

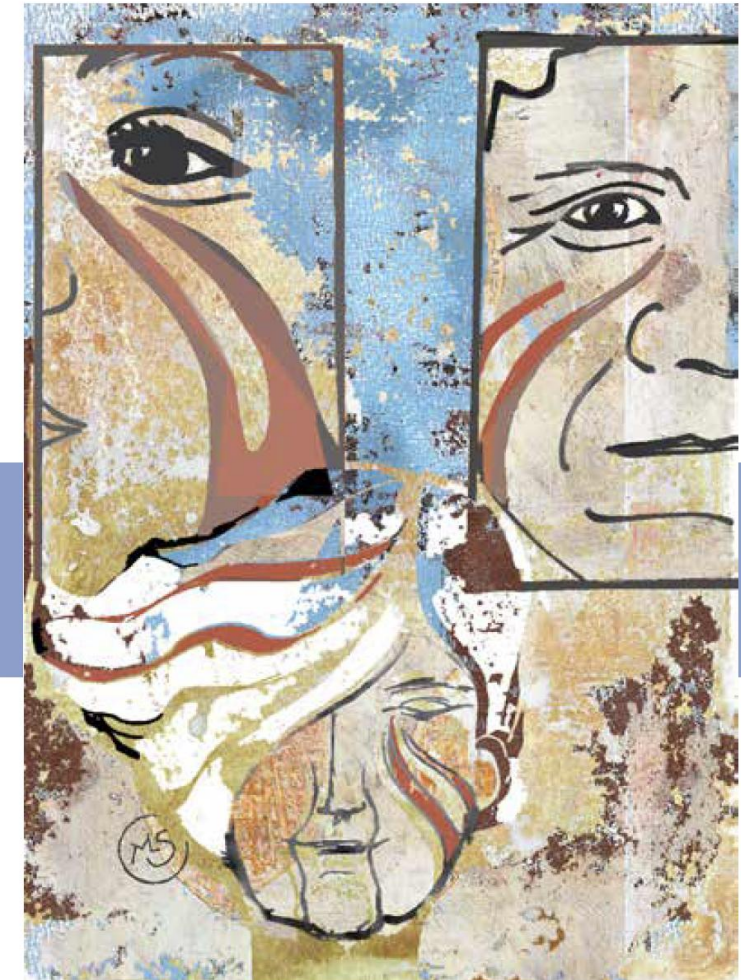
70° CONGRESSO
NAZIONALE
SIGG

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

UNIVERSITÀ
DEGLI STUDI
DI BRESCIA

LIBERI E LONGEVI

17-20
Dicembre
2025
Napoli



SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Università degli
Studi di Napoli
Federico II
Polo Didattico
di **SCAMPIA**

Prof Alessandro Padovani

Delirium e Malattia di Alzheimer: non solo amiloide

Neurology Unit

Department of Clinical and Experimental Sciences

University of Brescia

Department of Continuity of Care and Frailty

ASST Spedali Civili Brescia

Brain Health Center

University of Brescia

Disclosures

No conflicts of interest relative of this lecture

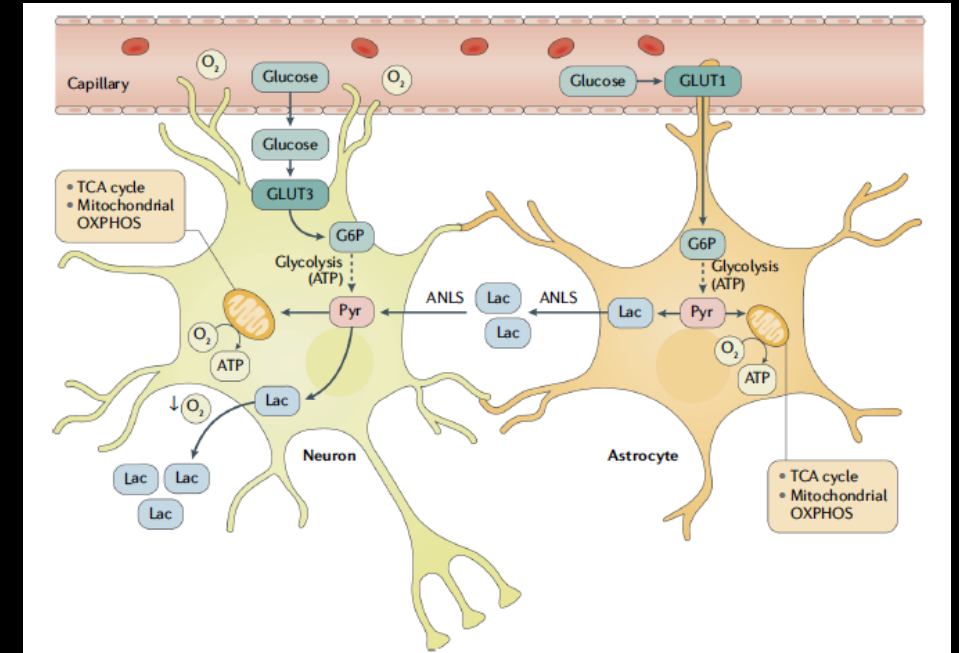
The real world experience in italy

- The mean sample age was 82.0 ± 7.5 years (58 % female). Overall, 429 patients (22.9 %) had delirium.
- **The prevalence was highest in Neurology (28.5 %)** and Geriatrics (24.7 %), lowest in Rehabilitation (14.0 %), and intermediate in Orthopedic (20.6 %) and Internal Medicine wards (21.4 %).
- In a multivariable logistic regression, **age** (odds ratio [OR] 1.03, 95 % confidence interval [CI] 1.01-1.05), **Activities of Daily Living dependence** (OR 1.19, 95 % CI 1.12-1.27), **dementia** (OR 3.25, 95 % CI 2.41-4.38), **malnutrition** (OR 2.01, 95 % CI 1.29-3.14), and use of antipsychotics (OR 2.03, 95 % CI 1.45-2.82), **feeding tubes** (OR 2.51, 95 % CI 1.11-5.66), **peripheral venous catheters** (OR 1.41, 95 % CI 1.06-1.87), urinary catheters (OR 1.73, 95 % CI 1.30-2.29), and **physical restraints** (OR 1.84, 95 % CI 1.40-2.40) were associated with delirium.
- **Admission to Neurology wards was also associated with delirium (OR 2.00, 95 % CI 1.29-3.14), while admission to other settings was not.**

The Energy Crisis Hypothesis (ie hypoglycemia, intoxication, hypoxia)

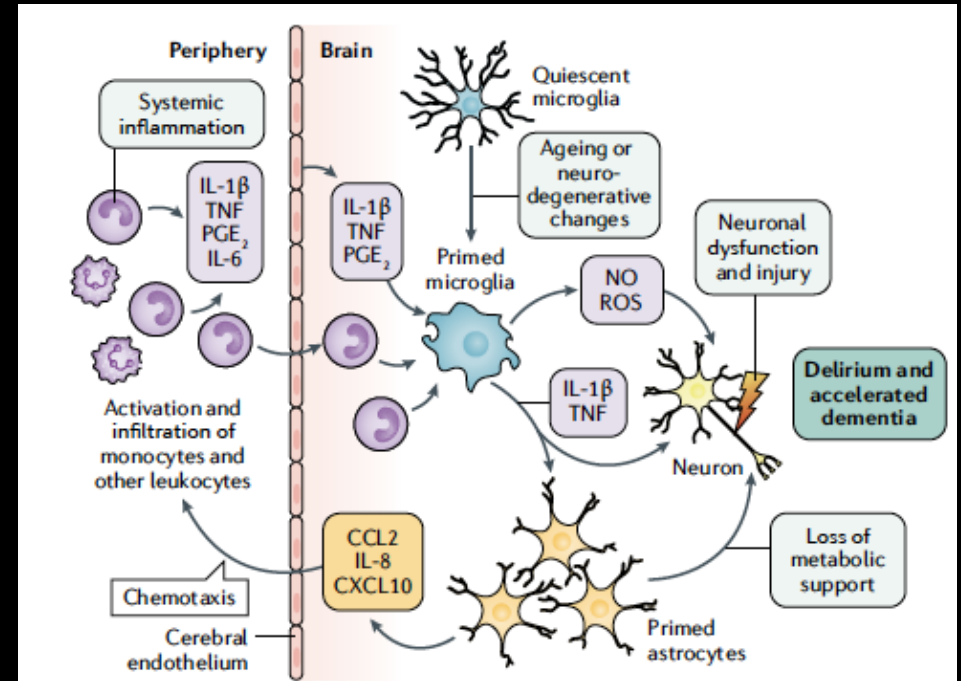
Il delirio potrebbe derivare dall'incapacità del cervello di
cervello di soddisfare le sue elevate esigenze energetiche.
energetiche.

- ↓ **Ipossia:** Ritiro di O₂ compromesso a causa di difficoltà respiratoria o shock.
- ↓ **Ipoglicemia:** Insufficiente apporto ->Compromissione
>Compromissione mitocondriale: Riduzione dell'efficienza di
dell'efficienza di produzione di ATP.
- ↓ **Disfunzione microvascolare:** Flusso sanguigno capillare in
capillare in declino.
- ↓ **Compromissione mitocondriale:** Riduzione dell'efficienza di
dell'efficienza di produzione di ATP.



The Neuroinflammatory Cascade (encephalitis, cytokines reactions)

L'infiammazione periferica innesca una cascata che interrompe la funzione cerebrale.



Peripheral Insult
(Trauma, Infection)



Inflammatory Mediators
(IL-1 β , TNF, HMGB1)



Brain Activation
(Endothelium, Microglia)

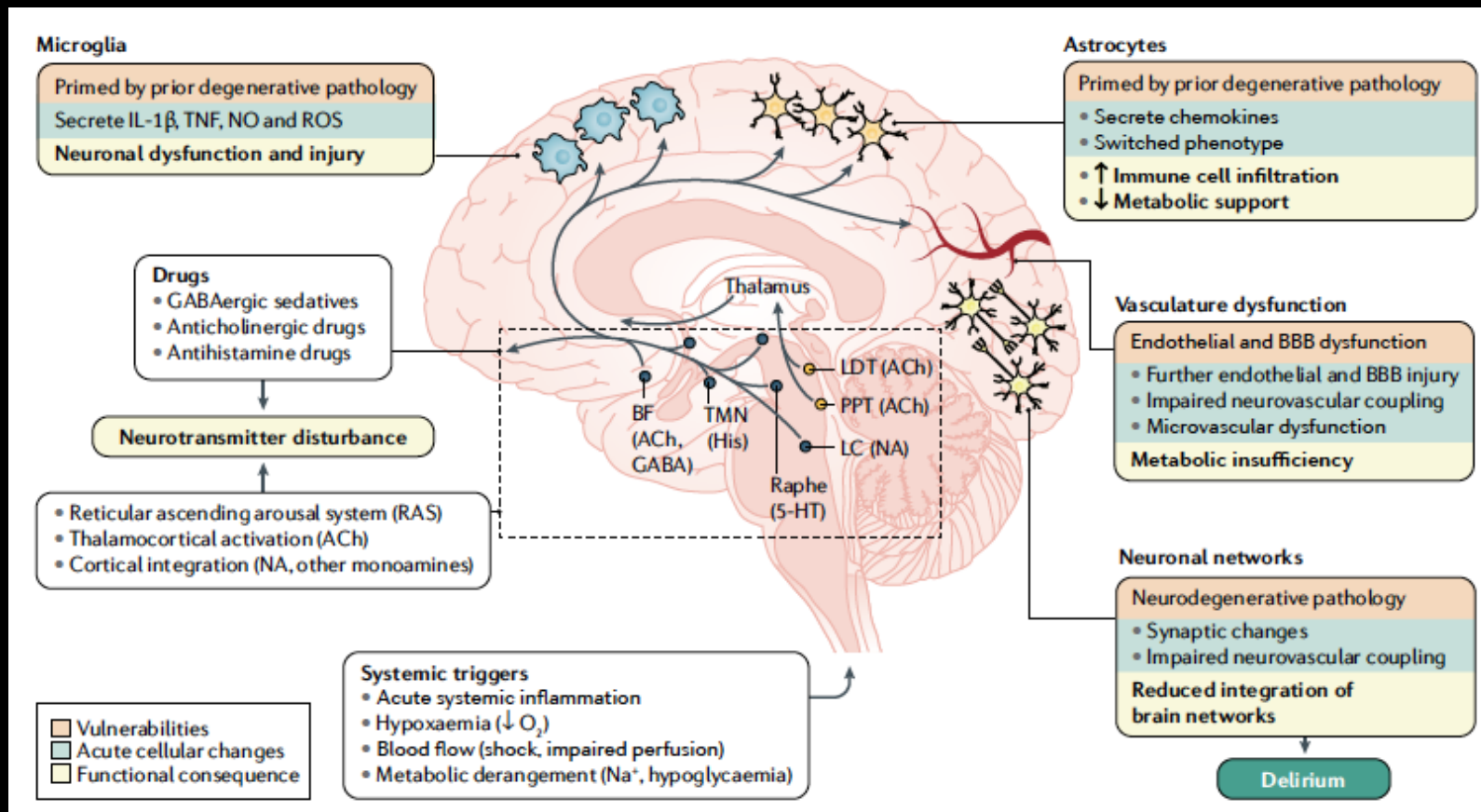


Network Disruption
(Delirium)

Network Disintegration

(ie Alzheimer Disease, Neurodegeneration Disorders, TBI, Stroke, Epilepsy, Epilepsy, Drugs, Alcohol)

L'ultimo percorso comune: la compromissione della connettività funzionale.



Connettività indebolita

La fMRI mostra una riduzione dell'integrazione tra reti in modalità executive, saliente e predefinita.

Perdita dei segnali di attivazione

L'EEG rivela una diminuzione dell'attivazione talamo-corticale e dell'efficienza globale.

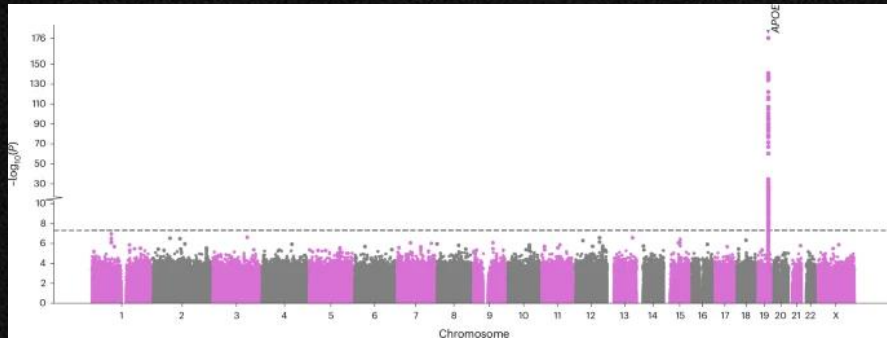
Esiste una predisposizione genetica al delirium?

Chi è il soggetto a rischio?

APOE ε4 as Lead Signal

Raptis, V., Bhak, Y., Cannings, T.I. et al. Dissecting the genetic and proteomic risk factors for delirium. Nat Aging (2025). <https://doi.org/10.1038/s43587-025-01018-6>

rs429358 definendo APOE ε4 mostra l'associazione più forte con il delirio, con aumento del rischio dipendente dalla dose.



rs429358 (APOE ε4)

OR 1.60

(95% CI 1.55–1.65)

$P = 9.7 \times 10^{-177}$

Le analisi condizionate eliminano ogni significatività incerta, confermando APOE ε4 come unico fattore indipendente sul cromosoma 19.

Shared Genes with Alzheimer Disease

L'analisi multi-caratteristica che sfrutta correlazioni genetiche ($r_g = 0,38$) identifica cinque loci replicati, suggerendo vie neuro-infiammatorie convergenti.

BIN1

Regulation of calcium homeostasis

CLU

Amyloid- β clearance

CR1

Complement activation

MS4A4A

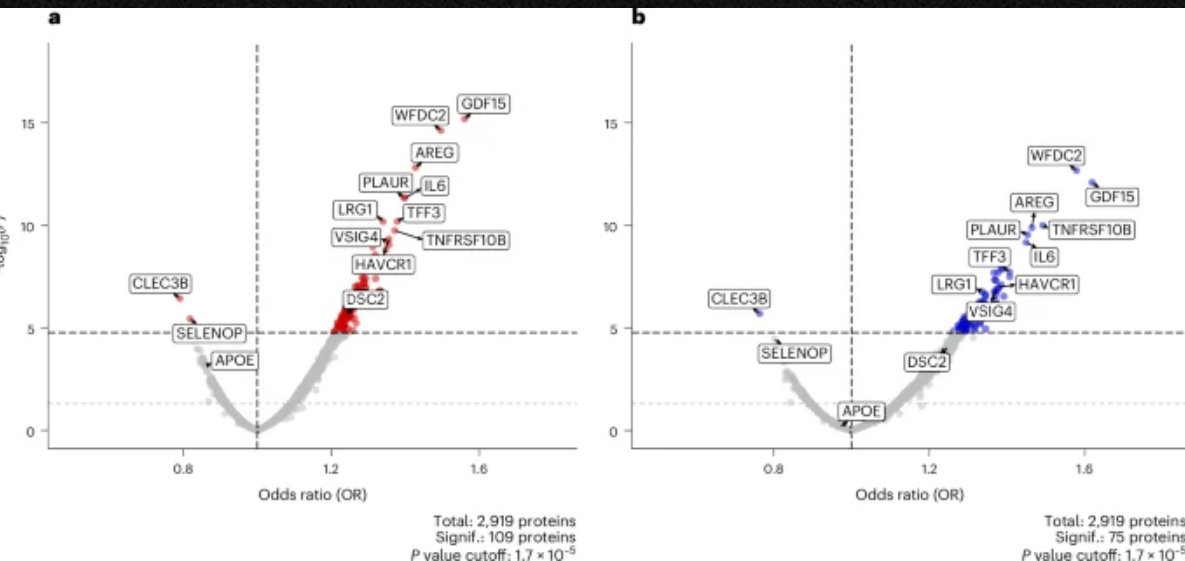
Myeloid function

TOMM40

Mitochondrial protein transport

Questi loci genetici sono tutti correlati ad aumentato rischio di M. Alzheimer

Proteome-Wide Screen Design



I livelli plasmatici basali di 2.919 proteine sono stati testati per l'associazione con delirio incidente in un follow-up di 16 anni.

This yielded **109 Bonferroni-significant hits** enriched for - interleukin signalling, TNF cascades, and ECM pathways, implicating **systemic inflammation and neural vulnerability** years before hospitalisation.

Proteome-Wide Screen

Raptis, V., Bhak, Y., Cannings, T.I. et al. Dissecting the genetic and proteomic risk factors for delirium. Nat Aging (2025). <https://doi.org/10.1038/s43587-025-01018-6>

Axonal Injury Biomarkers

Neurofilament Light Chain (NEFL)

Indicates subclinical axonal damage. Its persistence in dementia-free strata supports neuro-structural antecedents of delirium, positioning plasma NEFL as a long-range sentinel biomarker.

Glial Fibrillary Acidic Protein (GFAP) (GFAP)

Indicates astrogliosis. Its role suggests that astrocyte activation is a key activation is a key feature of the brain vulnerability that predisposes to delirium.

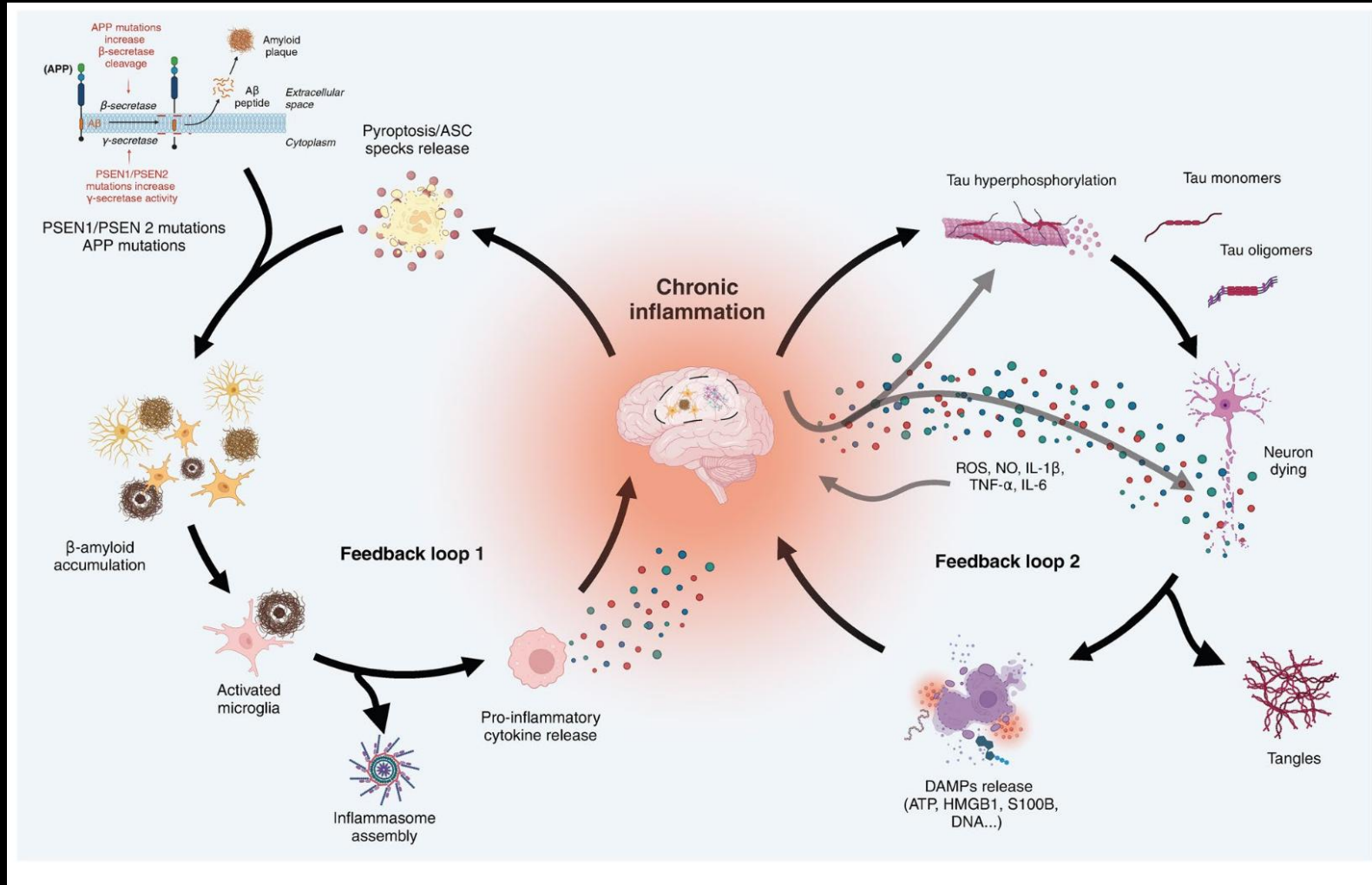
These findings encourage trials of neuro-protective interventions before acute stressors occur.

Raptis, V., Bhak, Y., Cannings, T.I. et al. Dissecting the genetic and proteomic risk factors for delirium. Nat Aging (2025). <https://doi.org/10.1038/s43587-025-01018-6>

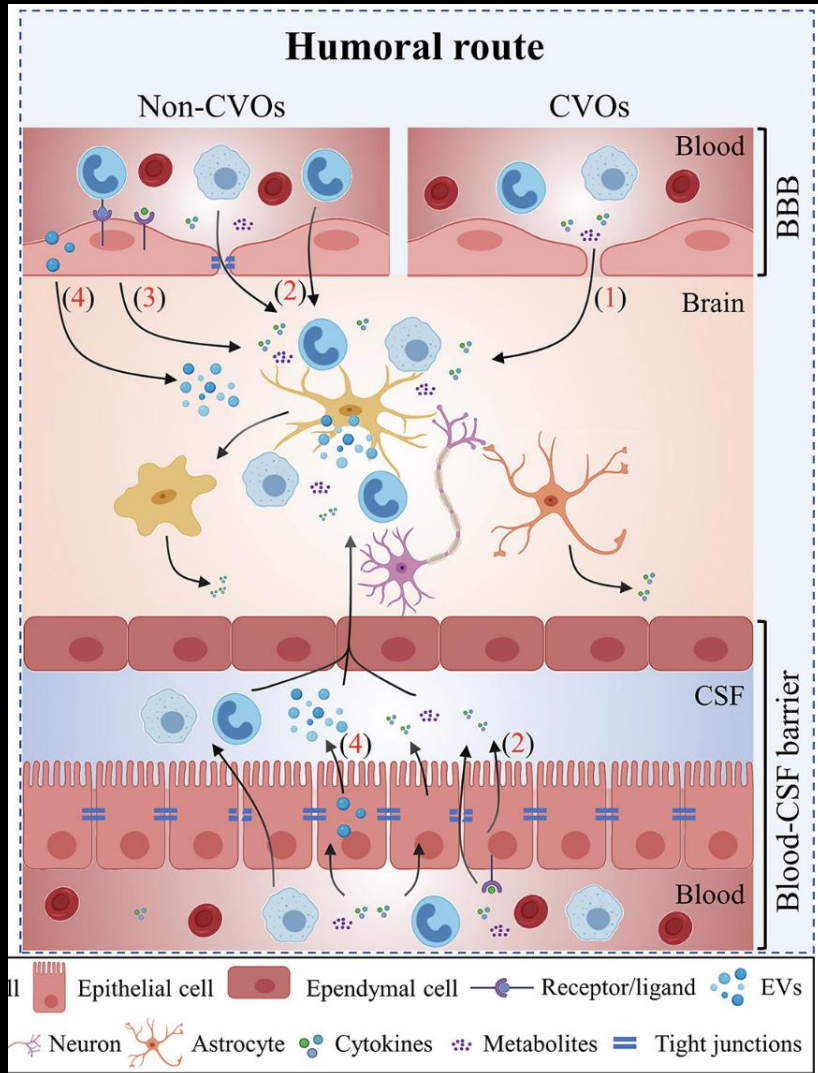
Inflammation, genetic alterations, metabolic compromise, brain damage

The complex interplay between amyloid, tau phosphorylation, neuronal degeneration and inflammation

Which are the mechanisms linking Delirium and Alzheimer? Amyloid?



Which are the mechanisms linking neuroinflammation and Amyloid?



L'amiloide è una risposta all'infiammazione del sistema nervoso centrale (e – potenzialmente – periferica)?



Is amyloid a response to CNS (and – potentially- peripheral) inflammation?

TABLE 2 CSF biomarkers according to the clinical diagnosis

| | HC (n = 18) | ENC (n = 42) | P |
|--------------------------------|---------------------|---------------------|-------|
| Inflammatory markers | | | |
| IL-6, pg/mL | 1.05 (0.56–1.64) | 2.36 (0.99–8.74) | .002 |
| IL-8, pg/mL | 33 (28–47) | 121 (59–516) | <.001 |
| TNF- α , pg/mL | 0.17 (0.17–0.17) | 0.37 (0.25–1.88) | <.001 |
| β -2 microglobulin, mg/L | 0.90 (0.71–1.01) | 1.82 (1.37–2.94) | <.001 |
| Amyloid markers | | | |
| A β 38, pg/mL | 1045 (858–1568) | 1338 (815–1652) | .67 |
| A β 40, pg/mL | 2961 (2806–4455) | 3672 (2627–4626) | .97 |
| A β 42, pg/mL | 243 (165–358) | 262 (136–373) | .92 |
| A β 42/40 ratio | 0.073 (0.058–0.083) | 0.068 (0.048–0.086) | .28 |
| sAPP- α , pg/mL | 131 (88–241) | 154 (103–227) | .64 |
| sAPP- β , pg/mL | 432 (291–786) | 409 (296–580) | .44 |
| Glial markers | | | |
| GFAP, pg/mL | 109 (76–151) | 323 (214–629) | <.001 |
| sTREM-2, pg/mL | 589 (478–1005) | 2573 (1465–4104) | <.001 |
| YKL-40, ng/mL | 64 (45–97) | 199 (145–422) | .004 |
| Neuronal markers | | | |
| NfL, pg/mL | 297 (229–437) | 1388 (496–3935) | <.001 |
| T-tau, pg/mL | 165 (127–183) | 327 (238–559) | <.001 |
| P-tau, pg/mL | 18.2 (14.2–24.1) | 25.5 (19.7–45.7) | .02 |

Abbreviations: ENC, encephalitis; GFAP, glial fibrillary acidic protein; HC, healthy controls; IL-6, interleukin 6; IL-8, interleukin 8; NfL, neurofilament light chain; p-tau, phosphorylated tau; sAPP- α , soluble amyloid precursor protein alpha, sAPP- β , soluble amyloid precursor protein beta; sTREM-2, triggering receptor expressed on myeloid cells 2; TNF- α , tumor necrosis factor alpha; t-tau, total tau; YKL-40, chitinase-3-like protein 1.

Notes: Data are presented as median (interquartile ranges).

P-values were calculated by Mann-Whitney test or Fisher's exact test, as appropriate.

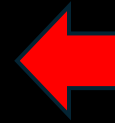


Inflammation

No amyloid alterations



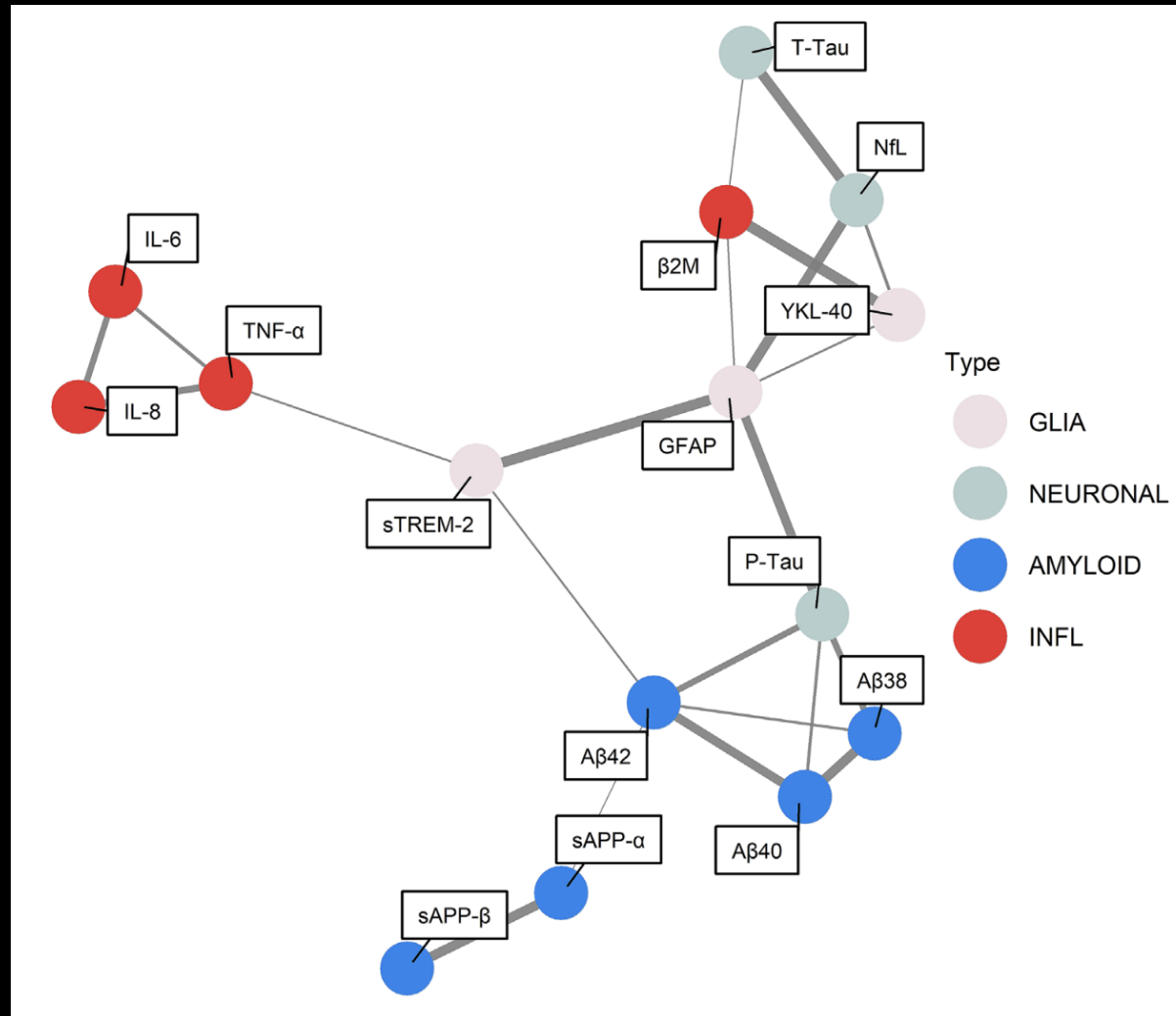
Glia



Neuronal

Inflammation does not impact on amyloid metabolism

Is amyloid a response to CNS (and – potentially- peripheral) inflammation?



Debunking the Myth

Acute inflammation is **NOT** associated with Amyloid deposition or alterations



Padovani et al. 2022

Is chronic inflammation associated with amyloid deposition?

What about chronic inflammation and AD?

(in)consistent studies indicating mild inflammation in AD

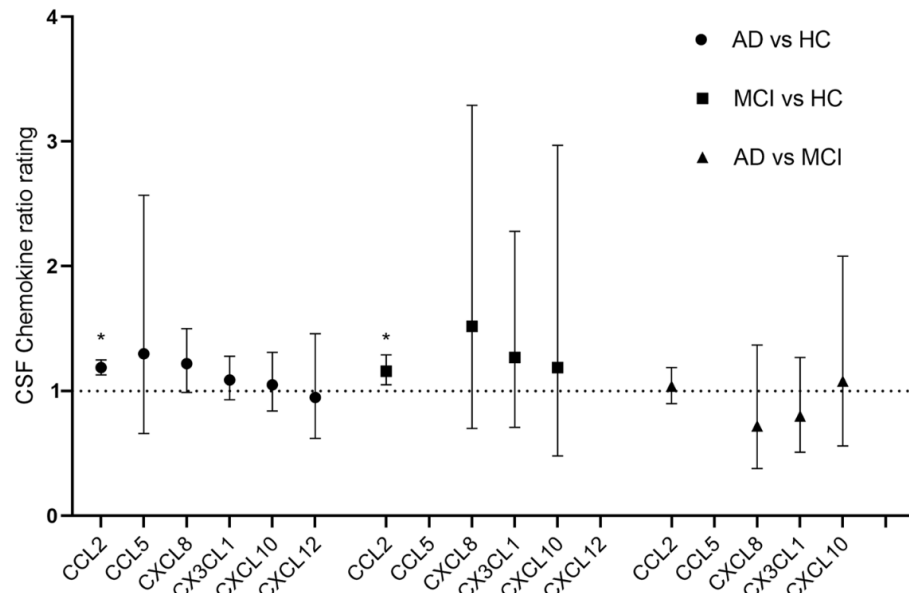


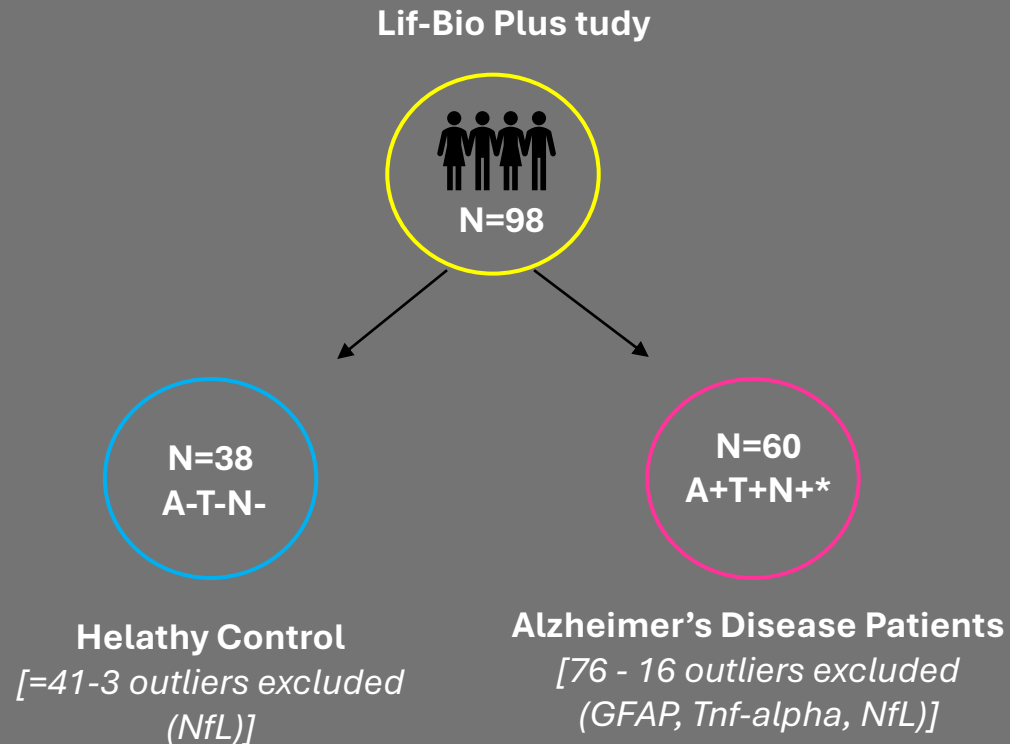
Fig. 4 The ability of CSF chemokines to distinguish AD from MCI. Average AD to MCI ratios were used to compare CSF chemokine performance. An asterisk indicates significance, $p < 0.05$

Why so inconsistent association?

Any relationship between Neuroinflammation and Neuronal, glial and synaptic markers?

PRIN PNRR- Collaboration with University of Milan

Sample characteristics



Inclusion criteria

AD: A+T+N+ patients with extensive clinical and imaging data

Inclusion criteria

Controls:

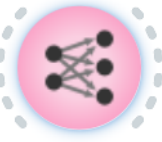
Matched subjects who underwent CSF analyses for headache
All negative markers including NfL

Objective 1:

Test the relationship between inflammatory and neuronal, synaptic and amyloid markers

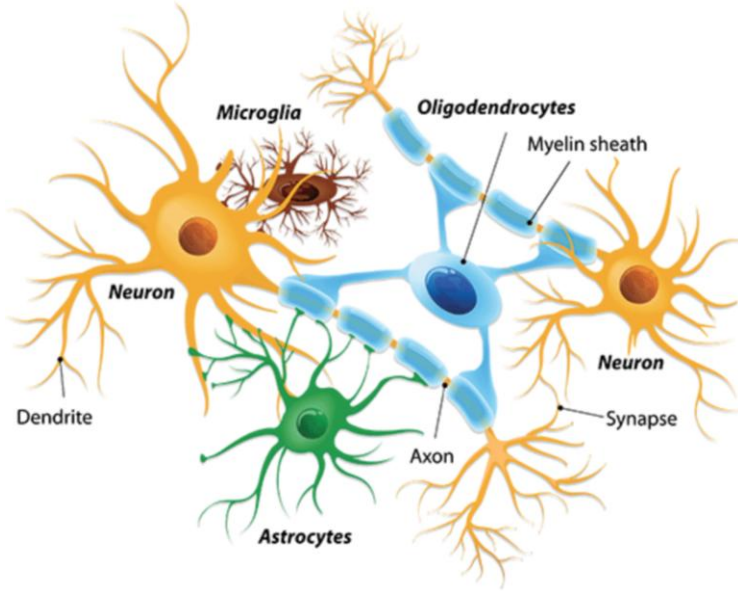
| Variable | HC (N=38) | AD (N=60) | p-value |
|--|-----------------------------|-------------------------------|---------------------|
| Age | 72.000(65.500-76.500) | 76.000(70.000-79.000) | 0.090 ^b |
| Sex (F:M) | 20:18 | 36:24 | 0.307 ^d |
| MMSE | 29.670(28.900-30.000) | 23.000(17.000-26.000) | < .001 ^c |
| AD CSF Core Biomarkers | | | |
| t-tau [pg/mL] | 187.500(143.500-272.500) | 708.000(532.000-1022.000) | < .001 ^a |
| p-tau 181 [pg/mL] | 24.400(20.400-39.850) | 108.000(86.000-171.800) | < .001 ^a |
| NfL [pg/mL] | 599.282(369.318-815.918) | 1386.292(795.304-2277.179) | < .001 ^a |
| Aβ42 [pg/mL] | 581.00(447.500-793.500) | 495.000(390.000-581.000) | 0.003 ^b |
| Aβ40 [pg/mL] | 6870.000(5886.00-8400.00) | 10127.000(8564.000-12357.750) | < .001 ^c |
| CSF Synaptic Biomarkers | | | |
| Neurogranin [pg/mL] | 767.605(554.775-1230.390) | 2221.510(1250.510-3747.840) | < .001 ^b |
| CAP2 [pg/mL] | 20.000(9.500-36.500) | 53.000(39.000-66.500) | 0.001 ^c |
| SNAP25 [pg/mL] | 52.938(37.198-67.475) | 104.999(79.892-133.642) | 0.001 ^b |
| CSF Inflammatory and Glial Biomarkers | | | |
| IL-1 alpha [pg/mL] | 1.000(0.515-1.573) | 0.920(0.670-1.190) | 0.569 ^a |
| IL-1 beta [pg/mL] | 0.885(0.735-1.270) | 1.370(1.210-1.770) | <.001 ^a |
| IL-8 [pg/mL] | 63.720(44.855-92.070) | 63.220(46.090-73.750) | 0.598 ^a |
| MCP1 [pg/mL] | 1038.525(670.605-1370.092) | 1212.760(972.260-1484.350) | 0.351 ^a |
| TNF alpha [pg/mL] | 3.835(2.905-4.953) | 6.920(4.720-8.480) | <.001 ^b |
| GFAP [pg/mL] | 4339.025(3100.992-6663.672) | 18662.644(5266.992-26664.460) | <.001 ^a |

Note: ^a Mann-Whitney U test, ^b Welch test, ^c Student's t test, ^d χ^2 Chi-squared test.

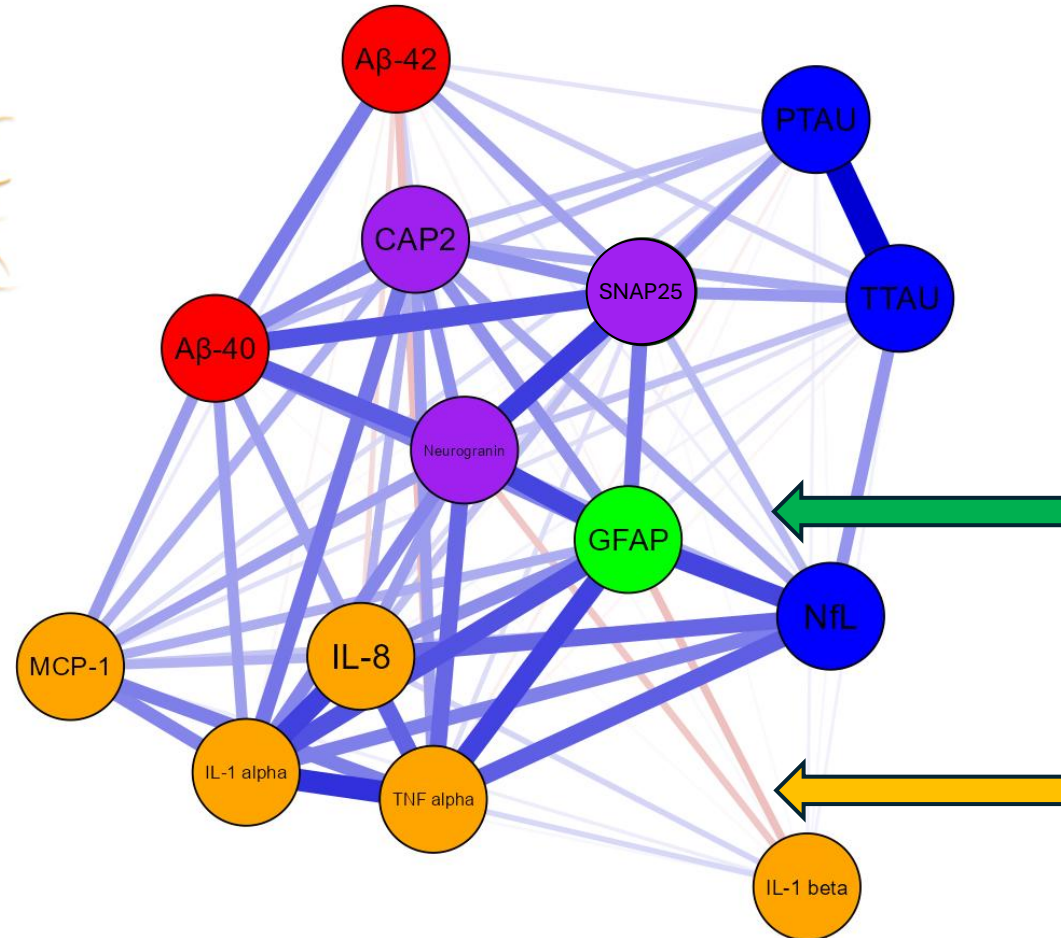


Network Analysis

(imputed and forced maintained distances for a direct comparison)



AD



GFAP mediates the relationship between mild inflammation, neuronal and synapse dysfunction

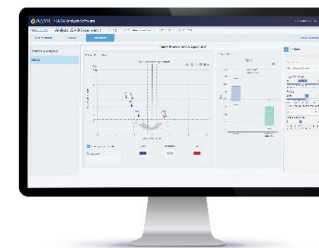
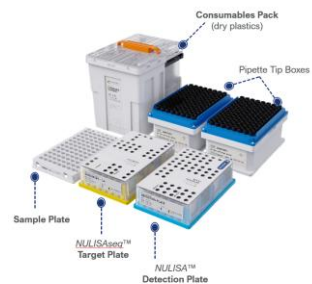
Final statement
Chronic inflammation is NOT associated with Amyloid markers

Are single markers the key?

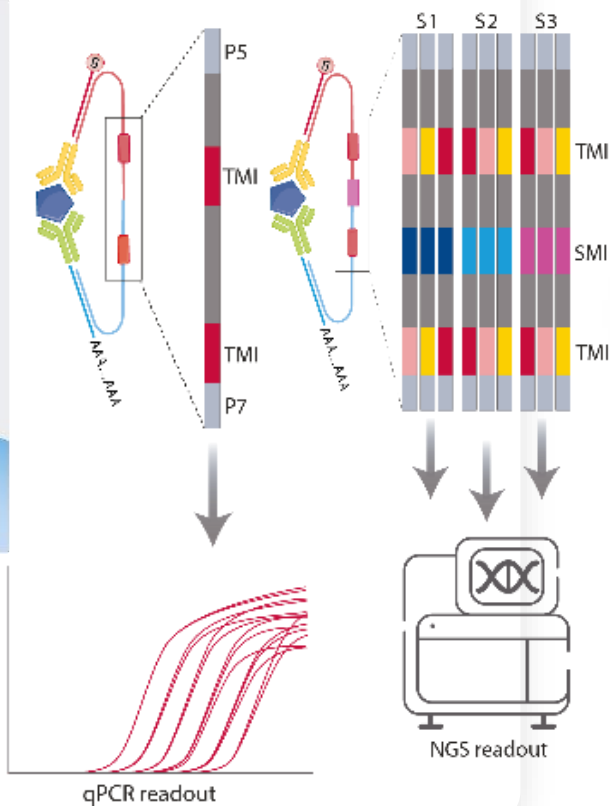
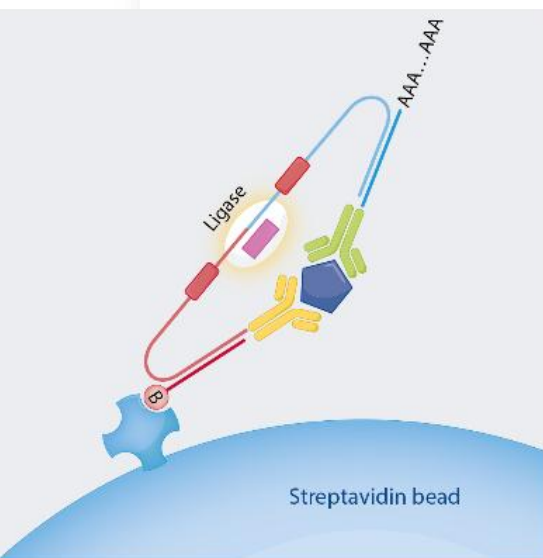
Which is the global signature related to Alzheimer's disease?



NULISA Workflow



Enabled by NULISA's combination of ultra-sensitivity and high-plex using 25 μ L



High Detectability:
~95% in plasma
~85% in CSF

| AMYLOID & TAU PATHOLOGIES | | |
|---------------------------|--------|----------------|
| Abeta38 (a β 38) | BACE1 | PSEN1 |
| Abeta40 (a β 40) | BASP1 | pTau181 |
| Abeta42 (a β 42) | CD63 | pTau217 |
| ACHE | CST3 | pTau231 |
| APOE | IGFBP7 | SFRP1 |
| APOE (APOE4) | KLK6 | tTau(totalTau) |

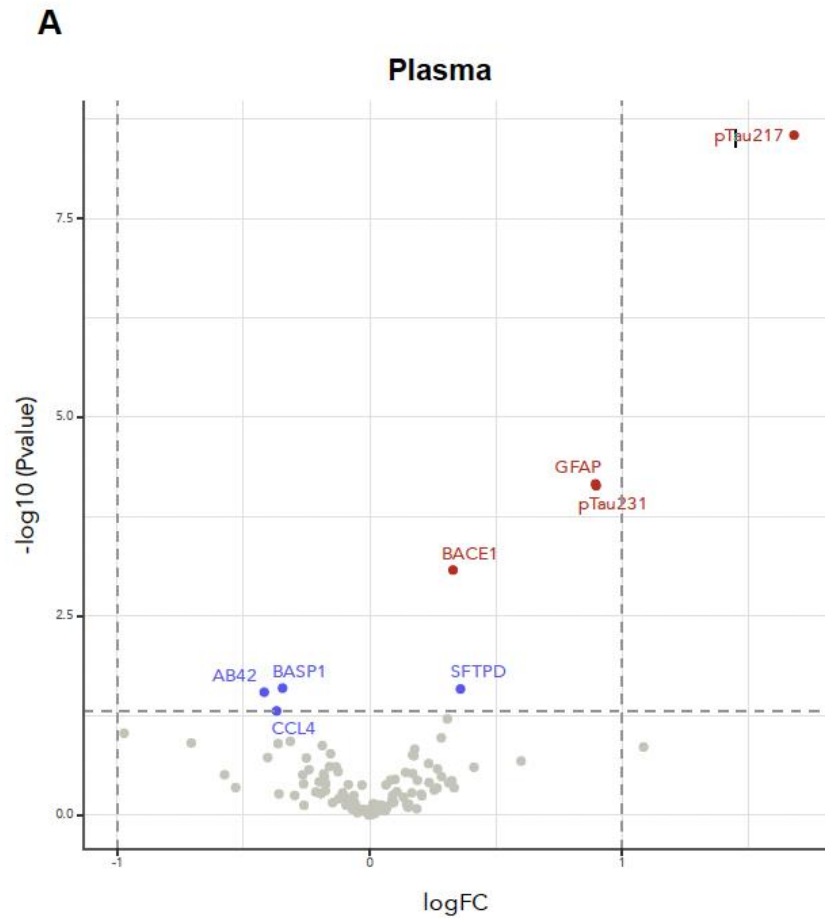
| SYNUCLEIN & SYNAPTIC | | |
|----------------------|-----------------------------------|----------------------|
| AGRN | IL6R (IL6Ra) | SNCB (β -Syn) |
| ARSA | MDH1 | SOD1 |
| BDNF | NGF | TDP43 |
| DDC | Oligo-SNCA (Oligo- α -Syn) | pTDP43-409 |
| FABP3 | PARK7 | UCHL1 |
| FOLR1 | pSNCA-129 | VEGF |
| HTT | SNCA (α -Syn) | VSNL1 (VILIP-1) |

| VASCULAR & METABOLISM | |
|-----------------------|--------|
| FLT1 (VEGF R1) | PGK1 |
| HBA1; HBA2 | POSTN |
| KDR (VEGF R2) | PTN |
| MME | SAA1 |
| PDGFRB | VEGF-A |
| PGF(PLGF) | VEGF-D |

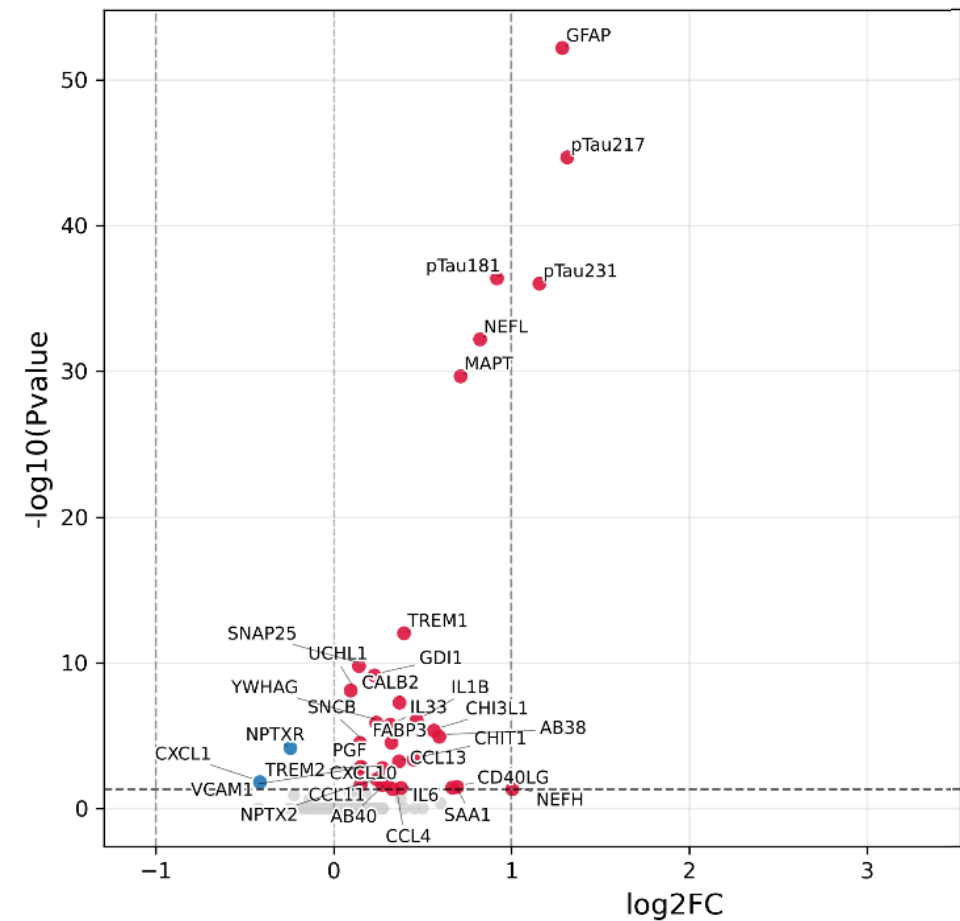
| NEURODEGENERATION | |
|-------------------|--------|
| ANXA5 | NPTX2 |
| CALB2 | NPTXR |
| CNTN2 | NPY |
| ENO2 | NRGN |
| FGF2 (FGF basic) | PDLIM5 |
| GDI1 | REST |
| GDNF | SMOC1 |
| GOT1 | SNAP25 |
| MSLN | SQSTM1 |
| NEFH | UBB |
| NFL | YWHAG |
| NPTX1 | YWHAZ |

| INFLAMMATION | | |
|-----------------------|-----------------------|------------------------|
| CCL2 (MCP1) | CSF2 (GM-CSF) | IL4 |
| CCL3 (MIP1a/CCL3) | CX3CL1 (Fractalkine) | IL5 |
| CCL4 (Mip1b/CCL4) | CXCL1 (GRO α) | IL6 |
| CCL11 (Eotaxin) | CXCL8 (IL8) | IL7 |
| CCL13 (MCP4) | CXCL10 (IP-10) | IL9 |
| CCL17 (TARC/CCL17) | FCN2 | IL10 |
| CCL22 (MDC) | GDF15 | IL12A/IL12B (IL-12p70) |
| CCL26 (Eotaxin-3) | GFAP | IL13 |
| CD40LG (CD40L/TNFSF5) | ICAM1 | IL15 |
| CHI3L1 (YKL40) | IFNG (IFN-gamma) | IL16 |
| CHIT1 | IGF1R | IL17A |
| CRH | IL1B(IL-1 beta) | IL18 |
| CRP | IL2 | IL33 |
| | | PRDX6 |
| | | RUVBL2 |
| | | S100A12 |
| | | S100B |
| | | SFTPD |
| | | SLIT2 |
| | | TAFI5 |
| | | TEK (Tie-2/TEK) |
| | | TIMP3 |
| | | TNF (TNF-a) |
| | | TREM1 (sTREM1) |
| | | TREM2 |
| | | VCAM1(CD106) |

Alzheimer's disease disease muldimodal plasma signature

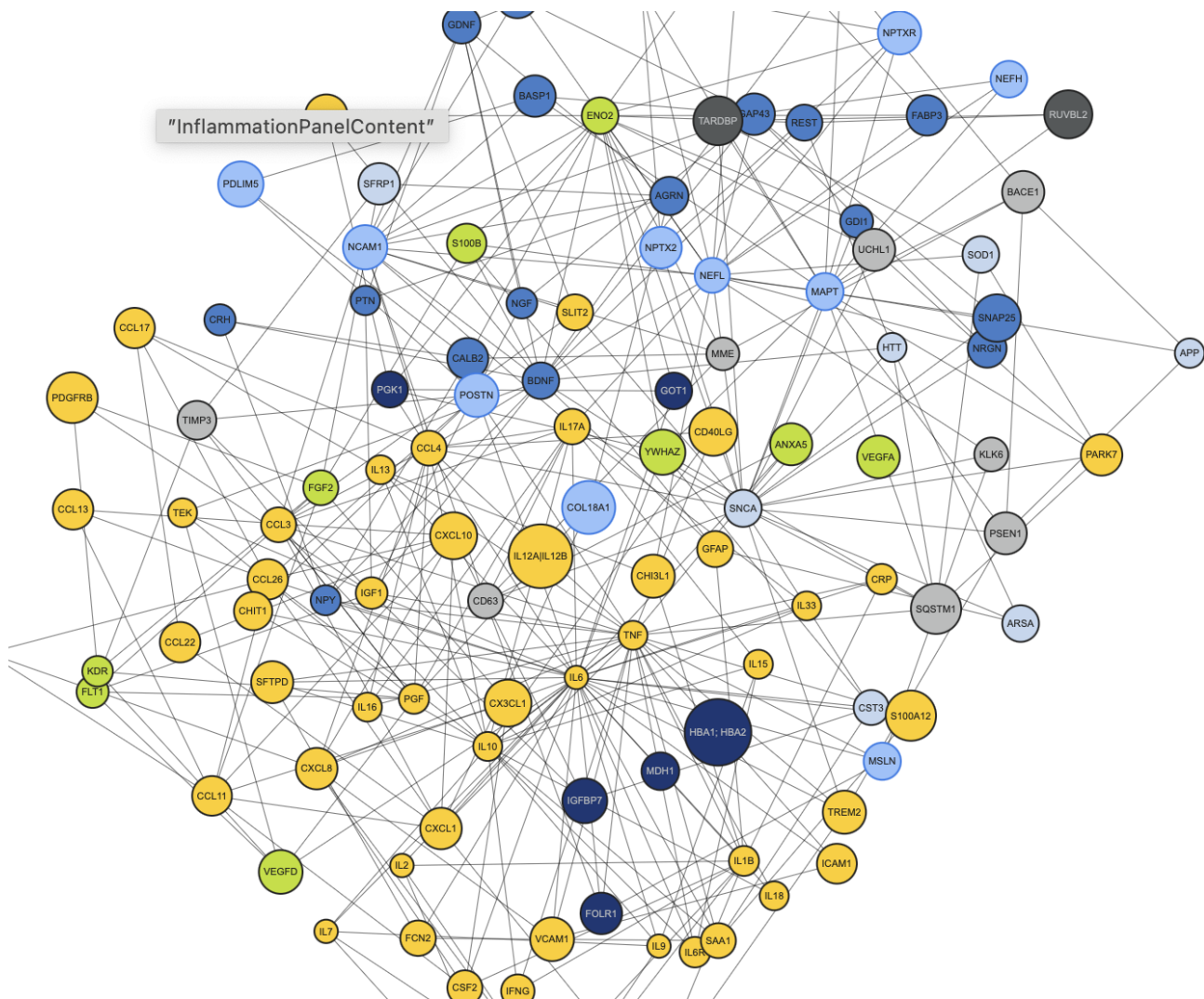


Plasma markers in life-Biocoohort 400 subjects including 170 A+T+N+ AD



In Life Bio cohort

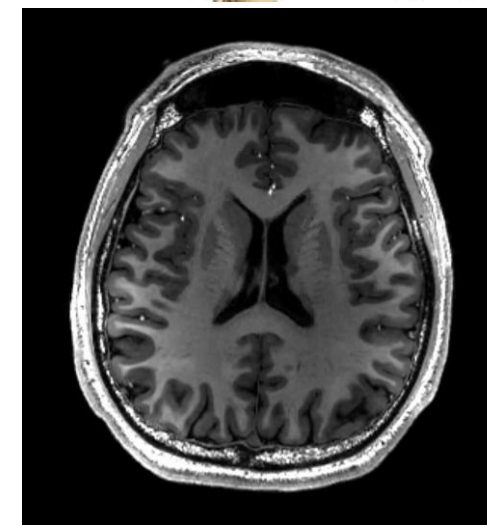
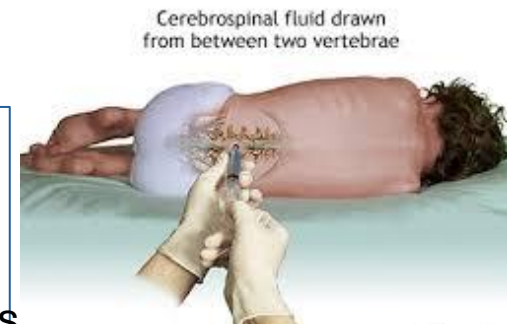
No clear relationship between inflammation and ..



Severity
comorbidities

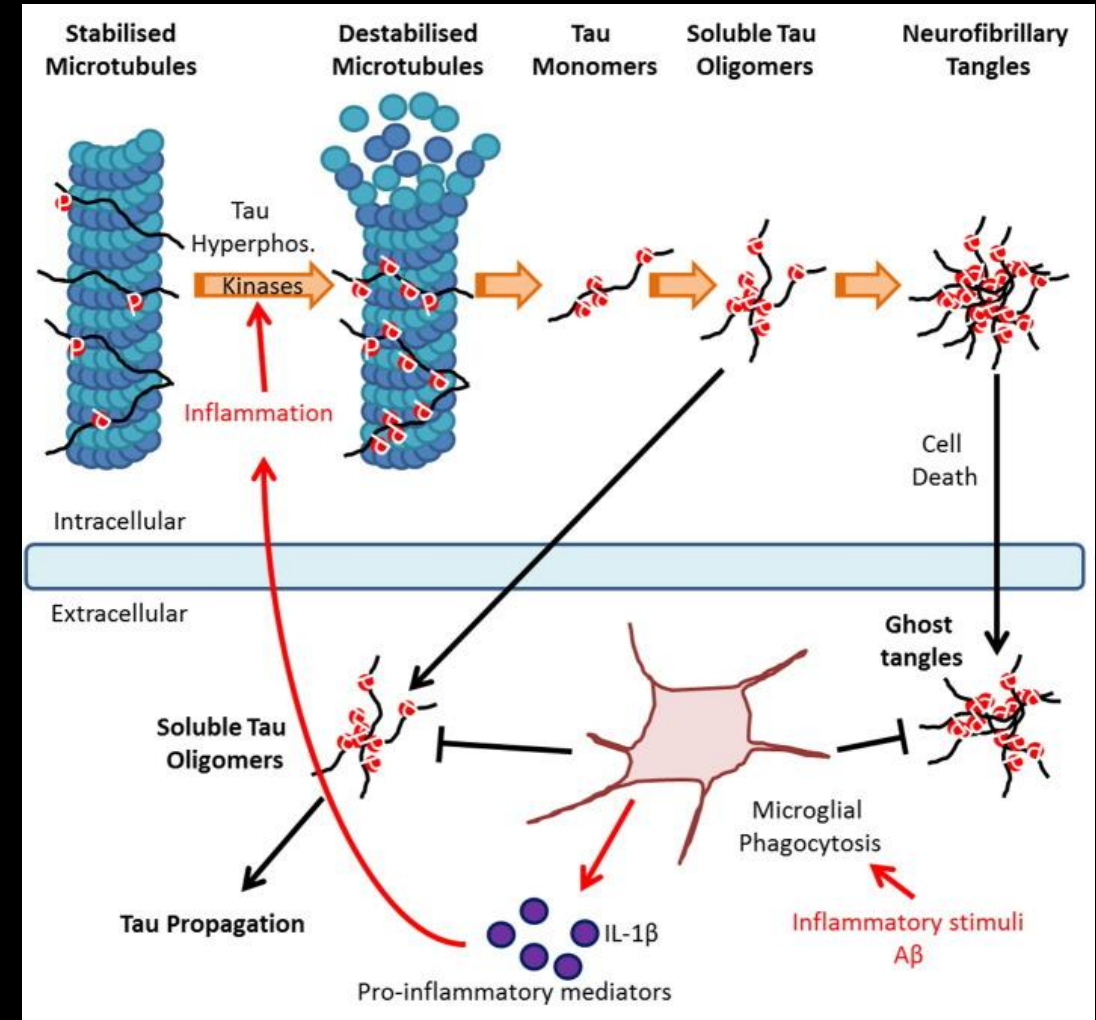
CSF core markers

MRI patterns



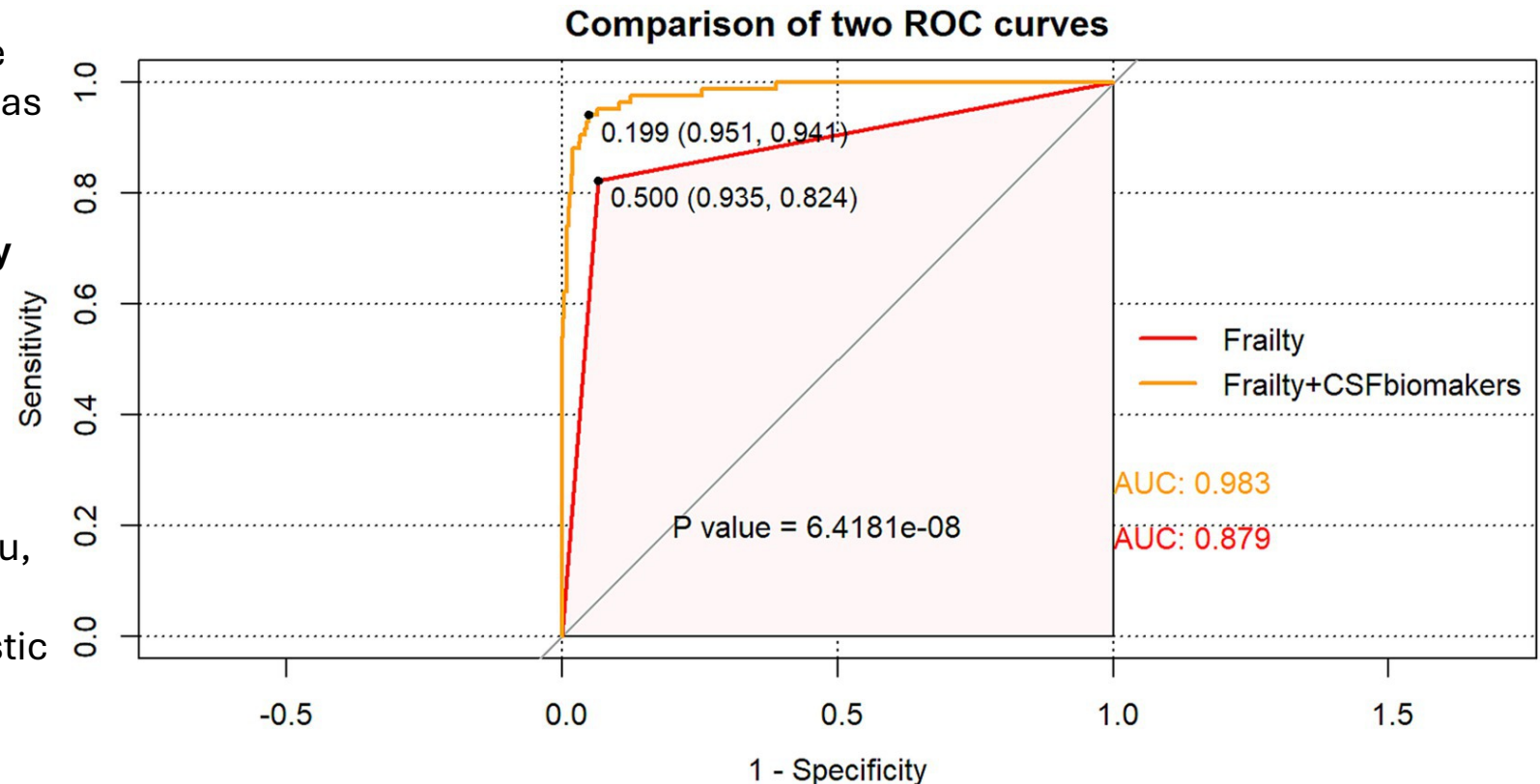
A state of delirium: Deciphering the effect of inflammation on tau pathology in Alzheimer's disease

- È stato suggerito che l'infiammazione possa avere un ruolo nello sviluppo della patologia tau, ma i meccanismi sottostanti restano poco compresi.
- Sebbene la segnalazione di IL-1 β nella microglia sembri essere dannosa, i dati qui discussi mettono in discussione la pertinenza dell'uso della fosforilazione tau come lettura per la patologia tau.
- **Gli stimoli pro-infiammatori inducono in modo robusto la fosforilazione dei tau nei sistemi modello, ma se ciò progredisca o meno nel processo patologico di aggregazione dei tau è in gran parte sconosciuto.**



The strong relationship with Tau Metabolism

- The incidence of POD was 14.7%. The study identified frailty, Tau, and P-tau as significant risk factors for POD
- **ROC curve analysis (AUC = 0.983) demonstrated that combining frailty with CSF biomarkers had strong predictive power for distinguishing POD.**
- Using Lasso regression for variable selection, we subsequently identified eight predictors—frailty, Tau, A β 42/Tau, A β 40, age, A β 42, P-tau, and drinking history—from the training set via logistic regression.
- Furthermore, **SHAP analysis confirmed that frailty and Tau were the key determinants influencing the machine learning model's predictions.**



Front. Neurol., 17 September 2025

Sec. Cognitive and Behavioral Neurology

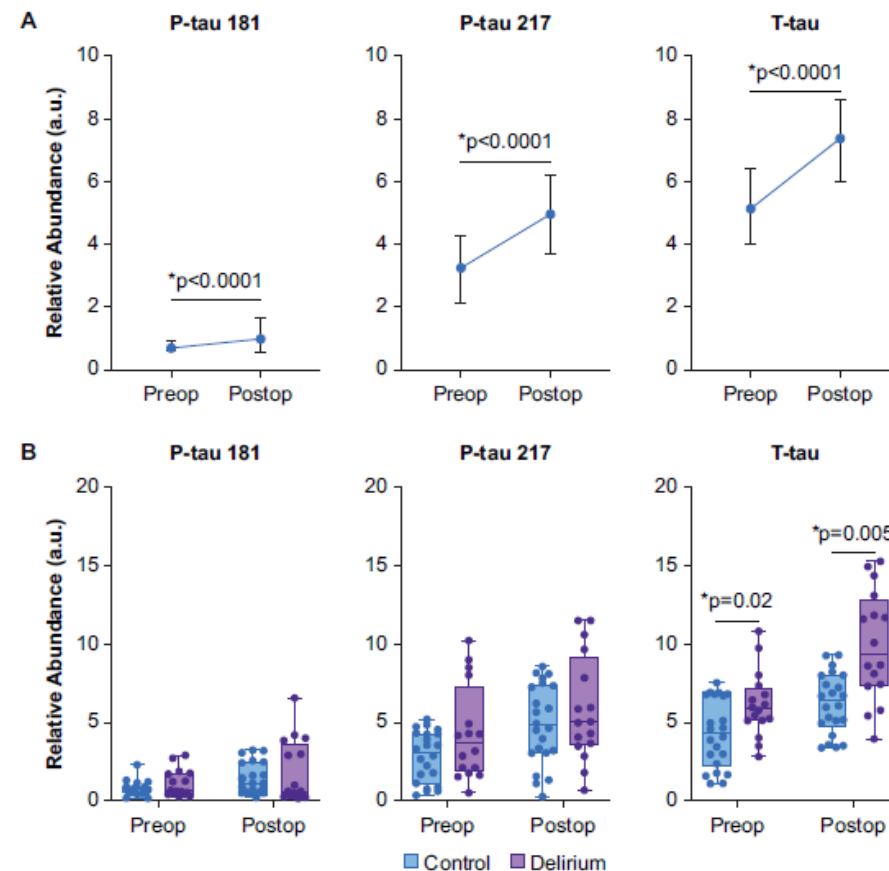
The strong relationship with Tau Metabolism

Only T-tau was associated with the incidence and severity of postoperative delirium, suggesting a mechanistic link between postoperative delirium and T-tau, upstream of tau hyperphosphorylation and cortical aggregation of these tau isoforms.

Our findings suggest that T-tau could be developed as a biomarker for postoperative delirium. Further, they suggest that the perioperative period may be leveraged to enable fundamental new insights into tau regulation and ADRD pathophysiology. F

Front. Neurol., 17 September 2025

Sec. Cognitive and Behavioral Neurology

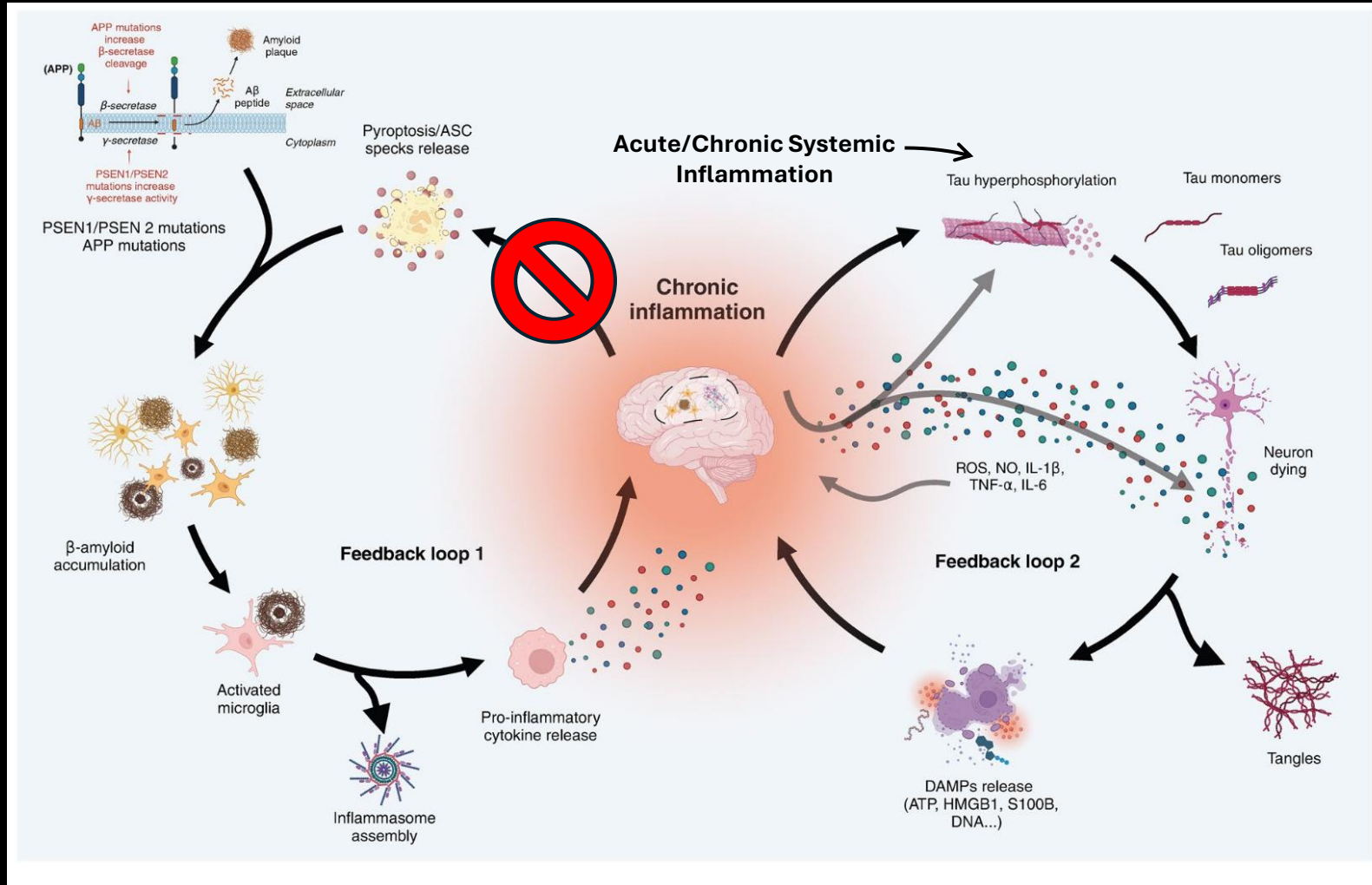


Cognitive Stability Among Plasma p-tau 181 Negative Individuals: A 5-year Analysis of the Multidomain Alzheimer Prevention Trial Study, Federico Bellelli, et al., for the MAPT/DSA Study Group

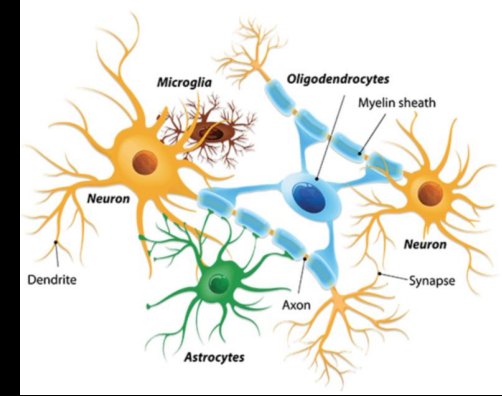
The Journals of Gerontology: Series A, Volume 80, Issue 7, July 2025, glaf113,

- This study aims to assess the evolution of cognitive performances over a 5-year follow-up period in community-dwelling older people with negative plasma p-tau181 levels and to determine whether frailty could discriminate between those who experience cognitive decline and those who do not, in the p-tau negative groups.
- In a population with an end-of-study median age of 79 years (interquartile range: 76–82), whatever the cut-off, the overall group with negative p-tau181 status did not develop cognitive decline over the follow-up. Among the p-tau181 negative groups, individuals who declined had a higher prevalence of frailty compared to those who did not decline.

Which are the mechanisms linking Delirium and Alzheimer? Amyloid?



Conclusions:



- L'infiammazione periferica fa parte della firma complessiva dell'AD
- L'infiammazione acuta NON è associata alla deposizione amiloidee allo sviluppo della Malattia di Alzheimer
- GFAP guida la correlazione tra neuroinfiammazione e disfunzione sinaptica/neuronale
- CSN e infiammazione periferica non sono correlate ma l'infiammazione acuta/cronica periferica agisce a valle sul metabolism della proteina tau
- Il delirium condivide gli stessi fattori di rischio della Malattia di Alzheimer confermando la stretta associazioni tra le due condizioni

Future Directions: Precision Subtyping

Moving beyond one-size-fits-all to target specific pathways.



Hypoxic Subtype

Target with oxygen support, vascular therapies.
therapies.



Inflammatory Subtype

Target with anti-cytokine agents.



Metabolic Subtype

Target with energy-supporting therapies.

