Corso di Aggiornamento AINV2024

La disautonomia nella pratica clinica: diagnosi e strategie terapeutiche

Ipoperfusione cerebrale e deficit cognitivo

G.VITICCHI

CLINICA NEUROLOGICA

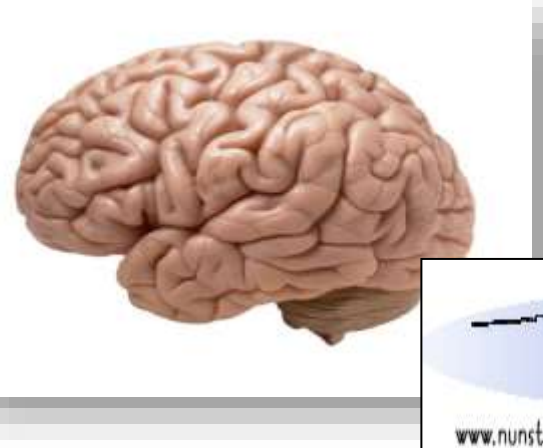
UNIVERSITA' POLITECNICA DELLE MARCHE

Treia, 4 ottobre 2024

Pure AD

- AD with severe cerebral amyloid angiopathy
- Mild AD with vascular involvement
- AD with vascular lesions
- AD with CVD
- VaD with vascular changes
- VaD with small-vessel diseases

Pure VaD



The Nun Study

www.nunstudy.org

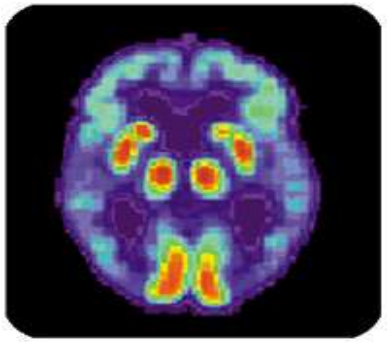
That you may have life to the full

Aggregation of vascular risk factors and risk of incident Alzheimer disease

J.A. Luchsinger, MD, MPH; C. Reitz, MD; L.S. Honig, MD, PhD; M.-X. Tang, PhD; Steven Shea, MD, MS; and R. Mayeux, MD, MSe

CONVERGING PATHOGENIC MECHANISMS IN VASCULAR AND NEURODEGENERATIVE DEMENTIA

C. Iadecola, Stroke 2003



ALZHEIMER'S DISEASE

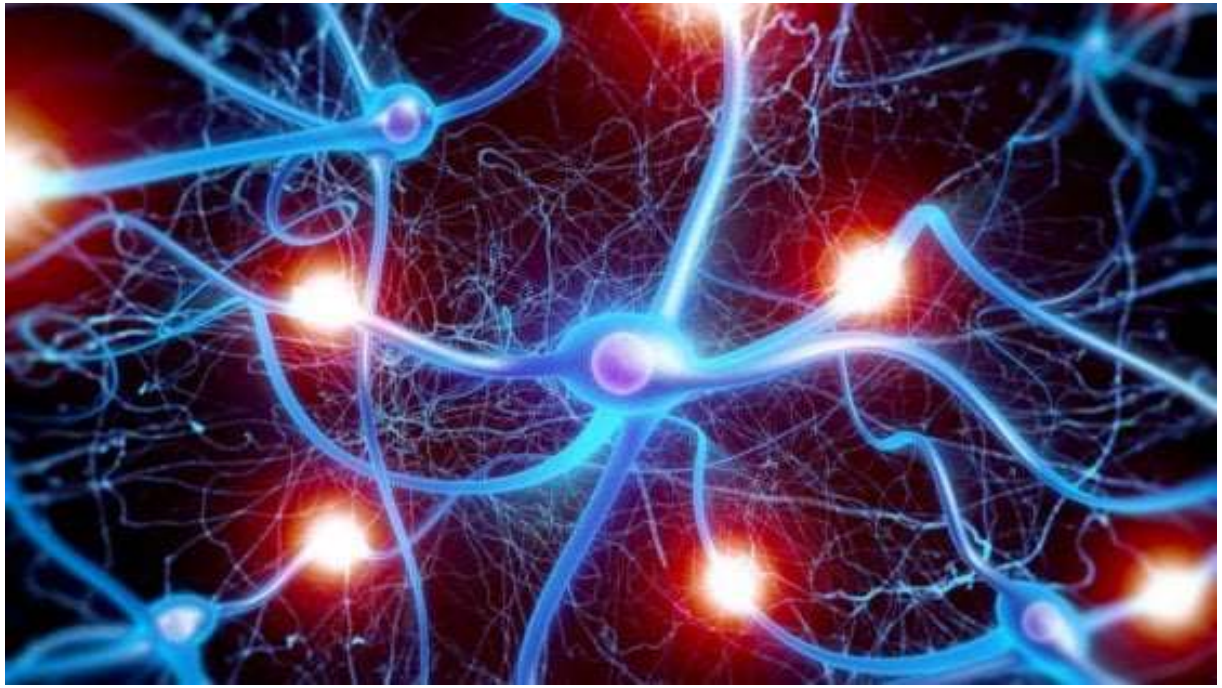
AMYLOID HYPOTESIS

- Abnormal APP cleavage
- Aβ deposition
- Senile plaques
- Neurodegeneration
- AD

VASCULAR HYPOTESIS

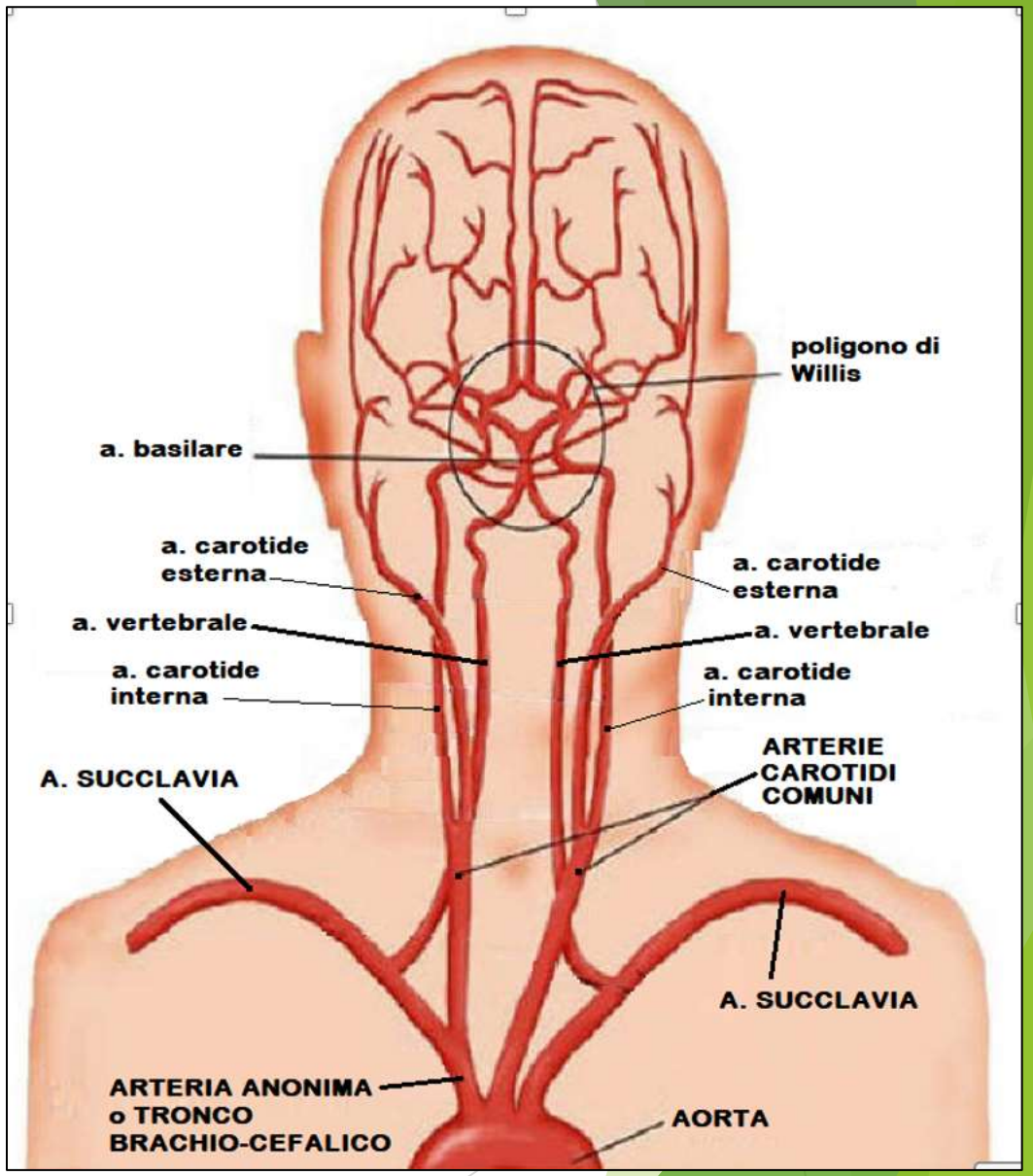
- Advanced ageing and vascular risk factor
- Brain hypoperfusion
- Neuroglial energy crisis
- Mild cognitive impairment
- Neurodegeneration
- AD

De La Torre 2000



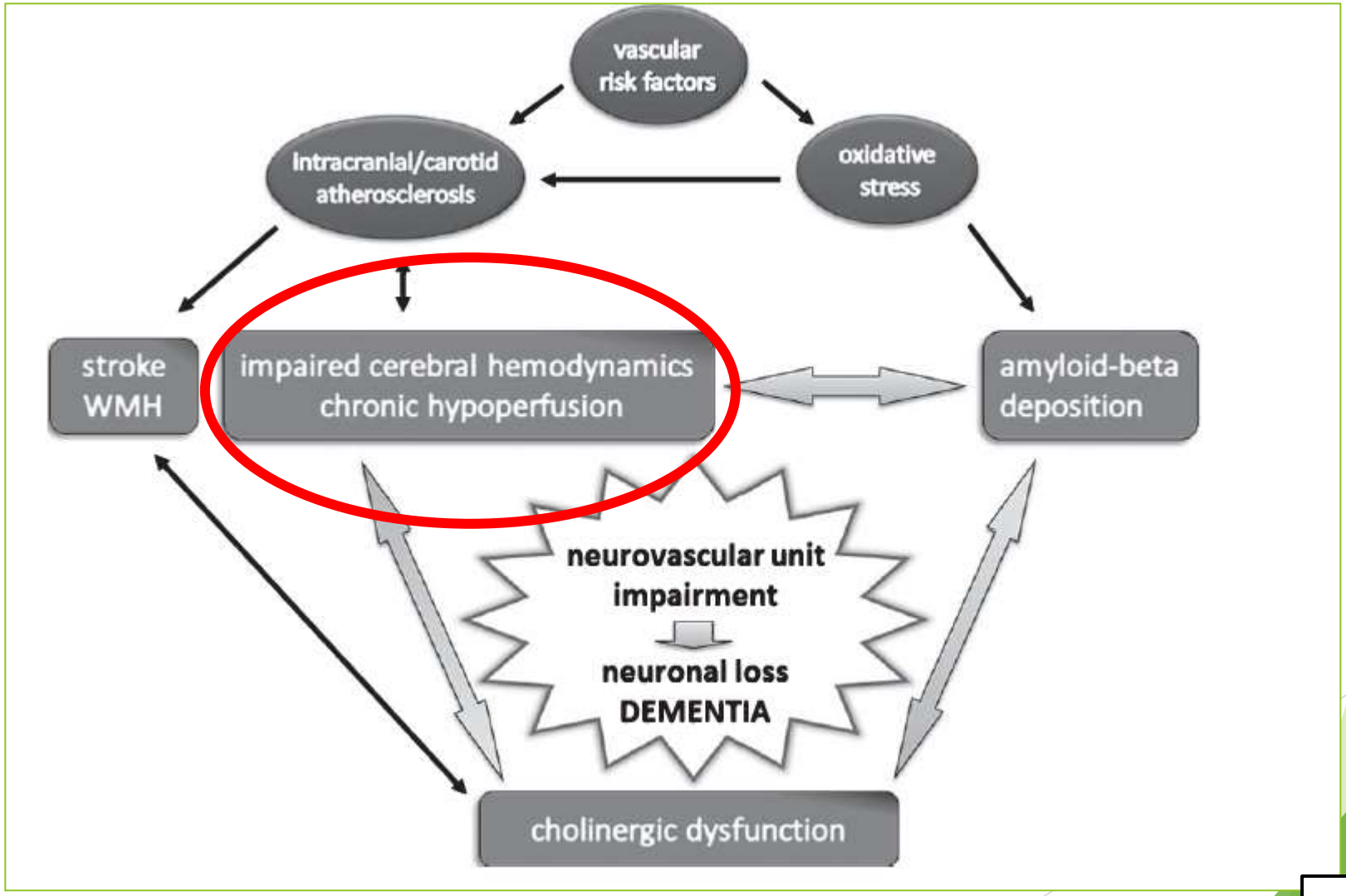
Cerebral hemodynamics play an important role in maintaining coordinated flow responses in the brain as neuronal tissues require tight coordination between neuronal activity and CBF within the brain parenchyma

(**NEUROVASCULAR COUPLING**).

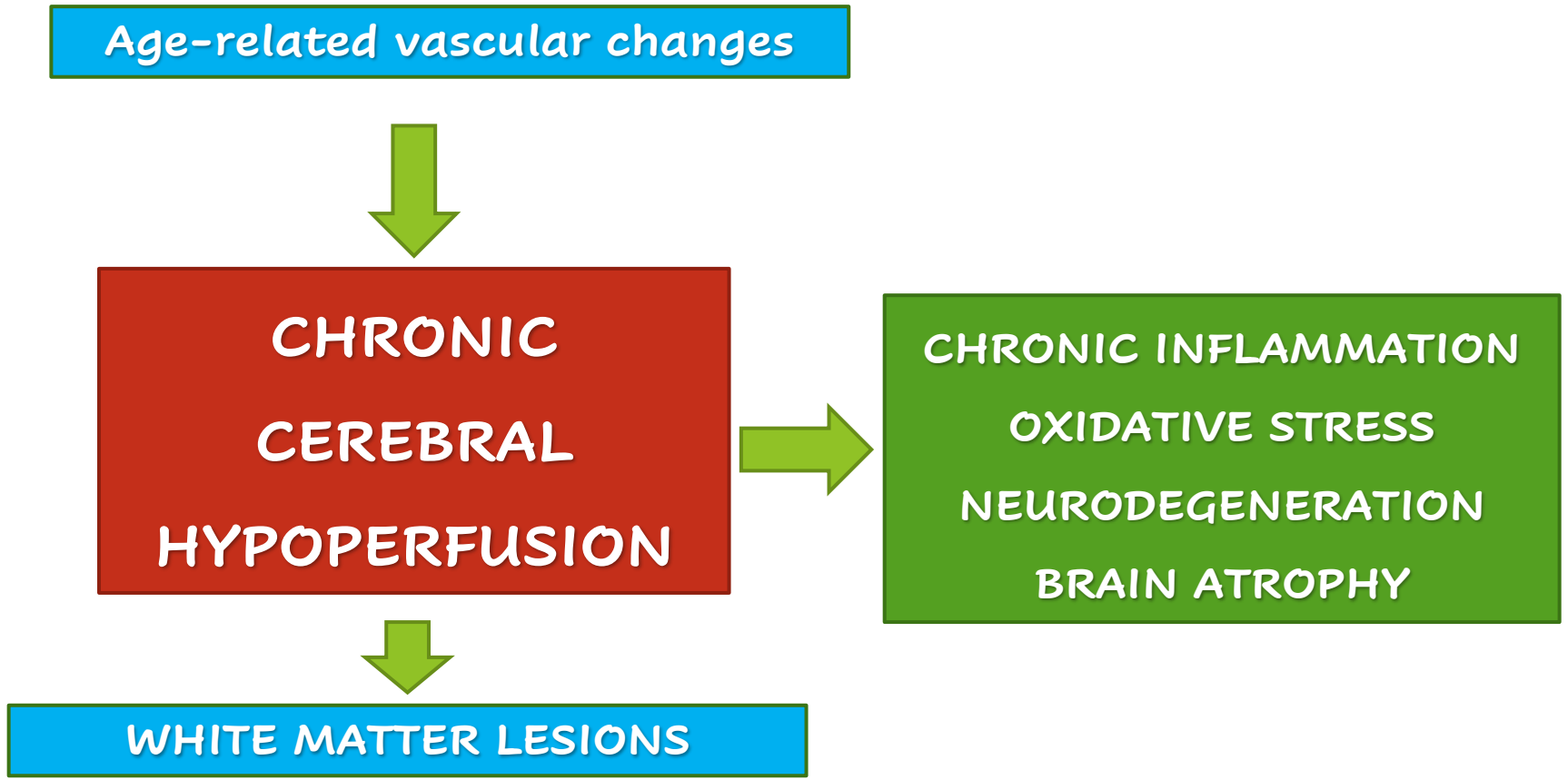


Ungvari 2010

VASCULAR RISK FACTORS & COGNITIVE IMPAIRMENT

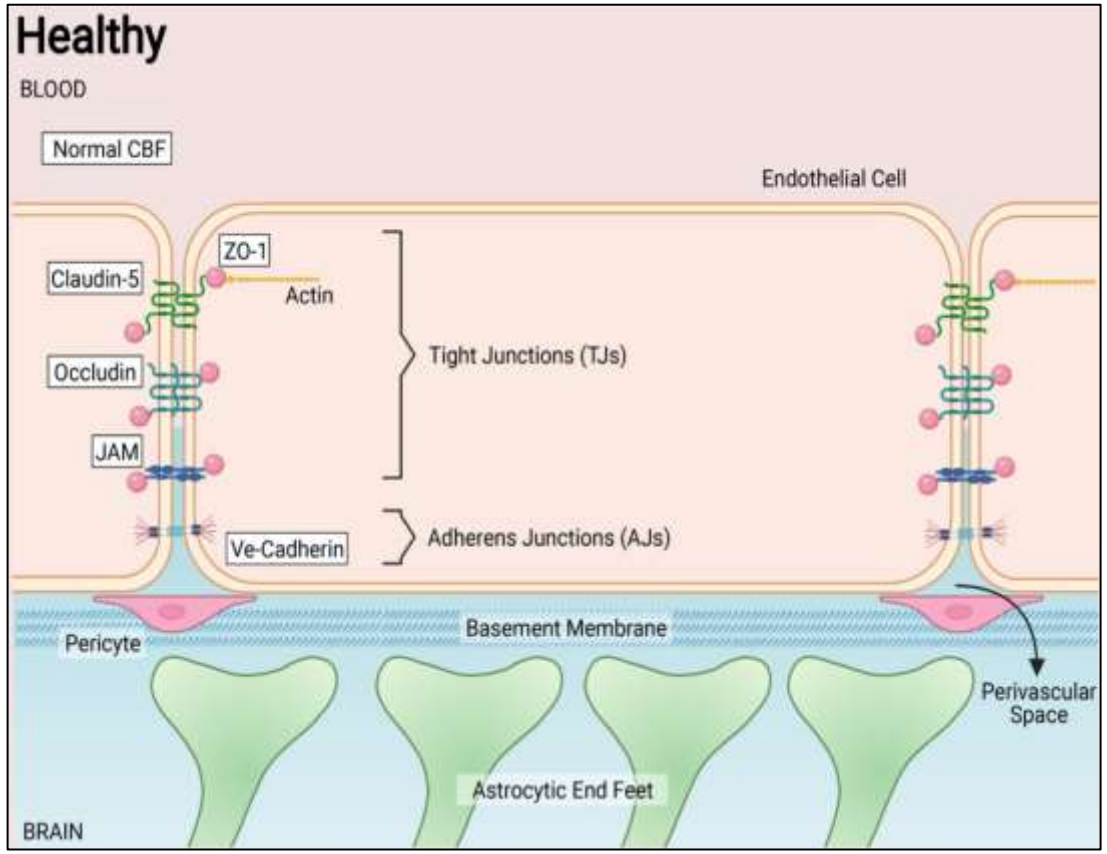


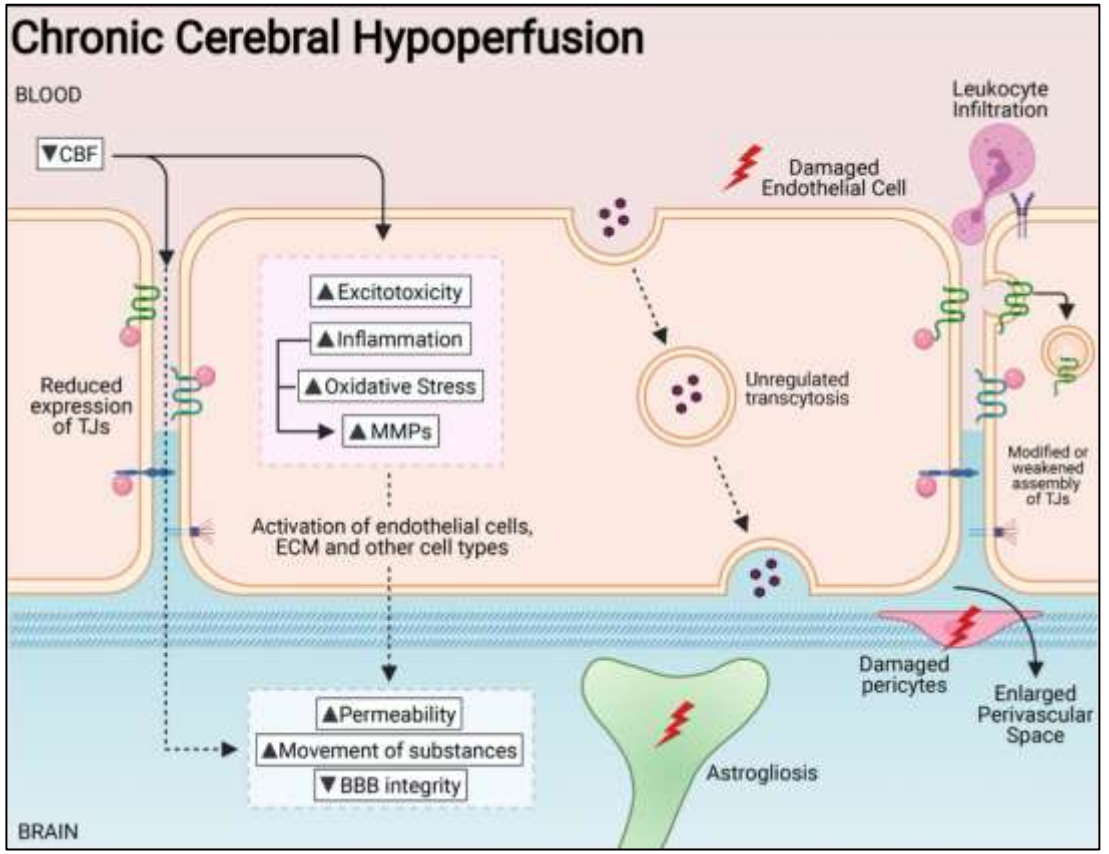
Viticchi 2012



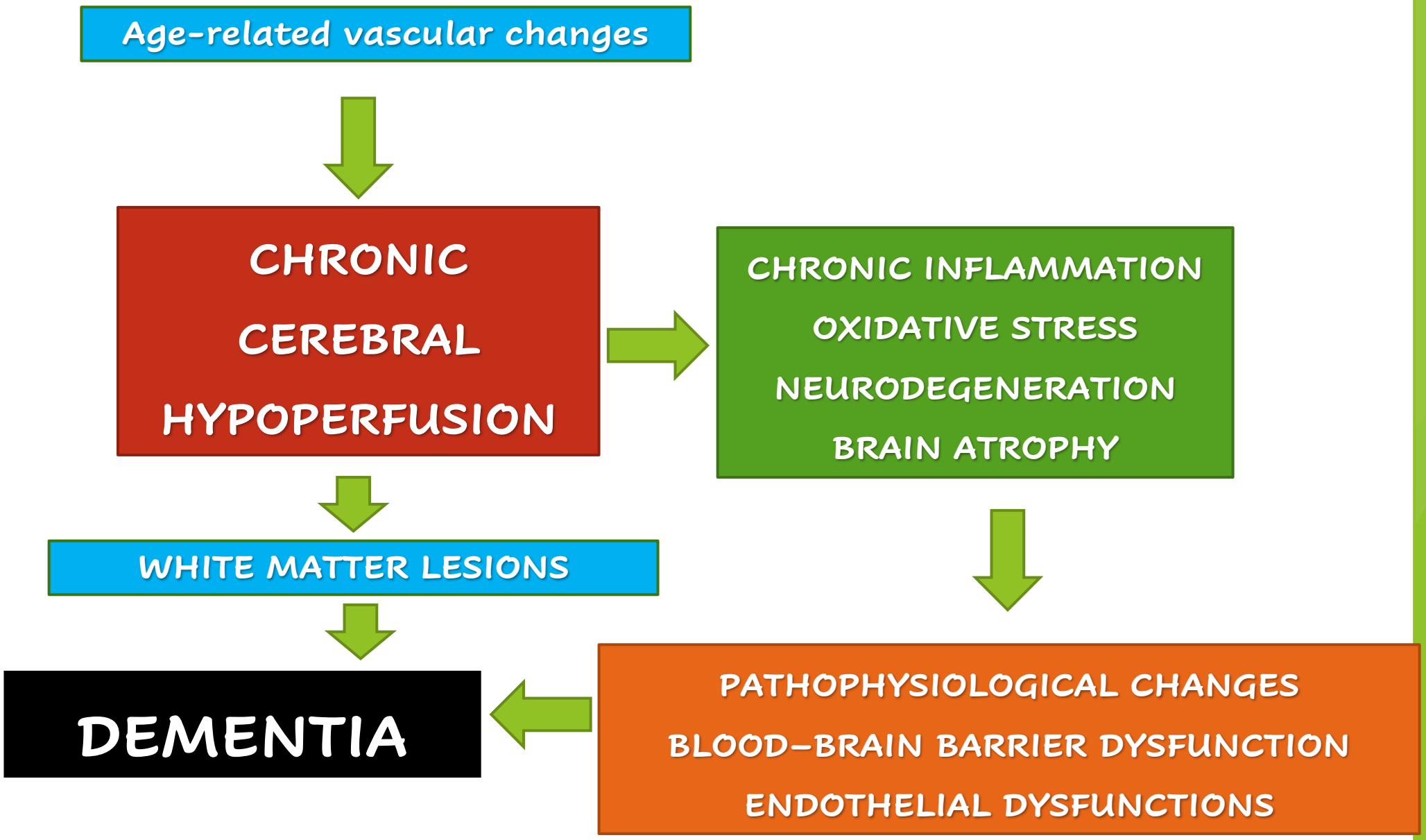
Ungvari 2010

BLOOD BRAIN BARRIER





Rajeev 2022



Ungvari 2010

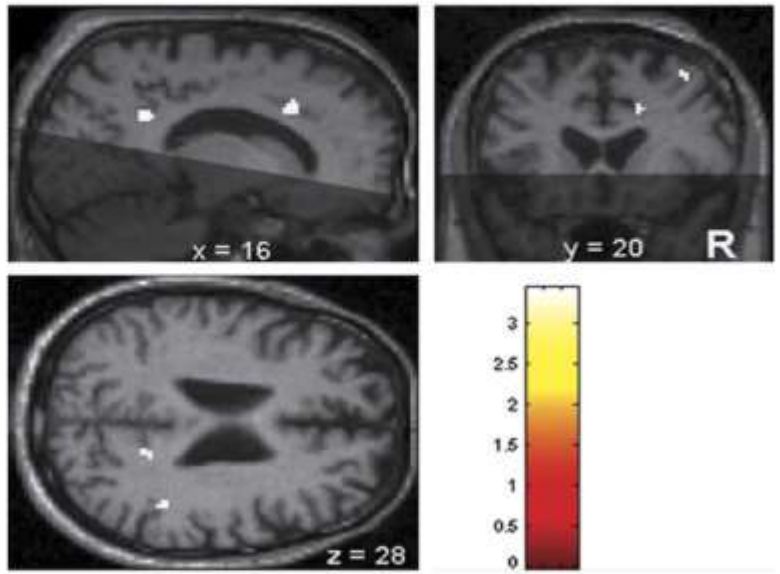
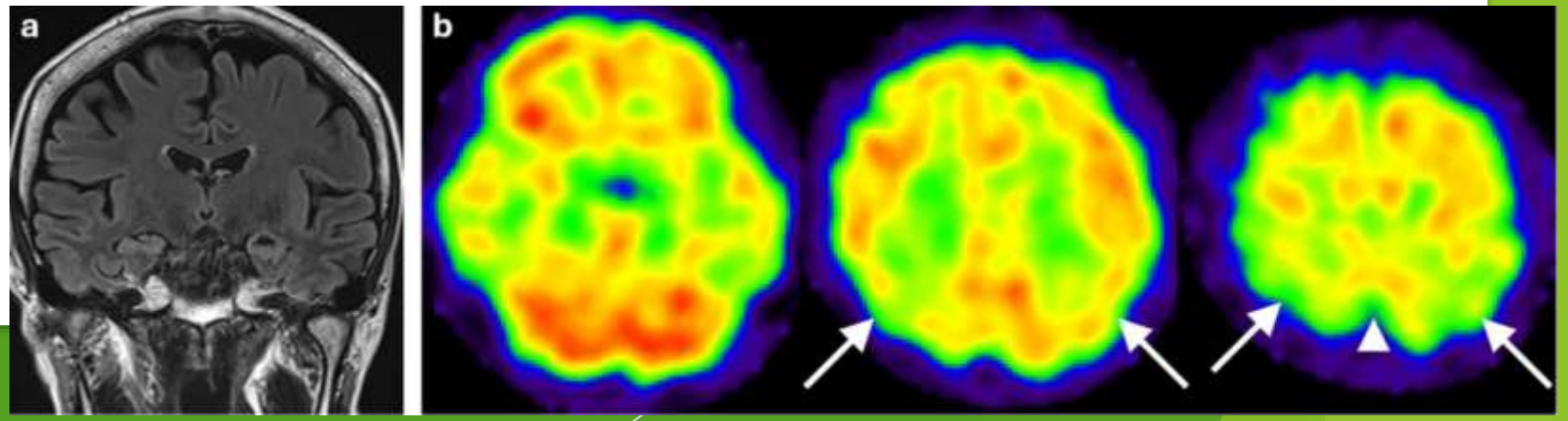


FIGURE 1.
Statistical parametric maps showing regions of hypoperfusion in the 13 mild cognitive impairment subjects who converted to dementia relative to the 35 mild cognitive impairment subjects who remain nondemented. Converters had hypoperfusion in the right precuneus/posterior cingulum (shown in the sagittal and axial slices), right middle cingulum (shown in the sagittal and coronal slices), right middle frontal cortex (shown in the coronal slice), and right inferior parietal cortex (shown in the axial slice). The shaded areas in the sagittal and coronal slices represent regions not covered by our implementation of arterial-spin labeling magnetic resonance imaging.

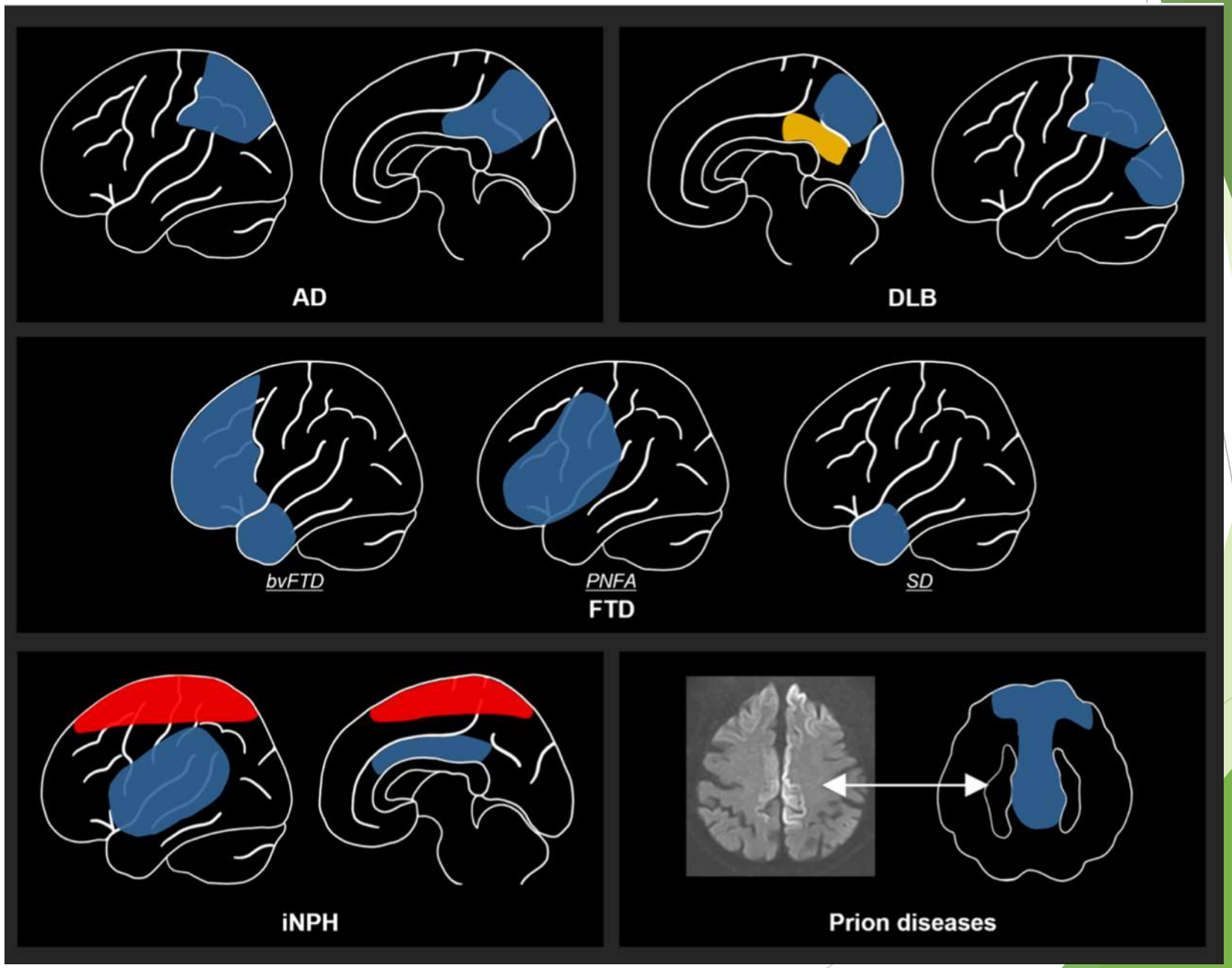
ALZHEIMER DISEASE
& ASSOCIATED DISORDERS
AN INTERNATIONAL JOURNAL

Chao 2010

Imokava 2024

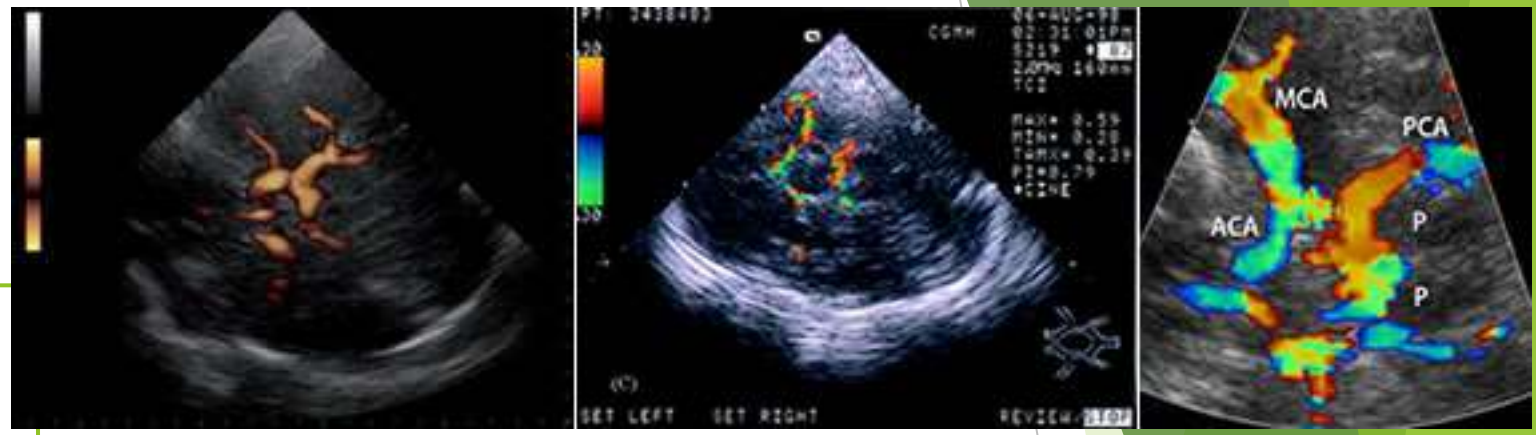


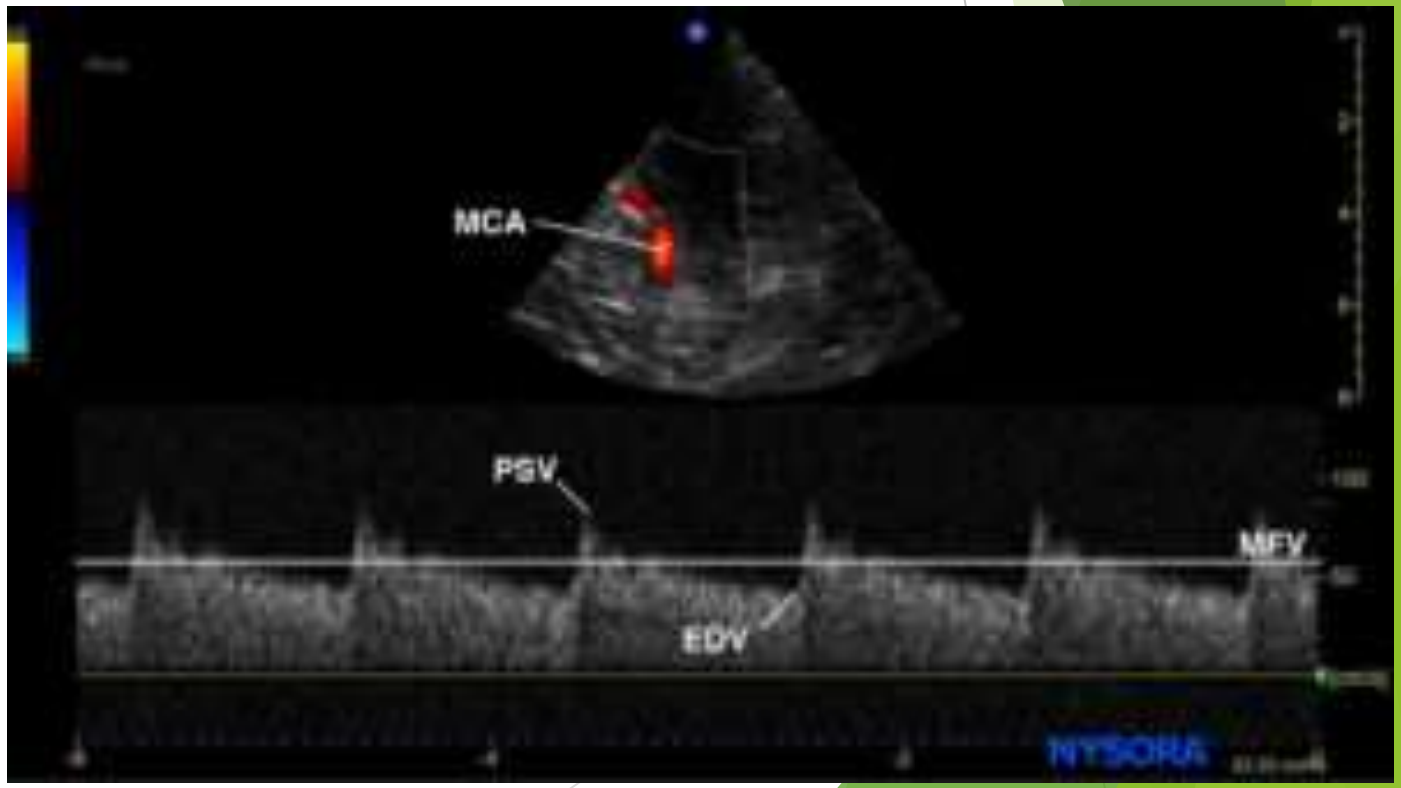
Schematic drawings of typical perfusion patterns



Imokava 2024

CEREBRAL BLOOD FLOW AND PERFUSION: TRANSCRANIAL ECODOPPLER AND ECOCOLORDOPPLER





Cerebrovascular Hemodynamics in Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of Transcranial Doppler Studies

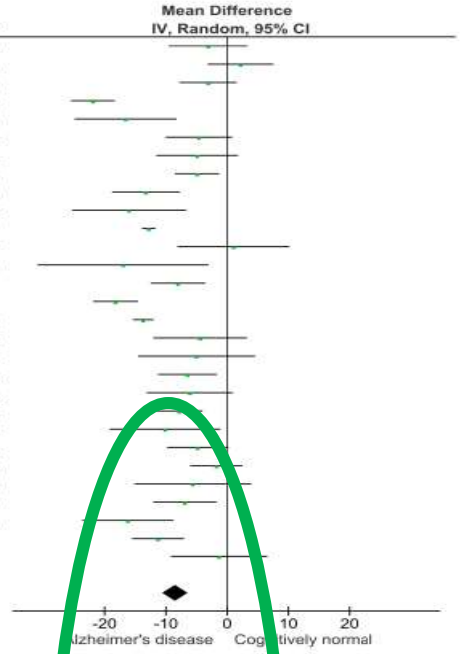
Dementia and Geriatric Cognitive Disorders

Fresnais 2023

a

Study or Subgroup	Alzheimer's disease Mean [cm/s]	SD [cm/s]	Total	Cognitively normal Mean [cm/s]	SD [cm/s]	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Foerstl 1989	47.6	9.8	9	50.7	1.3	14	3.3%	-3.10 [-9.54, 3.34]	1989
Provinciali 1990	56.8	11	20	54.6	6	25	3.7%	2.20 [-3.16, 7.56]	1990
Biedert 1990	47.6	9.8	17	50.7	1.3	27	3.9%	-3.10 [-7.78, 1.58]	1990
Bressi 1992	41.6	6.85	23	63.5	3.58	10	4.2%	-21.90 [-25.47, -18.33]	1992
Caamaño 1993	39.92	10.55	12	56.5	10.21	12	2.8%	-16.58 [-24.89, -8.27]	1993
Ries 1993	47.5	10.6	21	52.1	12.3	64	3.7%	-4.60 [-10.04, 0.84]	1993
Ni 1994	42.3	11.8	21	47.2	10	20	3.3%	-4.90 [-11.58, 1.78]	1994
Biedert 1995	45.5	8.8	23	50.4	1.2	36	4.2%	-4.90 [-8.52, -1.28]	1995
Franceschi 1995	46.55	10.24	17	59.81	6.09	20	3.6%	-13.26 [-18.81, -7.71]	1995
Doepp 2006	43	13	20	59	13	12	2.5%	-16.00 [-25.30, -6.70]	2006
Vicenzini 2007	39.3	3	60	52.1	3.2	62	4.7%	-12.80 [-13.90, -11.70]	2007
Lee 2007	56.14	14.2	17	55.1	12.9	17	2.6%	1.04 [-8.08, 10.16]	2007
Claassen 2009	38	7.1	9	55	19	8	1.6%	-17.00 [-30.96, -3.04]	2009
Roher 2011	32.83	10.93	42	40.85	10.87	50	4.0%	-8.02 [-12.49, -3.55]	2011
Kong 2011	36.5	6.8	30	54.7	8.9	40	4.2%	-18.20 [-21.88, -14.52]	2011
Gommer 2012	37.3	2.3	15	51	2.8	20	4.6%	-13.70 [-15.39, -12.01]	2012
Van Beek 2012	37.7	14.7	21	42.1	9.9	20	3.0%	-4.40 [-12.04, 3.24]	2012
Meel-van den Abeelen 2014	45	15	12	50	11	24	2.4%	-5.00 [-14.56, 4.56]	2014
Shim 2015	45.13	13.65	67	51.6	13.01	52	3.9%	-6.47 [-11.29, -1.65]	2015
Urbanova 2018	39.61	11.26	14	45.69	9.67	24	3.2%	-6.08 [-13.13, 0.97]	2018
De Heus 2018	38.8	10.4	53	46.6	8.93	47	4.2%	-7.80 [-11.59, -4.01]	2018
Gongora-Rivera 2018	38.88	14.95	26	49	15.52	19	2.6%	-10.12 [-19.16, -1.08]	2018
Kouzuki 2018	20.4	11.5	42	25.2	7.8	18	3.8%	-4.80 [-9.81, 0.21]	2018
Zhou 2019	61.37	0.36	31	63.13	11.89	30	4.0%	-1.76 [-6.02, 2.50]	2019
Albatwan 2019	49	8.6	10	54.6	12.1	9	2.5%	-5.60 [-15.13, 3.93]	2019
Cipollini 2019	45.1	8.6	35	52	9.1	17	3.7%	-6.90 [-12.08, -1.72]	2019
Battistella 2020	32.2	10.2	31	48.4	10.5	10	3.0%	-16.20 [-23.63, -8.77]	2020
Liu 2021	45.83	4.72	30	57.1	10.92	30	4.0%	-11.27 [-15.53, -7.01]	2021
Diomedi 2021	49.71	13.8	37	51.02	13.66	17	2.9%	-1.31 [-9.18, 6.56]	2021
Total (95% CI)			**765**			**754**	**100.0%**	**-8.42 [-10.56, -6.28]**	

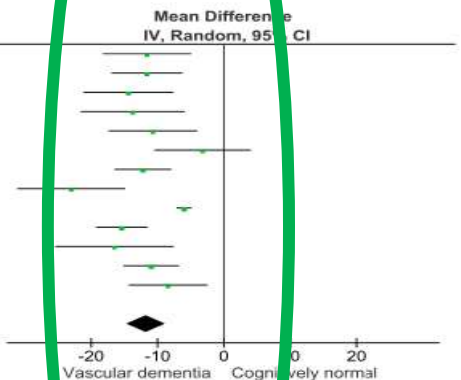
Heterogeneity: Tau² = 24.97; Chi² = 190.24, df = 28 (P < 0.00001); I² = 85%
Test for overall effect: Z = 7.71 (P < 0.00001)



b

Study or Subgroup	Vascular dementia Mean [cm/s]	SD [cm/s]	Total	Cognitively normal Mean [cm/s]	SD [cm/s]	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Foerstl 1989	39.1	10.2	9	50.7	1.3	14	7.1%	-11.60 [-18.30, -4.90]	1989
Biedert 1990	39.1	10.2	14	50.7	1.3	27	8.2%	-11.60 [-16.97, -6.23]	1990
Provinciali 1990	40.2	14.5	20	54.6	6	25	7.0%	-14.40 [-21.18, -7.62]	1990
Caamaño 1993	42.75	9.37	12	56.5	10.21	12	6.2%	-13.75 [-21.59, -5.91]	1993
Ries 1993	41.4	12.6	17	52.1	12.3	64	7.1%	-10.70 [-17.40, -4.00]	1993
Ni 1994	44	12.9	19	47.2	10	20	6.6%	-3.20 [-10.47, 4.07]	1994
Biedert 1995	38.2	9.5	19	50.4	1.2	36	9.1%	-12.20 [-16.49, -7.91]	1995
Doepp 2006	36	8	20	59	13	12	6.0%	-23.00 [-31.15, -14.85]	2006
Vicenzini 2007	46.1	3.2	58	52.1	3.2	62	11.0%	-6.00 [-7.15, -4.85]	2007
Kong 2011	39.3	8.2	34	54.7	8.9	40	9.4%	-15.40 [-19.30, -11.50]	2011
Battistella 2020	31.9	10.8	12	48.4	10.5	10	5.5%	-16.50 [-25.43, -7.57]	2020
Liu 2021	46.14	5.2	44	57.1	10.92	30	9.1%	-10.96 [-15.16, -6.76]	2021
Staszewski 2021	38.4	10.4	20	46.8	8.7	20	7.7%	-8.40 [-14.34, -2.46]	2021
Total (95% CI)			**298**			**372**	**100.0%**	**-11.75 [-14.68, -8.82]**	

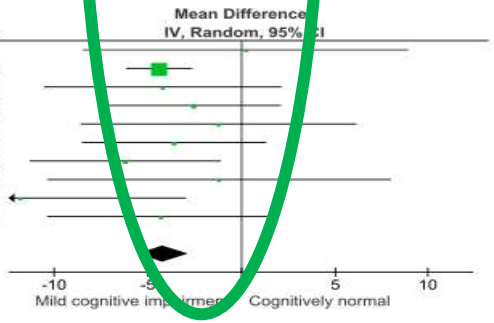
Heterogeneity: Tau² = 19.92; Chi² = 58.24, df = 12 (P < 0.00001); I² = 79%
Test for overall effect: Z = 7.86 (P < 0.00001)



c

Study or Subgroup	Mild cognitive impairment Mean [cm/s]	SD [cm/s]	Total	Cognitively normal Mean [cm/s]	SD [cm/s]	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Roher 2011	41.09	13.84	11	40.85	10.87	50	2.4%	0.24 [-8.48, 8.96]	2011
Gommer 2012	46.6	2.8	19	51	2.8	20	57.9%	-4.40 [-6.16, -2.64]	2012
Viola 2013	47.8	13.8	21	52	3.7	10	4.5%	-4.20 [-10.53, 2.13]	2013
Shim 2015	49.05	13.28	75	51.6	13.01	52	8.3%	-2.55 [-7.19, 2.09]	2015
Urbanova 2018	44.45	15.63	24	45.69	9.67	24	3.3%	-1.24 [-8.59, 6.11]	2018
De Heus 2018	43	13.03	37	46.6	8.93	47	7.4%	-3.60 [-8.51, 1.31]	2018
Kouzuki 2018	19	8.2	20	25.2	7.8	18	6.9%	-6.20 [-11.29, -1.11]	2018
Albatwan 2019	53.4	6.7	8	54.6	12.1	9	2.1%	-1.20 [-10.37, 7.97]	2019
Battistella 2020	36.6	12.9	18	48.4	10.5	10	2.3%	-11.80 [-20.62, -2.98]	2020
Tomoto 2020	48.7	9	53	53	13.3	22	4.9%	-4.30 [-10.36, 1.76]	2020
Total (95% CI)			**286**			**262**	**100.0%**	**-4.19 [-5.52, -2.85]**	

Heterogeneity: Tau² = 0.00; Chi² = 6.07, df = 9 (P = 0.73); I² = 0%
Test for overall effect: Z = 6.13 (P < 0.00001)



Dementia and Geriatric Cognitive Disorders

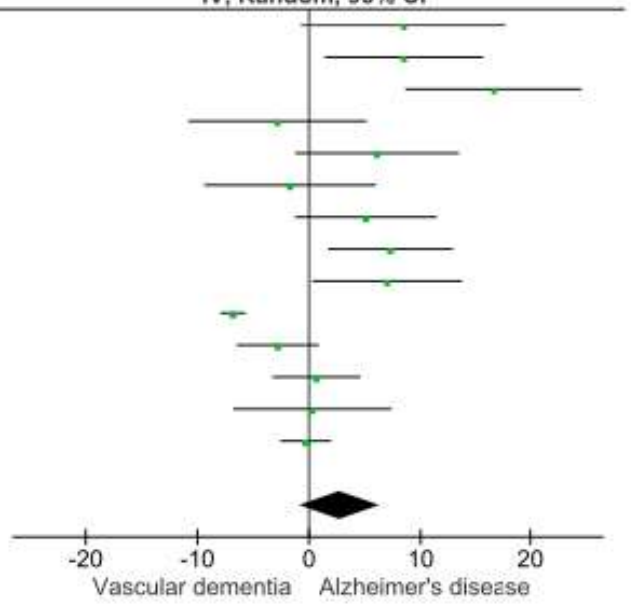
Cerebrovascular Hemodynamics in Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of Transcranial Doppler Studies

	Alzheimer's disease			Vascular dementia				Mean Difference	
Study or Subgroup	Mean [cm/s]	SD [cm/s]	Total	Mean [cm/s]	SD [cm/s]	Total	Weight	IV, Random, 95% CI	Year
Foerstl 1989	47.6	9.8	9	39.1	10.2	9	5.6%	8.50 [-0.74, 17.74]	1989
Biedert 1990	47.6	9.8	17	39.1	10.2	14	6.7%	8.50 [1.41, 15.59]	1990
Provinciali 1990	56.8	11	20	40.2	14.5	20	6.2%	16.60 [8.62, 24.58]	1990
Caamaño 1993	39.92	10.55	12	42.75	9.37	12	6.2%	-2.83 [-10.81, 5.15]	1993
Ries 1993	47.5	10.6	24	41.4	12.6	17	6.6%	6.10 [-1.24, 13.44]	1993
Ni 1994	42.3	11.8	21	44	12.9	19	6.4%	-1.70 [-9.39, 5.99]	1994
Rundek 1995	42.45	12.81	22	37.35	9.49	30	7.1%	5.10 [-1.24, 11.44]	1995
Biedert 1995	45.5	8.8	23	38.2	9.5	19	7.4%	7.30 [1.72, 12.88]	1995
Doepp 2006	43	13	20	36	8	20	6.9%	7.00 [0.31, 13.69]	2006
Vicenzini 2007	39.3	3	60	46.1	3.2	58	9.0%	-6.80 [-7.92, -5.68]	2007
Kong 2011	36.5	6.8	30	39.3	8.2	34	8.3%	-2.80 [-6.48, 0.88]	2011
Gao 2013	39.34	6.21	26	38.67	7.67	23	8.2%	0.67 [-3.27, 4.61]	2013
Battistella 2020	32.2	10.2	31	31.9	10.8	12	6.7%	0.30 [-6.79, 7.39]	2020
Liu 2021	45.83	4.72	30	46.14	5.2	44	8.8%	-0.31 [-2.59, 1.97]	2021
Total (95% CI)			**345**			**331**	**100.0%**	**2.79 [-0.78, 6.35]**	

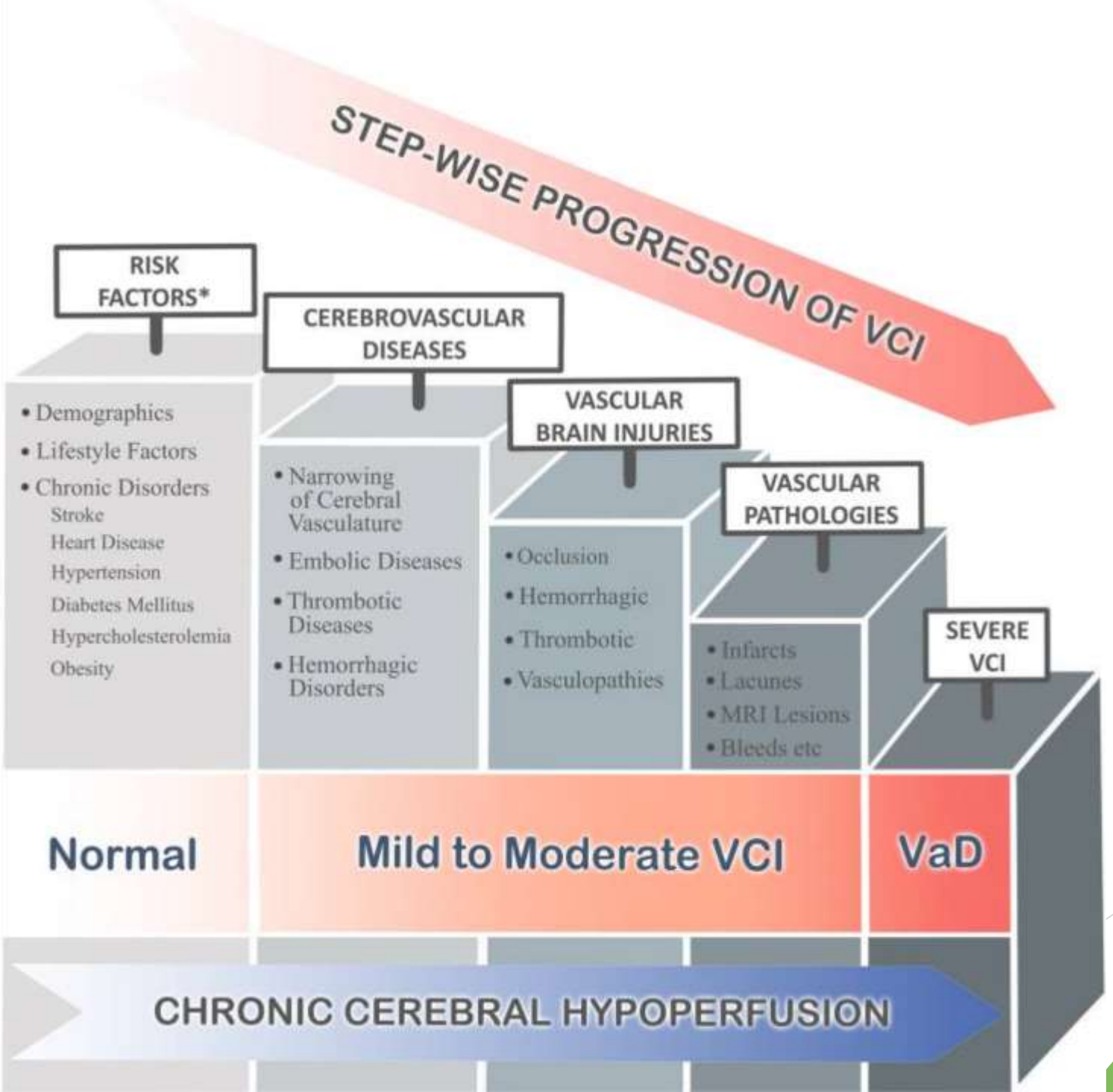
Heterogeneity: Tau² = 36.43; Chi² = 125.96, df = 13 (P < 0.00001); I² = 90%

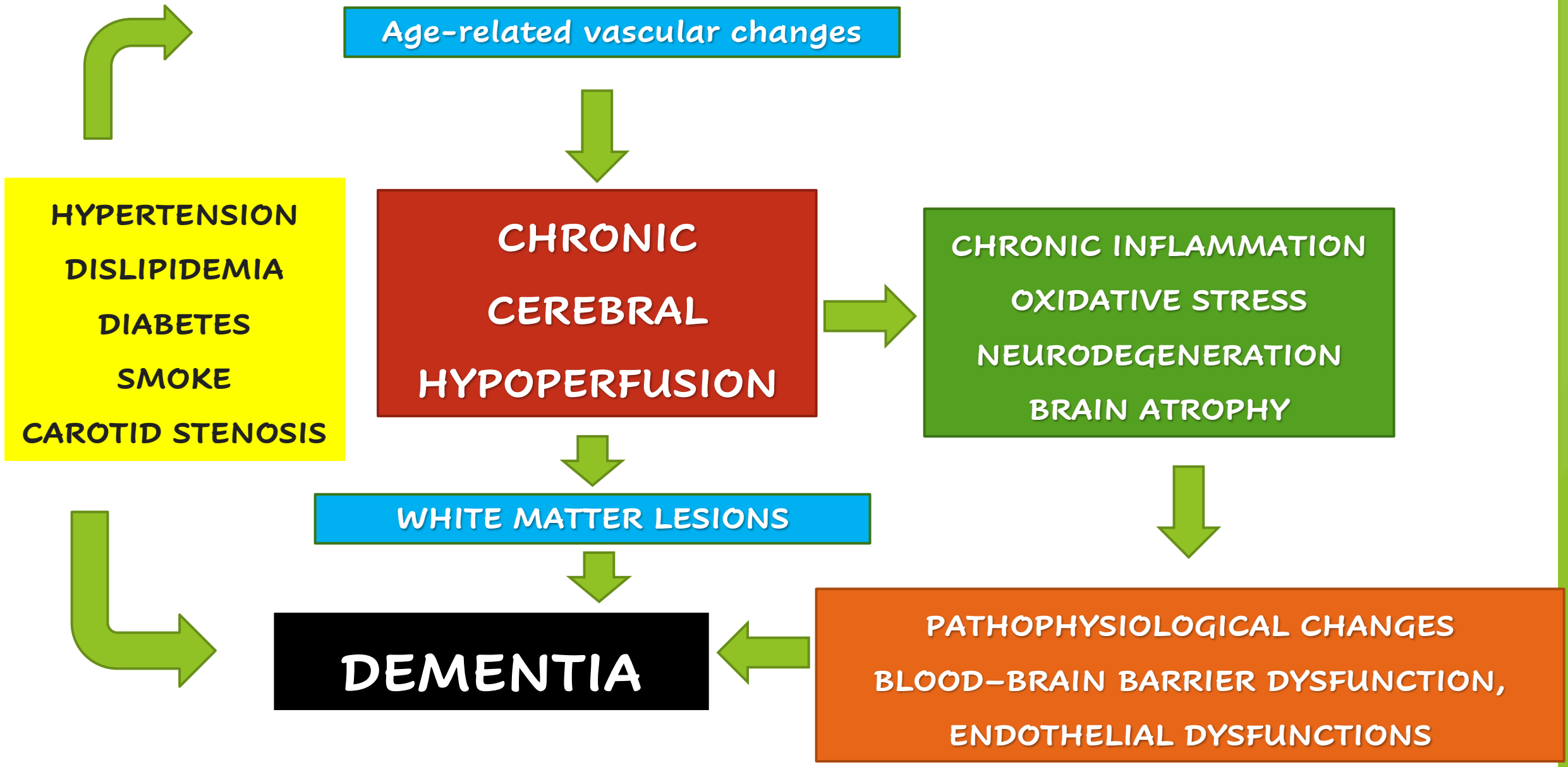
Test for overall effect: Z = 1.53 (P = 0.13)

d



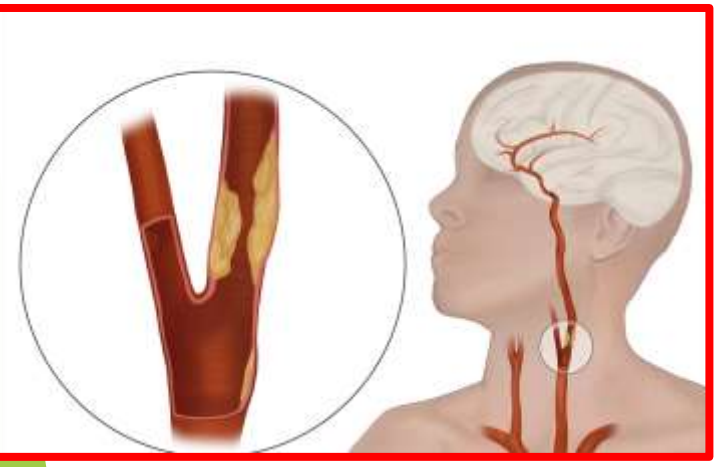
Fresnais 2023

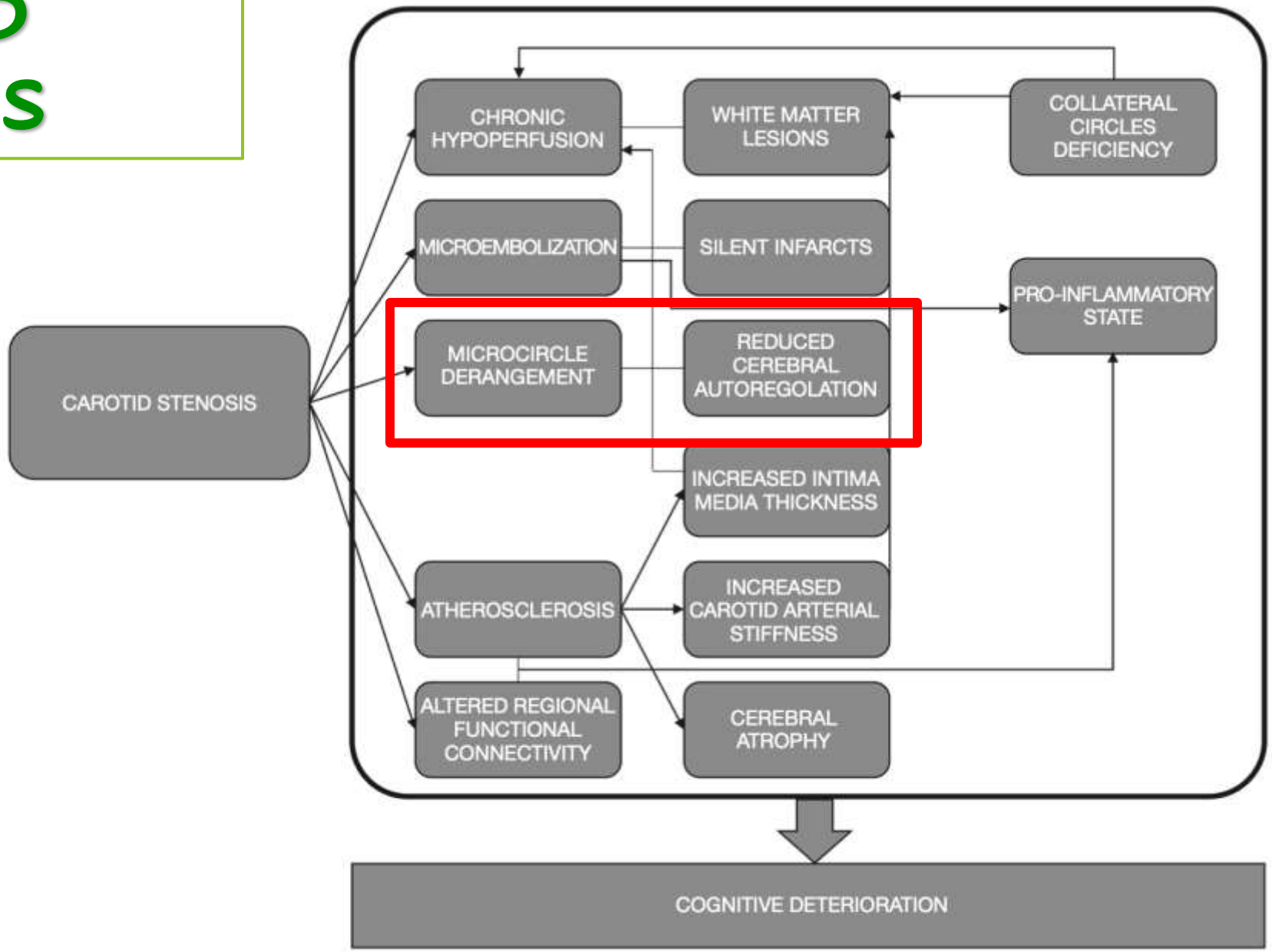

STEP-WISE PROGRESSION OF VCI
RISK FACTORS*
CEREBROVASCULAR DISEASES
VASCULAR BRAIN INJURIES
VASCULAR PATHOLOGIES
SEVERE VCI
• Demographics
• Lifestyle Factors
• Chronic Disorders
Stroke
Heart Disease
Hypertension
Diabetes Mellitus
Hypercholesterolemia
Obesity
• Narrowing of Cerebral Vasculature
• Embolic Diseases
• Thrombotic Diseases
• Hemorrhagic Disorders
• Occlusion
• Hemorrhagic
• Thrombotic
• Vasculopathies
• Infarcts
• Lacunes
• MRI Lesions
• Bleeds etc
Normal
Mild to Moderate VCI
VaD
CHRONIC CEREBRAL HYPOPERFUSION



Ungvari 2010

CAROTID STENOSIS



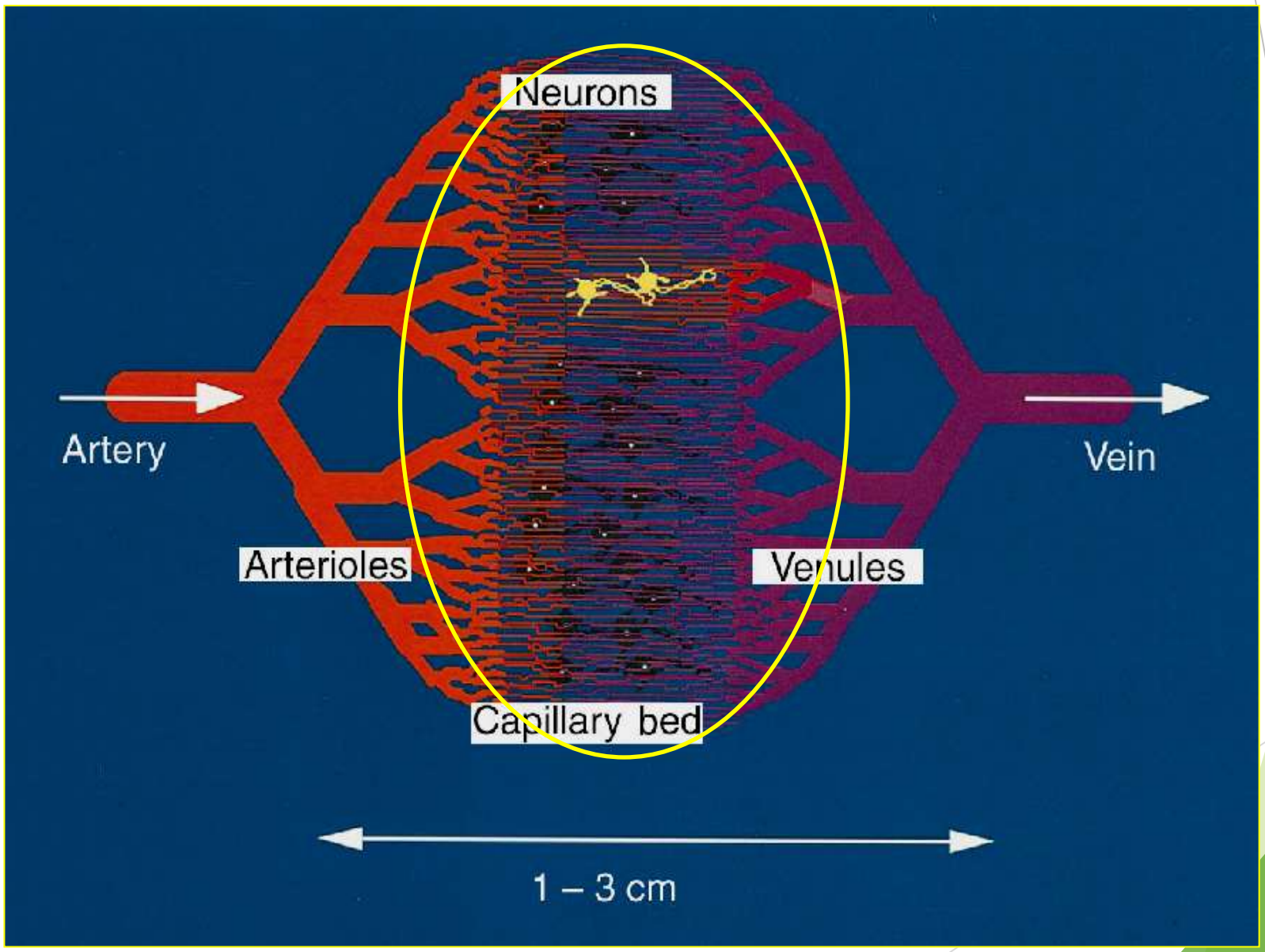


ATM | ANNALS OF TRANSLATIONAL MEDICINE

Figure 1 Proposed mechanisms for the association between carotid stenosis and cognitive impairment.

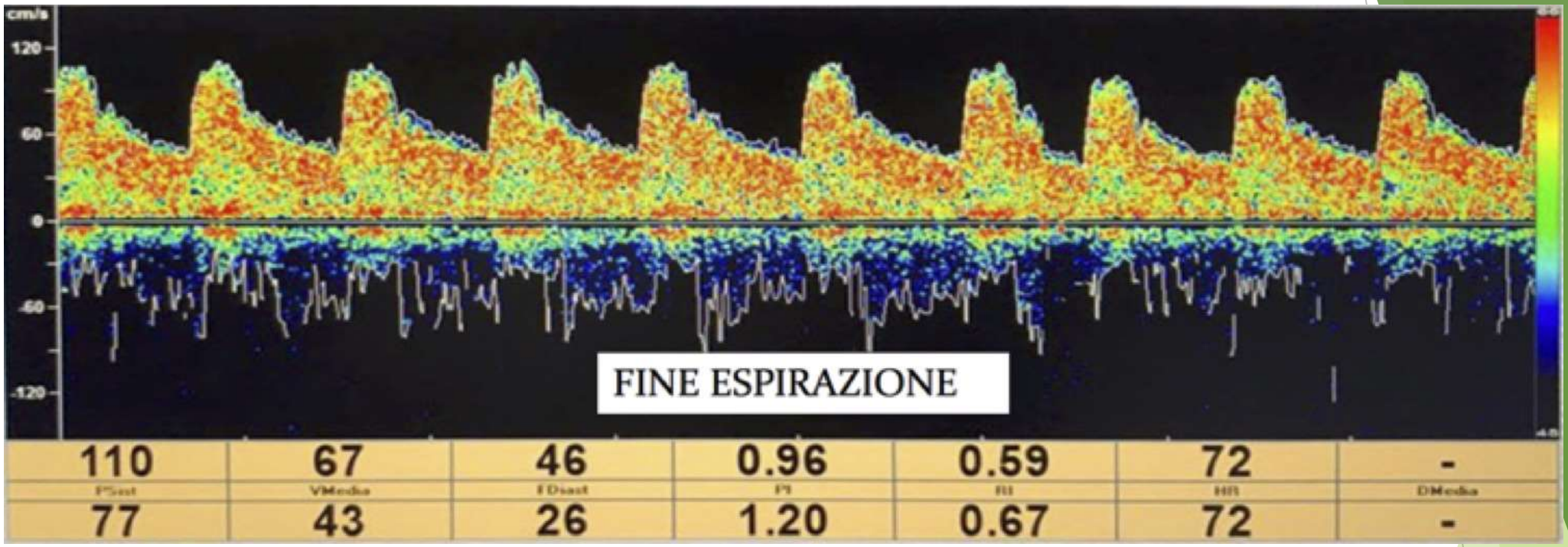
Viticchi 2021

CEREBROVASCULAR REACTIVITY



CO_2

BREATH-HOLDING INDEX (BHI)



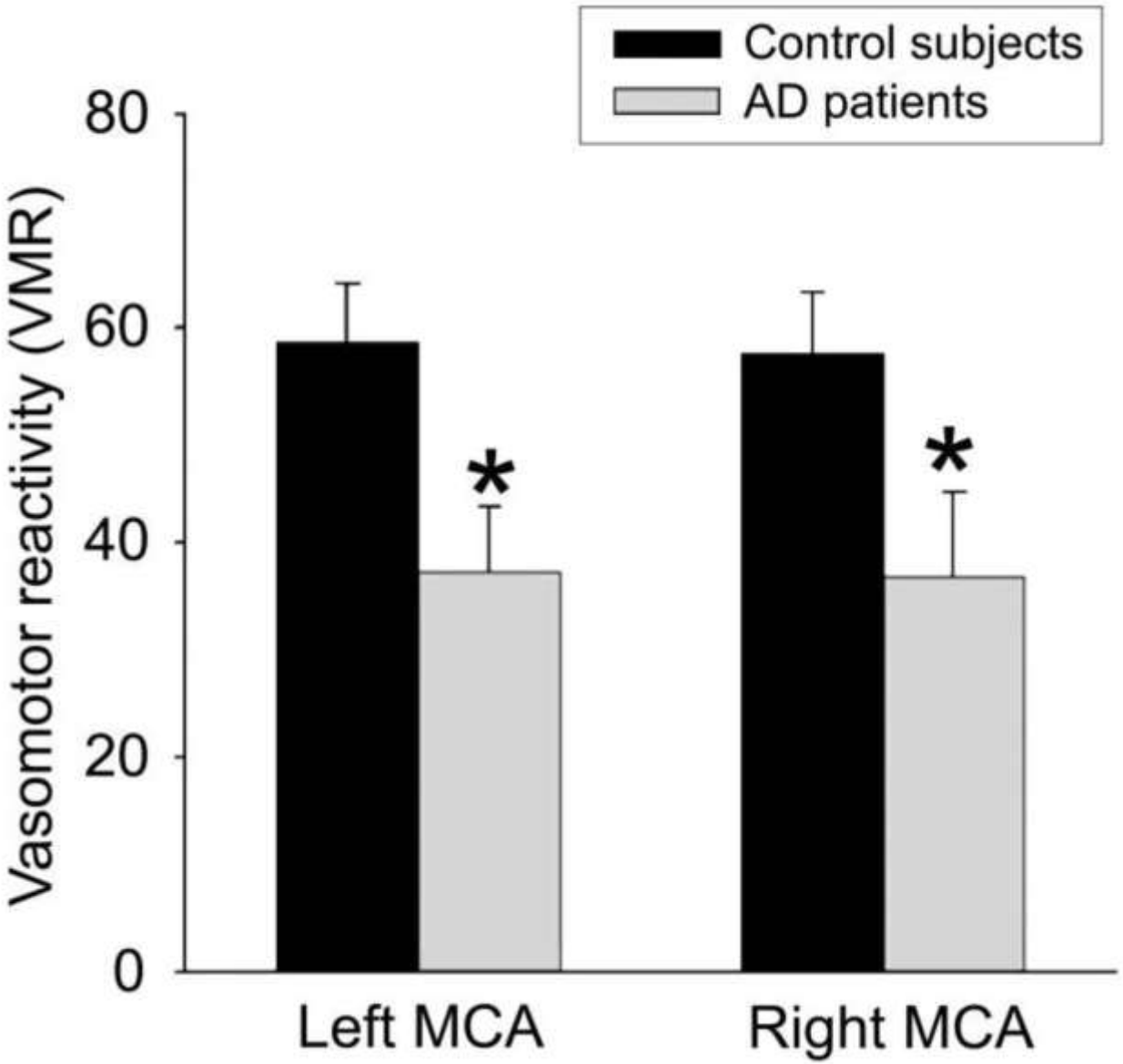
- BHI= (MFV alla fine dell'apnea- MFV a riposo/ MFV a riposo) x 100 / tempo di apnea in secondi

MFV= mean flow velocity

Il valore di BHI≤ 0.69 è stato preso come cut-off patologico.

Silvestrini 1999

Decreased Vasomotor Reactivity in Alzheimer's Disease

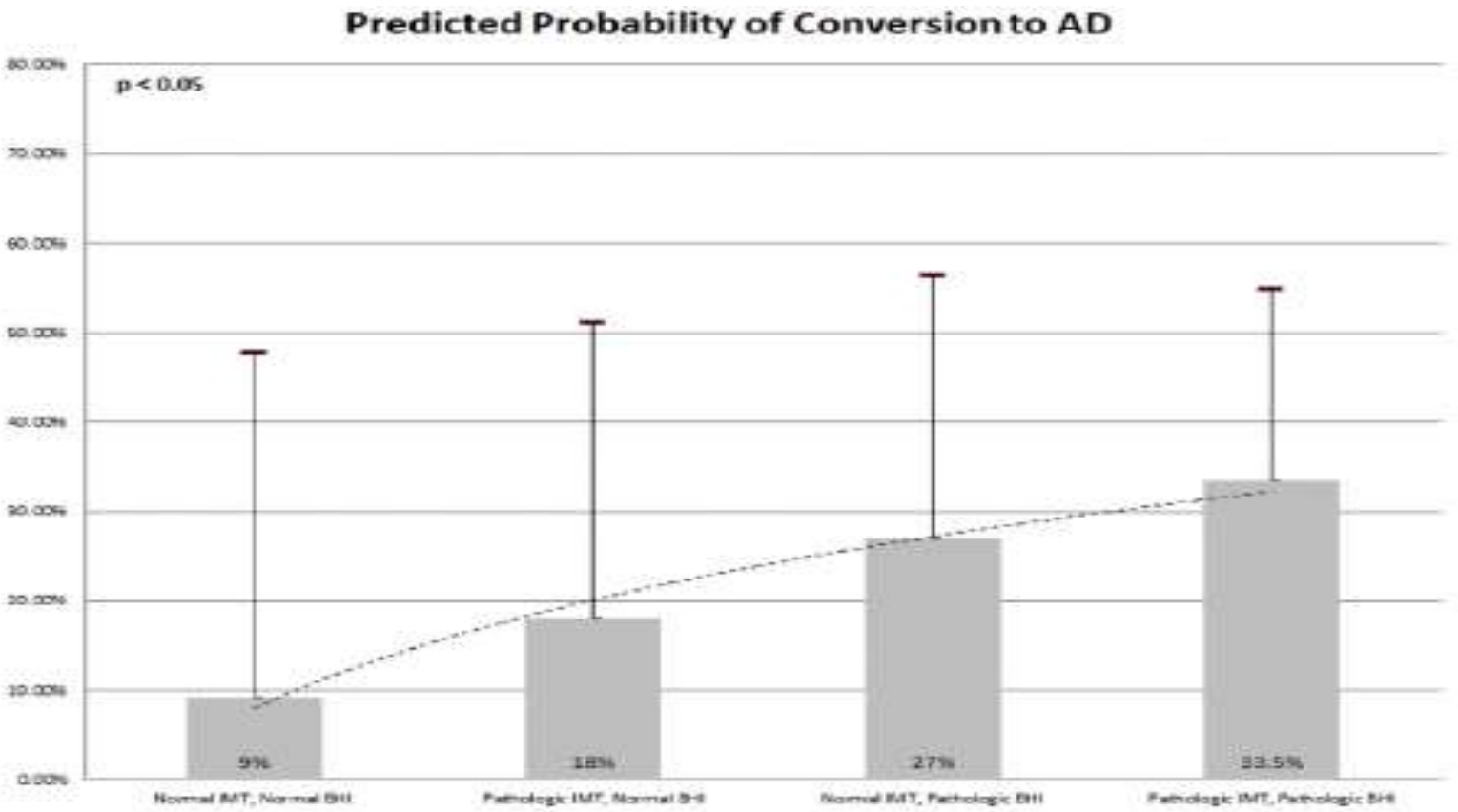


Soon-Tae 2007

NEUROBIOLOGY OF AGING

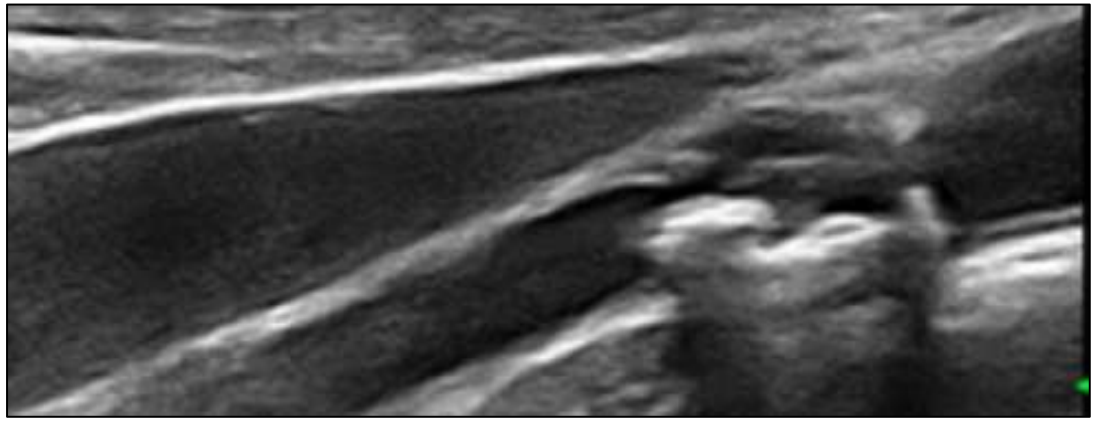
Vascular predictors of cognitive decline in patients with mild cognitive impairment

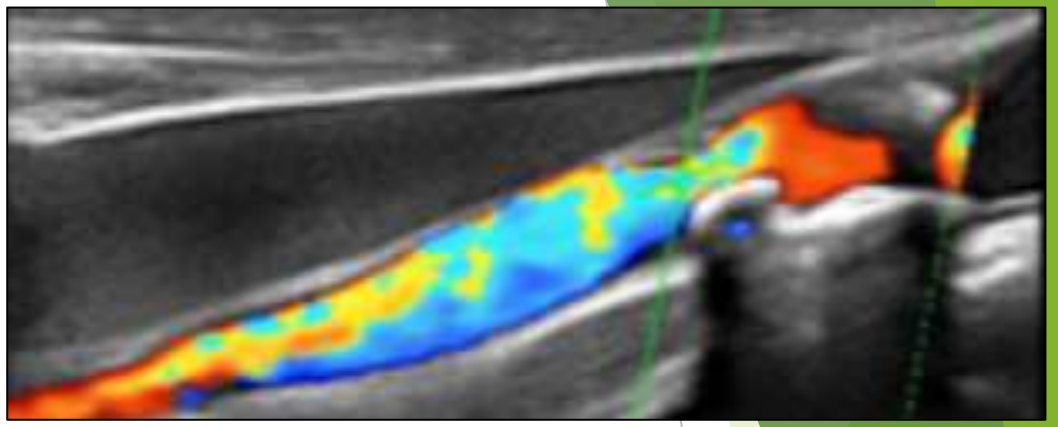
Giovanna Viticchi[a], Lorenzo Falsetti[b], Fabrizio Vernieri[c], Claudia Altamura[c], Marco Bartolini[a], Simona Luzzi[a], Leandro Provinciali[a], Mauro Silvestrini[a,*]

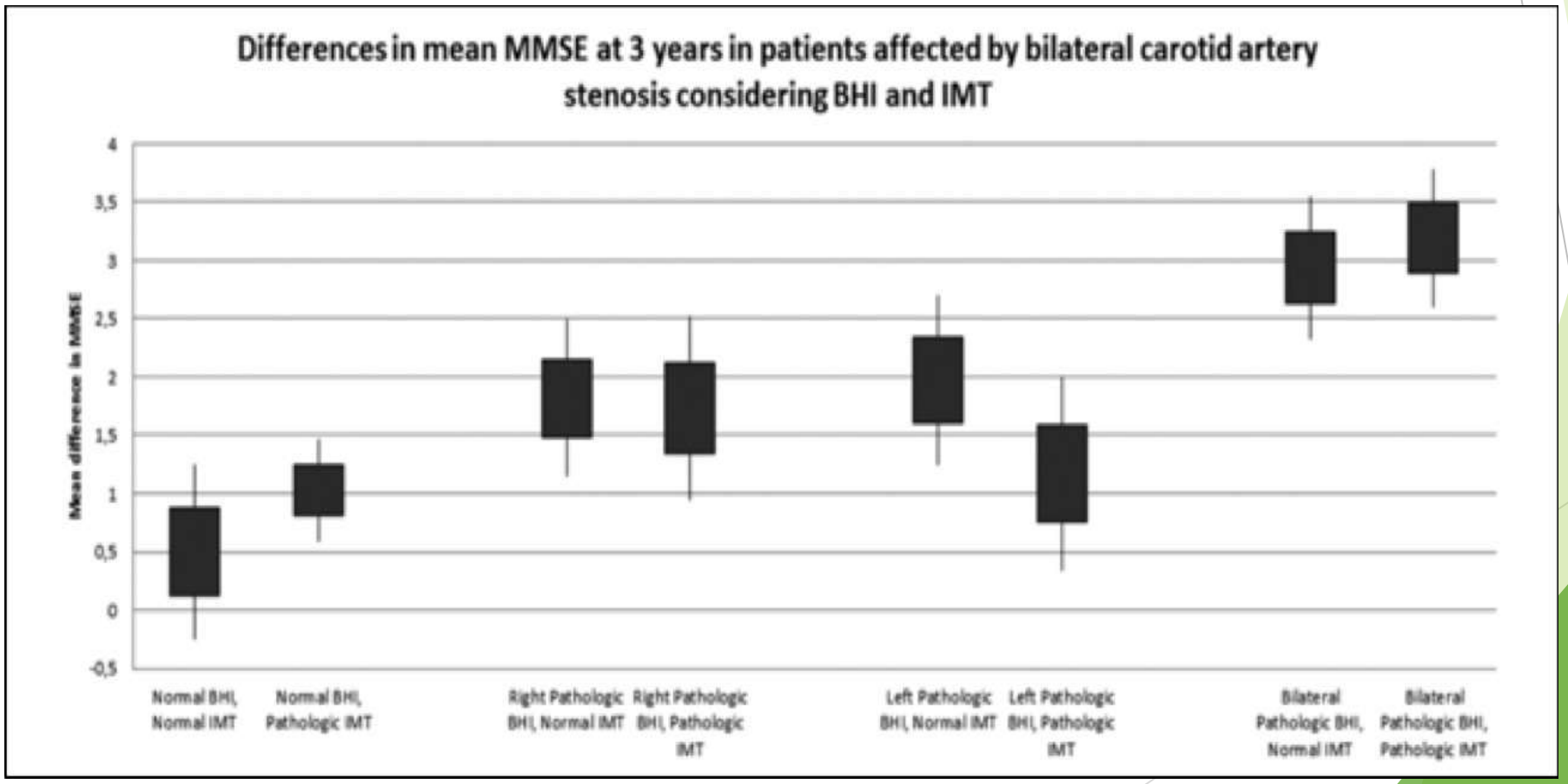


	(p < 0.05)	(p < 0.05)	(p < 0.05)	(p < 0.05)
P.Prob.	9.13%	18.05%	26.99%	33.50%
95%CI	1.09%-47.89%	4.41%-51.26%	9.51%-56.53%	17.07%-55.06%

Viticchi 2012





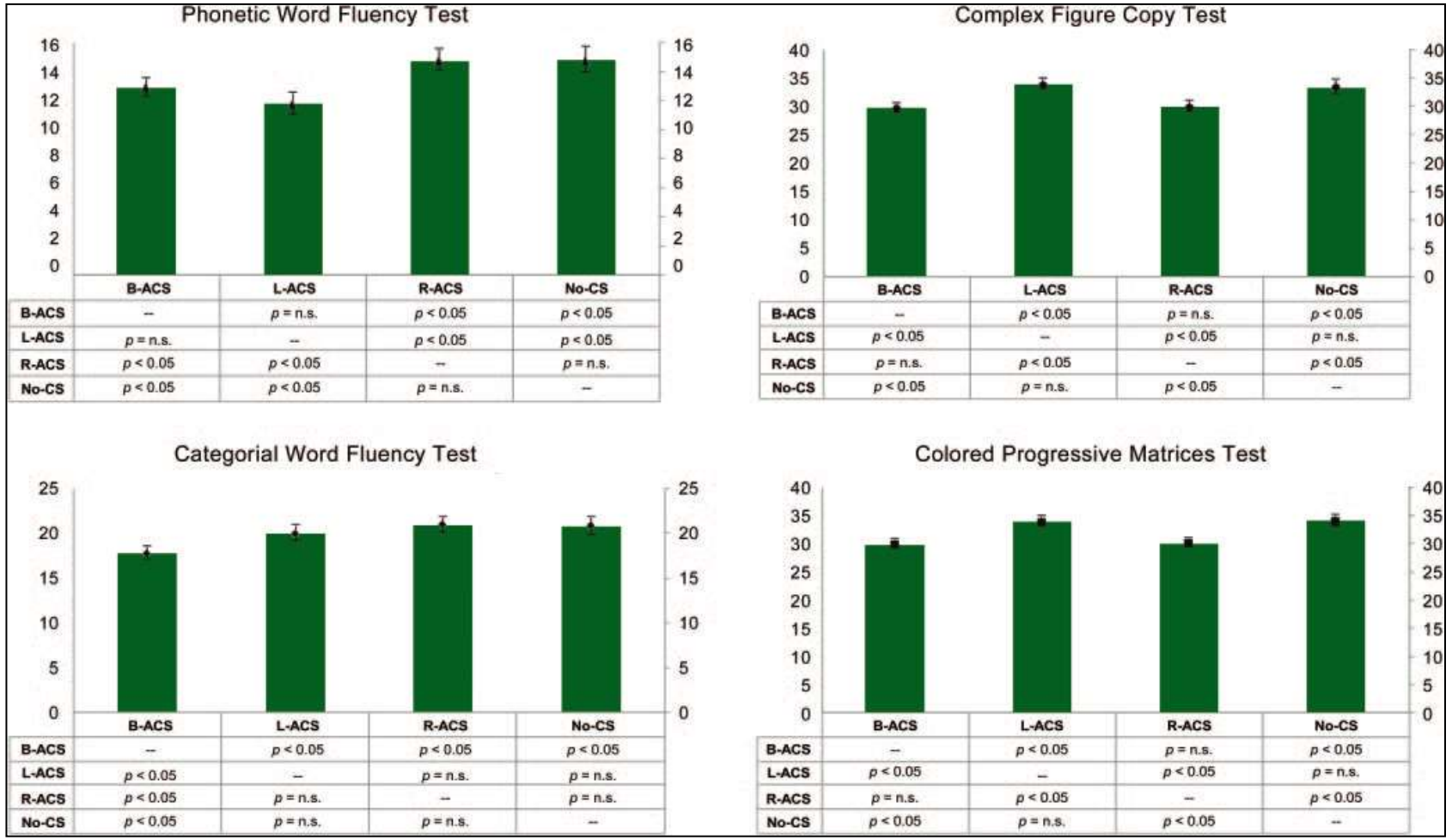

Differences in mean MMSE at 3 years in patients affected by bilateral carotid artery stenosis considering BHI and IMT
Mean difference in MMSE
4
3,5
3
2,5
2
1,5
1
0,5
0
-0,5
Normal BHI, Normal IMT
Normal BHI, Pathologic IMT
Right Pathologic BHI, Normal IMT
Right Pathologic BHI, Pathologic IMT
Left Pathologic BHI, Normal IMT
Left Pathologic BHI, Pathologic IMT
Bilateral Pathologic BHI, Normal IMT
Bilateral Pathologic BHI, Pathologic IMT

Stroke 2014

AMERICAN ACADEMY OF NEUROLOGY

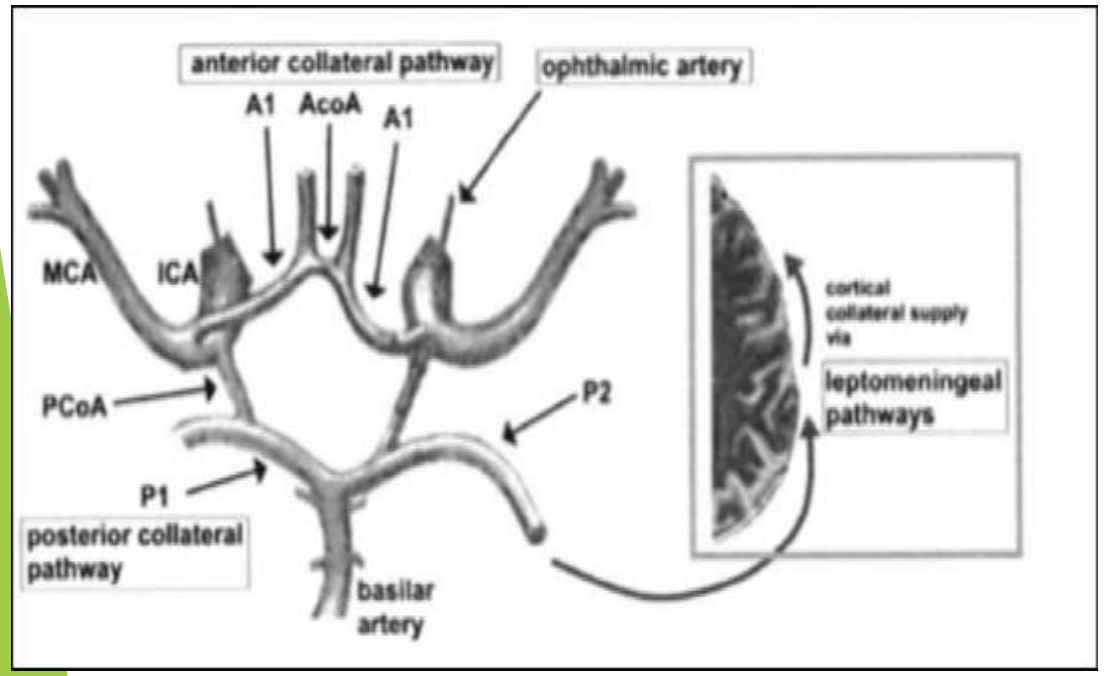
Cerebral hemodynamics and cognitive performance in bilateral asymptomatic carotid stenosis

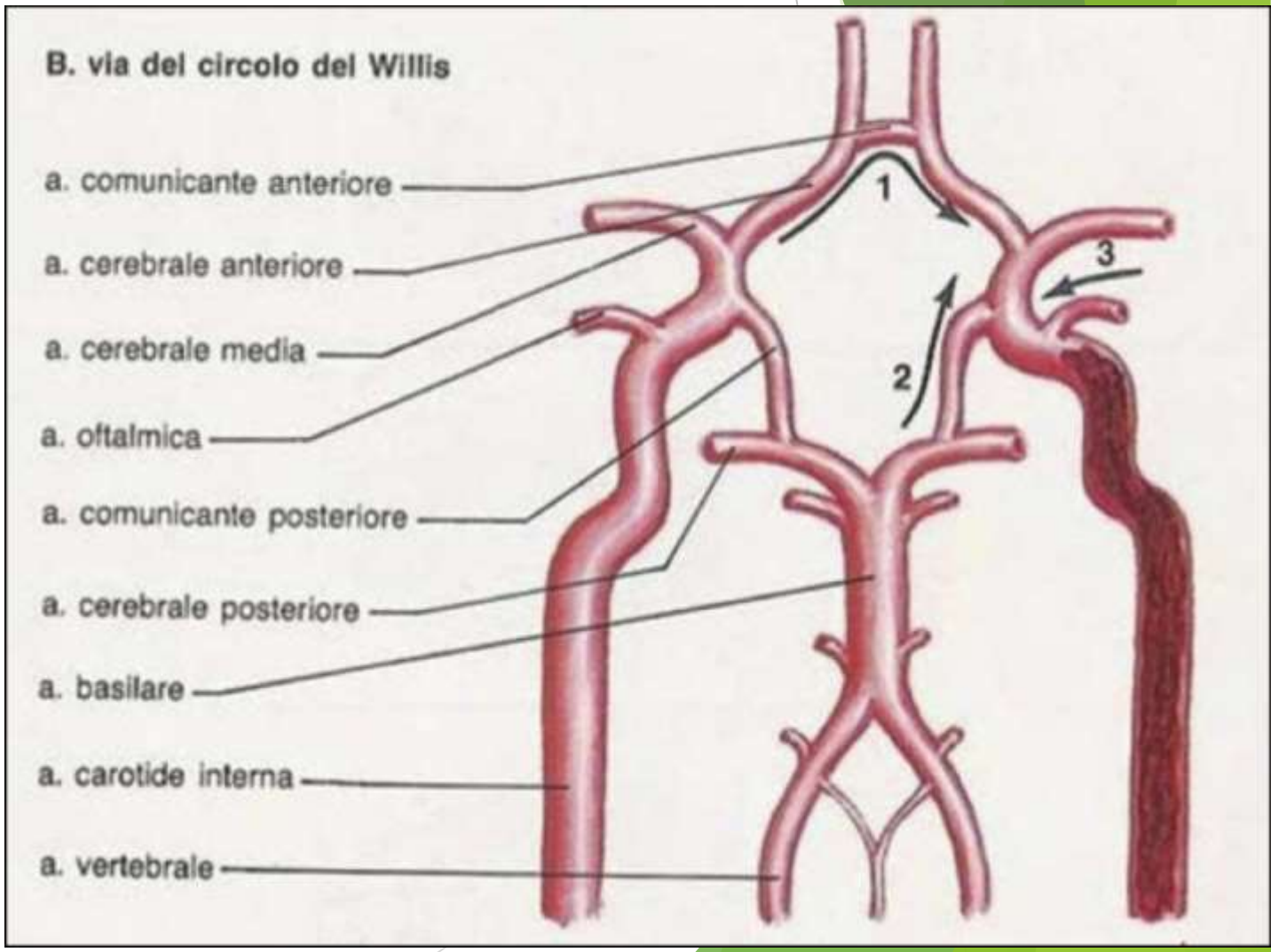
Clotilde Balucani, MD
Giovanna Viticchi, MD
Lorenzo Falsetti, MD
Mauro Silvestrini, MD



Balucani 2012

CAROTID OCCLUSION





➢ ECO-DOPPLER DEI TRONCHI SOVRAORTICI (TSA)

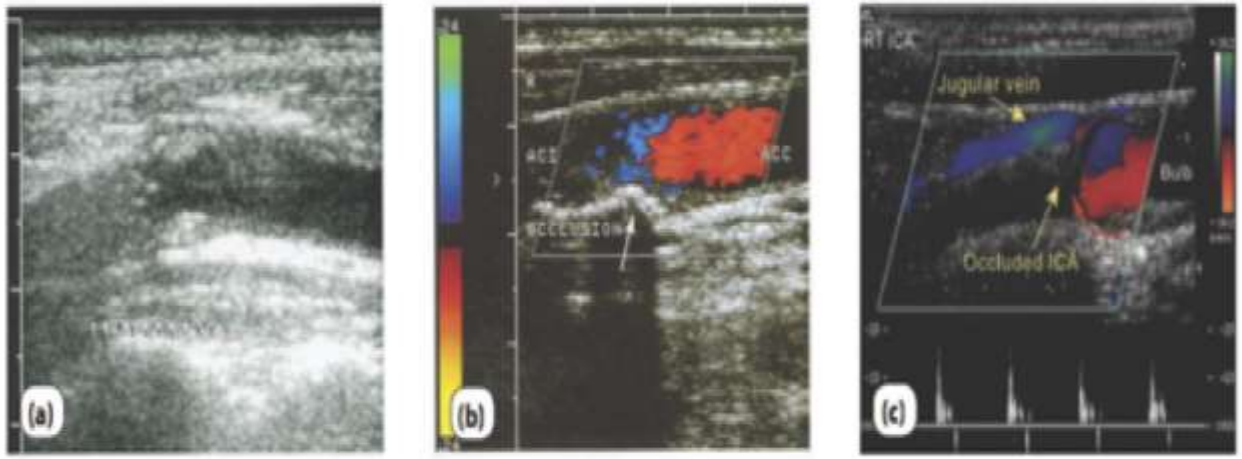
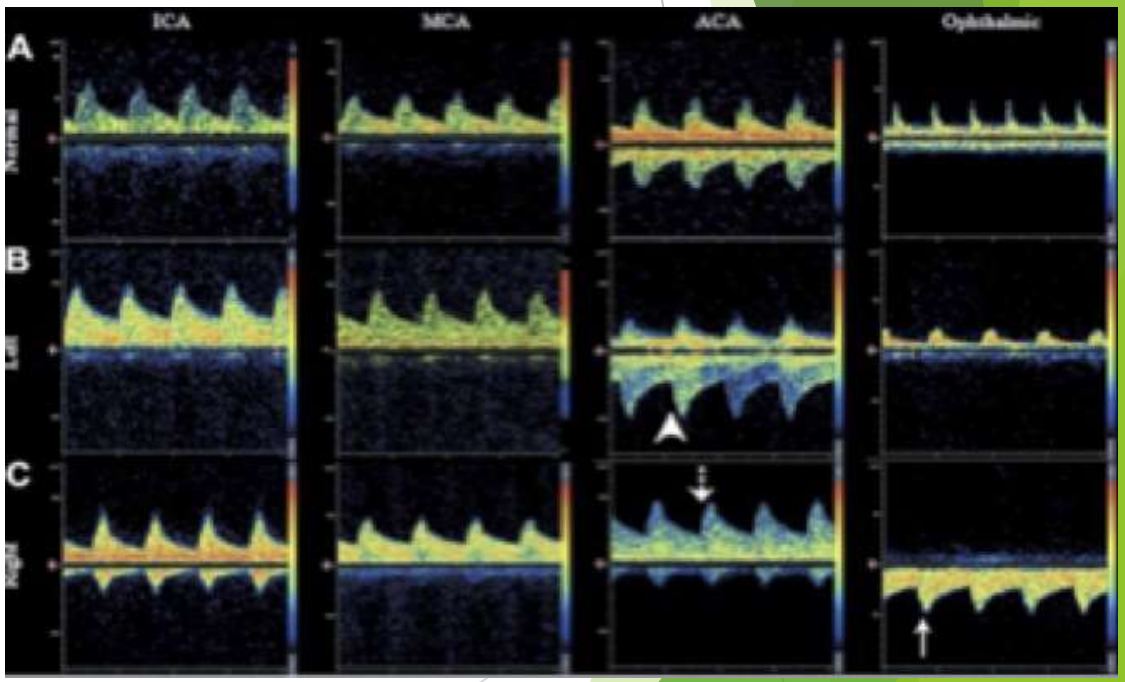


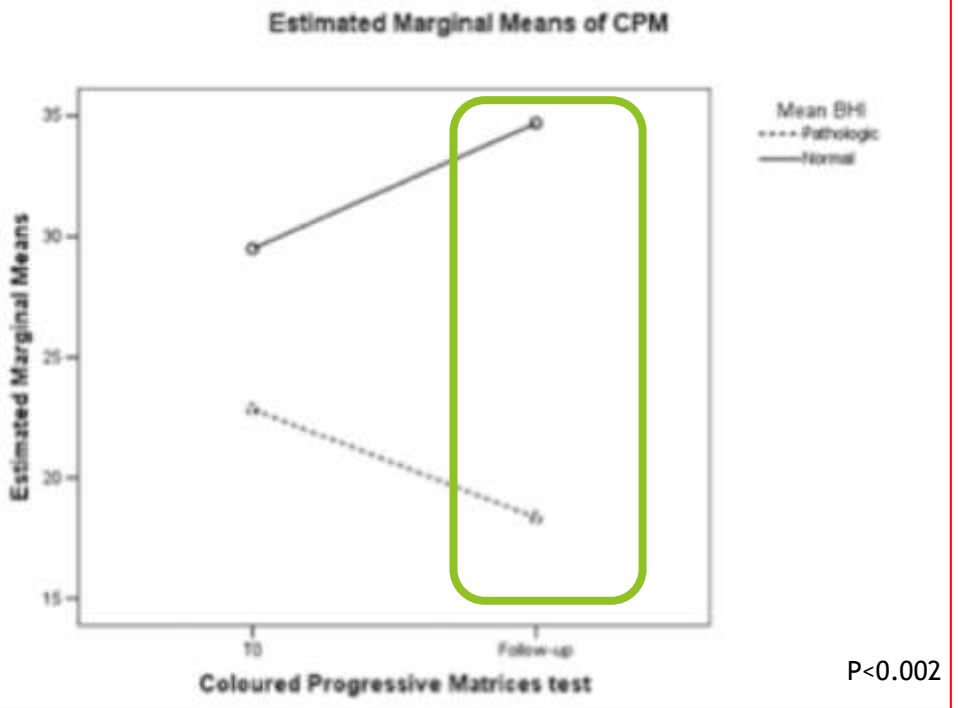
Figure 11. Occlusion of ICA. **(a)** In the case of an old occlusion, the occluded lumen can be well visualized in B-mode on account of the increased echogenicity. **(b)** In the case of a recently formed occlusion, the nonperfused lumen appears as a hypoechoic region in B-mode. The occlusion can only be detected by flow reversal using the color coding mode (arrow). **(c)** A biphasic Doppler signal can be recorded usually in the region of the reversed flow, just before the occluded segment (arrow).



➢ DOPPLER TRANSCRANICO (TCD)

Risultati

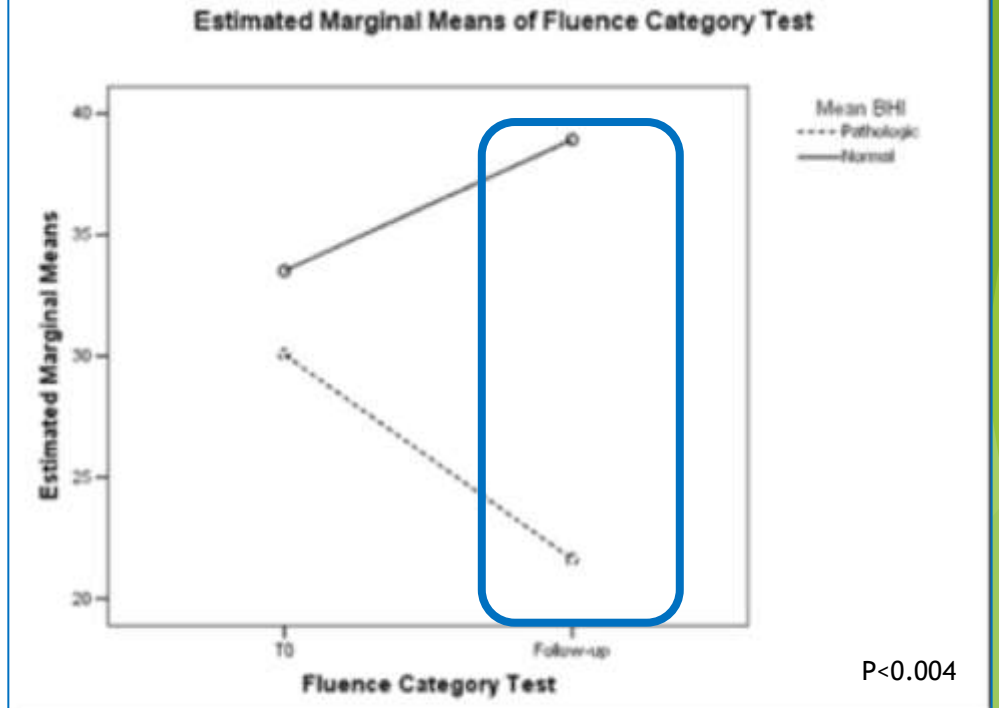
dx



P<0.002

MEAN BHI	TIME	MEAN	SE	95% CONFIDENCE INTERVAL	
				Lower	Upper
PATHOLOGIC	Baseline	2.504	0.36	1.689	3.319
	Follow-up	1.678	0.221	1.179	2.177
NORMAL	Baseline	4.487	0.736	2.823	6.151
	Follow-up	4.847	0.451	3.828	5.867

sx

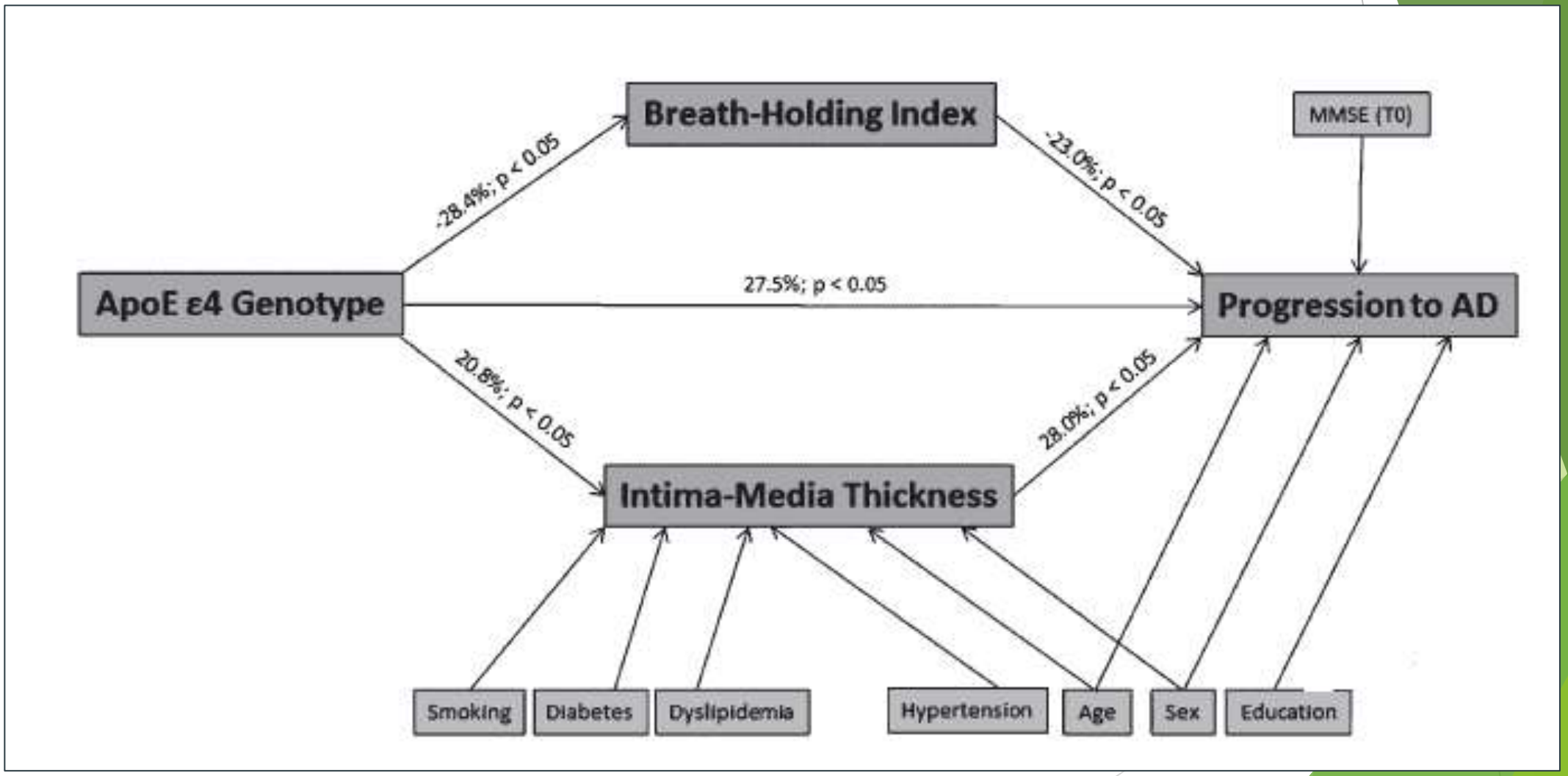


P<0.004

MEAN BHI	TIME	MEAN	SE	95% CONFIDENCE INTERVAL	
				Lower	Upper
PATHOLOGIC	Baseline	30.063	3.75	21.197	38.93
	Follow-up	21.625	2.334	16.107	27.143
NORMAL	Baseline	33.511	4.511	22.845	44.178
	Follow-up	38.925	2.807	32.287	45.563

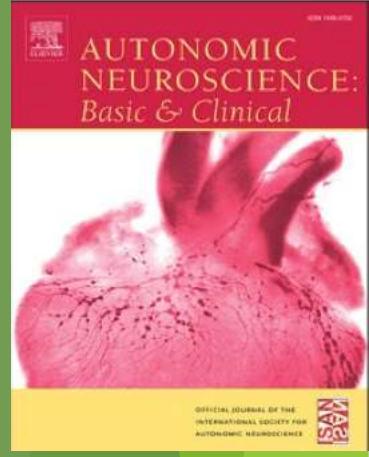
Viticchi 2021

MULTIFACTORIAL GENESIS



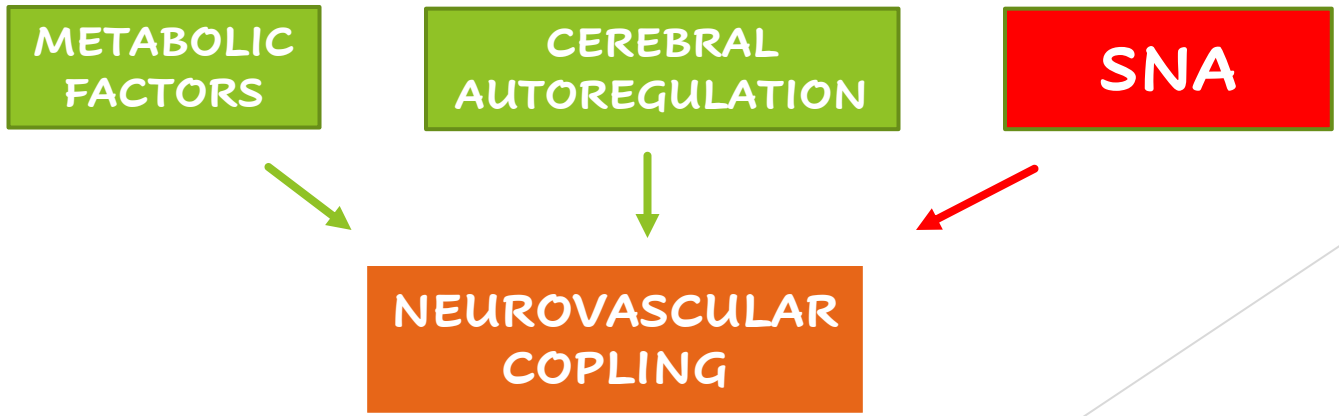
Viticchi 2014

The role of the autonomic nervous system in cerebral blood flow regulation in dementia: A review

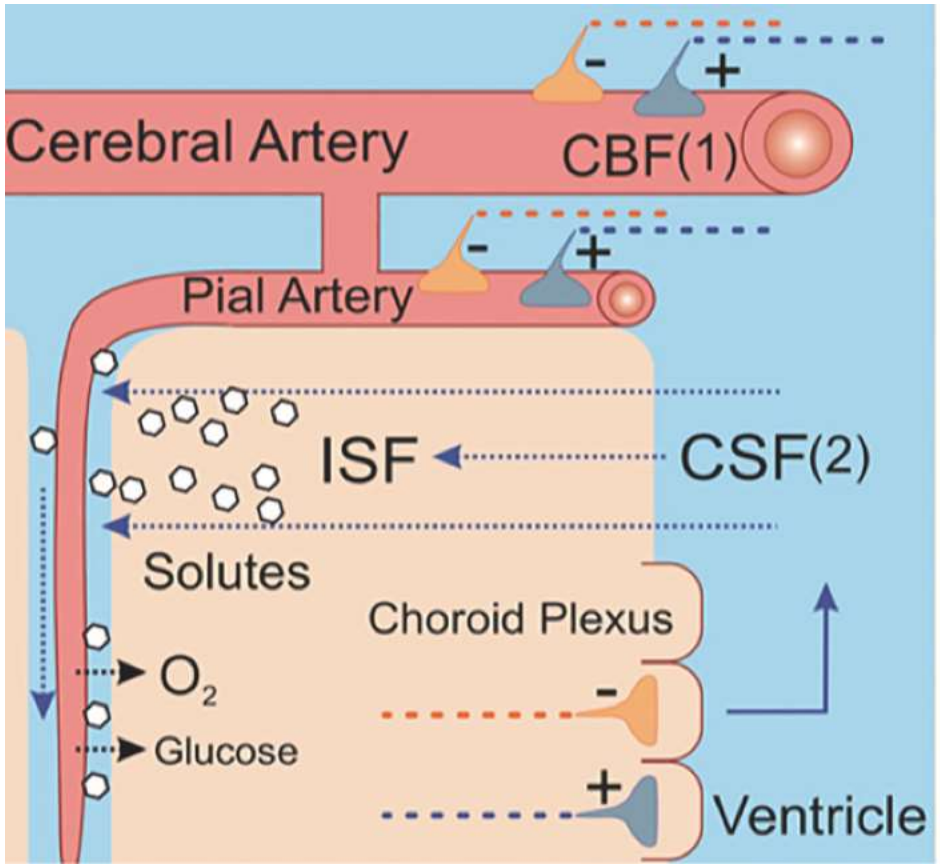


A B S T R A C T

In this review we will examine the role of the autonomic nervous system in the control of cerebral blood flow (CBF) in dementia. Worldwide, 55 million people currently live with dementia, and this figure will increase as the global population ages. Understanding the changes in vascular physiology in dementia could pave the way for novel therapeutic approaches. Reductions in CBF have been demonstrated in multiple dementia sub-types, in addition to increased cerebrovascular resistance and reduced vasoreactivity. Cerebral autoregulation (CA) is a key mechanism for the maintenance of cerebral perfusion, but remains largely intact in cognitive disorders, despite reductions in global and regional CBF. However, the tight coupling between neuronal activity and CBF (neurovascular coupling - NVC) is lost in dementia, which may be a key driver of cognitive dysfunction. Despite numerous studies investigating disturbances in the control of CBF in dementia, less is known about the specific mechanisms responsible for the observed changes. Disturbances could be related to one of a number of pathways and mechanisms including disruption of the autonomic component. In this review we will explore clinical and animal studies, which specifically investigated the autonomic component of CBF control in dementia, drawing on the clinical implications and potential for novel biomarker and therapeutic targets.



Beishon 2022



Autonomic innervation

Sympathetic

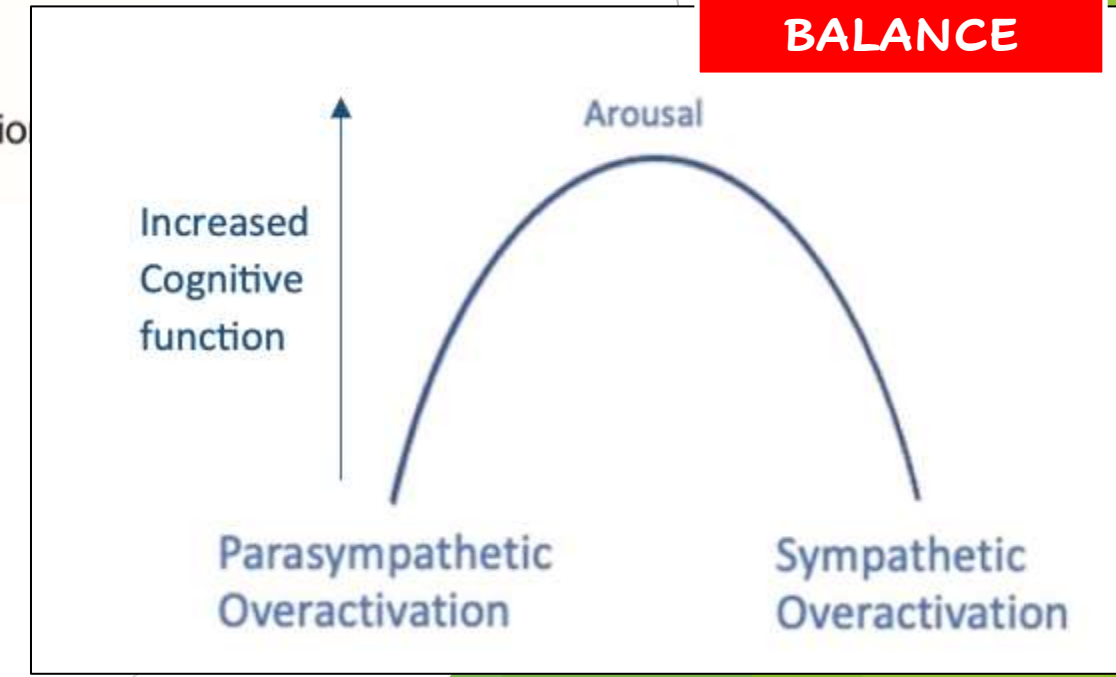
- ⊕ Aging
- ⊕ Cardiovascular disease
- ⊕ Diabetes

Parasympathetic

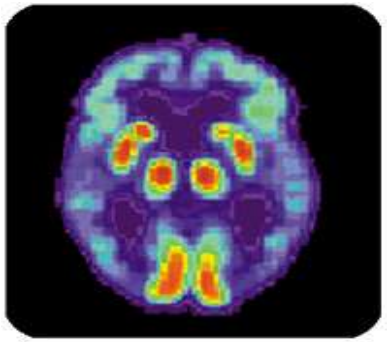
- ⊖ Aging
- ⊖ Cardiovascular disease
- ⊖ Diabetes

- ⊕ **Exercise**
- ⊕ Vagus Nerve Stimulatio

AUTONOMIC BALANCE



Beishon 2022



ALZHEIMER'S DISEASE

AMYLOID HYPOTESIS

- Abnormal APP cleavage
- Aβ deposition
- Senile plaques
- Neurodegeneration
- AD

VASCULAR HYPOTESIS

- Advanced ageing and vascular risk factor
- Brain hypoperfusion
- Neuroglial energy crisis
- Mild cognitive impairment
- Neurodegeneration
- AD

AUTONOMIC DYSFUNCTIONS IN CBF CONTROL

De La Torre 2000


GRAZIE
PER
L'ATTENZIONE!