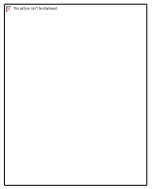
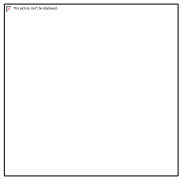
Post-Stroke Cognitive Neurology in the SSA Context





8th Regional Teaching Course in Sub-Saharan Africa
Maputo, Mozambique , 10 – 12 November 2016

Raj N Kalaria

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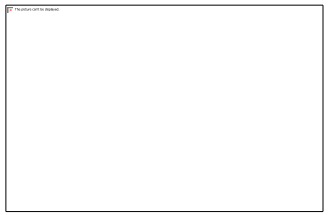
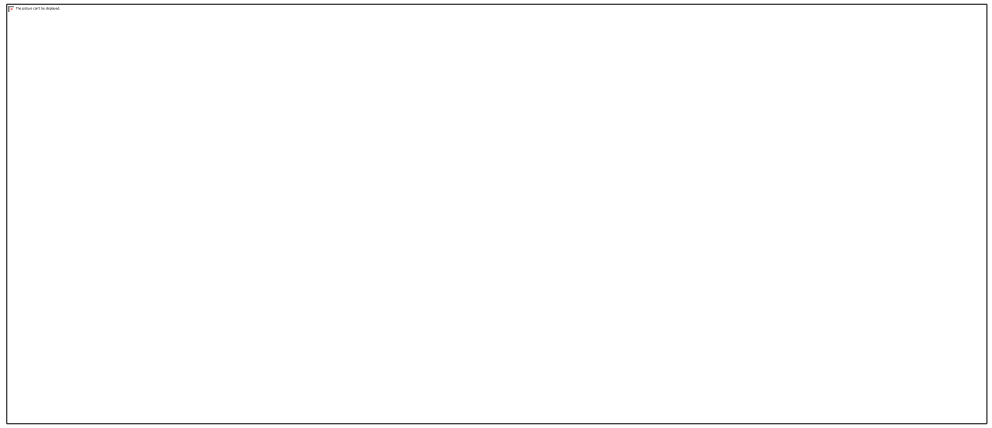
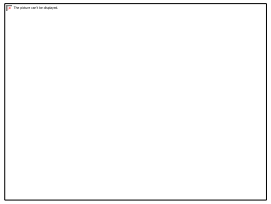
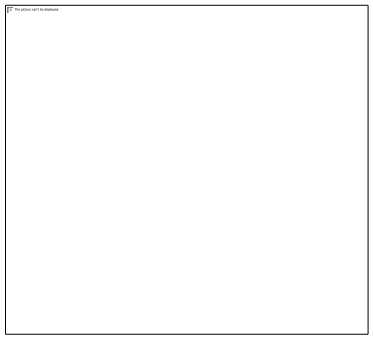
Newcastle Centre for Brain Ageing and Vitality





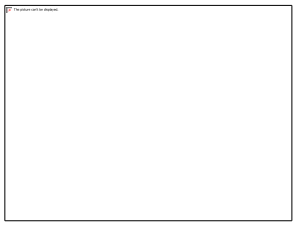


Newcastle University Campus for Ageing and Vitality



- Newcastle Brain Tissue Resource (NBTR)
- NIHR Biomedical Research Centre for Age Related Diseases (NBRB) and NE DenDRoN
- H Wellcome Laboratories for Biogerontology
- Clinical Ageing Research Unit (CARU)
- Newcastle Magnetic Resonance Centre (NMRC)

(old Newcastle General Hospital site)



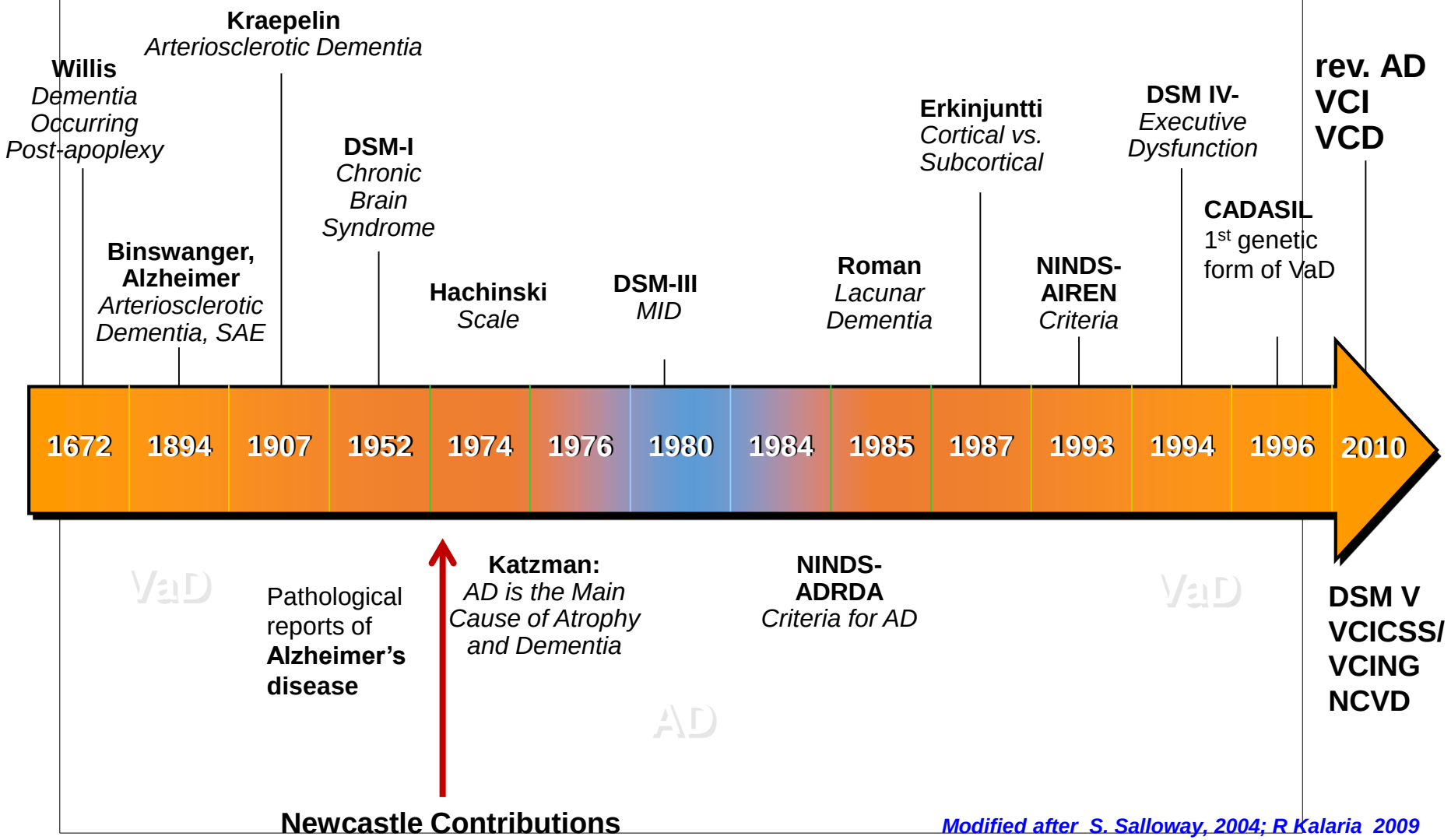
Institute for Ageing
Newcastle University

Plan: Cognitive Function after Stroke

Overview

- Introduction: Prevalence, Types and Classification
- Vascular Cognitive Impairment, VaD and SIVD
- Neuropsychometric assessment post-stroke
- **Newcastle and Ibadan (Nigeria) COGFAST studies**
  - Clinical and neuropsychological aspects
  - Cognitive Function in SVD, Dementia: Medial Temporal Lobe Atrophy (Hippocampus) and Frontal Lobe atrophy
  - Pathophysiology of Leukoencephalopathy, White matter changes
  - Post-stroke and VaD in SSA
- Take home message

The VaD-AD pendulum

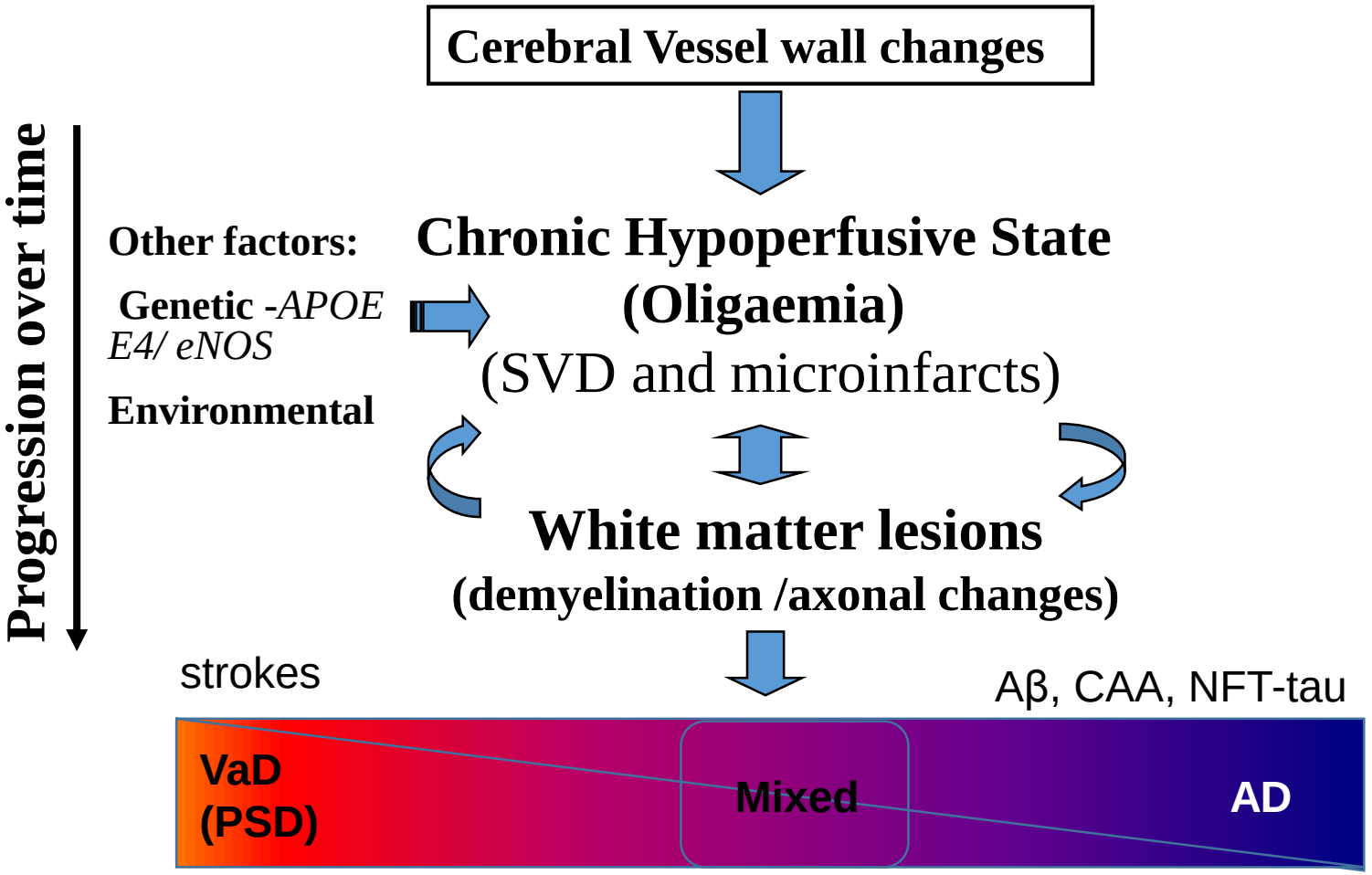


Modified after S. Salloway, 2004; R Kalaria 2009

Vascular Factors and Neurodegeneration

Vascular disease risk factors

hypertension, diabetes, dyslipidemia, obesity, atherosclerosis, CHD



Early Role of Vascular Dysregulation in Dementia and AD

Y Iturria-Medina et al , Nature Communications ,2016

Analysis of >7,700 brain images and tens of plasma and CSF biomarkers from ADNI;

Results suggest intra-brain vascular dysregulation is an early pathological event during disease development

High abnormality levels also observed for specific proteins associated with the vascular system's integrity

Vascular Factors in Dementia: What is the epidemiological and clinical evidence?

- Vascular disease risk during mid-life associated with dementia and AD; **hypertension** > dyslipidemia (high cholesterol) ≥ diabetes > hyperhomocysteinaemia > atrial fibrillation…obesity, smoking
- Strokes increase w/ age and dementia risk; AD risk by 3-fold
- Carotid atherosclerosis increases risk of AD
- Vascular risk factors promote conversion of MCI to AD
- Cardiovascular medications delay functional or slow decline in AD; statins and anti-hypertensives (beta-blockers)
- Vascular factors predict rate of progression in AD; some factors such as high cholesterol, atrial fibrillation and angina

Skoog I et al, Lancet 1996; Hofman A et al, Lancet 1997; Clarke R et al, Arch Neurol 1998; Breteler MM Neurobiol Aging 2000; Kalaria RN Neurobiol Aging 2000; Kivipelto M et al, BMJ 2001; Ott A et al, Neurology 1999; Rosenberg PB et al, Am J Geriatr Psychiatry 2008; *Khachaturian A et al, Arch Neurol 2006; Mielke MM et al, Neurology 2007; Helzner EP et al, Arch Neurol 2009; Deschanitre Y et al, Neurology; 2009; Purnell C et al, ADAD J 2009; Li J et al, Neurology 2011; Bettermann K et al, J Stroke Cerebrovascular Dis 2012;*

Evidence from longitudinal studies on Blood Pressure and Dementia

Previous high blood pressure

- The H70-study, Gothenburg, Sweden
  Skoog et al. Lancet 1996

5-15 years

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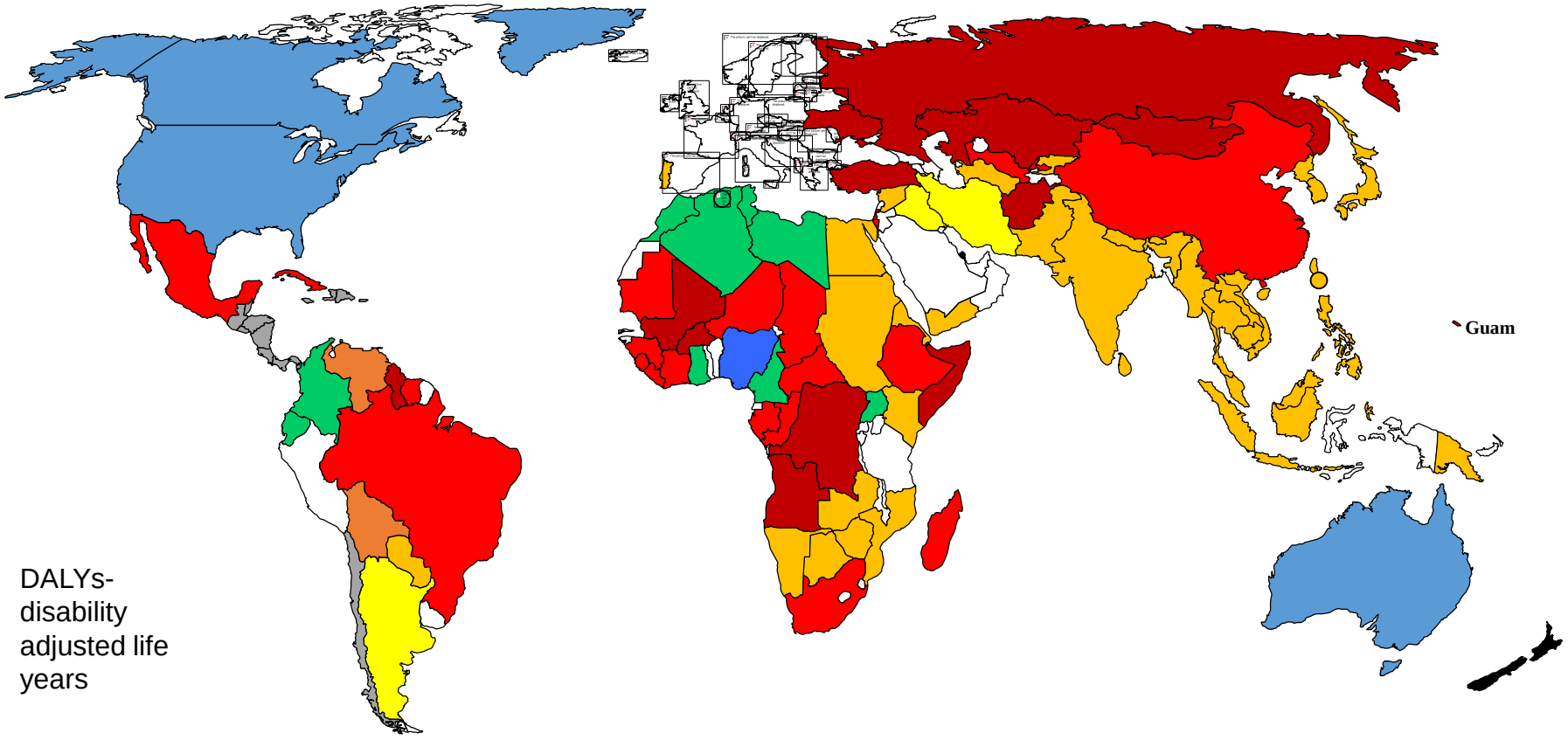
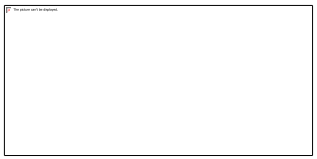
World-wide Stroke Incidence

Incidence decreased but total strokes increased worldwide



DALYs-disability adjusted life years

In HIC overall incidence, mortality and DALYs of all stroke types have declined in both younger (<75 years) and older (≥75 years) age groups, in LMIC these have increased (*Krishnamurthi RV et al, 2014; Feigin et al, 2014*)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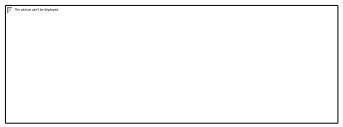
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Classification of Stroke

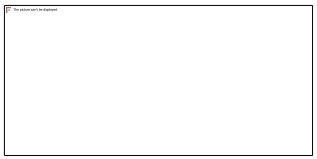
(Oxford Community Stroke Project (OSCP); also known as the Bamford or Oxford classification

Relies primarily on the initial symptoms; based on the extent of the symptoms, the stroke episode is classified as:

- **Total anterior circulation stroke (TAC)**
- **Partial anterior circulation stroke (PAC)**
- **Lacunar stroke (LAC)**
- **Posterior circulation stroke (POC)**

The type of stroke is then coded by adding a final letter to the above:
I – for infarct (e.g. TACI)
H – for haemorrhage (e.g. TACH)
S – for syndrome; intermediate pathogenesis, prior to imaging (e.g. TACS)

Entities predict extent of the stroke, area of brain affected, underlying cause, and the prognosis.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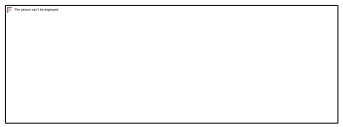
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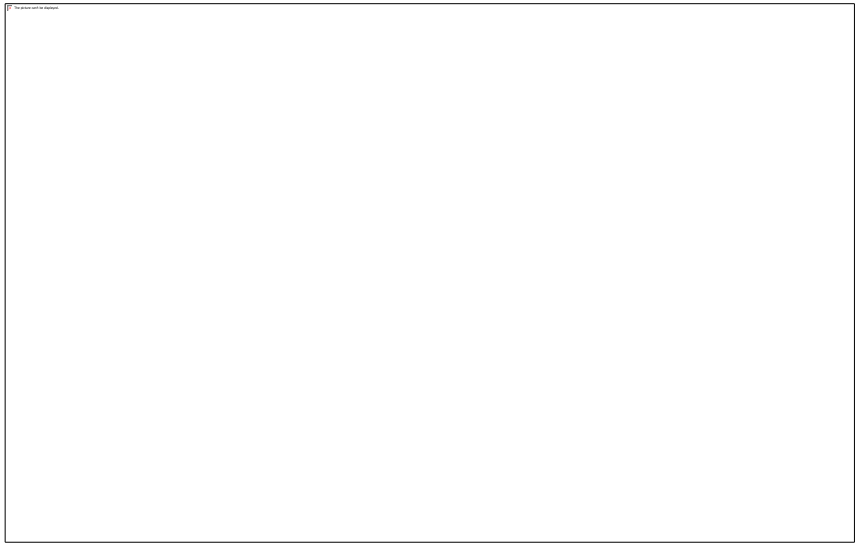
Frequency of Cognitive Impairment and Dementia after Stroke Injury

What type(s) of dementia do stroke survivors develop?

Cognitive Function after Stroke



Pooled cumulative incidence of post-stroke dementia excluding pre-stroke dementia in hospital-based cohorts Pooled cumulative incidence of PSD excluding pre-stroke dementia in hospital-based cohorts of any stroke (first-ever or recurrent stroke)

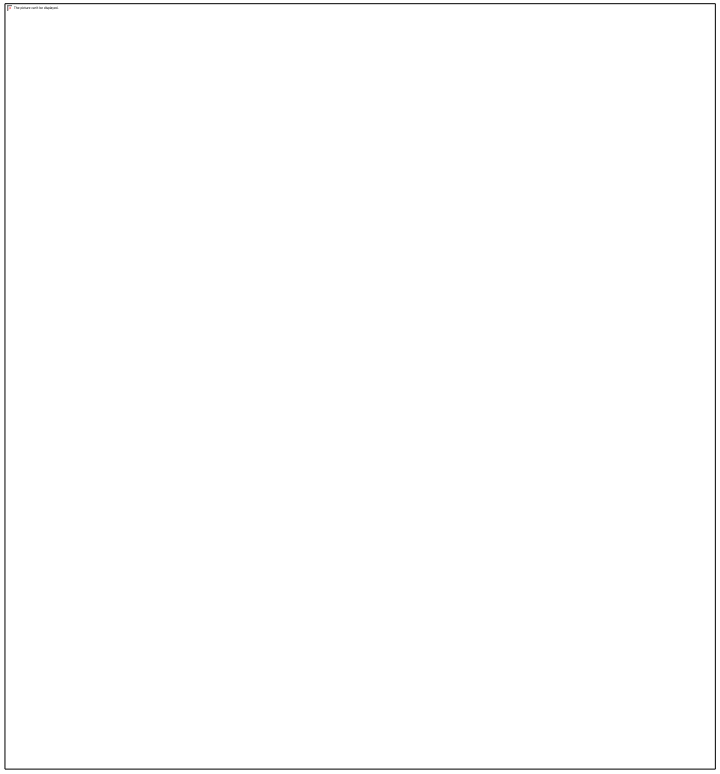
Causal role of stroke, optimum acute stroke care and secondary prevention important in reducing the burden of cognitive impairment

- Pre-stroke dementia ranged 9-14%
- PSD (≤1 year) rates ranged 7-41% in hospital-based studies of recurrent stroke
- Incidence of dementia >1st year was 3% per yr
- MTLA, female gender, family history of dementia strongly associated with pre-stroke dementia
- Characteristics and complications of stroke and multiple lesions in time and place strongly associated with PSD
- Interpretation: I0% of patients had dementia before first stroke, 10% developed new dementia soon after first stroke, and >third had dementia after recurrent stroke.

Pendlebury ST and Rothwell P, TLN, 2009

Cognitive Impairment in Lacunar Stroke

Makin SDJ, et al. J Neurol Neurosurg Psychiatry 2013;84:893–900.



- **24% had MCI or PSD**
- **Similar proportions: lacunar and non-lacunar strokes had MCI or dementia (1-4 yrs after stroke)**
- **Prevalence: 20% dementia after lacunar stroke**
- **Incidence: 37% MCI or dementia**

- **Limitations: short follow-up, subtype classification methods and confounding factors**

- **Conclusions: cognitive impairment common after lacunar strokes.**
- **New prospective studies required with accurate stroke subtyping to assess long term outcomes while accounting for co-factors**

OR of cognitive impairment in lacunar against cortical stroke for studies with particular characteristics

Neuropsychometric Assessment

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

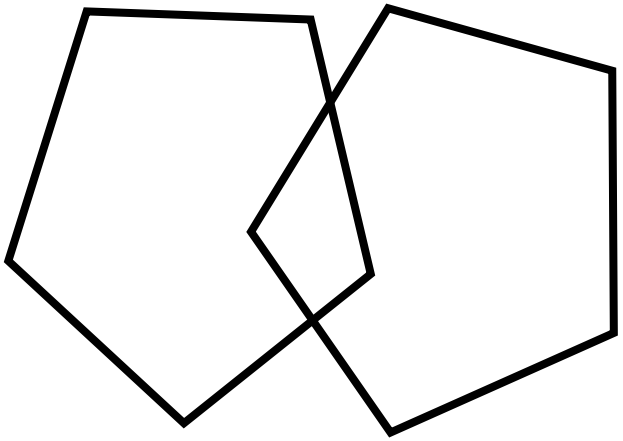
- Neuropsychometric batteries may contain several components to test different cognitive abilities, e.g. CANTAB, CAMCOG, ADAS-Cog etc.

- The Mini-Mental State Examination (MMSE)- widely used. Montreal Cognitive Assessment (MoCA) test.

- Value of informant questionnaires

Mini-Mental State Examination

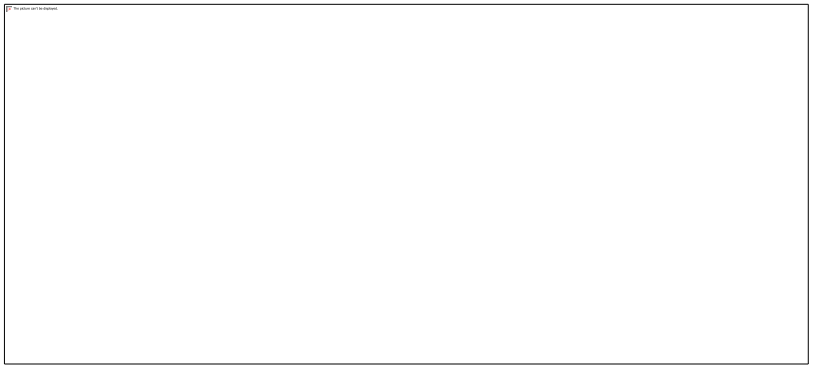
- MMSE is a short test which measures general cognitive status including short-term memory (Folstein, et al, 1975)

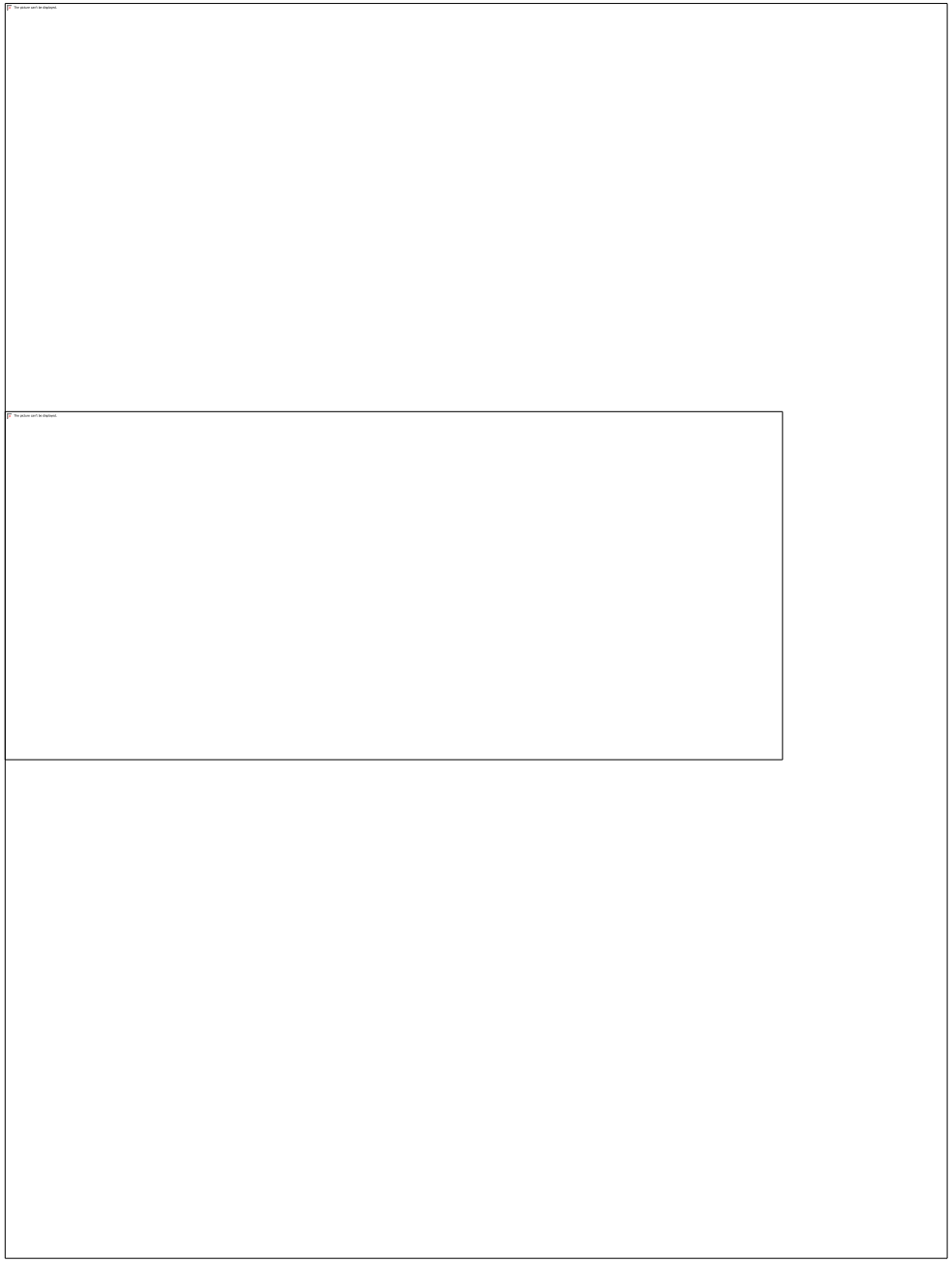


- MMSE includes tests for orientation (e.g. year, season, etc.), registration, attention and calculation, recall, and language

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

Montreal Cognitive Assessment (MoCA)





•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

Cognitive Function after Stroke

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

MoCA, ACE-R, and MMSE Versus the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery After TIA and Stroke

Sarah T. Pendlebury, Jose Mariz, Linda Bull, Ziyah Mehta and Peter M. Rothwell

Stroke. 2012;43:464-469; originally published online December 8, 2011;
doi: 10.1161/STROKEAHA.111.633586
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

MoCA = Montreal Cognitive Assessment (30 point test)

ACE-R= Addenbrooke's Cognitive Examination– Revised (100 point test)

MoCA and ACE-R had good sensitivity and specificity for MCI defined using the NINDS-CSN Battery (Hachinski et al, 2006) 1 year after TIA and stroke but MMSE showed a ceiling effect

Vascular Cognitive Impairment

Vascular = all causes of CVD

(cardiovascular also)

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

(VaD and MCI)

VCI Harmonisation Guidelines

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association
A Division of American Heart Association

Original Contributions

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

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

Background and Purpose—One in 3 individuals will experience a stroke, dementia or both. Moreover, twice as many individuals will have cognitive impairment short of dementia as either stroke or dementia. The commonly used stroke scales do not measure cognition, while dementia criteria focus on the late stages of cognitive impairment, and are heavily biased toward the diagnosis of Alzheimer disease. No commonly agreed standards exist for identifying and describing individuals with cognitive impairment, particularly in the early stages, and especially with cognitive impairment related to vascular factors, or vascular cognitive impairment.

Methods—The National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) convened researchers in clinical diagnosis, epidemiology, neuropsychology, brain imaging, neuropathology, experimental models, biomarkers, genetics, and clinical trials to recommend minimum, common, clinical and research standards for the description and study of vascular cognitive impairment.

Results—The results of these discussions are reported herein.

Conclusions—The development of common standards represents a first step in a process of use, validation and refinement. Using the same standards will help identify individuals in the early stages of cognitive impairment, will make studies comparable, and by integrating knowledge, will accelerate the pace of progress. (*Stroke*. 2006;37:2220-2241.)

VCI: Neuropsychological Tools

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association
A Division of American Heart Association

National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards
Vladimir Hachinski, Costantino Iadecola, Ron C. Petersen, Monique M. Breteler, David L. Nyenhuis, Sandra E. Black, William J. Powers, Charles DeCarli, Jose G. Merino, Raj N. Kalaria, Harry V. Vinters, David M. Holtzman, Gary A. Rosenberg, Anders Wallin, Martin Dichgans, John R. Marler and Gabrielle G. Leblanc
Stroke 2006;37;2220-2241; originally published online Aug 17, 2006;
DOI: 10.1161/01.STR.0000237236.88823.47
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

VCI may include all cognitive domains, but there is likely to be a preponderance of so called "executive" dysfunction (i.e. slowed information processing, impairments in the ability to shift from one task to another, and deficits in ability to hold and manipulate information or working memory)

Proposed 30-Minute and 5-Minute Neuropsychological Protocols

30-Minute Test Protocol

- Semantic Fluency (Animal Naming)
- Phonemic Fluency (Oral Word Association Test)
- Digit Symbol-Coding from the Wechsler Adult Intelligence Scale, Third Edition
- Hopkins Verbal Learning Test
- Center for Epidemiologic Studies-Depression Scale
- Neuropsych Inventory, Questionnaire Version (NPI-Q)
- Supplemental: MMSE, Trail Making Test

5-Minute Protocol

- MoCA subtests
- 5-Word Memory Task (registration, recall, recognition)
- 6-Item Orientation
- 1-Letter Phonemic Fluency
- Supplemental: Remainder of the MoCA, Semantic Fluency (Animal Naming),
- Trail Making Test, MMSE (to be administered at least 1 hour before or after the above tests).

Cognitive Function after Stroke

Neuropsychological Test Criteria: General considerations

- **Quality of the standardization sample**
- **Psychometric qualities**
- **Portability**
- **Brevity**
- **Cost**
- **Ease of use**
- **Domain specificity (for 1-hour battery)**
- **Availability of multiple forms**
- **International or cross-cultural capability**
- **The lack of ceiling and floor effects**
- **Previous use of the test in VCI samples**

Trialled and Tested in sub-Saharan Africa!

After Hachincki V et al, 2006

Diagnosis of VaD: NINDS-AIREN Criteria

Dementia
- Impaired memory
- ≥ 2 other cognitive domains impaired

Cerebrovascular disease
- Neurological exam
- Neuroimaging

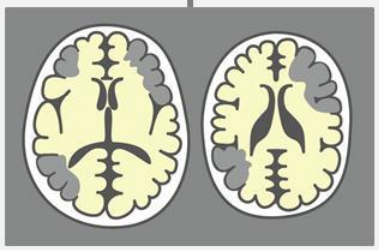
Probable/Possible diagnosis
- Temporal relationship between CVD and dementia
- Abrupt onset / stepwise progression
- Absence of disorders that could account for deficits (eg, AD)

Diagnosis of VaD

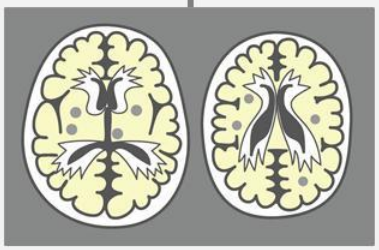
Definitive diagnosis by autopsy?

Román GC, et al. *Neurology.* 1993;43:250-260.

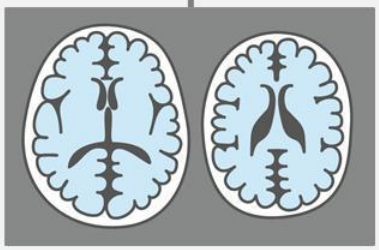
Vascular Dementia



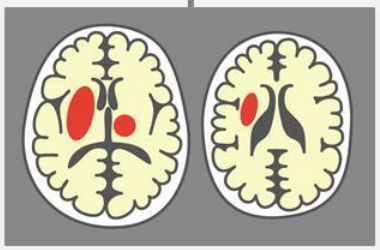
multi-infarct dementia



Small artery lesions

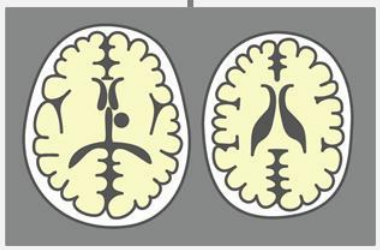


Hypoperfusion

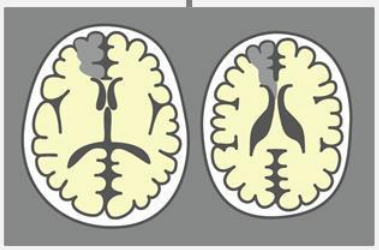


Brain hemorrhage

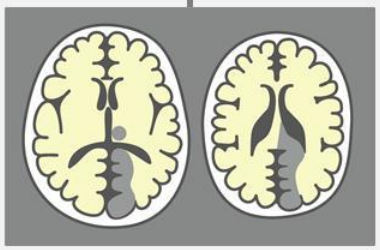
Strategic Lesions



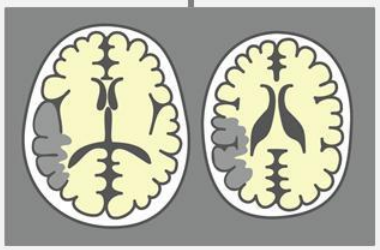
Thalamus



ACA territory



PCA territory



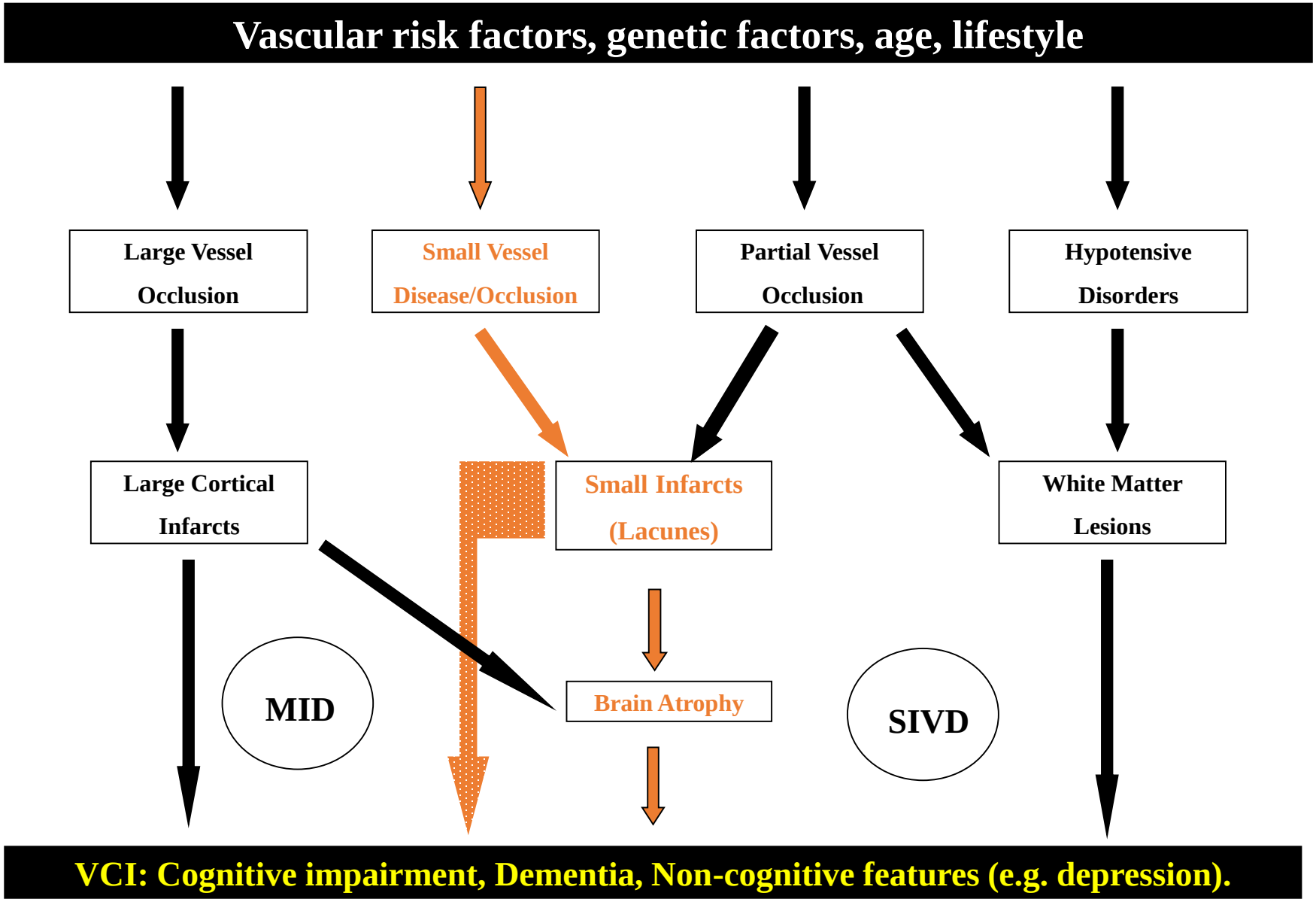
Angular gyrus

NINDS-AIREN criteria Roman et al. Neurology 43:250-260, 1993

Towards Clinicopathological Criteria and Mechanisms of Dementia in after Stroke (VaD)?

Dogma, problems, pitfalls

Mechanisms: Cerebral SVDs and Dementia



After O'Brien J et al, 2003

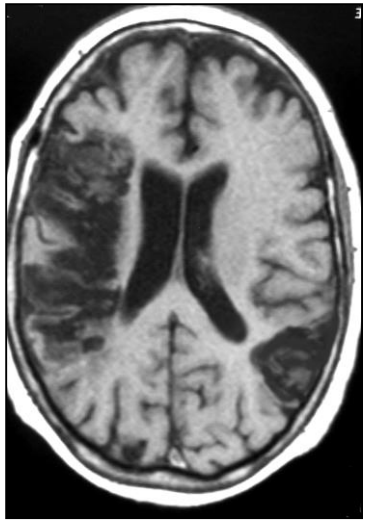
Cerebral Small Vessel Disease: Clinical Features

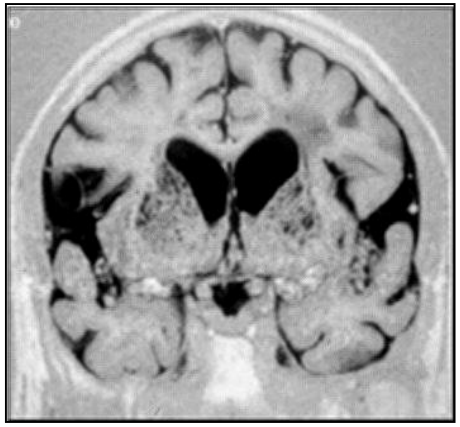
Varied manifestations

- Much of SVD can be clinically silent
- Sudden-onset stroke symptoms or syndromes e.g. lacunar syndrome
- Mostly covert neurological symptoms and signs
- Motor slowing, dysarthria, short-stepped gait
- *Cognitive: Self-reported cognitive difficulties e.g. executive slowing, processing speed, forgetfulness, dementia*
- *Behavioural: apathy (20-25%), depression (20-30%)*

Heterogeneity of CVD Changes

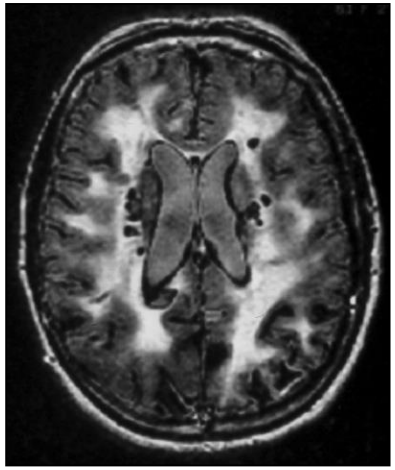
Multi-infarct dementia (MID)

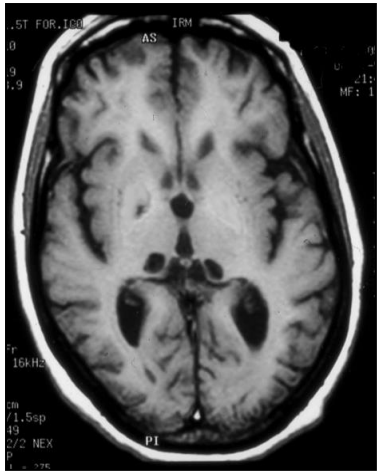




SVD - lacunar state

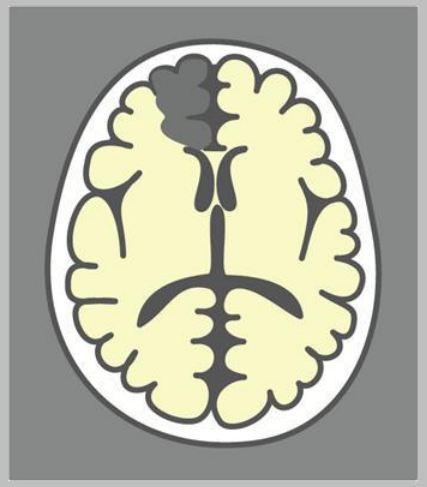
SVD -WMLs CADASIL



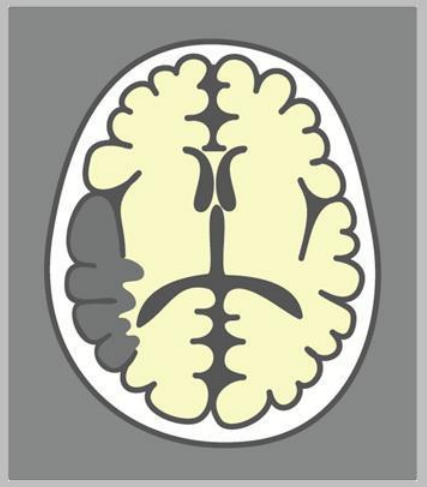


Strategic thalamic infarcts

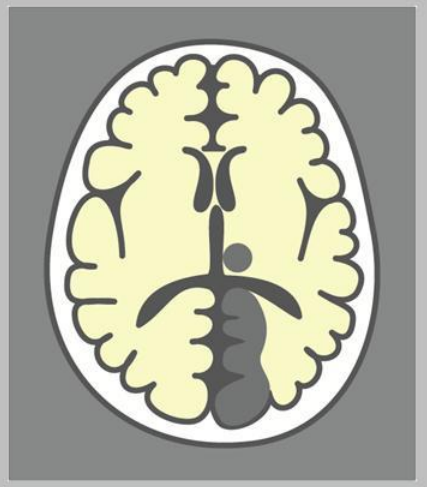
Large-vessel Disease



ACA territory

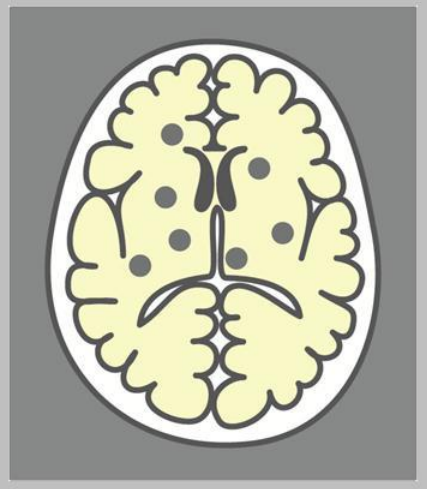


MCA territory

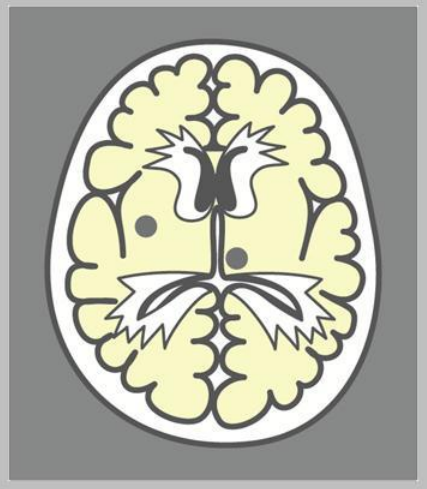


PCA territory

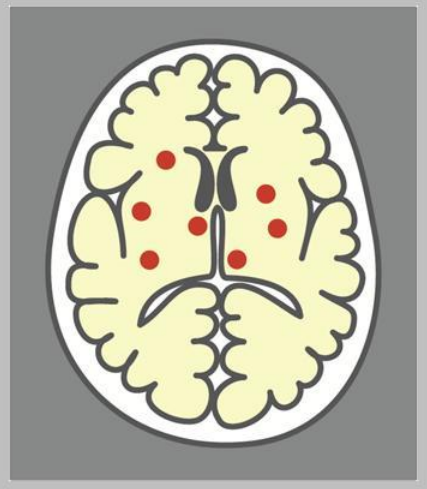
Small-vessel Disease



Lacunes



Leuko-araiosis

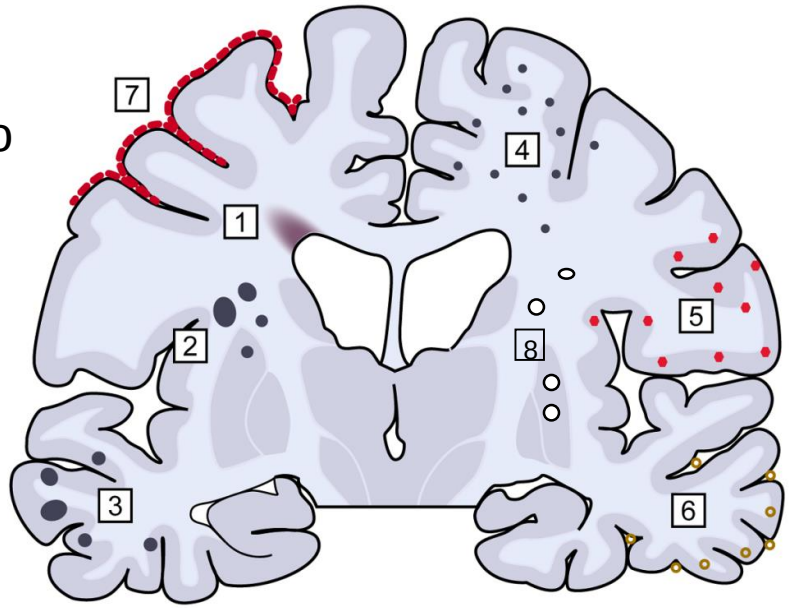


microbleeds

SVD Pathophysiology

Neuroimaging (MR)

1. Periventricular and Deep WMH
2. Lacunes and macro infarcts
3. Cortical: small infarcts
4. Subcortical: macroinfarcts
5. Cerebral Microbleeds
6. Amyloid deposition (PET)
7. Superficial siderosis
8. Perivascular spaces



Neuropathology

1. Periventricular WM changes (myelin loss)
2. Subcortical infarcts: Lacunes and macro infarcts
3. Cortical: small infarcts
4. Subcortical and cortical: microinfarcts
5. Microhaemorrhage/ haemosiderin
6. Superficial haemosiderin (some)
7. Cerebral Amyloid Angiopathy
8. Perivascular spaces

Arteriolosclerosis

Subtypes of VaD/VCI: Vascular Mechanisms and Brain Changes

Vascular mechanisms	Cortical VaD	Strategic infarct VaD	Subcortical ischemicVaD SVD
Large-vessel disease ✓	✓	×	
Cardiac embolic events	✓	✓	×
Hypoperfusion (focal or global)	✓	✓	✓
Small-vessel disease ×	✓	✓	
Clinical and Cognitive Features			
Focal neurological signs	✓	✓ / ×	×
Stepwise progression ✓	×	×	
Cognition (memory/executive)	✓	✓	✓
Changes in the brain			
Large cortico-subcortical	✓	×	×
Arterial territorial infarct	✓	✓	×
Distal field (watershed) infarct	✓	✓	×
Lacunar infarcts	×	✓	✓
Focal, diffuse WMLs ×	✓	✓	
Incomplete ischaemic injury	×	×	✓
Heterogeneity	++	+++	+

WMLs- white matter lesions

T Erinkinjuntti and R Kalaria, 2005

Accumulation of Focal Cortical Symptoms

Large-vessel disease

↓

Cortical infarcts in strategic locations

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

Cortical type of dementia

Non-Specific Disconnection of the Cortex

Small-vessel disease

↓

Diffuse white matter lesions

↓

Disruption of cortico-cortical pathways

↓

Frontal, temporal and parietal cortical deficits

Mixed cortical / subcortical type of dementia

Disruptions of Subcortico-cortical Circuits

Small-vessel disease

↓

Subcortical infarcts in strategic locations

Thalamus, caudate nucleus, internal capsule

↓

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

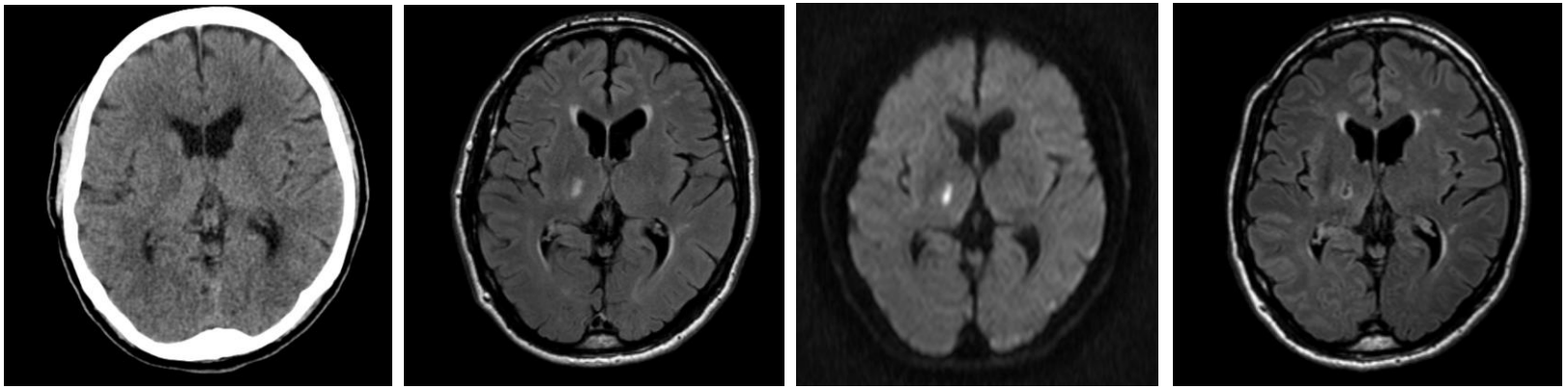
↓

Executive dysfunction Apathy Attentional deficit Personality change

Subcortical type of dementia

Neuroimaging of SVD: lacunar infarction

Male 61 yr old, lacunar infarct



CT 3 hours

MR-FLAIR 3 days

MR-DWI 3 days : ADC-low signal

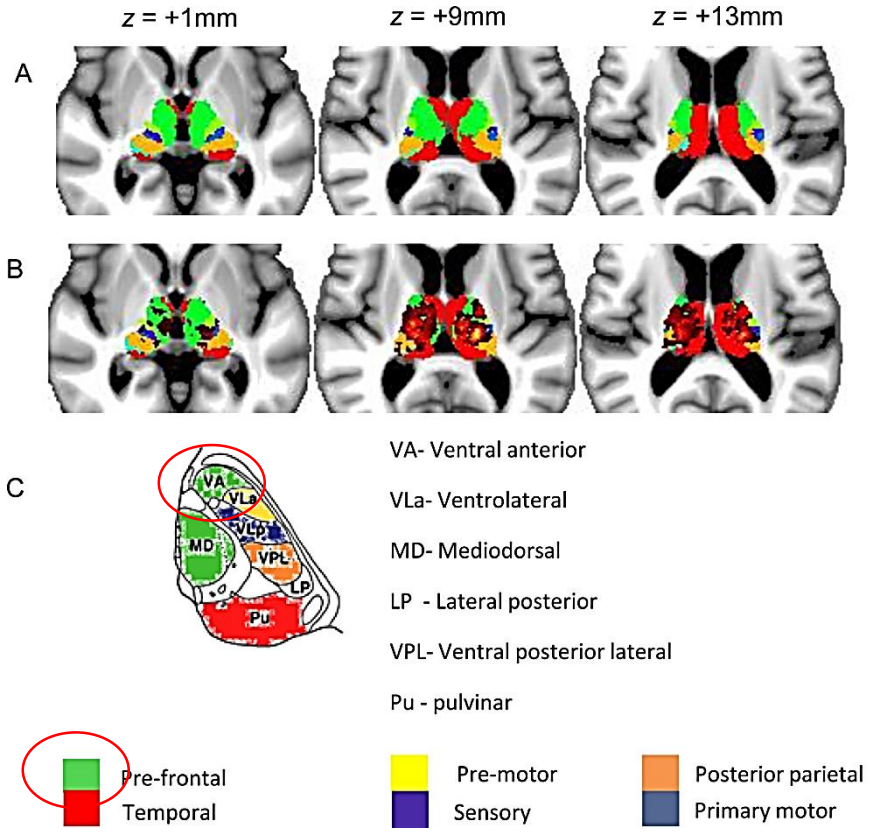
MR-FLAIR 2 years central caviatation of the infacrt → lacune

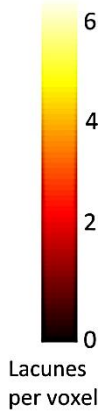
Symptoms: left side hemiparesis, dysarthria. Reported as normal, but with information later MRI a faint hypodensity discerned at lateral border of right thalamus

What Neuropsychometric changes can you predict?

Rathher than amnestic type memory impiarment features associated with frontal lobe function i.e. Executive Function tasks, processing speed, working memory are more eveident.

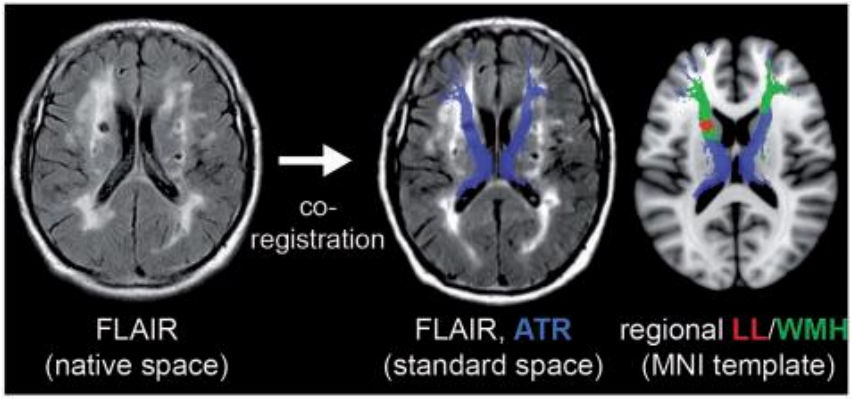
Strategic role of frontal white matter tracts in vascular cognitive impairment



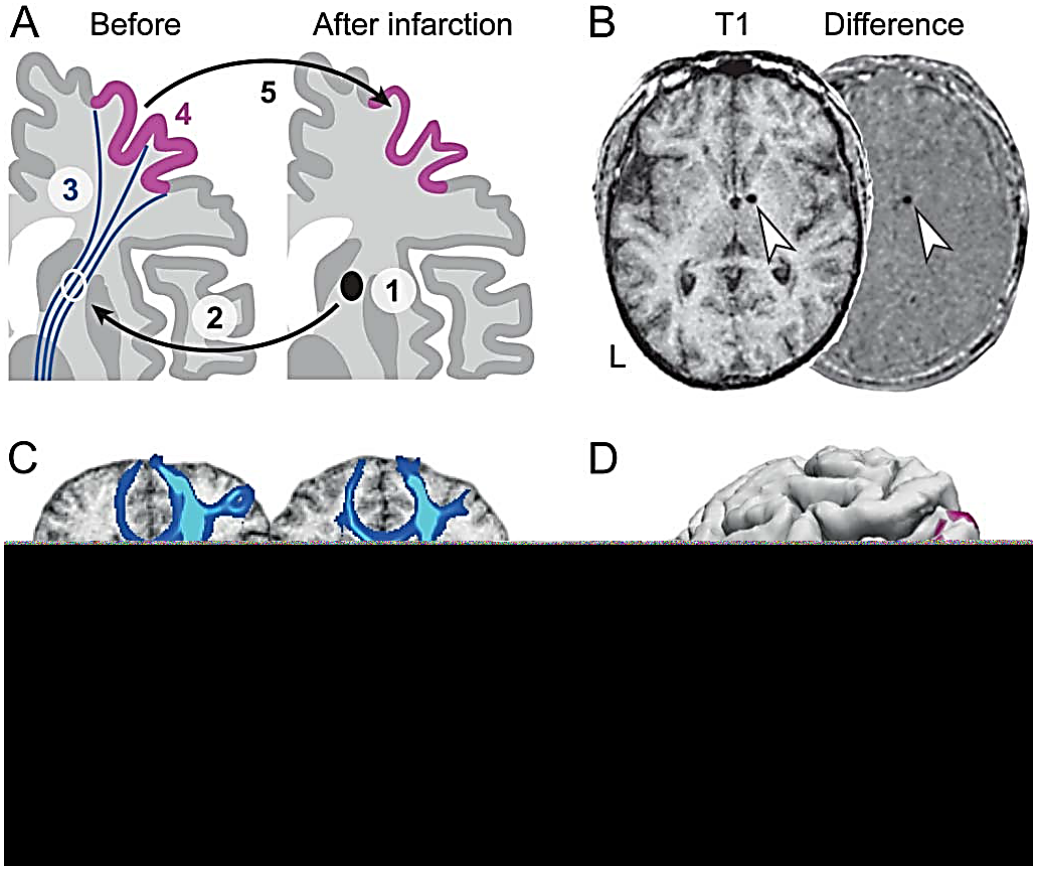


- Most prominent feature: processing speed
- Predominantly affected cognitive domain in lacunar stroke SVD and CADASIL
- Strategic locations included ***anterior parts of thalamus***, the genu and anterior limb of the internal capsule, anterior corona radiata and genu of the corpus callosum
- Interpretation: anterior thalamic radiation as a major anatomical structure impacting on processing speed.
- Strong support for a central role of frontal-subcortical circuits in SVD and VCI

Duering M et al, Brain, 2011; Benjamin et al, 2014



Secondary cortical neurodegeneration after subcortical ischemia (SVD) as a mechanism for brain atrophy



A causal relationship between incident subcortical infarcts and morphologic alterations in connected cortical regions

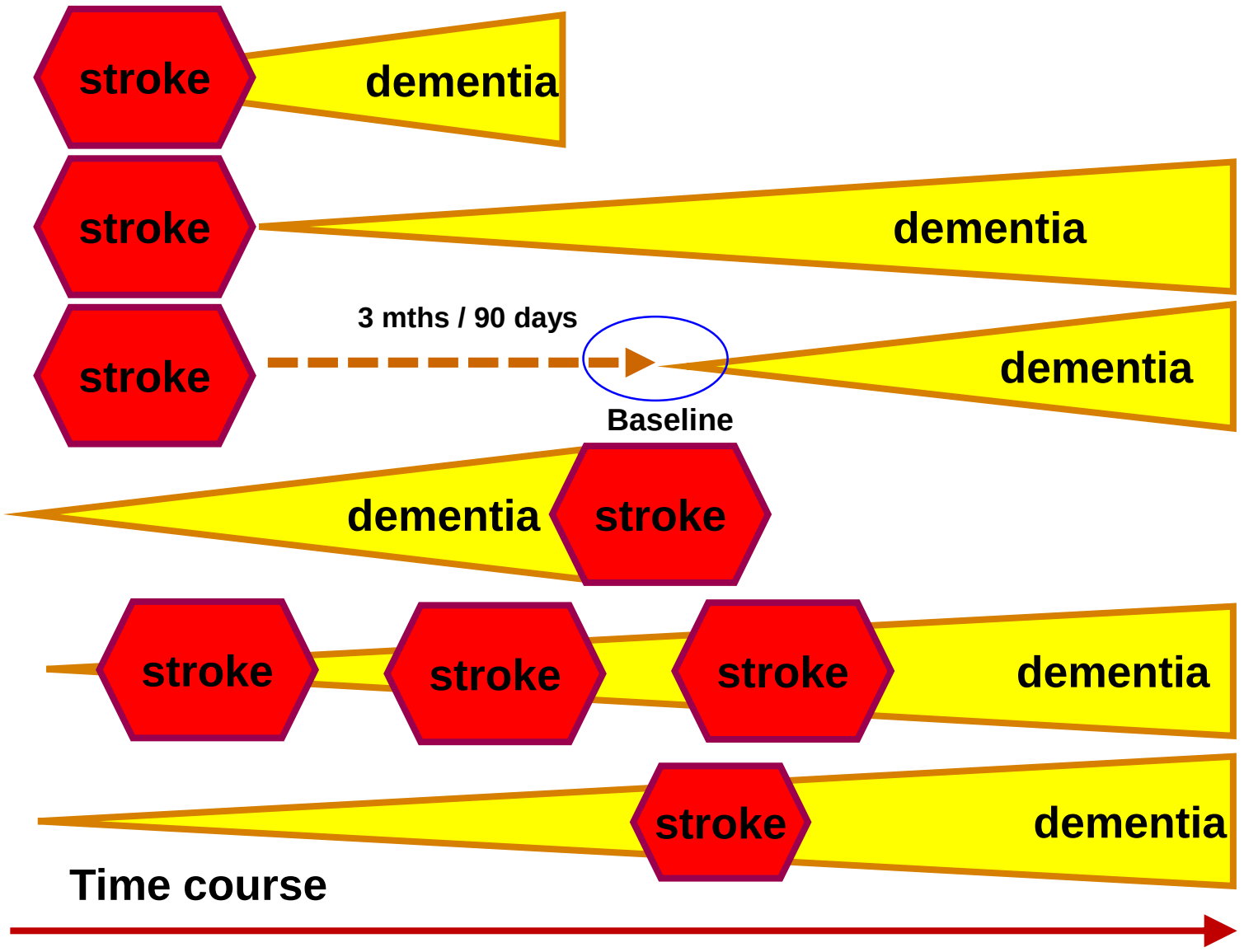
Implies a role for 2^{o} neurodegeneration within cortical GM (focal cortical thinning) after axonal damage e.g. infarct in WM

From M Duering et al, 2012

Vascular Basis for Dementia and Neurodegeneration in Stroke Survivors

What type(s) of dementia do stroke survivors develop?

Stroke and Dementia are risks for each other



Modified from K Nagata, 2007

COGnitive Function After STroke (COGFAST – Newcastle Study)

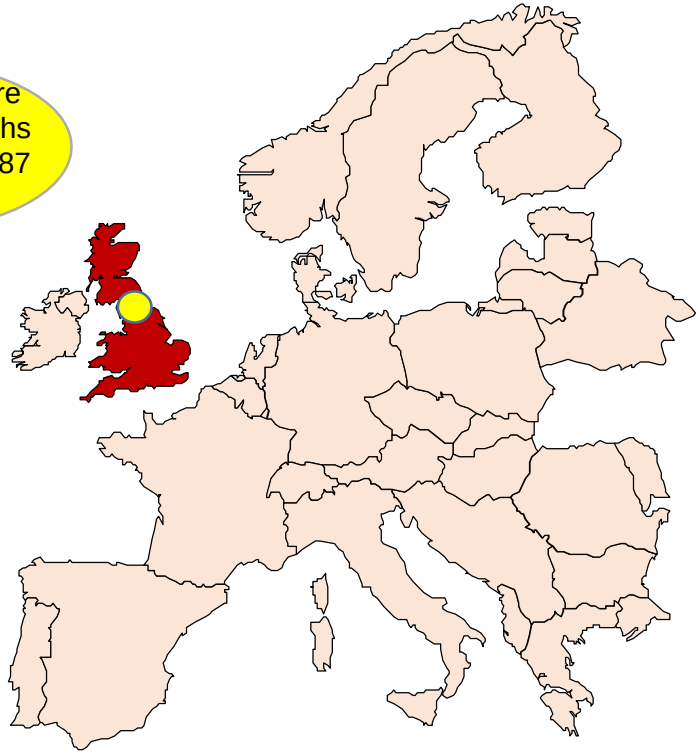
415 participants

Demented/severe disability 3 months post stroke: n=287 removed

356 stroke survivors (dementia free)

59 Vascular Dementia cases

103 sub study (MRI and Cardiovascular Assessment)



Baseline Recruitment at 3 months: COGFAST- first ever (overt) stroke

Original screen ~702 Non- demented elderly (>70 years) stroke survivors

COGFAST study: Overall Clinical and Neuropsychometric Findings

- Elderly group
- After 5 years, nearly half will have died.
- Only 1 third will be alive without dementia
- Greater decline to death or dementia if >2 vascular risk factors or baseline cognitive impairment but no dementia
- Incident depression 36.9 episodes per 100 person years

- Already lived to 80
- Improvement in cognitive function (CAMCOG) in ~25% post stroke
- Approx. 50% chance of another 5 years
- Better outcomes if no other risk factors (to CI or death)
- >60% free of depressive illness

MRC 15-year Longitudinal study of post-stroke survivors: Lead PI R Kalaria

Kalaria and Ballard, 2001; Ballard C et al, Stroke, 2003; Ballard C et al, Dementia 2003 ;Ballard et al, Neurology 2004; Stephens S et al, J Am Geriatr Soc, 2003; Kalaria RN et al, 2004; Allan LM et al, 2011; Kalaria RN 2012; Allan L et al, 2013

COGFAST study: Overall Clinical and Neuropsychometric Findings

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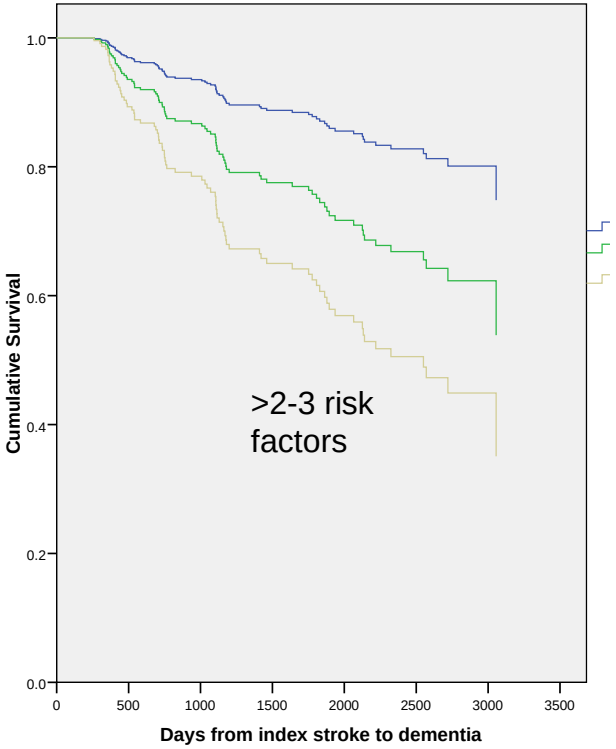
Time to dementia by number of cardiovascular risk factors



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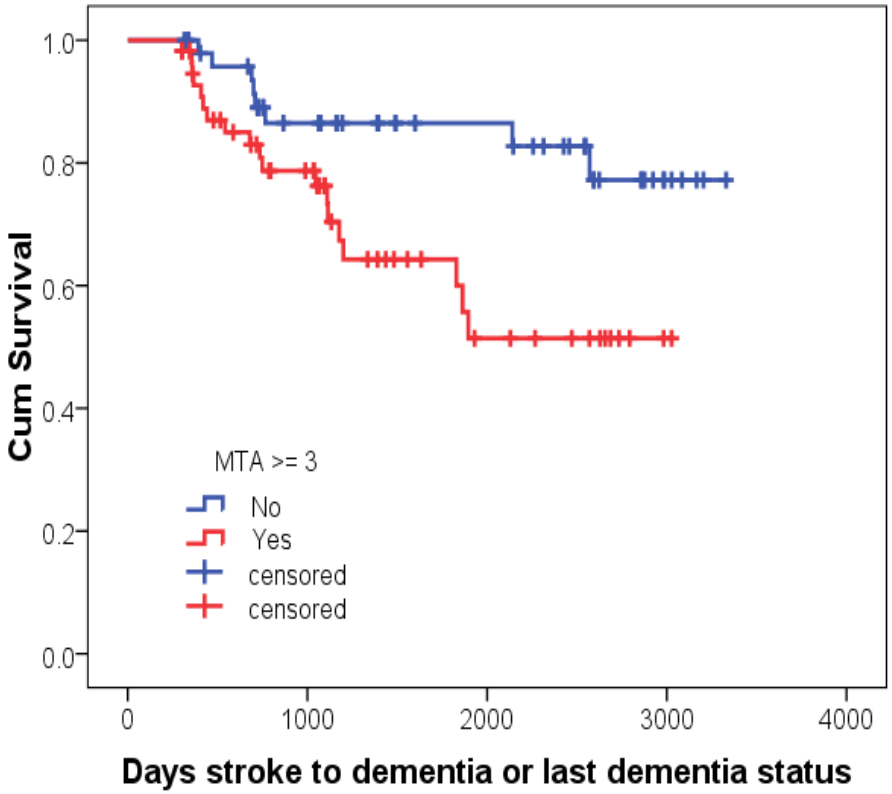
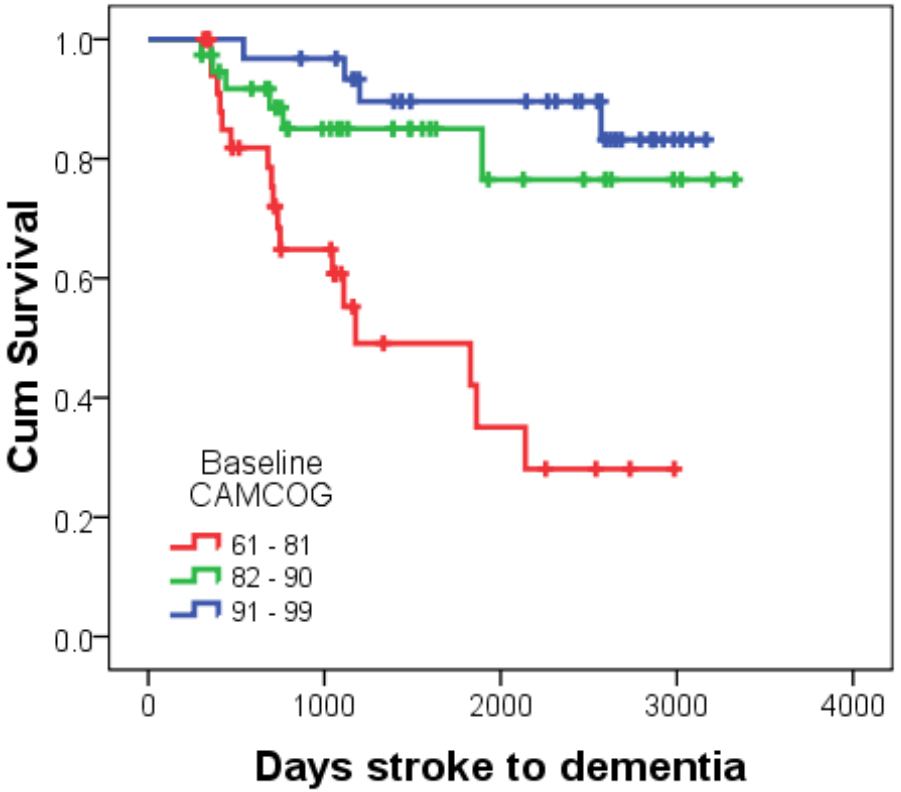
Neuroimaging in Elderly Stroke Survivors

How do the MRI features compare with AD?

MTA Predictor of survival to dementia





MTA associated with shorter time to dementia- a role for Alzheimer pathology in post-stroke dementia (PSD)?

Firbank MJ et al, 2011

Neuropathology in Elderly Stroke Survivors

Do the pathological findings compare with AD?

COGFAST study: Dementia, Vascular Risk Factors and Pathological Diagnosis of VaD

doi:10.1093/brain/awr273 Brain 2011: 134; 3713–3724 | 3713

BRAIN
A JOURNAL OF NEUROLOGY

Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors

Louise M. Allan, Elise N. Rowan, Michael J. Firbank, Alan J. Thomas, Stephen W. Parry, Tuomo M. Polvikoski, John T. O'Brien and Raj N. Kalaria

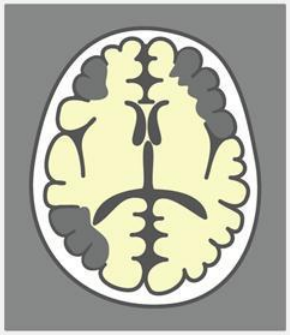
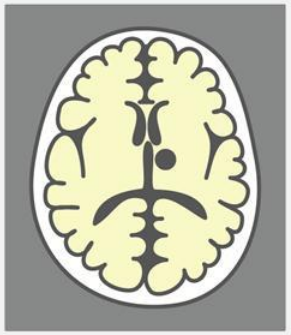
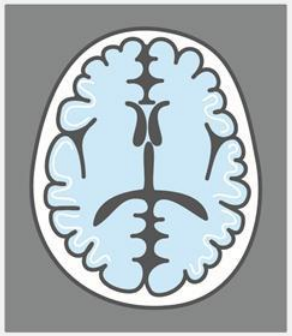
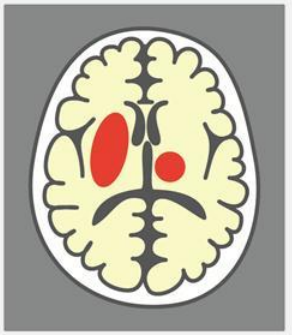
Institute for Ageing and Health, Newcastle University, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK

Correspondence to: Prof. Raj N. Kalaria

- During mean follow-up of 3.8 years, ~25% developed PSD
- Duration of survival (days from baseline stroke to death) or overall burden of vascular and minimal neurodegenerative pathology (Braak <2.5) similar between PSD and PSND
- Elderly stroke survivors in this age group likely to develop VaD: Pathological diagnosis indicated ~75% VaD, rest Mixed (AD type pathology with vascular lesions) and frontotemporal dementia (1)
- Microinfarction differentiated PSD from non-demented PS survivors

Ballard C et al, 2003; Kalaria RN et al, 2004; Firbank M et al, 2007, 2011, 2012; Allan L et al, 2012; 2013, Deramecourt V et al, 2012; Polvikoski T et al , in preparation

Newcastle Categorization of the Major CV lesions Associated with Cognitive Impairment

I	II	III	IV	V	VI
					
large infarct or several infarcts	multiple small or microinfarcts	strategic infarcts	cerebral hypoperfusion	cerebral hemorrhage	CV lesions with AD pathology
multi-infarct dementia	white matter lesions	thalamus hippocampus basal forebrain	hippocampal sclerosis	lobar ICH SAH	mixed dementia

Slide courtesy of Dr Ken Nagata

Kalaria, RN, et al. J Neuro Sci 226: 75-80, 2004

Staging and natural history of cerebrovascular pathology in dementia

V. Deramecourt, MD, PhD
J.Y. Slade, BSc
A.E. Oakley, MBiol
R.H. Perry, FRCPath
P.G. Ince, FRCPath
C.-A. Maurage, MD, PhD
R.N. Kalaria, FRCPath

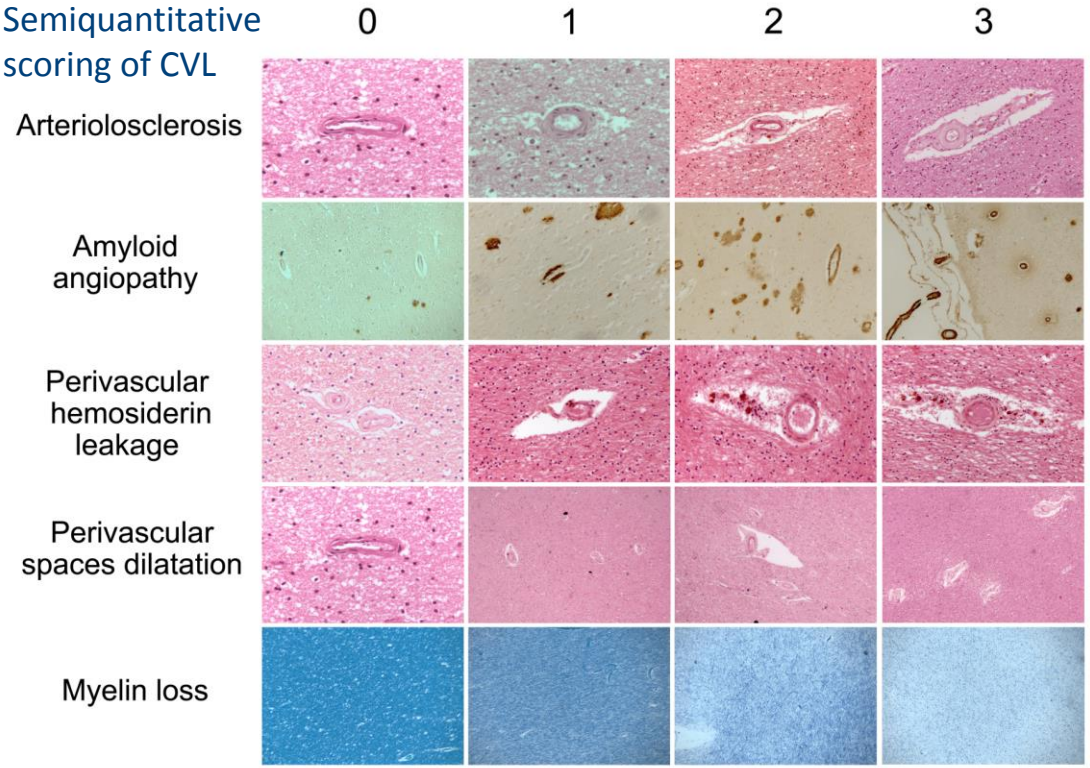
Deramecourt V et al, 2012

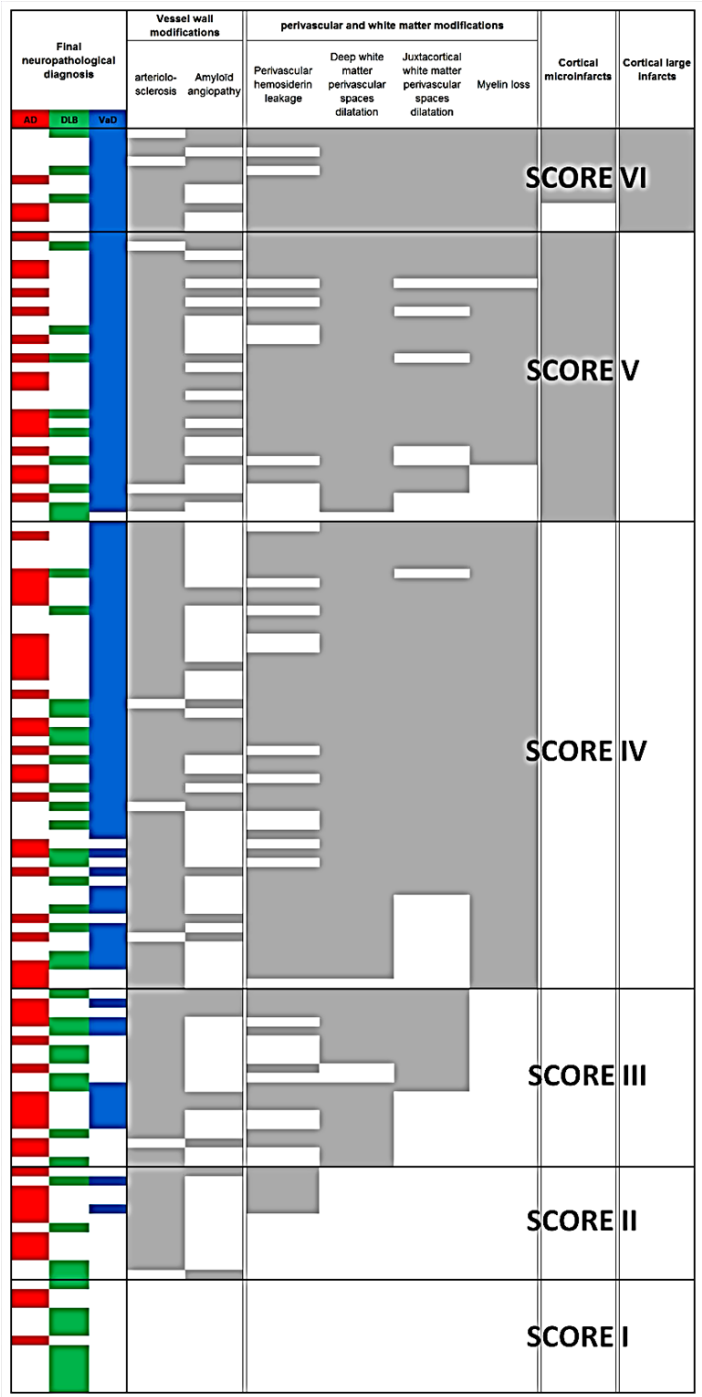
ABSTRACT

Objective: Most pathologic studies indicate that significant vascular changes are found in the majority of elderly persons, either alone or in association with neurodegenerative processes such as Alzheimer disease (AD) or dementia with Lewy bodies (DLB). Cumulative burden of cerebrovascular lesions can explain cognitive decline described as vascular cognitive impairment, but because there is a lack of consensus in the best way to quantify vascular pathology, the relationship between cognitive decline and cerebrovascular disease remains uncertain. We developed a rating scheme for cerebrovascular lesions using postmortem brains from patients with dementia from 2 European tertiary care memory clinics.

Staging and Natural history of cerebrovascular pathology

Semiquantitative scoring of CVL





Inheritance of Cerebrovascular disease

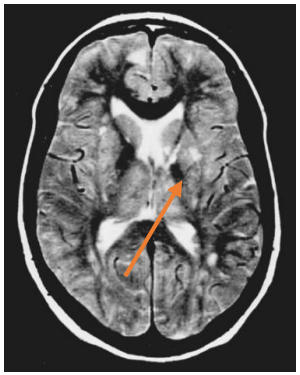
Group	Specific types	Genetics (gene /Chr.)
Stroke(s)	CADASIL, CARASIL, RVCL (HERNS, CRV, HRV)	*NOTCH 3 (Chr 19), HTRA1 TREX1 (Chr. 3);*
Hypertensive angiopathies	Familial Binswanger's/ Leukoencephalopathies	unknown
Amyloid angiopathies	Icelandic, Dutch, Flemish, Prion, Finnish, Hungarian, British, Danish, Others	*Cystatin C, AβPP, PrP, Gelsolin, TTR, BRI APOE*
Other angiopathies	Moyamoya disease	Gene unknown/ Chr 3
Aneurysms	Sacular (berry), large aneurysms	Genes unknown (also congenital forms)
Vascular malformations	Cavernous angiomas Cavernous malformations	KRIT1 and other genes loci on Chr 7 and 3

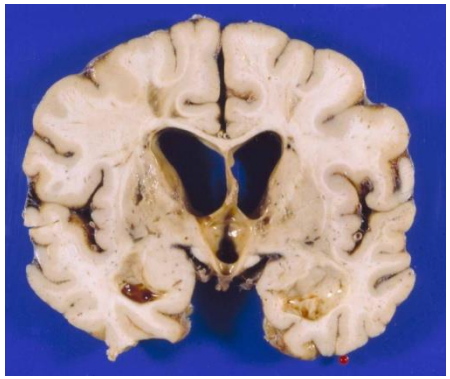
Familial SVDs of the Brain causing VCI: CADASIL is the most common

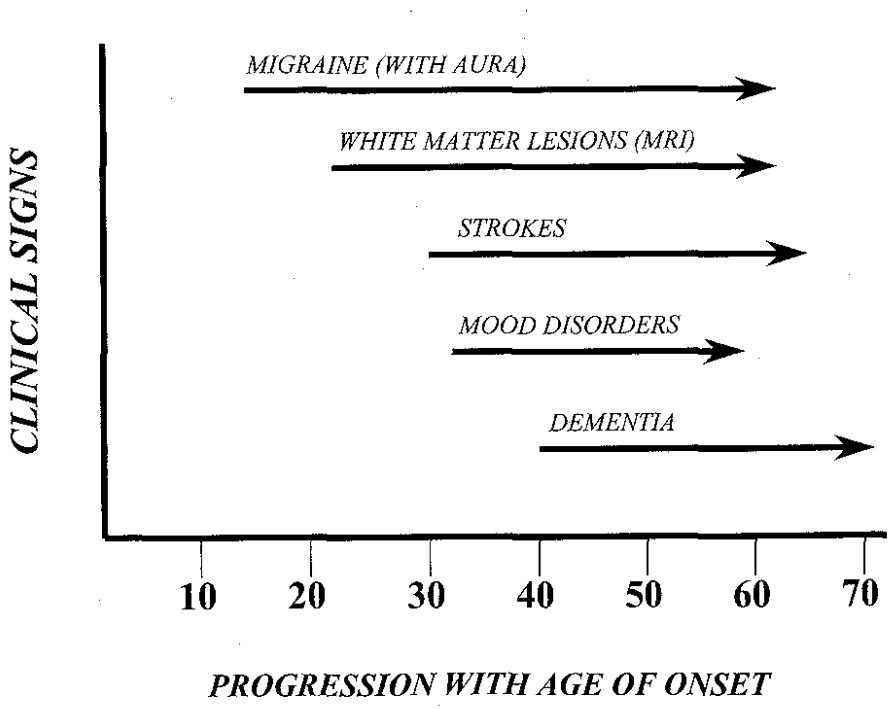
Type	Gene	Product
CADASIL	*NOTCH3*	Notch3
CARASIL (Maeda syndrome)* intervertebral disc herniations, kyphosis, ossification, alopecia	*HTRA1*	Htra1
AD Retinal Cerebral Vasculopathy with Leukodystrophy (RVCL)*	*TREX1*	DNA ex
Familial SVD- Portuguese-French type	?	?
Familial Multi-infarct dementia-Swedish type	?	?
Subcortical angiopathic encephalopathy (SAE/PADMAL)	?	?

* Described in Japanese, Chinese-American and Mutations also reported in American, French, and Dutch families

Key Features in CADASIL

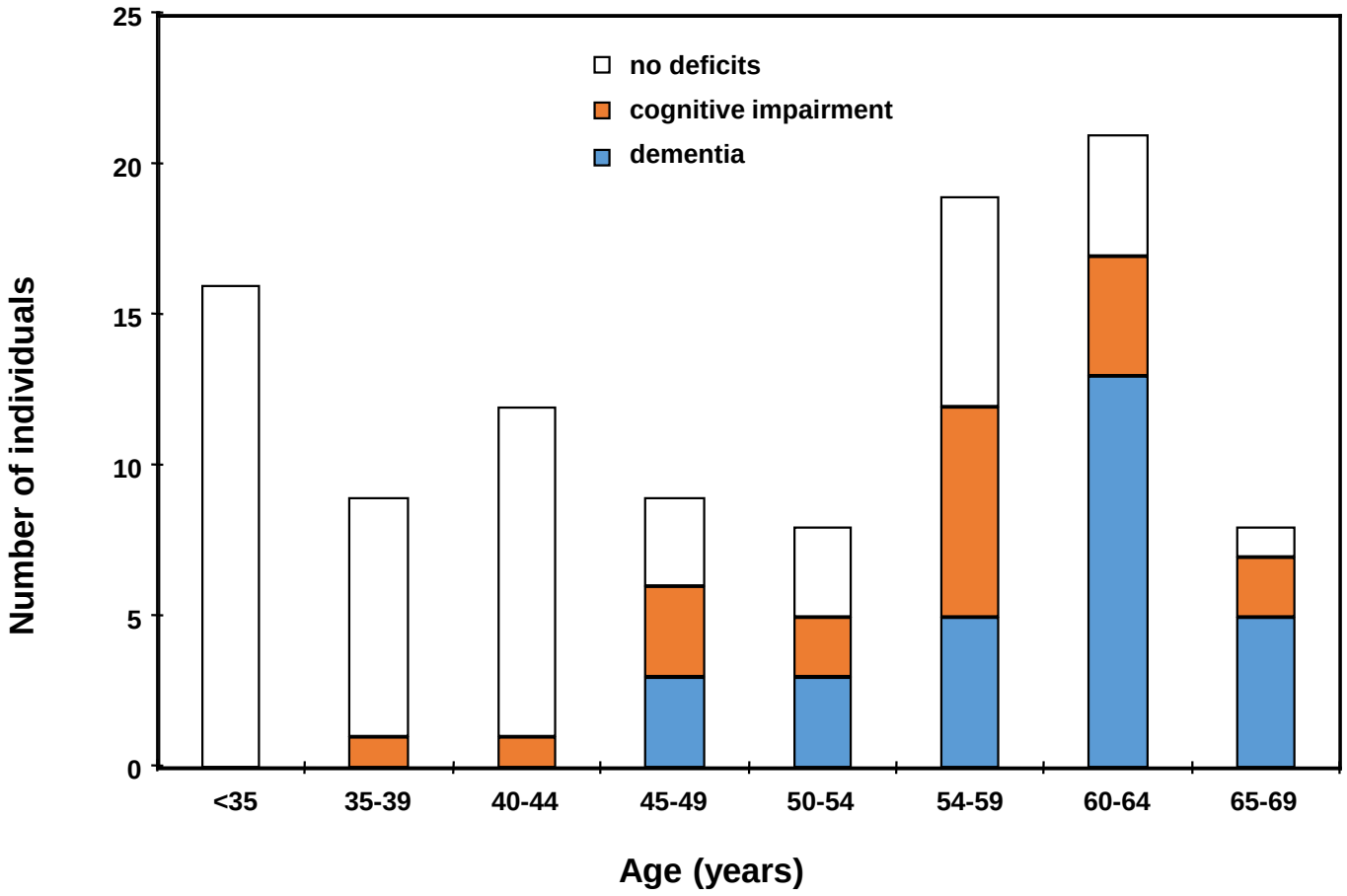




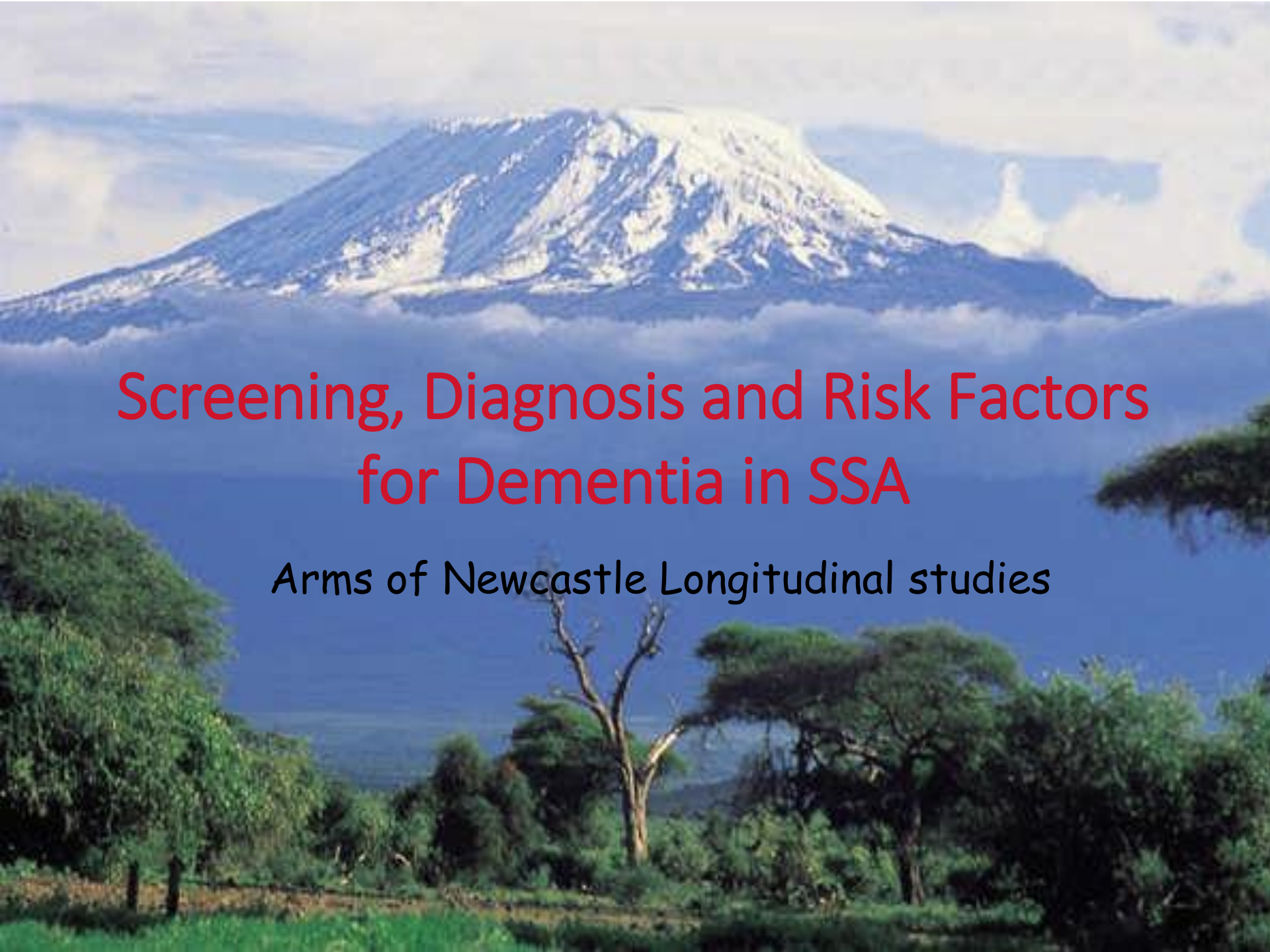


- Worldwide occurrence of CADASIL (>600 families)
- Variable clinical phenotypic features contributed by epigenetic and/or genetic factors.
- Commonly misdiagnosed as MS, cerebral vasculitis, Binswanger's disease, leukoencephalopathy of undetermined cause or AD.
- Mis-sense mutations in *NOTCH3*
- General absence of hypertension or hypercholesterolemia. Exceptions-some data on ↑ homocysteine and Type 2 diabetes

Cognition, Dementia and CADASIL



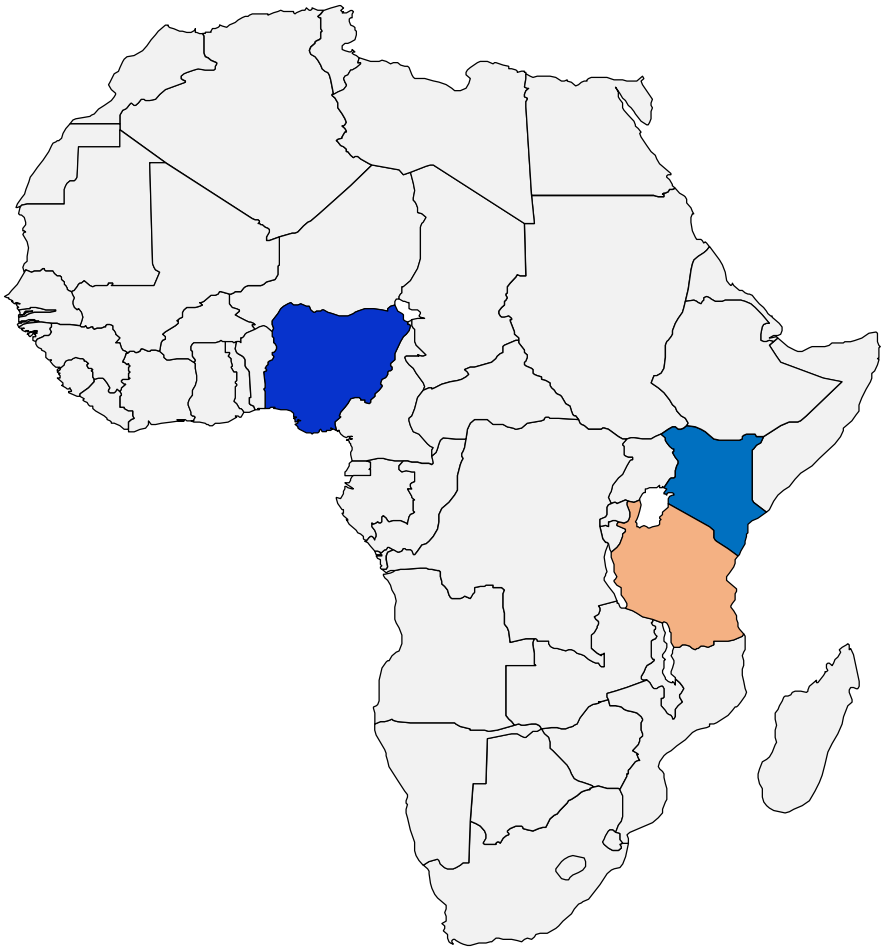
After Dichgans et al, 1998



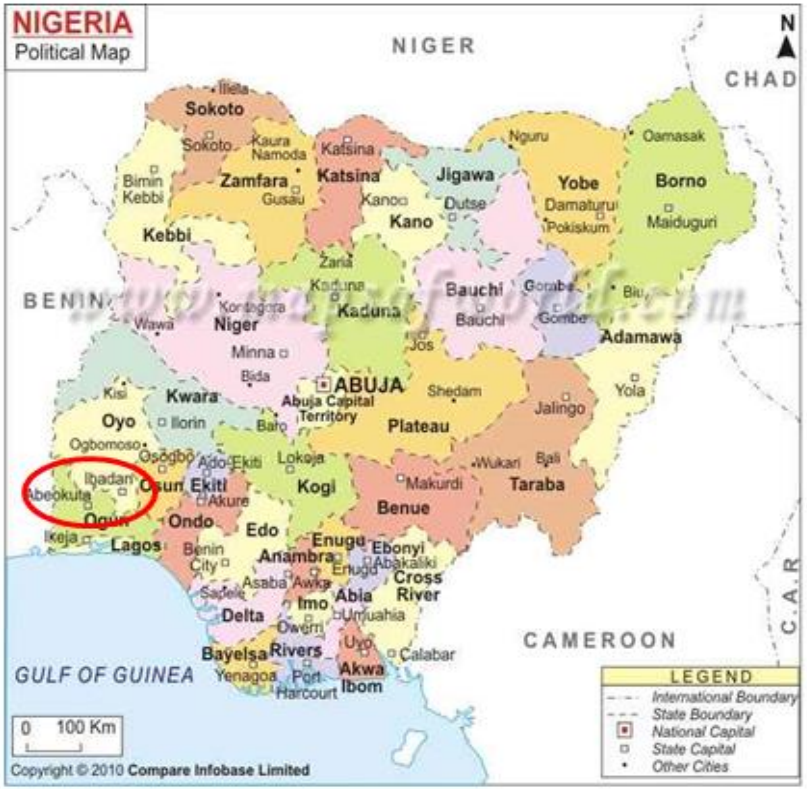
Screening, Diagnosis and Risk Factors for Dementia in SSA

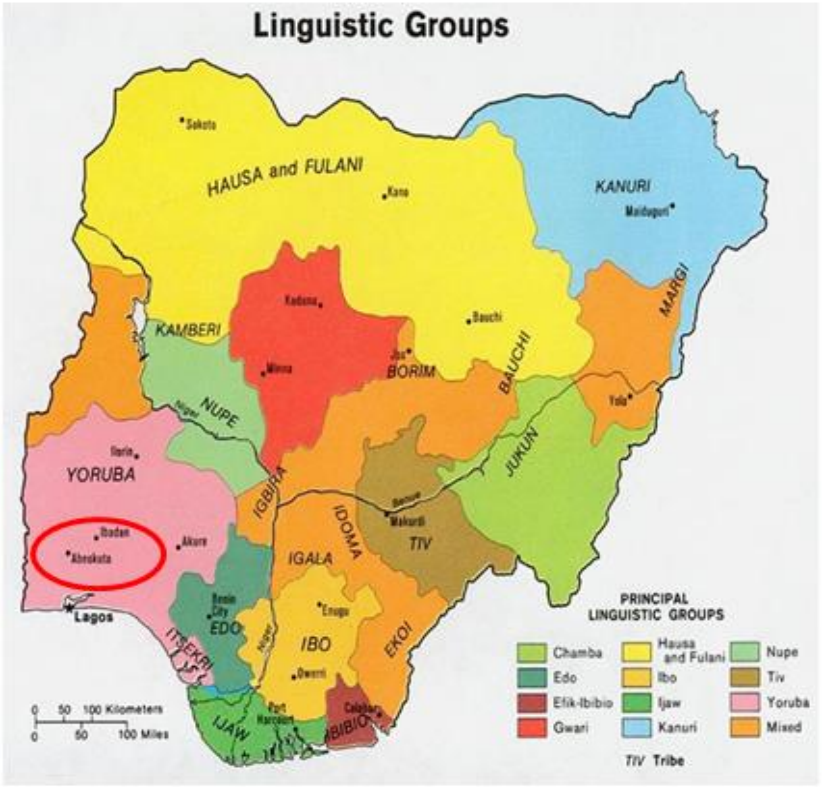
Arms of Newcastle Longitudinal studies

COGnitive Function After STroke (COGFAST – Nigeria Study)



Longitudinal study of post-stroke survivors in Africa (Ibadan, Nigeria, Nairobi, Kenya and Hai District Tanzania: PIs R Kalaria, A Ogunniyi, M Owolabi, R Akinyemi, R Walker





Map of Nigeria showing the study area in Southwestern part of the country [A] Political map of Nigeria showing Abeokuta and Ibadan north of Lagos [B] An ethno-linguistic map showing the Yoruba speaking Southwestern region of the country with location of study centres

CogFAST –Nigeria: Vascular Neuropsychological Battery

Cognitive Domain	Test
Executive Function	Category (Animal) Fluency Test
/Activation	
	Phonemic (Letter) Fluency Test
	Verbal Reasoning (Similarities Test)
	Ideational Fluency Test
Language/	Boston Naming Test (2nd version)
Lexical Retrieval	
Memory/ Learning	Word List Test (Learning, Recall,
	Recognition)
	Delayed Recall of Stick Design
Visuospatial/	Stick Design Test
Visuoconstruction	Modified Tokens Test
	(IU Token Test)
General Cognitive	Community Screening Instrument
Functioning	for Dementia (CSID
	Minimental State Examination
	(MMSE)

- Based on the 60 min VCI Harmonization Standards – Neuropsychological Protocol proposed by the NINDS – CSN (Hachinski et al, 2006).
- Multiple test items assessing each cognitive domain were selected in consonance with the recommendations of the Harmonization standards
- Utility of tests in previous cognitive evaluations in environment of study population

Refs: Folstein, 1995; Hall et al, 1993; 2000; Gureje et al., 1995; Blessed et al, 1991; Unverzagt et al., 1999; Ballard et al, 2002; Baiyewu et al., 2005; Akinyemi et al., 2008

CogFast- Nigeria: Stroke and Cognition

Journal of the Neurological Sciences 346 (2014) 241–249

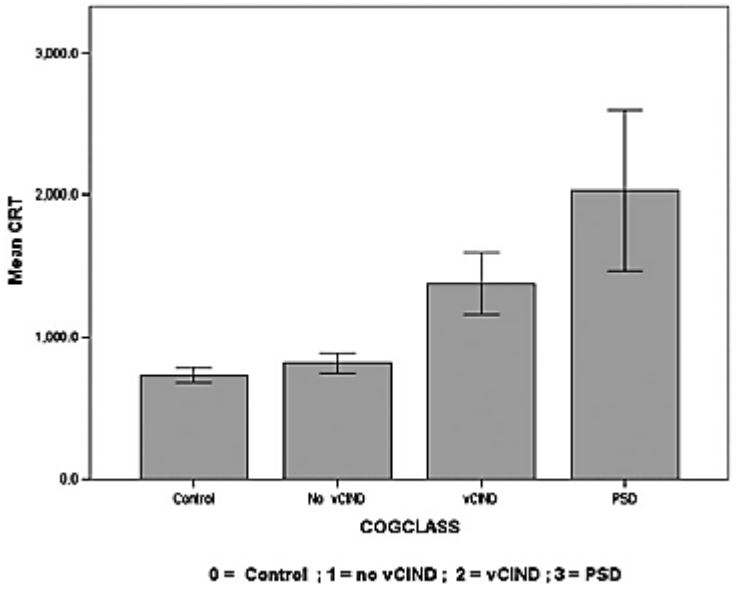
Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Profile and determinants of vascular cognitive impairment in African stroke survivors: The CogFAST Nigeria Study

Rufus O. Akinyemi [a,b,*,1], Louise Allan [b], Mayowa O. Owolabi [c], Joshua O. Akinyemi [d], Godwin Ogbole [e], Akinlolu Ajani [a], Michael Firbank [b], Adesola Ogunniyi [c], Raj N. Kalaria [b,*,1]



pattern of performance on Choice Reaction Time (CRT) in controls and impaired subjects.

- First ever stroke survivors mean age = 61 yrs
- 80% Ischaemic stroke; 41% lacunar stroke
- Median modified Rankin score=2)
- 8.4% demented at baseline and 30% cognitive impairment no dementia (CIND)
- Pre-stroke cognitive decline
- Medial temporal lobe atrophy (MTA) [OR = 2.25 (1.16–4.35)] was independently associated with cognitive dysfunction
- High frequency of early VCI

Akinyemi R et al, 204; 2015

Predictors of Post-stroke VCI - COGFAST Nigeria

Variable	Univariate analysis OR (95%CI)	Multivariate analysis: OR (95%CI)
Baseline Age (years)	**1.06 (1.02 – 1.10)**	**1.05 (1.00 – 1.09)**
Female Gender	**2.27 (1.15 -4.45)**	1.87 (0.80 – 4.40)
< 6 years of education	**4.84 (2.36 – 9.92)**	**5.09 (2.17 – 11.95)**
Hypertension	1.18 (0.30 4.58)	
DM	1.29 (0.59 -2.79)	
Previous stroke	1.38 (0.51 -3.10)	
Smoking	1.253 (0.51 – 3.10)	
Alcohol use	**2.01 (1.01 – 4.00)**	1.19 (0.47 -3.00)
Daily fish intake pre-stroke	**0.42 (0.20 – 0.88)**	**0.37 (0.15 -0.89)**
Moderate to strenuous physical activity pre - stroke	**0.17 (0.04 – 0.84)**	1.00 (0.99 -1.02)
Modified Rankin Score	1. 03 (0.53 – 1.98)	
Barthel Index	0.98 (0.90 -1.06)	
CESD score	1.04 (0.96 – 1.12)	

Significant results are shown in bold (p <0.01)

Factors associated with PS VCI include **older age at baseline, female gender and lower educational attainment**

While pre-stroke moderate- heavy physical activity and **daily fish intake were protective**

Akinyemi R et al, JNS, 2014; BMC Res Notes 2015

Neuroimaging in Nigerian Older Stroke Survivors

Medial temporal lobe atrophy (MTLA) was independently associated with VCI/VaD in PS survivors at 12 months

MTLA correlated significantly with cognitive performance and **white matter hyperintensities (WMH**s) on T2W MRI

Akinyemi et al. BMC Res Notes (2015) 8:625
DOI 10.1186/s13104-015-1552-7

BMC Research Notes

RESEARCH ARTICLE Open Access

Medial temporal lobe atrophy, white matter hyperintensities and cognitive impairment among Nigerian African stroke survivors

Rufus O. Akinyemi[1,2], Michael Firbank[2], Godwin I. Ogbole[3], Louise M. Allan[2], Mayowa O. Owolabi[4], Joshua O. Akinyemi[5], Bolutife P. Yusuf[3], Oluremi Ogunseyinde[3], Adesola Ogunniyi[4†] and Raj N. Kalaria[2*†]

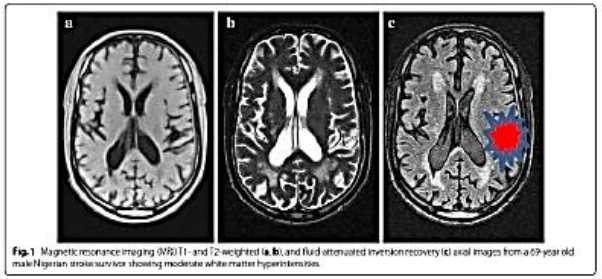


Fig. 1 Magnetic resonance imaging (MRI) T1- and T2-weighted (a, b) and fluid attenuated inversion recovery (c) axial images from a 69-year old male Nigerian stroke survivor showing moderate white matter hyperintensities

**MTLA vs WMH score showed positive correlation (r =0.461, p = 0.002) supporting a vascular basis for MTLA.

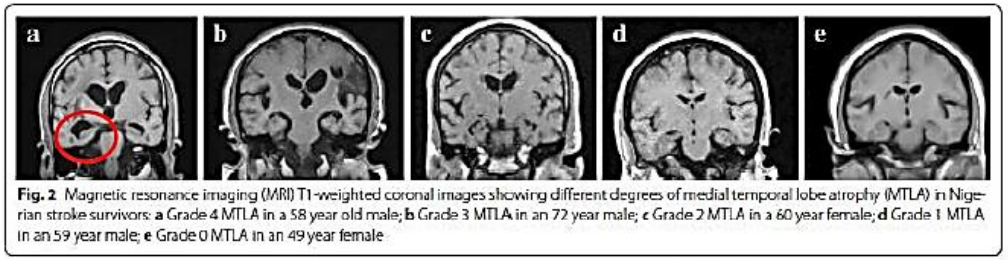


Fig. 2 Magnetic resonance imaging (MRI) T1-weighted coronal images showing different degrees of medial temporal lobe atrophy (MTLA) in Nigerian stroke survivors: **a** Grade 4 MTLA in a 58 year old male; **b** Grade 3 MTLA in an 72 year male; **c** Grade 2 MTLA in a 60 year female; **d** Grade 1 MTLA in an 59 year male; **e** Grade 0 MTLA in an 49 year female

Akinyemi et al, BMC Res Notes. 2015 ;8:625

	Normal vs vCIND			vCIND vs PSD			Normal vs (vCIND + PSD)		
Variable	**OR**	**95%CI**	***p value**	**OR**	**95%CI**	**p value**	**OR**	**95%CI**	***p value**
MTLA rating	2.02	1.05 – 3.87	**0.035**				2.25	1.16 – 4.35	**0.016**
Log _ TBV							0.01	0- 1996.50	0.260

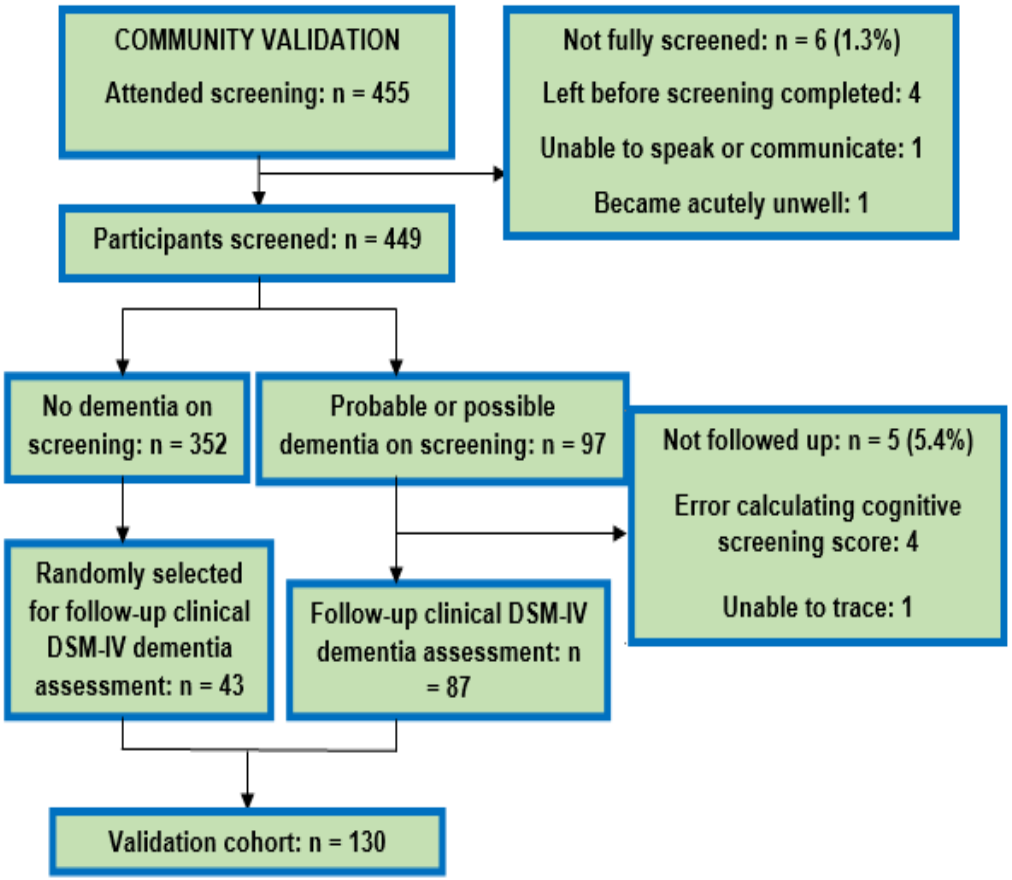
Hypertension and Incident dementia risk

Effect	Odds Ratio	95% CI
Hypertension	1.52	1.01- 2.30
Systolic BP, X 10 mm Hg	1.09	1.03 – 1.16
Diastolic BP, X 10 mm Hg	1.22	1.07 – 1.38
Pulse Pressure, X 10 mm Hg	1.10	1.01 – 1.21

Ogunniyi A et al. Acta Neurol Scand 2011

Screening and Diagnosis of Dementia in Hai, Tanzania

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

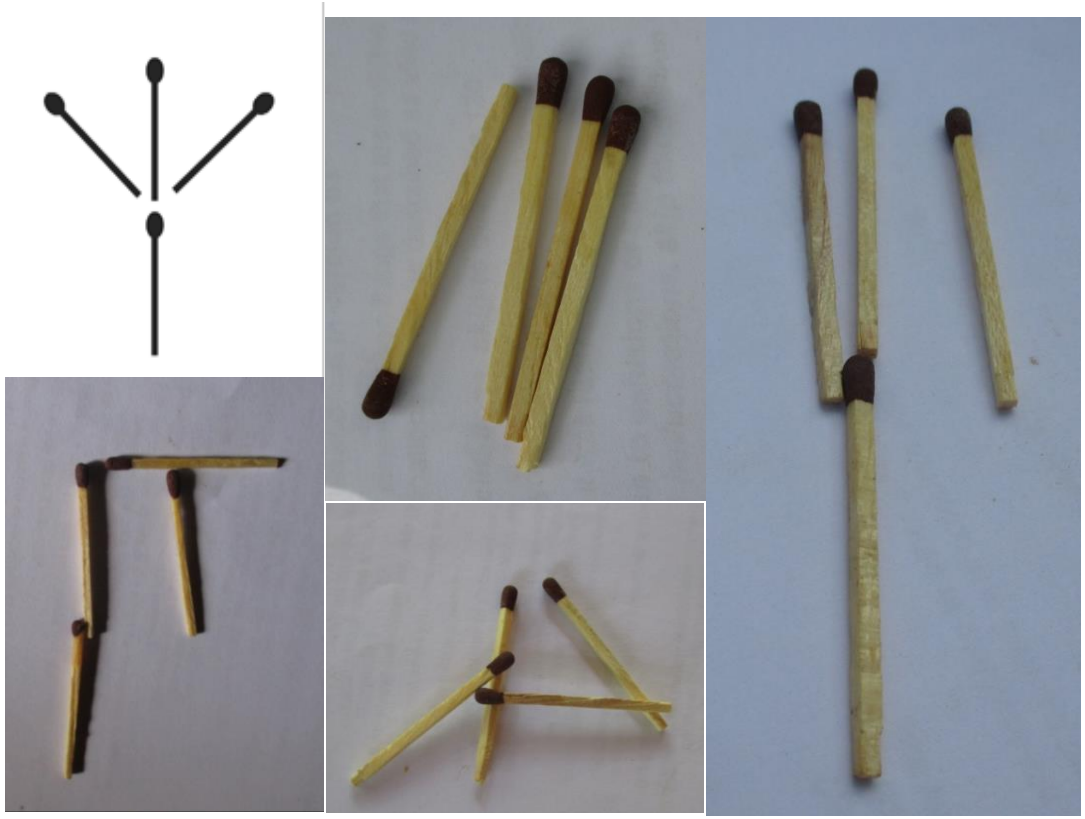
IDEA Study Screening Tools

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



2010 Dementia Prevalence in Hai

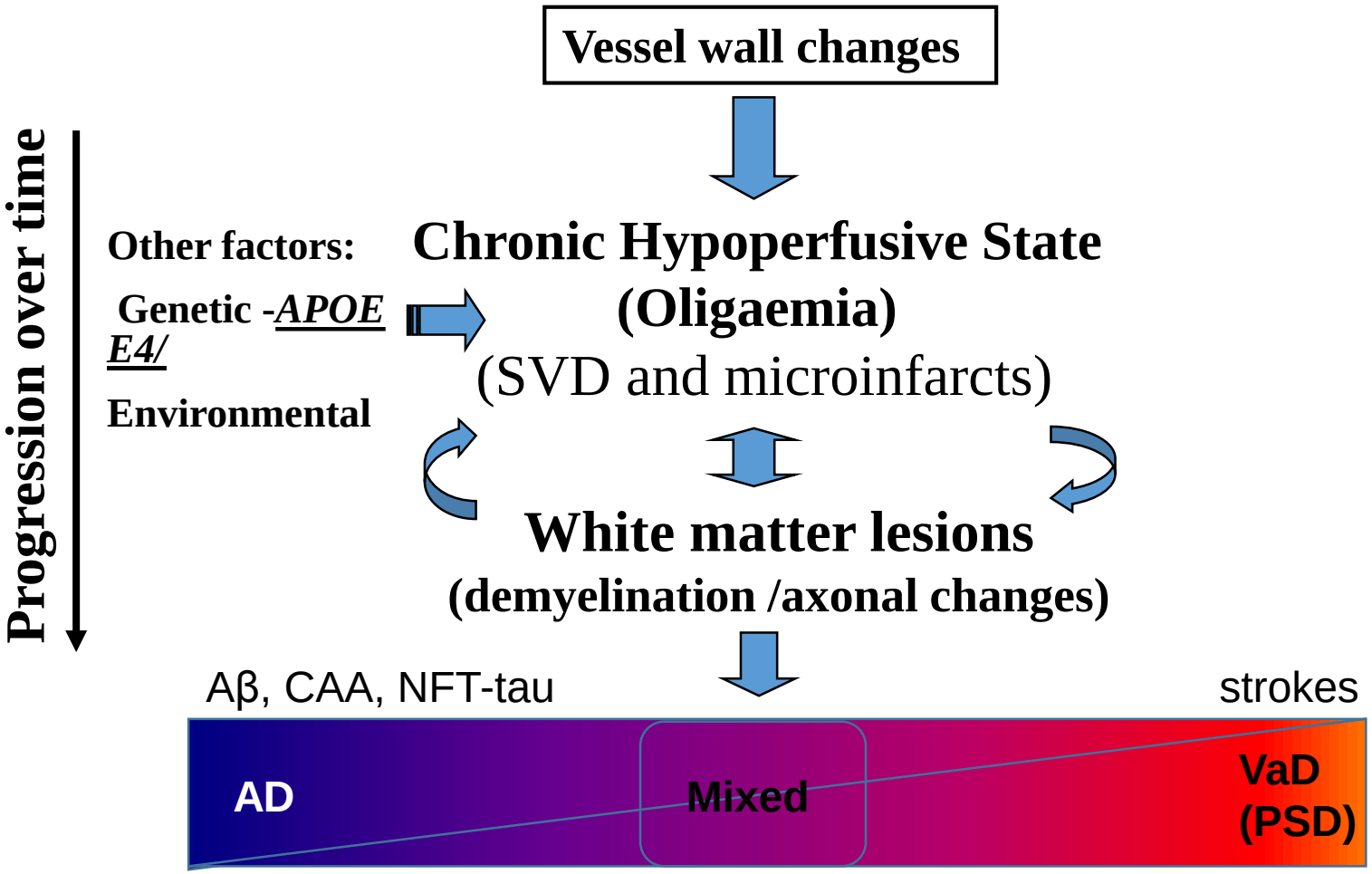
- Six villages -Total population 34,078
- 1260 eligible >70 yr on census (56% female)
- 1198 screened -184 Probable dementia, 108 possible dementia and rest no dementia
- 78 cases (22 male) ; DSM-IV
- Age-adjusted prevalence of dementia was 6.4% (95% CI: 4.9-7.9)
- Age-adjusted “10/66 dementia” prevalence 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

Vascular Factors and Neurodegeneration

Vascular disease risk factors

Stroke, hypertension, diabetes, dyslipidemia, obesity, atherosclerosis,



And Finally…

The Learning Objectives?

Summary: Post-stroke Cognitive Impairment and Dementia

- In tandem with ageing, stroke and dementia increased in LMICs
- Vascular risk factors associated with Dementia and Neurodegeneration; ***Hypertension is foremost in most studies***
- **Neuropsychometric assessement: MMSE, MoCA, CSI-D, CAMCOG-VCI**
- ~30% Stroke survivors develop dementia (PSD): ~75% in form of VaD; similar trends in SSA
- Medial Temporal and Frontal lobe atrophy caused by vascular disease irrespective of AD pathology; *Brain atrophy is an important target*
- Demographic transition suggests changing dementia trends in SSA: higher estimates of VCI and VaD than 10 years ago

Rufus Akinyemi et al, (2005): Dementing disorders in west Africa

Vascular Dementia in Africa

Knowledge and perception of stroke amongst hospital workers in an African community

Rufus O Akinyemi, OS Ogah, RF Ogundipe, OA Oyesola, AA Oyadoke, MO Ogunlan, FM Otubogun, TF. Odeyink, BS Alabi, JO Akinyemi, JK Osinfade & Raj N Kalaria *Eur J Neurology*, 2009

"This study demonstrates gaps in the knowledge of hospital workers about stroke, and treatment choice is influenced by cultural and religious beliefs"

"Health education is still important, even, amongst health workers and stroke awareness campaigns may need to involve faith-based organizations."

Acknowledgements

- CogFAST Study, IoN
- MRC VaD/PSD programme (NU)
- Neuropathology, Newcastle NHS Trust

Neurovascular Research Group: Arthur Oakley, Janet Slade, Yoshiki Hase, Masafumi Ihara, Rufus Akinyemi, Elizabeth Gemmell, Lucy Craggs, Matthew Burke, Yumi Yamamoto, Vincent Foster, Aiging Chen, **Louise Allan**

Neuropathology team: Robert Perry, Elaine Perry, **Tuomo Polvikoski**, Johannes Attems, Chris Morris, Evelyn Jaros

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

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- Aloyce Kisoli
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- Adesola Ogunniyi
- Richard Walker