

尋找形成記憶的分子元素

Searching for Memory Molecules

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高中生認知單元

Outlines 大綱

- 神經系統中的細胞學簡介
Neuron/ Glia/ microglia
樹突，軸突，突觸 (dendrite/axon/ synapse)
- 神經細胞間如何傳遞訊息？ Excitatory vs. inhibitory
興奮性 vs 抑制性
- 突觸可塑性 (Synaptic plasticity): 學習與記憶的分子
機制
- 長期記憶的分子本質
- 如何研究記憶的實驗方法

Learning and Memory- Making who we are

- Learning 學習：接受新的訊息
- Memory：將接受到的訊息存於腦中，可分為
陳述性（外顯）記憶：海馬體腦區

Declarative (explicit) memory

Cognitive memory- Facts and event

非陳述性（內隱）記憶：紋狀體腦區

Nondeclarative (implicit) memory

Procedural memory- skills, habits, behaviors

愛茲海默症：巴金森氏症

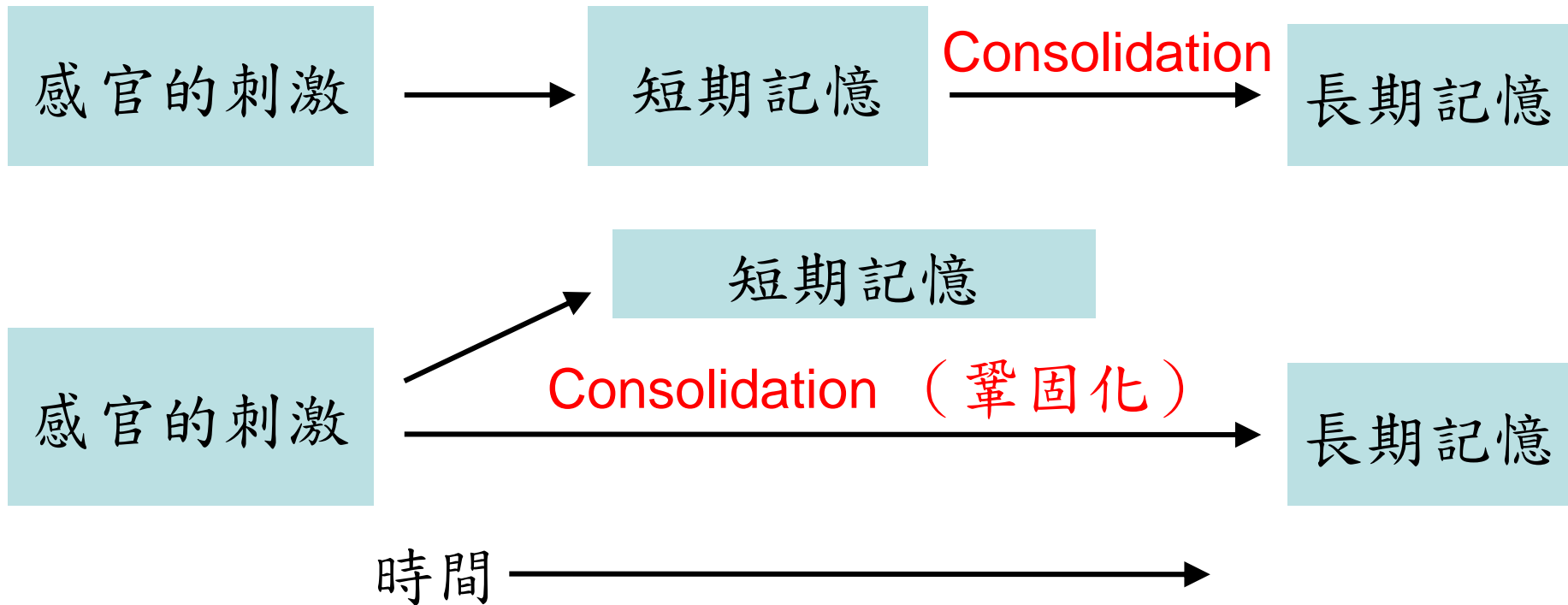
記憶存在腦中的時間可以有長有短

記憶可因存在時間的長短而又分成

長期記憶，短期記憶及暫時記憶

Long-Term, Short-Term, and Working (temporary) Memory

但長期記憶的形成不一定要經過短期記憶的過程



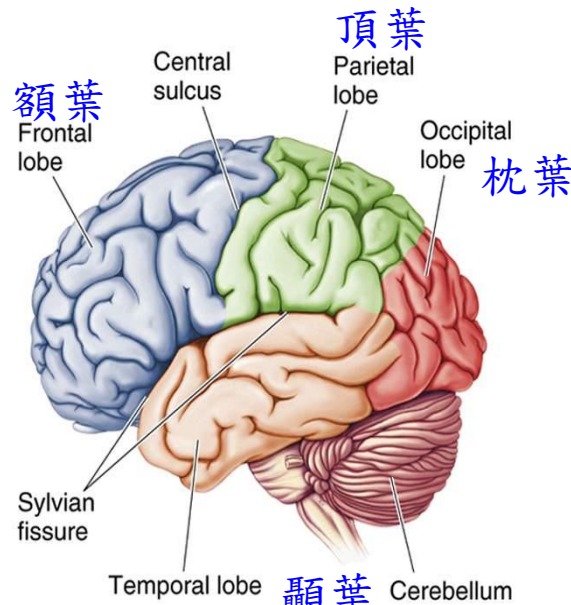
記憶可分成不同階段的過程

- **Acquisition (learning, encoding information)**
獲取資訊 (學習, 編碼信息)
- **Consolidation (鞏固化)**
- **Reconsolidation (再鞏固)**
- **Retrieval (取出記憶)**
- **Extinguish (是重新學習而非忘記)**

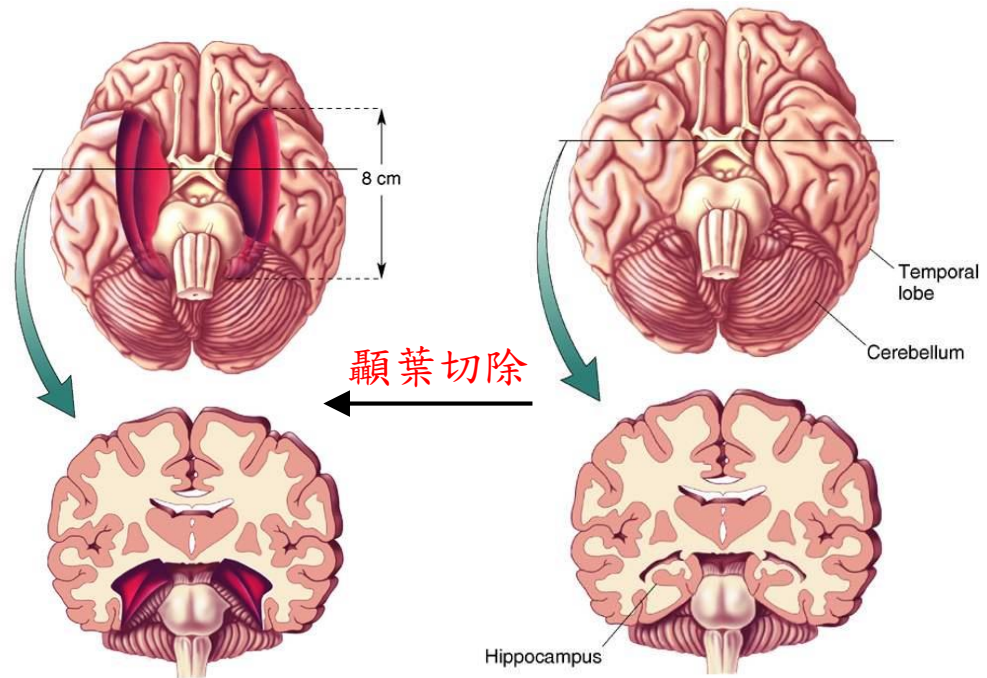
記憶痕跡：尋找記憶存在的大腦區域

人類研究：

1. 顳葉切除的病人 (H.M. patient, 1926-2008
work of Dr. Brenda Milner)
2. 電刺激於顳葉 (Dr. Penfield's experiments
sensations like hallucinations, recall past experiences)



Neuroscience: Exploring the Brain, 3rd Ed, Bear, Connors, and Paradiso Copyright © 2007 Lippincott Williams & Wilkins



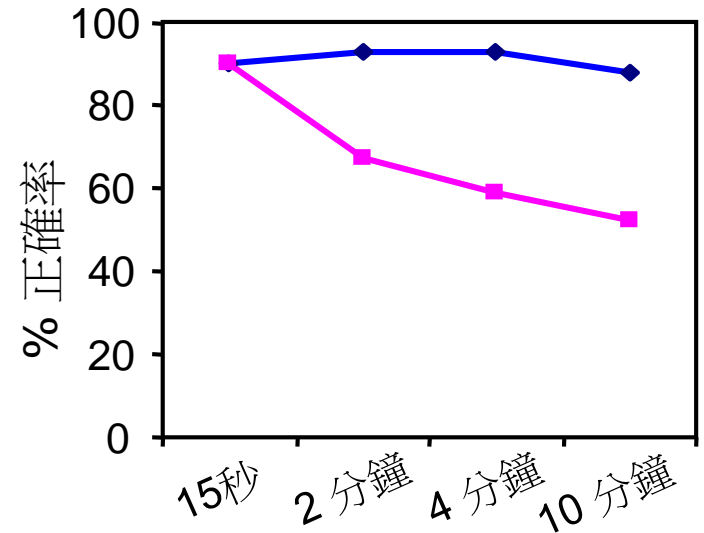
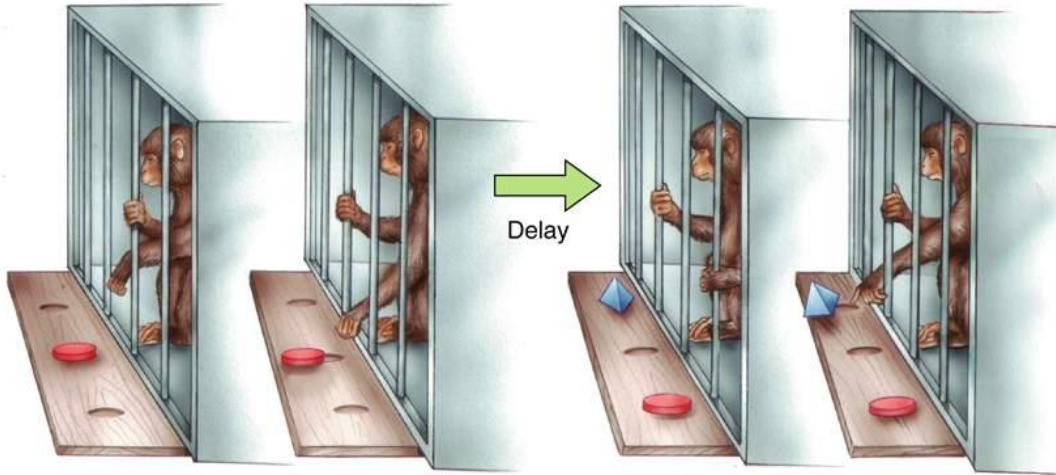
(a) H.M.'s brain

(b) Normal brain

Neuroscience: Exploring the Brain, 3rd Ed, Bear, Connors, and Paradiso Copyright © 2007 Lippincott Wi Neuroscience: Exploring the Brain, 3rd Ed, Bear, Connors, and Paradiso Copyright © 2007 Lippincott Williams & Wilkins

記憶痕跡：尋找記憶存在的大腦區域

- Recognition memory test:
 - DNMS: Delayed non-match to sample



教猴子學會在新的積木下有好吃的。所以猴子要能記住舊的積木才知新的積木是那一個。

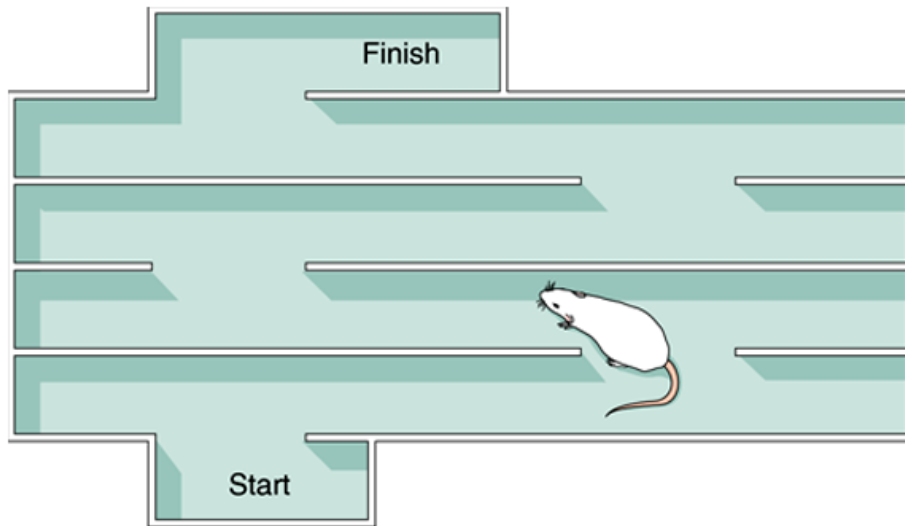
哪一條曲線代表猴子的顳葉是切除，而有記憶的問題？

搜索記憶痕跡：記憶是平均分配在大腦裡的嗎？

• Lashley's 大鼠的迷宮學習 (1920)

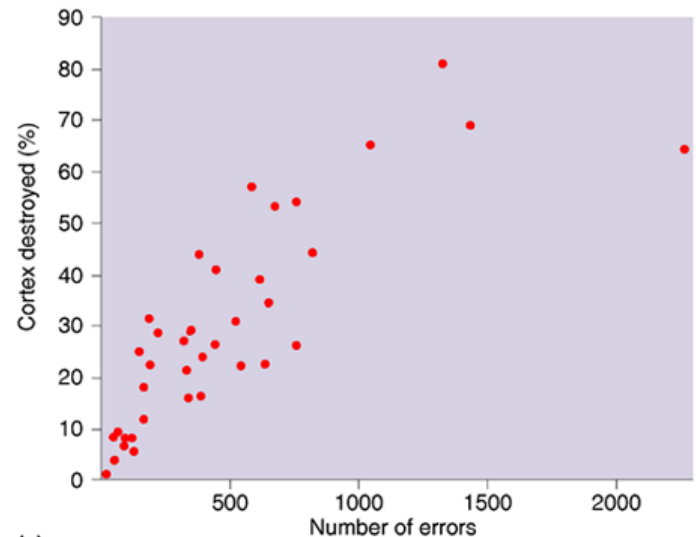
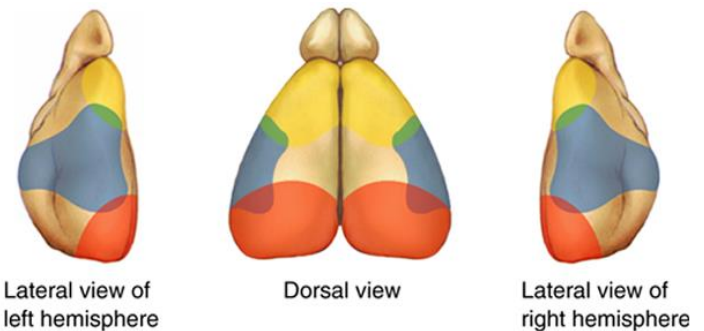
- 發現大腦切除的大小而非位置與記憶不良是相關的
- 結論“所有大腦皮質區域對記憶的貢獻相同”

Q : Is this true?



(a)

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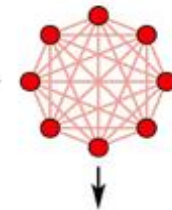
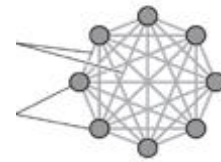
(c)

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記憶的分子基礎：赫布 (Donald Hebb) 的理論

- 外部歷經的事件會被記錄到一群大腦細胞中。
- 這群大腦細胞可以廣泛的分布，包含主司感官的神經細胞。
- 這群神經細胞，會相互溝通
- 持續溝通的過程會增強這群細胞的連結，最後有可能形成鞏固的迴路（記憶的軌跡）

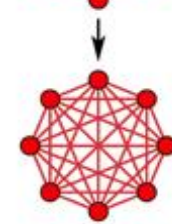
記憶存在一群相互連結的神經細胞間



Activation of the cell assembly by a stimulus.



Reverberating activity continues activation after the stimulus is removed.

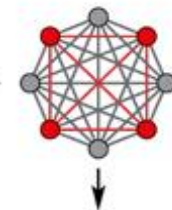


Hebbian modification strengthens the reciprocal connections between neurons that are active at the same time.



The strengthened connections of the cell assembly contain the engram for the stimulus.

(b)



After learning, partial activation of the assembly leads to activation of the entire representation of the stimulus.



= "Circle."

(c)

Neuron Doctrine: 神經元學說



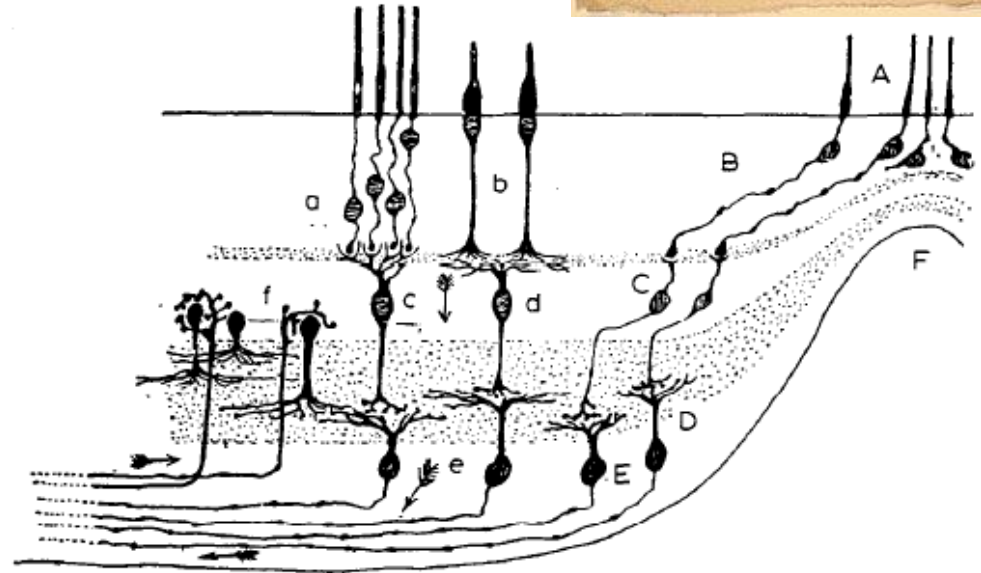
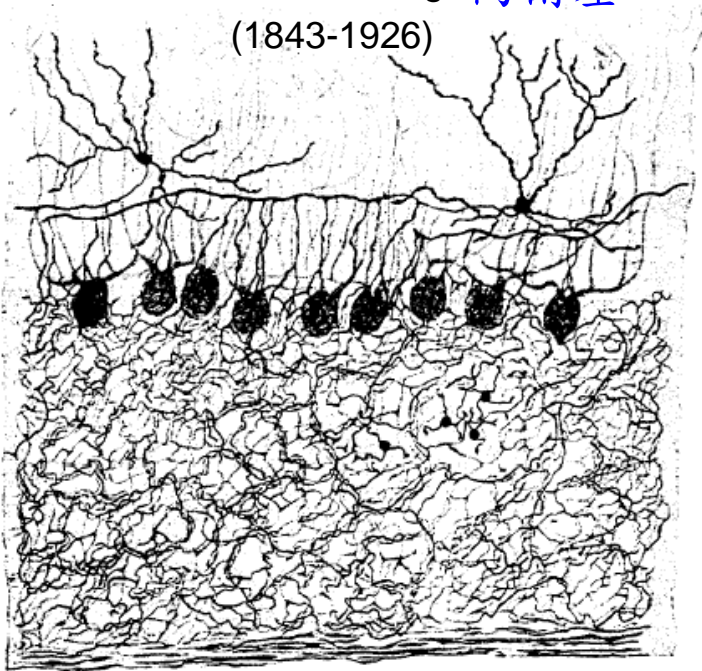
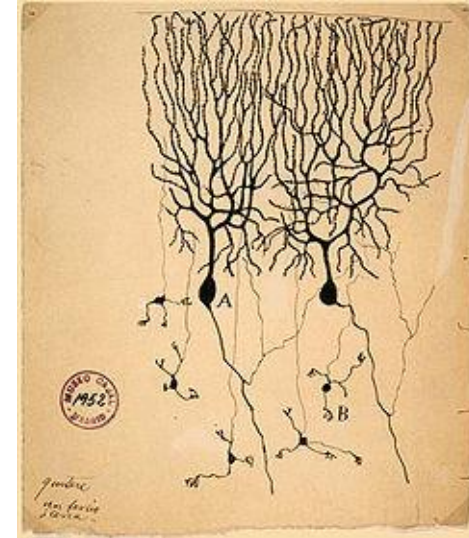
Camillo Golgi 高爾基
(1843-1926)



Medicine (1906)



Santiago Ramon Cajal
(1852-1934)

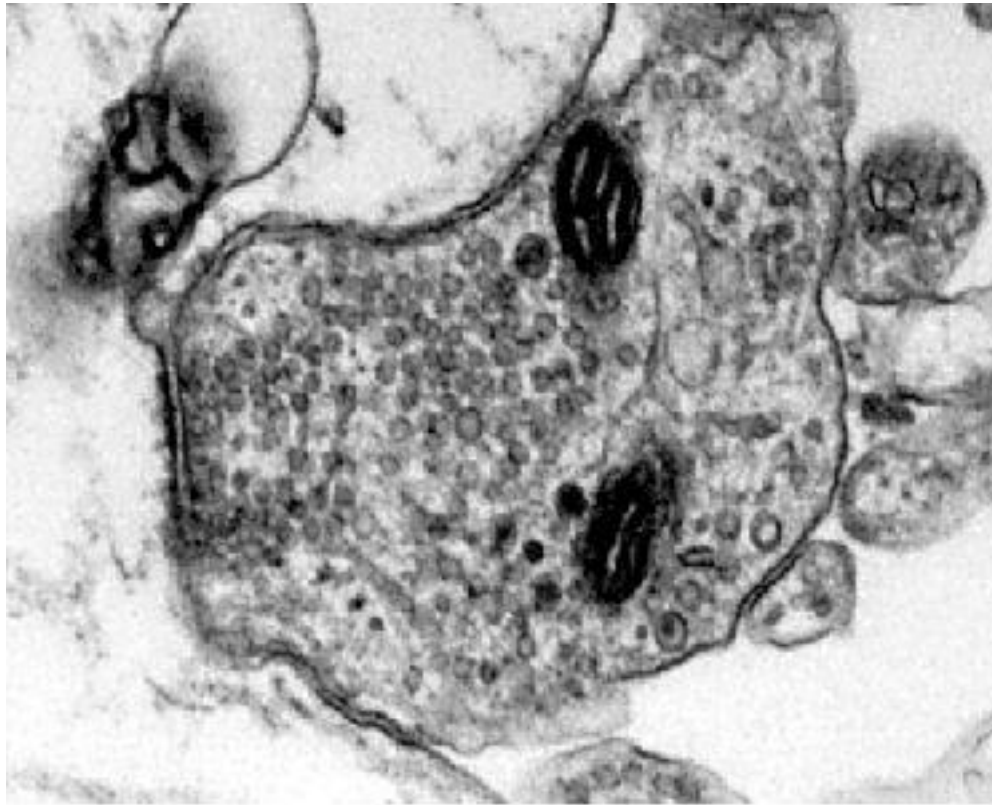


神經系統是一個細胞組成的

神經元通過接觸進行溝通，
而不是連續性

神經細胞是大腦中的功能單位

Q：哪個技術的發明（~1950年）奠定了Cajal的神經元學說理論？

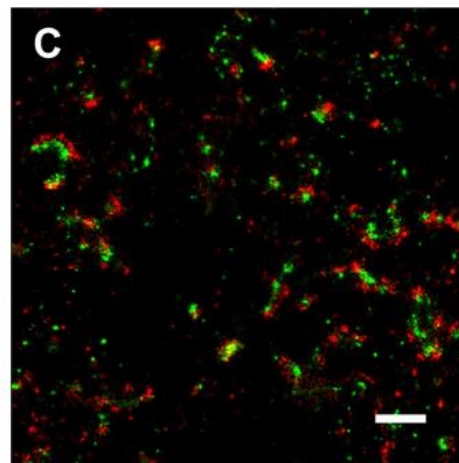
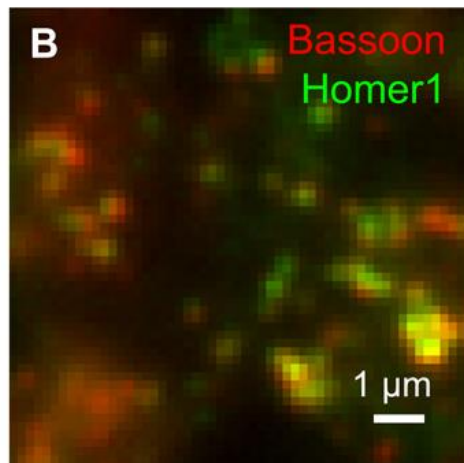
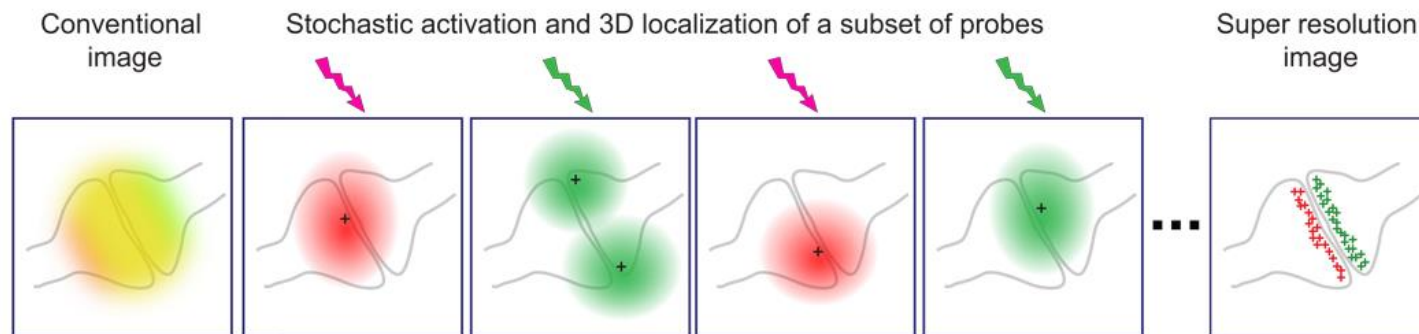


Chemistry (2008)

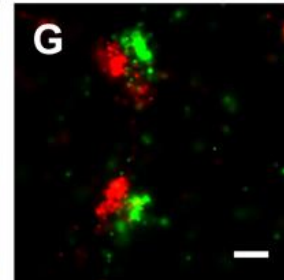
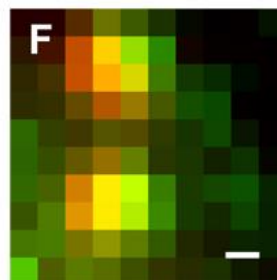
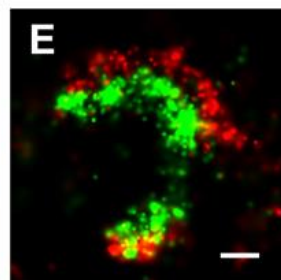
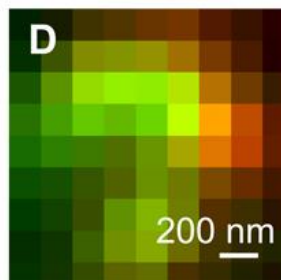


Physics (1986)

超解析度的顯微鏡 microscope (Nanoscope 奈米顯微)

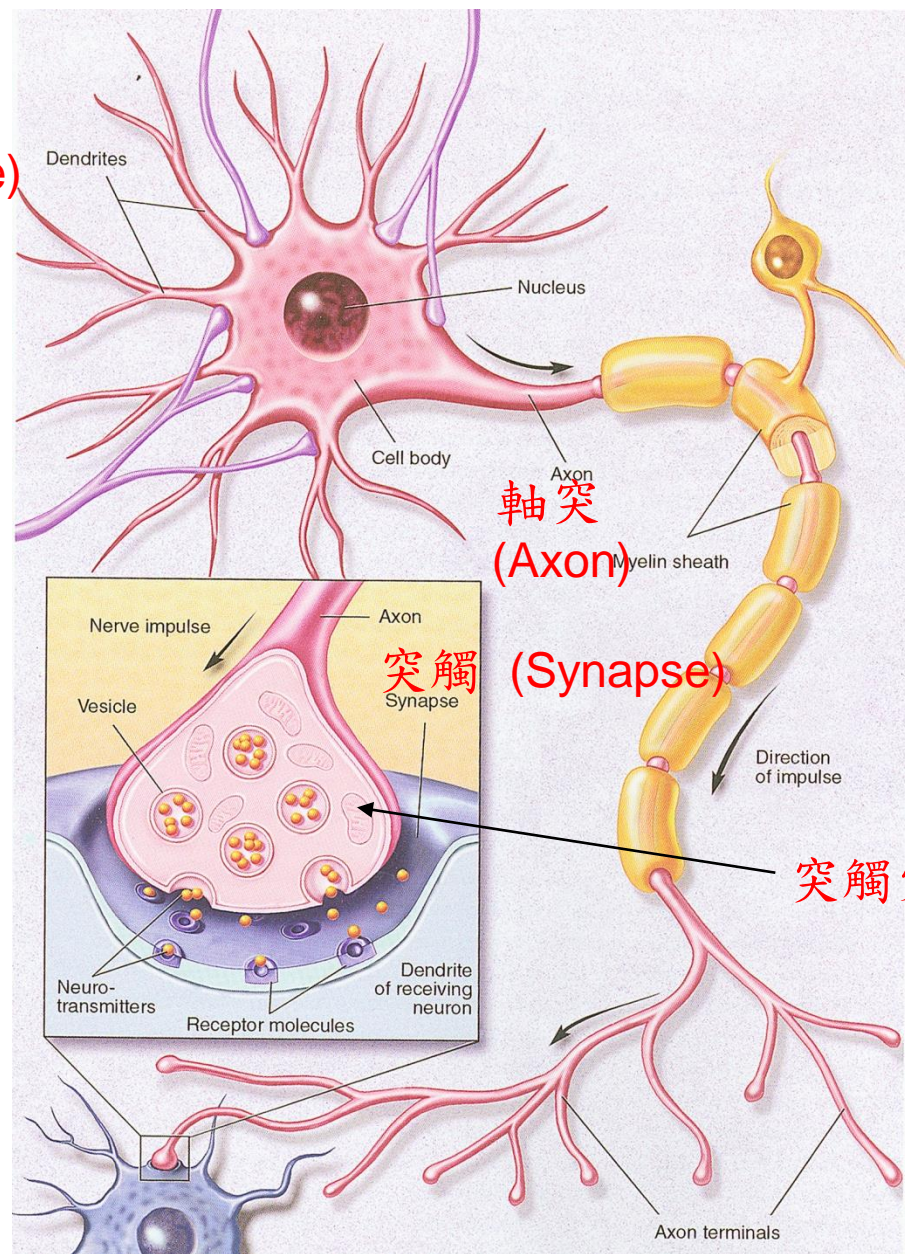


Chemistry (2014)



訊息傳遞: Axon, pre-synapse, post-synapse, dendrite, axon

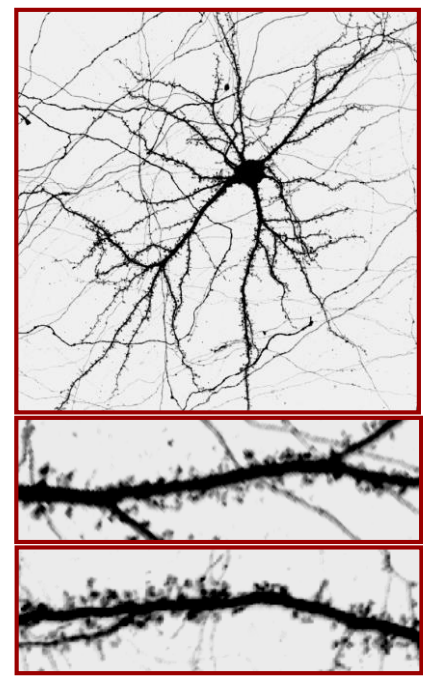
樹突
(Dendrite)



軸突
(Axon)

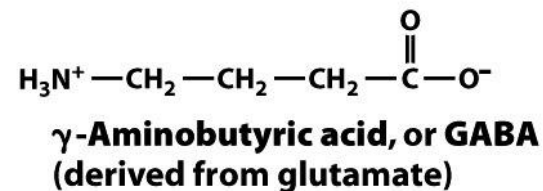
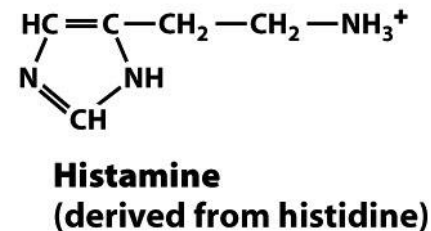
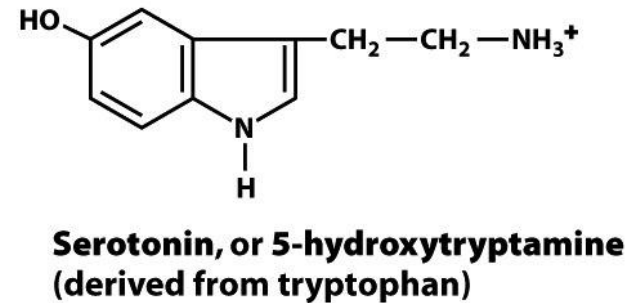
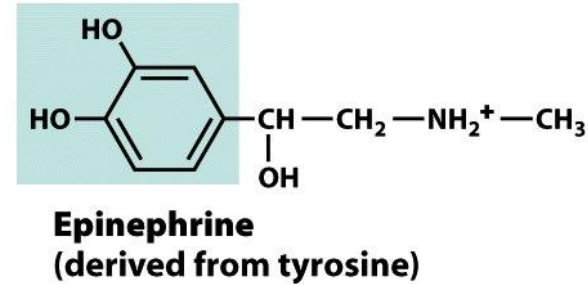
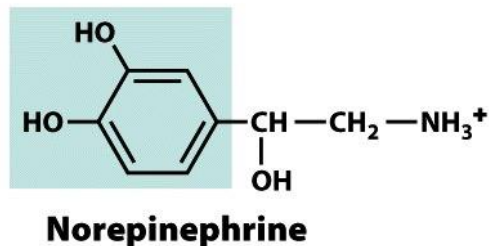
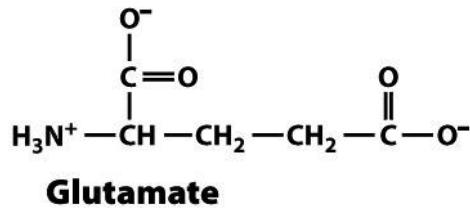
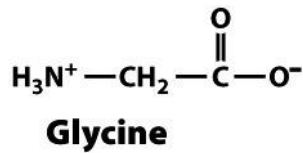
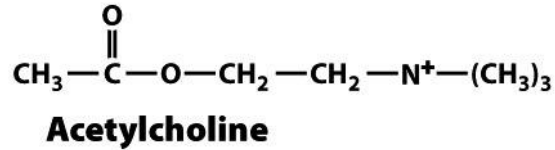
突觸
(Synapse)

突觸囊泡 (Synaptic vesicle)



樹突起
(Dendritic Spines)

神經傳導物質接起了突觸間的訊號傳遞 (電→化學)



Neurotransmitters: excitatory & inhibitory chemical signals at presynapses

神經傳導物質受體傳承了突觸間的訊號傳遞（化學→電）

神經傳導物質受體：皆會造成膜電位的改變

有些本身是離子通道，有些會間接造成其他離子通道的開啟

使膜電位更正（more positive）的是興奮性傳遞

反之是抑制性傳遞

神經傳導物質受體

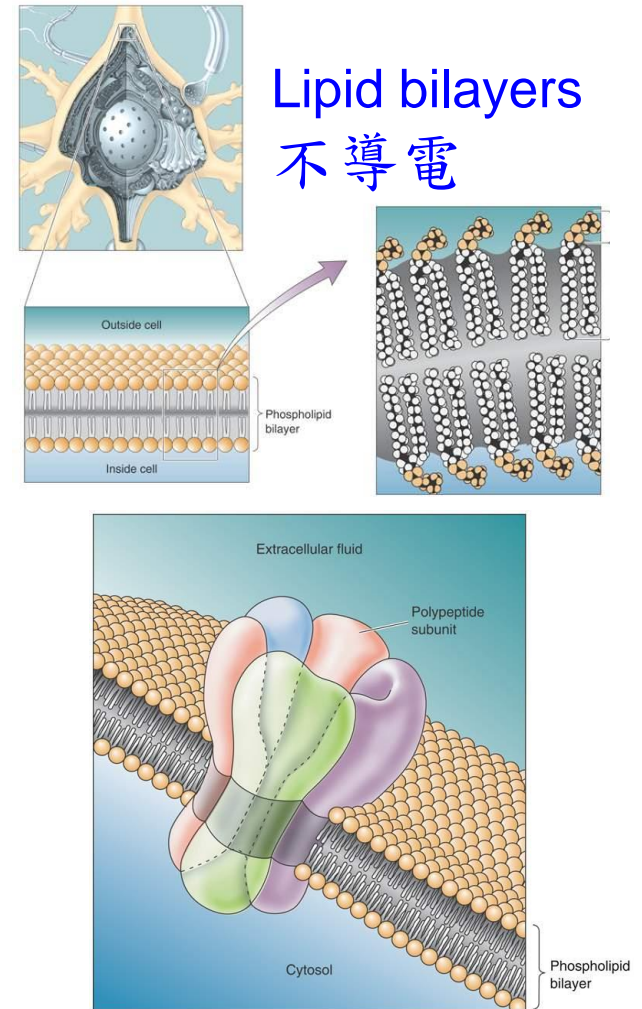
- Channel Proteins（離子通道）

Voltage-gated ion channel

Ligand (neurotransmitter)-gated ion channel

- Receptors（訊息傳遞的受體）

Neurotransmitter Receptors: excitatory & inhibitory receivers at postsynapses



電生理實驗檢測膜電位的變化來測量神經的活性

- **Principle: Ohm's Law** (歐姆定律)

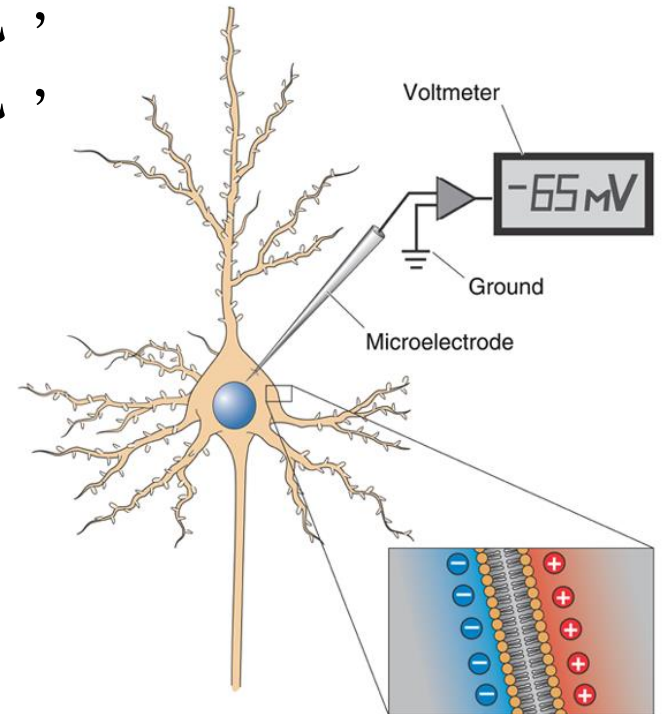
$V = IR$ V : voltage (電壓) R : resistance (電阻)

$I = Vg$ I : current (電流) g : conductivity (電導)

R: varies depending on channel open/close

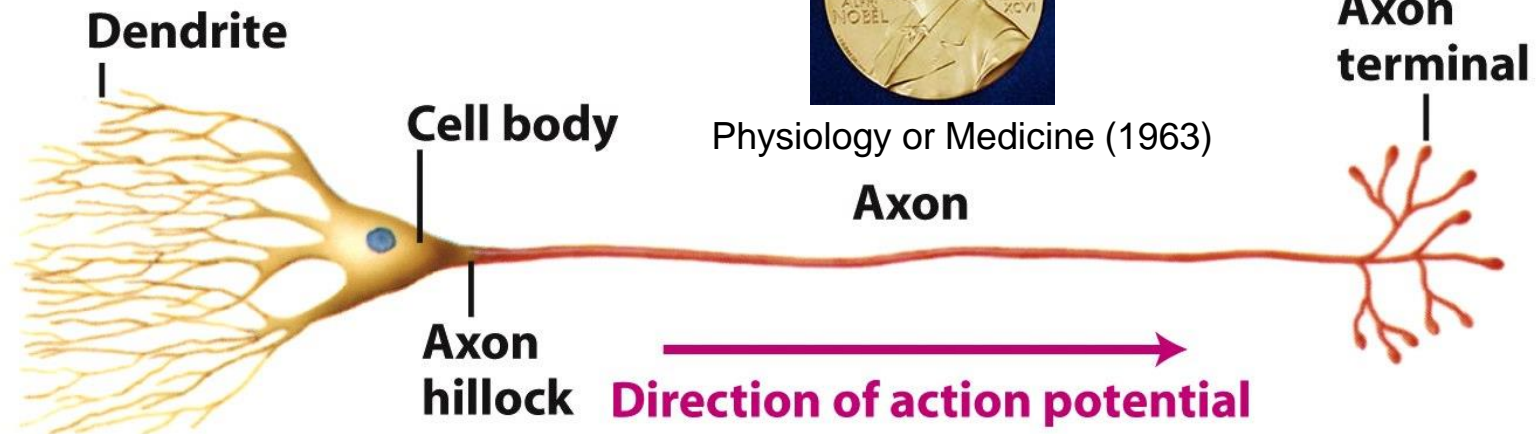
記錄時採固定電位然後記錄電流的變化，
或固定電流的方式然後記錄電位的變化，
由此可算出細胞膜電阻力的變化。

細胞膜電阻力的變化取決於
離子通道的開與關

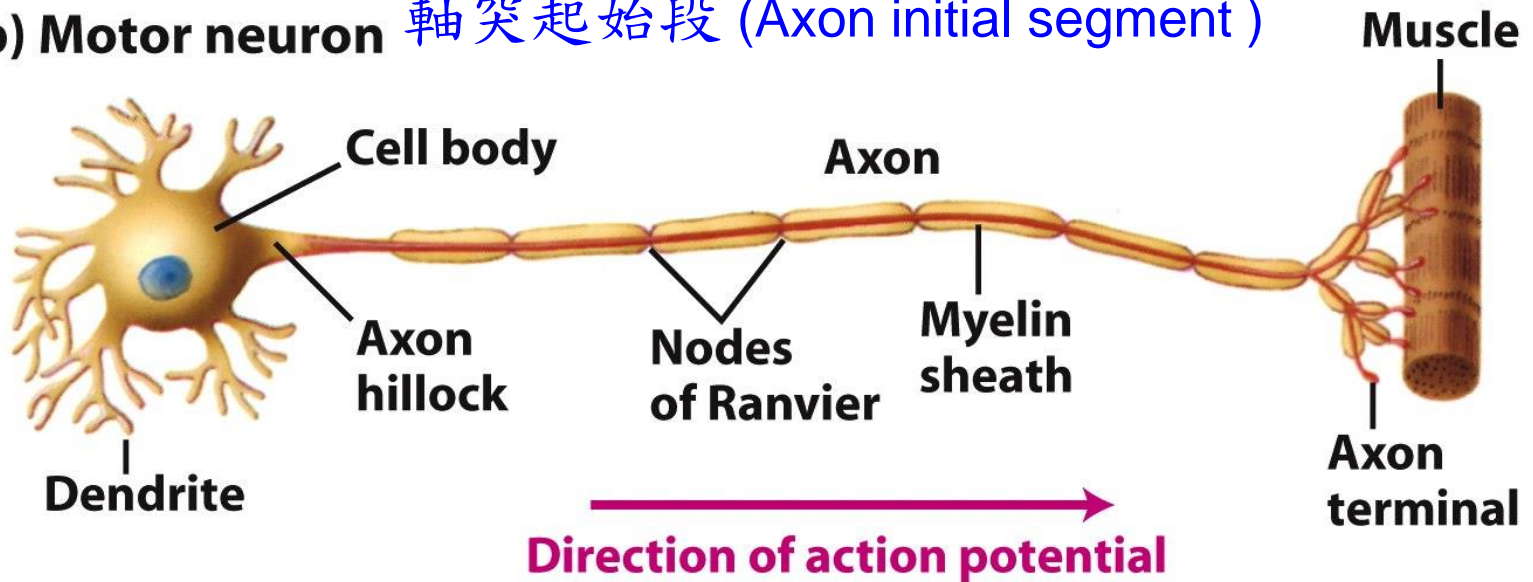


動作電位傳導：單方向/全無或有/跳躍式傳遞

(a) Multipolar interneuron

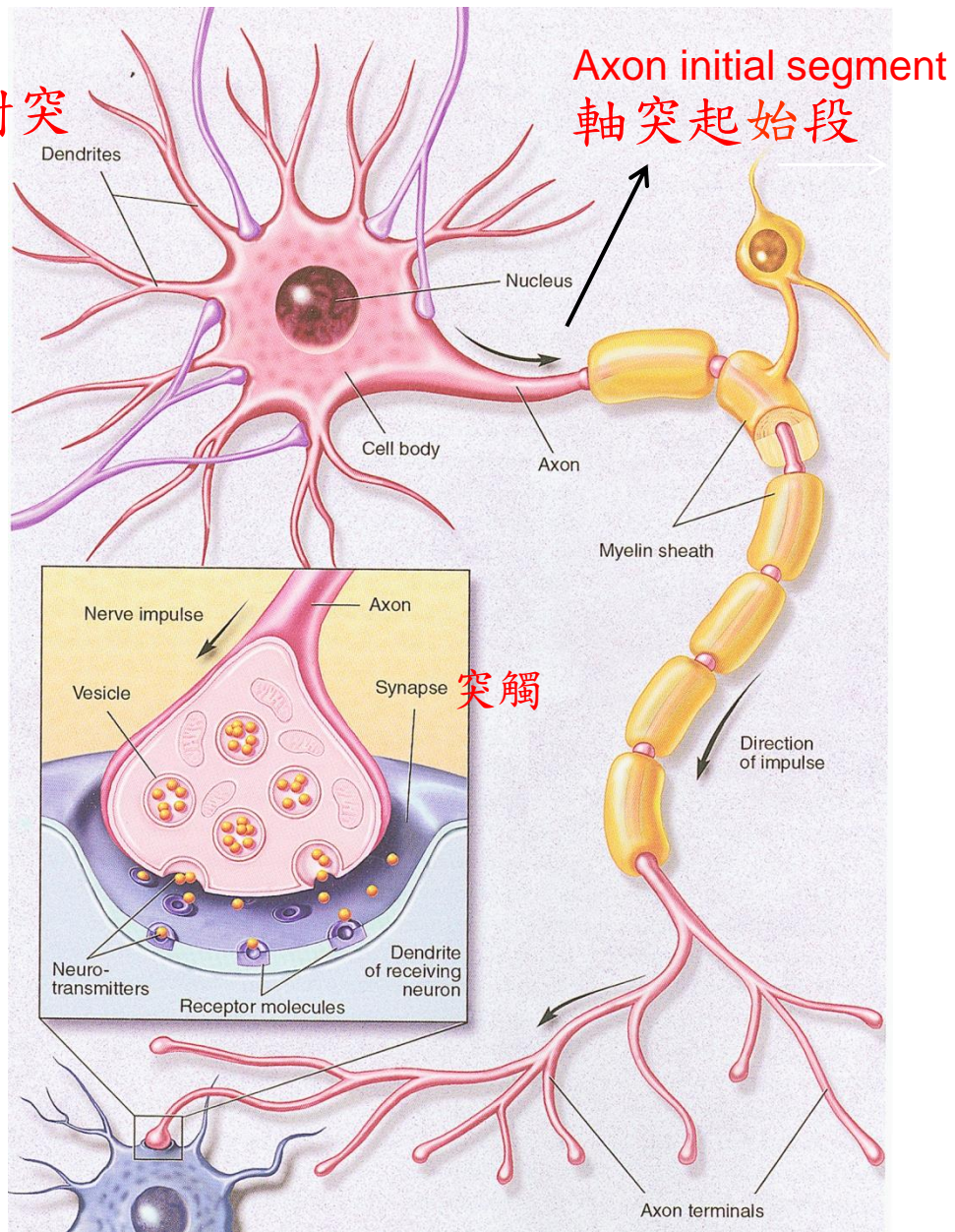


(b) Motor neuron 軸突起始段 (Axon initial segment)



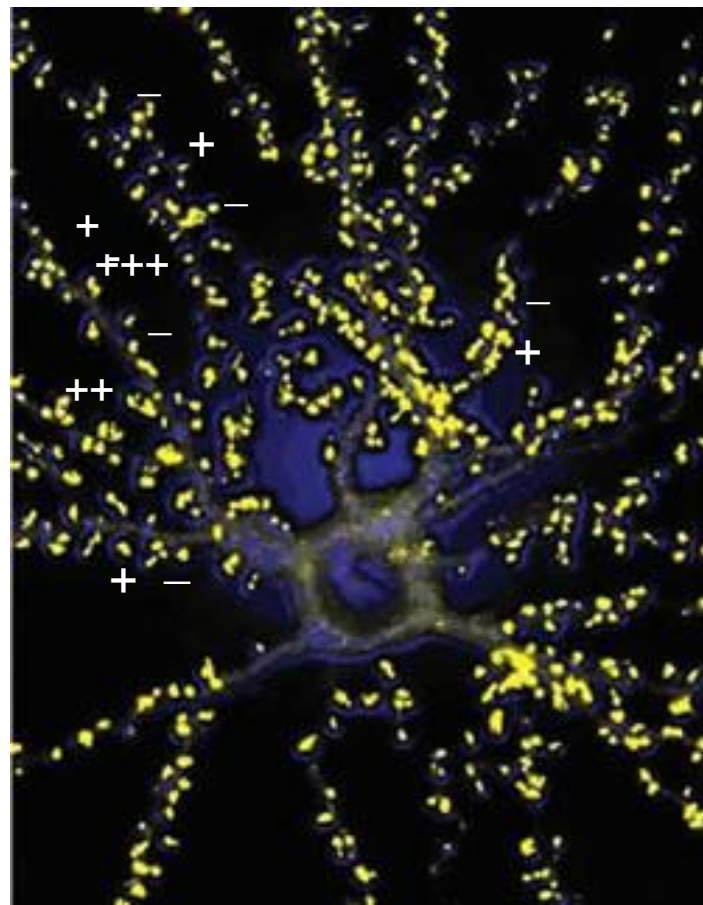
樹突接收計算突觸來的電訊號→軸突全有或無動作電位

樹突



Axon initial segment
軸突起始段

突觸

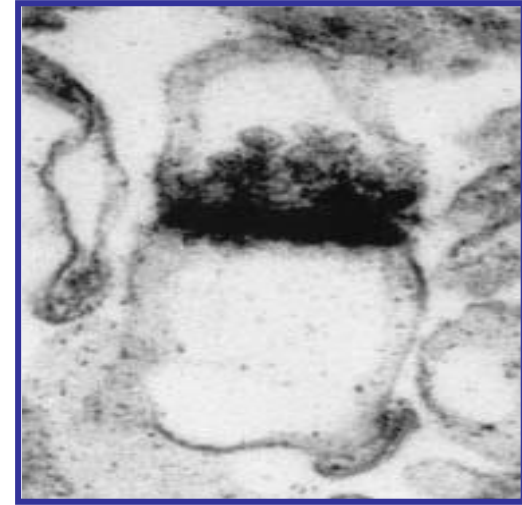


from Riken

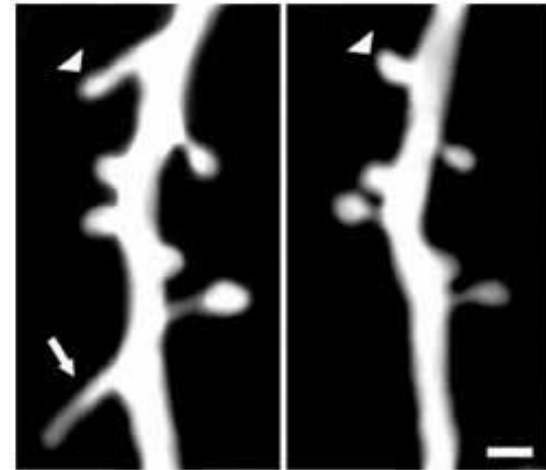
+ : 興奮性突觸
- : 抑制性突觸

突觸結構與神經活性是有關聯性

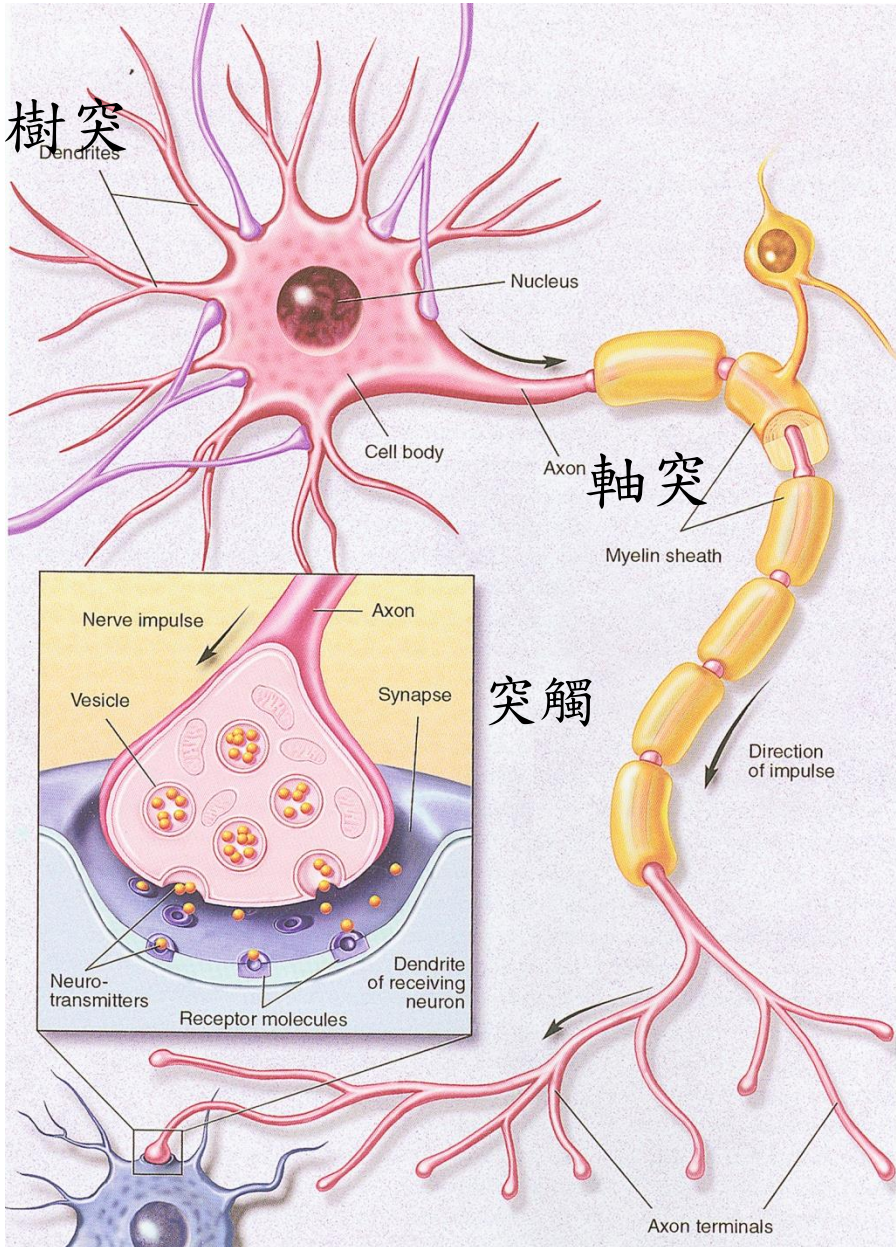
生化方法分離出的突觸部分



活體記錄突觸形狀的變化



from Wen-Biao Gan (in vivo image, 1 mon apart)

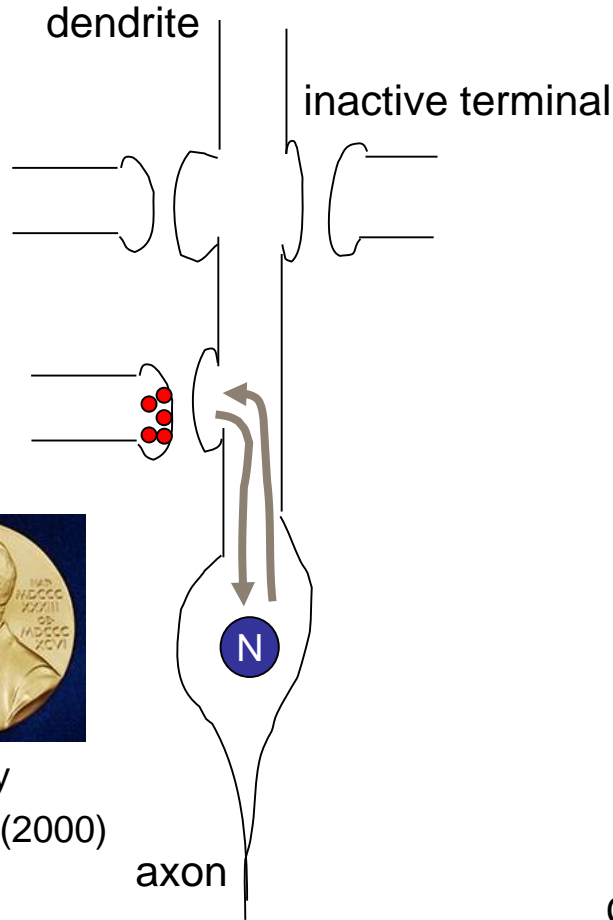


from www.sfn.org

概要總結：典型的神經細胞

- 細胞體 (Cell body 細胞體：細胞質 + 細胞核)
- 樹突 (dendritic tree, dendritic spine)
 - 神經細胞的“天線”
 - 突觸後位點 - 神經遞質受體 (從軸突端接收信號)
- 軸突 (axon)
 - 神經細胞的“電纜”，髓鞘：作為絕緣體
 - 軸突小丘 (開始：動作電位全部或無)
 - 軸突端 (信號：神經傳遞物質釋放)
 - 突觸前位點 (電 → 化學傳輸)
- 突觸 (synapse)
 - 神經細胞的通信位點
 - 神經細胞間：電 → 化學 → 電傳輸

如何調控突觸可塑性使其維持長期的變化



Physiology
/Medicine (2000)



Nerve system

~75 x10⁶ 神經細胞
~ 10¹¹ 突觸

Cerebral cortex (大腦)

~ 4 x10⁶ 神經細胞



Chemistry (1986)

Nerve system

~85 x10⁹神經細胞;
~10¹⁴-10¹⁵突觸

Cerebral cortex (大腦)

~ 20 x10⁹ 神經細胞

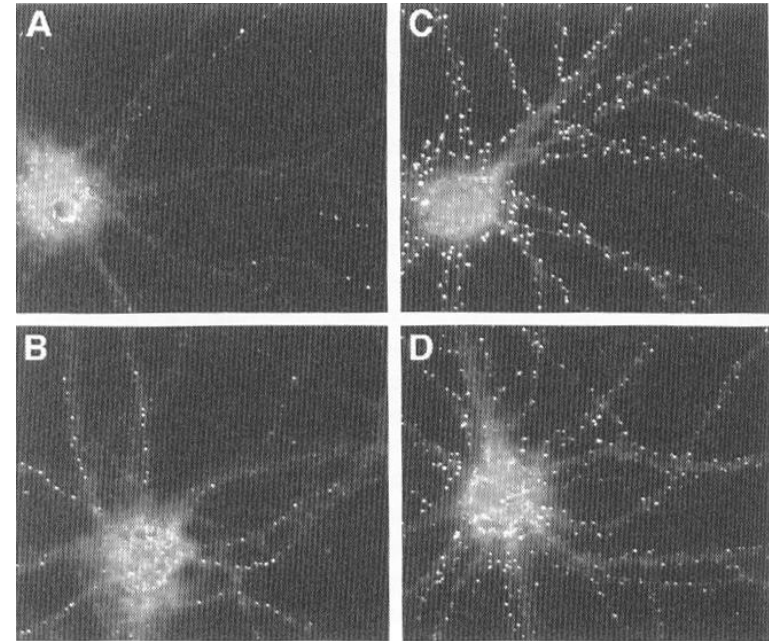
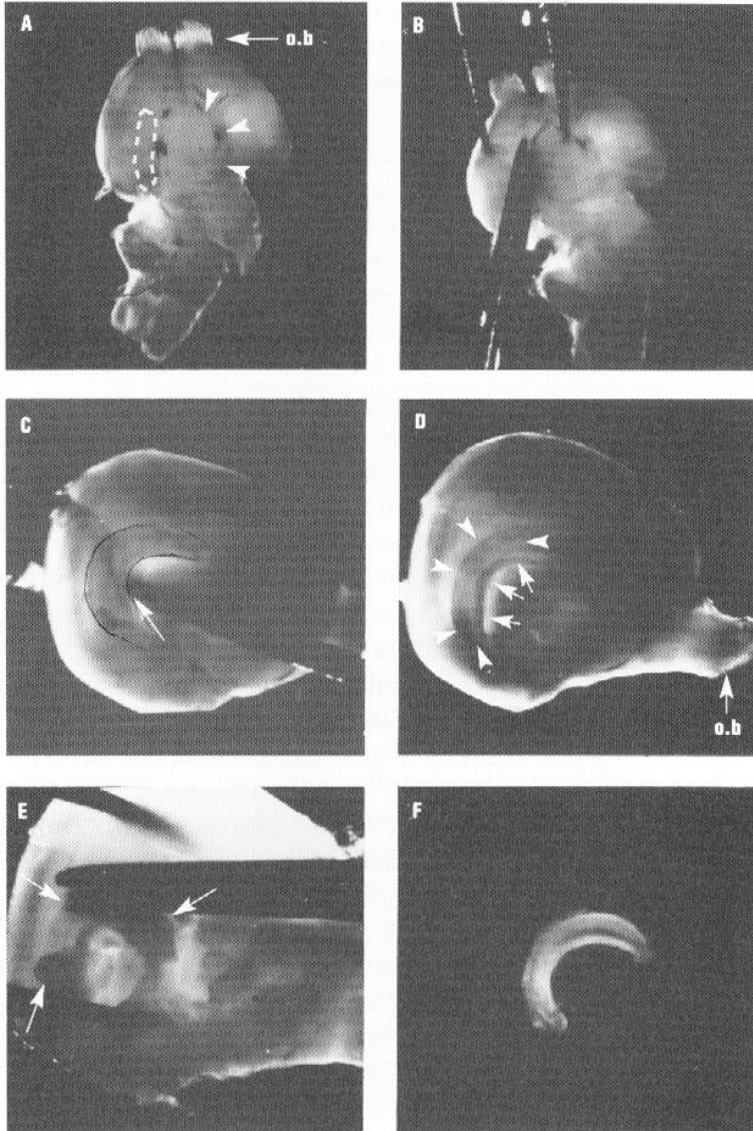
施打蛋白質合成抑制劑，抑制長期記憶的形成，
所以長期記憶的分子本質是蛋白質。

Flexner et al (1963) Science 141:57

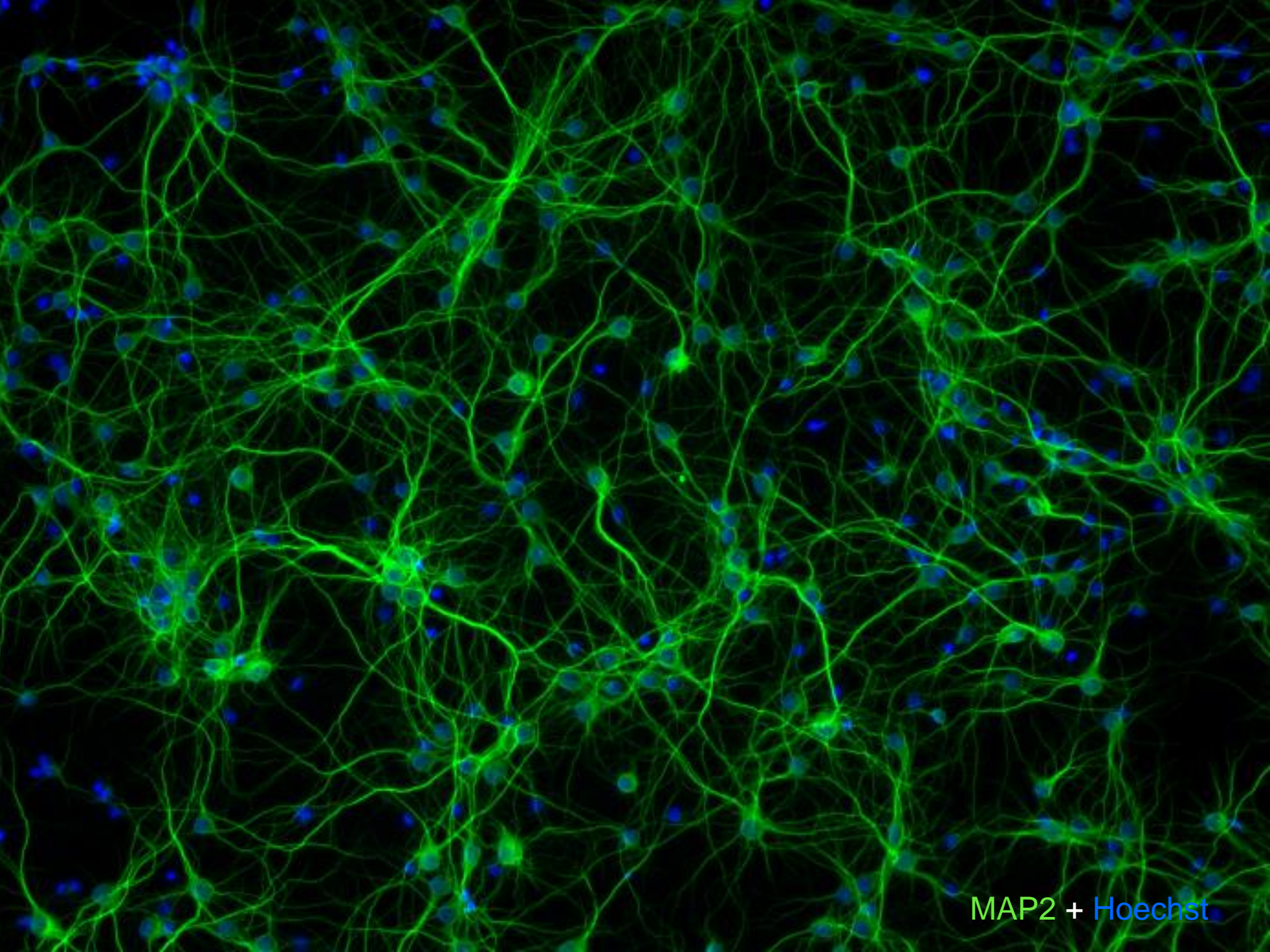
記憶中樞: Hippocampus 海馬體

取出胎鼠的腦，再分離出海馬體

Hippocampal neuron culture
海馬體神經培養

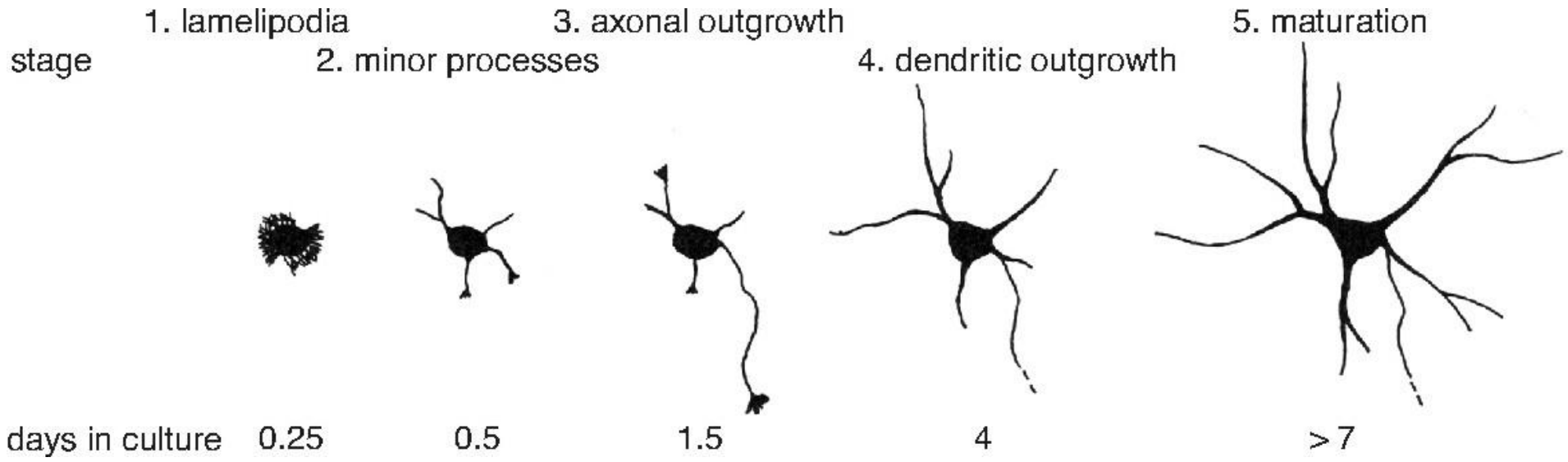


stained with lucifer yellow
to reveal tiny spines
rendered in artificial color

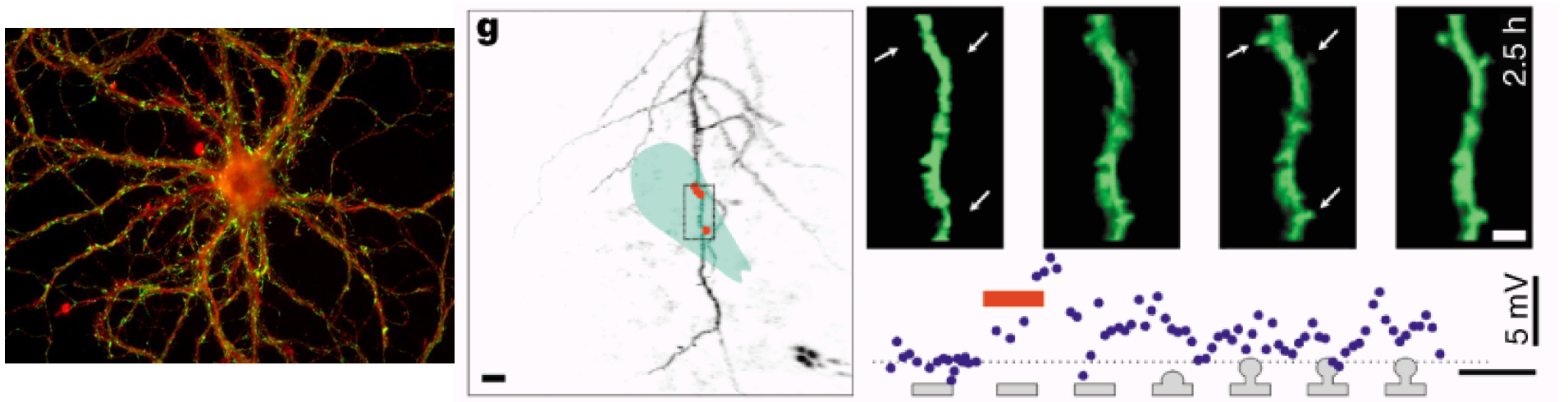


MAP2 + Hoechst

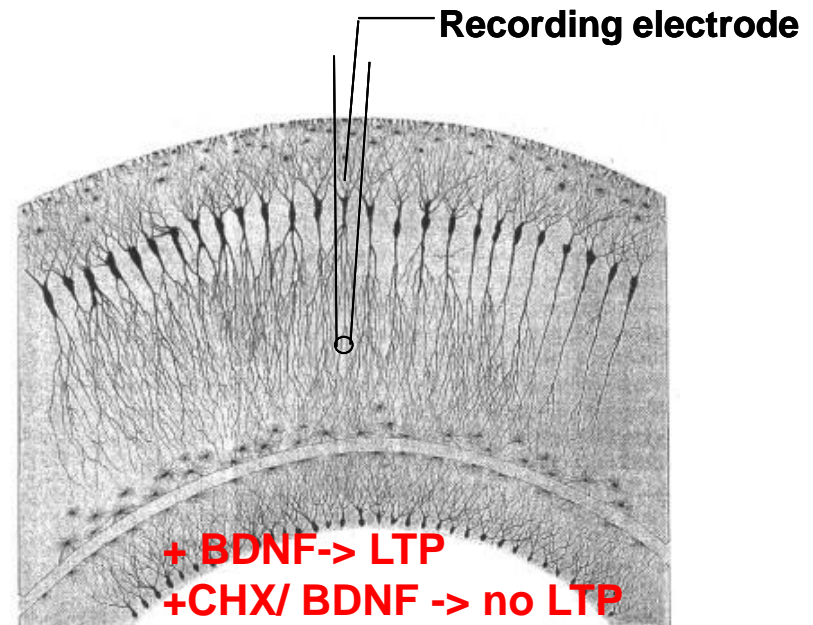
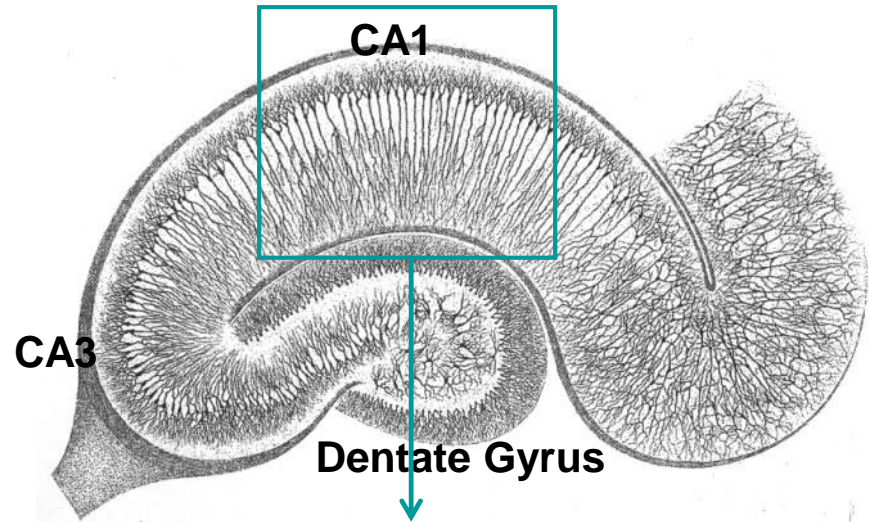
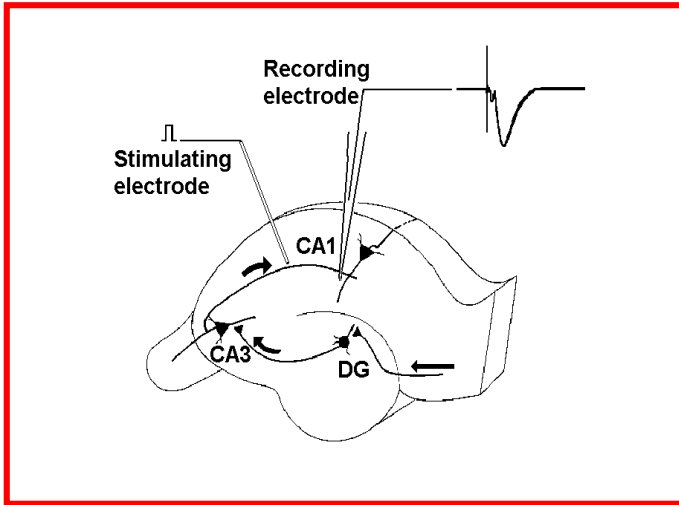
體外發育的海馬神經元：用其研究突觸形狀，大小，數目



morphological changes of synapses



用電生理來證明長期性的突觸可塑性是需要蛋白的合成



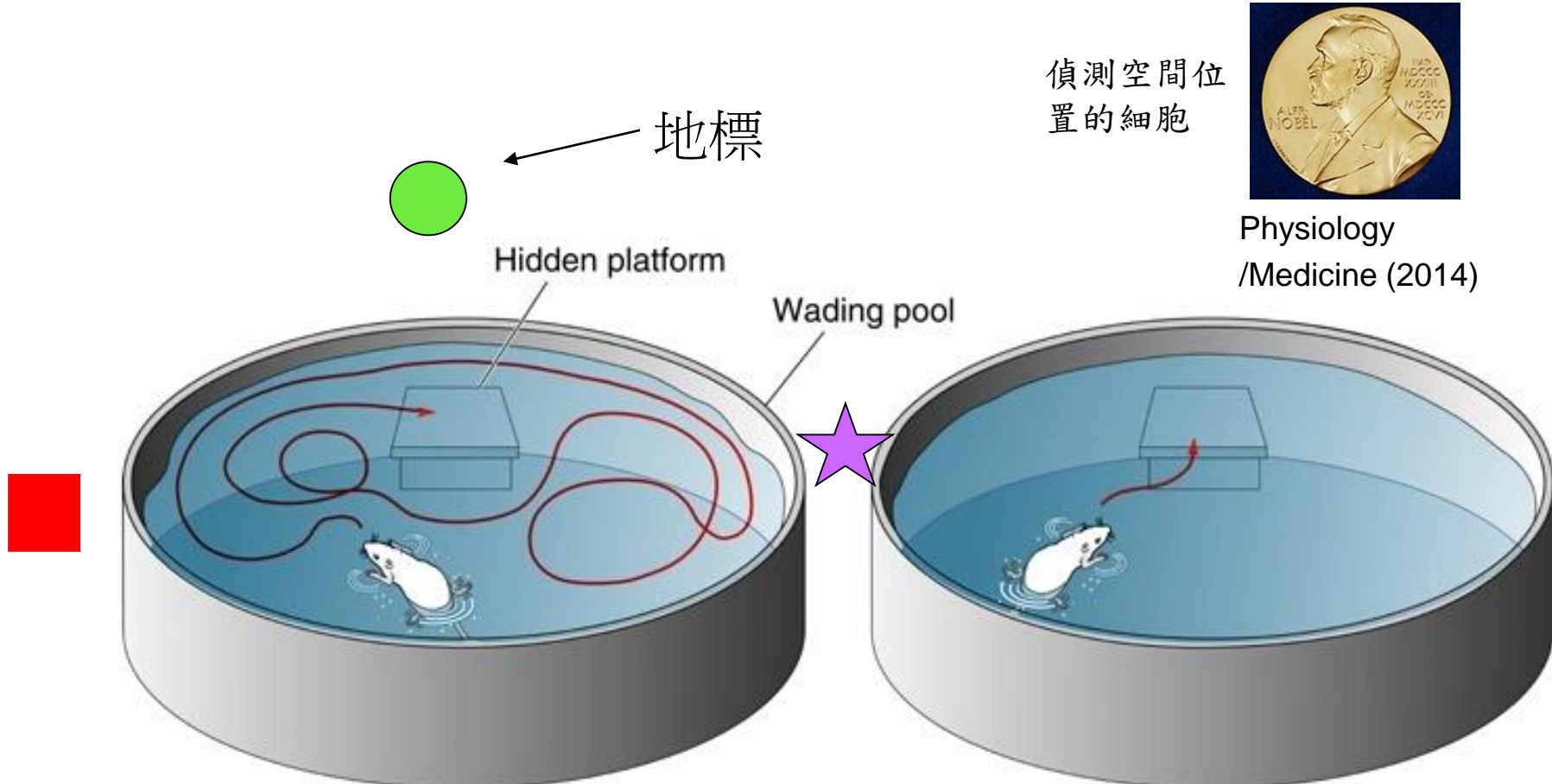
BDNF- induced LTP (long-term potentiation)

Kang and Schuman (1996) Science

DHPG- induced LTD (long-term depression)

Huber et al., 2000, Science

Morris water maze: 用水迷宮來測試老鼠的空間記憶



(a) Before learning

(b) After learning

偵測空間位置的細胞



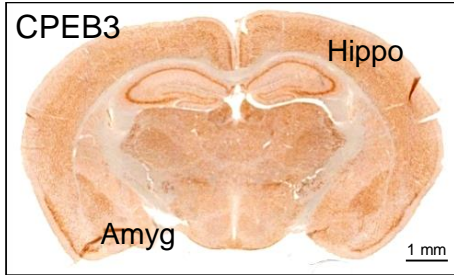
Physiology
/Medicine (2014)

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從分子（基因）到記憶

Translational Regulator



KO mouse model



PRAY for something wrong with my mice

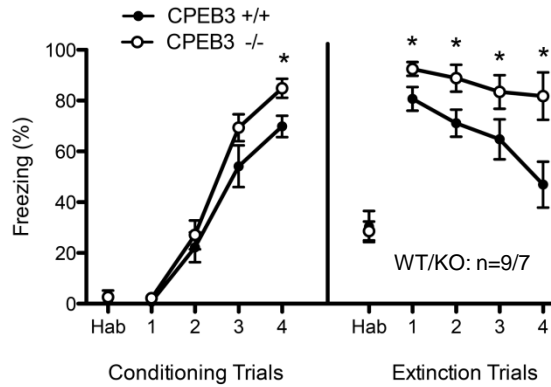
LOST IN TRANSLATION

行為測試

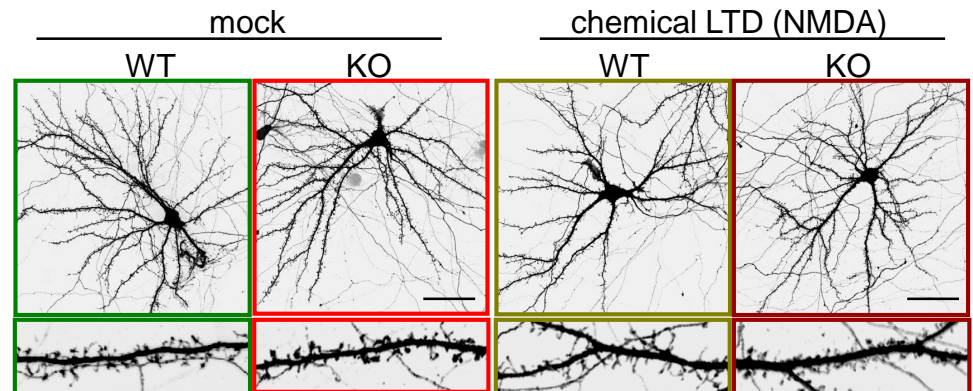
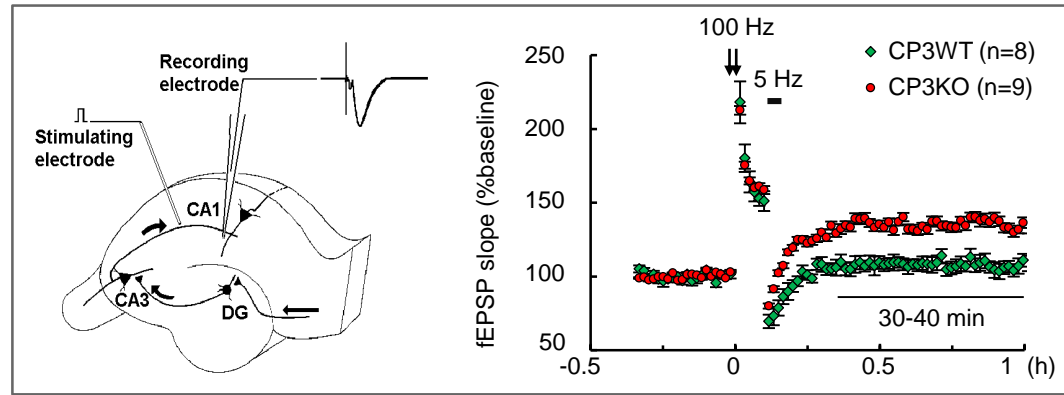
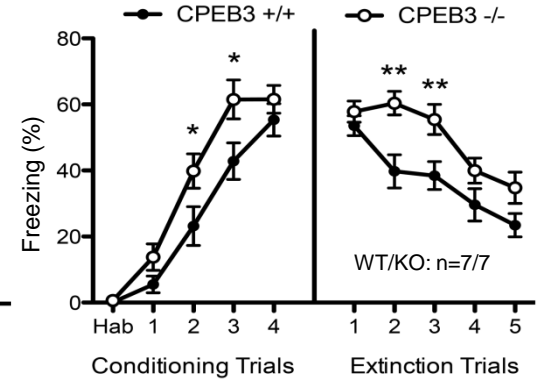
電生理分析

分子研究

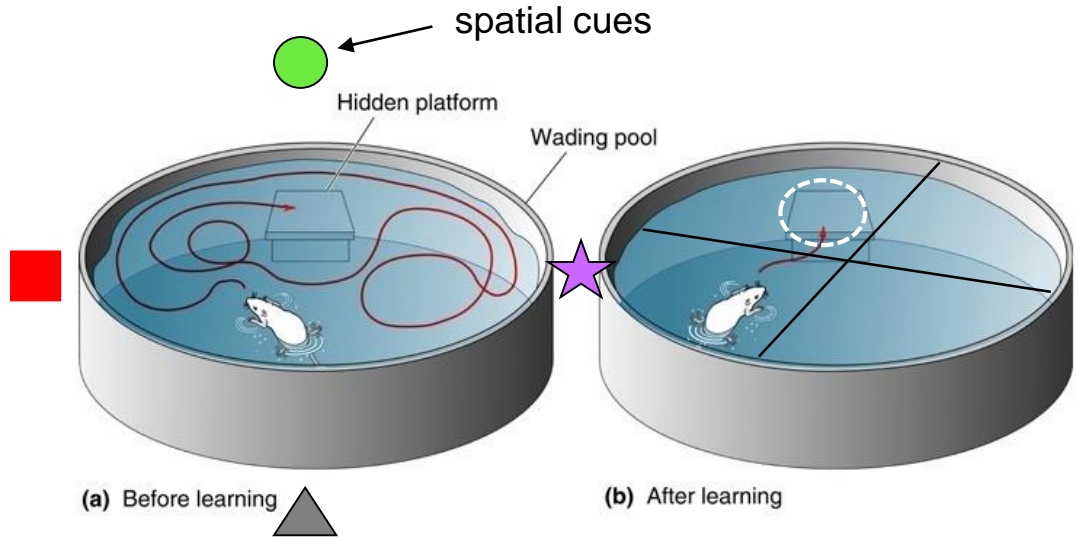
Cued fear conditioning



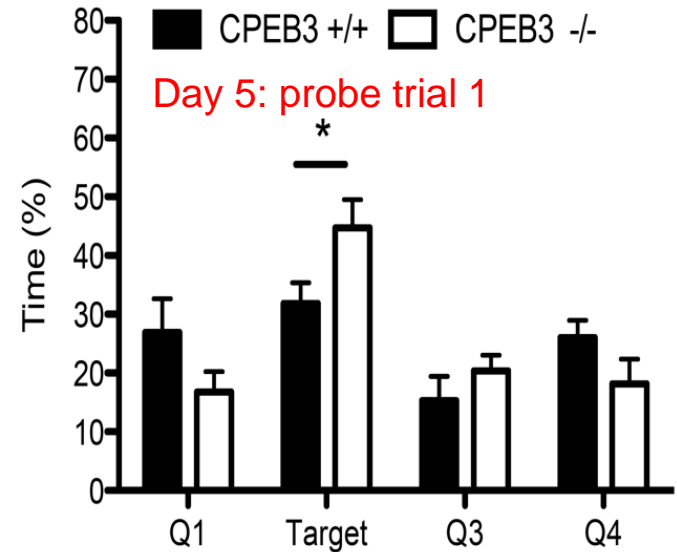
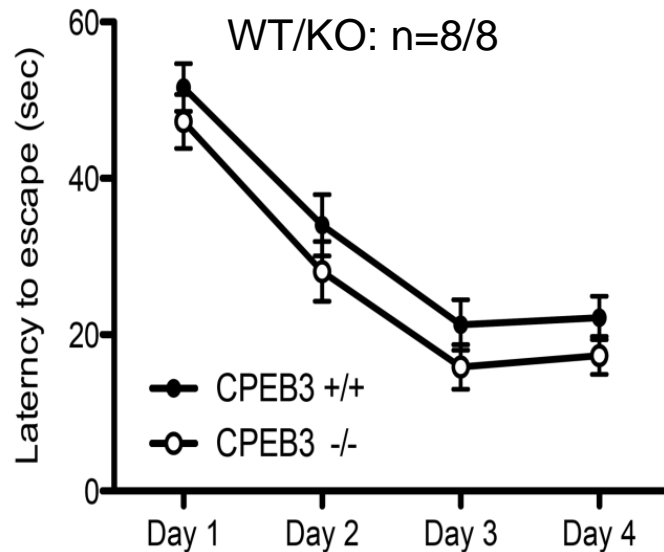
Contextual fear



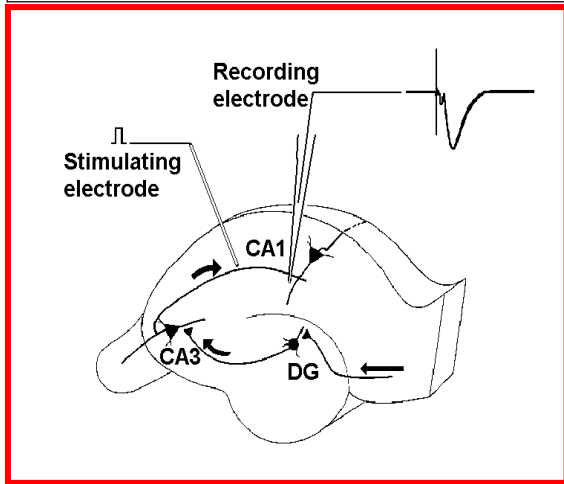
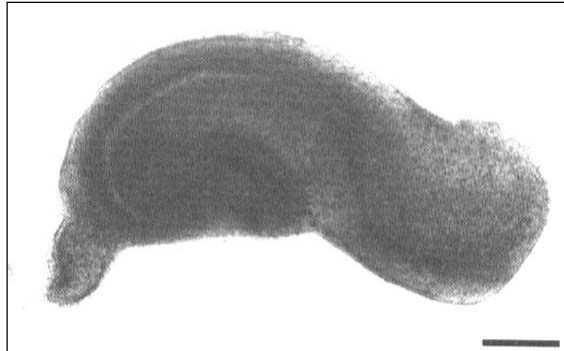
利用水迷宮來測試老鼠空間記憶的差異



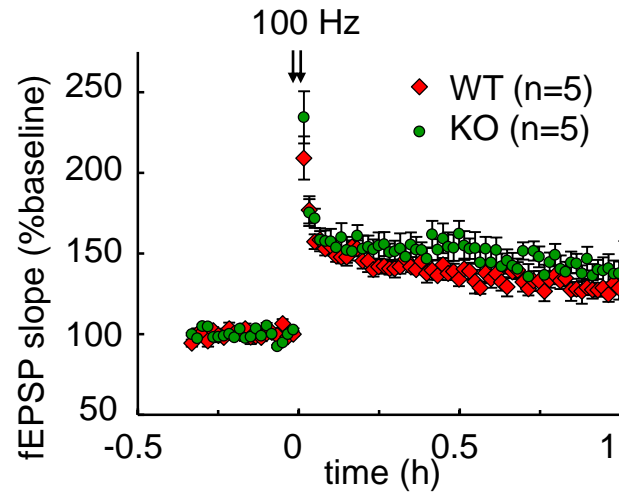
Swimming speed:
 WT: 16.6 ± 2.4 cm/sec
 KO: 17.3 ± 1.4 cm/sec



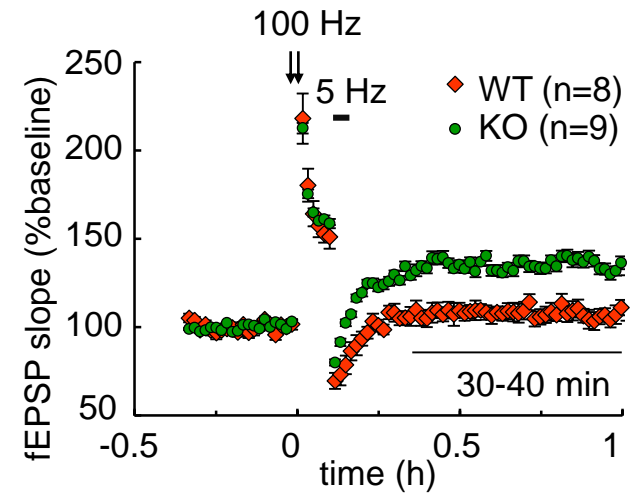
用電生理來研究基因剔除鼠的突觸可塑性是否不同於野生鼠



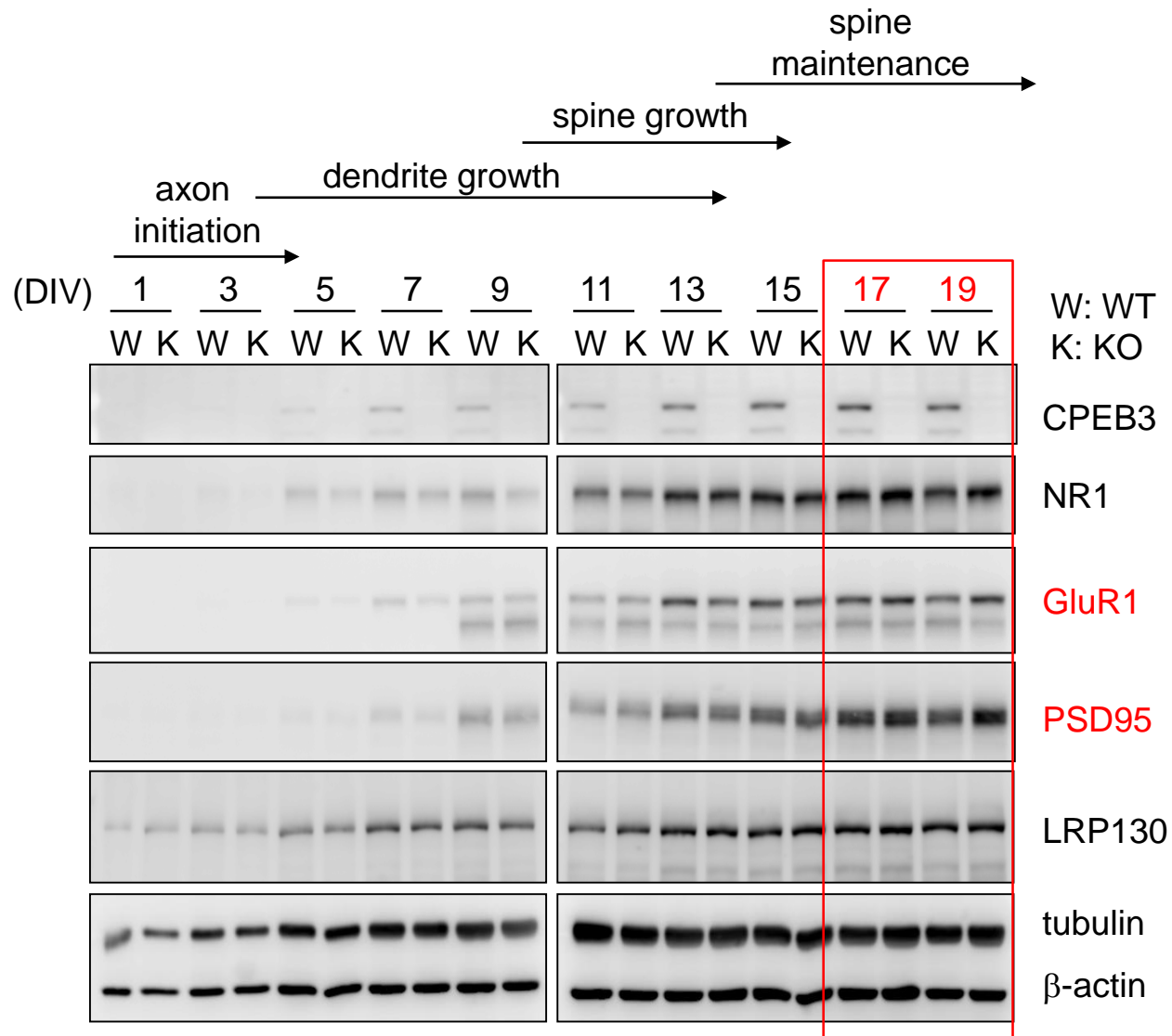
potentiation



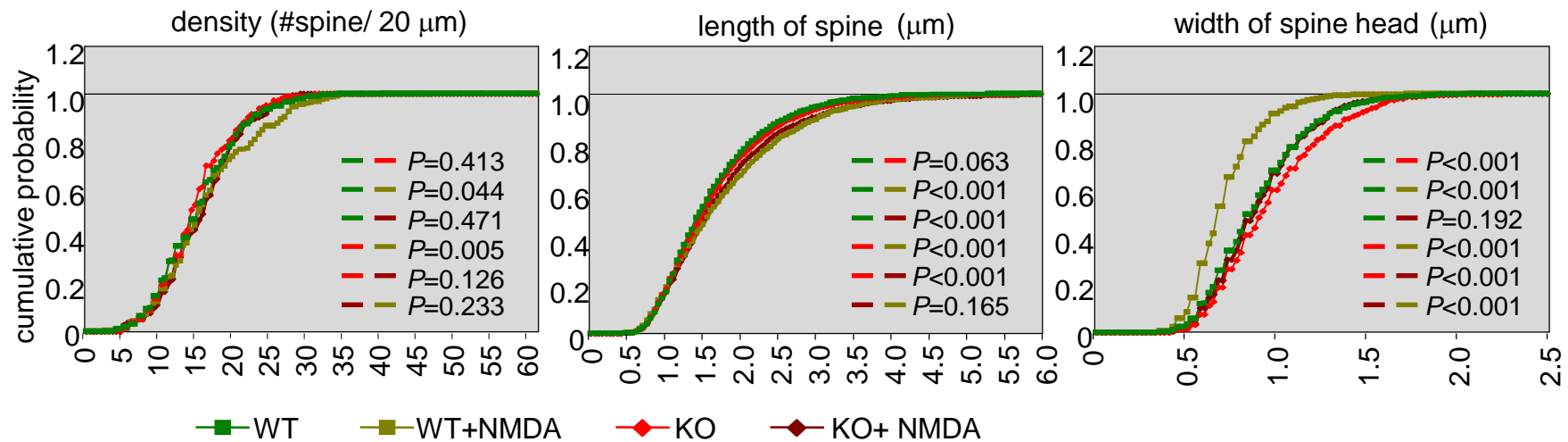
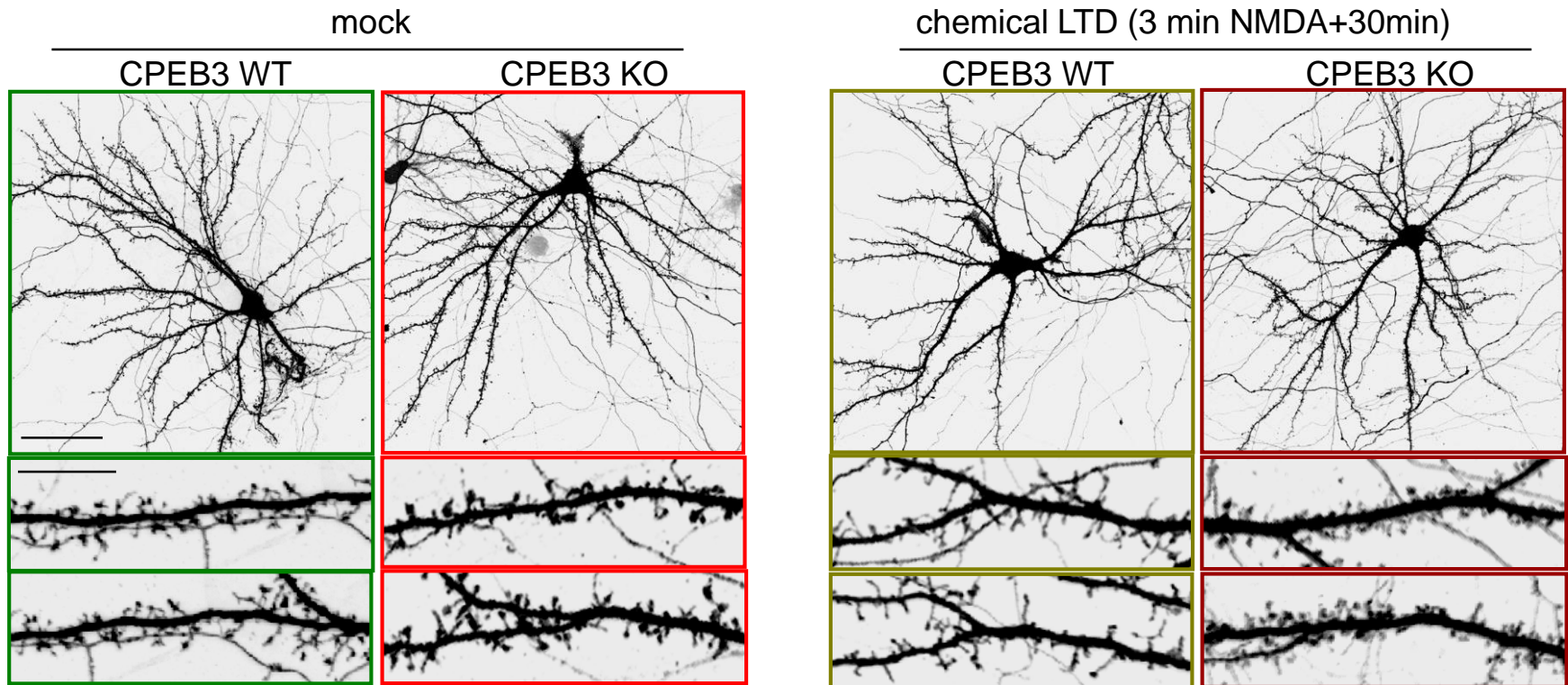
depotentialiation



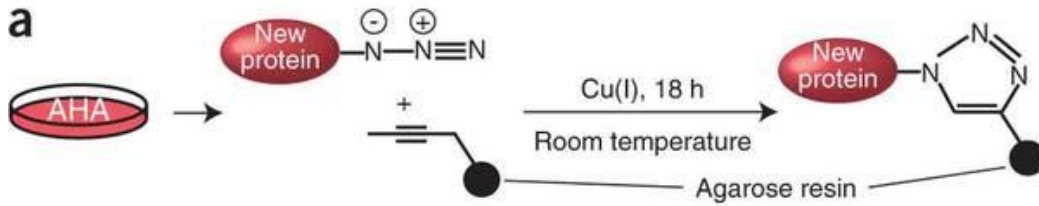
用生化方法來研究基因剔除鼠的神經蛋白組成是否不同於野生鼠



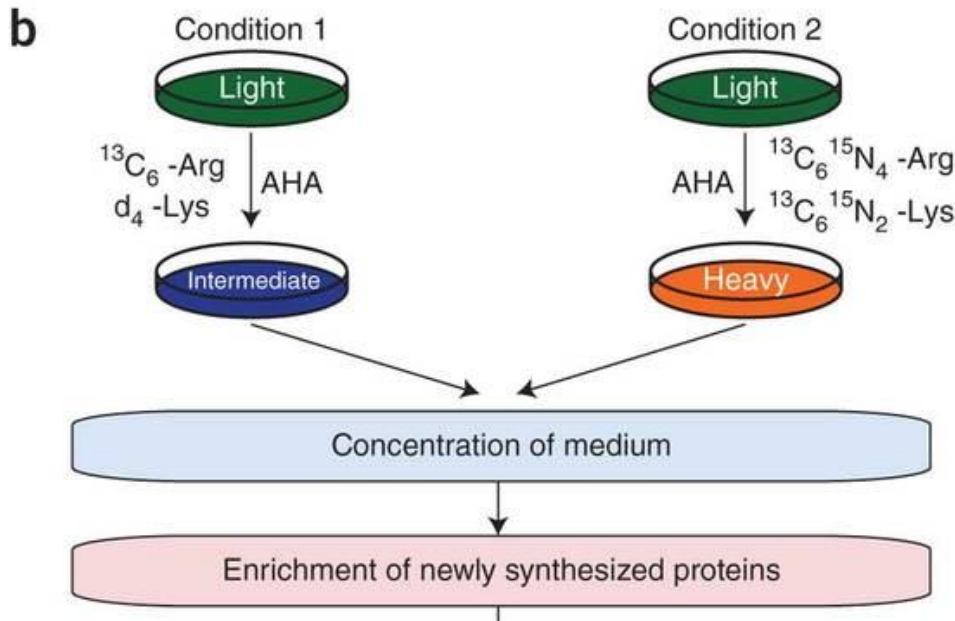
用型態分析來研究基因剔除鼠的突觸是否不同於野生鼠的突觸



在受刺激的神經中，研究蛋白質體（記憶分子）的變化

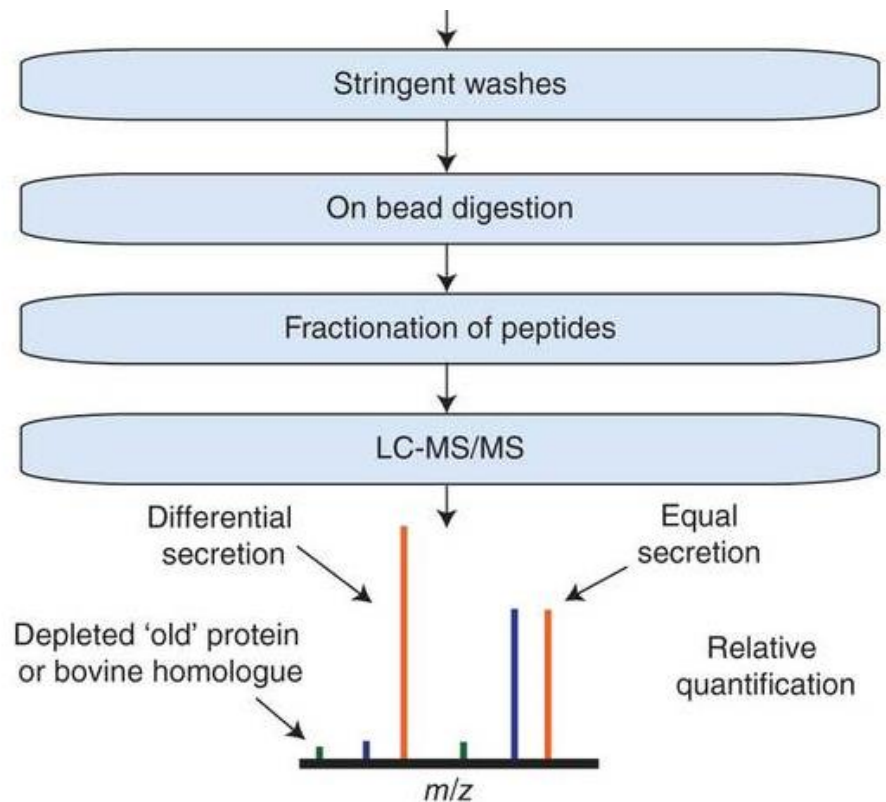


從記憶到分子（基因）

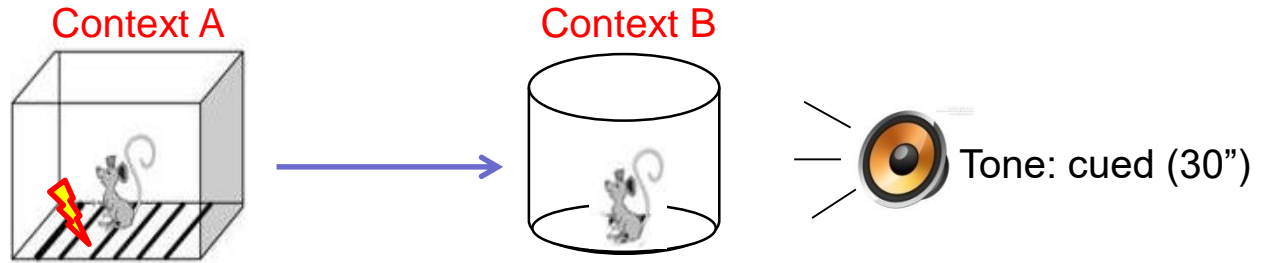


用化學方式來標定新合成的蛋白

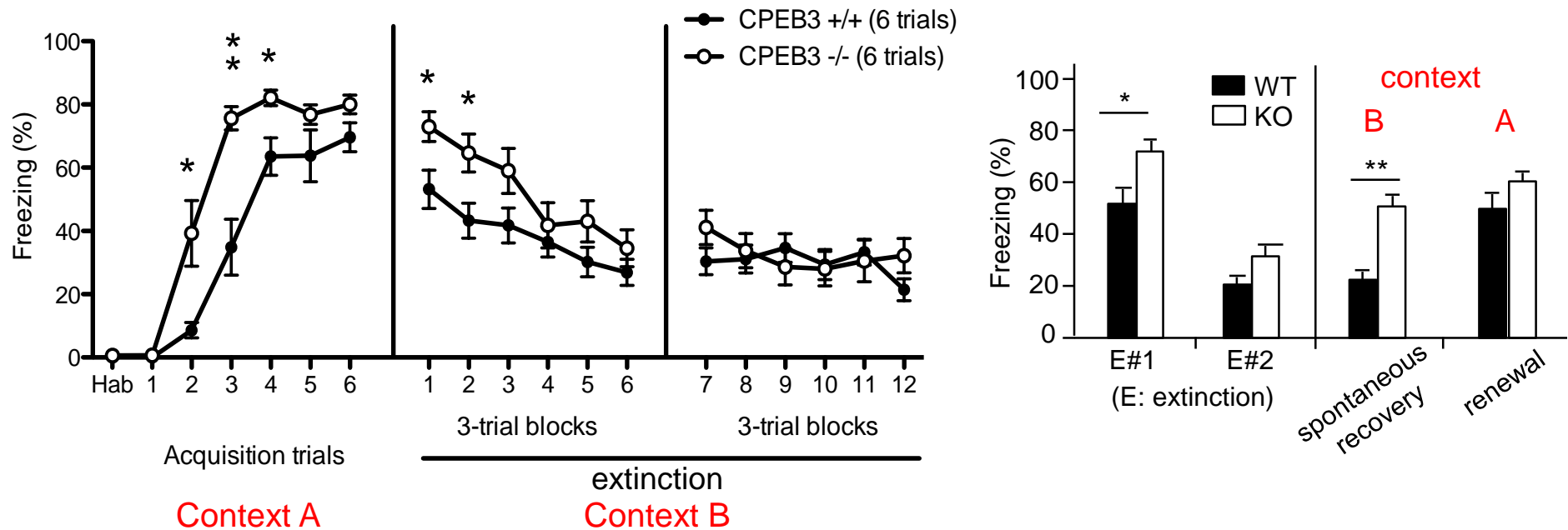
然後用質譜儀來分析這些新合成蛋白是什麼？



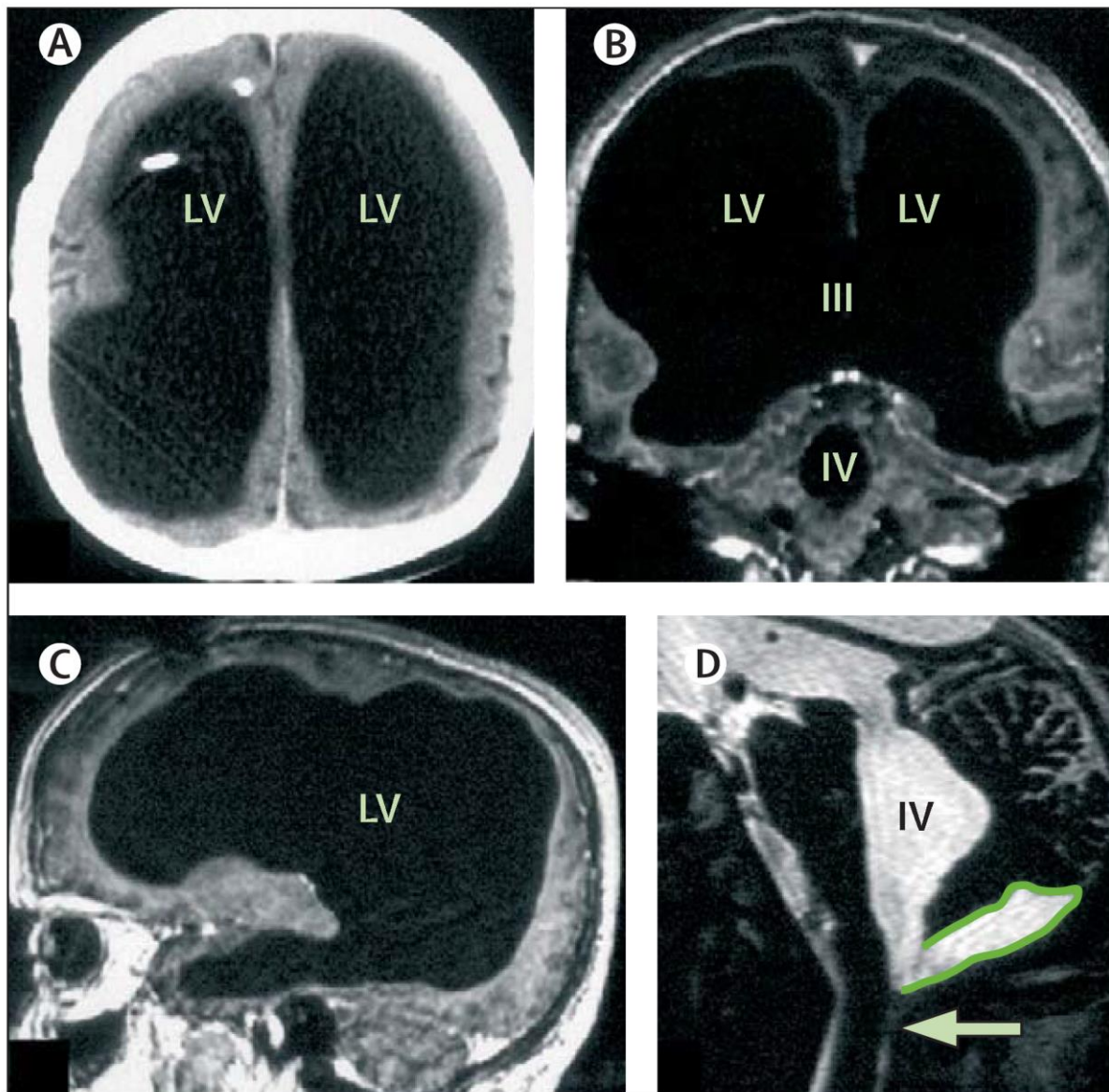
增強記憶有好無壞嗎？創傷後症候群



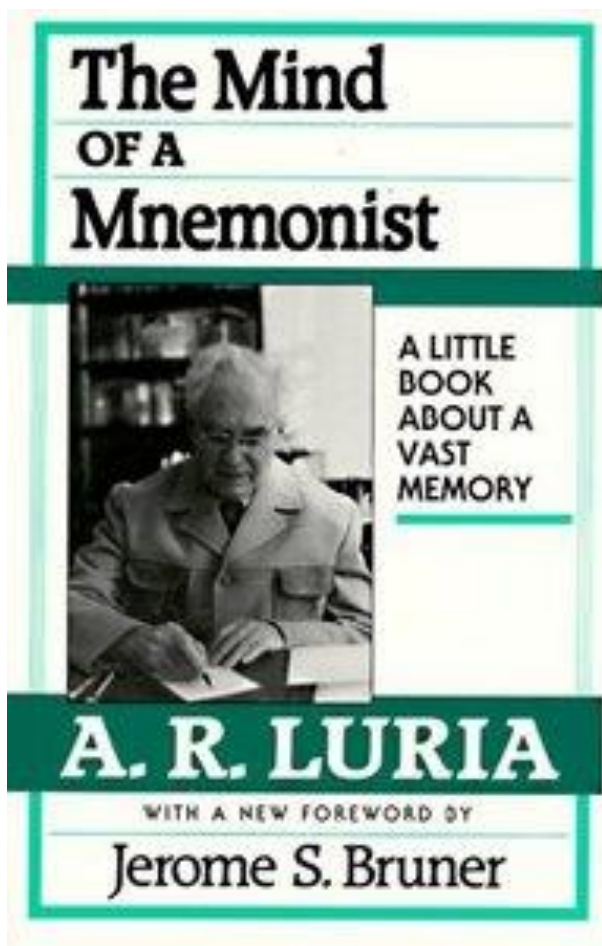
	Acquisition (Context A)	24h →	Extinction (Context B)	7d →	Memory recall	
	CS + US		CS 30min →	CS	Spontaneous recovery (Context B)	30min → Renewal (Context A)
WT (6 trials)	(Tone + shock) x 6		Tone x 18	Tone x 18	Tone x 4	Tone x 4
KO (6 trials)	(Tone + shock) x 6		Tone x 18	Tone x 18	Tone x 4	Tone x 4



猜猜看，這個水腦的成人的IQ是？30, 70, 100, 140



記憶有極限嗎？過目不忘（photographic memory）好嗎？



Stephen Wiltshire 史蒂芬·威爾特郡在20多分鐘的直升機俯瞰紐約城市後，從記憶中畫出了曼哈頓的素描。

終身記憶：普恩蛋白(Prion) 假說

Aplysia CPEB

MSQSPQTVDQAISVKTDYEDNQQEHIPSNFEIFRRINALLDNSLEANNVSCS**QSQSQQQQ**
QQTQQQQQQQQQQQQQHLQQVQQQQLLKQQQQQAQQQQIQQLLQQQQQKQQLQ
QQQQQEQLQQQQLQLQQQLQQQLQHIQKEPSSHTYTPGPSPELQSVLNYANVPLSKSAA
FNCNNSSSYSVGPTPVQSPVTPSPAASAVTVNSPSYGNFQLFGENAFDSTTPFQSDGTSQ
SHSRSLANDSDPMVVMSPGRDSIIPLSPTTEKILYQNFLLSKQAQGGENTALDPSPPHEIMPI S
PLEKKLYSNLLSKHTQGMRAINSTSPPLQTPLTPPRSPQEVLVA
RMDLSGRNQQADYSGTLAFLDAHNVLRRRTPSSSRSR SVM
ARLHRNAAVGEASCTWSGHLPPRNHENPVYSPKVFLGGV
KIEWPGKDG YVHLLFDVEKSVRSLLQACTHDFSN GDYFYKIS
SNHVFQPSQRLESNKTVFVGALHGMITAEALGRIMSDLFGNV
TFSSRKS YMKAVQAAFVEIKTPKFTKKLQVDPYLGDAICSLC
RSCWYWQHAPDSMRQHRPLTRNTK SSSL



有些蛋白的結構變形可改變其功能並使其不易水解，來增長蛋白分子的壽命。

Prion蛋白的另一特性是能將正常的蛋白轉為prion狀的蛋白

腦計畫：建構腦內的google map：結構，活性及分子

江安世院士

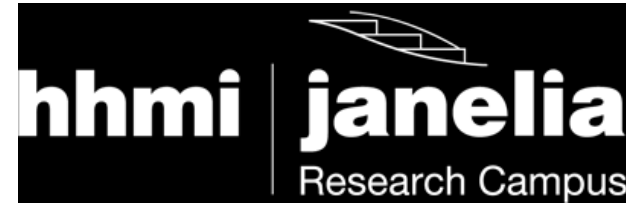
FlyCircuit 1.1

A Database of Drosophila Brain Neurons

果蠅迴路（果蠅記憶）



ALLEN INSTITUTE *for*
BRAIN SCIENCE



WE NEED

神經生物學家

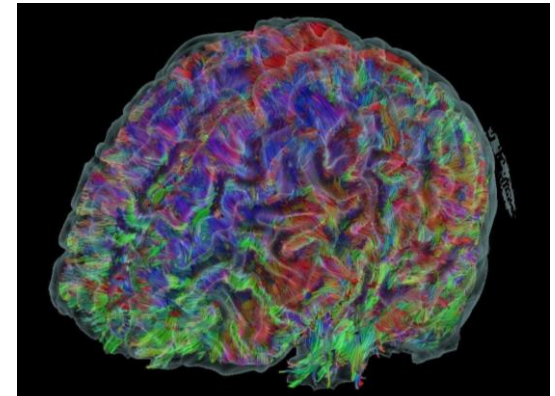
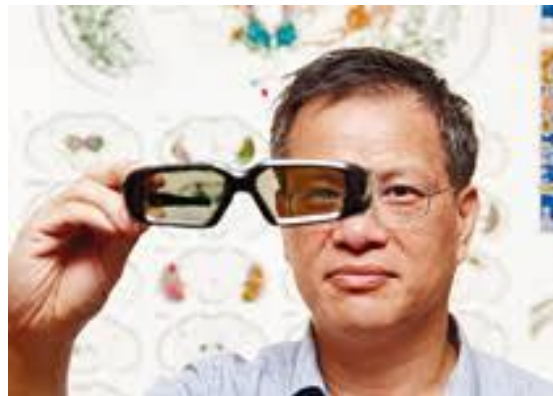
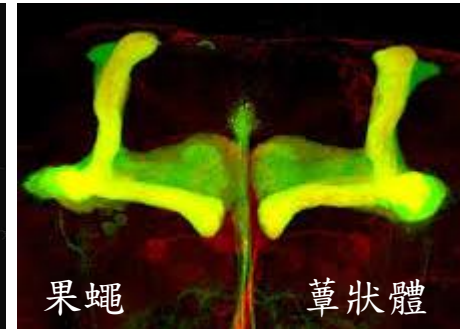
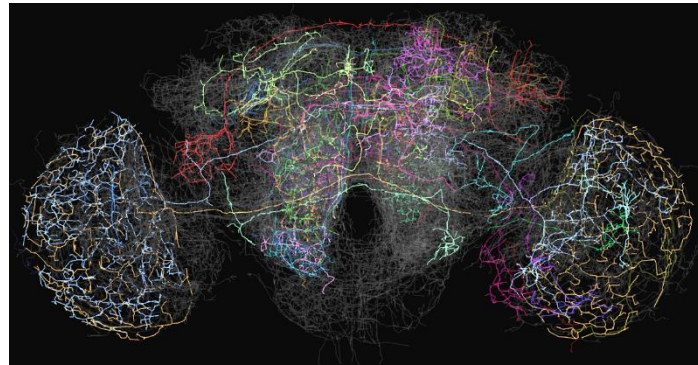
物理學家

化學學家

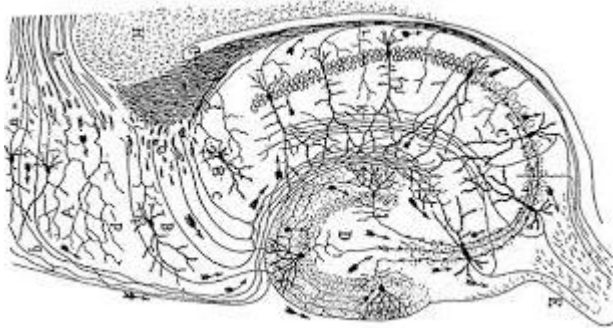
電機/機械工程師

電腦學家

生物資訊學家



Clarity: 透明化讓一切看的更清楚



Before

The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.

After

The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.

Optogenetics: 用光來影響動物的神經活性及行為

用基因工程的方式，將從藻類中找到的蛋白表達在老鼠或其他動物身上。此蛋白是以光波長來決定開關的離子通道，打開後正電流或負電流流入的兩種蛋白。

light-gated ion channel proteins such as channelrhodopsins. e.g. ChR2 (打開，正電流流入) , halorhodopsin, VChR1 (打開，負電流流入)



Year ??

Q: 爸媽常唸我們，要多動動腦，要不腦袋會生鏽。其所依據的神經學理是？