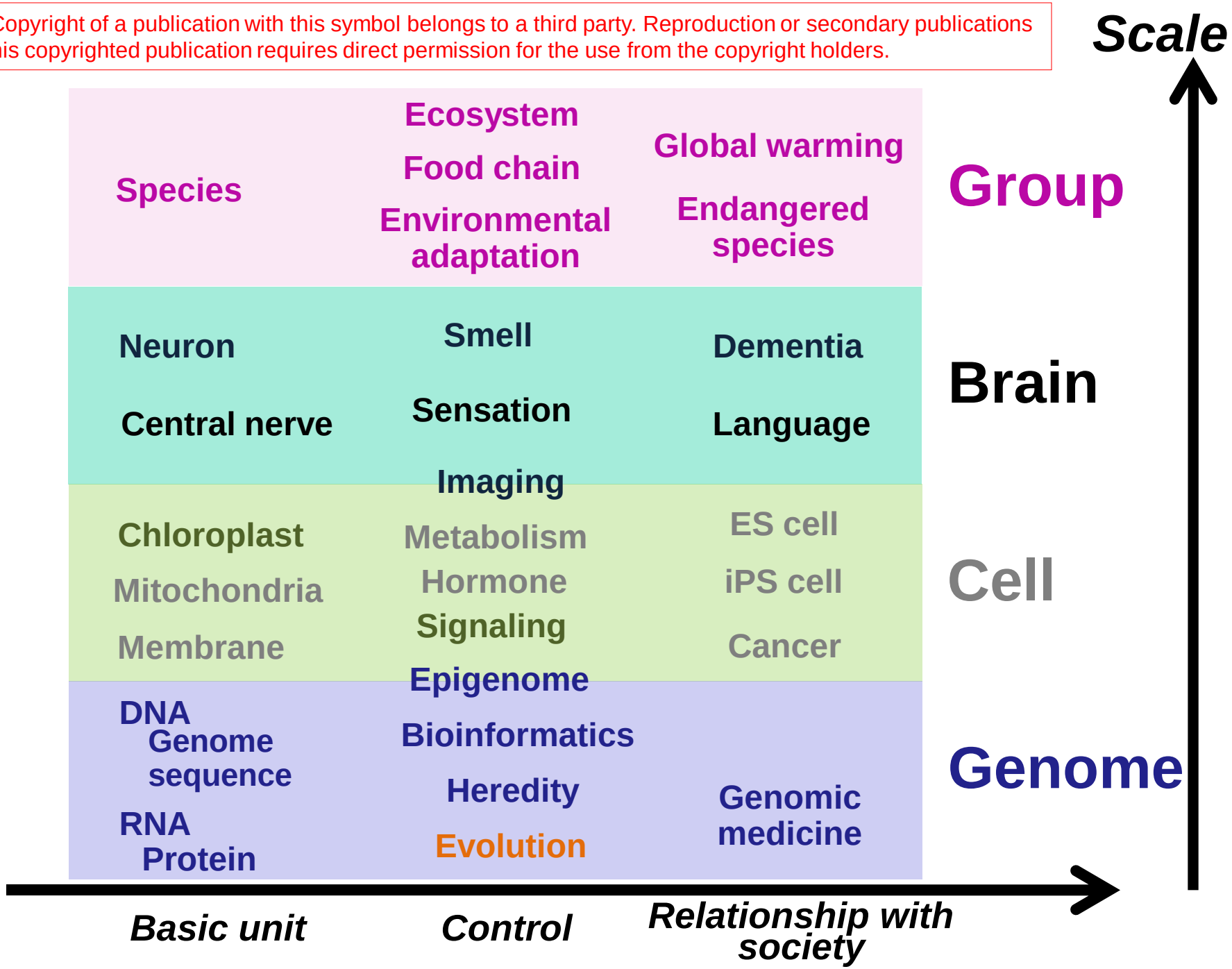
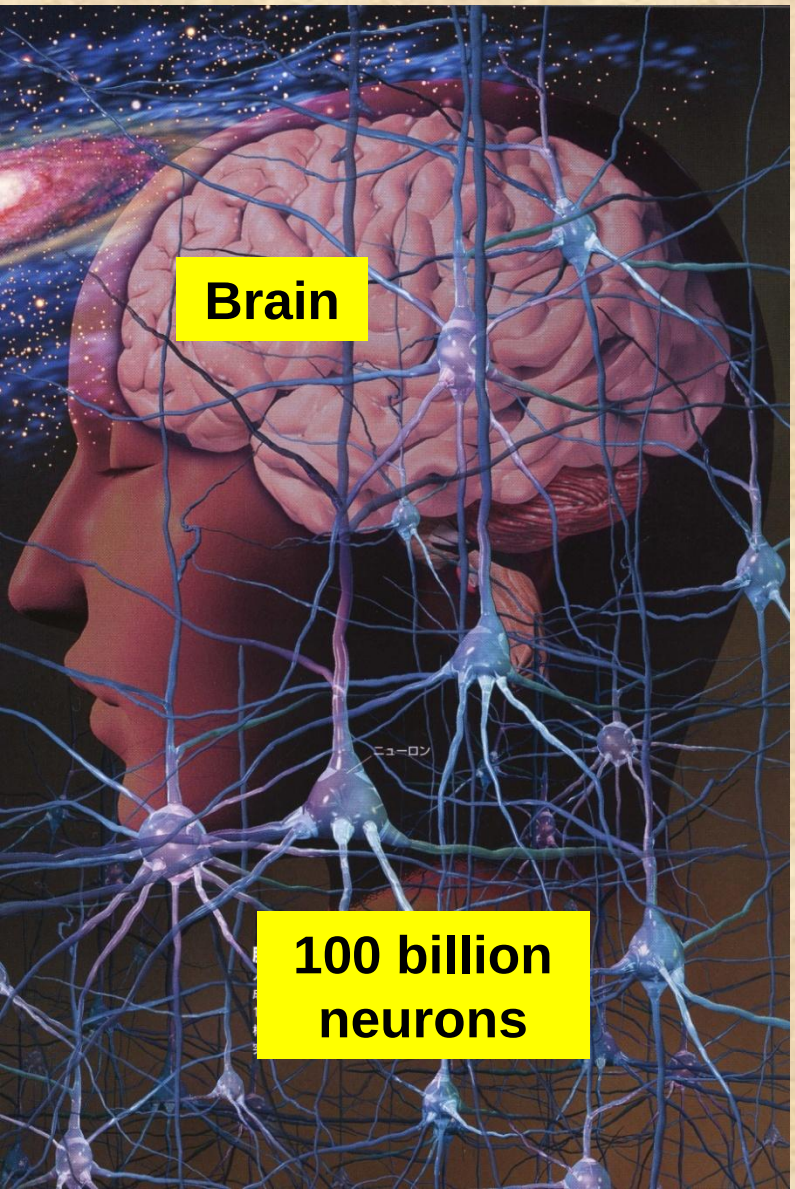


Higher Brain Function and Neuronal Activities

Print

Haruo Kasai hkasai@m.u-tokyo.ac.jp
Center for Disease Biology and Integrative Medicine, The University of Tokyo

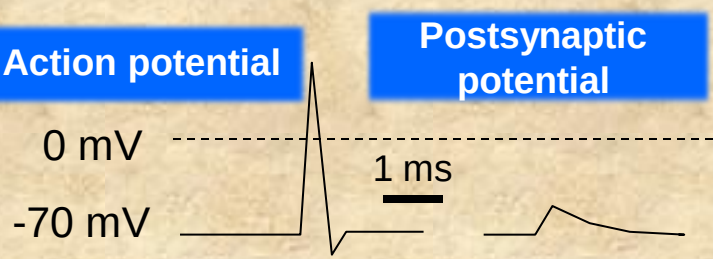
July 1, 2009



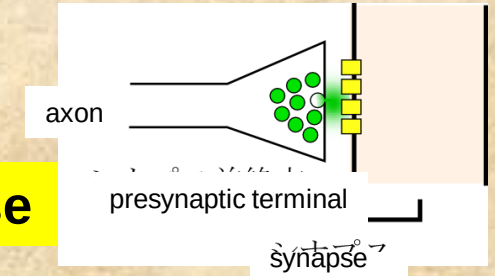
Brain activity

Action potential

Postsynaptic potential



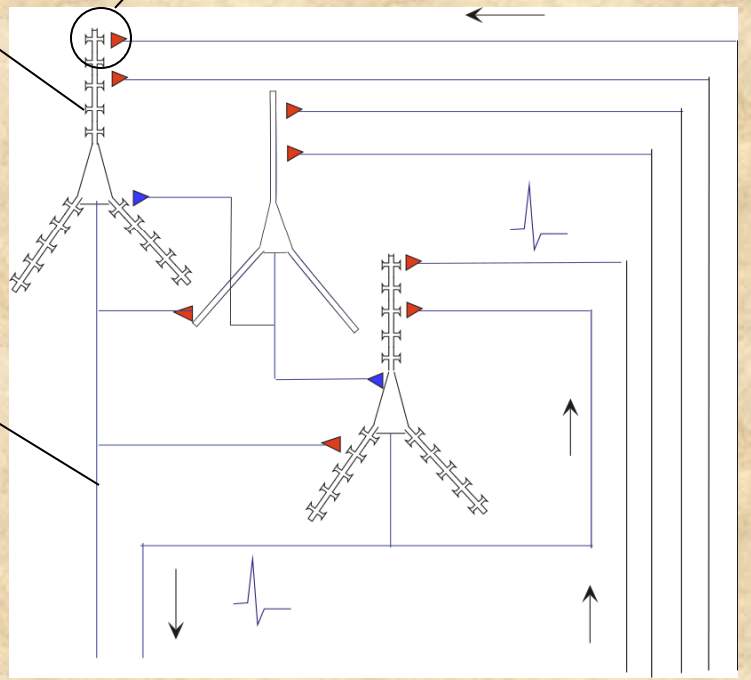
Connectionism



Dendrite

Synapse

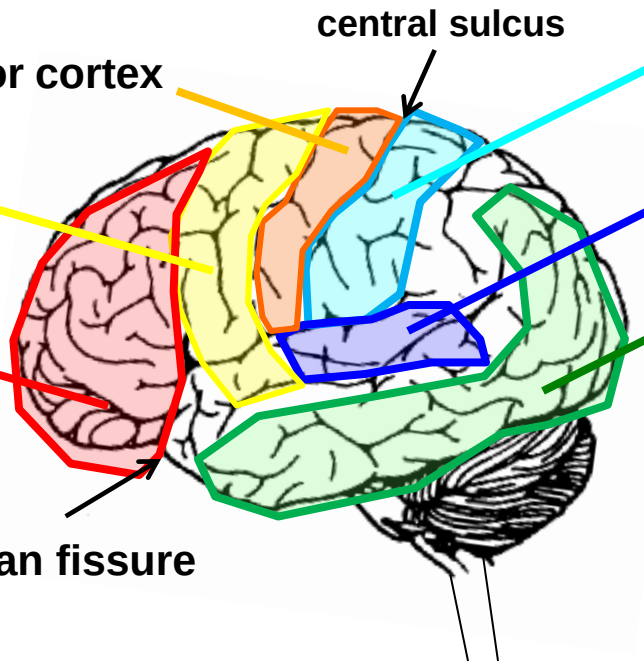
Axon



Localization of higher brain function

Print

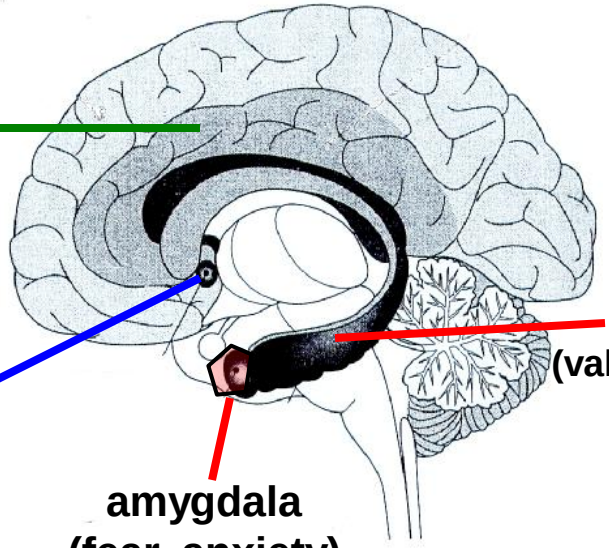
Cerebral neocortex



Intention

Perception

Limbic system



Emotion

Wilder Penfield's experiment (1954)

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Mystery of the Mind: A Critical Study of Consciousness and the Human Brain, Wilder Penfield
Princeton Univ Pr (1978)
p23 Figure3, Case M.M.

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Mystery of the Mind: A Critical Study of Consciousness and the Human Brain, Wilder Penfield
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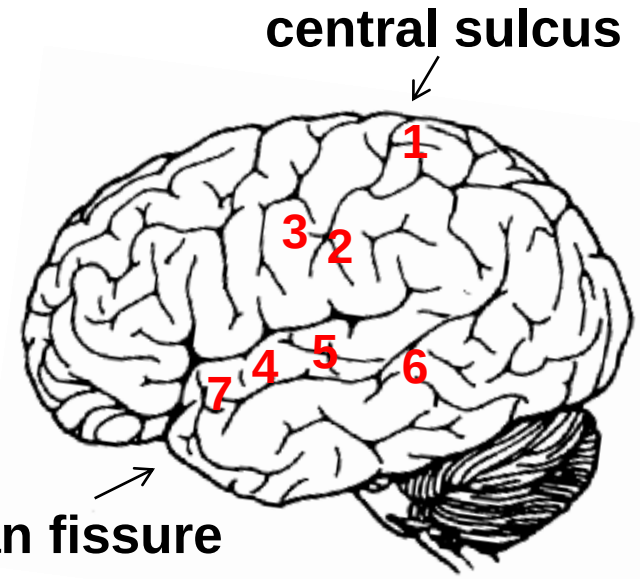
p24 Figure4, Case M.M.



1. Tactile sensation in the left thumb.
2. Tactile sensation in the tongue.
3. Motion of the tongue.
4. I hear a mother is calling a small child.
5. I hear a voice from somewhere near a river.
6. I first momentarily feel like I am in a familiar place and then feel that I can understand anything that will be happening in the immediate future.
7. Oh, this is a familiar scene that I always see when I have an attack. I can see many desks in some office. I am there and someone is calling me.

Biggest challenges in neuroscience (science of the mind)

Print

Higher brain function (=mind)

Functions localized to three regions (occipital-parietal lobe, frontal lobe, limbic cortex) of the cerebrum

Perception: vision, hearing, smell, taste, pain, balance, qualia (texture)

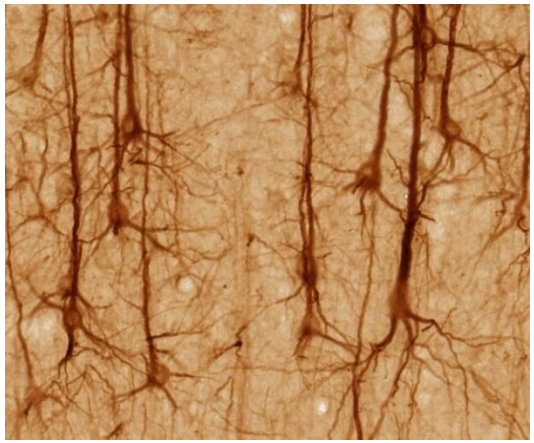
Intention: freedom, judgment, thinking

Emotion: pain, pleasure, love, hate, fear, anxiety, desire, anger

Functions found in all regions of the cerebrum

Memory, language, personality, intelligence, concentration, creativity, imagination

Scientific thinking, sense of beauty, religion, custom, sleep, laugh, philosophy, foul passion



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http://en.wikipedia.org/wiki/File:Smi32neuron.jpg

Higher brain function and subjective experience

A portion of higher brain function is accompanied by subjective experience (=awareness).

Numerous brain functions are highly computational but are not always accompanied by subjective experience.

Computational portions of brain function can be explained by connectionism.

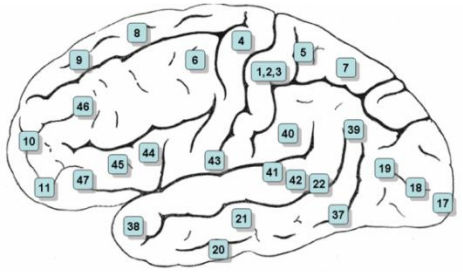
Subjective experience has higher information connection capability (binding) and activity.

These two characteristics are difficult to explain by connectionism.

Can a computer have a mind?

The electric properties of brain activity have been considered the absolute basis of explaining brain function, but other explanations are possible.

Functional localization of the brain indicates that physical states are responsible for subjective experience.



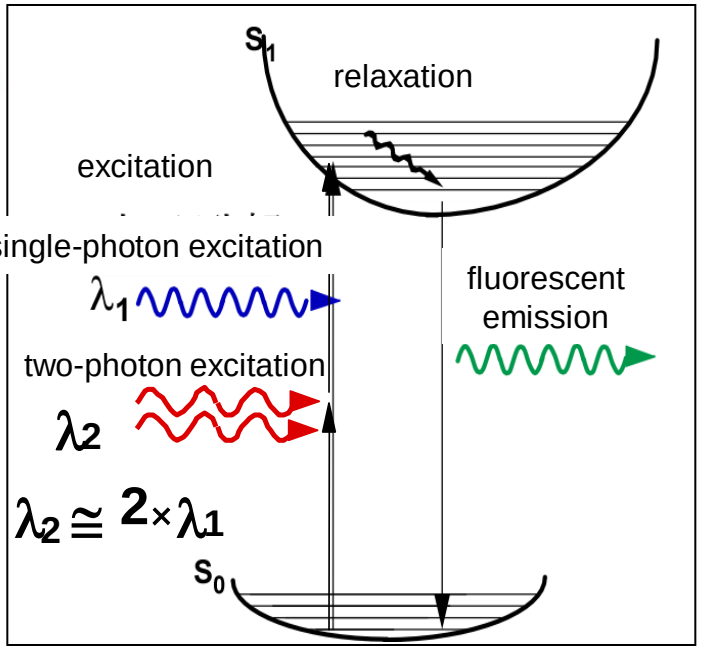
Brodmann's classification
Reproduced from Wikipedia
(July 7, 2009)
http://en.wikipedia.org/wiki/File:
Gray726-Brodman.png

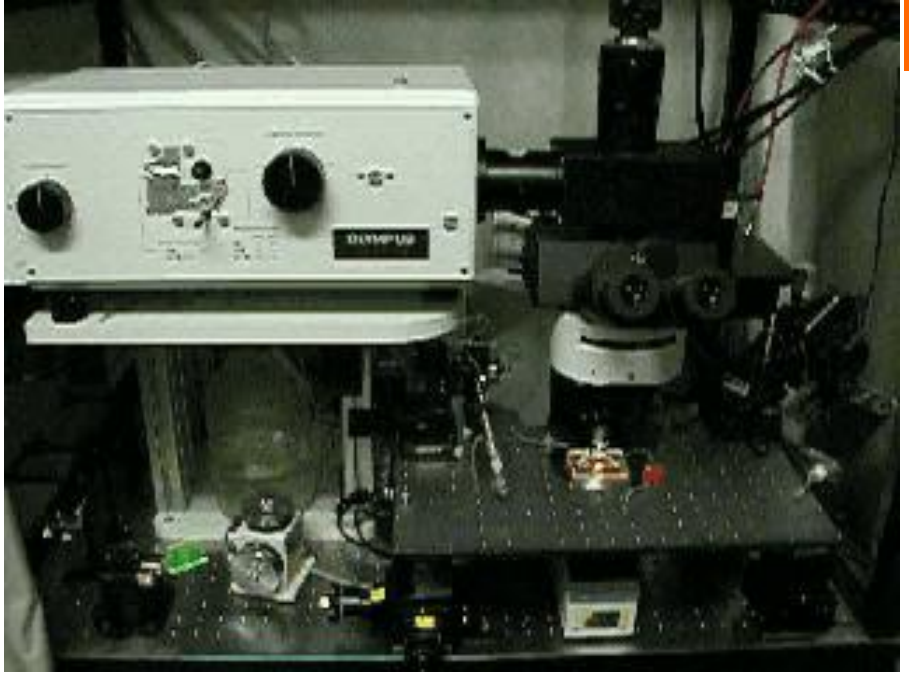
Goal:

To identify the physical state of brain that is undergoing subjective experience.

Two-photon microscope

Print





visible continuous light (laser)

t

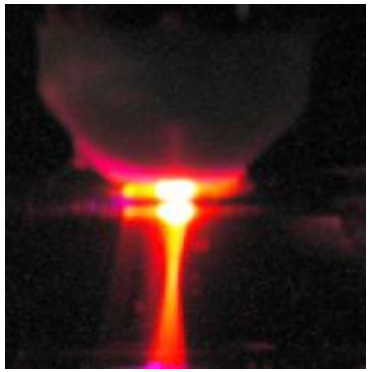
Near-infrared femto-second ultra-intense pulsed light (laser)

100 fs

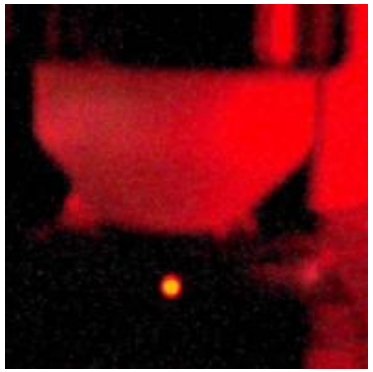
t

object lens

Sulforhodamine

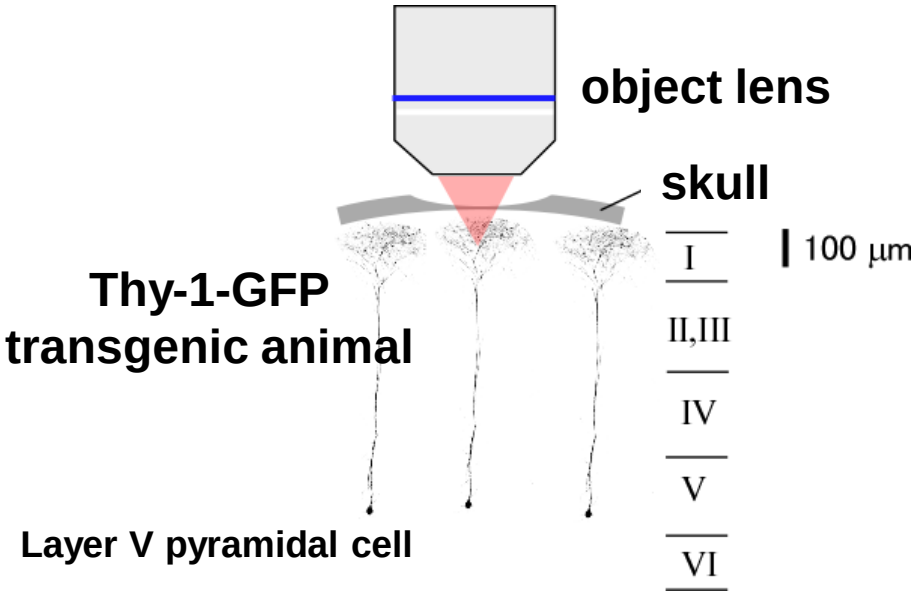


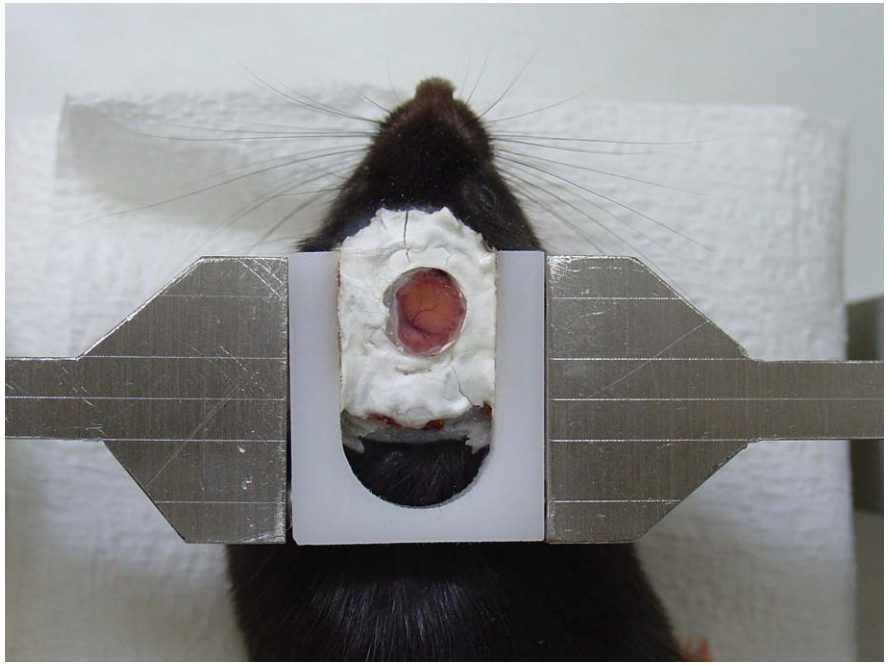
Single-photon excitation

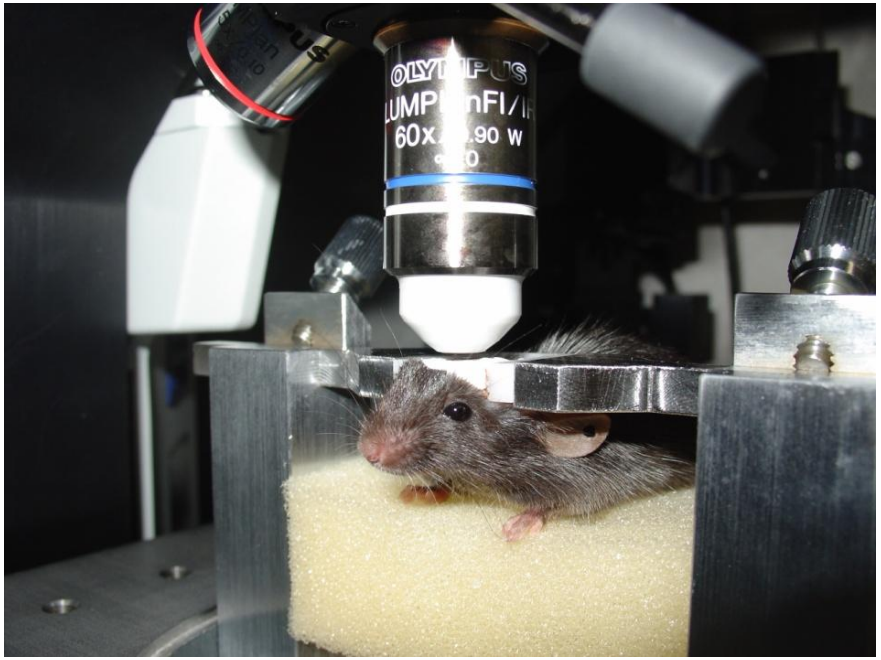


Two-photon excitation

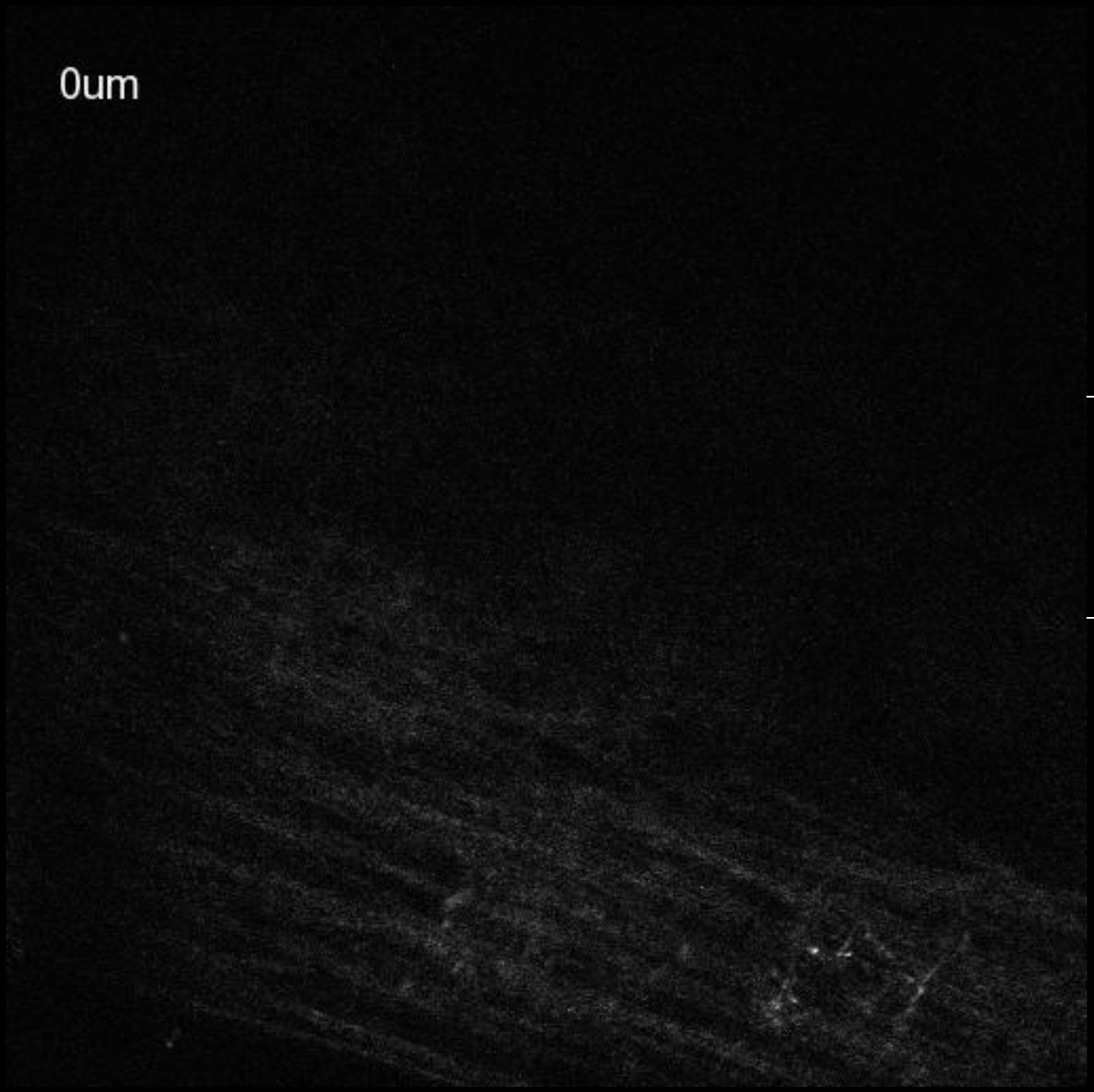
Examining interior of the brain using a two-photon microscope

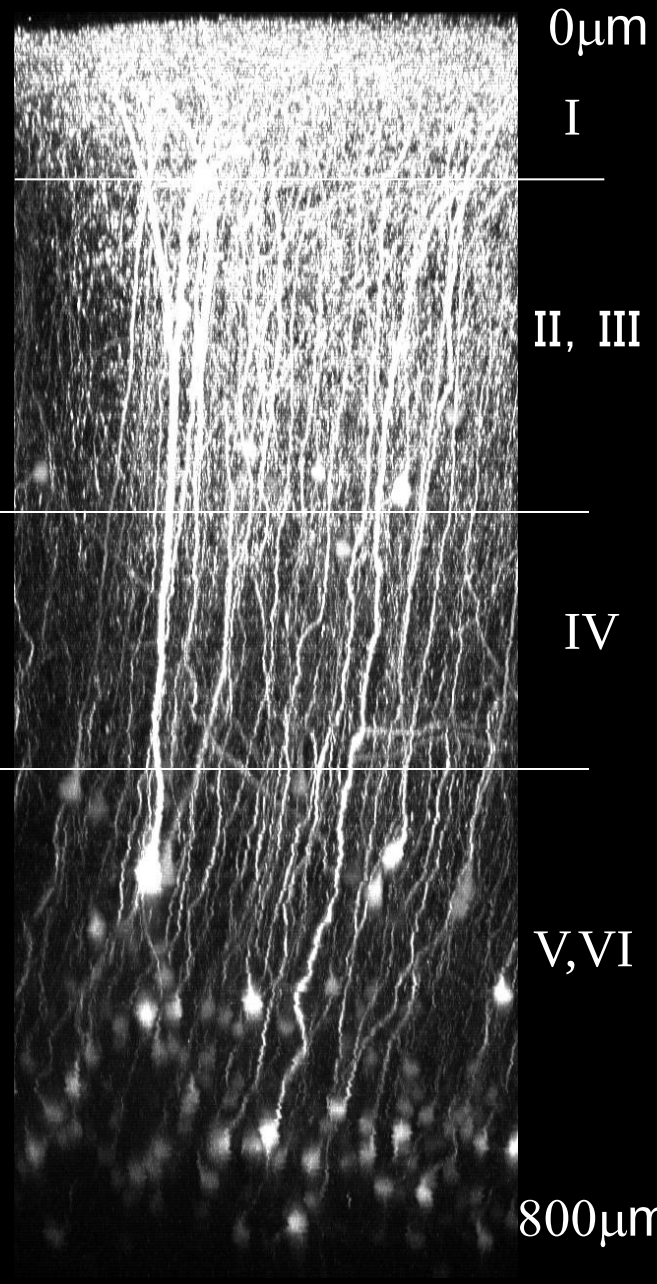


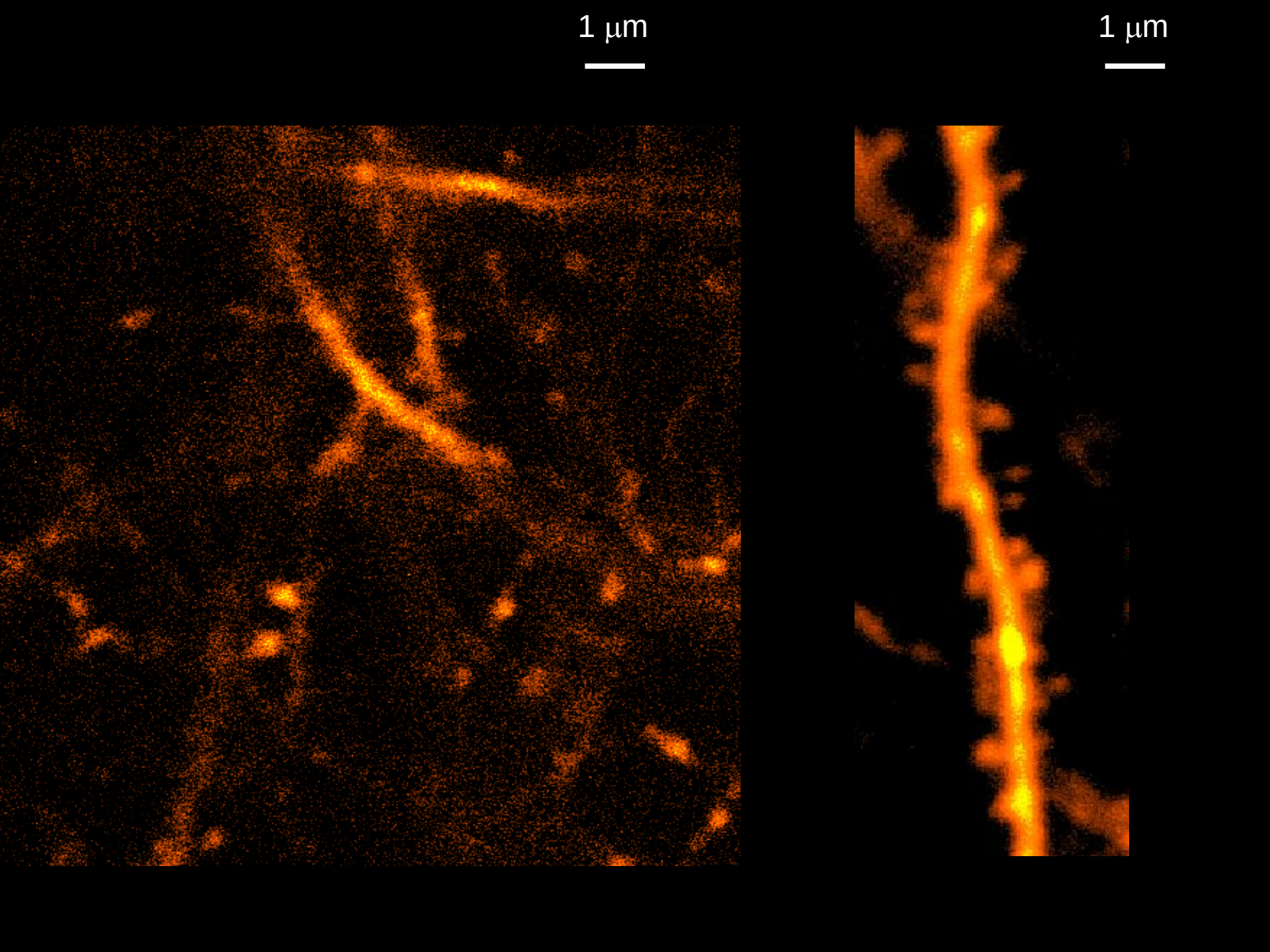




Thy-1-GFP transgenic animal

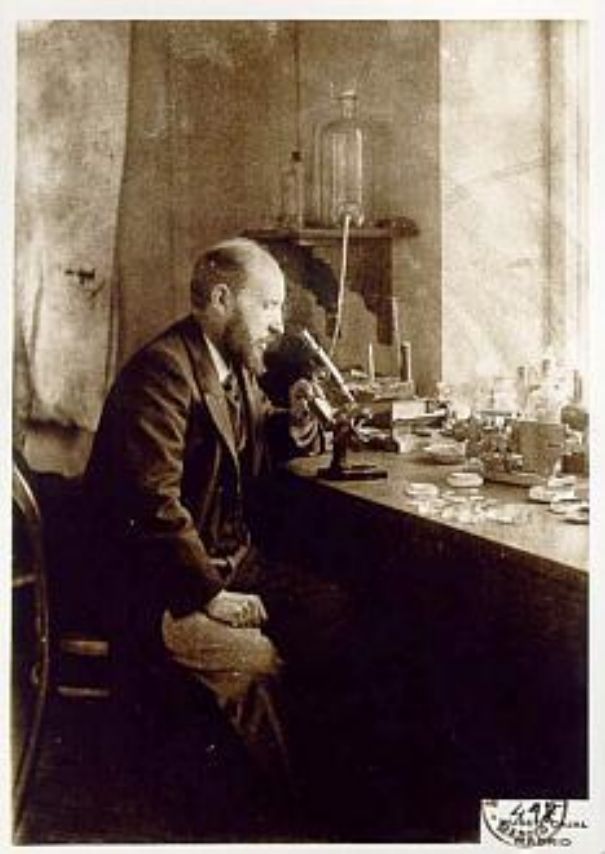





1 μm
1 μm

Santiago Ramón y Cajal (1852-1934)

Cerebral cortex pyramidal cell



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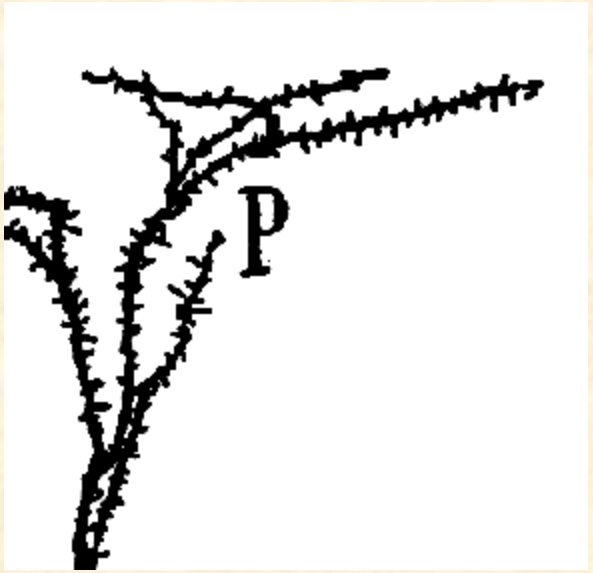
http://en.wikipedia.org/wiki/File:Cajal-mi.jpg

Dendritic spine



Pleomorphic

Cell-specific

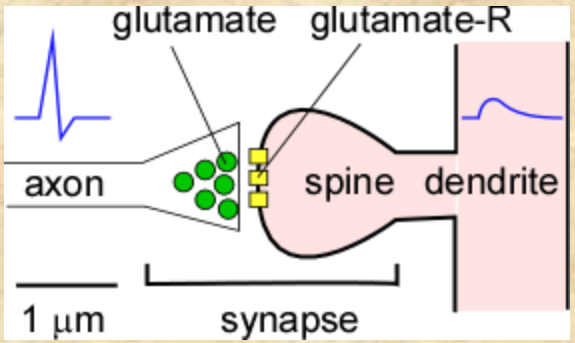
Unique to higher animal

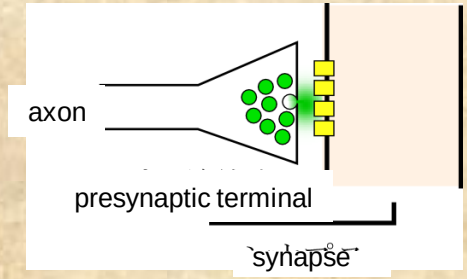
Properties of dendritic spines

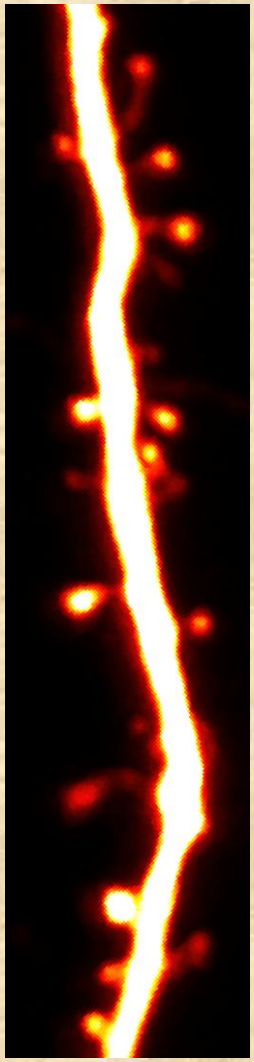
Print

1mm

1. Glutamatergic postsynaptic side
2. Cell-specificity—highly developed in three types of cells:
   - Cerebral cortex pyramidal cell
   - Basal ganglia medium spiny neuron
   - Cerebellar Purkinje cell
3. Rarely found in the spinal cord or in lower animals
4. Pleomorphic (brain, neck)
5. Have the largest number of actin filaments in neurons
6. Morphological defects have been reported in many neuropsychiatric disorders
   - Mental retardation: cognitive impairment determined by IQ







Normal

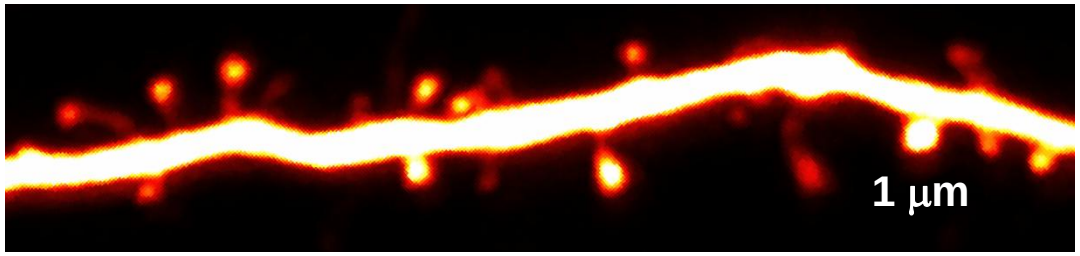
Fragile-X syndrome

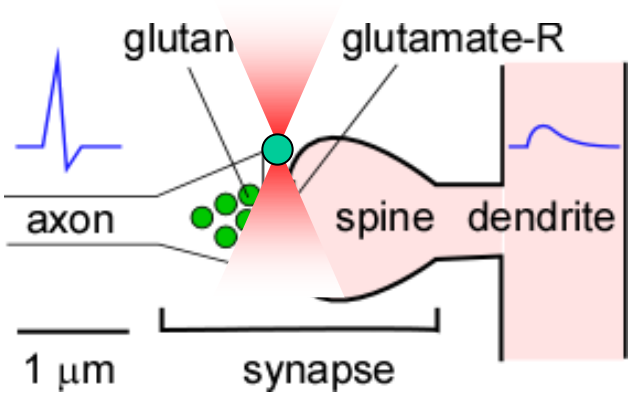
Mental retardation: anomaly in volumetric distribution of spines.

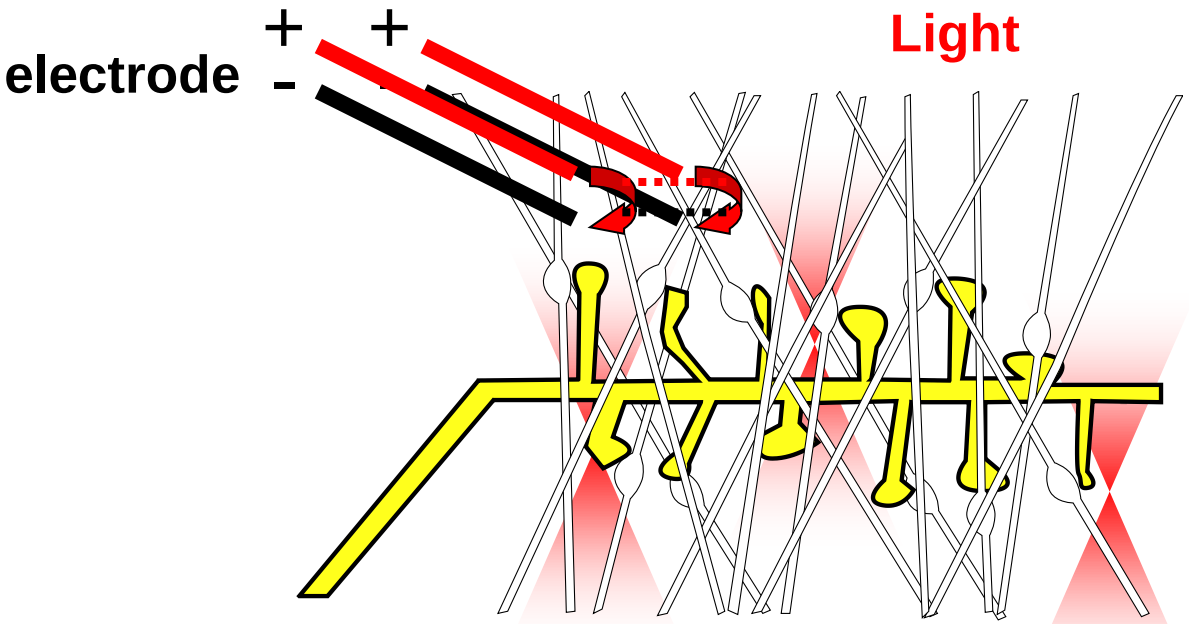
Other mental disorders: anomaly in the density of spines.

Spines hold the key to understanding cerebral functions.

20th century's techniques cannot stimulate a single spine. A new technique for this stimulation using light is being developed.

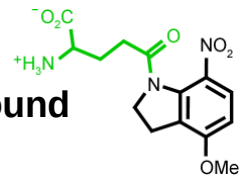




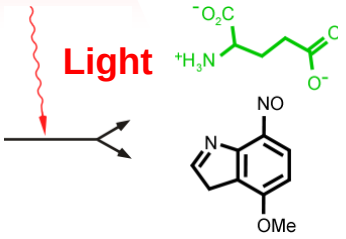


1997–1999

Caged-glutamate compound



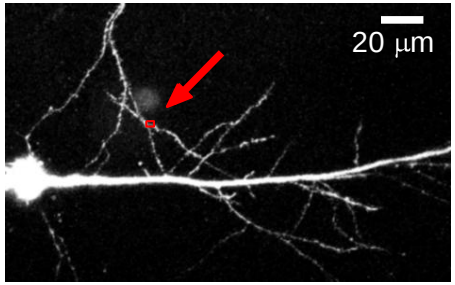
(MNI-glutamate)

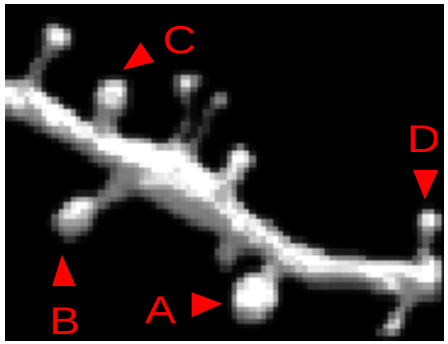


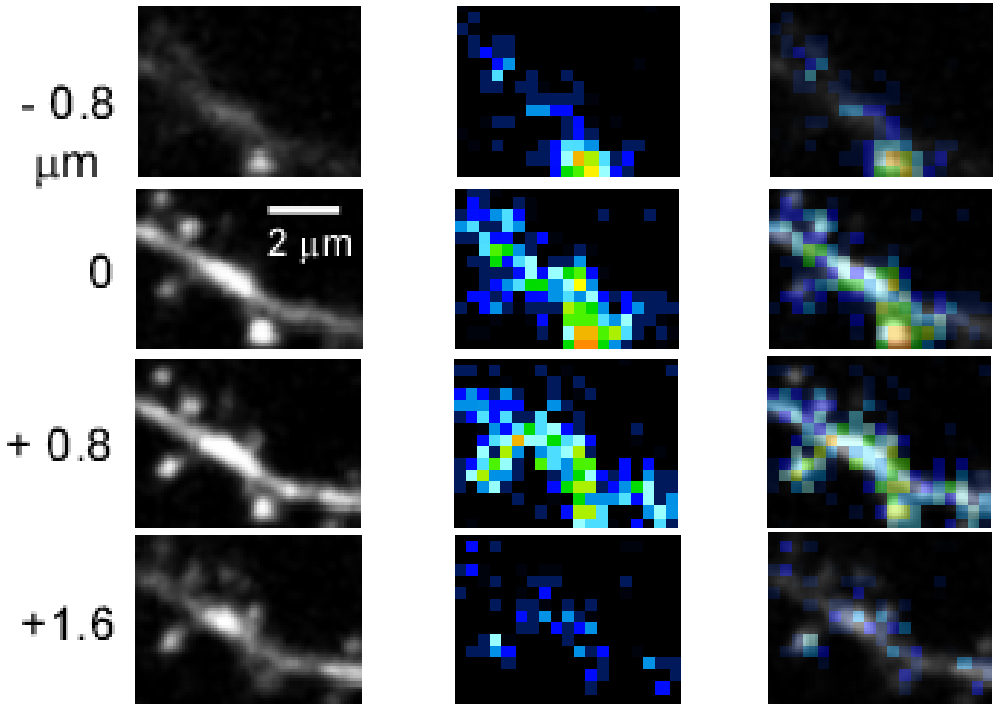
glutamate

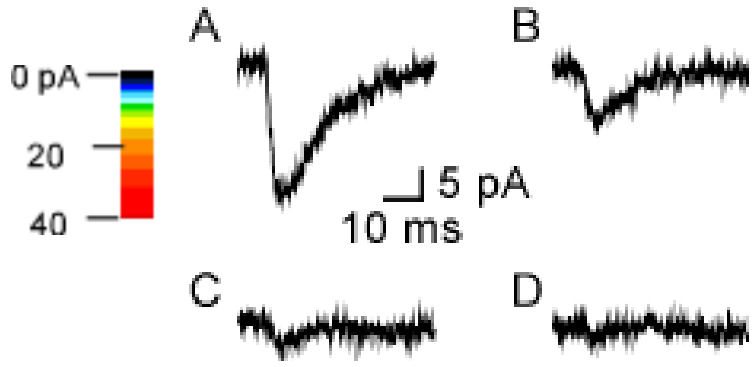
inert group

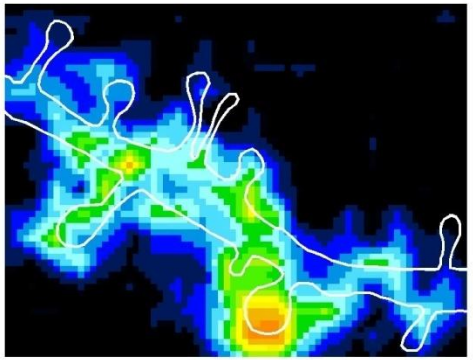
3D mapping of glutamate-susceptibility

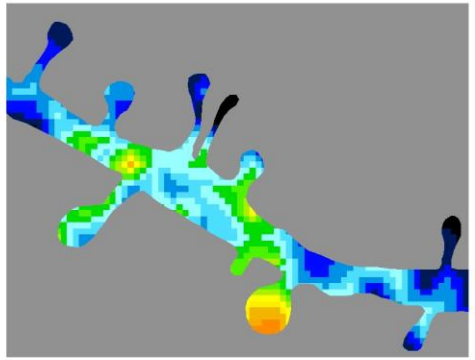












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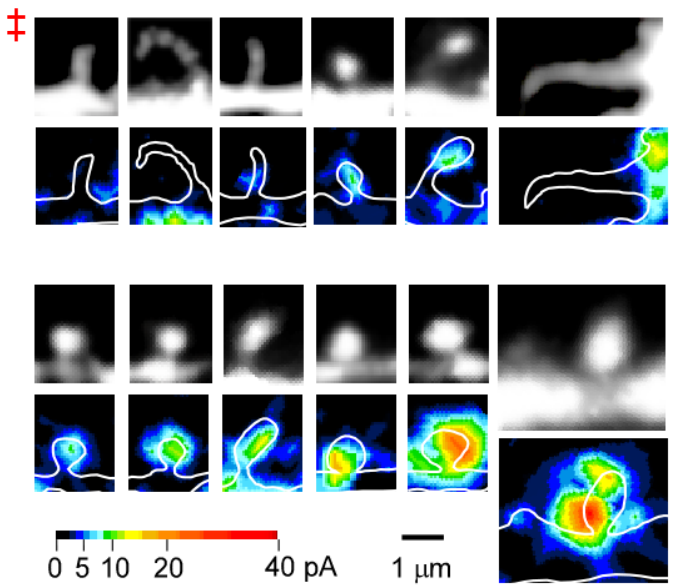
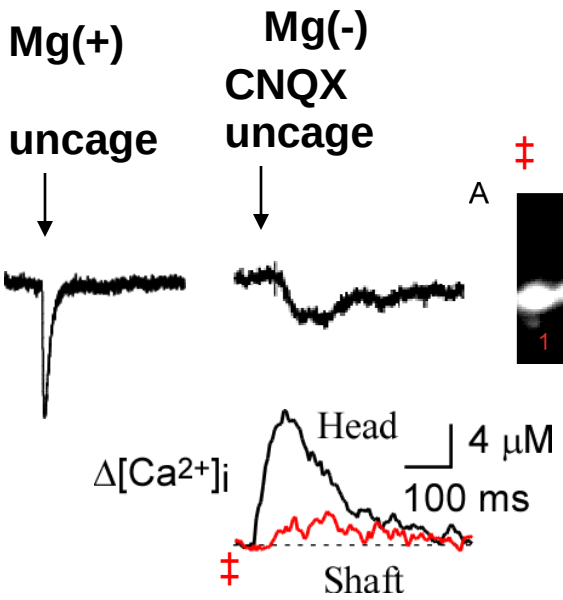
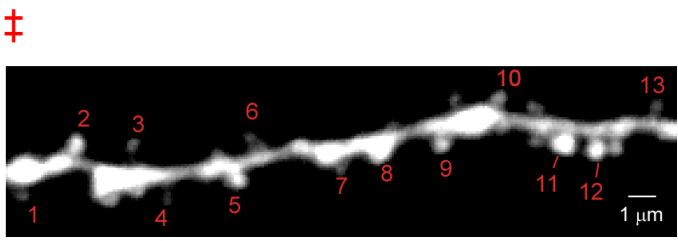
Functional expression of 2 types of glutamate receptors (AMPA receptor, NMDA receptor)

Print







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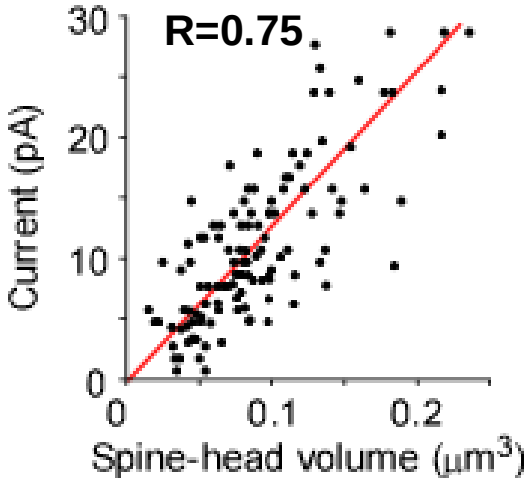
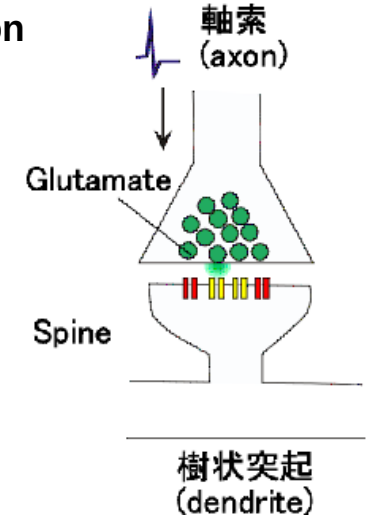
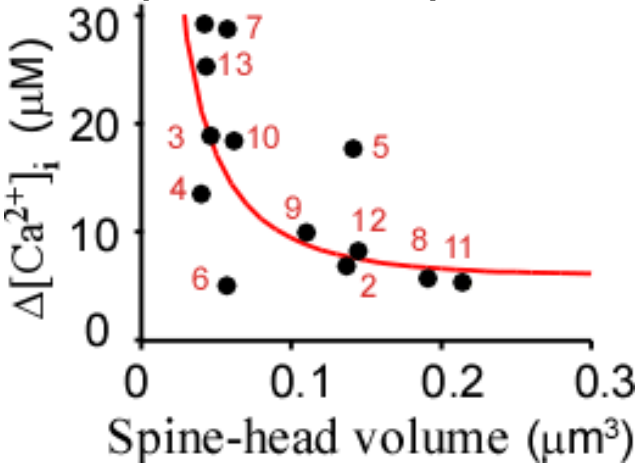
AMPA
Expression of receptor function





NMDA
Expression of receptor function



Discovery of fast volume increases specific to stimulated spines (2004)

GFP-expressing cells

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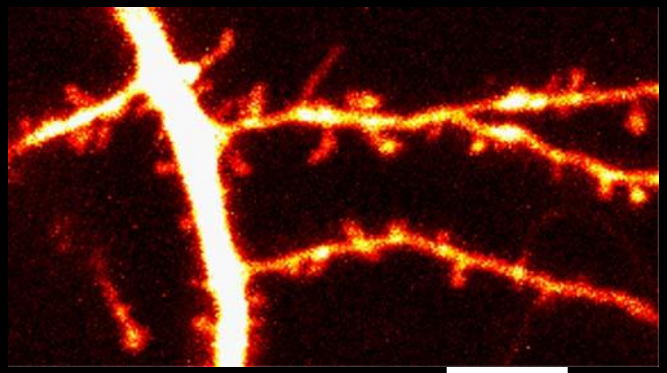
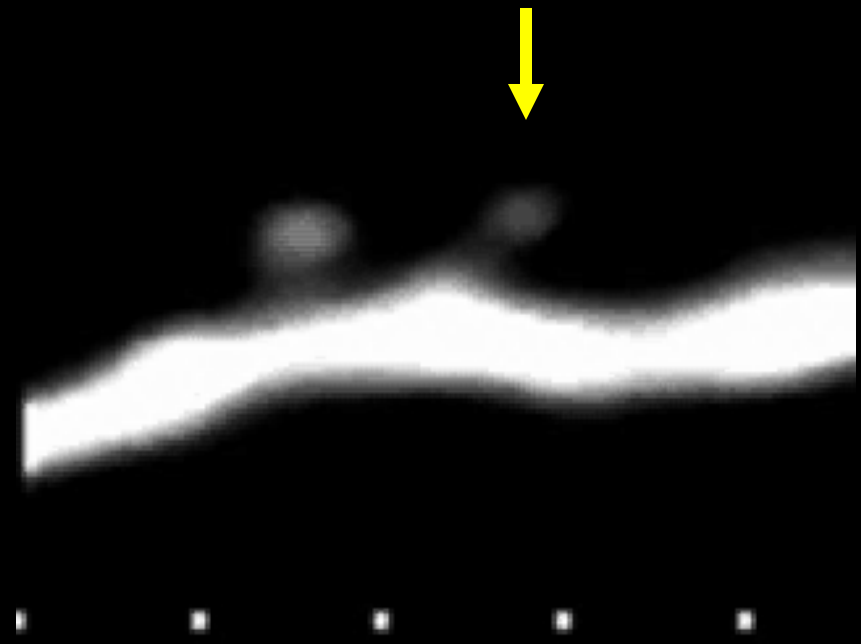
100 mm



4 mm

0 Mg, 1Hz, 60 times



1 mm

0 30 60 90 120 min

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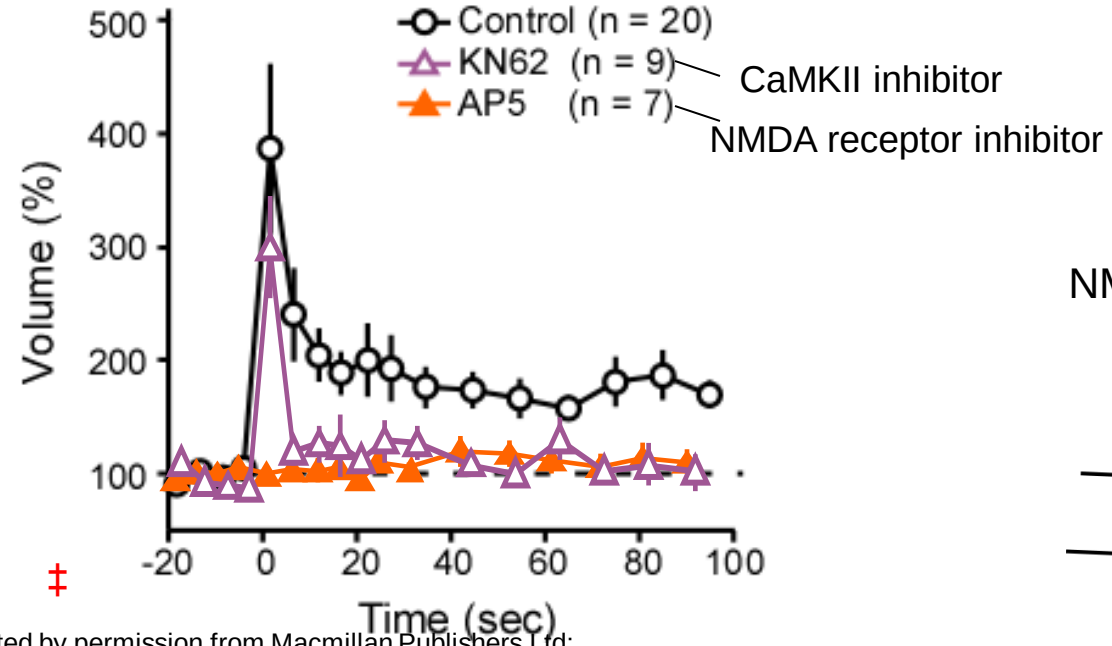
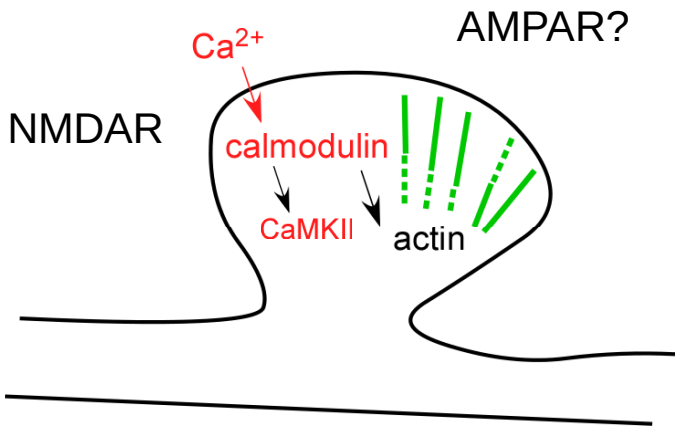
Mechanisms of fast and slow enlargement of the spine-head

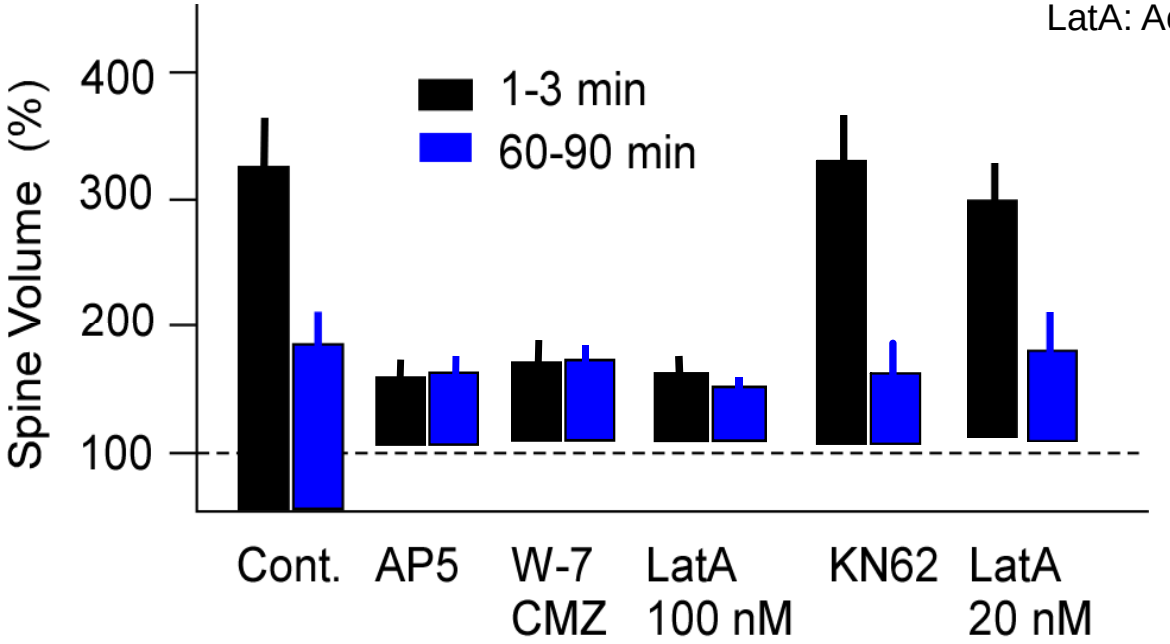


Enlargement of spine-head



W7, CMZ: Calmodulin inhibitor

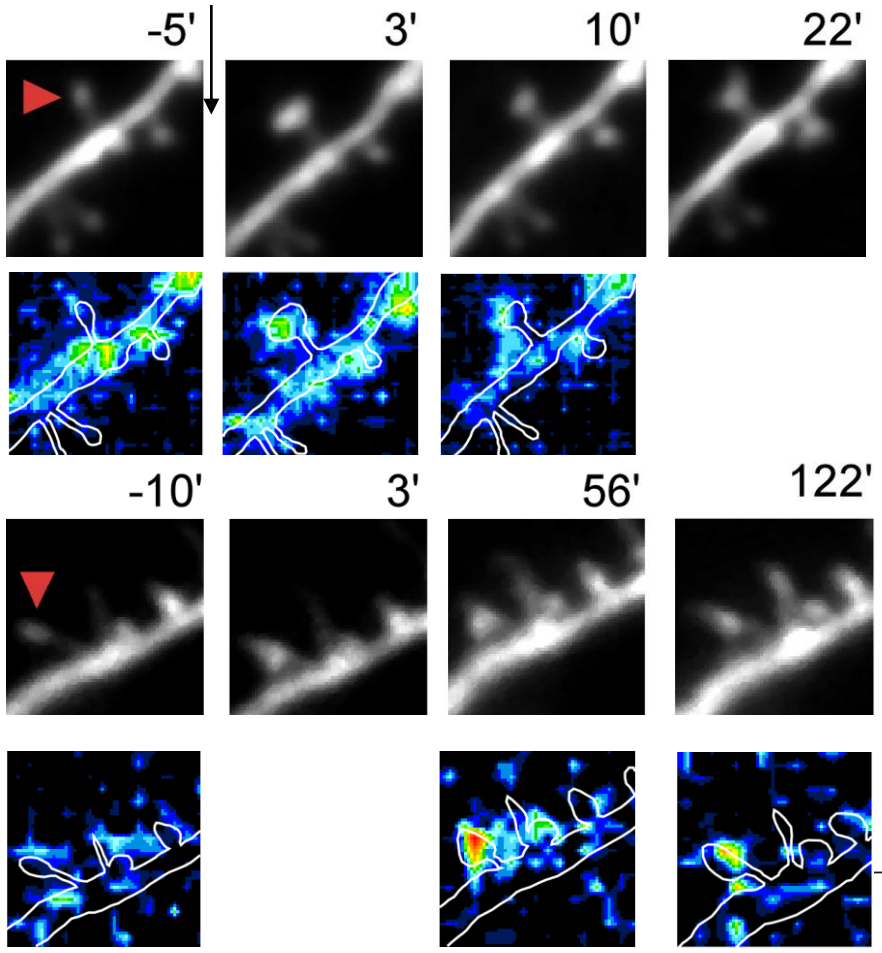
LatA: Actin polymerization inhibitor



Enlargement of spine-head and long-term potentiation

Print

Two-photon excitation of glutamate with repeated stimulations: 0 Mg



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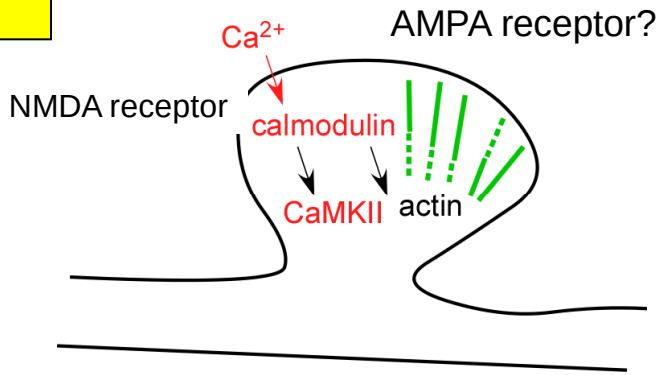
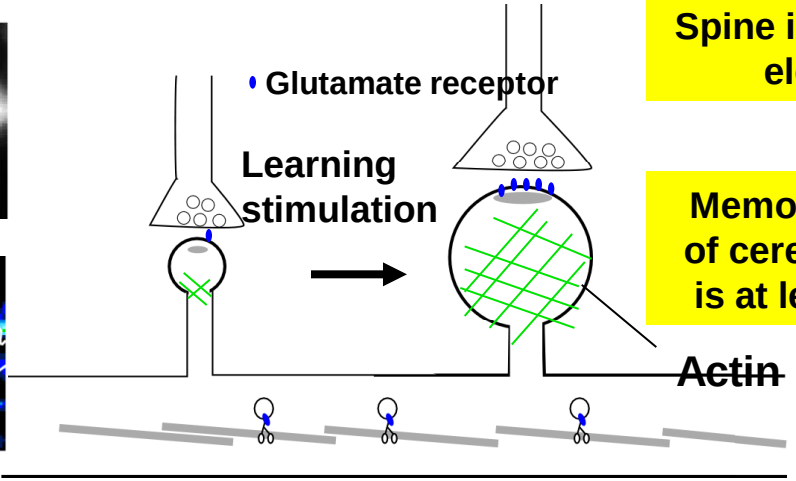
Enlargement of spine-head



Long-term potentiation ≈ Long-term enlargement of spine-head



Spine is a memory element.

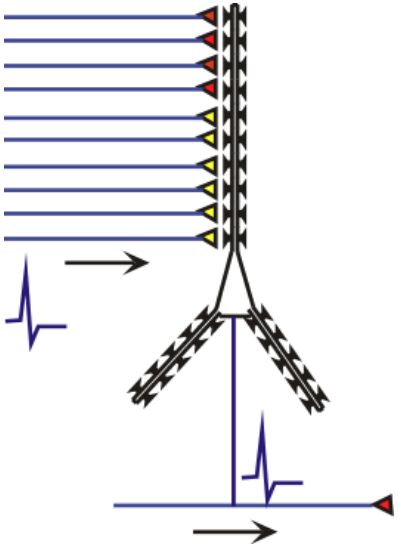
Memory capacity of cerebral cortex is at least 10 TB.

Small spine
II
Structure responsible for learning

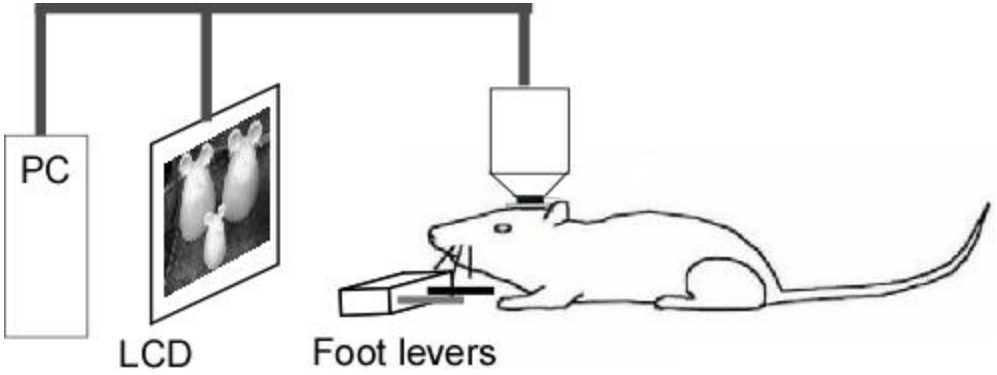
Large spine
II
Physical traces of memory

Cognitive phenomena and synchronous neuronal firing

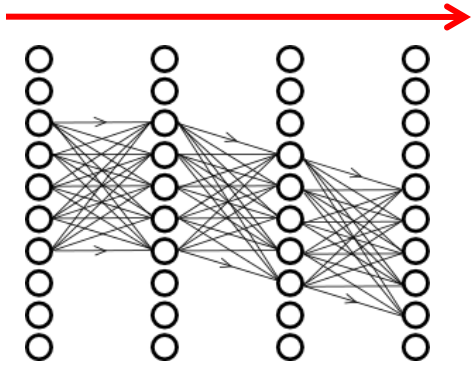
1. Synchronization of signals from input cells effectively induces the firing of neurons.



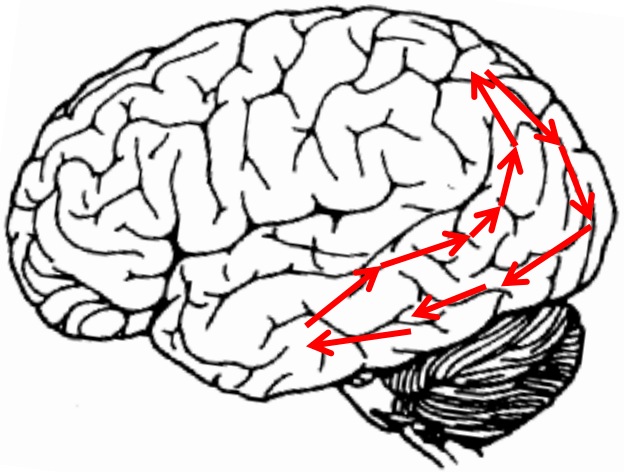
Visual perception



2. A chain of synchronous firings can be easily propagated.



3. Cell assembly (Hebb,1949)

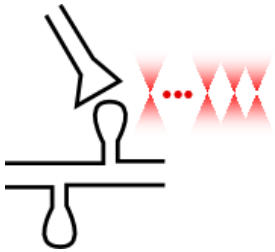


Spine-head enlargement is induced by synchronous firing stimulation

Print

0 Mg stimulation

0 Mg, 1Hz, 60 times



-5 min → 10 min → 60 min

Tanaka, J., Horiike, Y., Matsuzaki, M., Miyazaki, T., Ellis-Davies, GCR & Kasai, H. (2008).
Science, 319:p1683-1687, figure1

- 0 Mg stimulation
- Protein synthesis

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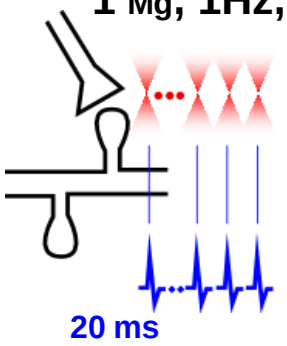
Tanaka, J., Horiike, Y., Matsuzaki, M., Miyazaki, T., Ellis-Davies, GCR & Kasai, H. (2008).
Science, 319:p1683-1687, figure1

Synchronous firing stimulation

1 Mg, 1Hz, 80 times



-5 min → 10 min → 60 min

Copyrighted materials have been removed.

Tanaka, J., Horiike, Y., Matsuzaki, M., Miyazaki, T., Ellis-Davies, GCR & Kasai, H. (2008).
Science, 319:p1683-1687, figure1

- Synchronous firing stimulation
- Protein synthesis inhibitor

Copyrighted materials have been removed.

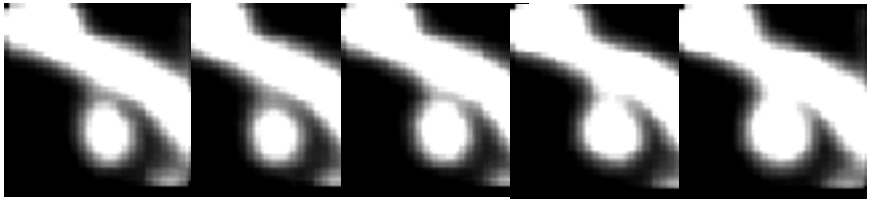
Tanaka, J., Horiike, Y., Matsuzaki, M., Miyazaki, T., Ellis-Davies, GCR & Kasai, H. (2008).
Science, 319:p1683-1687, figure1

Spine twitches by promptly detecting the synchronous firing of neurons.

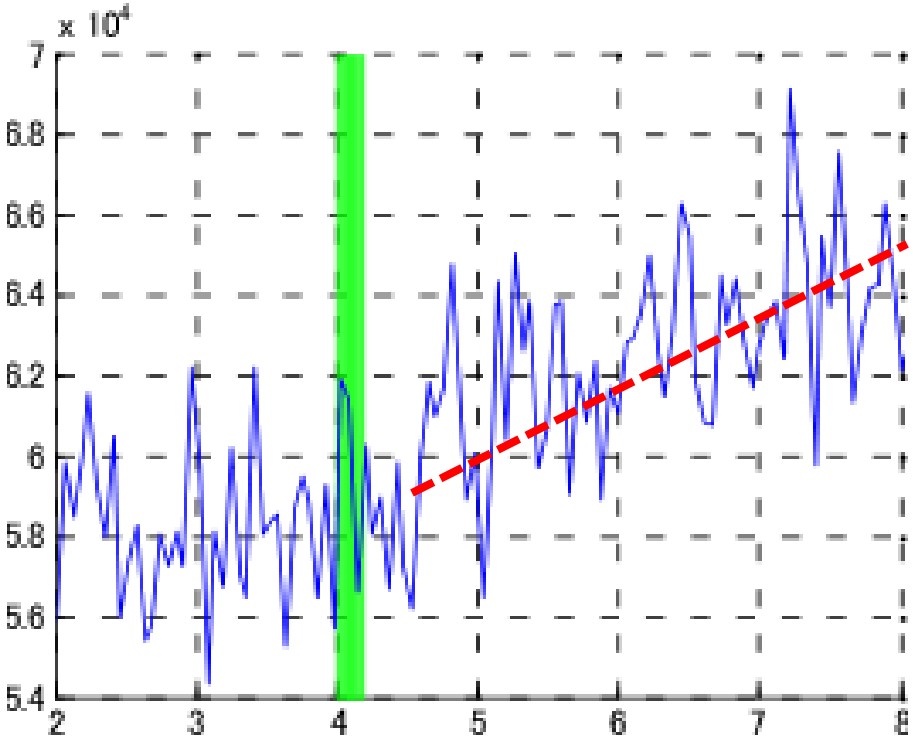
Spine twitching is protein synthesis-dependent and a suitable player of long-term memory.

Tanaka, J., Horiike, Y., Matsuzaki, M., Miyazaki, T., Ellis-Davies, GCR & Kasai, H. (2008).
Science, 319:1683-1687.

Head enlargement promptly begins with about 0.5 sec latency



-1.5 s -0.5 s 0.5 s 1.5 s 2.5 s

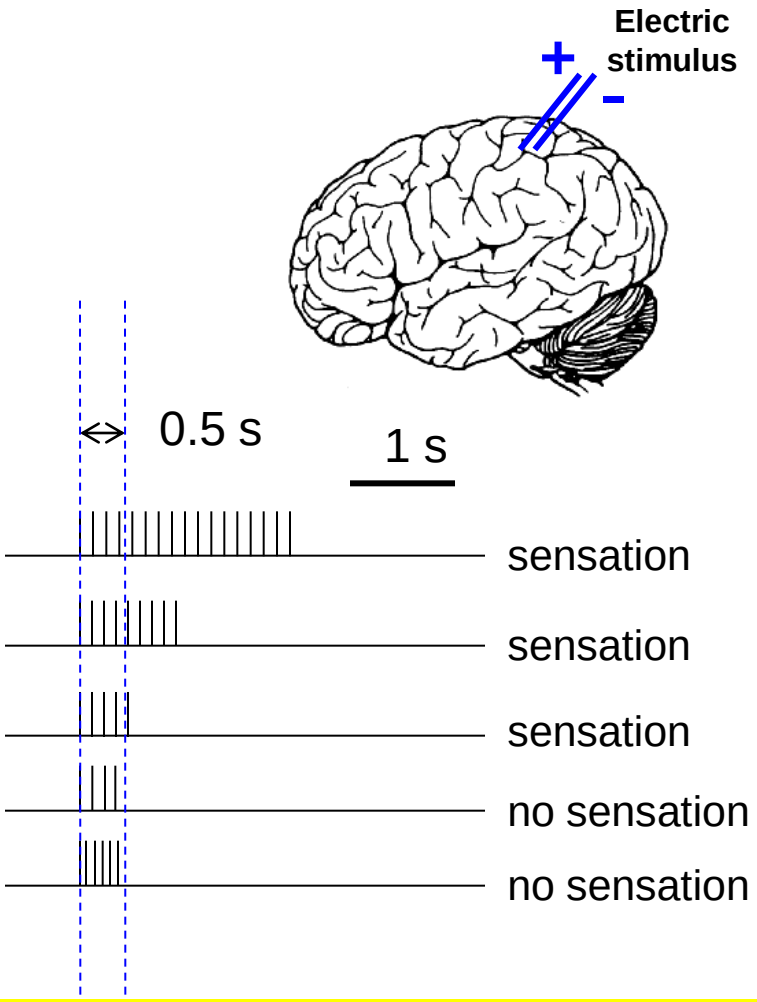


Uncaging 50 Hz, x10 ↑ **0.5 sec**

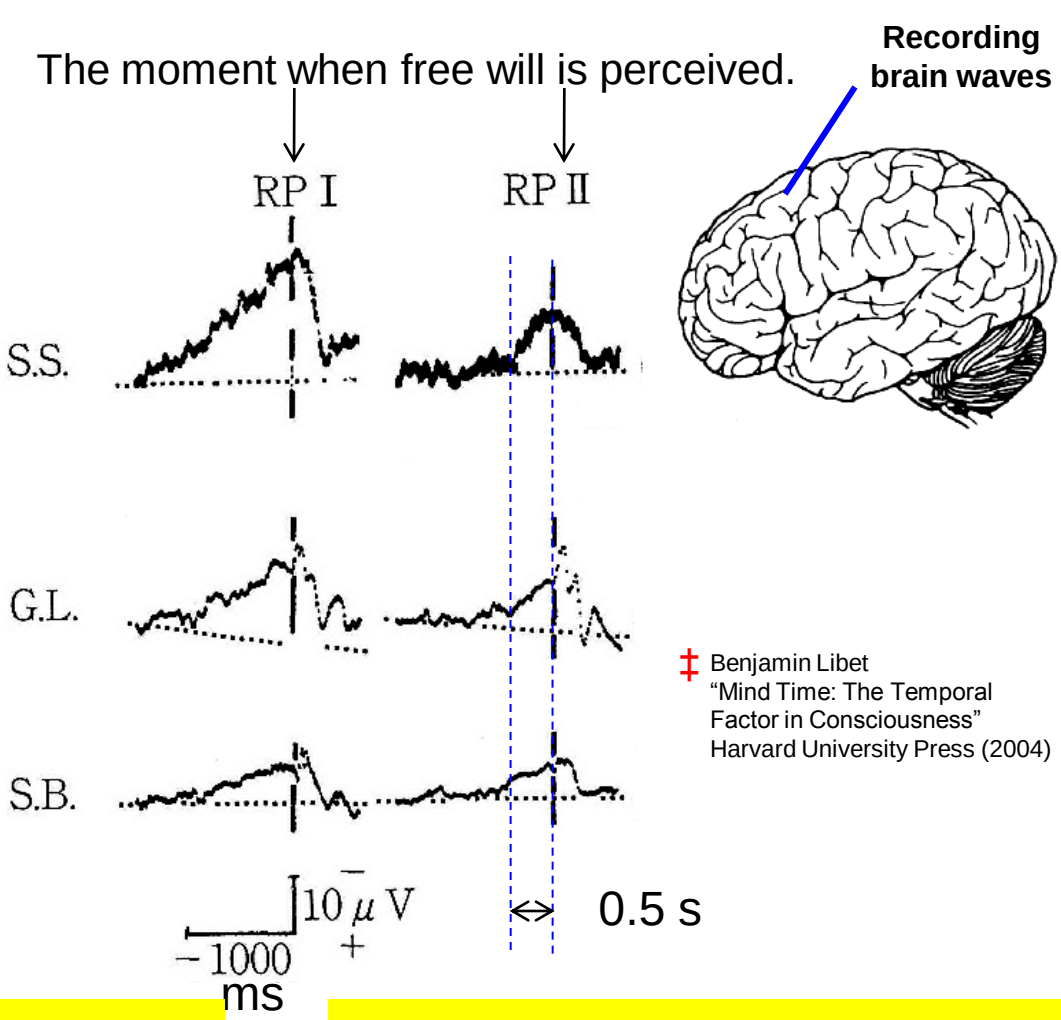
Benjamin Libet's experiment: Subjective experience is delayed by about 0.5 sec with respect to the electrical activity of brain

Print

1. Stimulation of the somatosensory area and delayed subjective perception (1966)



2. Brain waves in the motor area precede free will (1983)

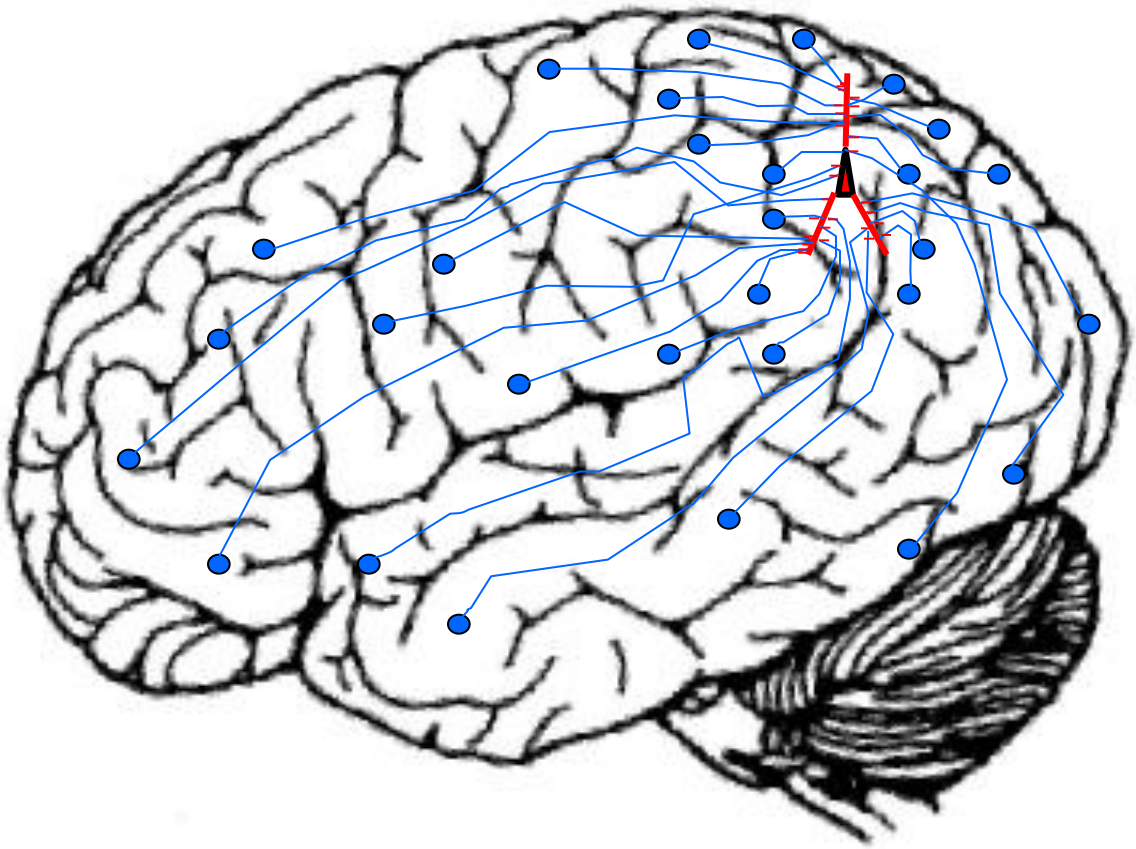


‡ Benjamin Libet
"Mind Time: The Temporal Factor in Consciousness"
Harvard University Press (2004)

Subjective experience is delayed by about 0.5 sec with respect to the electrical activity of brain.

Free will is delayed by 0.5 sec with respect to electrical activity.

Detecting synchronous firing by cell movement



- Other neurons

30 cells

2000 cells in actual brain → Extremely high Information connection capability

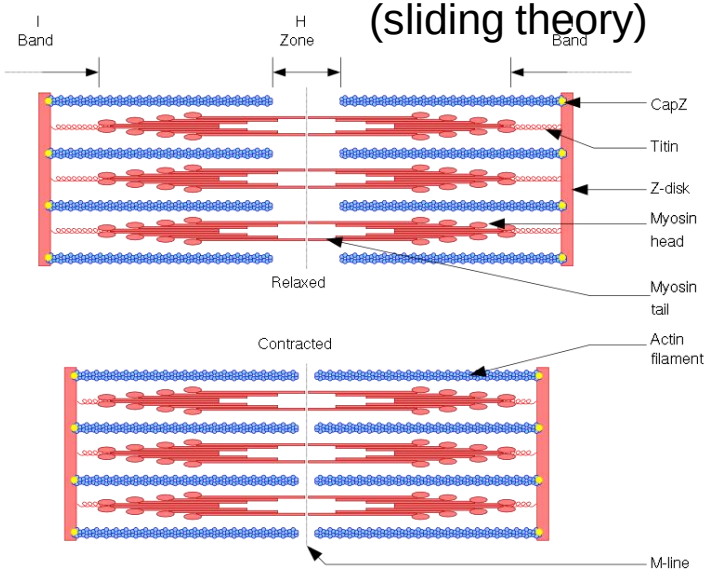
There are 10 billion of these pyramidal cells.

Cell movement is a type of self-expression of a cell

Print

Skeletal muscle cells

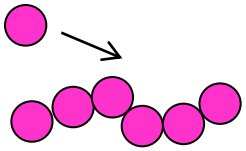
Muscle contraction is explained by the sliding of actin and myosin. (sliding theory)



‡ http://en.wikipedia.org/wiki/File:Sarcomere.svg

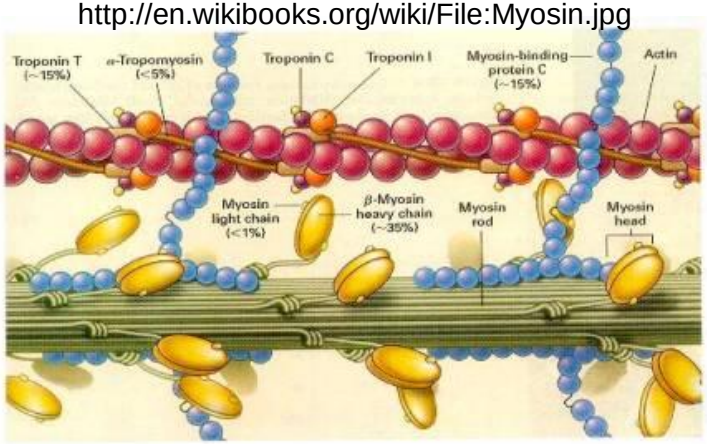
Other cells

Globular actin (G-actin) 42kDa

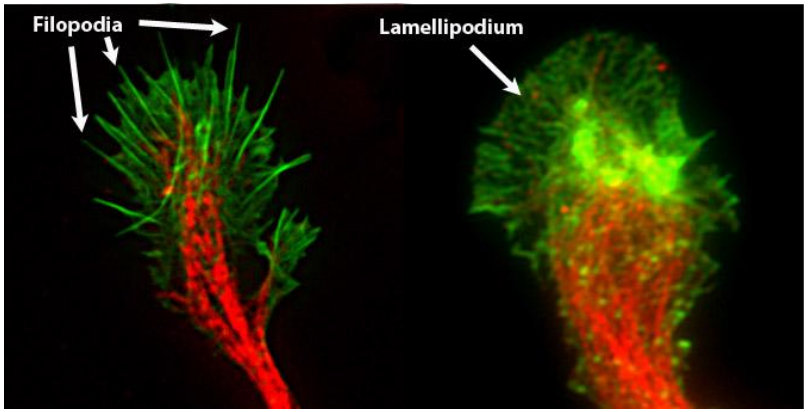


Filamentous actin (F-actin, actin fiber)

http://en.wikibooks.org/wiki/File:Myosin.jpg



‡ http://en.wikipedia.org/wiki/File:GrowthCones.jpg



Cell movement is a self-expression of a whole cell and morphologically acts on surrounding cells.

Electrical activity of a cell is limited to the region within the cell membrane and provides only a restrictive action on the surrounding cells.

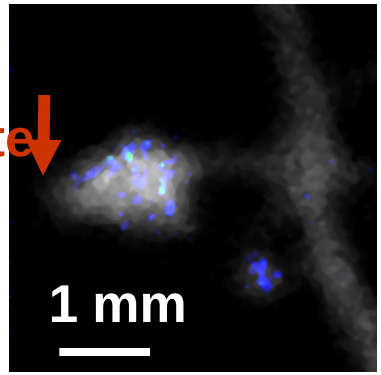
Construction of actin fiber in the spine

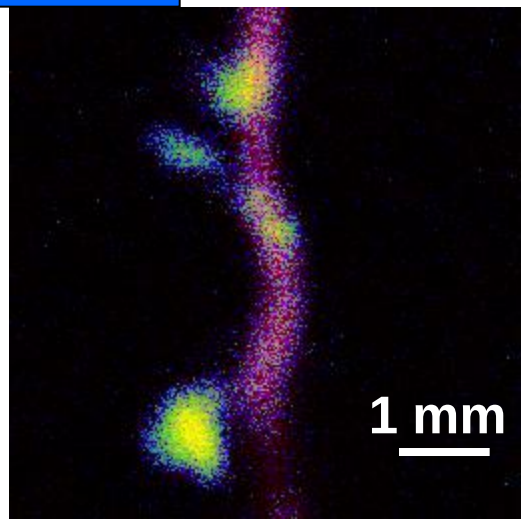
Print

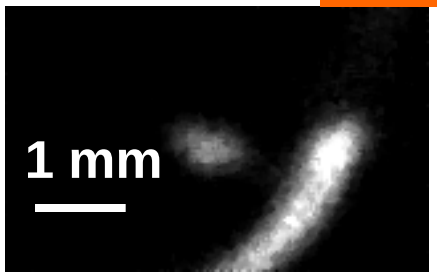
PAGFP-actin

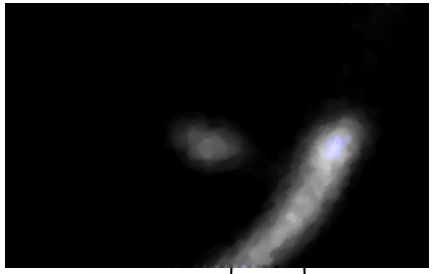
Photoactivate

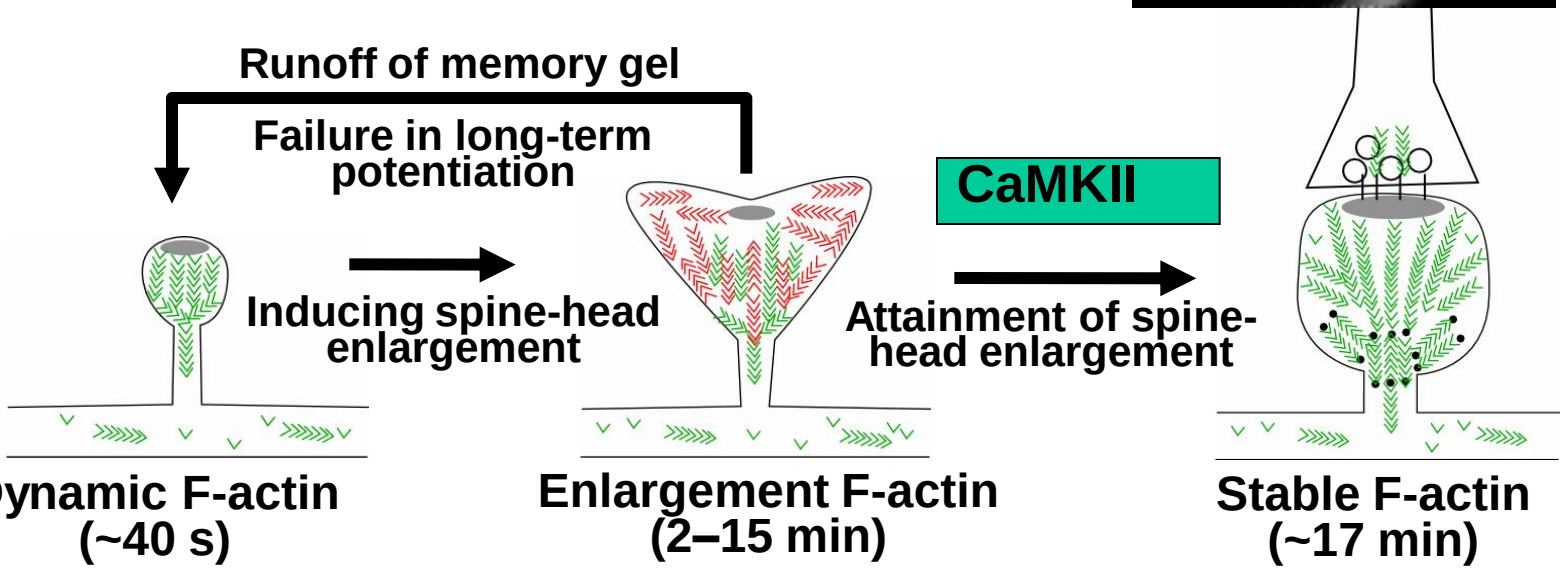
time







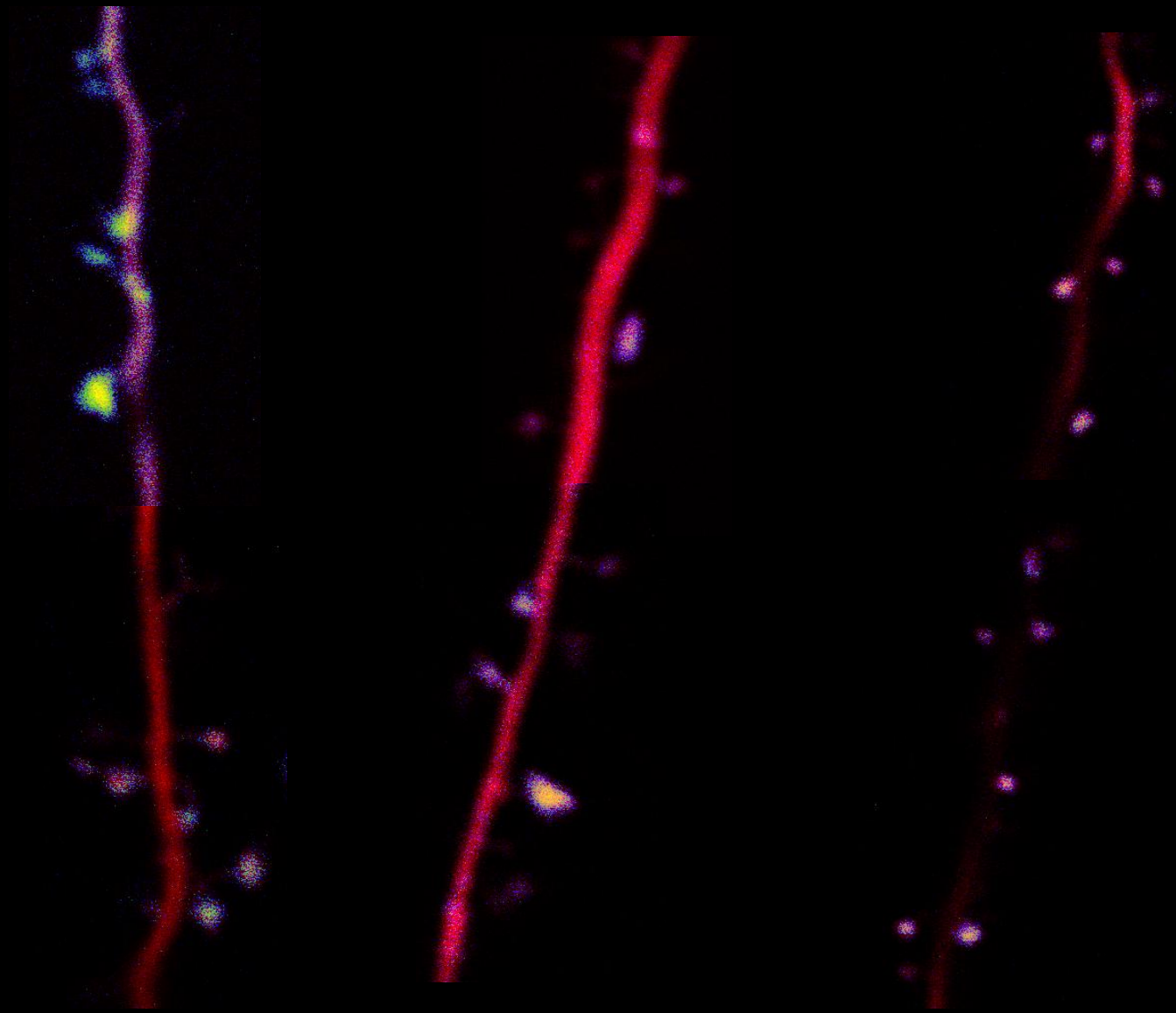




The spine synapse in not only electrical; it is also dynamical.

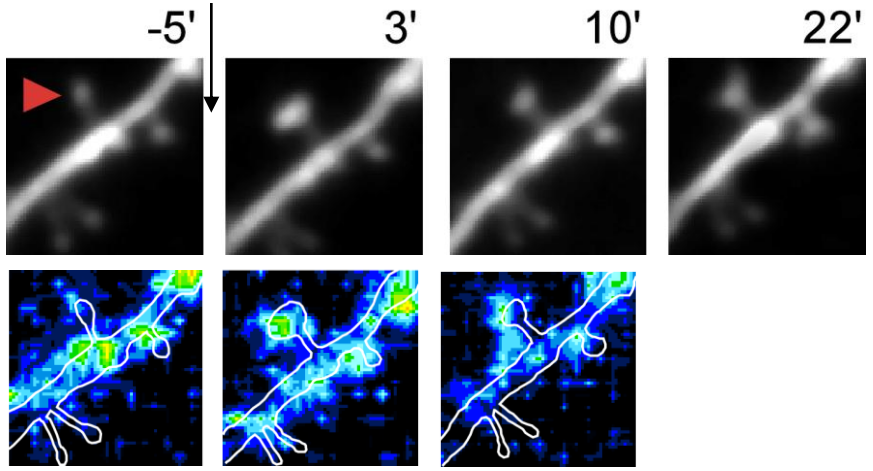
Dendrite movement upon stimulation

Neuron movement occurs in a great variety of ways



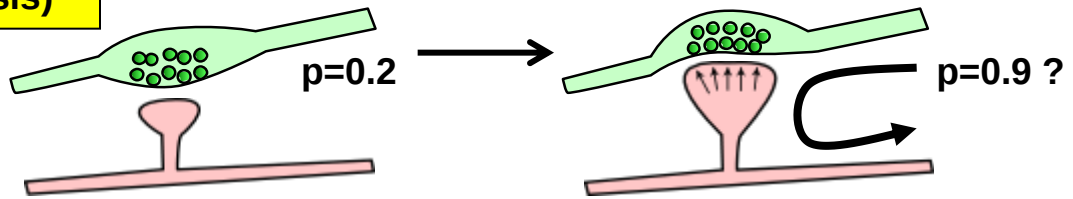
Spine-head enlargement acts on a synapse

Action on the function of postsynaptic site (verified)



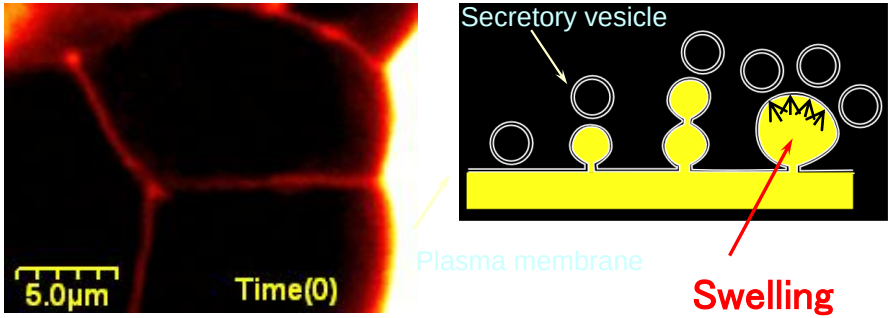
‡ Reprinted by permission from Macmillan Publishers Ltd: Matsuzaki, Honkura, Ellis-Davies & Kasai, Nature 429, 761-766, copyright （2004)

Action on the function of presynaptic terminal (hypothesis)



Adrenal medulla
Adrenaline-producing cells

‡



"There is no such conquering weapon as the necessity of conquering."

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Similarity between subjective experience and neuron movement

Print

Subjective experience

Temporal-spatial firing specific to neuronal populations.

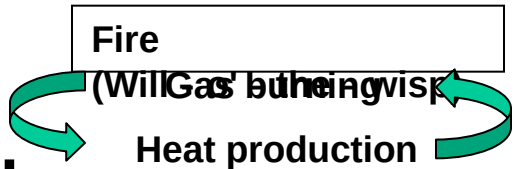
Although this is a standard way of thinking, it can hinder understanding phenomenological or active aspects.

Characteristics of neuron movement that are similar to those of subjective experience are:

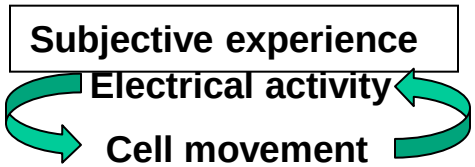
1. Induced by synchronous firing that represents neural activities (this is in agreement with the standard concept). It has high information connectivity.
2. Tens of billions of pyramidal cells, each with 2000 spines, in the brain, allow rich expression.
3. Spine movement is delayed by about 0.5 sec with respect to neural activities. (Benjamin Libet, 1966 &1983)
4. Associated with memory (fast movement of spines is responsible for subjective experience and slow and long-lasting movement is for memory).
5. Developed in the cerebrum, but not found in the anesthetized brain. NMDA receptor-dependent movement is impossible for principal cells in the cerebellum.
6. Movement provides actions on the functions of neural circuits.

Cell movement can be observed and controlled.

Let's conduct experiments!



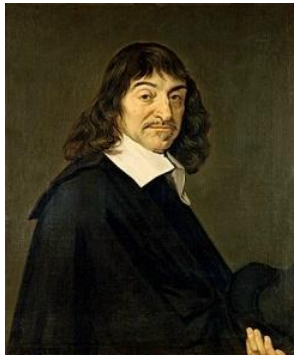
Identity



Identity

La Mettrie “Machine Man” (1747)

Print



Rene Descartes (1596-1650)

Discourse on Method (1637)

- Mind-body dualism: Body and the mind are different.
- Animals do not have the mind and can be completely understood as a machine.

Julien Offray de La Mettrie (1709-1751)

Machine Man (1747)

- “The leg has muscles to walk, so does the brain to think.”
- Brain activity is the mind and there is no spirit or gods (materialism).

Luigi Galvani (1737-1798)

Discovery of electric phenomena in frog’s skeletal muscles (1780)

↓

Golden years of electrophysiology
1780–2009

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http://en.wikipedia.org/wiki/File:Frans_Hals_-_Portret_van_René_Descartes.jpg
http://en.wikipedia.org/wiki/File:Julien_Offray_de_La_Mettrie.jpg
http://en.wikipedia.org/wiki/File:Luigi_Galvani,_oil-painting.jpg

Summary

1. Higher brain function (the mind) consists of a region that is subjectively experienced and a region that is not.

2. The region that is subjectively experienced has yet to be elucidated.

Two aspects: phenomenological and active aspects.

Active aspect may be explained by cell movement.

An abundance of cell movement helps to understand the phenomenological aspect; however, extensive and long-term studies are still required.

3. To enable objective observations of subjective experience is neuroscience's (and my) purpose.

4. Research explained in this presentation will advance the understanding of the mind, help cure mental illness, and eventually enhance human culture.

5. I would like to encourage you to pay attention to such a frontier of neuroscience, and your participation is highly appreciated, either directly or indirectly.

The information presented in today's lecture will be published in *Trends in Neuroscience*, a neuroscience journal, in this fiscal year.

Additionally, I am preparing another review article to be published in *Kagaku* (publisher: Iwanami Shoten) and your questions and comments are welcome. Hkasai@m.u-tokyo.ac.jp

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