Cerebral Small Artery Disease: An Update

Gordon R. Kelley MD FAAN
Medical Director
AHSM Stroke Program

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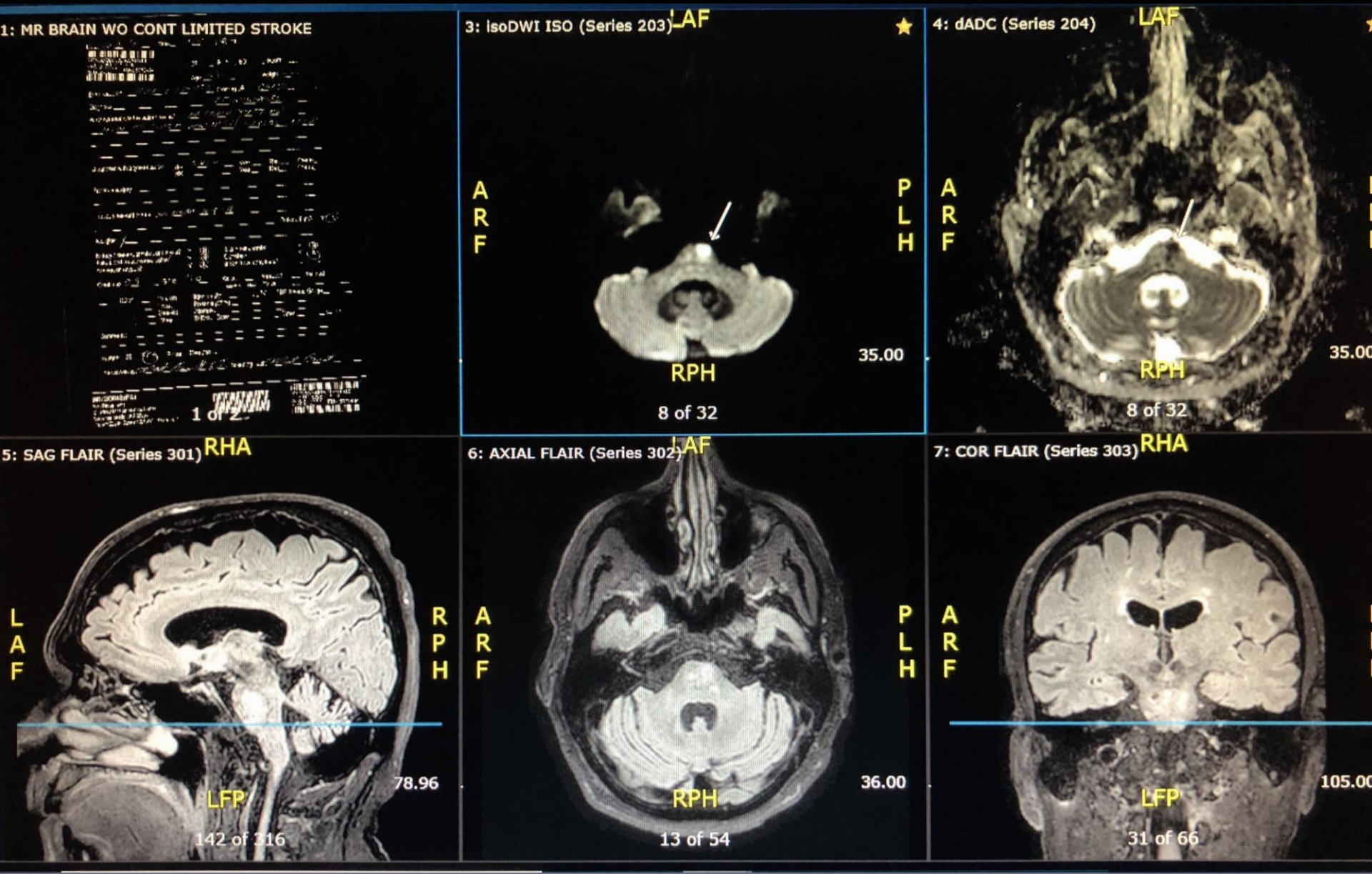
63 yo RH Caucasian male

- Presents 10/08 with three brief spells of slurred speech
- No health care for decades but BP was elevated when basal cell ca excised 1 year ago
- NIHSS 0
- BP 242/106
- MRI: moderate chronic white matter signal hyperintensities in the cerebral hemispheres and brainstem

- After admission fluctuating R facial droop, slurred speech and pure motor R hemiparesis
- At 24 hours after admission the right arm and leg were completely flaccid, speech severely dysarthric NIHSS: 13
- BP's ranged 103-208 systolic
- Echo: severe concentric LVH
- TC: 162, HDL: 43, LDL: 120, Trig: 63
- Hgb A1c: 5.7


1: MR BRAIN WO CONT LIMITED STROKE
1 of 2
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PLH
RPH
35.00
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4: dADC (Series 204)
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5: SAG FLAIR (Series 301)
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RPH
LFP
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6: AXIAL FLAIR (Series 302)
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7: COR FLAIR (Series 303)
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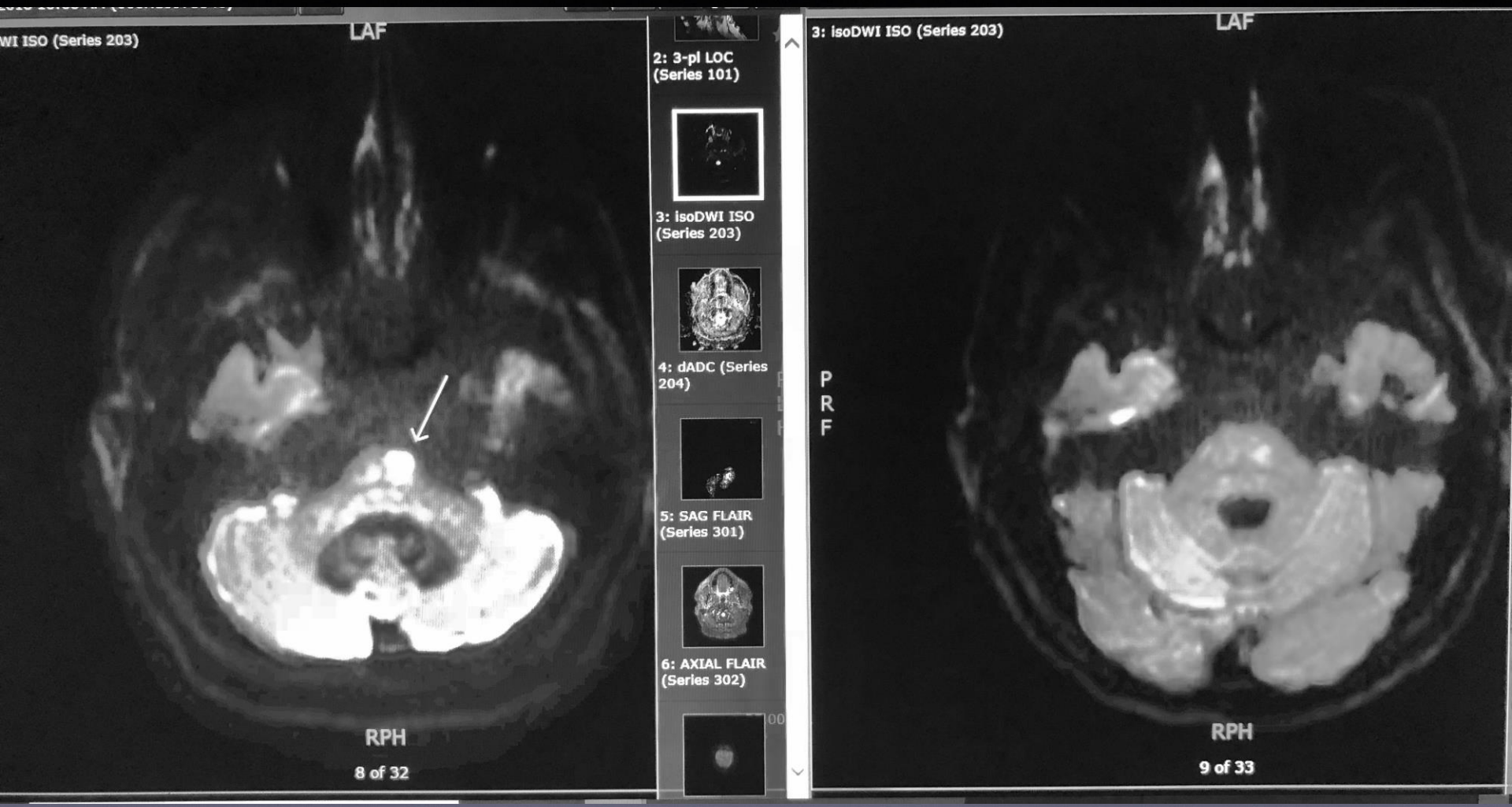
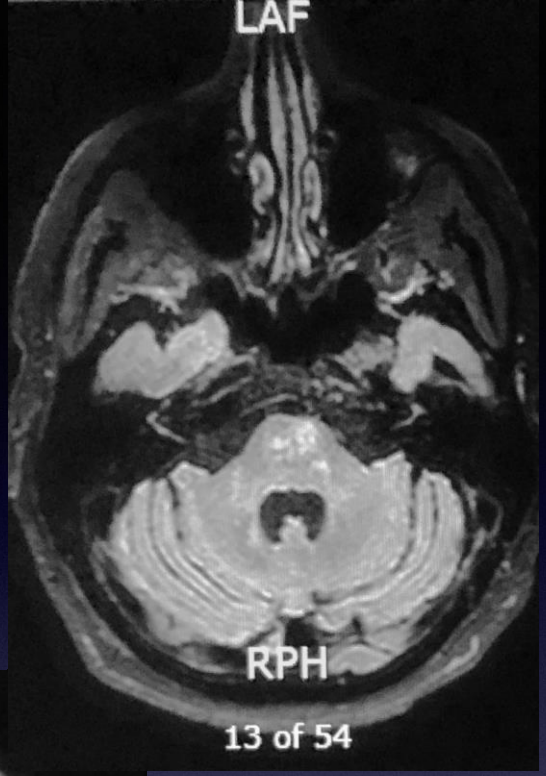


DWI: 1 day after admission

DWI: day of admission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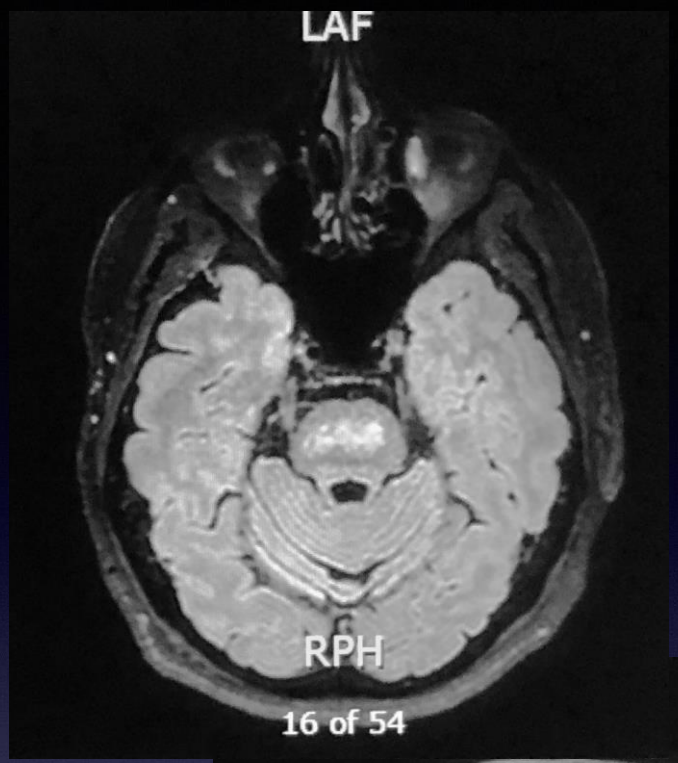
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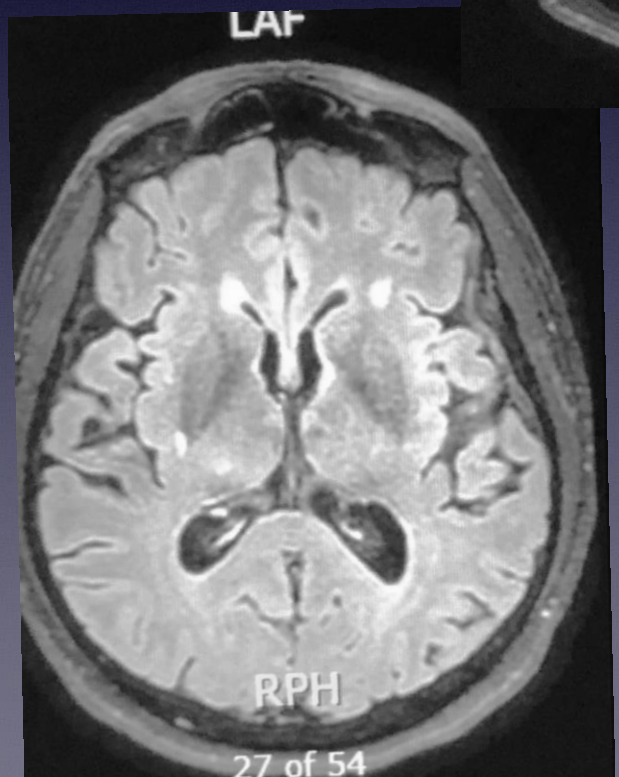
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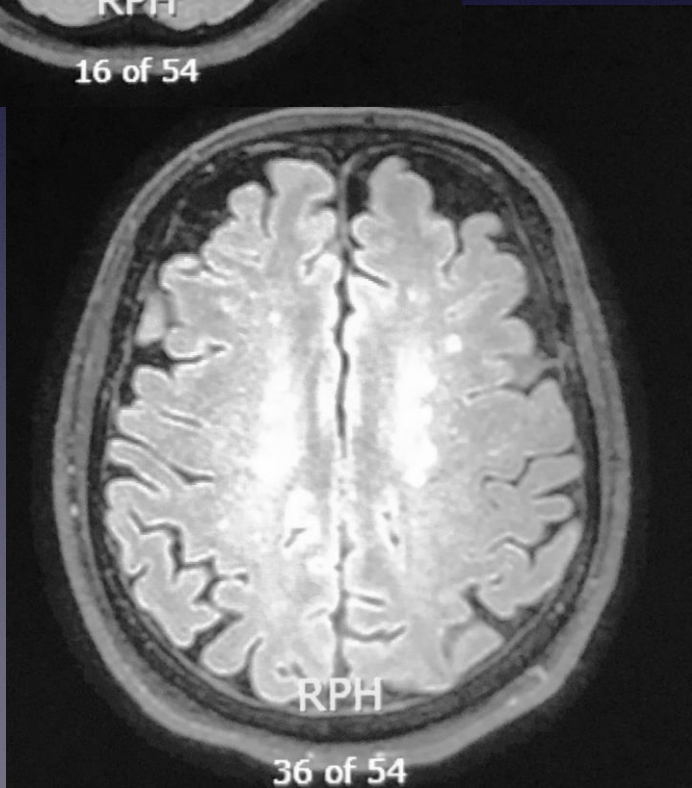

RPH
36 of 54

STROKE

Primary Hemorrhage
15%
-intraparenchymal
-subarachnoid

Ischemic Stroke
85%

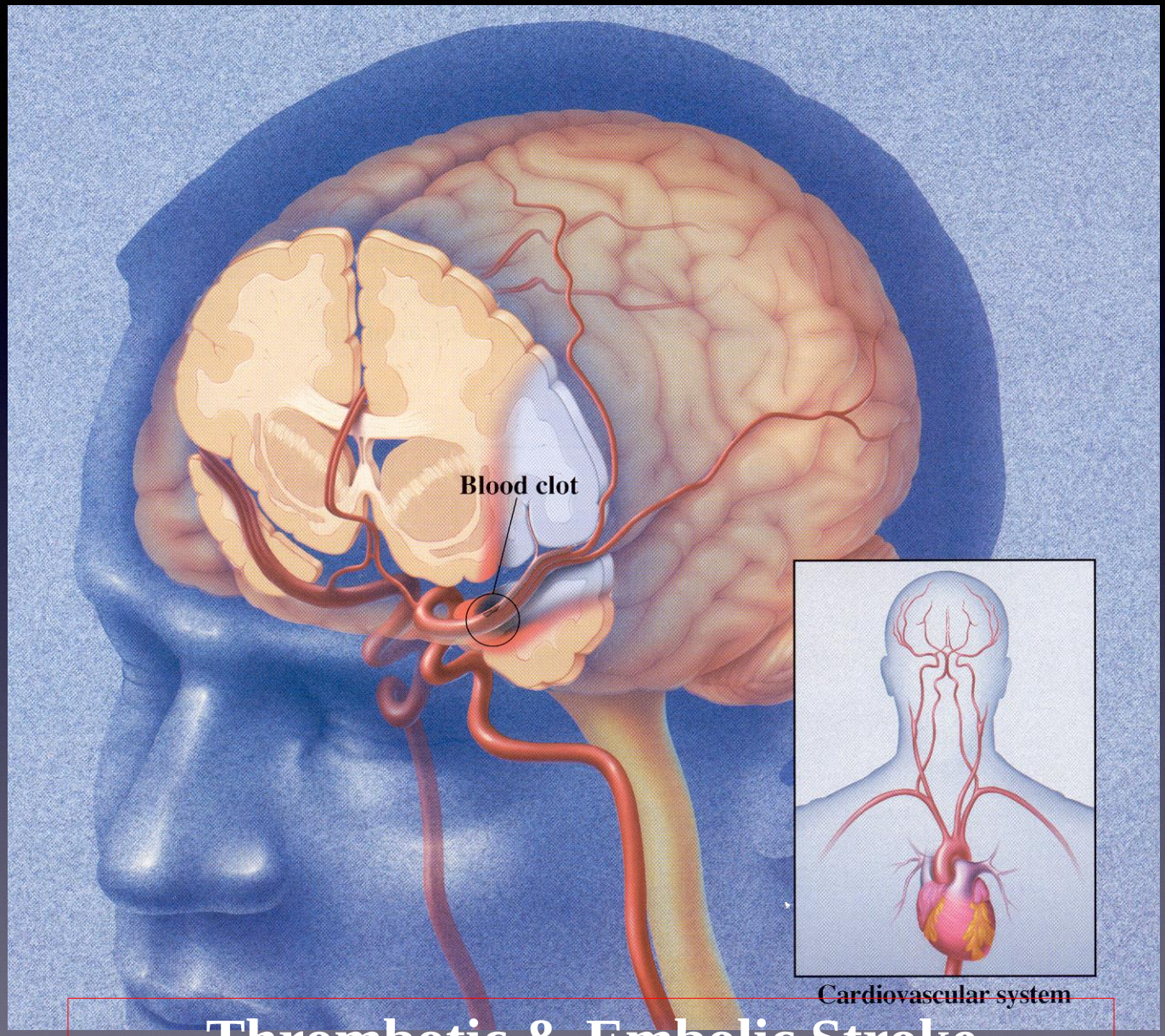
Atherosclerosis
20%
-thrombosis
-arteriogenic emboli

Small Artery Disease
25%
"lacunes"

Cardiogenic Embolism
20%
-atrial fib.
-many others

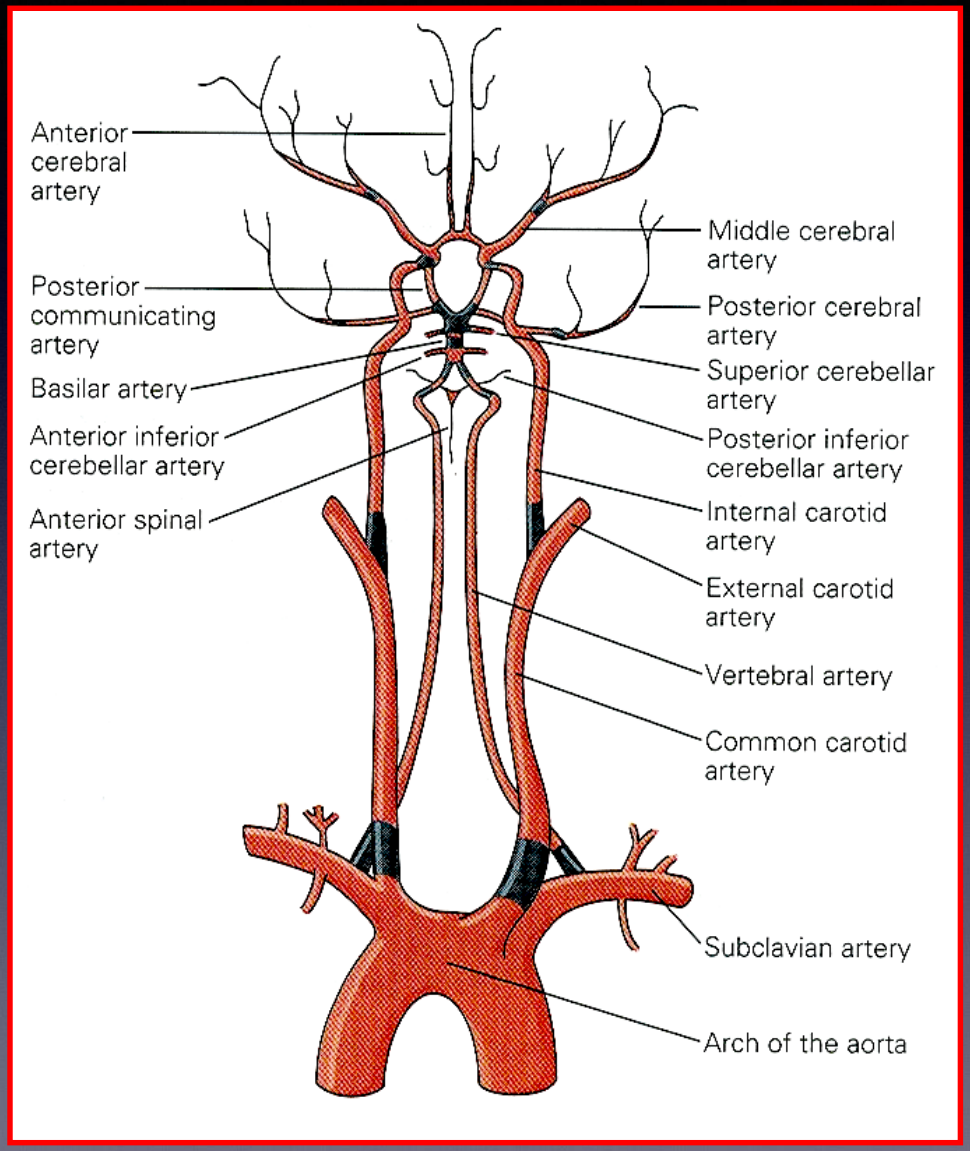
Cryptogenic Stroke
30%
-? aortic emboli

Other, Unusual Causes
5%
-dissections, arteritis, migraine
-hypercoaguability, drug abuse, more



Thrombotic & Embolic Stroke

Sites of Atherosclerosis



- Especially above bifurcations
- At sites of maximum turbulence and sheer stress

Inflammation & Atherosclerosis

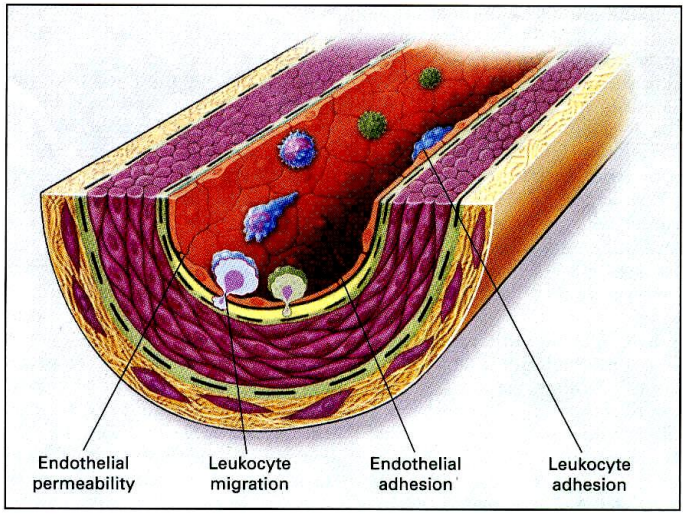


Figure 1. Endothelial Dysfunction in Atherosclerosis.

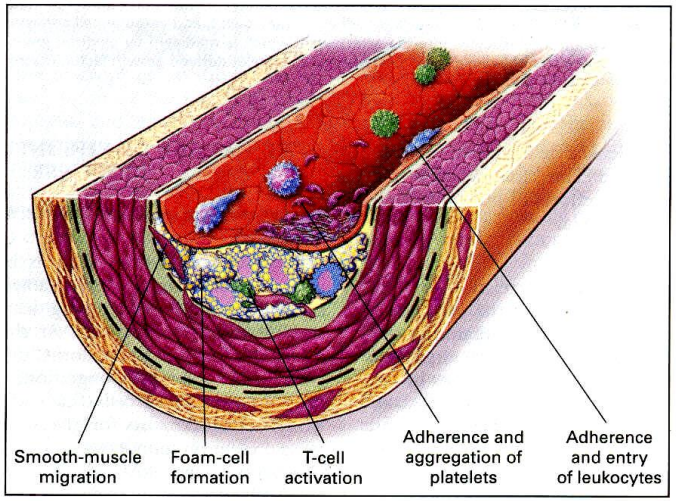


Figure 2. Fatty-Streak Formation in Atherosclerosis.

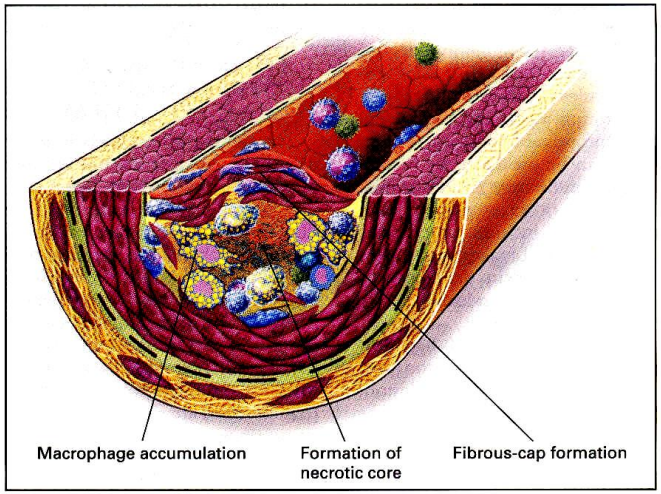


Figure 3. Formation of an Advanced, Complicated Lesion of Atherosclerosis.

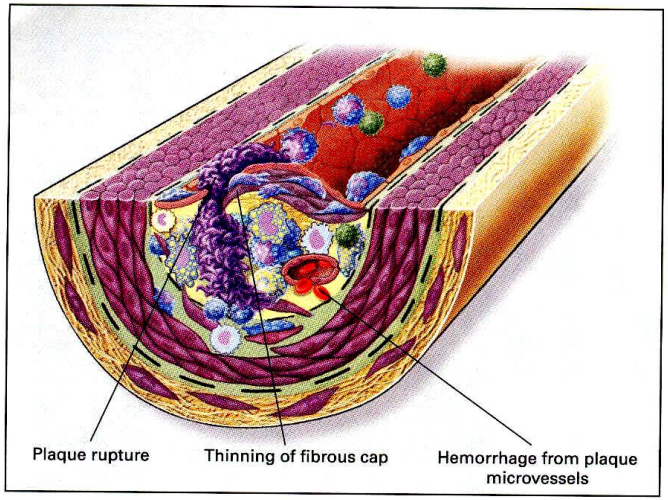
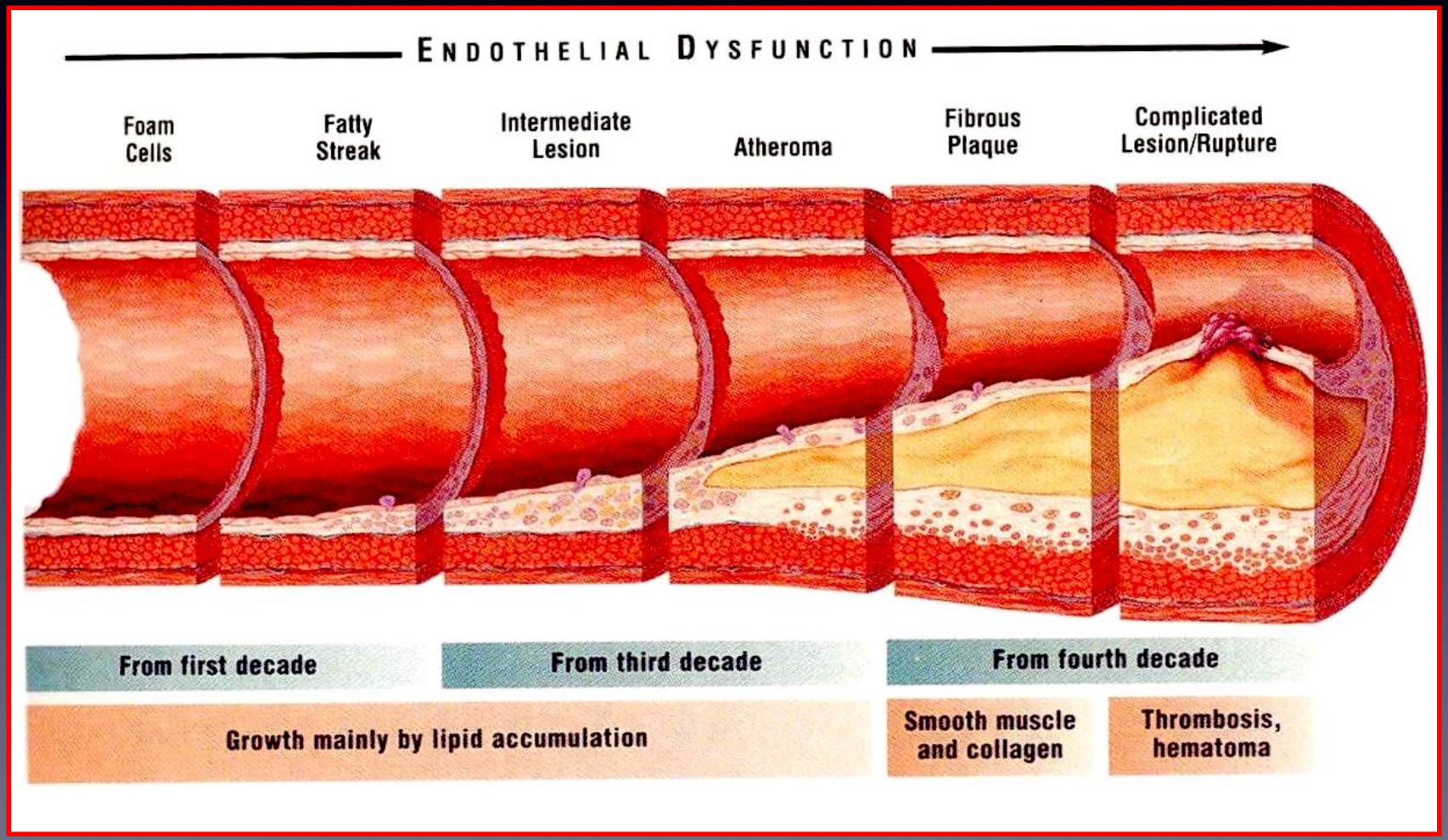
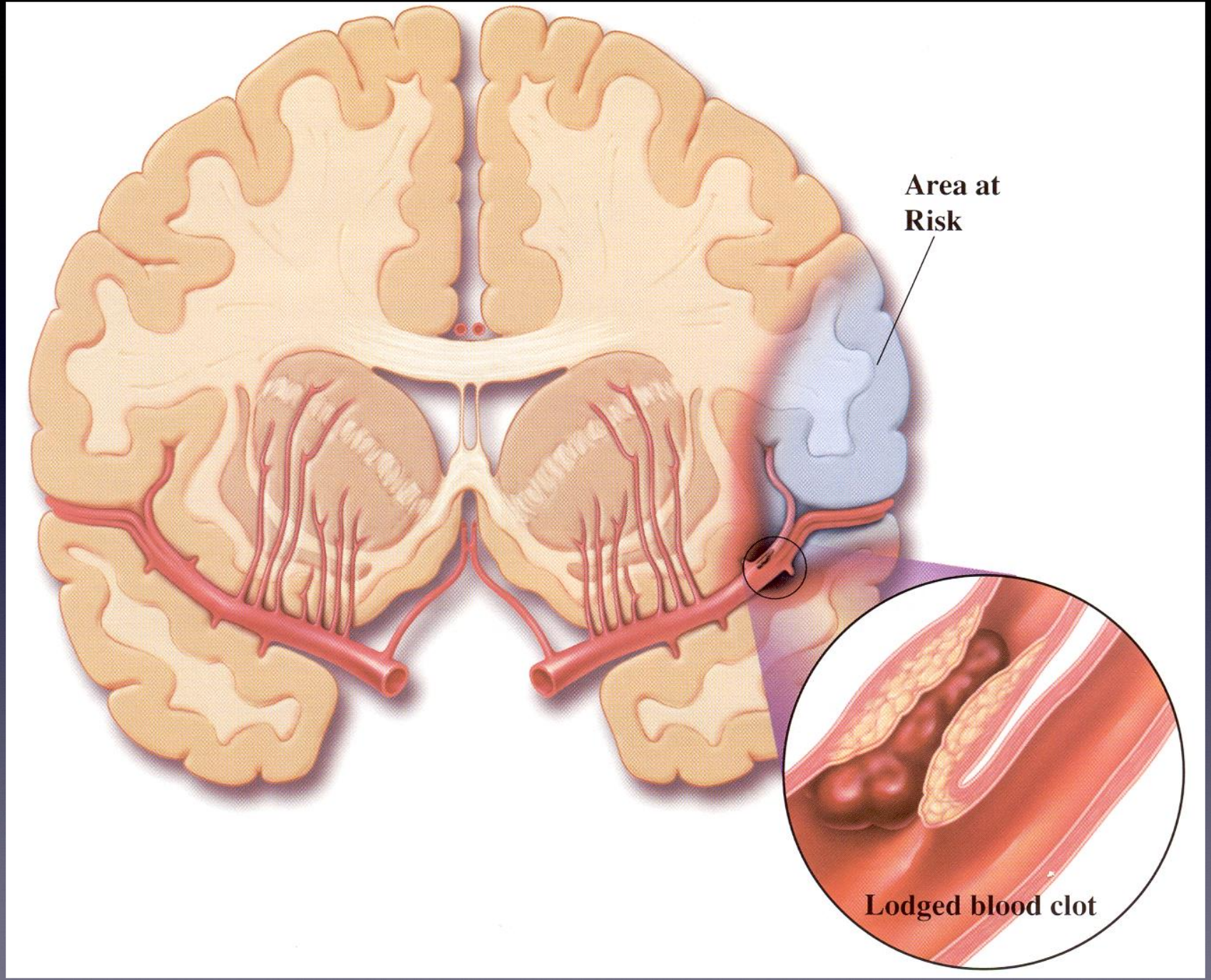


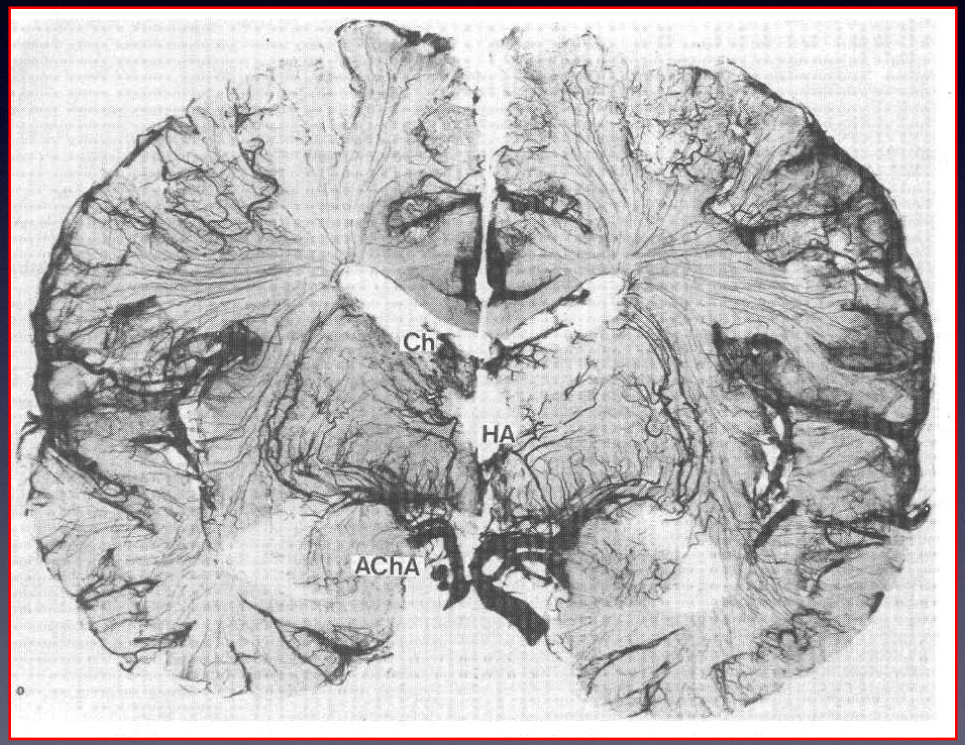
Figure 4. Unstable Fibrous Plaques in Atherosclerosis.

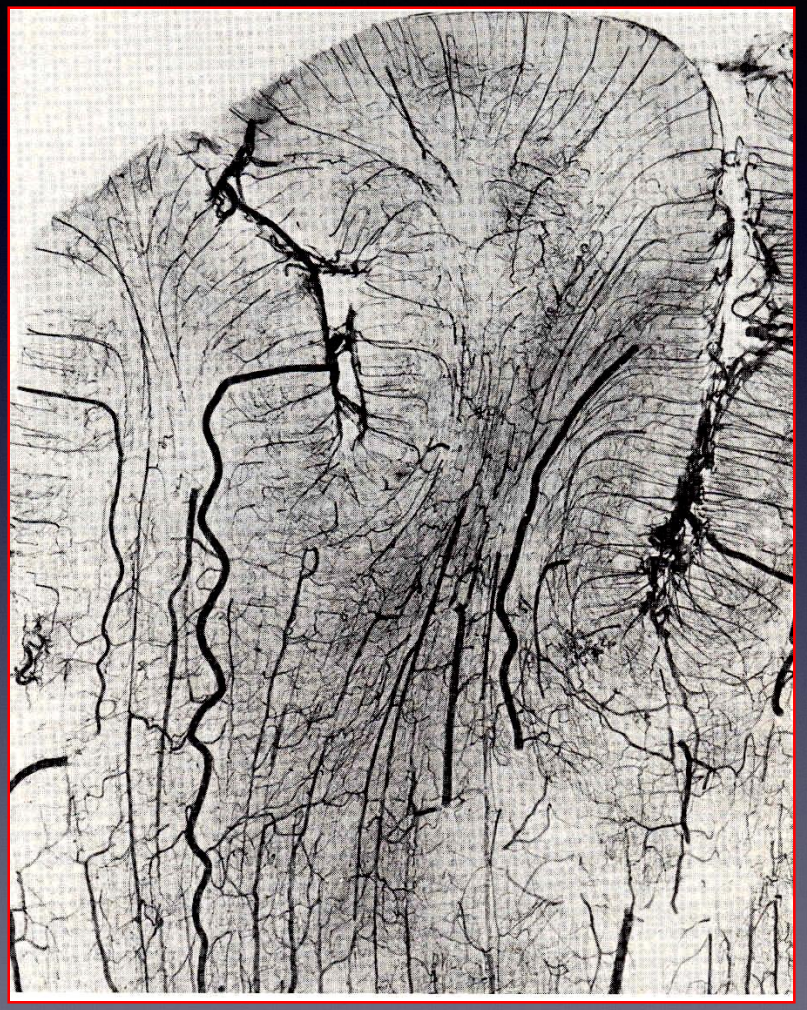
Atherosclerosis Timeline



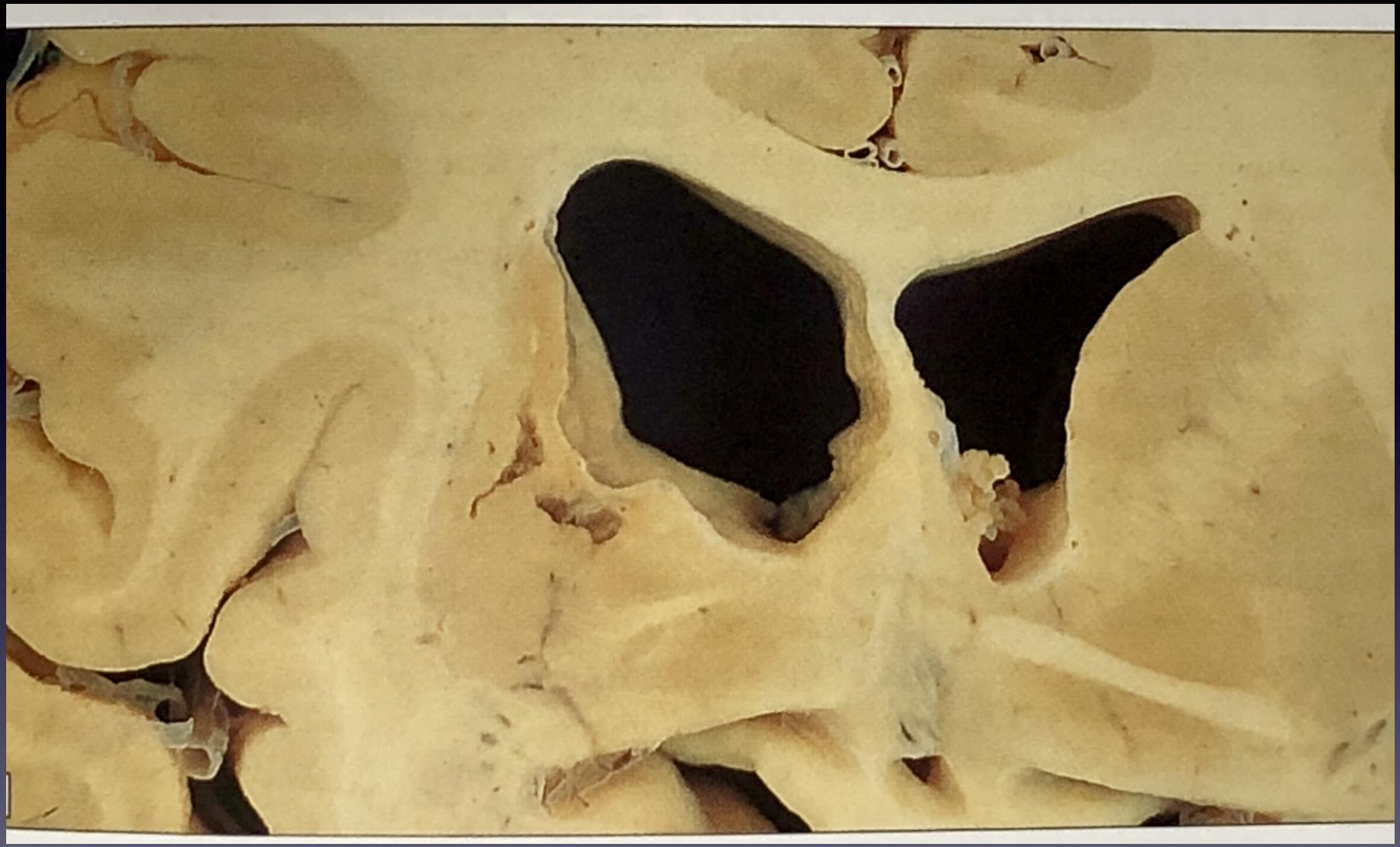

Area at
Risk
Lodged blood clot

Deep penetrating small vessels

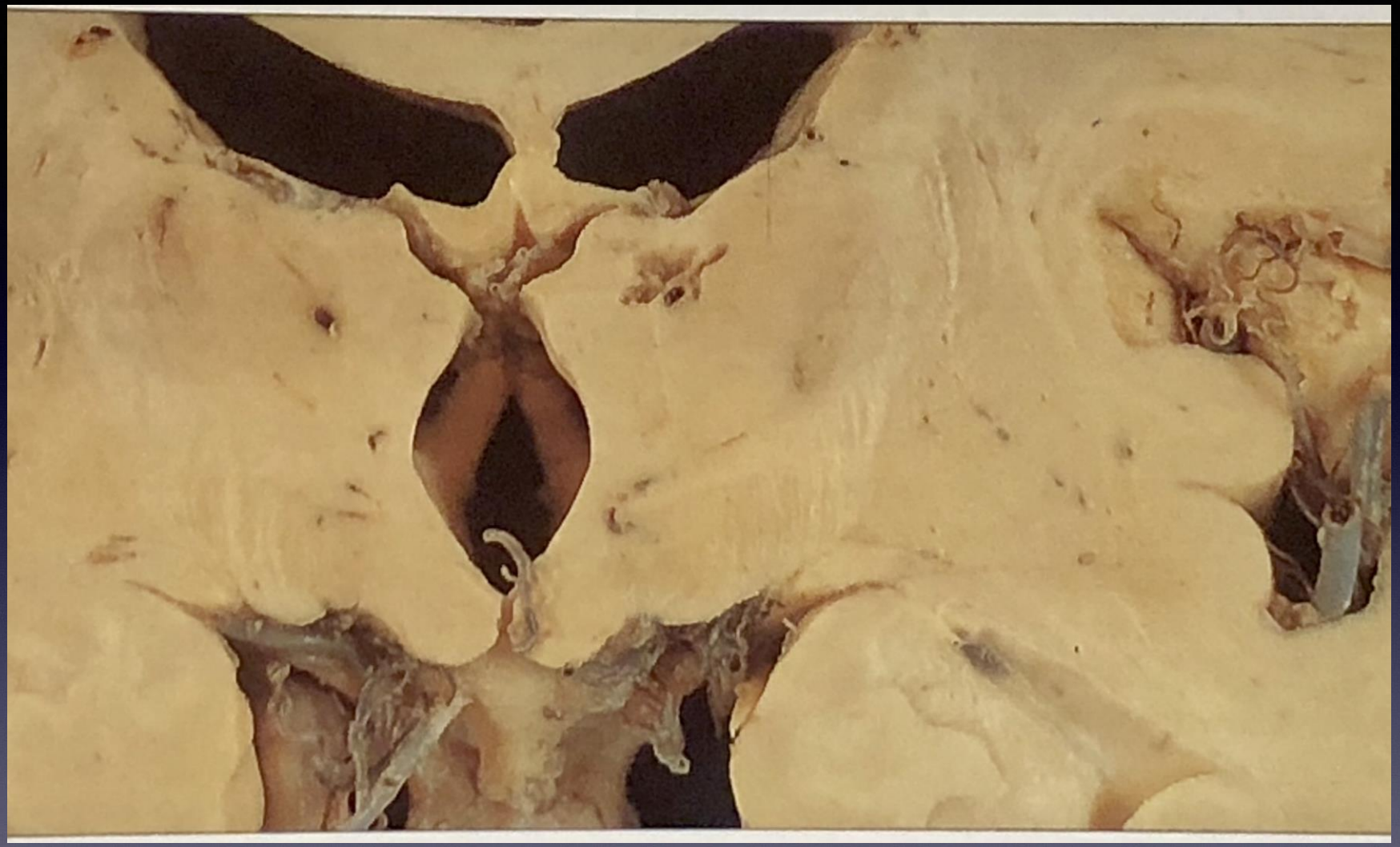




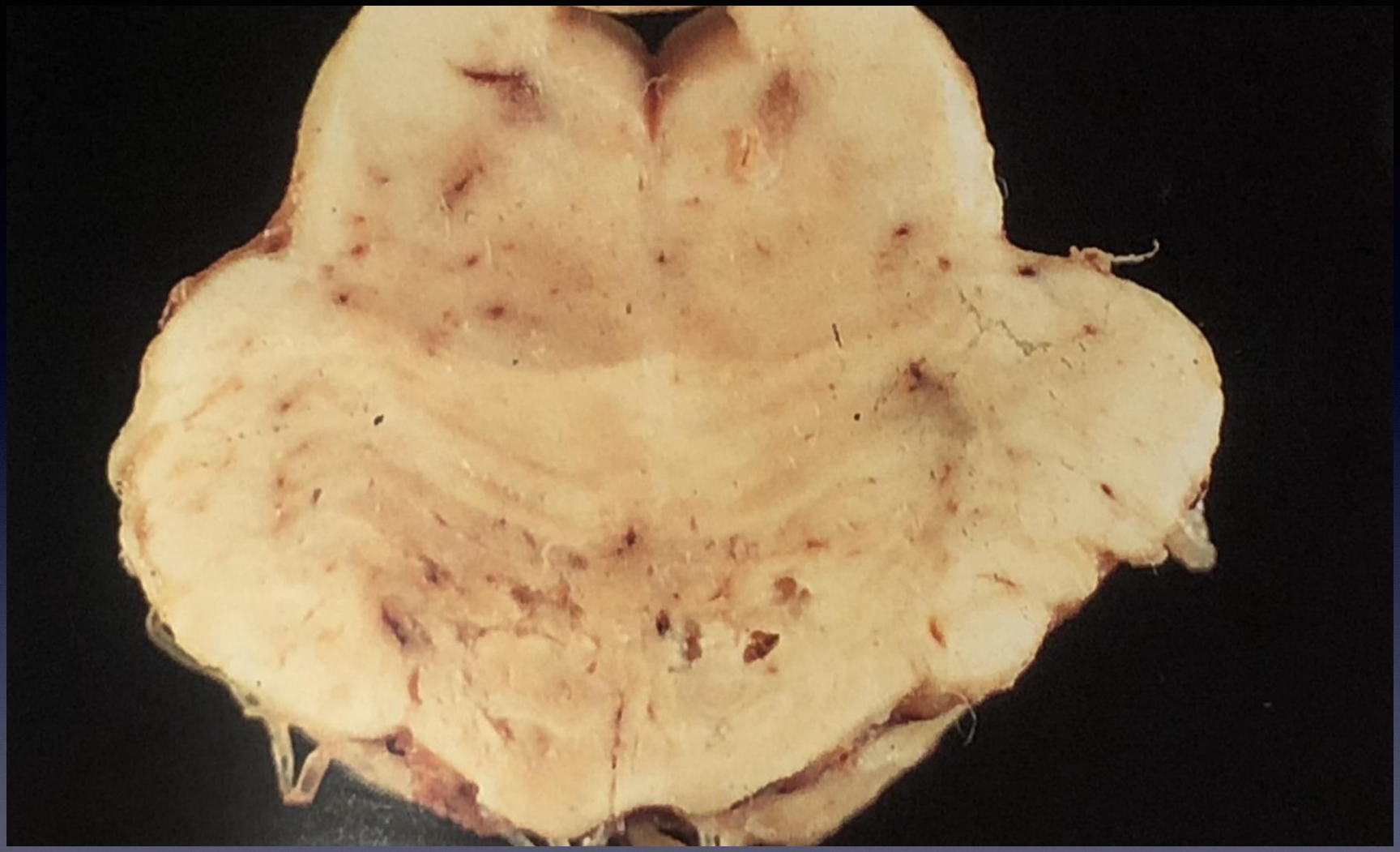
Temporal cortex



Old lacunar Strokes (Lacunae)
Right Caudate & Putamen



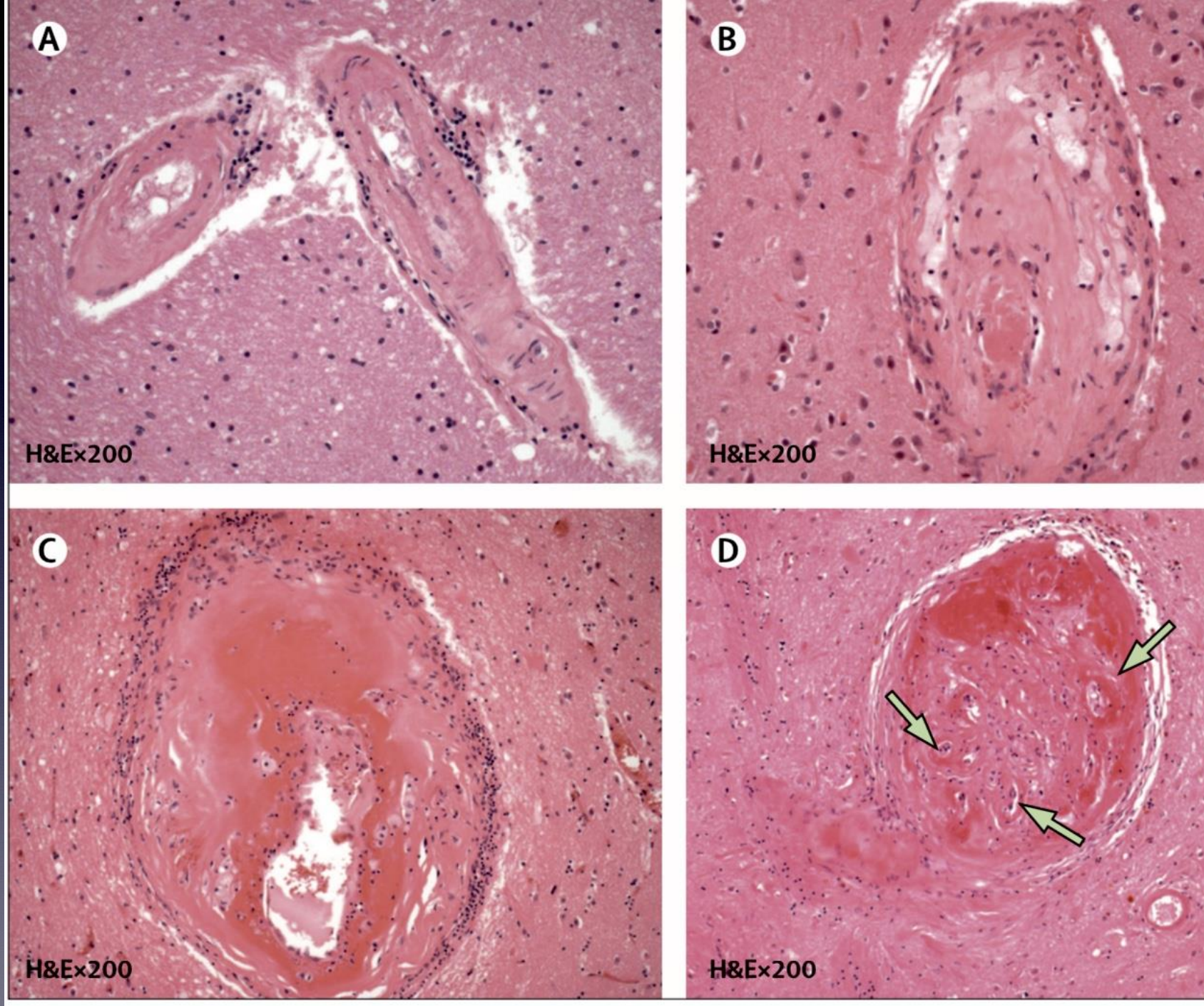
Lacunar infarcts: thalamus



Lacunar Infarcts Pons

C. Miller Fisher

- Meticulous dissections of lacuna strokes (LS)
- 1950-1960's
- Described classic lacunar stroke syndromes
- Most LS found distal to occlusive lesions of small perforating arteries
- "Lipohyalinosis"—he believed due to hypertension: fibrinoid necrosis and segmental arteriolar disorganization
- 3 overlapping findings:
  - Vessel enlargement
  - Hemorrhage
  - Fibrinoid deposition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H&E×200
B
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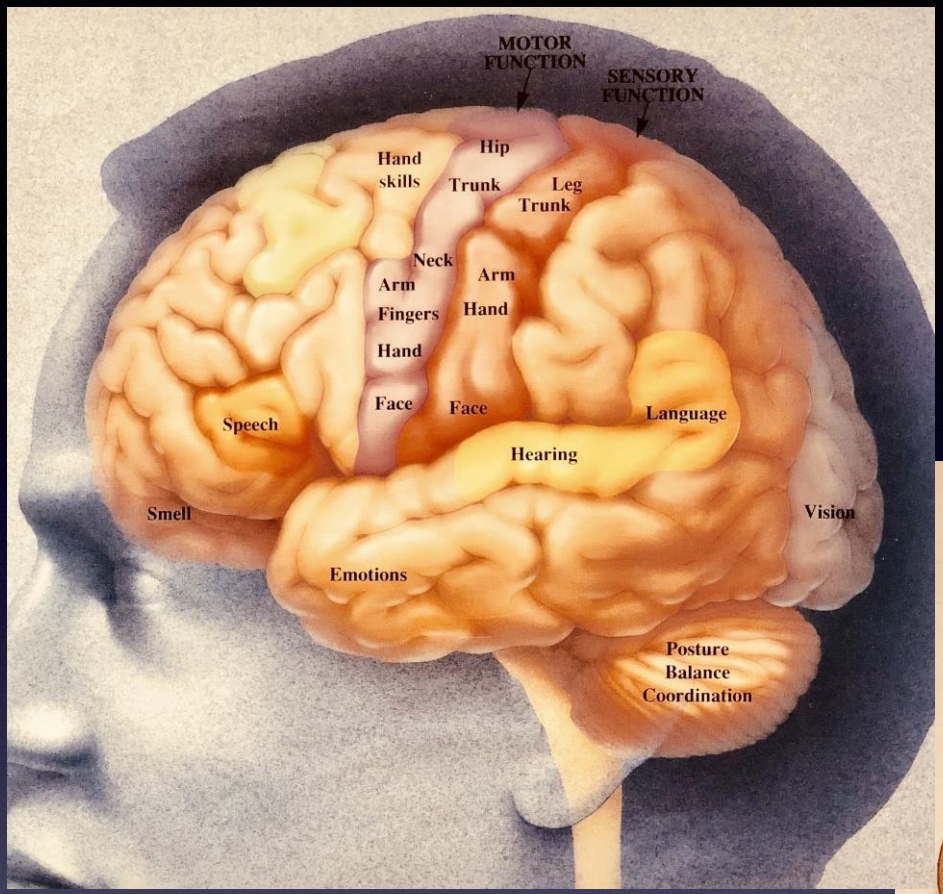
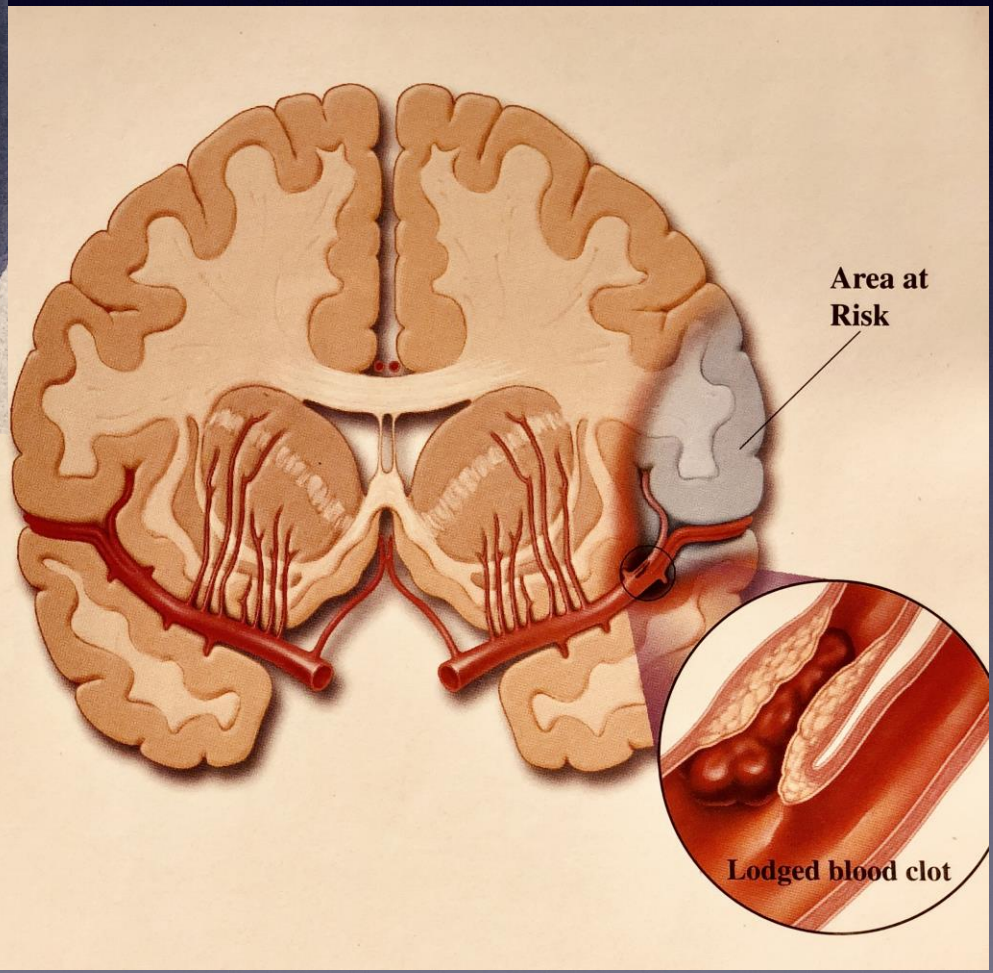
C
H&E×200
D
H&E×200

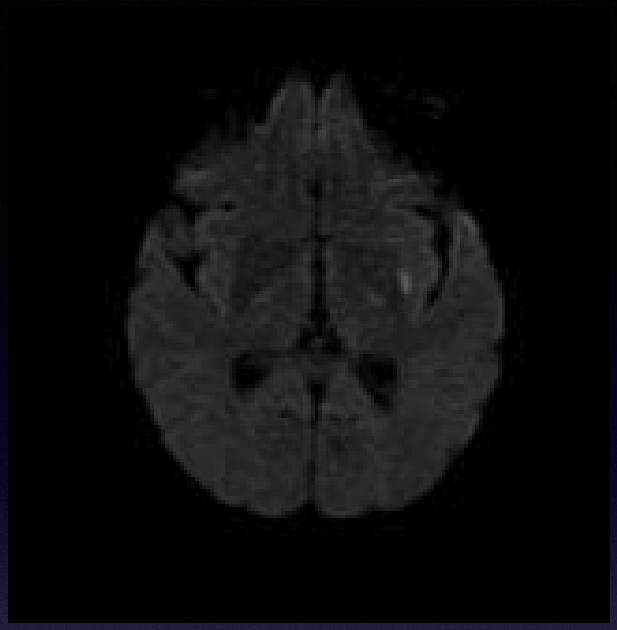
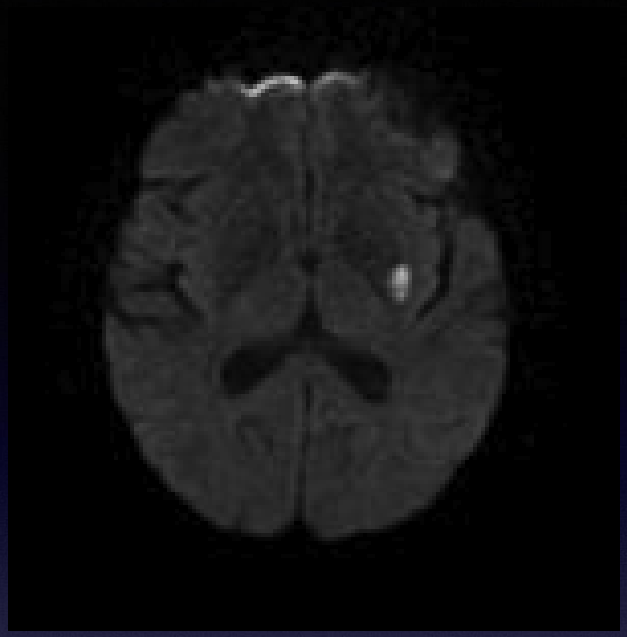
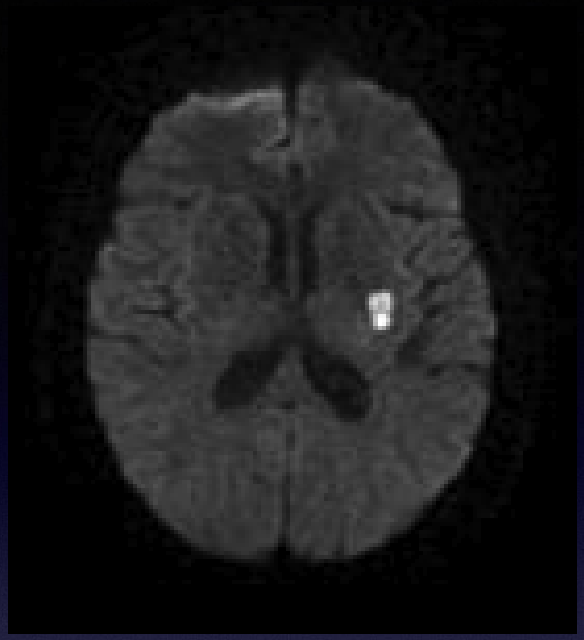
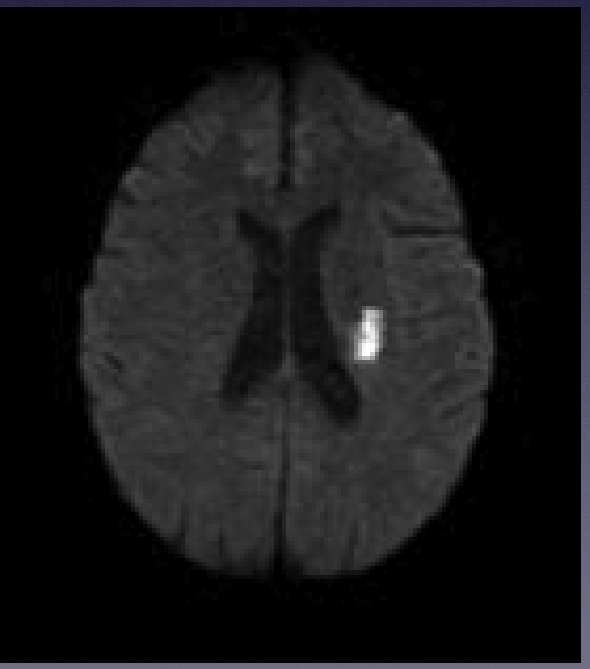
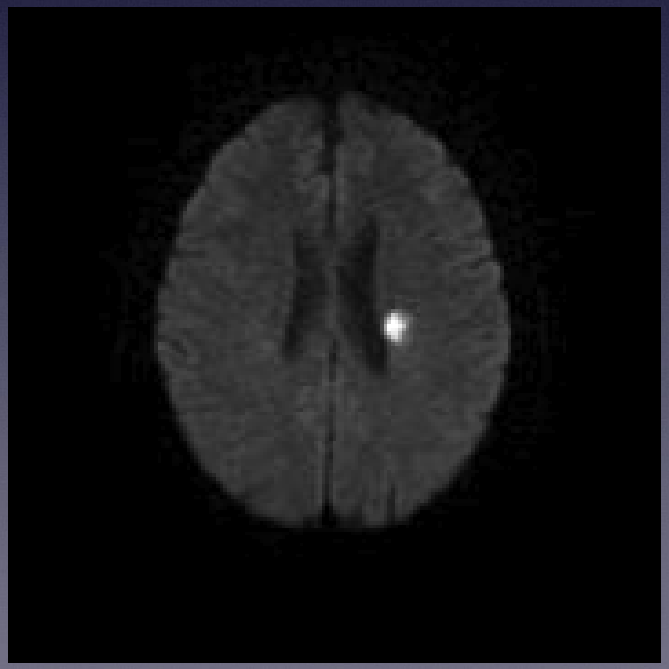
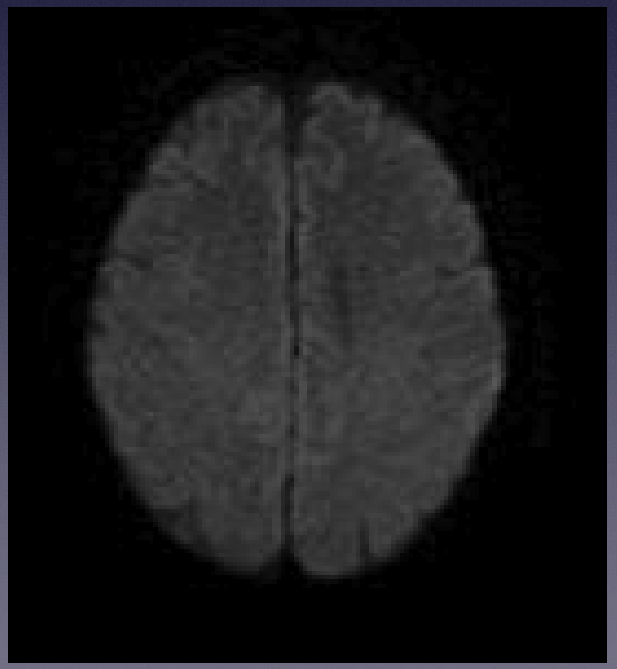


Common Lacunar Stroke Syndromes

- pure motor hemiparesis
- pure hemisensory loss
- clumsy hand/dysathria
- crural hemiparesis/ataxia

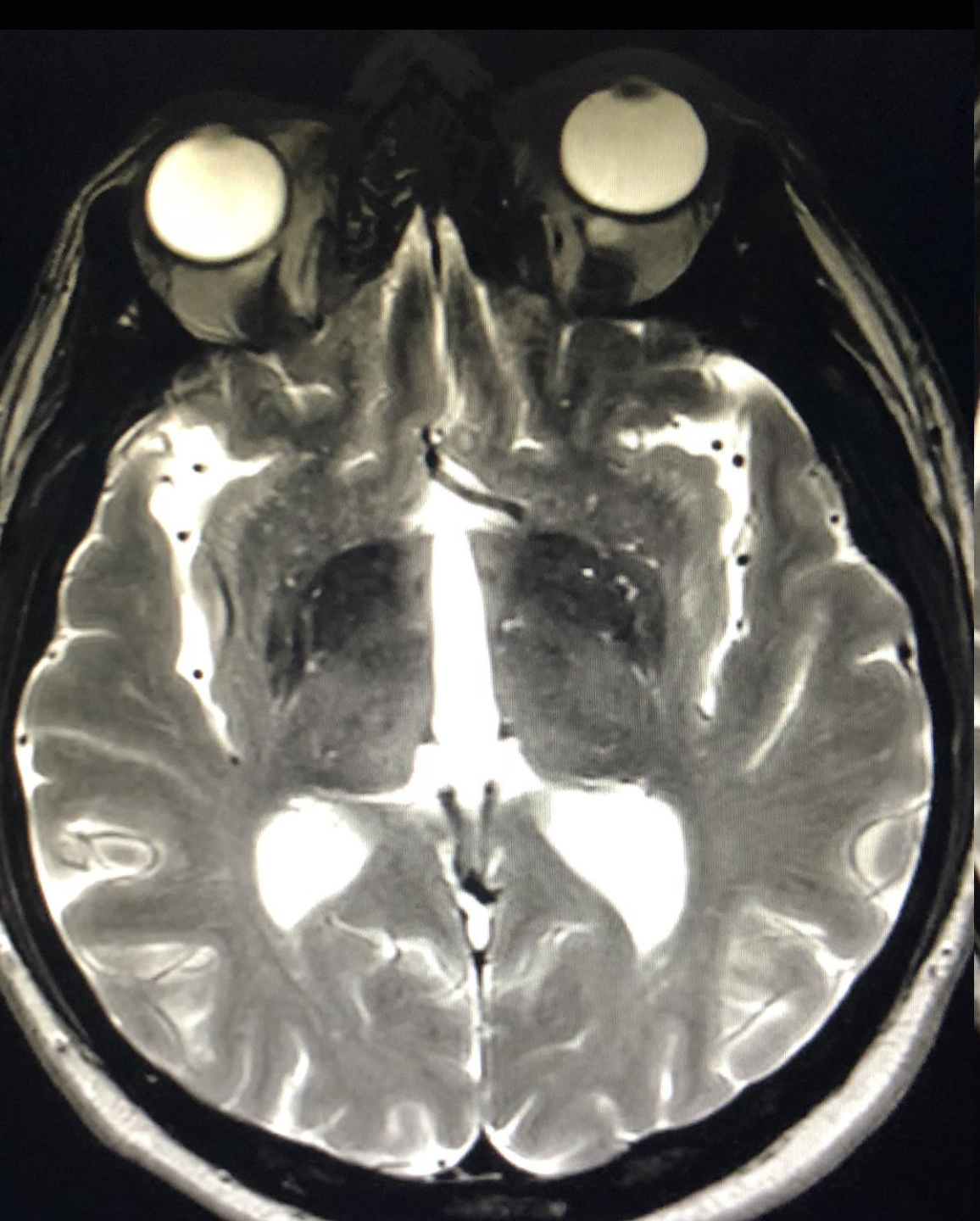
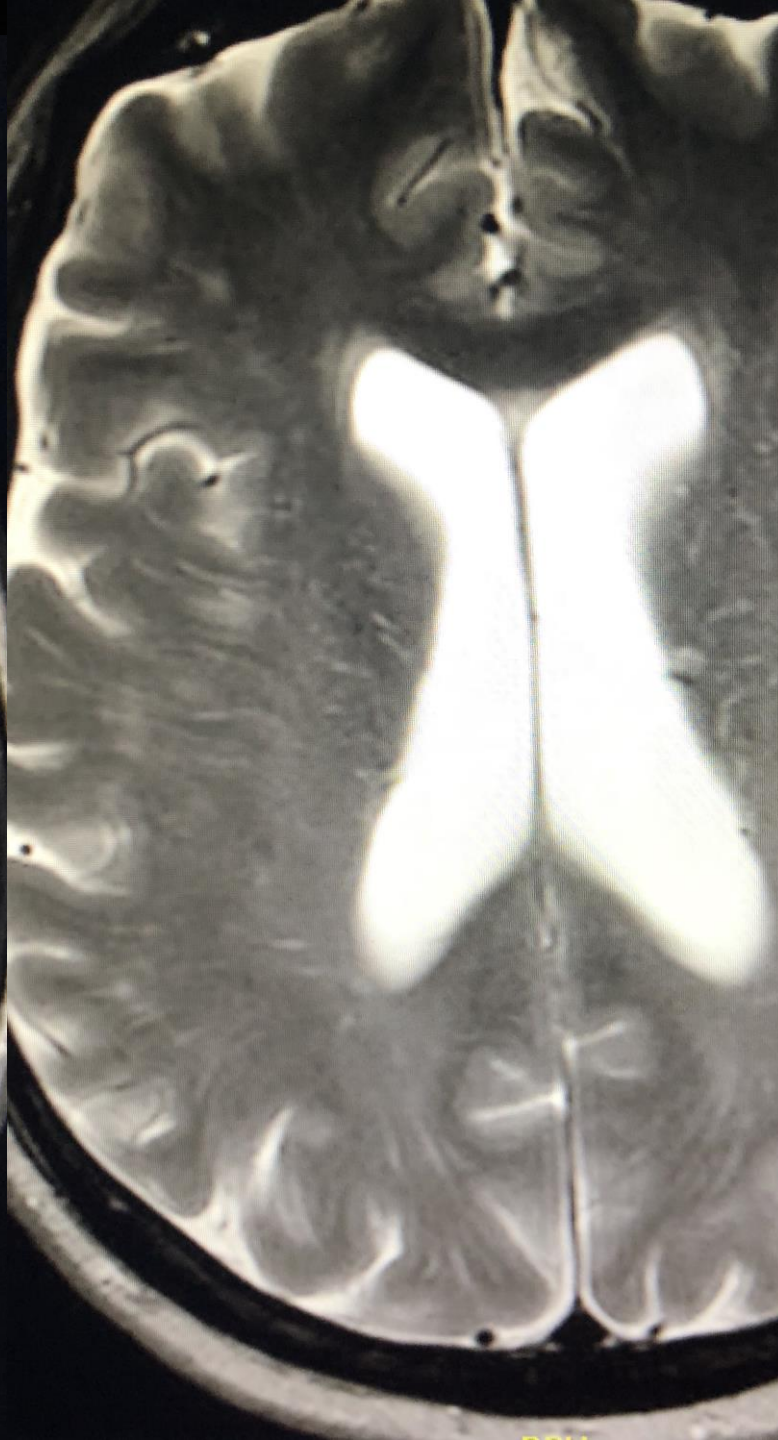


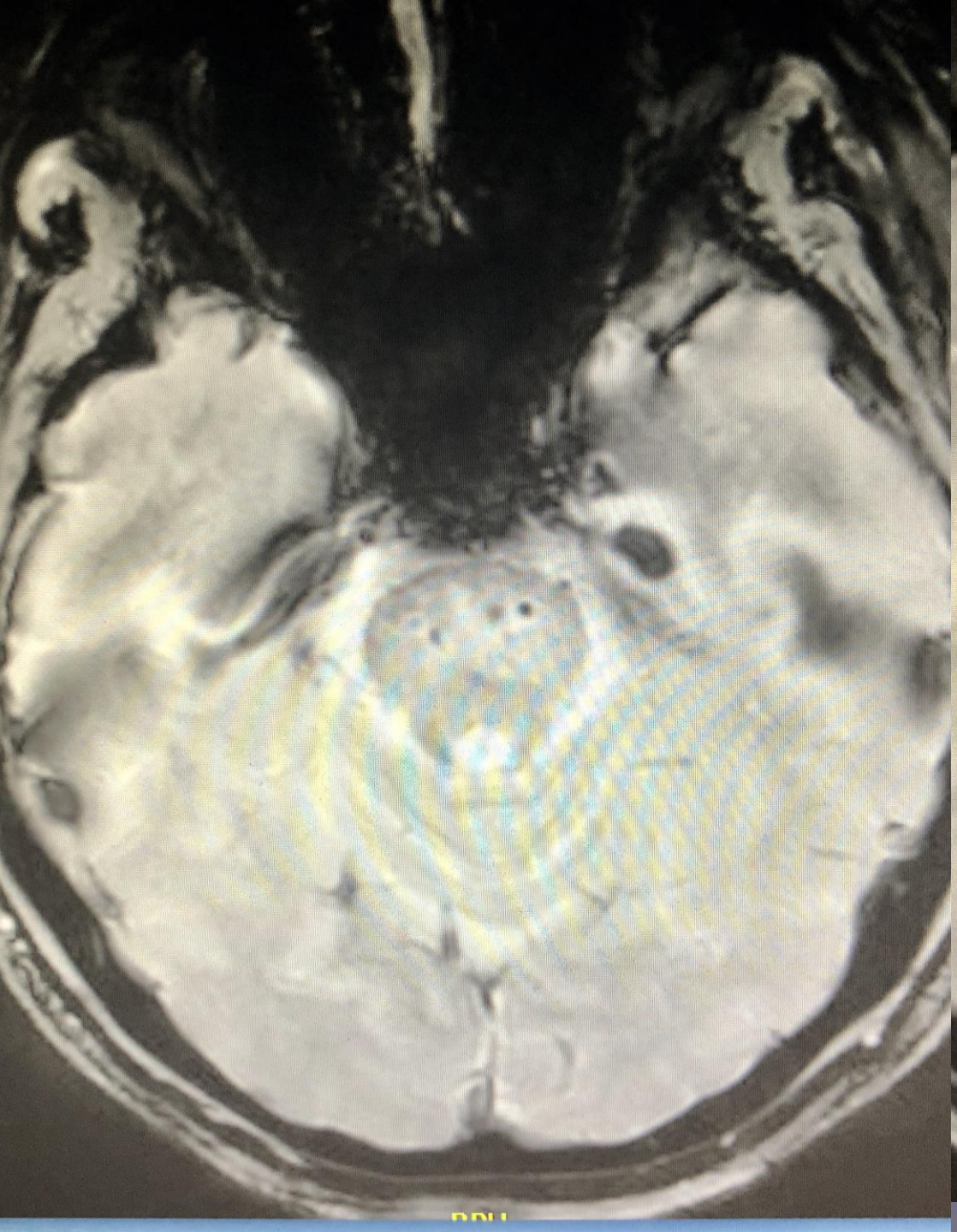
- May evolve over 24-72 hours
- “Stroke in Evolution ”

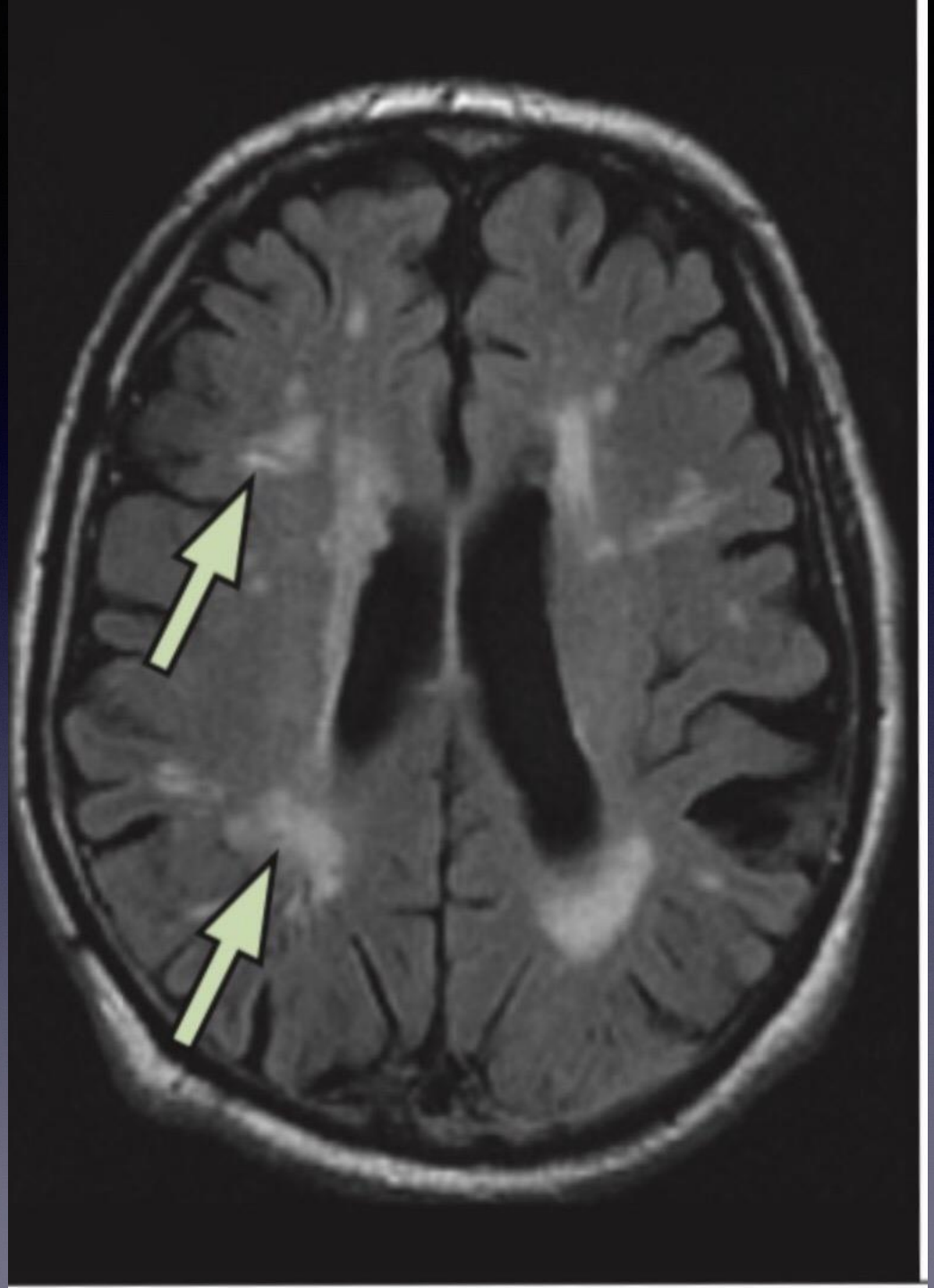







63 yo RH Caucasian Male

- Fluctuating R hemiparesis
- Treated with reclined bed rest, aspirin, atorvastatin
- Improved over next 24 hours: NIHSS stabilized at 3-4 (down from 13 at worst)
- Treatment of BP started several days after stabilization
- Ambulatory, marginal dysarthria and using RUE though fingers slightly clumsy at d/c

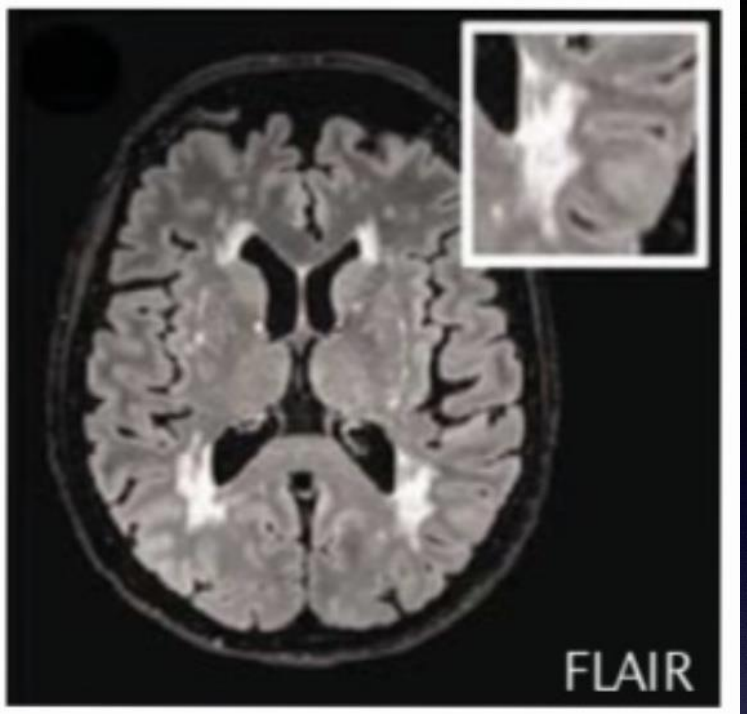


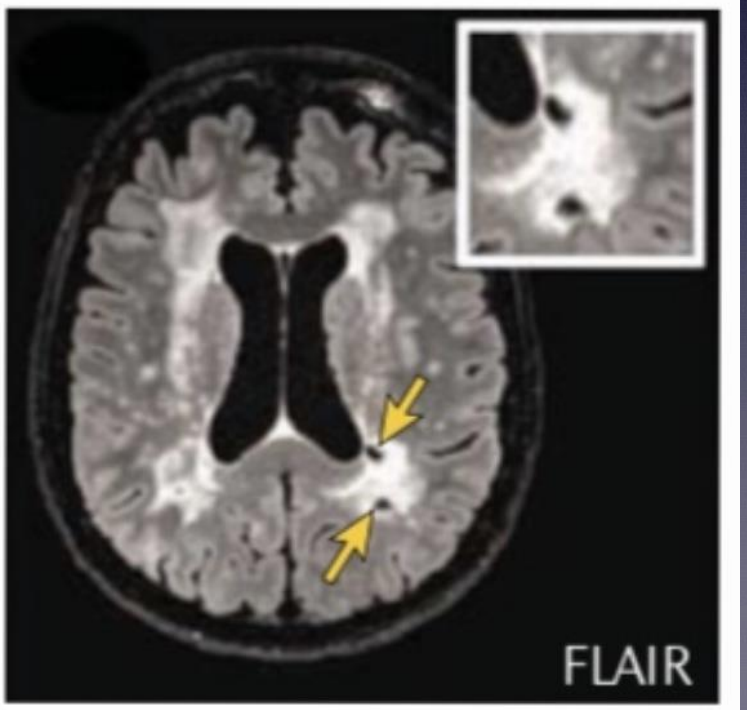


STRIVE Criteria

STandards for **R**eporting **V**ascular Changes on N**E**uroimaging

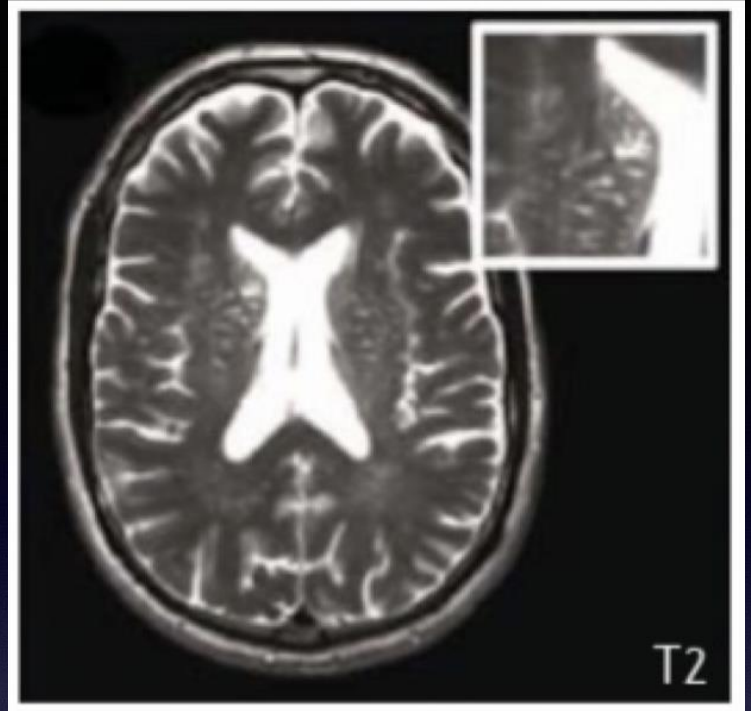
- Published 2013
- 36 authors

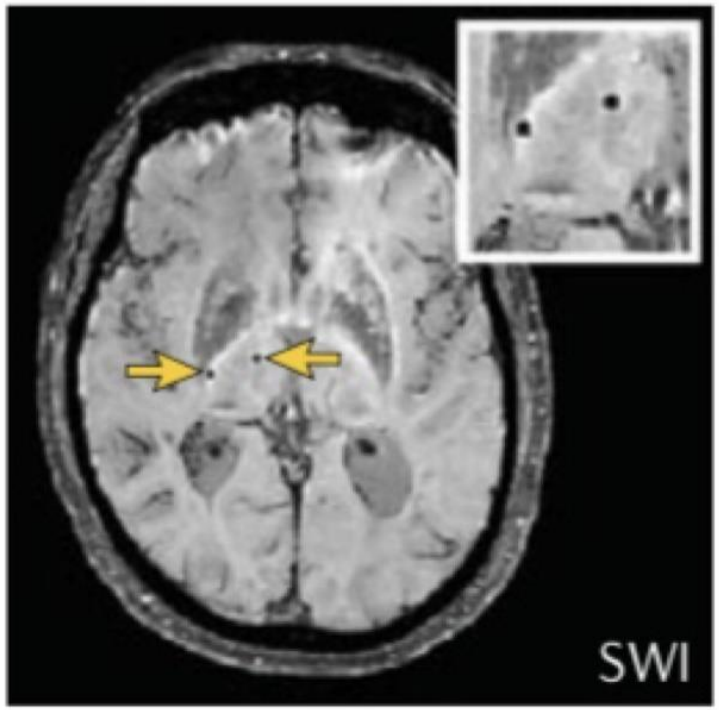




White Matter Hyperintensities
of presumed Vascular Origin

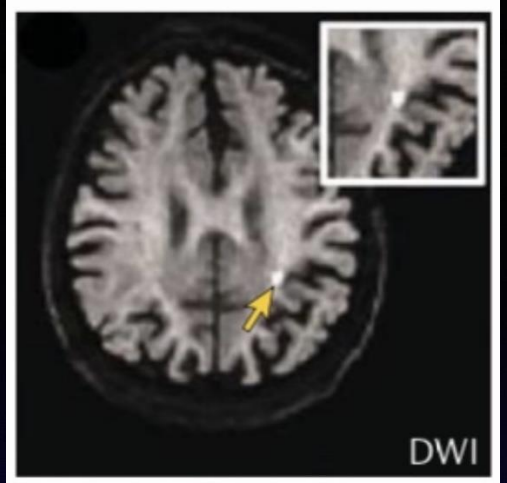
Lacunes

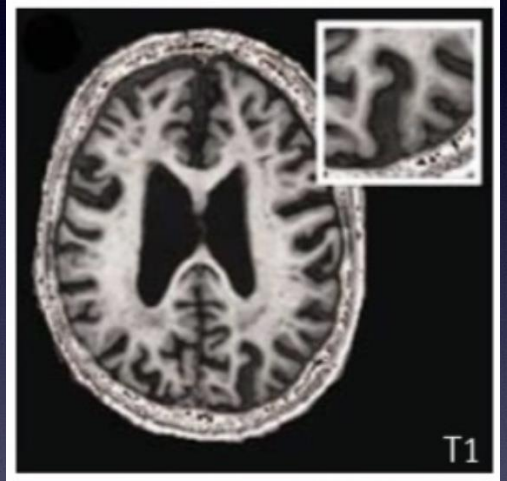


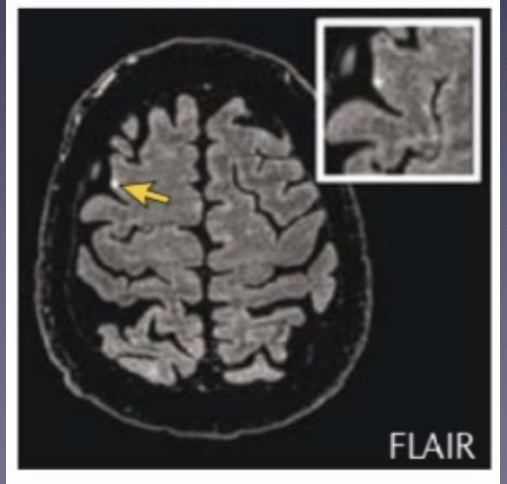


Enlarged Perivascular Spaces

Microbleeds



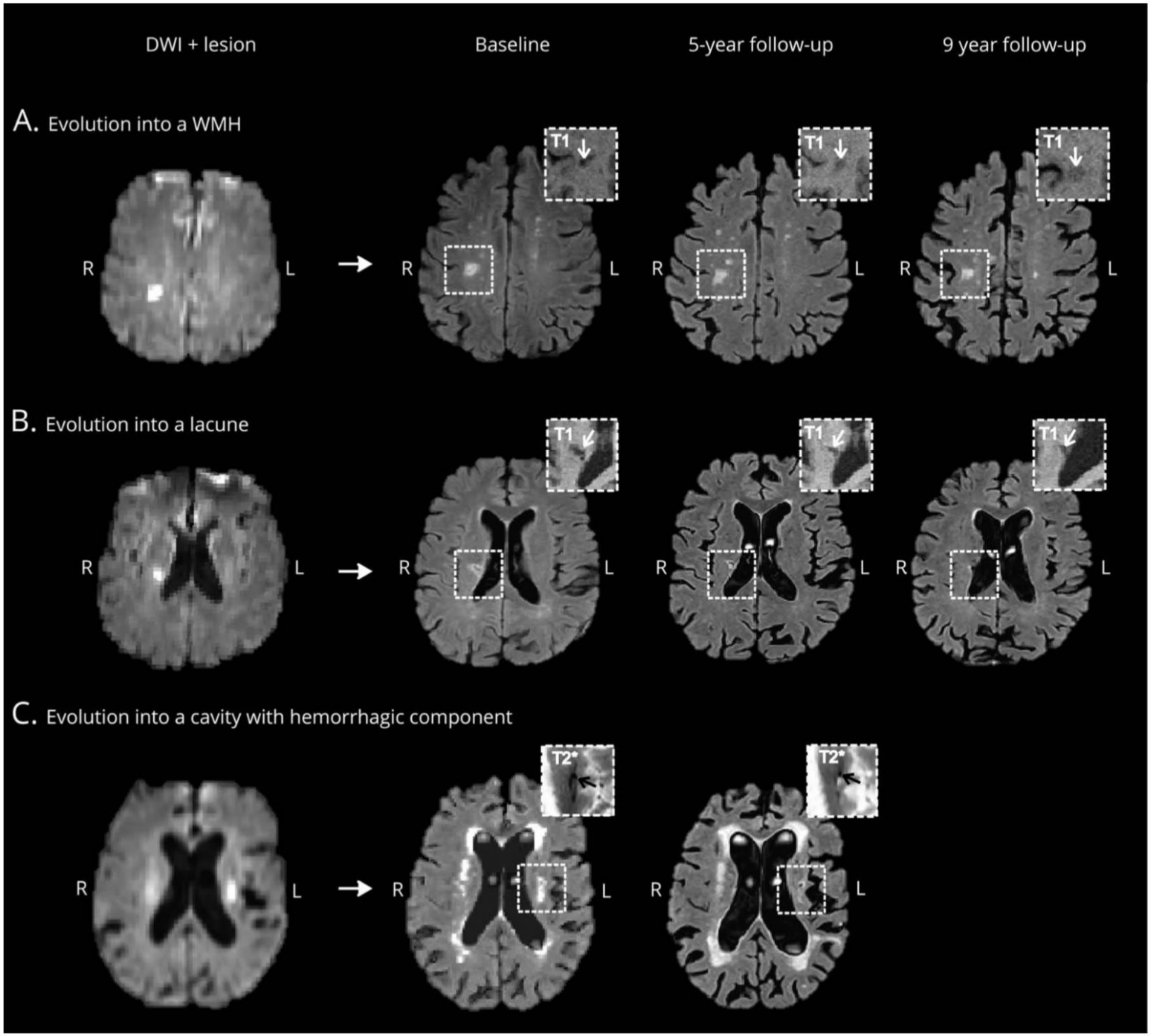




Recent Small Subcortical Infarcts

Brain Atrophy

Cortical Microinfarcts


DWI + lesion
Baseline
5-year follow-up
9 year follow-up
A. Evolution into a WMH
T1
R
L
B. Evolution into a lacune
T1
C. Evolution into a cavity with hemorrhagic component
T2*

Joanna M Wardlaw MD, Edinburgh

William M Feinberg Award for Excellence in Clinical Stroke
2018

Small vessel disease IS NOT just atherosclerotic disease in little vessels

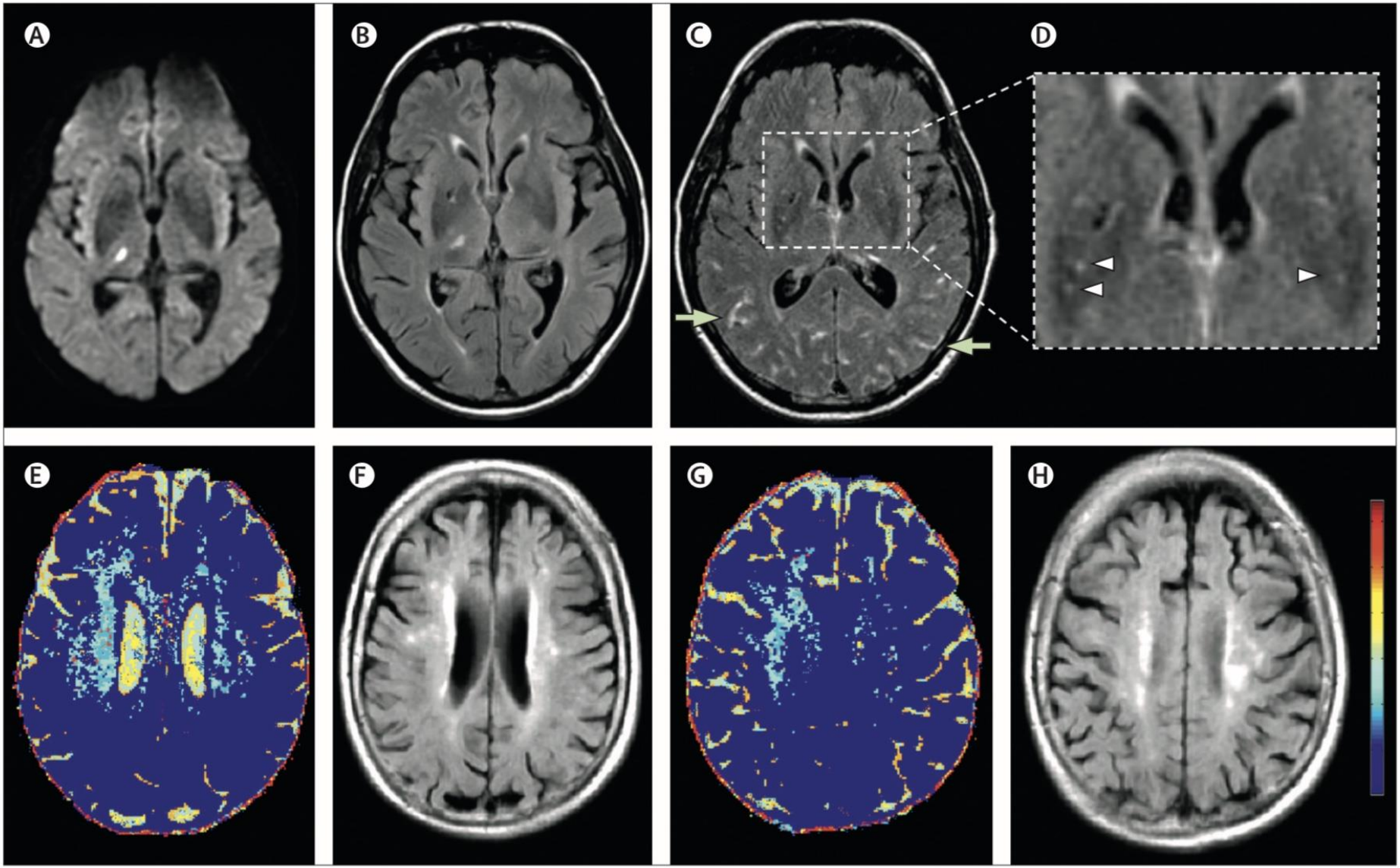


Figure 7: **MRI of cerebrovascular endothelial permeability**

Top row: 56-year-old patient with a right thalamic lacunar infarct. (A) Diffusion-weighted imaging. (B) FLAIR 2 days after symptom onset. (C) 2 months later, FLAIR image after intravenous gadolinium showing gadolinium in the perivascular spaces (D; arrowheads) and sulci (arrows) and (D) inset magnified image of (C). Bottom row: older patient with left internal capsule lacunar infarct (not shown). (E) Colour mapping of cerebrovascular permeability after intravenous gadolinium and (F) corresponding FLAIR images showing white matter hyperintensities. Blue shows low cerebral vascular endothelial permeability, yellow and red show increasing permeability. Permeability changes are diffuse. (G) Permeability and (H) corresponding FLAIR image on the slice adjacent to (E) and (F). Panels E and G courtesy of Dr Maria Valdes Hernandez. FLAIR=fluid-attenuated inversion recovery.

Transcranial Doppler

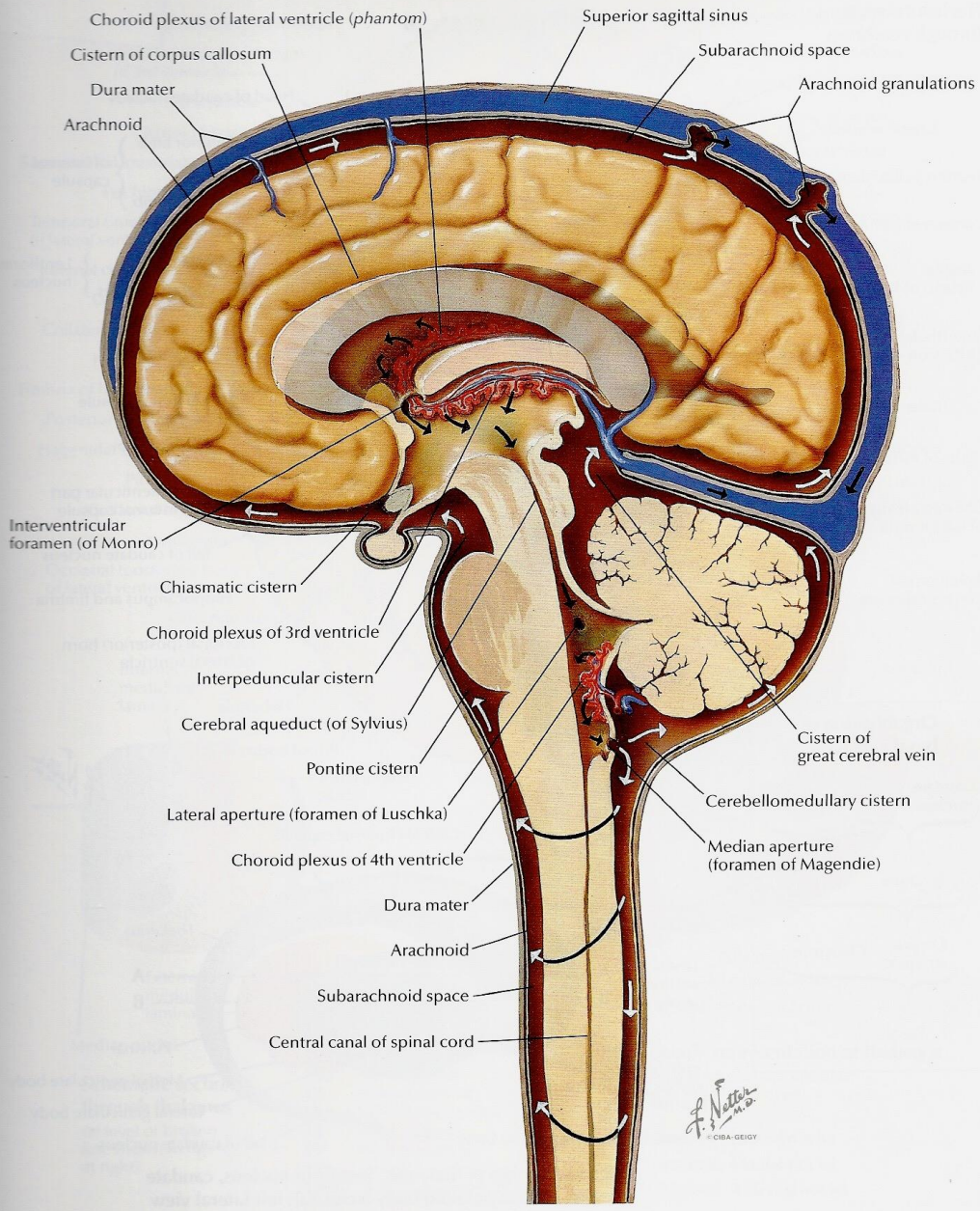
- No evidence for decreased resting cerebral blood flow beyond that expected from tissue damage
- Decreased MCA vasoreactivity with advancing age is greater with LS or WMI
- Increased vessel pulsatility
- Combination of impaired cerebrovascular vasoreactivity and increased vessel stiffness contributes to endothelial dysfunction

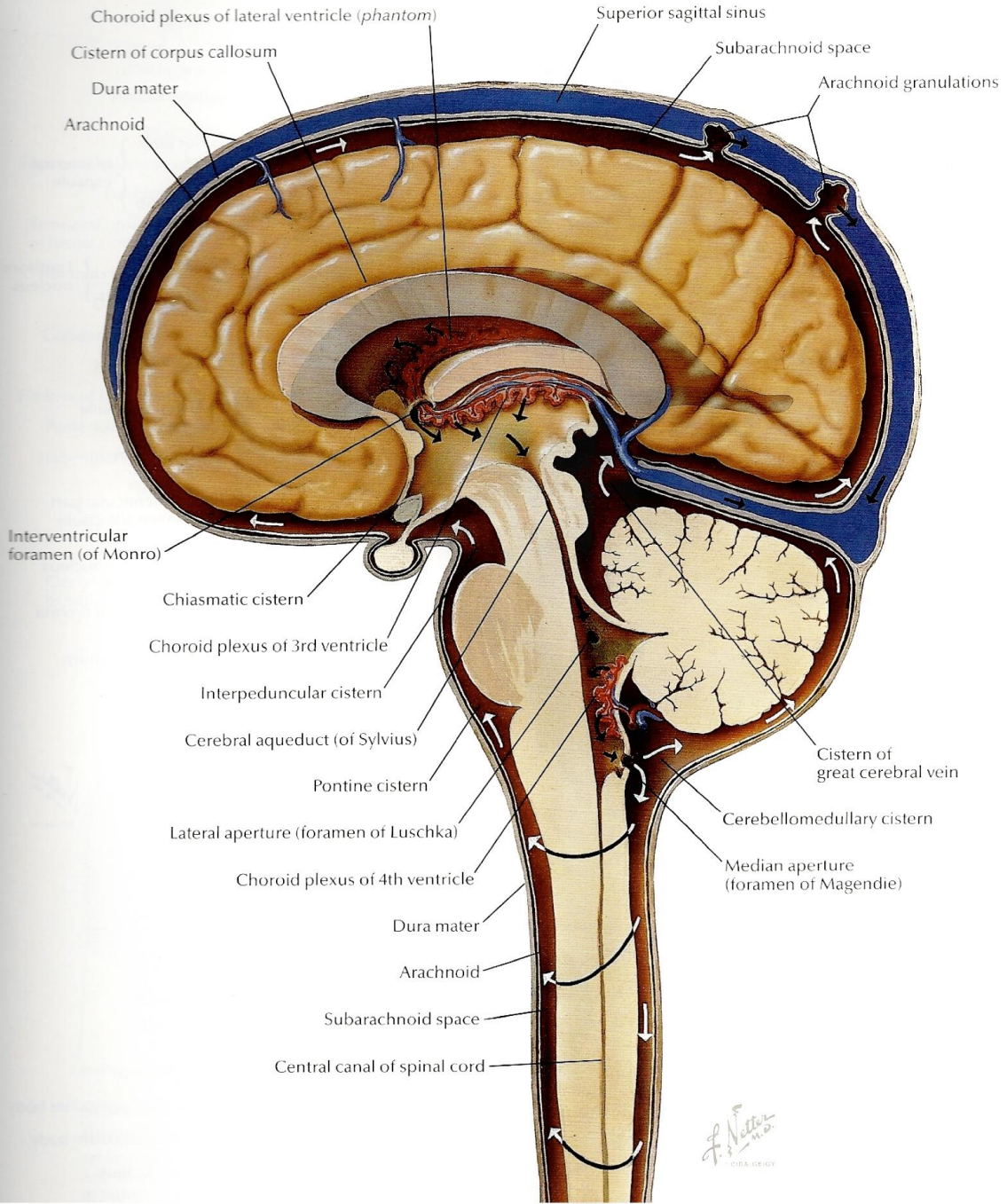
SVD Evolution

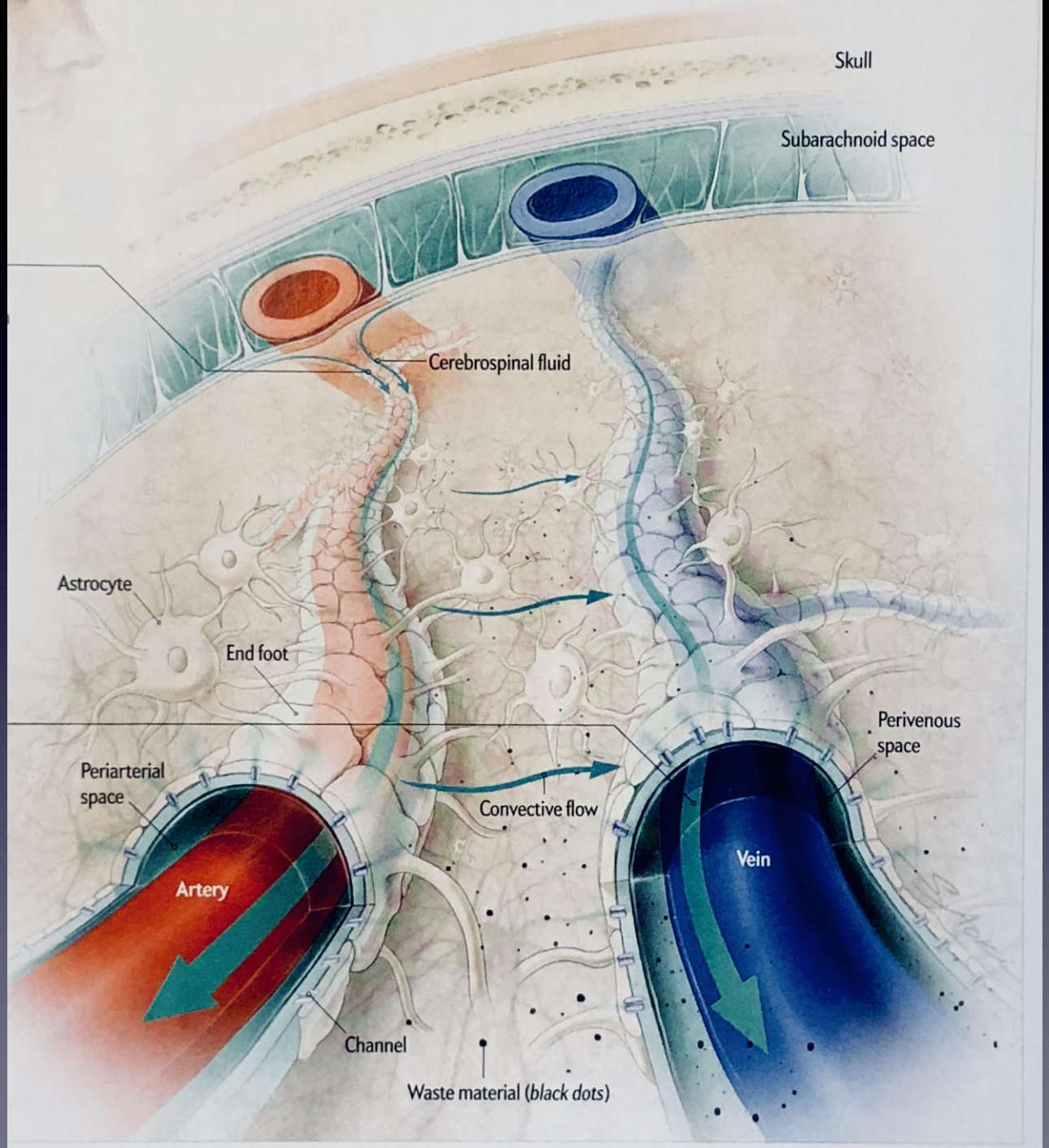
- Diffuse endothelial injury occurs early
- Leads to breakdown of the “Blood Brain Barrier”
- Extravasation of plasma proteins
- Injury to blood vessel wall, surrounding cells — especially glia (demyelination), inflammation, glial scarring, thickening and stiffness of the vessel wall, impaired autoregulation
- Late luminal narrowing & occlusion

What is the Glymphatic System?

Circulation of Cerebrospinal Fluid




Choroid plexus of lateral ventricle (*phantom*)
Cistern of corpus callosum
Dura mater
Arachnoid
Superior sagittal sinus
Subarachnoid space
Arachnoid granulations
Interventricular foramen (of Monro)
Chiasmatic cistern
Choroid plexus of 3rd ventricle
Interpeduncular cistern
Cerebral aqueduct (of Sylvius)
Pontine cistern
Lateral aperture (foramen of Luschka)
Choroid plexus of 4th ventricle
Dura mater
Arachnoid
Subarachnoid space
Central canal of spinal cord
Cistern of great cerebral vein
Cerebellomedullary cistern
Median aperture (foramen of Magendie)


Skull
Subarachnoid space
Cerebrospinal fluid
Astrocyte
End foot
Perivenous space
Periarterial space
Convective flow
Vein
Artery
Channel
Waste material (*black dots*)

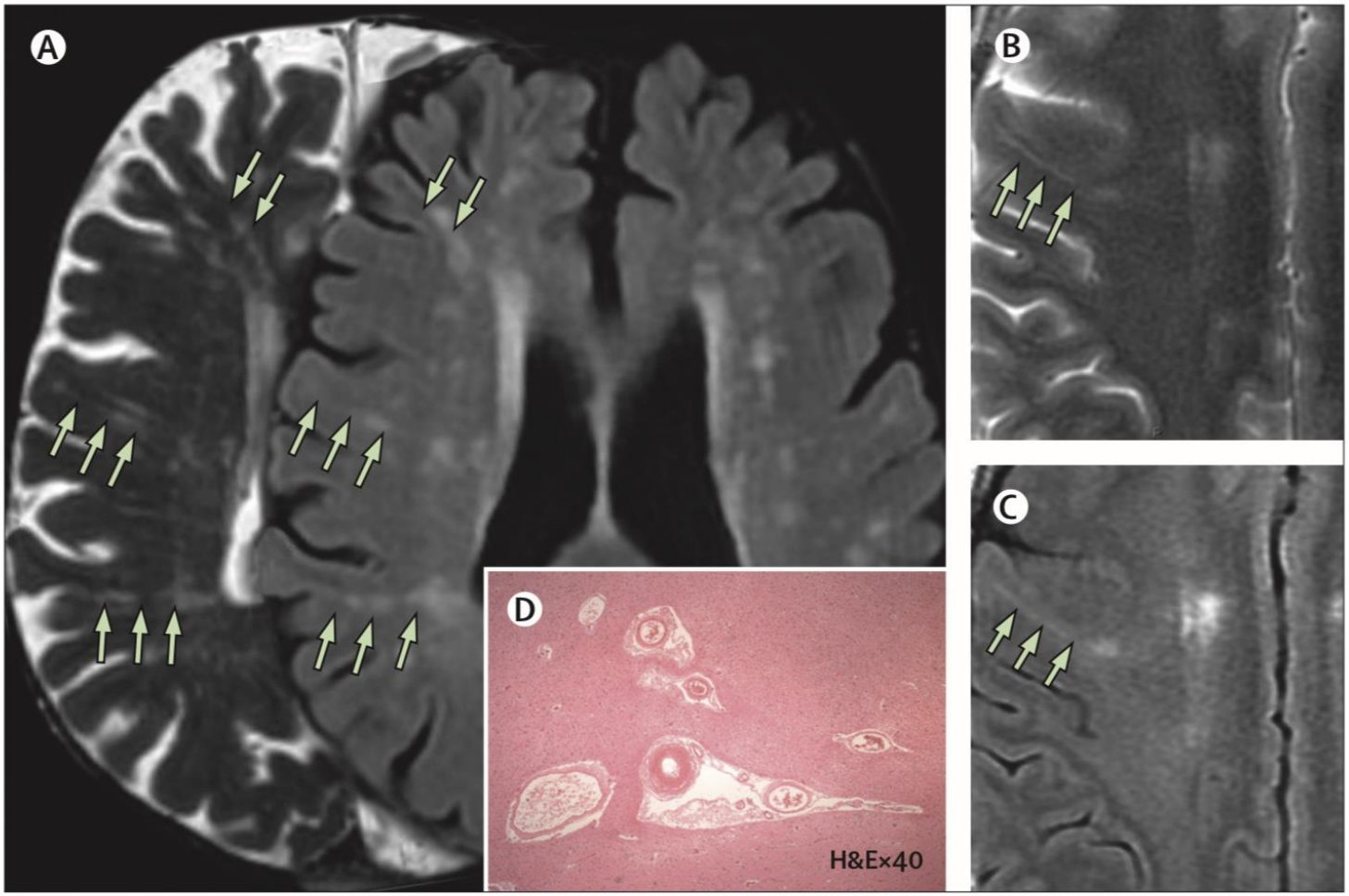
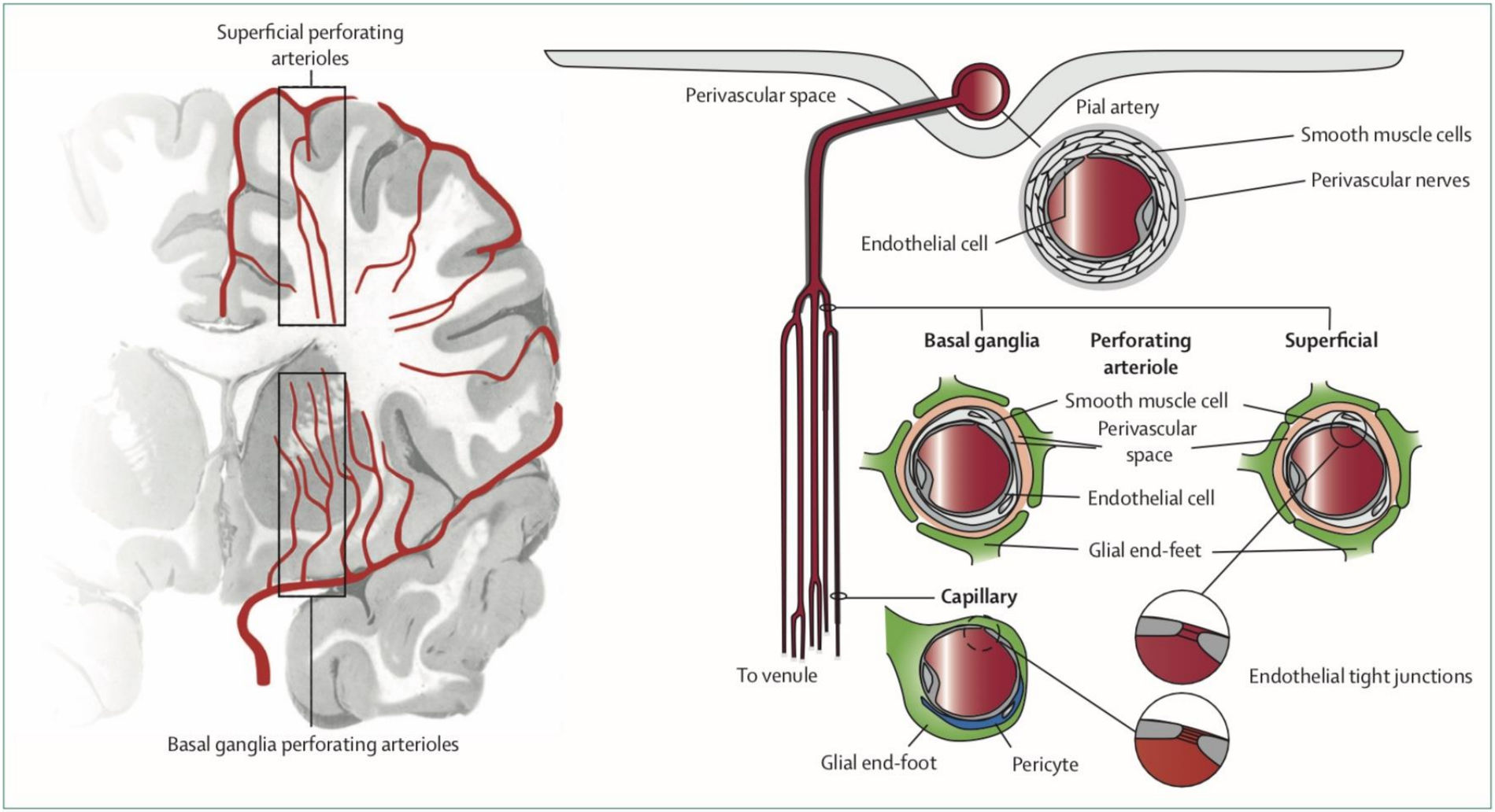
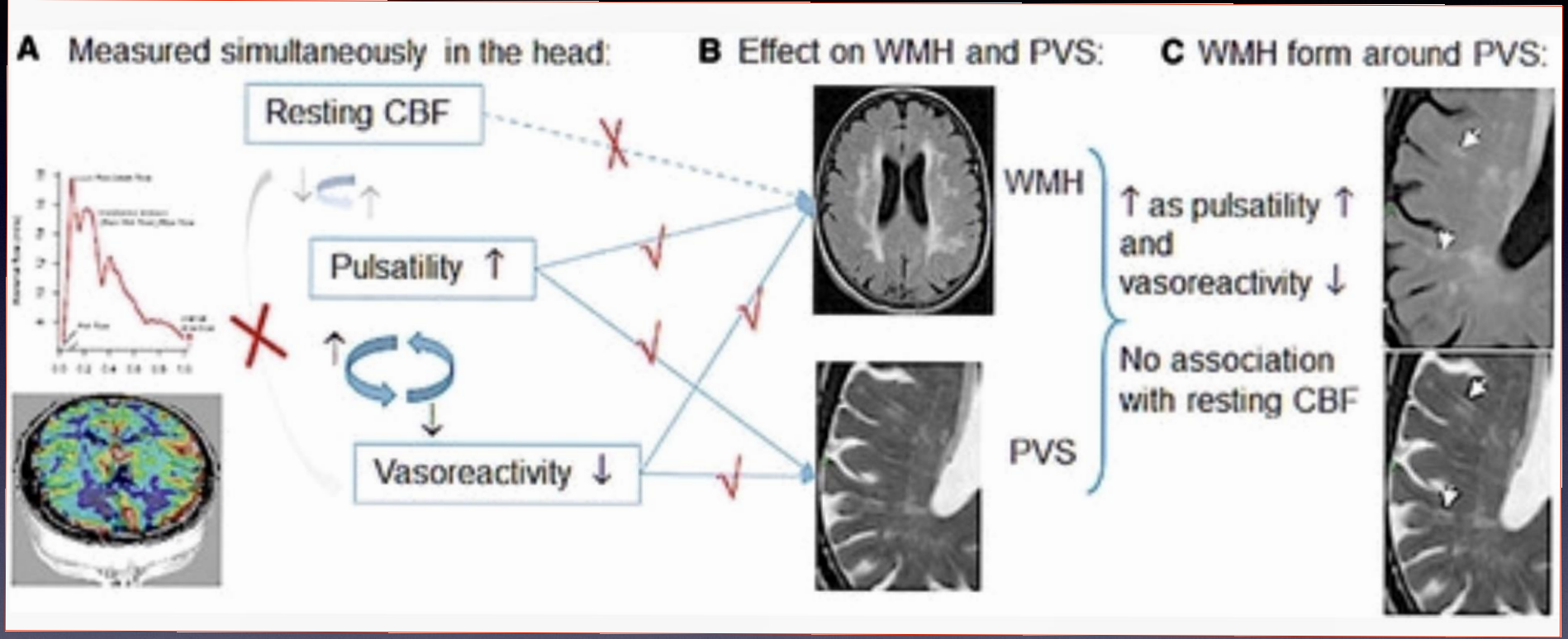


Figure 4: **Examples of visible perivascular spaces on MRI and histology**
(A) 72-year-old asymptomatic patient, T2-weighted image (right) shows linear visible perivascular spaces in the plane of the image, and FLAIR (left) shows white matter hyperintensities around the perivascular spaces.
(B) T2-weighted imaging of a 49-year-old man with left internal capsule acute small deep infarct (not shown) shows a perivascular space extending from the periventricular to subcortical tissues and (C) on the corresponding FLAIR image, one white matter hyperintensity running longitudinally around the visible perivascular spaces.
(D) Visible perivascular spaces on histology showing parenchymal tissue retraction from around small perforating vessels; these have been dismissed as a processing artifact but are typically seen in ageing brain sections, and are often associated with cerebral small vessel disease. FLAIR=fluid-attenuated inversion recovery. H&E=haemotoxylin and eosin staining.

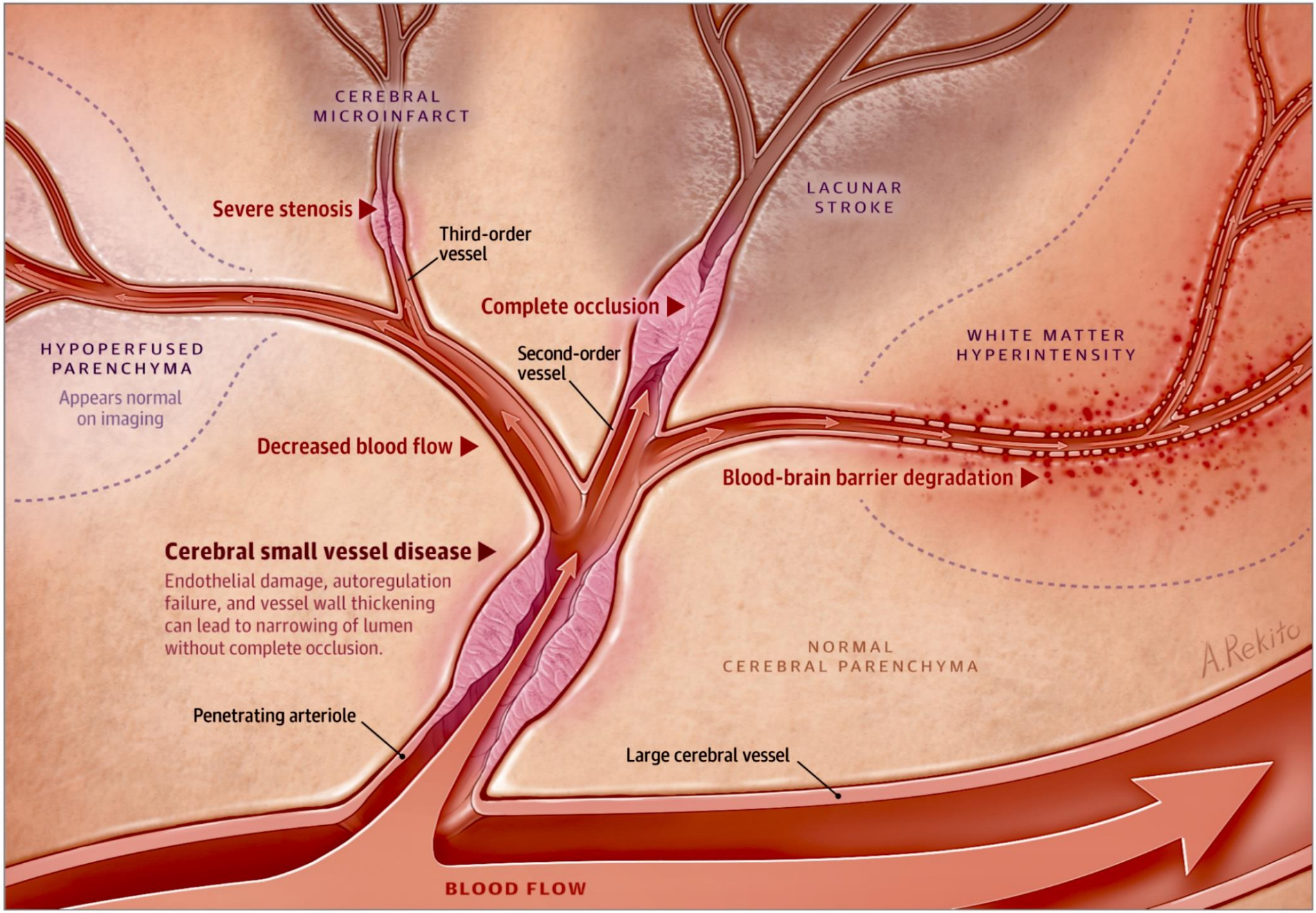
What is the Blood Brain Barrier?


Superficial perforating arterioles
Basal ganglia perforating arterioles
Perivascular space
Pial artery
Smooth muscle cells
Perivascular nerves
Endothelial cell
Basal ganglia
Perforating arteriole
Superficial
Smooth muscle cell
Perivascular space
Endothelial cell
Glial end-feet
Capillary
To venule
Endothelial tight junctions
Glial end-foot
Pericyte


A Measured simultaneously in the head:
Resting CBF
Pulsatility ↑
Vasoreactivity ↓
B Effect on WMH and PVS:
WMH
PVS
↑ as pulsatility ↑ and vasoreactivity ↓
No association with resting CBF
C WMH form around PVS:

SVD Evolution

- Diffuse endothelial injury occurs early
- Leads to breakdown of the “Blood Brain Barrier”
- Extravasation of plasma proteins
- Injury to blood vessel wall, surrounding cells — especially glia (demyelination), inflammation, glial scarring, thickening and stiffness of the vessel wall, impaired autoregulation
- Late luminal narrowing & occlusion


CEREBRAL MICROINFARCT
Severe stenosis
Third-order vessel
LACUNAR STROKE
Complete occlusion
HYPOPERFUSED PARENCHYMA
Appears normal on imaging
Second-order vessel
WHITE MATTER HYPERINTENSITY
Decreased blood flow
Blood-brain barrier degradation
Cerebral small vessel disease
Endothelial damage, autoregulation failure, and vessel wall thickening can lead to narrowing of lumen without complete occlusion.
NORMAL CEREBRAL PARENCHYMA
A. Rekito
Penetrating arteriole
Large cerebral vessel
BLOOD FLOW

Etiology/Risk Factors

- **Endothelial dysfunction & permeability increase exponentially with age**
- **Hypertension & smoking are important treatable risk factors but 90% OF DISEASE SEEMS UNACCOUNTED BY CONVENTIONAL RISK FACTORS**
- **High sodium intake>HBP; increased oxidative stress, vascular stiffness & impaired vasodilation**
- **Likely genetics plays a large role**
- **Low education, childhood poverty**

Table. Recent Genetic Studies of Lacunar Stroke and Cerebral Small Vessel Disease

Source	Study Type	Related Gene	Biomarker(s) Studied	SNP	Locus
Weng et al,[40] 2012	Single gene	*COL4A1*	LS, ICH	rs515201	13q34
Rannikmäe et al,[41] 2017	Single gene	*COL4A2*	LS, ICH	rs4771674	13q34
Lv et al,[42] 2014	Single gene	*COL3A1*	LS	rs1800255	2q32.2
Rannikmäe et al,[41] 2017	Single gene	*HTRA1*	LS, ICH	rs79043147	10q26.13
Zhao et al,[43] 2014	Single gene	*ACE*	LS	rs464994	17q23.3
Rutten-Jacobs et al,[44] 2016	Single gene	*MTHFR*	LS, WMH	rs1801133	1p36.22
Luo et al,[45] 2017	Single gene	*APOE*	WMH	rs429358	19q13.32
Traylor et al,[46] 2017	GWAS	*ZCCH14*	LS, WHM	rs12445022	16q24.2
Lopez et al,[47] 2015	GWAS	*TRIM65*	WMH	rs3744028	17q25
Lopez et al,[47] 2015	GWAS	*TRIM47*	WMH	rs1055129	17q25
Lopez et al,[47] 2015	GWAS	*PMF1*	WMH	rs1052053	1q22
Verhaaren et al,[48] 2015	GWAS	*SH3PXD2A*	WMH	rs12357919	10q24.33
Verhaaren et al,[48] 2015	GWAS	*HAAO*	WMH	rs11679640	2p21
Verhaaren et al,[48] 2015	GWAS	*PMF1-BGLAP*	WMH	rs2984613	1q22
Verhaaren et al,[48] 2015	GWAS	*EFEMP1*	WMH	rs78857879	2p16.1
Zhang et al,[49] 2014	WES	*C1ORF156*	Stroke	rs1048177	1q24.2
Zhang et al,[49] 2014	WES	*XYLB*	Stroke	rs17118	3p21.3
Cole et al,[50] 2012	WES	*CSN3*	LS	NA	4q13.3
Cole et al,[50] 2012	WES	*HLA-DPB1*	LS	NA	6p21.32
Fornage et al,[51] 2015	WES	*SH3TC1*	WMH	NA	4p16.1

SVD Treatments

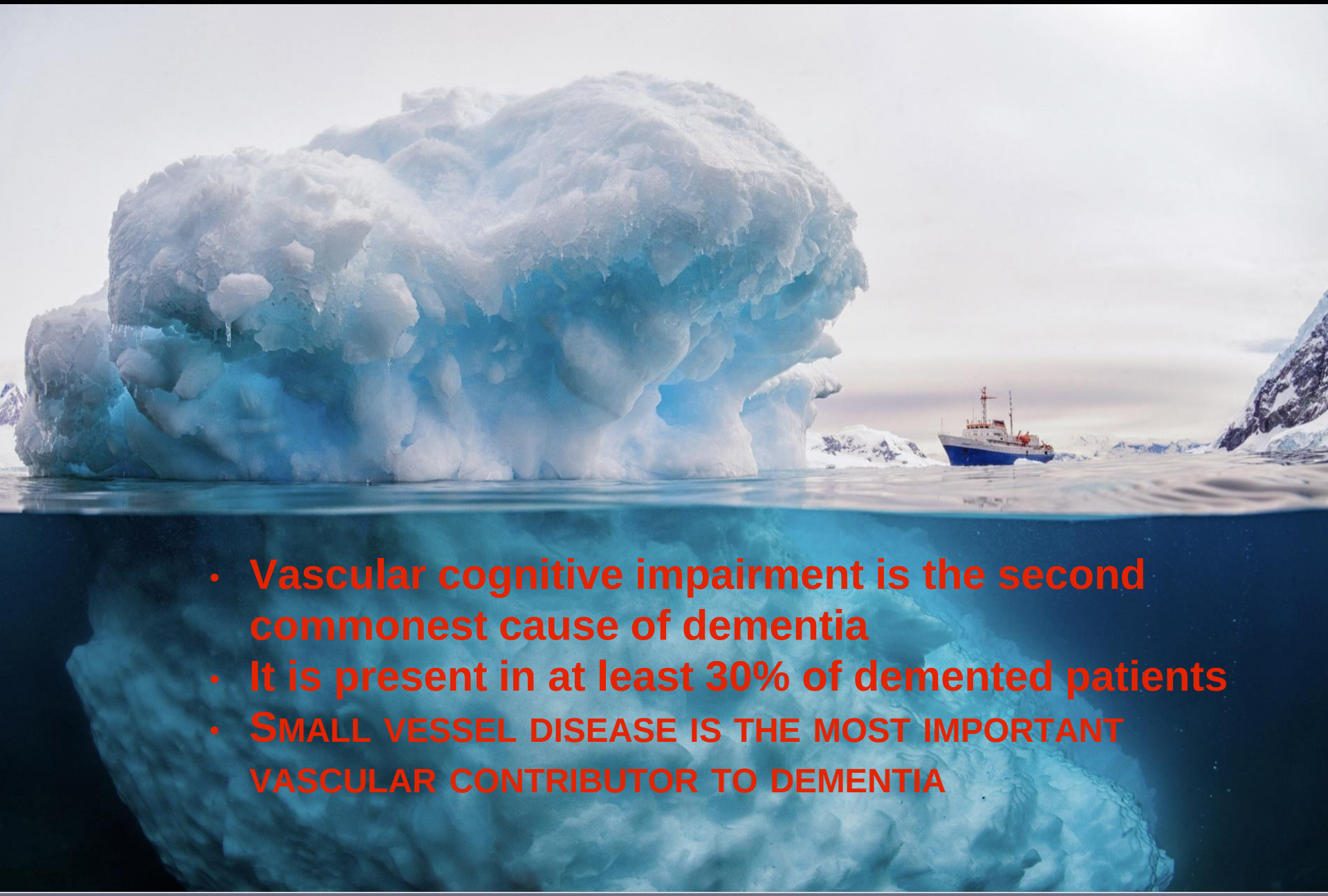
- Control BP
- Stop smoking
- Exercise
- Avoid XS salt intake
- Dual antiplatelet therapy is harmful

SVD: New treatments?

- **Isosorbide mononitrate**
  - oxide donor
  - Potentially improves BBB integrity, vasodilation, reduces inflammation and neuroprotection
- **Cilostazol**
  - Phosphodiesterase 3 inhibitor
  - Improves BBB integrity, vasodilation, reduces vessel stiffness and inflammation
- LACI-2 (LACunar stroke Intervention) Phase 2 trial now ongoing

The commonest form of cerebrovascular disease is dementia, not stroke.

-Vladimir Hachinski



- **Vascular cognitive impairment is the second commonest cause of dementia**
- **It is present in at least 30% of demented patients**
- **SMALL VESSEL DISEASE IS THE MOST IMPORTANT VASCULAR CONTRIBUTOR TO DEMENTIA**

SVD and Cognition

Historically felt to affect frontal-subcortical networks with:

- **Loss of mental processing speed**
- **Decreased executive function**
- **Slowed motor performance**
- **Impaired mood regulation**
- **Apathy and depression common**

SVD and Cognition

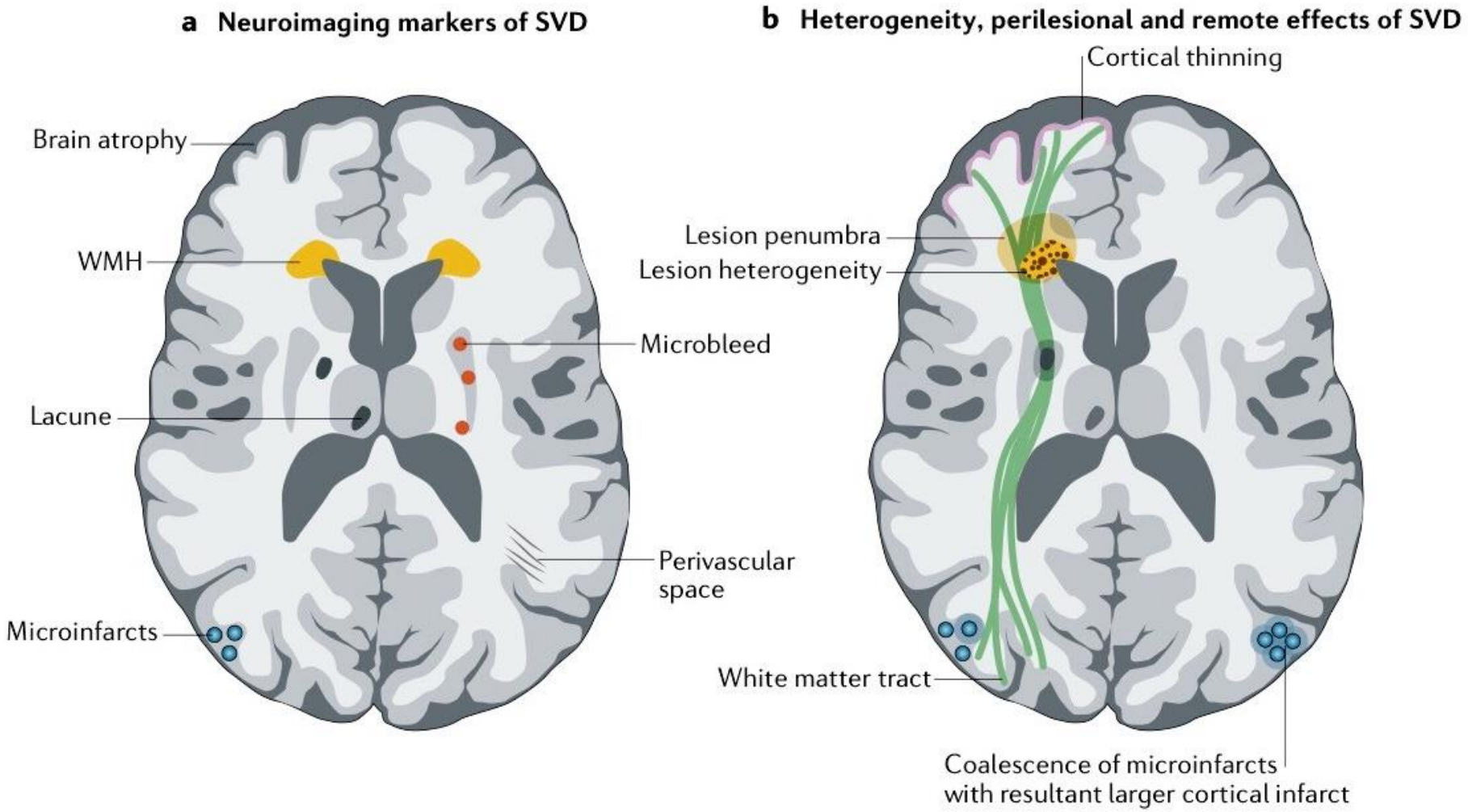
Effects more diverse that previously recognized. Include deficits in:

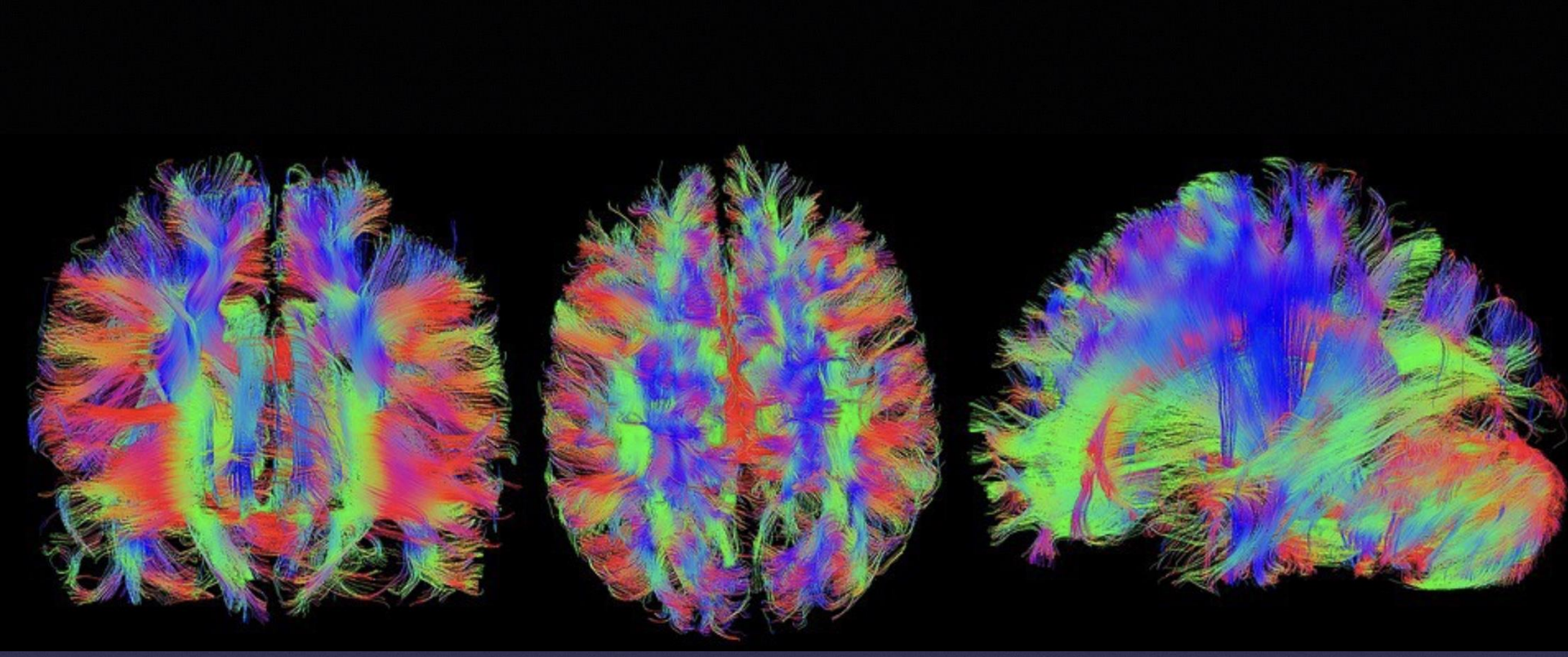
- **Language**
- **Memory**
- **Attention**
- **Visuospatial abilities**

Remarkable heterogeneity in patients with radiologically similar degrees of SVD

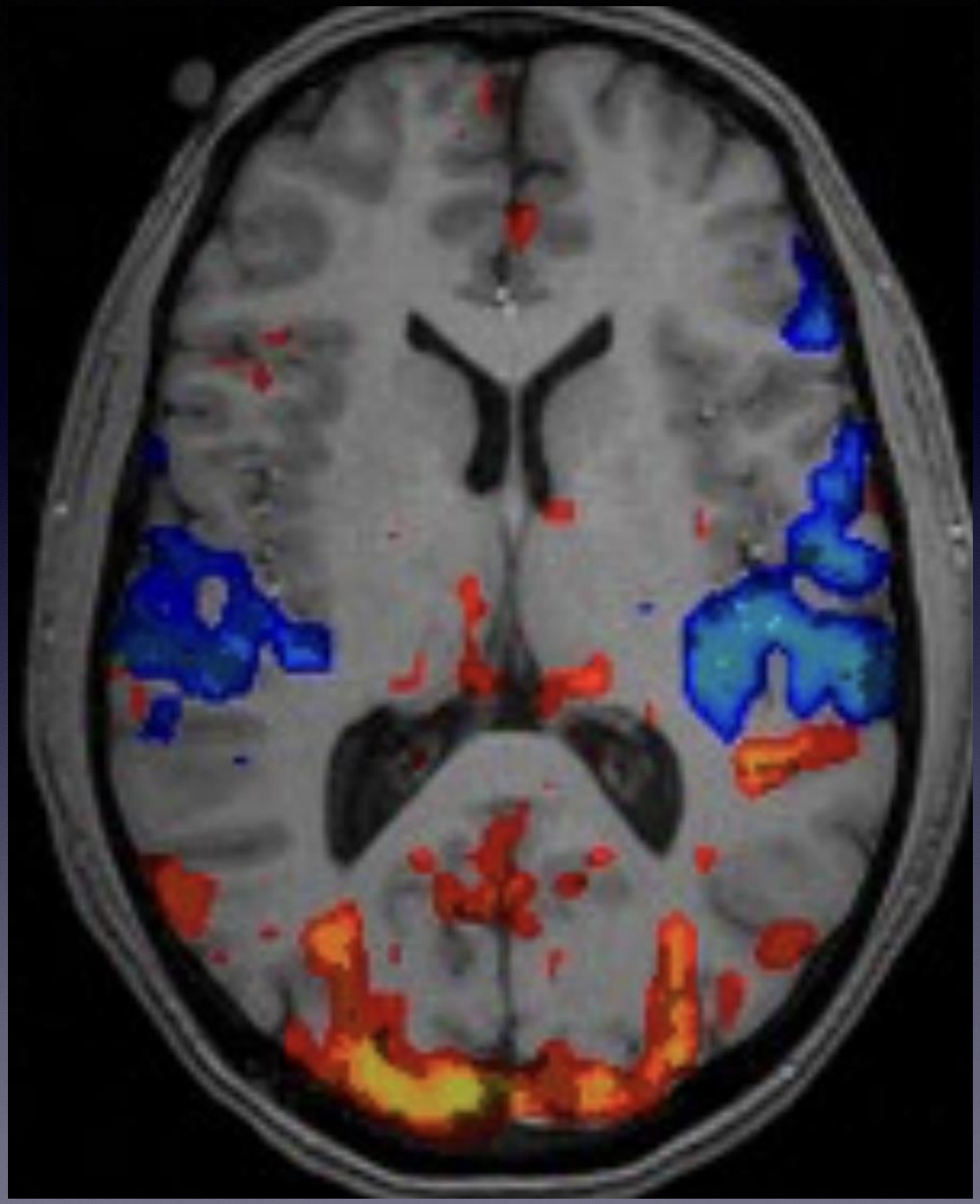
Frank-Erik de Leeuw

Radboud University Medical Center
The Netherlands

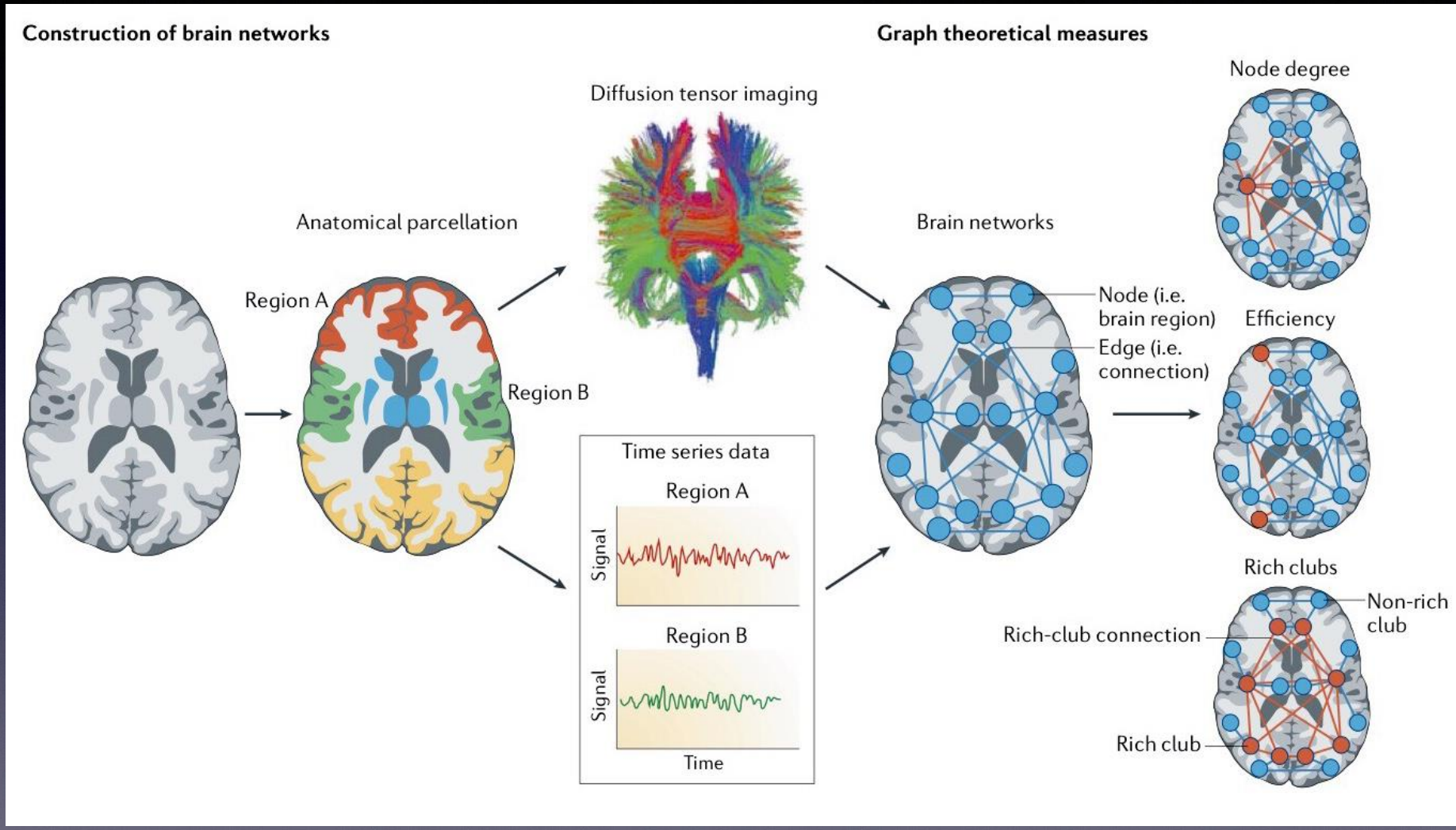

a Neuroimaging markers of SVD
Brain atrophy
WMH
Microbleed
Lacune
Perivascular space
Microinfarcts
b Heterogeneity, perilesional and remote effects of SVD
Cortical thinning
Lesion penumbra
Lesion heterogeneity
White matter tract
Coalescence of microinfarcts with resultant larger cortical infarct

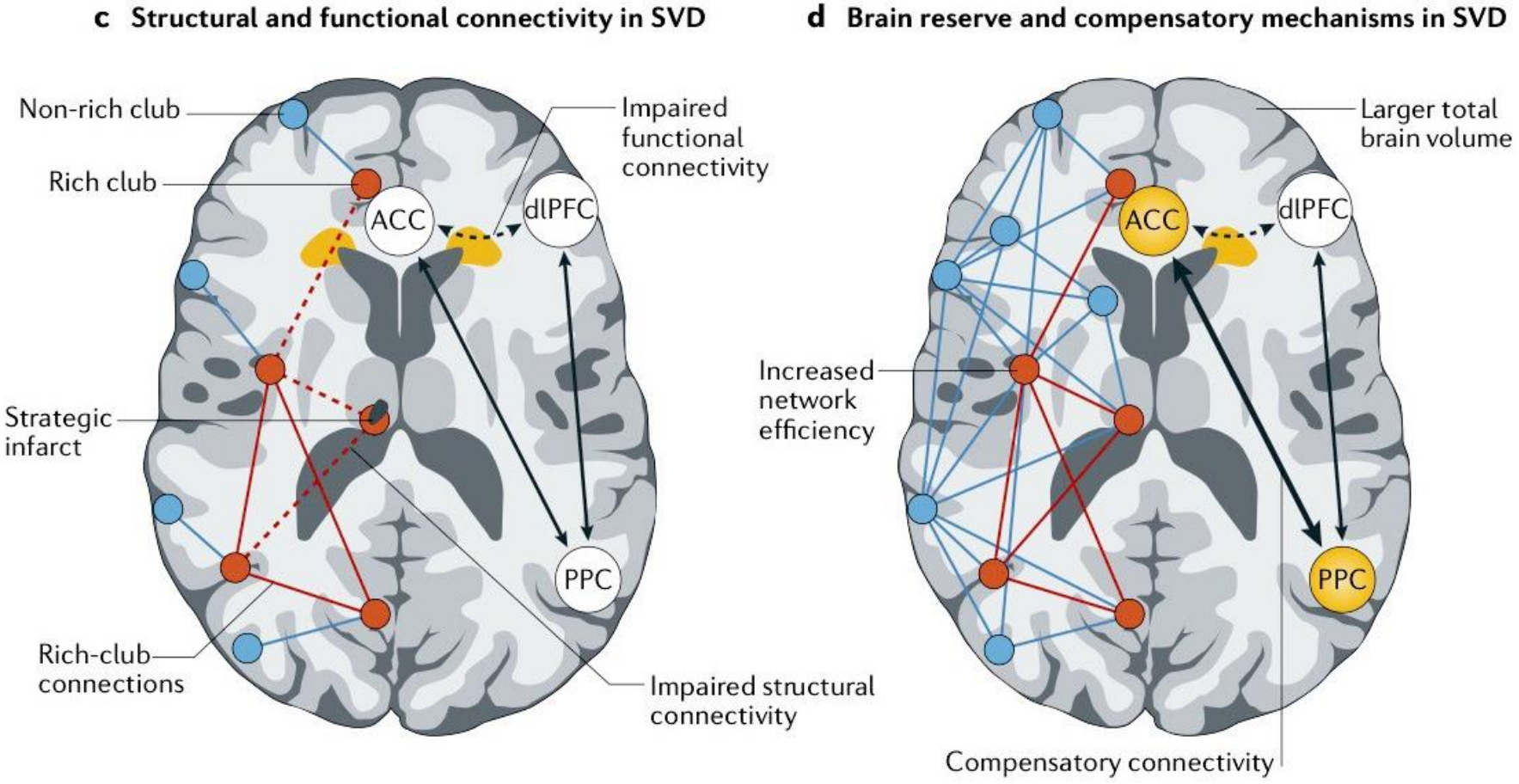


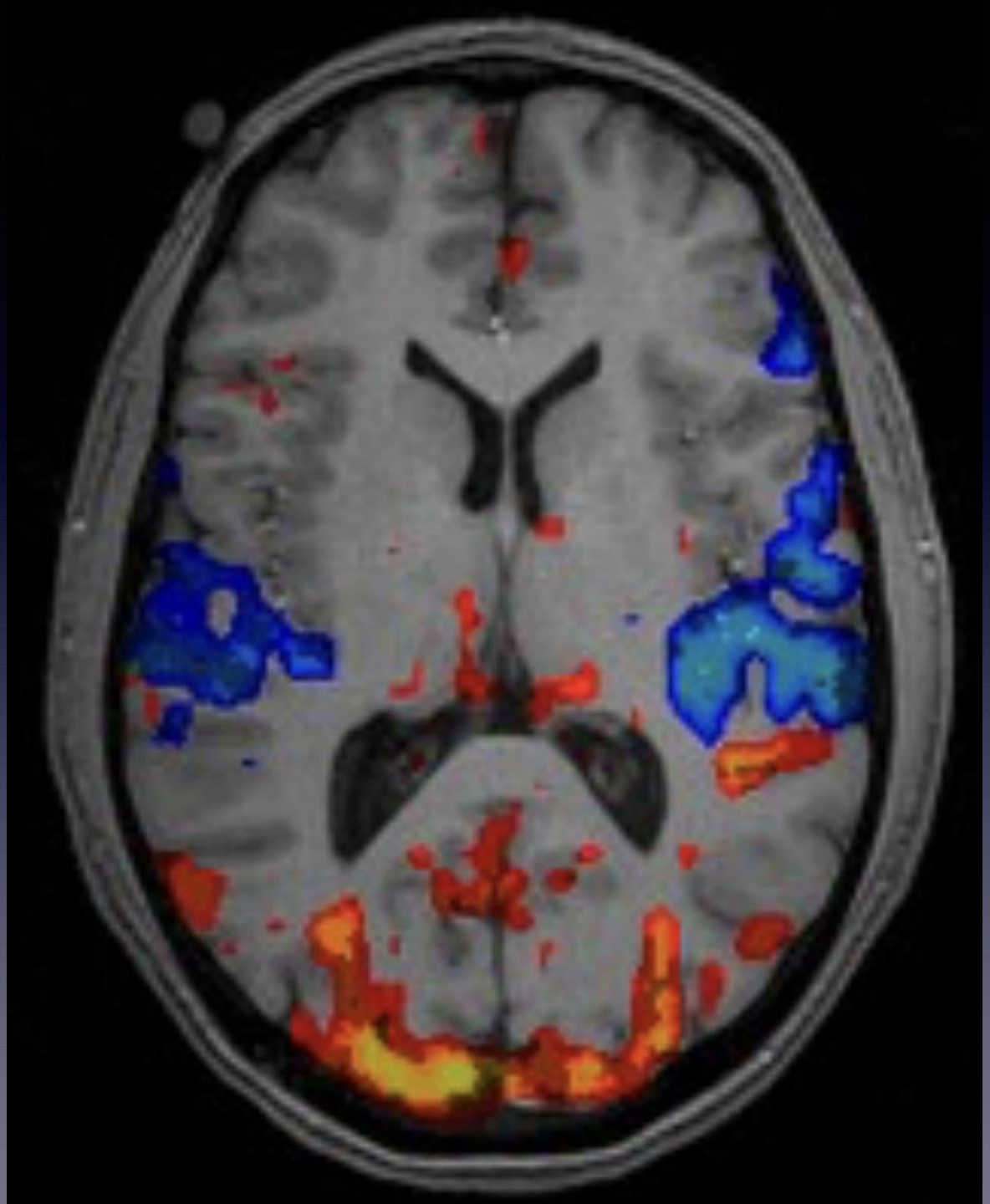
Diffusion Tensor Imaging



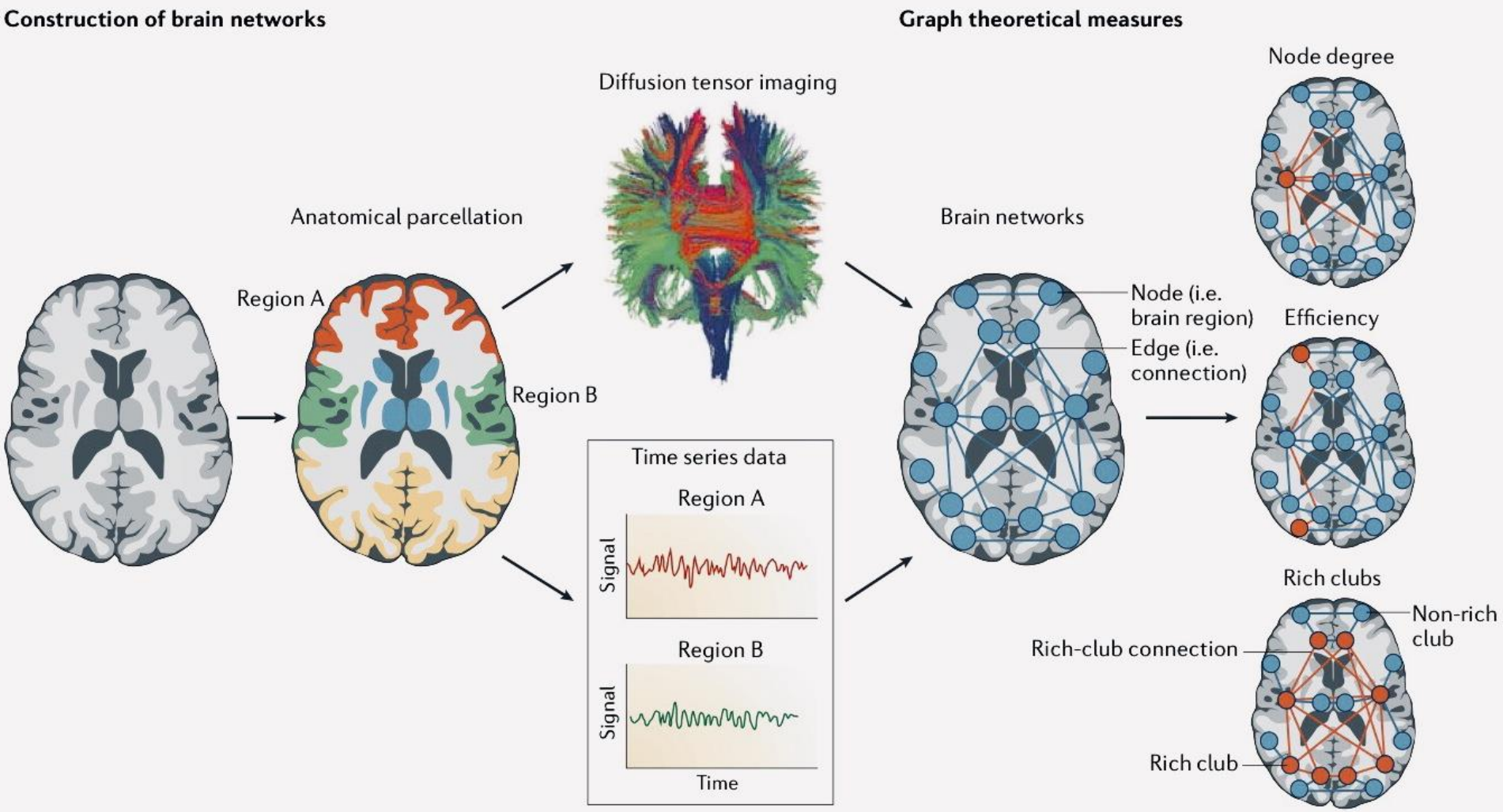
Functional MRI


Construction of brain networks
Graph theoretical measures
Diffusion tensor imaging
Anatomical parcellation
Region A
Region B
Brain networks
Node degree
Node (i.e. brain region)
Edge (i.e. connection)
Efficiency
Time series data
Region A
Signal
Region B
Signal
Time
Rich clubs
Non-rich club
Rich-club connection
Rich club


c Structural and functional connectivity in SVD
Non-rich club
Rich club
Strategic infarct
Rich-club connections
ACC
dlPFC
PPC
Impaired functional connectivity
Impaired structural connectivity
d Brain reserve and compensatory mechanisms in SVD
Increased network efficiency
Larger total brain volume
ACC
dlPFC
PPC
Compensatory connectivity



Functional MRI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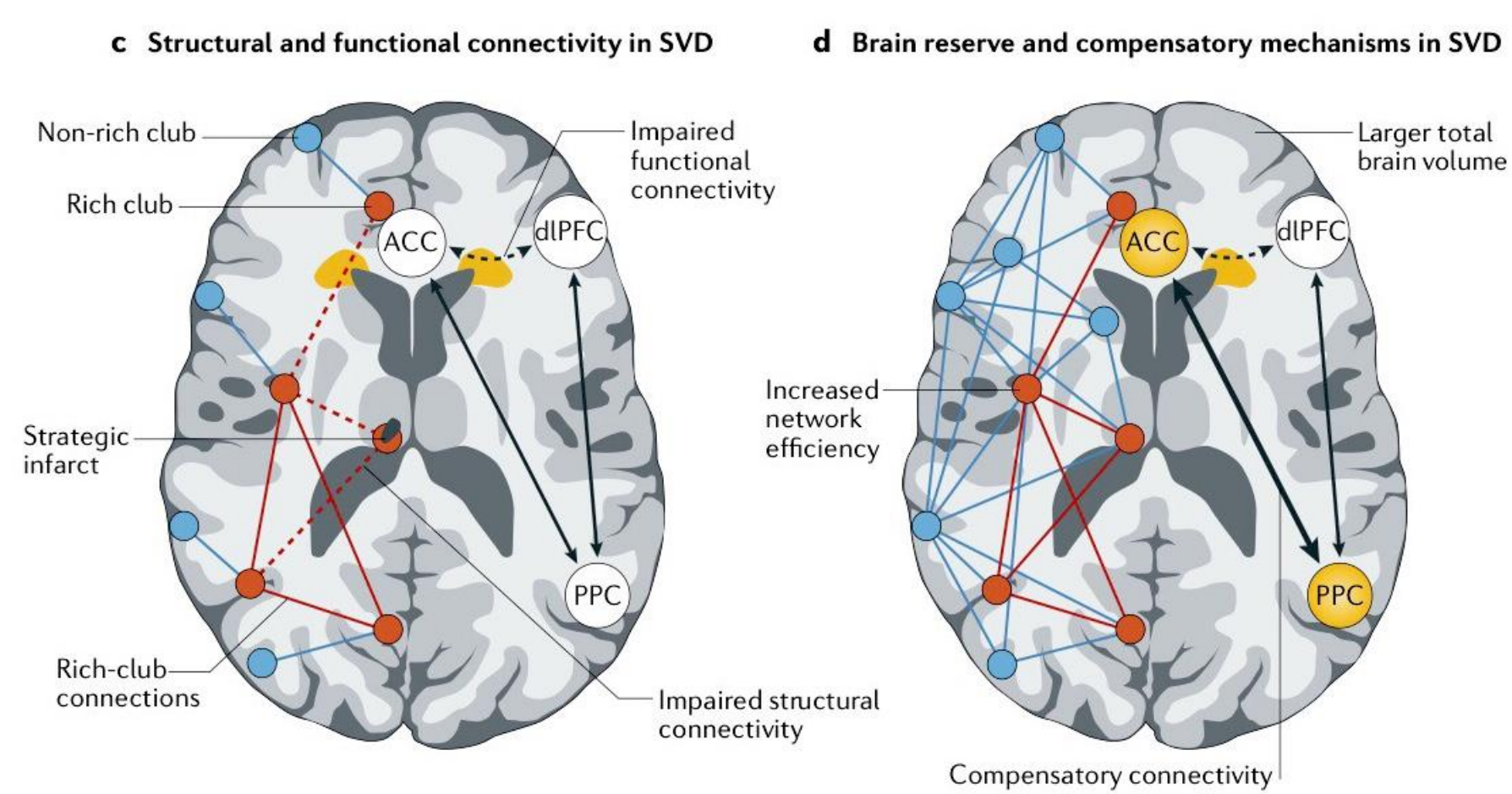
Construction of brain networks

Graph theoretical measures



SVD: Summary

- SVD accounts for
  - about 25% of strokes
  - at least 30% of dementia
- Endothelial failure>BBB permeability>vessel damage>tissue damage, demyelination, scarring, damage to connectome
- Lacunar infarcts are late events
- SVD pathology probably has an additive interaction with other degenerative diseases—especially Alzheimer’s

SVD Treatment

- Control BP
- Stop smoking
- Exercise
- Avoid XS salt intake
- Dual antiplatelet therapy is harmful
- Possibly isosorbide dinitrate and cilostasol


Thank you
for your attention