Dementias in SSA: clinical diagnosis, pathology & therapeutics

9th RTC in Sub-Saharan Africa
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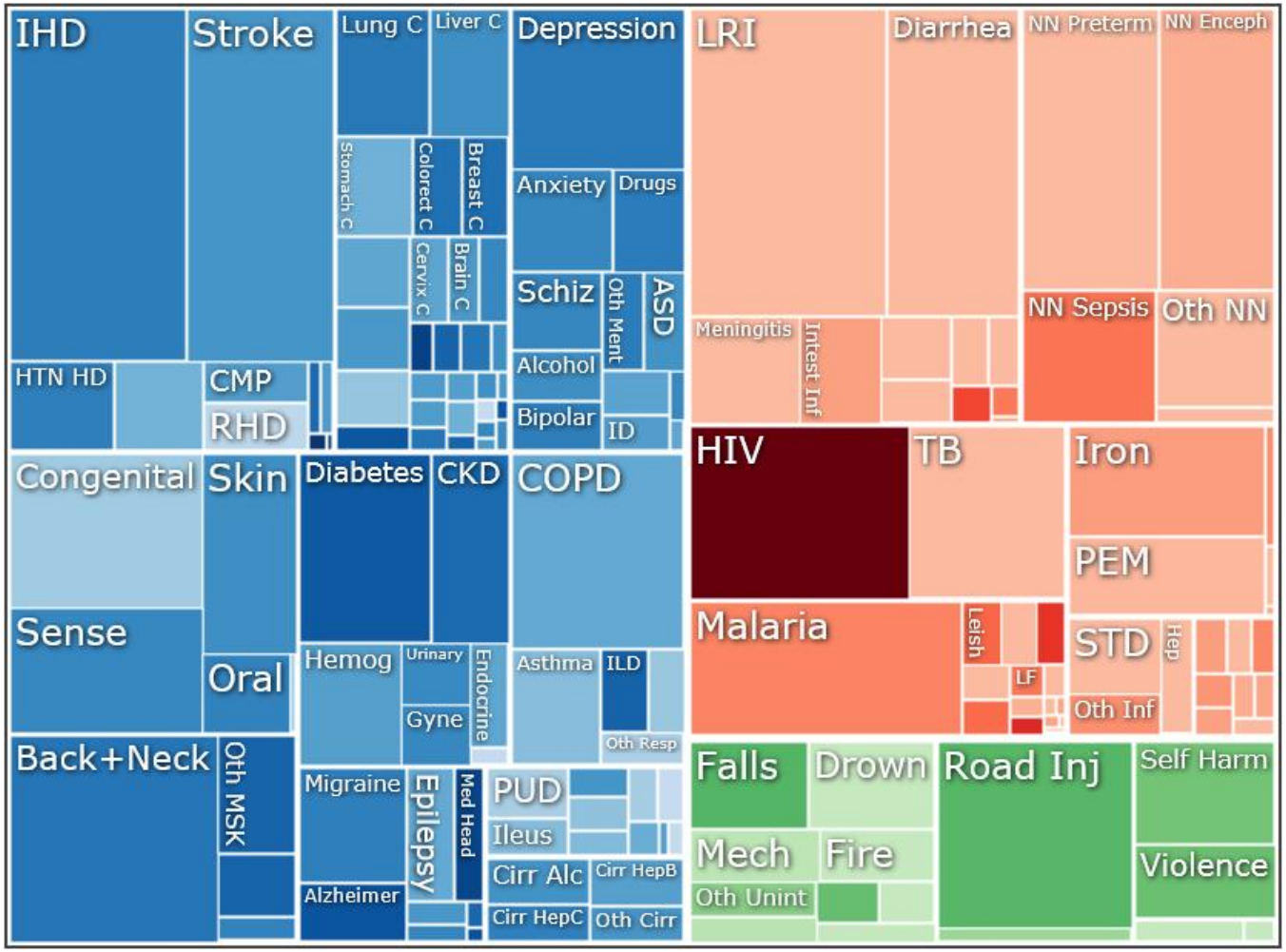
Newcastle Centre for Brain Ageing and Vitality

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

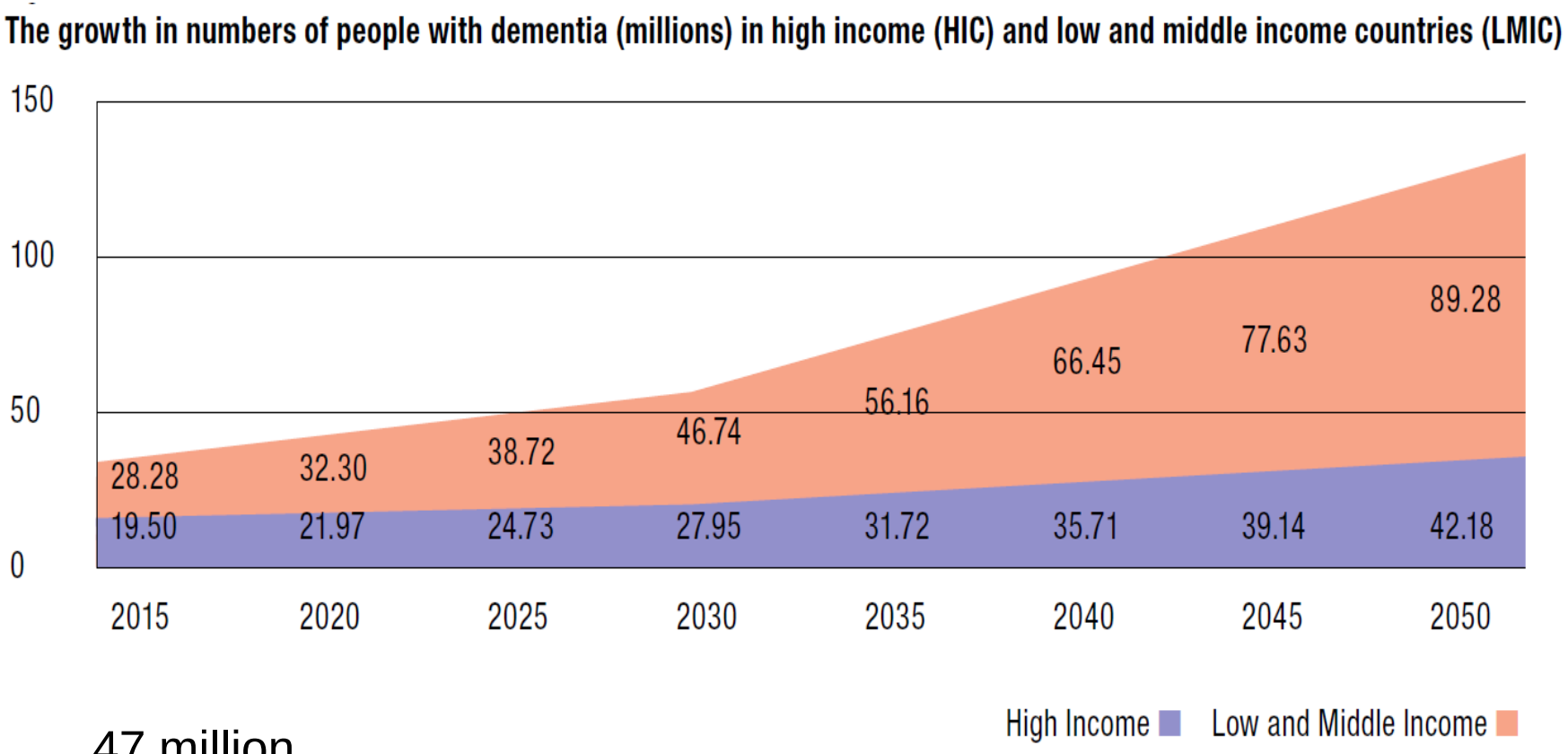
GBD 1990-2013: DALYs for all Causes



Tree Map of Low and Middle Income Countries: All ages 70+ years and Both sexes

Murray et al, 2012; Whiteford et al, 2013

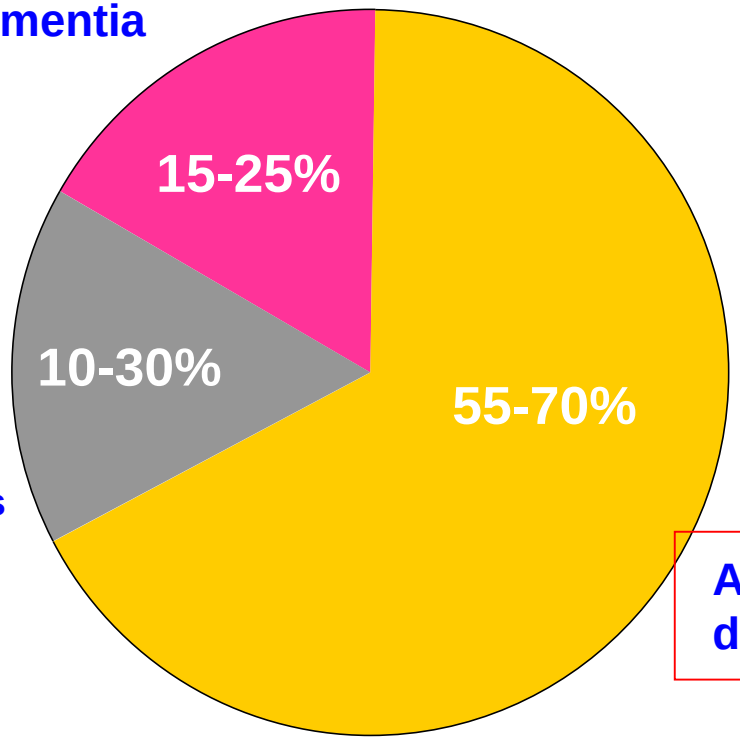
Numbers of People with Dementia

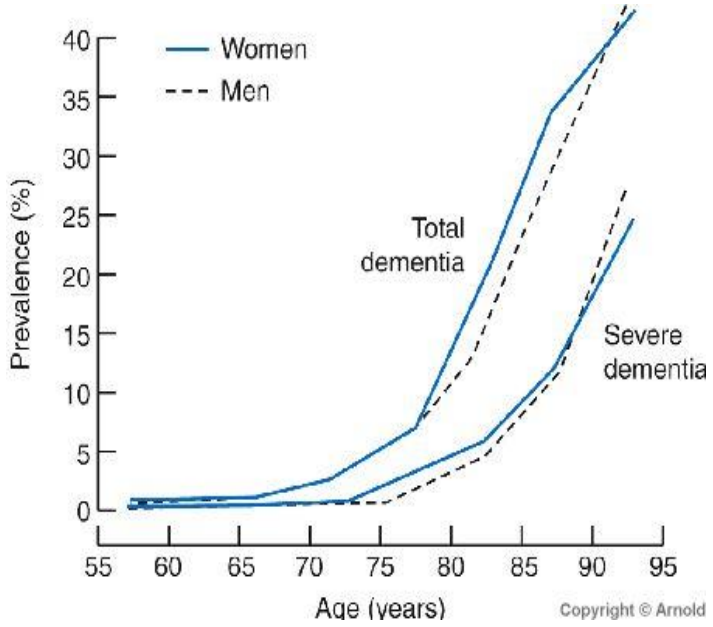


47 million

Wimo A et al 2015

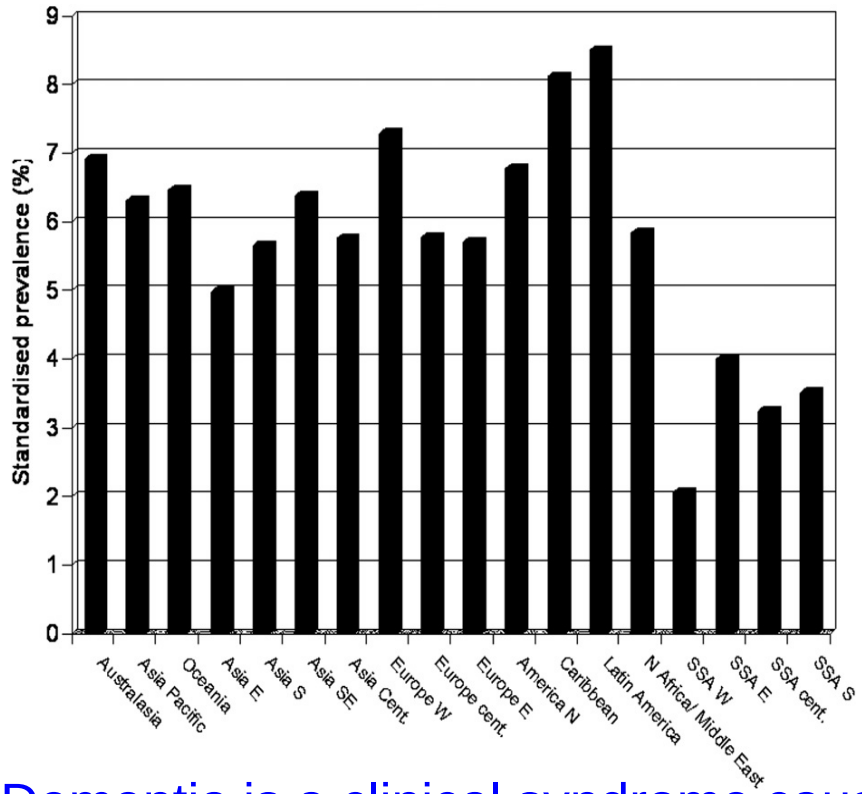
What Are the Most Common causes of Degenerative Dementias?

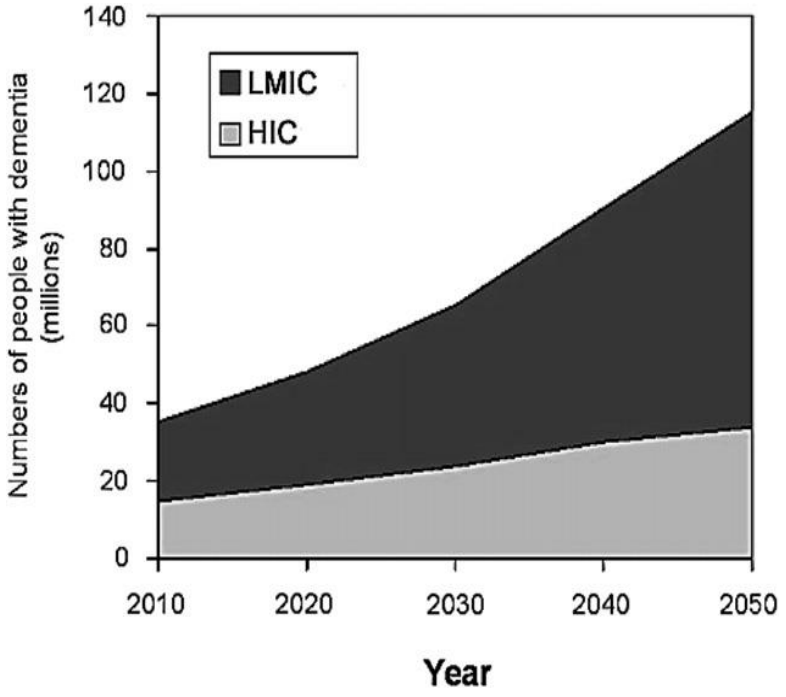




Frataglioni L, et al. Neurology. 2000;54:S10-15
Rarer dementias not shown but do not amount to >15 of total.

Prevalence of Dementia Worldwide

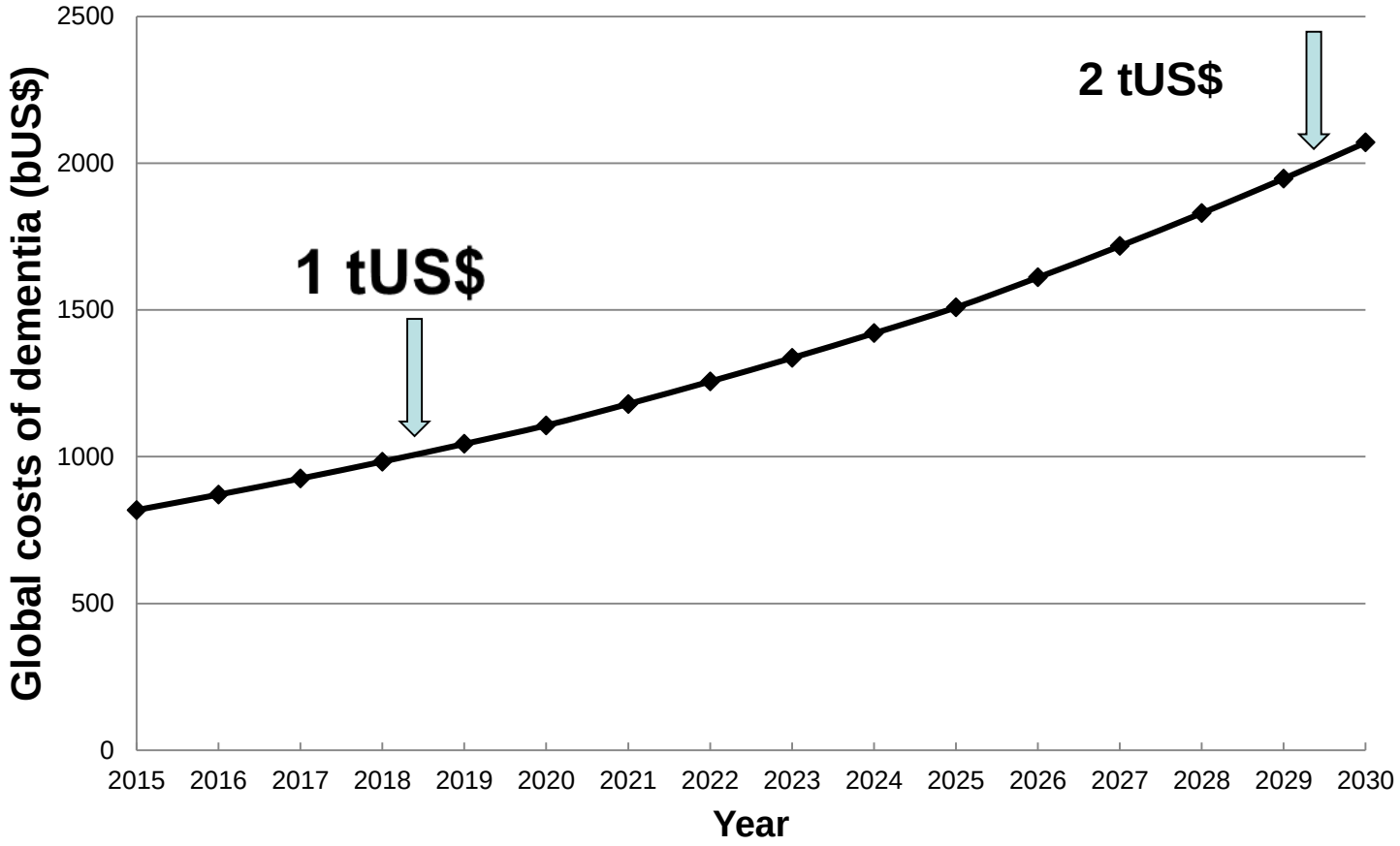




Dementia is a clinical syndrome caused by neurodegeneration . Alzheimer's disease (AD) is the most common type followed by vascular dementia (VaD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD).

Prince M et al, 2010

Worldwide costs of dementia forecast?



Dementia in Infectious Disease

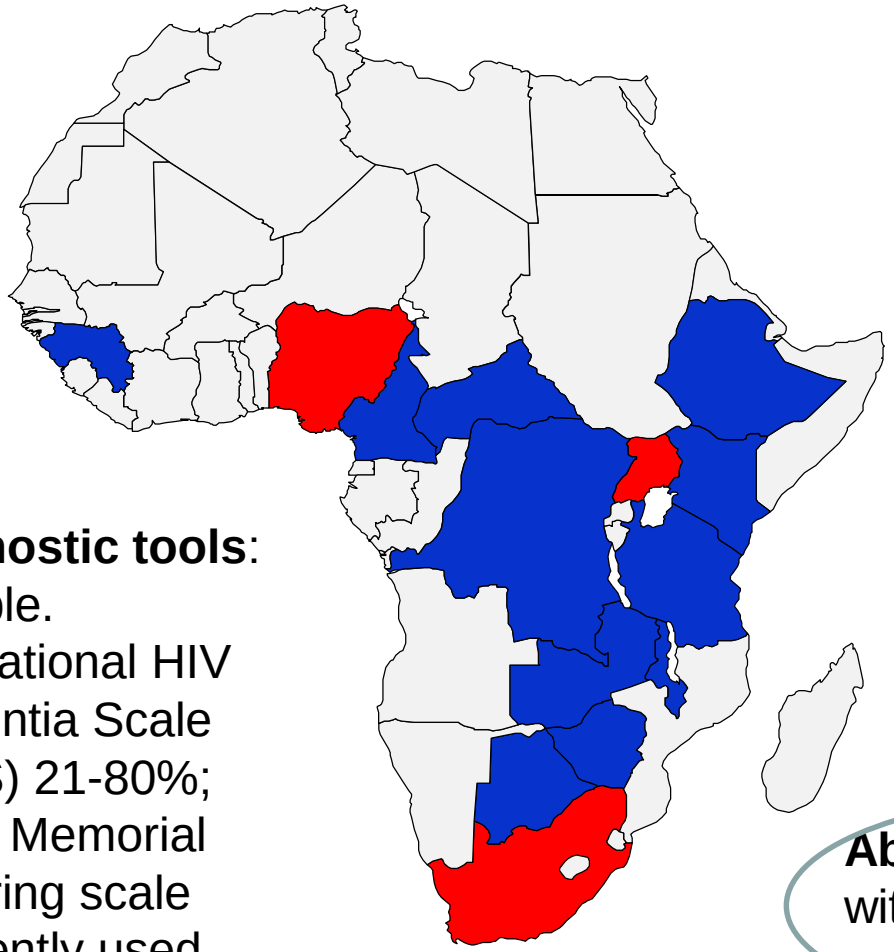
- Factors include viral, bacterial, fungal, and parasitic organisms

  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 (2014): 51 hospital-based studies case-control (10), cohort (6), 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

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

Sub-Types of HIV and Cognitive Impairment

HIV Subtype D Is Associated with Dementia, Compared with Subtype A, in Immunosuppressed Individuals at Risk of Cognitive Impairment in Kampala, Uganda

Ned Sacktor,[1] Noeline Nakasujja,[7] Richard L. Skolasky,[2] Mona Rezapour,[4] Kevin Robertson,[5] Seggane Musisi,[7] Elly Katabira,[8] Allan Ronald,[9] David B. Clifford,[6] Oliver Laeyendecker,[3,4] and Thomas C. Quinn[3,4]

Departments of [1]Neurology, [2]Orthopedic Surgery, and [3]Medicine, Johns Hopkins University School of Medicine, Baltimore, and [4]Laboratory of Immunoregulation, Division of Intramural Research, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland; [5]Department of Neurology, University of North Carolina, Chapel Hill; [6]Department of Neurology, Washington University, St. Louis, Missouri; Departments of [7]Psychiatry and [8]Medicine, Makerere University, Kampala, Uganda; and [9]Department of Medicine, University of Manitoba, Winnipeg, Canada

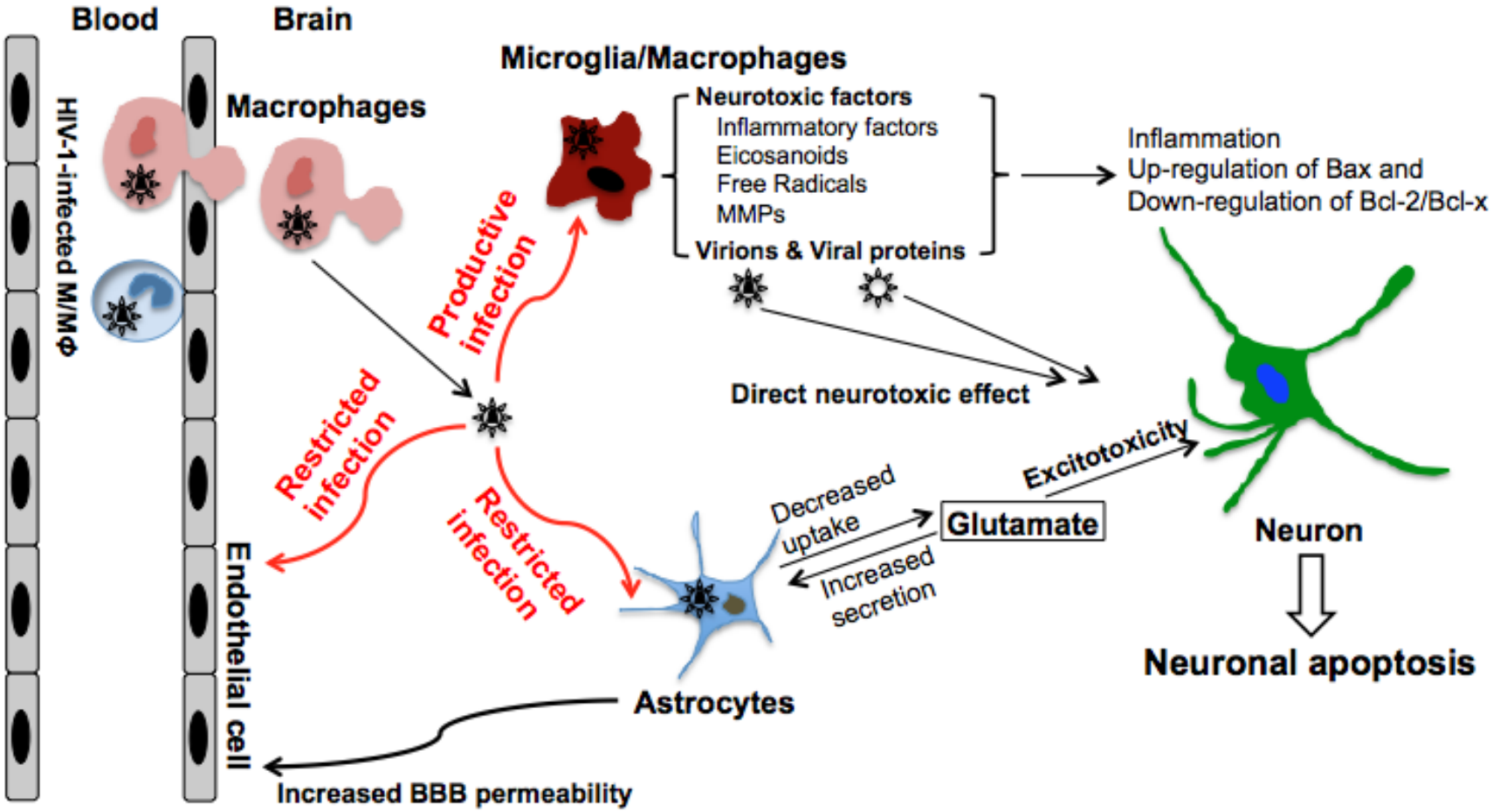
Background. In the United States, clade B is the predominant human immunodeficiency virus (HIV) subtype, whereas in sub-Saharan Africa, clades A, C, and D are the predominant subtypes. HIV subtype may have an impact on HIV disease progression. The effect of HIV subtype on the risk of dementia has, to our knowledge, not been examined. The objective of this study was to examine the relationship between HIV subtype and the severity of HIV-associated cognitive impairment among individuals initiating antiretroviral therapy in Uganda.

Methods. Sixty antiretroviral-naive HIV-infected individuals with advanced immunosuppression who were at risk of HIV-associated cognitive impairment underwent neurological, neuropsychological, and functional assessments, and *gag* and *gp41* regions were subtyped. Subtype assignments were generated by sequence analysis using a portion of the *gag* and *gp41* regions.

Results. Thirty-three HIV-infected individuals were infected with subtype A, 2 with subtype C, 9 with subtype D, and 16 with A/D recombinants. Eight (89%) of 9 HIV-infected individuals with subtype D had dementia, compared with 7 (24%) of 33 HIV-infected individuals with subtype A ($P = .004$).

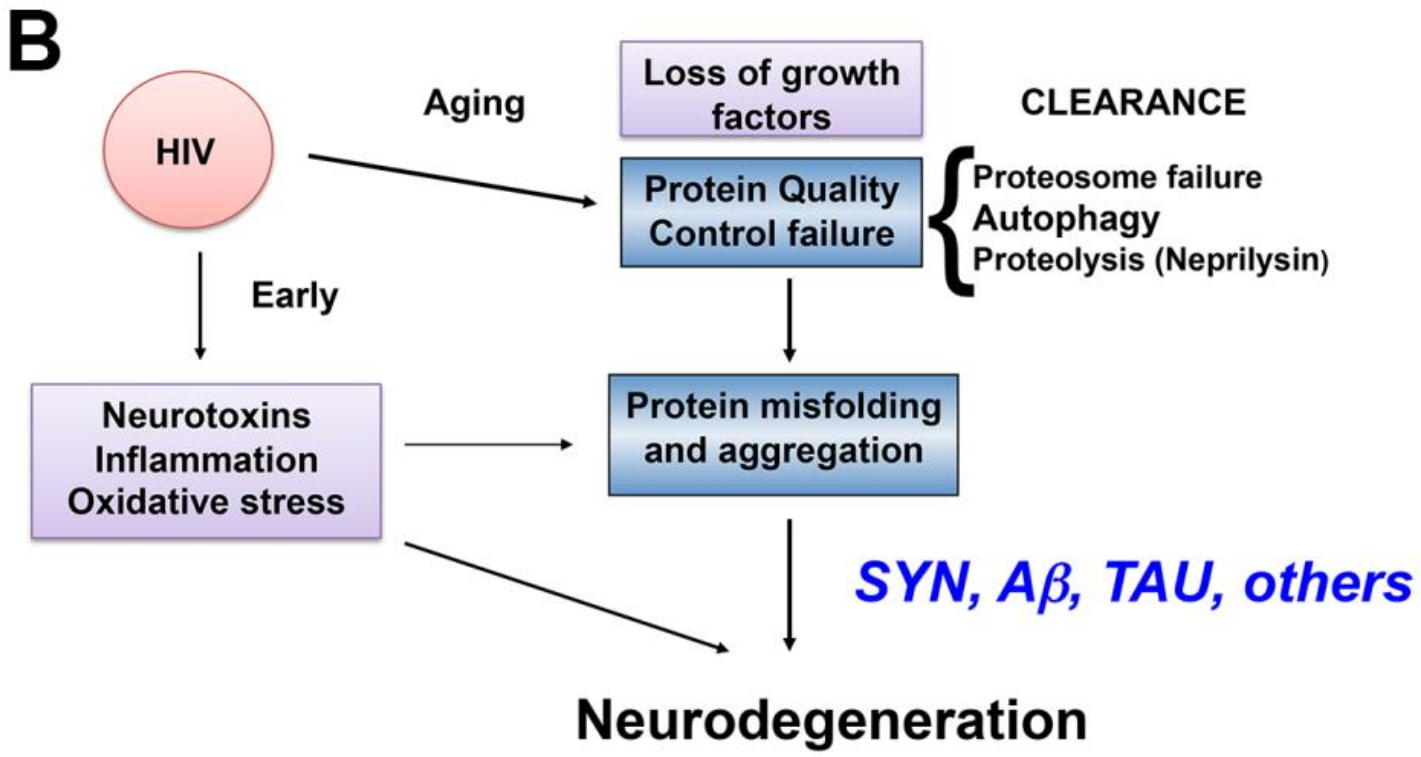
Conclusions. These results suggest that, in untreated HIV-infected individuals with advanced immunosuppression who are at risk of developing HIV-associated cognitive impairment, HIV dementia may be more common among patients infected with subtype D virus than among those infected with subtype A virus. These findings provide the first evidence, to our knowledge, to demonstrate that HIV subtypes may have a pathogenetic factor with respect to their capacity to cause cognitive impairment. Additional studies are needed to confirm this observation and to define the mechanism by which subtype D leads to an increased risk of neuropathogenesis.

Pathogenesis and Cellular Mechanisms



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

Mechanisms in HAND with Age



Mechanisms leading to HAND are exacerbated in >50 yr olds with years of chronic neuroinflammation. Neurotoxins, inflammation and OS combined with normal aging processes increase HAND burden in ageing HIV patients

Fields J et al, 2014

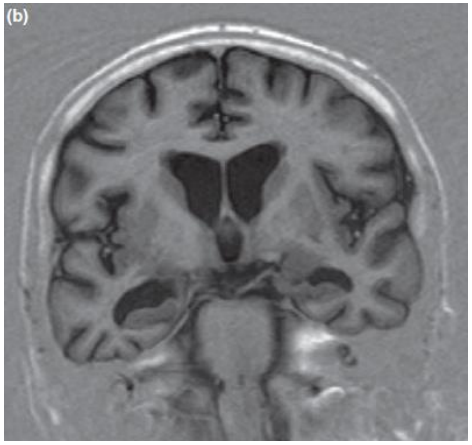
Rapidly Progressing Dementia

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]

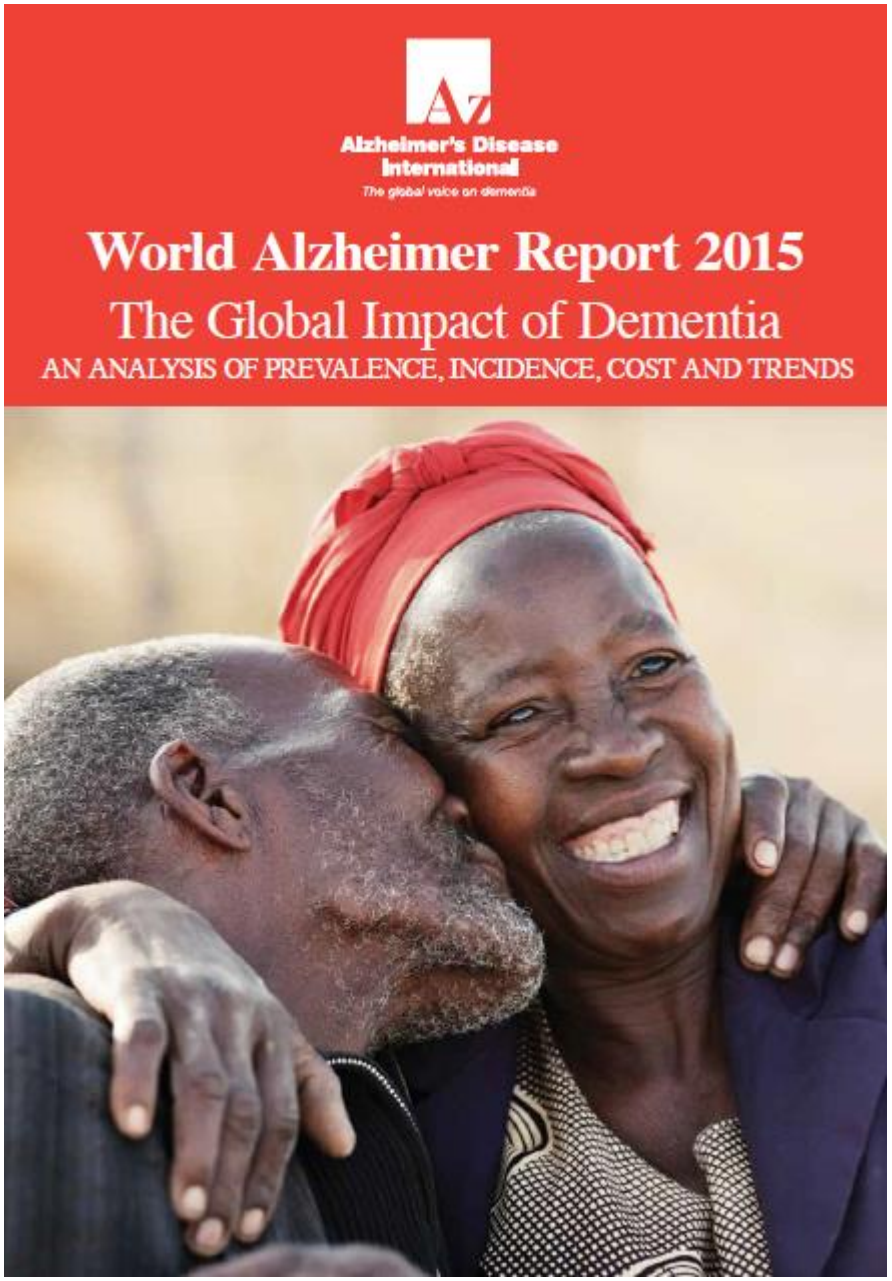


Cognitive/behavioral symptoms and neuropsychological profile were compatible with diagnosis of AD (DSM IV-TR).

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



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
- Failure rates to detect dementia: Clinicians fail to detect in 21%-72% of patients
- 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

Diagnosis of Alzheimer's Disease:

NINCDS-ADRDA Criteria

Dementia

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

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Probable/Possible diagnosis

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

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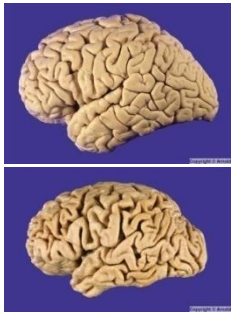


Definitive diagnosis by autopsy →

Diagnosis of AD

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

Diagnosis of Dementia

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

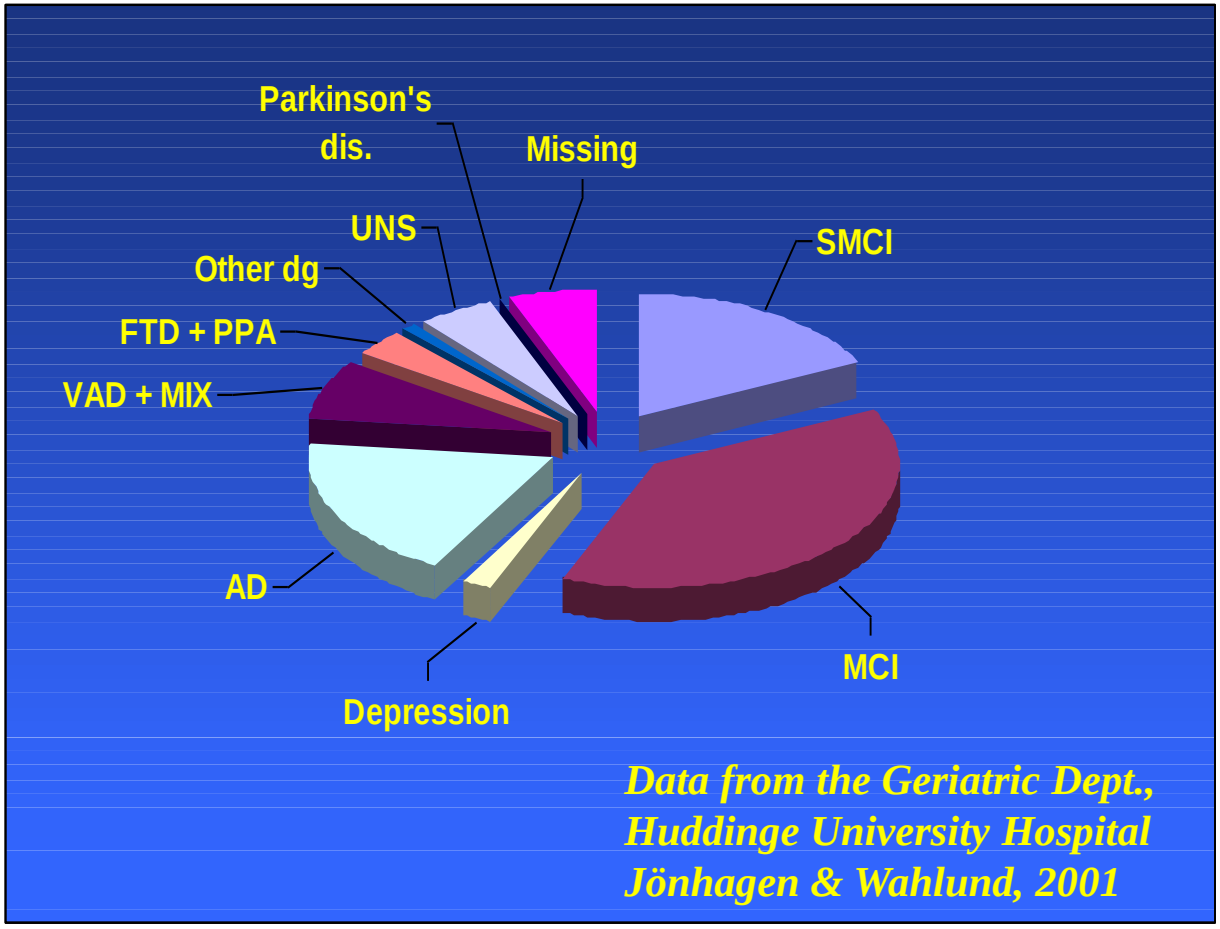
Development of multiple cognitive deficits manifested by both:

- **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

AD Versus VaD: "Classical" Clinical Features

	AD	VaD
Presence of vascular conditions and risk factors	✓	✓✓
Onset and progression	Insidious and gradual	Abrupt and stepwise
Neuroimaging positive for CVD	X	✓
Psychiatric comorbidity	May be present	Frequent
Executive dysfunction	None or mild	✓
Focal neurological signs and symptoms	X	✓
Memory impairment	✓✓	May not be prominent
Gait disturbances	X	✓
Emotional lability	X	✓
Increased urinary frequency	X	✓
Diagnostic criteria	DSM-IV, NINCDS-ADRDA	DSM-IV, NINDS-AIREN

Cross-section Through a Memory Clinic



SMCI--subjective memory impairment

MCI-mild cognitive impairment

AD-Alzheimer's disease

VaD-vascular dementia

MIX-"mixed" dementia

FTD-frontal lobe dementia

PPA-primary progressive aphasia

UNS-dementia of unspecified origin

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)

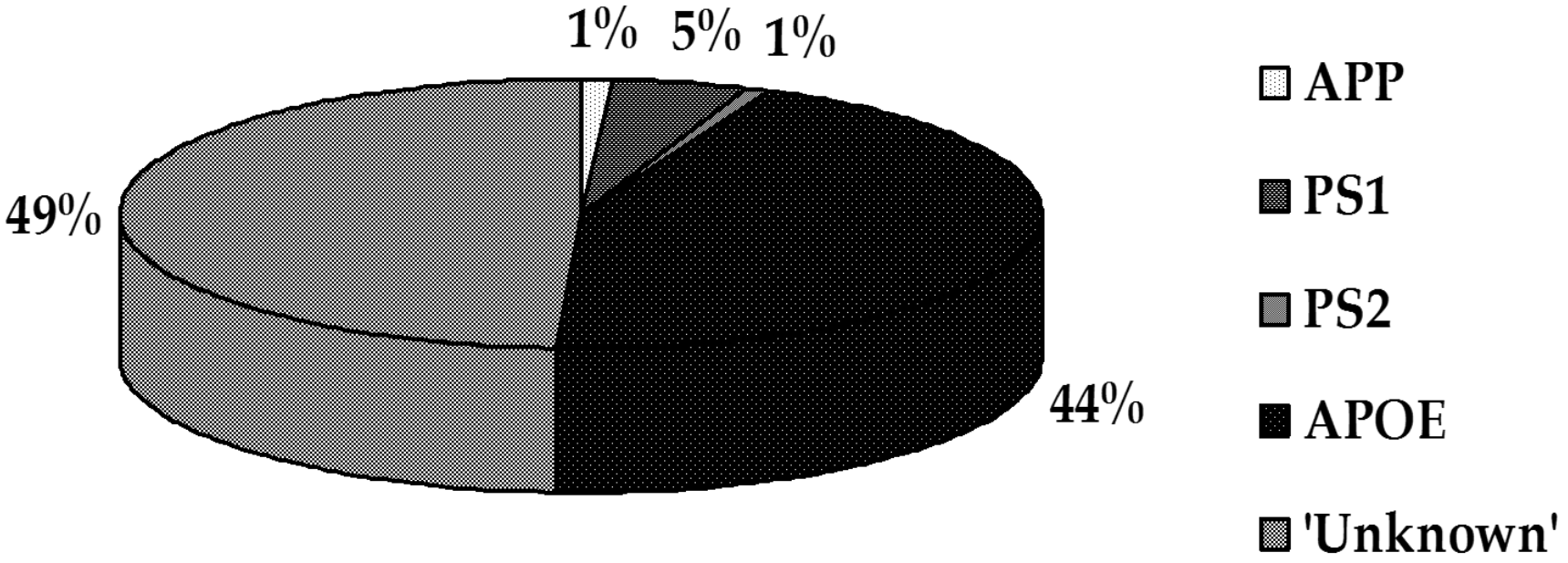
LOAD (>65 years)

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)

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

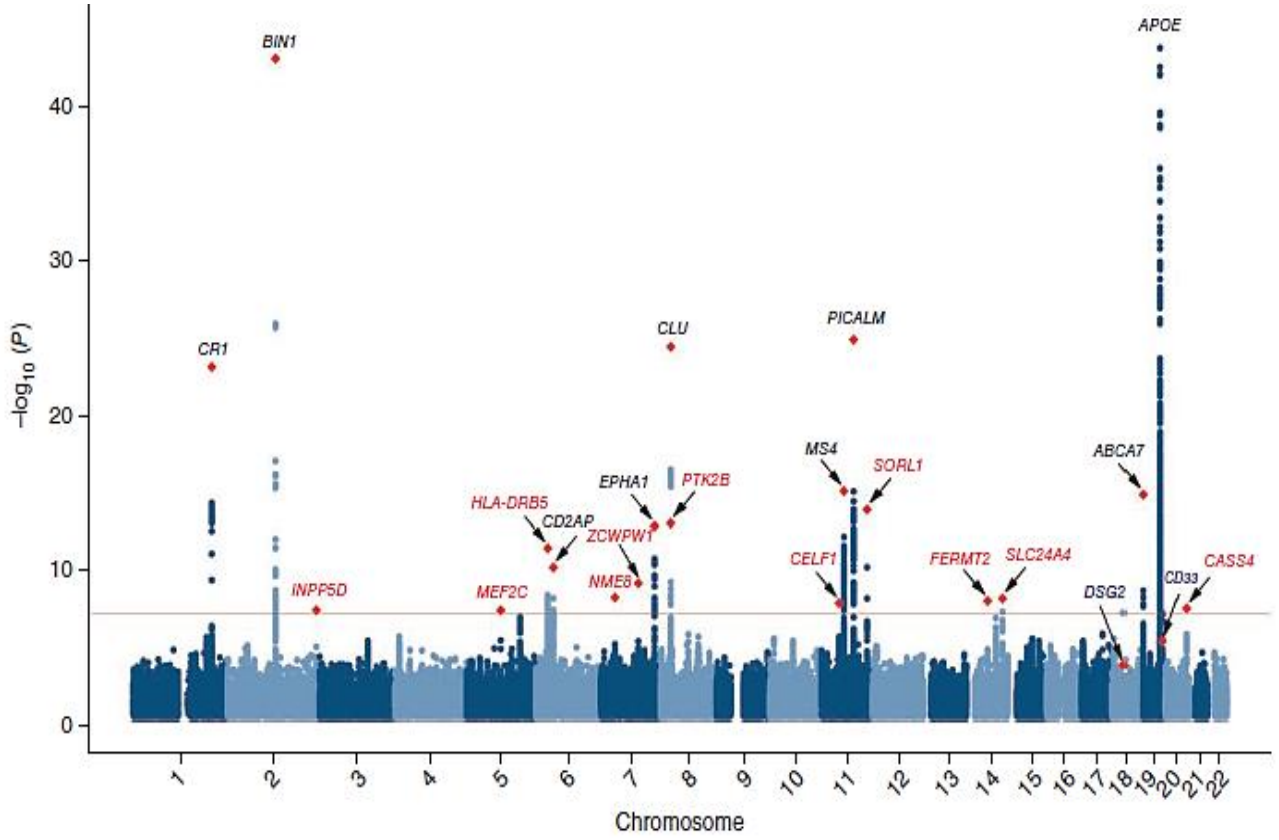
Sporadic AD 90-95%;

Familial AD ~5-10%



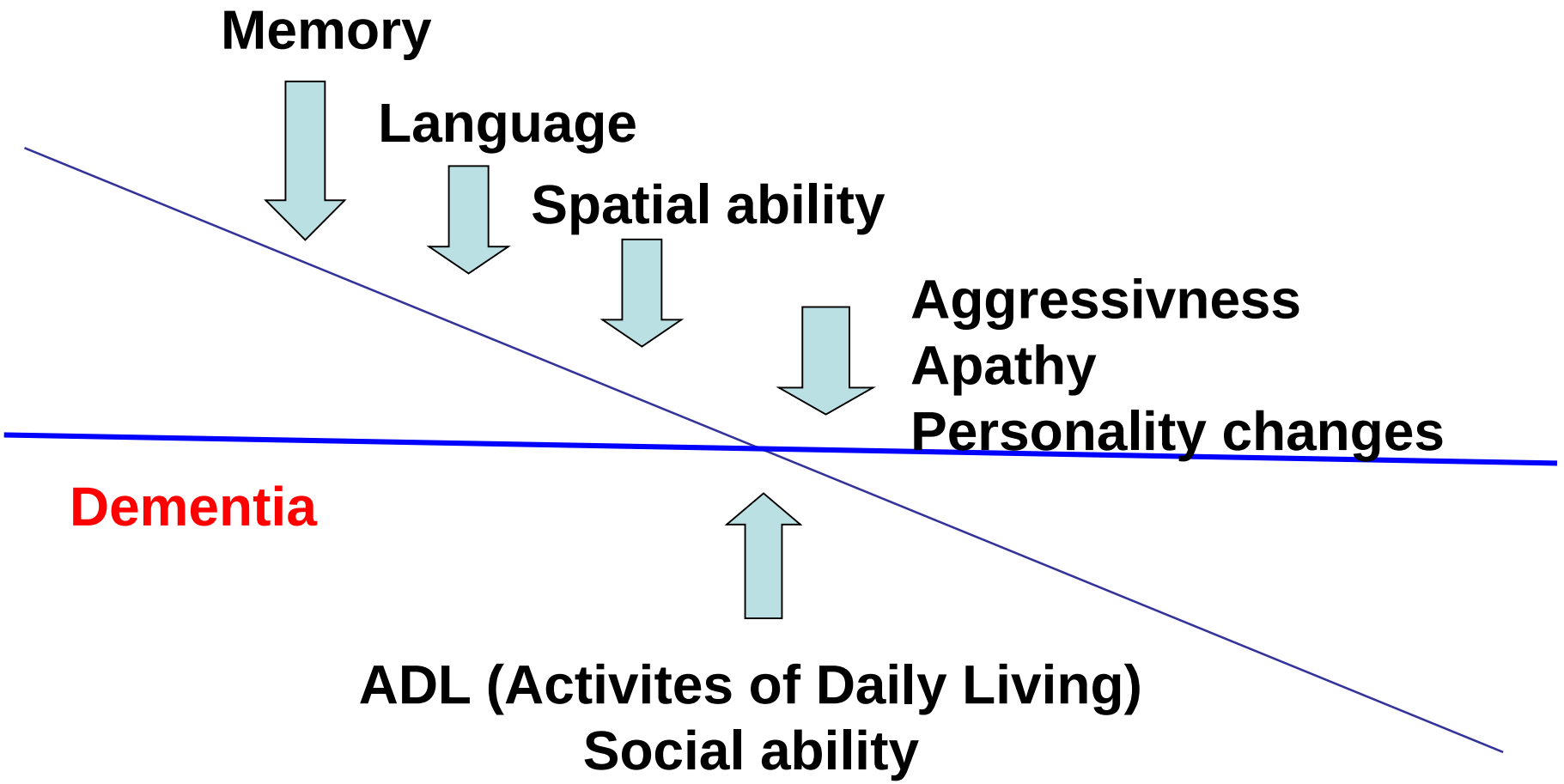
***Current estimates from ~500 families world-wide**

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.

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

Objectives for Neuropsychometry screening

- Cognitive function tests have been used and developed over several years

- Neuropsychometric batteries may contain several components to test different cognitive abilities, e.g. CANTAB, CAMCOG, ADAS-Cog etc.

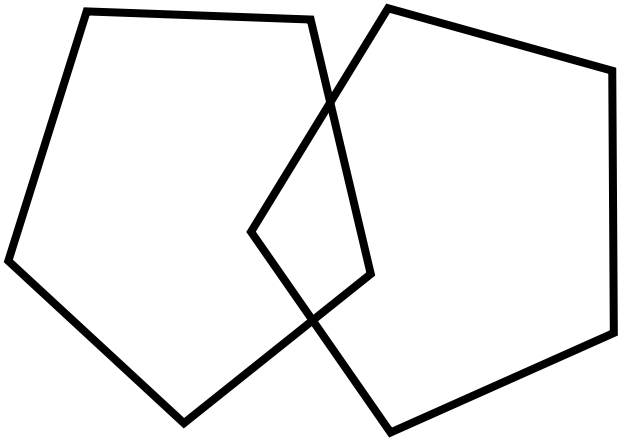
- The Mini-Mental State Examination (MMSE)-widely used; Others Montreal Cognitive Assessment (MoCA)

- Value of informant questionnaires

Mini-Mental State Examination

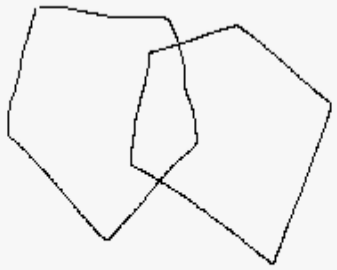
- MMSE is a short test which measures general cognitive status including short-term memory (Folstein, et al, 1975)

- 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

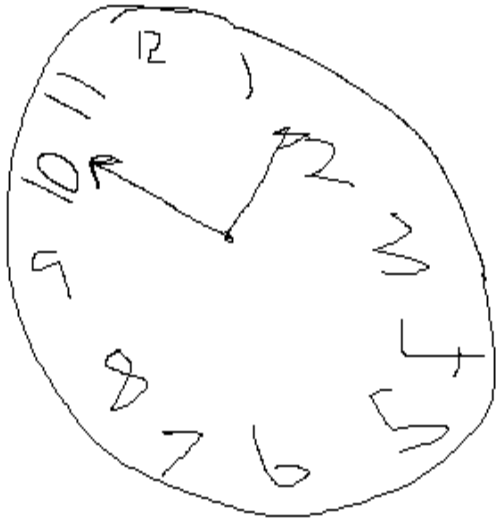
Dementia with Lewy Bodies (DLB)

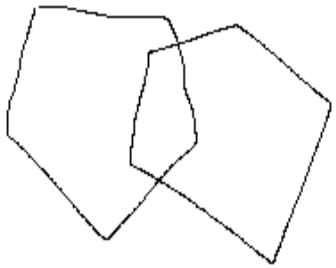
MMSE 20/30

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

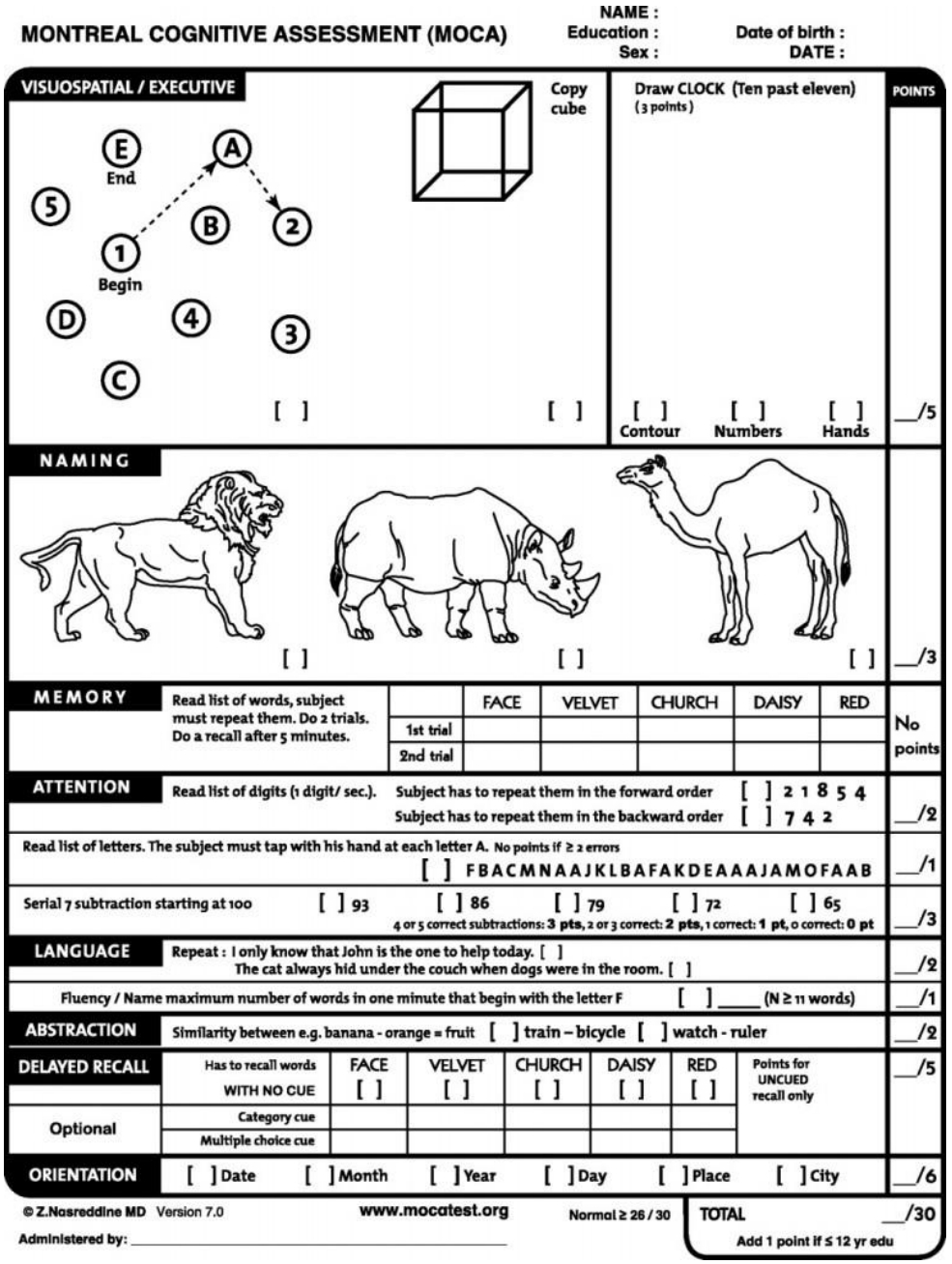
Short term memory 2/3

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

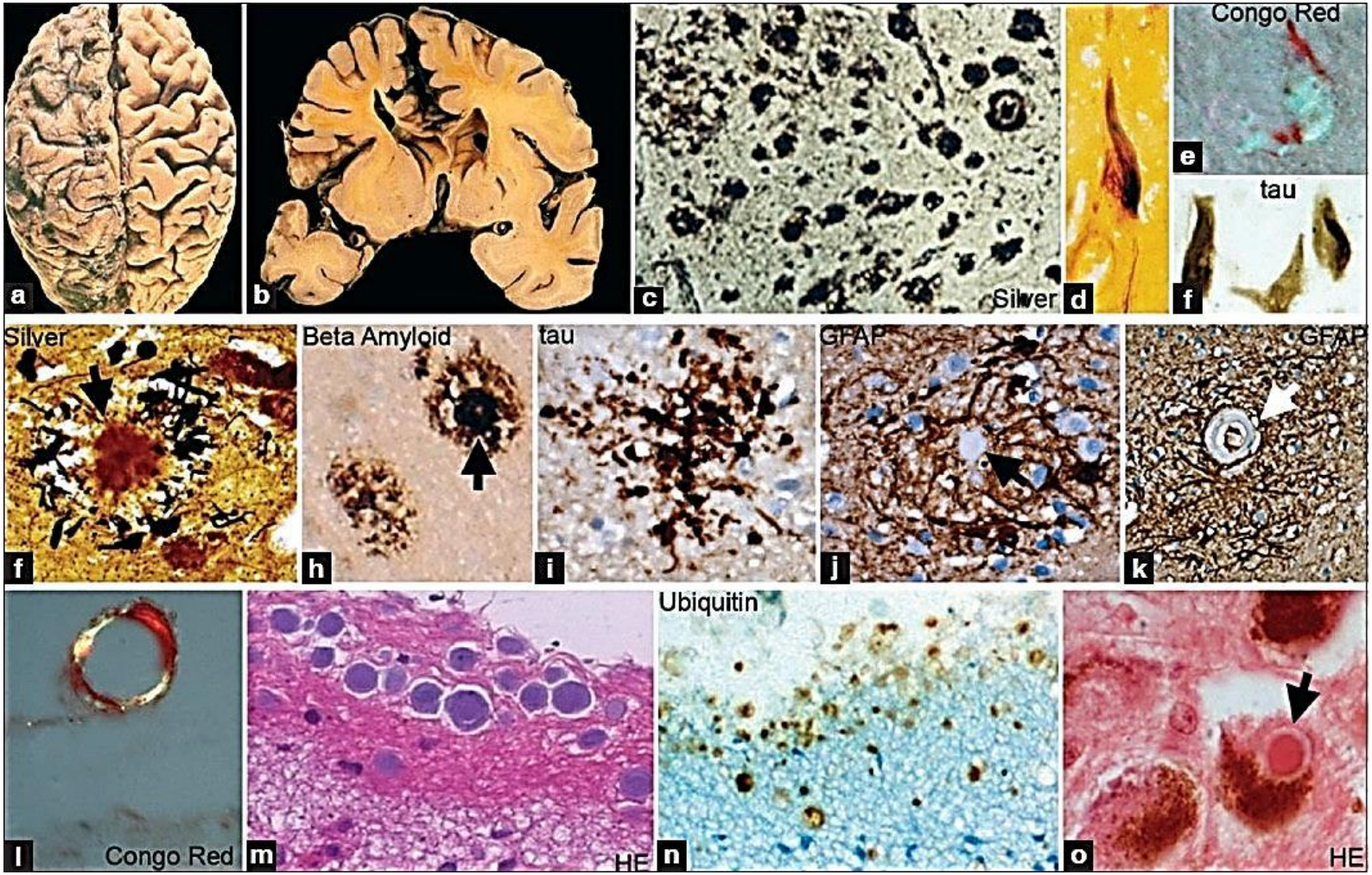


Tests of Cognition in Dementia (1)

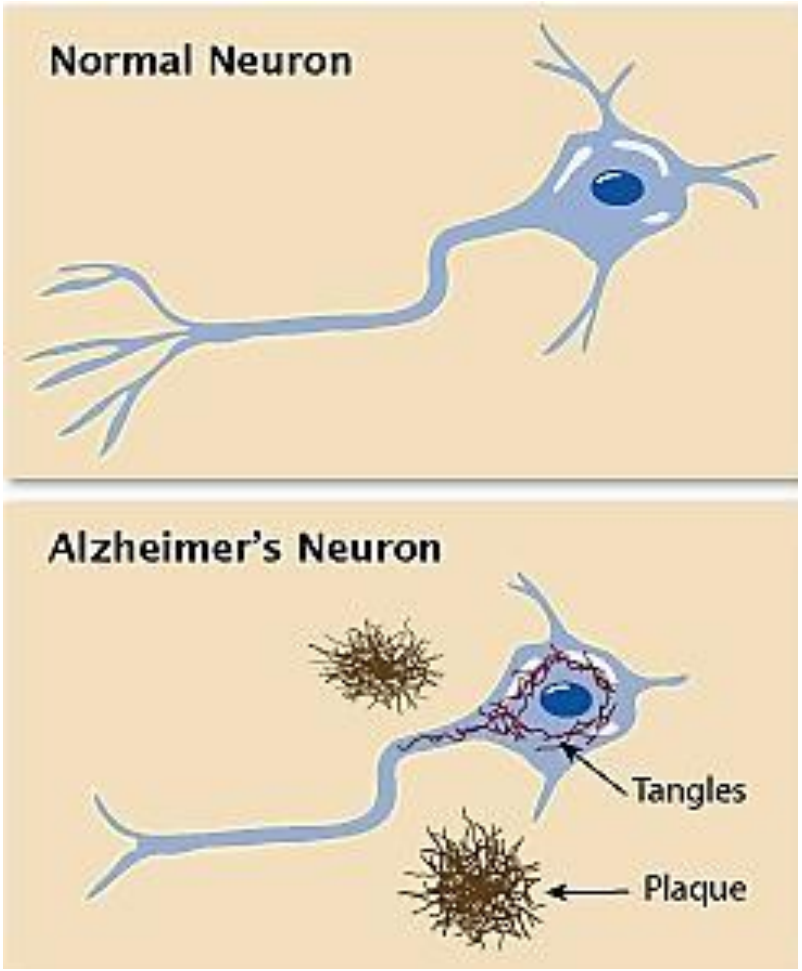
ADAS-Cog is used to test several features of cognition in subjects suspected with dementia

1. **First 10 min conversation- travel, weather, exercise, other**
2. **Word recall task –words shown on card**
3. **Naming fingers and objects – asked to name**
4. **Command –make a fist, point ceiling etc**
5. **Delayed word-recall task –recall previous words**
6. **Constructional praxis –ability to copy geometric forms**
7. **Ideational praxis –do something (fold letter)**
8. **Orientation – person, day, month, year**
9. **Word-Recognition task**

Accumulation of Different Types of Brain Pathology during Ageing

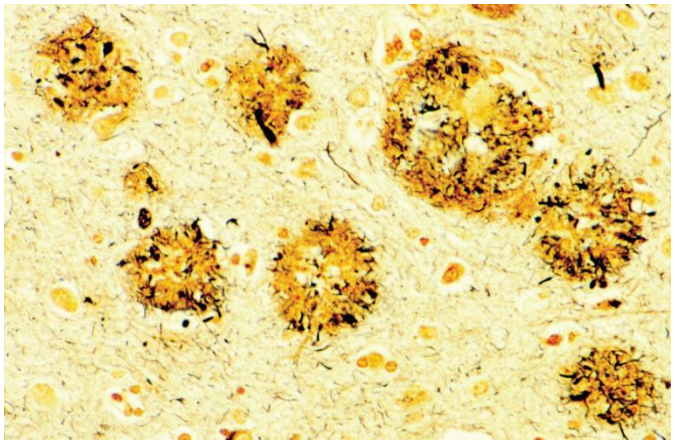


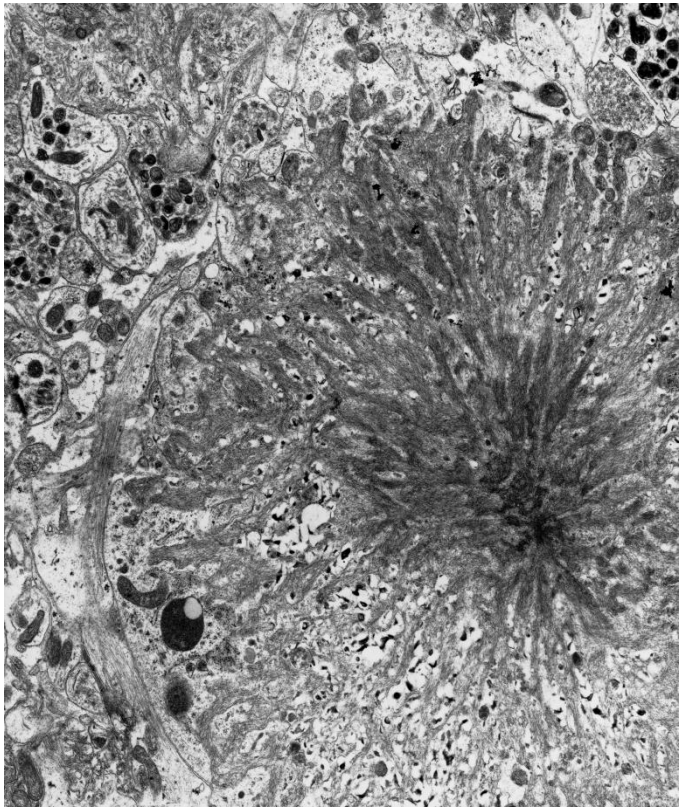
Key Pathological Hallmarks of AD



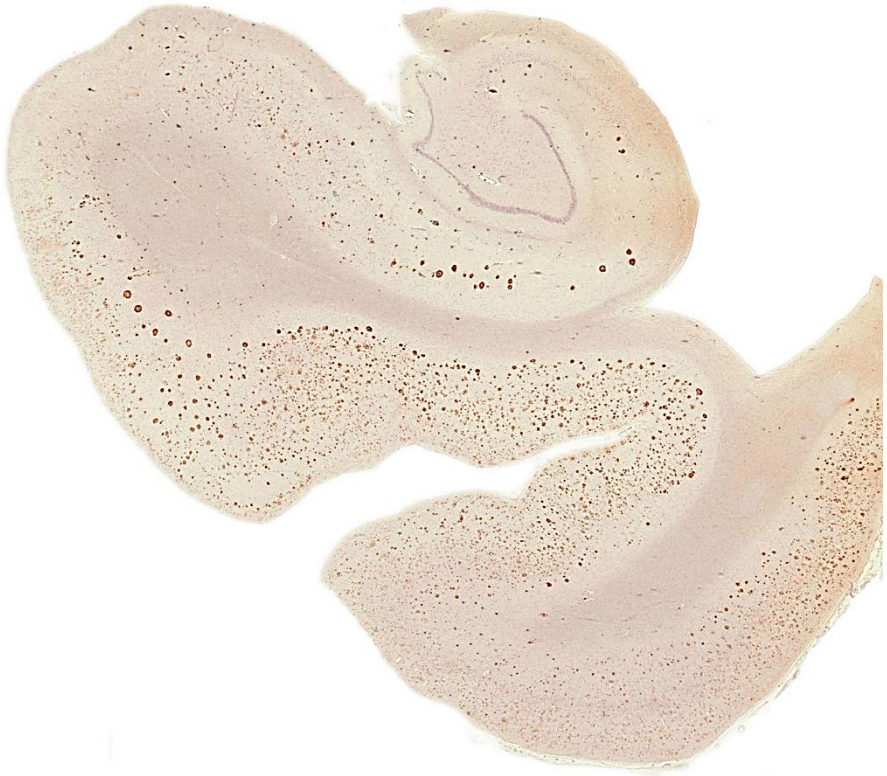
Accumulation of Brain Pathology with Age

- Amyloid or Neuritic plaques (NP)
- Neurofibrillary tangles (NFT)





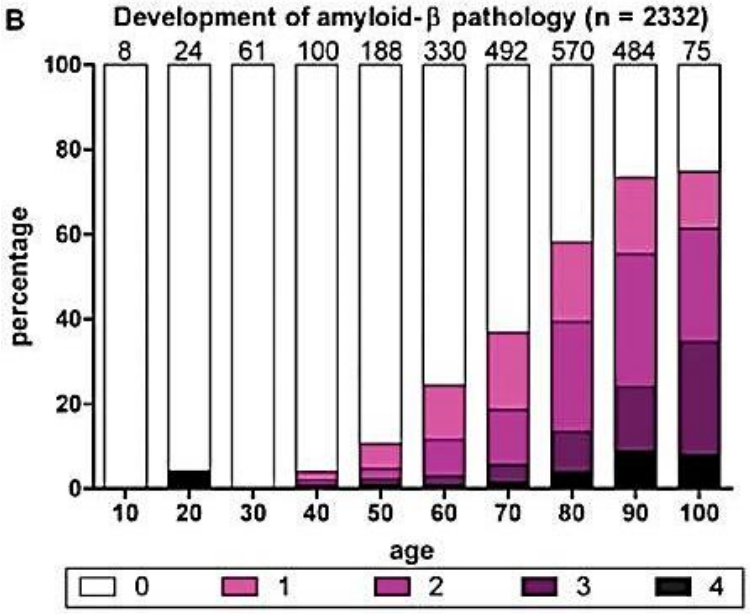
Amyloid Plaques
(Aβ protein deposits)

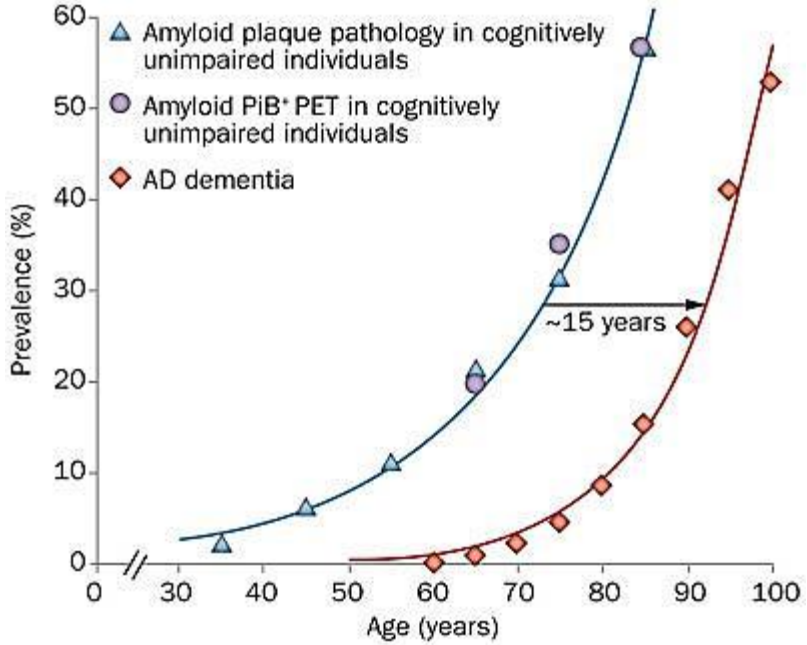


Aβ in neocortex and hippocampal formation. EM shows fibirillar amyloid

Brain amyloid plaques with Ageing

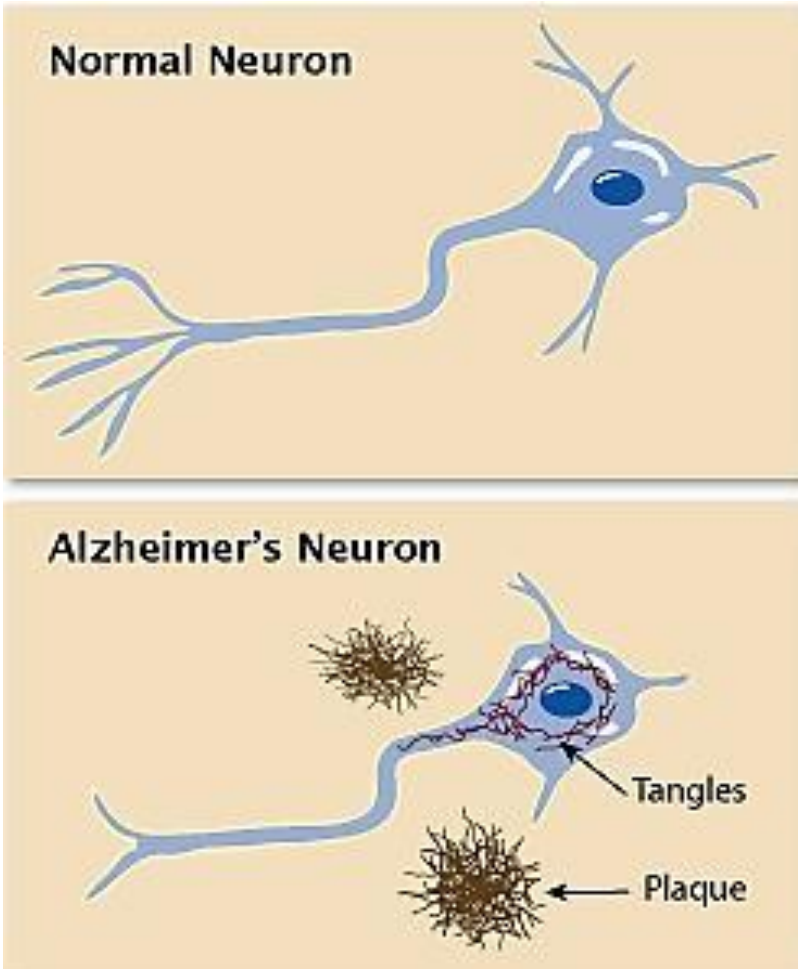
Cortical accumulation of NPs





Nelson PT et al, JNEN, 2012

Key Pathological Hallmarks of AD

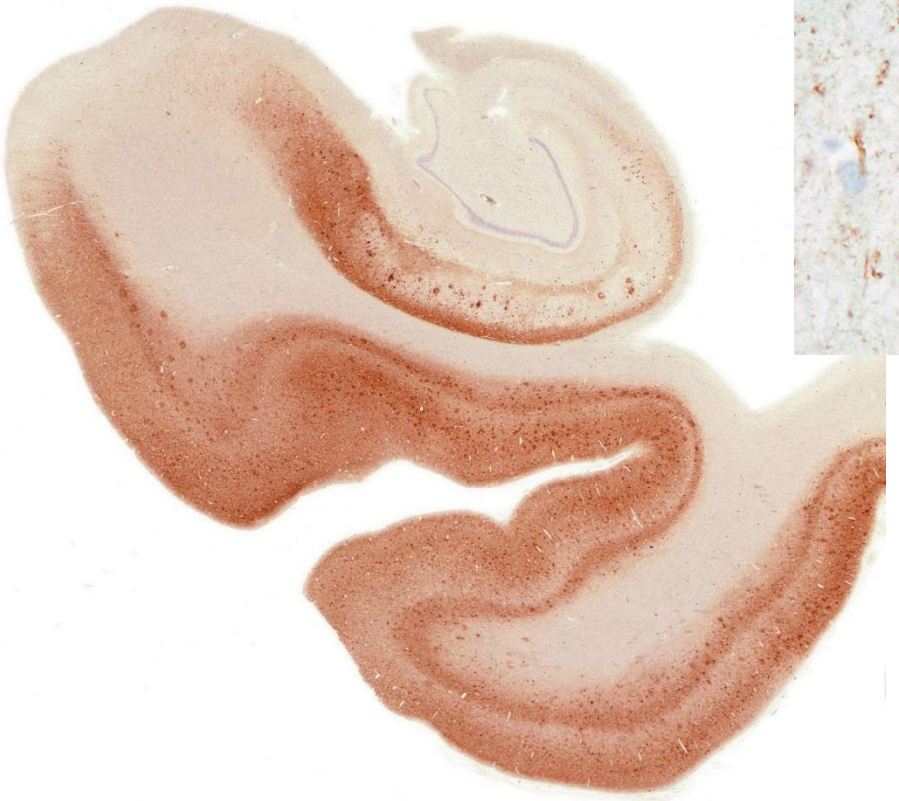


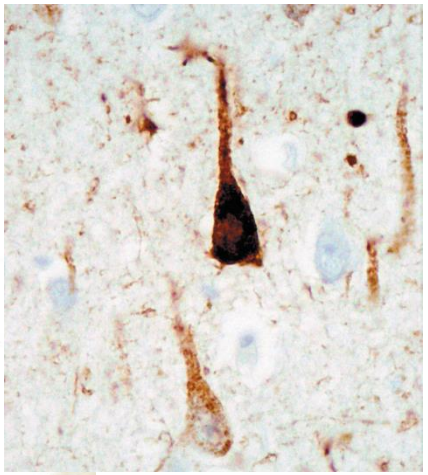
Accumulation of Brain Pathology with Age

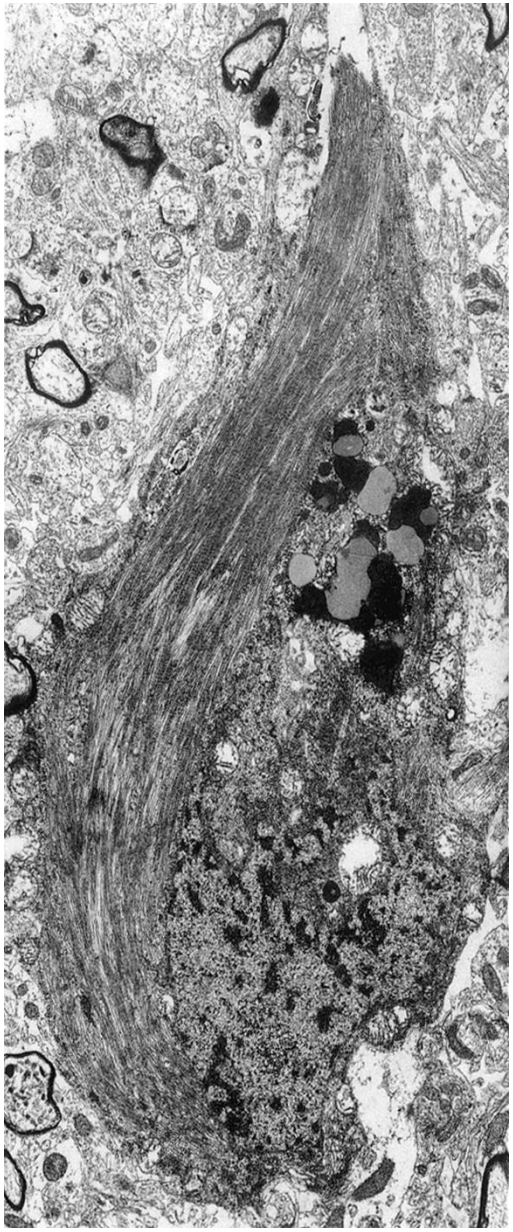
- Amyloid or Neuritic plaques (NP)
- Neurofibrillary tangles (NFT)

Neurofibrillary tangles

(Hyperphosphorylated tau protein)

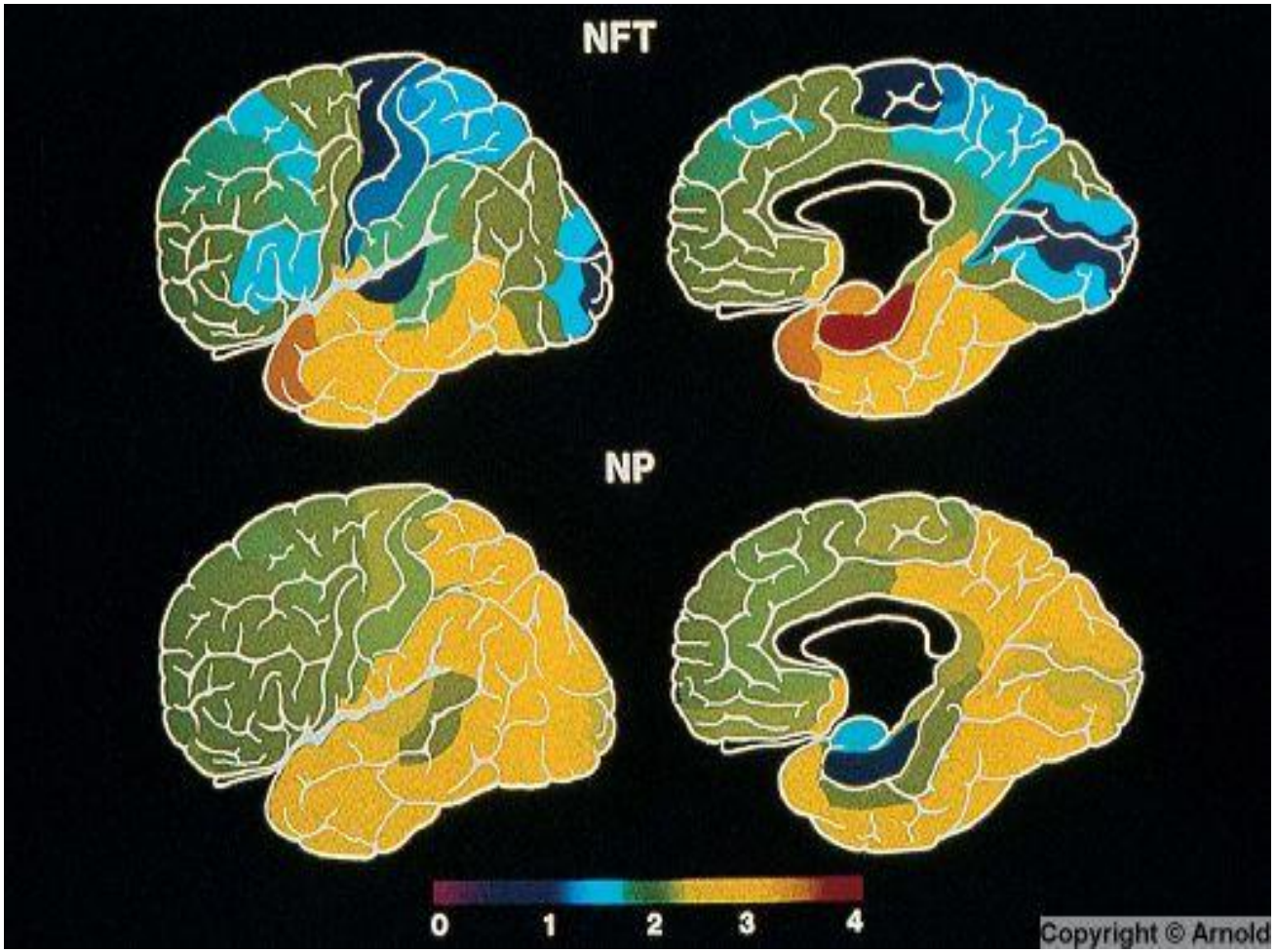






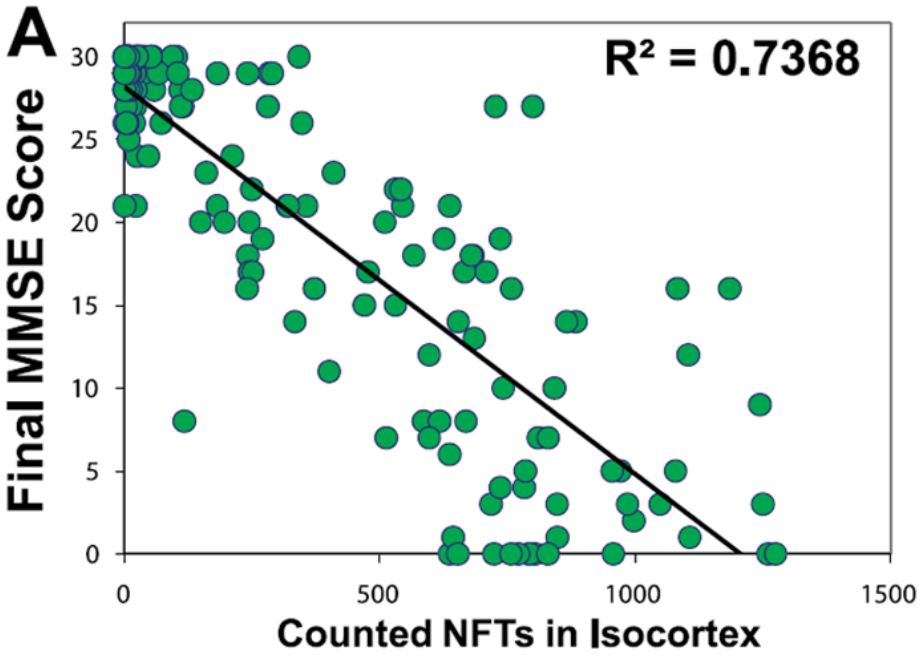
NFT in neocortex and hippocampal formation.
EM shows neurofibirillar twisted fillaments (tangles)

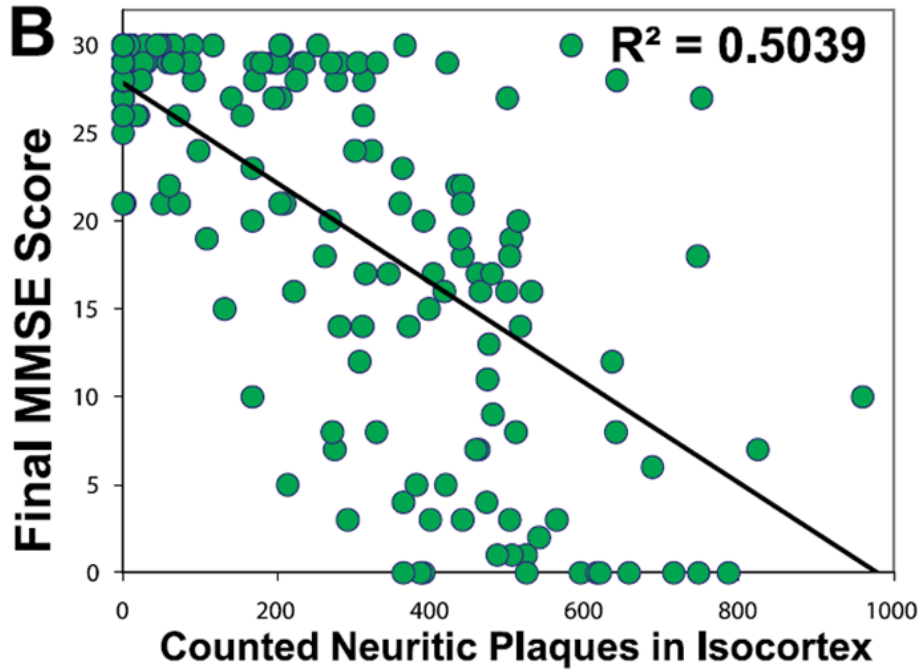
Topographic distribution of NFT and NP in AD



Thirty-nine cytoarchitectural fields were assessed on a 0-4+ scale for the presence of NFT or NP in 17 hemispheres.

A consistent hierarchical distribution was observed.



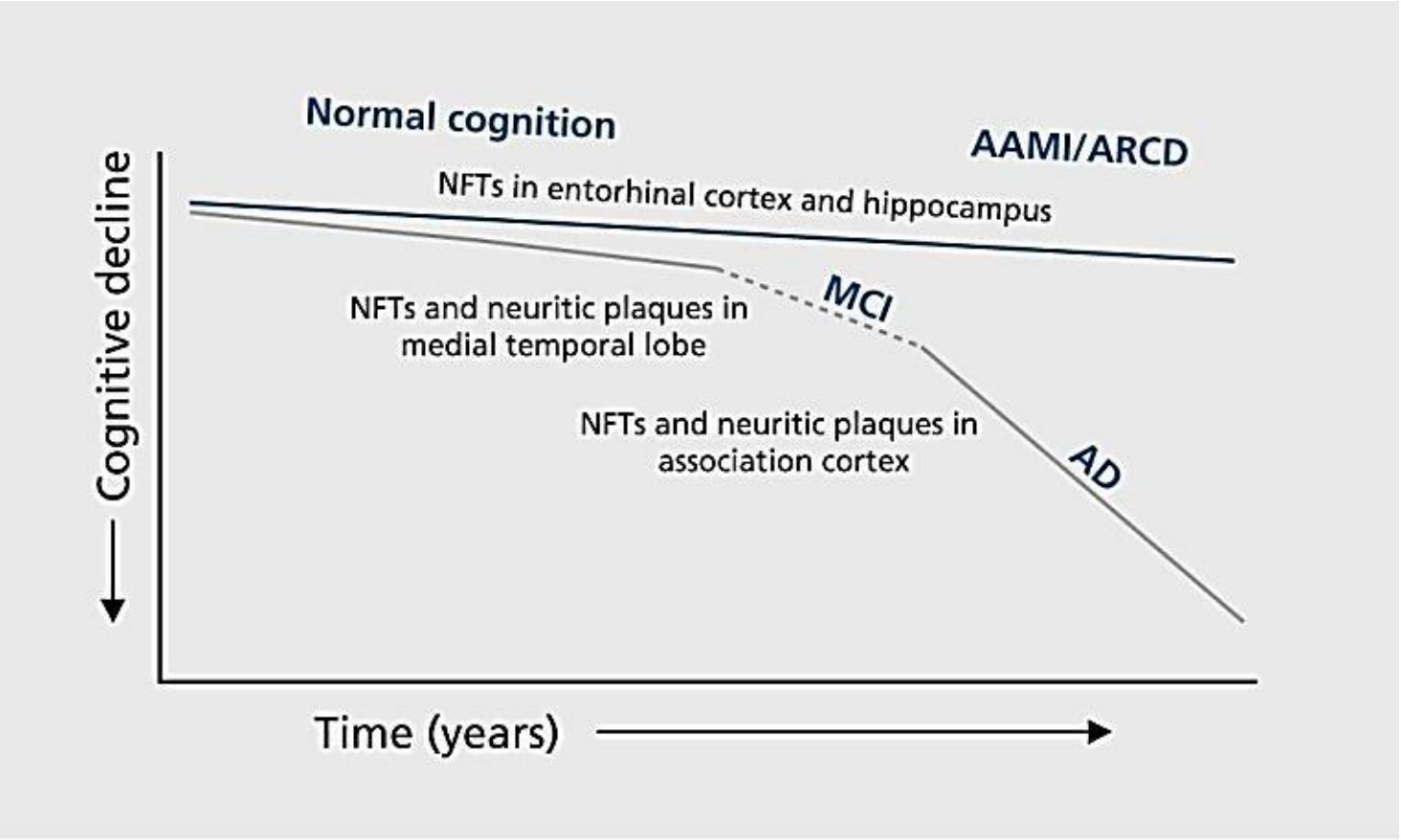


Correlation of AD Neuropathological Changes With Cognitive Status

- Correlations between antemortem cognitive status (MMSE), and counted neocortical NFTs (**A**) and neuritic β-amyloid plaques (NPs; **B**)
- Correlation between final MMSE scores and neocortical NFT counts is stronger than that between MMSE scores and NP counts

Nelson PT et al, 2012

Cognition and Brain Pathology during Ageing



Progressive accumulation of brain pathology increases damage and decreases cognitive functions

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

Articles

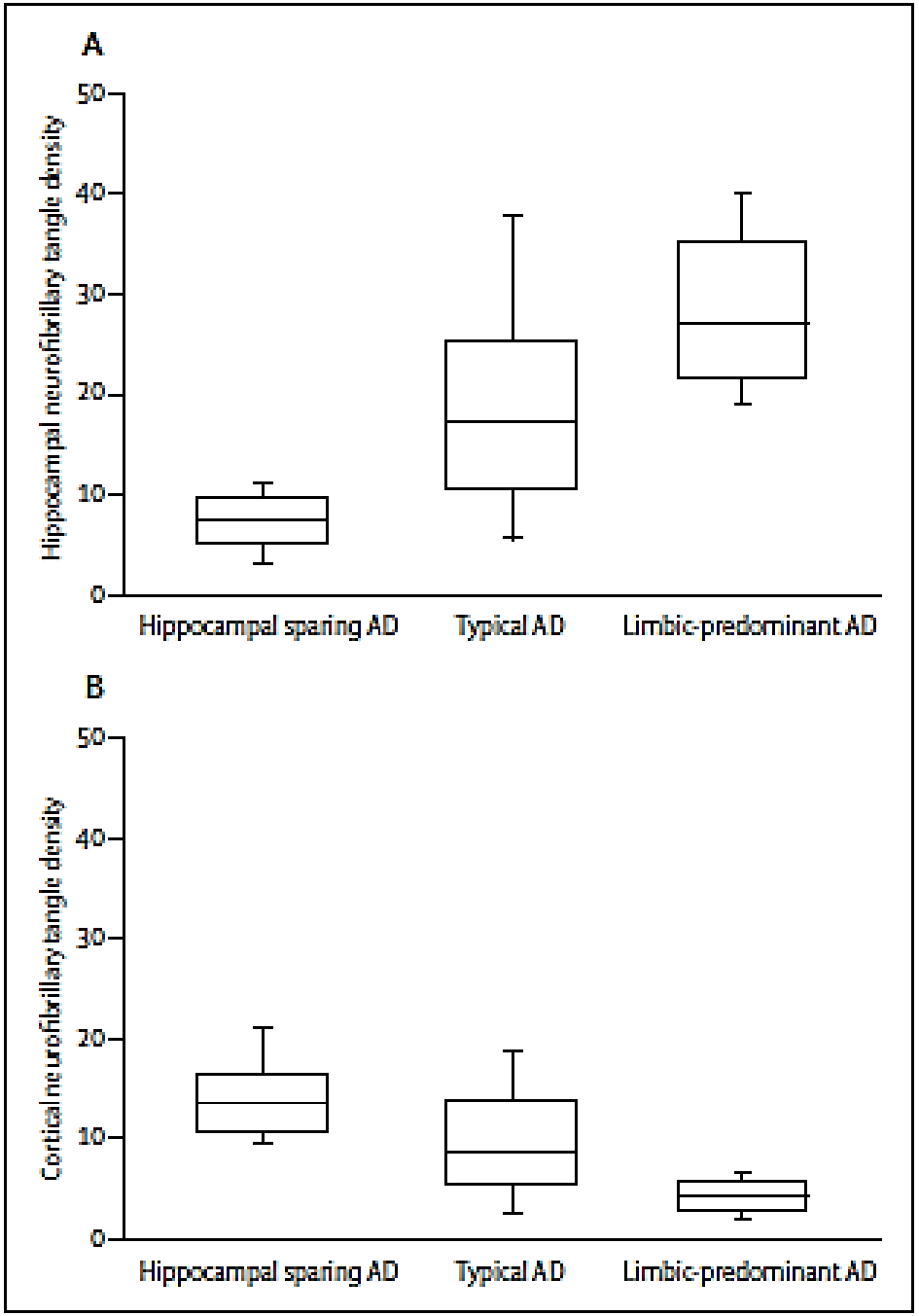
Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study

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



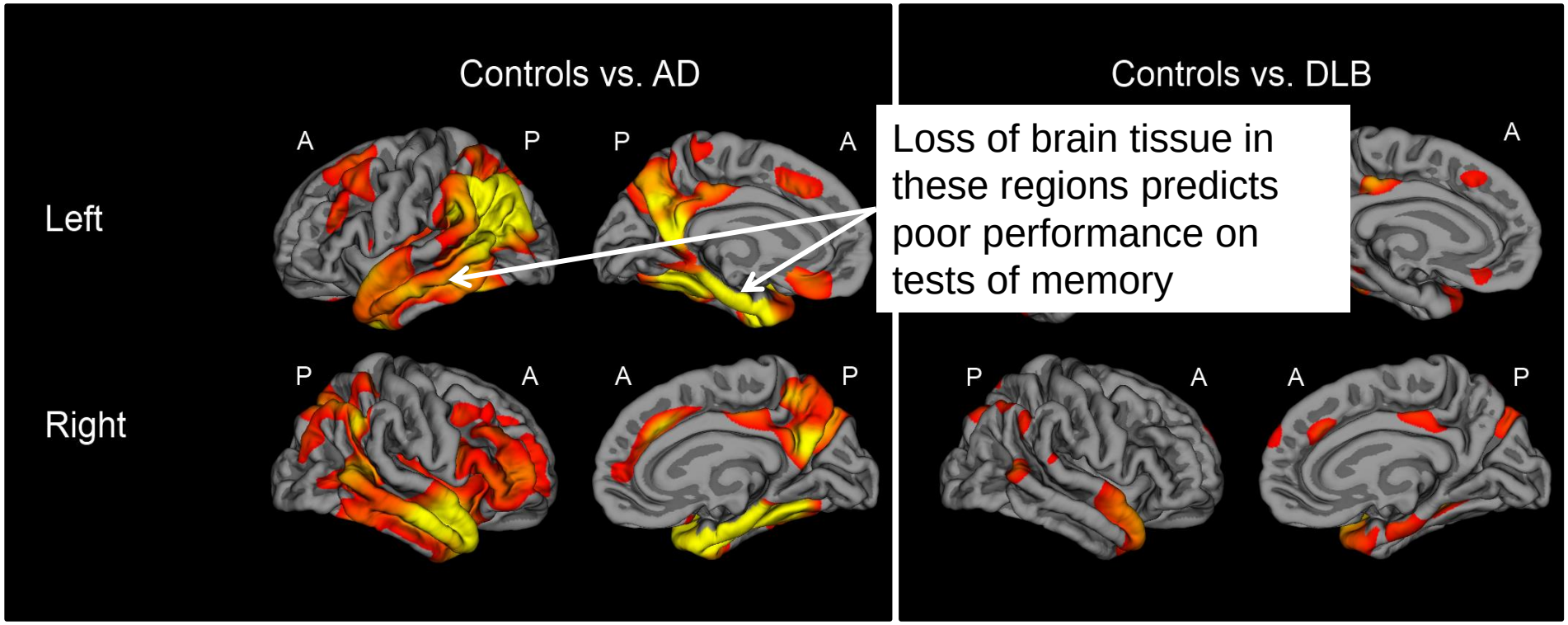
www.thelancet.com/neurology **Vol 11 October 2012**

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

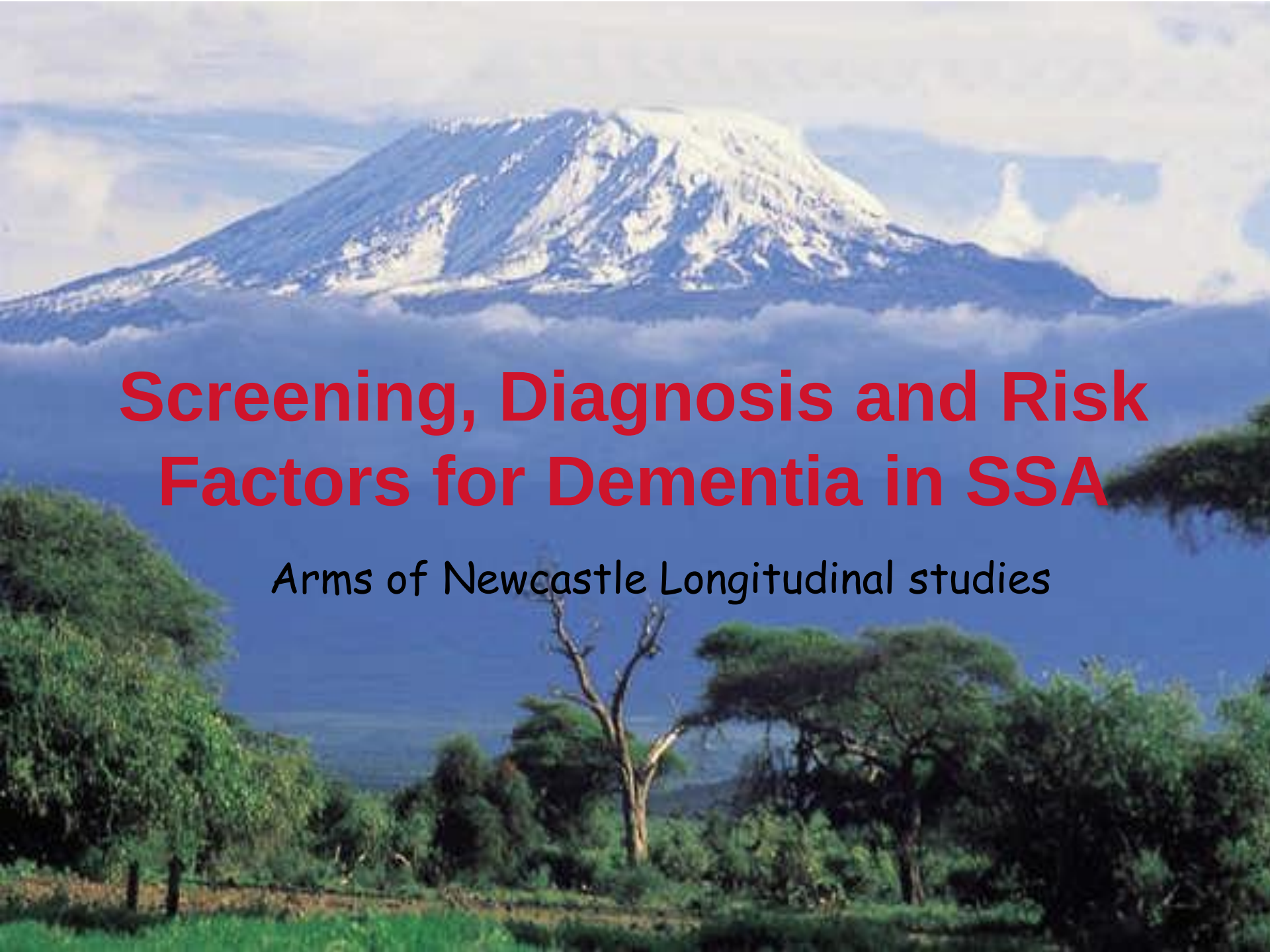
Jennifer L Whitwell, Dennis W Dickson, Melissa E Murray, Stephen D Weigand, Nirubol Tosakulwong, Matthew L Senjem, David S Knopman, Bradley F Boeve, Joseph E Parisi, Ronald C Petersen, Clifford R Jack Jr, Keith A Josephs

- 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

Patterns of Atrophy in Dementia



- **Pattern of atrophy is different between types of dementia**



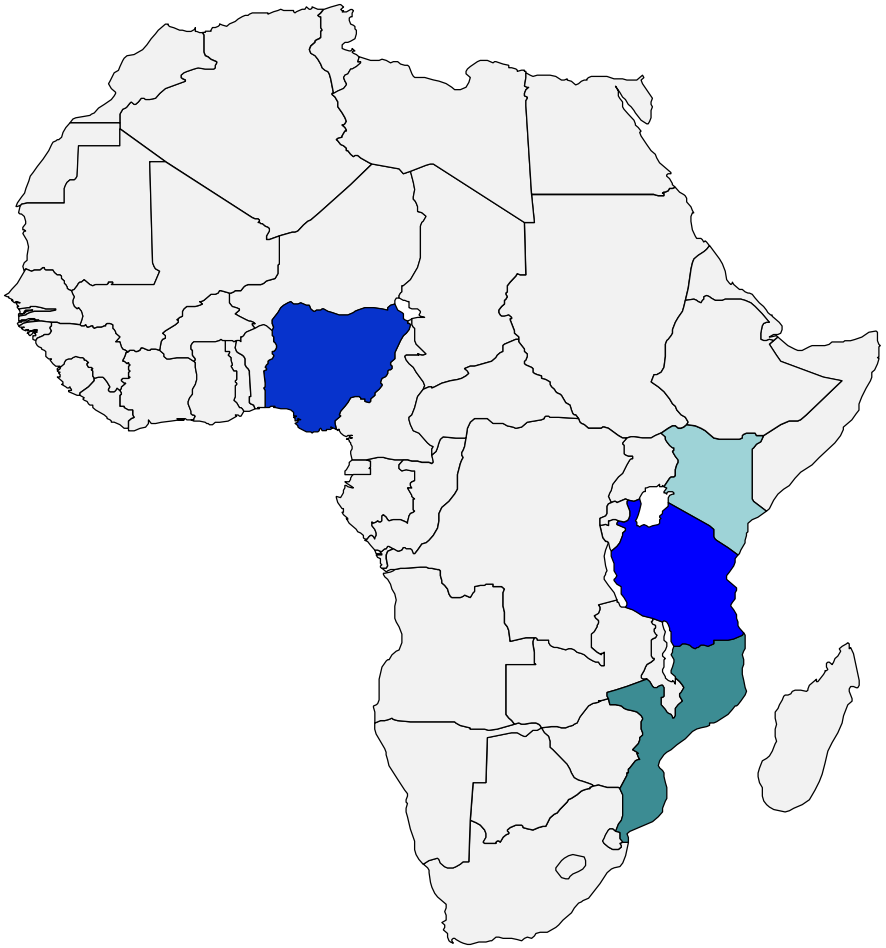
Screening, Diagnosis and Risk Factors for Dementia in SSA

Arms of Newcastle Longitudinal studies

COGFAST

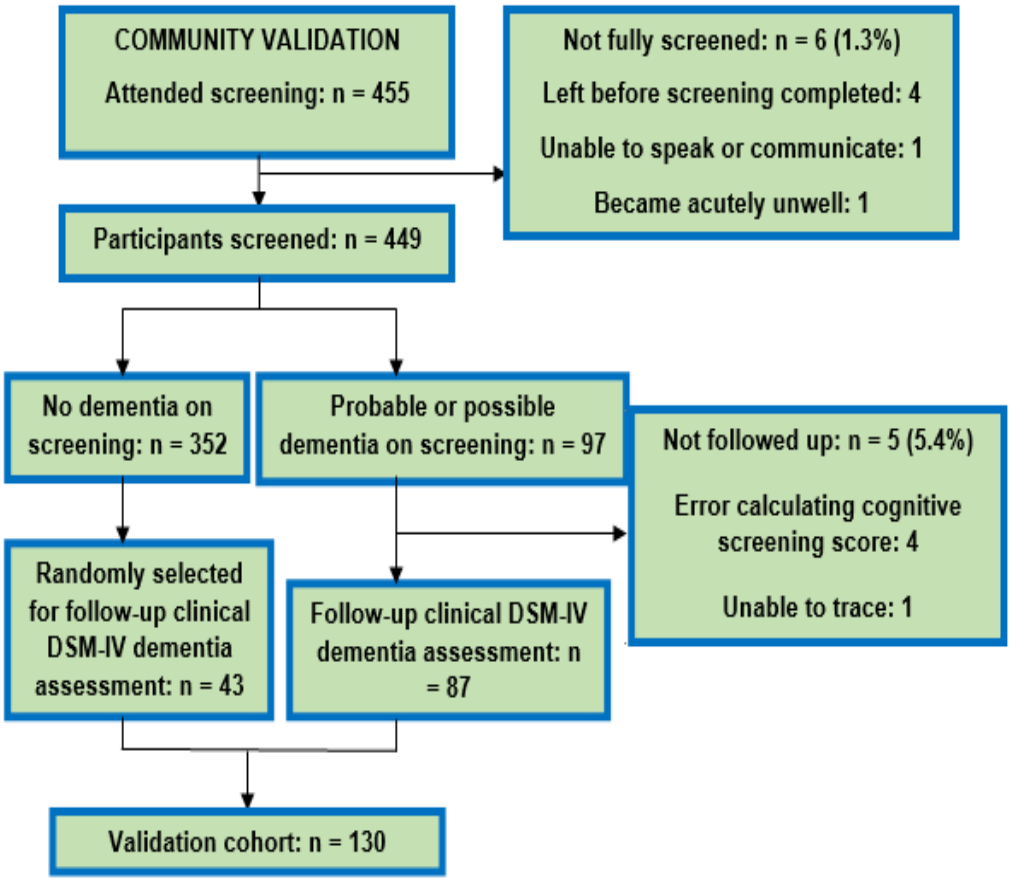
Memory After Stroke Study

Extensions of Newcastle Dementia Studies in SSA



Longitudinal studies in Dementia in Africa (Ibadan, Nigeria, Nairobi, Kenya and Hai District Tanzania: PIs R Kalaria, A Ogunniyi, M Owolabi, R Akinyemi, R Walker

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

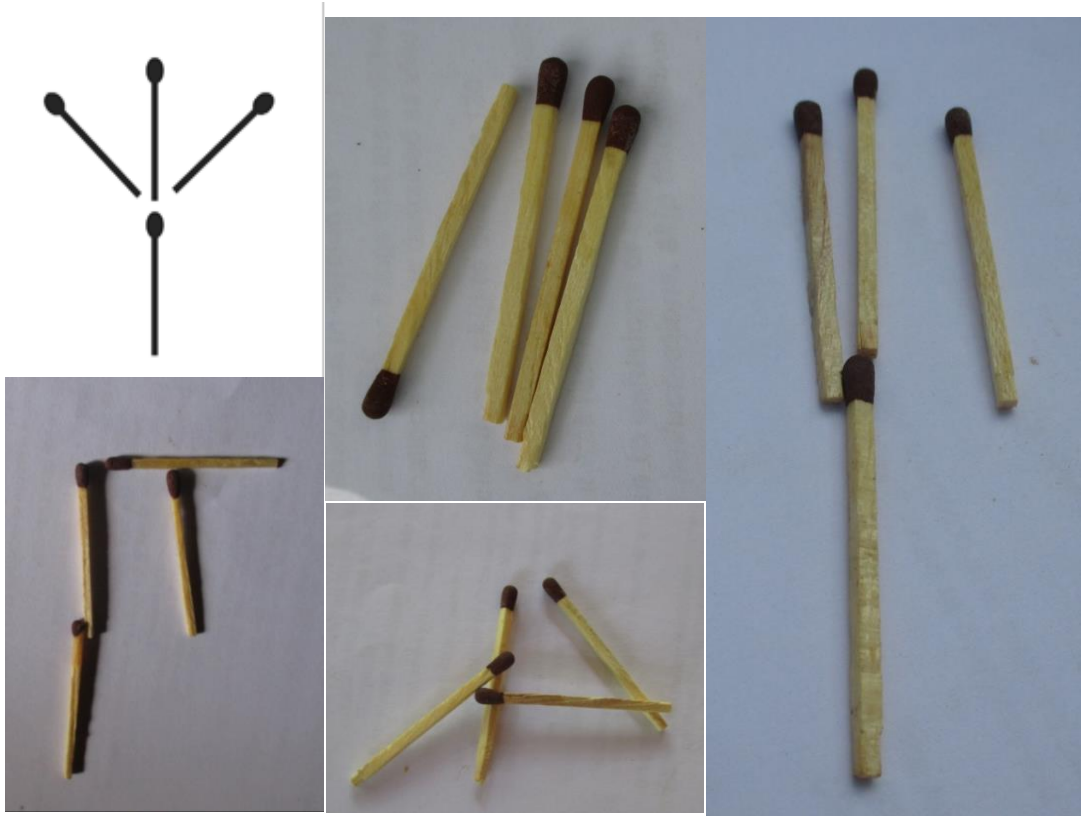
IDEA Study Screening Tools

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

2010 Dementia Prevalence in Hai

- Six villages -Total population 34,078
- 1260 eligible >70 yr on census (56% female)
- 1198 screened -184 Probable dementia, 108 possible dementia and rest no dementia
- 78 cases (22 male) ; DSM-IV
- Age-adjusted prevalence of dementia was 6.4% (95% CI: 4.9-7.9)
- Age-adjusted “10/66 dementia” prevalence 21.6% (95% CI 17.5-25.7%)
- Dementia Subtypes: 48.7% AD; 41.0% VaD; prevalence 3.9% AD and 2.9% VaD
- Vascular Risk Factors: *Diabetes; Cholesterol and Hypertension*

Longdon AR et al, 2013

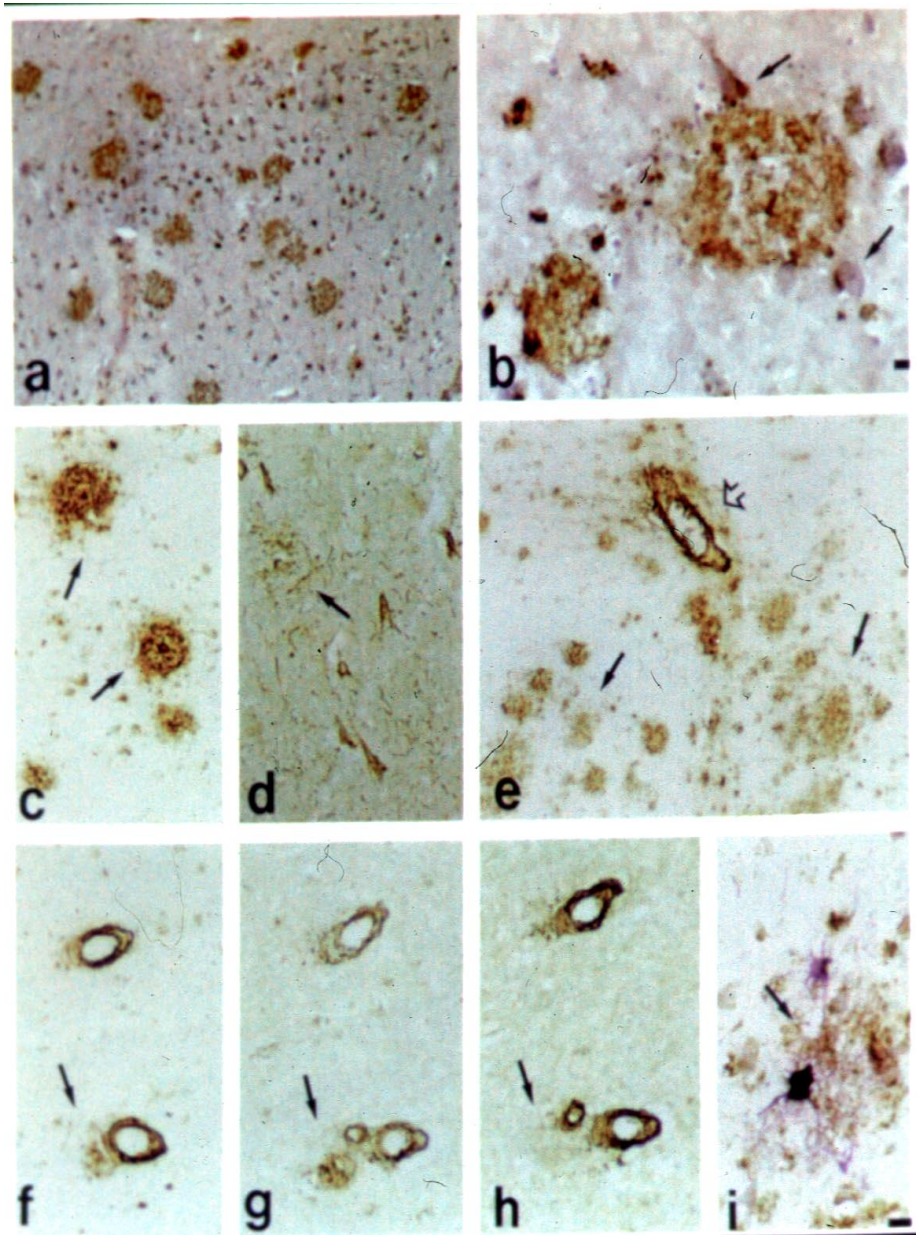
Prevalence Estimates of Dementia in sub-Saharan Africa (~2.1 million people)

Study	Country	Age range	Screening tool used	Dementia prevalence
Longdon, 2013	Rural Tanzania	70 +	CSI-D	6.4% (age-adjusted)
Paraiso, 2011	Benin, urban	65+	CSI-D, 5WT	3.7%
Guerchet, 2009	Benin, rural	65+	CSI-D, 5WT	2.6%
Guerchet, 2010	CAR Congo Brazaville	65 +	CSI-D, 5WT	8.1% (CAR) 6.7% (Congo).
Yusuf, 2011	Nigeria, Zaria	75.5 ± 9.4	CSI-D	2.79%
Ochayi & Thacher	Nigeria, Jos	65 +	CSI-D	6.4%
Ogunniyi, 2000	Nigeria, Ibadan	65+	CSI-D	2.29% (age-adjusted)
Gureje, 2006	Nigeria, Ibadan		10 word learning list	'Probable Dem' 10.1%

Brain AD lesions in East Africans

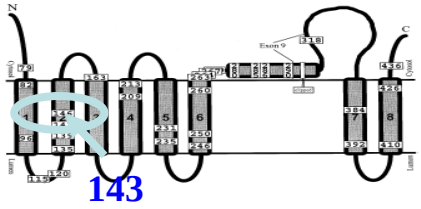
- **Comparable to a US sample, ~18%of elderly East Africans exhibit Aβ(42) deposits (9/50 cases)**
- **Severe CAA was evident in brains of two subjects**
- **Typical τ +ve NFT pathology was evident in the hippocampus and neocortex**
- **These findings suggest that elderly East Africans are unlikely to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

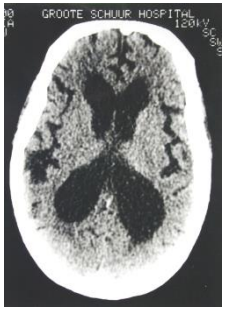
(Ogeng'o J et al, 1996)

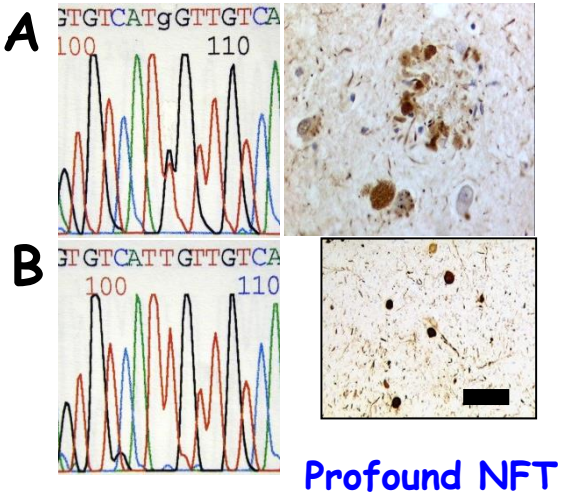


Hereditary AD in a large Xhosa Family, SA

Heckmann J et al, 2004

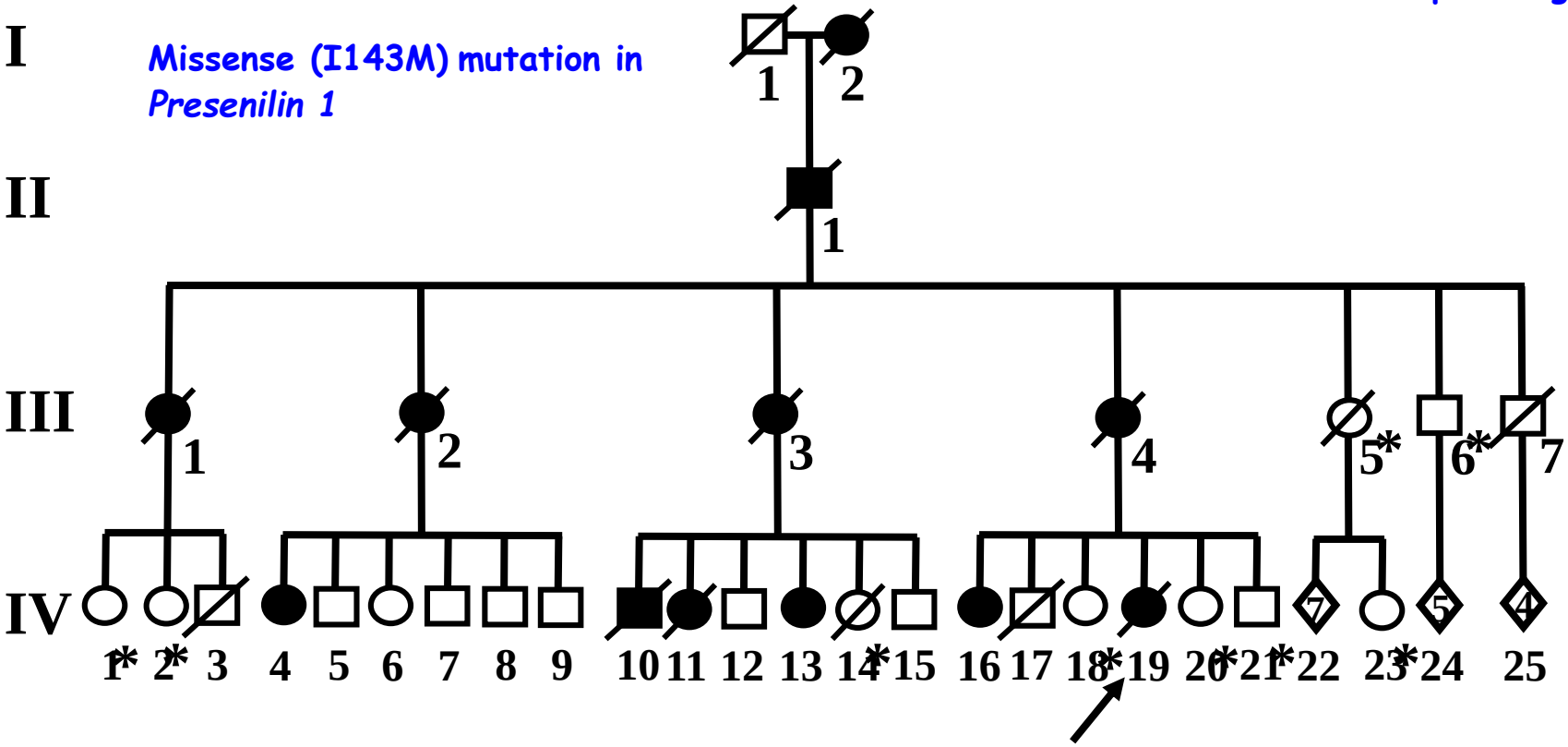




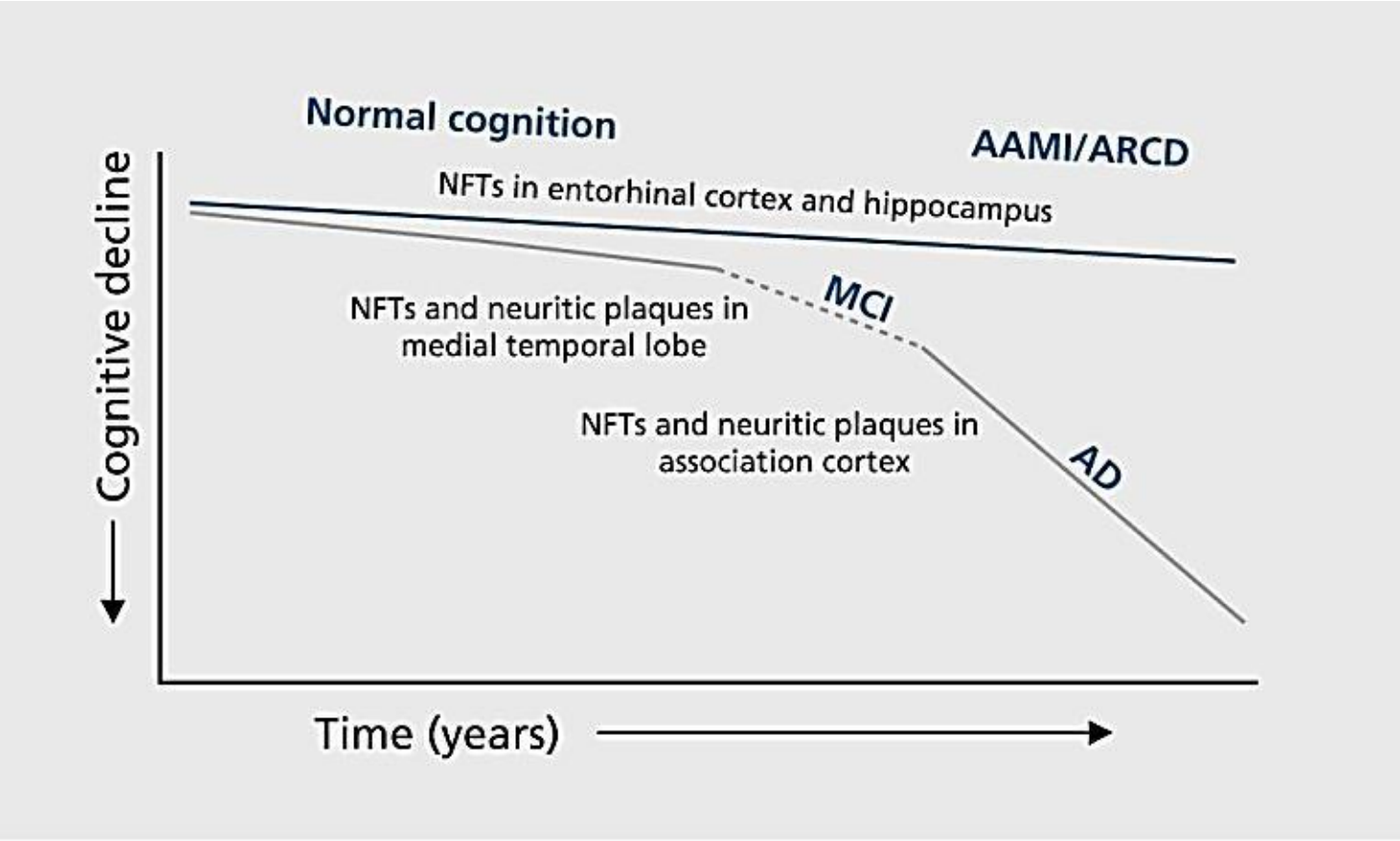


Profound NFT pathology

Missense (I143M) mutation in *Presenilin 1*

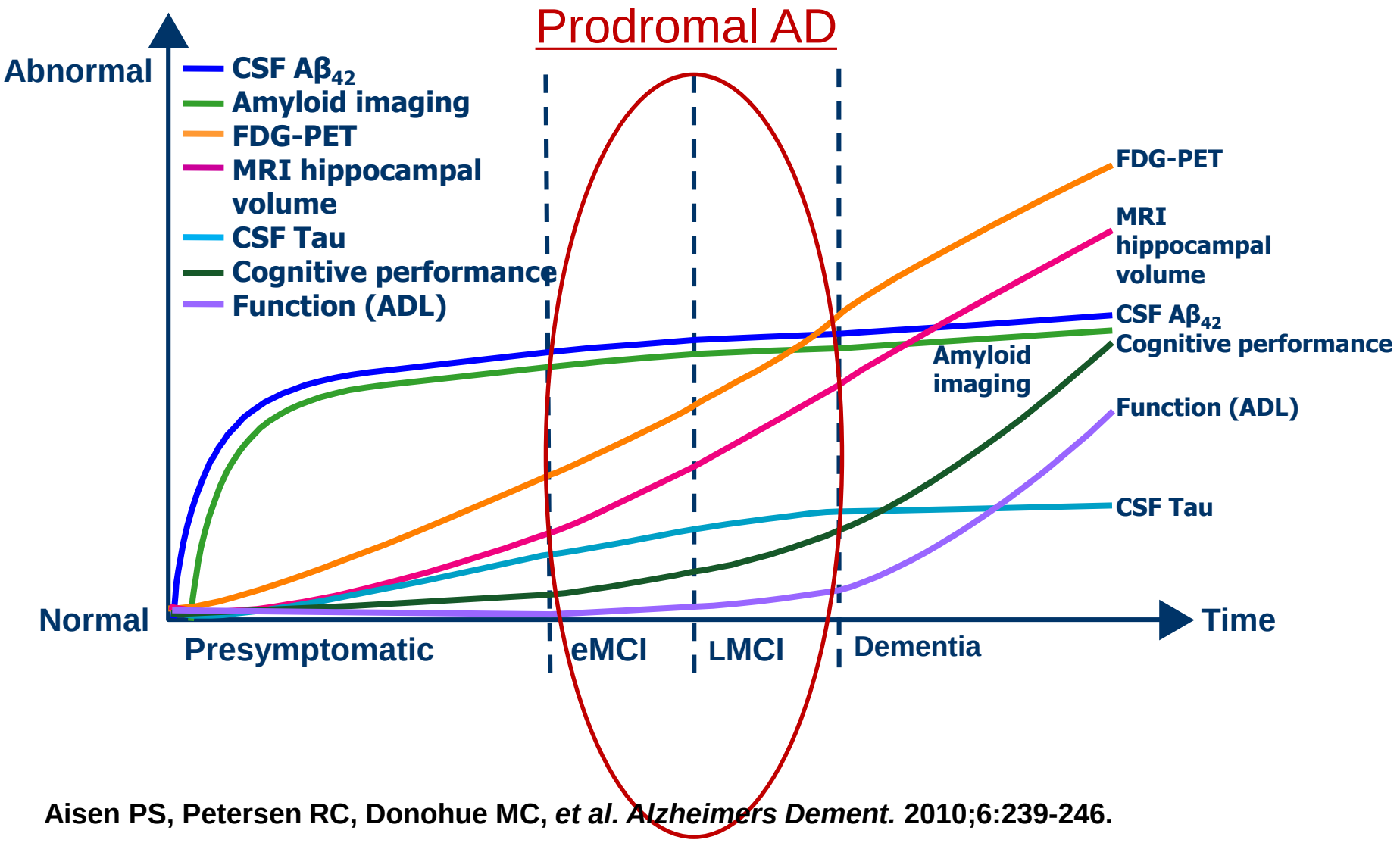


Progression of Dementia



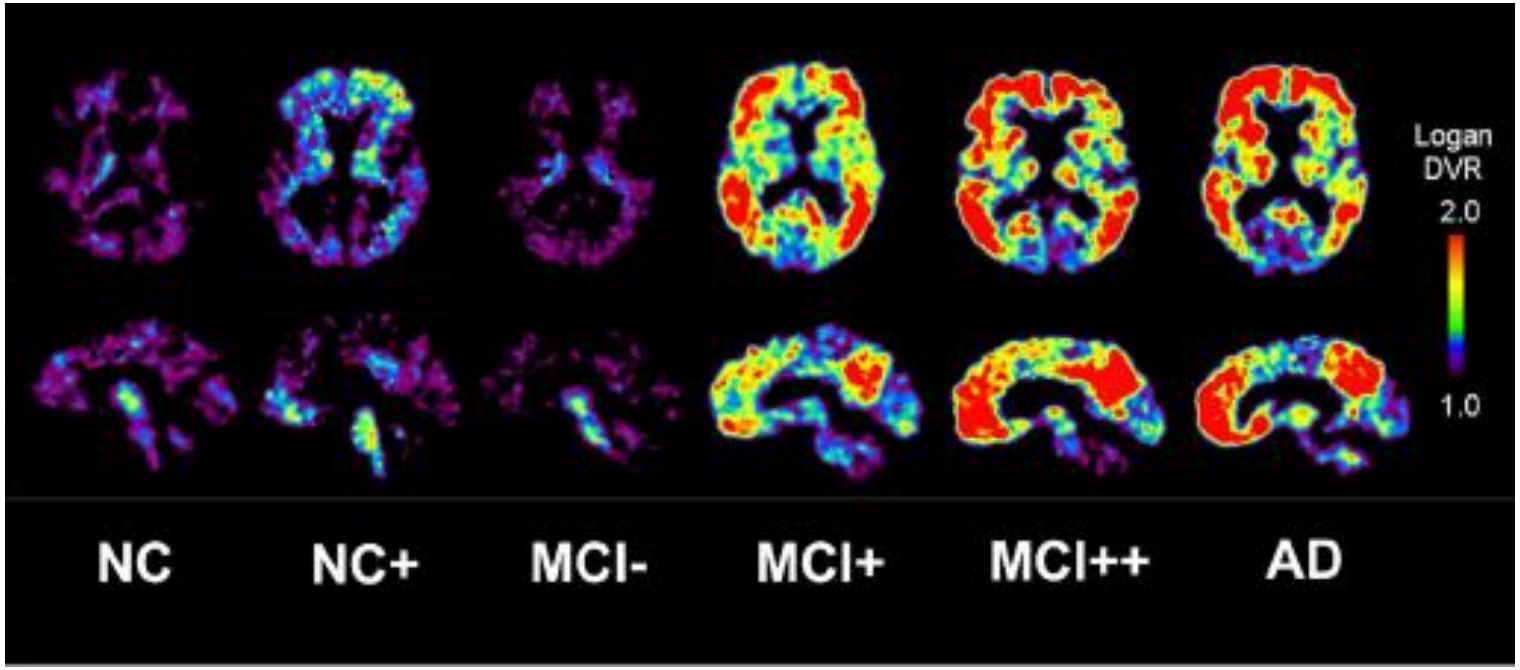
Progressive accumulation of brain pathology increases damage and decreases cognitive functions

Progression of Dementia



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

Amyloid Deposition precedes Clinical Dementia by Years



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

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

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

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

Side Effects of AChEIs

Mild sedation (initially)	Dizziness/ Postural hypotension
Abdominal discomfort	Anxiety, insomnia
Anorexia, nausea, vomiting	Depression
Diarrhoea	Increased salivation, sweating, cramps

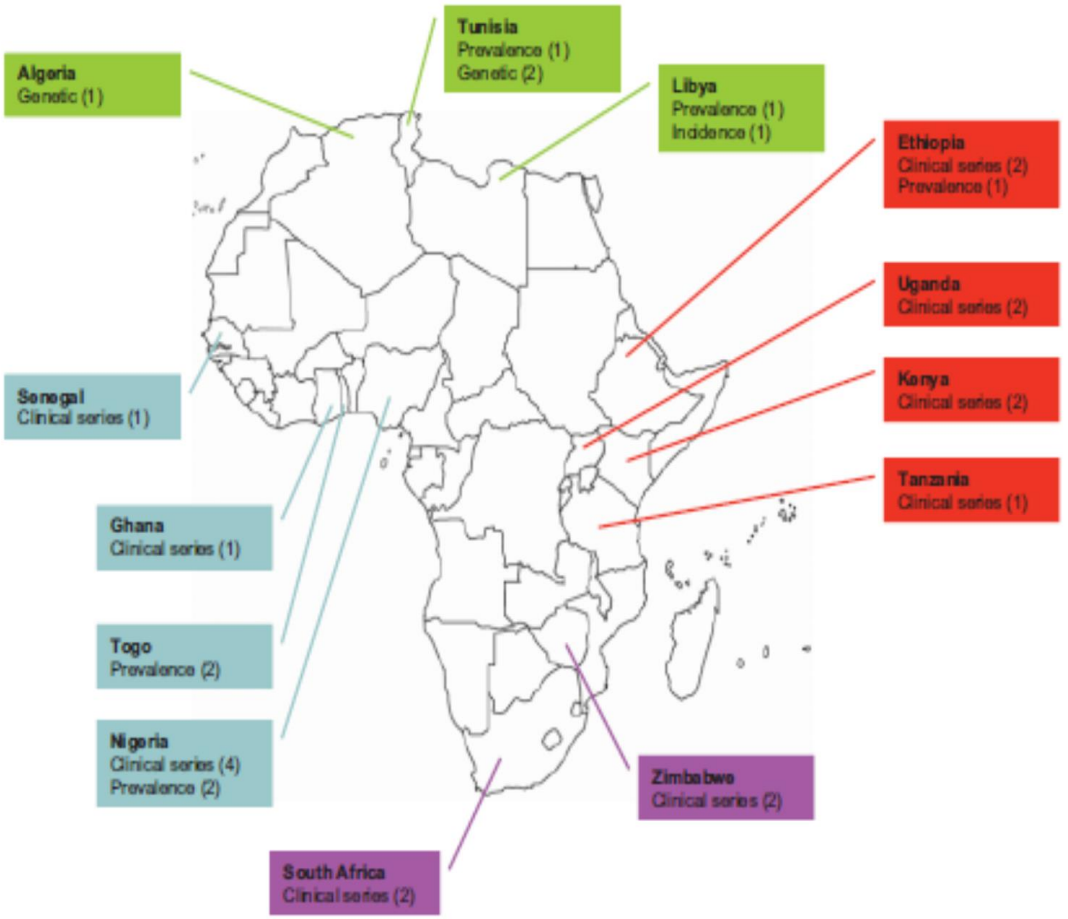
Maladies Neurodégénératives dans Afrique

- **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

Parkinson's Disease in Africa

- Okubadejo et al. Mov Disord 2006;21: 2150-6
- Okubadejo. Parkinsonism and Rel Disord 2008; 14: 177-182

- 12 studies describing genetics of PD in Africa
- 2 studied inheritance patterns of familial PD
- 10 focused on one of Parkin, PINK 1 and LRRK2 genes in familial PD
- All studies were from North Africa, mostly powered by the French PD Genetics Study Group (Lesage et al)
- Most sig. finding was very high freq. of LRRK2 mutation (41%)
- Parkin and PINK 1 mutations were also documented



After Akinyemi R, 2009

Dementia with Lewy Bodies in Africa

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

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

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

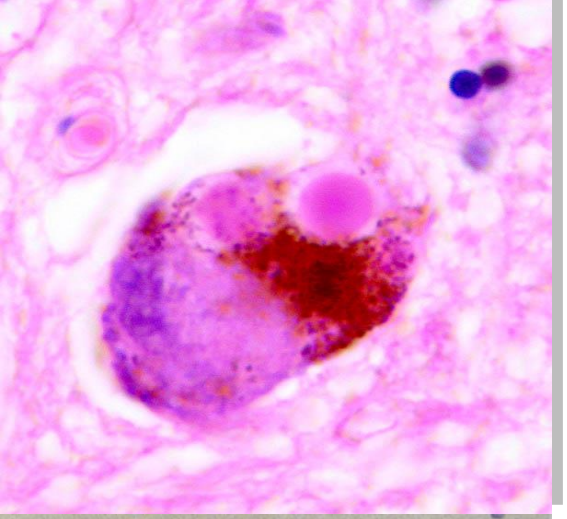
- **Cognitive decline & reduced social/occupational function**
  - Attentional, executive and visuo-spatial dysfunction prominent
- **CORE features**
  - Fluctuation
  - Recurrent visual hallucinations
  - Spontaneous parkinsonism
- **Suggestive features:**
  - REM sleep behaviour disorder
  - Neuroleptic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

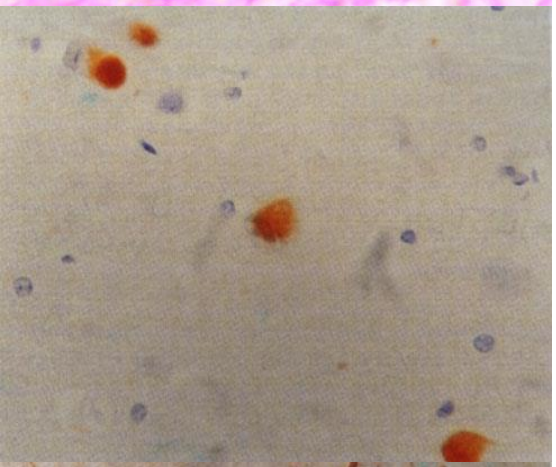
At least one core + one suggestive or 2 core features for Probable DLB

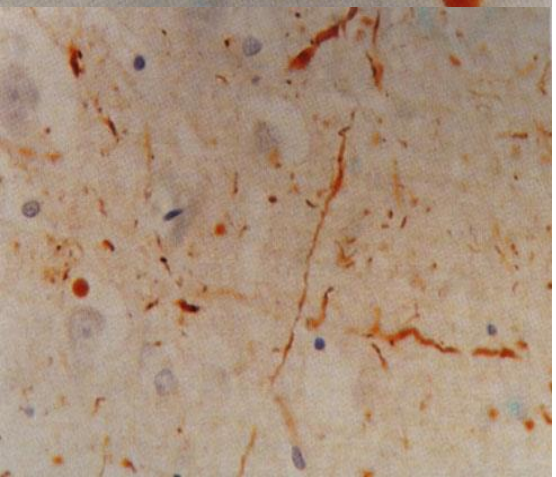
One core or suggestive feature sufficient for Possible DLB

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

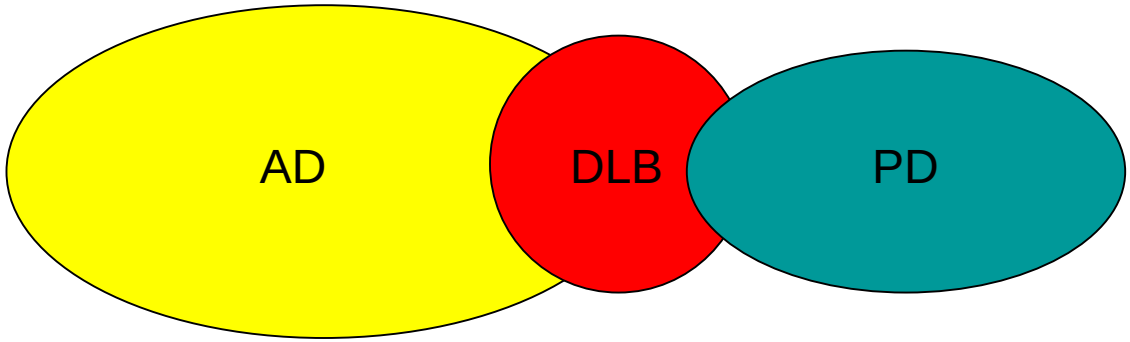




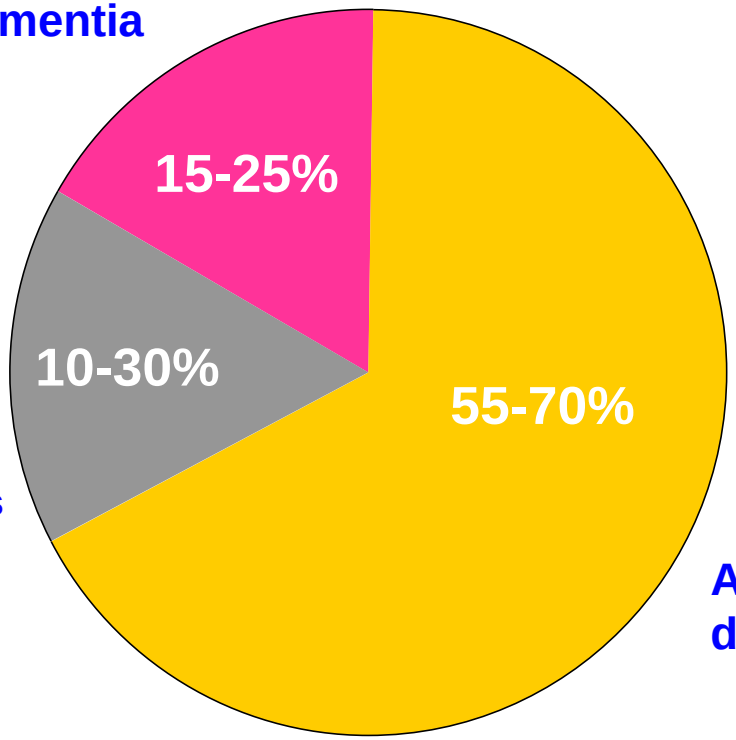


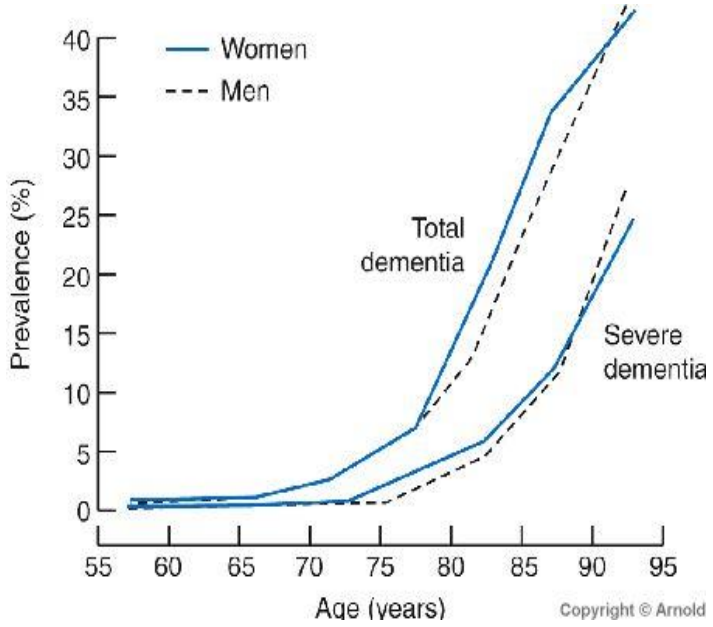
AD-DLB-PDD continuum

- 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



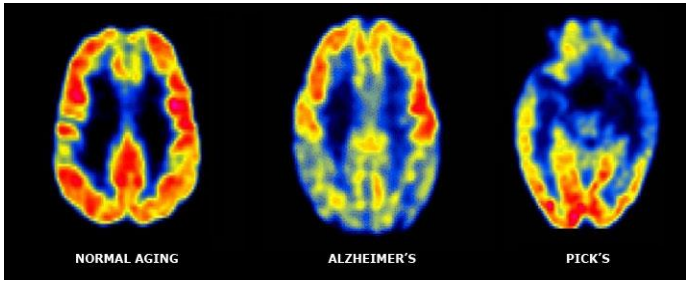
What Are the Most Common causes of Degenerative Dementias?





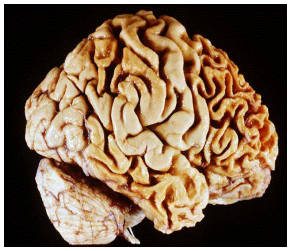
Frataglioni L, et al. *Neurology.* 2000;54:S10-15
Rarer dementias not shown but do not amount to >15 of total.

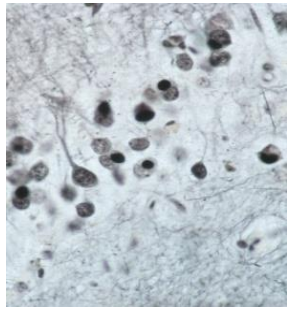
Frontotemporal Dementias (FTD)



Arnold Pick
1854- 1924

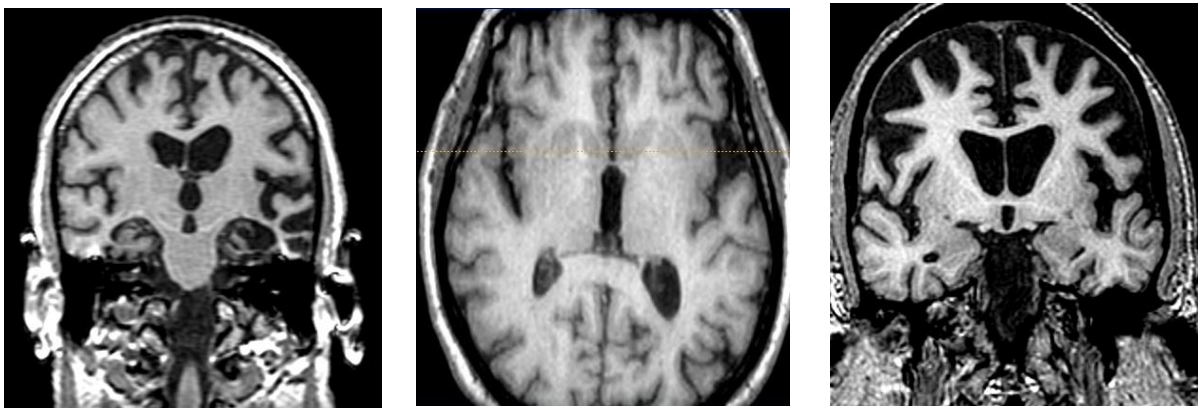
- Pick (1892) and bilateral frontal lobe atrophy
- FTD is a focal degenerative disorder (cause FTLD)
- Alteration in personality, social conduct and executive function
- Non-Alzheimer pathology disorder
- Related FTD syndromes –Semantic dementia, Primary Progressive non-fluent Aphasia,
- FTLDs are tauopathies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

- Frontotemporal dementia (frontal variant; FTD; bvFTD)
- Semantic dementia (SD)
- Progressive non-fluent aphasia (PNFA)



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.

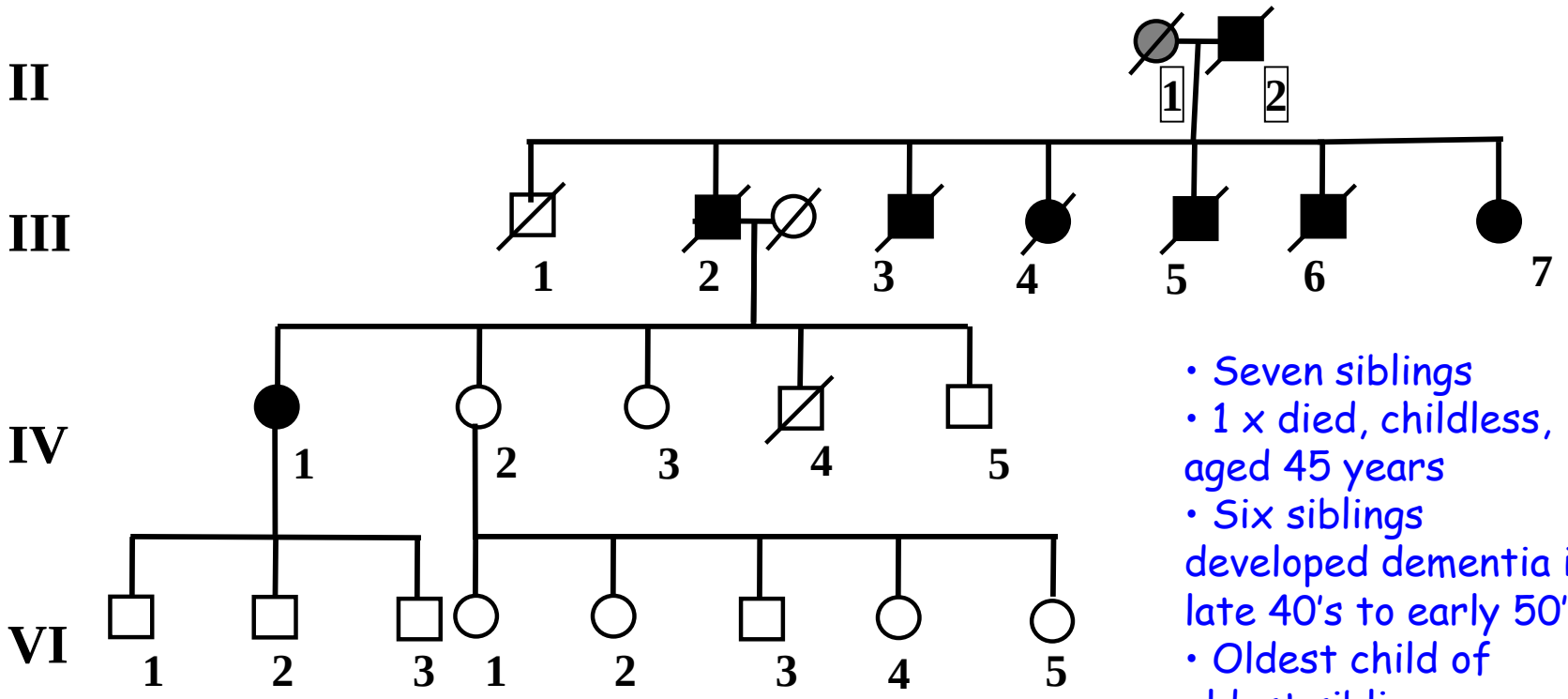
RO Akinyemi[1,4], MO Owolabi[1], VA Makanjuola[2], AO Ogunseyinde[3] and A Ogunniyi[1].

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)

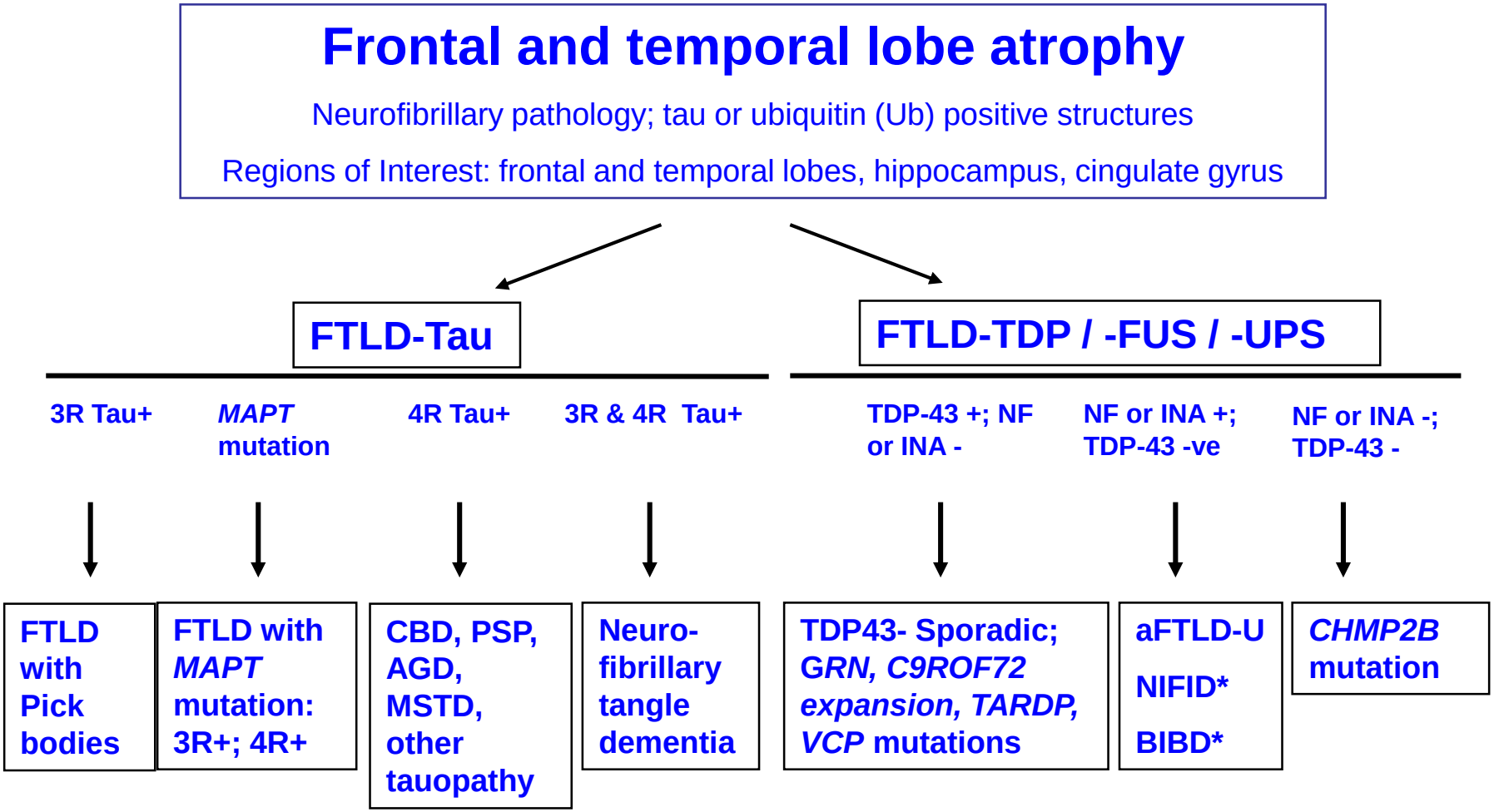
Family Tree



- 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)

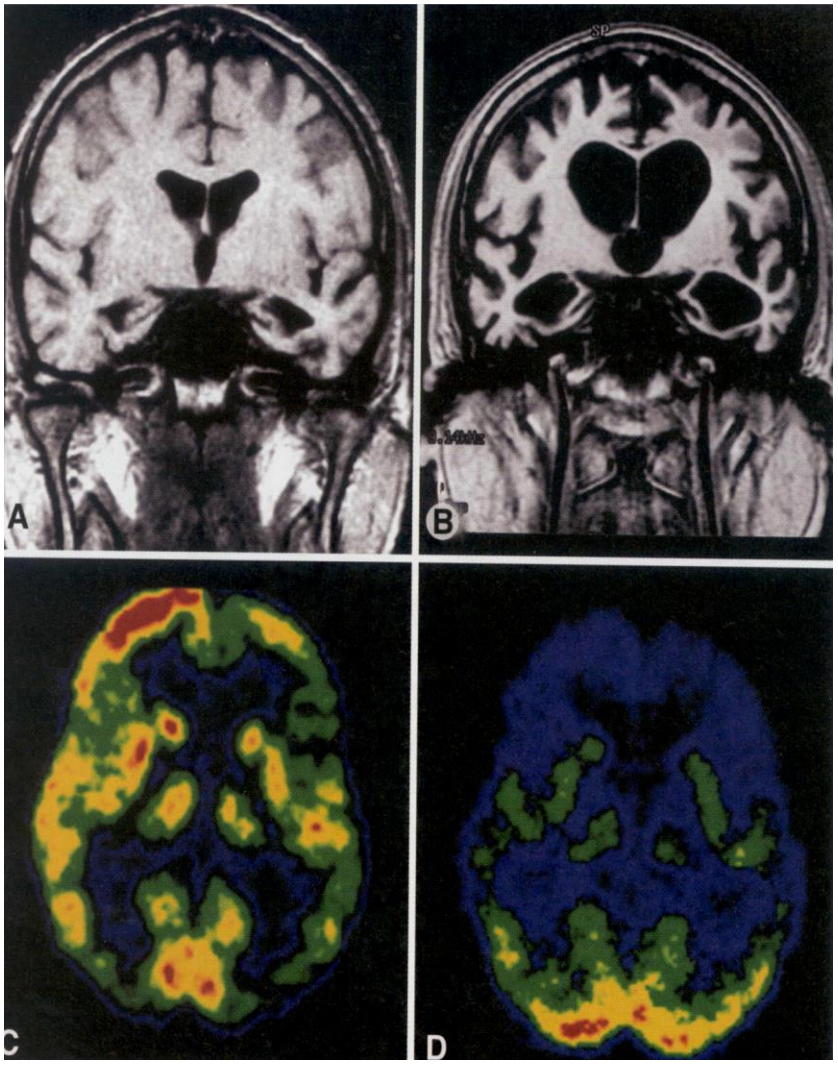
Family tree has been disguised to preserve individual patient identity. Family tree x 300 years genealogical Institute of South Africa (Dr Leon Endeman)

Frontotemporal Lobar Degeneration



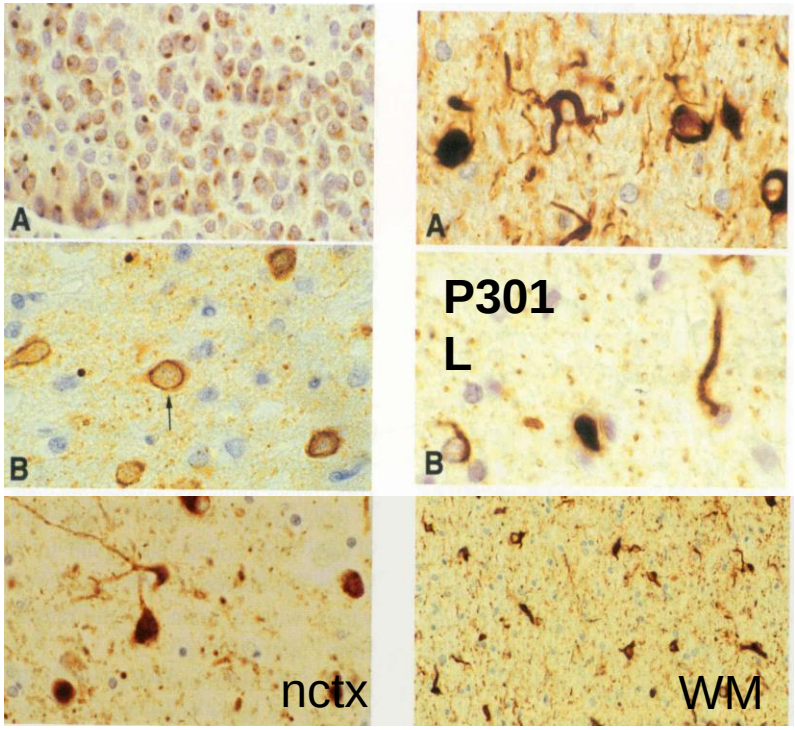
** BIBD, basophlic inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; TDP-43 transactivation response DNA binding protein with M(r) 43 kD; PGRN, progranulin; VCP, Valosin-containing protein*

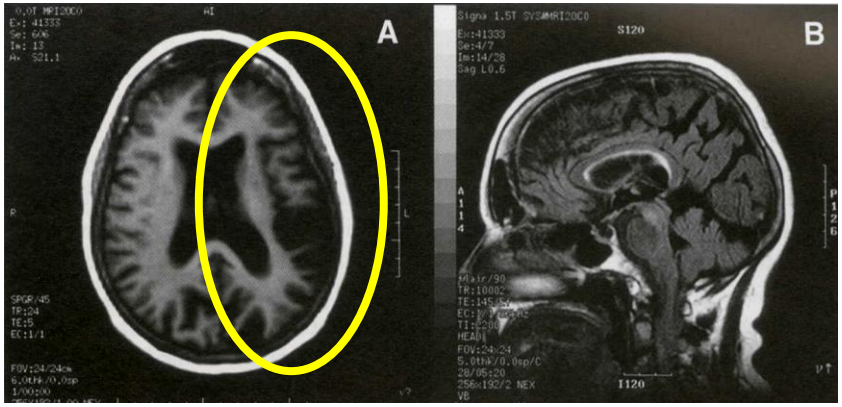
G389R mutation A→B 3 yrs

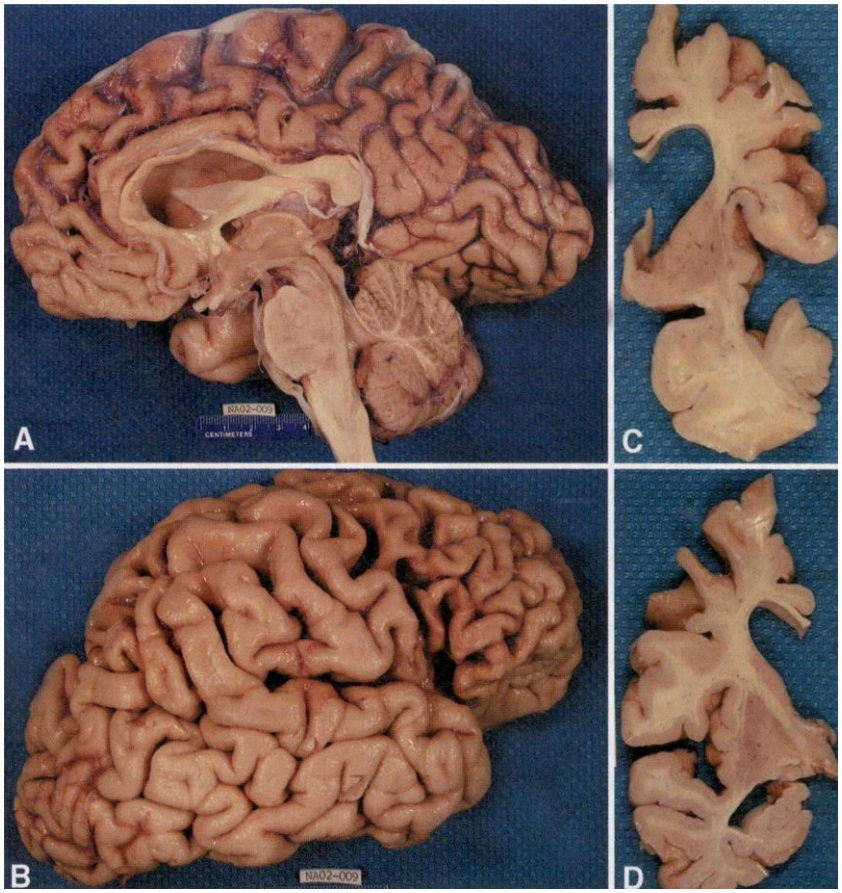


FTD linked Parkinsonism- Chr 17

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

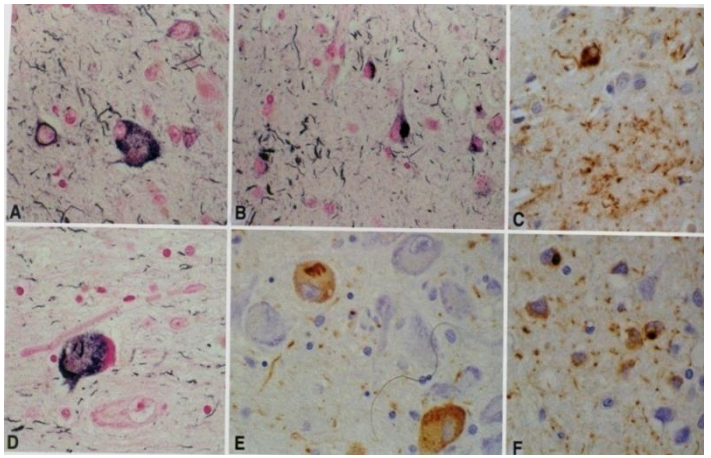




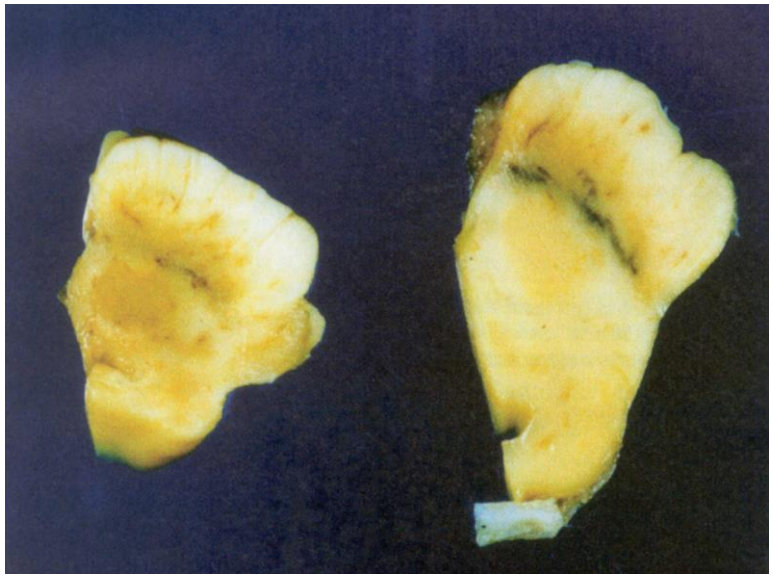


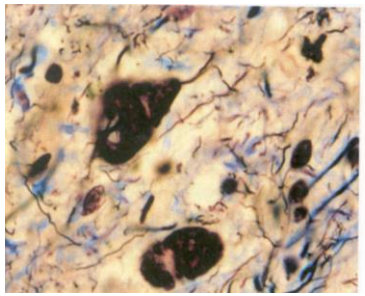
Corticobasal Degeneration

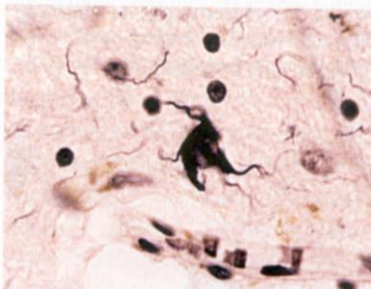
- Slowly progressive dementia
- Asymmetric lesions (Apraxia)
- Frontal and Parietal atrophy
- Corpus Callosum thining
- Heterogeneity of neuronal inclusions
- Balloned neurones (H&E)
- Neuronal vacuolation



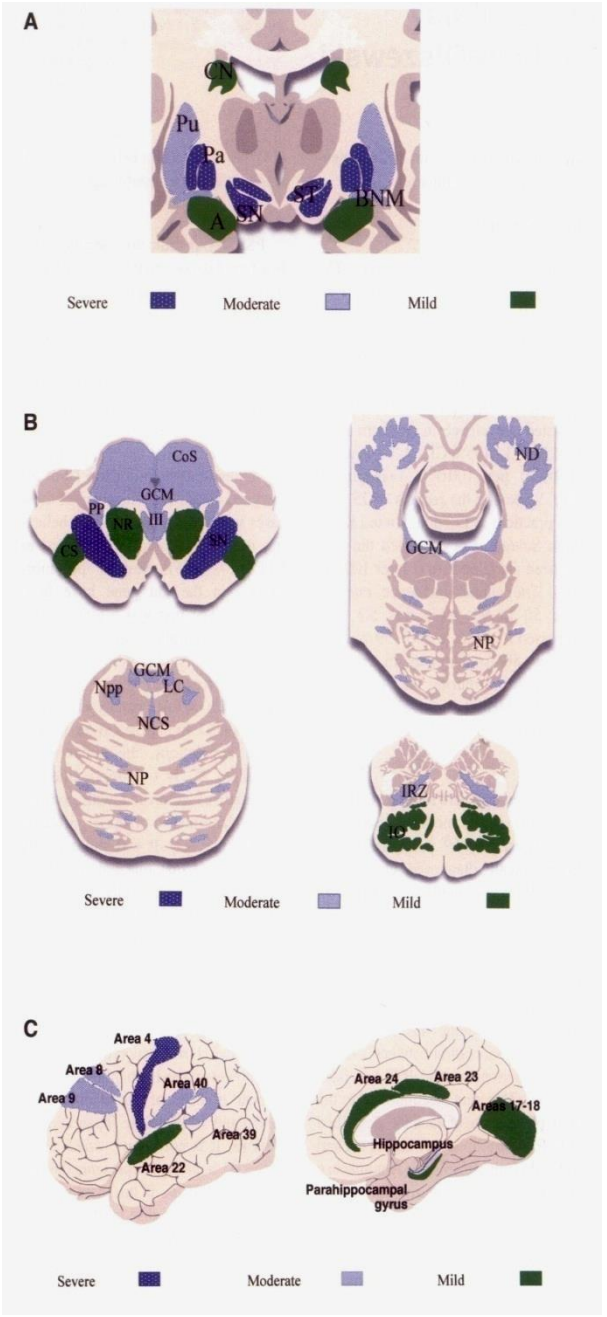
Progressive Supranuclear Palsy



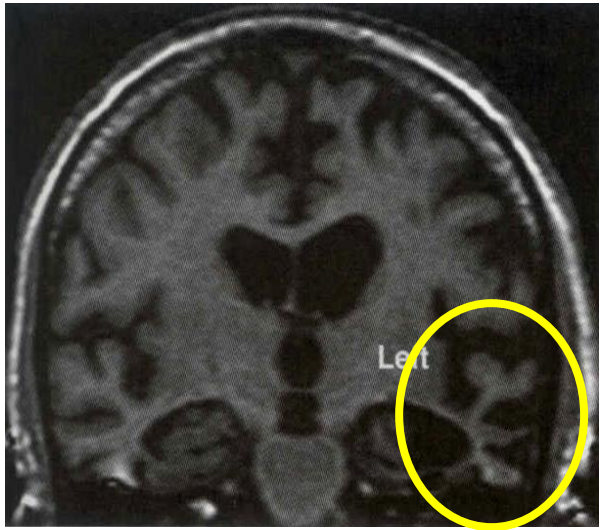


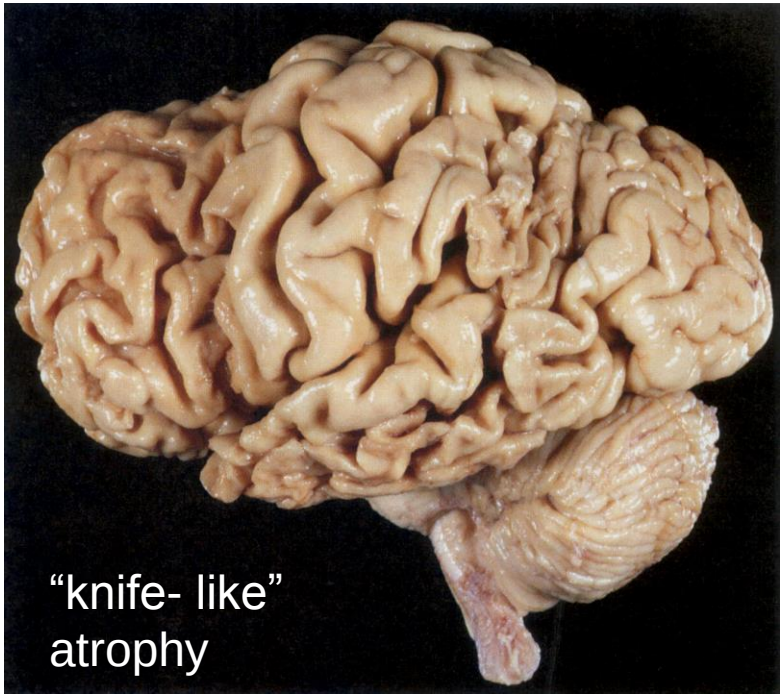


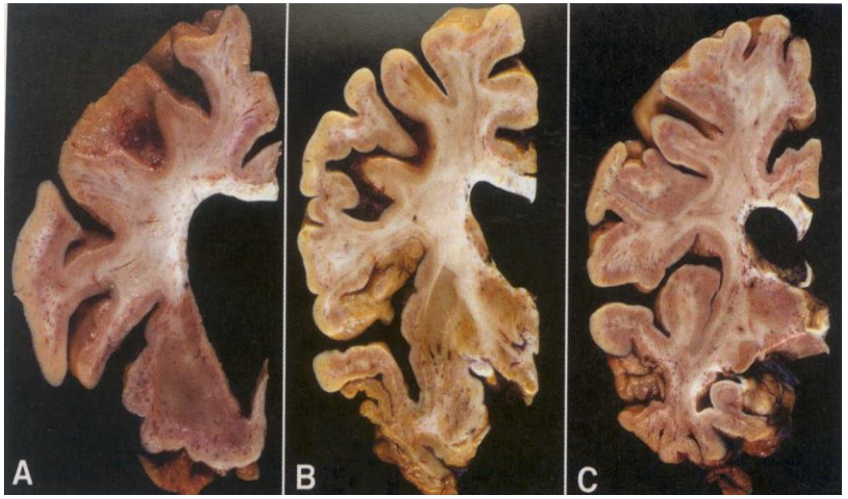
• S-R-O Syndrome; Midbrain (SN) degeneration; Neuronal Inclusions (*Tau*)

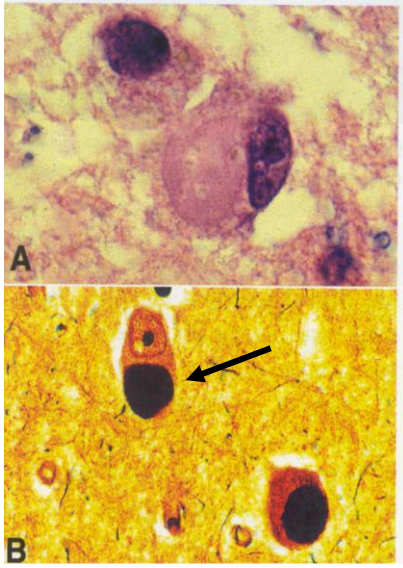


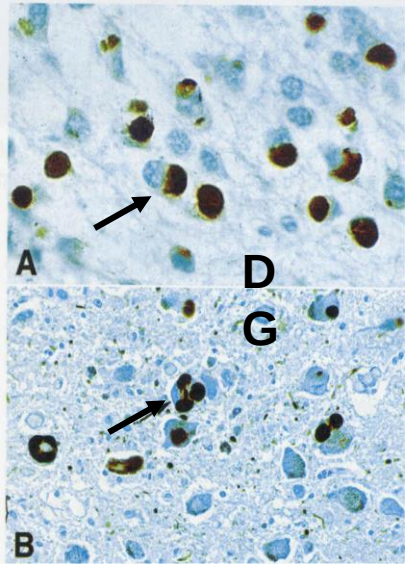
Pick's Disease







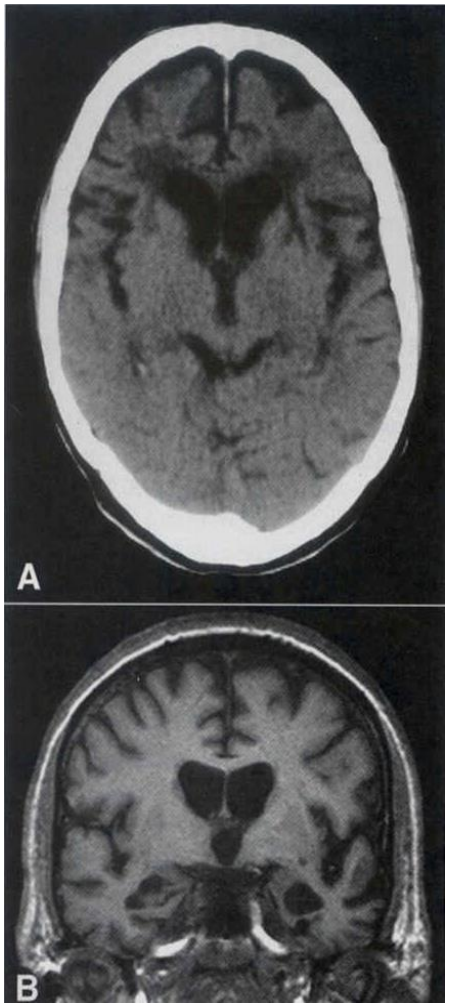


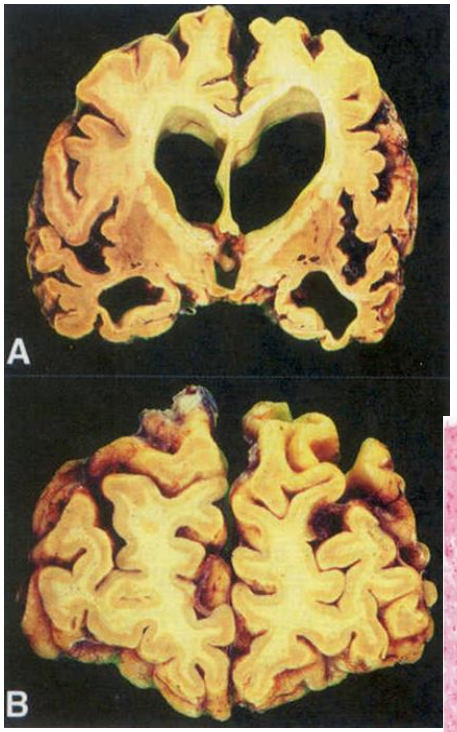


Tauopathies- CBD, PSP and Pick's

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



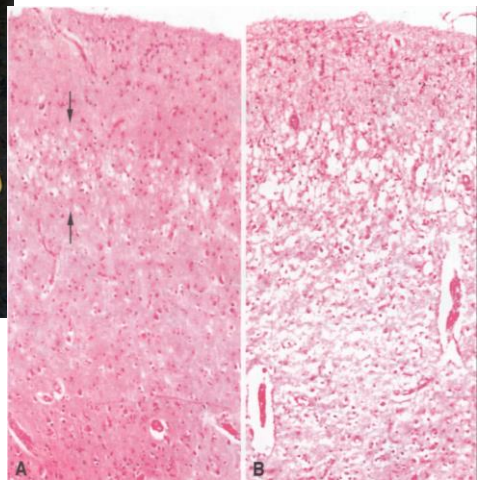


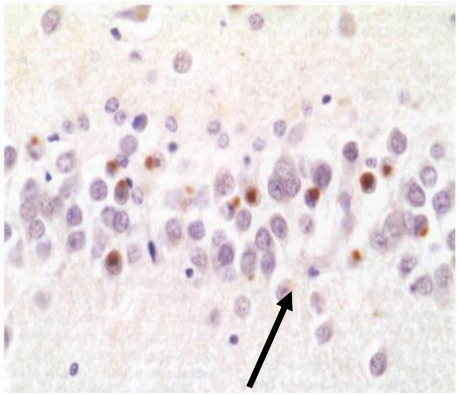
“Progranulin”

Most mutations null alleles, FTD results from PGRN haploinsufficiency

FTLD: Tau –ve

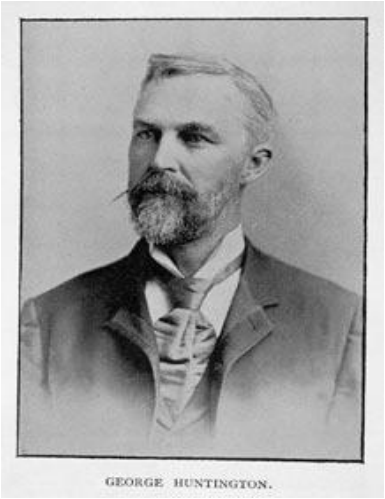
- Originally all as Pick’s disease
- 10-15% of all dementias
- Clinical presentation FTD, semantic dementia, primary aphasia, corticobasal-like syndrome
- Subtypes- FTLD, FTLD-U, FTLD-MND
- Marked frontotemporal atrophy
- Neuronal loss and astrogliosis
- Progranulin (PGRN) cases +ve for TDP-43





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

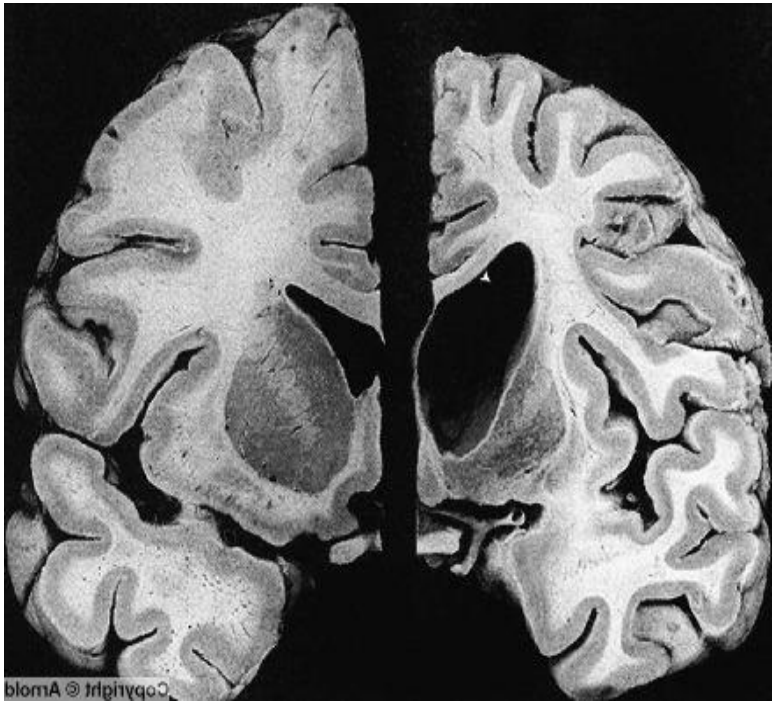
Huntington's Disease (HD)

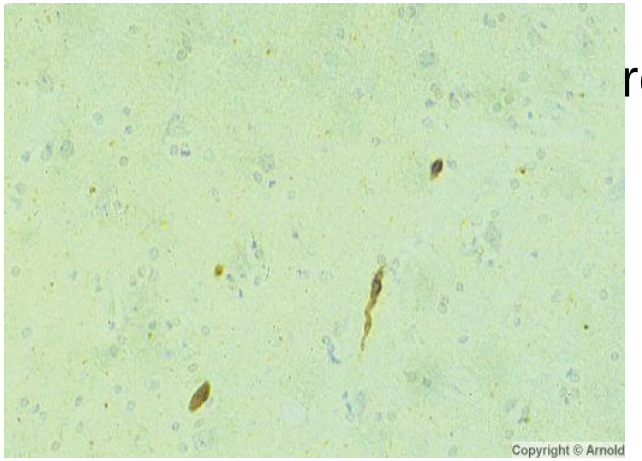


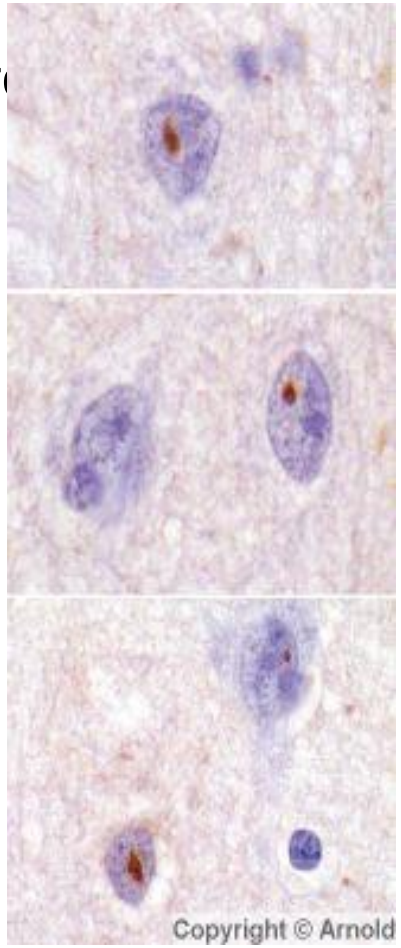
George Huntington 1850-1916

- 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

Huntington's Disease- pathology

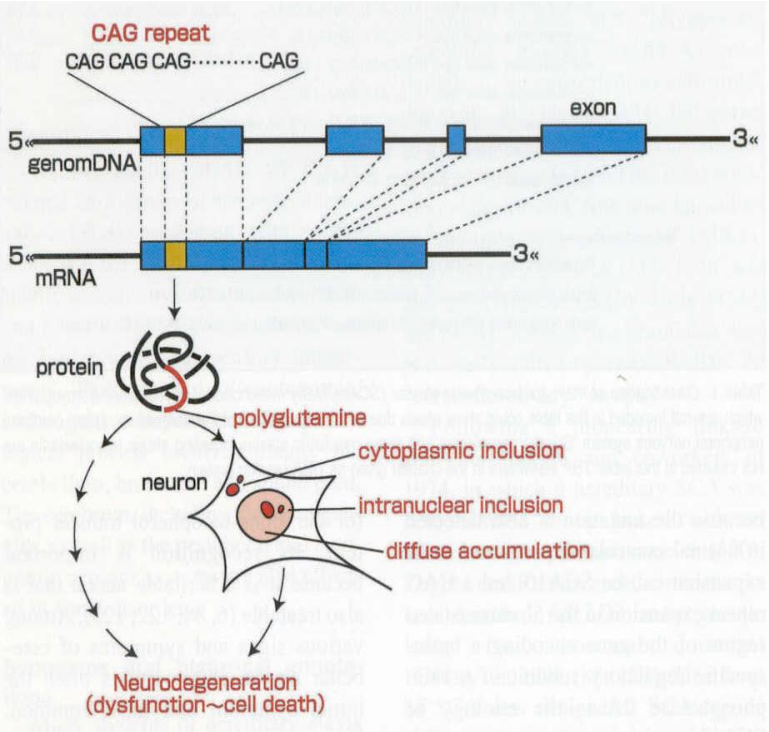


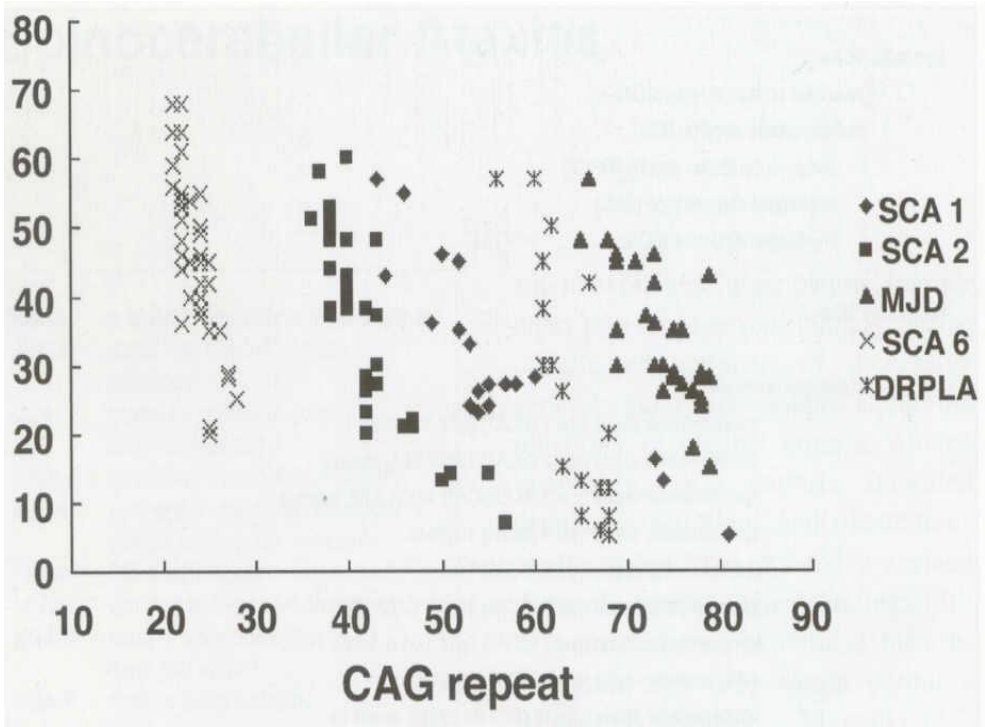




- HD patients exhibit severe caudate and considerable putaminal atrophy due to loss of medium spiny neurones.
- Anti-ubiquitin staining reveals abnormal cortical neurites in wide distribution.

HD and Polyglutamine (PG) pathogenesis





PG domains lead to cytoplasmic inclusions. Huntingtin has many roles- protein trafficking, vesicle transport, postsynaptic signaling, transcriptional regulation, and apoptosis-multiple intracellular pathways are disrupted.

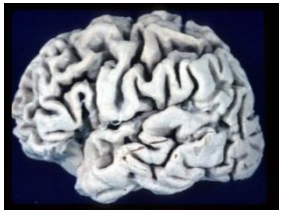
- Inverse correlation between age of onset and CAG repeat numbers.

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



Prion Disorders

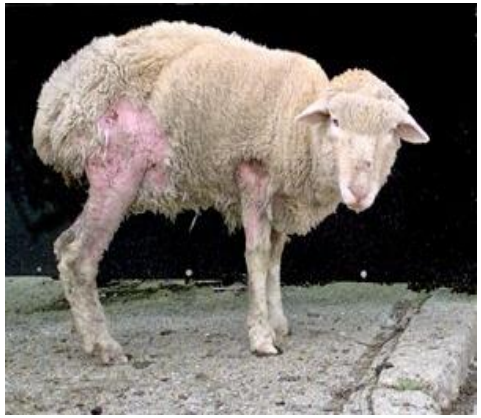
The Nobel Prize in Physiology or Medicine 1997

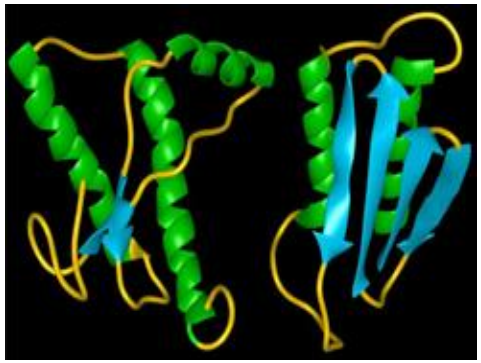
Stanley Prusiner, Born 1942

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

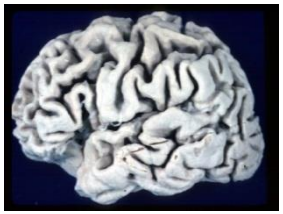
Carlton Gadjusek, Nobel Prize in 1976- Kuru Studies

- 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

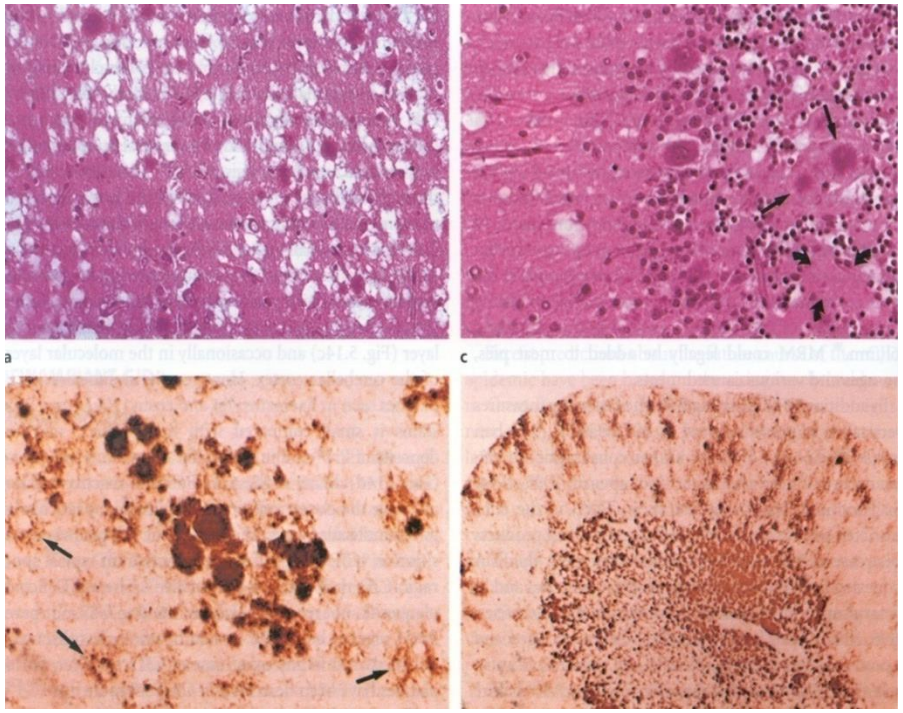


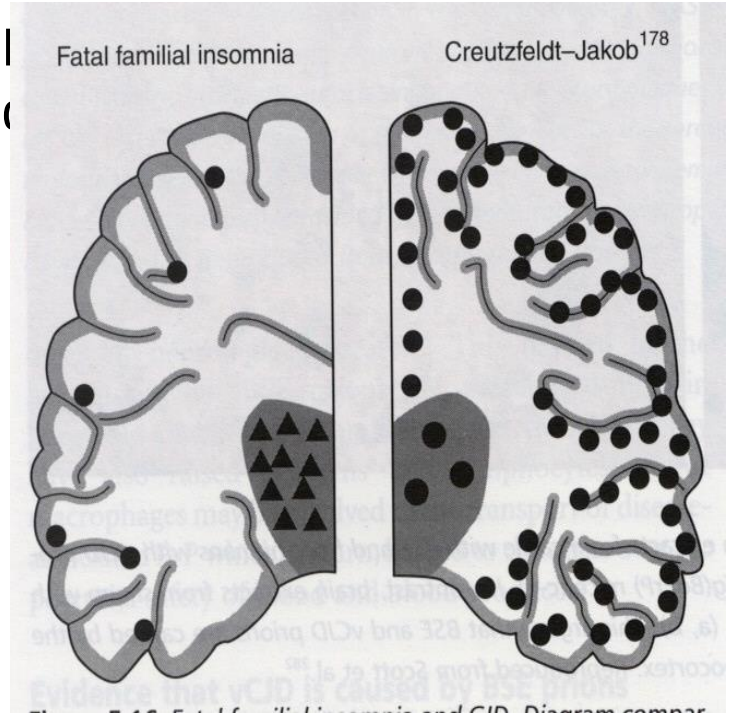


The normal (left) and disease-carrying forms of human prion protein with beta-strands in blue and alpha-helices in green



Pathology of Prion Disorders





- CJD, FFI and nvCJD as Prion disorders; Severe atrophy may involve all lobes; Spongiform change; Florid prion plaques (with angiopathy). Sometimes restricted regional pathology

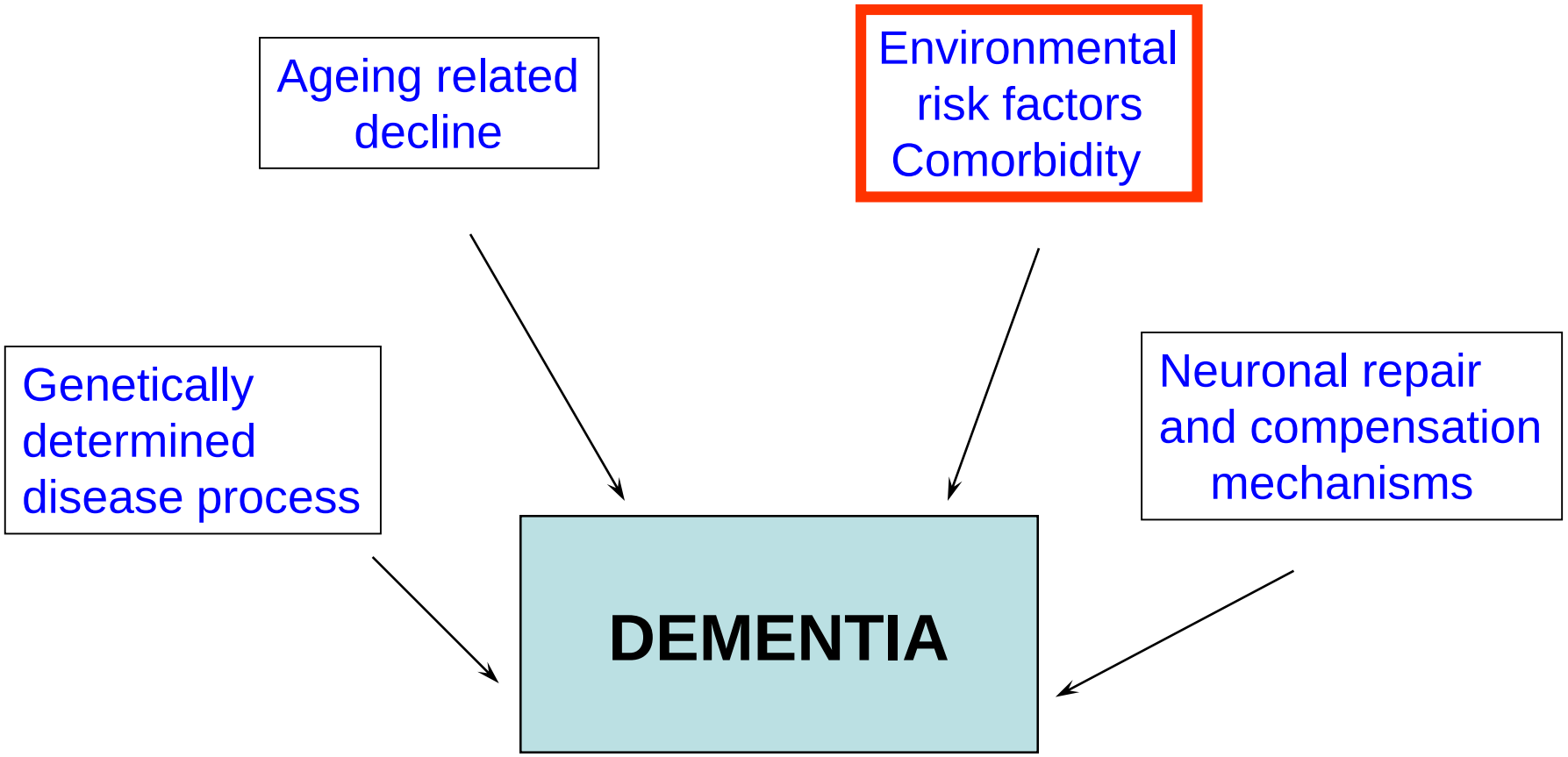
Pathological Expression of Disease: Disorders of protein accumulation or proteinopathies

- 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)

Processes influencing clinical expression of dementia

Additional opportunities for interventions



Learning Objectives

Overview of Neuropathology of Dementia

- Ageing related decline 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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- **Neuropathology, Newcastle NHS Trust**

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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)

Asante Sana!

The IDEA study team

- Stella-M Paddick
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