WCN 2013
TEACHING COURSE 21: UPDATE ON DIFFERENT TYPES OF DEMENTIA

Vascular Cognitive Impairment: From WML to Full-Blown Dementia

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Outline

- Definitions
- Pathology & Pathogenesis
- Clinical Manifestations
- Treatment and Prevention

What is in a name?

NOMENCLATURE: DEFINITIONS

Nomenclature

- Dementia
- Senile & Presenile Dementia
- Atherosclerotic (Senile) Dementia
- Multi-infarct Dementia vs AD
- Vascular Cognitive Impairment
- Vascular Cognitive Disorder
- Major Neurocognitive Disorder

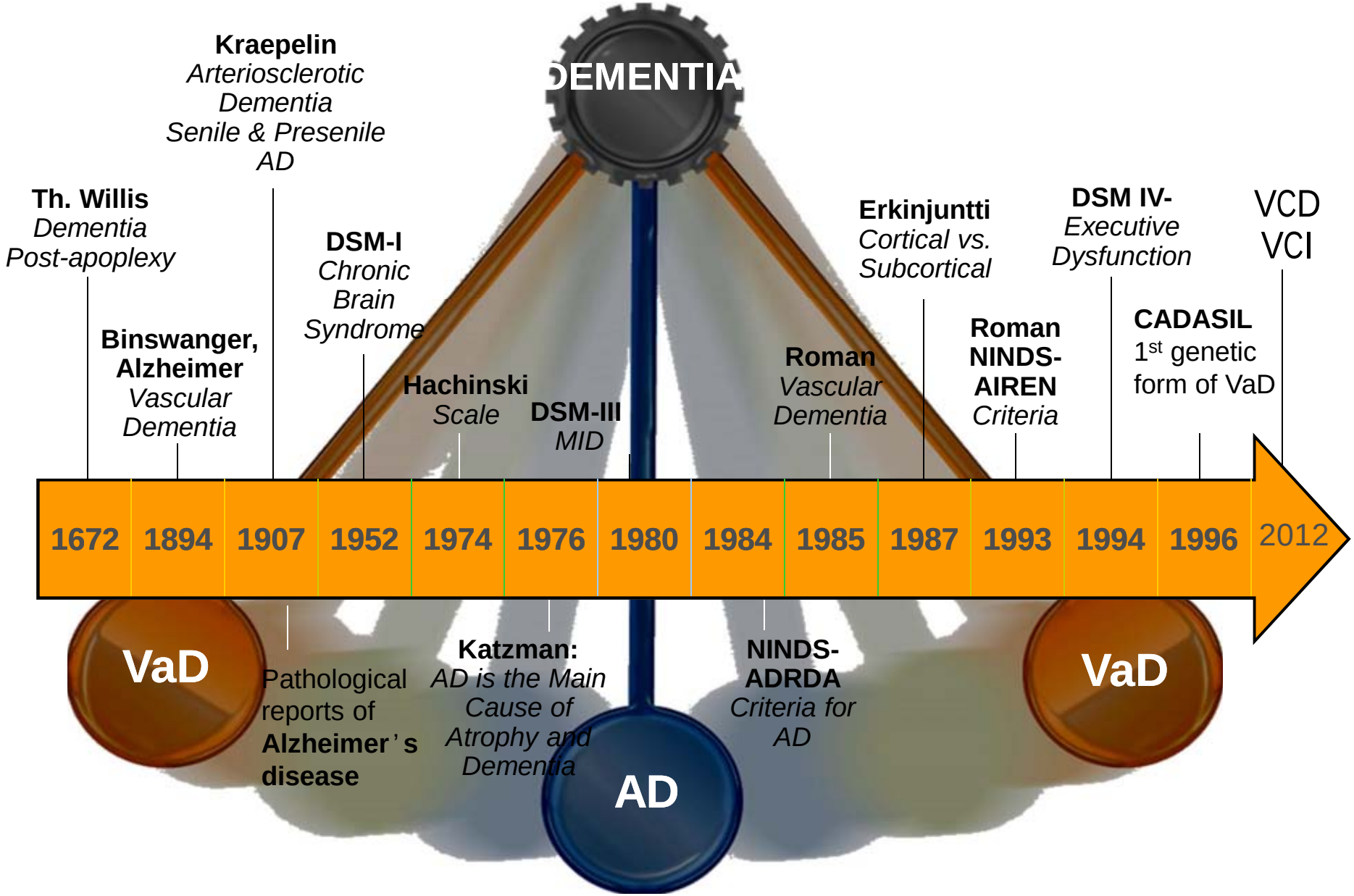
Th. Willis on Dementia

Some at first crafty and ingenuous become by degrees dull, and at length foolish by the mere declining of age... from great strokes or bruising of the head such as happen from a fall from high place...frequent drunkenness... frequent use of opiates very much troubles the sharpness of the mind... and cruel diseases of the head, such as a great and long epilepsy...

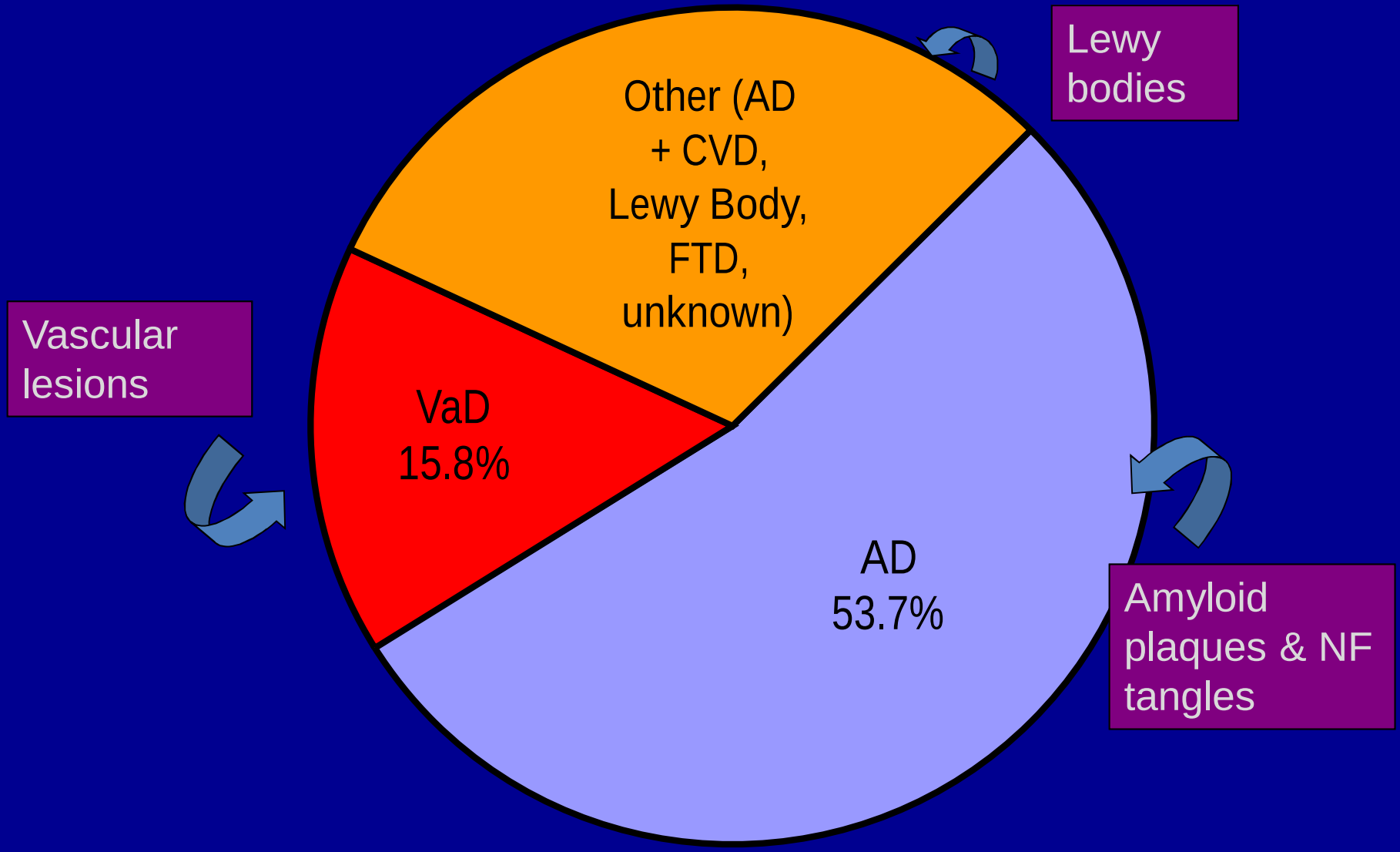
Th. Willis 1672

Thomas Willis at age 45 (1667)
Willis coined the name NEUROLOGY

A BRIEF HISTORY OF DEMENTIA



Prevalence of Dementia



Source: Lobo A. et al. Neurology 2000; 54: S4-9

Post-stroke Dementia

- Stroke is an important cause of dementia
- H/O stroke doubles the Incidence of new-onset dementia from 7% after 1 year to 48% after 25 years
- 30% of stroke survivors aged >60 yrs develop dementia
- 19-61% of patients with post-stroke dementia also have Alzheimer's disease

Savva et al. *Stroke* 2010; 41: e41-46
Leys et al. *Lancet Neurol* 2005;11:752-9

Secondary Prevention of Small Subcortical Strokes (SPS3)

Almost half (47%) of all participants (N=1,636) had vascular mild cognitive impairment (MCI)

-amnestic (36%)

-amnestic multi-domain (37%)

-non-amnestic (28%)

MCI was seen even in those with minimal or no motor disability

Jacova et al. *Ann Neurol* 2012;72:351-62

There has been significant evolution of the terminology to characterize the cognitive syndrome associated with risk factors for cerebrovascular disease and its manifestations, especially the description of dementia. Approximately 30 years ago, the term *MID*[11] was used to identify patients who developed dementia after multiple strokes, although it was also used for patients with a single vascular insult. More recently, the term *VaD* has been used, regardless of the pathogenesis of the vascular lesion—ischemic or hemorrhagic or single or multiple infarct(s).[10,19,20]

Cerebrovascular disease can also cause mild cognitive deficits that can affect multiple cognitive functions, and some authors have proposed the term *vascular mild cognitive impairment* (*VaMCI*).[21,22] This is the "vascular" equivalent of mild cognitive impairment (MCI) commonly used to identify subjects in the transition from normalcy to Alzheimer dis-

THE LANCET, JULY 27, 1974

Mental Health

MULTI-INFARCT DEMENTIA
A CAUSE OF MENTAL DETERIORATION IN THE ELDERLY

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special article

20 years!

Vascular dementia: Diagnostic criteria for research studies

Report of the NINDS-AIREN International Workshop

GC Román TK Tatemichi, T Erkinjuntti, JL Cummings, JC Masdeu, JH García, L Amaducci, J-M Orgogozo, A Brun, A Hofman, DM Moody, MD O'Brien, T Yamaguchi, J Grafman, BP Drayer, DA Bennett, M Fisher, J Ogata, E Kokmen, F Bermejo, PA Wolf, PB Gorelick, KL Bick, AK Pajeau, MA Bell, C DeCarli, A Culebras, AD Korczyn, J Bogousslavsky, A Hartmann, P Scheinberg

NEUROLOGY 1993;43:250-260

ELSEVIER

Journal of the Neurological Sciences 226 (2004) 81–87

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia

Gustavo C. Román[a,*], Perminder Sachdev[b], Donald R. Royall[c], Roger A. Bullock[d], Jean-Marc Orgogozo[e], Secundino López-Pousa[f], Raul Arizaga[g], Anders Wallin[h]

In Medicine, well-defined disorders are treated — not impairments (i.e., pulmonary diseases: asthma, COPD, not impairments of pulmonary function)

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Original Contributions

National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards

Vladimir Hachinski, MD, DSc; Costantino Iadecola, MD; Ron C. Petersen, MD, PhD; Monique M. Breteler, MD, PhD; David L. Nyenhuis, PhD; Sandra E. Black, MD; William J. Powers, MD; Charles DeCarli, MD; Jose G. Merino, MD; Raj N. Kalaria, PhD, FRCP; Harry V. Vinters, MD; David M. Holtzman, MD; Gary A. Rosenberg, MD; Anders Wallin; Martin Dichgans, MD; John R. Marler, MD; Gabrielle G. Leblanc, PhD

Stroke. 2006;37:2220-2241; originally published online August 17, 2006;
doi: 10.1161/01.STR.0000237236.88823.47

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association℠

A Division of American Heart Association

Vascular Contributions to Cognitive Impairment and Dementia : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Philip B. Gorelick, Angelo Scuteri, Sandra E. Black, Charles DeCarli, Steven M. Greenberg, Costantino Iadecola, Lenore J. Launer, Stephane Laurent, Oscar L. Lopez, David Nyenhuis, Ronald C. Petersen, Julie A. Schneider, Christophe Tzourio, Donna K. Arnett, David A. Bennett, Helena C. Chui, Randall T. Higashida, Ruth Lindquist, Peter M. Nilsson, [redacted] Frank W. Sellke and Sudha Seshadri

Conclusions—Vascular contributions to cognitive impairment and dementia are important. Understanding of VCI has evolved substantially in recent years, based on preclinical, neuropathologic, neuroimaging, physiological, and epidemiological studies. Transdisciplinary, translational, and transactional approaches are recommended to further our understanding of this entity and to better characterize its neuropsychological profile. There is a need for prospective, quantitative, clinical-pathological-neuroimaging studies to improve knowledge of the pathological basis of neuroimaging change and the complex interplay between vascular and Alzheimer disease pathologies in the evolution of clinical VCI and Alzheimer disease. Long-term vascular risk marker interventional studies beginning as early as midlife may be required to prevent or postpone the onset of VCI and Alzheimer disease. Studies of intensive reduction of vascular risk factors in high-risk groups are another important avenue of research. (***Stroke*****. 2011;42:2672-2713.)**

American Psychiatric Association (APA)

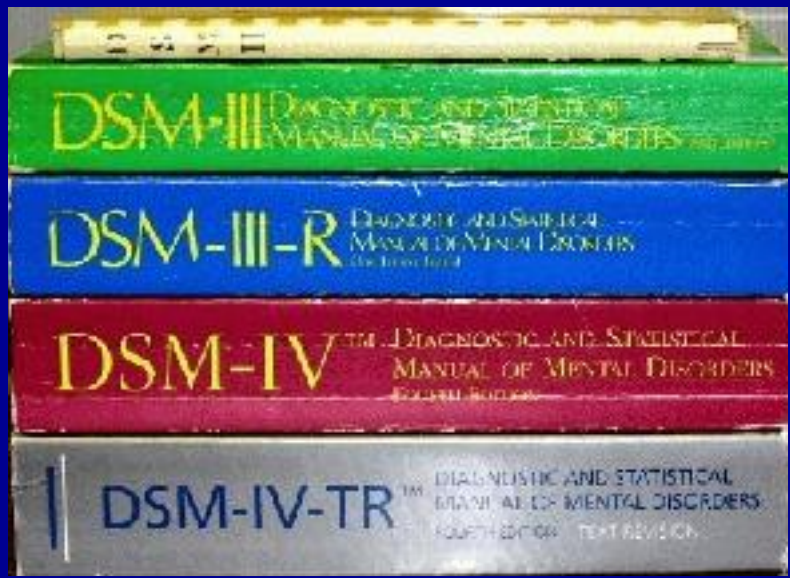
1952: Diagnostic and Statistical Manual of Mental Disorders (DSM-I).

Major Neurocognitive Disorder (DSM-V)

Chronic brain syndrome

with impairment of memory, orientation, affect, judgment, and intellectual function (comprehension, calculation, knowledge, learning)

Román GC, 2002

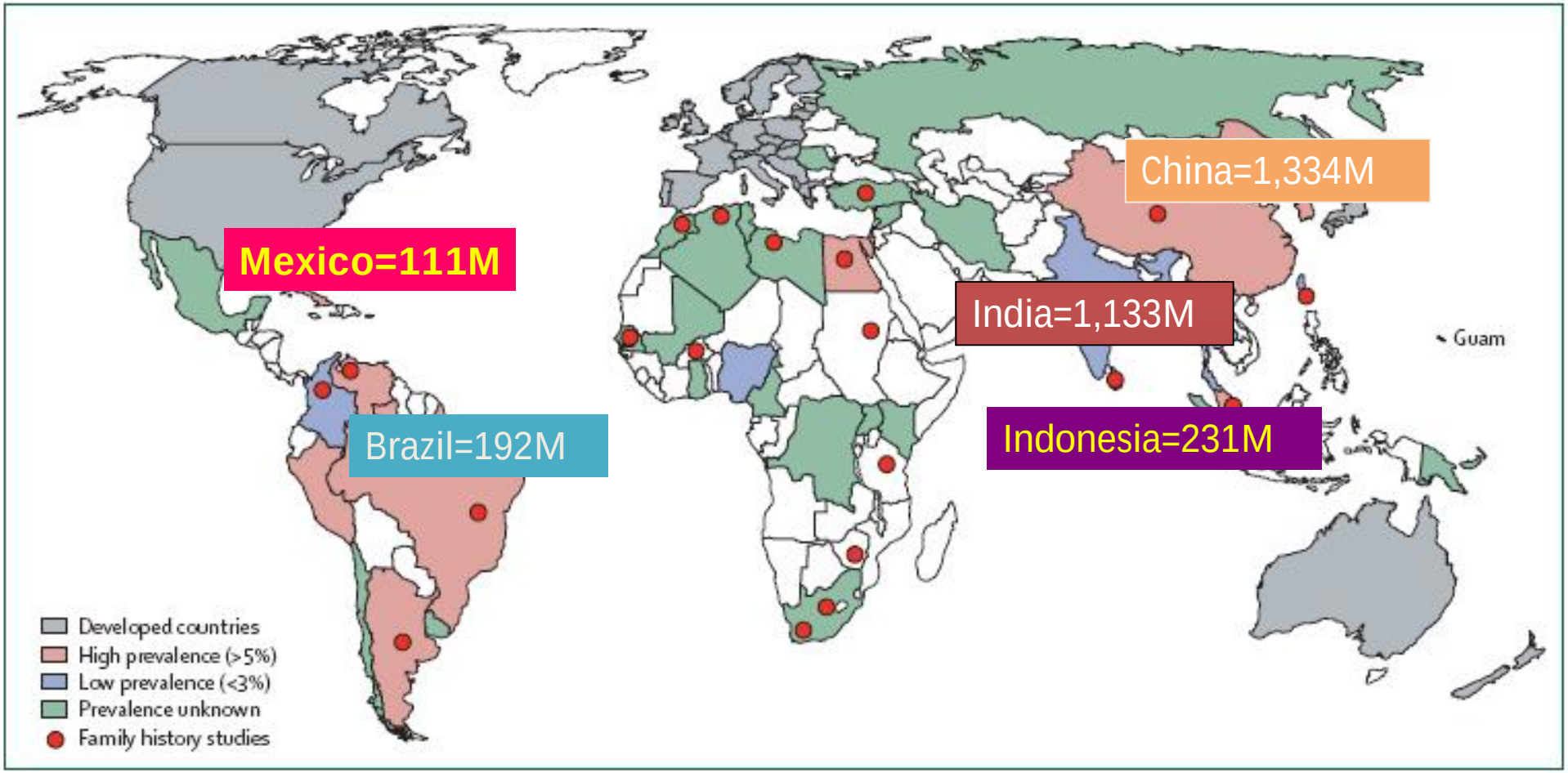


Epidemiology of VaD

- VaD represents 10-20% of all dementias
- Second cause after Alzheimer's disease
- Growing incidence/prevalence of «pure» and «mixed» cases of AD
- Is AD declining?

Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors

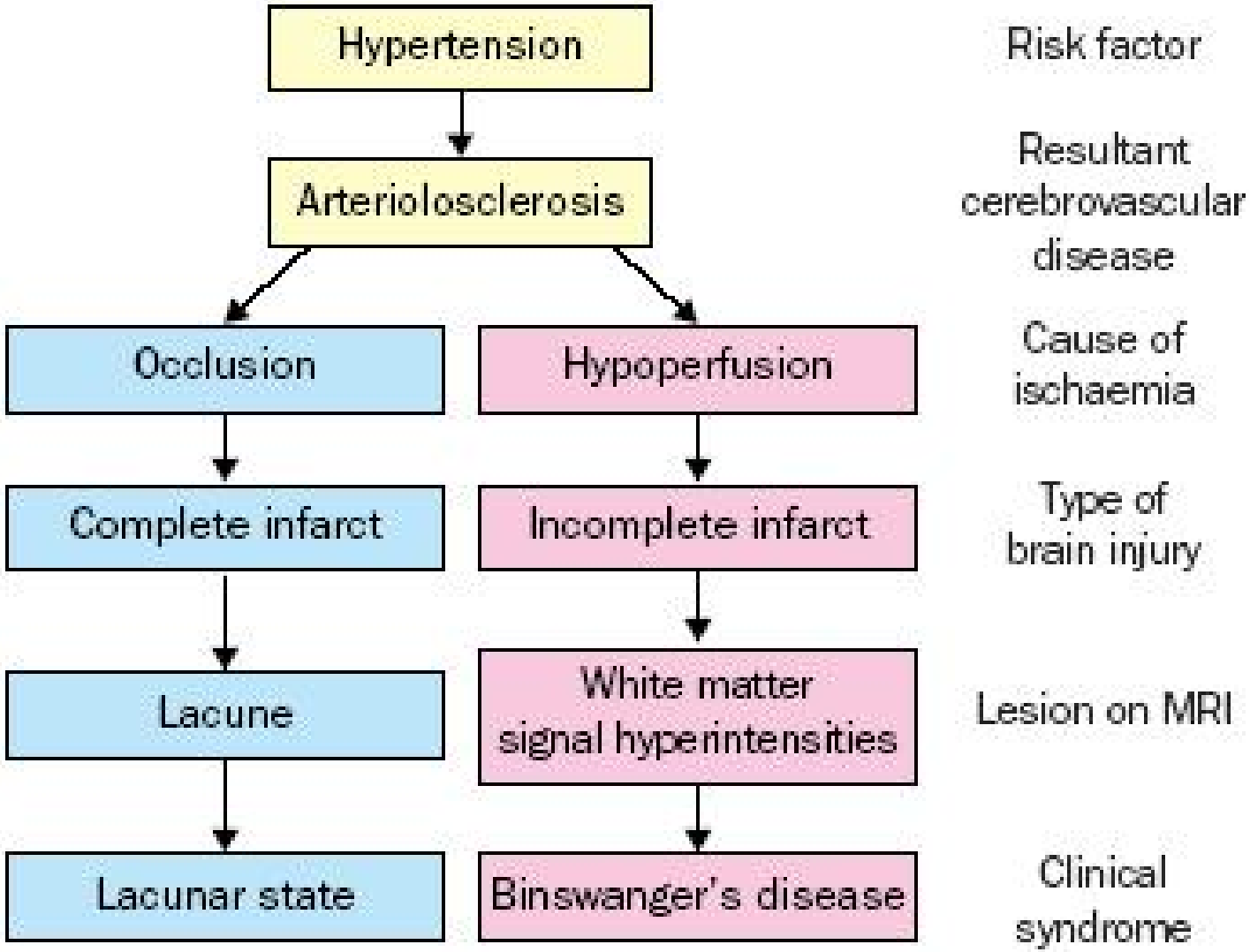
*Raj N Kalaria, Gladys E Maestre, Raul Arizaga, Robert P Friedland, Doug Galasko, Kathleen Hall, José A Luchsinger, Adesola Ogunniyi, Elaine K Perry, Felix Potocnik, Martin Prince, Robert Stewart, Anders Wimo, Zhen-Xin Zhang, Piero Antuono, for the World Federation of Neurology Dementia Research Group**



The Lancet Neurology 2008;7: 812

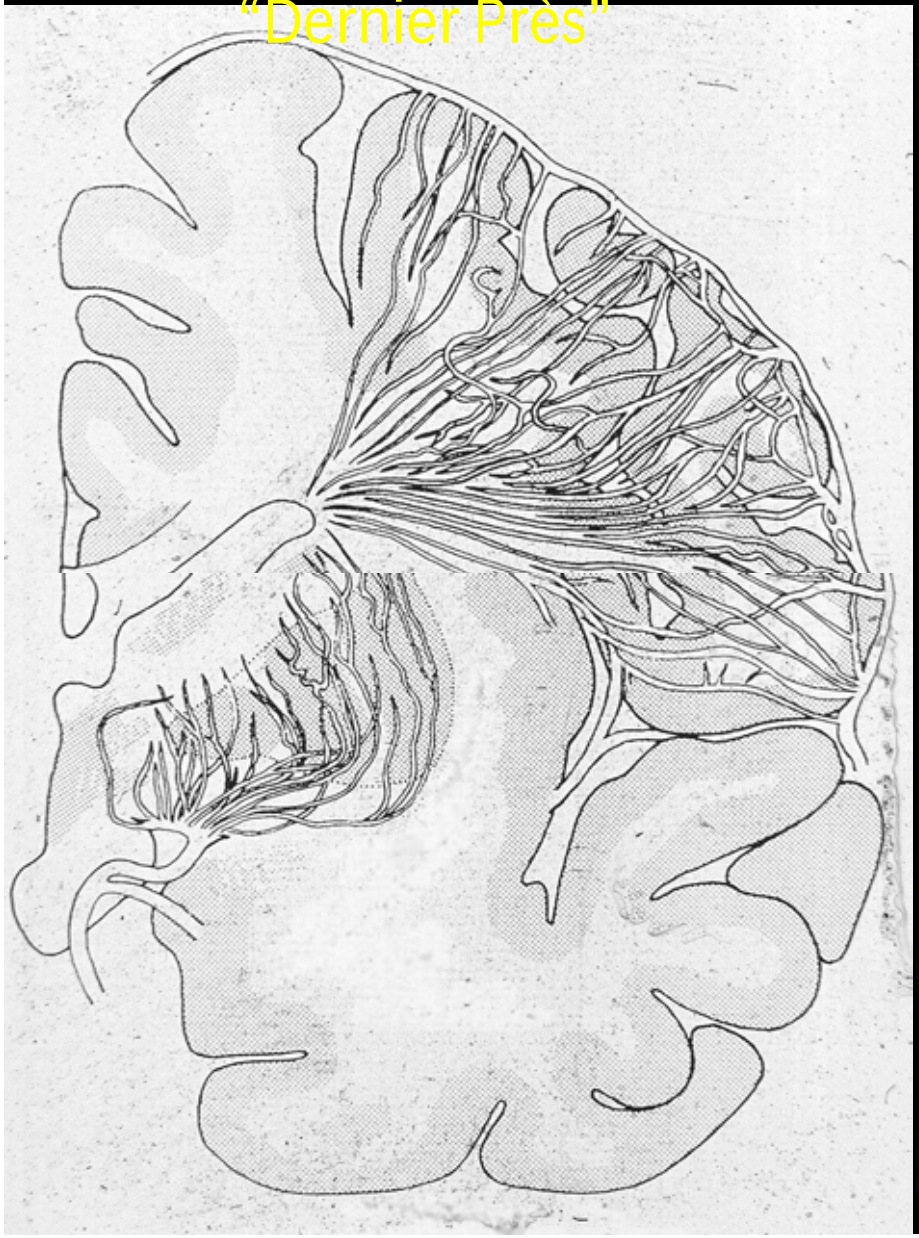
VaD and AD are tightly associated

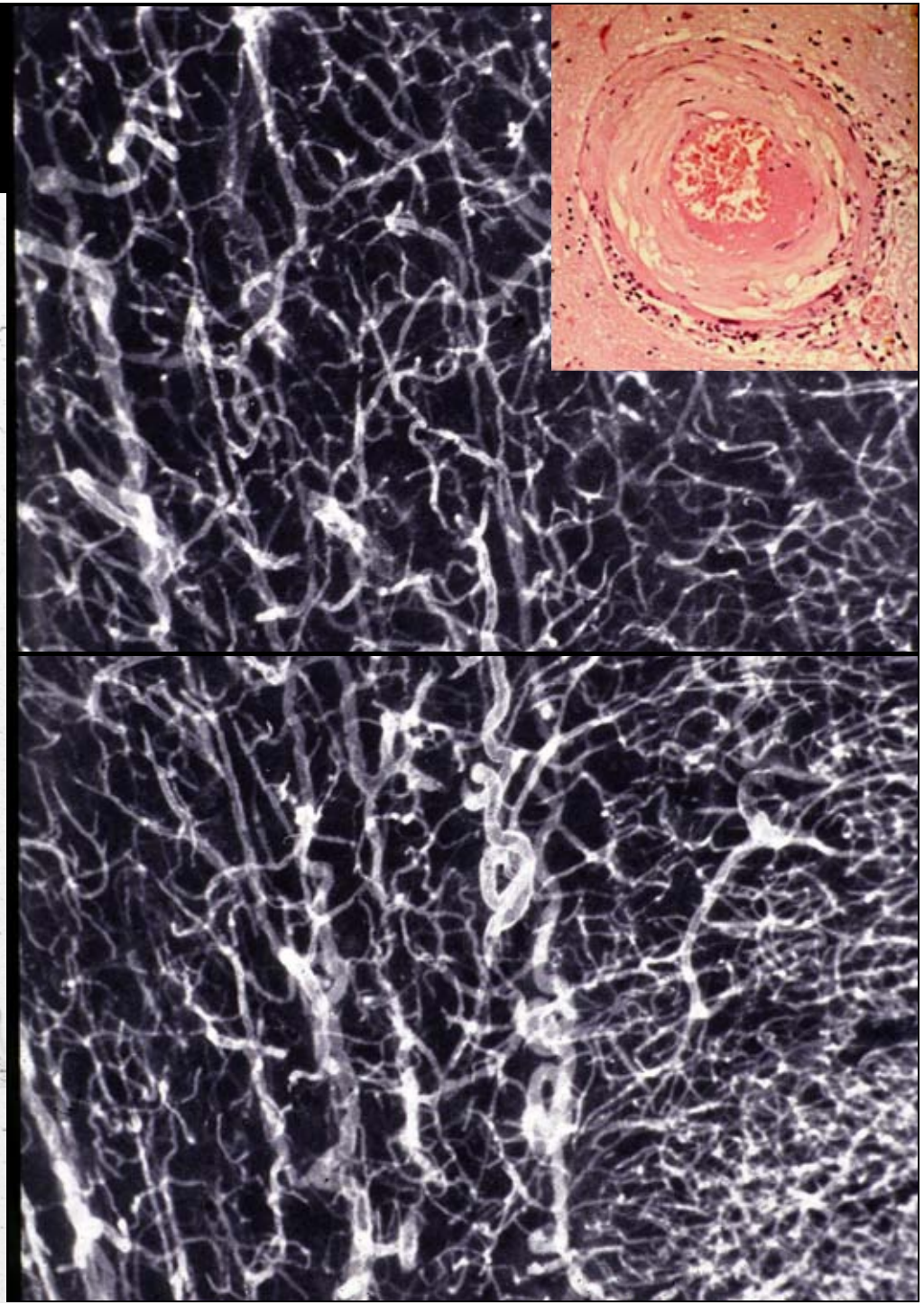
NEUROPATHOLOGY
PATHOGENESIS



From: Román et al. Subcortical ischaemic vascular dementia. Lancet Neurology 2002; 1: 426-436.

Distal Vascular Territories
"Dernier Près"





AD Pathology and Macroscopic Cerebral Infarctions in 153 Persons With and Without Dementia in the Religious Orders Study

Parameters	No Dementia n=86	Dementia n=67
AD pathology (SD)	0.55 (0.48)	1.15 (0.77)
Neuritic plaques	0.51 (0.59)	1.24 (1.05)
Tangles	0.39 (0.46)	0.98 (1.00)
Cerebral infarctions (%)	**22 (25.58)**	**32 (47.76)**
One infarction only	12	14
Multiple infarctions, range: 2–9	10	18
Cortical	7	10
Subcortical	19	28
Left hemispheric	12	18
Right hemispheric	16	21

Julie Schneider et al. Neurology. 2004;62:1148-1155.

Age, Neuropathology, and Dementia

George M. Savva, Ph.D., Stephen B. Wharton, F.R.C.Path., Paul G. Ince, M.D., Gillian Forster, B.Sc., Fiona E. Matthews, Ph.D., and Carol Brayne, M.D., for the Medical Research Council Cognitive Function and Ageing Study

The NEW ENGLAND JOURNAL of MEDICINE

RESULTS

The difference in the prevalence of moderate and severe Alzheimer's-type pathological changes between persons with and those without dementia decreased with increasing age. The association between neocortical neuritic plaques and dementia was strong at 75 years of age (odds ratio, 8.63; 95% confidence interval [CI], 3.81 to 19.60) and reduced at 95 years of age (odds ratio, 2.48; 95% CI, 0.92 to 4.14), and similar attenuations with advancing age were observed in the association between other pathological changes related to Alzheimer's disease and dementia in all brain areas. In contrast, neocortical cerebral atrophy maintained a relationship with age in persons with dementia at both 75 years of age (odds ratio, 5.11; 95% CI, 1.94 to 13.46) and 95 years of age (odds ratio, 6.10; 95% CI, 2.80 to 13.28) and thus distinguished the cohort with dementia from the cohort without dementia.

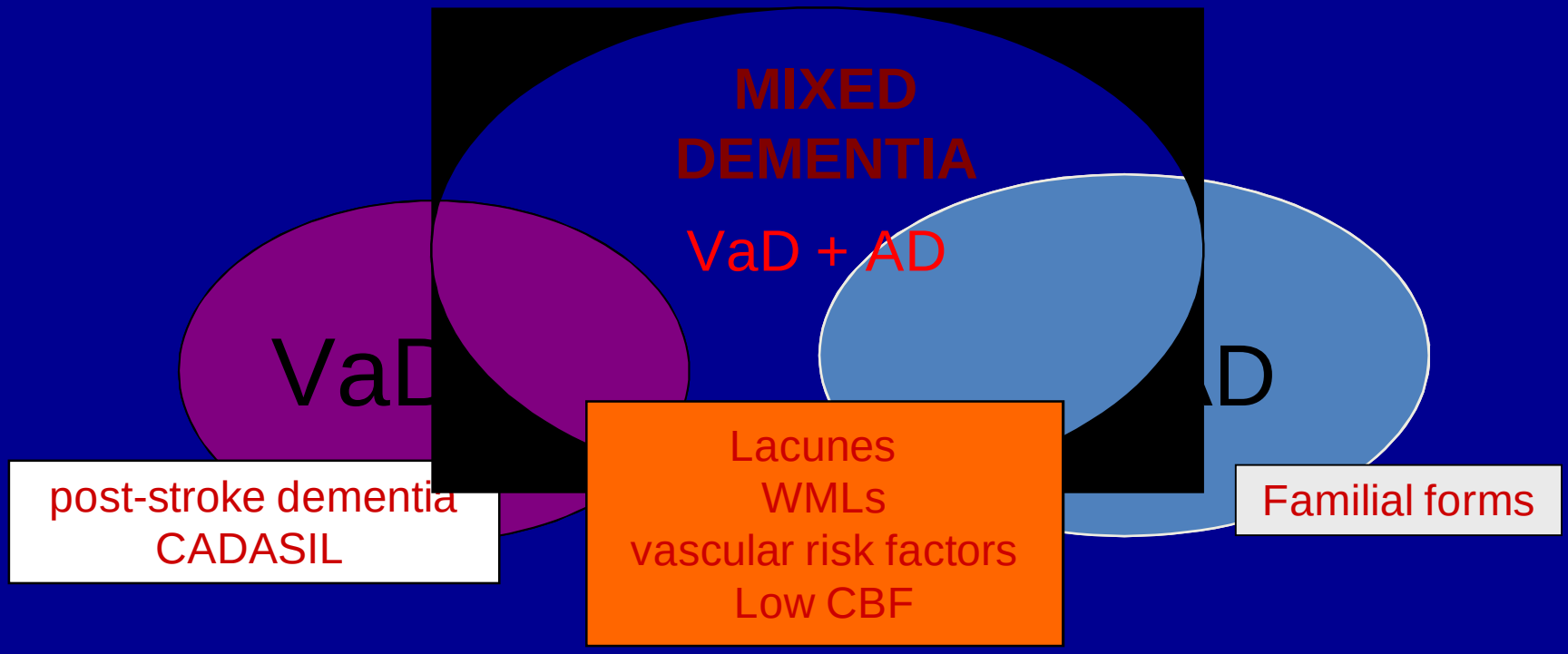
CONCLUSIONS

The association between the pathological features of Alzheimer's disease and dementia is stronger in younger old persons than in older old persons. Age must be taken into account when assessing the likely effect of interventions against dementia on the population.

VaD and AD are tightly linked

- Population-based studies have demonstrated the frequent contribution of cerebrovascular disease, in particular lacunar strokes and ischemic leukoencephalopathy to AD
- The natural history of dementia in the elderly must explore the role of “silent” ischemic brain lesions demonstrated by imaging

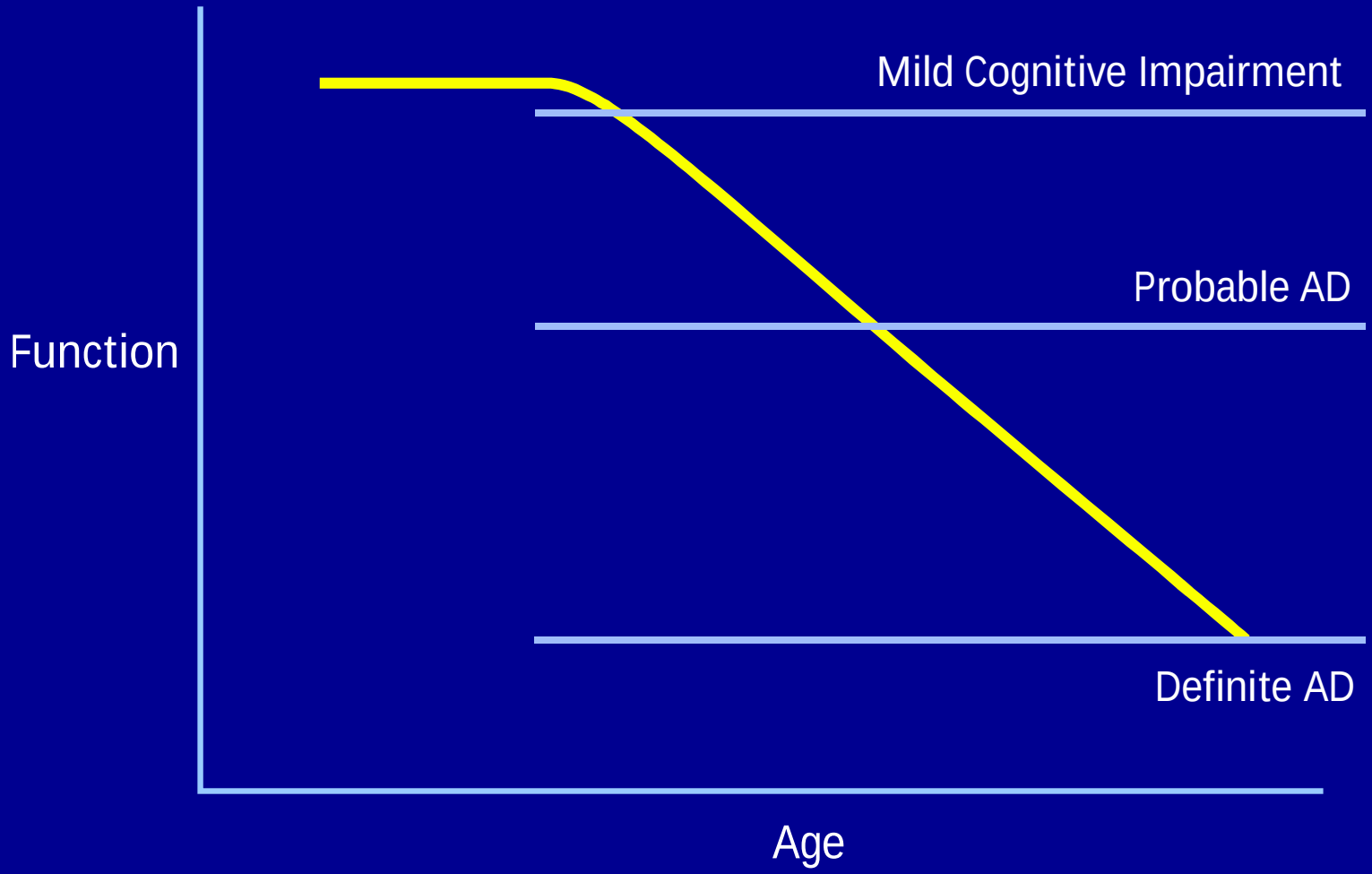
Interactions Between VaD and AD



Source: T. Erkinjuntti modified by GC Roman

AD: Conceptual Framework

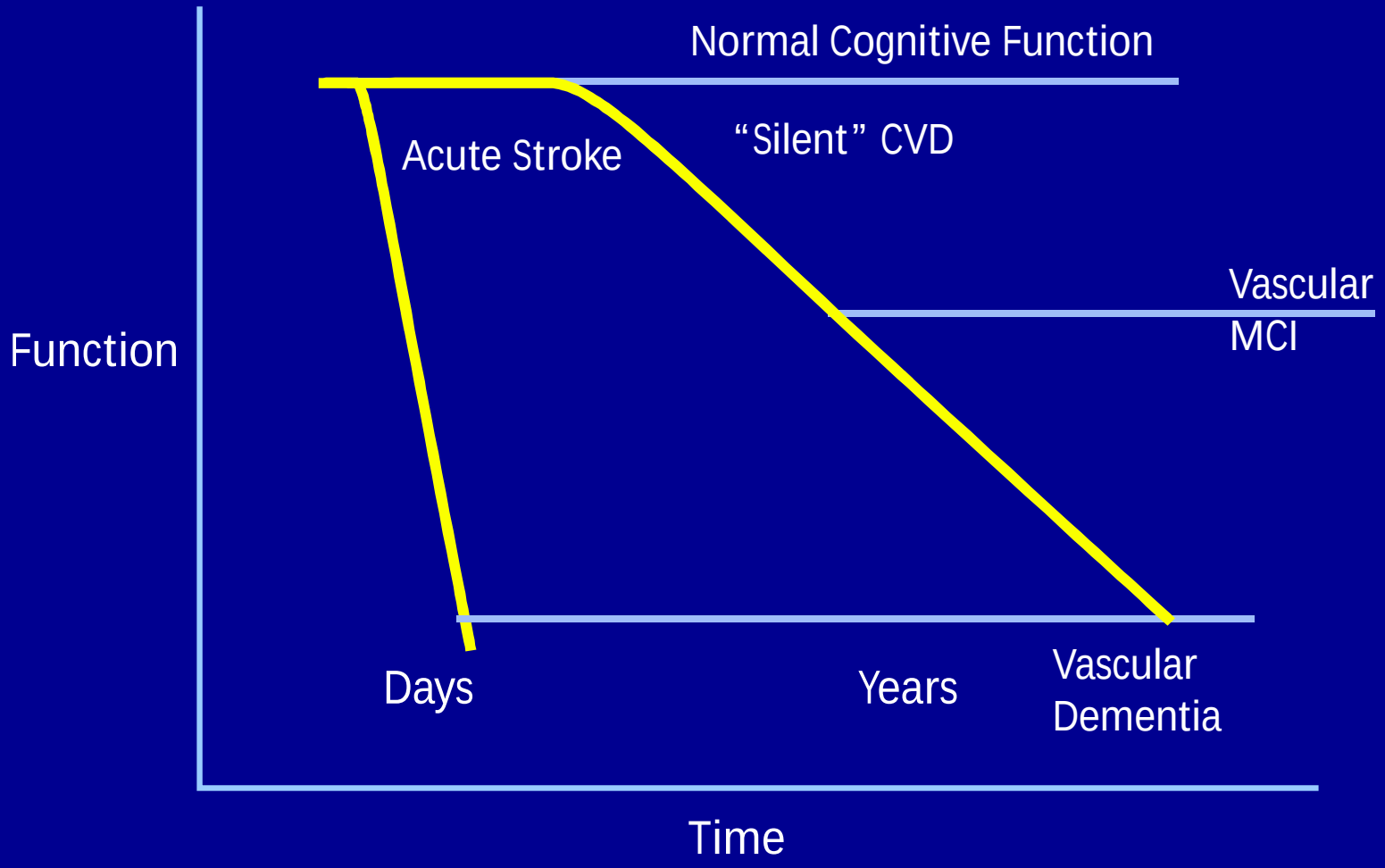
Cognitive Continuum



Petersen RC. *Neurol Clin.* 2000;18:789-805.

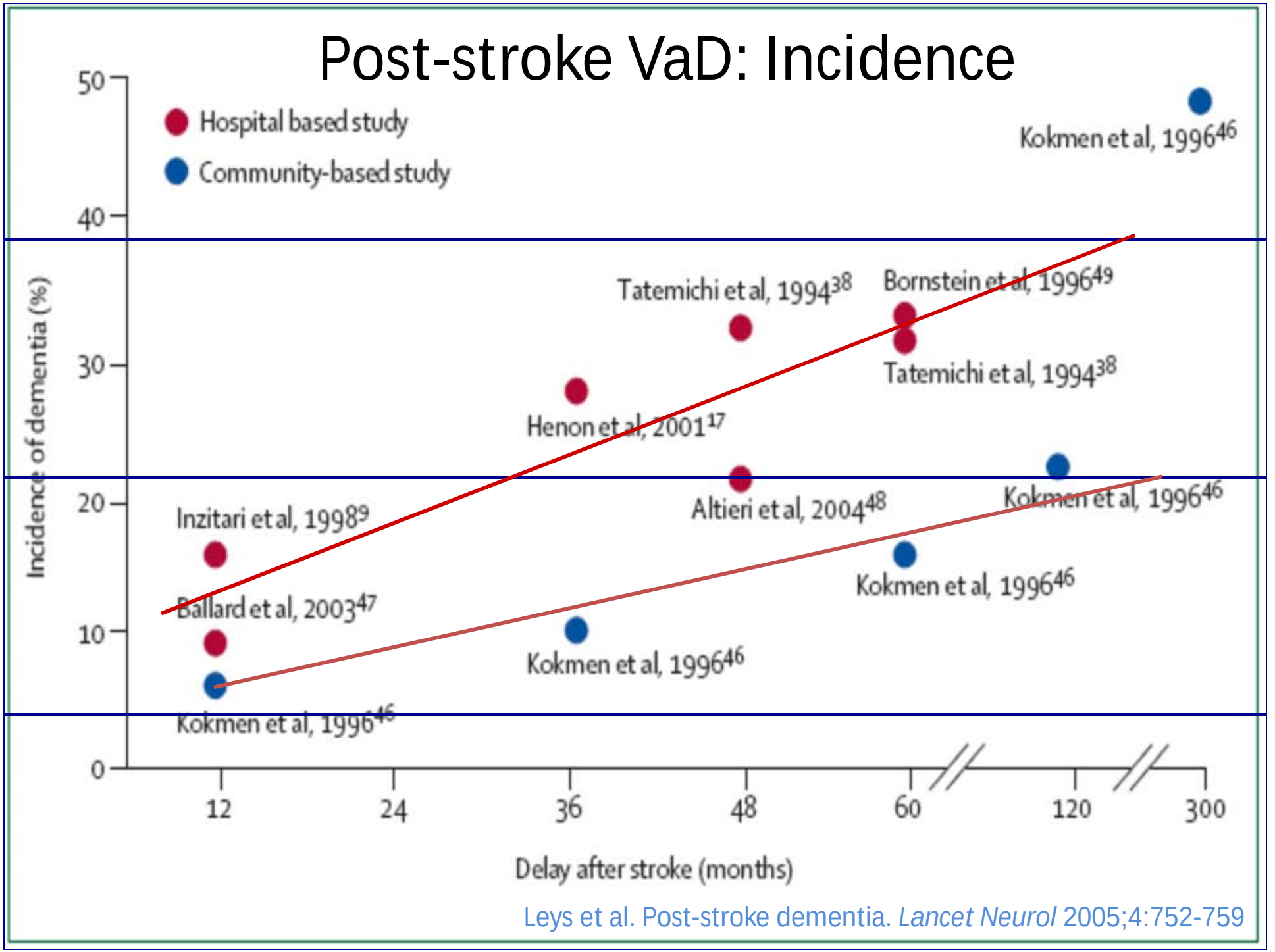
VaD: Conceptual Framework

Cognitive Continuum



Concept by Román GC

Post-stroke VaD: Incidence



Leys et al. Post-stroke dementia. *Lancet Neurol* 2005;4:752-759

Stroke—both silent and clinically eloquent—is one of the most important determinants of dementia in the elderly

Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. *Nat Rev Neurol* 2009;5:649-658.

Risk Factors for Post-Stroke Dementia

Patients' demographic & clinical characteristics

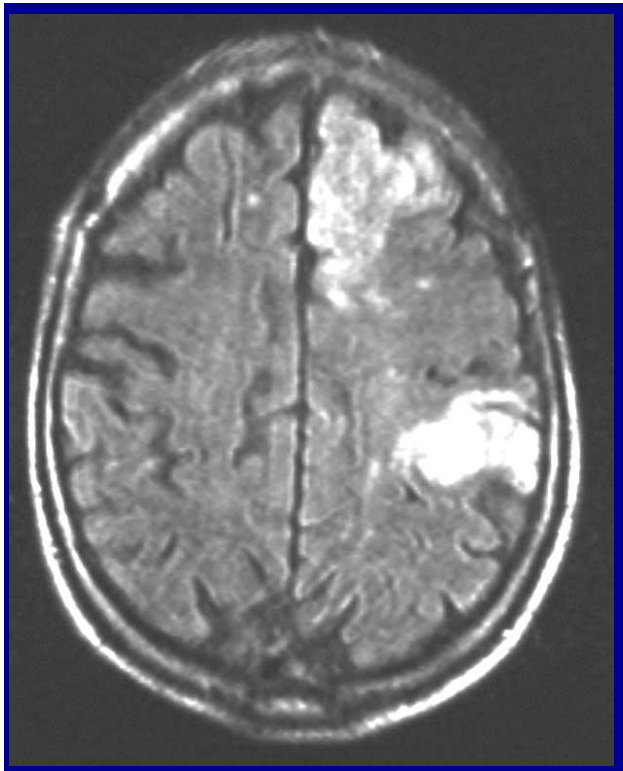
- Older age
- Low education
- Pre-stroke dependency
- Pre-stroke cognitive decline–no dementia
- High blood pressure
- Diabetes mellitus
- Atrial fibrillation
- Myocardial infarction
- Epileptic seizures
- Sepsis
- Cardiac arrhythmias
- Congestive heart failure

Patients' neuroimaging & stroke characteristics

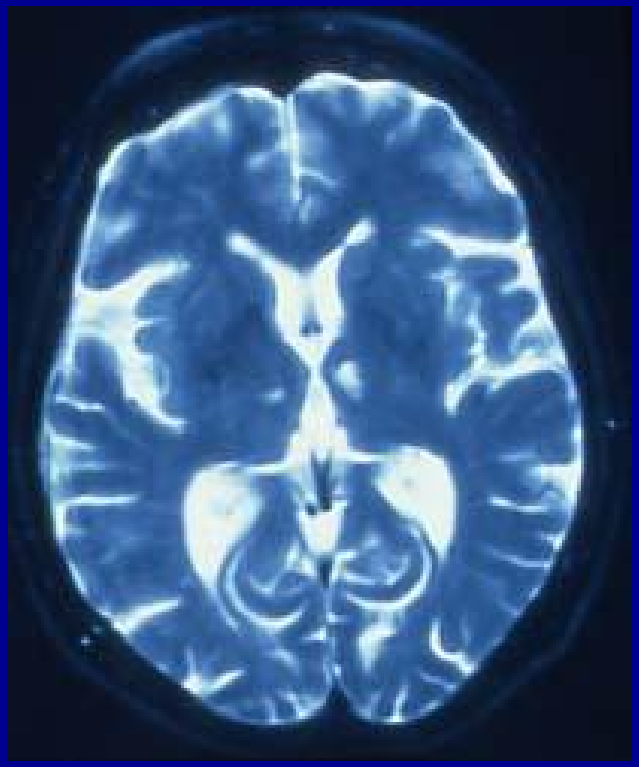
- Silent infarcts
- Global cerebral atrophy
- Medial-temporal-lobe atrophy
- White-matter changes
- More severe clinical deficit at stroke onset
- Stroke recurrences
- Supratentorial lesions
- Left hemispheric lesions
- Anterior and posterior cerebral artery territory infarcts
- Strategic infarcts
- Multiple lesions

Leys et al. Post-stroke dementia. *Lancet Neurol* 2005;4:752-759

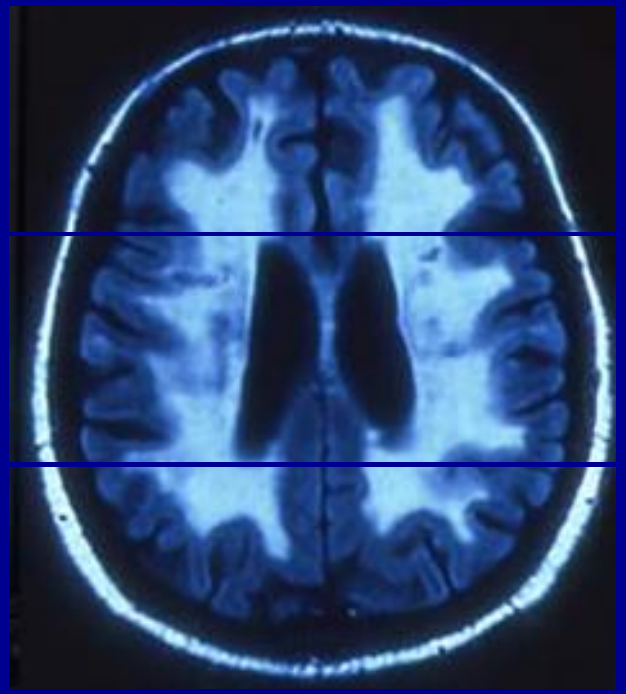
Vascular Dementia



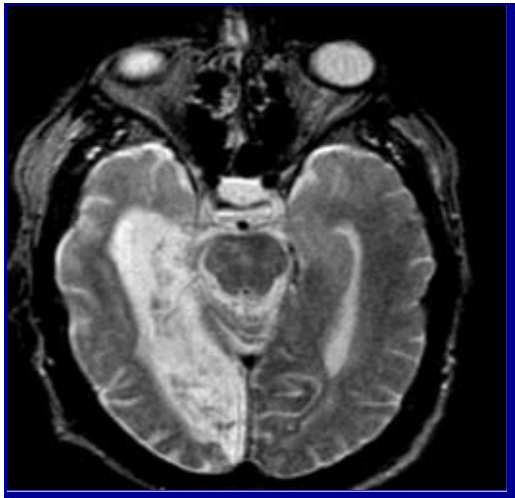
Multi-Infarct Dementia (MID): multiple large vessel infarctions (ischemic strokes)



Bilateral strategic thalamic infarcts



Binswanger's disease



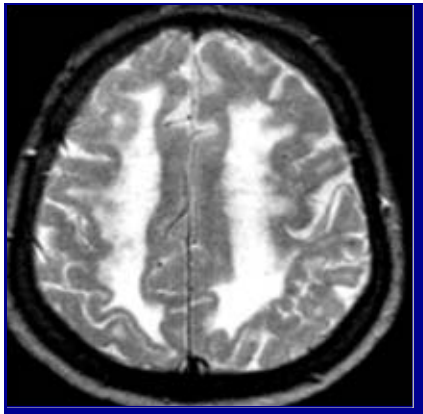
Large cortical lesions

Large-vessel disease

Cortical infarcts in strategic locations

- Frontal lobe → Aphasia, apraxia, disinhibition, apathy
- Hippocampus, basal forebrain → Amnesia
- Gyrus angularis → Constructional problems
- Parietal lobe → Alexia, agraphia

Cortical type of dementia



Small-vessel Disease Subcortical VaD

Small-vessel disease

↓

Subcortical infarcts in strategic locations
Thalamus, caudate nucleus, internal capsule

↓

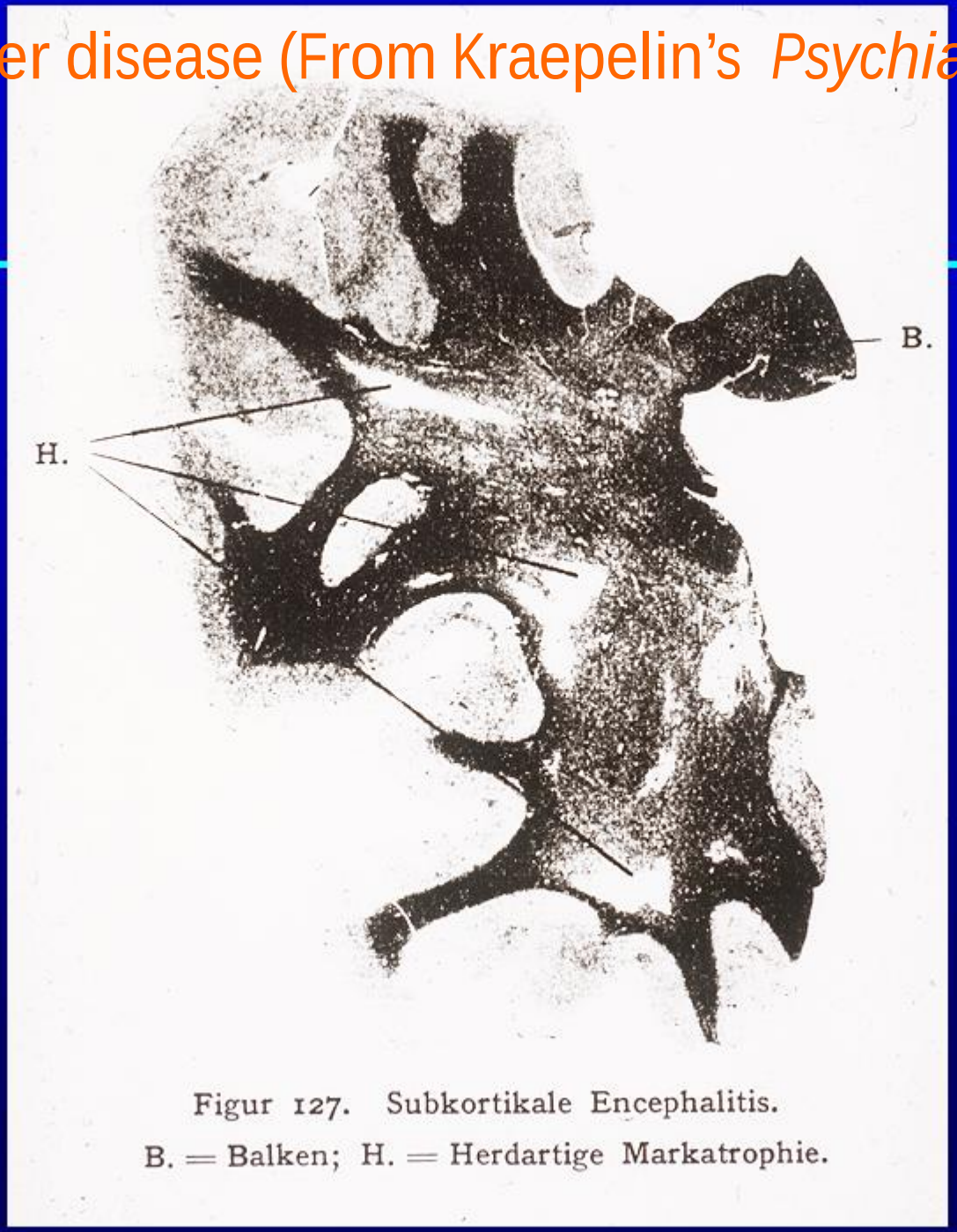
Disruption of specific fronto-subcortical circuits or non-specific thalamo-cortical projections

↓

Executive dysfunction — Apathy — Attentional deficit — Personality change

Subcortical type of dementia

Binswanger disease (From Kraepelin's *Psychiatrie*, 1910)



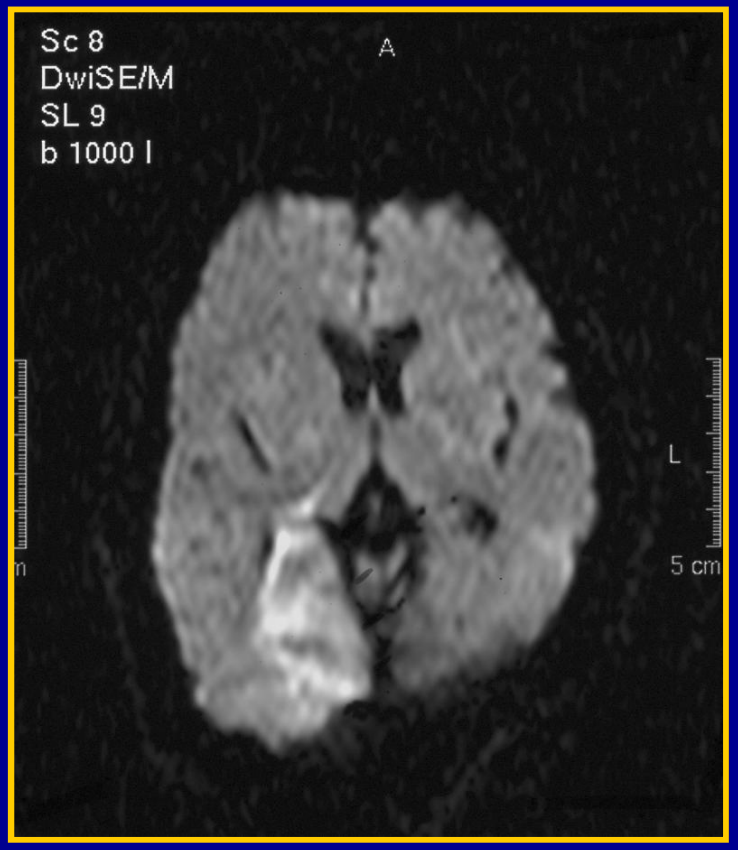
Figur 127. Subkortikale Encephalitis.
B. = Balken; H. = Herdartige Markatrophie.

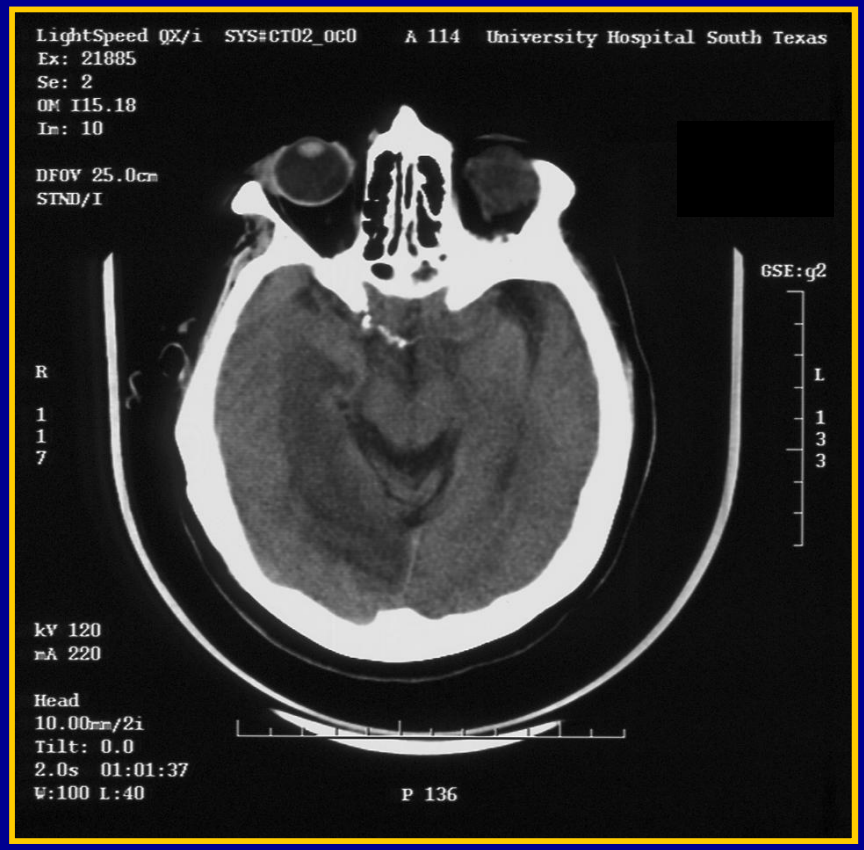
J. Delay and S. Brion (1962): 3 stroke locations may cause VaD

1) Posterior form: PCA infarction involving ventral-medial temporal lobe, occipital structures and thalamus
2) Anterior form: ACA territory infarction involving medial frontal lobe
3) Basal form: with bilateral involvement of basal ganglia and thalamus (thalamic VaD)

Patients with large lesions of the left (dominant) hemisphere have almost a five-fold risk of developing post-stroke dementia, an effect not explained by aphasia (Tatemichi et al. 1993)

Right Posterior Cerebral Artery Infarction



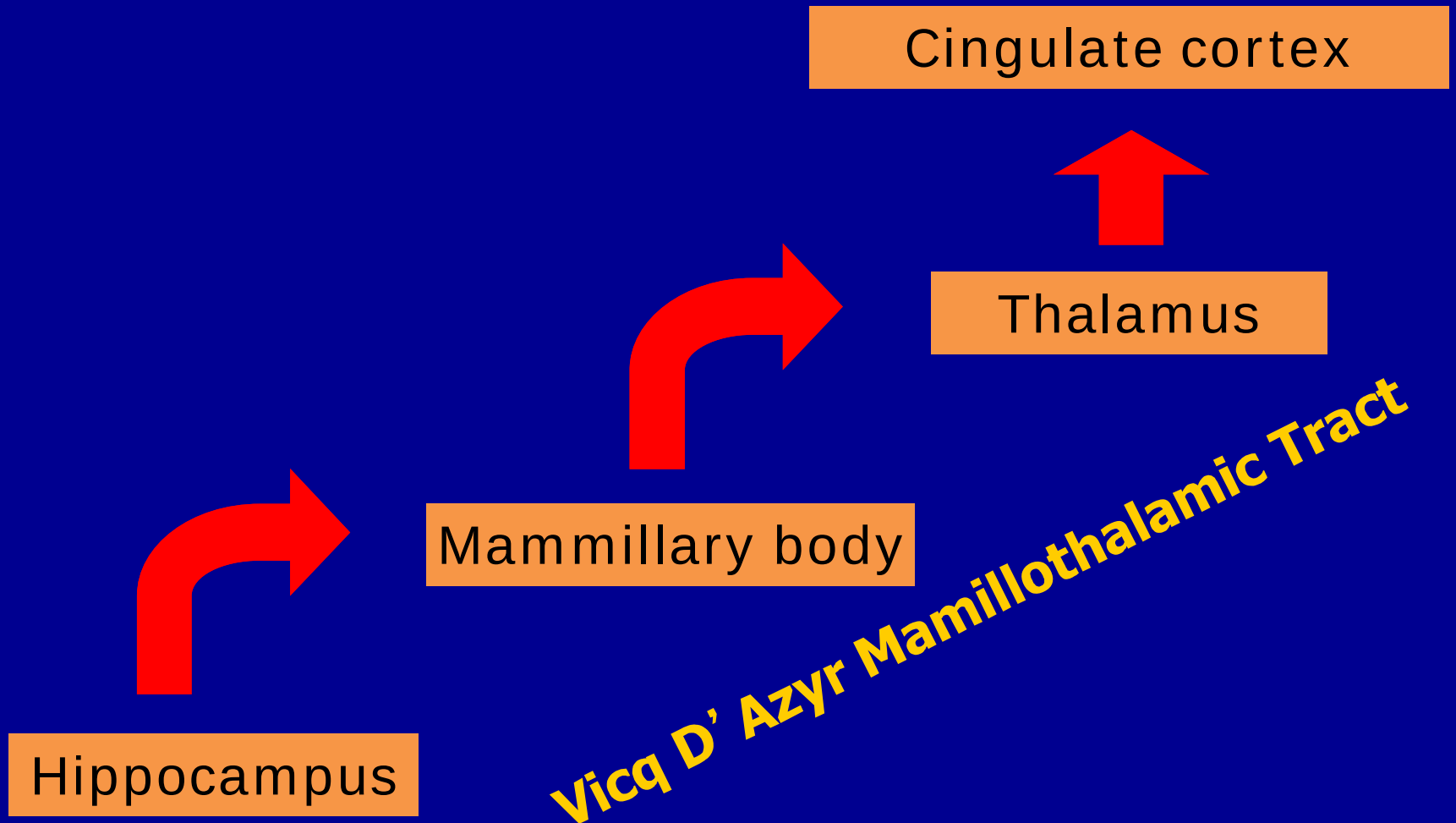


Posterior Cerebral Artery (PCA)

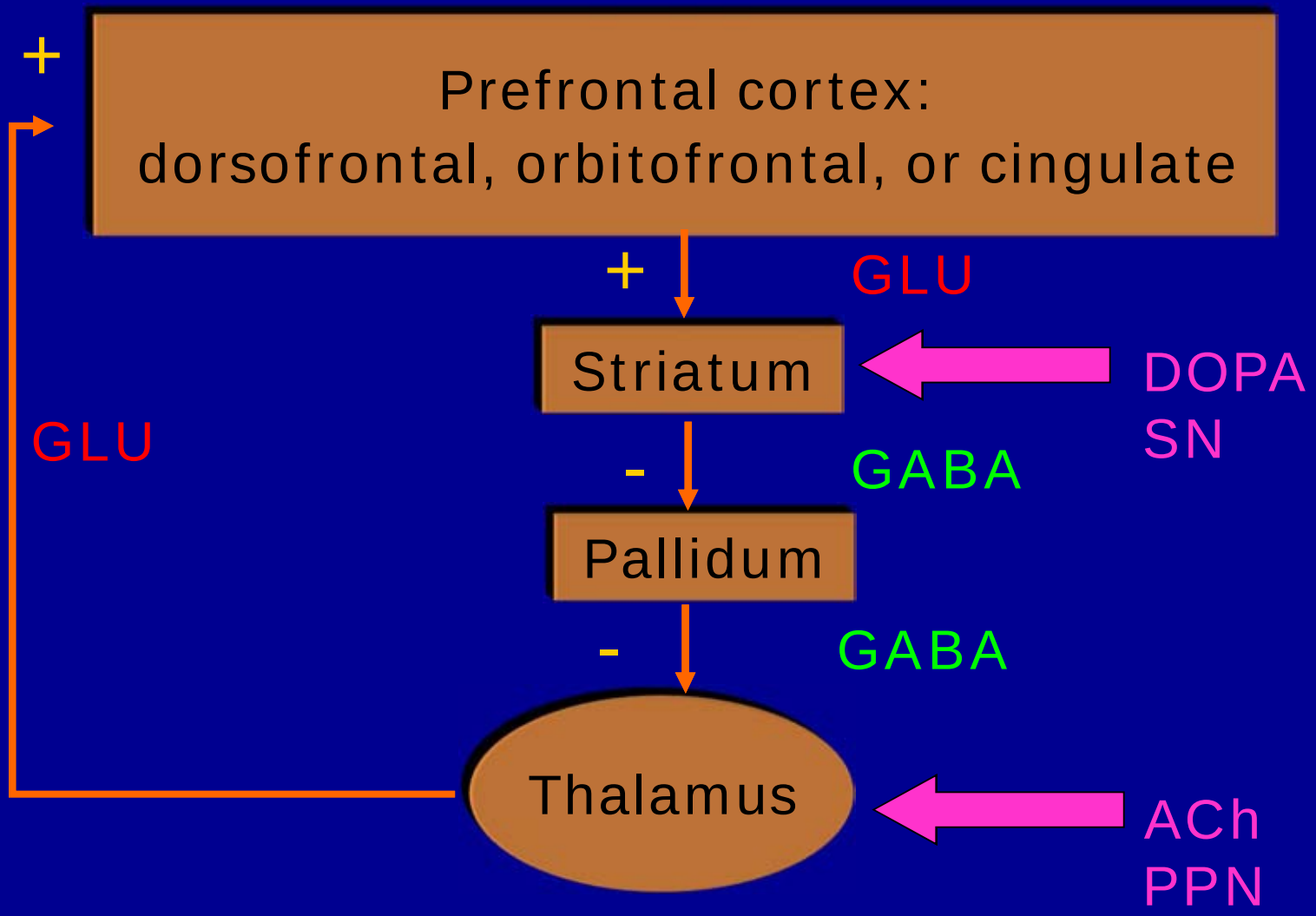
- 25% of patients with PCA infarcts present with memory problems
- (L) Verbal amnesia
- (R) Visuospatial memory and memory for locations
- Bilateral: global amnesia
- Damage to portions of the memory circuit due to temporal lobe lesions (hippocampus and its projections)
- Episodic anterograde amnesia—sometimes confused with that of AD

Brandt et al. Cerebrovasc Dis. 2000;10:170-182.

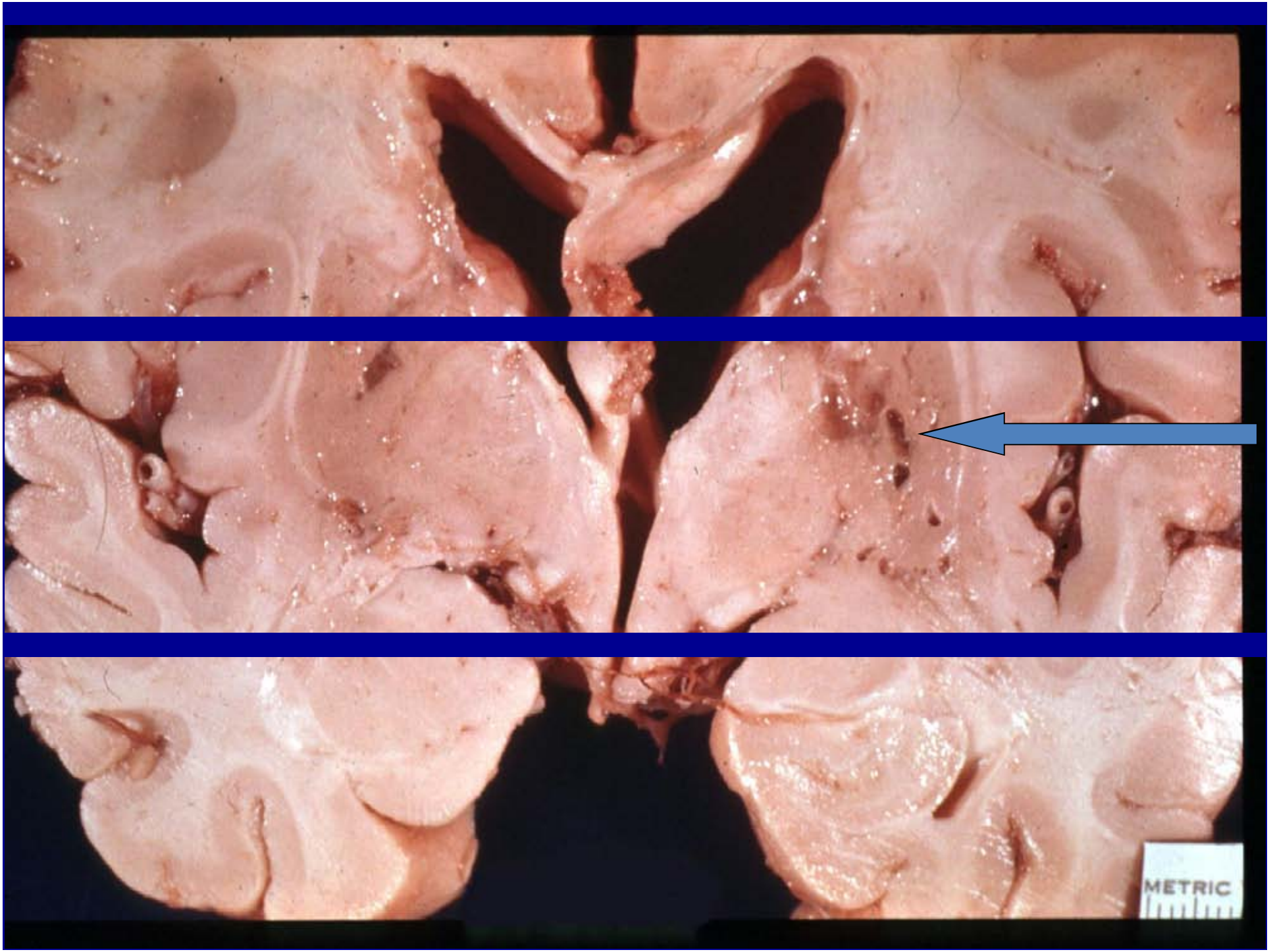
The Memory Circuit



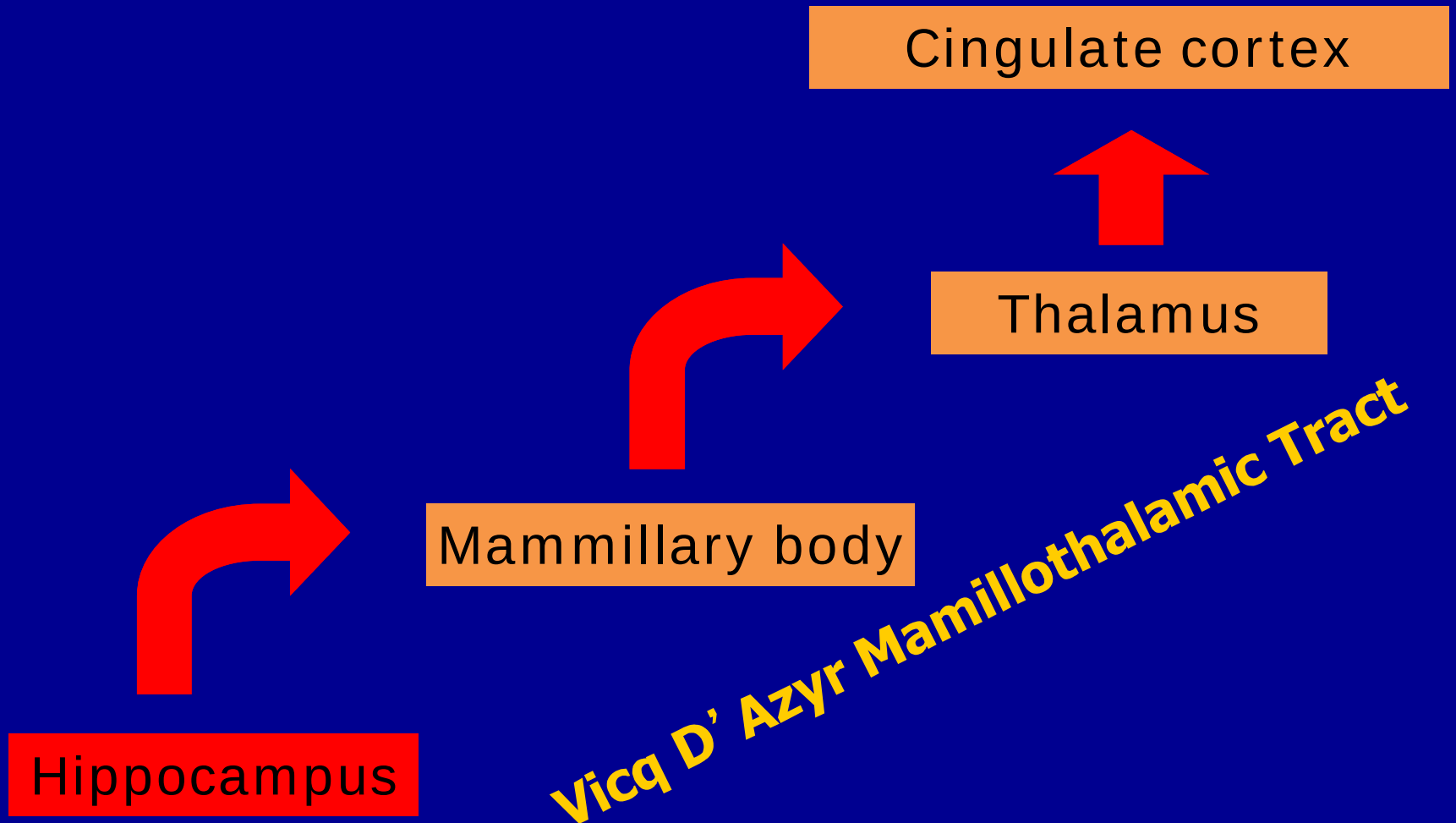
Behavioral Frontal Circuits



Román GC, Royall DR. Executive control function: a rational basis for the diagnosis of vascular dementia. *Alzh Dis Assoc Dis* 1999;13(supp 3):S69-80.

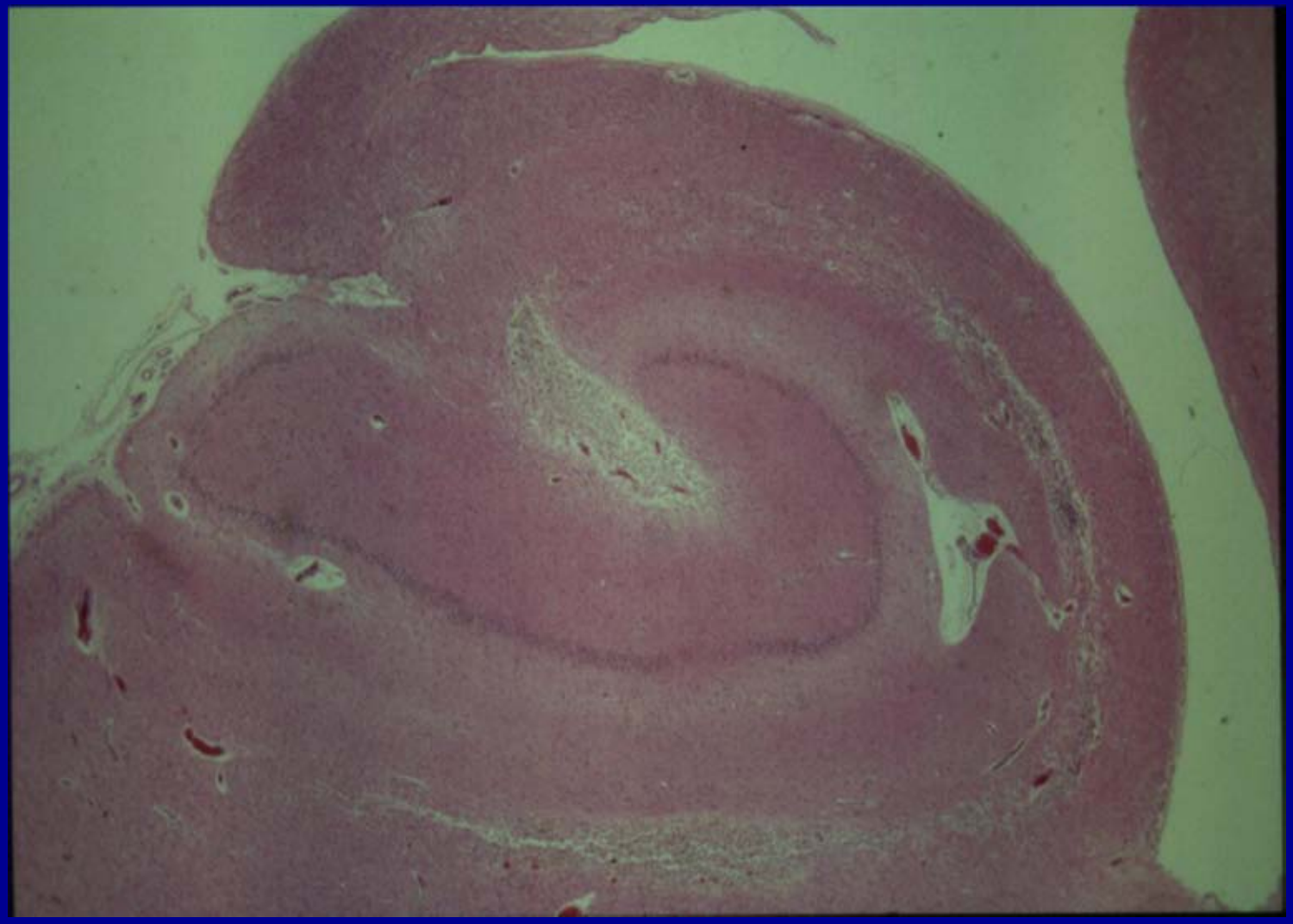

METRIC

The Memory Circuit



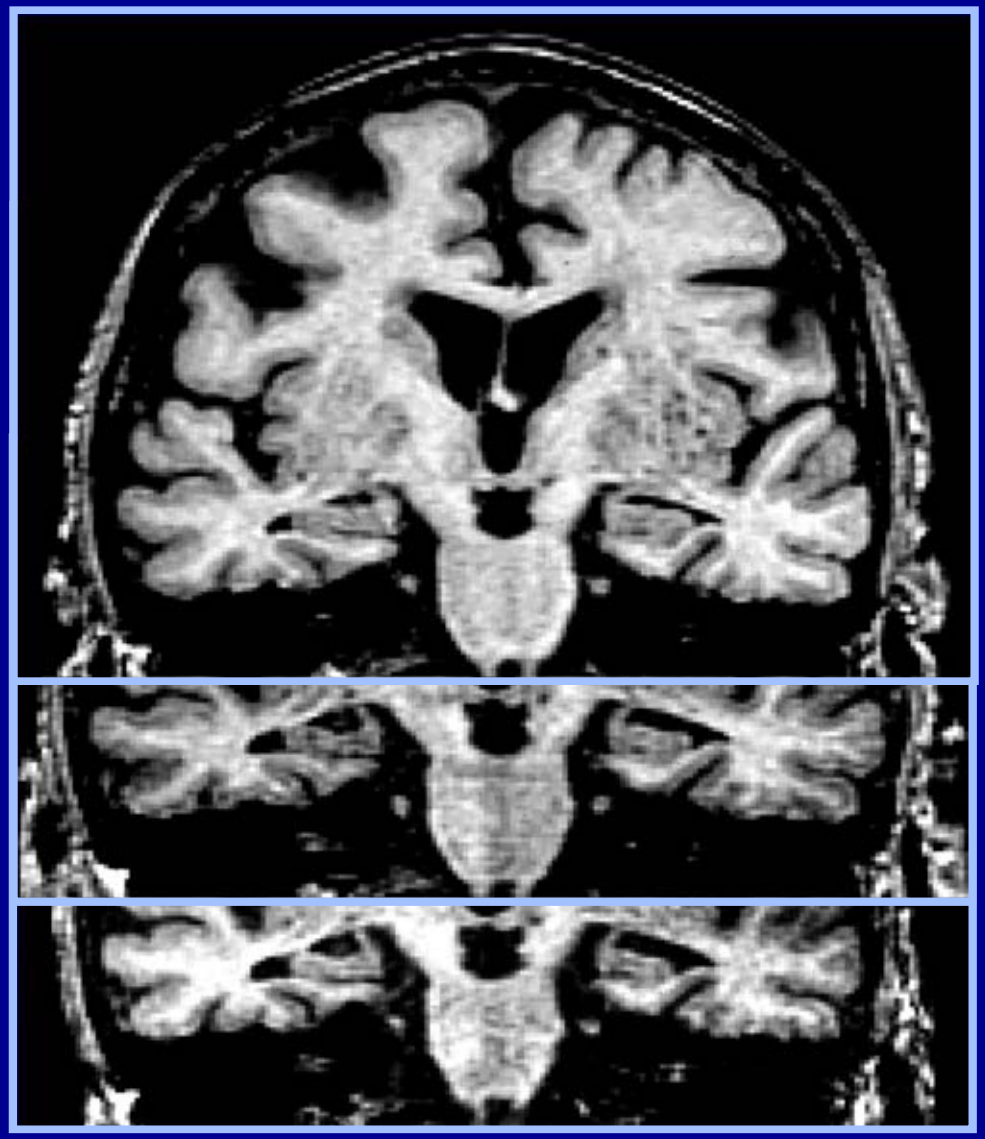
Hippocampal lesions causing memory loss

- Alzheimer's disease
- Hippocampal sclerosis
- (aka mesial temporal lobe sclerosis)
- Herpes encephalitis
- Head injury
- Stroke
- Syphilis
- Tumor



Hypotension and ischemia result in hippocampal atrophy: Mesial Temporal Lobe Sclerosis

Hippocampal Volumes

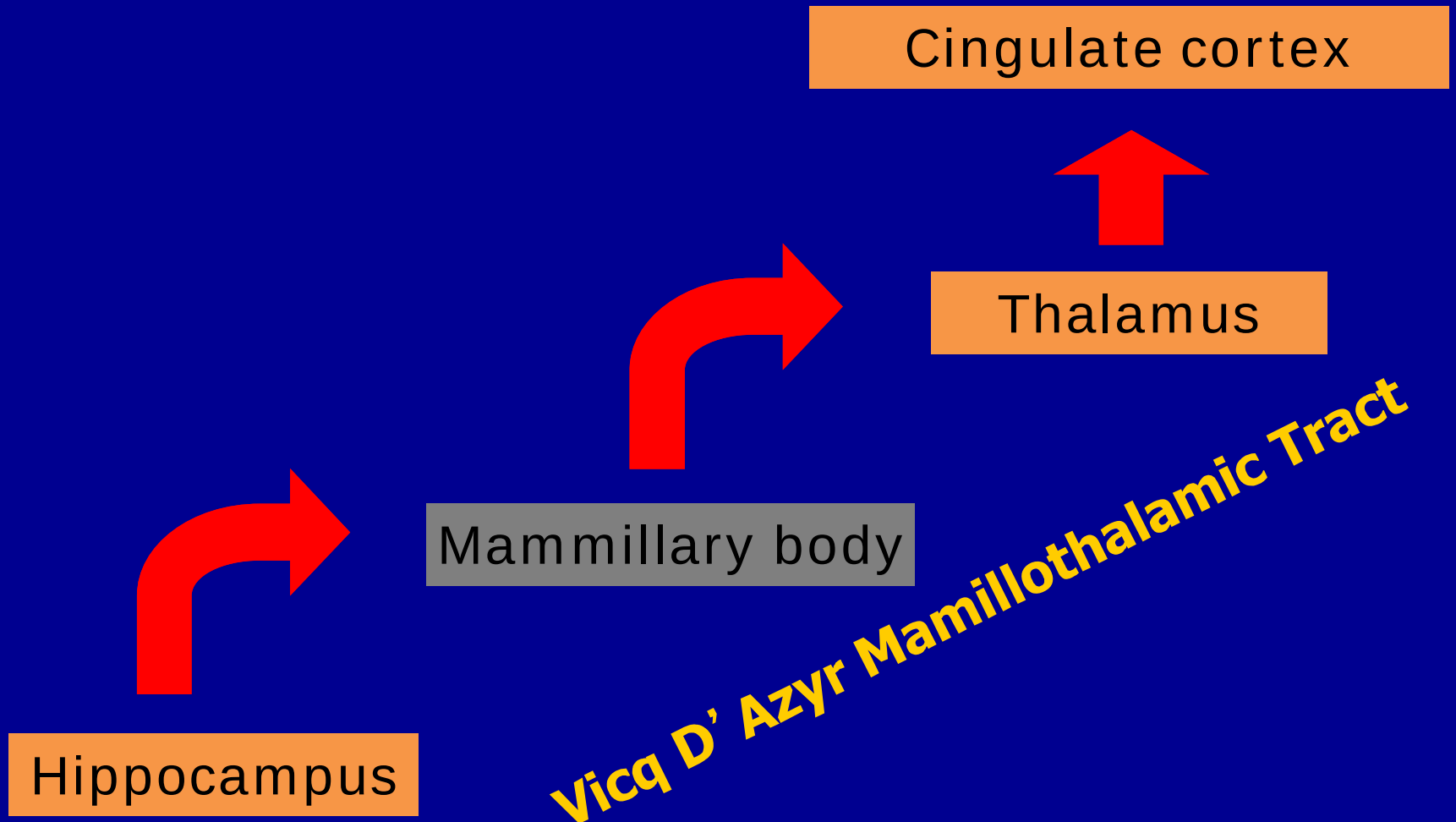


Clinically Normal

MCI

AD

The Memory Circuit

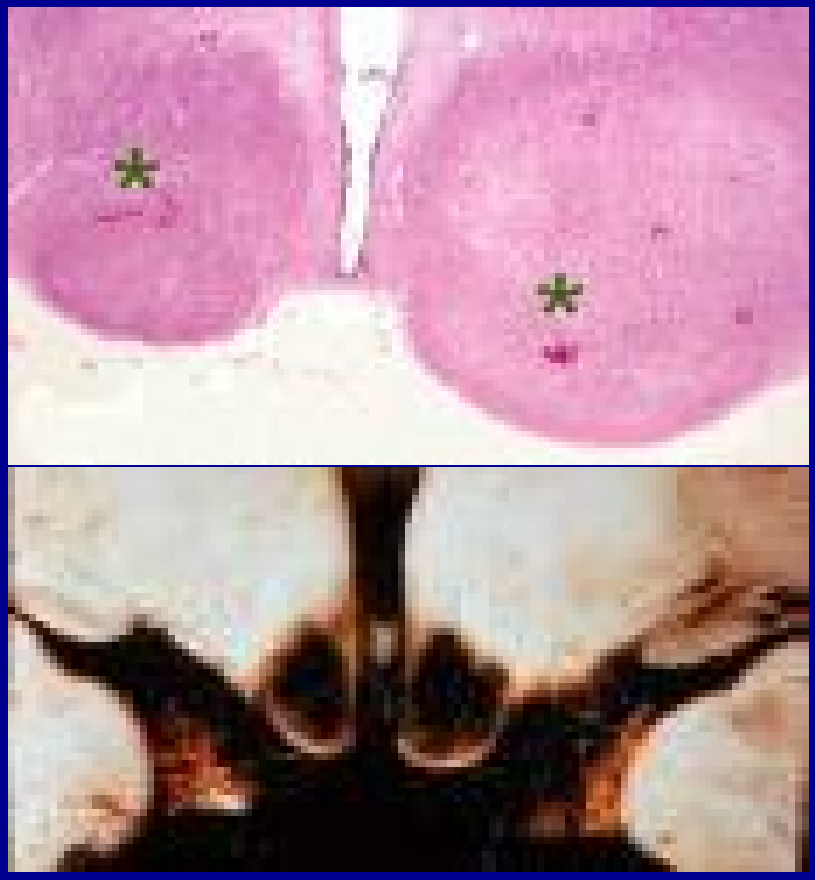


Mammillary Body Lesions

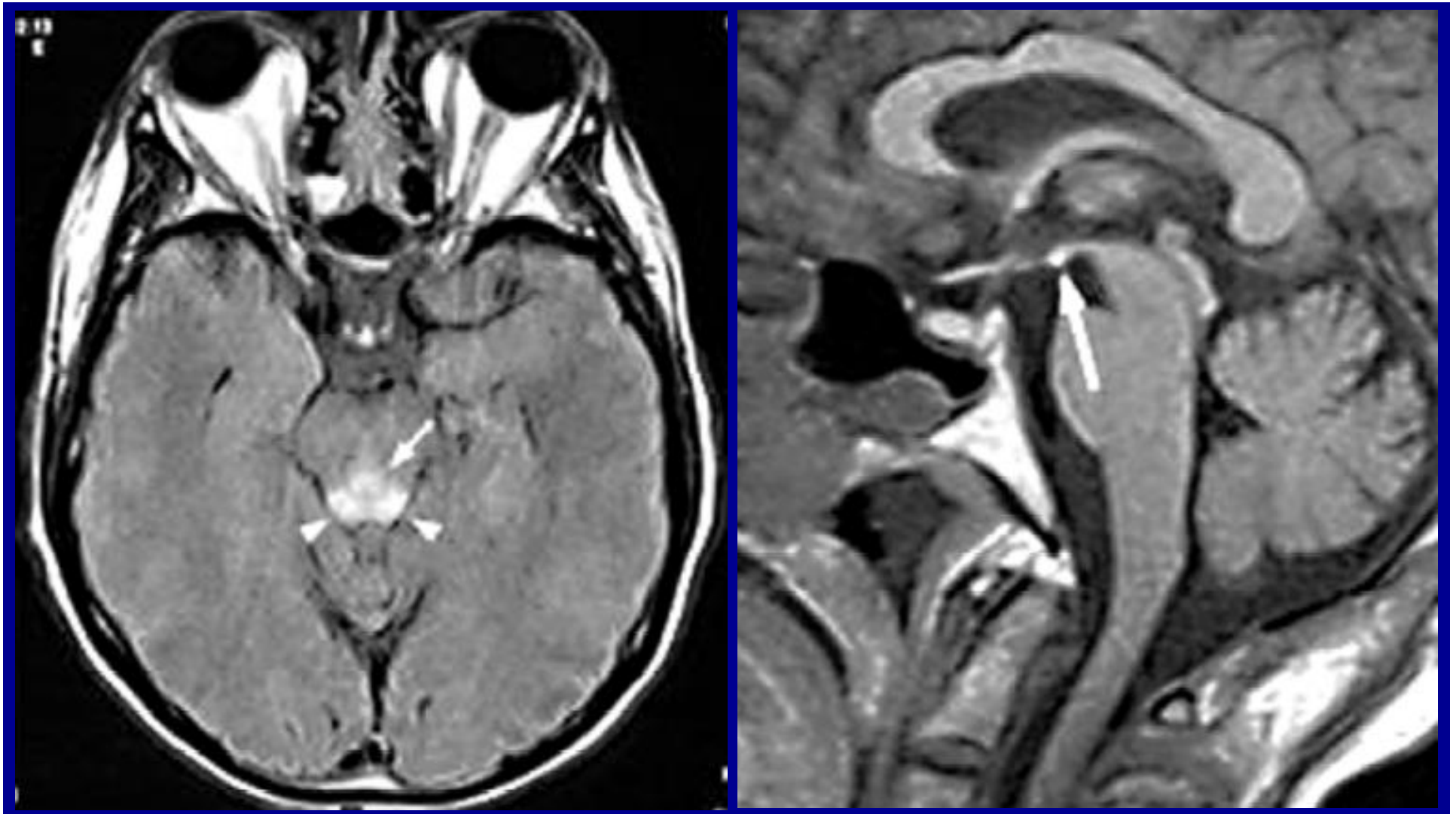
- Thiamine (Vitamin B1) deficiency
  - Alcohol
  - Nutritional (“tea & cookies”)
  - ICU lactic acidosis
  - Hyperemesis gravidarum
  - Cancer
- Wernicke’s encephalopathy
- Wernicke-Korsakoff syndrome

Wernicke's Encephalopathy in Nonalcoholic Patients

- Ocular abnormalities, ataxia, confusion (16%)
- Nystagmus down-beat (85%), bilateral lateral rectus palsy (54%), conjugate gaze palsies (45%)
- Vestibular dysfunction (OCF reflexes, cold water), loss of equilibrium, followed by ataxic wide-base gait (cerebellum)
- Confusion, apathy, inattention, loss of executive function, restlessness
- Coma, hypothermia
- No clinical signs in 19% of 131 cases (JNNP 49:341,1986)

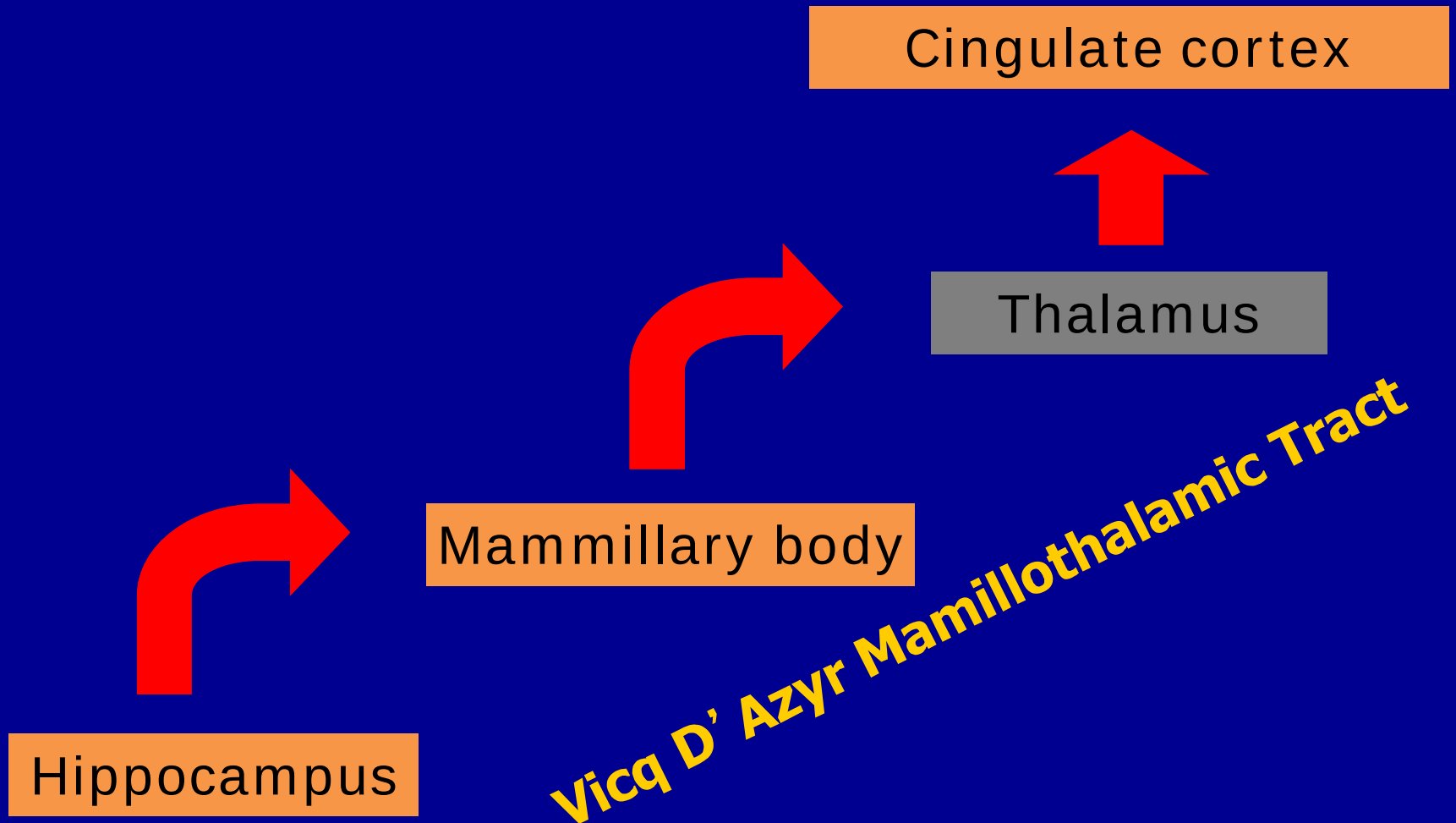


"polioencephalitis hemorrhagica superioris"
Carl Wernicke, 1881

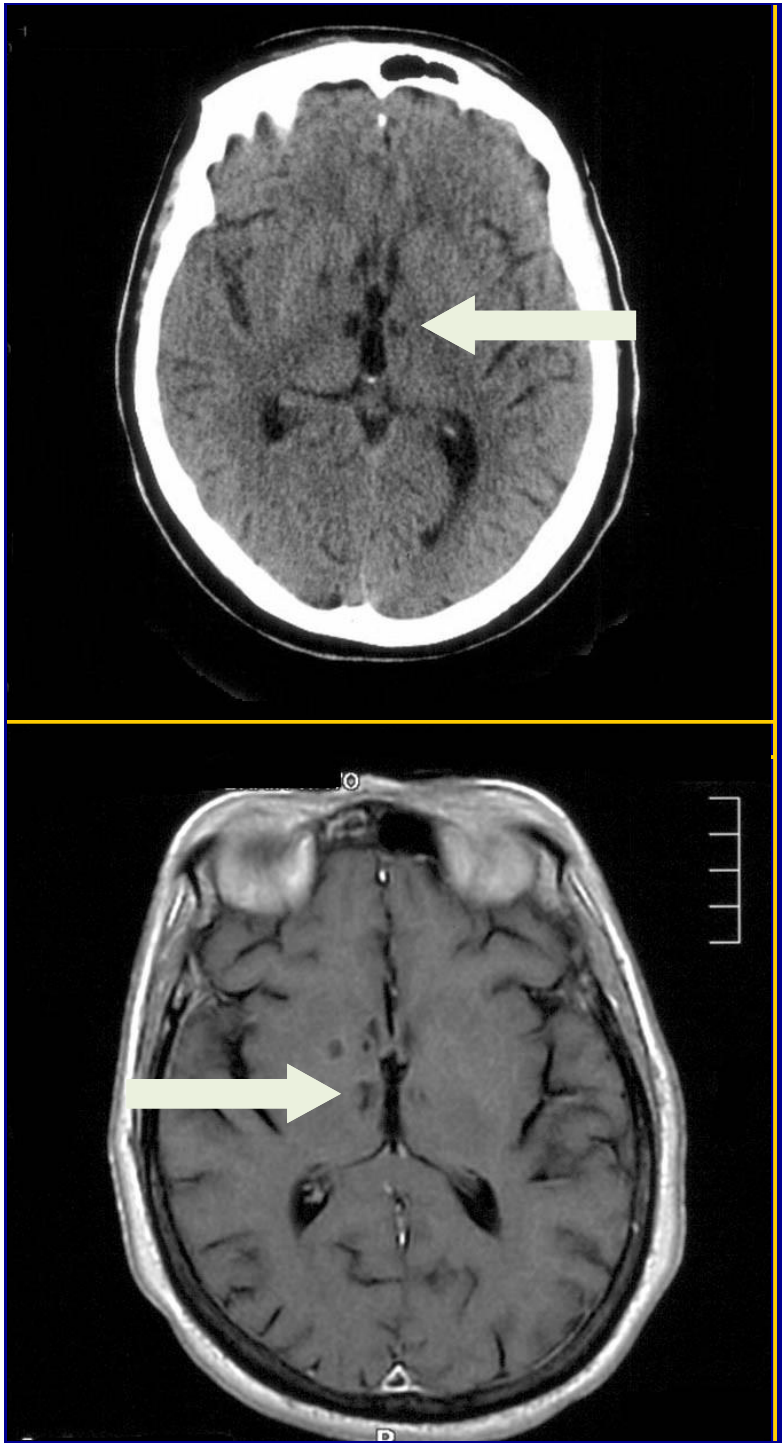


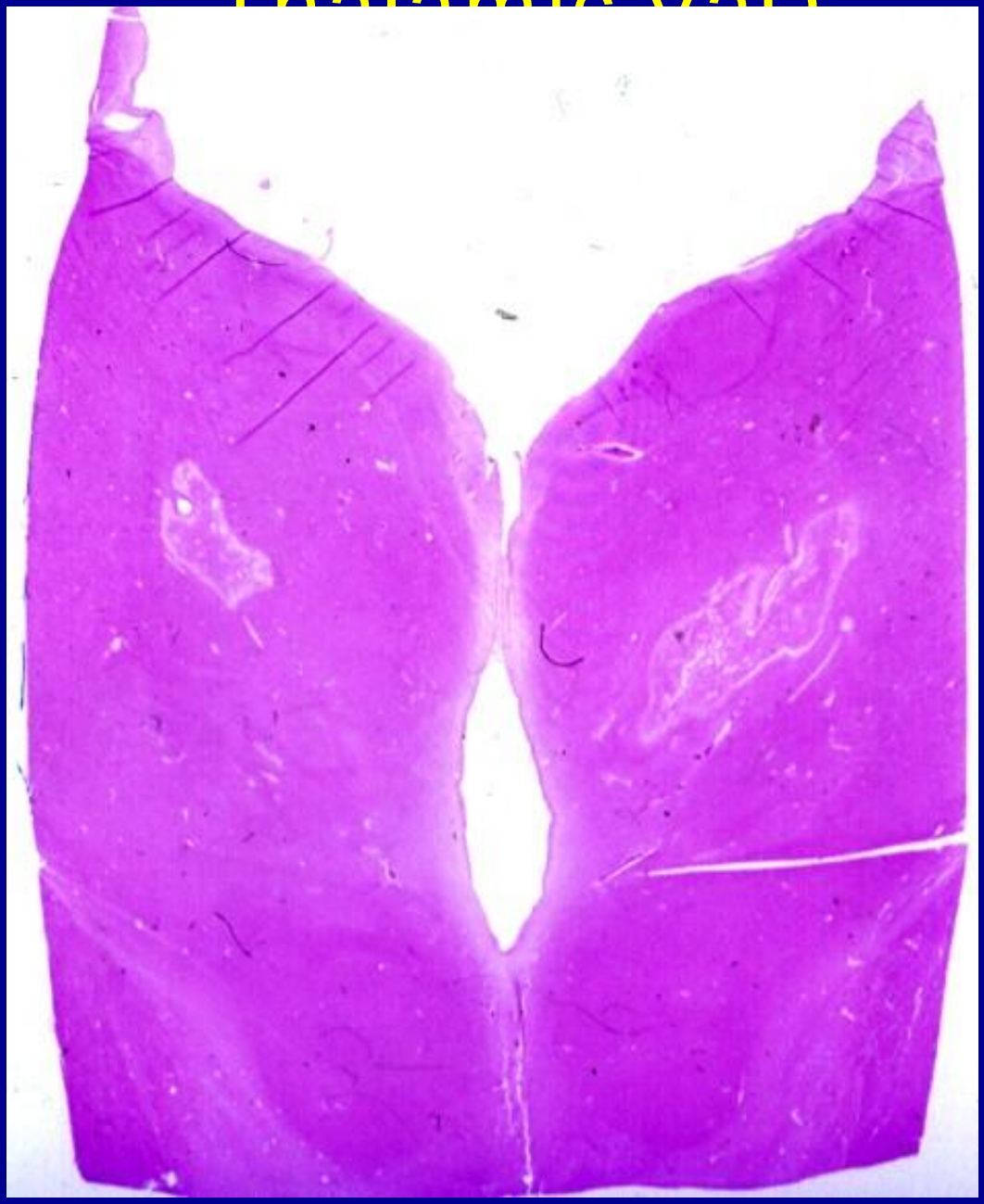
Nolli M et al. Wernicke's encephalopathy in a malnourished surgical patient. *Acta Anesthesiol Scand* 2005;49:1566-70.

The Memory Circuit



Thalamic VaD

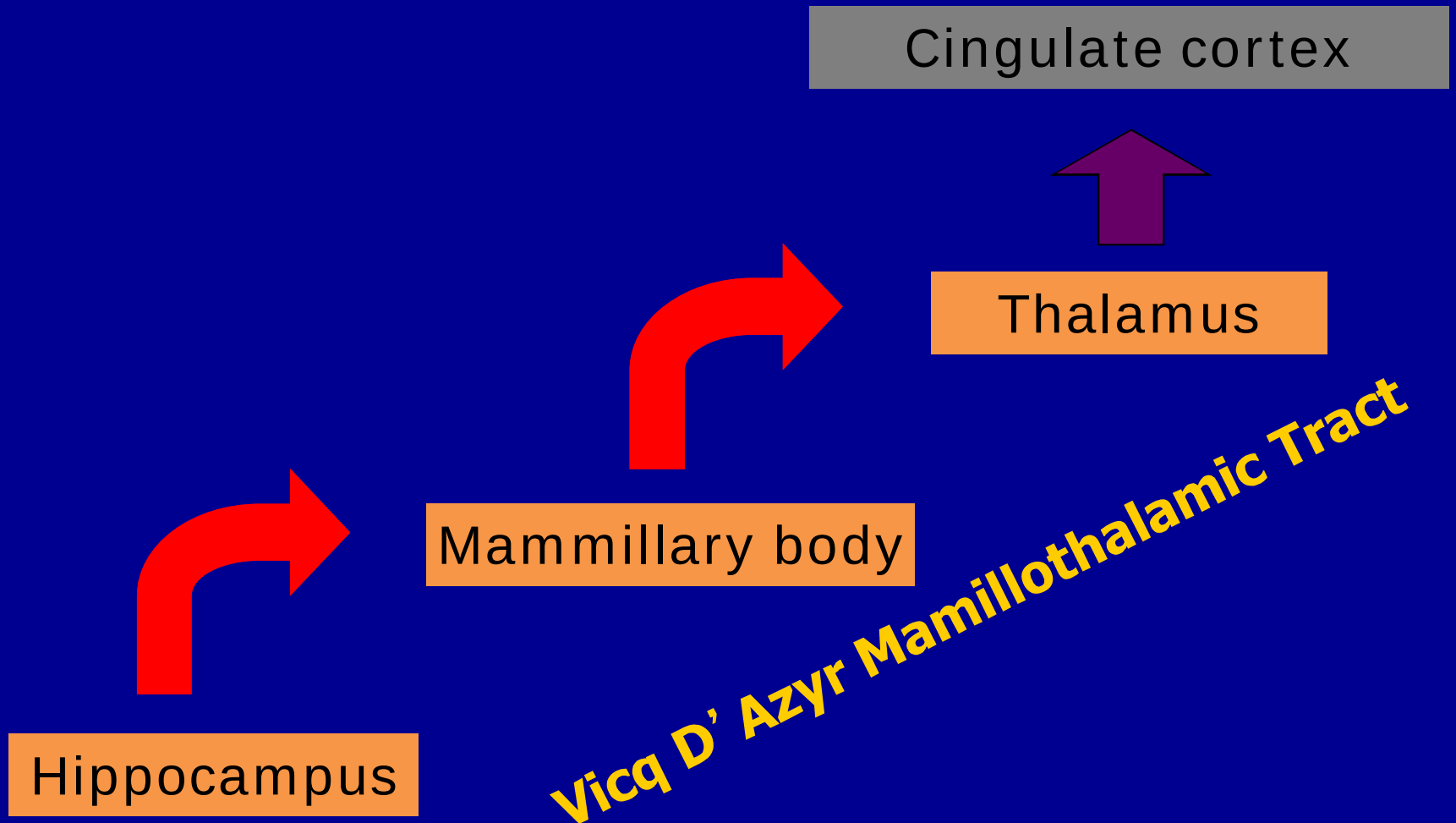


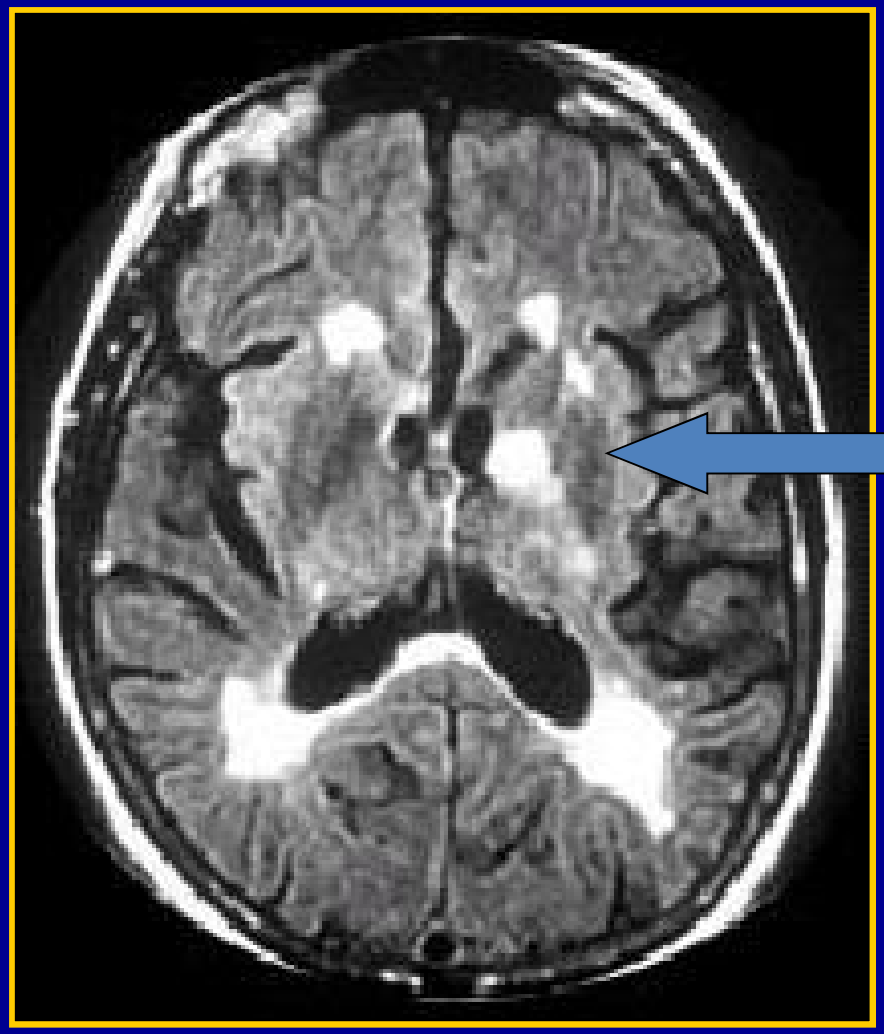


Thalamic Lesions

- Ischemic stroke
  - Thalamic Vascular Dementia
  - PCA infarct
- Alcohol/beriberi
- Creutzfeldt-Jakob disease

The Memory Circuit

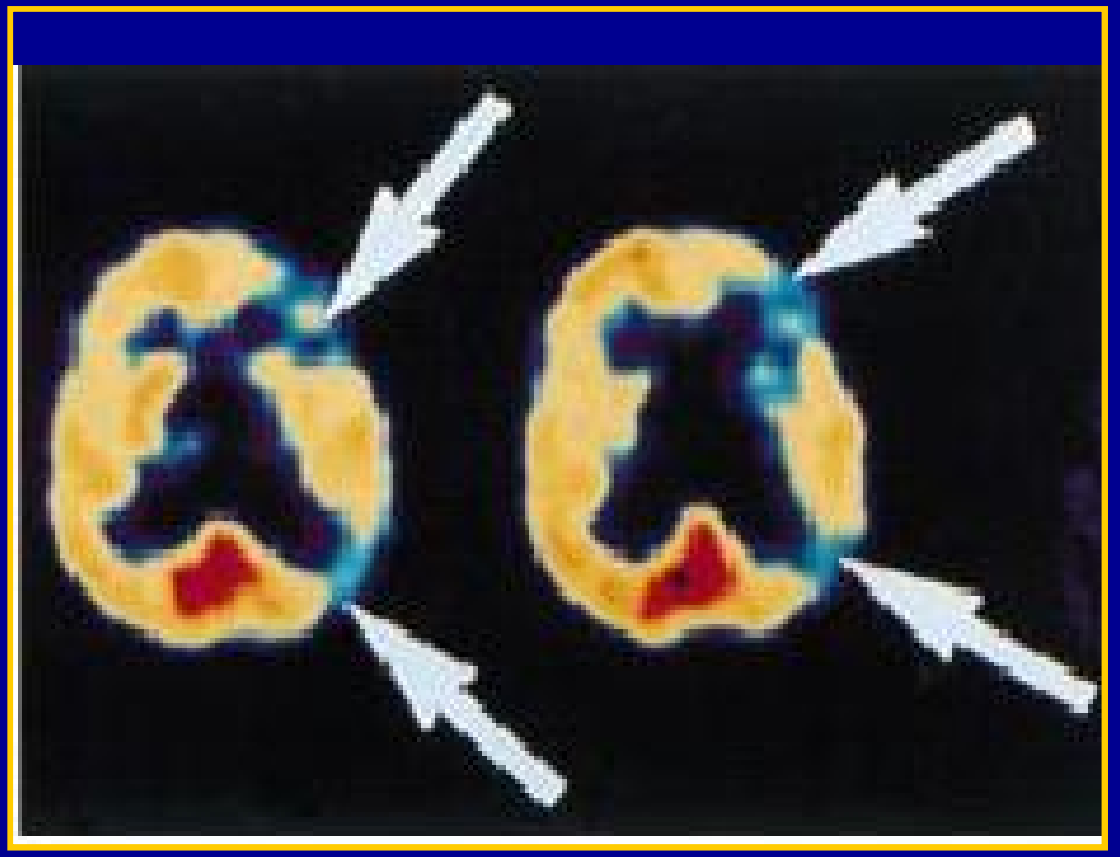




Genu of the Internal Capsule

MRI

Chukwudelunzu et al. *J Neurol Neurosurg Psychiatry*. 2001;71:658-662



18FDG Positron Emission Tomography (PET) images of the brain; decreased cortical metabolic activity is apparent *two weeks after* stroke

Chukwudelunzu et al. *J Neurol Neurosurg Psychiatry*. 2001;71:658-662.

VaD From Inferior Genu Stroke

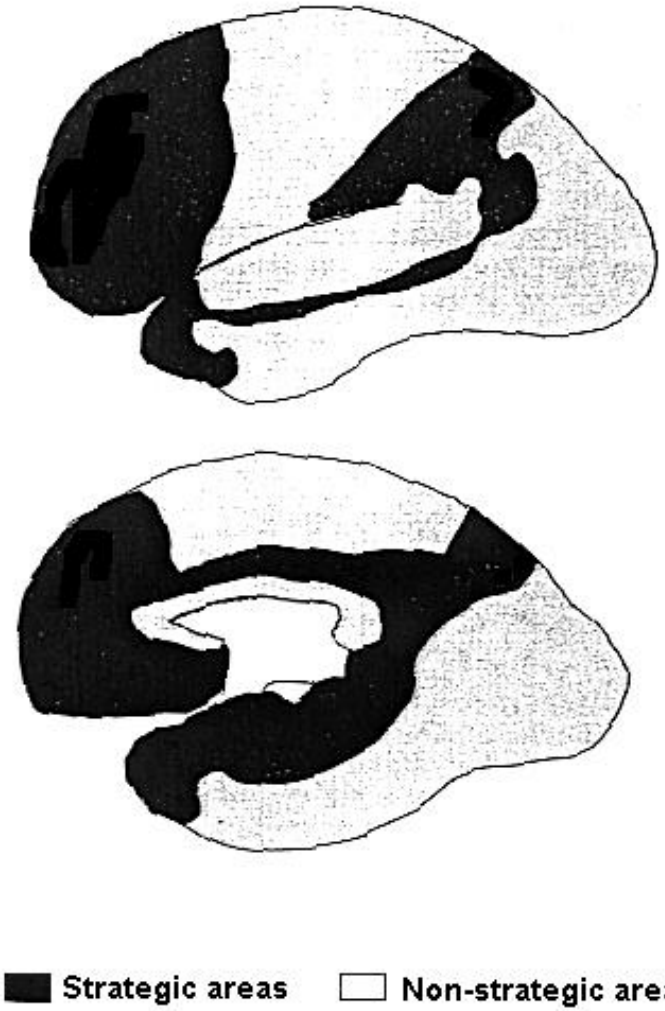
Capsular genu infarction causes a thalamocortical syndrome

- Sudden change in cognitive function, often associated with fluctuating attention, confusion, abulia, striking psychomotor retardation, inattention, executive dysfunction, and other features of frontal lobe dysfunction
- No focal findings (hemiparesis, dysarthria) or mild
- Memory loss in all cases: left-sided infarcts had severe verbal memory loss and right-sided infarcts caused visuospatial memory loss

Tatemichi et al. *Neurology.* 1992;42:1966

Volume and Location of Vascular Lesions Affect Cognition

- Severity of cognitive loss was correlated with total volume of infarcts
- Volume destroyed in limbic and heteromodal association areas (frontal cortex and FWM) explained 50% of the variance of MMSE and GDS
- Total ischemic-lesion volume explained 0.1-5% of the variance
- Age: 0.1-1.6%.
- Infarcts in strategic areas play a role in cognitive impairment



Zekry et al., Neuro Biol Aging 2003;24:213-219

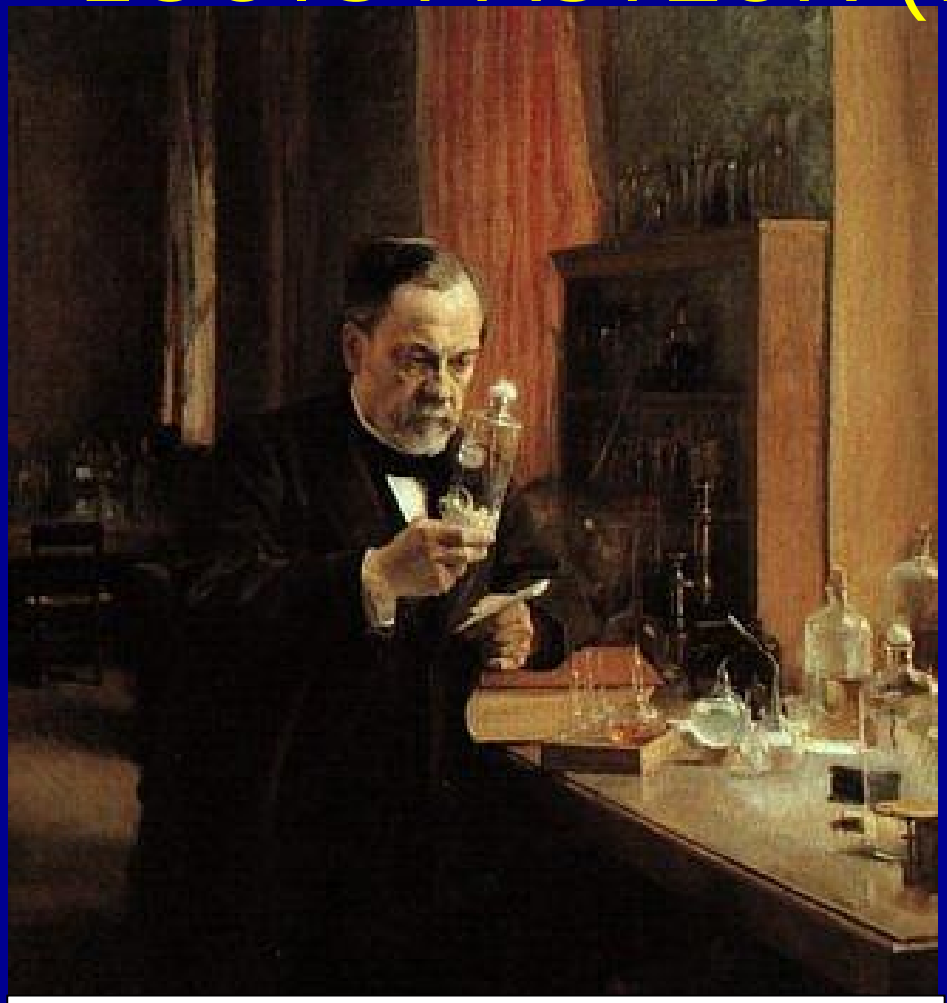
Look for Executive Dysfunction

CLINICAL MANIFESTATIONS

Paradox: “Clinically eloquent” strokes may not produce cognitive deficits

- Motor deficits
- Sensory complaints
- Speech problems
- Cranial nerves involvement
- Alterations of gait
- Coordination loss

LOUIS PASTEUR (1822-1895)



Pasteur at his laboratory working on the rabies vaccine (portrait by Edelfelt).

1854-57 Professor of Chemistry, Lille

1857-67 Director École Normale Supérieure, Paris

1865-70 Silkworm diseases

19 Oct 1868 First stroke, L hemiplegia (Age 46)

Pasteur’s left hemiparesis

Paradox: “Clinically silent” strokes cause behavioral and cognitive manifestations

- Behavioral manifestations: depression, agitation, crying spells, apathy
- Cognitive loss:

  inattention, dysexecutive syndrome, memory problems

Subtle Clinical Signs

- Subtle manifestations such as behavioral and mood changes
- Executive dysfunction due to subcortical ischemic disease must be recognized
- Bedside simple tests include the “Show me” Luria’s kinetic melody test and the CLOX test
- Imaging is critical for the correct diagnosis

TREATMENT AND PREVENTION

THE ROLE OF HCY B_{12} AND OSA IN THE PATHOGENESIS OF VAD

Homocysteine is a Vascular Risk Factor

Each increase of 5 micromol/L in homocysteine level (above 10 ?6mol/L) increases the risk of CHD events by approximately 20%, independently of traditional CHD risk factors

Helfand M, et al. Screening for Intermediate Risk Factors for Coronary Heart Disease: Systematic Evidence Synthesis. Evidence Synthesis No. 73. AHRQ Publication No. 10-05141-EF-1. Rockville, Maryland: Agency for Healthcare Research and Quality, October 2009

Humphrey LL, Fu R, Rogers K, Freeman M, Helfand M. Homocysteine level and coronary heart disease incidence: a systematic review and meta-analysis. *Mayo Clin Proc.* 2008;83:1203–1212.

The New England Journal of Medicine February 14, 2002

PLASMA HOMOCYSTEINE AS A RISK FACTOR FOR DEMENTIA AND ALZHEIMER'S DISEASE

SESHADRI S, BEISER A, SELHUB J, JACQUES PF, et al.

A total of 1092 subjects without dementia (667 women and 425 men; mean age, 76 years) from the Framingham Study. Plasma total Hcy at base line and 8 yrs earlier and risk of newly diagnosed dementia (adjusted for age, sex, ApoE, vascular risk, folate and vit. B_{12} and B_6.)

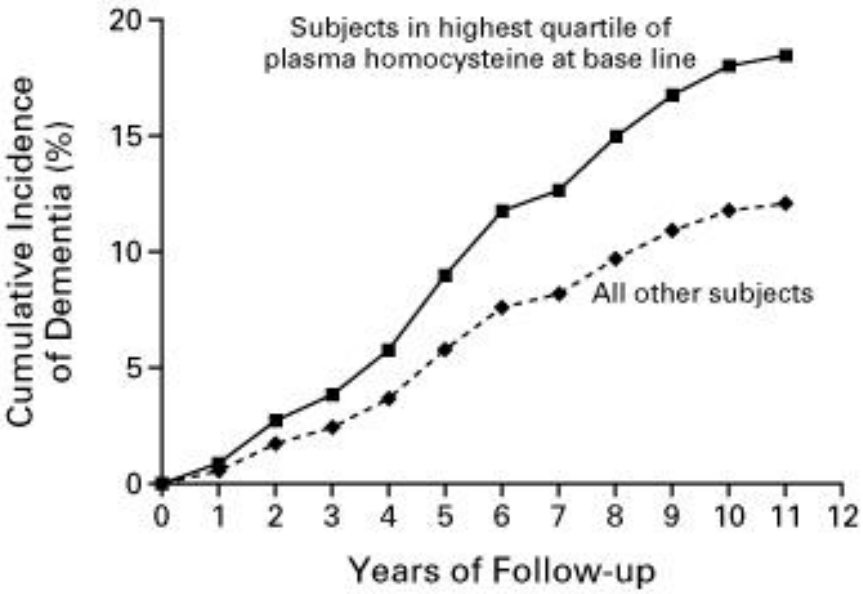
Conclusion Plasma tHcy level > 14 μmol/L ⇒2X the risk of AD

NEJM 2002;346:476-83

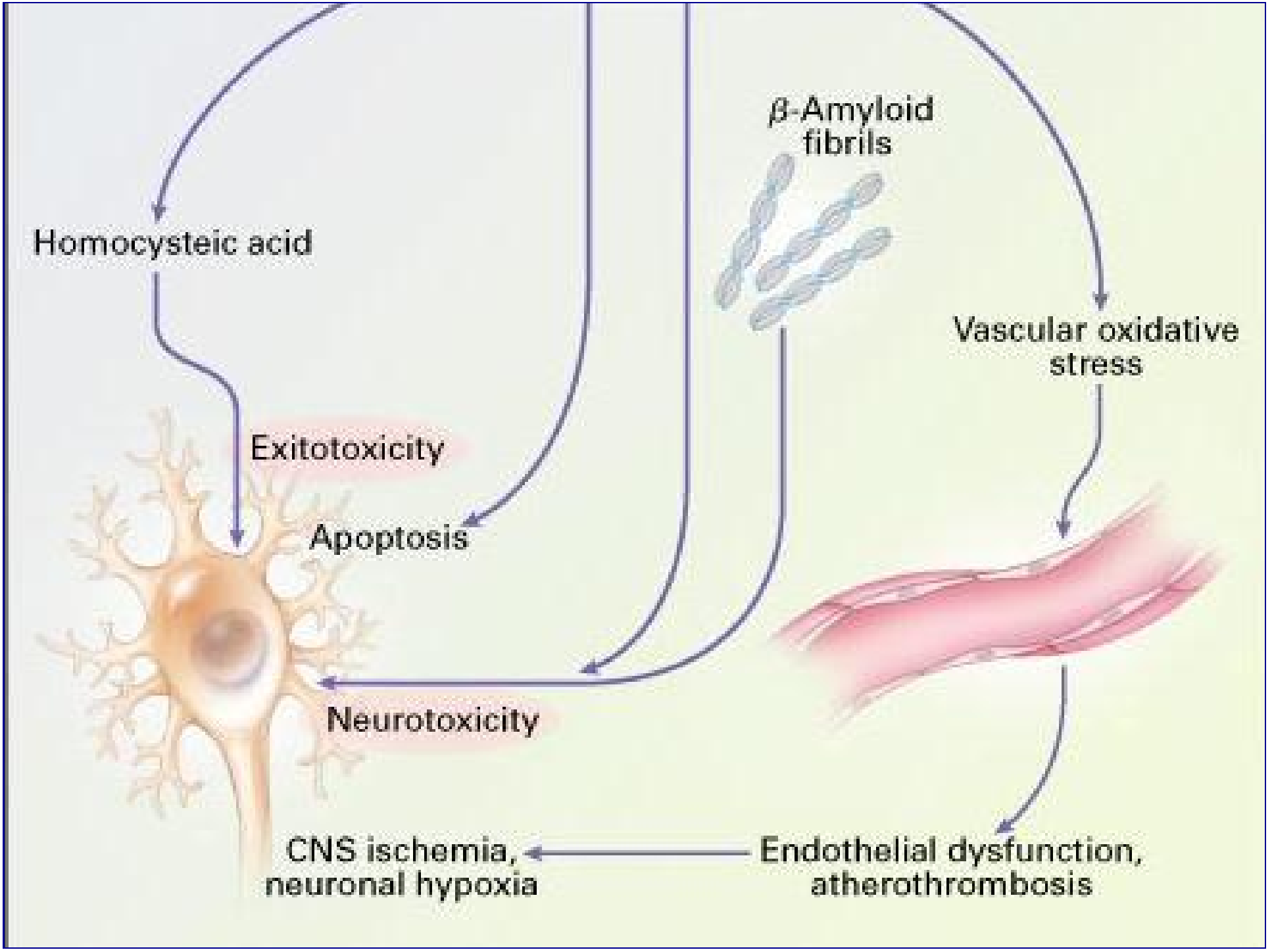
TABLE 2. DISTRIBUTION OF BASE-LINE PLASMA HOMOCYSTEINE LEVELS WITHIN FIVE-YEAR AGE GROUPS *

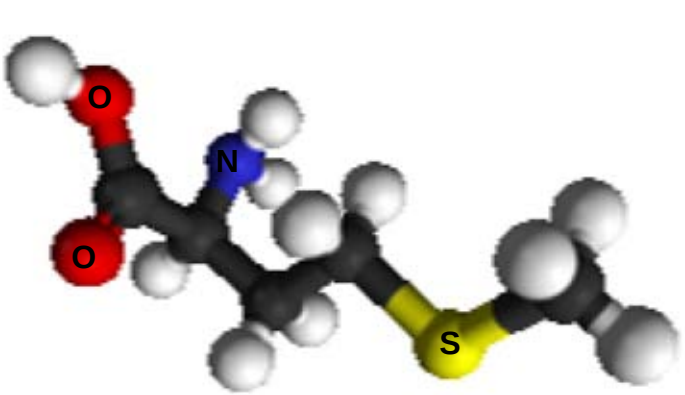
PLASMA HOMOCYSTEINE LEVEL			AGE		No. of SUBJECTS
±SD	RANGE	75TH PERCENTILE		MEAN	
μmol per liter					
5.4–25.5	13.2		65–69 yr	46	11.5±3.9
6–66.7	13.8		70–74 yr	457	12.1±5.9
9	14.5		75–79 yr	315	12.6±5.9
	16.5		80–84 yr	179	14.2±7.3
19.3			85–89 yr	66	15.3±8.0
6			90–94 yr	29	22.3±12.6

*The difference in mean values between men and women was not significant.



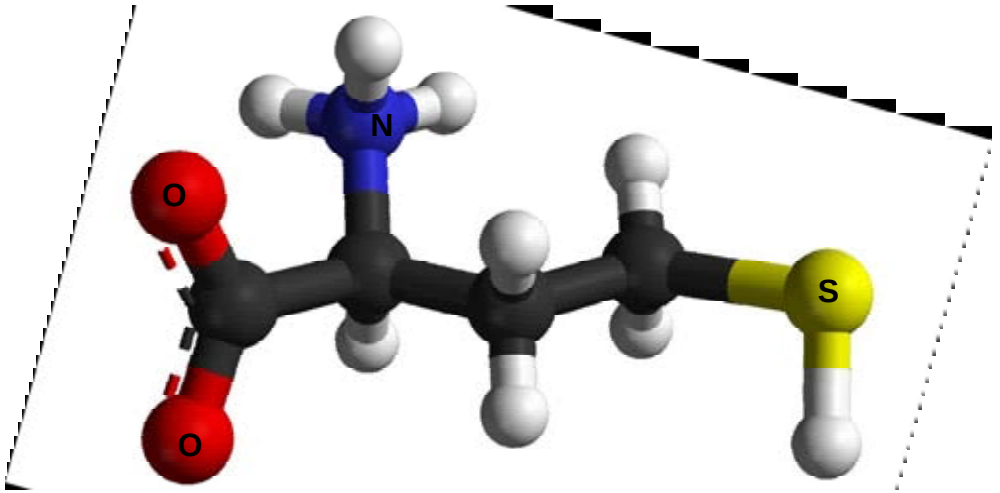
NEJM 2002;346:476-83


β-Amyloid fibrils
Homocysteic acid
Vascular oxidative stress
Exitotoxicity
Apoptosis
Neurotoxicity
CNS ischemia, neuronal hypoxia
Endothelial dysfunction, atherothrombosis



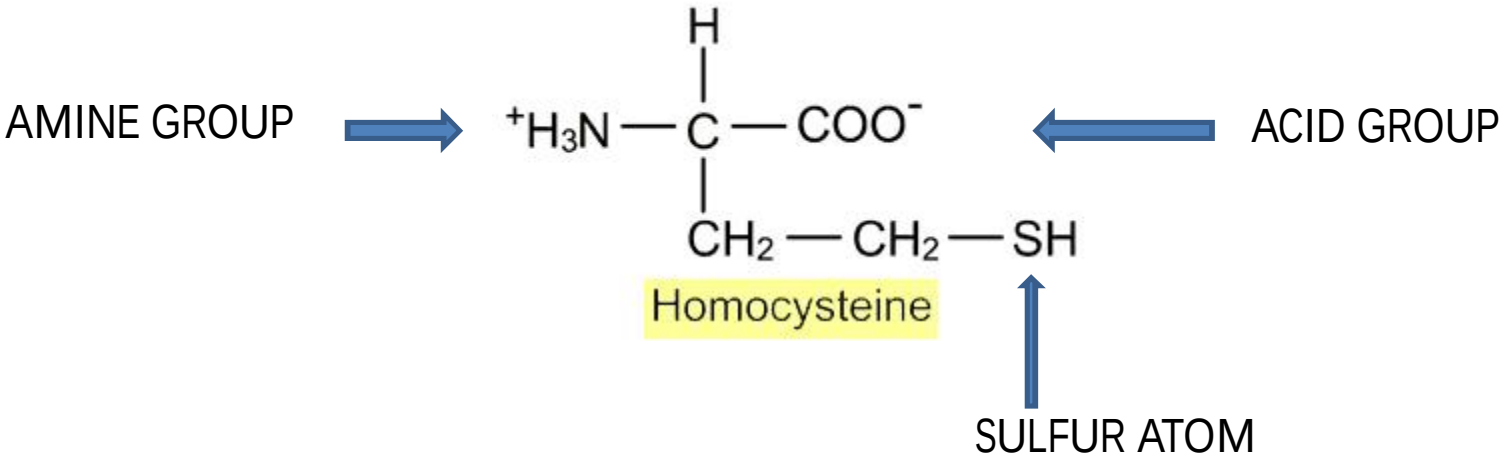
METHIONINE

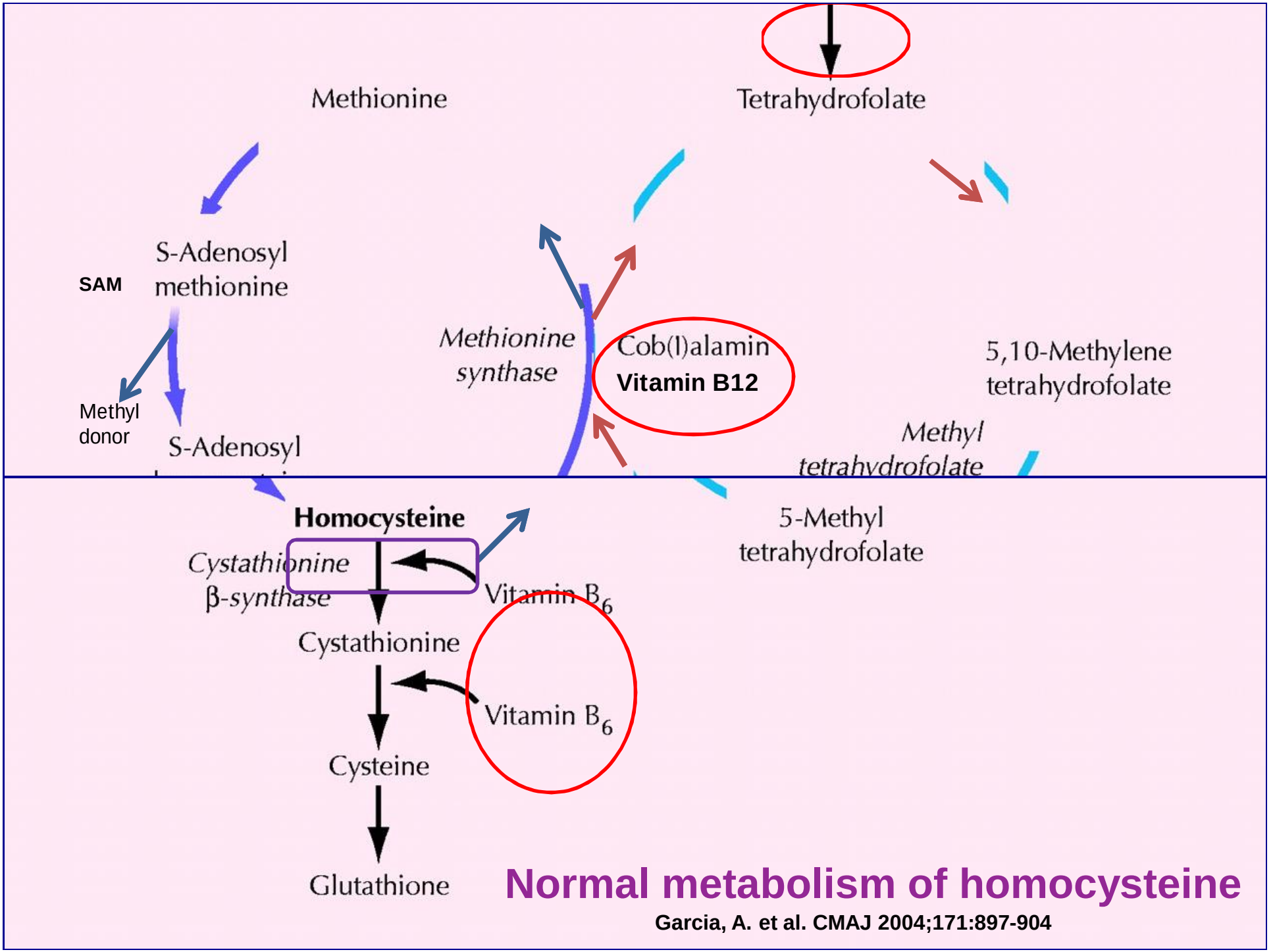
essential amino acid not synthesized in humans



HOMOCYSTEINE

Homocysteine degrades and inhibits formation of collagen, elastin and proteoglycans by affecting cysteine disulfide bridges and lysine amino acid residues in proteins





Normal metabolism of homocysteine

Garcia, A. et al. CMAJ 2004;171:897-904

Plasma vitamin B_{12} status and cerebral white-matter lesions

L M L de Lau,[1,2] A D Smith,[3] H Refsum,[3,4] C Johnston,[3] M M B Breteler[1]

modestly weakened the associations. No association was observed for any of the studied markers of vitamin B_{12} status with presence of brain infarcts and baseline cognition or cognitive decline during follow-up.

Conclusions: These results indicate that vitamin B_{12} status in the normal range is associated with severity of white-matter lesions, especially periventricular lesions. Given the absence of an association with cerebral infarcts, it is hypothesised that this association is explained by effects on myelin integrity in the brain rather than through vascular mechanisms.

JNNP 2009;80:149

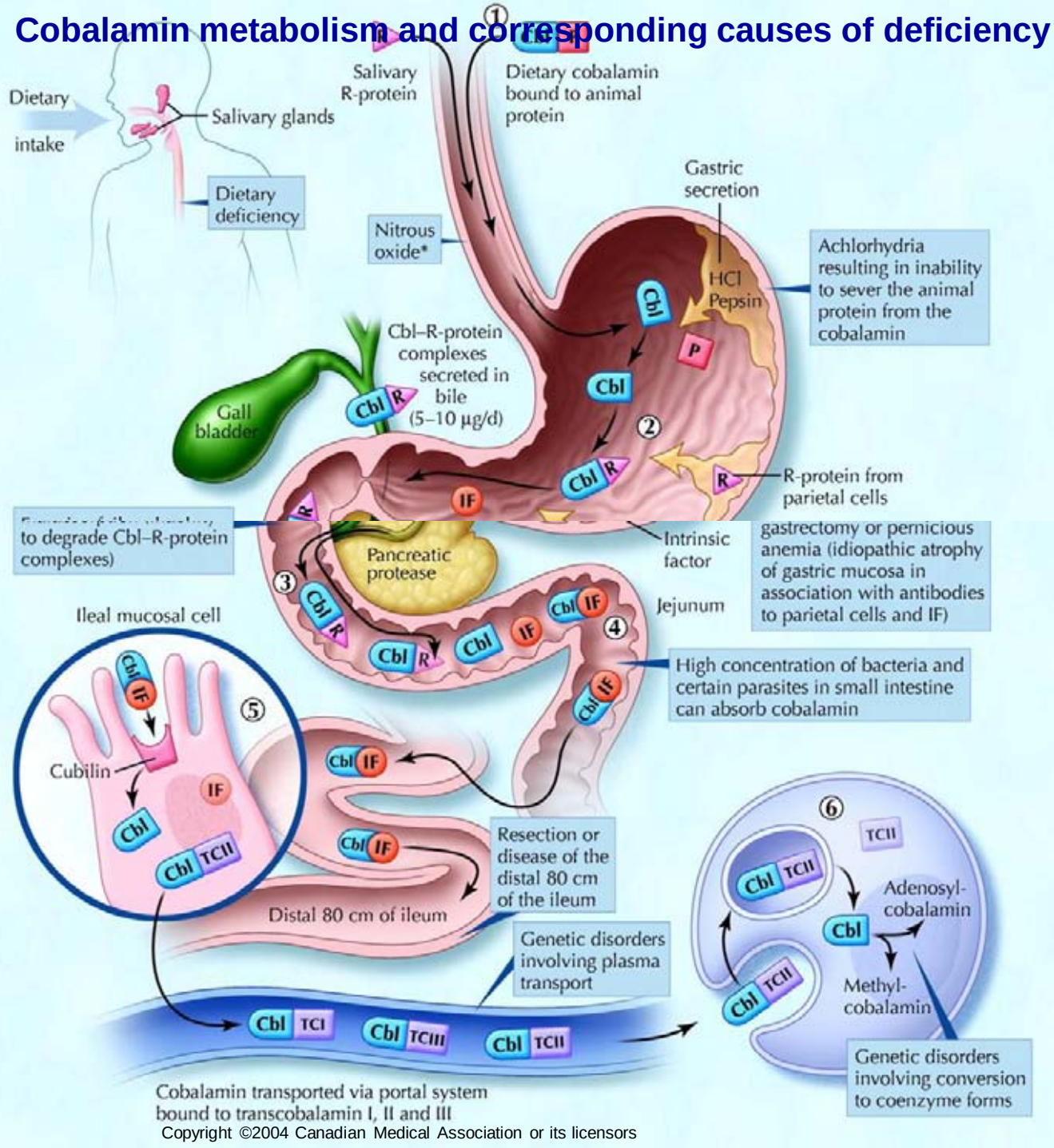
Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease

E P Quinlivan, J McPartlin, H McNulty, M Ward, J J Strain, D G Weir, J M Scott

Fortification of food with folic acid to prevent neural-tube defects in babies also lowers plasma total homocysteine, which is a risk factor for vascular disease. We investigated the effect of folate and vitamin B12 on homocysteine concentrations. 30 men and 23 women received sequential supplementation with increasing doses of folic acid. After supplementation, the usual dependency of homocysteine on folate diminished, and vitamin B12 became the main determinant of plasma homocysteine concentration. This finding suggests that a fortification policy based on folic acid and vitamin B12, rather than folic acid alone, is likely to be much more effective at lowering of homocysteine concentrations, with potential benefits for reduction of risk of vascular disease.

Lancet 2002; **359:** 227–228

Cobalamin metabolism and corresponding causes of deficiency



PLoS Hub for Clinical Trials

Homocysteine-Lowering by B Vitamins Slows the Rate of Accelerated Brain Atrophy in Mild Cognitive Impairment: A Randomized Controlled Trial

David Smith, Stephen M. Smith, Celeste A. de Jager, Philippa Whitbread, Carole Johnston, Grzegorz Agacinski, Abderrahim Oulhaj, Kevin M. Bradley, Robin Jacoby, Helga Refsum

Oxford Project to Investigate Memory and Ageing (OPTIMA), University of Oxford, Oxford, United Kingdom, Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

September 2010 | Volume 5 | Issue 9 | e12244

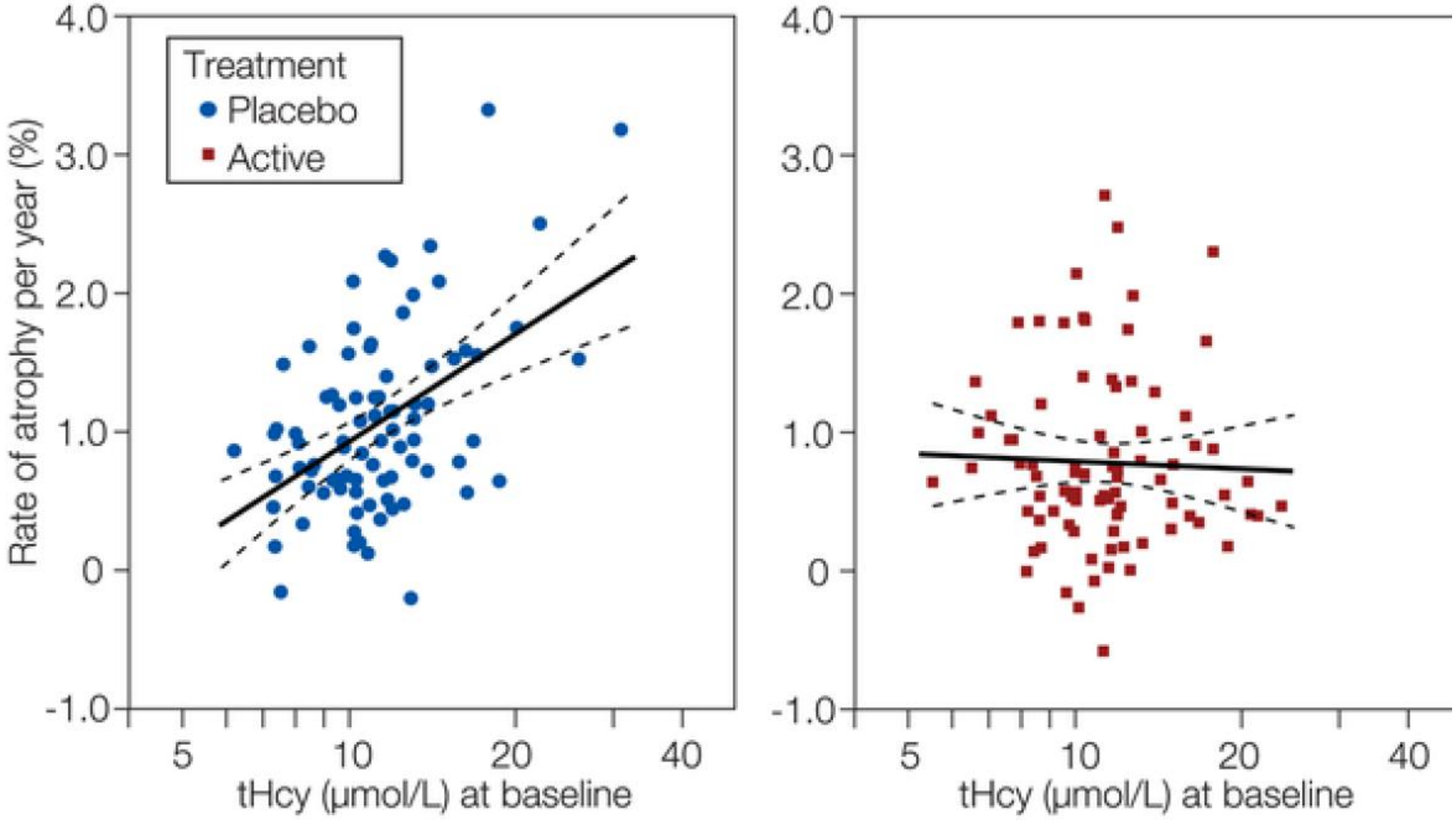
PLoS 2010;5(9):e12244

Methods and Findings

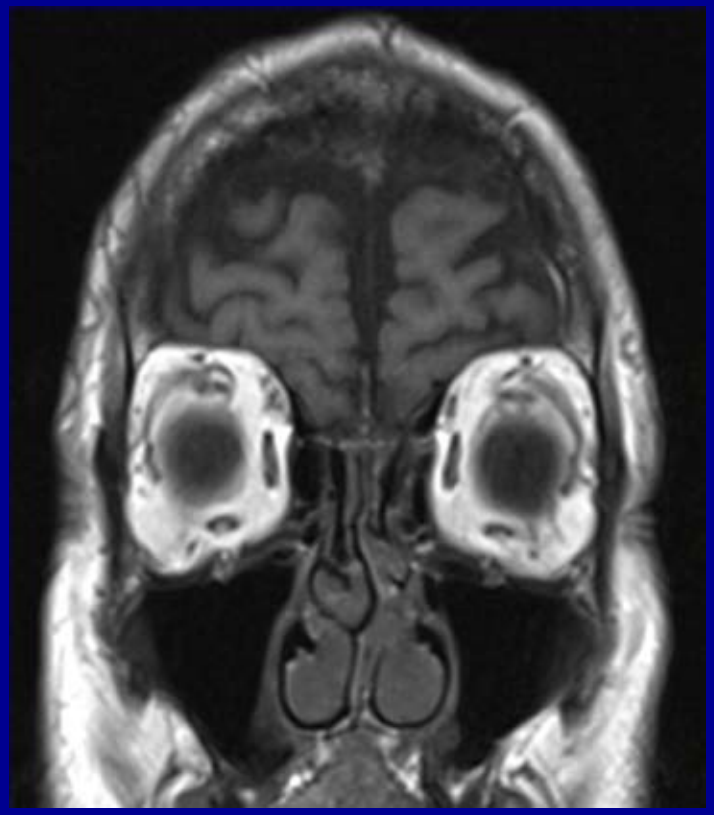
Single-center, randomized, double-blind controlled trial of high-dose folic acid, vitamins B_6 and B_{12} in 271 individuals (of 646 screened) over 70 y old with mild cognitive impairment. A subset (187) volunteered to have cranial MRI scans at the start and finish of the study. Participants were randomly assigned to two groups of equal size, one treated with folic acid (0.8 mg/d), vitamin B_{12} (0.5 mg/d) and vitamin B_6 (20 mg/d), the other with placebo; treatment was for 24 months. The main outcome measure was the change in the rate of atrophy of the whole brain assessed by serial volumetric MRI scans.

Results

A total of 168 participants (85 in active treatment group; 83 receiving placebo) completed the MRI section of the trial. The mean rate of brain atrophy per year was 0.76% [95% CI, 0.63–0.90] in the active treatment group and 1.08% [0.94–1.22] in the placebo group ($P = 0.001$). The treatment response was related to baseline homocysteine levels: the rate of atrophy in participants with homocysteine >13 µmol/L was 53% lower in the active treatment group ($P = 0.001$). A greater rate of atrophy was associated with a lower final cognitive test scores. There was no difference in serious adverse events according to treatment category.


Treatment
Placebo
Active
Rate of atrophy per year (%)
4.0
3.0
2.0
1.0
0
-1.0
5
10
20
40
tHcy (µmol/L) at baseline

OBSTRUCTIVE SLEEP APNEA



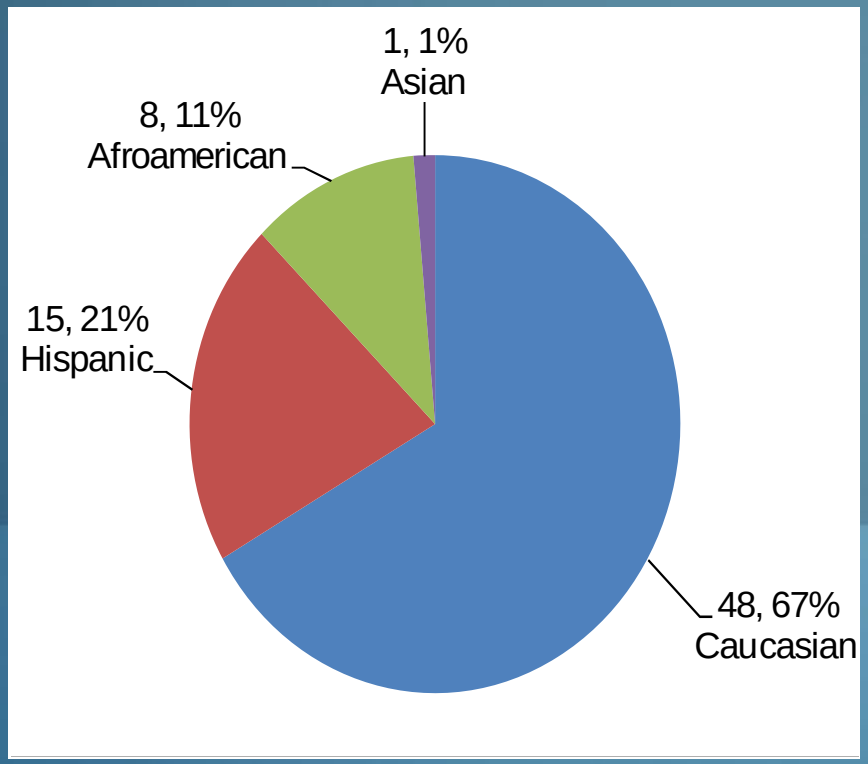
POLYSOMNOGRAPHY

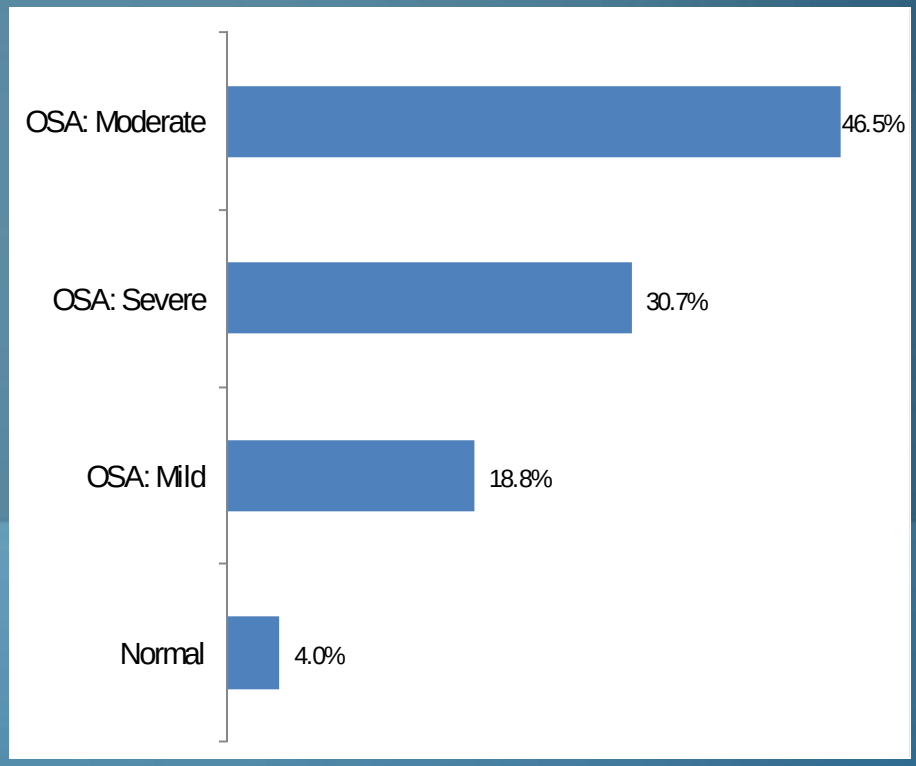
JAMA®
The Journal of the American Medical Association

Original Contribution

Yaffe et al. Sleep-Disordered Breathing, Hypoxia, and Risk of Mild Cognitive Impairment and Dementia in Older Women. JAMA 2011; 306 (6): 613-619

Sleep Evaluation (Polysomnography) in 106 consecutive Patients from the A&D Clinic Methodist Neurological Institute Houston TX 2010-2011



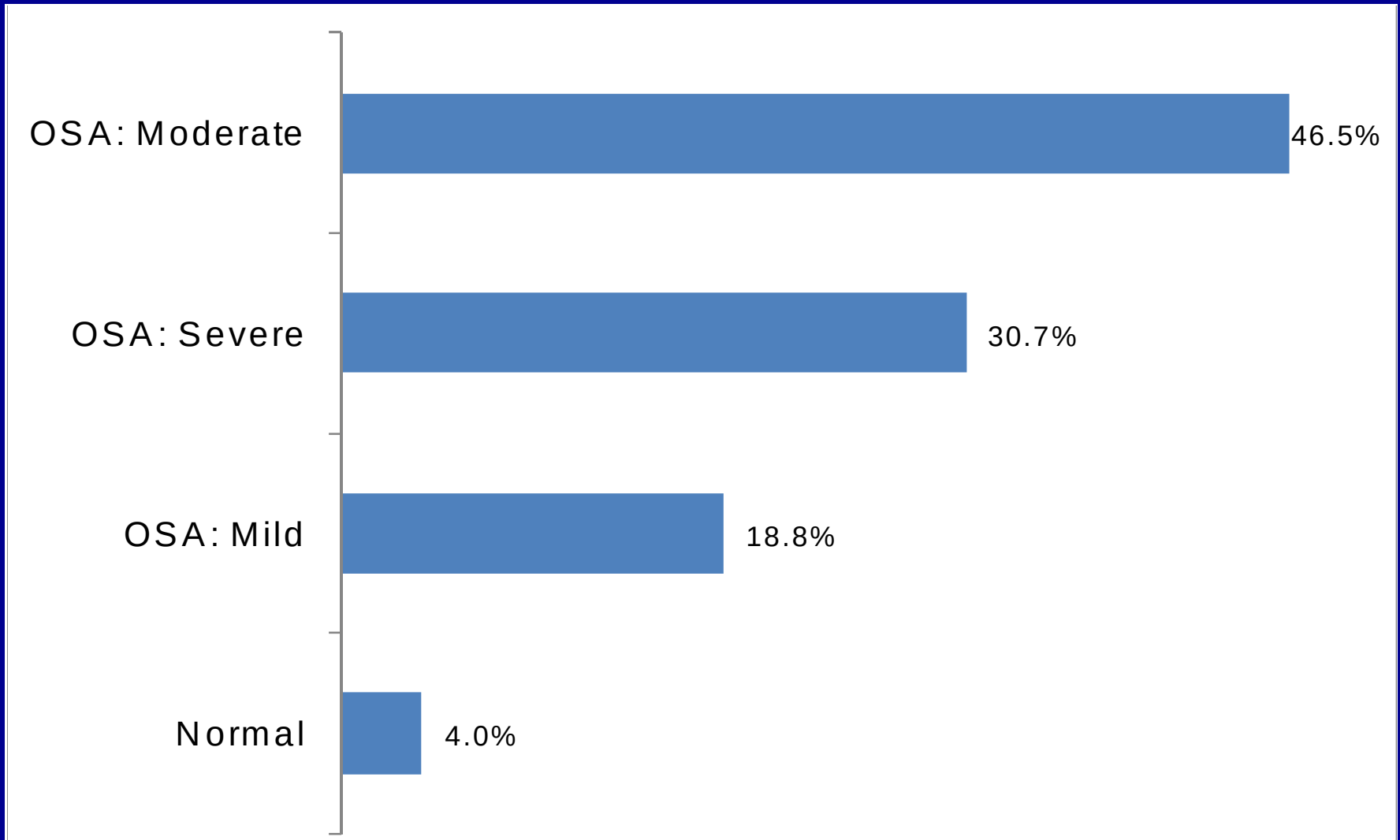


N=106 Mean age=73 F=51% M=49%

PSG Results N=106

- Mean age: 72.9 years
- 51.5% men and 48.5% women.
- Mean Body Mass Index: 27.5 kg/m2 [range=19–41].
- Caucasian (59%), Hispanics (25%), African Americans (12%) and Asian (4%)
- Vascular risk factors: hypertension (77%), hypercholesterolemia (45%), cardiovascular disease (33%), diabetes (28%), prior stroke (22%)

PSG RESULTS



COGNITIVE DIAGNOSES

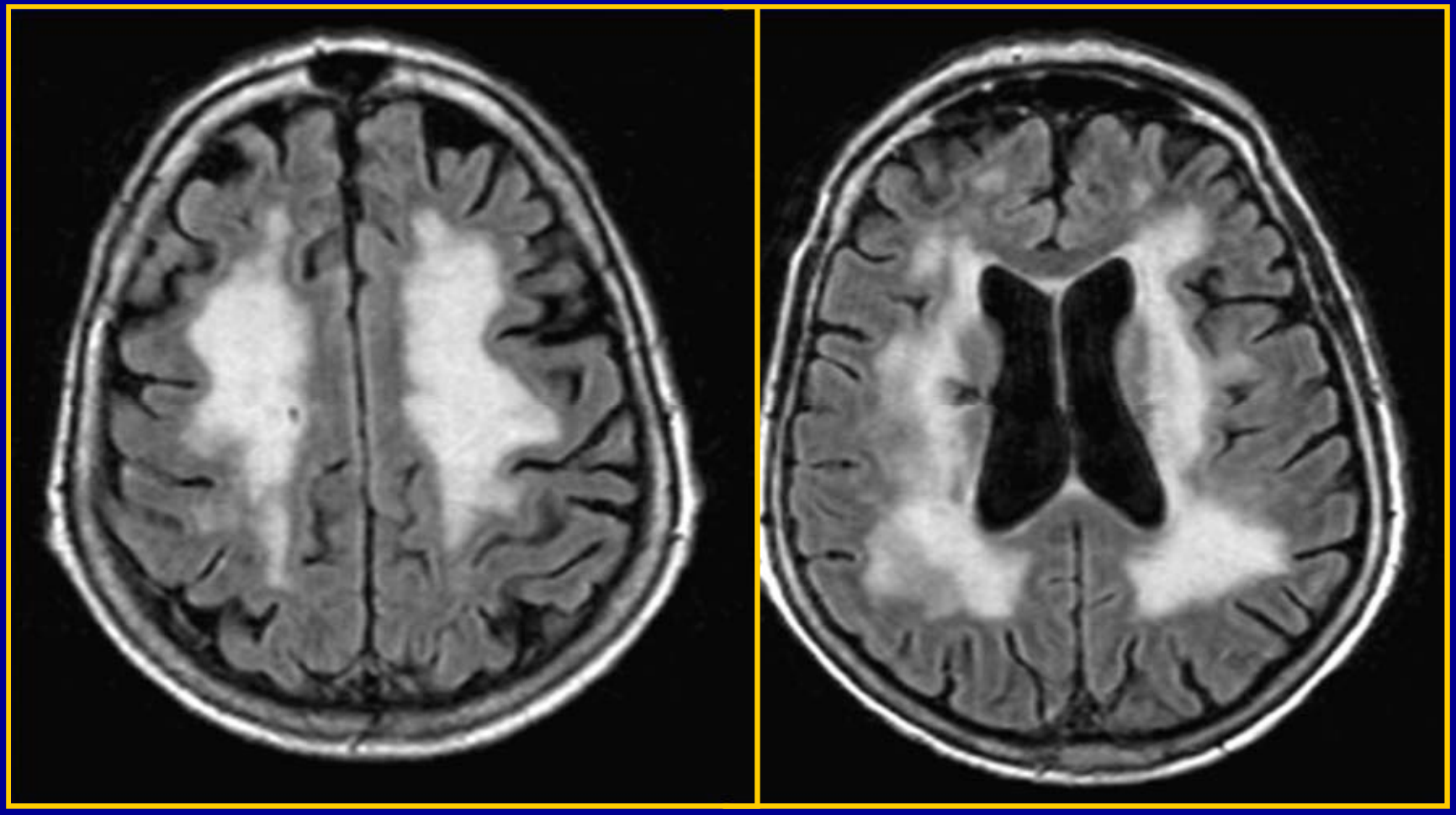
- MCI Dysexecutive type (24%)
- Mixed AD + VaD (20%)
- MCI Amnestic type (17%)
- Vascular Dementia (12%)
- Alzheimer's disease (9%)
- Normal Pressure Hydrocephalus (7%)

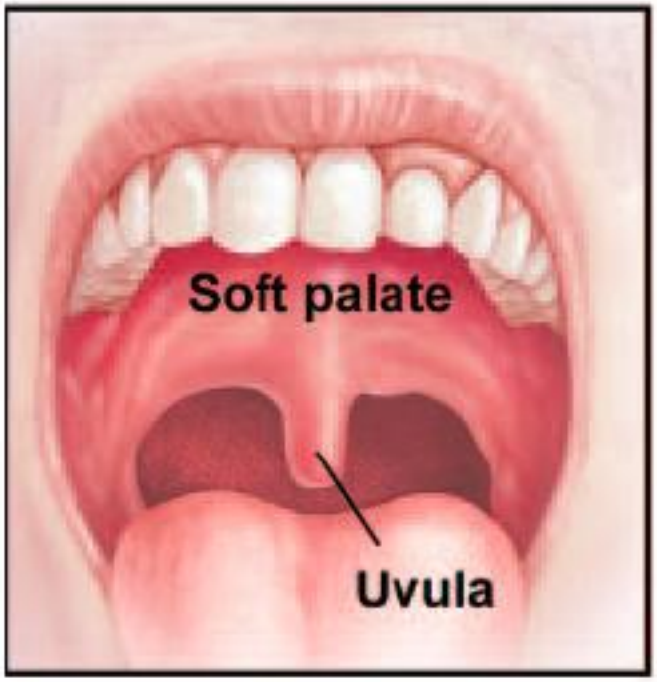
Cognitive test scores according to OSA severity

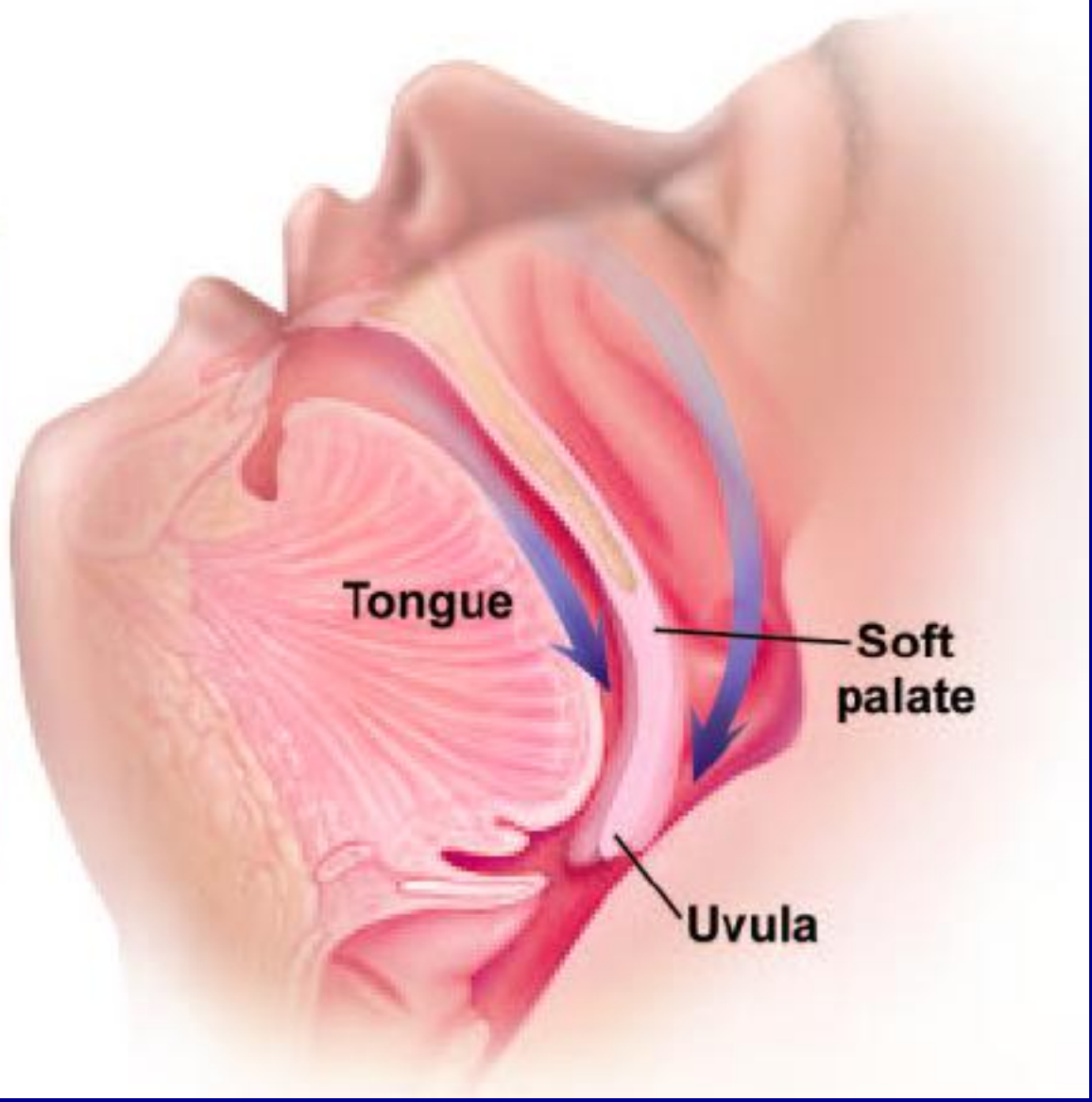
	MMSE	CLOCK	VF Animals	Luria
Normal <5 apneas/hr				
Mean	27.3	13.0	17.5	2.3
Std. Dev.	3.8	1.0	0.7	1.2
Obs	3	3	2	3
Mild 5-15 apneas/hr				
Mean	25.8	8.1	12.0	3.3
Std. Dev.	4.7	4.5	3.5	0.7
Obs	14	15	11	15
Moderate 16-30 apneas/hr				
Mean	24.2	8.1	12.7	3.2
Std. Dev.	6.6	4.7	4.3	0.9
Obs	42	41	21	37
Severe >30 apneas/hr				
Mean	23.2	6.3	12.0	3.4
Std. Dev.	6.1	4.9	6.8	0.8
Obs	26	27	11	26

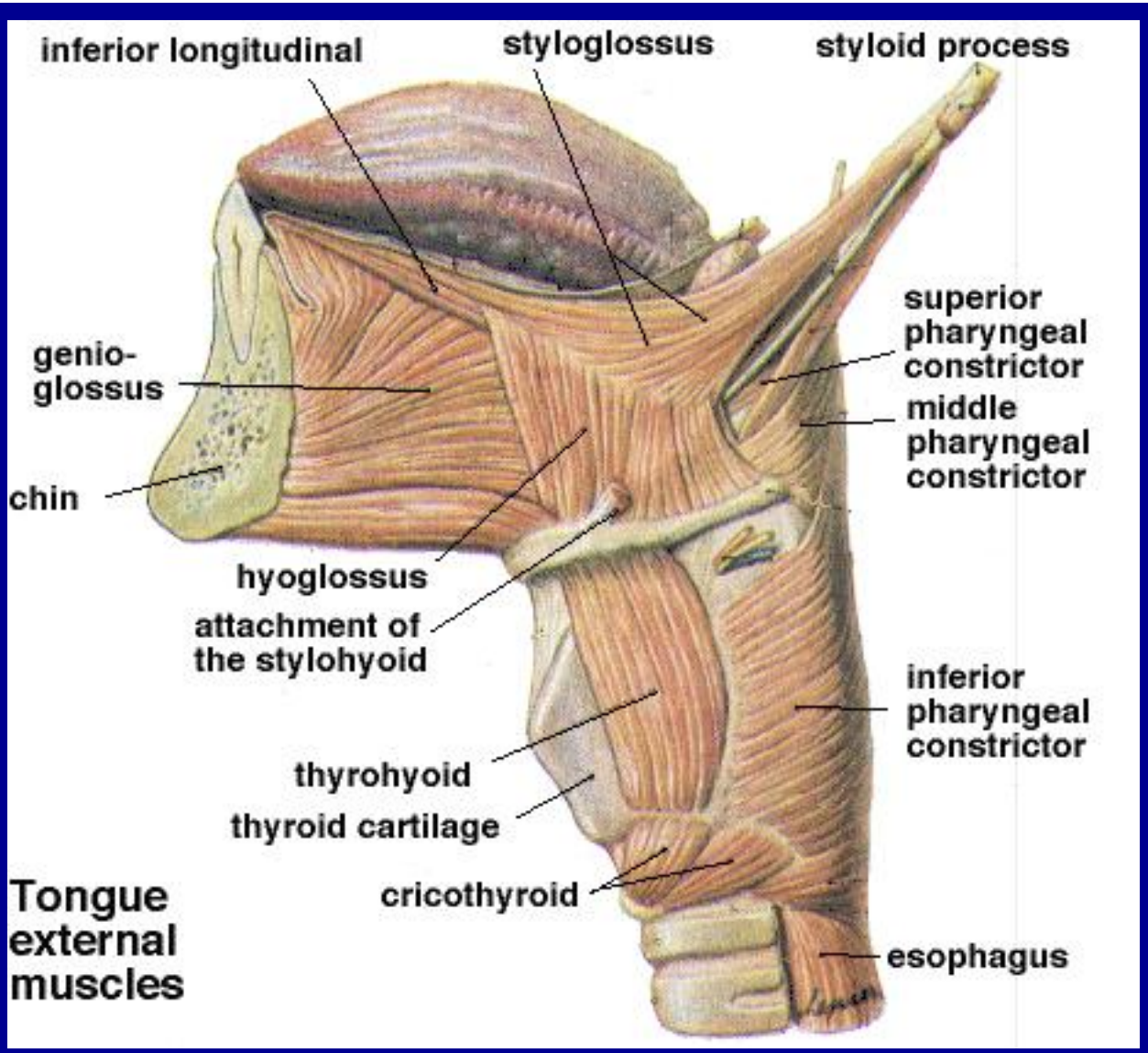
MRI

- Extensive small vessel disease (86%)
- Isolated white matter hyperintensities (34%)
- Large-vessel strokes (17%)




Soft palate
Uvula


Tongue
Soft palate
Uvula

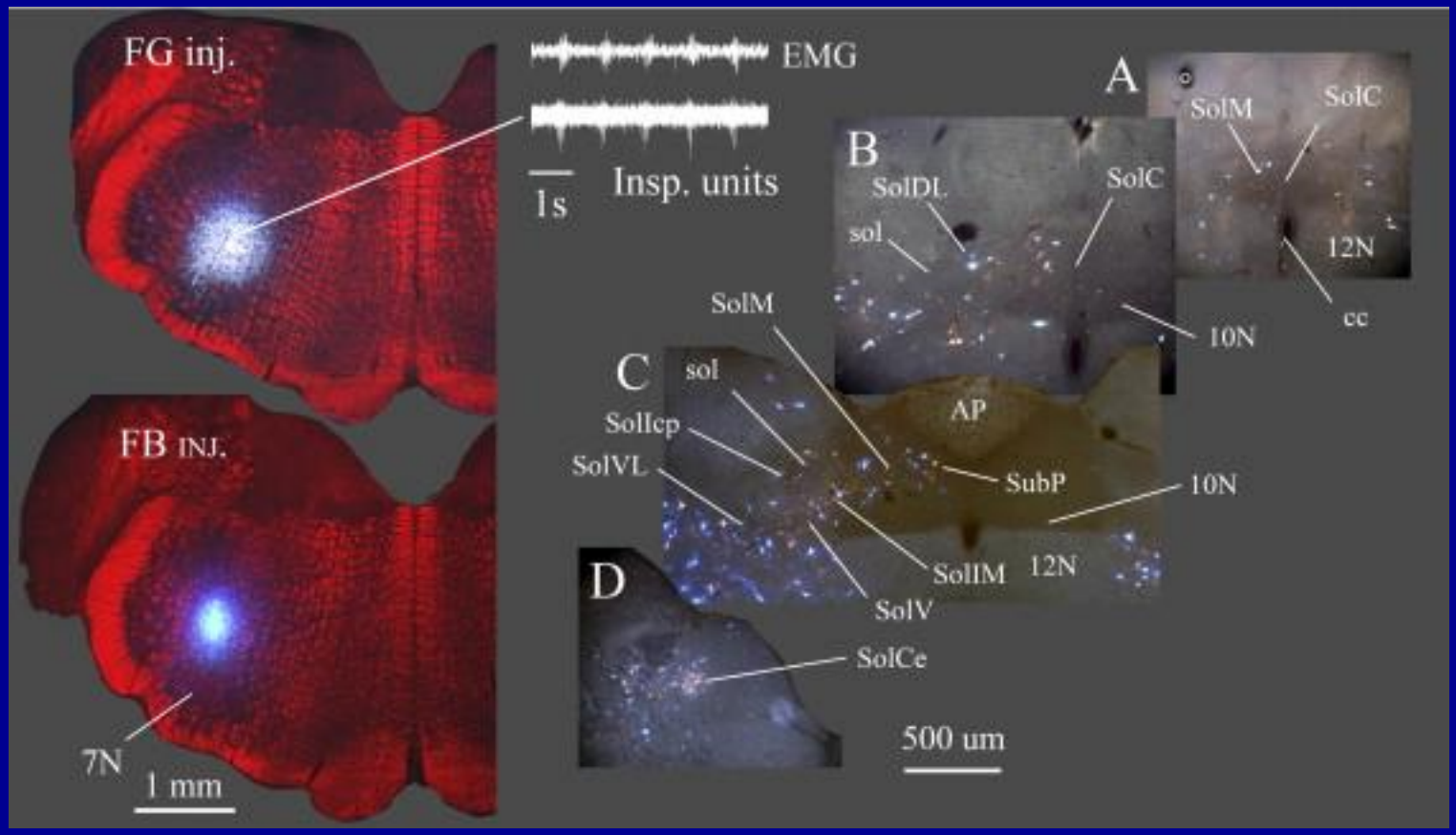


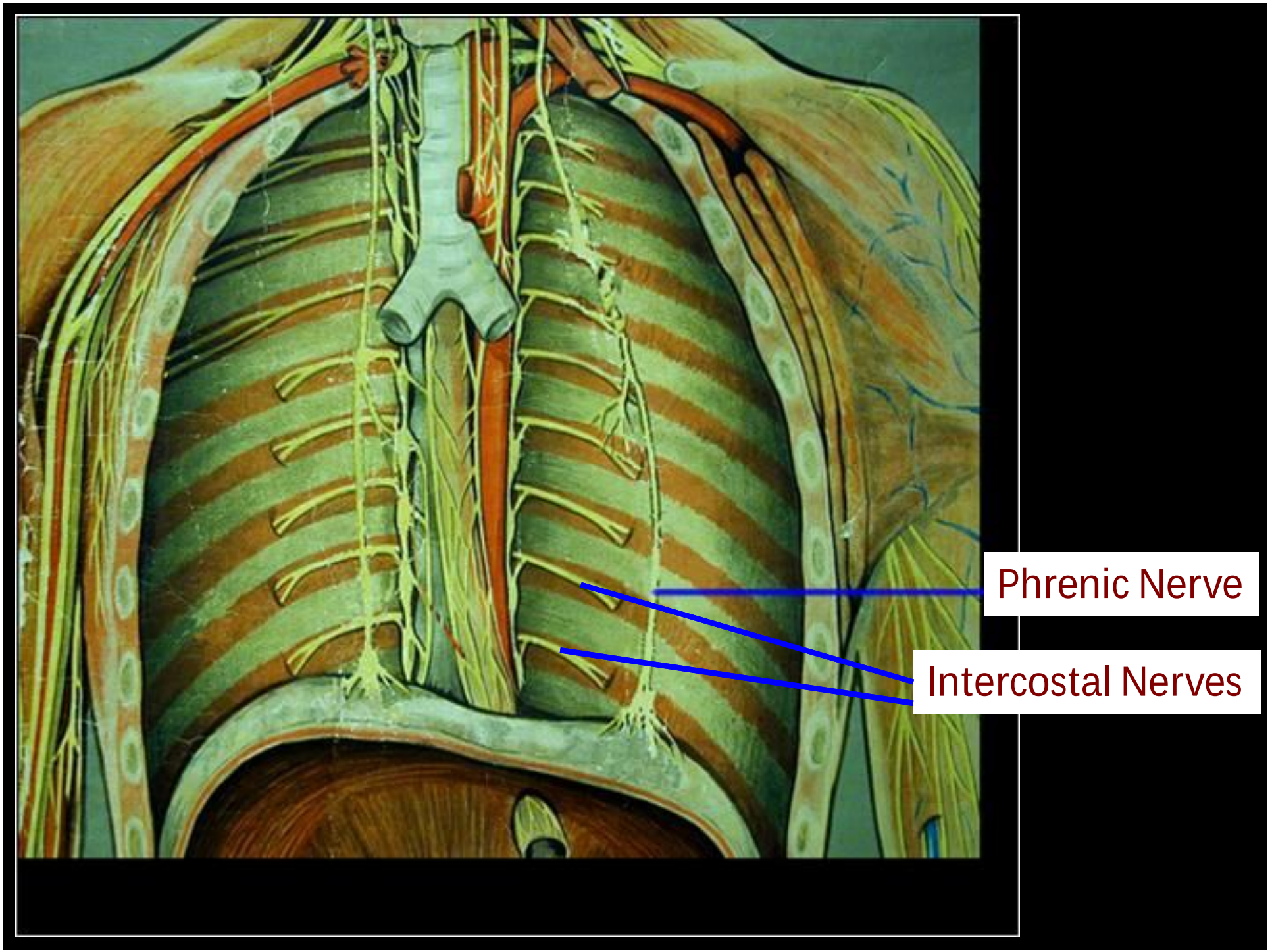
Extrinsic muscles of the tongue (genioglossus, geniohyoid) insert on the mandible's inner surface. NREM and REM sleep induce muscle relaxation causing the jaw to drop and the tongue to fall back blocking the airway

Aortic and carotid chemoreceptors and baroreceptors

http://anatomyandphysiology.blogspot.com/2008/08/aortic-and-carotid-bodies.html

Alheid GF, Jiao W, McCrimmon DR: Caudal nuclei of the rat nucleus of the solitary tract differentially innervate respiratory compartments within the ventrolateral medulla. *Neuroscience* 2011;190:207-27




Phrenic Nerve
Intercostal Nerves

Consequences of Airway Obstruction

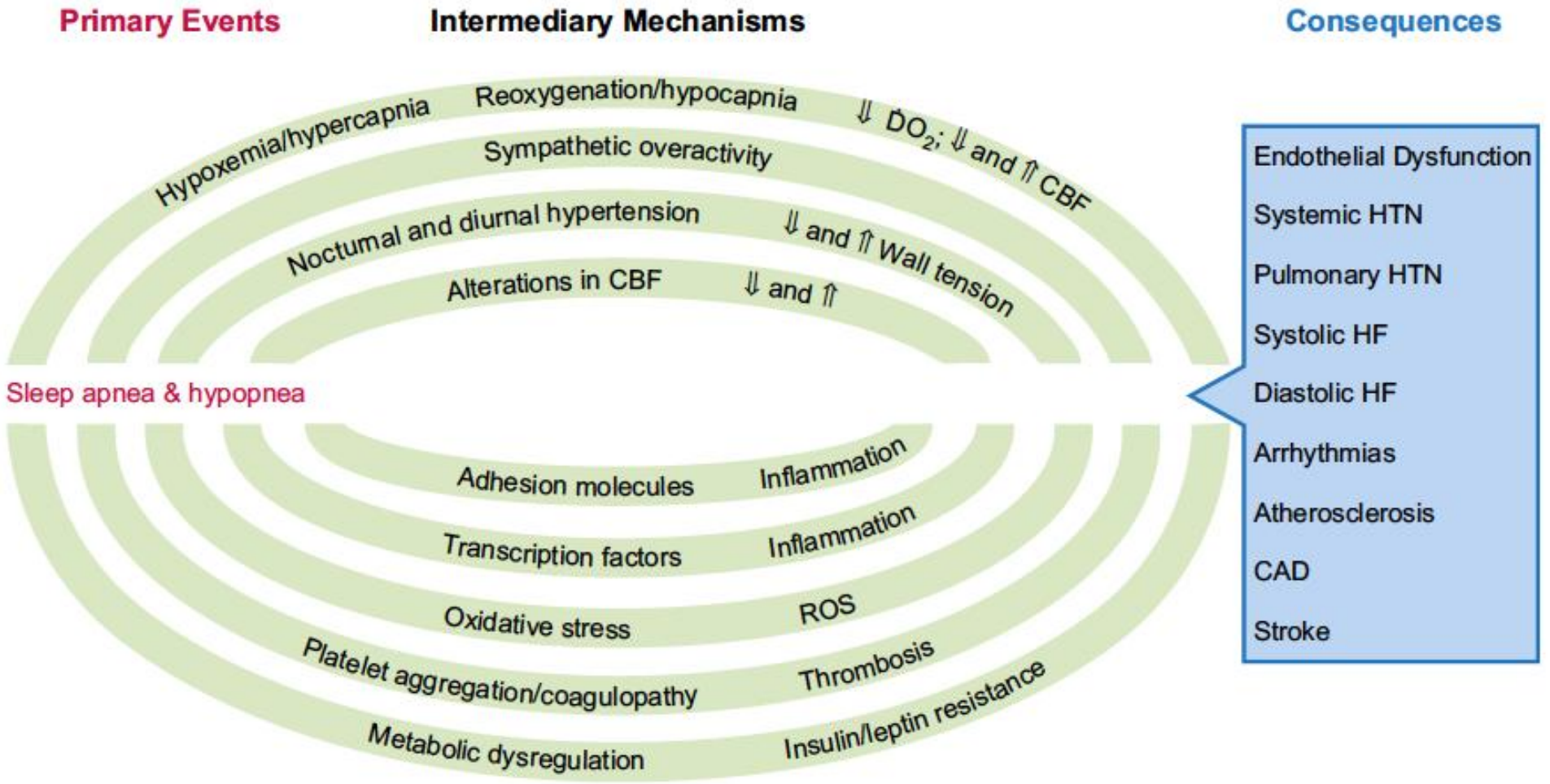
- Interruption of ventilation.
- Repetitive hypoxemia due to low PaO_2, concomitant $PaCO_2$ retention (hypercapnia) and respiratory acidosis.
- Intermittent, often violent and strenuous, respiratory efforts from reflex attempts involving chest and abdominal musculature to overcome the obstruction of the airway and to restore airflow.
- This is the *Mueller maneuver** that generates severely negative intrathoracic pressure (–60 to –80mm Hg), a risk factor for ATRIAL FIBRILLATION
- The end result of these respiratory events is suffocation that produces an acute stress reaction, disrupting sleep.

* Inverse Valsalva

Alterations induced by Apneas and Hypopneas during Sleep

- ?á Recurrent hypoxemia (low PaO_2) hypercapnia (elevated $PaCO_2$) and respiratory acidosis (low blood pH)
- ?á Activation of carotid and aortic chemoreceptors
- ?á Reflex contractions of respiratory chest and abdominal muscles
- ?á Severely increased negative intrathoracic pressure
- ?á Tachycardia from atrial Bainbridge reflex
- ?á Sympathetic (adrenergic) outburst
- ?á Arterial hypertension
- ?á Baroreceptor reflex activation
- ?á Peripheral vasoconstriction
- ?á Hyperglycemia, hypercoagulability

From Roman; in, *Sleep, Stroke, and Cardiovascular Disease,* Culebras A, ed. Cambridge U Press, 2013



Sleep Med Clin 2007; 2:539

STROKE RISK FACTORS

- Over 300 risk factors have been associated with atherosclerosis and its major complications, coronary heart disease and stroke.
- 70-90% of the risk can be explained by conventional risk factors, such as smoking, abnormal lipids, hypertension, diabetes, obesity, psychosocial factors, unhealthy diet, and lack of physical activity

Vinereanu: Risk factors for atherosclerotic diseases. Herz 2006:31 Suppl 3:5-24

Obstructive sleep apnea (OSA)

- Significant association with stroke risk
- Independent of other risk factors, including hypertension, atrial fibrillation and T2DM
- Direct relation of OSA severity and increased risk of stroke
- Higher risk of death following stroke
- Stroke incidence is 2-3X higher in OSA patients than in the general population

Yaggi et al. *N Engl J Med* 2005;353: 2034–41; Muñoz et al. *Stroke* 2006;37:2317–21; Redline et al. Am J Respir Crit Care Med 2010;182:269–77 Wallace DM, Ramos AR, Rundek T. *Int J Stroke* 2012;7:231-42. Epub 2012 Feb 15.

Obstructive sleep apnea (OSA)

- Meta-analysis: 5 studies N=8435 participants
- OSA is associated with incident stroke

  OR 2.24; 95%CI, 1.57-3.19
- Significant association predominantly in men

  OR 2.87; 95%CI, 1.91-4.31
- Data on women were sparse
- Relationship with ischemic heart disease and cardiovascular mortality needs further research

Loke et al. *Circ Cardiovasc Qual Outcomes* 2012 Sep 1;5(5):720-8. Epub 2012 Jul 24

OSA: Complications

- Hypertension
- Coronary artery disease
- Congestive heart failure
- Myocardial infarction
- Pulmonary hypertension
- Atrial fibrillation
- Carotid Atherosclerosis
- Stroke
- Ruptured aortic aneurysms
- Sudden cardiac death

Traditional Stroke Risk Factors

- Age
- Hypertension
- Atherosclerosis
  - Atrial fibrillation
  - Carotid disease
  - CAD, CHF
- Hyperlipidemia
- Diabetes mellitus
- Smoking

Non-traditional risk factors

- Infection
- Homocysteine
- Markers of inflammation (CRP)
- Renin angiotensin system (RAS)
- Coagulation/platelet-related factors
- Lipoproteins
- Diet (Vitamins)
- Lack of Exercise (sedentary lifestyle)
- Obstructive sleep apnea

Gorelick PB. *Stroke* 2002 Mar;**33**(3):862-75.

Is Sleep the New Vital Sign?

Does it seem as though everybody is tired all the time? In a nation where people value long hours of hard work, guzzle more than 100 million cups of coffee a day, and watch television obsessively, sleep has suffered. Average nightly sleep duration has fallen from approximately 9 hours in 1910 to 7 hours in 2002. Many people often sleep no more than 5 to 6 hours a night, even though studies show that most people need between 7 and 8 hours.

Najib Ayas, MD, assistant professor of medicine, University of British Columbia School of Medicine in Vancouver, British Columbia, Canada. His epidemiologic research has identified a 30% increased relative risk for myocardial infarction or symptomatic diabetes among people who report reduced nightly sleep. These relationships are associations, which means that no one has proved that sleep deprivation causes myocardial infarction or diabetes.

ONE TAKE HOME MESSAGE:

ASK THE FAMILY:

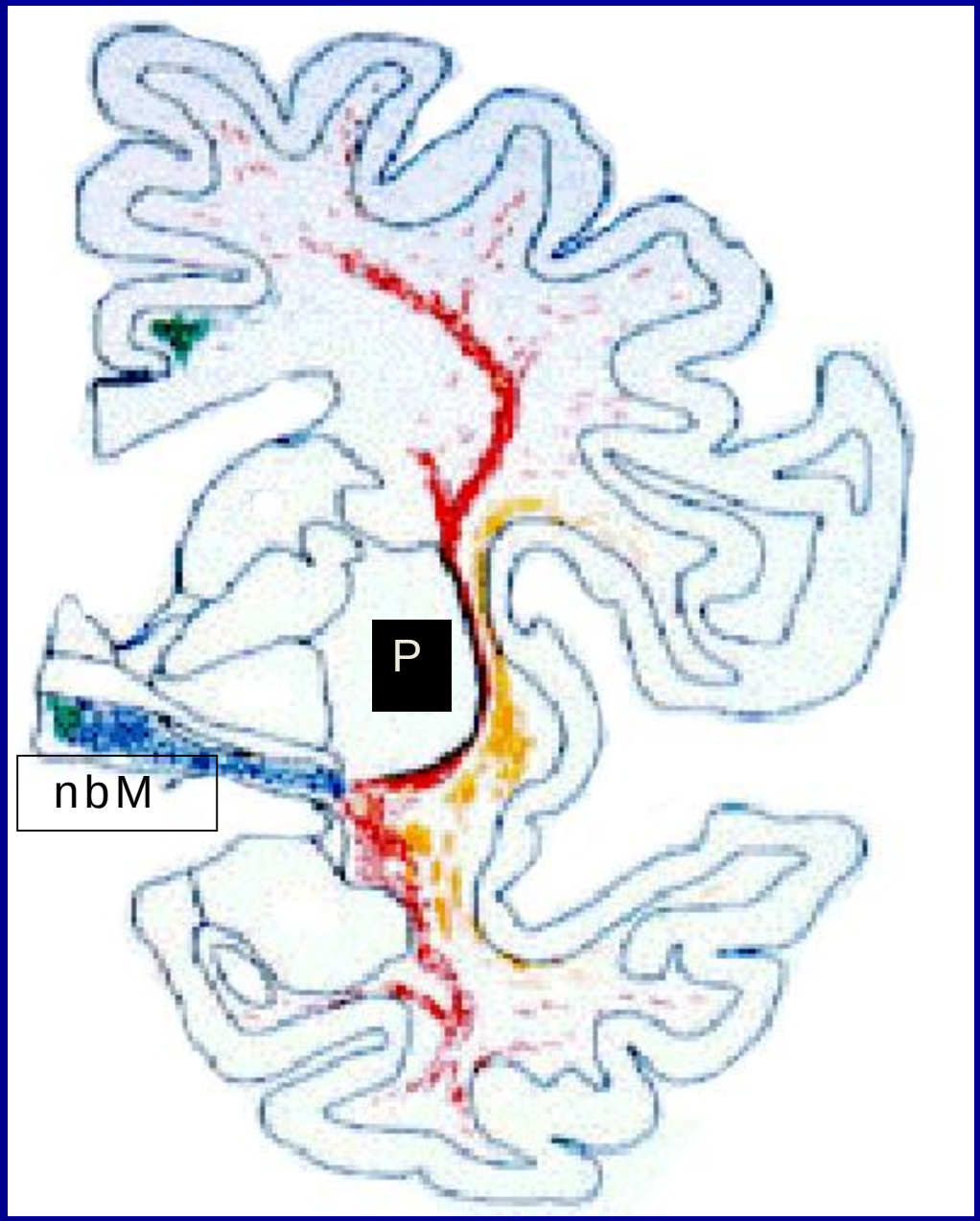
— IS THERE A HISTORY OF SNORING IN THIS PATIENT?

The Goal is Symptomatic Improvement

FARMACOLOGICAL TREATMENT

Treatment

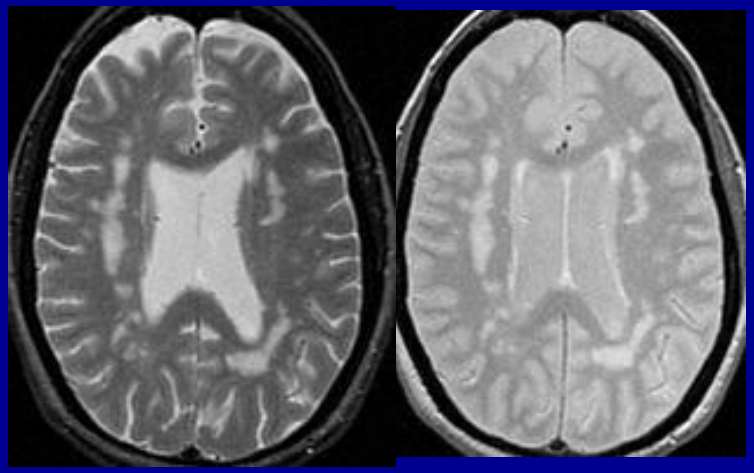
- Cholinesterase inhibitors (Aricept, Excelon) for cholinergic deficits secondary to ischemic subcortical white matter lesions
- Sertraline for treatment of executive dysfunction, mood changes and apathy
- Citicoline
- Exercise
- Adequate control of classic VRF:
  - OSA
  - Smoking cessation
  - B_{12} for hyperhomocysteinemia



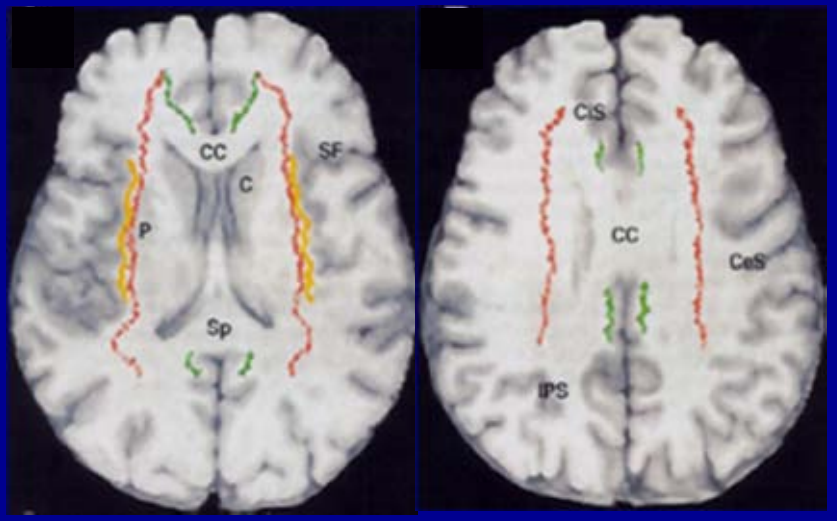
Selden et al. Brain. 1998;121:2249-2257.

Hyperintensities affecting ACh WM tracts

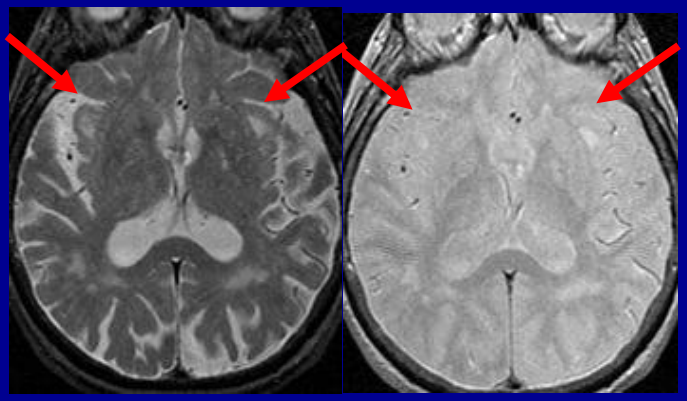
Extensive DW HI



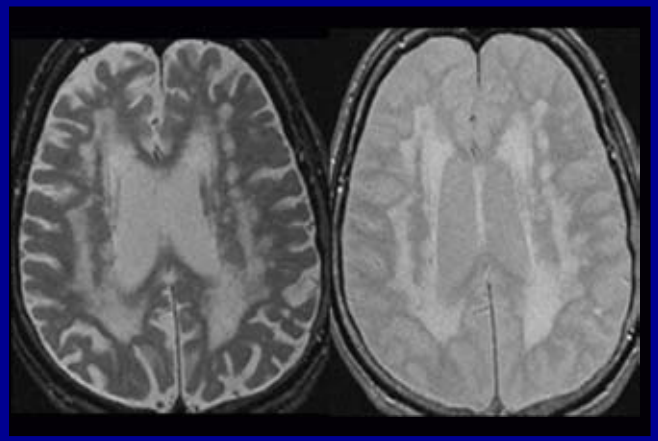
Selden, et al., Brain (1998), 121, 2249-2257



External capsule HI



Extensive periventricular HI

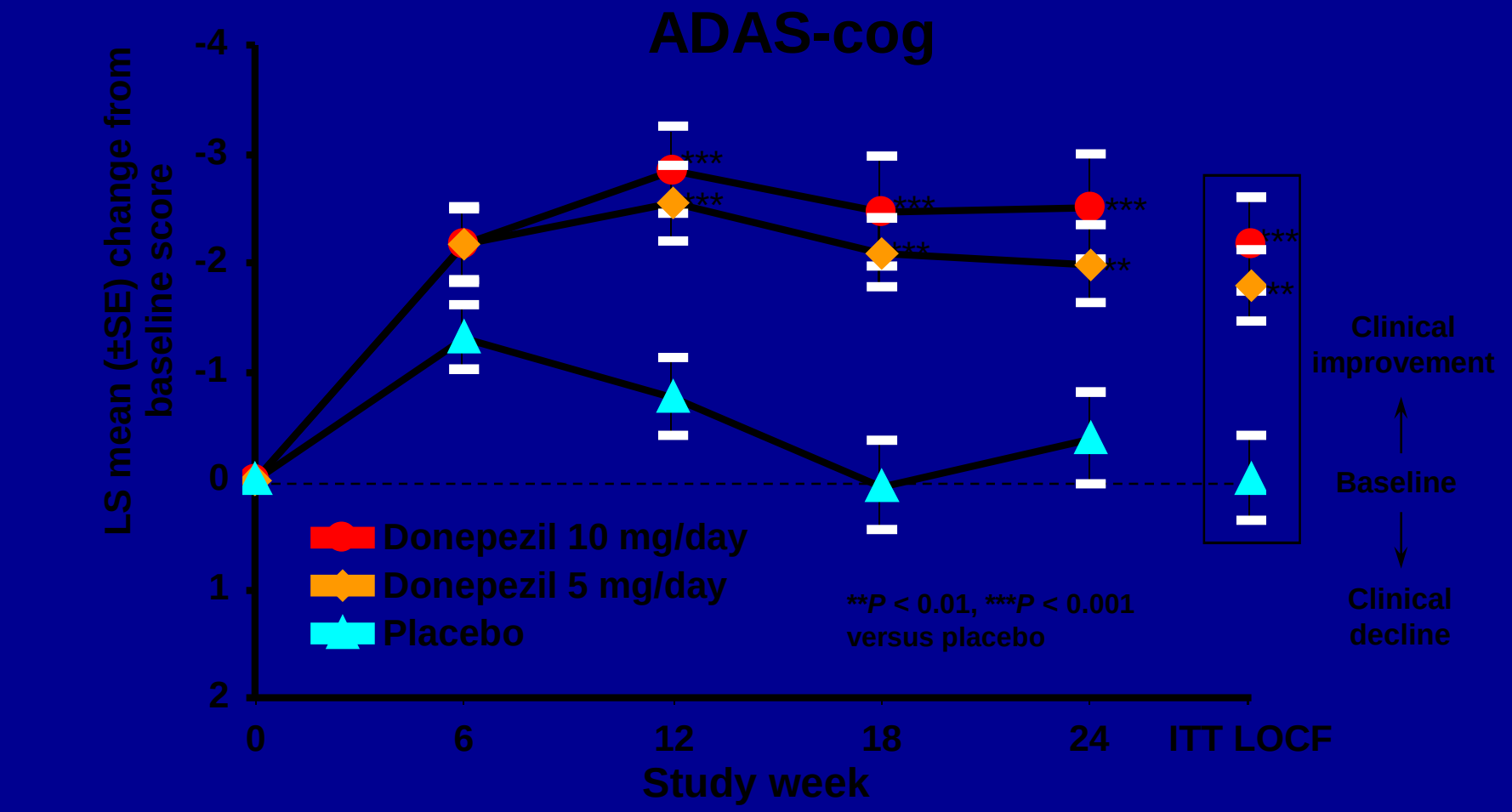


Swartz, Sahlas, Black, J Stroke CVD, 2003

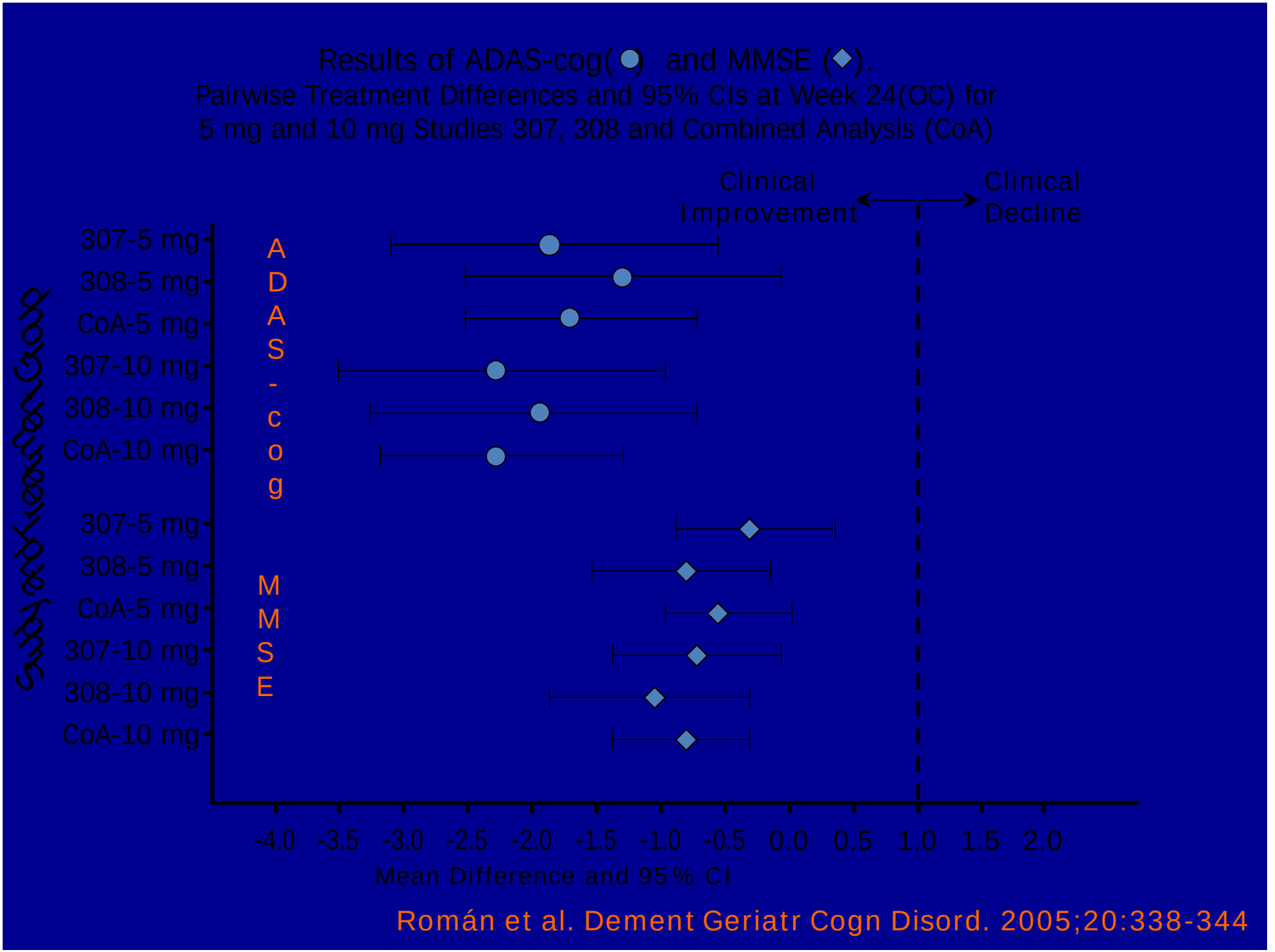
ChoE-inhibitor studies in VaD or AD+CVD

- Donepezil → Pure VaD (probable and possible cases by NINDS-AIREN)
  - 2 double-blind studies
  - (1200 subjects)
- Galantamine → AD+CVD & pure VaD
  - 1 double-blind study
  - AD with vascular risk factors
  - 2 double-blind studies
- Rivastigmine → Pure VaD
  - 2 open studies

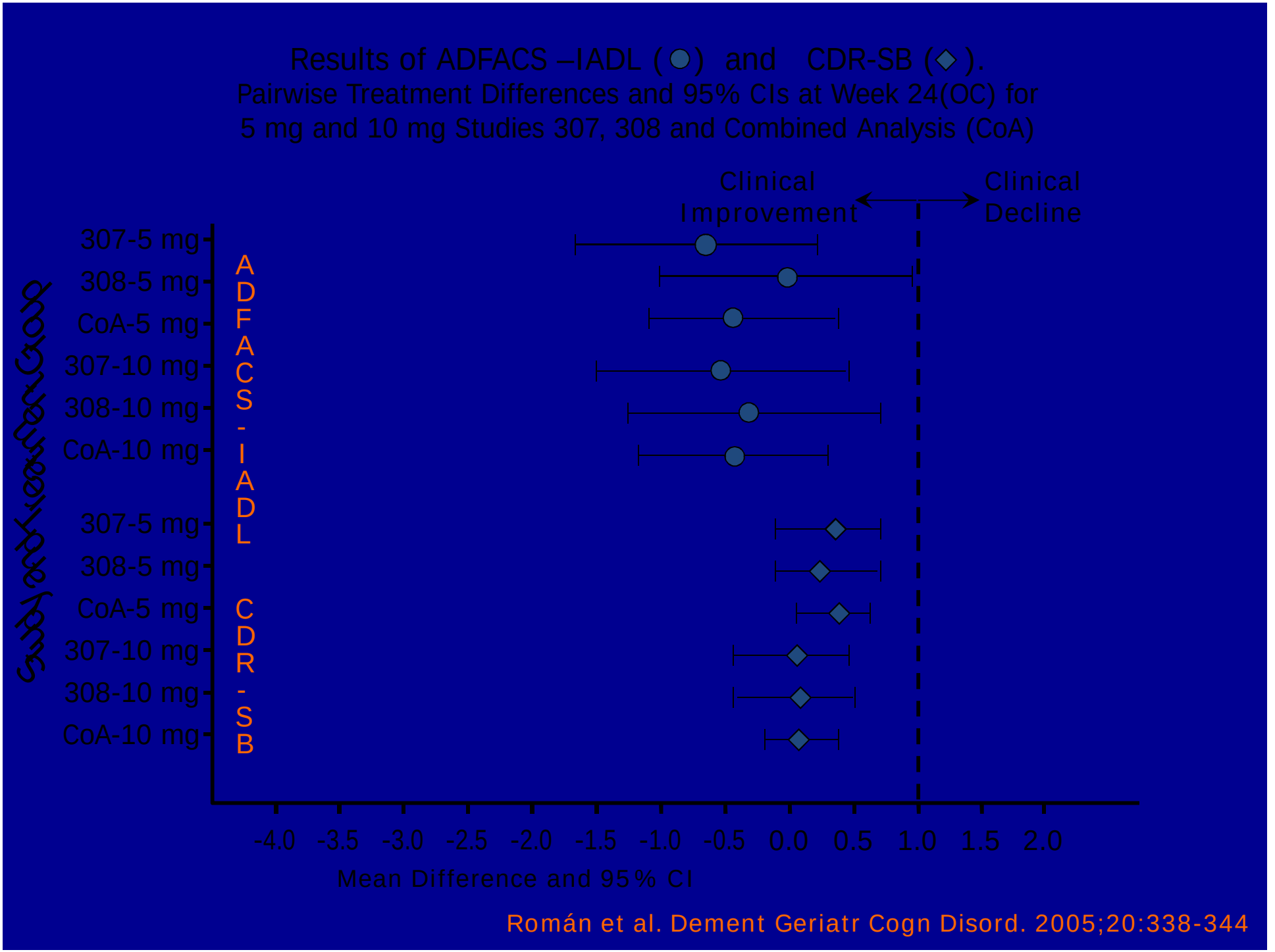
Effects of donepezil on cognitive function in cases of probable and possible VaD



Don 10 mg	n = 194	188	172	163	155	194
Don 5 mg	n = 201	193	183	173	164	199
Placebo	n = 181	180	167	160	150	180



Román et al. Dement Geriatr Cogn Disord. 2005;20:338-344



Román et al. Dement Geriatr Cogn Disord. 2005;20:338-344

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
Stroke 2010;41:1213-1221

American Heart Association | American Stroke Association

Randomized, Placebo-Controlled, Clinical Trial of Donepezil in Vascular Dementia

Differential Effects by Hippocampal Size

Gustavo C. Román, MD; Stephen Salloway, MD, MS; Sandra E. Black, MD, FRCPC; Donald R. Royall, MD; Charles DeCarli, MD; Michael W. Weiner, MD; Margaret Moline, PhD; Dinesh Kumar, MS; Rachel Schindler, MD; Holly Posner, MD, MS

Background and Purpose—We sought to assess the efficacy and safety of donepezil in patients with vascular dementia (VaD) fulfilling National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria.

Methods—This international, multicenter, 24-week trial was conducted from March 2003 to August 2005. Patients (N=974; mean age, 73.0 years) with probable or possible VaD were randomized 2:1 to receive donepezil 5 mg/d or placebo. Coprimary outcome measures were scores on the Vascular-Alzheimer Disease Assessment Scale–Cognitive Subscale and Clinician's Interview–Based Impression of Change, plus carer interview. Analyses were performed for the intent-to-treat population with the last-observation-carried-forward method.

Results—Compared with placebo, donepezil-treated patients showed significant improvement from baseline to end point on the Vascular-Alzheimer Disease Assessment Scale–Cognitive Subscale (least-squares mean difference, −1.156; 95% CI, −1.98 to −0.33; $P<0.01$) but not on the Clinician's Interview–Based Impression of Change, plus carer interview.

Patients with hippocampal atrophy who were treated with donepezil demonstrated stable cognition versus a decline in the placebo-treated group; in those without atrophy, cognition improved with donepezil versus relative stability with placebo. Results on secondary efficacy measures were inconsistent. The incidence of adverse events was similar across groups. Eleven deaths occurred in the donepezil group (1.7%), similar to rates previously reported for donepezil trials in VaD, whereas no deaths occurred in the placebo group.

Cognitive Impairment

Donald R. Royall, M.D.
Jeffrey A. Cordes, M.D.
Gustavo Román, M.D.
Angela Velez, M.D.
Aaron Edwards, M.D.
Jason S. Schillerstrom, M.D.
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sion. Our findings suggest that sertraline may have both statistical and clinically meaningful effects on executive control function in ischemic cerebrovascular disease. The authors discuss the implications for future clinical trials.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2009; 21:445–454)

Apr 18, 2005;(2):CD000269

Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly (Review)

Fioravanti M, Yanagi M

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2013;35:146–154
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Long-Term Treatment with Citicoline May Improve Poststroke Vascular Cognitive Impairment

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Olga Maisterra[a] Marc Ribo[a] Carlos Molina[a] Manuel Quintana[a]
Gustavo C. Román[c]

...ents with first-ever ischemic stroke is safe and probably effective in improving poststroke cognitive decline. Citicoline appears to be a promising agent to improve recovery after stroke. Large clinical trials are needed to confirm the net benefit of this therapeutic ap-

The Goal is Prevention of Vascular Dementia

PREVENTION

Translating Current Knowledge Into Dementia Prevention

Gustavo C. Román, MD,† David T. Nash, MD,‡ and Howard Fillit, MD§‖*

Abstract: Considerable knowledge has been gained from epidemiologic studies and randomized clinical trials regarding risk factors for dementia, including Alzheimer disease (AD) and vascular dementia (VaD). Most identified risk factors for dementia are similar to vascular disease risk factors for heart disease and stroke. In 2010, the National Institutes of Health Conference concluded that there are no validated modifiable factors to reduce the incidence of AD or to change its course. This research perspective specifically concerning AD disregards the fact that in community-dwelling elderly, the most common forms of dementia involve the cerebral macrovasculature and microvasculature, manifesting as VaD and mixed dementia (the combination of VaD and AD) in autopsy-confirmed cases. Thus, prevention of dementia in clinical practice should be considered from this broader and more relevant view and not just a research perspective on "pure" AD. Practicing clinicians can reasonably state to patients that, although more definitive research is clearly needed, the management and treatment of vascular disease risk factors are likely beneficial not only to prevent heart disease and stroke, but also common forms of dementia in the community.

Key Words: Alzheimer disease, diet, exercise, homocysteine, hyperlipidemia, hypertension, smoking, vascular diseases risk factors, vascular dementia

(*Alzheimer Dis Assoc Disord* 2012;00:000–000)

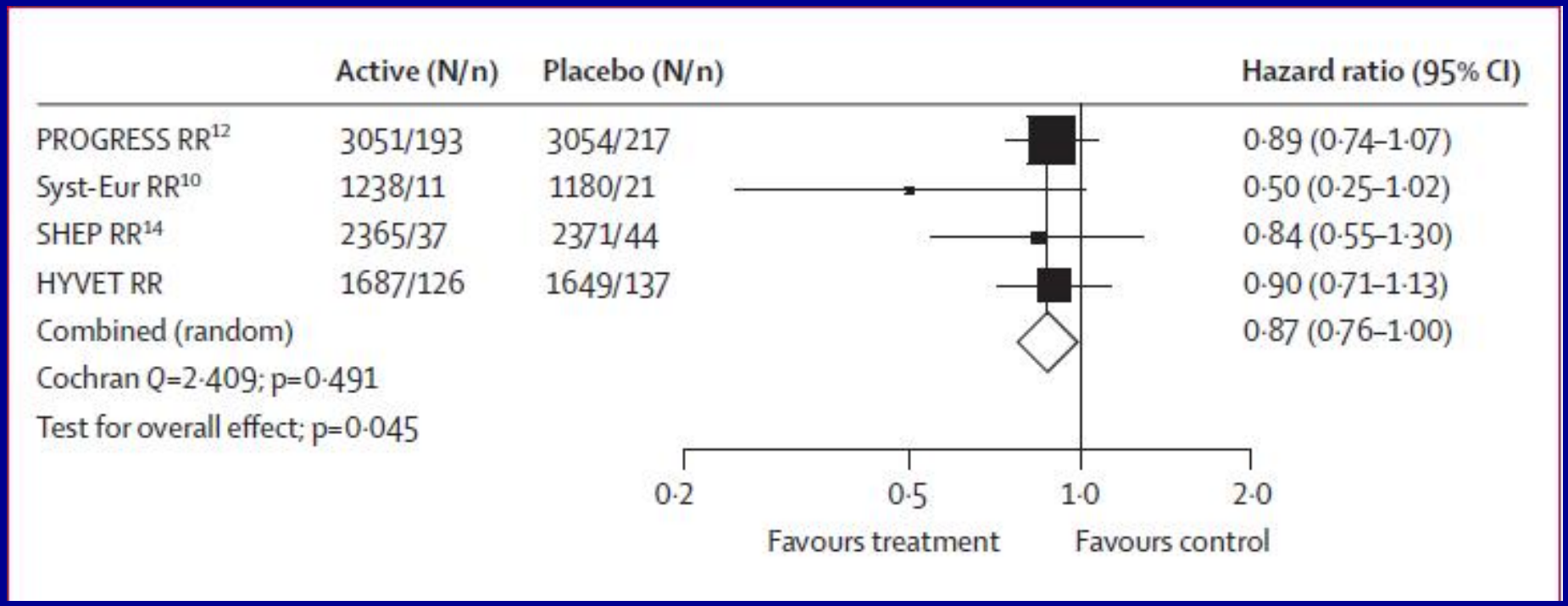
and AD pathology, predominates in autopsy-confirmed cases of dementia in the elderly.[2–5] The conference undervalued evidence that vascular disease risk factors (VDRFs) predispose not only to heart disease and stroke, but also to dementias that involve the vasculature, such as vascular dementia (VaD) and mixed dementia, which together comprise the most common forms of dementia at autopsy in community-based studies.[2–5] Recently, a comprehensive review and position paper by the American Heart Association/American Stroke Association[6] confirmed the importance of vascular factors in cognitive impairment and dementia and the complex relationships existing between AD and cerebrovascular pathology.

THE MANY VASCULAR CAUSES OF DEMENTIA IN THE ELDERLY

The trend toward increasing population age is well known[7]; the potential benefits of a long life are countered by many burdens including a 100-fold increase in stroke incidence from 3/10,000 population in the third and fourth decades to 300/10,000 at age 80 to 90 years.[8] Poststroke cognitive decline is more common than stroke recurrence and affects 30% of survivors older than 65 years; new-onset dementia incidence increases from 7% after 1 year to 48% after 25 years.[9] More troublesome is the fact that "silent"

Dementia prevention: Anti-hypertensive treatment

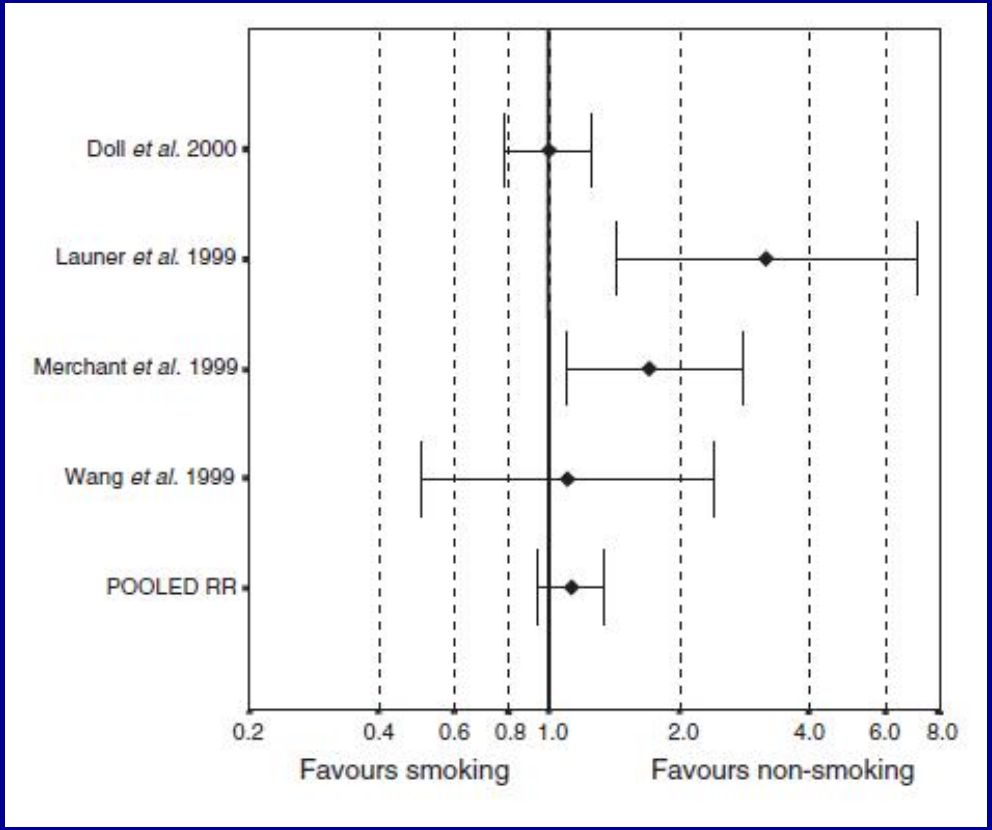
- Pooled 13% reduction in incident dementia



Peters et al., Lancet Neurol. 2008 Aug;7(8):683-9;
Peters et al., PLoS One. 2010 Jul 26;5(7):e11775. From Rockwood

Dementia prevention: No smoking/smoking cessation

Cohort studies



From Rockwood

Anstey et al., *Am J Epidemiol*. 2007 Aug 15;166(4):367-78.

Exercise Improves Your Memory and Could Become a Promising Treatment for Alzheimer's Disease

Gustavo C. Román, M.D.
The Jack S. Blanton Distinguished Endowed Chair
Director, Nantz National Alzheimer Center

Bravata et al. Auto-CPAP in Acute Stroke. *Sleep* 2011;34:1271-7

Acute stroke patients were randomized to 2 nights of auto-CPAP; OSA patients received auto-CPAP for 30 days. End-point: NIHSS baseline vs 30 d

RESULTS:

- Intervention N = 31, control N = 24 similar NIHSS (3.0)
- Most stroke pts had OSA: baseline 13/15 (86.7%); 30 d, 24/35 (68.6%)
- CPAP improved NIHSS (-3.0) more than in controls (-1.0); P = 0.03
- NIHSS improved in OSA with auto-CPAP use: -1.0 for controls no auto-CPAP; -2.5 for some auto-CPAP use; -3.0 for acceptable auto-CPAP use

BRAVATA ET AL. AUTO-CPAP IN ACUTE STROKE. *SLEEP* 2011;34:1271-7

CONCLUSIONS:

- The majority of acute stroke patients had sleep apnea.
- Auto-CPAP was well tolerated and appears to improve neurological recovery from stroke
- Auto-CPAP may represent a new therapeutic approach for selected patients with acute cerebral infarction

Cognitive Effects of Treating Obstructive Sleep Apnea in Alzheimer's Disease: A Randomized Controlled Study

Sonia Ancoli-Israel, PhD,† Barton W. Palmer, PhD,*† Jana R. Cooke, MD,†‡ Jody Corey-Bloom, MD, PhD,†§ Lavinia Fiorentino, PhD,‖ Loki Natarajan, PhD,# Lianqi Liu, MD,*† Liat Ayalon, PhD,* Feng He, MS,# and Jose S. Loredo, MD†‡*

JAGS 2008;56:2076-2081

Obstructive Sleep Apnea: Brain Structural Changes and Neurocognitive Function before and after Treatment

Nicola Canessa[1,2,3,4*], Vincenza Castronovo[5*], Stefano F. Cappa[1,2,3,4], Mark S. Aloia[6], Sara Marelli[5], Andrea Falini[3,7], Federica Alemanno[1,3,4], and Luigi Ferini-Strambi[4,5]

Am J Respir Crit Care Med 2011;183:1419-1426

Reduced Brain Gray Matter Concentration in Patients With Obstructive Sleep Apnea Syndrome

Eun Yeon Joo, MD, PhD[1]; Woo Suk Tae, PhD[2]; Min Joo Lee, MS[1]; Jung Woo Kang, MD[1]; Hwan Seok Park, MD[1]; Jun Young Lee, MD[1]; Minah Suh, PhD[3]; Seung Bong Hong MD, PhD[1]

SLEEP 2010;33(2):235-241

Sleep, Stroke, and Cardiovascular Disease

Edited by

Antonio Culebras

Professor of Neurology, SUNY Upstate Medical University, and Consultant, The Sleep Center at Upstate University Hospital at Community General, Syracuse, NY, USA

Chapter 8

Pathogenesis of cerebral small-vessel disease in obstructive sleep apnea

Gustavo C. Román