

ΕΠΙΣΤΗΜΟΝΙΚΗ ΕΚΔΗΛΩΣΗ

Εγκέφαλος
και Νεφρός

10-11 Νοεμβρίου 2023
Pantelidis Hotel, Πλατεία



Αρτηριακή υπέρταση και υποκλινικές βλάβες του εγκεφάλου. Παθοφυσιολογικοί μηχανισμοί

Όλγα Μπαλάφα

Νεφρολόγος-Διευθύντρια ΕΣΥ

Πανεπιστημιακό Νοσοκομείο Ιωαννίνων

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

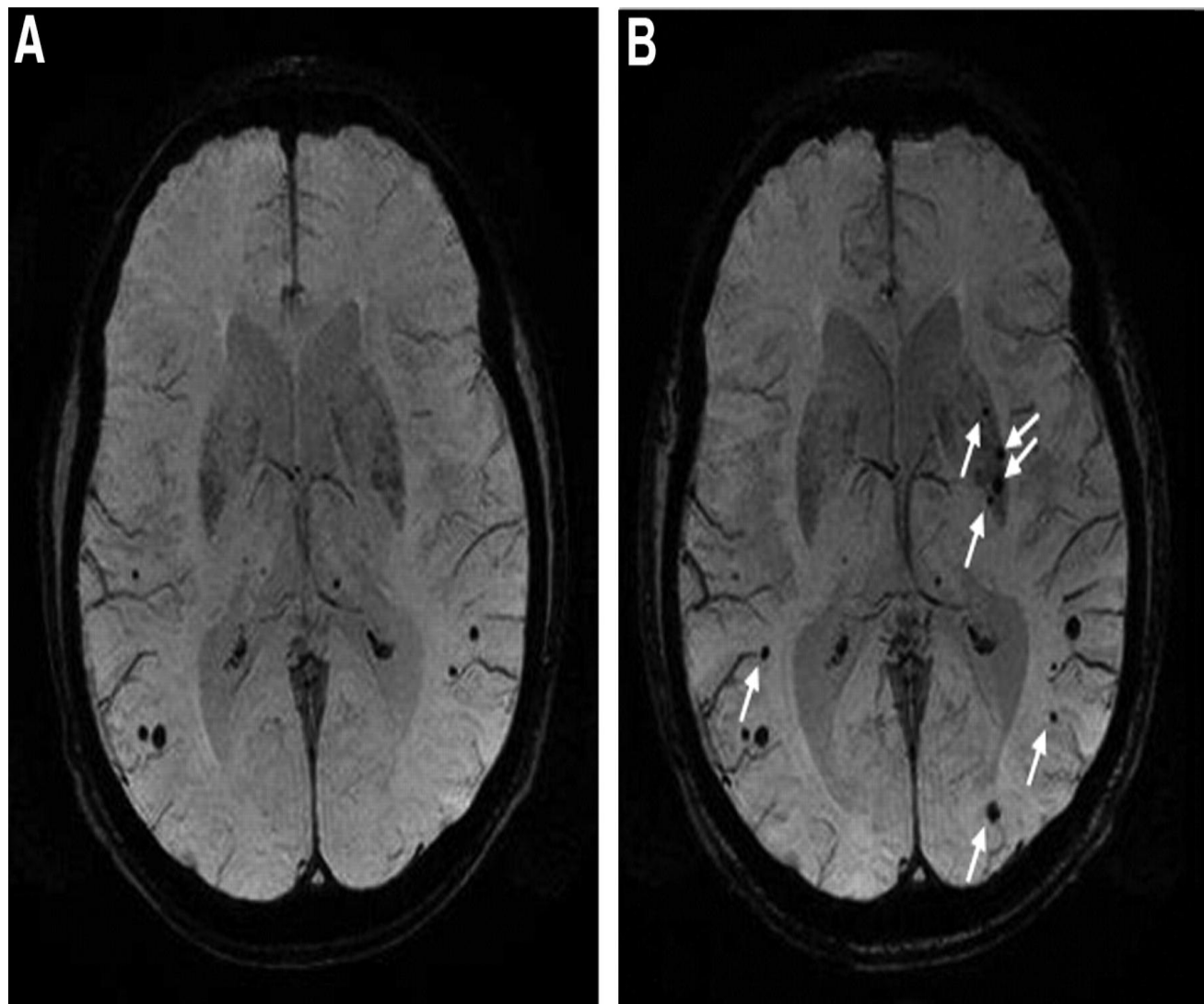
Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

HMOD in the brain

Hypertension is a major risk factor, not only for acute cerebrovascular events such as ischemic stroke, intracranial hemorrhage and TIA, but also for chronic and asymptomatic or oligosymptomatic brain damage, which may ultimately lead to dementia. In particular, long-standing arterial hypertension is known to exert a cumulative effect on cerebrovascular damage, including atherosclerosis, white matter lesions, silent brain infarcts, microinfarcts, microbleeds and brain atrophy [300], especially hippocampal atrophy .

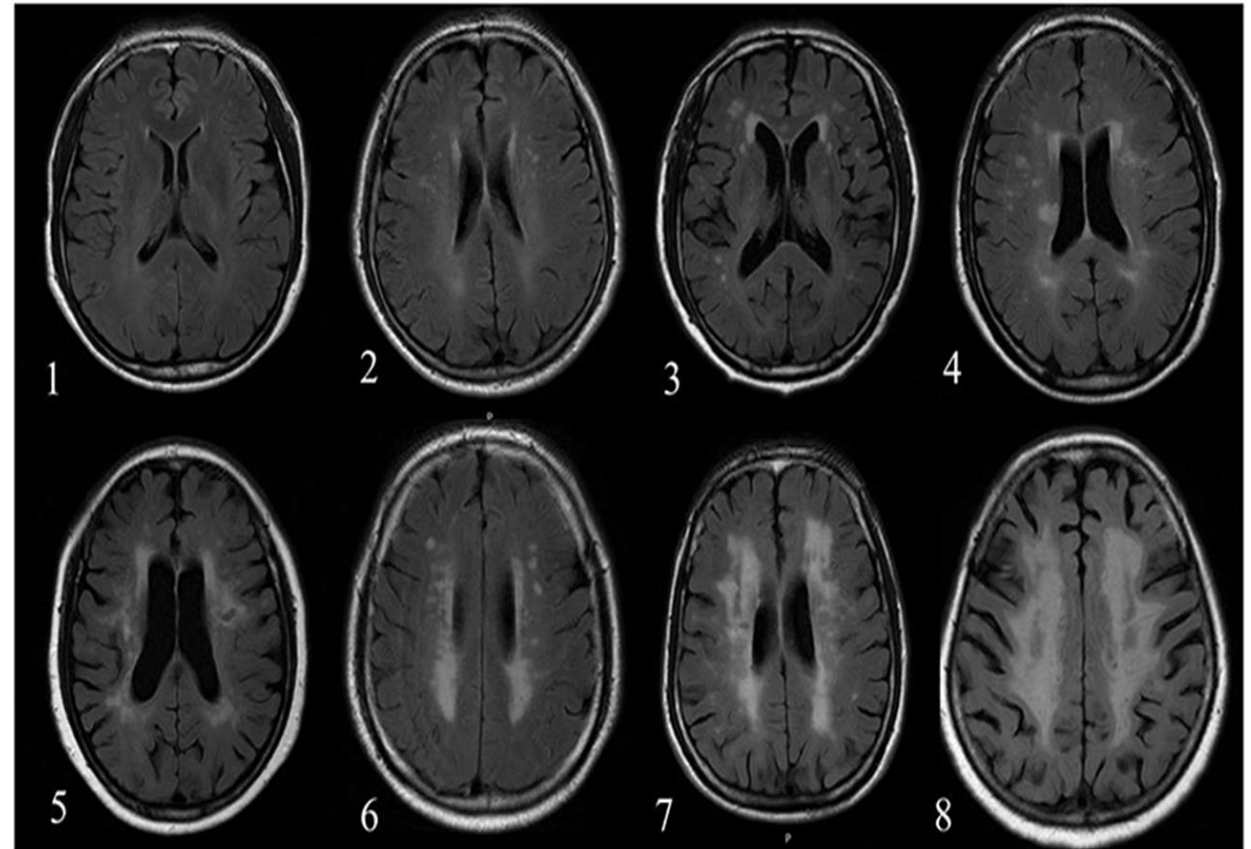
Μικροαιμορραγίες

- Εστιακές αιμορραγίες <5 mm διάμετρο
- T2* MRI ακολουθίες
- Σχετίζονται με διάρκεια υπέρτασης
- >50% σε ασθενείς υπέρτατικούς >65 ετών
- ΧΝΝ



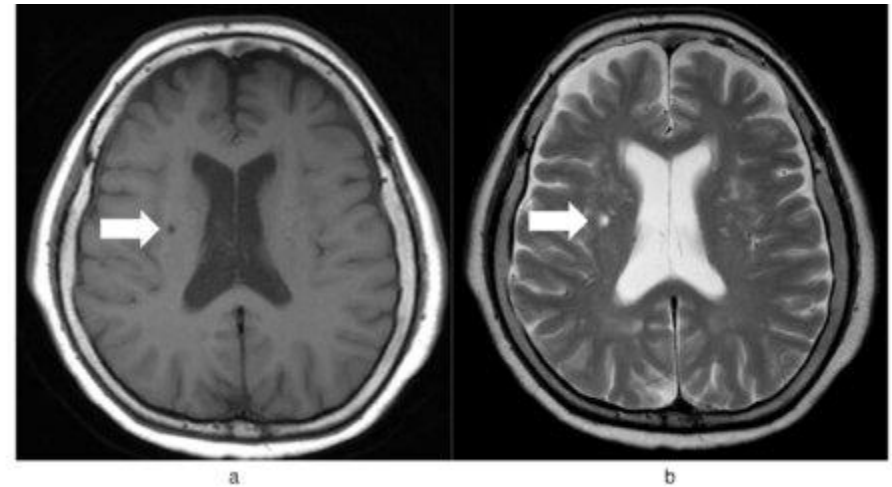
White matter lesions (WML) – βλάβες λευκής ουσίας

- περικοιλιακά και βαθειά λευκή ουσία
- συμμετρικά
- 60–70 ετών με >20 χρόνια υπέρτασης
- συσχέτιση με γνωσιακή δυσλειτουργία
- x 3 φορές κίνδυνος εγκεφαλικού και x2 κίνδυνος άνοιας



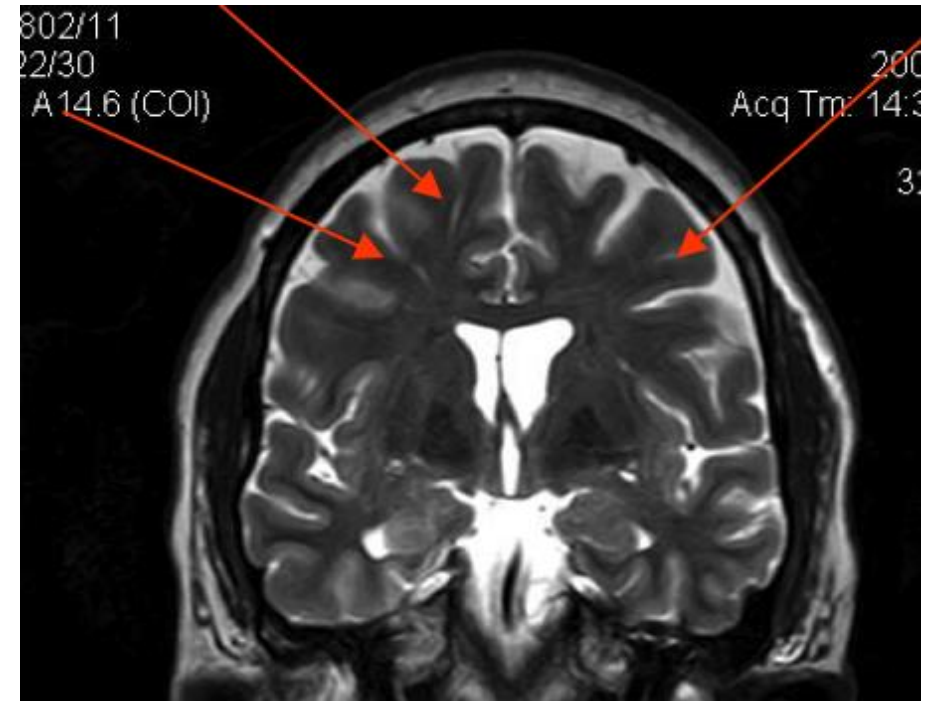
'Silent' brain infarcts

- lacunar/ Εστιακά
- λευκή ουσία και υποφλοιικές περιοχές (βασικά γαγγλία, θάλαμος, στέλεχος).
- >20% σε υγιείς >60 ετών
- Μικρή συσχέτιση WMHs και εμφράκτων
- και οι δυο βλάβες ανεξάρτητα συσχετίζονται με γνωσιακή δυσλειτουργία σε ηλικιωμένους

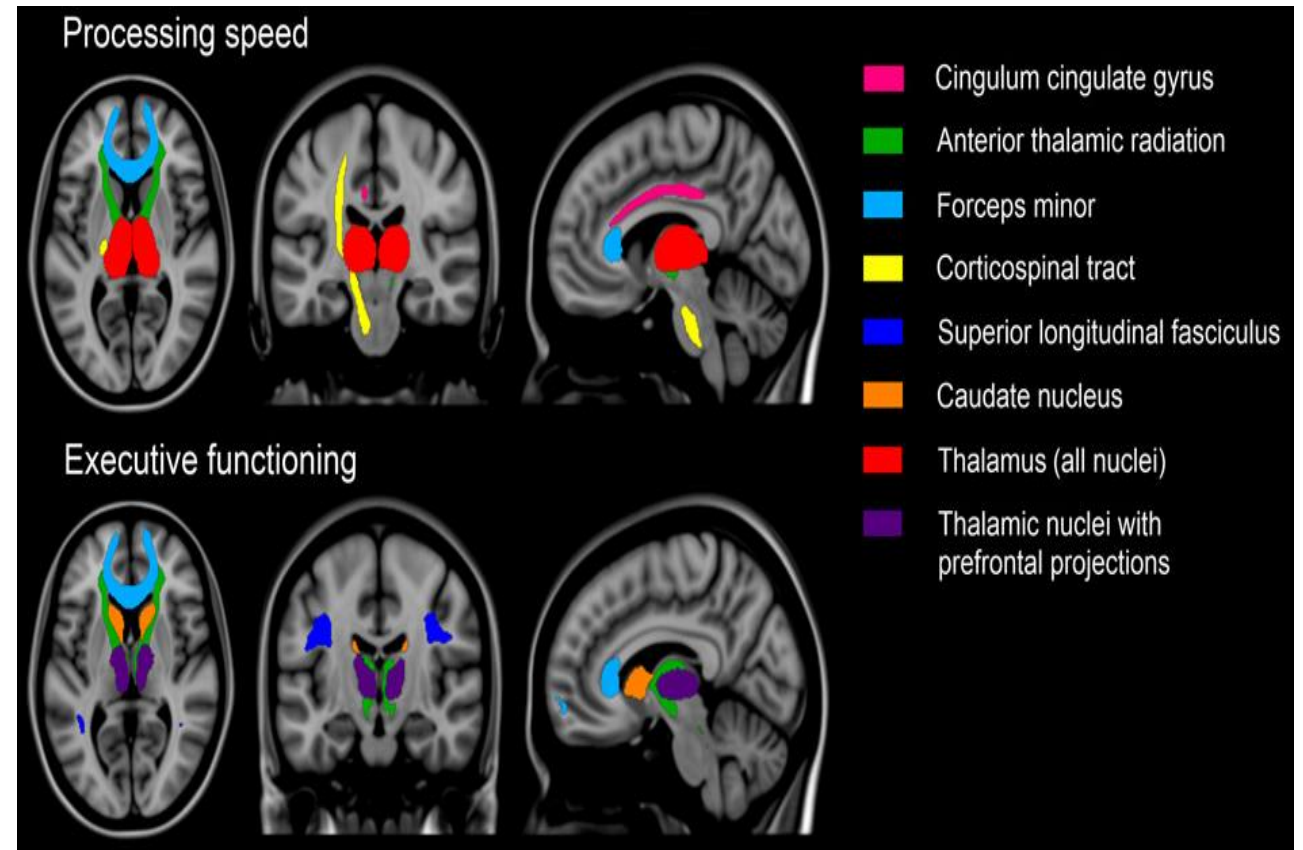
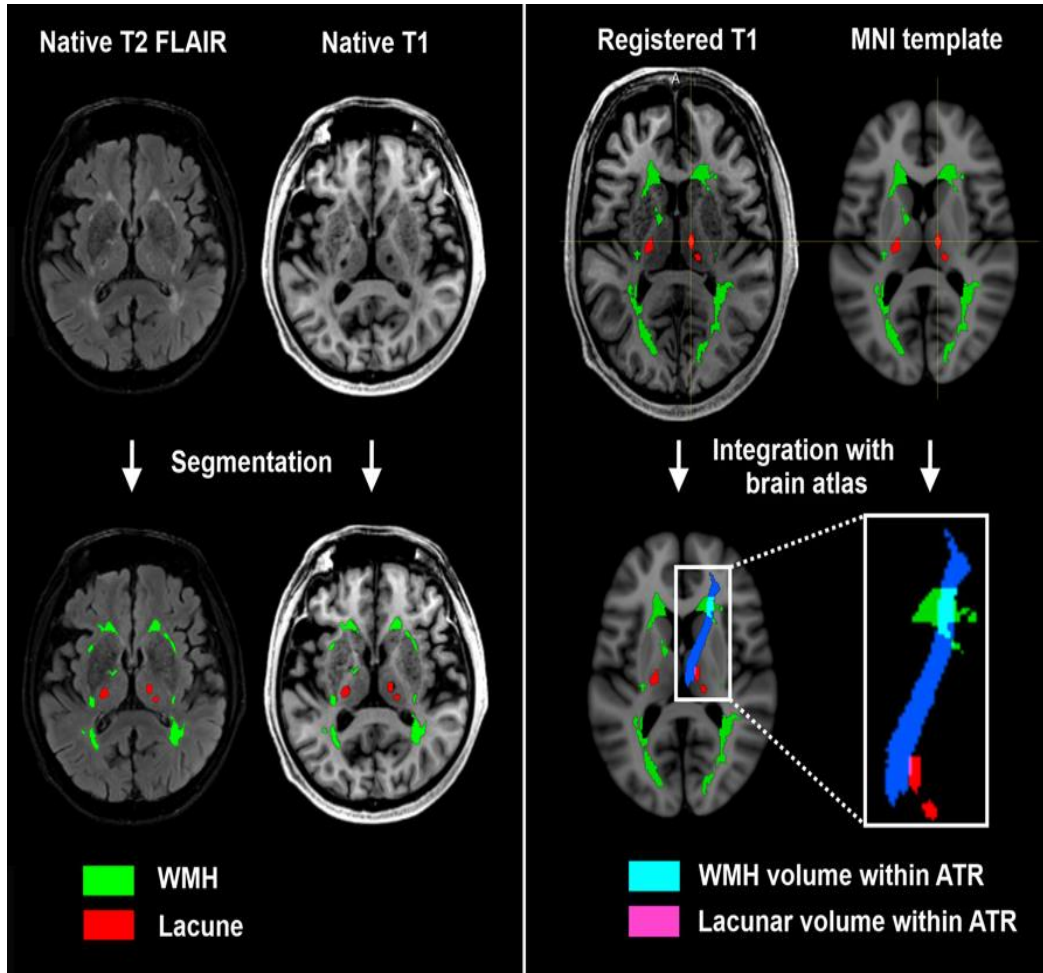


Διεύρυνση περιαγγειακών χώρων

- Συσσώρευση πρωτεϊνών και υγρού (αιματοεγκεφαλικός φραγμός)
- T2 MRI(κατά μήκος αγγείων, δ 3mm)
- Διαταραχή απομάκρυνσης ουσιών
- Συσχέτιση με υπέρταση και γνωσιακή δυσλειτουργία
- Λίγες μελέτες

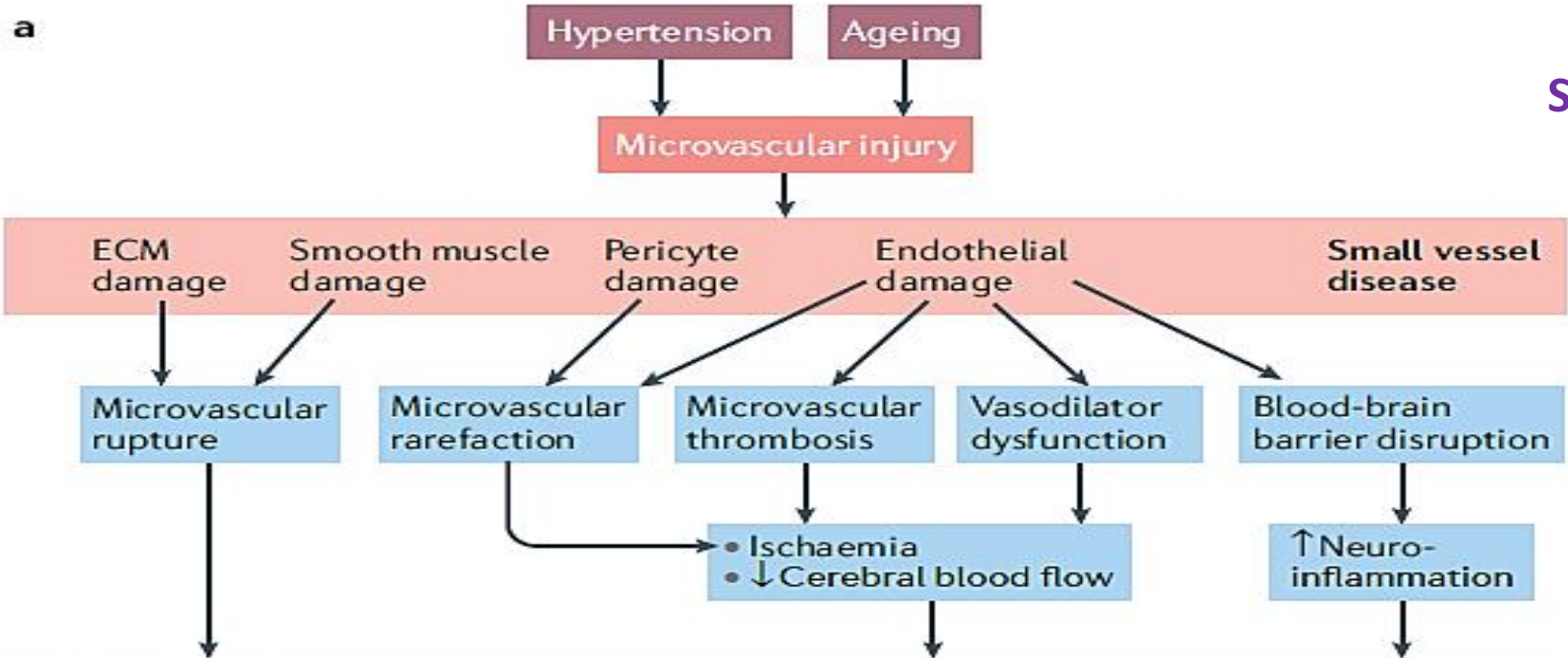


Lesion location and cognitive impact of cerebral small vessel disease



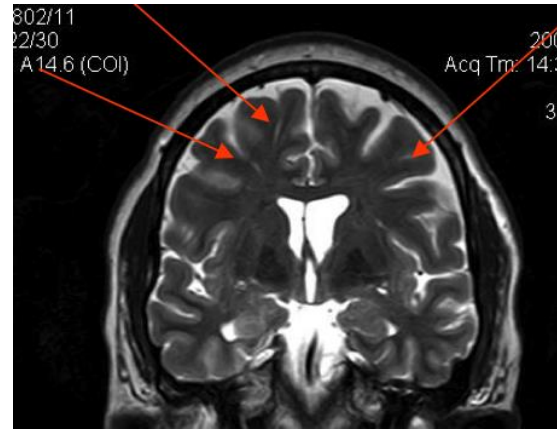
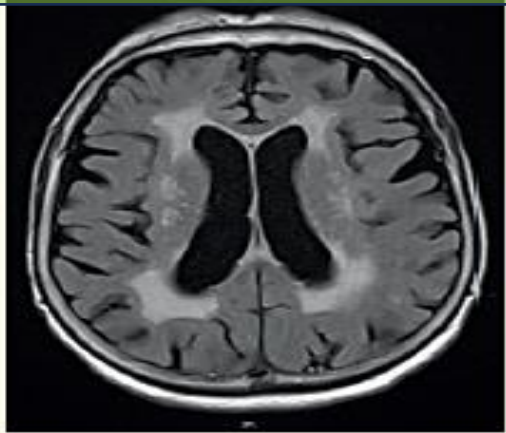
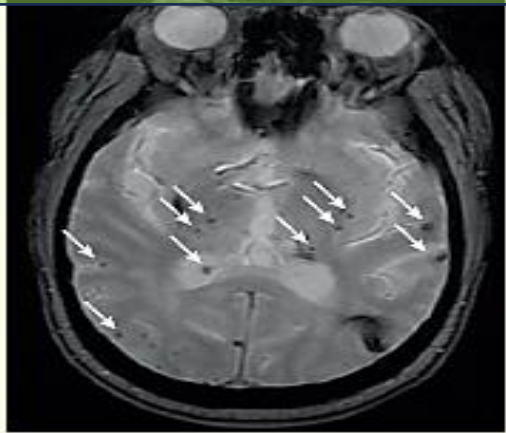
Small vascular disease (SVD)

a

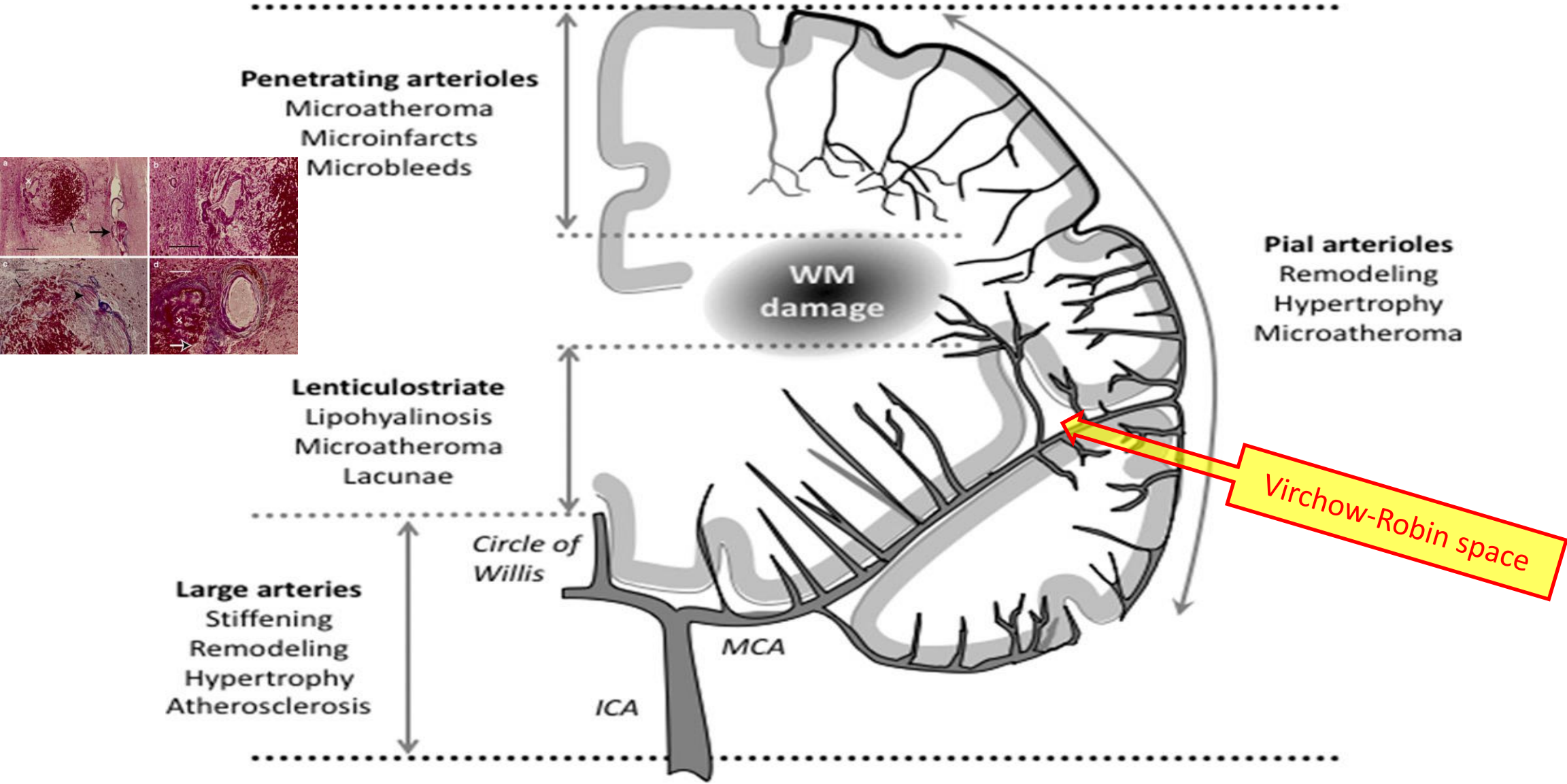


Imaging signs

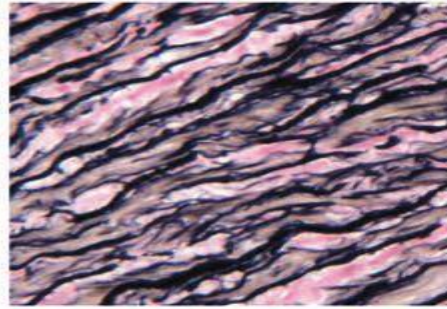
b Microhaemorrhages **c Lacunar infarcts** **d White matter damage** **increased perivascular spaces**



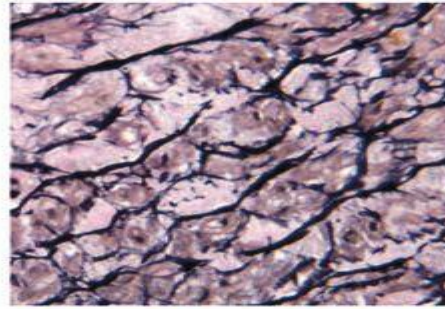
Υπέρταση και εγκεφαλικά αγγεία



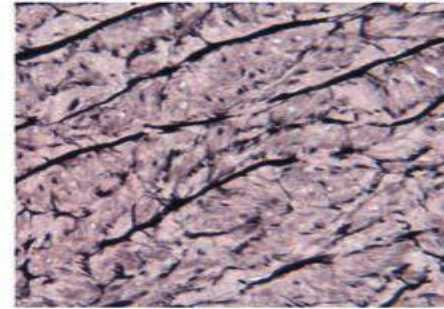
Arterial wall
(aorta/carotid)



Young Adult



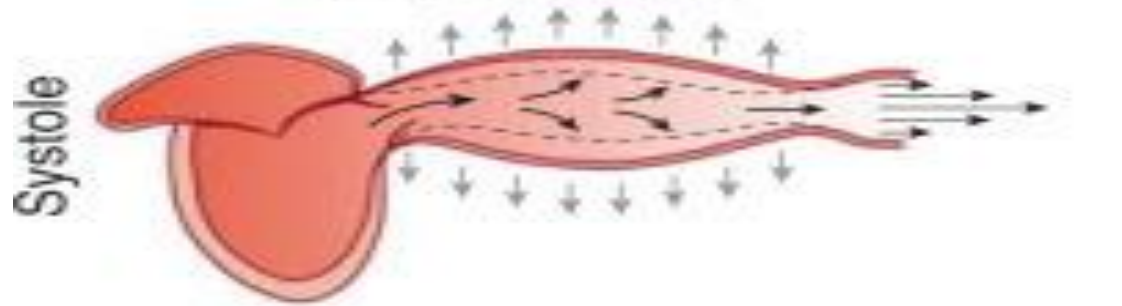
Middle Aged



Elderly

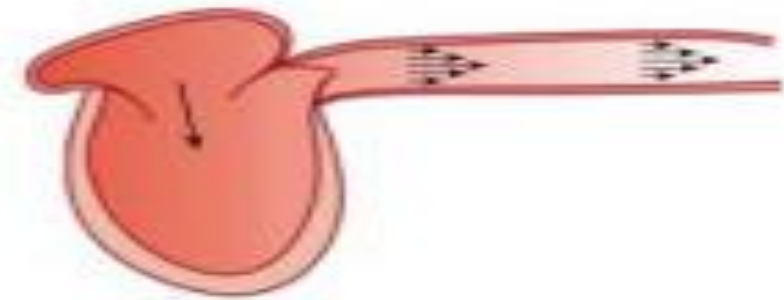
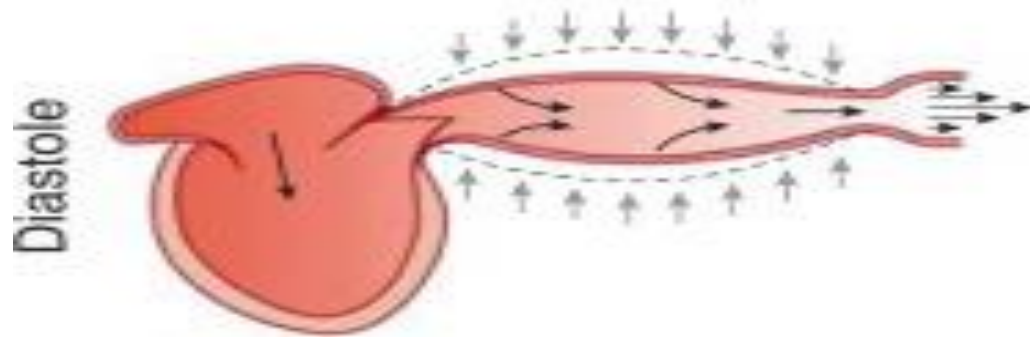
Elastic arteries

Stiff arteries

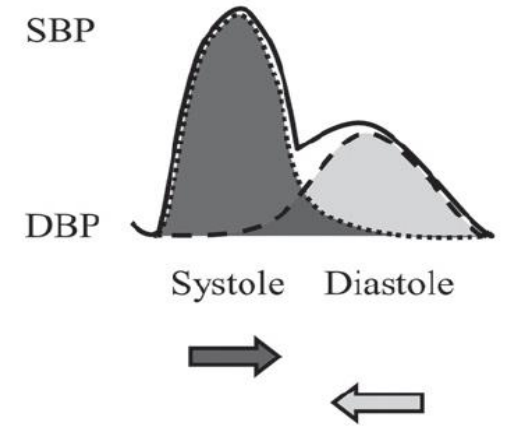
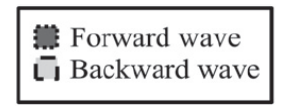
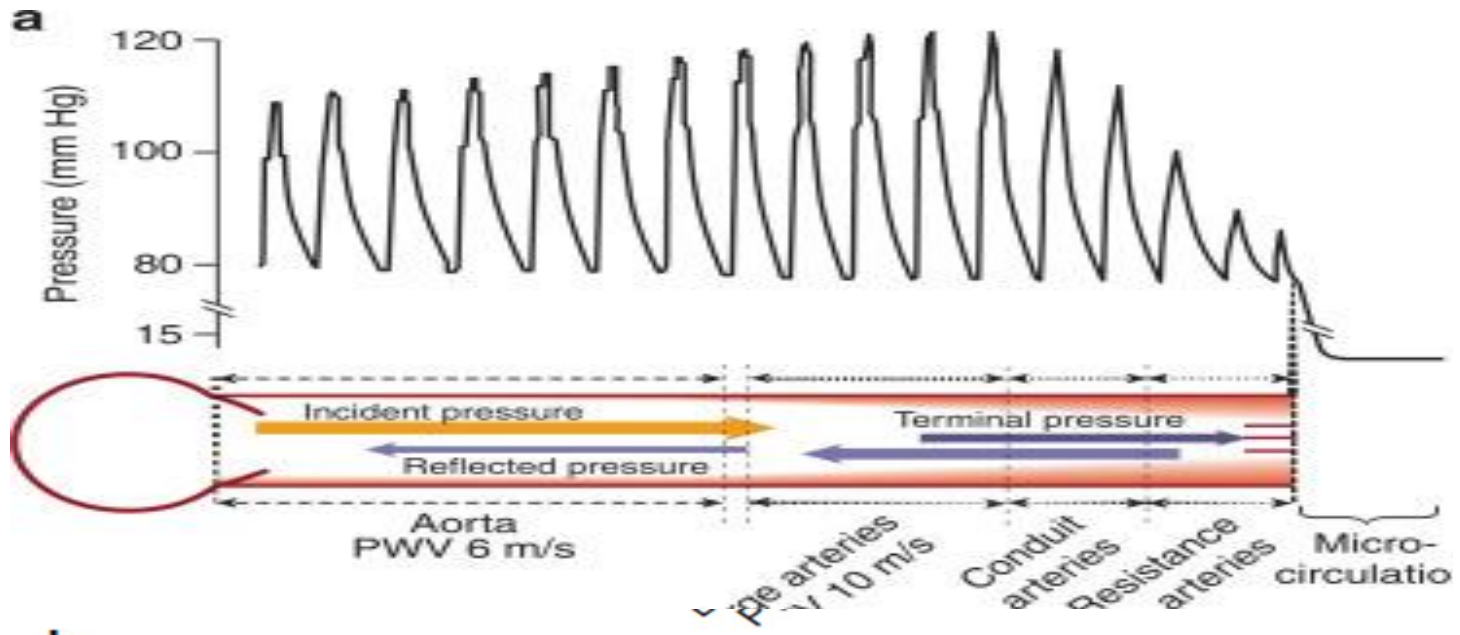


↘ Systolic/pulse pressure
↗ Diastolic flow

↗ Systolic/pulse pressure
↘ Diastolic flow

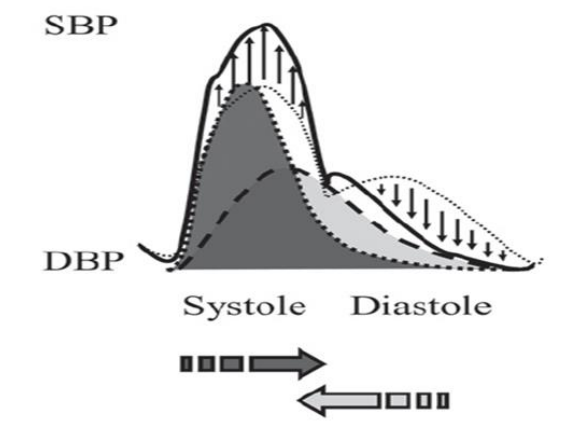
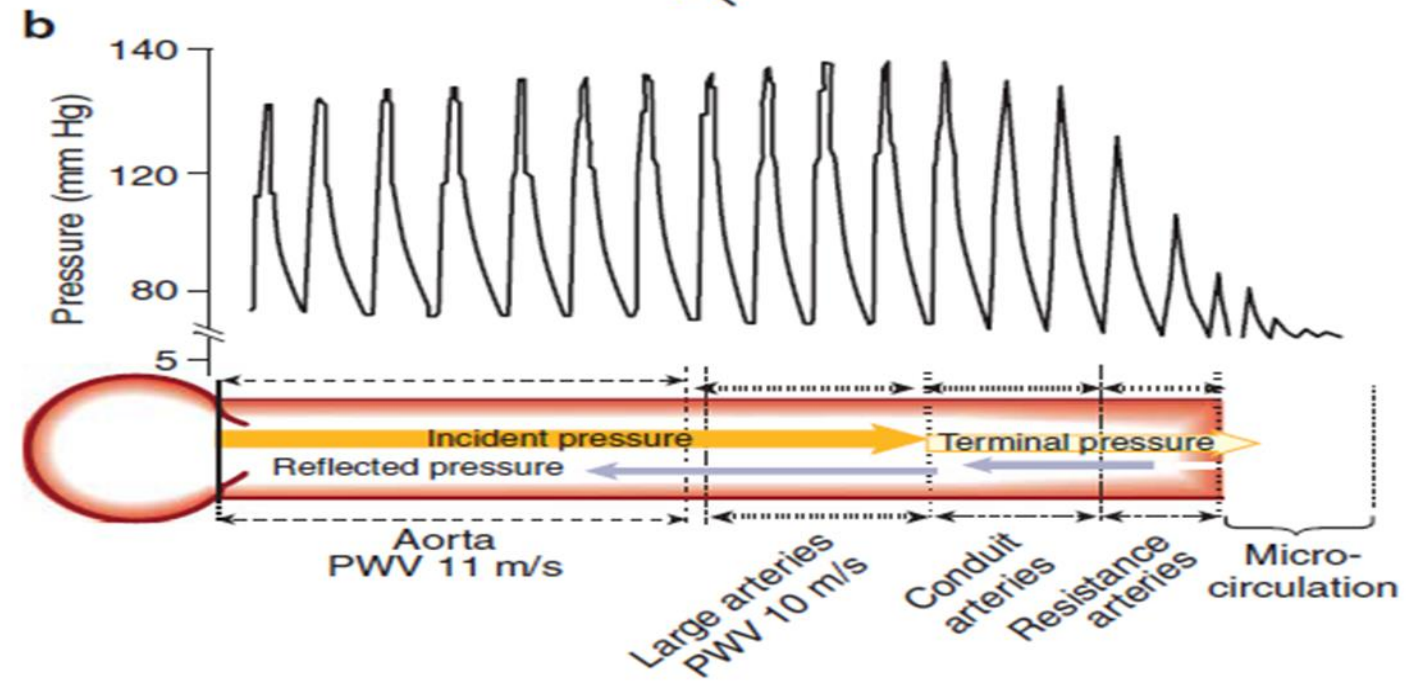


Elastic arteries



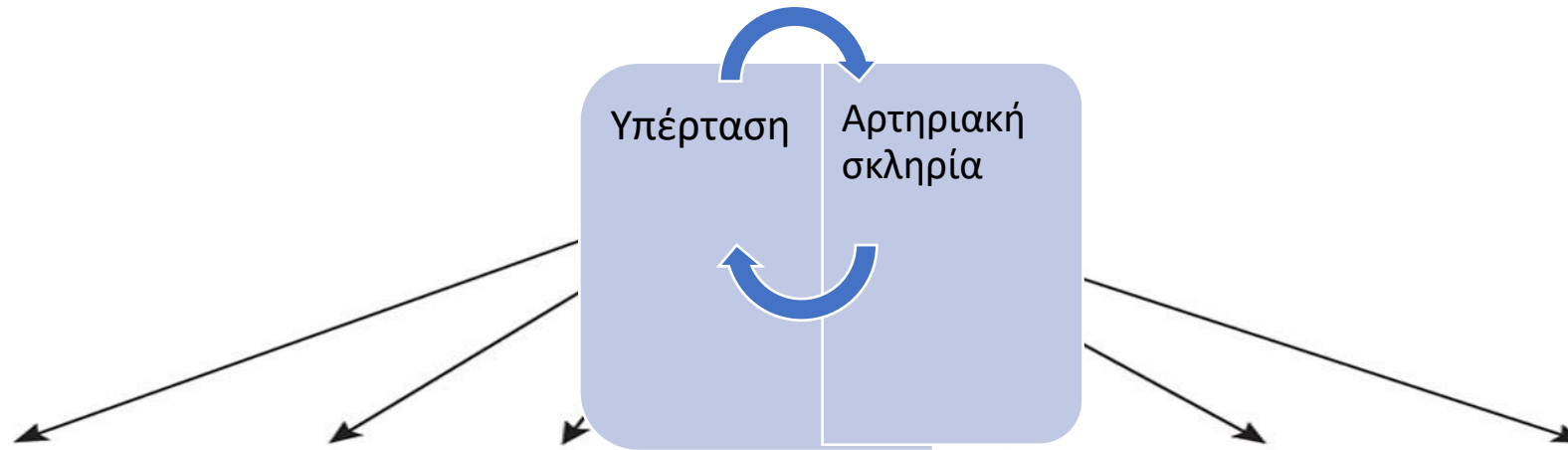
Normal arterial stiffness

Stiff arteries



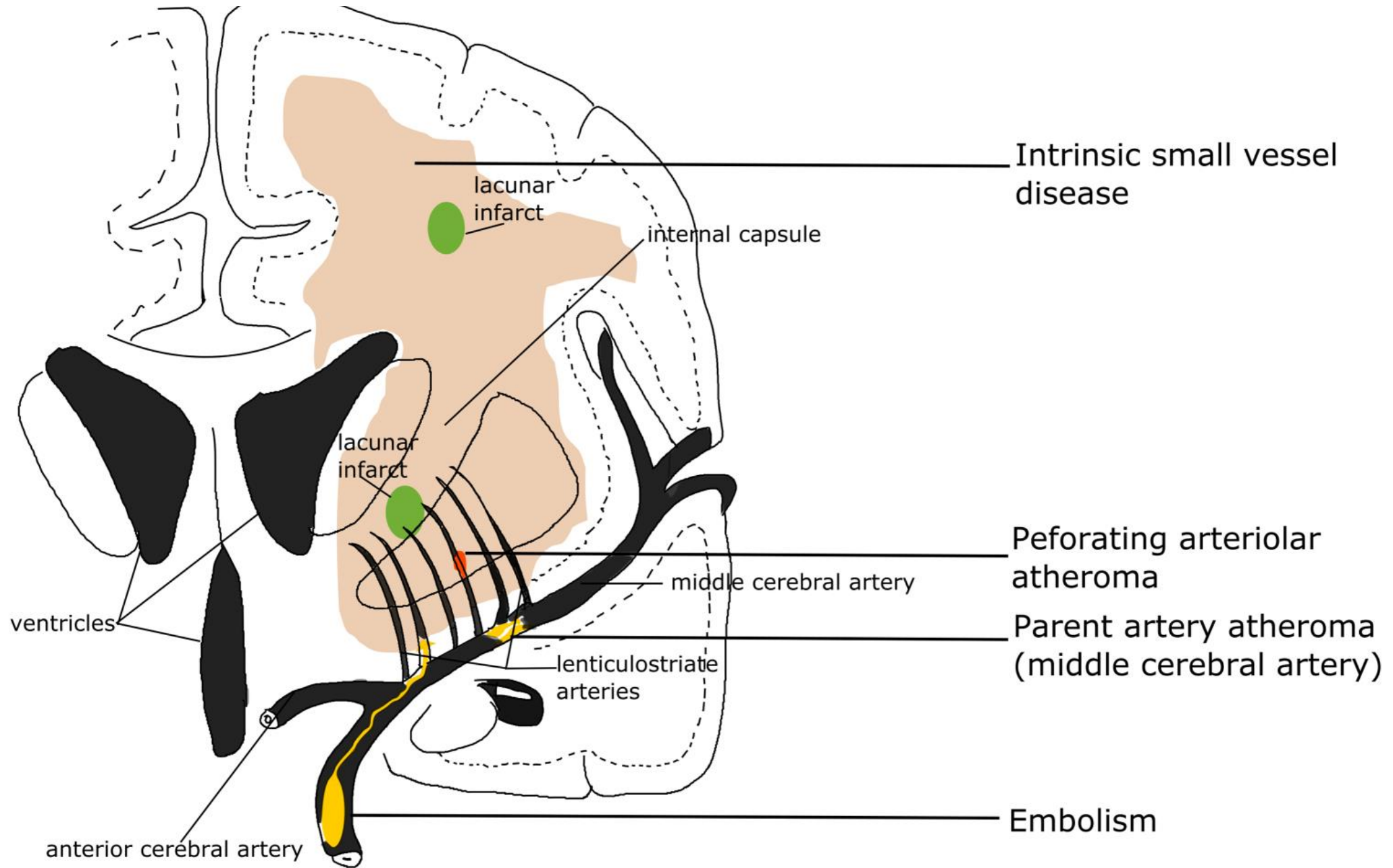
Increased arterial stiffness

Remodelling and stiffening of the arterial wall



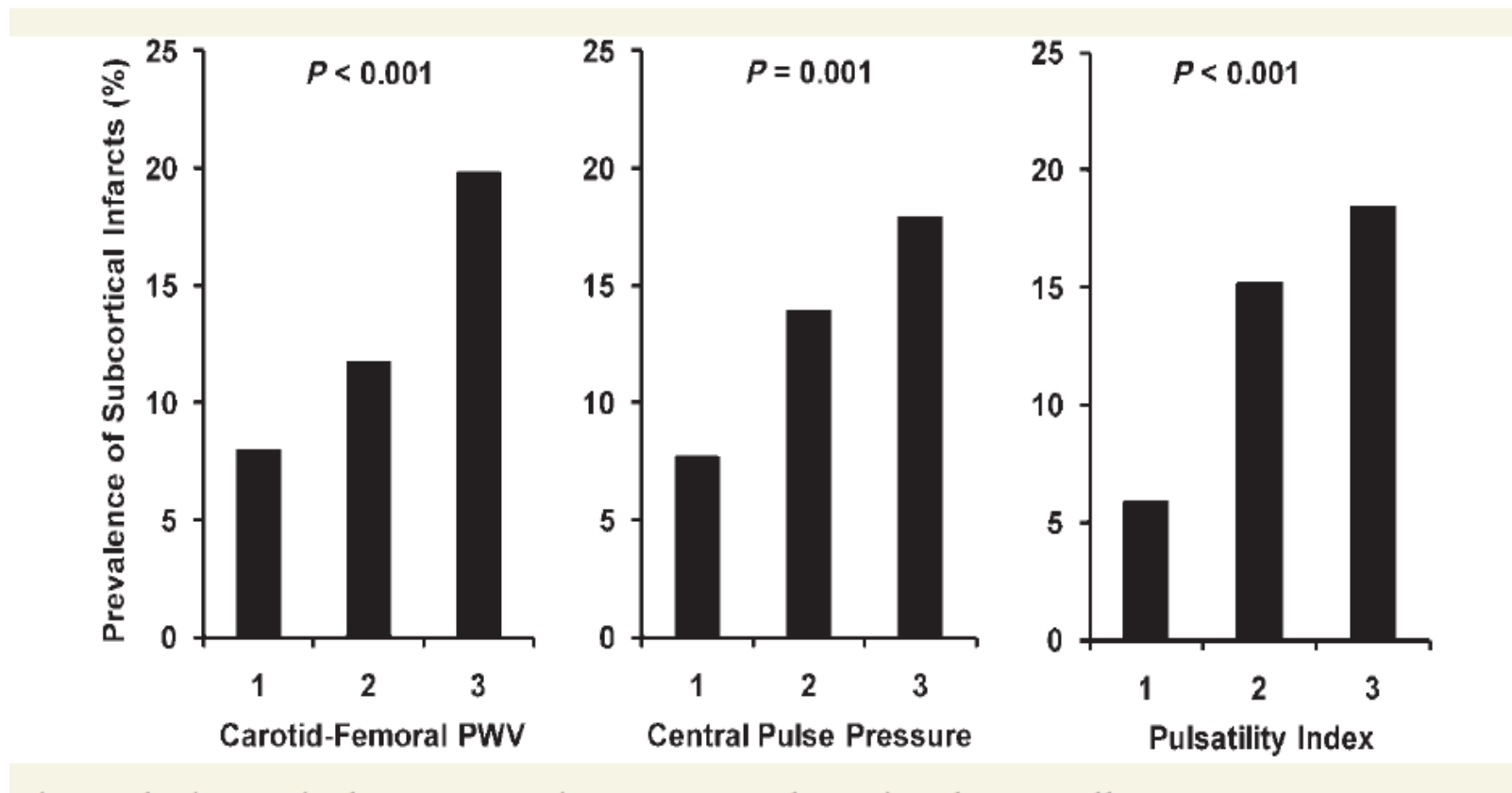
Adipokines	Ca ²⁺	Ang II/RAAS	ET-1	MR	SNS	Inflammation
↓ Adiponectin ↑ Resistin	Ca ²⁺ signaling dysregulation ↓ Ca ²⁺ handling ↑ Ca ²⁺ sensitivity ↑ PDE1 activity	↑ Sensitivity + signaling	↑ Production	↑ Aldosterone production + MR activation	↑ Activity ↑ ATP production ↑ NE response	↑ Infiltration of T cells + macrophages ↑ Pro-inflammatory cytokines
Eutrophic	Hypertrophic + Eutrophic	Hypertrophic + Eutrophic	Hypertrophic	Hypertrophic	Hypertrophic + Eutrophic	Hypertrophic
Resistance	Conductive + Resistance	Conductive + Resistance	Resistance	Conductive + Resistance	Conductive + Resistance	Conductive

- Υπερτροφία
- αύξηση του λόγου τοίχωμα/αυλός (αύξηση πάχους τοιχώματος και μείωση αυλού)



Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/ Environment Susceptibility – Reykjavik Study

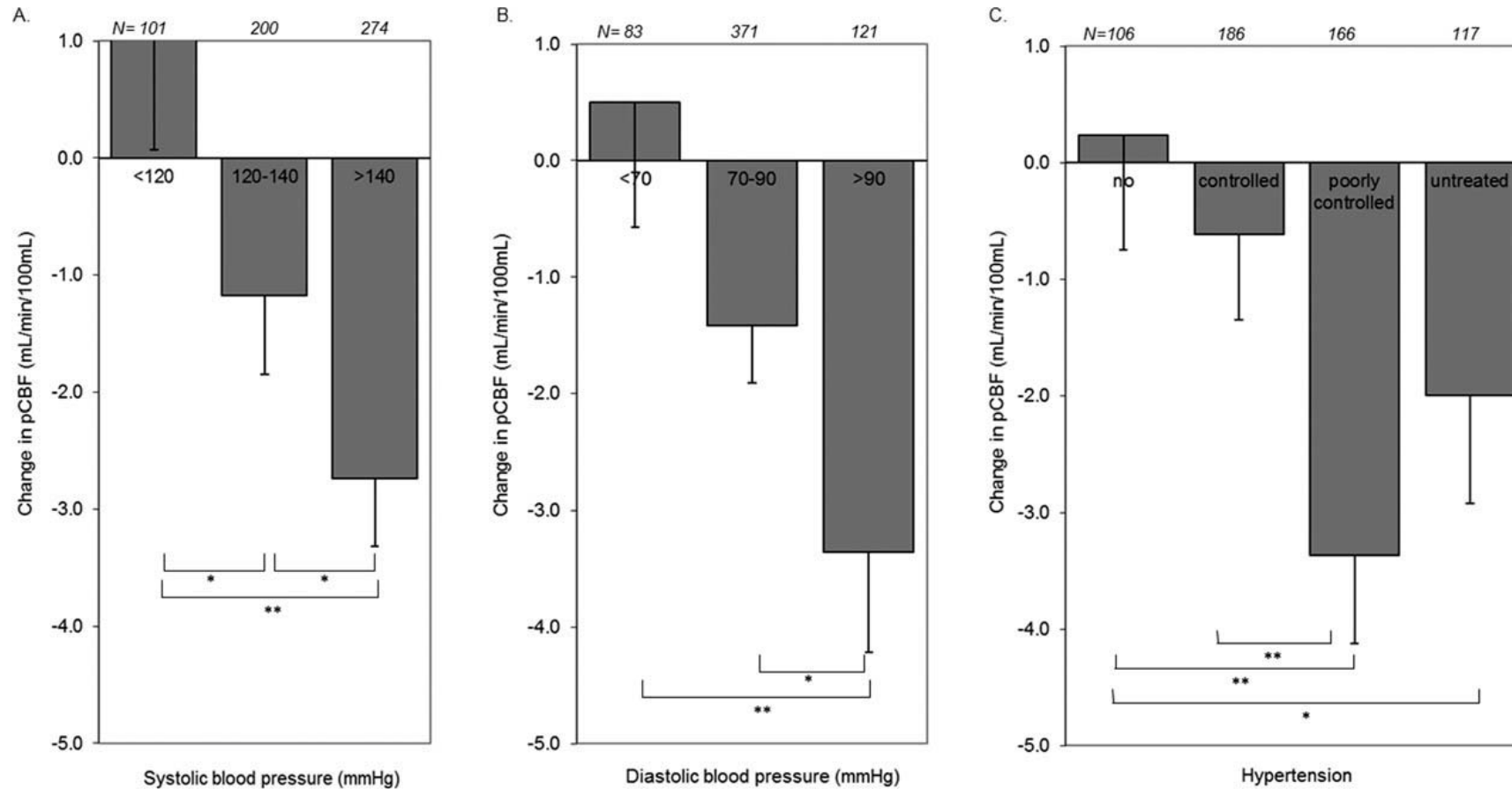
Gary F. Mitchell,¹ Mark A. van Buchem,² Sigurdur Sigurdsson,³ John D. Gotal,¹ Maria K. Jonsdottir,^{3,4} O'lafur Kjartansson,³ Melissa Garcia,⁵ Thor Aspelund,^{3,6} Tamara B. Harris,⁵ Vilundur Gudnason,^{3,6} and Lenore J. Launer



Carotid–femoral pulse wave velocity was associated with higher white matter hyperintensity volume

Hypertension and Longitudinal Changes in Cerebral Blood Flow: The SMART-MR Study

Majon Muller, MD, PhD,^{1,2} Yolanda van der Graaf, MD, PhD,² Frank L. Visseren, MD, PhD,³ Willem P. Th. M. Mali, MD, PhD,⁴
and Mirjam I. Geerlings, PhD² for the SMART Study Group

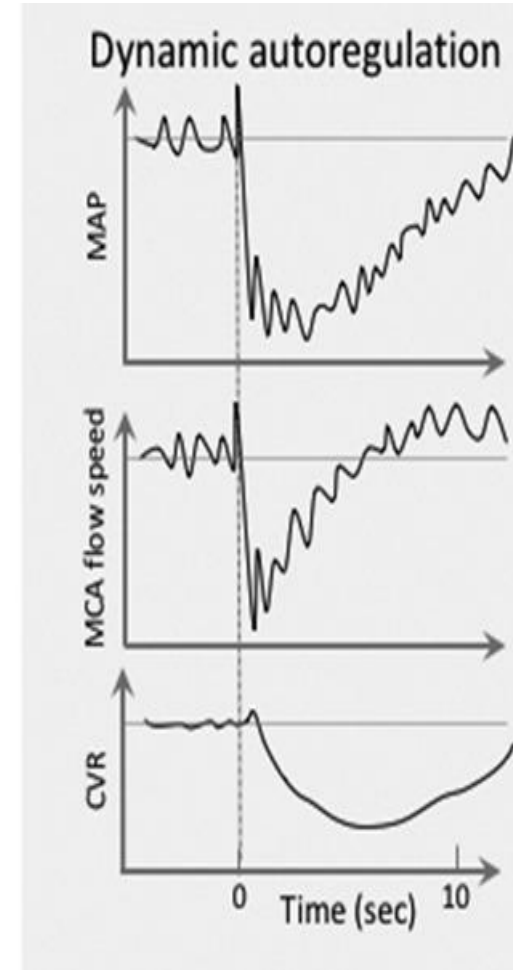
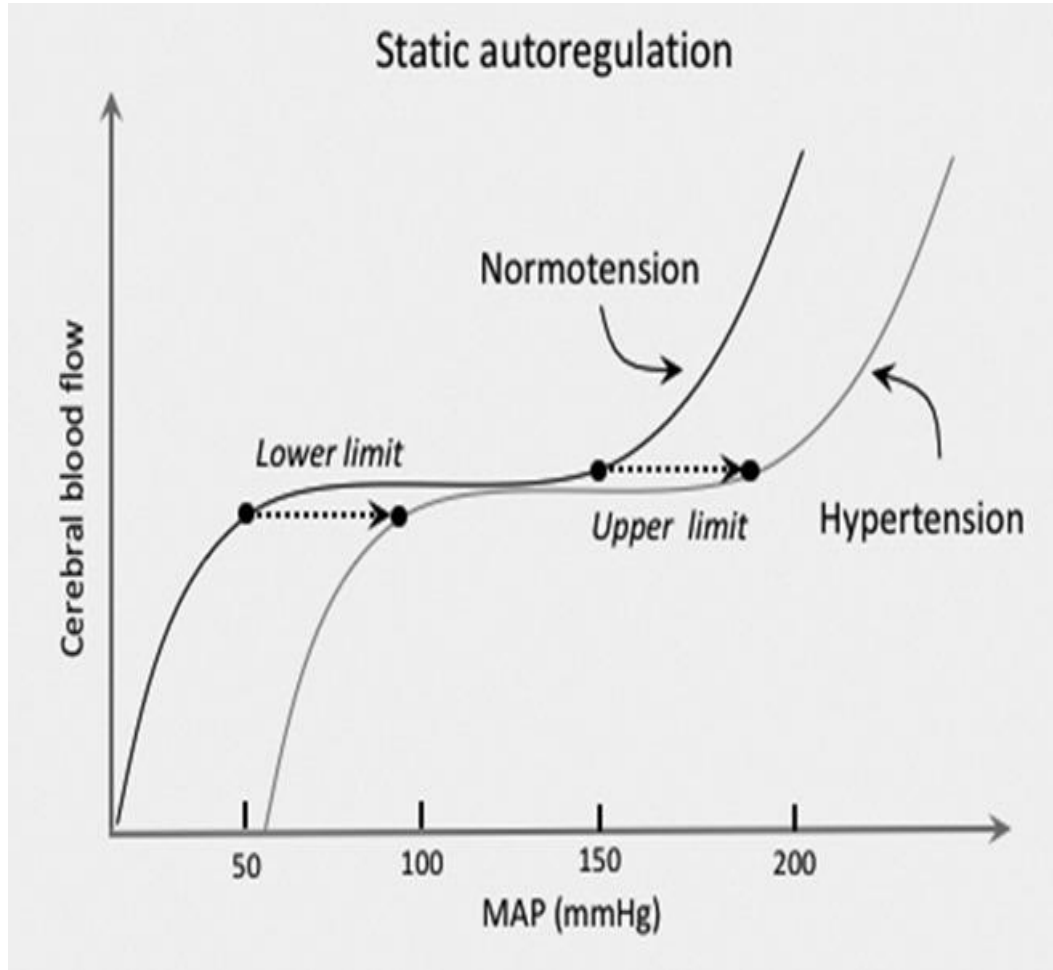


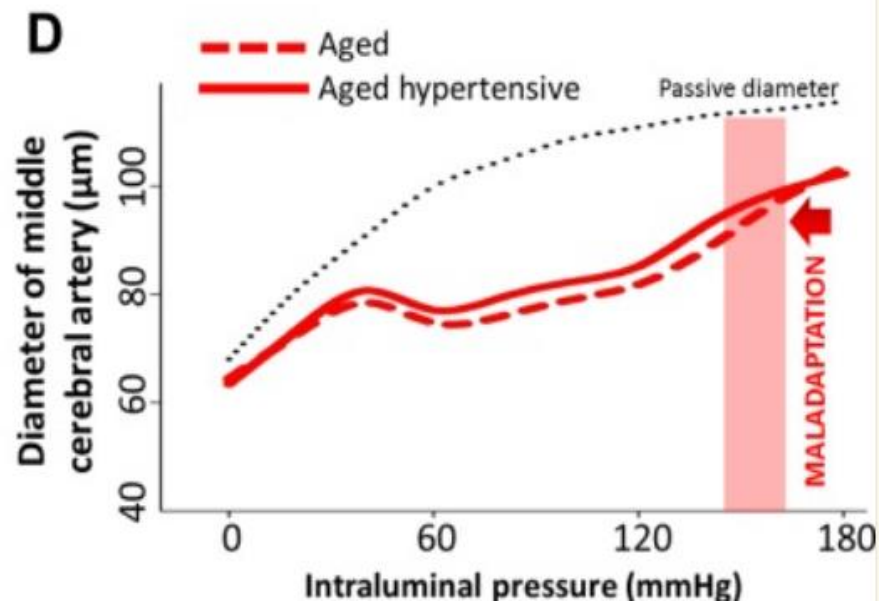
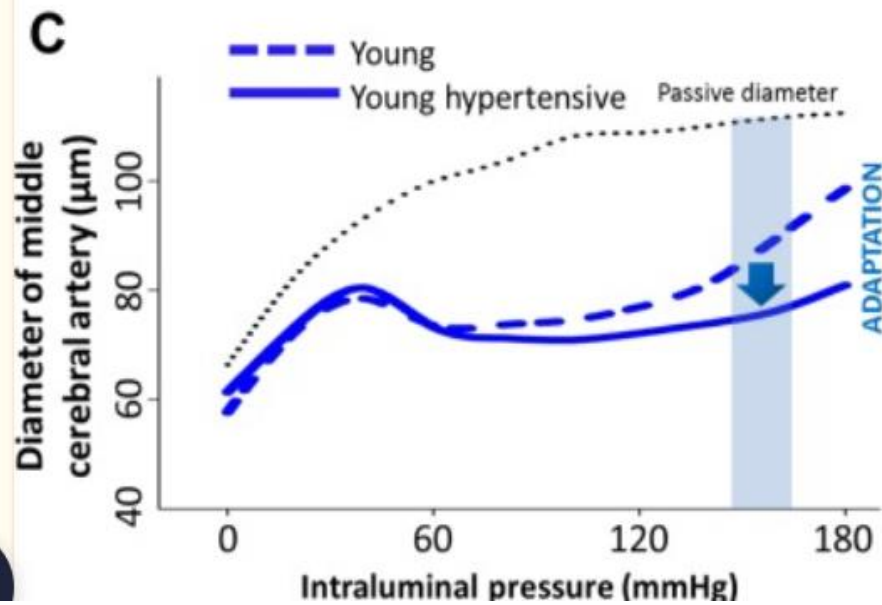
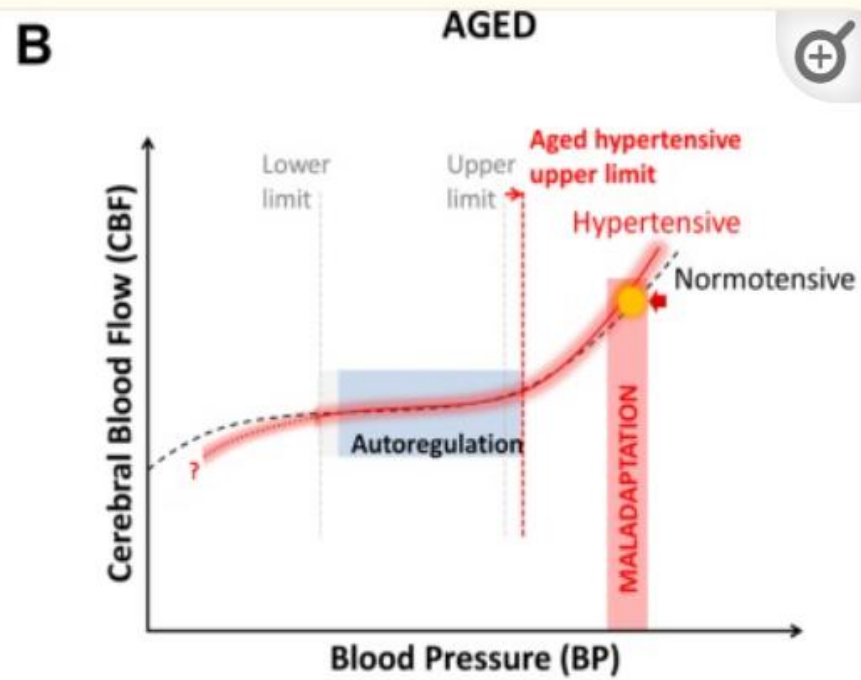
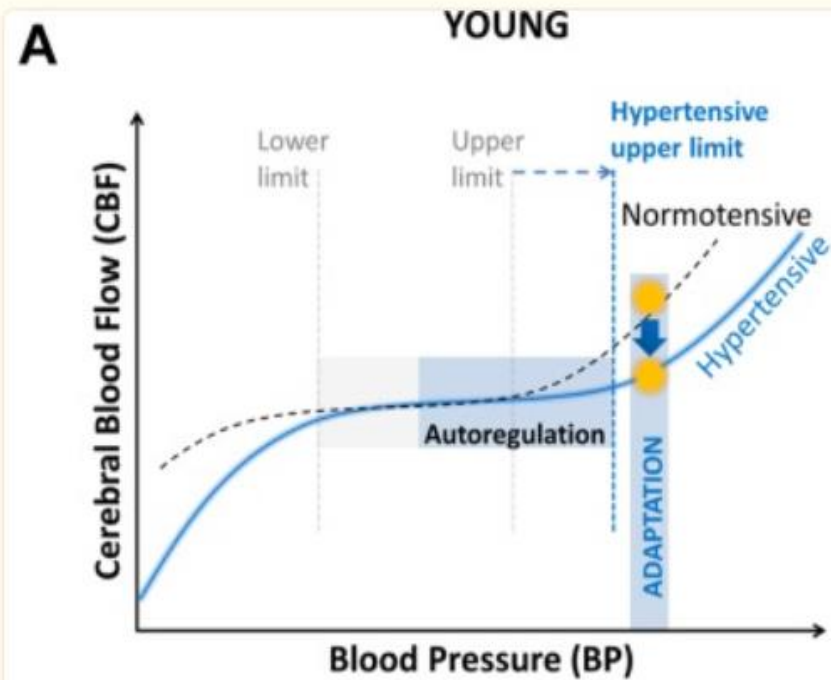
Εγκεφαλική αιματική ροή

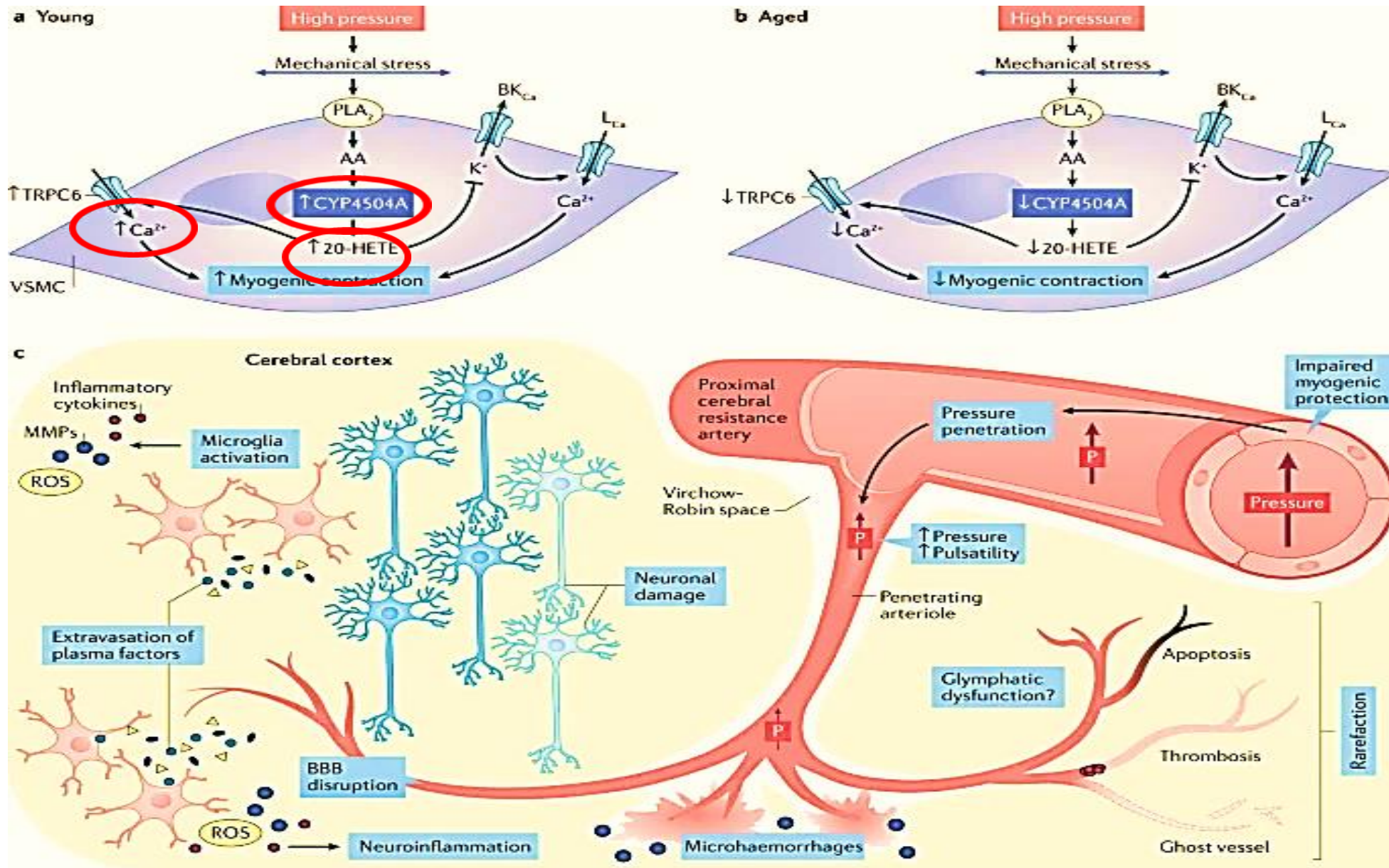
- Μήκος τριχοειδών εγκεφάλου ~600 km -κάθε νευρώνας έχει το δικό του τριχοειδές
- Υψηλές ανάγκες οξυγόνου (2% ΒΣ, αλλά 25% αναγκών γλυκόζης και 20% οξυγόνου)
- Δεν υπάρχουν αποθέματα ενέργειας στους νευρώνες
- Οι μεταβολικές ανάγκες των νευρώνων αλλάζουν ανάλογα με τη δραστηριότητα
- Ο χώρος του κρανίου είναι περιορισμένος (σταθερή ροή και ενδοκράνια πίεση)

Ρύθμιση της εγκεφαλικής αιματικής ροής

- ✓ Προστασία της μικροκυκλοφορίας
- ✓ Σταθερή ροή







Longitudinal Relationship Between Cerebral Small-Vessel Disease and Cerebral Blood Flow

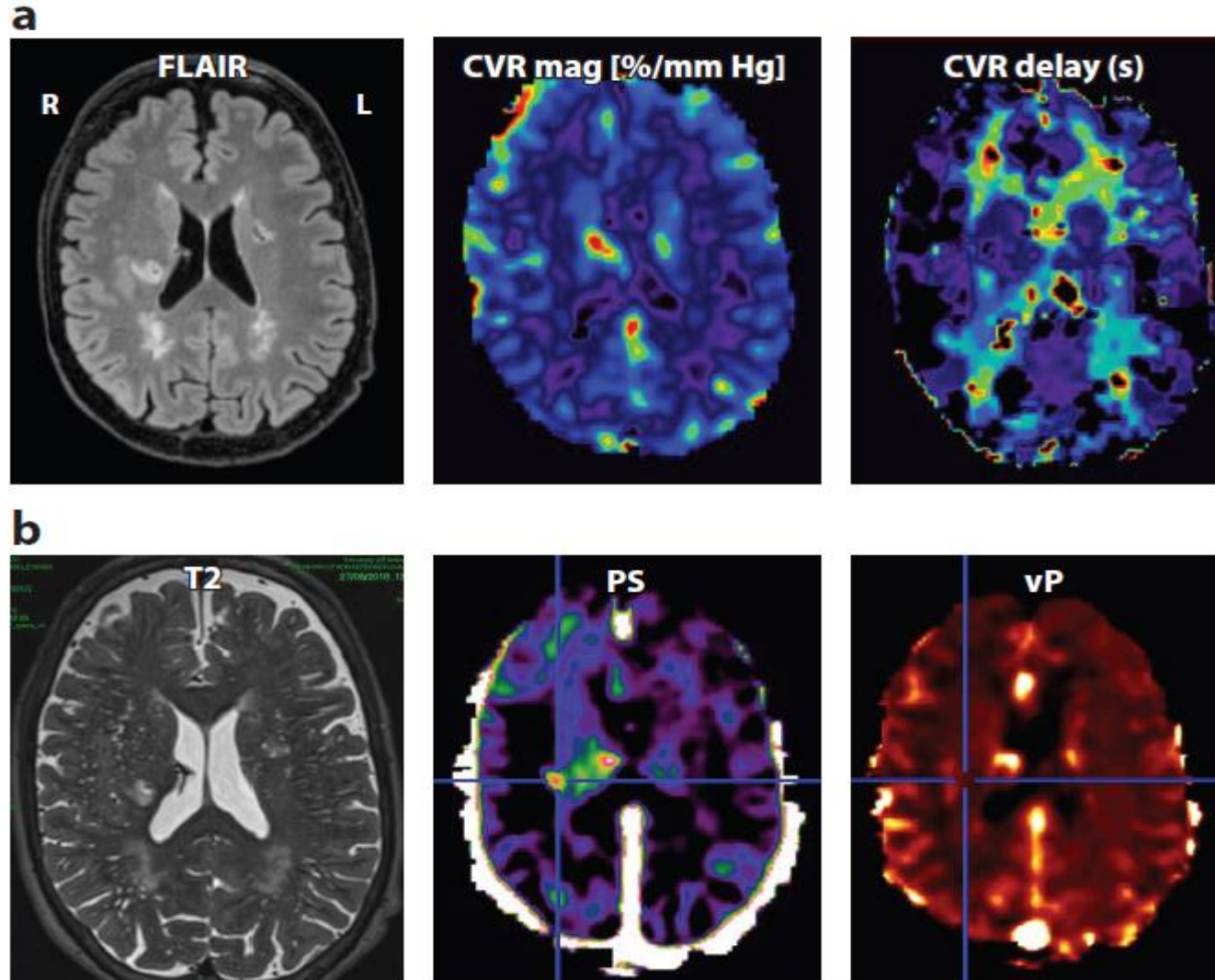
The Second Manifestations of Arterial Disease-Magnetic Resonance Study

[Pieterella H. van der Veen](#), [Majon Muller](#), [Koen L. Vincken](#), [Jeroen Hendrikse](#), [Willem P.T.M. Mali](#), [Yolanda van der Graaf](#), [Mirjam I. Geerlings](#)

SMART Study Group

In patients with manifest arterial disease, baseline periventricular and deep WMH volumes were associated with decline in pCBF over time, but baseline pCBF was not associated with progression of WMHs and lacunes over time.

Cerebrovascular reactivity



- ✓ PS, permeability surface area product, a measure of blood–brain barrier leakage
- ✓ vP, plasma volume fraction;

Μηχανισμοί υποκλινικών βλαβών

- Ατελή έμφρακτα ?

*Δεν επιβεβαιώνεται σε ιστολογικό υλικό
Γονιδιακή συσχέτιση-οικογένειες*

- Υποάρδευση ?

Ασαφή δεδομένα

- Βλάβη μικρών αγγείων

Inflammatory biomarkers, cerebral microbleeds, and small vessel disease

Framingham Heart Study

Table 2

Median levels (with interquartile range within parentheses) of hsCRP, neopterin and adhesion molecules in different patient groups, classified by MRI

	Asymptomatic lacunar infarcts		Extensive WML		Both asymptomatic lacunar infarcts and WML		Healthy control subjects (n = 43)
	Yes (n = 117)	No (n = 229)	Yes (n = 81)	No (n = 265)	Yes (both) (n = 48)	No (none) (n = 196)	
hsCRP (mg/L)	2.13 (4.14)	1.90 (3.19)	1.95 (4.09)	1.94 (2.59)	2.21 (4.30)	1.92 (3.12)	2.70 (4.04)
Neopterin (ng/mL)	2.01 (1.96)***	1.65 (0.62)	1.97 (1.01)***	1.71 (0.70)	2.05 (1.05)***	1.63 (0.62)	1.70 (0.66)
sP-selectin (ng/mL)	54.6 (62.1)*	42.9 (46.9)	45.3 (58.8)	47.3 (47.5)	45.6 (63.1)	42.8 (45.6)	62.0 (54.5)
sE-selectin (ng/mL)	24.2 (23.3)	25.0 (21.3)	28.4 (24.6)	24.1 (20.4)	28.9 (26.2)	24.6 (22.3)	28.8 (15.0)
sICAM-1 (ng/mL)	548.7 (219.4)***	459.7 (192.0)	517.3 (176.7)	473.7 (218.8)	509.7 (171.7)**	453.6 (187.8)	524.3 (99.3)
sVCAM-1 (ng/mL)	731.6 (274.5)**	687.9 (212.3)	758.3 (305.7)***	692.4 (222.1)	742.5 (283.5)**	681.6 (198.9)	637.8 (147.1)

Data are median (interquartile range). Statistically significant differences are indicated in bold.

Key: CRP, C-reactive protein; hs, high sensitivity; WML, white matter lesions.

* $p < 0.05$ (yes vs. no).

** $p < 0.01$.

*** $p < 0.001$.

Ln myeloperoxidase	1	0.8	0.7-1.0	0.06
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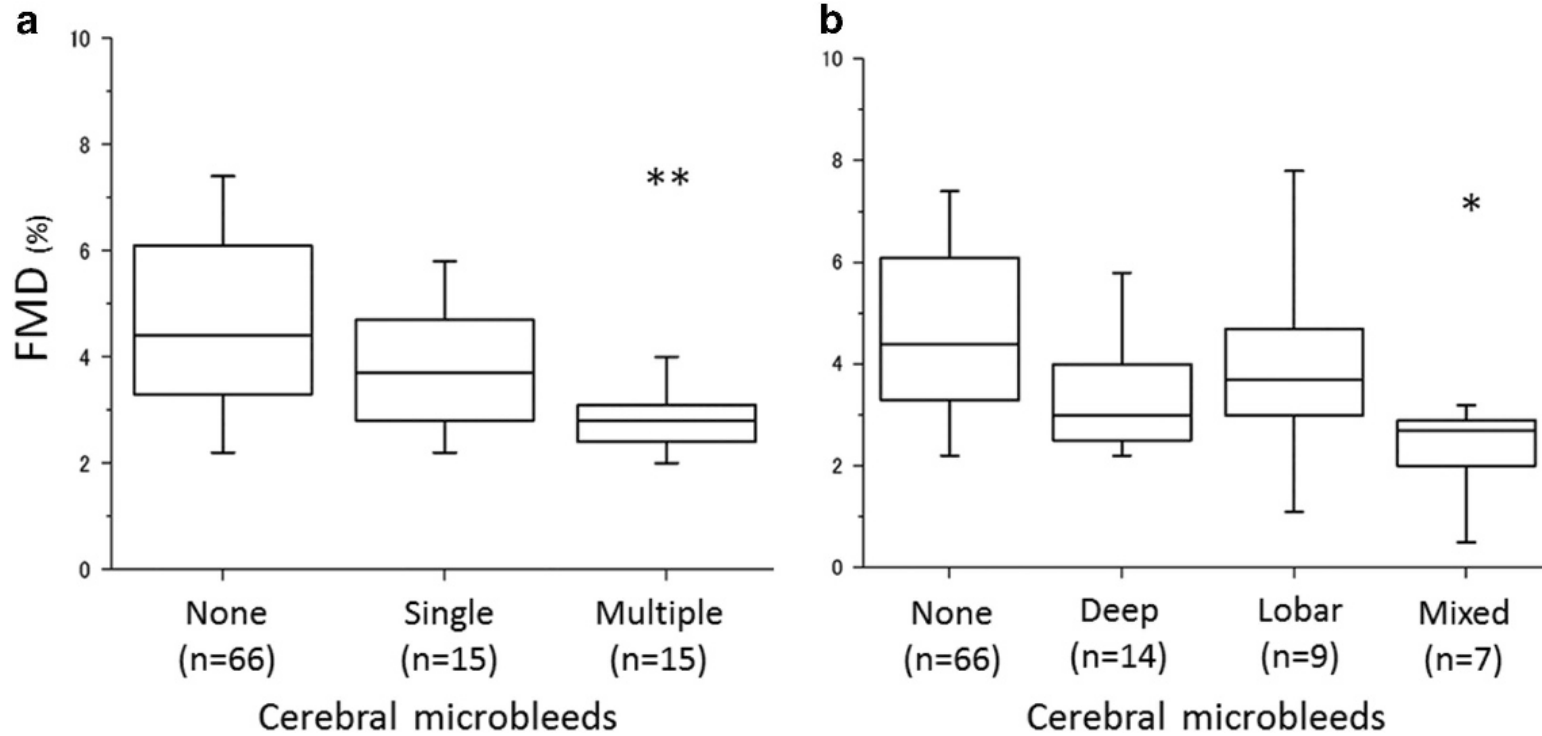
Abbreviations: CI = confidence interval; ICAM-1 = intercellular adhesion molecule 1; ln = natural logarithm; Lp-PLA₂ = lipoprotein-associated phospholipase A₂; OR = odds ratio.

^a Model 1 is adjusted for age at examination 7, sex, and time between examination 7 and MRI.

^b ORs for biomarkers designated as ln correspond to 1-unit increase on ln scale.

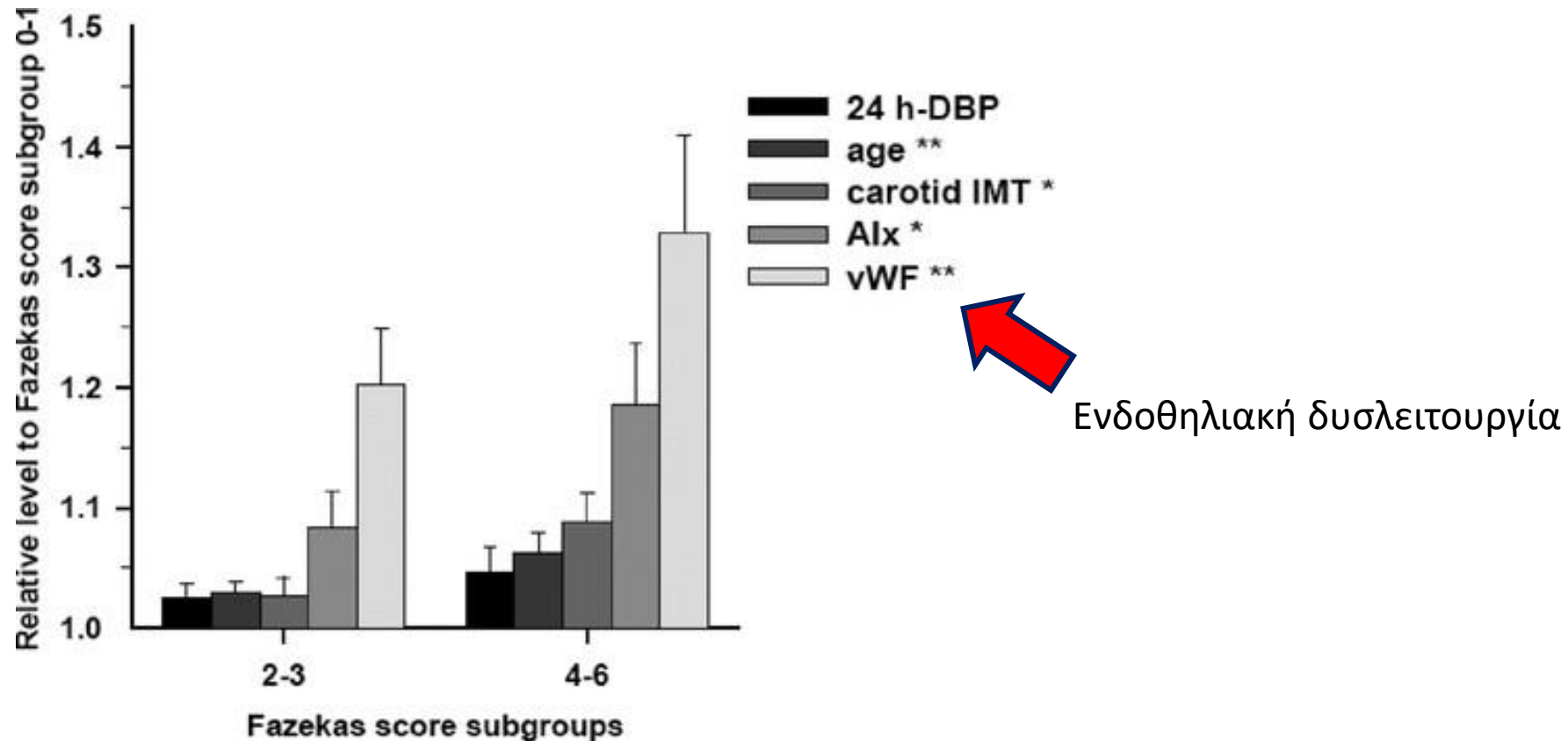
Endothelial dysfunction is associated with the severity of cerebral small vessel disease

Tomohisa Nezu, Naohisa Hosomi, Shiro Aoki, Satoshi Kubo, Mutsuko Araki, Tomoya Mukai, Tetsuya Takahashi, Hirofumi Maruyama, Yukihiro Higashi and Masayasu Matsumoto

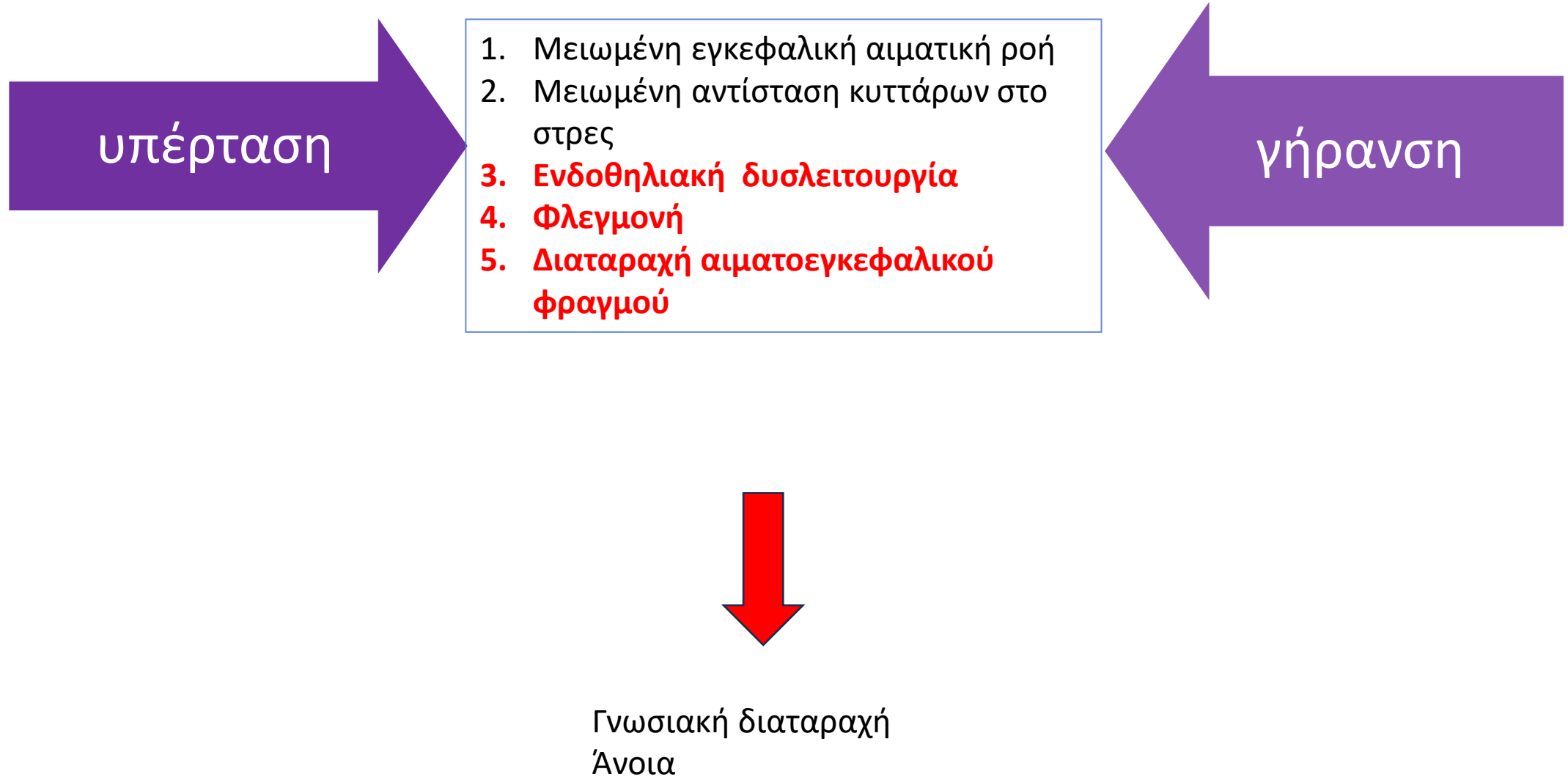


Vascular Structure and Function Is Correlated to Cognitive Performance and White Matter Hyperintensities in Older Hypertensive Patients With Subjective Memory Complaints

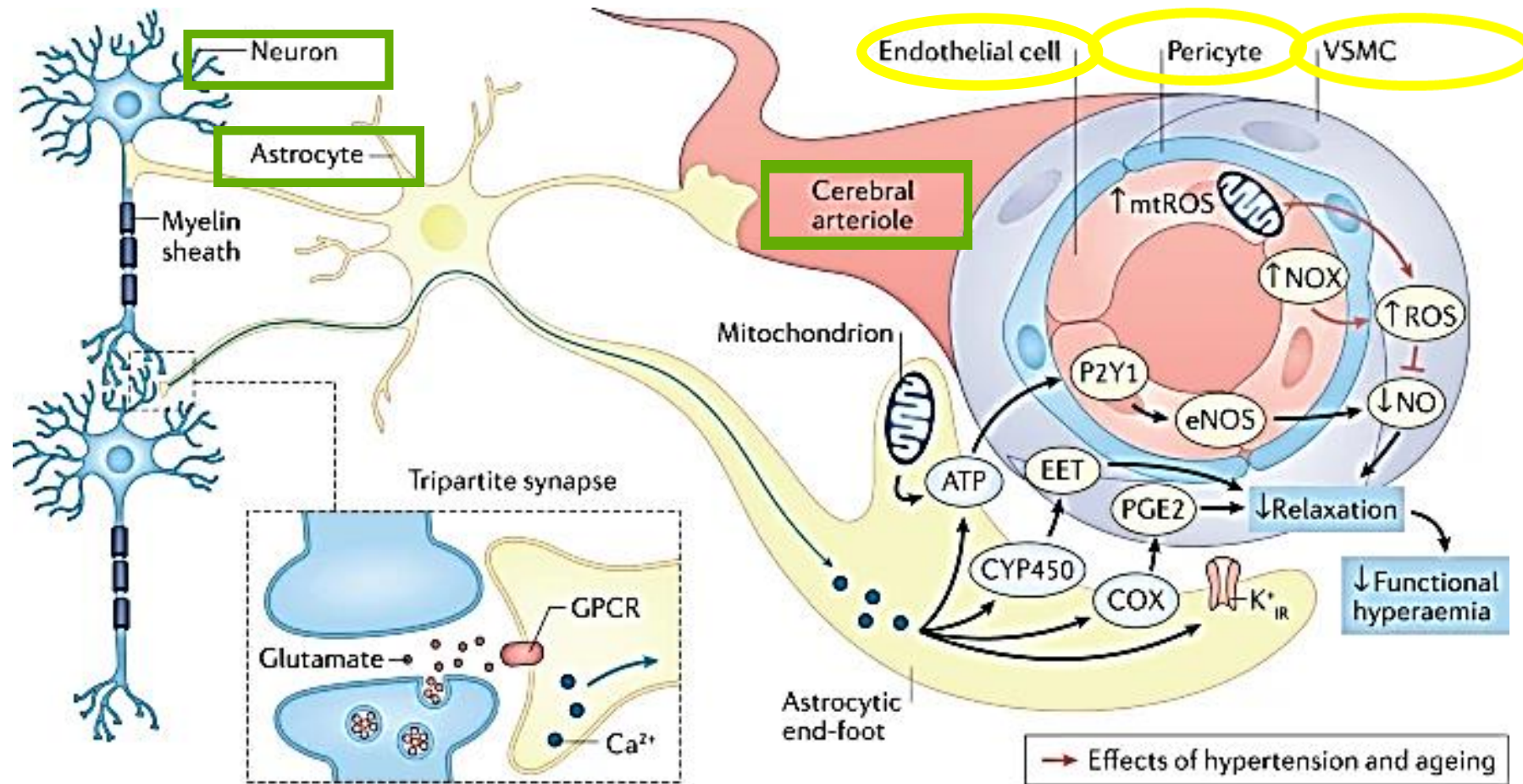
Anna Kearney-Schwartz, Patrick Rossignol, Serge Bracard, Jacques Felblinger, Renaud Fay, Jean-Marc Boivin, Thomas Lecompte, Patrick Lacolley, Athanase Benetos and Faiez Zannad



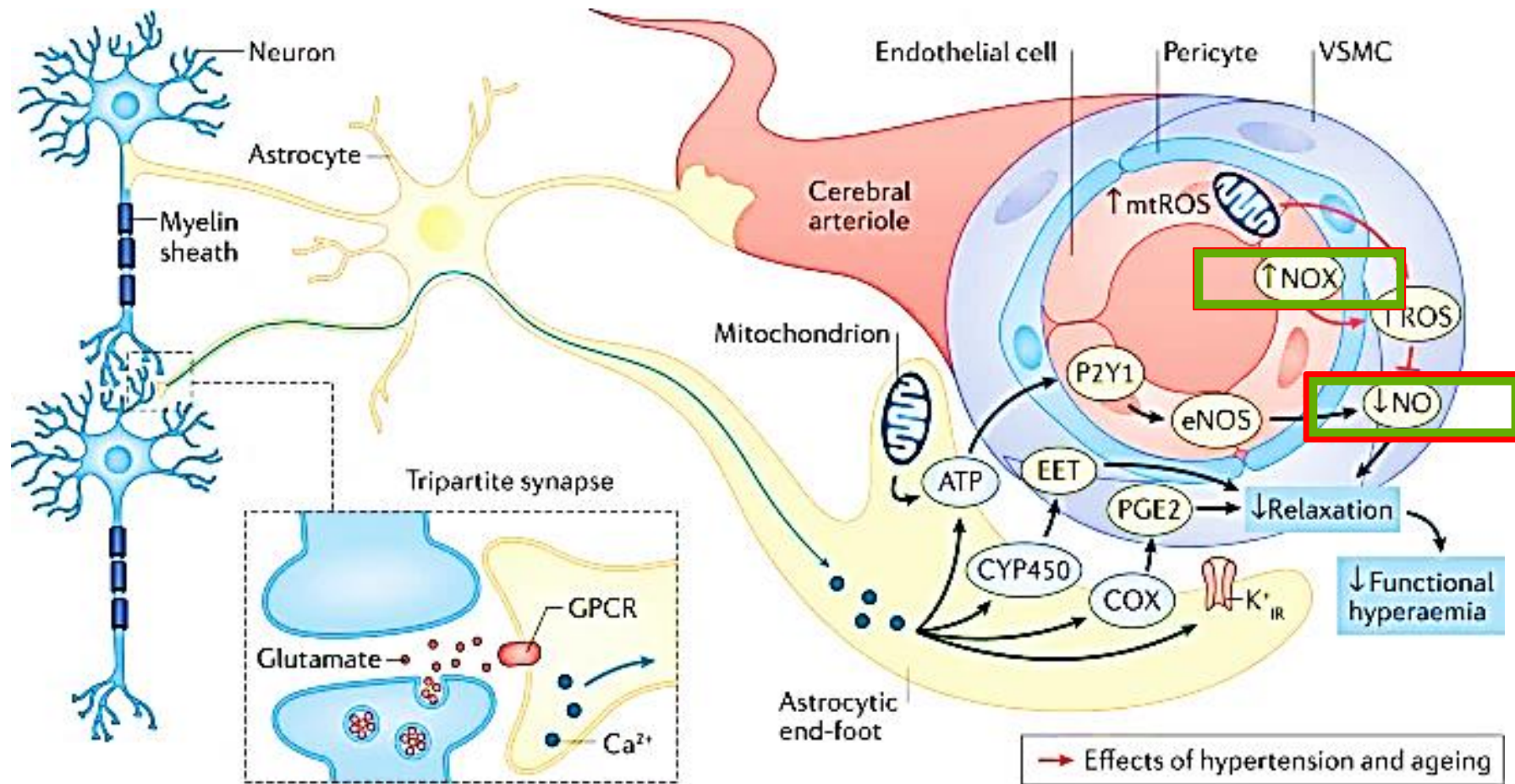
Νόσος μικρών αγγείων εγκεφάλου



Neurovascular unit



Neurovascular uncoupling

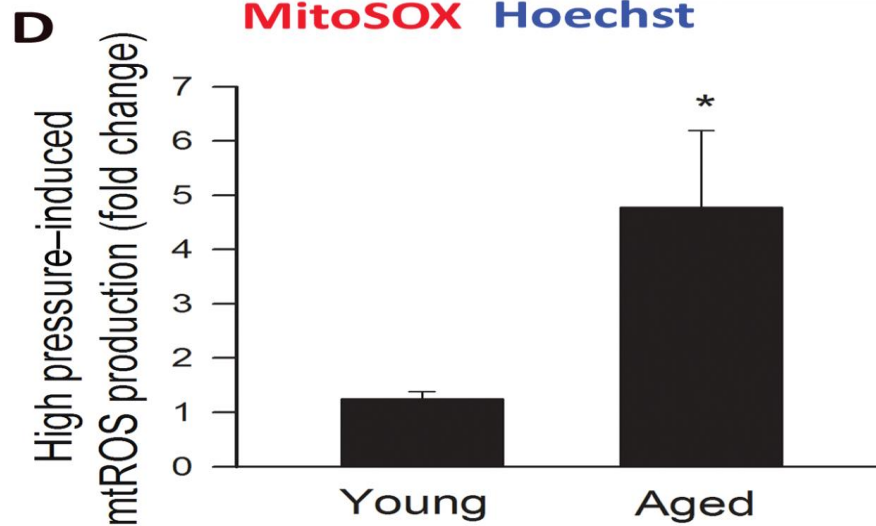
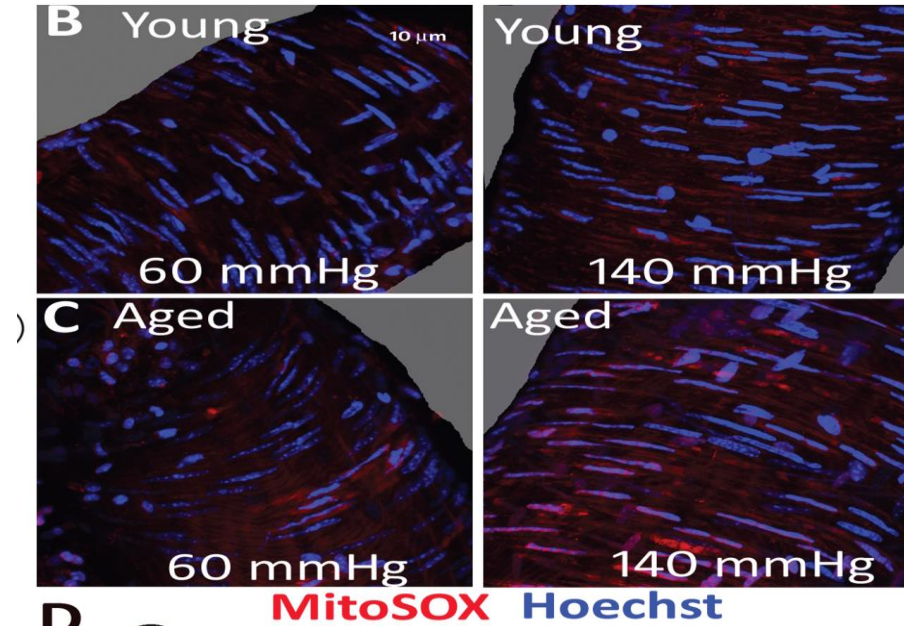


Neurovascular uncoupling

- Ομοστατικός μηχανισμός αύξησης αιματικής ροής σε αυξημένες ενεργειακές ανάγκες δυσλειτουργεί
- Υπέρταση προκαλεί απώλεια μηχανισμού μέσω παραγωγής ROS (αύξηση NADPH, μείωση διαθέσιμου NO)
- Απώλεια του μηχανισμού σχετίζεται με γνωσιακή δυσλειτουργία

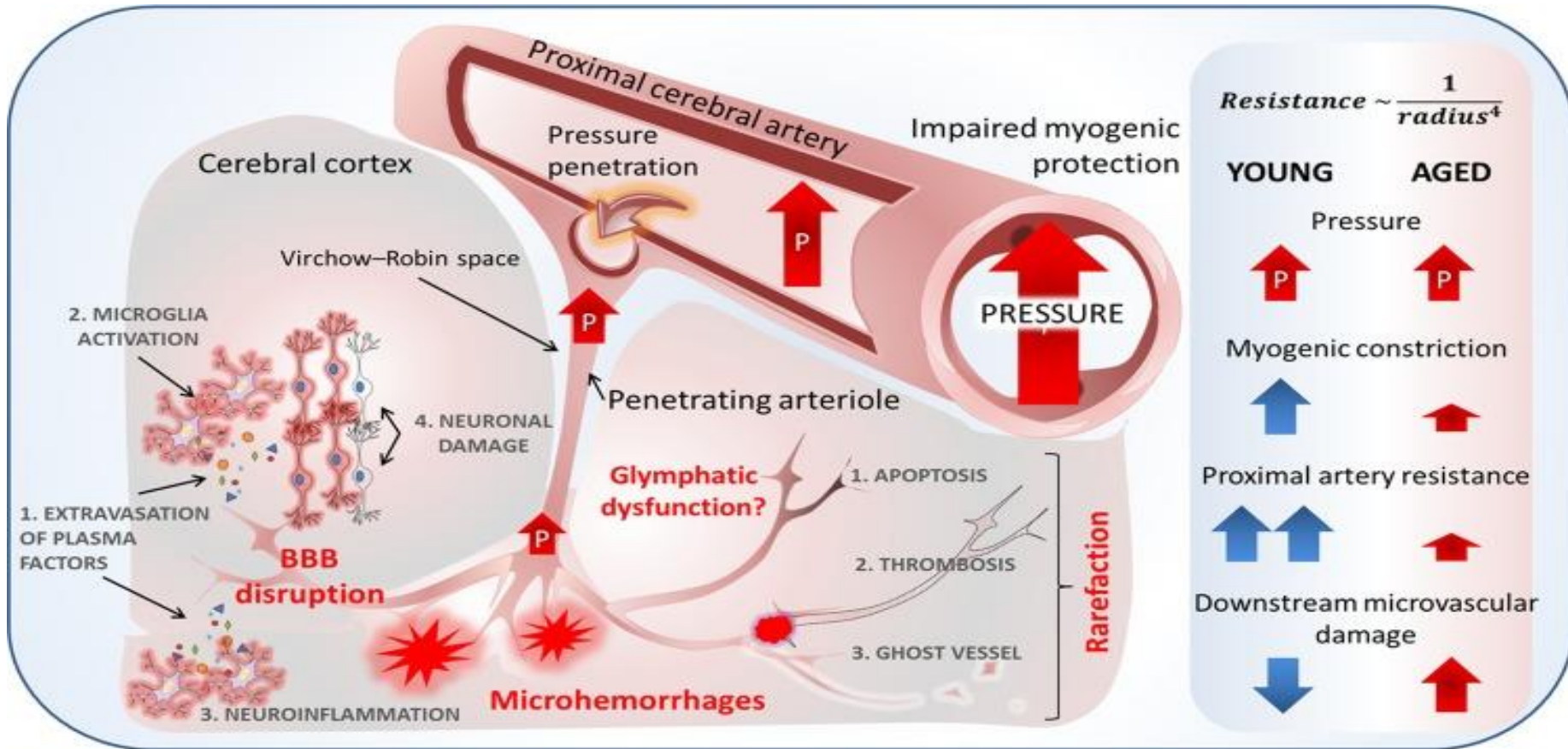
Aging Exacerbates Pressure-Induced Mitochondrial Oxidative Stress in Mouse Cerebral Arteries

Zsolt Springo,^{1,2,*} Stefano Tarantini,^{1,*} Peter Toth,^{1,*} Zsuzsanna Tucsek,¹ Akos Koller,² William E. Sonntag,^{1,3} Anna Csiszar,^{1,2,3} and Zoltan Ungvari^{1,2,3}

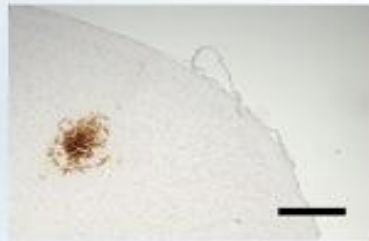
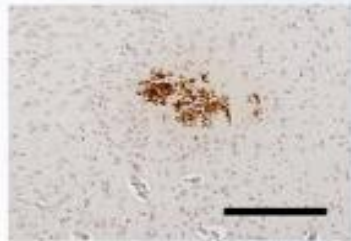
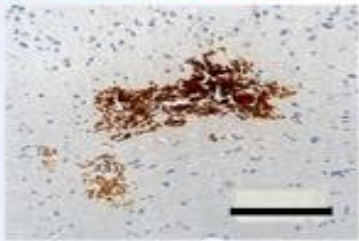


Υπέρταση, γήρανση και οξειδωτικό στρες

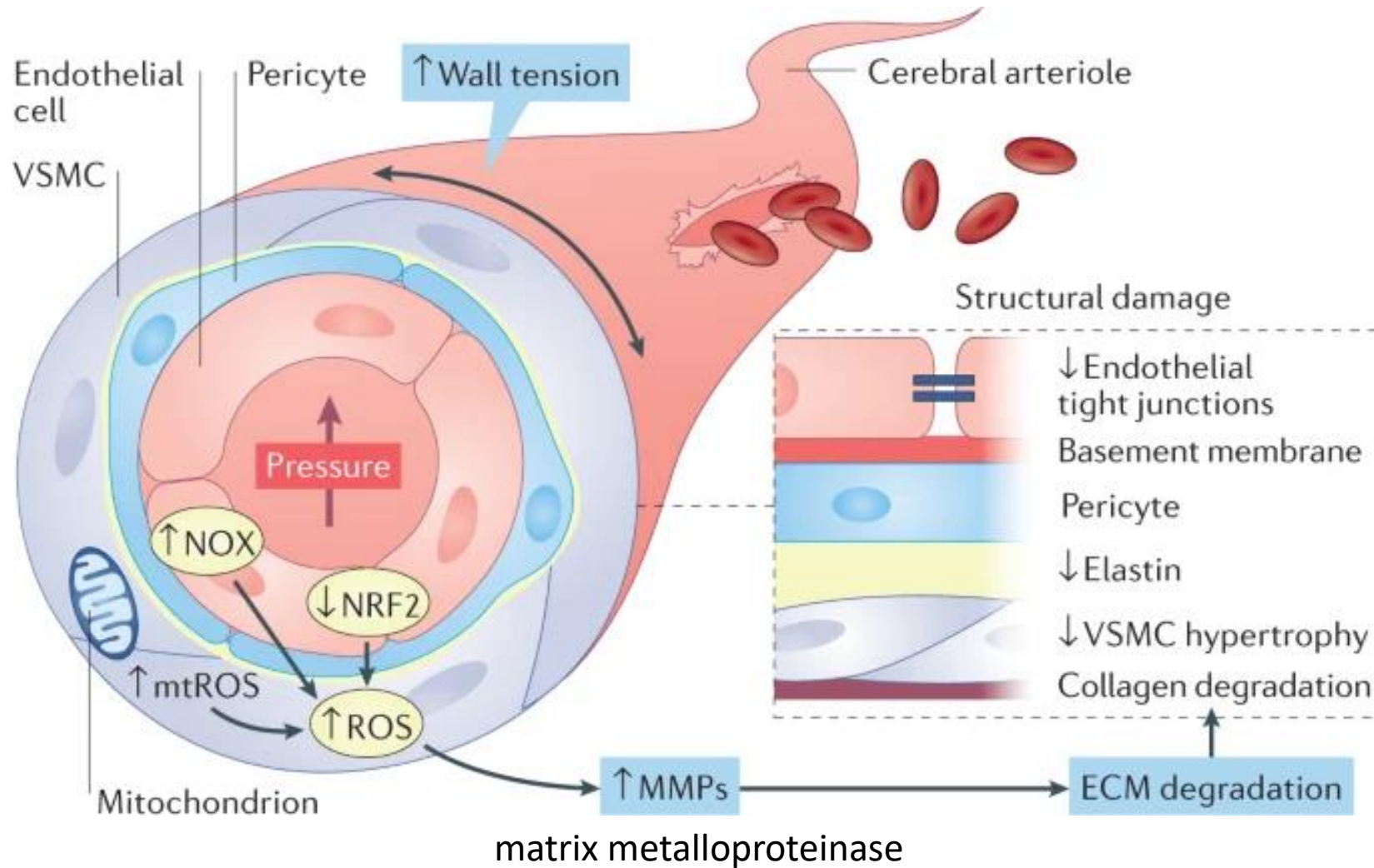
- NF-E2-related factor-2 (Nrf2) είναι μεταγραφικός παράγοντας, παράγεται στα αγγεία από ελεύθερες ρίζες οξυγόνου και ρυθμίζει αντι-οξειδωτικά γονίδια
- Γήρανση συνοδεύεται από $O_2^{\cdot-}$ παραγωγή και μειώνει mRNA έκφραση του Nrf2 και ενεργότητα Nrf2
- Μειώνει έκφραση γονιδίων NAD(P)H:quinone oxidoreductase 1, γ -glutamylcysteine synthetase και heme oxygenase-1



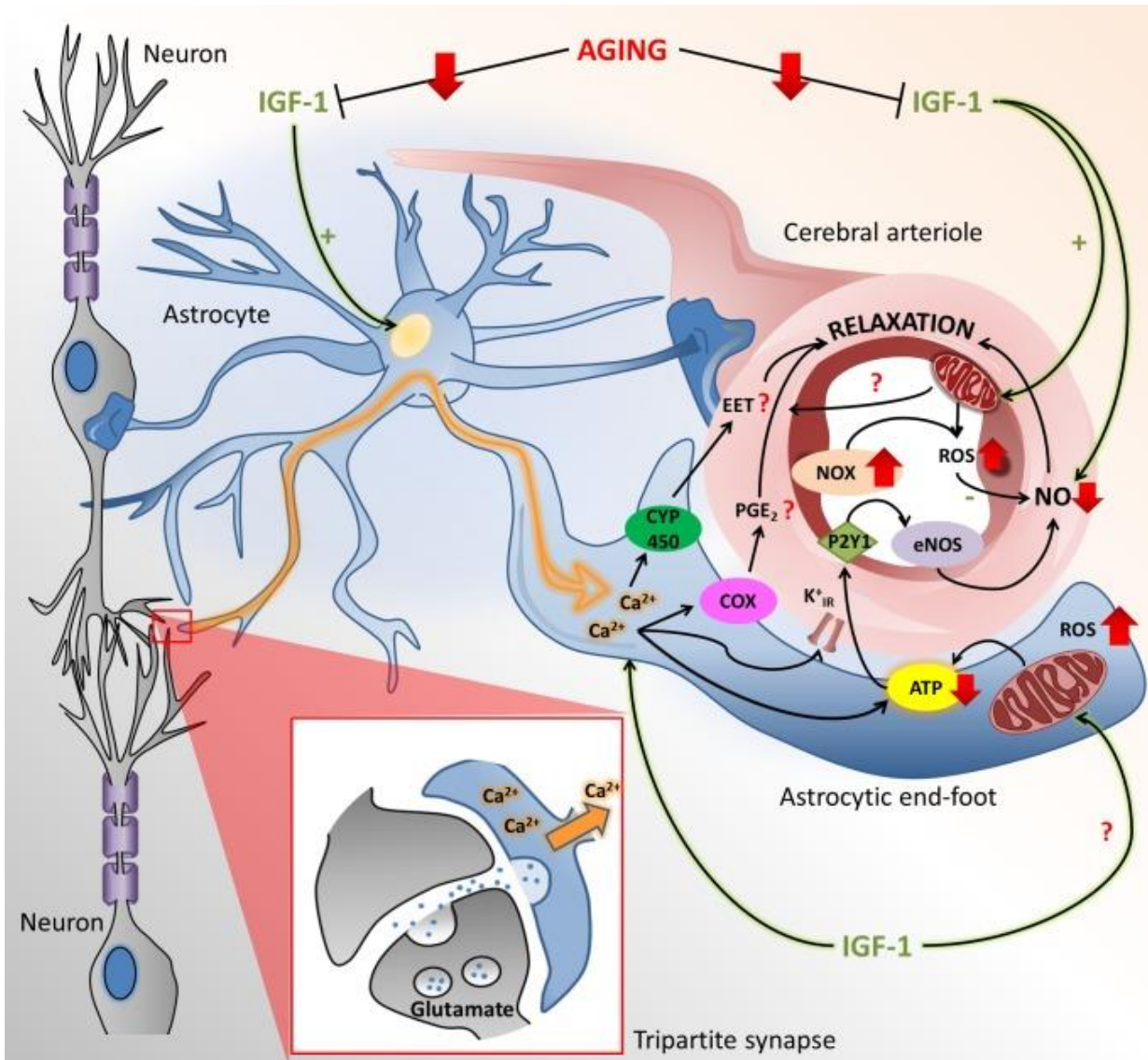
Microhemorrhages



Μικροαιμορραγίες

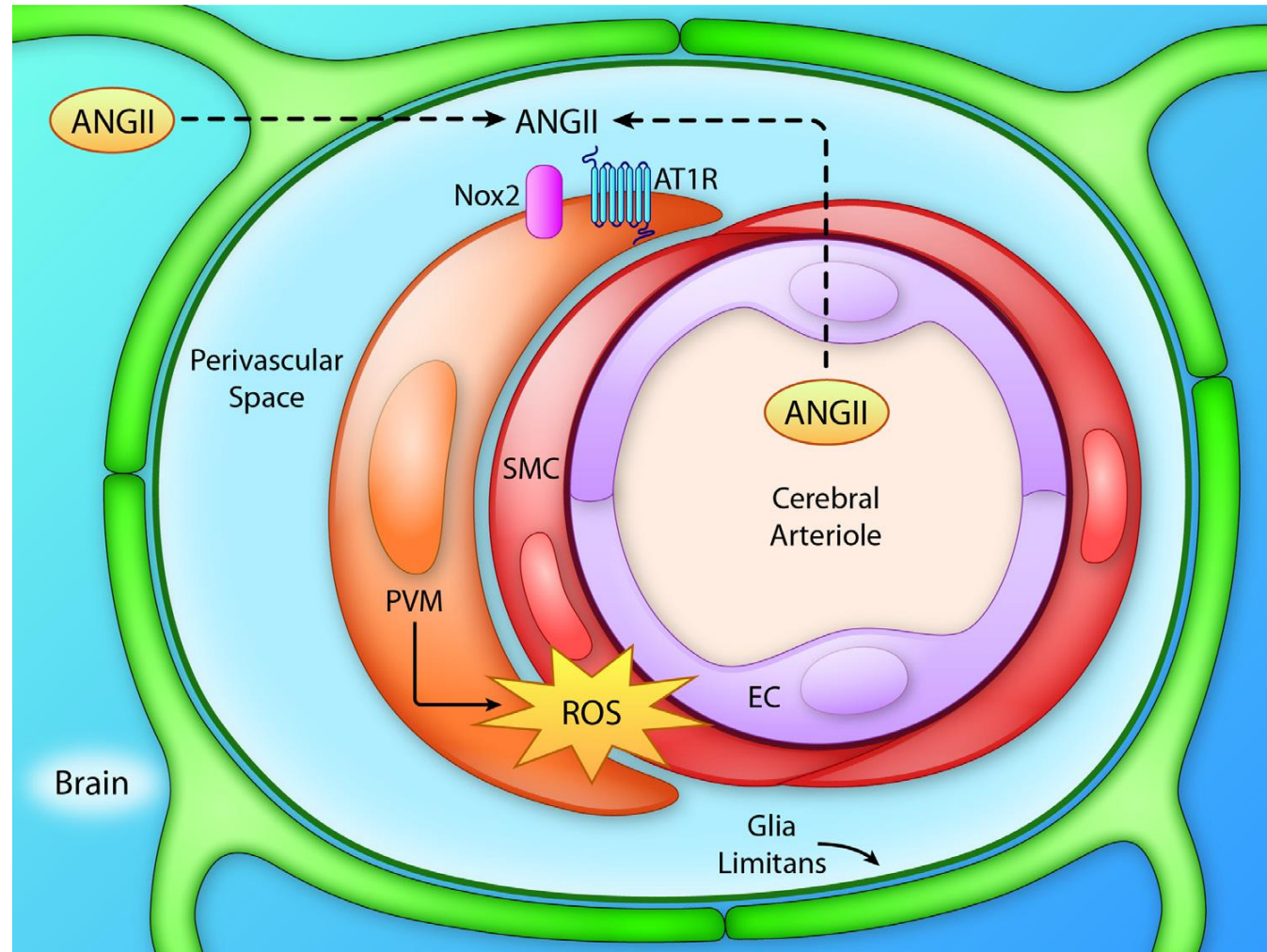


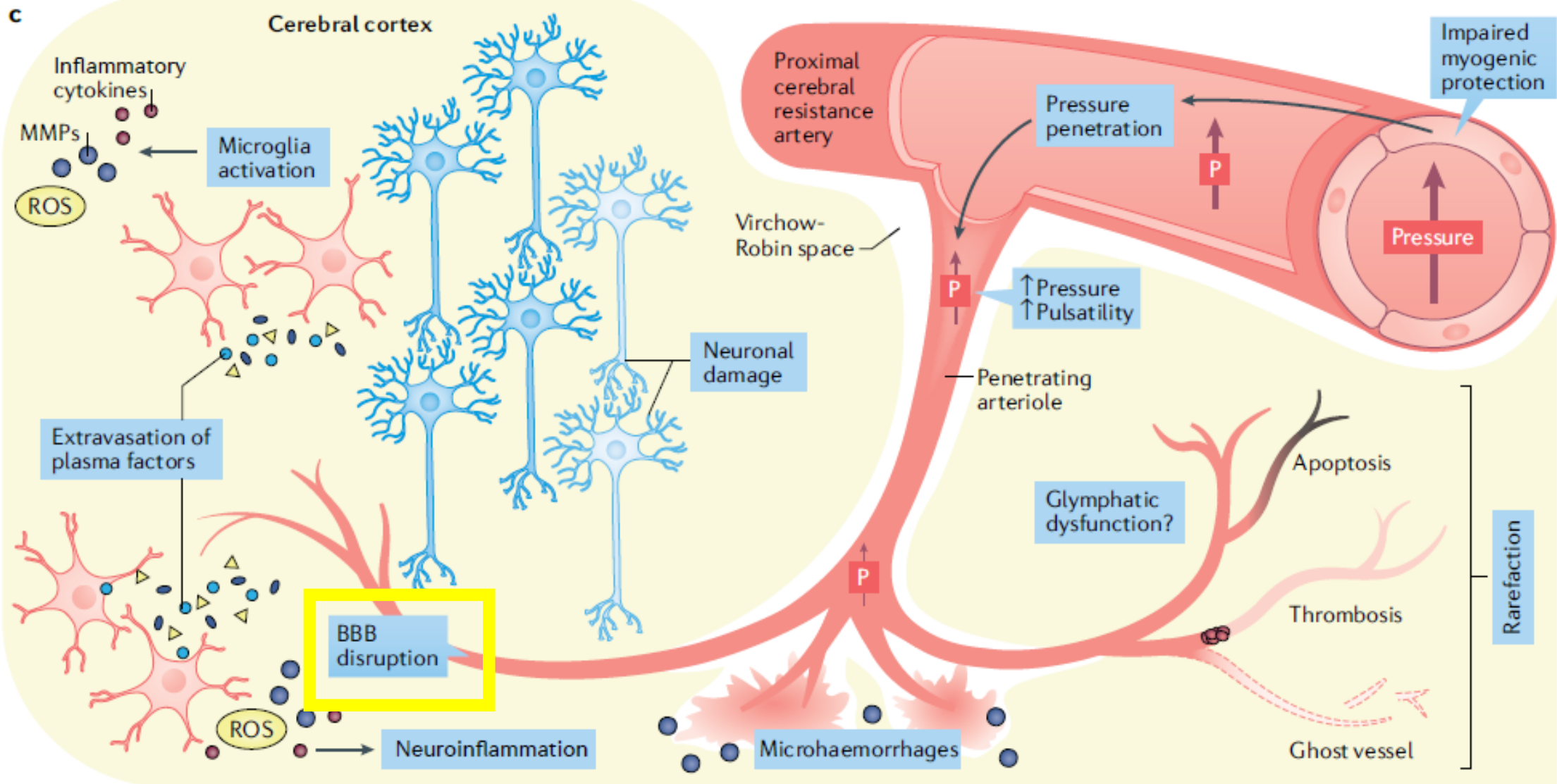
Ο ρόλος του IGF1



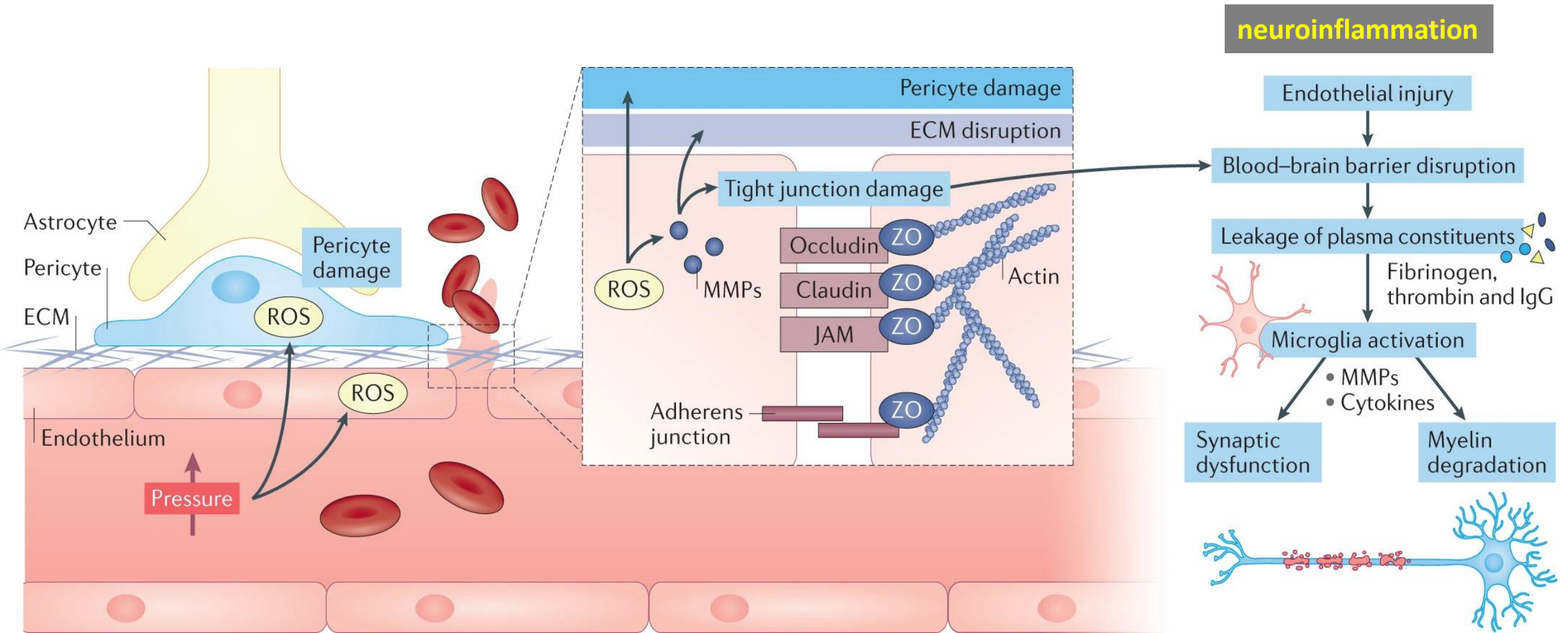
IGF1 υποδοχείς στα VSMCs και ενδοθηλιακά κύτταρα
IGF1 προάγει υπερπλασία και υπερτροφία VSMCs
ρυθμίζει συσπαστικότητα και παραγωγή matrix
μειώνει οξειδωτικό στρες

Ο ρόλος της αγγειοτενσίνης II



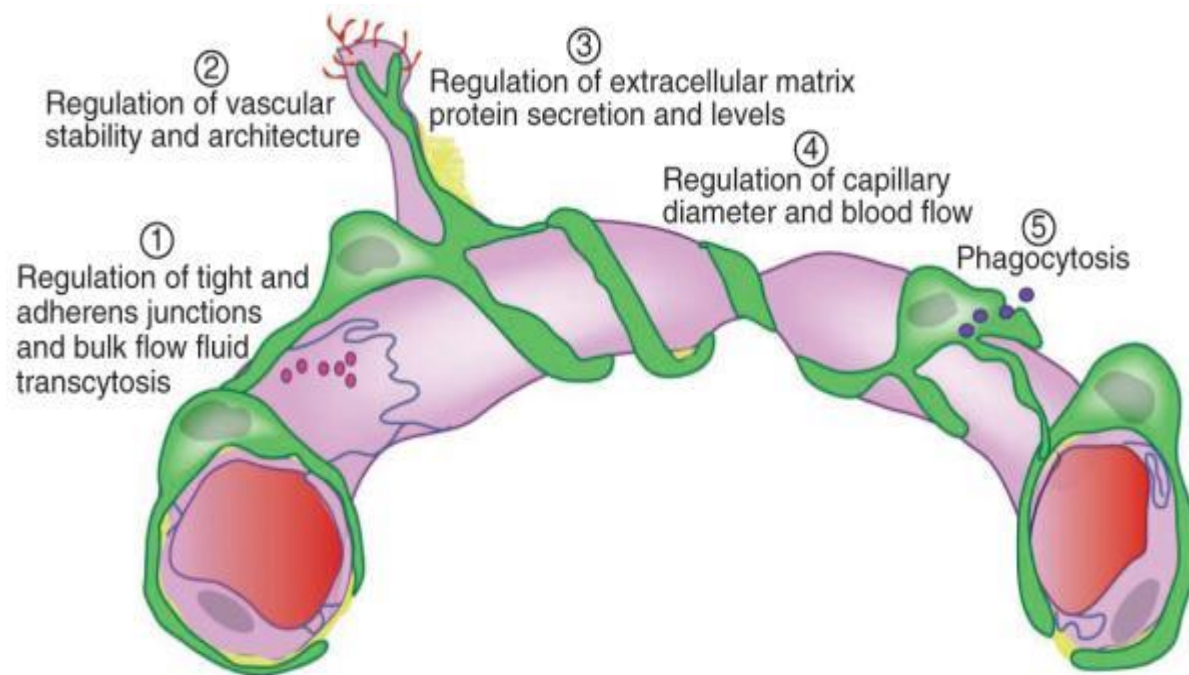


Διαταραχή αιματοεγκεφαλικού φραγμού (ΑΕΦ)

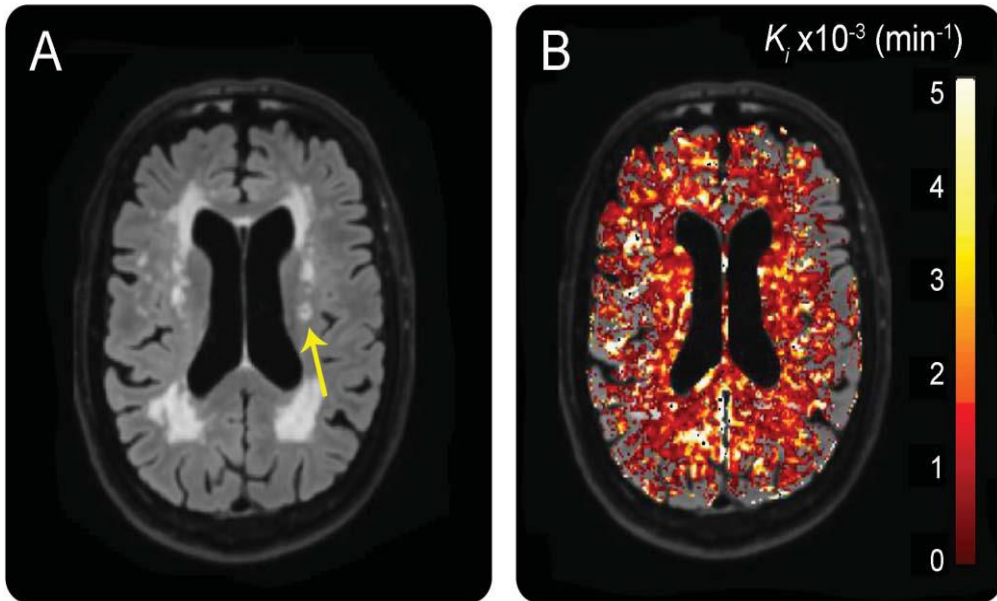


Διαταραχή αιματοεγκεφαλικού φραγμού

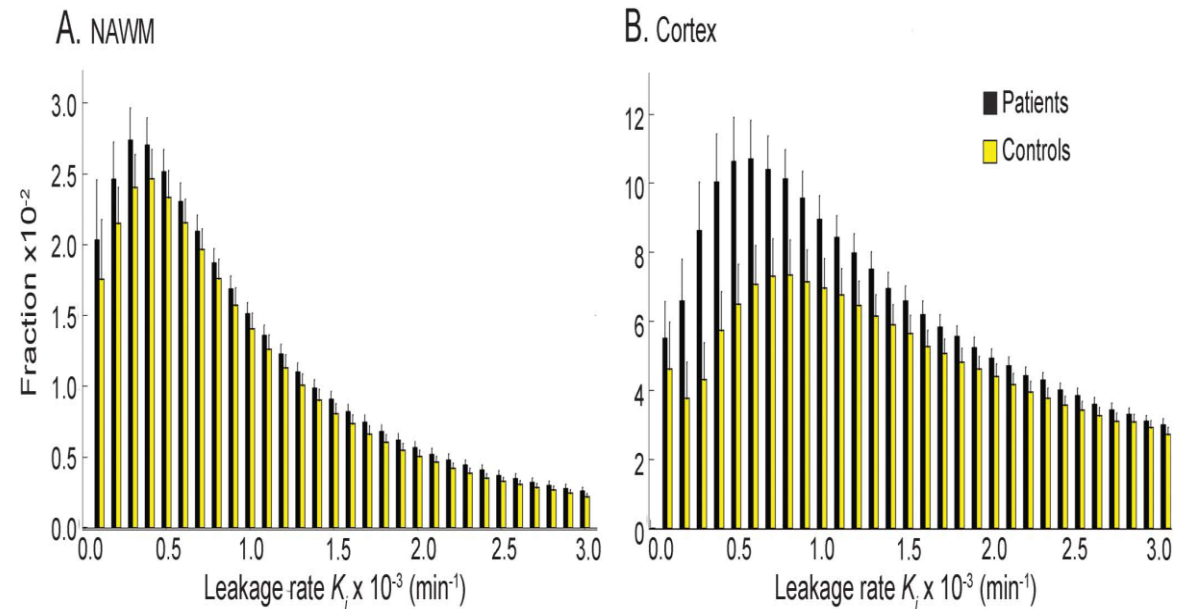
- βλάβη γλυκοκάλυκα ενδοθηλίου και βασικής μεμβράνης
- Απώλεια περικυττάρων



Blood–brain barrier leakage is more widespread in patients with cerebral small vessel disease

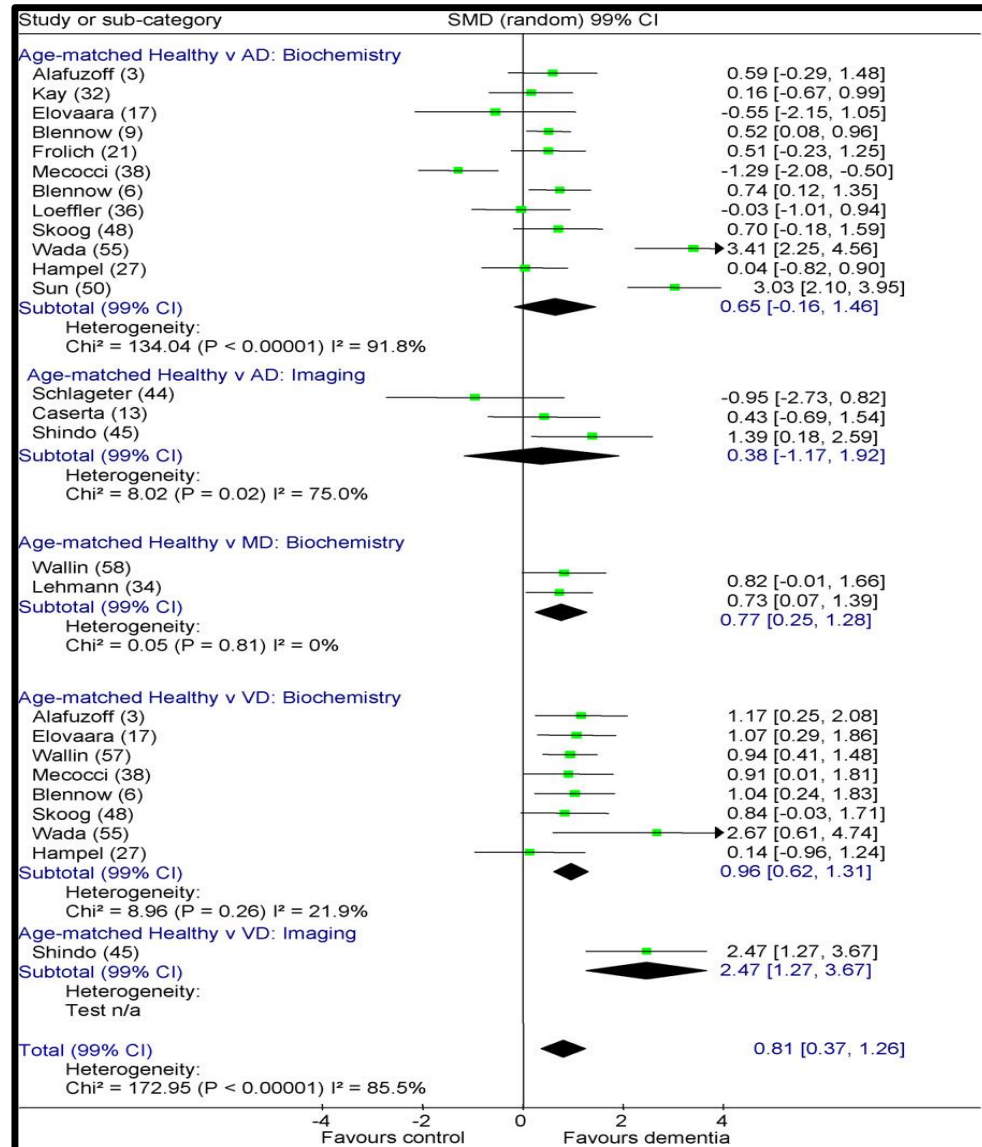


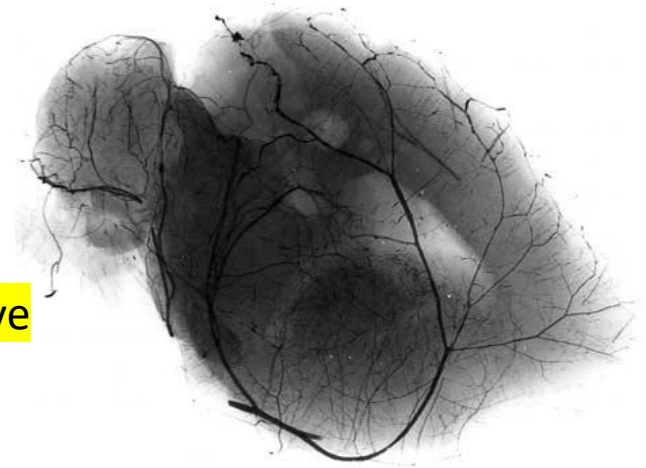
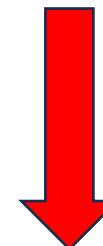
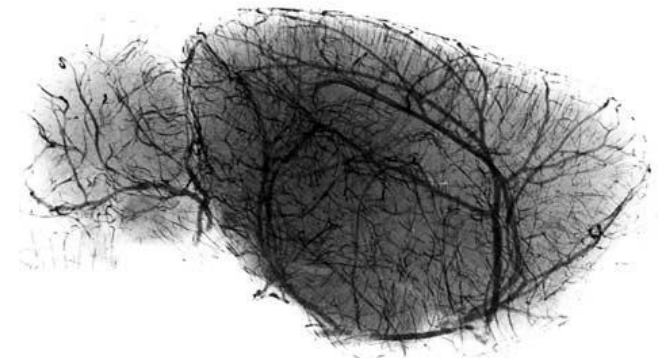
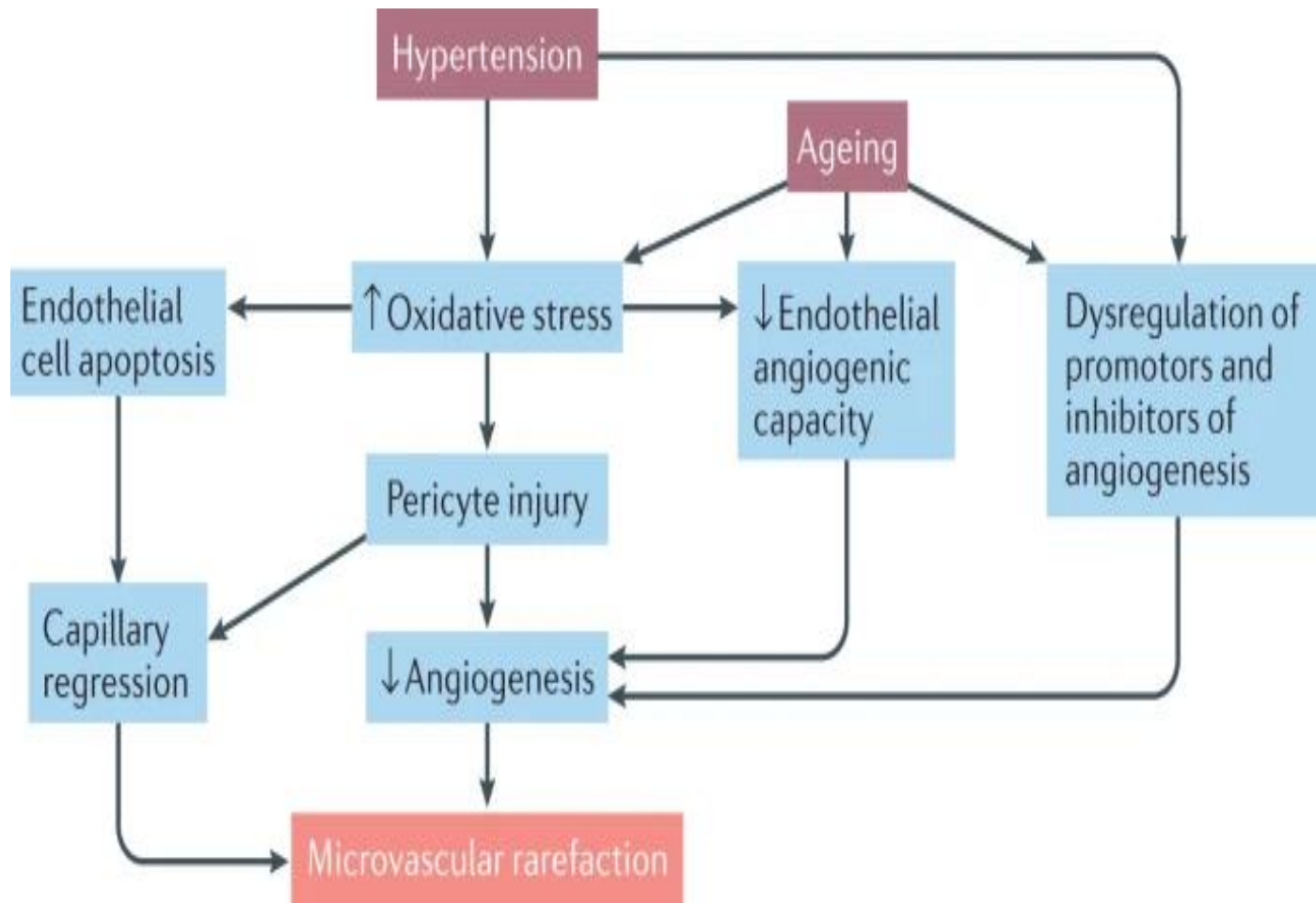
(A) Example of a FLAIR image and (B) a leakage map of one patient with cerebral small vessel disease with extensive WMH and a lacunar infarct



Leakage rate in patients with cerebral small vessel disease (cSVD) and controls

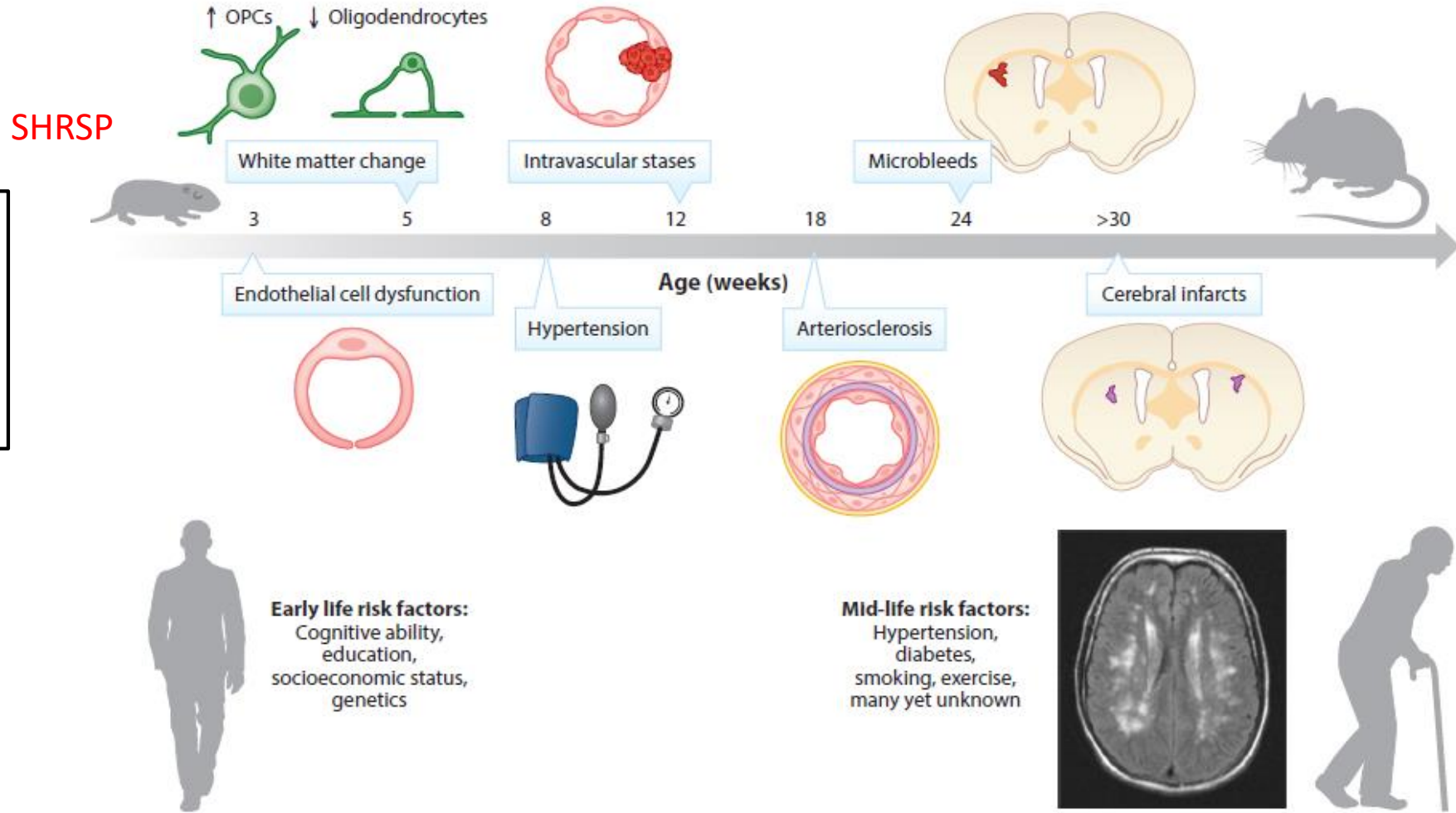
Διαταραχή αιματοεγκεφαλικού φραγμού, ηλικία, άνοια





hypertensive

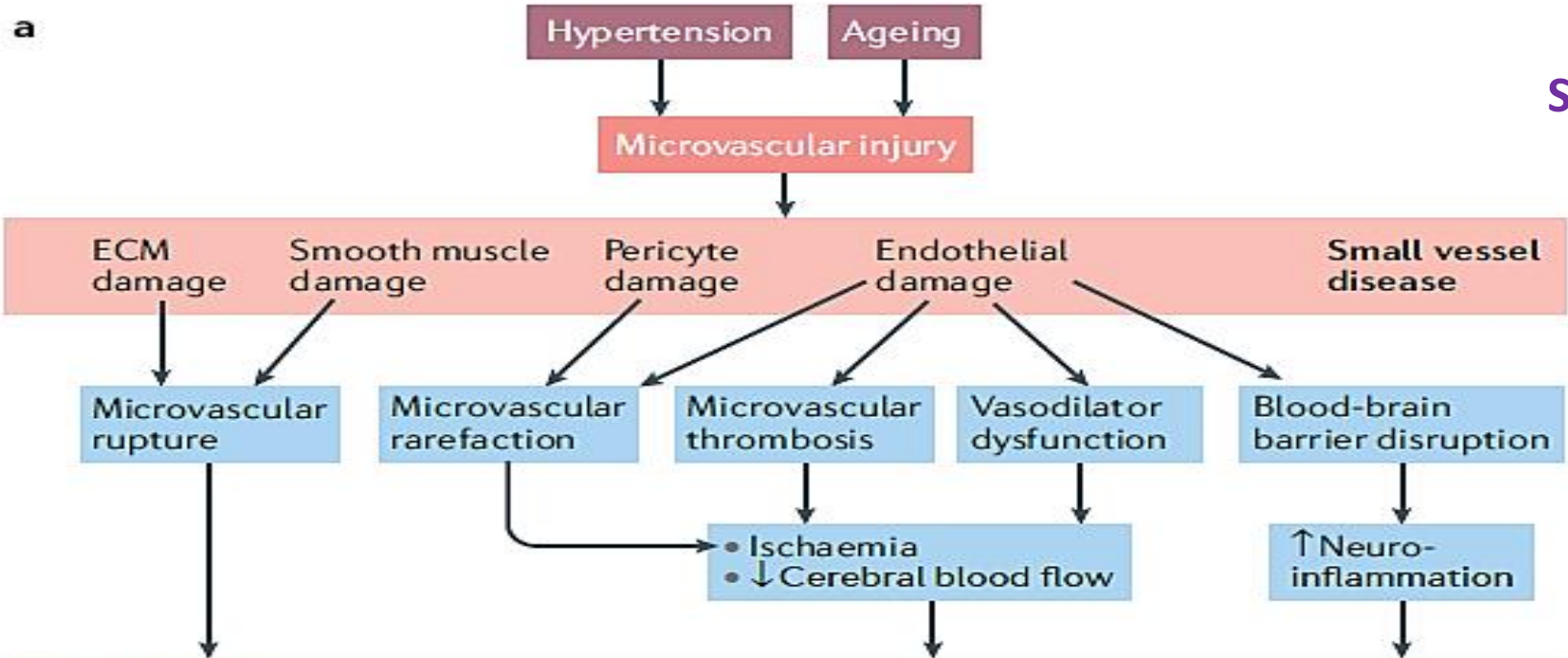
Complex Models of Complex Human Small Vessel Disease: A Translational Story



Endothelial cell dysfunction due to the loss of Atp11b, causing OPC maturation block and impaired myelination

Small vascular disease (SVD)

a

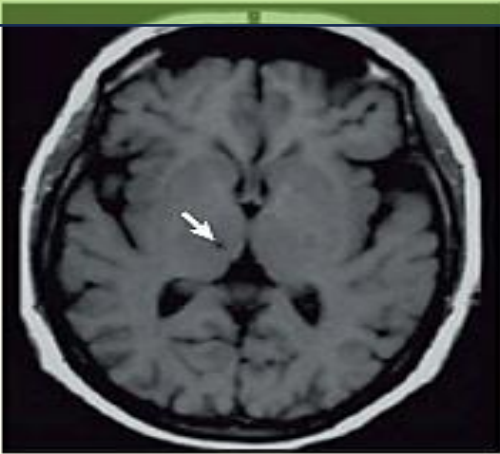


Imaging signs

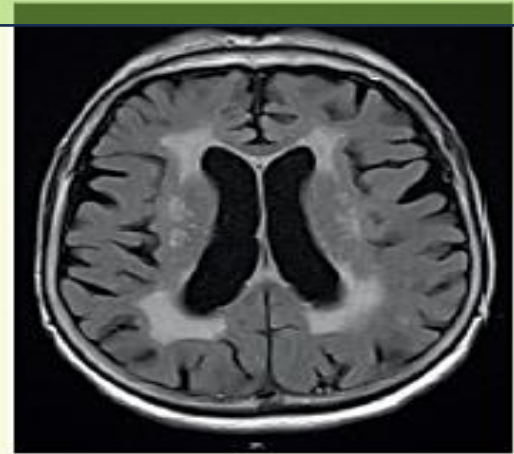
b Microhaemorrhages



c Lacunar infarcts



d White matter damage



increased perivascular spaces

