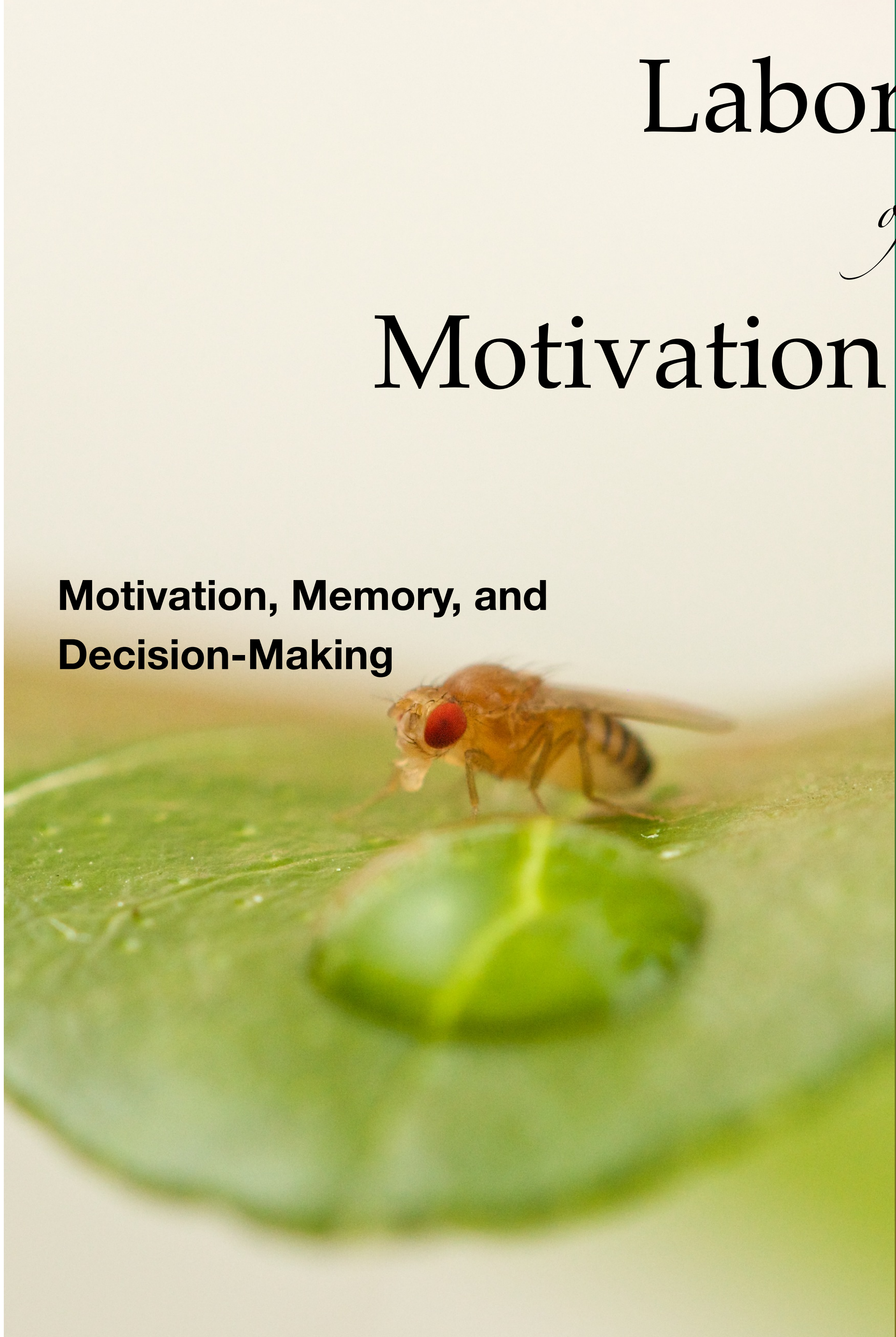
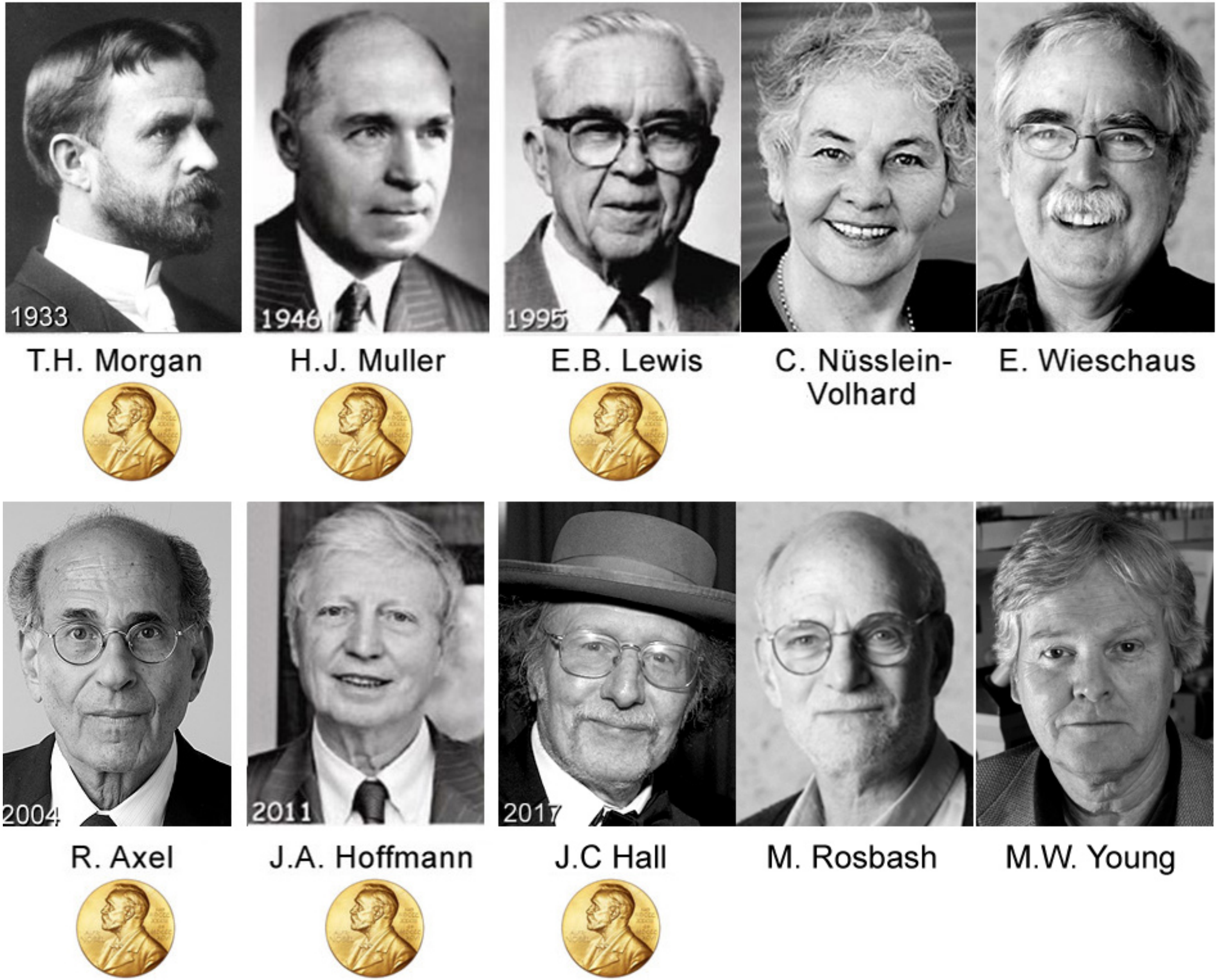
那些年果蠅教我們的事

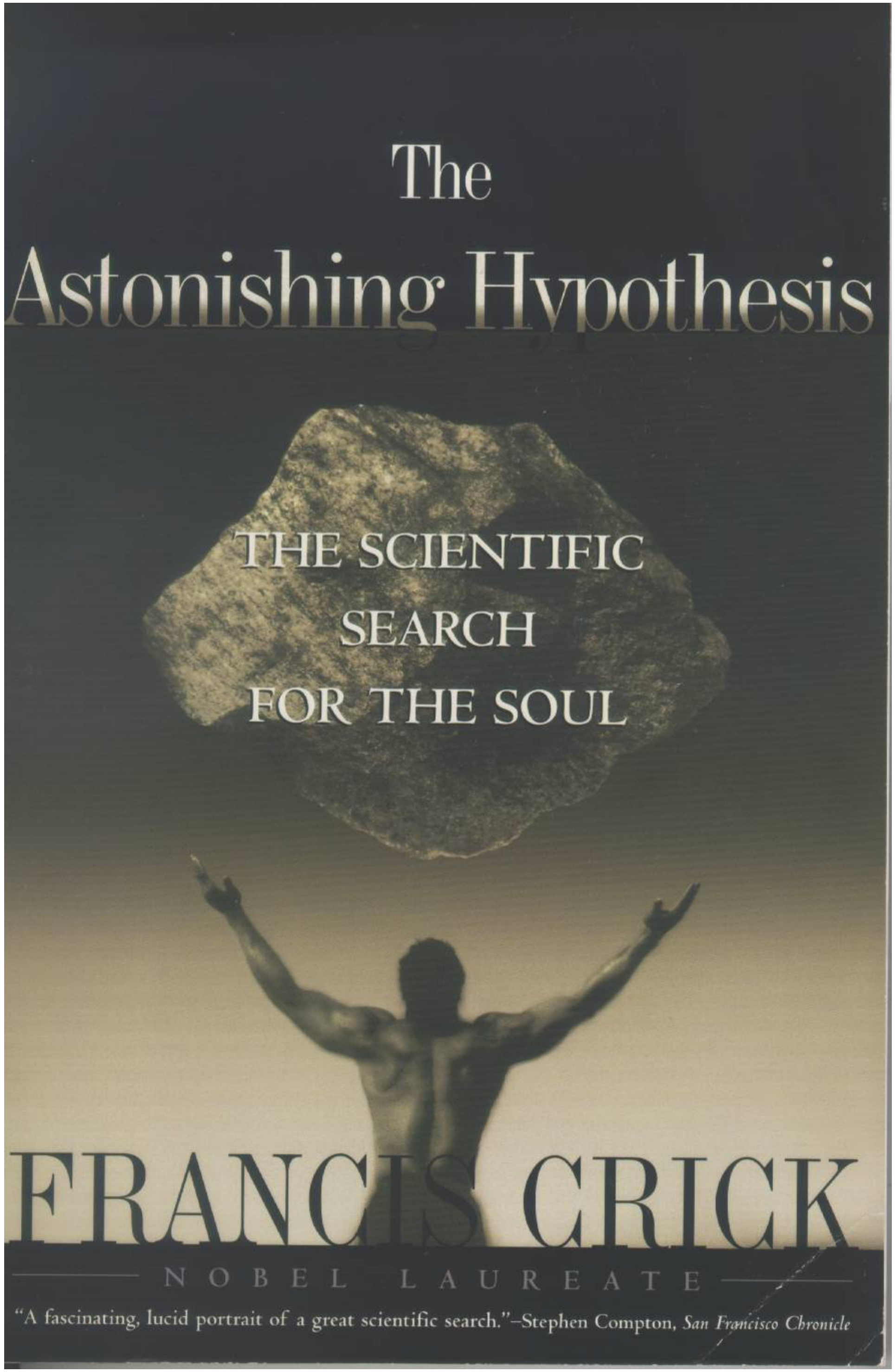
：神經科學的前沿探索

中研院分子生物研究所
林書葦 副研究員

Laboratory *of* Motivation & Memory

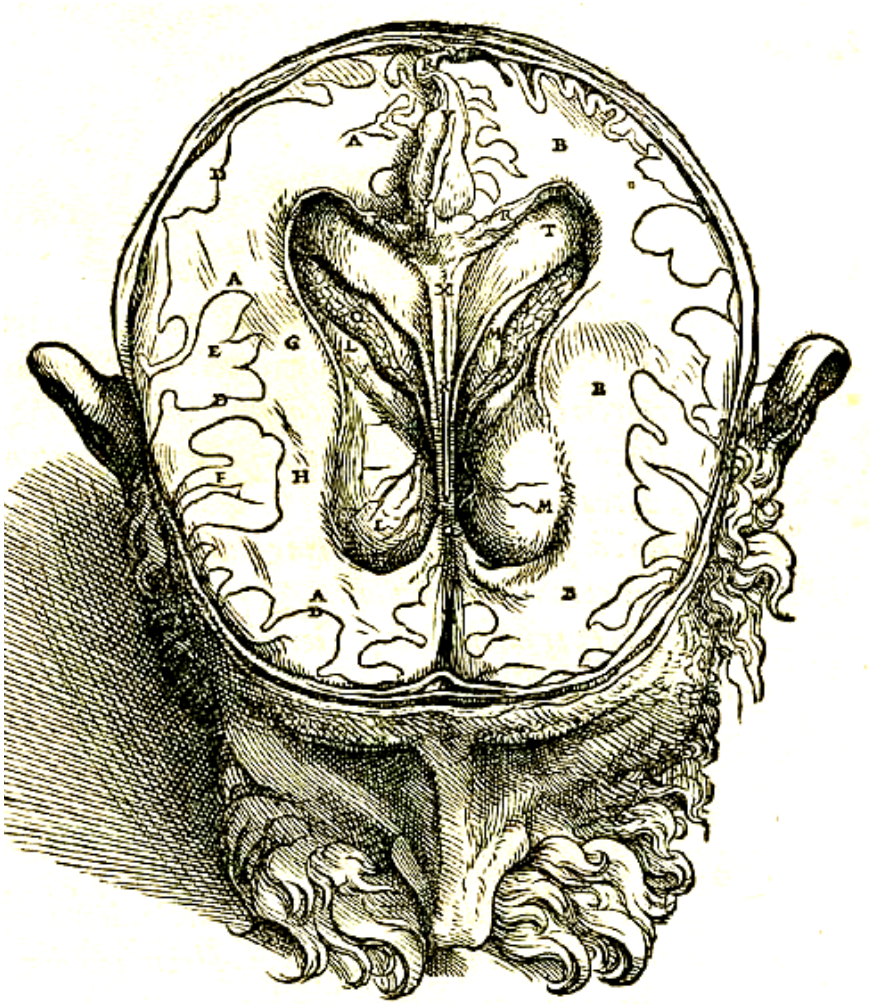



1933
T.H. Morgan
1946
H.J. Muller
1995
E.B. Lewis
C. Nüsslein-Volhard
E. Wieschaus
2004
R. Axel
2011
J.A. Hoffmann
2017
J.C Hall
M. Rosbash
M.W. Young



You are nothing but a pack of neurons!

Francis Crick, 1994



..tempers the heat and seething of the heart.

- Aristotle (384–322 BC.)

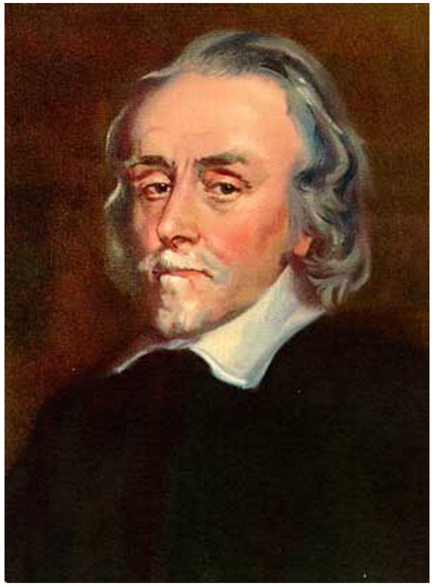
René Descarte (1596-1650)

To think that our soul excites the movements is like to think that there is a soul in a clock which causes it to show the hours…

- René Descartes (1596-1650)

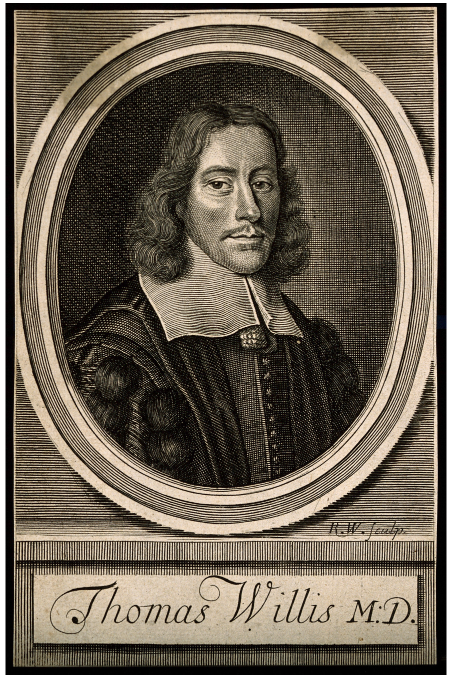
René Descarte (1596-1650)

William Harvey (1578-1657)



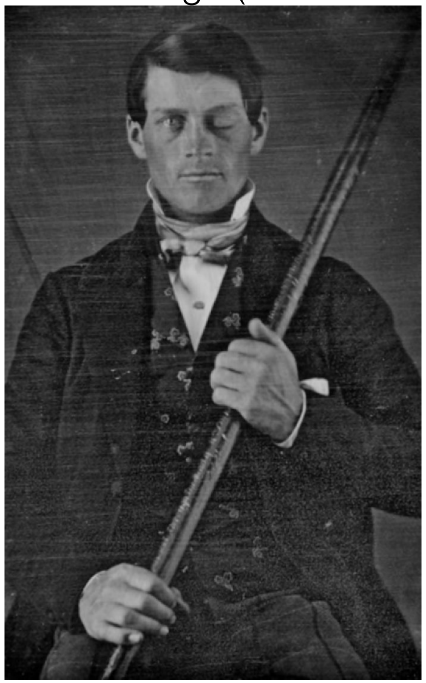
Robert Hooke (1635-1703)

Thomas Willis (1621-1675)

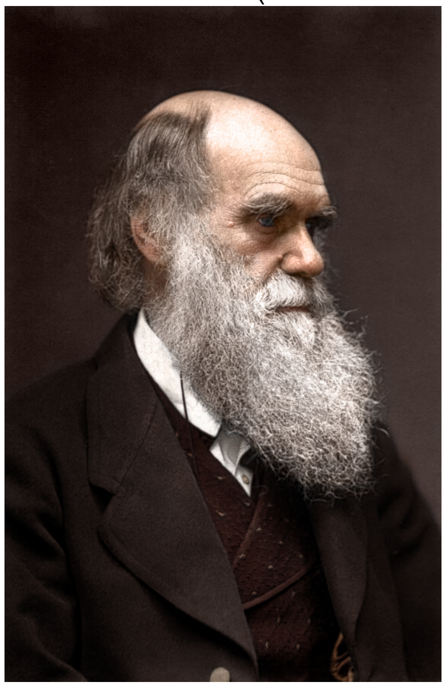


Luigi Galvani (1737-1798)

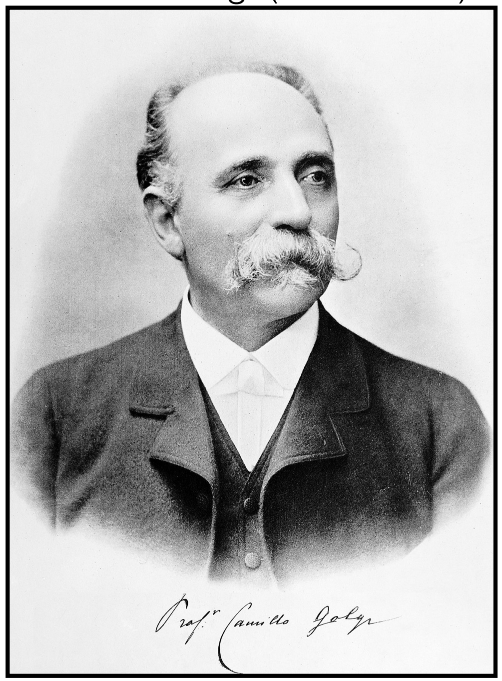
Phineas Gage (1823-1860)



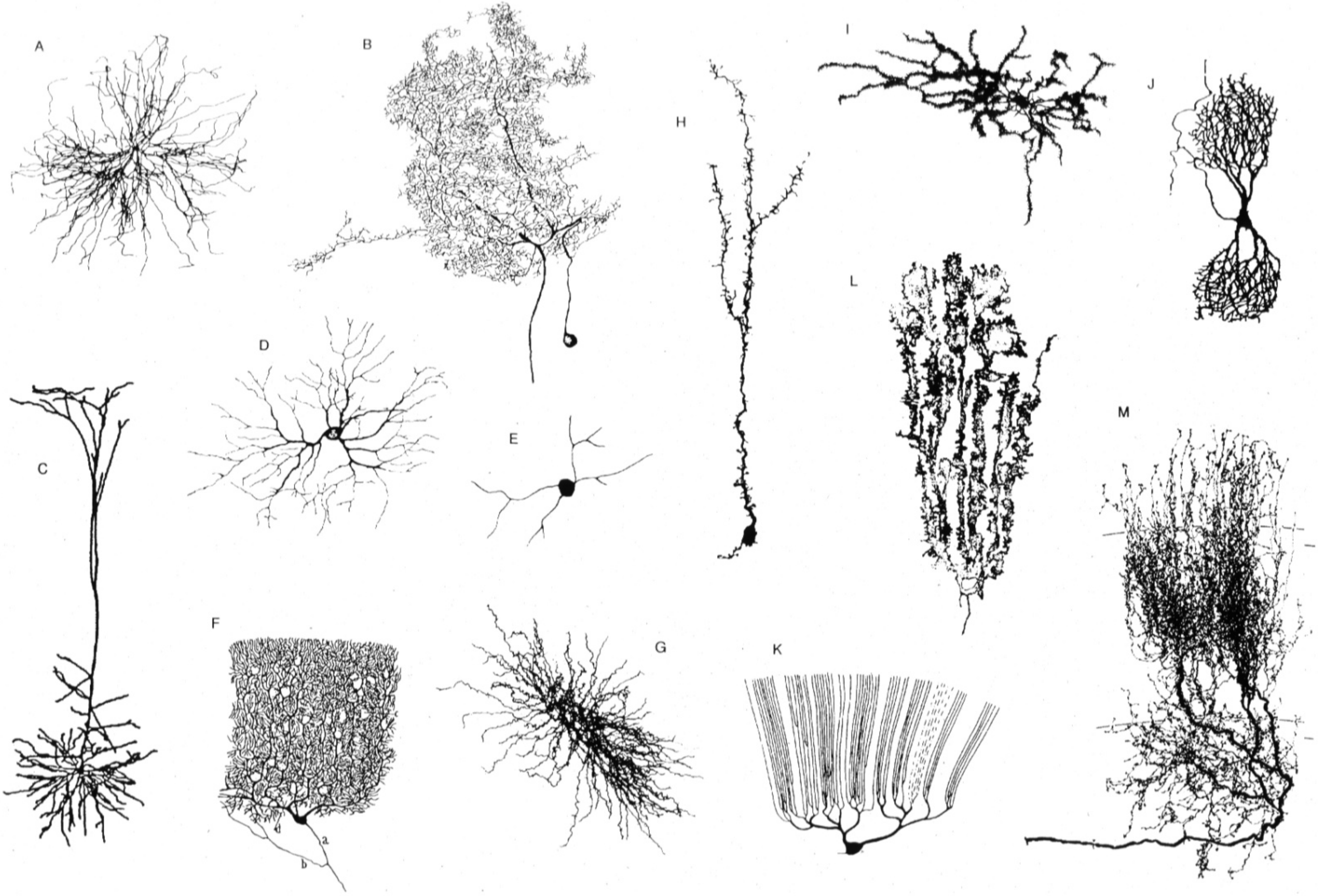
Charles Darwin (1809-1882)



Camillo Golgi (1843-1926)



Santiago Ramón y Cajal (1879-1930)


A
B
I
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H
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a
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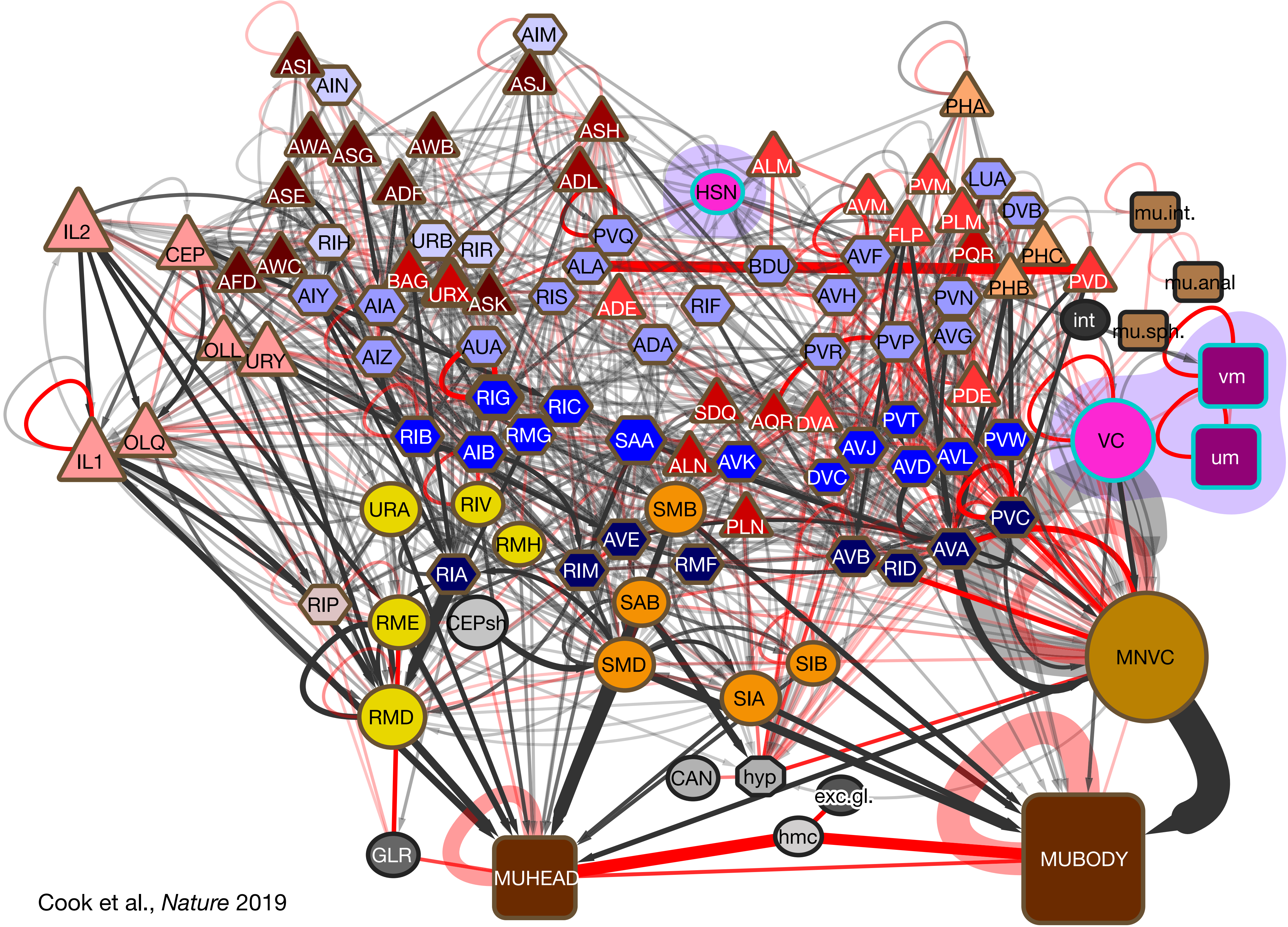
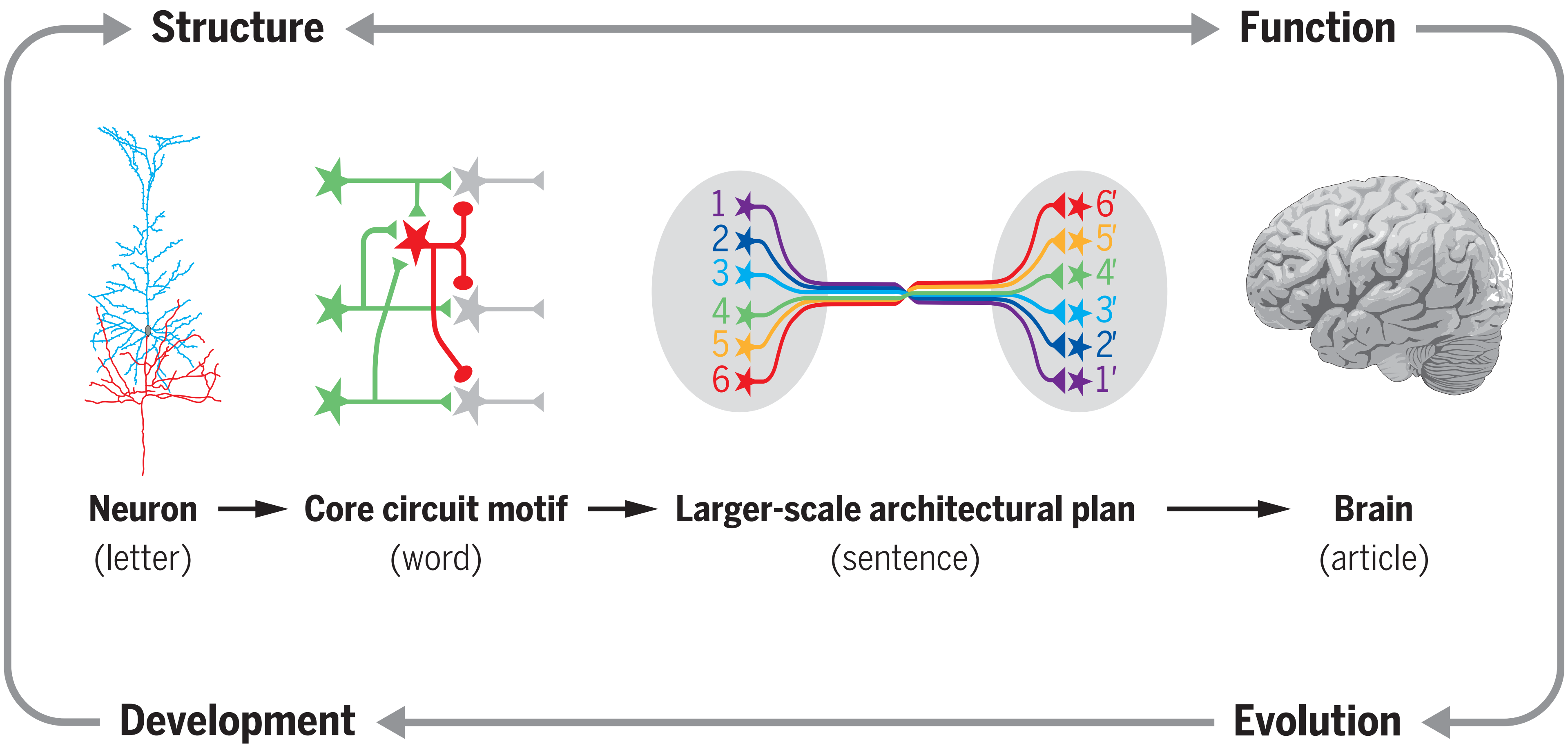
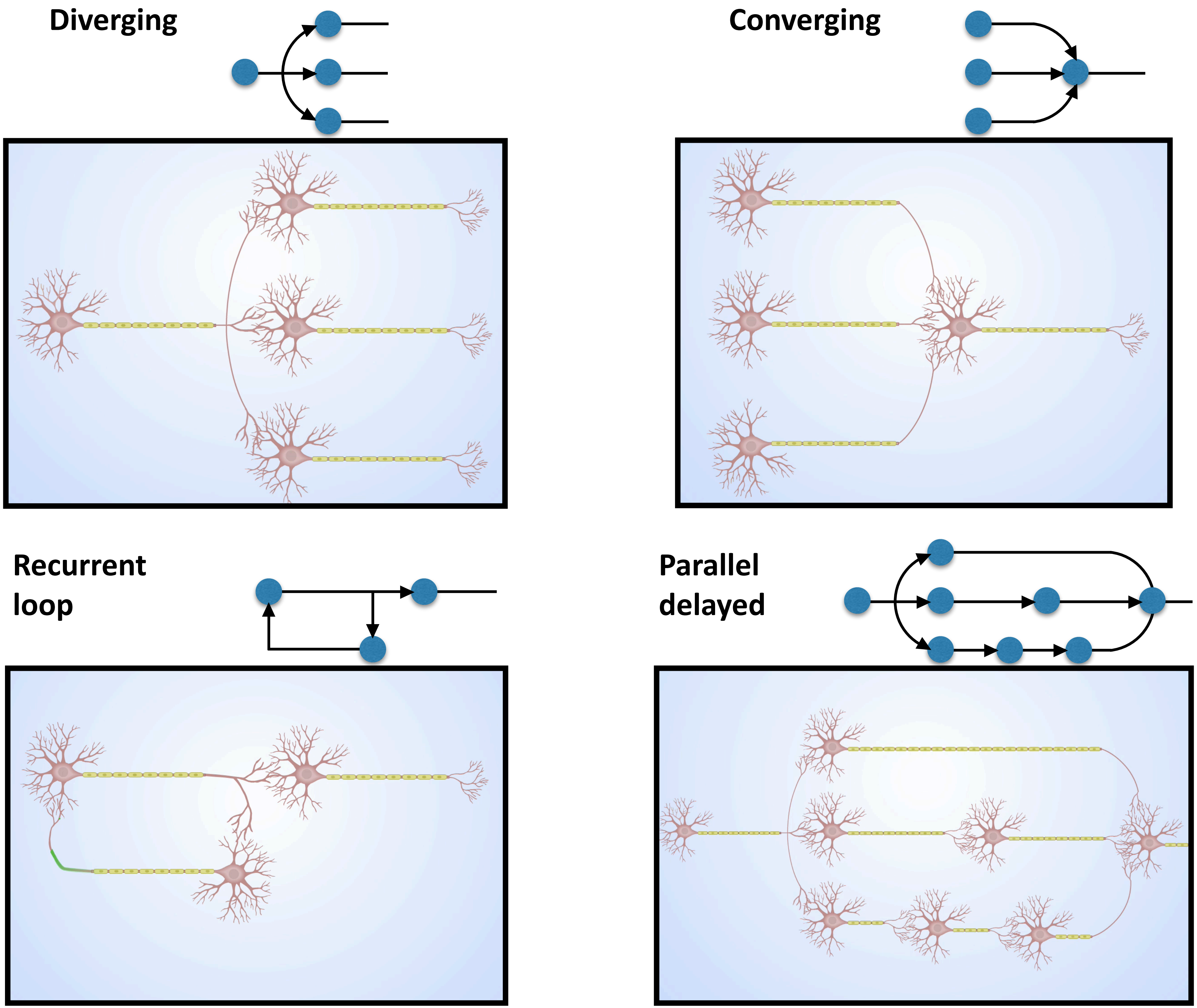


Cook et al., *Nature* 2019

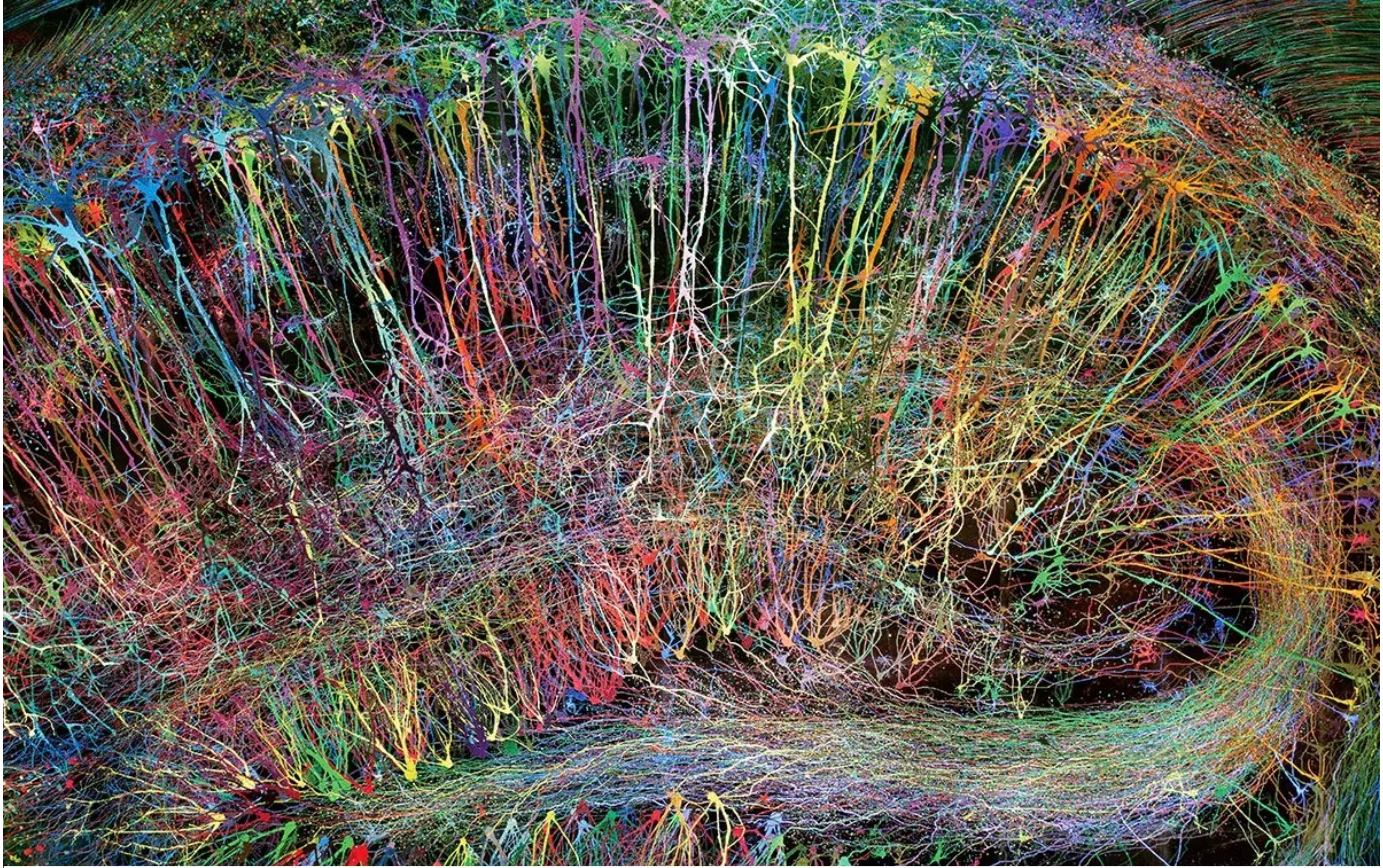
From neurons to a brain



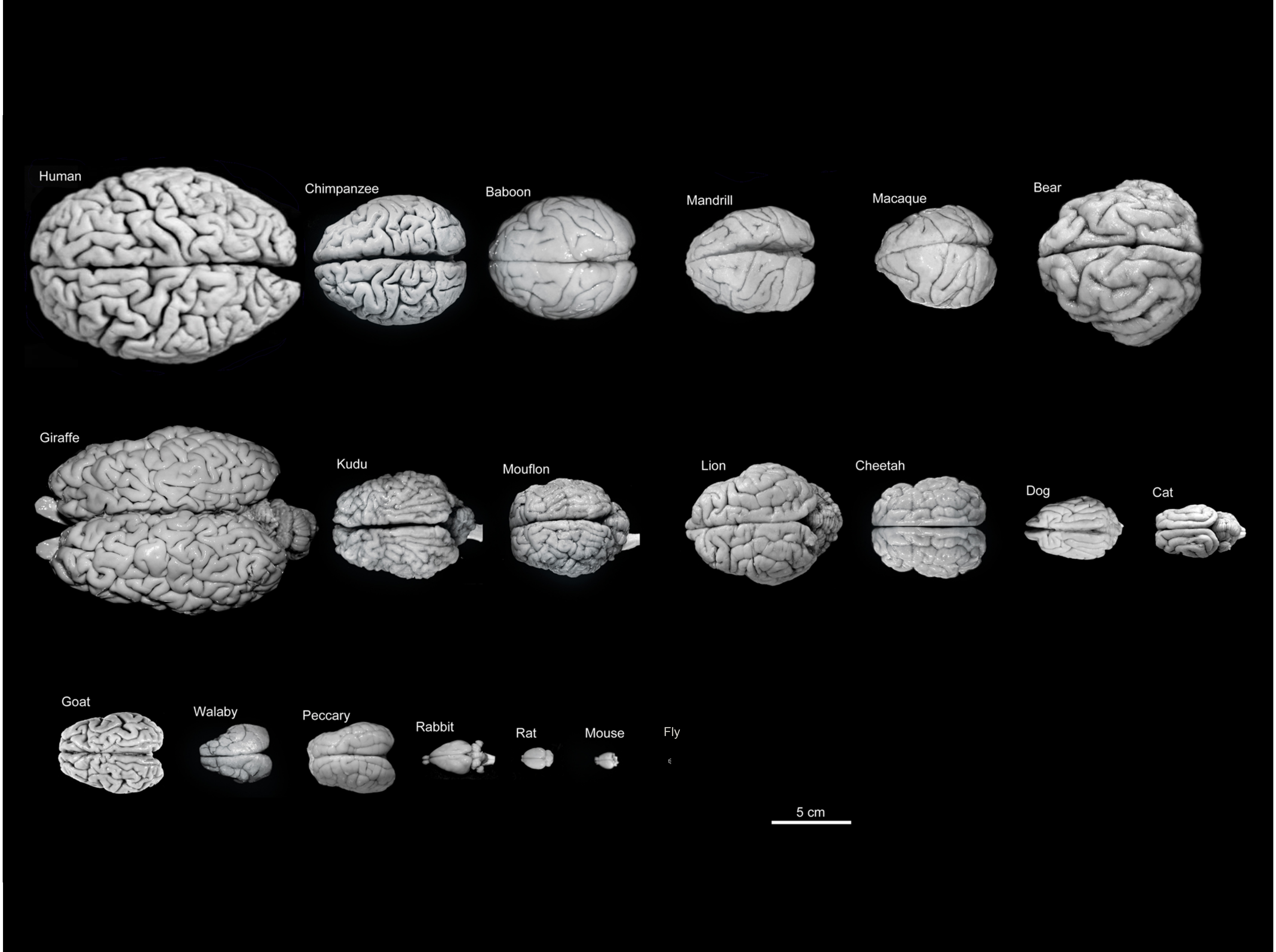
Luo, Science 2021



Diverging
Converging
Recurrent loop
Parallel delayed



86 billion neurons • 100 trillion synapses • one neuron can connect with up to 10,000 other neurons


Human
Chimpanzee
Baboon
Mandrill
Macaque
Bear
Giraffe
Kudu
Mouflon
Lion
Cheetah
Dog
Cat
Goat
Walaby
Peccary
Rabbit
Rat
Mouse
Fly
5 cm

- 71,000,000 neurons
- Complex behavior
- Genetic tools available
- A human-like brain

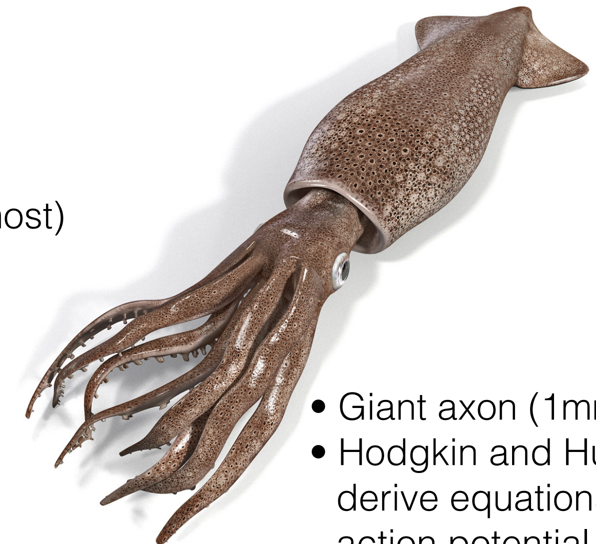
- 1,000,000 neurons
- Complex behavior
- Genetic tools available
- Larva is transparent
- Vertebrate

302 neurons •
Transparent •
Wiring diagram solved •

- 250,000 neurons
- Complex behavior
- Genetic tools available
- Brain connectome solved (almost)

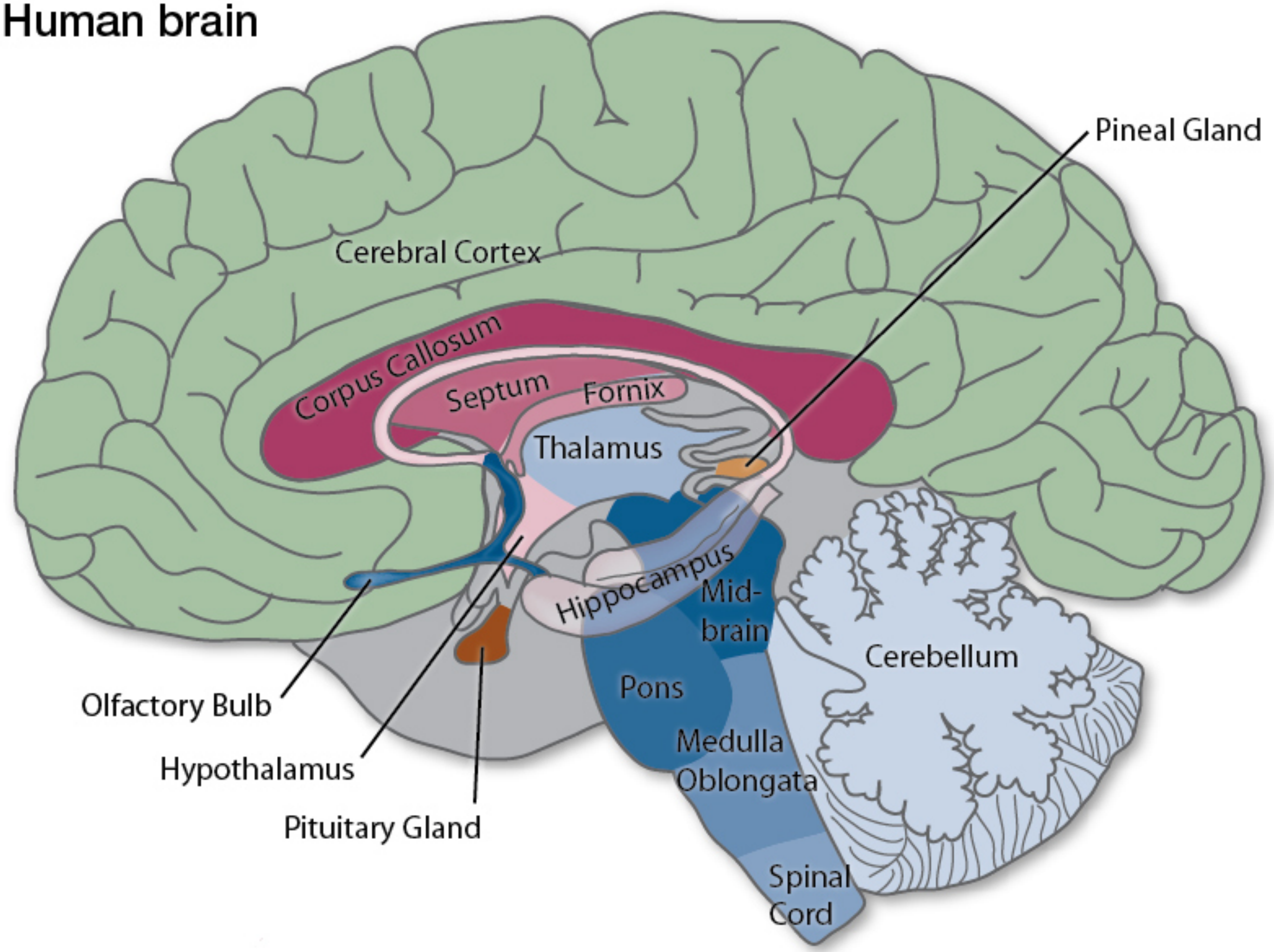
- 100,000 neurons
- Central pattern generator

- 20,000 neurons
- Eric Kandel's favorite
- Neurobiology of memory



- Giant axon (1mm in diameter)
- Hodgkin and Huxley used to derive equations to describe action potential

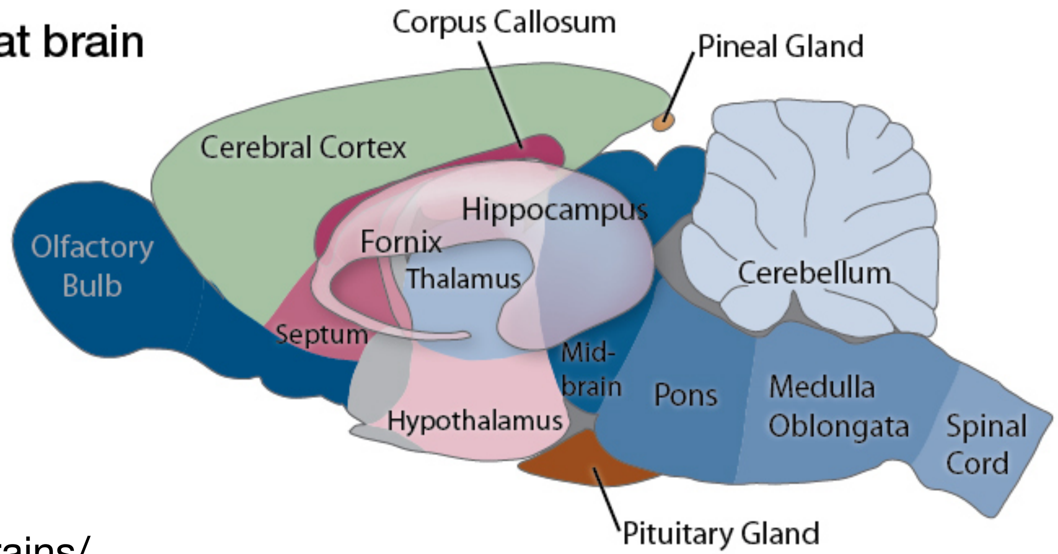
Human brain



1500g

86000 M

Rat brain



1.8g (0.5g)

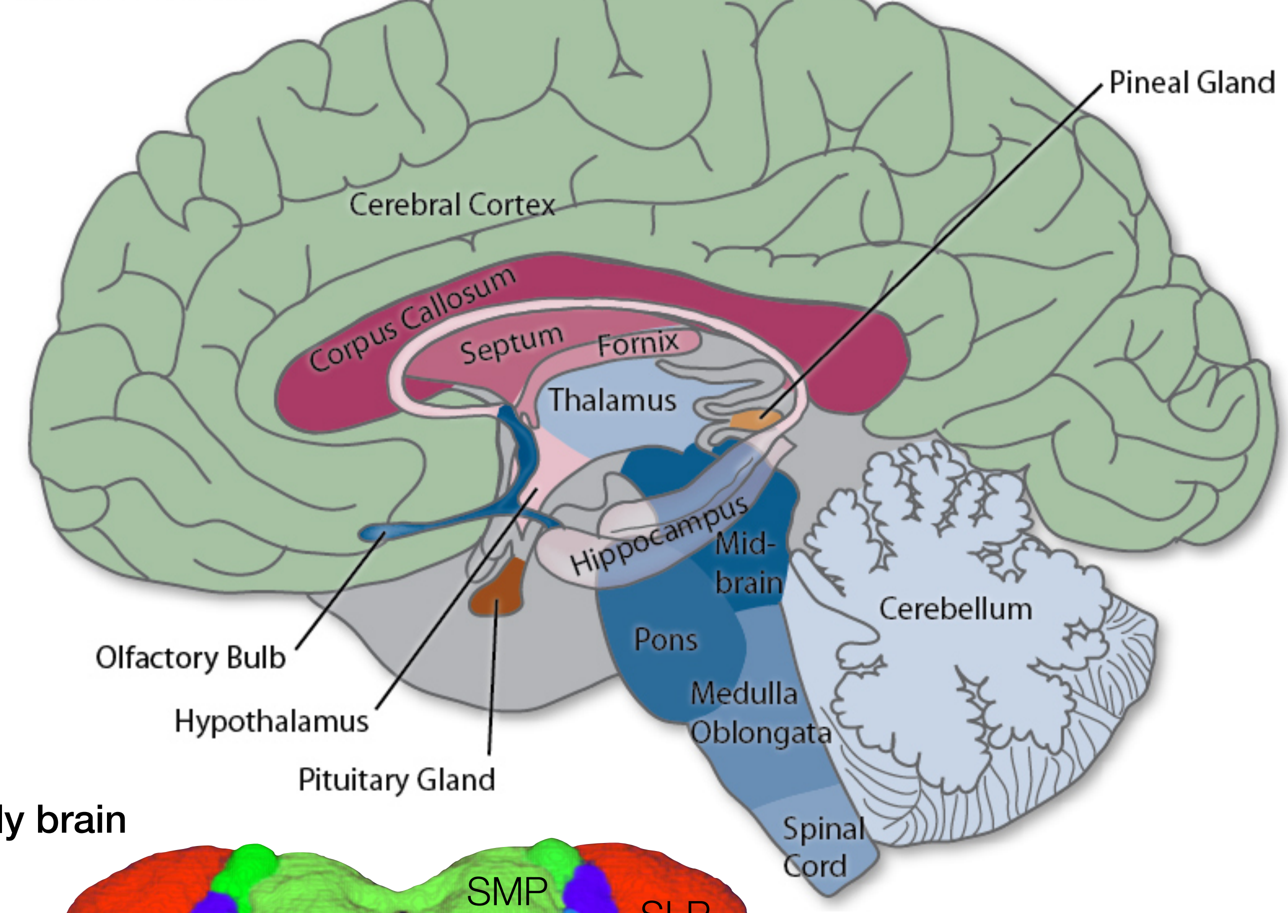
200 M (70 M)

https://sites.bu.edu/bryantlab/brains/

Human brain

1500g

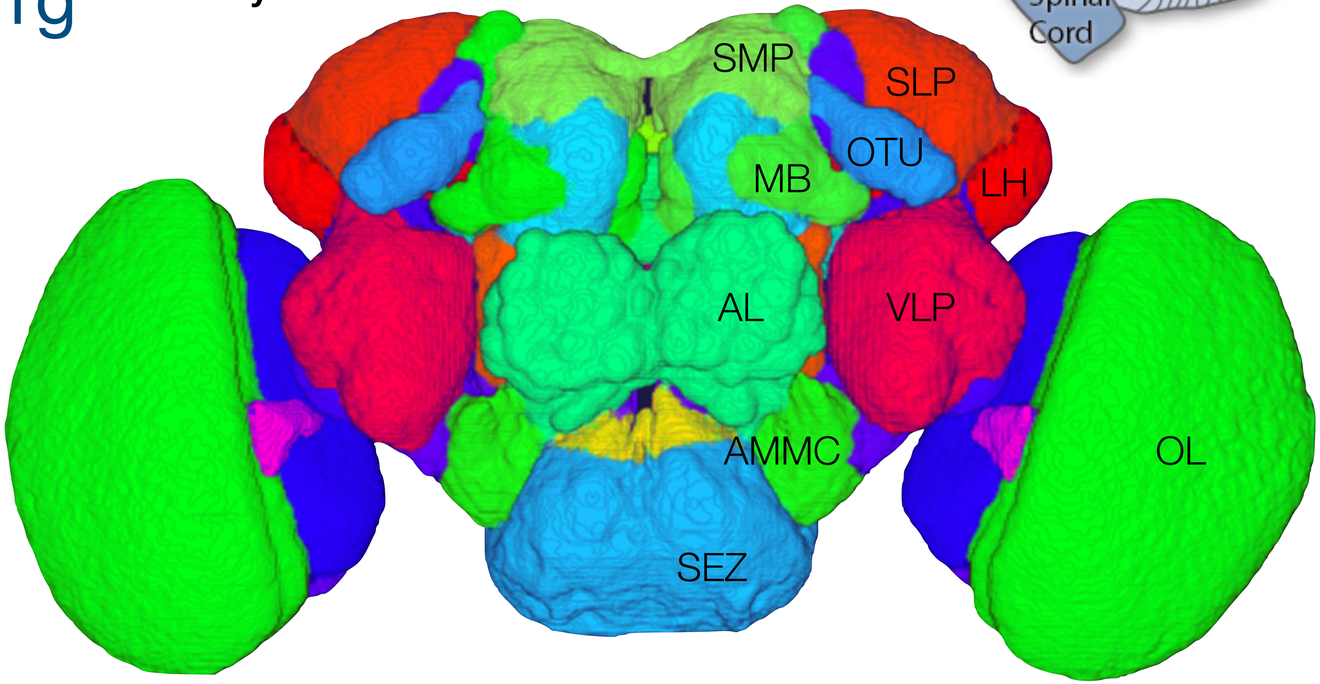
86000 M



Fly brain

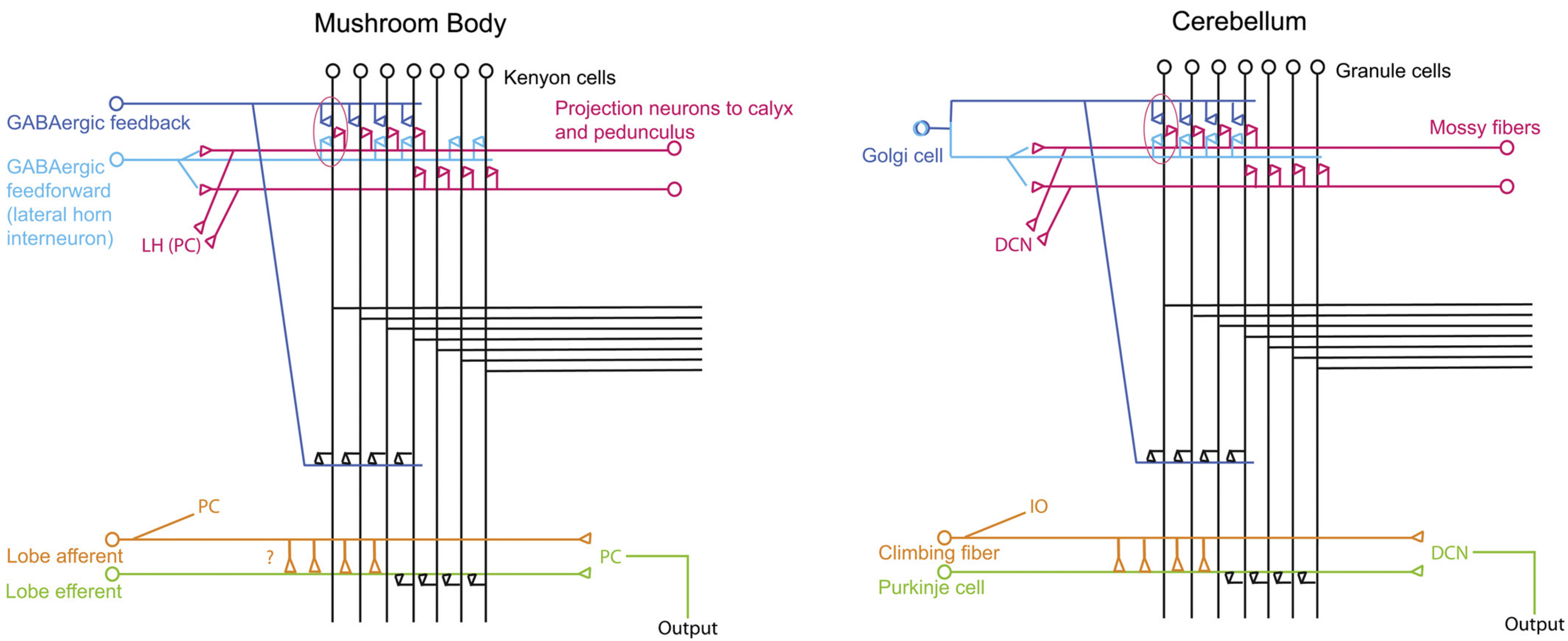
0.0001g

0.1 M



Givon & Lazar, 2016

Fly mushroom body and mammalian cerebellum share similar circuit structure



Farris, 2011

Scientists research man missing 90% of his brain who leads a normal life

CBC Radio · Posted: Jul 14, 2016 5:27 PM EDT | Last Updated: April 17, 2023

Brain of a white-collar worker

Lionel Feuillet, Henry Dufour, Jean Pelletier

Lancet 2007; 370: 262

Department of Neurology (L Feuillet MD, J Pelletier PhD), **and Department of Neurosurgery** (H Dufour PhD), **Faculté de Médecine de Marseille, Université de la Méditerranée, Assistance Publique hôpitaux de Marseille—Hôpital de la Timone, Marseille, France**

Correspondence to: Dr Lionel Feuillet, Department of Neurology, Faculté de Médecine de Marseille, Université de la Méditerranée, Assistance Publique hôpitaux de Marseille—Hôpital de la Timone, Marseille, France
lionel.feuillet@mail.ap-hm.fr

A 44-year-old man presented with a 2-week history of mild left leg weakness. At the age of 6 months, he had undergone a ventriculoatrial shunt, because of postnatal hydrocephalus of unknown cause. When he was 14 years old, he developed ataxia and paresis of the left leg, which resolved entirely after shunt revision. His neurological development and medical history were otherwise normal. He was a married father of two children, and worked as a civil servant. On neuropsychological testing, he proved to have an intelligence quotient (IQ) of 75: his verbal IQ was 84, and his performance IQ 70. CT showed severe dilatation of the lateral ventricles (figure); MRI revealed massive enlargement of the lateral, third, and fourth ventricles, a very thin cortical mantle and a posterior fossa cyst. We diagnosed a non-communicating hydrocephalus, with probable stenosis of Magendie's foramen (figure). The leg weakness improved partly after neuroendoscopic ventriculocisternostomy, but soon recurred; however, after a ventriculoperitoneal shunt was inserted, the findings on neurological examination became normal within a few weeks. The findings on neuropsychological testing and CT did not change.

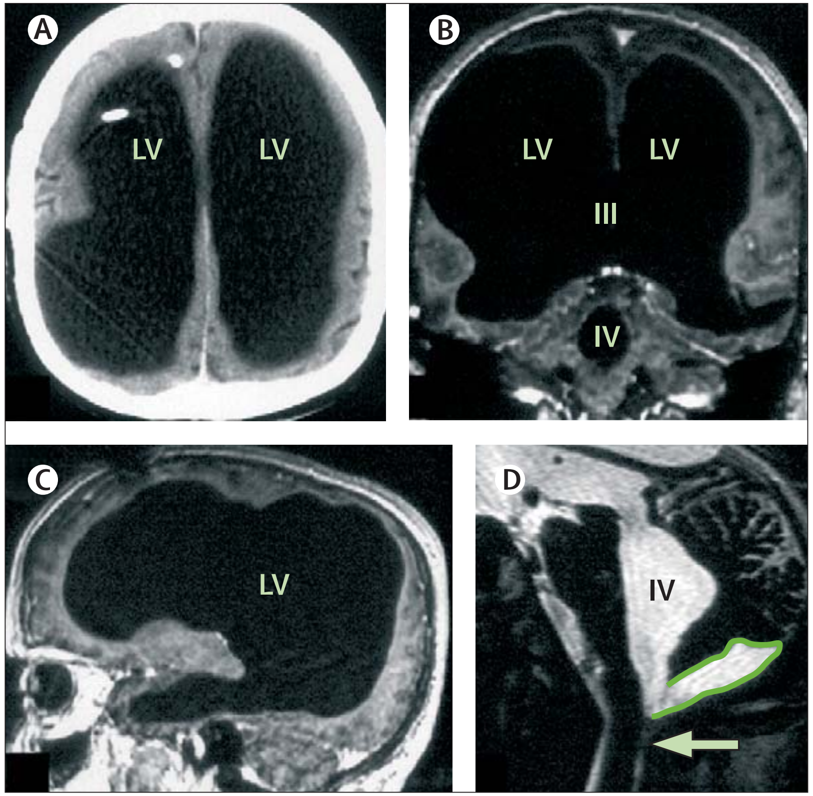


Figure: **Massive ventricular enlargement, in a patient with normal social functioning**
(A) CT; (B, C) T1- weighted MRI, with gadolinium contrast; (D) T2-weighted MRI. LV=lateral ventricle. III=third ventricle. IV=fourth ventricle. Arrow=Magendie's foramen. The posterior fossa cyst is outlined in (D).

Advantages of studying small brains

1. Reduced system = efficient in discovering general principles
2. High cellular resolution
3. Less redundancy
4. More stereotyped
5. Visualize the complete system in a single field of view
6. Clear interface between circuit motifs and complex systems (words to sentence; emergent properties)

Small but complex. It is like the atom of behavior

What tools do we have?

Behavioral tracking

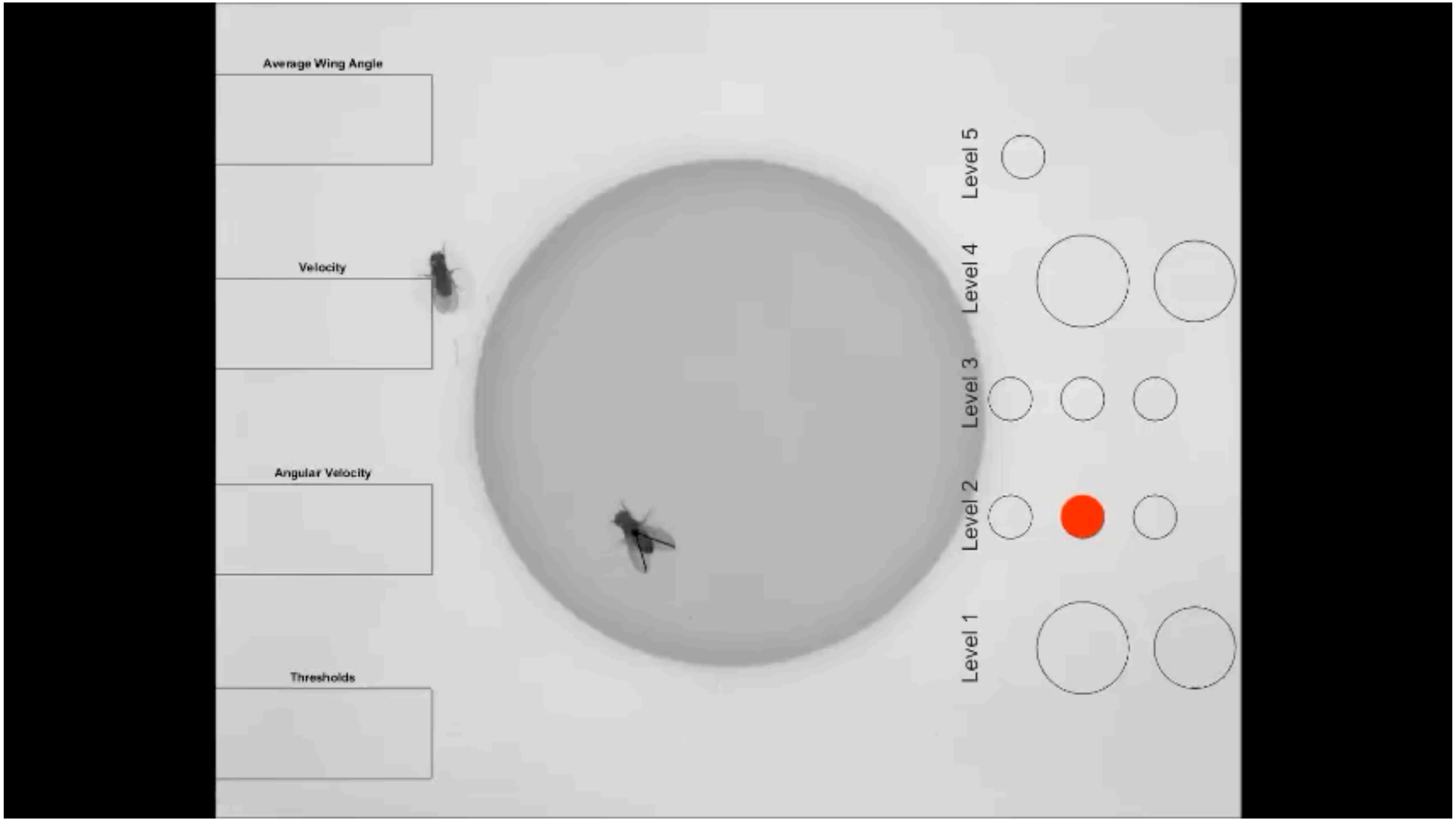
Genetics

Circuit tracing

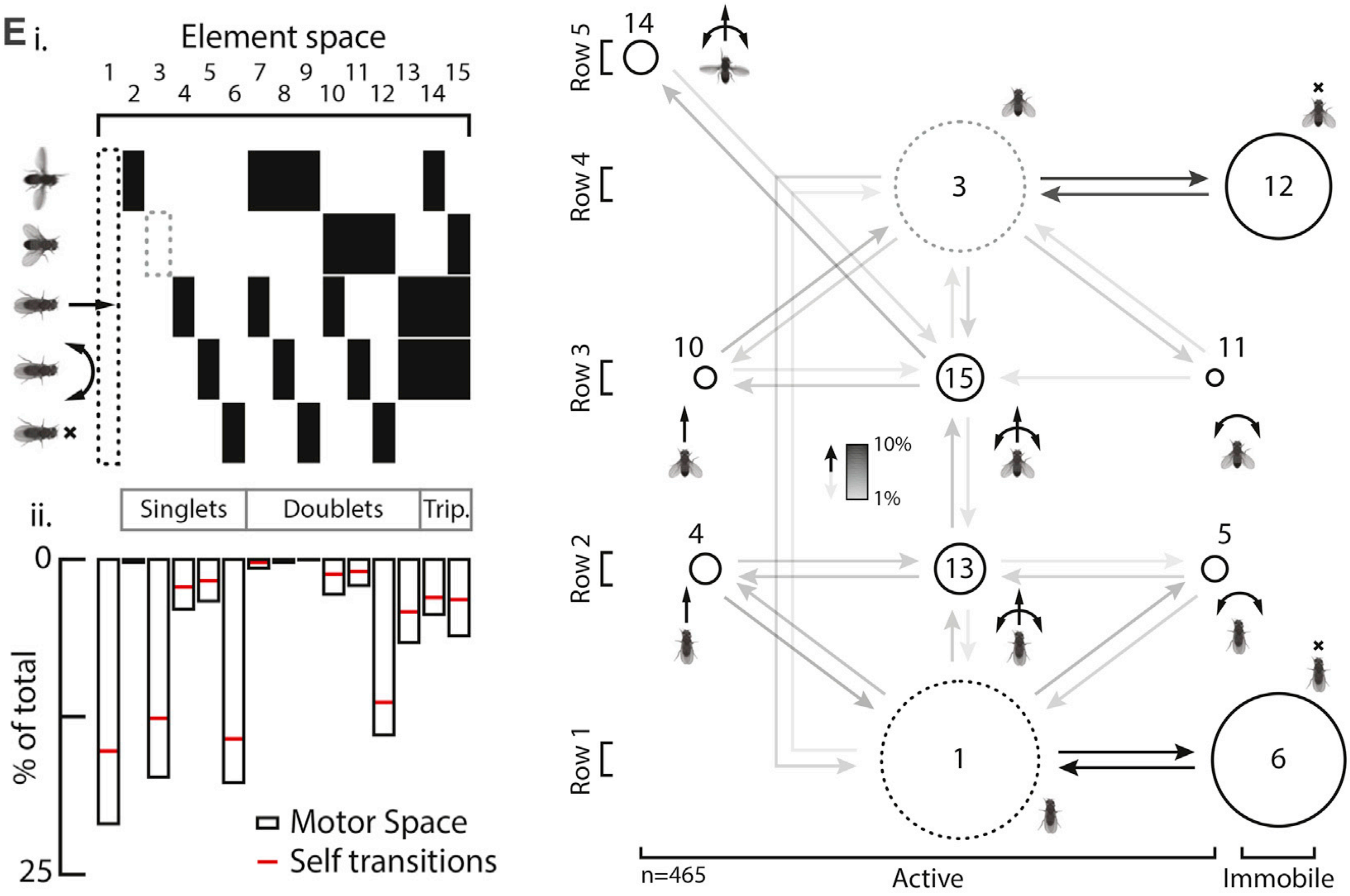
Neuron recording

Neuron manipulation

Threat behavior of the male fly



Duistermars et al., Neuron 2018



Duistermars et al., Neuron 2018

What tools do we have?

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Circuit tracing

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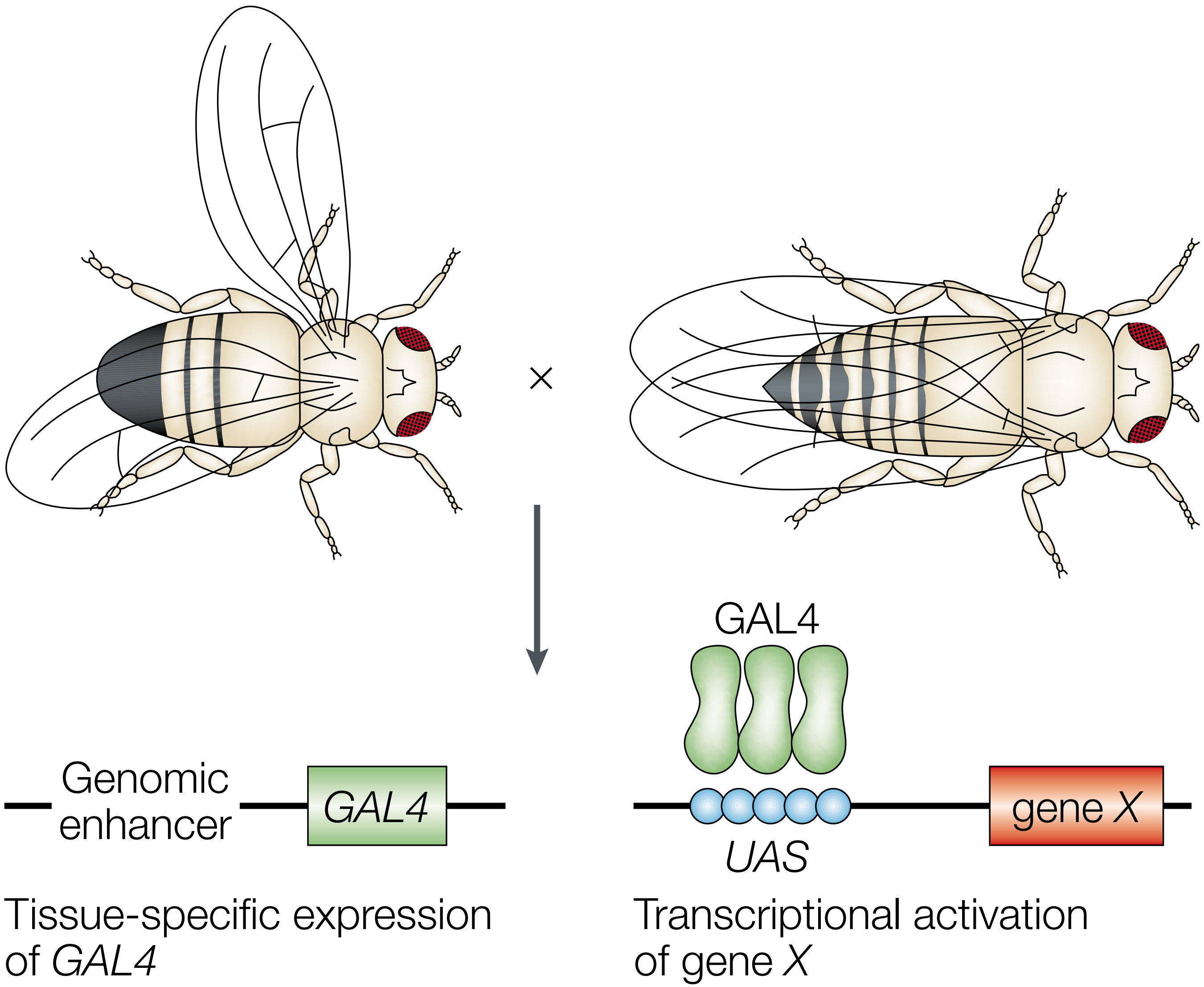
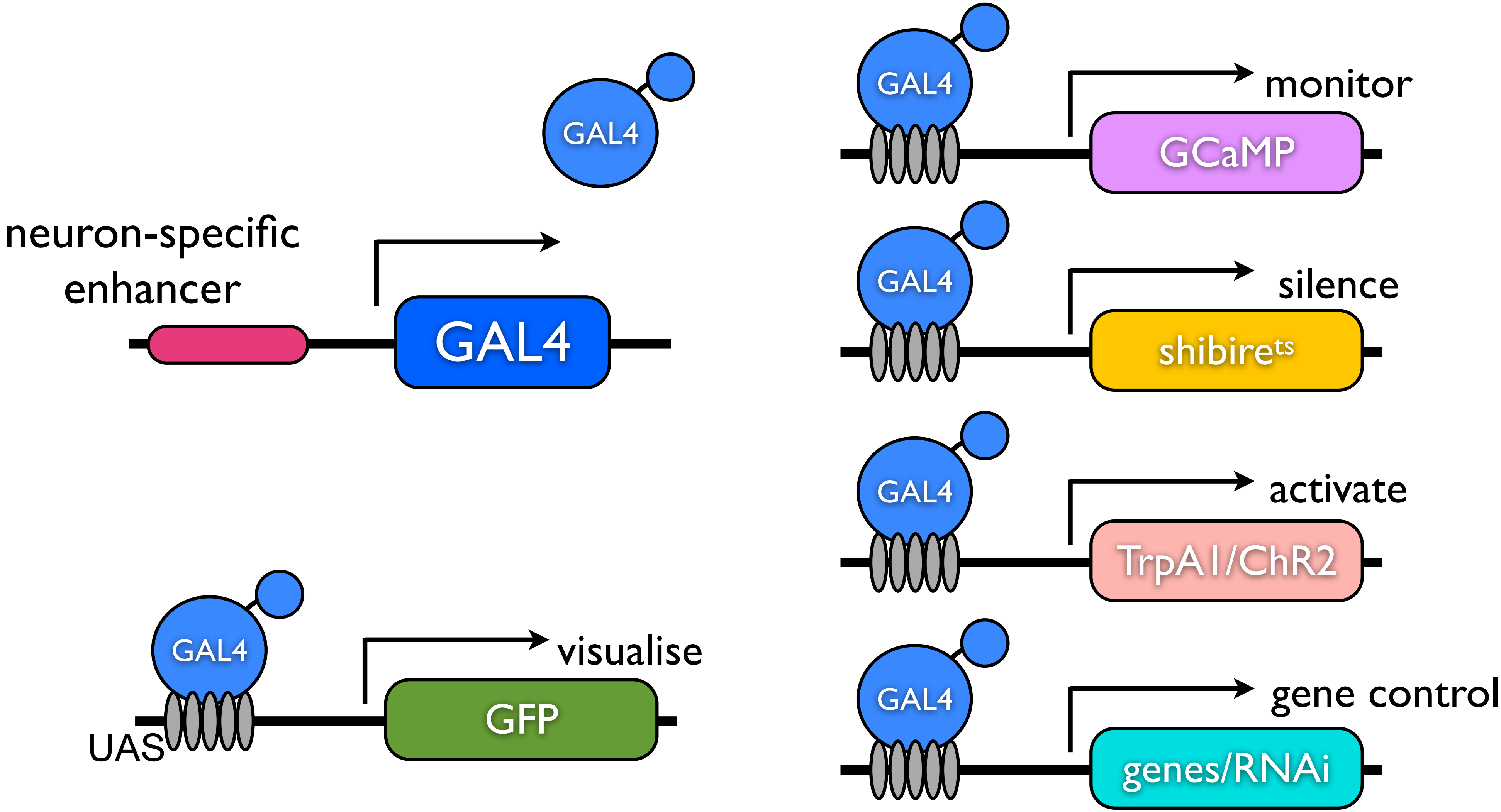
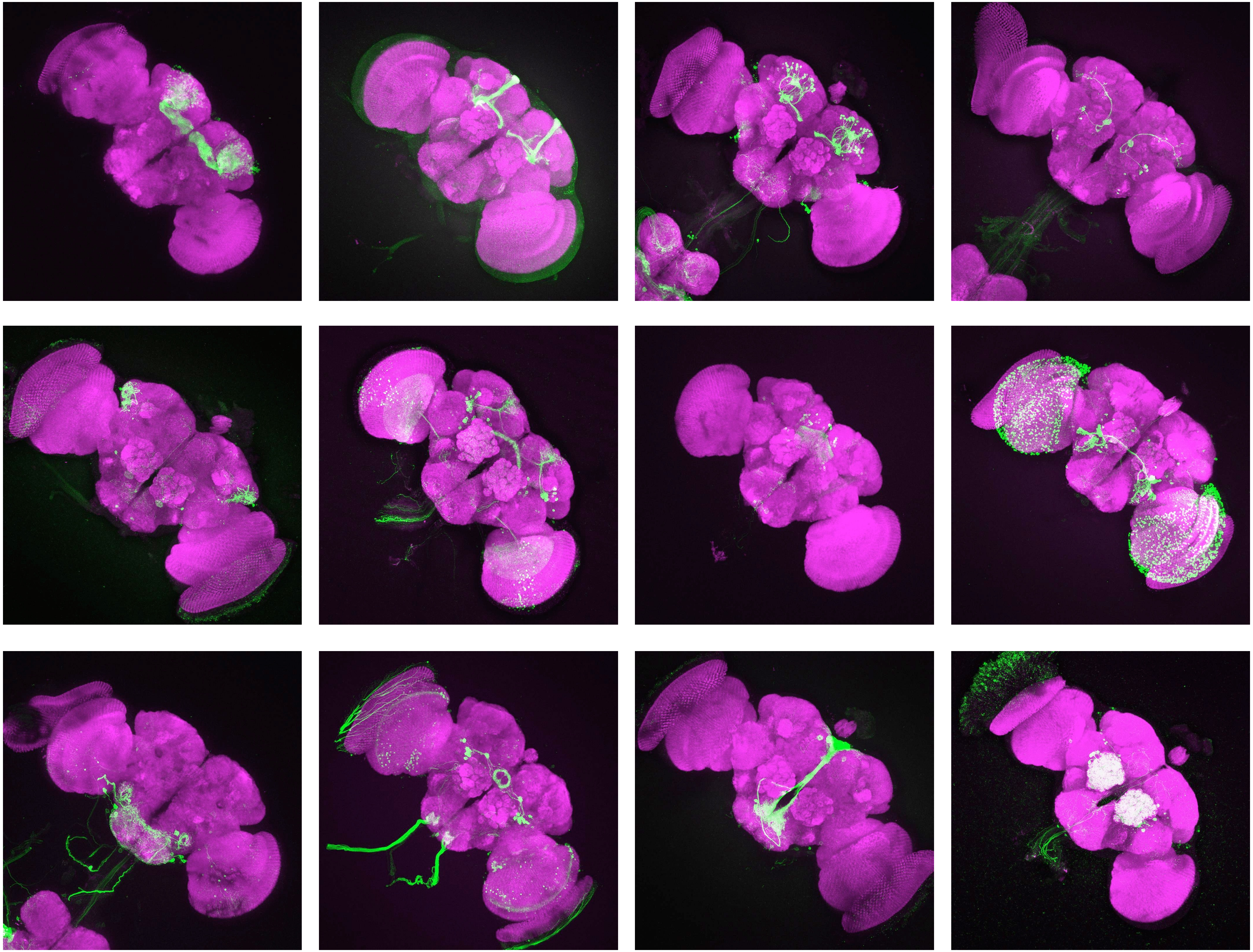
Neuron manipulation

The GAL4/UAS system



Genetic toolkits for manipulating specific neurons in the fly brain





What tools do we have?

Behavioral tracking

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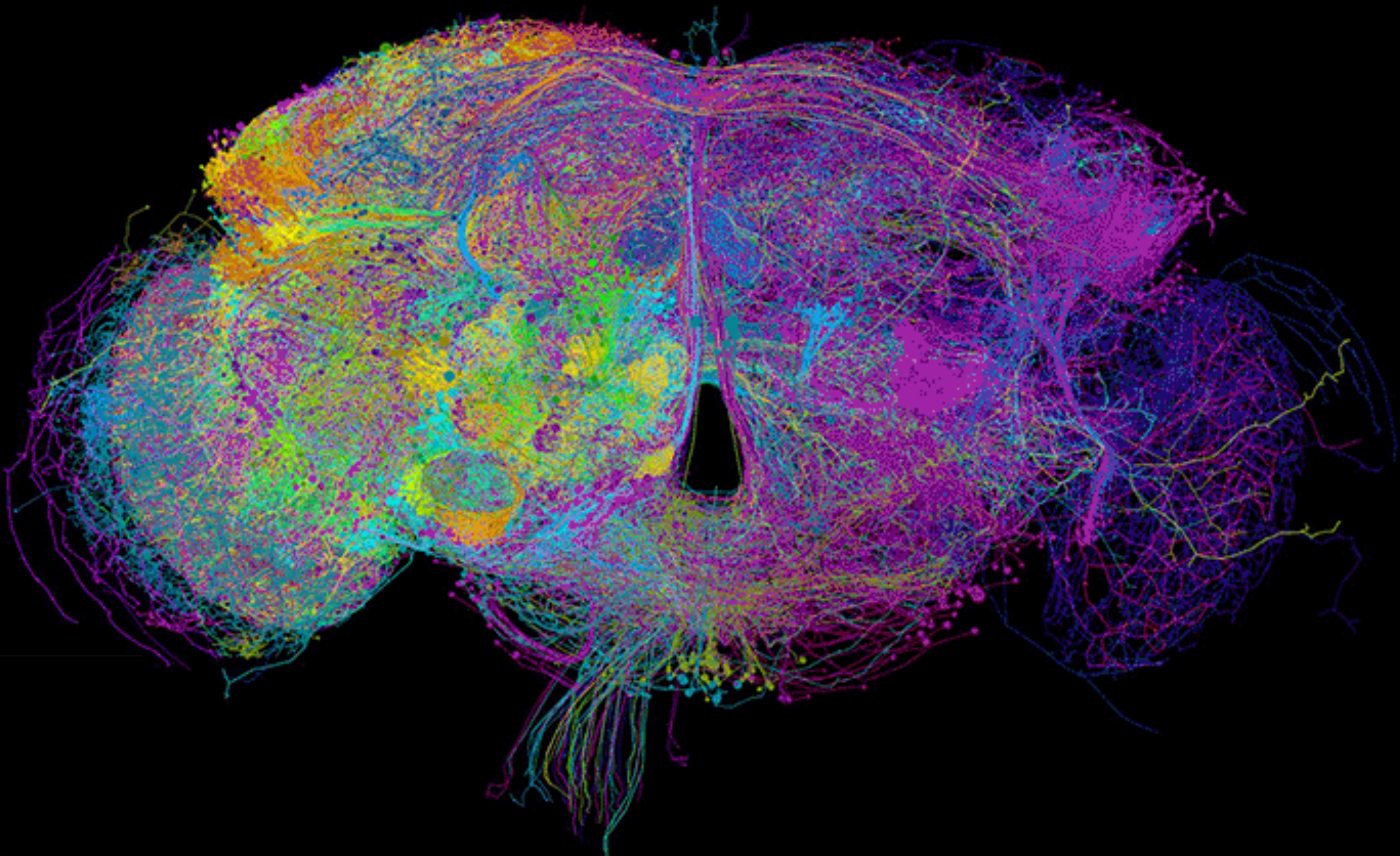
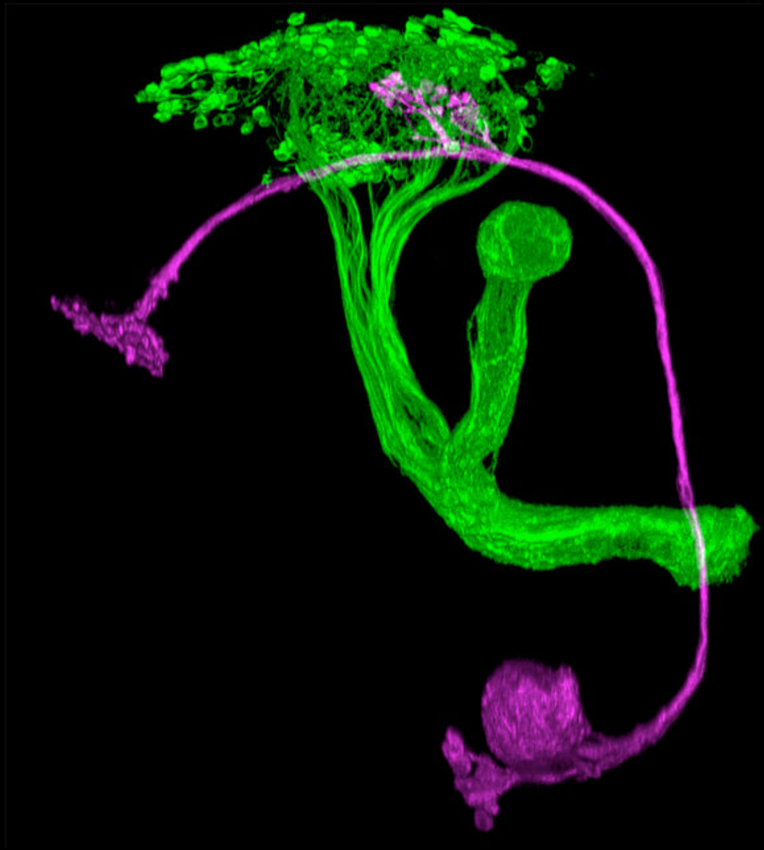
Circuit tracing

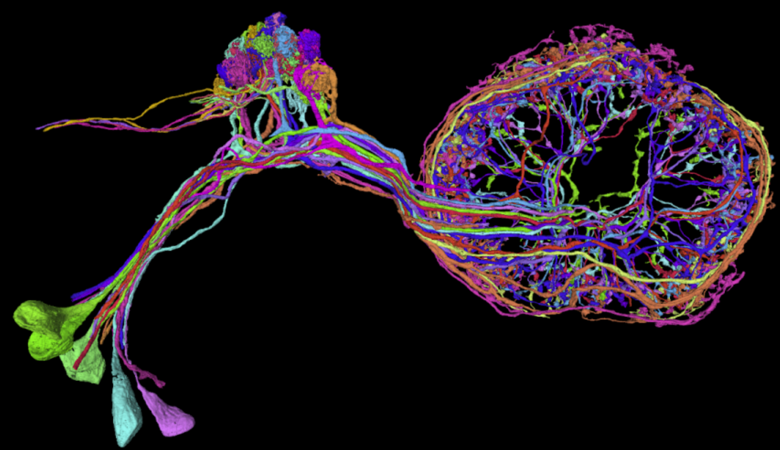
Neuron recording

Neuron manipulation

Whole brain connectome







What tools do we have?

Behavioral tracking

Genetics

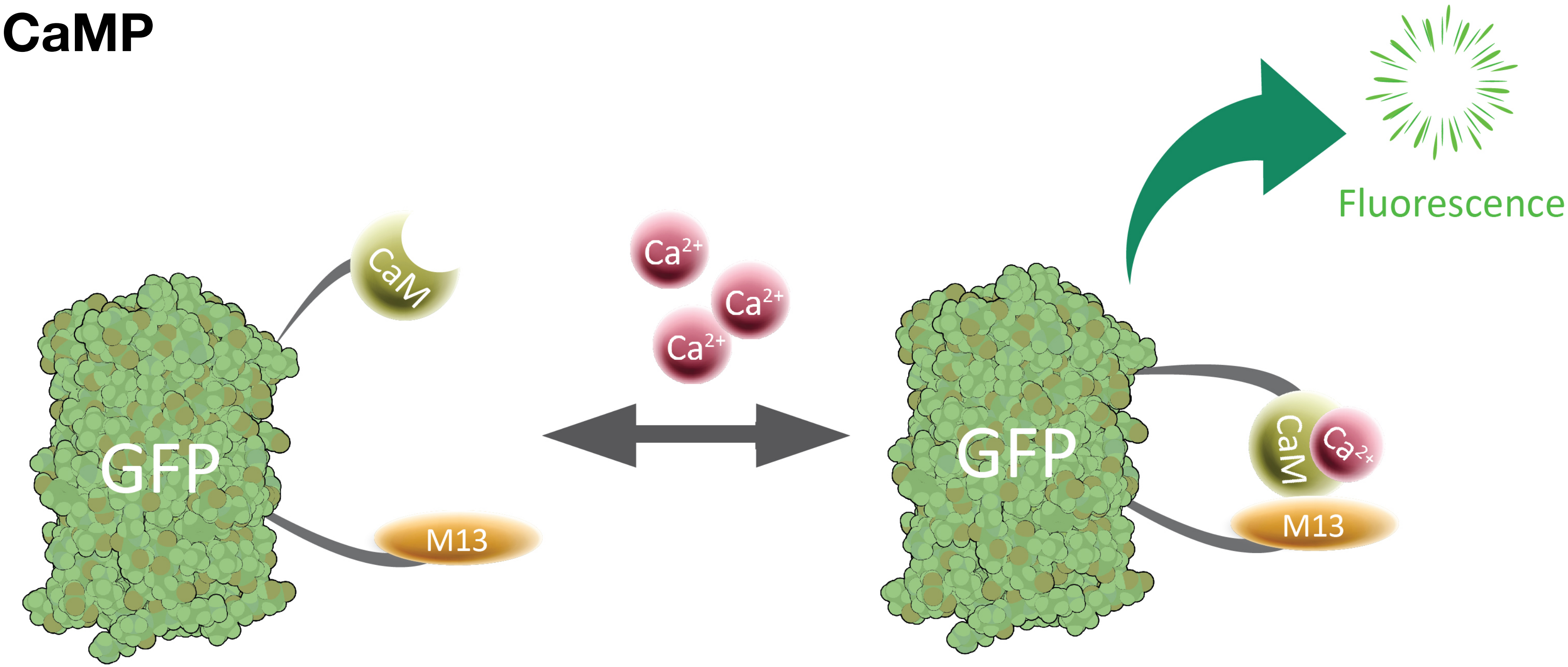
Circuit tracing

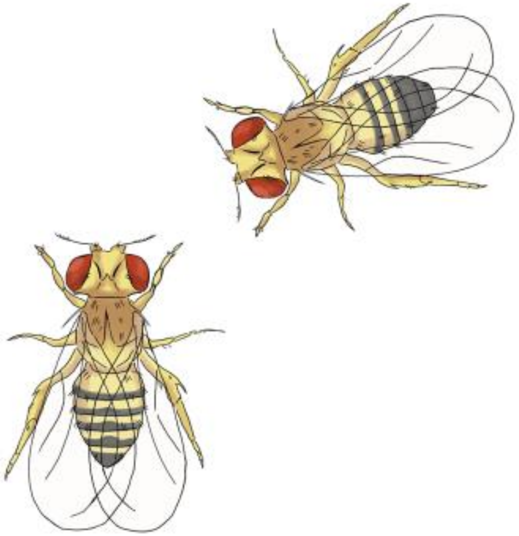
Neuron recording

Neuron manipulation

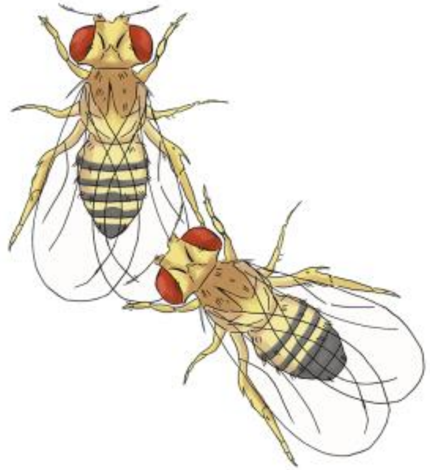
Genetically-encoded calcium indicator

GCaMP

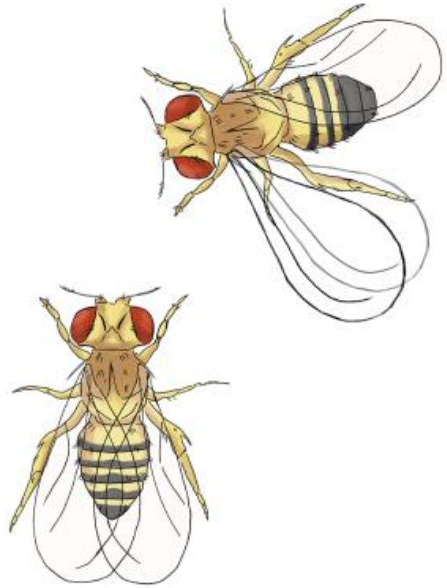




a. Orienting



b. Tapping



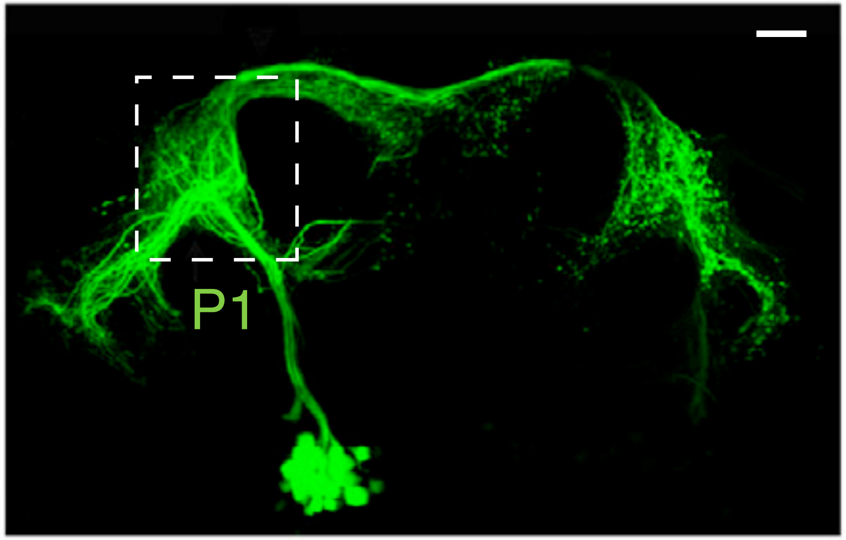
c. Singing

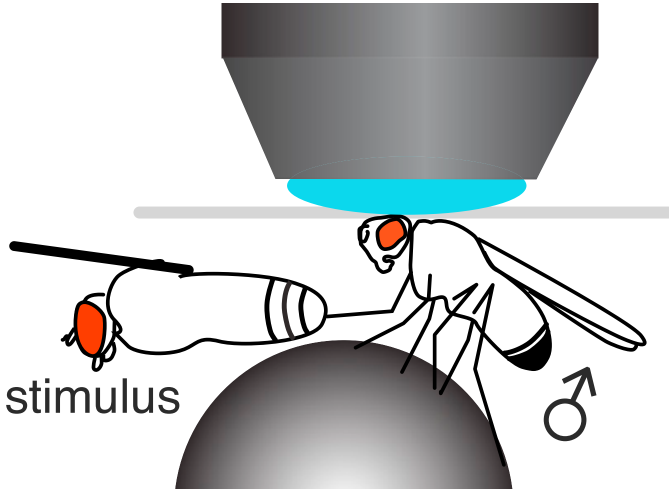
d. Licking

e. Attempting Copulation

f. Copulation

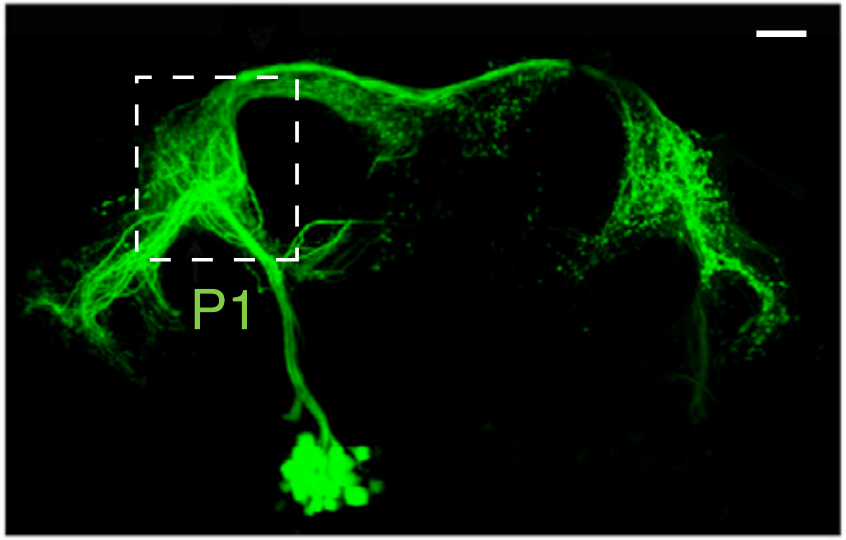
P1 > GCaMP6

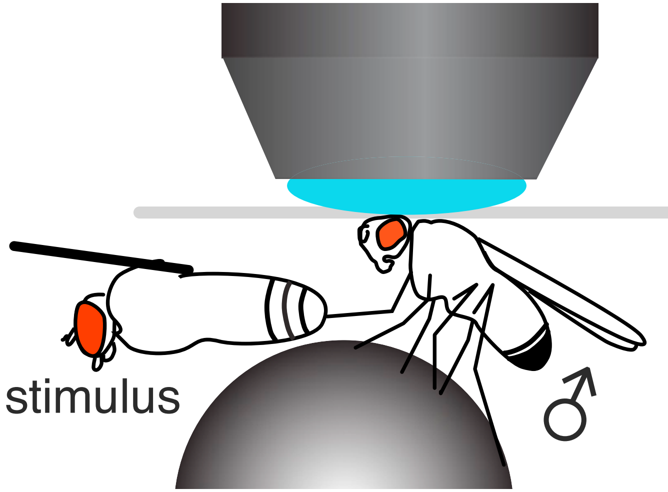


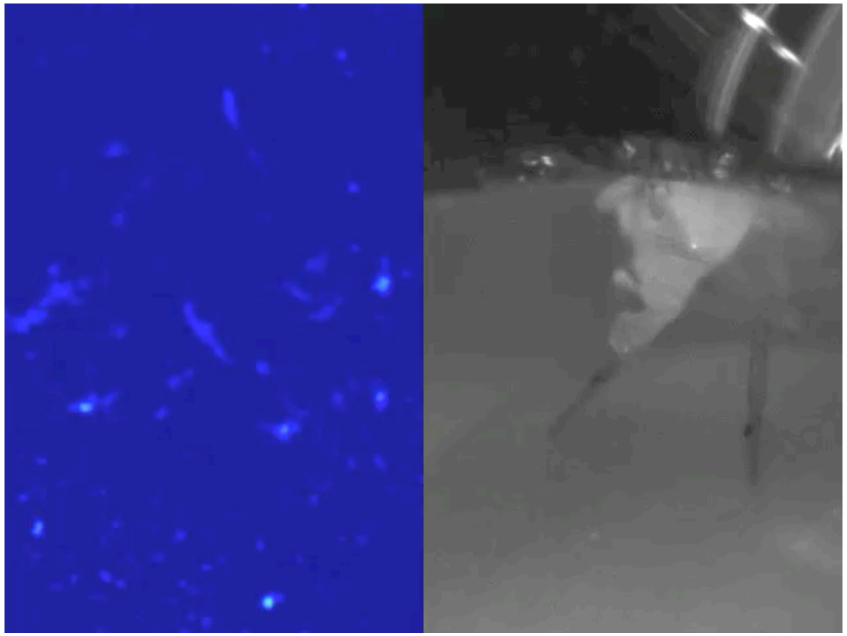


Clowney et al., 2015

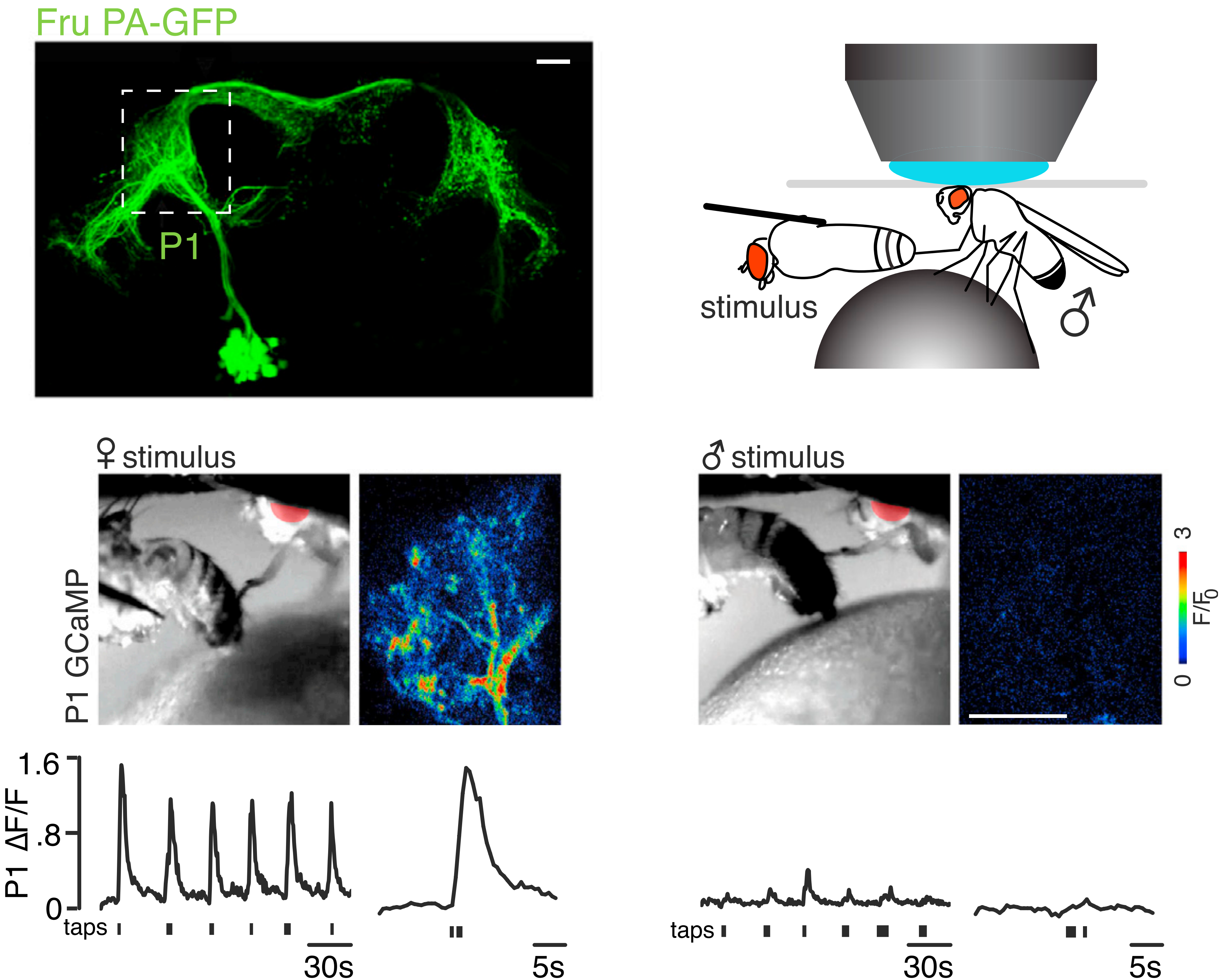
P1 > GCaMP6







Clowney et al., 2015



What tools do we have?

Behavioral tracking

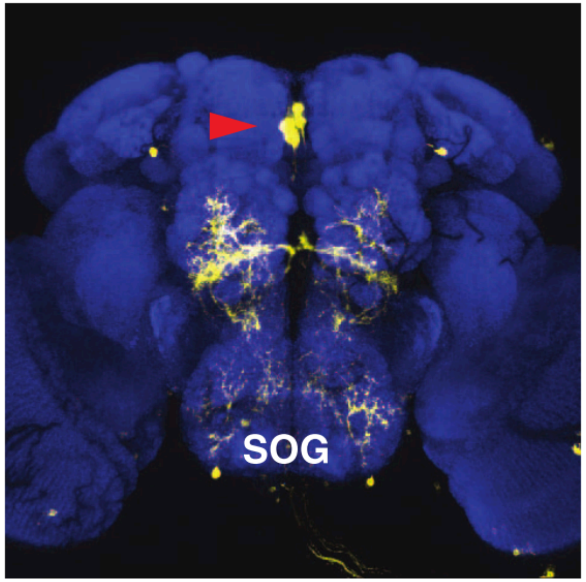
Genetics

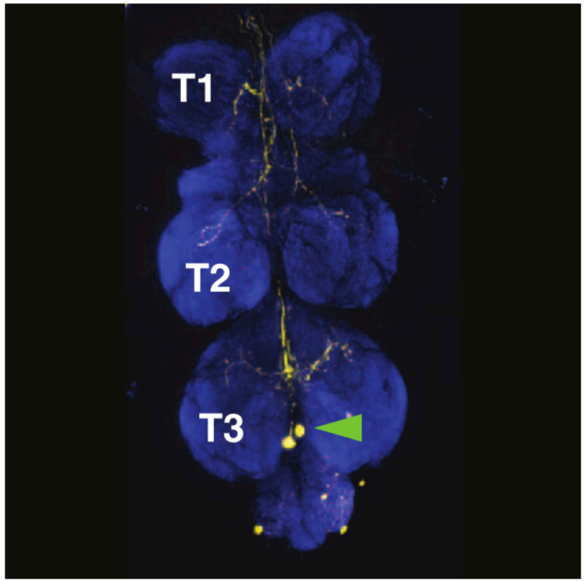
Circuit tracing

Neuron recording

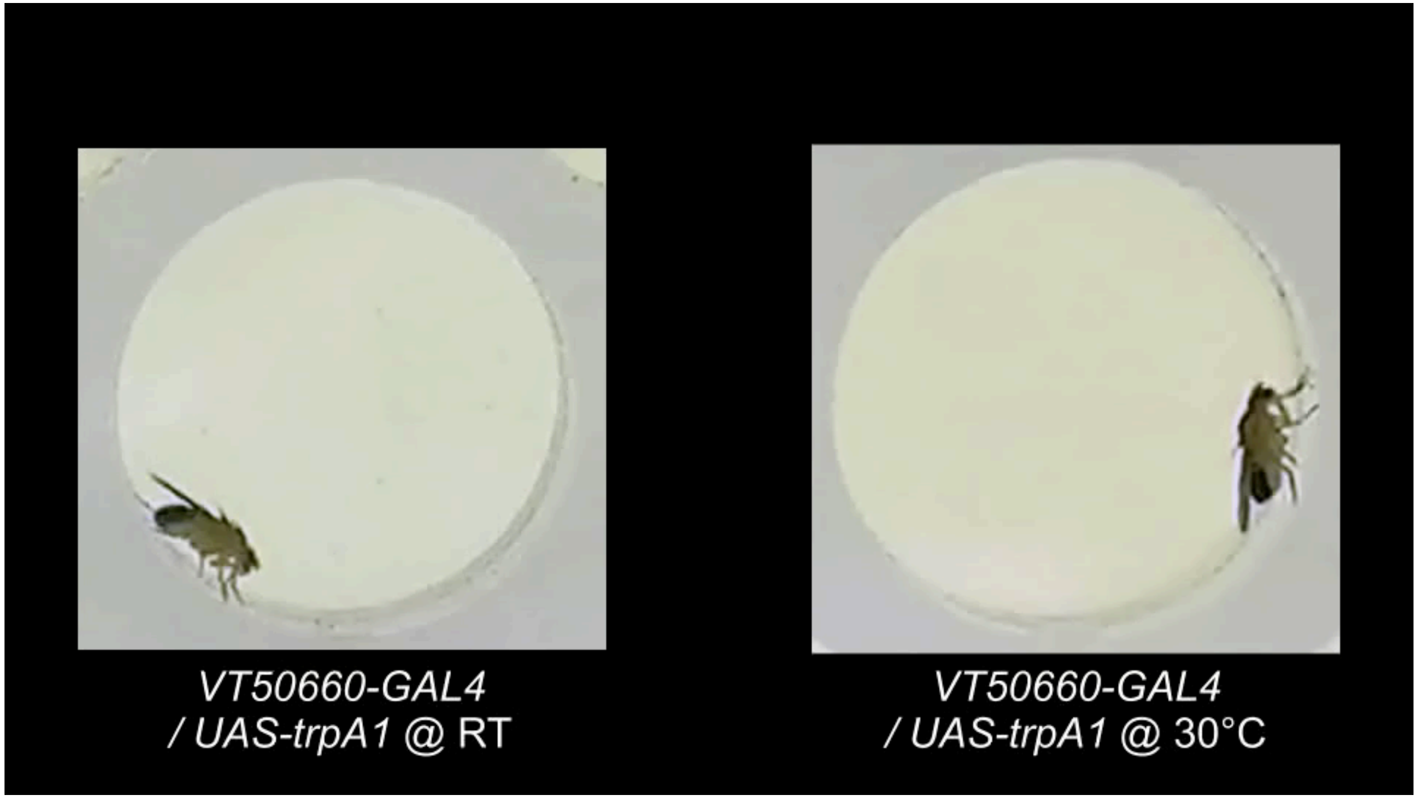
Neuron manipulation

Controlling flies by heat





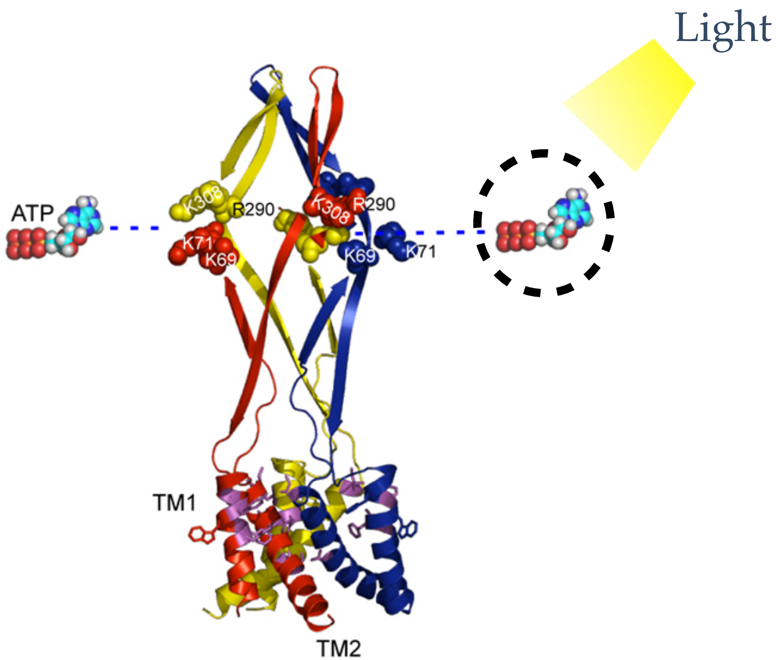
TrpA1: heat-sensitive channel

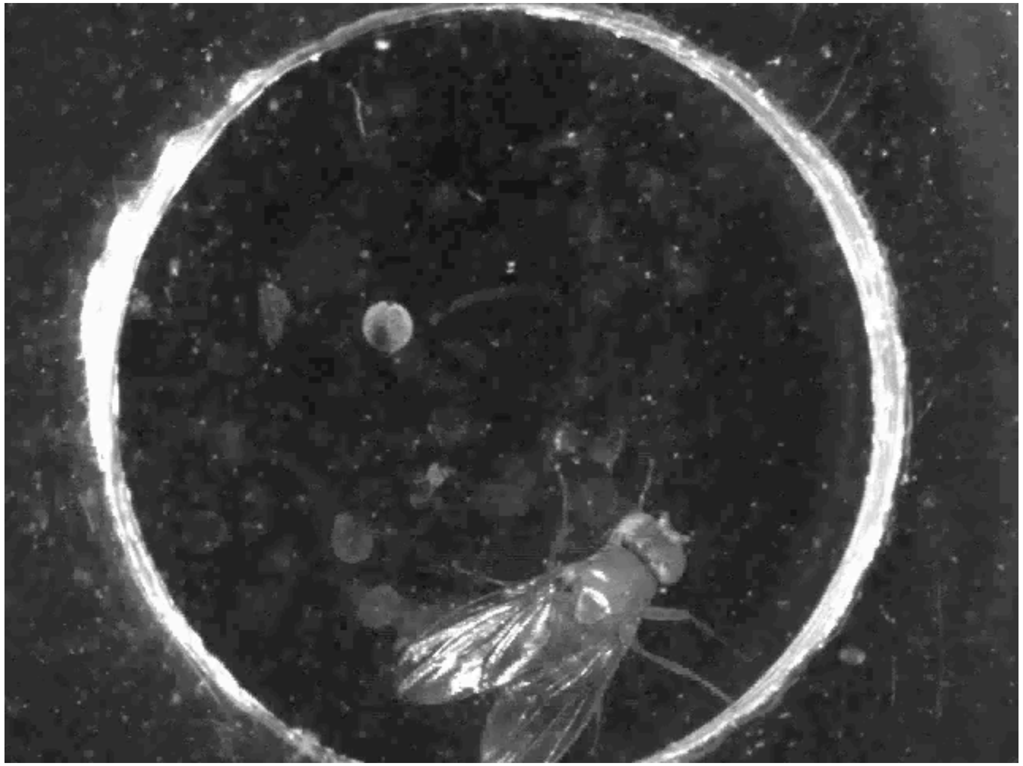


Bidaye et al., Science 2014

Activating neurons by light

ATP-gated ion channel $P2X_2$

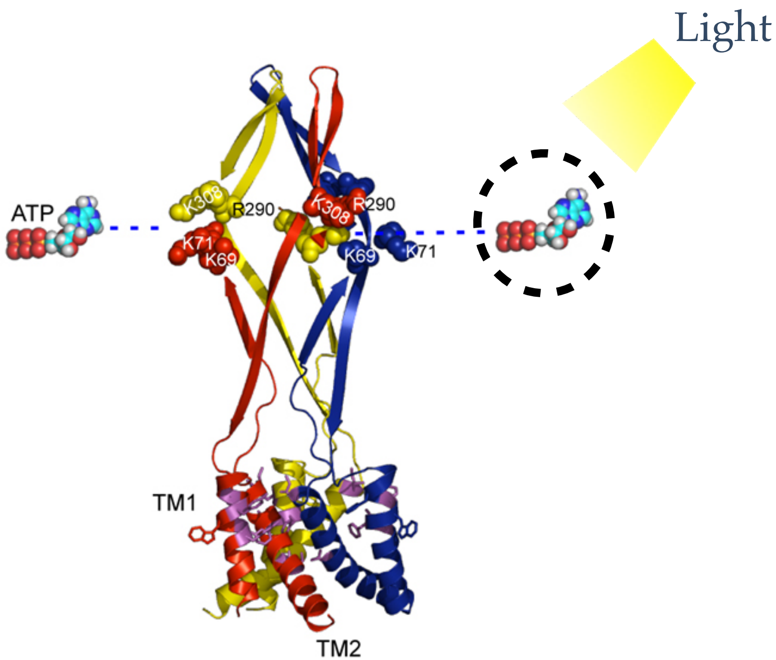




Susana & Miesenböck, Cell 2005

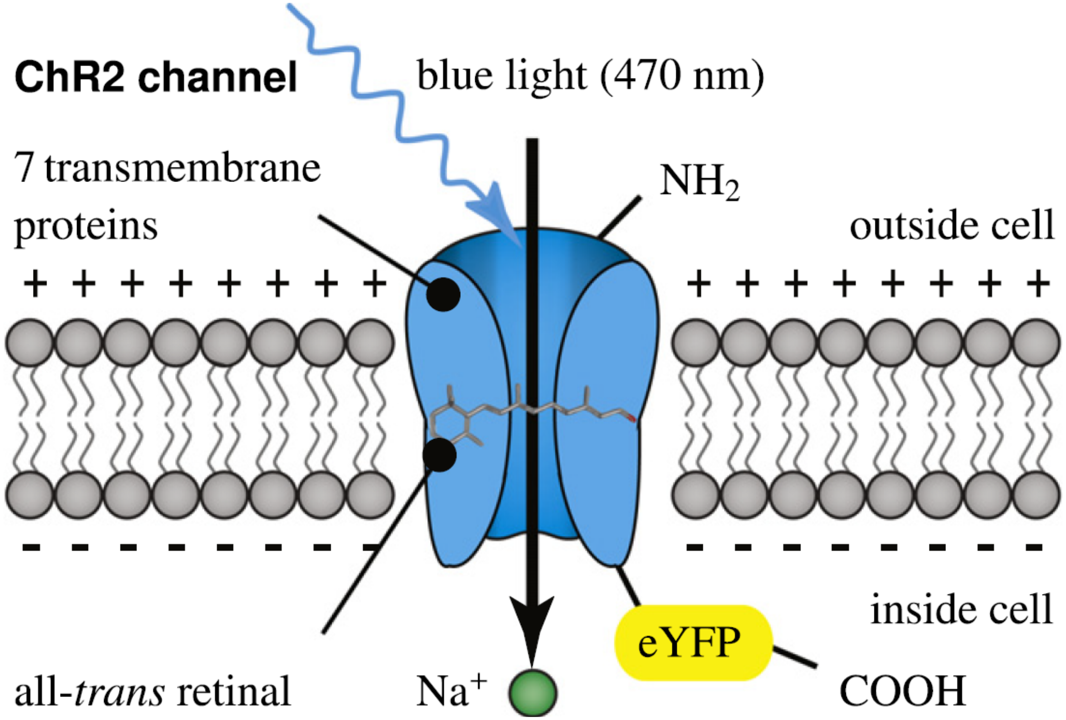
Activating neurons by light

ATP-gated ion channel P2X$_2$

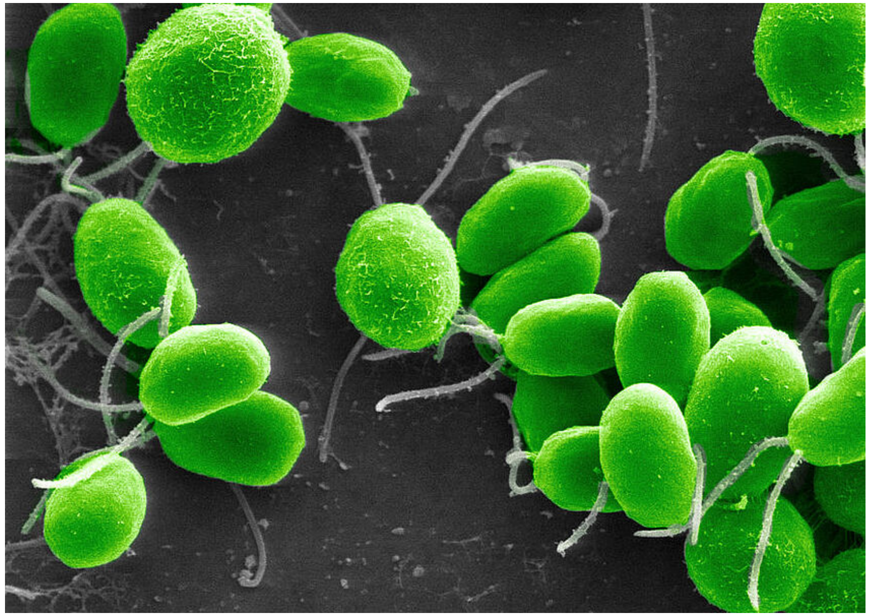


Susana & Miesenböck, Cell 2005

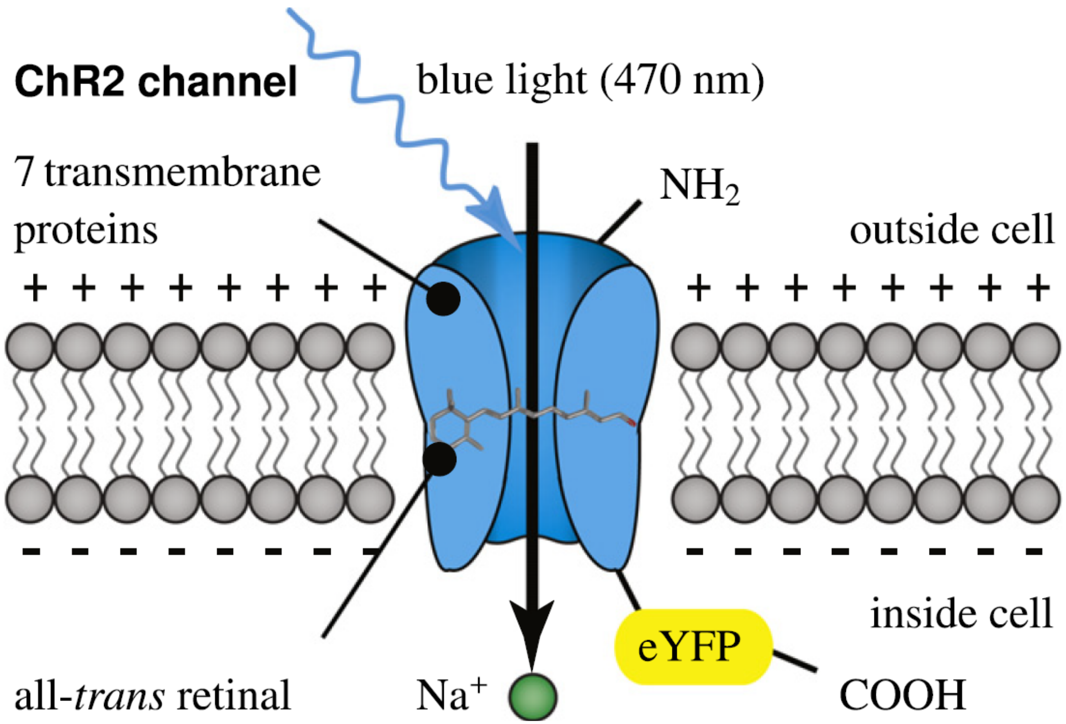
The Revolutionary Channelrhodopsin



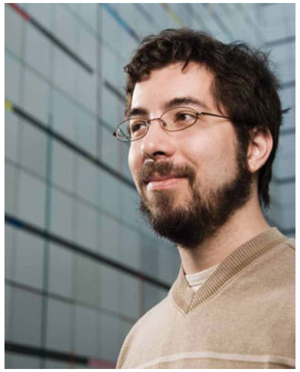
Chlamydomonas reinhardtii



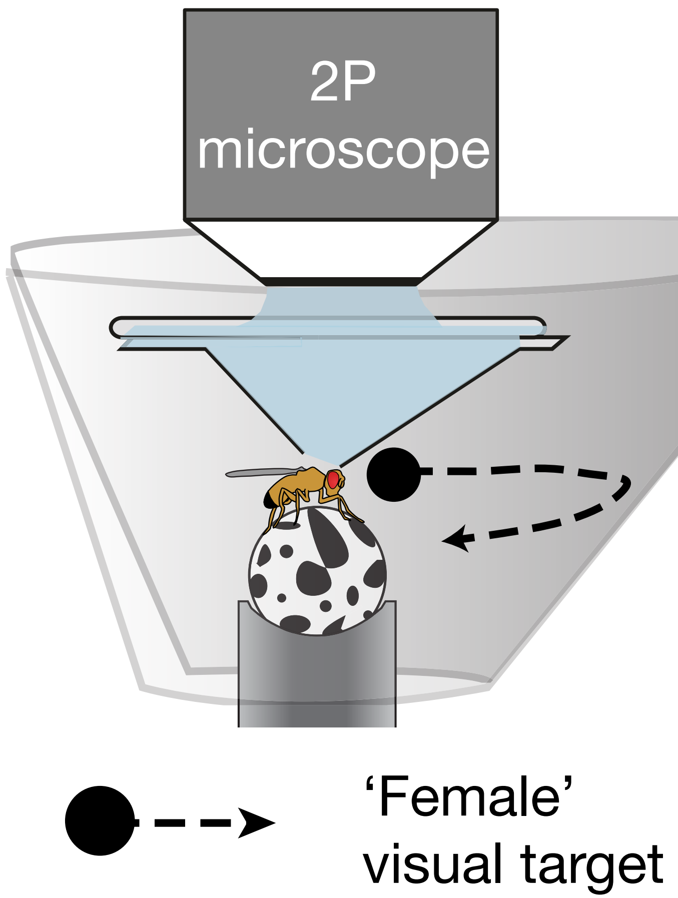
The Revolutionary Channelrhodopsin

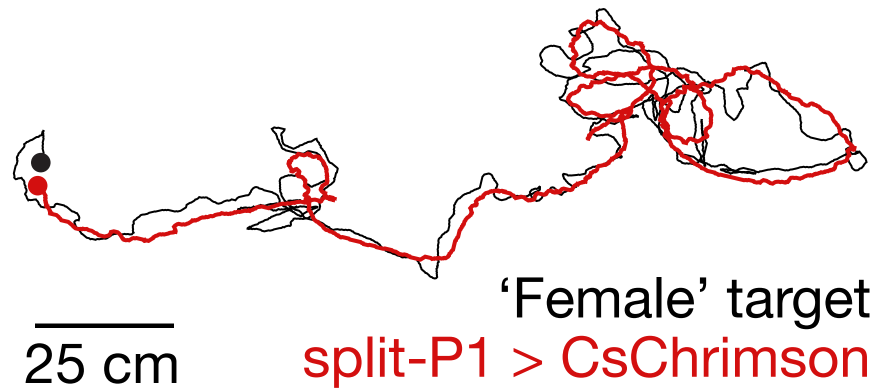


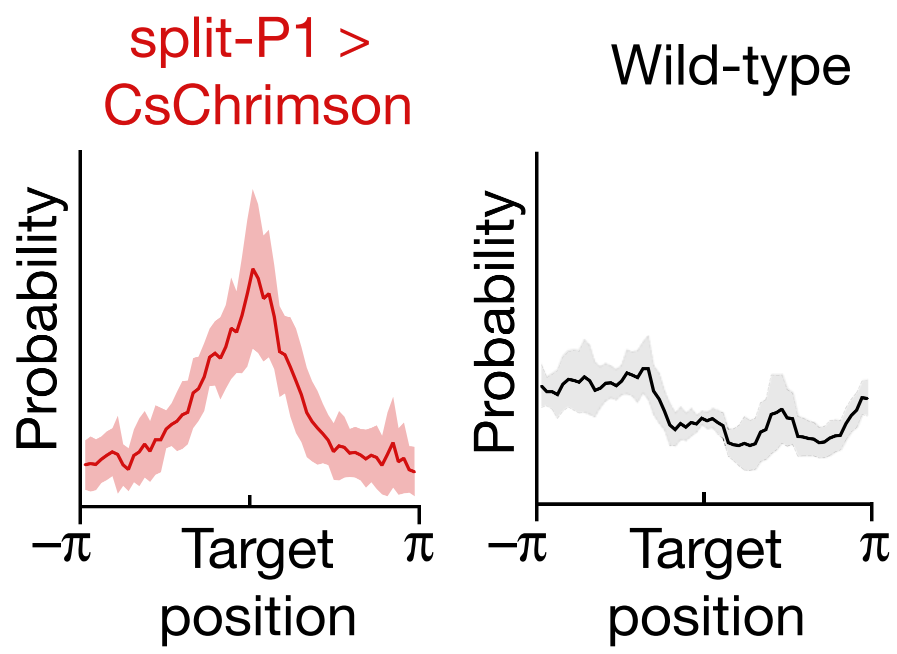
Pioneers of optogenetics



P1 activity gates courtship-related visual processing

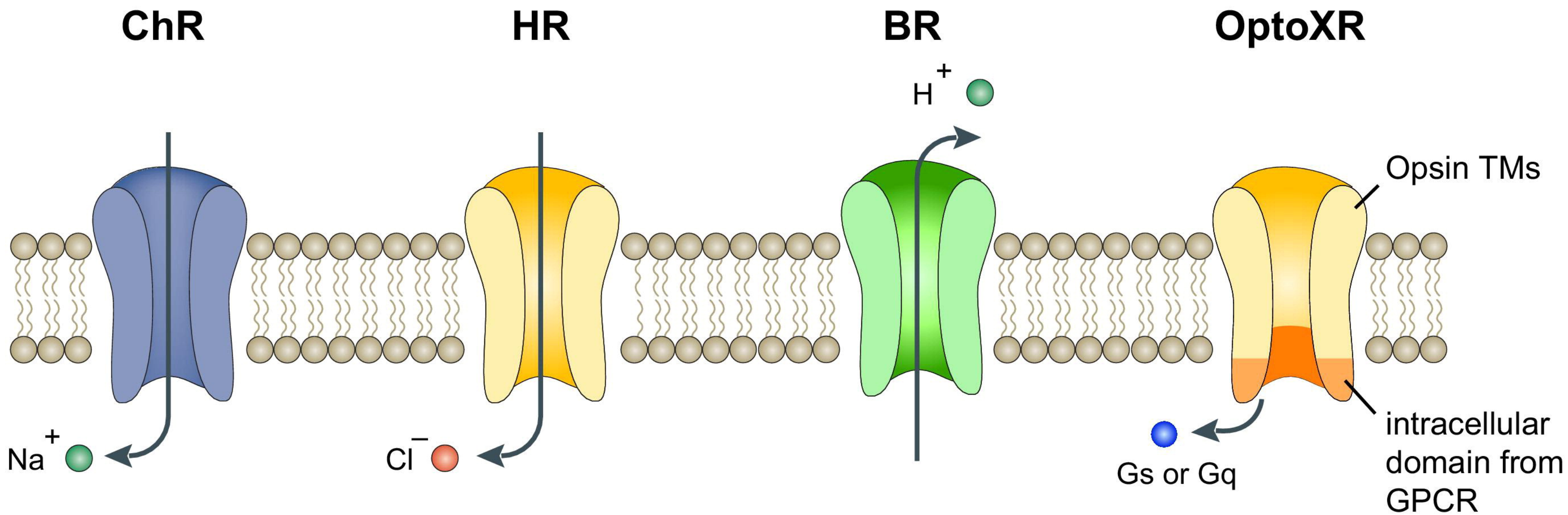


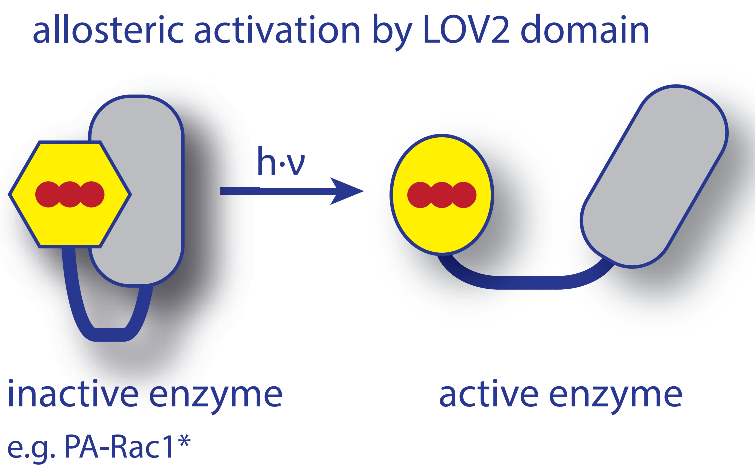


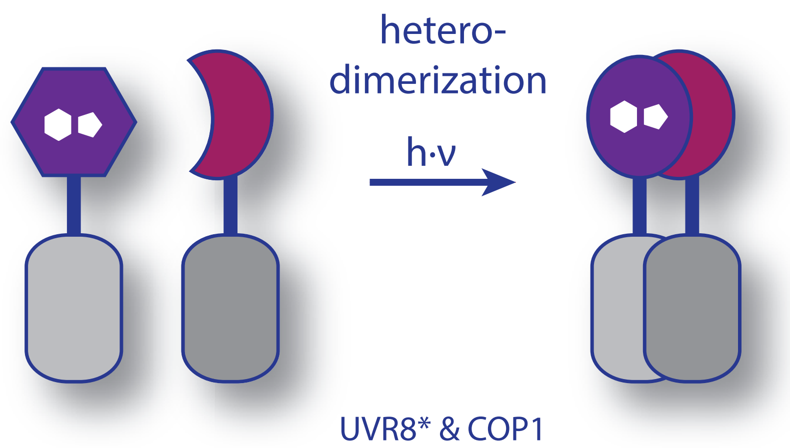


Sten et al., 2020

Optogenetic tools are still expanding

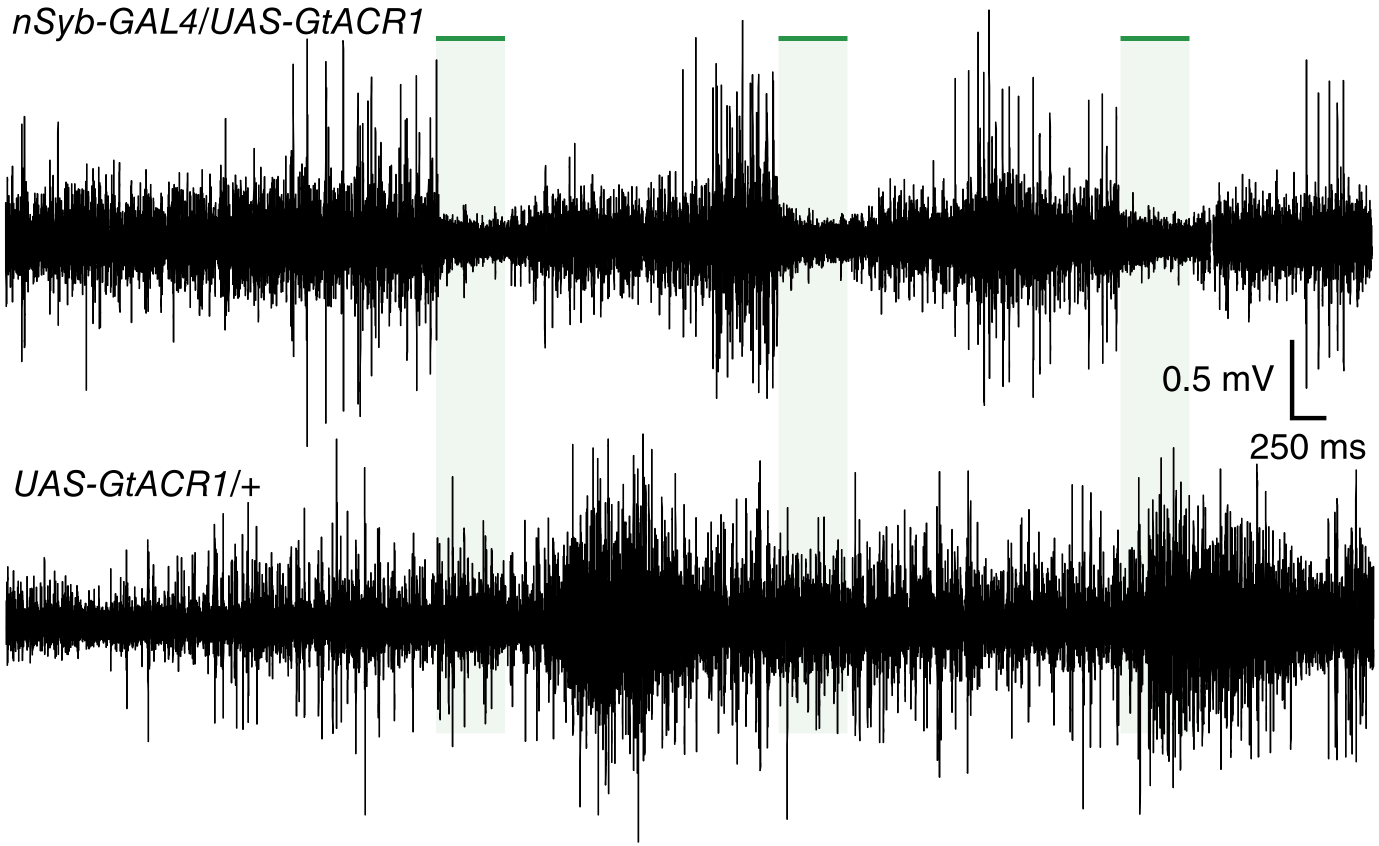






GtACR: an optogenetic silencer

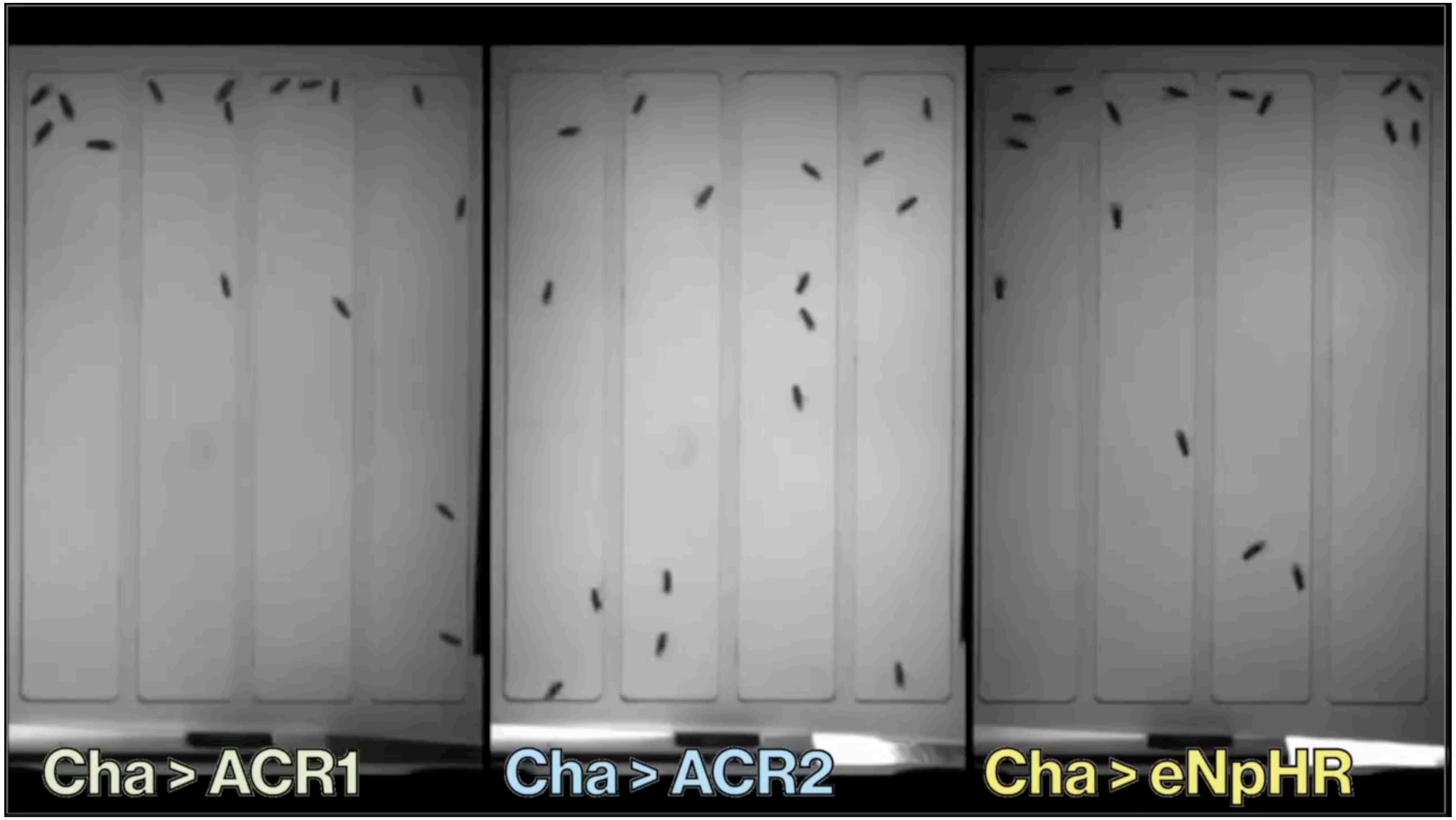
GtACR: alga Guillardia theta anion channelrhodopsins



Mohammad et al., Nature methods 2017

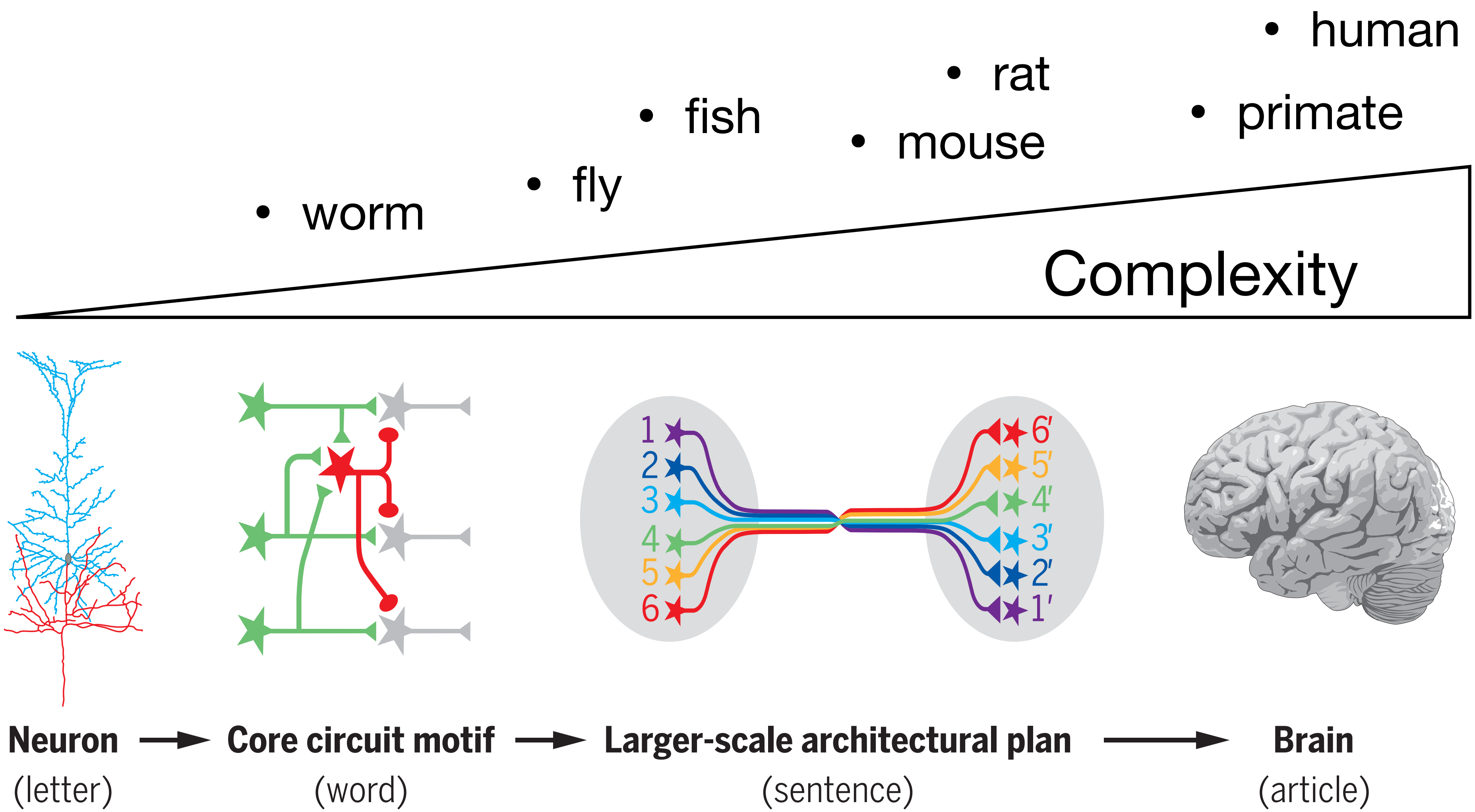
Optogenetic silencer—GtACR

GtACR: alga *Guillardia theta* anion channelrhodopsins



Mohammad et al., Nature methods 2017

From neurons to a brain



Luo, *Science* 2021