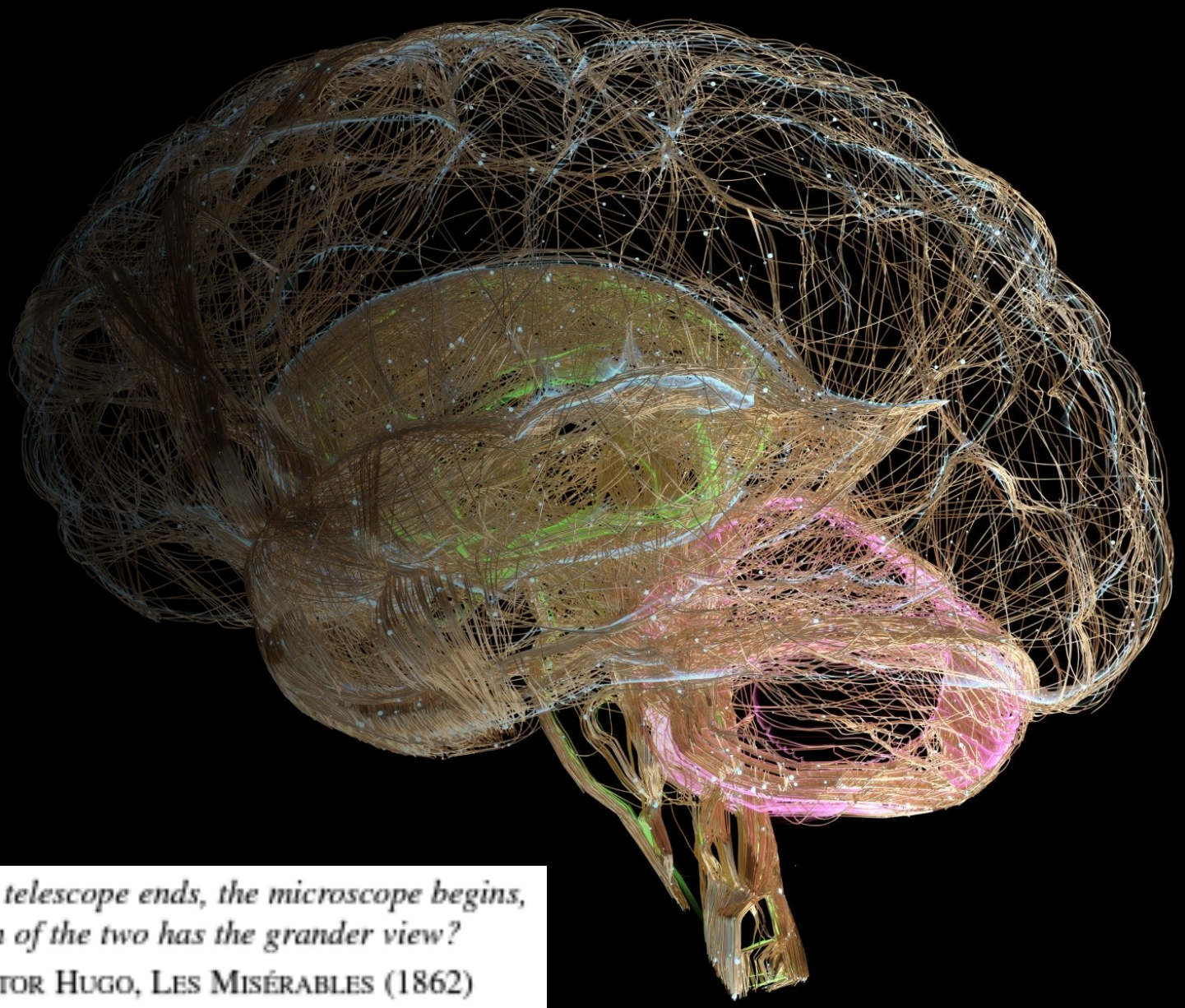
Voltage and calcium imaging of brain activity



Where the telescope ends, the microscope begins, which of the two has the grander view?

—Victor Hugo, Les Misérables (1862)

Calcium signaling basics:

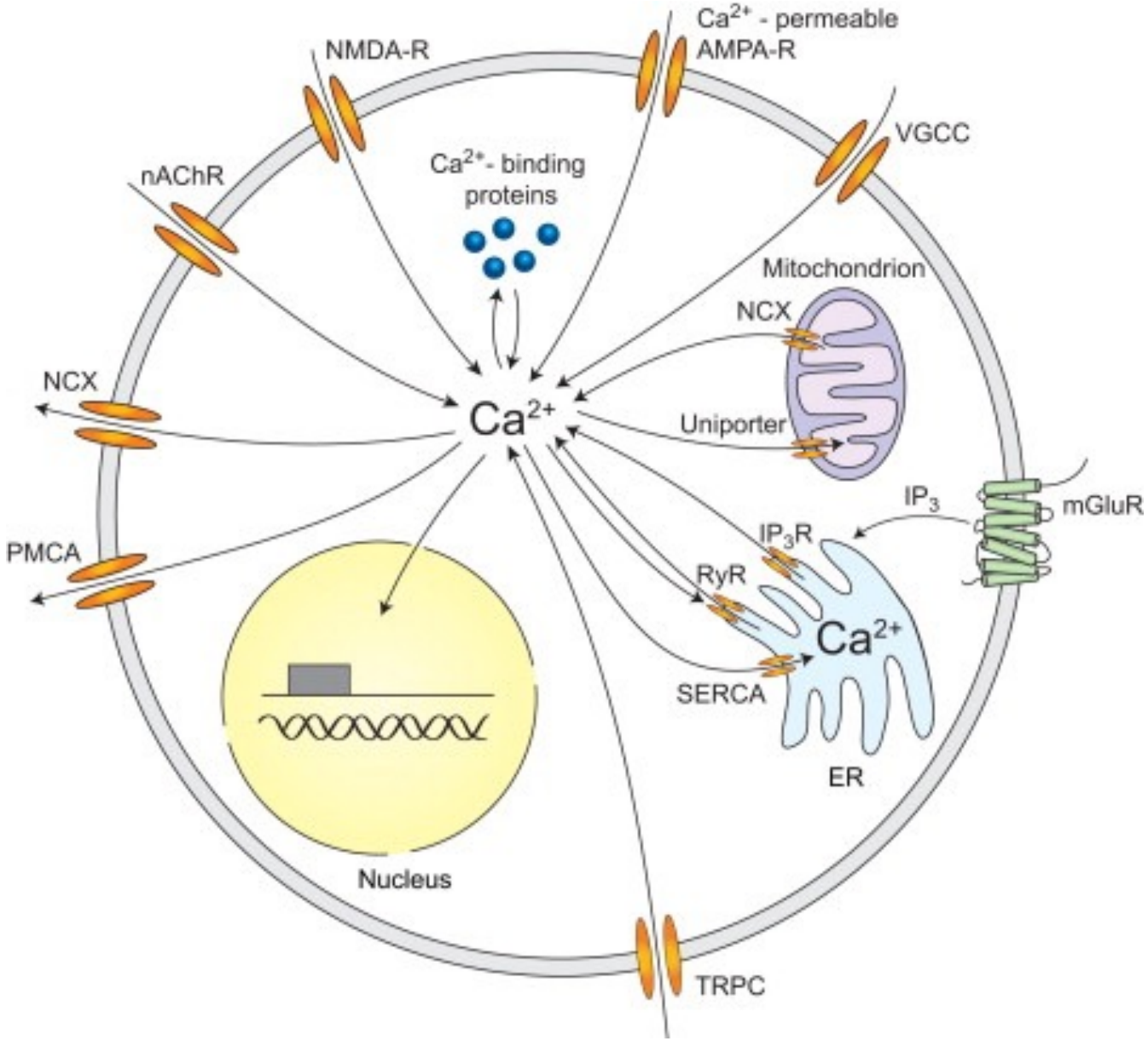
- Calcium ions (Ca2+) are vital for cell signaling.
- Sensor proteins bind to Ca2+ to relay signals.
- Ca2+ can bind in various shapes, unlike Mg2+

Neuronal calcium levels:

- At rest, neurons have low Ca2+ levels.
- Upon activation, Ca2+ levels can spike.

Calcium in cellular functions:

- Calcium signaling affects metabolism, gene transcription, and more.
- It is crucial for neuron-specific processes like synaptic transmission and memory formation.



C Grienberger, A Konnerth, 2012

How is Ca2+ important to neurons?

Neurotransmitter Release:

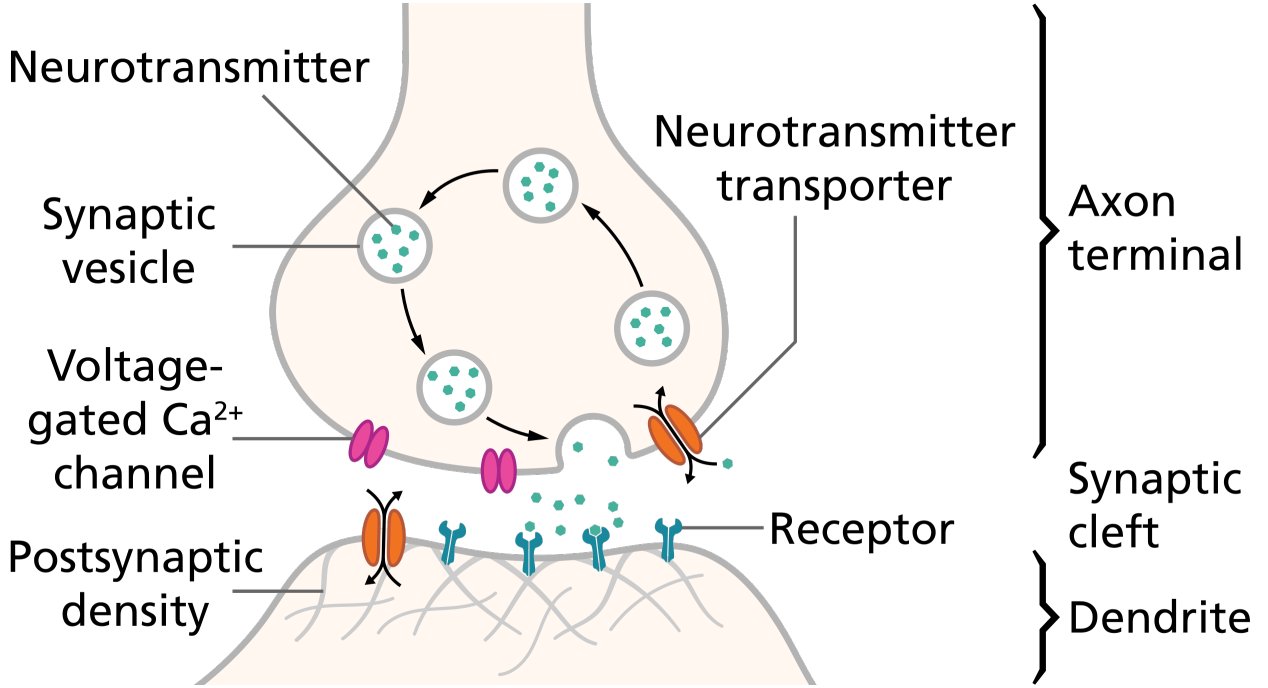
- Ca2+ enters neurons, prompting neurotransmitters to release into the synapse.
- Synaptotagmin senses Ca2+ to trigger this release.

Synaptic Plasticity:

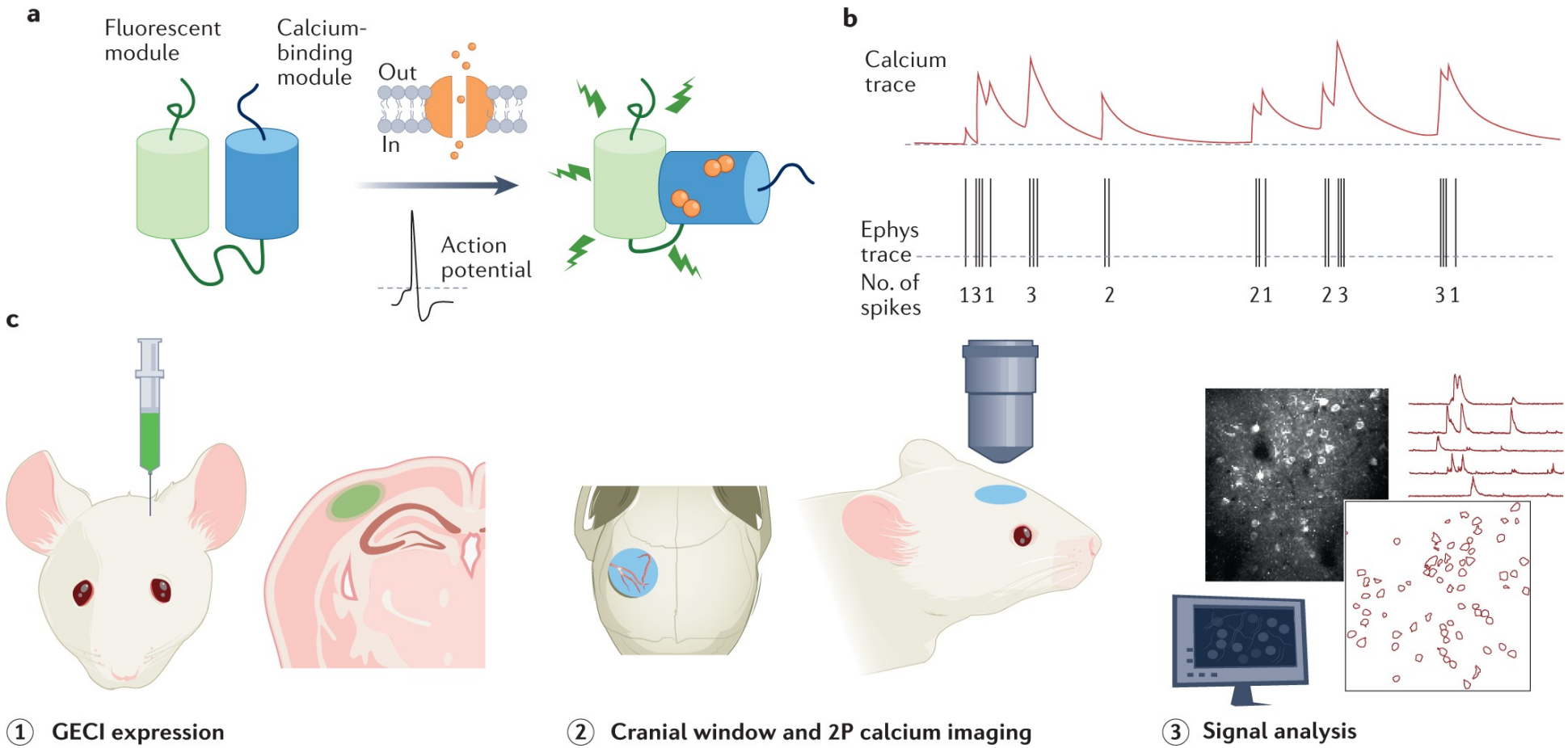
- **LTP:** Ca2+ strengthens synaptic connections.
- **LTD:** Ca2+ weakens synaptic connections.

Gene Regulation:

- Ca2+ travels to the nucleus to turn on genes affecting neuron function.



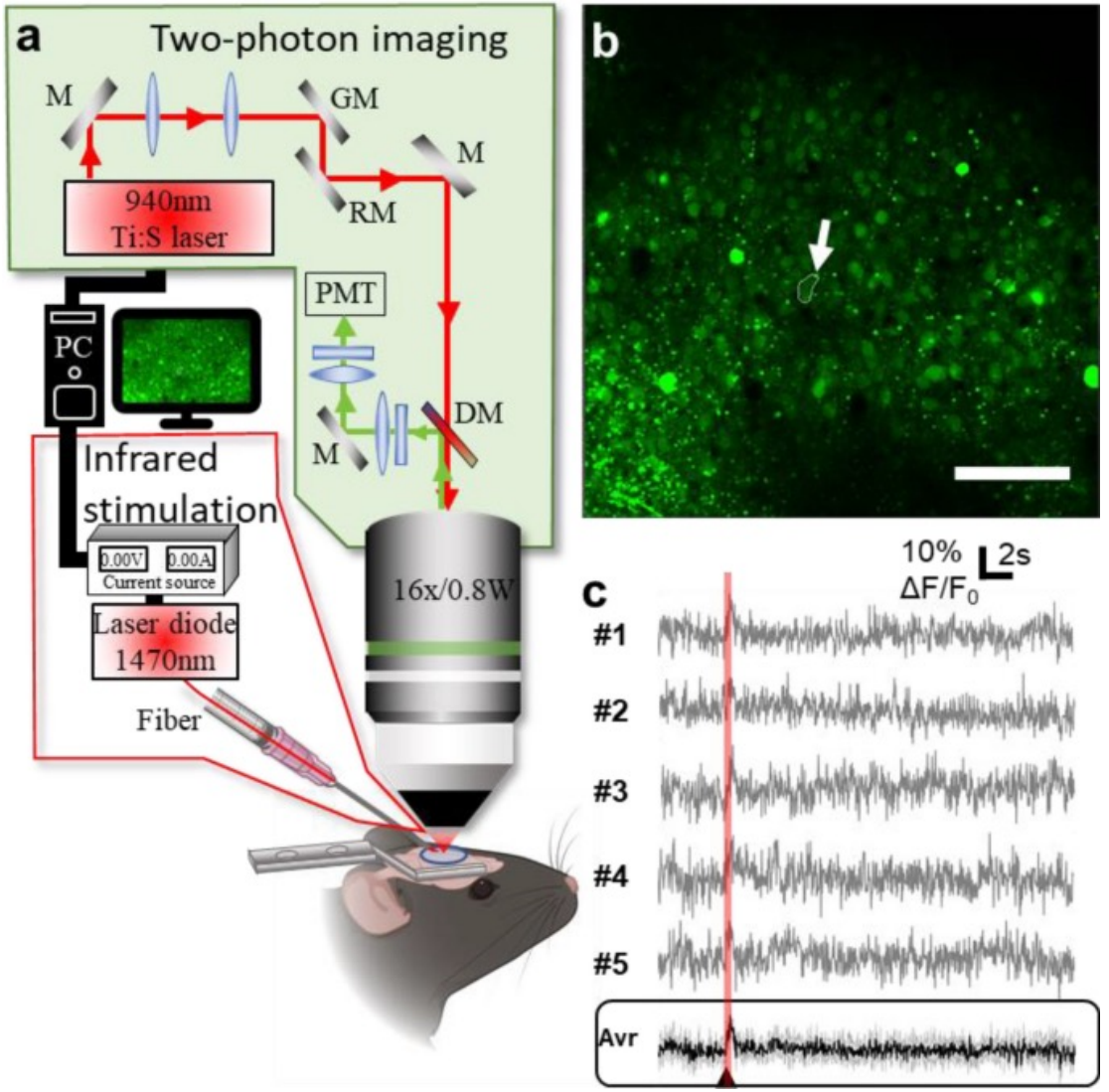
The principles of fluorescence calcium imaging



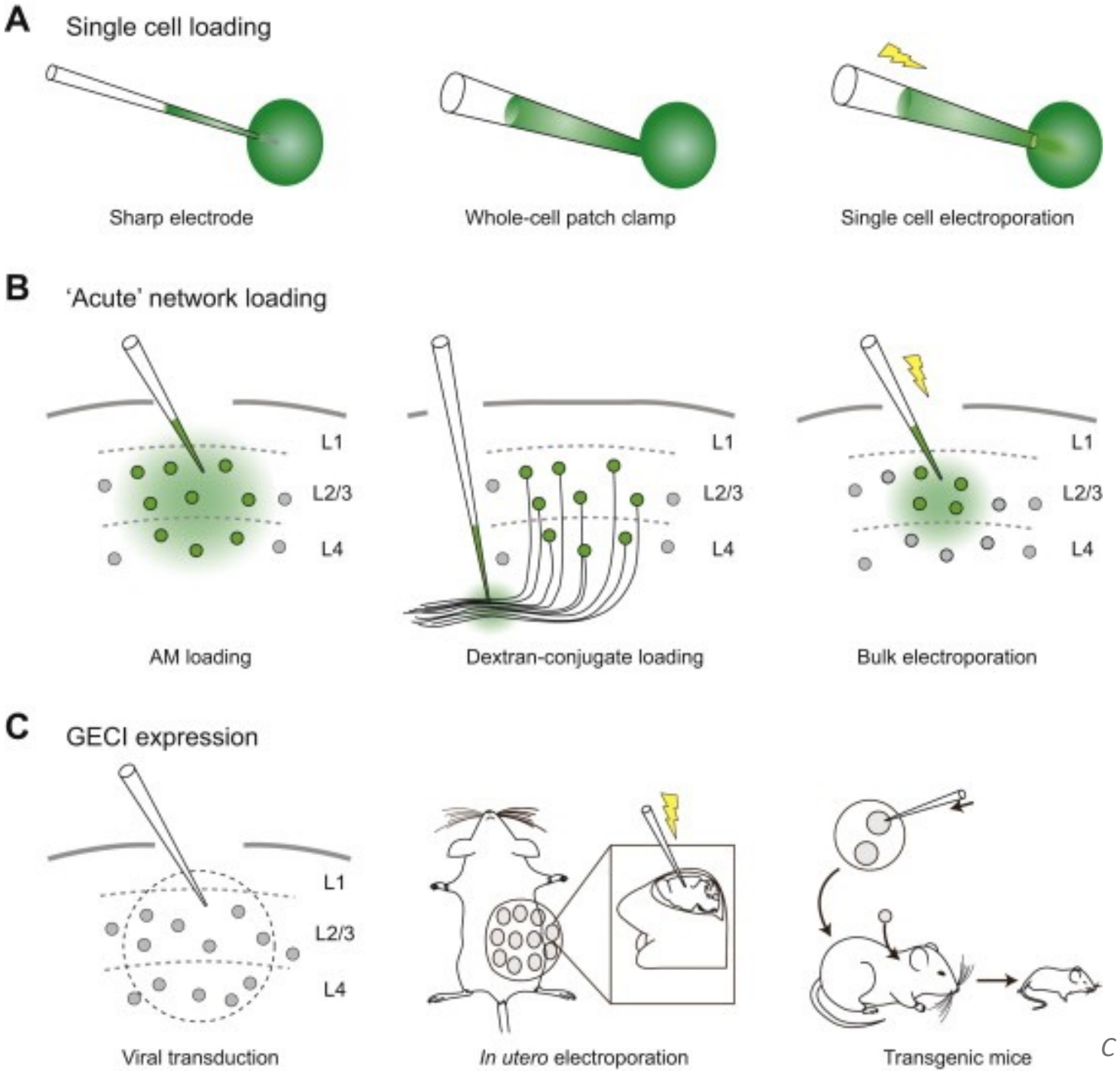
Grienberger et al., 2022

Advantages of two photon calcium imaging

- Minimal invasiveness
- Genetic targeting
- Subcellular and non-neuronal imaging
- Longitudinal studies
- Non-invasiveness
- Genetic specificity
- Subcellular resolution
- Long-term and wide-area imaging
- Cost-effectiveness
- Improved indicators
- Data processing
- Flexibility



Kaszas et al., 2021



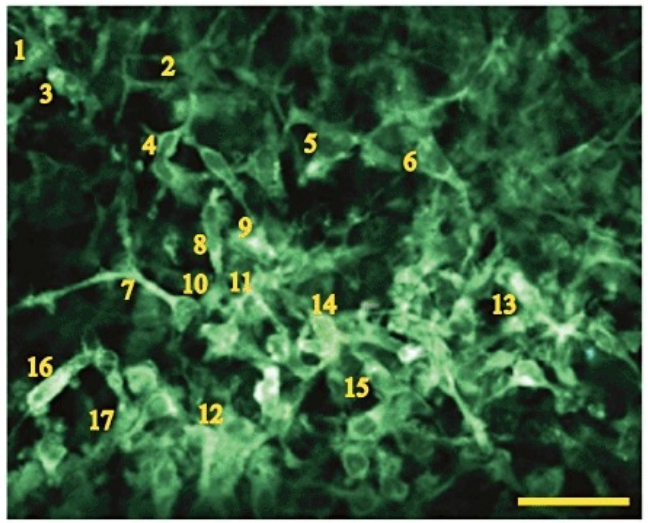
C Grienberger, A Konnerth, 2012

How do we measure optical calcium signaling?

C

D

E



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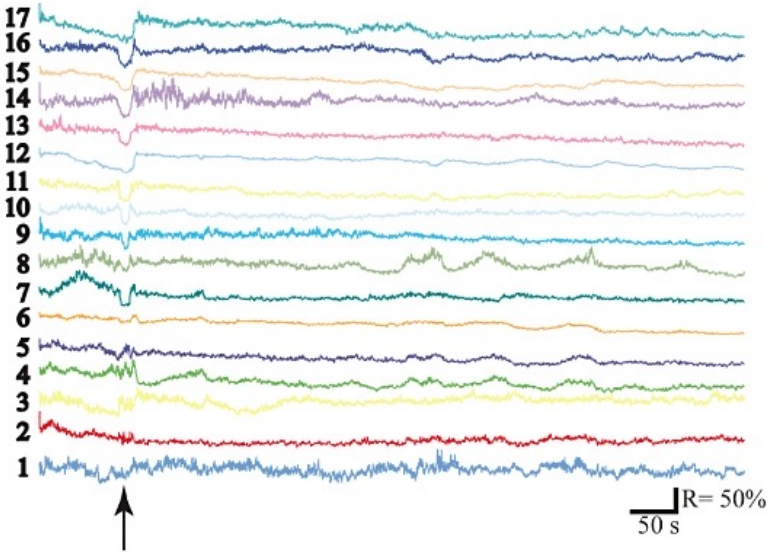

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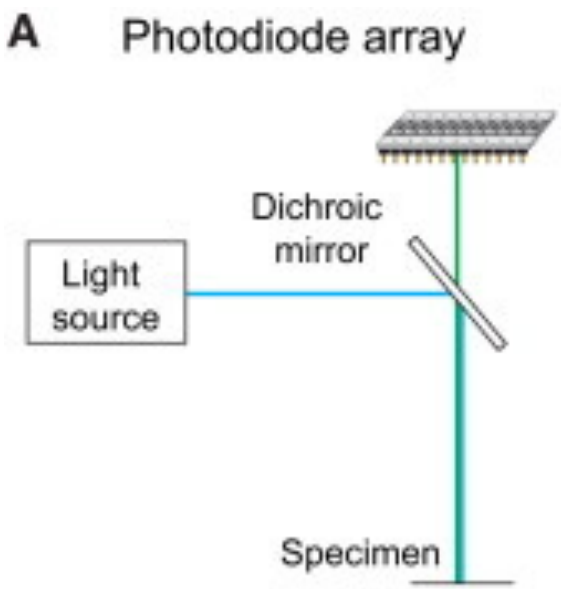
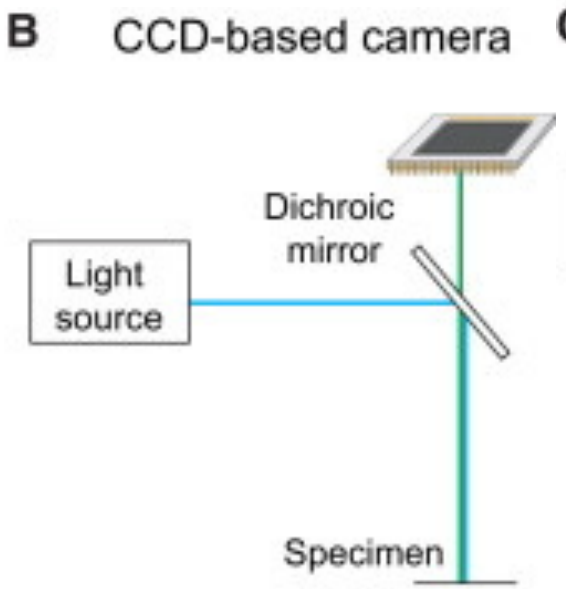
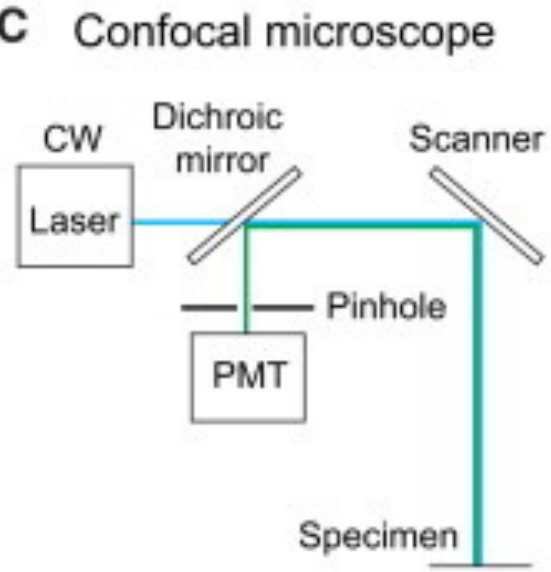


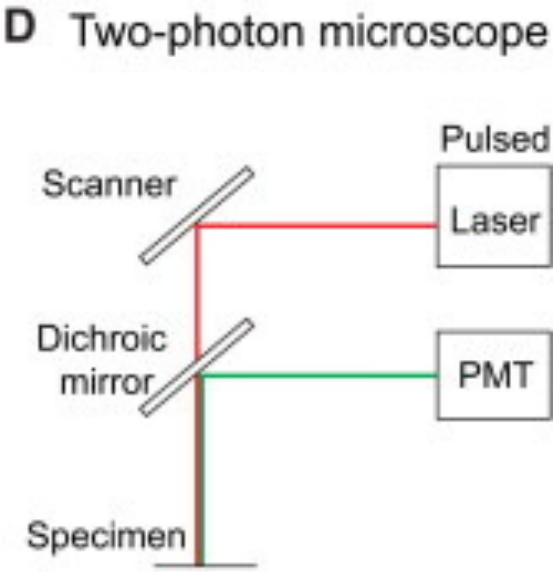
- **High dynamic range**
- **Low spatial resolution**



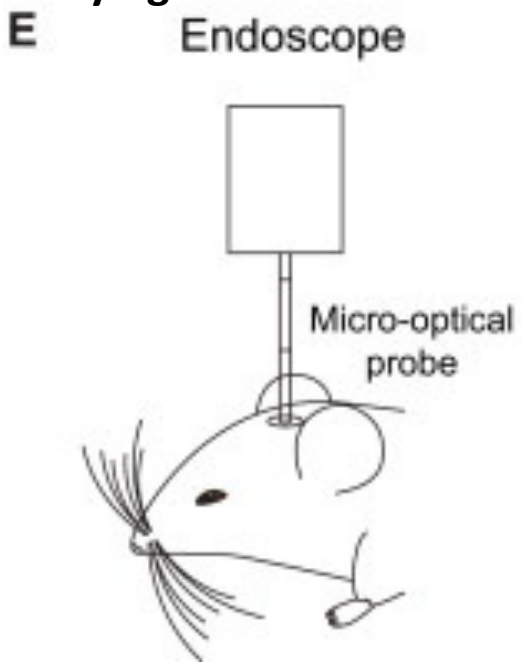
- **High spatio-temporal resolution**
- **Varying level of noise**



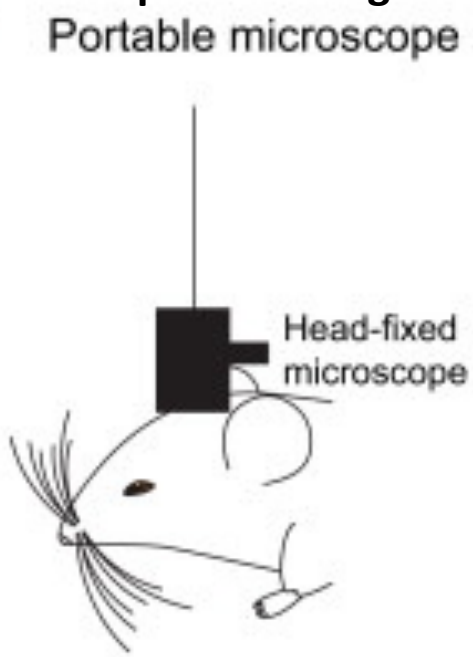
- **Pinhole for optical sectioning**
- **Risk of photodamage**



- **Deeper imaging**
- **Reduced background fluorescence**



- **Imaging in freely behaving animals**
- **Lower spatial resolution**



C Grienberger, A Konnerth, 2012

Dysregulation of Ca2+ signaling in the brain and neuronal degeneration

Huntington's Disease

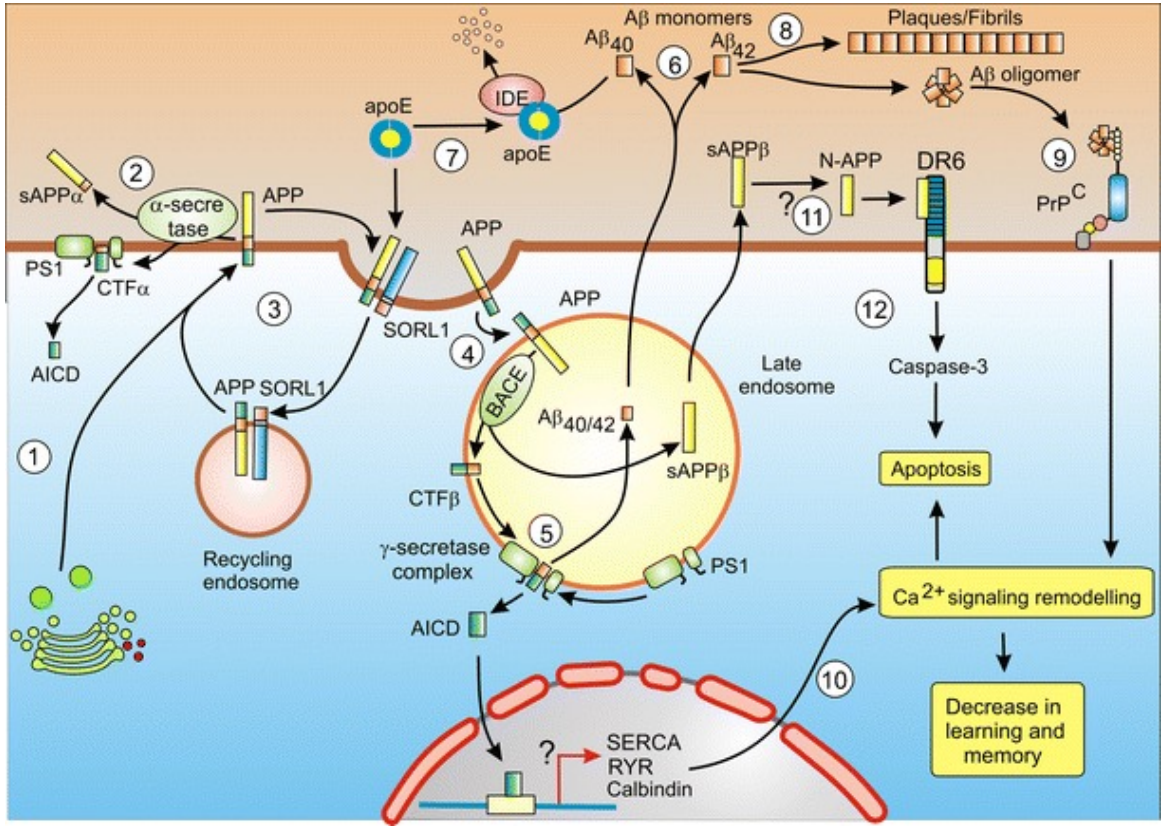
HD involves loss of striatal neurons and is associated with polyglutamine expansions in the huntingtin protein

Mutant huntingtin protein can result in proteolytic cleavage

Dysregulation of Ca^{2+} in HD may involve Ca^{2+} buffering proteins and channels, excitotoxicity, and mitochondrial Ca^{2+} handling defects.

Alzheimer's Disease

- The "calcium hypothesis" of AD suggests that dysregulation of Ca2+ release from the ER is involved in the pathogenic mechanisms, potentially through mutations in presenilin genes or amyloid metabolism.
- Mutations in presenilin genes may affect the expression and sensitivity of ER Ca2+ release channels



Parkinson's Disease

- Abnormal Ca2+ homeostasis in dopaminergic neurons
- Mutations in genes related to mitochondrial function and Ca2+ signaling are linked to PD, and aberrant Ca2+ signaling