THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA

- **Sandra Black, OC, O.Ont., MD, FRCPC, FRSC, Senior Scientist**

- **Mario Masellis, MSc, MD, PhD, FRCPC, Clinician Scientist & Associate Professor, Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto**

Alzheimer's and Vascular Dementia: what you need to know

Sandra E. Black, O.C., O.Ont., MD, FRCP(C),
Professor of Medicine, Neurology, Sunnybrook Health Science Centre, University of Toronto

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HEART & STROKE FOUNDATION Canadian Partnership for Stroke Recovery

TDRA Toronto Dementia Research Alliance

UNIVERSITY OF TORONTO

Disclosure of Potential Conflict of Interest

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CME Lecturer: Novartis, Eli Lilly, Medscape (Biogen)

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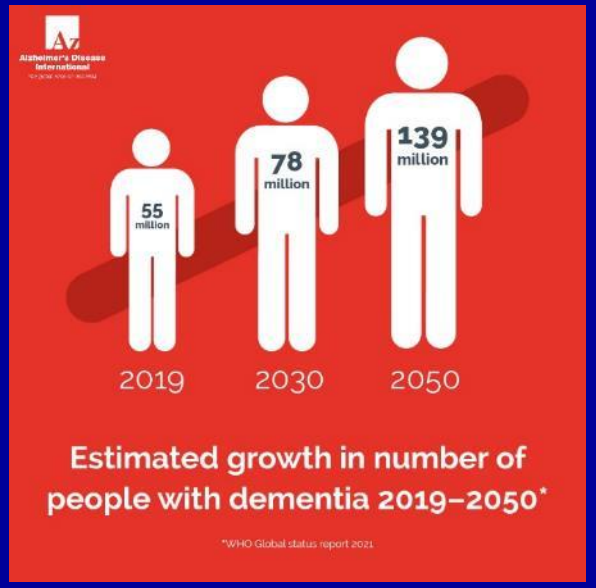
The Global Impact of Dementia



World Alzheimer Report 2021, Alzheimer's Disease International

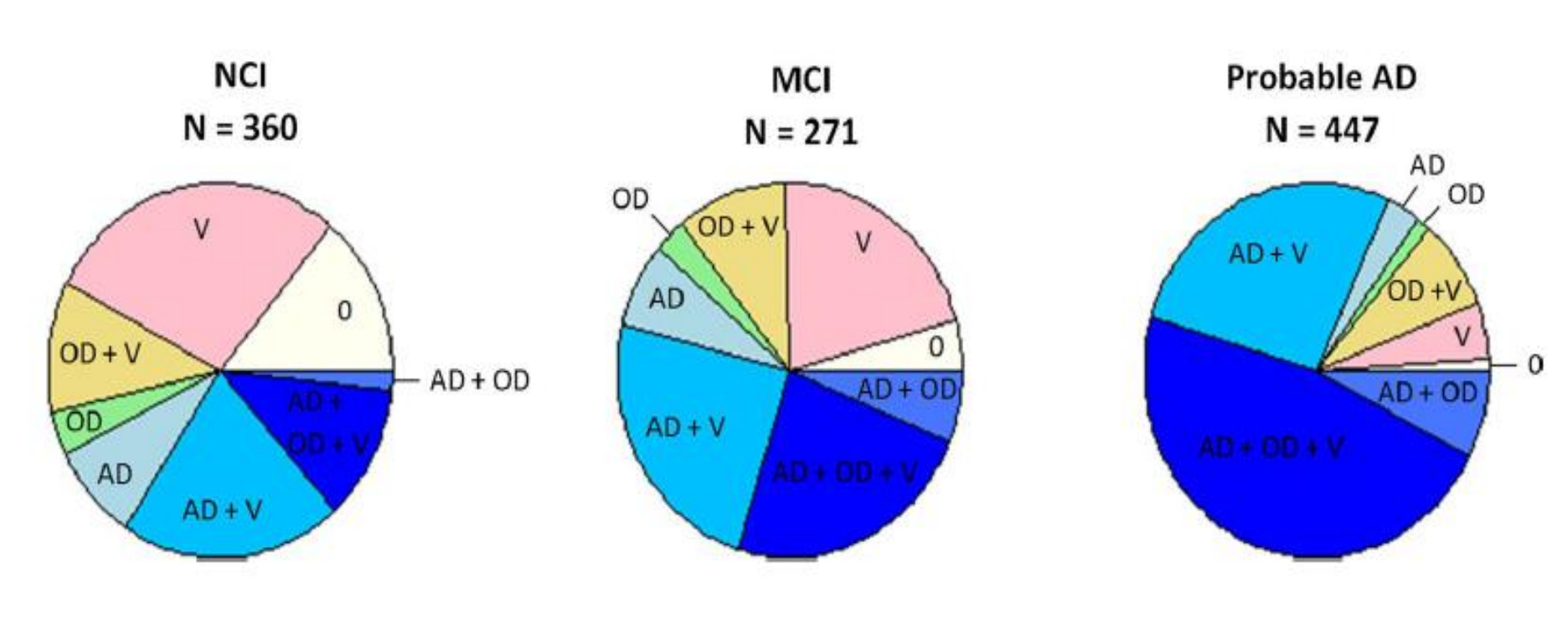
Learning Objectives

1) Review the clinical symptoms that occur in Alzheimer's Disease with case examples
2) Highlight emerging diagnostic criteria that incorporate brain imaging and blood tests, while also emphasizing the heterogeneity in AD
3) Briefly discuss rapid recent development of AD blood tests, that can allow early detection and complement brain imaging including brain Magnetic Resonance Imaging and PET scanning
4) Likewise describe criteria for Vascular Dementia related to focal stroke or small vessel disease

Biomarkers

- Molecular biology advances enable detection of genetic risk markers and biochemical abnormalities at birth and throughout life that may facilitate disease modifying therapies.
- Biomarker-driven approaches, advancing quickly in cancer and cardiovascular disorders, are just emerging in dementia.
- Can be useful for diagnosis, identifying therapeutic targets, monitoring patterns of progression and response to therapies---concept of theragnostics.
- *Challenge in our field: heterogeneity with complex etiologies involving multiple misfolded proteins combined with vascular pathologies and innate immune reactions*

Mixed pathologies are common in the Alzheimer Disease Syndrome



From the Religious Order Study/Memory Aging Program (Chicago)

Kapasi A. *Acta Neuropath.*, 2017

Clinical Stages of AD

Preclinical/Pre Symptomatic

Prodromal (MCI)

Dementia – mild, moderate, severe

Clinical means: assessment of cognition, mood, behaviour and function

AD: Clinical Manifestations

- Short term memory loss
- Word finding difficulty
- Way finding difficulty
- Diminished insight

Diagnosis of Probable Alzheimer's Disease: old and new criteria

- Dementia clinically and by appropriate testing
- Deficits in two or more areas of cognition
- Progressive loss of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40-90
- Absence of other causes

(McKhann et al 1984)

Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

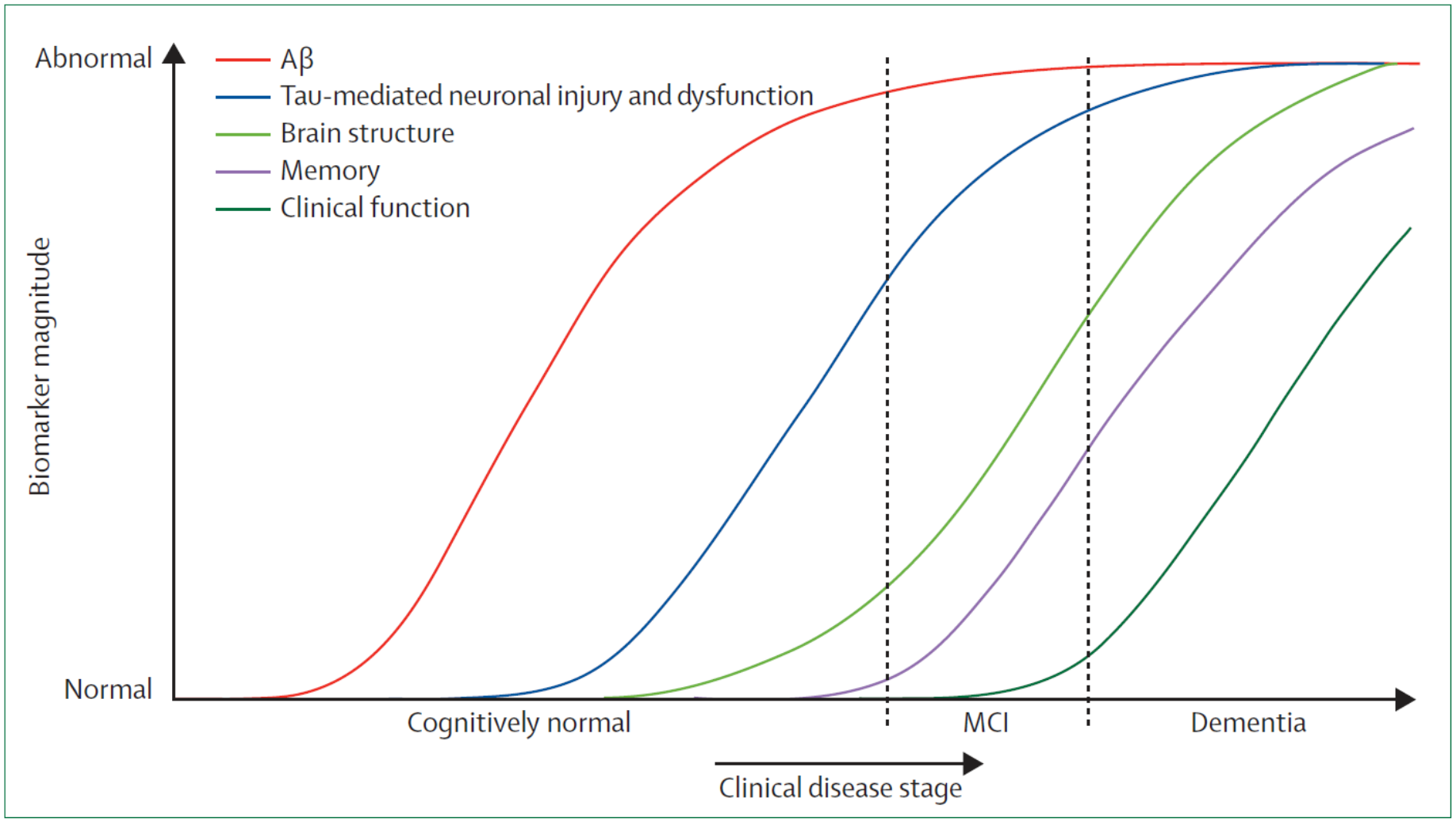
Jack CR et al, Alz & Dem, 2018

Amyloid, Tau, Neurodegeneraion: syndromal cognitive staging combined with biomarkers

		Cognitive stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	$A^- T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+ T^-(N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^+ (N)^-$ $A^+ T^+(N)^+$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^- (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^- T^+(N)^-$ $A^- T^-(N)^+$ $A^-T^+(N)^+$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia

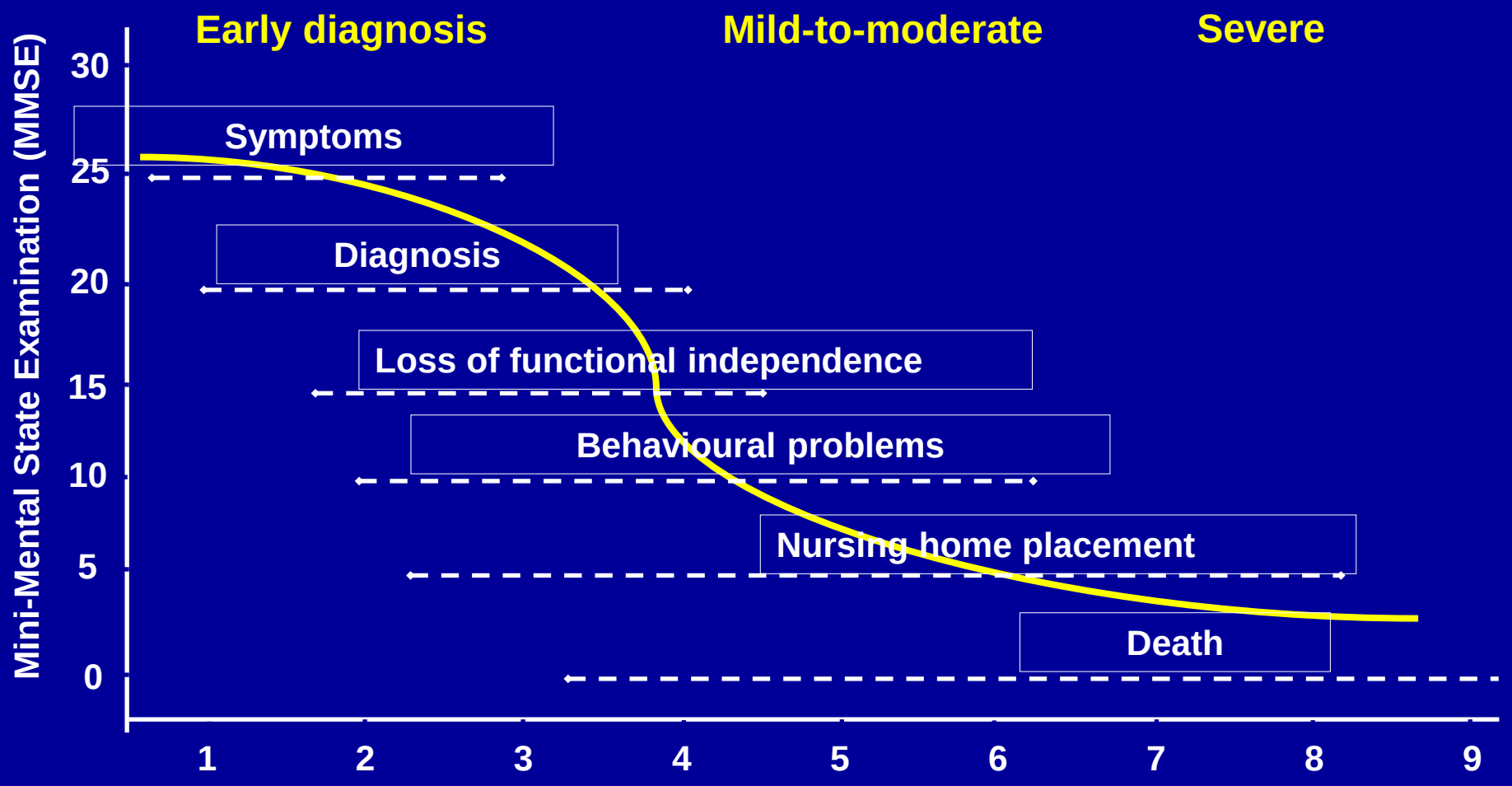
Jack, CR *Alzheimer& Dement*, 2018

Model of dynamic biomarkers of the Alzheimer's disease pathological cascade



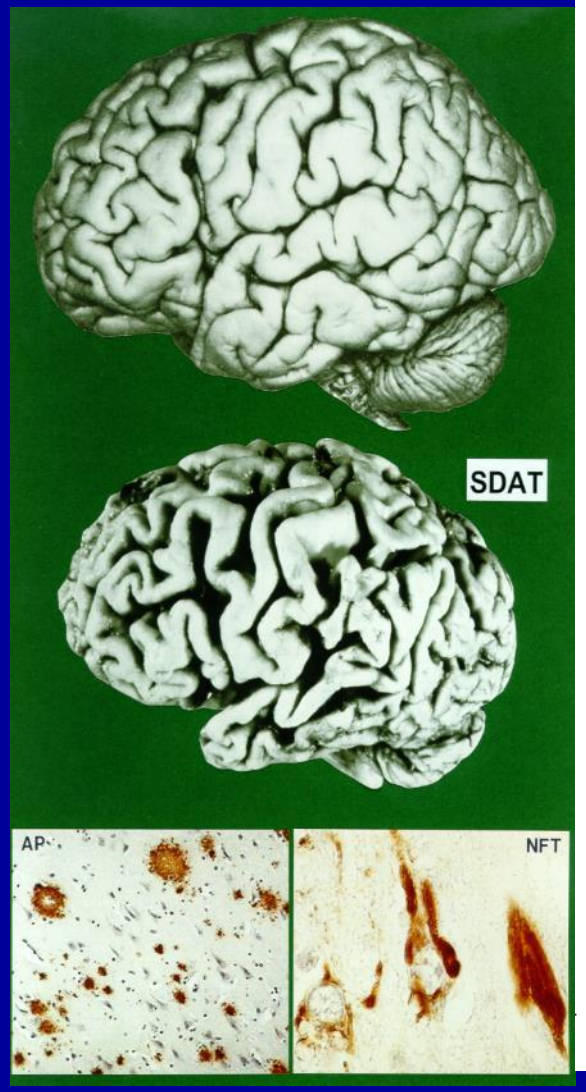
Jack et al *Lancet Neurol* 2013

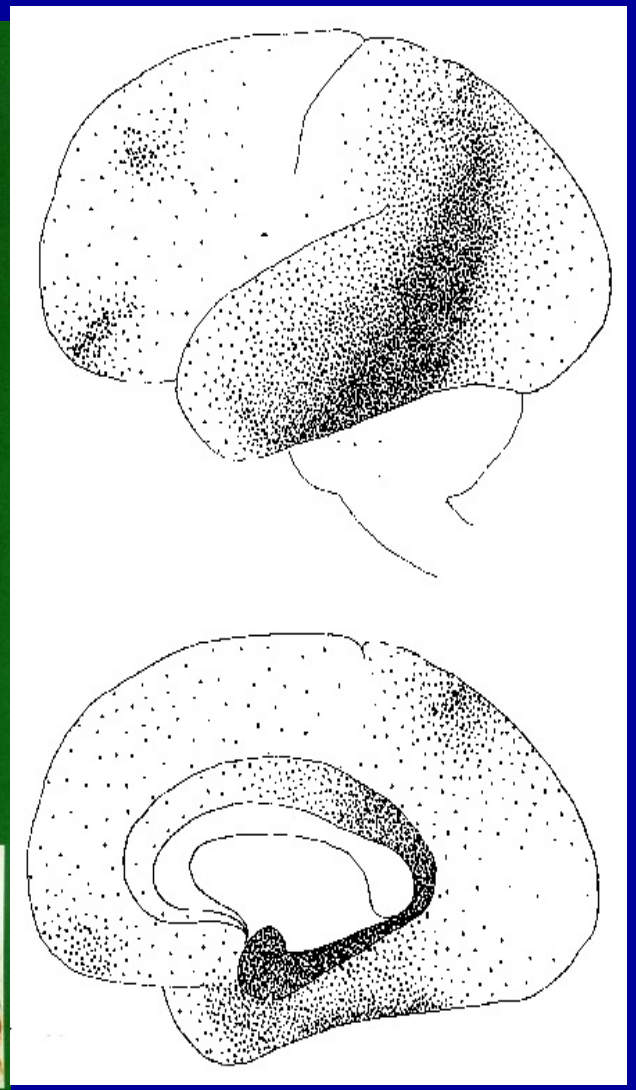
Natural history of Alzheimer's disease



Reproduced with permission from Feldman and Gracon, 1996

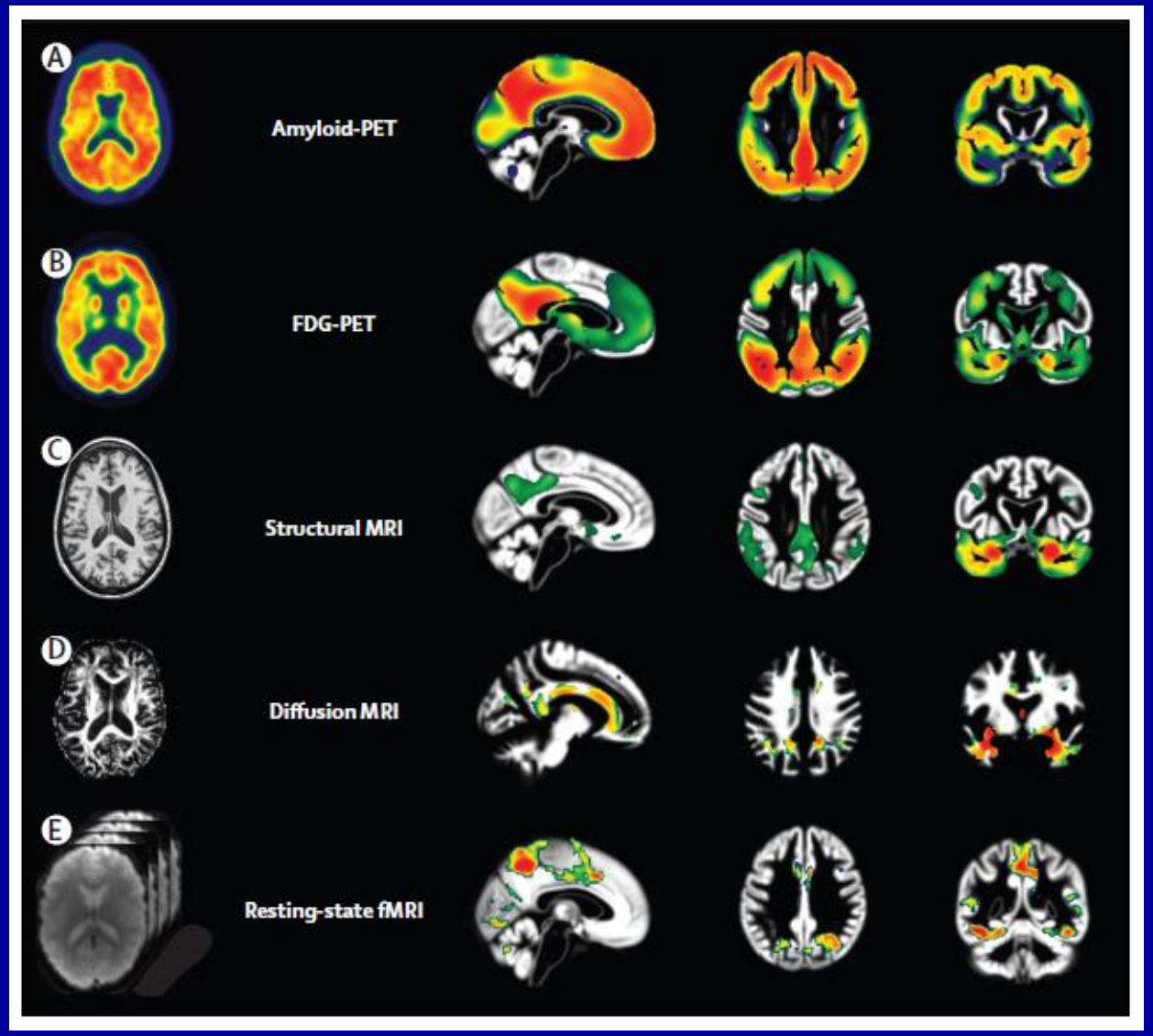
Imaging Alzheimer's Disease topography and the hallmark misfolded proteins





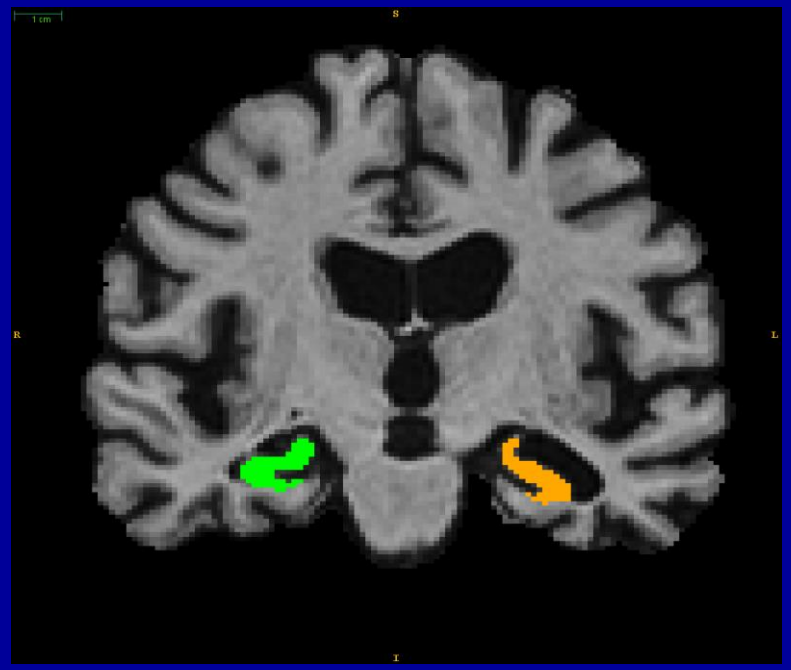
- Neurofibrillary Tangles
  - Insoluble aggregates of tau deposit in neurons interfering with cellular functions
- Amyloid-β Plaques
  - Toxic fragments from cleavage of Amyloid Precursor Protein forms fibrillar deposits in vessels and extracellularly

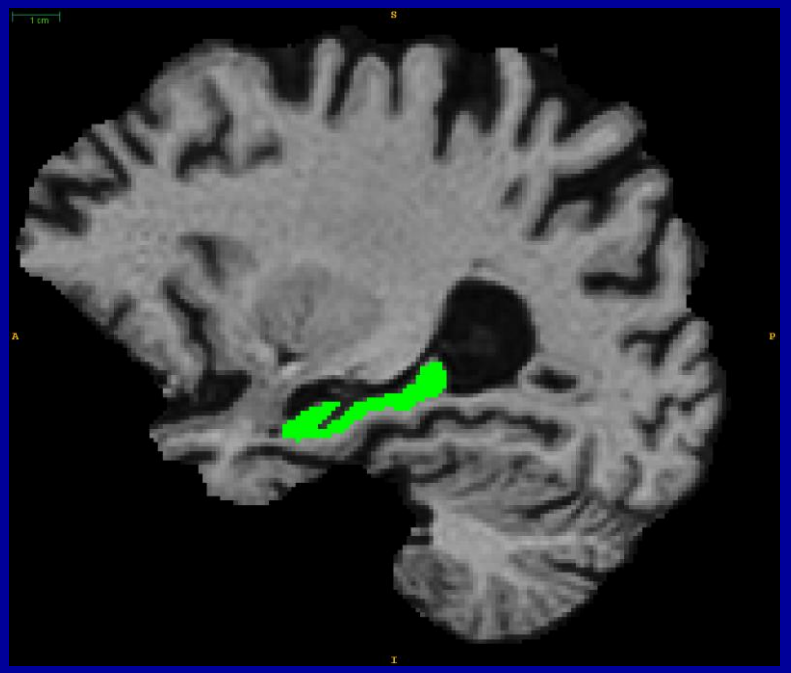
Multimodal signature of Alzheimer's disease

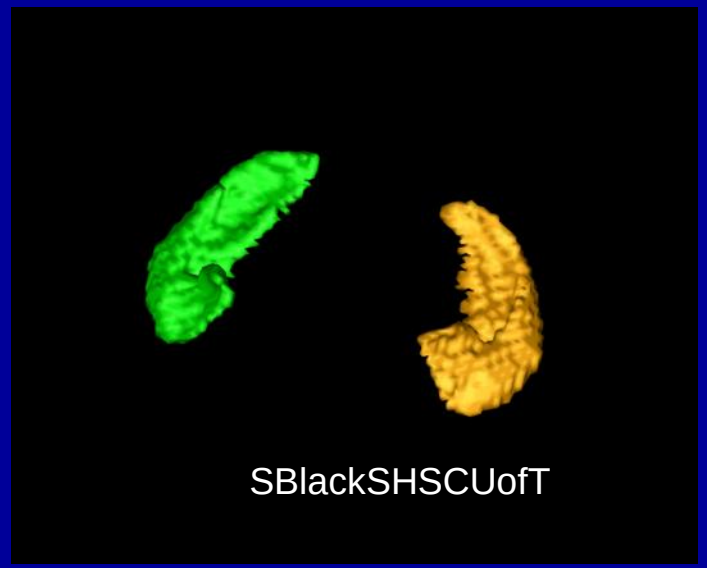


Teipel S. *Lancet Neurol*, 2015

Fully Automatic Hippocampal Segmentation



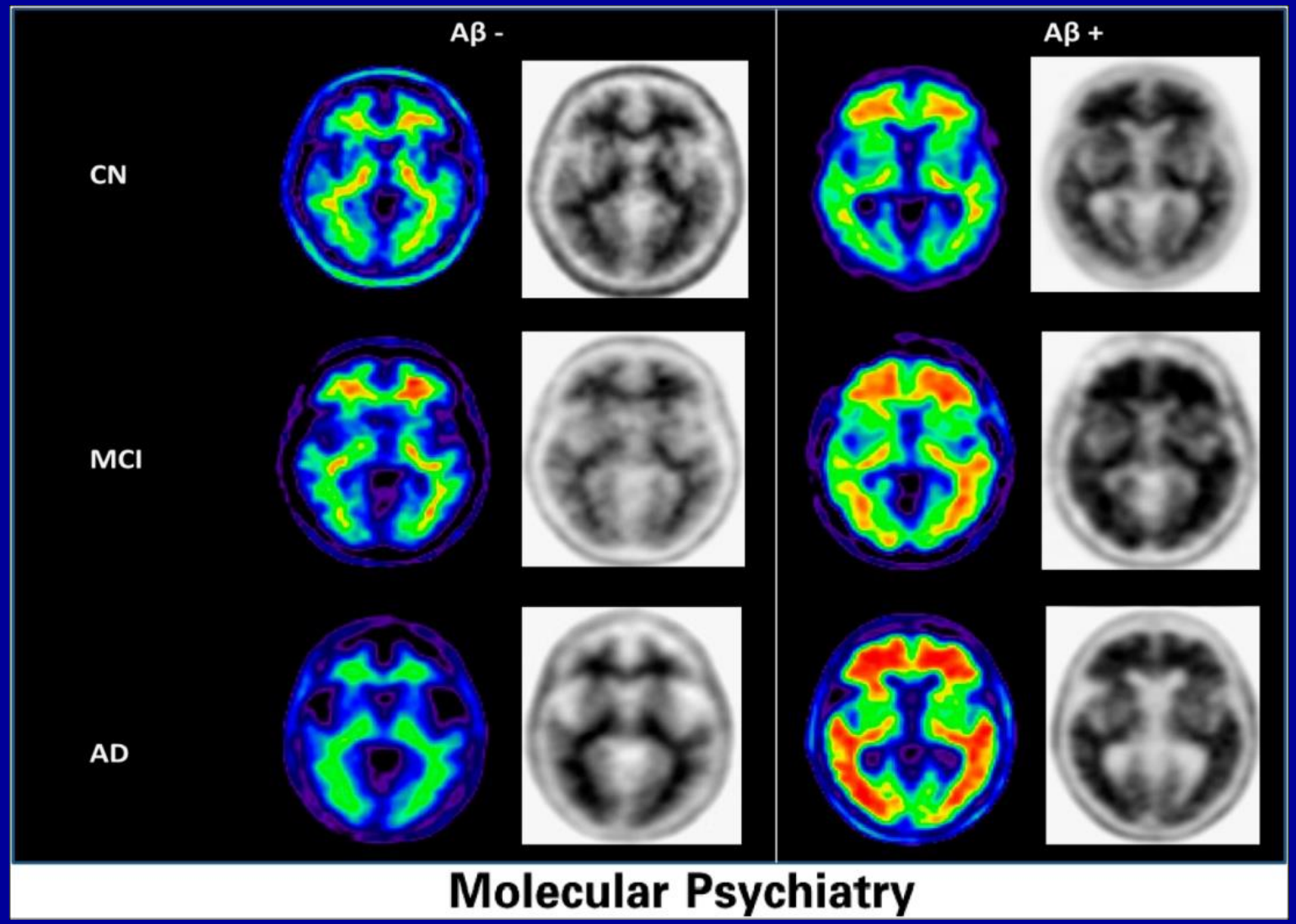




Images displayed in ITK-SNAP

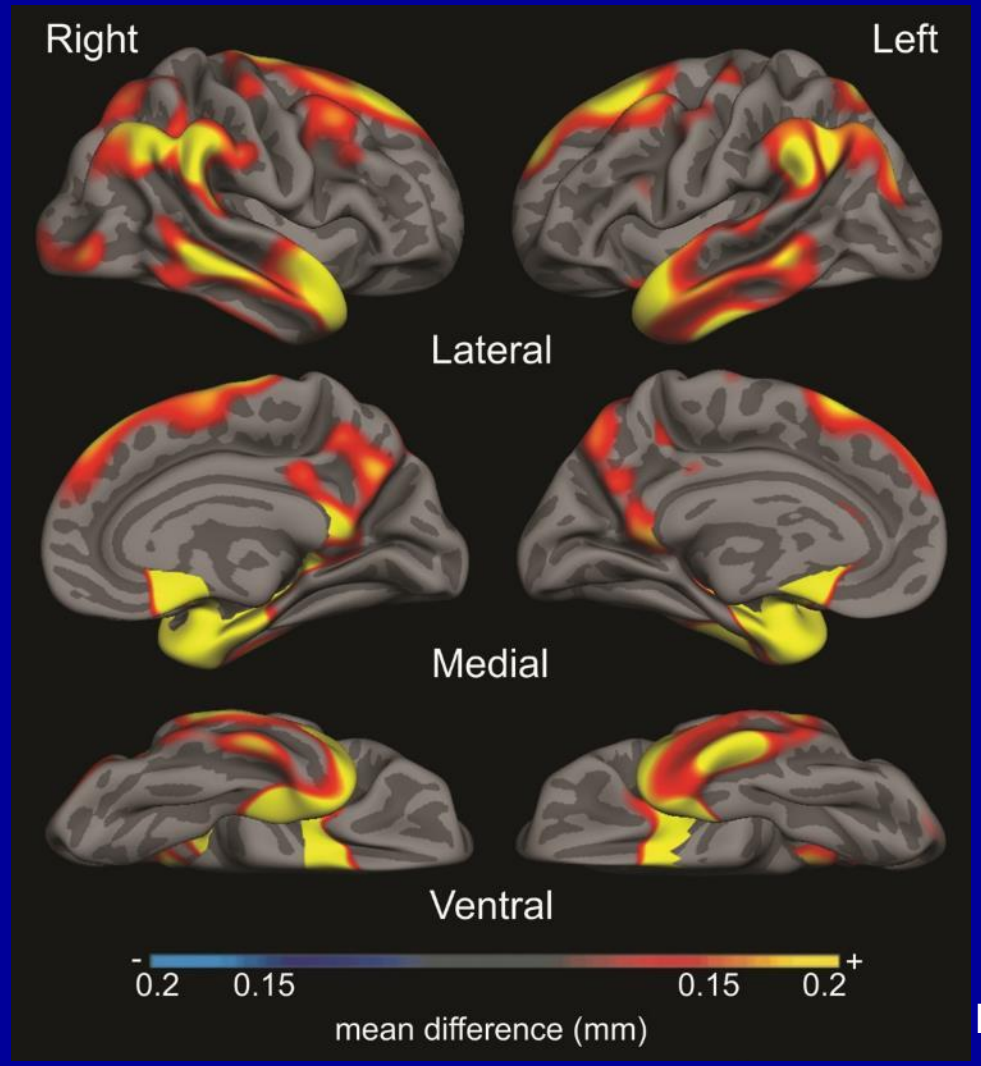
Nestor et al Neuroimage 2012

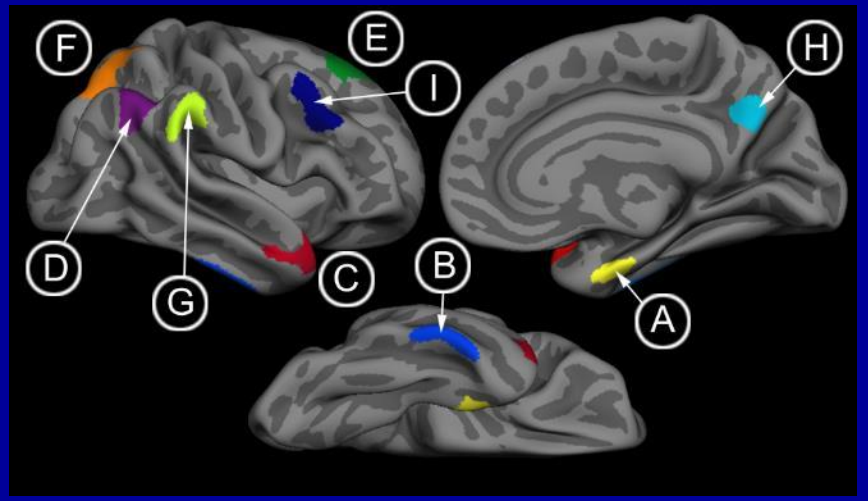
Florbetapir (amyvid) amyloid PET



Doraiswamy Molec Psych 2014

AD cortical signature:
Cortical thinning compared to older normals

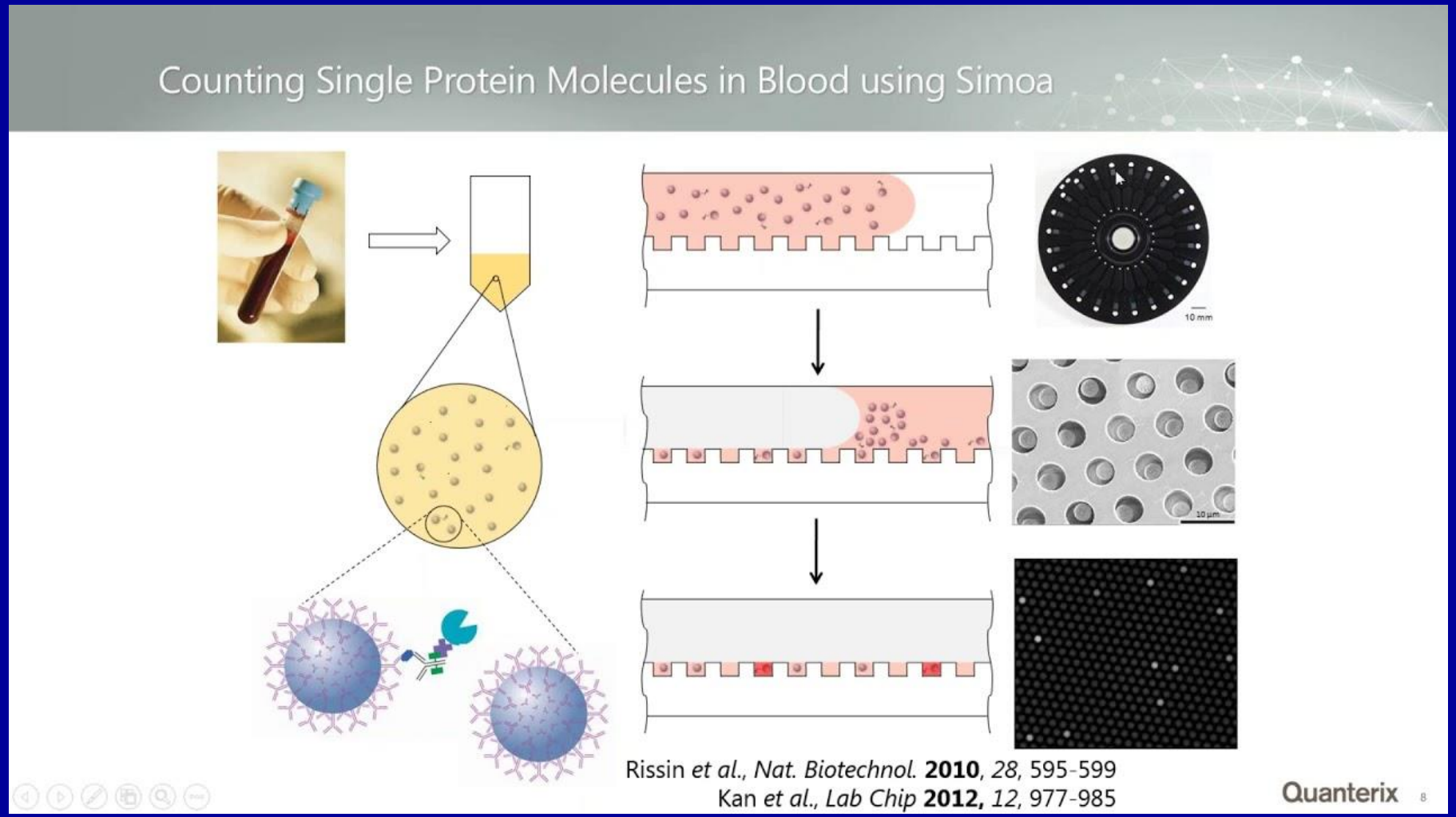




115 NC (CDR=0) vs 29 AD (CDR=1)

Dickerson Cerebral Cortex 2009; Neurol 2009

SIMOA



I billionth of a microgram (1/ I,000,000,000)

Current advances in plasma and CSF biomarkers in Alzheimer's disease

KEY POINTS

- Advances for CSF Alzheimer's disease biomarkers include fully automated assays, certified reference materials for Aβ42 and a unified protocol for preanalytical handing of samples.
- Alzheimer's disease biomarkers, including Aβ, T-tau, P-tau and NfL can now be measured reliably in both CSF and blood.
- Among plasma measures, P-tau is especially promising, with potential utility in both clinical practice and in clinical trials.

Leuzy A. *Curr Opin Neurol.*, 2021

Phospho-tau Isoforms emerge

First in csf and then in plasma

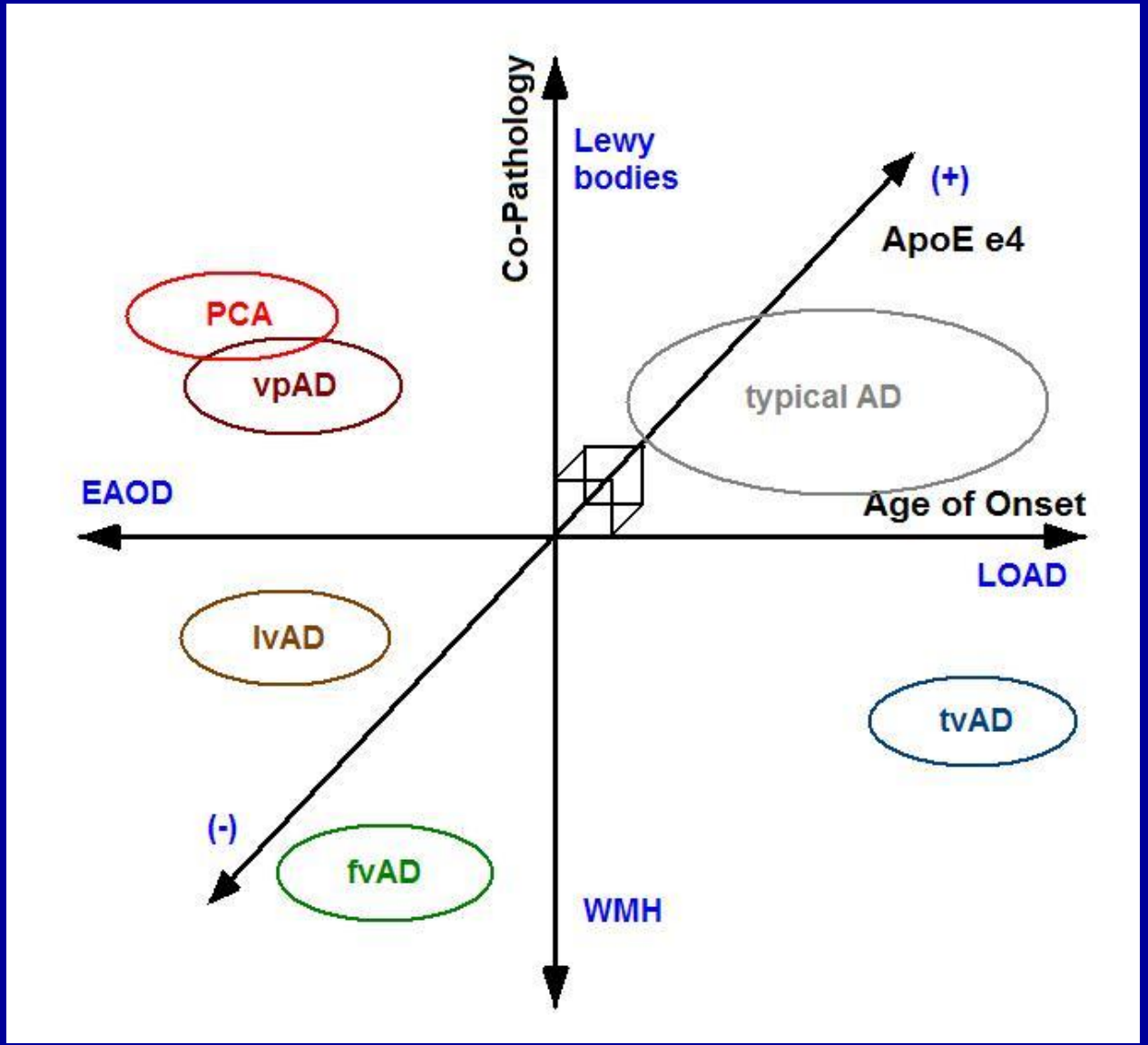
SIMOA: Quanterix chip (ptau 181, NFL, GFAP)

With Mass Spect can also measure amyloid Abeta plasma

C_2N Precivity AD

Case Examples

Axis of pathological heterogeneity



Lam Alz Res Therapy 2013

69 yo married insurance broker

One year history of forgetfulness. Needs lists, poor recall of names, streets and what he has just read. Difficulty with street directions. Still independent in ADL.

PMH: Ca prostate - radical prostatectomy, retinal surgery.

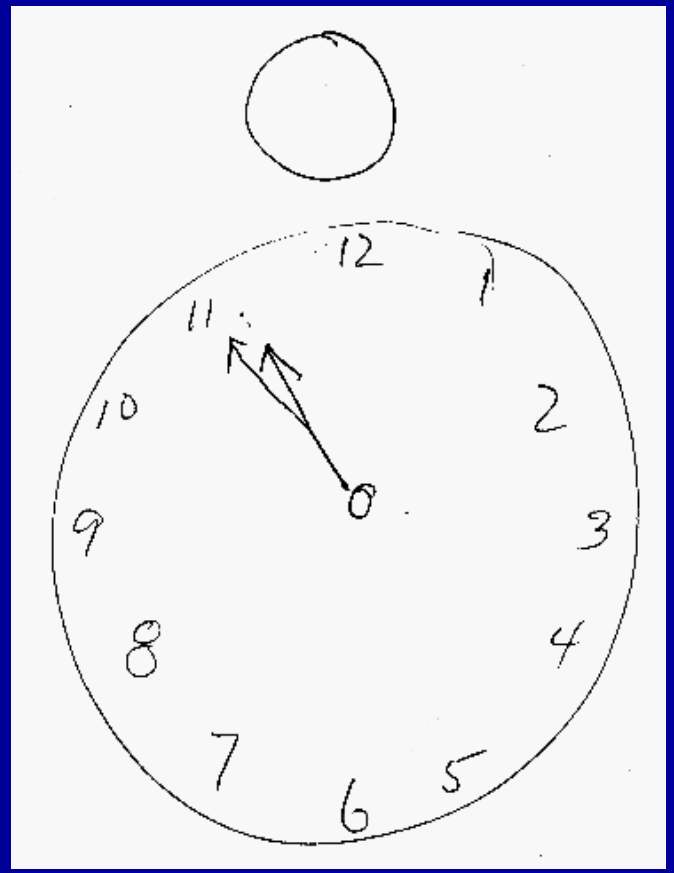
Quit smoking 25 years ago.

Meds: None.

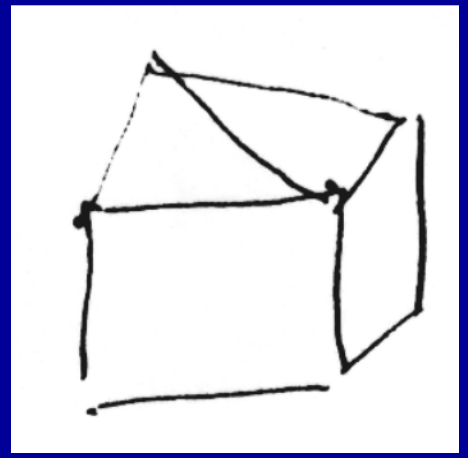
FH: Father had memory loss in his 80s.

Exam: Neurological + general exam normal

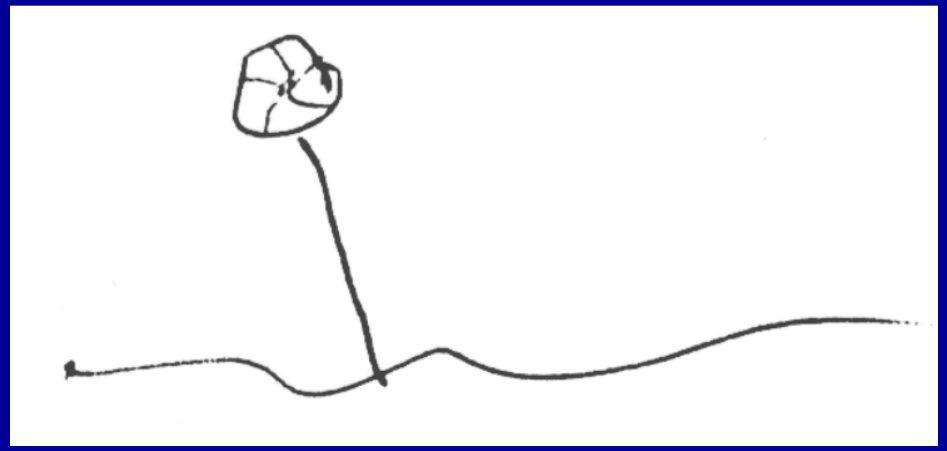
Free Drawn Clock



Drawings to Command



Cube

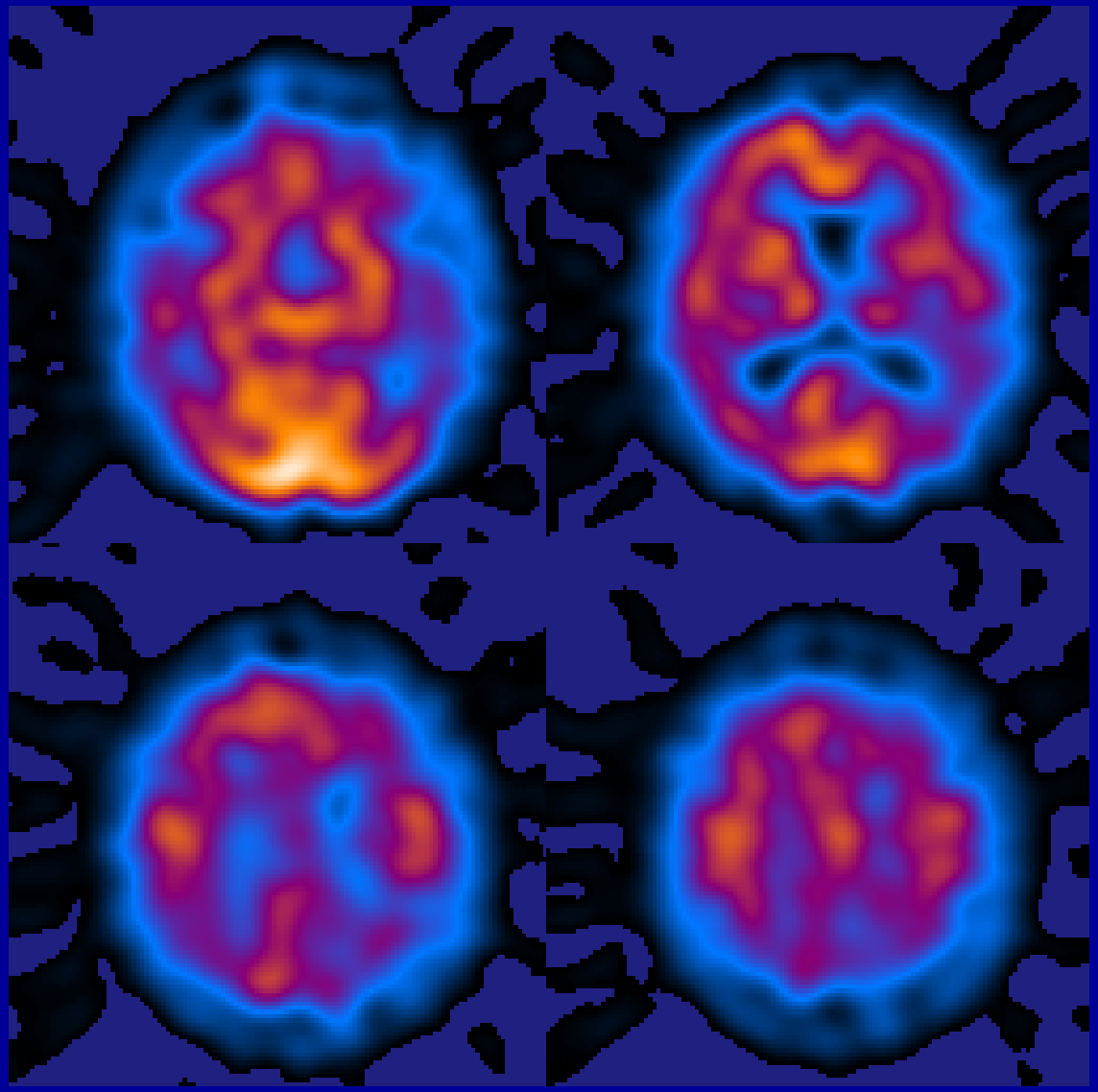


Daisy

50 y.o. married electrician

- Presents in 1993 with progressive language loss over last 4-5 years (anomia, comprehension difficulty).
- Med. Hx – treated for depression
- Family Hx - aunt has dementia
- Patient unable to work but still active and independent, (excellent homemaker, simple errands, does volunteer work).

SPECT at first assessment



First Assessment

- Mental Status: impaired language functioning, semantic/verbal fluency, nonverbal learning/recall, and mental flexibility. MMSE = 6/30, DRS = 80/144
- MRI – No abnormalities
- SPECT – global decreased perfusion more pronounced in L frontal and temporal regions.
- Neurological exam - Normal

Course over next few years

- Continuous decline in speech (non-fluent aphasia) and comprehension (MMSE = 1/30).
- MRI: perisylvian atrophy L > R
- Remained functional in activities of daily living (DAD = 70%)

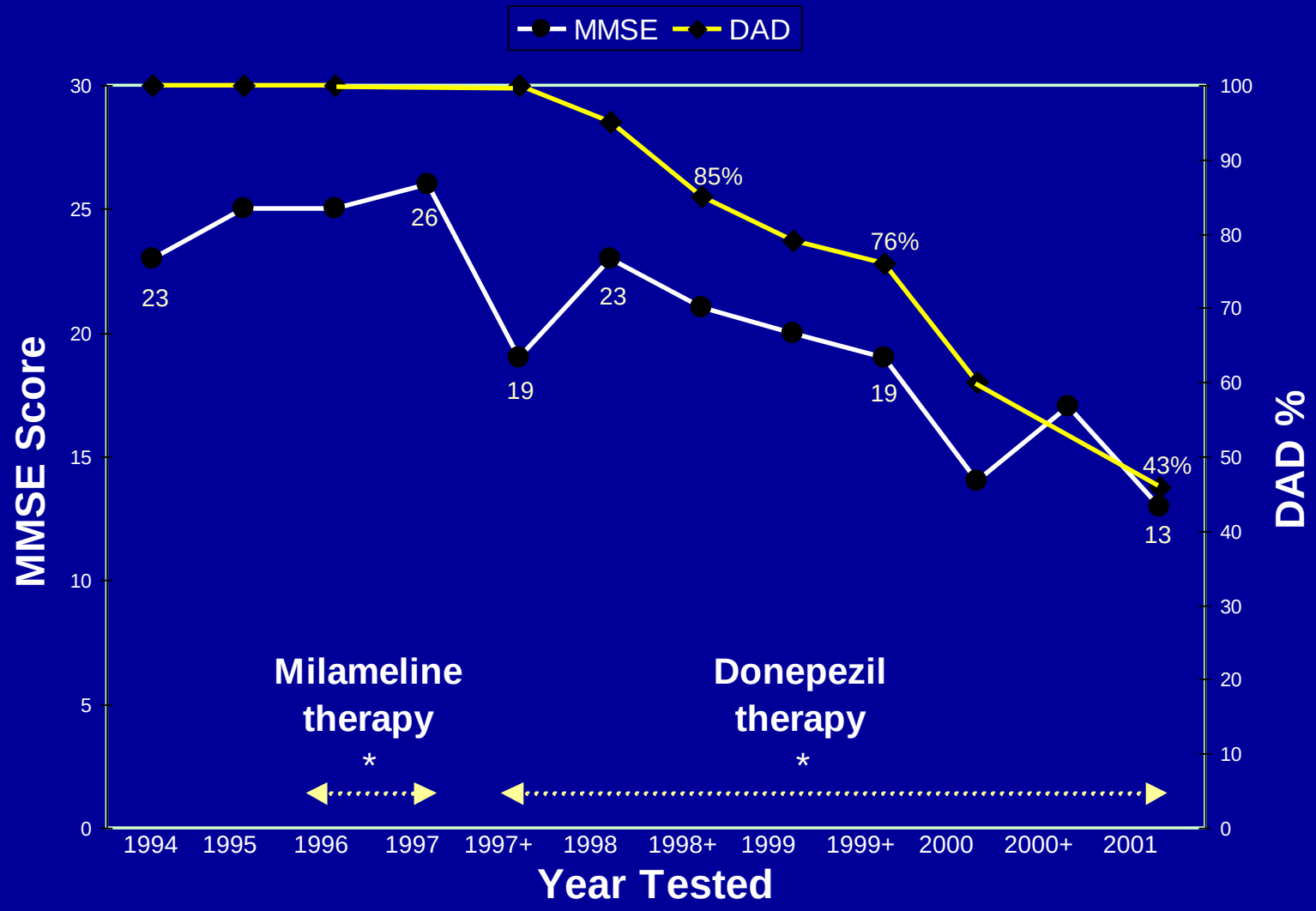
Subsequent decline

By 1997:

- No speech output or comprehension (globally aphasic)
- Rapid deterioration in self-care skills (Bathing, toileting)
- Tonic-clonic seizures, controlled on dilantin
- Changes in behavior – agitated, aggressive
- Needed 24-hour care; placed in nursing home.

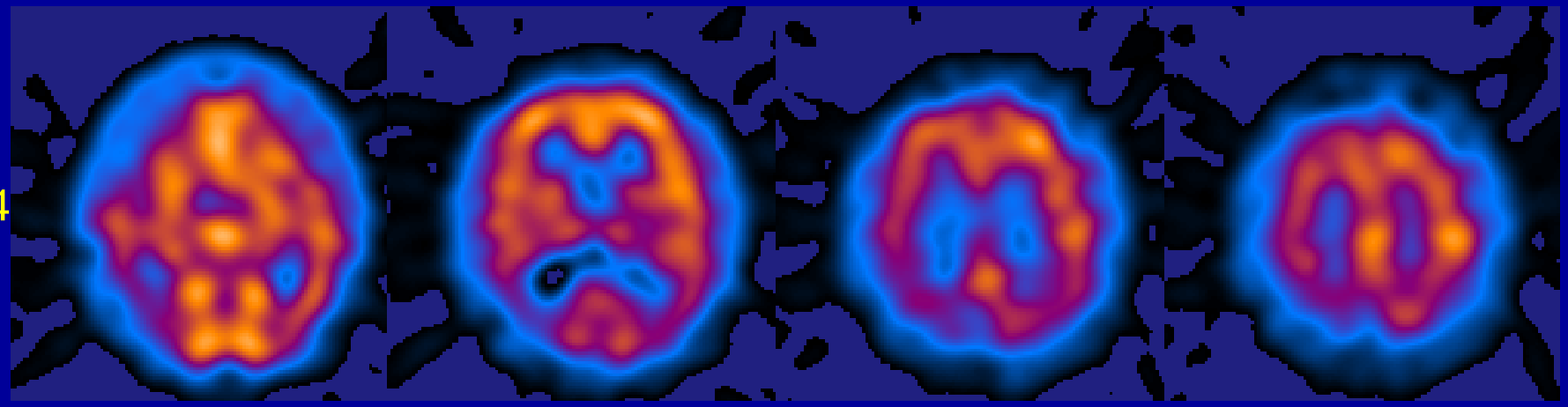
Died in 2001: autopsy revealed classical AD pathology

Test Performance Over Time

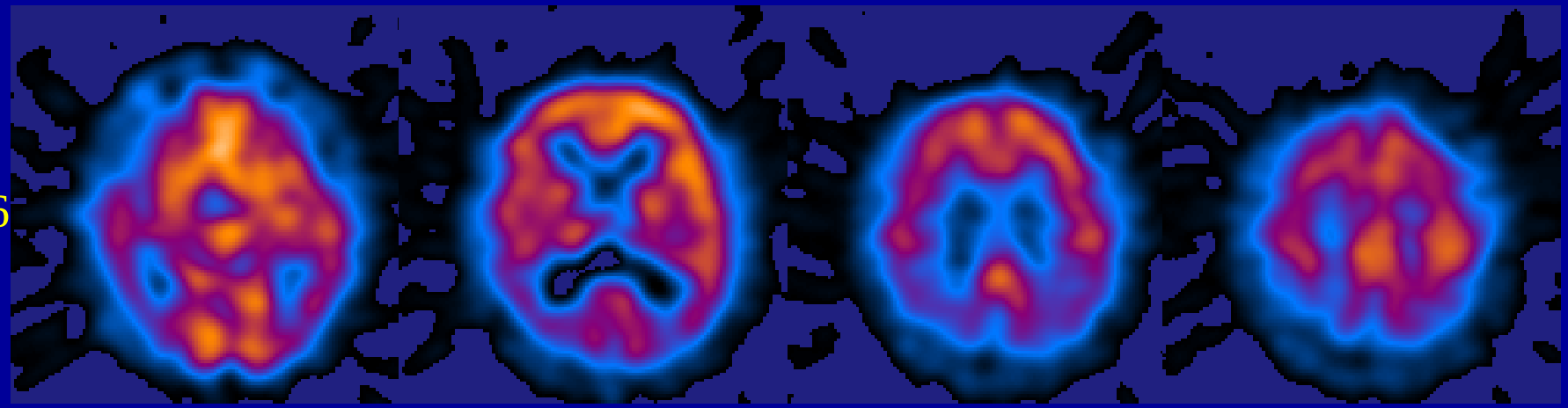


SPECT over Two Years

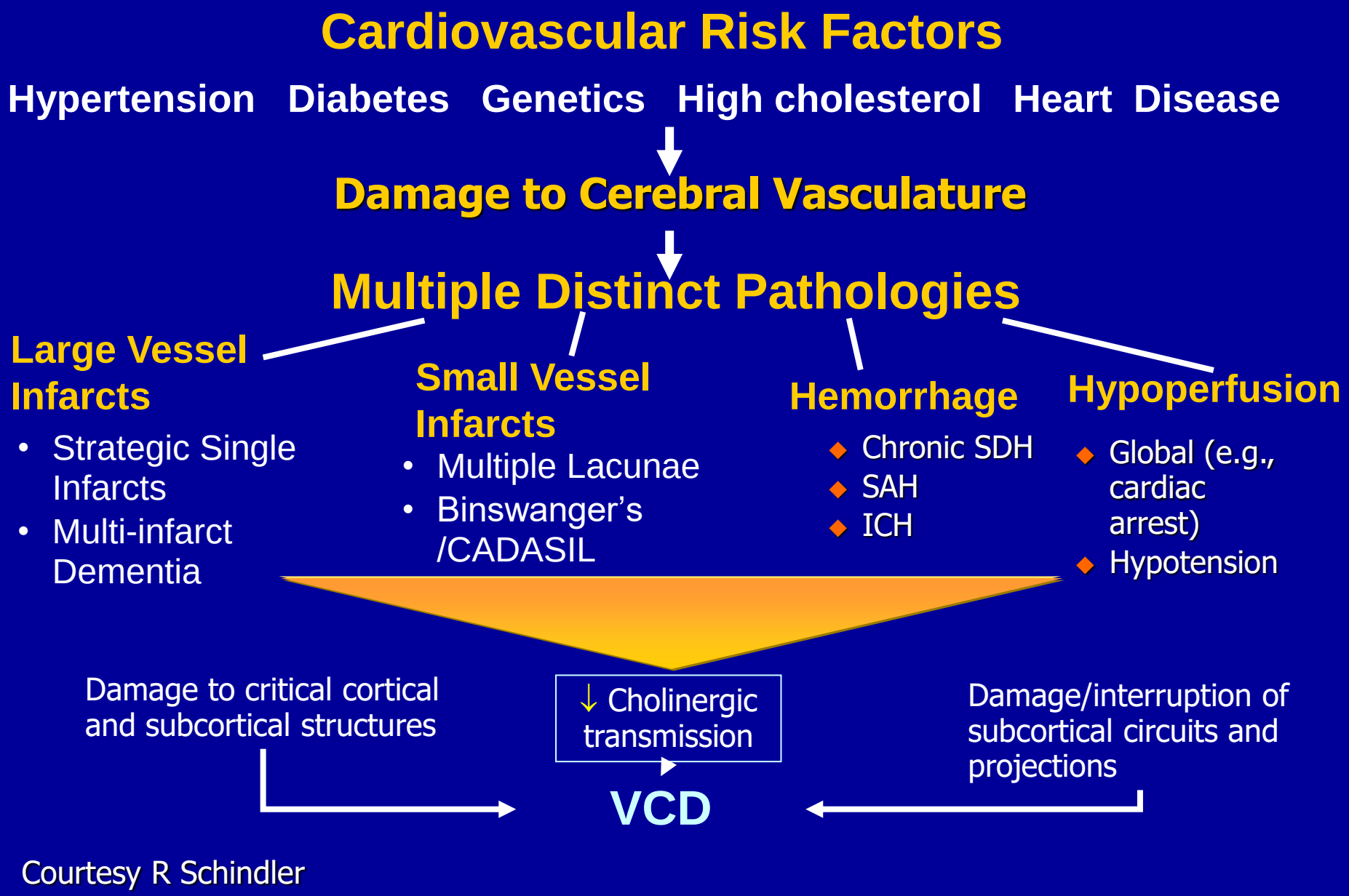
1994



1996



Vascular Cognitive Disorders



Courtesy R Schindler

Vascular Dementia

- “Multi-infarct Dementia” arises from multiple (often cortical) cerebral infarctions
- “Strategic placed infarcts” can result in dementia arising from discrete lesions (bilateral thalamic or angular gyrus)
- Multiple subcortical lacunar infarcts occur following occlusion of penetrating arteries

Diagnosis of Probable Vascular Dementia NINDS – AIREN Criteria

1. ***Dementia –*** memory loss plus 2 other areas of cognitive dysfunction sufficient to interfere with ADL (not due to physical effects of stroke alone)
2. ***Cerebrovascular Disease***

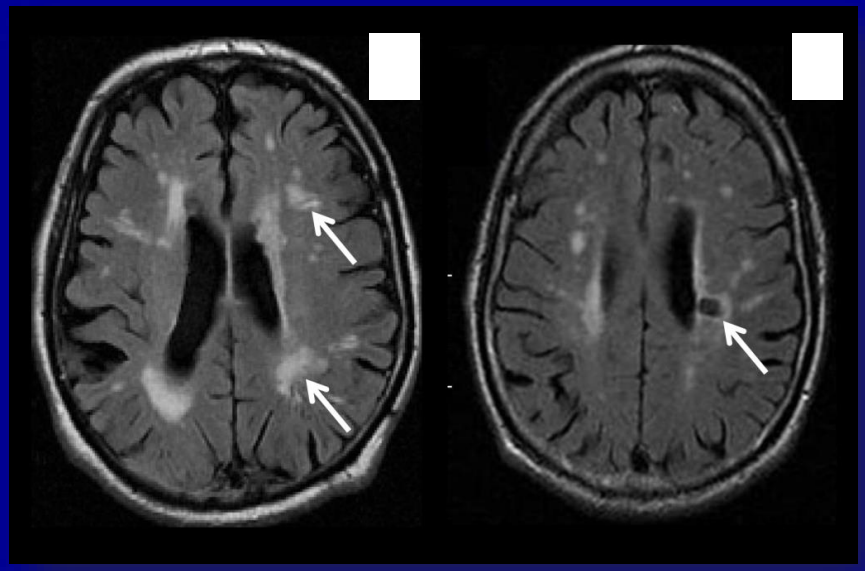
   -Neuroimaging (Cortical and/or subcortical infarcts and/or extensive periventricular white matter disease)

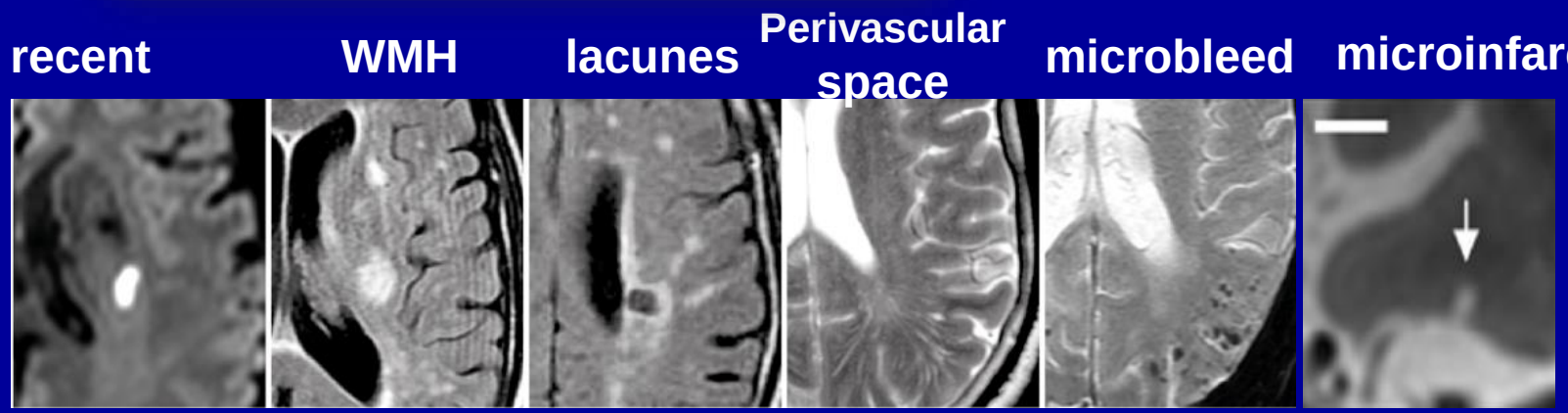
   -Focal signs
3. ***Temporal relationship*** between the above

   -onset within 3 months of a recognized stroke

   - abrupt or stepwise deterioration (Roman et al 1993)

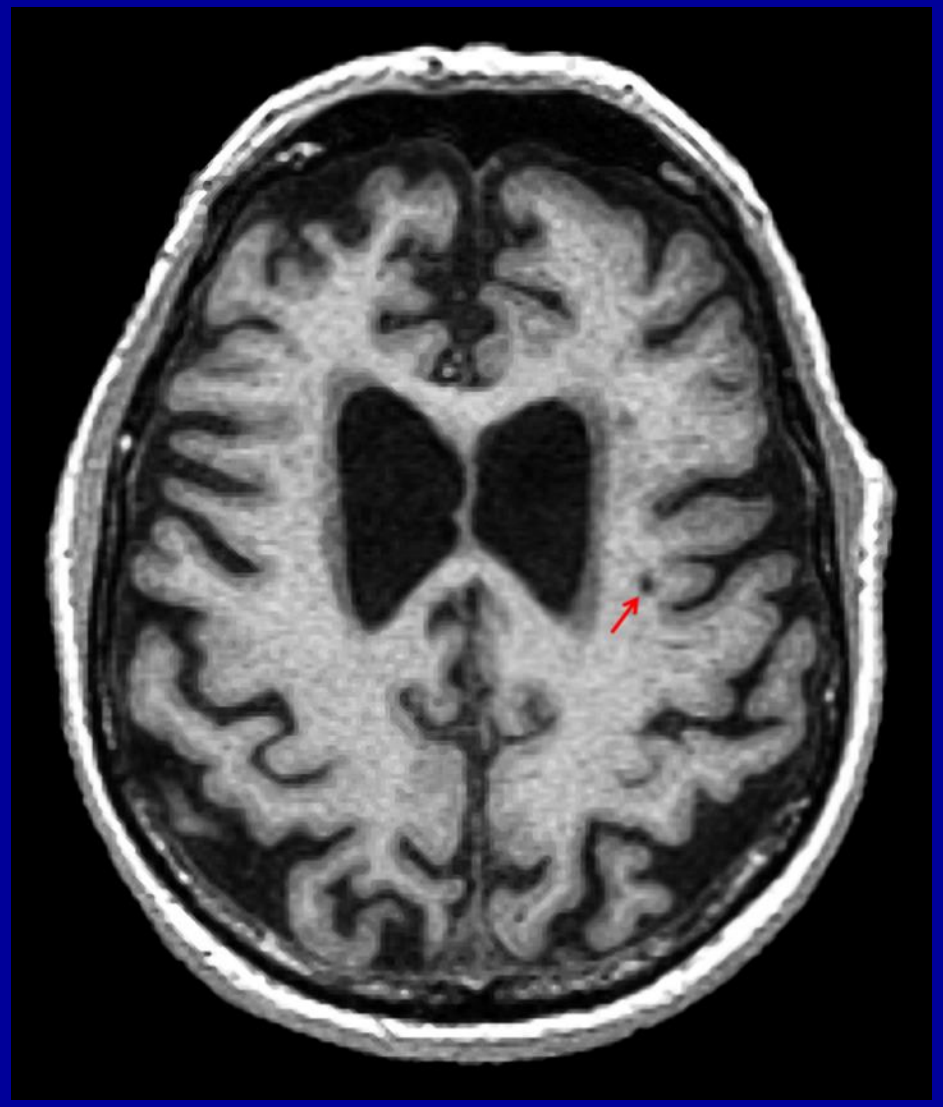
Multiple Faces of Small Vessel Disease





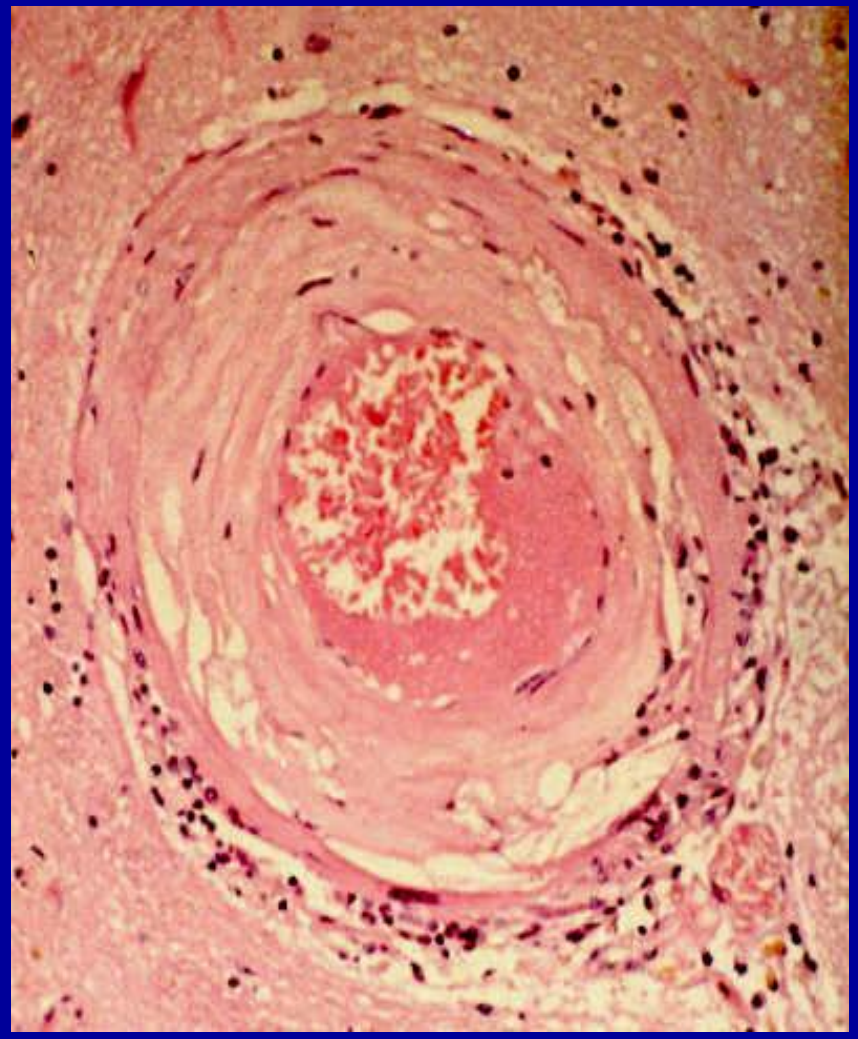
Wardlaw, *Lancet Neurol,* 2013

Incidental silent lacune found in an 85 year old man with probable AD



Small Vessel Disease

- Obliteration and occlusion
- Tortuosity, coiling
- Increased resistance
- Decreased autoregulation
- Endothelial changes
- BBB leakage
- Perivascular changes



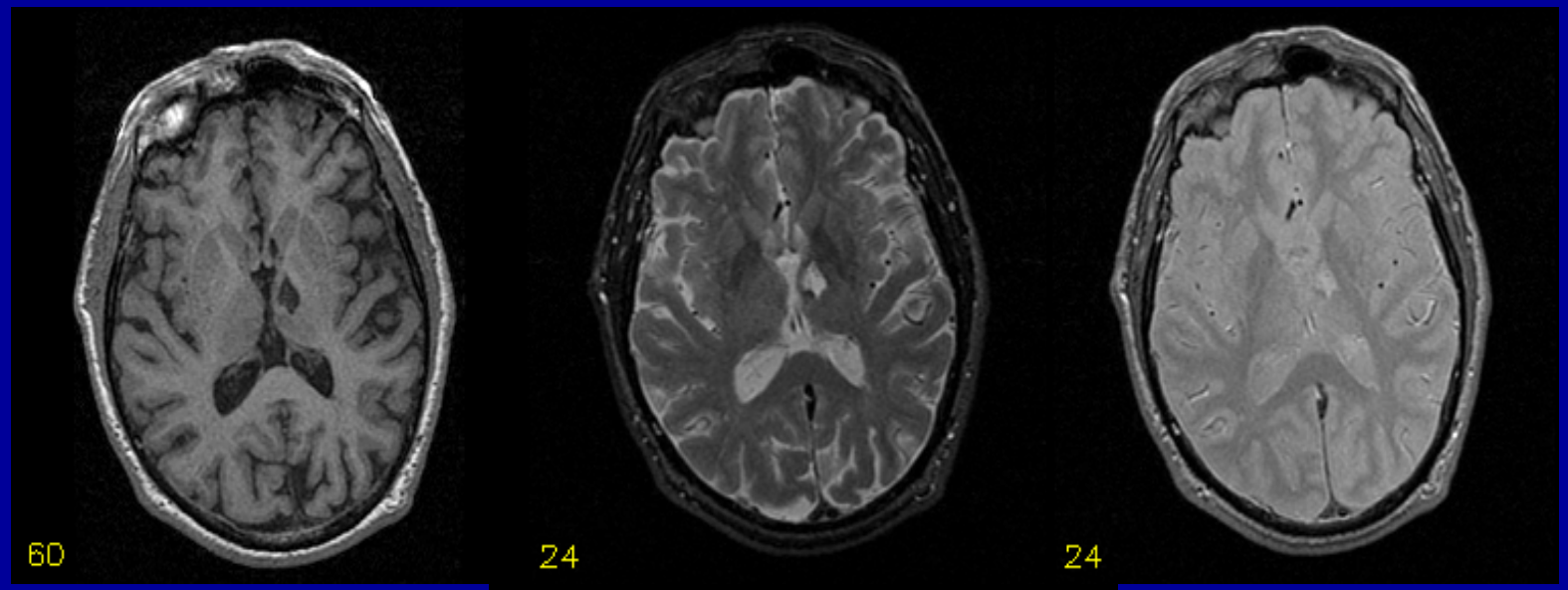
Silent Lacunes: Prevalence

- 3 mm diameter lesions (hypointense on T1, hyperintense on T2) potentially relevant even if “silent”
- Baseline MRI shows silent lacunes in 28% of seniors (3660 > 65, mean age 75, in Cardiovascular Health Survey) ie 10X as prevalent as overt stroke
  Longstreth 1998
- Frequency depends on age --12% seen in Framingham mean age 62 DeCarli Neurobiol Aging 2005
- In those with no baseline infarcts, 18 % showed them on rescan 5 years later Longstreth 2002

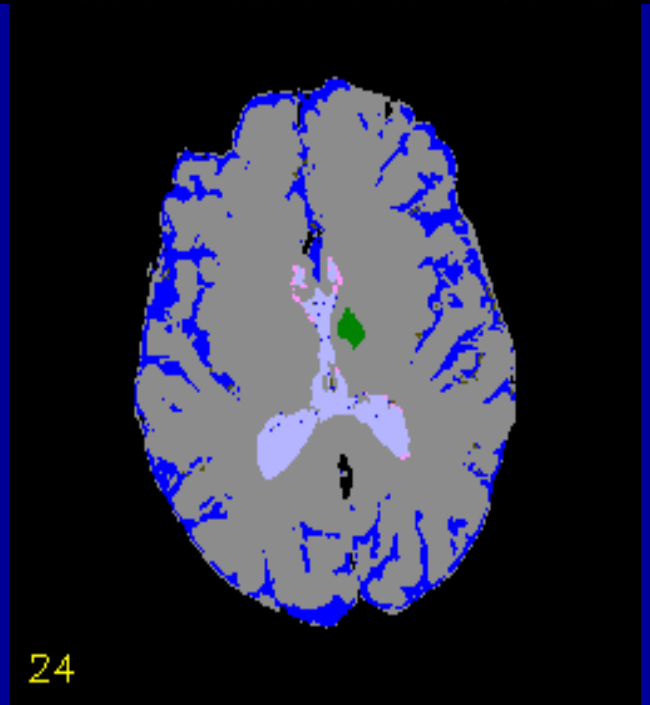
Case Example

- 76 year old man presents with sudden onset of a confusional state which improves over a day or two, but leaves him with persisting word-finding difficulty and short-term memory loss

Strategic Infarct Dementia



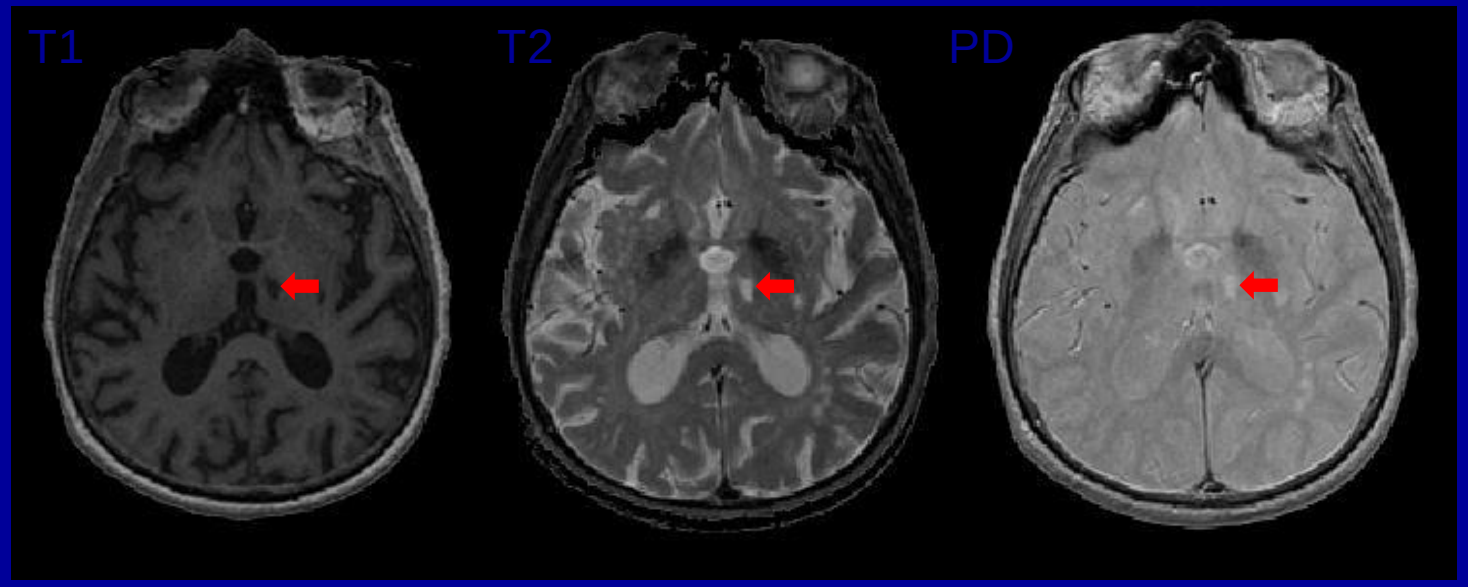
72 yr old man presented with sudden onset confusion

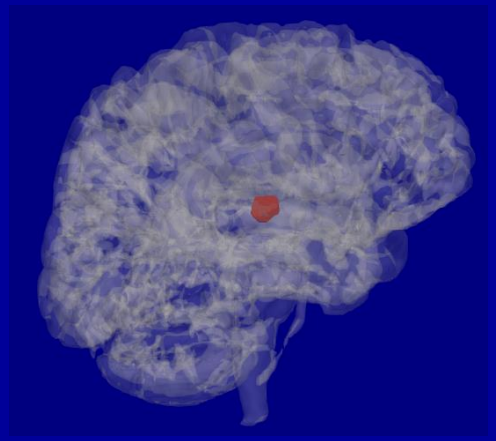


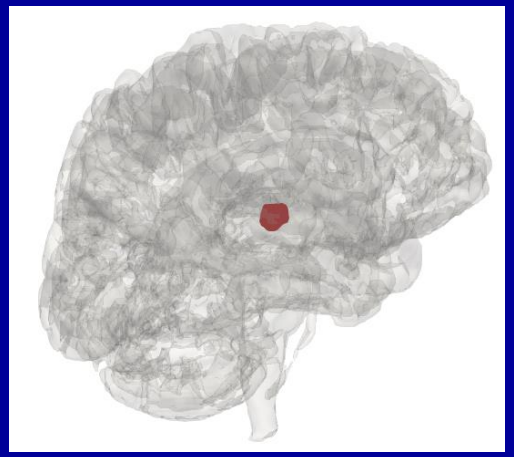
Short term Memory Loss, anomia and executive dysfunction persisted

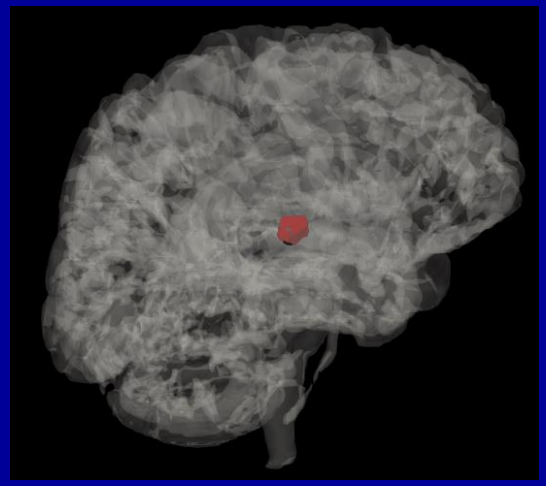
Courtesy of RH Swartz

A Strategic small lesion can have big cognitive impact



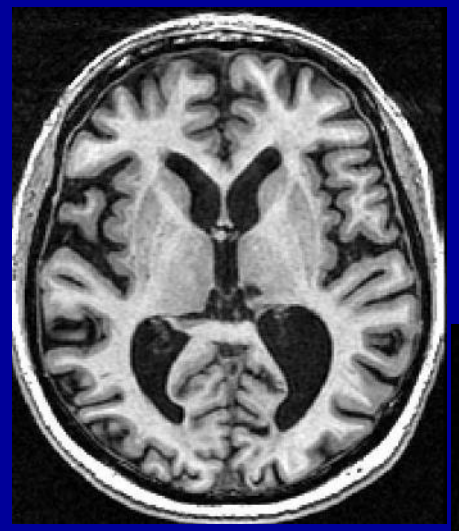




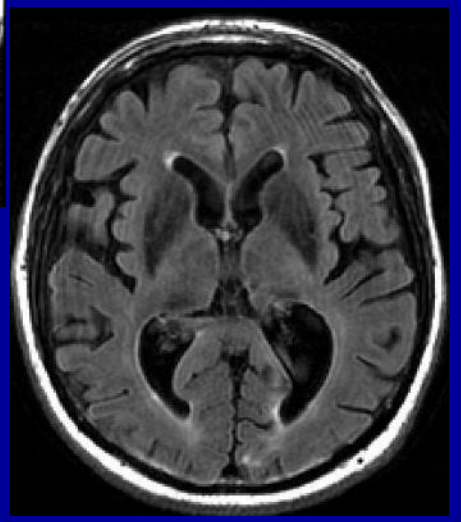


Courtesy of Melissa Holmes

Thalamic infarcts --a significant and under recognized contributor to cognitive impairment in elderly

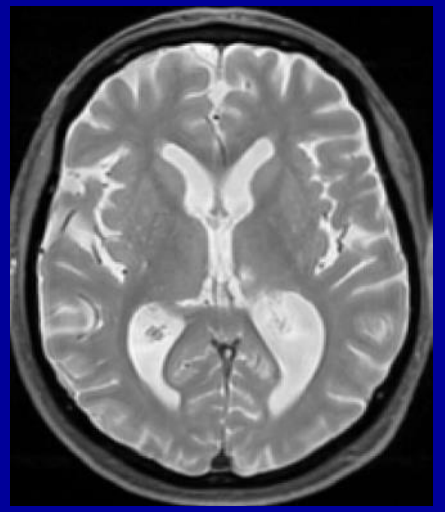


T1

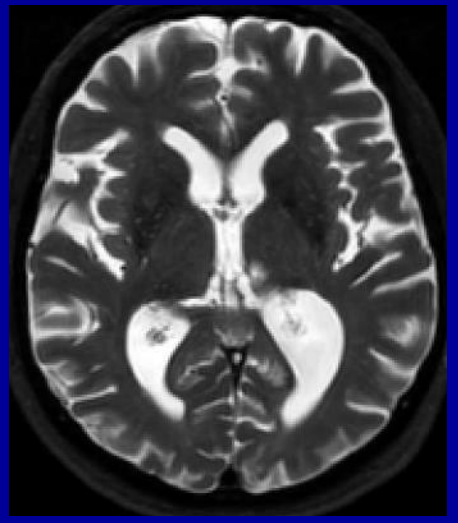


FLAIR

FLAIR can fail to detect thalamic and basal ganglia lesions



PD



T2

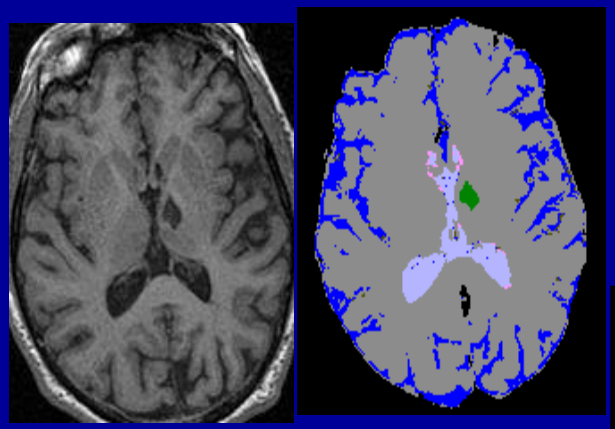
Antero medial thalamic hyperintensities ***>55mm^3*** *result in symptomatic decline; while smaller lesions go unrecognized*

Swartz JNNP 2006

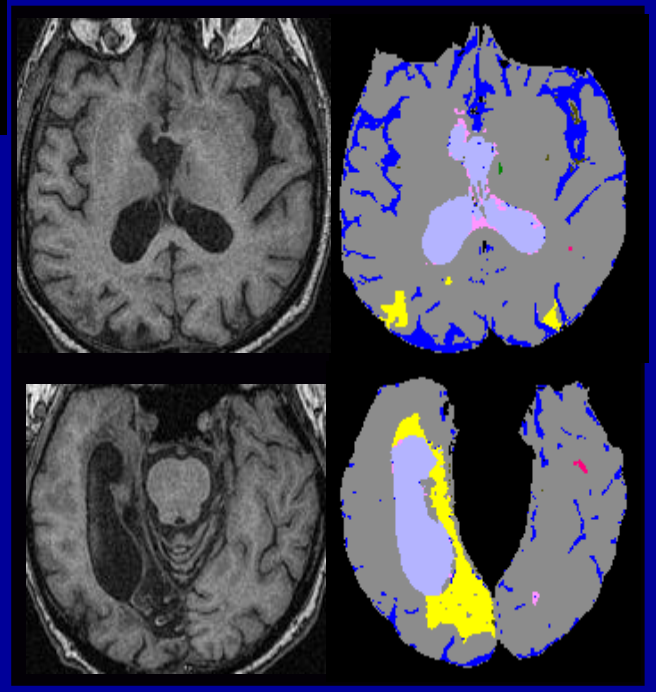
Anteromedial thalamic hyperintensities independently correlated with executive and memory function

Swartz Stroke 2008

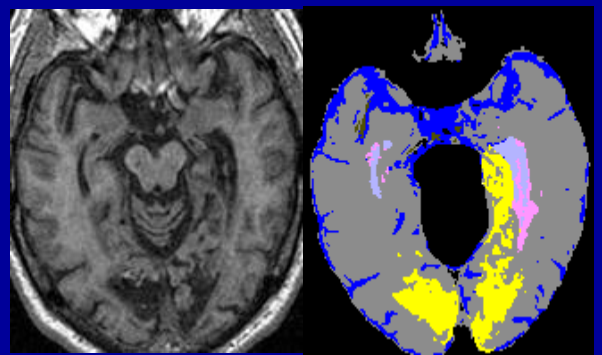
Anterior-medial Thalamic



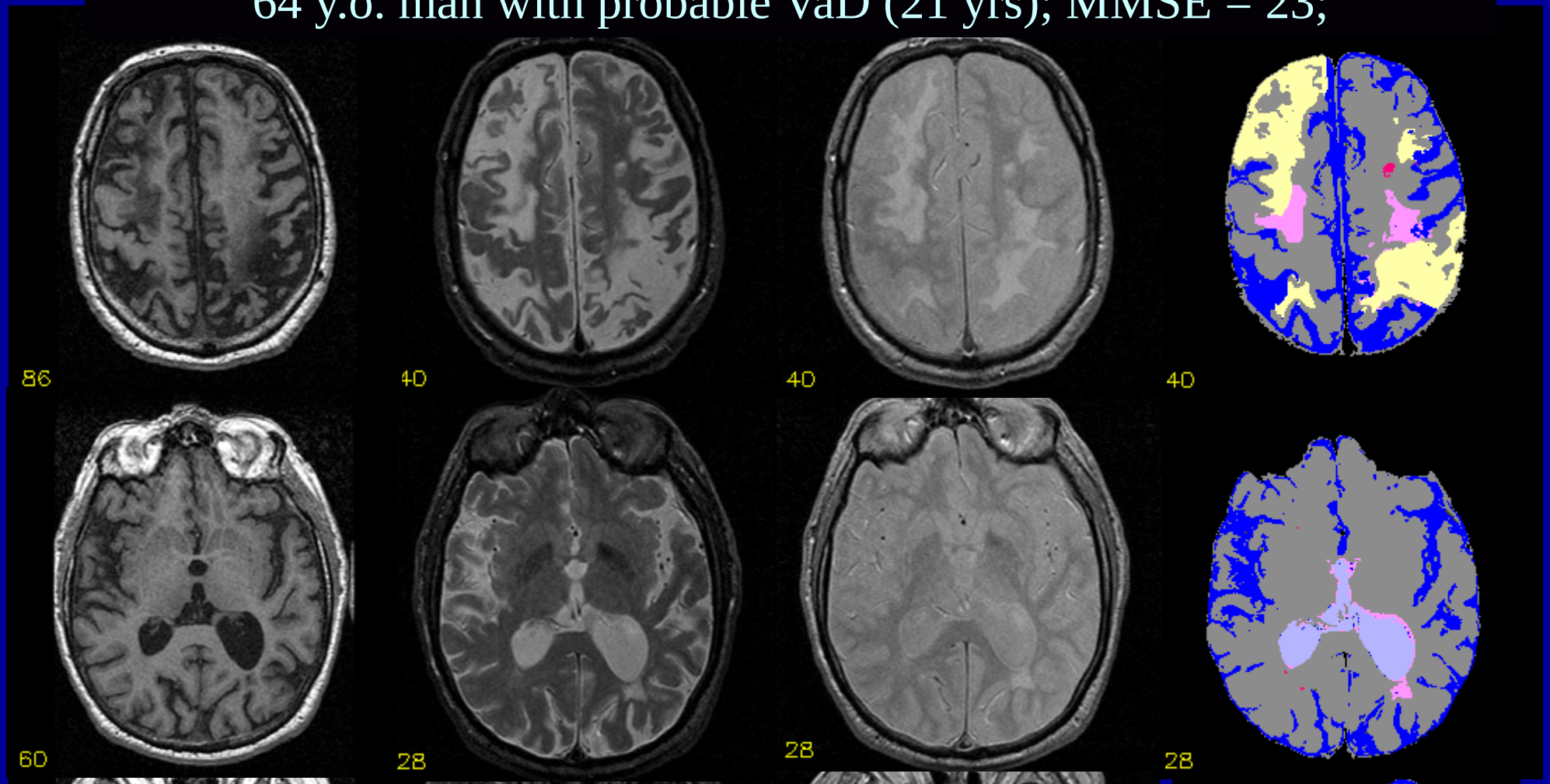
R. Hippocampus



L.Hippocampus



64 y.o. man with probable VaD (21 yrs); MMSE = 23;



081kenr

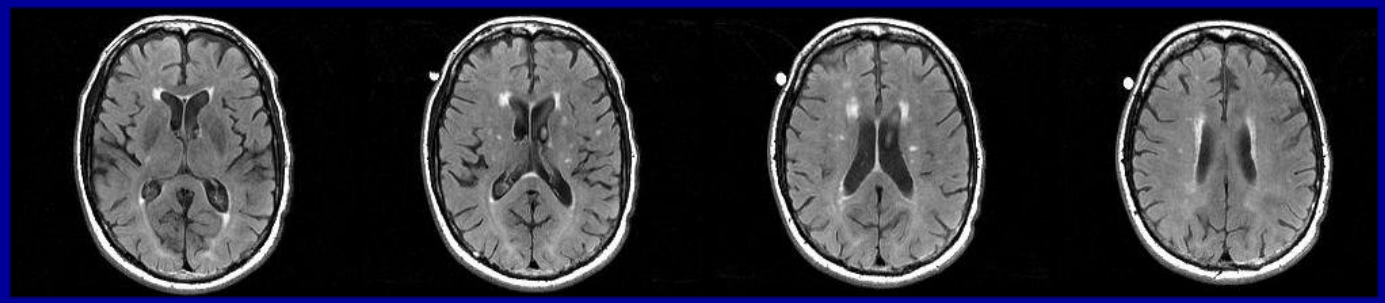
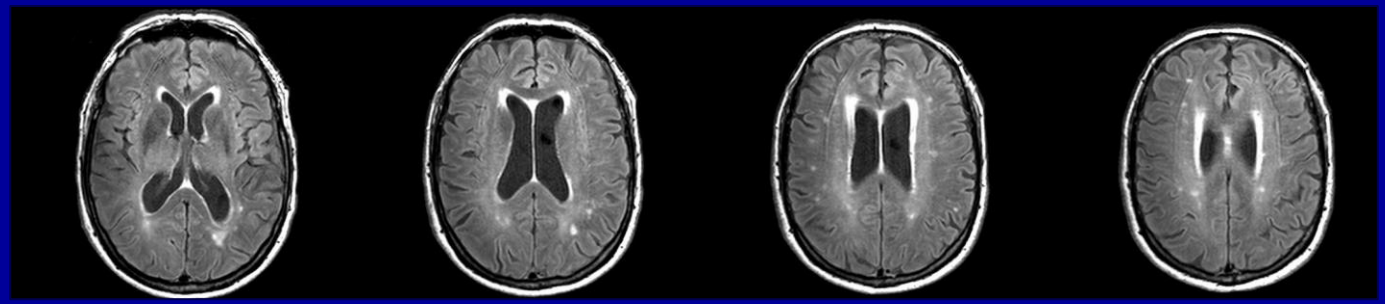
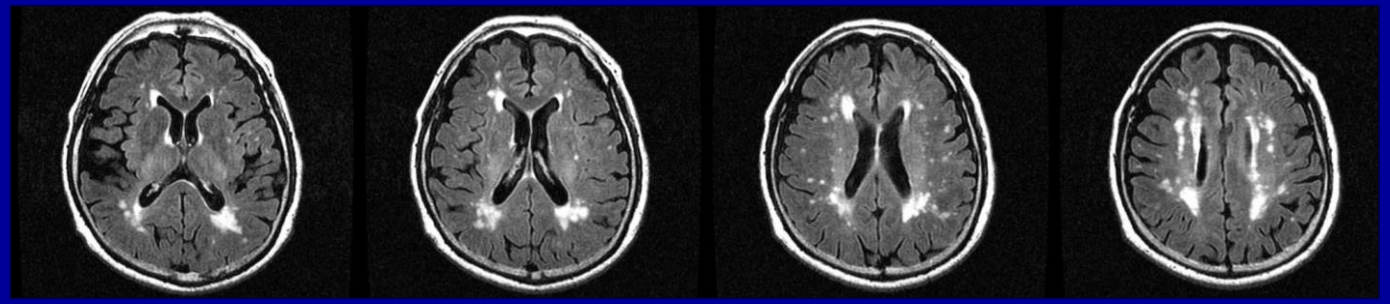
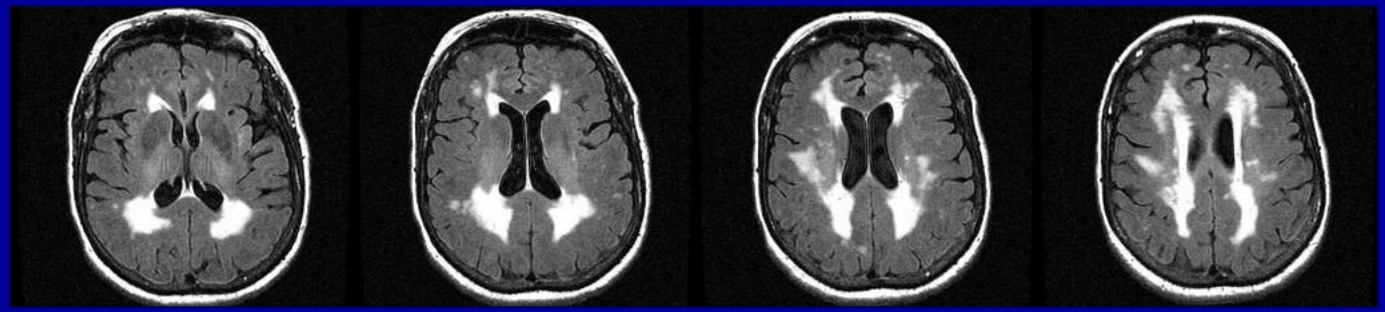
Clinical Course

- Diagnosis: Vascular Dementia
- Treatment: ASA, Trental
- R.K. was cognitively stable over 7 yrs ; average MMSE = 23/30
- Functional abilities maintained at high level over same period; average DAD = 90%
- Status epilepticus – Died 2000
- Autopsy results: cerebral and cerebellar infarct, remote, multiple, small and medium size predominantly involving the cortex (R frontal, both parietal regions). Cerebral senile changes.

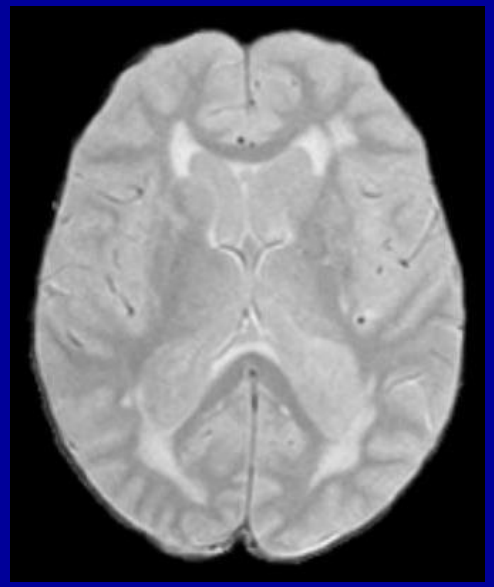
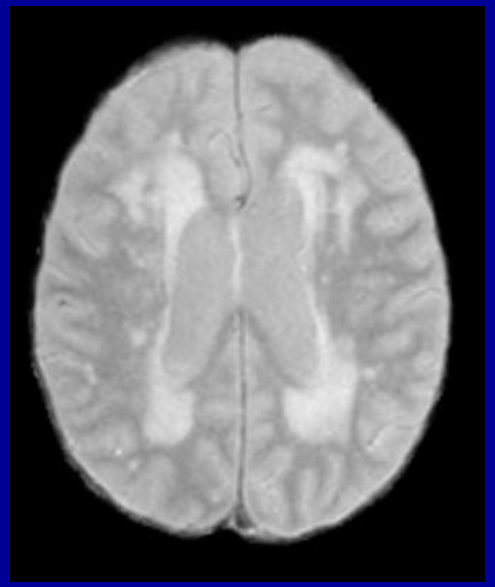
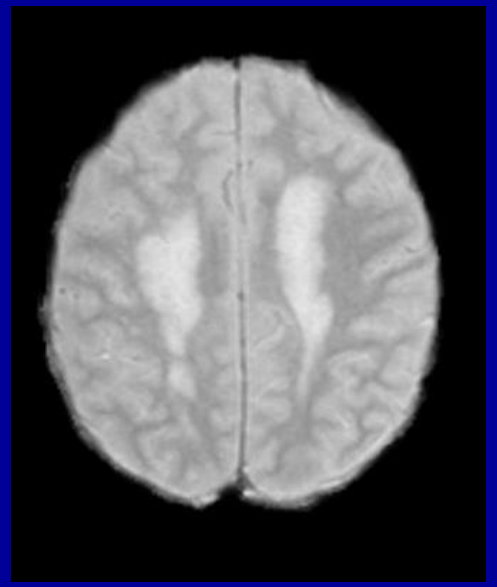
Coexisting AD and Cerebrovascular Disease (CVD)

- Prevalence of post-stroke dementia
  - 26 - 36% prevalence
- Approximately 1/3 of these due to AD
- CVD present in ~ 50% AD autopsies; considered significant in up to 28%
- 55% of Vascular Dementia subjects had AD pathology in recent autopsy series

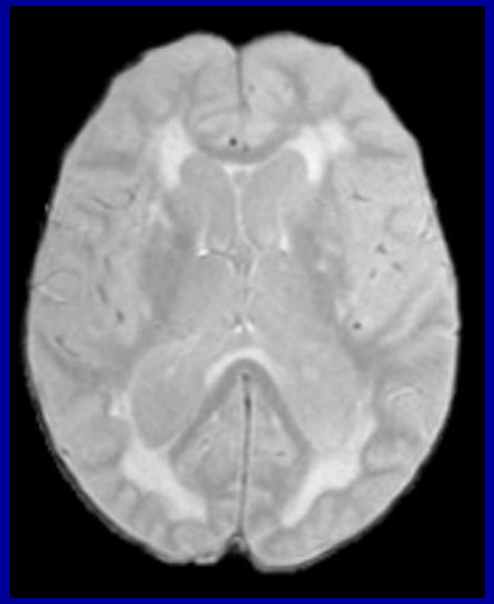
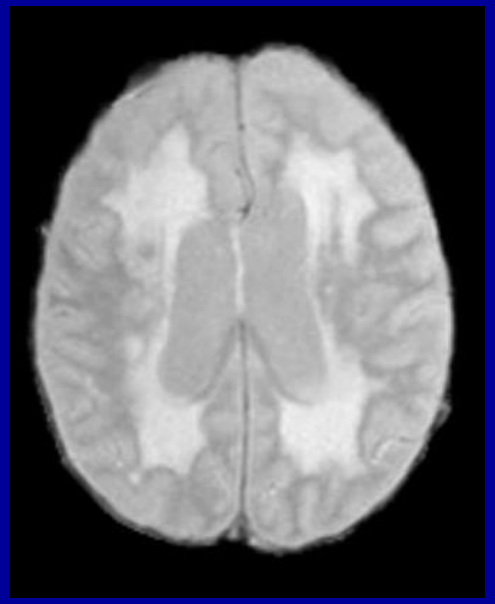
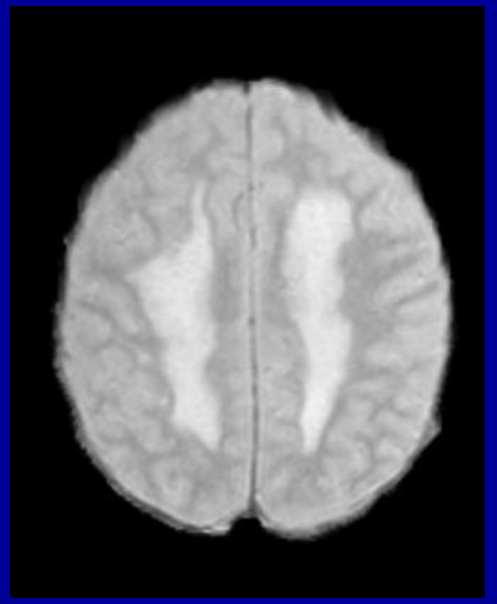
Periventricular White Matter Hyperintensity

Fazekas score		WMH volume
1		5 cm^3
2		10 cm^3
3		25 cm^3
3		50 c

Courtesy of FQ Gao

1996
55cc
4.1%

1999
71cc
5.2%

Clinical Significance of WMH

- In 22 longitudinal studies WMH associated with increased risk of
  - stroke (X3)
  - dementia (X2),
  - death (X2)

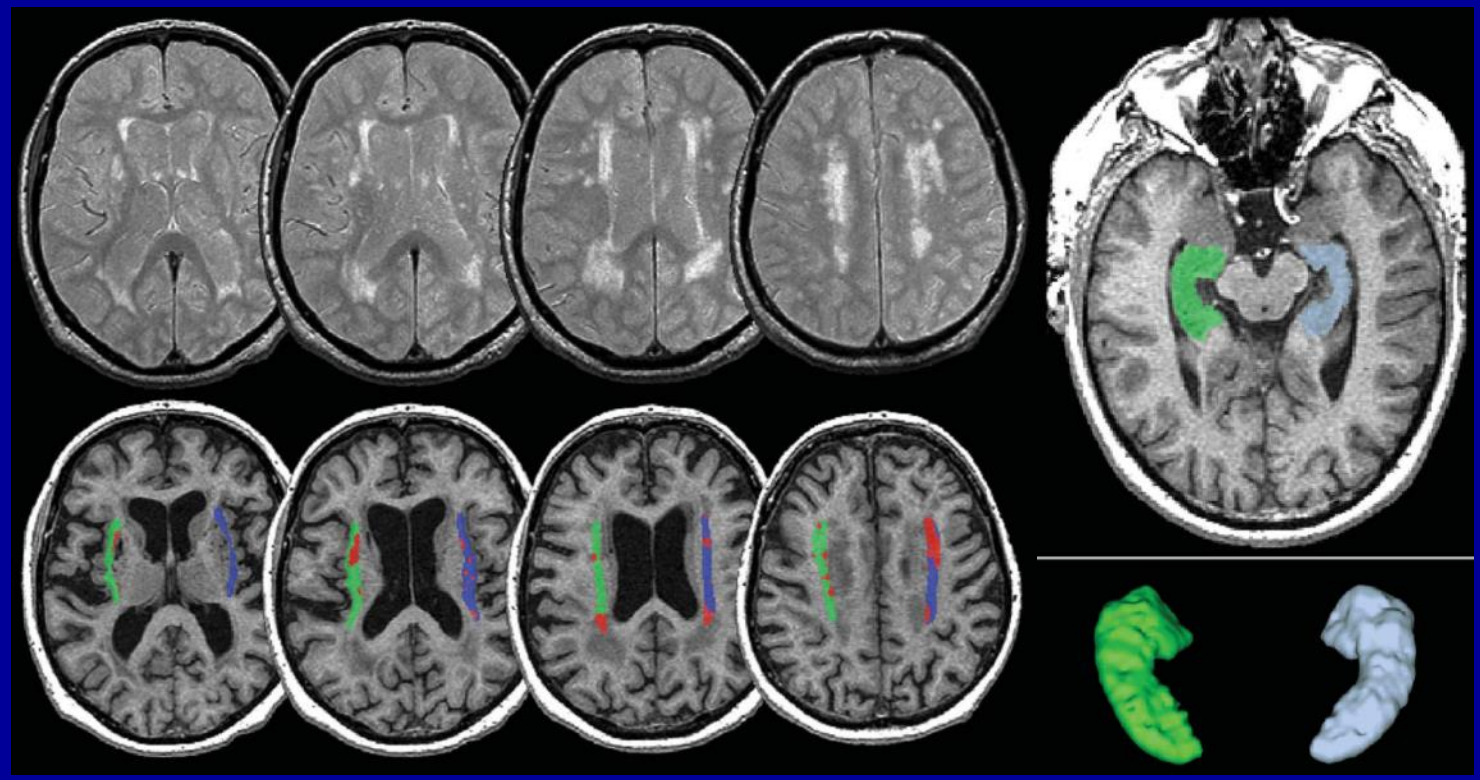
  Debette&Markus *BMJ* 2010

- worse recovery after ischemic stroke Rost Stroke 2010

- Faster decline in global cognitive performance, executive function, and processing speed also noted

  Debette&Markus *BMJ* 2010

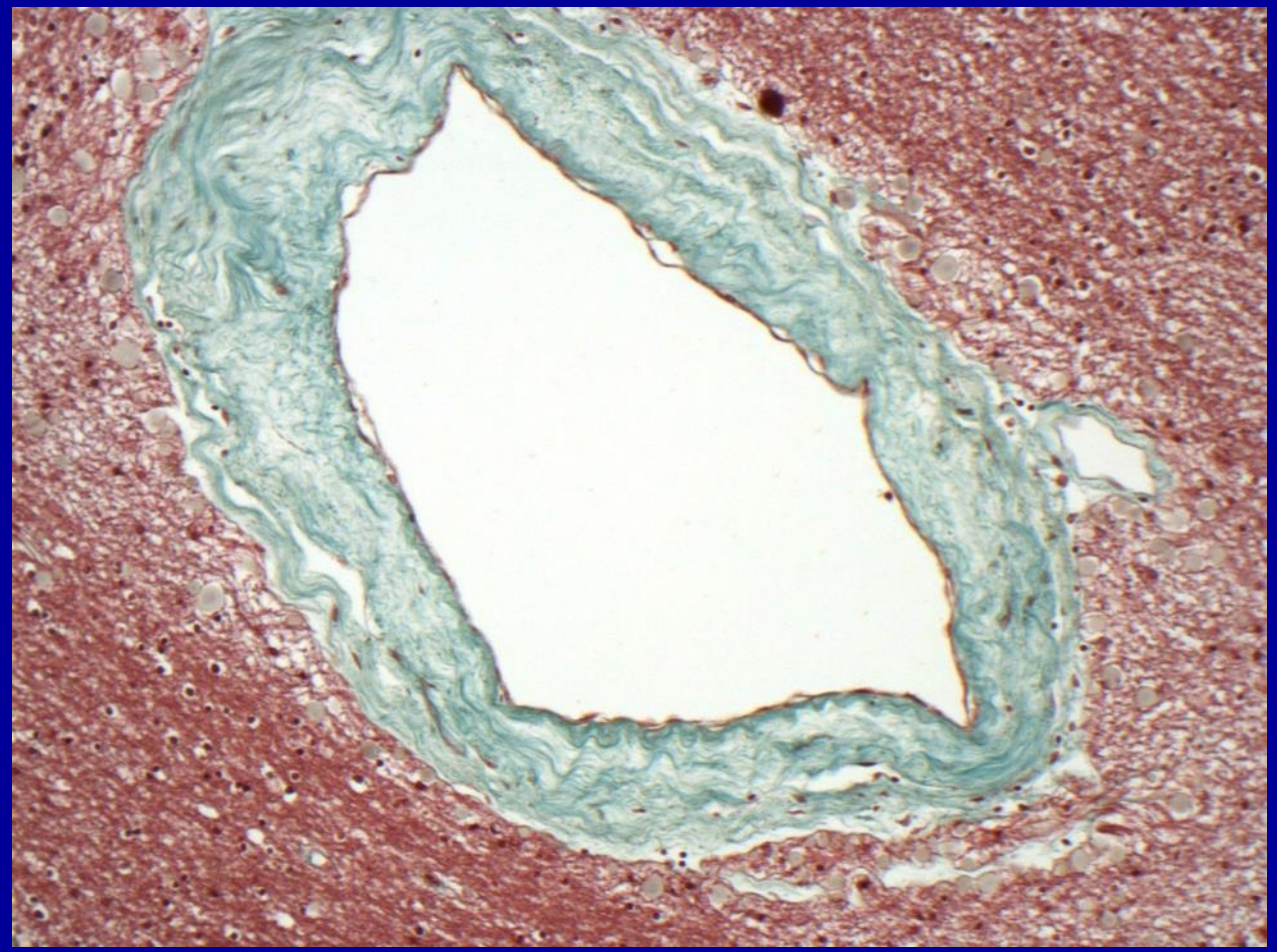
Cholinergic Subcortical Hyperintensities in Alzheimer's Disease



- AD patients with high chSH burden had poorer memory function (p=.03) and smaller total hippocampal volumes (p=.03) McNeely & Ramirez *JAD* 2015

- Cholinergic pathway Involvement in a post-stroke sample correlated with set-shifting on Trails B, whereas total stroke volume and overall WMH volumes correlated with Trails A (speed of processing) Muir, Stroke. 2015

Stenosis of large deep venules correlated with WMH volume



Large venular stenosis best correlated with PvWMH volume

Keith JNEN 2017 in press

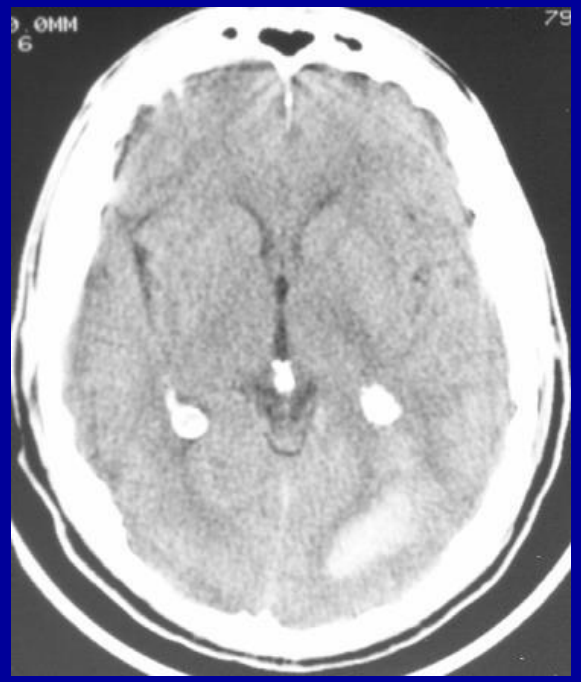
VC also seen in CADASIL

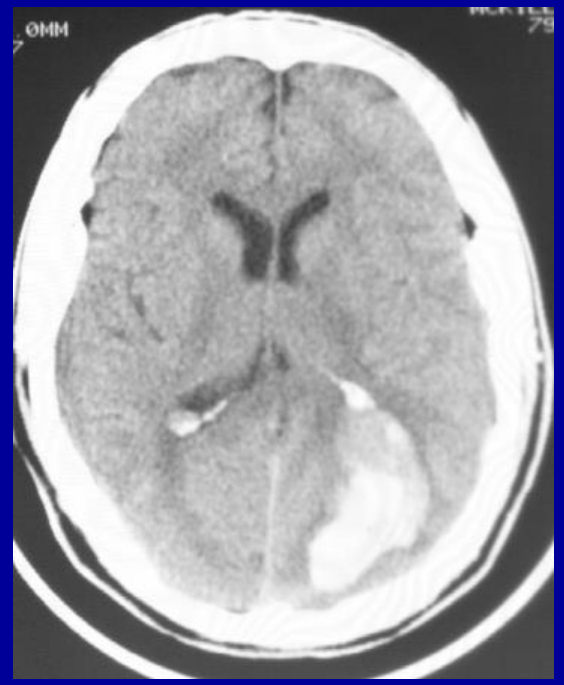
Pettersen Neur 2017

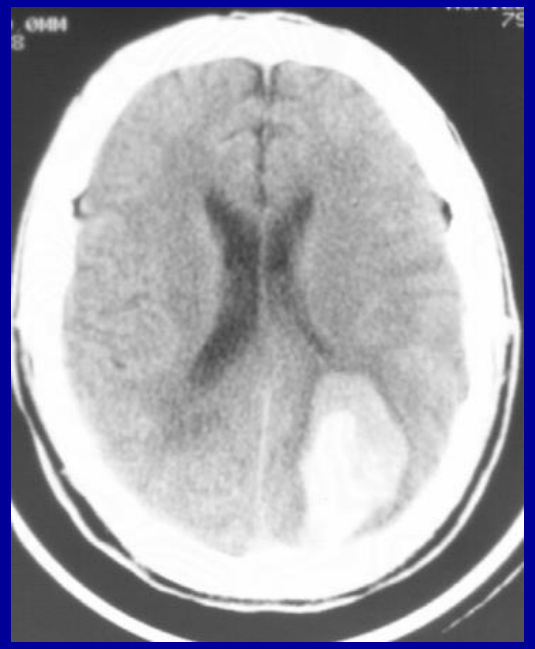
Courtesy of J Keith

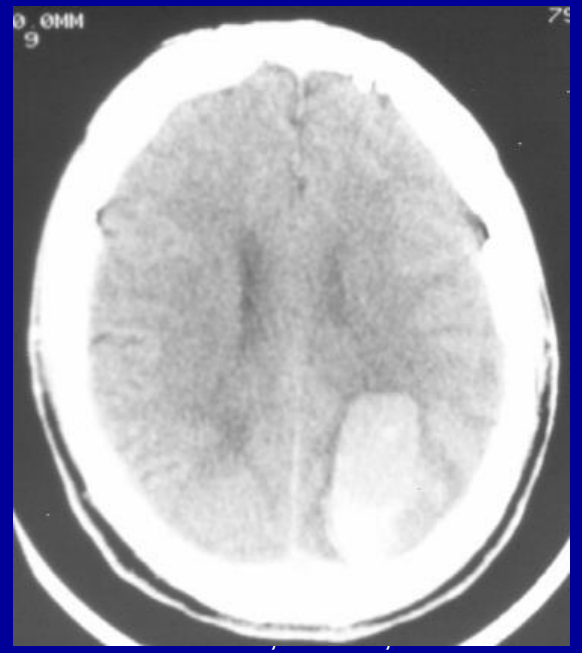
69 year lawyer presenting with confusion and bumping into desks

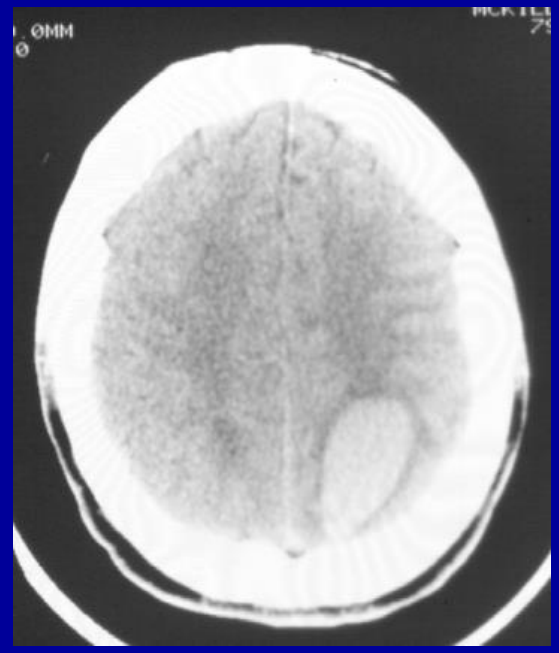
CT in ER





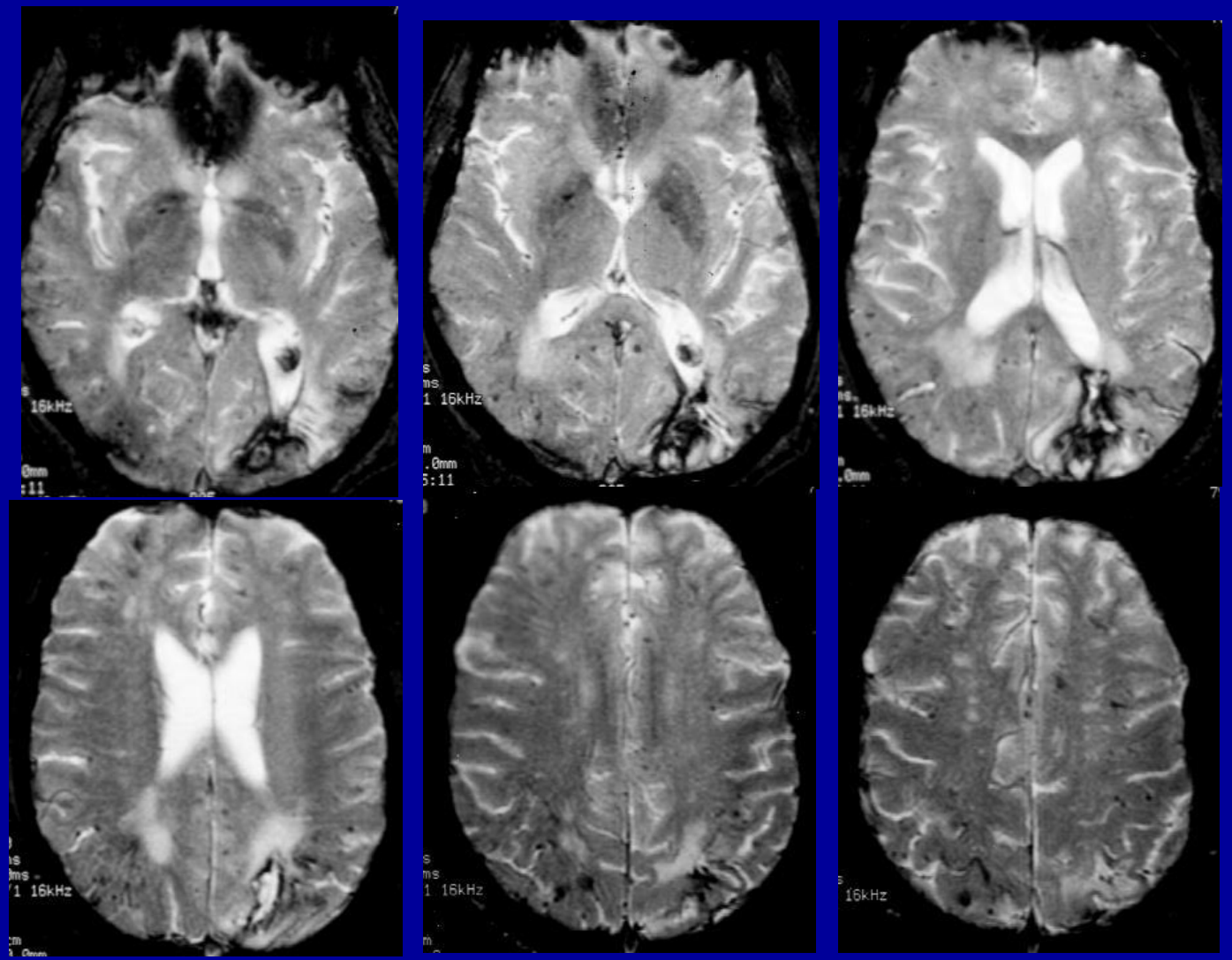






SEBlack,SHSC,UofT

Gradient Echo MRI 2 weeks later



Microbleeds: *hemosiderin deposits seen as black spots*

SEBlack,SHSC,UofT

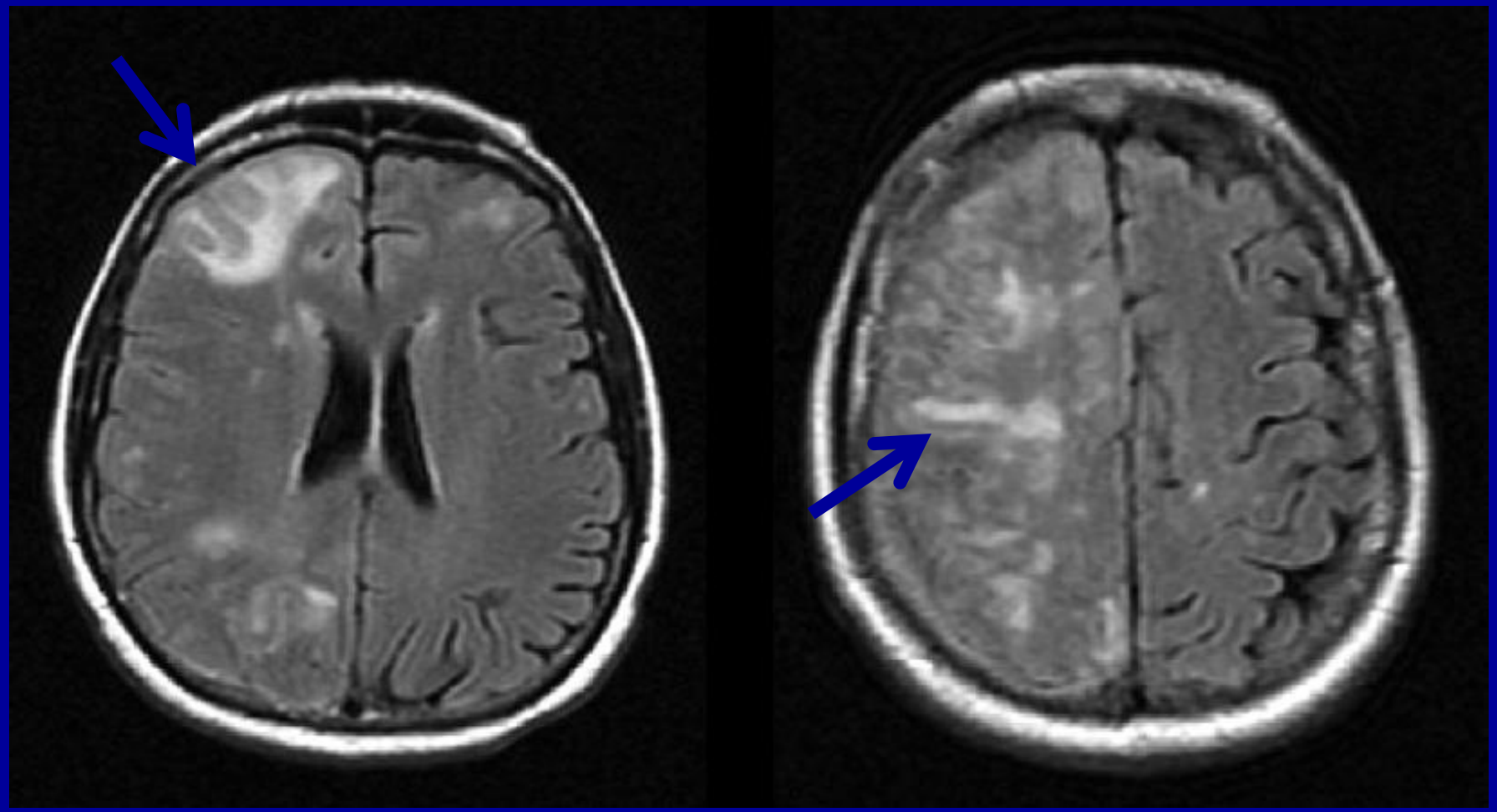
Amyloid Related Imaging Abnormalities (ARIA)

- **ARIA-E**: vasogenic **e**dema (extravasated fluid)
- **ARIA-H**: micro**h**emorrhage (hemosiderin)

- Observed cases in anti-amyloid antibody and gamma secretase inhibitor trials

- Spontaneous anti-Aβ antibodies associated with CAA progression

Sperling RA et al. *Alzheimers Dement* 2011; Piazza F et al. *Ann Neurol* 2013



The Nun Study

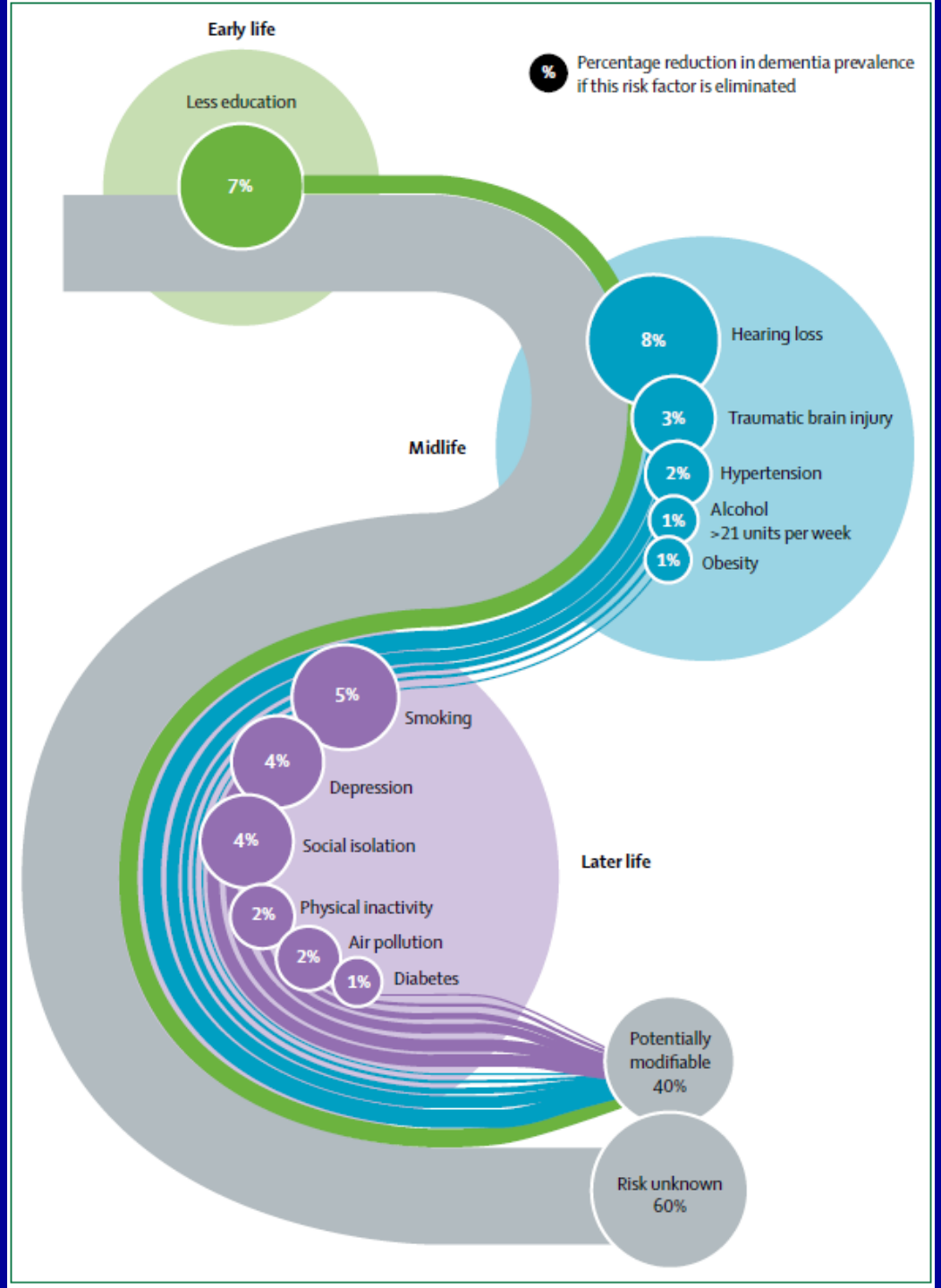
- 102 college-educated women, aged 76 to 100 years, cognitively followed to autopsy
- 45 of 102 met criteria for dementia
- AD pathology in 61 of 102
- Coexisting AD/CVD had 20X likelihood of dementia

from Snowdon et al. (1997) JAMA 277(10):813-817

The Nun Study (con’t)

- only 57% with AD pathology alone were demented
- 75% with AD and a cortical stroke were demented
- 93% of nuns with AD and at least one subcortical stroke were demented
- only 2.5% of those with dementia had only cerebrovascular lesions present

from Snowdon et al. (1997) JAMA 277(10):813-817



Population attributable fraction of potentially modifiable risk factors for dementia

Mukadam N. The Lancet Commissions., 2020

Common Vascular Risk Factors for Cognitive Impairment (Alzheimer's and Vascular Dementia:

proposed term "Vascular-Alzheimer Spectrum Disorders"

Age

Hypertension (**Kivipelto et al, 2001; Launer et al, 2001)**

Elevated cholesterol **(Kivipelto et al, 2001)**

Apolipoprotein E e4 (Slooter et al,1998)

Diabetes (Arvanitikas et al, 2004)

Homocysteinemia (Seshradi et al, 2002)

Cardiac (atrial fibrillation)

Previous stroke

Smoking

Poor dietary habits (fat, sugar, salt)

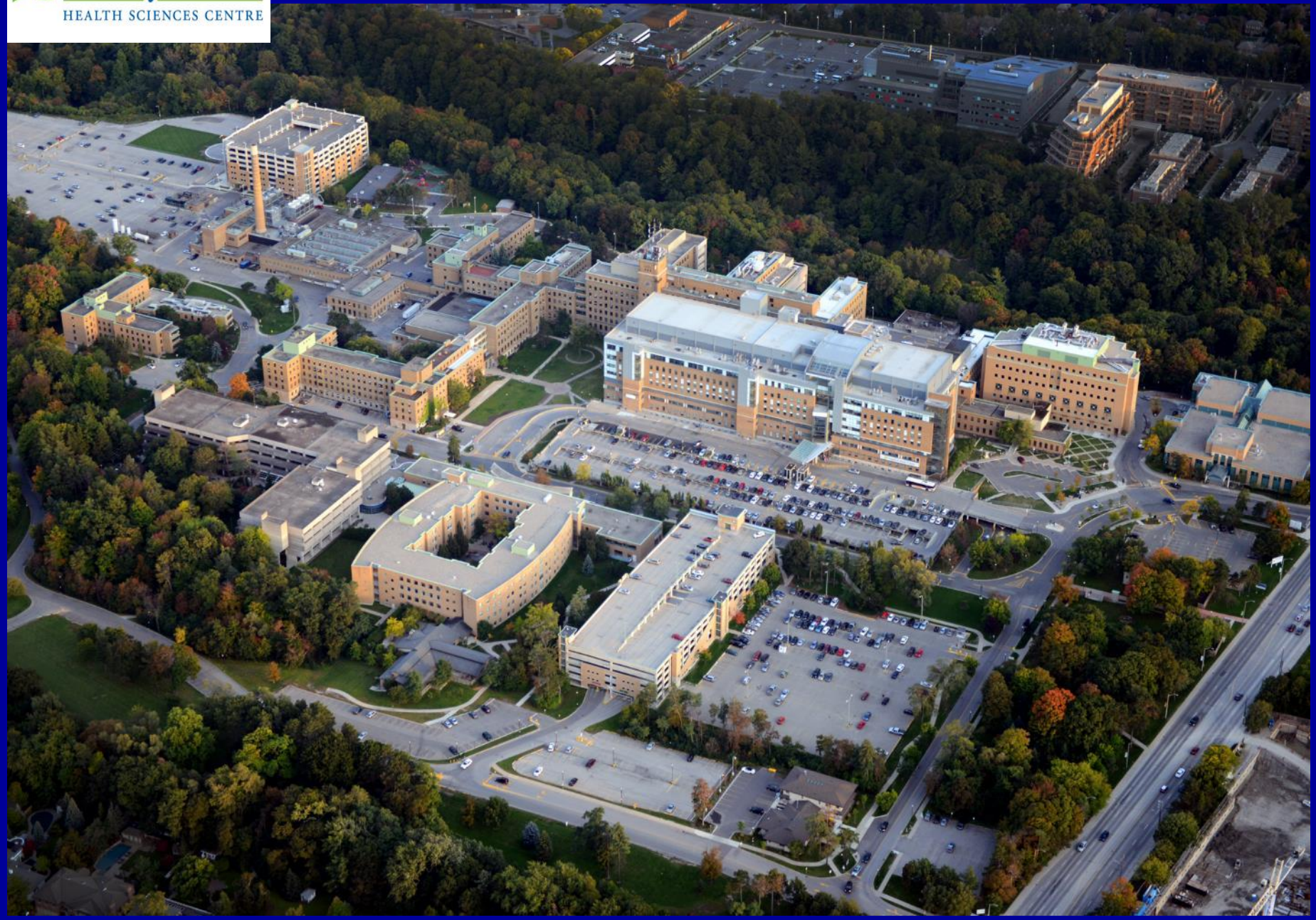
Poor sleep, obstructive sleep apnea

Physical inactivity

* Hearing loss has also emerged as risk factor

Sunnybrook
HEALTH SCIENCES CENTRE

Hurvitz Brain Sciences Research Program



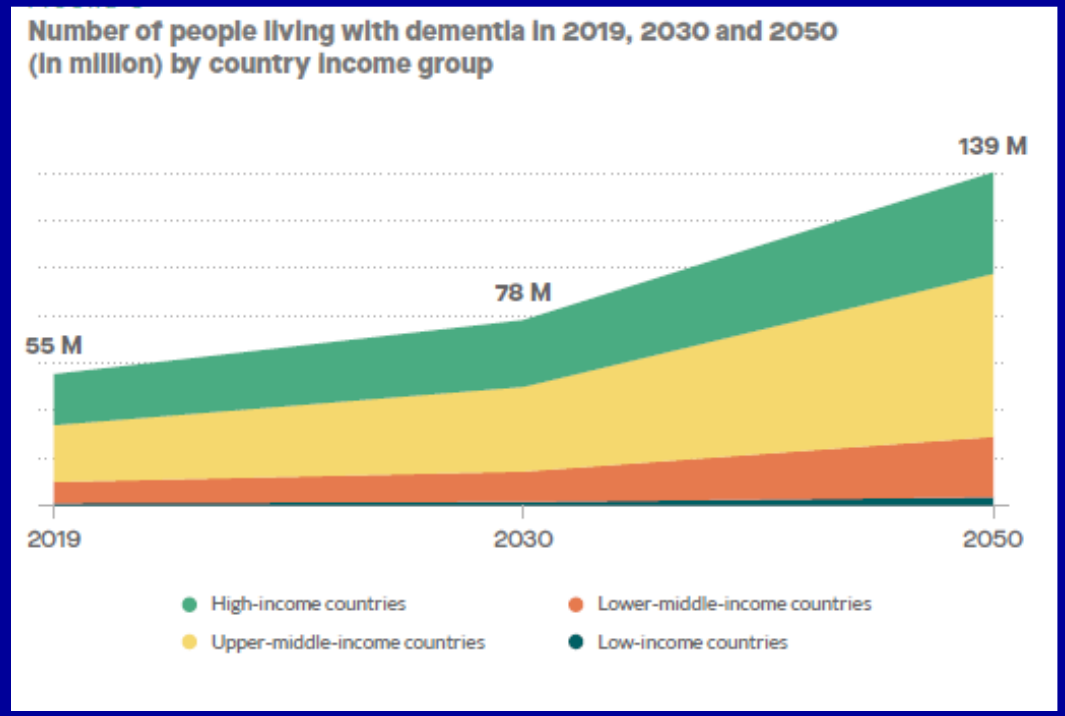
Aging of our Population

- Over 861,000 people aged 85 and older were counted in the 2021 Census, more than twice the number observed in the 2001 Census.
- The population aged 85 and older is one of the fastest-growing age groups, with a 12% increase from 2016. Currently, 2.3% of the population is aged 85 and older.
- Over the next 25 years (by 2046), the population aged 85 and older could triple to almost 2.5 million people.
- Over 9,500 centenarians are now living in Canada — a 16% increase from 2016. Centenarians represent 0.03% of the Canadian population.
- As more seniors are living to 85 and beyond, an increasing number of individuals will face limitations and long-term health challenges.

Statistics Canada, Census 2021

WHO Report on Dementia

- 55 million people with dementia worldwide
- 61% live in low and middle-income-countries
- Global cost 1.3 trillion US$
- 50% of costs by informal care
- 74% of costs in high-income countries



World Alzheimer Report 2021, Alzheimer's Disease International

Dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD): Clinical approach

Mario Masellis, MSc, MD, PhD, FRCPC
Associate Professor of Medicine (Neurology)
Sunnybrook Health Sciences Centre
University of Toronto

ASC/CCNA Webinar
June 21, 2023

Frontotemporal dementia

Case

Case

- Identifying data: 64 y.o. R-handed M; working as managing director; 16 years of education
- Chief complaint: “slowness, apathy, and somnolence”
  - Age at onset 62 y.o.
- Past Medical History:
  - None
- Family history:
  - +ve for FTD

Case

History of Presenting Illness (age 64):

- Insidious onset and gradual change in personality and behaviour for two years
- Initially withdrawn; less talkative
- Gave up his hobbies
- Troubles with handling familiar objects
- Months later, social judgement deteriorated:
  - Breakdown in formalities – poor table manners
  - Disinhibited – went outside without his clothes on
  - Irritability when opposed

Case

Examination (age 64):

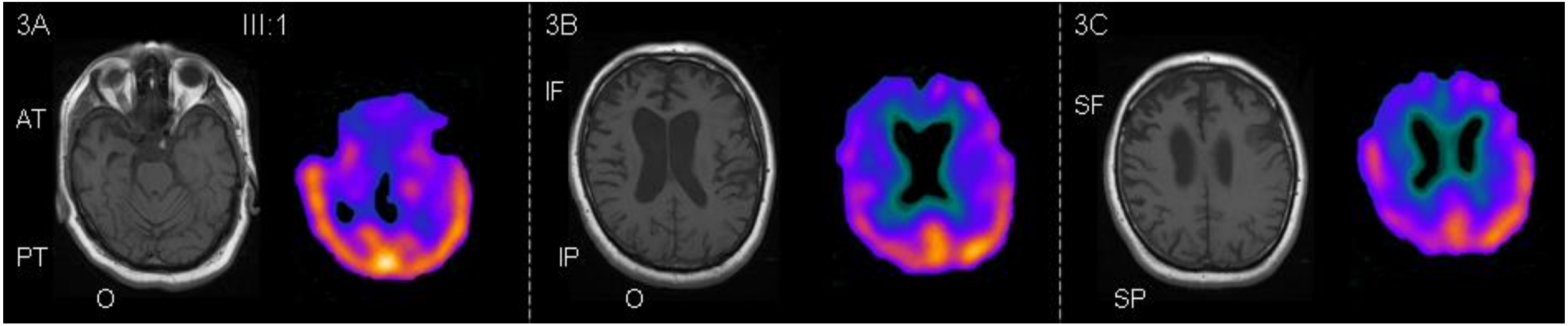
- Cognitive testing:
  - Impaired executive functions
  - Difficulties switching between categories
  - Poor attention
  - Visuospatial difficulties
  - F-word list generation – perseverated on “specific F word”
  - Relatively intact delayed memory
  - Neuropsychiatric Inventory = 23/144
- Impaired daily functions

Case

Examination (age 64):

- General exam - normal
- Neurological exam:
  - moderately impaired monotone, slurred speech
  - minimal loss of expression on his face
  - Tremor at rest of upper extremities, moderate in amplitude
  - moderate rigidity/stiffness
  - severe motor slowness of gait
  - multi-step turning with postural instability

Neuroimaging



What is the clinical diagnosis?

- Behavioural variant FTD with parkinsonism

Frontotemporal Dementia

- Second most common cause of dementia under age 65 – Age At Onset = 45 to 65
- Predominant frontal and/or temporal lobe symptoms:
  - Behavioural variant
  - Language variant (Neary et al., 1998)
- May be associated with motoneuron disease and/or Parkinsonism
- Up to 40% of cases are familial (Seelar et al., 2011)

doi:10.1093/brain/awr179 Brain 2011: 134; 2456–2477 | 2456

BRAIN
A JOURNAL OF NEUROLOGY

Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

Katya Rascovsky,[1] John R. Hodges,[2] David Knopman,[3] Mario F. Mendez,[4,5] Joel H. Kramer,[6] John Neuhaus,[7] John C. van Swieten,[8] Harro Seelaar,[8] Elise G. P. Dopper,[8] Chiadi U. Onyike,[9] Argye E. Hillis,[10] Keith A. Josephs,[3] Bradley F. Boeve,[3] Andrew Kertesz,[11] William W. Seeley,[6] Katherine P. Rankin,[6] Julene K. Johnson,[12] Maria-Luisa Gorno-Tempini,[6] Howard Rosen,[6] Caroline E. Prioleau-Latham,[6] Albert Lee,[6] Christopher M. Kipps,[13,14] Patricia Lillo,[2] Olivier Piguet,[2] Jonathan D. Rohrer,[15] Martin N. Rossor,[15] Jason D. Warren,[15] Nick C. Fox,[15] Douglas Galasko,[16,17] David P. Salmon,[16] Sandra E. Black,[18] Marsel Mesulam,[19] Sandra Weintraub,[19] Brad C. Dickerson,[20] Janine Diehl-Schmid,[21] Florence Pasquier,[22] Vincent Deramecourt,[22] Florence Lebert,[22] Yolande Pijnenburg,[23] Tiffany W. Chow,[24,25] Facundo Manes,[26] Jordan Grafman,[27] Stefano F. Cappa,[28,29] Morris Freedman,[24,30] Murray Grossman[1,*] and Bruce L. Miller[6,*]

Table 3 International consensus criteria for behavioural variant FTD (FTDC)

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behaviour
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviours
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

The Banana Lady

and other stories of curious behaviour and speech

ANDREW KERTESZ

Classification of primary progressive aphasia and its variants

M.L. Gorno-Tempini, MD, PhD
A.E. Hillis, MD
S. Weintraub, PhD
A. Kertesz, MD
M. Mendez, MD
S.F. Cappa, MD
J.M. Ogar, MS
J.D. Rohrer, MD
S. Black, MD
B.F. Boeve, MD
F. Manes, MD
N.F. Dronkers, PhD
R. Vandenberghe, MD, PhD
K. Rascovsky, PhD
K. Patterson, PhD
B.L. Miller, MD
D.S. Knopman
J.R. Hodges, MD*
M.M. Mesulam, MD*
M. Grossman, MD*

Neurology® 2011;76:1006-1014

Table 2 Diagnostic features for the nonfluent/agrammatic variant PPA

I. Clinical diagnosis of nonfluent/agrammatic variant PPA
At least one of the following core features must be present:
1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)
At least 2 of 3 of the following other features must be present:
1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

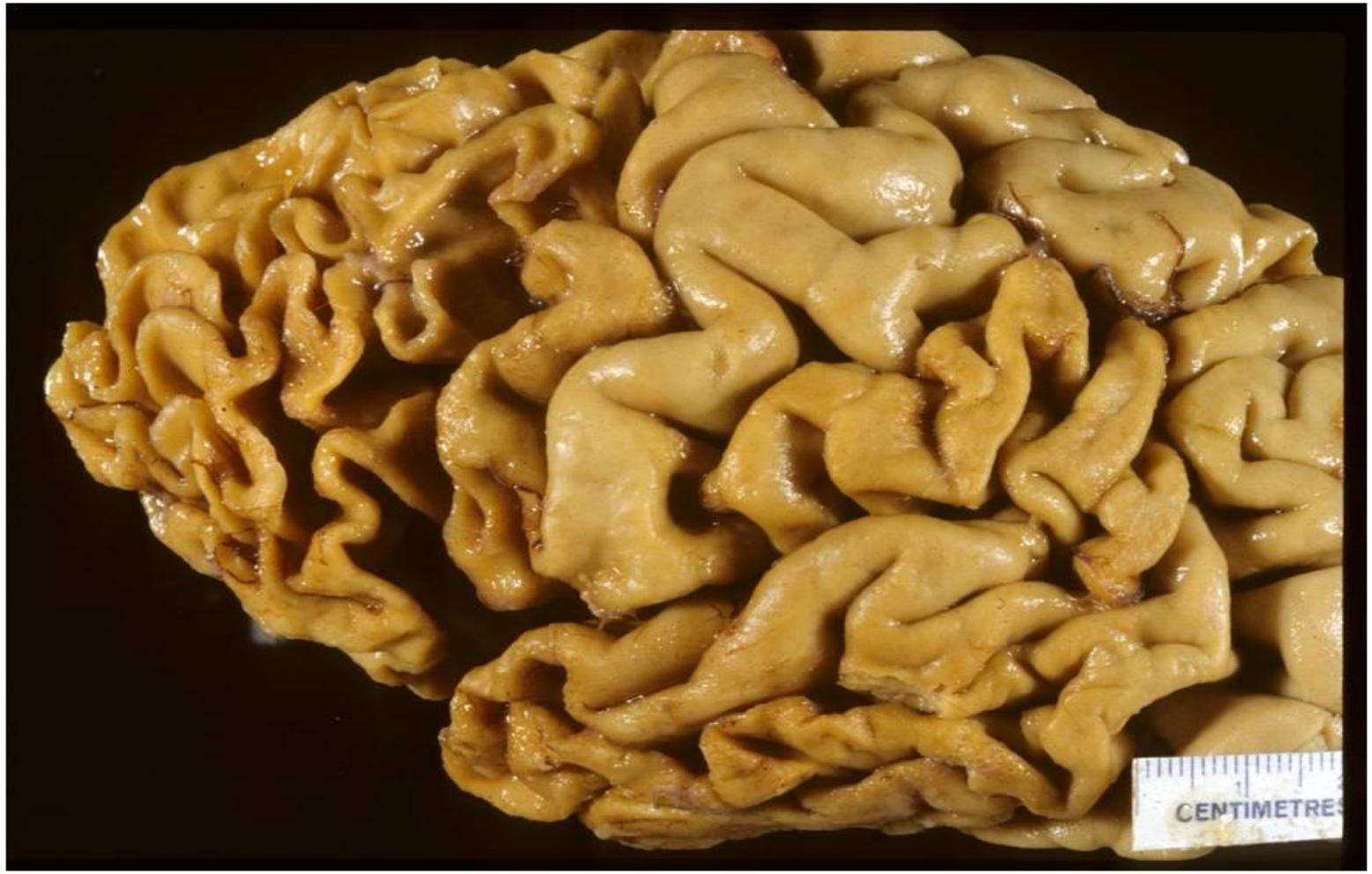
Table 3 Diagnostic criteria for the semantic variant PPA

I. Clinical diagnosis of semantic variant PPA
Both of the following core features must be present:
1. Impaired confrontation naming
2. Impaired single-word comprehension
At least 3 of the following other diagnostic features must be present:
1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)

How common is FTD?

- Prevalence ranges from 0.01 to 4.61 per 1000
  - 2.7% (range 0-9.1%) of all dementia cases older than 65 years of age
  - 10.2% (2.8-15.7%) in those younger than 65 and approaches the prevalence of Alzheimer's disease in this age group
- Incidence rate 0.00 to 0.33 per 1000 person-years
- Behavioural variant presentation is 4 times more common than the language variant (Hogan et al., 2016)
- Rare disease but impact to society is huge

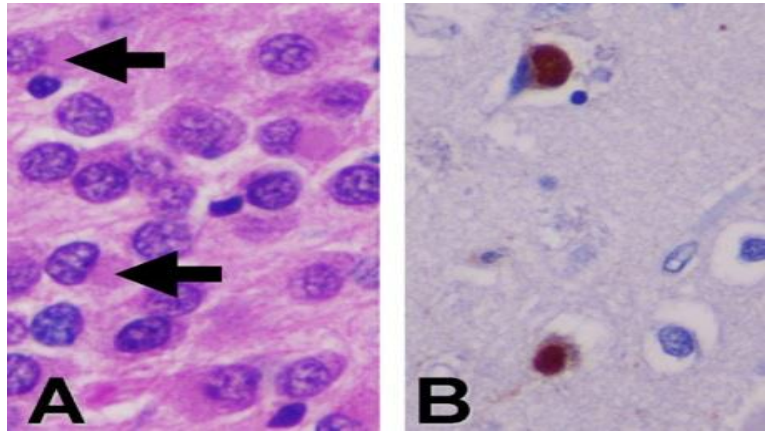
Frontotemporal shrinkage



Genetics of FTD and neuropathology

Tauopathies

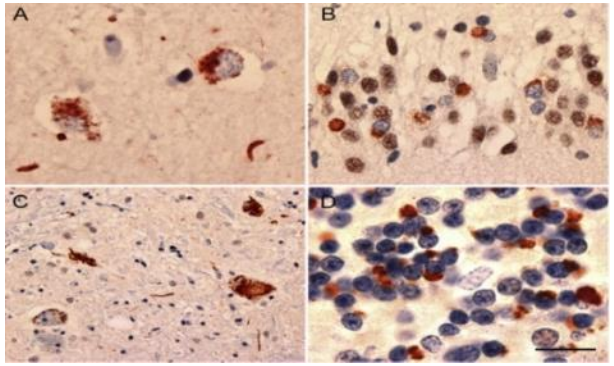
MAPT mutations



Montine et al., 2014

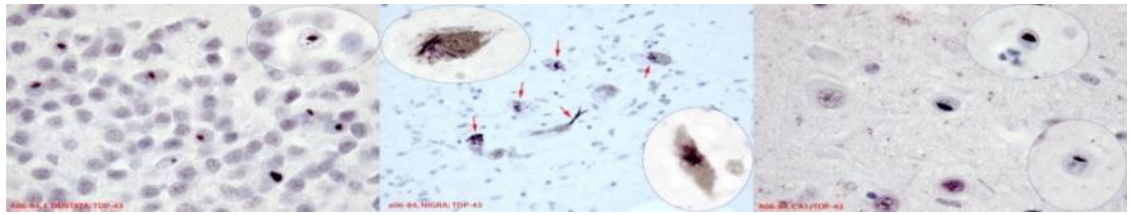
TDP43 proteinopathies

C9orf72 G_4C_2 repeat expansions



DeJesus-Hernandez et al., 2011

GRN mutations



Dementia with Lewy bodies

Case

Case

- **ID:** 78 y.o. R-handed woman; married; gr 7/8 education
- **RFR:** Cognitive decline, visual hallucinations, parkinsonism affecting iADLs
- **PMH:**
  - Vitamin B12 deficiency; adequately treated
  - Depression/anxiety x 6 years; paroxetine responsive
  - No known CV risk factors, except obesity
- **Medications:** vitamin B12 1000 mcg/d; paroxetine 30 mg od

Case

- **HPI:**
  - Acting out dreams; flail arms and legs; being chased (3 years)
  - Insidious onset and gradual decline in cognition (2 years)
    - Losing train of thought
    - Word-finding troubles
    - Difficulties understanding complex instructions/written text
    - Mild ST memory loss – benefits from cueing
    - Cognitive fluctuations – occasional confusional episodes

Case

- **HPI (con't):**
  - Visual hallucinations (2 years)
    - Insects crawling on floor and on skin; ½ inch long; change colour; wings
    - Small cats
  - Motor symptoms (2 years)
    - Left > right-sided rest tremor
    - AM stiffness
    - Slowed movements and gait
    - Stooped posture
    - Difficulties with buttons, rolling over, getting out of chair
    - Spontaneous falls

Case

- **Exam:**
  - Vitals normal; no postural change
  - General exam normal
  - Cognitive exam
    - MMSE = 22/30
    - MOCA = 21/30
    - Behavioural Neurology Assessment-sf = 71/114
      - Inattention
      - Visuospatial dysfunction
      - Executive functions impaired
      - Naming
      - Verbal memory – benefited from cueing

Case

- **Exam:**
  - Neurological exam
    - Full EOM with no vertical gaze restrictions
    - Horizontal saccadic pursuit
    - Mild hypomimia & reduced blink
    - Hypophonia
    - L > R rest tremor; intermittent tremor R foot
    - L > R rigidity
    - L > R bradykinesia
    - Multiple attempts to arise from chair; posture stooped
    - Gait slow, festinating, reduced arm swing
    - Pull test – fall if not caught

Diagnosis?

Dementia with Lewy Bodies

Diagnosis and management of dementia with Lewy bodies

Neurology® 2017;89:88-100

Fourth consensus report of the DLB Consortium

Central Feature

- Dementia

Core features (1=possible; 2=probable)

- Fluctuating cognition
- Recurrent visual hallucinations
- REM behavioural disorder
- Spontaneous parkinsonism

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Supportive clinical features
Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.
Indicative biomarkers
Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy. Polysomnographic confirmation of REM sleep without atonia.
Supportive biomarkers
Relative preservation of medial temporal lobe structures on CT/MRI scan. Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging. Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Diagnosis and management of dementia with Lewy bodies

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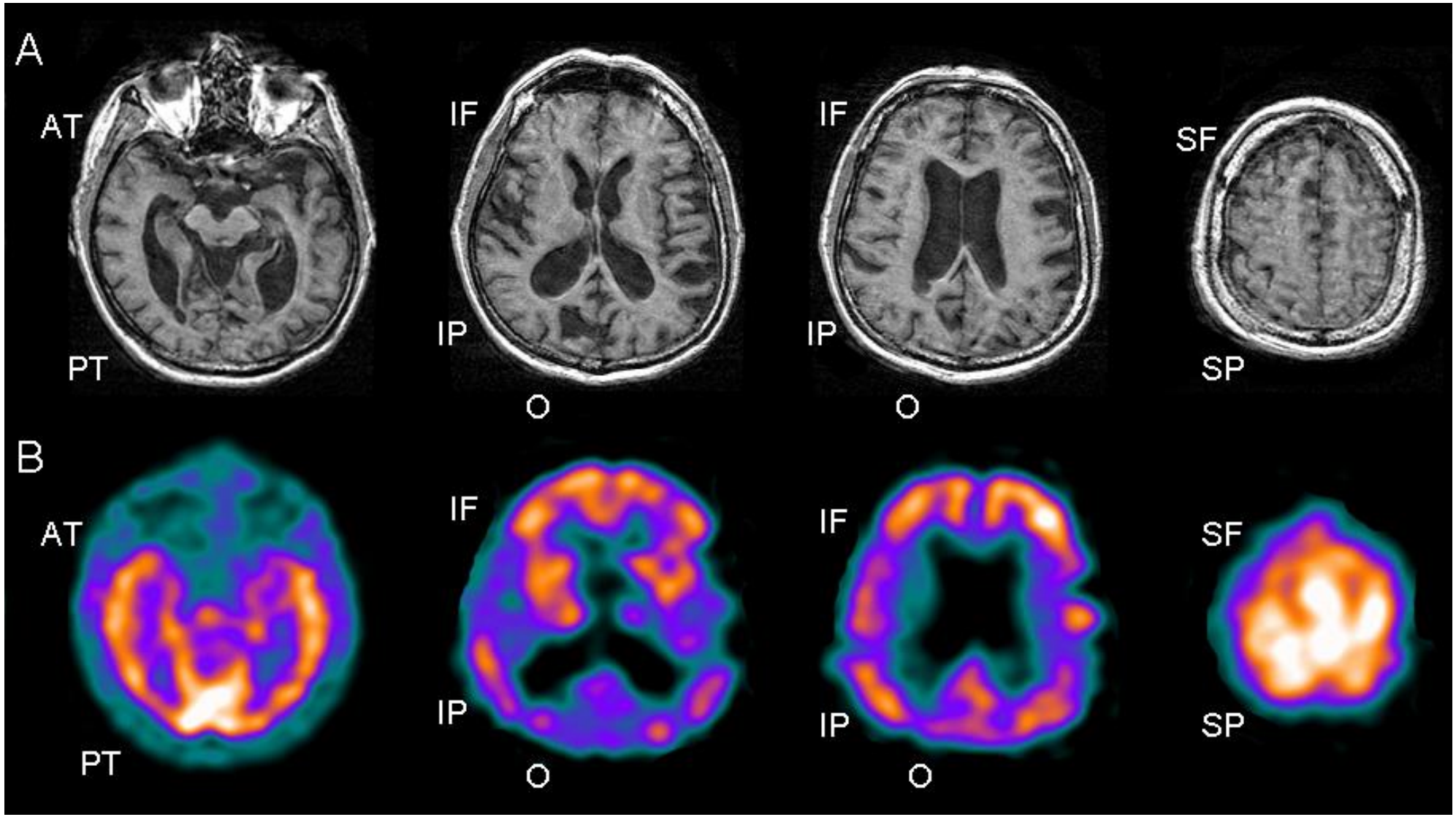
Probable DLB can be diagnosed if:
a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or
b. Only one core clinical feature is present, but with one or more indicative biomarkers.
Probable DLB should not be diagnosed on the basis of biomarkers alone.
Possible DLB can be diagnosed if:
a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or
b. One or more indicative biomarkers is present but there are no core clinical features.

Epidemiology of DLB

- Second most common form of degenerative dementia
- 10-15% of dementia cases at autopsy (McKeith et al., 1996)
- Community-based study 5% met consensus criteria of DLB (age > 85 years); represents ~ 22% of all demented cases (Rahkonen et al., 2003)

Neuroimaging



Conclusions

- DLB is the second most common form of neurodegenerative dementia
- FTD is a common form of early onset dementia
- They present with both overlapping and different symptoms from AD
- Both diseases cause devastation for patients and their families and place a huge burden on society