Dementias: clinical diagnosis, pathology & therapeutics

13th RTC in Sub-Saharan Africa
CAN, Douala, Cameroon
20th October 2022

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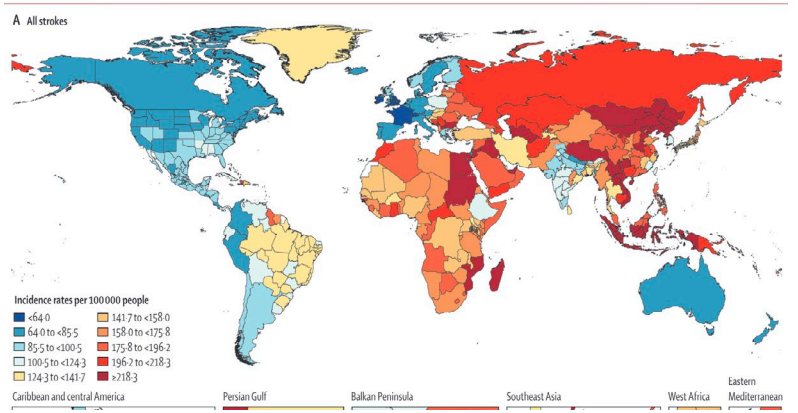
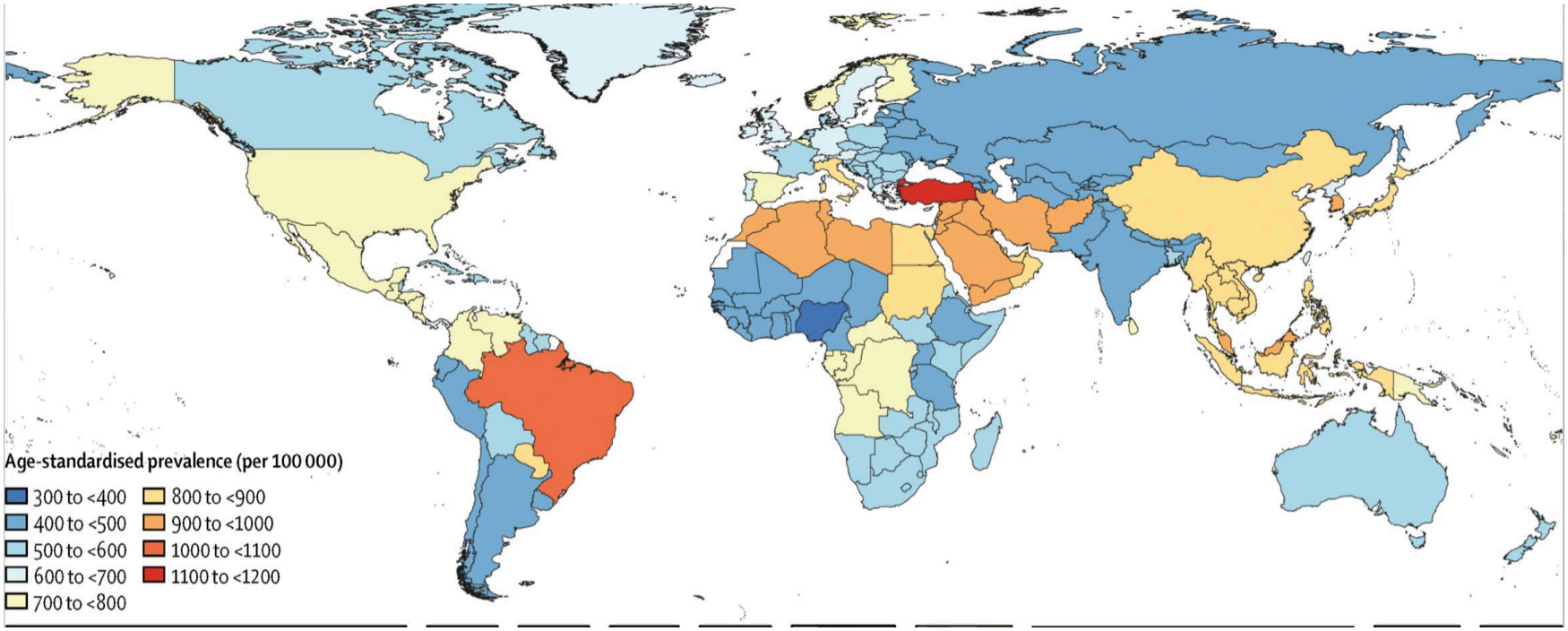
How do we Define Dementia?

- Memory problems in the healthy elderly do not mean they have dementia
- Dementia is more than forgetfulness or a subjectively poor memory
- Impairment in any of these:
  - memory
  - language
  - visual processing and orientation
  - mood, personality, and social skills
  - frontal executive function, including planning and problem solving
- Causes inability to function independently

Global Burden of Dementia



Doubling of Prevalence between 1990 and 2016



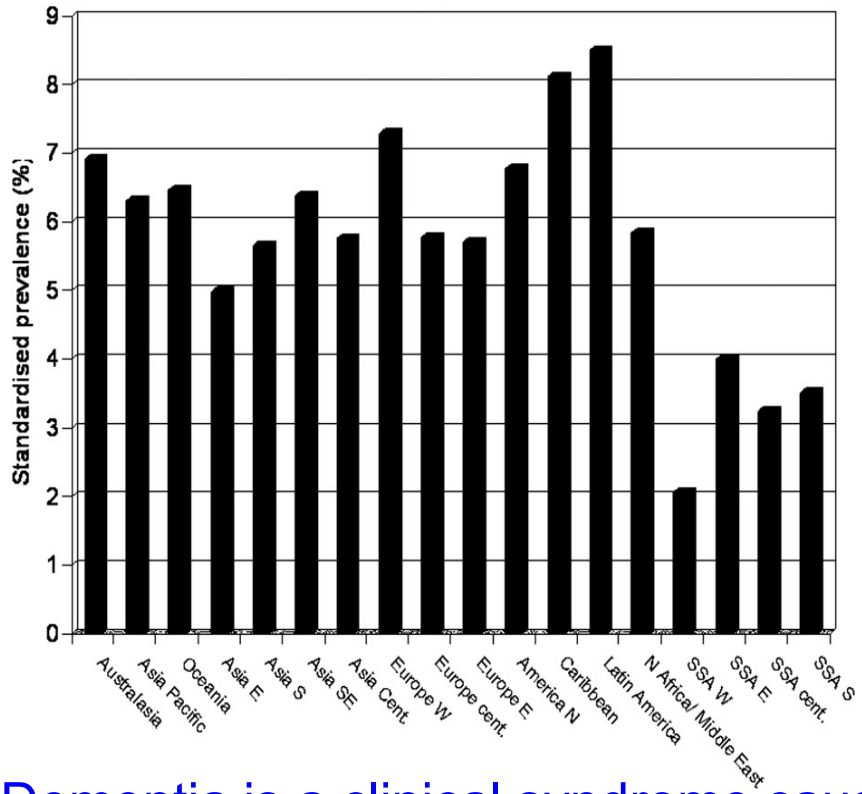
Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

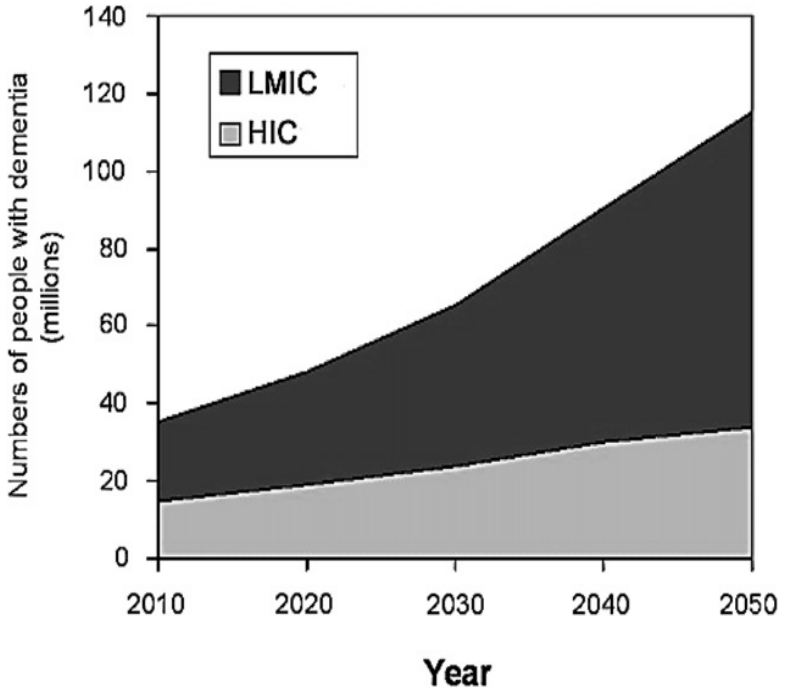
1 in 3 Dementia or Stroke

Lancet Neurol 2019; 18: 88–106

*GBD 2016 Dementia Collaborators**

Prevalence of Dementia Worldwide

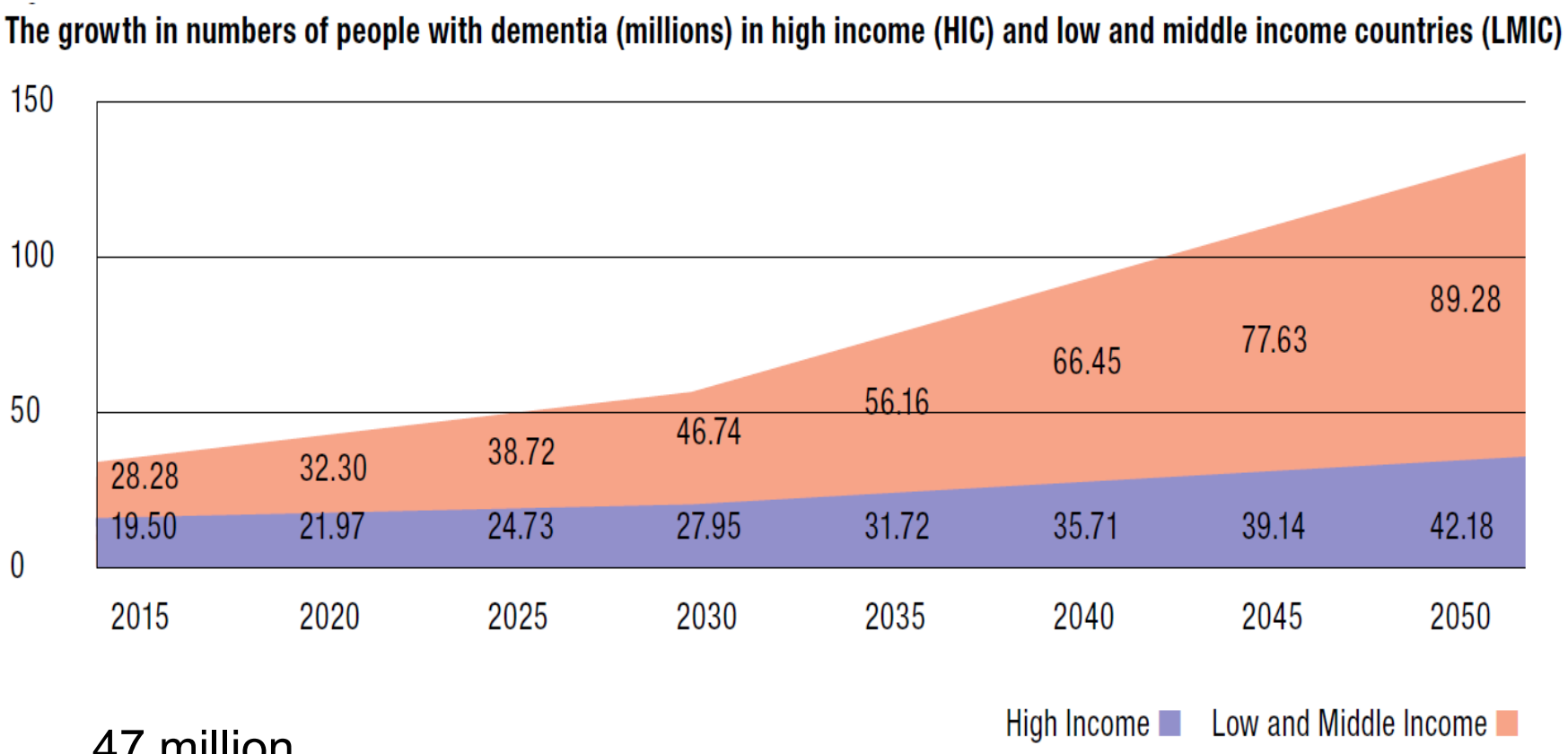




Dementia is a clinical syndrome caused by neurodegeneration . Alzheimer's disease (AD) is the most common type followed by vascular dementia (VaD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD).

Prince M et al, 2010

Numbers of People with Dementia



47 million

Wimo A et al 2015

Global Burden of DALYS and Deaths

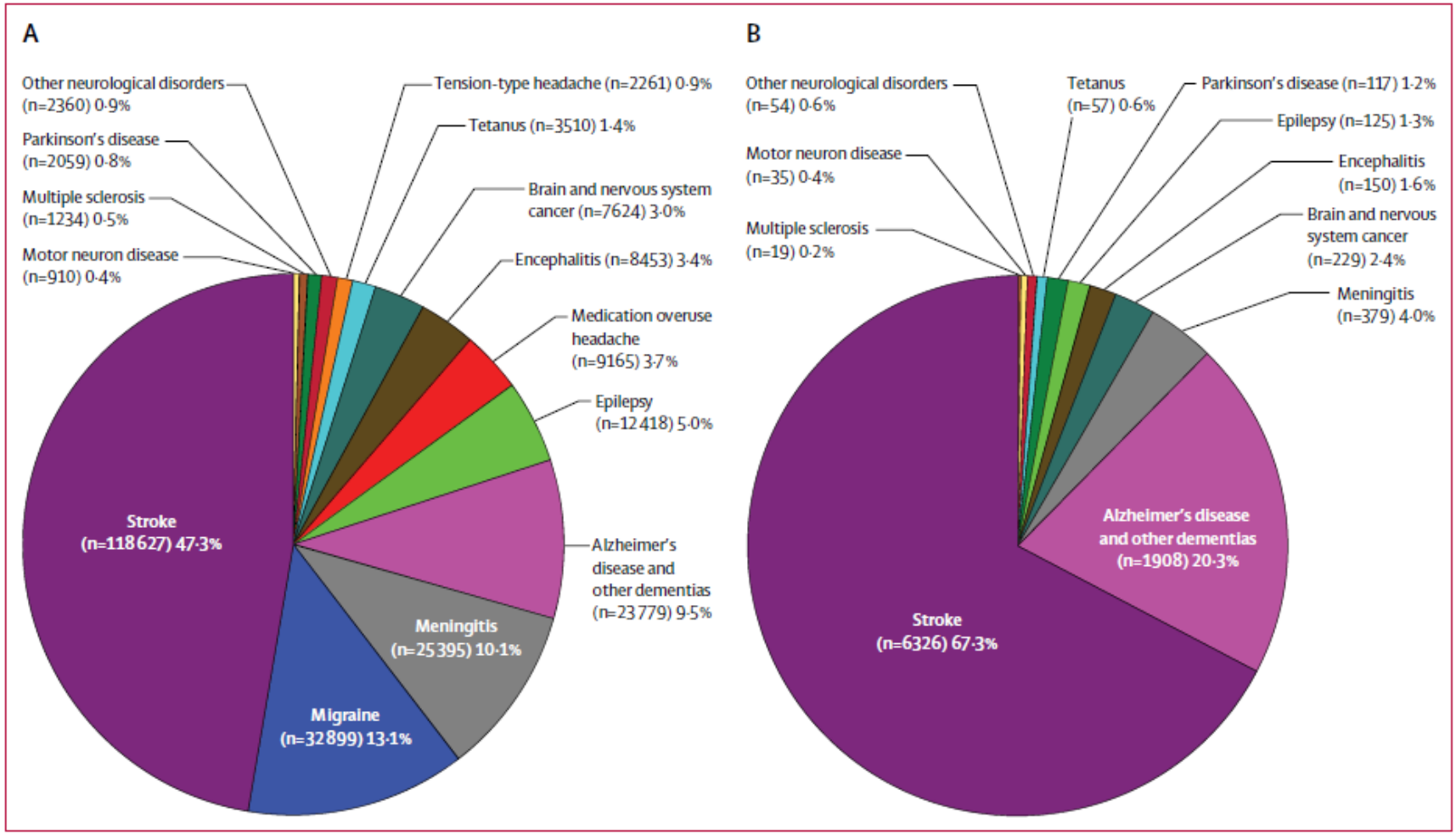
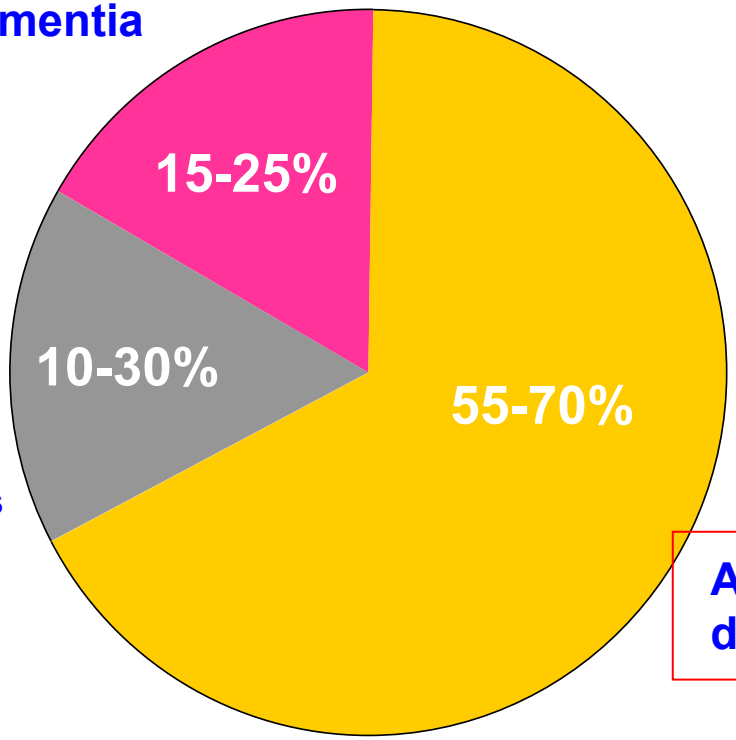
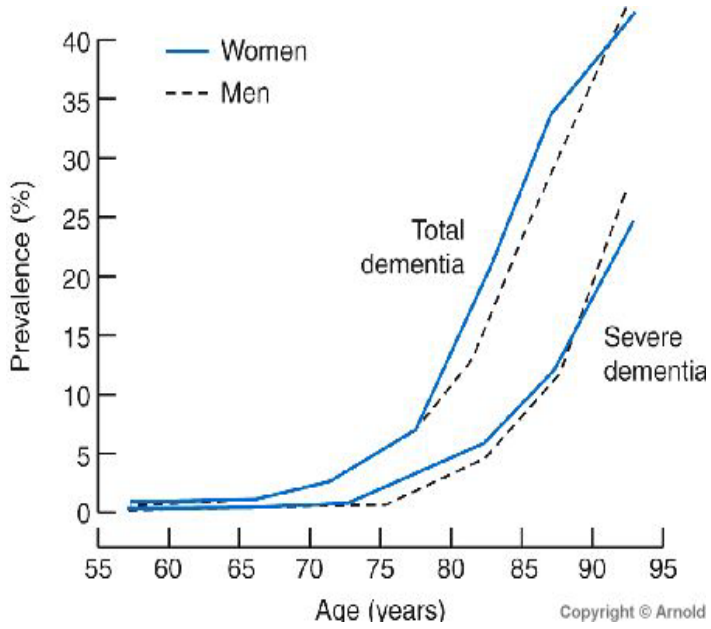


***Figure 2*: Contribution of various neurological disorders to the overall burden from neurological disorders in 2015**
Estimates are for (A) disability-adjusted life-years and (B) deaths.

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

What Are the Most Common causes of Degenerative Dementias?

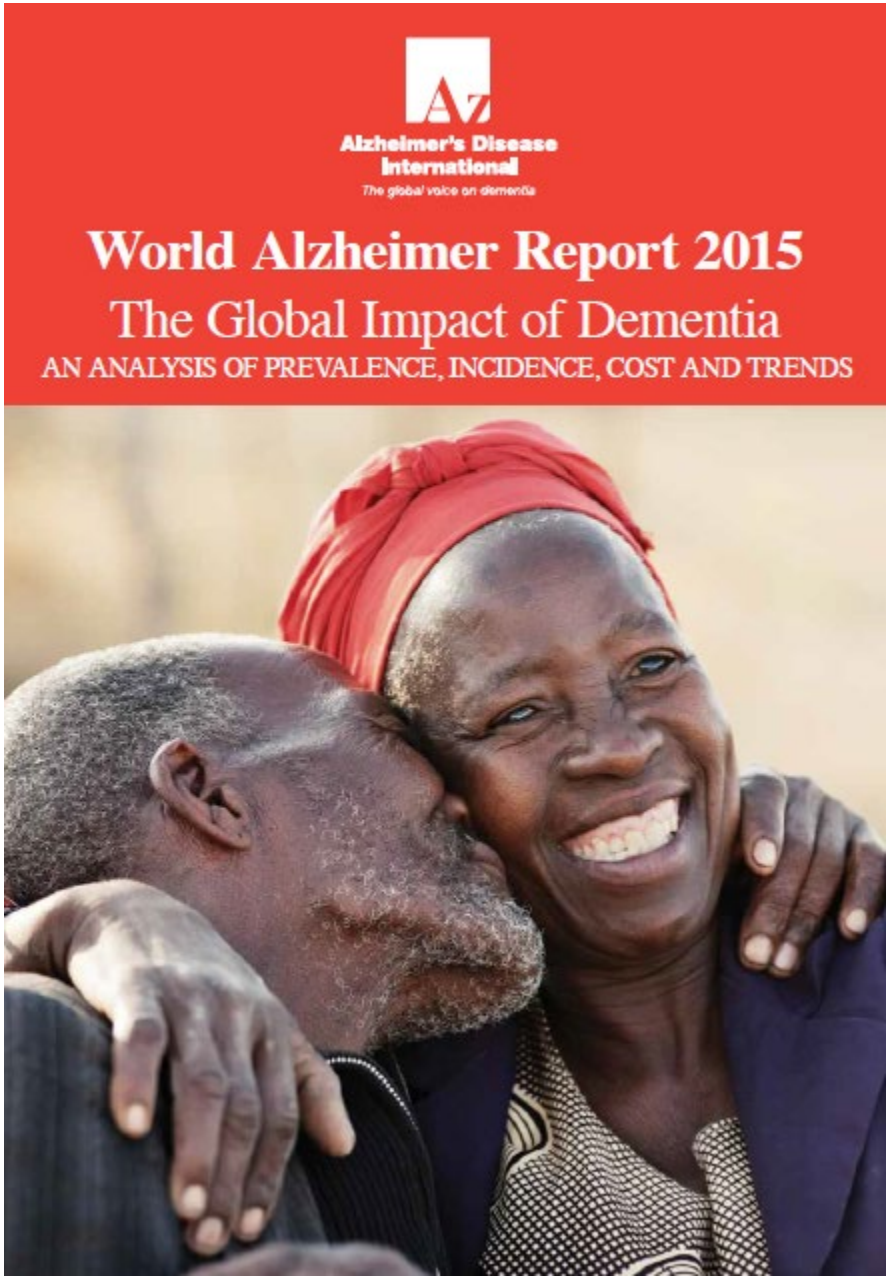




Frataglioni L, et al. Neurology. 2000;54:S10-15
Rarer dementias not shown but do not amount to >15 of total.

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)

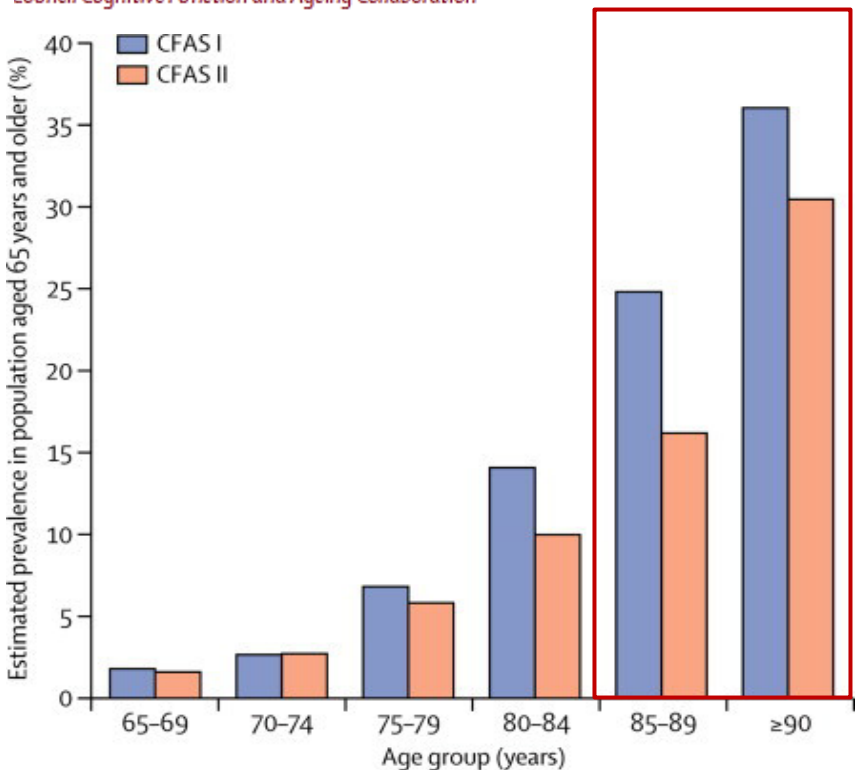
- Age
- Family history
- Down's syndrome
- Head injury
- Apolipoprotein E-ε4
- Vascular factors
- Smoking
- Female gender

	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, TLN 2008; 2012

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

Alzheimer's Disease International

The global voice on dementia

Dementia in sub-Saharan Africa

Challenges and opportunities

frontiers in Neurology

SYSTEMATIC REVIEW
published: 25 March 2021
doi: 10.3389/fneur.2021.627761

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

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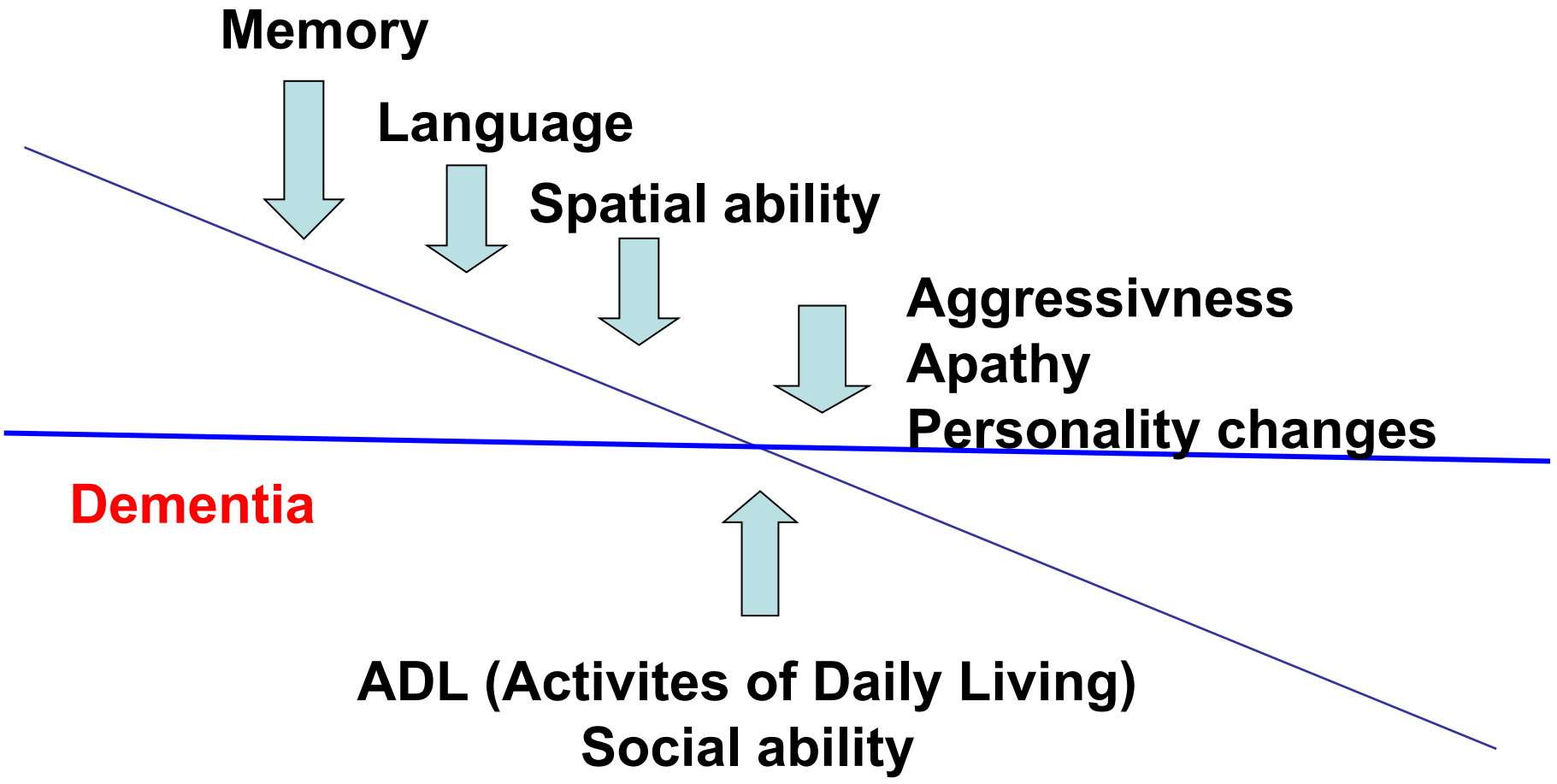
Background: Sub-Saharan Africa (SSA) is projected to have a rapid increase in the number of people living with dementia by 2050. Yet, there is currently no robust evidence on the risk factors for dementia in the sub-region that could inform context specific interventions.

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

CognitiveAgeing related thresholds leading to Alzheimer's Disease (AD)



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-NIA-AA Criteria

Dementia

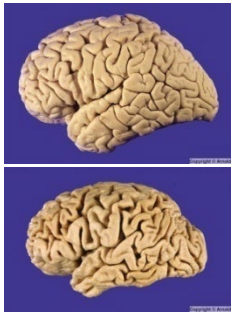
- Impaired memory
- ≥ 1 other cognitive domain impaired
- Clinical examination
- Neuropsychological tests

↓

Probable/Possible diagnosis

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

↓



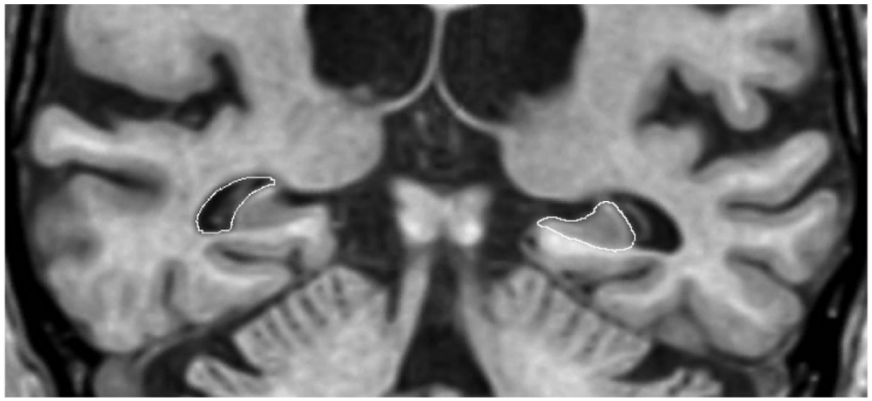
Definitive diagnosis by autopsy

Diagnosis of AD

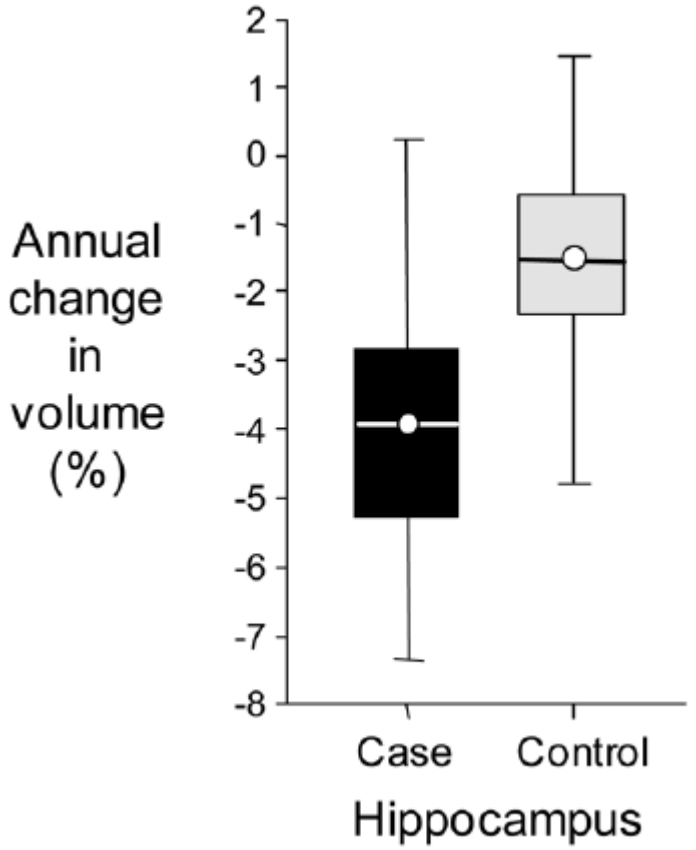
A, T, N (V) criteria

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

Rates of Medial Temporal Lobe Atrophy in Ageing and AD



- Mean annualized rate of hippocampal volume loss ~1.6% ± 1.4%/year
- Rates were greater in AD patients: hippocampus ~4.0% ± 1.9%/year
- Rates approximately 2 x times greater in AD than in age and gender matched controls.



Jack et al, 1998

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

Articles

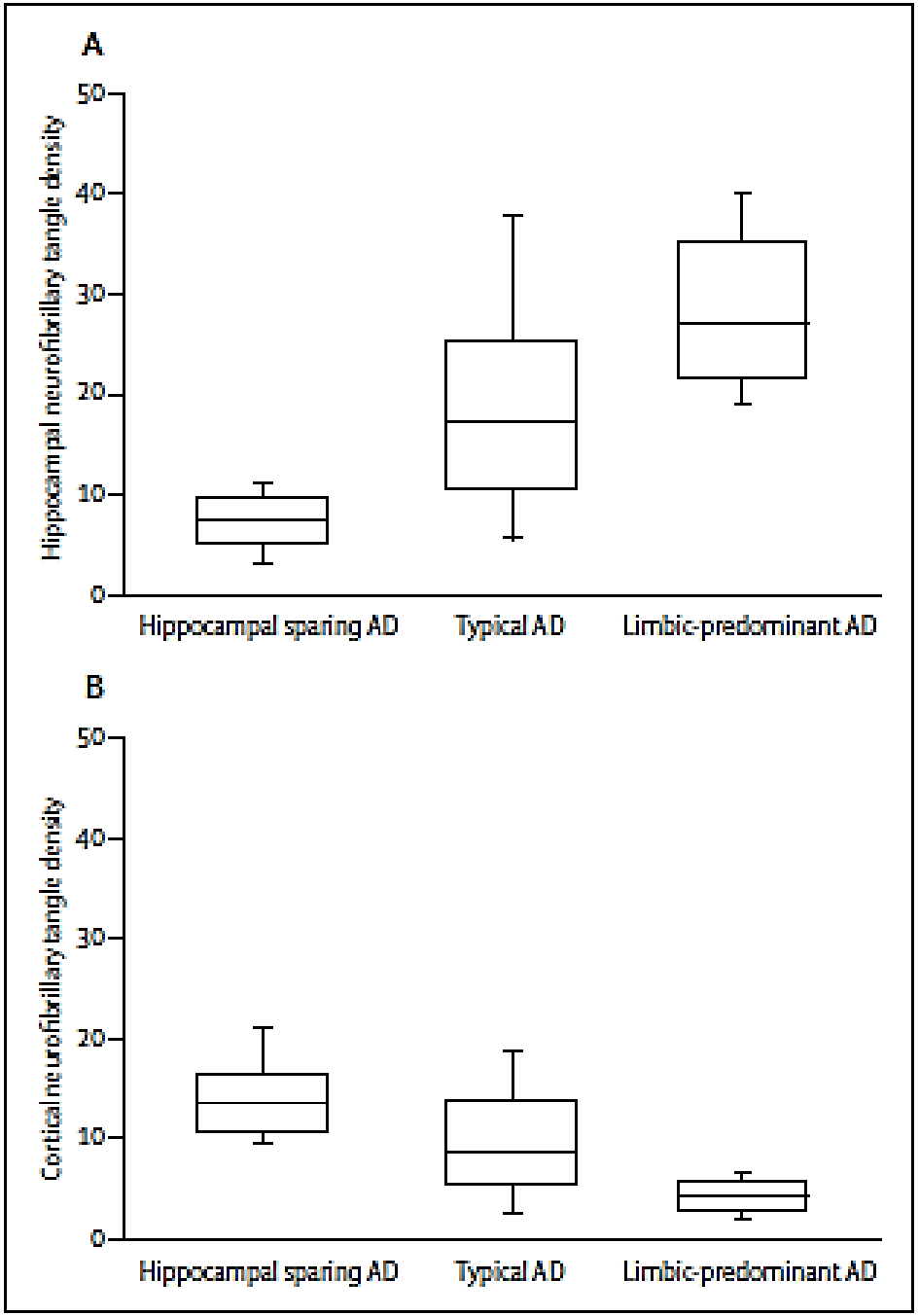
Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study

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



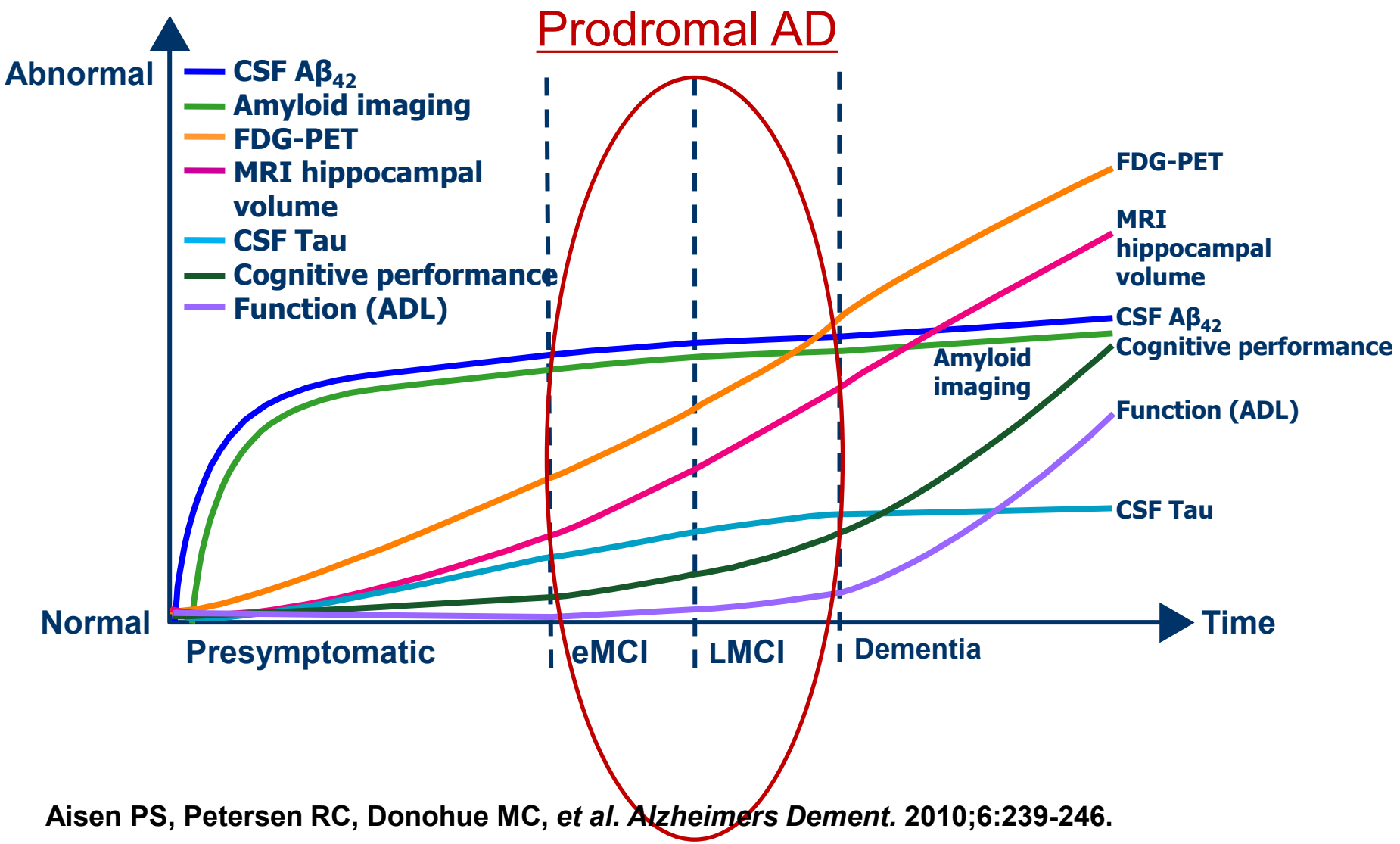
www.thelancet.com/neurology **Vol 11 October 2012**

Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study

Jennifer L Whitwell, Dennis W Dickson, Melissa E Murray, Stephen D Weigand, Nirubol Tosakulwong, Matthew L Senjem, David S Knopman, Bradley F Boeve, Joseph E Parisi, Ronald C Petersen, Clifford R Jack Jr, Keith A Josephs

- Patterns of atrophy on MRI differ across the pathological subtypes of AD
- MRI regional volumetric analysis can reliably track the distribution of NFT pathology and can predict pathological subtype of AD at autopsy

Progression of Dementia

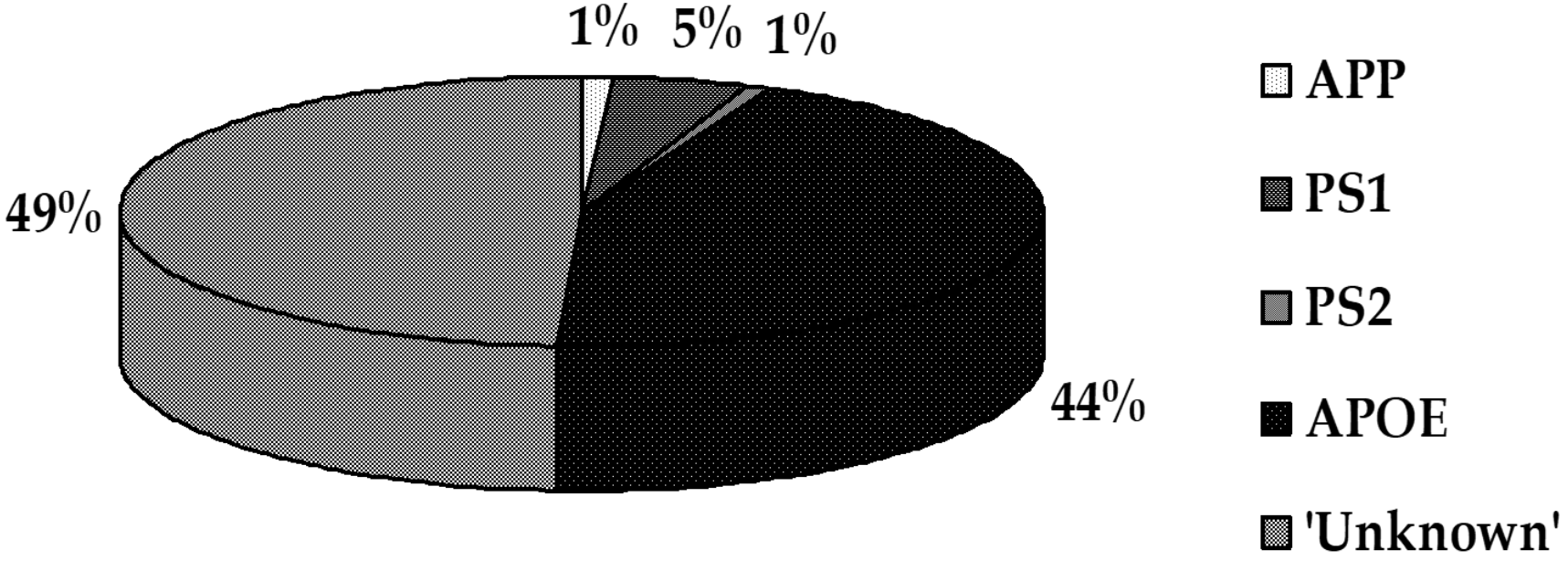


Aisen PS, Petersen RC, Donohue MC, *et al. Alzheimers Dement.* 2010;6:239-246.

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

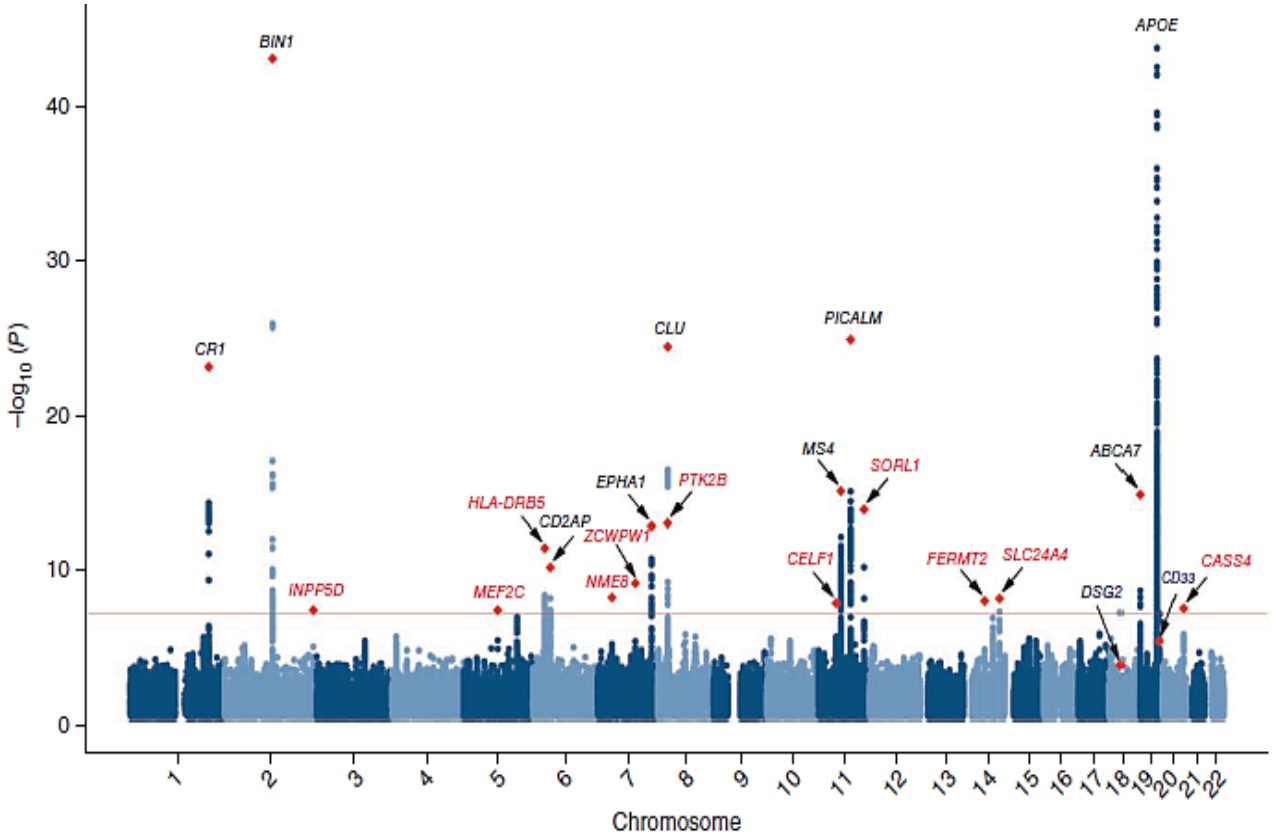
Sporadic AD 90-95%;

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.

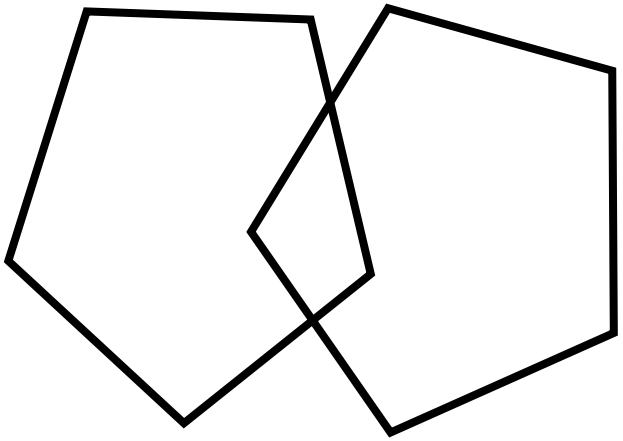
- Value of informant questionnaires; IQCODE

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

Mini-Mental State Examination

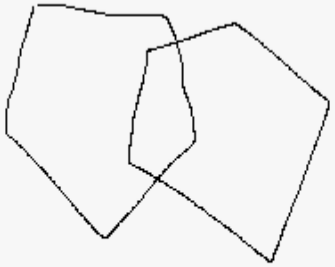
- MMSE is a short test which measures general cognitive status including short-term memory (Folstein, et al, 1975)

- 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

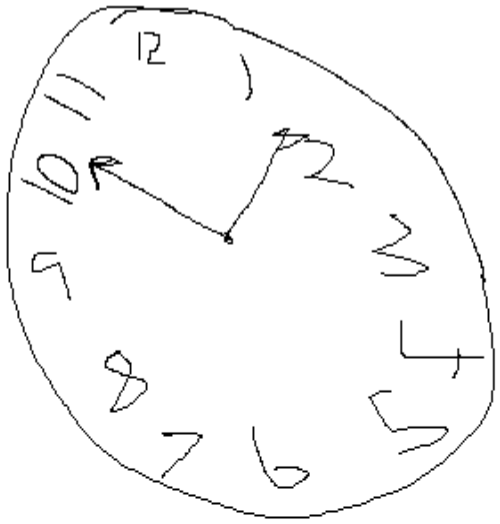
Dementia with Lewy Bodies (DLB)

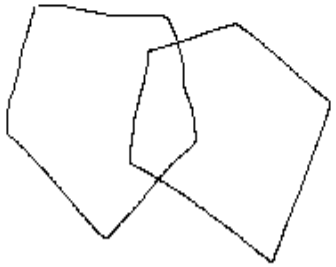
MMSE 20/30

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

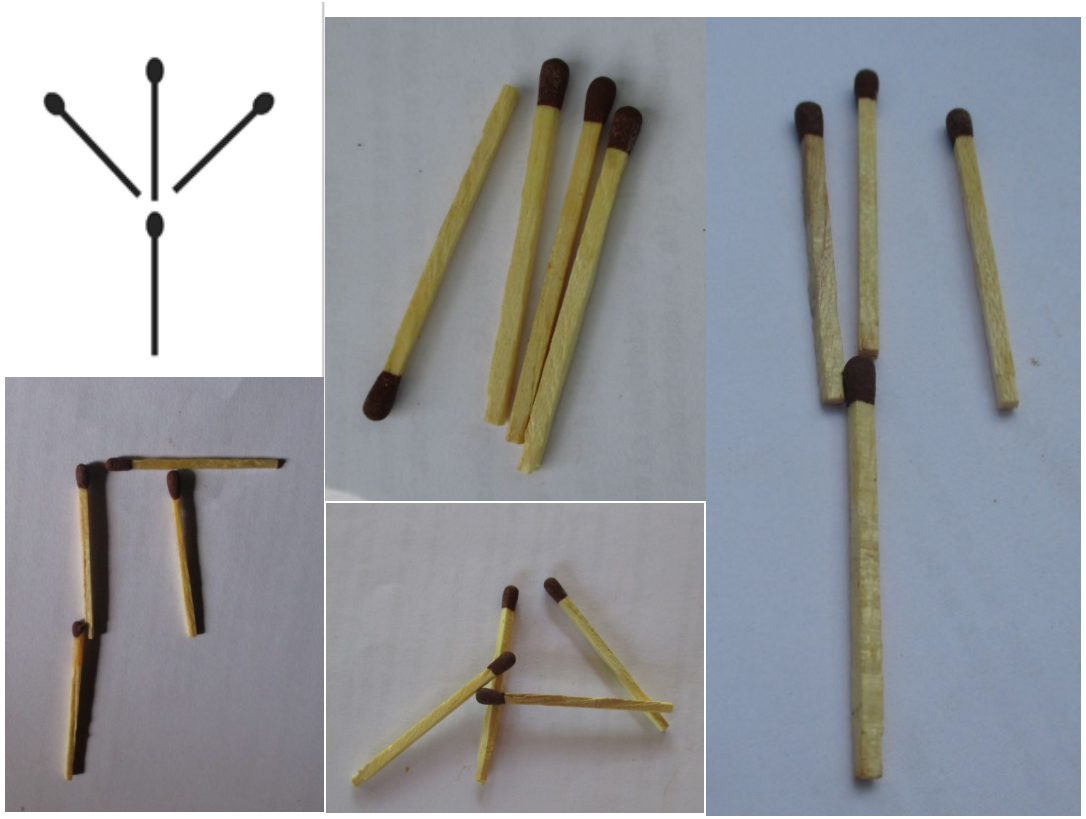
IDEA Study Screening Tools

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



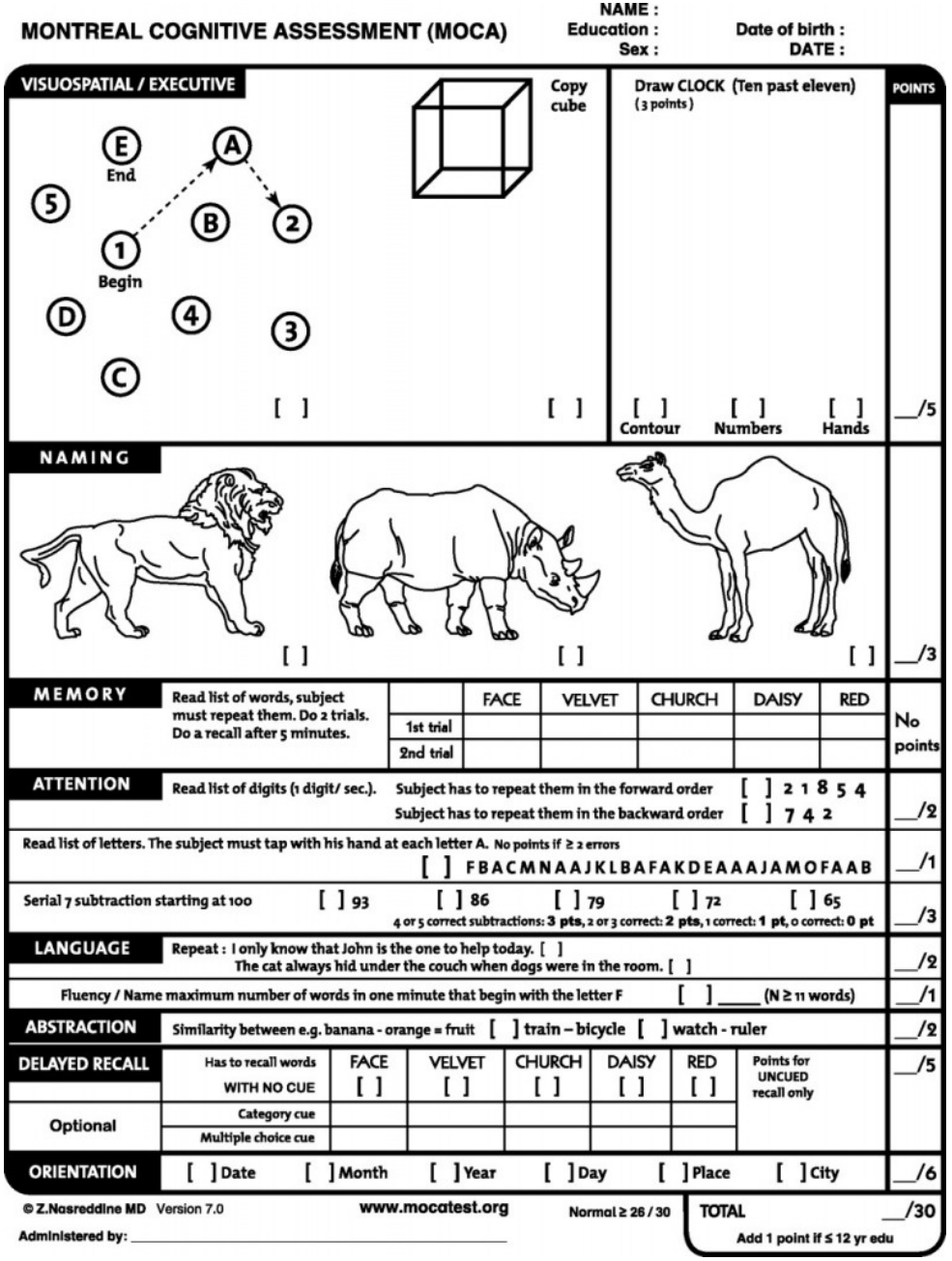
Observe examples of stick design in 4 impaired subjects

Montreal Cognitive Assessment (MoCA)

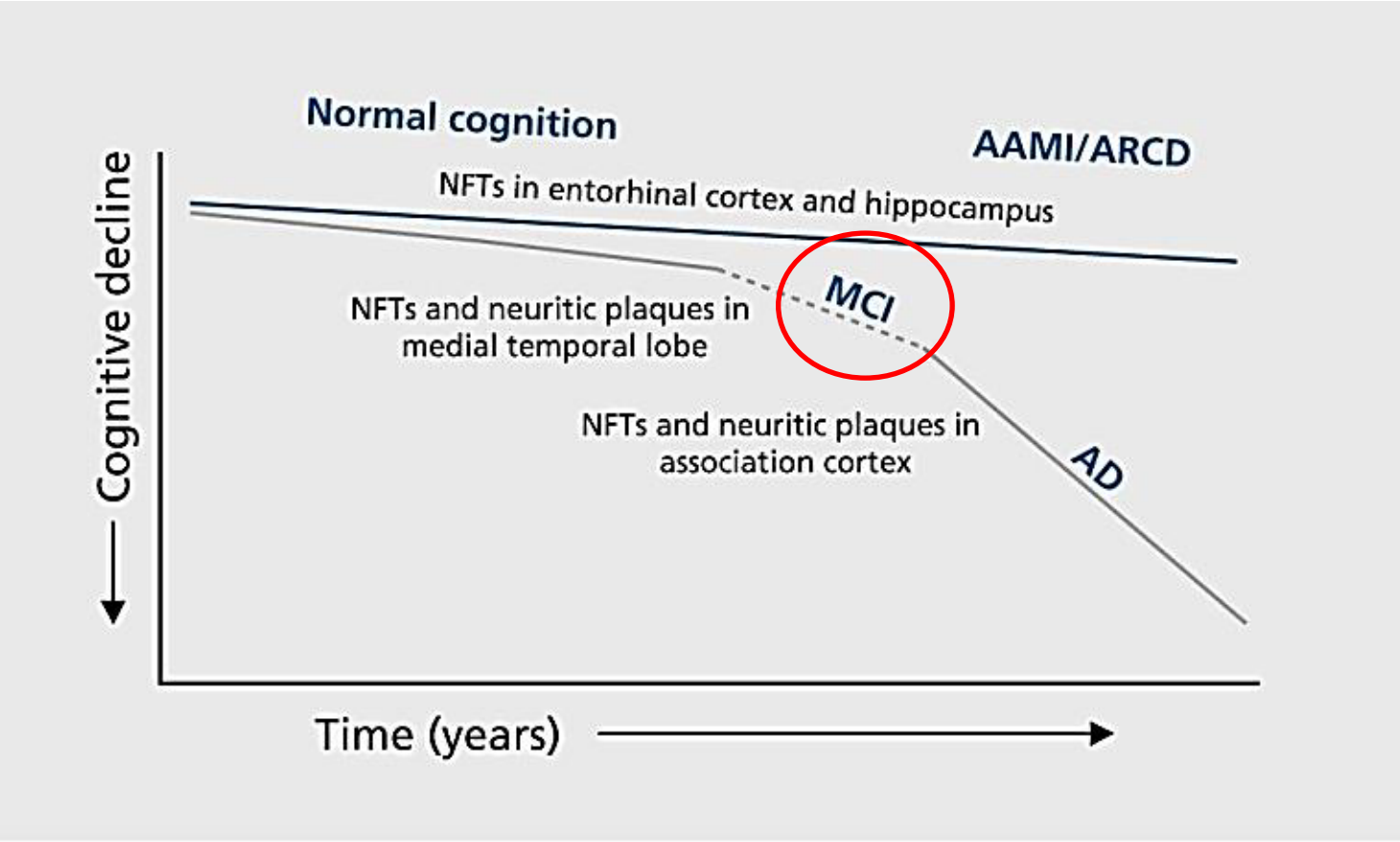
MoCA
MONTREAL
COGNITIVE ASSESSMENT

- 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; MCI, mild cognitive impairment

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, HTN, 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); lecanamab (Sept 2022)

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

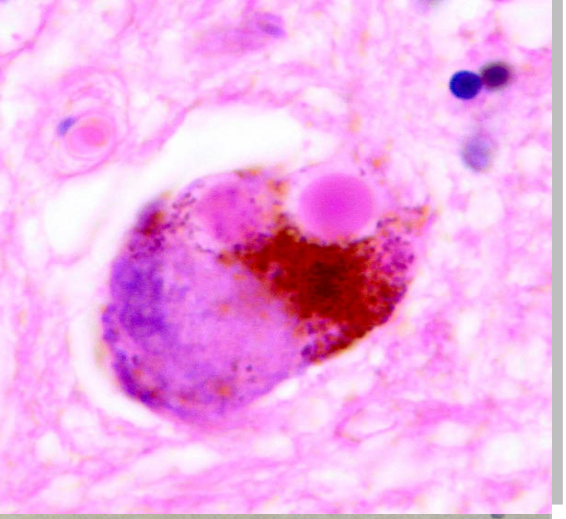
- **Cognitive decline & reduced social/occupational function**
  - Attentional, executive and visuo-spatial dysfunction prominent
- **CORE features**
  - Fluctuation
  - Recurrent visual hallucinations
  - Spontaneous parkinsonism
- **Suggestive features:**
  - REM sleep behaviour disorder
  - Neuroleptic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

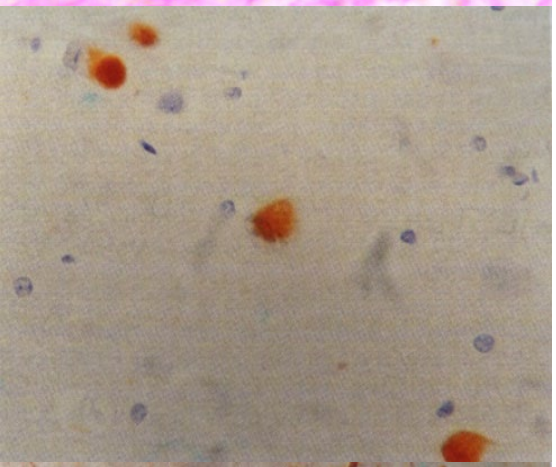
At least one core + one suggestive or 2 core features for Probable DLB

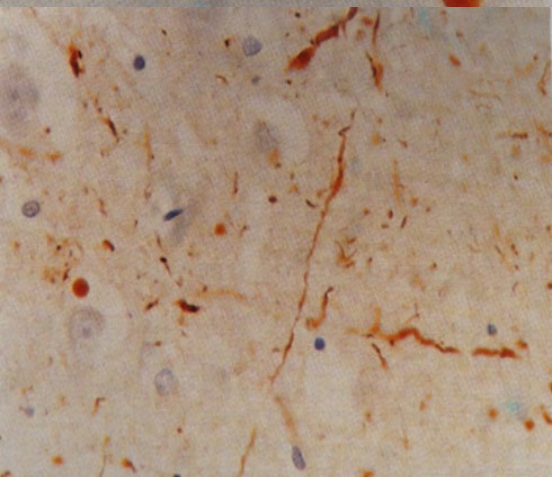
One core or suggestive feature sufficient for Possible DLB

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

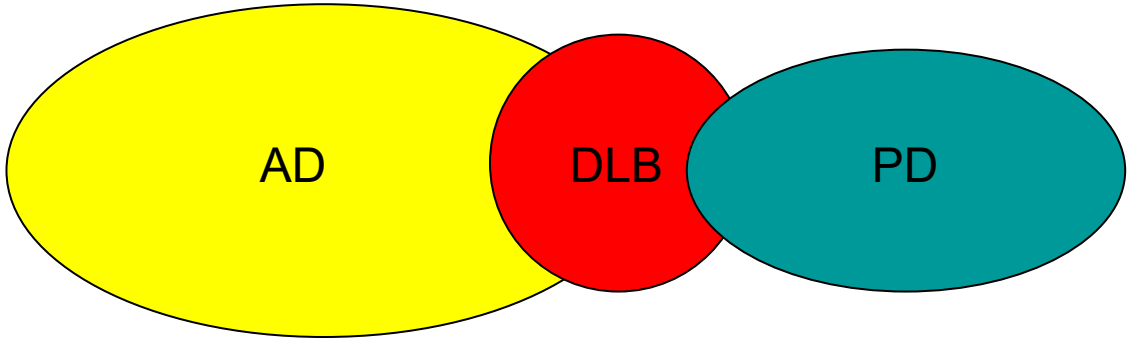






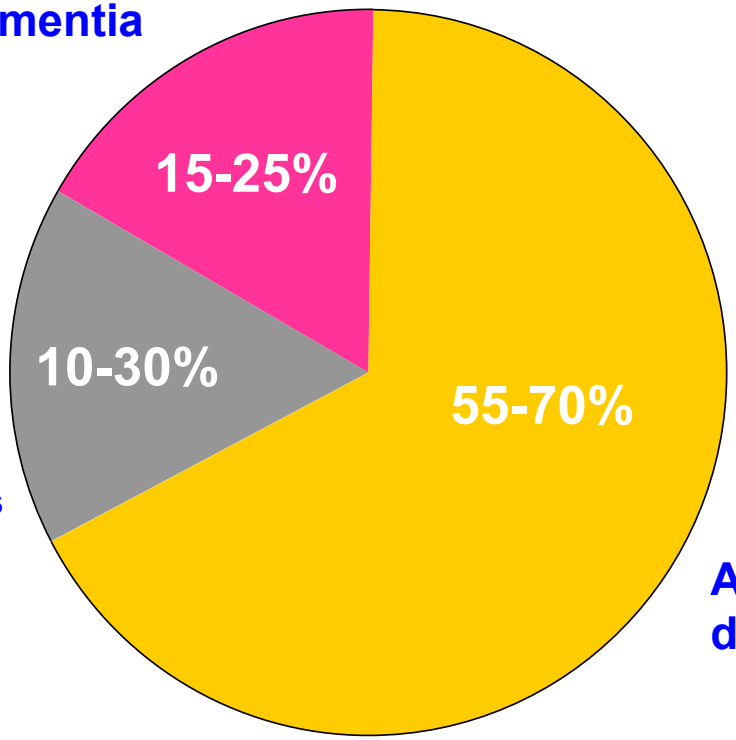
AD-DLB-PDD continuum

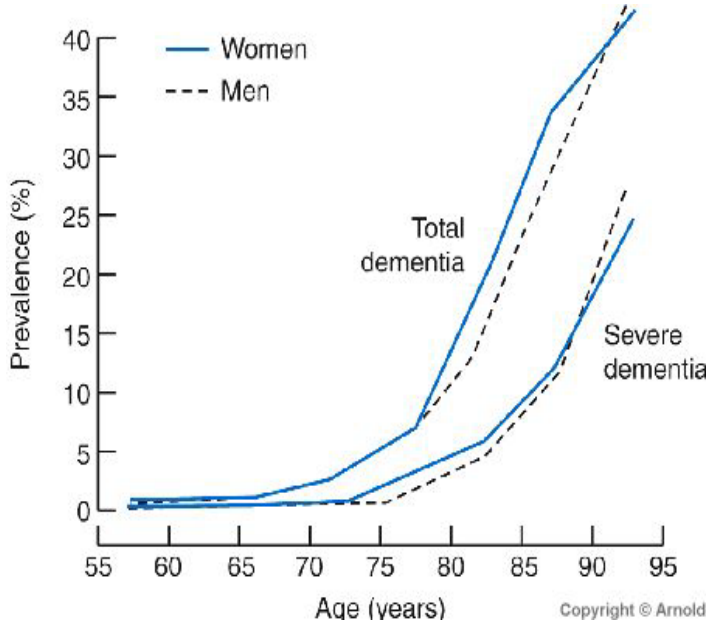
- Lewy bodies and Lewy neurites seen in ~ 15% of all autopsy cases of dementia
- One in seven cases of dementia is due to DLB
- One case of DLB for every 4 of AD and 2 of PD



McKeith I et al, 2017

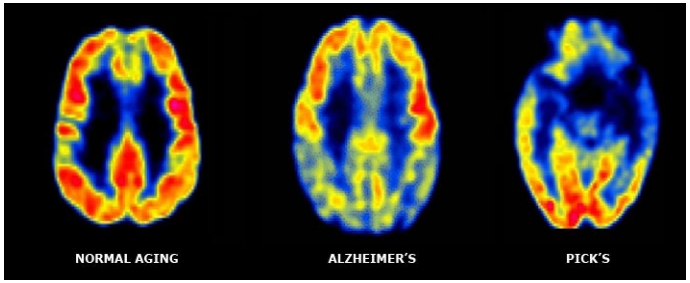
What Are the Most Common causes of Degenerative Dementias?





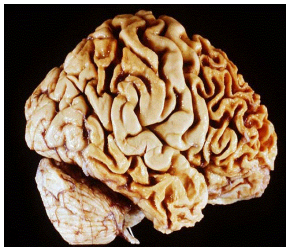
Frataglioni L, et al. *Neurology*. 2000;54:S10-15
Rarer dementias not shown but do not amount to >15 of total.

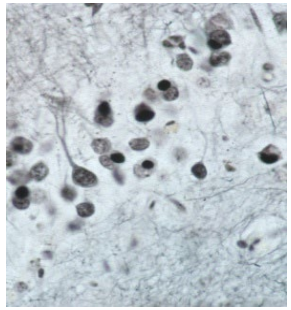
Frontotemporal Dementias (FTD)



Arnold Pick
1854- 1924

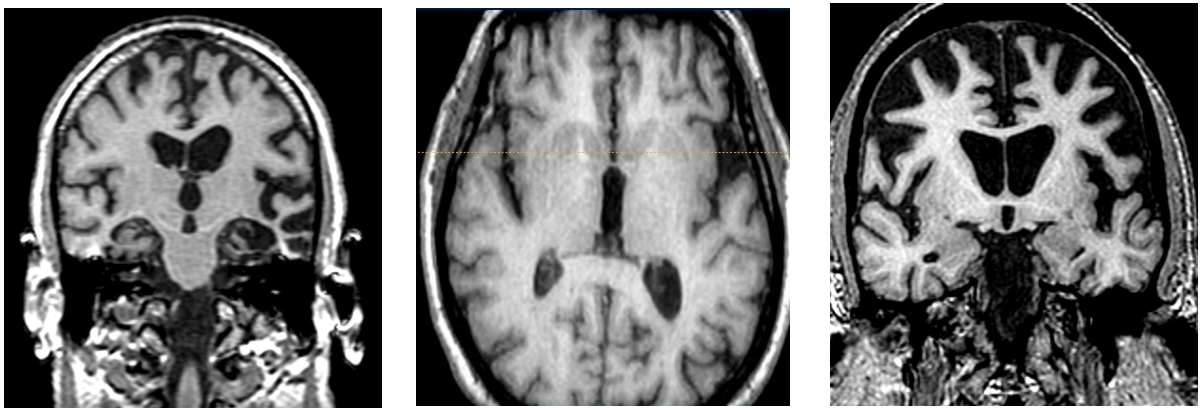
- Pick (1892) and bilateral frontal lobe atrophy
- FTD is a focal degenerative disorder (cause FTLD)
- Alteration in personality, social conduct and executive function
- Non-Alzheimer pathology disorder
- Related FTD syndromes –Semantic dementia, Primary Progressive non-fluent Aphasia,
- FTLDs are tauopathies 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





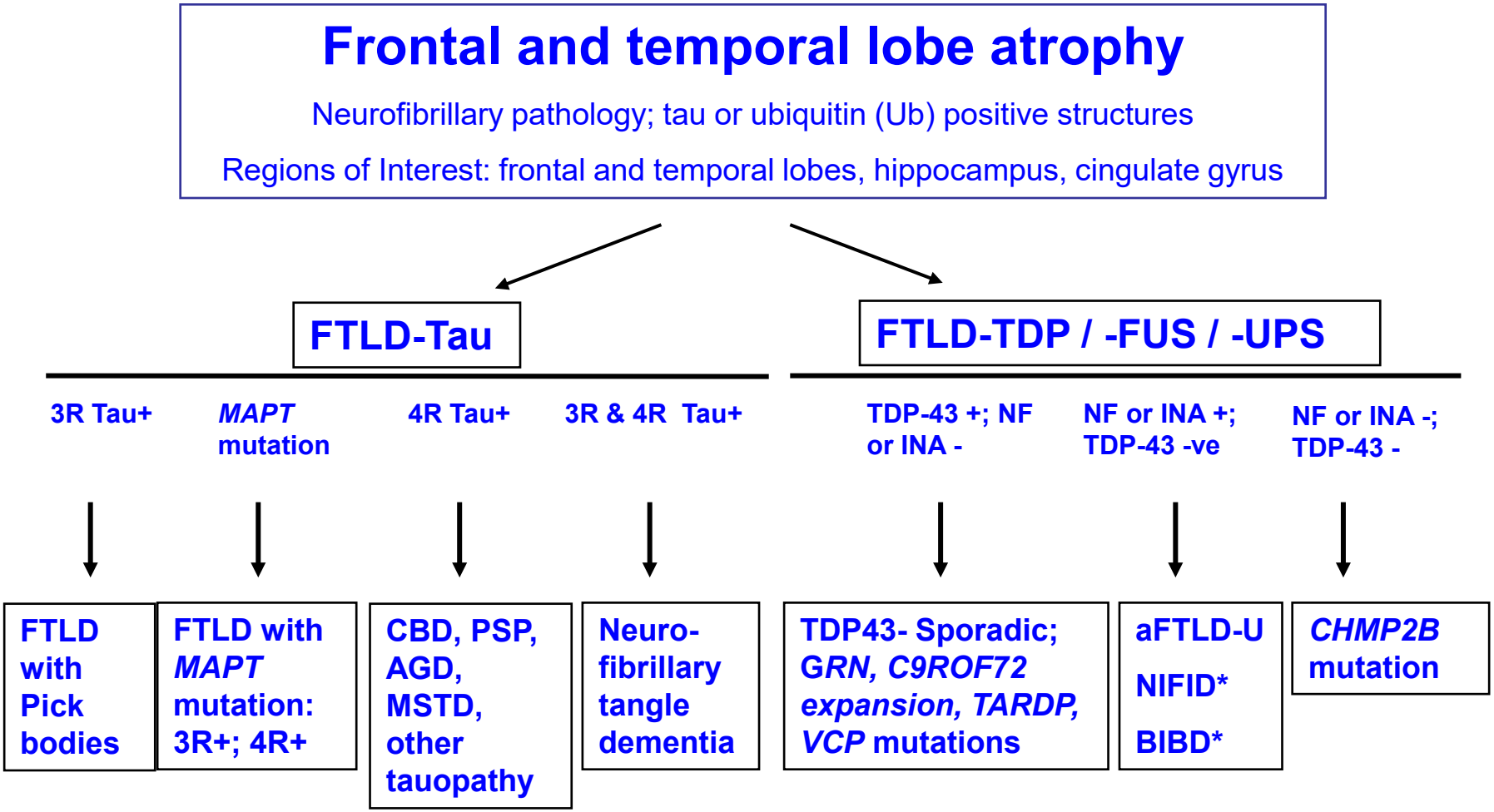
Clinical Syndromes in FTD

- 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

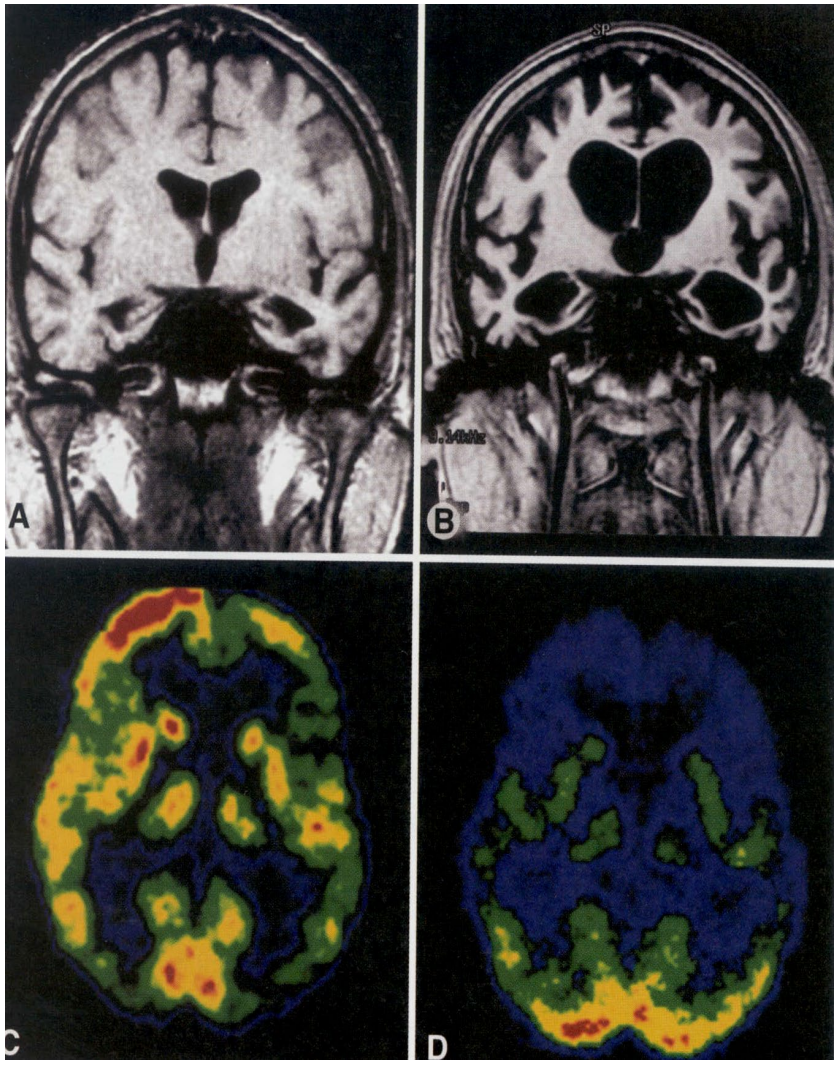
Frontotemporal Lobar Degeneration



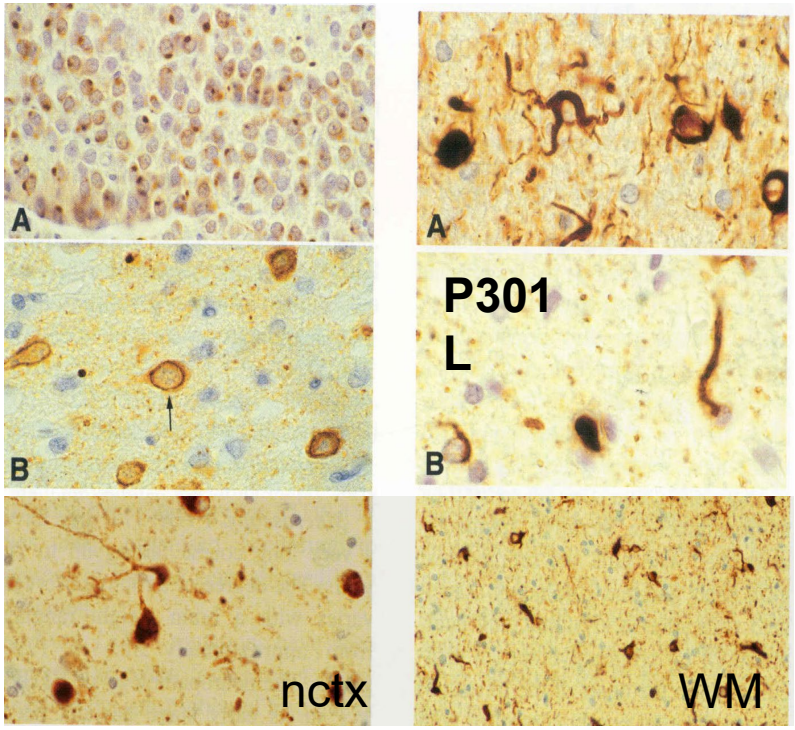
** BIBD, basophlic inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; TDP-43 transactivation response DNA binding protein with M(r) 43 kD; PGRN, progranulin; VCP, Valosin-containing protein*

FTD linked Parkinsonism- Chr 17

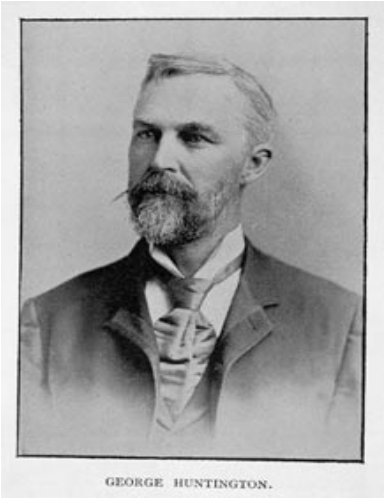
G389R mutation A→B 3 yrs



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



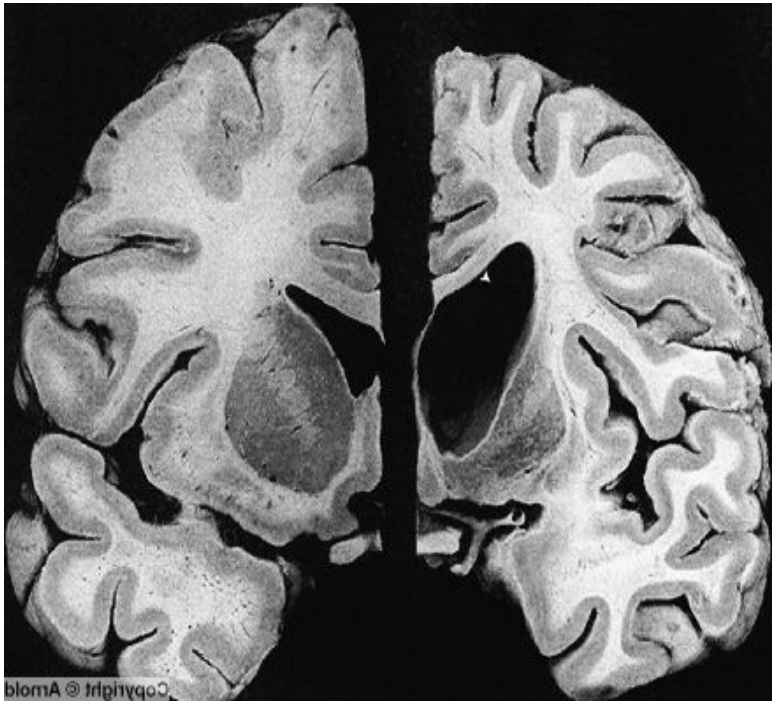
Huntington's Disease (HD)

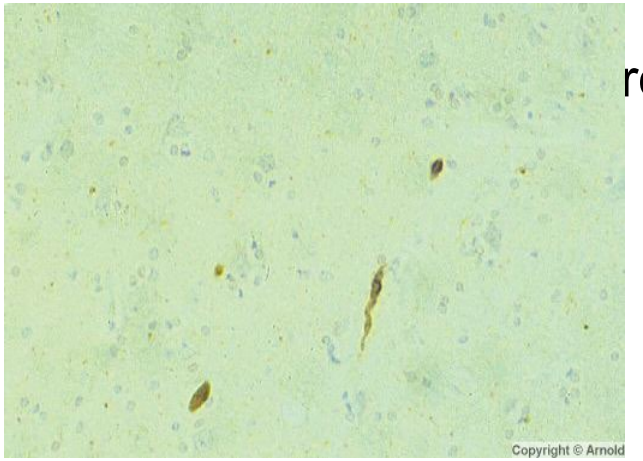


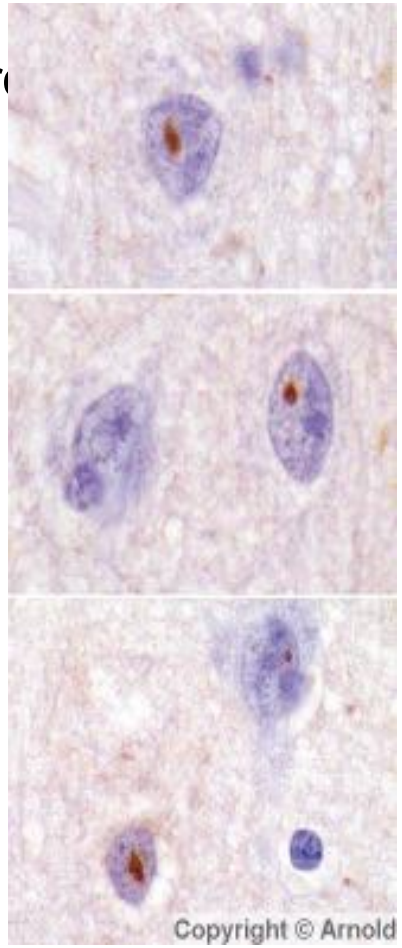
George Huntington 1850-1916

- 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

Huntington's Disease- pathology







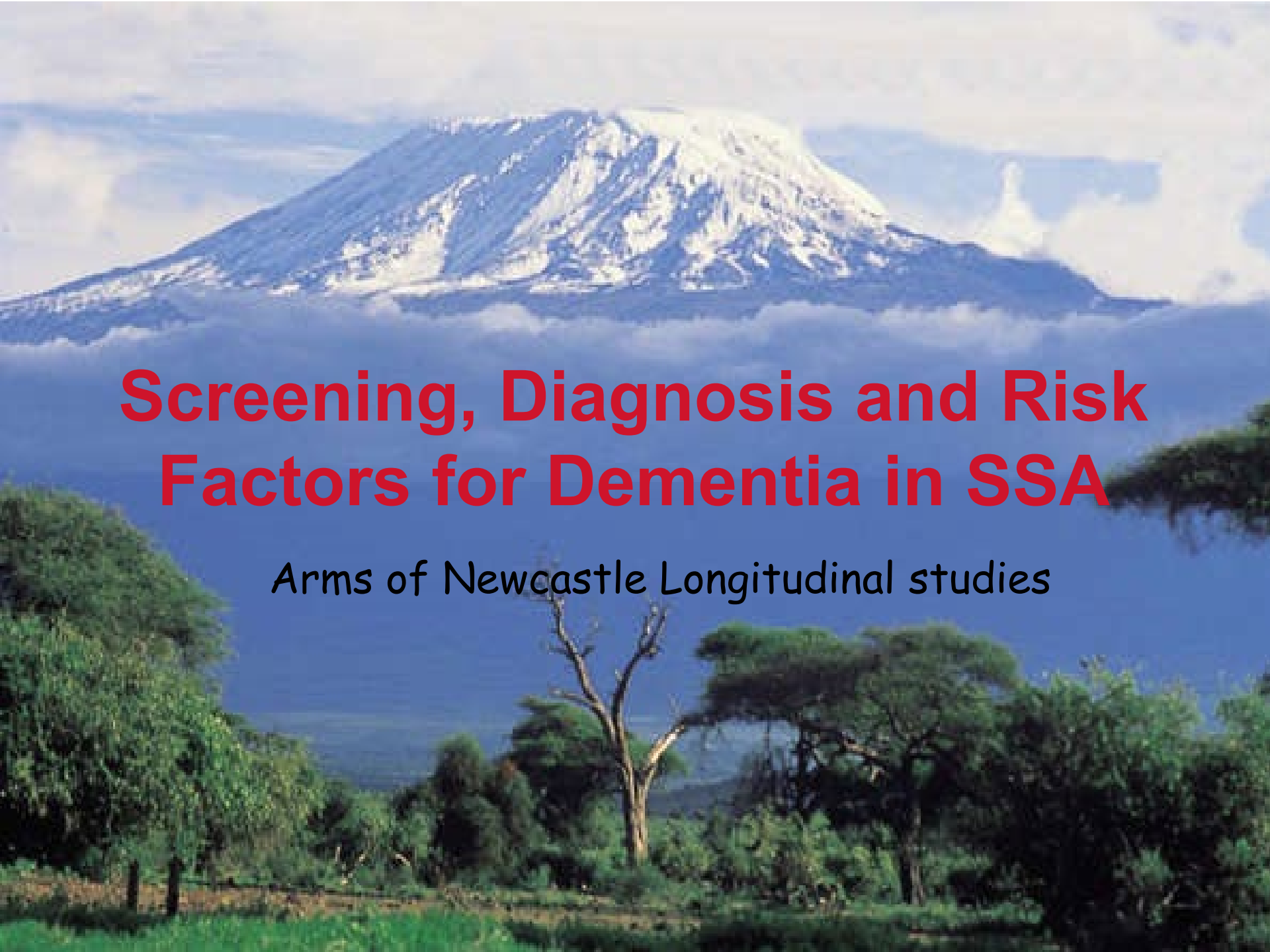
- HD patients exhibit severe caudate and considerable putaminal atrophy due to loss of medium spiny neurones.
- Anti-ubiquitin staining reveals abnormal cortical neurites in wide distribution.

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

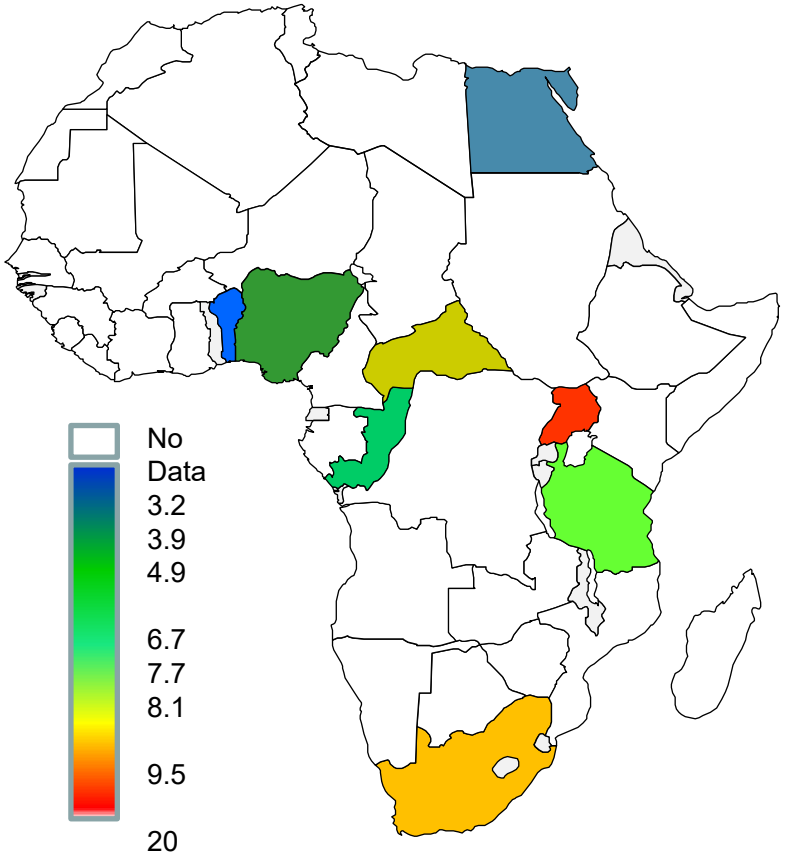
Lowe J and Kalaria R, 2015

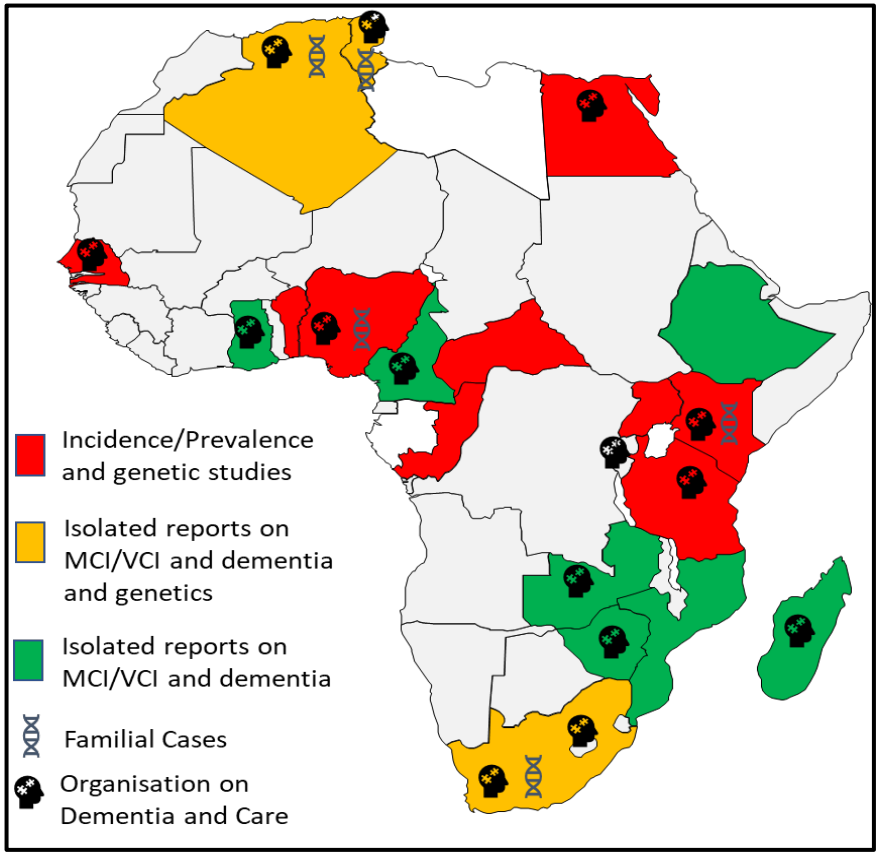


Screening, Diagnosis and Risk Factors for Dementia in SSA

Arms of Newcastle Longitudinal studies

Variation in Dementia Prevalence estimates in Africa





Akinyemi R 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

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)

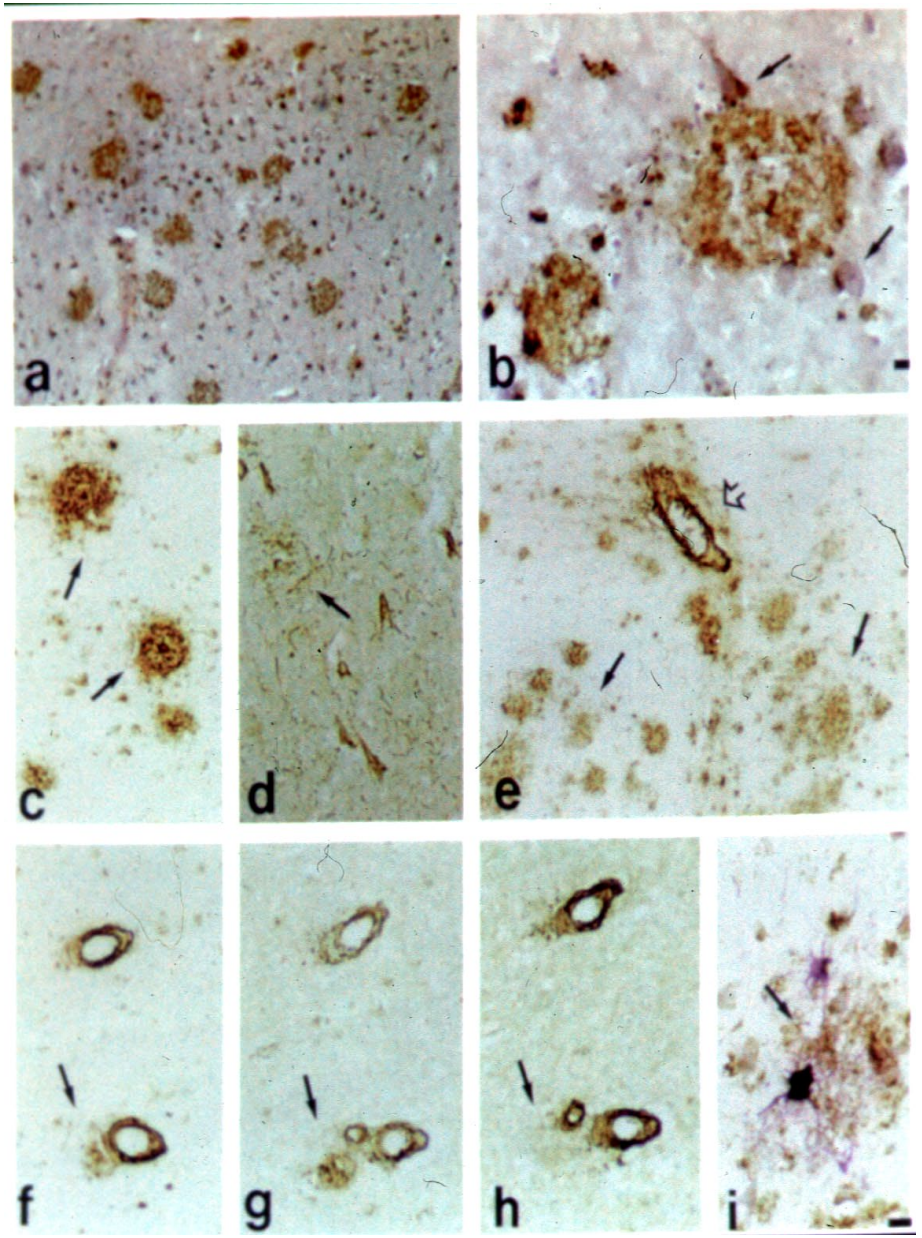
Country, Location; Type of sample	Sample size, Age (yrs)[a]	Dementia Prevalence (%)	Alzheimer's Disease (%)	VaD (%)	Reference
Africa, 10 countries; Community		2.4%	57%	27%	(George-Carey et al., 2012)
SSA, 5 countries (Benin, Botswana, CAR, Congo, Nigeria); Community/clinic[b]	10,413; > 65 yrs	0–10%	54–83%	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

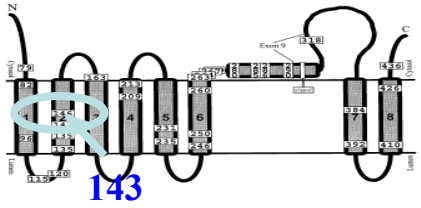
- Comparable to a US sample, ~18%of elderly East Africans exhibit Aβ(42) deposits (9/50 cases)
- Severe CAA was evident in brains of two subjects
- Typical τ +ve NFT pathology was evident in the hippocampus and neocortex
- These findings suggest that elderly East Africans are unlikely to escape AD (even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

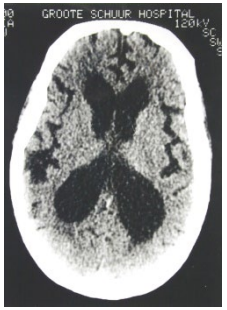
(Ogeng'o J et al, 1996)

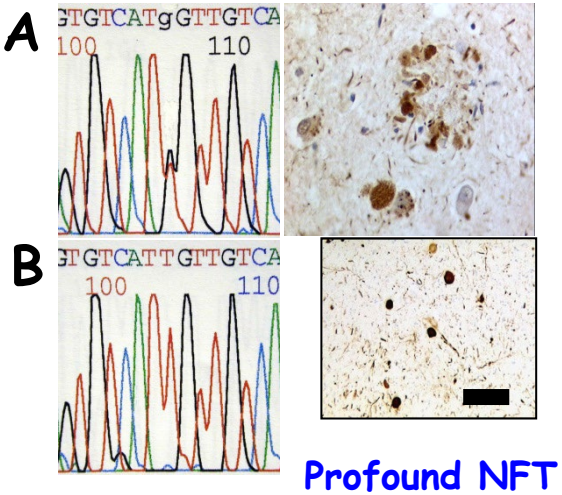


Hereditary AD in a large Xhosa Family, SA

Heckmann J et al, 2004

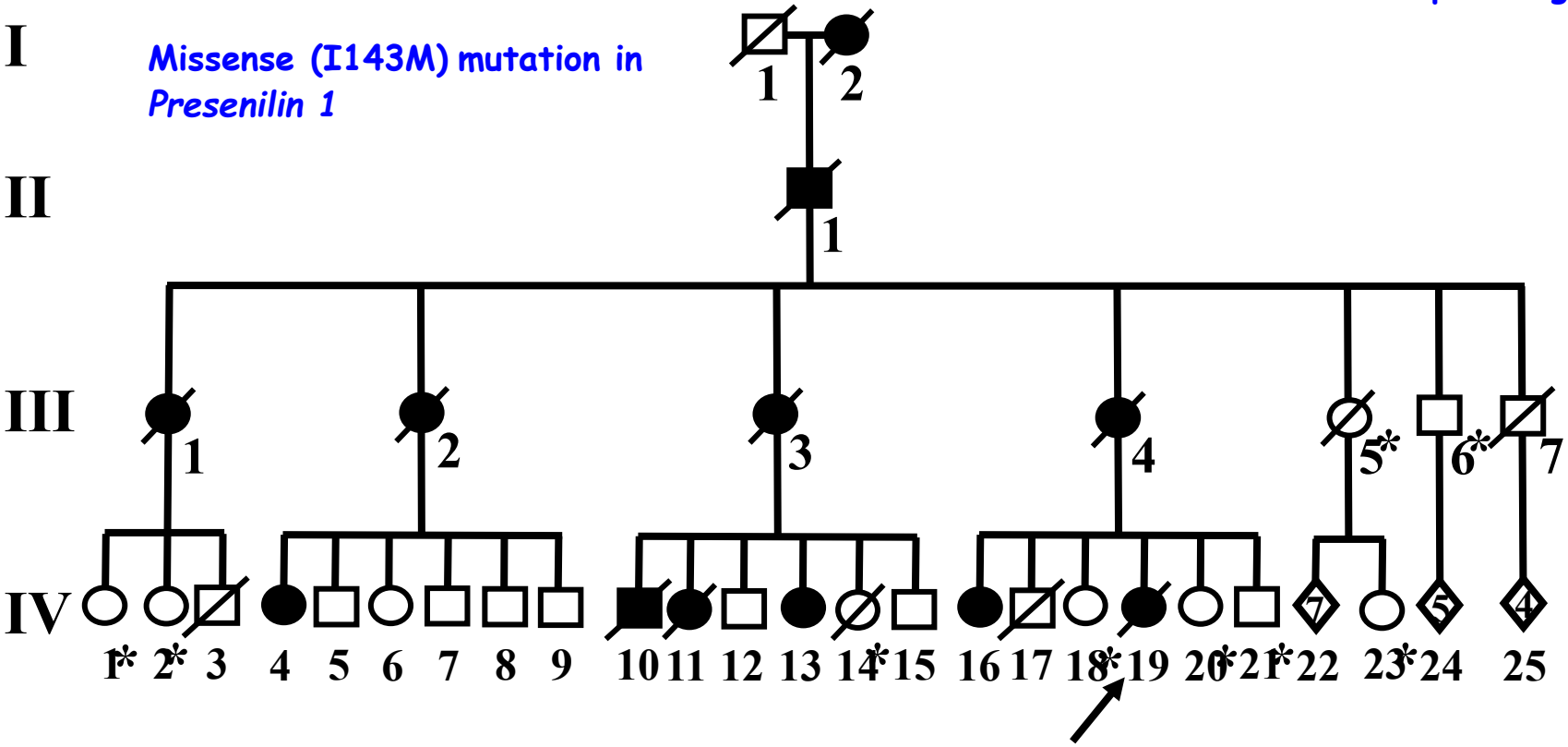






Profound NFT pathology

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.

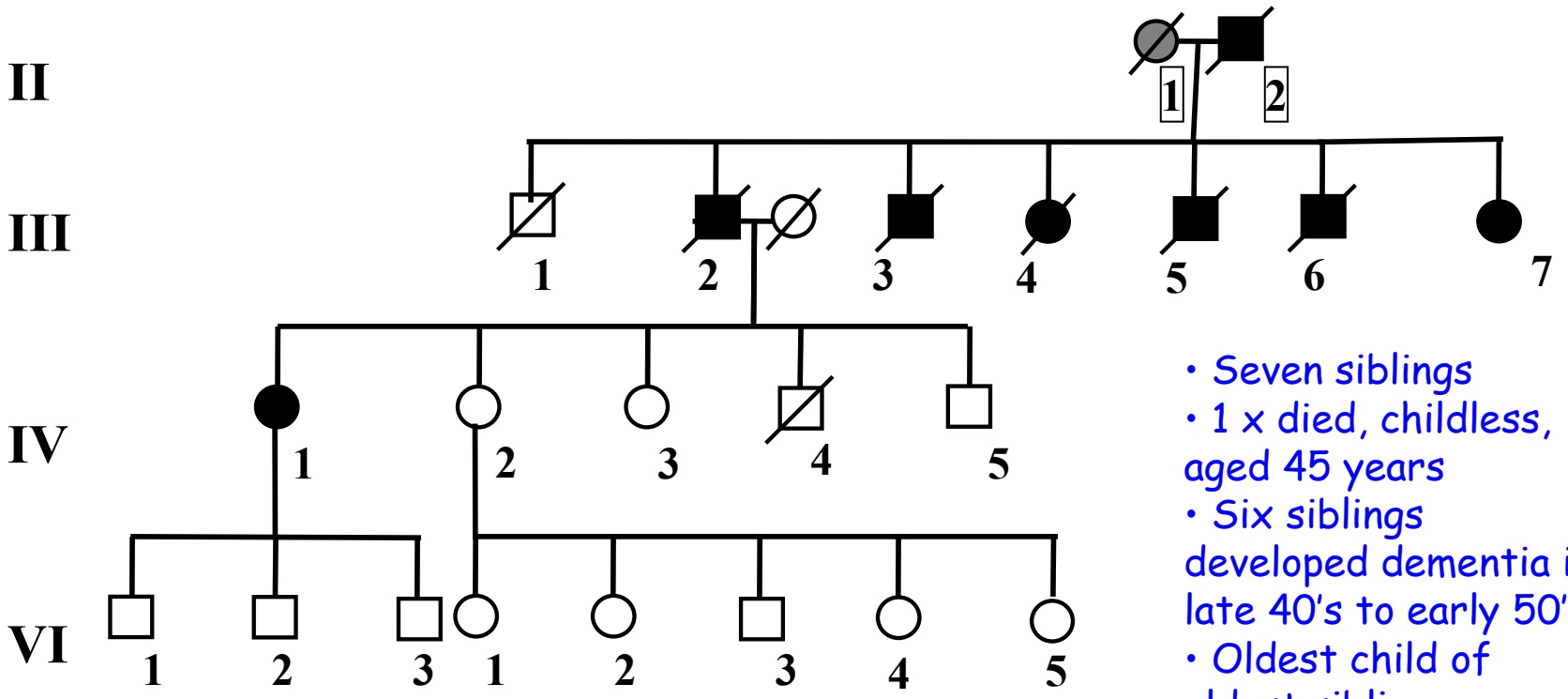
RO Akinyemi[1,4], MO Owolabi[1], VA Makanjuola[2], AO Ogunseyinde[3] and A Ogunniyi[1].

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

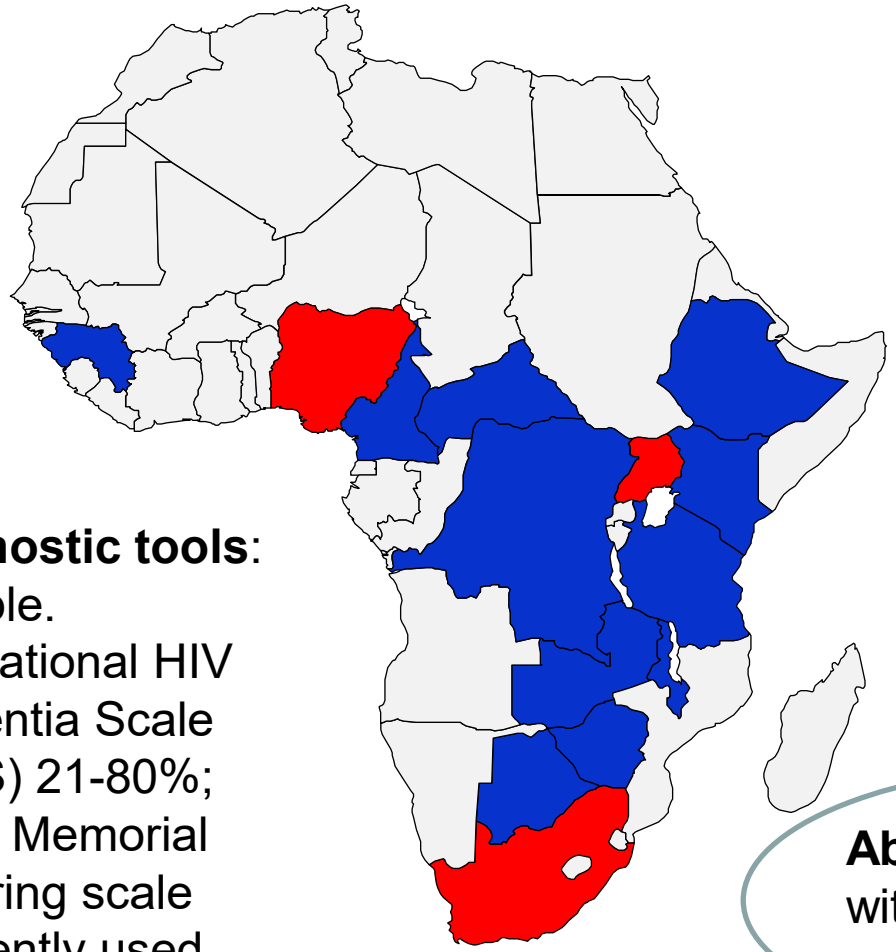
- Factors include viral, bacterial, fungal, and parasitic organisms

  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

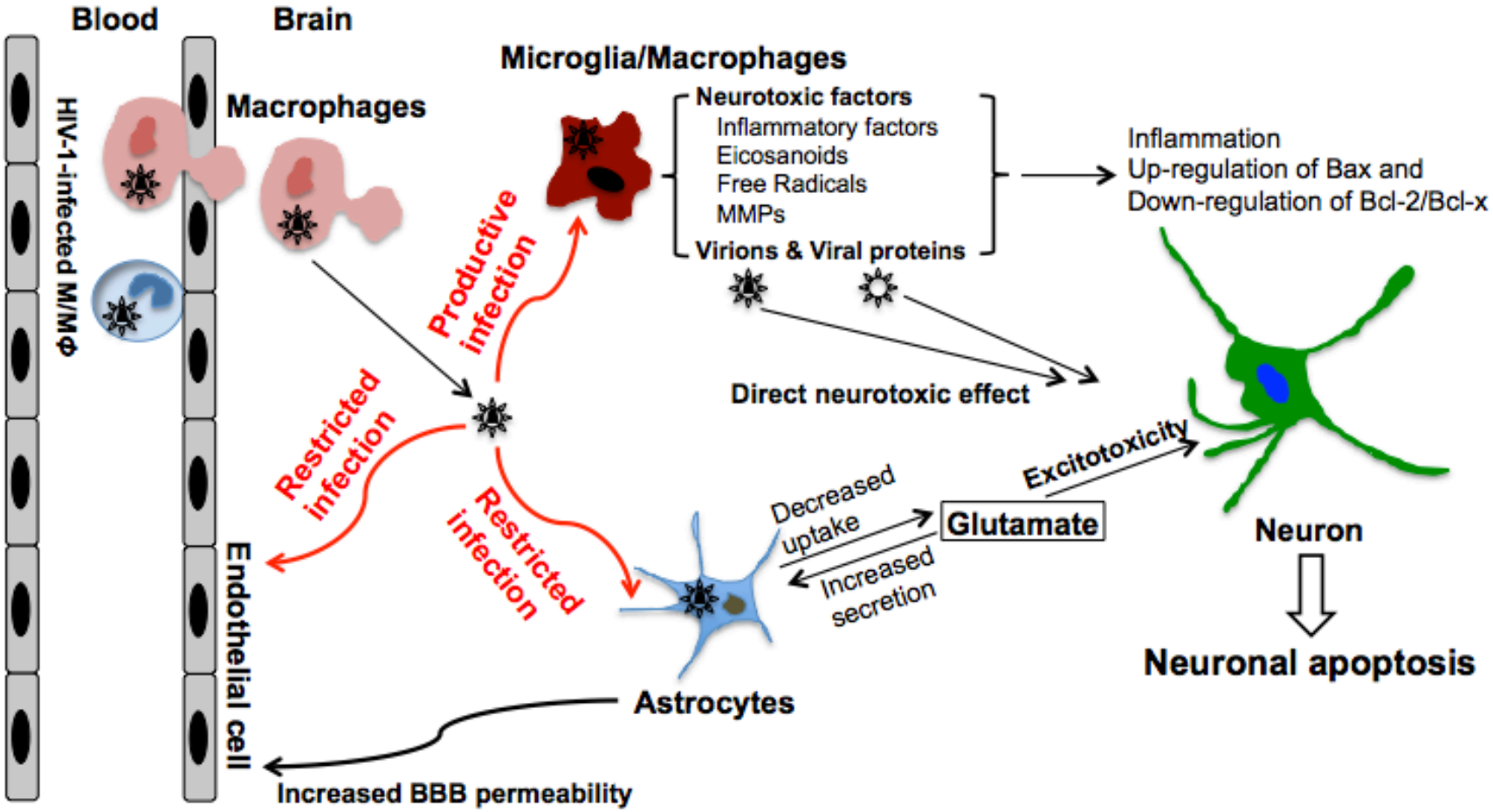
Absolute participants with HAND 0-396; prevalence 0%-80%

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

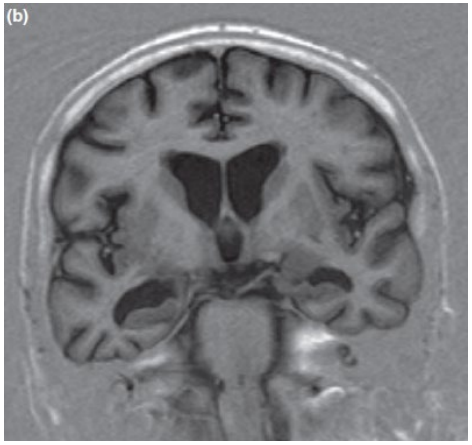
Rapidly Progressing Dementia

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]

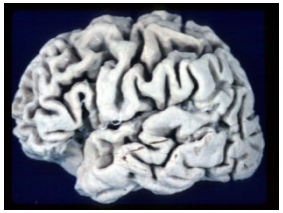


Cognitive/behavioural symptoms and neuropsychological profile were compatible with diagnosis of AD (DSM IV-TR).

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

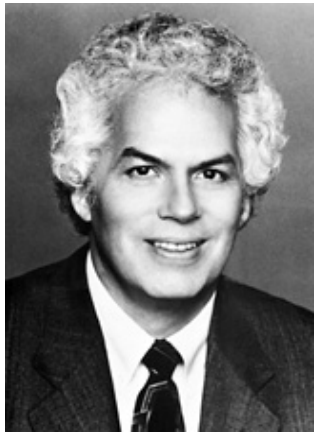
Treponema pallidum hemagglutination and VDRL in CSF +

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***



Prion Disorders

The Nobel Prize in Physiology or Medicine 1997

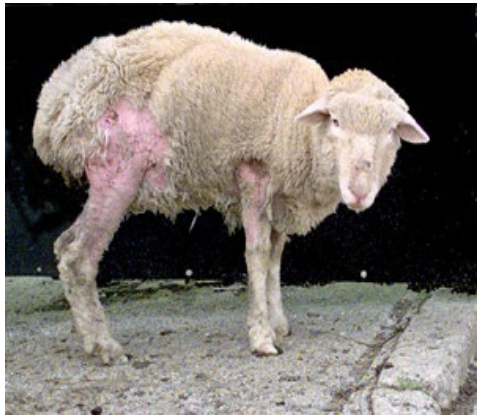


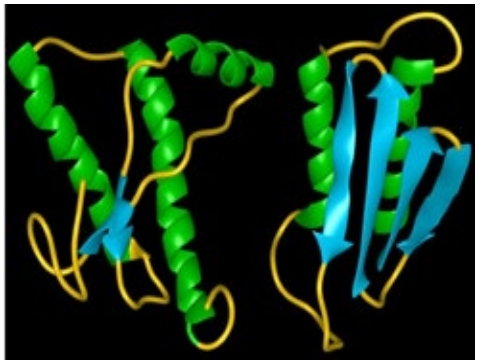
Stanley Prusiner, Born 1942

"for his discovery of Prions - a new biological principle of infection"

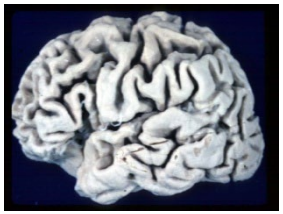
Carlton Gadjusek, Nobel Prize in 1976- Kuru Studies

- Fatal degenerative conditions; transmissible spongiform encephalopathies (TSEs)
- Sporadic (85%) and familial types; CJD, FFI, GSS, Kuru, BSE, Scrapie
- Rapid insidious onset; duration of illness 6-9 months
- Neurological features: myoclonus, seizures, motor involvement, ataxia
- Progressive dementia
- Definitive diagnosis at autopsy

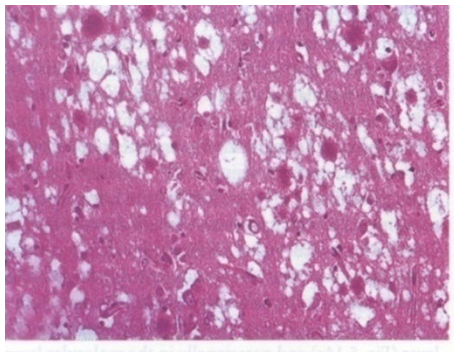


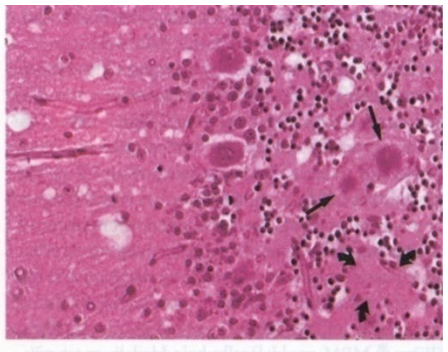


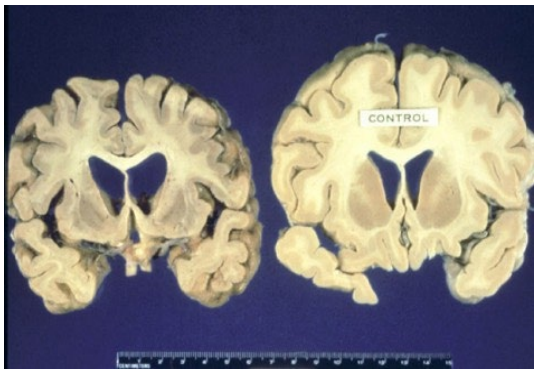
The normal (left) and disease-carrying forms of human prion protein with beta-strands in blue and alpha-helices in green

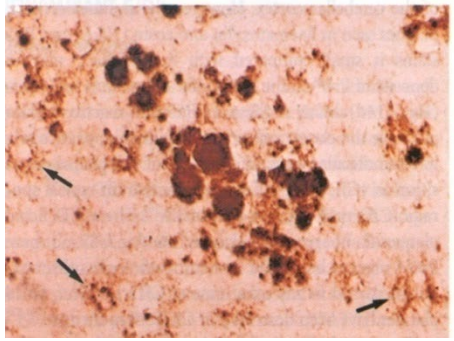


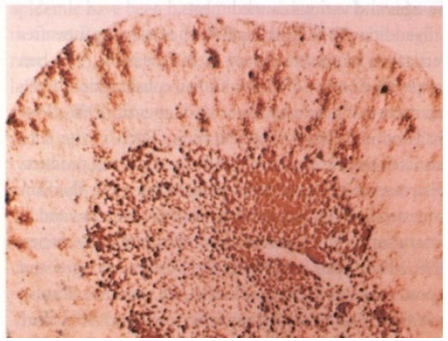
Neuropathology of Prion Disorders

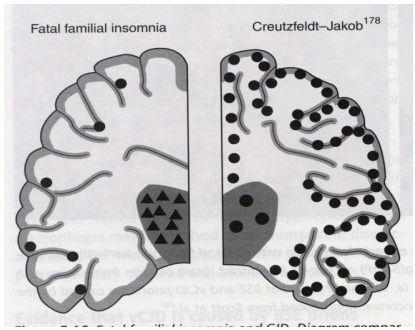












- Cruetzfeldt-Jacob Disease (CJD), Fatal Familial Insomnia (FFI), Gerstmann Sträussler Scheinker syndrome (GSS), nvCJD , Bovine Spongiform Encephalopathy (BSE) as Prion disorders;
- Severe atrophy may involve all lobes; Spongiform change; Florid prion plaques (with angiopathy). Sometimes restricted regional pathology

Neurodegenerative Dementias

(specific molecular pathologies causing dementia)

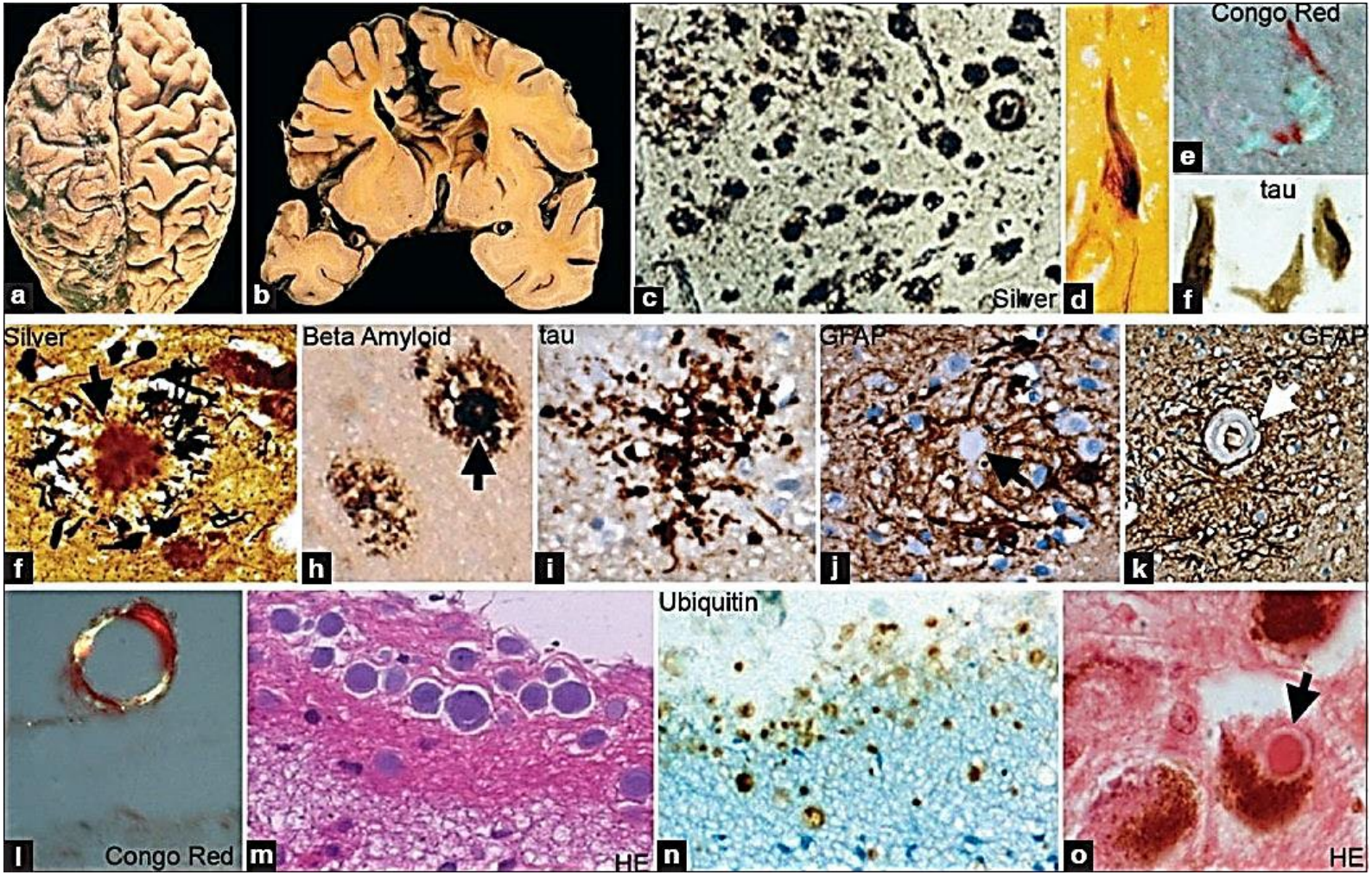
- Alzheimer's disease and age-related disorders
- Dementia with Lewy bodies (DLB); Parkinson disease with dementia (PDD) -The synucleinopathies
- Frontotemporal dementia (+tau) / Tauopathies
  - FTD and Parkinsonism Chr. 17, CBD, PSP, Pick's disease
  - Argyrophilic grain disease (AGD) and Tangle only 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

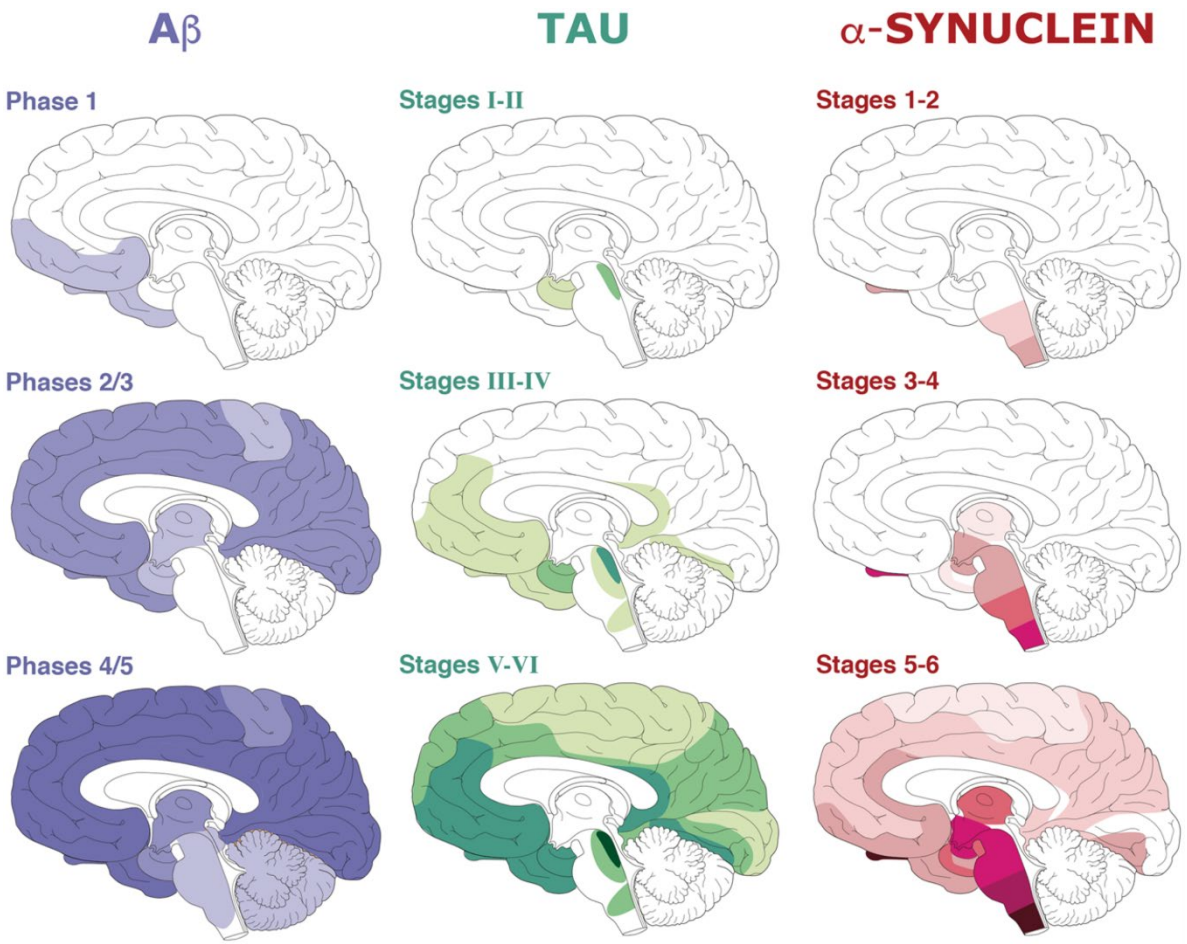
- Alzheimer disease - Aβ plaques, tau
- Parkinson's/ DLB - LBs (α-synuclein)
- FTD I: FTDP-17/ Pick's CBD, PSP - Tau+, Pick bodies (3R and 4R tau)
- FTDs II: - Tau-, ubiqutin, PGRN, TDP-43
- Prion diseases - PrP plaques, tau, CAA
- Multiple System Atrophy - Glial synuclein inclusions
- Polyglutamine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



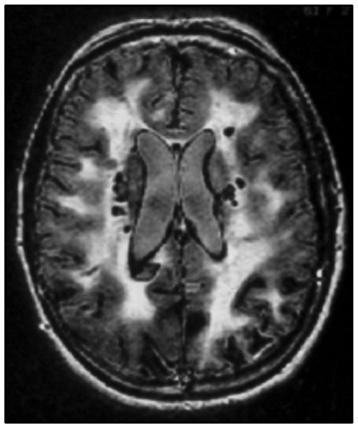
- Highest stages are diagnostic for the dementia type

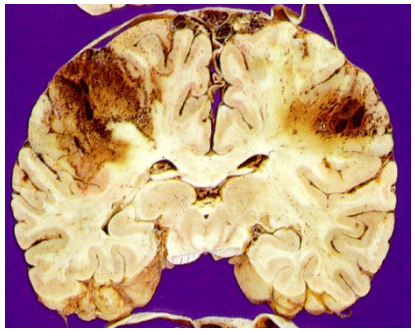
Goedert M et al, 2015

Vascular Dementia (VaD)

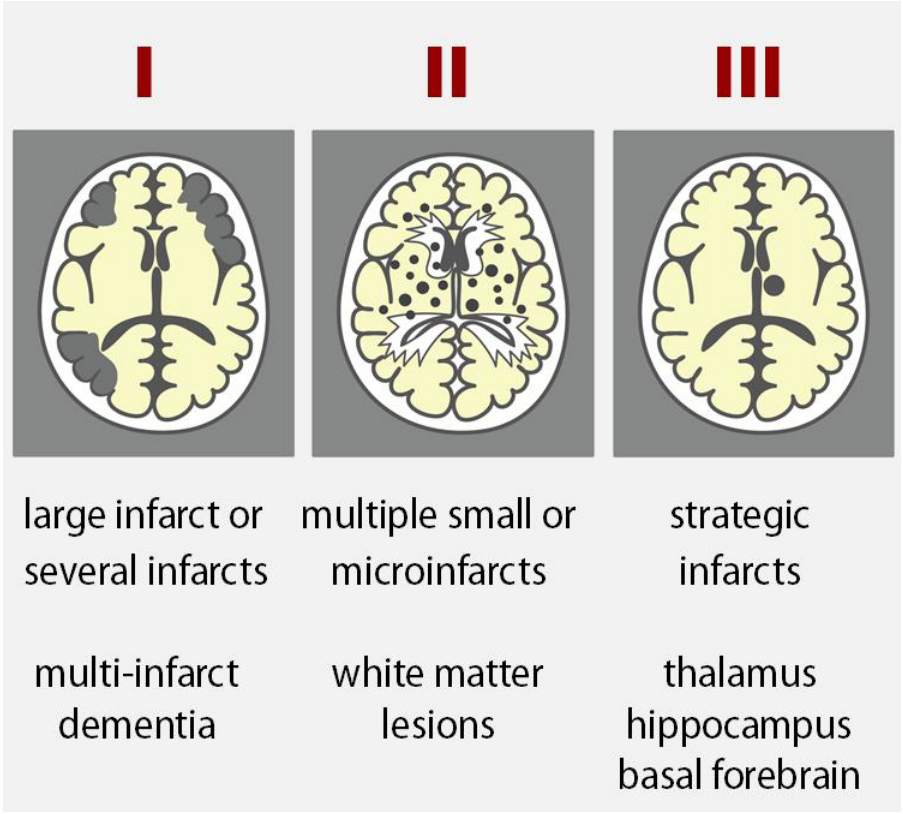
The *conventional definition of VaD is deficient* as stroke may produce a spectrum of cognitive changes but not necessarily prominent memory loss as in Alzheimer's Disease (AD)

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)

Vascular Cognitive Impairment

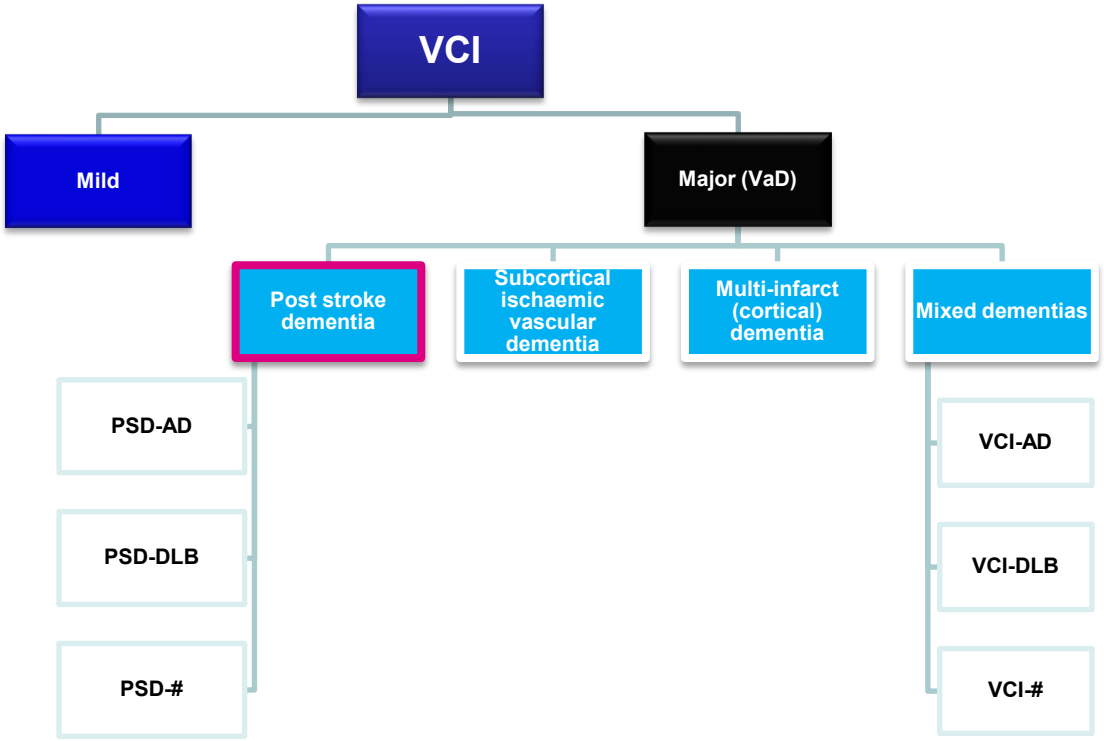
Vascular = all causes of CVD

(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)

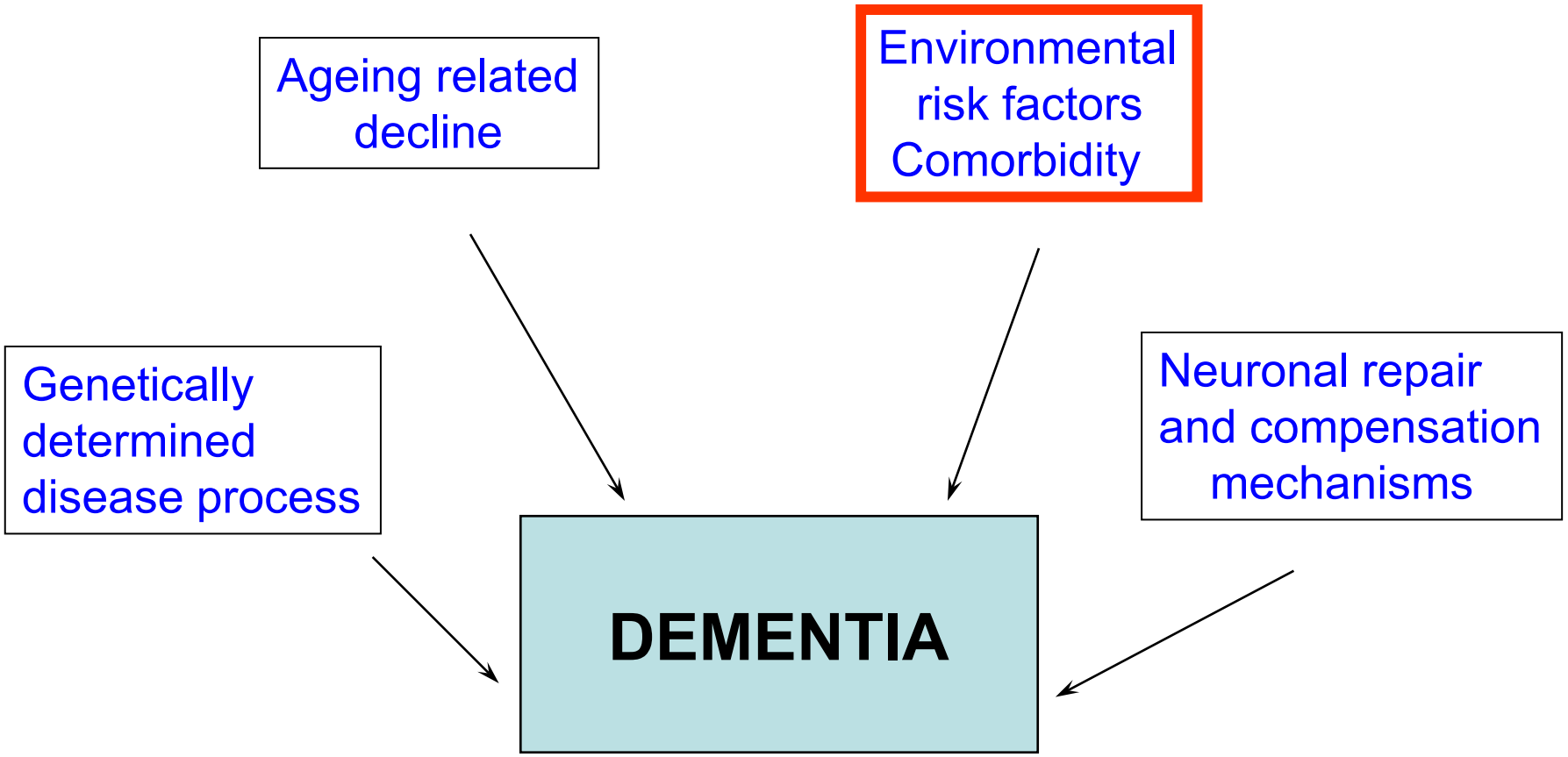
Major VCI (VaD): Clinically significant deficits of sufficient severity in *at least* ONE cognitive domain (deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event)

- **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

Processes influencing clinical expression of dementia

Additional opportunities for interventions



Learning Objectives

Overview of Neurology/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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Asante Sana!

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BRAIN AGEING AND DEMENTIA IN LMICs 2022

THEMES: EPIDEMIOLOGY, GENETICS, RISK FACTORS, PATHOPHYSIOLOGY, PREVENTION, CARE

This in-person conference will provide a forum to discuss risk factors and increasing burden of vascular and neurodegenerative diseases including HIV Dementias in the context of incidence and prevention in cross-cultural populations in Low and Middle Income Countries compared to Europe, North America and Japan

Grants and Policy Workshop 5th December

Symposium 6-9 December, 2022

(Safari Park Hotel, Nairobi, Kenya)

Registration:

Email: advascular@ncl.ac.uk

Website: https://conferences.ncl.ac.uk/advascular/

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