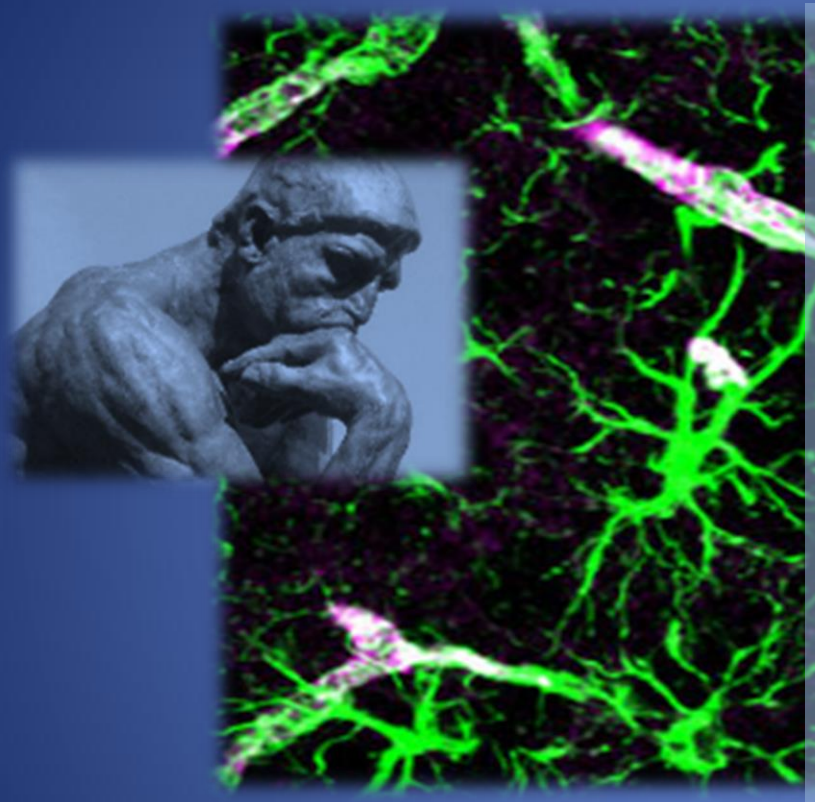
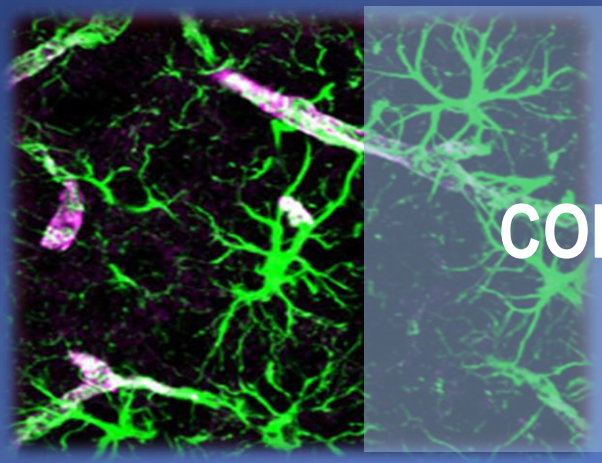


NEURO-DEGENERATIVE *diseases*

Susanna Melkas

specialist in neurology, assistant professor in neurological rehabilitation

Helsinki University Hospital and University of Helsinki



CONTENTS

Alzheimer’s disease

Vascular cognitive impairment

OVERLAP, INTERACTION

Fronto-temporal dementia

Dementia with Lewy bodies and Parkinson’s disease

Huntington´s disease

Creutzfeld-Jakob´s disease

ALS and other motor neuron diseases

Neurodegeneration in general

- Misfolding, aggregation, and accumulation of proteins in the CNS
- Accumulation of misfolded proteins leads to
  - synaptic dysfunction,
  - neuronal apoptosis,
  - brain damage,
  - and disease

- Exact mechanism?
- Regeneration within the nervous system is very slow compared to other body systems

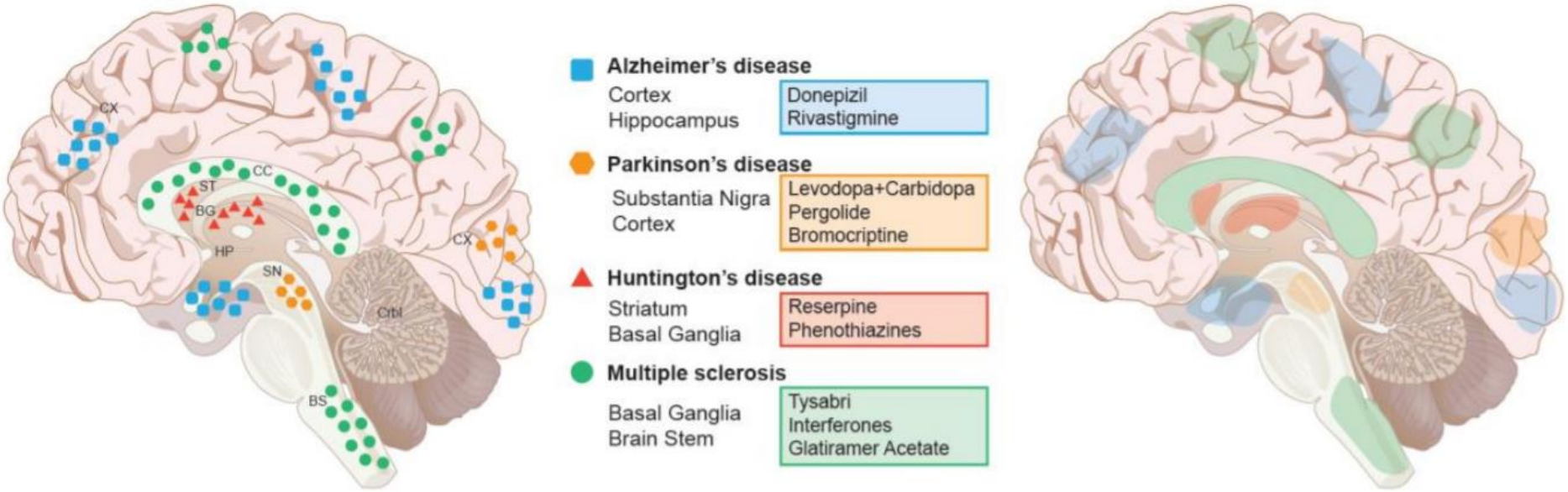


Figure 1. Major Neurodegenerative diseases, their associated regions, and current therapeutic interventions. Left panel: Brain disorders are color and shown in representative areas of the brain. Right panel: current pharmacological treatments and their areas of activity within the brain. Abbreviations: Basal ganglion (BG), Brain Stem (BS), Cerebellum (Crbl), Corpus callosum (CC), Cortex (Cx), Hippocampus (Hp), Striatum (St), Substantia Nigra (SN).

Hussain R, Zubair H, Pursell S, Shahab M.
Neurodegenerative Diseases: Regenerative Mechanisms and Novel Therapeutic Approaches
Brain Sci. 2018, 8, 177; doi:10.3390/brainsci8090177

Over 100 million people are likely to be affected by dementia by 2050.

About 9 million cases less if interventions could delay both disease onset and progression by just one year.

The more advanced old age,

…the more Alzheimer, vascular and other pathologies coexist.

Prevention and early intervention.

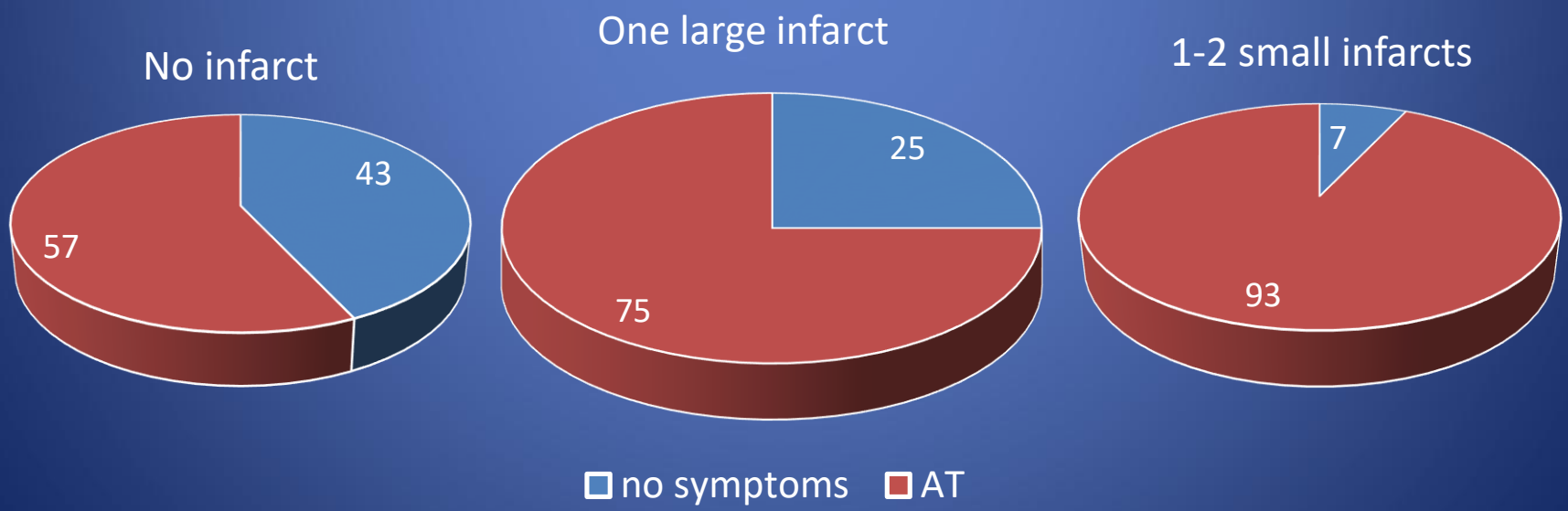
The patient must be encouraged to control vascular risk factors, not least by life-style modification.

Vascular contribution to neurodegeneration

WHEN THE PATIENT HAS ALZHEIMER PATHOLOGY:

Small vessel disease defines whether the Alzheimer pathology is symptomatic or not.

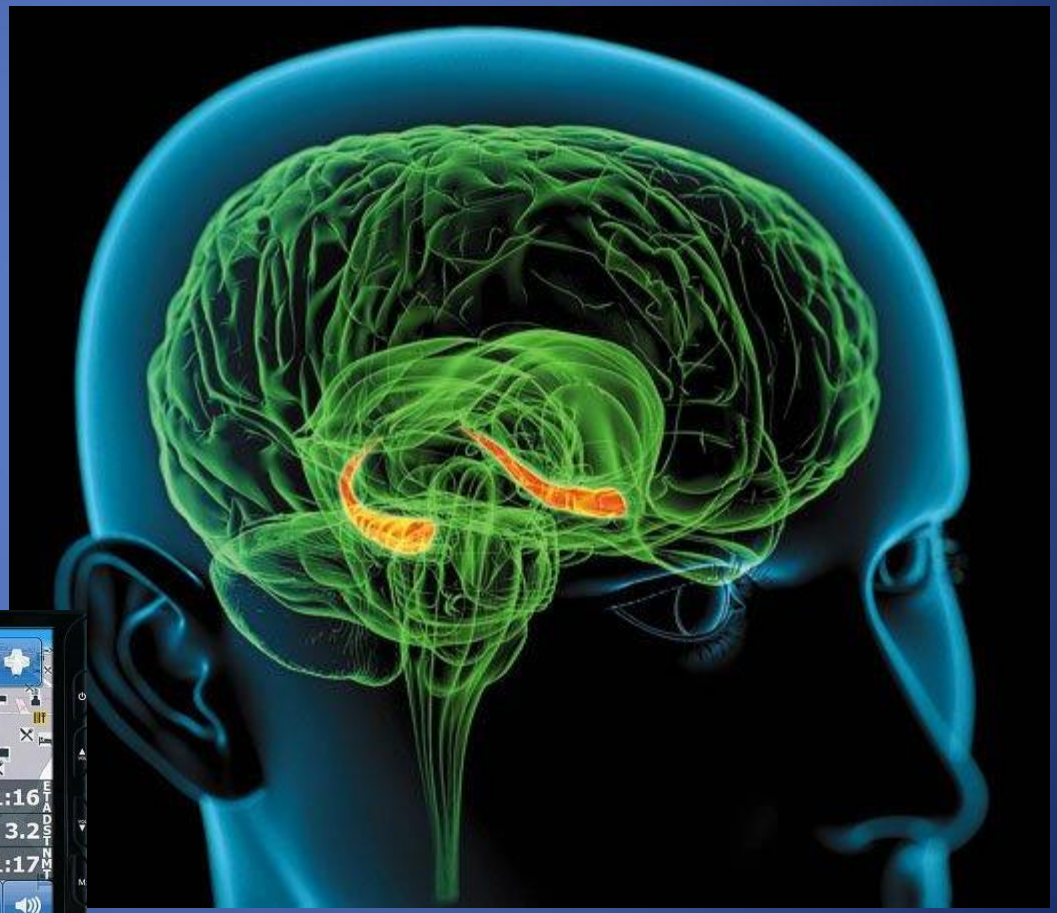
The Nun Study. Snowdon et al JAMA 1997



Alzheimer´s disease

Hippocampus in
inner temporal lobe

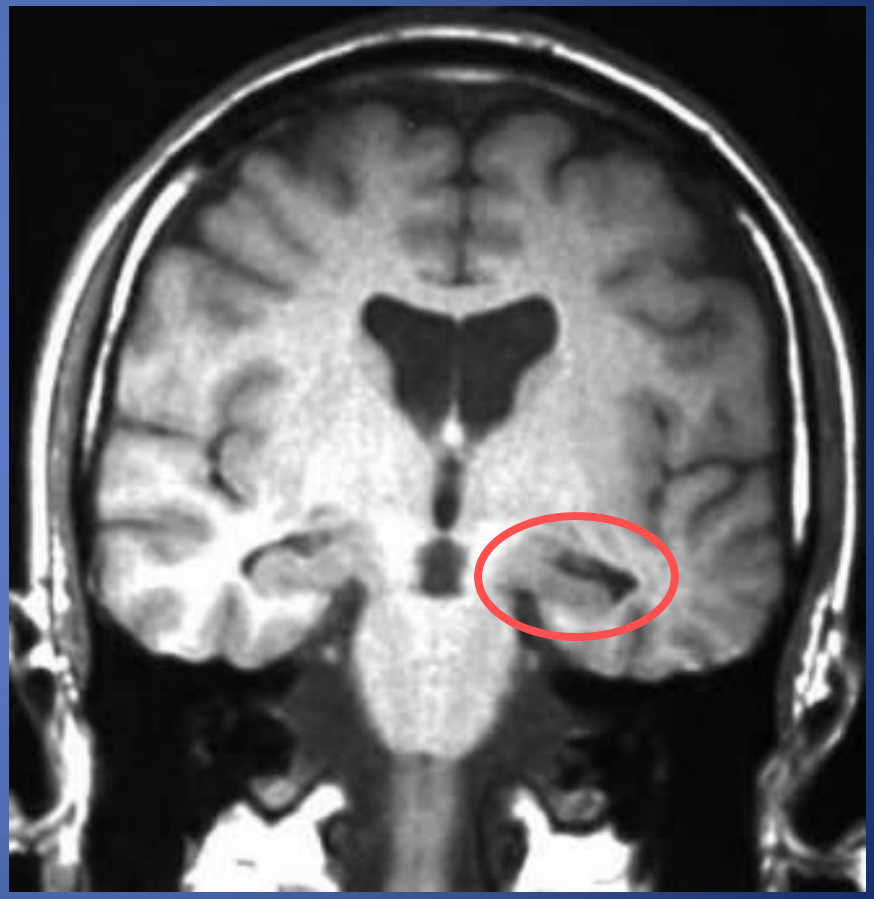
- Episodic memory
- Semantic memory
- Cognitive map



mgitecetech.wordpress.com

Alzheimer's disease

- Early AD: anterograde episodic amnesia
- Atrophy in the inner temporal lobe
- Decreased beta-amyloidpeptid 42 in CSF, elevated Tau and phosphorylated Tau

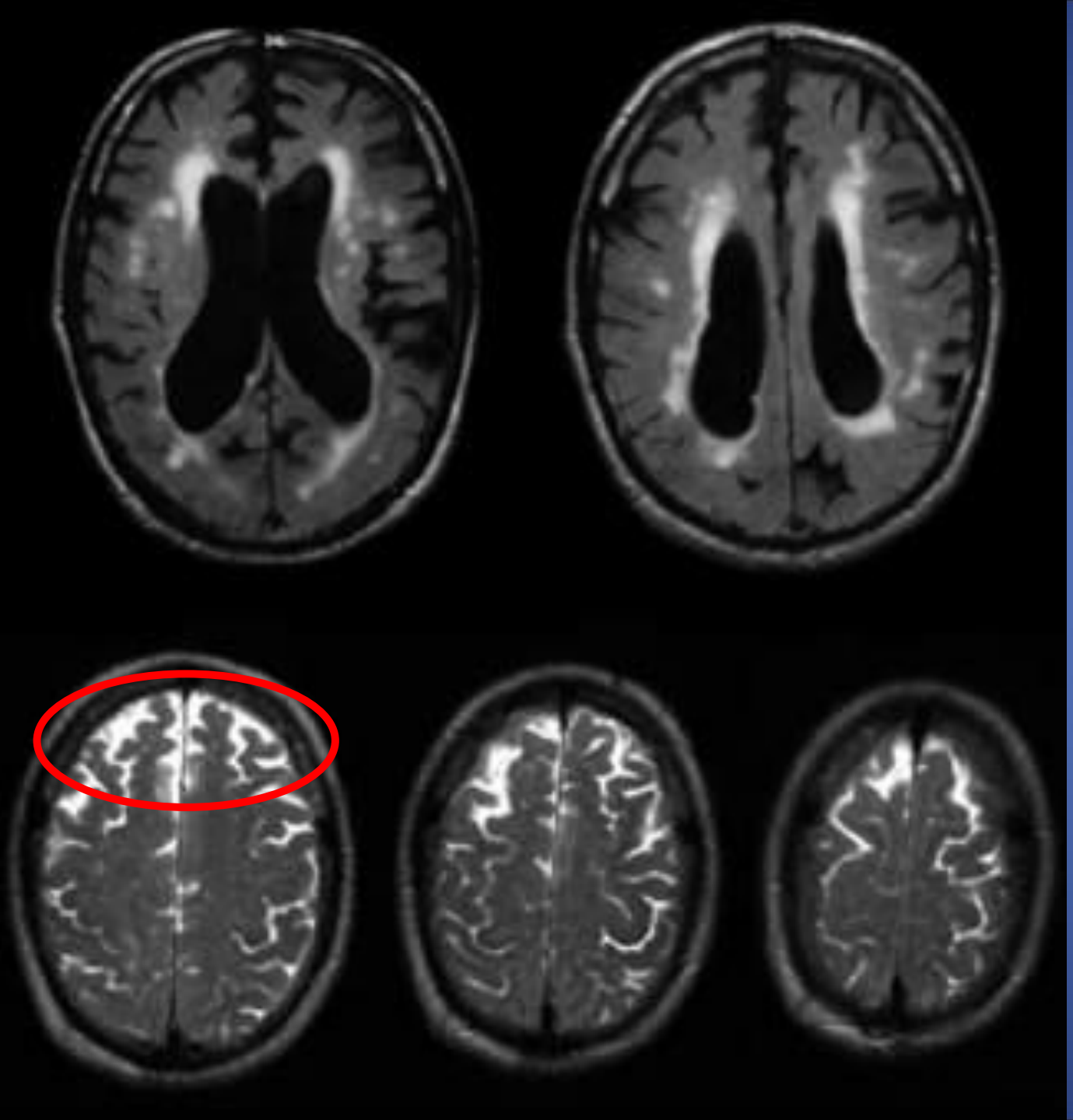


Alzheimer's disease

- Depression
- Psychotic symptoms
- Behavioural abnormalities:
  - agitation,
  - wandering,
  - sleep disturbances and
  - disinhibition

Frontotemporal dementia

- Behavioral variant frontotemporal dementia (bvFTD) – affects personality and behavior
- Primary progressive aphasia (PPA) – first affects speech, then behavior
- Progressive nonfluent aphasia – causes loss of ability to recall and speak words



- etiology: tau or ubiquitine pathology

Patient

- 53 year-old man, works in economy branch
- had 2 mild concussions, 2014 and 2016. Brain MRI normal.
- since 2015 problems in work in social contacts, unemployed since 2017

Patient, continued

- examined on traumatic brain injury outpatient clinic:
  - 3T brain MRI normal -> mild concussions do not explain the symptoms
  - neuropsychological examination: no specific cognitive defects, but was distressed
  - CSF: normal

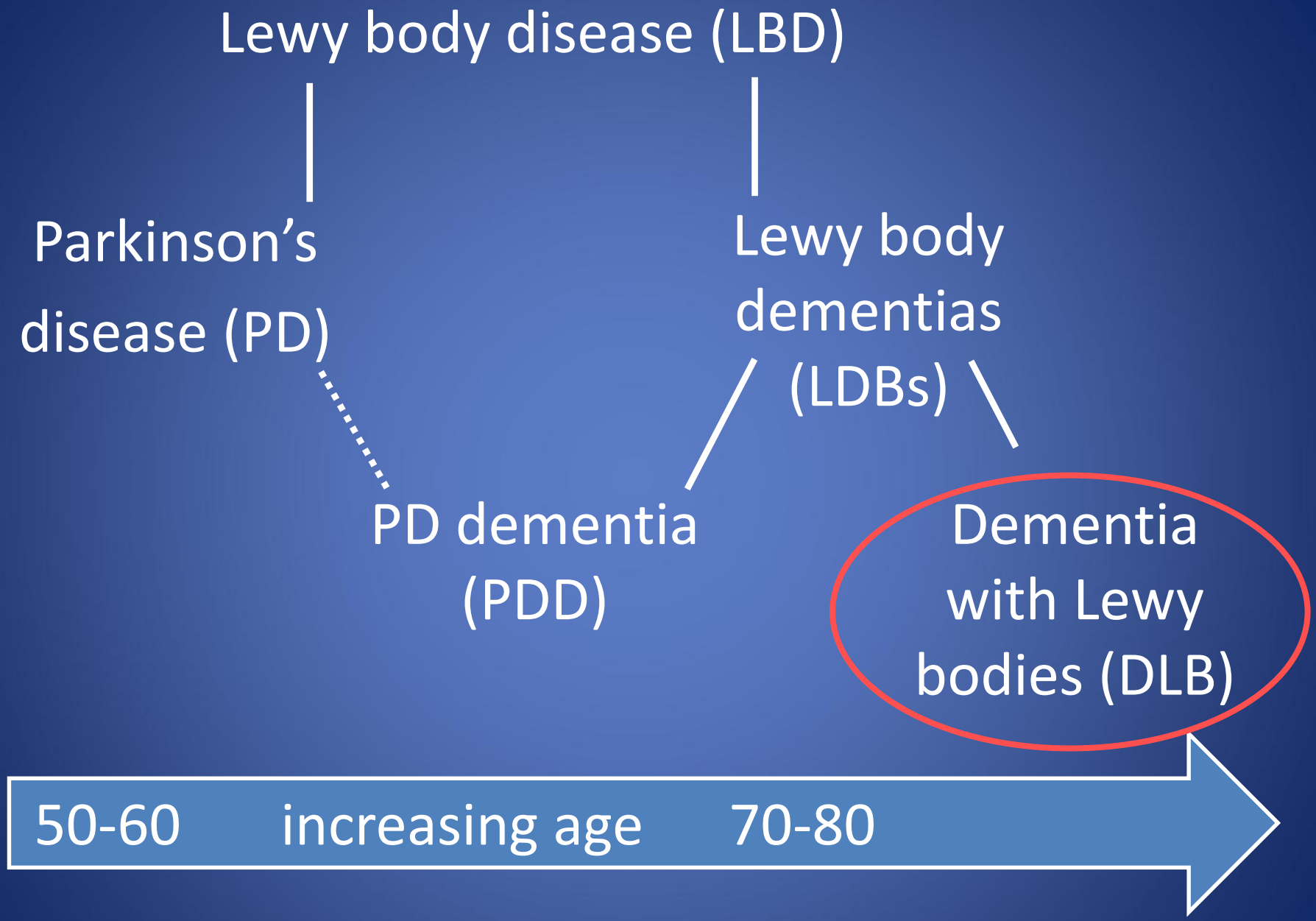
Patient, continued

- psychiatric evaluation: difficulties in social contacts, suspicion of degenerative process
- neuropsychiatric examination: emotional dysregulation, working memory easily overloaded
- PET-TT of brain metabolism: showed decreased metabolism in the both frontal lobes

-> Frontal degeneration, beginning frontotemporal dementia

Dementia with Lewy bodies and Parkinson's disease

- Neurobehavioural syndrome
- Psychotic features such as depression, hallucinations and paranoia
- Parkinsonian features, above all rigidity


Lewy body disease (LBD)
Parkinson's disease (PD)
Lewy body dementias (LDBs)
PD dementia (PDD)
Dementia with Lewy bodies (DLB)
50-60
increasing age
70-80

Vascular cognitive impairment

- Critical region infarct
- Large vessel disease
- Small vessel disease
- AD + vascular (mixed)

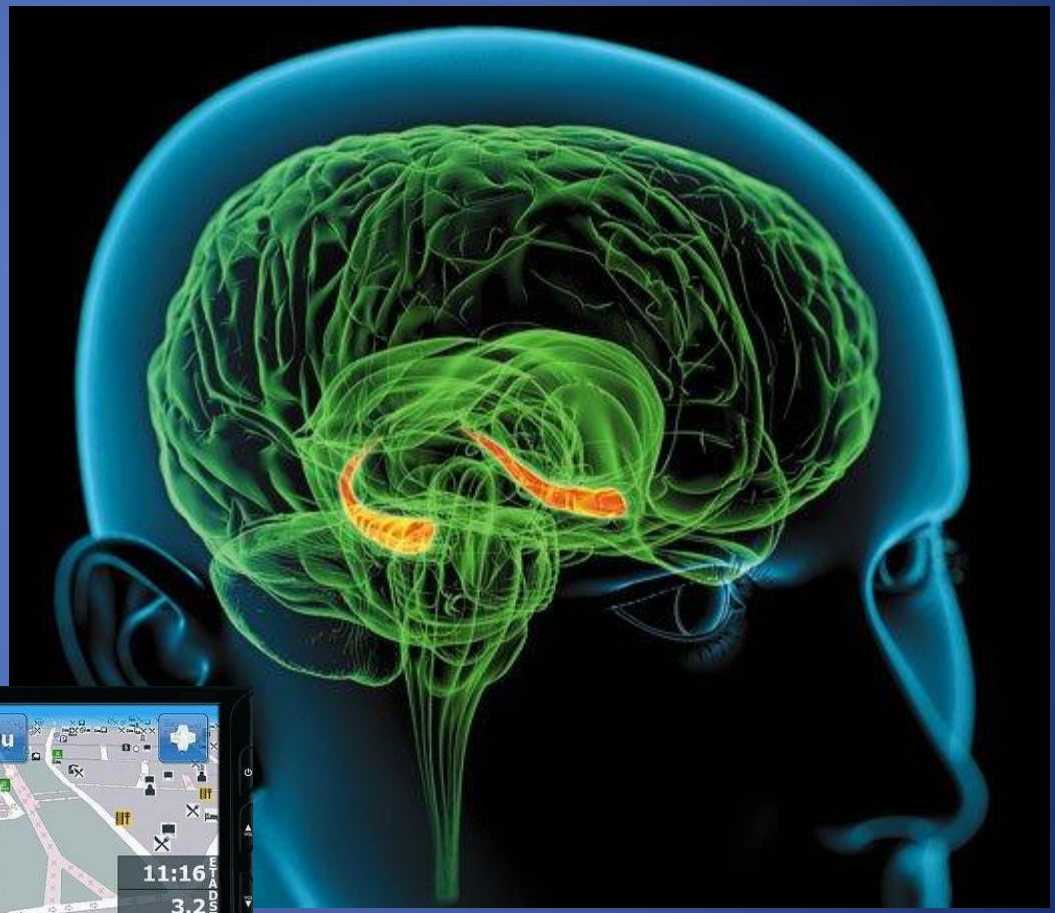
Vascular cognitive impairment

- Critical region infarct
- Large vessel disease
- Small vessel disease
- AD + vascular (mixed)

Critical regions: cortical

- hippocampus
- gyrus angularis
- gyrus cinguli

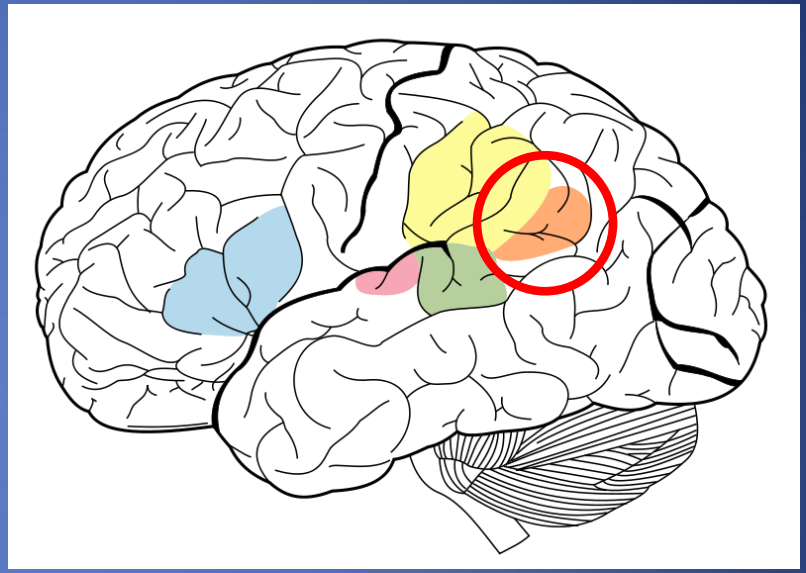
Episodic memory
Semantic memory
Cognitive map



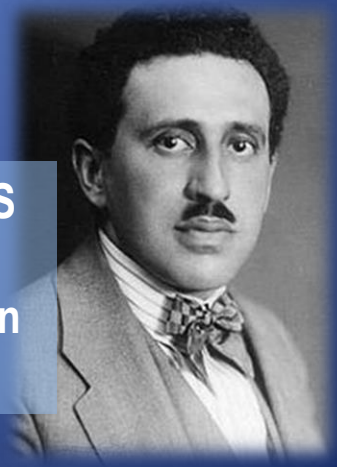
mgitecetech.wordpress.com

Critical regions: cortical

- hippocampus
- gyrus angularis
- gyrus cinguli



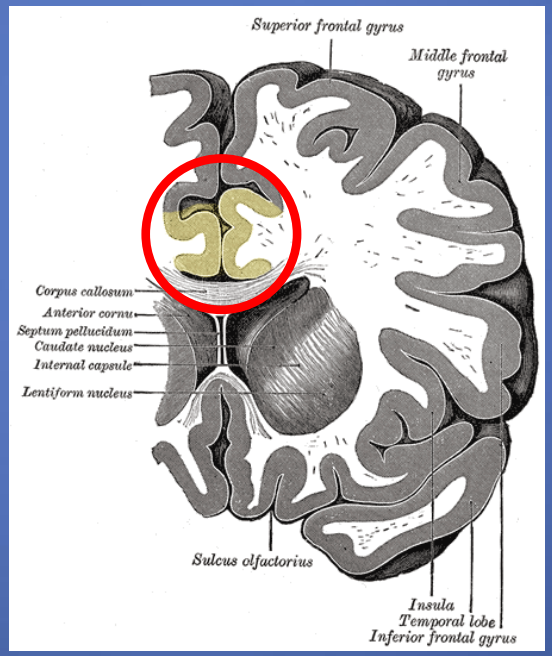
Aphasia (amnestic)
Alexia
Agrafia*
Acalculia*
Agnosia (fingeragnosia*, prosopagnosia)
Asomatognosia
Left-right-desorientation*



***GERSTMANN´S SYNDROME**
Josef Gerstmann
1887-1969

Critical regions: cortical

- hippocampus
- gyrus angularis
- gyrus cinguli

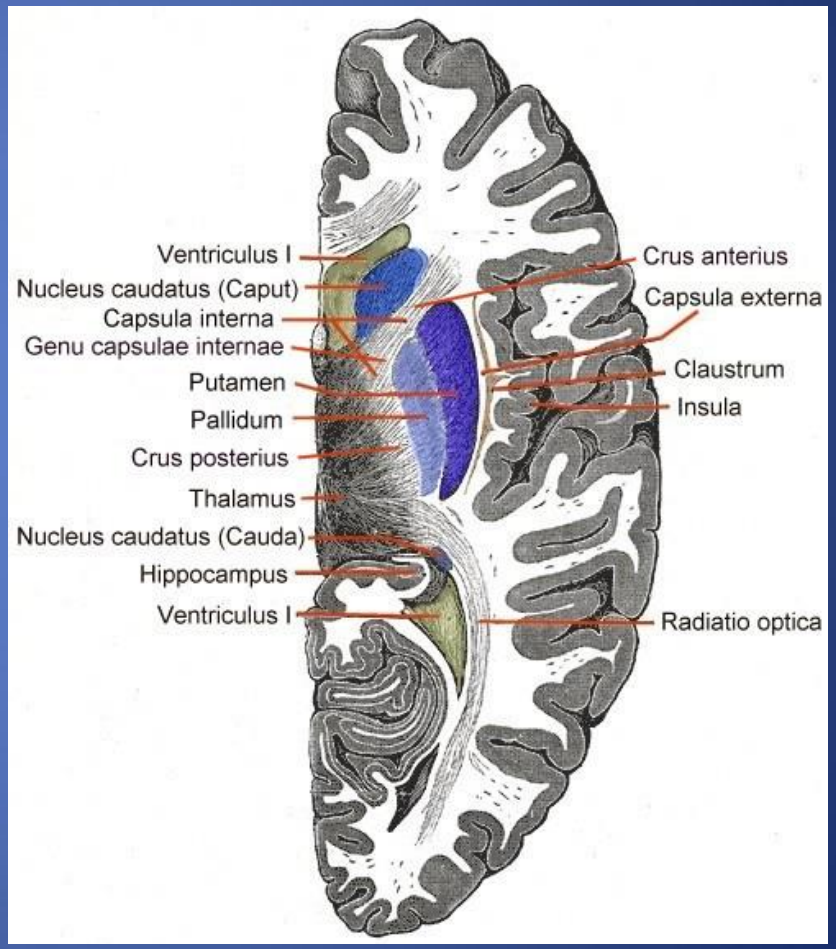


Part of limbic system.

Emotions, learning, memory, executive functions.

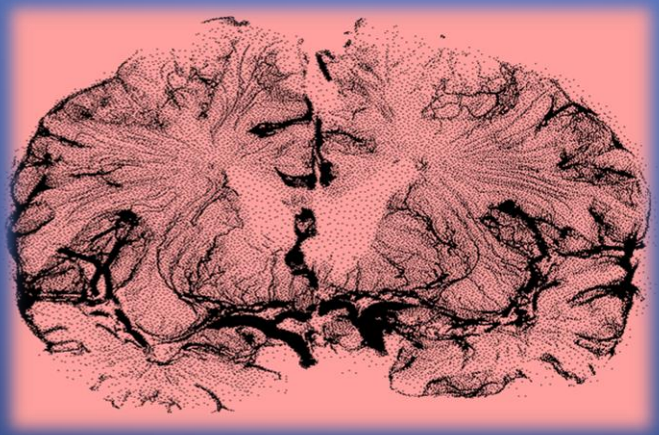
Critical regions: subcortical

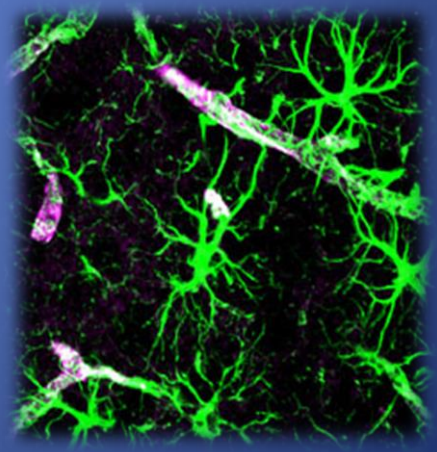
- thalamus
- fornix
- frontobasal regions
- nucleus caudatus
- pallidum
- anterior capsula interna/ genu



Vascular cognitive impairment

- Critical region infarct
- Large vessel disease
- Small vessel disease (SVD)
- AD + vascular (mixed)





SVD: arterioles

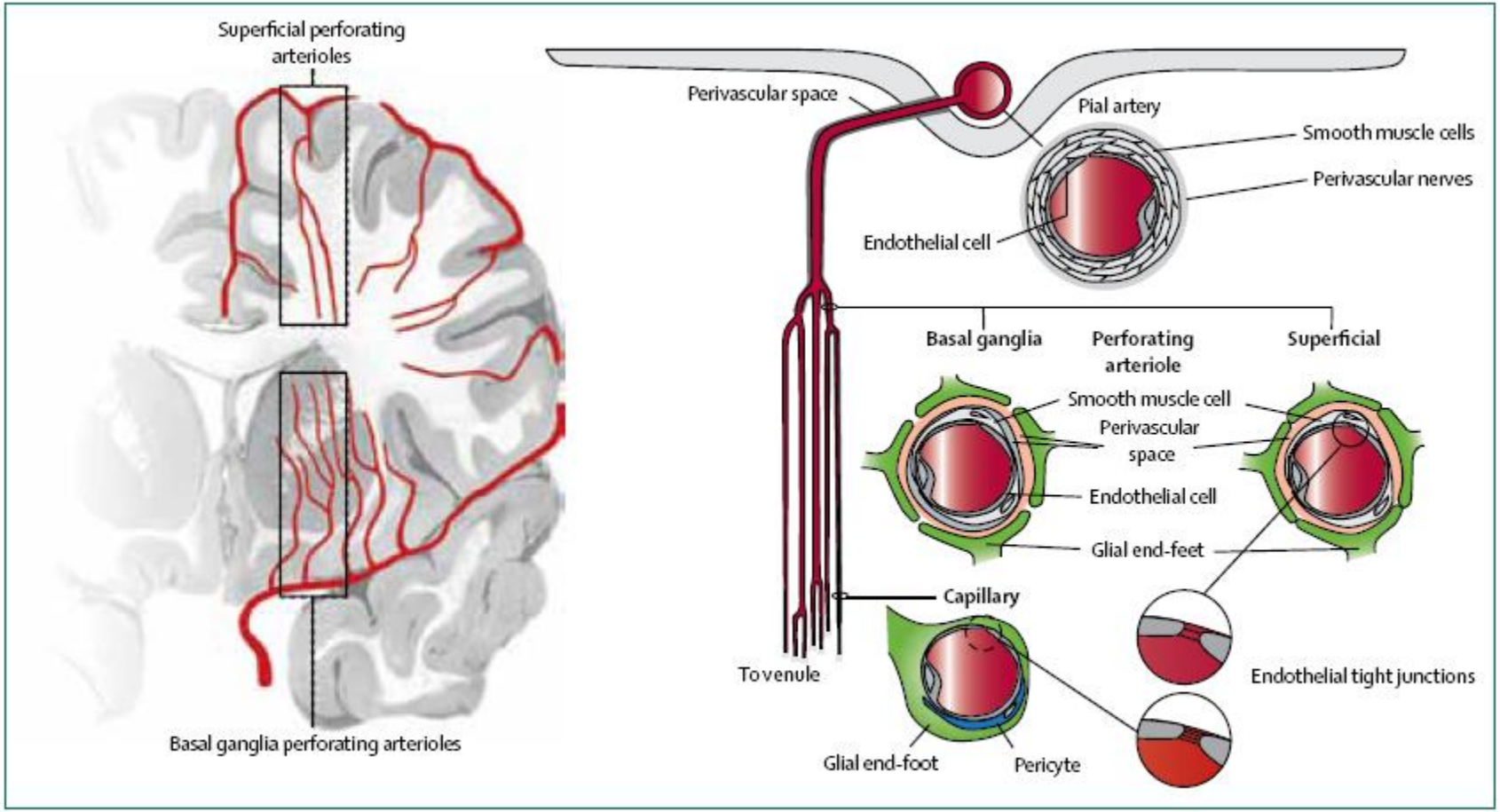
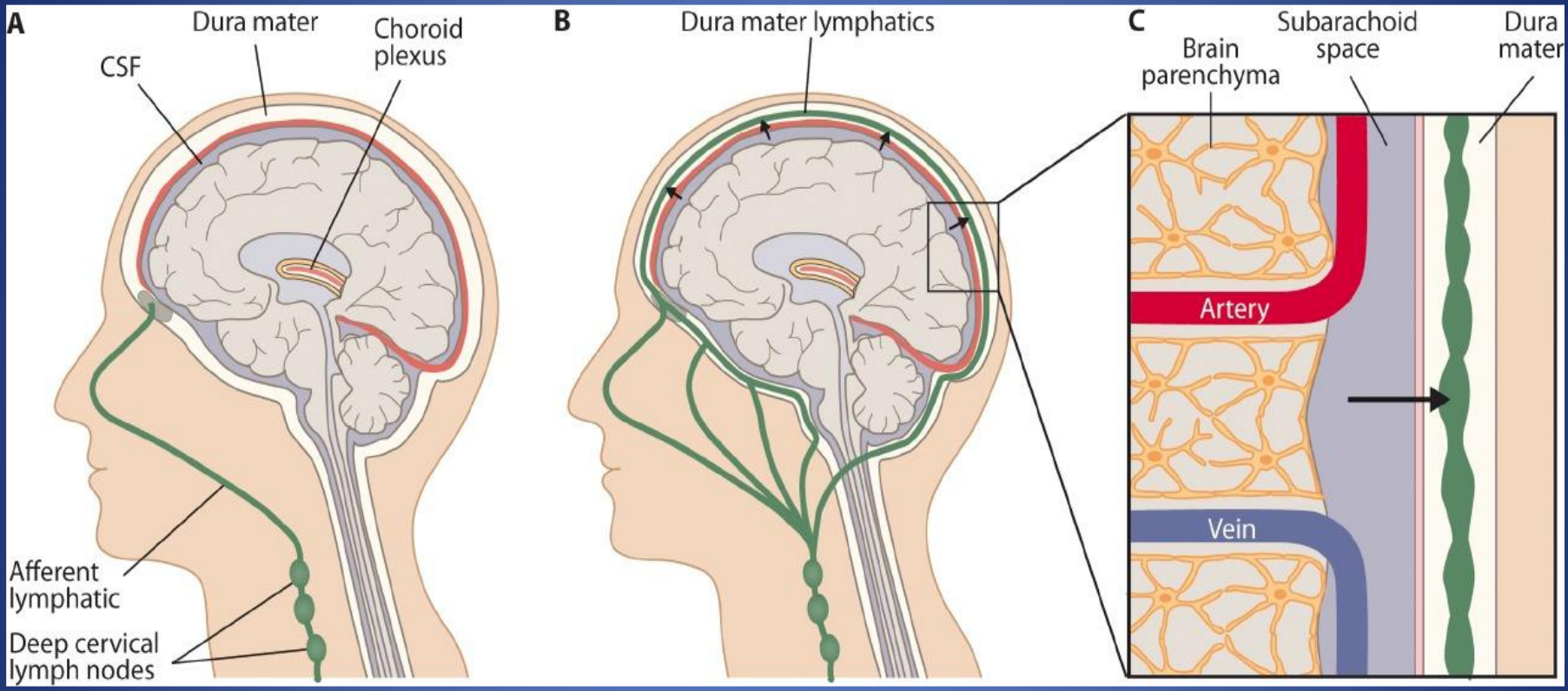


Figure 6: Key features of the arteriolar and capillary wall

Courtesy by Joanna M Wardlaw.

SVD: glymphatic vessels



- Decrease with advancing age
- Aquaporine-4 –system degrades, beta-amyloid elimination decreases

Kress BT et al. Ann Neurol 2014

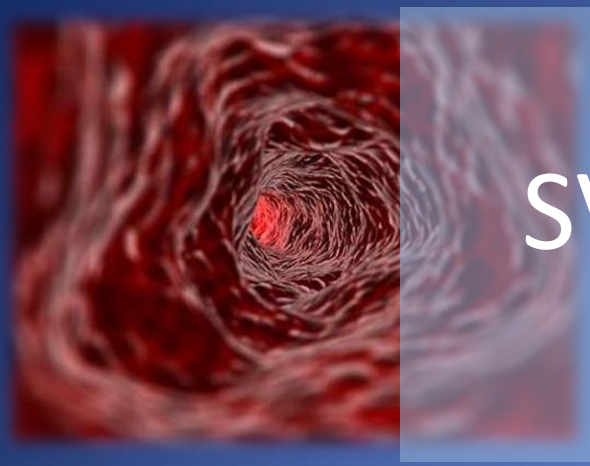
SVD: inflammation

- Inflammation affects blood-brain-barrier
- Different inflammatory paths in ischemic and hemorrhagic lesions?

SVD: genetic

- Notch3 – CADASIL

  (Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)



SVD: clinical image

- Executive dysfunction
- Amnesia less than in AD
- Behavioral symptoms: depression, change in personality, slowing down

LADIS

Leucoaraiosis And DISability in the Elderly, N=639 (65-84 v)

Review

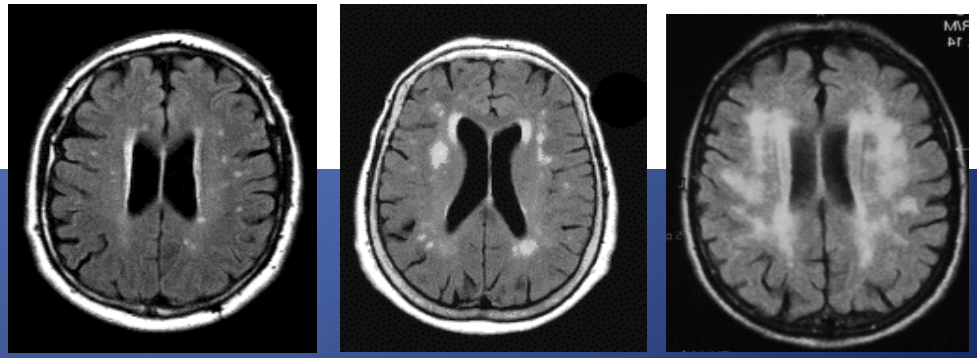
Cerebrovascular Diseases

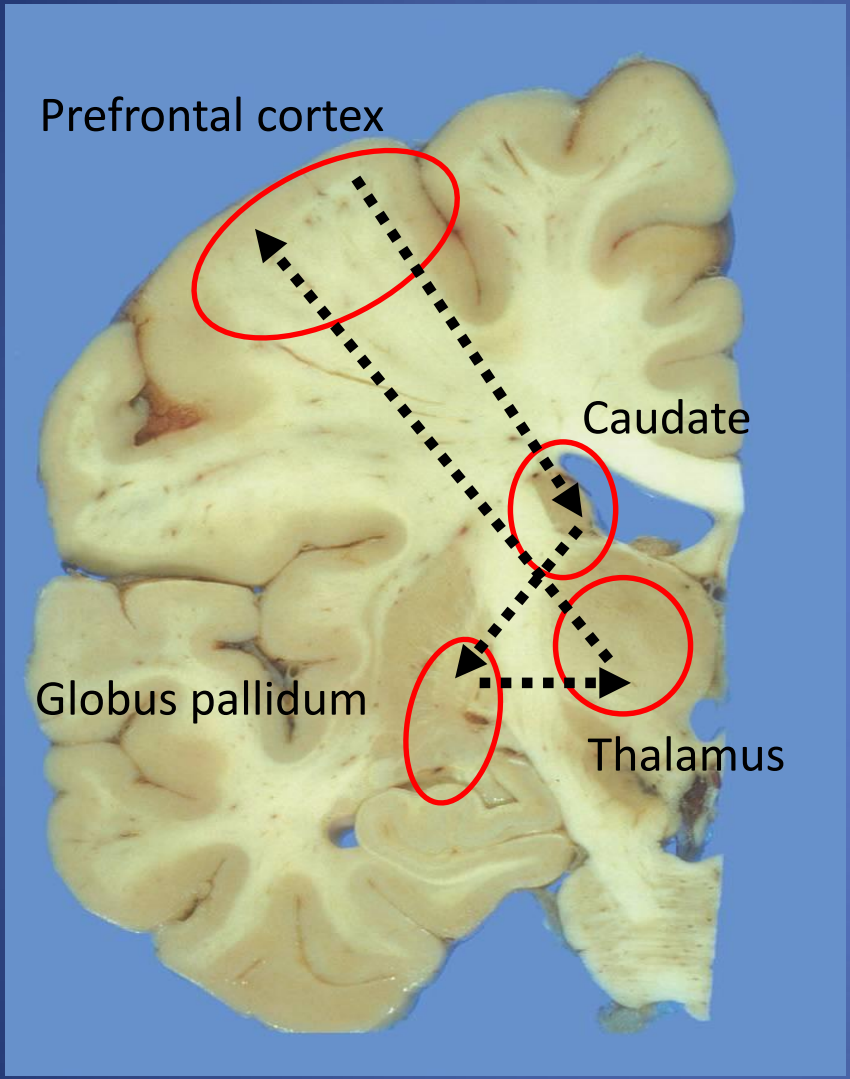
Cerebrovasc Dis 2011;32:577–588
DOI: 10.1159/000334498

Received: September 21, 2011
Accepted: October 18, 2011
Published online: December 1, 2011

2001–2011: A Decade of the LADIS (Leukoaraiosis And DISability) Study: What Have We Learned about White Matter Changes and Small-Vessel Disease?

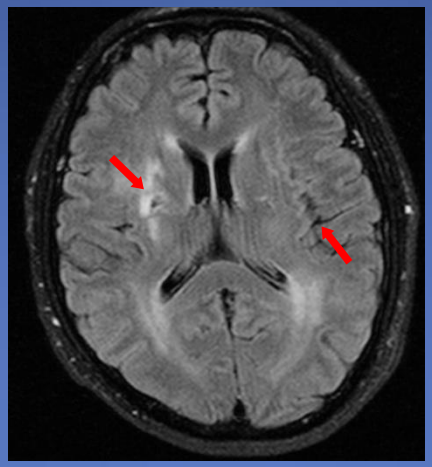
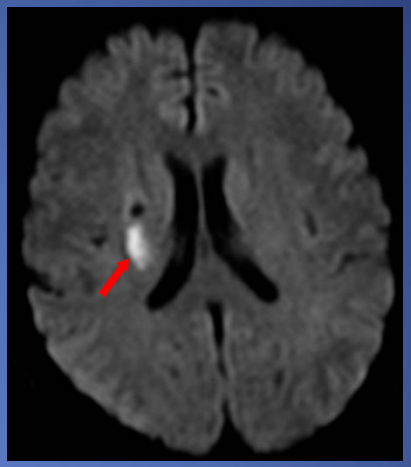
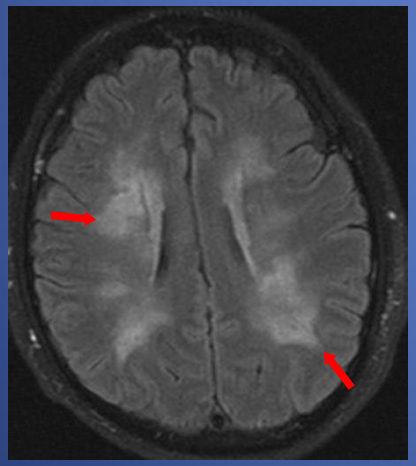
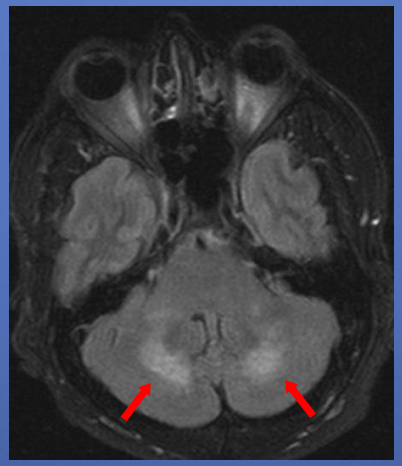
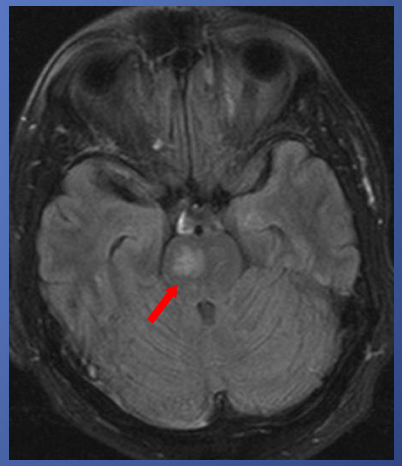
The LADIS Study Group[1]





Courtesy by Timo Erkinjuntti

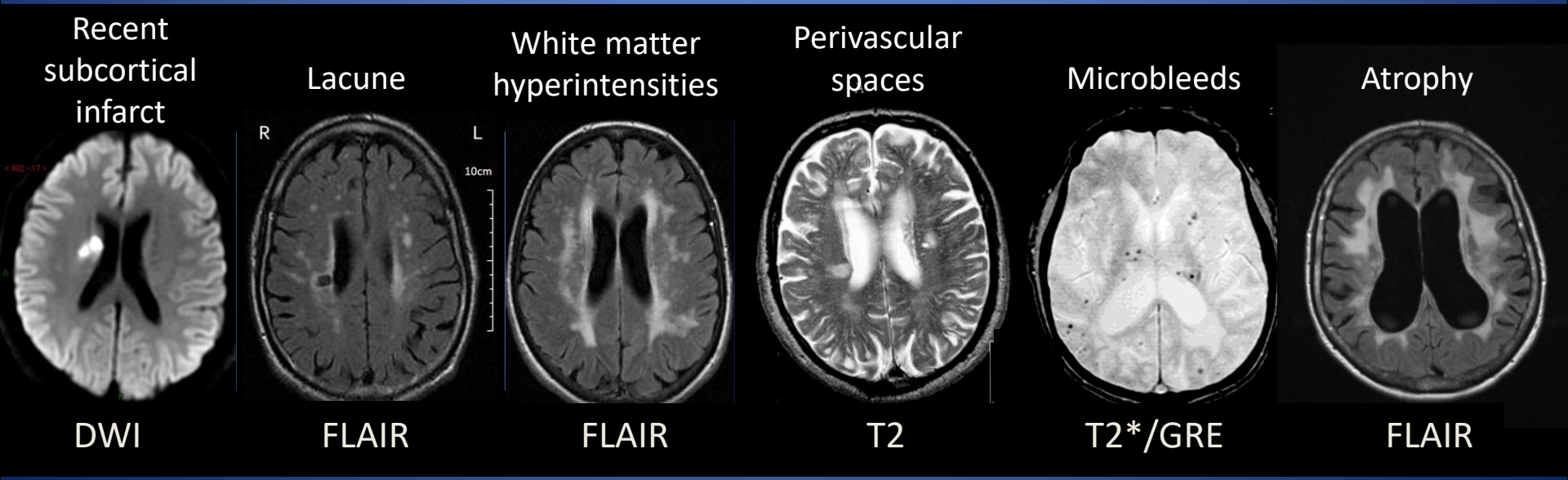
Prefrontal subcortical network

Recent advances in SVD

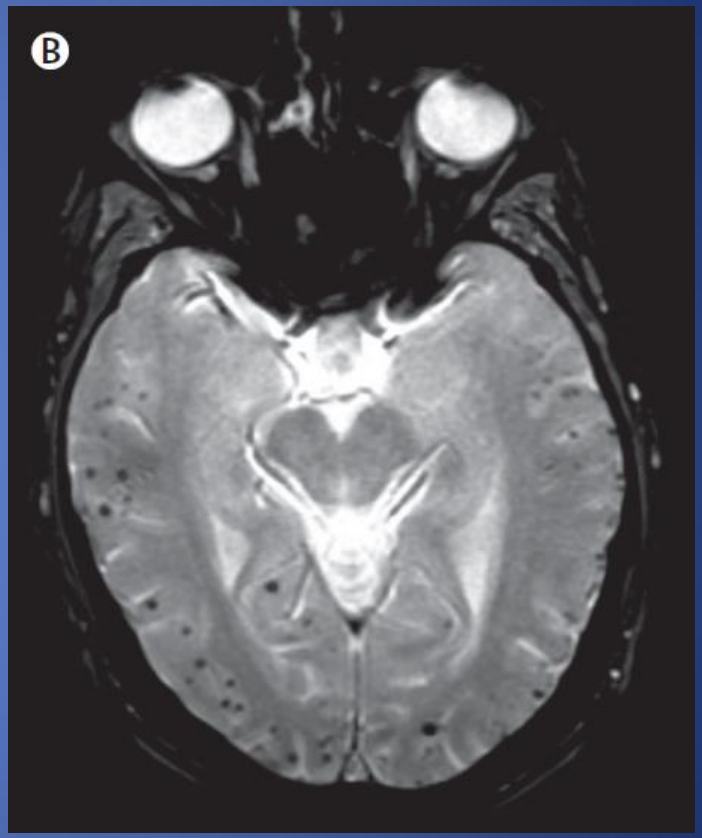
- Radiologic criteria implemented: Standards for Determining the Vascular Contribution to Neurodegeneration –project (STRIVE)
- Total load -thinking

Wardlaw JM et al. Lancet Neurology 2013



Amyloid angiopathy

- Aβ40 accumulates within cerebral vessel walls.
- Associated with intracerebral hemorrhage.
- Severe amyloid angiopathy is found in one out of four Alzheimer patients.



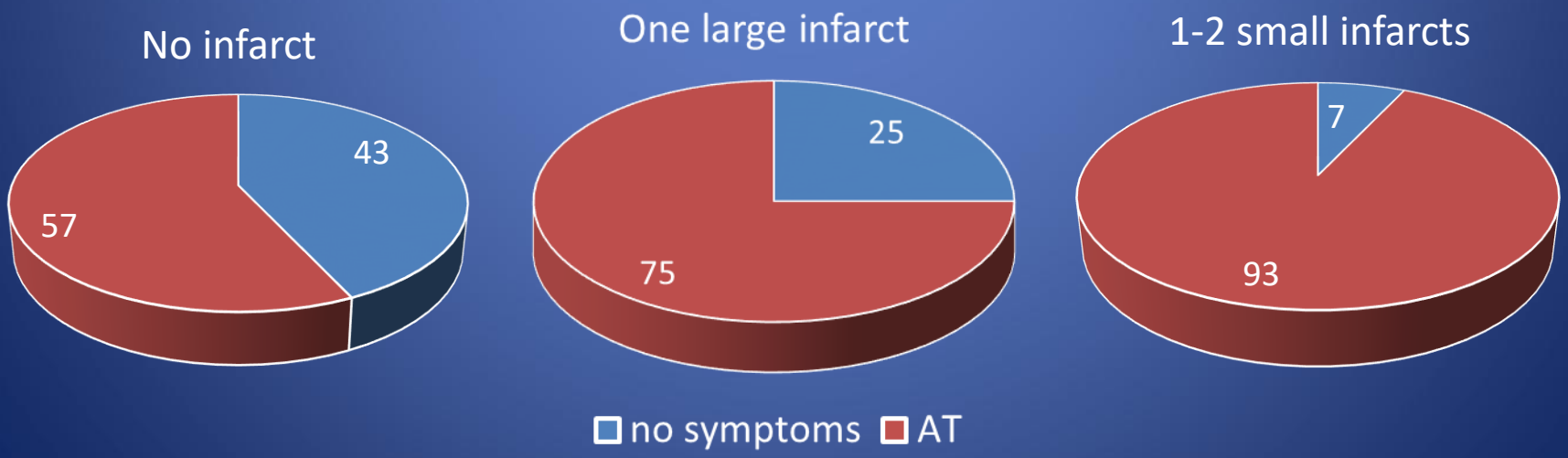
SVD risk factors

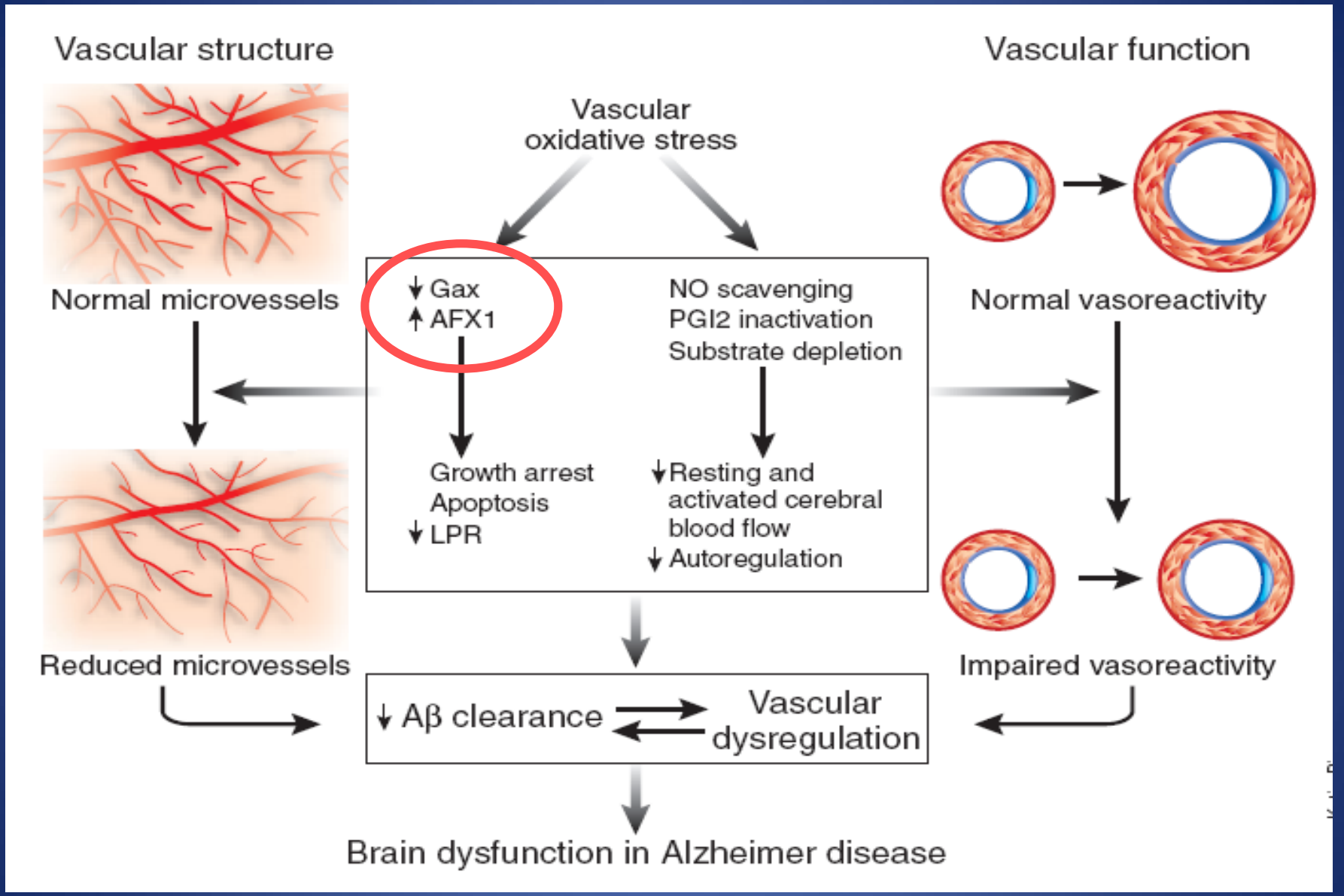
	Lacune	WMH	Microbleed
Age	x	x	
Male sex	x		
Hypertension	x	x	x
Hypercholesterolemia		contradictory	contradictory
Low LDL			x
Statin use			contradictory
Diabetes	x	x	
Atrial fibrillation	x		
Smoking	x	x	x (deep CMB)
Internal carotid artery stenosis	x		
High homocysteine		contradictory	
Low vitamin B12/folate		x	

Mok V, Kim JS. Journal of Stroke 2015

Vascular cognitive impairment

- Critical region infarct
- Large vessel disease
- Small vessel disease
- AD + vascular (mixed)





Iadecola C, Nature Med 2005;11:923-924

Huntington's disease

- unbalanced cytosine-adenine-guanine (CAG) repeat expansion in the Huntingtin gene (HTT)
- autosomal dominant inheritance, anticipation
- uncontrolled movements, emotional problems, and loss of thinking ability (cognition)

Creutzfeld-Jakob's disease

- prion from "protein", "infectious"
- sporadic, hereditary or acquired
- failing memory, behavioral changes, lack of coordination, visual disturbances
  - Remember: myoclonic movements and cognitive changes -> rule out CJD
- MRI, CSF, EEG findings suggestive, but only PAD is conclusive (biopsy/autopsy)

Cognitive tests

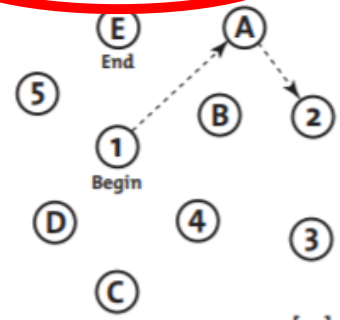
- MMSE (Minimental State Examination)
- MoCA (Montreal Cognitive Assessment)
- CERAD (The Consortium to Establish a Registry for Alzheimer's Disease, USA 1986)

- Golden standard: Neuropsychological examination

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE



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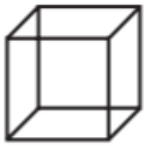


Copy cube

[ ]

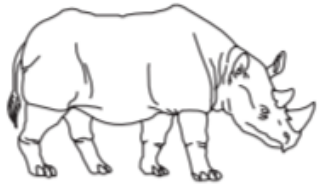
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING

[ ]



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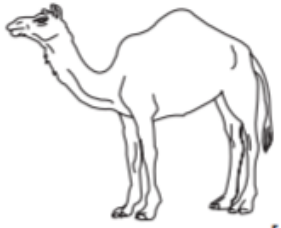


[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

		FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
	Has to recall words WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

 Version November 7, 2004

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Treatment of Alzheimer's disease

- 200 therapeutic agents tested for AD
- Five have been approved for clinical use: the cholinesterase inhibitors (donepezil, galantamine, rivastigmine and tacrine) and the N-methyl-d-aspartate (NMDA) antagonist memantine.
- Of the remainder: 87 active in current trials.
- Six Phase IV trials of agents already approved for use in other conditions (including prazocin, carvedilol and simvastatin).

In all cognitive symptoms

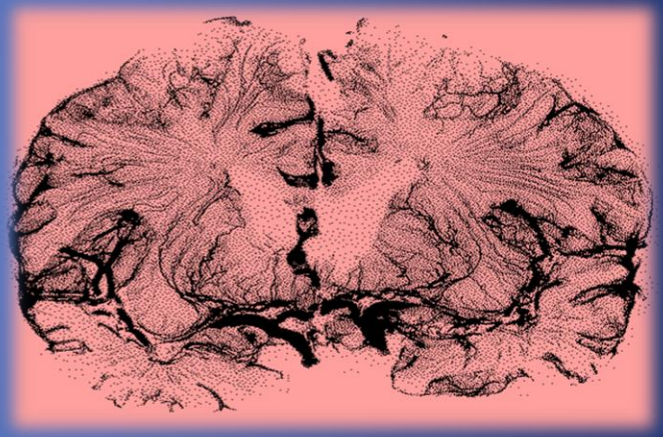
Important to

- avoid opiates, digoxin, beta-blockers etc.
- take care of the small vessels
- treat mood disorders

Most important in management of SVD

4 P by professor Leonardo Pantoni

- Predictive
- Personalized
- Preventive
- Participatory



”...regular exercise promotes the structural integrity of CNS and, thereby, counteracts age-related decline.”

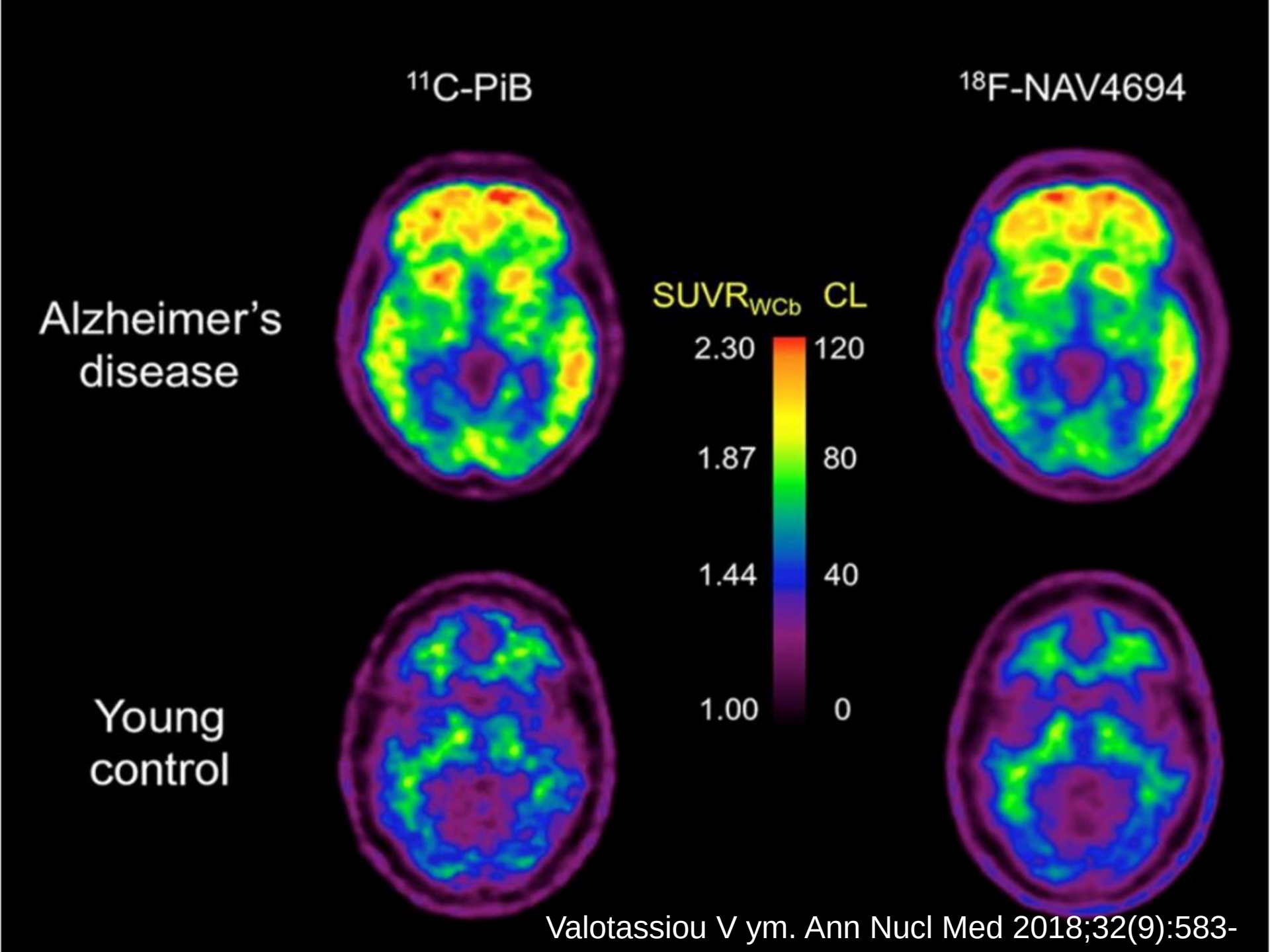
What could help in developing treatments against dementia?

- Identify genetic variants -> identify multiple causes of what had appeared to be a single dementia syndrome.

- Develop evaluation of earliest symptoms -> reshape the assessment of therapeutics.

New radiologic methods

- Positron Emission Tomography (PET) uses ligands specific for the molecular abnormalities characteristic of dementias.
  - Amyloid-PET-TT
  - FDG-PET-TT

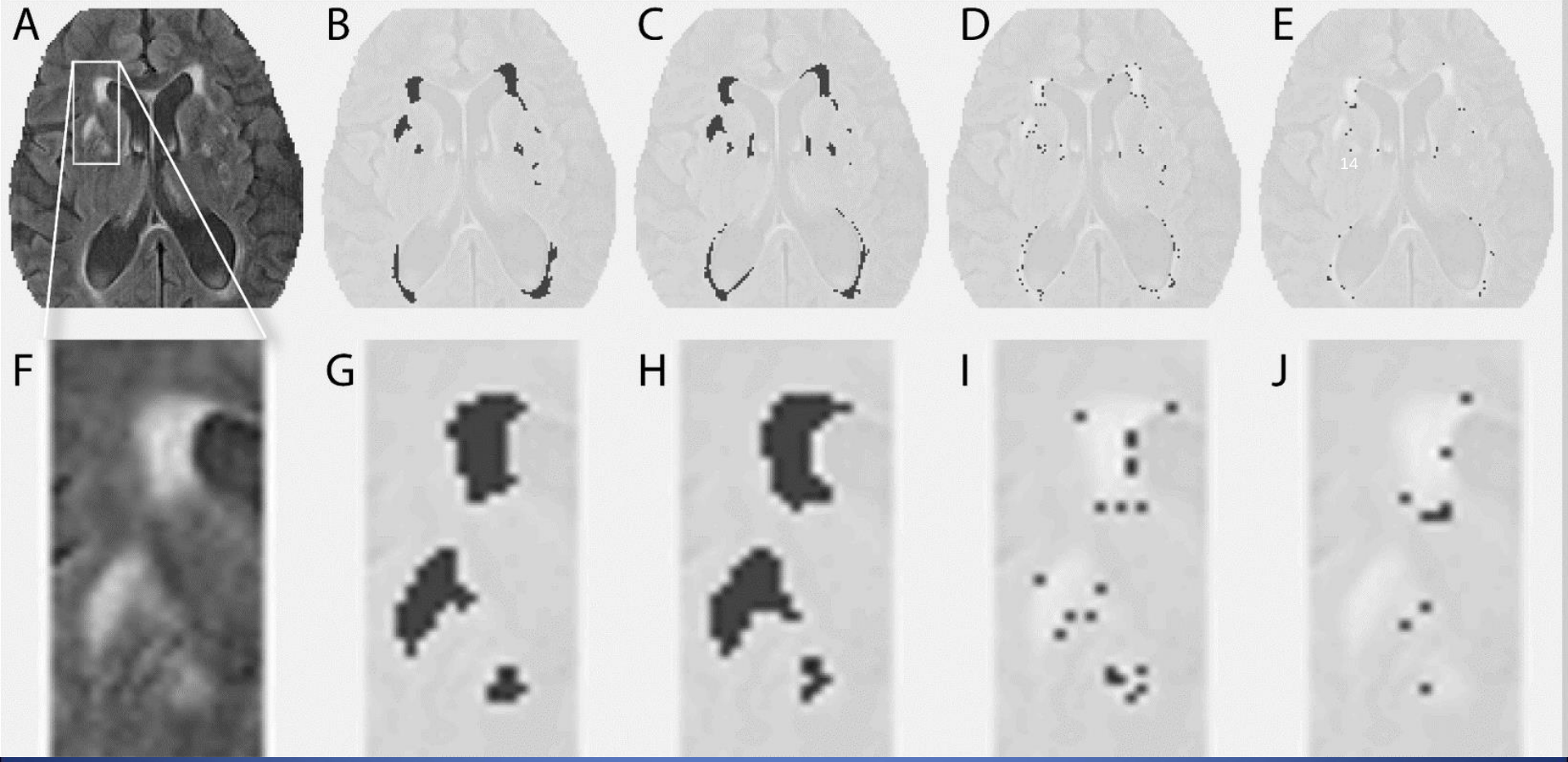


Valotassiou V ym. Ann Nucl Med 2018;32(9):583-

A new multispectral tissue segmentation method

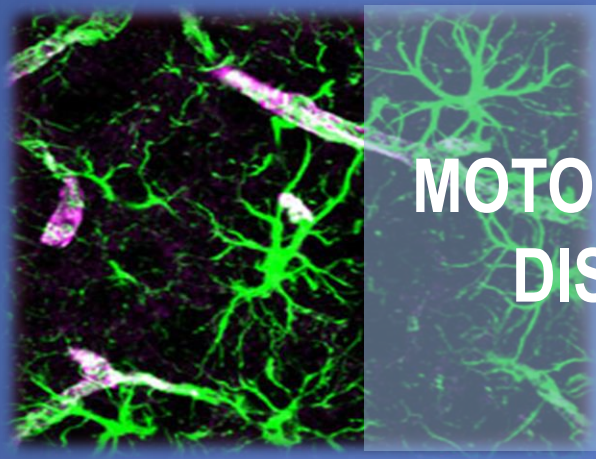
Gonçalves N et al. Int J Neural Syst 2014; Jokinen H et al. Front Neurosci 2015

- Detects *partial WML volumes* representing very early-stage changes in normal-appearing brain tissue
- MRI scans of 78 subjects from the LADIS study were analyzed using multispectral segmentation to identify tissue types and partial WML volumes
- Each lesion voxel was classified as having a small (33%), intermediate (66%), or high (100%) proportion of lesion tissue



(A) FLAIR image
(B) Conventionally estimated WML
(C-E) Estimated WML, using the segmentation algorithm, for high, intermediate and small proportion of lesion

Jokinen H et al. Front Neurosci 2015.



MOTOR NEURON DISEASES

ALS, amyotrophic lateral sclerosis

- affects nerve cells in the lateral spinal cord and in the brain
- sporadic (95%) or familial
- symptoms: muscle weakness and atrophy, spasticity, muscle cramps, and fasciculations.

ALS continued

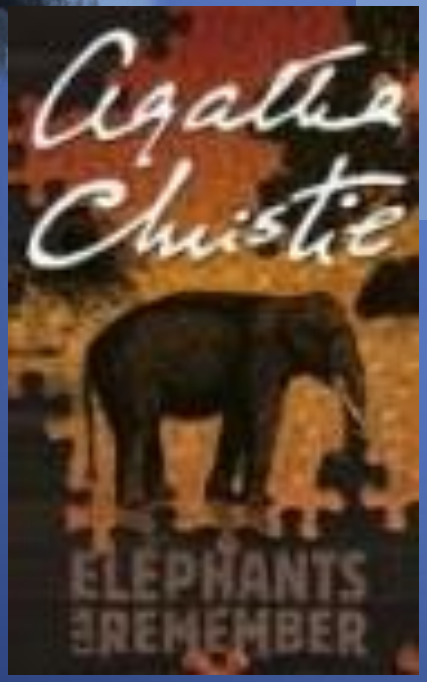
- diagnosis: cervical spine MRI and brain MRI normal, ENMG is diagnostic
- may be associated with fronto-temporal dementia

Other motor neuron diseases

- Primary lateral sclerosis
- Progressive bulbar palsy
- Spinal muscle atrophy

Take home message

- Neurodegeneration means misfolding, aggregation, and accumulation of proteins in the CNS.
- In brain, vascular contribution to neurodegeneration can be managed.
- Although the diseases are progressive, there is substantial variation in prognosis.



”Memory is a wonderful thing, but pity those who cannot forget.”

Olli Kortekangas, composer

Thank you