Advances in Neuroimaging for Cognitive Impairment and Dementia

DR CHRISTOPHER CHEN
DIRECTOR, MEMORY AGING & COGNITION CENTRE
DEPARTMENT OF PHARMACOLOGY
NATIONAL UNIVERSITY OF SINGAPORE

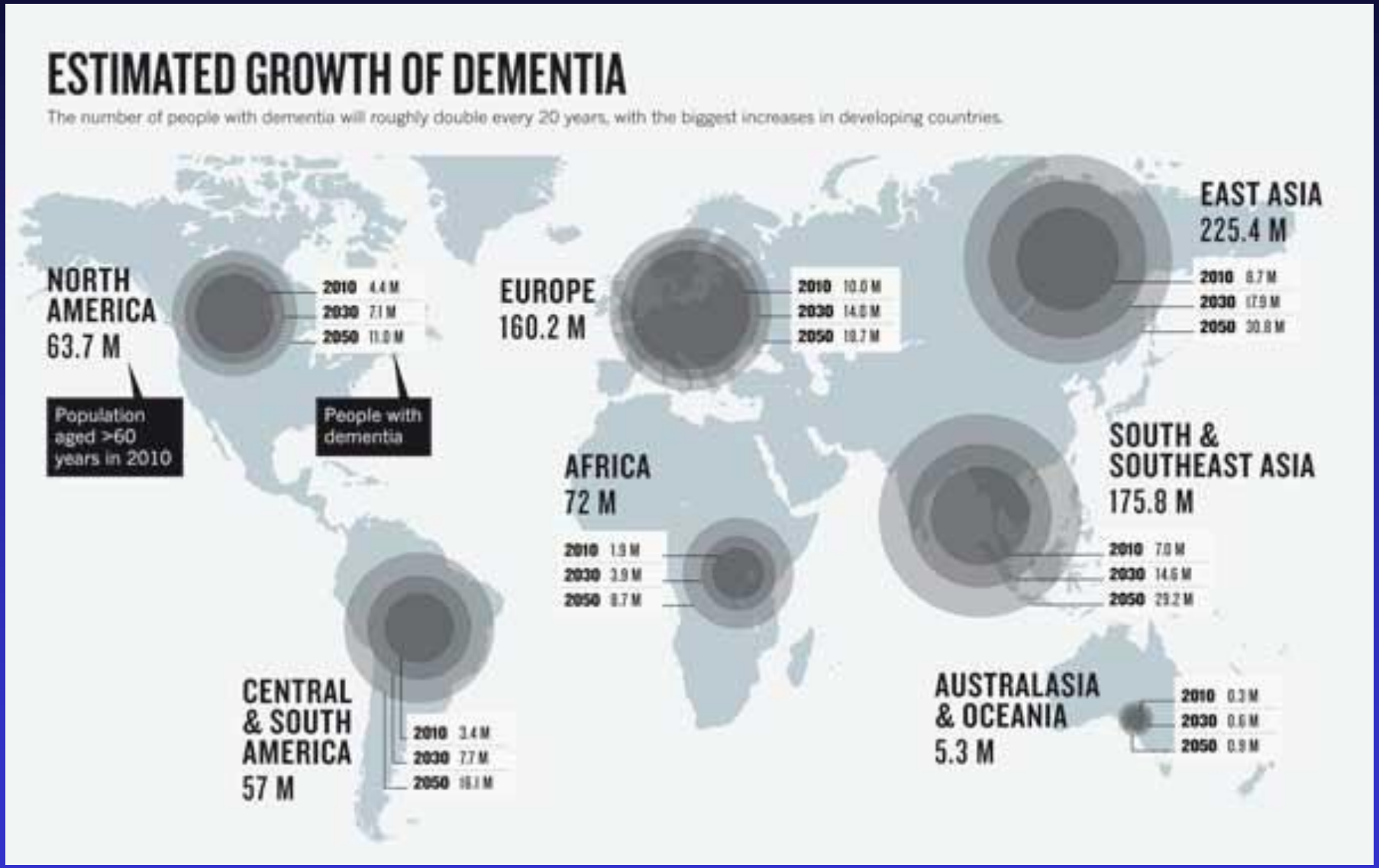
SENIOR CLINICIAN SCIENTIST
NATIONAL MEDICAL RESEARCH COUNCIL

National University Hospital

NUS National University of Singapore

NMRC National Medical Research Council

Largest increases in dementia burden will be in Asia



ADI, 2010

Memory Aging & Cognition Centre (MACC)

- 4 Themes focusing on "Asian" (actually global) phenotype of dementia & cognitive impairment due to neurodegeneration and cerebrovascular disease
- Collaboration of NUHS, NUS, A*STAR and
  - other institutions in Singapore
    - St Luke's, SERI, Duke-NUS, NNI
  - and internationally
    - King's London, Oxford, UCLA, Utrecht, Rotterdam

Memory Aging & Cognition Centre

Biomarker Discovery & Mechanisms of Disease

Mitchell Lai, Peter Wong, Sze Siu Kwan

Neuroimaging Theme

MRI : Helen Zhou, H Vroomans

Retinal : Wong Tien Yin, Carol Cheung

Clinical Theme

Christopher Chen, NV Ramani

Epidemiology Theme

NV Ramani, CY Cheng, TY Wong

Funded by the NMRC 2010-13 (Centre Grant) and
renewed for 2013-17 (NUHS Centre Grant)
and 2017-2022 (NUHS Centre Grant)

NUS National University of Singapore

NUHS National University Health System


Yong Loo Lin School of Medicine
A member of the NUHS

Harmonisation
Baseline = 580
Yr1 = 515
Yr2 = 417
Yr3 = 331
Yr4 = 206
Yr5 = 145

Other Observational Studies
MoH AD8
Phase 1=1072
Phase2 =309
ADOS Study = 40
DANONE
Asian Nutritional Status Study= 180

LONGITUDINAL COHORTS
a) post acute stroke patients (COAST, COAST-E) followed up for up to 6 years
b) controls, MCI and dementia (HARMONISATION) followed up for up to 5 years

COAST = 400
COAST E = 318

EPIDEMIOLOGY COHORT
multi-ethnic community based study of the prevalence of dementia, dementia subtypes risk factors, biomarkers

As of 31st Mar 2018

N= 959
Chinese=300
Malay= 323
Indian=336

CLINICAL TRIALS
MissionAD=2
NEURITES = 62
Athene = 101
Starbright = 19
Mindset= 13
Mindset Ext= 11
TauRx = 7
OLEX= 5
AB Science =1

MACC Clinical Research Core :
Clinical & Neuropsychological Assessments

NUS- ASPIRATION

NMRC-IRG

BIOMARKERS : neurochemical epigenetic and genetic markers for dementia subtypes

NEUROIMAGING : (**in close collaboration with CIRC**) Identifying MRI markers associated with dementia subtypes & cerebrovascular contribution to dementia

RETINAL IMAGING : Identifying retinal markers associated with dementia subtypes

NMRC CSA

GSK ACE Award

918 community based subjects with MRI

567 baseline, 395year 2, 236 year 4/5 longitudinal cohort subjects with MRI

Cross-sectional (429)
Longitudinal (140)

170 subjects with amyloid PET : ABRI= 157, PIB= 24

NUS National University of Singapore

Memory Aging & Cognition Centre

NUHS National University Health System

Neuroimaging Methodologies for Cognitive Impairment and Dementia

Structural Imaging

- CT
- MRI
- MRA
- DTI

Functional Imaging

- PET
- SPECT
- fMRI

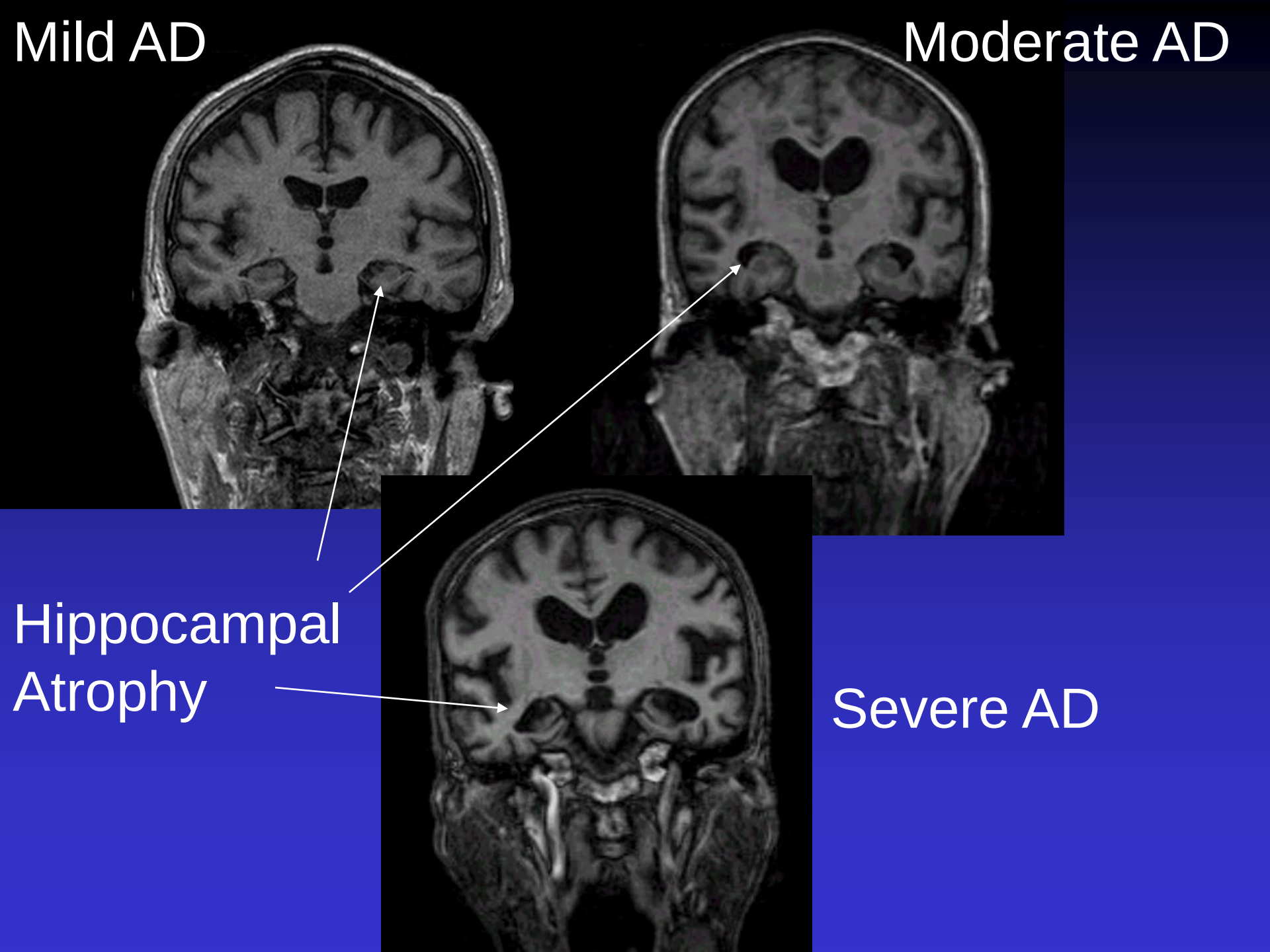
Molecular Imaging

- PET

Imaging Methodologies for Dementia

Structural imaging may be helpful in identifying particular causes of dementia

- Alzheimer's Disease
  - cortical and hippocampal atrophy
- Fronto-temporal Dementia
  - asymmetrical frontal / temporal atrophy
- Vascular Dementia
  - infarcts and vessel occlusion

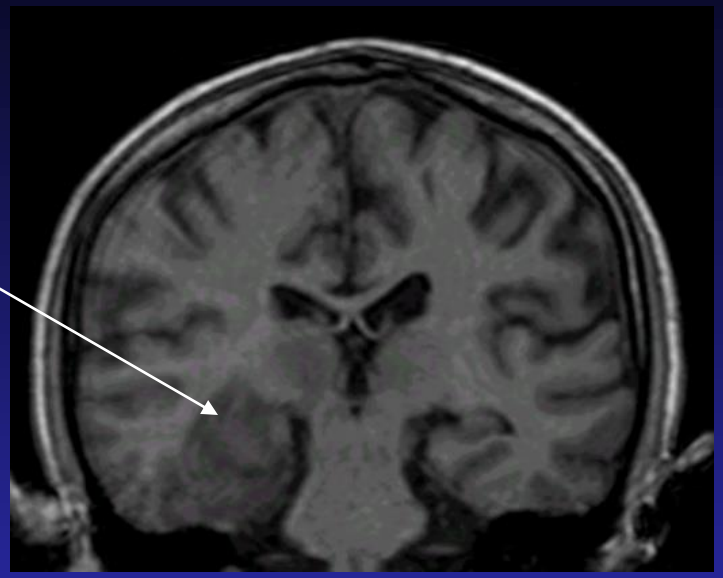

Mild AD
Moderate AD
Hippocampal Atrophy
Severe AD

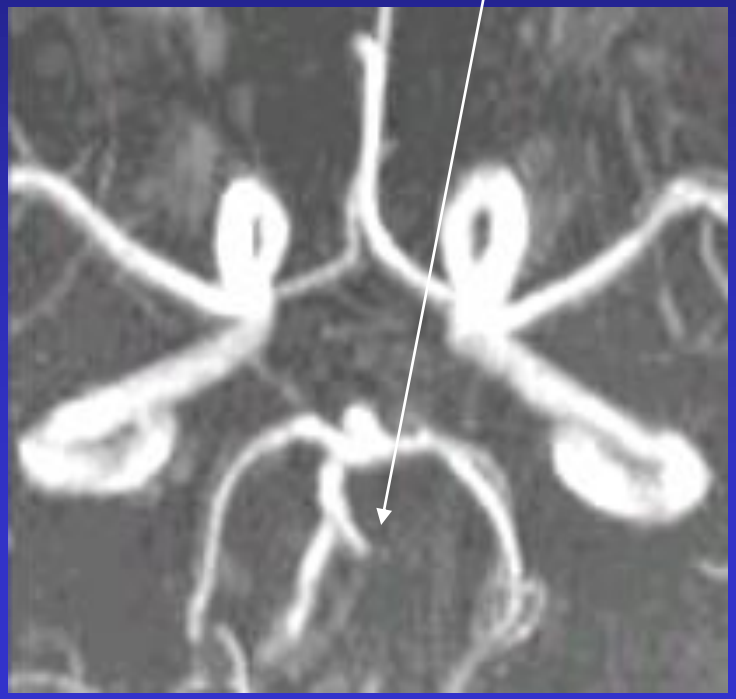
LARGE-VESSEL INFARCT DEMENTIA

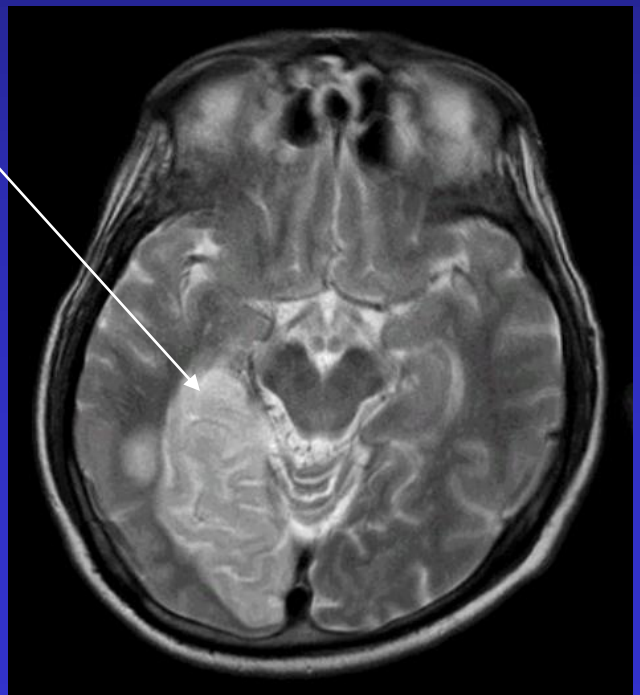
Hippocampal infarct

Right cortical infarct

Vertebral artery occlusion







Cerebrovascular Contributions to Cognitive Impairment and Dementia

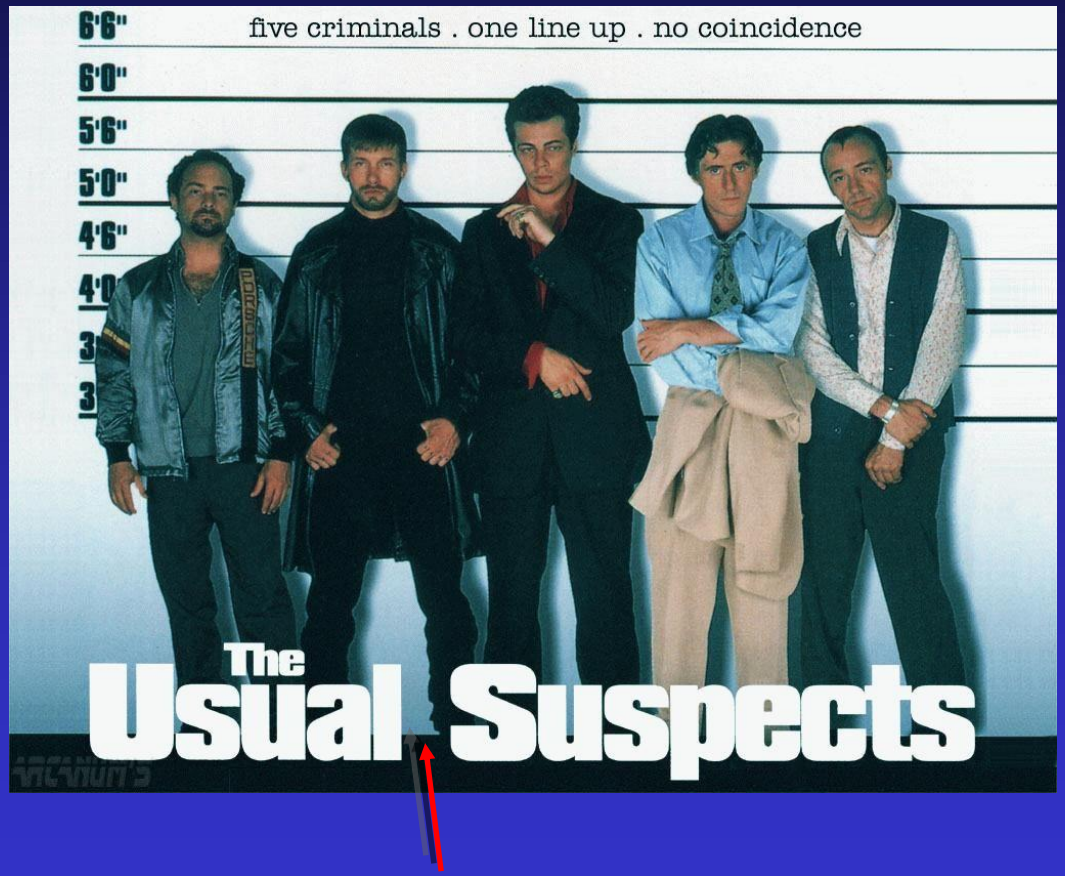
- Vascular pathology is highly prevalent in elderly people
- Vascular contributions to cognitive impairment and dementia in later life are important
- Evidence that vascular risk factors (hypertension, diabetes, and hypercholesterolaemia) increase the risk of Alzheimer's Disease suggests a role of vascular factors in potentiating or even triggering neurodegenerative disease
- Many people with dementia have mixed pathology (commonly AD and cerebral small vessel disease)
- Vascular pathology can be additive with AD pathology in impairing cognitive function and increasing the likelihood of dementia

CoEN, Lancet Neurology 2012

The Importance of Covert Stroke

- Overt stroke is what most often demands attention and consumes resources
- However, advances in neuroimaging have shown that more needs to be learned about covert vascular disease that erodes brain structure and function in less dramatic ways
  - These MRI findings are common in the elderly and not benign
  - Need to identify etiologic risk factors so that they be prevented with preservation of brain function

Imaging Biomarkers of Vascular Cognitive Disorders



and less usual

- Cortical Infarcts
- Lacunar Infarcts
- White Matter Lesions
- Atrophy
- DTI
- Cerebral Microbleeds
- Cerebral Micro-Infarcts
- Intracranial Stenosis
- Retinal Imaging
- Amyloid Imaging

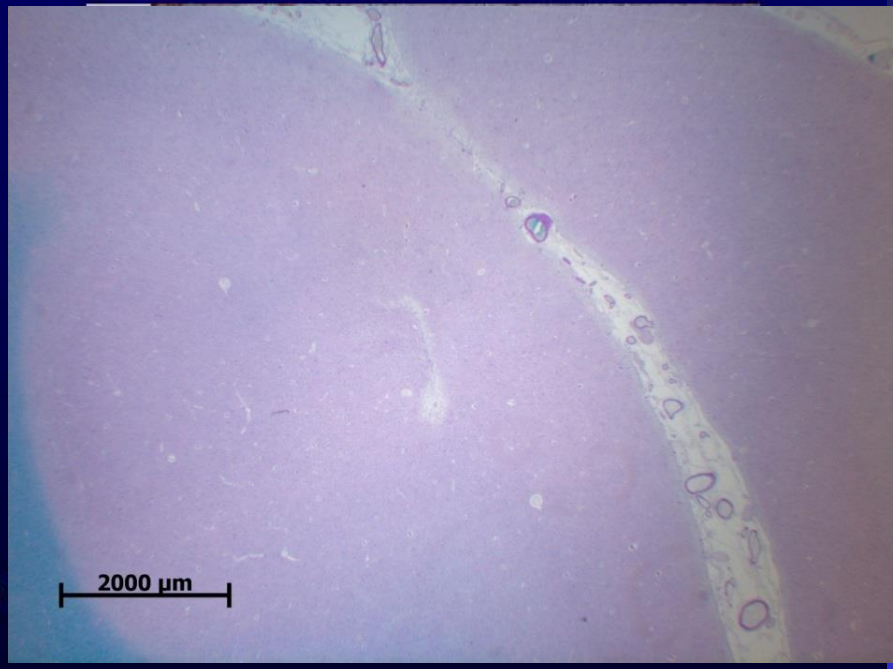
Microinfarcts : Important but previously invisible during life

systematic review autopsy studies

- cystic or gliotic
- 100-200 µm to a few mm

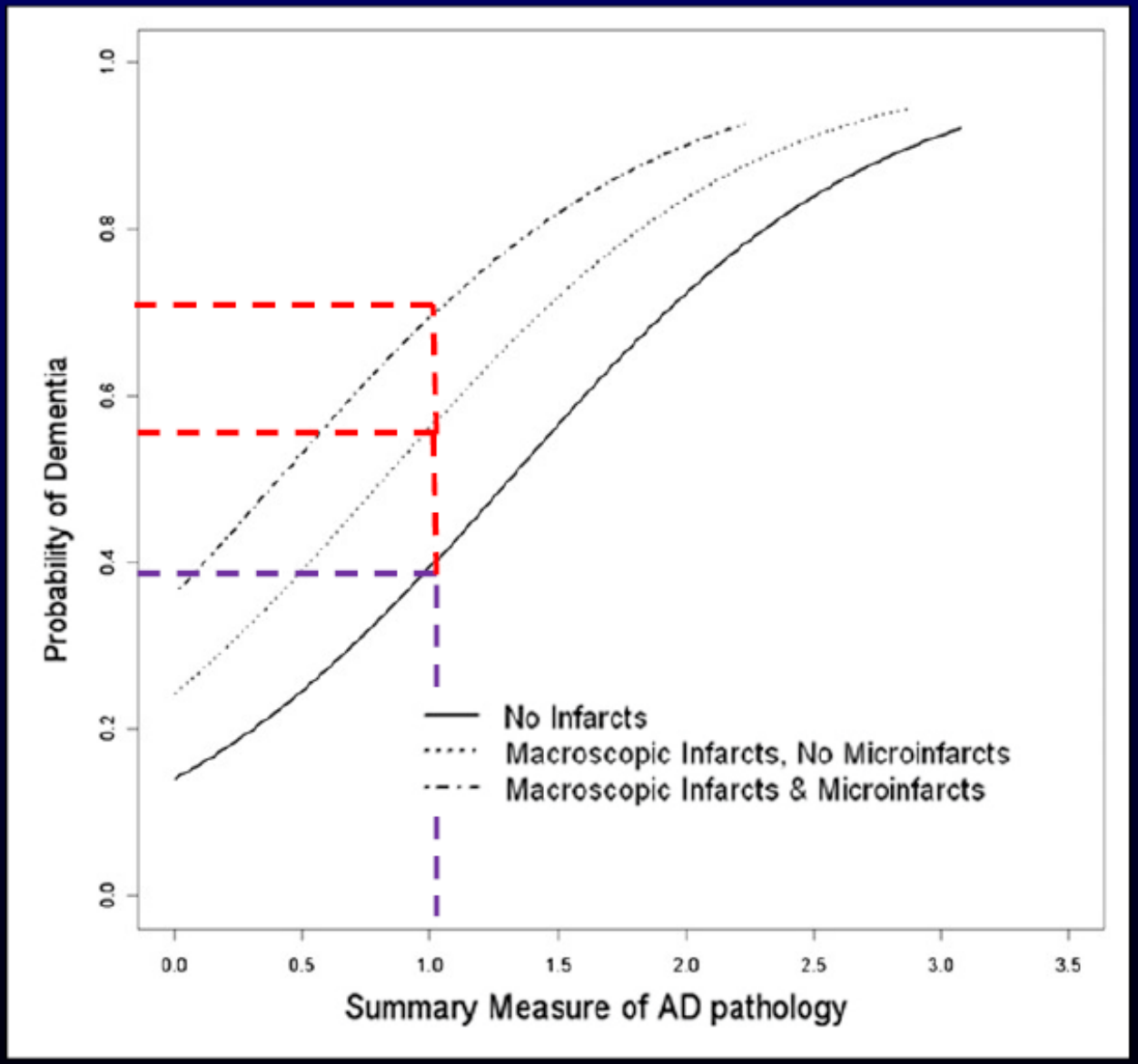
prevalence:

- Alzheimer's - 43%
- vascular dementia – 62%
- non-demented elderly – 24%



Brundel et al JCBFM 2012

ADDITIVE EFFECT OF MICROINFARCTS AND AD PATHOLOGY



Religious Orders Study

Probability dementia:
AD + vascular pathology

Arvanitakis et al Stroke 2011

Review

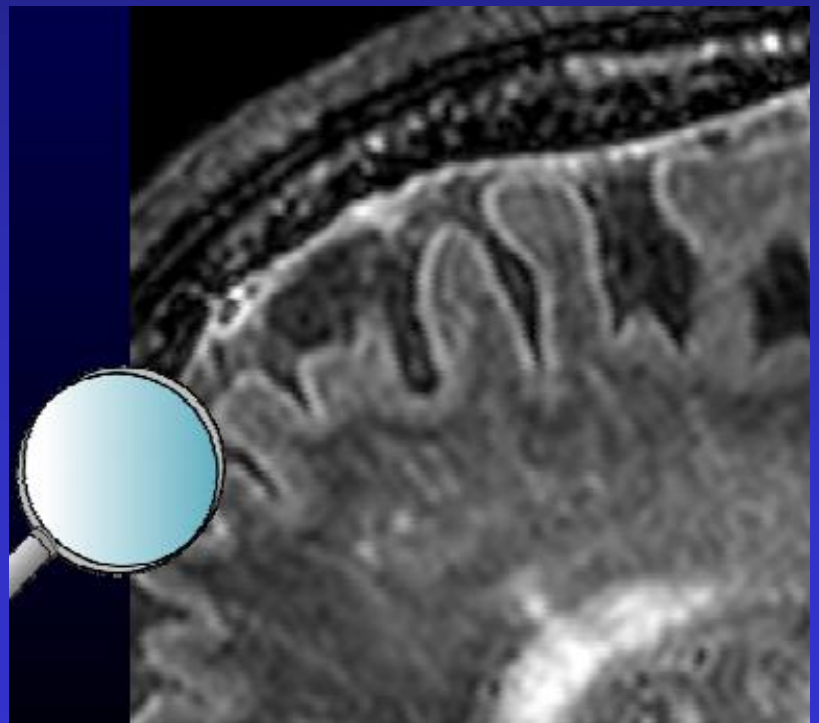
Cerebral microinfarcts: the invisible lesions

Eric E Smith, Julie A Schneider, Joanna M Wardlaw, Steven M Greenberg

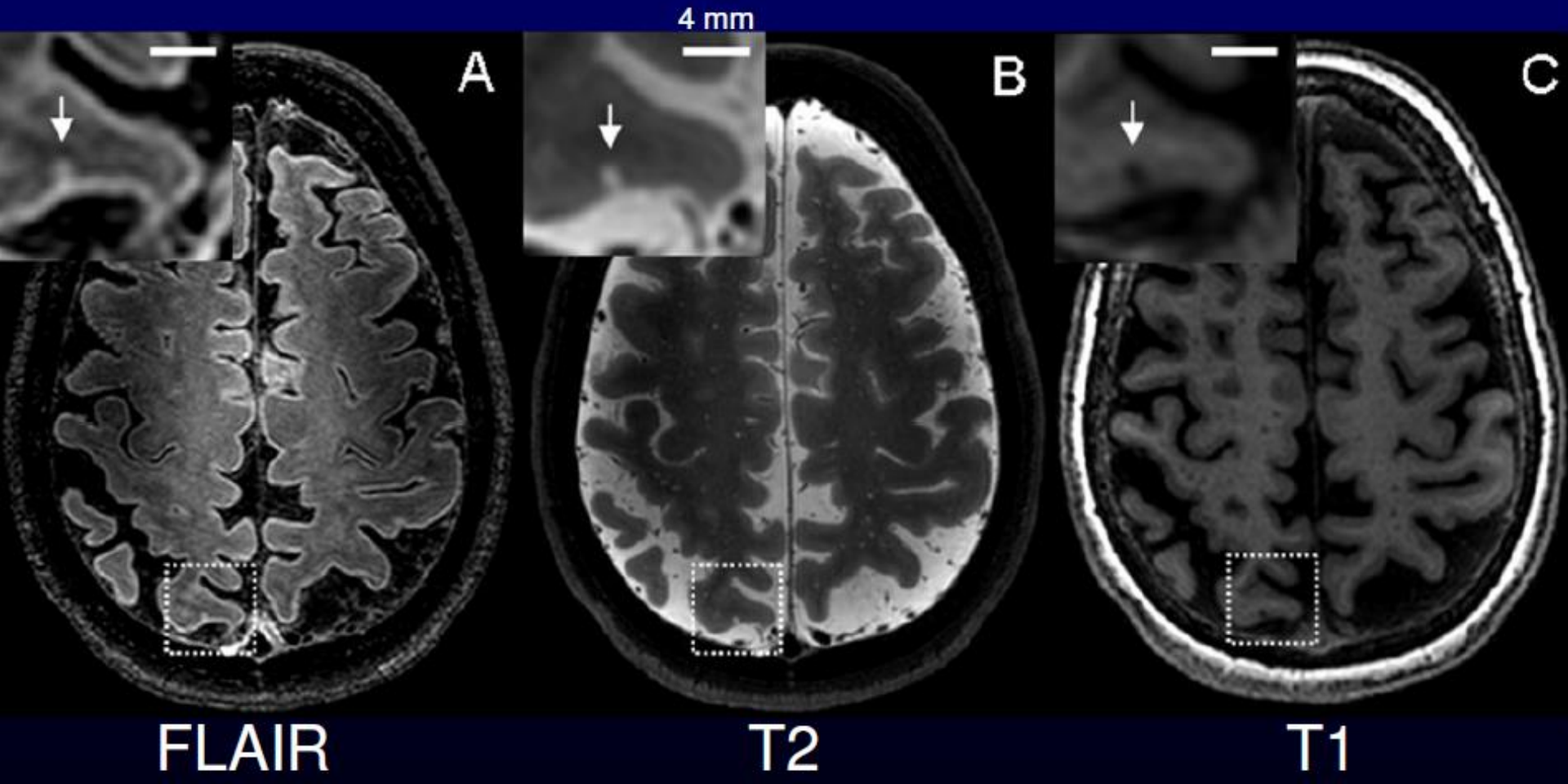
Lancet Neurol 2012; 11: 272–82

The association between small but still visible lacunar infarcts and cognitive decline has l

Until the advent of high field strength 7T MRI

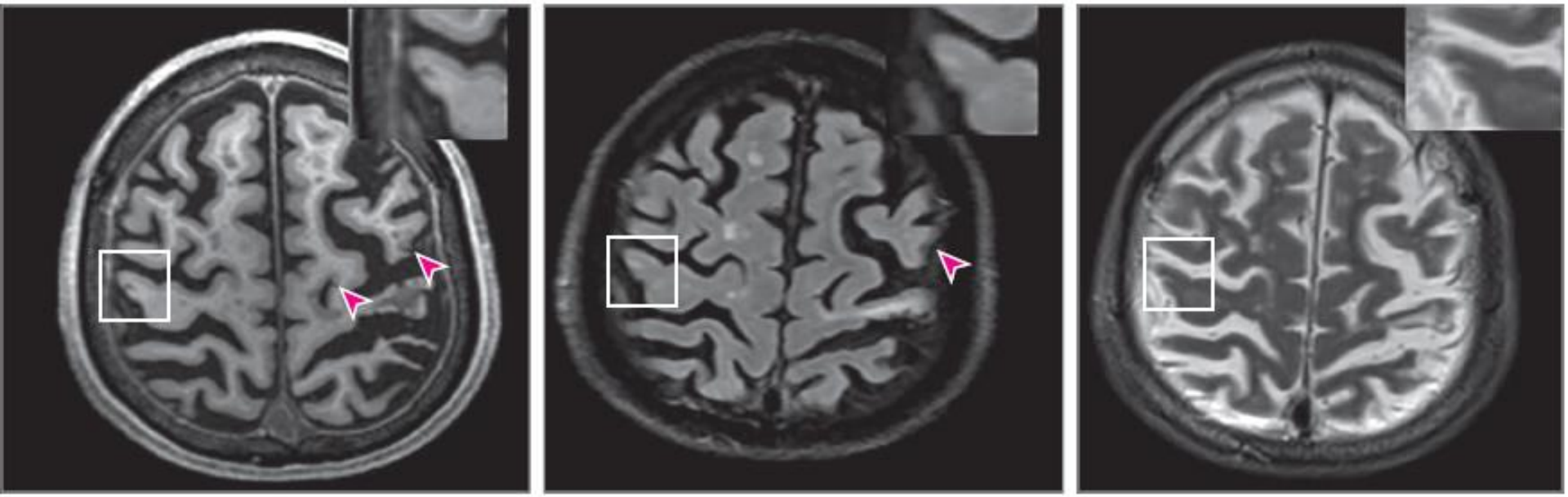


Cortical Microinfarcts are Visible on 7T MRI



van Veluw JCBFM 2013

Cortical Microinfarcts also Visible on 3T MRI



Three cortical microinfarcts detected in 70 year old male with vascular cognitive impairment
Depicted are a 3D T1 (A), FLAIR (B), and T2 (C) image

27% of 7T detected CMIs also seen on 3T
87% of 3T detected CMIs also seen on 7T

The Importance of Funding Academic Meetings

2nd Translational Strategies for Therapeutics Discovery in Dementia

Date : 1 February 2013

Venue : NUS Centre of Life Sciences Auditorium Level 1

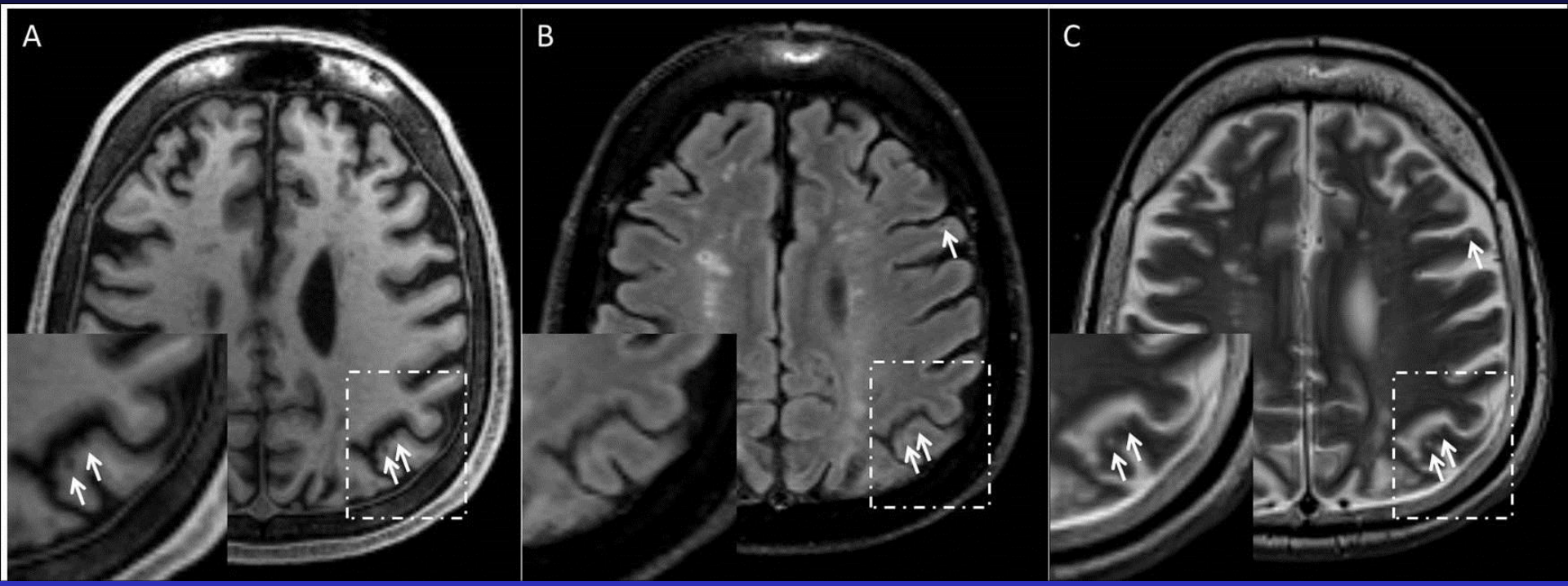
Time	Speakers	Presentation Topics
0800 - 0830 hrs	Registration	
Chairperson : A/Prof Christopher Chen		
0830 - 0835 hrs	A/Prof Christopher Chen	Introduction
0835 - 0930 hrs	Prof Duk L.Na	Plenary Lecture 1 - Prediction of PiB Negative Subcortical Vascular Dementia Using Clinical And MRI Variables
0930 - 1000 hrs	Dr Helen Zhou	Predicting regional neurodegeneration from healthy functional connectome
1000 - 1030	Dr Kamran Ikram	Association of Retinal Imaging with Neuroimaging and Cognition
1030 - 1100 hrs	Coffee break	
Chairperson : Prof Carlos Ibanez		
1100 - 1130 hrs	Dr Andrea Lim	Animal and Cell Culture Models of Alzheimer's Disease
1130 - 1200hrs	Dr Mitchell Lai	Genome wide microarray approaches toward biomarkers discovery in dementia
1200 - 1300 hrs	Lunch break	
Chairperson : Prof Barry Halliwell		
1300 - 1400 hrs	Prof Paul Francis	Plenary Lecture 2 - Neurochemical studies of dementia: clues for new biomarkers
1400 - 1430 hrs	A/Prof Newman Sze	Degenerative protein post-translational modifications in human disease and ageing
1430 - 1500 hrs	Coffee break	
Chairperson : Prof David Townsend		
1500 - 1600 hrs	Prof. Geert Jan Biessels	Plenary Lecture 3 - Imaging cortical microinfarcts and cerebrovascular lesions
1600 - 1630 hrs	Dr Qiu Anqi	Cortical Atrophy and White Matter Lesions in Vascular Cognitive Impairment : Preliminary Results from the Memory Aging & Cognition Centre Harmonisation Study
1630 - 1700 hrs	Dr Chuang Kai Hsiang	Development of Arterial Spin Labeling Perfusion MRI for Translation Study of Dementia
	End of Conference	

Clinical Significance of Cortical Microinfarcts

- 238 consecutive patients (72.5±9.1 years, 49% men) from a memory clinic in Singapore between December 2010 and September 2013.
- All patients underwent extensive neurological and neuropsychological testing and 3T MRI on the same day
- Cortical CMI rating criteria were adapted from a previous study at 7T MRI.

Van Veluw et al (2015)

Cortical Cerebral Microinfarcts



Three cortical CMIs on the 3T MR images of a 63-year old Singaporean male with ‘vascular cognitive impairment no dementia’.
Depicted are a 3D T1 (A), FLAIR (B), and T2 (C) image.
This patient had 32 cortical CMIs, of which 3 are captured in these images (arrows).

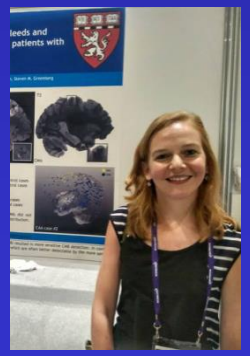
Van Veluw et al (2015)

Cortical Microinfarcts : Cognition

Characteristics	without CMIs (N=163)	with CMIs (N=75)	B [95% CI]	P-value
Cognitive profile				
Mini-mental state examination	21.0 ± 6.2	19.5 ± 5.9	-1.49 [-2.89; -0.08]	**0.038**
Montreal Cognitive Assessment	16.5 ± 7.2	15.2 ± 6.9	-1.38 [-2.96; 0.20]	0.086
Composite z-score	0.08 ± 1.05	-0.17 ± 0.10	-0.20 [-0.42; 0.01]	0.067
Executive function	0.06 ± 1.00	-0.13 ± 1.00	-0.18 [-0.41; 0.05]	0.133
Attention	0.03 ± 1.00	-0.07 ± 1.02	-0.11 [-0.34; 0.13]	0.375
Language	0.09 ± 1.04	-0.21 ± 0.89	-0.28 [-0.53; -0.04]	**0.023**
Verbal memory	0.05 ± 1.05	-0.11 ± 0.88	-0.13 [-0.37; 0.10]	0.268
Visual memory	0.07 ± 1.06	-0.15 ± 0.84	-0.21 [-0.45; 0.03]	0.086
Visuoconstruction	0.10 ± 1.03	-0.21 ± 0.89	-0.30 [-0.52; -0.08]	**0.008**
Visuomotor speed	0.07 ± 1.06	-0.15 ± 0.83	-0.19 [-0.40; 0.01]	0.067

Prevalence of 32% in Memory Clinic patients

Characteristics	Without CMIs (N=163)	With CMIs (N=75)	OR [95%CI]	P-value
Referral diagnosis				
No cognitive impairment	26 (16)	4 (5)	0.27 [0.09 ; 0.85]	**0.025**
CIND, without stroke	29 (18)	5 (7)	0.34 [0.12 ; 0.92]	**0.033**
CIND with stroke	32 (20)	23 (31)	1.80 [0.94 ; 3.47]	0.078
Alzheimer's disease	66 (40)	31 (41)	1.13 [0.60 ; 2.12]	0.708
Vascular dementia	10 (6)	12 (16)	2.86 [1.17 ; 6.99]	**0.021**



van Veluw, Hilal S et al. 2015, Alz and Dem

Cortical Microinfarcts : Risk Factors

Prevalence of 6.3% in population based study

Risk factors	CMI (presence vs. absence) OR (95%CI)*	CMI (counts) RR (95%CI)†
Demographics		
Age, (per year increase)	**1.09 (1.05-1.14)**	**1.09 (1.06-1.12)**
Gender (men vs. women)	1.47 (0.83-2.62)	**1.77 (1.22-2.56)**
Ethnicity,		
Malay vs. Chinese	**2.38 (1.17-4.84)**	**2.29 (1.42-3.69)**
Malay vs. Indian	1.84 (0.87-3.89)	**1.79 (1.14-2.81)**
Chinese vs. Indian	0.83 (0.35-1.99)	0.78 (0.44-1.38)
Cardiovascular risk factors		
Hypertension, (yes vs. no)	**3.36 (1.02-11.09)**	**4.33 (1.58-11.83)**
Hyperlipidemia, (yes vs. no)	0.71 (0.36-1.39)	0.91 (0.56-1.45)
Diabetes, (yes vs. no)	1.40 (0.77-2.54)	**1.59 (1.10-2.31)**
Smoking (ever vs. never)	1.68 (0.79-3.54)	1.36 (0.85-2.17)
BMI (kg/m^2)	0.96 (0.88-1.05)	0.98 (0.93-1.04)
History of stroke, (yes vs. no)	**5.56 (2.59-11.96)**	**4.85 (3.17-7.43)**
History of cardiovascular disease, (yes vs. no)	1.02 (0.39-2.65)	0.90 (0.52-1.58)
MRI markers		
Cortical infarct, (yes vs. no)	**14.91 (6.40-34.71)**	**13.64 (9.40-19.78)**
Lacunar infarct, (yes vs. no)	**3.53 (1.87-6.63)**	**4.94 (3.25-7.50)**
WMH volume, ml, log transformed	**2.61 (1.40-4.85)**	**2.28 (1.55-3.33)**
Cerebral microbleed (yes vs. no)	1.34 (0.74-2.43)	**1.72 (1.15-2.57)**
Intracranial stenosis (yes vs. no)	**1.97 (1.02-3.80)**	**3.57 (2.40-5.31)**

*Adjusted for age, gender, ethnicity, hypertension, history of stroke (significant from model I)
†Adjusted for age, gender, ethnicity, hypertension, diabetes and history of stroke (significant from model I)

Hilal S, et al. (Neurology, 2016)

Review

Detection, risk factors, and functional consequences of cerebral microinfarcts

Susanne J van Veluw, Andy Y Shih, Eric E Smith, Christopher Chen, Julie A Schneider, Joanna M Wardlaw, Steven M Greenberg, Geert Jan Biessels

Cerebral microinfarcts are small lesions that are presumed to be ischaemic. Despite the small size of these lesions, affected individuals can have hundreds to thousands of cerebral microinfarcts, which cause measurable disruption to structural brain connections, and are associated with dementia that is independent of Alzheimer's disease pathology or larger infarcts (ie, lacunar infarcts, and large cortical and non-lacunar subcortical infarcts). Substantial progress has been made with regard to understanding risk factors and functional consequences of cerebral microinfarcts, partly driven by new in-vivo detection methods and the development of animal models that closely mimic multiple aspects of cerebral microinfarcts in human beings. Evidence from these advances suggests that cerebral microinfarcts can be manifestations of both small vessel and large vessel disease, that cerebral microinfarcts are independently associated with cognitive impairment, and that these lesions are likely to cause damage to brain structure and function that extends beyond their actual lesion boundaries. Criteria for the identification of cerebral microinfarcts with in-vivo MRI are provided to support further studies of the association between these lesions and cerebrovascular disease and dementia.

Lancet Neurol 2017

Published Online
July 14, 2017
http://dx.doi.org/10.1016/S1474-4422(17)30196-5

Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands (S J van Veluw PhD, Prof G J Biessels MD); **Department of Neurology, Massachusetts General Hospital and Harvard Medical School**

Cortical Cerebral Microinfarcts : Future Studies

cross sectional studies of CMI and
- molecular imaging (amyloid, tau PET)
- **brain connectivity**,
- **brain perfusion,**
- lesion symptom mapping,
- Retinal imaging and
- **blood biomarkers**

longitudinal studies of CMI and
- **cognition**,
- MRI markers,
- Retinal imaging

Plasma NTproBNP and hs-cTnT are associated with dementia and CIND, only when accompanied by presence of CeVD

Hilal et al, Medicine 2015

	CIND (n = 78) OR (95% CI)*	Dementia (n = 80) OR (95% CI)*
Pro brain natriuretic peptide		
1st tertile	1	1
2nd tertile	1.52 (0.57–4.04)	0.79 (0.23–2.69)
3rd tertile	3.12 (0.61–15.99)	5.44 (0.98–30.21)
High sensitivity Troponin T		
1st tertile	1	1
2nd tertile	1.64 (0.60–4.43)	1.04 (0.27–4.01)
3rd tertile	2.66 (0.69–10.29)	4.13 (0.83–20.51)

CI = confidence interval, CIND = cognitive impairment no dementia, OR = odds ratios.
* Adjusted for age, gender, education, hypertension, and cardiovascular diseases (atrial fibrillation, congestive heart failure, and myocardial infarction).

	Presence of Significant Cerebrovascular Diseases			
	Absence		Presence	
	CIND (n = 37), OR (95% CI)*	Dementia (n = 34), OR (95% CI)*	CIND (n = 41), OR (95% CI)*	Dementia (n = 46), OR (95% CI)*
Pro brain natriuretic peptide				
1st tertile	1	1	1	1
2nd tertile	0.87 (0.28–2.77)	0.51 (0.11–2.39)	2.35 (0.72–7.66)	1.50 (0.38–5.99)
3rd tertile	2.52 (0.44–14.35)	4.77 (0.63–36.06)	4.59 (0.75–27.93)	7.74 (1.23–48.58)
High sensitivity Troponin T				
1st tertile	1	1	1	1
2nd tertile	0.96 (0.28–3.29)	0.61 (0.12–3.08)	4.36 (1.14–16.71)	3.62 (0.47–27.69)
3rd tertile	1.35 (0.28–6.47)	3.82 (0.55–26.38)	9.05 (1.64–49.79)	16.89 (2.02–142.67)

CI = confidence interval, CIND = cognitive impairment no dementia, OR = odds ratios.
* Adjusted for age, gender, education, hypertension, and cardiovascular diseases (atrial fibrillation, congestive heart failure, and myocardial infarction).

Association of subclinical cardiac biomarkers and clinical cardiac diseases with CMIs (Hilal et al, JAMA Neurology 2017)

	CMI counts	CMI (presence vs. absence)	CMI (≥3 vs. <3)
	RR (95%CI)	OR (95%CI)	OR (95%CI)
Subclinical cardiac diseases			
Log pro brain natriuretic peptide			
Model I	3.85 (3.18-4.66)	2.71 (1.49-4.93)	5.34 (2.37-12.06)
Model II	3.19 (2.62-3.90)	2.51 (1.34-4.69)	4.63 (1.98-10.83)
Log high sensitivity Troponin T			
Model I	7.98 (5.08-12.53)	3.99 (1.30-12.22)	13.23 (2.38-73.64)
Model II	4.86 (3.03-7.08)	3.19 (0.94-10.75)	9.41 (1.54-57.32)
Clinical cardiac diseases			
Atrial fibrillation			
Model I	2.14 (1.59-2.88)	4.42 (1.73-11.32)	4.99 (1.72-14.47)
Model II	1.62 (1.20-2.18)	3.76 (1.42-9.91)	3.94 (1.32-11.74)
Ischemic heart disease			
Model I	5.61 (4.41-7.14)	3.28 (1.43-7.54)	7.24 (2.67-19.63)
Model II	4.31 (3.38-5.49)	2.64 (1.12-6.22)	5.67 (2.05-15.65)
Congestive heart failure			
Model I	2.94 (1.86-4.65)	9.98 (1.09-91.56)	15.37 (2.24-105.38)
Model II	2.05 (1.29-3.25)	7.23 (0.78-66.77)	10.68 (1.54-74.06)

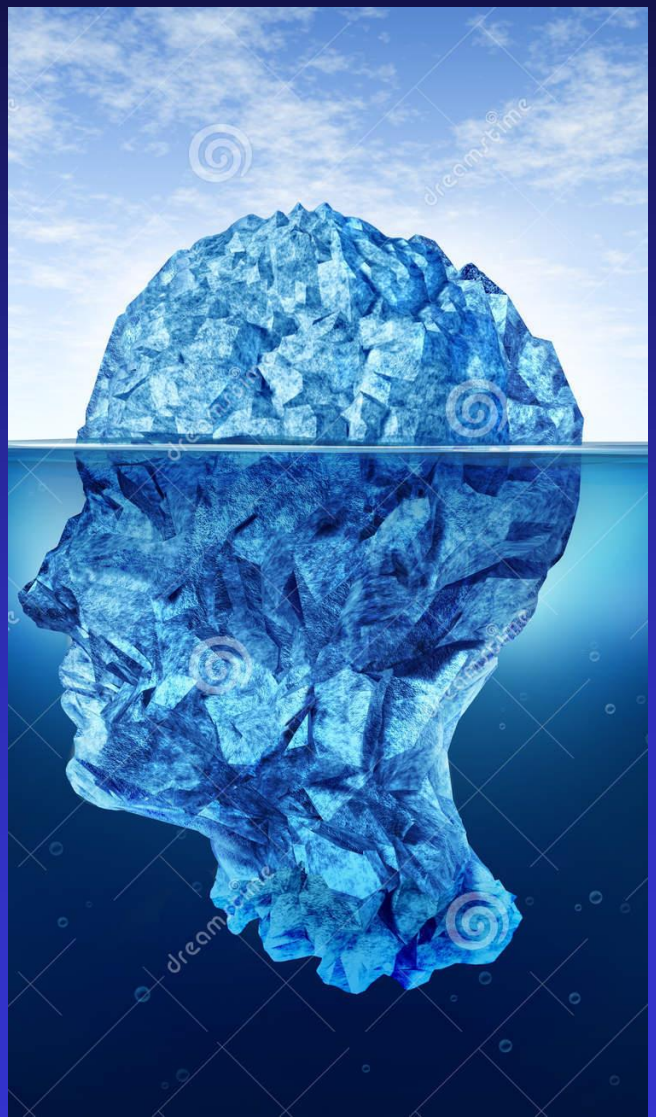
The Brain-Heart Axis : Future Studies

- cross sectional studies of CeVD markers and
  - molecular imaging brain connectivity,
  - brain perfusion,
  - retinal imaging
  - **blood biomarkers**
  - **Cardiac and vascular biomarkers**
- longitudinal studies of brain and heart biomarkers with
  - cognition
  - brain, cardiac and vascular biomarkers
- Interventional studies

SINGapore intervention study to prevEnt coGnitive impairment and disability (SINGER) study

- Based on the ground breaking FINGER study in collaboration with World Wide FINGERS
- Randomised controlled study of multiple interventions in elderly patients at risk of cognitive decline (E Koo and C Chen)
  - Cognitive (X Xu)
  - Diet (CJ Henry)
  - Exercise (E Chew)
  - Vascular risk modification (C Chen)
- Pilot proof of concept and feasibility studies to be proposed and executed prior to larger scale study
- FINGER vs SINGER adaptations

The burden of “silent” cerebrovascular disease

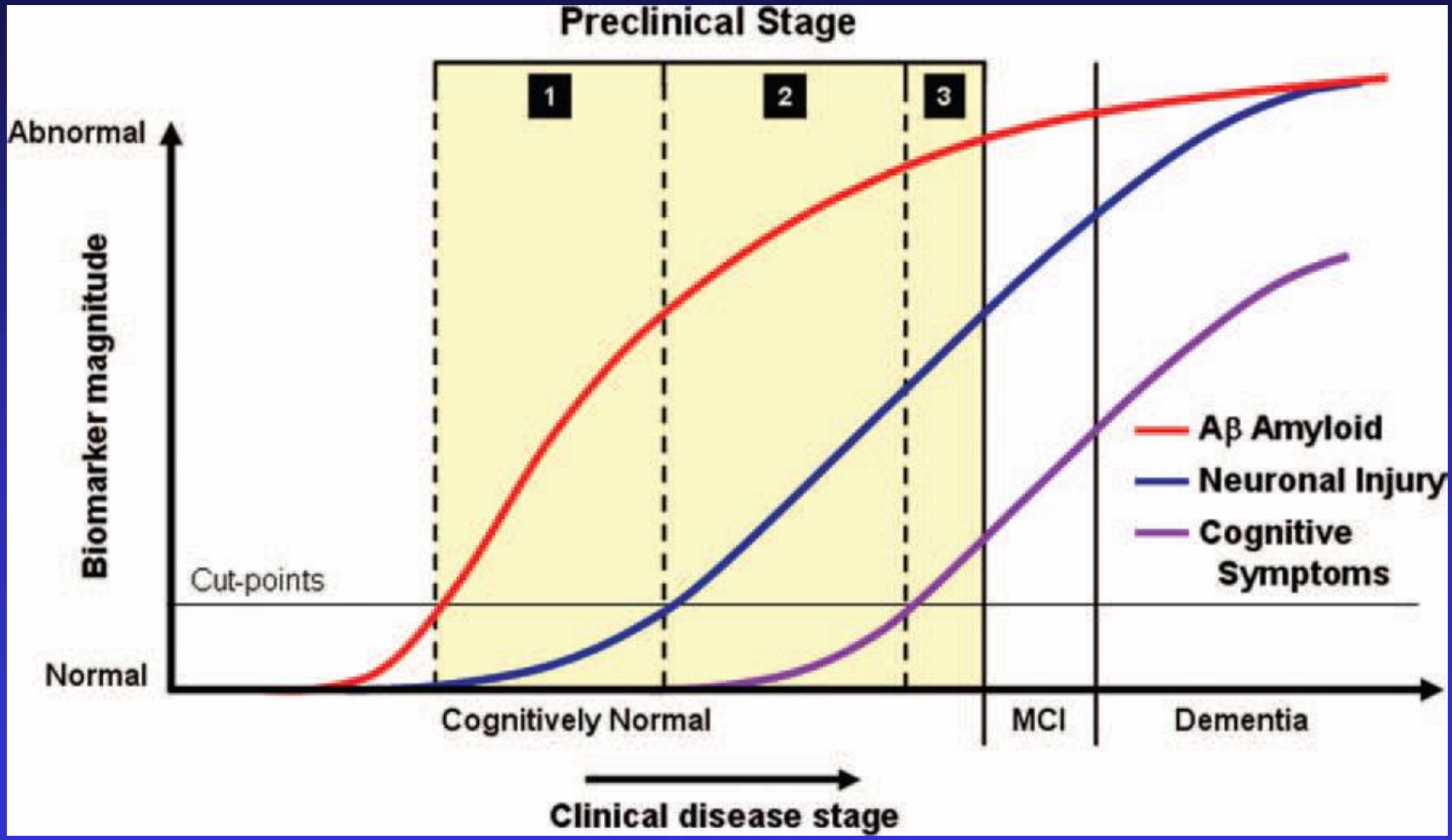


Under-recognized

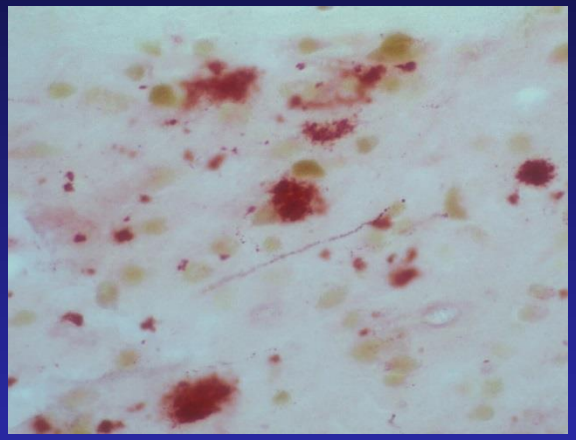
Ignored

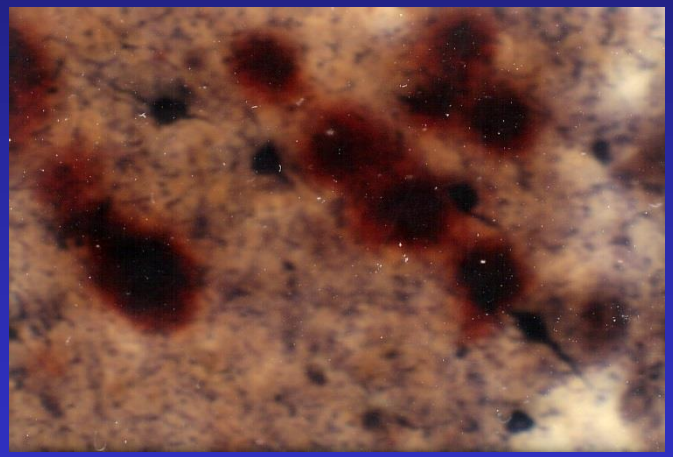
Important

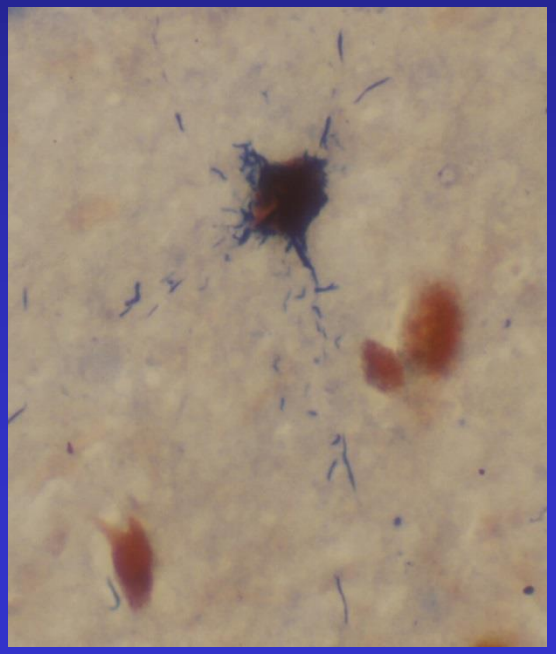
Model of AD Progression



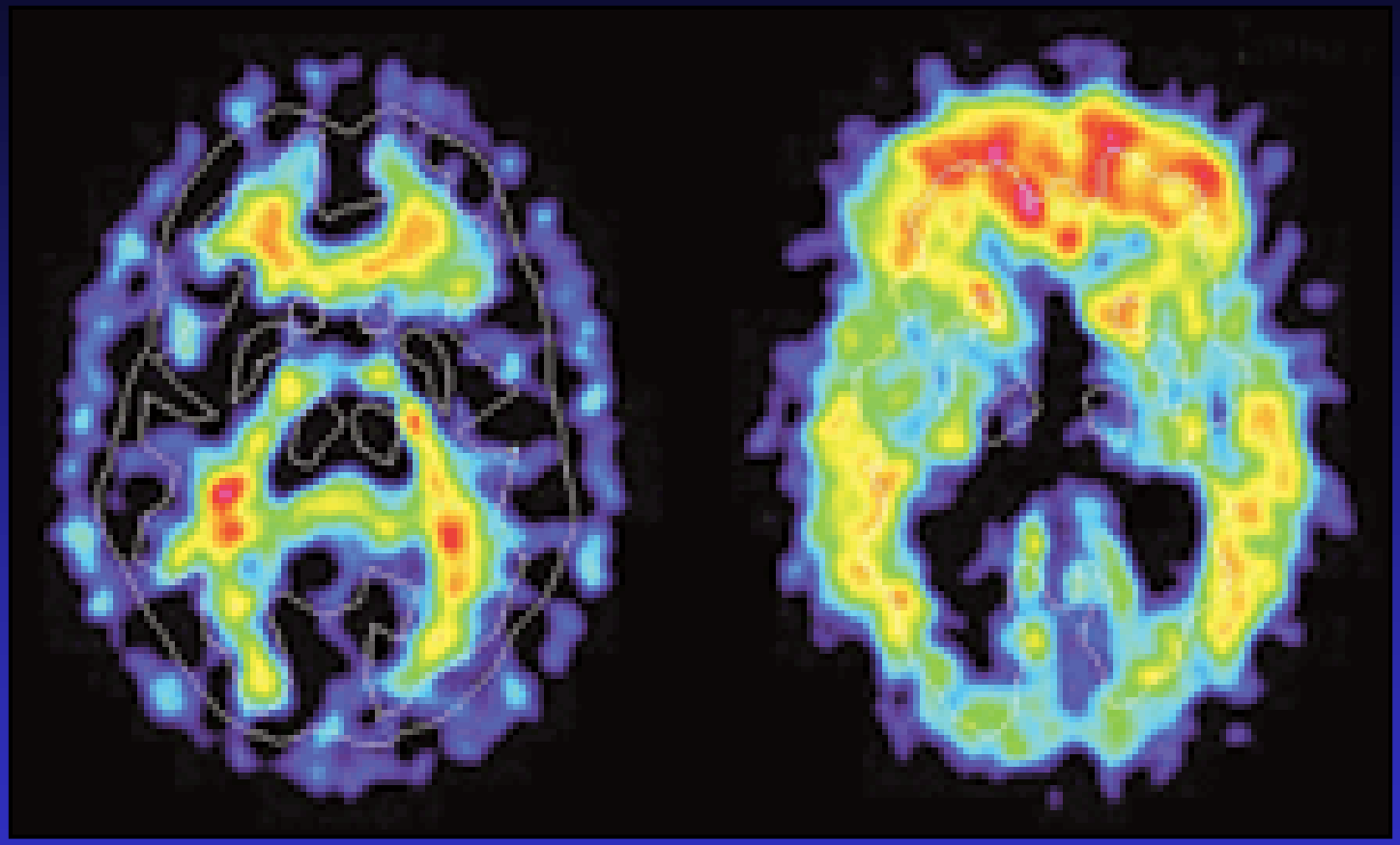
AMYLOID PLAQUES AND NEUROFIBRILLARY TANGLES







MOLECULAR IMAGING



Aglow with Alzheimer's. The first images of a β-amyloid tracer in humans show an ominous signal in the brains of patients with early symptoms of Alzheimer's disease.
Helmuth, L. Science, **297**, 752-3 (2002).

Utility of Amyloid PET

- To define molecular pathology in vivo for diagnostic purposes
  - Identifying pre-clinical subjects with early AD pathology
  - Differentiating MCI due to AD from non AD-MCI
  - Differentiating AD from late onset FTD
  - Differentiating VaD from AD+CVD
- To identify patients for anti-amyloid trials
- To identify contribution of other pathologies to progression
  - Ideally as part of complete diagnostic workup which includes MRI and FDG-PET
- NOT for persons without cognitive impairment (except in research)

Amyloid PET Research Objectives in NUS

- Investigating the natural history of individuals with mild cognitive impairment (MCI) with high amyloid PET signal
  - Is their progression affected by concomitant vascular pathology?
- Prevalence of amyloid PET in ApoE4 negative AD and MCI subjects
- Prevalence of amyloid PET in VaD and vascular MCI subjects
- Prevalence of Suspected Non-Alzheimer Pathophysiology (SNAP) and association with CeVD

Amyloid PET Research Objectives in NUS

This study will help develop molecular neuroimaging at NUHS which would be an important platform for the development of other molecular ligands such as

- tau (neurofibrillary tangles)
- microglia (neuroinflammation)
- neurotransmitters
- Synaptic / neuronal density

which would facilitate important translational research

Amyloid PET Research Objectives in NUS

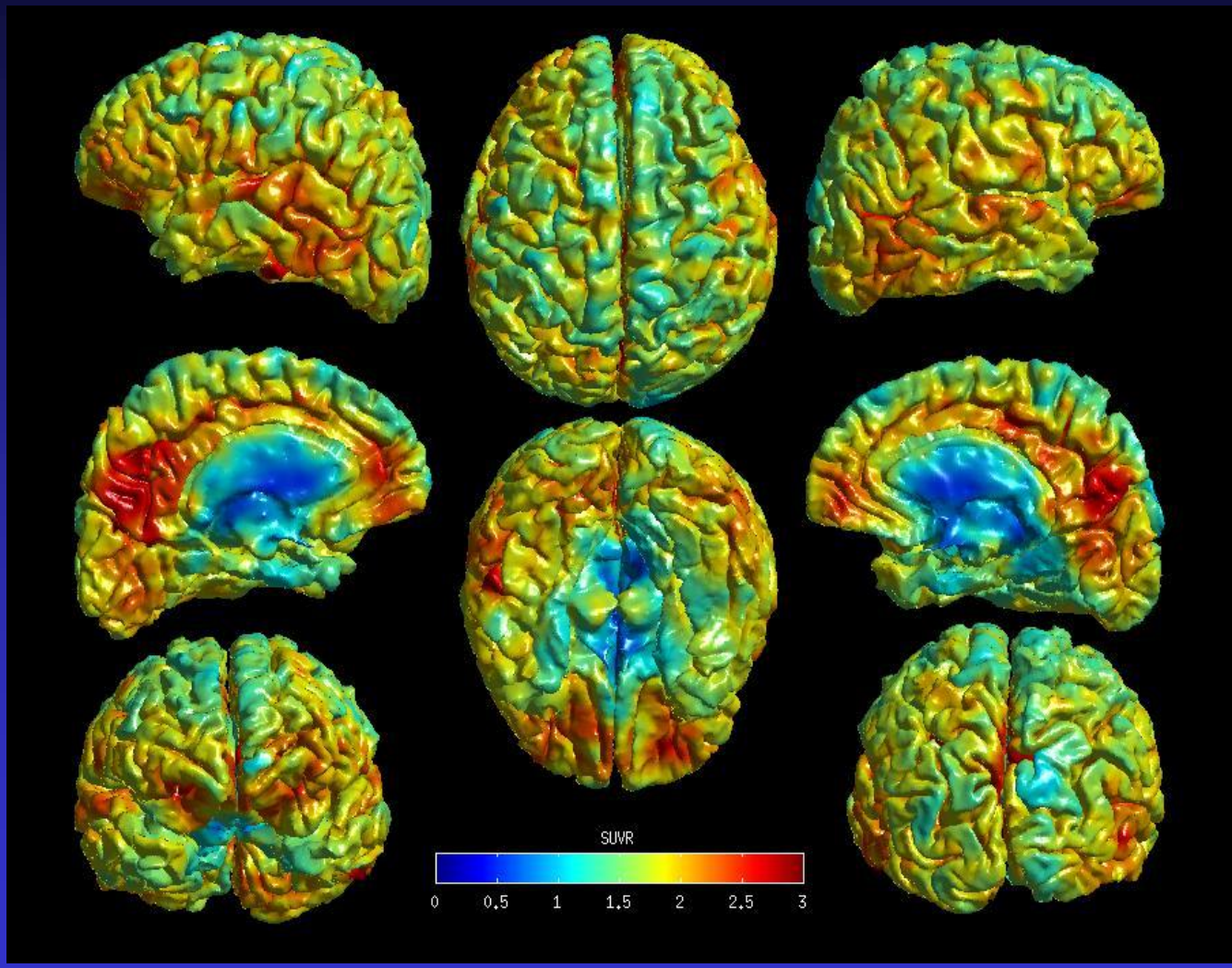
- Accelerating the discovery/validation of accessible and cost-effective biomarkers such as retinal imaging and in body fluids.
  - To examine the relationship between alterations in retinal ganglion cell (RGC) neuronal and axonal structure as well as in the retinal microvascular network to prognostic neuroimaging biomarkers of AD (PiB-PET)
  - To examine the relationship between blood biomarkers of inflammation, vascular disease (and amyloid) to PiB-PET

C11-PIB PET in NUS
First Scans in April 2016

Composite
SUVR = 1.92

Clinical Dx: AD

ApoE4 +



NOT FOR DIAGNOSTIC USE

PET Recruitment status

Target: 215 (100 MCI, 45 AD, 25 VAD, 45 NCI)

	Completed	Scheduled	To recruit
AD	**45**	0	10
MCI	100	0	0
VAD	**25**	0	5
NCI	**45**	0	20
Total	170		**45**

Completion date: end December 2018

Funded by NUS Aspiration Grant

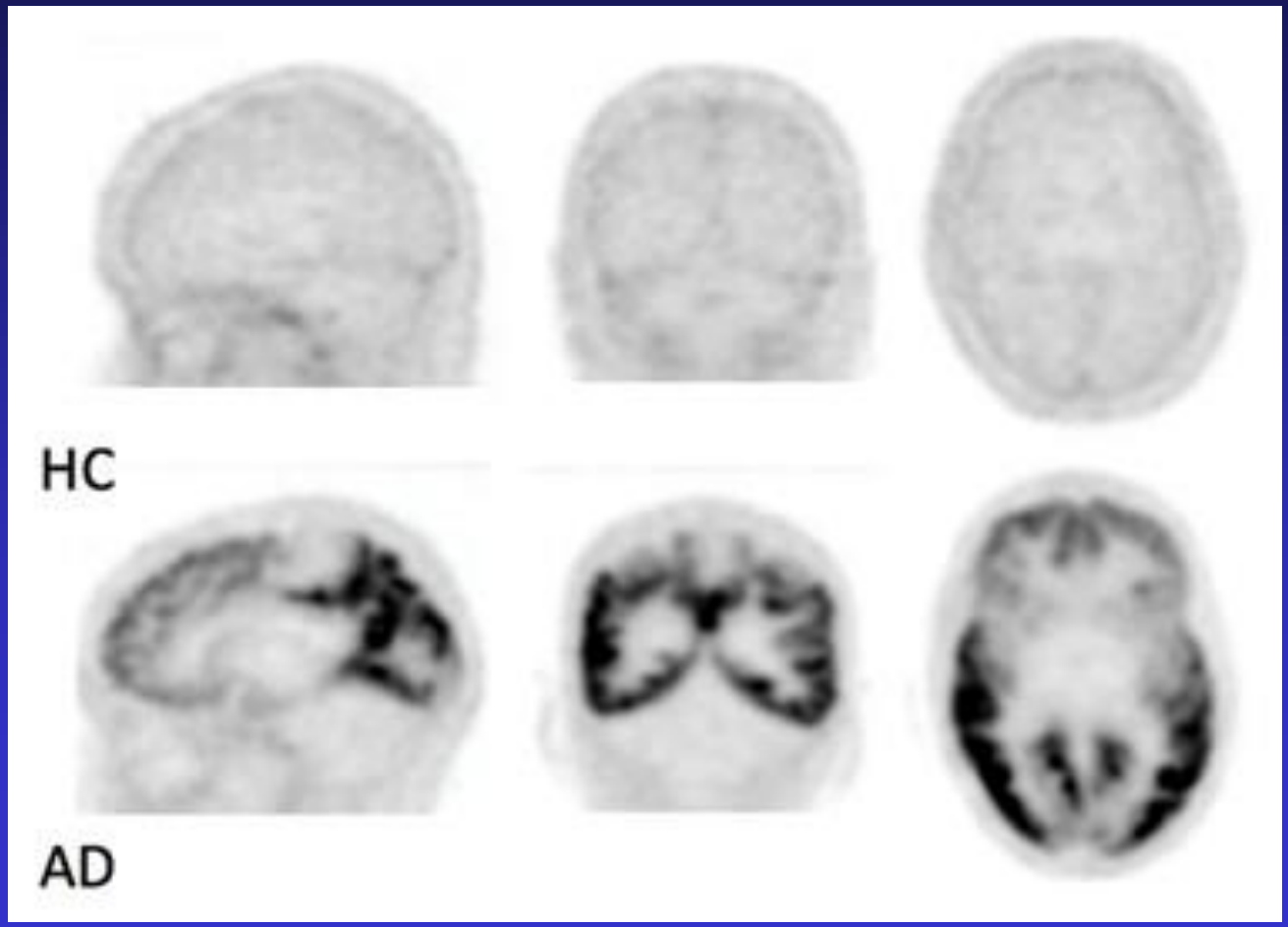
CONCLUSIONS

- Neuroimaging (including amyloid PET) is useful for the management of and research into dementia & cognitive impairment
  - Diagnosis
  - Prognosis
  - Drug discovery
  - Monitoring of treatment

Future Directions

- Papers on the
  - Impact of amyloid PET on diagnosis
  - Association of CeVD with amyloid
  - Prediction of cognitive decline
- Funding applications to
  - Investigate mechanisms of SNAP, successful aging
  - Blood biomarkers
  - Tau PET
  - F18 amyloid PET

MK-6240, a tau PET tracer developed by Merck and now Cerveau Technologies



Courtesy of Christopher Rowe

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

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

Detecting and intervening in prodromal dementia is important

An early or premonitory symptom or sign (Neuroimaging / Blood biomarkers) that indicates the onset or development of disease