Dementias: clinical diagnosis, pathology & therapeutics

12th RTC in Sub-Saharan Africa
Makerere University, Kampala, Uganda,
10 – 11 September 2021

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Newcastle University
Institute of Neuroscience

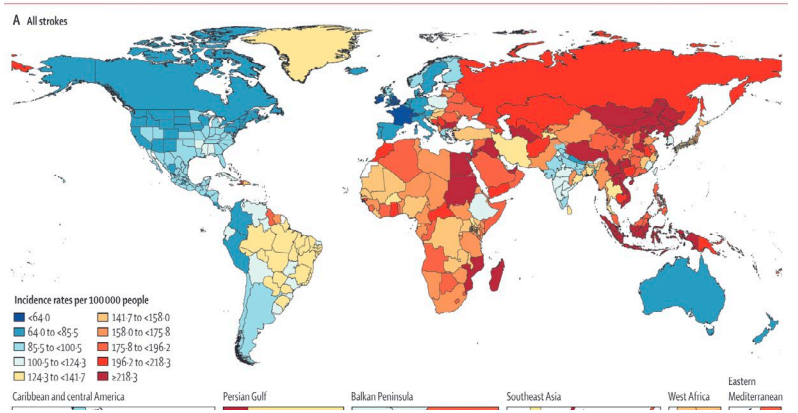
MRC Medical Research Council

COGFAST Memory After Stroke Study

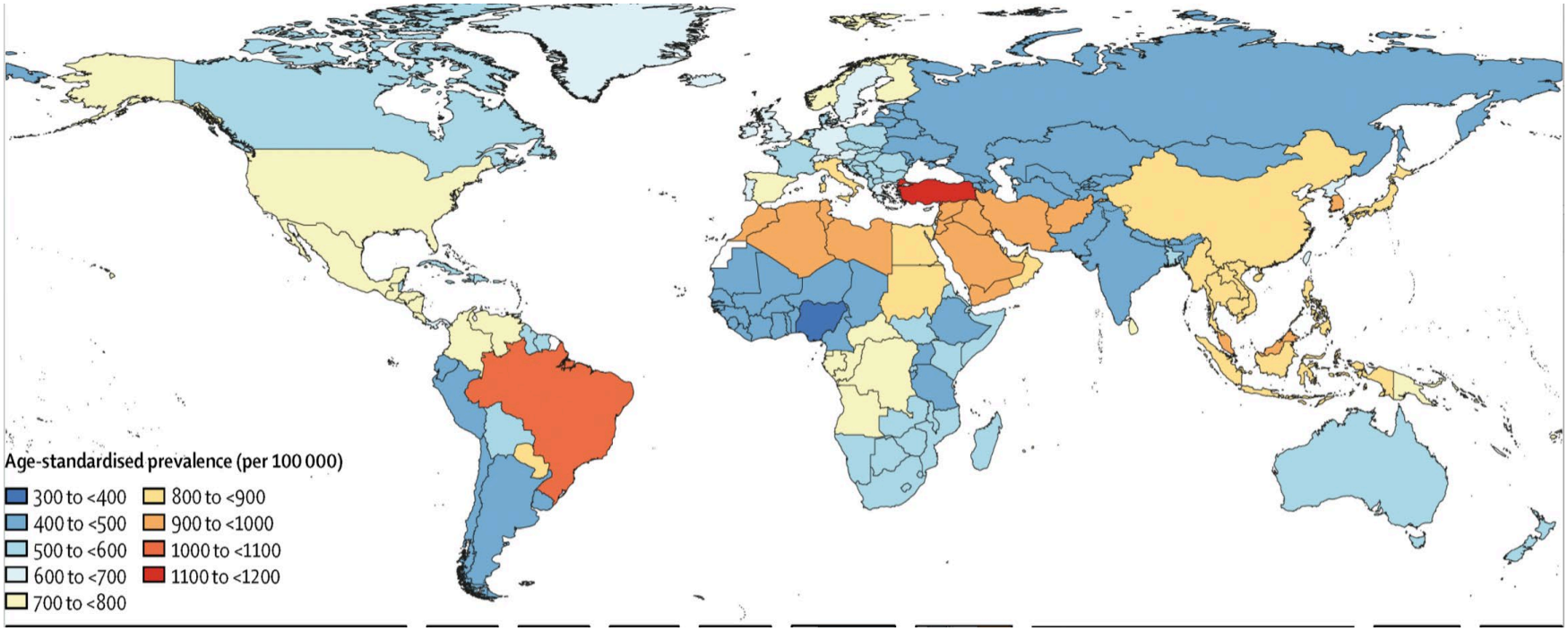
Dementia

IS GLOBAL

Global Burden of Dementia



Doubling of Prevalence between 1990 and 2016



Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

*GBD 2016 Dementia Collaborators**

Lancet Neurol 2019; 18: 88–106

Global Burden of DALYS and Deaths

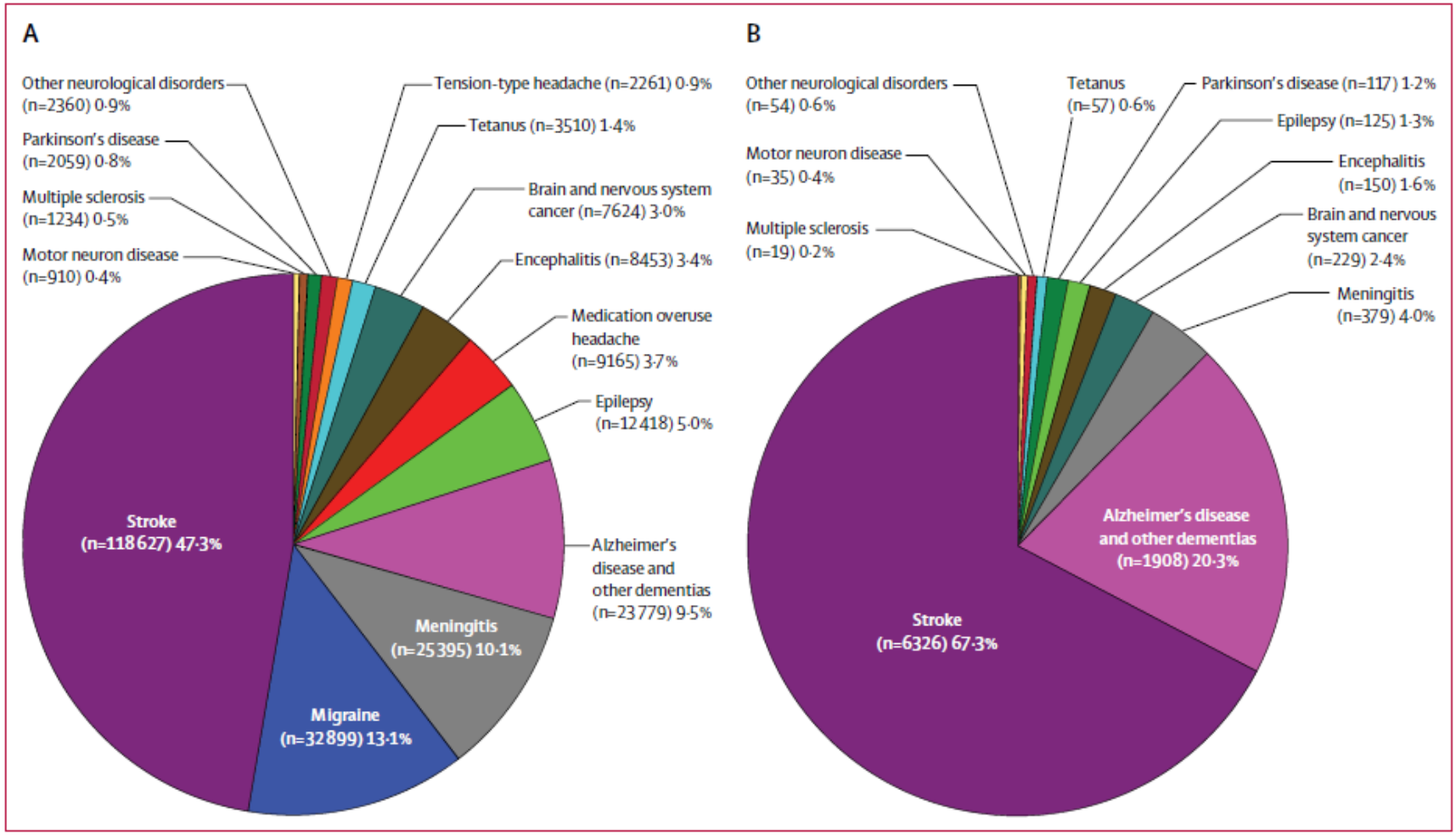
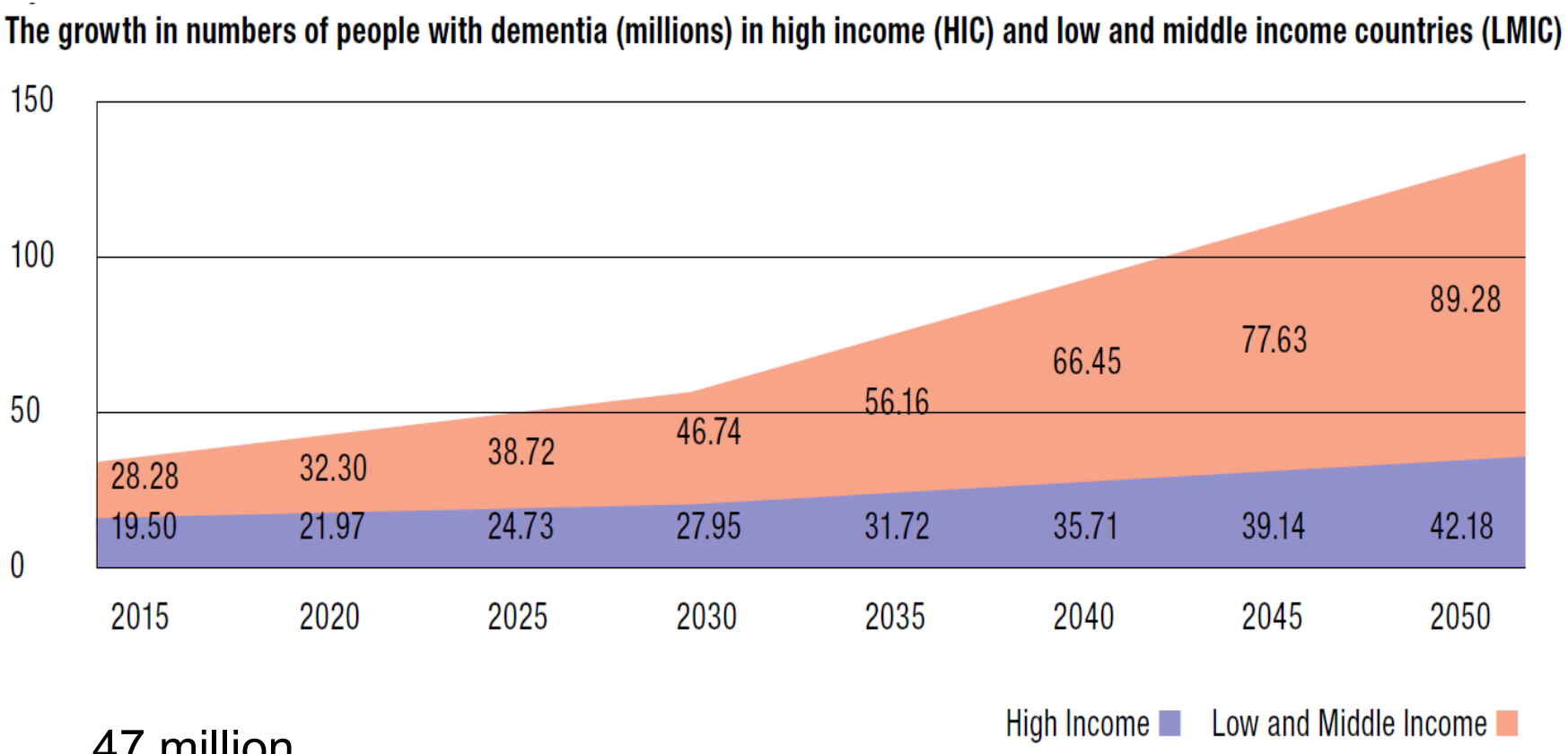


***Figure 2*: Contribution of various neurological disorders to the overall burden from neurological disorders in 2015**
Estimates are for (A) disability-adjusted life-years and (B) deaths.

*GBD 2015 Neurological Disorders Collaborator Group** **Lancet Neurol 2017; 16: 877–97**

Numbers of People with Dementia

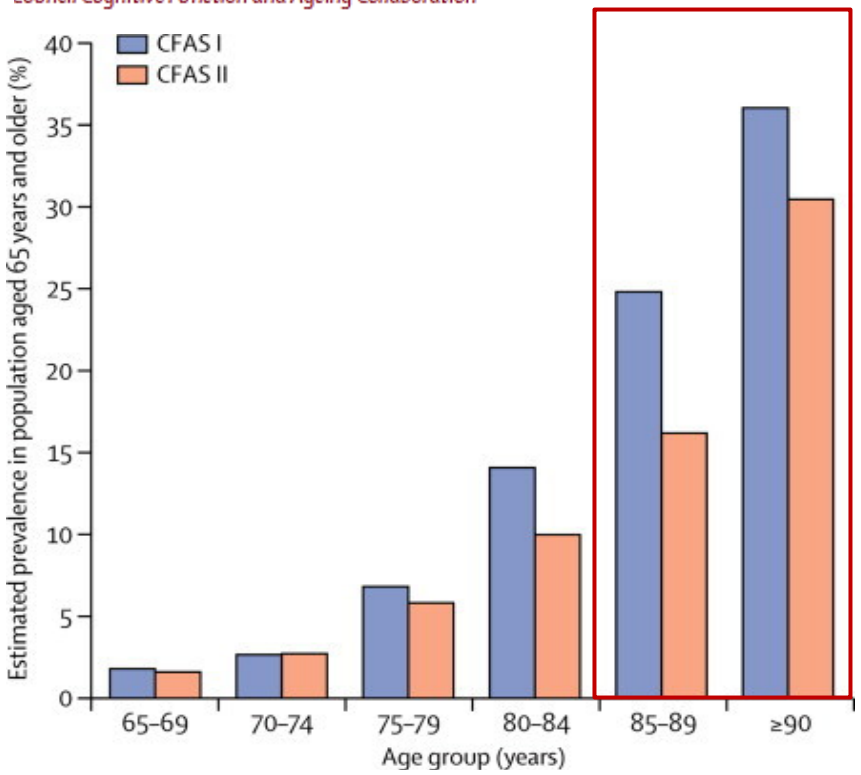


47 million

Wimo A et al 2015

A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II

Fiona E Matthews, Antony Arthur, Linda E Barnes, John Bond, Carol Jagger, Louise Robinson, Carol Brayne, on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration



Dementia prevalence can be modified by societal changes…..many factors increase dementia prevalence at specific ages (e.g. those associated with diabetes, survival after stroke, and vascular incidents),

Factors, which could decrease prevalence, such as improved prevention of vascular morbidity, higher levels of education, seem to have had a greater effect

Matthews FE, Arthur A, Barnes LE, MRC CFA S Collaboration. *Lancet* 2013; 382: 1405-1412.

"CFAS results suggest that prevention is possible and that we can have agency in this most complex of disorders." Sube Banerjee, Editorial Lancet, 2013

Unexpected Impact of COVID-19

Received: 20 May 2020 | Revised: 11 June 2020 | Accepted: 15 June 2020

DOI: 10.1002/alz.12143

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

PERSPECTIVES

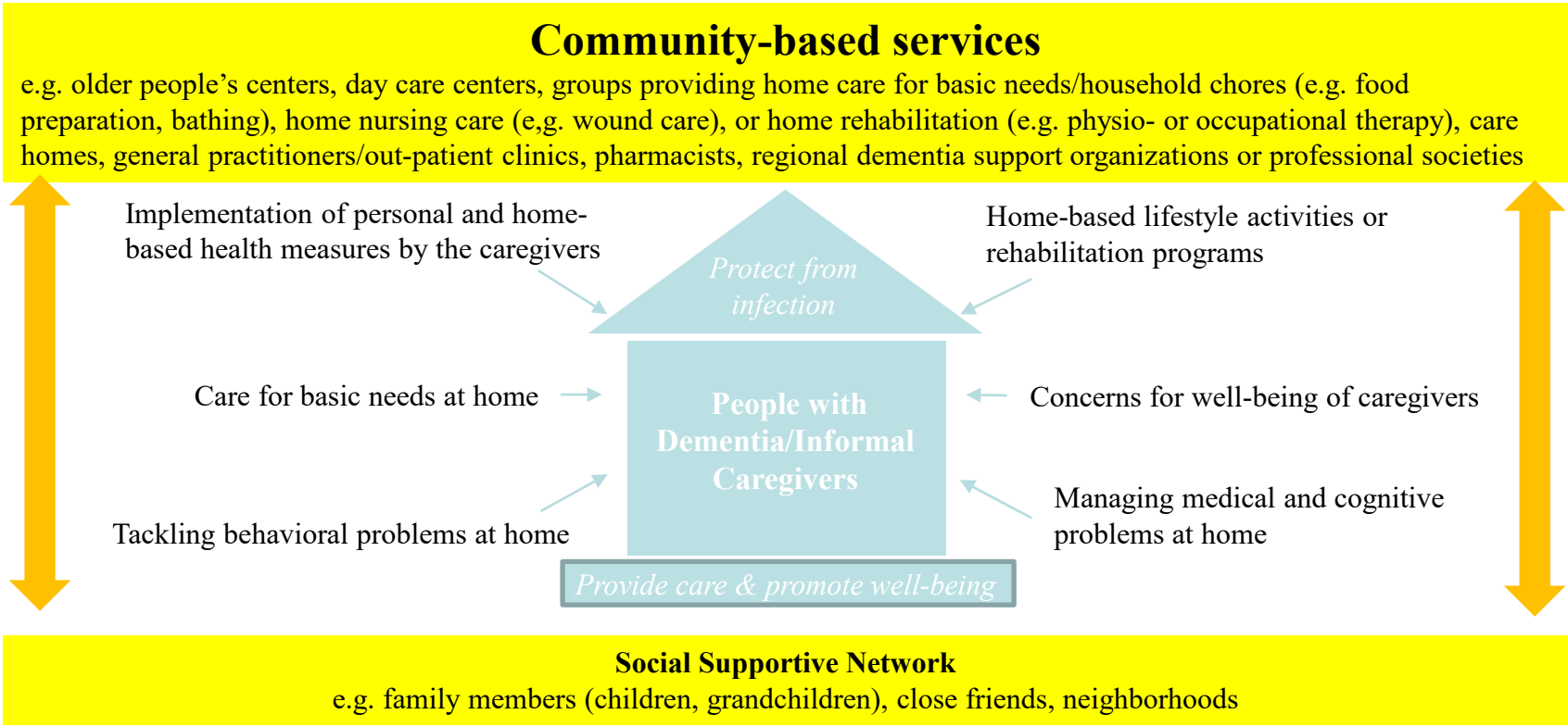
Tackling challenges in care of Alzheimer's disease and other dementias amid the COVID-19 pandemic, now and in the future

Vincent C.T. Mok[1,2,3] | Sarah Pendlebury[4,5,6] | Adrian Wong[1,2] | Suvarna Alladi[7] | Lisa Au[1,2] | Philip M Bath[8] | Geert Jan Biessels[9] | Christopher Chen[10] | Charlotte Cordonnier[11] | Martin Dichgans[12,13,14] | Jacqueline Dominguez[15] | Philip B. Gorelick[16,17,18] | SangYun Kim[19] | Timothy Kwok[20] | Steven M. Greenberg[21] | Jianping Jia[22] | Rajesh Kalaria[23] | Miia Kivipelto[24,25,26] | Kandiah Naegandran[27] | Linda C.W. Lam[28] | Bonnie Yin Ka Lam[1,2] | Allen T.C. Lee[28] | Hugh S. Markus[29] | John O'Brien[30] | Ming-Chyi Pai[31] | Leonardo Pantoni[32] | Perminder Sachdev[33] | Ingmar Skoog[34] | Eric E. Smith[35] | Velandai Srikanth[36] | Guk-Hee Suh[37] | Joanna Wardlaw[38] | Ho Ko[1,2,3] | Sandra E. Black[39] | Philip Scheltens[40]

- Likely profound impact of COVID-19 upon dementias- nature not certain?
- Proposal for a conceptual framework and practical suggestions for health-care providers
- Provides strategic directions and set standards for health-care leaders in dementia

Mok V et al, 2020

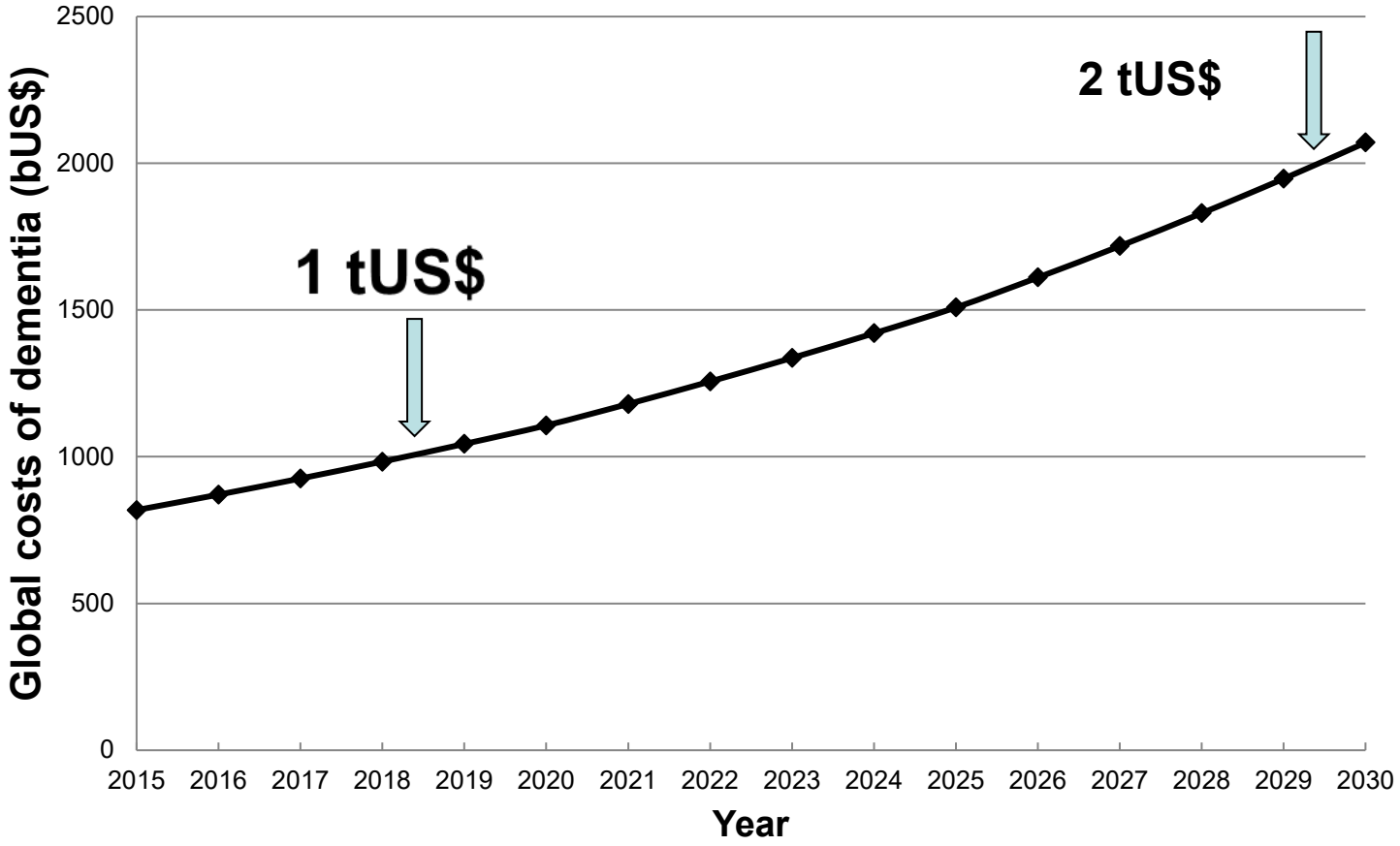
Conceptual framework of ”home-based” care strategies during lockdown period



Providing care for people with dementia/caregivers at home can be achieved by a dynamic interaction/partnership between patients' social supportive network and available community-based services, focus areas: implement infection control measures, care for basic needs, tackling behavioral problems, maintaining brain-healthy activities, concerns for caregivers, managing medical/cognitive problems. Simple and user-friendly telehealth technologies can facilitate better care delivery in many ways, making simple phone calls may sometime serve a similar purpose.

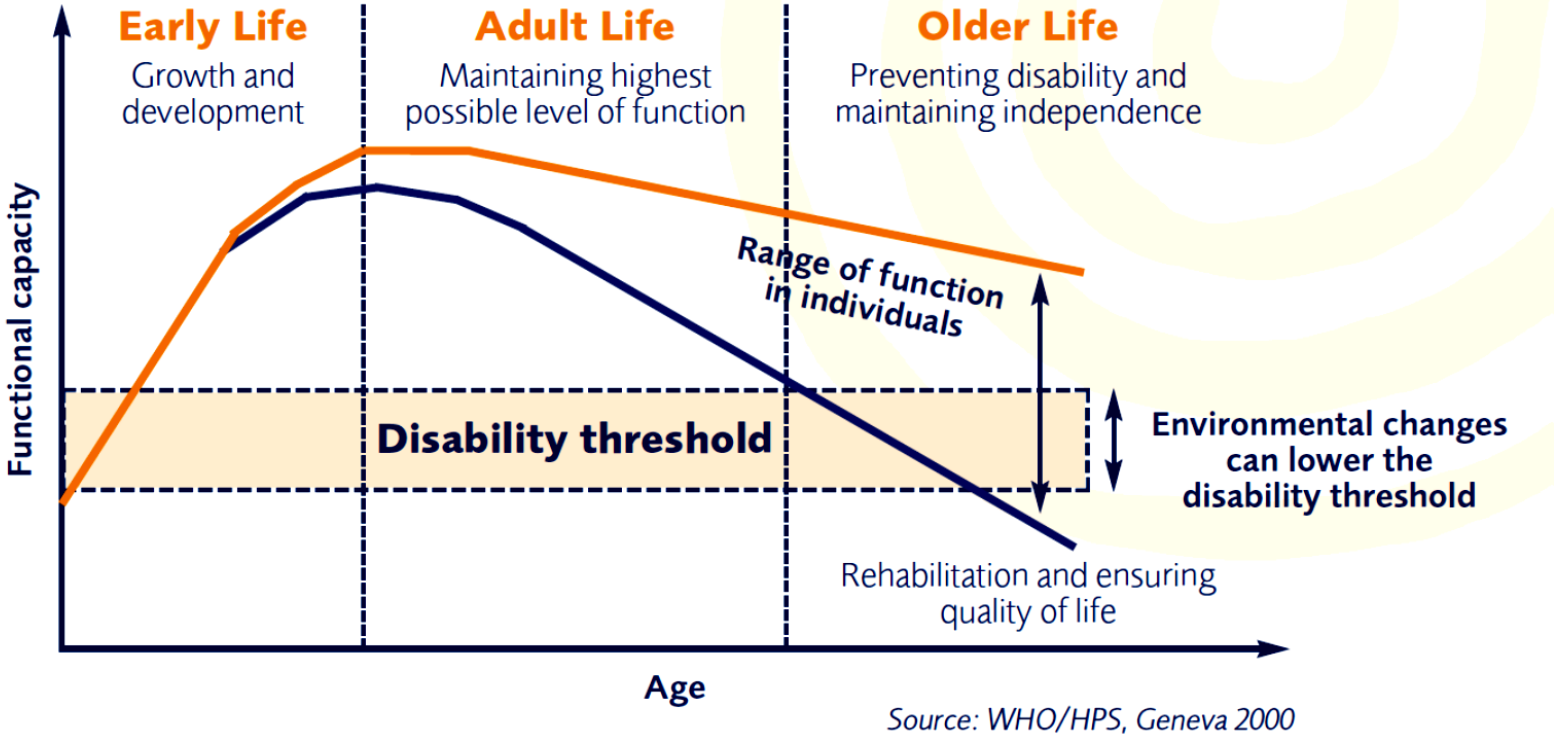
Mok V et al, 2020

Worldwide costs of dementia forecast

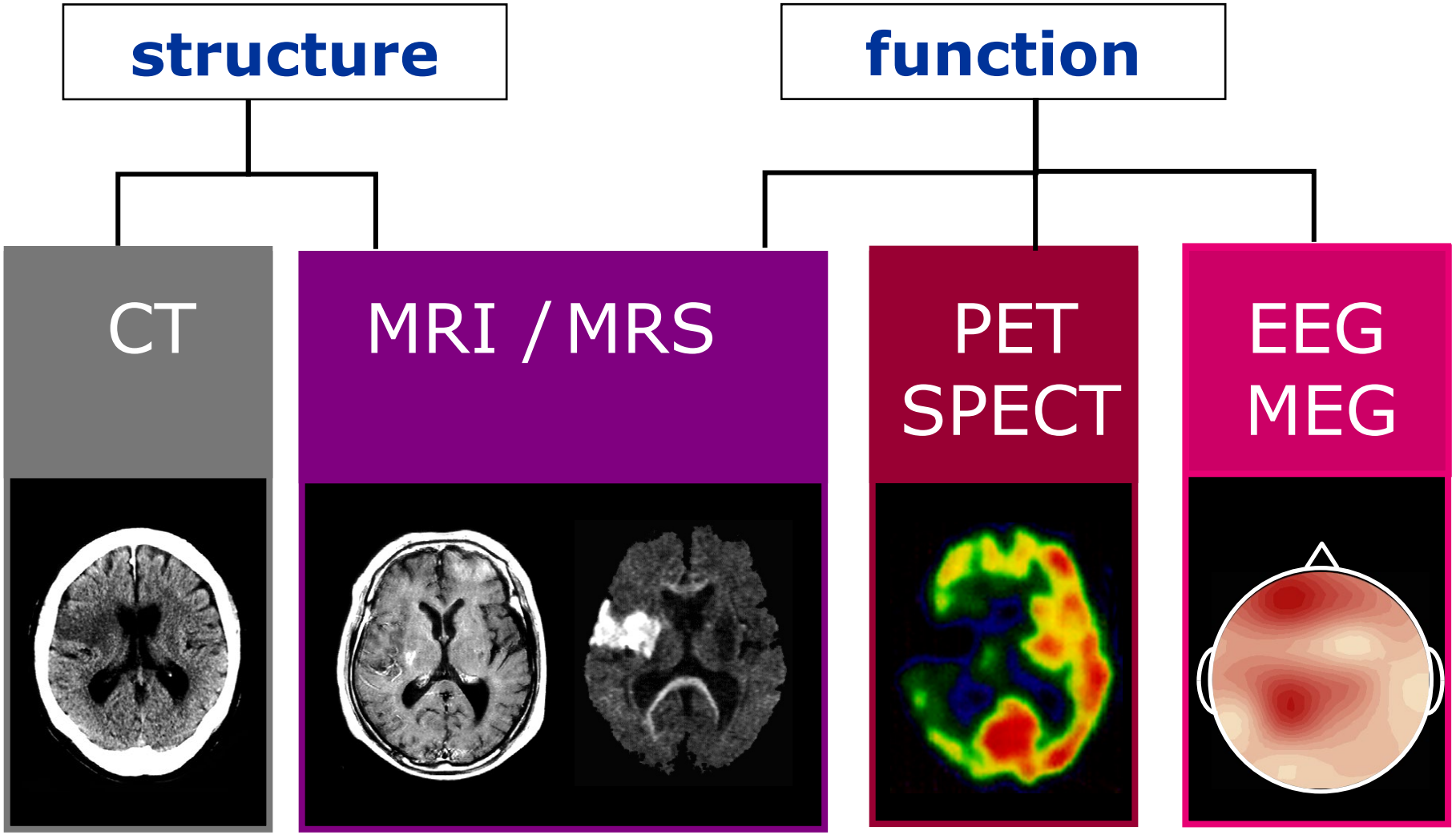


Wimo A et al, 2015

The Brain: an essential organ to maintain functional capacity during life

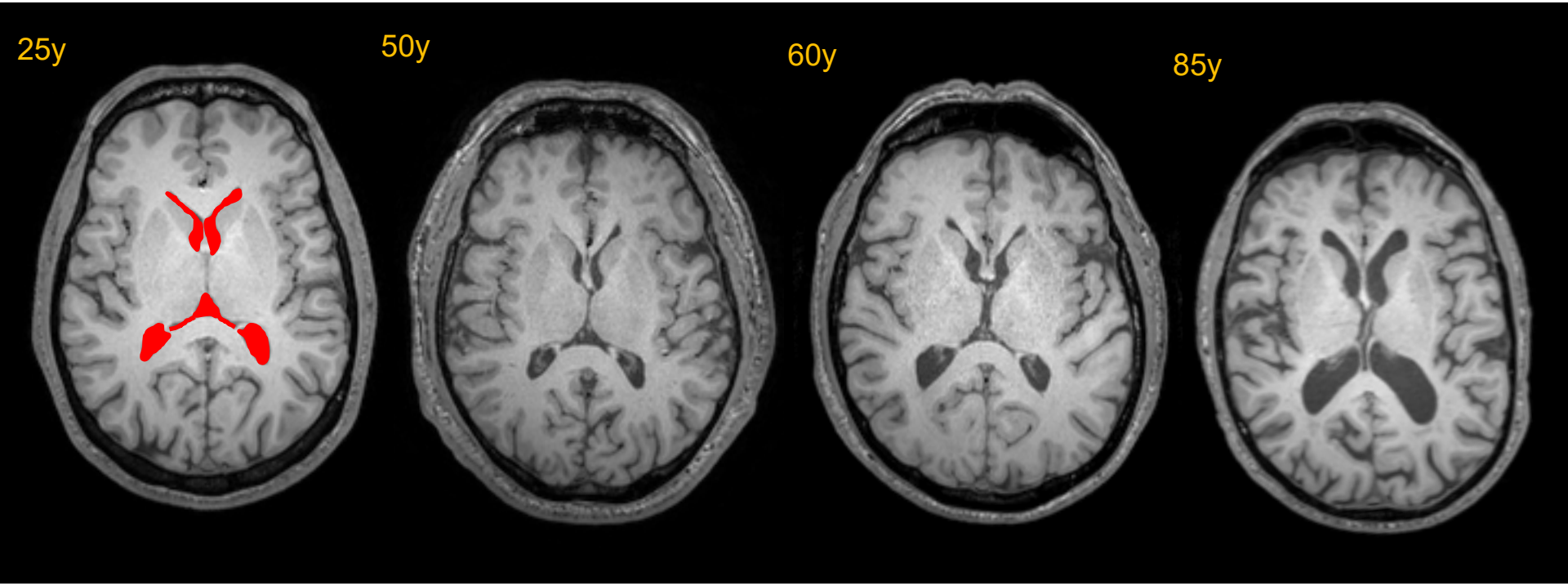


Diagnostic Brain Imaging Techniques



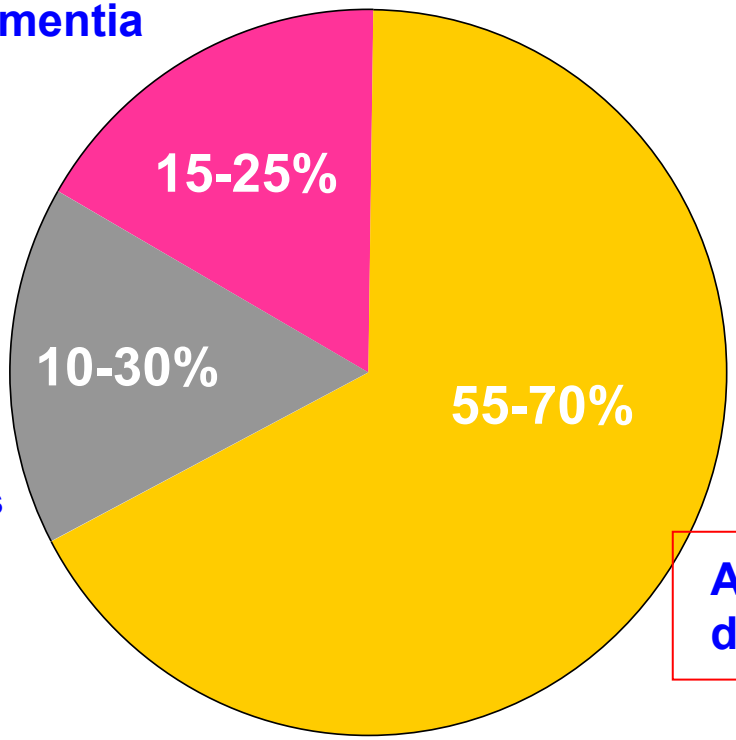
In addition other MR methods have been developed, e.g. DTI, MTI, T2* and fMRI

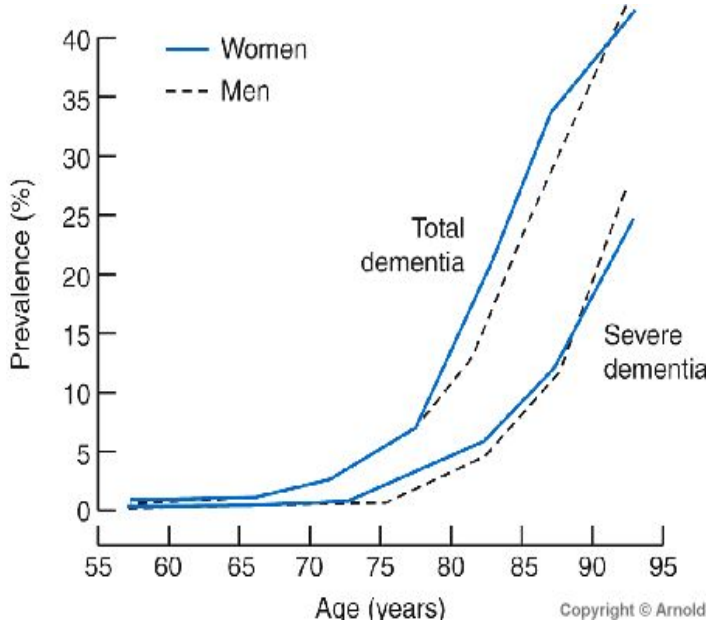
What happens to the brain as we age?



- Ventricles enlarge
- Cortex gets thinner – lose about 0.5% per year

What Are the Most Common causes of Degenerative Dementias?





Frataglioni L, et al. Neurology. 2000;54:S10-15
Rarer dementias not shown but do not amount to >15 of total.

Neurodegenerative Dementias

(specific molecular pathologies causing dementia)

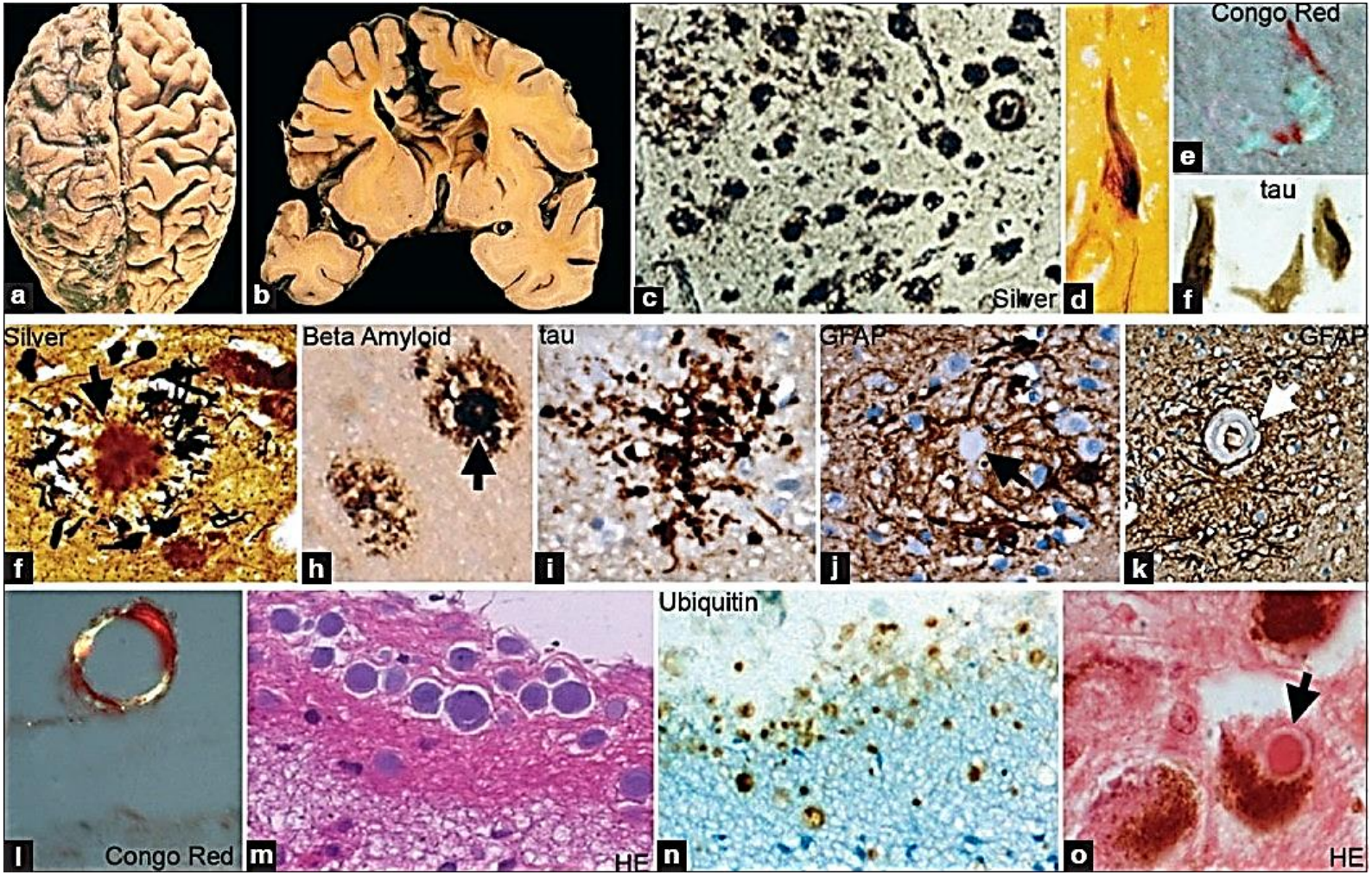
- Alzheimer's disease and age-related disorders
- Dementia with Lewy bodies (DLB); Parkinson disease with dementia (PDD) -The synucleinopathies
- Frontotemporal dementia (+tau) / Tauopathies
  - FTD and Parkinsonism Chr. 17, CBD, PSP, Pick's disease
  - Argyrophilic grain disease (AGD) and Tangle only dementia
- Frontotemporal dementias (-tau)
  - FTDs with ubiquitin, progranulin and TDP-43 inclusions
- Prion diseases
  - Creutzfeldt-Jakob disease, Fatal familial insomnia, GSS, Kuru
- Trinucleotide Repeat disorders (polyglutamine diseases)
  - Huntington's disease (HD), Spinocerebellar ataxias, Friedreich's Ataxia
- HIV-related Neurocognitive Disorders; HAND, HAD, HIVE
- Motor Neurone Disorders; ALS, PLS, SMA with dementia

Pathological Expression of Disease: Disorders of protein accumulation or proteinopathies

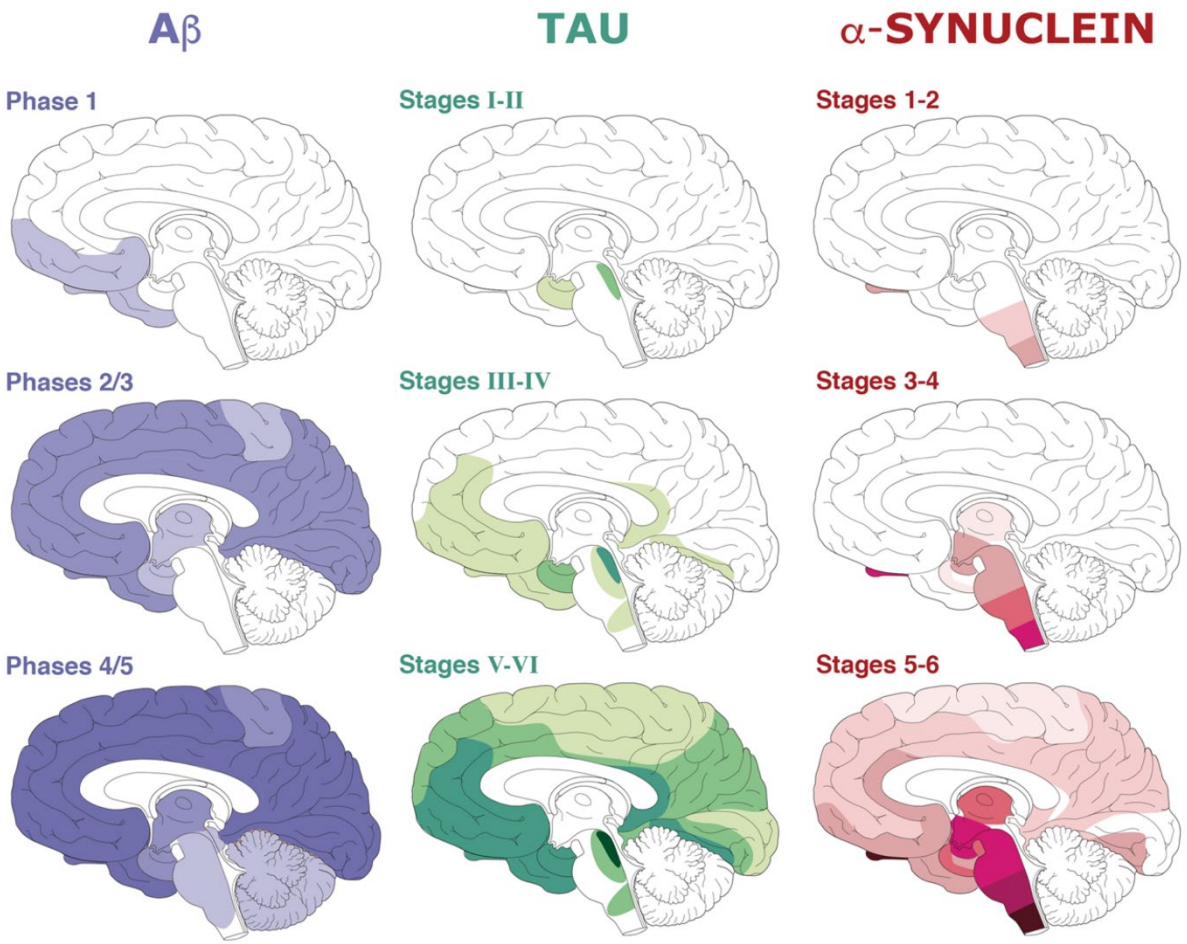
- Alzheimer disease - Aβ plaques, tau
- Parkinson's/ DLB - LBs (α-synuclein)
- FTD I: FTDP-17/ Pick's CBD, PSP - Tau+, Pick bodies (3R and 4R tau)
- FTDs II: - Tau-, ubiqutin, PGRN, TDP-43
- Prion diseases - PrP plaques, tau, CAA
- Multiple System Atrophy - Glial synuclein inclusions
- Polyglutamine diseases - HD and Spinocerebellar Ataxias

(as extracellular deposits or intracellular inclusions; insoluble (or protein misfolding) products that form aggregate by "seeding" mechanism)

Accumulation of Different Types of Brain Pathology during Ageing



Propagation of Neurodegenerative Pathologies in Common Dementias

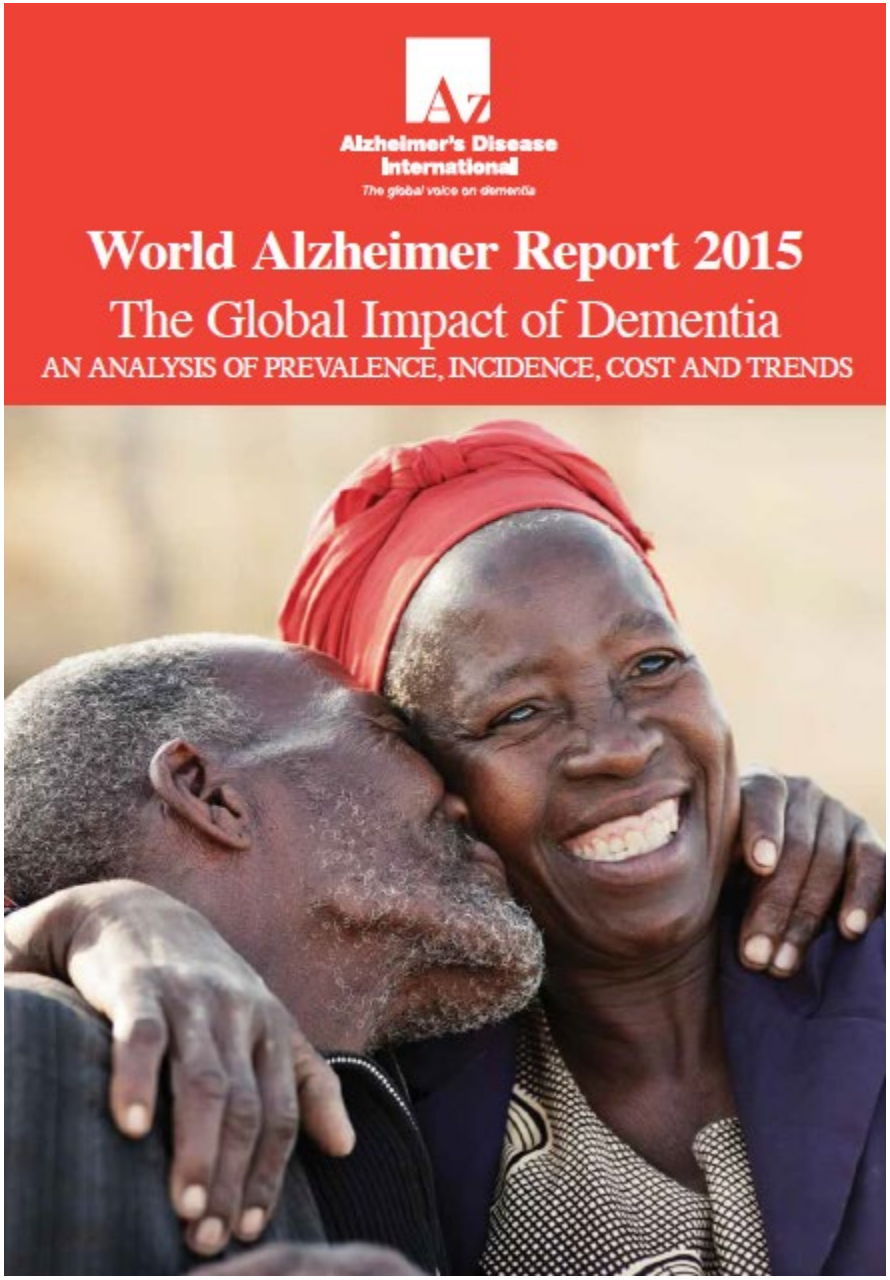


- Highest stages are diagnostic for the dementia type

Goedert M et al, 2015

Ageing-related Brain Disorders and Dementias

- Alzheimer's Disease
- Parkinson's Disease
- Dementia with Lewy Bodies
- Frontotemporal Dementias
- Prion Diseases
- Vascular Dementia



What is Alzheimer's Disease?

A progressive degenerative brain disorder and the most common cause of dementia

Alzheimer's Disease: Main features

- Alzheimer type of dementia: 55%-60% of all dementia cases
- AD ~doubles after age 65 yrs:
  - >65 yrs 5% (3%- 11%); >75 yrs: 10% (7%-15%); >85 yrs: 20%...
- Majority of AD late-onset: Slow gradual onset and progression;
  - Predominance of memory impairment (a. over intellectual impairment or b. meet general criteria for dementia)
  - 5% estimated to be of familial form: autosomal dominant inheritance
  - Mild cognitive impairment ('early stage' of AD) 63%-80% will progress to AD
- Diagnosis of exclusion: no evidence of CVD, HIV, PD, HD, NPH
- Definitive diagnosis by neuropathological examination
  - presence of amyloid plaques and neurofibrillary pathology

Age and Illiteracy are the strongest risks

Alzheimer's disease
(common dementia)

- Age
- Family history
- Down's syndrome
- Head injury
- Apolipoprotein E-ε4
- Vascular factors
- Smoking
- Female gender

	Developed regions (North America, Europe, Japan)	Asia (China, Guam, India, South Korea, Taiwan*)	Africa (Egypt, Nigeria, Kenya, South Africa)	Latin America (Argentina, Brazil, Venezuela)
Increasing age	Positive	Positive	Positive	Positive
Female sex	Positive	Positive	Unclear	Unclear
Family history	Positive	Positive	..	Positive
Head injury	Positive	..	..	Positive
Genes (APOE ε4 allele)	Positive	Positive	No risk	Unclear
Illiteracy or lack of education	Positive	Positive	Positive	Positive
MCI or cognitive impairment without dementia	Positive	Positive	..	Positive
Urban living	Unclear	Unclear	Negative	Positive
Low socioeconomic status or poverty	Unclear	Positive	..	Positive
Occupation as housewife	Negative	Positive	Unclear	Positive
Depressive illness	Positive	Positive	Positive	Positive
Vascular disease†	Positive	Positive	Positive	Unclear
Low fibre diet	Unclear	Positive	Positive	..
Smoking	Positive	Positive	..	Unclear

Kalaria RN et al, 2008; 2012

Alzheimer's Disease International

The global voice on dementia

Dementia in sub-Saharan Africa

Challenges and opportunities

frontiers in Neurology

SYSTEMATIC REVIEW
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Dominant and Modifiable Risk Factors for Dementia in Sub-Saharan Africa: A Systematic Review and Meta-Analysis

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OPEN ACCESS

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Background: Sub-Saharan Africa (SSA) is projected to have a rapid increase in the number of people living with dementia by 2050. Yet, there is currently no robust evidence on the risk factors for dementia in the sub-region that could inform context specific interventions.

Methods: We conducted a systematic review and meta-analysis of observational studies to determine the dominant and modifiable risk factors for dementia in SSA. We searched MEDLINE, EMBASE, PsychINFO, and African Journals Online using keywords for dementia and Alzheimer's disease as well as the.mp operator for all 47 SSA countries

Diagnosis of Dementia

Criteria (NINCDS-ADRDA, 1984; ICD-10, 1993; APA, 1994; 2011)

Development of multiple cognitive deficits manifested by both:

- **Memory impairment** (impaired ability to learn new information or to recall previously learned information)
- One (or more) of the following cognitive disturbances: a. **Aphasia** (language disturbances); b. **Apraxia** (impaired ability to carry out motor activities despite intact motor function); c. **Agnosia** (failure to recognize or identify objects despite intact sensory function); d. **Disturbance in executive functioning** (i.e., planning, organizing, sequencing, abstracting)
- Cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning

Diagnostic issues in AD (2)

Early and Late-onset

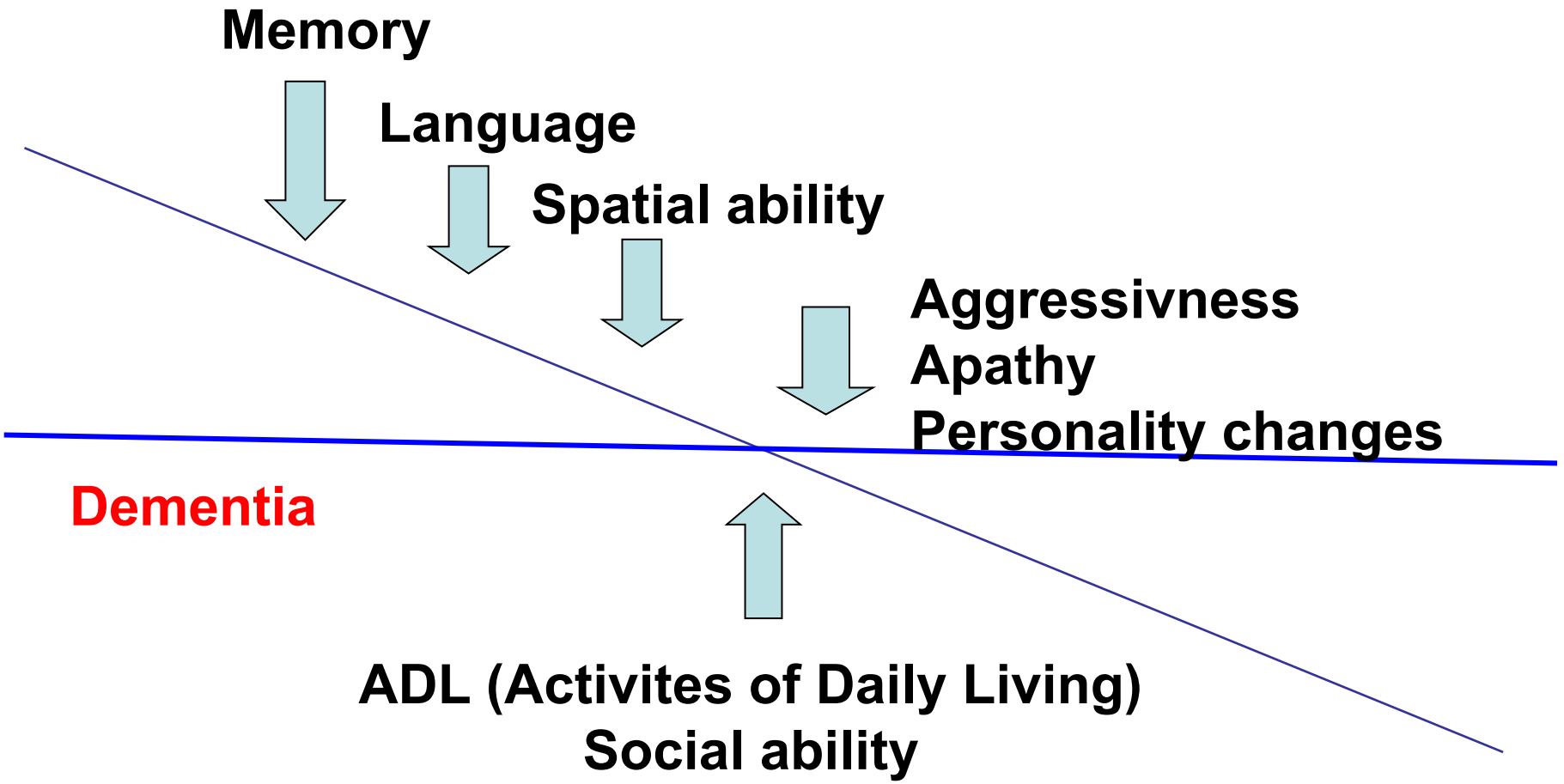
EOAD (<65 years; usually familial)

Relatively rapid onset and progression; memory impairment; aphasia; agraphia; alexia; acalculia or apraxia (presence of temporal, parietal and frontal lobe involvement)

LOAD (>65 years)

1. Evidence of very slow gradual onset and progression (may only be obvious retrospectively)
2. Predominance of memory impairment (a. over intellectual impairment or b. meet general criteria for dementia)

CognitiveAgeing related thresholds leading to Alzheimer's Disease



Signs of Dementia vs Age-Related Changes

- Memory loss that disrupts daily life: forgetting recently learned information
- Challenges in planning or solving problems: changes in their previous abilities and concentrating
- Difficulty completing familiar tasks: difficulties in daily tasks in familiar environments
- Confusion with time and place: lose track of dates, seasons and passage of time
- Trouble undertstanding visual images and spatial relationships: difficulty reading, judging distance, colour, contrast
- New problems with words in speaking or writing: difficulty following/joining conversation, vocabulary problems..
- Misplacing things and losing ability to retrace steps: losing things and the way
- Decreased or poor judgement: experience changes in decision-making
- Withdrawl from work or social activities: cannot keep up with social activities, hobbies, work projects, sports etc.
- Changes in mood and personality: become confused, suspicious, aggressive, fearful, anxious, easily upset

Alzheimer's Association, Alzheimers Dement 2017;13:325-373.

Terminal stages of AD

How can we tell?

- Limited vocabulary (six words or less)
- Absence of smiling
- Inability to walk without substantial assistance
- Inability to sit up independently
- Difficulty eating or swallowing
- Recent weight loss
- Decreased consciousness or coma
- Bowel or urinary incontinence
- Recurrent respiratory or urinary infections
- Inability to hold up the head or track objects with the eyes

Presentation of AD
Neuropsychiatric Inventory (NPI)

❶Apathy	72%	Appetite	31%
❷Agitation	60%	❷Disinhibition	30%
❷Anxiety	45%	Night-time	24%
❸Irritability	42%	❹Delusions	22%
❹Depression	38%	❹Hallucinations	10%
❸Motor behaviour	38%	Euphoria	2%

J Cummings, 2010

Diagnosis of Alzheimer's Disease:
NINCDS-ADRDA Criteria

Dementia

- Impaired memory
- ≥ 1 other cognitive domain impaired
- Clinical examination
- Neuropsychological tests

↓

Probable/Possible diagnosis

- Progressive worsening
- Absence of other disorders that could account for deficits

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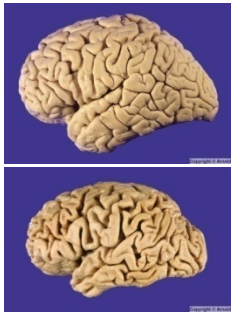


Definitive diagnosis by autopsy →

Diagnosis of AD

McKhann G, et al. Neurology. 1984;34:939-944
McKhann G et al, Alzheimers Dement 2011;7:257-62.

www.thelancet.com/neurology **Vol 11 October 2012**

Articles

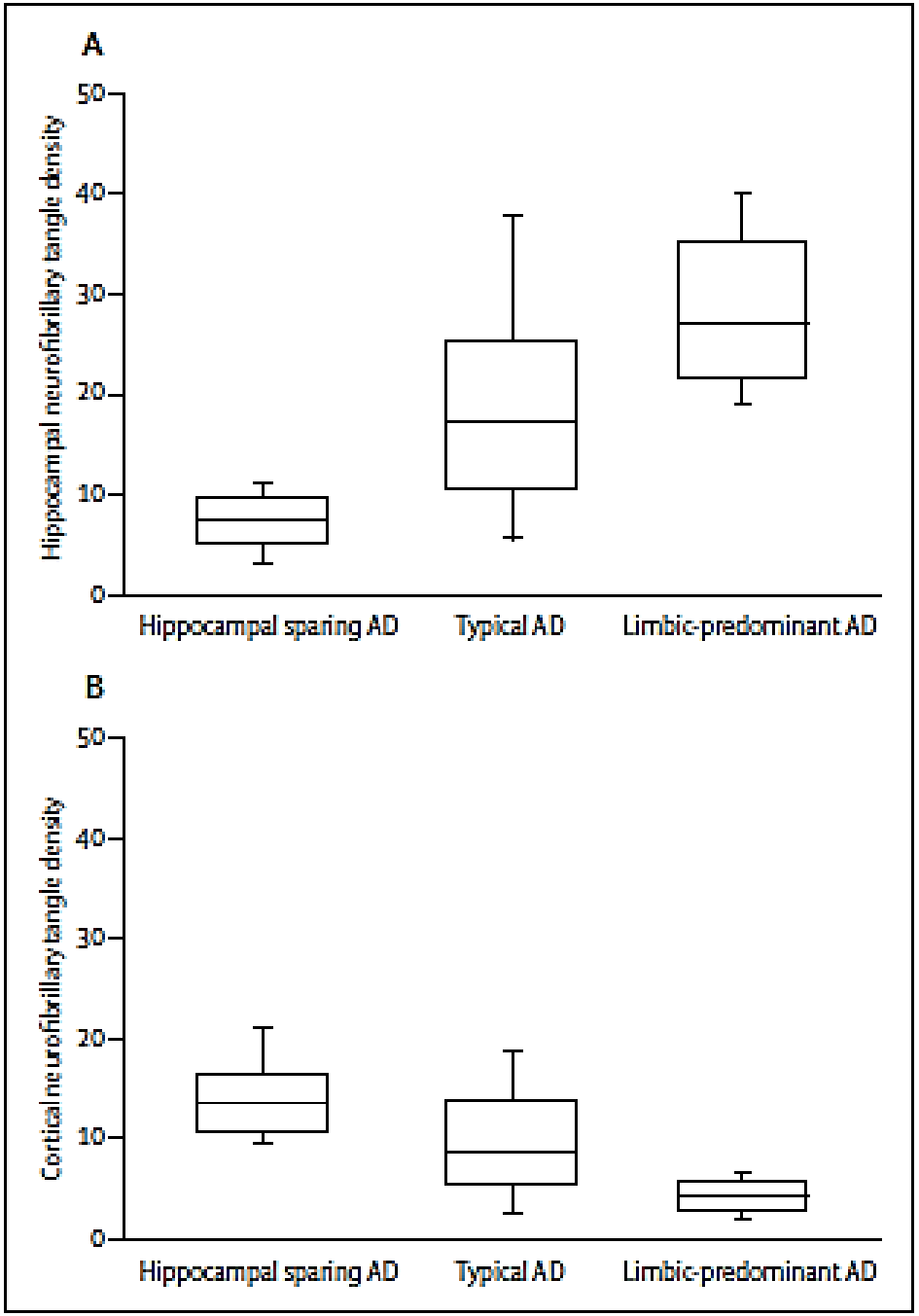
Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study

Melissa E Murray, Neill R Graff-Radford, Owen A Ross, Ronald C Petersen, Ranjan Duara, Dennis W Dickson

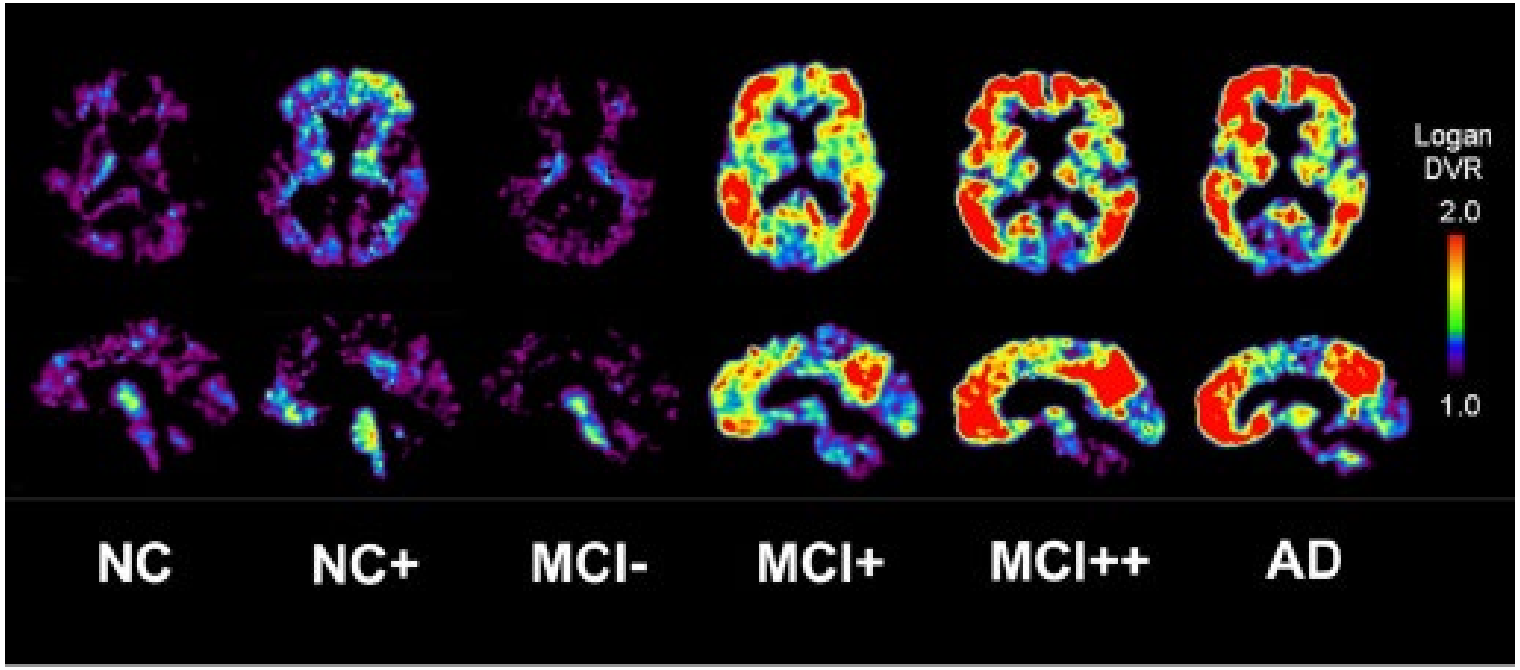
- Hippocampal sparing and limbic-predominant AD subtypes account for ~25% of cases
- Supports hypothesis that AD has distinct clinicopathological subtypes
- Implications for designing clinical, genetic, biomarker, and treatment studies

Hippocampal and cortical NFT densities by AD subtype

- Hippocampus: average NFT count per 0.125 mm2 for the CA1 and subiculum regions.
- Cortex: average NFT count per 0.125 mm2 for the superior temporal, middle frontal, and inferior parietal regions
- Box plots: median (IQR) and error bars represent 10–90th percentile

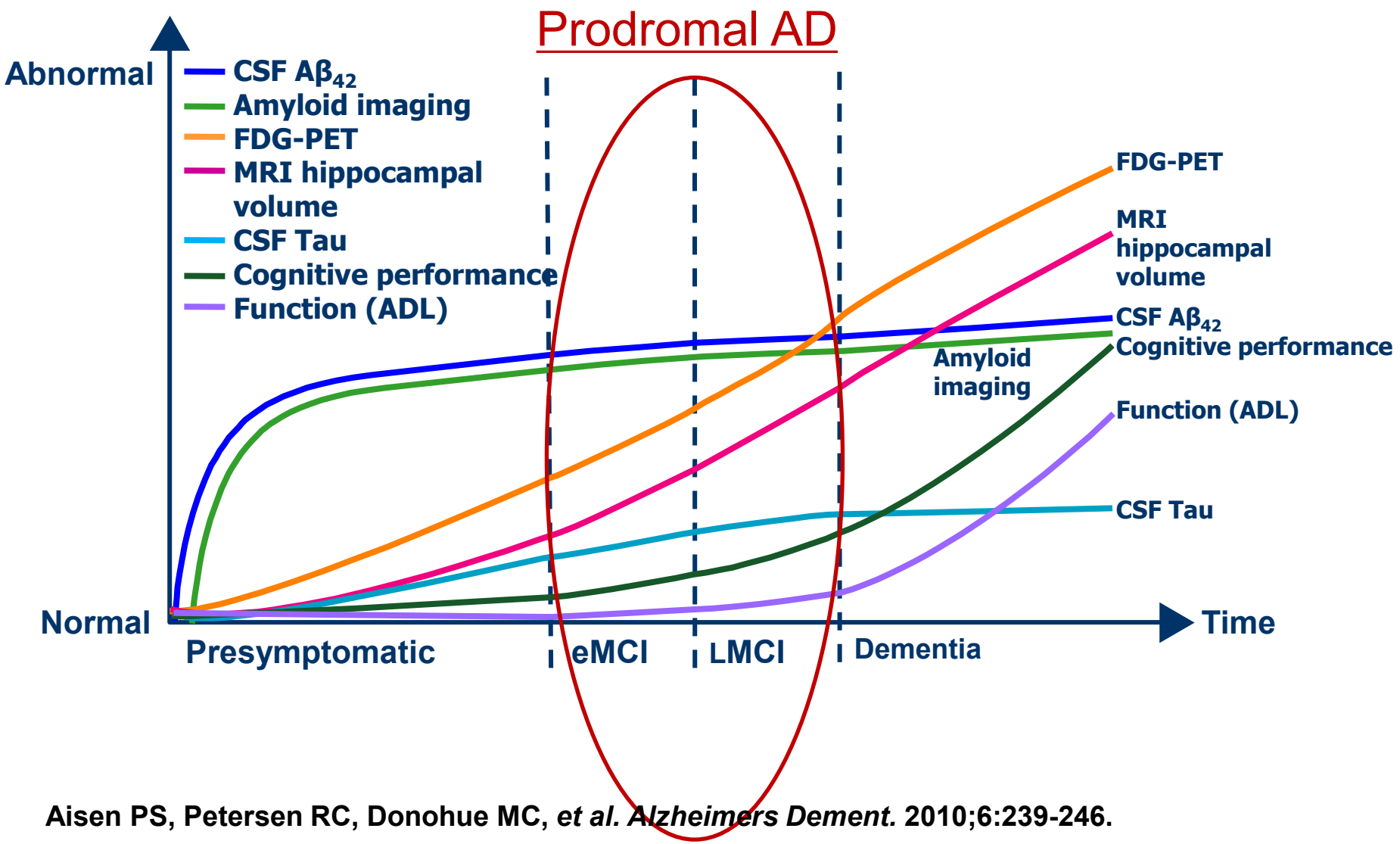


Amyloid Deposition precedes Clinical Dementia by Years



Mathis *et al.*,*Nucl Med Biol* 2007;**34**(7);809-22

Progression of Dementia

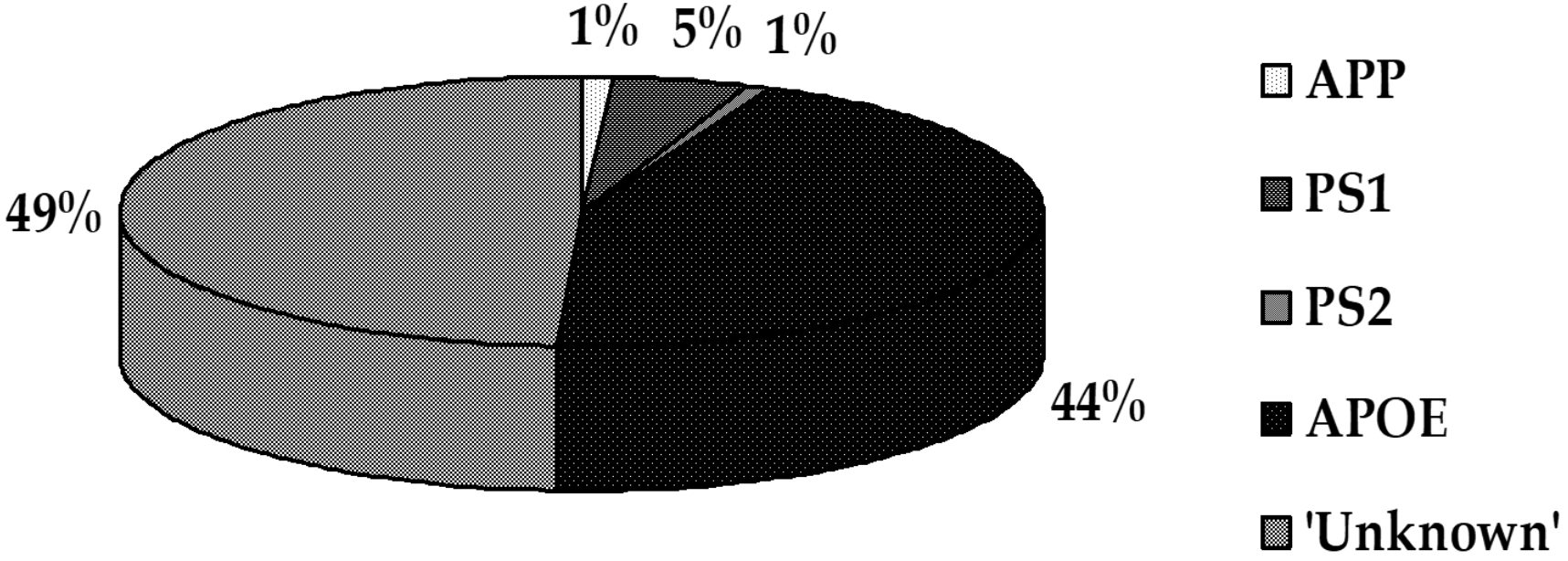


Aisen PS, Petersen RC, Donohue MC, *et al. Alzheimers Dement.* 2010;6:239-246.

Genetics of AD: how much of AD is explained by autosomal dominant or recessive patterns?

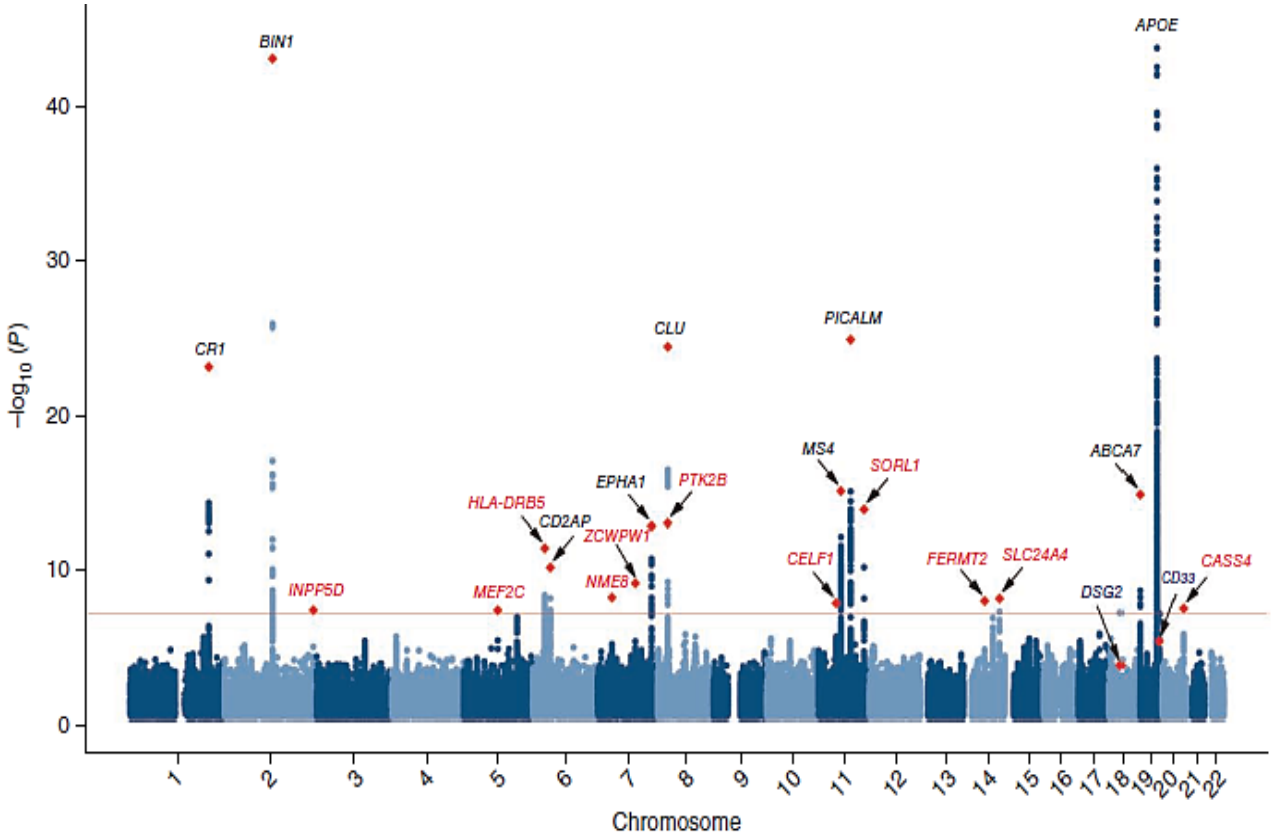
Sporadic AD 90-95%;

Familial AD ~5-10%



***Current estimates from ~500 families world-wide**

Genes and Molecular Genetics of AD



Manhattan plot of stage 1 for genome-wide association with Alzheimer's disease (17,008 cases and 37,154 controls). Red line- The threshold for genome-wide significance ($P < 5 \times 10^{-8}$). Newly associated genes (Red) and previousyl identified genes (Black) are shown. Red diamonds represent SNPs with the smallest *P* values in the overall analysis.

Neuropsychometric Test and Screening*

- Cognitive function tests have been used and developed over several years, many translated in local languages

- First stop: Mini-Mental State Examination (MMSE)-widely used; Others Montreal Cognitive Assessment (MoCA)

- Neuropsychometric Batteries/Tools contain several components to test different cognitive abilities, e.g. CANTAB, CAMCOG, ADAS-Cog, CASI, **IDEA** etc.

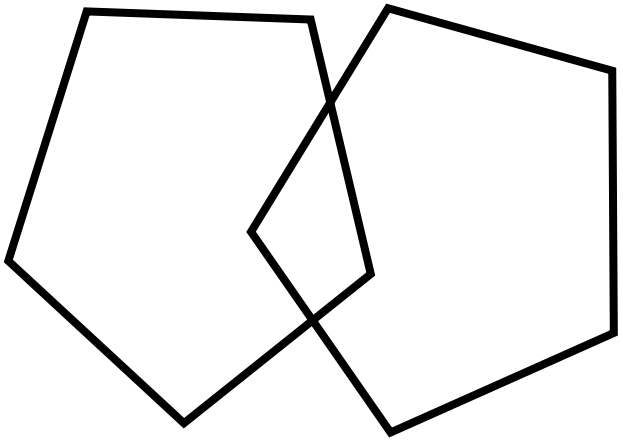
- Value of informant questionnaires; IQCODE

**Most tools widely available online; main obstacles availability of trained staff*

Mini-Mental State Examination

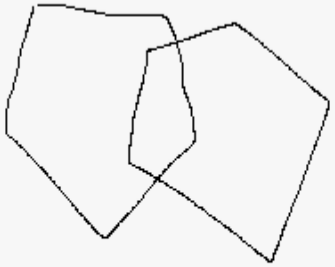
- MMSE is a short test which measures general cognitive status including short-term memory (Folstein, et al, 1975)

- MMSE includes tests for orientation (e.g. year, season, etc.), registration, attention and calculation, recall, and language



- MMSE is a 30 points score test. Mildly cognitively impaired subjects can have scores 26 to 21

Alzheimer's Disease (AD)



MMSE 18/30

Orientation 5/10

Short term memory 0/3

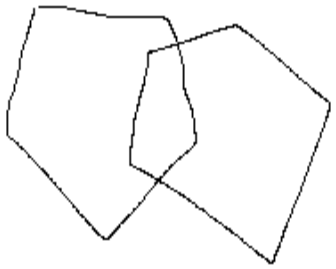
Dementia with Lewy Bodies (DLB)

MMSE 20/30

Orientation 8/10

Short term memory 2/3

Alzheimer's disease



MMSE 18/30

Orientation 5/10

Short term memory 0/3

Dementia with Lewy Bodies

MMSE 20/30

Orientation 8/10

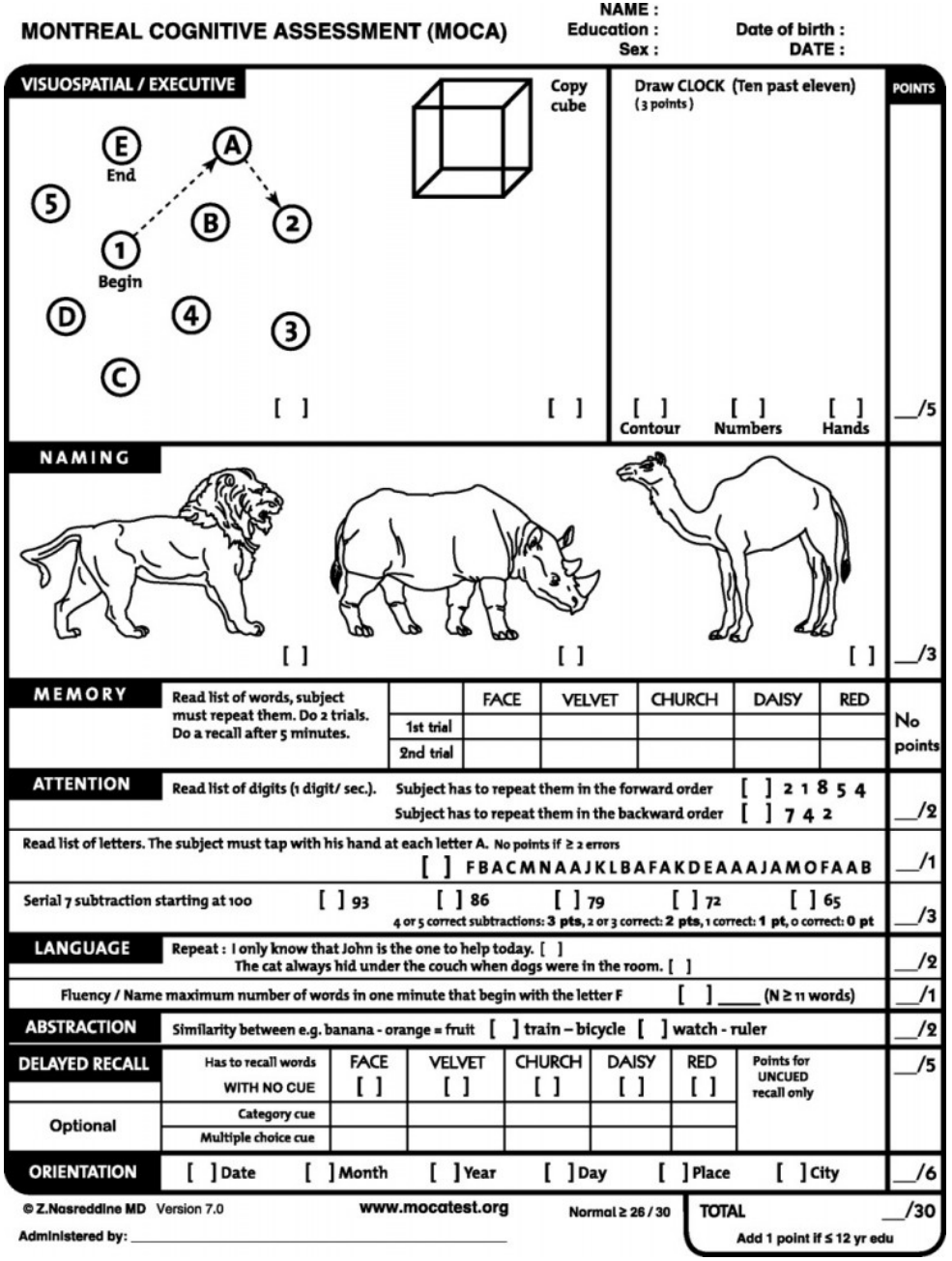
Short term memory 2/3

Montreal Cognitive Assessment (MoCA)

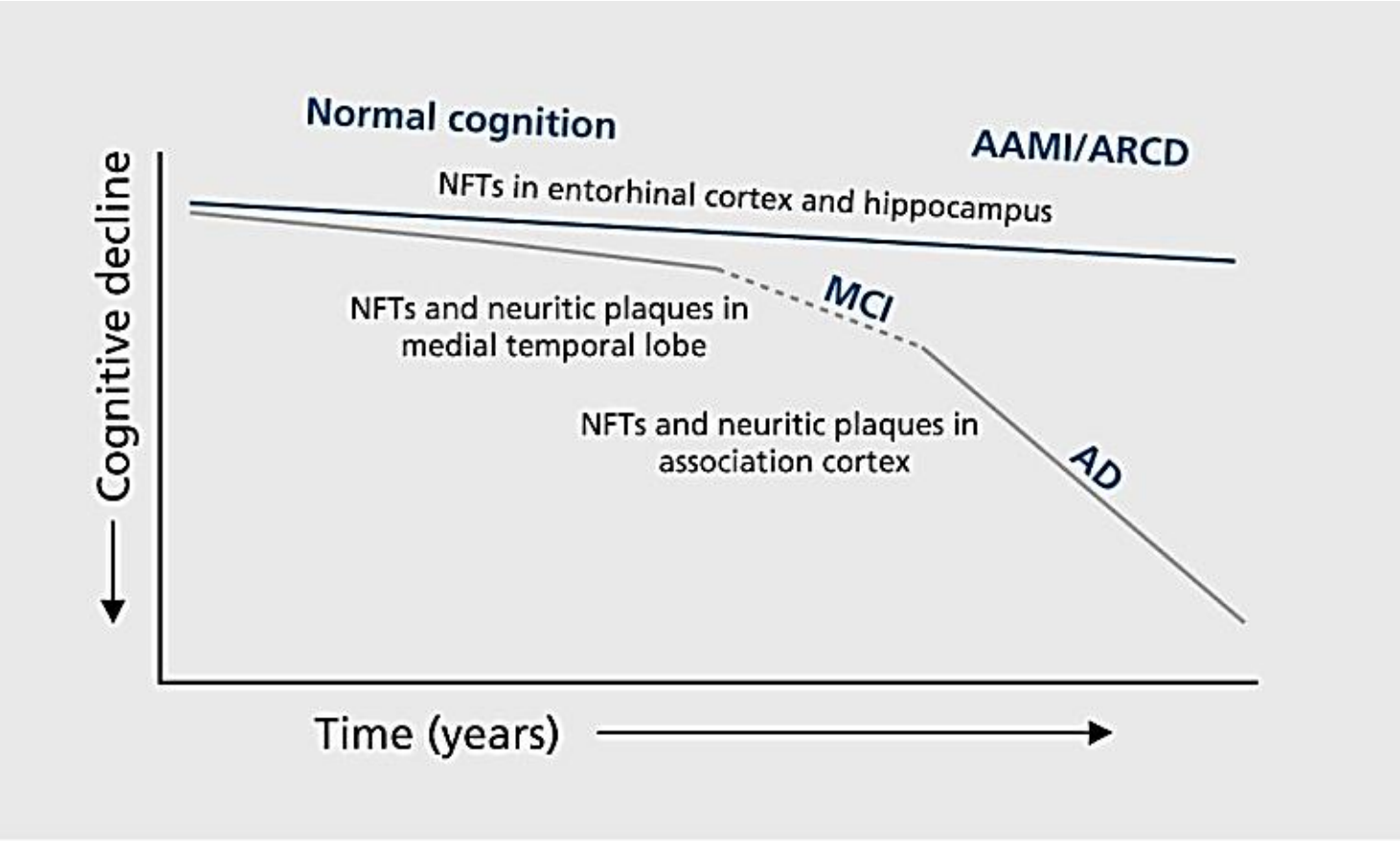
MoCA
MONTREAL
COGNITIVE ASSESSMENT

- MoCA also includes tests for orientation (e.g. year, season, etc.), registration, attention and calculation, recall, and language biased towards **Executive Dysfunction**

- MoCA a 30 points score test. Mildly cognitively impaired subjects can have scores 26 to 21



Progression of Dementia



Progressive accumulation of brain pathology increases damage and decreases cognitive functions

Why focus on MCI?

- Mild cognitive impairment (MCI) is an intermediate between normal ageing and dementia
- Area of intervention to prevent or delay progression of dementia
- Earlier treatment will lead to better prognosis
- Caregiver support and planning (Wills etc.)

Stephan, Minett, Pagett et al. BMJ Open 2013;3:e001909

MCI patients at higher risk for AD

- Older age (but not older than 85 yrs)
- Lower education
- Lower physical activity
- Recurrent depression
- Uncontrolled vascular risk factors (DM2, HPT, AF)
- Use of inappropriate medications
- MRI hippocampal atrophy
- CSF and PET indicating amyloid accumulation

Medications for MCI and AD

1. Memory enhancers:

Acetylcholinesterase inhibitors (AChEI's):

a. Donepezil ('Aricept') 5-10mg at night

b. Rivastigmine ('Exelon') 3-6mg twice daily

c. Galantamine ('Reminyl') 16-24mg daily

NMDA-receptor antagonist:

d. Memantine ('Ebixa') 10mg twice daily

2. Psychotropic agents for residual symptoms (BPSDs) i.e. mood (depression & irritability) and behavioural disturbances (restlessness, agitation, psychotic symptoms, insomnia)- ***antidepressants, neuroleptics, anticonvulsants***

3. Control of cardiovascular risk factors e.g. HTN

4. Aβ lowering vaccines: aducanumab (June 2021)

Ageing-related Brain Disorders and Dementias

- Alzheimer's Disease
- Parkinson's Disease
- Dementia with Lewy Bodies
- Frontotemporal Dementias
- Prion Diseases
- Vascular Dementia

Dementia with Lewy Bodies (DLB)
(PDD-AD continuum)

- Dementia syndrome (early neuropsychiatric features)
- Mild Parkinsonism
- Visual hallucinations and fluctuations in conscious level
- Cortical Lewy Bodies
- Relatively little tangle burden
- Marked cholinergic deficits but preserved M1 receptors

Diagnostic Criteria for DLB

McKeith et al, Neurology, 2005; 2017

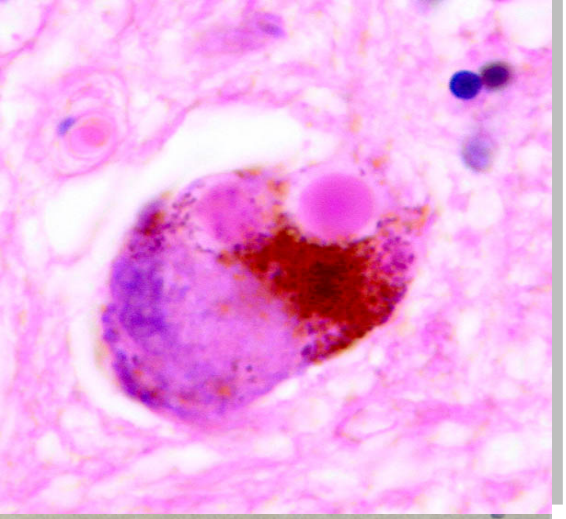
- **Cognitive decline & reduced social/occupational function**
  - Attentional, executive and visuo-spatial dysfunction prominent
- **CORE features**
  - Fluctuation
  - Recurrent visual hallucinations
  - Spontaneous parkinsonism
- **Suggestive features:**
  - REM sleep behaviour disorder
  - Neuroleptic sensitivity
  - Dopaminergic abnormalities in basal ganglia on SPECT/PET

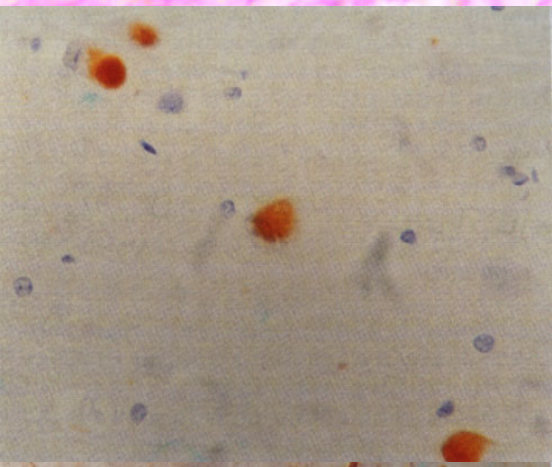
At least one core + one suggestive or 2 core features for Probable DLB

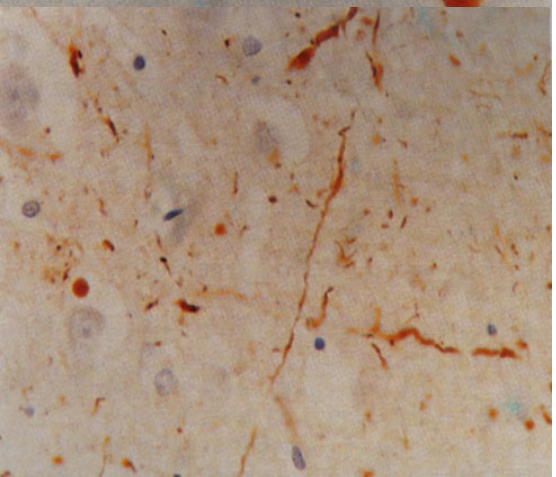
One core or suggestive feature sufficient for Possible DLB

Dementia with Lewy Bodies

- ~15% of all dementia cases have Lewy body pathology at autopsy
  - Lewy body variant of Alzheimer's disease
  - Lewy body dementia
  - Diffuse Lewy body disease
- Most are not recognised clinically during life
  - Diagnosed as Alzheimer's or vascular dementia

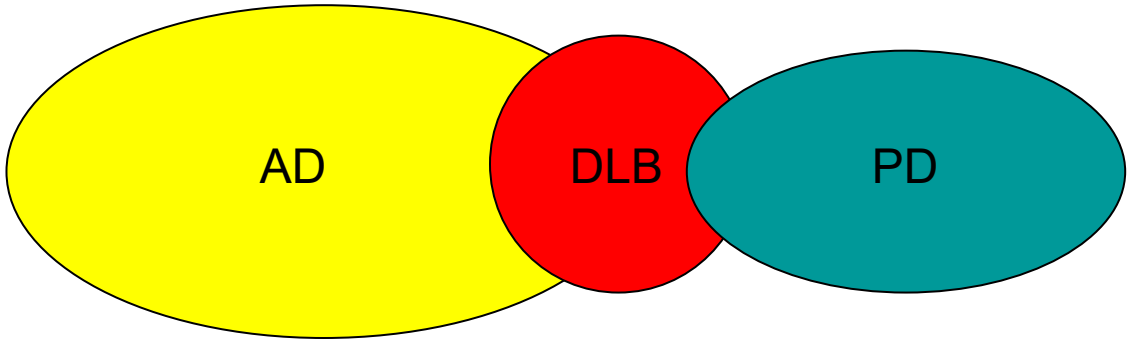






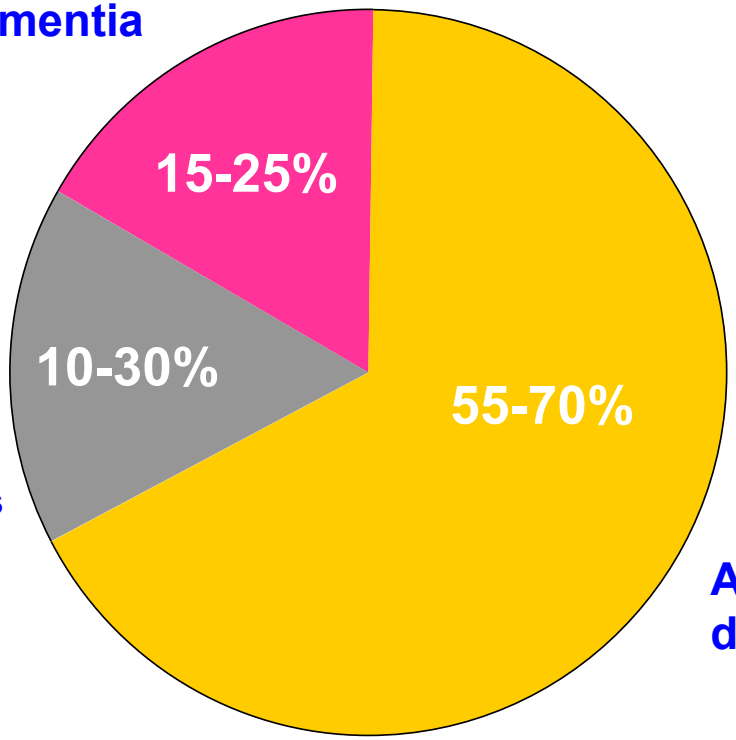
AD-DLB-PDD continuum

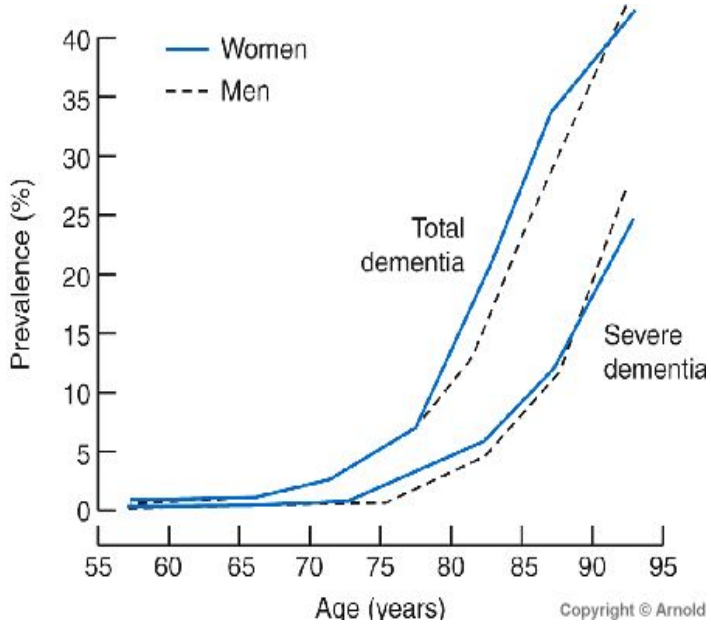
- Lewy bodies and Lewy neurites seen in ~ 15% of all autopsy cases of dementia
- One in seven cases of dementia is due to DLB
- One case of DLB for every 4 of AD and 2 of PD



McKeith I et al, 2017

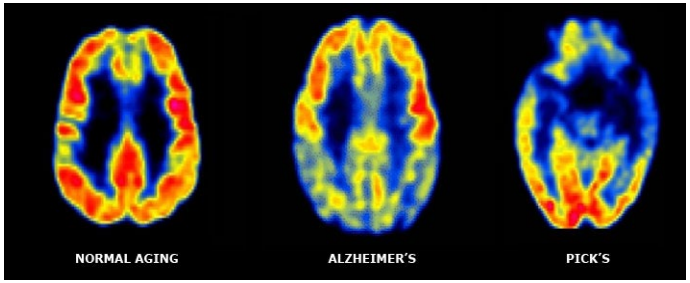
What Are the Most Common causes of Degenerative Dementias?





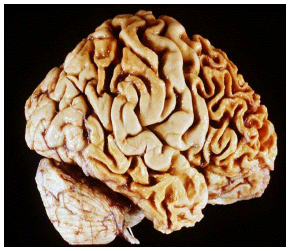
Frataglioni L, et al. *Neurology*. 2000;54:S10-15
Rarer dementias not shown but do not amount to >15 of total.

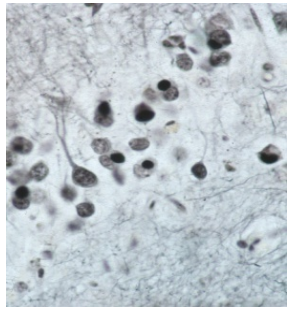
Frontotemporal Dementias (FTD)



Arnold Pick
1854- 1924

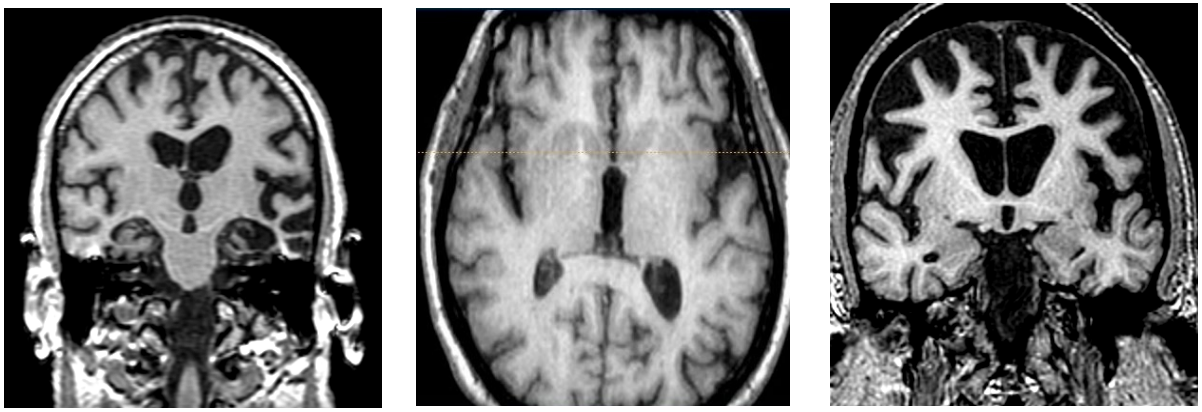
- Pick (1892) and bilateral frontal lobe atrophy
- FTD is a focal degenerative disorder (cause FTLD)
- Alteration in personality, social conduct and executive function
- Non-Alzheimer pathology disorder
- Related FTD syndromes –Semantic dementia, Primary Progressive non-fluent Aphasia,
- FTLDs are tauopathies which include:
  - FTLD with Pick bodies, Corticobasal Degeneration (CBD), Progressive Supranuclear Palsy (PSP), Sporadic multiple system tauopathy, Argyrophilic Grain Disease (AGD), NFT dementia, FTDP-17





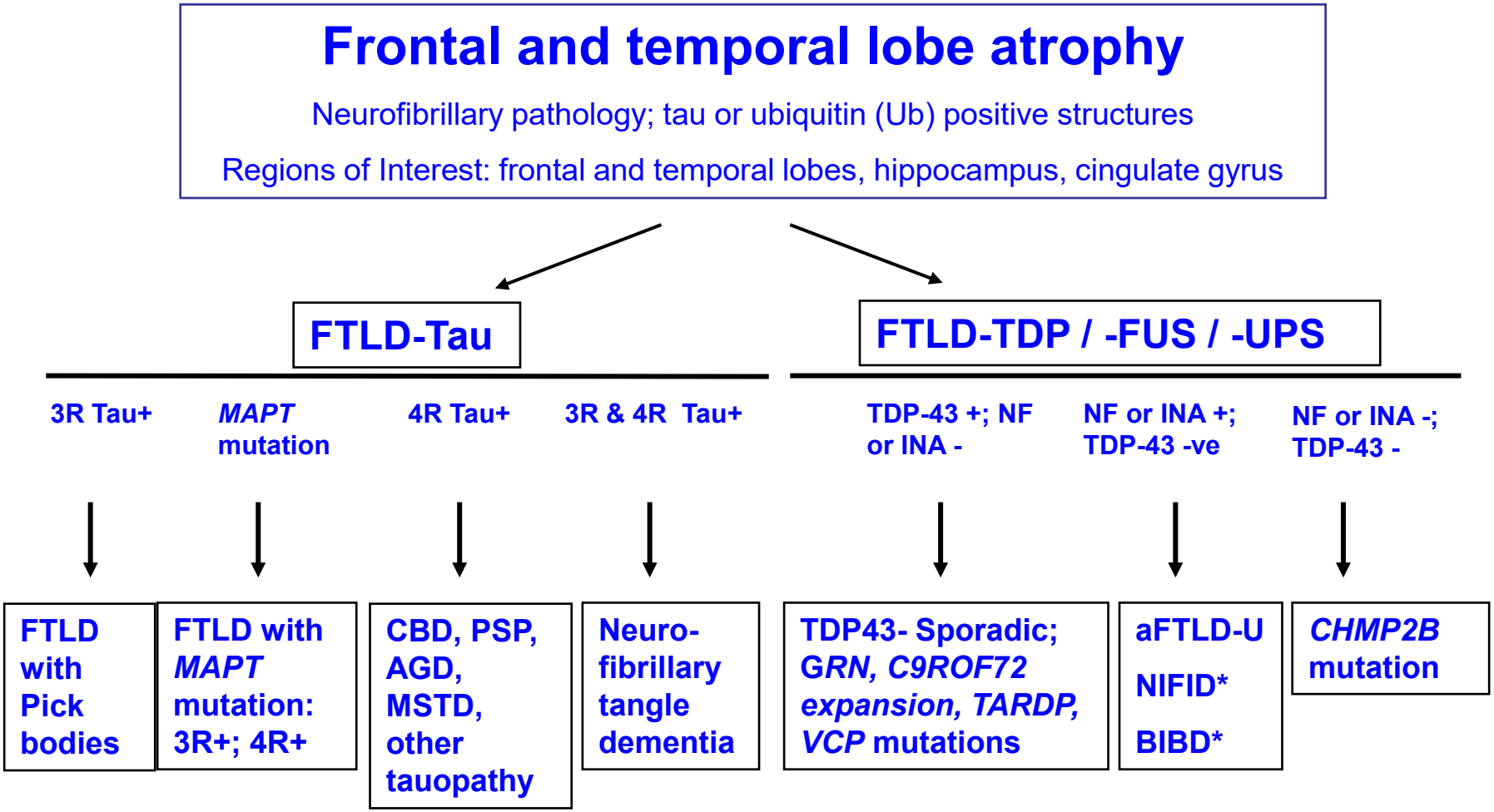
Clinical Syndromes in FTD

- Behavioural-variant of FTD -associated with early behavioural and executive deficits
- Semantic dementia (SD) -with progressive deficits in speech, grammar, and word output
- Progressive non-fluent aphasia (PNFA) -progressive disorder of semantic knowledge and naming



Bang J et al, 2015

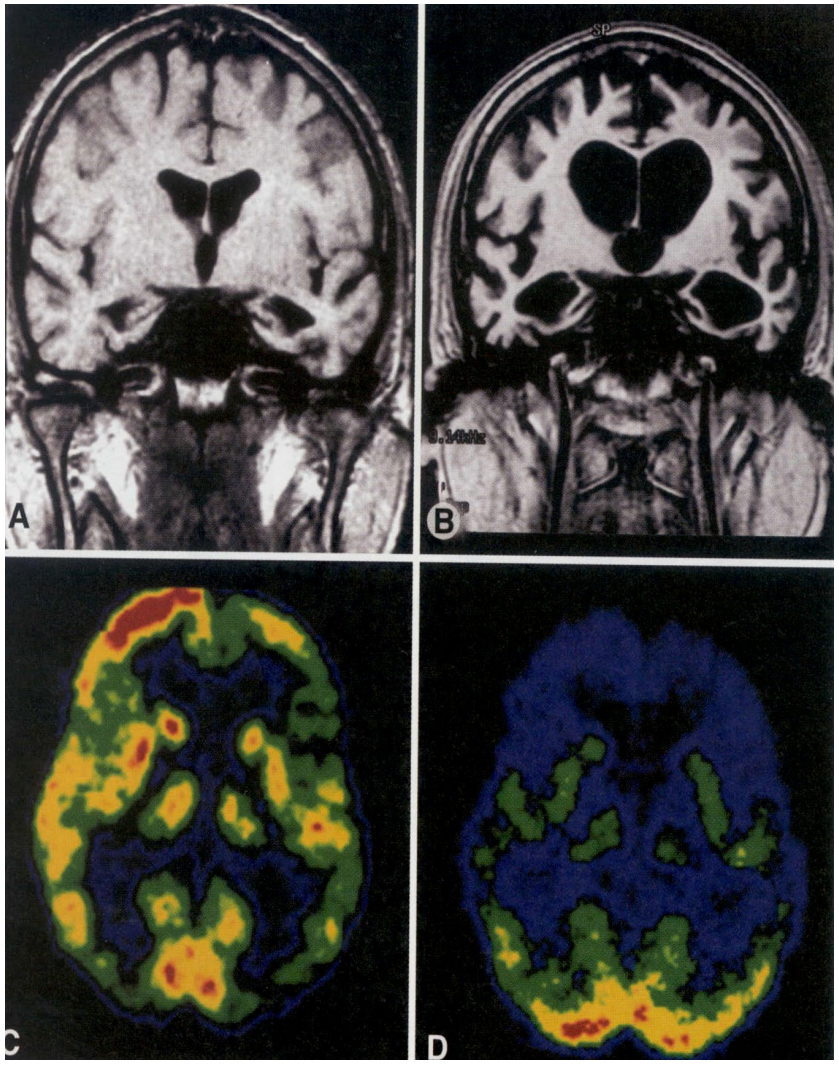
Frontotemporal Lobar Degeneration



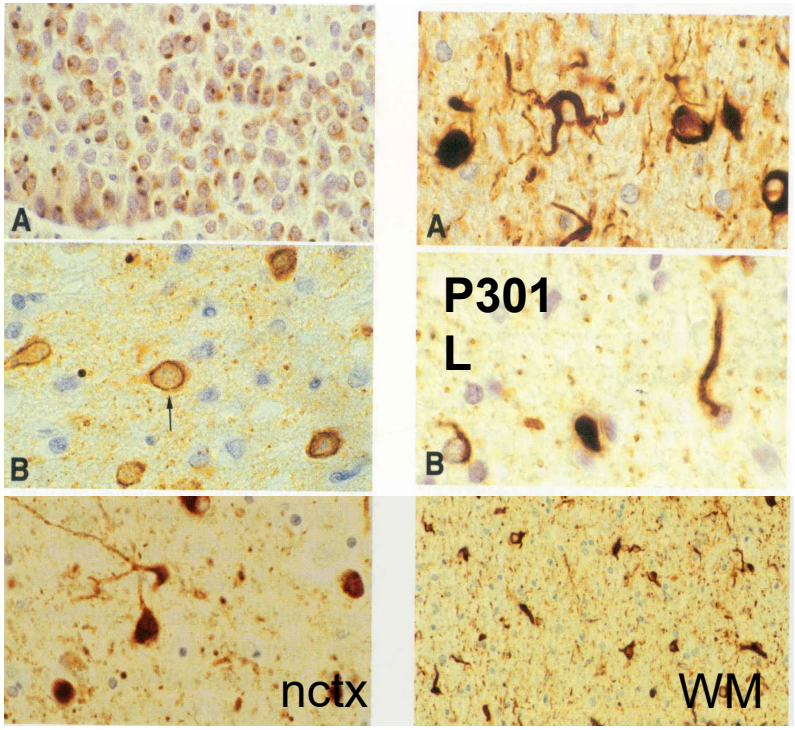
** BIBD, basophlic inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; TDP-43 transactivation response DNA binding protein with M(r) 43 kD; PGRN, progranulin; VCP, Valosin-containing protein*

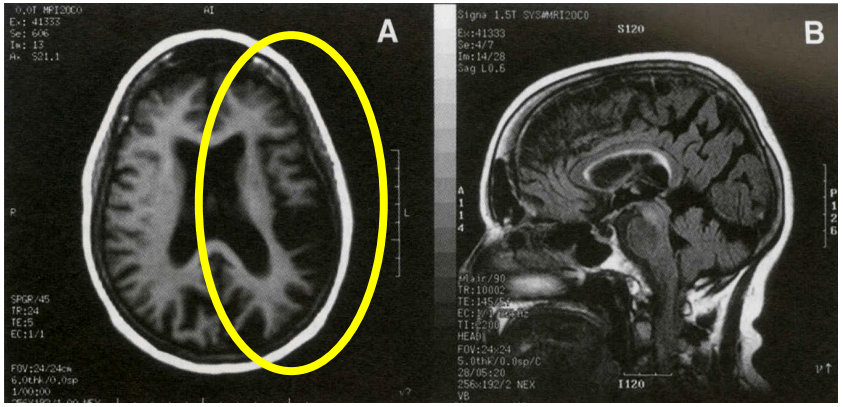
FTD linked Parkinsonism- Chr 17

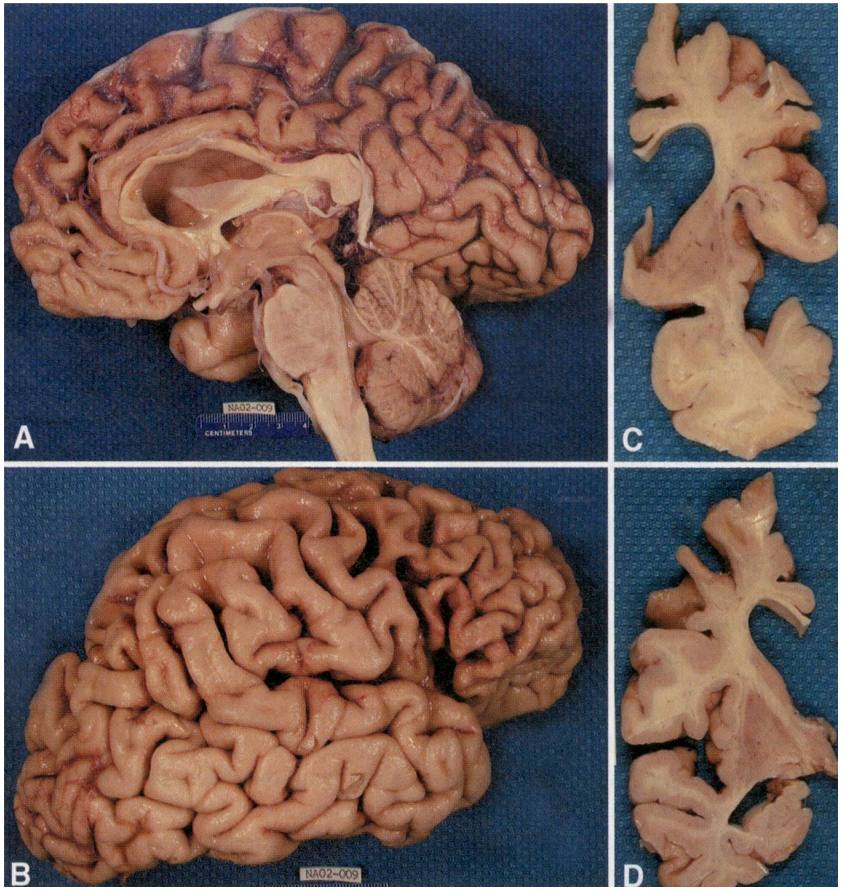
G389R mutation A→B 3 yrs



- Features of Parkinsonian tremor
- Progressive cerebral atrophy
- Increased hypometabolism
- Tau-IR deposits in neocortex as well as white matter (oligos)

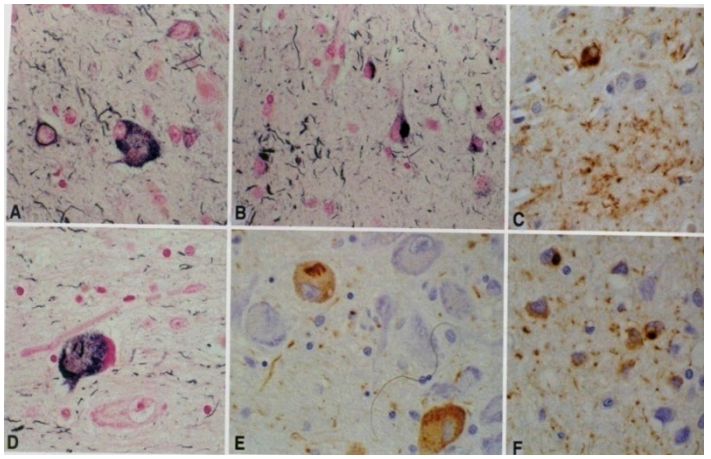




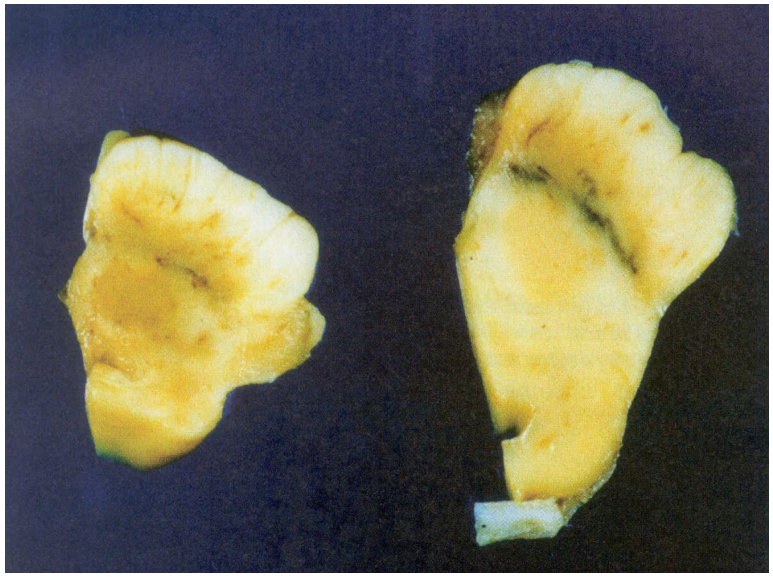


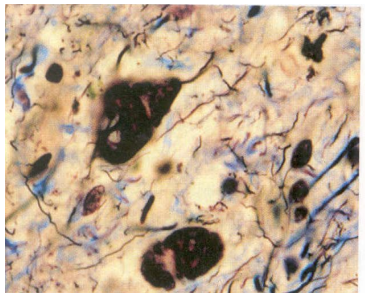
Corticobasal Degeneration

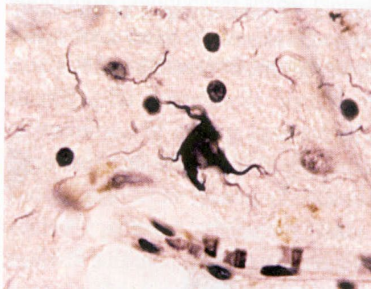
- Slowly progressive dementia
- Asymmetric lesions (Apraxia)
- Frontal and Parietal atrophy
- Corpus Callosum thining
- Heterogeneity of neuronal inclusions
- Balloned neurones (H&E)
- Neuronal vacuolation



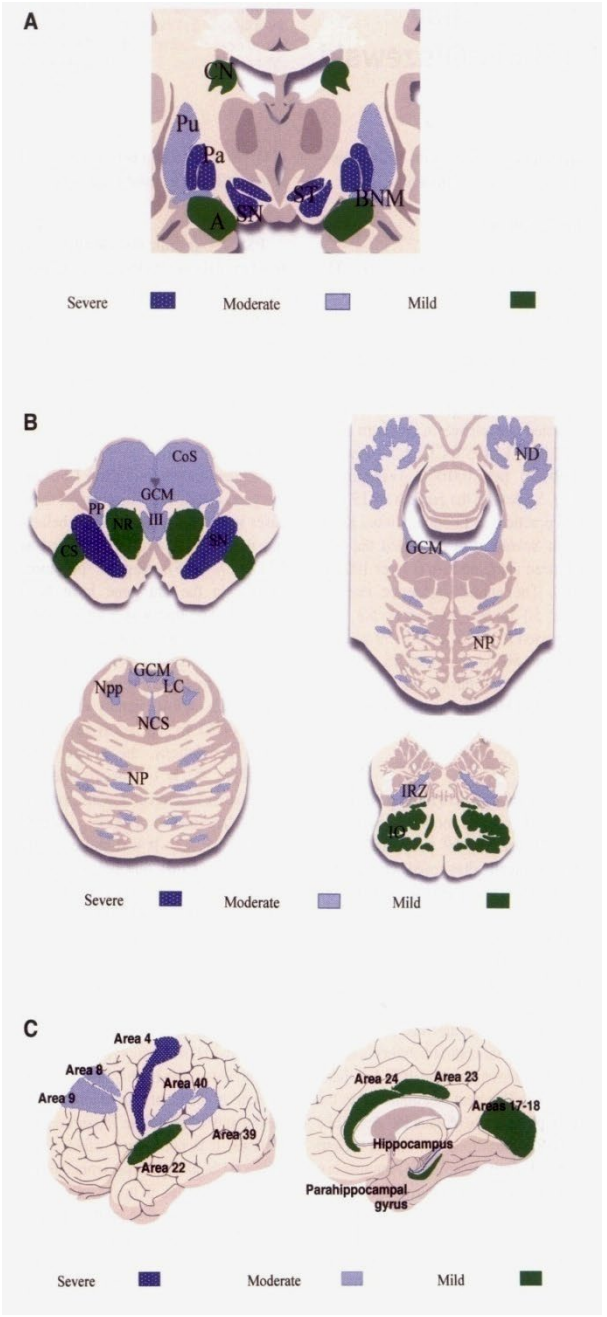
Progressive Supranuclear Palsy



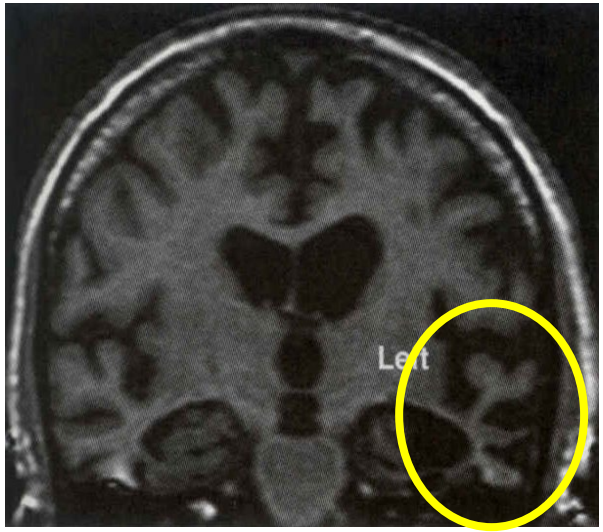


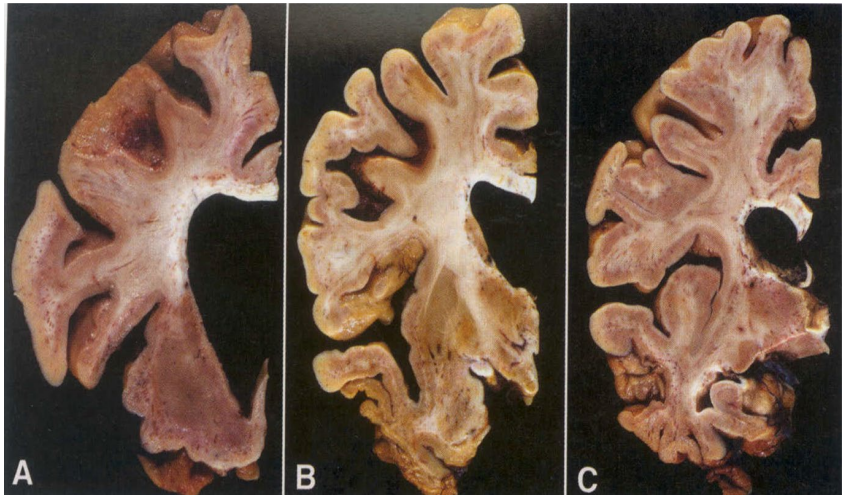


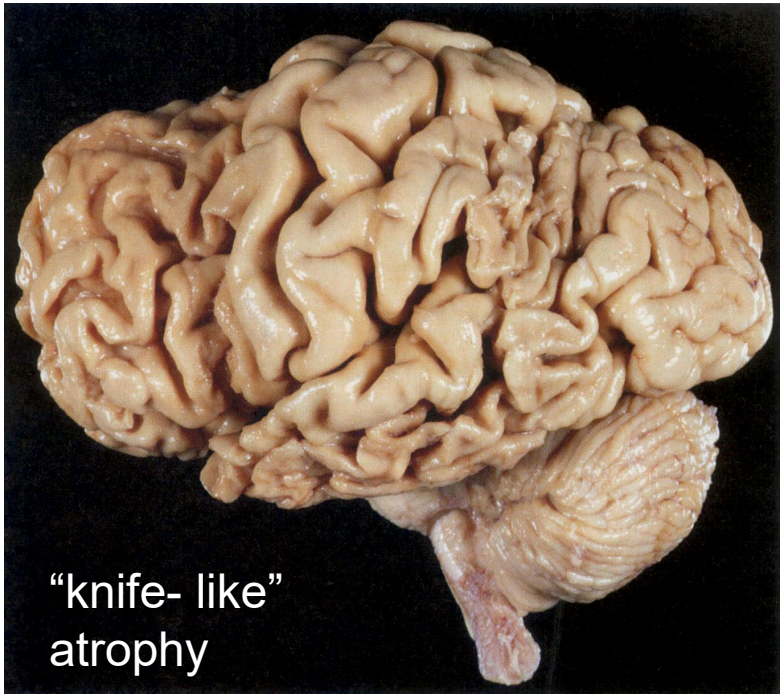
• S-R-O Syndrome; Midbrain (SN) degeneration; Neuronal Inclusions (*Tau*)

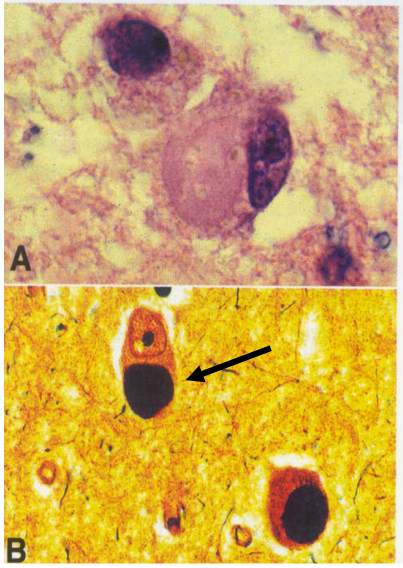


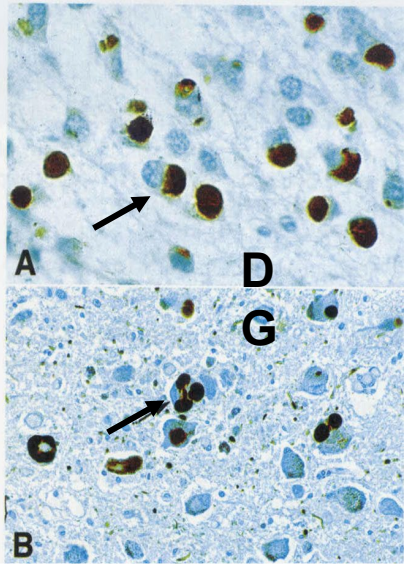
Pick's Disease







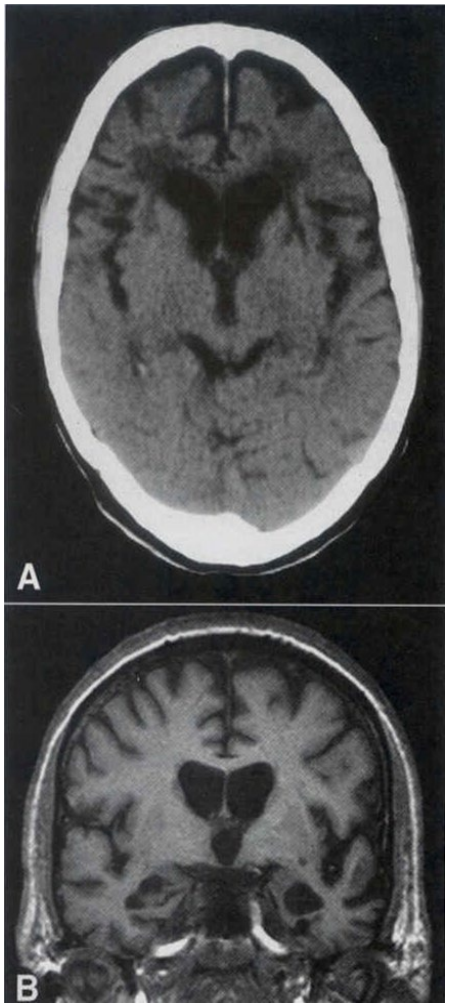


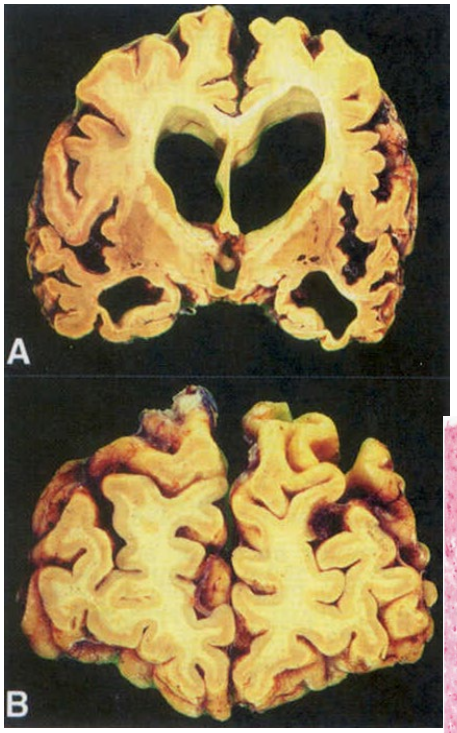


Tauopathies- CBD, PSP and Pick's

Feature	CBD	PSP	Picks
Cortical atrophy	++	+	++
WM pathology	Frontal	Cerebral	Frontal lobe
Basal Ganglia changes	Caudate atrophy	Pallidus pigmented	Caudate atrophy
Cortical changes	superior	middle +	severe
Tau reactivity	++	++ (NFT)	Pick bodies
Threads	+++	+	Variable
Astrogliosis	+++	+++	Variable
Microgliosis	++	++	++
Oligodendrocytes	+++	++	Variable

Frontotemporal Lobar Degeneration

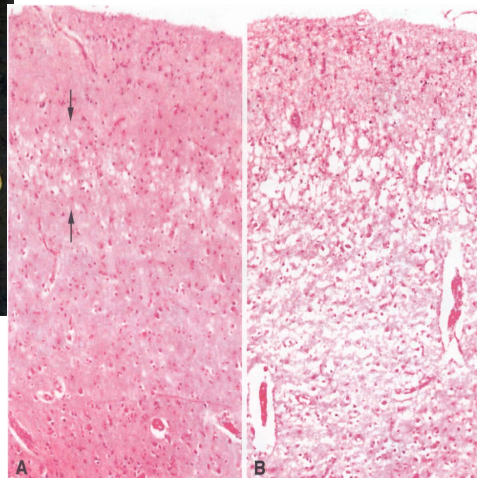


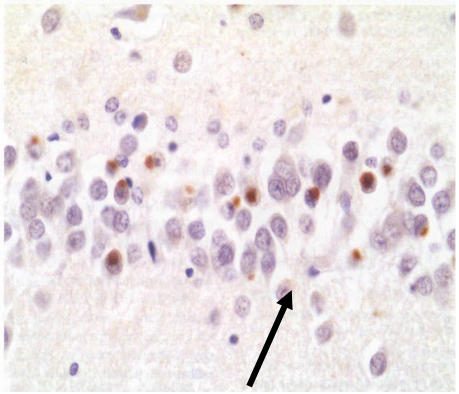


"Progranulin"
Most mutations null alleles, FTD results from PGRN haploinsufficiency

FTLD: Tau –ve

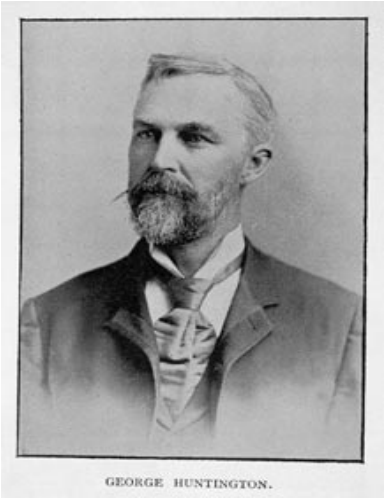
- Originally all as Pick's disease
- 10-15% of all dementias
- Clinical presentation FTD, semantic dementia, primary aphasia, corticobasal-like syndrome
- Subtypes- FTLD, FTLD-U, FTLD-MND
- Marked frontotemporal atrophy
- Neuronal loss and astrogliosis
- Progranulin (PGRN) cases +ve for TDP-43





PGRN (FL) many functions: trophic and anti-inflammatory activity,

Huntington's Disease (HD)



George Huntington 1850-1916

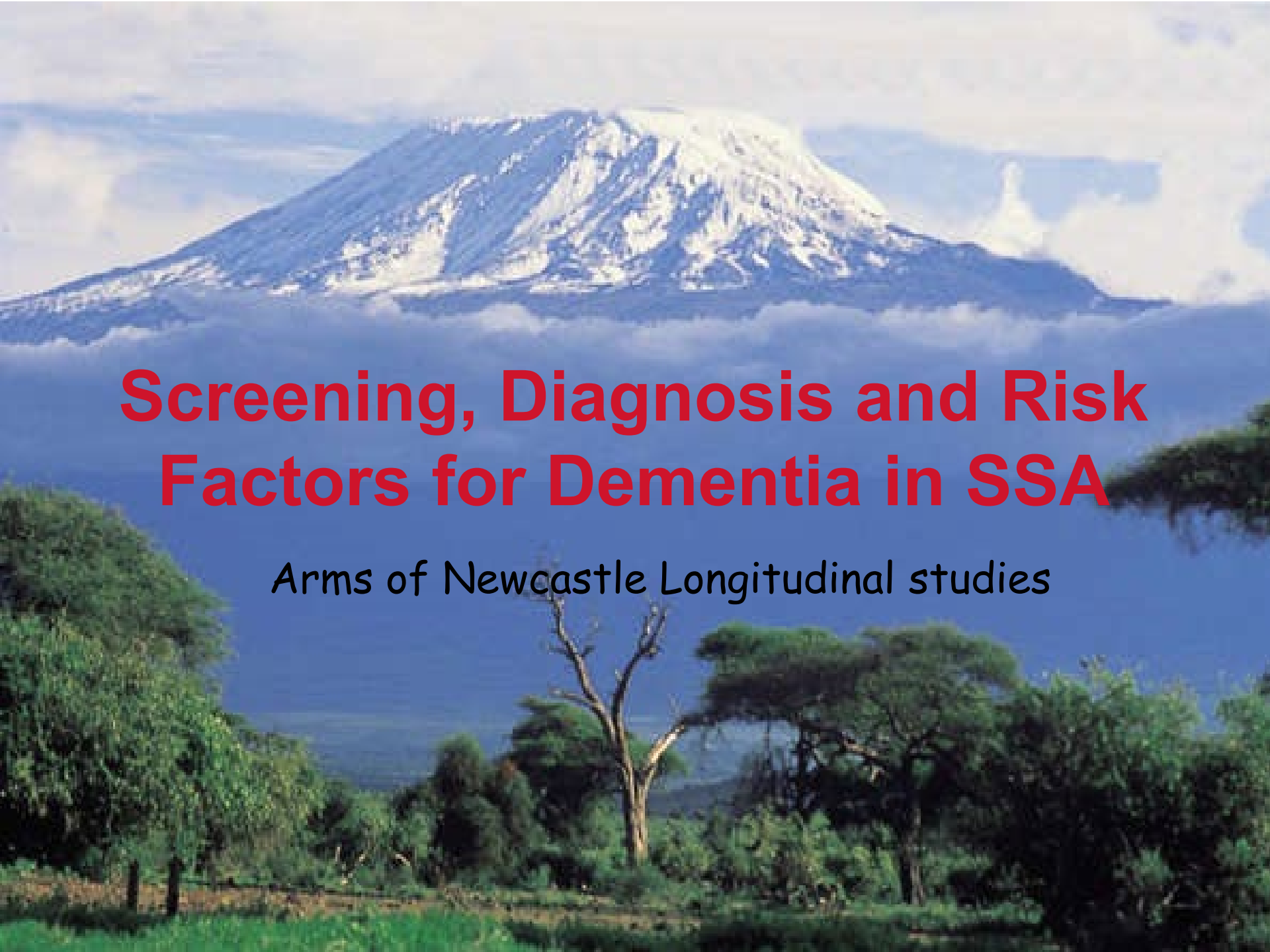
- HD is an autosomal dominant disorder; prevalence 3-10 per 100,000.
- HD phenotype = chorea (brief, irregular contractions that appear to flow between muscles), psychiatric abnormalities and cognitive decline
- Linked to *Huntingtin* gene on chromosome 4
- "Mutation" involves expansion of CAG repeats (>36) normal up to 26). HD is most common polyglutamine (PG) disorder.
- Expansion of PG tract (N-terminal) confers "gain of toxic function" in full-length huntingtin product

Causes of Dementia: clues from neurological features and cognitive decline

Clinical and pathological presentations and possible diagnosis of dementia

Clinical presentation	Diagnostic considerations
Dementia with myoclonus	Prion disease Autosomal dominant AD
Dementia with ataxia	Inherited forms of ataxia including SCA2, SCA3, SCA17, DPRLA
Dementia with chorea	Huntington's disease SCA3, SCA17, DPRLA, neuroferritinopathy, neuroacanthocytosis
Dementia with dystonia	Wilson's disease Niemann–Pick disease (NPC1 and NPC2)
Dementia with progressive myoclonic epilepsy	Mitochondrial disease, Lafora body disease, Neuronal ceroid lipofuscinosis

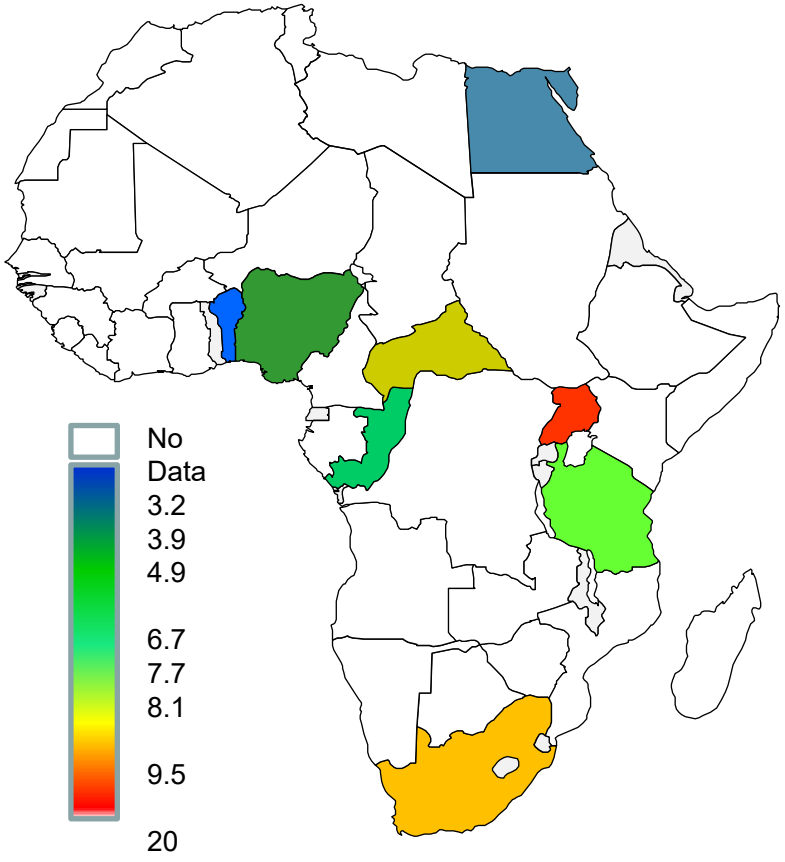
Lowe J and Kalaria R, 2015

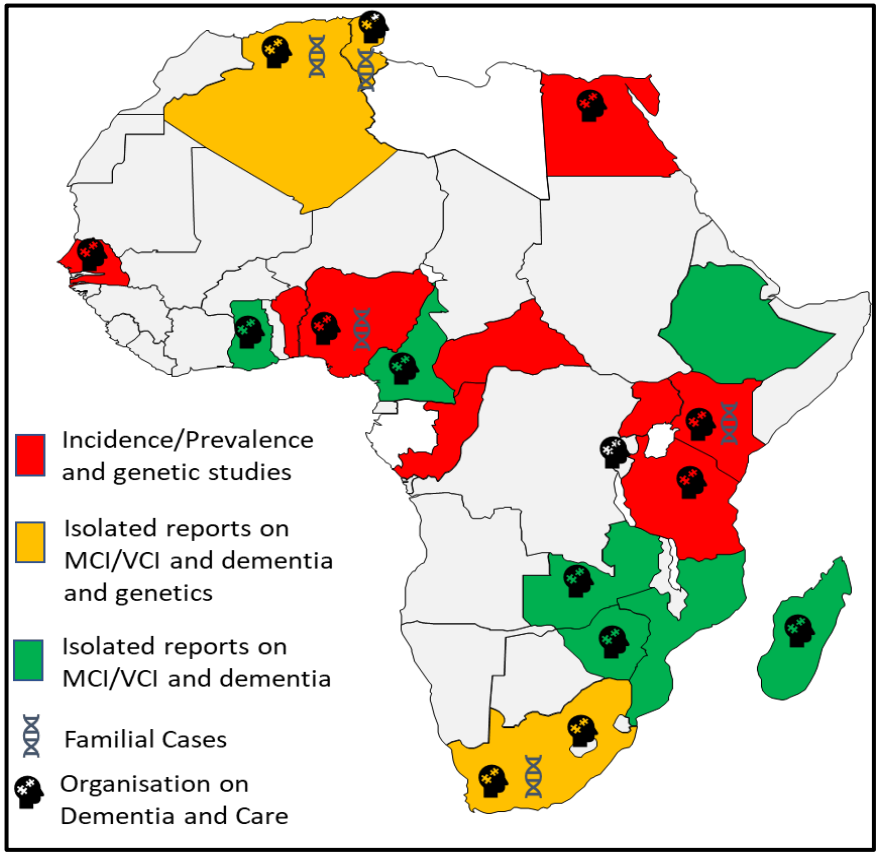


Screening, Diagnosis and Risk Factors for Dementia in SSA

Arms of Newcastle Longitudinal studies

Variation in Dementia Prevalence estimates in Africa





Akinyemi et al, Alz & Dementia, 2021

Meta-Analysis of SSA dementia epidemiological datasets

Guerchet et al 2017

- Prevalence
- ✓ (All Studies) : 5.5 %
- ✓ (DSM criteria) = 6.38%

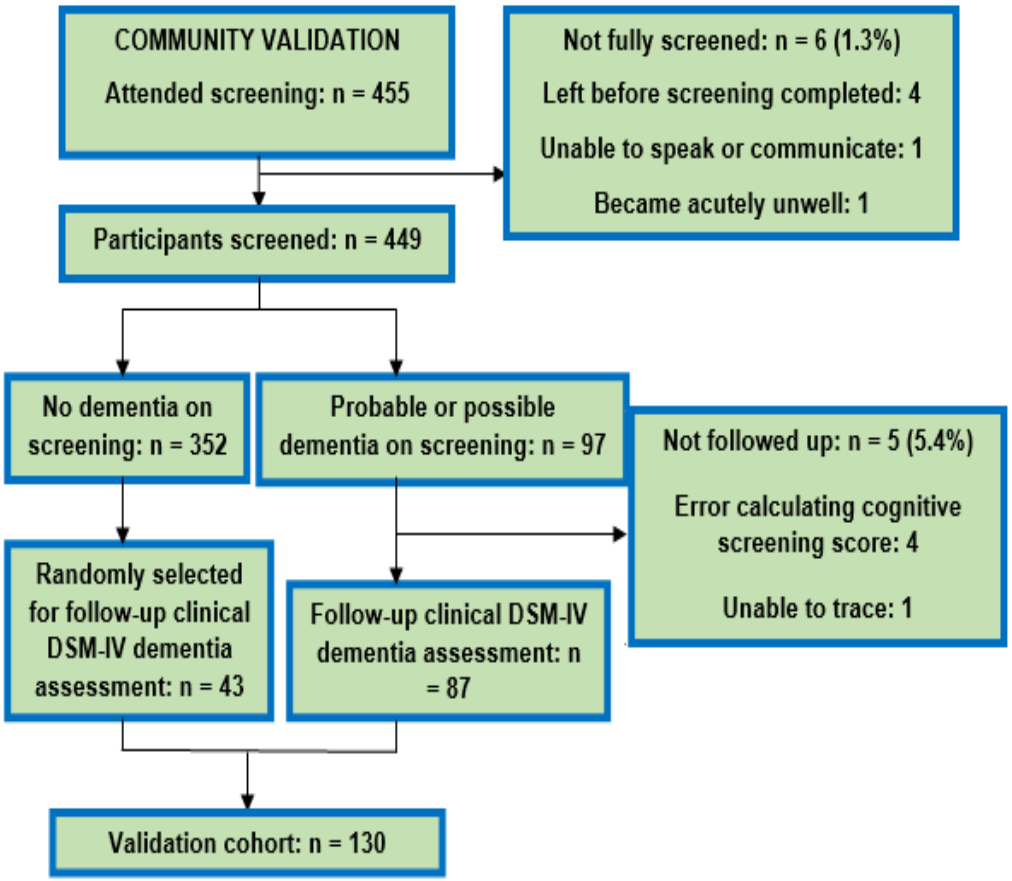
Incidence : 1.3%

Ojagbemi et al 2021

- Prevalence
- ✓ Hospital-based studies : 3% (CI 1% - 5%)
- ✓ Community (clinically diagnosed) : 5% (C1 2%-7%)
- ✓ Community (rating scales): 9% (CI 6% - 11%)
- Incidence : 2% (CI 1% - 4 %)

Guerchet et al, ADI Technical Report, 2017
Ojagbemi et al, Frontiers Neurology, 2021

Community Validation, Hai Dementia screening Study



Cut-off of ≤ 7	
Sensitivity	60.0%
Specificity	84.2%
LR	3.80
Cut-off of ≤ 8	
Sensitivity	88.6%
Specificity	64.2%
AUROC curve	0.846 (95%CI 0.776 - 0.915)
	Educational level no association

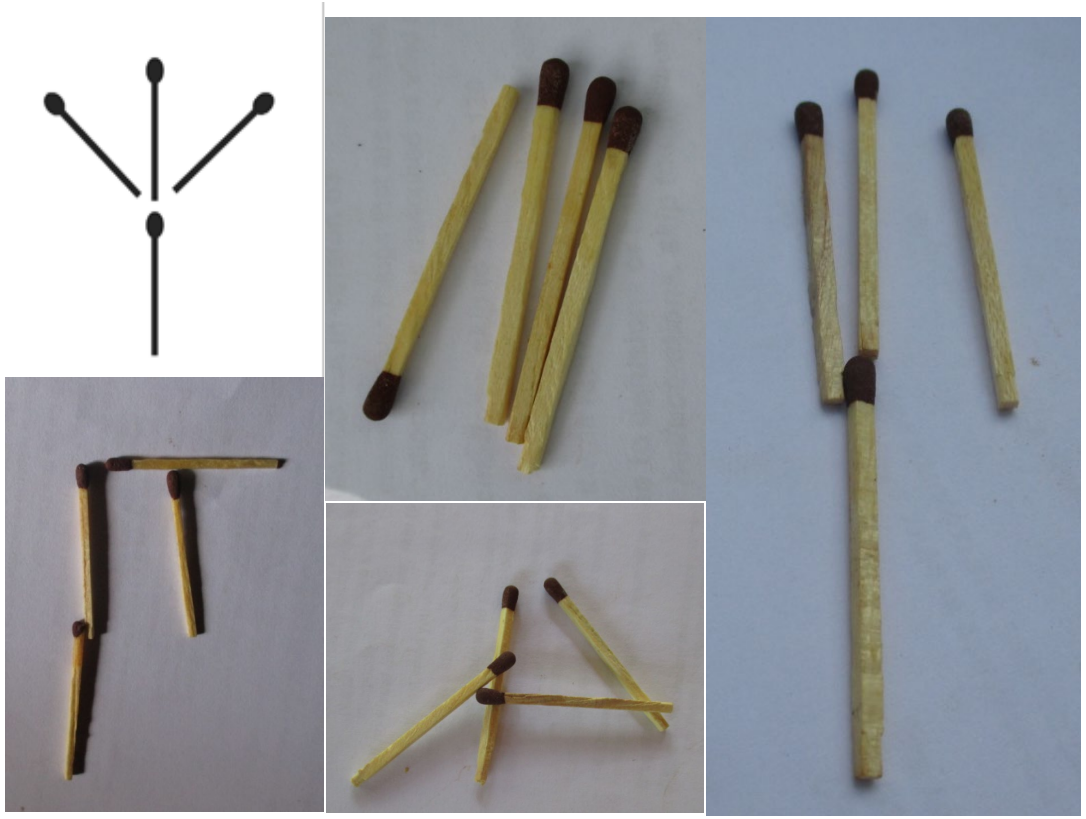
IDEA Study Screening Tools

Matchsticks (Orientation) Test

(Baiyewu et al 2003)

Subject asked to make the design shown above using four matchsticks. He/She is shown once and then they have **to** copy exactly

Score 1 for each part of the design that is performed correctly



Observe examples of stick design in 4 impaired subjects

Subtypes of Dementias in Africa

- **Alzheimer's disease-** Several countries
- **Parkinson's disease-** Several countries
- **Dementia with LBs-** Nigeria, Tunisia
- **Frontotemporal Dementias** Nigeria, South Africa
- **Huntington's disease LBs-** Tunisia, Senegal, South Africa
- **Prion diseases** Tunisia, South Africa
- **Ataxias (SCAs) and MNDs-** North Africa, West, Central & East Africa

Proportions of AD as a Dementia Subtype in Africa (Community and Hospital-based Studies)

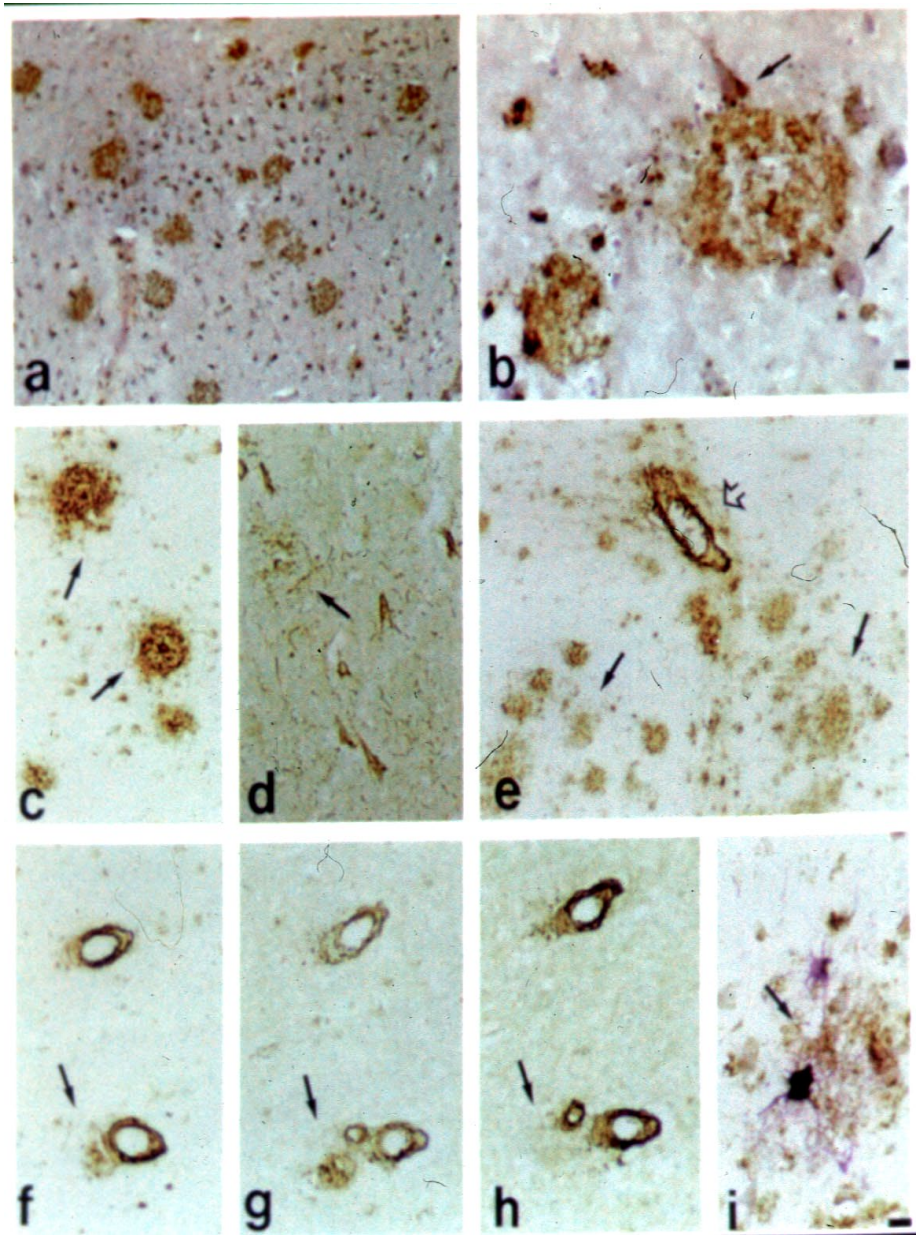
Country, Location; Type of sample	Sample size, Age (yrs)[a]	Dementia Prevalence (%)	Alzheimer's Disease (%)	VaD (%)	Reference
Africa, 10 countries; Community		2.4%	57%	27%	(George-Carey et al., 2012)
SSA, 5 countries (Benin, Botswana, CAR, Congo, Nigeria); Community/clinic[b]	10,413; > 65 yrs	0–10%	54–83%	8–31%	(Mavrodaris et al., 2013)
Nigeria, Abeokuta/Ibadan; Hospital/Clinic	240,294;	0.05%	57%	17%	(Amoo et al., 2011)
Egypt, Al Kharga District; Community	8173, > 50 yrs	2.3%	51%	29%	(El Tallawy et al., 2012)
South Africa, Durban; Hospital	140; > 60 yrs[e]	8%	–	40%	(Ramlall et al., 2013)
Egypt, Al-Quseir city,	2222; > 60 yrs[c]	3.8%	48%	37% (1.4%)[c]	(El Tallawy et al., 2014)
Tanzania, Hai District; Community	1198; > 60 yrs	6.4%	48%	41% (2.6%)[d]	(Paddick et al., 2013),(Paddick et al., 2014)
Egypt, Quena/Aswan; Community	691; > 60 yrs[c]	5.1%	–	–	(Khedr et al., 2015)
Congo, Brazzaville, Bangui, CAR; Community	910;	6.1%	69,%, 83%	31%, 18%	(Samba et al., 2016)

Longdon AR et al, 2013; Akinyemi et al. BRB 2019

Brain AD lesions in East Africans

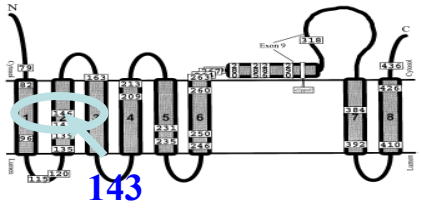
- Comparable to a US sample, ~18%of elderly East Africans exhibit Aβ(42) deposits (9/50 cases)
- Severe CAA was evident in brains of two subjects
- Typical τ +ve NFT pathology was evident in the hippocampus and neocortex
- These findings suggest that elderly East Africans are unlikely to escape AD (even if incidence is low)

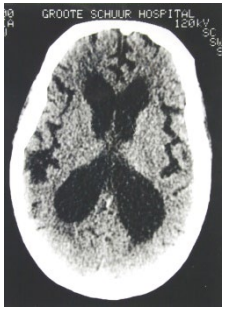
(Ogeng'o J et al, 1996)

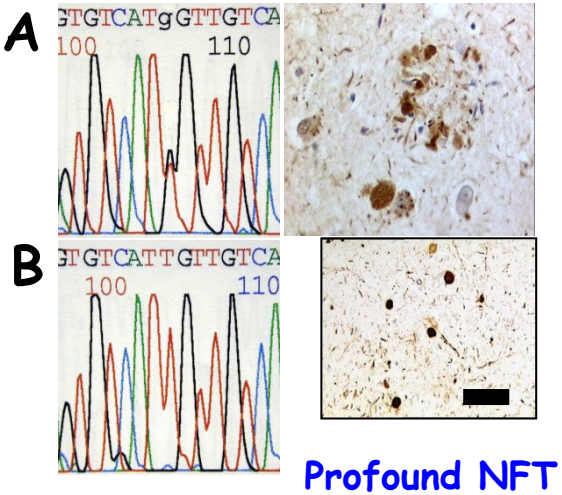


Hereditary AD in a large Xhosa Family, SA

Heckmann J et al, 2004

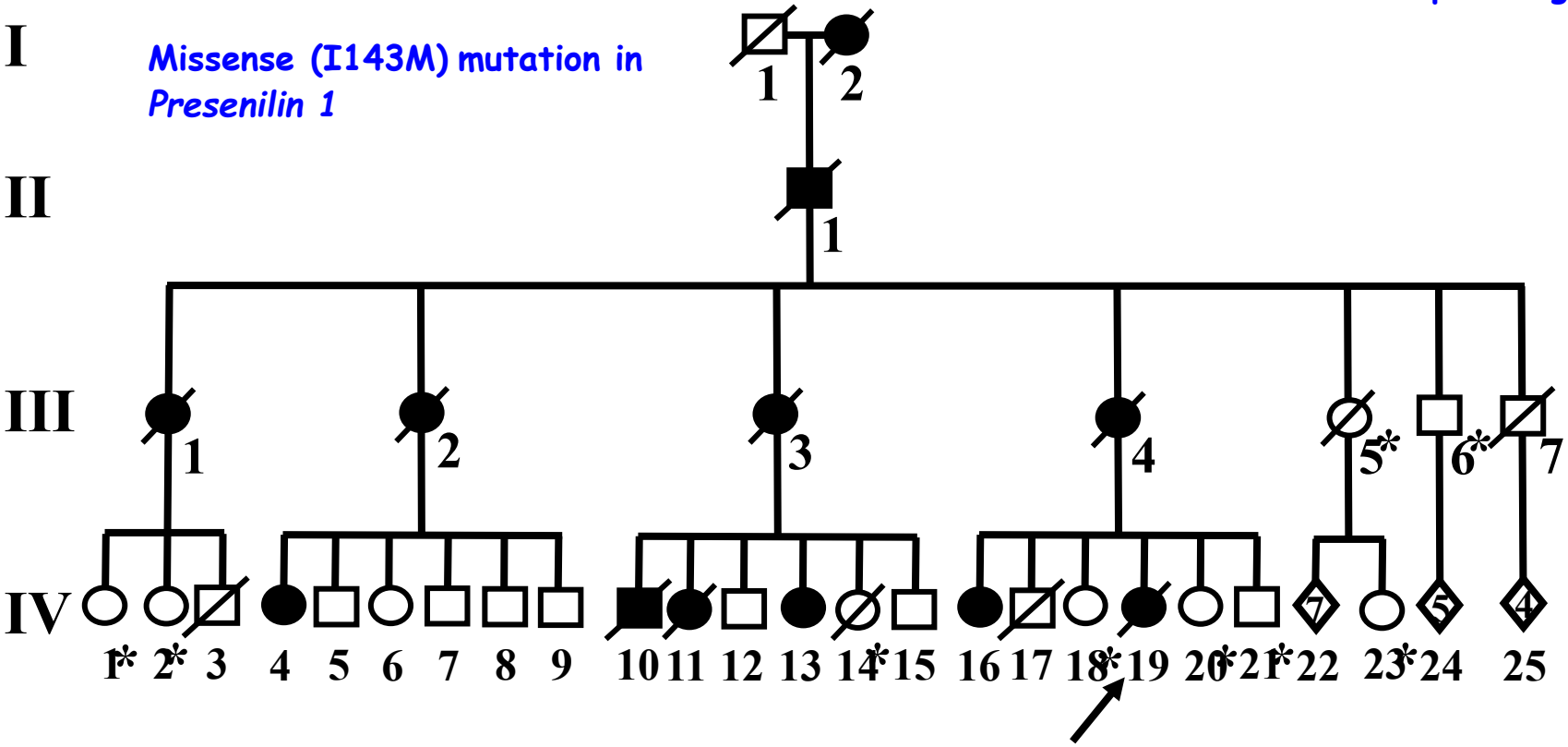






Profound NFT pathology

Missense (I143M) mutation in *Presenilin 1*



Dementia with Lewy Bodies in Africa

International Psychogeriatrics, Vol. 14, No. 2, 2002, pp. 211-218

Dementia With Lewy Bodies in a Nigerian: A Case Report

ADESOLA OGUNNIYI, EFFIONG E. U. AKANG, OYE GUREJE, MASAKI TAKAO, PEDRO PICCARDO, OLUSEGUN BAIYEWU, KATHLEEN S. HALL, BERNARDINO GHETTI, AND HUGH C. HENDRIE

- Isolated cases of DLB may exist with PD
- Full spectrum of DLB-PDD likely exist in Africa

Frontotemporal Dementias in Africa

Afr. J. Med. Med. Sci. (2009) **38**, 71-75 *Reports*

Frontotemporal dementia in a Nigerian woman: case report and brief review of the literature.

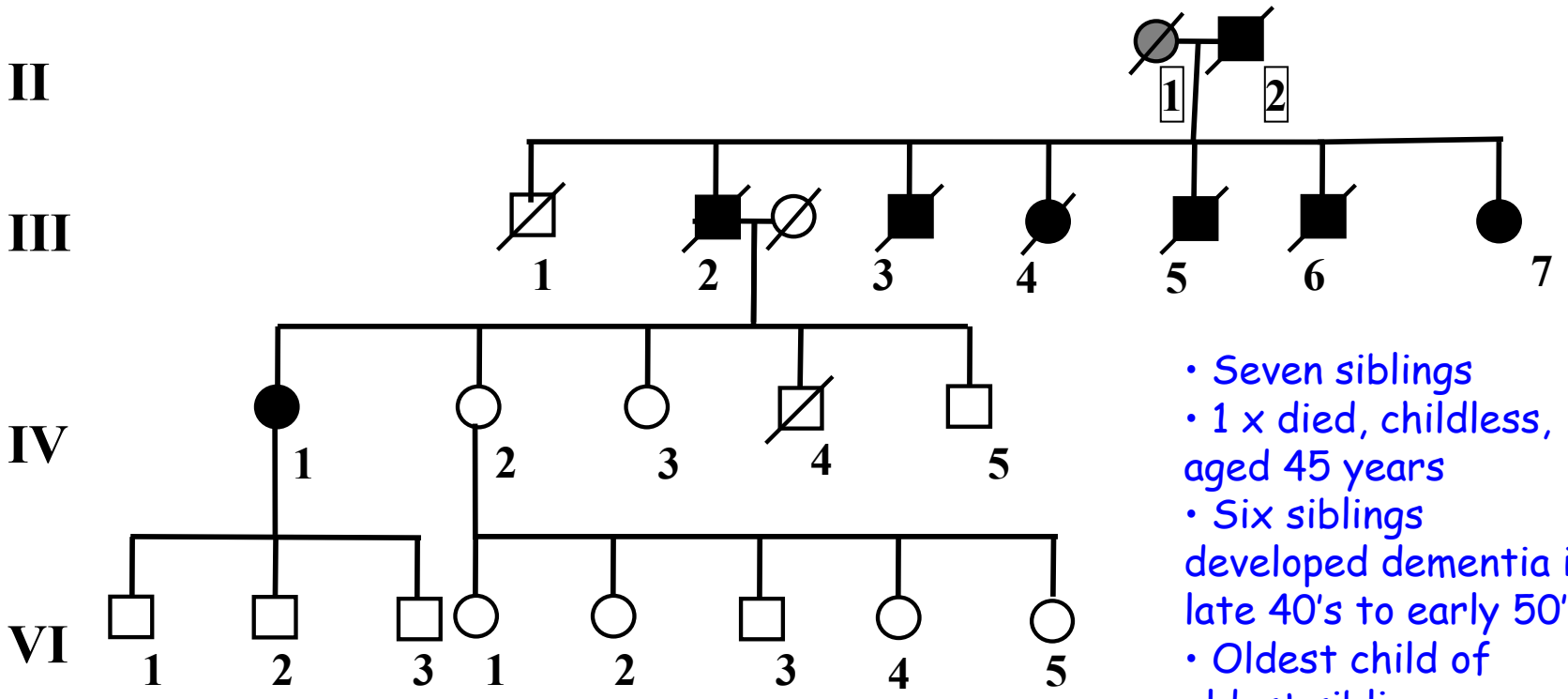
RO Akinyemi[1,4], MO Owolabi[1], VA Makanjuola[2], AO Ogunseyinde[3] and A Ogunniyi[1].

Departments of Medicine[1], Psychiatry[2] and Radiology[3], University College Hospital, Ibadan and Department of Medicine[4], Federal Medical Centre, Abeokuta, Nigeria

- Isolated cases of FTD described in North Africa
- Unknown if full spectrum of FTDs exist in Africa

SA family with history of dementia (FTD)

Family Tree



- Seven siblings
- 1 x died, childless, aged 45 years
- Six siblings developed dementia in late 40's to early 50's
- Oldest child of oldest sibling dementing (at 54)

Family tree has been disguised to preserve individual patient identity. Family tree x 300 years genealogical Institute of South Africa (Dr Leon Endeman)

Dementia in Infectious Disease

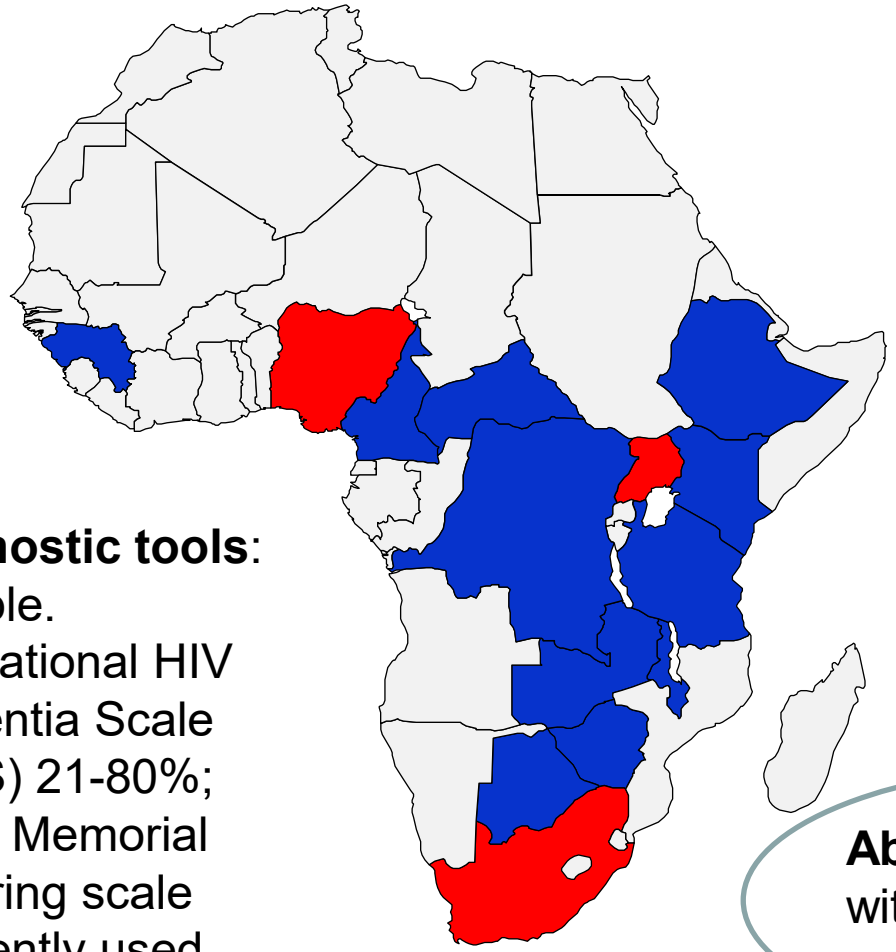
- Factors include viral, bacterial, fungal, and parasitic organisms

  HIV is the most common cause

- Presence of fever, peripheral leukocytosis, or CSF pleocytosis should prompt investigation for an infectious agent

- Consequences on behavioural and cognitive function most frequent in immunocompromised patients

HIV-related Neurocognitive Impairment in SSA



Total reports (2020): 51 hospital-based studies case-control (10), cohort (7), cross-sectional (31)

14 countries: South Africa (14), Uganda (8), Nigeria (6), Zambia (4), Kenya (4), Cameroon (3) DRC (3), Ethiopia (2), Malawi (2), CAR (1), Botswana (1), Guinea Bissau (1), Tanzania (1), Zimbabwe (1)

Diagnostic tools: variable. International HIV Dementia Scale (IHDS) 21-80%; Sloan Memorial Kettering scale frequently used

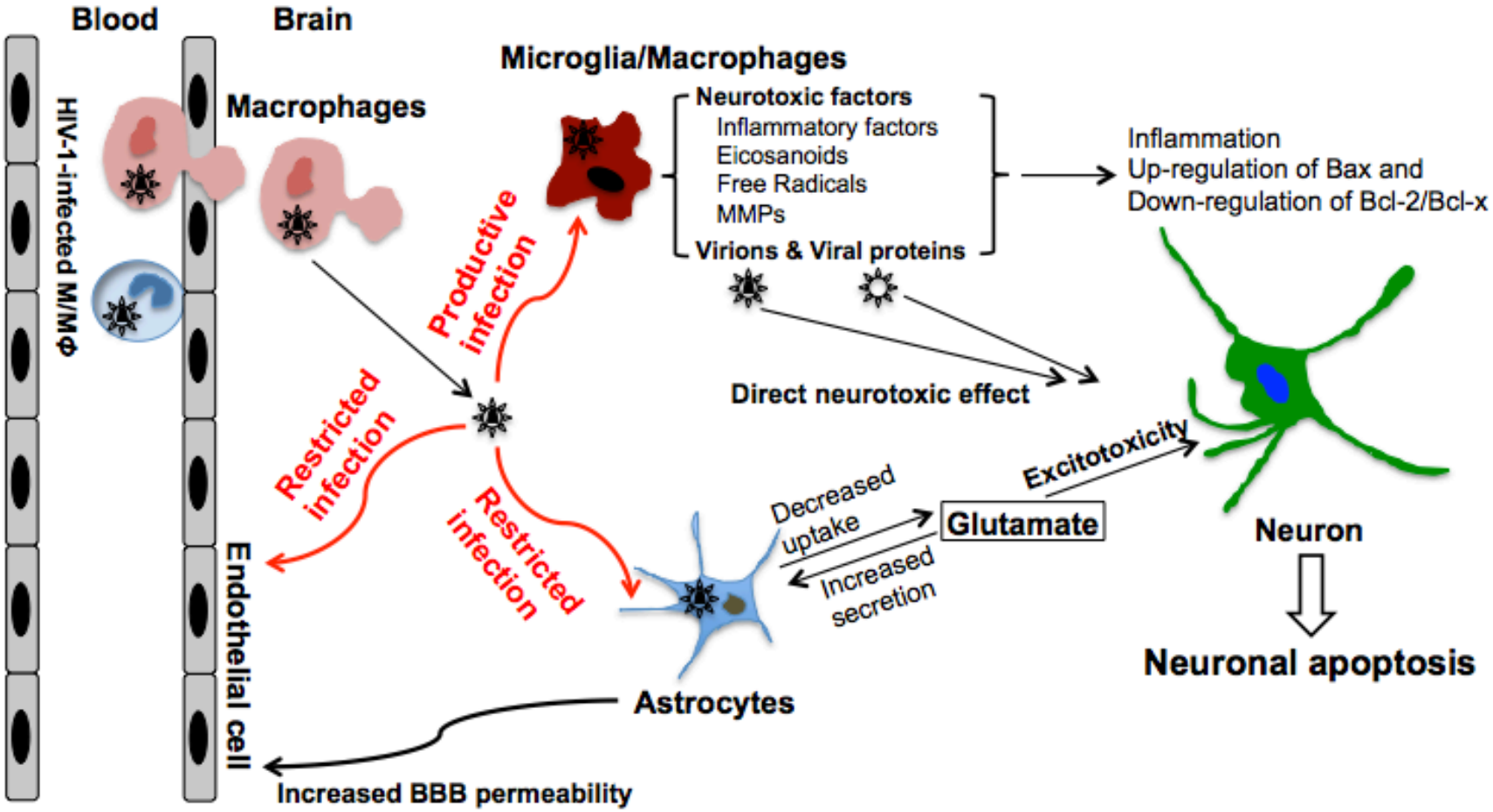
Absolute participants with HAND 0-396; prevalence 0%-80%

Lekoobou A et al, BMC Public Health, 2014; Paddick SM et al, 2021 (submitted)

Frequency of HIV Meningoencephilitis

- ~50% HAND- HIV-associated neurocognitive disorders
- ~20% HAD- HIV associated dementia
- ~2% HAD with ART treatment
- >50% HIVE- HIV encephalitis as less severe HAND
  - Persistent immune activation, inflammation, viral escape / blipping in treated subjects,
  - comorbid conditions show HIV disease progression and ↑ HAND risk

Pathogenesis and Cellular Mechanisms



Note: This figure was modified from Jones G. & Power C. Neurobiology of Disease, 2006; 1 – 17
M/MΦ: monocytes/macrophages

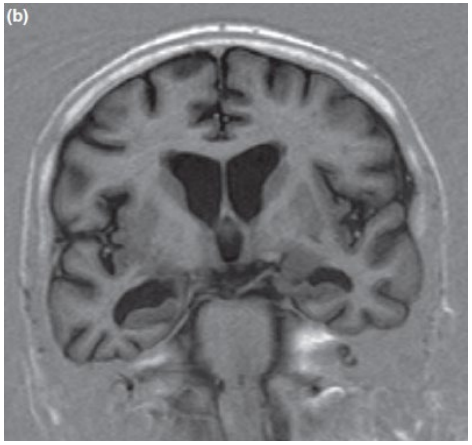
Rapidly Progressing Dementia

European Journal of Neurology 2008, **15:** e14–e15

LETTER TO THE EDITOR

Progressive dementia and mesiotemporal atrophy on brain MRI: Neurosyphilis mimicking pre-senile Alzheimer's disease?

P. van Eijsden[a], J. H. Veldink[b], F. H. Linn[b], P. Scheltens[c] and G. J. Biessels[b]



Cognitive/behavioural symptoms and neuropsychological profile were compatible with diagnosis of AD (DSM IV-TR).

MRI scan medial temporal lobe atrophy (MTA) = highest atrophy rating scale

Treponema pallidum hemagglutination and VDRL in CSF +

Treated w/ 0.15 · 106 IU/kg benzylpenicillin for 2 wks. 6 months later, MMSE 27/30
slight improvement of language-related skills, but little improvement in memory

Vascular Cognitive Impairment

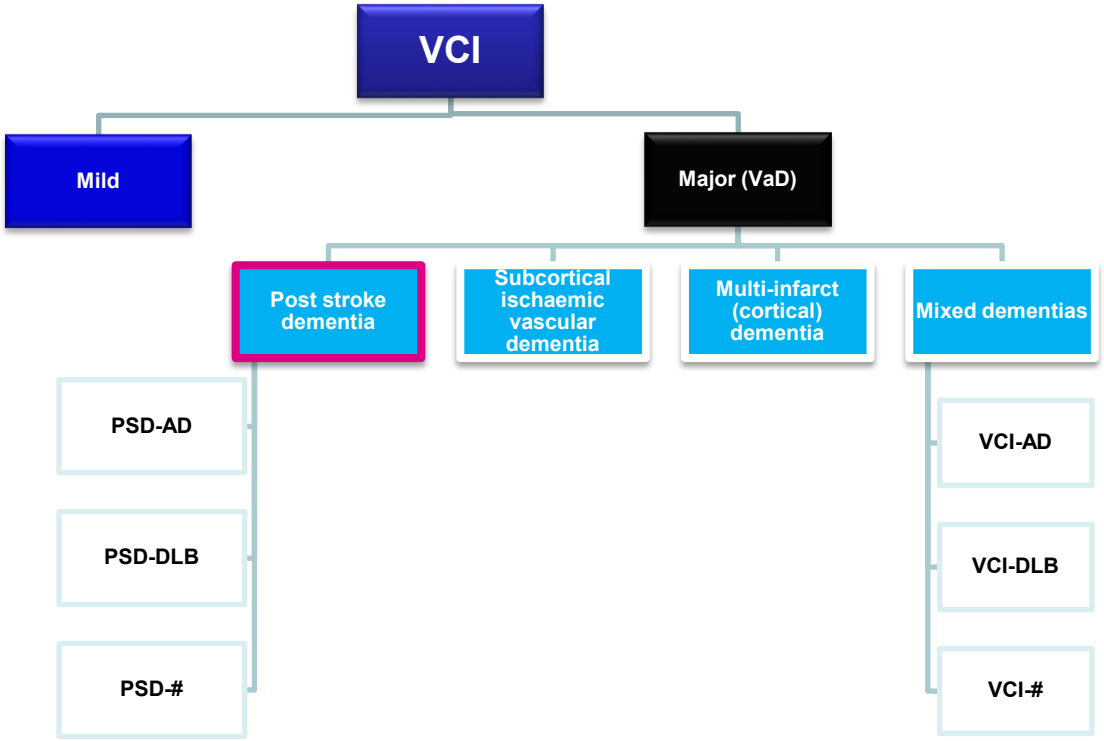
Vascular = all causes of CVD

(cardiovascular also)

Cognitive Impairment = early to late and severe forms of dementia syndromes

(VaD and MCI)

Progress towards standardised diagnosis of VCI guidelines from VICCCS



Mild VCI: Impairment in at least ONE cognitive domain and mild to no impairment in ADL (independent of motor/sensory sequelae of vascular event)

Major VCI (VaD): Clinically significant deficits of sufficient severity in *at least* ONE cognitive domain (deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event)

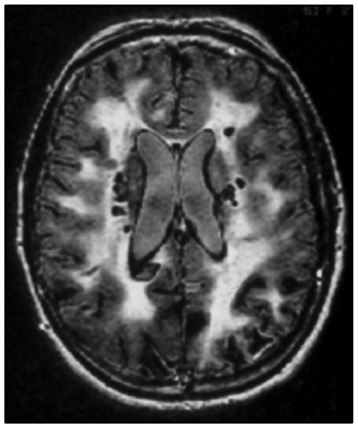
- **Diagnosis of VICCCS-revised *Mild and Major forms of VCI* and endorsed the NINDS-CSN (Hachinski et al, 2006) neuropsychological assessment protocols and recommendations for imaging**
- **Core domains for assessment should include: *executive function, attention and memory as well as language and visuospatial function***

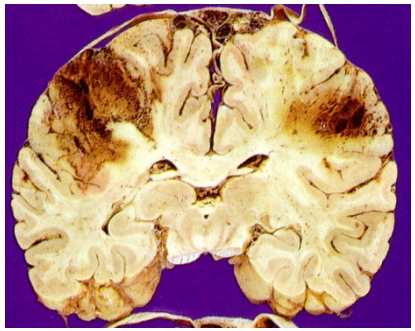
O Skrobot et al, 2017. 2018

Vascular Dementia (VaD)

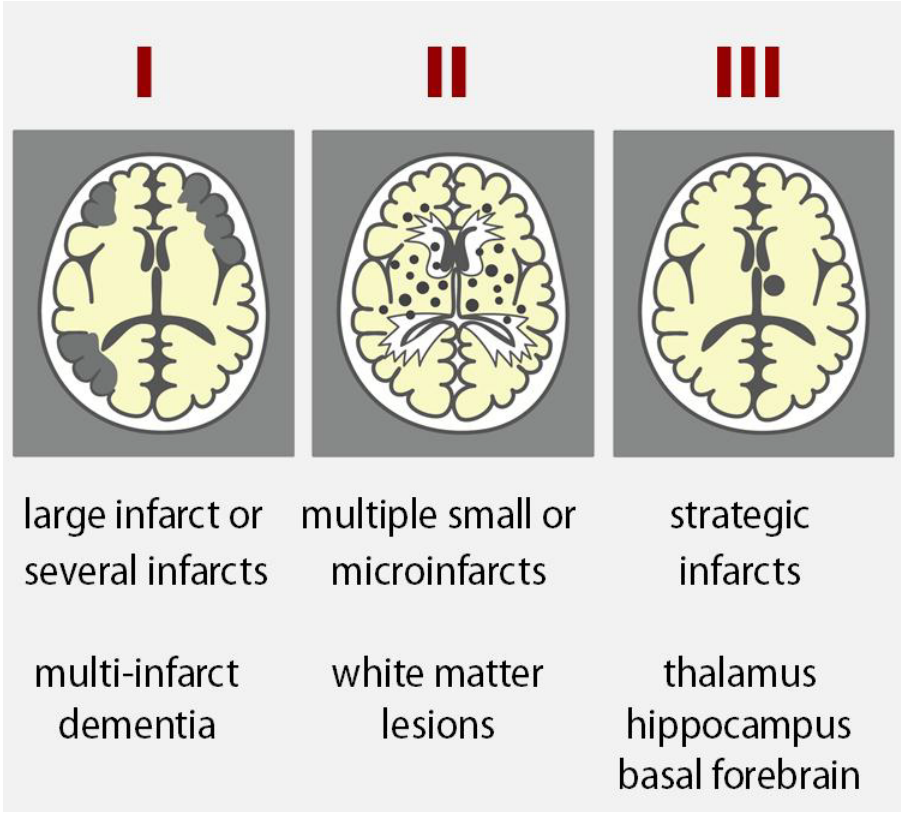
The *conventional definition of VaD is deficient* as stroke may produce a spectrum of cognitive changes but not necessarily prominent memory loss as in Alzheimer's Disease (AD)

Vascular Dementia





Main Types: I Multi-infarct Dementia, II Subcortical Ischaemic Vascular Dementia, III Strategic infarct dementia



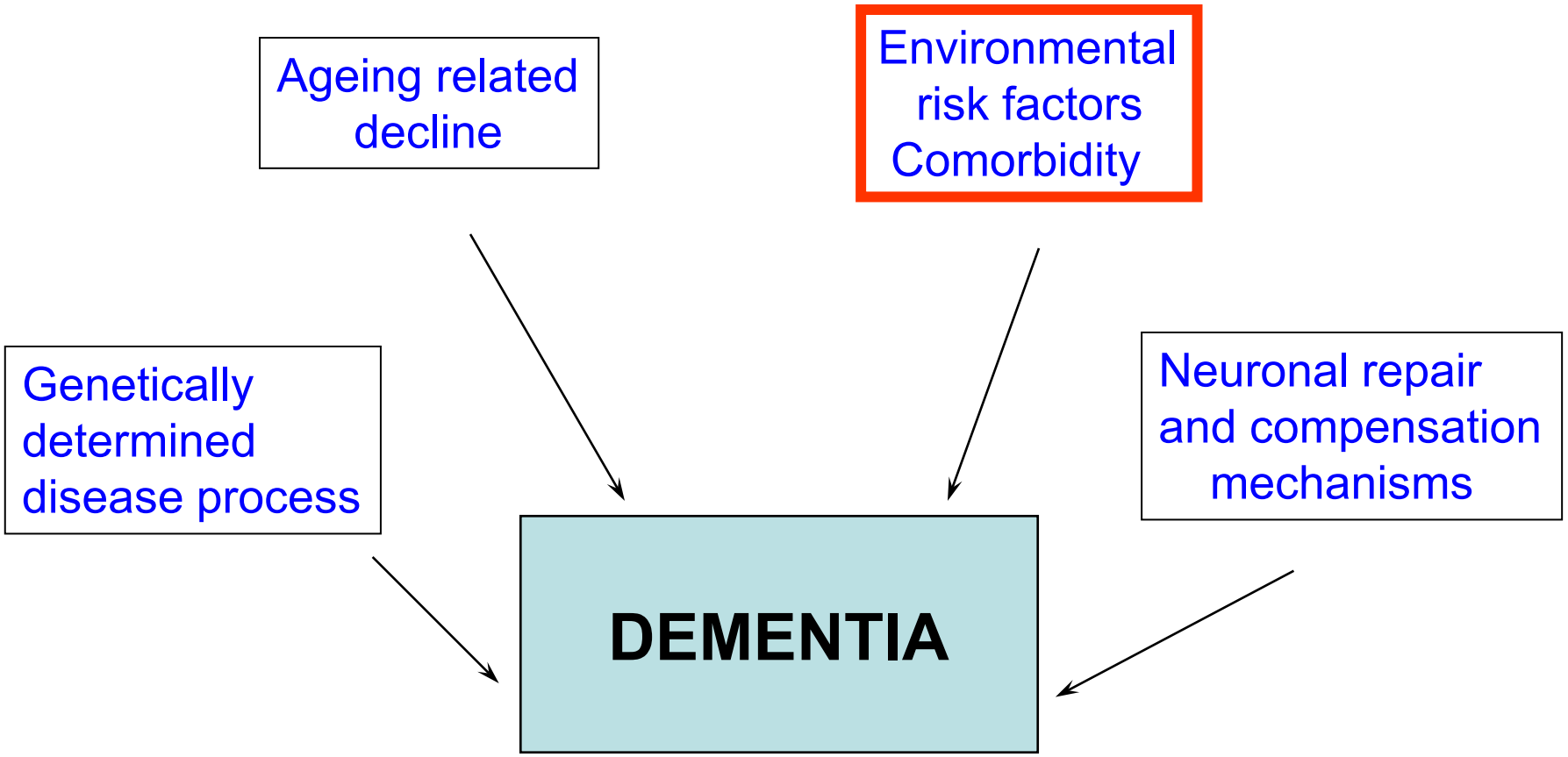
Worldwide prevalence 10-15% (as high as~35%)

Causes:

- Large infarcts (Atherothromboembolism)
- Lacunar infarcts
- Small vessel disease (SVD) (arteriolosclerosis)
- Multiple microinfarcts
- White matter changes (lesions)

Processes influencing clinical expression of dementia

Additional opportunities for interventions



Learning Objectives

Overview of Neuropathology of Dementia

- Ageing related decline, atrophy and neuronal attrition
- AD as most common form of neurodegenerative dementia
  - Amyloid, Tau and other factors in AD
- Parkinson's disease, Dementia with Lewy bodies
- FTDs (tau + /tau –), Huntington's disease and Prion diseases
- HAND, HAD, HIVE common in some parts of SSA
- Overlap between degenerative disorders, e.g. AD, DLB, VaD

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Collaborators: **Ahmad Khundakar**, Alan Thomas, John O'Brien (Camb), Paul Francis (KCL), Clive Ballard (KCL), Paul Ince (Sheff), RA Kenny (Dublin)

Alzheimer's Research UK
Defeating Dementia

MRC Medical Research Council

The Dunhill Medical Trust

COGFAST
Memory After Stroke Study

Asante Sana!
The IDEA study team

- Stella-M Paddick
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- Godfrey Mbowe
- Sarah Mkenda
- John Kisima
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- Bingileki Lwezuala
- Laura Ternent
- Catherine Dotchin
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