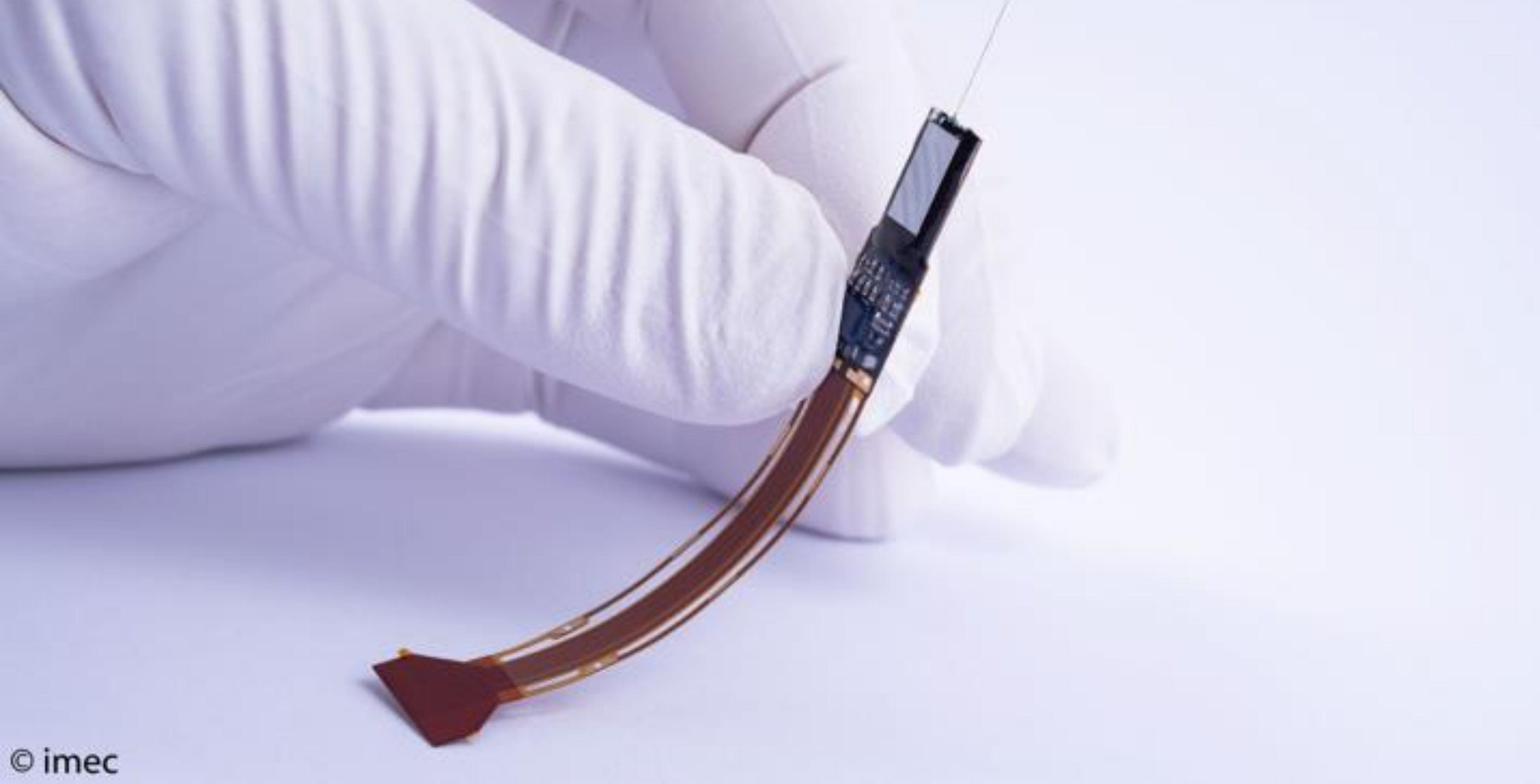
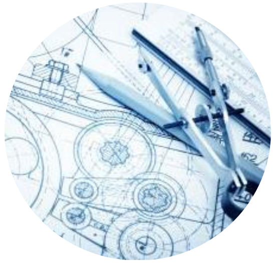
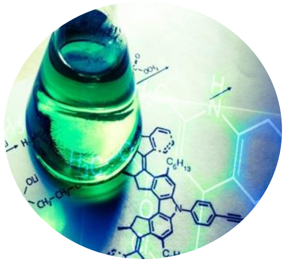
Tools & technology to study neuroscience



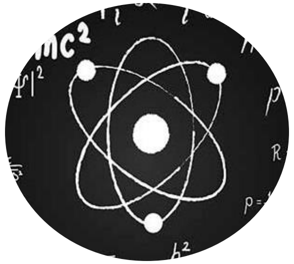
Tools & technology to study neuroscience



Engineering



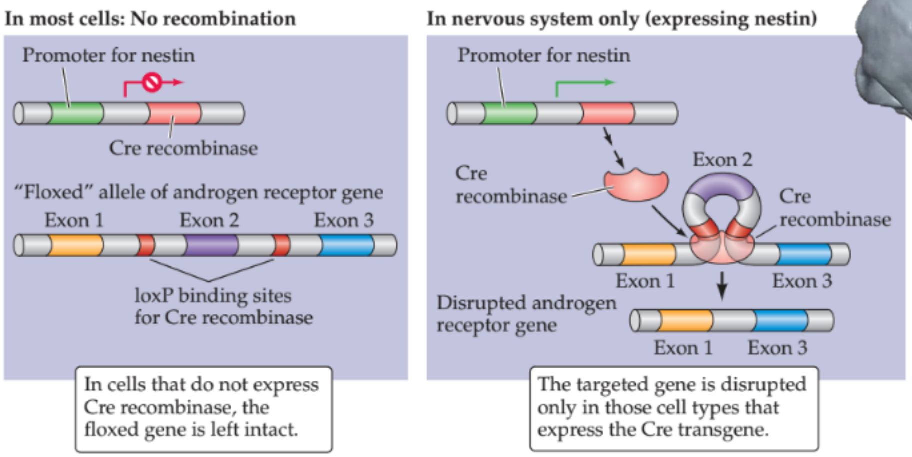
Chemistry

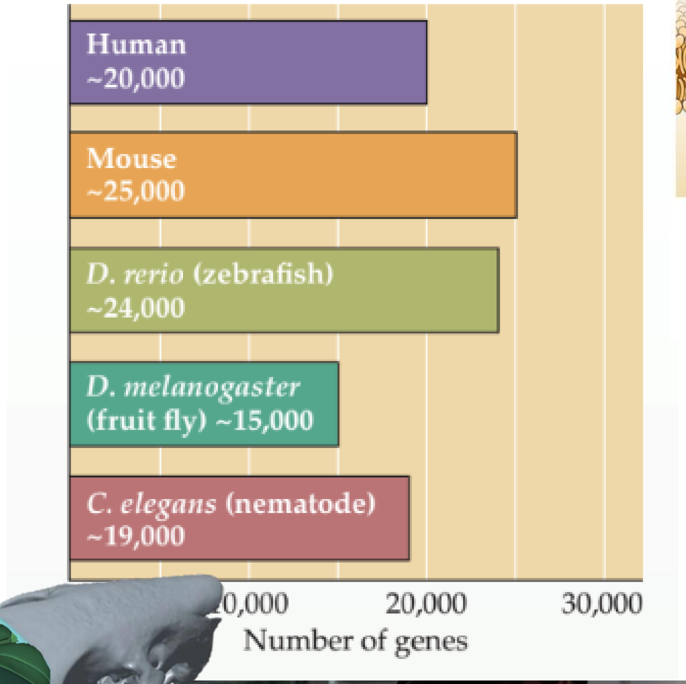


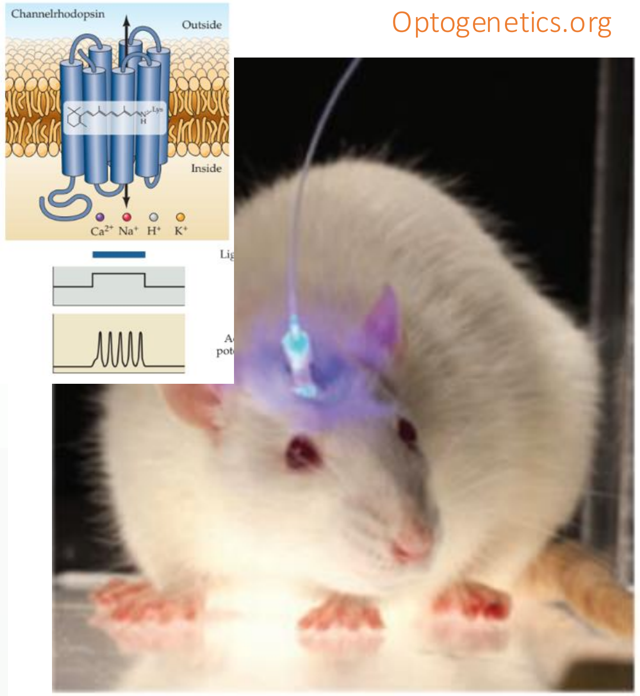
Physics

Biology

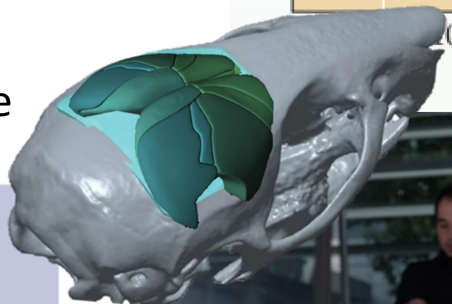
Computer Science

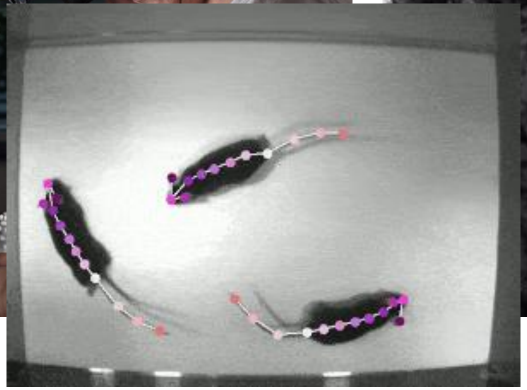


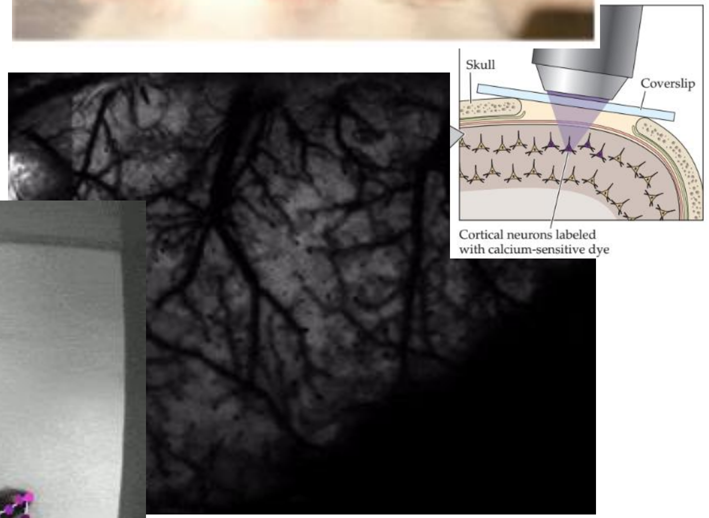




Optogenetics.org



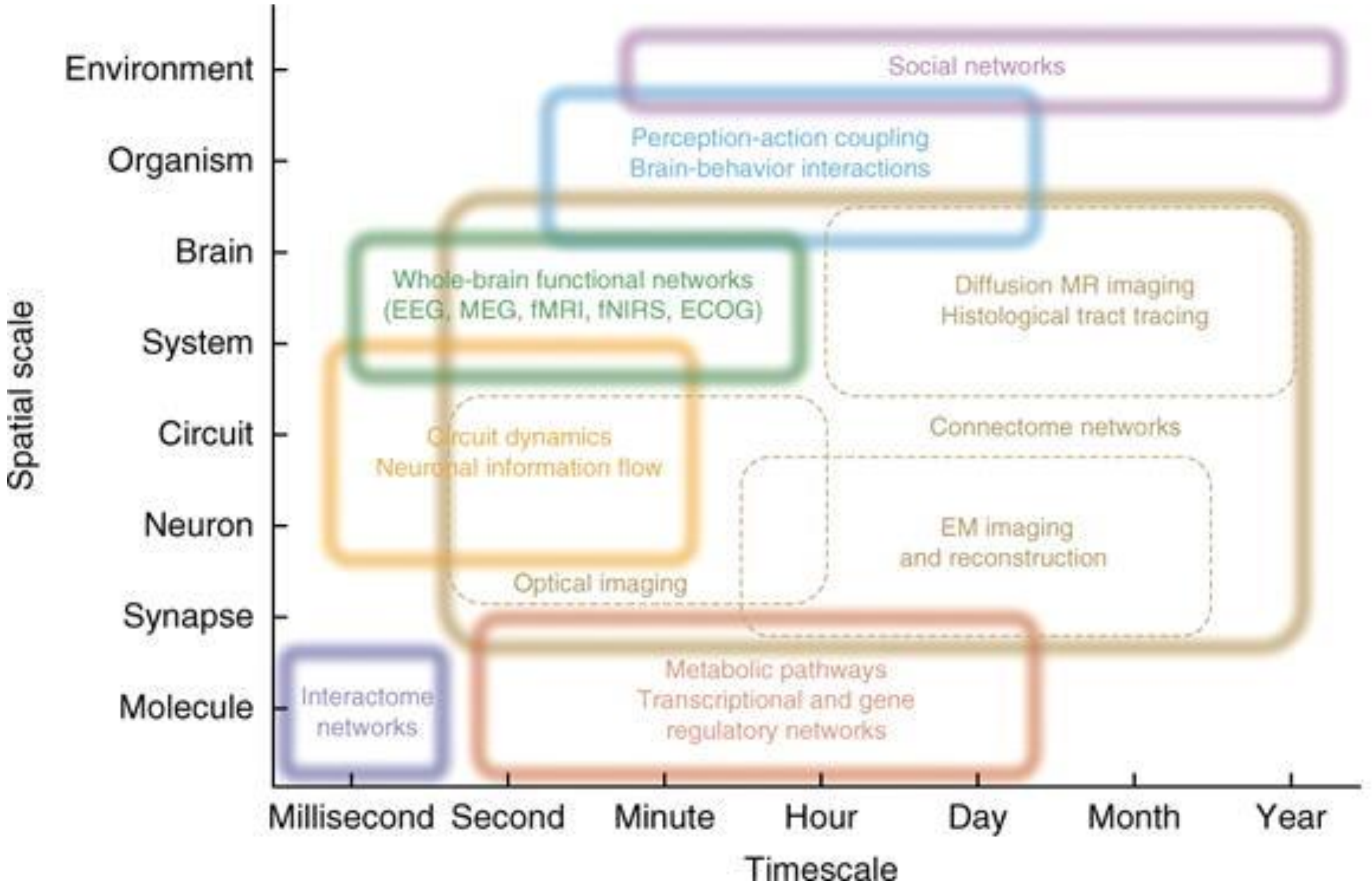




Sofroniew et al 2016 eLife

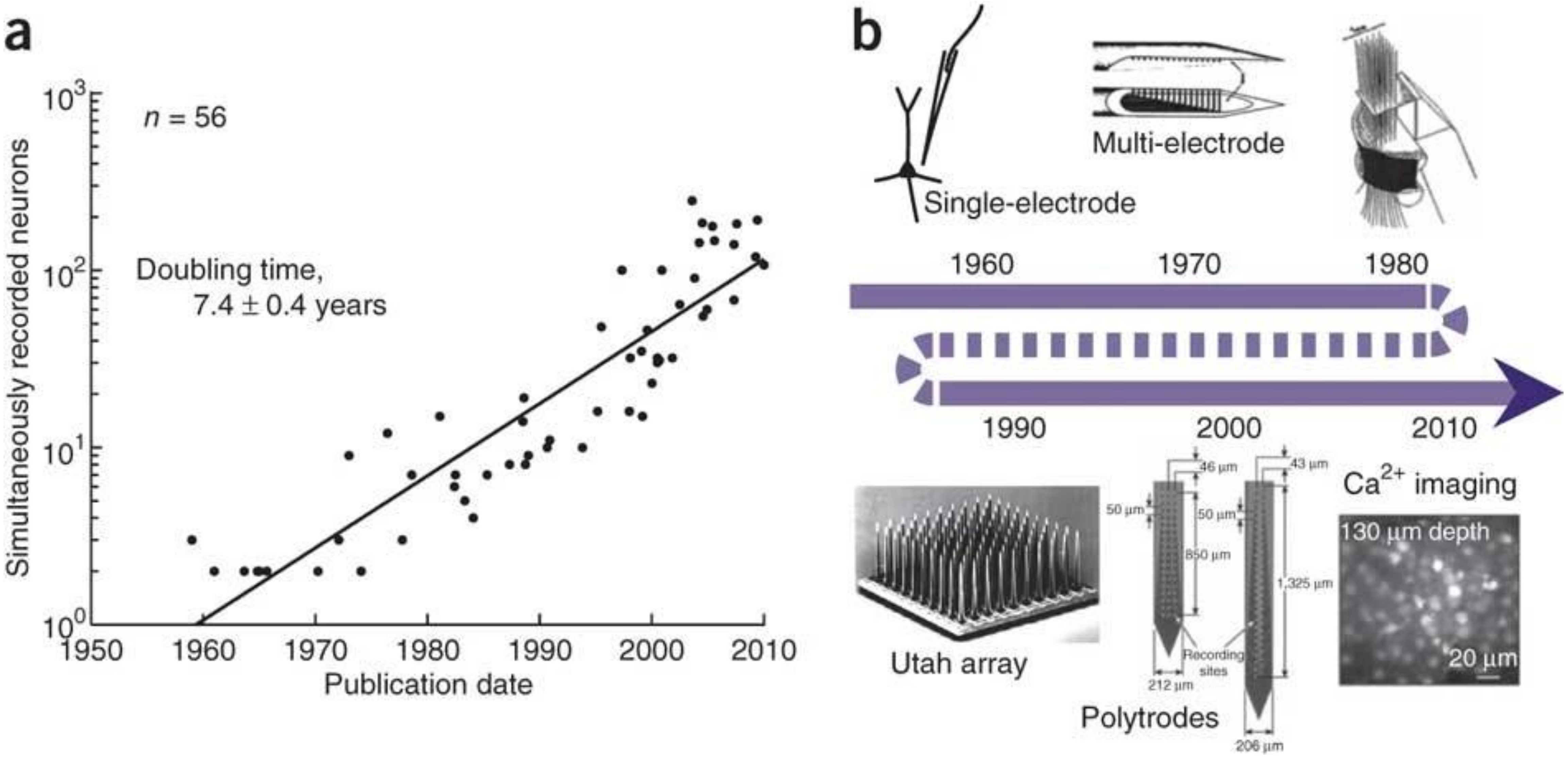
How do we record neural data?

Methods for measuring brain function



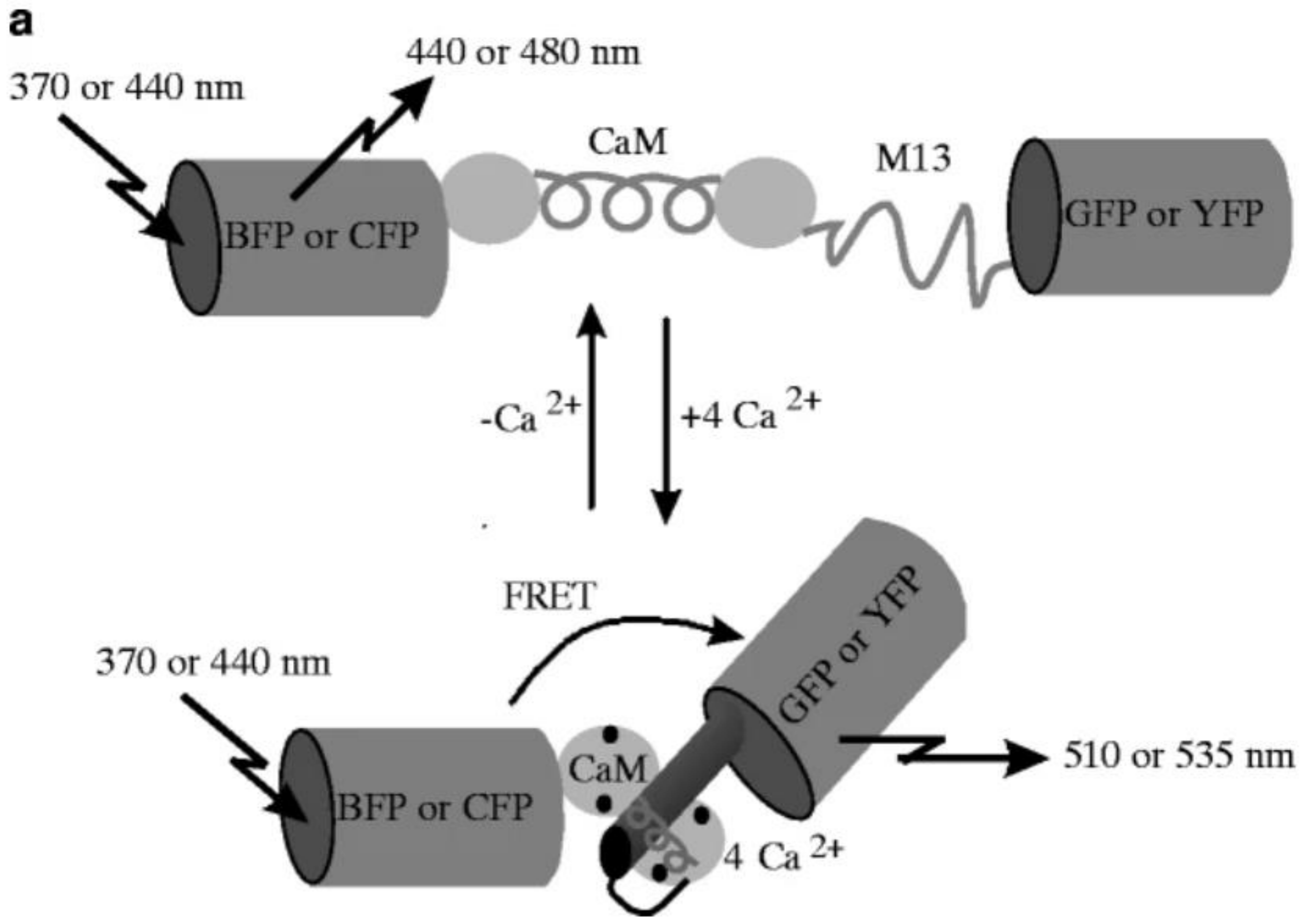
Basset, Nat Neuro 2017

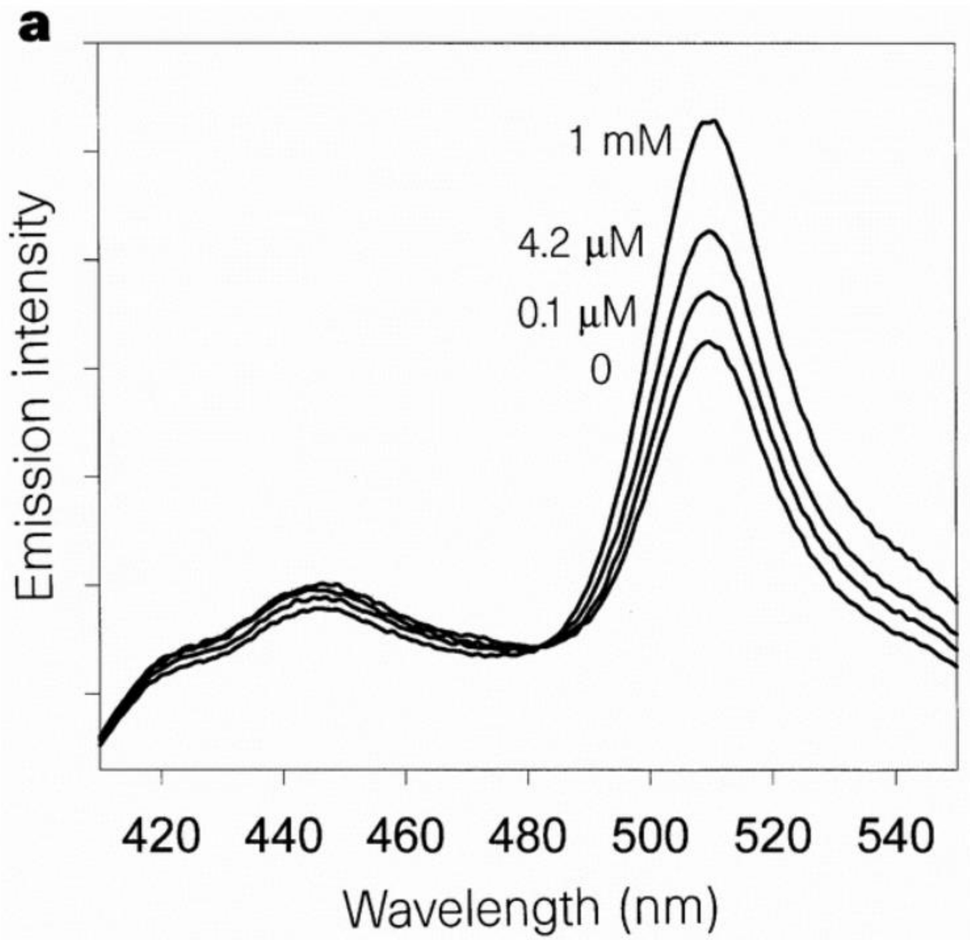
Single unit recoding: “Moore’s law”



How advances in neural recording affect data analysis, Stevenson & Kording Nature Neuroscience 2011

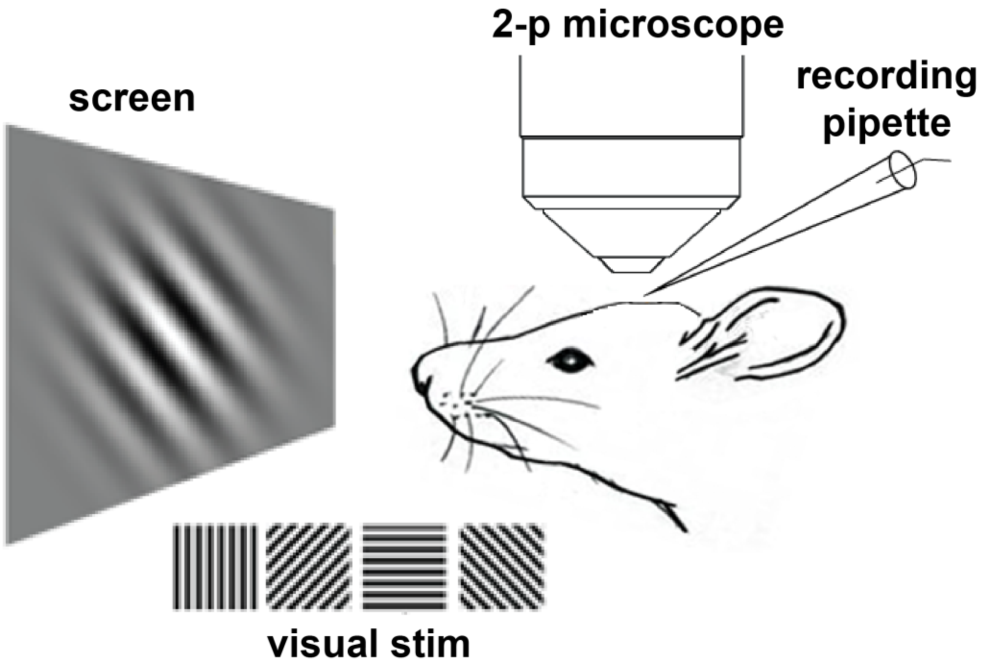
Tools & technology to study neuroscience: **calcium imaging**

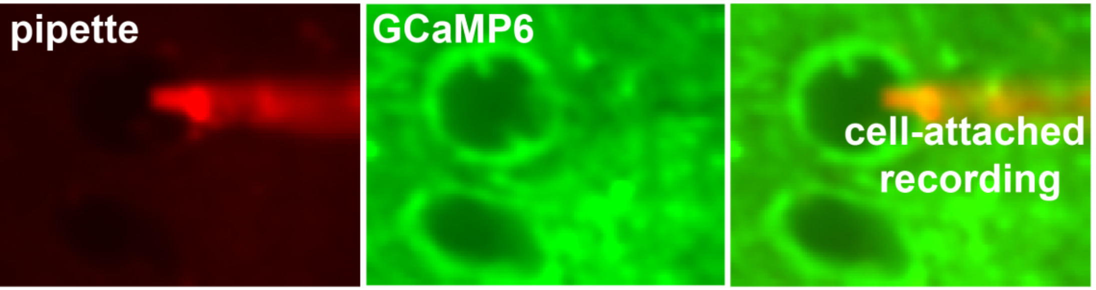




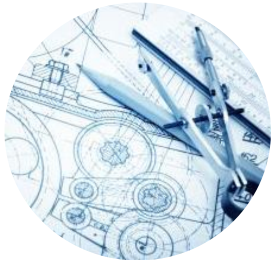
Miyawaki, A., Llopis, J., Heim, R. *et al.* Fluorescent indicators for Ca^{2+}based on green fluorescent proteins and calmodulin. *Nature* **388**, 882–887 (1997).

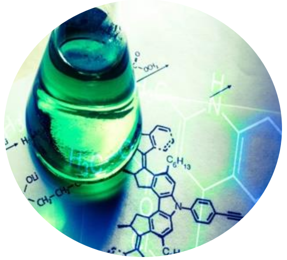
GCaMP imaging in mice

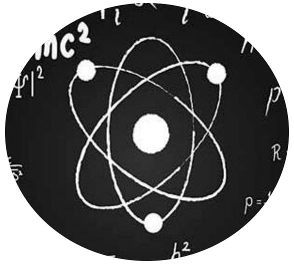




Tools & technology to study neuroscience: **mesoscopic imaging**


Engineering

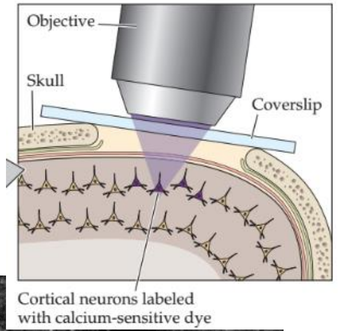

Chemistry

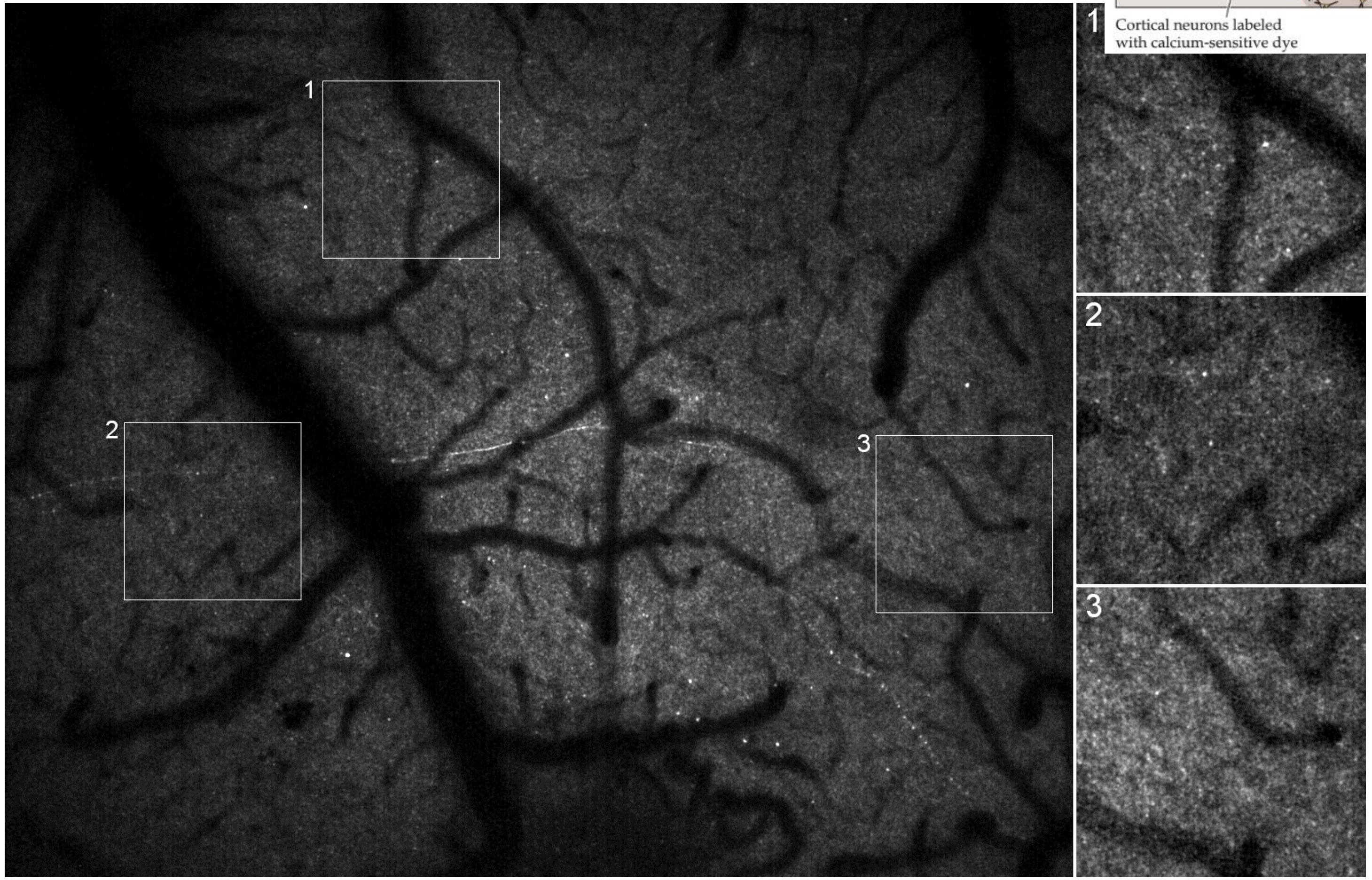

Physics


Biology

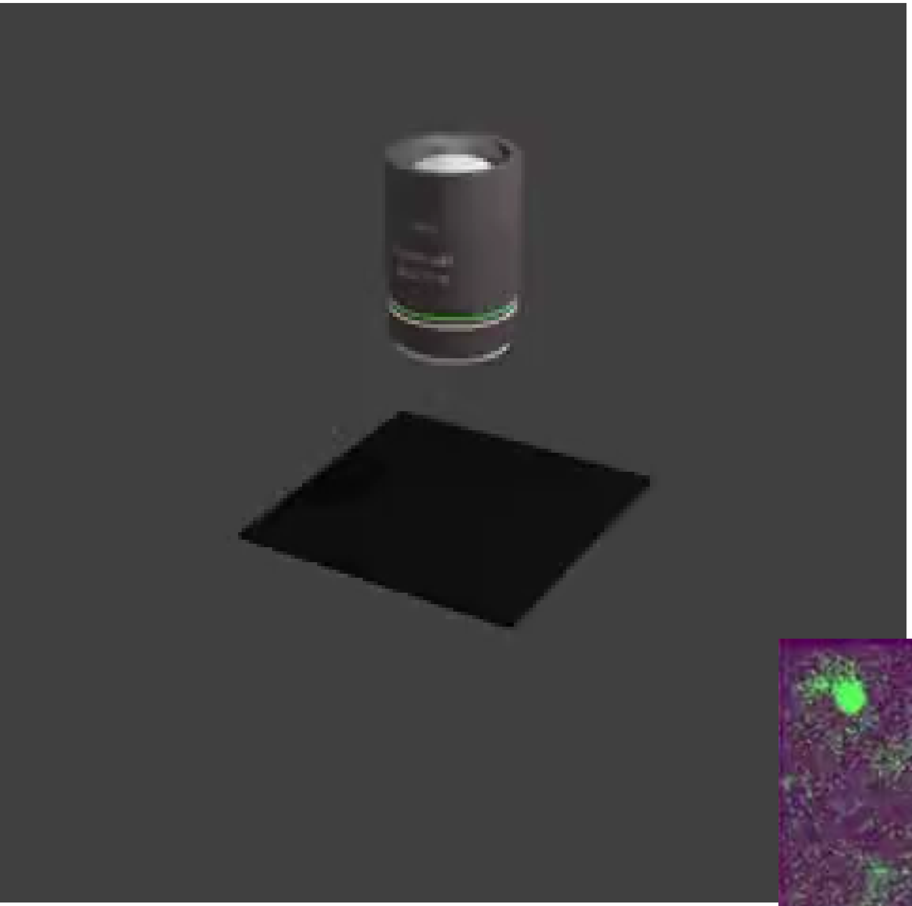

Computer Science

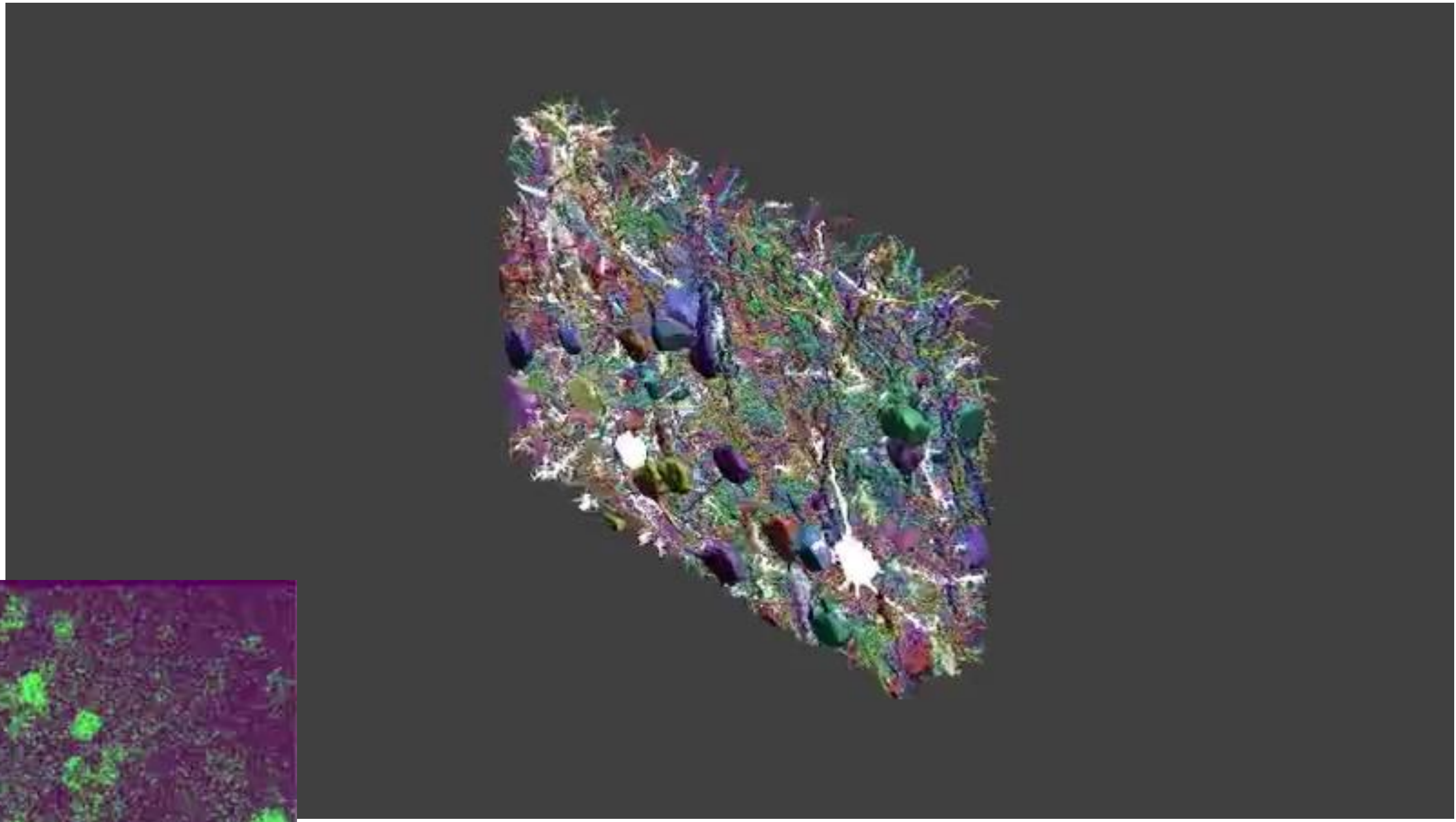
Yoshida et al., 2018
Scientific Reports

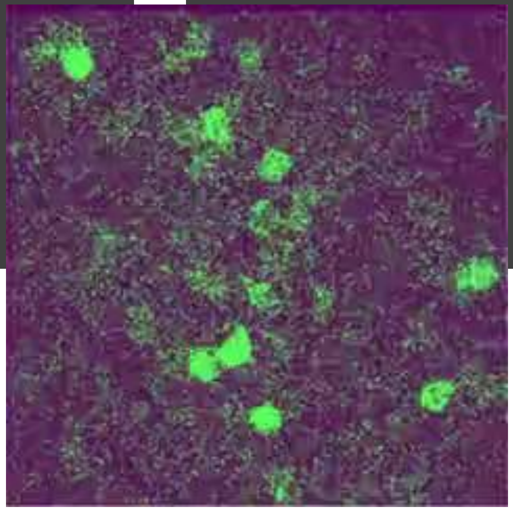




Calcium imaging allows for great spatial resolution of neurons



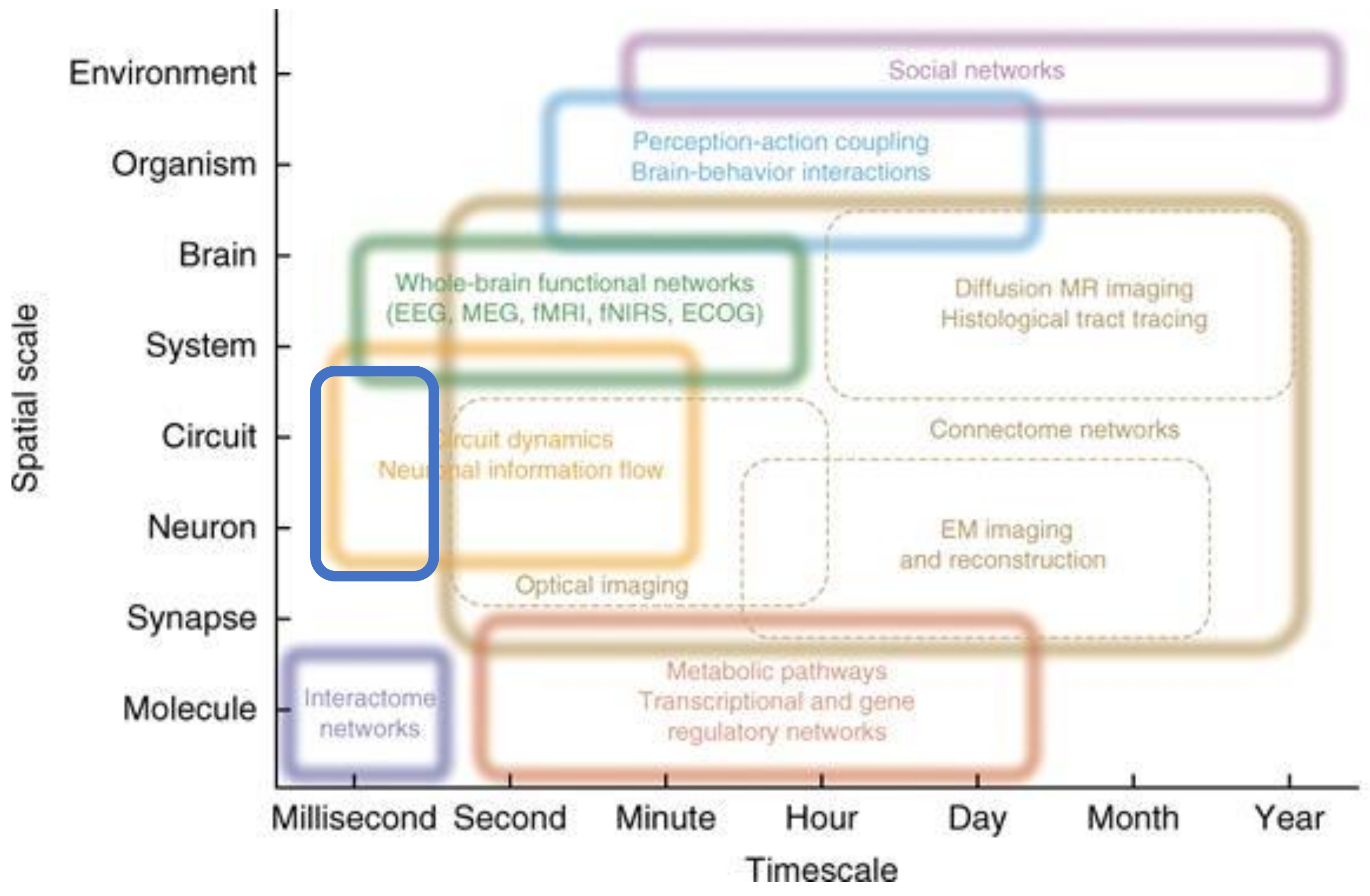




Courtesy of Prof. Andreas Tolias

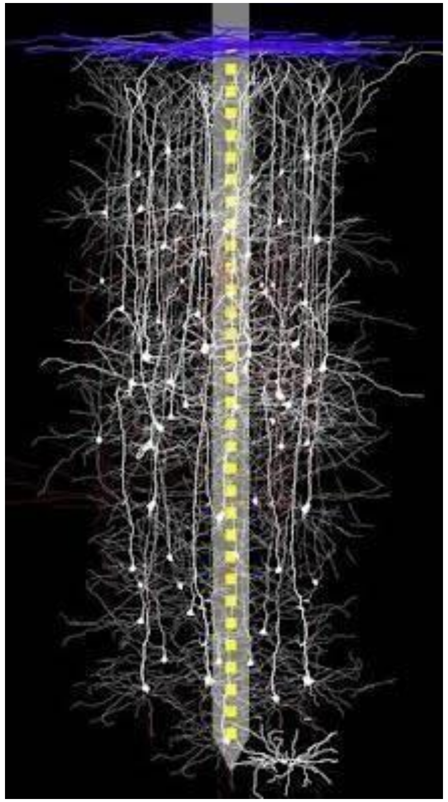
https://www.microns-explorer.org/

Methods for measuring brain function



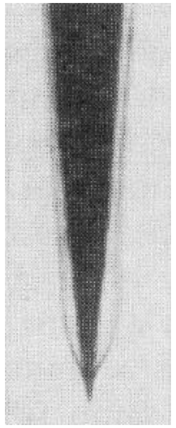
Basset, Nat Neuro 2017

Extracellular Electrophysiology: a brief history



Microelectrode (1953)

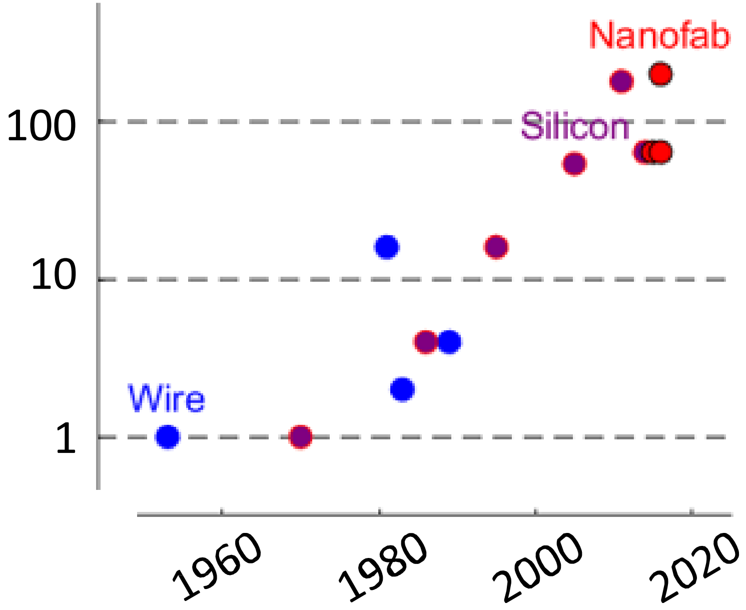
5 μm wires



Polytrode (2005)

1.5 μm wires

Sites



Slide from Matteo Carandini University College London

Hubel
Science 1953

Blanche et al
J Neurophys 2005

Steinmetz et al, *Curr Op Neurobiol* 2018

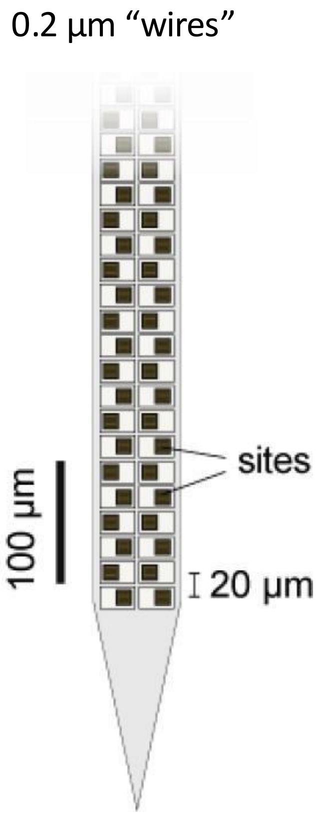
New technologies facilitate new tools: Neuropixels

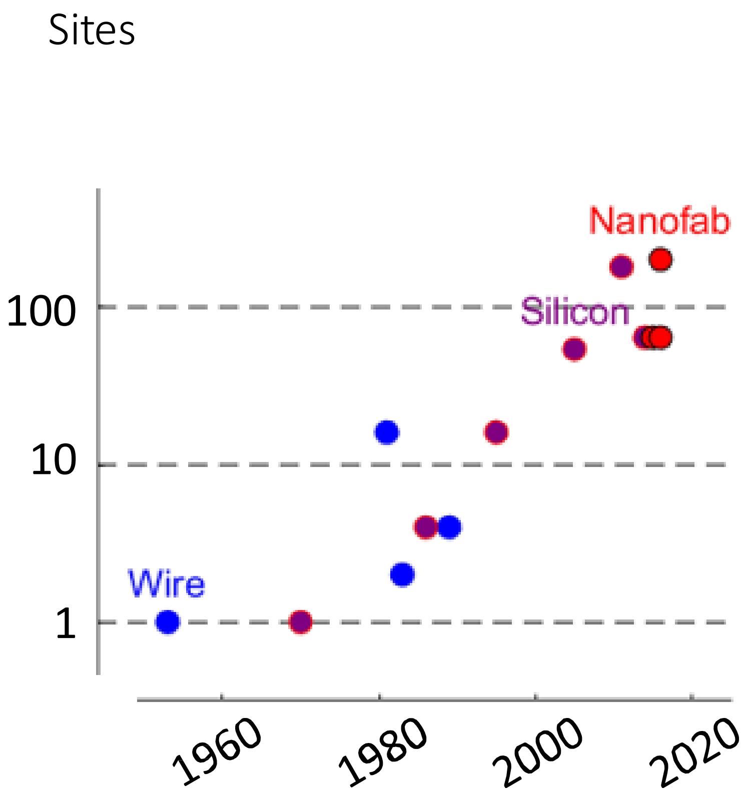
LETTER

doi:10.1038/nature24636

Fully integrated silicon probes for high-density recording of neural activity

James J. Jun[1]*, Nicholas A. Steinmetz[2,3,4]*, Joshua H. Siegle[5]*, Daniel J. Denman[5]*, Marius Bauza[6,7]*, Brian Barbarits[1]*, Albert K. Lee[1]*, Costas A. Anastassiou[5,8], Alexandru Andrei[9], Çağatay Aydın[10,11], Mladen Barbic[1], Timothy J. Blanche[5,12], Vincent Bonin[9,10,11,13], João Couto[10,11], Barundeb Dutta[9], Sergey L. Gratiy[5], Diego A. Gutnisky[1], Michael Häusser[3,14], Bill Karsh[1], Peter Ledochowitsch[5], Carolina Mora Lopez[9], Catalin Mitelut[5,8], Silke Musa[9], Michael Okun[2,3,15], Marius Pachitariu[2,3], Jan Putzeys[9], P. Dylan Rich[1], Cyrille Rossant[2,3], Wei-lung Sun[1], Karel Svoboda[1], Matteo Carandini[4], Kenneth D. Harris[2,3], Christof Koch[5], John O'Keefe[6,7] & Timothy D. Harris[1]





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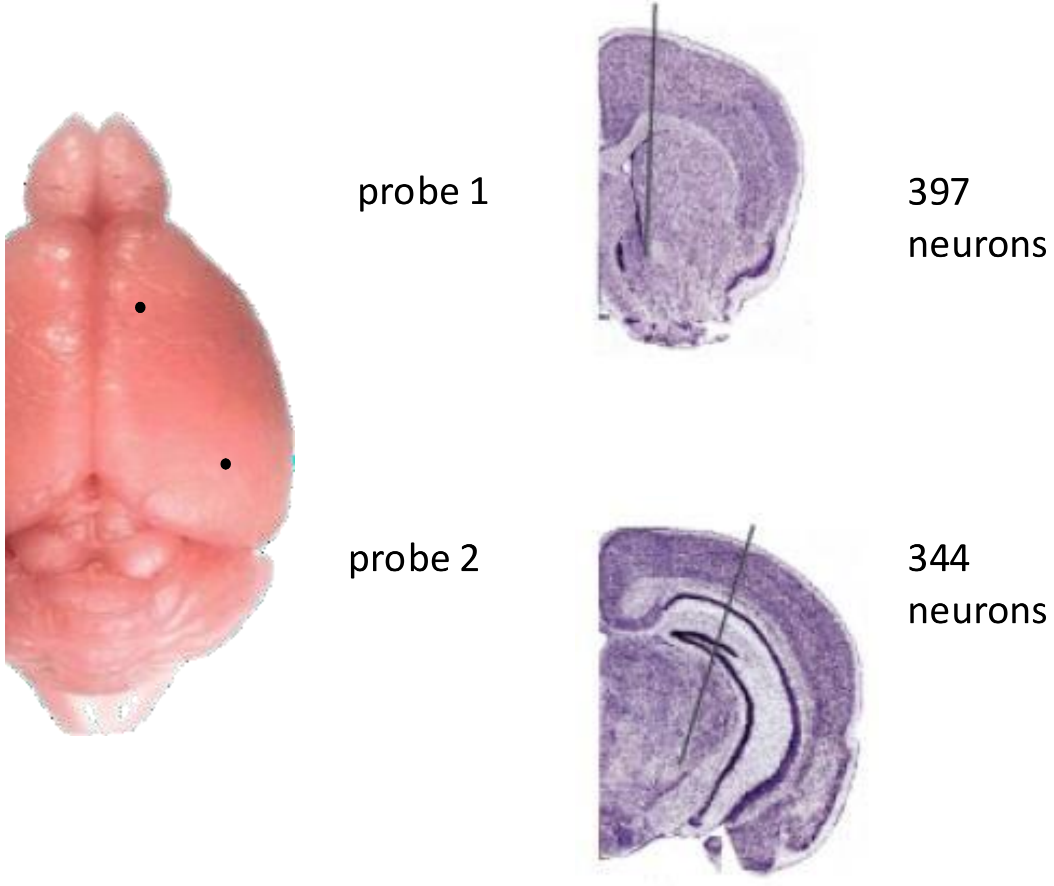
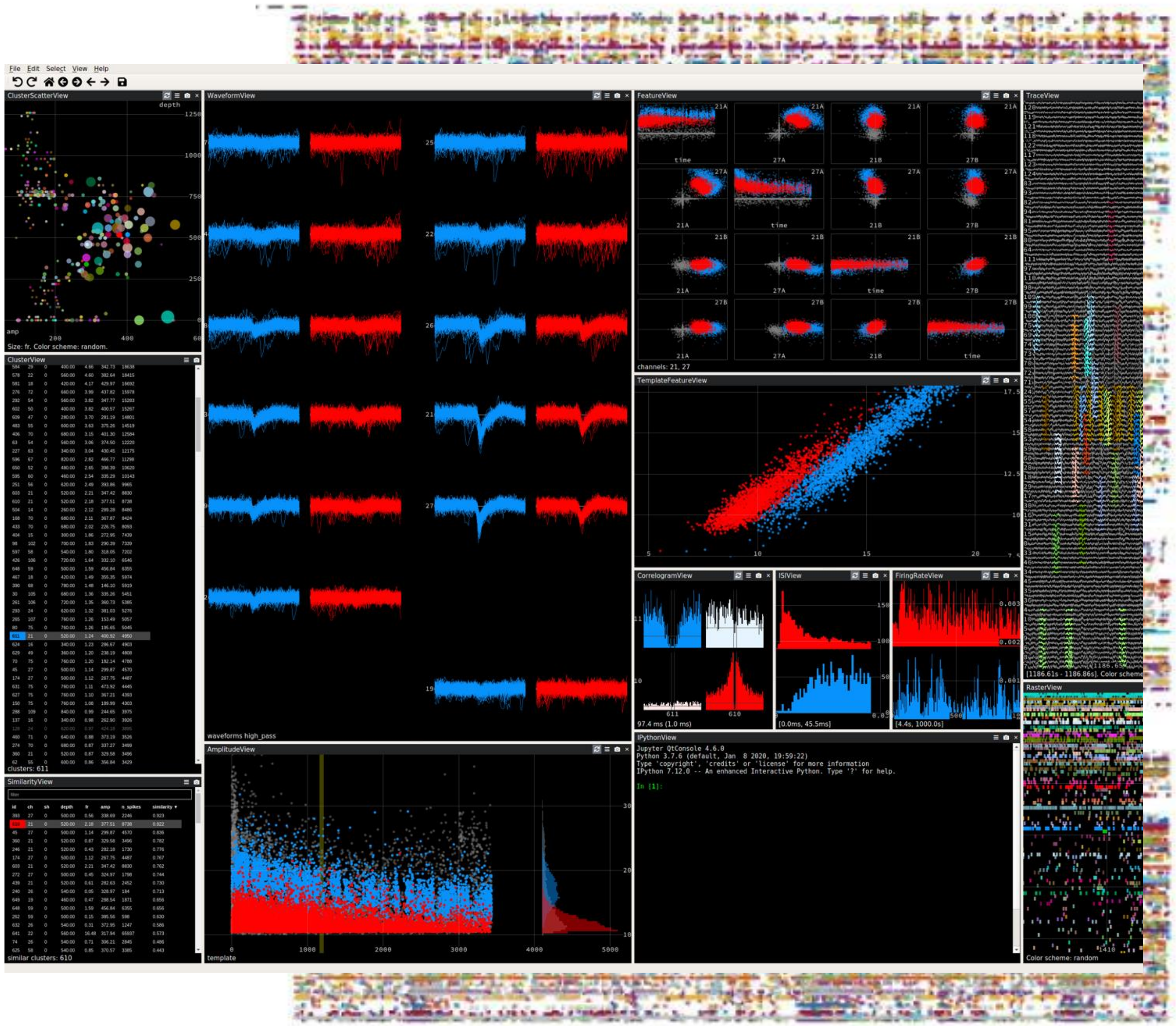
Steinmetz et al, *Curr Op Neurobiol* 2018
Jun, Steinmetz, Siegle, Denman, Bauza, Barbarits, et al, *Nature* 2017

New technologies facilitate new tools: Neuropixels



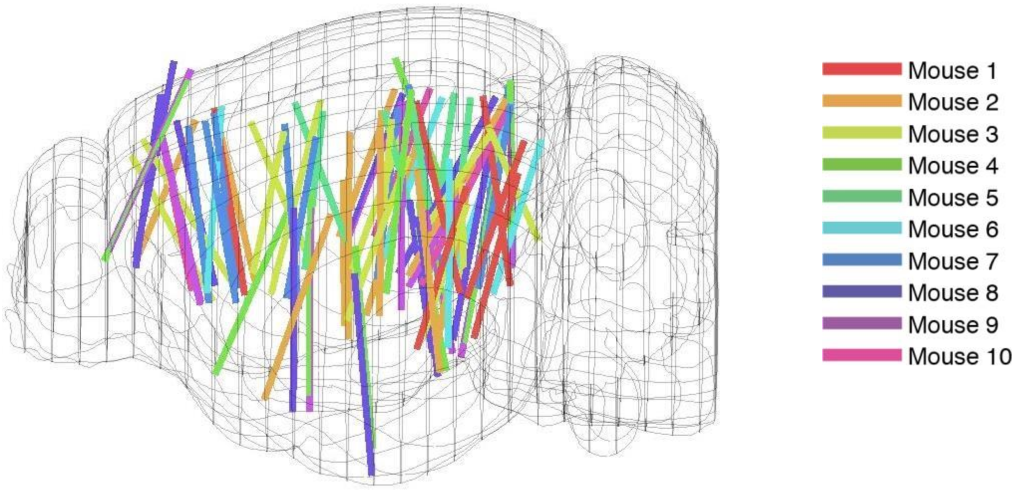


Slide from Matteo Carandini University College London

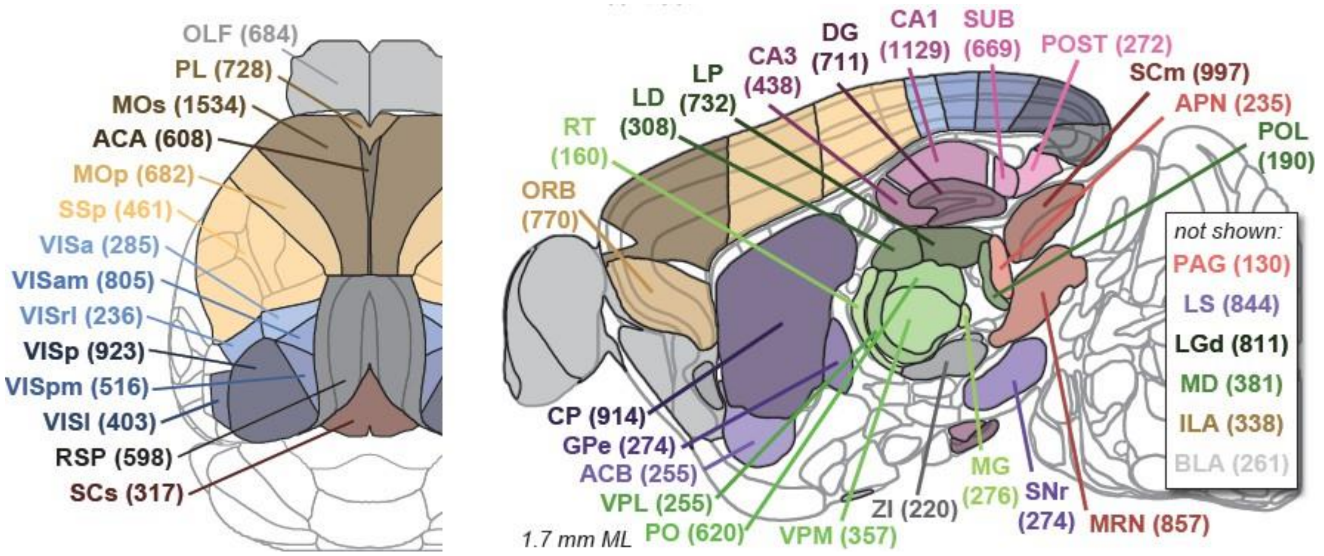
Jun, Steinmetz, Siegle, Denman, Bauza, Barbarits, et al, *Nature* 2017

Collaborative recording projects allow the creation of brain-wide datasets

92 insertions in 10 mice



30,000 neurons in 42 regions



Many of these datasets are open source! Check them out if you want to explore real data:

- IBL Brain Map
- Allen Vision Dataset

Slide from Matteo Carandini University College London

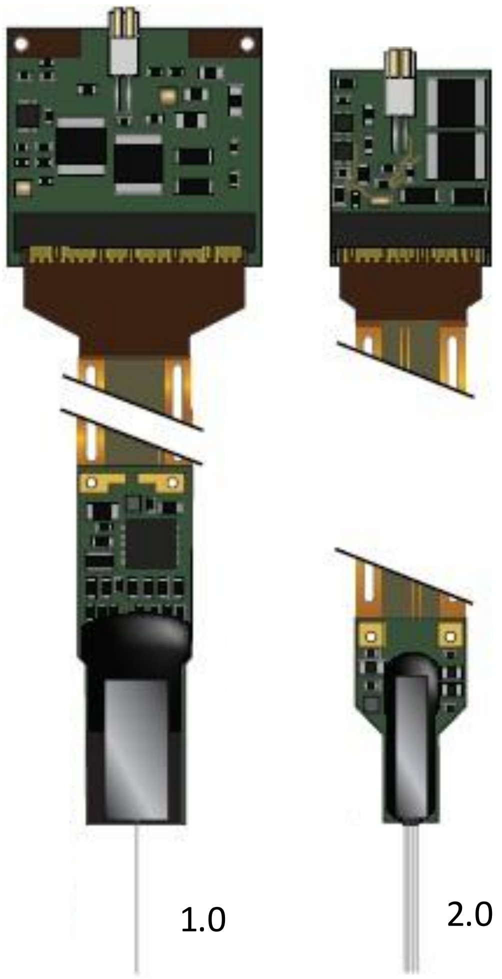
Steinmetz et al, *Nature*, 2019

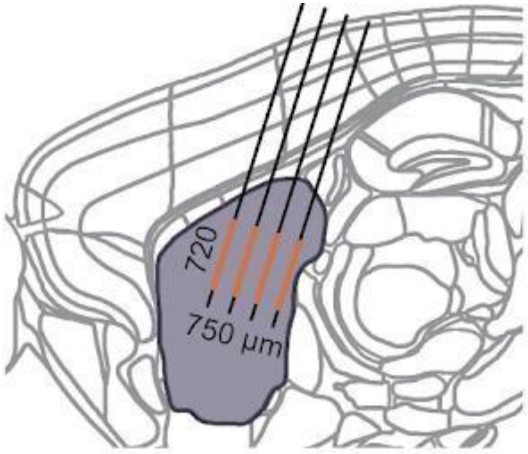
New technologies facilitate new tools: Neuropixels 2.0

NEUROSCIENCE

Neuropixels 2.0: A miniaturized high-density probe for stable, long-term brain recordings

Nicholas A. Steinmetz*,†,1,2, Cagatay Aydin*,3, Anna Lebedeva*,4, Michael Okun*,5,6, Marius Pachitariu*,7, Marius Bauza4, Maxime Beau8, Jai Bhagat6, Claudia Böhm7, Martijn Broux3, Susu Chen7, Jennifer Colonell7, Richard J. Gardner9, Bill Karsh7, Fabian Kloosterman3, Dimitar Kostadinov8, Carolina Mora-Lopez10, John O'Callaghan10, Junchol Park7, Jan Putzeys10, Britton Sauerbrei7, Rik J. J. van Daal11,3,14, Abraham Z. Vollan9, Shiwei Wang10, Marleen Welkenhuysen10, Zhiwen Ye2, Joshua Dudman7, Barundeb Dutta10, Adam W. Hantman7, Kenneth D. Harris6, Albert K. Lee7, Edvard I. Moser9, John O'Keefe4, Alfonso Renart12, Karel Svoboda7, Michael Häusser8, Sebastian Haesler3,13, Matteo Carandini†,1, Timothy D. Harris†,7,15





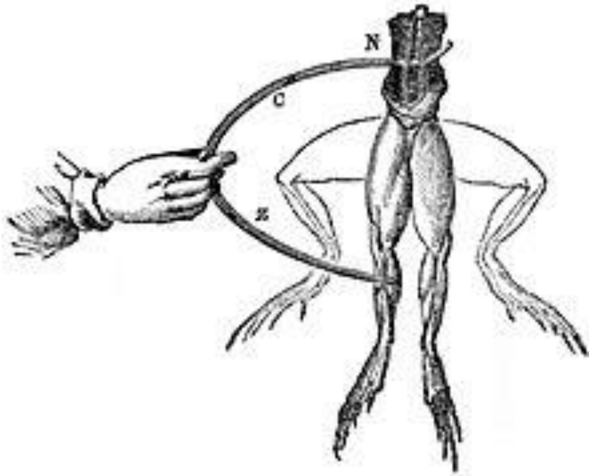
	1.0	2.0
shanks	*1*	***4***
sites	*1,000*	***5,000***
channels	*384*	*384*

Slide from Matteo Carandini University College London

Steinmetz, Aydin, Lebedeva, Okun, Pachitariu et al, *Science* 2021

How can we modulate the brain?

Tools & technology to study neuroscience: **Electrical Stimulation of neurons**



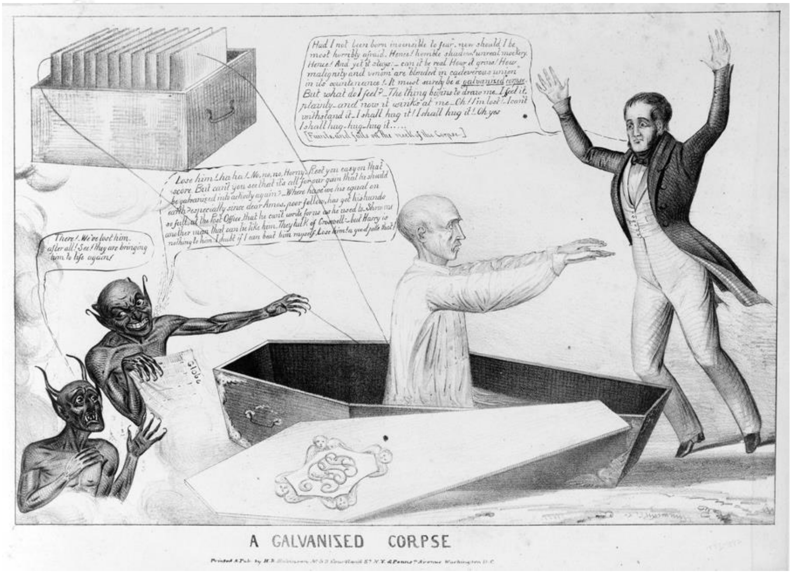
Alessandro Volta

Stimulate a neuron = **trigger an action potential**, AP

(…neurons are electrically excitable)

We often want to electrically stimulate a neuron at a specific (ms-defined) time

- e.g. to observe synaptic transmission after the stimulation
- e.g. to observe the effect on behavior *in-vivo* (when a neuron *population* is stimulated)



https://en.wikipedia.org/wiki/Galvanism

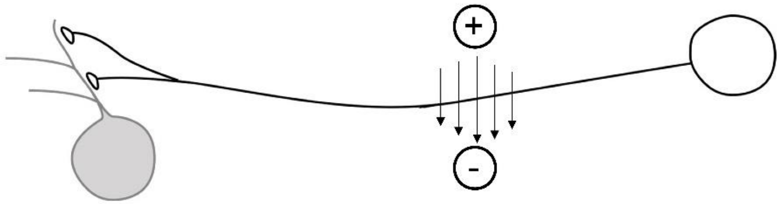
electrical stimulation

- 1a) with *intracellular* electrode -> current clamp
- 1b) with *extracellular* (stimulation) electrode e.g. "microstimulation" experiments *in-vivo*

Courtesy of Ralf Schneggenburger

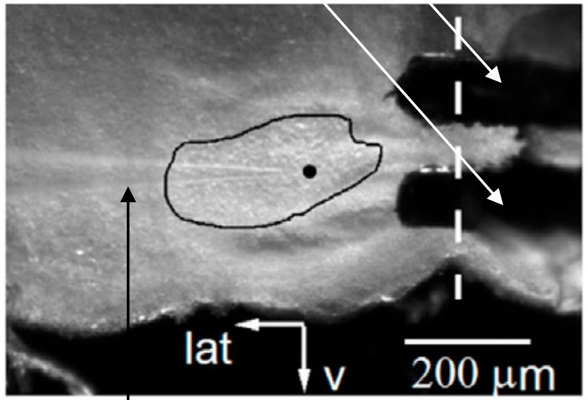
Stimulation by extracellular (stimulation) electrode

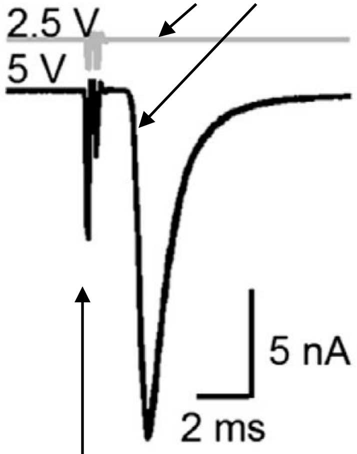
Example: "bipolar" stimulation of axons in a brain slice preparation



stimulation electrode
(2 poles)

recording of EPSC after 2.5 V and 5V
stimulation ("all-or-none" event)





Advantage: high timing precision

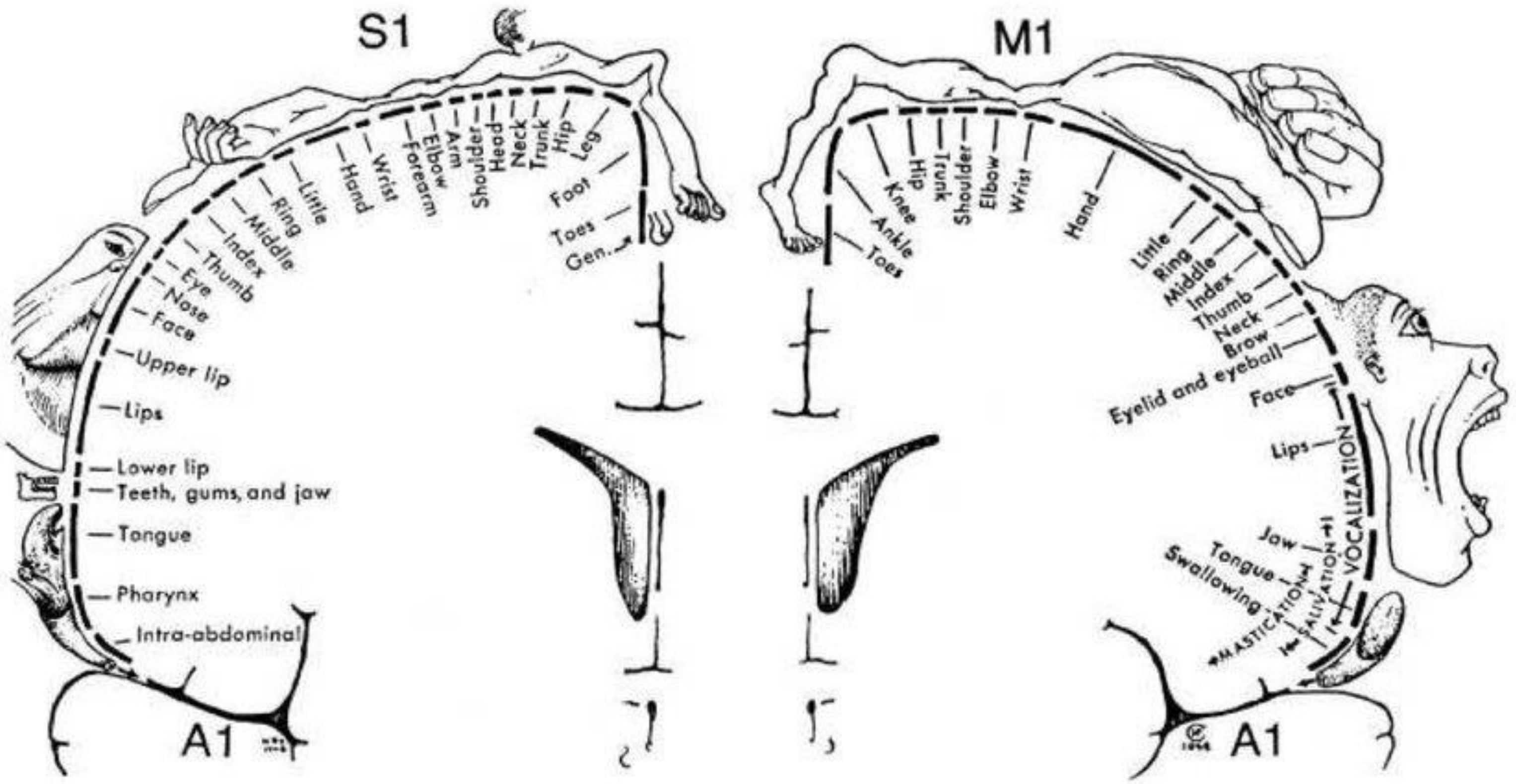
Disadvantage:
- no control over *which* (molecularly defined) presynaptic neuron gets stimulated

whole-cell patch-clamp
glass electrode
(for recording of EPSC)

stimulation artefact
(duration ~ 0.3 ms)

Figure from Michalski N, Babai N et al. 2013 *Neuron*

Electrical stimulation (Wilder Penfield)



From Penfield and Rasmussen (1950). THE CEREBRAL CORTEX OF MAN.

Old documentation about Penfield:
https://www.youtube.com/watch?v=Rqxhdffo_0c

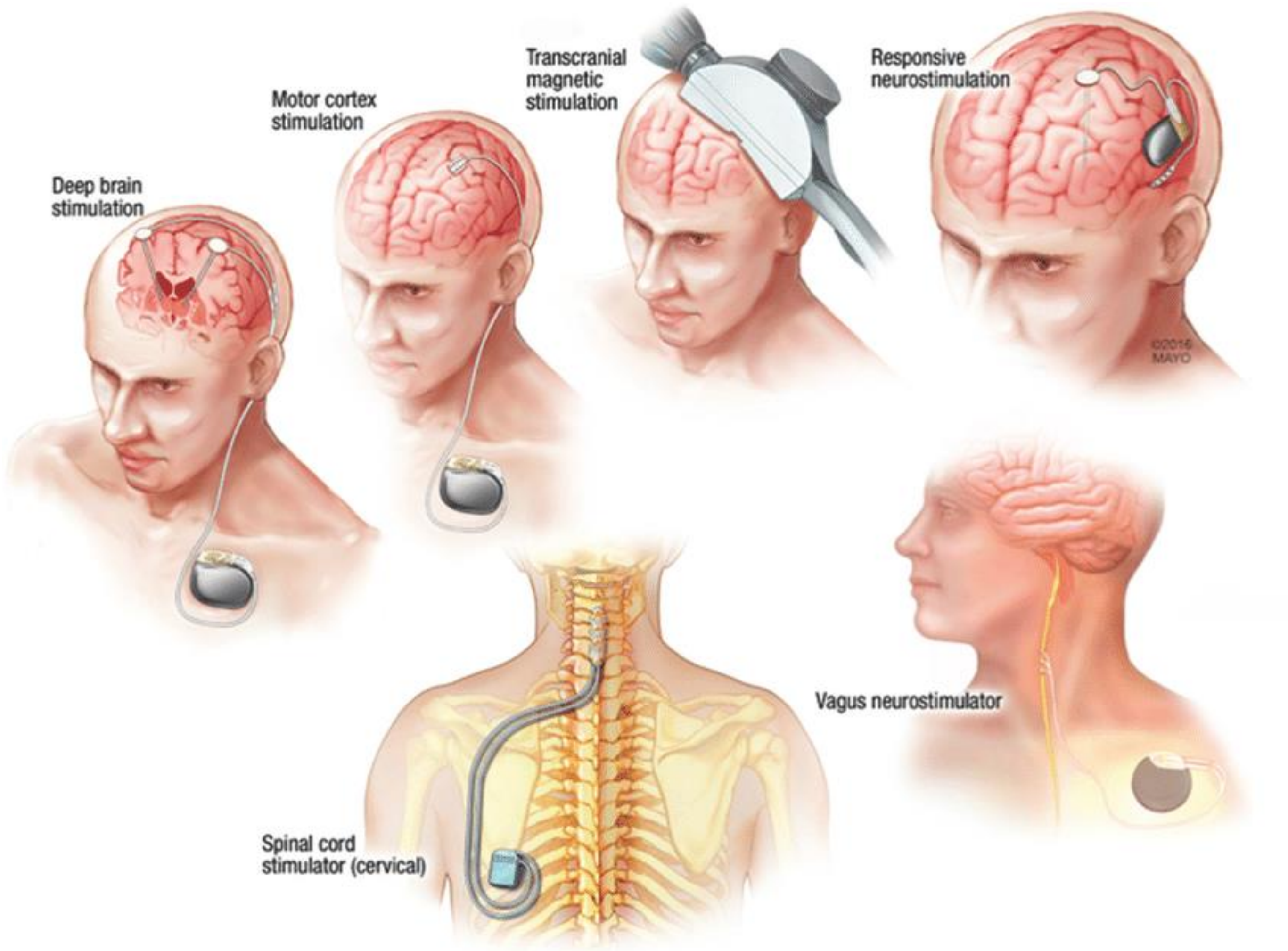
https://en.wikipedia.org/wiki/Wilder_Penfield

Electrical stimulating the fusiform face area

https://www.youtube.com/watch?v=O7AQ8NjSnTo&t=2s

This remarkable video clip was released to accompany the 2012 paper **“Electrical stimulation of human fusiform face-selective regions distorts face perception.”** Onscreen is the patient, who has undergone a surgical implantation of subdural electrodes in an effort to localize the focus of his seizures. Offscreen is the neurologist, Josef Parvizi, whose voice is heard asking about the effects of administering electrical stimulation (variously "4mAmp" or "3mAmp") to the targeted region of the FFA, or "SHAM" stimulation (a switch is clicked, but no current is passed), while the patient looks first at Parvizi's face, then the face of another person in the room, then non-face objects in the hospital room.

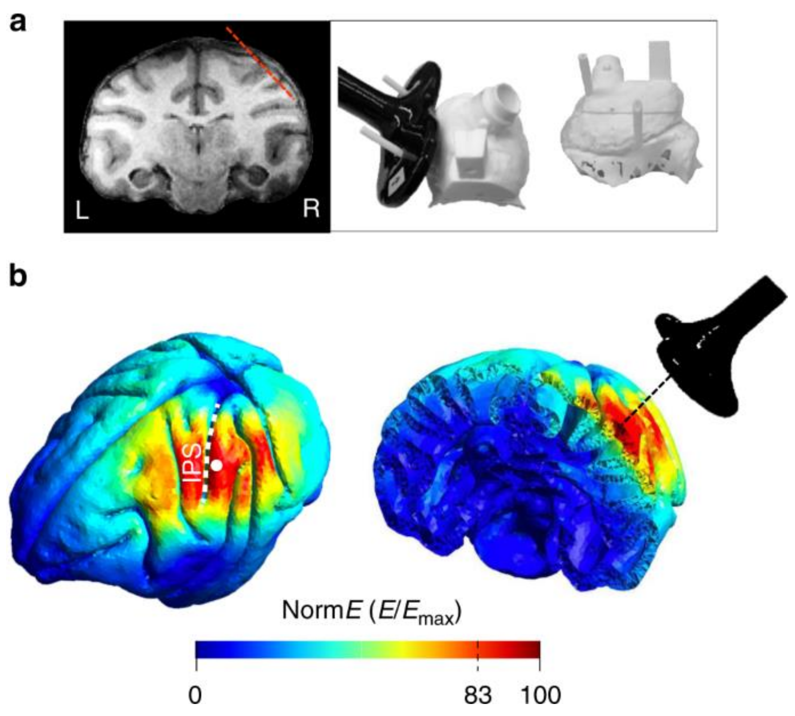
Neurostimulation Methods for Research and Treatment of Neurologic Disorders



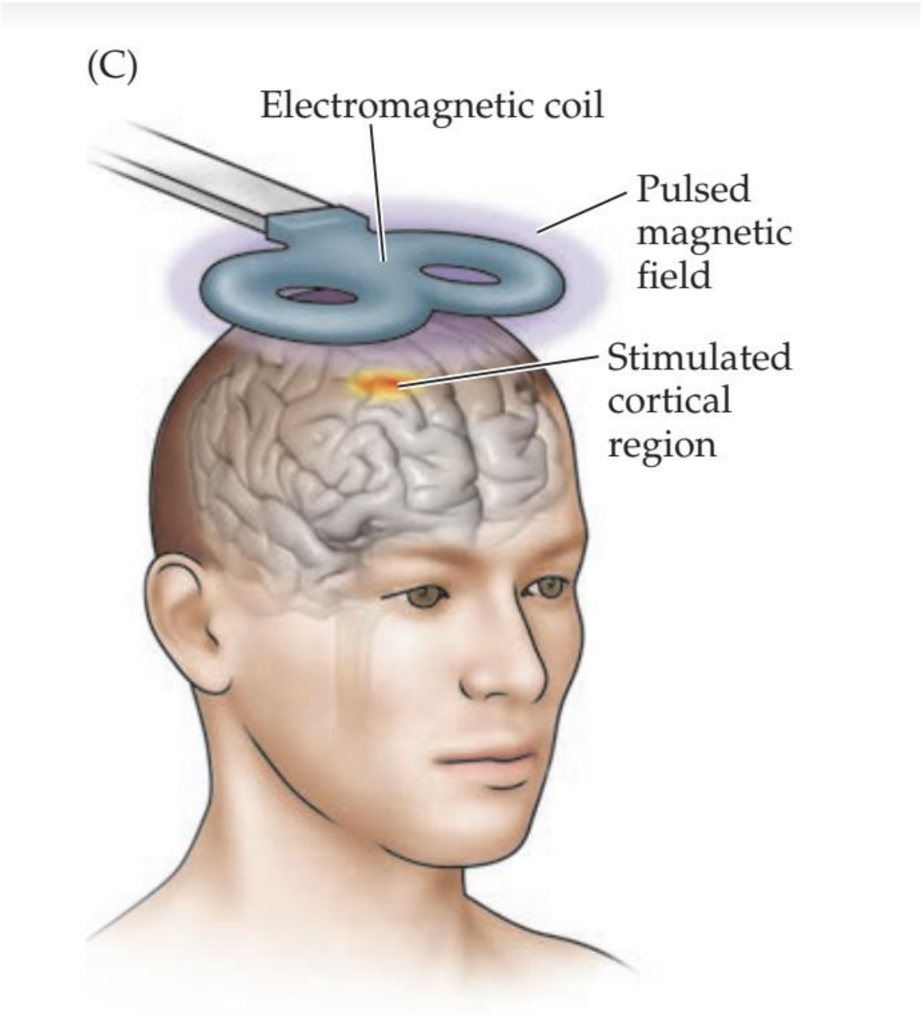
Edwards et al., 2017

The majority of these methods are invasive, but research into noninvasive stimulation is growing.

TMS is used as a non-invasive method in humans to modulate neuron activity

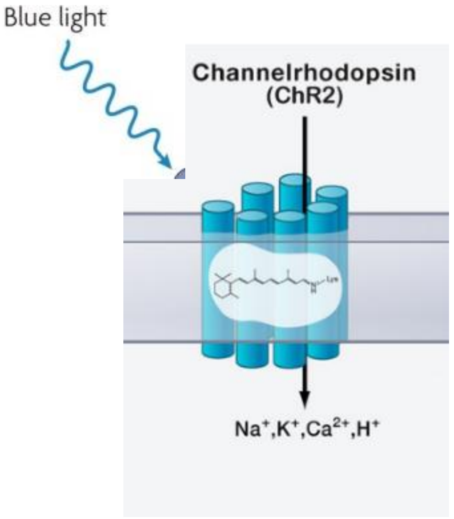


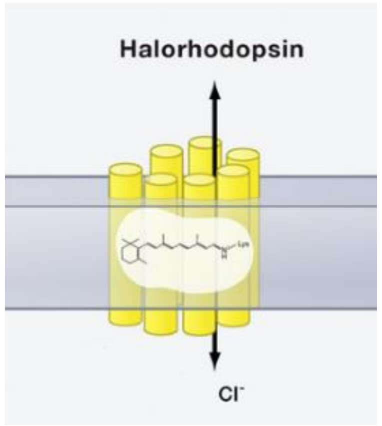
- **Transcranial magnetic stimulation** (**TMS**) is a noninvasive form of brain stimulation in which a changing magnetic field is used to cause electric current at a specific area of the brain through electromagnetic induction.



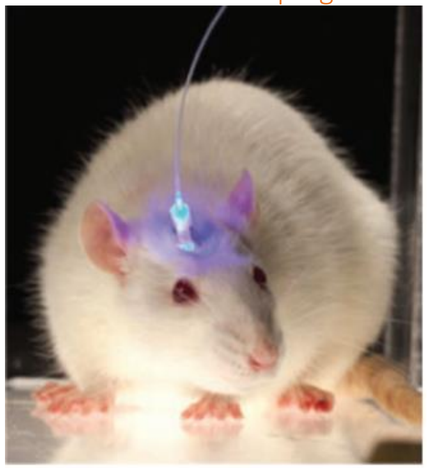
https://www.nature.com/articles/s41467-019-10638-7

Opsins: Light-activated ion channels / pumps





Optogenetics.org



- Type I opsins:
  - in prokaryotes, algae, fungi
  - for phototaxis, energy storage

Channelrhodopsin:
From alga
Chlamydomonas reinhardtii

Halorhodopsin:
From Natromonas pharaonis
(NpHR)

- Type II opsins: - in higher eukaryotes, for vision (e.g. rhodopsin; a GPCR)

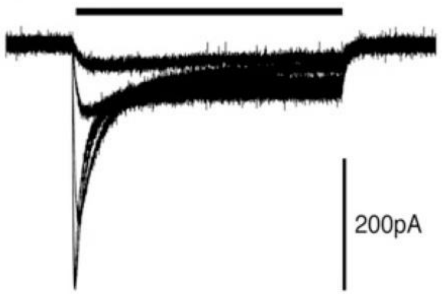
Bamberg, Boyden, Deisseroth, Hegemann, Nagel and others

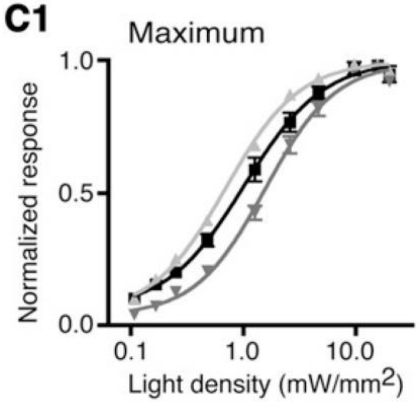
Courtesy of Ralf Schneggenburger

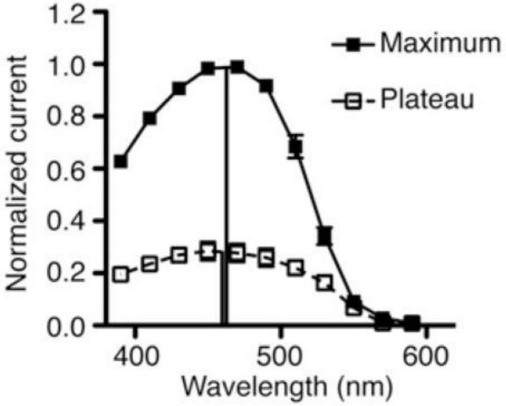
Channelrhodopsin-2 (ChR2) is a light-activated cation channel

- blue light λ 470 nm, 500 ms
- different intensities

B1







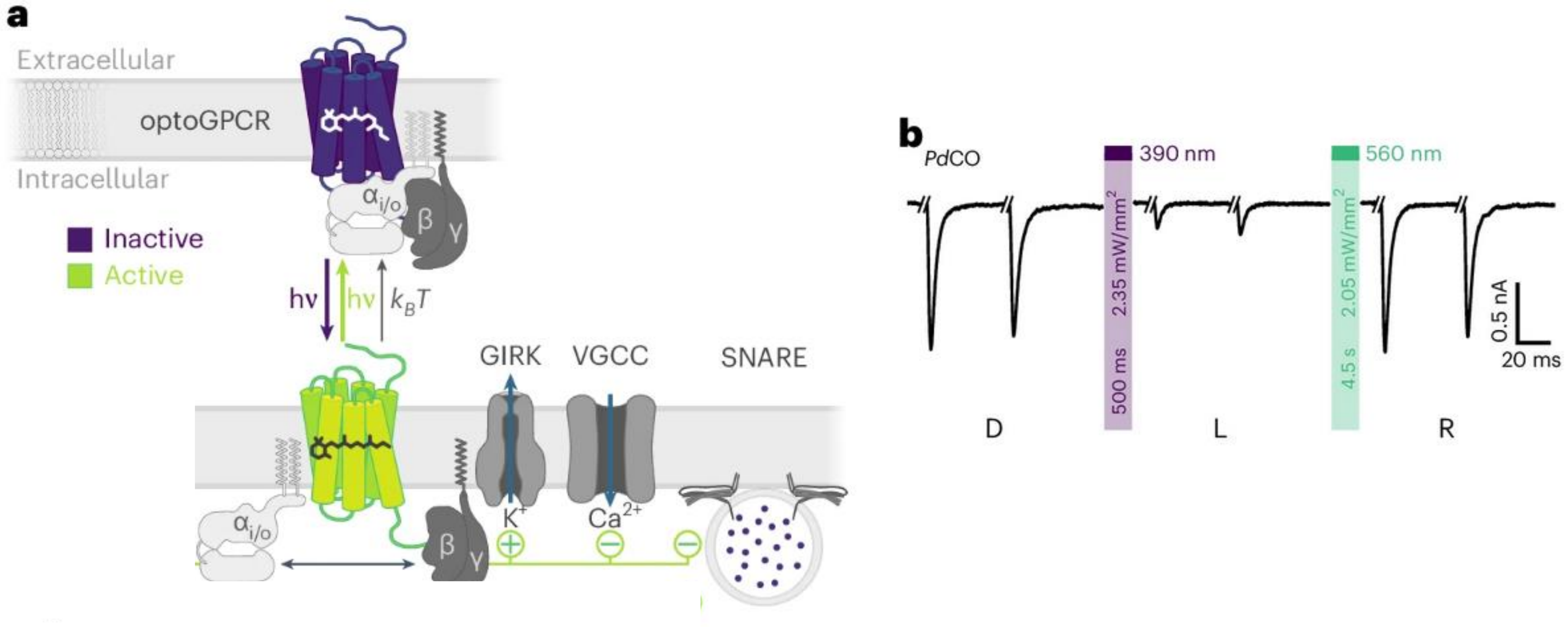
Nagel et al., 2003 *PNAS*; Lin et al. 2009 *Biophysical J.*

- From green alga, *Chlamydomonas reinhardtii*
  - ChR2 expressed in HEK293 cells
  - Whole-cell voltage clamp recording
  - Light exposure with LED / monochromator

Take Homes:
- absorption maximum ~ 470 nm
- inward currents (**nonselective cation channel**)
- channel activates fast ~ 2 ms
- channel *inactivates* with prolonged light

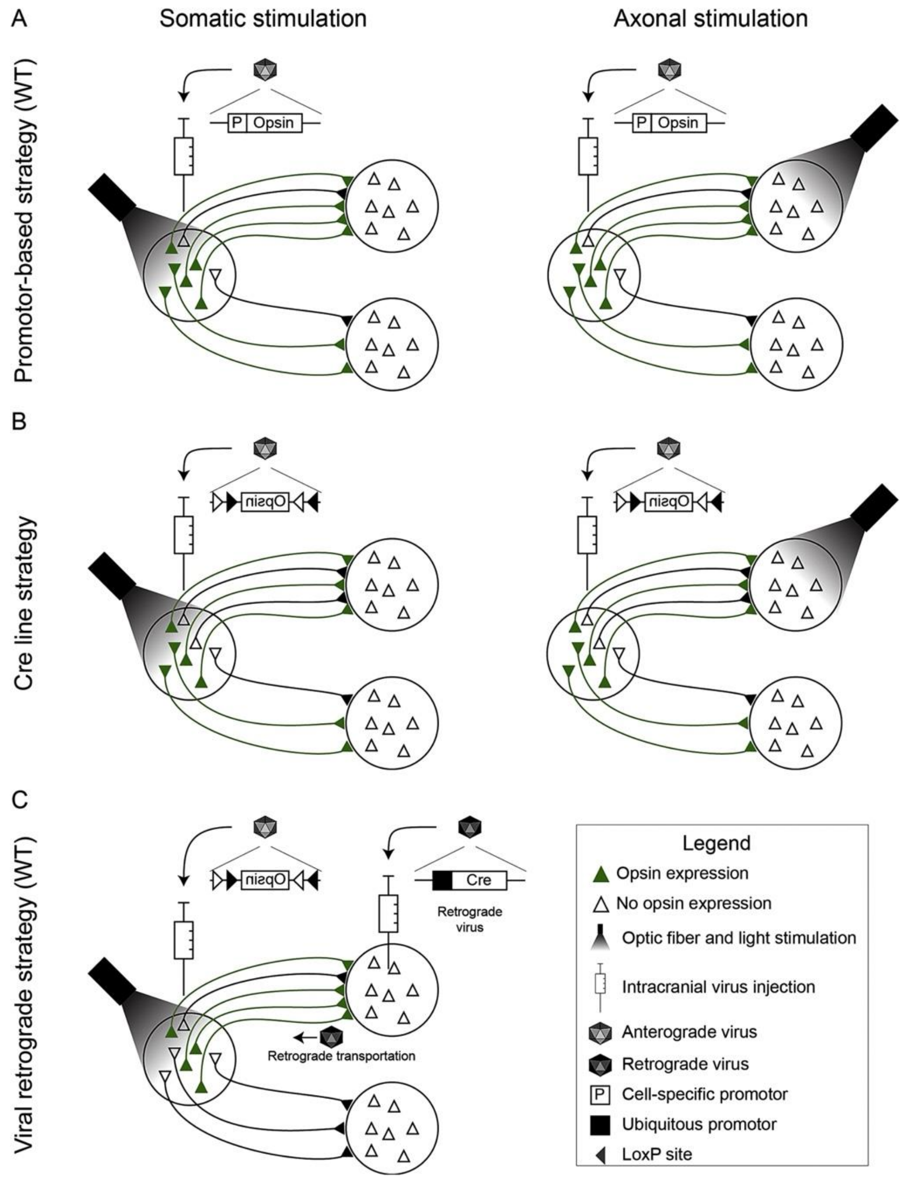
Courtesy of Ralf Schneggenburger

G-protein coupled opsins enable presynaptic inhibition

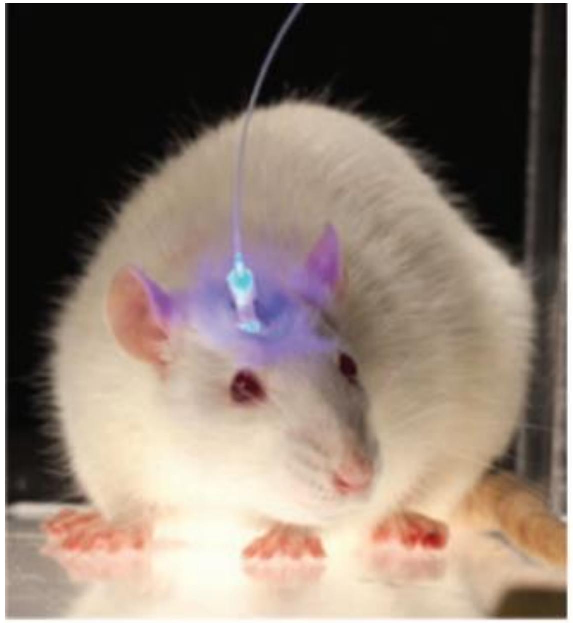


Wietek, J., Nozownik, A., Pulin, M. *et al.* A bistable inhibitory optoGPCR for multiplexed optogenetic control of neural circuits. *Nat Methods* (2024).

Optogenetics enable high spatio-temporal precision for circuit interogation



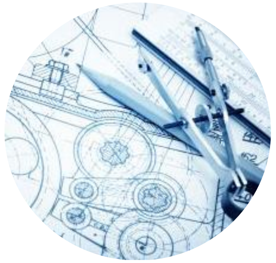
Optogenetics.org



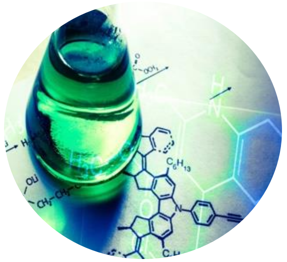
Brice De La Crompe, Philippe Coulon, Ilka Diester. Functional interrogation of neural circuits with virally transmitted optogenetic tools (2020)

How do we measure behavior precisely?

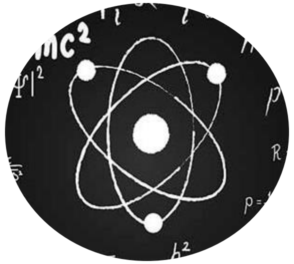
Tools & technology to study neuroscience: **behavioral tracking**



Engineering



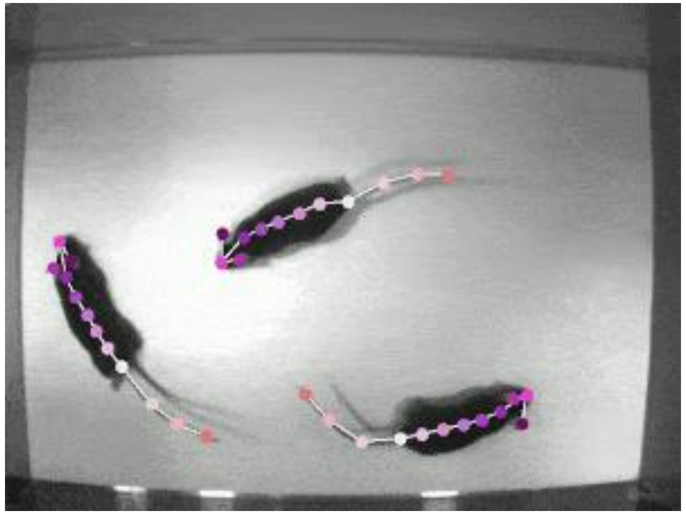
Chemistry



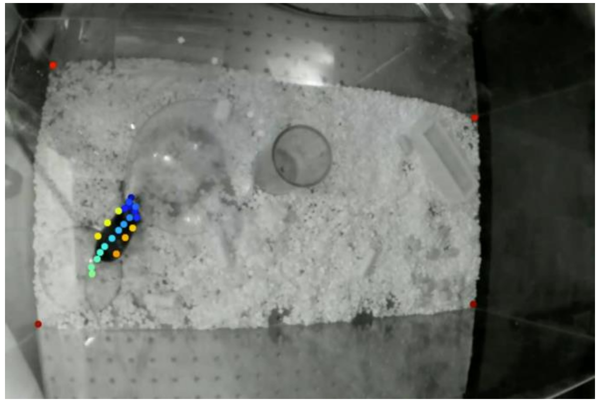
Physics

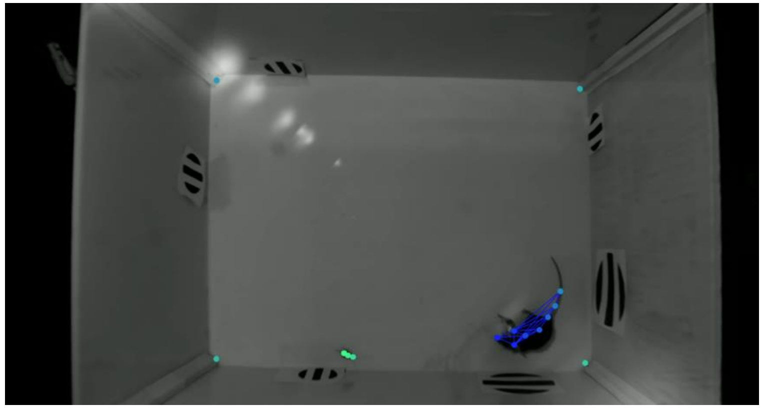
Biology

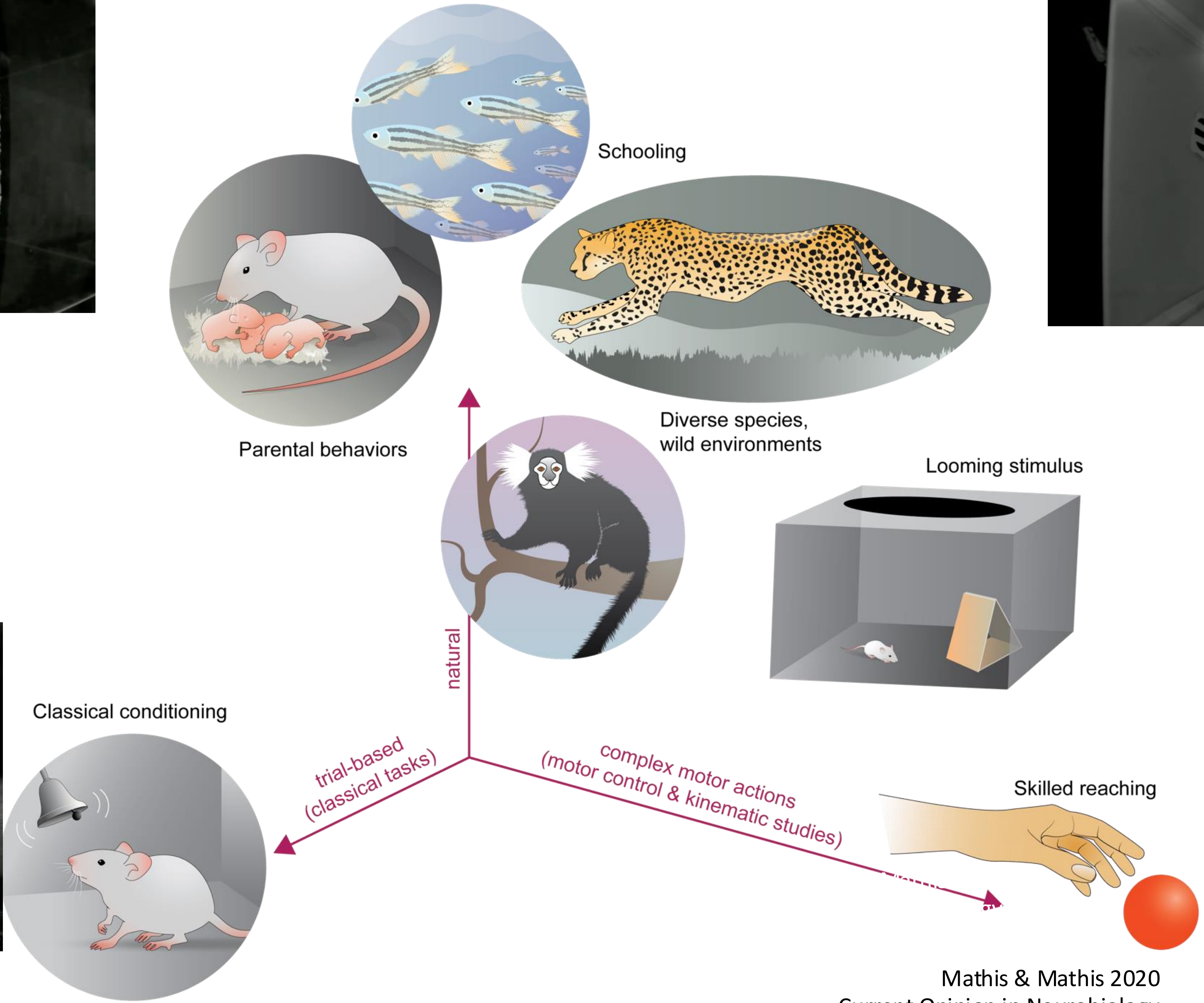
Computer Science

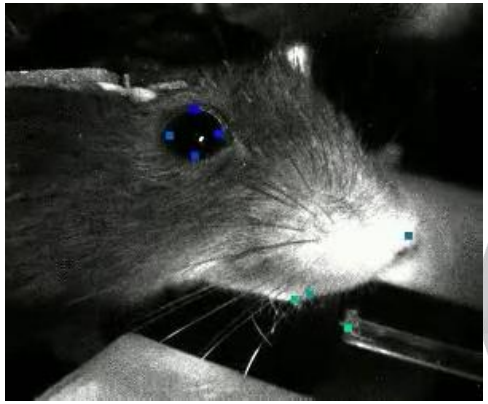


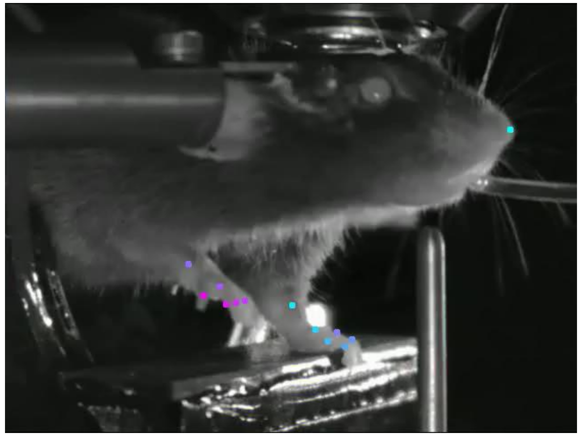
Behavior as a lens into neural function





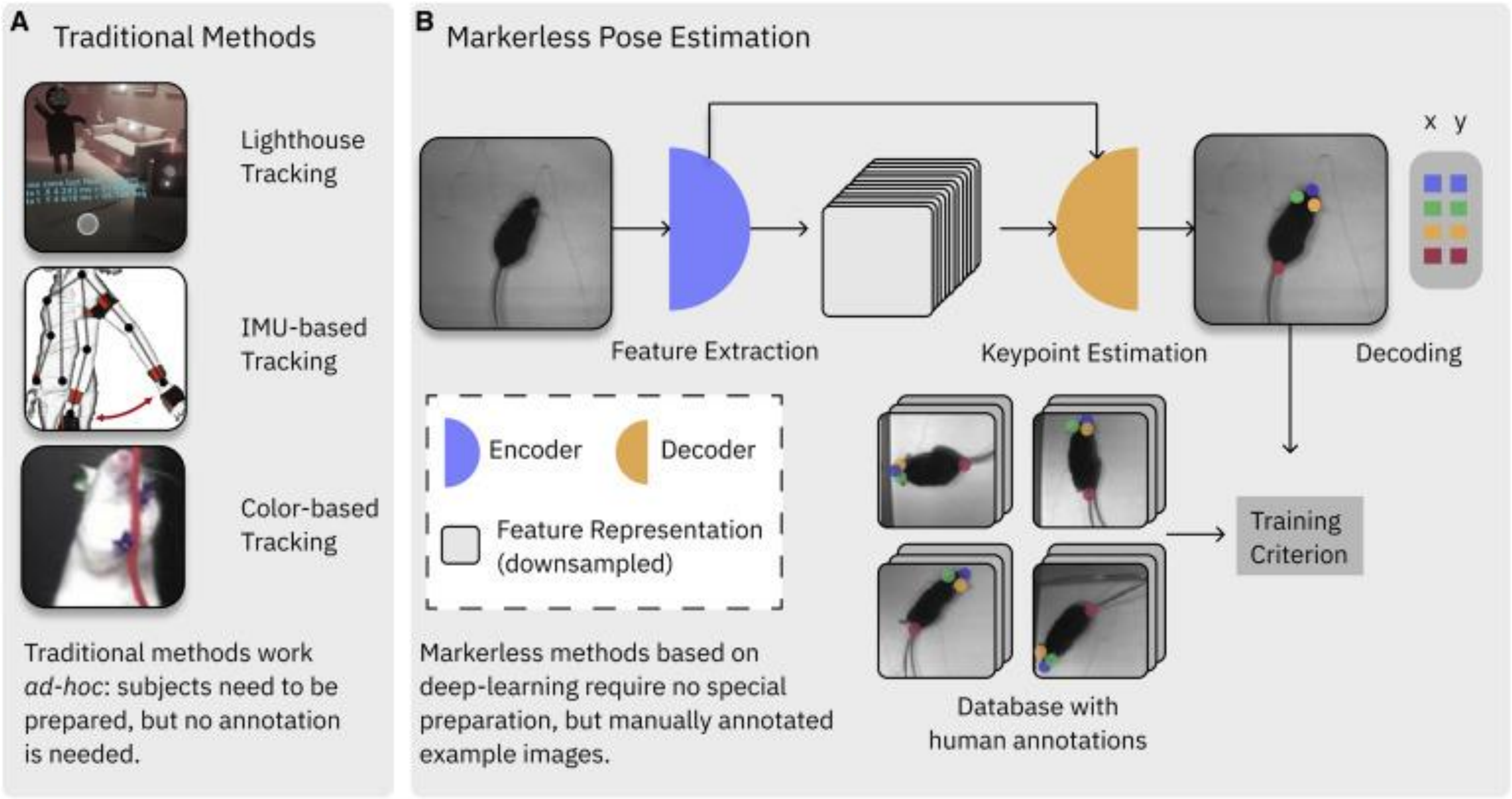






Mathis & Mathis 2020
Current Opinion in Neurobiology

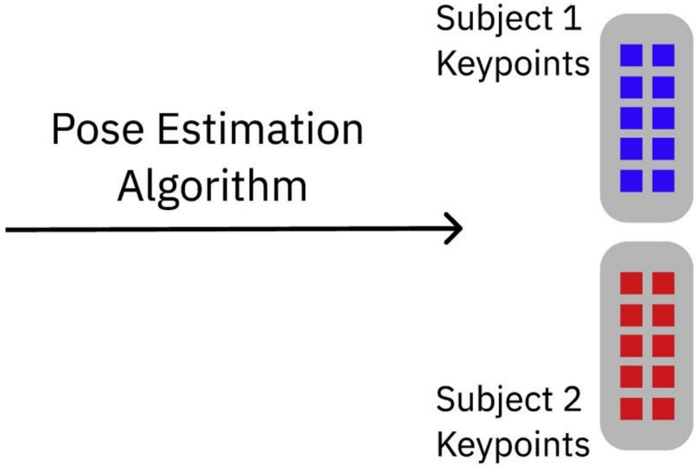
Deep learning for measuring behavior



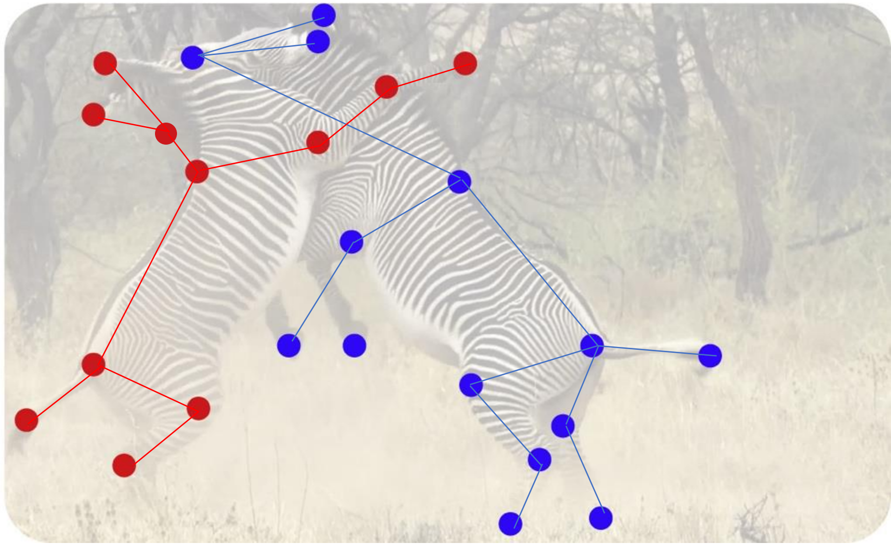
Schematic Overview of Markerless Motion Capture, aka Pose Estimation

Pixel Representation

Pose Estimation Algorithm



Keypoint Representation



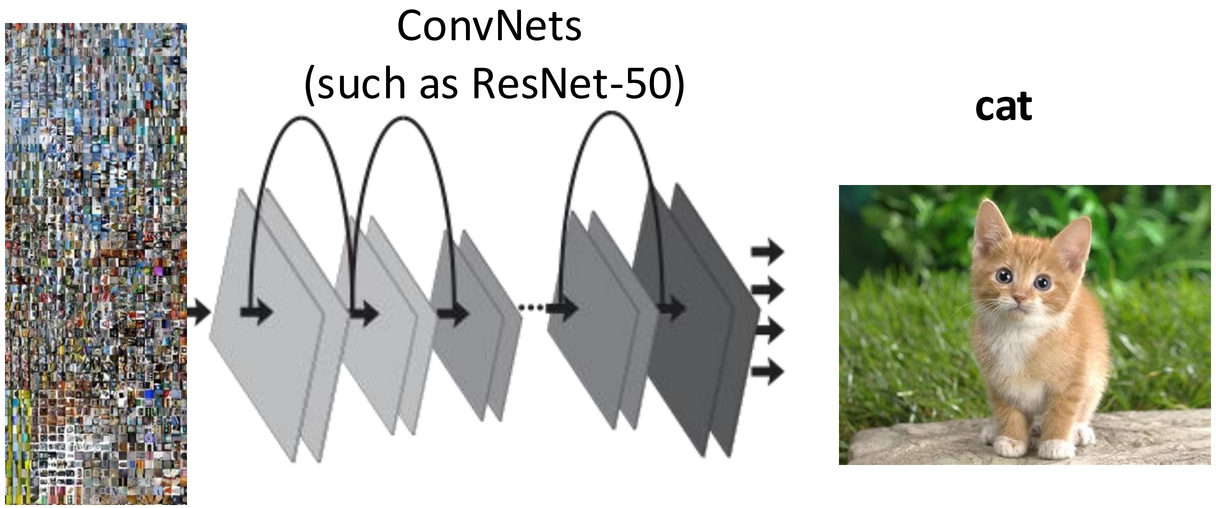
Primer

A Primer on Motion Capture with Deep Learning: Principles, Pitfalls, and Perspectives

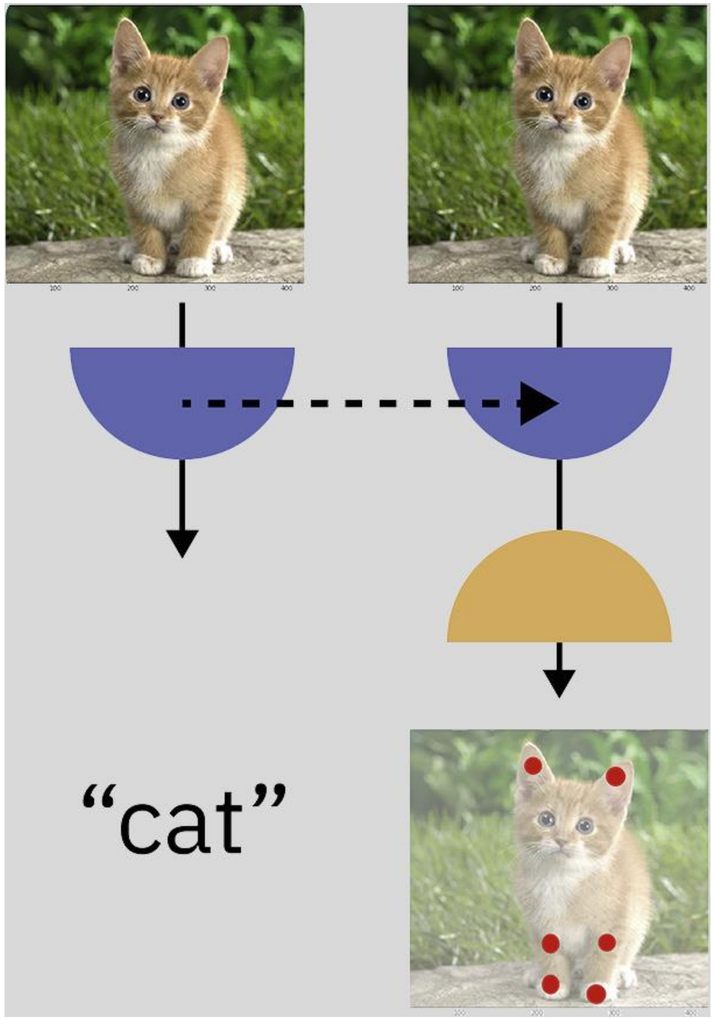
Alexander Mathis,[1,2,3,*] Steffen Schneider,[3,4] Jessy Lauer,[1,2,3] and Mackenzie Weygandt Mathis[1,2,3,*]
[1]Center for Neuroprosthetics, Center for Intelligent Systems, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland
[2]Brain Mind Institute, School of Life Sciences, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland
[3]The Rowland Institute at Harvard, Harvard University, Cambridge, MA, USA
[4]University of Tübingen and International Max Planck Research School for Intelligent Systems, Tübingen, Germany
*Correspondence: alexander.mathis@epfl.ch (A.M.), mackenzie.mathis@epfl.ch (M.W.M.)
https://doi.org/10.1016/j.neuron.2020.09.017

High performance pose estimation by **transfer learning**

IMAGENET based transfer learning



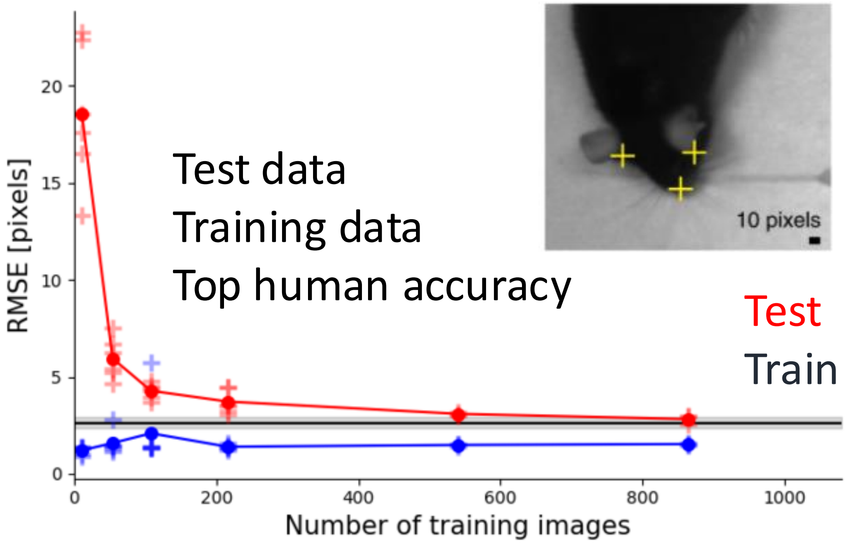
Olga Russakovsky*, Jia Deng*, Hao Su, Jonathan Krause, Sanjeev Satheesh, Sean Ma, Zhiheng Huang, Andrej Karpathy, Aditya Khosla, Michael Bernstein, Alexander C. Berg and Li Fei-Fei. (* = equal contribution) **ImageNet Large Scale Visual Recognition Challenge**. *International Journal of Computer Vision*, 2015.



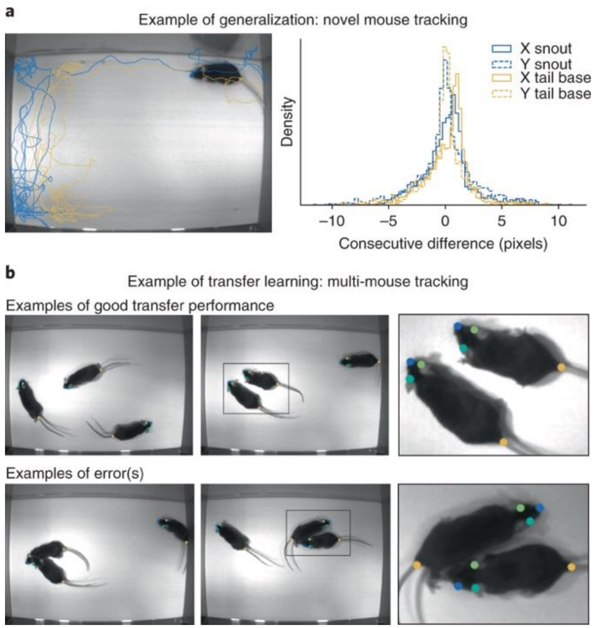
Mathis et al. Neuron 2020

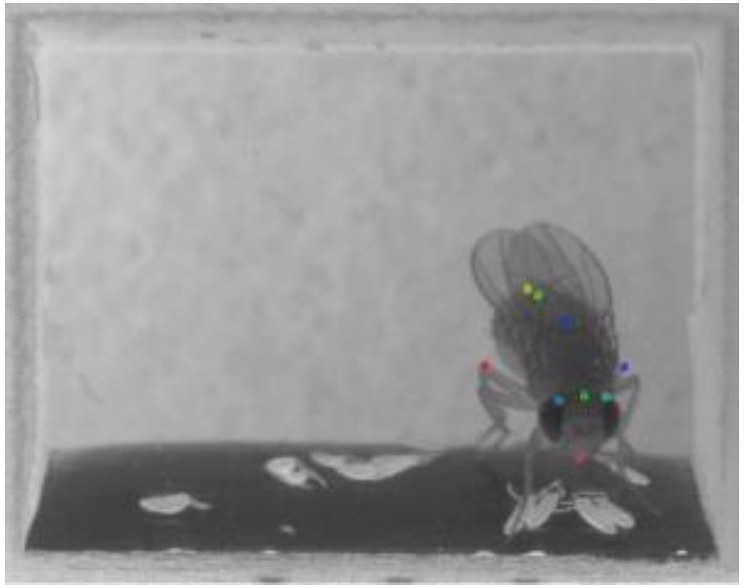
DeepLabCut: a toolbox for efficient markerless pose estimation

A small amount of training data is required to match human-level performance



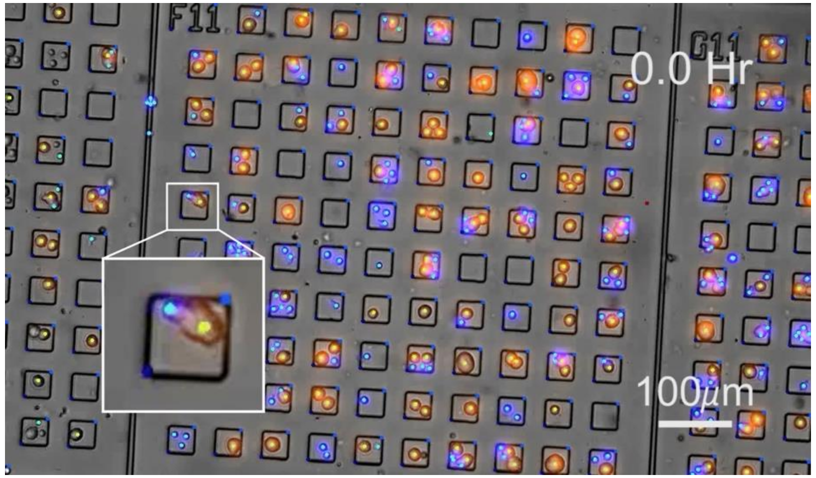
Generalizes to new animals



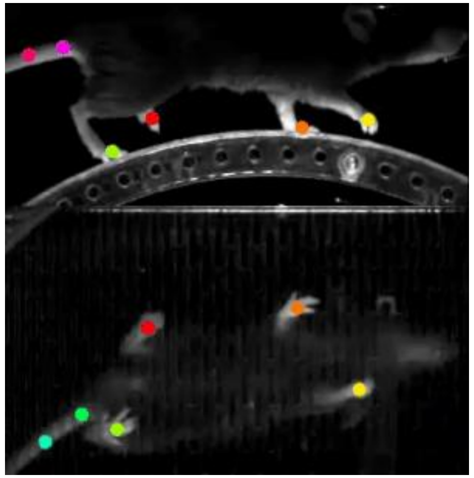


A. Mathis et al 2018

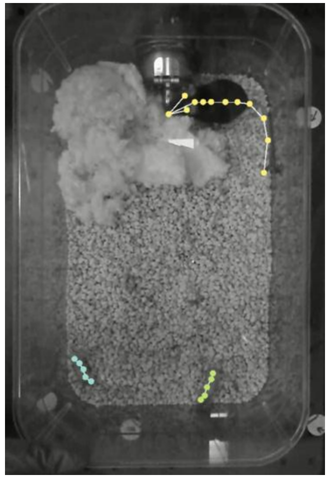
DeepLabCut: high performance markerless motion capture

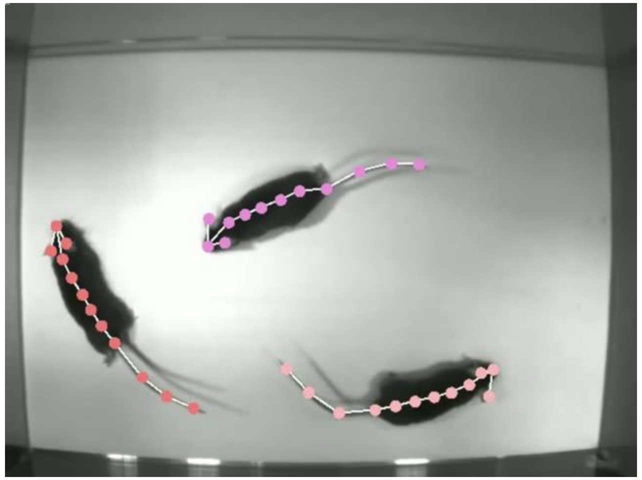


Cachot et al. 2021
Science Advances



Mathis & Warren 2018
bioxiv



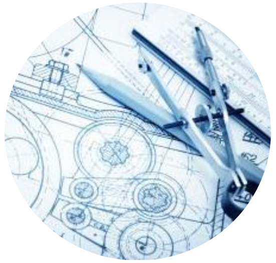


Lauer et al. 2022
Nature Methods

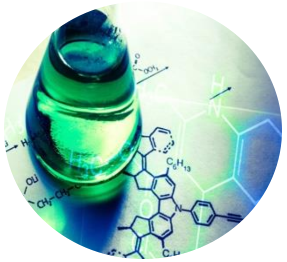
Nature Neuro 2018, Nature Prot. 2019, Neuron 2020, WACV 2021, ICRA, 2021, CVPR-W 2021

Nature Methods 2022

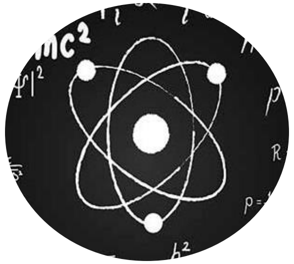
Tools & technology to study neuroscience: **modeling neural dynamics**



Engineering



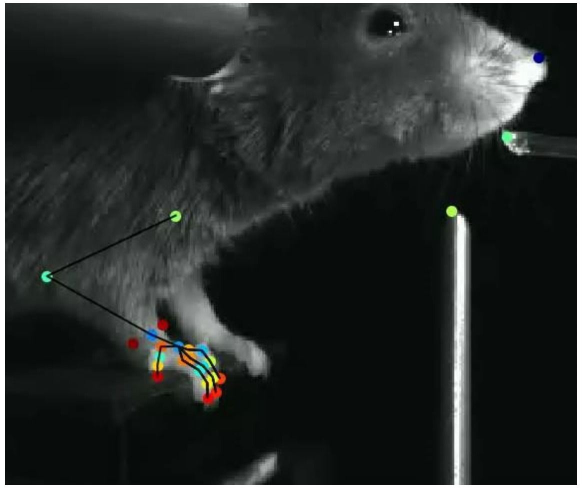
Chemistry



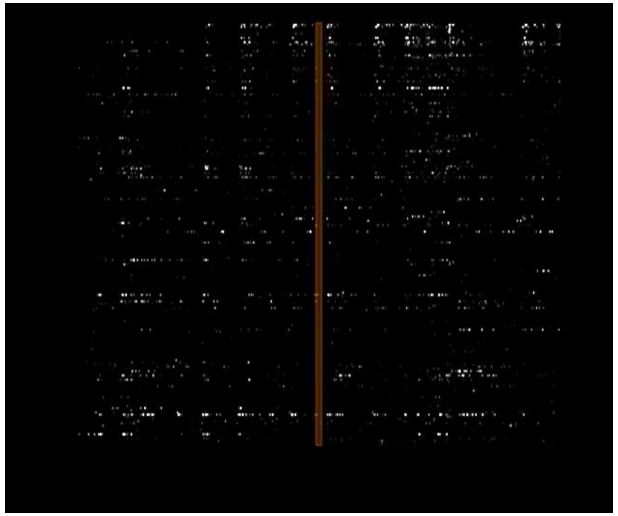
Physics

Biology

Computer Science



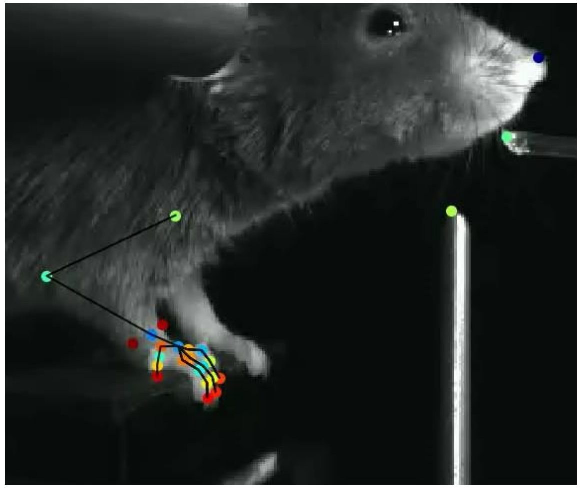
Keypoint tracking with DeepLabCut



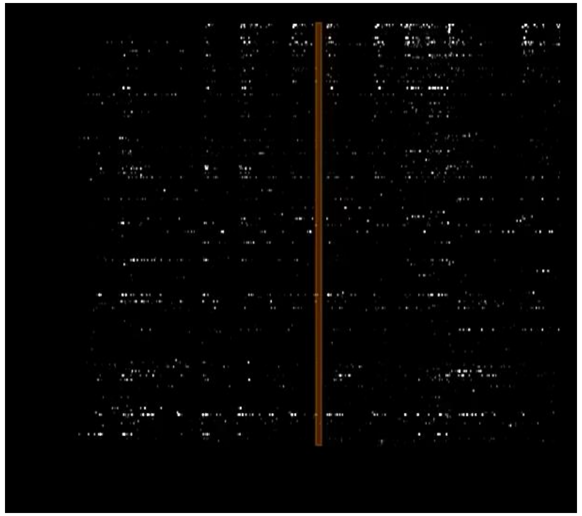
Neural recording in vivo (Calcium imaging)

Large-scale behavioral & neural recordings call for new methods to link neural dynamics and behavior

Mapping behavioral actions to neural computations



Keypoint tracking with DeepLabCut



Neural recording in vivo (Calcium imaging)

20 neurons → over one million possible instantaneous ON/OFF patterns of spiking (2^{20}) for a small time bin; one billion for 30 neurons (2^{30})

↓

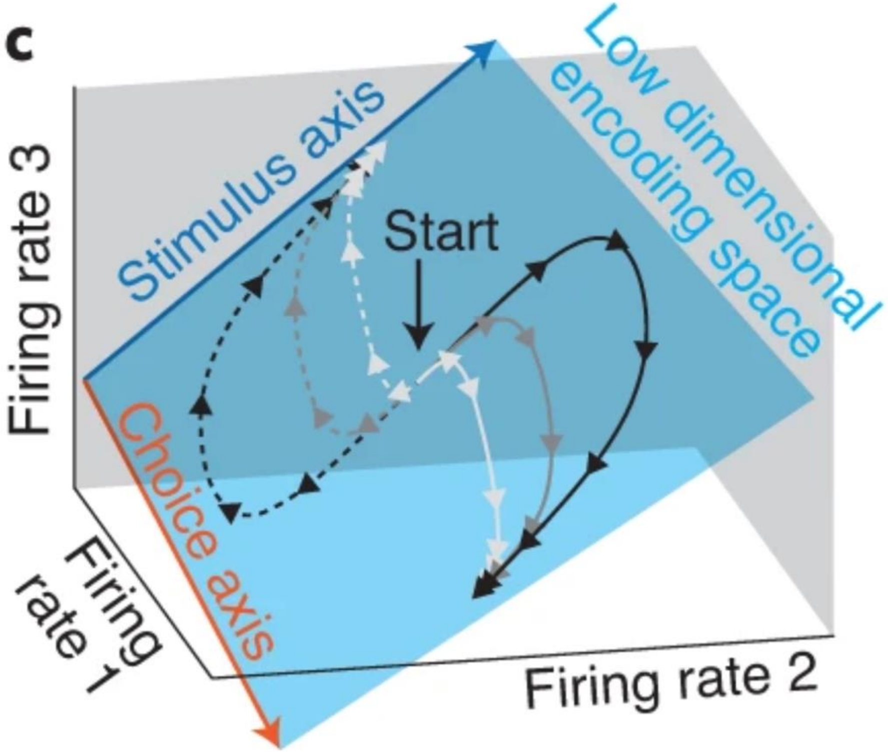
In reality: much smaller due to neural connectivity constraints, but **interpreting all neural patterns reliably from typical recordings is impossible** even for small populations!

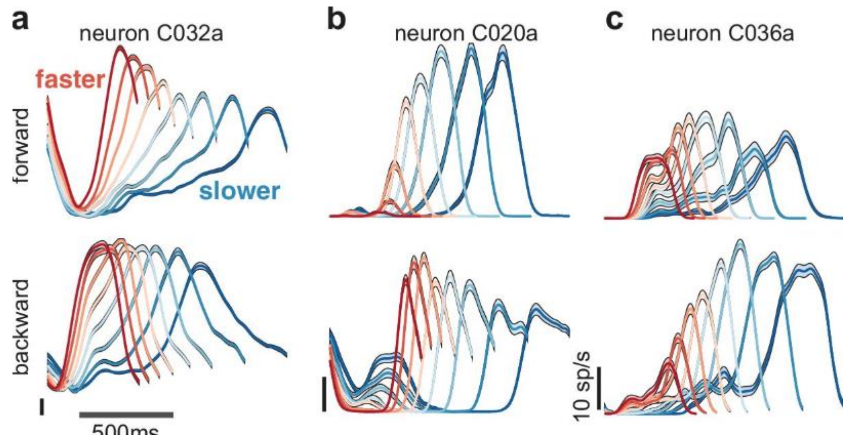
↓

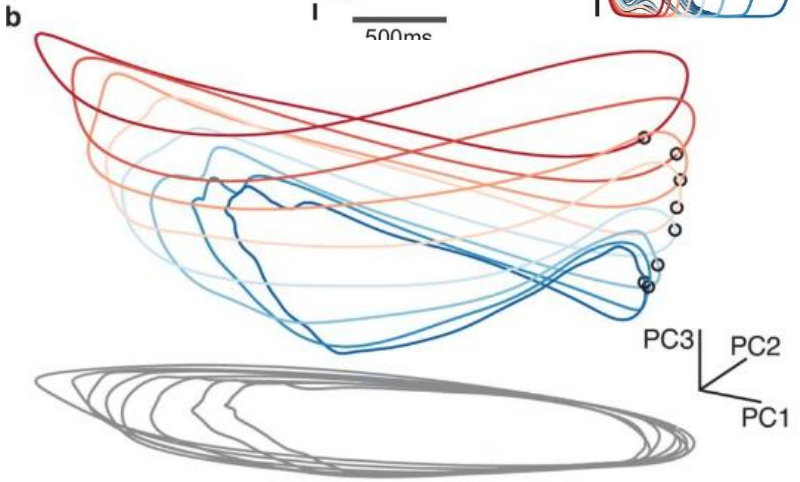
Statistical models can allow us to find patterns of activity in the neural data with reasonable constraints.

Adapted from C. Hurwitz 2021 Current Opinion Neuro

Population analysis can reveal core principles of neural coding







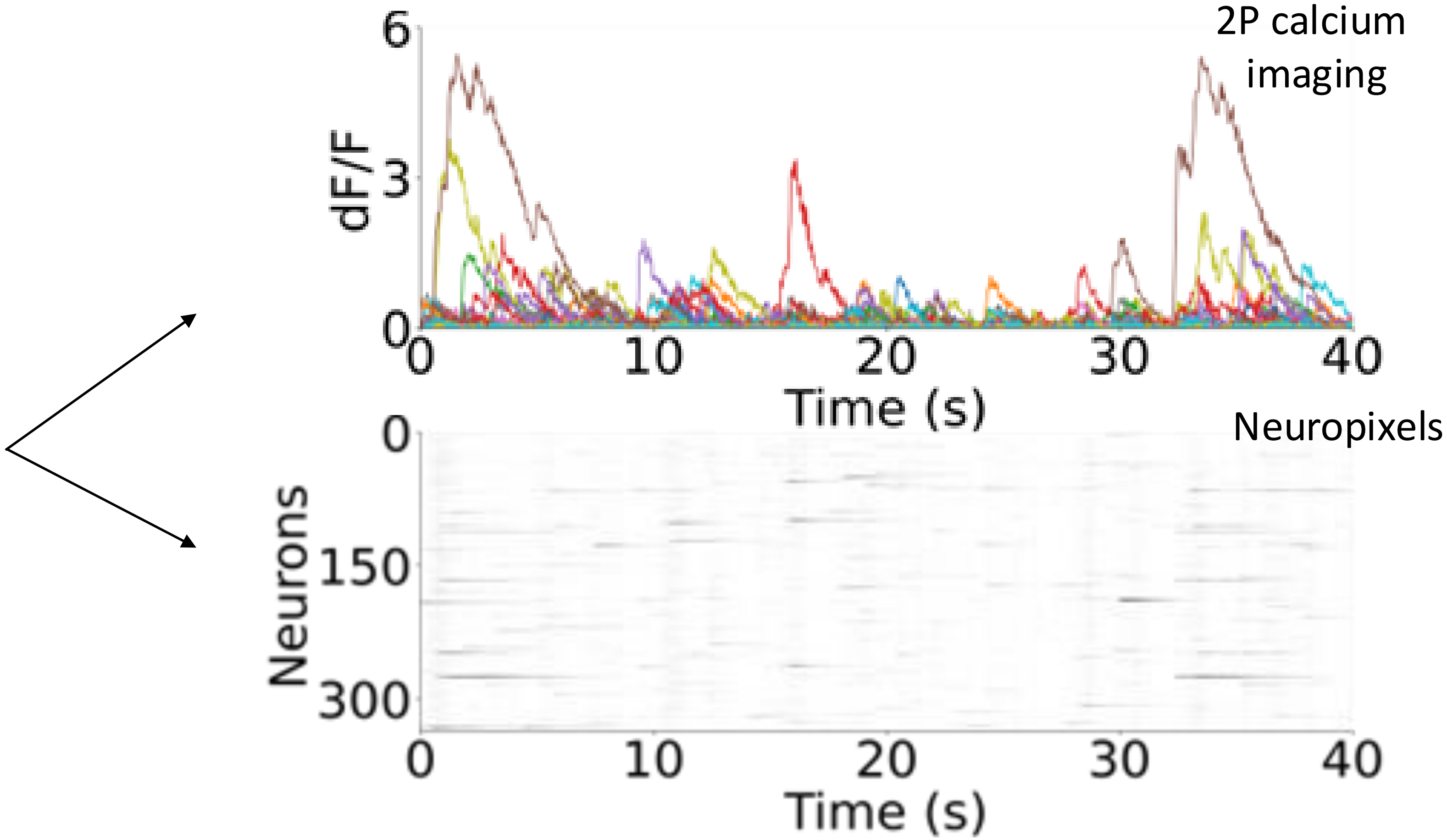
Behaviorally relevant neural variance explained by a **small number of dimensions**.

Neural computations at population dynamics in a **latent space,** but not in single-neuron firing rates.

Urai et al., Nature Neuroscience, 2022

See also: Mante et al Nature (2013), Churchland et al Nature (2012), Sadtler et al Nature (2014), Elsayed & Cunningham Nat Neurosci (2017)

Learnable latent embeddings from **V1**: mapping naturalistic video to latent spaces



Data: de Vries et al. (2020)
Deitch, Rubin, and Ziv (2021)
Siegle et al. (2021)

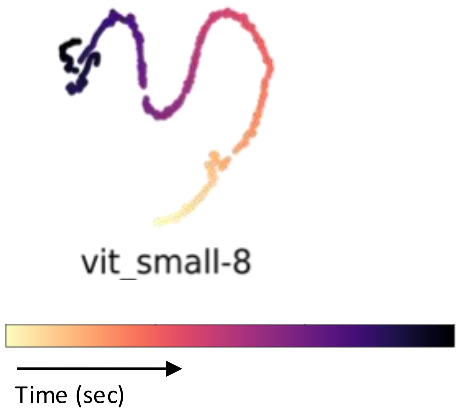
CEBRA: leverage visual features to guide latent embeddings

Movie frames

Caron et al 2021 arxiv

Emerging Properties in Self-Supervised Vision Transformers

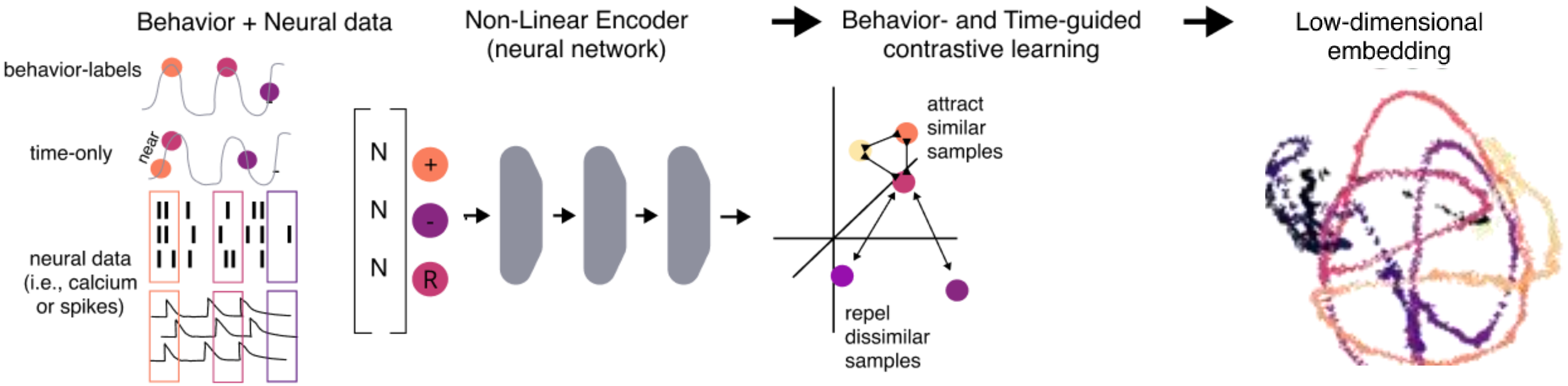
Pre-trained DINO



Extract global visual features of the images

A self-supervised learning algorithm

Hypothesis: Neural activity at a given timepoint is similar to neural activity at another timepoint IF the behavior it encodes is similar.



Schneider, Lee, Mathis Nature 2023

CEBRA : leverage visual features to guide latent embeddings

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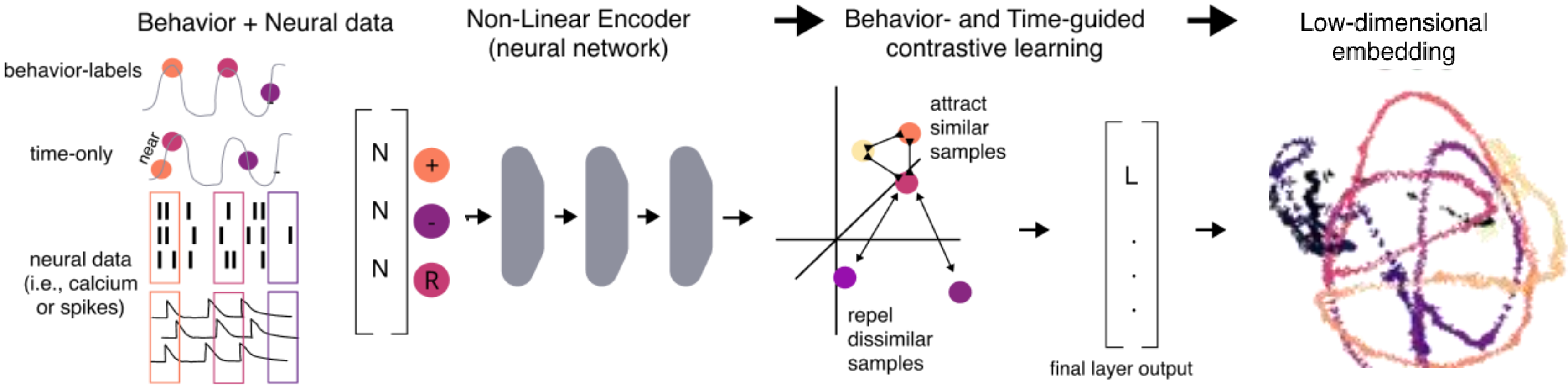
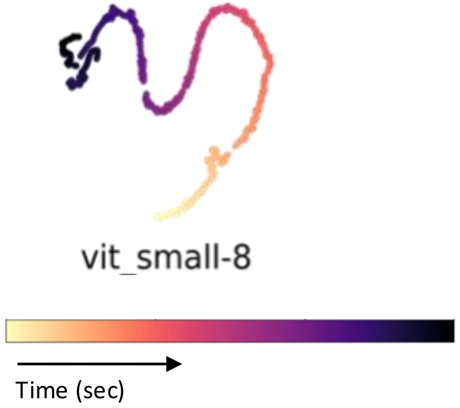
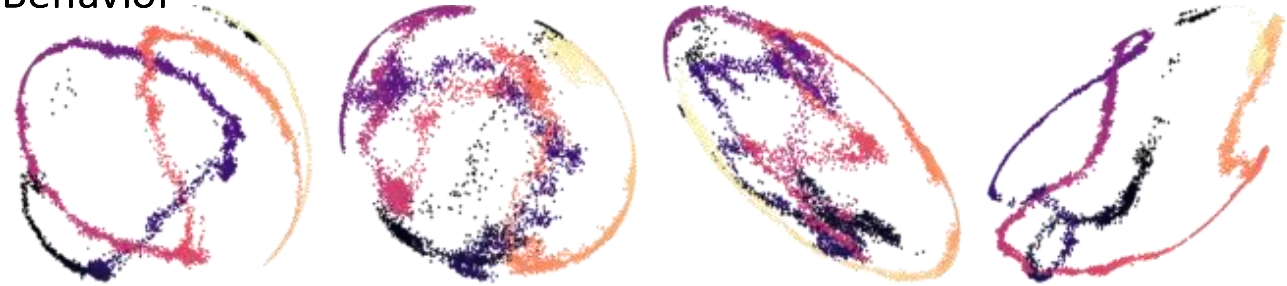
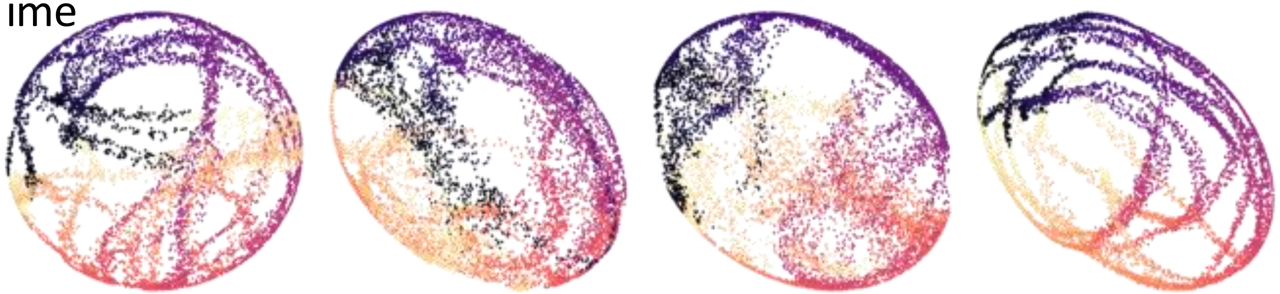




CEBRA-Behavior



CEBRA-Time



Extract global visual features of the images

Schneider, Lee, Mathis Nature 2023

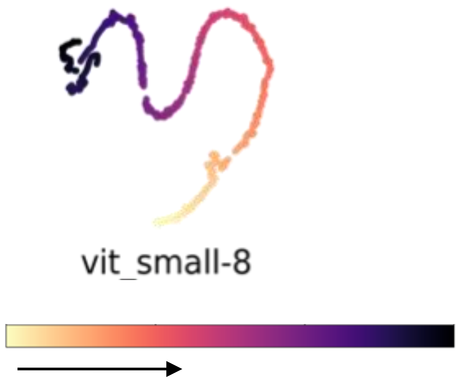
CEBRA : leverage visual features to guide latent embeddings

Movie frames

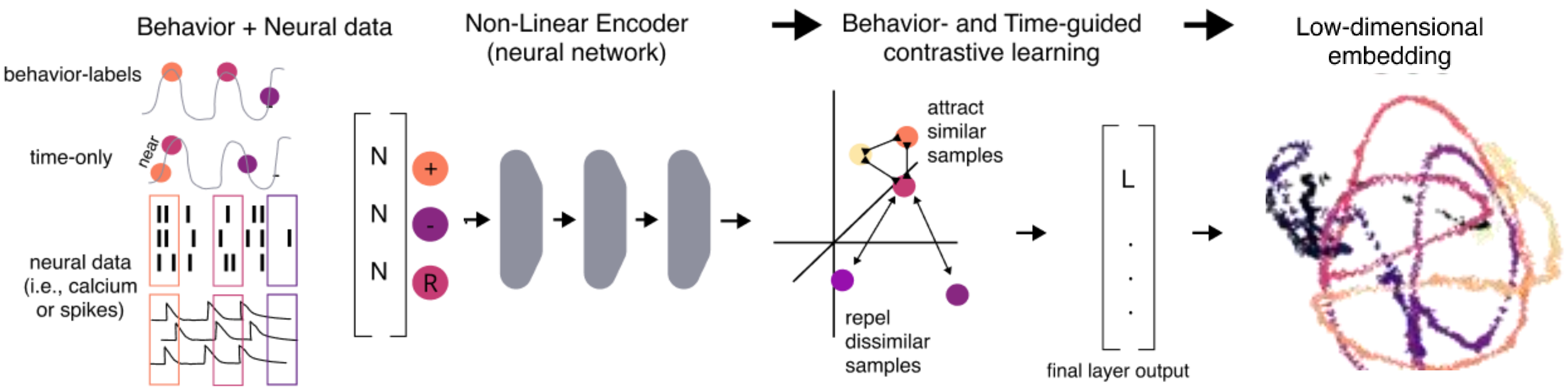
Caron et al 2021 arxiv

Emerging Properties in Self-Supervised Vision Transformers

Pre-trained DINO



Extract global visual features of the images

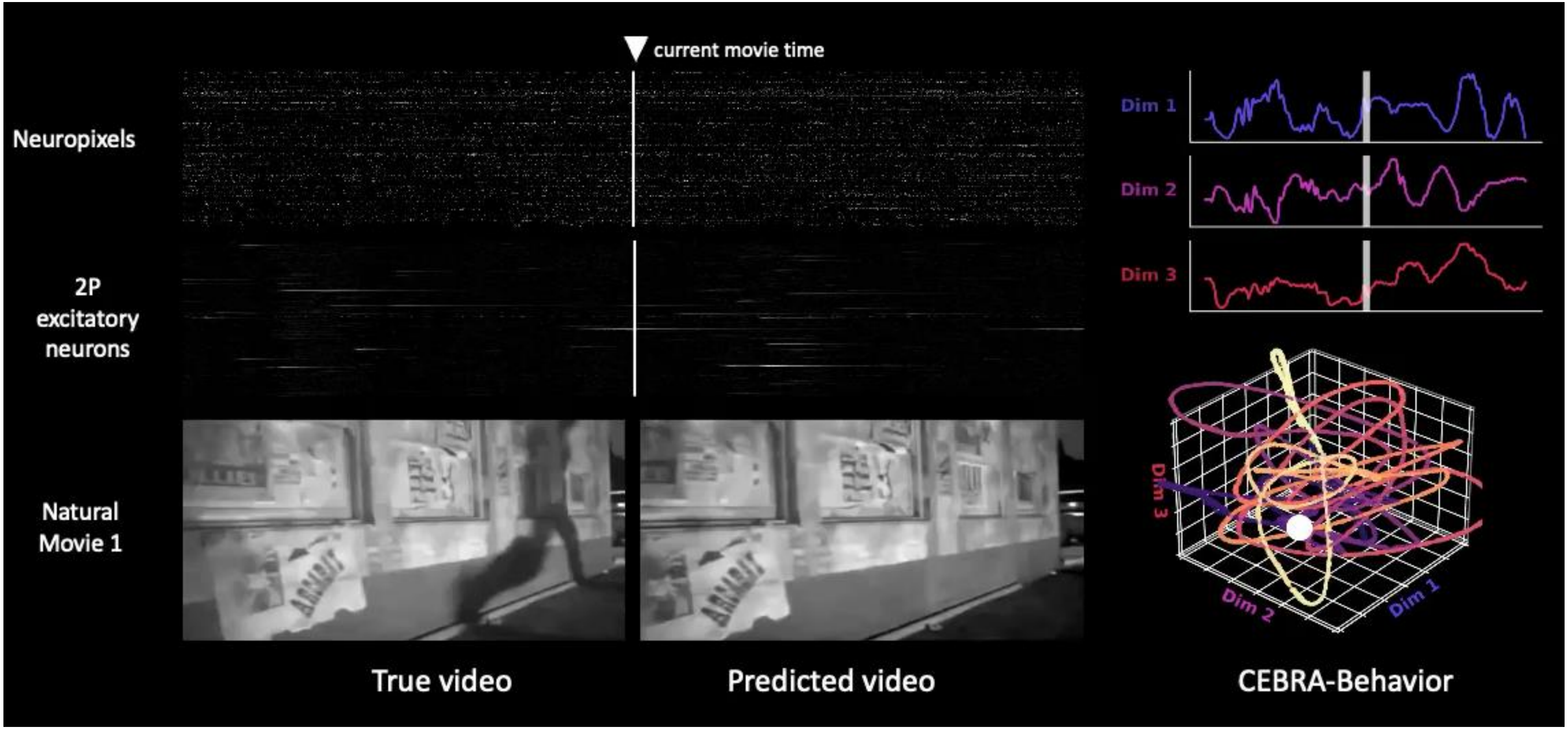


- Can we find evidence for movie-feature representations in V1 using CEBRA-Behavior, CEBRA-Time?

→ Can we decode the natural movie frames from the neural latent embeddings?

Schneider, Lee, Mathis Nature 2023

High performance decoding with CEBRA



Schneider, Lee, Mathis Nature 2023

Take homes: Unit 9

- How things change during injury or disease can tell you about what the circuit does (examples: memory, motor system changes)
- Many ways to stimulate neurons and see changes in behavior: 3 shown → electrical stimulation, optogenetics, and TMS
    - Electrical: Volta – driving all or none response, fast, can't control easily which neuron is stimulated
    - Optogenetics – light gated ion channel/pumps, can target precise neurons
    - TMS – non-invasive magnet stimulation used in humans; changes single cell activity, but targets large areas
- Genetic tools for model organisms (optogenetics, gene knock outs, calcium imaging)
- Computer vision for behavioral monitoring
- Computational neuroscience to link neural dynamics to behavior