UNIVERSITÀ DI PISA

SCUOLA DI MEDICINA

Corso di Laurea Magistrale in Medicina e Chirurgia

# LA NEUROPATOLOGIA DELLE MALATTIE NEURODEGENERATIVE

**Dott. Alessandro Galgani**

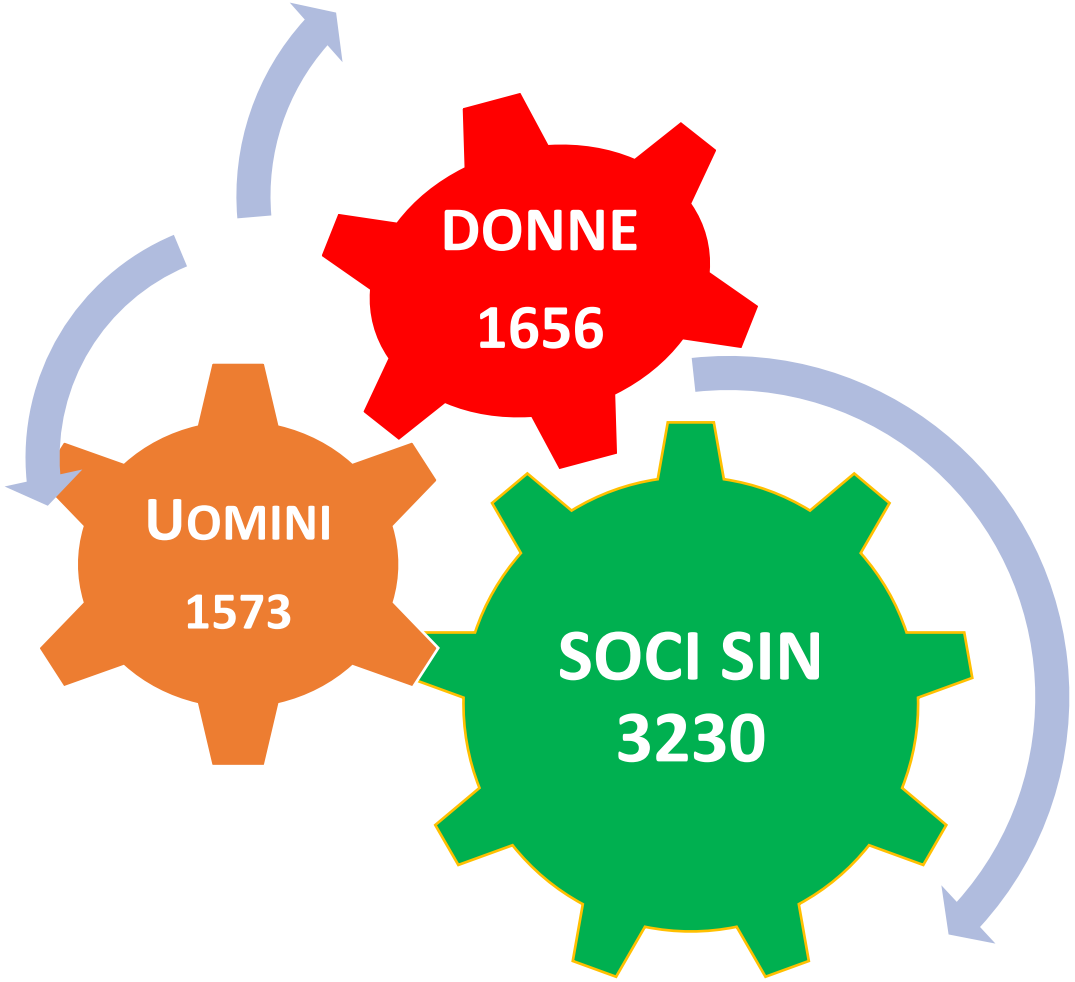
**Prof. Gabriele Siciliano**

# Fotografia al 10 maggio 2022

**Sin , NUMERO ASSOCIATI COMPLESSIVO ALLA DATA DEL 10.05.2022**

**Presidente: Prof. Alfredo Berardelli**

In attesa di approvazione a questo CD , al momento sono ulteriori **43** candidati




Sin

# Il problema dell'invecchiamento

**POPOLAZIONE OVER-60**

2000 → 600 MLN

2025 → 1,2 MLD

2050 → 2 MLD

# Perché invecchiamo?

**Aspettativa di vita alla nascita**

- Neolitico: 18 anni
- Età del ferro: 28-36 anni
- Età classica: 20-30 anni
- Medioevo: 30-35 anni
- XIX secolo: 40 anni ca.
- **Italia 2019: 82,54 anni**

**Aspettativa dopo i 15 anni**

- Neolitico: 25-37 anni
- Età del ferro: 50-60 anni
- Età classica: 60 anni
- Medioevo: 64 anni
- XIX secolo: 65 anni ca.
- **Italia 2019: 82,54 anni**

**Aspettativa di vita massima***
**125 anni ca.**

* Weon BM, Je JH (February 2009). "Theoretical estimation of maximum human lifespan". Biogerontology

# Perché invecchiamo?

$$\Delta S > 0$$

**Lucrezio:** la vecchiaia e la morte consentono il rinnovamento del mondo, cosicché i vecchi possano fare posto ai giovani

Dal De Rerum Natura – I sec. a.C.

**C. Darwin** pubblica l'Origine della Specie nel 1859

**A. Weismann:** la senescenza e la morte hanno una spiegazione evolutiva, poiché l'eliminazione degli individui anziani, più deboli e malati, consente agli individui giovani, più forti e sani, di sfruttare le risorse a disposizione, a vantaggio della specie.

Da Ober die Dauer des Lebens -1881

# Il problema dell'invecchiamento

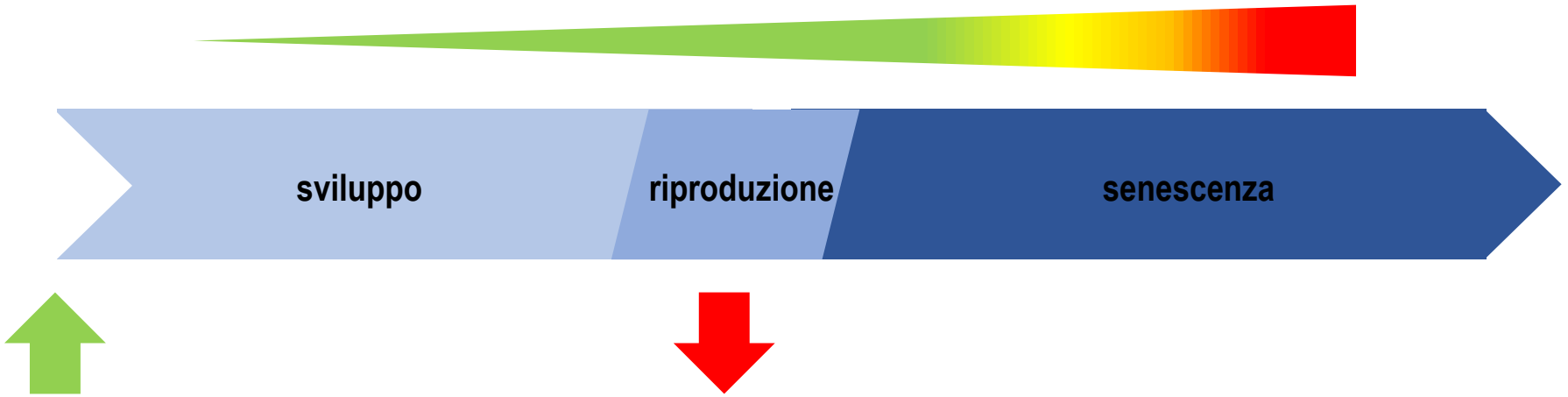
World Health Organization

Healthy Ageing is about creating the environments and opportunities that enable people to be and do what they value throughout their lives. Everybody can experience Healthy Ageing. Being free of disease or infirmity is not a requirement for Healthy Ageing as many older adults have one or more health conditions that, when well controlled, have little influence on their wellbeing.

i. cerebrale

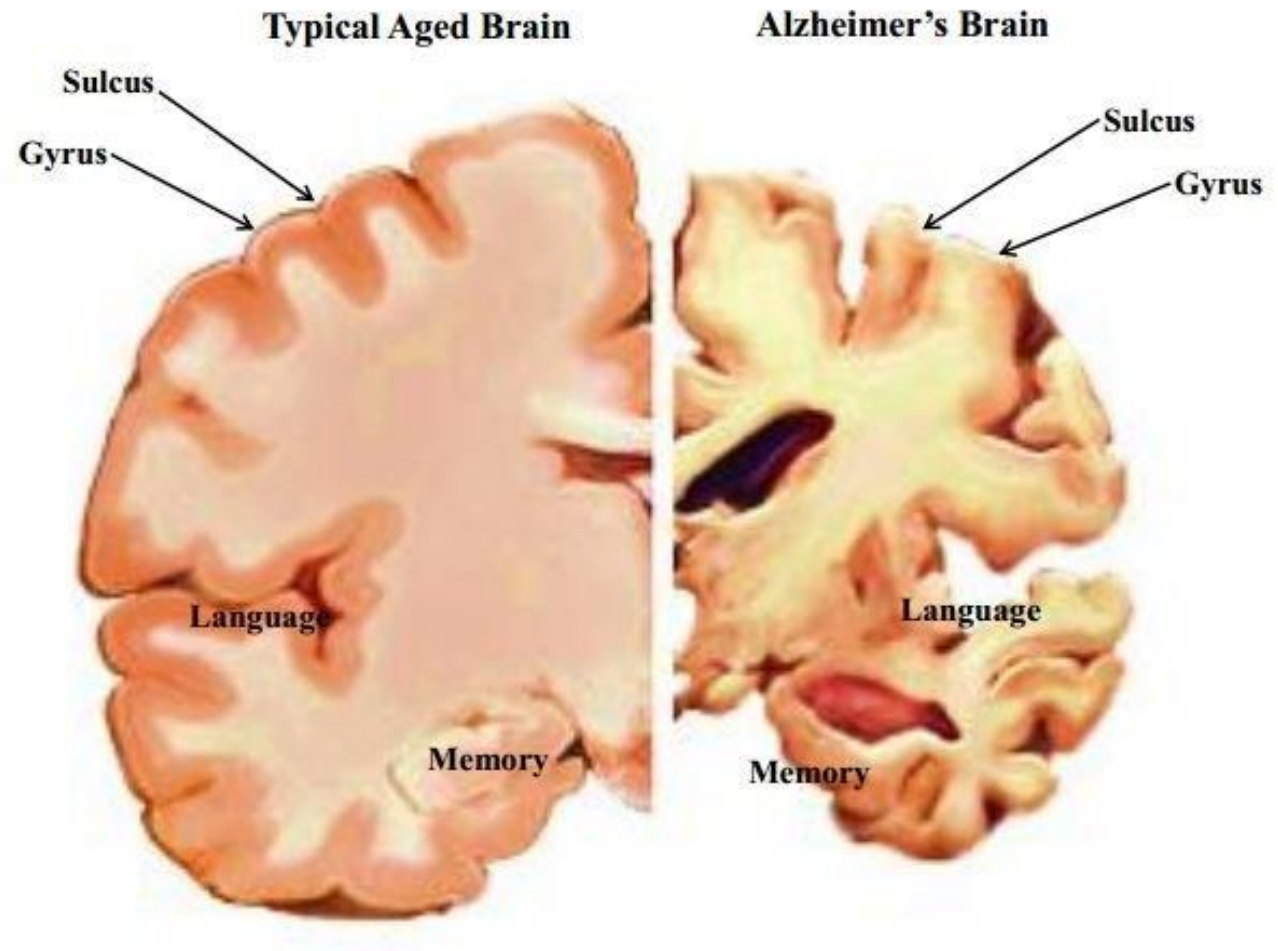
# Perché invecchiamo?

**Accumulo del danno**




**Geni antagonisti pleiotropi**

# Senescenza cerebrale o neurodegenerazione



I Primary degenerative dementias

A: Dementia 'pure': neurodegenerative disorders primarily involving cerebral cortex

Alzheimer's disease

Focal degenerations

Frontotemporal lobar degenerations (FTD)

Behavioural subtype

Primary progressive aphasia

Semantic dementia

Posterior cortical atrophies

Primary progressive visual-spatial impairment

Primary progressive apraxia

B: Dementia 'plus': neurodegenerative disorders involving additional brain areas such as basal ganglia or other subcortical structures

Dementia with Lewy bodies

Parkinson's disease dementia

Multiple system atrophy

FTD-Parkinsonism-17

FTD with motor neuron disease

Corticobasal degeneration

Progressive supranuclear palsy

Familial multiple system tauopathy

Huntington disease

Progressive subcortical gliosis

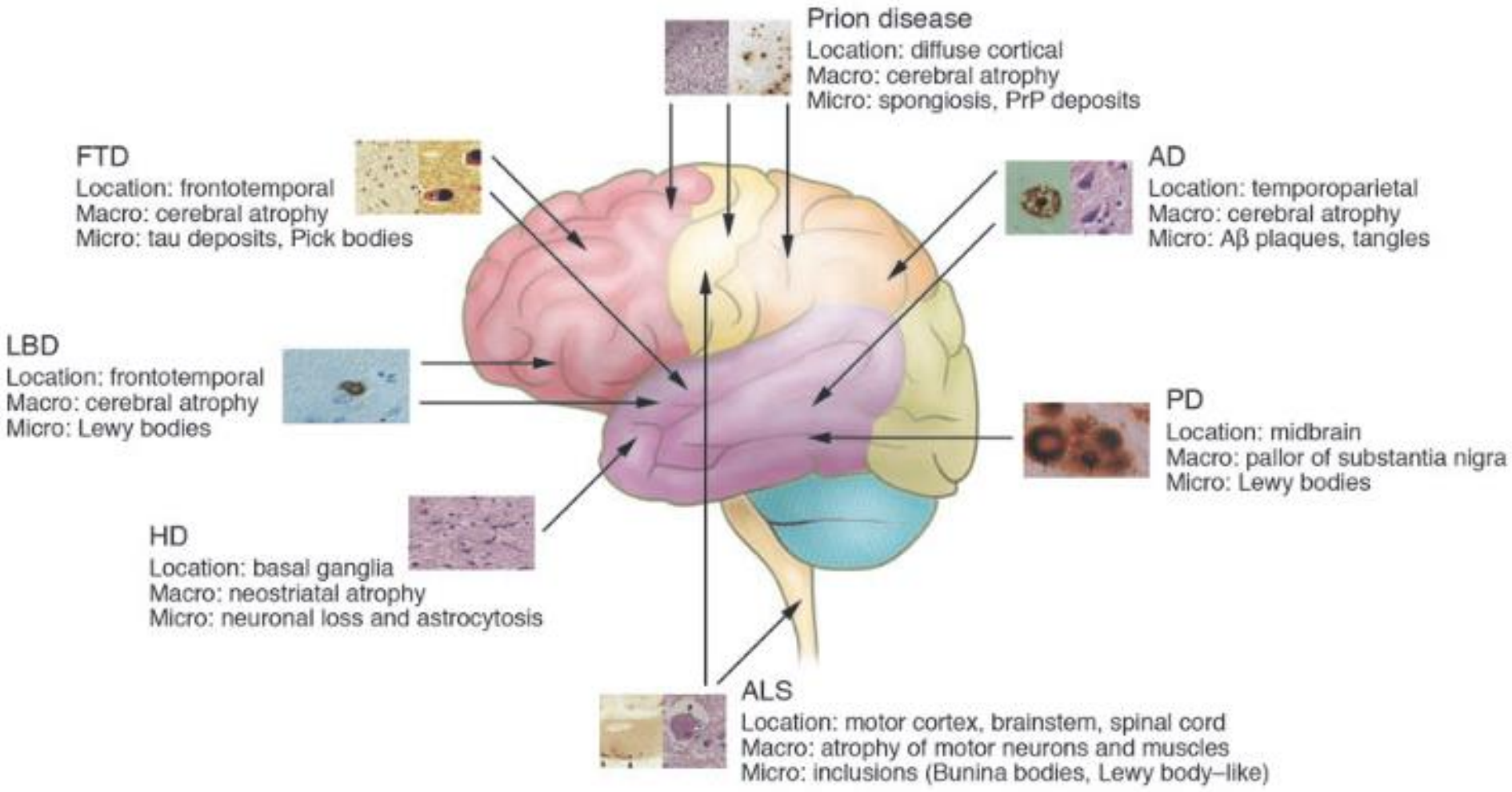
Dementia lacking distinctive histopathological features

Some forms of spinocerebellar ataxias (such as SCA 1-3, DRPLA)

# The genetic epidemiology of neurodegenerative disease

**Lars Bertram and Rudolph E. Tanzi**

The Journal of Clinical Investigation http://www.jci.org Volume 115 Number 6 June 2005



- Amiloidopatie:
  - Malattia di Alzheimer (MdA)
  - Malattie da Prioni (CJD, GSS, FI, vCJD, kuru)

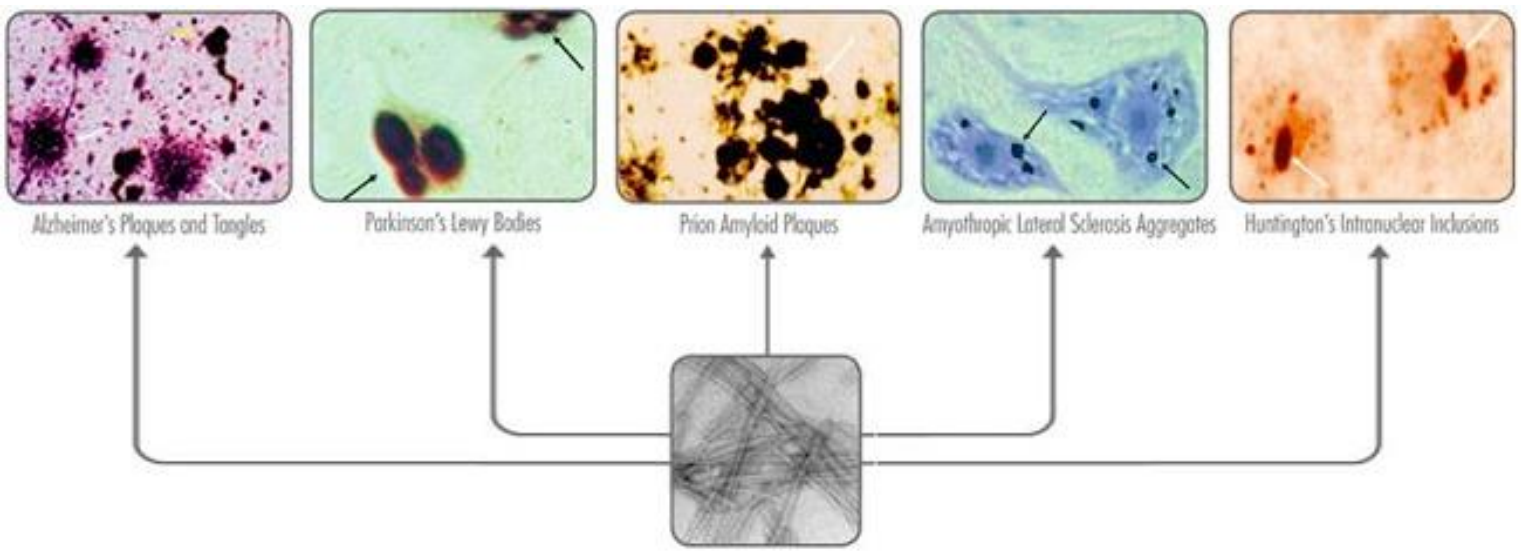
- Sinucleinopatie:
  - Demenza a corpi di Lewy (LBD)
  - Demenza associata alla malattia di Parkinson (PDD)

- Taupatie:
  - Demenza di Pick
  - Demenza fronto-temporale con parkinsonismo legata al cromosoma 17 (FTDP-17)
  - Paralisi sopranucleare progressiva (PSP)
  - Degenerazione corticobasale (CBGD)

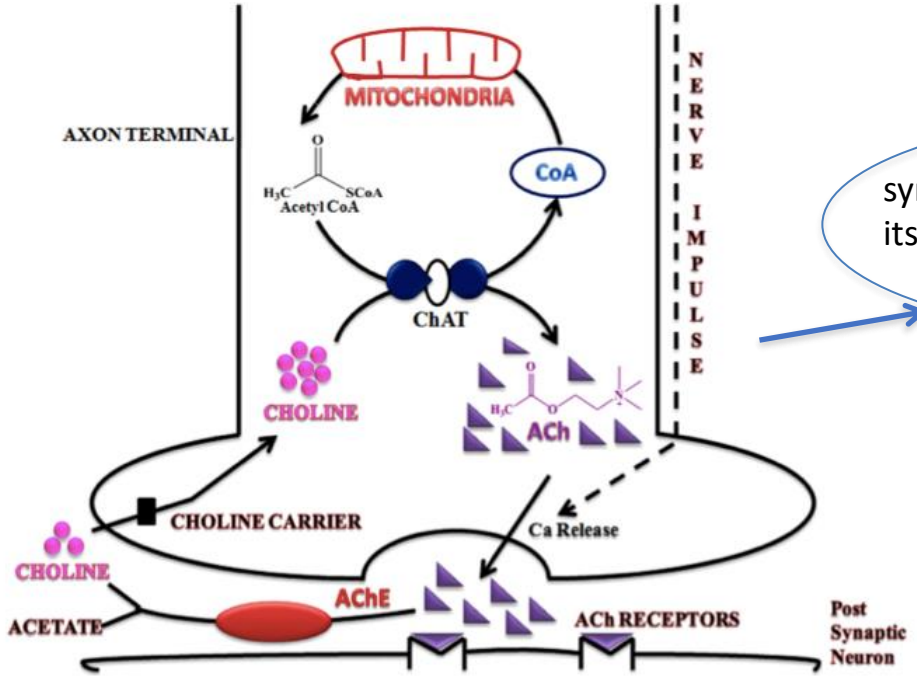
**CLASSIFICAZIONE PER PATHWAY MOLECOLARI**

↓

TERAPIA ?



# Pathogenesis of Alzheimer's disease: The cholinergic hypothesis




synthesis of acetylcholine in the axon and its hydrolytic pathway

**Key Targets for Multi-Target Ligands Designed to Combat Neurodegeneration**

*Rona R. Ramsay[1]*, Magdalena Majekova[2], Milagros Medina[3] and Massimo Valoti[4]**

Frontiers in Neuroscience
August 2016 | Volume 10 | Article 375

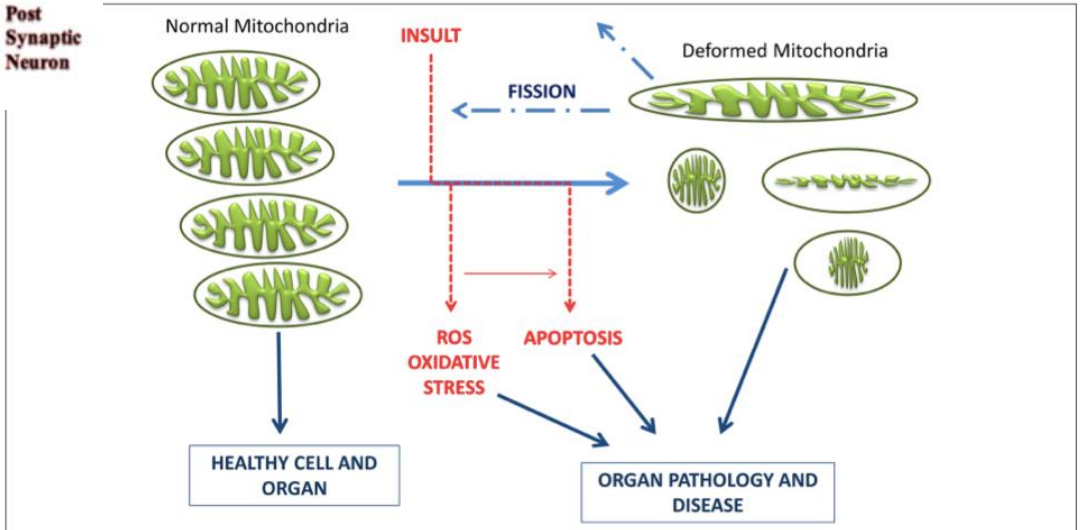
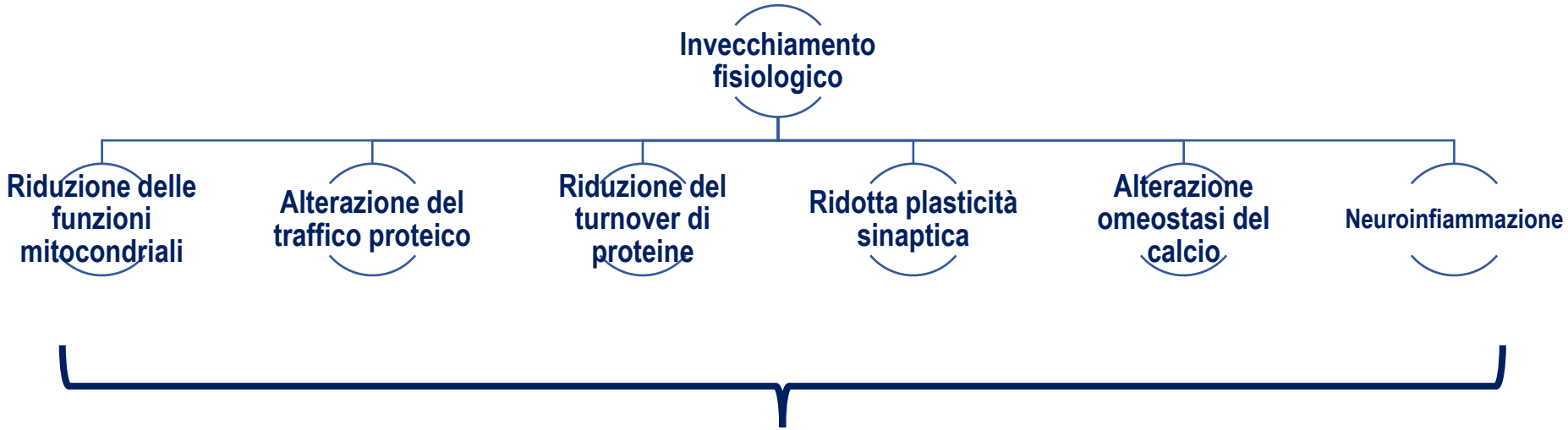



**FIGURE 4 | Schematic representation of the timeline of mitochondrial bioenergetics and morphological changes inducing pathologies.** Electrons leaking from the electron transport chain generate ROS, which damage mitochondrial membrane, mitochondrial DNA, and proteins. Neurons have limited defense against oxidative damage and are highly vulnerable to ROS. Damaged/depolarized mitochondria release cytochrome c that triggers cell death by activating caspases as well as AIF that initiates apoptosis in a caspase independent manner.

# Invecchiamento cerebrale fisiologico

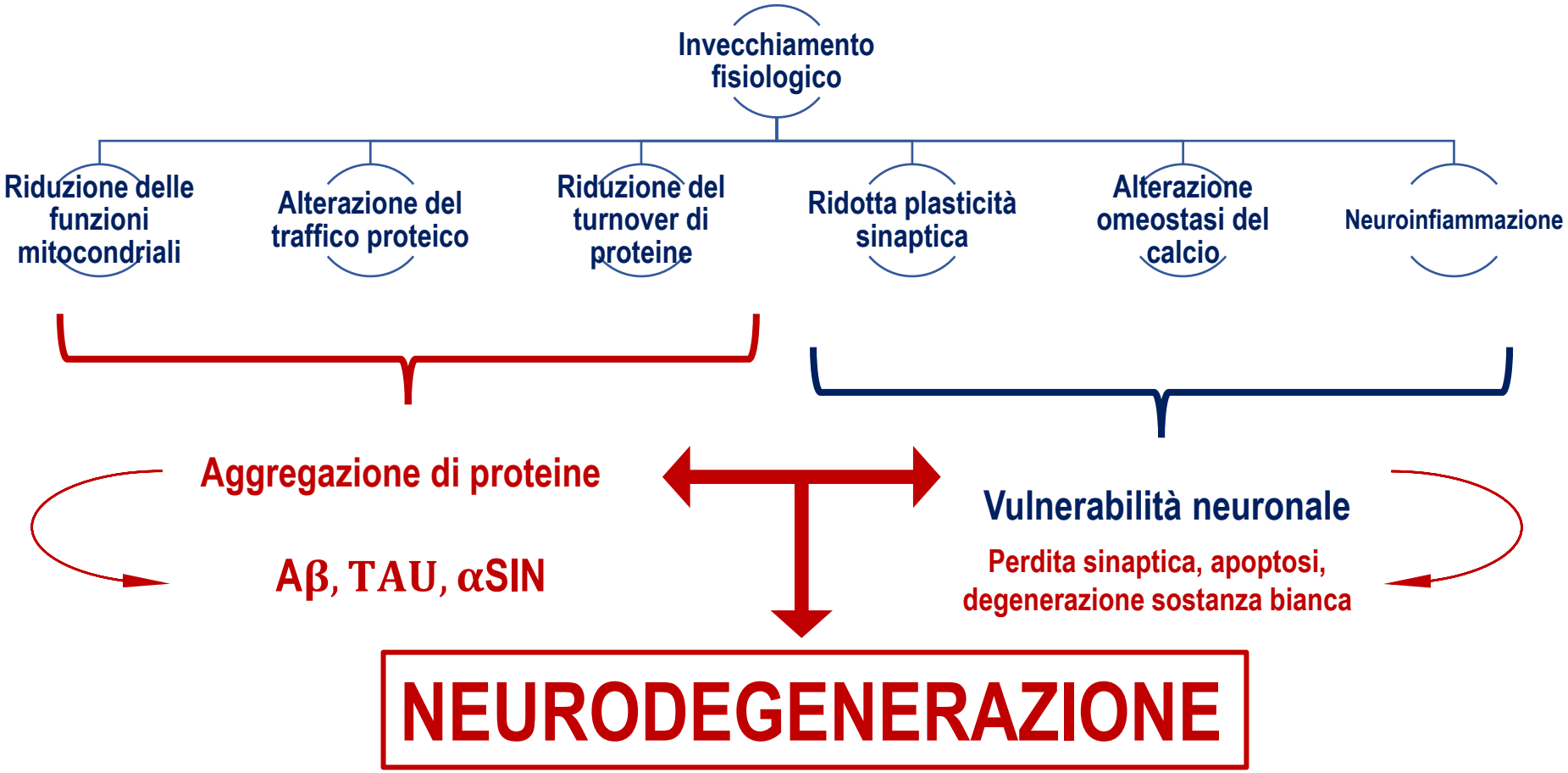



**Perdita di sinapsi, apoptosi neuronale, degenerazione della sostanza bianca**

**Deficit cognitivi**

The Aging Brain, Bruce A. Yankner, Tao Lu, and Patrick Loerch, Annu. Rev. Pathol. Mech. Dis. 2008

# Invecchiamento cerebrale patologico




The Aging Brain, Bruce A. Yankner, Tao Lu, and Patrick Loerch, Annu. Rev. Pathol. Mech. Dis. 2008

# Espressione genetica ed epigenetica

**ESPRESSIONE GENICA ANZIANO ≠ ESPRESSIONE GENICA GIOVANE**

Invecchiamento geneticamente programmato?

**= ESPRESSIONE GENICA NELLO STRESS CELLULARE**

- **Proteine sinaptiche** (subunità del recettore del glutammato, proteine delle vescicole sinaptiche, sistemi di trasduzione della LTP
- **Proteine associate al segnale Ca2+ dipendente** (calmodulina 1 e 3, CAM chinasi II e IV, calcineurina)
- **Proteine implicate nel trasporto delle vescicole sinaptiche**
- **Proteine correlate alla funzione mitocondriale**

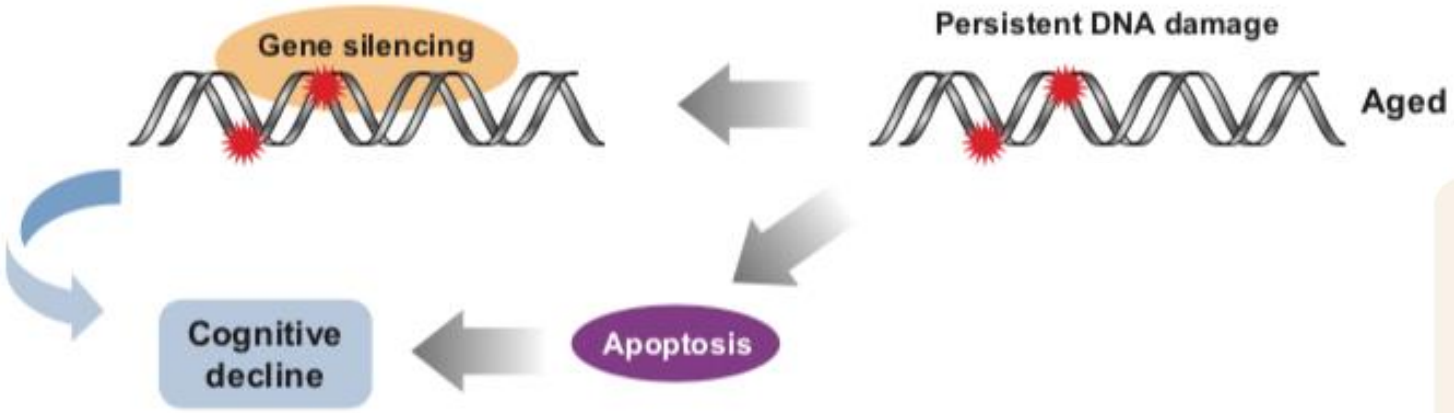
- **Riparazione DNA**
- **Protezione stress ossidativo**
- **Risposta immunitaria**

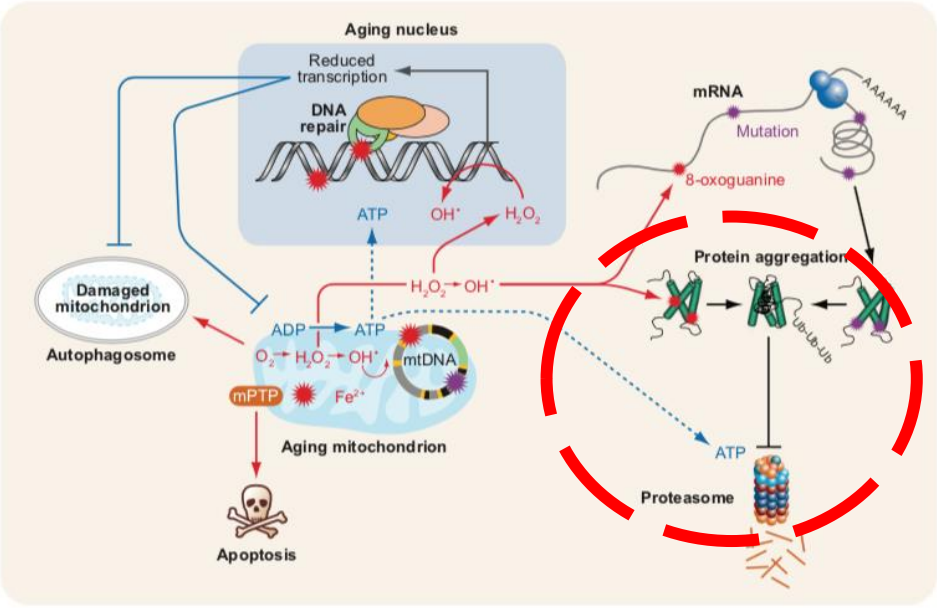
**Gene regulation and DNA damage in the ageing human brain**. Lu T, Pan Y, Kao SY, Li C, Kohane I, et al. **Nature 2004**

**vulnerabilità**

# Danno genetico

**Does oxidative damage to DNA increase with age?** Hamilton ML,VanRemmen H,Drake J A,Yang H,Guo ZM, et al. **Proc. Natl. Acad. Sci. 2001**



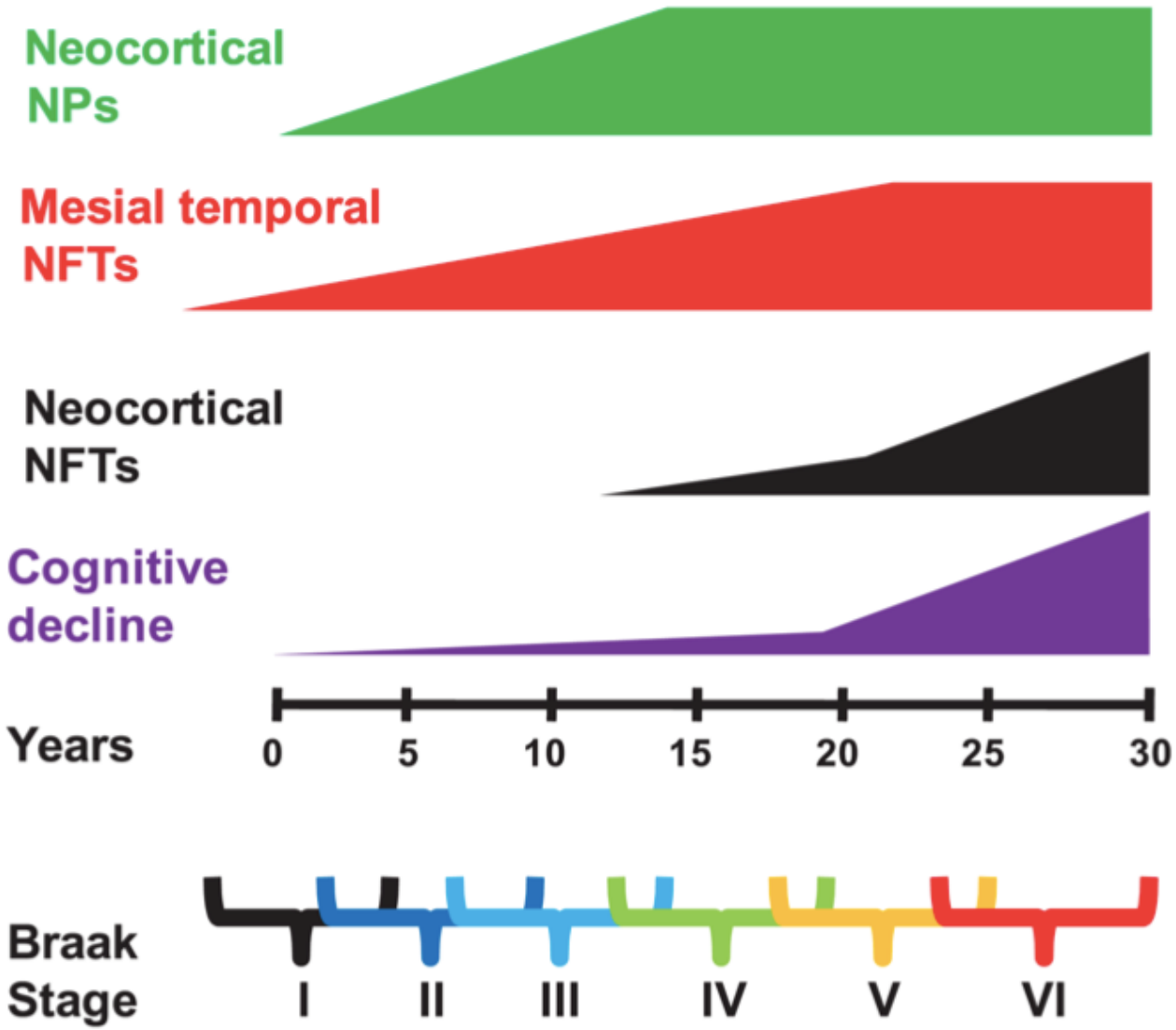

- **Principale tipo di danno al DNA neuronale: ossidazione**
- **Principale specie ossidativa prodotta: 8- oxoguanina**
- **Se il danno non viene riparato due possono essere le conseguenze**
  - silenziamento del gene
  - apoptosi neuronale
- **Esistono geni selettivamente danneggiati dal danno ossidativo?**

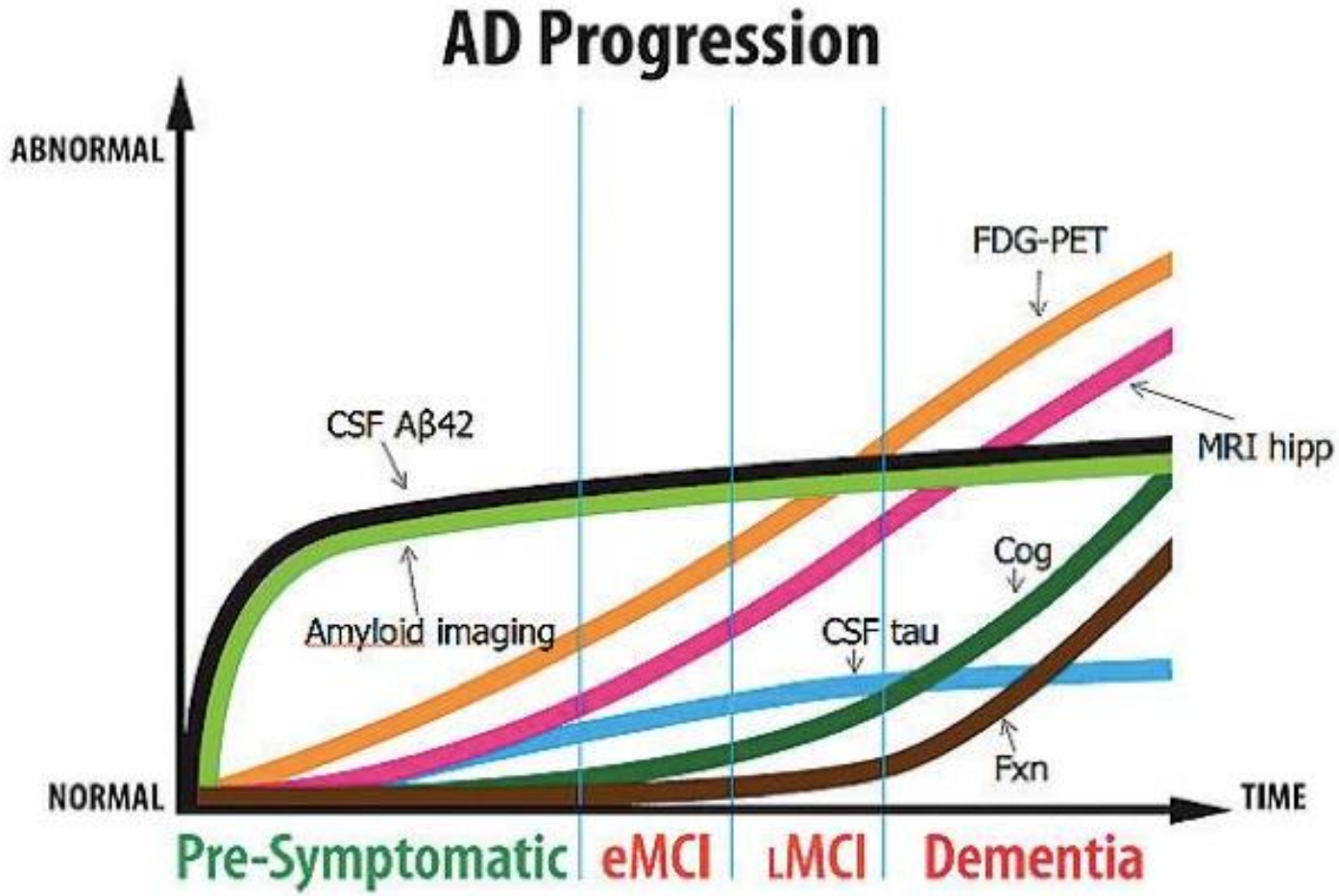
**vulnerabilità**

# Neuropathology and Cognitive Impairment in Alzheimer Disease: A Complex but Coherent Relationship

*J Neuropathol Exp Neurol*. 2009 January ; 68(1): 1–14.

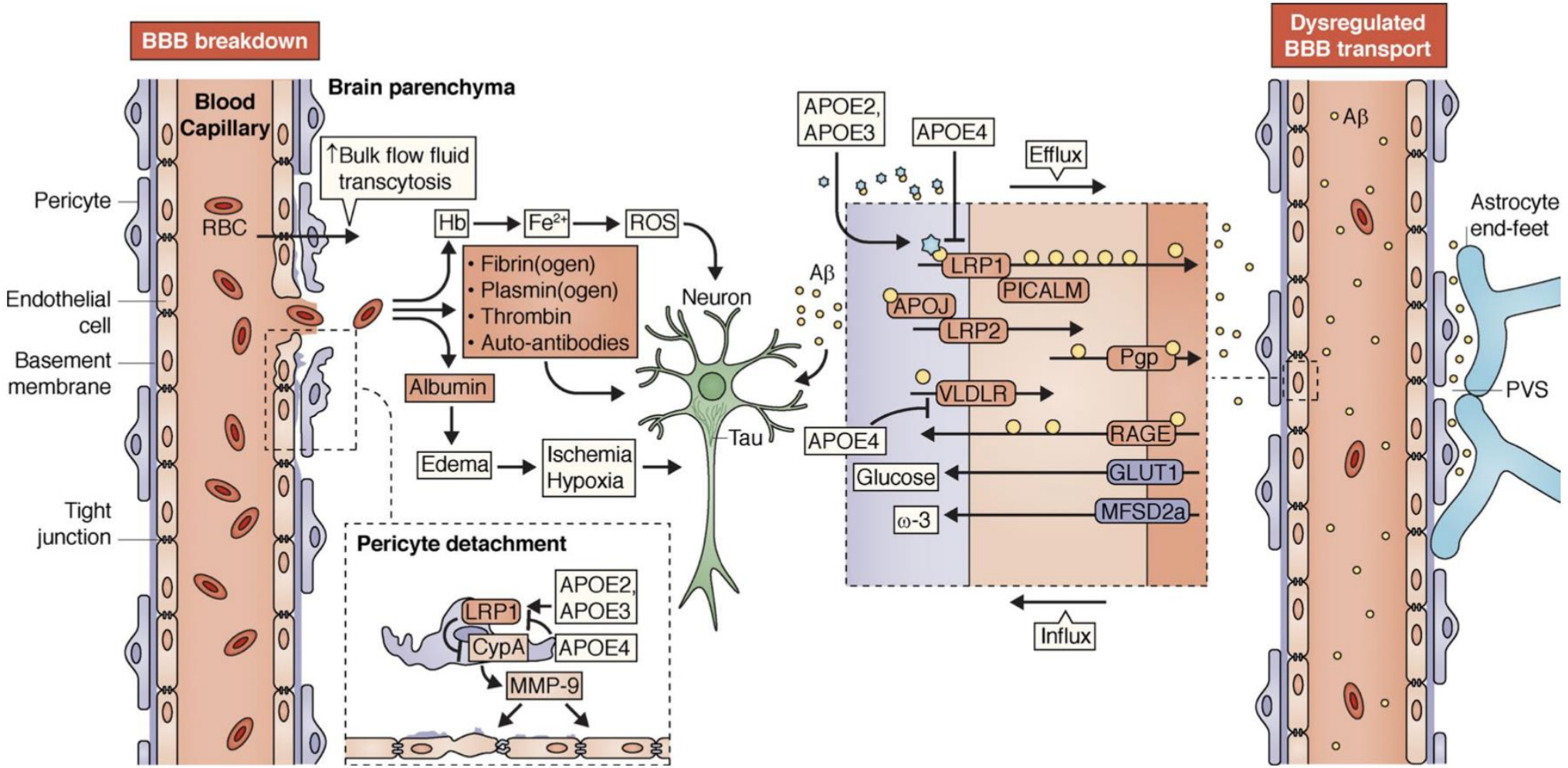
**Peter T. Nelson, MD, PhD**, **Heiko Braak, MD**, and **William R Markesbery, MD**



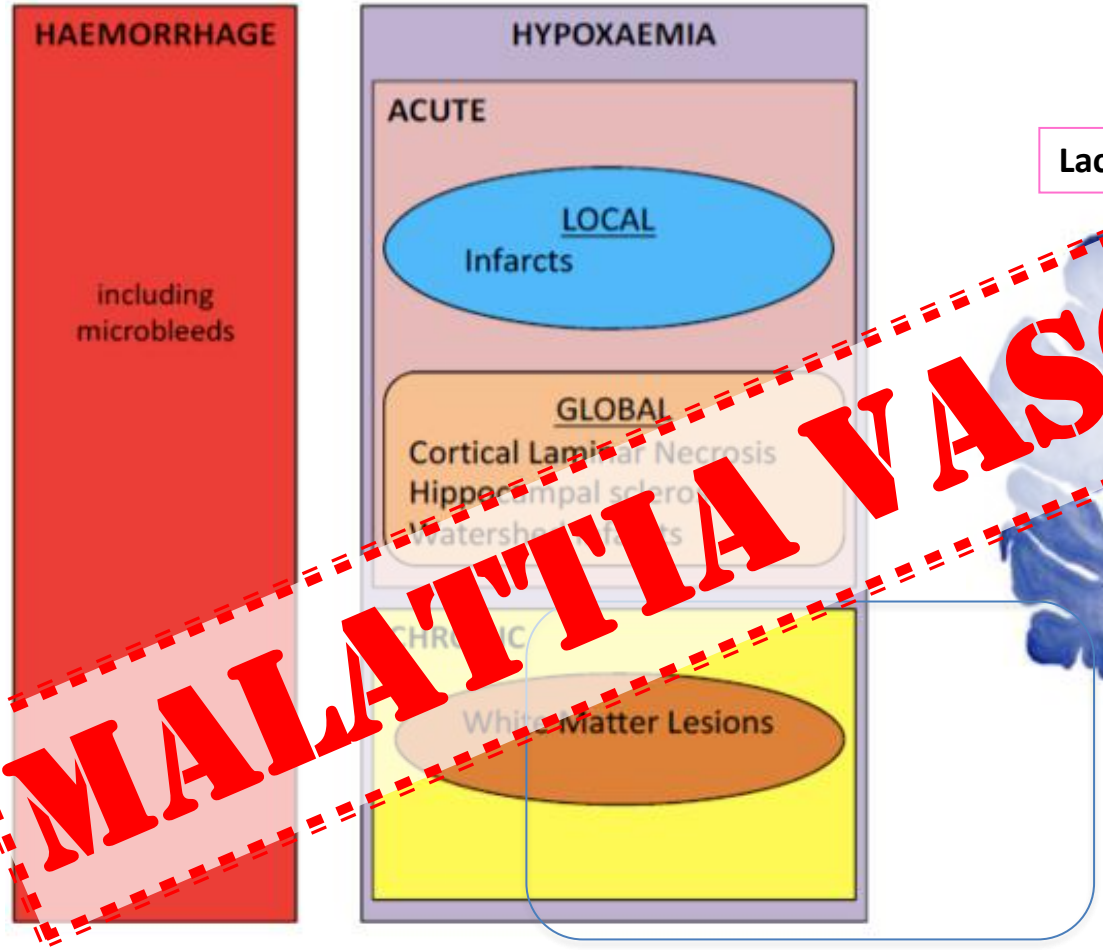



Courtesy of Paul Aisen, M.D., Alzheimer's Disease Cooperative Study, University of California, San Diego.

# Danno dell'unità neurovascolare



# Danno dell'unità neurovascolare





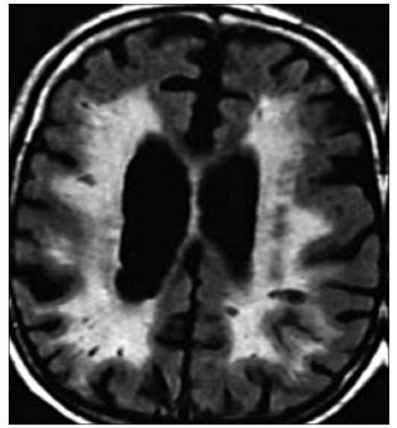
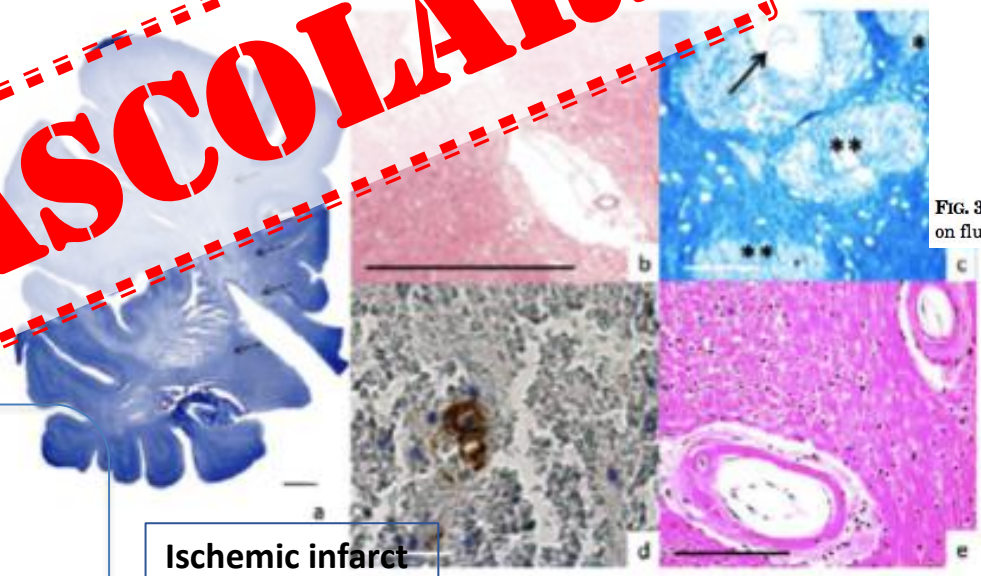



FIG. 3. Subcortical vascular dementia type of vascular dement on fluid attenuated inversion recovery (FLAIR) brain MRI.



Lacunar infarct

White matter lesion

Ischemic infarct

Cerebral amyloid angiopathy

Small vessel disease

## Vascular dementia

Major pathological findings underlying vascular dementia

Amos D Korczyn[1], Veronika Vakhapova[2], and Lea T Grinberg[3,4]

# Neuroinfiammazione

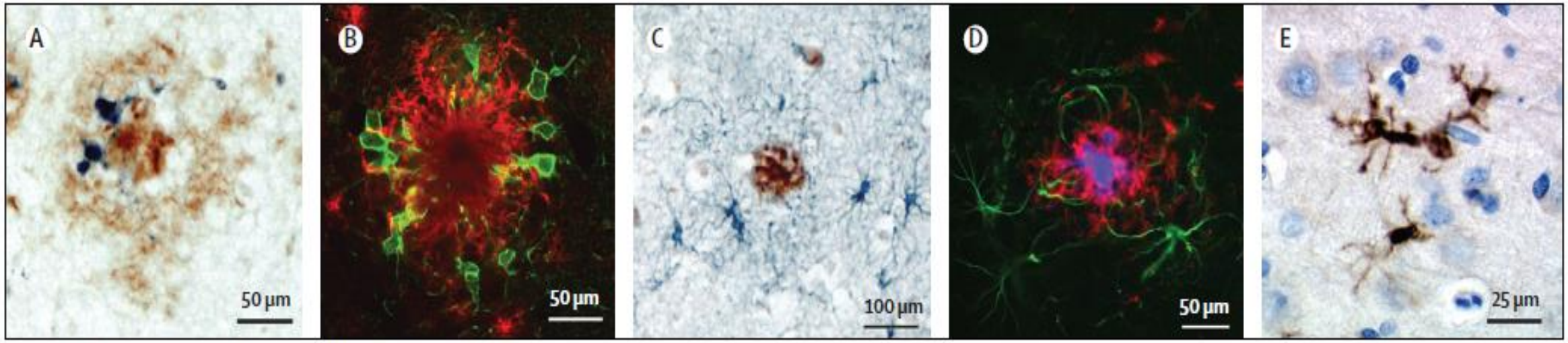
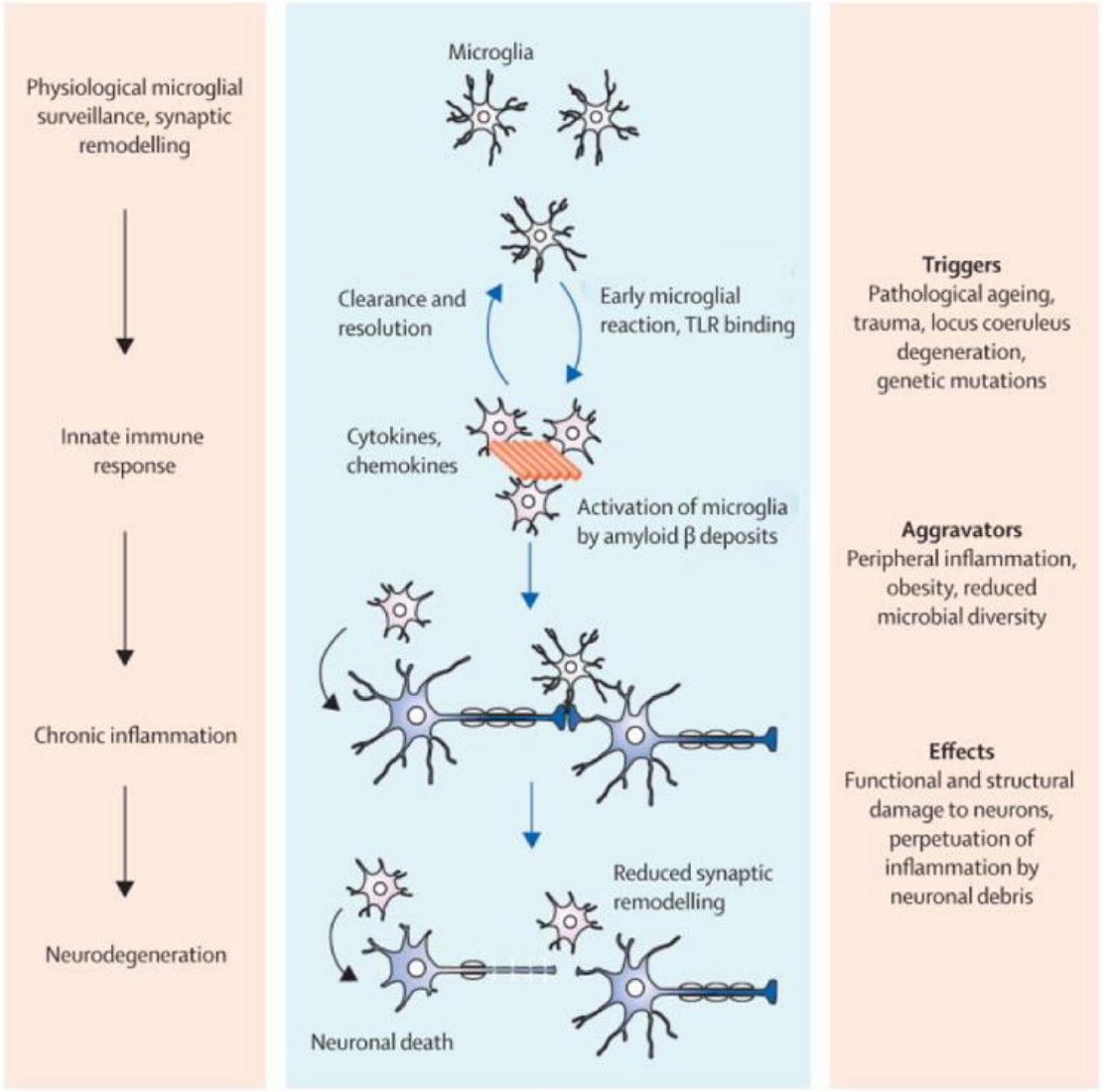


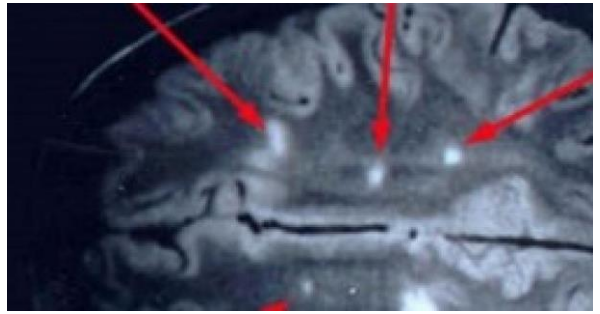

***Figure 2:*** **Changes in microglia and astroglia in Alzheimer's disease**

Microglia and astroglia are key players in the inflammatory response: changes in microglia and astroglia are evident in the post-mortem brains of patients with Alzheimer's disease and in animal models of the disorder. (A) CD11b-positive microglia (blue) within an amyloid β (Aβ) deposit (brown) in the parietal cortex of a brain section from a patient with Alzheimer's disease. (B) Activated, IBA1-positive microglia (green) at an Aβ plaque site (red) in a brain section from an APP/PS1 transgenic mouse. (C) GFAP-positive astrocytes (blue) surround the site of Aβ deposition (brown) in the parietal cortex of a brain section from a patient with Alzheimer's disease. (D) GFAP-positive astrocytes (green) at an Aβ plaque site (red) in a brain section from an APP/PS1 transgenic mouse. (E) Interleukin-1β-positive microglia (brown) in the frontal cortex of a brain section from a patient with Alzheimer's disease.

# Neuroinfiammazione




**La microglia partecipa attivamente alla regolazione della funzione neuronale, agendo sul rimodellamento sinaptico e rilasciando fattori trofici per i neuroni**



**La presenza di DAMPs (***damage associated molecular patterns***) che si accumulano nell'invecchiamento (**proteine ossidate o aberranti, acidi nucleici mutati o detriti cellulari/lisosomiali**) porta all'attivazione della neuroinfiammazione da parte della microglia, tramite Toll-like receptors**

**Neuroinflammation in Alzheimer's disease.** Heneka et al. 2015 **Lancet Neurology**

**vulnerabilità**

# Neuroplasticità e ambiente

- prevenzione primaria e secondaria
- igiene e costumi di vita
- fattori di rischio, inquinanti

# ALCUNI ESEMPI DI ARTICOLI PUBBLICATI


Il Messaggero

L'INTERVISTA ALFREDO BERARDELLI

ALLENIAMO IL CERVELLO CON LO SPORT E LA LETTURA AUMENTA LA PLASTICITÀ

Il presidente della Società italiana di Neurologia: «Pensiamo poco a tutelare la mente, che è attaccabile oltre che dalle malattie, anche da abitudini killer Dobbiamo aumentare le nostre riserve cognitive accumulando informazioni»


la Repubblica Salute

Settimana del cervello, gli esperti: "Proteggiamolo sempre, non solo in età avanzata"


DIVA eDONNA


Cibo, sonno, sport: i 3 alleati del nostro cervello

Come tutti gli organi, anche l'encefalo invecchia. **La scienza ha però dimostrato che lo stile di vita, oltre il corpo, influenza anche la salute della nostra mente.** Ecco i test per migliorarla e misurare le nostre capacità

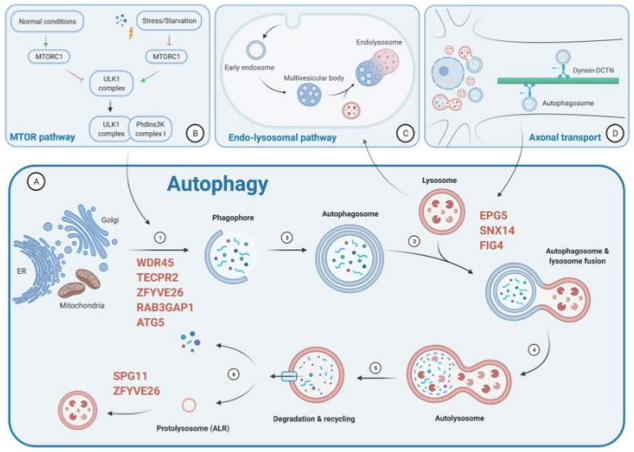
# 7. Corso giovani 2022: gruppo SIN-Africa- Dott. Massimo Leone


**200 posti** disponibili per i soci SIN Junior, iscritti alle scuole di specializzazione e/o under 40, in regola con il versamento delle quote associative

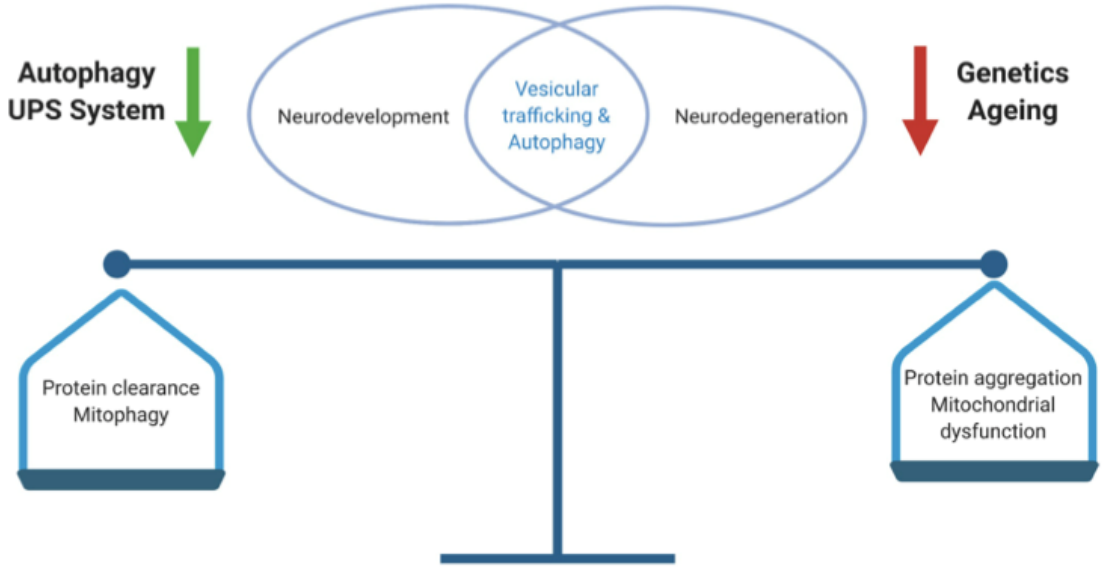
Dead line iscrizione, fino ad esaurimento dei posti disponibili

**18 aprile**

# AUTOFAGIA



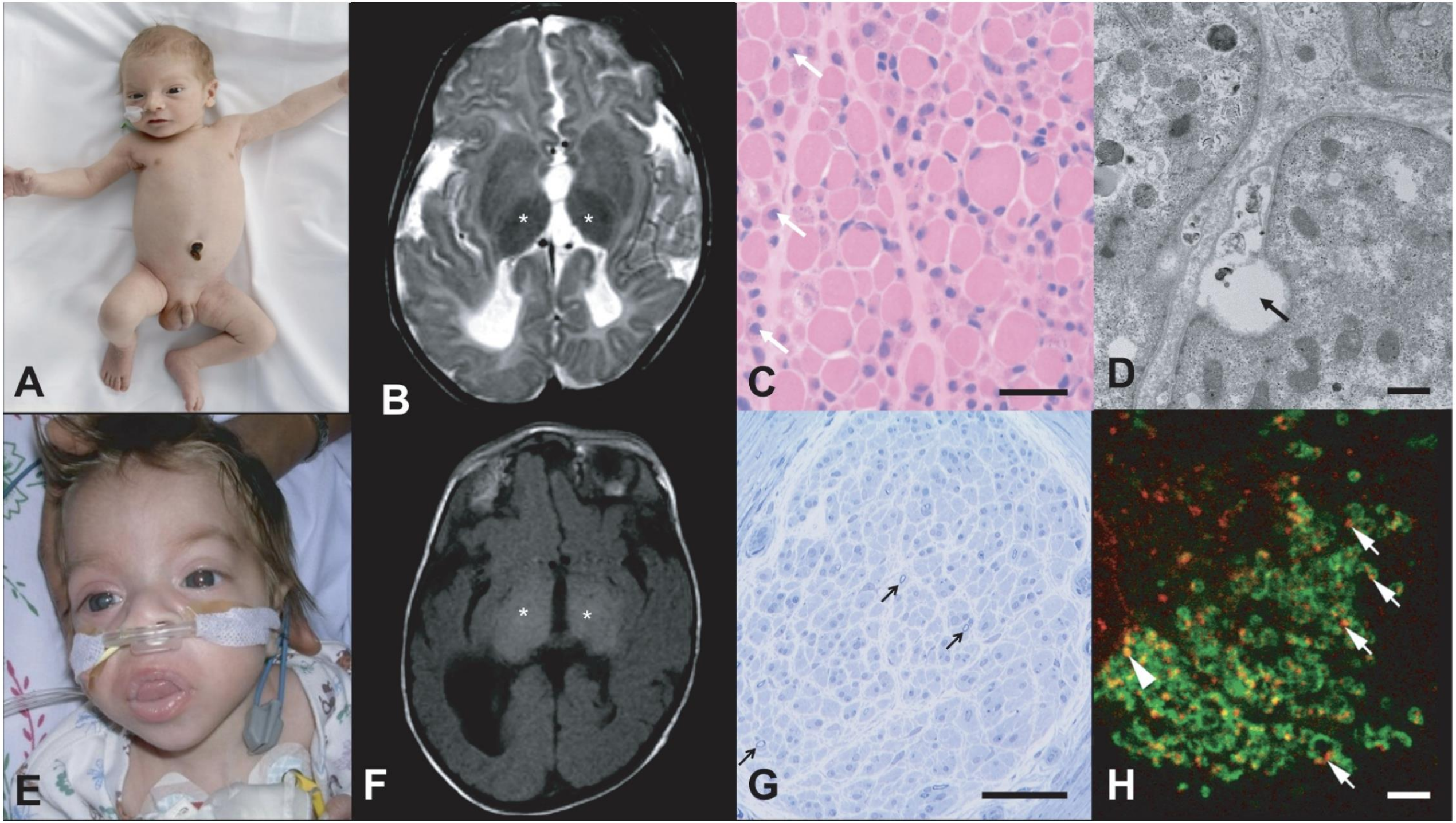

**Neurodevelopmental and neurodegenerative disorders with defects in intracellular trafficking and autophagy.**




→The accumulation of abnormal protein aggregates and defective organelles (in particular mitochondria) with age is counterbalanced by intracellular quality control mechanisms including mitophagy and aggregate removal through autophagy and/or the ubiquitin-proteasome (UPS) system.

→ In genetic conditions impairing the effective actions of these intracellular pathways, the balance is shifted, resulting in neurodegenerative changes usually occurring later in life.

→ Early-onset neurodevelopmental and adult-onset neurodegenerative disorders with defects in autophagy thus represent a highly interconnected spectrum of disorders associated with premature neuronal aging presenting throughout life


A
B
C
D
E
F
G
H

# Beyond autophagy: a novel role for autism-linked Wdfy3 in brain mitophagy

SCIENTIFIC REPORTS | (2018) 8:11348

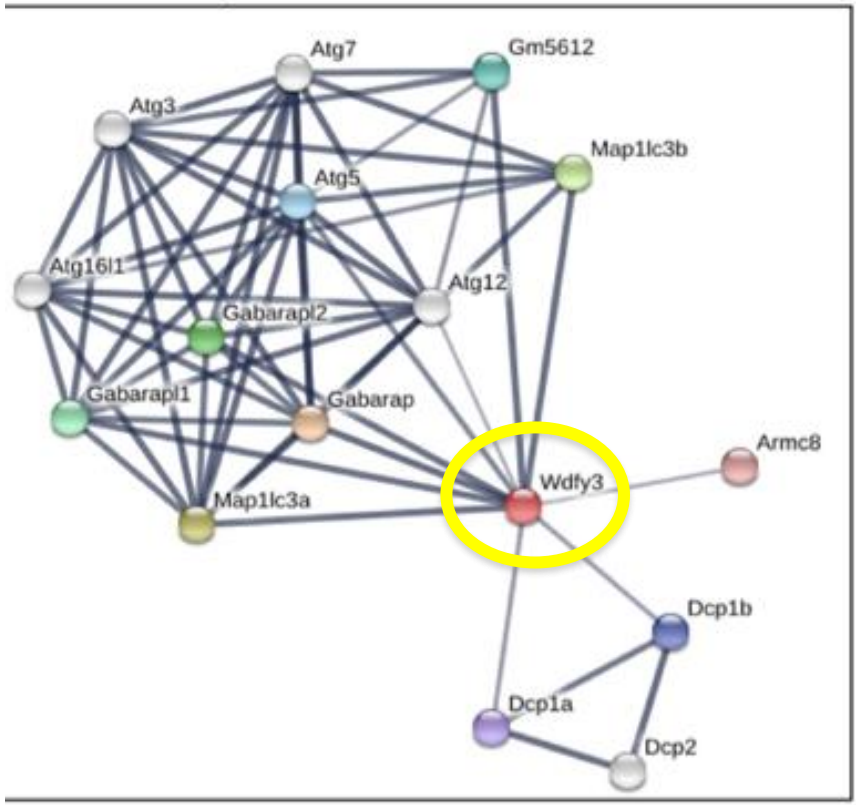
Eleonora Napoli[1], Gyu Song[1], Alexios Panoutsopoulos[2,3], M. Asrafuzzaman Riyadh[2,3], Gaurav Kaushik[2,3], Julian Halmai[1], Richard Levenson[2], Konstantinos S. Zarbalis[2,3,4] & Cecilia Giulivi[1,4]

→ Mitochondrial trafficking, dynamics and remodeling have key roles in synaptic plasticity

→ WD repeat and FYVE domain-containing 3 (*WDFY3*; also known as Autophagy-Linked FYVE or Alfy) is an identified intellectual disability, developmental delay and autism risk gene.

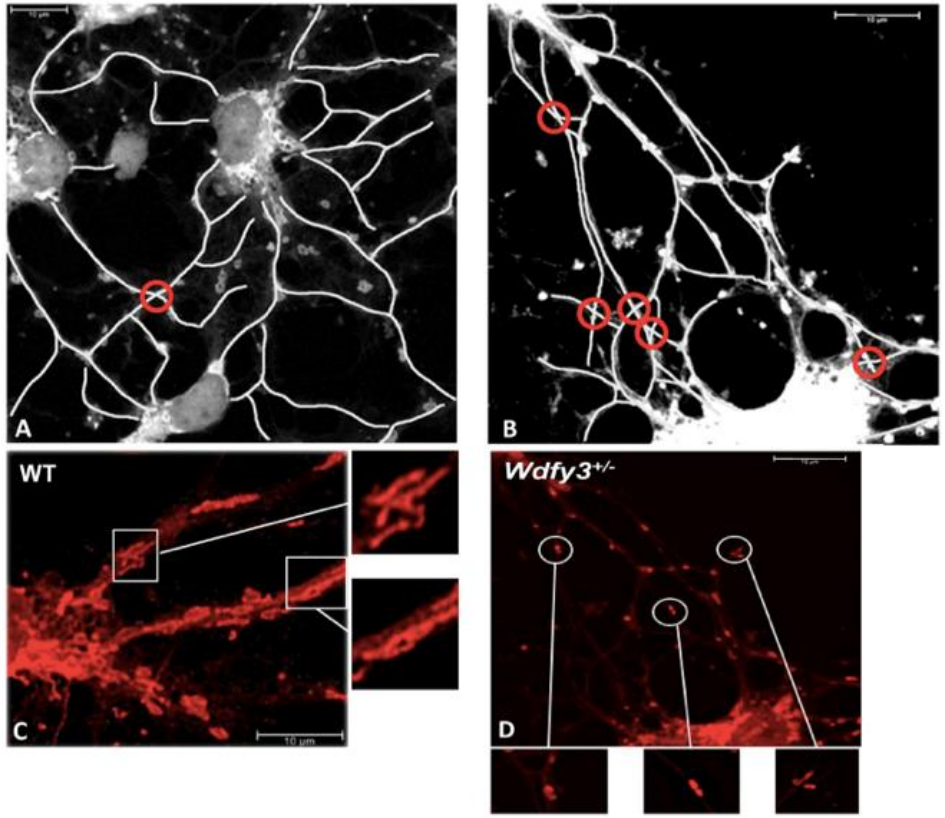
→ This gene encodes for a scaffolding protein that is expressed in both the developing and adult central nervous system and required for autophagy and aggrephagy with yet unexplored roles in mitophagy.

**B. Protein-protein interaction network**



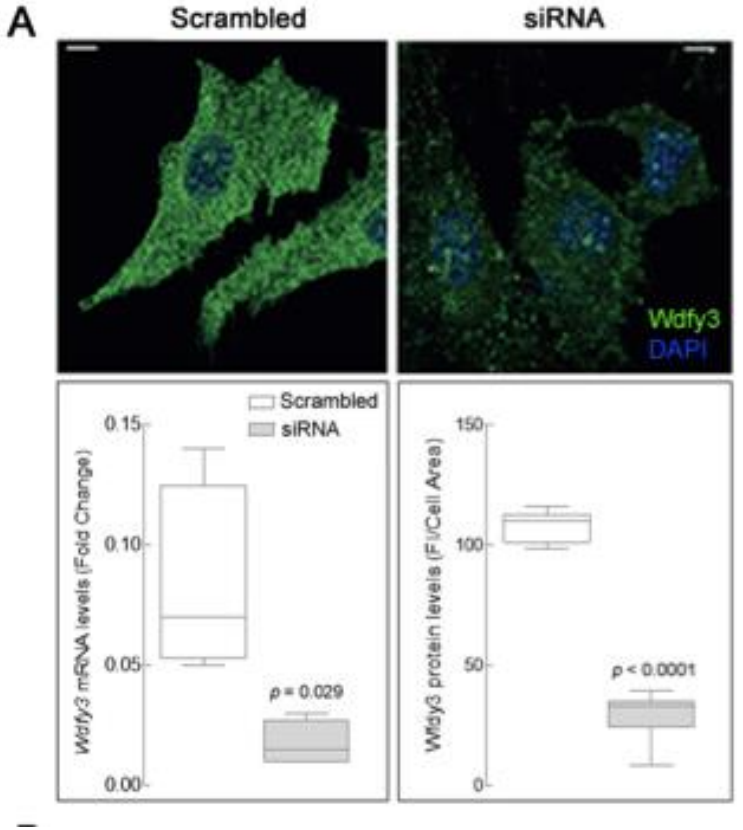

| Entry name | Protein names | Involvement in human disease from OMIM (a) | Involvement in human disease from GWAS, DECIPHER and DisGeNet (b) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | BPD | ALZ | ASD | ALS | Epilepsies | PD | SZ | Other |
| *WDFY3* | *WD repeat and FYVE domain-containing protein 3 (Autophagy-linked FYVE protein) (Alfy)* | | ✔ | ✔ | ✔ | | | | | *intellectual disability* |

# Critical role for Wdfy3 in mitochondrial homeostasis with implications for neuron differentiation, neurodevelopment and age-dependent neurodegeneration




*Mitochondrial morphology, distribution and projection pattern of cortical primary neurons in Wdfy3-haploinsufficient mice. Mitochondrial staining of primary cortical neurons from WT (**A**,**C**) or Wdfy3-haploinsufficient mice (**B**,**D**)*

*Dampening of autophagy activation in Wdfy3-deficient neuronal progenitor cells is accompanied by decreased mitophagy. (**A**) Wdfy3 immunofluorescent labeling in striatal neuronal progenitor cells (NPCs) shows ubiquitous expression (scrambled). A significant down regulation of Wdfy3 was observed in siRNA-transfected cells*



# Cell Therapy Targets for Autism Spectrum Disorders: Hopes, Challenges and Future Directions

Adv Exp Med Biol - Cell Biology and Translational Medicine 2020

Bagher Larijani, Najmeh Foroughi Heravani, Sepideh Alavi-Moghadam, Parisa Goodarzi, Mostafa Rezaei-Tavirani, Moloud Payab, Mahdi Gholami, Farideh Razi, and Babak Arjmand