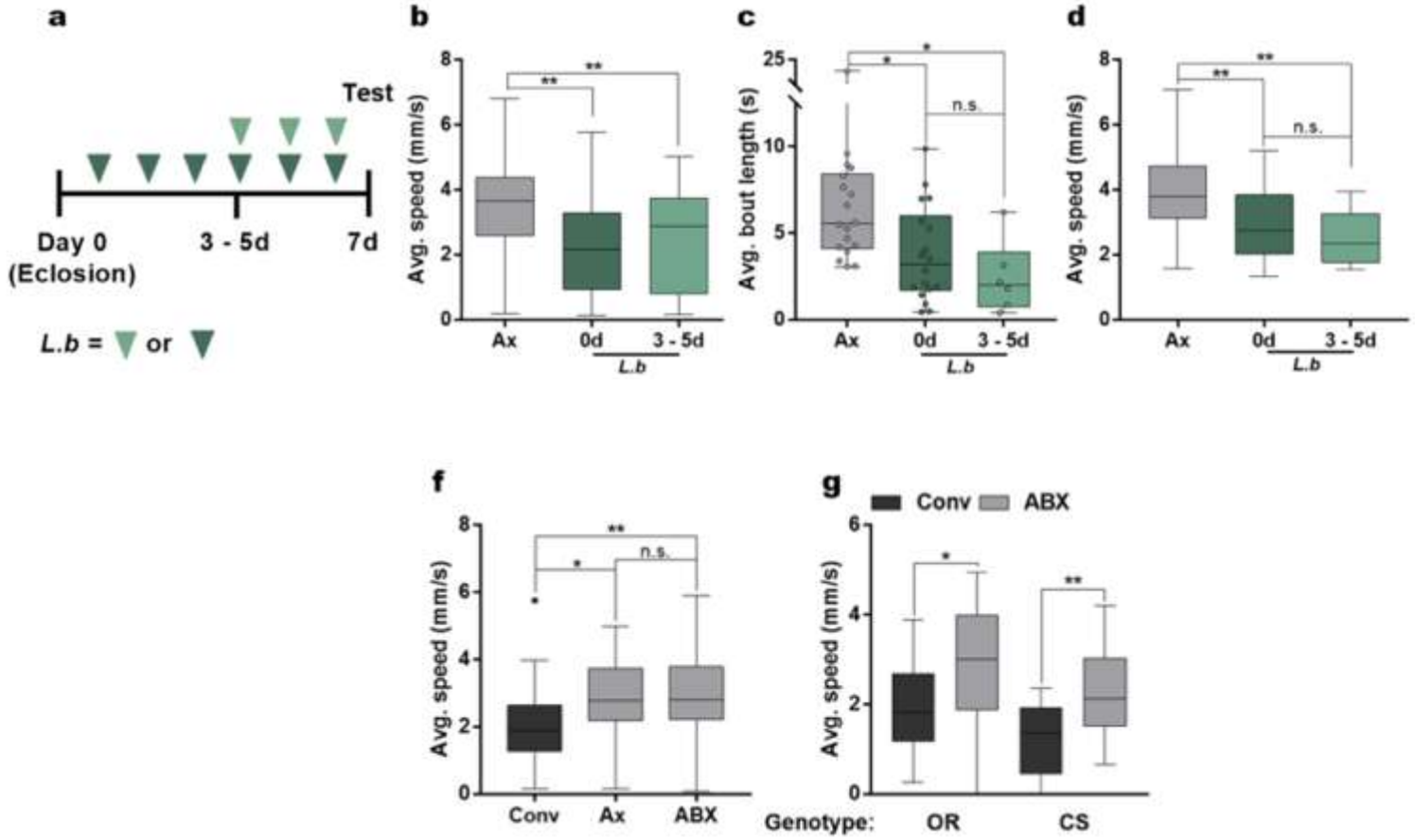
A gut microbial factor modulates locomotor behaviour in *Drosophila*

Catherine E. Schretter[1]*, Jost Vielmetter[2], Imre Bartos[3], Zsuzsa Marka[3], Szabolcs Marka[3], Sulabha Argade[4] & Sarkis K. Mazmanian[1]*

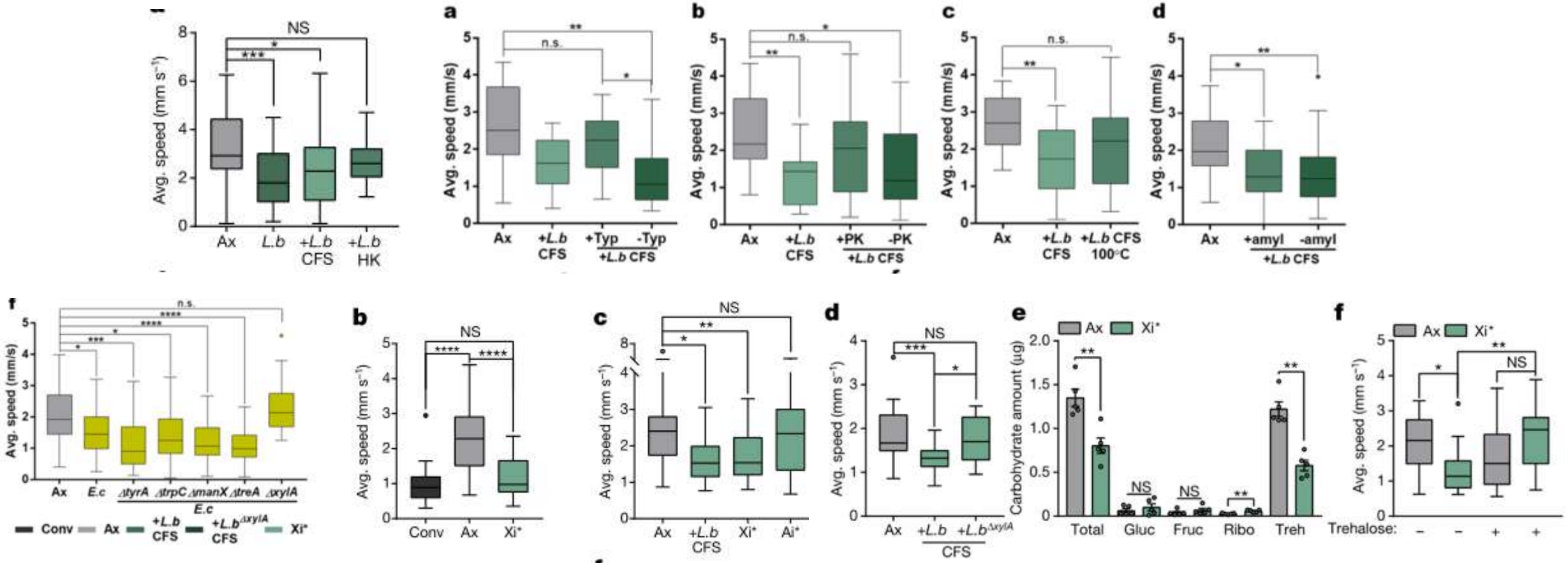
- Select gut bacteria modulate locomotor behavior in flies



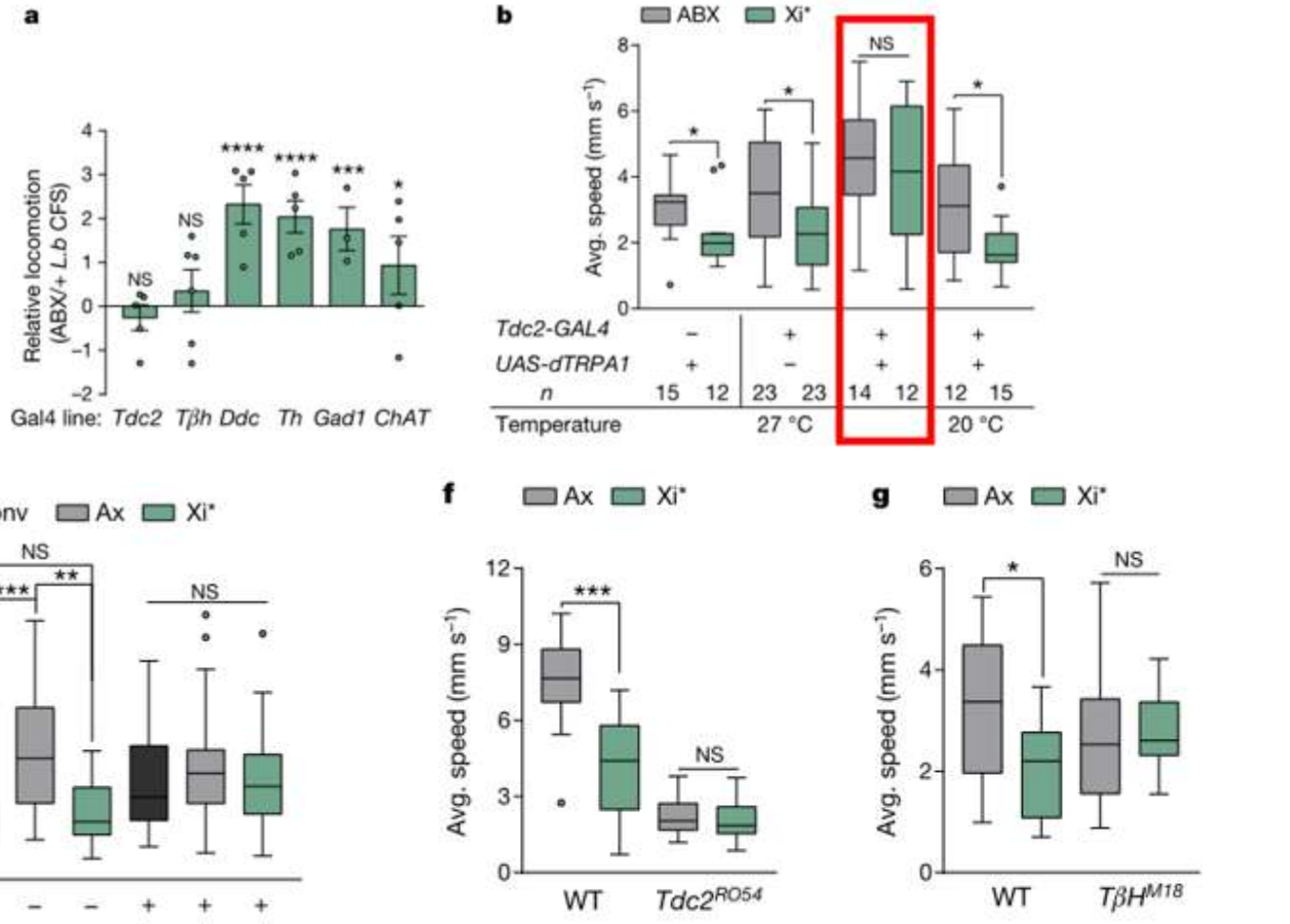
- Post-eclosion microbial signals decrease host locomotion

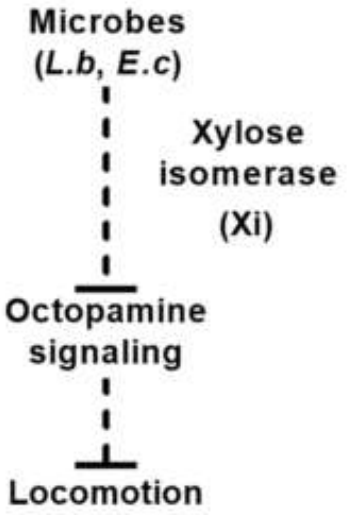


- Xylose isomerase from *L. brevis* alters host locomotion



- Octopamine mediates Xi-induced changes in locomotion.





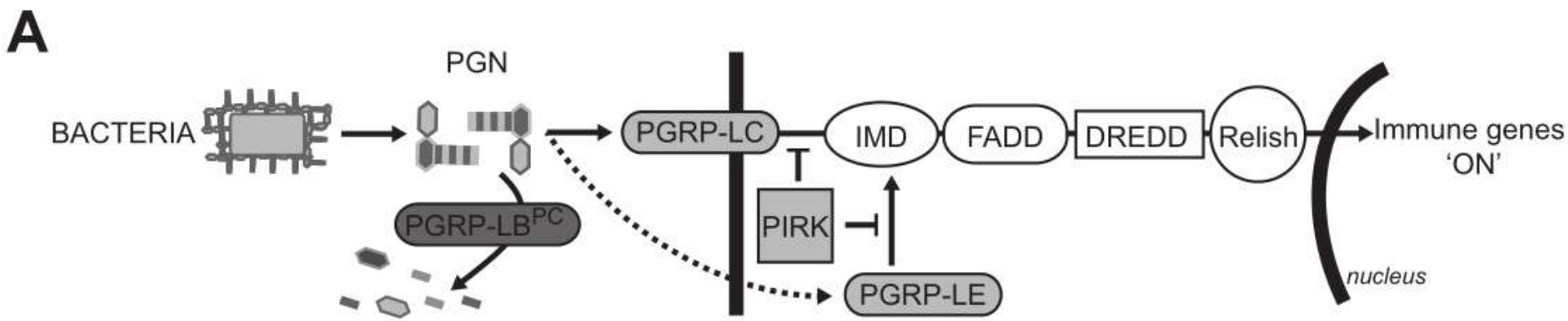
eLIFE elifesciences.org

RESEARCH ARTICLE

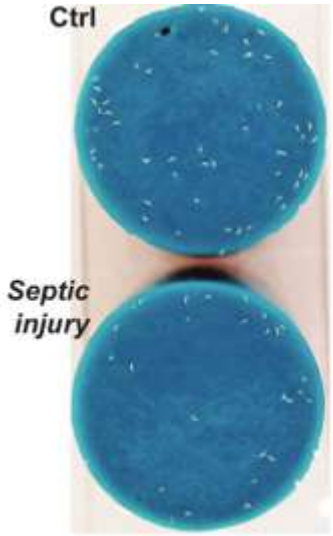
Peptidoglycan sensing by octopaminergic neurons modulates *Drosophila* oviposition

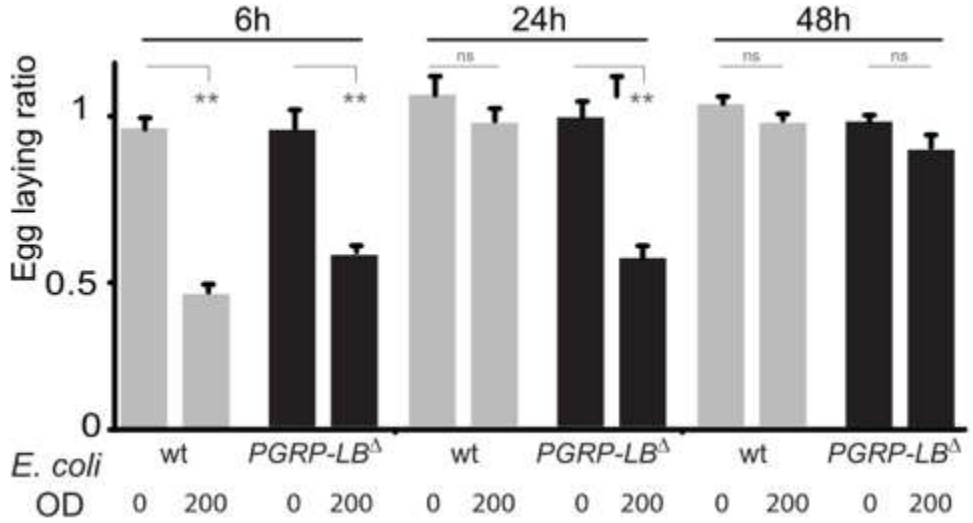
C Leopold Kurz†, Bernard Charroux†, Delphine Chaduli, Annelise Viallat-Lieutaud, Julien Royet*

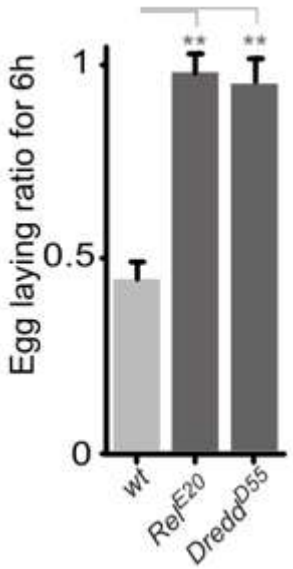
Aix-Marseille Université, Centre National de la Recherche Scientifique, UMR 7288, Institut de Biologie du Développement de Marseille, Marseille Cedex, France



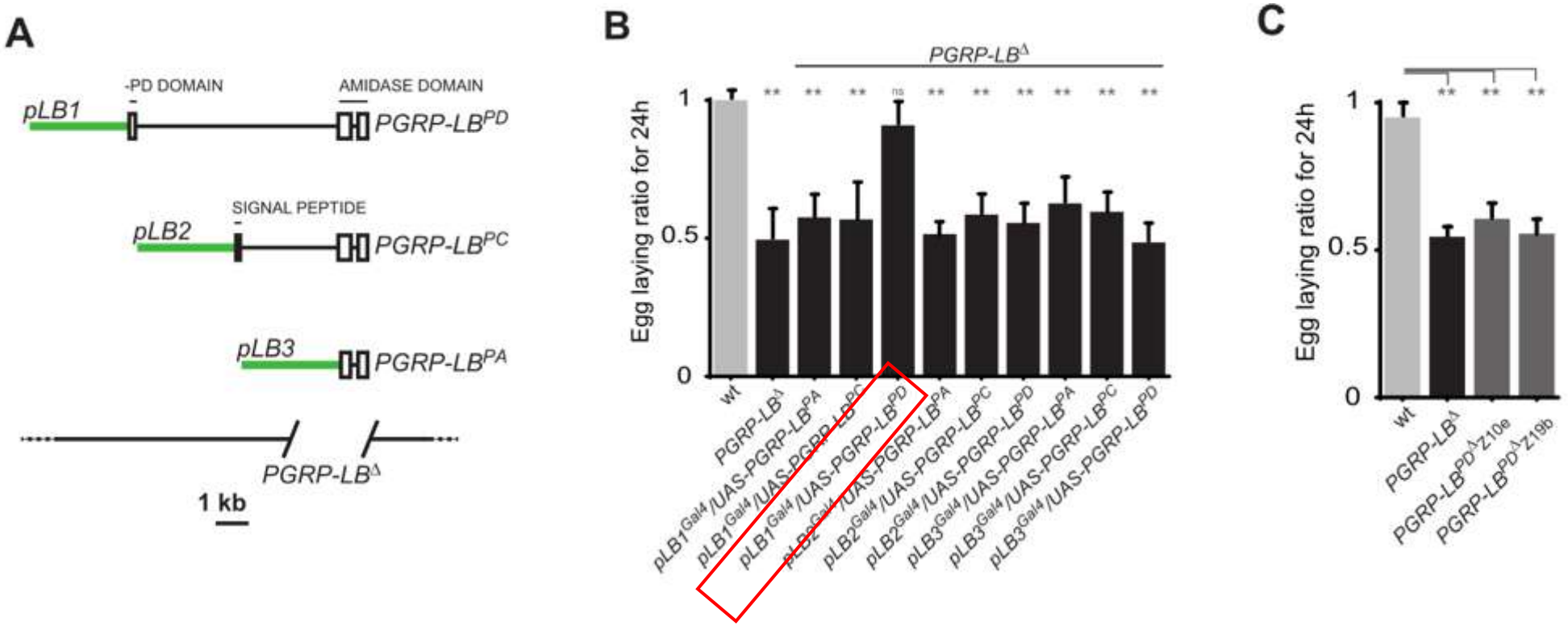
- PGN-mediated NF-kB pathway activation decreases female oviposition.



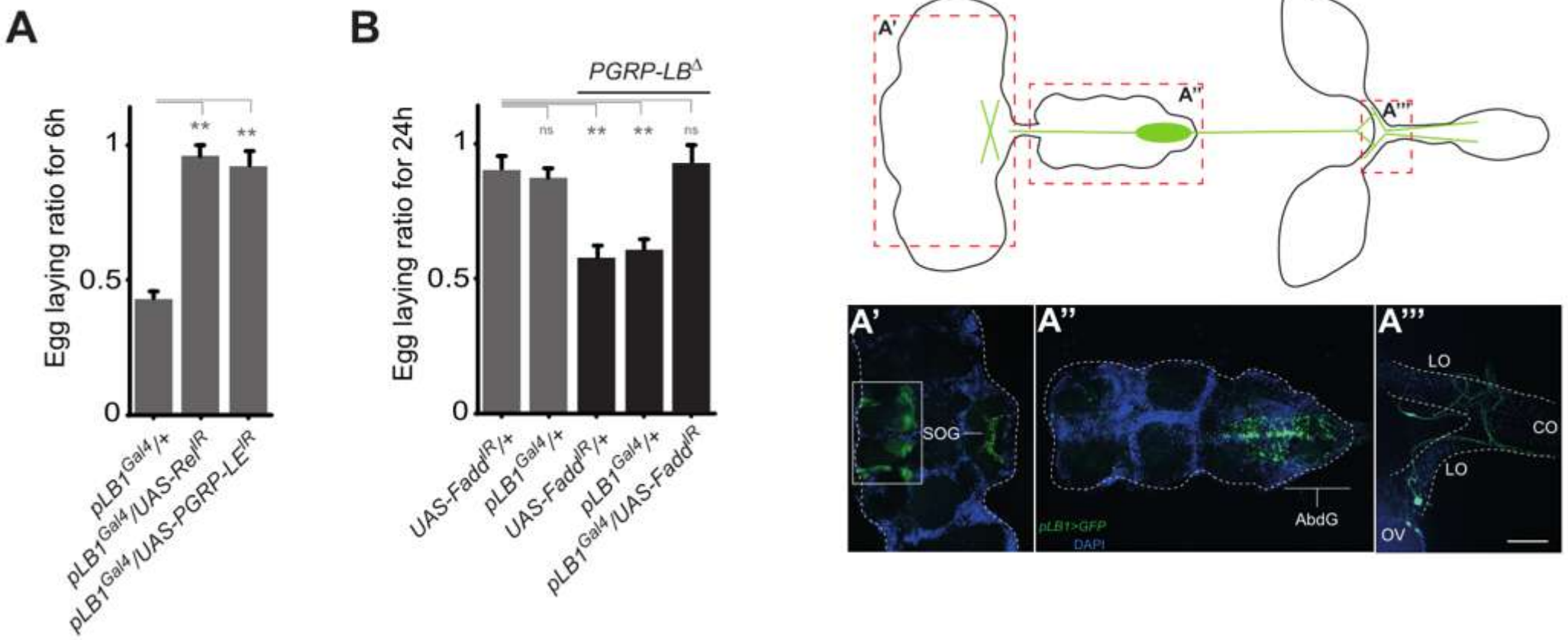


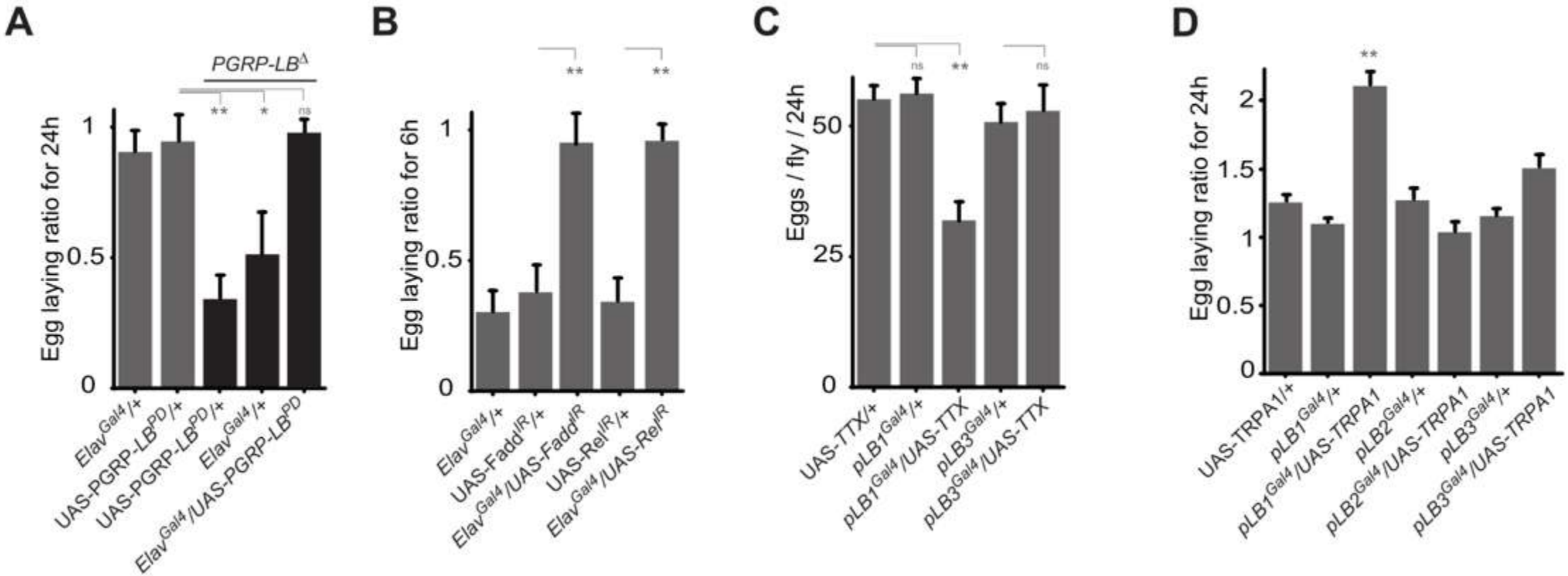


- One specific PGRP-LB isoform controls oviposition

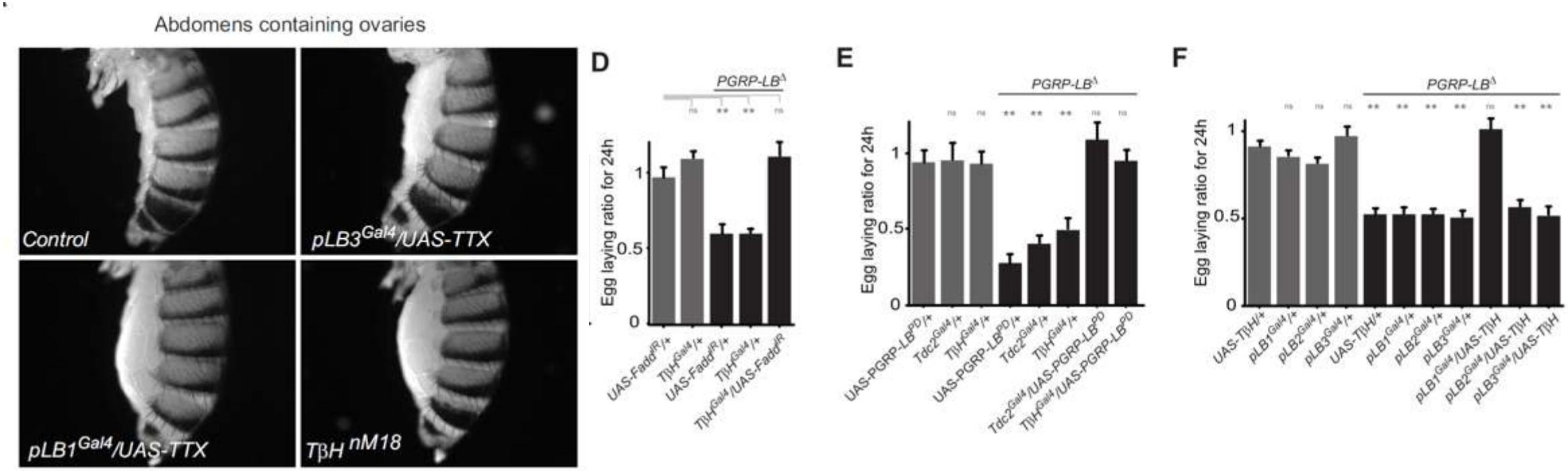


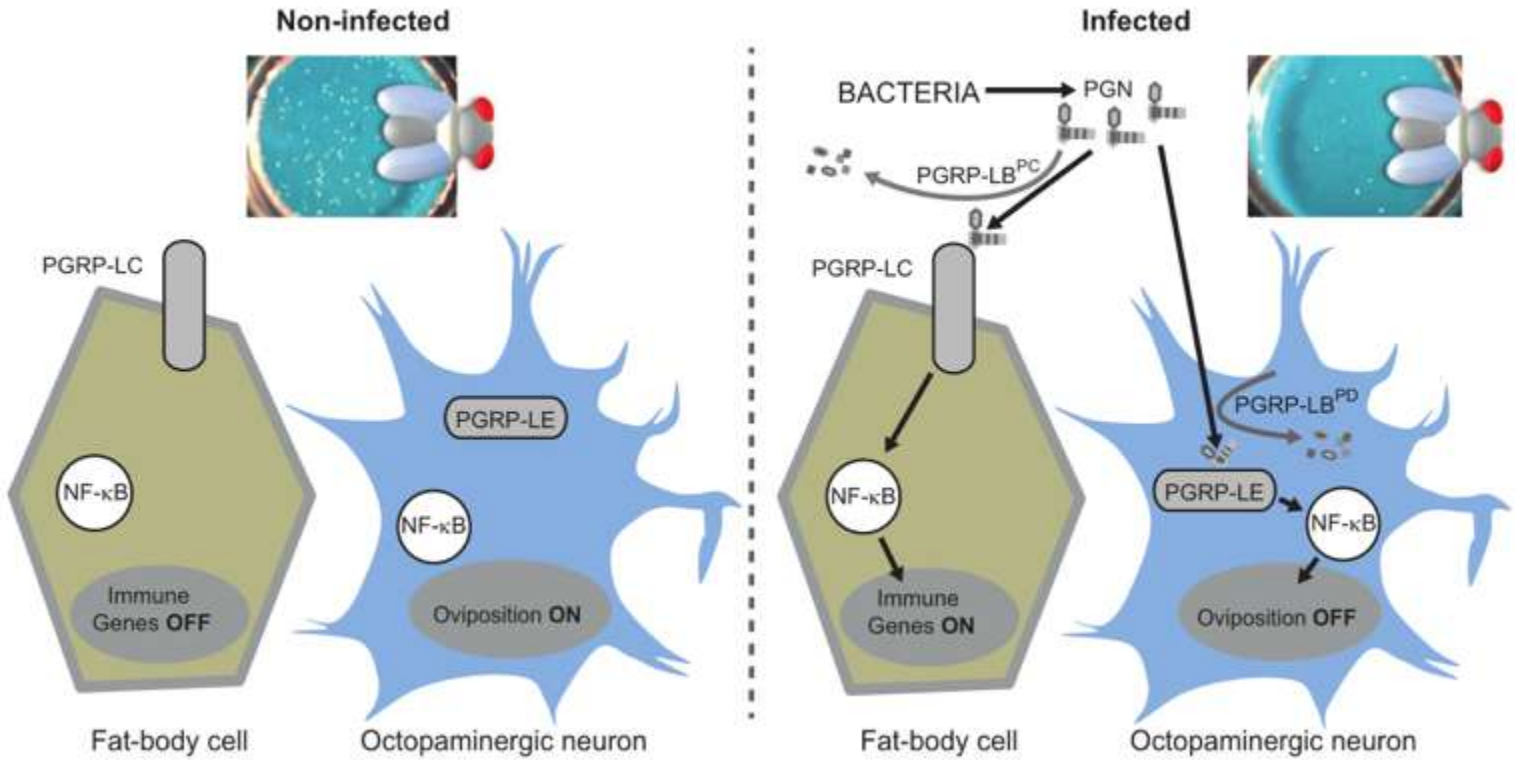
- NF-κB acts in neurons to regulate infection-dependent egg laying




A
PGRP-LB^Δ
**
*
ns
Egg laying ratio for 24h
1
0.5
0
Elav^Gal4/+
UAS-PGRP-LB^PD/+
UAS-PGRP-LB^PD/+
Elav^Gal4/+
Elav^Gal4/UAS-PGRP-LB^PD
B
**
**
Egg laying ratio for 6h
1
0.5
0
Elav^Gal4/+
UAS-Fadd^IR/+
Elav^Gal4/UAS-Fadd^IR
UAS-Rel^IR/+
Elav^Gal4/UAS-Rel^IR
C
ns
**
ns
Eggs / fly / 24h
50
25
0
UAS-TTX/+
pLB1^Gal4/+
pLB1^Gal4/UAS-TTX
pLB3^Gal4/+
pLB3^Gal4/UAS-TTX
D
**
Egg laying ratio for 24h
2
1.5
1
0.5
0
UAS-TRPA1/+
pLB1^Gal4/+
pLB1^Gal4/UAS-TRPA1
pLB2^Gal4/+
pLB2^Gal4/UAS-TRPA1
pLB3^Gal4/+
pLB3^Gal4/UAS-TRPA1

- Bacteria modulate egg-laying behavior via the octopamine pathway.



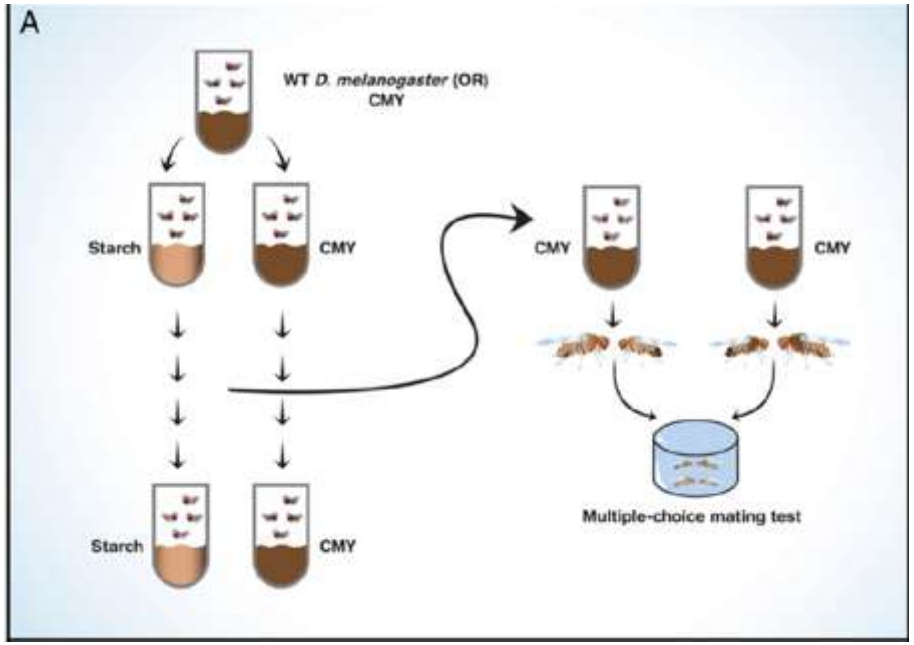

Non-infected
PGRP-LC
NF-κB
Immune
Genes OFF
PGRP-LE
NF-κB
Oviposition ON
Fat-body cell
Octopaminergic neuron
Infected
BACTERIA
PGN
PGRP-LB^PC
PGRP-LC
NF-κB
Immune
Genes ON
PGRP-LB^PD
PGRP-LE
NF-κB
Oviposition OFF
Fat-body cell
Octopaminergic neuron

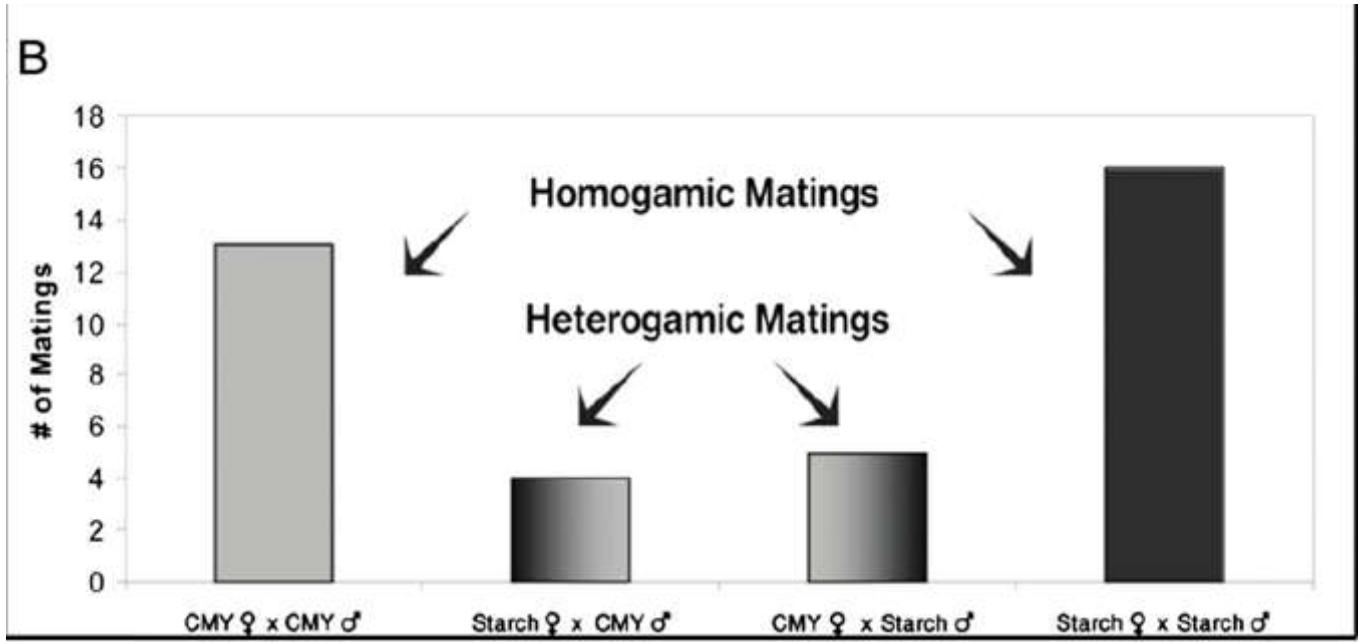
Commensal bacteria play a role in mating preference of *Drosophila melanogaster*

Gil Sharon[a], Daniel Segal[a], John M. Ringo[b], Abraham Hefetz[c], Ilana Zilber-Rosenberg[d], and Eugene Rosenberg[a,1]

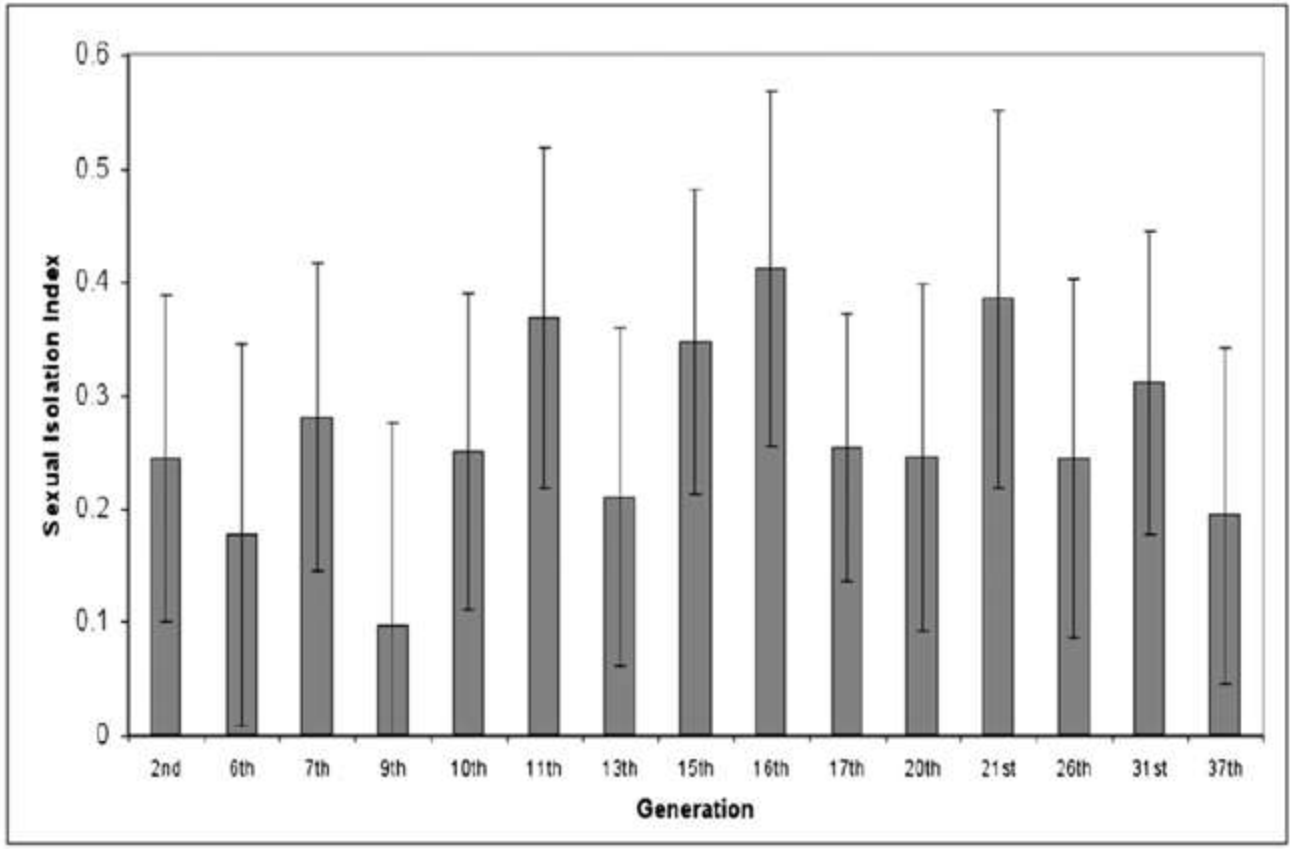
[a]Department of Molecular Microbiology and Biotechnology, Tel Aviv University, Tel Aviv 69978, Israel; [b]School of Biology and Ecology, University of Maine, Orono, ME 04469; [c]Department of Zoology, Tel Aviv University, Tel Aviv 69978, Israel; and [d]18 Rachavat Ilan St., Givat Shmuel 51905, Israel

Edited by R. John Collier, Harvard Medical School, Boston, MA, and approved September 28, 2010 (received for review July 12, 2010)





- Mating preference tests of D. melanogaster after growth for different numbers of generations on either starch or CMY medium.



$$SII = \frac{homogamic\ matings - heterogamic\ matings}{n(total\ matings)} \qquad [1]$$

Table 1. The role of bacteria in diet-induced mating preference of *D. melanogaster*

Experiment	Fly treatment*	Matings	SII, mean ± SEM	*P* value†
1	Starch-grown × CMY-grown	18	0.27 ± 0.02	<0.0001
2	Experiment 1 after antibiotics	10	0.01 ± 0.03	0.4483
3	Experiment 2 after infection with homologous bacteria‡	4	0.22 ± 0.03	0.0024
4	Experiment 3 with *Lactobacillus* replacing homologous bacteria in starch-bred flies	4	0.16 ± 0.06	0.0392
5	Experiment 3 with *Lactobacillus plantarum* replacing homologous bacteria in starch-bred flies	5	0.19 ± 0.05	0.0004
6	Infection control (no added bacteria)	4	−0.04 ± 0.08	0.4052

*After all treatments, the flies were grown for one generation in CMY medium before performing the mating preference test.
†*P* value of the normal approximation to the binomial test. $P < 0.05$ was considered to indicate significant mating preference.
‡Antibiotic-treated starch- and CMY-grown flies were infected with bacteria isolated from their respective growth medium (before antibiotic treatment).

Table 2. Bacterial communities in *D. melanogaster* grown on CMY or starch

Closest match (accession no.)	Identity, %	Representation in clone library, %*	
		CMY†	Starch‡
Acetobacter pomorum strain EW816 (EU096229.1)	89.81	1.49	—
Acetobacter pomorum strain EW816 (EU096229.1)	93.99	1.49	—
Acetobacter pomorum strain EW816 (EU096229.1)	94.00	1.49	—
Acetobacter pomorum strain EW816 (EU096229.1)	100.00	14.93	—
Bacillus firmus strain XJSL2-8 (GQ903397.1)	100.00	11.94	—
Enterococcus faecalis strain 3–12 (GU177628.1)	100.00	1.49	—
Lactobacillus plantarum strain IMAU:10272 (GU138600.1)	100.00	2.99	26.09
Low G+C Gram-positive bacterium T135 (AB116139.1)	99.44	5.97	—
Weissella paramesenteroides strain CTSPL5 (EU855224.1)	97.24	1.49	—
Weissella paramesenteroides strain CTSPL5 (EU855224.1)	99.64	4.48	—
Wolbachia endosymbiont of *Drosophila melanogaster* (AB360385.1)	100.00	47.77	73.91

16S rRNA gene analysis was performed on files (third generation) grown on CMY medium for one generation before mating preference tests.
*Sequences with ≥99% identity were clustered by DOTUR (9).
†Based on 64 clones.
‡Based on 23 clones.

Table 3. Major differences in CH profiles of CMY and starch bred flies

			Mean CH per fly ± SEM, ng			
			No antibiotic treatment		Treated with antibiotics	
Peak name	Retention time (min)	Identified compound[a]	CMY (n = 3)	Starch (n = 2)	CMY (n = 3)	Starch (n = 3)
Females						
F16	17.92	7-Tricosene	44.7 ± 10.1	22.6 ± 0.5	25.8 ± 2.3	16.2 ± 0.8
F24	21.08	7-Pentacosene	37.1 ± 7.7	11.1 ± 2.3	20.3 ± 2.5	10.5 ± 0.8
FF12	23.77	7,11-Heptacosadiene	117.4 ± 21.8	172.0 ± 5.6	50.6 ± 8.1	59.4 ± 8.8
F40	26.54	2-Methyloctacosane	87.2 ± 2.5	136.2 ± 4.3	34.2 ± 4.3	49.0 ± 6.1
Males						
M12	16.4	Cis-vaccenyl acetate	9.9 ± 6.2	51.6 ± 7.8	16.2 ± 5.7	32.4 ± 14.0
M16	17.92	7-Tricosene	259.1 ± 59	495.4 ± 39.9	181.2 ± 15.8	415.0 ± 10.5
M24	21.08	7-Pentacosene	146 ± 29.8	61.5 ± 8.4	93.1 ± 3.5	69.7 ± 4.8

[a]Based on the GC CH profiles of *D. melanogaster* (12) and on GC-MS analyses.

Reference:

- Martino M , Ma D , Leulier F . Microbial influence on Drosophila biology[J]. Current Opinion in Microbiology, 2017, 38:165.
- Shin S C , Kim S H , You H , et al. Drosophila Microbiome Modulates Host Developmental and Metabolic Homeostasis via Insulin Signaling[J]. ence, 2011, 334(6056):670-674.
- Xu J , Hopkins K , Sabin L , et al. ERK signaling couples nutrient status to antiviral defense in the insect gut[J]. Proceedings of the National Academy of Sciences, 2013, 110(37):15025-15030.
- Xu, Jie, Osbom, et al. Microbiota-Dependent Priming of Antiviral Intestinal Immunity in Drosophila[J]. Cell Host & Microbe, 2015.
- Douglas, Angela E . The Drosophila model for microbiome research[J]. Lab Anim, 2018, 47(6):157-164.
- Sharon G , Segal D , Ringo J M , et al. Commensal bacteria play a role in mating preference of Drosophila melanogaster (vol 107, pg 20051, 2010)[J]. Proceedings of the National Academy of ences, 2013, 110(12):4853-4853.
- Catherine, E, Schretter, et al. A gut microbial factor modulates locomotor behaviour in Drosophila.[J]. Nature, 2018.

Thank you !