

Dipartimento di Neuroscienze del Farmaco e della Salute del Bambino

Azienda Ospedaliero Universitaria Careggi
Dipartimento di Neuroscienze

Dalla ricerca sperimentale alle applicazioni cliniche: limiti dell'uso delle cellule staminali per la riparazione delle lesioni del sistema nervoso.

Prof. Luca Massacesi

Firenze, 14 Marzo 2014

Il lungo e affascinante viaggio della
ricerca sulle cellule staminali

Sommario

- Danno/malattia del Sistema Nervoso Centrale
- Il Sistema Nervoso Centrale:
 - forma macroscopica e microscopica
 - funzioni
- Riparazione o protezione?

sim



Settimana Mondiale del Cervello

10 - 16 Marzo 2014



www.neuro.it

Medicina moderna

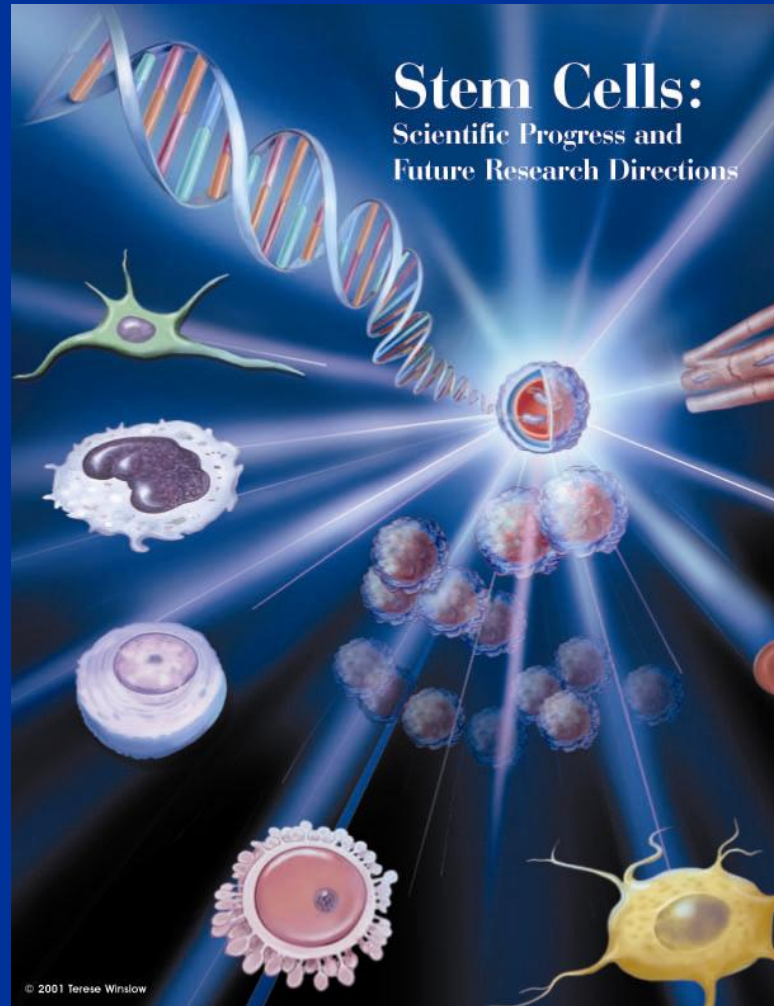
- Sintomi

- Lesioni

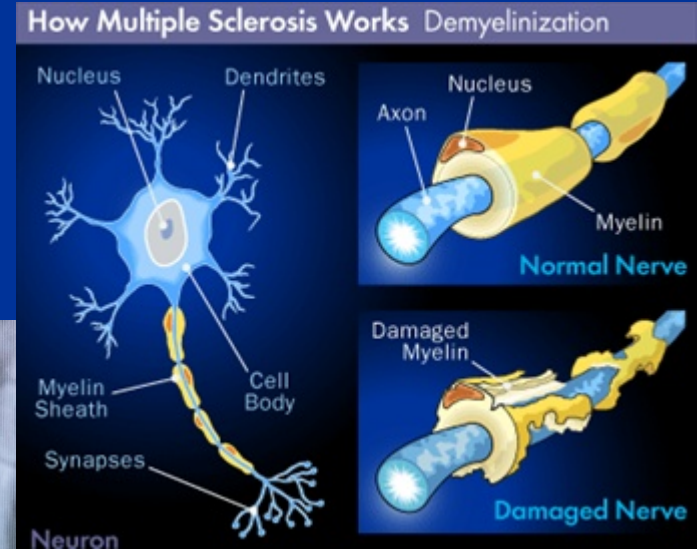
- Terapie

- Terapie:
 - Raramente curative:
 - Infezioni
 - Chirurgia
 - Spesso:
 - preventive di:
 - malattia (vaccini)
 - progressione
 - sintomatiche
 - Mai riparative del danno instauratosi
 - eccezioni:
 - autoriparazione
 - trapianti d'organo

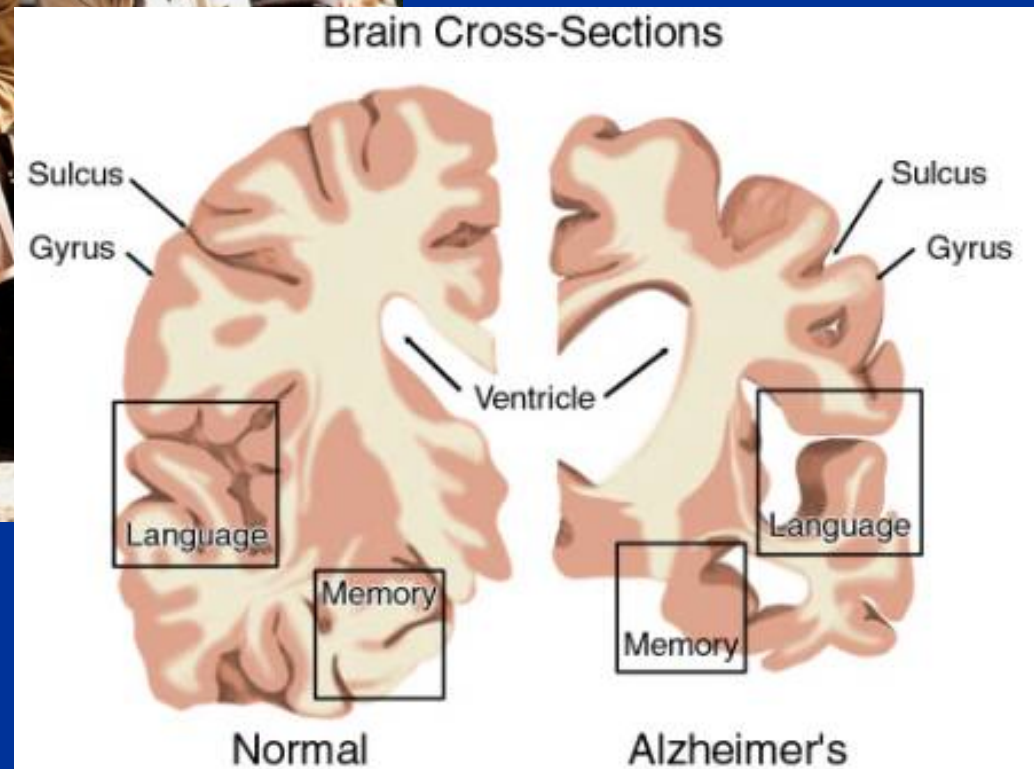
Cellule Staminali e riparazione di tessuti umani



Paraplegia = lesione midollo spinale



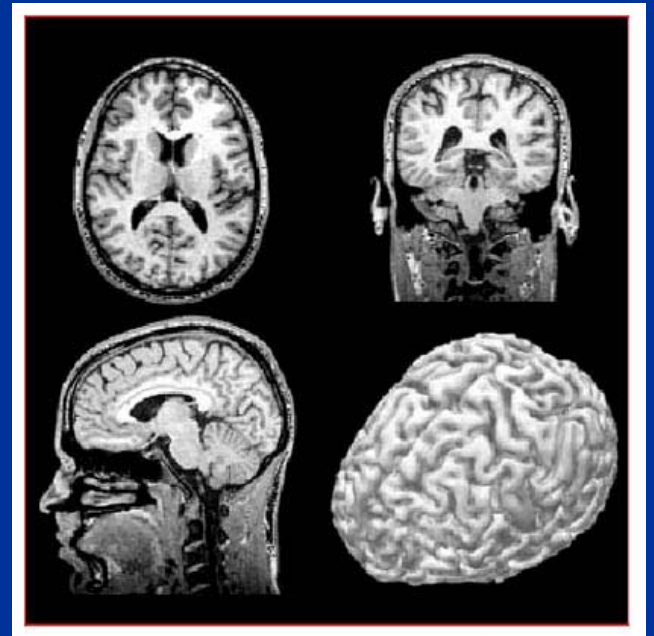
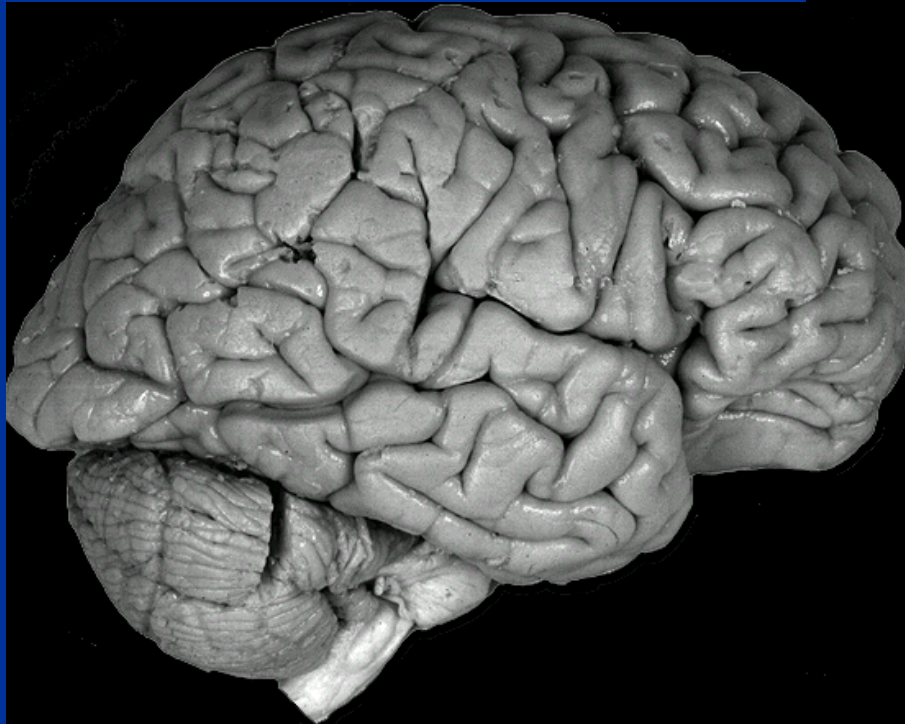
Demenza senile = atrofia cerebrale



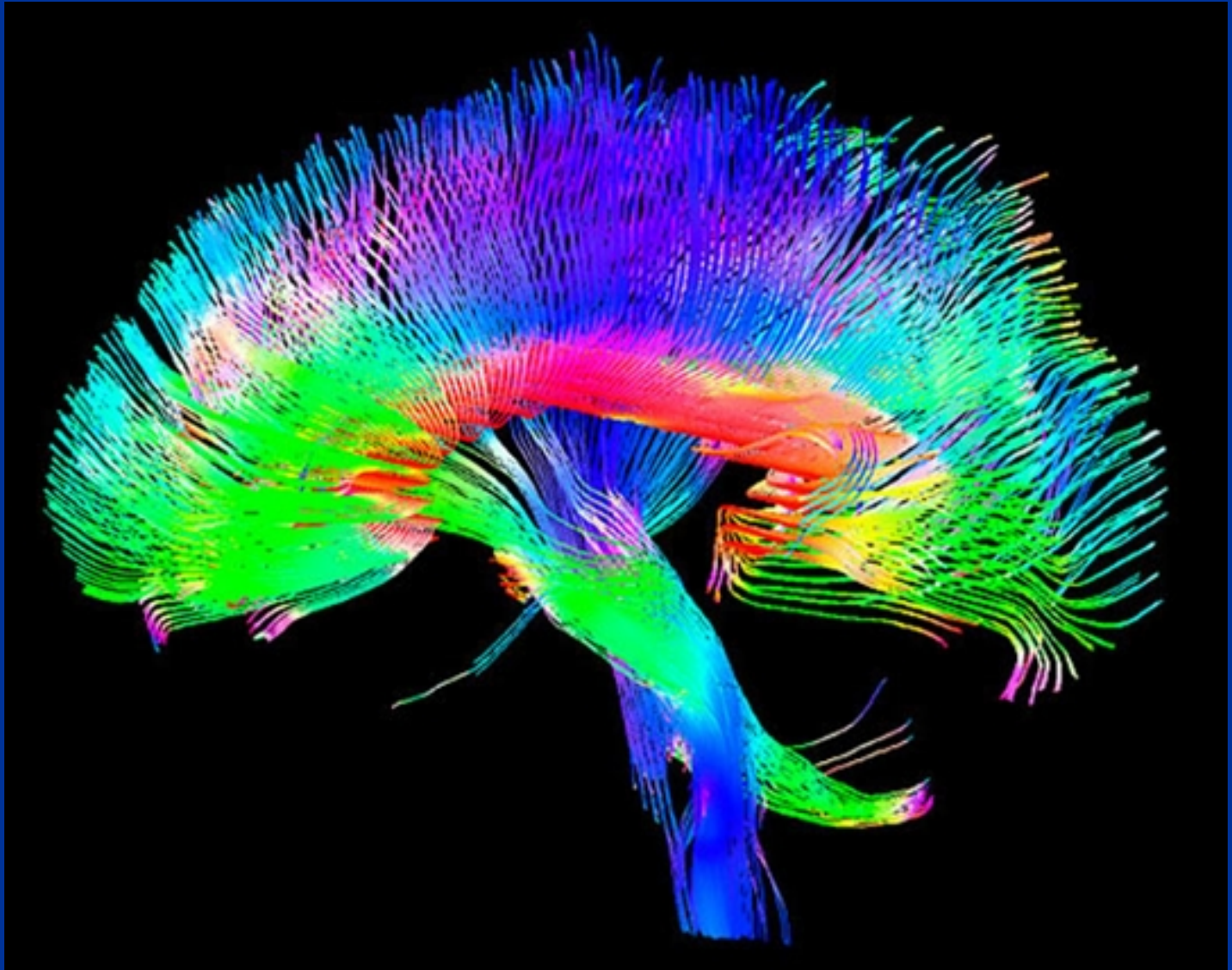
Problemi aperti della terapia delle malattie neurologiche

- E' possibile riparare il sistema nervoso?
- Probabilmente no
- E' possibile proteggere il sistema nervoso dai danni delle malattie prima che questi si manifestino?
- Probabilmente sì, ma dipende da costante tempo

Cervello umano

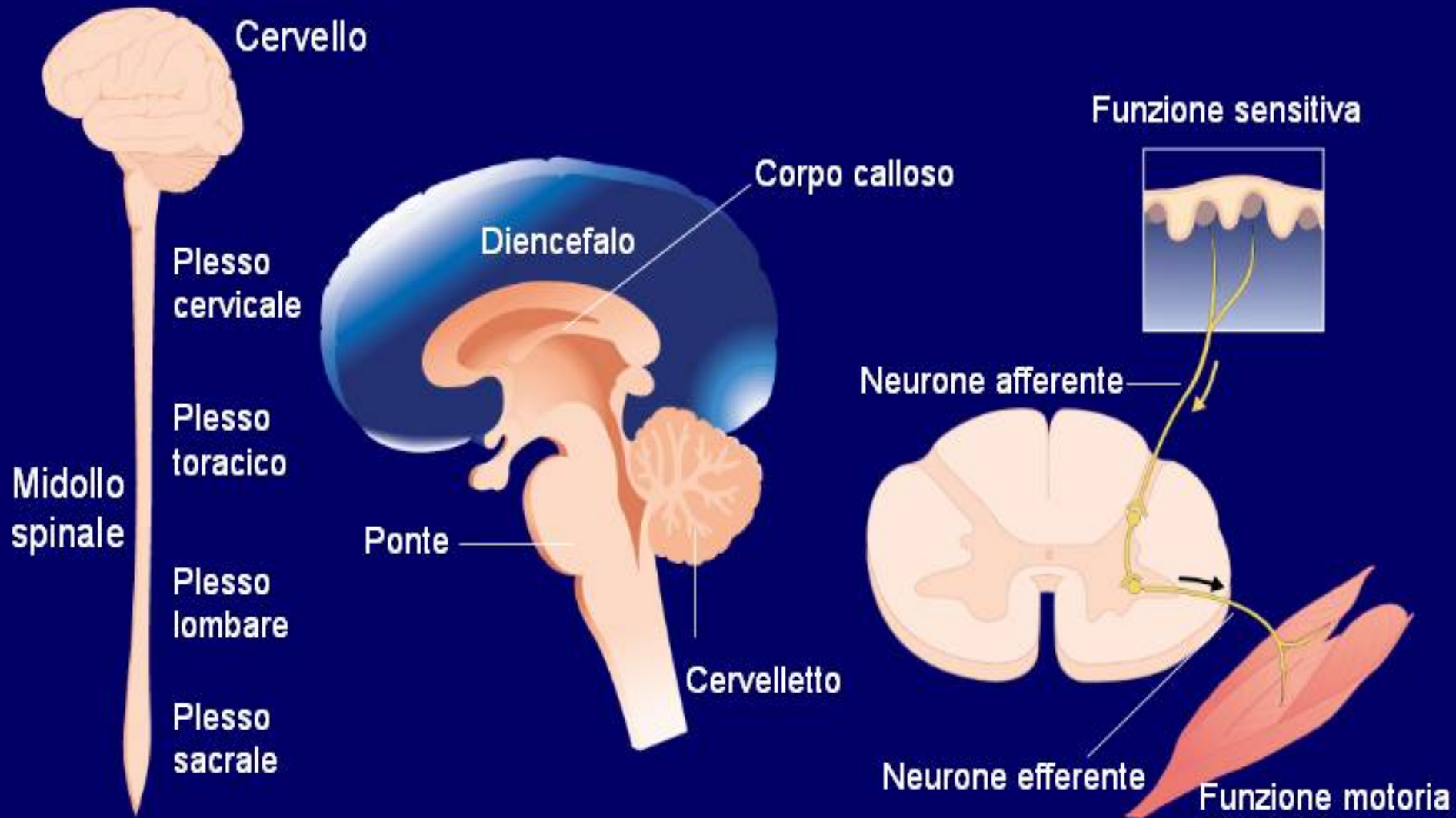


Trattografia MRI





Struttura del sistema nervoso centrale





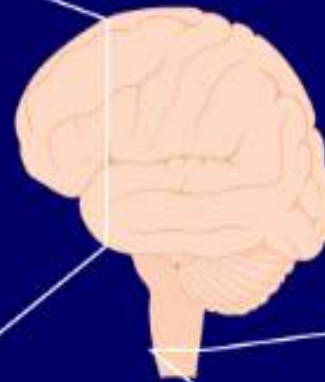
Sostanza grigia e bianca nel SNC

Sostanza grigia

Cervello



Sostanza bianca



Midollo spinale

Sostanza grigia

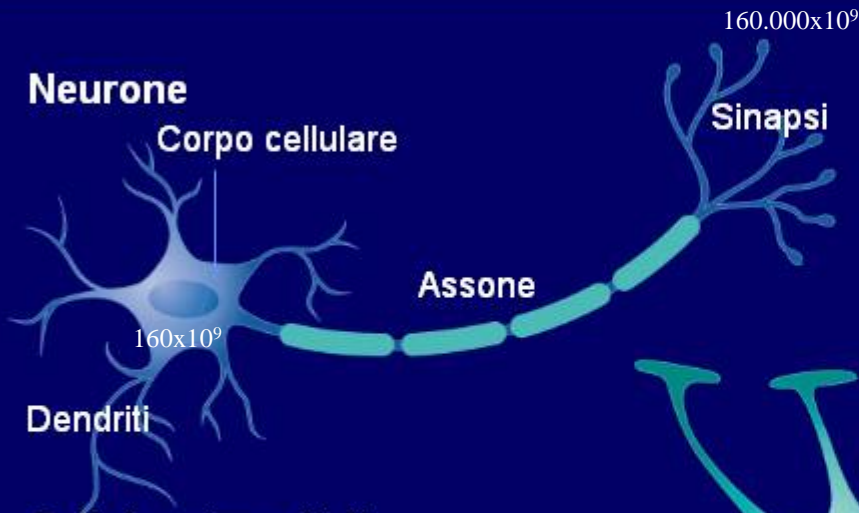


Sostanza bianca



Neurone e differenti tipi di cellule neurogliali

Neurone



Cellule microgliali

Inattive nel SNC normale, proliferano in condizioni patologiche e nella fagocitosi



Astrociti

Formano una struttura di supporto, hanno una funzione fagocitaria, prendono il posto dei neuroni morti



Oligodendrociti

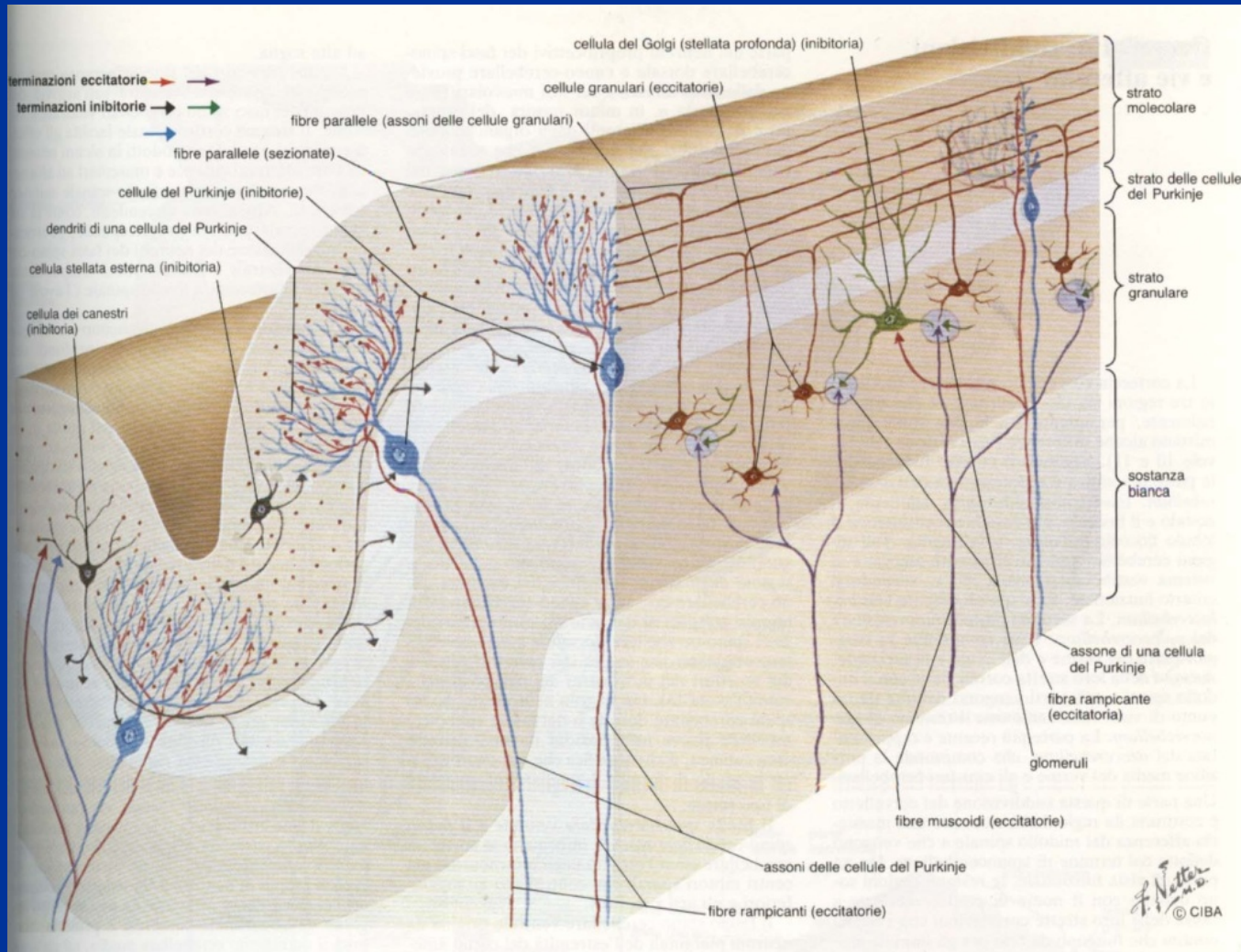
Formano la mielina nel SNC, influenzano la biochimica dei neuroni



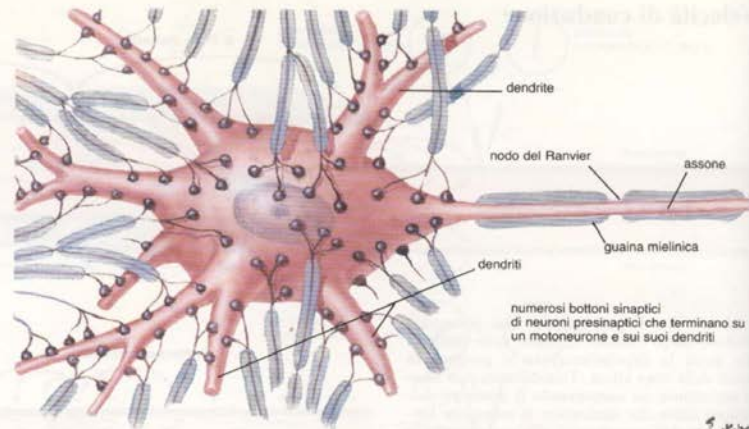
Camillo Golgi



Componenti cellulari del tessuto nervoso

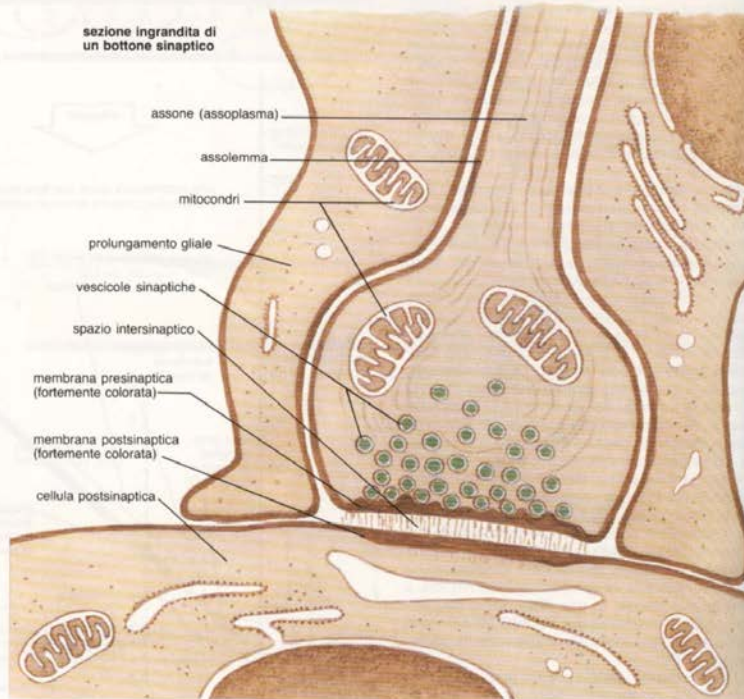


sinapsi

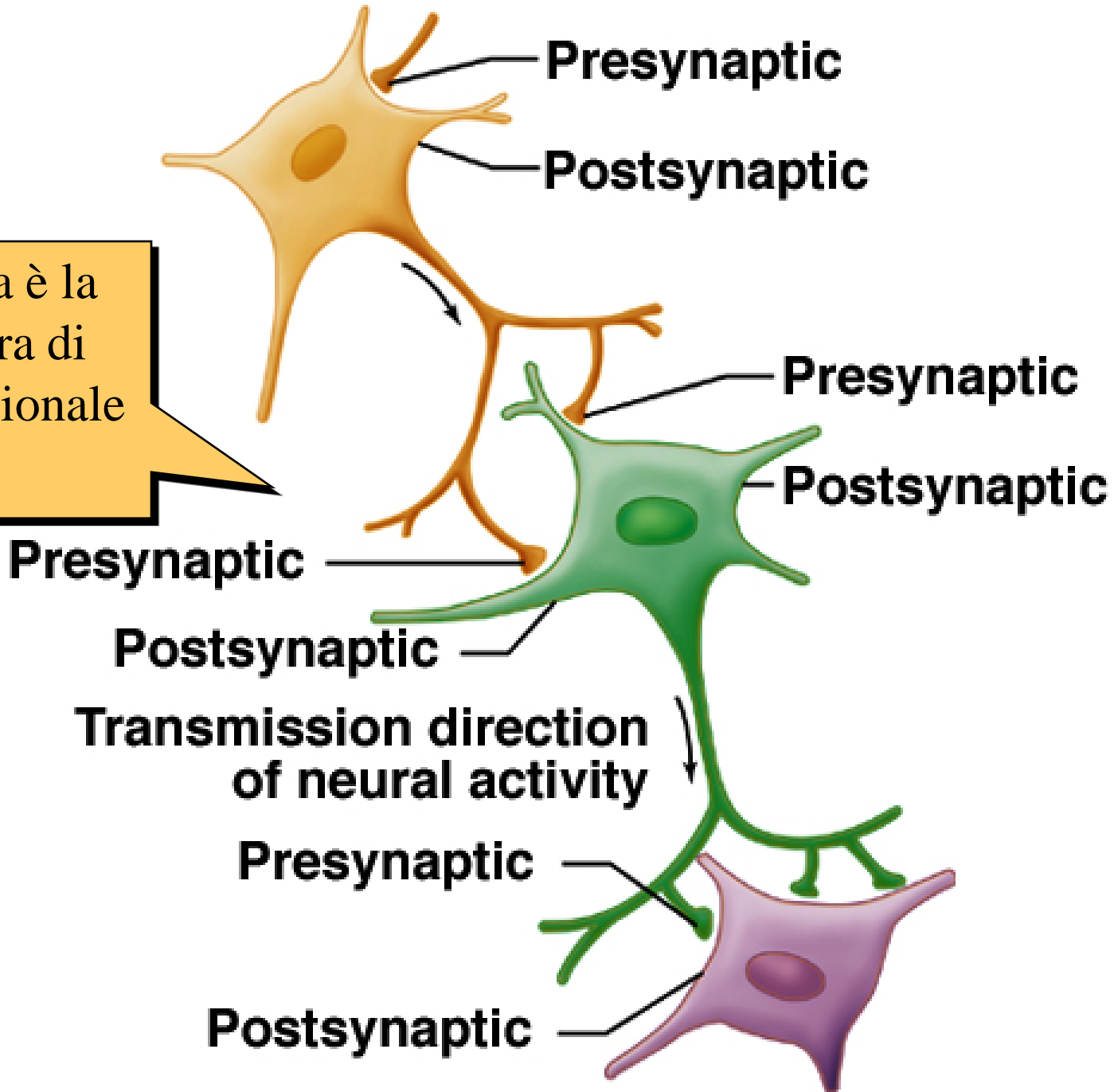


F. Netter
M.D.
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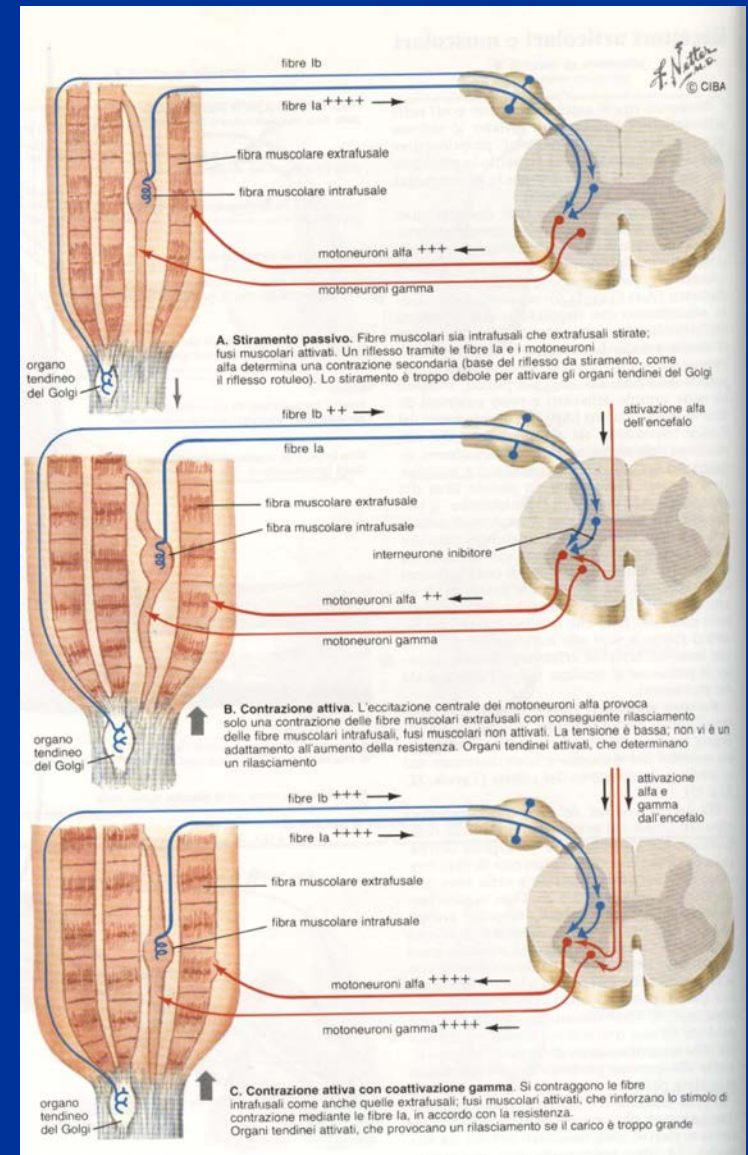
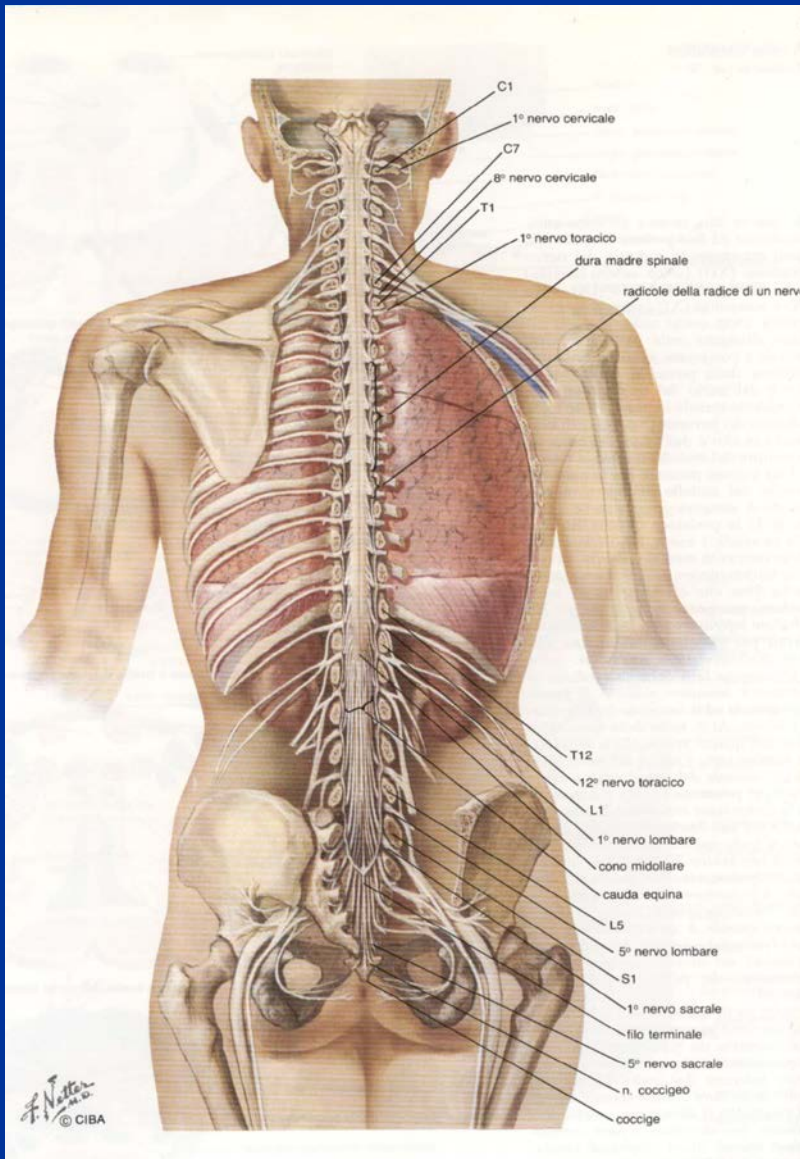
sezione ingrandita di un bottone sinaptico

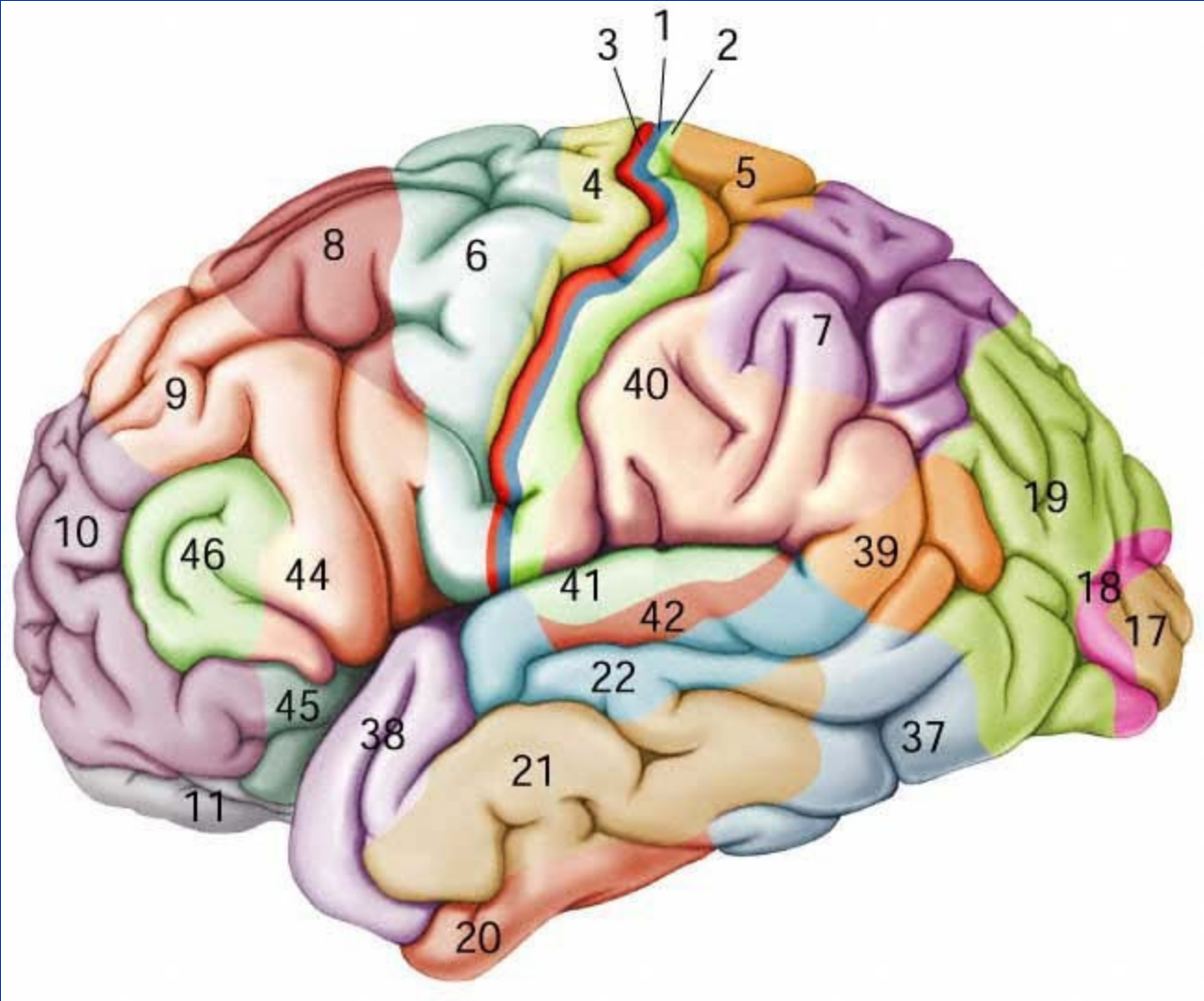


la sinapsi chimica è la principale struttura di connessione funzionale fra neuroni



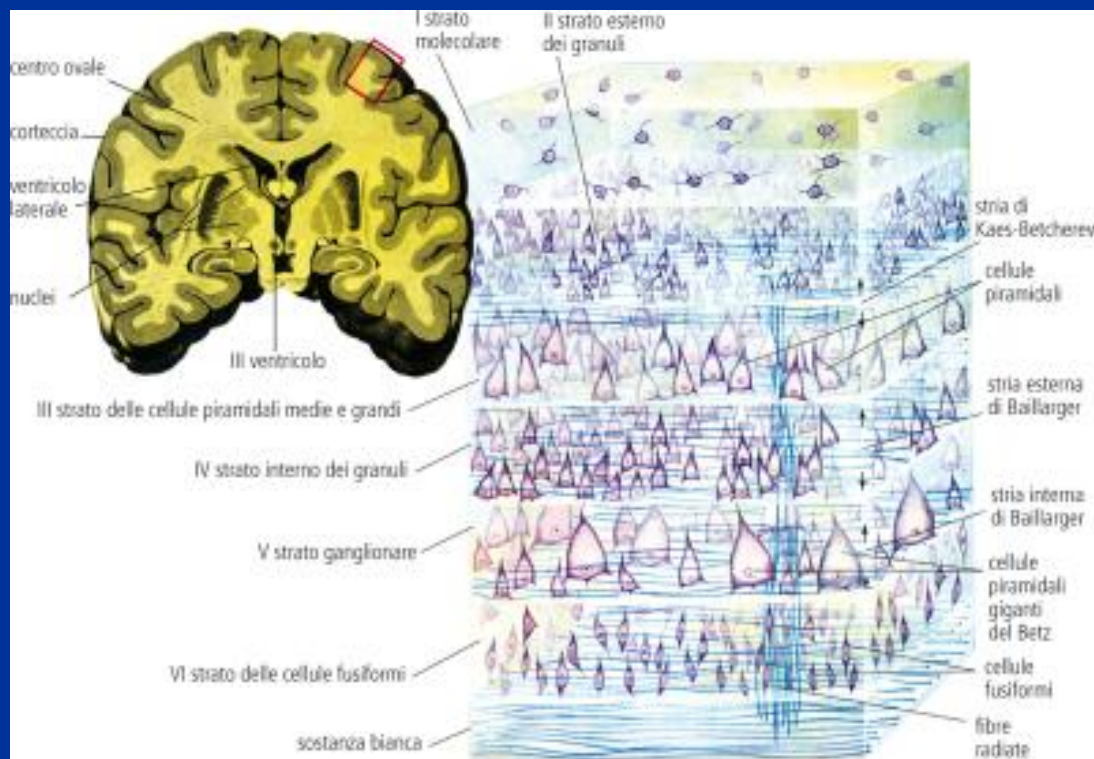
Midollo spinale e sistema nervoso periferico

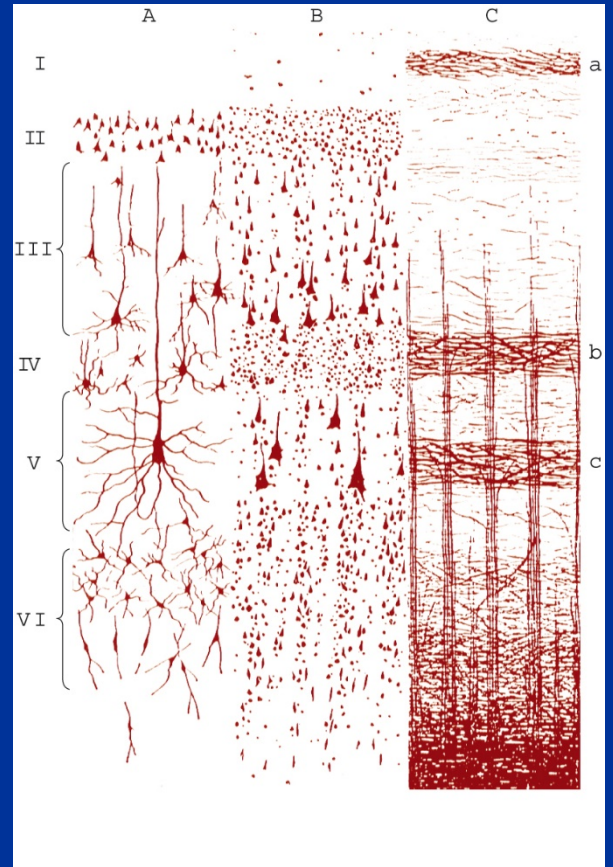
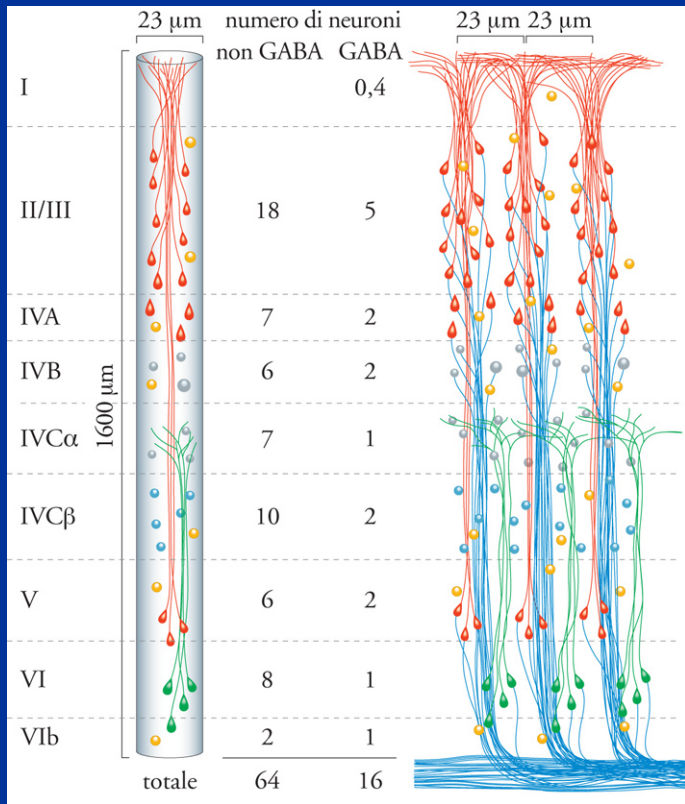




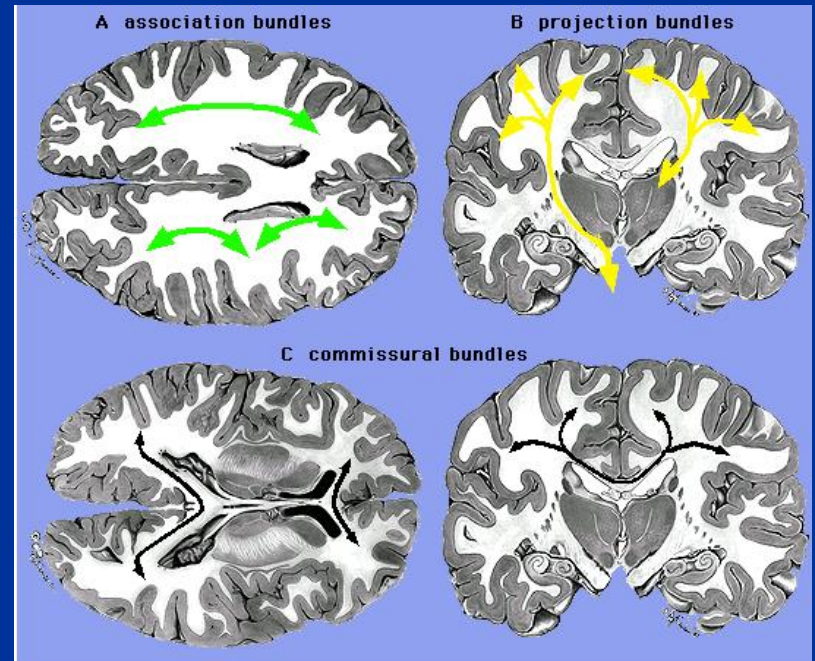
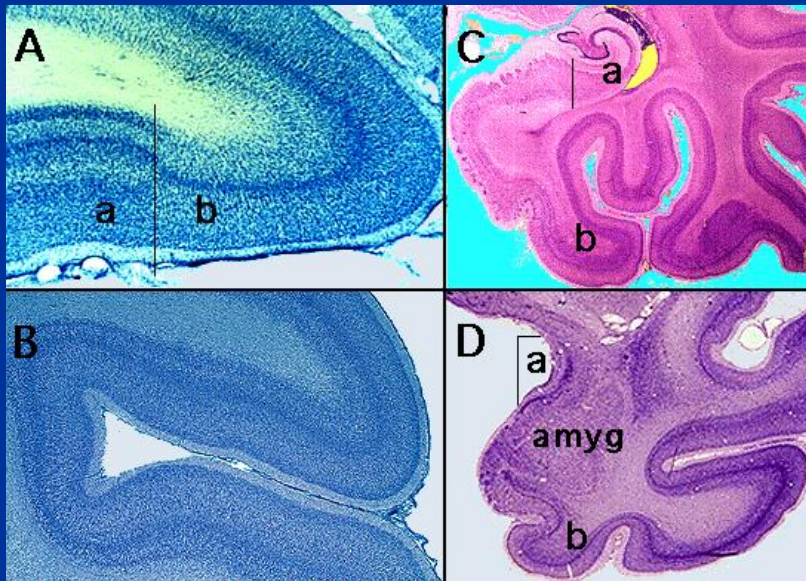
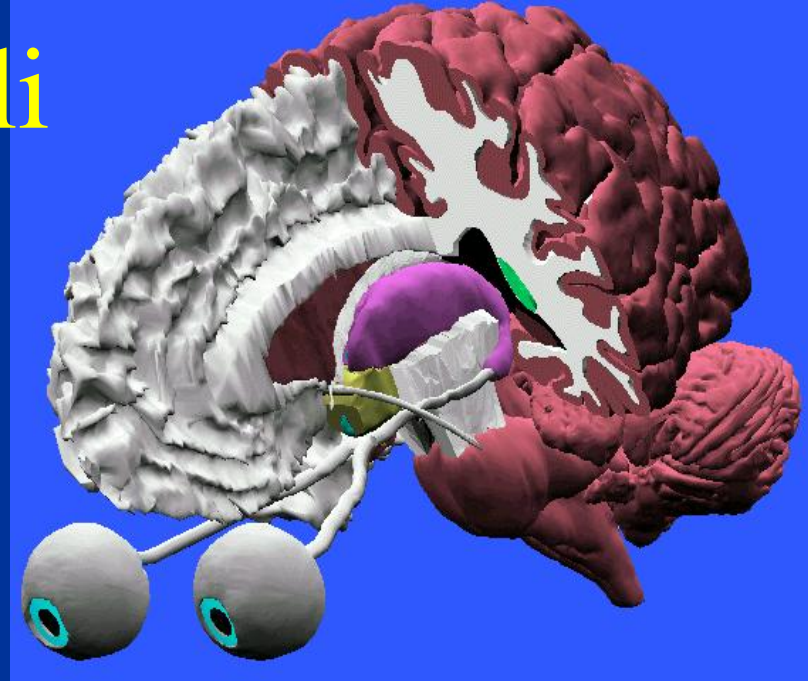
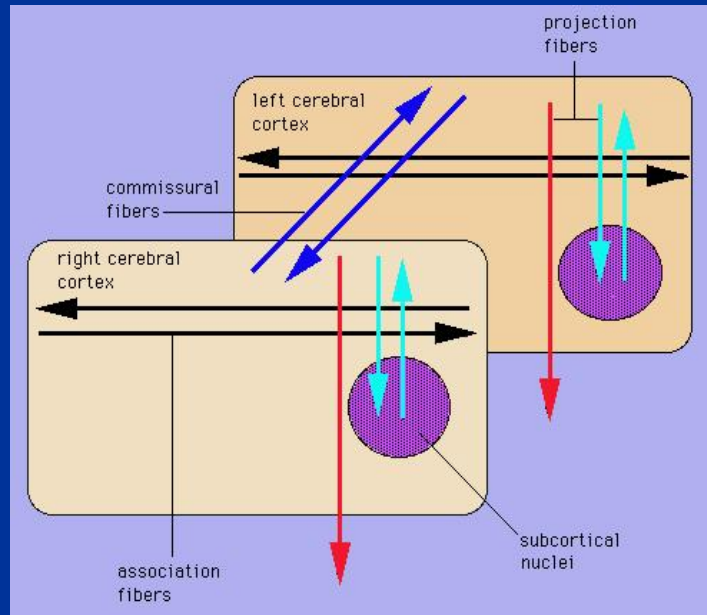
Corteccia Cerebrale

- 2600 cm²,
- Spessore, 3÷4 mm;
- 60×10⁹ neuroni (100×10⁹ nel cervelletto);
- 10¹² cellule gliali e dei vasi
- 100-1000 x10¹¹ 'sinapsi'
- 1.6 x10⁹ cm di fibre

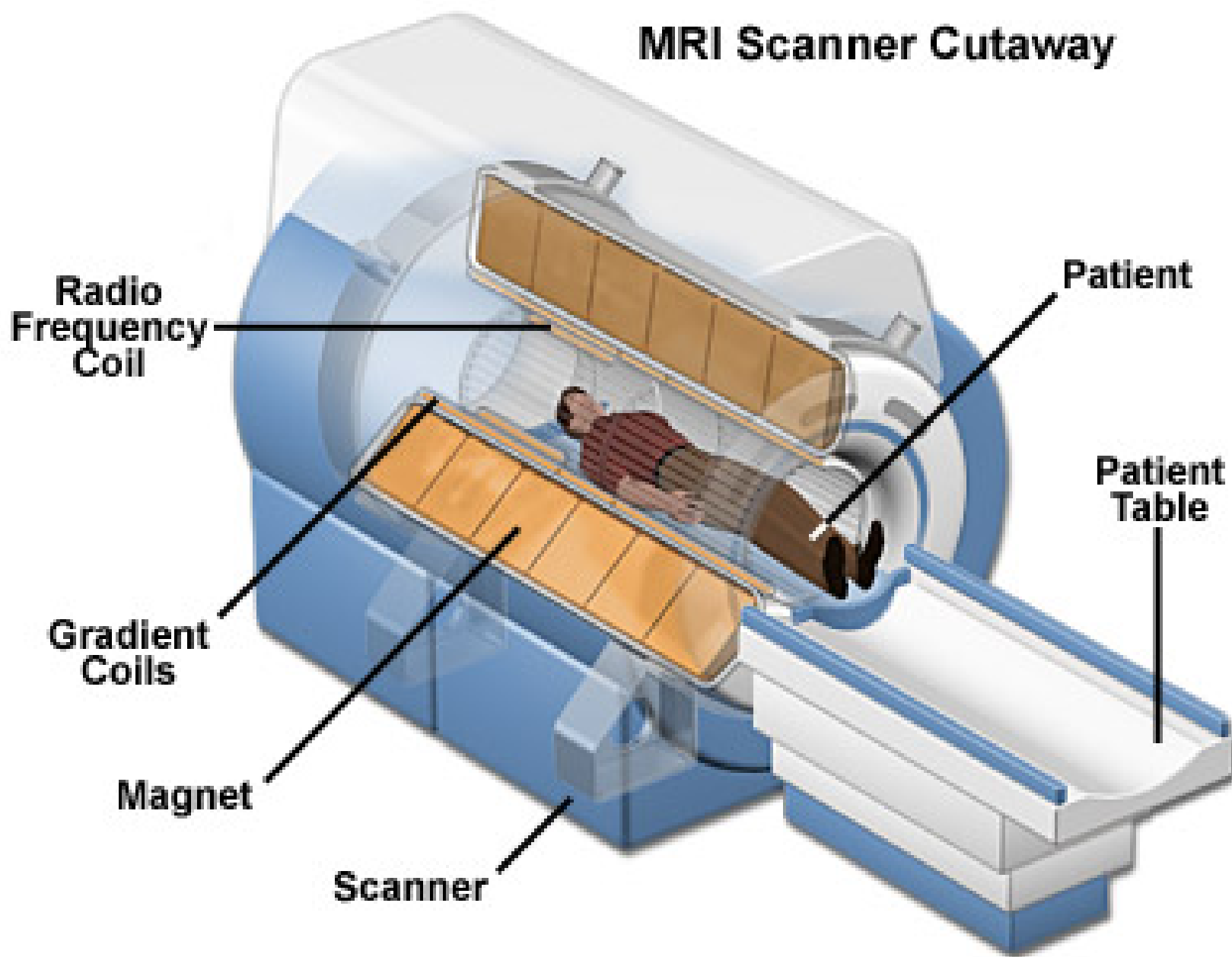




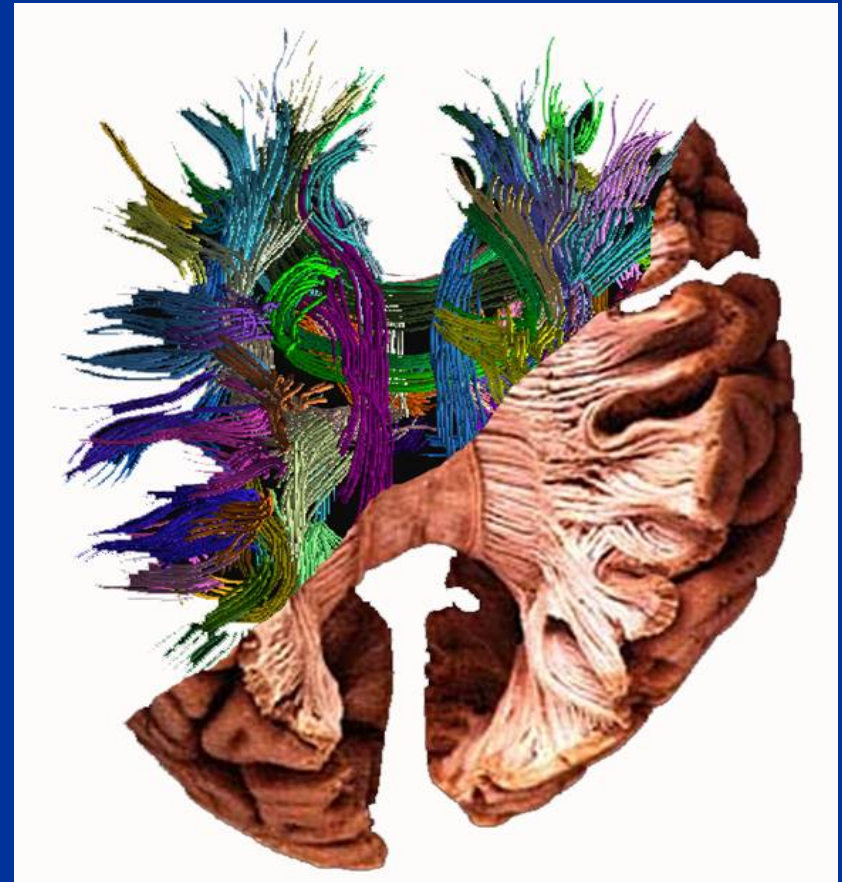
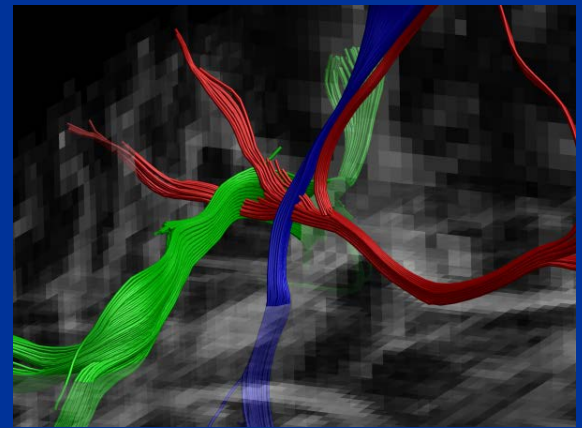
connessioni cerebrali



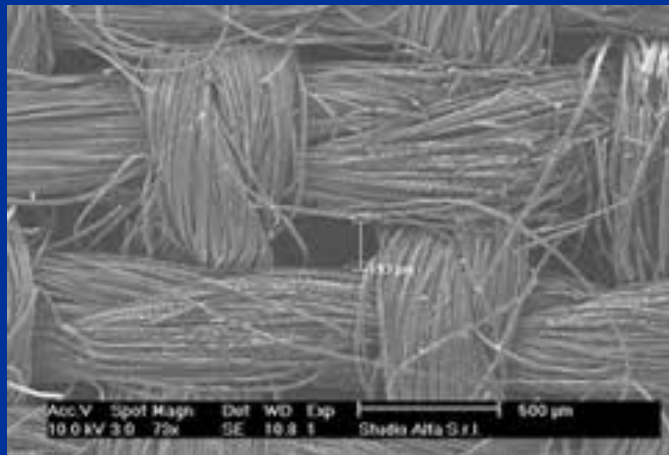
MRI Scanner Cutaway



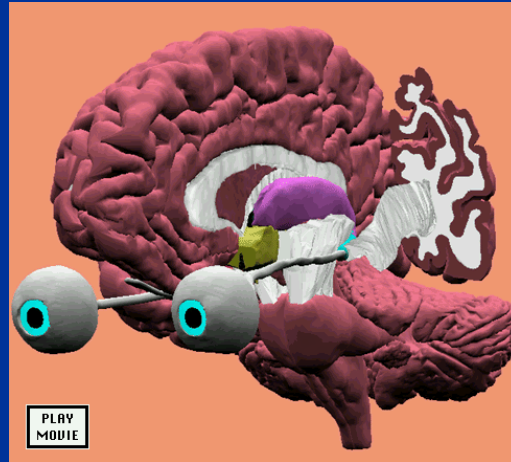
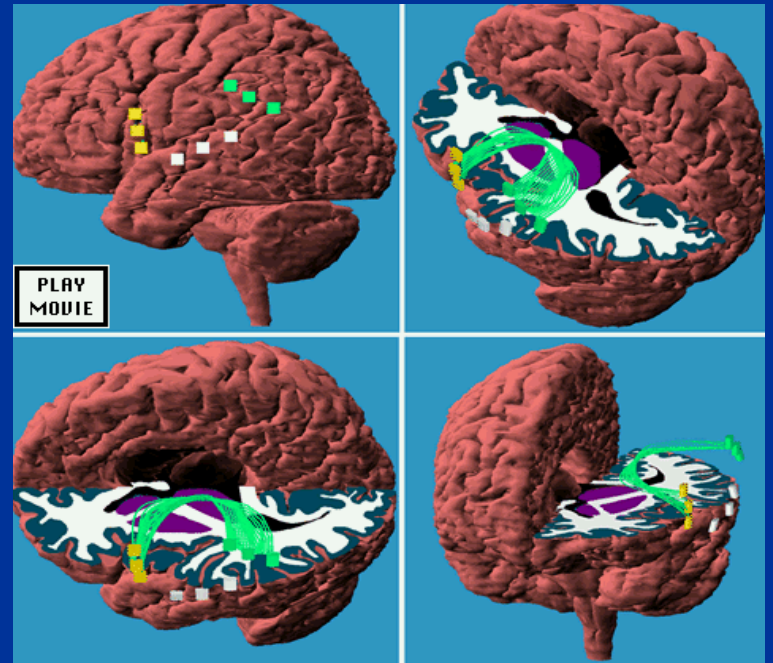
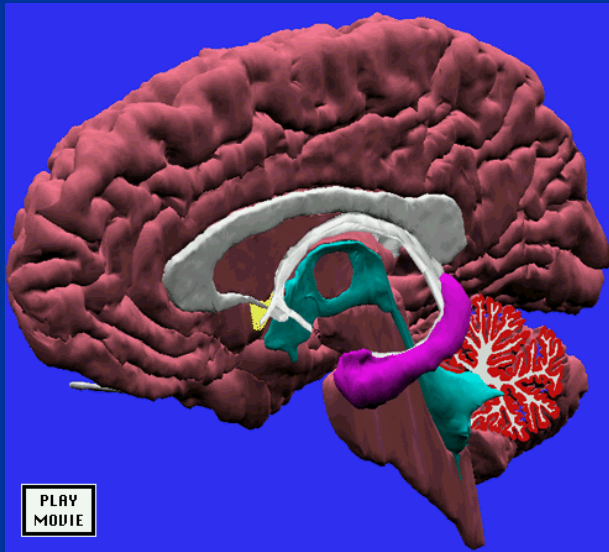
MRI tractography and connectome



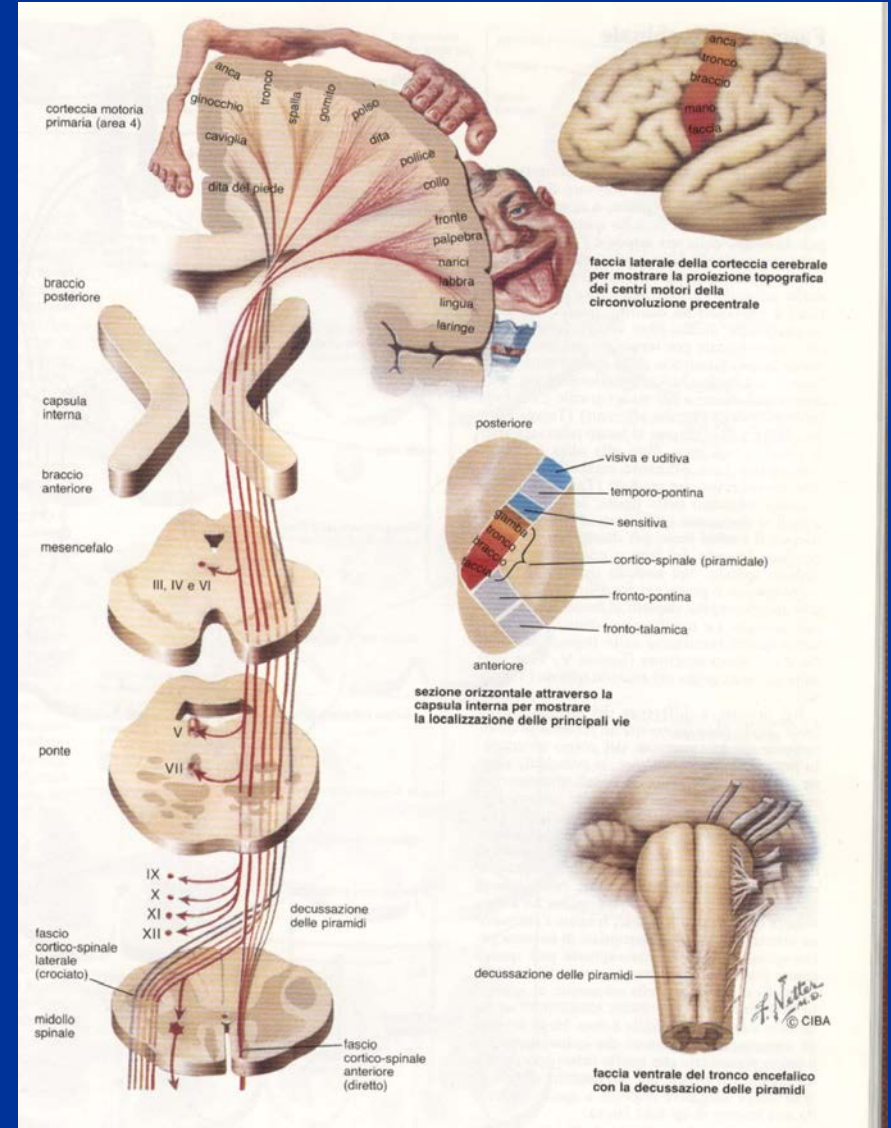
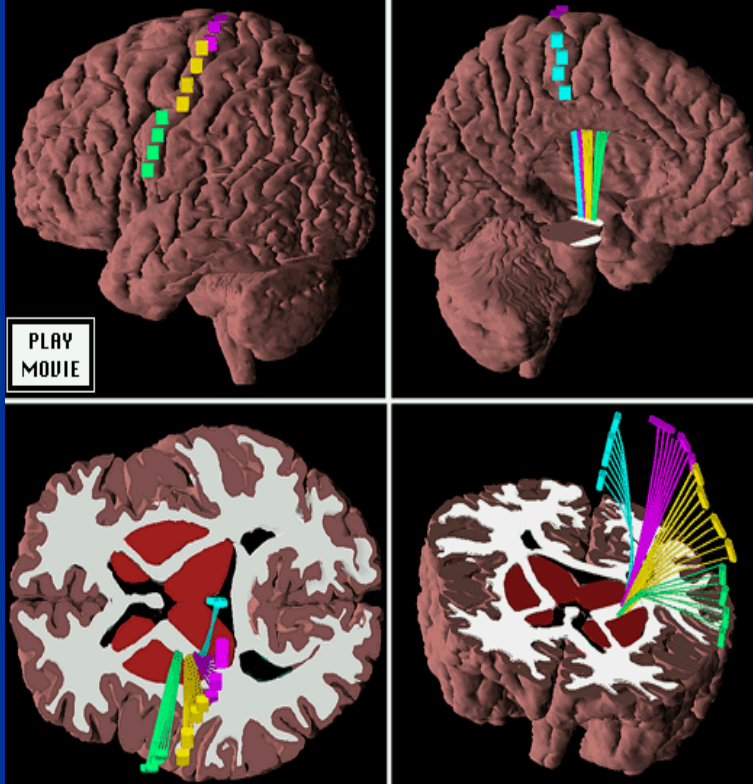
La sostanza bianca cerebrale è proprio un gomitolo di tessuto



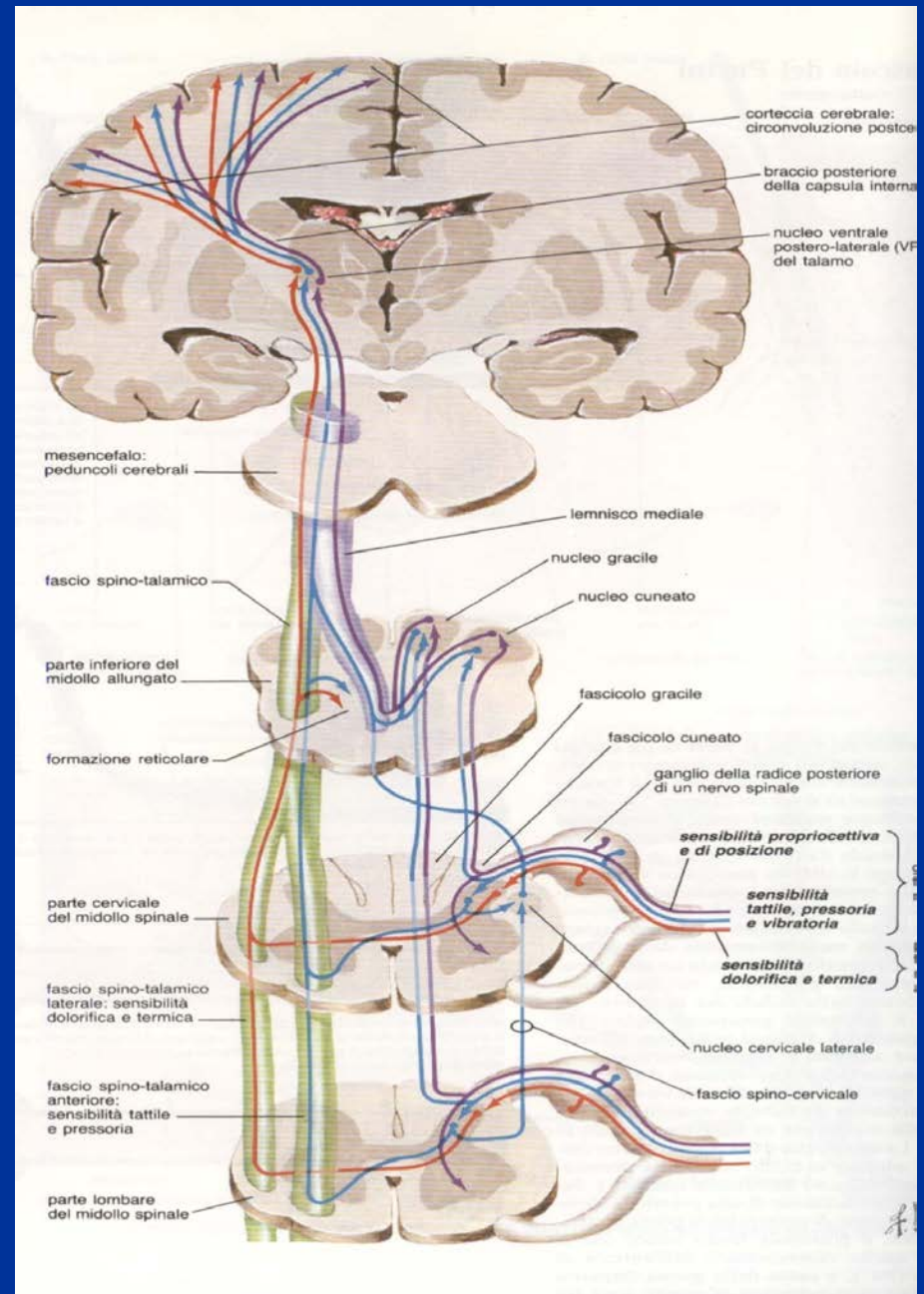
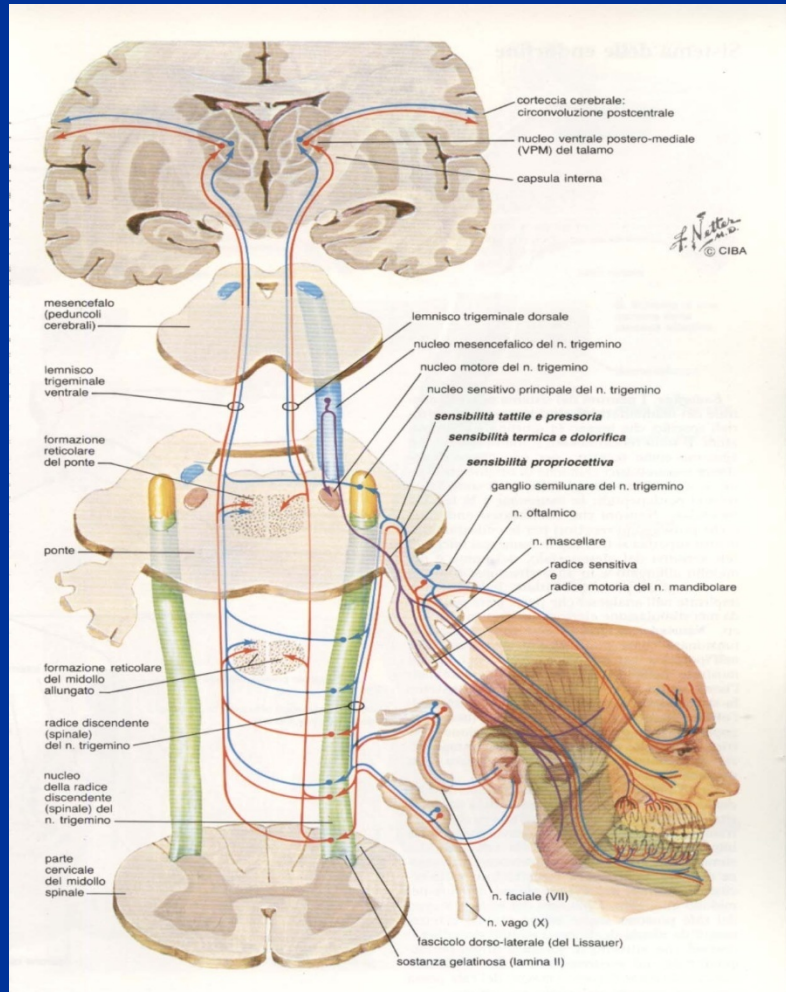
Altre vie nervose



Via motoria primaria



Vie sensibilità



Aspetti quantitativi

- **Neuroni :**

- Corpo, diametro: 10-15 μ
- Assone, lunghezza: fino a dm
- n.= 160×10^9
- cervelletto > cervello
- 10 % peso totale

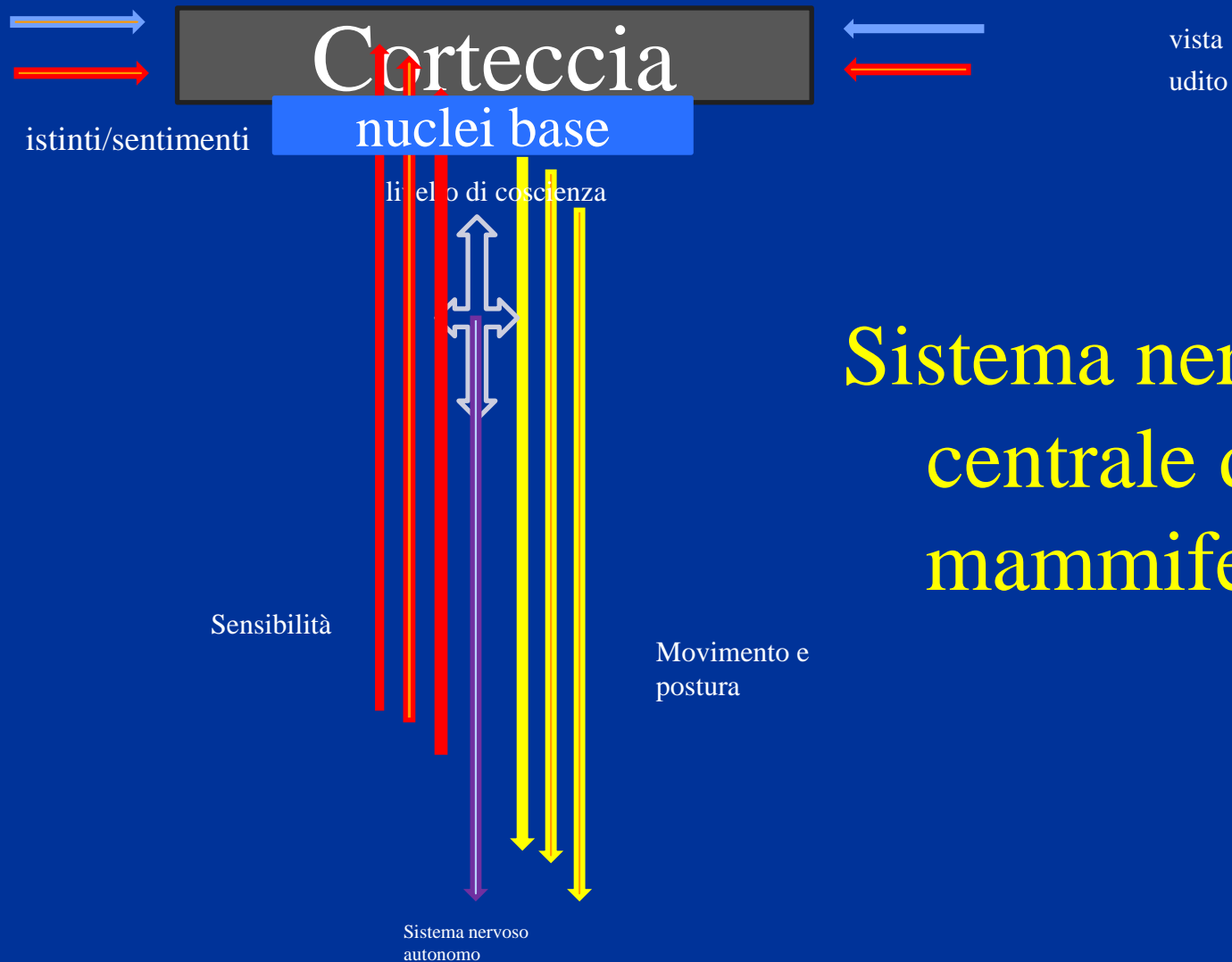
• **Peso cervello: 1.500 g**

- **Sinapsi:** 10^{12-14}

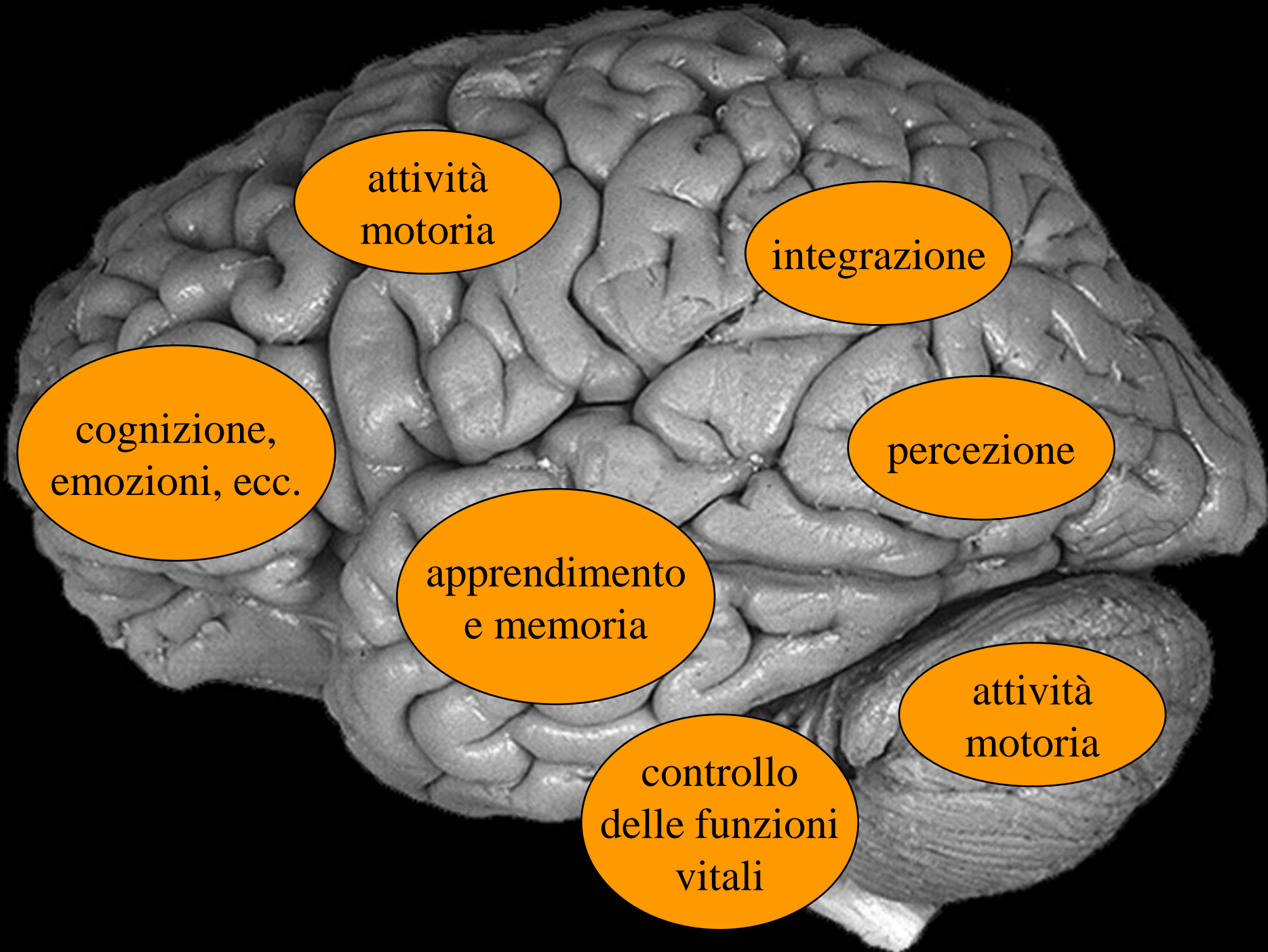
- **Assoni : 16×10^9** **(160.000 km)**

- **Glia vasi e sangue:**

- cellule: 10^{12}
- 90% peso



Sistema nervoso centrale del mammifero



attività
motoria

integrazione

cognizione,
emozioni, ecc.

percezione

apprendimento
e memoria

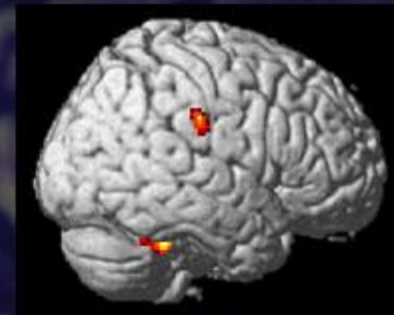
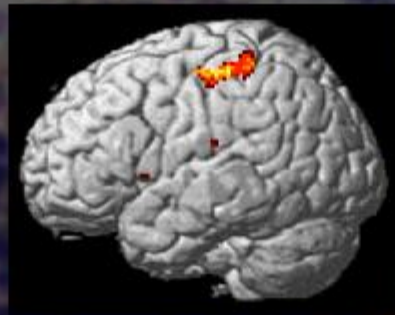
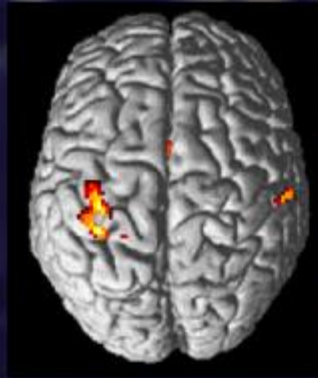
controllo
delle funzioni
vitali

attività
motoria

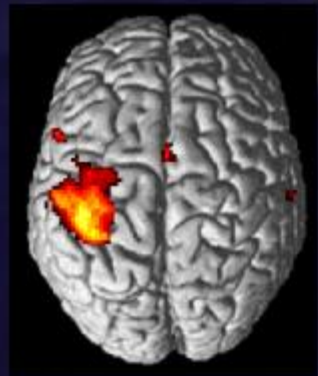
RM funzionale

Pazienti CIS

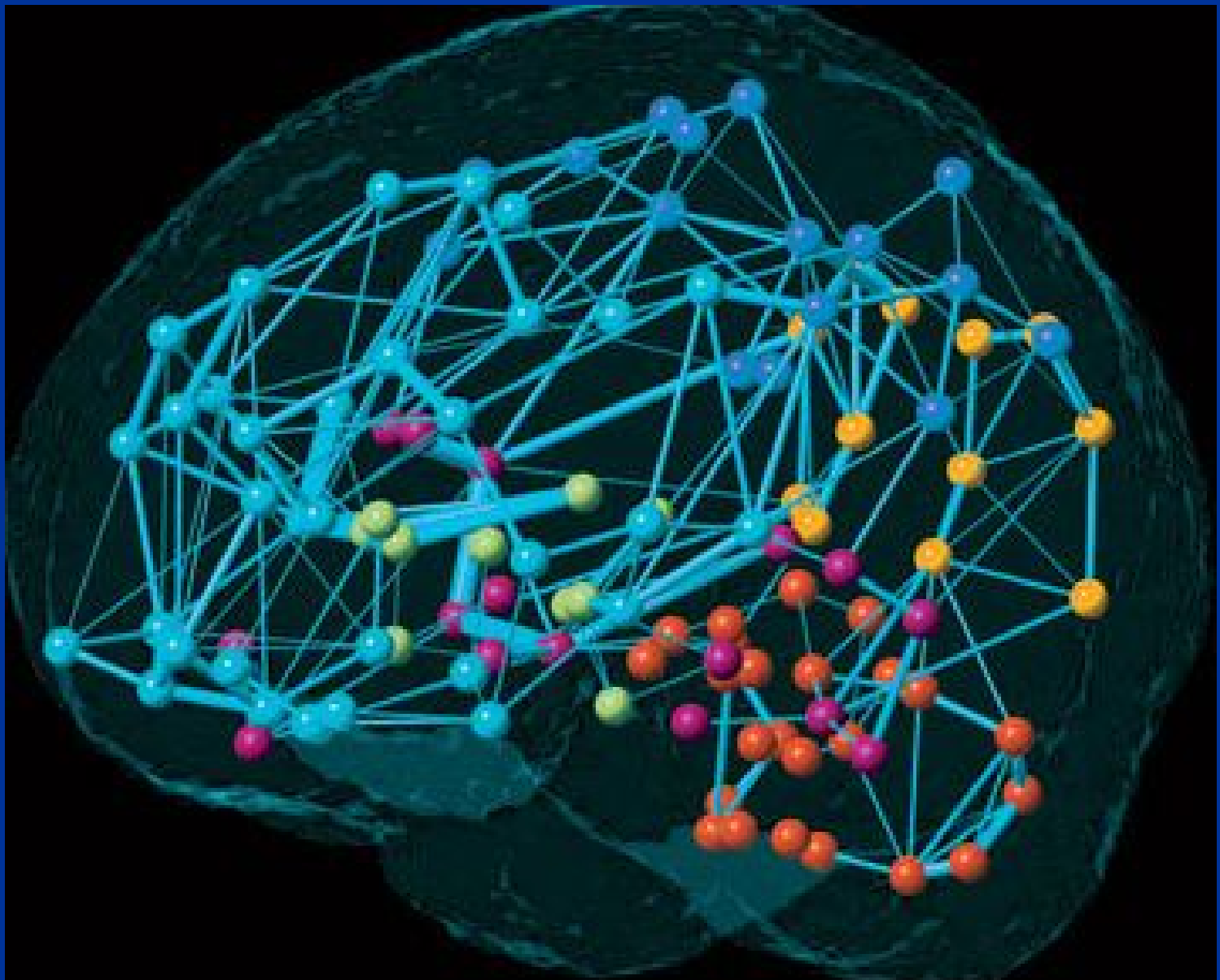
Controlli sani



CIS

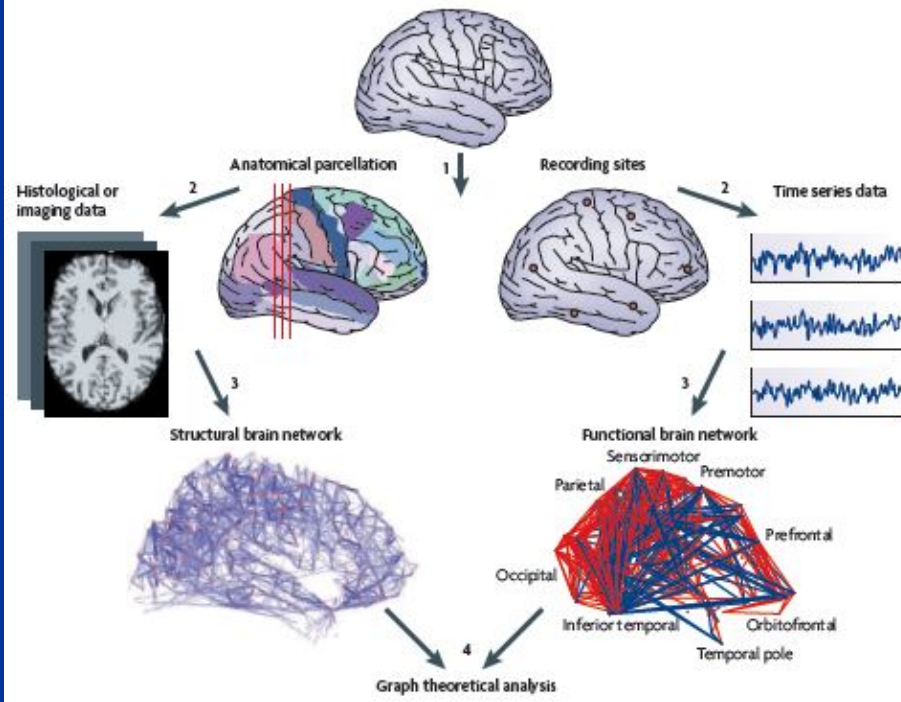


Rocca et al., Neurology (in press)

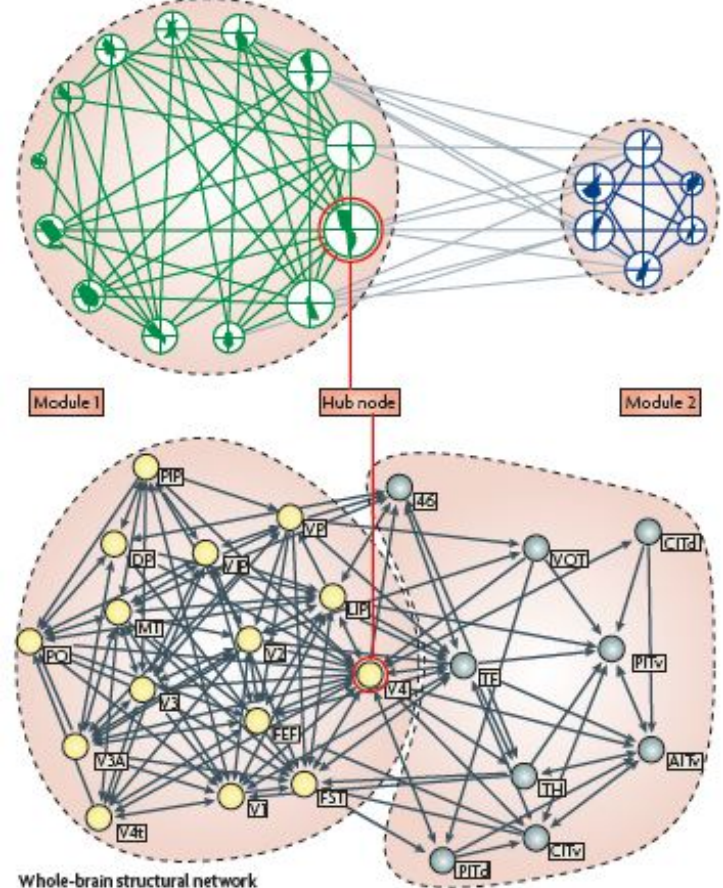


Organizzazione circuiti: hub e spoke

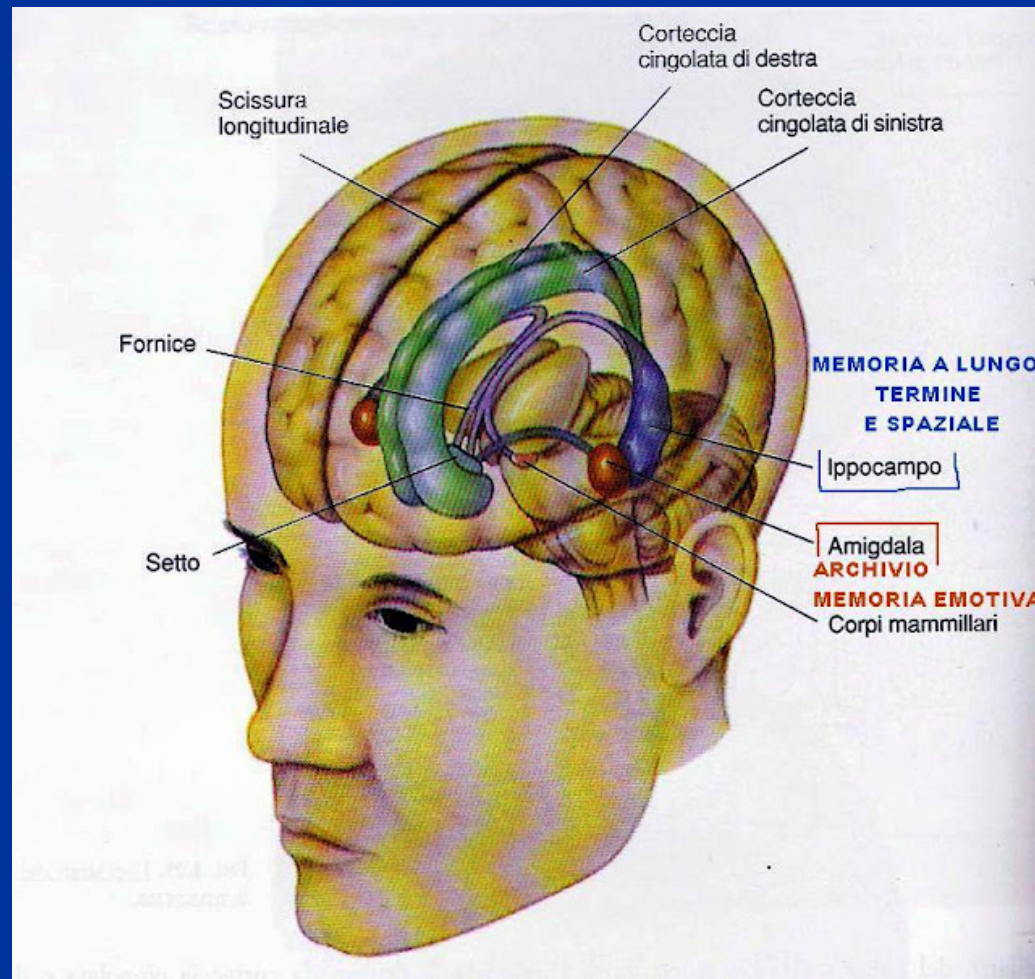
Box 1 | Structural and functional brain networks



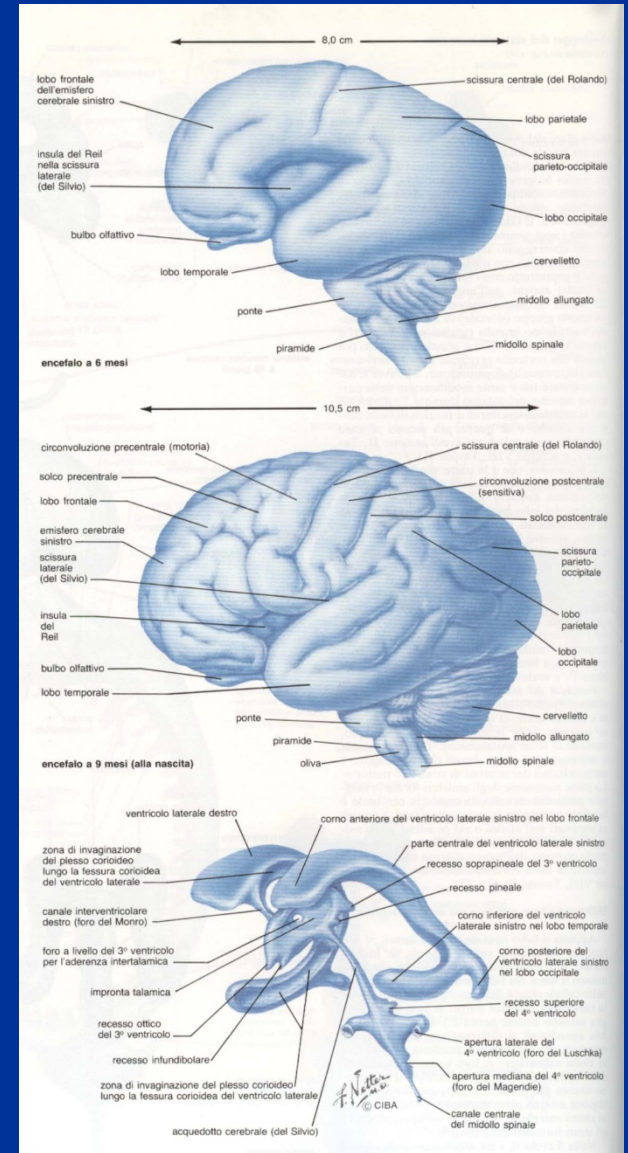
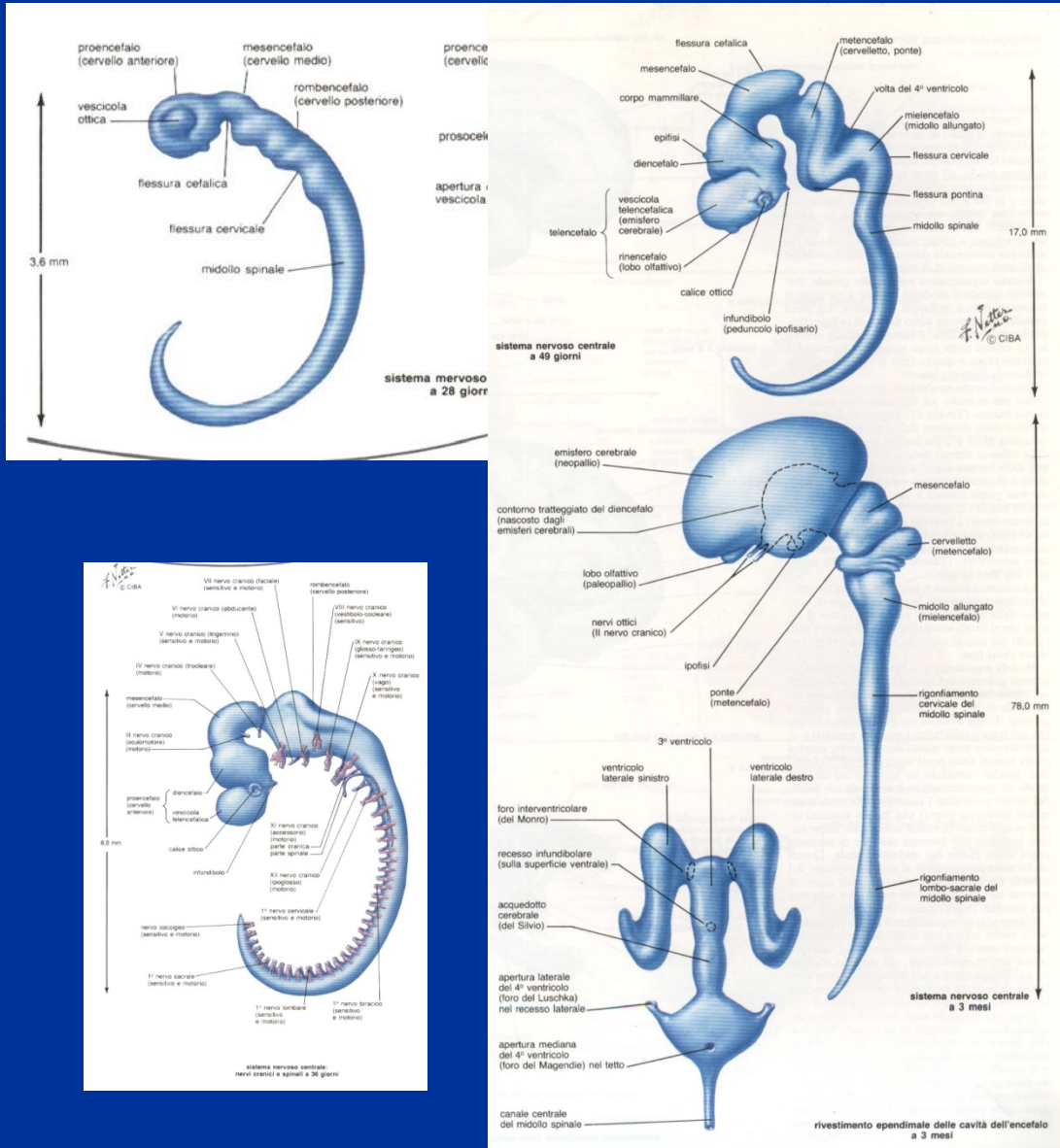
Cellular functional network



Nucleo dell'amigdala e memoria



Sviluppo embriologico



Ontogenesi e filogenesi

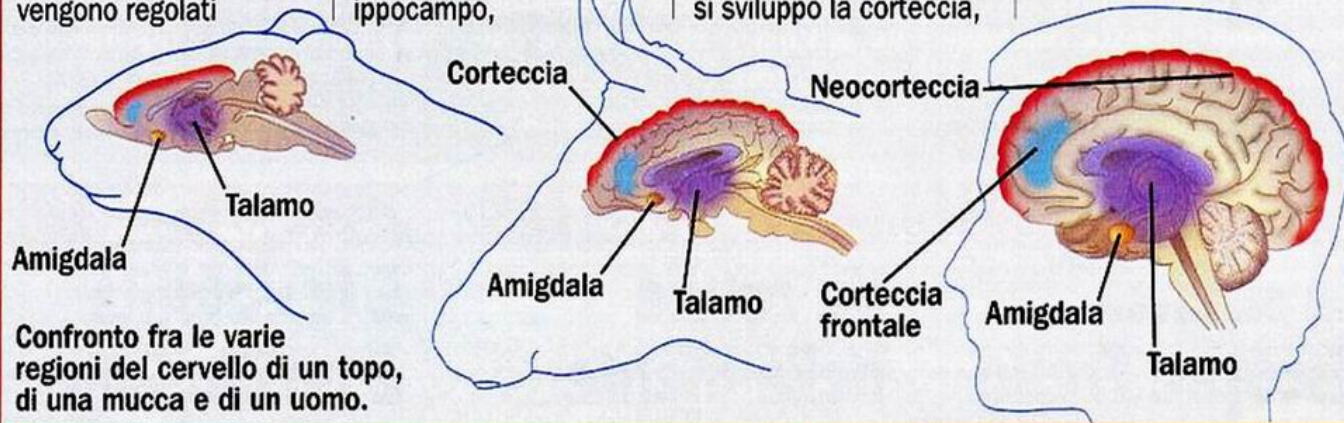
Dentro il cervello strati antichissimi

Che emozioni e ragionamento siano collegati lo dimostra l'architettura del cervello umano. Il suo nocciolo più antico, lo strato più interno posto al termine della spina dorsale, il tronco cerebrale, è la "stanza caldaie e contatori": lì vengono regolati

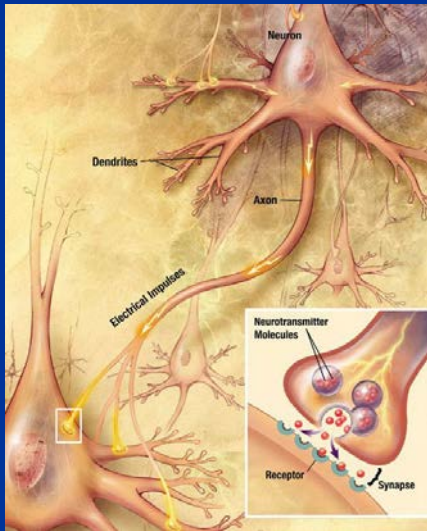
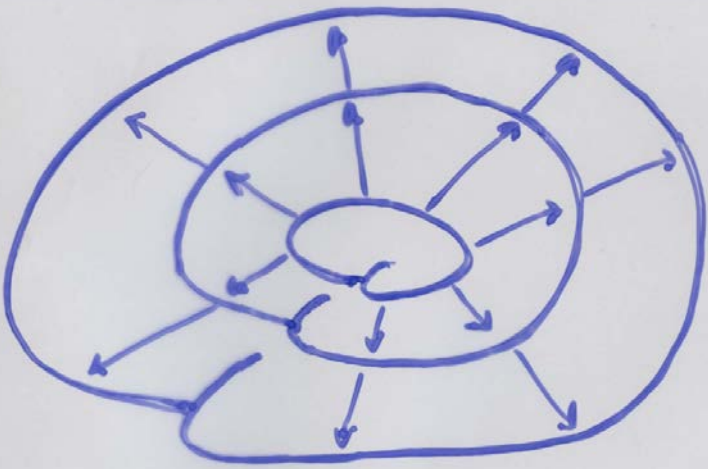
battito cardiaco, respirazione, erezione. **Sistema limbico.** Milioni di anni dopo, questo primo nucleo, presente già nei rettili, fu avvolto da una formazione ad anello, il sistema limbico, dove hanno sede i centri delle emozioni: ippocampo,

amigdala, talamo e ipotalamo. Il talamo è un relais di smistamento, nell'amigdala sono depositate paure e ansie; nell'ippocampo i ricordi dei contesti di quelle paure. Attorno al sistema limbico, presente nei primi mammiferi (come i topi) si sviluppò la corteccia,

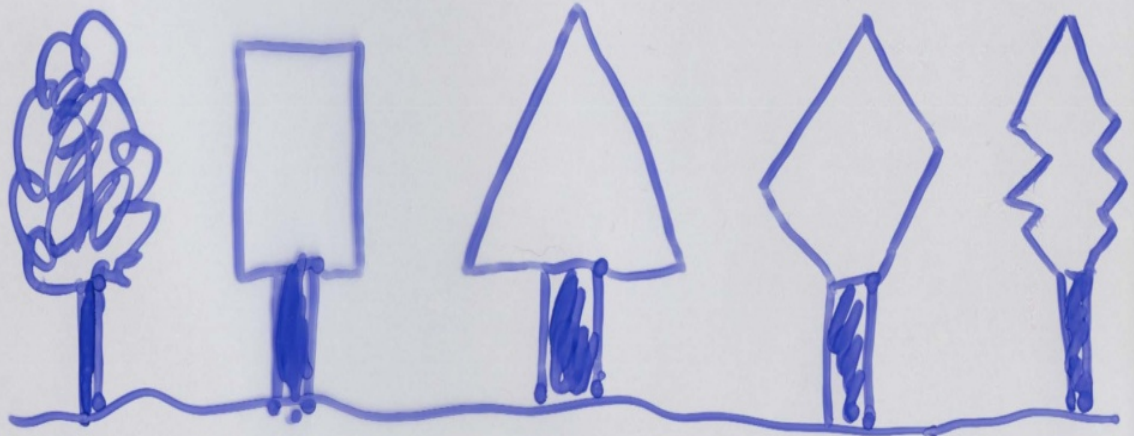
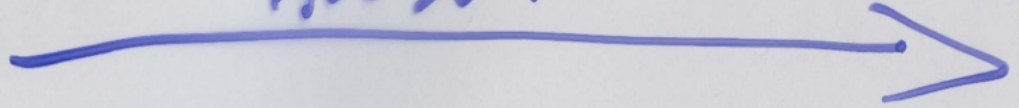
dove vengono elaborate le informazioni giunte dai 5 sensi. Infine, 100 milioni di anni fa, tutto è stato avvolto con l'ultimo strato, la neocorteccia, che nell'uomo è particolarmente sviluppata: qui risiedono ragione, morale, volontà, senso di colpa.



Neuronal Darwinism



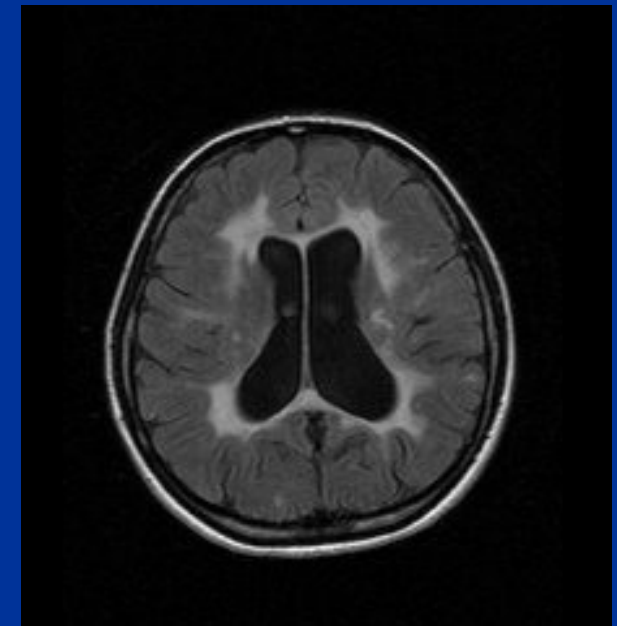
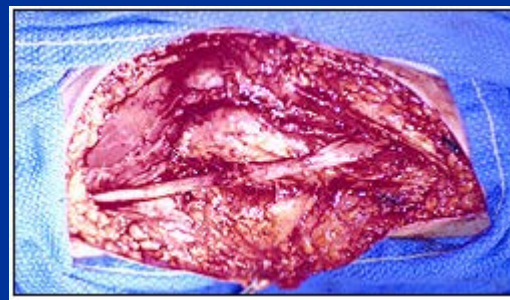
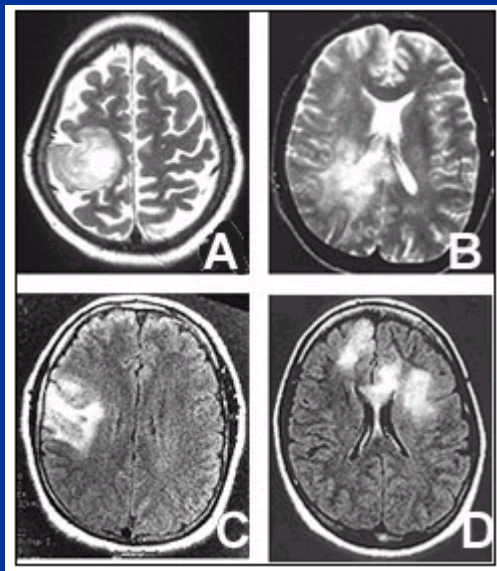
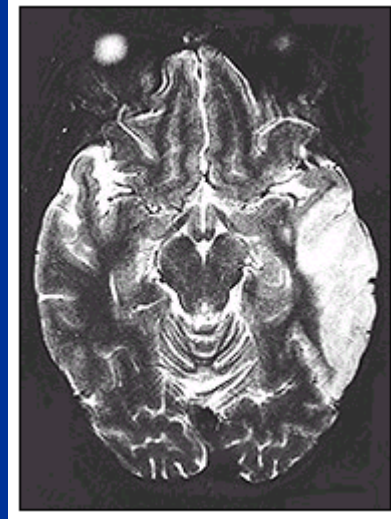
ANNI



Malattie neurologiche: perdita di tessuto nervoso



Gross brain atrophy in Alzheimer disease



Conduzione Normale



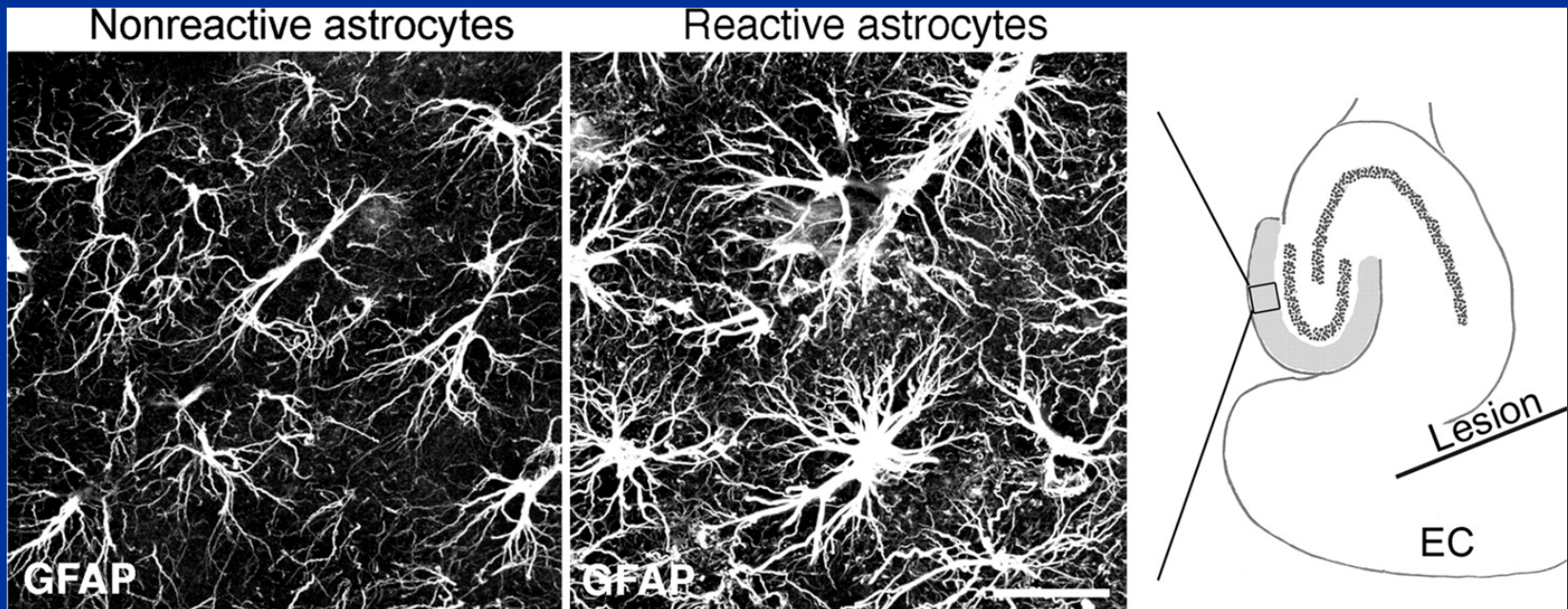
Conduzione Rallentata



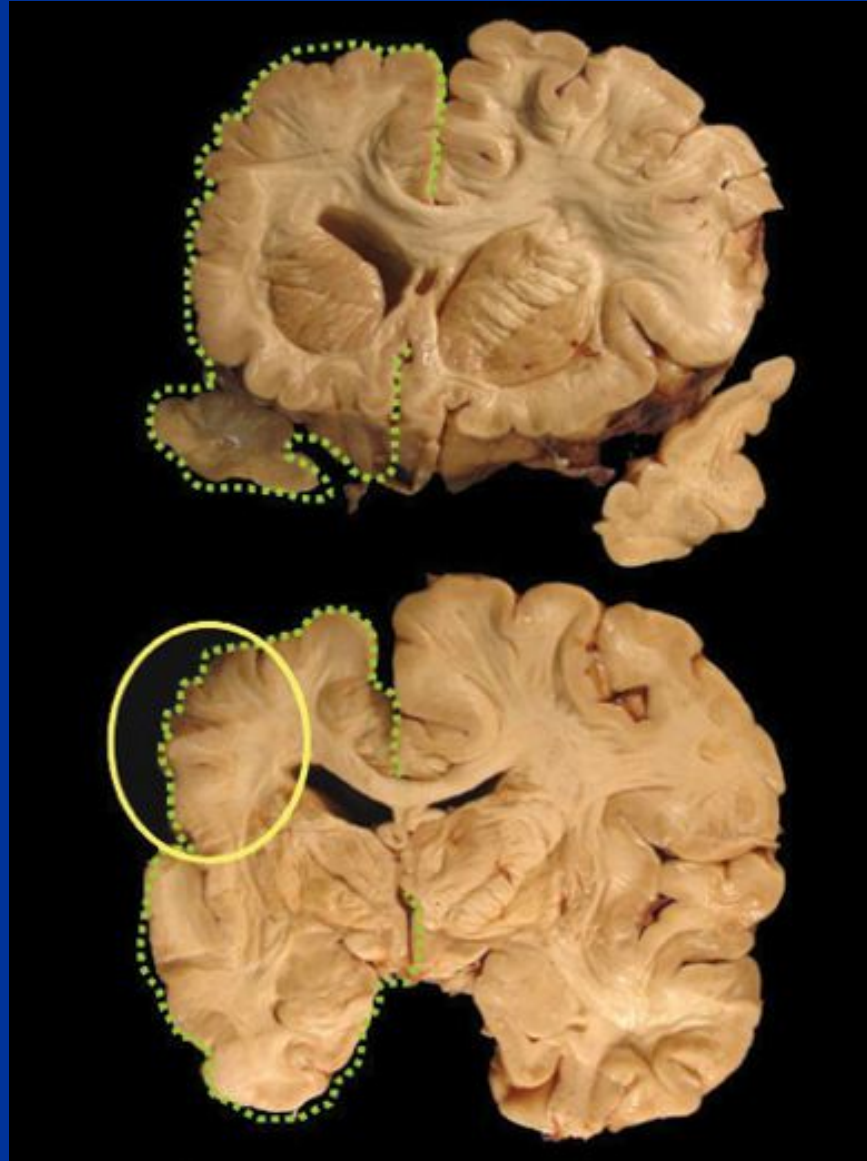
Conduzione Interrotta



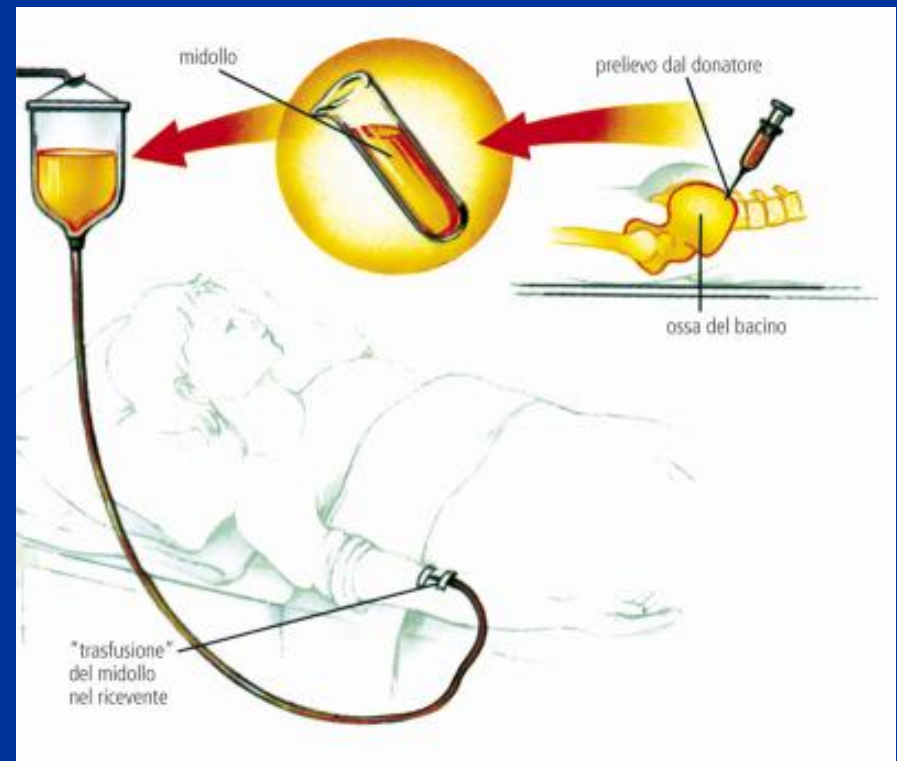
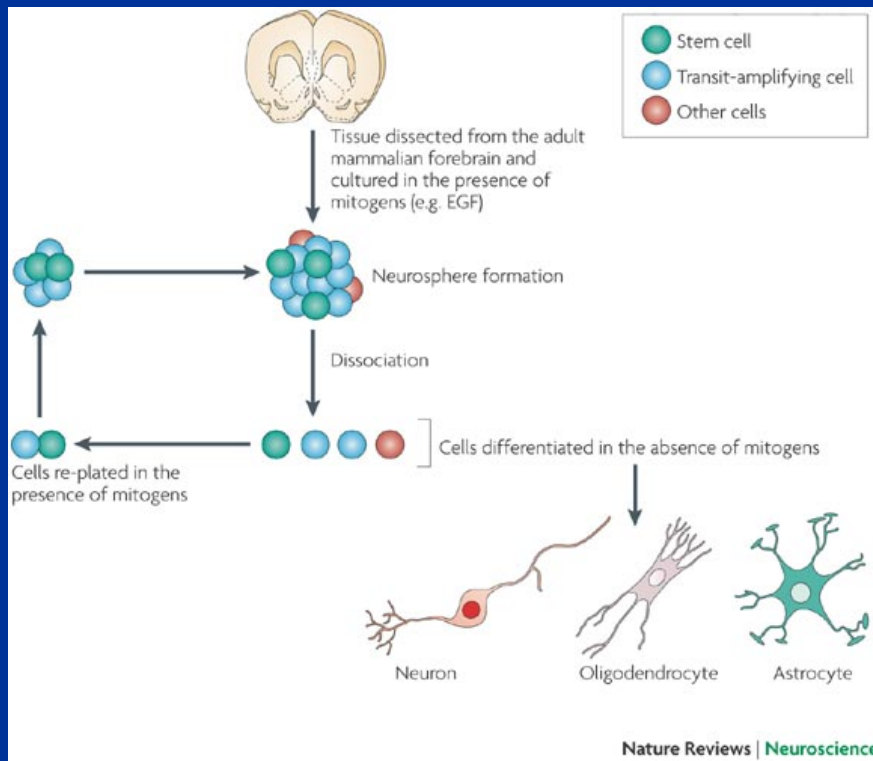
Gliosis as biological basis of neurodegeneration



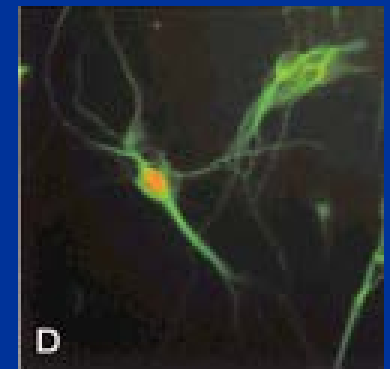
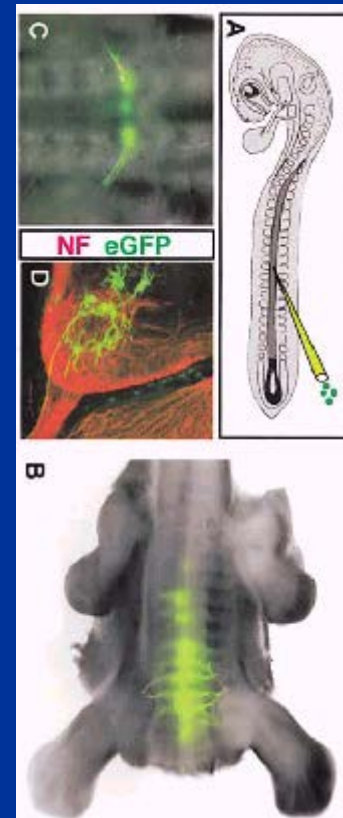
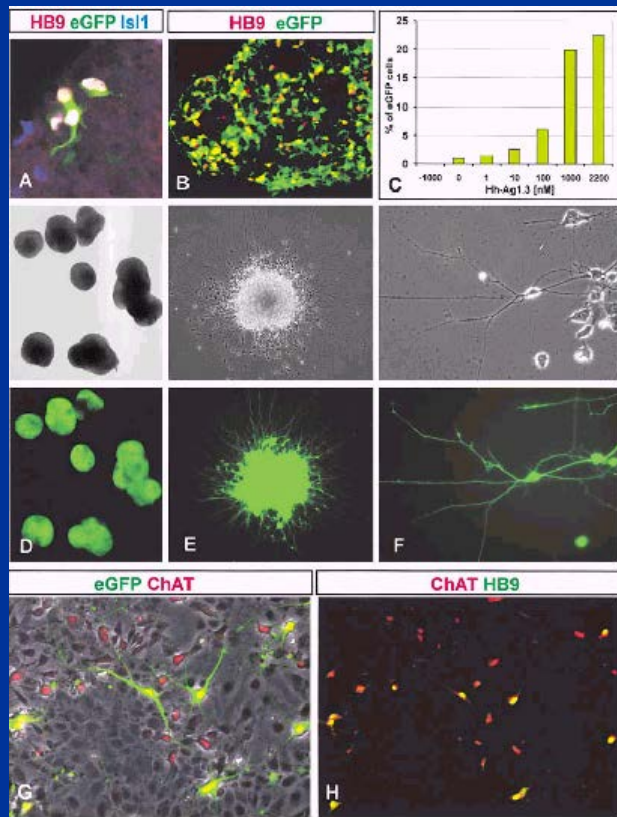
Brain scars



Cellule staminali neuronali e cellule staminali ematopoietiche



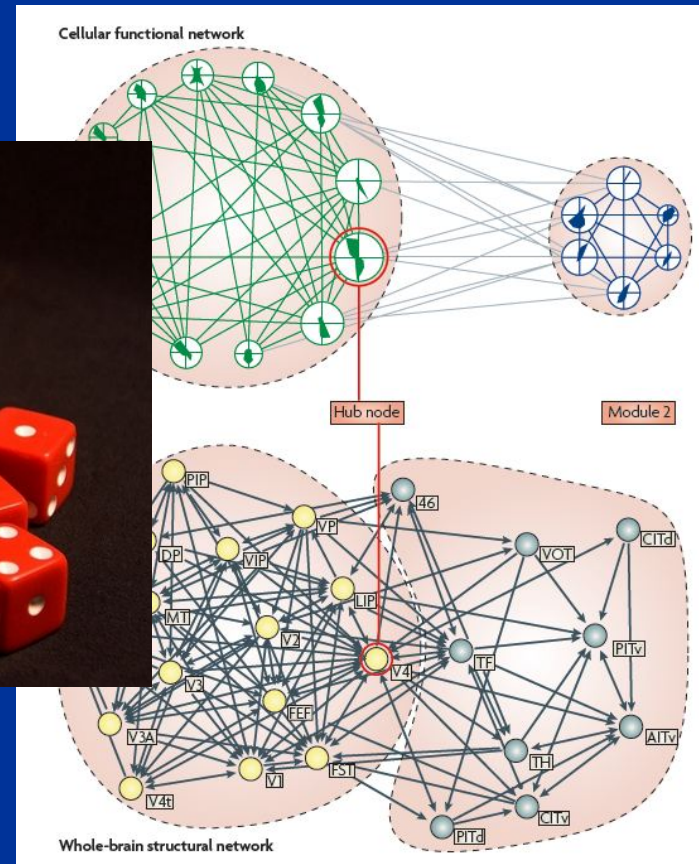
Cellule staminali generano nuovi neuroni



Neuron repair and stem cell therapy

- Based on the assumption that the lack of spontaneous neuroregeneration is mainly due to neuron specificity of being perennial
- Limitations
 - Cell number (this will be overcome in a few years)
 - How to reach the right place
 - How to develop the right connections

Stem cell therapy



Trapianto di cellule neuronali nella Corea di Huntington

JNNP Online First, published on December 17, 2013 as 10.1136/jnnp-2013-306533

Movement disorders

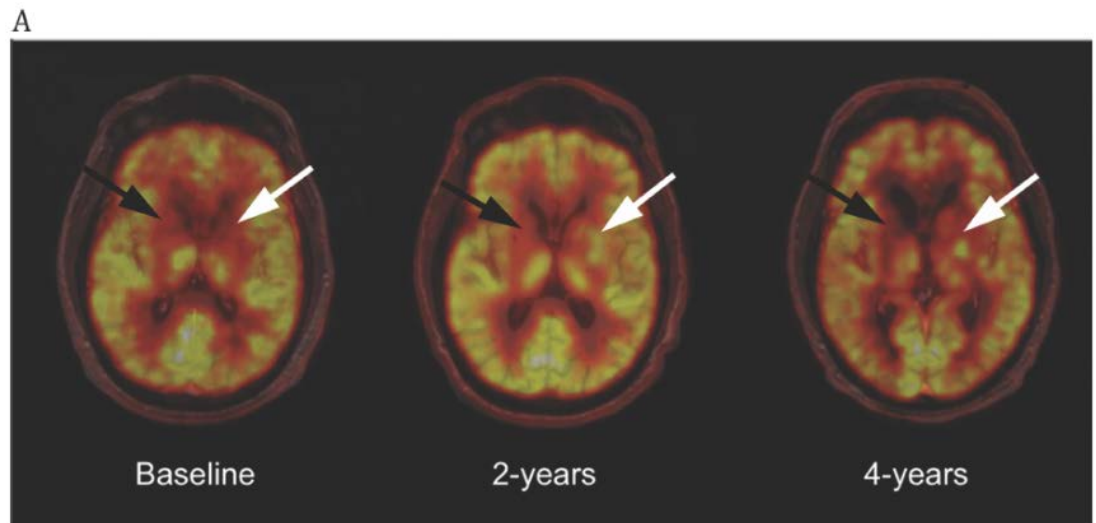


OPEN ACCESS

RESEARCH PAPER

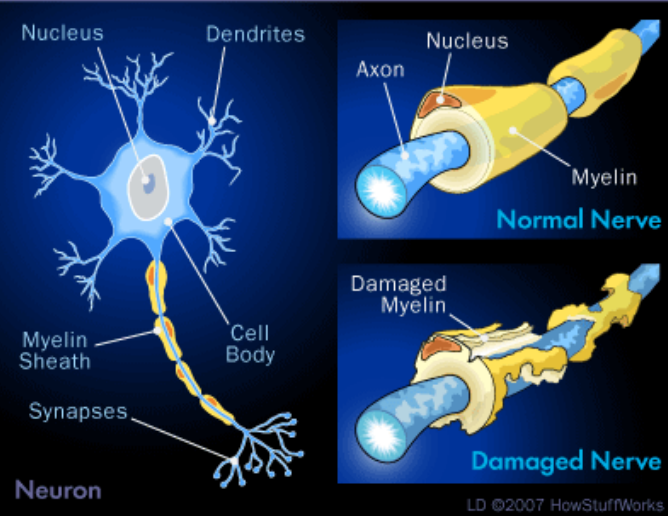
Fetal striatal grafting slows motor and cognitive decline of Huntington's disease

Marco Paganini,^{1,2} Annibale Biggeri,^{3,4} Anna Maria Romoli,¹ Claudia Mechi,¹ Elena Ghelli,¹ Valentina Berti,⁵ Silvia Pradella,¹ Sandra Bucciantini,² Dolores Catelan,^{3,4} Riccardo Saccardi,² Letizia Lombardini,^{2,6} Mario Mascalchi,⁵ Luca Massacesi,^{1,2} Berardino Porfirio,^{2,5} Nicola Di Lorenzo,⁷ Gabriella Barbara Vannelli,⁸ Pasquale Gallina^{2,7}



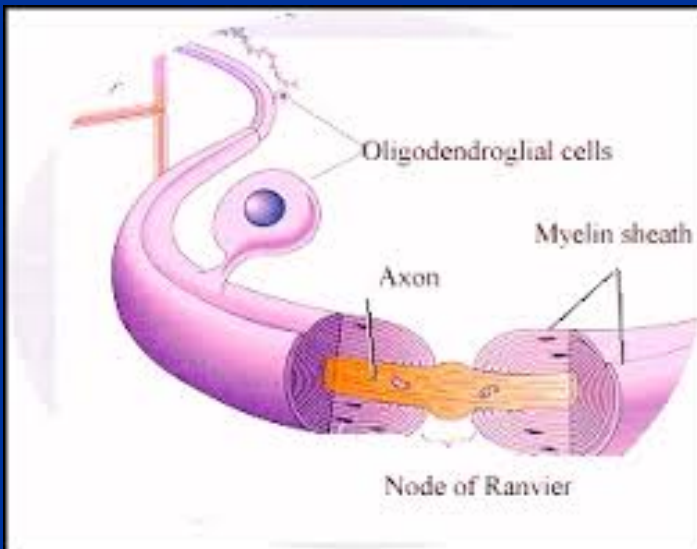
B

How Multiple Sclerosis Works Demyelination



Myelin repair/protection by stem cells

- Feasible
- Limitation
 - Cell number (this will be overcome in a few years)



Discussione

- Danni definitivi dei neuroni o dei loro assoni non sono riparabili
- Questo è probabilmente un limite invalicabile intrinseco alla biologia del sistema nervoso
- Terapie protettive dei neuroni, delle loro fibre e della mielina sono già in corso di sperimentazione, ma devono essere instaurate precocemente, già in pronto soccorso
- Danni della guaina mielinica sono probabilmente riparabili con cellule staminali, ma la terapia deve essere intrapresa precocemente e comunque prima della formazione della cicatrice gliale

Cellule staminali neuronali e cellule staminali ematopoietiche

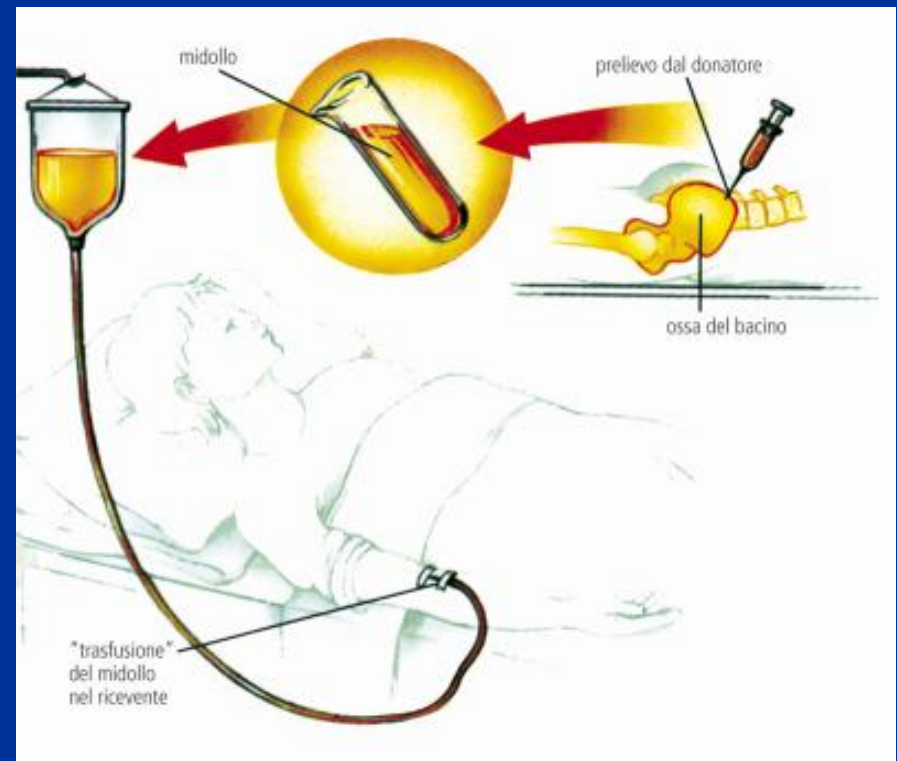
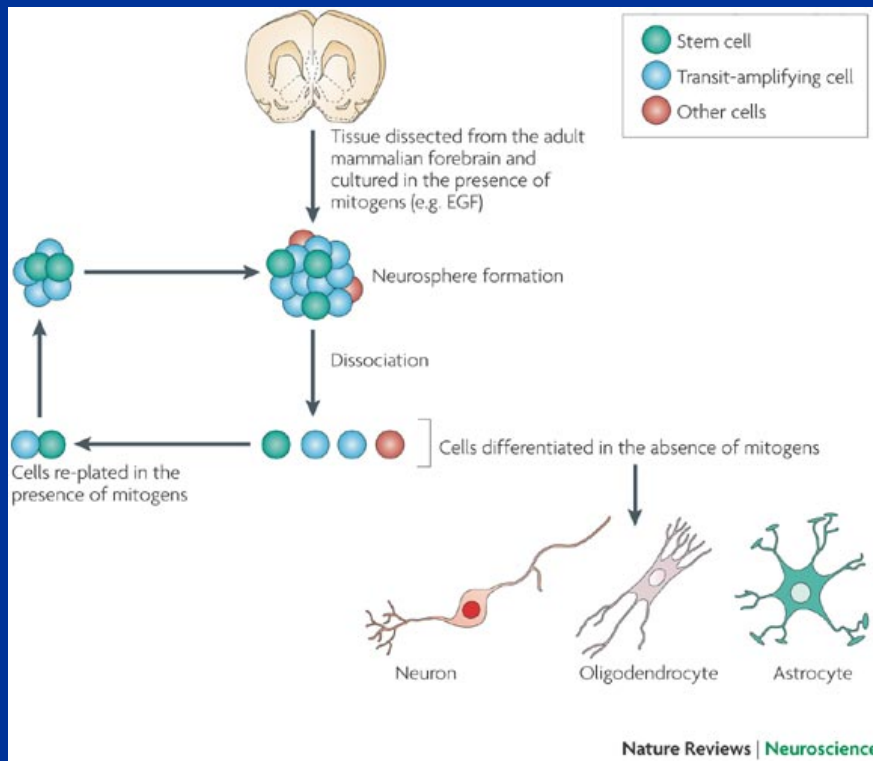
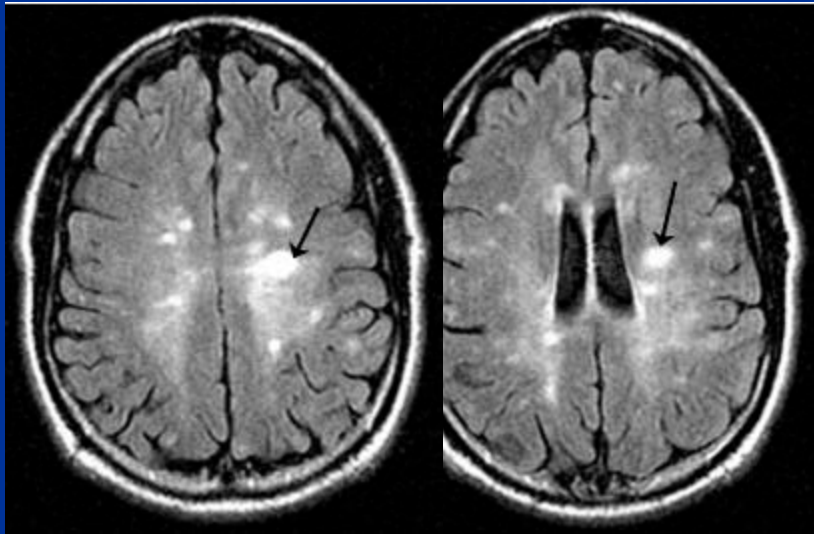
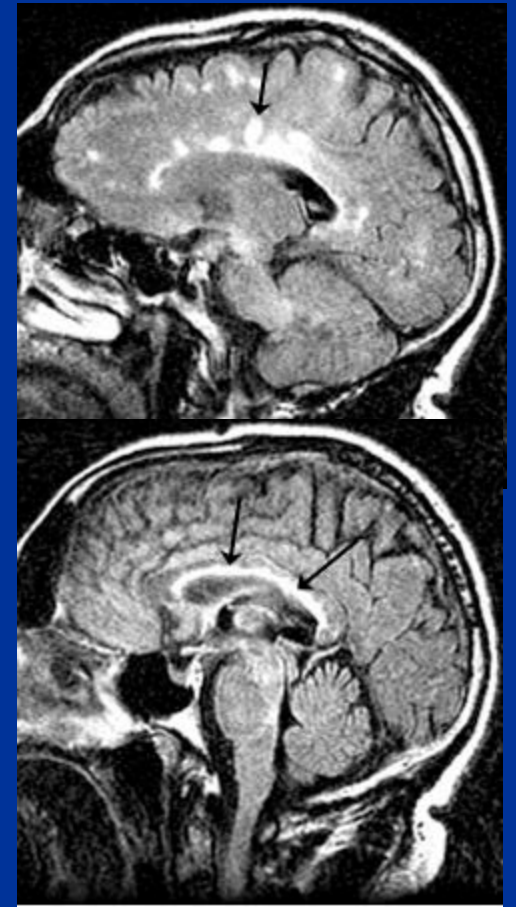
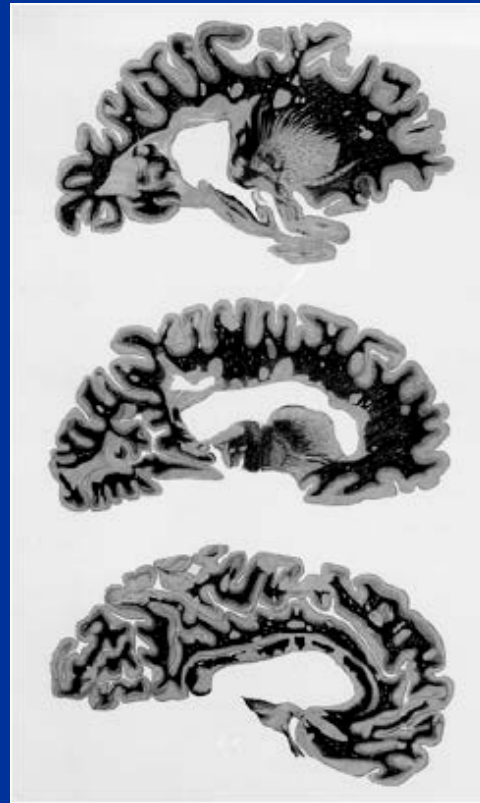
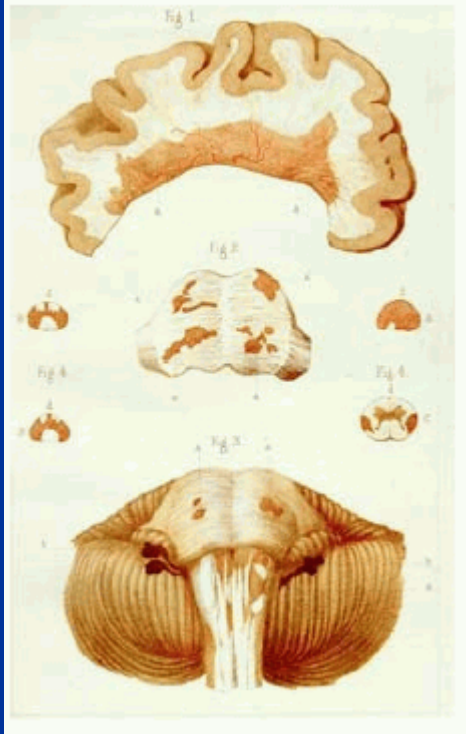
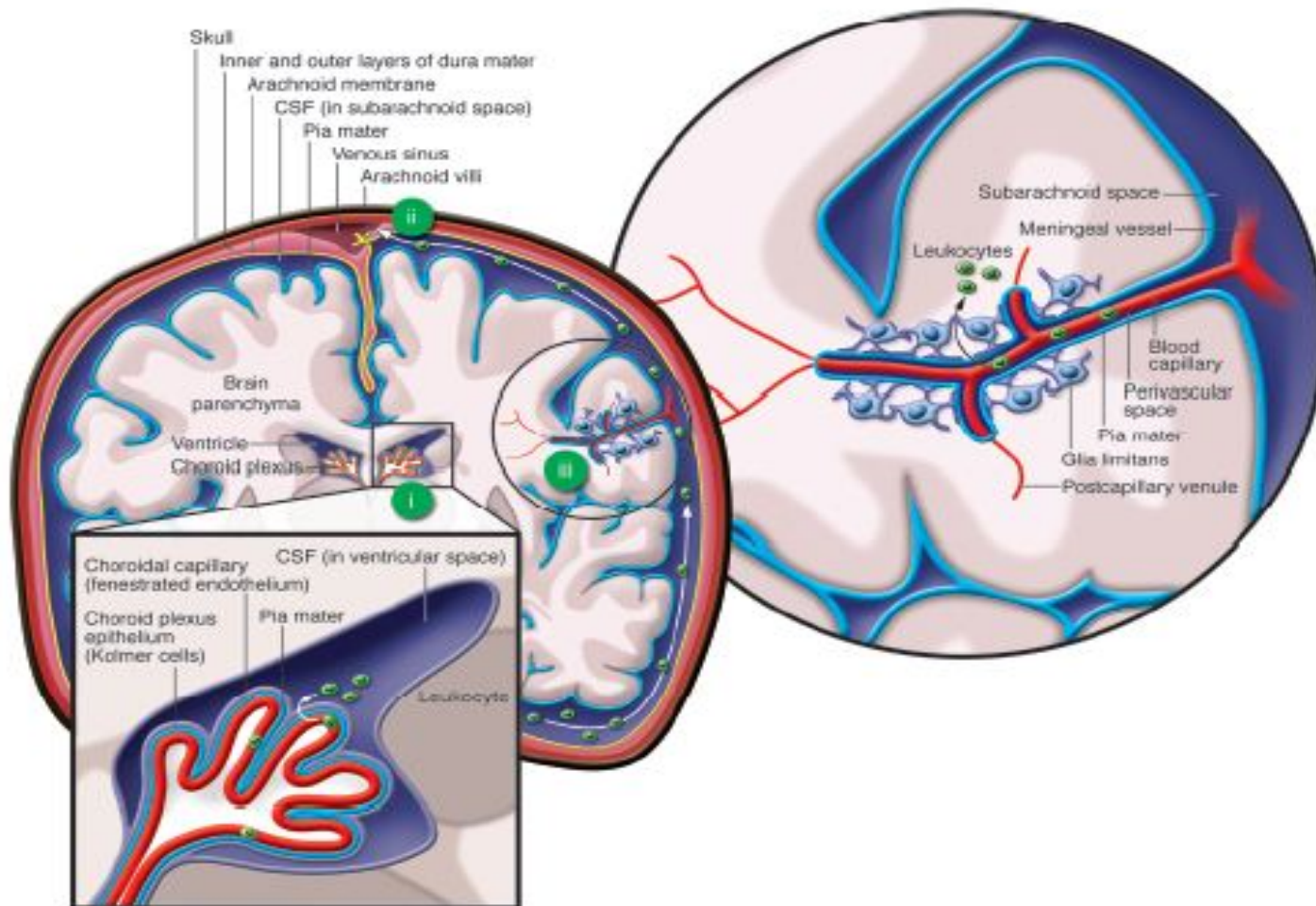


Plate IV: Charcot's First Illustration of Multiple



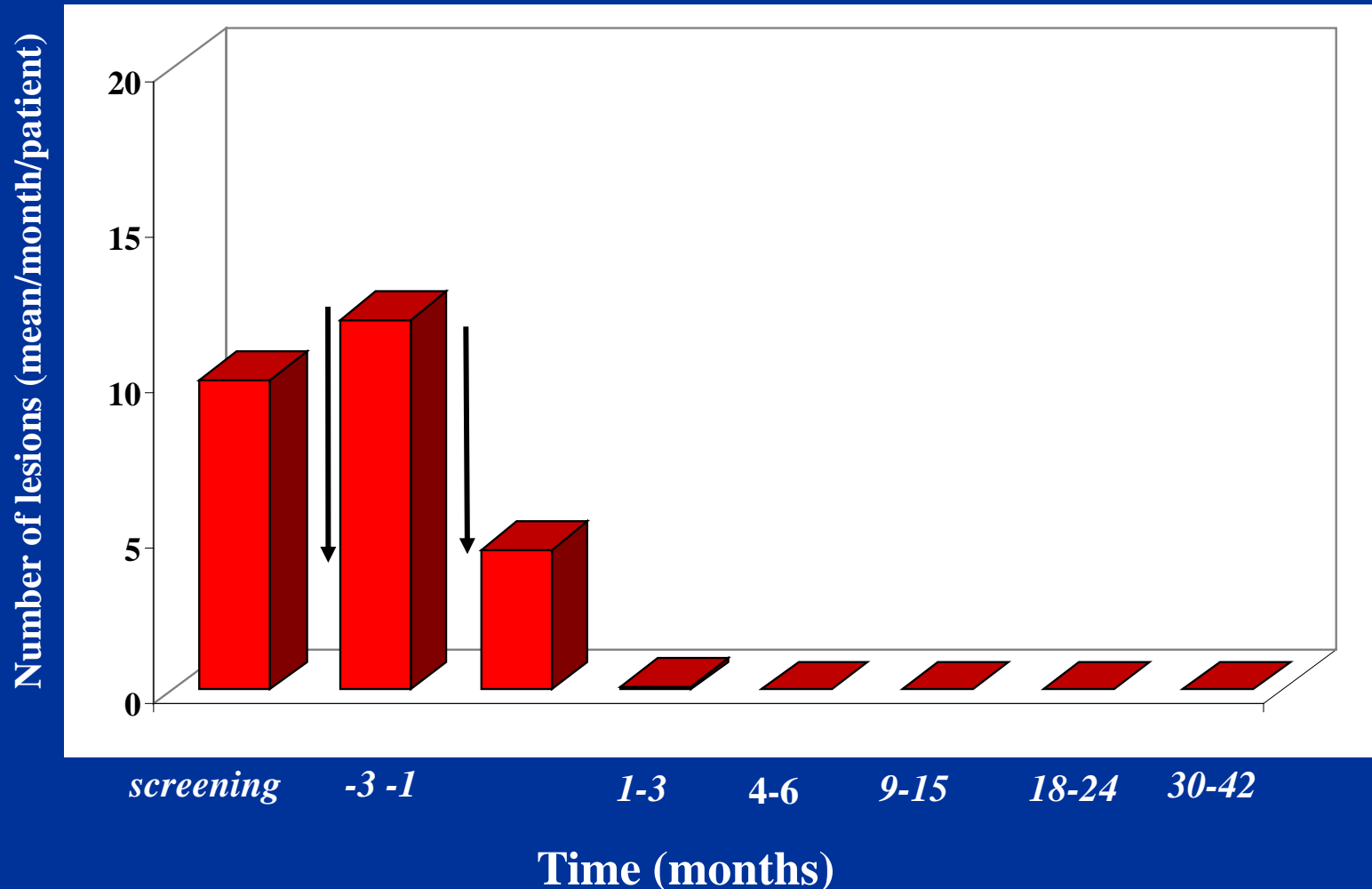
Infiammazione SNC

science in medicine



Neuro-GITMO: MRI Results

Complete suppression of MRI activity and this effect is sustained with time



Grazie per l'attenzione

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Non si studia la Natura perché è utile, ma perché se ne trae diletto,
e se ne trae diletto perché la Natura è bella.
Se non fosse bella non varrebbe la pena conoscerla....

Henry Poincarè, matematico, fisico teorico e naturalista