

# Perspectivas y Desafíos en la Investigación del Cerebro

Granada, 2010

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CSIC

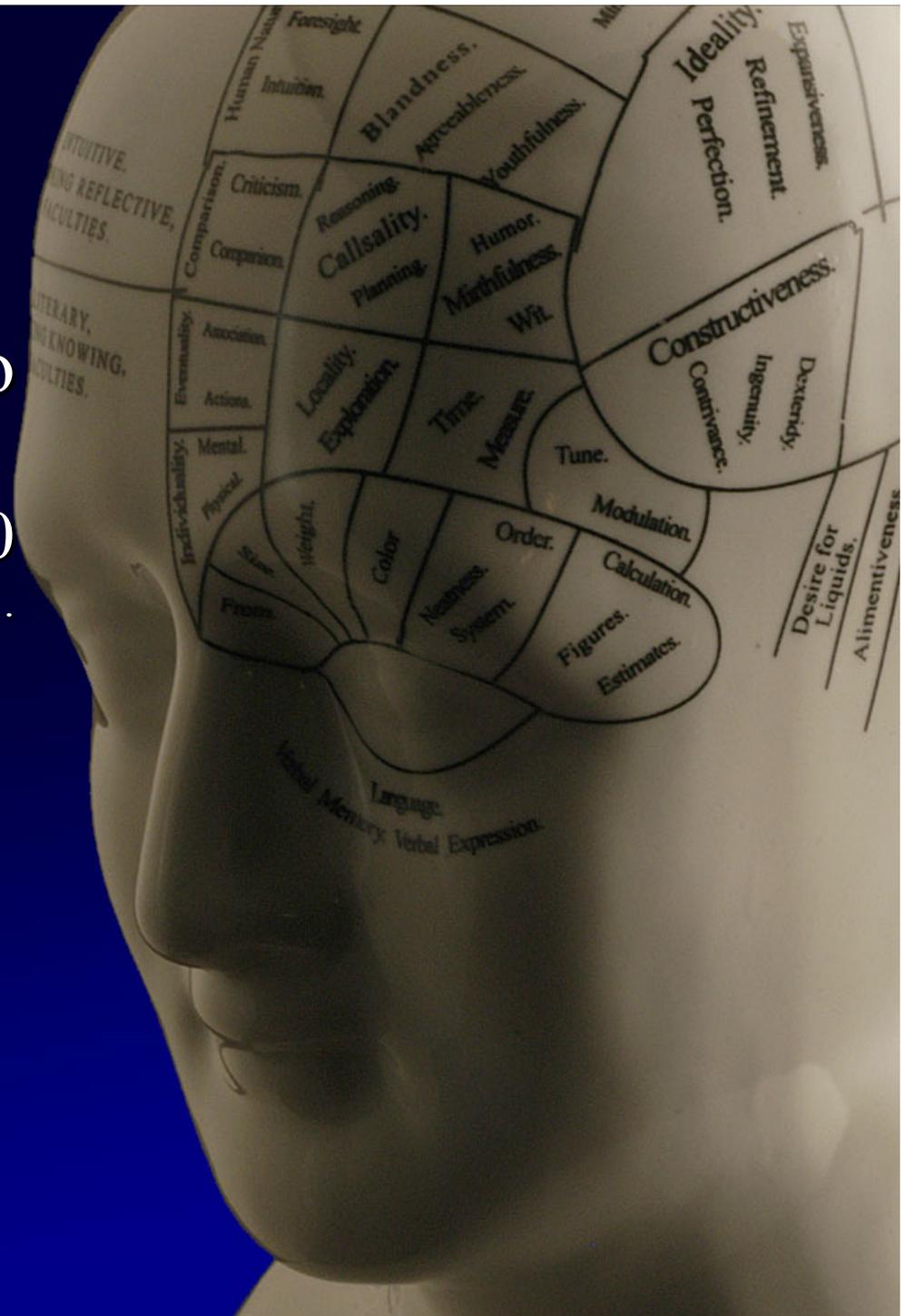
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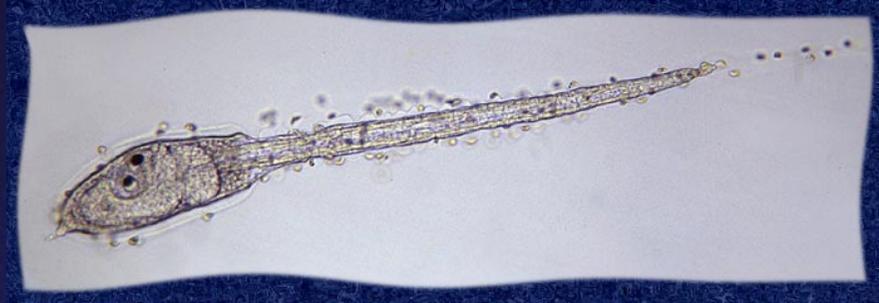


UNIVERSITAS  
Miguel  
Hernández



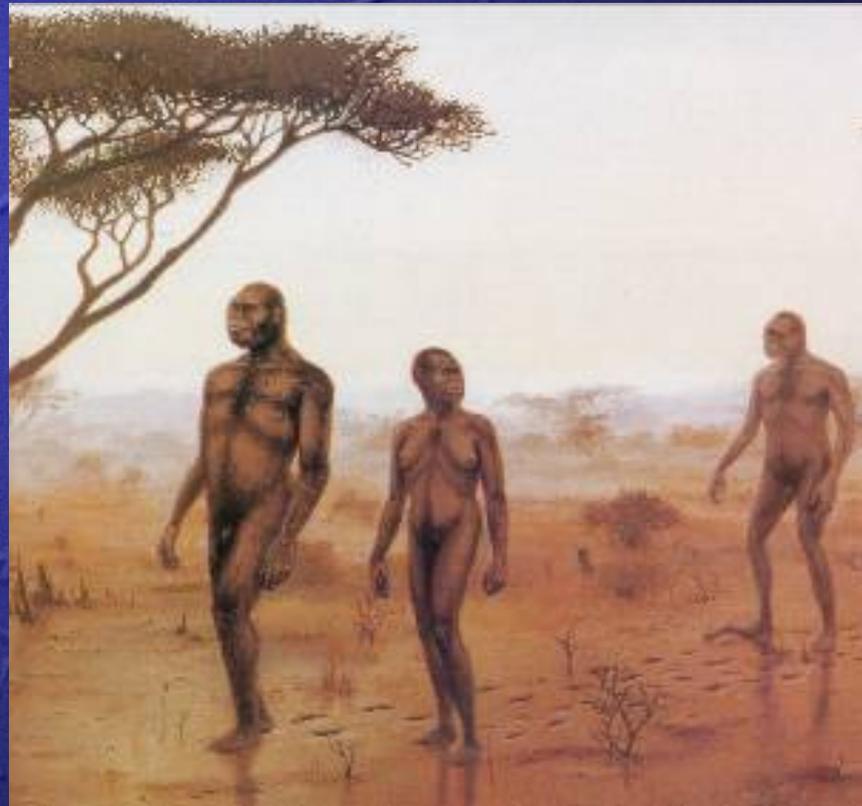
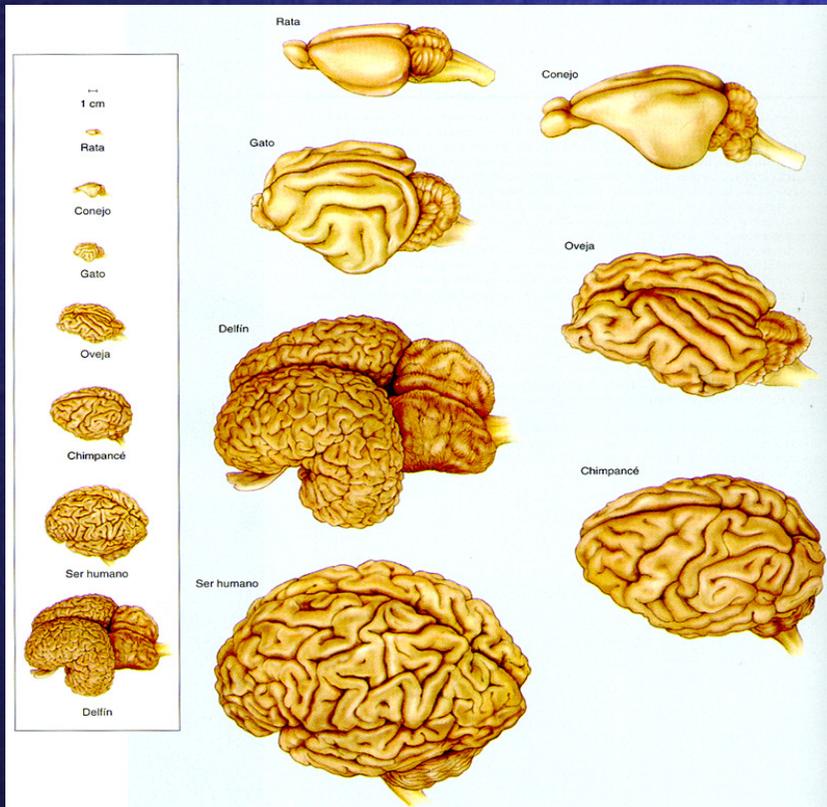
INSTITUTO DE NEUROCIENCIAS





Ascidia

## El cerebro, una conquista evolutiva





**Exploración del mundo exterior**



## Desarrollo de actividades motoras complejas

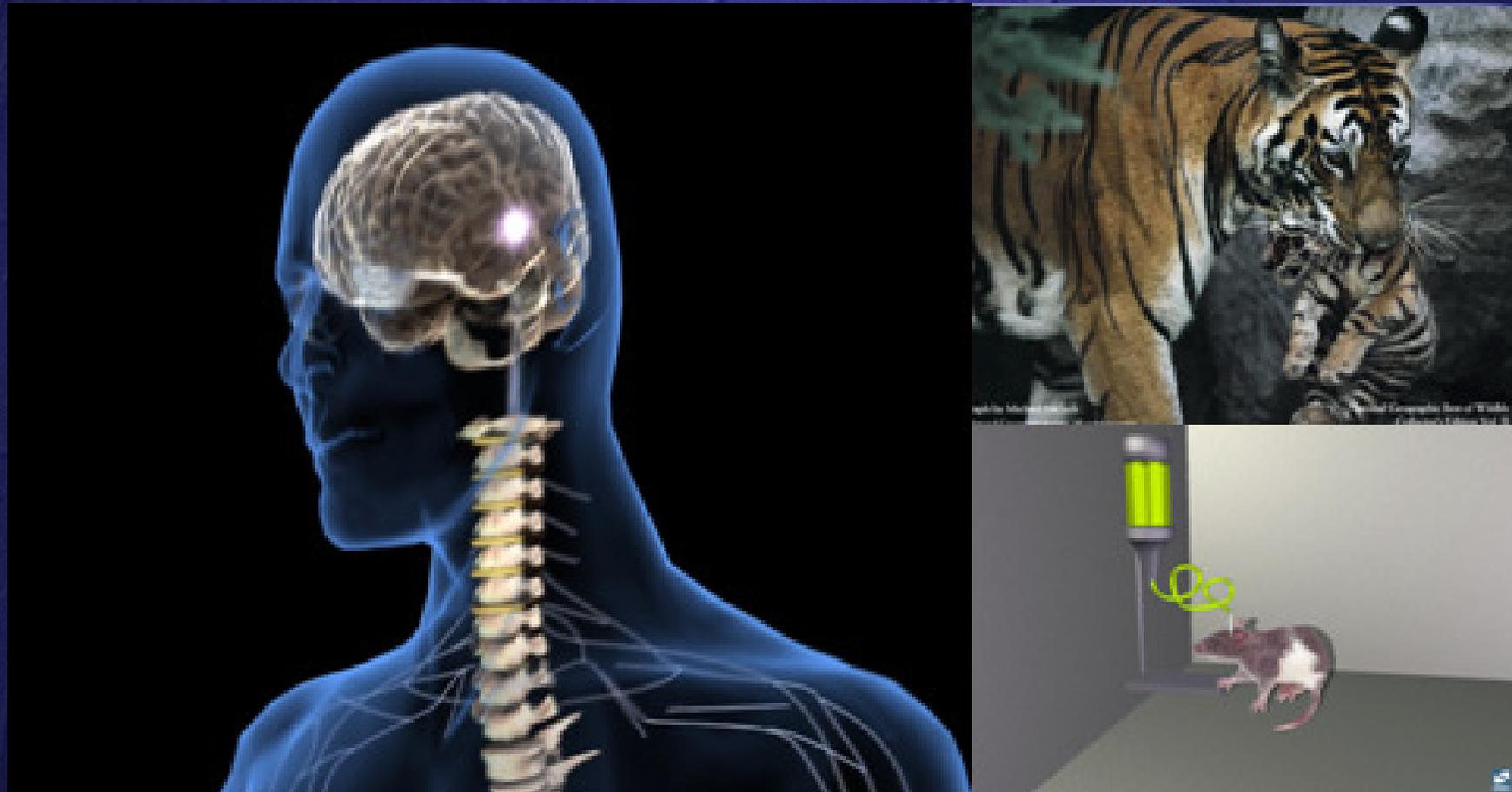




## Desarrollo de conductas sociales



**Desarrollo de sistemas neurales de  
Protección (dolor) y de recompensa (placer)  
Para potenciar las conductas de supervivencia y  
reproducción**



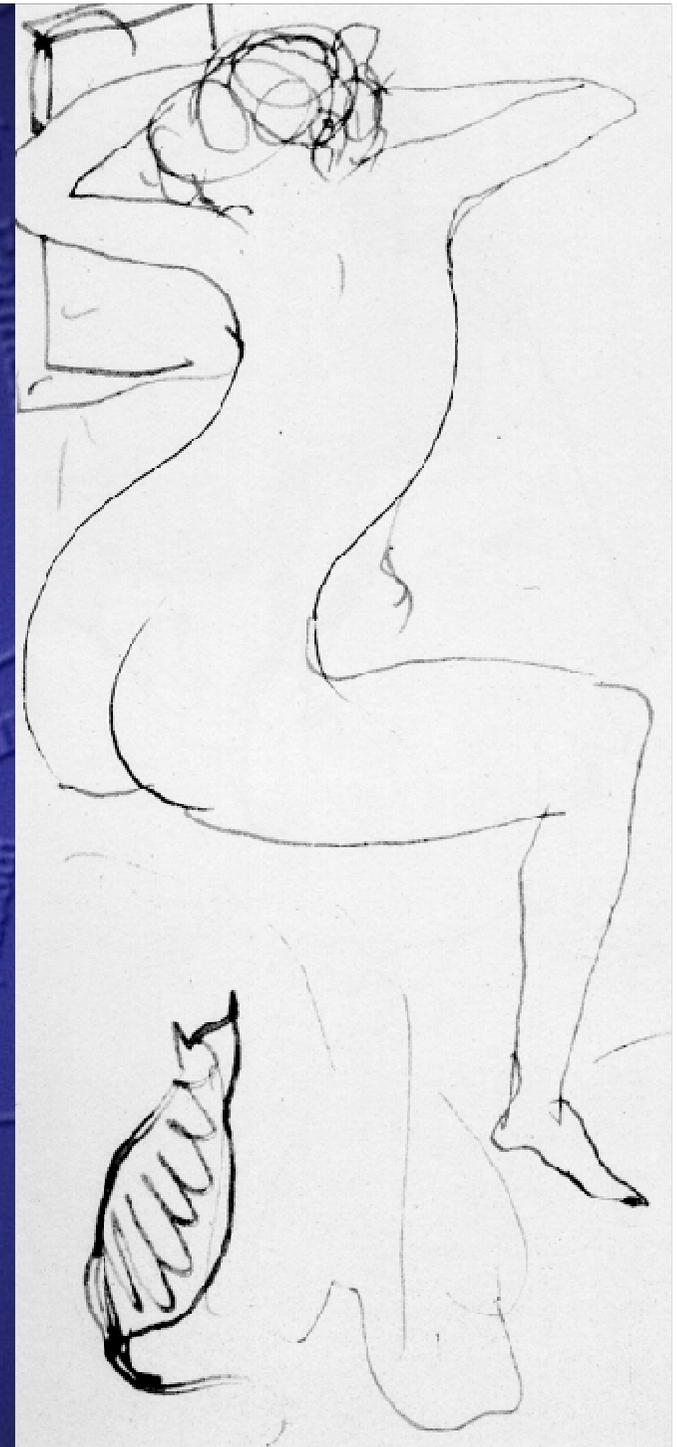


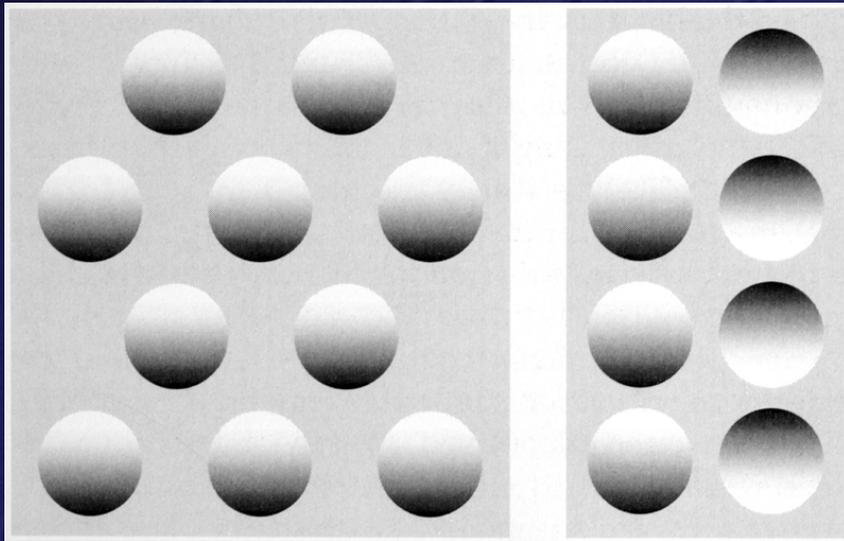
**El cerebro construye una visión distorsionada del mundo**

**Proporciona una información sintética, coherente y continuada del mundo (qualia)**

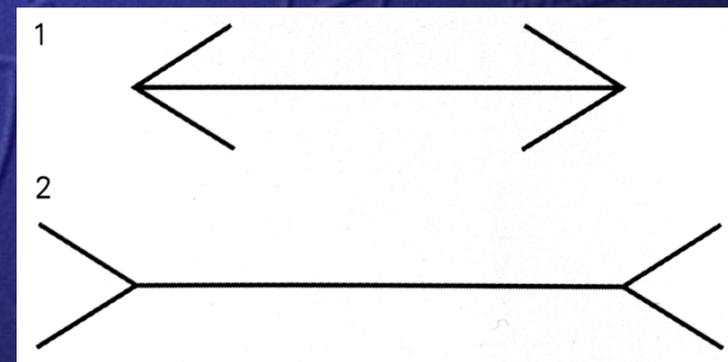
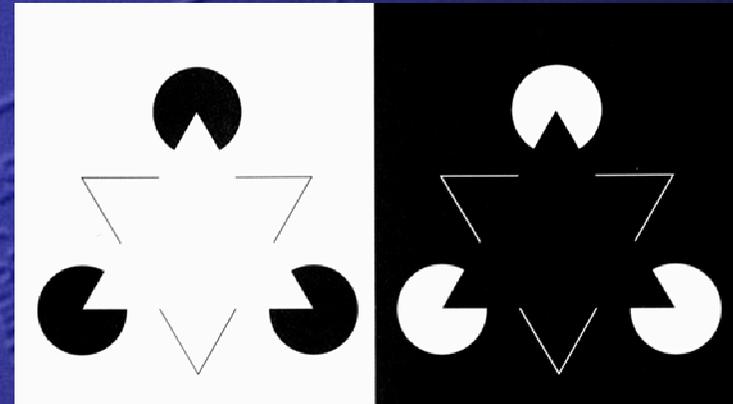
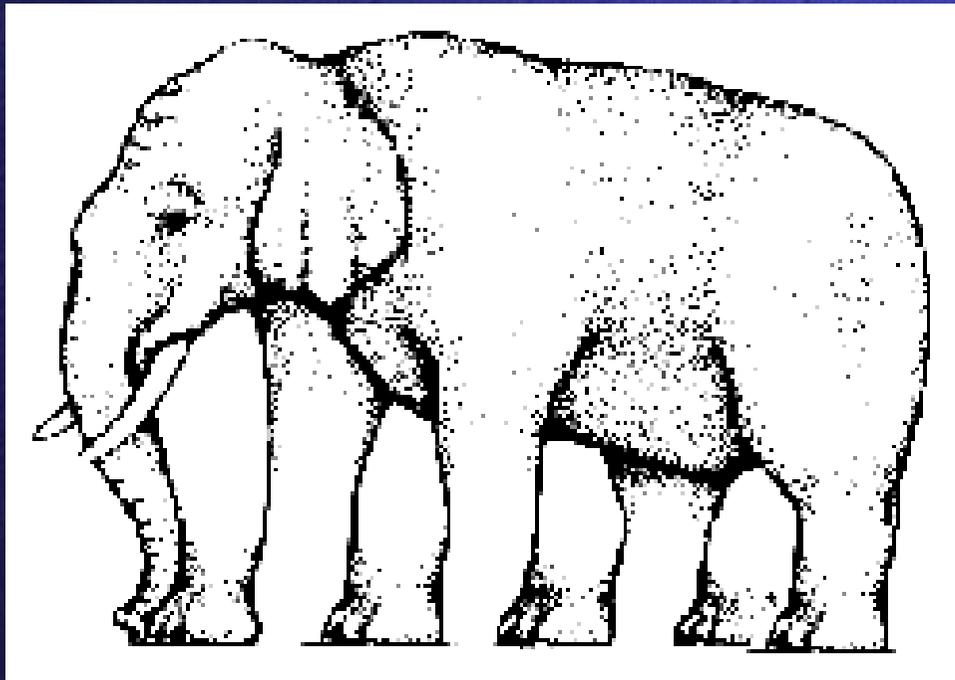


**Y genera la consciencia: una percepción unificada y subjetiva de la realidad**





Y tambien nos engaña ...

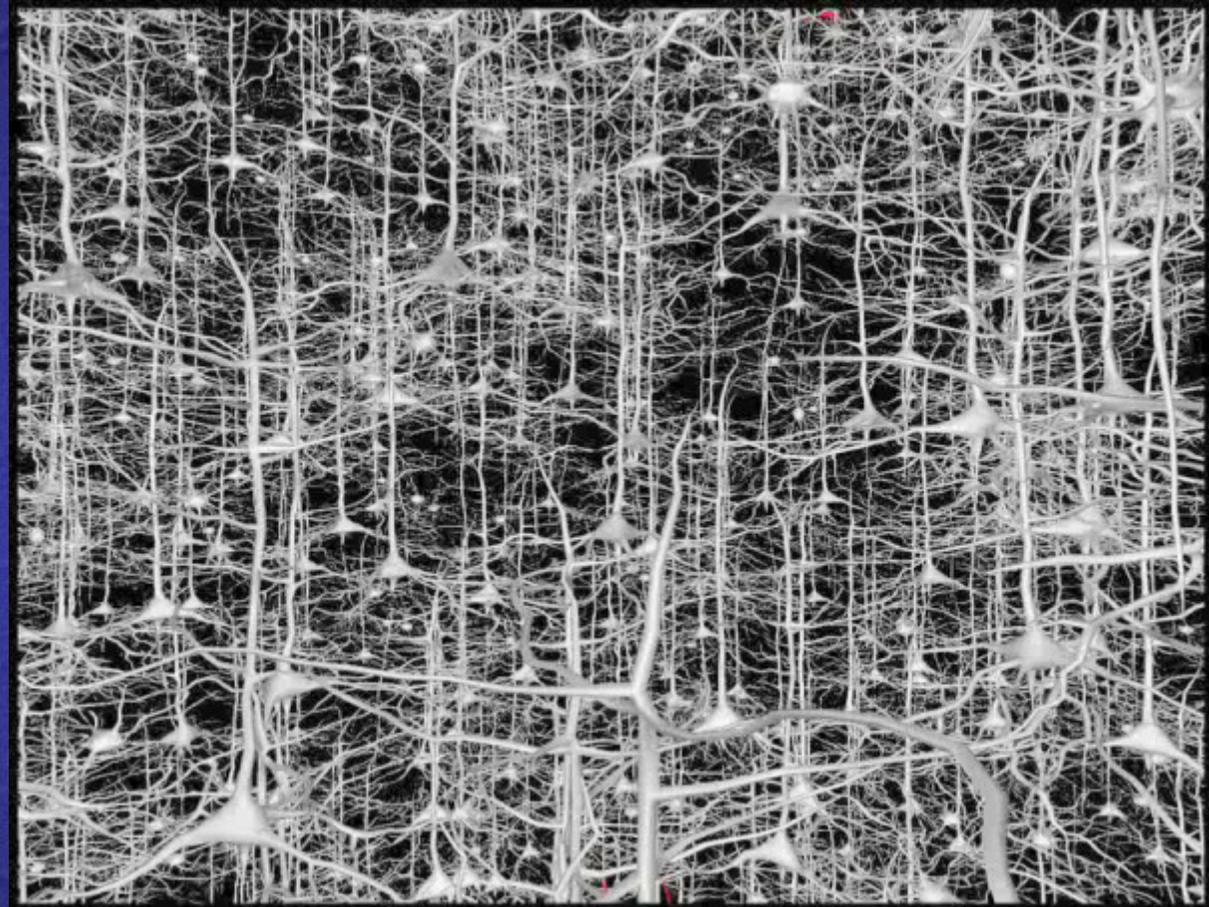
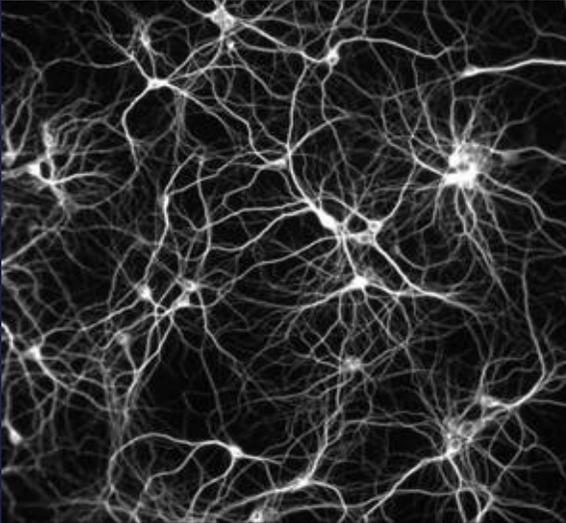
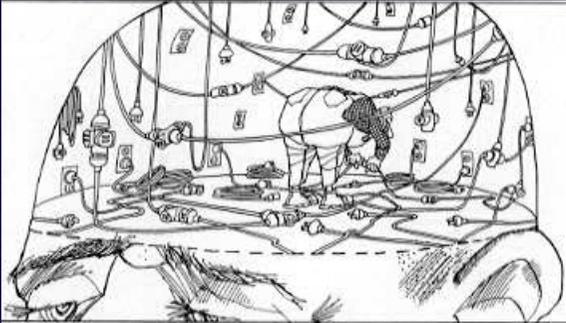




## **Santiago Ramón y Cajal (1852-1934), fundador de la neurociencia moderna**

“Solo el conocimiento exacto de la textura del sistema nervioso permitirá averiguar el cauce material del pensamiento y de la voluntad y sorprender la historia íntima de la vida, en su duelo perpetuo con las energías exteriores..” (« Recuerdos de mi vida »)

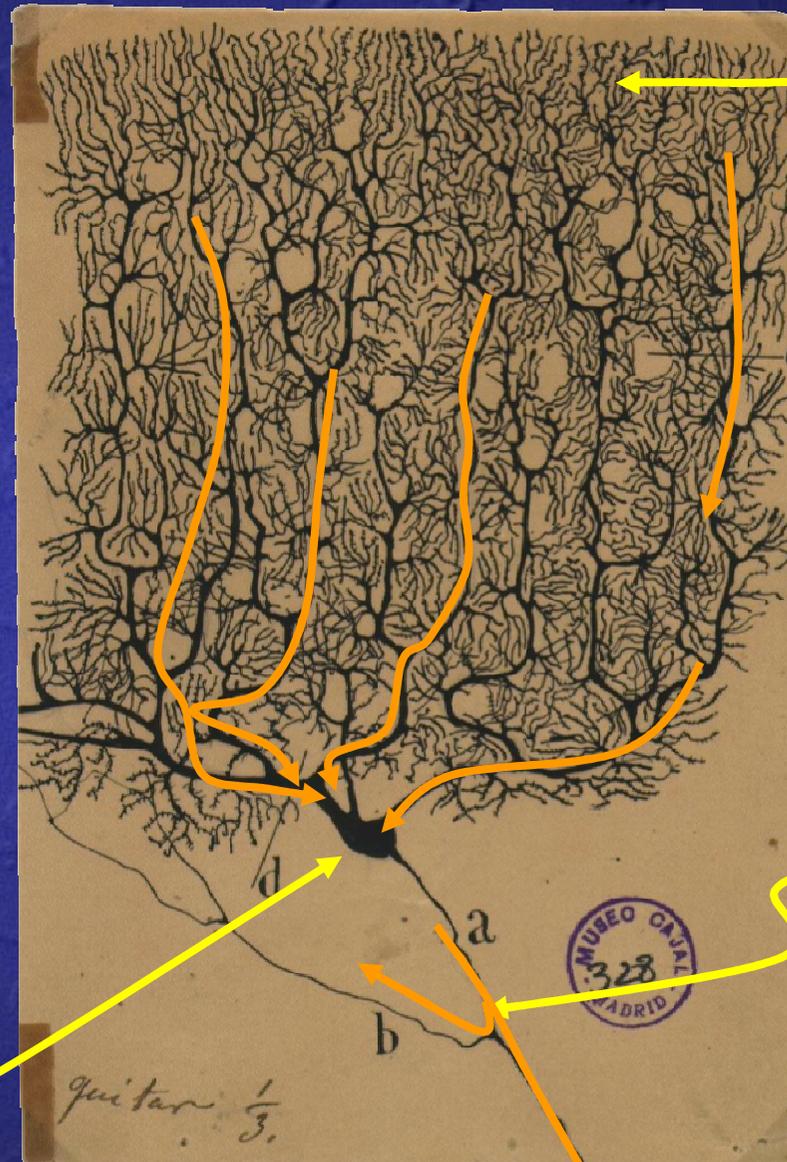
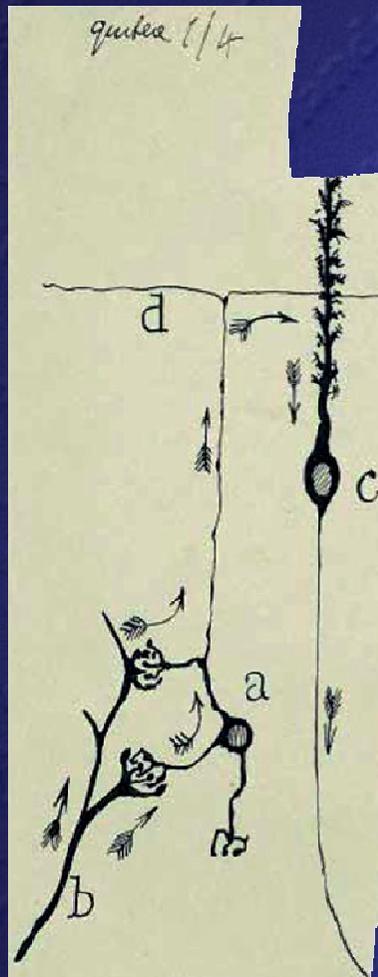
# Aproximaciones experimentales al estudio del cerebro: Reduccionistas y Holísticas



El cerebro humano:  
 $\approx 100.000.000.000$  neuronas

Javier de Felipe:  
Bosque neuronal

# Doctrina neuronal y ley de la polarización dinámica de la neurona

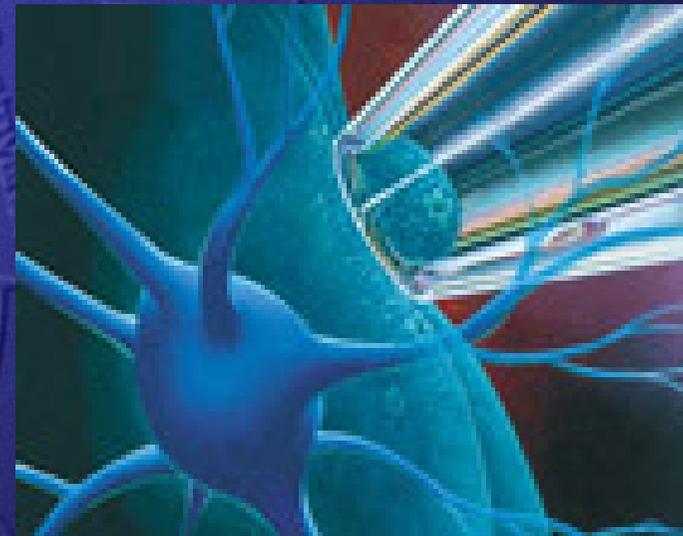
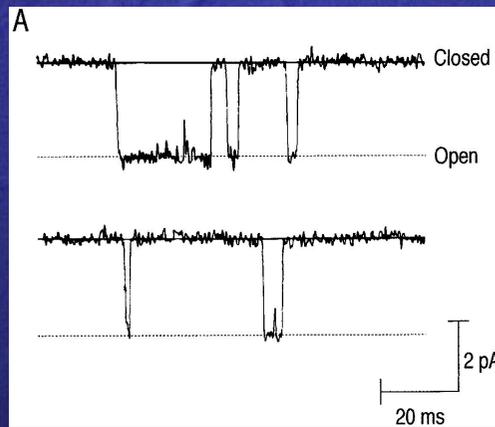
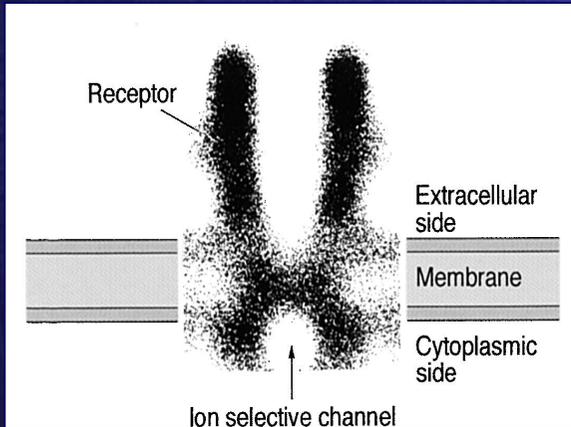
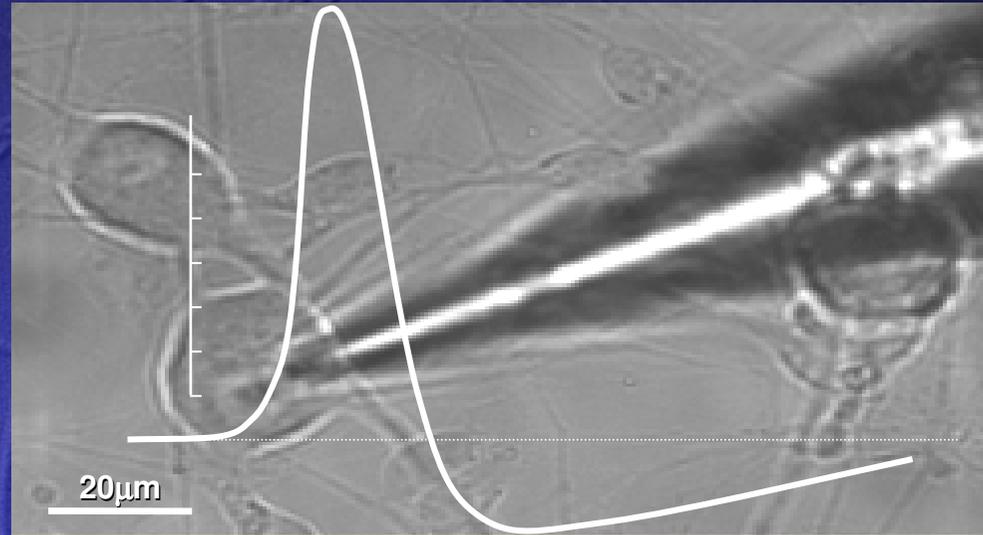


Dendritas: Entrada

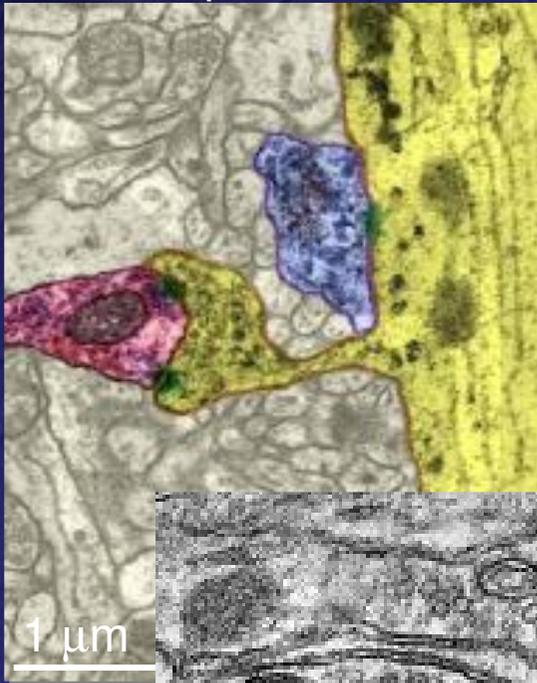
AXÓN: Salida

SOMA

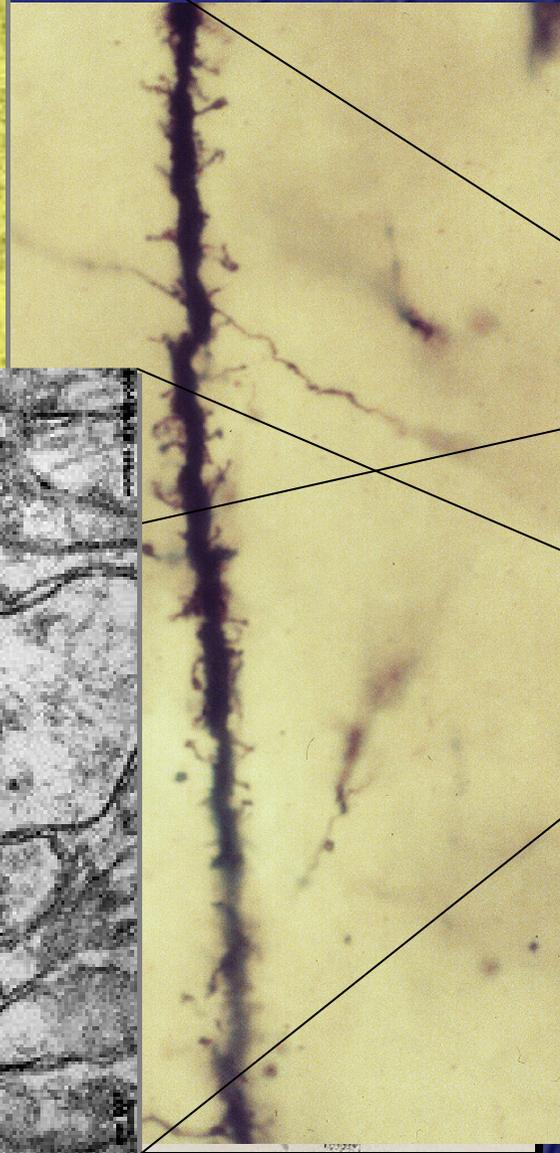
# El lenguaje neuronal: impulsos nerviosos



Microscopía Electrónica



## Comunicación neuronal: Conexiones sinápticas

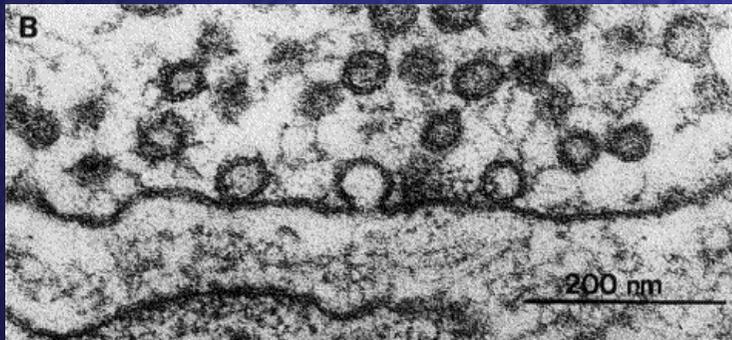
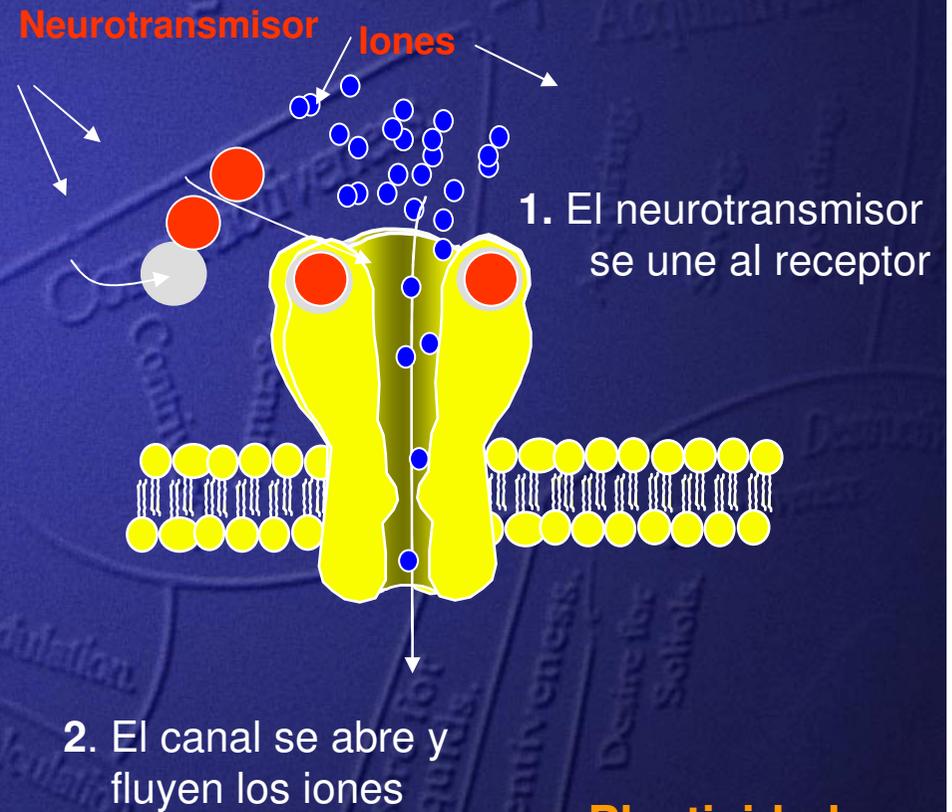


Preparación original de Cajal

Cortesía de J. Lerma

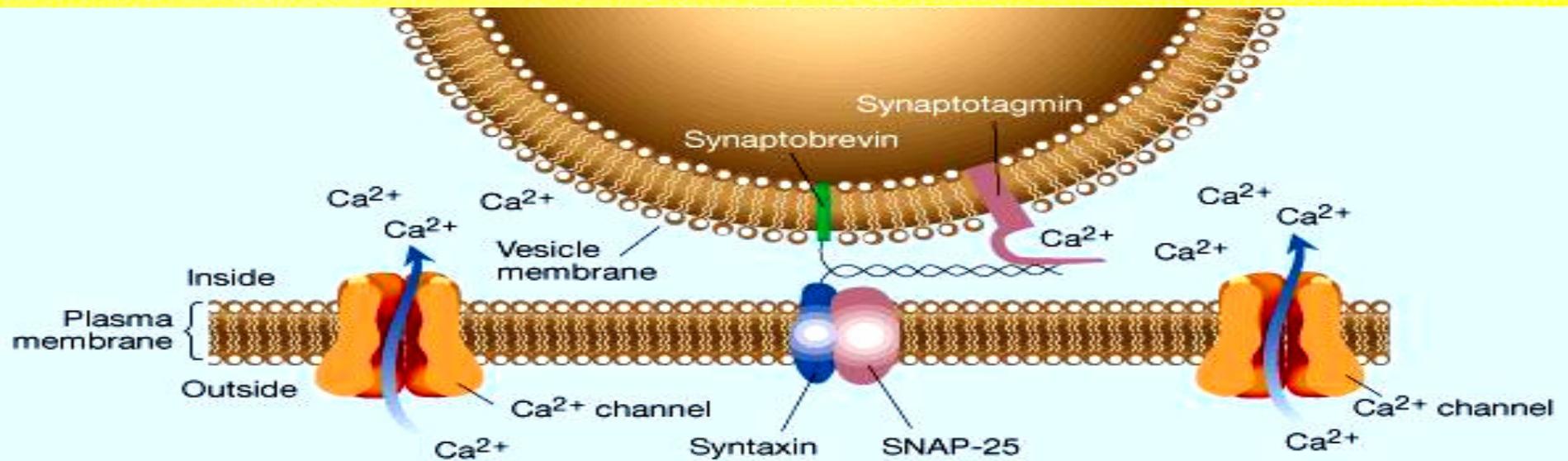
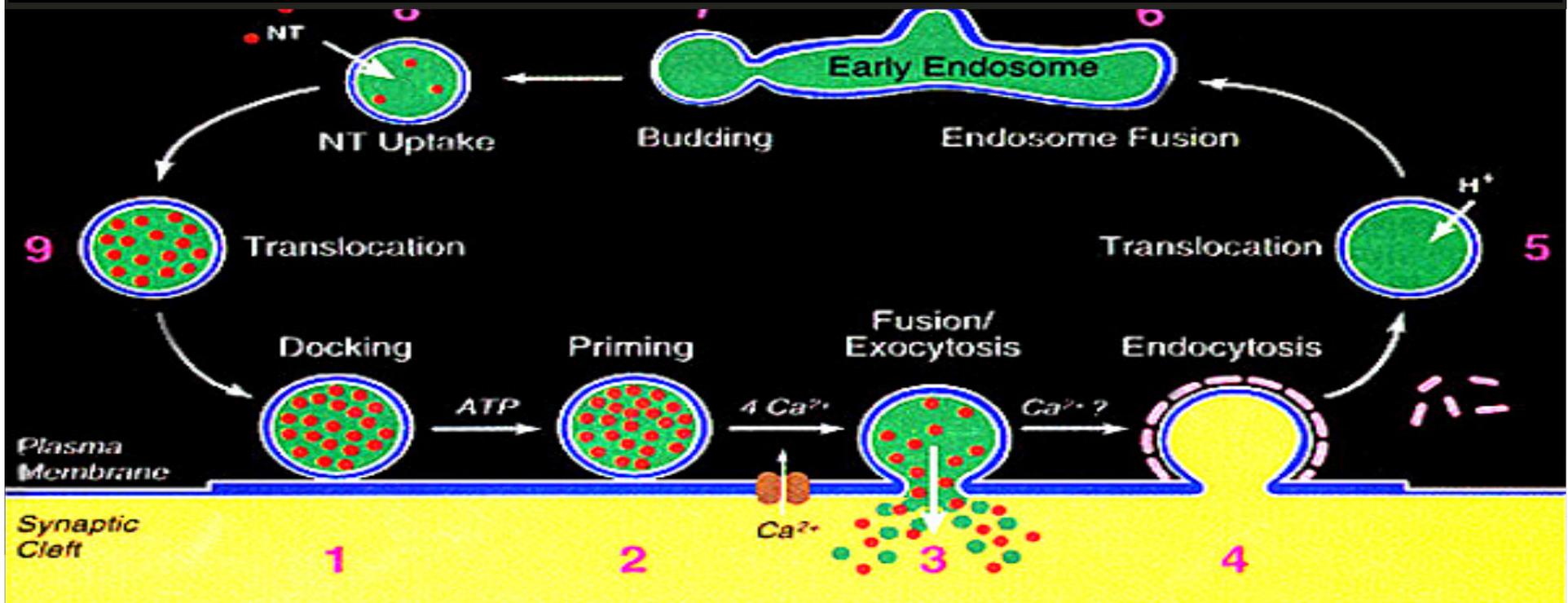
# La transmisión sináptica

- 1-Almacenamiento vesicular
- 2-Liberación del neurotransmisor
- 3-Interacción con receptor



**Plasticidad....**

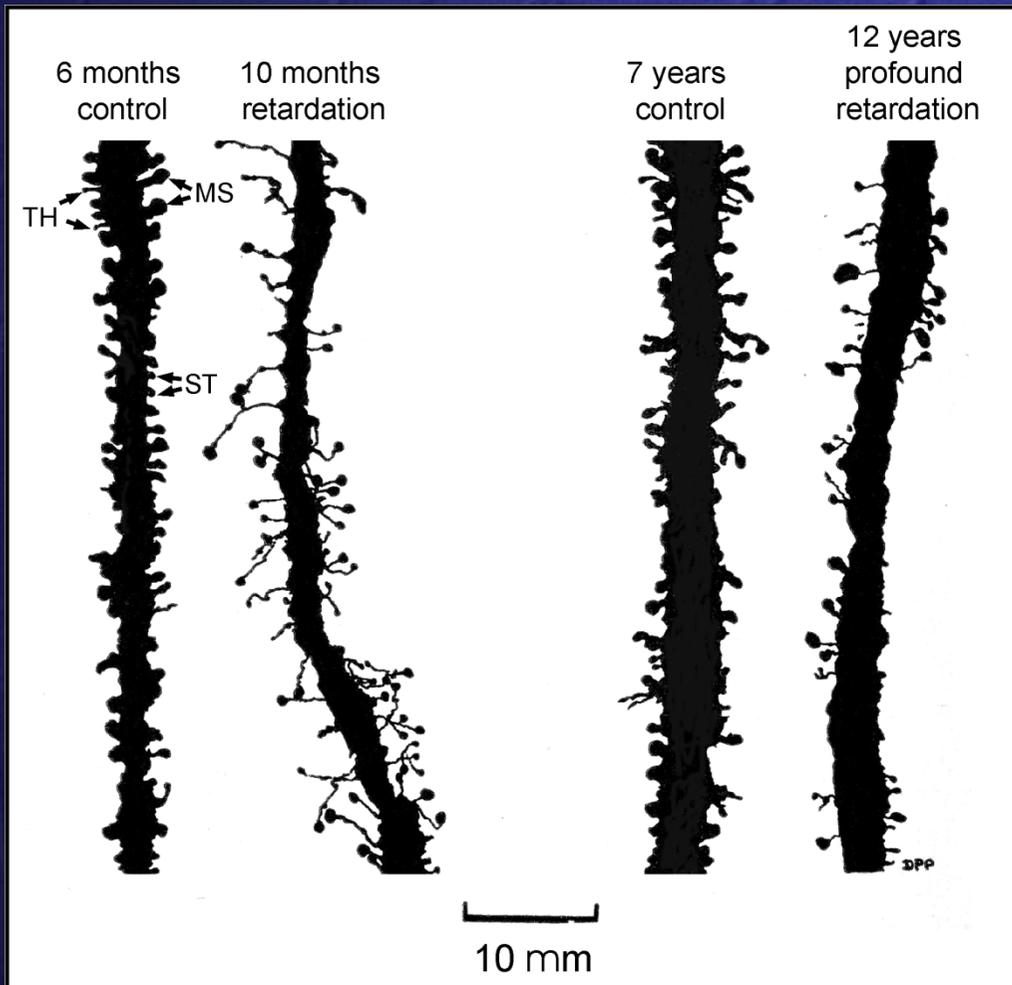
# Caracterización molecular de la sinapsis



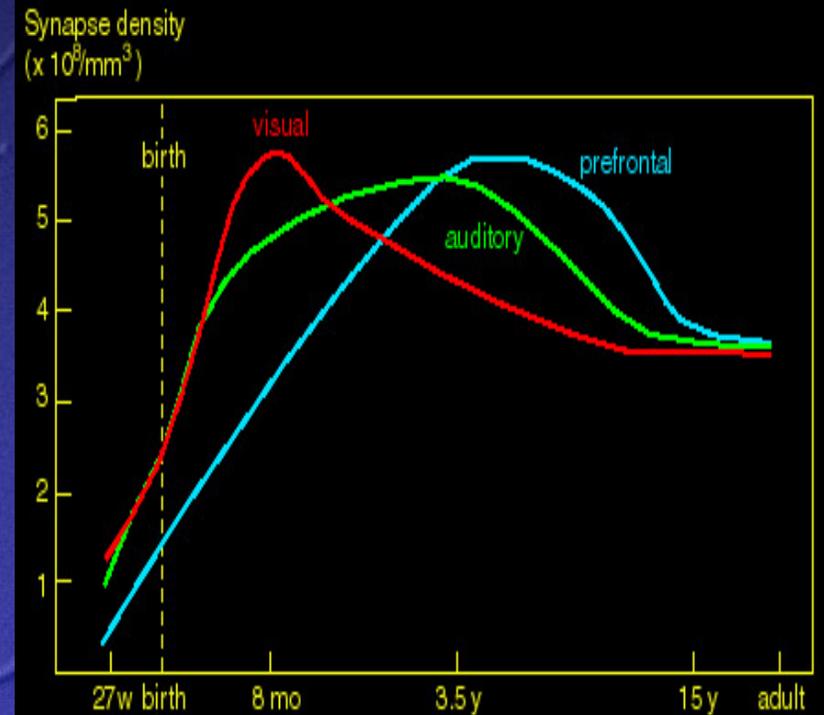
# Principales Neurotransmisores

Molécula Transmisora	Efecto	Localización
Acetilcolina (ACh)	-,+	SNC, unión neuromuscular
→ Serotonina 5-Hydroxytryptamina (5-HT)	-,+	SNC, otras células
→ GABA	-	SNC
→ Glutamato (Glu)	+	SNC
Glicina (Gly)	+,-	Médula Espinal
Noradrenalina (Norepinefrina)	+	SNC, nervios simpáticos
Dopamina	+,-	SNC
Adenosina	+,-	SNC, nervios periféricos
ATP	+,-	Neuronas simpáticas, sensoriales
Oxido Nítrico (NO)	+,-	SNC, tracto gastrointestinal, corazón

# Relación entre densidad de espinas dendríticas y retraso mental



Purpura, 1974



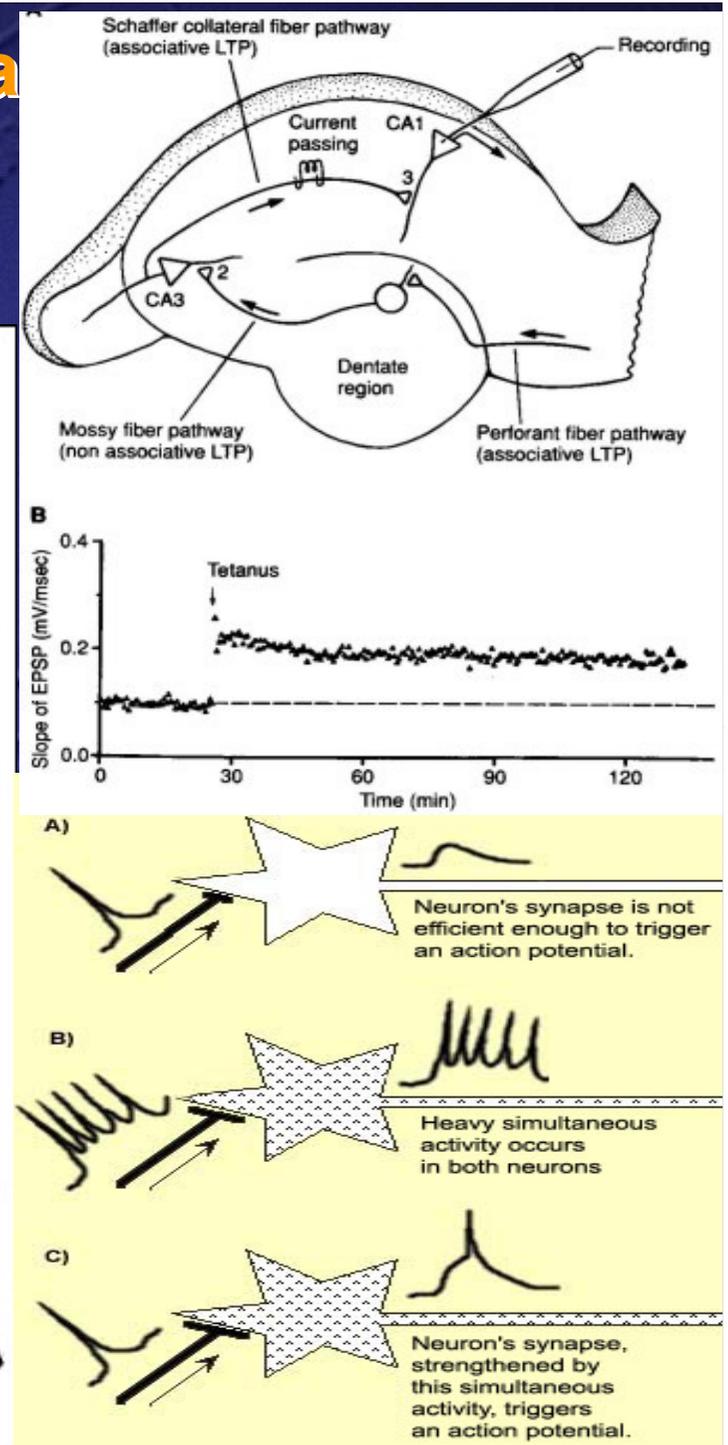
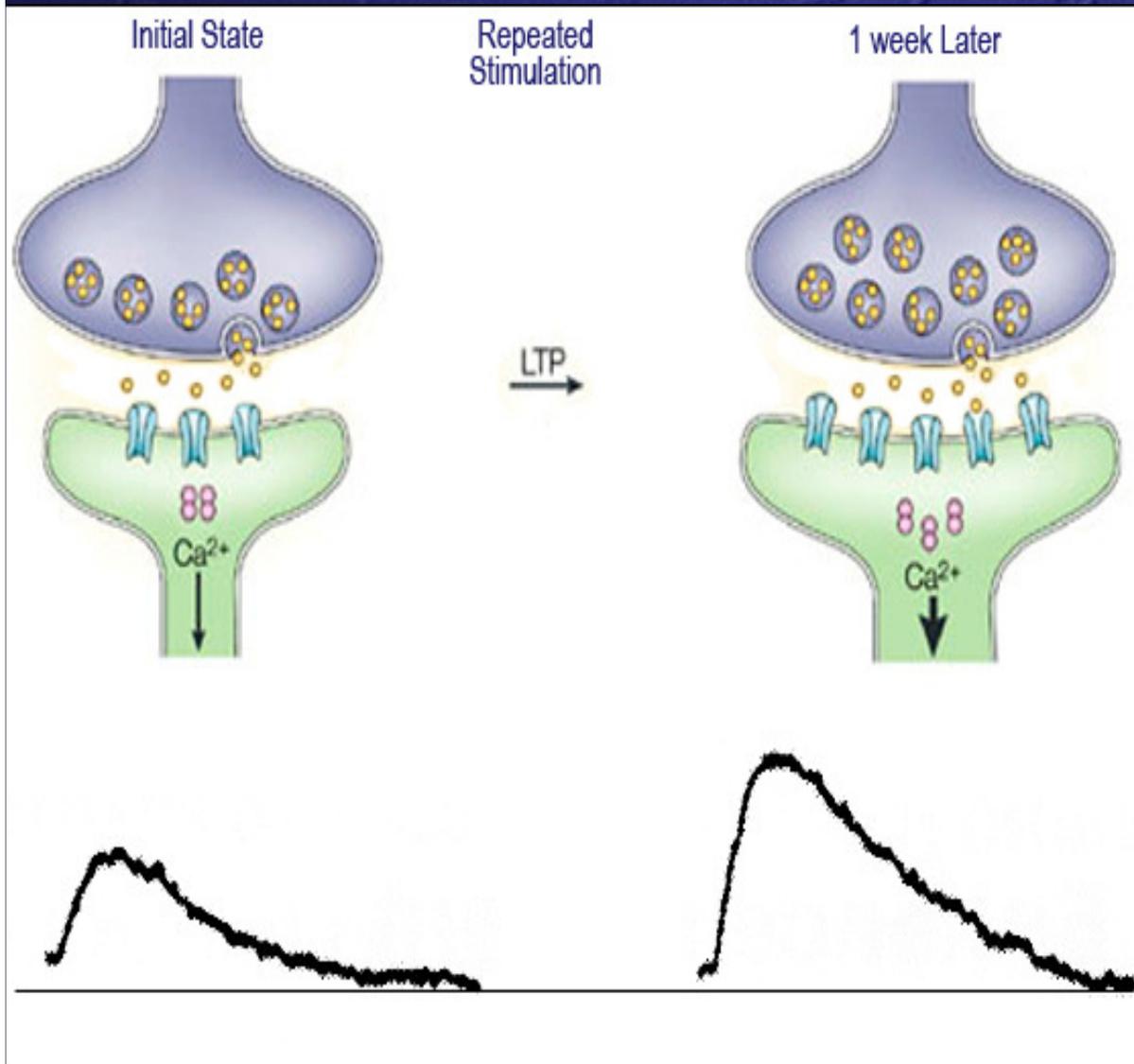
Huttenlocher, 1999

## Síndromes de Down, fragil X, Rett

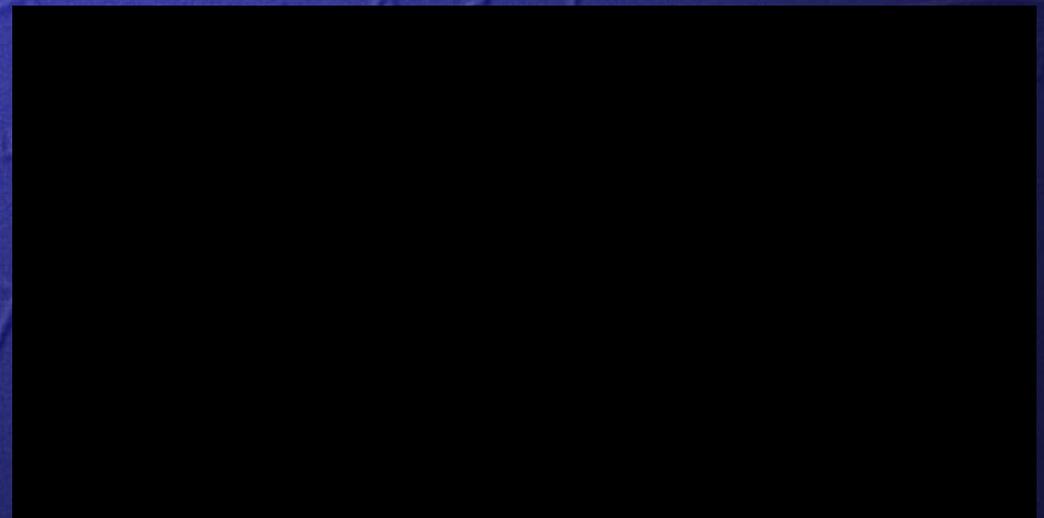
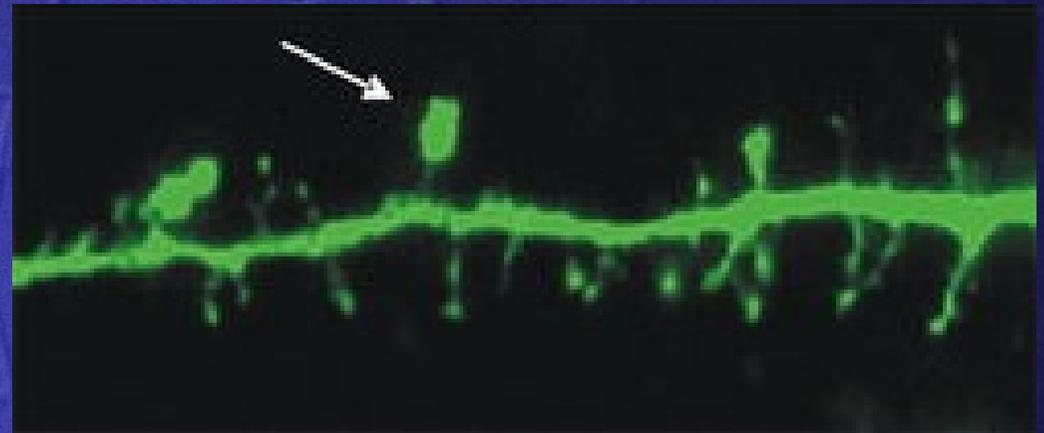
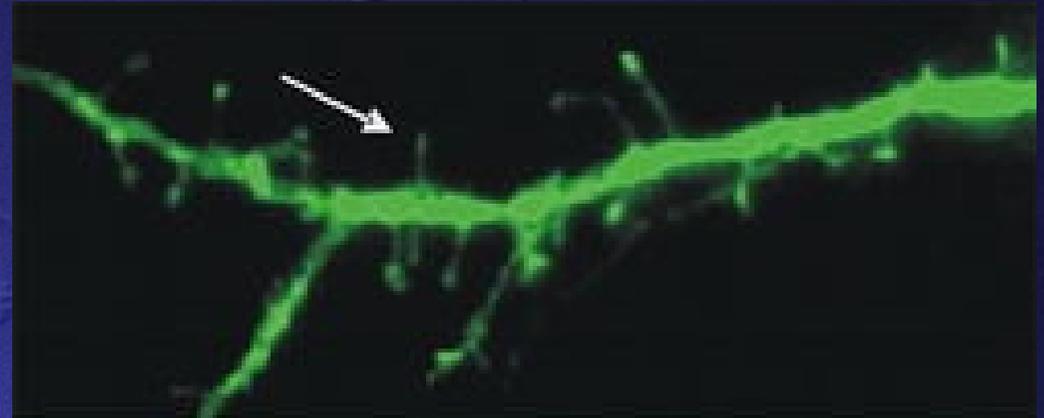
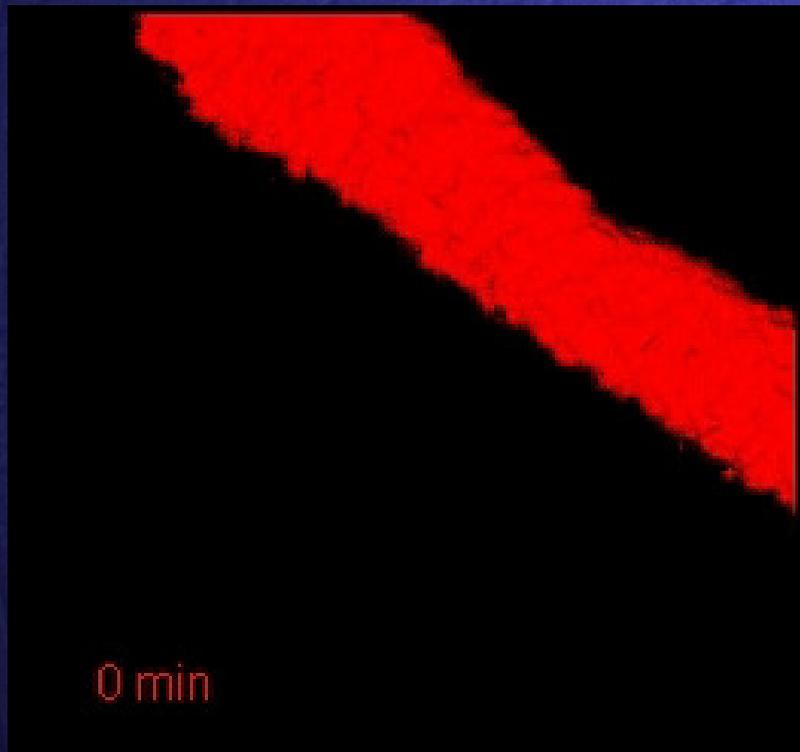
- Reducción en el número y longitud de las espinas
- Anormalias morfológicas (espinas largas, finas, en forma de hongo)
- 'disgenesia de las espinas'

Courtesy of Ger Ramakers

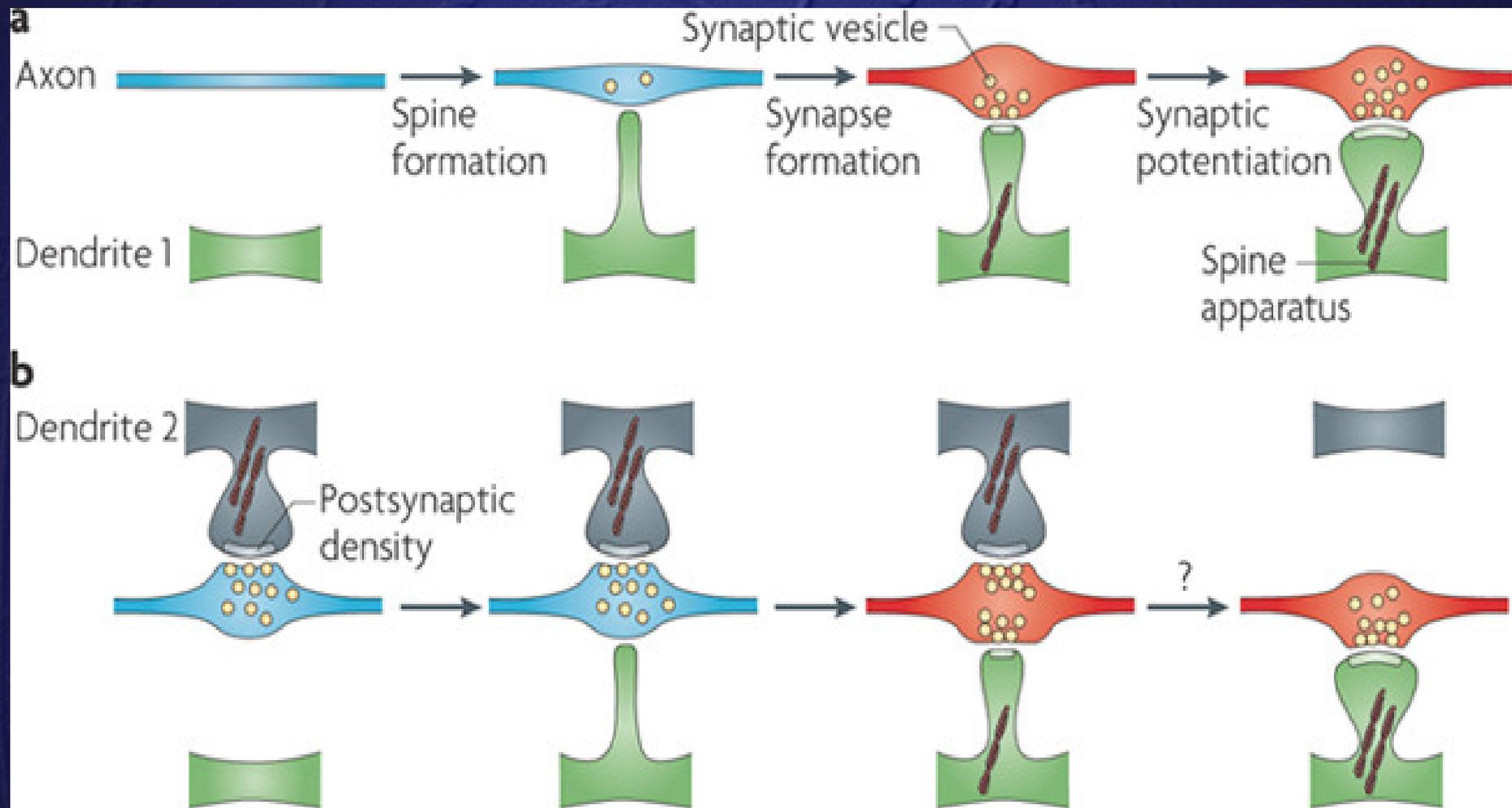
# Correlato funcional de la memoria Long Term Potentiation (LTP)



## Formación de sinapsis durante el aprendizaje



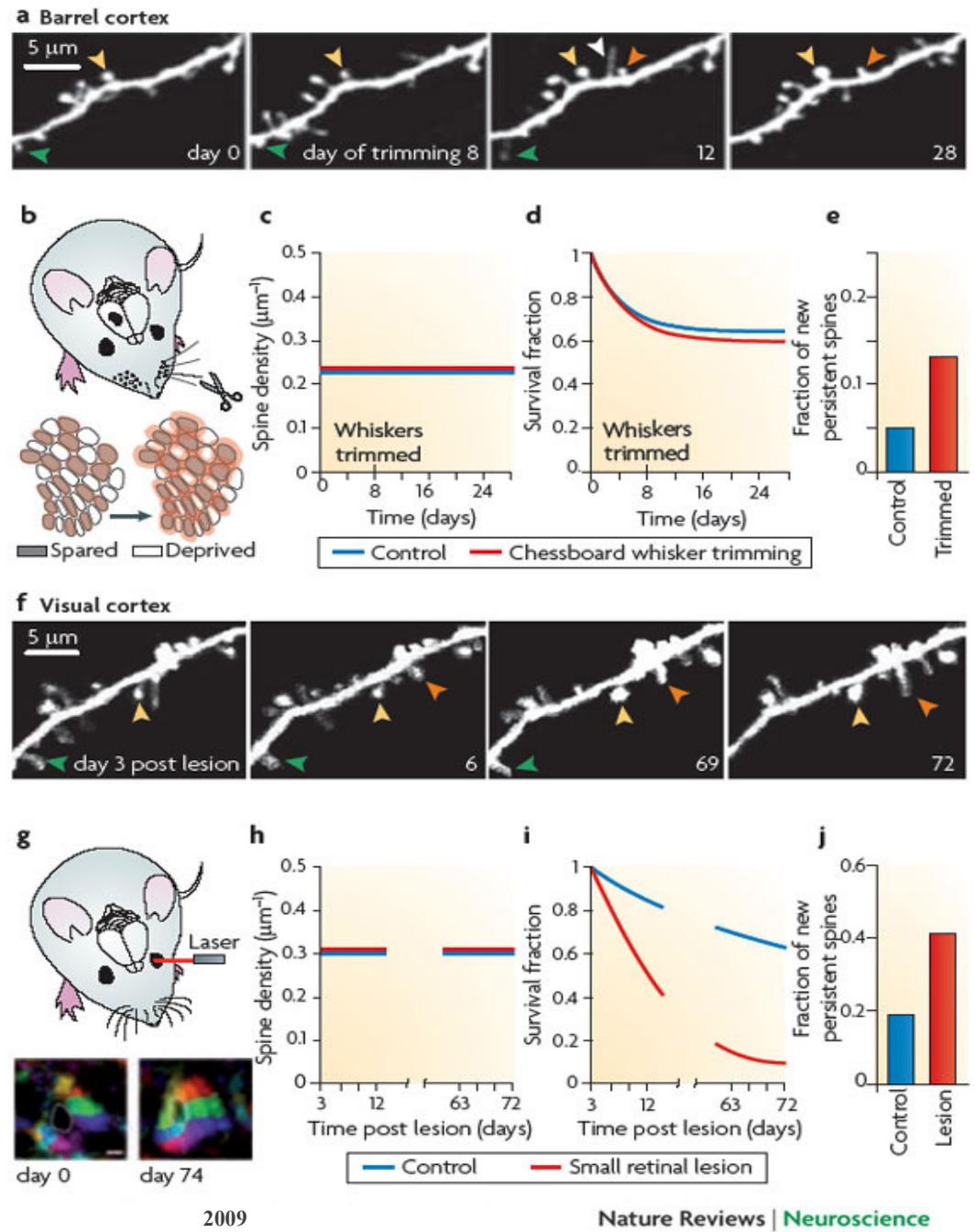
# Mecanismos de Formación de Nuevas Sinapsis



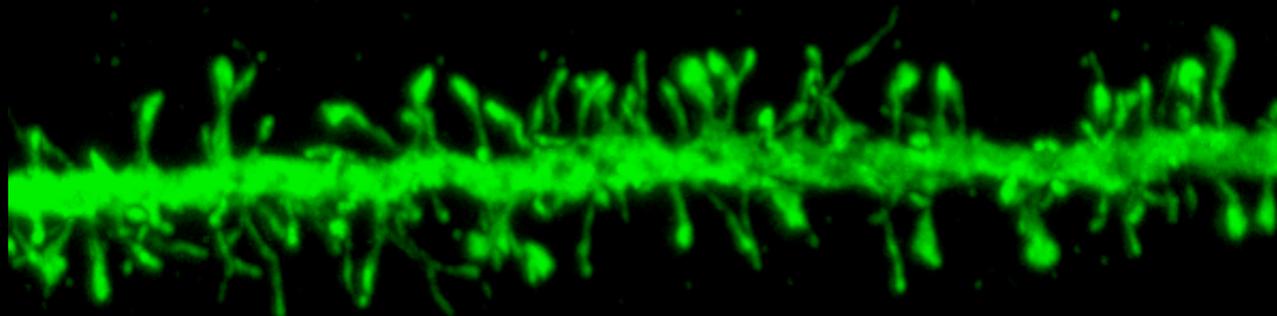
# Corteza sensorial

## Plasticidad sináptica dependiente de la información en el neocortex cerebral

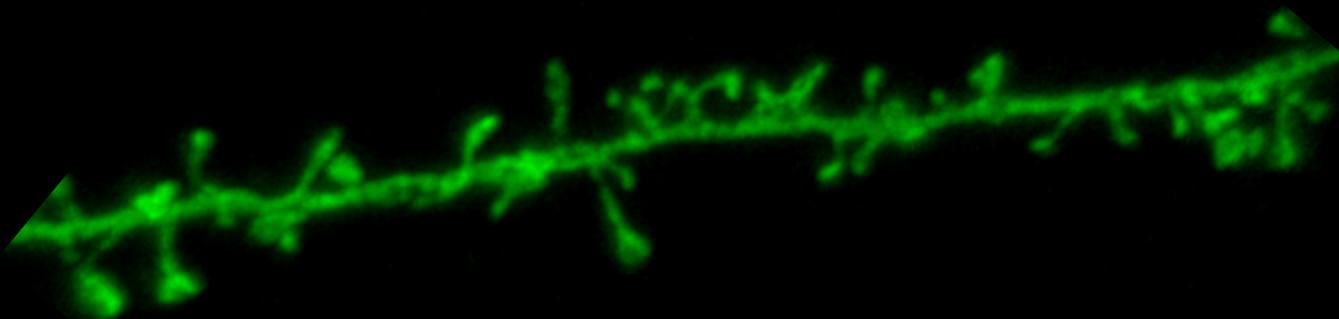
# Corteza visual



## Cambios con la edad en la densidad y la morfología de las espinas dendríticas



41 años

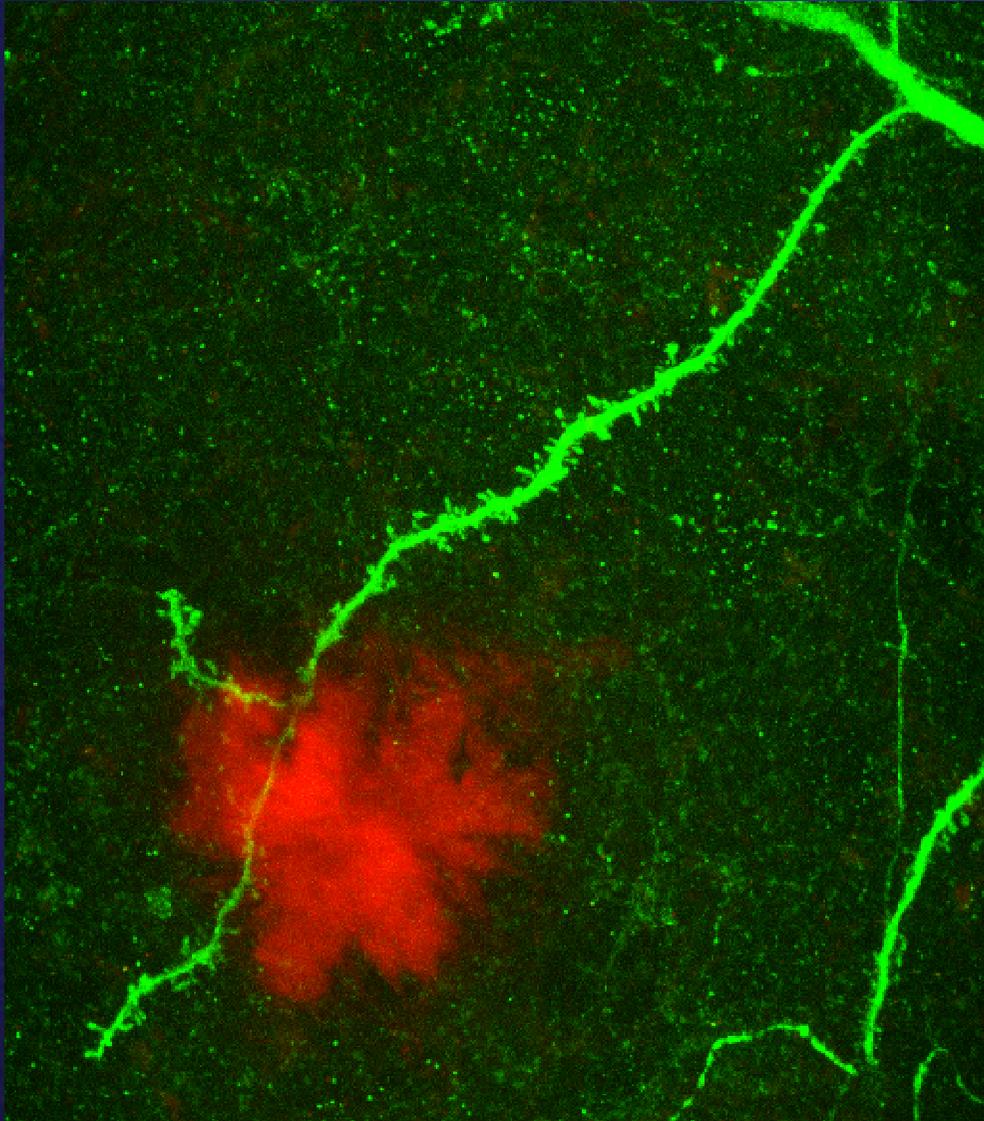


84 años

# Reproducción de la enfermedad de Alzheimer

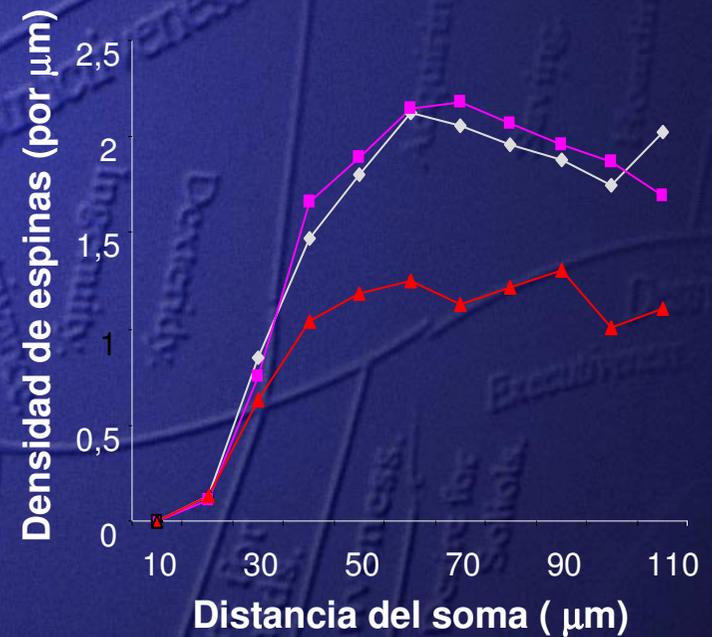
## Ratón doble transgénico APP/PS-1

Cortex Frontal

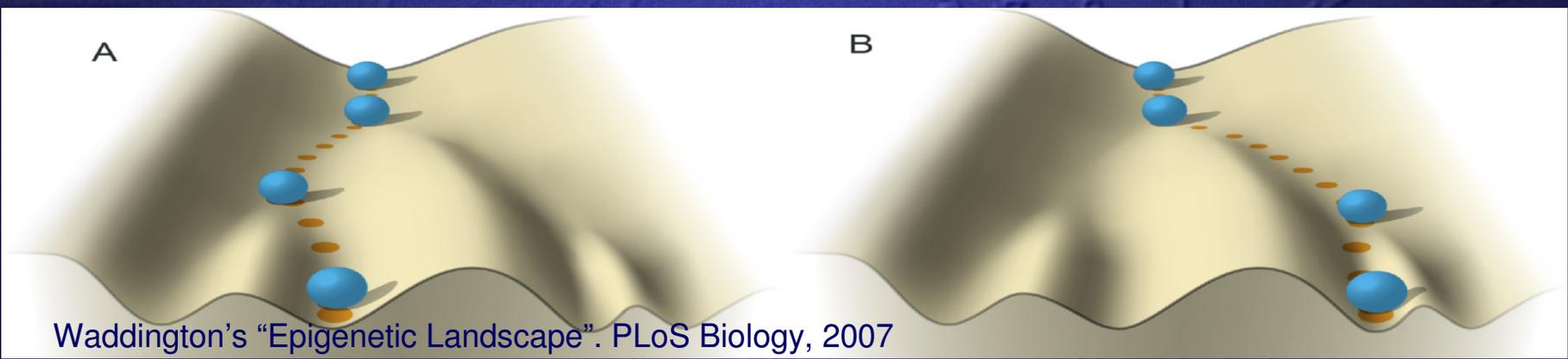
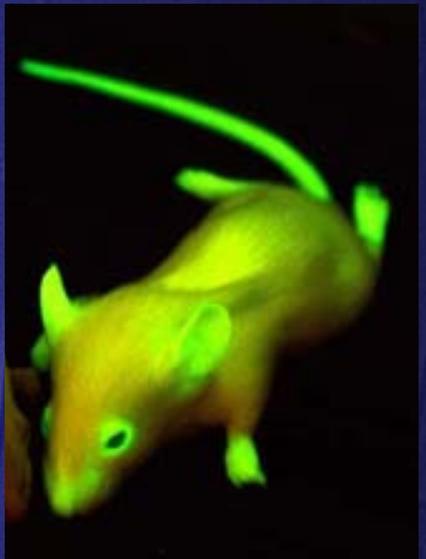
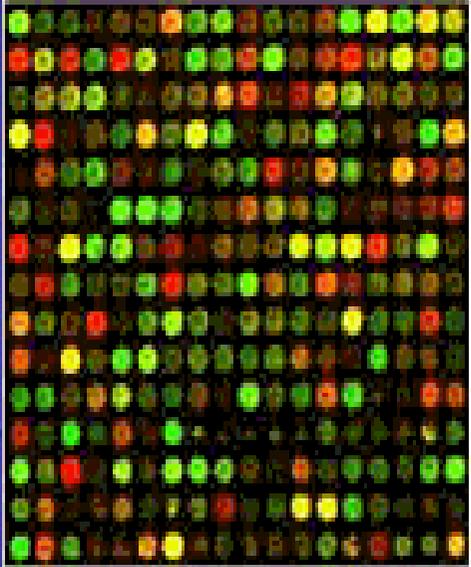
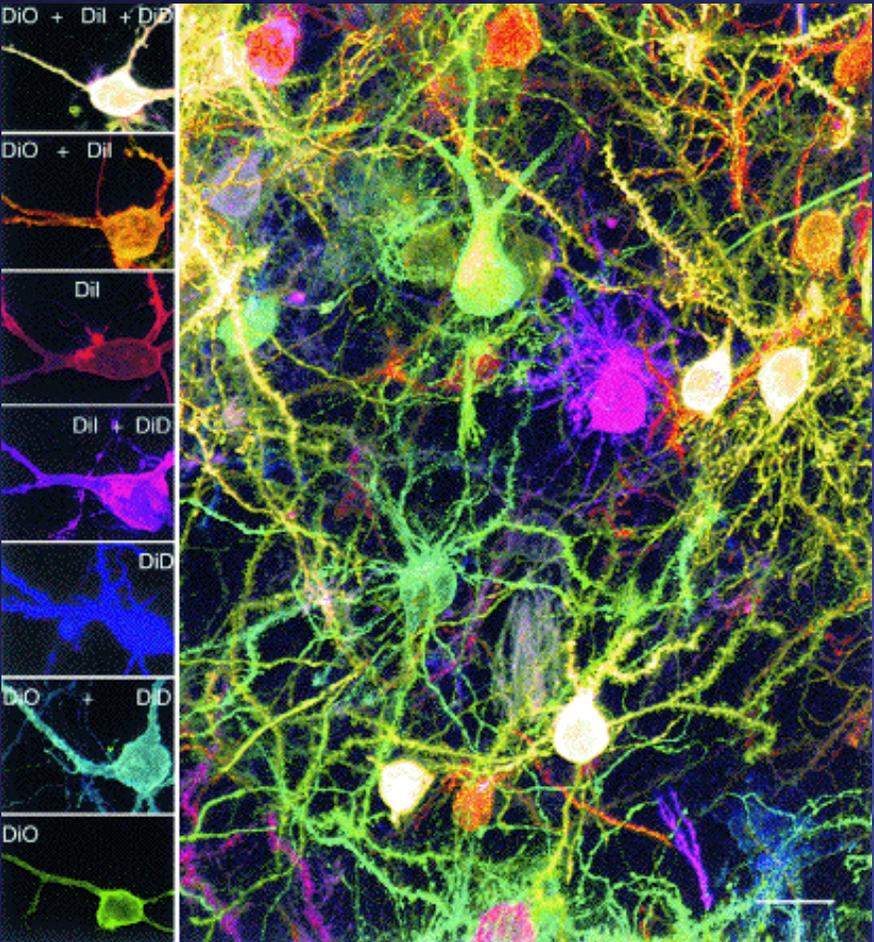


Las dendritas pueden estar o no en contacto con las placas

- ◇— Wt
- Tg Sin placas
- ▲— Tg En contacto con placas

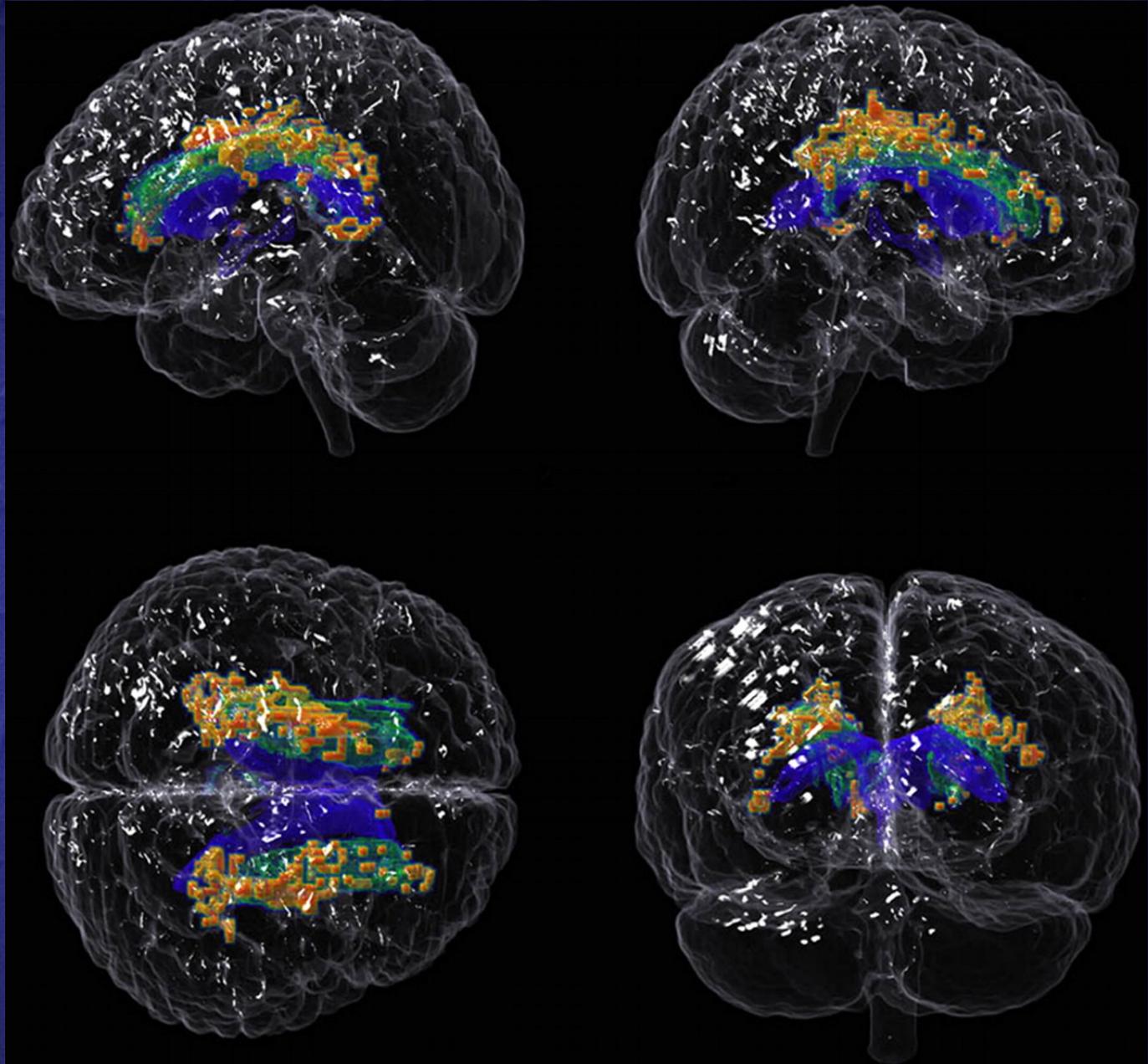


# Caracterización genética y molecular del cerebro

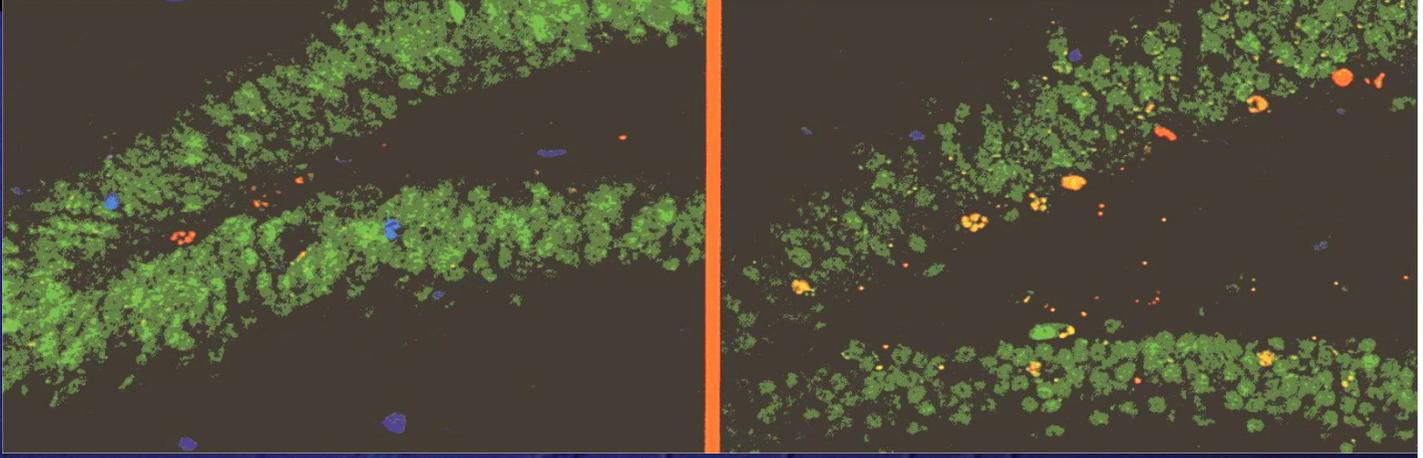
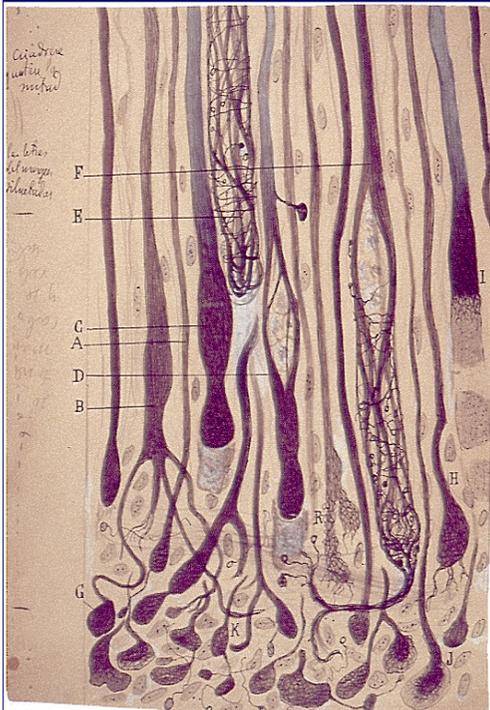
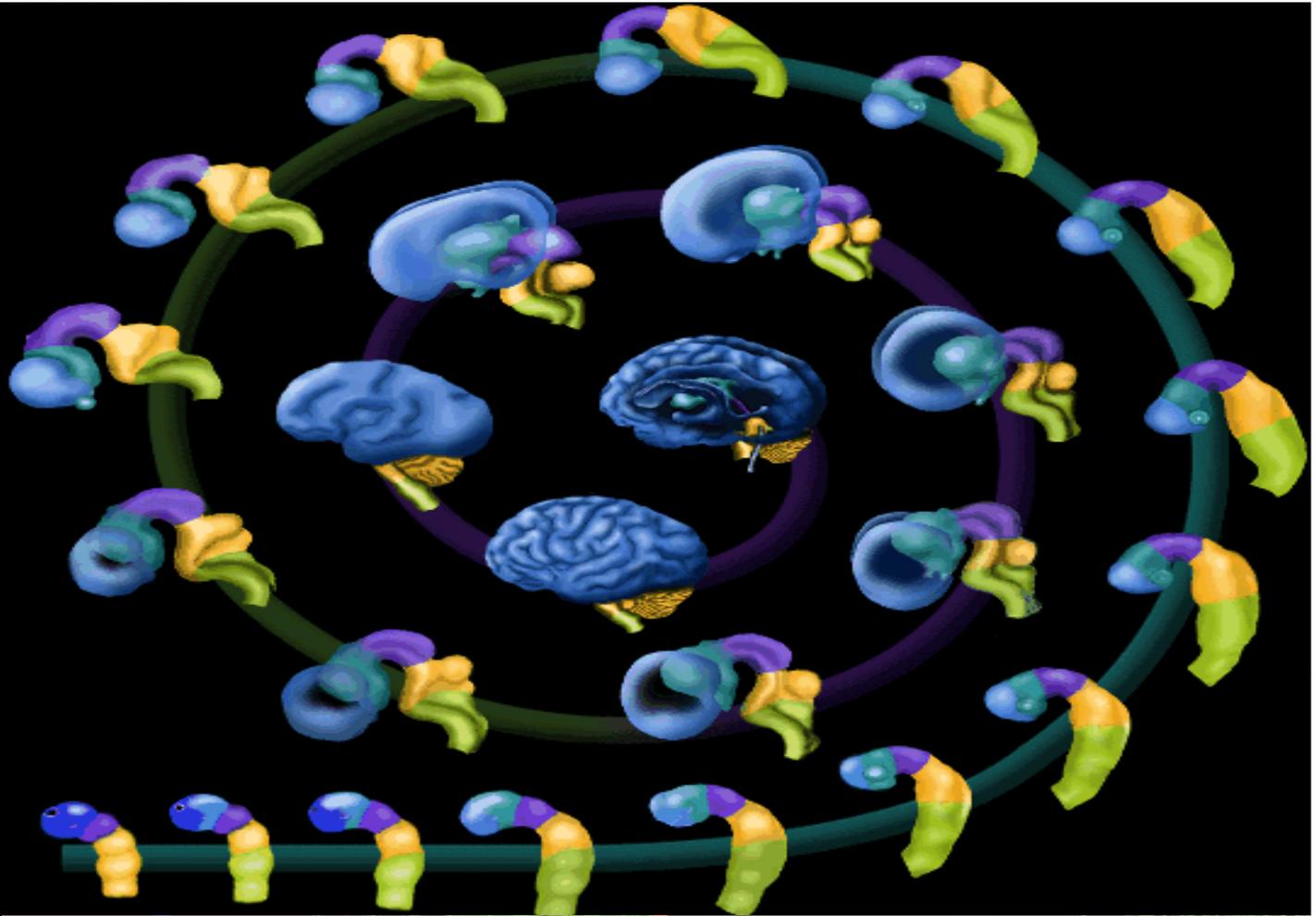


## Genes, morfología del cerebro e inteligencia

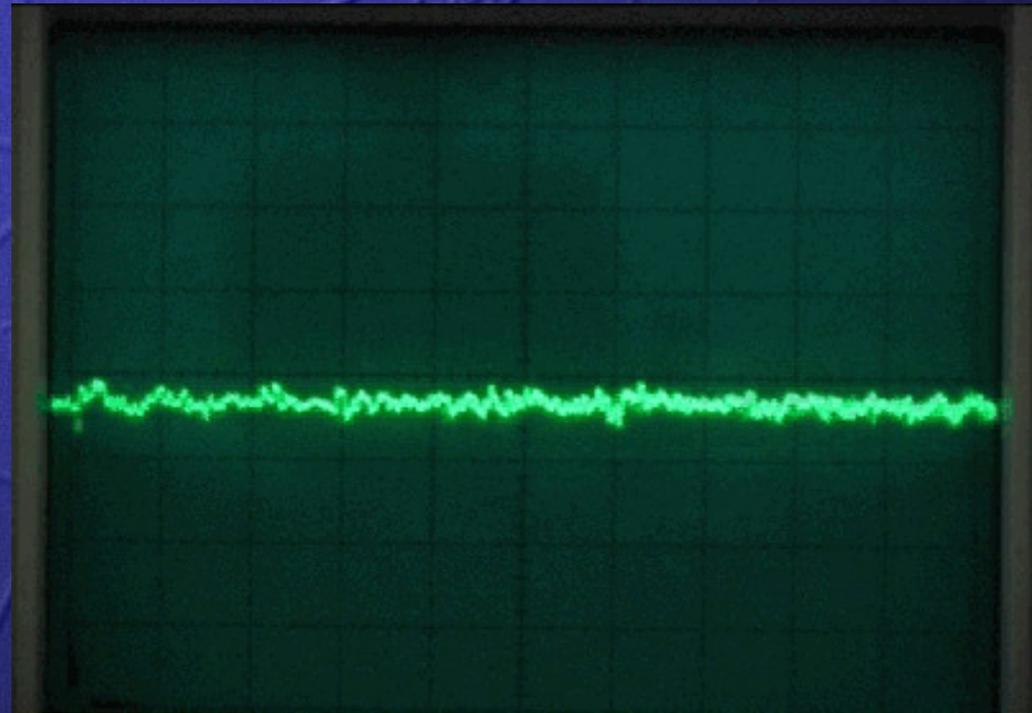
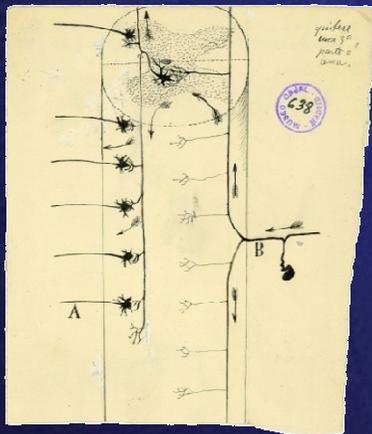
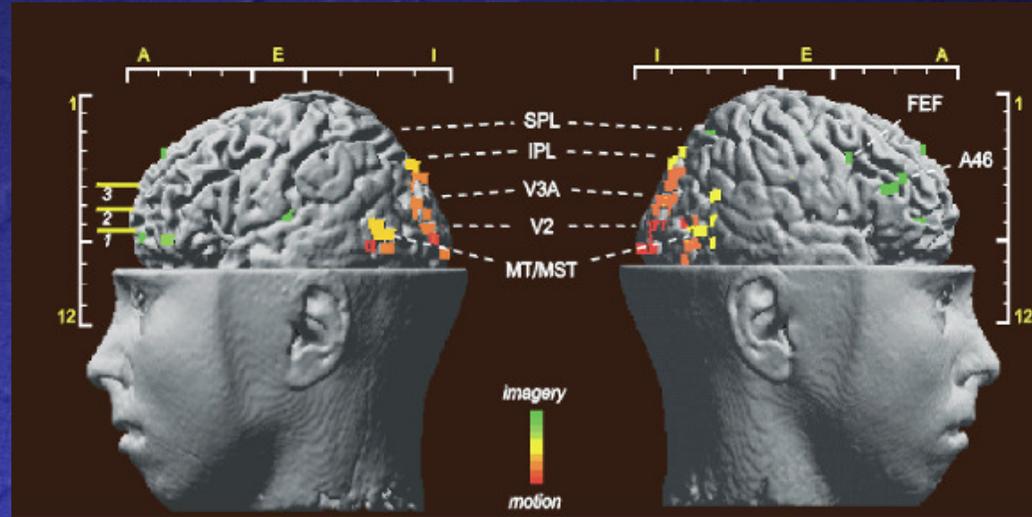
Determinación  
genética del  
cociente  
intelectual  
(VIQ/PIQ) y de la  
densidad de la red  
neural formada por  
la sustancia gris  
frontal, occipital y  
parahipocámpica



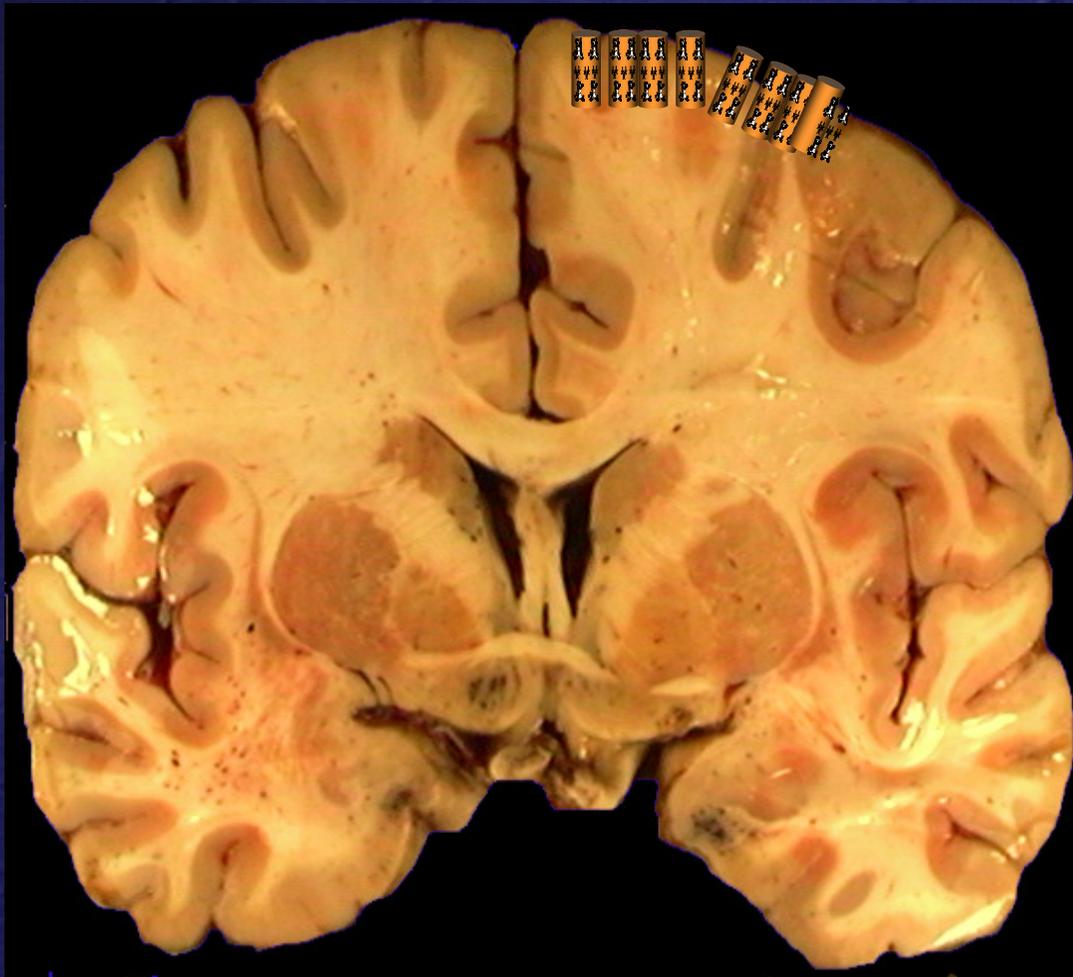
# Desarrollo y regeneración del cerebro



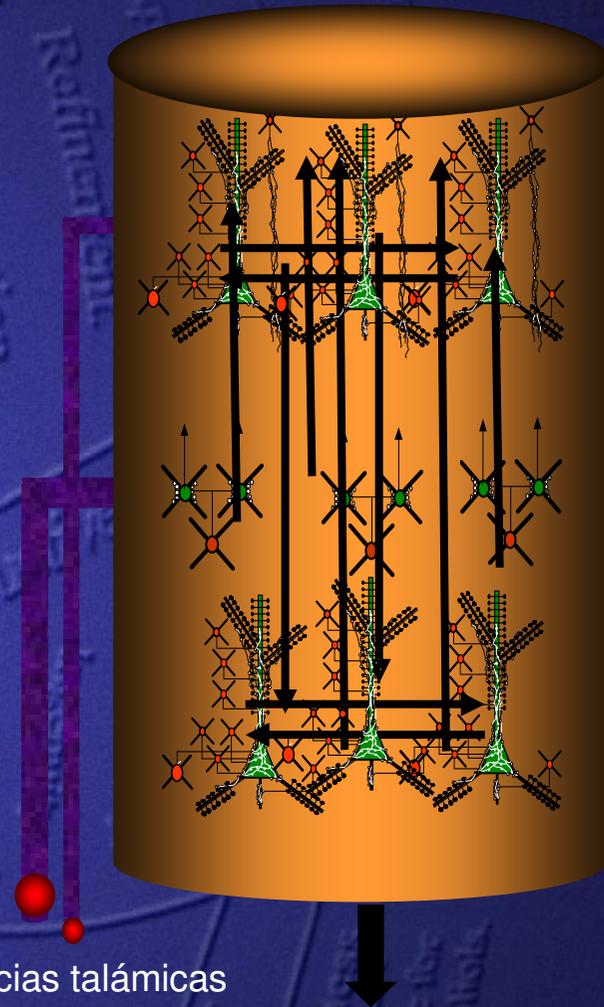
# Características funcionales de los circuitos neurales



# Circuitos corticales



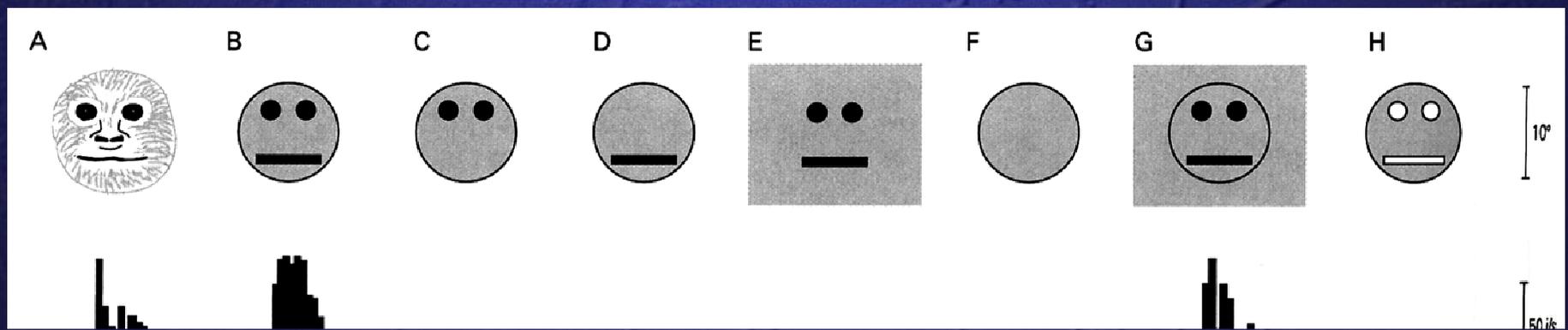
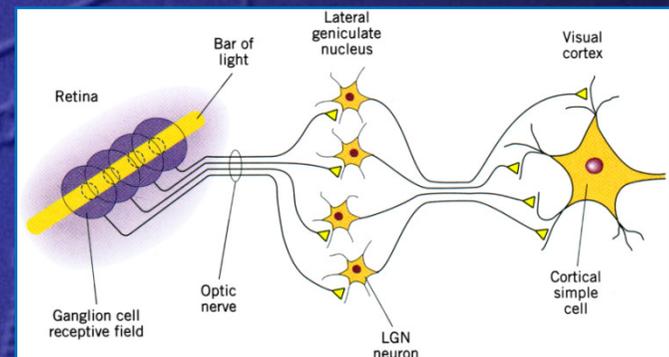
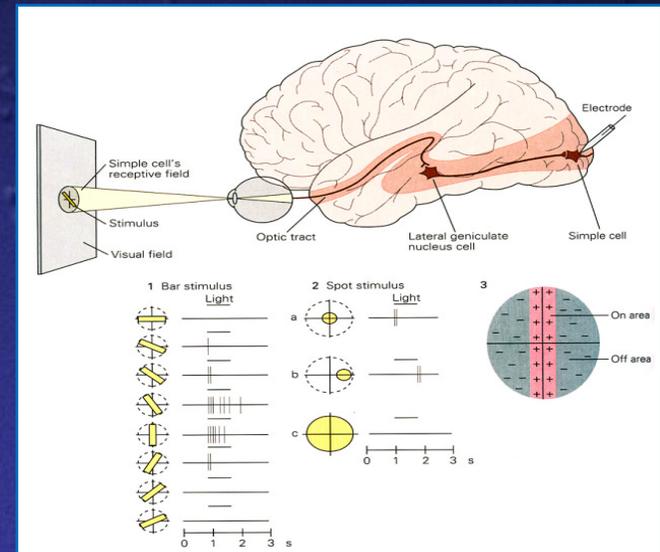
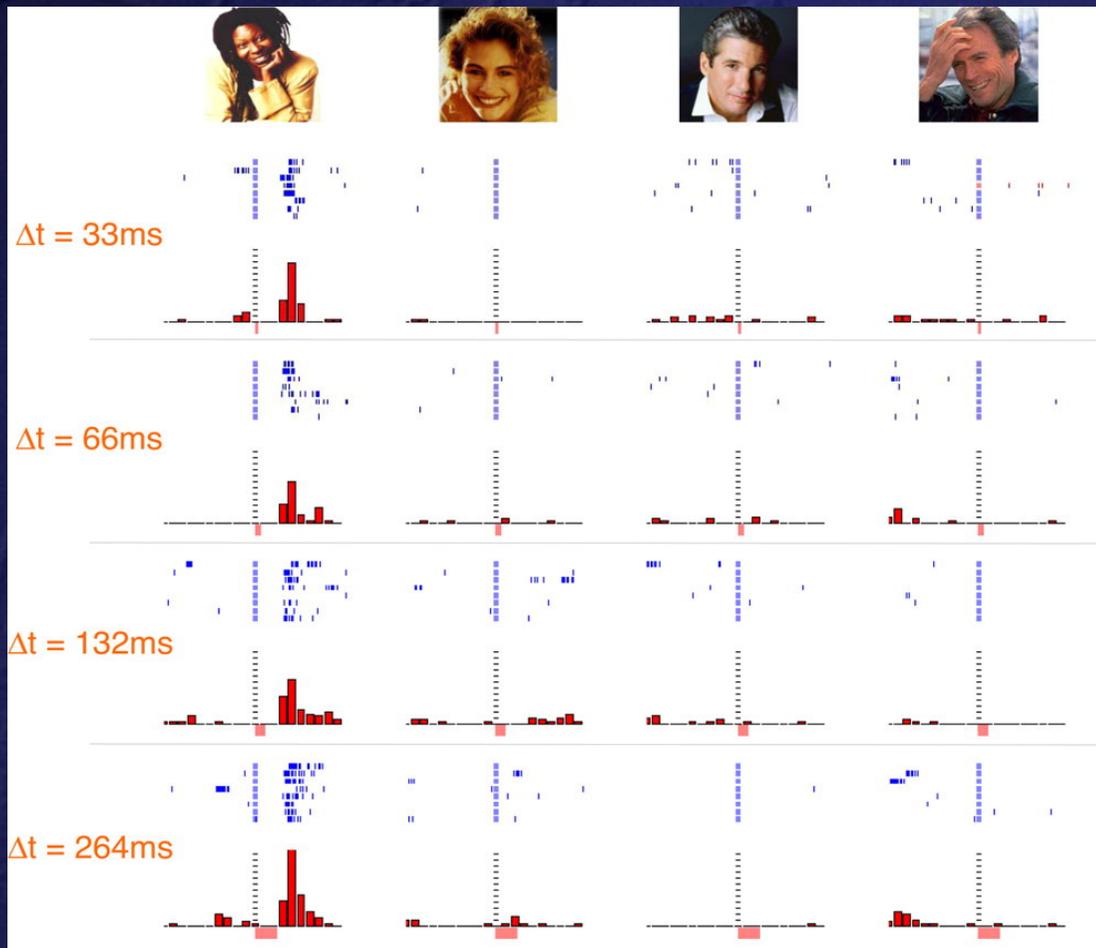
## Macrocolumna cortical



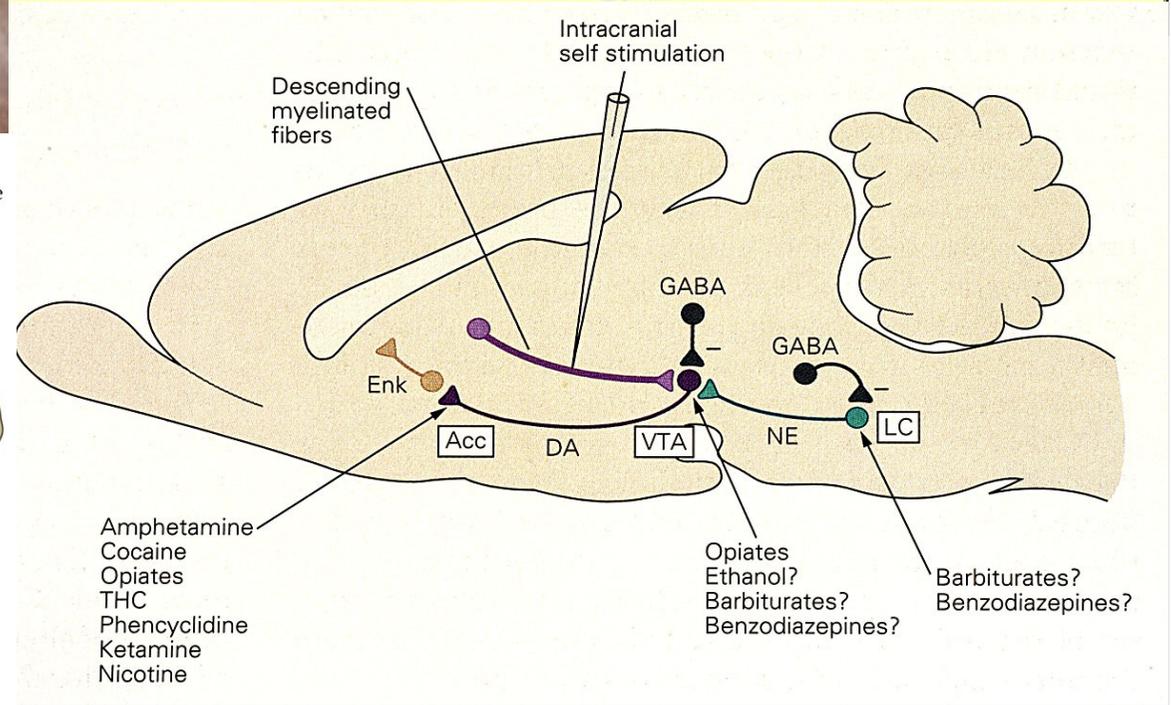
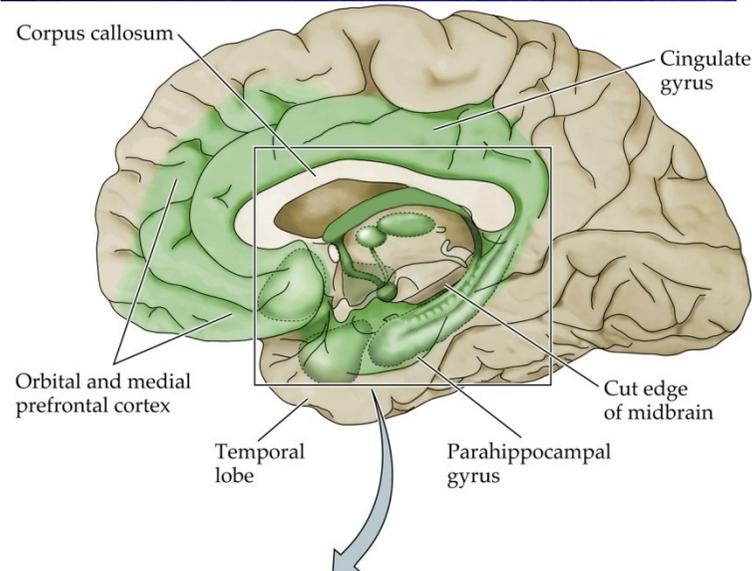
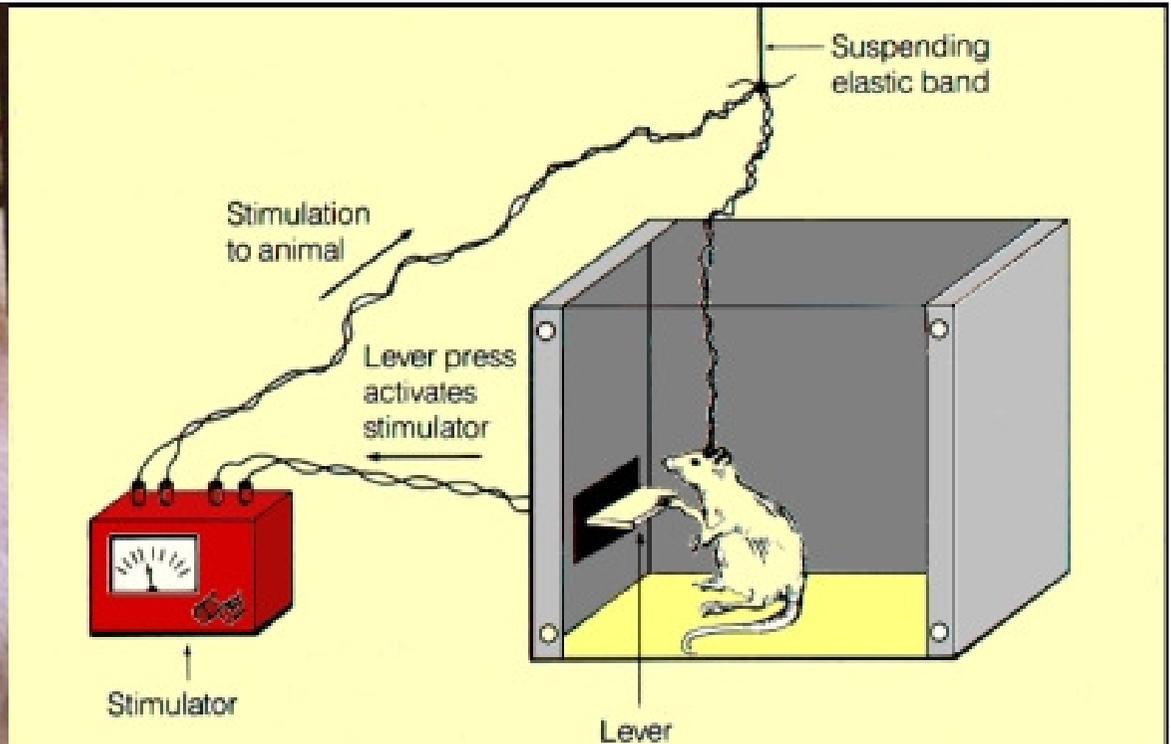
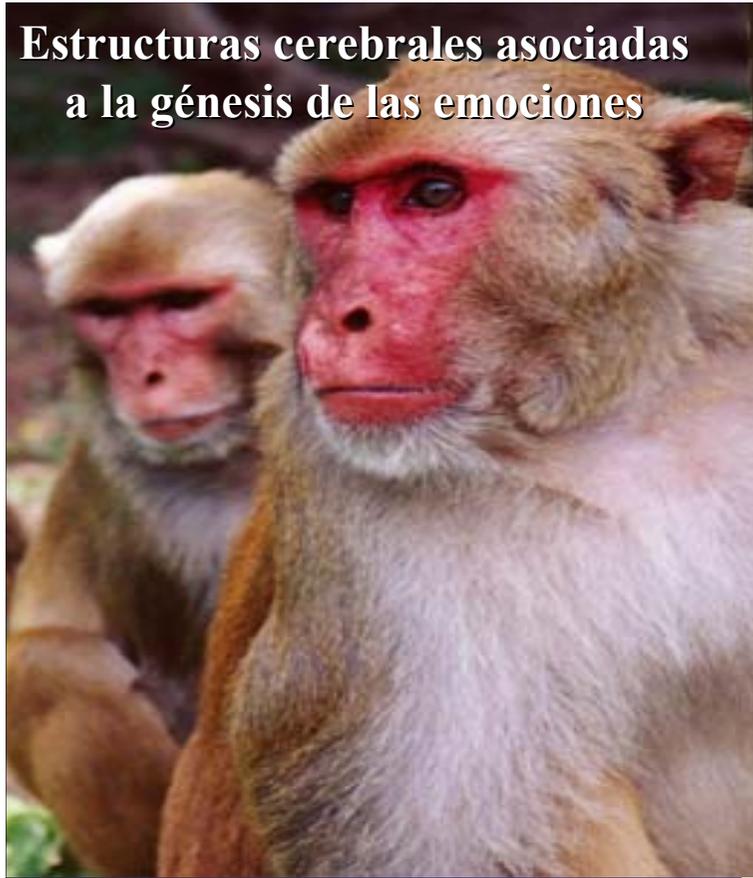
La corteza cerebral se compone de multiples microcircuitos que se repiten en cada columna cortical

Cortesía de J. de Felipe

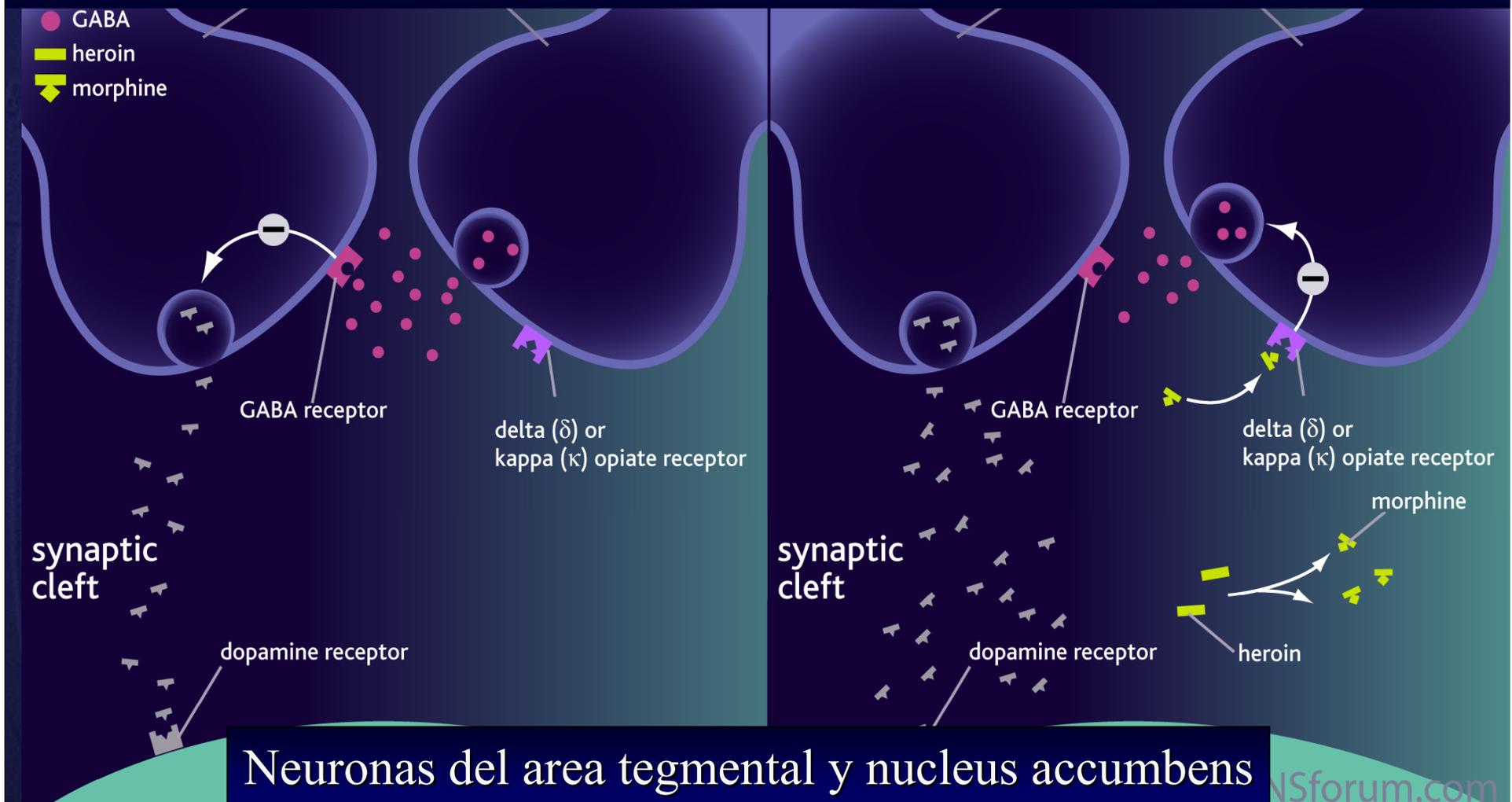
Aferencias talámicas



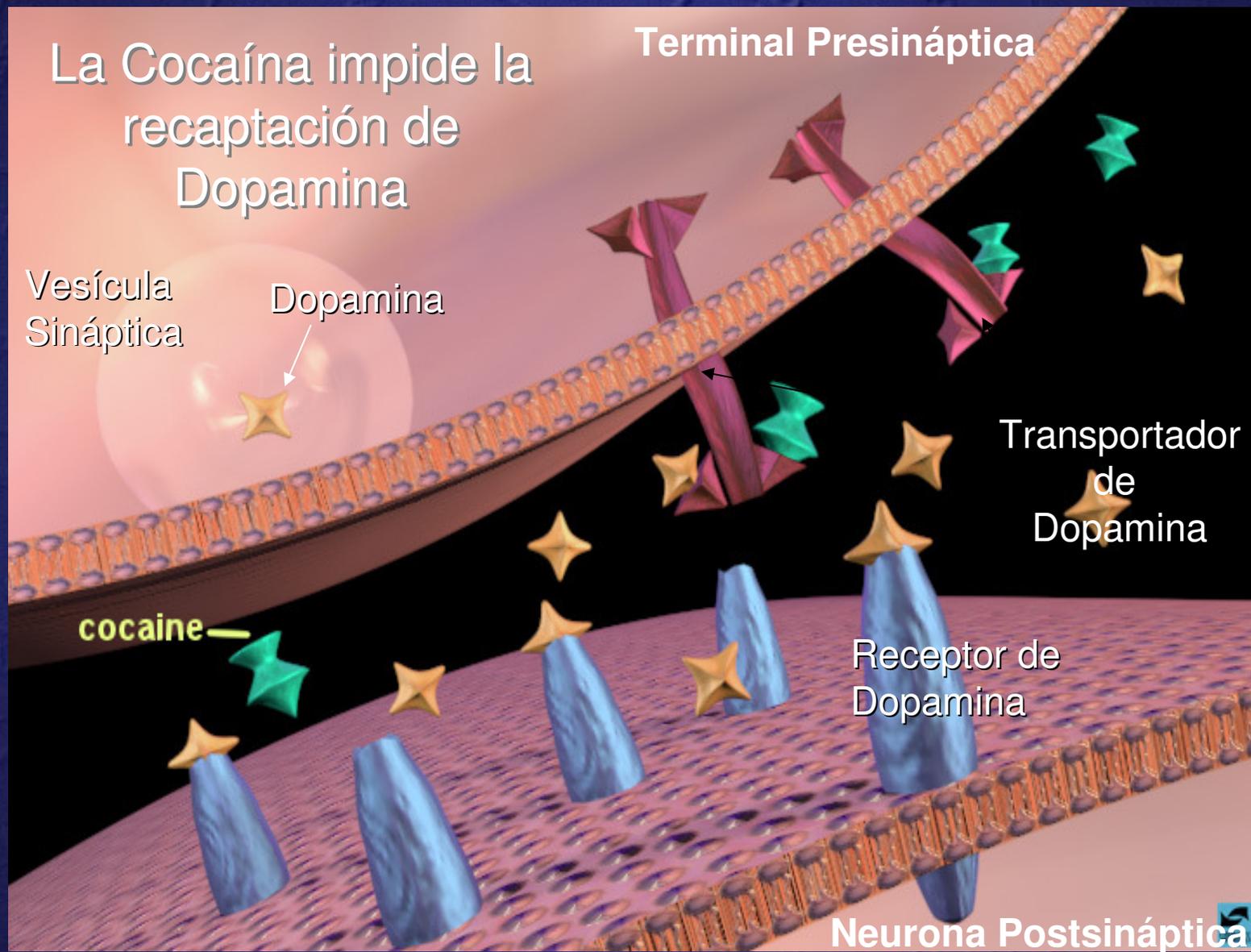
# Estructuras cerebrales asociadas a la génesis de las emociones



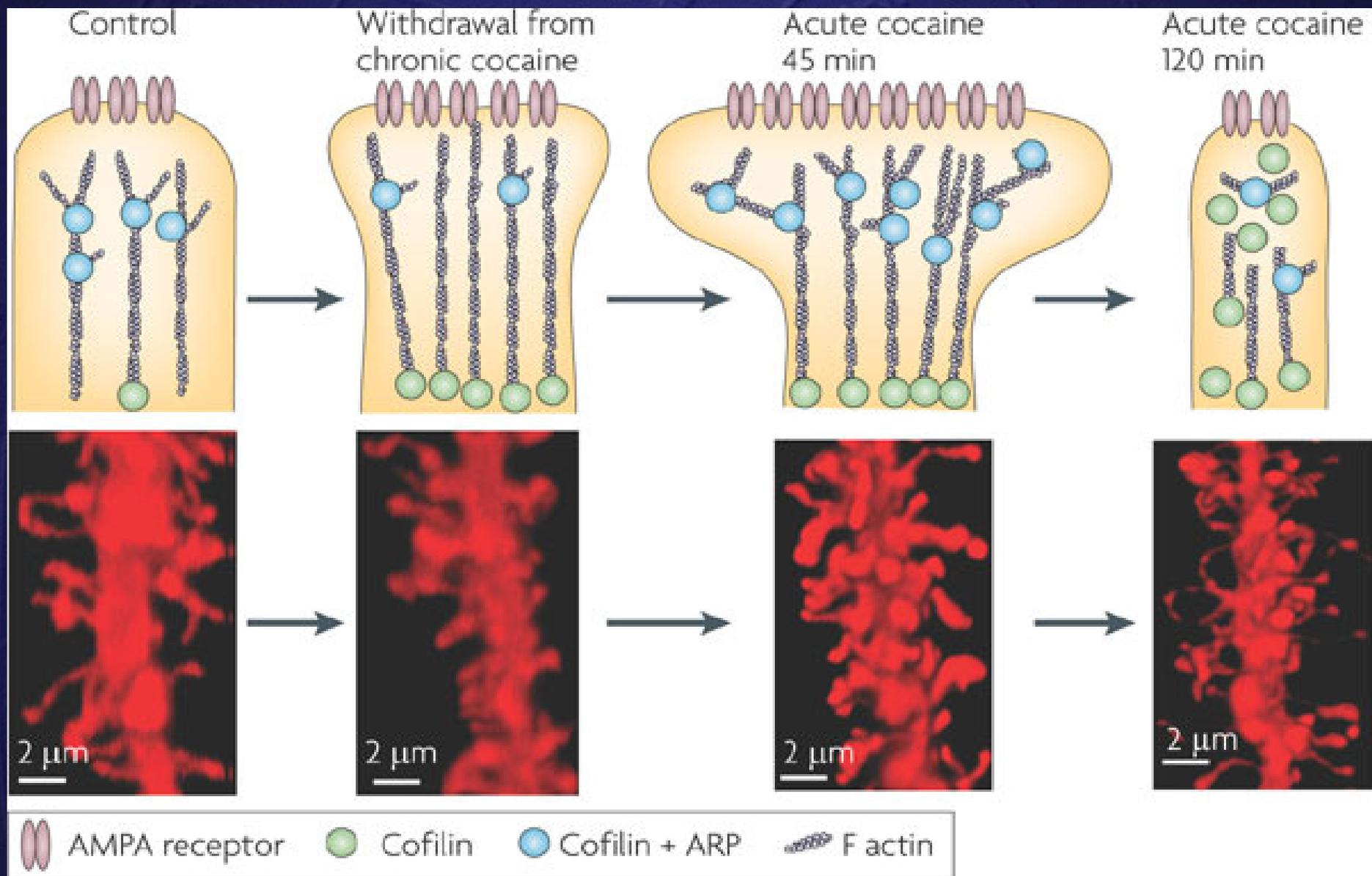
# Los opioides endógenos actúan sobre los receptores opioides delta ( $\delta$ ) y kappa ( $\kappa$ ) y mu ( $\mu$ ) e inhiben a los receptores GABA, que frenan la secreción de DA. La morfina y la heroína, mimetizan este efecto



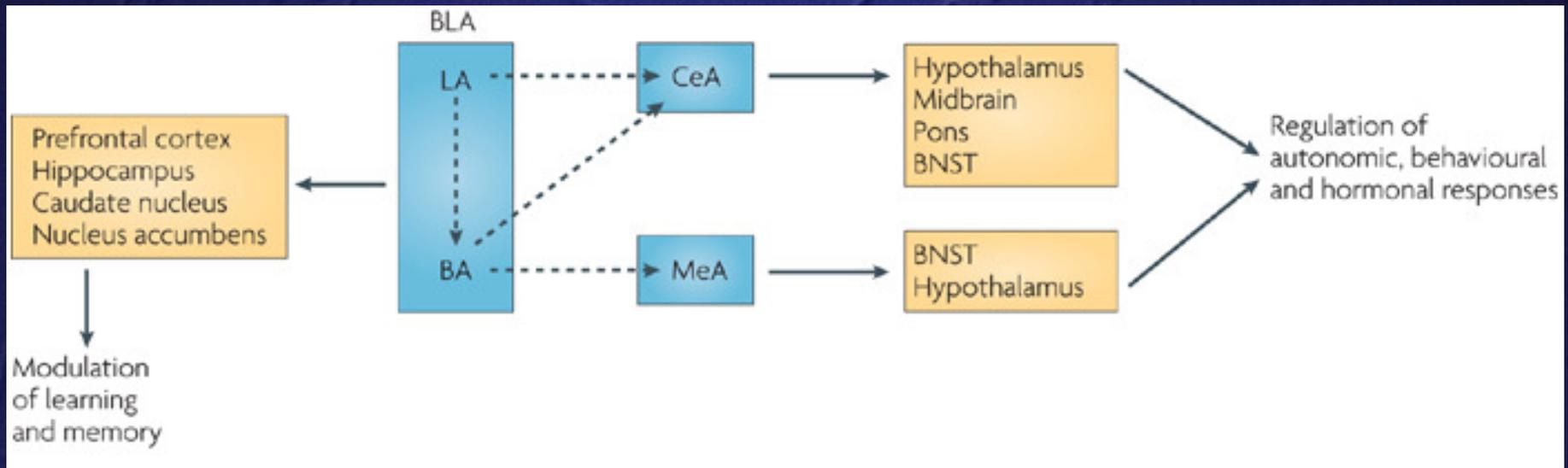
## Las drogas de abuso actúan sobre la sinapsis



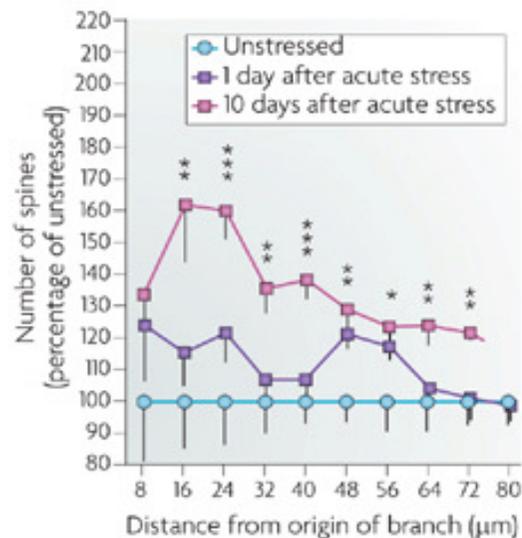
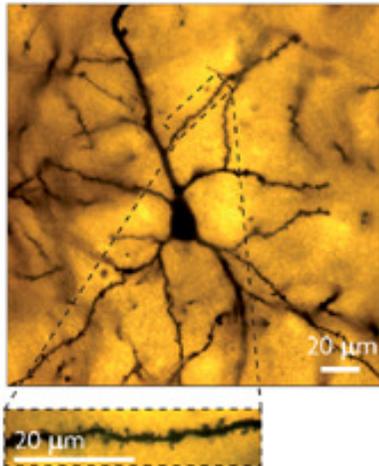
# Efectos sinápticos de la administración crónica de cocaína



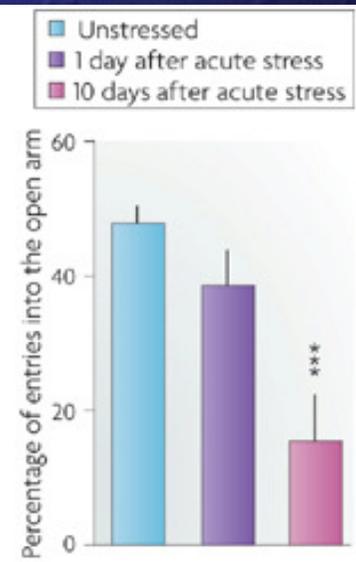
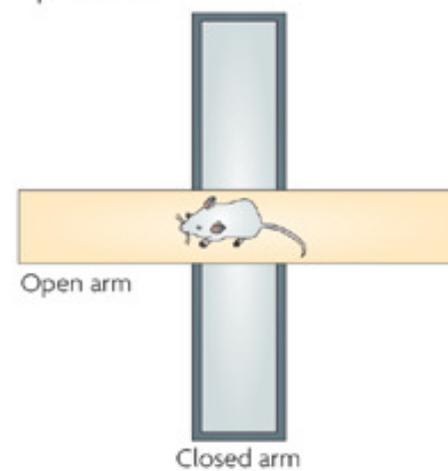
# Consolidación de las memorias por el estrés



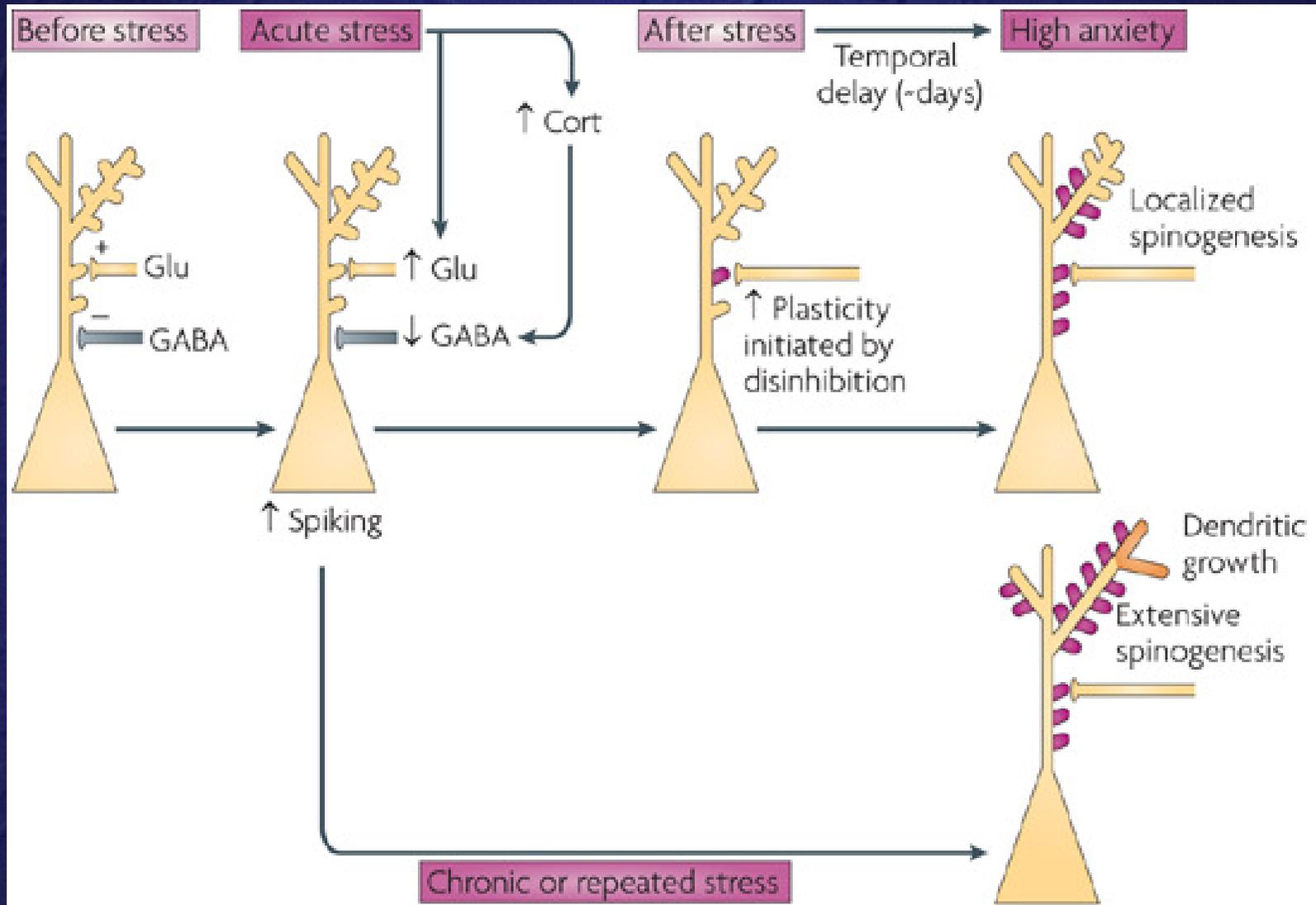
**a** A Golgi-stained pyramidal neuron in the BLA



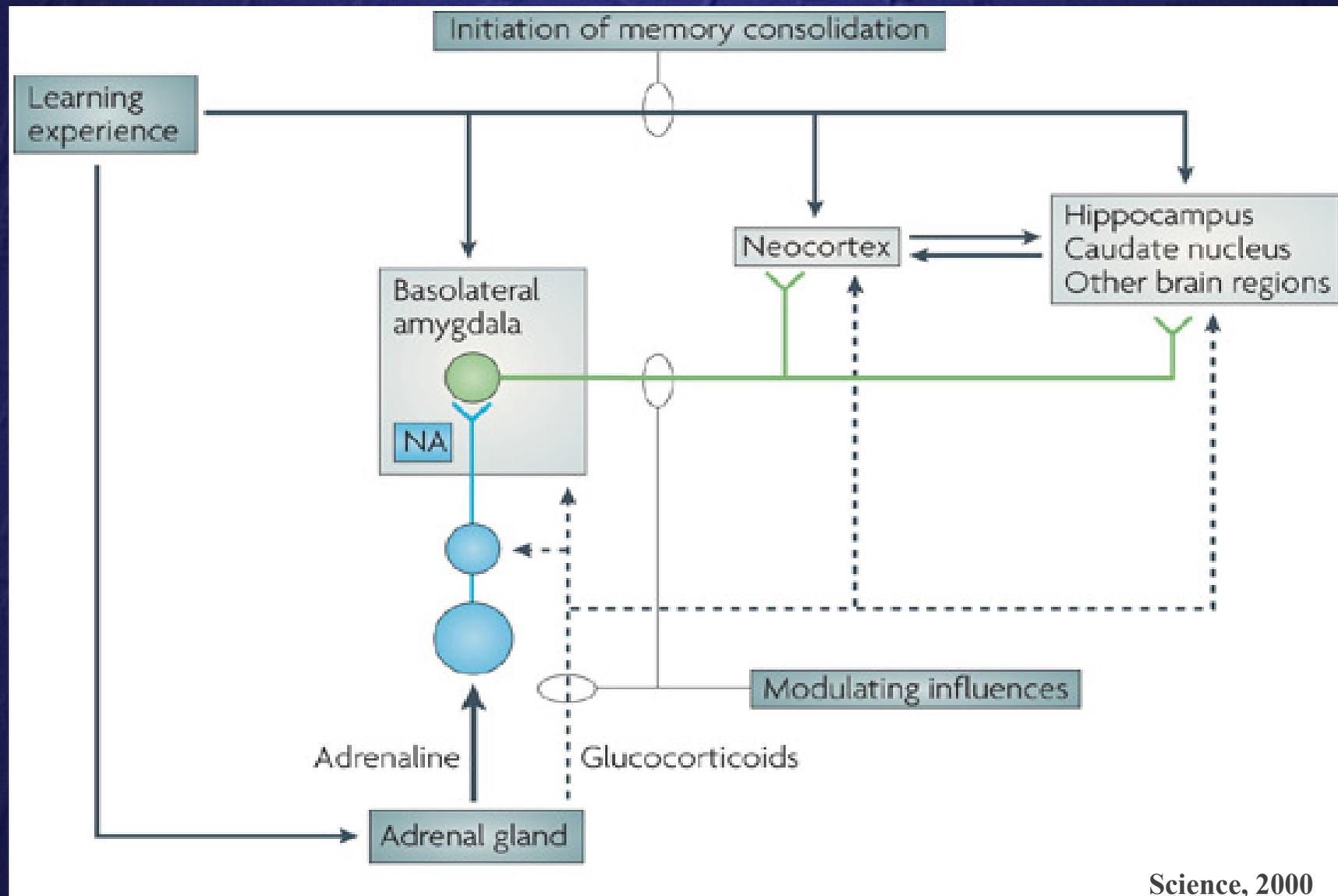
**b** Anxiety-like behaviour on an elevated plus maze



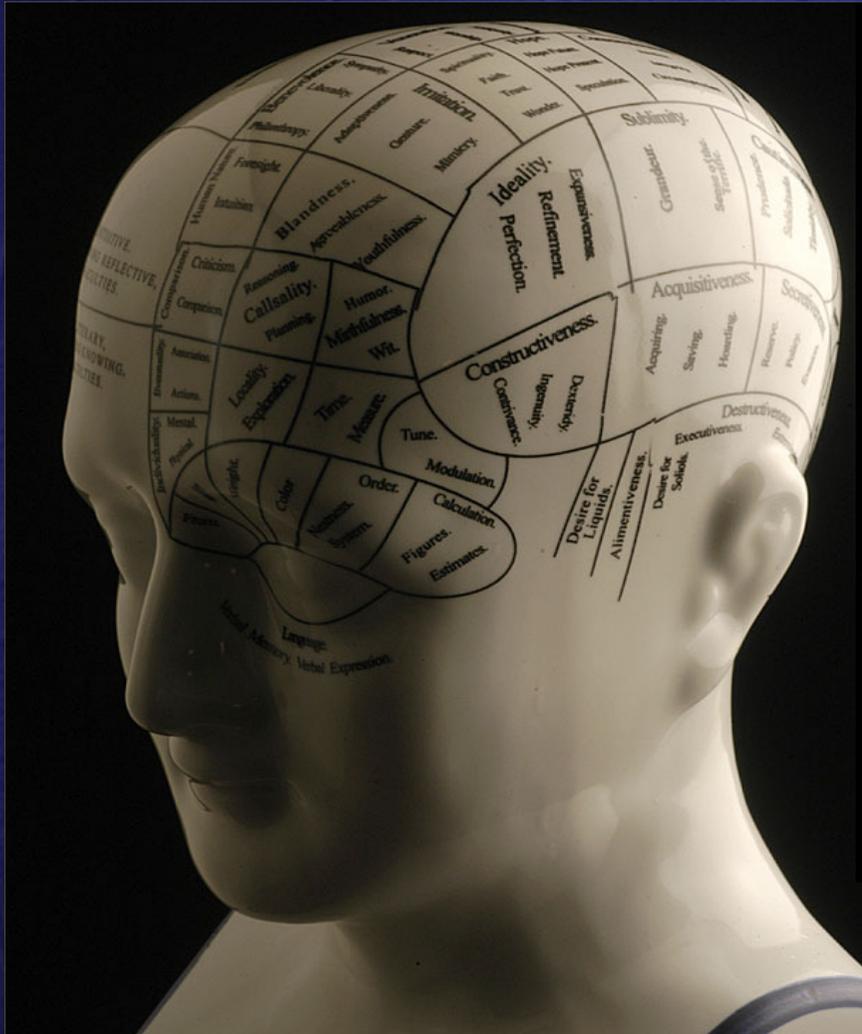
# Mecanismo de consolidación de las memorias por el estrés



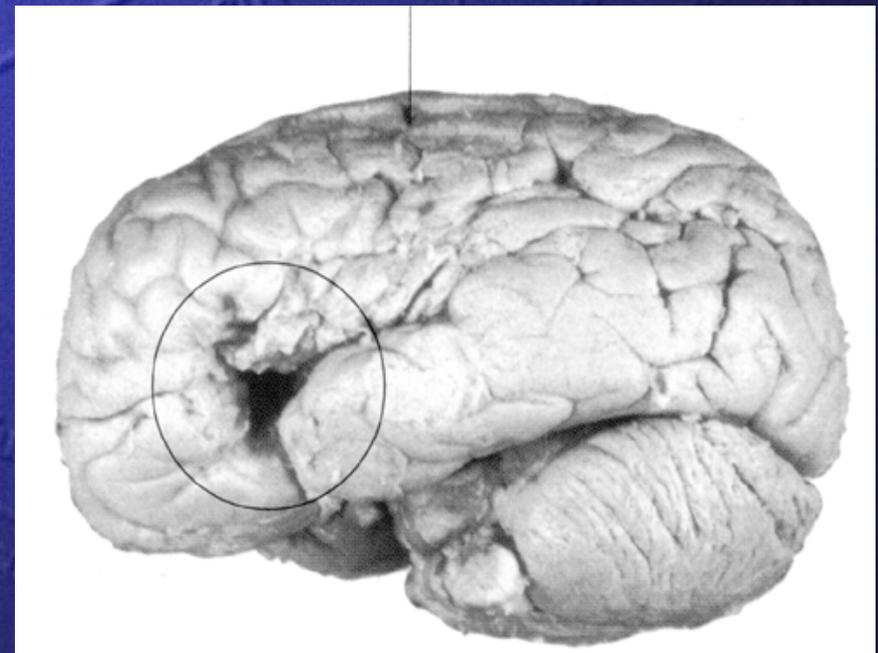
# Modulación de la consolidación de la memoria por la emoción



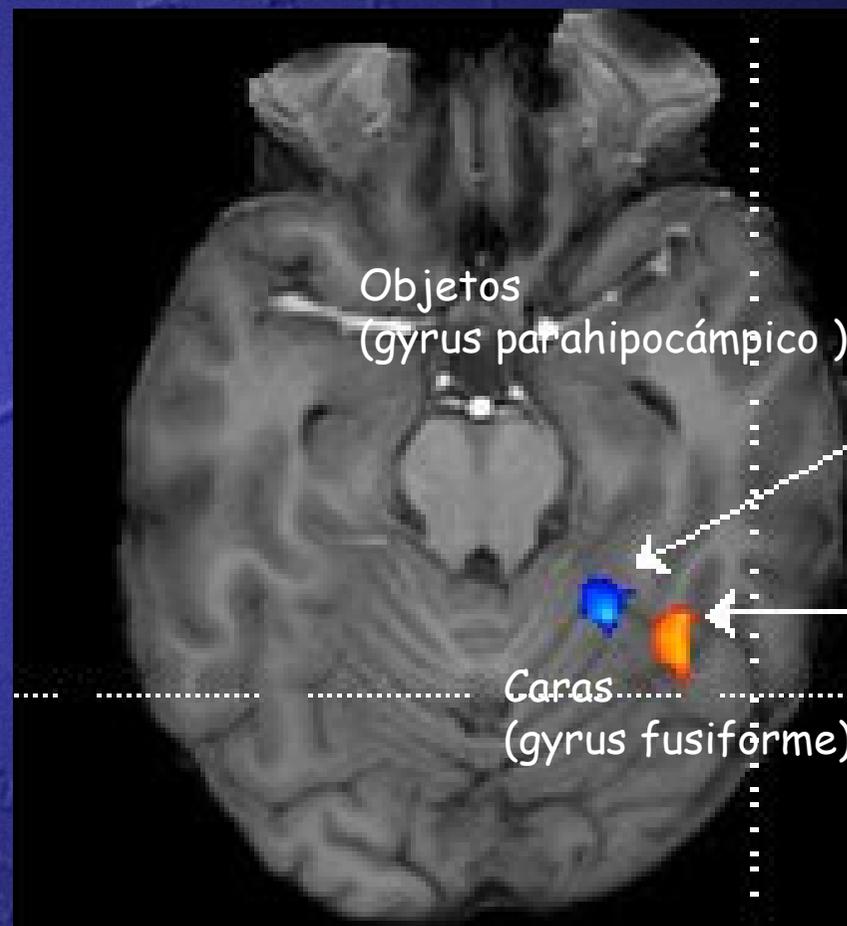
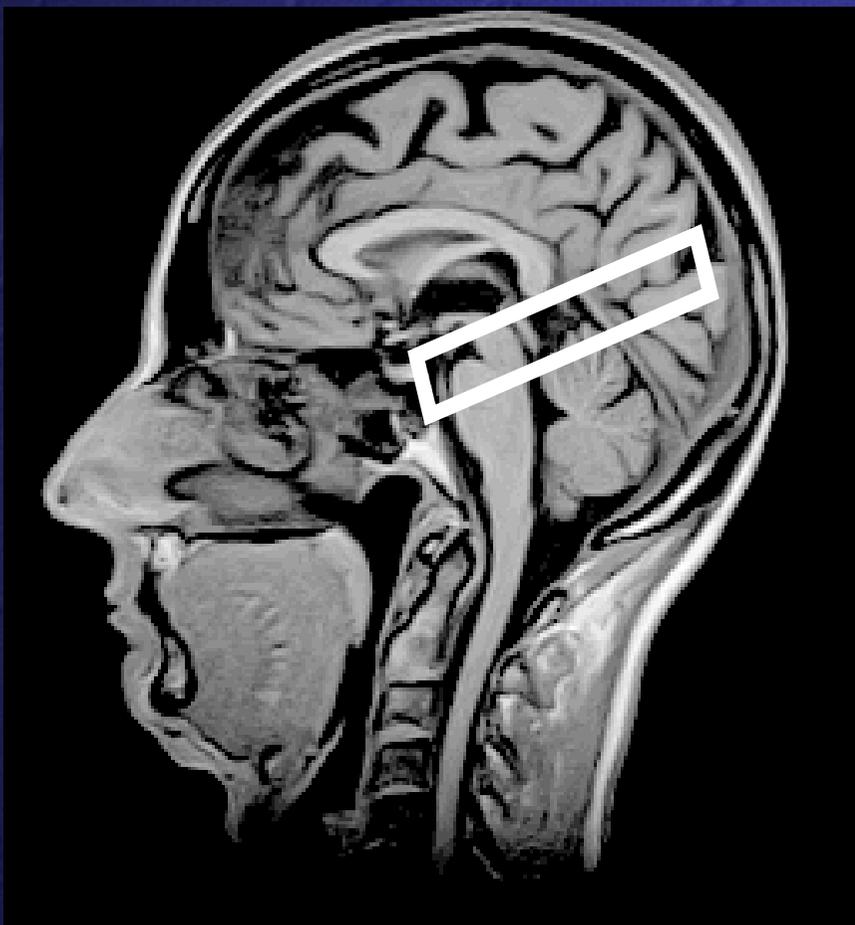
# La patología cerebral como método de estudio del cerebro



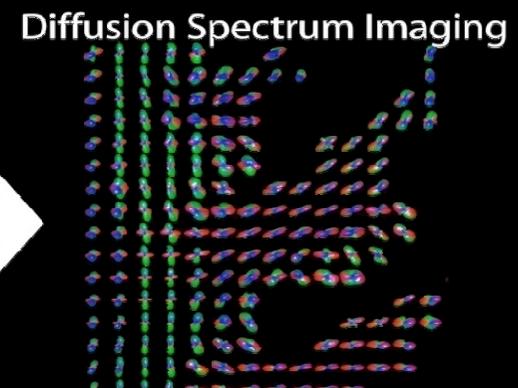
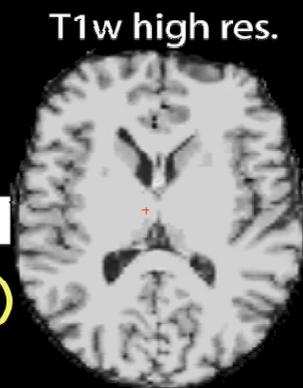
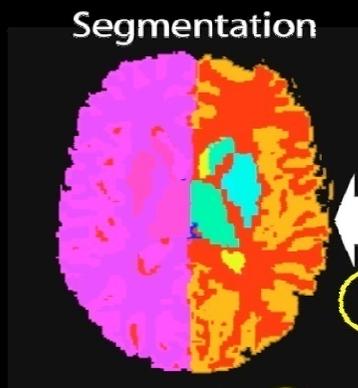
Phineas P. Gage



# Correlación estructura-función: La imagen cerebral



# Técnicas de imagen cerebral



2

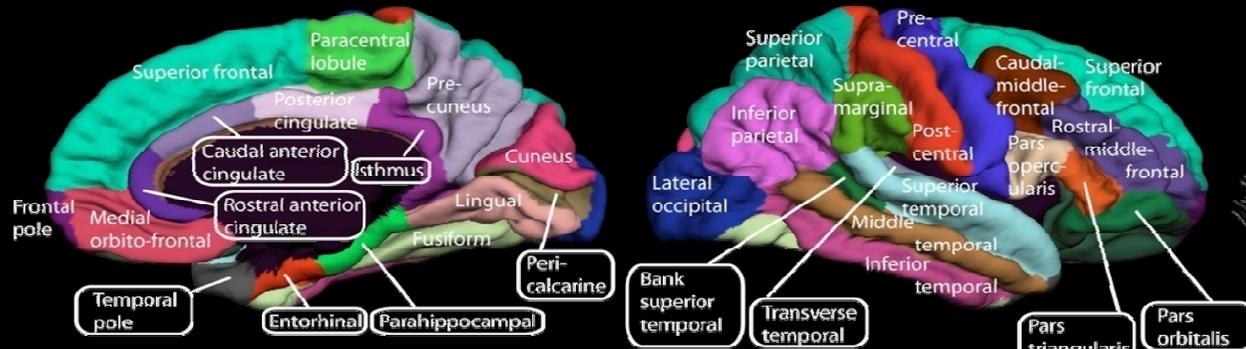
1

3a

4

Partition into 66 anatomical subregions

Tractography

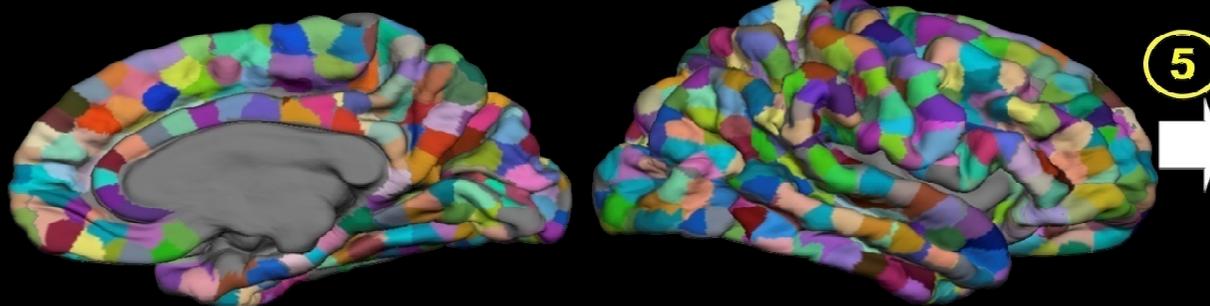


3b

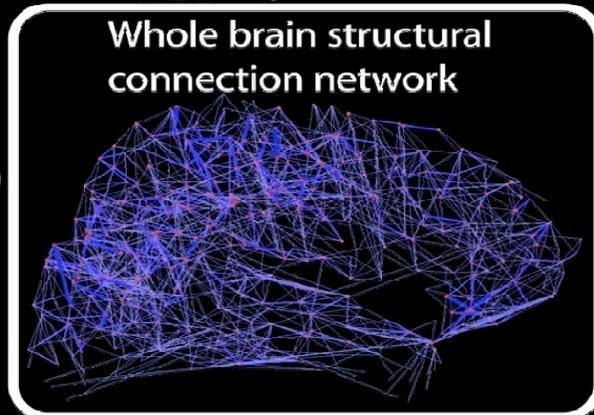
5

Partition into 1000 ROIs

Whole brain structural connection network

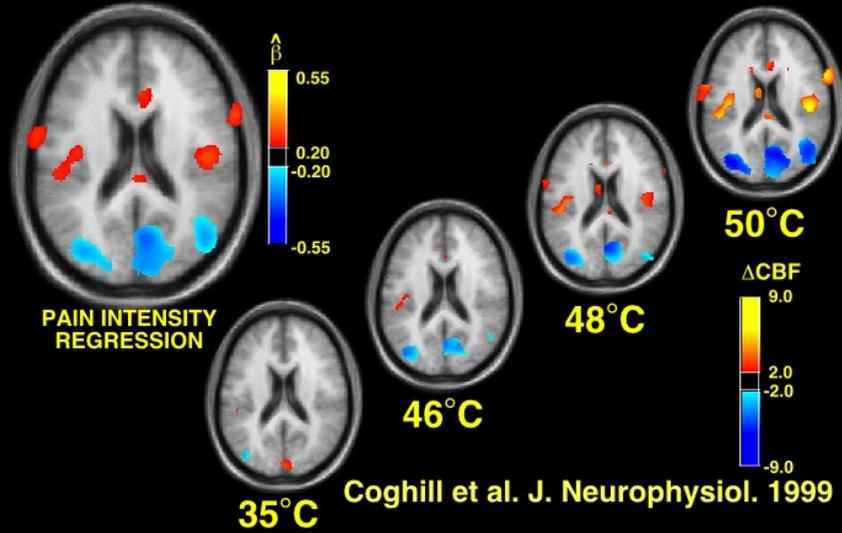


5

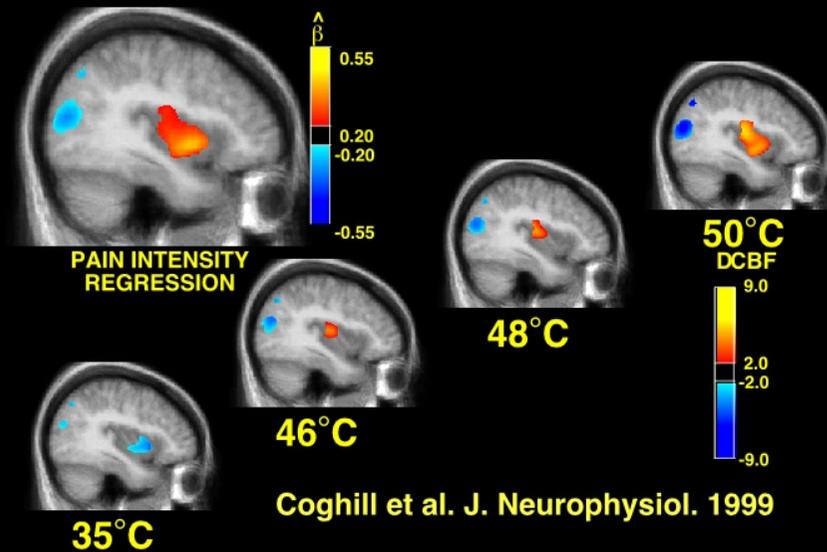


# Activación cortical por el dolor

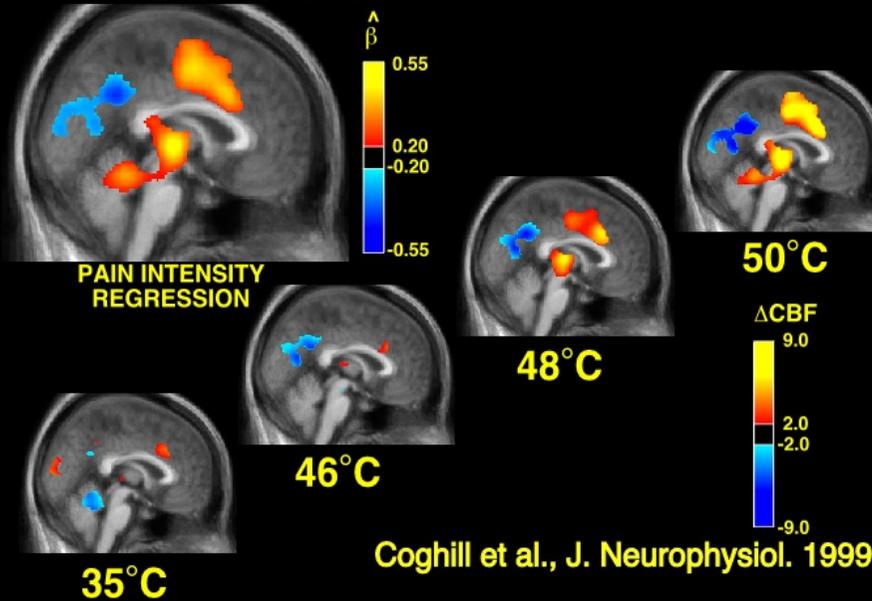
## SECONDARY SOMATOSENSORY CORTEX



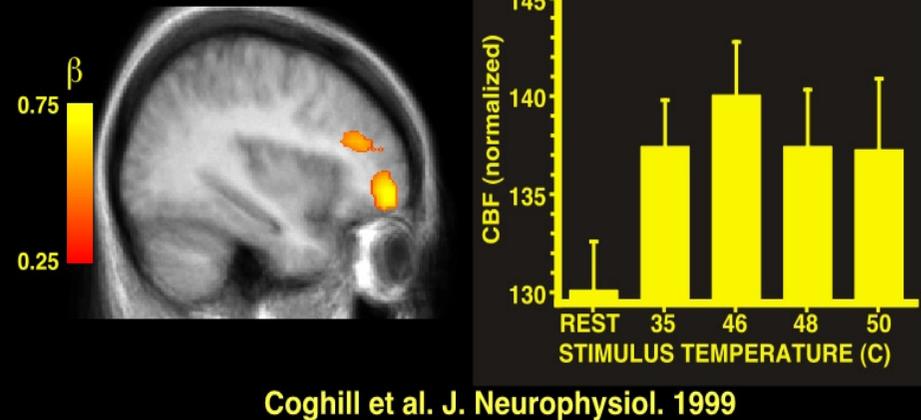
## INSULAR CORTEX

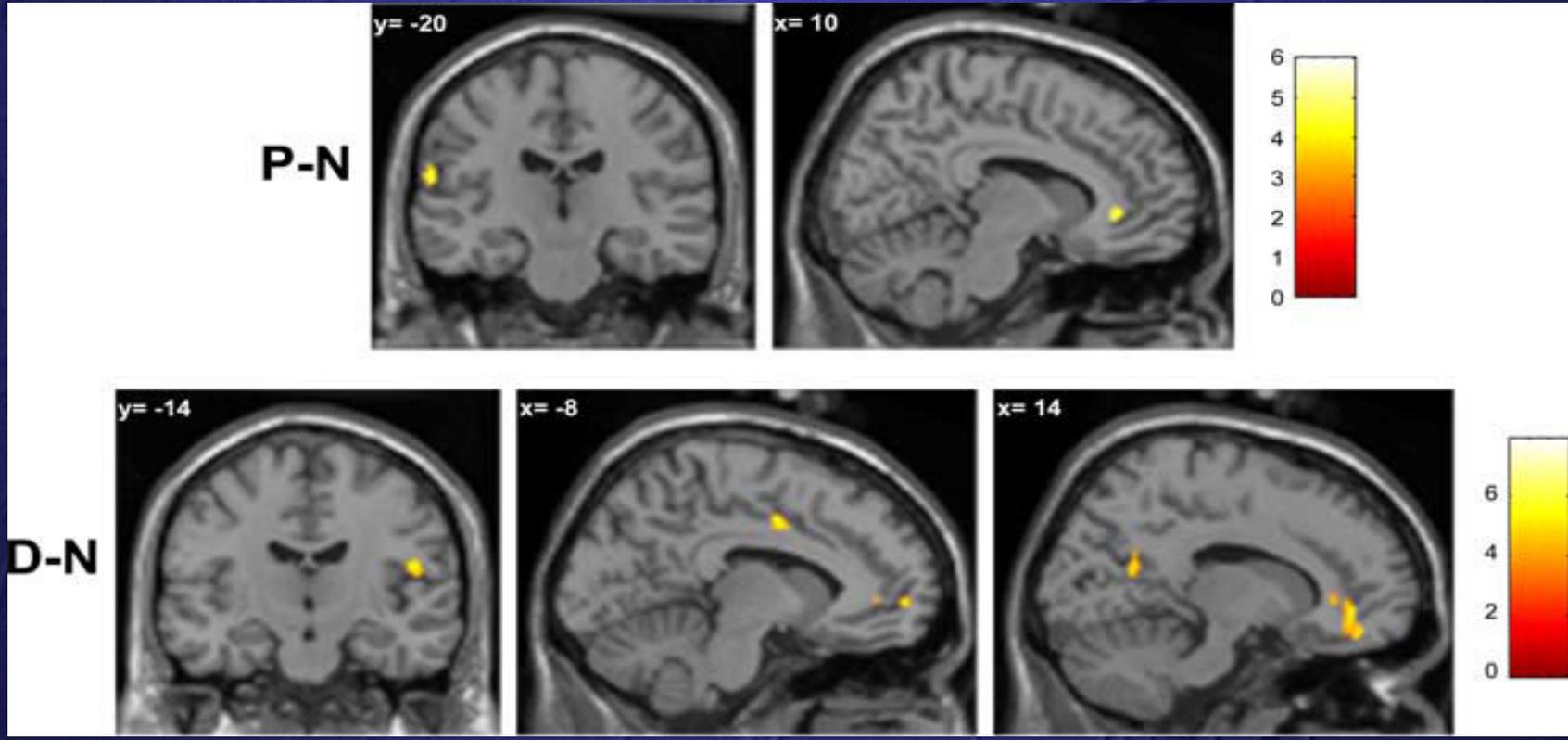


## ANTERIOR CINGULATE CORTEX



## PREFRONTAL CORTEX





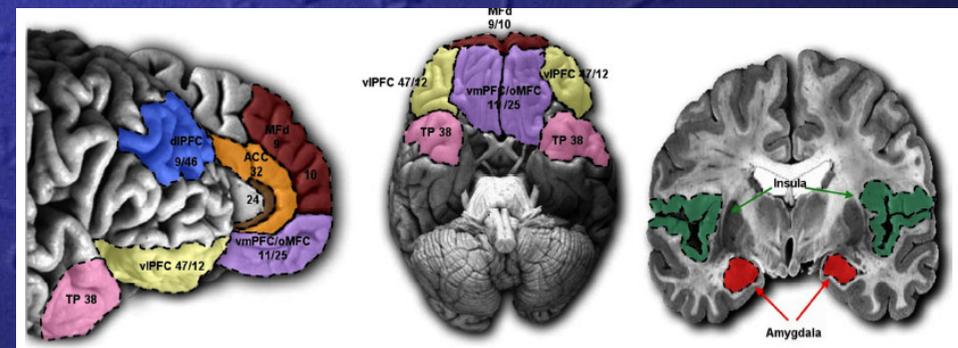
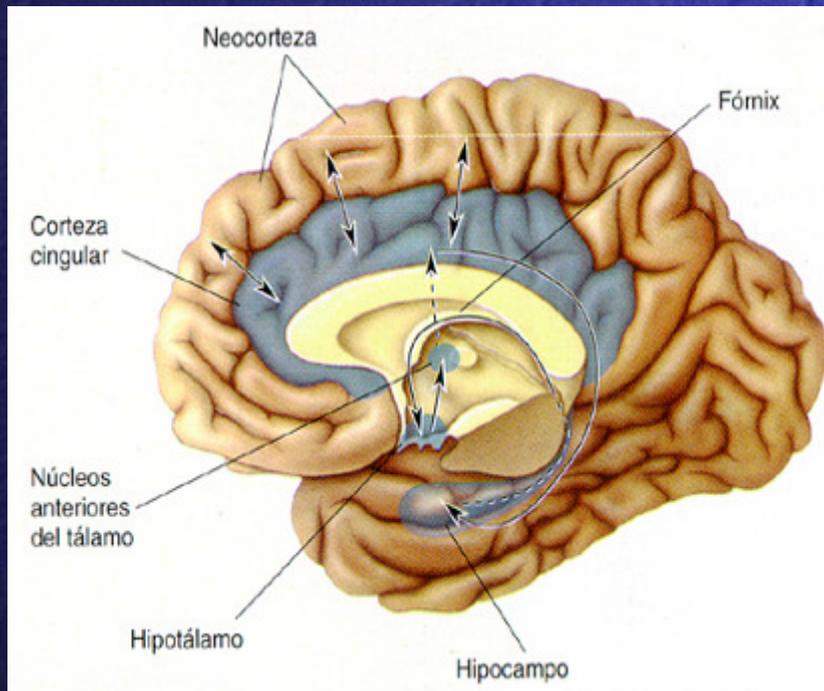
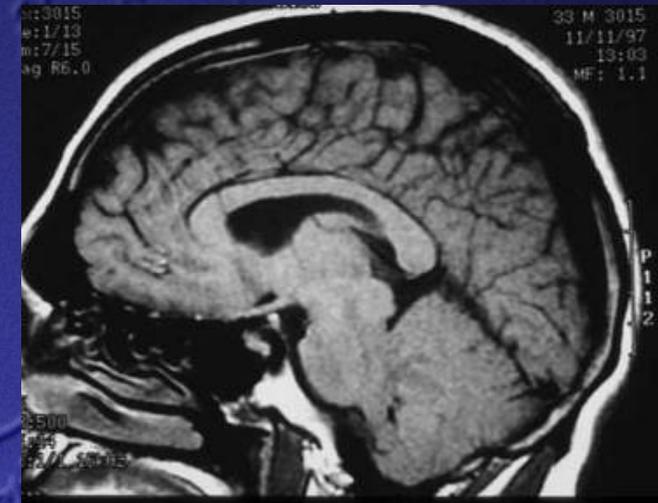
# Áreas cerebrales implicadas en las conductas sociales

## Región cerebral

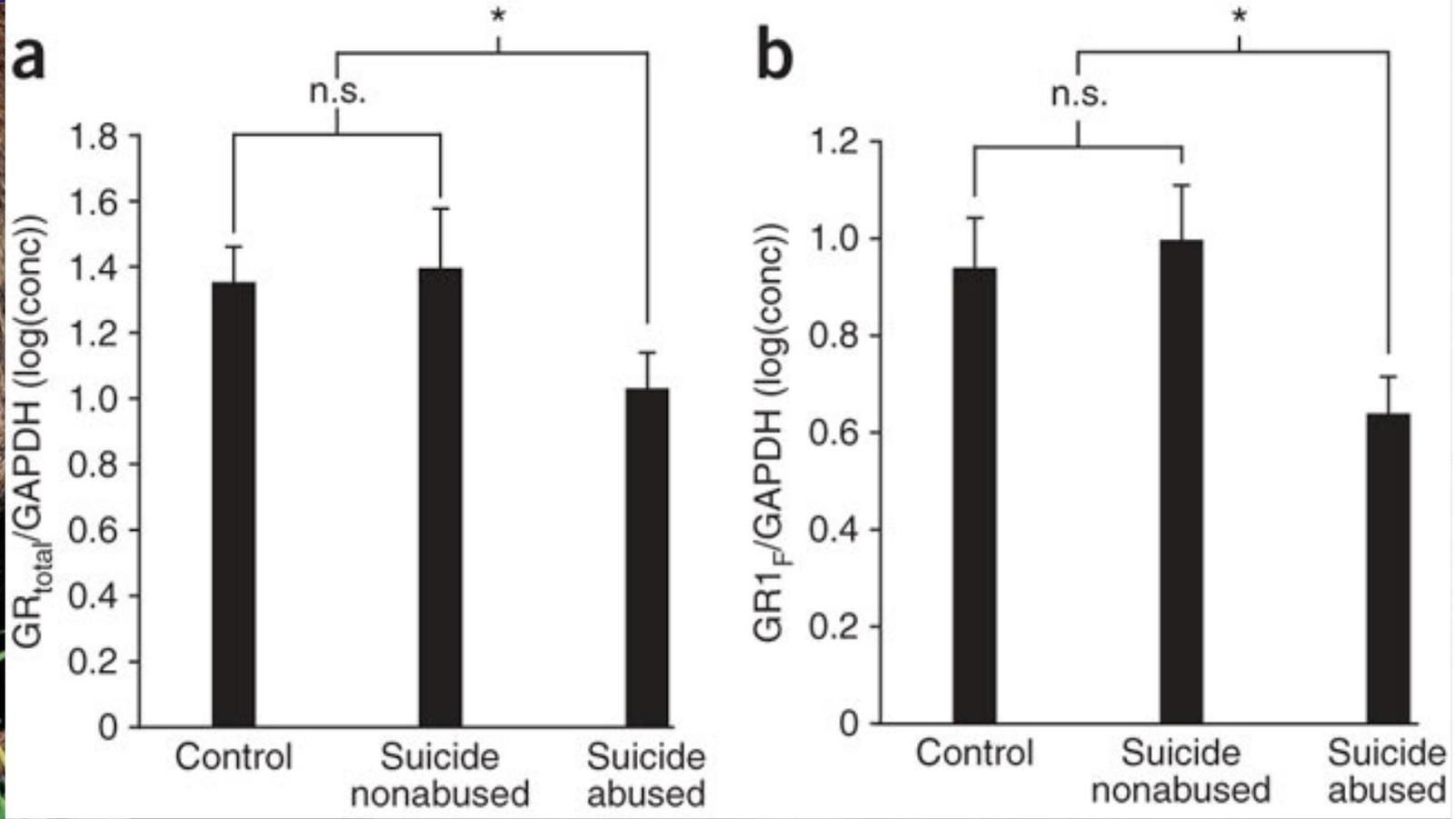
C cingular anterior  
 CPF orbitaria  
 CPF Ventromedial  
 CPF Ventrolateral  
 CPF Dorsolateral

## Conducta social

Empatía  
 Arrepentimiento  
 Decisiones éticas  
 Inhibición de conductas  
 Razonamientos



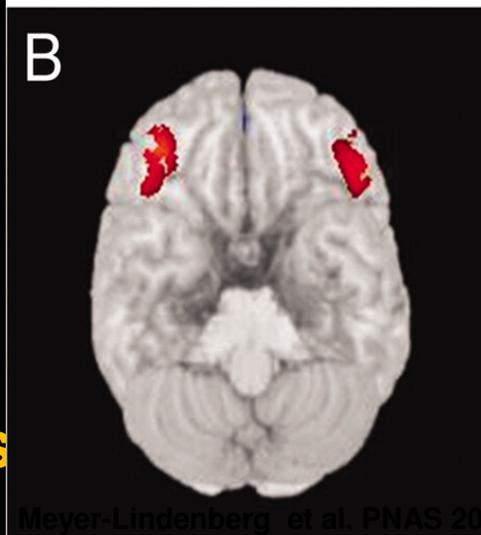
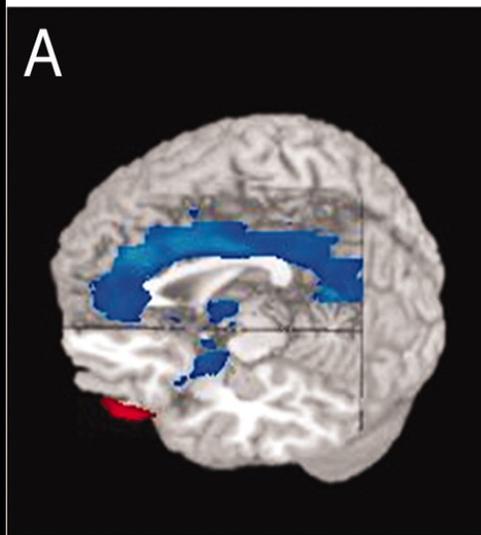
# El cuidado maternal modifica epigenéticamente la expresión del receptor a glucocorticoides (NR3C1) en hipocampo en ratas



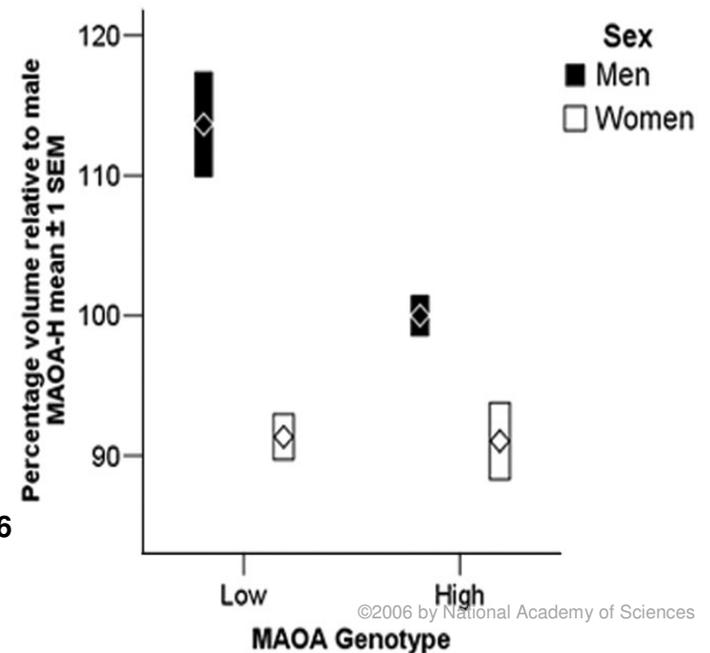
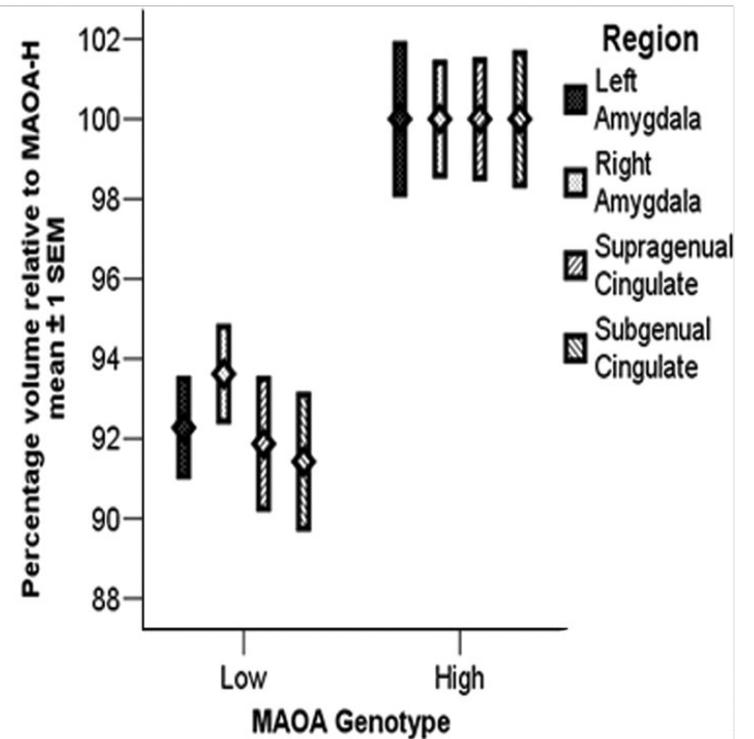
En humanos, el abuso infantil modifica las respuestas del eje hipotalamo-hipofisis-adrenal al estrés y reduce la expresión del receptor NR3C1

McGowan et al. Nature Neuroscience (2009)

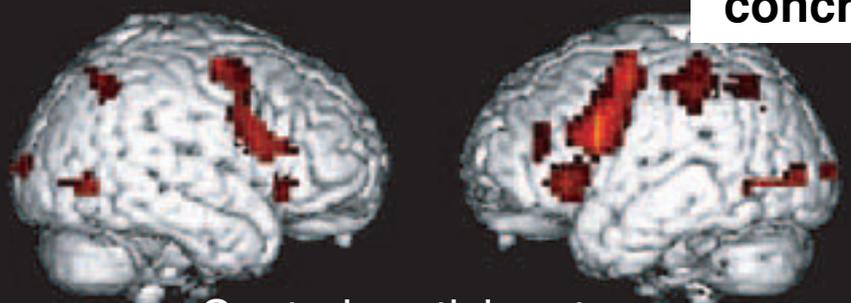
El grado de expresión del gen monoamine oxidase A (MAOA) predice la conducta agresiva tras la provocación. Los datos morfológicos muestran cambios de volumen en las regiones límbica y paralímbica en sujetos MAOA-L.



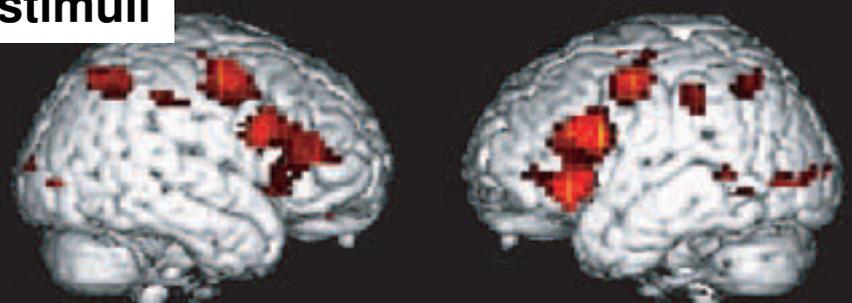
Meyer-Lindenberg et al. PNAS 2006



**concrete stimuli**

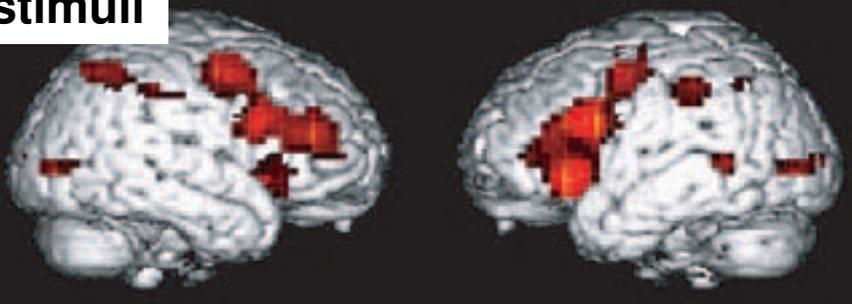
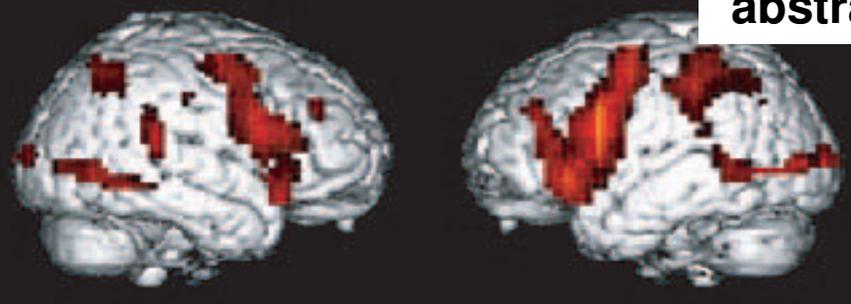


Control participants



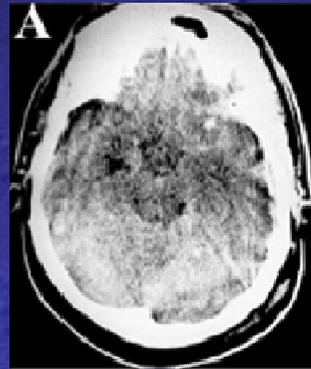
Criminal psychopaths

**abstract stimuli**

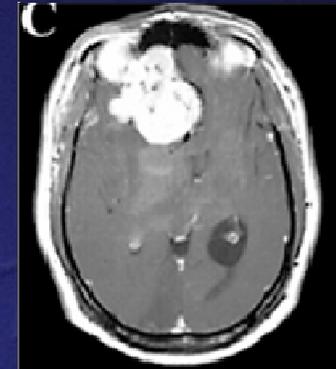
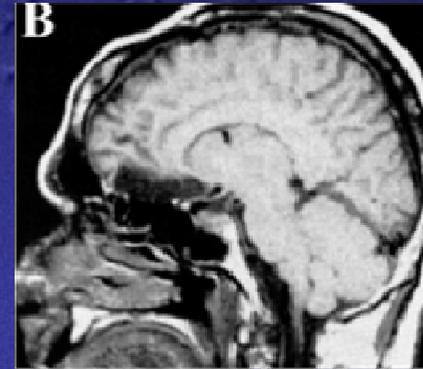


# Anomalías cerebrales asociadas a conductas antisociales

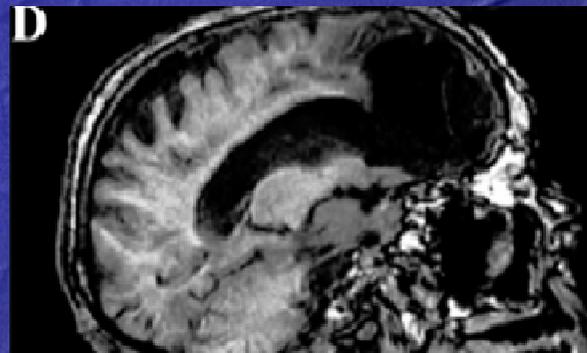
**A- Conducta sociopática  
Tramática**



**B. Post-extirpación tumor  
hipofisario**

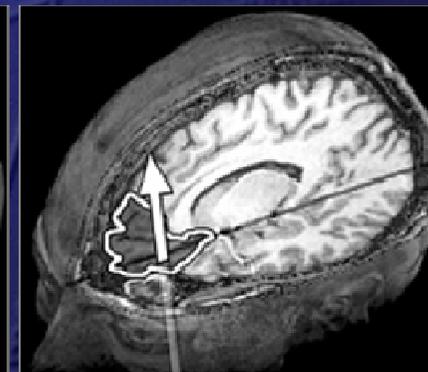
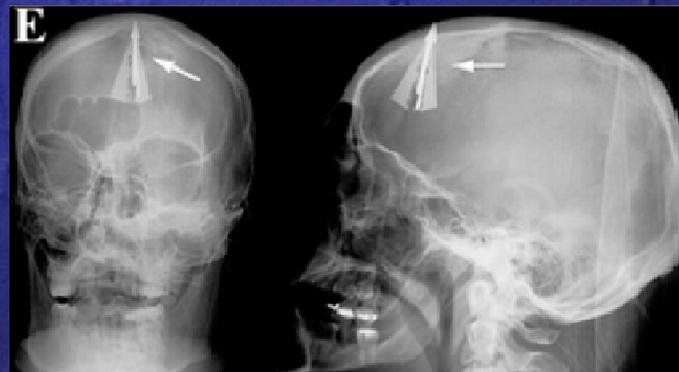


**C. Pedofilia secundaria a  
tumor**



**D. Trauma orbitofrontal con  
cambio de personalidad  
no antisocial**

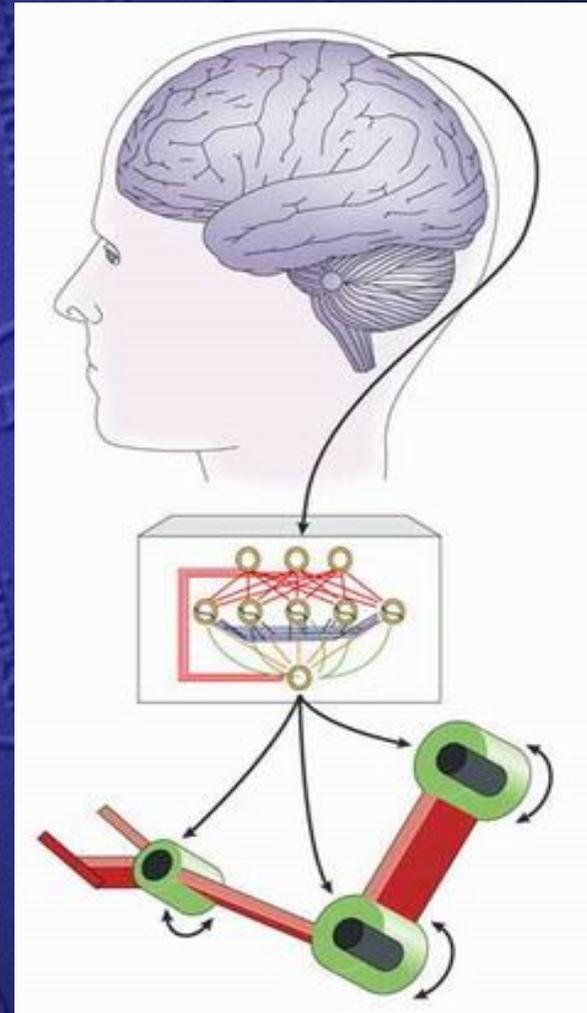
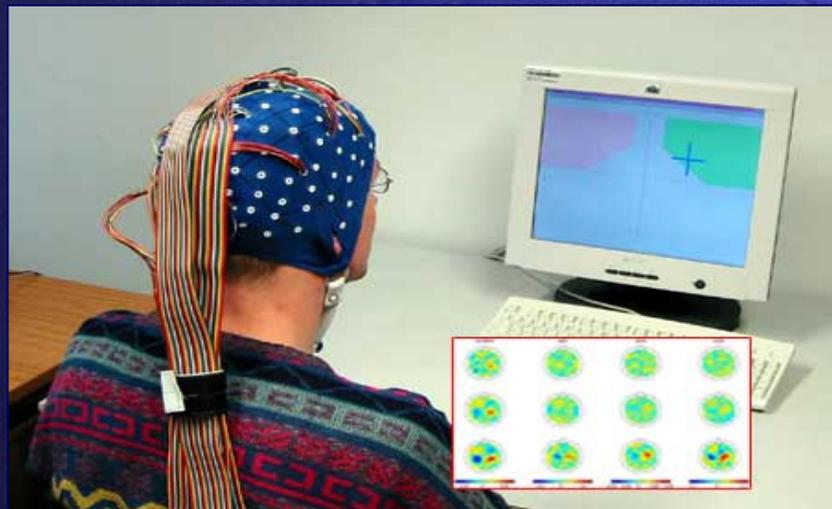
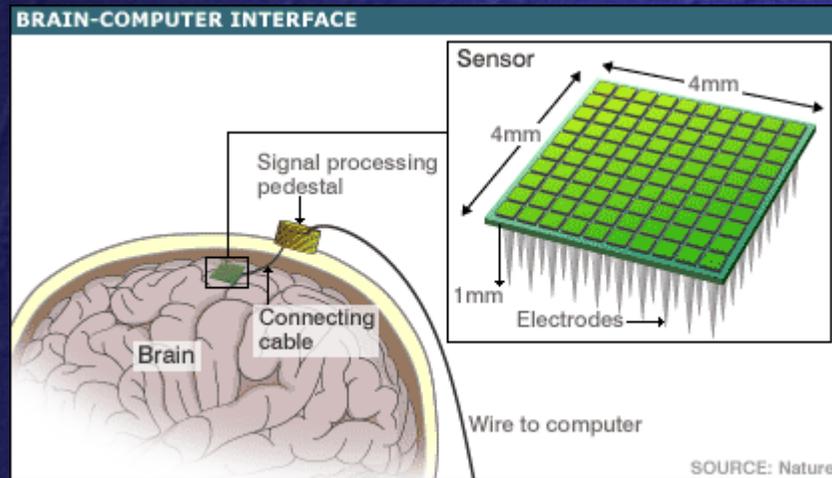
**E. Intento de suicidio con una  
ballesta que eliminó la  
conducta antisocial previa**



## Brain-computer interface

Velliste et al. Cortical control of a prosthetic arm for self-feeding. *Nature*,2008

Hochberg et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature*,2006



## A Foreign-language exposure

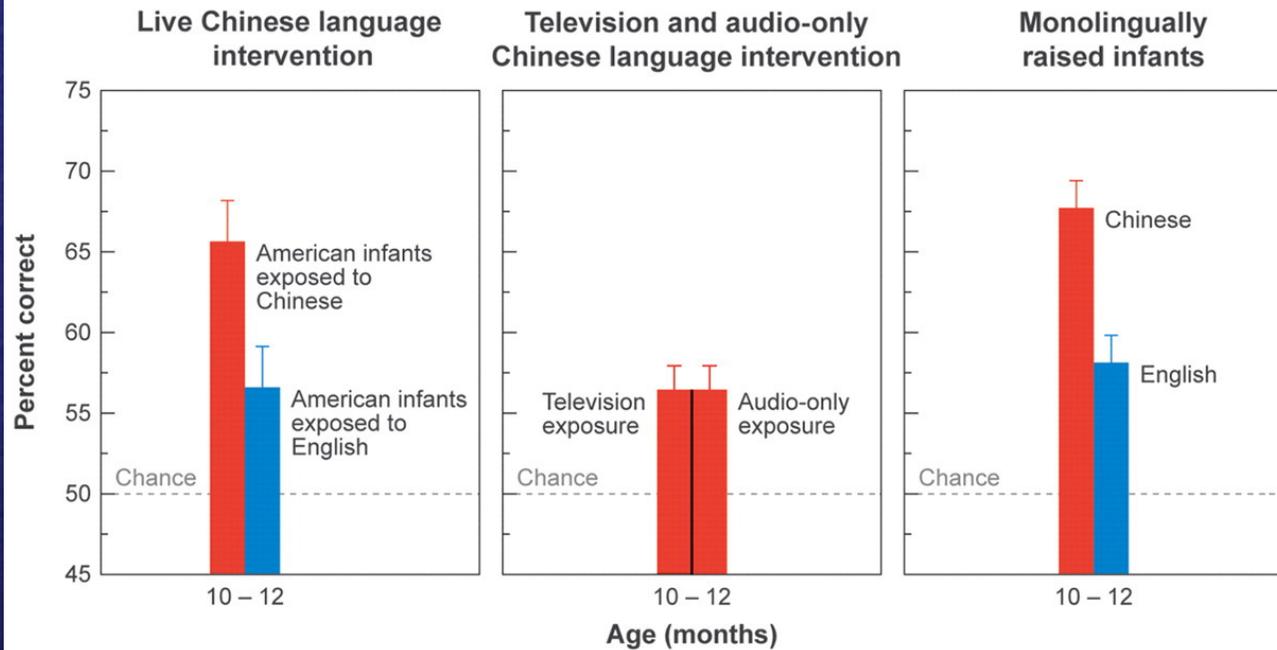
Live exposure



Television exposure



## B Mandarin Chinese phonetic discrimination



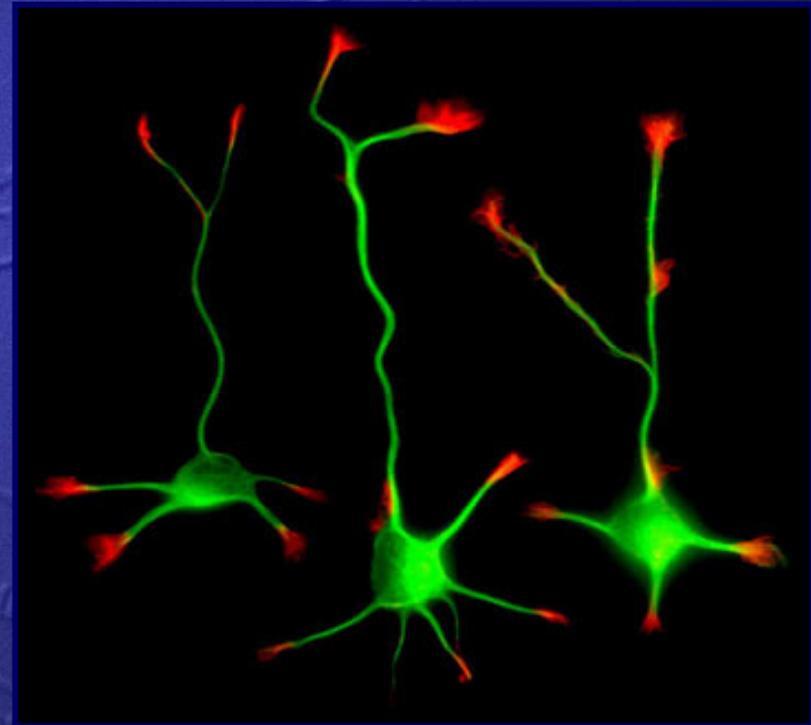
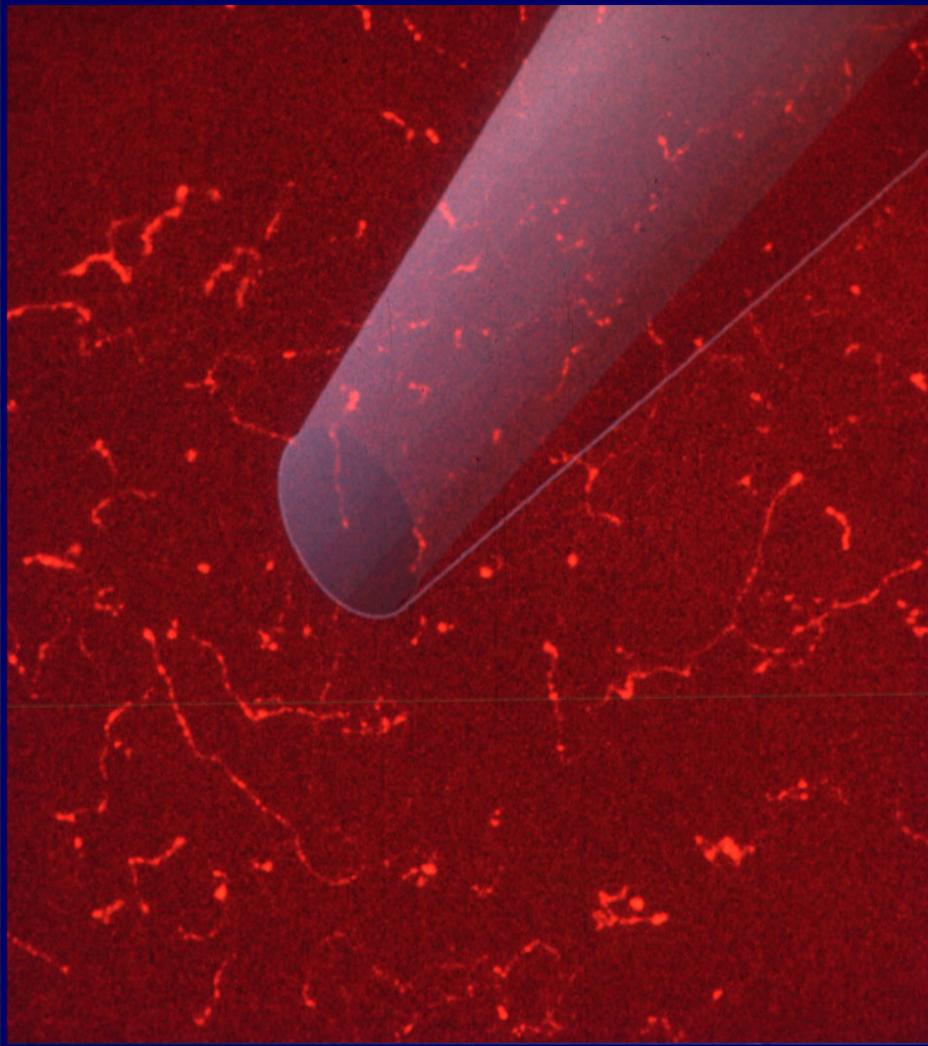
# Desafíos futuros



Fomentar las aproximaciones multidisciplinares y la investigación traslacional para favorecer el paso de la genómica a la clínica y viceversa

Cortesía de D. Mendlewicz

## Repercusiones de la investigación del cerebro



## La Factura de los Desórdenes del Cerebro\*

Desarreglo	Casos Totales (Millones)	Coste Anual (billones \$ USA)
Audición	28	5,6
Depresión	18,8	4,4
Enfermedad de Alzheimer	4	10
Accidentes Cerebro- Vasculares	4	3
Esquizofrenia	3	3,2
Enfermedad de Parkinson	1,5	1,5
Traumatismos Craneoencefálicos	1	4,8
Esclerosis Múltiple	0,35	0,7
Lesiones Espinales	0,25	1

\*Datos del NIH y fuentes varias, recogidos en "Brain Facts" publicado por la SFN

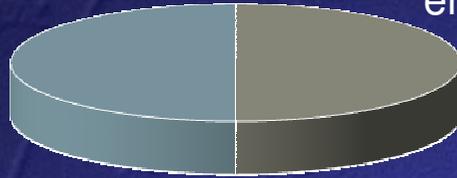
## Carga sanitaria de las enfermedades psiquiátricas

- Aproximadamente el 20% de la población adulta de los Estados Unidos presentará un problema mental grave a lo largo de su vida.
- Esta cifra es mas alta si se incluye a niños y adolescentes.
- Una de cada cuatro familias tiene al menos un pariente que padece una enfermedad.
- De todas las enfermedades mentales, la depresión genera la mayor carga sanitaria.
  - 33 millones de personas al año padecen depresión severa.
  - Mas de 100000 suicidios anuales por esta causa
- Se subestima la carga sanitaria que representan las enfermedades psiquiátricas

Enfermedades  
cerebrales  
50%

## Europa

Otras  
enfermedades  
50%



Prevalencia durante toda la vida de las  
enfermedades del S. Nervioso Central

0.5%



Parkinson

0.8%



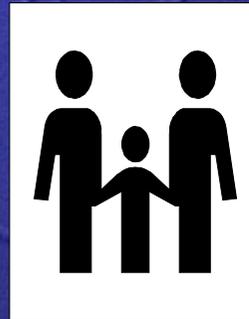
SDAT  
(Alzheimer)

1%



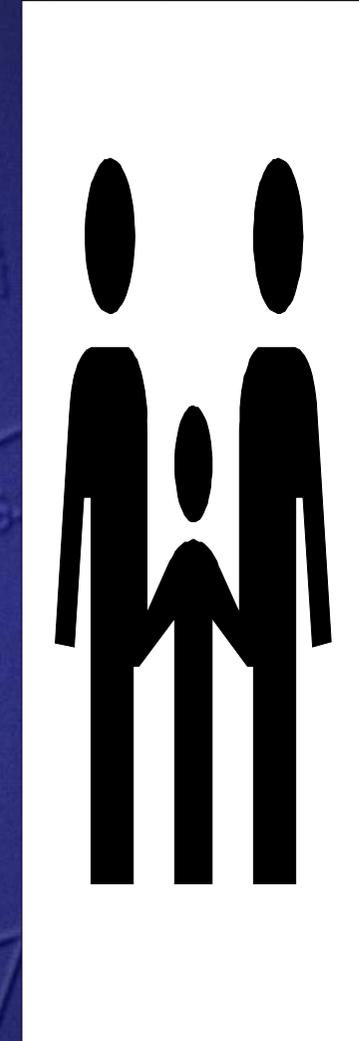
Schizophrenia

4%



Bipolar  
Disorder

14%

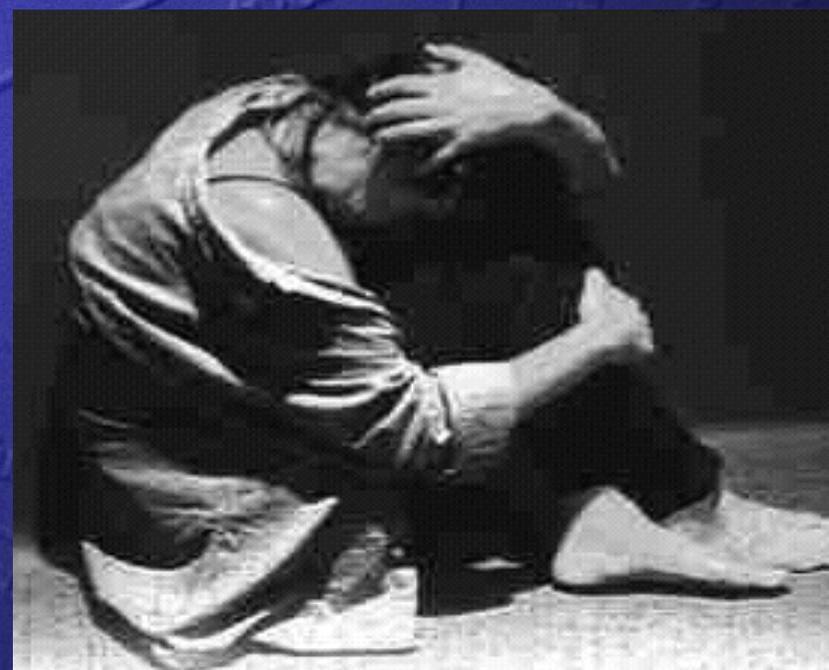
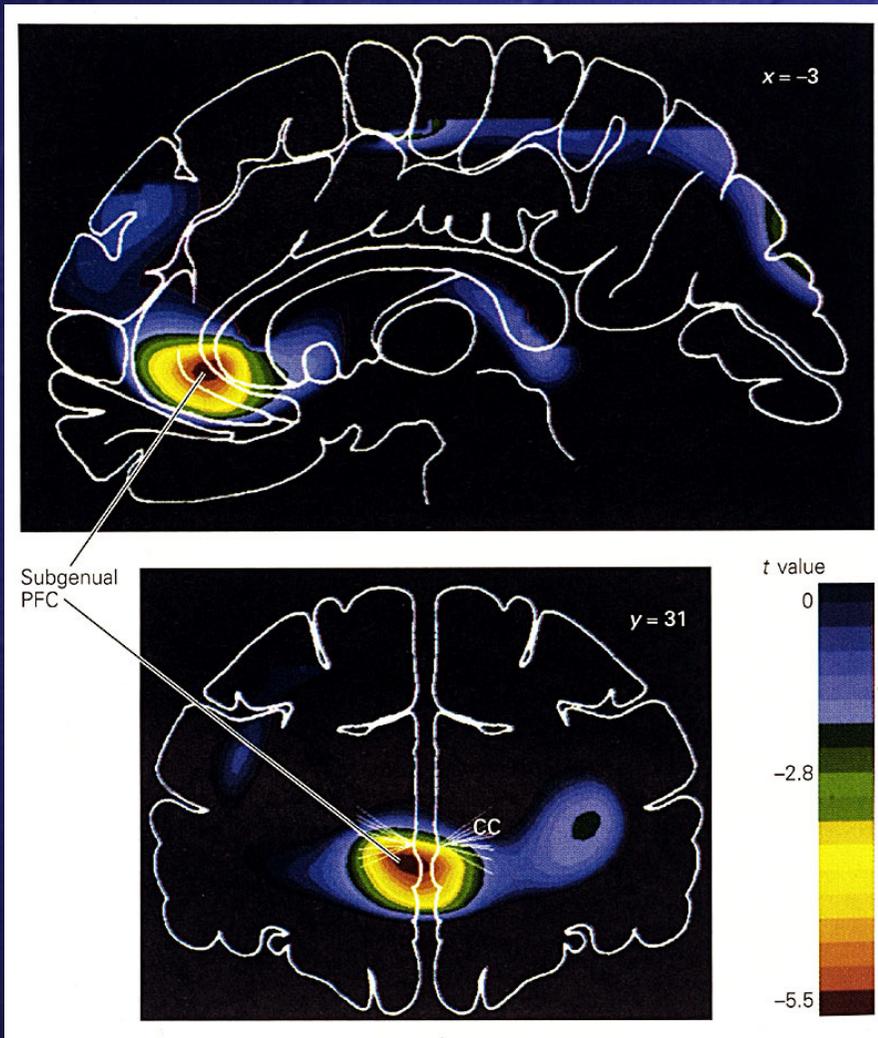


Major  
Depression

## Control de los mecanismos cerebrales de la violencia



# Control de las sustancias de abuso



# Fármacos que modulen los estados emocionales

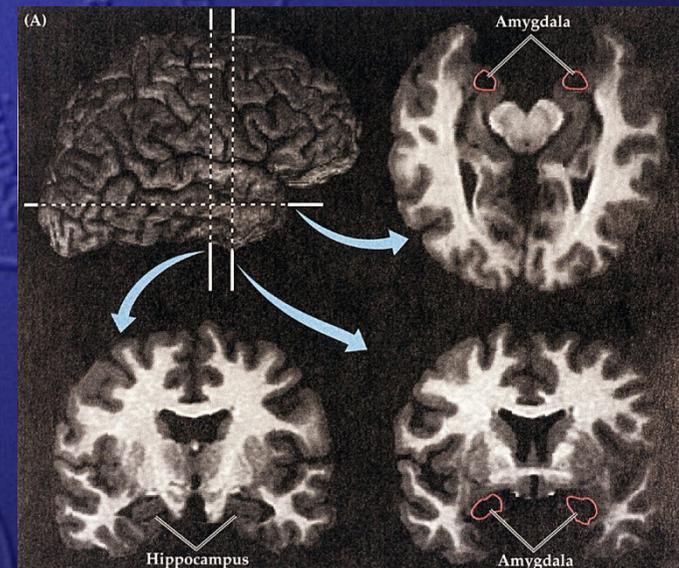
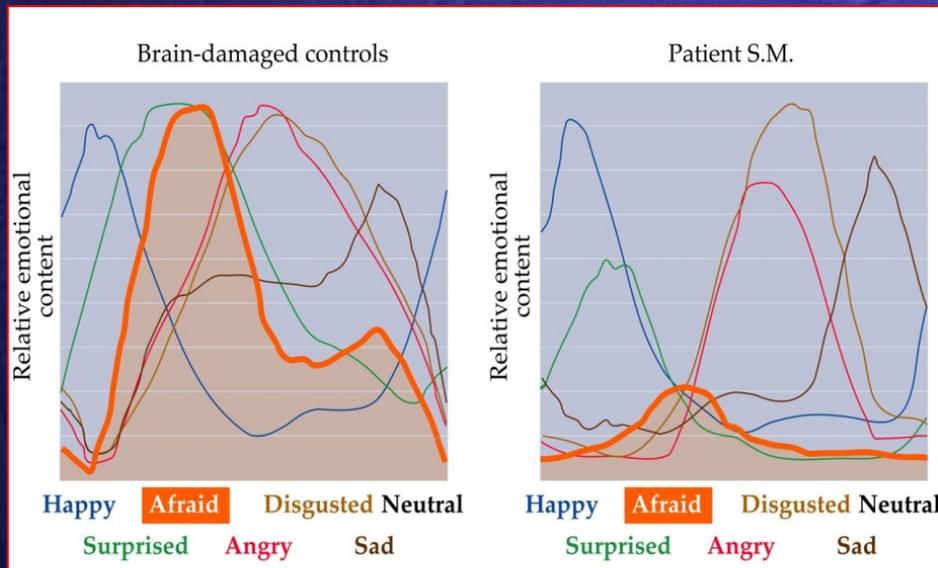


Edvard Munch The dance of life

# Valoración de la empatía emocional

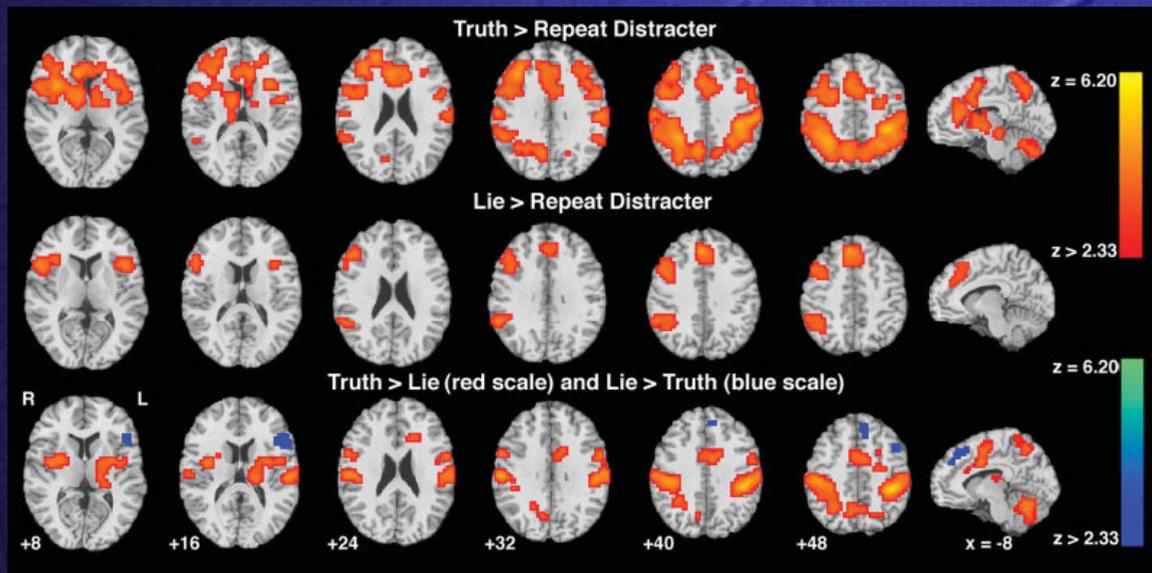


CONDUCTA VIOLENTA: Agresión afectiva  
Agresión predatoria

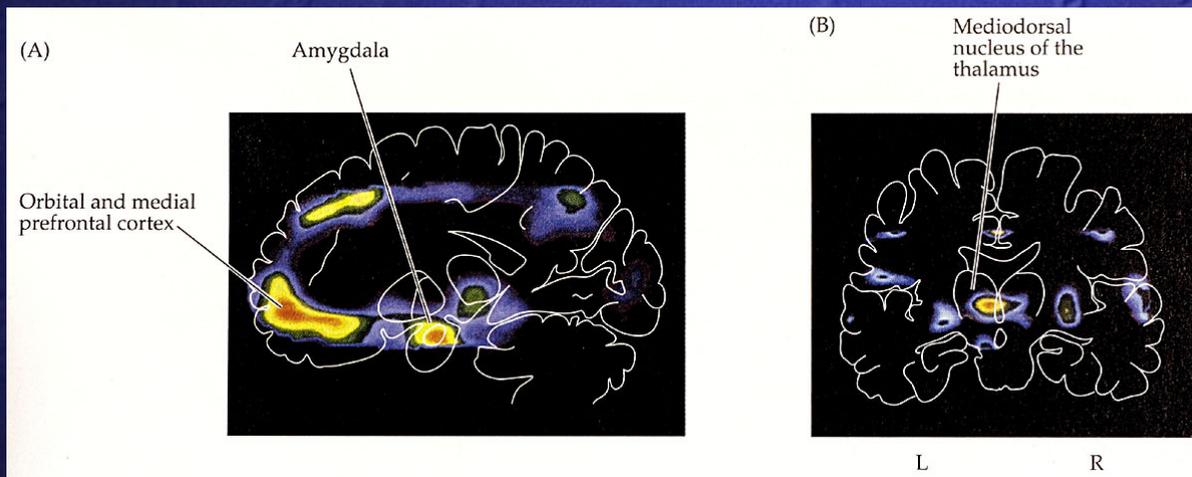


## Determinación de la responsabilidad legal

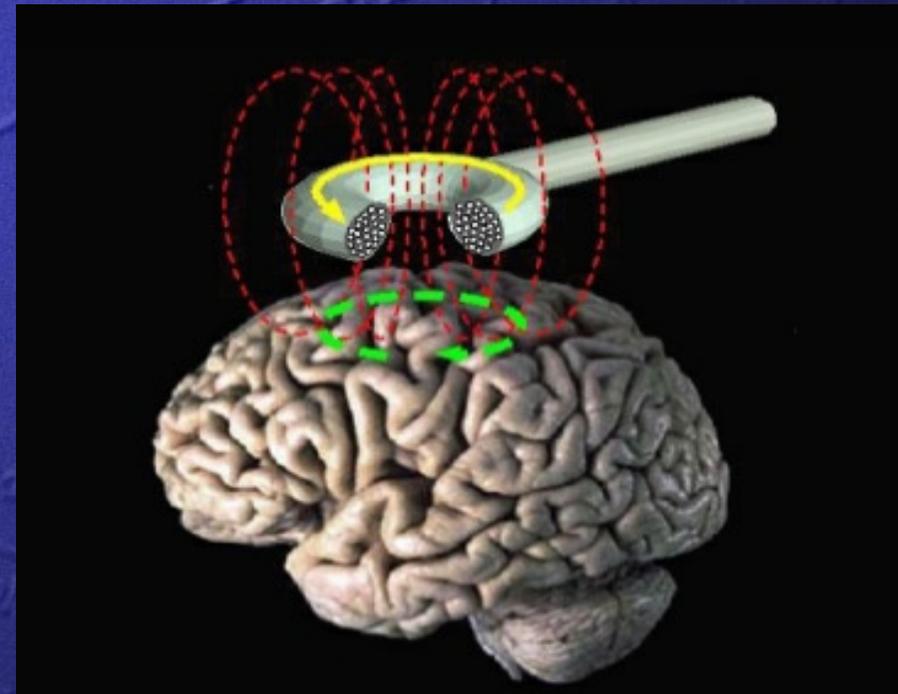
- Presencia de lesiones neurológicas
- Correspondencia entre daño cerebral y conducta antisocial
- Simulaciones
- Falsedades asociadas a un delito
- Possibilidades de reincidencia



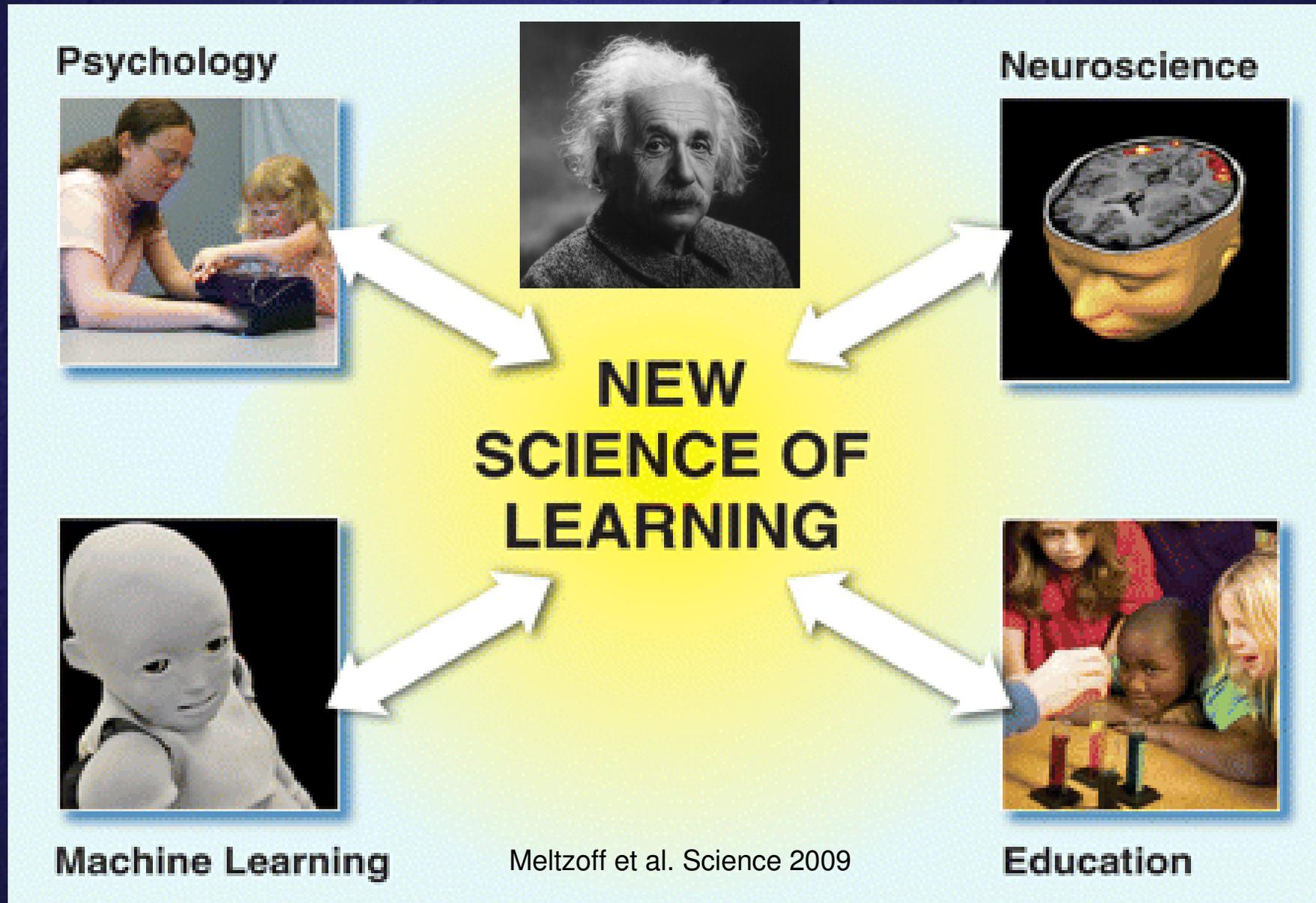
# Detección de preferencias (Neuroeconomía)



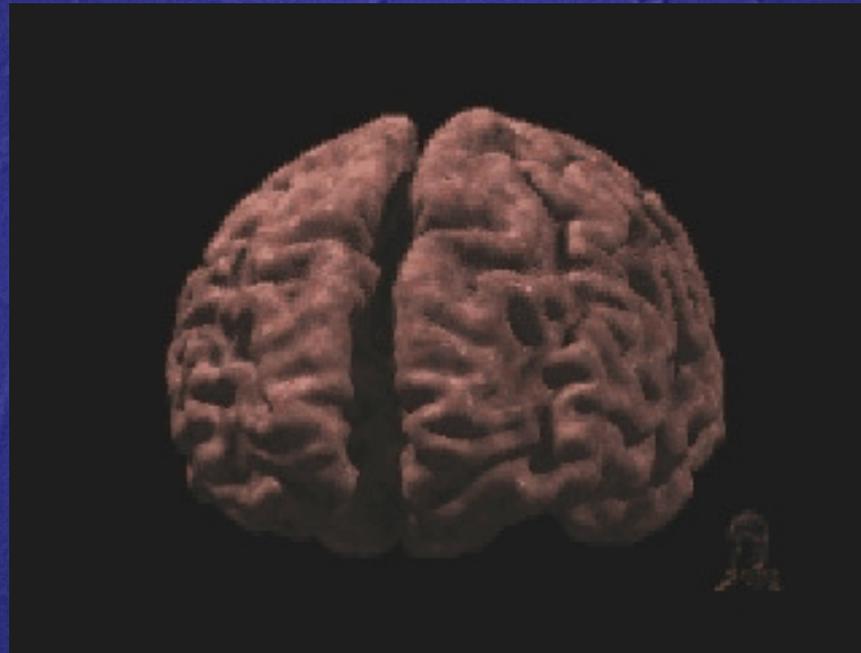
# Modulación externa de la actividad cerebral



# Optimización del aprendizaje y del desarrollo de la inteligencia

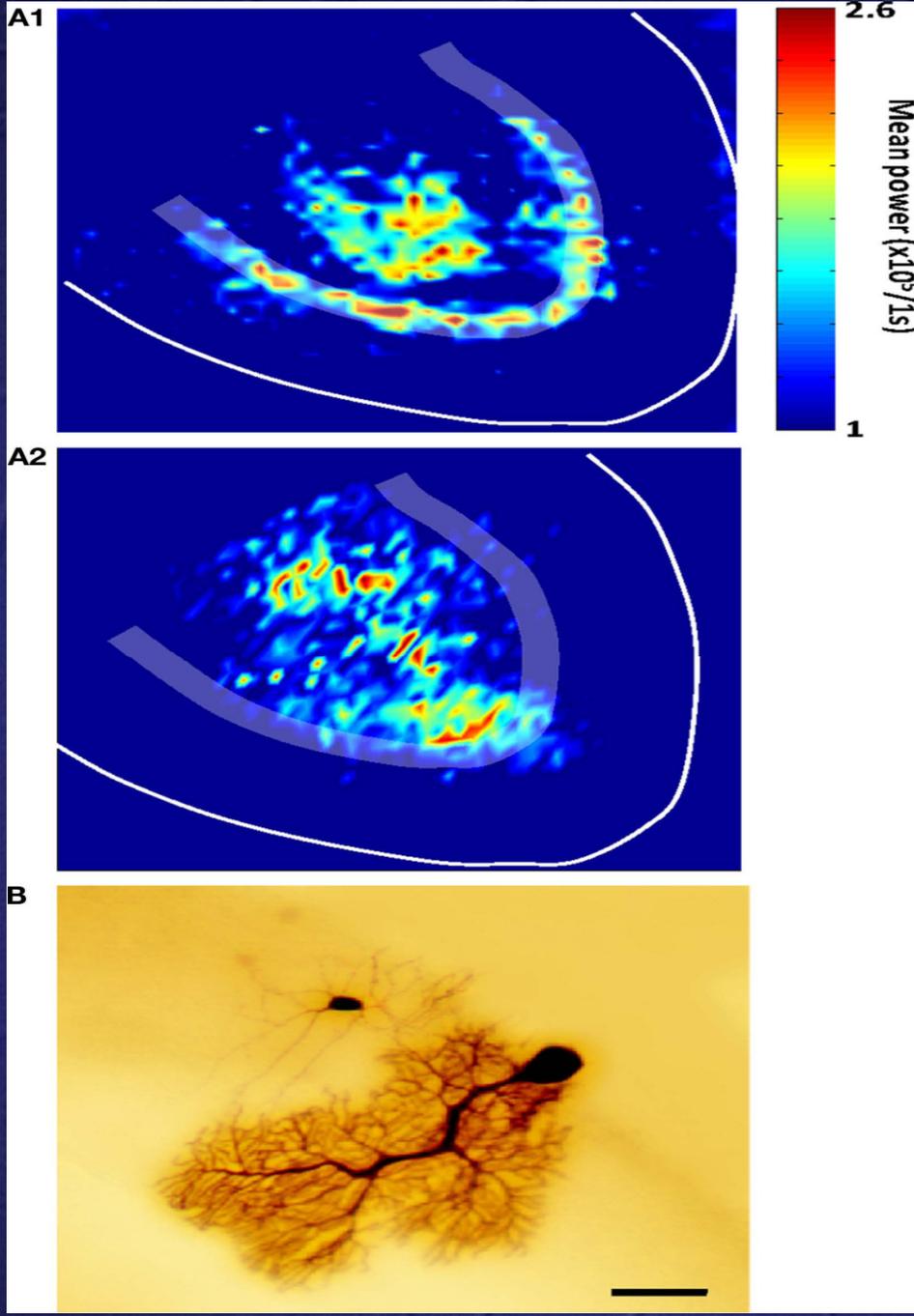


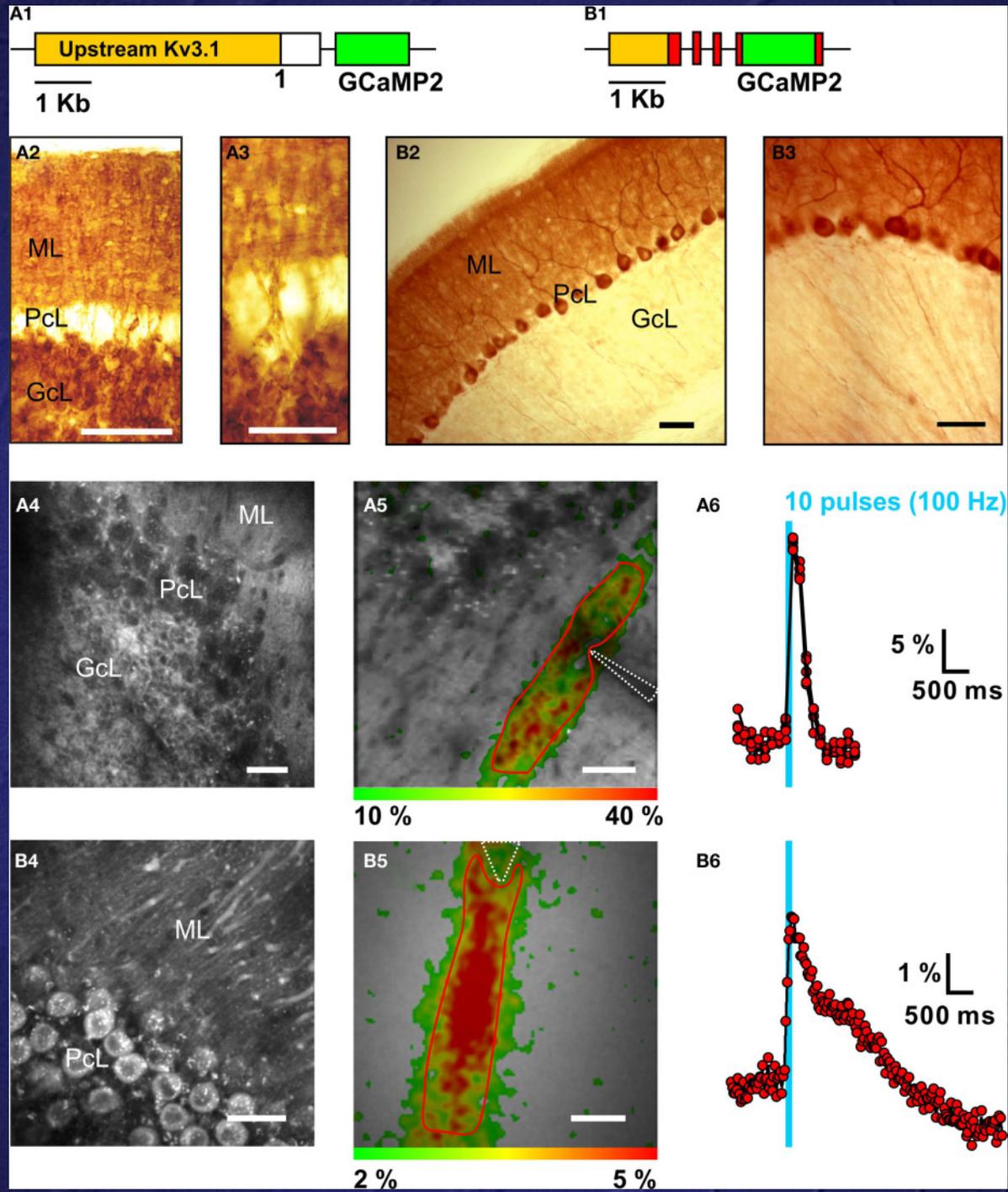
El conocimiento del cerebro condicionará  
la sociedad del futuro....

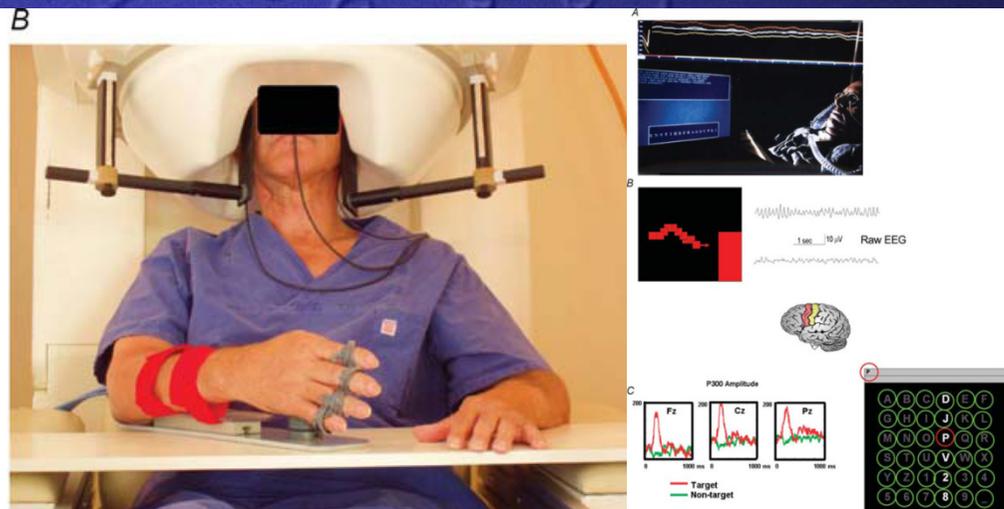
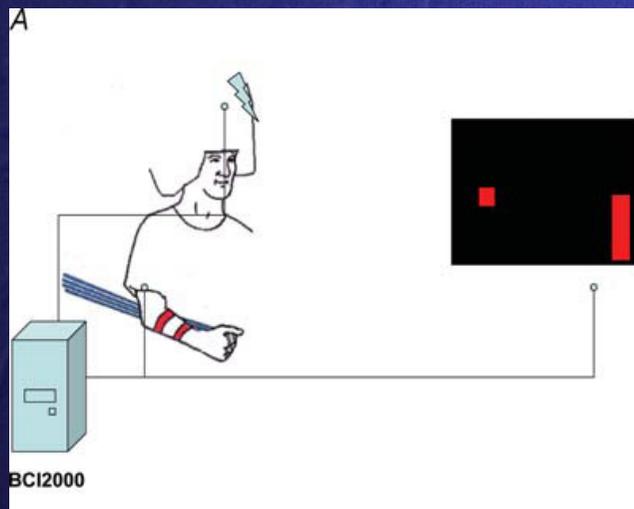
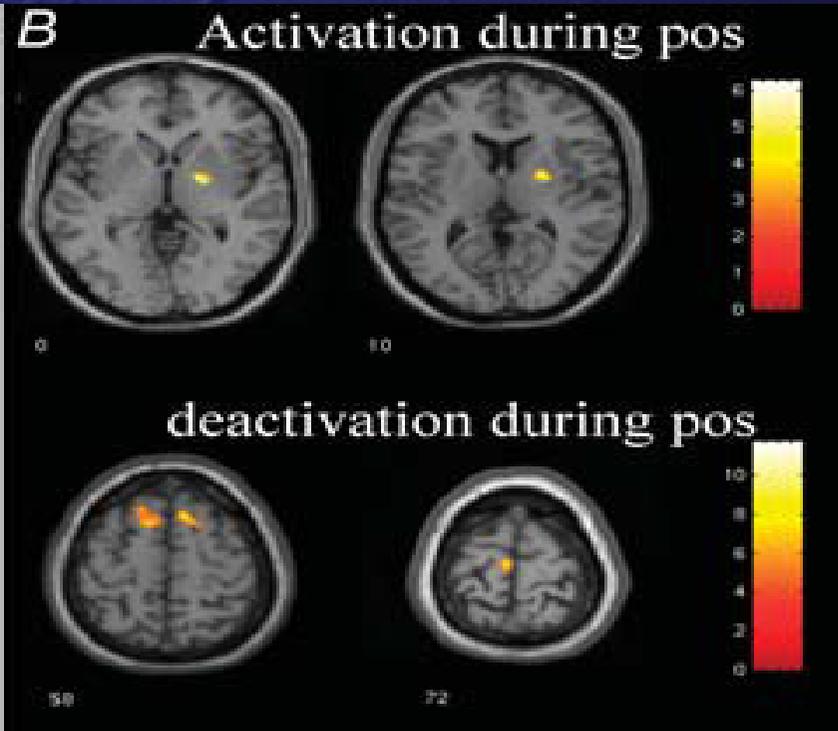
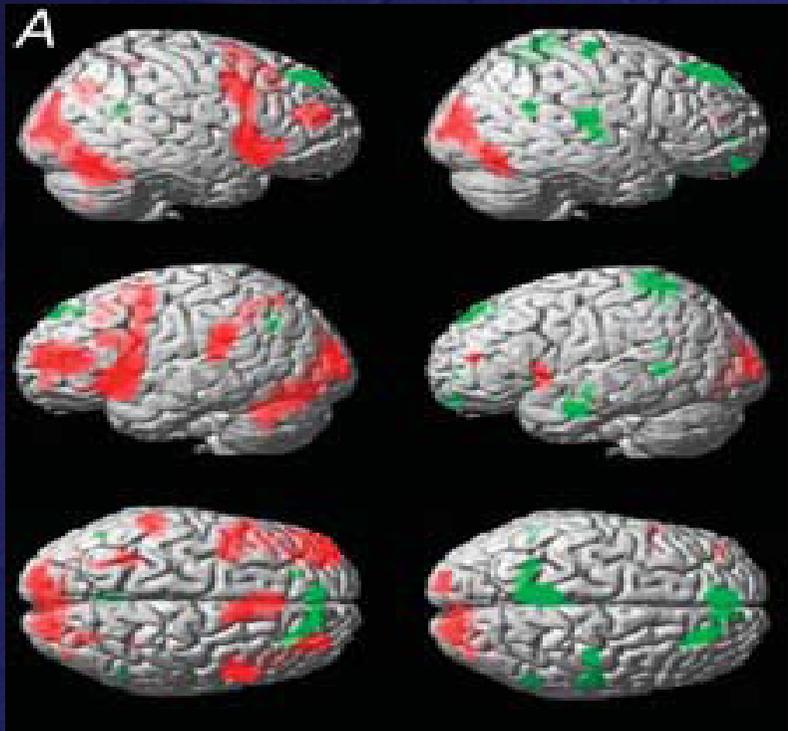


¡Muchas gracias!









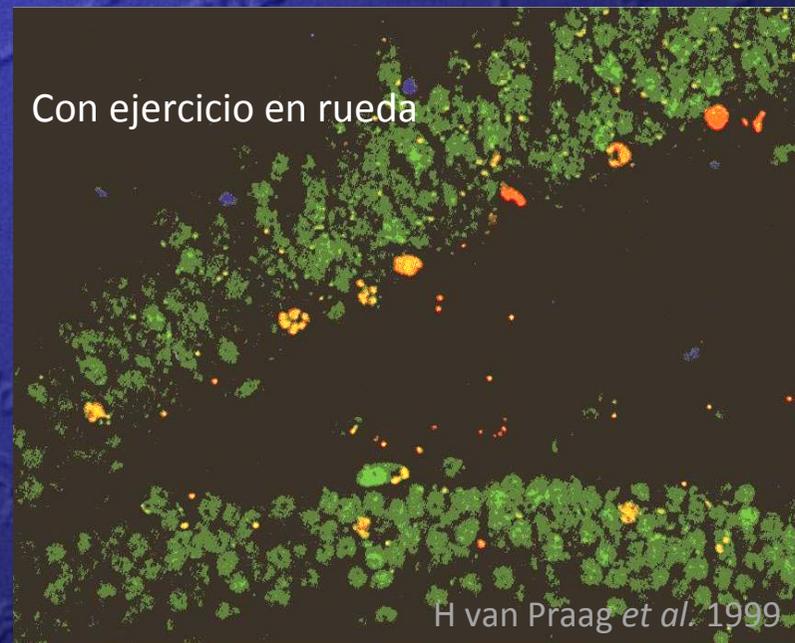
# Regeneración y plasticidad del sistema nervioso

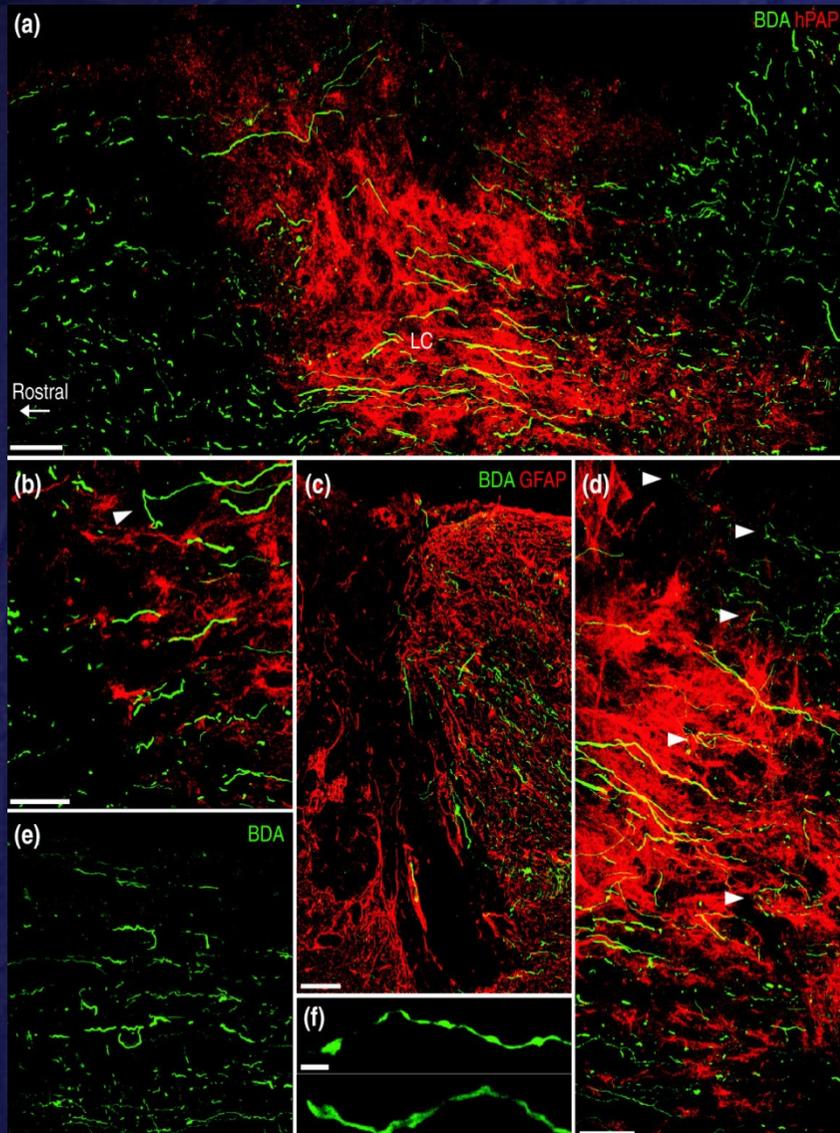


Cerebro de ratón adulto  
Sin ejercicio en rueda

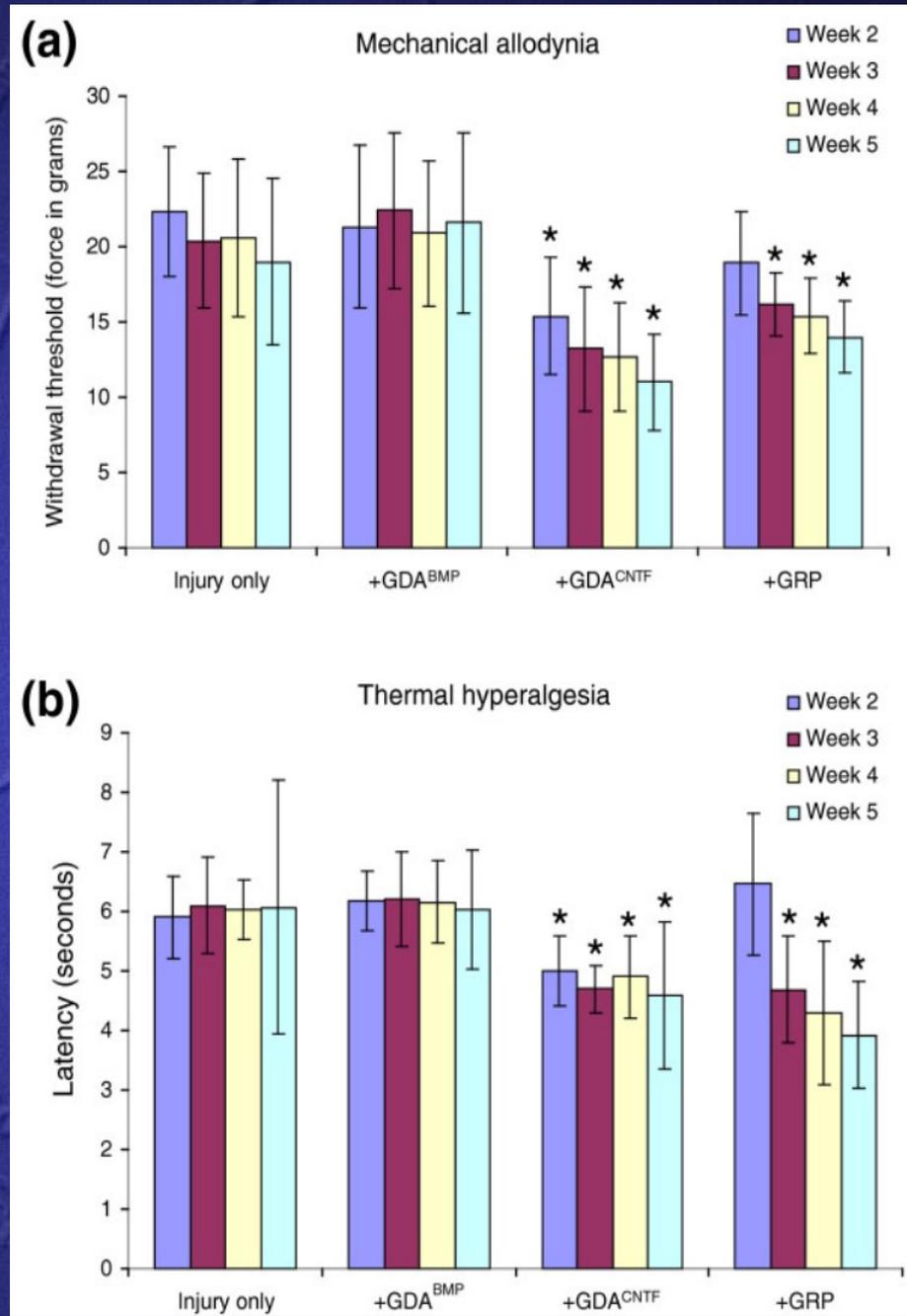


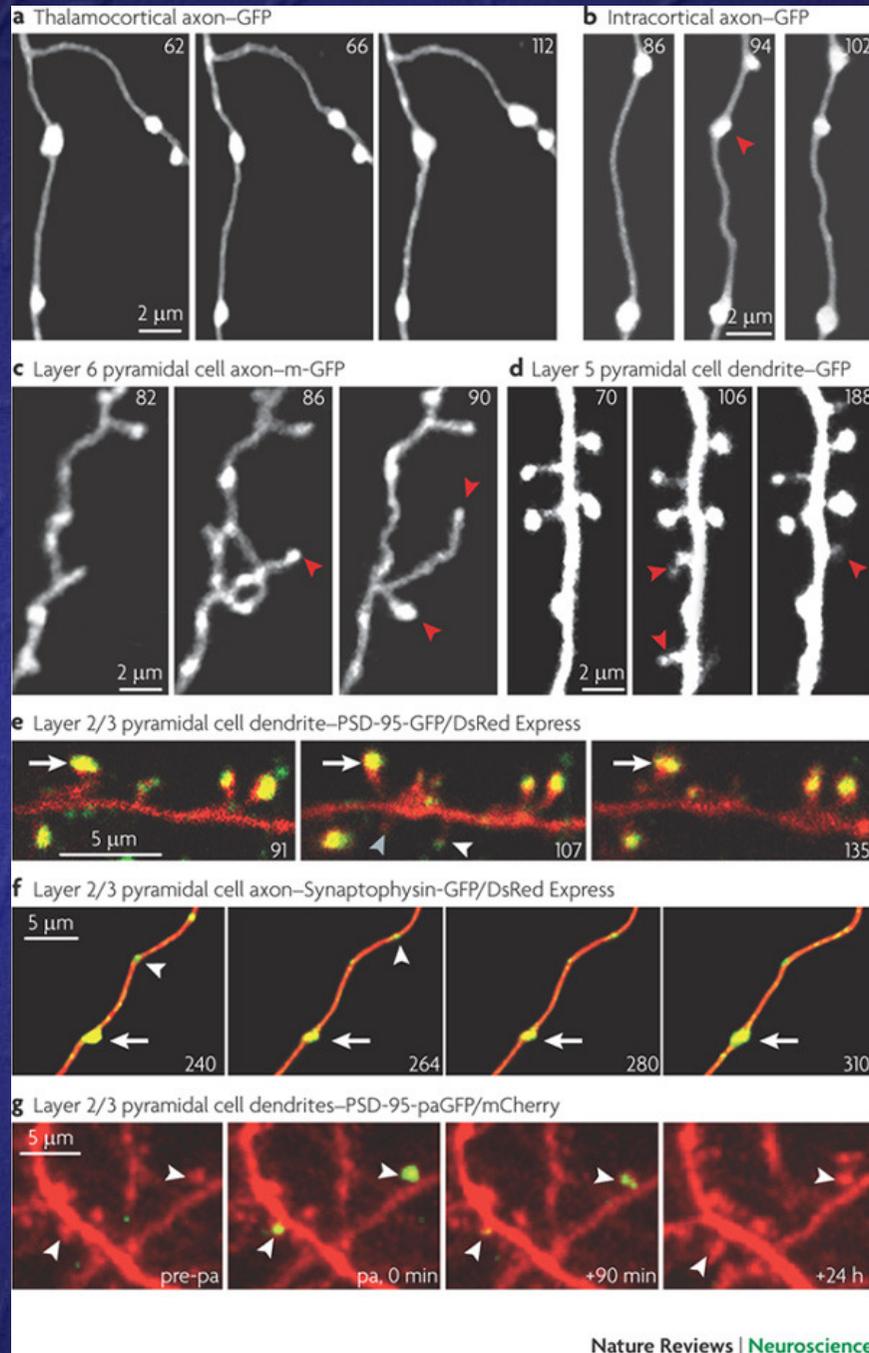
Con ejercicio en rueda



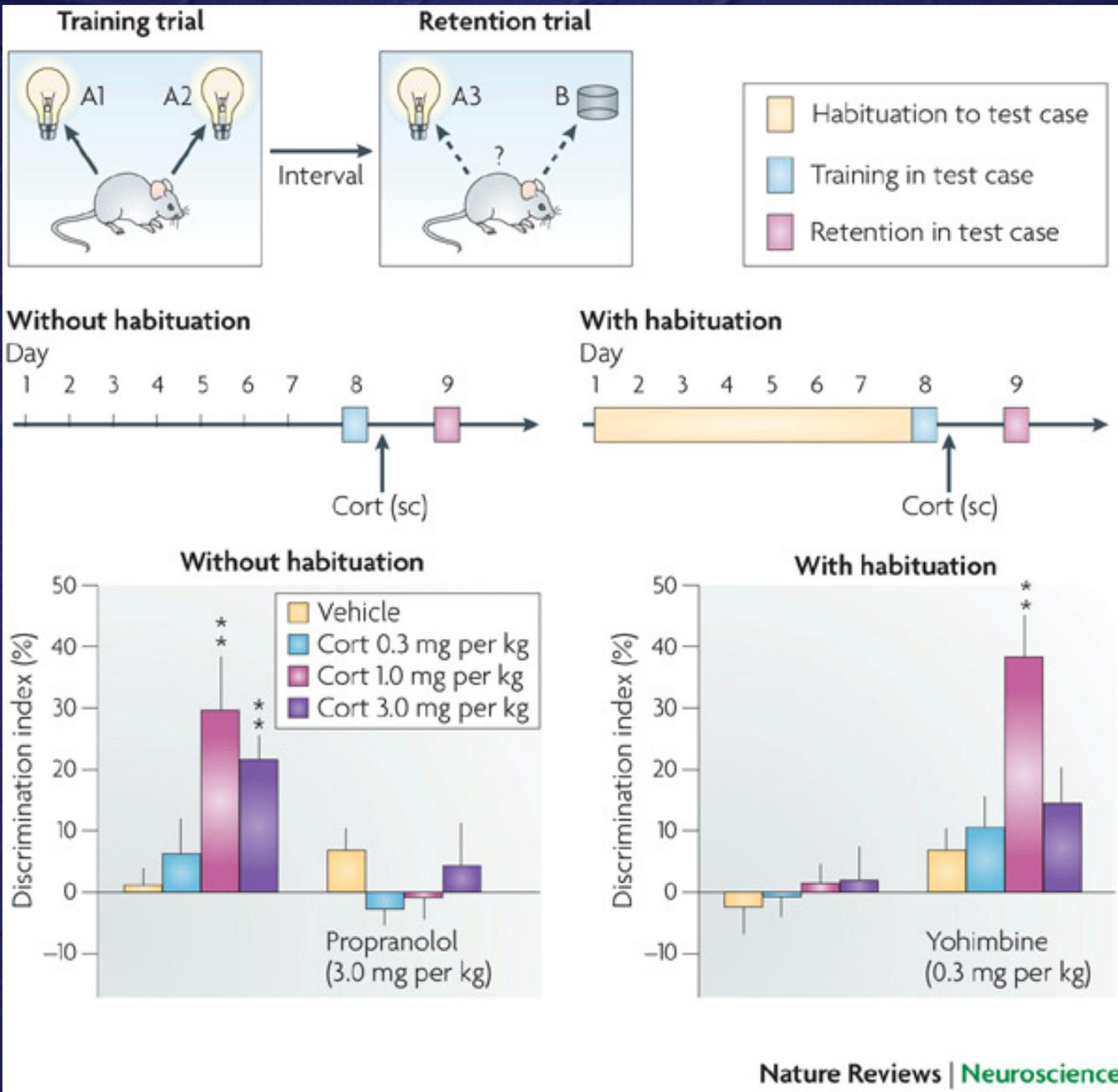


Transplanted astrocytes (GDAs) derived from glial-restricted precursors cells  
 Davies et al. J Biol., 2006; 2008









**Psychology**



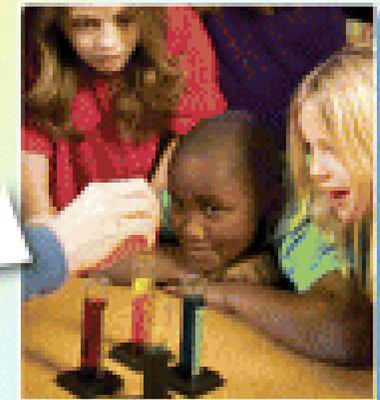
**Neuroscience**



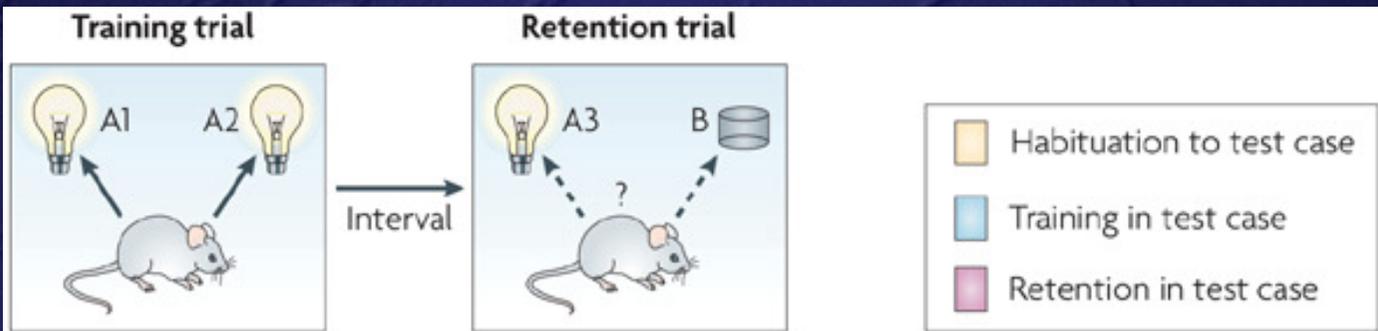
**NEW  
SCIENCE OF  
LEARNING**



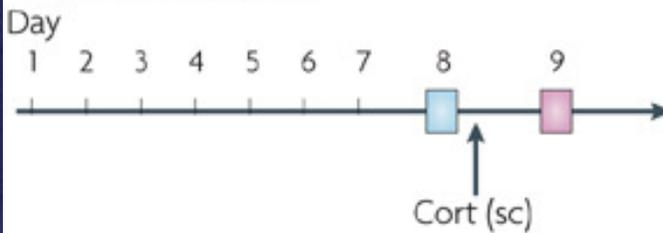
**Machine Learning**



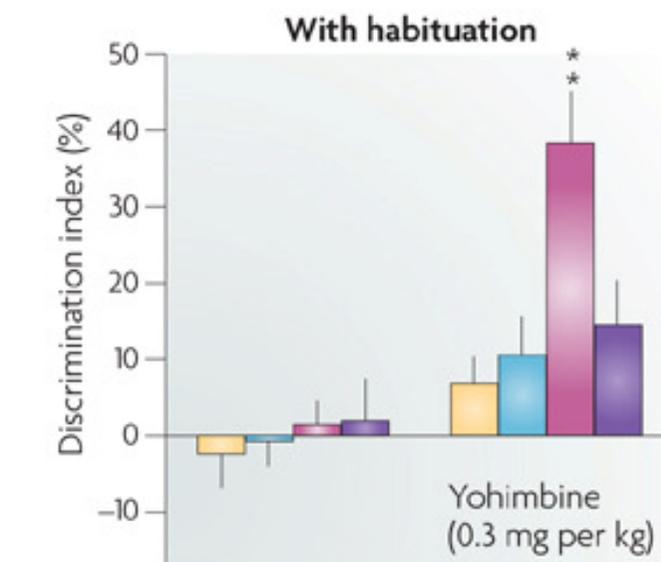
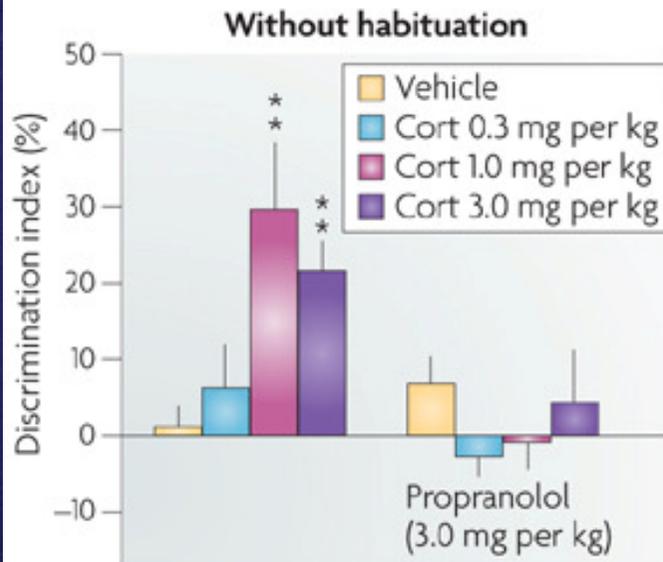
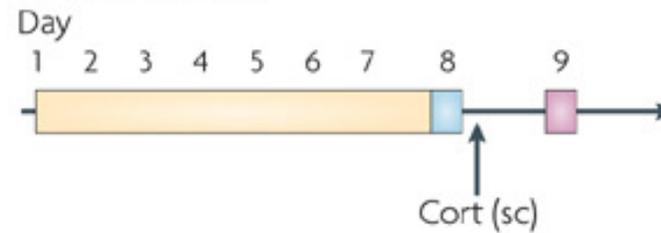
**Education**



**Without habituation**



**With habituation**







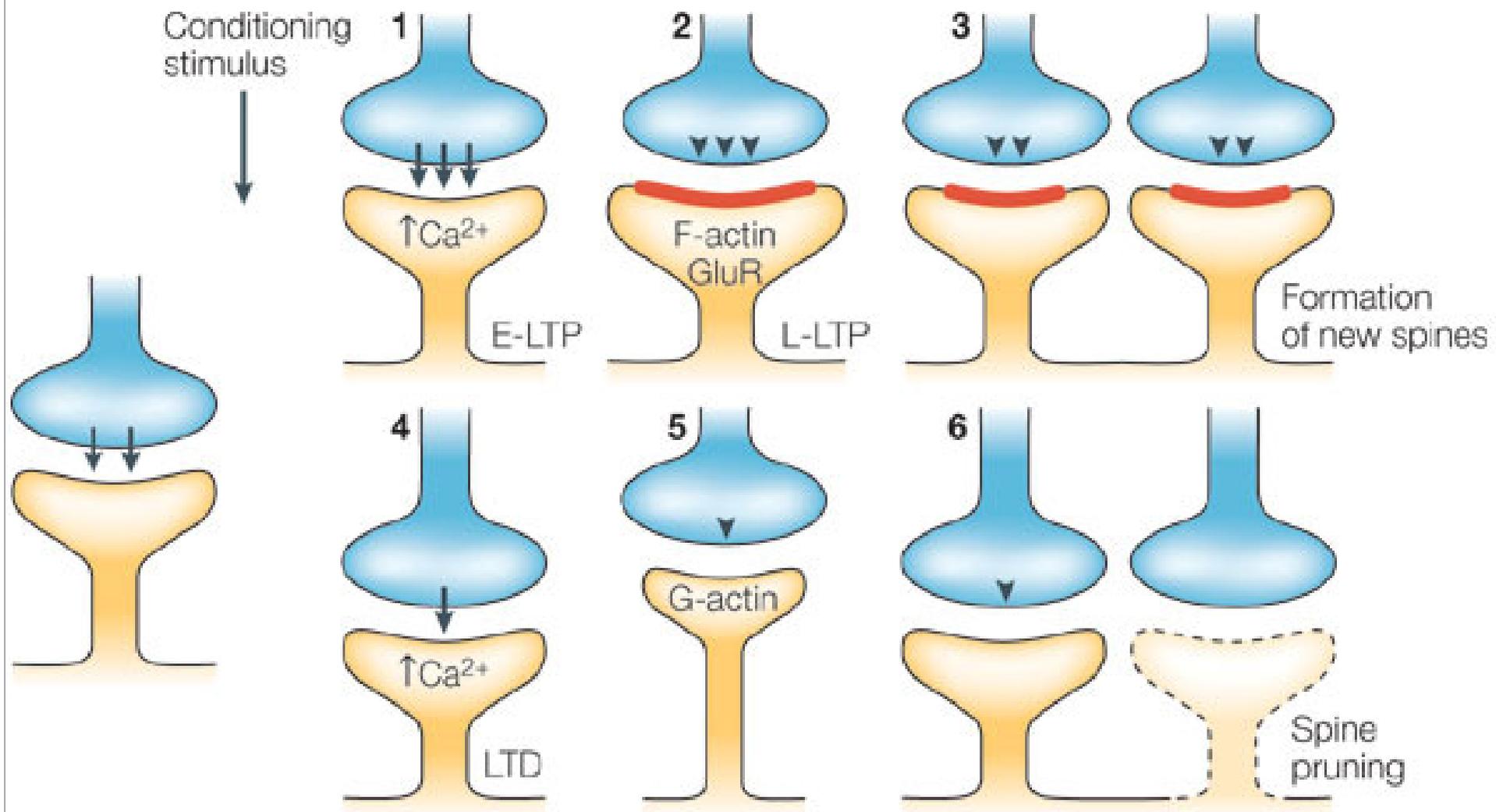








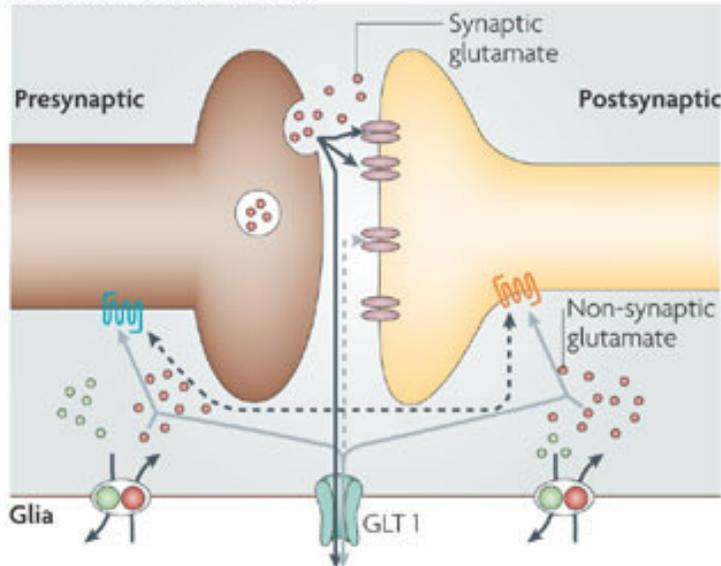




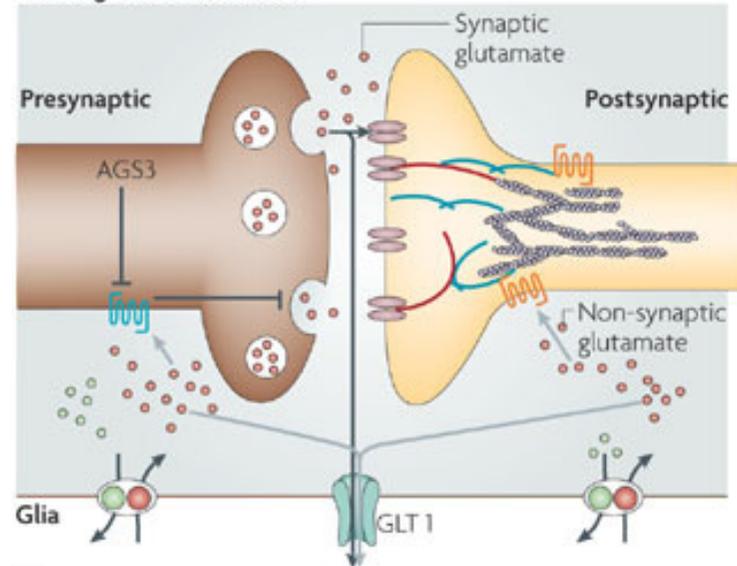
# Las drogas de abuso modifican la sinapsis

iGluR	
mGluR5	
mGluR2/3	
Synaptic vesicle	
Glutamate	
Cystine	
Homer	
PSD95	
F actin	
Glutamate exchanger	

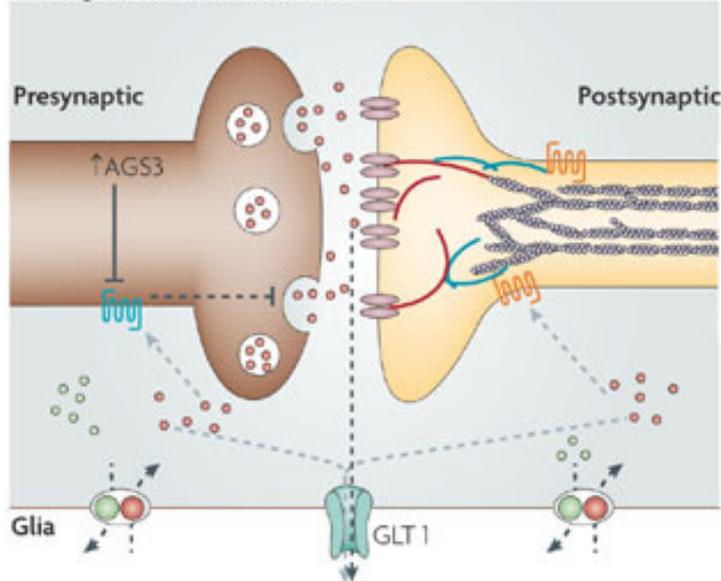
**a** Glutamate homeostasis



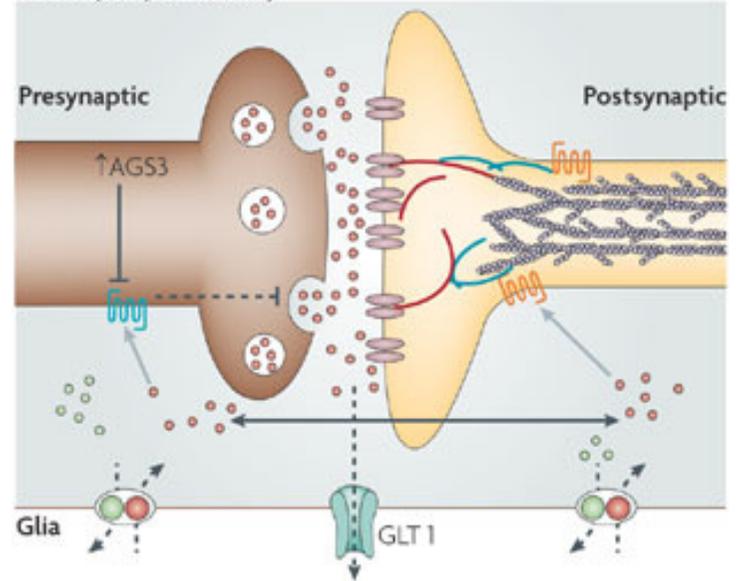
**b** Drug-naive conditions



**c** Drug-withdrawal conditions



**d** Relapse (30–60 min)



2009