Imaging Changes Associated with Alzheimer's and Cerebrovascular Disease

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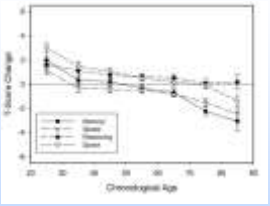
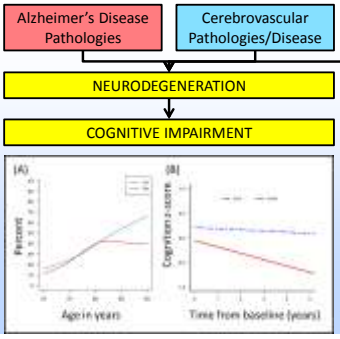
Nashville, TN
Nothing to disclose

Aging and Cognition



Longitudinal changes in different cognitive variables

Salthouse TA, Psychol Bull 2011



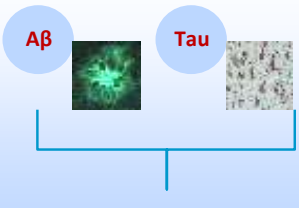
Vemuri P, Alzheimer's Res Ther 2018

Learning Objectives

- Imaging methodologies that are available for evaluation of
  - Alzheimer's disease pathophysiology
  - Cerebrovascular disease
- Studying Risk Factors for Alzheimer's disease changes
- Open questions and directions in this research area

ALZHEIMER'S DISEASE

Brain Changes in Alzheimer's Disease



Surrogate Markers Considered for Research

Aβ

Amyloid PET Imaging
CSF Aβ
*Plasma Aβ (New)

Tau

Tau PET Imaging
CSF p-tau
*Plasma p-tau (New)

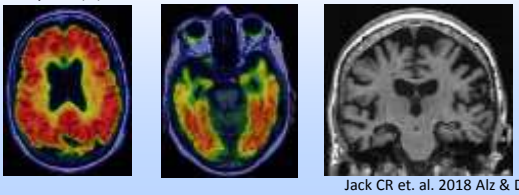
ND

Structural MRI
FDG PET
CSF t-tau
*CSF NFL (New)
*Plasma t-tau and NFL (New)

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

New 2018 Biological Definition of Alzheimer's uses A/T/N classification scheme

Amyloid (A) | Tau (T) | Neurodegeneration (N)

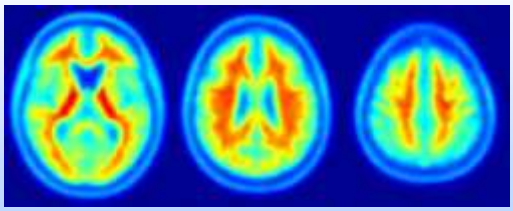


Jack CR et. al. 2018 Alz & Dem

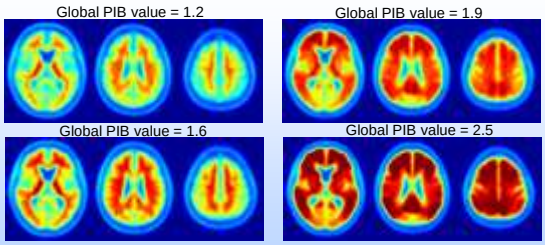
Amyloid Deposition (PET)

Amyloid Scans along the AD spectrum

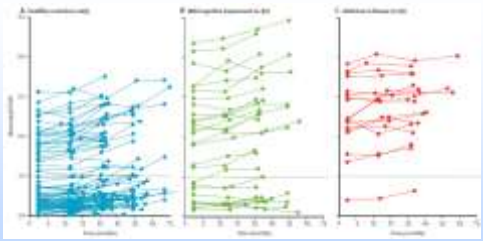
Amyloid PET tracers measure brain amyloid load by binding to fibrillar Aβ [Ikonomovic et al. Brain 2008]
Mayo Clinic Data - 670 population based individuals along the AD spectrum



Amyloid Deposition (PET tracers)

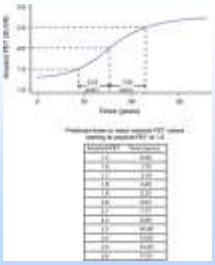


Amyloid Deposition in AD



Aβ deposition is slow and protracted, likely to extend for more than two decades. Villemange et al. Lancet Neurology 2013

Amyloid Deposition Reaches a Plateau

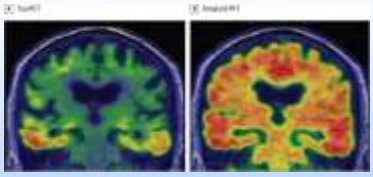


15-year interval over which amyloid deposition occurs.

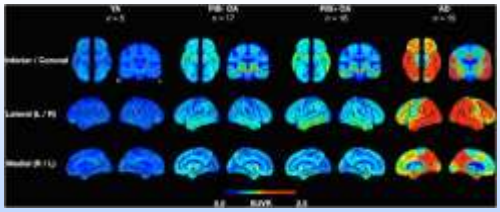
Jack CR et al. Neurology 2013

Tau Deposition (PET)

Tau Deposition (new kid on the block)



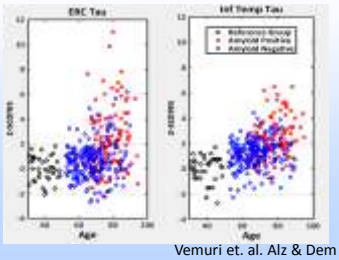
Tau PET changes in AD



Scholl M et. al., Neuron 2016

Tau Biomarkers – Temporal Lobes

Amyloid →Tau



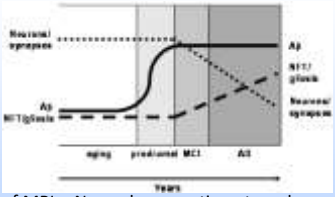
Vemuri et. al. Alz & Dem DADM 2017

Neurodegeneration (MRI)

MRI – measure of neuronal injury

Neurodegeneration due to AD

Pathological Progression in AD



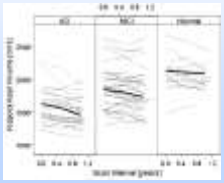
Advantages of MRI - Neurodegeneration strongly correlates with clinical symptoms (disease tracking); low variability of MR signal (high reproducibility)

Ingelsson et al. Neurology 2004

Cross-sectional Biomarker: Extracting Information from MRI scans

I. **VISUAL ASSESSMENT** (Scheltens et al. 92)

II. **QUANTITATIVE ROI BASED: E.g. Hippocampal Volume** (Jack et al 92, De Leon et al 93, Fox et al 96)



Schuff et. al. Brain 2009

Cross-sectional Biomarker: Extracting Information from MRI scans

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III. **QUANTITATIVE VOXEL BASED:** Pattern differences: VBM – MCI < CN

IV. **AUTOMATED DIAGNOSTIC SYSTEMS:** Creation of composites across voxels or regions to aid individual subject diagnosis

E.g. Each patient's MRI scan is given a single number

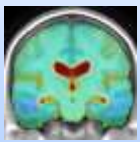
(Alexander et al 94, Fan et al 05, Duchesne et al 05, Vemuri et al 08, Kloppel et al 09, Schwarz et al 16.....)

e.g. STructural Abnormality iNDex (STAND) –scores

Longitudinal Biomarker

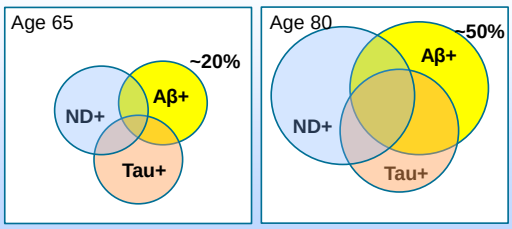
Difference between two scans (two components – register the scans and summarize the change)

Global atrophy quantification over time - BSI (Freeborough and Fox 97) – vent vol, brain vol.



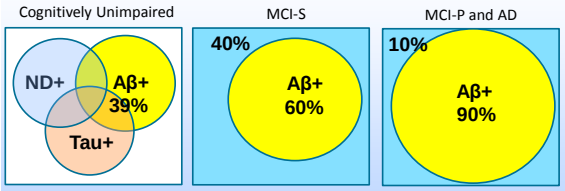
Tensor-based morphometry - TBM (Hua X, NeuroImage 2011)- Voxel level-differences.

Biomarker Based Detection in Cognitively Unimpaired: Sensitivity



Jack Jr. CR Lancet Neurology 2017

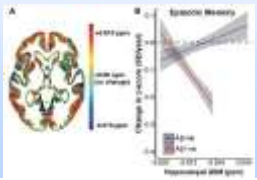
Amyloid Based Detection in Cognitive Impairment: Specificity



Ekman U et. al. Sci Rep 2018

What about other MRI modalities ?

- DTI
- fMRI
- QSM



Ayton et. al. Brain 2017

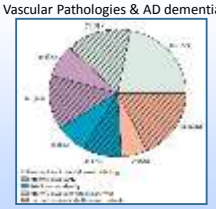
Future work for AD Imaging markers

- Biomarker-Pathology Studies
- Standardization
- Operationalization

CEREBROVASCULAR DISEASE

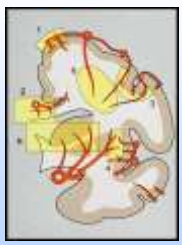
Vascular Disease and Cognitive Impairment

Vascular Pathologies & AD dementia



Arvanitakis Z. et. al.
Lancet Neurology 2016

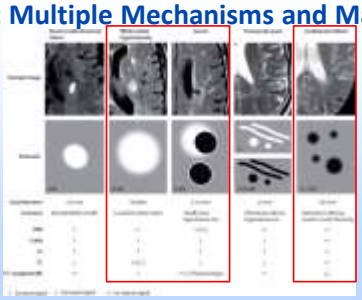
Assessing Cerebrovascular Pathologies



Regional vulnerability to global ischemia. Less vulnerable are the (1) cerebral cortex , (2) the corpus callosum , (3) the subcortical cortical u-fibers, and (4) the external capsule. More vulnerable are (5) the deep white matter and (6) basal ganglia and thalamus.

Moody et. al. AJNR 1990
Brown et. al. Neuropath & Appl. Neurobiology 2011

CVD: Multiple Mechanisms and Markers

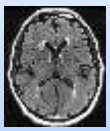


Wardlaw et. al. 2013
STRIVE CRITERIA

FLAIR MRI Images

White matter hyper intensities (WMH)
Surrogates for small-vessel ischemic disease

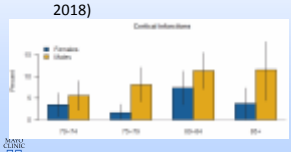
Macroinfarcts
Size and Location

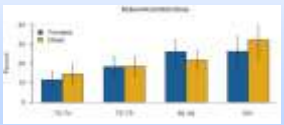


Gorelick et. al. Stroke 2011

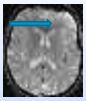
Mechanistic heterogeneity

- Regional white matter hyperintensities (McAleese et. al. 2017 Acta Neuropathol, van Westen et. al. 2016 Scientific Reports)
- Cortical vs. subcortical infarctions (Fatemi et. al. Neurology 2018)





T2* GRE MRI



Blood leakage from weakened vessels

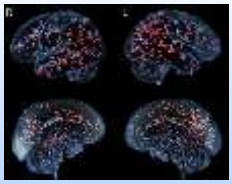
Subcortical microbleeds are associated with small vessel disease pathologies

Lobar cortical microbleeds are associated with cerebral amyloid angiopathy (CAA)

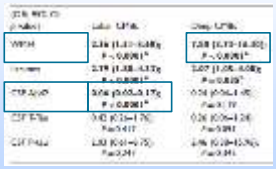
Yates PA et. al. Front Neurol 2014

Mechanistic heterogeneity

Microbleeds: Regional differences (Lobar vs. Deep)



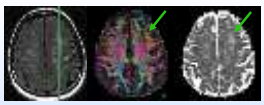
Kantarci et. al. Alz & Dem 2013



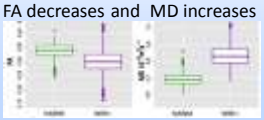
Shams et. al. JCBFM 2017

Diffusion Tensor Imaging (DTI) MRI

Microstructural changes



FA decreases and MD increases



Maniega et. al. 2015

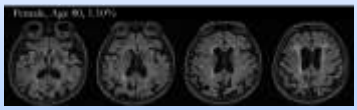
Early CVP changes

Maillard et. al. 2013

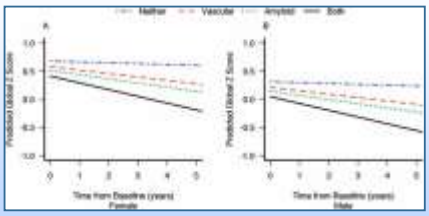
Lack of Scales for Cerebrovascular Disease

BASIC SCALE (FLAIR)

- Brain infarct (Large Cortical and Subcortical)
- How much white matter disease ?
  - Sample of 1082 non-demented elderly
    - Degree of cognitive impairment in a year



Vascular Positivity based on FLAIR

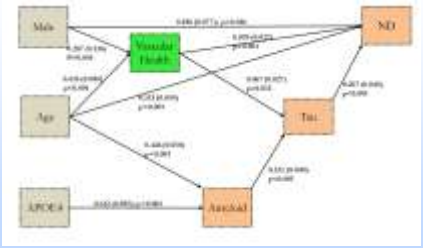


The effect of A+ and V+ on cognitive trajectories appears to be additive

Vemuri et. al. Brain 2015

RISK FACTORS FOR ALZHEIMER'S DISEASE: DESIGNING EFFECTIVE TRIALS

Vascular Risk and the "ATN" Framework



Vemuri et. al., Annals of Neurology 2017

Sleep and Amyloid

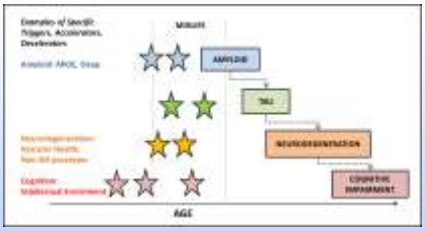
Poor sleep quality and the risk for cognitive decline and AD

- Sleep drives metabolite clearance (Xie L Science 2013)
- Cross-sectional biomarker studies (Varga AW Sleep 2016; Spira JAMA Neuro. 2013; Sprecher KE NBA 2015)

Longitudinal Amyloid Deposition vs. Sleep

Carvalho DZ JAMA Neurology 2018

Understanding Risk Factors



- Effect size estimation
- Appropriate end-points
- Better subject recruitment (subpopulation effects)

Summary: Vemuri, P. Exceptional Aging: Triggers, Accelerators, and the Net Sum Game Alz, Res & Therapy 2018

Imaging in aging and dementia

- Alzheimer's Disease (A-T-N) Framework
  - Accuracy
  - Effective trials
- Cerebrovascular Disease
  - Visible pathologies – many and heterogeneous
  - Invisible damage due to vascular health – utility of ASL and DTI

Open Questions

- Development of sensitive and specific tools for detecting early damage
- Robust Automated Diagnostic Systems
  - Large dimensionality, better learning
- Development of scales for Cerebrovascular Disease

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