Neuroscience

From Mysteries of the Brain to Diseases of the Nervous System

Yi Rao

人脑

宇宙中已知最神奇

National Geographic

Soul/Mind/Brain

Long before biology was born, people/philosophers/great minds were thinking about it

Long after major problems in other branches of biology have been solved, the brain will remain mysterious

Neuroscience

highly interdisciplinary

哲学、经济、社会、
认知、心理、
物理、化学、数学、信息、
分子、遗传、成像、生化、结构
神经内科、神经外科、精神健康、老年病、
眼科、耳鼻喉科

NINDS，NIMH，NEI，NIDCD，NIDA，NIAMSD，NIBIB，NIA，NCI，NIAAA，NICHD，NIDCR，NIEHS，NHGRI

神经科学可以是其他科学的：用武之地

注意其他学科：而不是只知道鼻子底下一点

比如，

学生化的知道神经：蛋白质纯化
学分子的知道神经：克隆基因
学结构的知道神经：解结构

反过来，

学神经的知道生化：蛋白质纯化
学神经的知道分子：克隆基因
学神经的知道结构：解结构

还有好多交叉，

物理、化学、成像、数据分析…….

神经科学带动其他学科：有时

Schwann先发现包裹神经纤维的Schwann细胞，
其后1839年提出细胞学说，全身都是细胞组成

细胞程序性死亡，最初Victor Hamburger和
Rita Levi-Montanici于1940年代在神经系统发现，
70年代见于其他系统，最后发现普遍存在

生长因子1940到1960年代首先发现于神经系统
Rita Levi-Montanici 的NGF
以后普遍发现生长因子参与多种过程，包括癌症，
生长因子下游：药物Gleevec ，抑制蛋白激酶

Axonal Transport原先是神经生物的问题，
Ron Vale等1980年代发现kinesin后，
原来是细胞普遍用的微管依赖的分子和细胞器运动的基本机理，是细胞生物学普遍问题

等……

神经科学：人类健康和医药工业

如

心血管药物: 心得安等

精神健康
抑郁症Prozac, 21 billion for Eli Lilly from 1988-2001

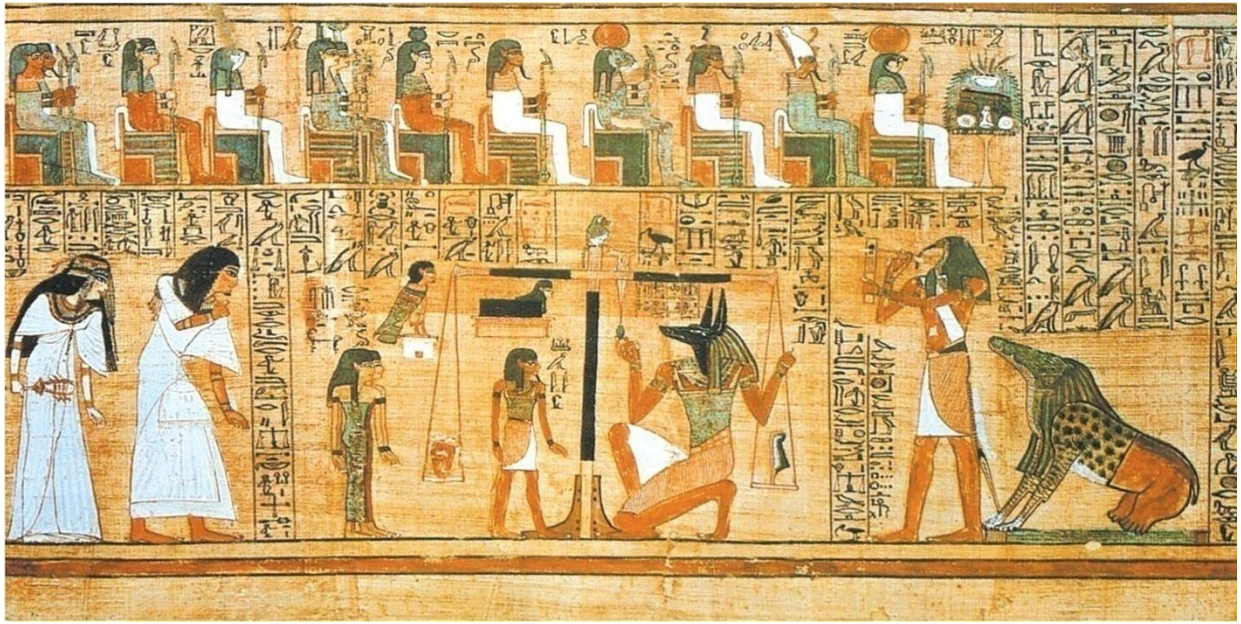
等……

神经科学

如果你对脑感兴趣，自然要学

非神经科学专业，学了也可能有好处

Soul



心 脑

埃及
Homer (胸 肺心)
Aristotle Plato

Galen

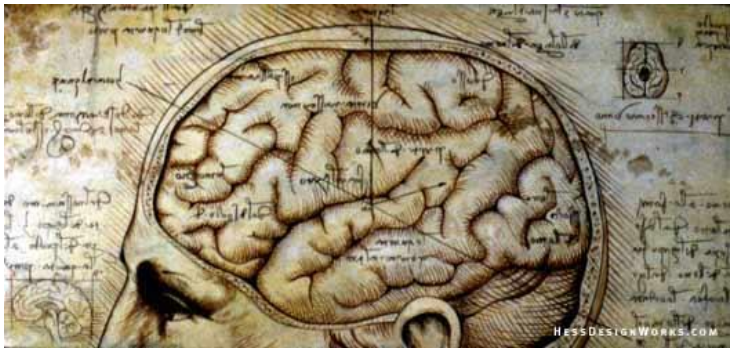
Leonardo Da Vinci and Michelangelo

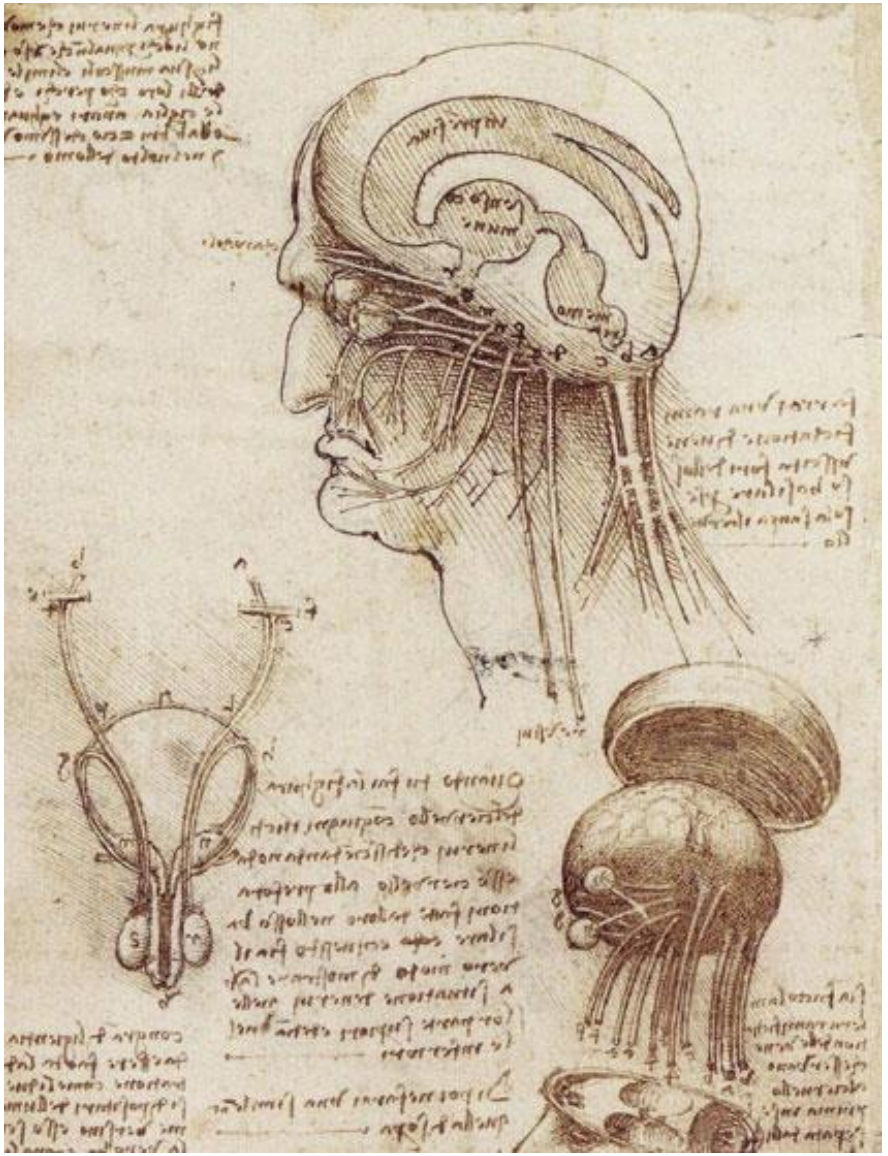
Leonardo Da Vinci:
(April 15, 1452 – May 2, 1519)

Michelangelo Buonarroti
(1475–1564)

Leonardo Da Vinci

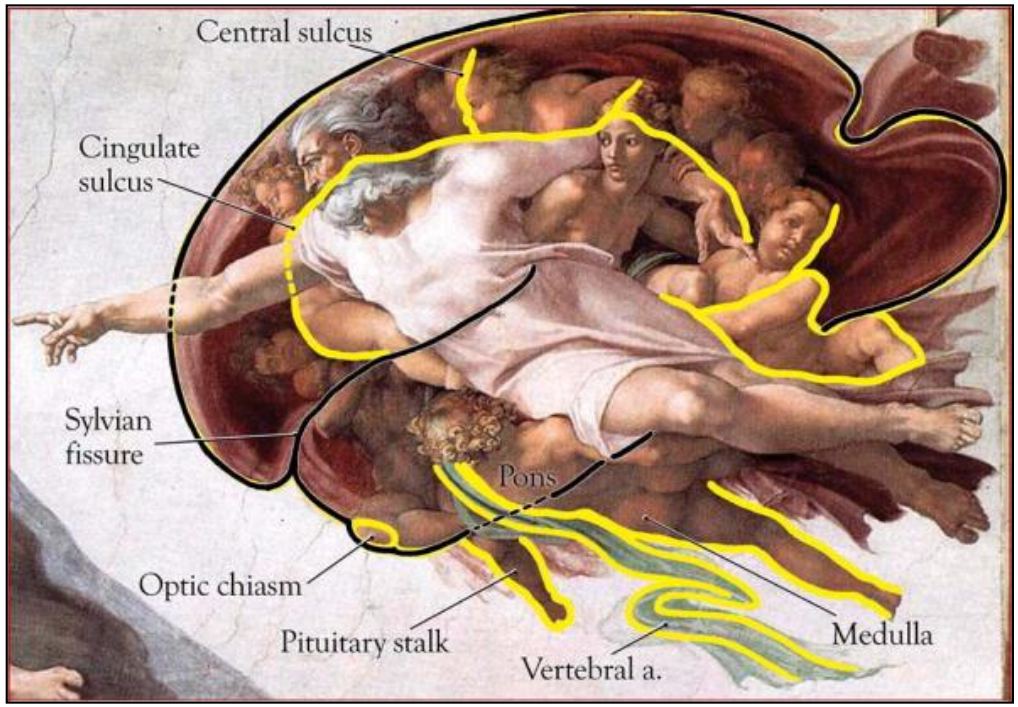
大量作品未出版
可以看他的草图

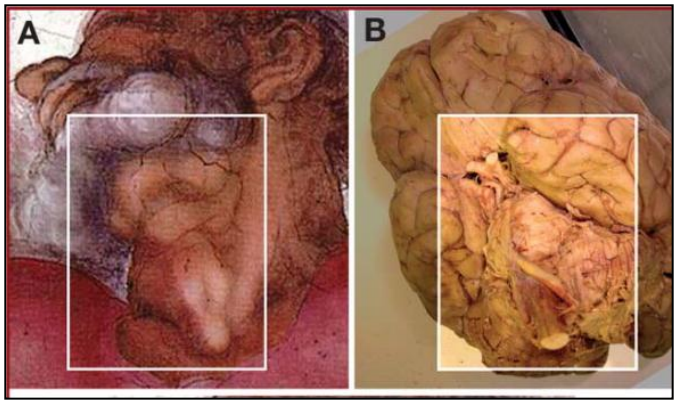




Michelangelo: Sistine Chapel Ceiling 1508-1512

Michelangelo: hidden images of the brain in the ceiling?





Meshberger FL (1990) An interpretation of Michelangelo's Creation of Adam based on neuroanatomy. *JAMA* 264:1837–1841

Suk I, Tamargo RD (2010) Concealed Neuroanatomy in Michelangelo's Separation of Light From Darkness in the Sistine Chapel. *Neurosurgery* 66:851-861

Leonardo Da Vinci: Search for the Soul

达芬奇对神经科学的思考和实验研究

1487-1489
drawing from books

1489-1505
locating the soul (*senso comune*)

1508-1514
其他系统的解剖, 还有脑室

1487达芬奇的实验:
蛙实验 sharp scalpio, spinal medulla (medulla oblongata延髓），即刻死亡
“运动和生命的foundation”

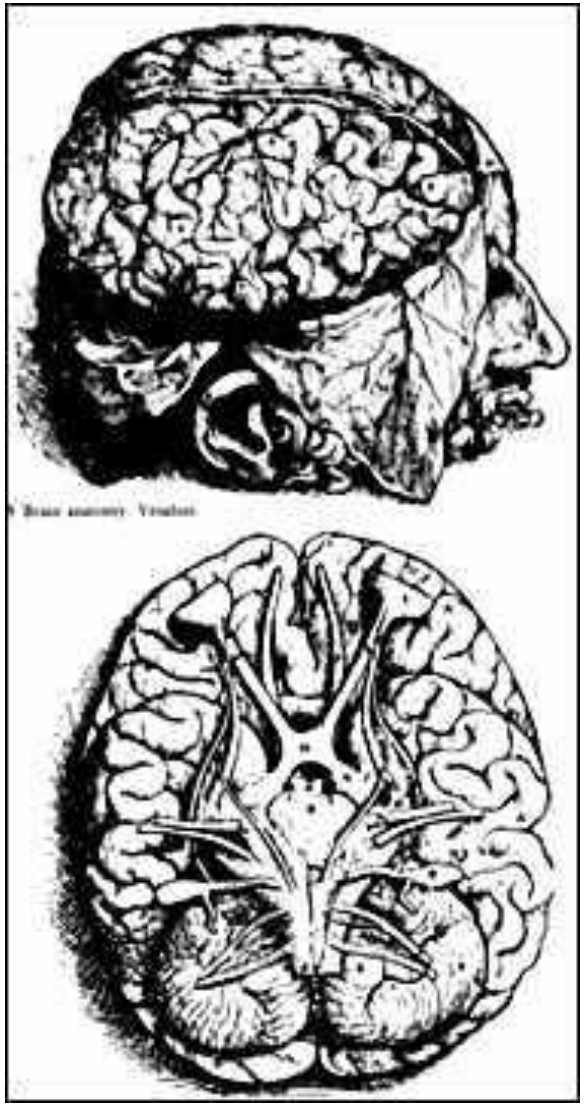
Stuard重复 1739

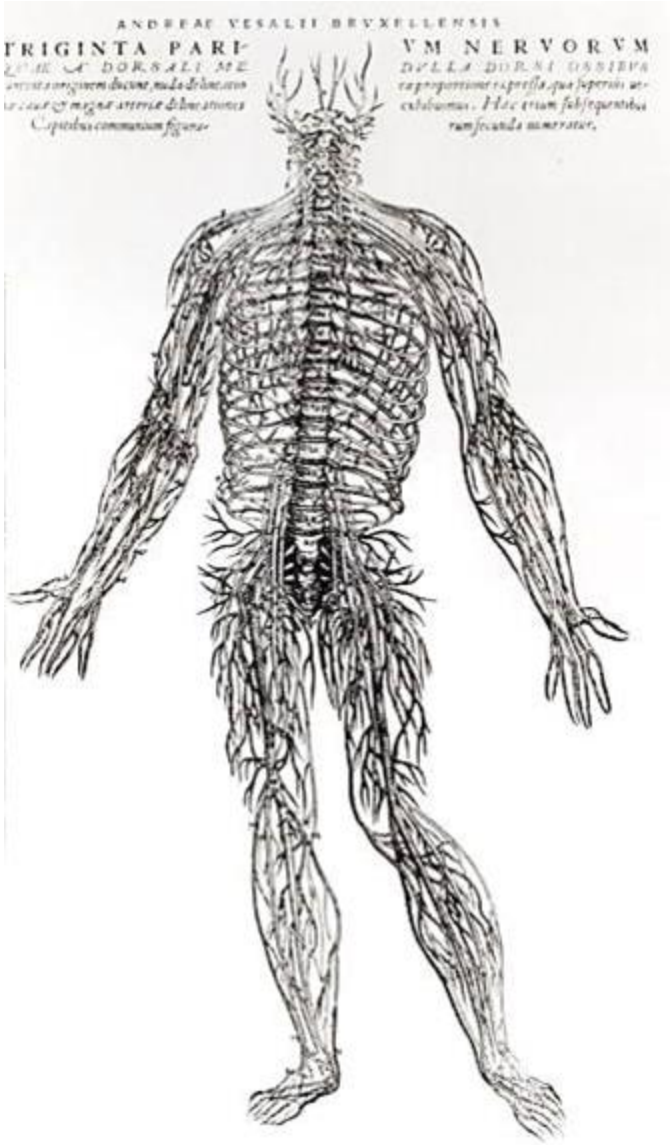
Del Maestro RF (1998): Leonardo da Vinci: the search for the soul. *J Neurosurg* 89:874–887.

Andreas Vesalius: De Humani Corporis Fabrica

Library of Congress

Andreas Vesalius
(1514 – 1564)





Rene Descartes: hydraulic powered mechnics

笛卡尔对神经科学的思考

不仅 I think, therefore I am

提出神经传导的理论和模型

Rene Descartes

(1596 – 1650)

RENATUS DES CARTES

DE

HOMINE

FIGVRIS

ET

LATINITATE DONATUS

A

FLORENTIO SCHUYL,

Inclytæ Urbis Sylvæ Ducis Senatore, & ibidem Philosophiæ Professore.

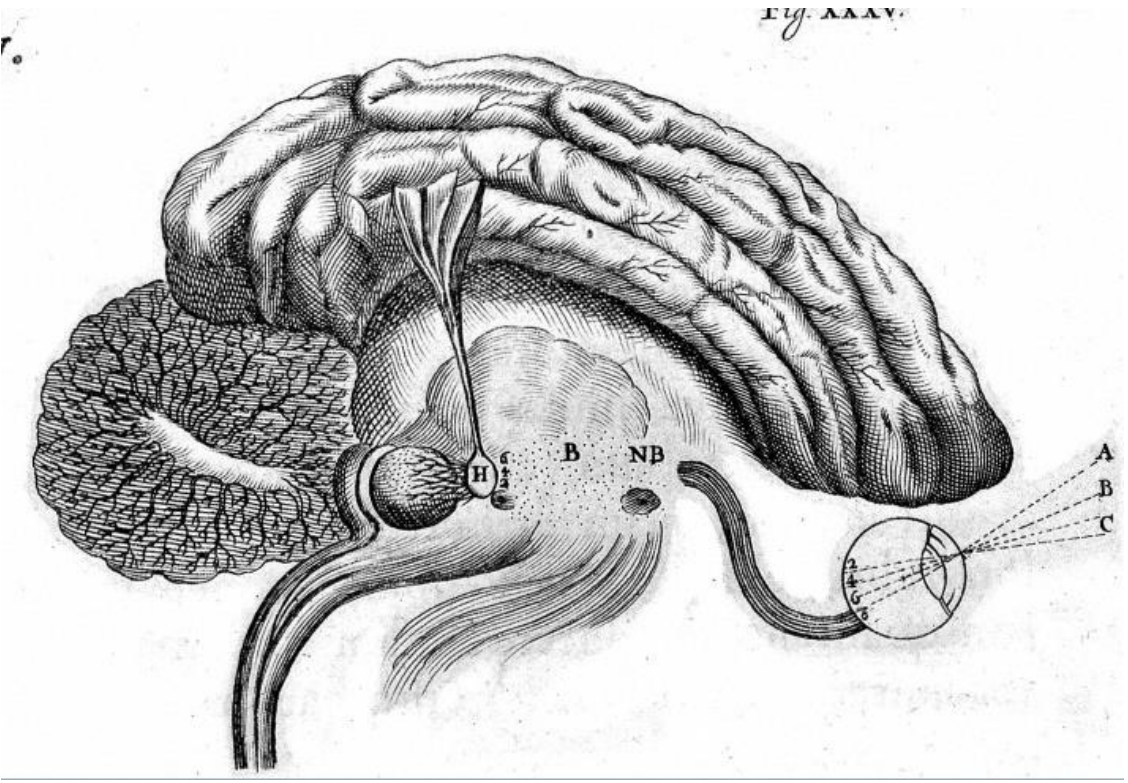
LVGDVNI BATAVORVM,

Apud PETRVM LEFFEN & FRANCISCVM MOYARDVM.

1662 *De Homine* (The Treatise on Man)

Rene Descartes: the pineal gland

松果体灵魂所在：唯一不对称的脑结构



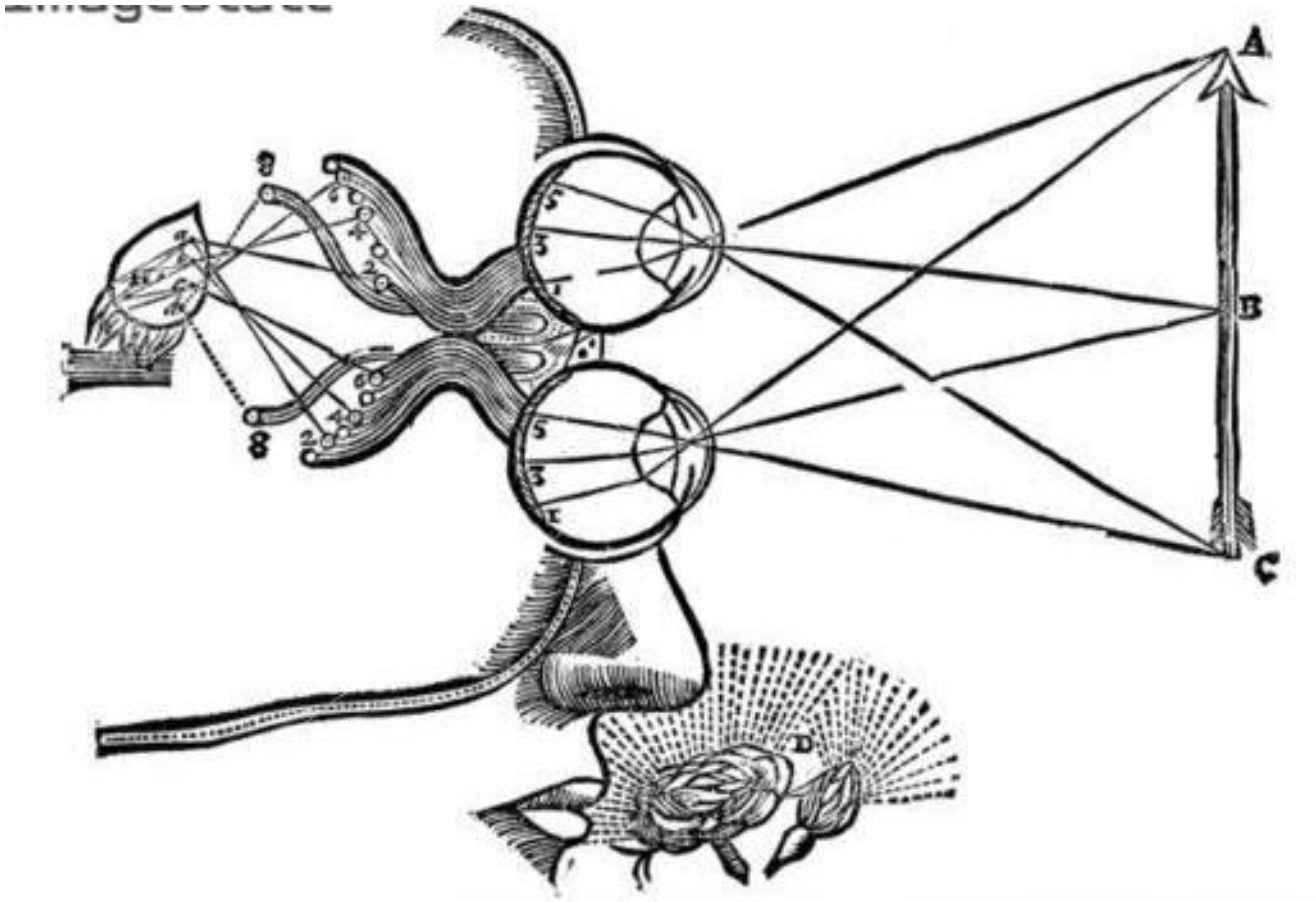
Rene Descartes

(1596 – 1650)

I have plainly found out that that part of the body wherein the soul immediately exercises her function is not a jot of the heart, nor yet al the brain, but only the most interior part of it, which is a certain very small kernel [pineal gland] situated in the middle of the substance of it and so hung on the top of the conduit by which the spirits of its anterior cavities have communication with those of the posterior, whose least motions in it cause the course of the spirits very much to change, and reciprocally, the least alteration befalling the course of the spirits cause the motions of the kernel very much to alter. The reason which persuades me that the soul can have no other place in the whole body but this kernel where she immediately exercises her functions is for that I see: all the other parts of our brain are paired, as also we have two eyes, two hands, two ears; lastly, all the organs of our exterior senses are double and for as much as we have but one very thing at one and the same time

Descartes R: *The Passions of the Soul. Indianapolis, Hackett, 1989*

Rene Descartes



Neuroscience

问题

结构

- 形态
- 神经环路

功能

- 神经传递
- 自主功能
- 高级功能

来源

- 进化
- 发育

方法

结构

- 解剖
- 现代成像

物理化学数学信息

功能

- 物理、化学
- 生物
- 心理、认知

来源

- 比较
- 实验

Neuroscience

神经解剖
神经生理
神经生化
神经药理
神经病理

心理学
神经病学
精神病学
神经经济学
社会?
政治?

Neuroscience

研究的层次

分子
细胞
环路
系统
整体
群体

体外　*in vitro*
体内　*in vivo*

Neuroscience

结构

- 形态
  - 大体
  - 细胞
- 神经环路

功能

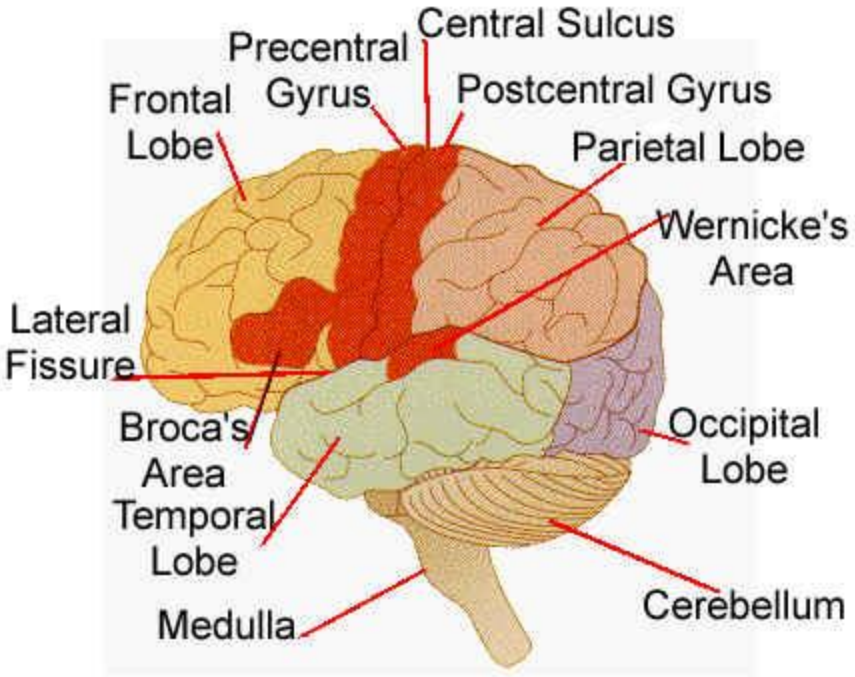
- 神经传递
- 自主功能
- 高级功能

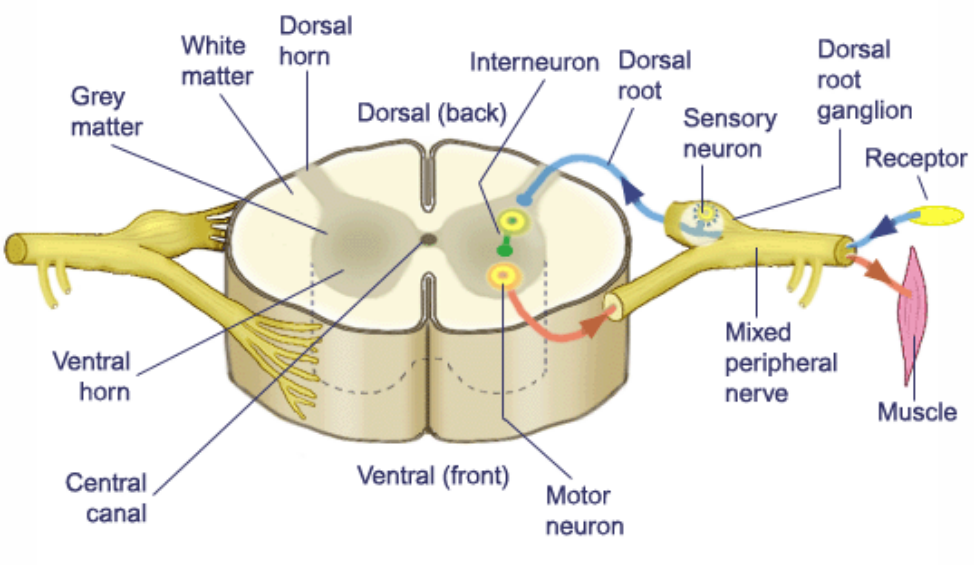
来源

- 进化
- 发育

中枢神经系统 CNS


C1
T1
L1
S1


Central Sulcus
Precentral Gyrus
Postcentral Gyrus
Frontal Lobe
Parietal Lobe
Wernicke's Area
Lateral Fissure
Broca's Area
Occipital Lobe
Temporal Lobe
Cerebellum
Medulla


Dorsal horn
White matter
Grey matter
Interneuron
Dorsal root
Dorsal root ganglion
Dorsal (back)
Sensory neuron
Receptor
Ventral horn
Mixed peripheral nerve
Muscle
Central canal
Ventral (front)
Motor neuron

脑的功能分区：达芬奇的思考

Ventricles	
Anterior	**intelletto and imprensiva**
Middle	**volonta and senso comune**
Posterior	**memoria**

imprensiva: 对智力直接作用的感觉信息
volonta : will, voluntary motion or action

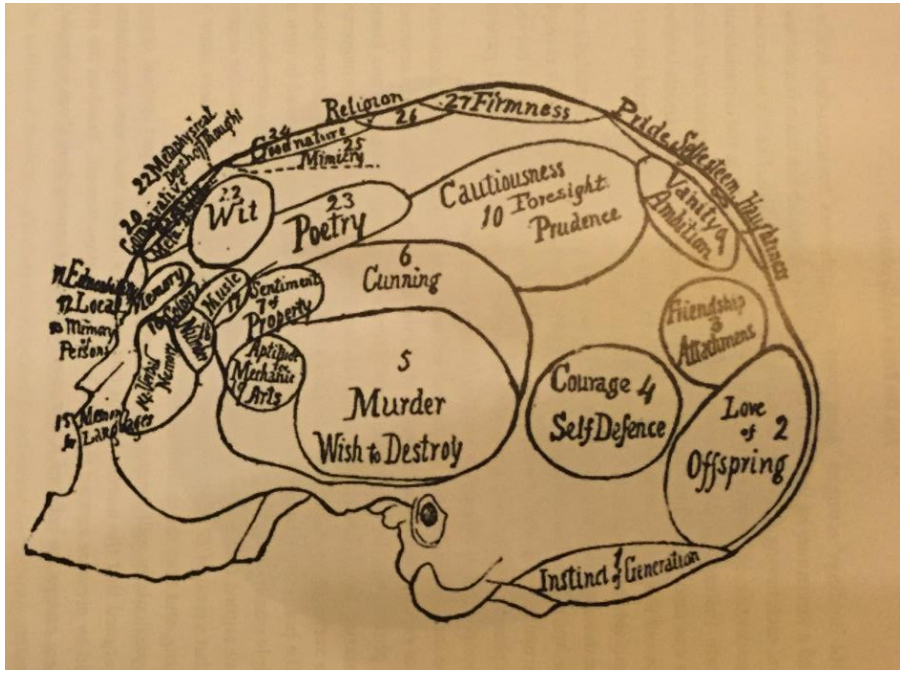
Ventricles	
Anterior	**接受视觉输入**
Middle	**接受听觉和嗅觉输入**

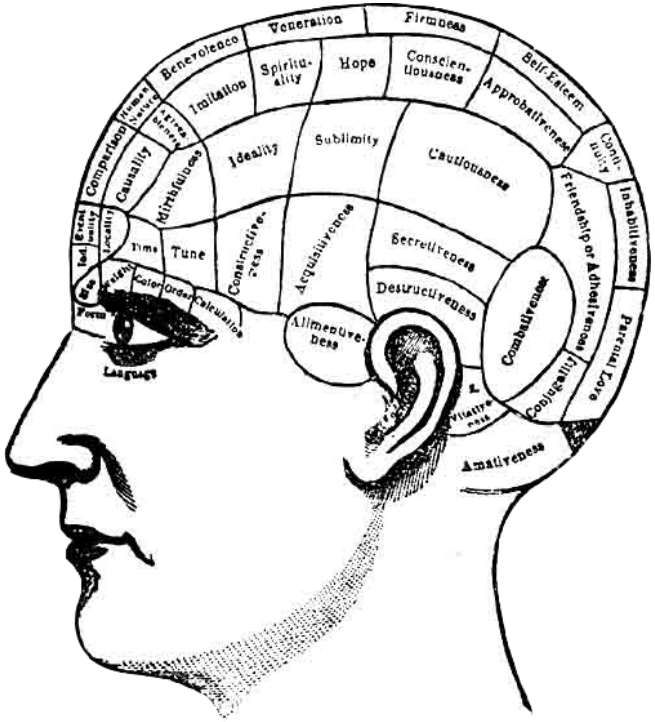
Leonardo Da Vinci
(April 15, 1452 – May 2, 1519)

脑的功能分区

Phrenology　颅相学

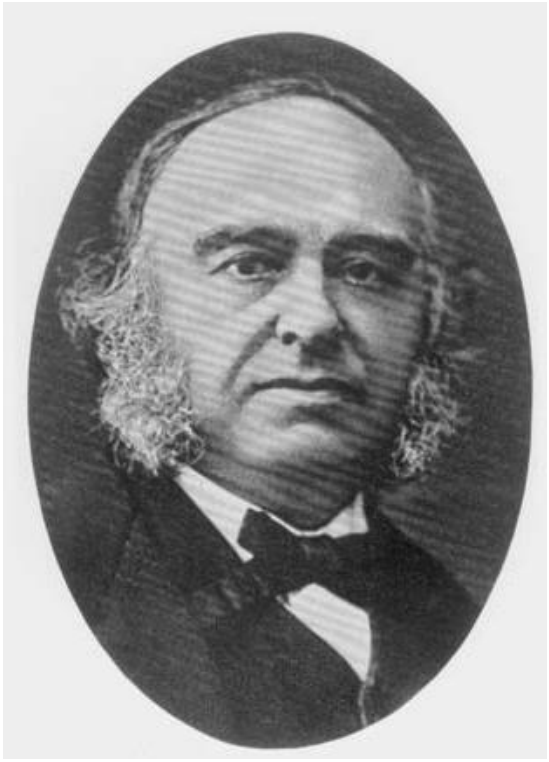
德国医生 Franz Josehp Gall 1796





Gall and Spurzheim (1810)

脑的功能分区: Broca'aphasia失语



Paul Broca
(1824-1880)
法国医生

1861 4月12日,
见51岁的 M Leborgne
青年起癫痫
31岁后不能自主说话.
以后还有瘫痪、右侧无感觉 语言障碍，诱导下可骂人,

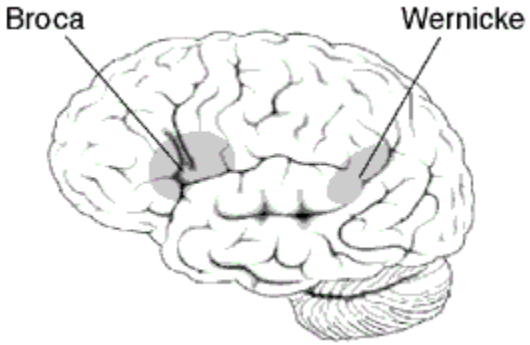
6天后去世
病理解剖：脑区损失、其它软化

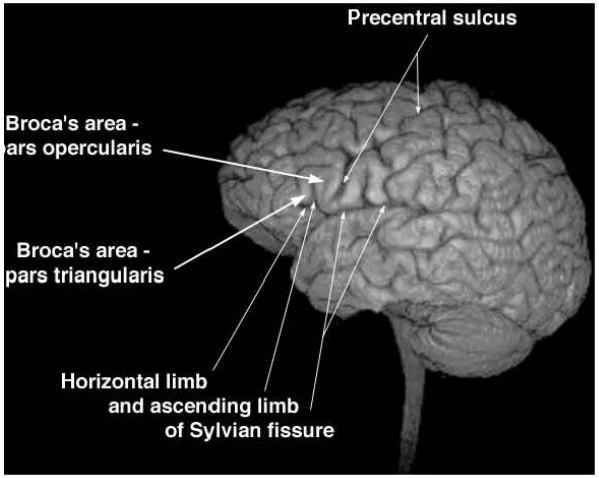
同年，病人Lelong

至1863，有8个语言障碍病例： 皆左半球损

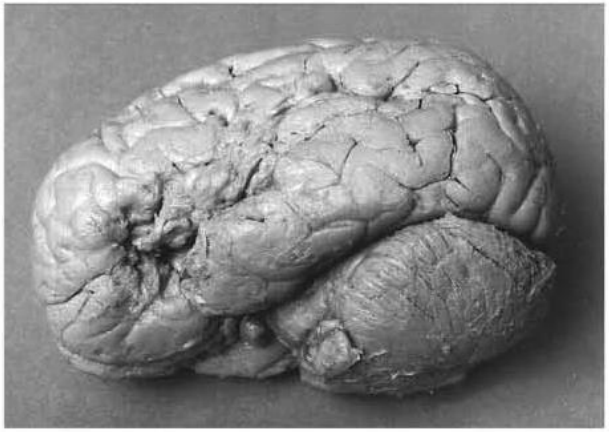
Broca P (1861) Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). Bulletins de la Société Anatomique (Paris) 6:330–357,398–407
Broca P (1865) Sur le siège de la faculté du langage articulé. Bulletins de la Société d'Anthropologie 6:337–393.
Finger S (2004). Paul Broca (1824-1880). *Journal of Neurology* 251: 769–70

脑的功能分区: Broca's area

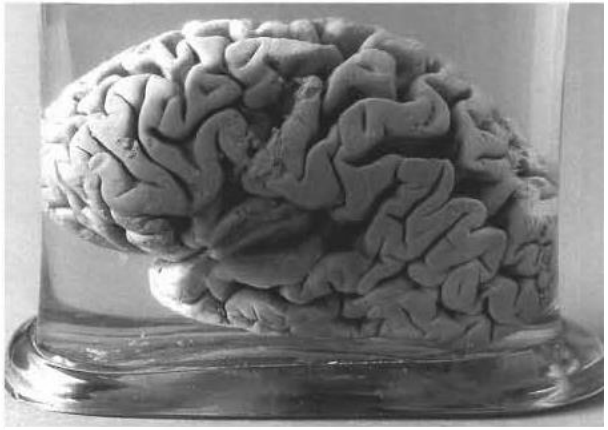


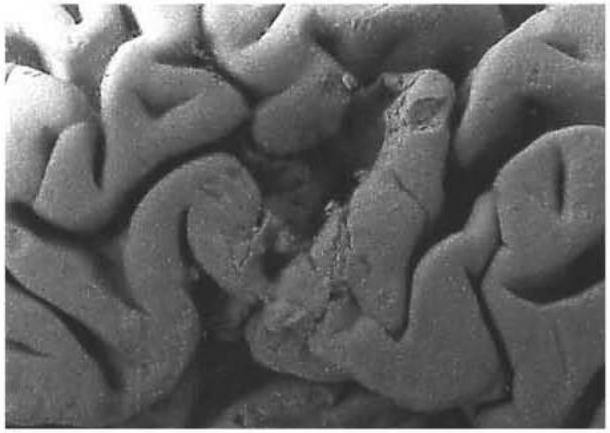


Leborgne



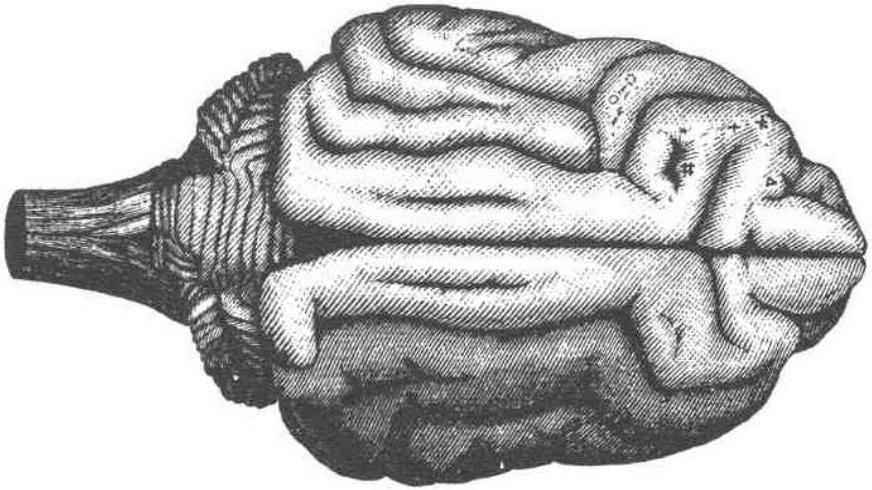
Lelong



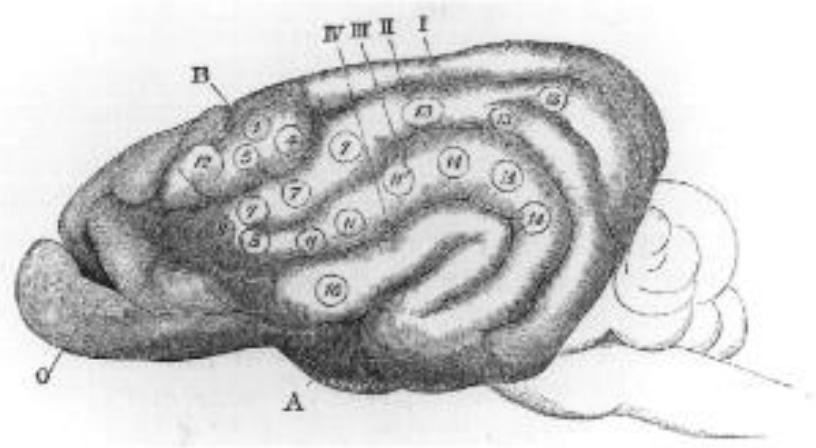


Dronkers NF, Plaisant O, M. T. Iba-Zizen, &E. A. Cabanis (2007). Paul Broca's Historic Cases: High Resolution MR Imaging of the Brains of Leborgne and Lelong. *Brain* 130:1432–1441.

脑的功能分区

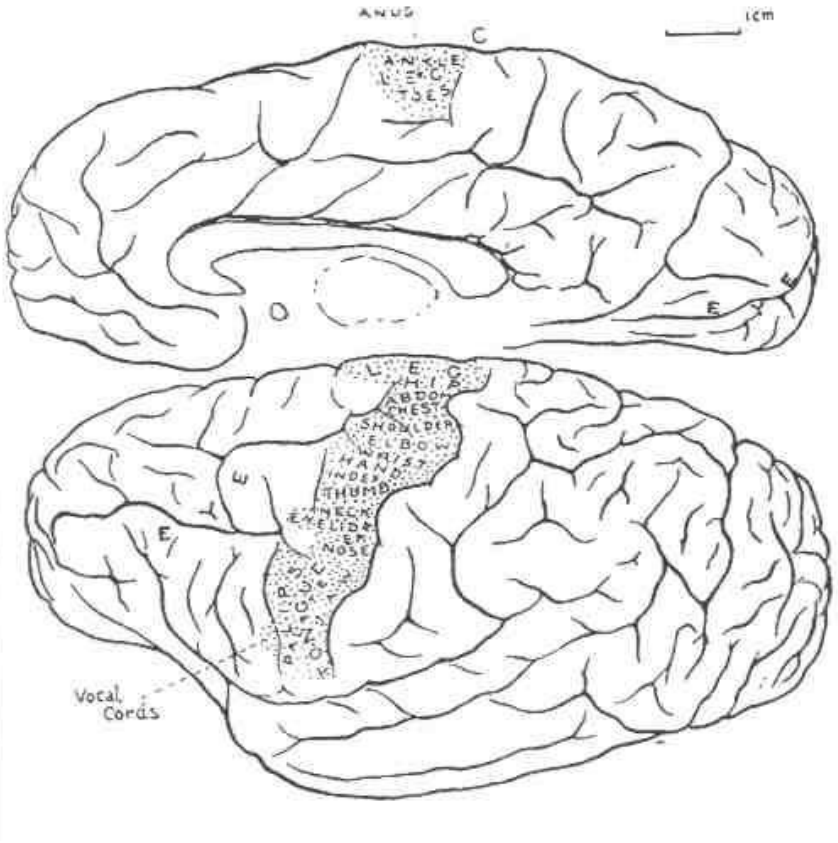


沟脑分区
德国生理学家
Gustav Theodor Fritsch (1838-1927)
Julius Eduard Hitzig (1838-1907).
Über die elektrische Erregbarkeit des Grosshirns
(About the Electrical Excitabilty of the Brain).



猴脑29个功能分区， 1875
英国生理学家和医生
David Ferrier (1843-1924),

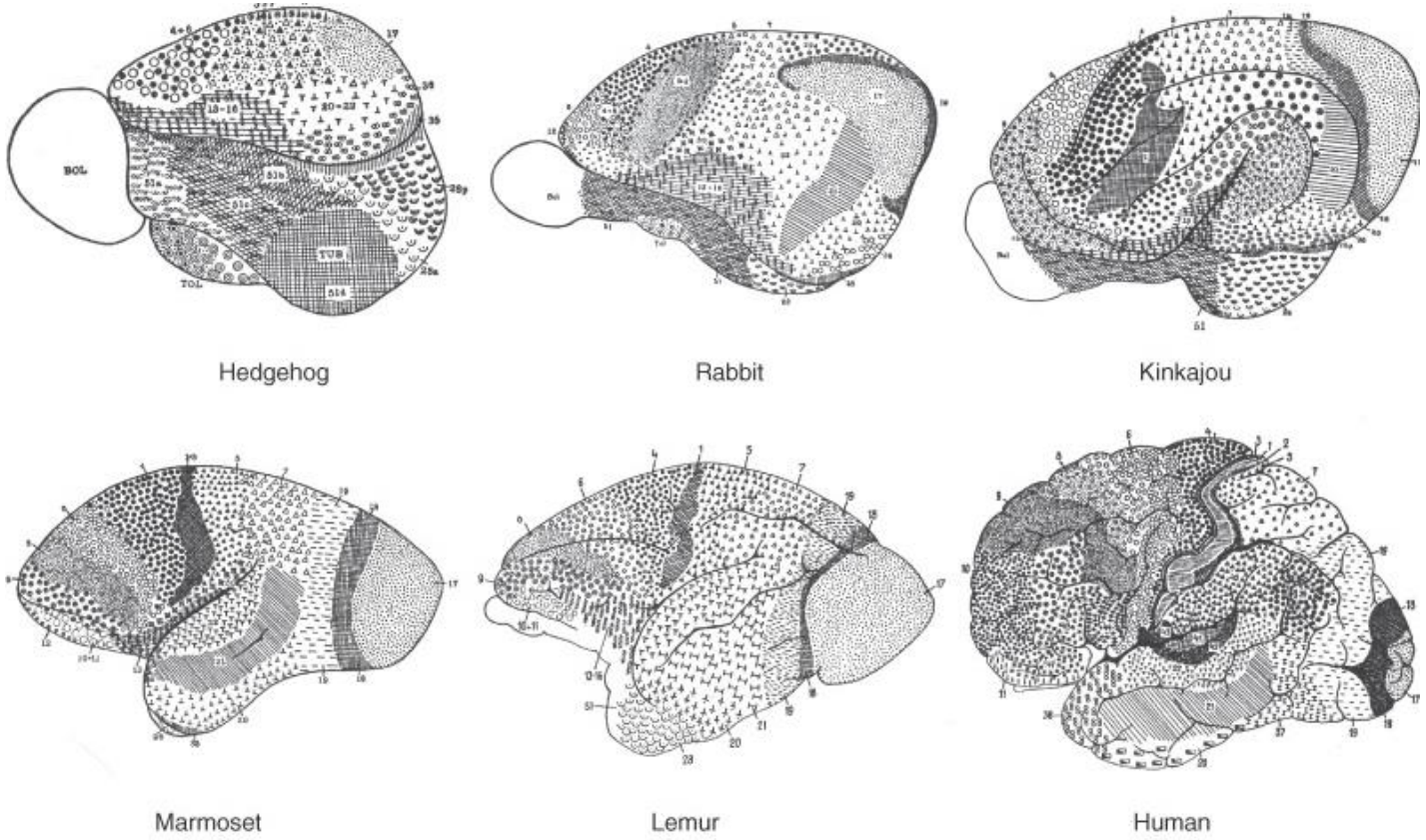
脑的功能分区：灵长类运动皮层分区，1901



英国生理学家
Charles Scott Sherrington (1852-1952)

医生
Harvey W. Cushing (1869-1939)

脑的功能分区1909：cytoarchitectonics



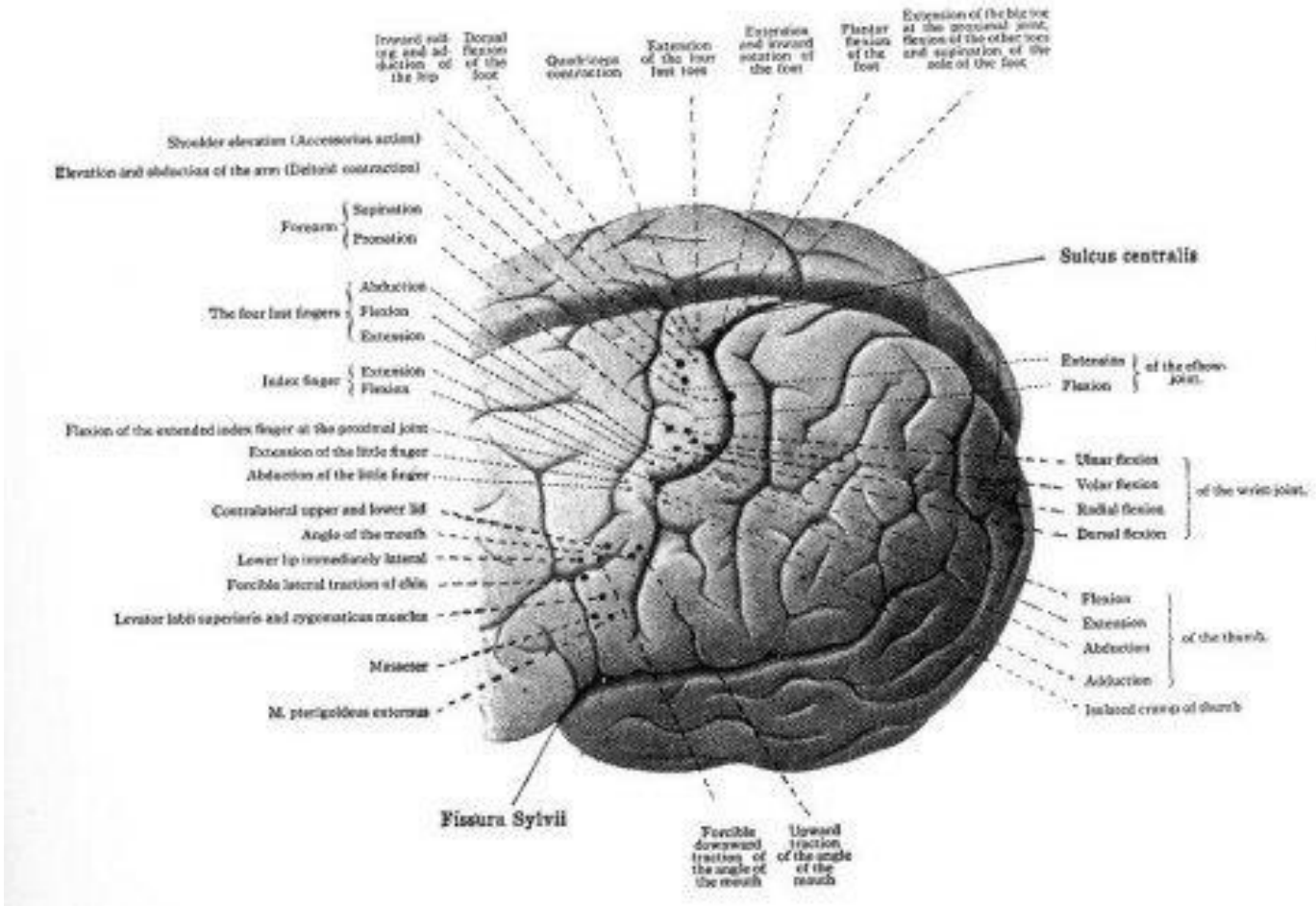
德国神经内科医生 Korbinian Brodmann (1868-1918)

1903-1908发表6篇文章在 *Journal für Psychologie und Neurologie.*

Brodmann, K. (1909) *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*, Leipzig: J. A. Barth. Translated by Laurence Garey as Localisation in the Cerebral Cortex (1994), London: Smith-Gordon.

Squire et al. (2008) *Fundamental Neuroscience*

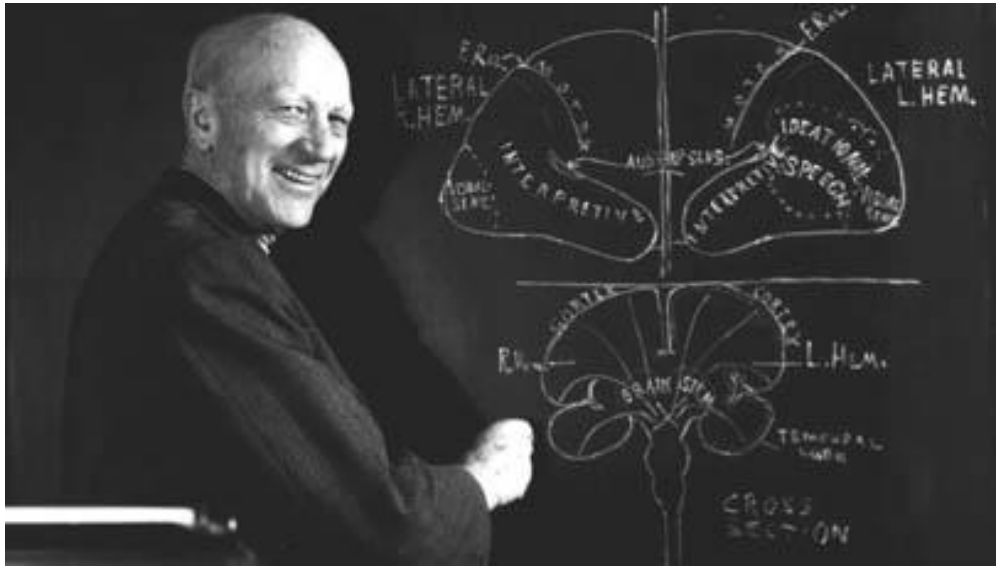
脑的功能分区：142人脑， 1902-1912



德国神经外科医生
Fedor Krause (1857-1937)

脑的功能分区

Wilder Graves Penfield
(1891 – 1976)



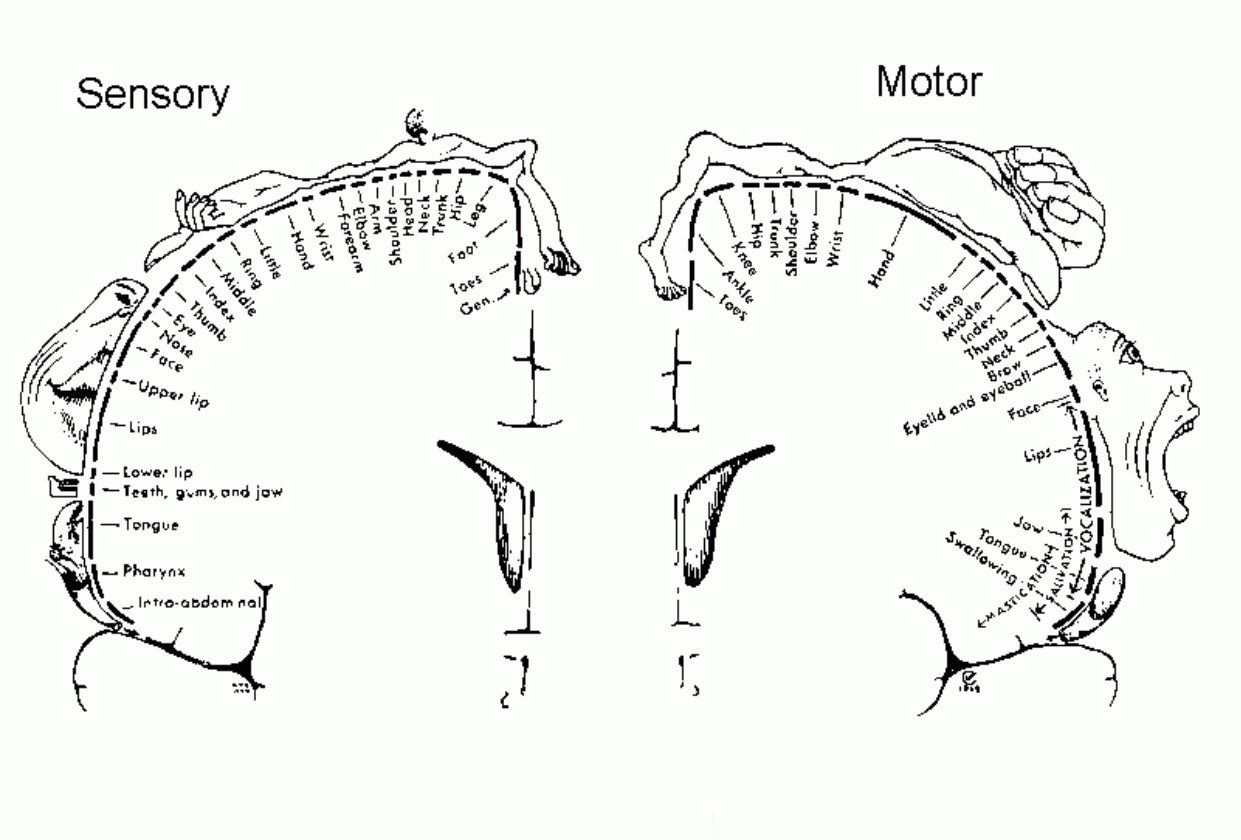
Jasper, H., and Penfield, W. (1951). *Epilepsy and the Functional Anatomy of the Human Brain.* 2nd edition. Little, Brown and Co.

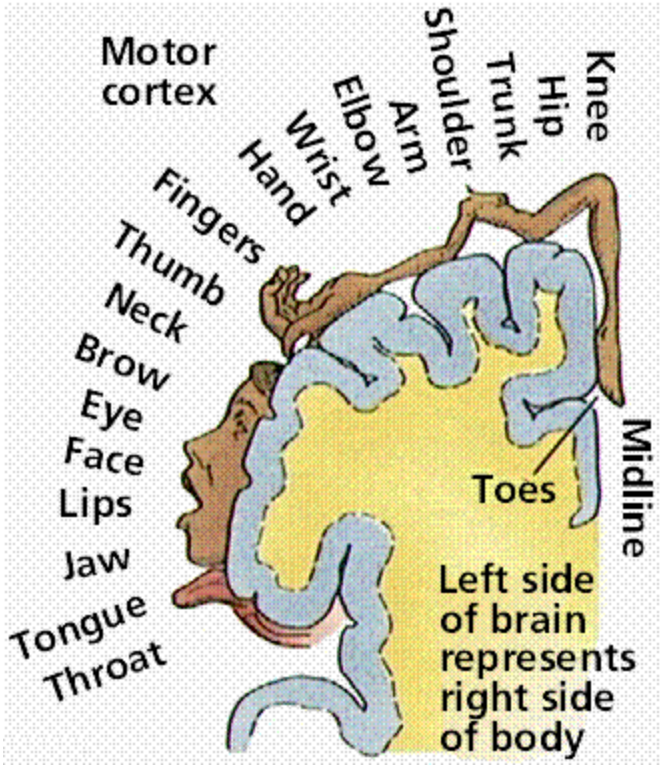
治疗癫痫病人
治疗前刺激脑区

Montreal Neurological Institute, 1934
Rockefeller Foundation
McGill University

脑的功能分区

Cortical Homunculus





W. Penfield and T. Tasmussen, 1950

Purves et al., Life: The Science of Biology, 4th Edition, Sinauer Associates

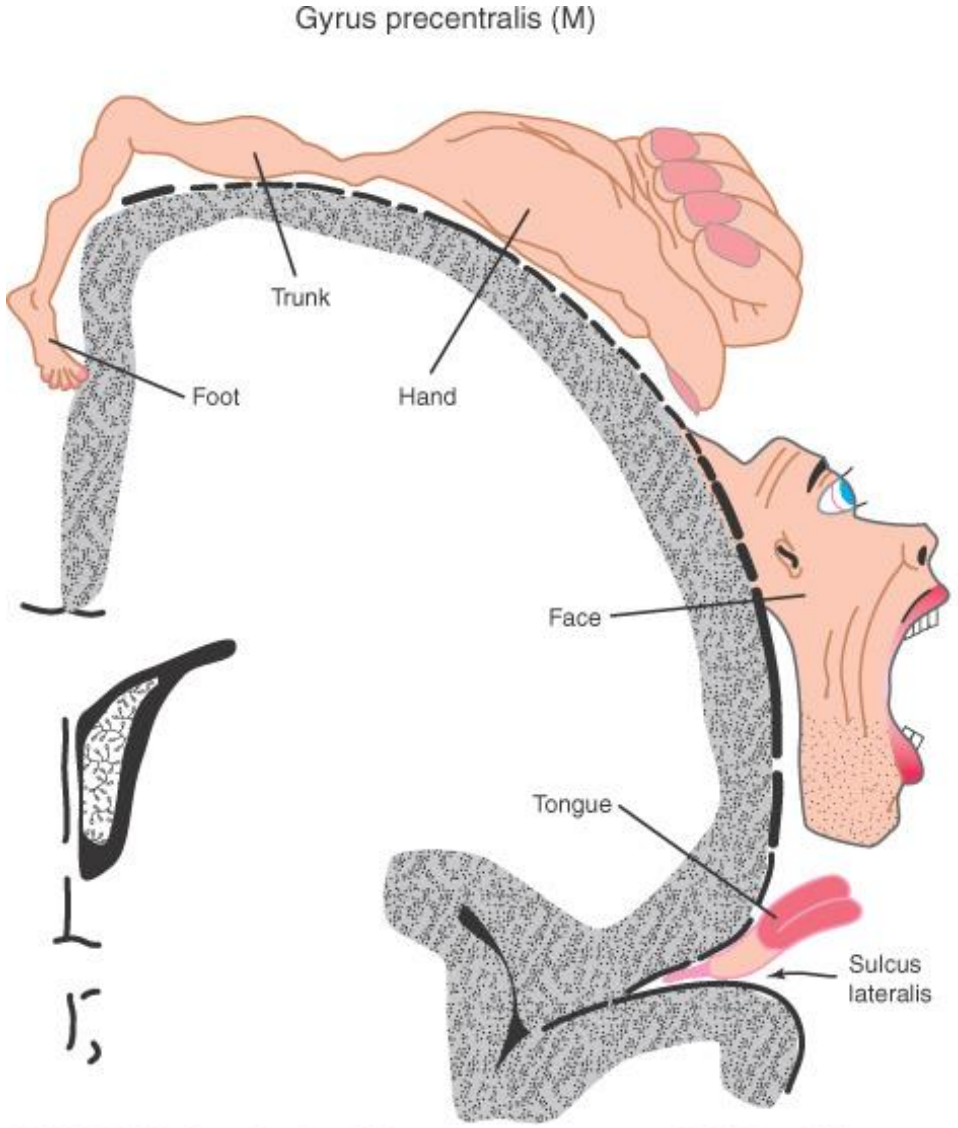
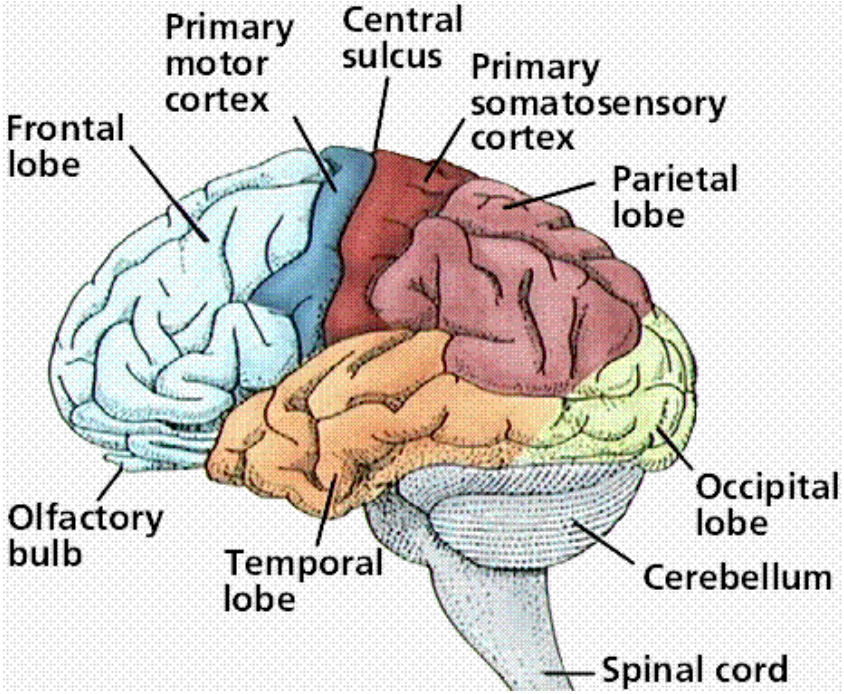
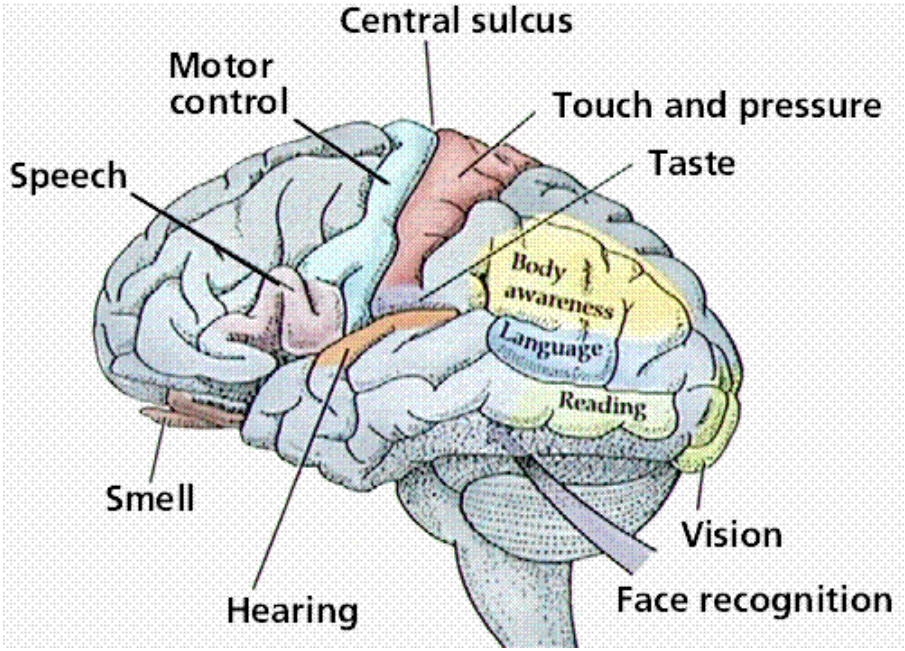


FIGURE 28.6 Organization of the primary motor cortex (M1). The different parts of the body are represented in a somatotopic fashion in M1, with the legs represented most medially, arms and hand more laterally, and the oral cavity and face even more so. Note that the two areas that are represented with disproportionally large regions are the hand with fingers and the oral cavity. They are represented in this way due to the fine control required in speech and fine manipulation of objects with the fingers. Adapted from Penfield and Rasmussen (1950).

Squire et al. (2008) *Fundamental Neuroscience*

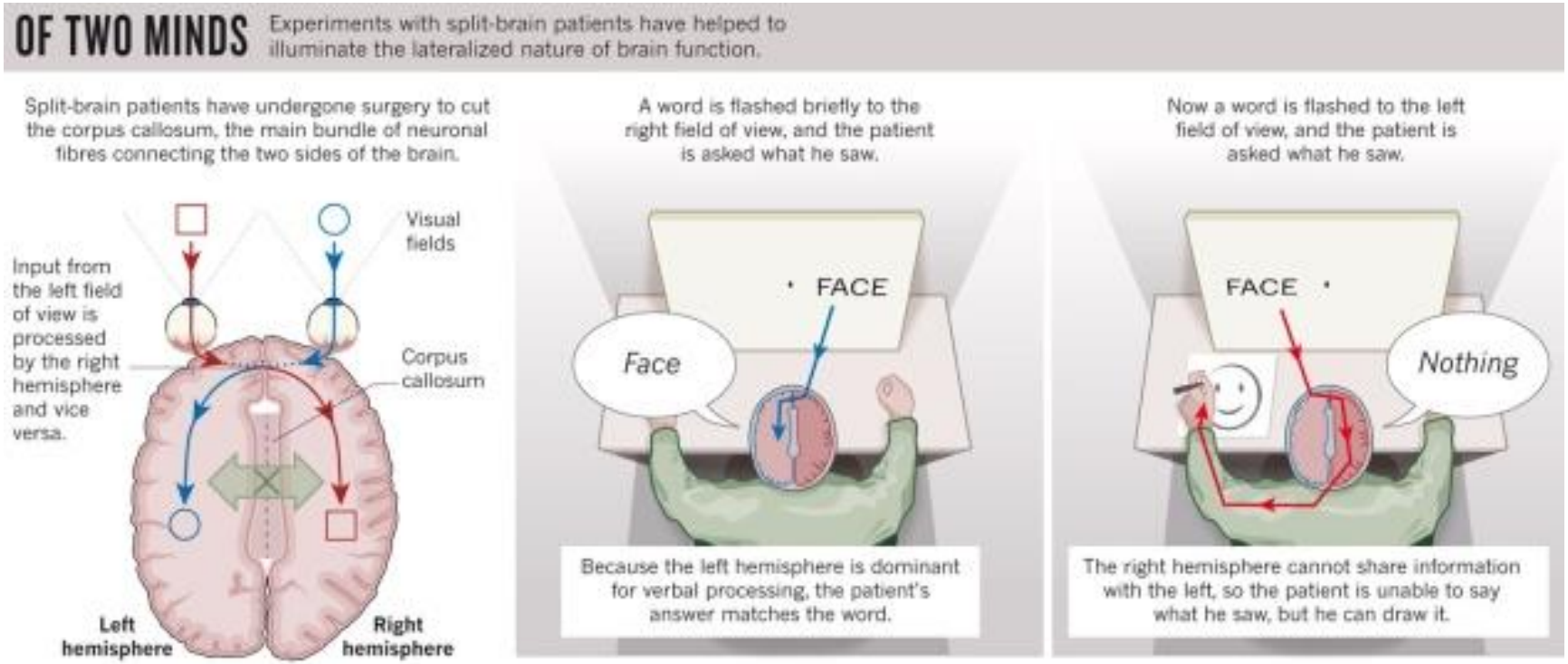
脑的功能分区:现在





Purves et al., Life: The Science of Biology, 4th Edition, Sinauer Associates

脑的功能分区：两半球的差别

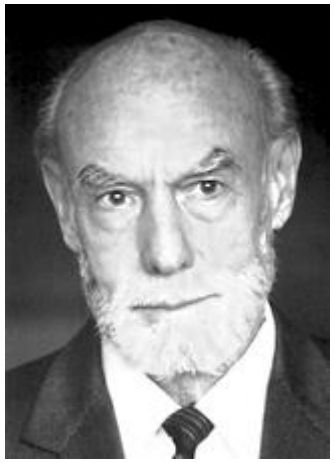


Wolman D (2012) Nature 483

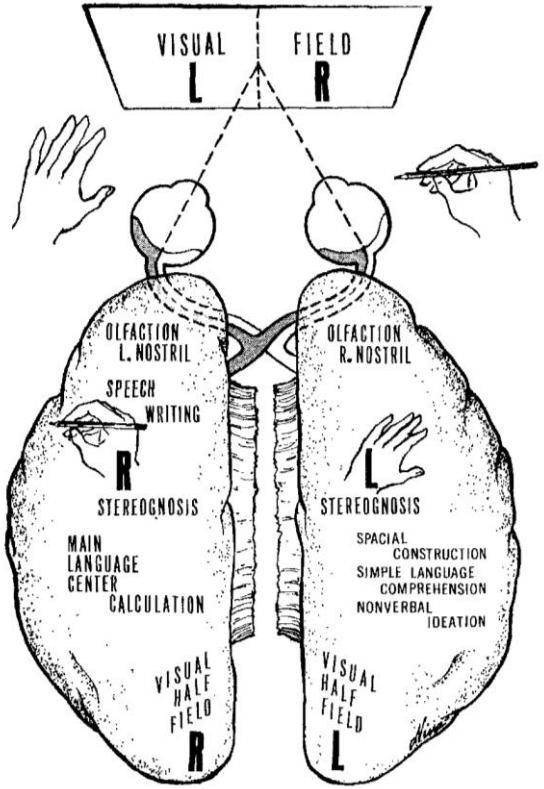
脑的功能分区：两半球的差别

Michael Gazzaniga

脑的功能分区：两半球的差别



Roger Sperry



Michael Gazzaniga

Gazzaniga, M. S., Bogen, J. E. and Sperry, R. W. (1962) Some functional effects of sectioning the cerebral commissures in man. Proc. Natl. Acad. Sci. 48, Part 2, 1765-1769

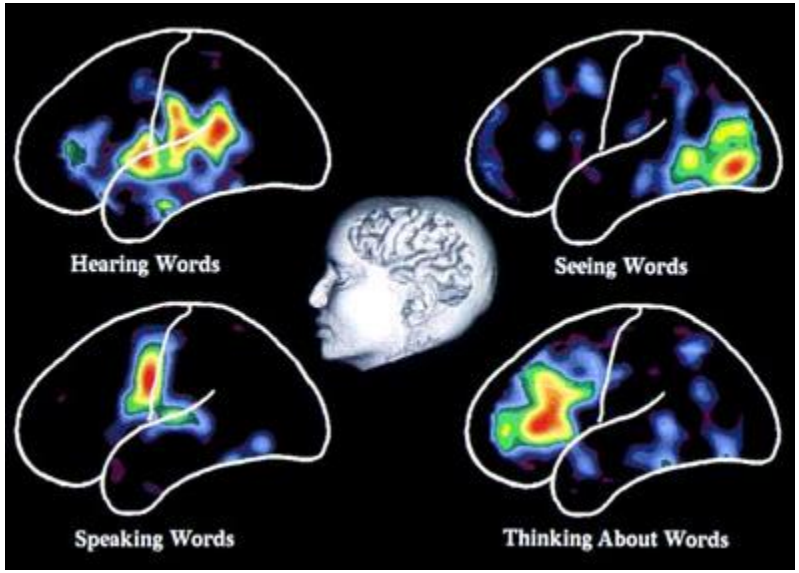
Gazzaniga, M. S., Bogen, 3. E. and Sperry, R. W. (1963) Laterality effects in somesthesis following cerebral commissurotomy in man. Neuropsychologia 1, 209-215.

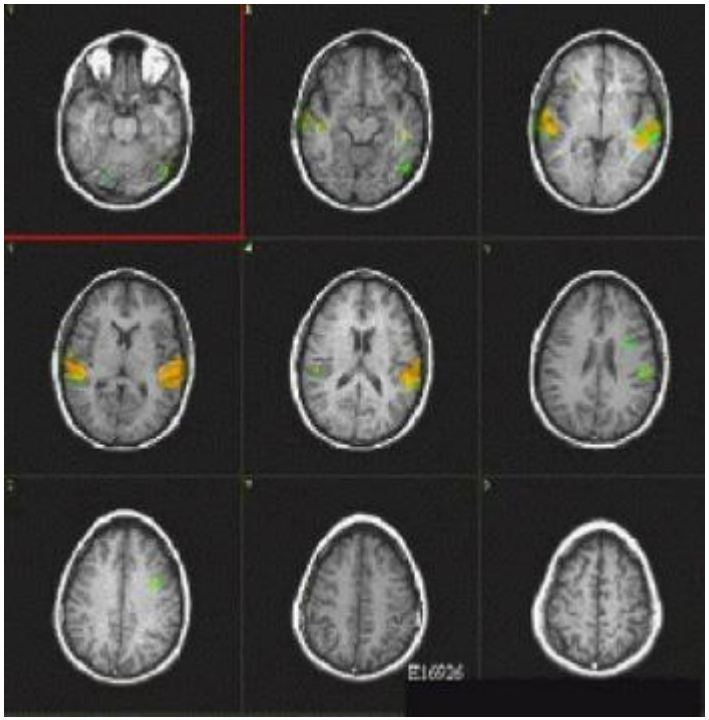
Gazzaniga, M. S., Bogen, 3. E. and Sperry, R. W. (1965) Observations on visual perception after disconnection of the cerebral hemispheres in man. Brain 88, Part 2, 22 1-236

Gazzaniga, M. S. and Sperry, R. W. (1967) Language after section of the cerebral commissures. Brain 90(1), 13 1-148.

脑的功能分区

PET & fMRI



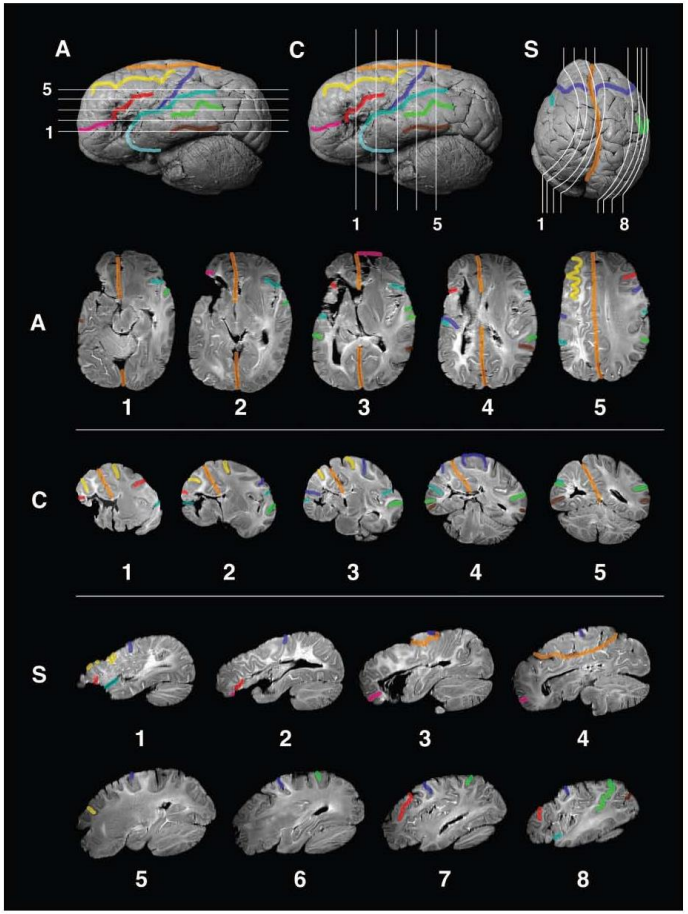


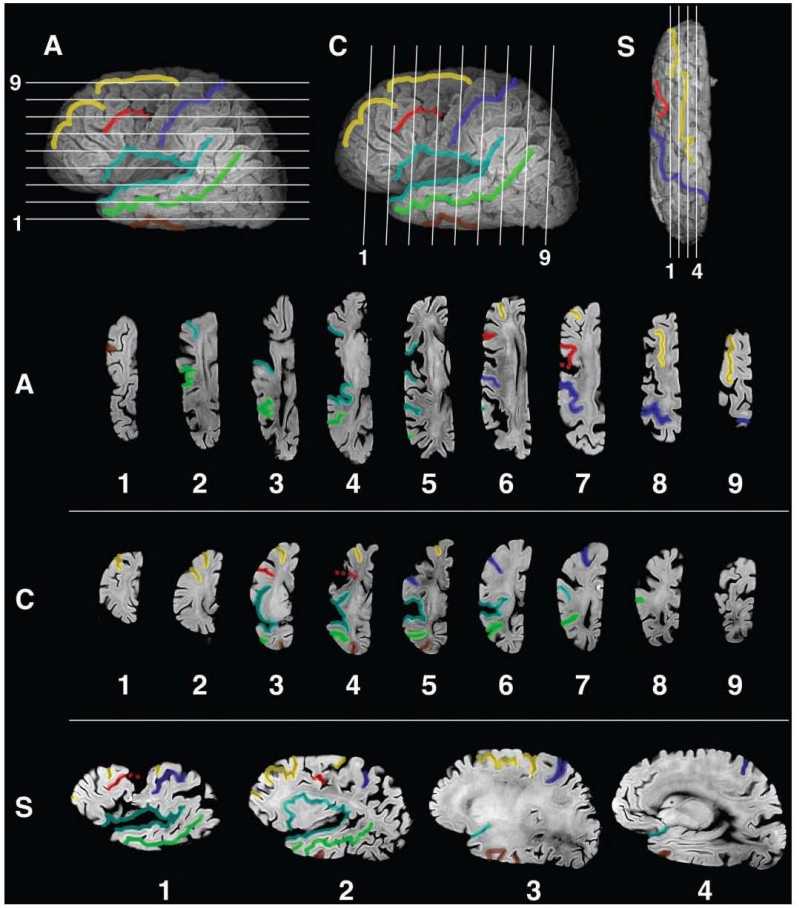
S. E. Petersen, P. T. Fox, M. 1. Posner, M. A. Minmn, M. E. Raichle （1988） *Nature* 331:585

Ogawa, S., Lee, T.M., Nayak, A.S., and Glynn, P. (1990). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magnetic Resonance in Medicine* 14: 68–78

重访150年前的大脑: MRI

We found that both patients' lesions extended significantly into medial regions of the brain, in addition to the surface lesions observed by Broca. Results also indicate inconsistencies between the area originally identified by Broca and what is now called Broca's area





Dronkers NF, Plaisant O, M. T. Iba-Zizen, &E. A. Cabanis (2007). "Paul Broca's Historic Cases: High Resolution MR Imaging of the Brains of Leborgne and Lelong". *Brain* 130:1432–1441.

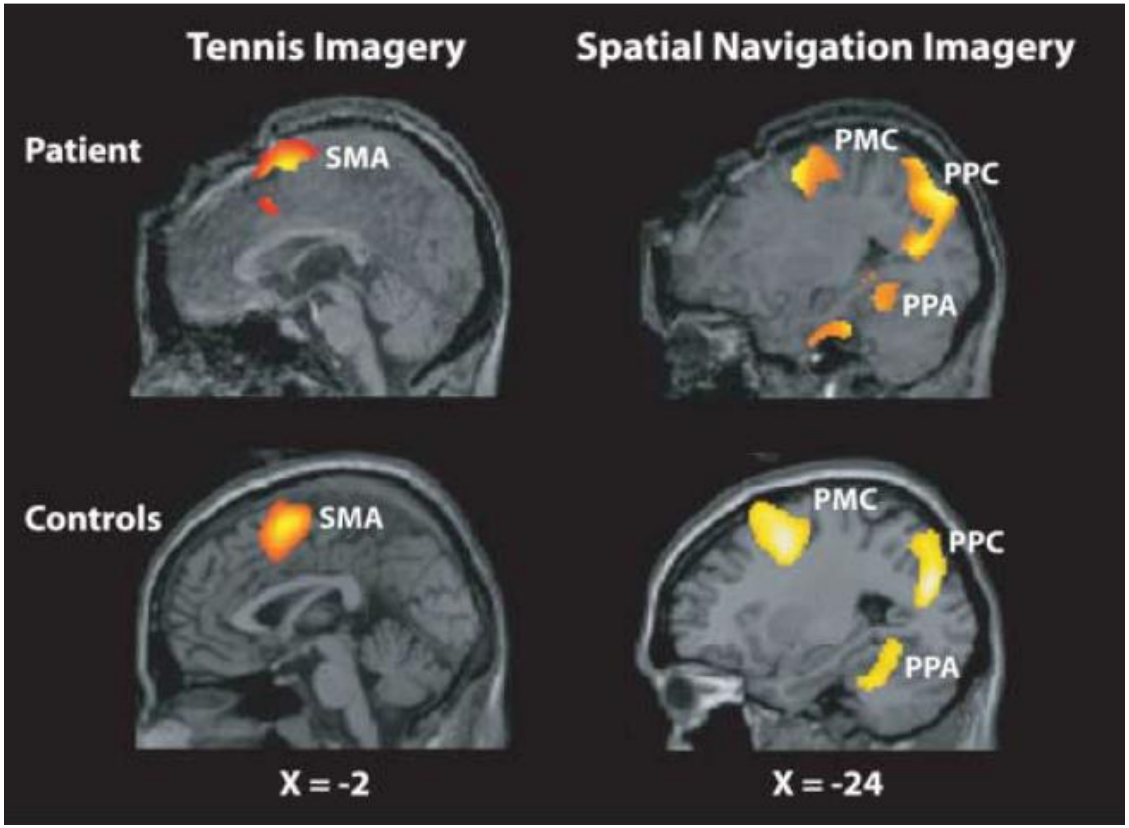
脑的功能分区：没有完结

PET & fMRI

音乐家和普通人听音乐
大师和普通人下棋
人们做经济决定
…

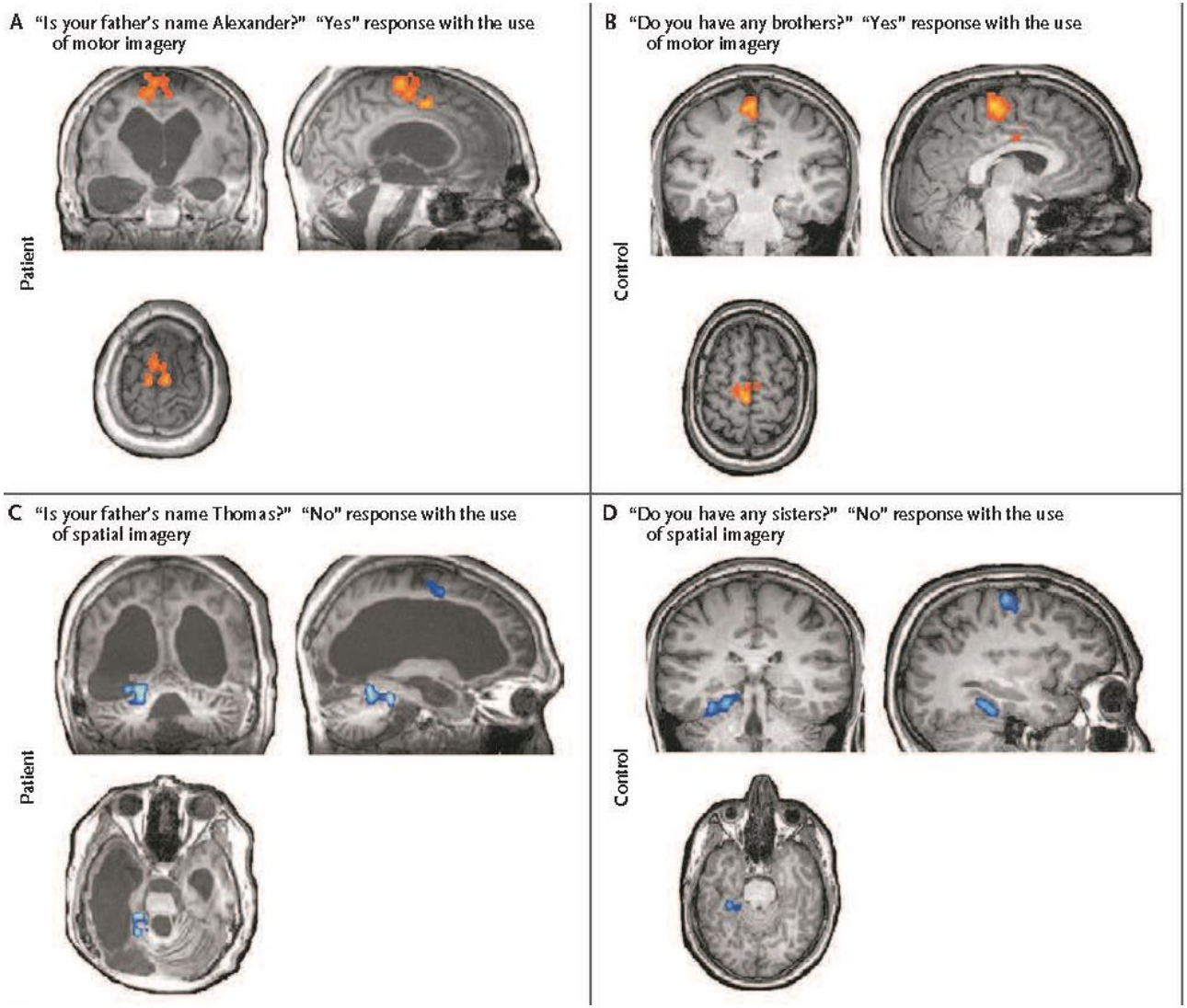
哪个脑区亮了
哪些脑区亮的相关性
哪些暗了
…

见证奇迹：与植物人交流



Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD (2006). Detecting awareness in the vegetative state. *Science* 313:1402.

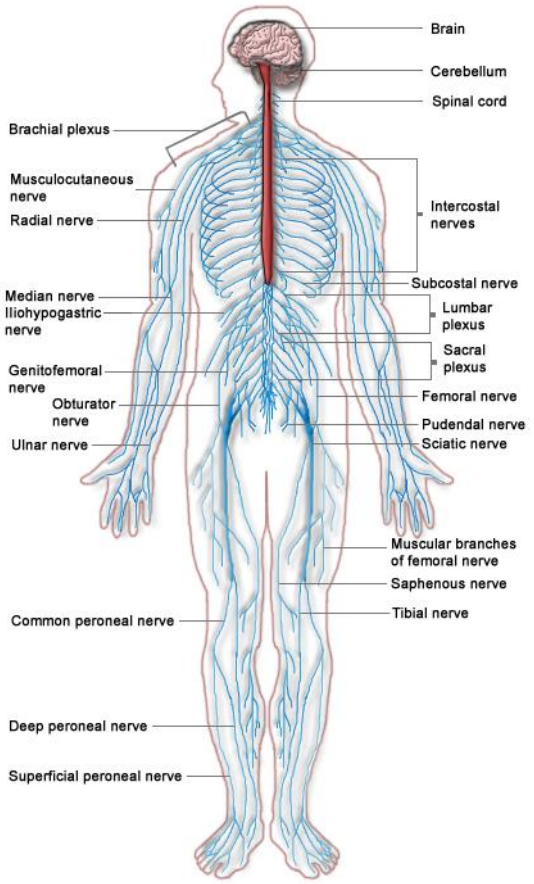
见证奇迹：与植物人交流



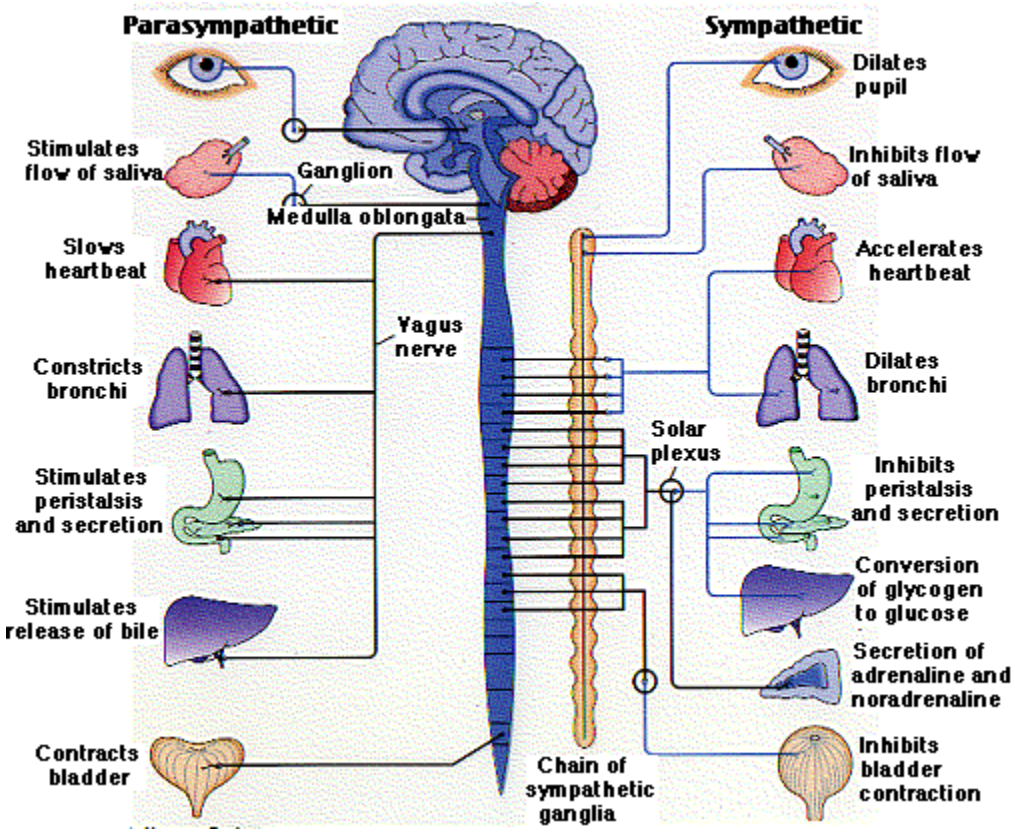
Monti MM, Vanhaudenhuyse A, Coleman MR, BolyM, Pickard JD, Tshibanda L, Owen AM, Laureys S (2010) Willful modulation of brain activity in disorders. *NEJM* 362:579-589.

外周神经系统
Peripheral Nervous System

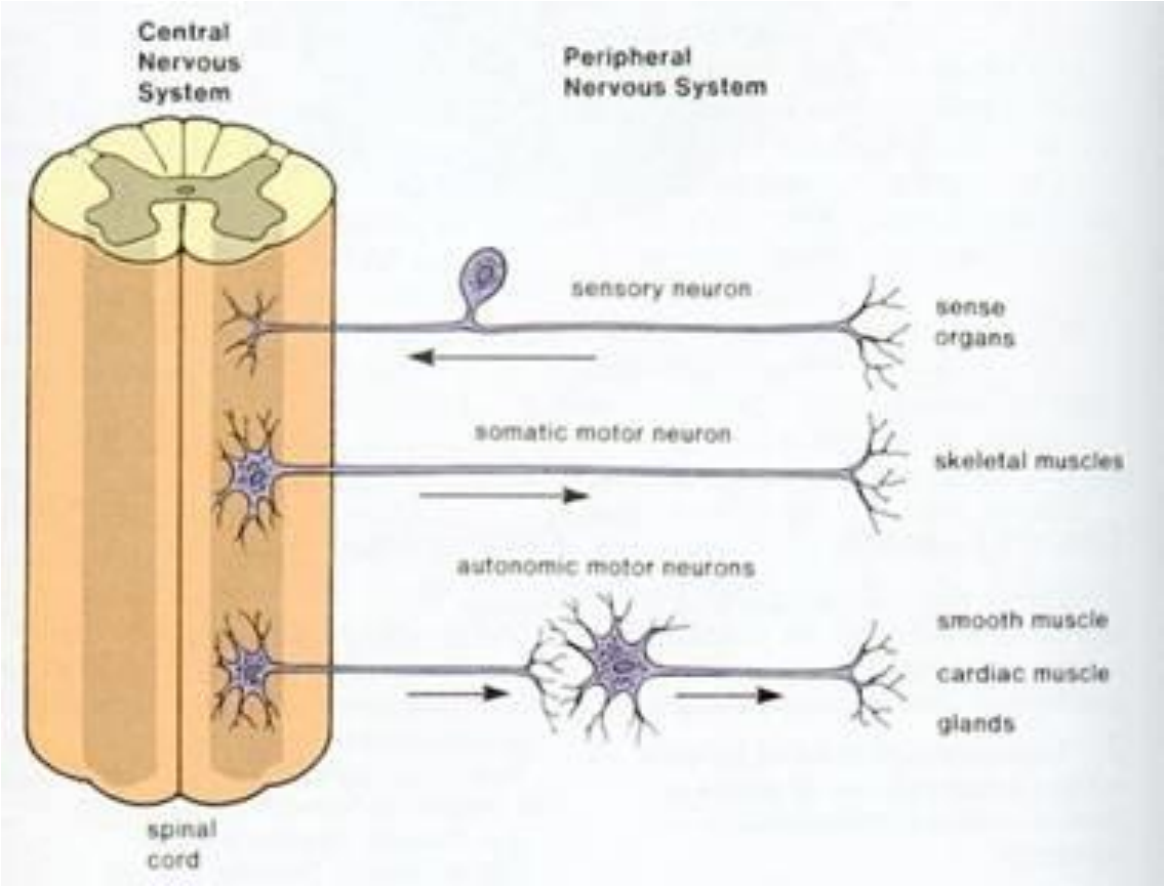
外周感觉和运动神经



自主神经系统
Automic Nervous System



外周神经系统 PNS



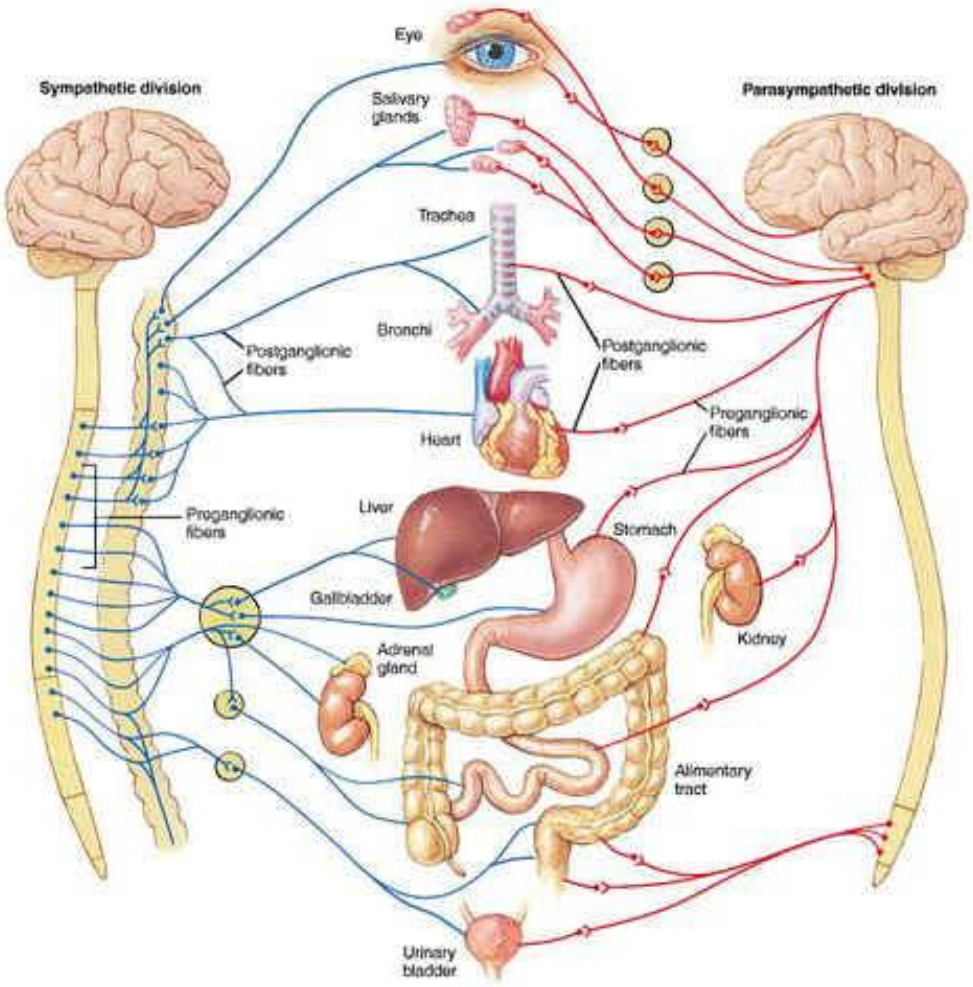
外周感觉神经

外周运动神经

自主神经系统

自主神经系统

交感神经　　副交感神经



sympathetic　　**parasympathetic**

Neuroscience

结构

形态

大体

细胞

神经环路

功能

神经传递

自主功能

高级功能

来源

进化

发育

Neuron Theory vs Reticular Theory

Santiago Ramón y Cajal (1852 –1934)

1839, the cell theory
M.J. Schleiden and T. Schwann

Camillo Golgi (1843-1926)

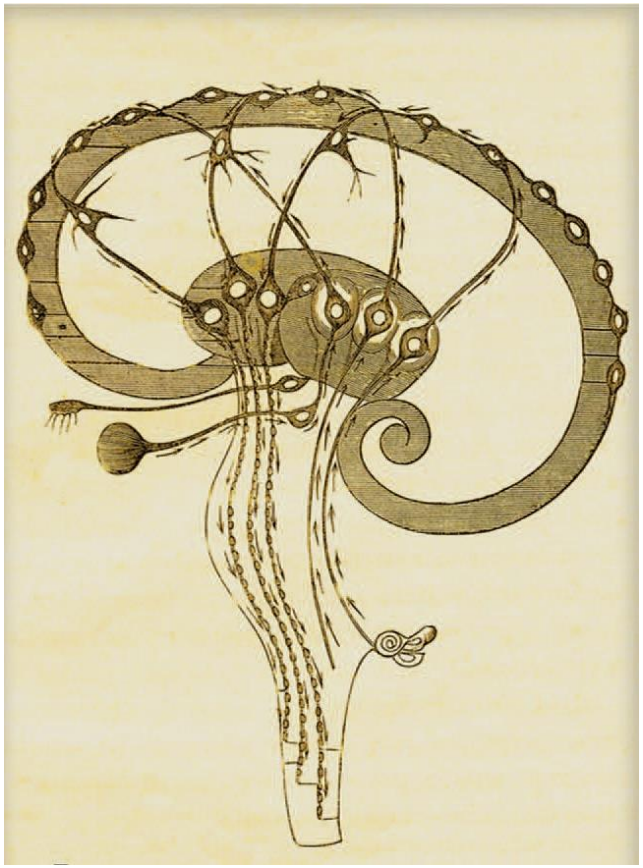
1906

Golgi C (1873). Sulla struttura della sostanza grigia del cervelo, *Gazzetta Medica Italiana. Lombardia* 33:244–246.

1871, the reticular theory by Josef von Gerlach

De Carlos JA, Borrell J (2007) A historical reflection of the contributions of Cajal and Golgi to the foundations of neuroscience. Brain Res Rev 5 5 : 8 – 1 6

The Reticular Theory



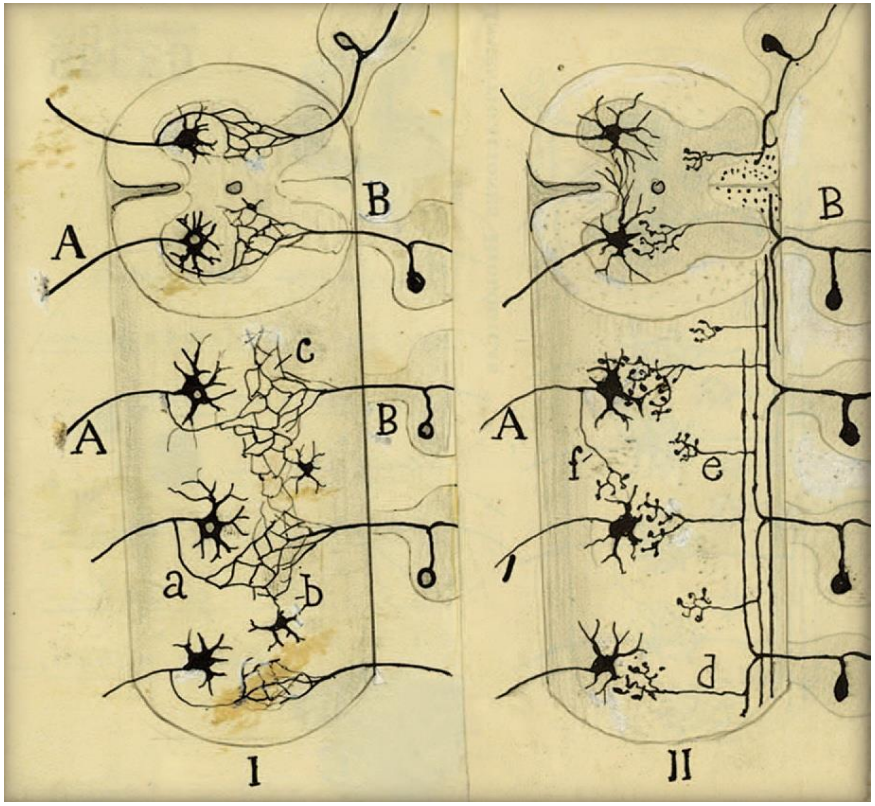
Luys, 1878

Josef von Gerlach, 1871

Dogiel ,1893 and 1899

DeFelipe J (2010). *Science* 330:1198-1201

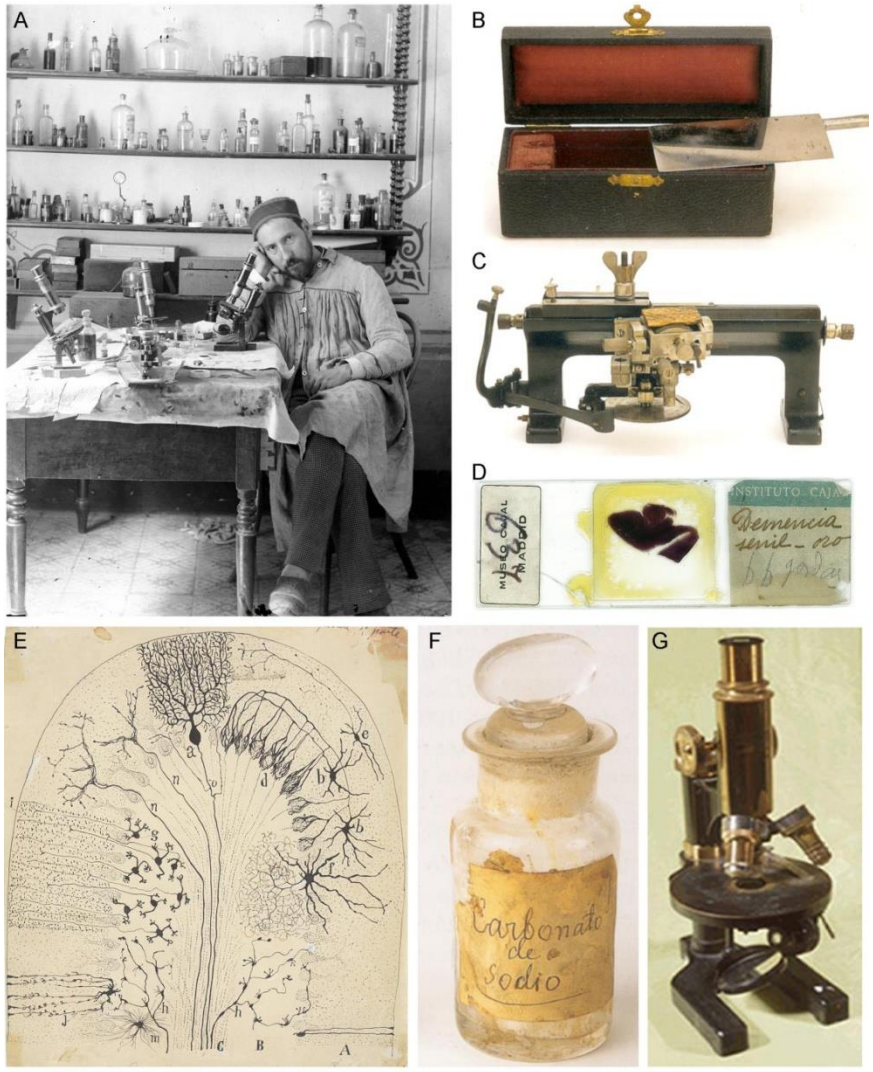
Neuron Theory vs Reticular Theory



Scheme to compare Golgi's concept regarding the sensorymotor connections in the spinal cord (I) with the results of my own studies (II). A, anterior roots; B, posterior roots; a, collateral of a motor root; b, cells with a short axon that, according to Golgi, would intervene in the formation of the network; c, diffuse interstitial network; d, our long collaterals in contact with the motor cells; e, short collaterals; f, collateral of a motor root."

Ramón y Cajal, S(1917). *Recuerdos de mi Vida*, Moya, Madrid.
DeFelipe, J. (2010). *Science* 330:1198-1201

Cajal

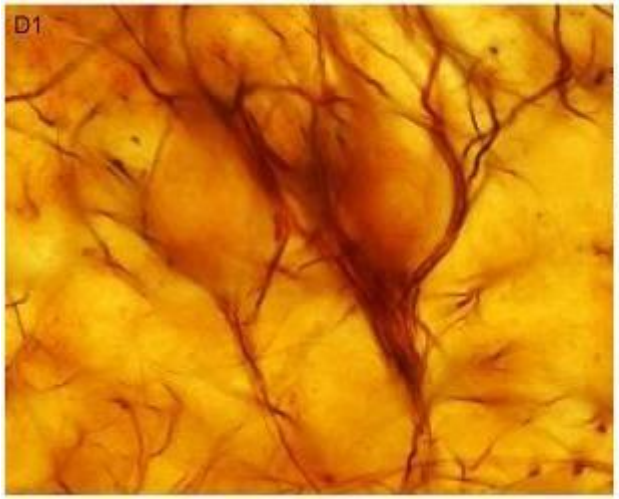


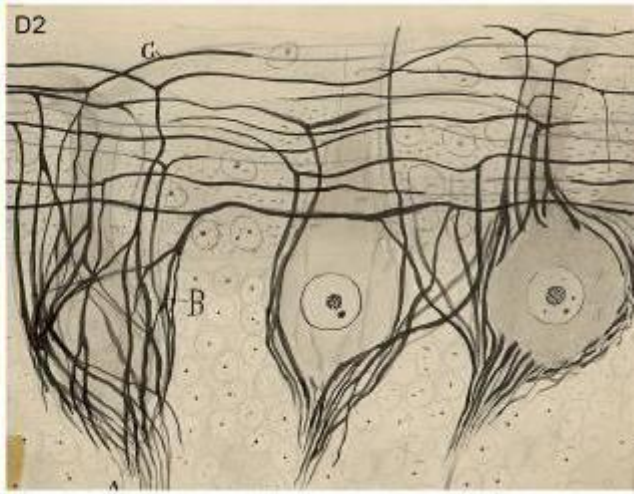
简陋的工具
无限的热情
丰富的想象
长期的影响

Garcia-Lopez P, Garcia-Marin V, and Freire M.(2010) The Histological Slides and Drawings of Cajal. *Frontiers in Neuroanatomy* 4:9

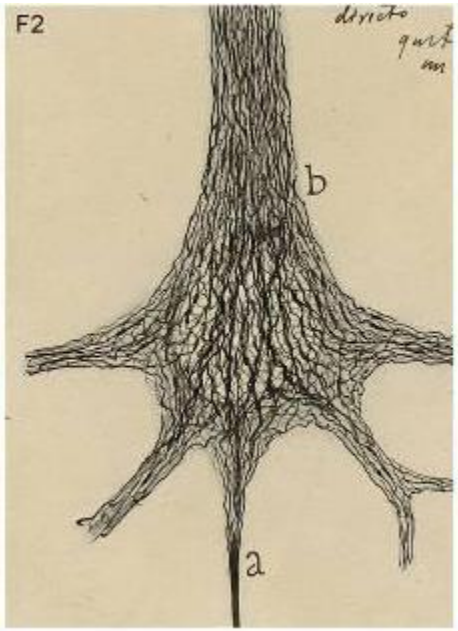
Cajal's slides today

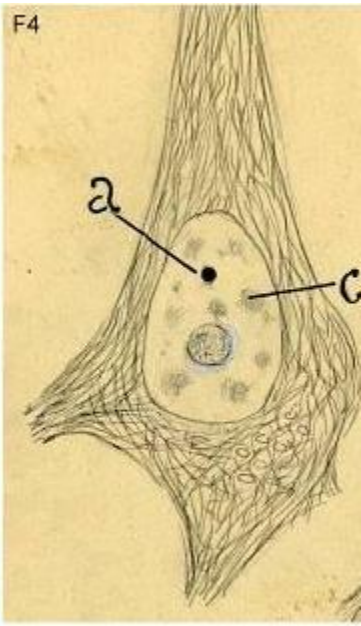
今人重新看其切片





Cajal 当时发表的图





Garcia-Lopez P, Garcia-Marin V, and Freire M.(2010) The Histological Slides and Drawings of Cajal. *Frontiers in Neuroanatomy* 4:9

Neuronal Polarity: directional flow of current

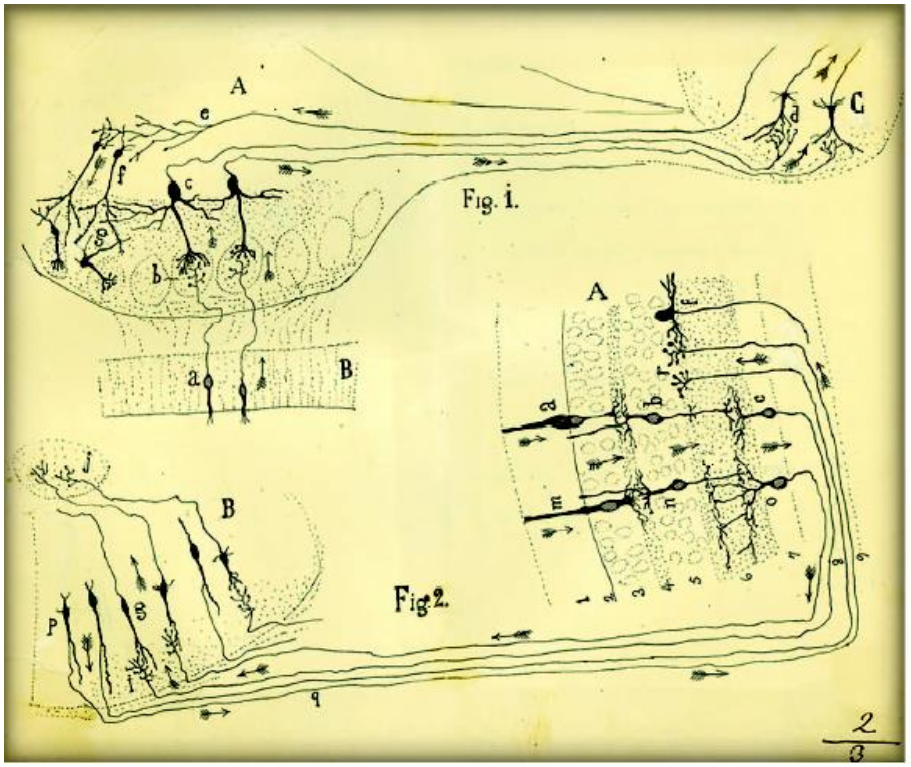
Cajal proposed in 1891 that neurons showed a morphological and functional polarization in such a way that neurons could be divided in general into three functionally distinct regions: a receptor apparatus (formed by the dendrites and soma), the emission apparatus (the axon), and the distribution apparatus (terminal axonal arborization).

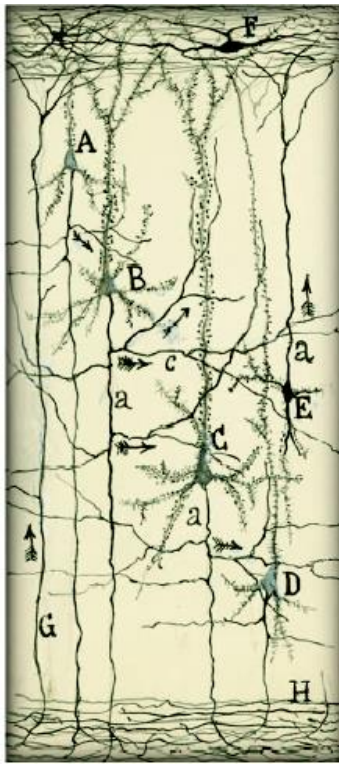
设想神经信号传递方向：

嗅觉

和

视网膜



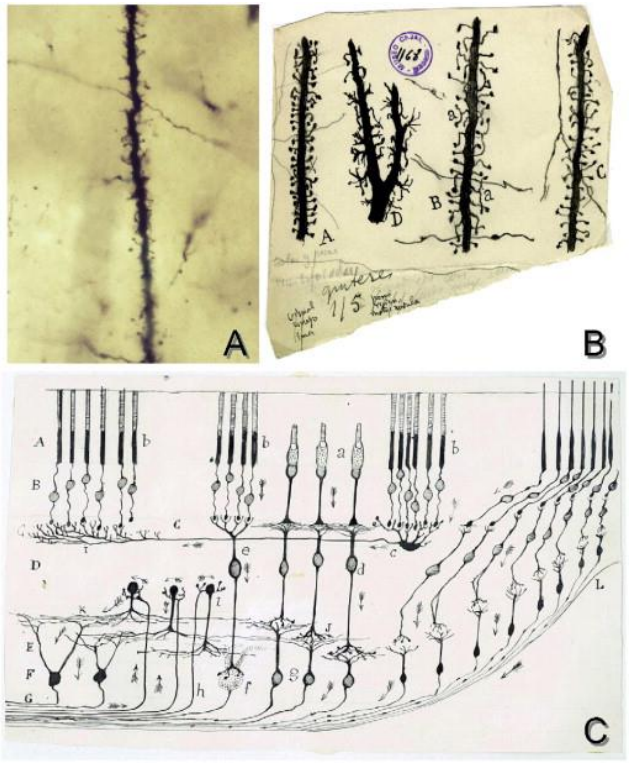


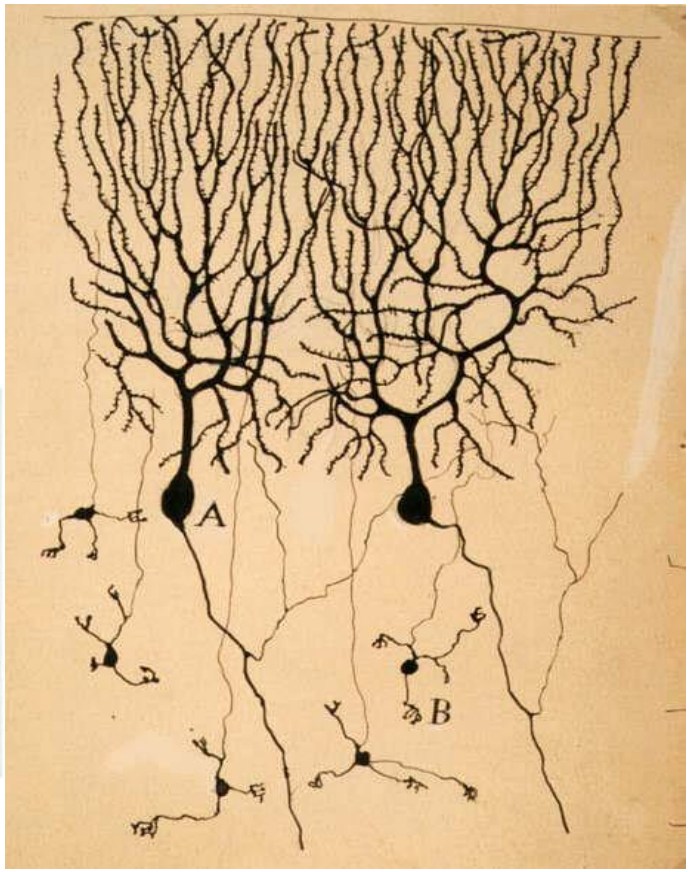
大脑皮层

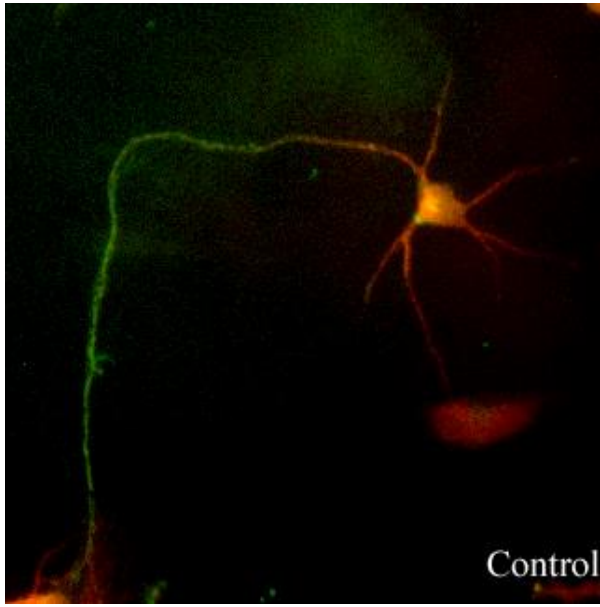
Cajal's scheme showing the flow of current (arrows) in the visual and olfactory systems to support the Law of Dynamic Polarization.

DeFelipe, J. (2010). *Science* 330:1198-1201

The Neuron Doctrine

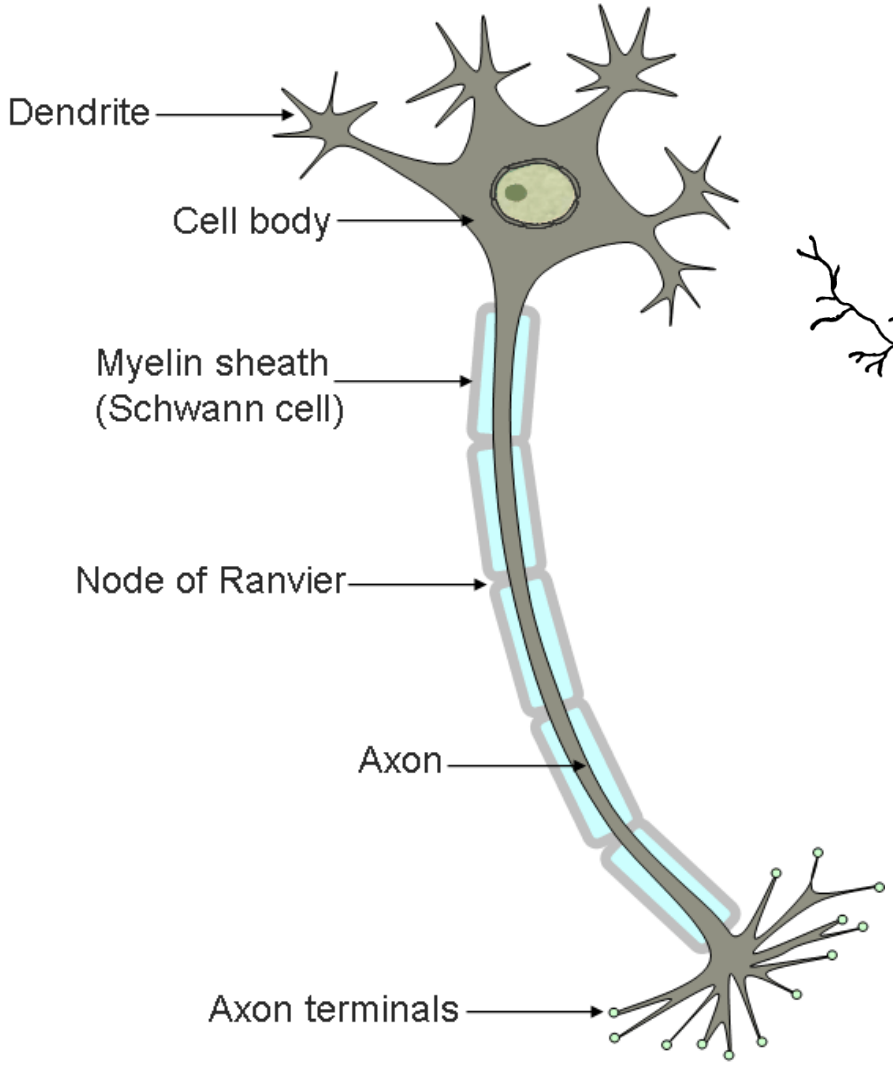


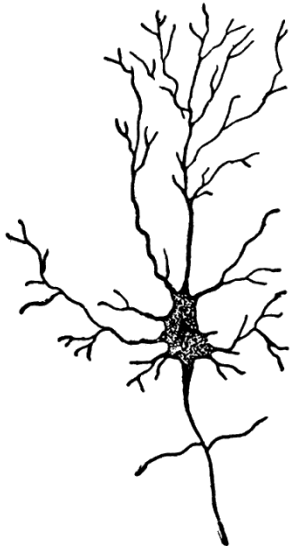


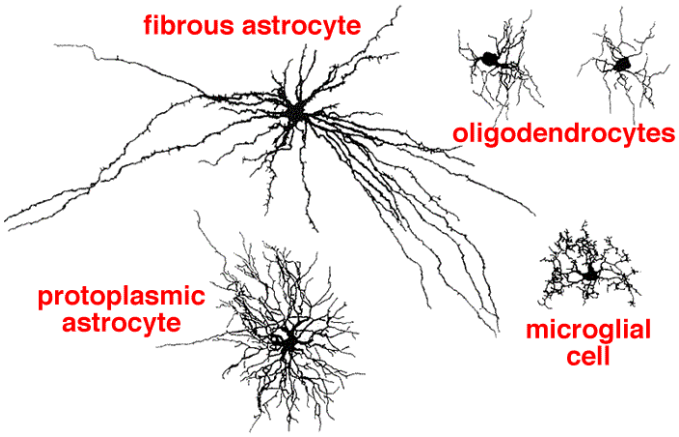


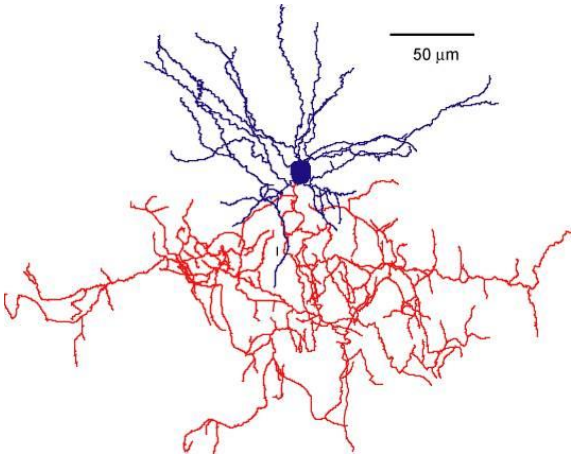
Functional Polarity

神经细胞　神经胶质细胞


Dendrite
Cell body
Myelin sheath
(Schwann cell)
Node of Ranvier
Axon
Axon terminals




fibrous astrocyte
oligodendrocytes
protoplasmic
astrocyte
microglial
cell


50 µm

Neuroscience

结构

形态

大体

细胞

神经环路

功能

神经传递

自主功能

高级功能

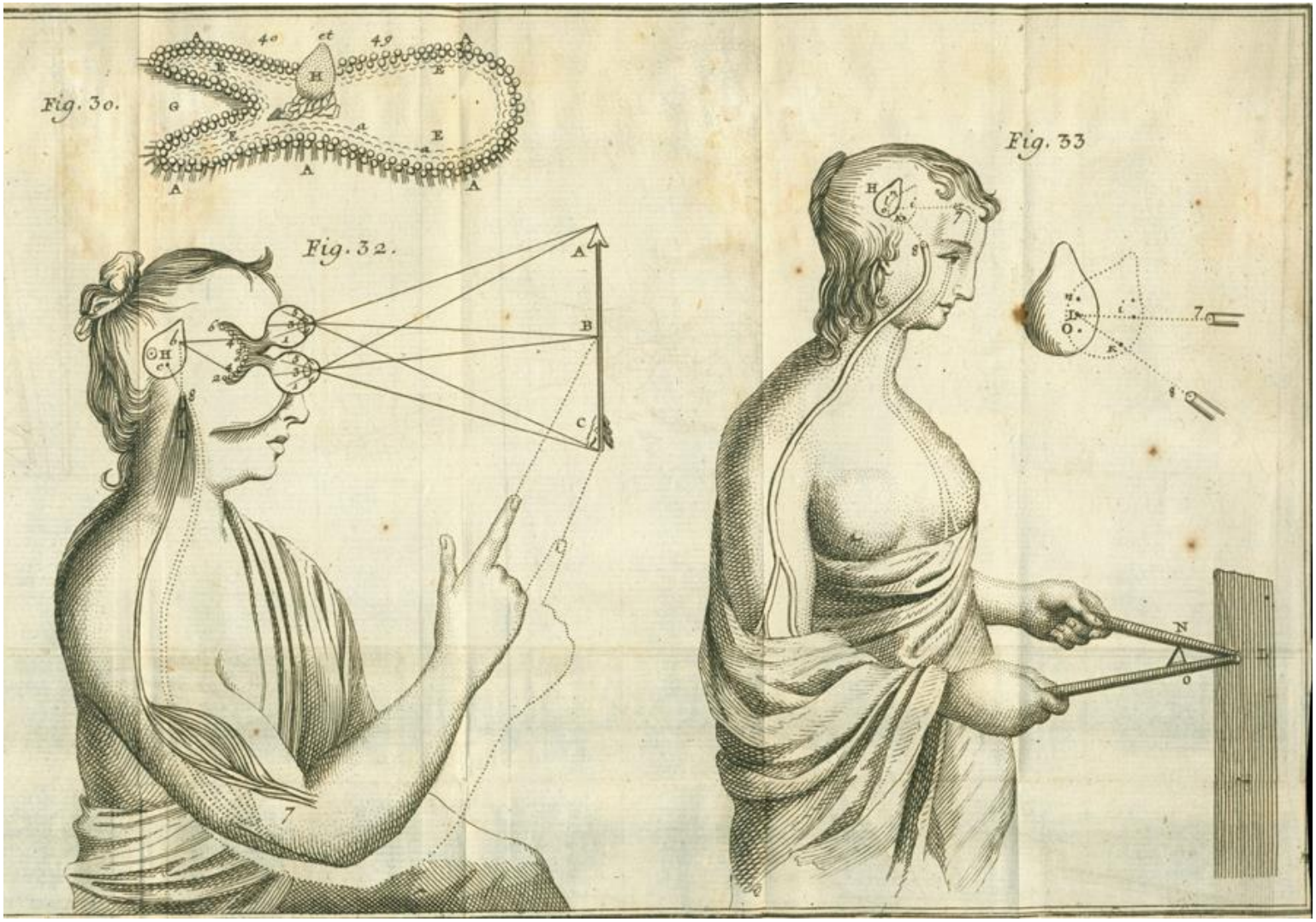
来源

进化

发育

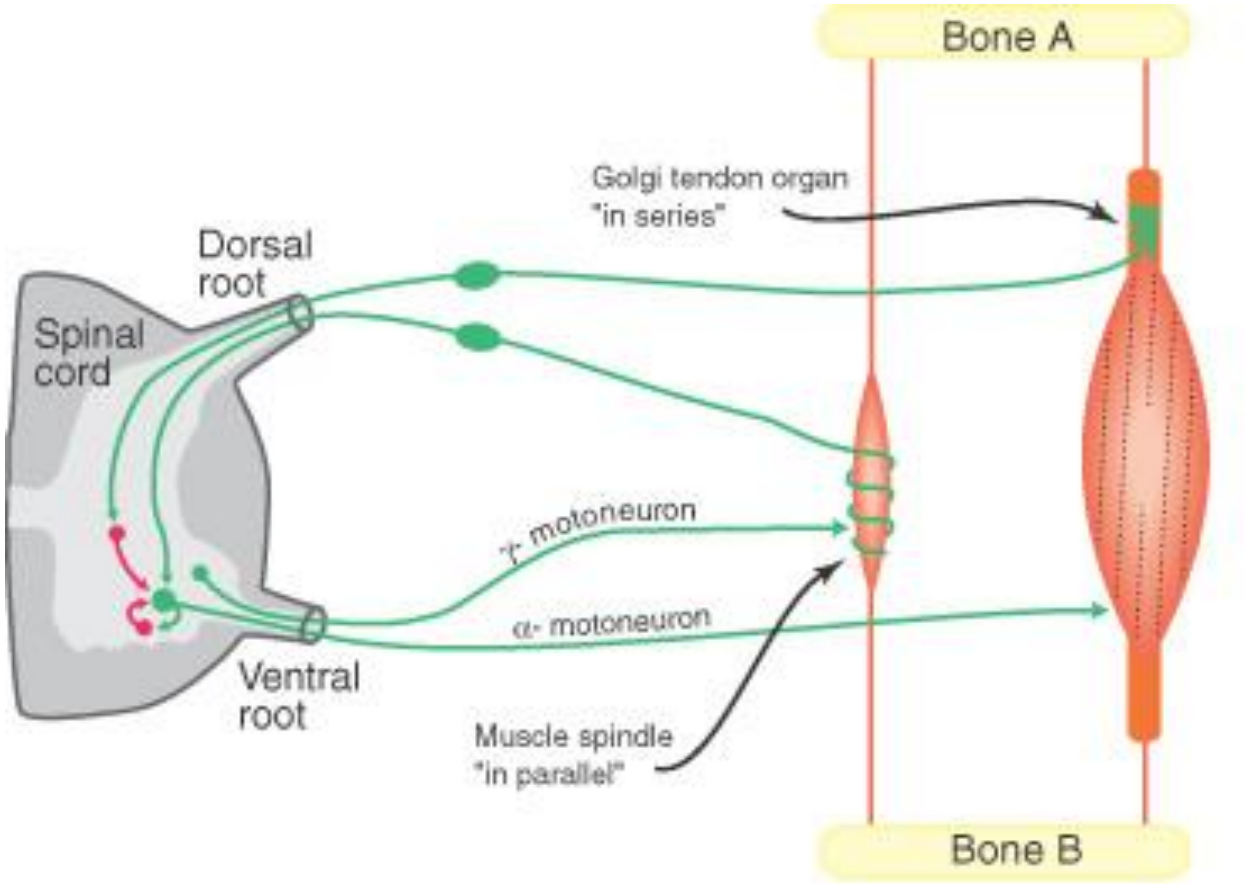
神经环路

Rene Descartes的想象



简单已知神经环路：牵张反射

Vertebrate Stretch Reflex

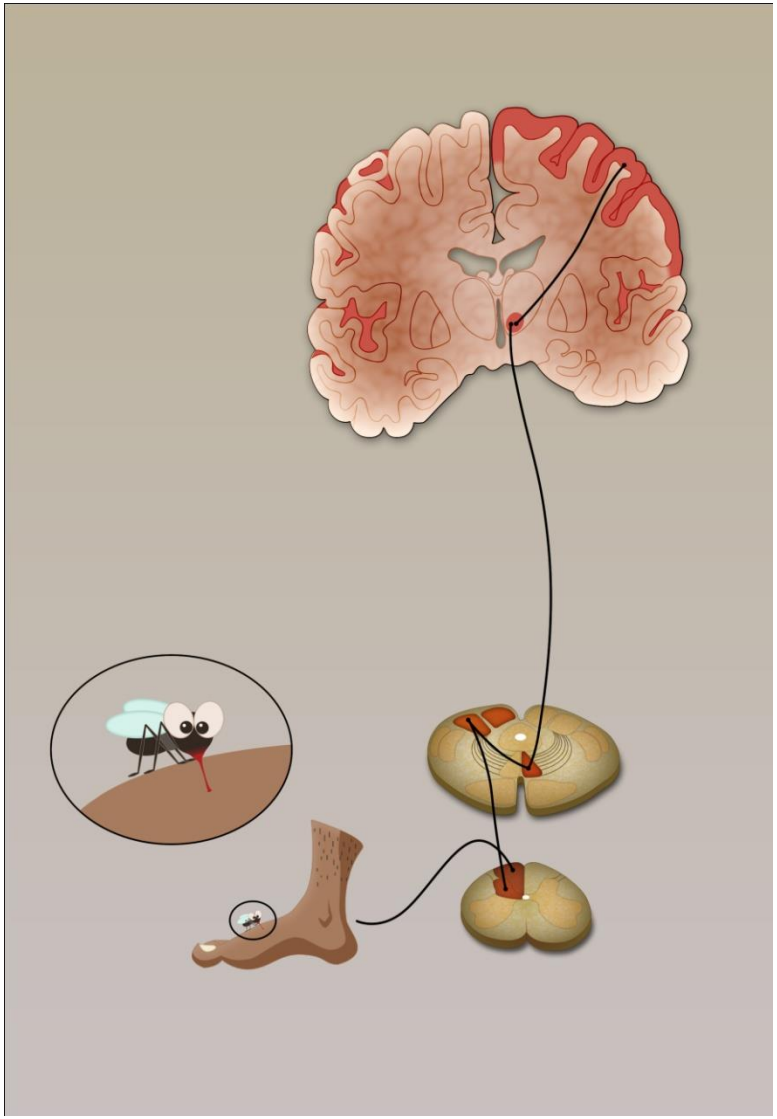


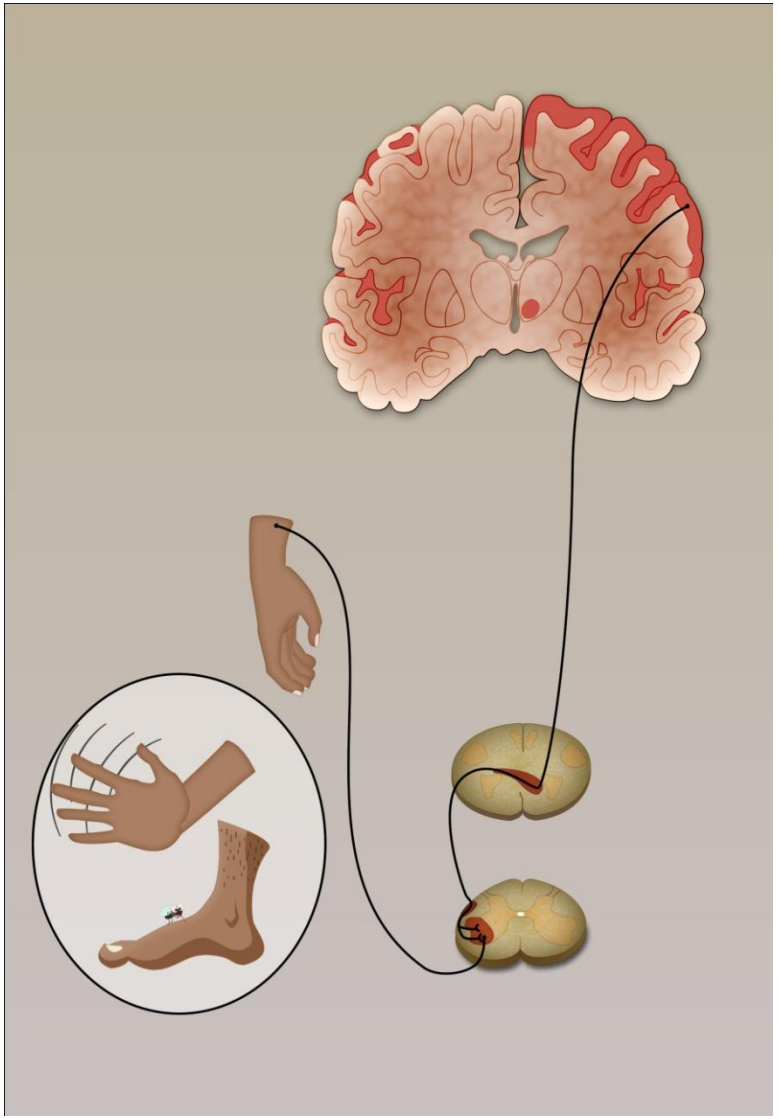
Negative length feedback by muscle spindle: stretch reflex

Negative force feedback by Golgi tendon organ

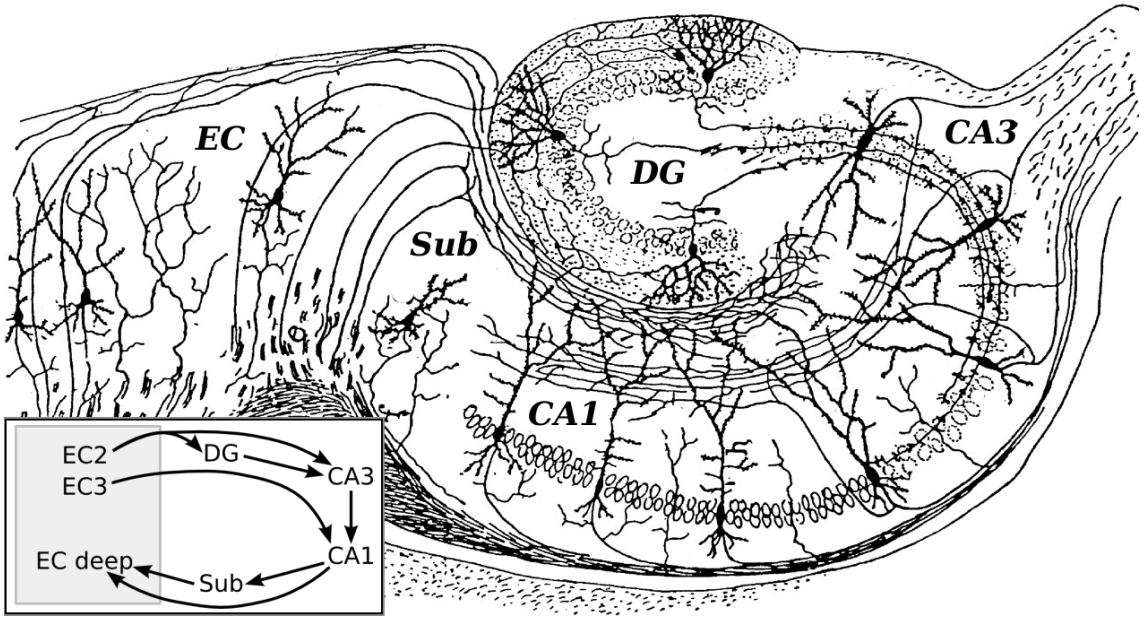
Squire et al. (2008) *Fundamental Neuroscience*

神经环路:体躯感觉和运动

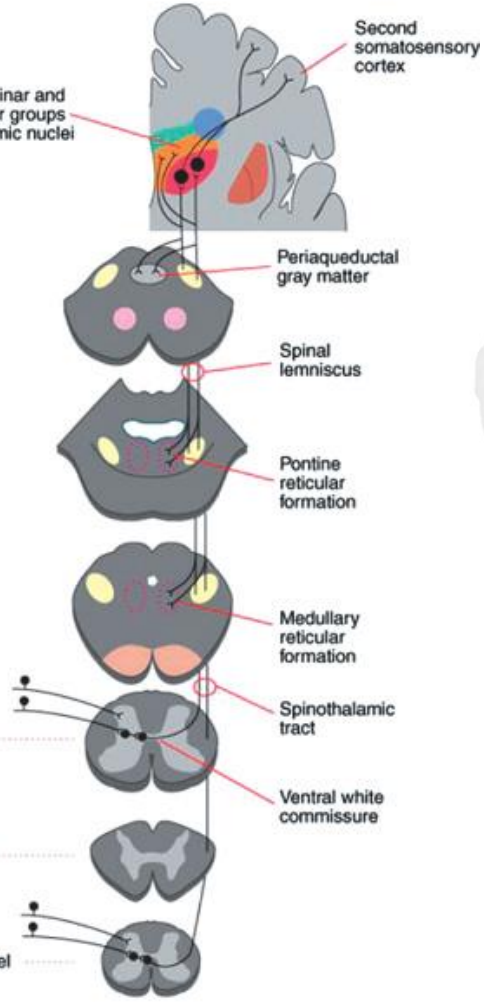


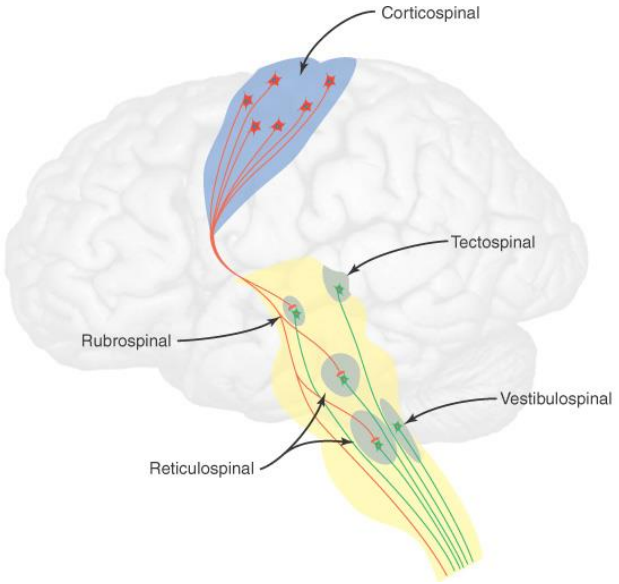


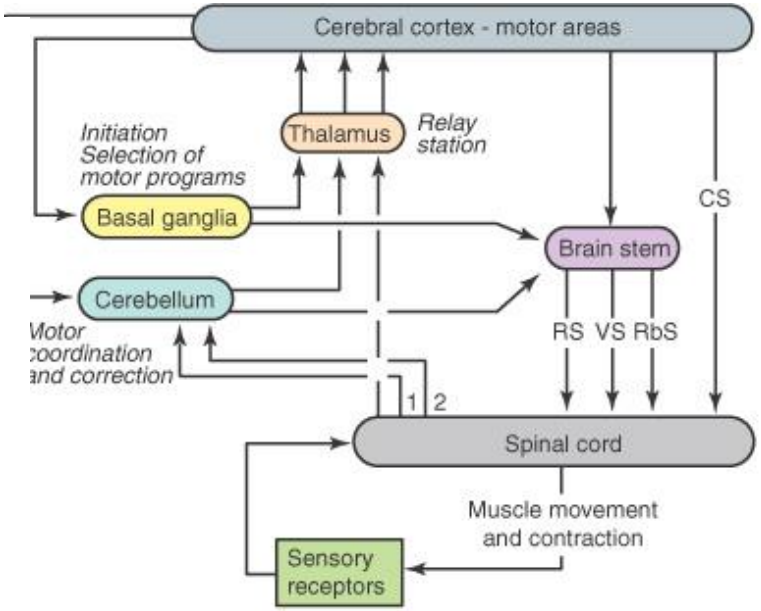
Hippocampus:海马环路



神经环路：多数迄今不全清楚







Squire et al. (2008) *Fundamental Neuroscience*

确定神经环路：神经生物学的目标之一

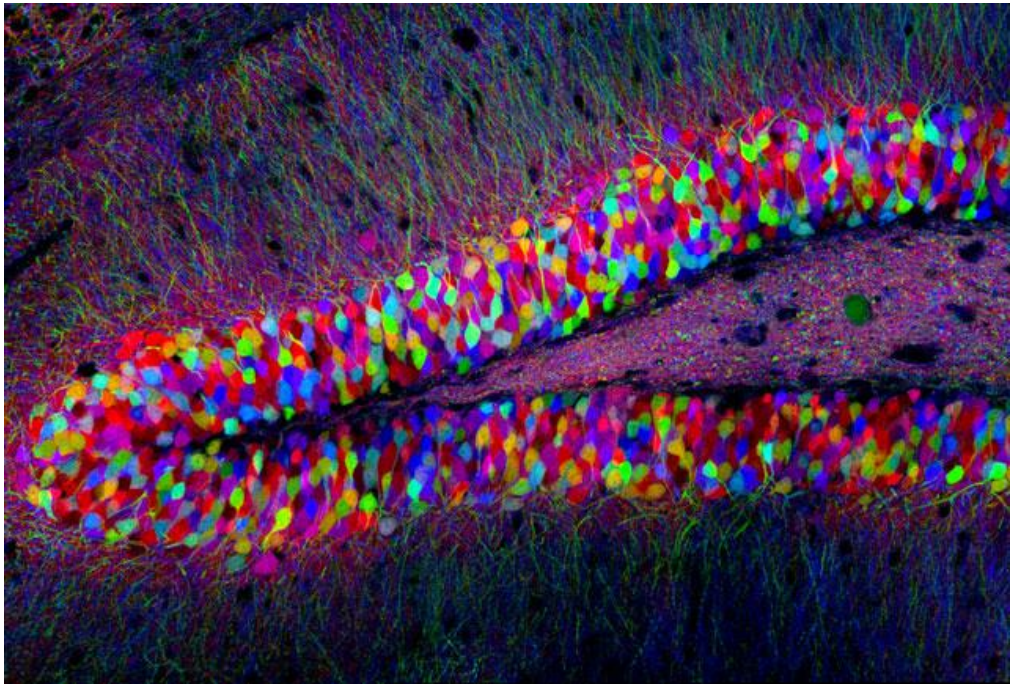
科学：

解剖—重要环路的形态基础
功能—环路及其成分的功能
动态—环路的实时和动态变化
发育—环路的形成和修饰
进化—环路的来源和演化

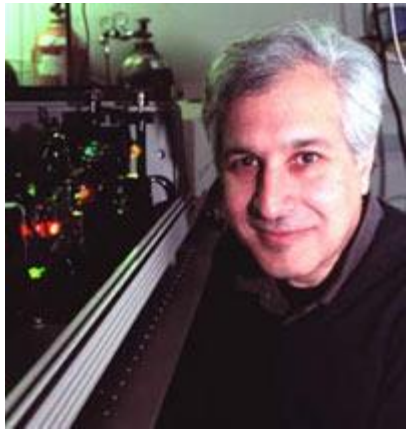
brainbow
connectomics

技术：

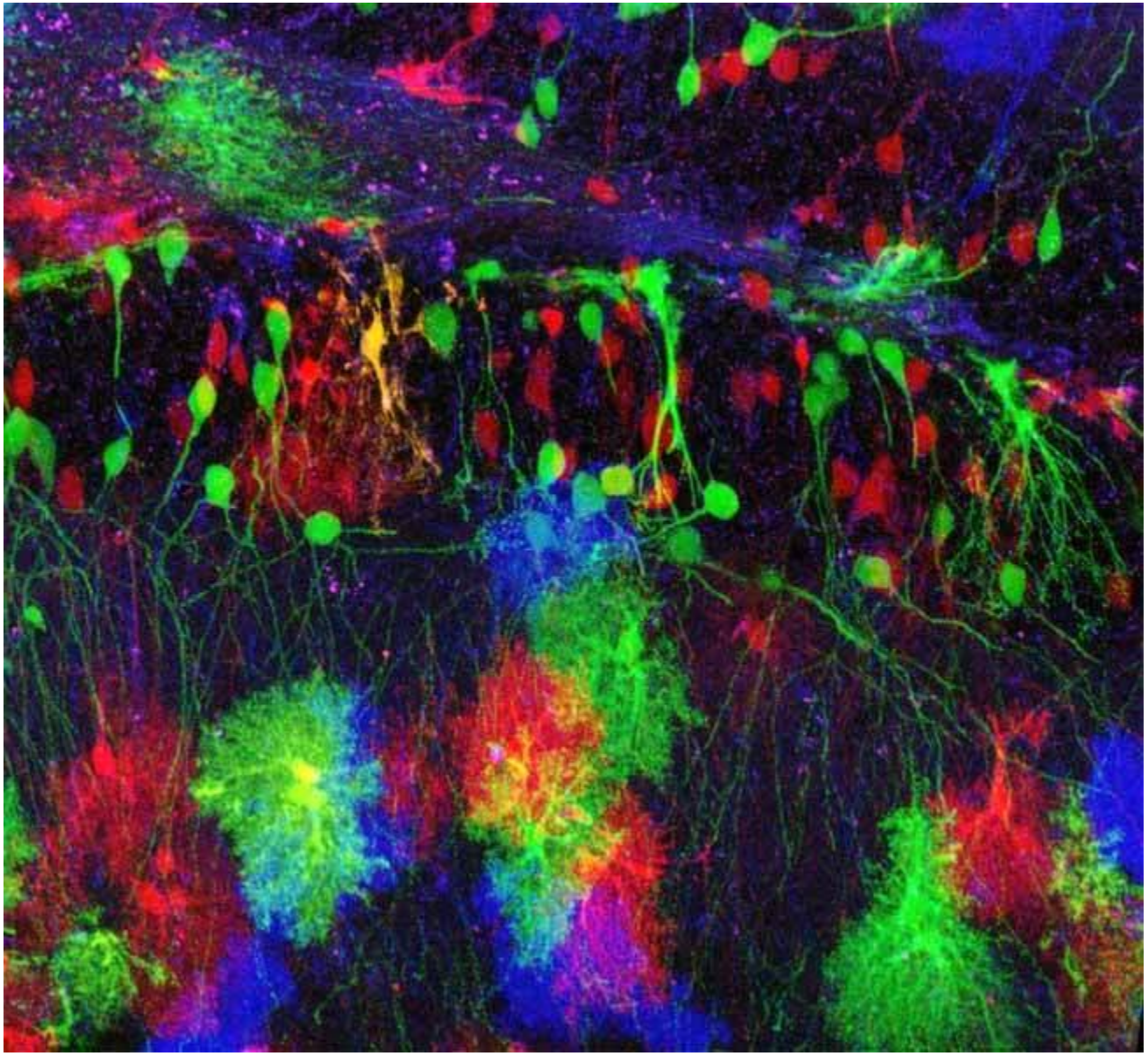
以前：染料标记、HRP、损毁
光学
探针
计算
…

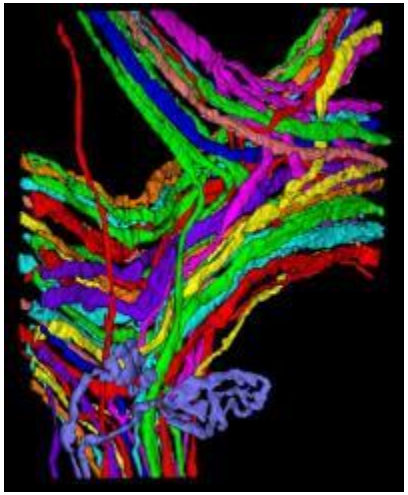


Jeff Lichtman



Livet et al (2007). Transgenic strategies for combinatorial expression of fluorescent proteins in the nervous system. *Nature* 450:56-62.





Neuroscience

结构

- 形态
  - 大体
  - 细胞
- 神经环路

功能

- 神经传递
- 自主功能
- 高级功能

来源

- 进化
- 发育

神经信息传递

轴突:

传导conductance

细胞间:

传递 transmission

神经元与神经元之间
神经元与靶细胞之间

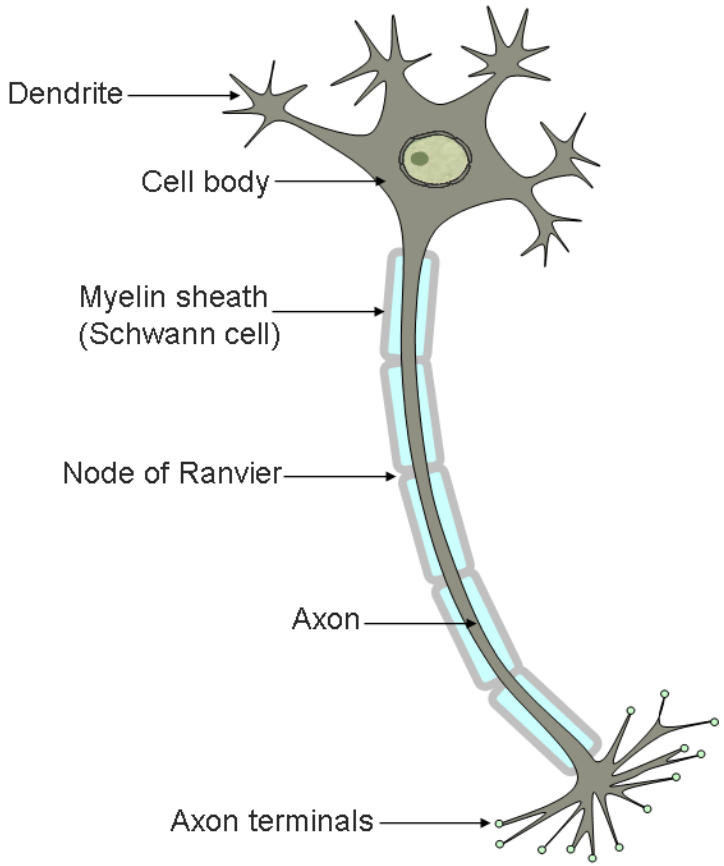
化学传递 chemical
电传递 electric

树突和胞体:

接收和整合

神经冲动（nerve impulse）

轴突（神经纤维）上的电信号传导



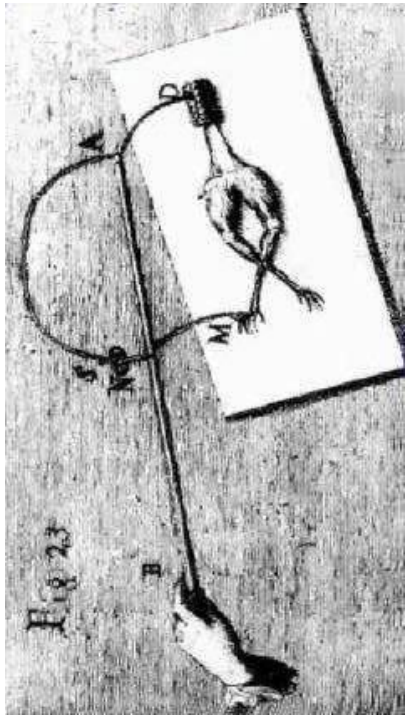
Gotch: the wave of activity accompanied by a change of potential, lasts milliseconds, followed by a refractory state, all-or-nothing

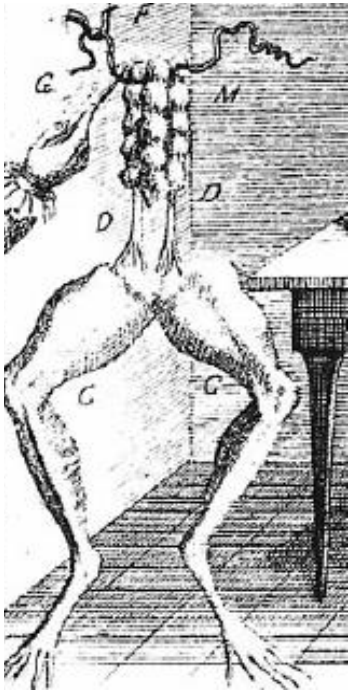
Keith Lucas: all or nothing,
Contraction of muscle innervated by a bundle of nerve fibers
with an increasing stimulus the contraction increased in sudden steps.
The number of steps was never greater than the number of fibres in the preparation

动作电位：全或无

电和神经：物理与生物的早期交叉

Galvani



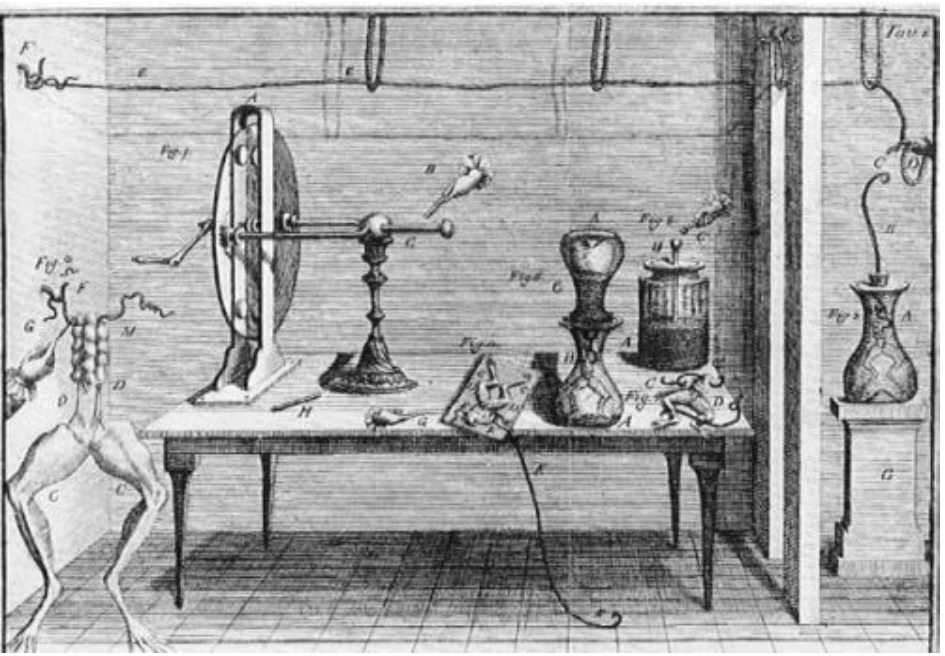


More:

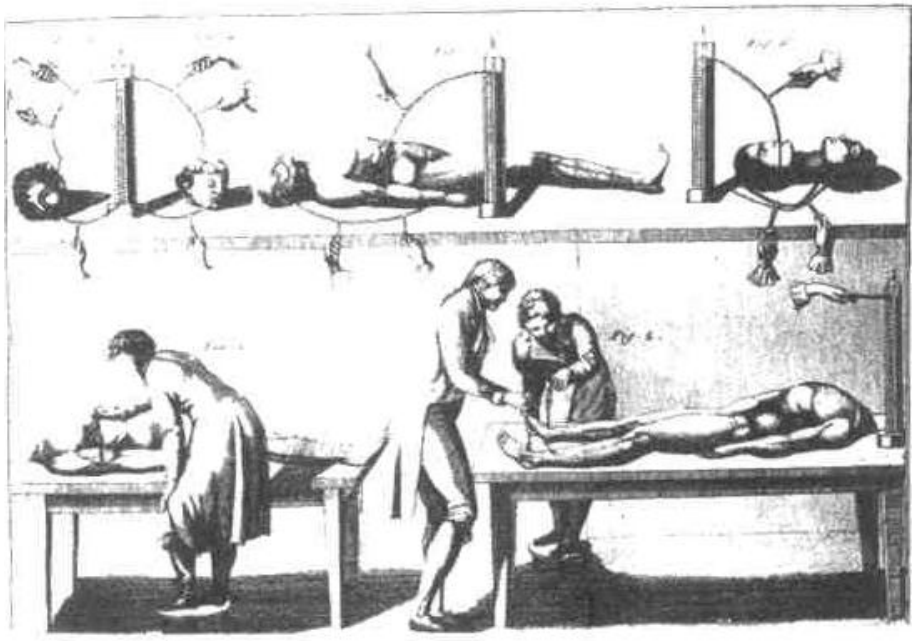
While one of those who were assisting me touched lightly, and by chance, the point of his scalpel to the internal crural nerves of the frog, suddenly all the muscles of its limbs were seen to be so contracted that they seem to have fallen into tonic convulsions.

Galvani L(1791). De viribus electricitatus in motu musculari commentarius, English translation (Commentary on the effects of electricity on muscular motion) by Margaret Glover Foley. Burndy Library: Norwalk, 1953

Galvani的侄子：Giovanni Aldini (1762-1834)



Luigi Galvani



Giovanni Aldini, 1802

有人用电击治病：**Charles Darwin** “被”用过

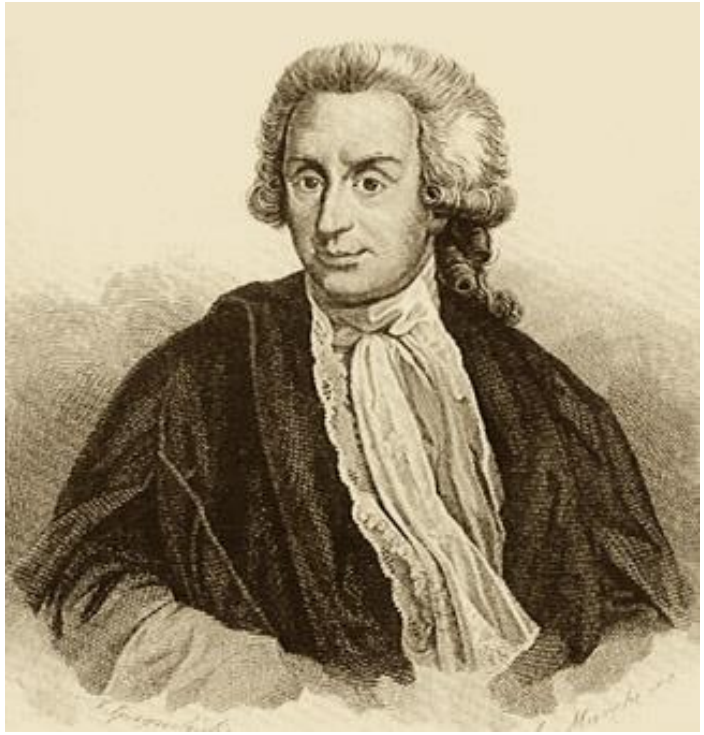
Mary W Shelley (1818) *Frankenstein, or Modern Prometheus*

Shelley (1797-1851), consulting the poet Percy Shelley雪莱 (1792-1822), said:
“Perhaps, a corpse would be reanimated; galvanism had given token of such things”

电化学和电生理：不同解释导致的两个学科

Volta：电化学之父　　vs　　Galvani神经生理之父

Alessandro Volta (1745-1827)

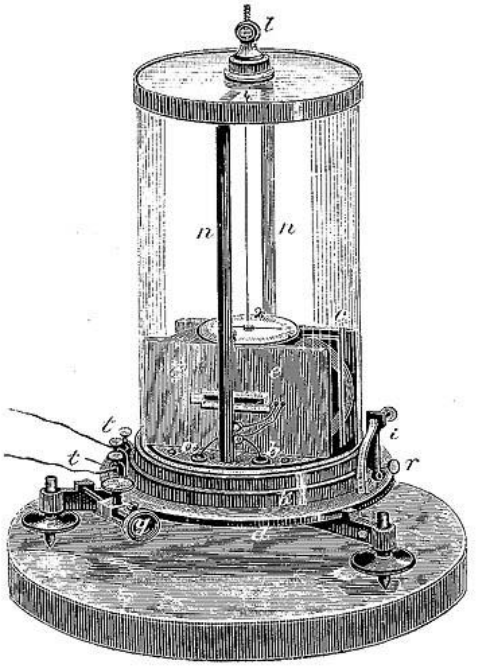


Luigi Galvani (1737-1798)

Action Current：

Emil du Bois-Reymond
(1818-1896)
Univ Berlin

发明灵敏的检测器
发明和刺激诱导圈

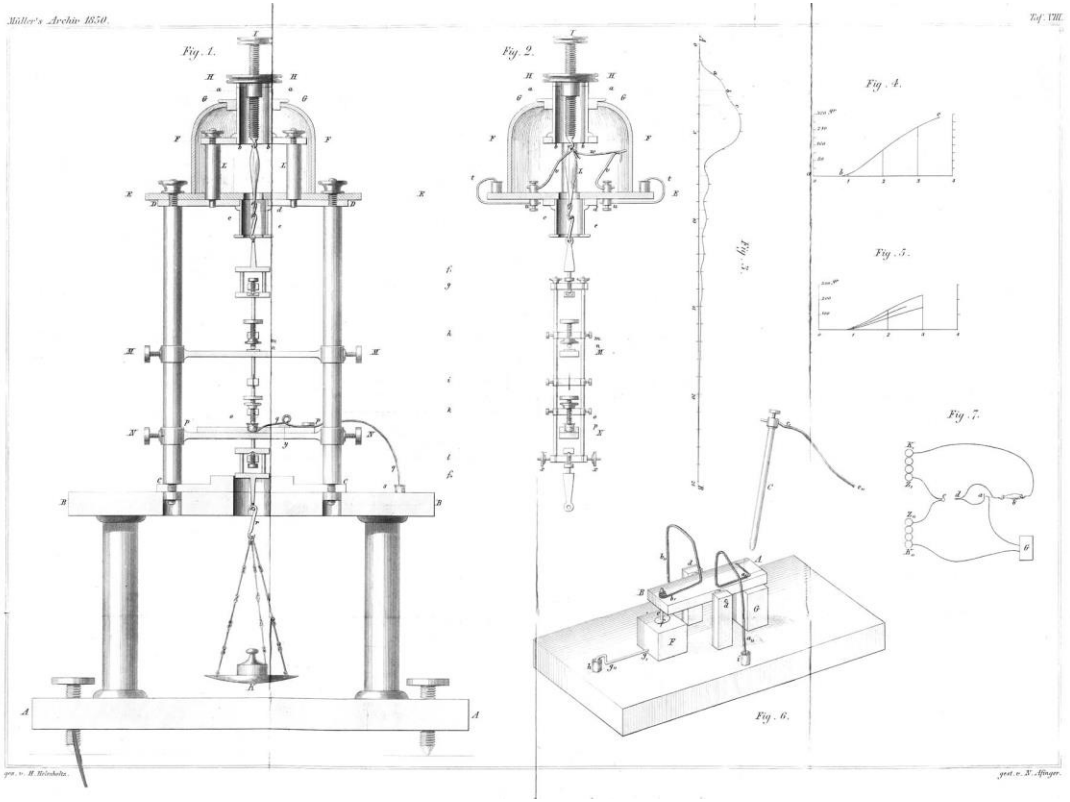


1843：　检测到神经中有电流

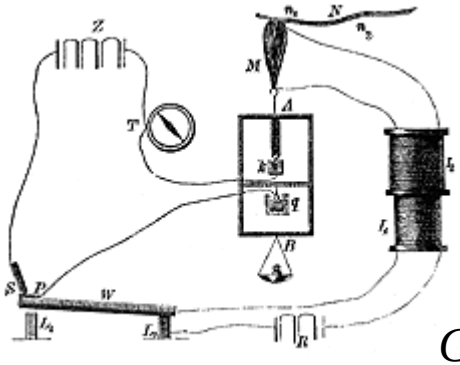
du Bois-Reymond discovered that the voltage across a nerve cell membrane diminished upon stimulation of the nerve. With his galvanometer, he also detected what he called the "action current" - the change in transmembrane current that occurred when a nerve was stimulated - and noticed that this was propagated along the length of the nerve fibre, and in muscle

Meltzer, SJ (1897). EMIL DU BOIS-REYMOND. *Science* 5: 217–219

神经冲动传导速度



离肌肉不同距离的部位刺激神经，
由肌肉收缩时间
推测神经传导速度
27/秒



Herman von Helmholtz
(1821–1894)

Contemporary reconstruction

动作电位：全或无

Gotch:
the wave of activity accompanied by a change of potential, lasts milliseconds, followed by a refractory state,
all-or-nothing

Keith Lucas:
all or nothing,
contraction of muscle innervated by a bundle of nerve fibers with an increasing stimulus
the contraction increased in sudden steps
the number of steps was never greater than the number of fibres in the preparation

动作电位：编码

Edgar Adrian:
Frequency, not size or shape, of action potential encodes the strength of sensory stimuli

适用于多数情况，
但非所以情况：视网膜有两级没有动作电位，电位变化的大小就影响神经信息的传递
现在，有新技术的情况下，对于复杂的、以前没有很好研究的区域，比如脑内，是否此原理还完全适用？

技术与科学

阴极射线示波器the cathode-ray oscillograph：
改进并应用于神经电生理

Joseph Erlanger
(1874-1965)

Herbert S Gasser
(1888-1963)

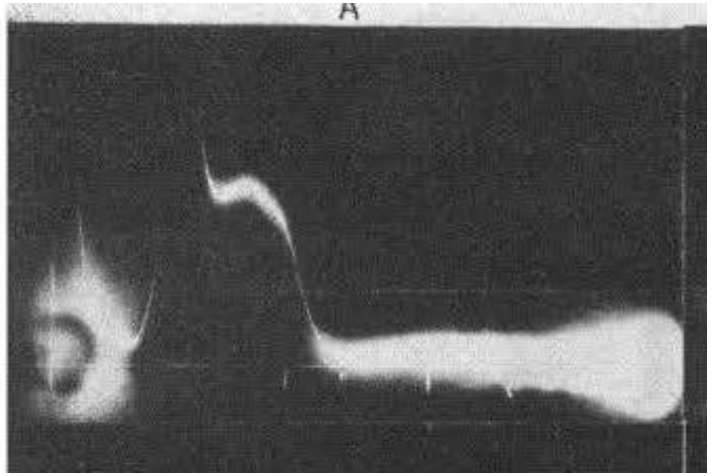
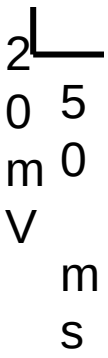


Fig. 1a. The action current in the phrenic nerve of the dog.

Gasser HS, and Erlanger J (1922) A study of the action currents of nerve with the cathode ray oscillograph. *Am J Physiol* 62:496-524

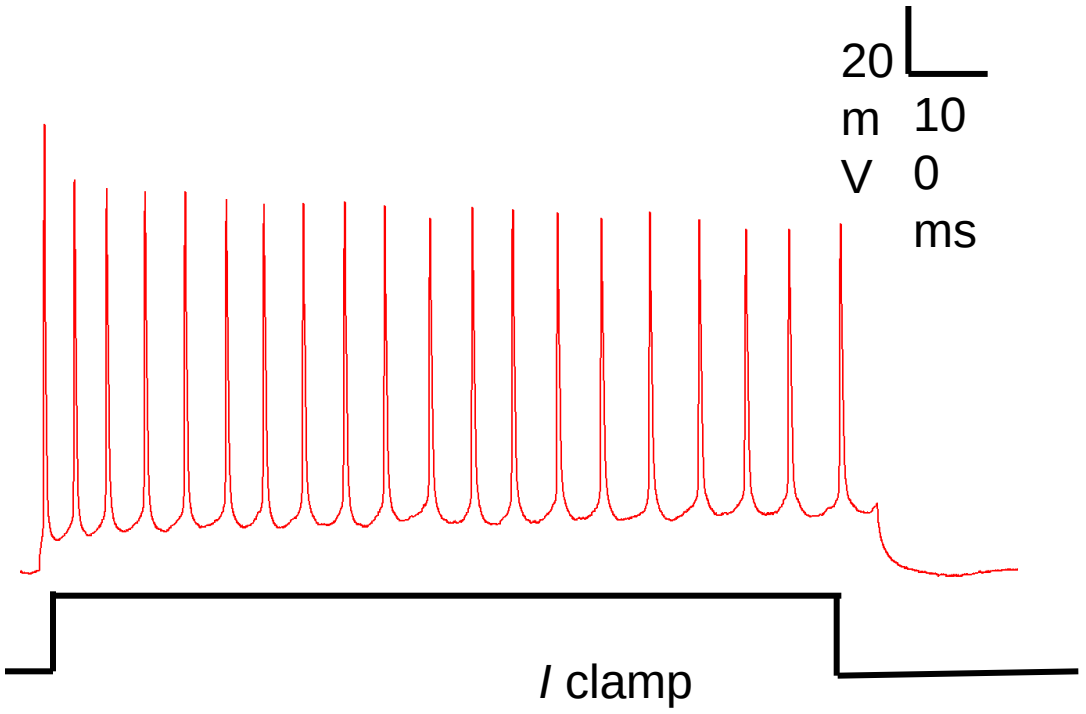
Erlanger J and Gasser HS, Bishop, GH (1924) The compound nature of the action current of nerve as disdosed by the cathode ray cacillograph. *Am. J. Physiol*. 70:624-666

动作电位 action potential



20天SD大鼠急性海马脑片

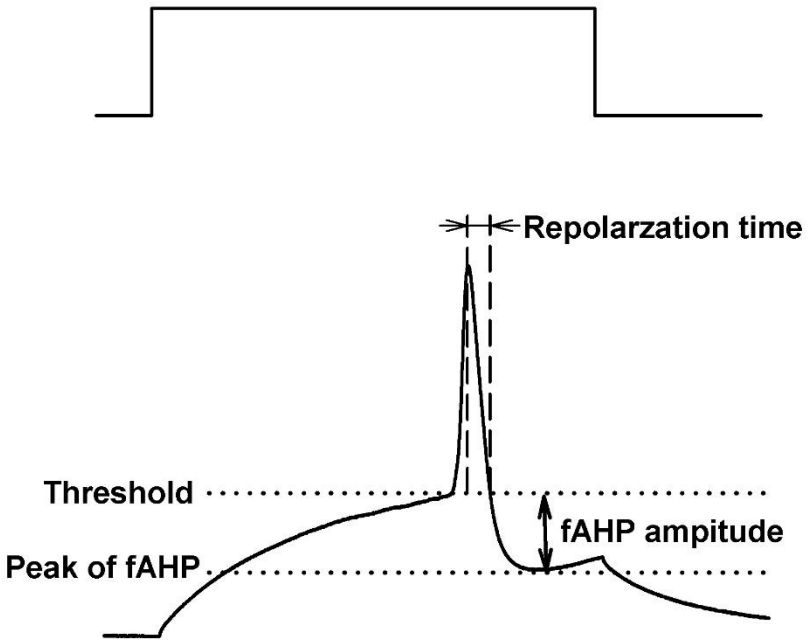
CA1区锥体神经元的记录



电流钳下的动作电位簇状发放

柴真实验室

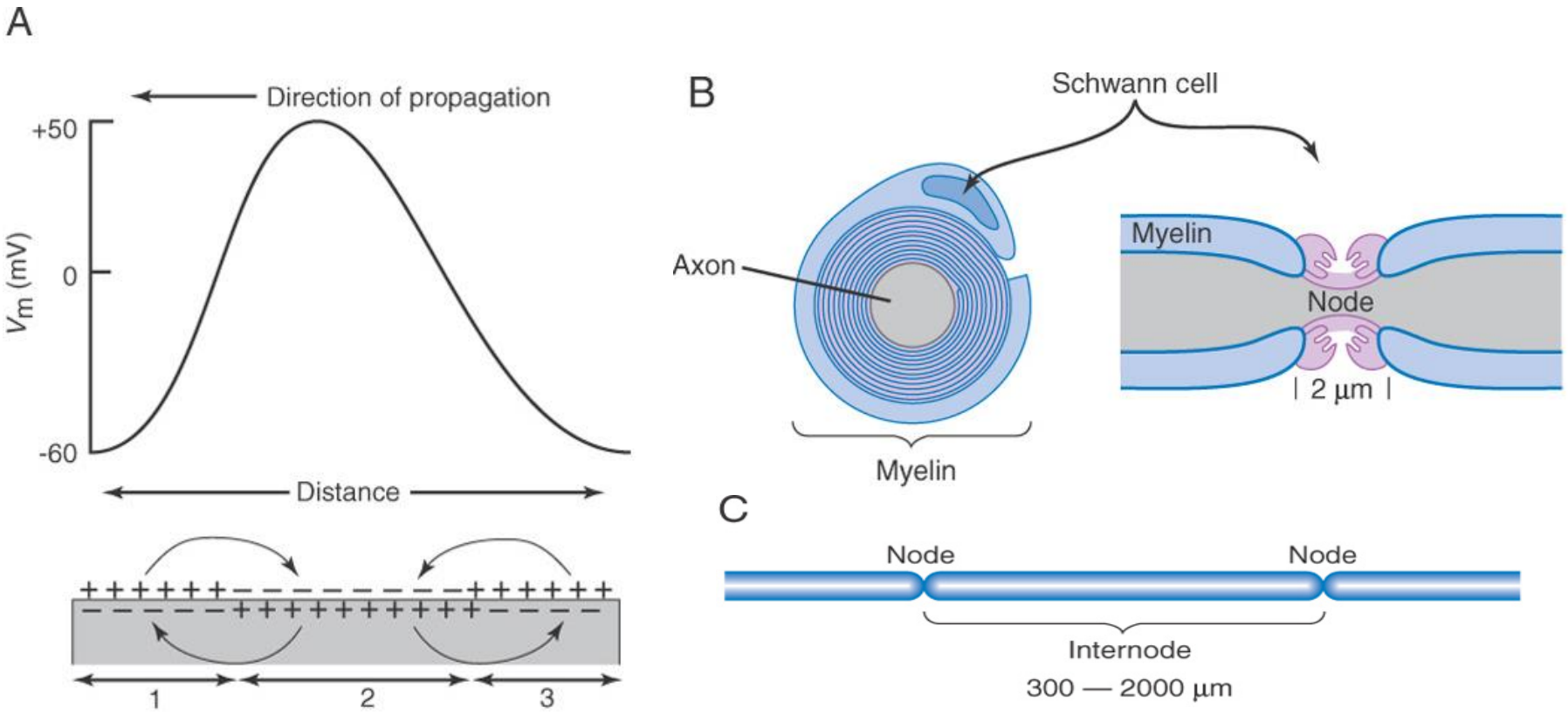
动作电位　action potential



培养的大鼠皮层神经元，培养时间在7到12天之间。记录方式为电流钳，神经元钳制在-70mV下，输入去极化电流（图片上侧方波表示）引发动作电位。阈值、后超极化峰值和复极化时间

柴真实验室

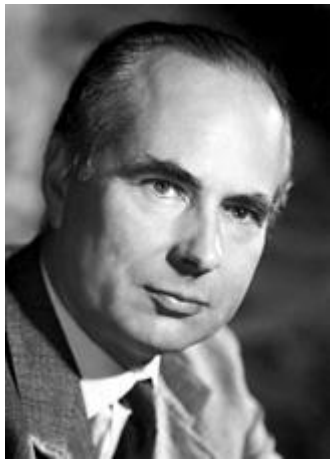
动作电位的传播：局部电流



Squire et al. (2008) *Fundamental Neuroscience*

动作电位的离子基础

Alan L Hodgkin (1914–1998)



Andrew F Huxley (1917-)

Hodgkin AL & Huxley AF (1939). Action Potentials Recorded from Inside a Nerve Fibre. Nature 144:710-711

Hodgkin AL, Katz B 1949. The effect of sodium ions on the electrical activity of the giant axon of the squid. J. Physiol108:37-77

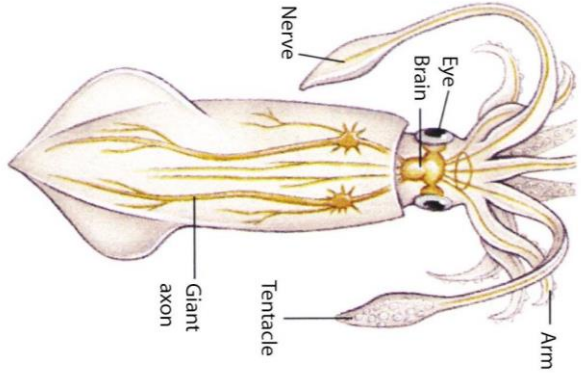
Hodgkin AL, Huxley AF & Katz B (1949). Ionic currents underlying activity in the giant axon of the squid. *Arch. Sci. Physiol*. 3:129-150.

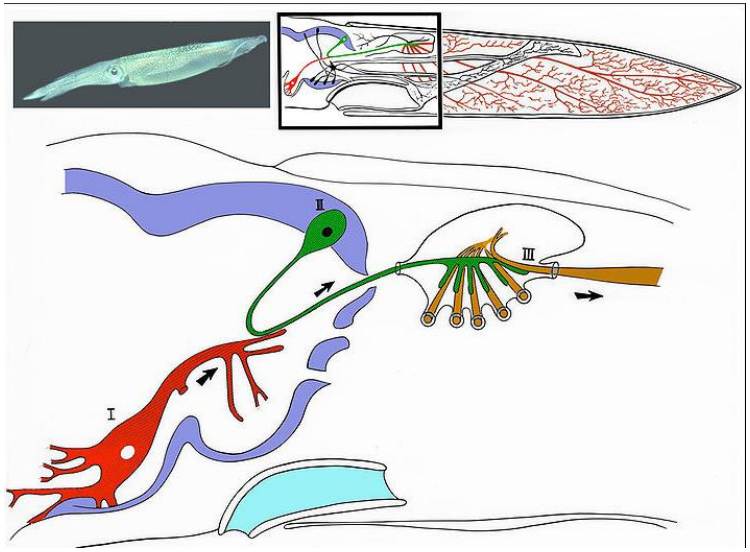
Hodgkin AL & Huxley AF (1952a). Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. J. Physiol. 116:449-472.

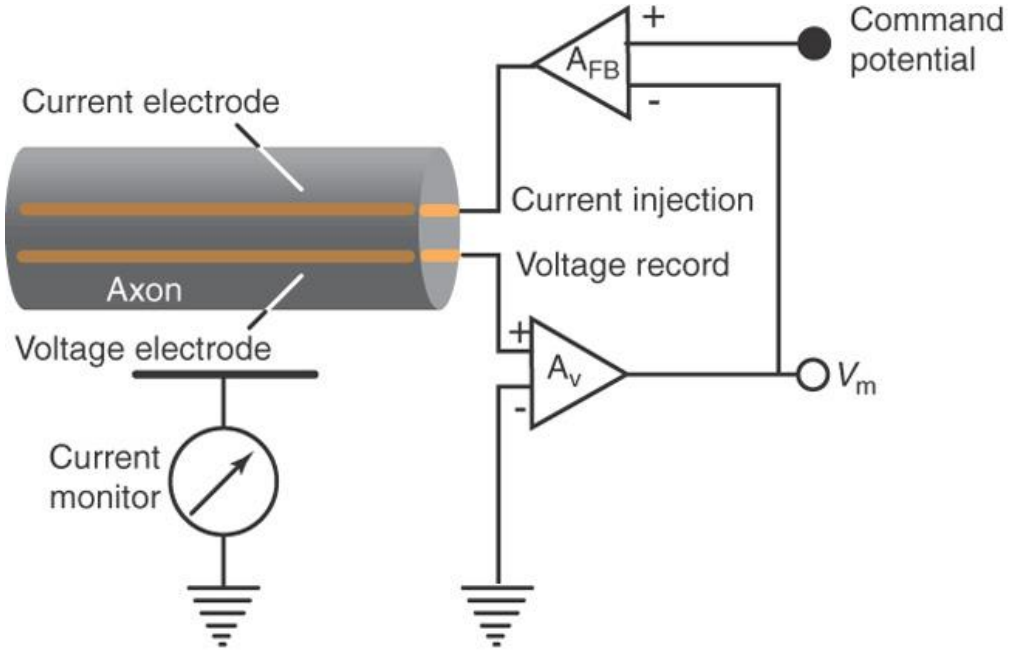
Hodgkin AL & Huxley AF (1952b). The components of membrane conductance in the giant axon of Loligo. J. Physiol. 1I6:473-496.

Hodgkin AL & Huxley AF (1952c). The dual effect of membrane potential on sodium conductance in the giant axon of Loligo. J. Physiol. 116:497-506.

Voltage Clamp & Squid Giant Axon:枪乌贼巨大轴突





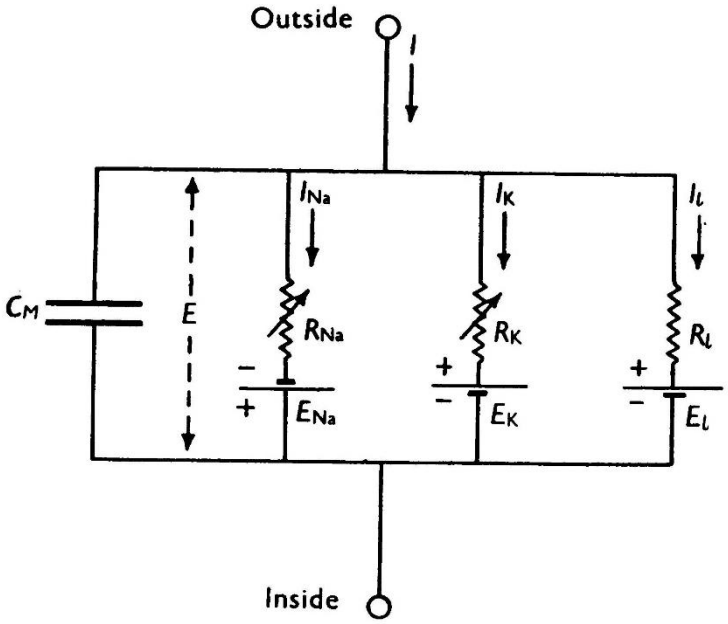


Cole KS, Curtis HJ (1937). Wheatstone bridge and electrolytic resistor for measurements over a wide frequency range.Rev. Sci Inst. 8:333-39.
Cole KS, Curtis H J (1939). Electric impedance of squid giant axon during activity. J. Gen. Physiol 22:649-70.
Cole KS (1949)

Squire et al. (2008) *Fundamental Neuroscience*

数学模型

This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952 a-c). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).



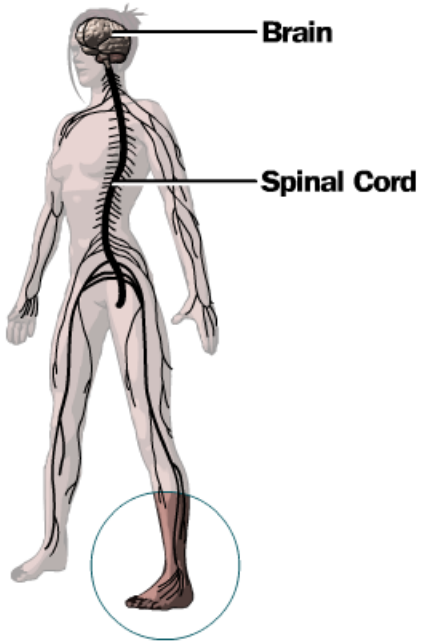
Hodgkin AL & Huxley AF (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117:500–544

数学模型

Hodgkin AL & Huxley AF (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117:500–544

动作电位的离子基础

Action Potential

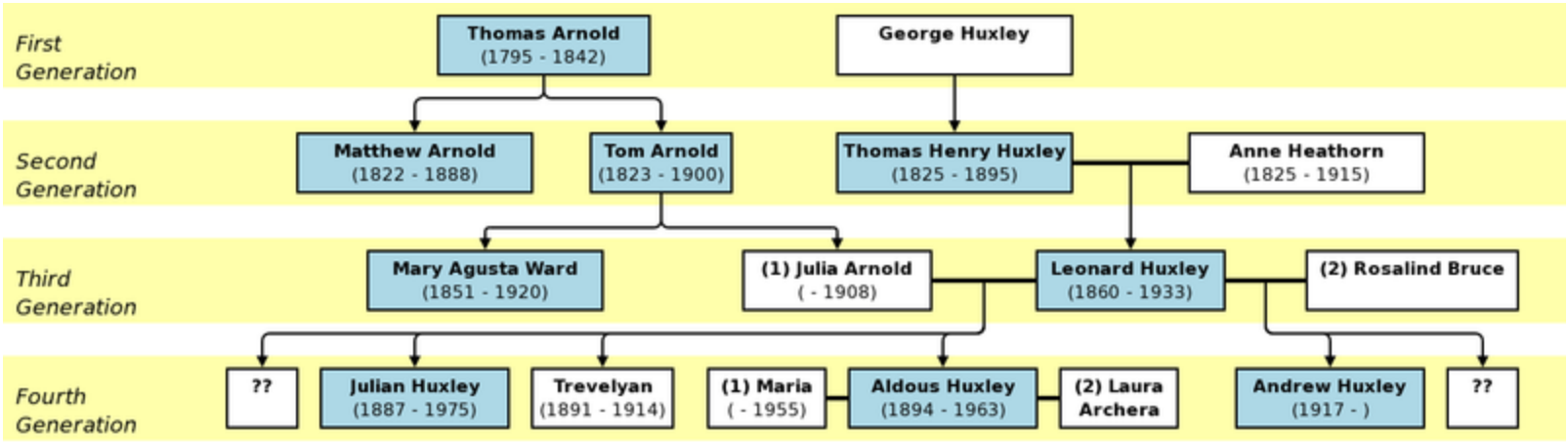


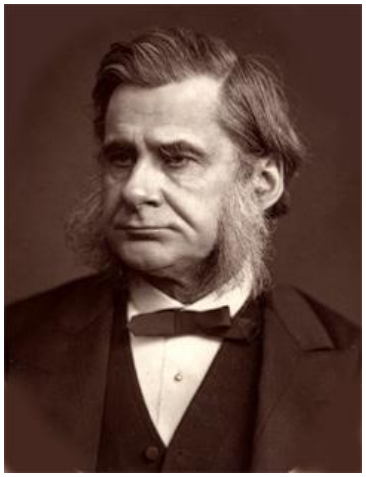
This woman is moving her foot. Her brain sends a message to certain muscles of her foot. They contract and the foot moves. What is this message? How does it travel so quickly?

Glossary
Credits

Matthew Bohan, Harvard

英国科学世家: Huxley





Thomas H Huxley (1825– 1895), biologist, “Darwin's Bulldog”

Julian Huxley (1887 –1975), evolutionary biologist, humanist, and the first UNESCO Director.

Aldous Huxley (1894 –1963), author (Brave New World1932, Eyeless in Gaza1936, the Doors of Perception1954).

Andrew Huxley, Nobel1963, the second Huxley to become President of the Royal Society.

英国科学世家

Alan L Hodgkin (1963 Med/Physiol)

Dorothy Hodgkin (1964 Chem), wife of Thomas Hodgkin, historian & communist

Payton Rous (1966, Med/Physiol)

Jonathan Hodgkin (C elegans, MRC)

(1879-1972)

(1879-1972)

Thomas Hodgkin (1798 - 1866)

Hodgkin's Lymphoma (1832)

Alan L Hodgkin (1963 Med/Physiol) **Andrew F Huxley** (1963 Med/Physiol)

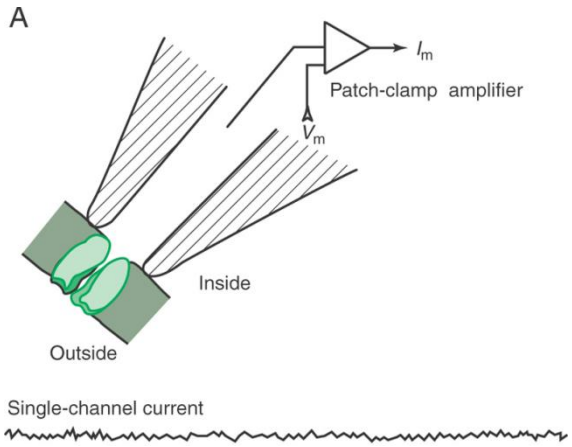
Bernard Katz (1970)

Darwin **英国:76位**

Mitchison **剑桥:25位**

离子通道：单分子活动记录

Patch Clamp



Neher E, Sakmann B (1976): Single-channel currents recorded from membrane of denervated frog muscle fibres. Nature 260:779-802

Neher E, Sakmann B, Steinbach JH (1978). The extracellular patch clamp: a method for resolving currents through individual open channels in biological membranes. *Pflügers Archiv* 375: 219–28.

Max Planck Society: (institutes)

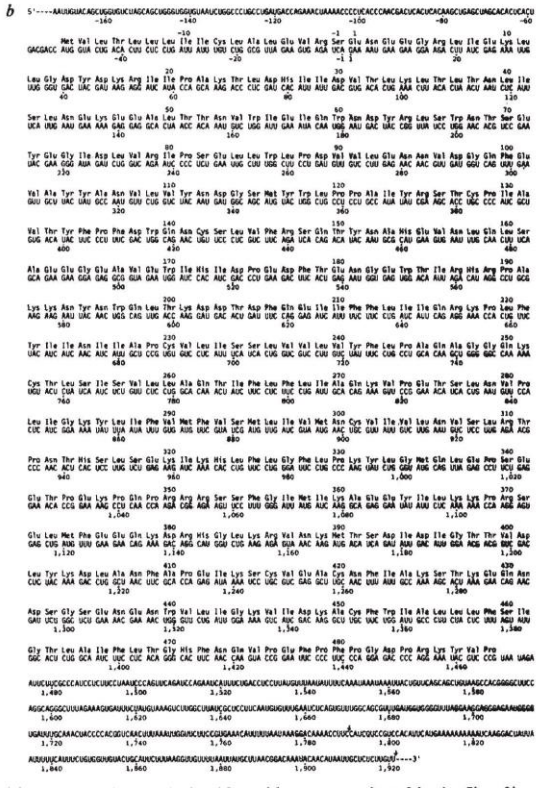
Bert Sakmann (1942-)

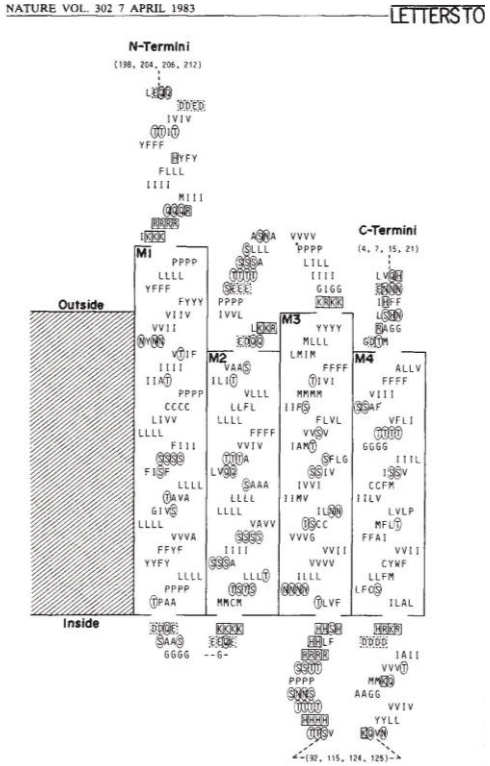
Erwin Neher (1944-)

离子通道&递质受体：cDNA,蛋白质

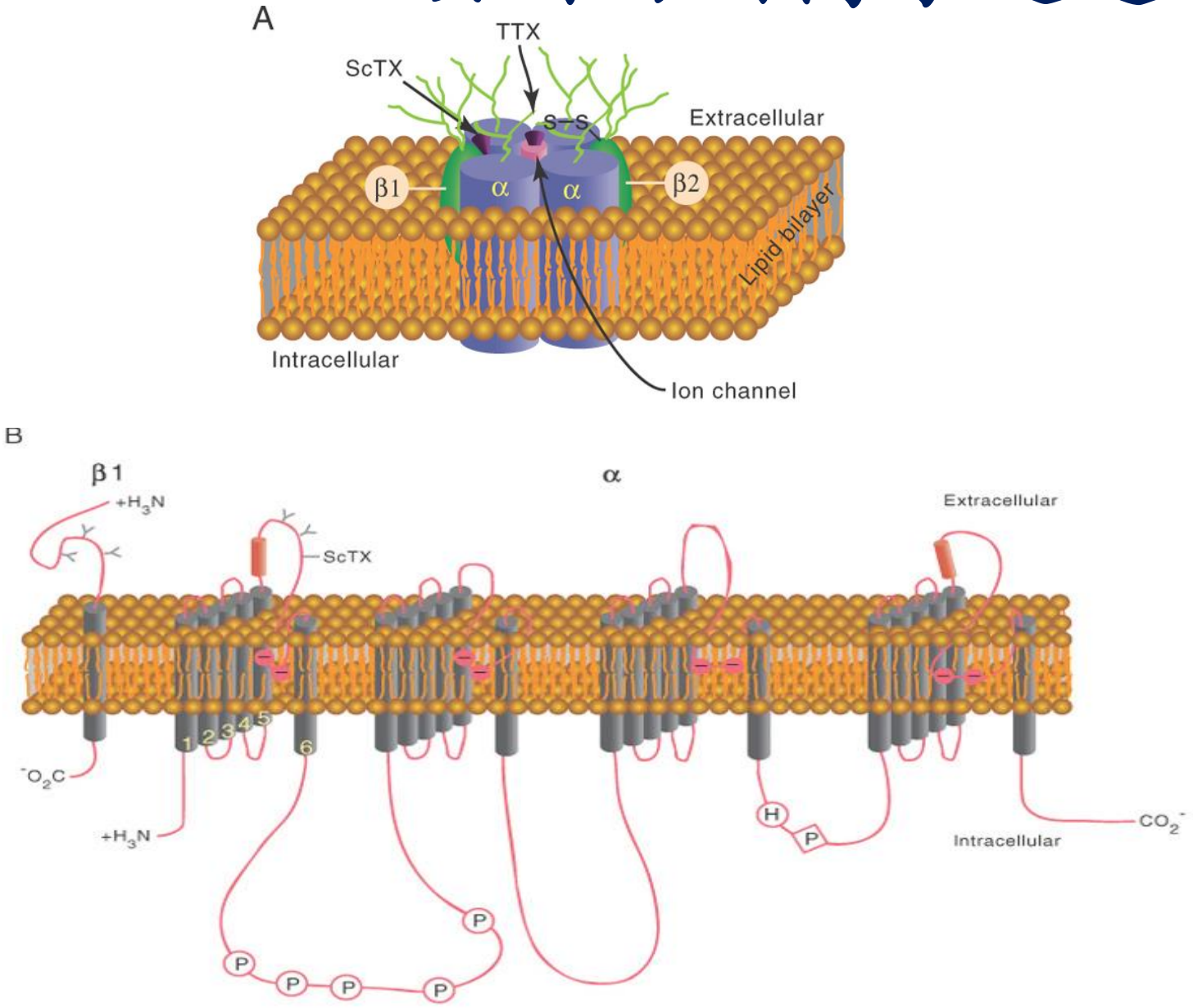
Shosaku Numa (1929-1992)

(1979)
(1980s)





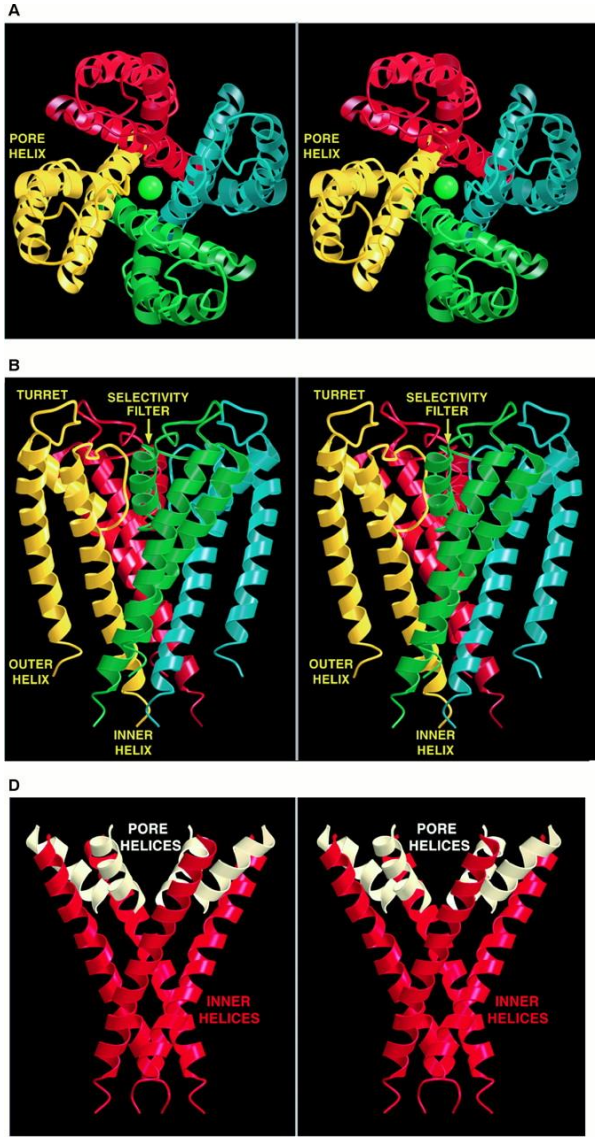
cDNA 预测的钠离子通道



Squire et al. (2008) *Fundamental Neuroscience*

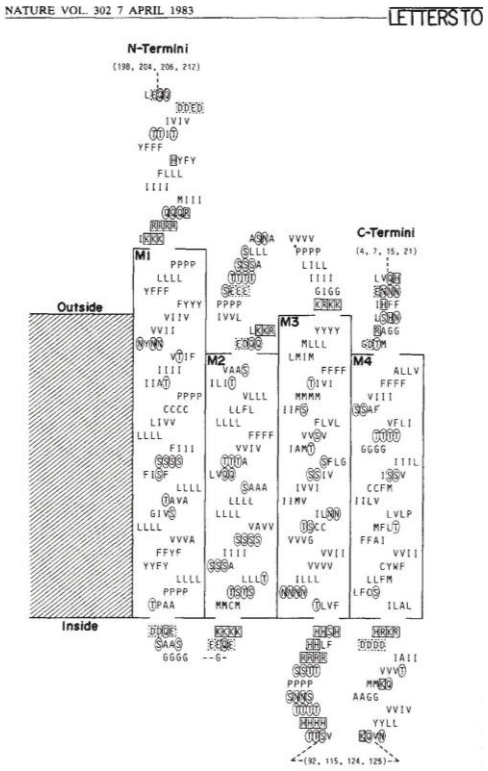
离子通道：结构

Rod MacKinnon (1956-)



Doyle DA, Morais Cabral JH, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, Chait BT, and MacKinnon R (1998). The structure of the potassium channel: molecular basis of K+ conduction and selectivity. Science *280*, *69–77*.

离子通道：结构与功能的关系



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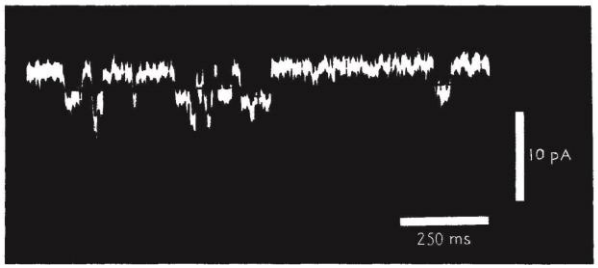
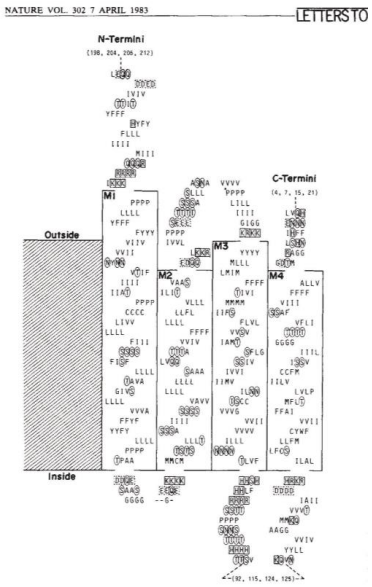


改变通道氨基酸序列，观察通道特性的改变

隔靴搔痒？



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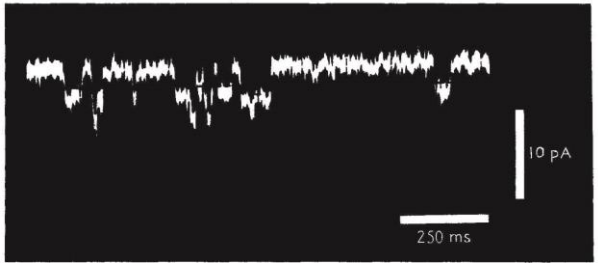
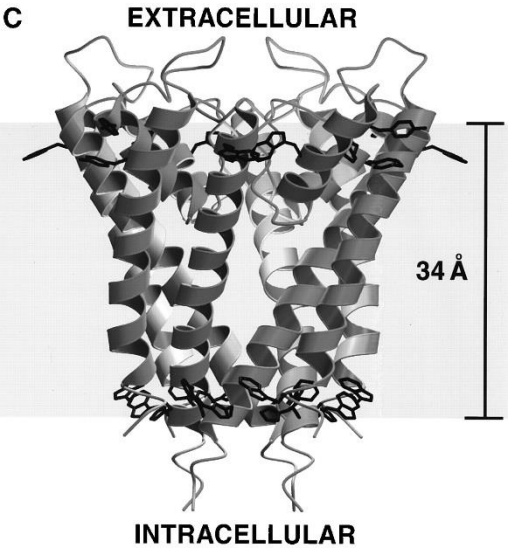
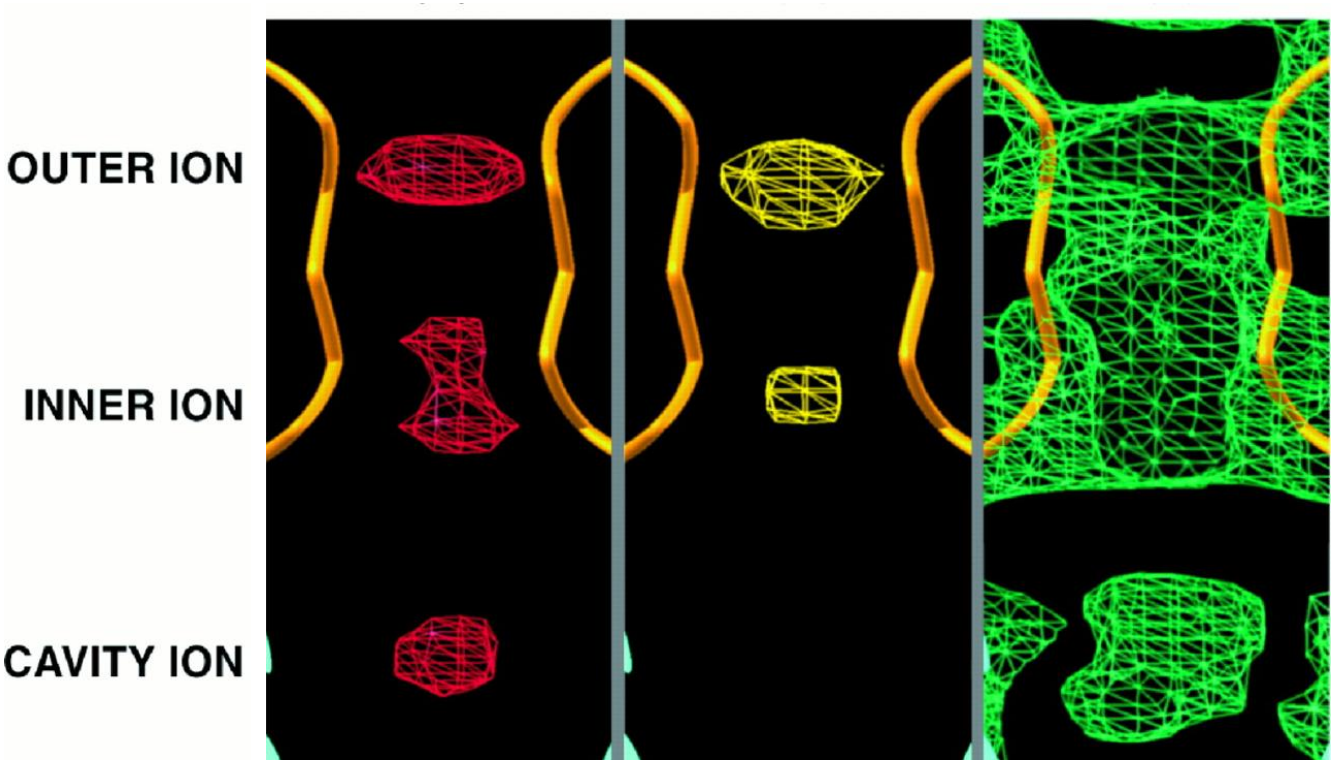


间接推测，不如直接看

离子通道：眼见为实





Doyle DA, Morais Cabral JH, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, Chait BT, and MacKinnon R (1998). The structure of the potassium channel: molecular basis of K+ conduction and selectivity. Science *280*, *69–77*.

学科交叉

注意其他学科：而不是只知道鼻子底下一点

比如，

学生化的知道神经：蛋白质纯化
学分子的知道神经：克隆基因
学结构的知道神经：解结构

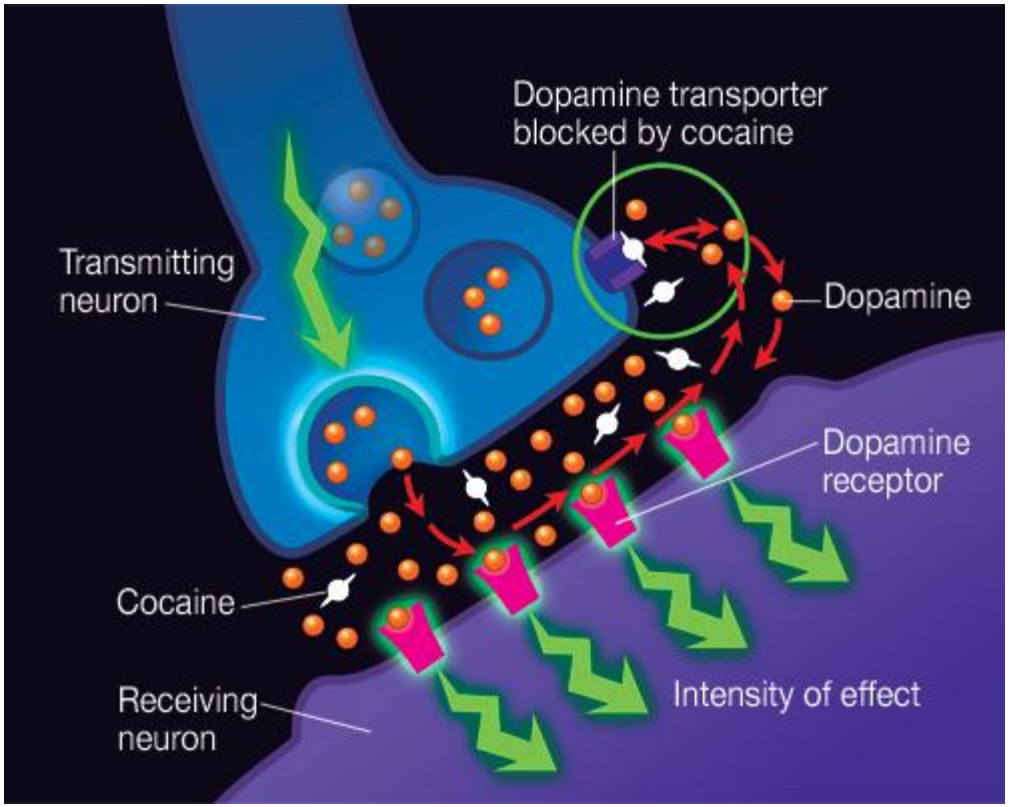
反过来，

学神经的知道生化：蛋白质纯化
学神经的知道分子：克隆基因
学神经的知道结构：解结构

还有好多交叉，

化学、成像、数据分析…….

突触　Synapse：神经细胞与靶细胞间



Charles Sherrington

化学传递和神经递质

Henry Dale
（1875-1968）

英国人

1902朋友

Otto Loewi
（1873-1961）

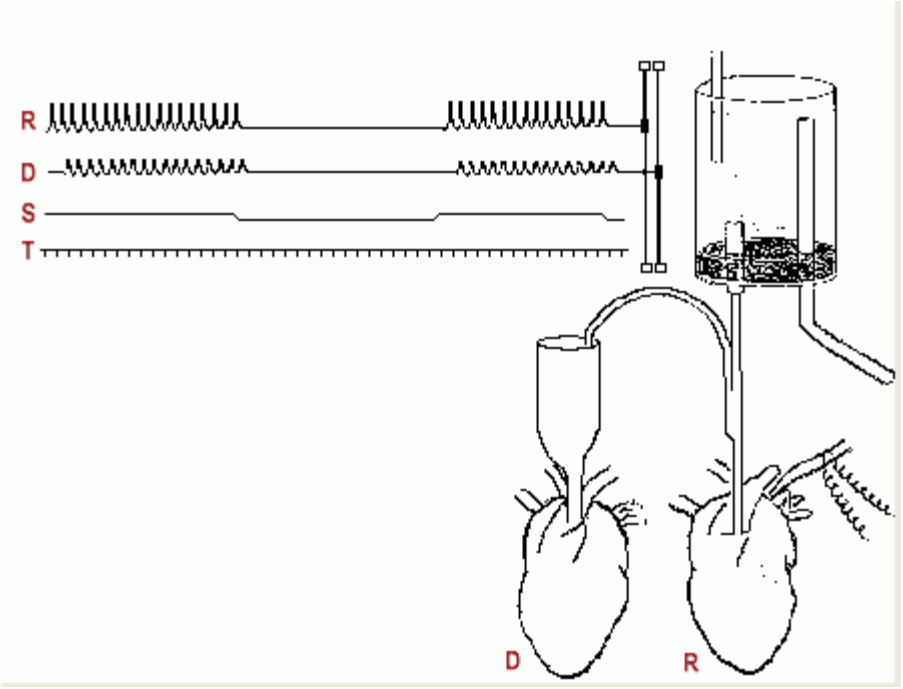
德国犹太人

1936诺贝尔奖

证明化学传递：梦中设计的实验

Otto Loewi,
University of Graz,
Austria

‘the night before Easter Sunday of that year (1920) I woke, turned on the light and jotted down a few notes on a tiny slip of thin paper. Then I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl.’
He tried unsuccessfully to recall the dream or interpret his note. On the Sunday night he went to bed and read for a time before turning out the light. He then awoke between two and three in the morning, which was unusual for him, and he knew what the nature of his dream had been that night and the previous night. He got out of bed and immediately went to the laboratory to put into action his new idea
Todman D (2008) I J Neurol

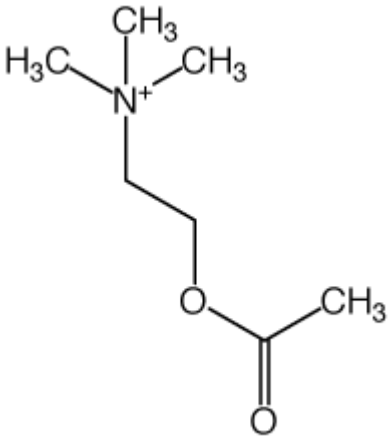


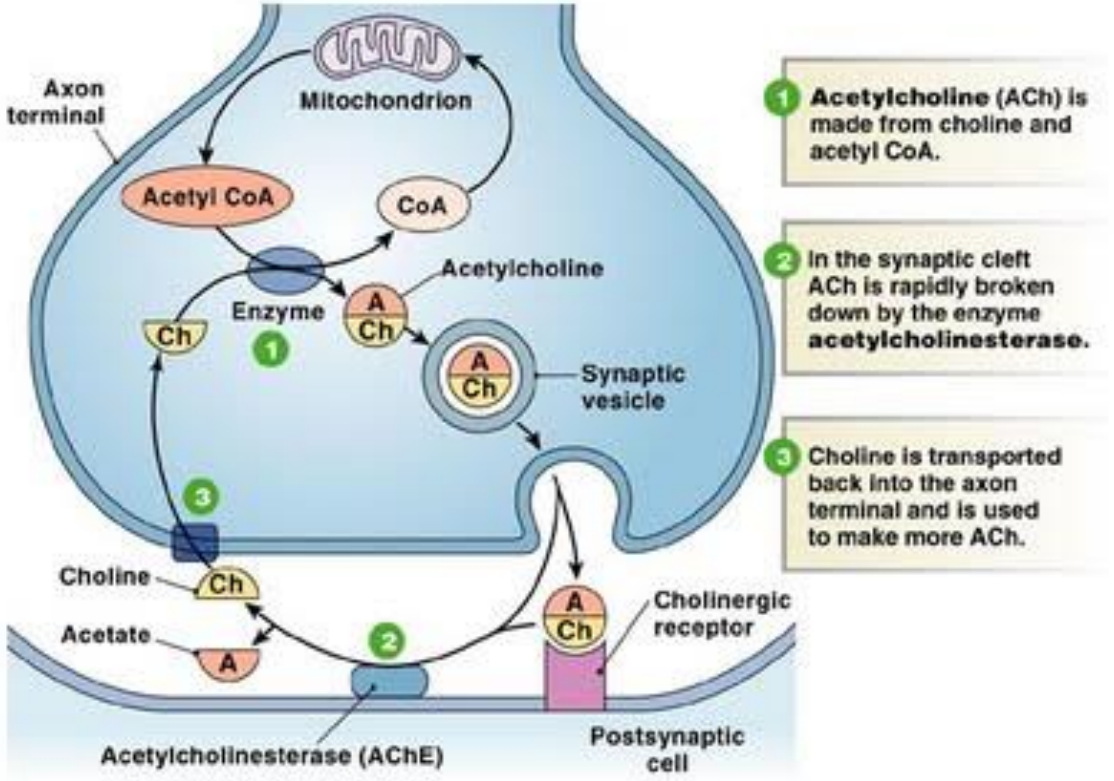
Vagusstoff (vagal substance)

O. Loewi (1921) "Über humorale Übertragbarkeit der Herznervenwirkung. I." *Pflügers Archiv*, 189, pp. 239-242

Acetylcholine：乙酰胆碱

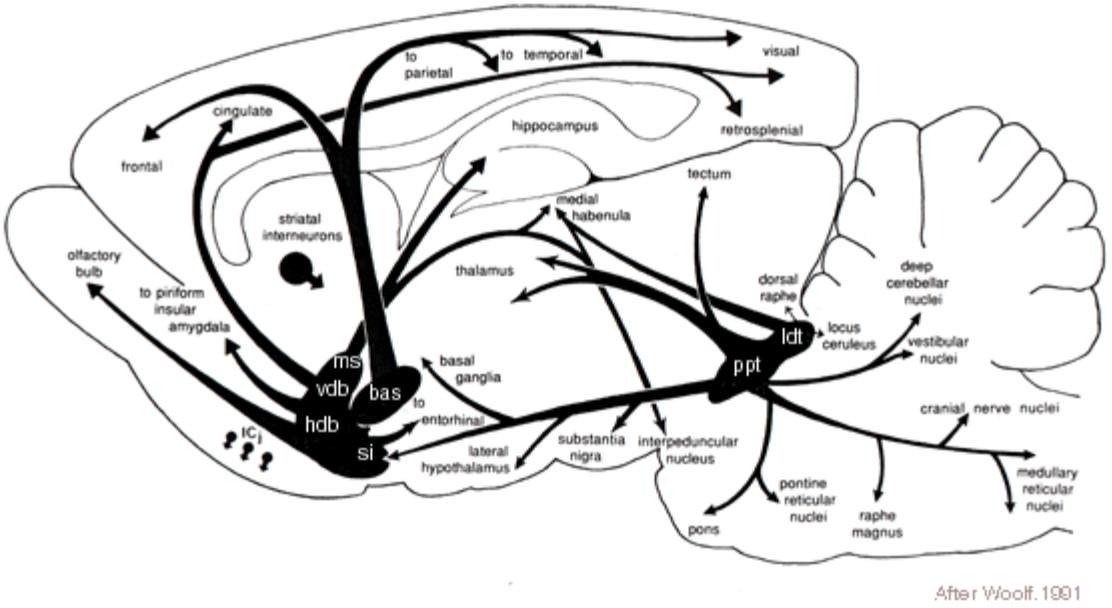
Vagusstoff 迷走物质
(vagal substance)





Choline acetyltransferase: ChAT
Acetylcholinesterase: AChE

ACh



中枢神经系统

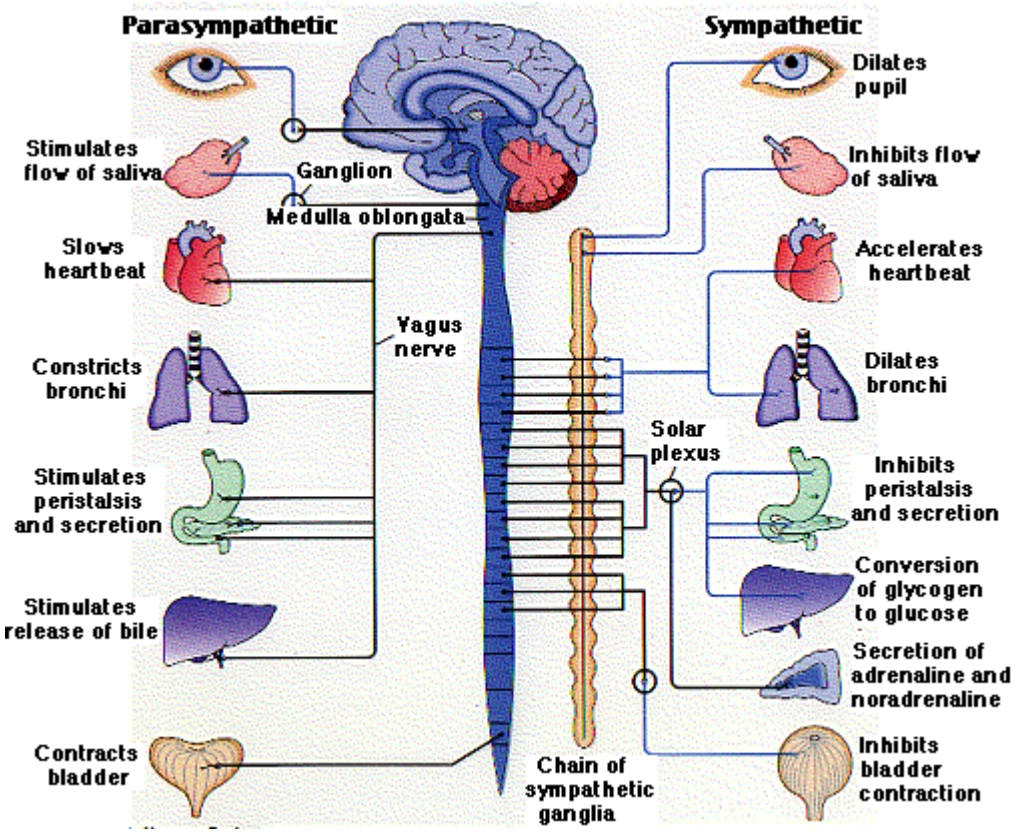
外周神经系统:

外周运动神经元

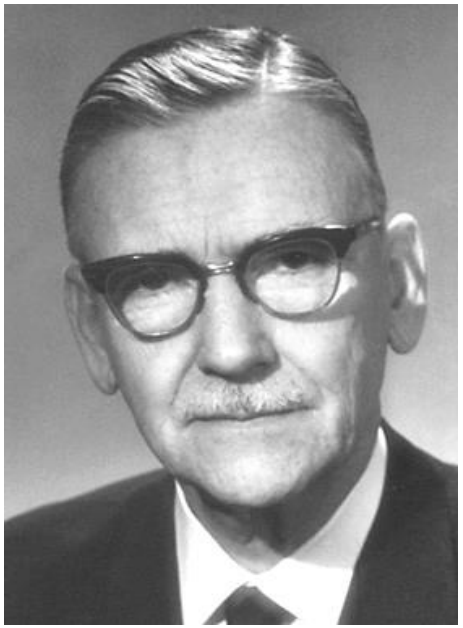
副交感神经系统

NA和ACh：交感对副交感

自主神经系统
Automic Nervous System



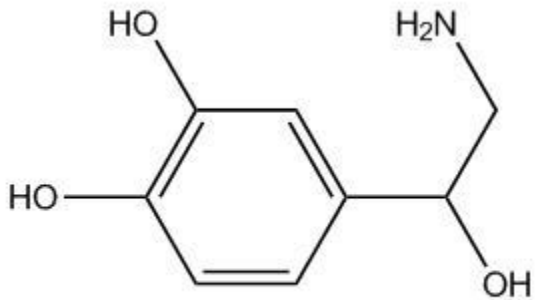
Noradrenaline/Norepinephrine：去甲肾上腺素



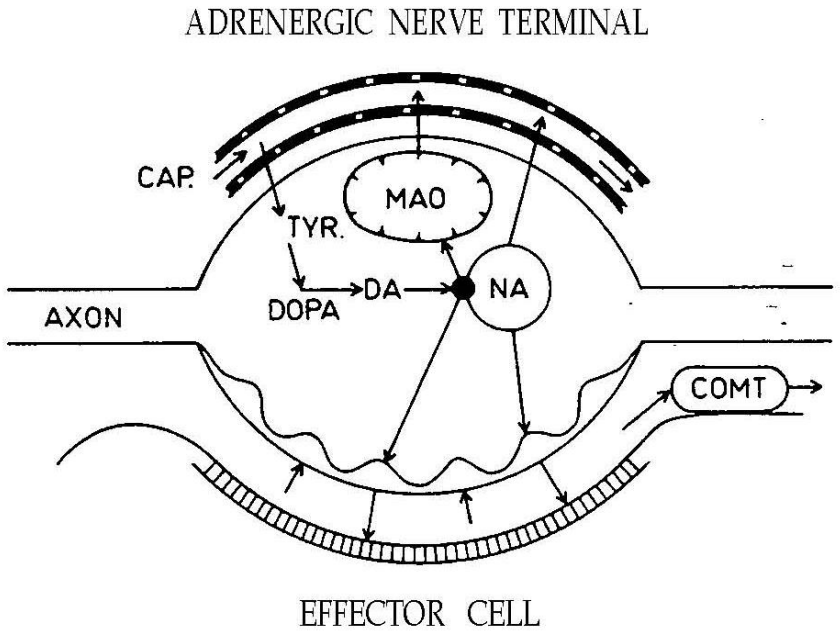
Ulf von Euler （1905-1983）

亲上加亲
父亲：1929化学
自己：1970
秘书：1960-1965
主席：1965-
徒子徒孙：1982

5代曾祖：数学家欧拉（1707-1783）

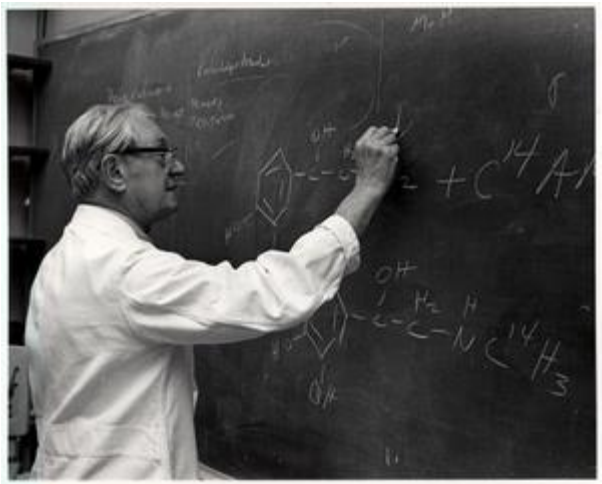


norepinephrine

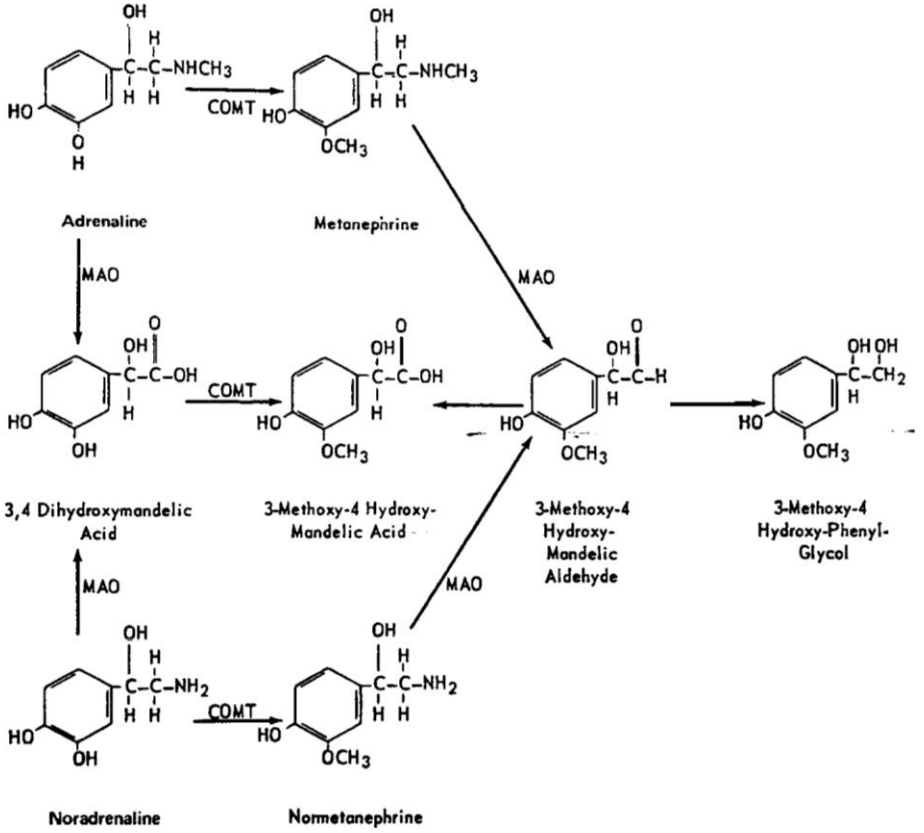


U.S. von Euler, *Acta Physiol. Scand., 12 (1946) 73-97.*
U.S. von Euler, *Acta Physiol. Scand., 16 (1948) 63-74.*

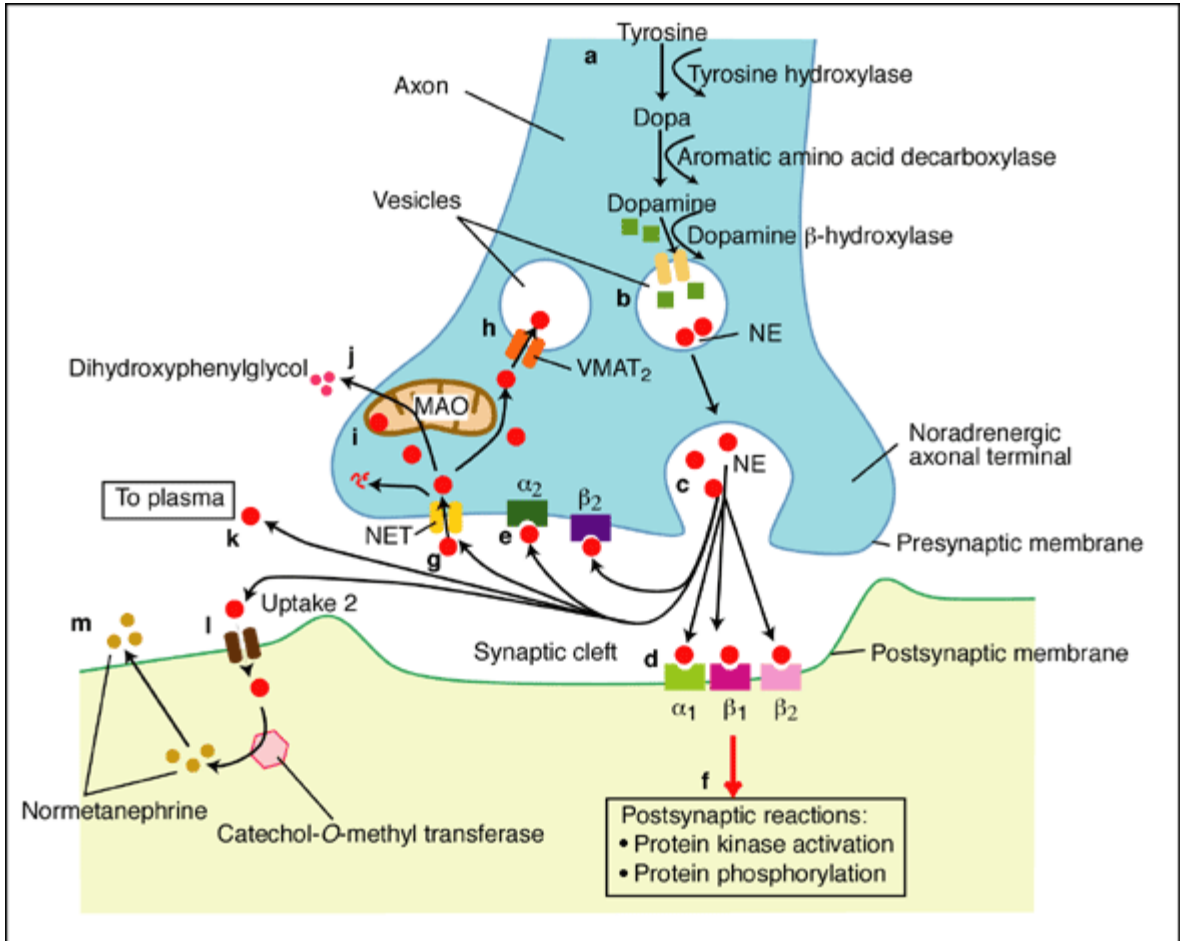
Noradrenaline/Norepinephrine：去甲肾上腺素



Julius Axelrod （1912-2004）



Noradrenaline/Norepinephrine：去甲肾上腺素



T Tellioglu and D Robertson

神经科学和药物：心血管~神经

β-blockers， 1962

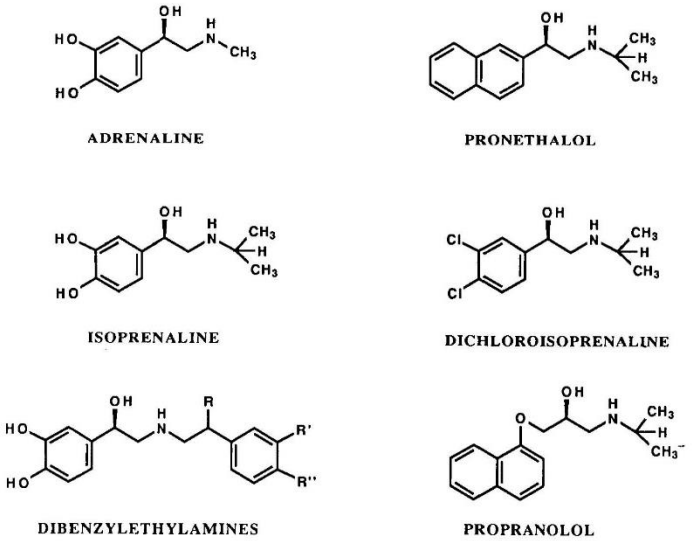
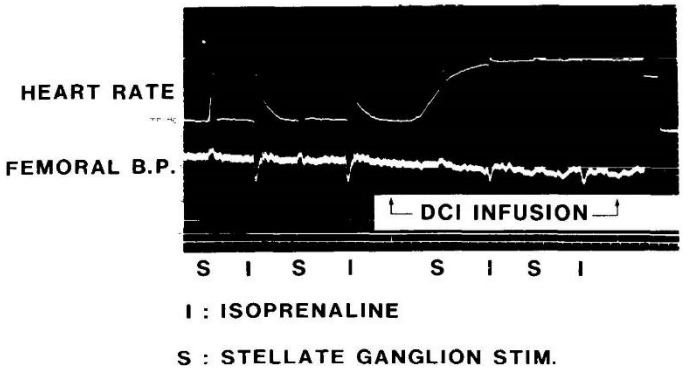


Figure 1. Chemical structures of adrenaline-related compounds.



James Black
（1924-2010）
1988

Transmitters/Modulators

Excitatory/Inhibitory

Monoamines

- **Catecholamines: NE, E, DA**
- **Histamine**
- **Serotonin (5-HT, 5-hydroxytryptophane)**
- **octopamine, tyramine**

Amino Acids

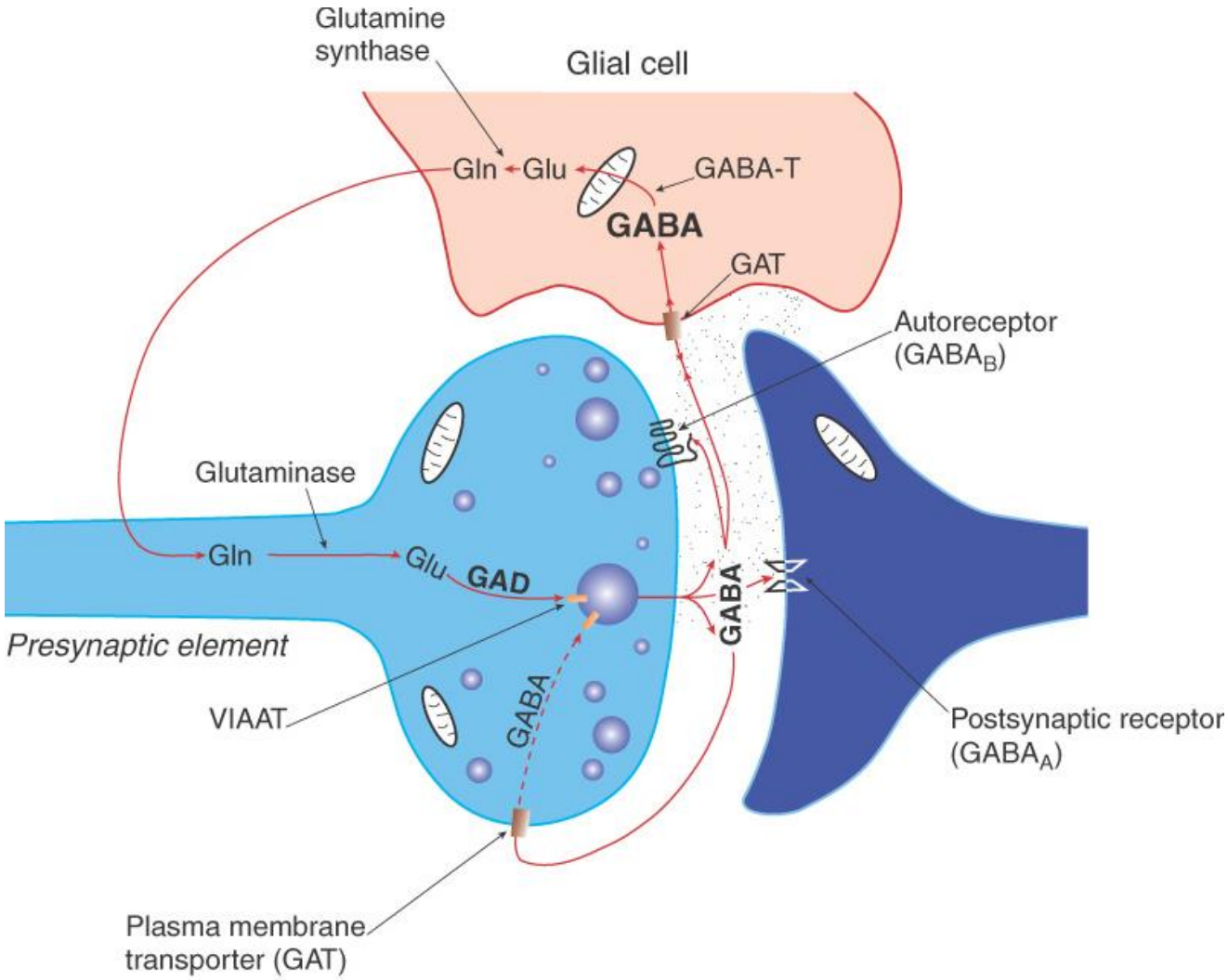
- **glutamate**
- **GABA (γ-amino butyric acid)**

ACh, Adenosine, nitric oxide, endocannibinoids

Neuropeptides

- **Opioid peptides, substance P, VIP, NPY, oxytocin and vasopressin,…~50**

脑内主要抑制性递质：GABA



Schematic depiction of the life cycle of a GABAergic neuron. a-Ketoglutarate formed in the Krebs cycle is transaminated to glutamate (Glu) by GABA transaminase (GABA-T). The transmitter GABA is formed from the Glu by glutamic acid decarboxylase (GAD). GABA that is released is taken by high-affinity GABA transporters (GAT) present on neurons and glia.

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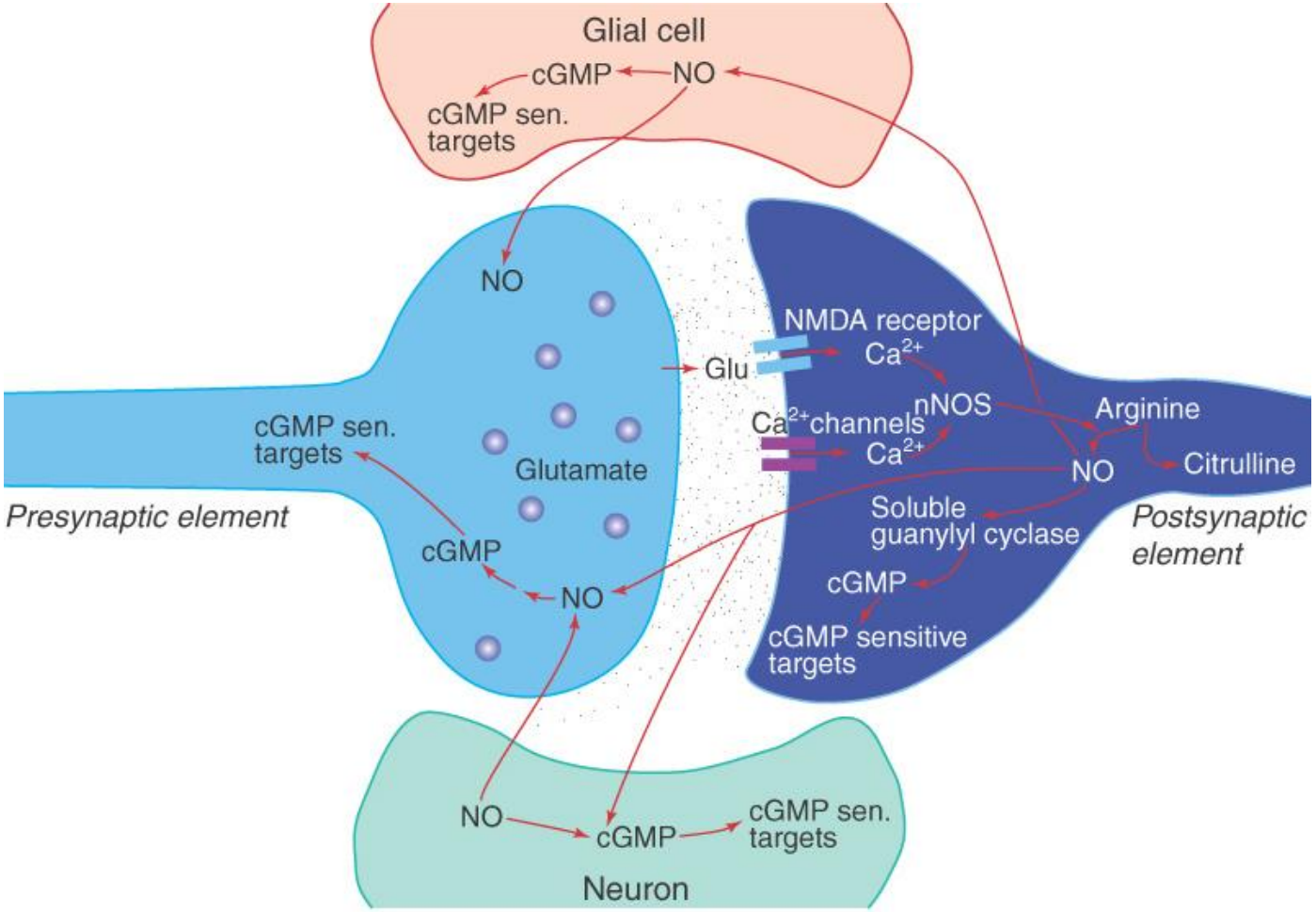
Glutamate and NO



Schematic representation of a nitric oxide (NO)-containing neuron. NO is formed from arginine by the actions of different nitric oxide synthases (NOS). NO diffuses freely across cell membranes and can thereby influence both presynaptic neurons (such as the glutamatergic presynaptic neuron in the figure) or other cells that are not apposed

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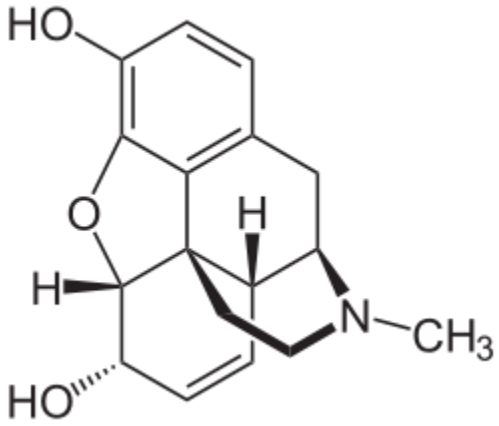
Neuropeptides 神经肽：鸦片和吗啡的历史

~3400 B.C. Mesopotamia, “joy plant” by Sumerians, passed to Assyrians, Babylonians, Egyptians.
460 B.C. Hippocrates. 鸦片的医学应用：镇静、内科疾病.
330 B.C. Alexander the Great 鸦片带到波斯和印度
400 阿拉伯人将鸦片首次引入中国
1500 葡萄牙人将吸鸦片带到中国.
1601 伊丽莎白女王雇船买印度鸦片运到英国
1700 荷兰人出口印度鸦片到中国
1729 雍正皇帝禁止鸦片
1750 英属东印度公司对华销售印度鸦片 1767达一年两千箱，1793获得印度鸦片垄断.
1799 嘉庆皇帝严禁鸦片
1800 英国 Levant 公司销售鸦片到欧洲和美国.
美国人加入对中国的鸦片贸易：Charles Cabot （1805）, John Cushing (1818), John Jacob Astor(1816)
1830 英国每年进口鸦片22,000 磅.
Jardine-Matheson 洋行垄断印度鸦片
1839年3月18日，林则徐发布谕：外公商人交出鸦片，虎门销烟
第一次鸦片战争
1840 美国新英格兰地区进口24,000 磅鸦片
1841 中国败于英国，赔款、割让香港
1842 中英南京条约
1856 英法联军，第二次鸦片战争，中国赔款、并鸦片进口合法化
1878 英国通过鸦片法，只能给注册的中国和印度吸毒者卖鸦片。
1890 美国国会通过法律对鸦片和吗啡加税.
1905 美国国会禁止鸦片， 1909年禁止进口
1906 中英限制印度-中国鸦片贸易
1909 年2月1日 上海，国际鸦片会议.
1910 英国取消经印度对华贸易鸦片
1950s 美国、法国支持金三角（缅甸、老挝、泰国）反共武装、允许其鸦片贸易，美国非法进口海洛因增加、吸毒人口增加。
1962 缅甸禁止鸦片.
1965-1970 美国打越战，中情局进口鸦片，美国海洛因吸毒人数达到高峰. 750,000
迄今没有完全解决，另外还有其他吸毒、成瘾

Neuropeptides 神经肽:内源性阿片肽



鸦片的活性成分 Morphine
(1806，德国Friedrich Sertürner)
有多种作用

镇痛作用的位点:
阿司匹林作用于外周
吗啡作用于中枢

Goldstein A et al,1971.
Pert CB, Snyder SH,1973
Simon et al, 1973
Terenius L 1973

Opiate receptors
defined
isolated

Endogenous opioid peptides
enkaphalin
endophin
dynophin

Hughes & Kosterlitz et al,1975.
Goldstein,1979
Nakanishi et al 1979
Kakinani et al 1982
Noda et al 1982

阿片受体和内源性阿片肽

Sertürner FWA (1806) Darstellung der reinen Mohnsäure (Opiumsδure), nebst einer chemischen Untersuchung des Opiums. *J Pharmacol 14:47–93*

Goldstein A, Lowney LI & Pal, BK (1971) Stereospecific and Nonspecific Interactions of the Morphine Congener Levorphanol in Subcellular Fractions of Mouse Brain. PNAS 68, 1742-1747.

Pert CB, Snyder SH (1973) Opiate receptor: Demonstration in nervous tissue. Science 179:1011–1014

Simon EJ, Hiller JM, Edelman I (1973) Stereospecific binding of the potent narcotic analgesic (3H) Etorphine to rat-brain homogenate. PNAS 70:1947–1949.

Terenius L (1973) Stereospecific interaction between narcotic analgesics and a synaptic plasma membrane fraction of rat cerebral cortex. Acta Pharmacol Toxicol 32:317–320.

Hughes J. Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. *Brain Res.* 1975;88:295-308

Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature.* 1975;258:577-580.

Bradbury AF, Smyth DG, Snell CR, Birdsall NJM, Hulme EC (1976) C-fragment of lipotropin has a high affinity for brain opiate receptors. *Nature (Lond) 260:793–795.*

Van Ree JM, De Wied D, Bradbury AF, Hulme EC, Smyth DC, Snell *CR (1976) Induction of tolerance to the analgesic action of lipotropin C-fragment. Nature (Lond) 264:792–794.*

Wei E, Loh H (1976) Physical dependence of opiate-like peptides. *Science (Wash DC) 193:1262–1263.*

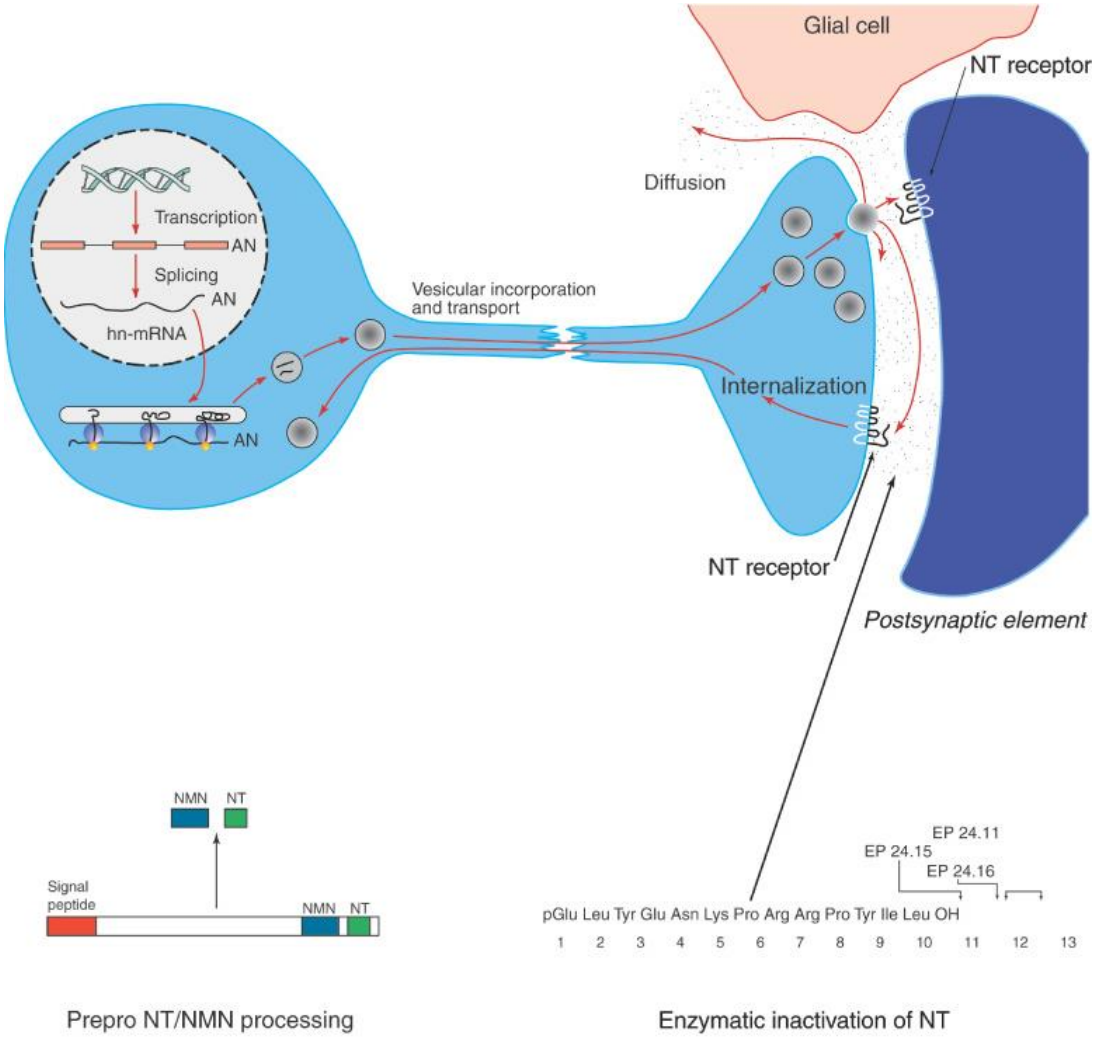
Goldstein A, Tachibana S, Lowney LI, Hunkapiller M, Hood L(1979) Dynorphin-(1–13), an extraordinarily potent opioid peptide. *PNAS* 76:6666–6670

Nakanishi S, Inoue A, Kita T, Nakamra M, Chang AC, Cohen SN, Numa S(1979) Nucleotide sequence of cloned cDNA for bovine corticotropin-β-lipotropin precursor. *Nature* (Lond) 278:423–427.

Kakidani H, Furutani Y, Takahashi H, Noda M, Morimoto Y, Hirose T, Asai M, Inayama S, Nakanishi S, Numa S(1982) Cloning and sequence analysis of cDNA for porcine β-neo-endorphin/dynorphin precursor. *Nature* (Lond) 298:245–249.

Noda M, Furutani Y, Takahashi H, Toyosato M, Hirose T, Inayama S, Nakanishi S, Numa S(1982) Cloning and sequence analysis of cDNA for bovine adrenal preproenkephalin. *Nature* (Lond) 295:202–206.

神经肽作为递质



Schematic illustration of the synthesis, release, and termination of action of the peptide transmitter neurotensin (NT). The illustrative panels of the bottom show processing of NT from the prohormone *(left)* and enzymatic inactivation of NT *(right)*.

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Neuropeptides 神经肽

~50

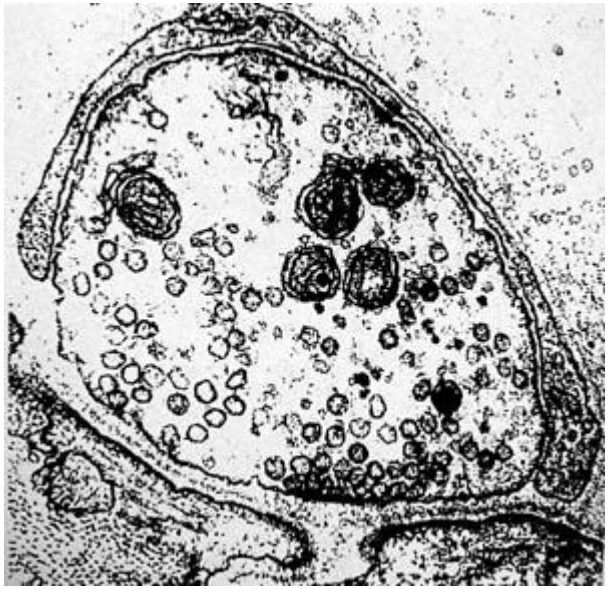
substance P,
VIP,
NPY,
oxytocin and vasopressin

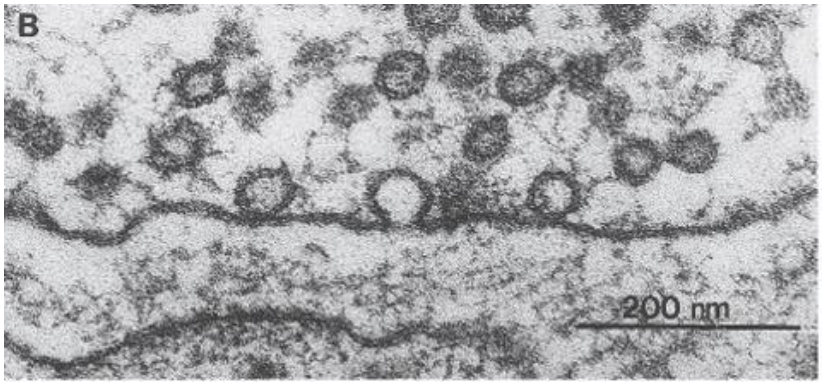
…

突触间隙　Synaptic Cleft

EM

10 to 20 nm

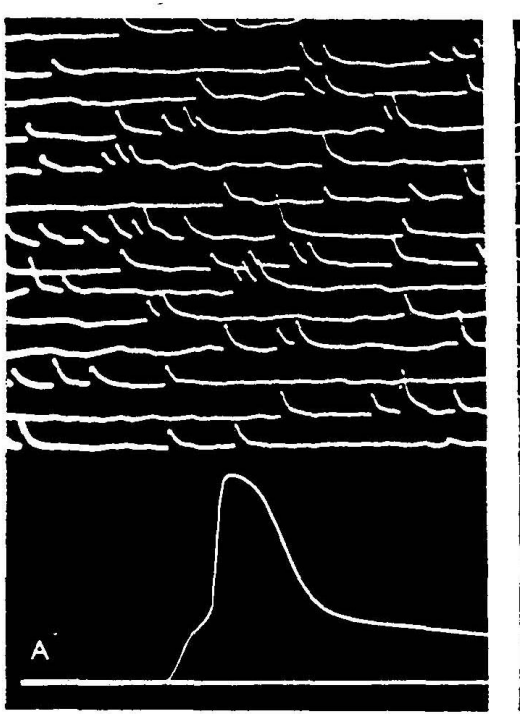




J. D. Robertson (1953). Proc. Soc. Exp. Biol. Med. 82:219
G. E. Palade, S. L. Palay (1954). Anat. Rec. 118:335

量子释放: Quantal Release

Benard Katz
(1911 – 2003)



vesicles

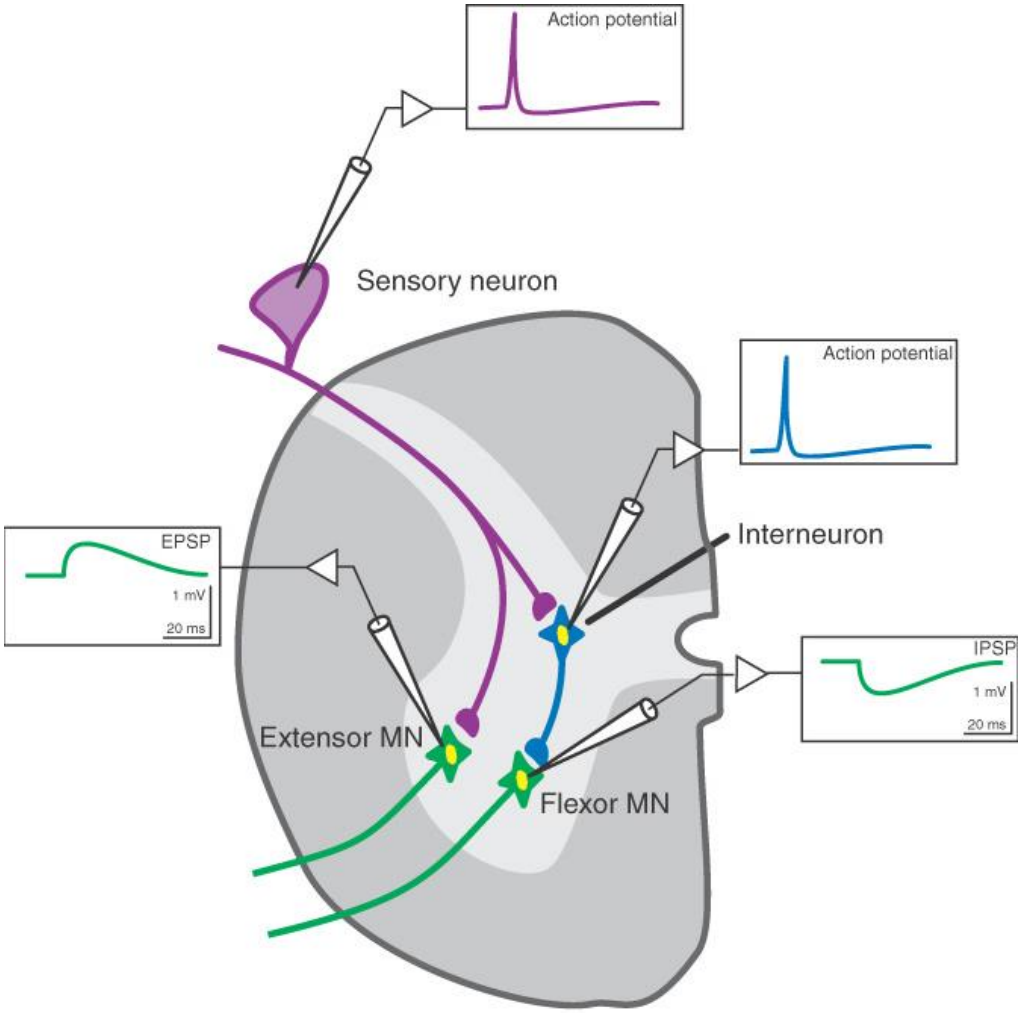
Spontaneous "miniature end-plate potentials"

犹太人的诺贝尔奖记录

P. Fatt and B. Katz (1952) *J. Physiol. (London),* 117:109.
E.D.P. deRobertis and H.S. Bennett (1954) *Federation Proc.*, 13 :35.
G.E. Palade and S.L. Palay (1954) *Anat. Record*, 118 :335.

化学传递和电反应

John C Eccles
(1903 – 1997)



Excitatory (EPSP) and inhibitory (IPSP) postsynaptic potentials in spinal motor neurons. Idealized intracellular recordings from a sensory neuron, interneuron, and extensor and flexor motor neurons (MNs). An action potential in the sensory neuron produces a depolarizing response (an EPSP) in the extensor motor neuron. An action potential in the interneuron produces a hyperpolarizing response (an IPSP) in the flexor motor neuron.

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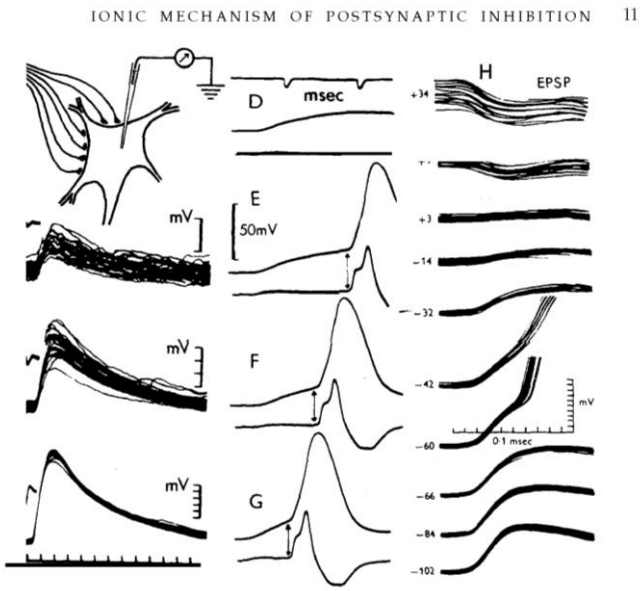
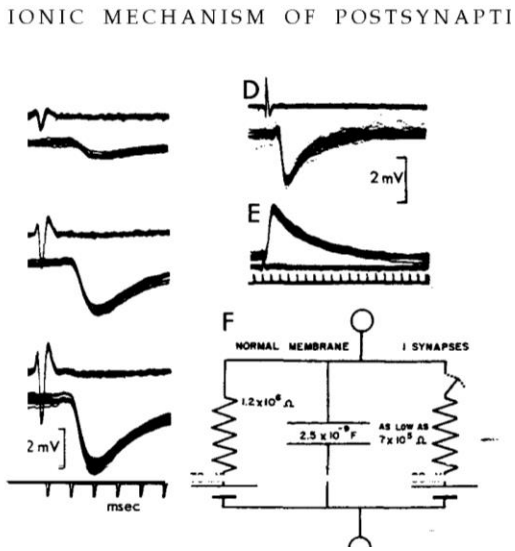
兴奋性和抑制性突触后电位





EPSP **IPSP**

John C Eccles
(1903 – 1997)

突触后反应机理：递质受体

两种：

ionotrophic： 离子通道

metabotrophic：第二信使 cAMP, CA and cGMP

John Langley (1852-1925):

1901 nicotine not acting on nerve ending

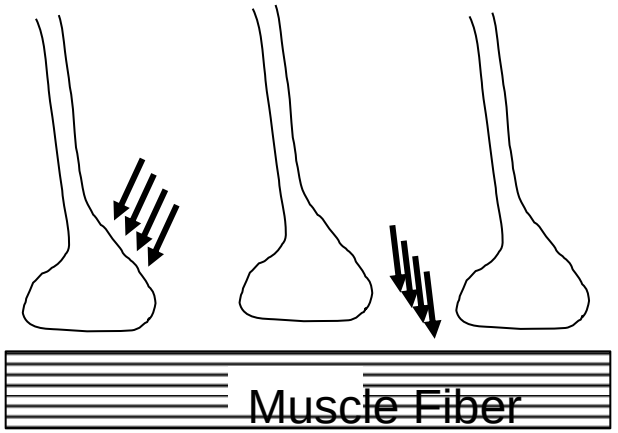
renal extract (adrenaline)

1905

curare & nicotine on muscles

1909

receptive substance



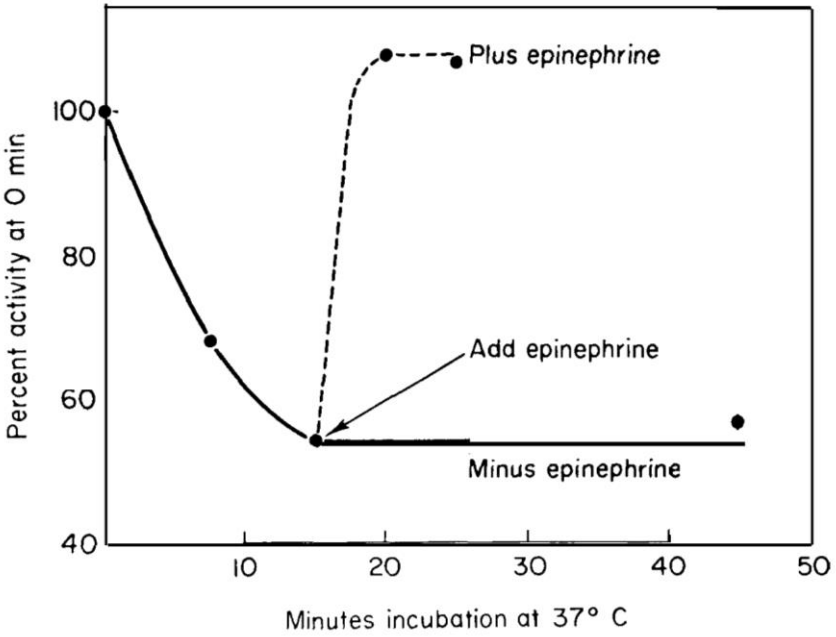
Langley JN. (1909). On the contraction of muscle, chiefly in relation to the presence of 'receptive' substances. Part IV. The effect of curari and of some other substances on the nicotine response of the sartorius and gastrocnemius muscles of the frog. J Physiol 39, 235-295

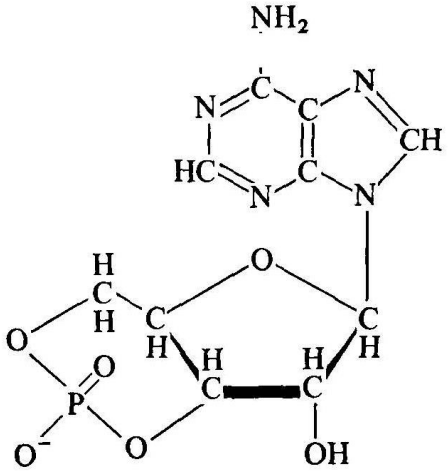
递质受体：第二信使

Earl Sutherland (1915-1974):

cAMP (1957/1958)

Epinephrine & glucagon activation of phosphorylase

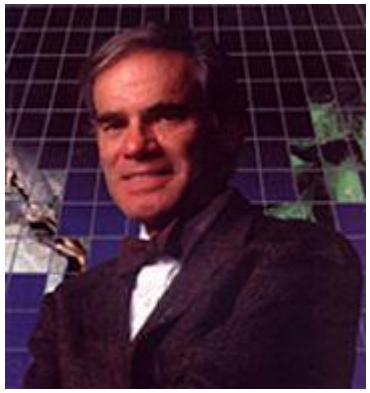




Carl and Gety Cori, Washington Univ, St. Louis

Sutherland, E. W. and Rall, T. W., JACS 79, 3608 (1957) ; IBC 232, 1077 (1958).
Rall, T. W. and Sutherland, E. W., JBC 232, 1065 (1958).
Lipkin, D., Cool, W. H. and Markham, R., JACS 81, 6198 (1959)

递质受体: G proteins介导



Martin Rodbell
(1925-1998)
GTP requirement
(1971)

Alfred Goodman Gilman
(1941-)
hetertrimeric G proteins

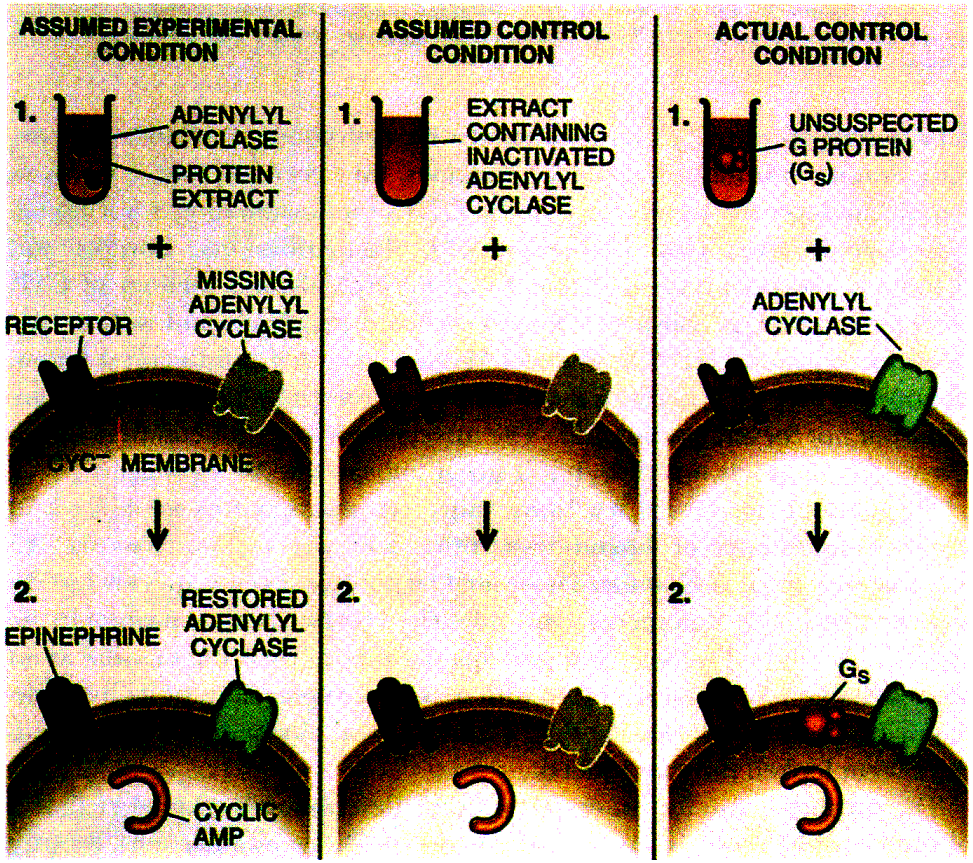
Rodbell M, Bimbaumer L, Pohl SL, Krans, HMJ. 1971 .JBC 246: 1877-82
Rodbell M. , Krans HMJ, Pohl SL, Bimbaumer L 1971 JBC 246: 1872-76
Bourne, H. R., Coffino, P., and Tomkins, G. M. (1975) Science 187,750 - 752
Ross, EM, Gilman AG 1977. PNAS 74:3715-1 9
Ross EM, Gilman AG 1 977 JBC252:6966-69
Ross EM, Howlett AC, Ferguson KM, Gilman AG 1978. JBC 253:6401 -12
Northup JK , Sternweis PC, Smigel MD, Schleifer LS, Ross EM , Gilman AG 1980. PNAS 77:6516-20

Discovery of Gs

做实验结果与预期不同，而且是对照实验

放弃还是重复、改变假设，继续跟踪

Experiments leading to the discovery of Gs. A: Cartoon of the protocols. In the first experiments, Elliott M. Ross added a detergent extract of membrane proteins to so-called cyc- membranes (left, I), which were thought to lack adenylyl cyclase. Epinephrine stimulated cyclic AMP production (2). which seemed to indicate that adenylyl cyclase had been inserted into the deficient membranes. In the control experiment, the adenylyl cyclase in the extract was inactivated (center, 1). Even without it, epinephrine caused the cyc- membranes to make cyclic AMP. This puzzling finding led to the discovery that the cyc‘ membranes did contain adenylyl cyclase (right, 1) but lacked a third component necessary to activate it - a G protein that persisted in the extract after adenylyl cyclase had been inactivated. Restoration of the G protein to the membranes enabled adenylyl cyclase to synthesize cyclic AMP



Bourne, H. R., Coffino, P., and Tomkins, G. M. (1975) Science 187,750 - 752

Ross, EM, Gilman AG 1977. PNAS 74:3715-1 9

Northup JK , Sternweis PC, Smigel MD, Schleifer LS, Ross EM , Gilman AG 1980. PNAS 77:6516-20

不要丢掉不符合老师、或你预计的结果

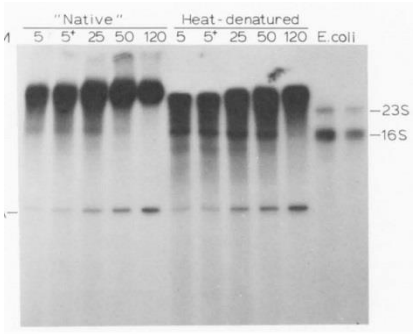
做实验结果与预期不同，而且是对照实验
放弃还是重复、改变假设，继续跟踪

结果比老师厉害、结果比科学家厉害

不要忘记、或藏起
这种结果

有些没有预计到的是更重要的：
天上掉下来的机遇

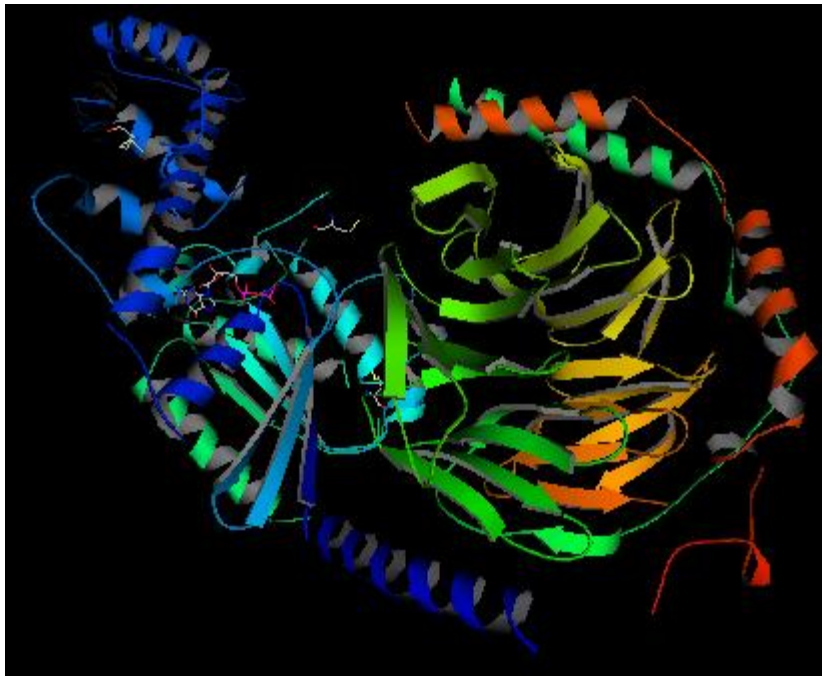
Ross and Gilman 1977
Tom Cech (1980, 1981): RNA 酶活性
RNAi, 1997
…但愿下一个是你

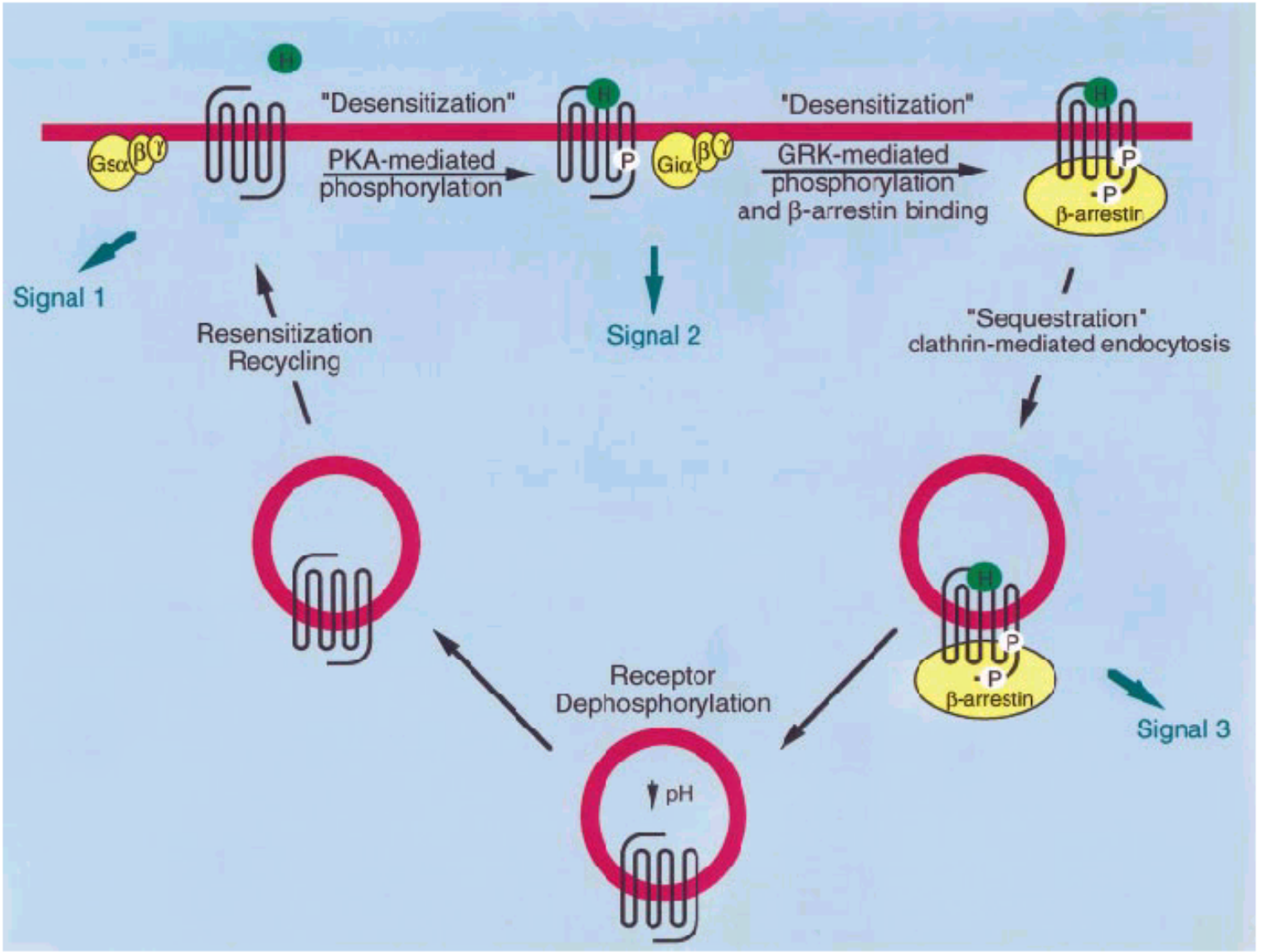


Zaug, A. J. & Cech, T. R. (1980) *Cell* 19, 331-338
Cech, T. R., Zaug, A. J. & Grabowski, P. J. (1981) *Cell* 27, 487-496

http://www.ibiomagazine.org/index.php/issues/august-issue/discvering-ribozymes

G proteins: three subunits





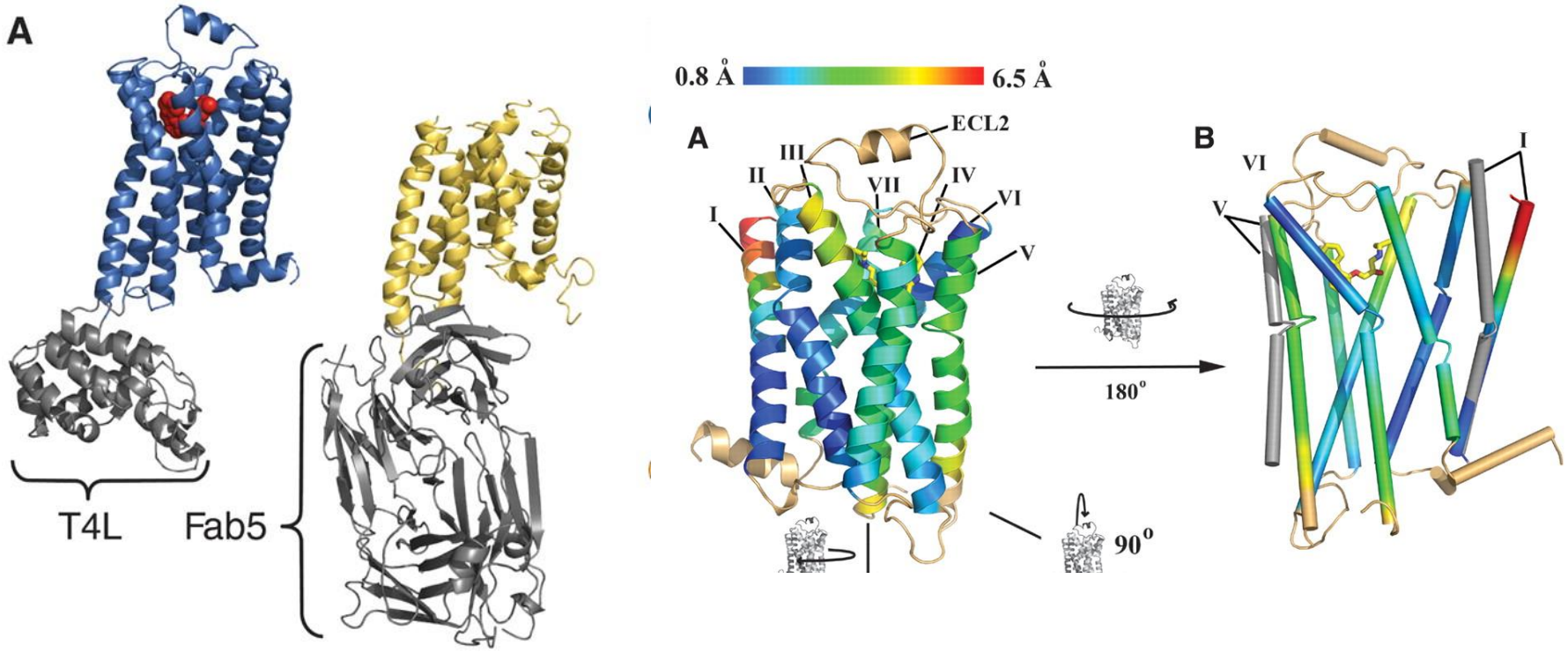
Lefkowitz, 1998 (JBC 273)

科学最激动人心:不是过去

至少生命科学
神经科学
最激动人心的
是现在
是未来
最好是你带来的未来

递质受体结构:突飞猛进的几年

递质受体：晶体结构



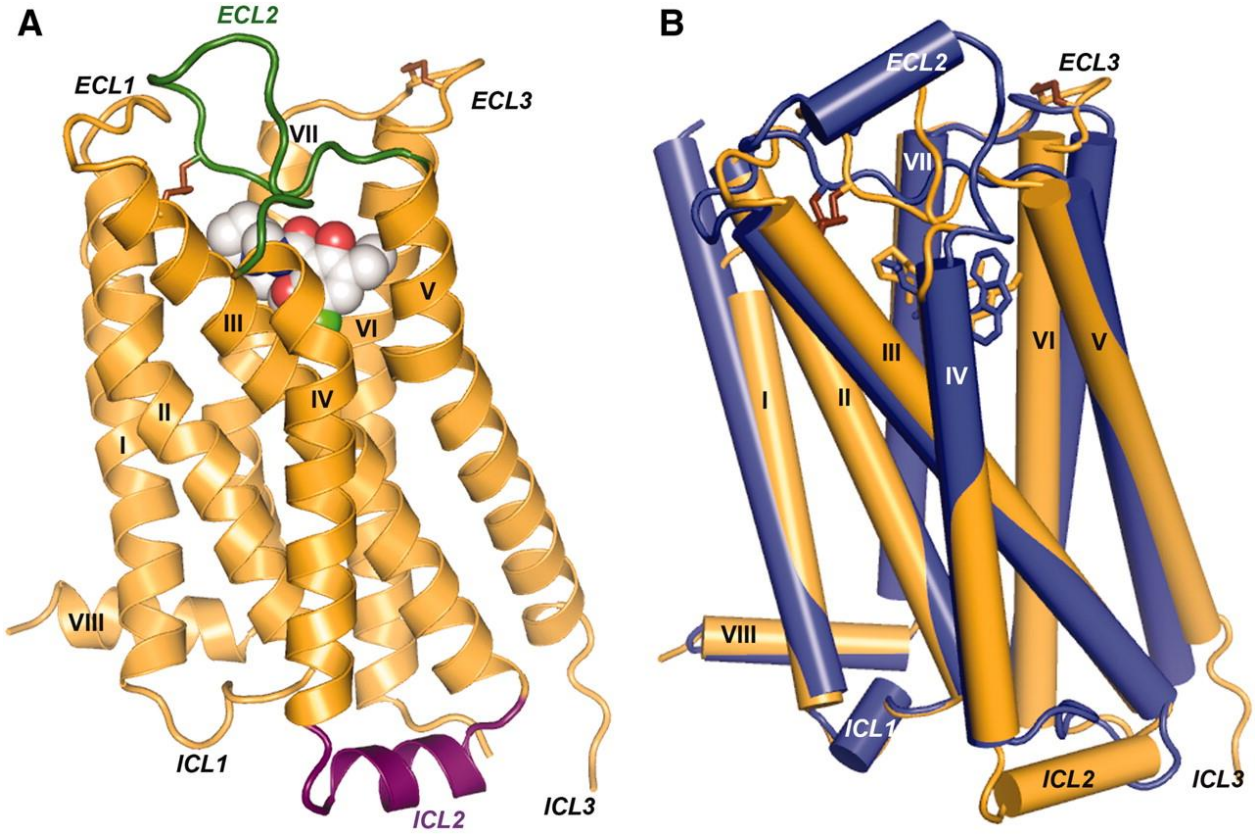
Rosenbaum, DM, Cherezov V, Hanson MA, Rasmussen SGF, Thian FS, Kolbilka ST, Choi H-J, Yao X-J, Weis WI, Stevens RC Kolbika BK (2007). GPCR engineering yields high-resolution structural insights into β_2-adrenergic receptor function. *Science* **318**, 1266–1273

Cherezov V, Rosenbaum, DM, Hanson MA, Rasmussen SG, Thian FS, Kobilka TS, Choi HJ, Kuhn P, Weis WI, Kobilka BK and Stevens RC (2007). High-resolution crystal structure of an engineered human β_2-adrenergic G protein-coupled receptor Science 318, 1258–1265.

Rasmussen, S. G. *et al.* (2007) Crystal structure of the human β_2 adrenergic G-protein-coupled receptor. *Nature* **450**, 383–387

Jaakola, V. P. *et al.* (2008) The 2.6 angstrom crystal structure of a human A2A adenosine receptor bound to an antagonist. *Science* **322**, 1211–1217

递质受体和配体结合的结构



Overall D3R structure with eticlopride

Hanson MA, Cherezov V, Griffith MT, Roth CB, Jaakola VP, Chien EY, Velasquez J Kuhn P and Stevens RC (2008). Structure 16, 897–905.

Roth CB, Hanson MA, and Stevens RC (2008). J. Mol. Biol. 376, 1305–1319.

Chien EYT et al (2010) Science 2010;330:1091-1095

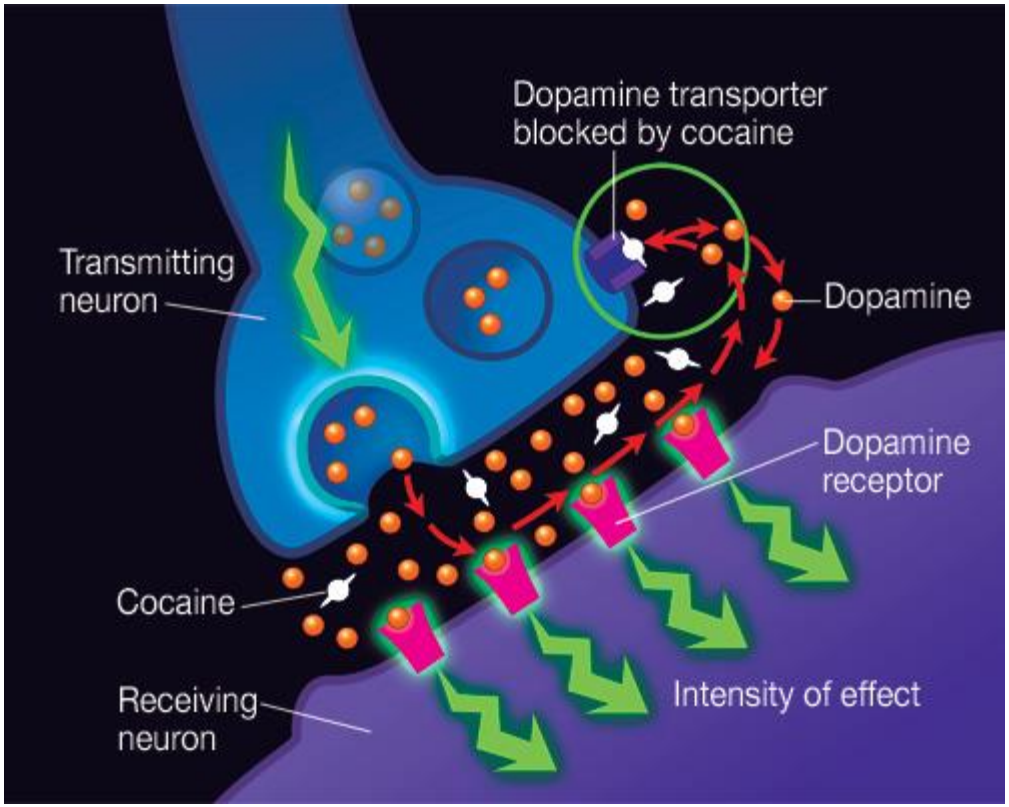
递质受体和人类健康：

市场上药物

30-40%

针对**GPCR**

Synaptic Transmission



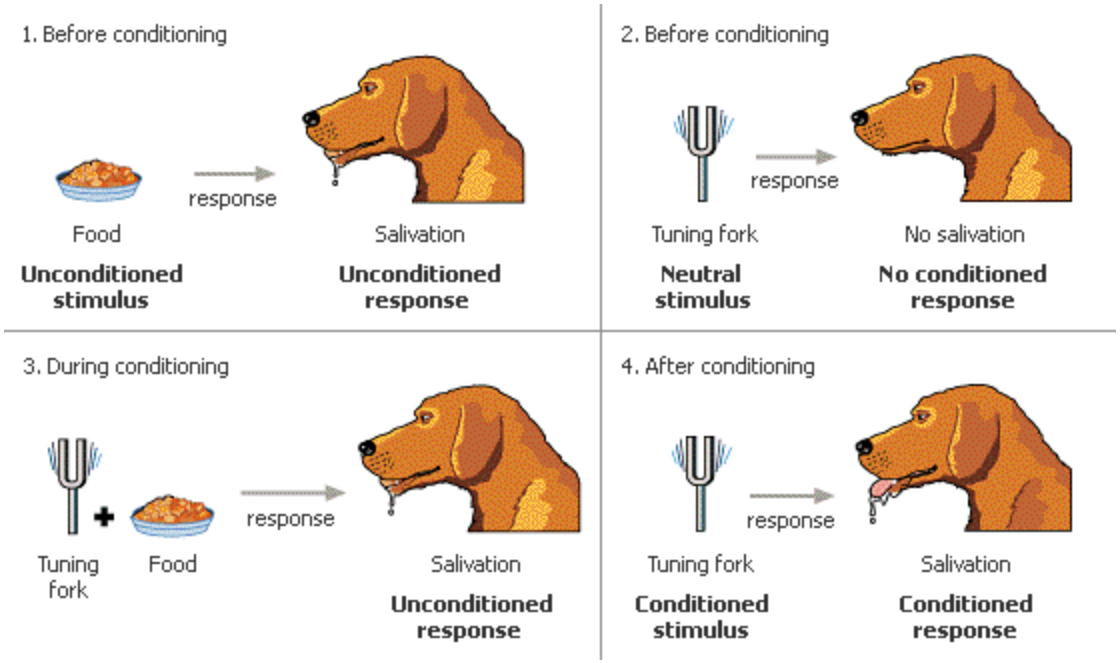
Synaptic Plasticity

learning & memory

Long Term Potentiation

Learning & Memory

Ivan Petrovich Pavlov
Nobel 1904



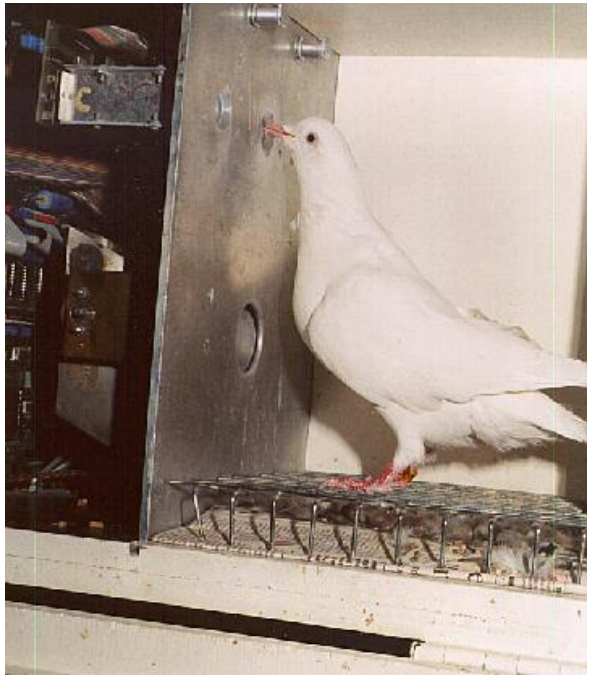
Learning & Memory

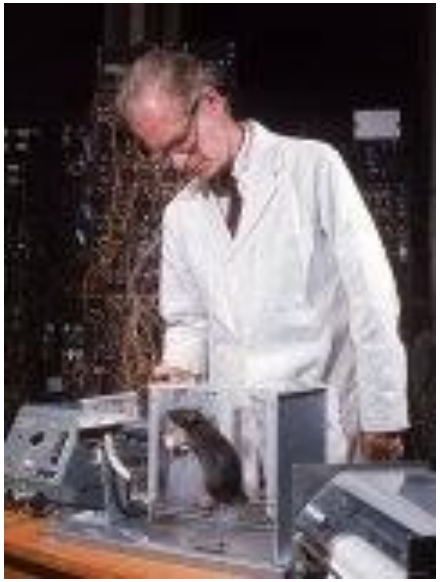
Experimental analysis of behavior

radical behaviorism

stimulus-response

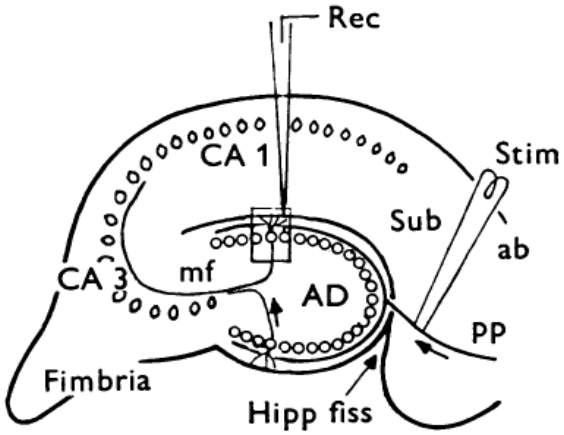
Operant Conditioning

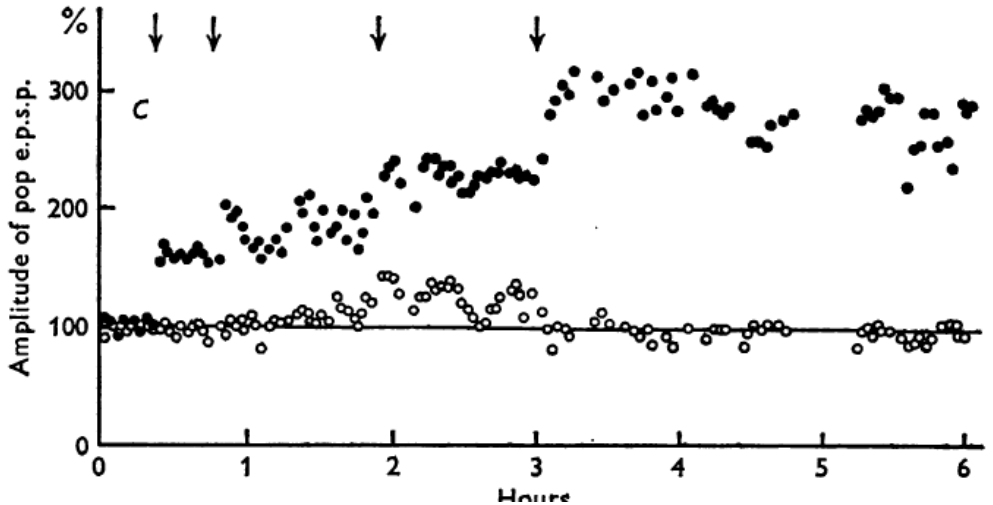




BF Skinner
1904-1990

Long Term Potentiation





Bliss TVP and Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rahbit following stimulation of the perforant path. J. Physiol. 232 : 33 1-56

Bliss, T. V. P., Gardner-Medwin, A. R. 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the unanaesthetized rabbit following stimulation of the perforant path. J. Physiol. 232 :357-74

Long Term Potentiation

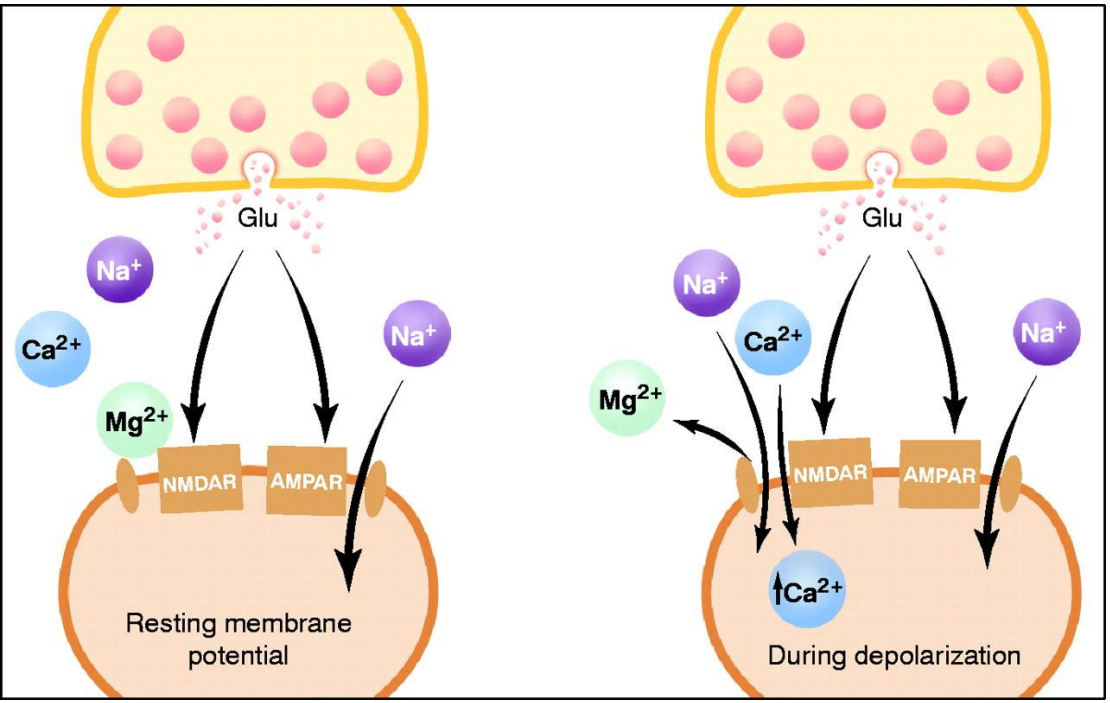
Long lasting

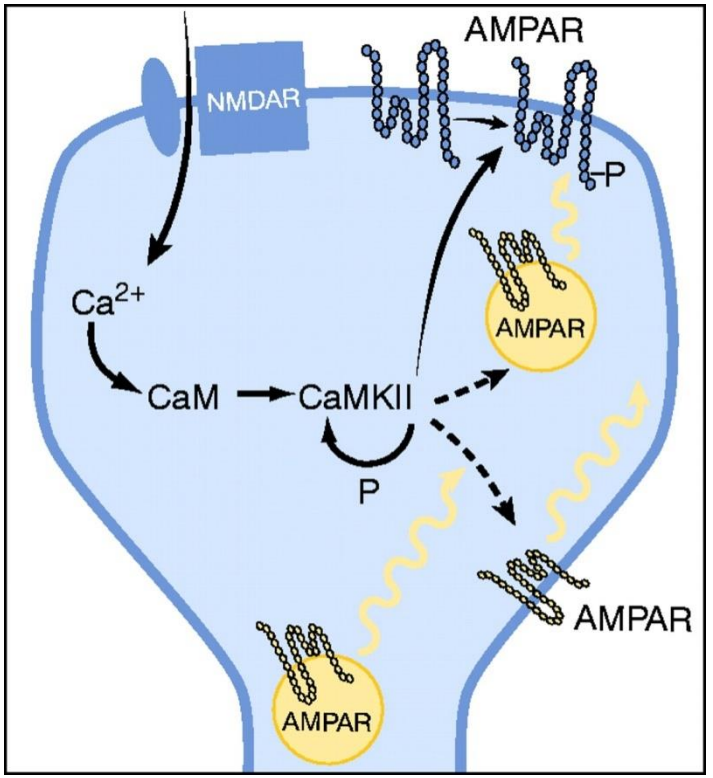
Coactivation: coincidence detector

postsynaptic depolarization & presynaptic stimulation

Input specificity

LTP：mechanisms 1999





1999年以前的重要发现：

NMDA，Ca，protein kinase

突触后变化、突触前变化

有兴趣者自己读现在的文章

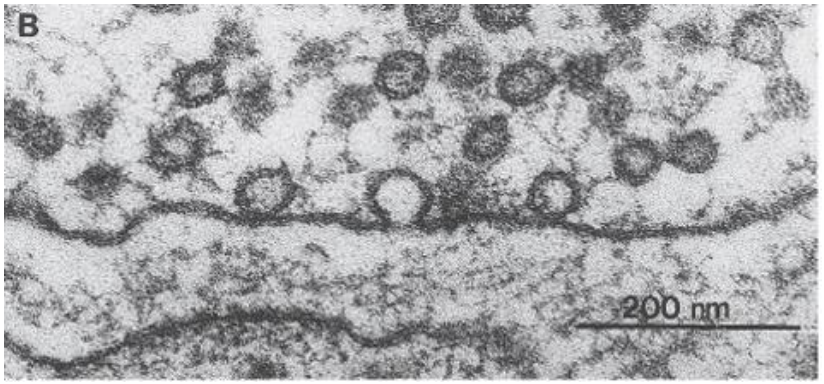
R C Malenka, & R A Nicoll (1999) Science 285:1870-1874

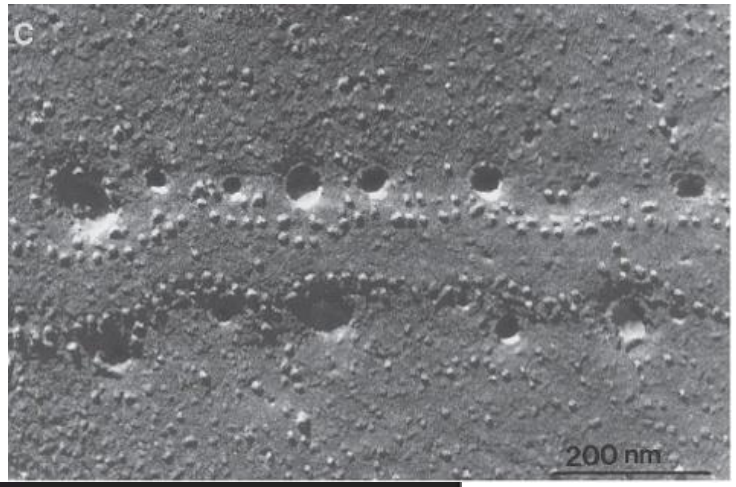
Neuroscience

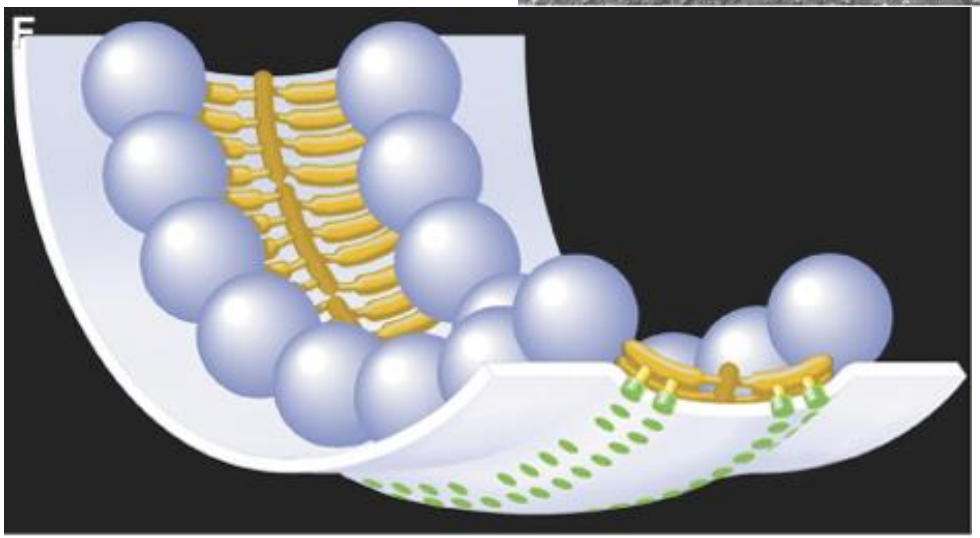
- 结构
  - 形态
    - 大体
    - 细胞
  - 神经环路
- 功能
  - 神经传递
  - 自主功能
  - 高级功能
- 来源
  - 进化
  - 发育

神经和其他学科相互促进

Vesicle Release & Recycling

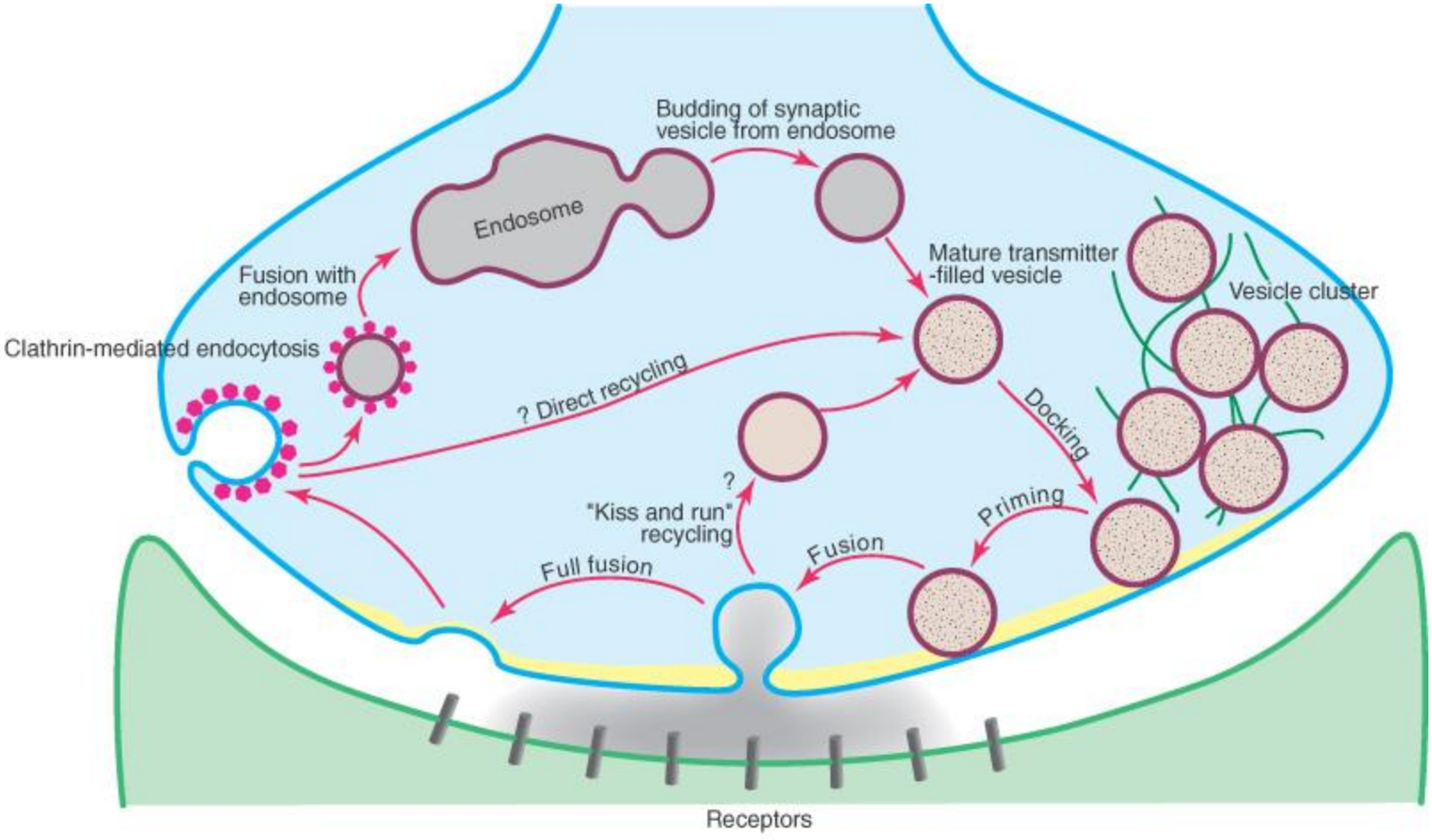






Squire et al. (2008) *Fundamental Neuroscience*

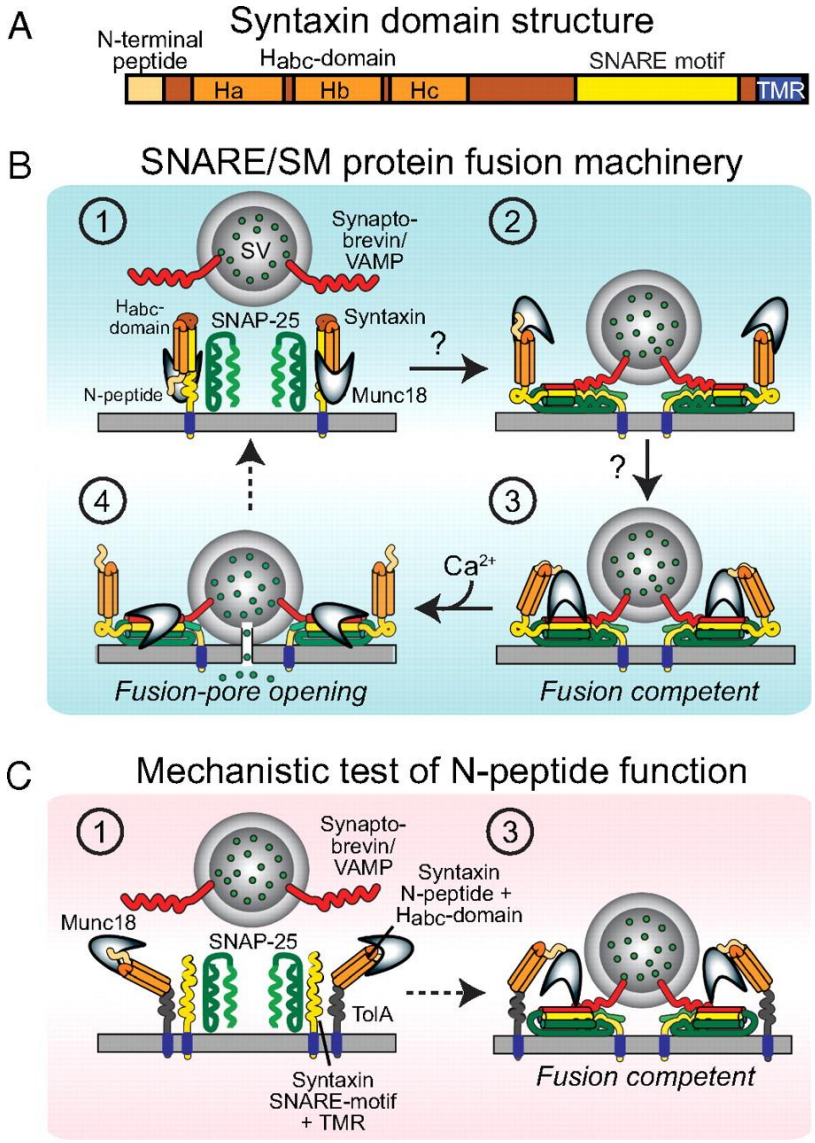
Vesicle Recycling

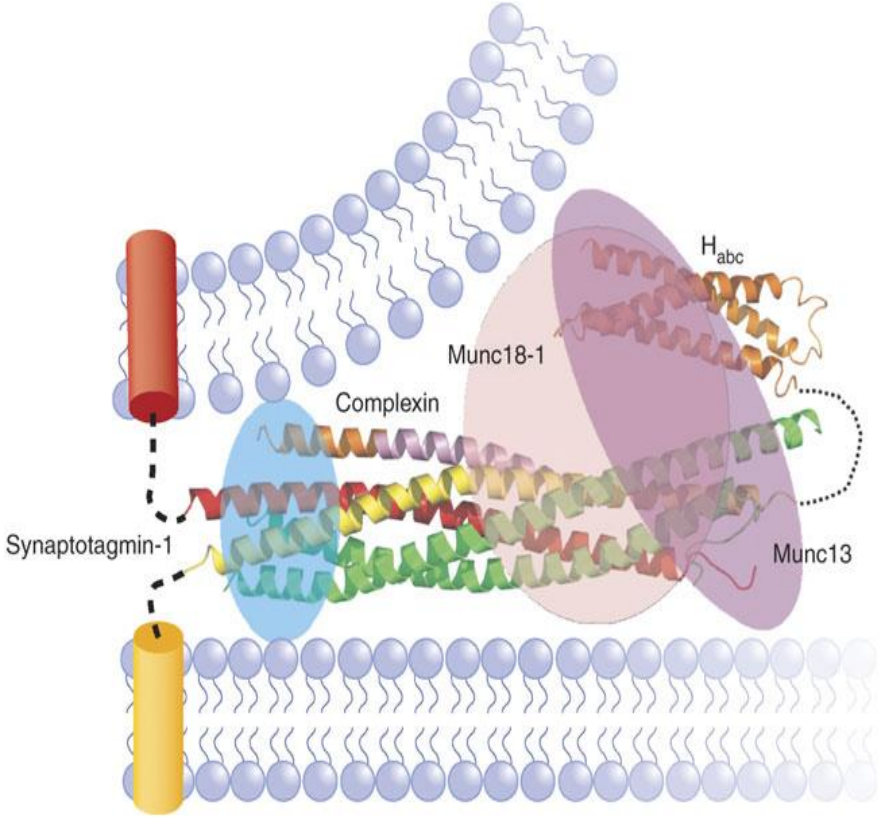


The life cycle of synaptic vesicles. Transmitter-filled vesicles can be observed in clusters in the vicinity of the

Squire et al. (2008) *Fundamental Neuroscience*

Tom Sudhof: neurons/Jim Rothman: biochem/Randy Schekman: yeast genetics





Rizo J & Rosenmund C (2008) *Nature Structural & Molecular Biology* 15, 665 - 674

Bacaj T, Pang ZP, Sudhof TC. (2010) PNAS 107:22365-22366

神经科学对一般生物学普遍意义发现

Axonal Transport

轴浆转运：axonal transport

首先因为神经纤维长而提出：

支配脚趾的神经：从脊髓到脚

继而因为神经纤维有好材料而好研究

枪乌贼巨大轴突

技术进步：

Nina & Robert Allen (1981), Inoue (1981), VE-DIC

挤牙膏

在轴浆中不同亚细胞器运动速度不同

轴浆挤出来，无障碍时，运动速度相同，

>>机理相同

体外assay

运动的相对性：珠子在微管上走/微管在玻璃上走

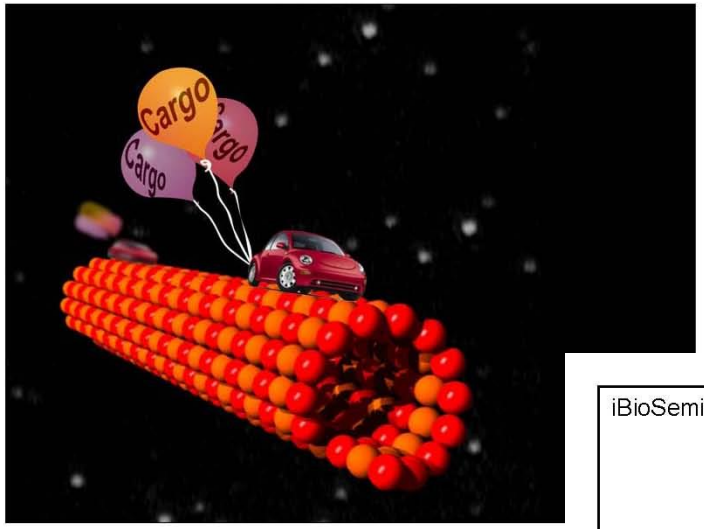
生物化学：1985　　获得分子

最后发现是基本的分子细胞生物学

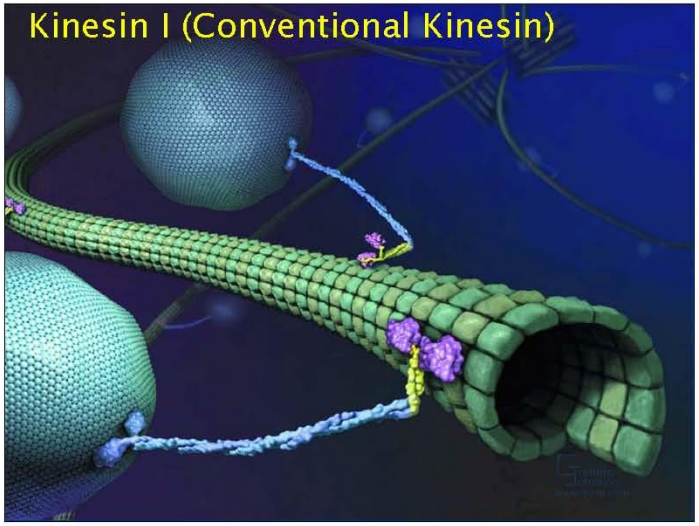
kinesin

Allen and Inoue

Nina & Robert Allen (1981), Inoue (1981), VE-DIC



iBioSeminars: Ron Vale, July 2007 Cytoskeletal Motor Proteins, Part 1



In vitro assays: cell free

beads on MT

Ron Vale (1983)

MT on glass

Ron Vale 1984

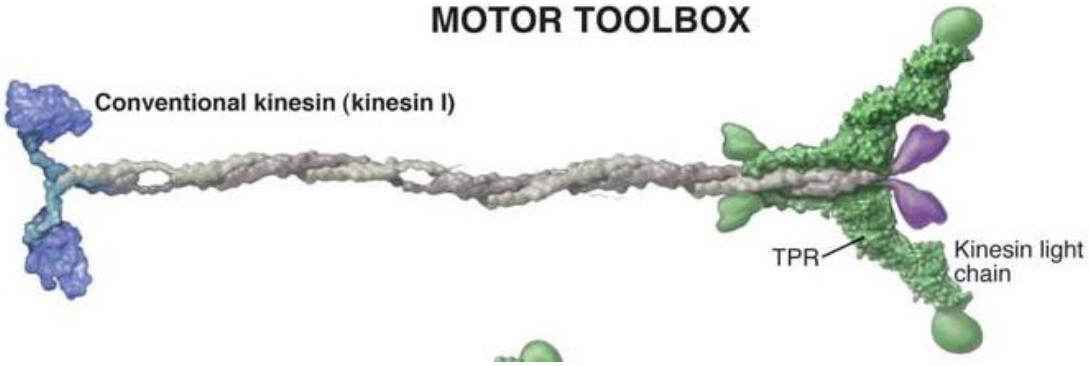
Vale, R.D., Schnapp, B.J., Sheetz, M.P. and Reese, T.S. (1985) Movement of organelles along filaments dissociated from the axoplasm of the squid giant axon. ***Cell*** 40: 449-454.

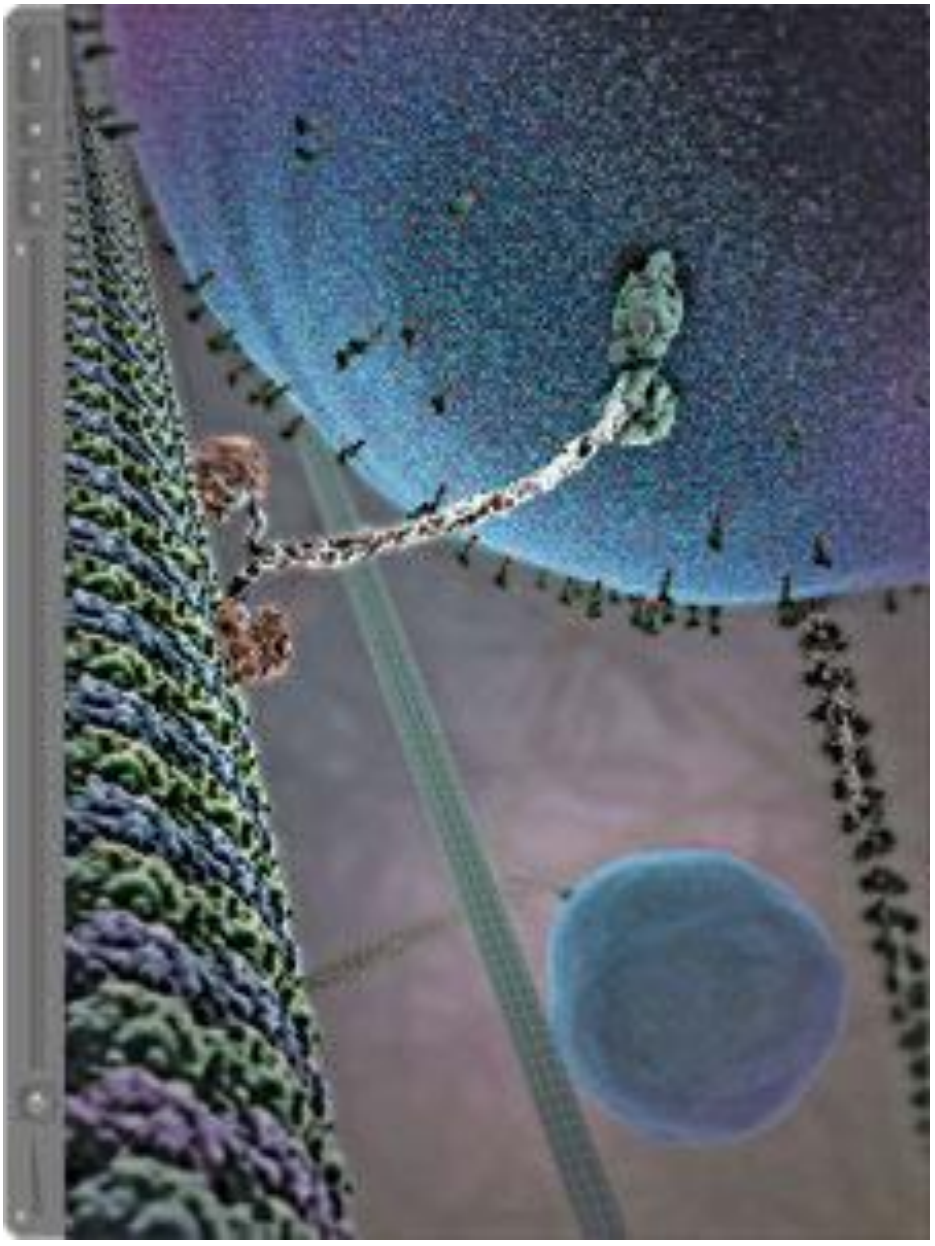
Schnapp, B.J., **Vale, R.D**., Sheetz, M.P. and Reese, T.S. (1985) Single microtubules from squid axoplasm support bidirectional movement of organelles. ***Cell*** 40: 455-462.

Vale, R.D., Schnapp, B.J., Reese, T.S. and Sheetz, M.P. (1985) Organelle, bead and microtubule translocations promoted by soluble factors form the squid giant axon. ***Cell*** **40:559-569.**

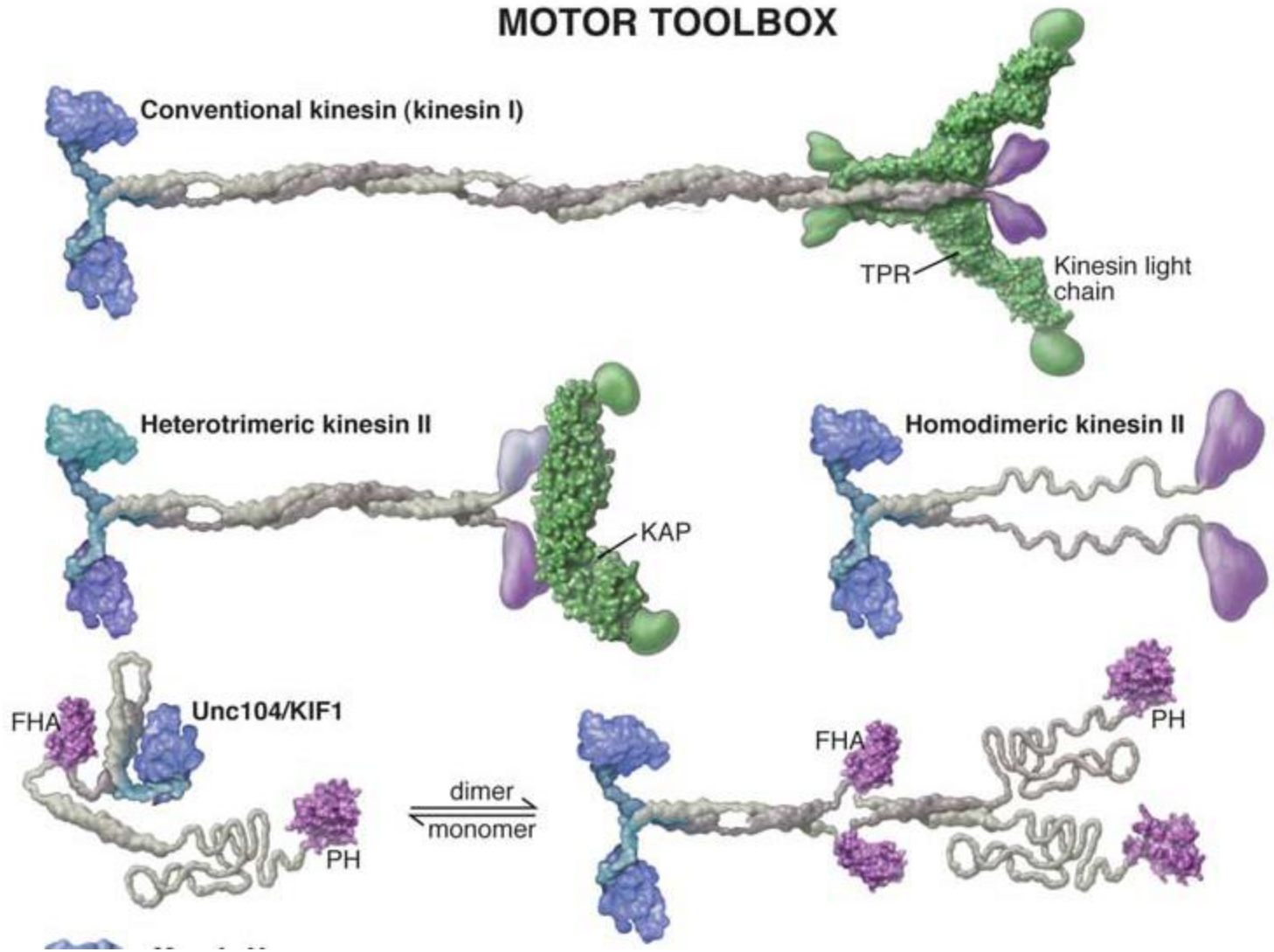
Vale, R.D., Reese, T.S. and Sheetz, M.P. (1985) Identification of a novel force generating protein, kinesin, involved in microtubule-based motility. *Cell* 42: 39-50.

Vale, R.D., Schnapp, B.J., Mitchison, T., Steuer, E., Reese, T.S. and Sheetz, M.P. (1985) Different axoplasmic proteins generate movement in opposite directions along microtubules in vitro. ***Cell*** 43: 623-632.


MOTOR TOOLBOX
Conventional kinesin (kinesin I)
TPR
Kinesin light chain



Vale R (2007)

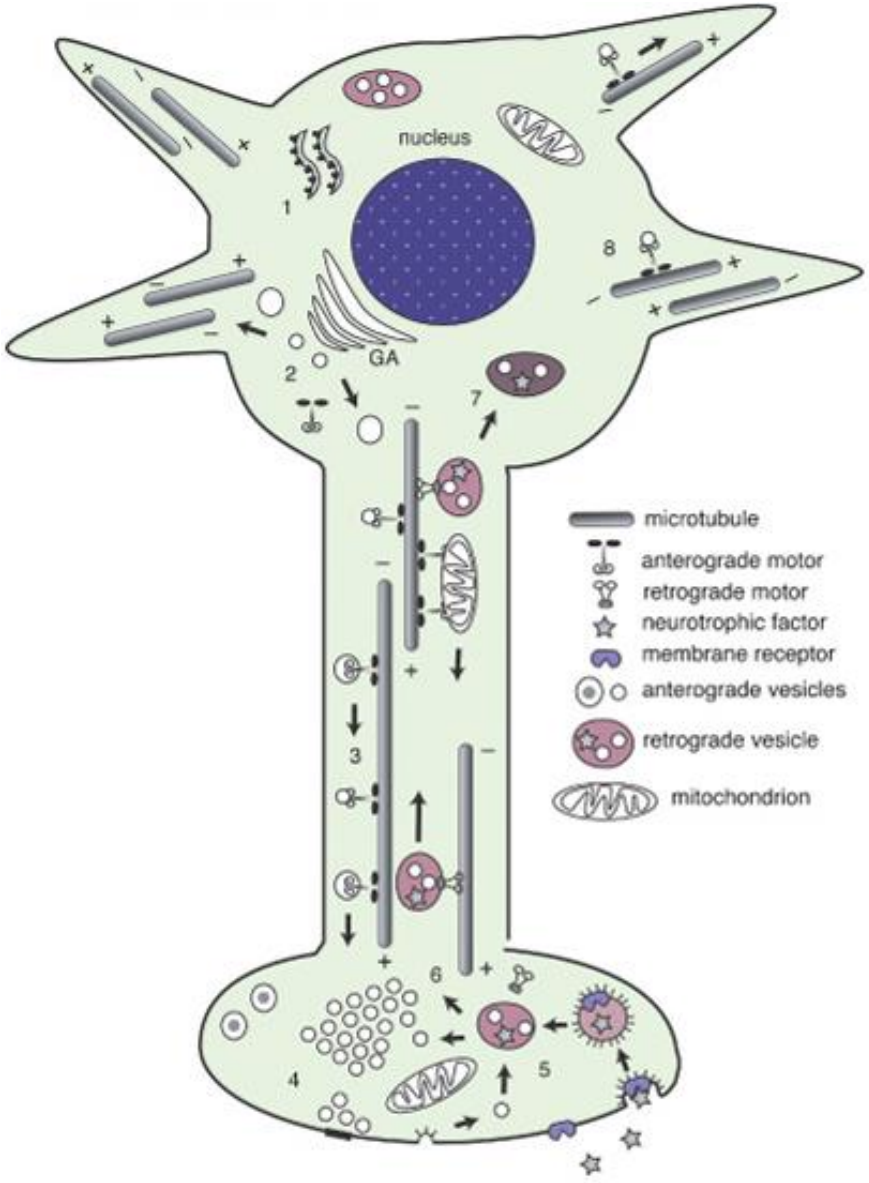

MOTOR TOOLBOX
Conventional kinesin (kinesin I)
TPR
Kinesin light chain
Heterotrimeric kinesin II
KAP
Homodimeric kinesin II
FHA
Unc104/KIF1
PH
dimer
monomer
FHA
PH

Vale R (2007)

Kinesin走路

	Kinesin	Automobile Engine
Size	10^{-8} m	1 m
Fuel	ATP	Hydrocarbons
Speed	4 x 10^{-3} m/hr	10^{5} m/hr
	4 x 10^{5} lengths/hr	10^{5} lengths/hr
Work Efficiency	~60%	~10%

Vale R (2007)



Squire et al. (2008) *Fundamental Neuroscience*

神经发育：略

神经细胞命运决定
神经诱导
神经母细胞
神经干细胞
神经细胞迁移
神经轴突导向
神经连接形成
突触形成
突触去除

神经科学与疾病：略

先天痴呆
神经内科疾病
精神疾病
神经损伤
老年痴呆
……

神经科学：何时突破

感情
语言
思维
意识
……

好难啊：等谁突破