EXPRESSION OF TIGHT JUNCTION PROTEINS IN DEMENTIA BRAINS

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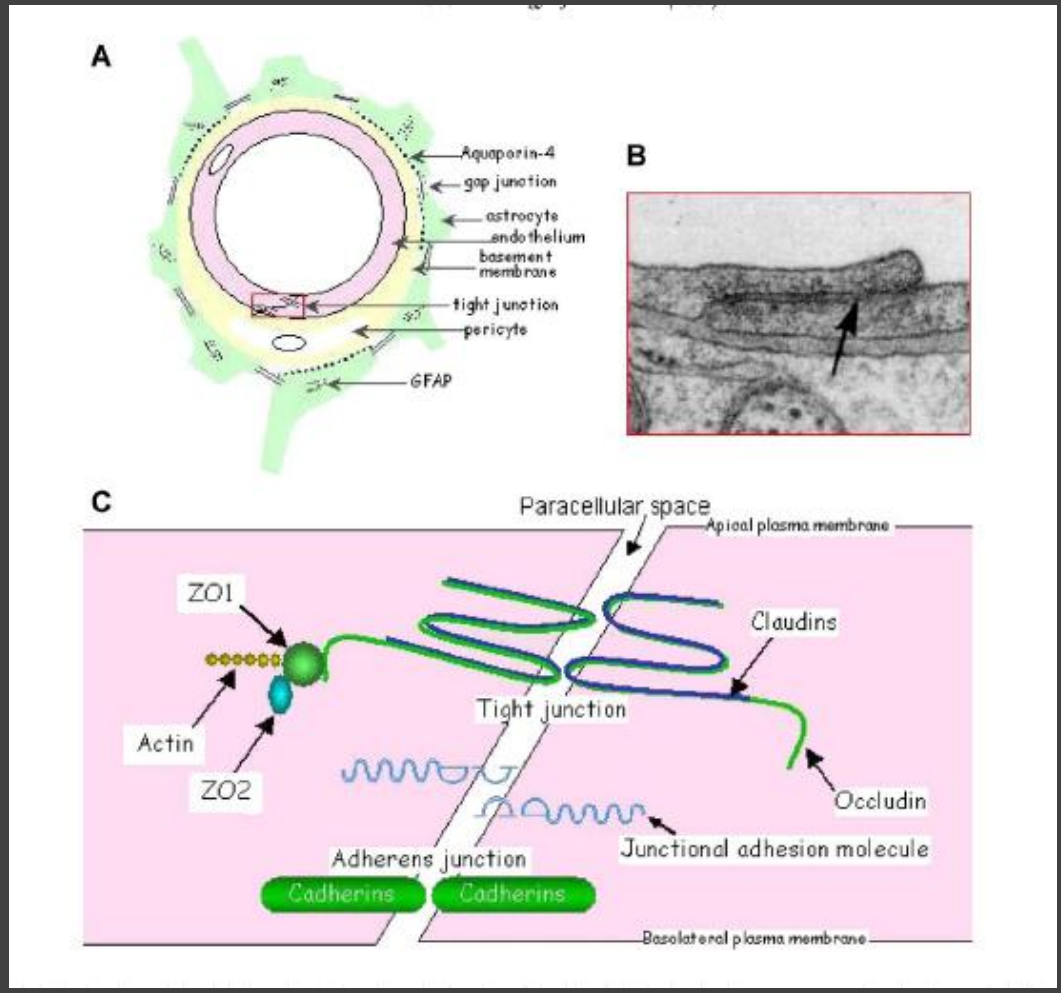
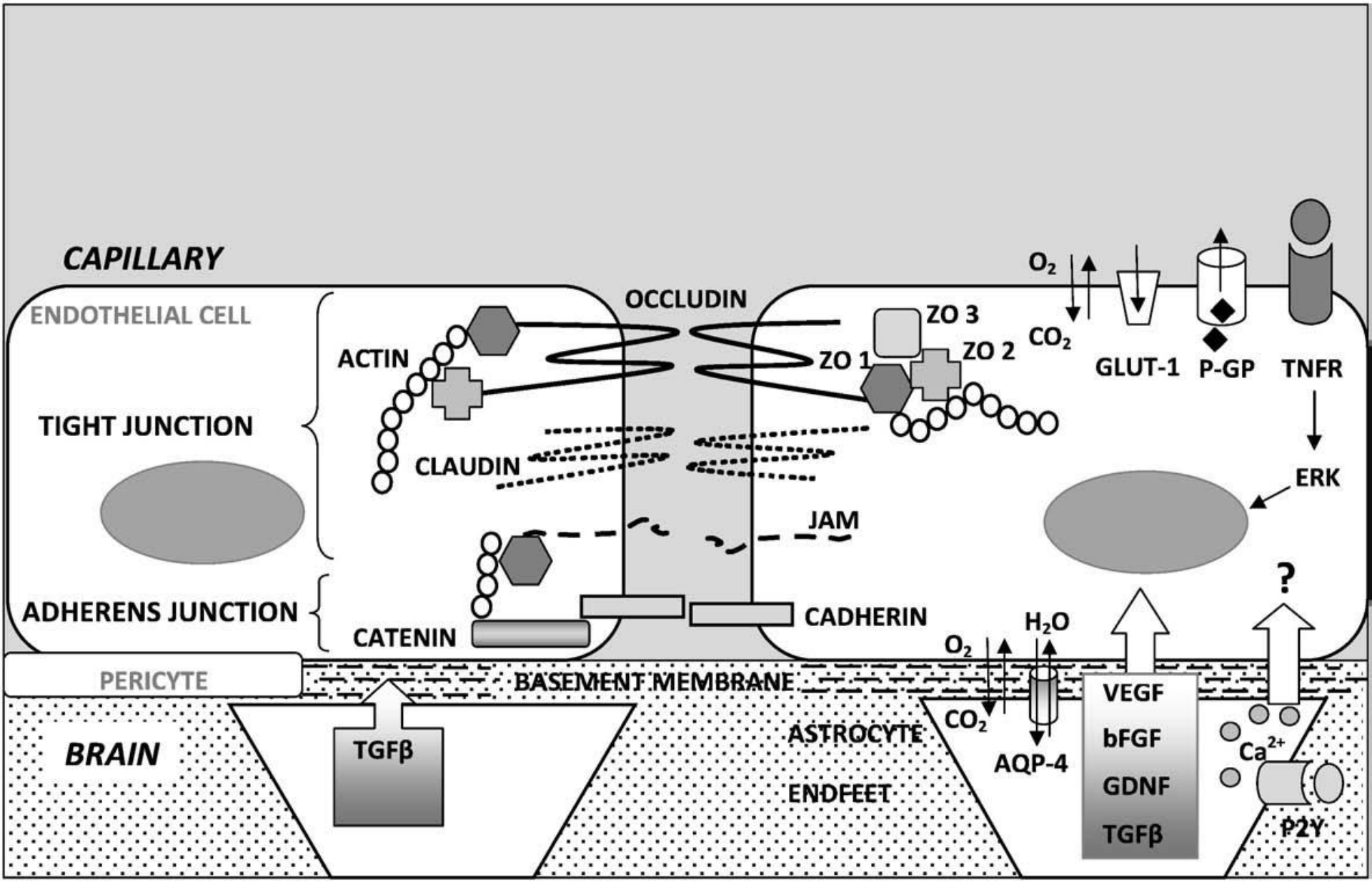
Why should we consider BBB?

- two ways diffusion barrier
- essential for the normal function of the nervous system
- peculiar endothelial cells and tight junctions
- low vesicular transport (transcytosis)
- O_2, CO_2 – gradient diffusion
- aa, glucose – transporters
- larger – endocytosis (receptor)



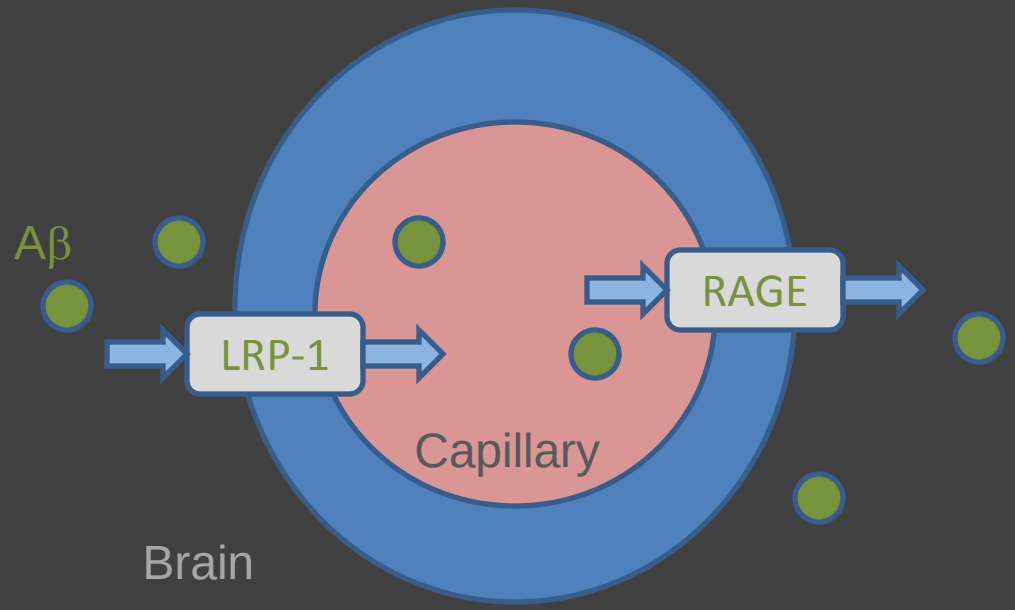
Ballabh et al, Neurobiol Dis, 2004



Popescu et al, J Neurol Sci, 2009

Aβ and BBB

LRP-1 = low density lypoprotein receptor-related protein
RAGE = receptor for advanced glycation end-products

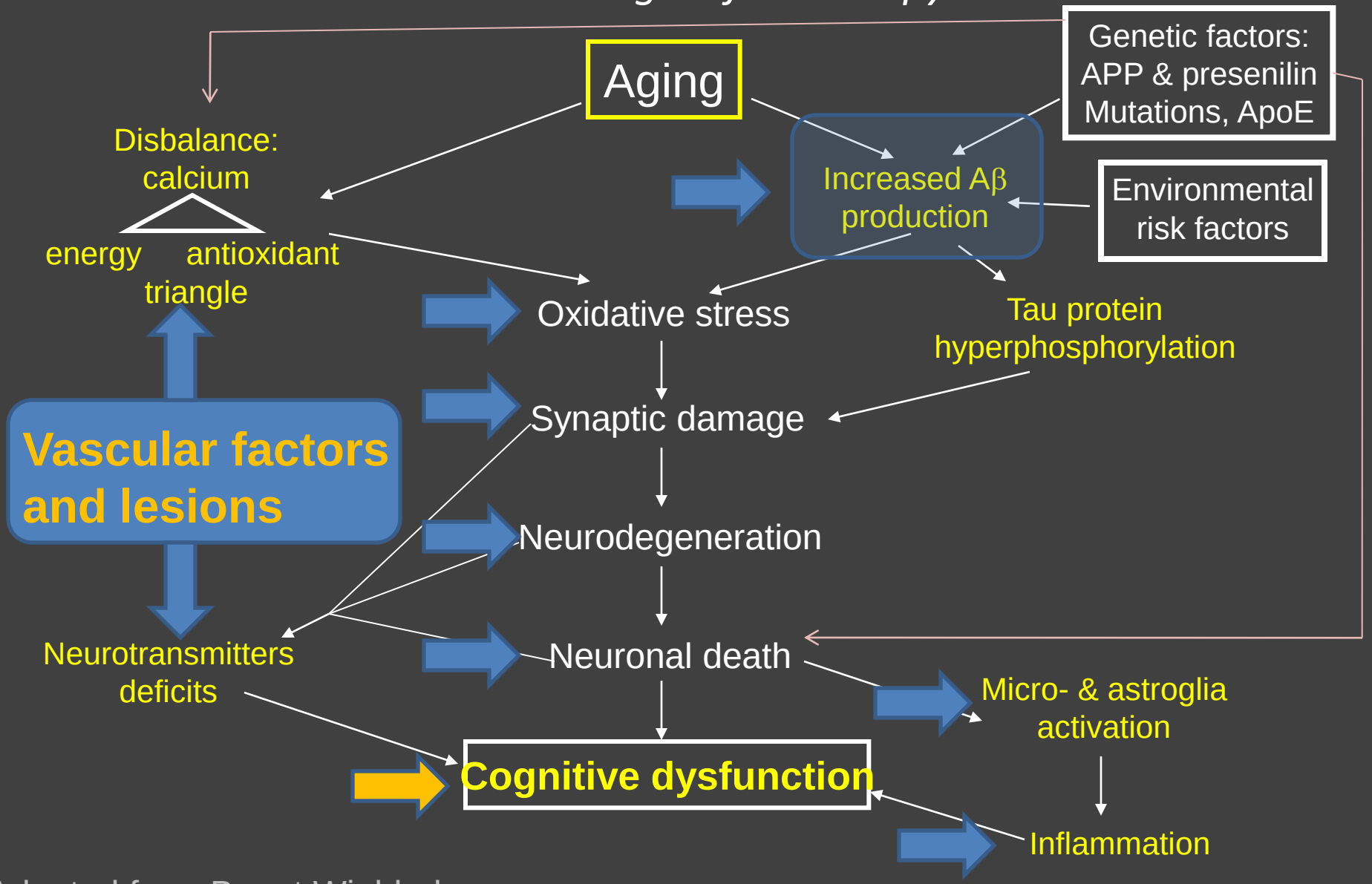


Aβ in:
-blood
-vessels (CAA)
-brain tissue

Drawing following the concept of
Deane et al., Nature Med, 2003

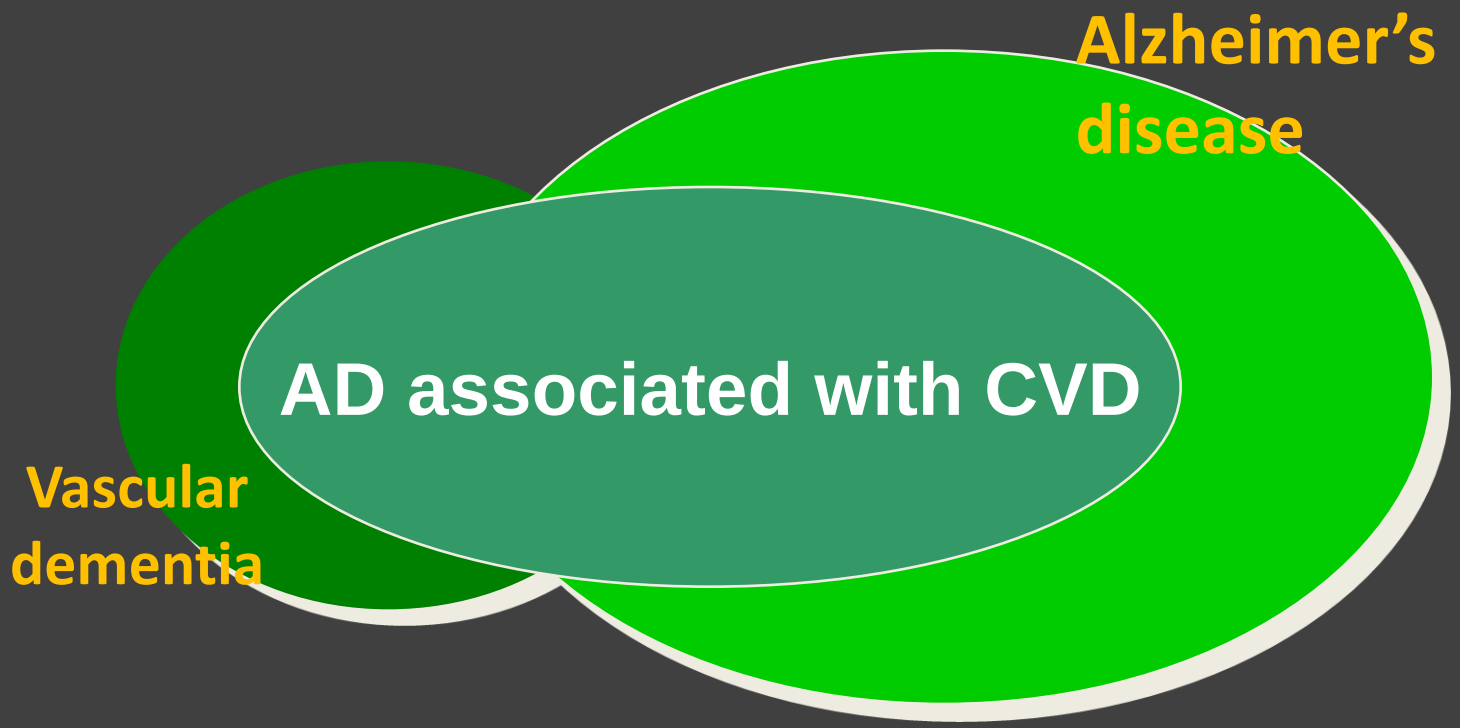
Pathophysiological Processes Leading to AD

Possible Targets for Therapy



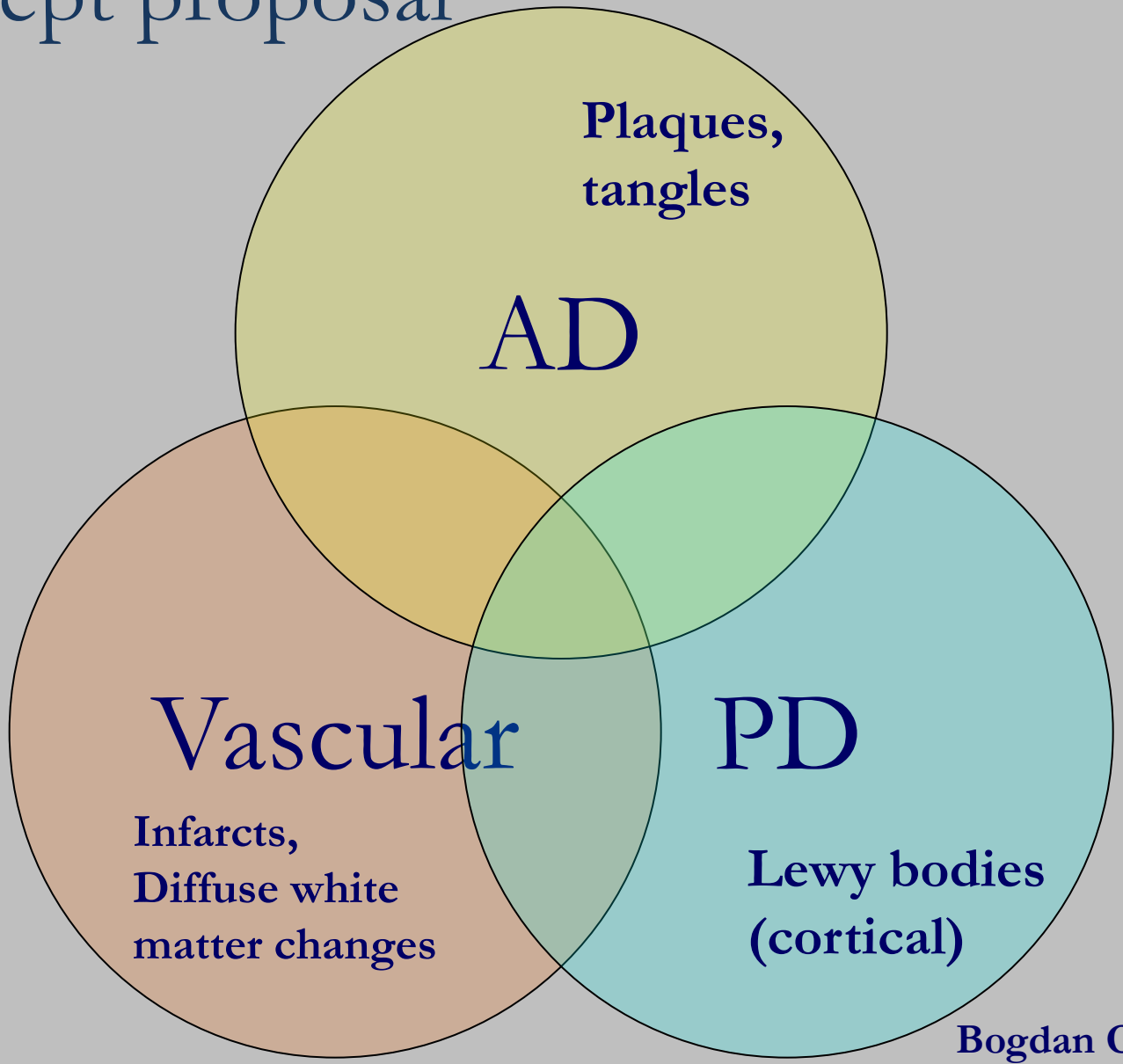
Adapted from Bengt Winblad

Present view of vascular dementia and Alzheimer's disease



- Cerebrovascular disease should not lead directly to diagnosis of vascular dementia
- Vascular dementia without typical AD pathology is a rare condition
- Many patients with vascular risk factors or cerebrovascular disease have typical AD clinical evolution
- This overlap represents in fact AD with CVD

An even broader dementia spectrum concept proposal



Bogdan O. Popescu, 2006

But how is BBB doing?

Acta Neurol Scand 2007: 115: 403–408 DOI: 10.1111/j.1600-0404.2007.00823.x

ACTA NEUROLOGICA
SCANDINAVICA

The integrity of the blood–brain barrier in Alzheimer's disease

Algotsson A, Winblad B. The integrity of the blood–brain barrier in Alzheimer's disease.
Acta Neurol Scand 2007: 115: 403–408.

A. Algotsson, B. Winblad

Division of Clinical Geriatrics, Department of Neurobiology, Caring Sciences and Society, Karolinska Institutet, Stockholm, Sweden

- Evaluated by CSF/plasma albumin ratio in 157 AD patients
- Patients with CT/MRI evidence of vascular disease excluded
- Lab ref value < 9.2 (no age-matched controls)

BBB leakage in AD

Table 1 Demographic and clinical characteristics

	Men	Women	
Number	71	86	
Age (years)	70.0 (9.3)	69.4 (9.5)	NS
MMSE*	20.7 (5.2)	22.0 (4.2)	NS
Plasma creatinine (μmol/L)	98.2 (15.0)	86.0 (12.4)	$P<0.001$
Albumin ratio	9.6 (4.33)	7.1 (1.9)	$P<0.001$
IgG index†	0.42 (0.1)	0.41 (0.1)	NS
Dysfunction of the BBB (%)	42	13	$P<0.001$
One ApoE 4 allele (%)‡	71	59	NS
Two ApoE 4 alleles (%)‡	18	15	NS
At least one vascular riskfactor/disease (%)§	52	53	NS
At least two vascular riskfactor(s)/disease(s) (%)§	16	12	NS
Early debut of the disease (%)	46	43	NS

Values are given as mean (SD) or percent. Reference values of the laboratory: plasma creatinine, men: < 120 μmol/L; women: < 110 μmol/L; albumin ratio: < 9.2; IgG index: < 0.7. SD, standard deviation. NS, not significant.

*Mini-Mental State Examination. Data missing for two women.

†Data missing for one man and one woman.

‡One (or two) apolipoprotein E ε4 allele(s) was present. Data missing for three men.

§Presence of at least one (or two) vascular risk factor(s)/disease(s) (hypertension, heart disease, diabetes mellitus). Data missing for 10 men and 8 women.

Algotsson & Winblad, 2007

BBB leakage in AD

Algotsson & Winblad

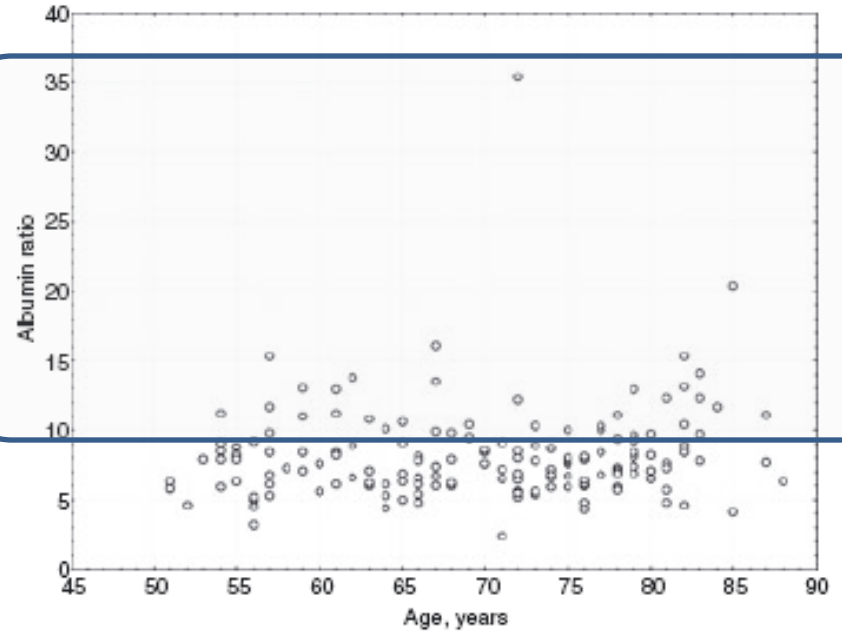


Figure 2. The association between age (years) and albumin ratio for all patients (r_s = 0.13; not significant).

Table 2 Multiple regression analysis with albumin ratio (natural logarithms) for all patients as the dependent variable

	B	SE of *B*	*P*-value
Intercept	1.434	0.249	0.000
Age	0.000	0.003	0.935
Plasma creatinine	0.005	0.002	0.009
Gender*	0.191	0.059	0.002
Presence of 0, at least one or two vascular risk factor(s)/disease(s)†	0.043	0.041	0.302

Non-dependence on age!

BRAIN RESEARCH 1142 (2007) 223–236

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BRAIN RESEARCH

Research Report

Aβ peptides can enter the brain through a defective blood–brain barrier and bind selectively to neurons

Peter M. Clifford[a], Shabnam Zarrabi[a], Gilbert Siu[a], Kristin J. Kinsler[a], Mary C. Kosciuk[a], Venkateswar Venkataraman[b], Michael R. D'Andrea[c], Steven Dinsmore[a], Robert G. Nagele[a,*]

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[b]Department of Cell Biology, University of Medicine and Dentistry of New Jersey, Stratford, NJ 08084, USA

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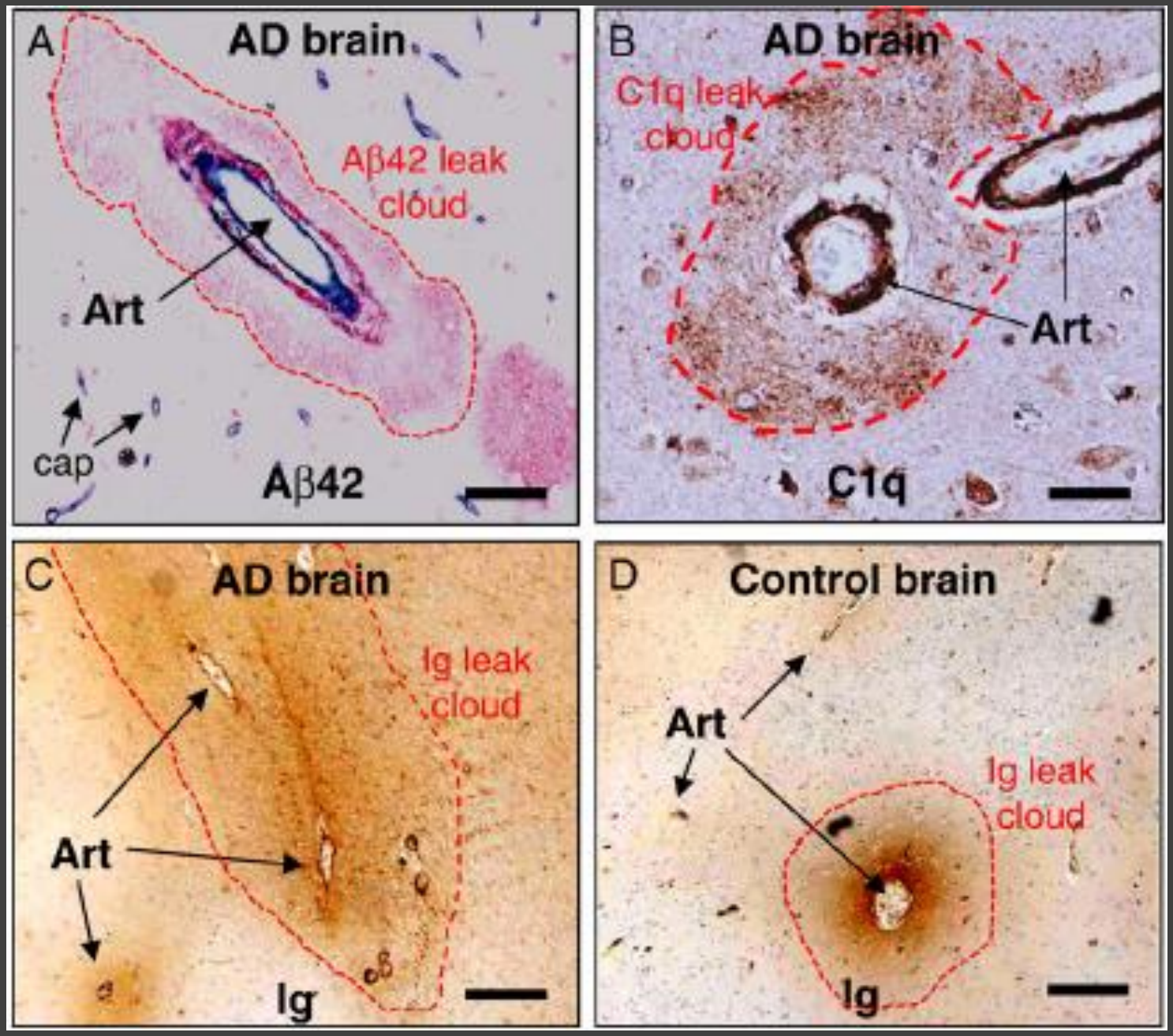

Clifford et al, 2007

NBA-6887; No. of Pages 16

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Neurobiology of Aging xxx (2007) xxx–xxx

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Review

Blood–brain barrier: Ageing and microvascular disease – systematic review and meta-analysis

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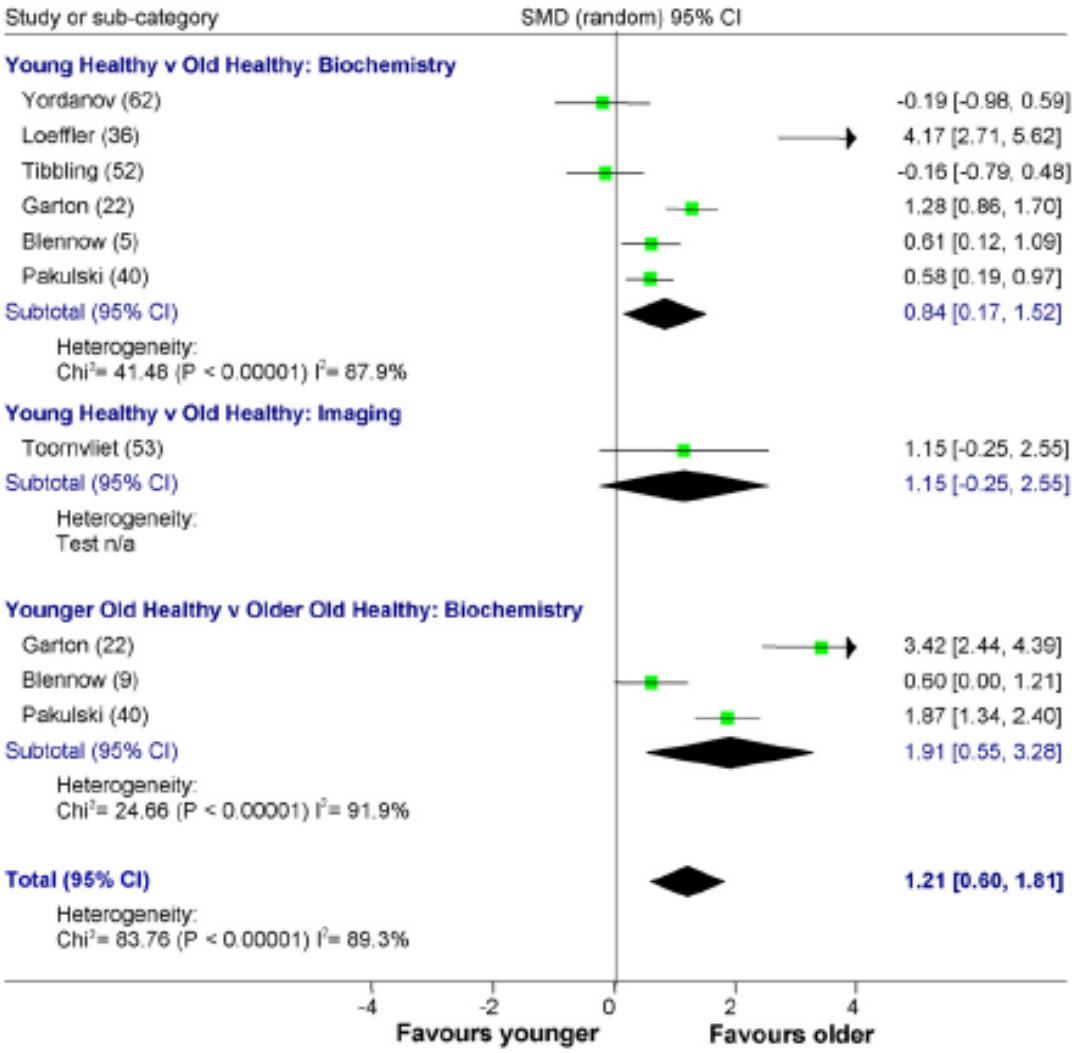
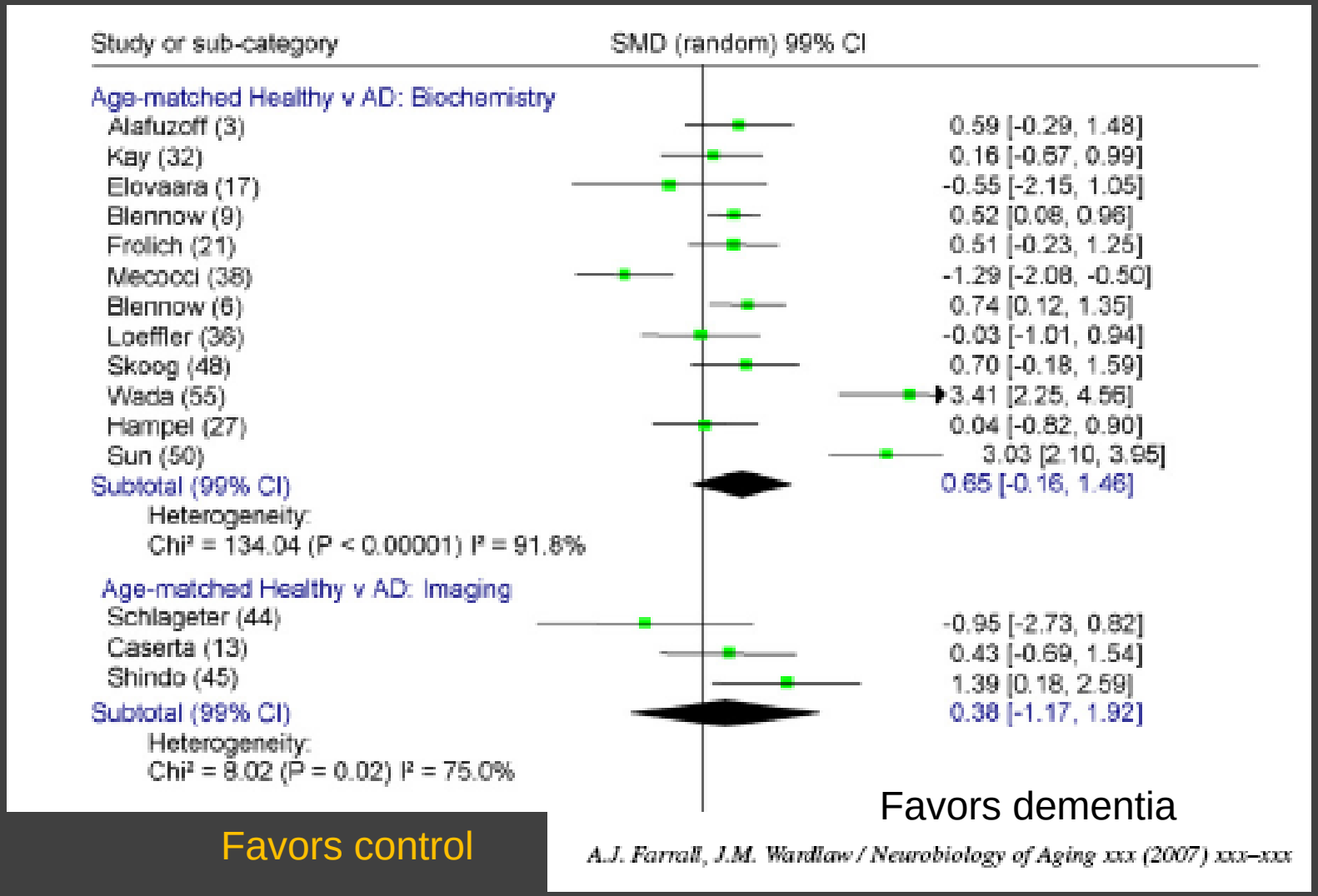
BBB permeability with age

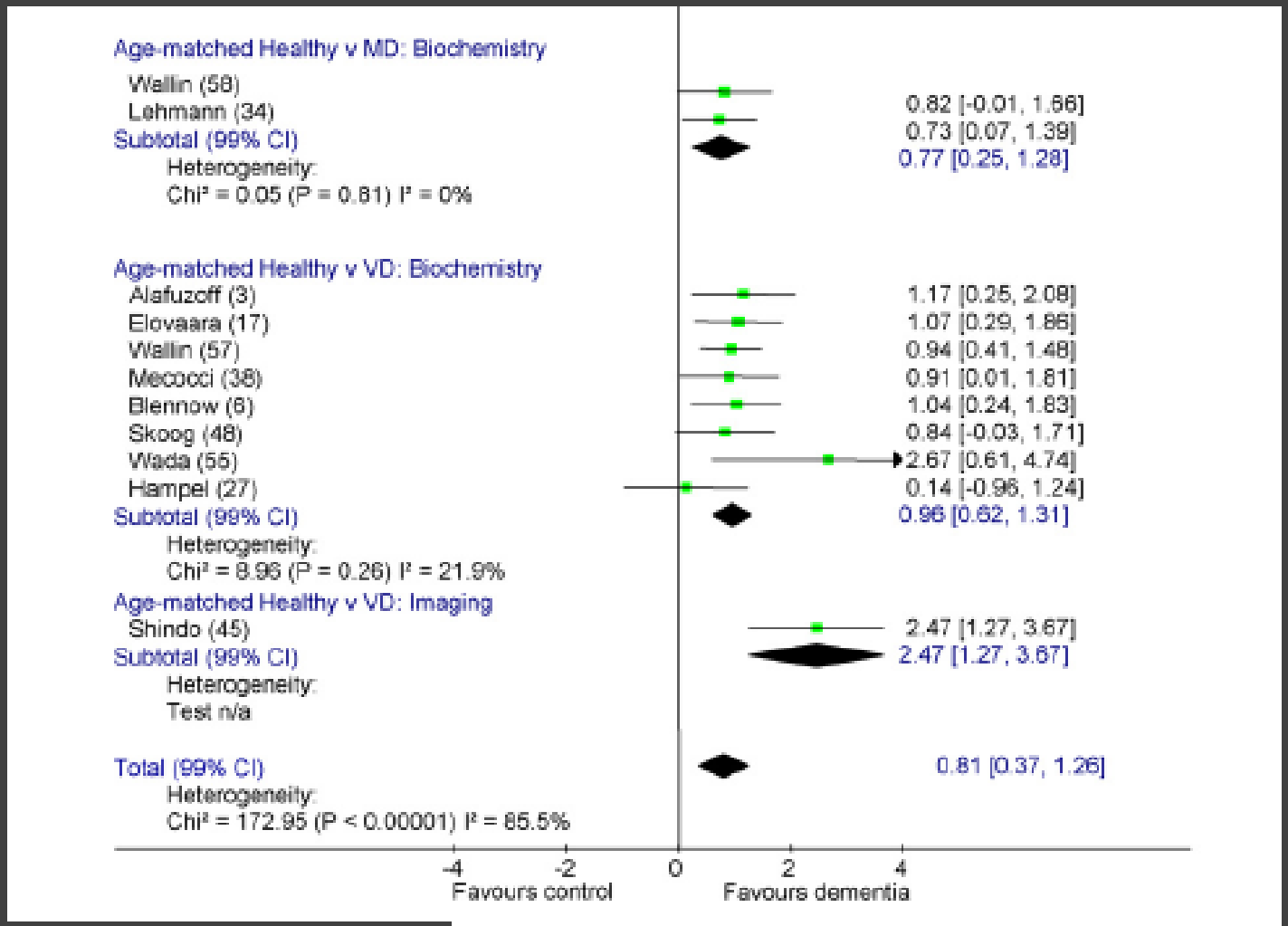


A.J. Farrall, J.M. Wardlaw / Neurobiology of Aging xxx (2007) xxx–xxx

BBB permeability with dementia: AD



BBB permeability with dementia: MD and VaD



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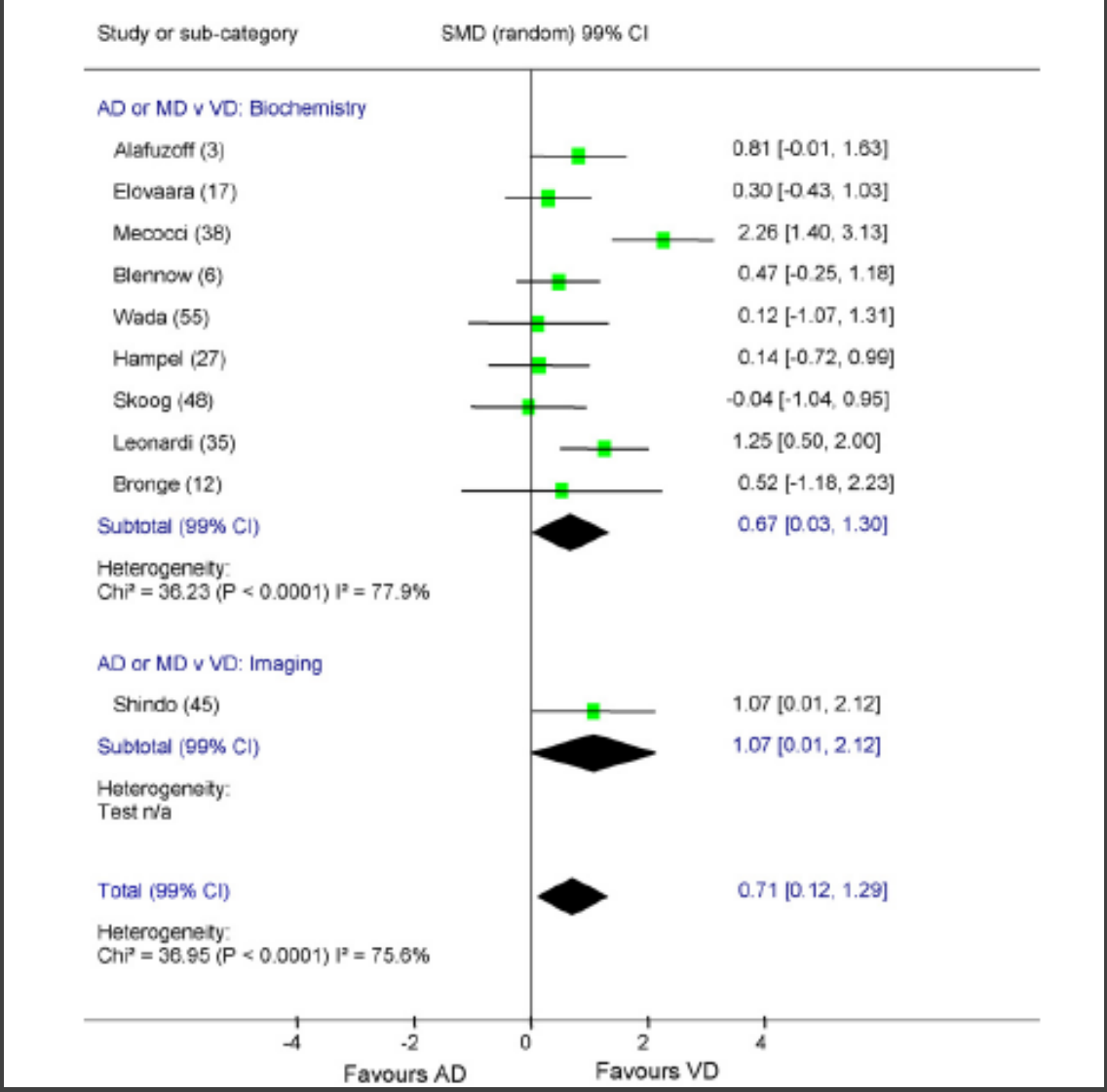
BBB permeability : AD vs VaD



A.J. Farrall, J.M. Wardlaw / Neurobiology of Aging xxx (2007) xxx–xxx

A fast look at the TJPs

In Focus

J. Cell. Mol. Med. Vol 11, No 3, 2007 pp. 569-579

Occludin is overexpressed in Alzheimer's disease and vascular dementia

Mihaela Oana Romanitan [a, b], Bogdan O. Popescu [b, c], Bengt Winblad [a], Ovidiu Alexandru Bajenaru [b], Nenad Bogdanovic [a, *]

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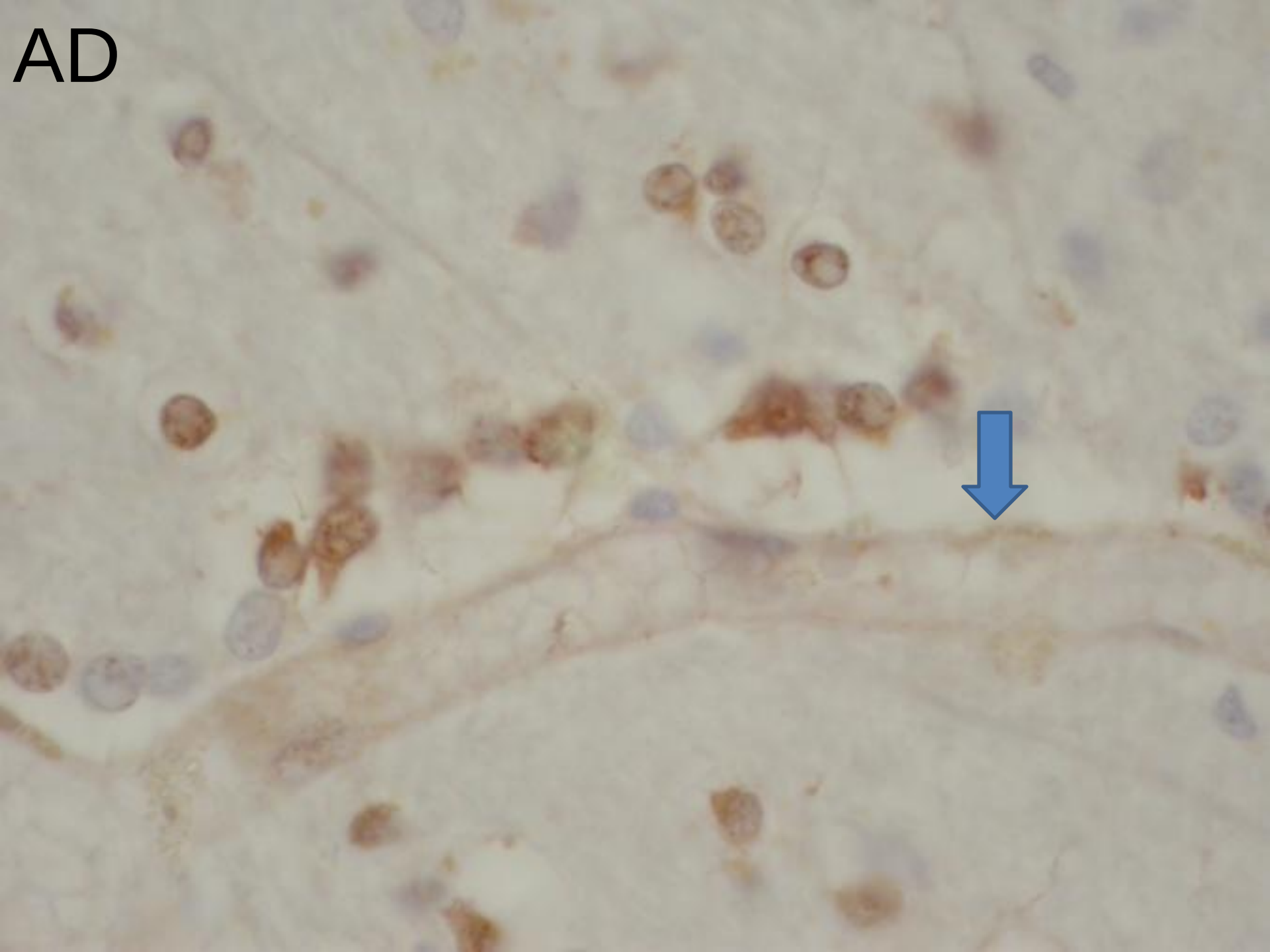
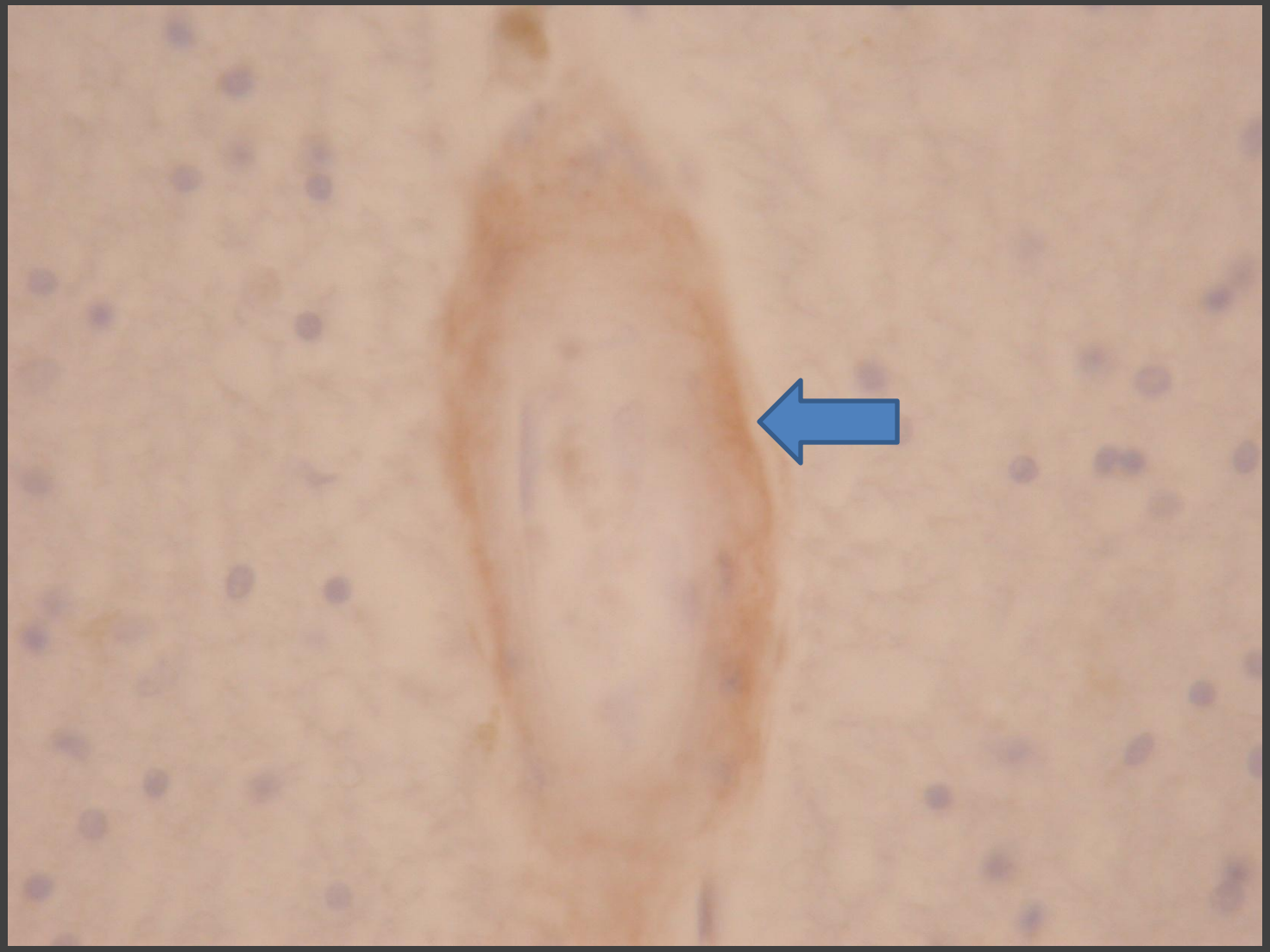
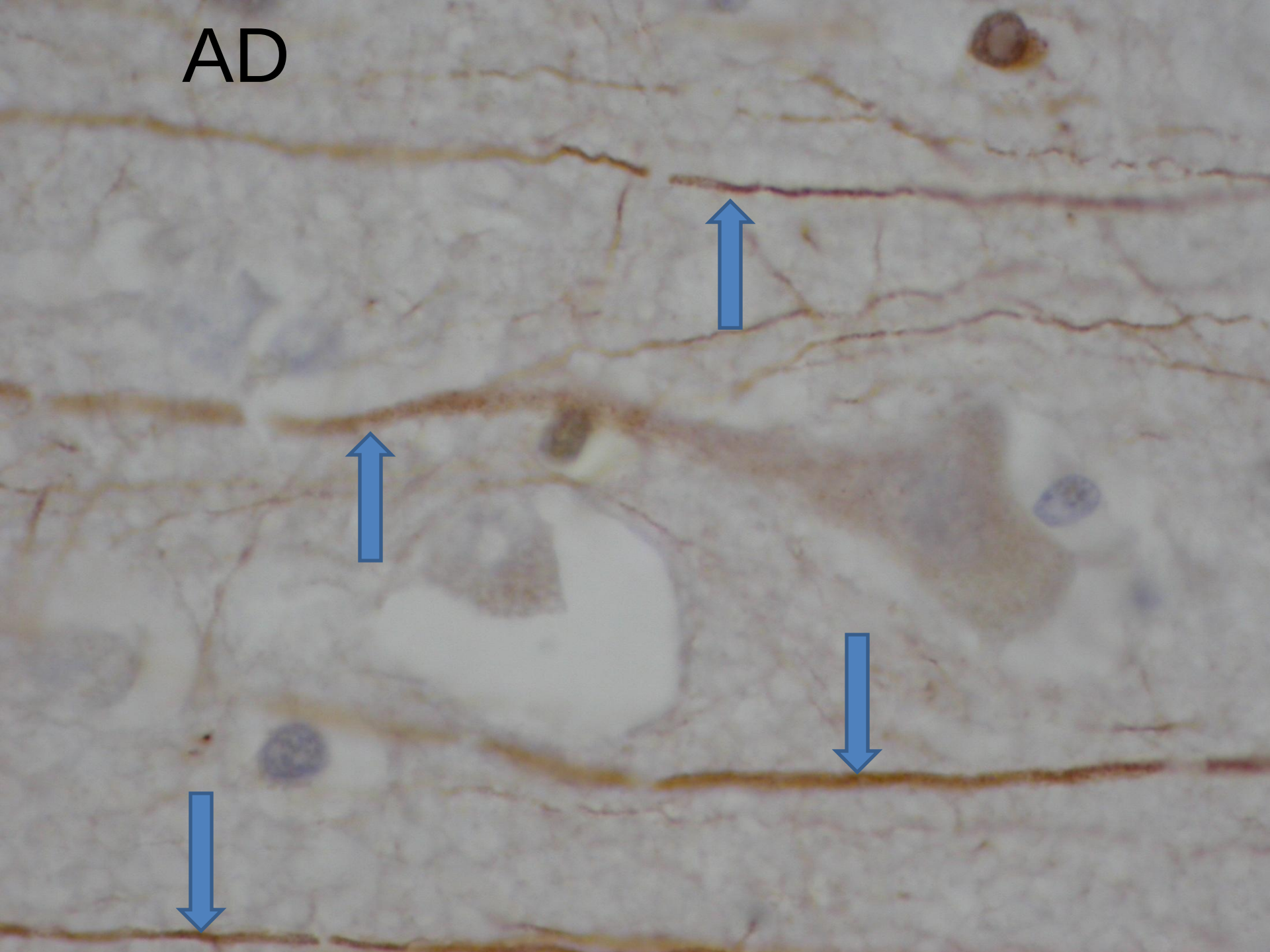
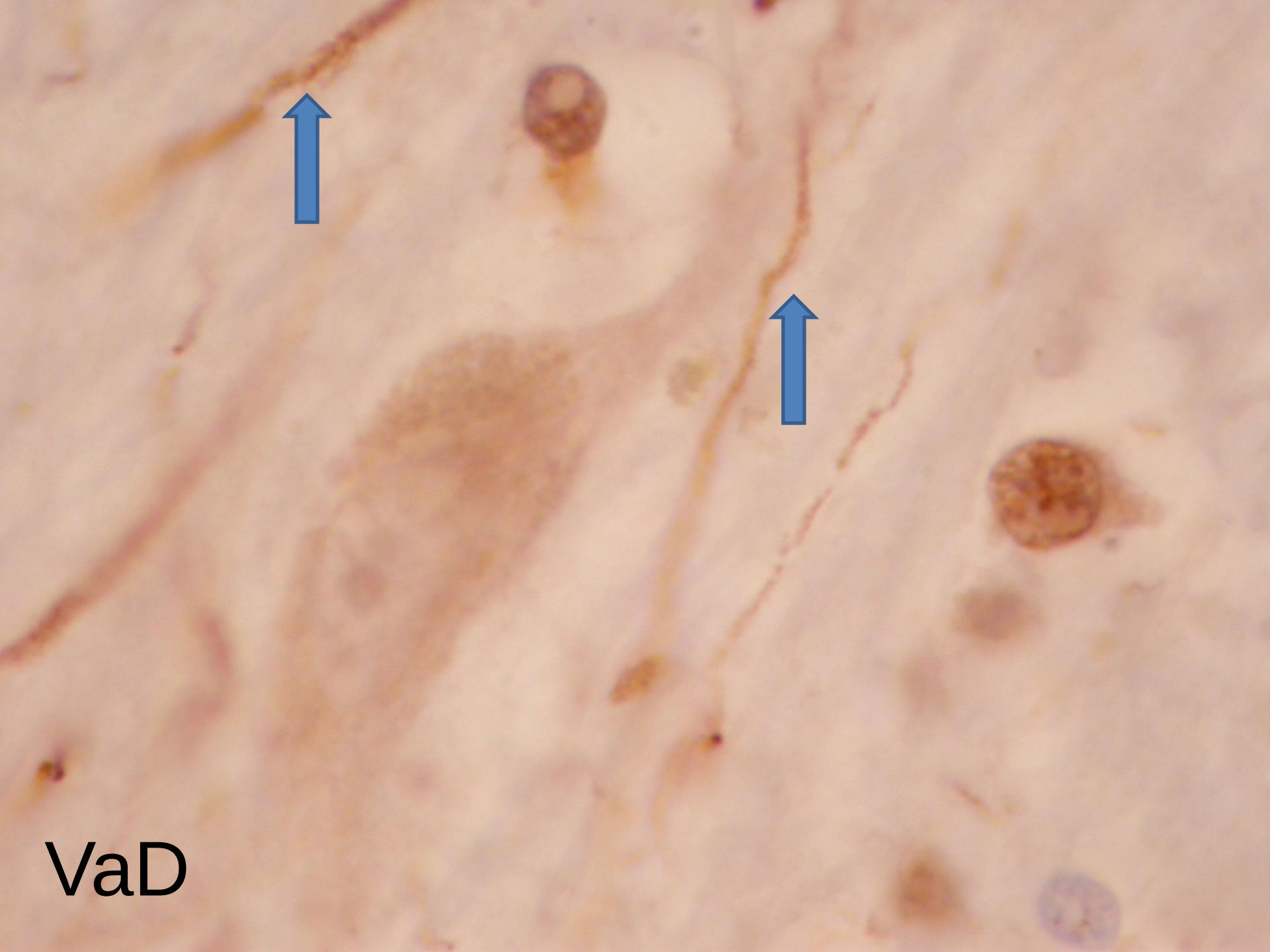
AGE-MATCHED CONTROL


AD

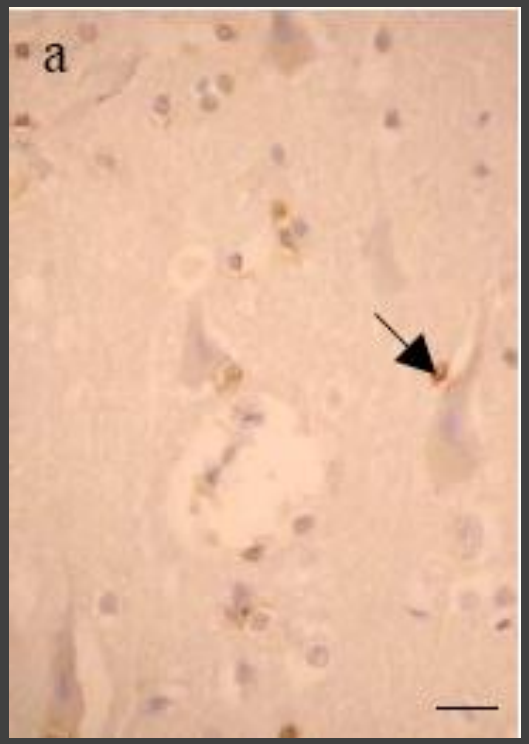
VaD vessel - Occludin



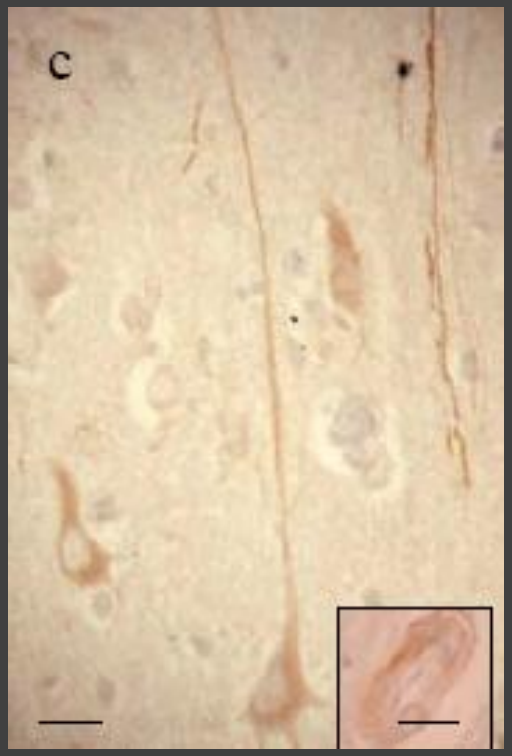

AD


VaD

Occludin expression in ctr and dem



CTR



AD

VaD

Table 2 Quantification of total number of neurons and occludin-expressing neurons (positive neurons) in frontal cortex (FC) and striatum (STR) regions in control (5 cases), Alzheimer's disease (AD, 4 cases) and vascular dementia (VD, 6 cases) groups. All values were truncated to two decimals

Group	Region	Total number of neurons				Number of positive neurons			
		mean	SD	SEM	CE	mean	SD	SEM	CE
CONTROL	FC	23.17	3.14	1.57	6.79	5.58	1.52	0.76	13.65
	STR	31.58	4.32	2.16	6.84	1.04	0.08	0.04	4
AD	FC	20.67	4.55	2.27	11	11.25	3.13	1.57	13.92
	STR	34.33	4.22	2.11	6.14	18.88	2.76	1.38	7.31
VD	FC	22	5.56	2.78	12.65	11.25	2.71	1.36	12.06
	STR	24.8	10.57	4.32	17.78	9.28	8.57	3.5	37.69

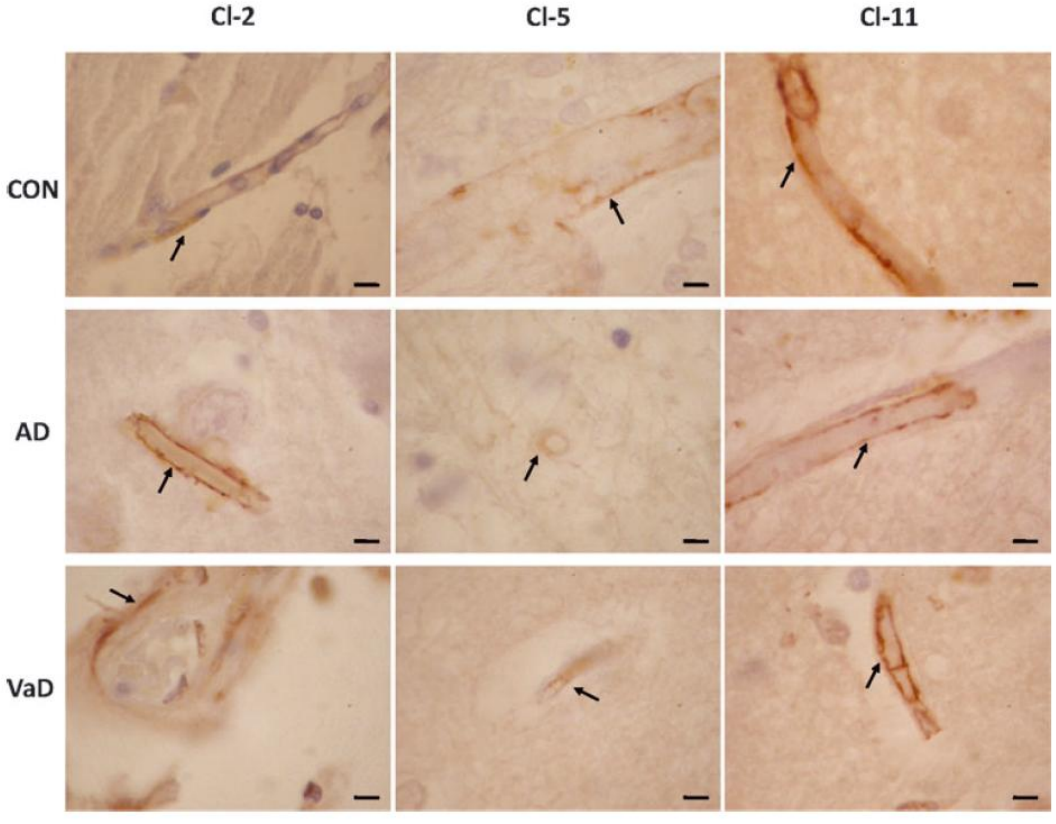
SD = standard deviation, SEM = standard error of the mean, CE = coefficient of error (multiplied by 100).

Romanitan et al, 2007

J. Cell. Mol. Med. Vol XX, No XX, 2009 pp. 1-13

Altered expression of claudin family proteins in Alzheimer's disease and vascular dementia brains

Mihaela O. Romanitan [a, b], Bogdan O. Popescu [a, b, *], Tefan Spulber [c], Ovidiu Băjenaru [b], Laurenţiu M. Popescu [a, d], Bengt Winblad [c], Nenad Bogdanovic [c]



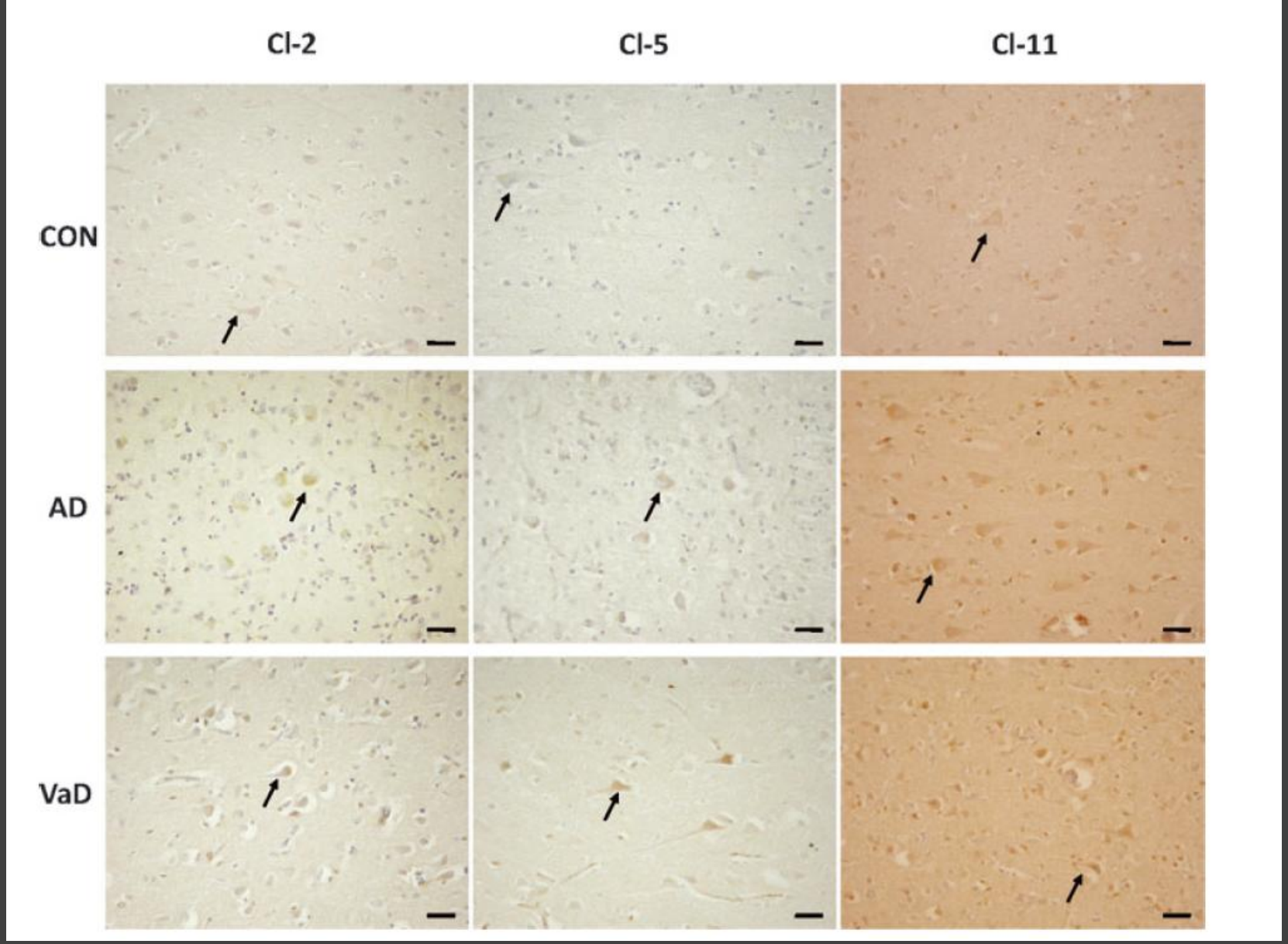
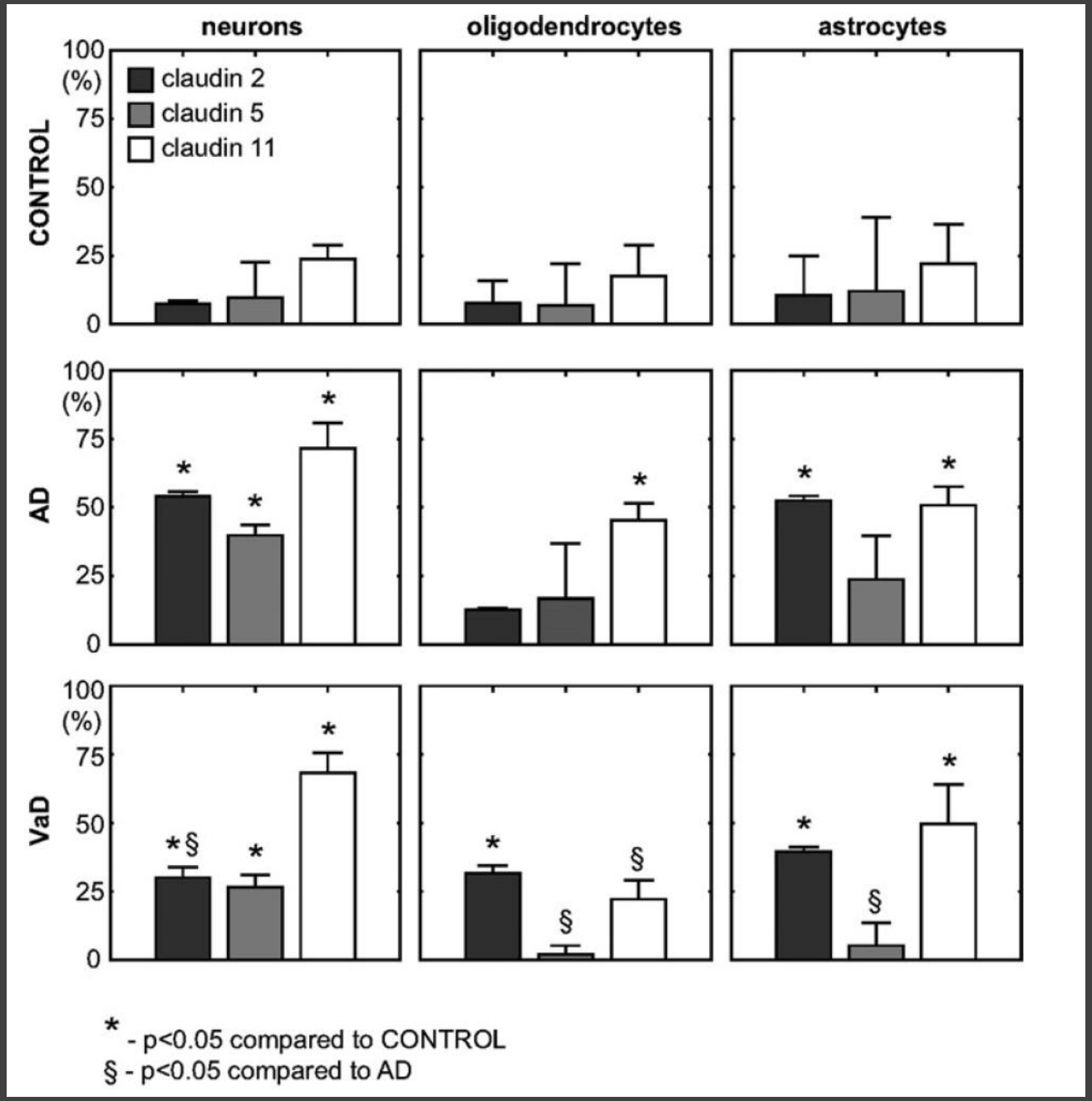
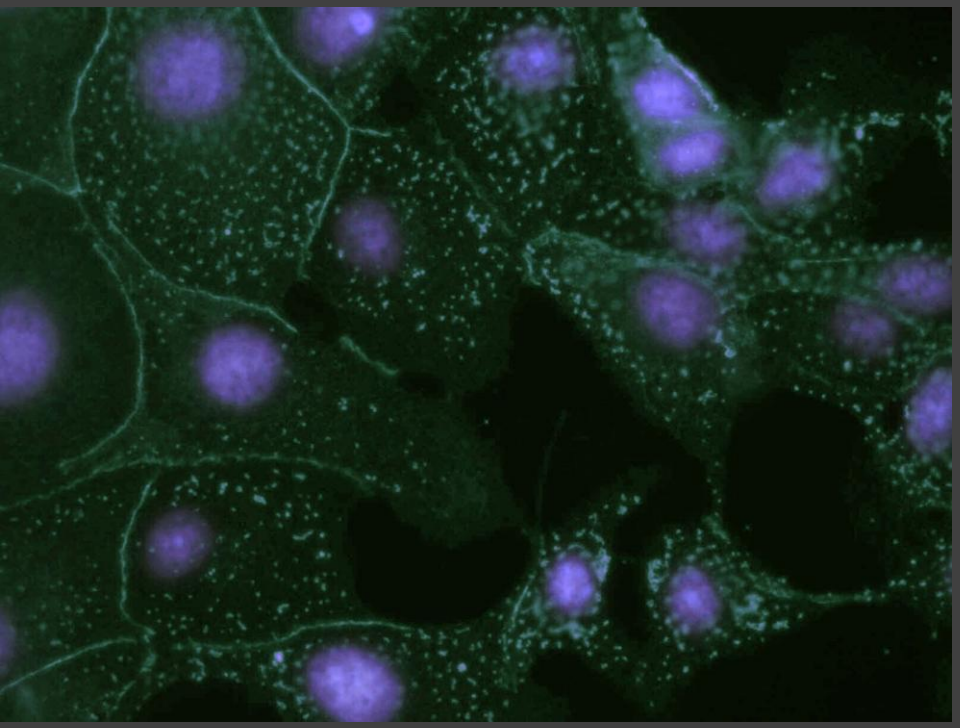


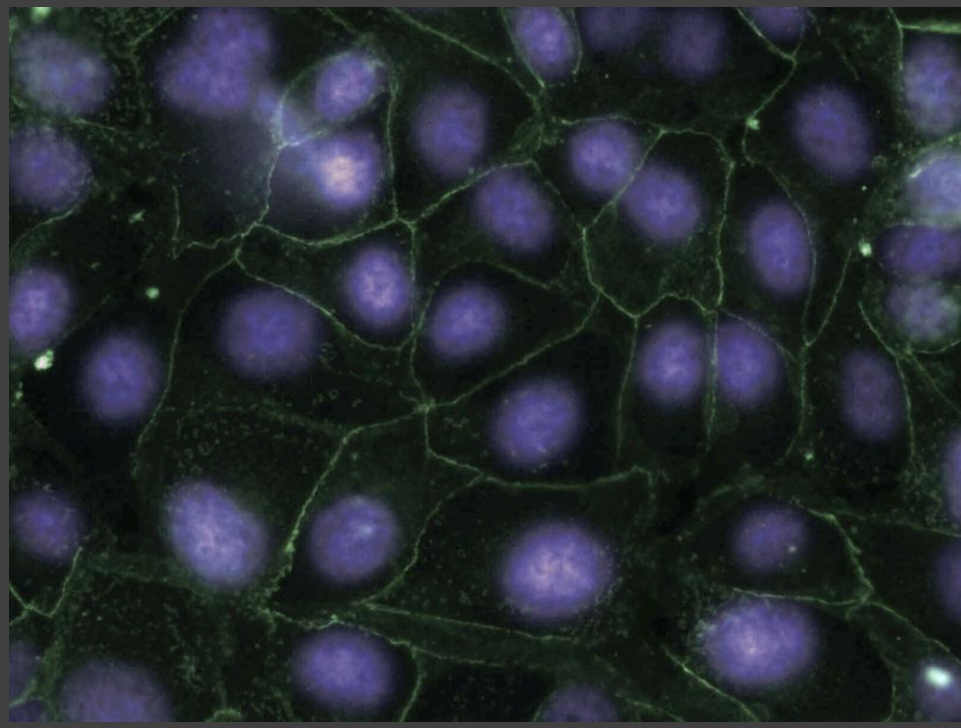
Fig. 1 Expression of Cl-2, Cl-5 and Cl-11 in control (CON), AD and VaD brains, in the frontal cortex, Brodmann area 46/9. Cl-expressing cells are brownish, as a result of the immunohistochemical staining method with anti-Cl sera detected with avidin–biotin-peroxidase complex kit and DAB substrate. Expression of Cl-2, Cl-5 and Cl-11 was increased in neurons and neuronal fibres in AD and VaD brains, as compared to control brains. Expression of Cls was noticed mainly in the pyramidal neurons in CON, AD and VaD. Arrows are indicating Cl-expressing neurons. Bars: 30 μm.

Table 2 Quantification of total number of neurons and CI-expressing neurons (positive neurons) in the frontal cortex region in control (CON, five cases), AD (four cases) and VaD (six cases) groups. All values were truncated to two decimals. S.D. = standard deviation

Group	Total number of neurons						Number of positive neurons					
	CI-2		CI-5		CI-11		CI-2		CI-5		CI-11	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
CON	33.47	4.79	31.33	4.82	32.53	5.78	2.47	0.73	3.20	4.56	7.80	2.64
AD	32.17	3.87	33.58	2.20	32.58	0.32	17.42	2.63	13.33	0.98	23.33	3.02
VaD	27.00	4.49	27.83	3.13	28.44	2.93	10.44	3.12	7.39	1.48	19.44	2.93


neurons
oligodendrocytes
astrocytes
CONTROL
AD
VaD
100
(%)
75
50
25
0
claudin 2
claudin 5
claudin 11
*
§
* - p<0.05 compared to CONTROL
§ - p<0.05 compared to AD





Conclusions

- TJP are expressed not only in endothelial cells, but in neurons, astrocytes and oligodendrocytes as well
- TJP expression is increased in AD and VaD brains
- There is a specific profile of TJP expression in controls, AD and VaD
- TJP might have a function in defense against cellular stress

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