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Alzheimer's Disease

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Introduction to Alzheimer's disease (AD)

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- **1906**: Dr. Alois Alzheimer's identifies the first case
- **1980s**: Introduction of the first diagnostic criteria (PMID: 6610841)
- **2000s-present**: Emergence of genetic, molecular, and imaging techniques (PMID: 20083042, PMID: 21514249)

The first reported AD

Dr. Alois Alzheimer, The pioneer in AD research
https://en.wikipedia.org/wiki/Alzheimer's_disease

Table 1. Criteria for clinical diagnosis of Alzheimer's disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

- dementia established by clinical examination and documented by the Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:
  - normal lumbar puncture as evaluated by standard techniques,
  - normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and
  - evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

- the clinical criteria for probable Alzheimer's disease and
- histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- familial occurrence;
- onset before age of 65;
- presence of trisomy-21; and
- coexistence of other relevant conditions such as Parkinson's disease.

Introduction to Alzheimer's disease (AD)

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Table 2

Biomarkers under examination for AD

Biomarkers of Aβ deposition
CSF $A\beta_{42}$
PET amyloid imaging
Biomarkers of neuronal injury
CSF tau/phosphorylated-tau
Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
Rate of brain atrophy
FDG-PET imaging
SPECT perfusion imaging
Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures
Associated biochemical change
Inflammatory biomarkers (cytokines)
Oxidative stress (isoprostanes)
Other markers of synaptic damage and neurodegeneration such as cell death

Introduction to Alzheimer's disease (AD): significance

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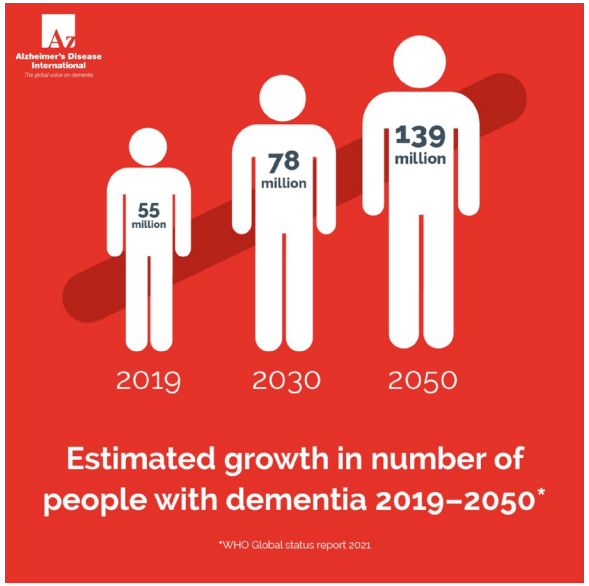
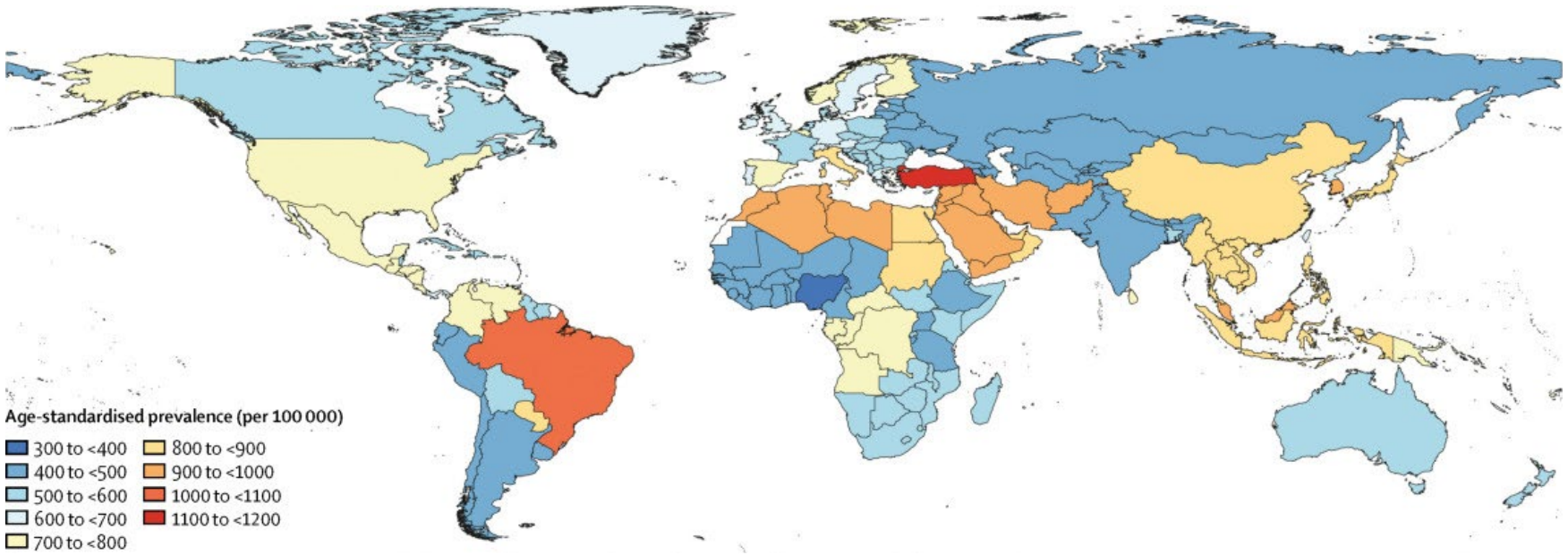
- **Prevalence**: AD affects millions worldwide (55M in 2020) (PMID: 30497964)
- **Economic impact**: Billions spent on care, treatment, and lost productivity. $321 billion cost in US for only 2022. (PMID: 37458371)
- **Potential for breakthrough**: Early diagnosis, treatment avenues, and eventual cure. (PMID: 32695874, PMID: 21514248)





Age-standardised prevalence for Alzheimer's disease and other dementias per 100 000 population

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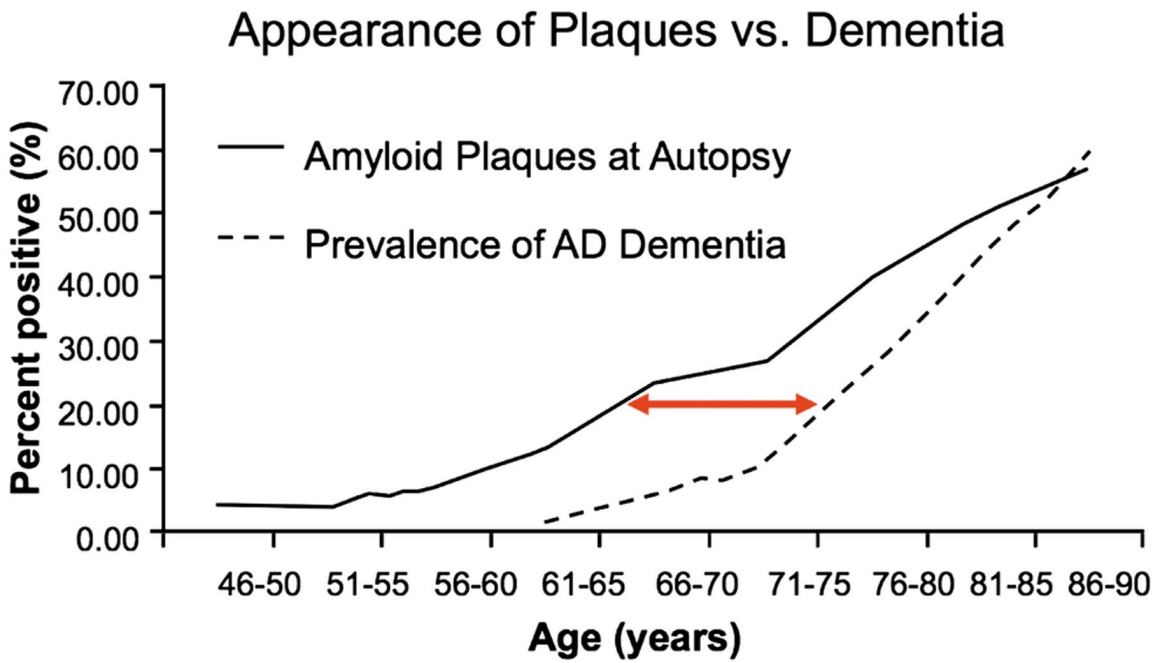

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II. AD diagnosis: A/T/N framework

Working Model of AD: A/T/N framework

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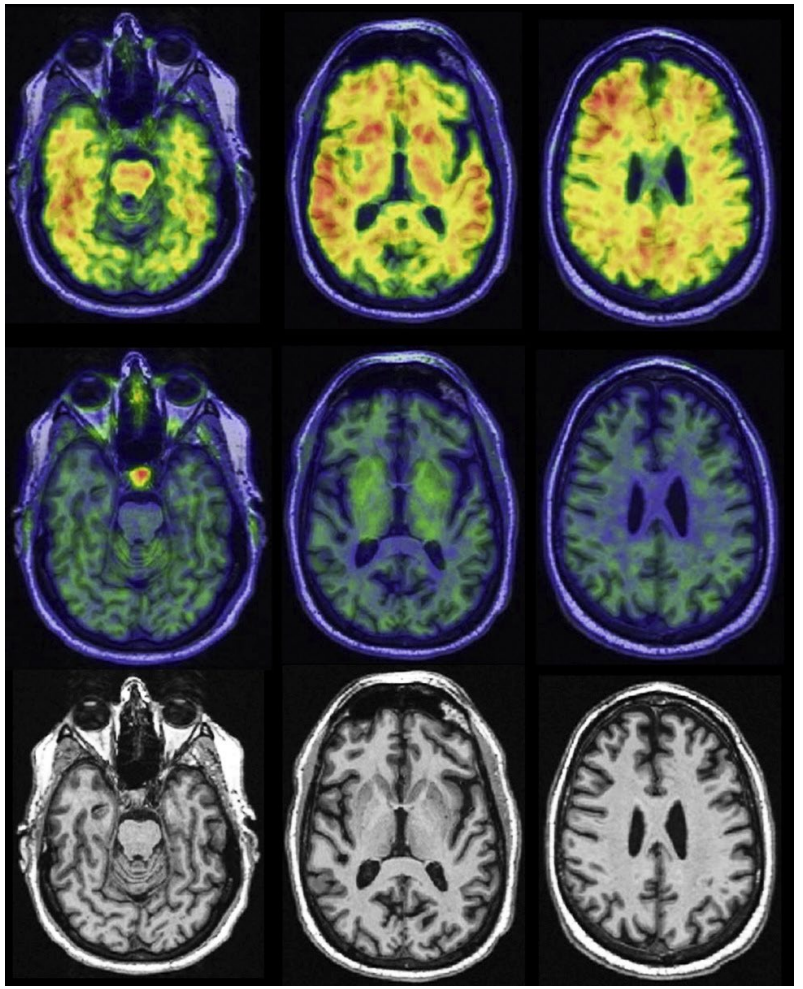
- **A:** Aggregated Aβ or associated pathologic state
  - CSF Aβ42, or Aβ42/ Aβ40 ratio
  - Amyloid PET
- **T:** Aggregated tau (neurofibrillary tangles) or associated pathologic state
  - CSF phosphorylated tau
  - Tau PET
- **N**: Neurodegeneration or neuronal injury
  - Anatomic MRI
  - FDG PET
  - CSF total tau

(PMID: 29653606)



67Yo, M, Cognitively unimpaired
PiB Ab, Flortaucipir tau, T1w
A+T-N-

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Working Model of AD: A/T/N framework

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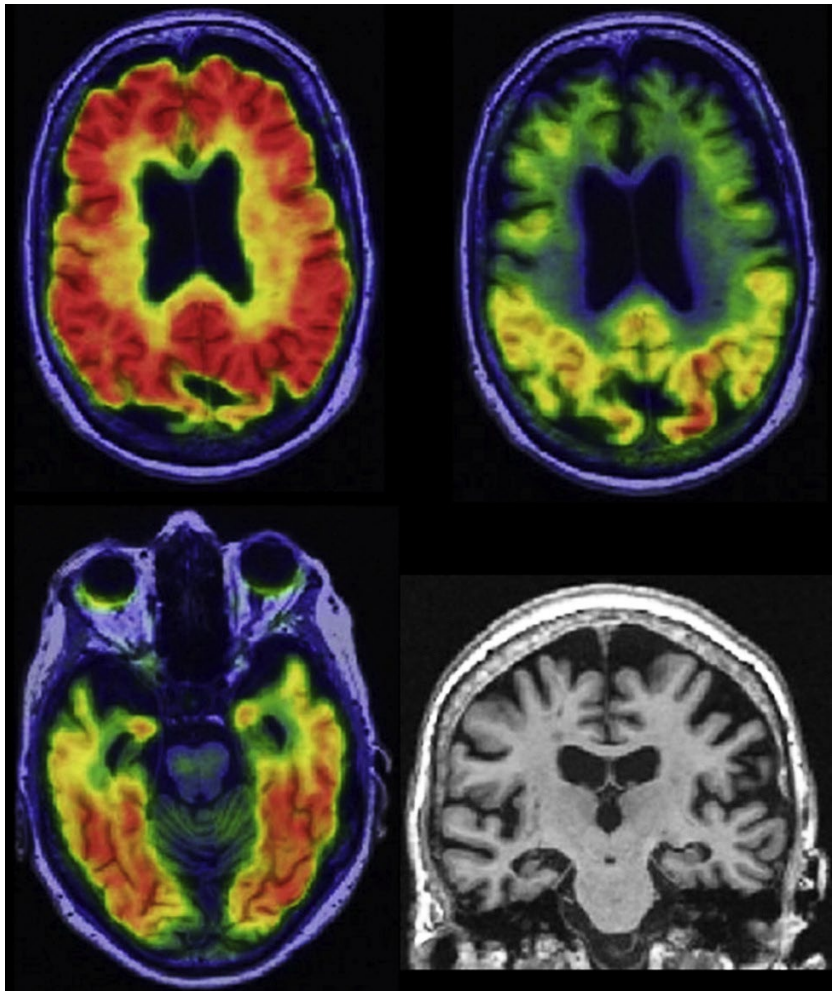

75Yo, F, AD dementia
PiB Ab, Flortaucipir tau, T1w
A+T+N+

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Hypothetic Sequence of AD: A/T/N framework

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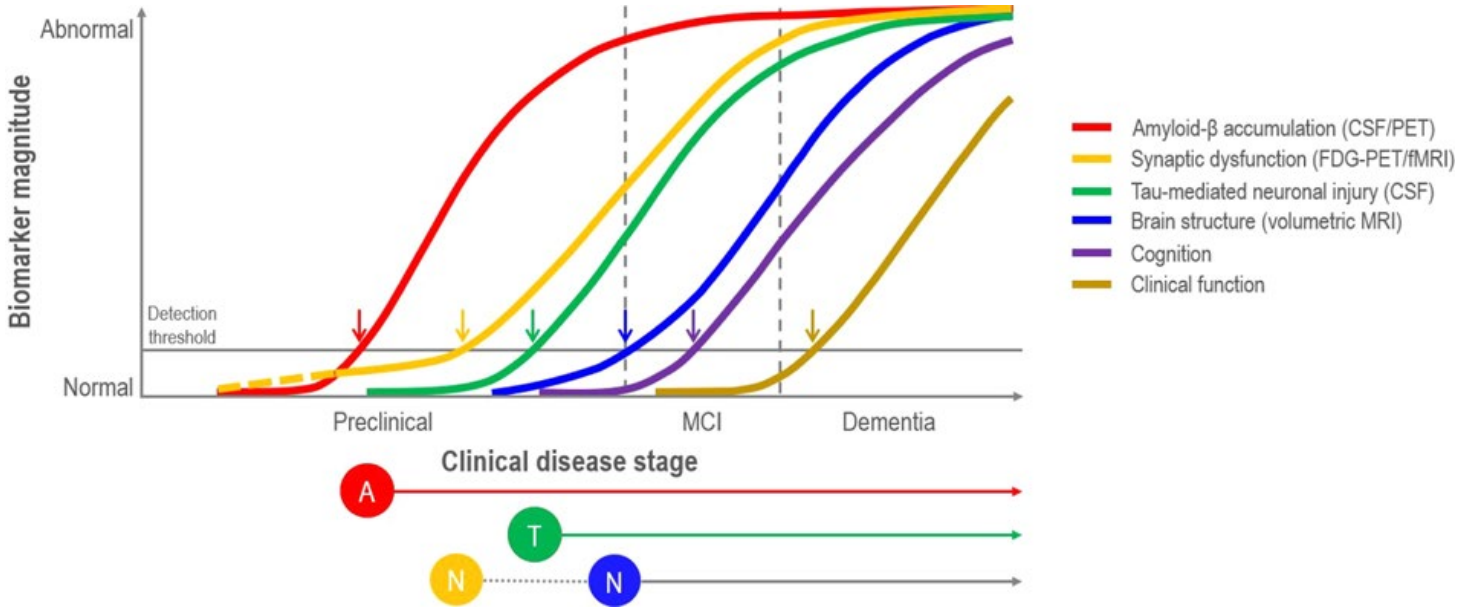

(PMID: 34456336

Definition of AD: A/T/N biomarker profile

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AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

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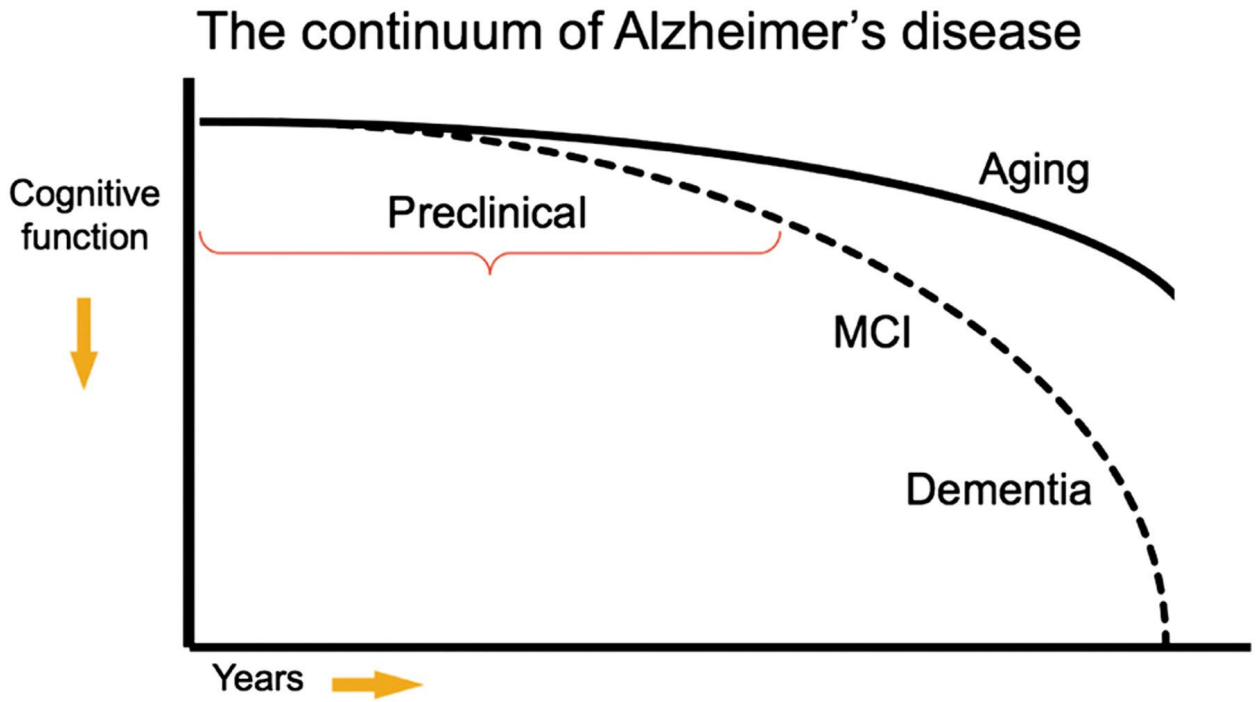

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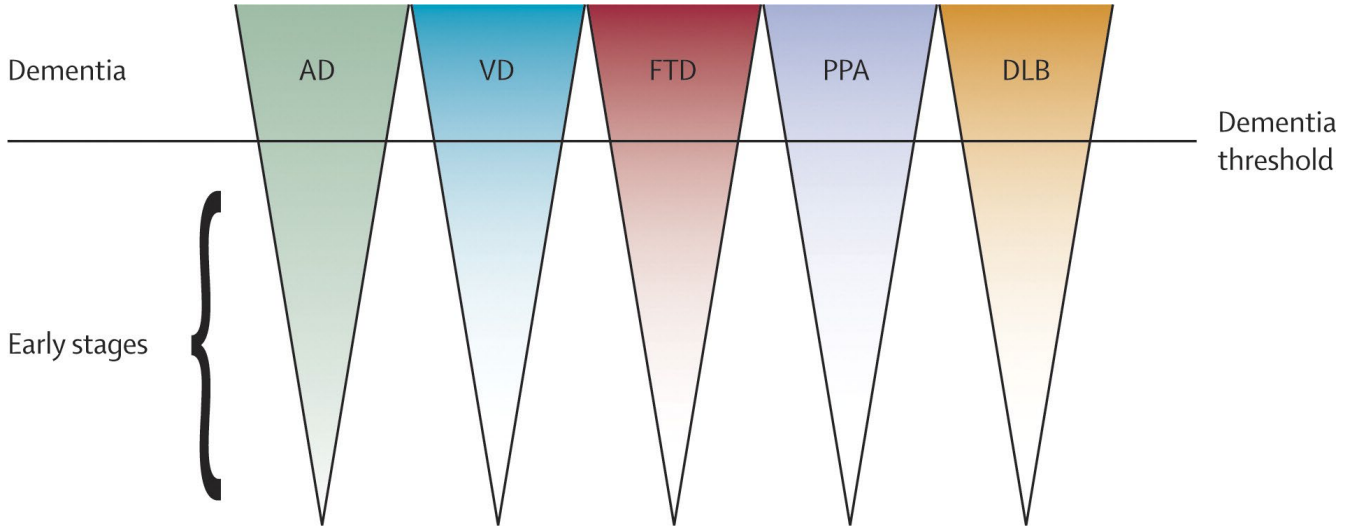

AD starts early and should be identified before the occurrence of full-blown dementia (PMID: 21514248)

AD=Alzheimer's disease;
VD=vascular dementia;
FTD=frontotemporal dementia;
PPA=primary progressive aphasia;
DLB=dementia with Lewy bodies.

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III. AD Pathologies

Pathology: Aβ plaques

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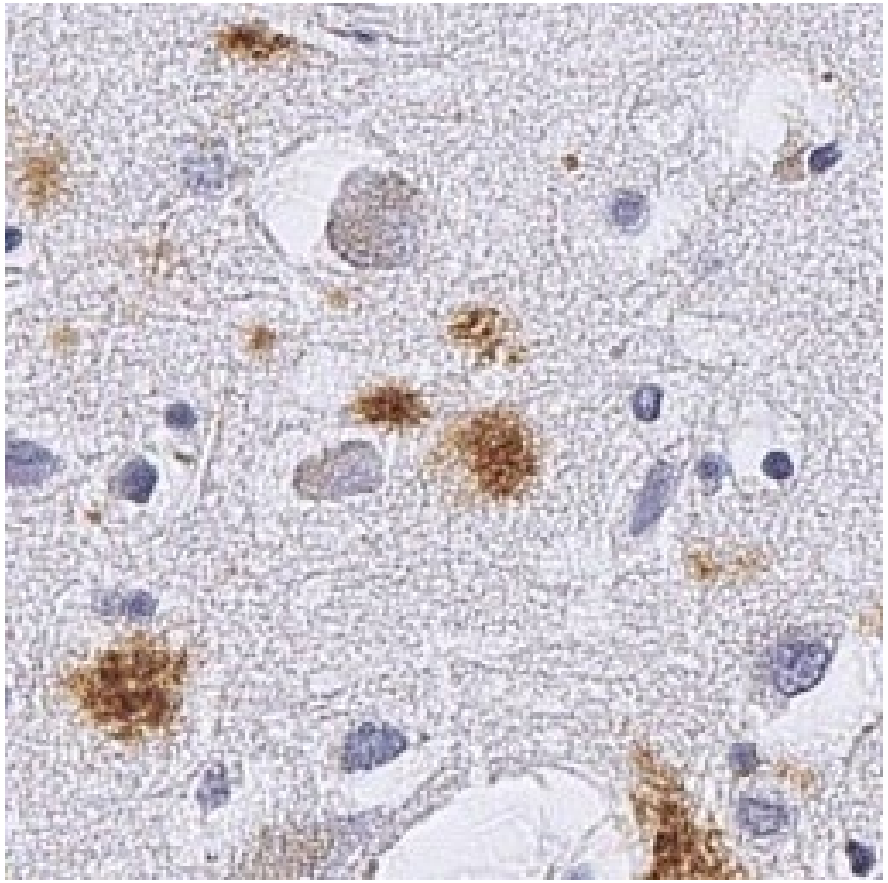
- **Definition**: Aggregates of Aβ protein that accumulate in the spaces between nerve cells (extracellular space). (PMID: 12130773, PMID: 15734686)
- **Formation**: Abnormal processing of the amyloid precursor protein (APP) leads to production of Aβ (PMID: 21456963, PMID: 22896675, PMID: 21148344)
- **Clearance**: Clearance deficit results in accumulation of Aβ(PMID: 21148344)
- **Impact**: Leads to neuronal damage, inflammation, and disrupts cell communication. (PMID: 12399581, PMID: 30643230)



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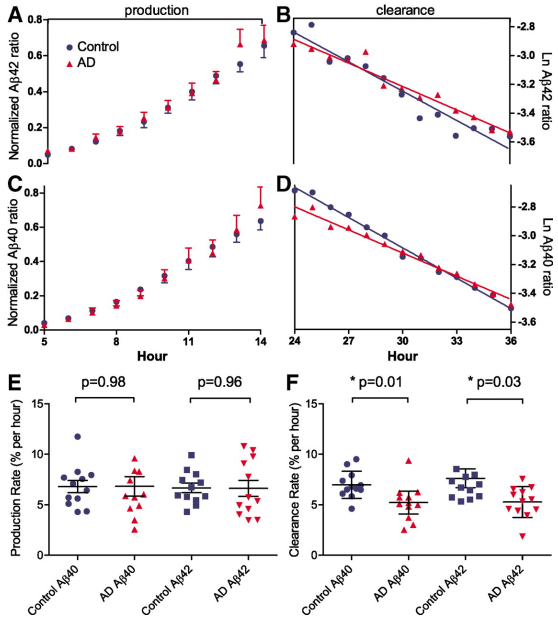

Aβ kinetics show the accumulation is due to clearance deficits.

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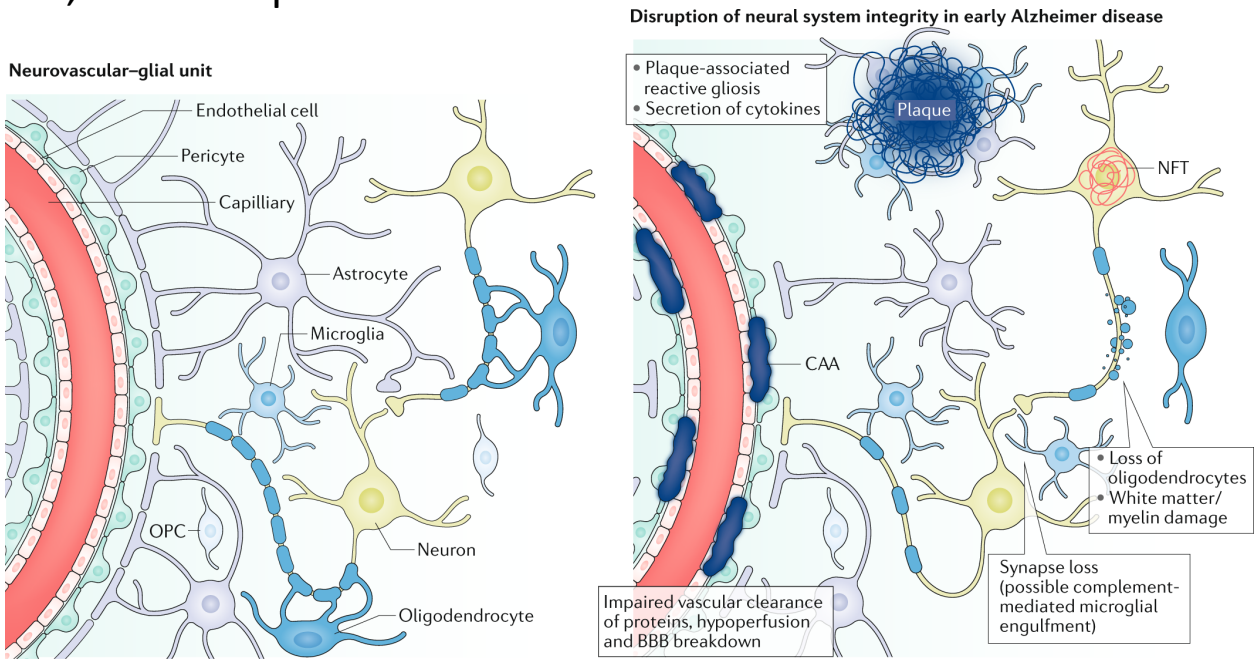

All of the cell types in the brain interact in a complex web to maintain brain function (left). During the early stages of Alzheimer disease (right).

Pathology: Tau tangles

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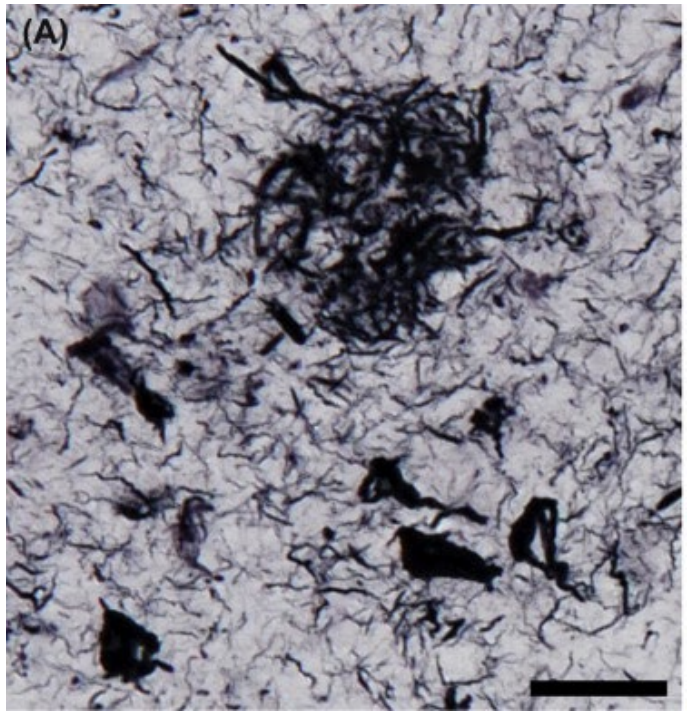
Radiology

- **Definition**: Twisted protein strands formed by hyperphosphorylated tau inside nerve cells (intracellular space). (PMID: 21456963, PMID: 11520930)
- **Formation**: Abnormal phosphorylation of tau protein leads to tangle formation, causing structural support collapse. (PMID: 3088567, PMID: 33422896, PMID: 33422896)
- **Impact**: Disrupt nutrient transport in cells, leading to cell death. (PMID: 9854307)



The classical triad of tau pathology in Alzheimer disease (AD) consists of neurofibrillary tangles, neuritic plaques, and neuropil threads. The image is a Gallyas silver-stained section taken from the temporal lobe of a severe AD case.

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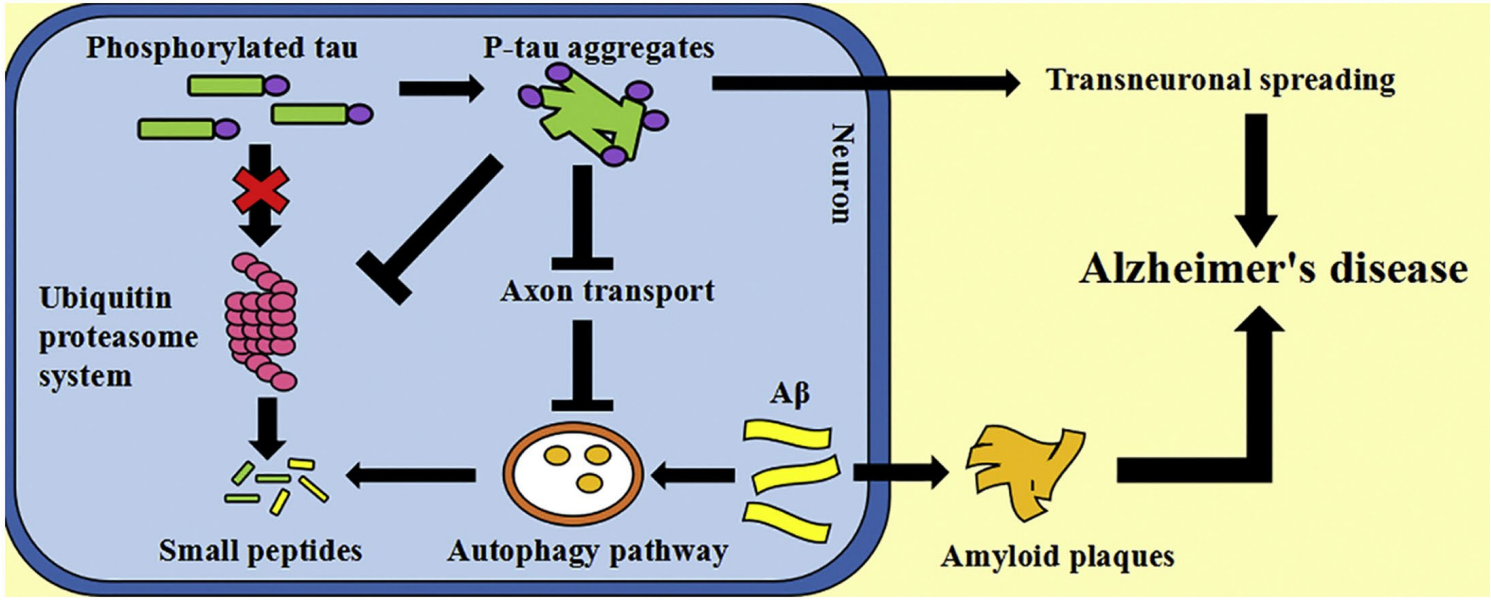
Abnormal phosphorylation and aggregation of tau are closely related to the impairment of axonal transport, further impede autophagy in neurons, interrupting the autophagic clearance of amyloid beta.



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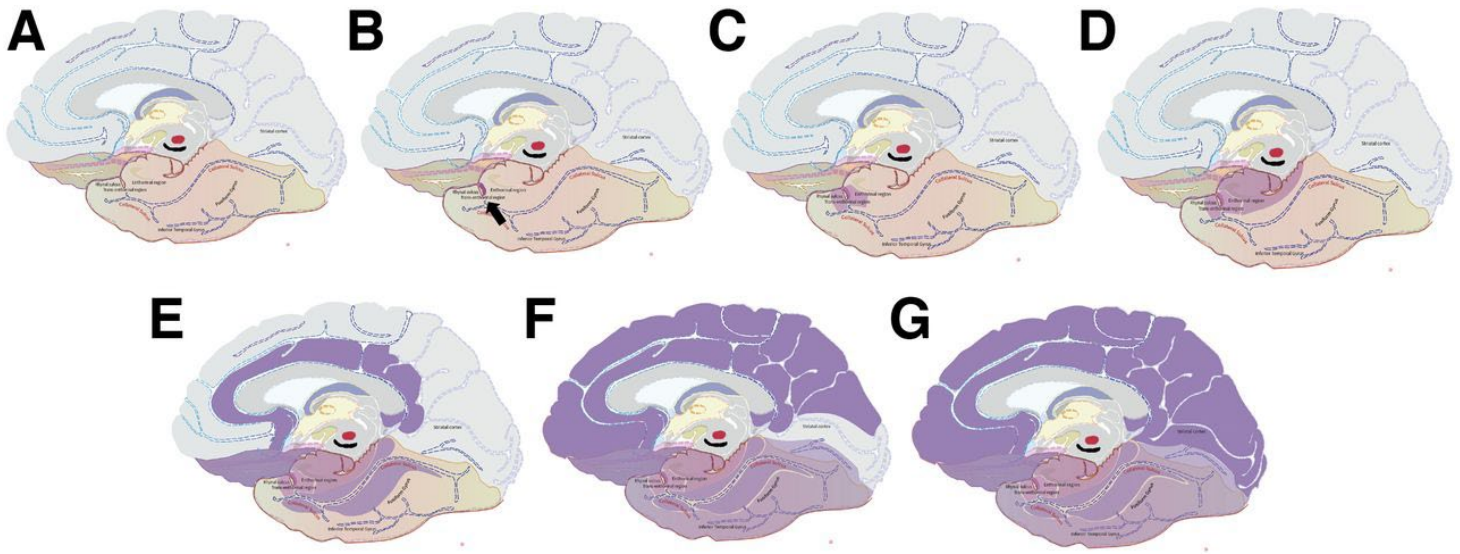

Braak stage of tau progression (PMID 1759558)
(B) I entorhinal
(C) II hippocampus
(D) III parahippocampal, fusiform, amygdala
(E) IV middle and inferior temporal
(F) V frontal, temporal, occipital, precunes
(G) VI pre-, post-, para-central, cuneus, pericalcarine

Pathology: Neurodegeneration/neuronal injury

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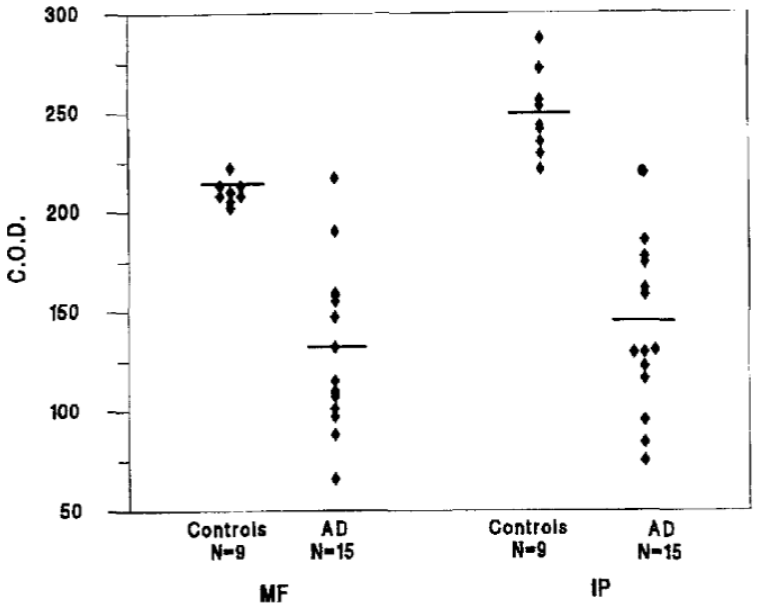
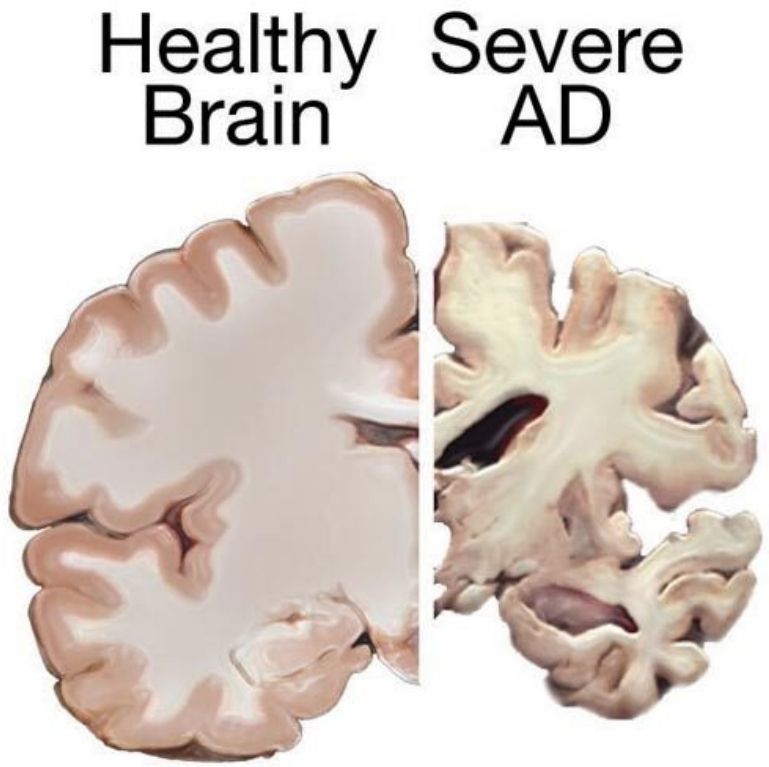
- **Definition**: Degradation of synapses, the critical junctions where nerve cells communicate. (PMID: 1789684)
- **Cause**: Accumulation of amyloid plaques and neurofibrillary tangles that damage and kill nerve cells. (PMID: 2360787, PMID: 24493463)
- **Impact**: Decline in cognitive functions like memory, thinking, and behavior due to decreased communication between neurons.

(PMID: 12399581, PMID: 33302541)



Corrected optical density (COD) show AD has lower synaptophysin-like immunoreactivity than CN.



https://www.ncbi.nlm.nih.gov/books/NBK499922/

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AD Risk Factors

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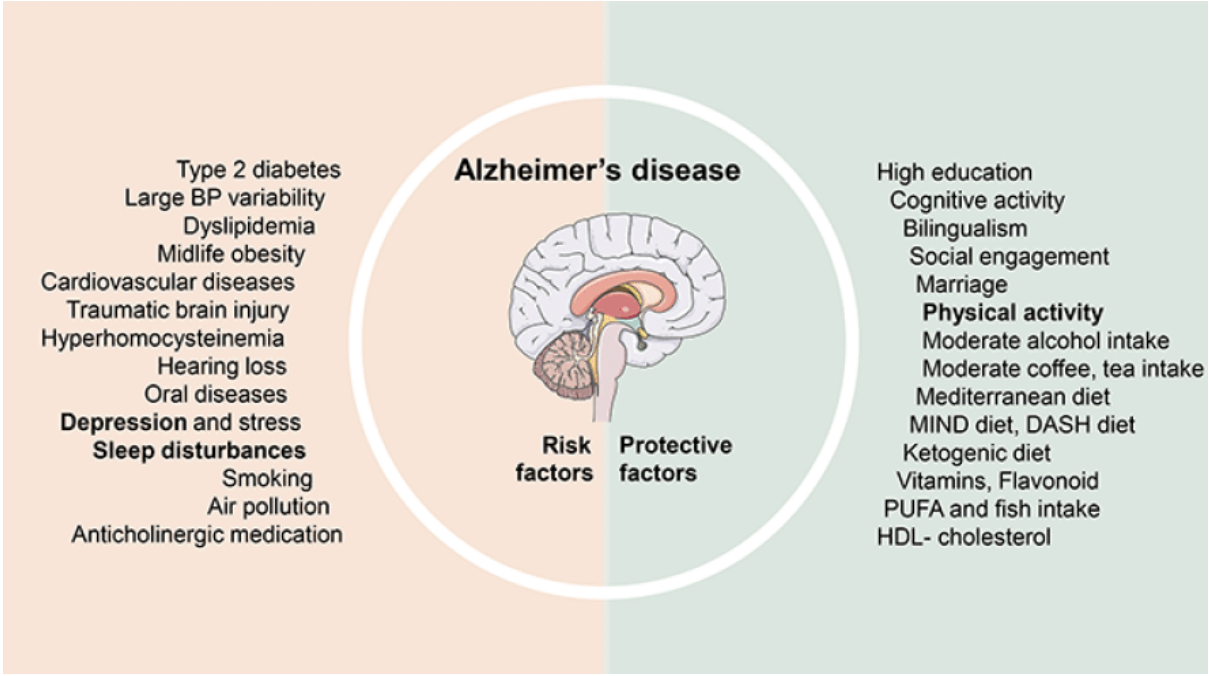
- ❑ Genetic: 75+ risk genes including APOE allele 4, APP
- ❑ Demographic: age, gender (F), race (black/Hispanic)
- ❑ Diseases: Obesity, hypertension, diabetes type 2, depression, hearing loss, traumatic brain injury (TBI), cardiovascular diseases, sleep disorders
- ❑ Environmental: cigarette smoking, excessive alcohol, small particle air pollution (PM25)
- ❑ Lifestyle: lack of exercise, unhealthy diets (PMID: 34101789)



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IV. Neuroimaging in Alzheimer's Disease

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Neuroimaging in AD: importance of imaging

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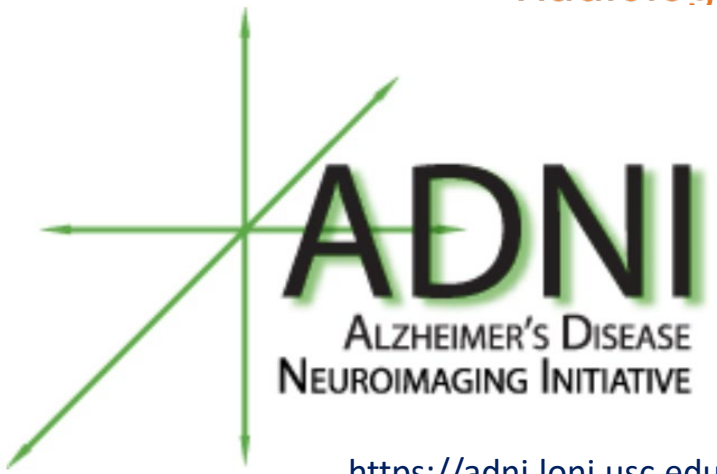
- **Early detection**: Imaging can reveal structural and functional changes before noticeable symptoms appear. (PMID: 20083042)
- **Differential diagnosis**: Helps differentiate AD from other neurodegenerative disorders and conditions. (PMID: 23897875)
- **Tracking progression**: Monitors the course of the disease, enabling better treatment planning and management. (PMID: 26073027)
- **Objective Biomarkers**: Offers quantitative data, vital for patient assessment, treatment decisions, and research. (PMID: 14991808)
- **Personalized treatment**: Imaging findings can guide tailored interventions for individual patients. (PMID: 27332958)



https://adni.loni.usc.edu/

https://www.humanconnectome.org/

https://www.alzheimersdata.org/

Neuroimaging in AD: molecular imaging using PET

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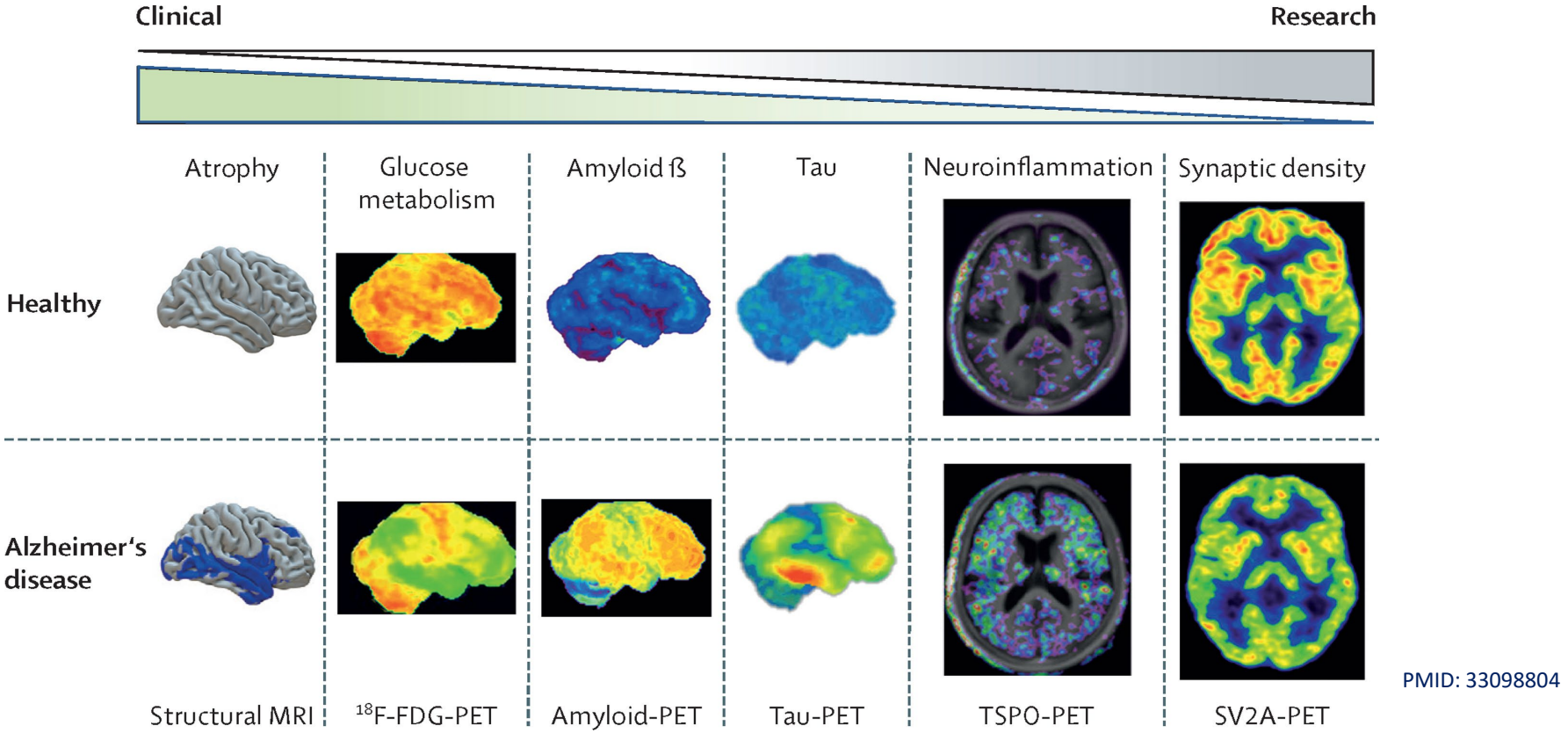
- Purpose: Visualizes and measures physiological functions, e.g., glucose metabolism and amyloid or tau accumulation. (PMID: 14991808, PMID: 27230925, PMID: 25199063)
- Applications: Amyloid PET imaging, tau PET imaging, and metabolic (FDG-PET) imaging. Predictive in assessing risk and progression. (PMID: 24825318, PMID: 32671408)



PMID: 33098804

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Neuroimaging in AD: structural MRI

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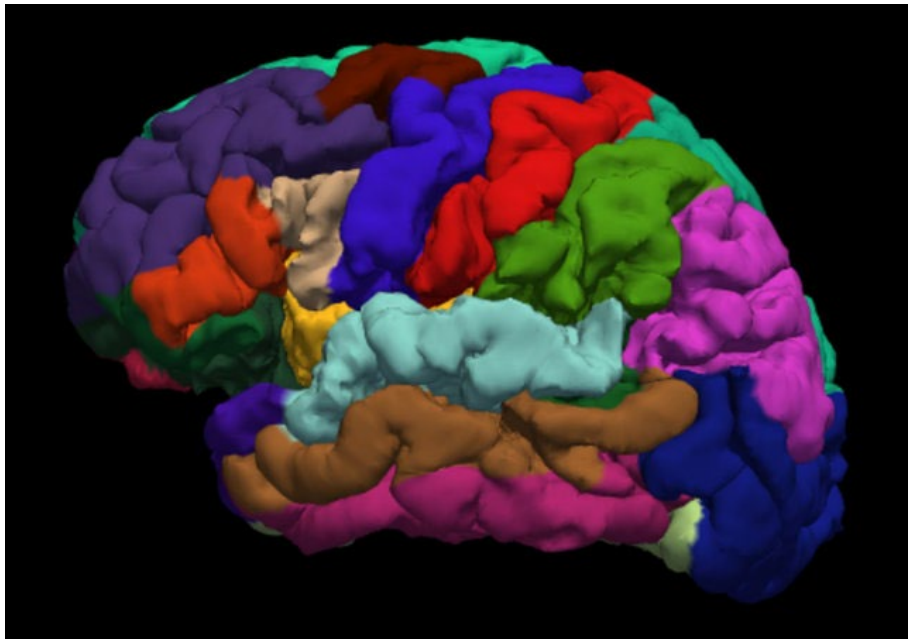
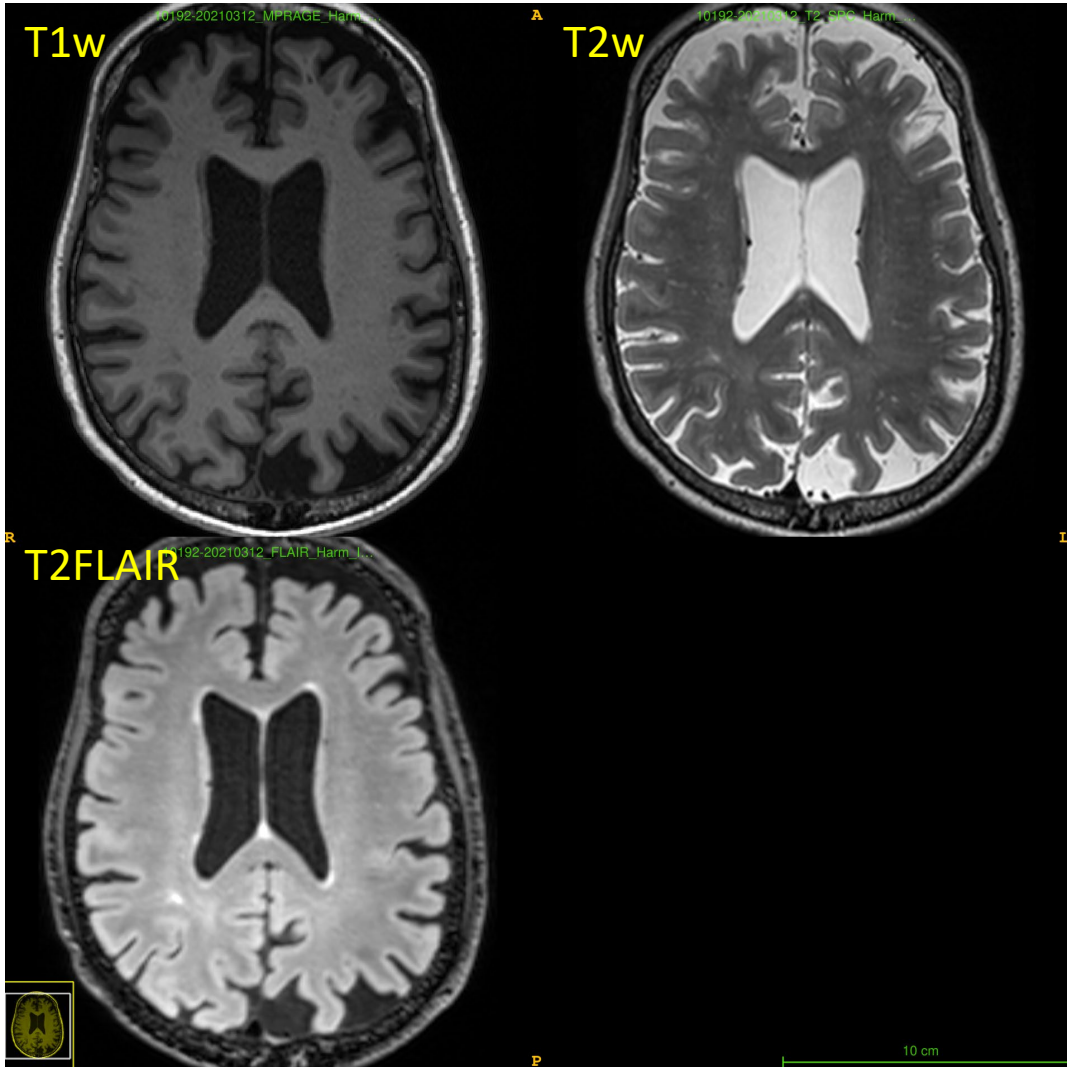
- Purpose: Captures detailed images of brain structures; detects shrinkage in specific brain regions. (PMID: 20139996, PMID: 9931268)
- Applications: Atrophy assessment (hippocampus), differential diagnosis, and disease progression tracking. (PMID: 20083042)



Brain regions segmentation



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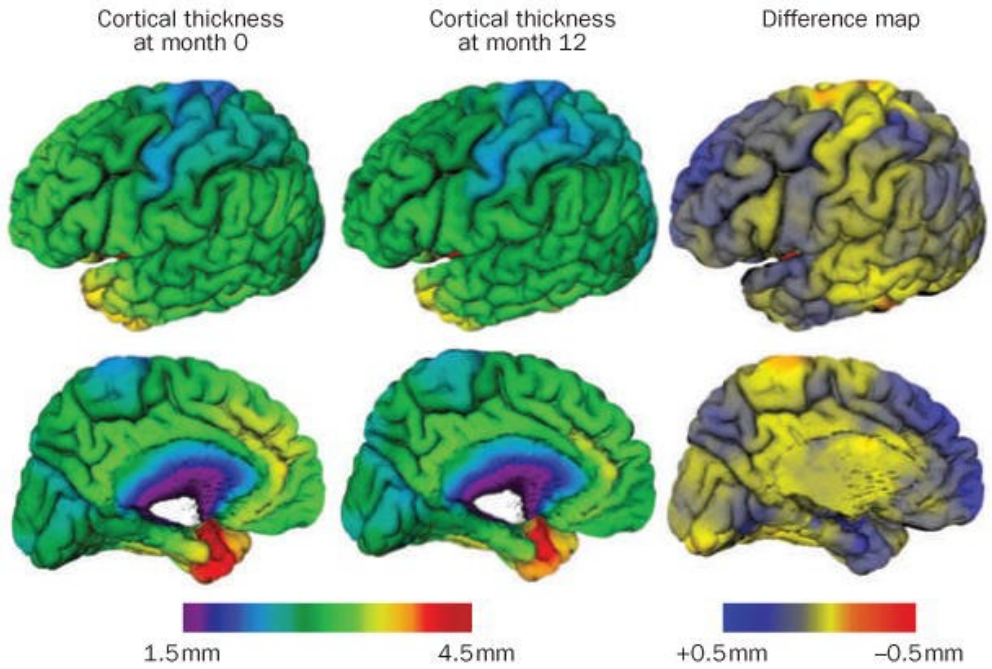

Cortical thinning as MCI progression

Neuroimaging in AD: functional MRI

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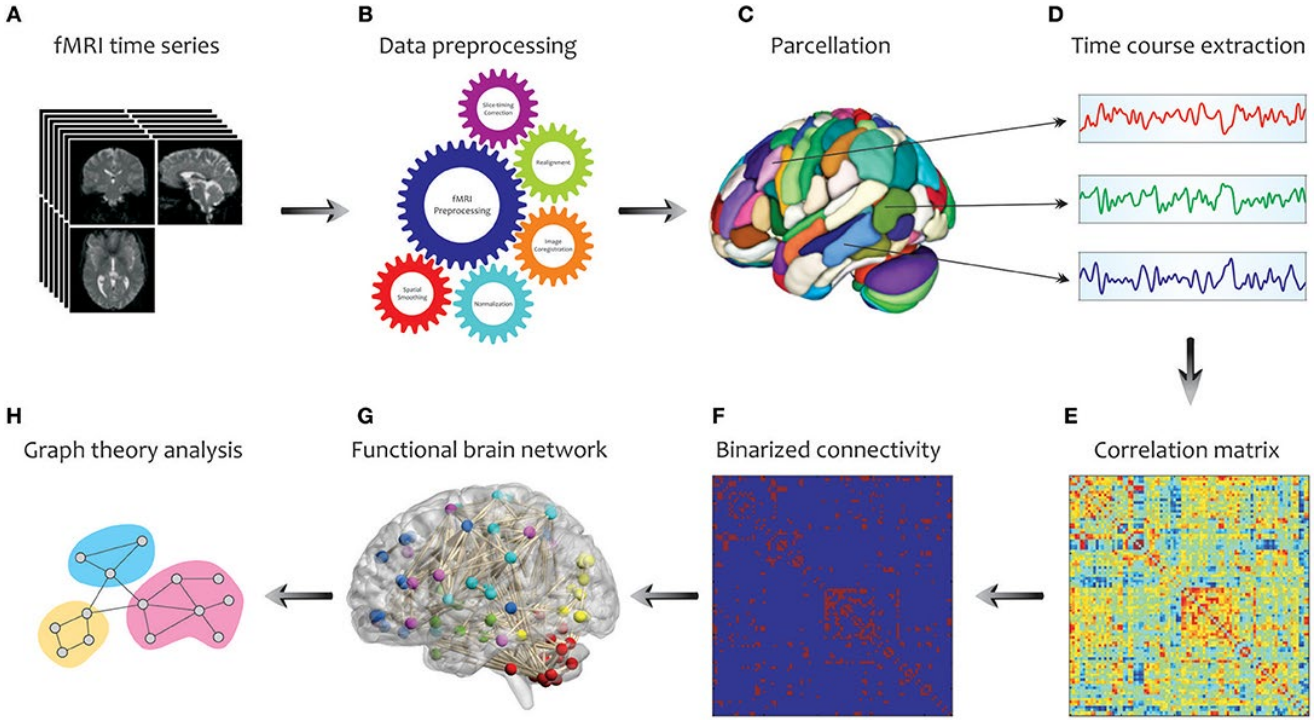
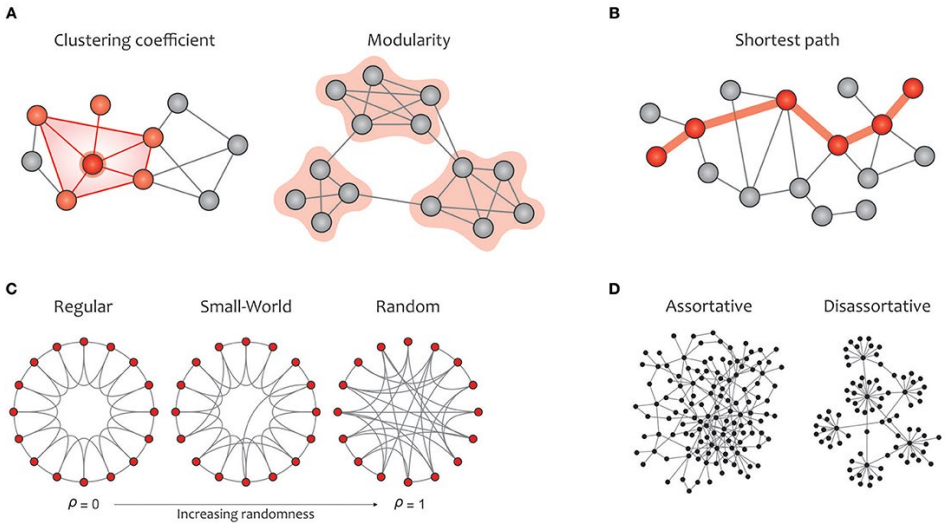
- Purpose: Measures and maps the brain's activity. Unlike standard MRI, it captures rapid dynamic changes in the brain. (PMID: 15070770, PMID: 31249501)
- Applications: Examines connectivity in brain networks, especially the default mode network (DMN); often disrupted in AD. (PMID: 18400922)



Modeling the functional brain network.



Small world network characterization.

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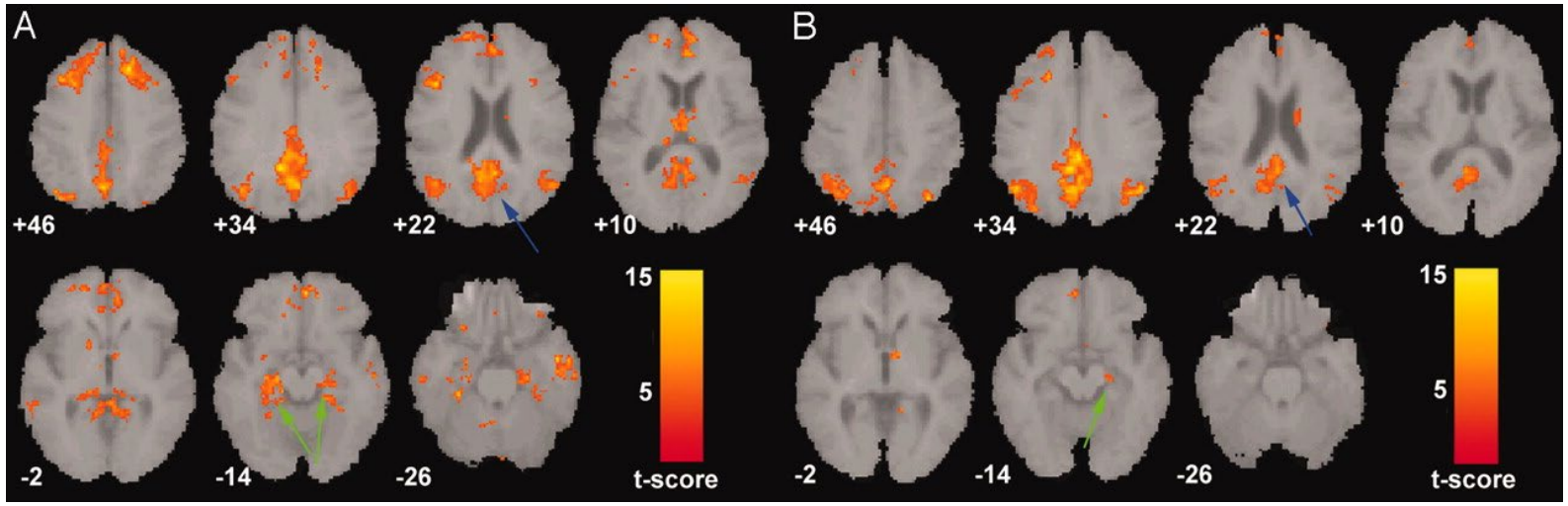
- Purpose: Measures and maps the brain's activity. Unlike standard MRI, it captures rapid dynamic changes in the brain. (PMID: 15070770, PMID: 31249501)
- Applications: Examines connectivity in brain networks, especially the default mode network (DMN); often disrupted in AD. (PMID: 18400922)



(B) AD shows altered DMN compared with (A) CN.

Neuroimaging in AD: other modalities and contrast mechanisms

Weill Cornell Medicine
Radiology

- MRI
  - T1w: anatomic structure
  - T2w: perivascular space
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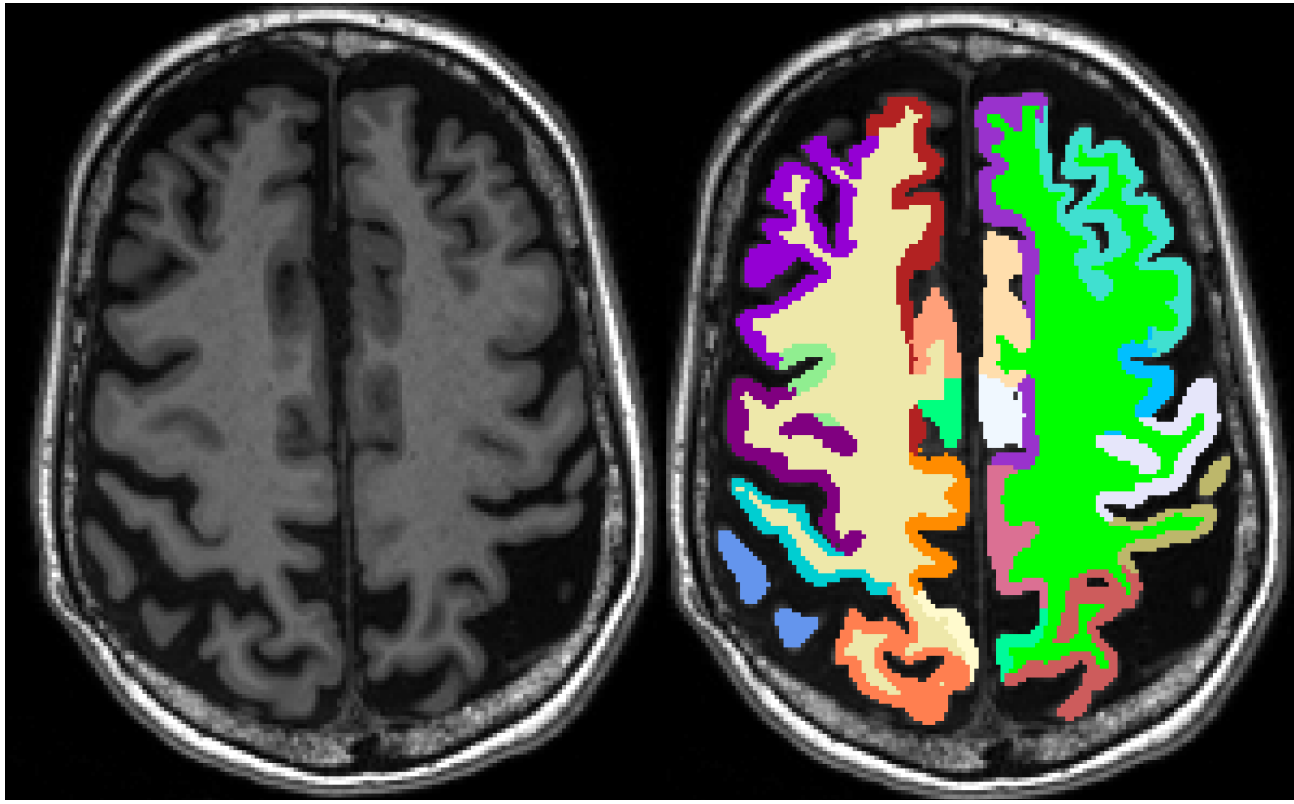
  - CSFF: parenchymal CSF fraction (PMID: 37396667)
- PET
  - PK11195 PET: neuroinflammation
  - O_2/Butanol PET: blood perfusion



T1w for regional parcellation

L. Zhou, Brain Health Imaging Institute (BHII)

Neuroimaging in AD: other modalities and contrast mechanisms

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Radiology

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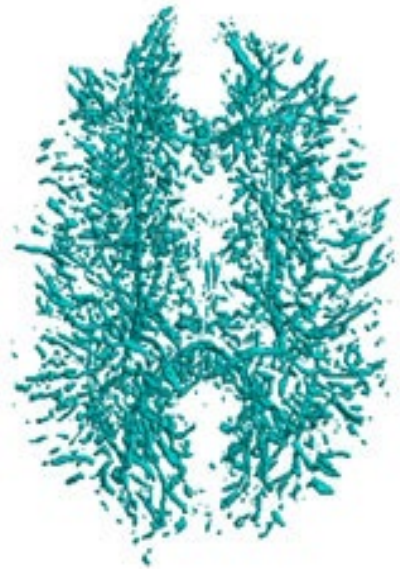

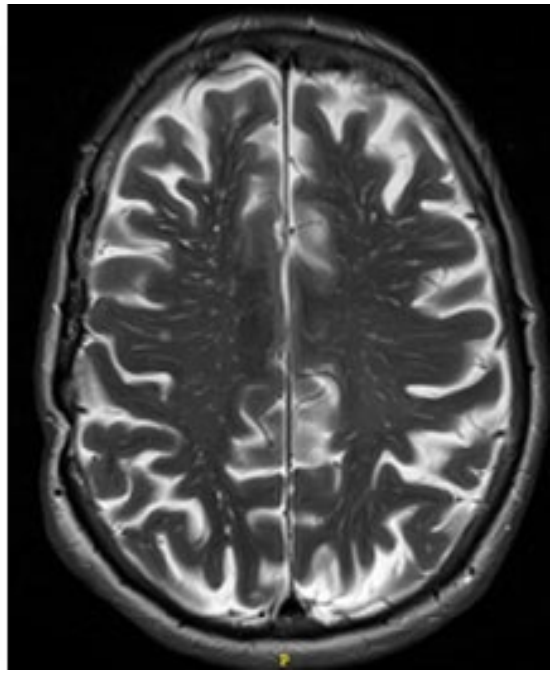

T2w for PVS

L. Zhou, Brain Health Imaging Institute (BHII)

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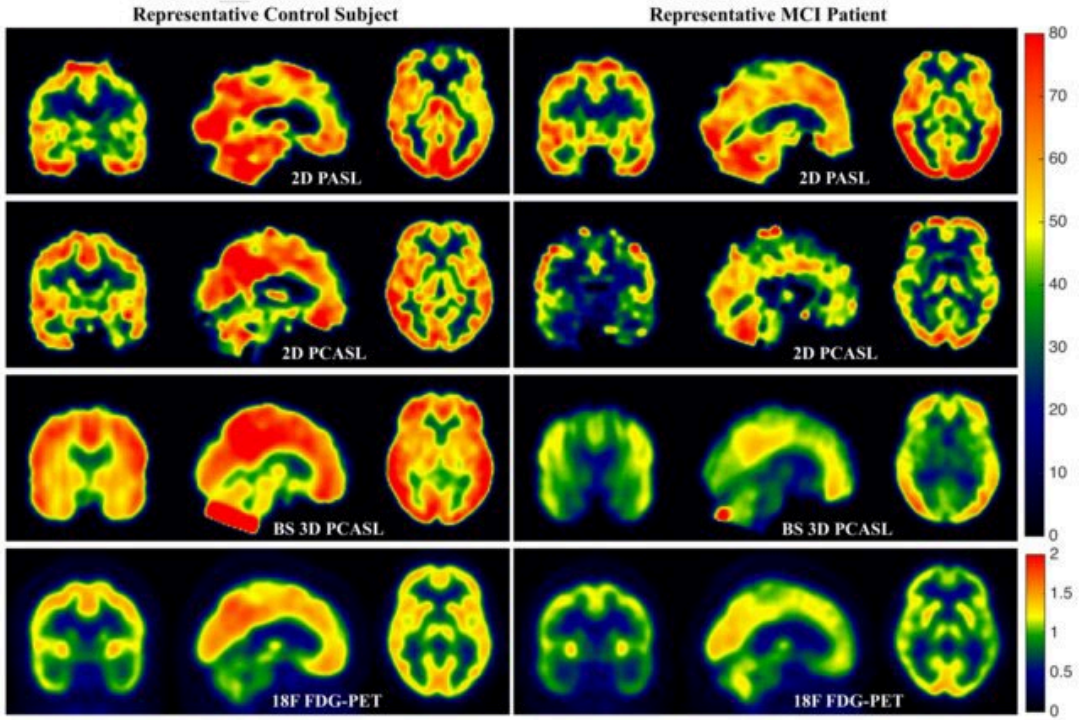

pcASL for CBF

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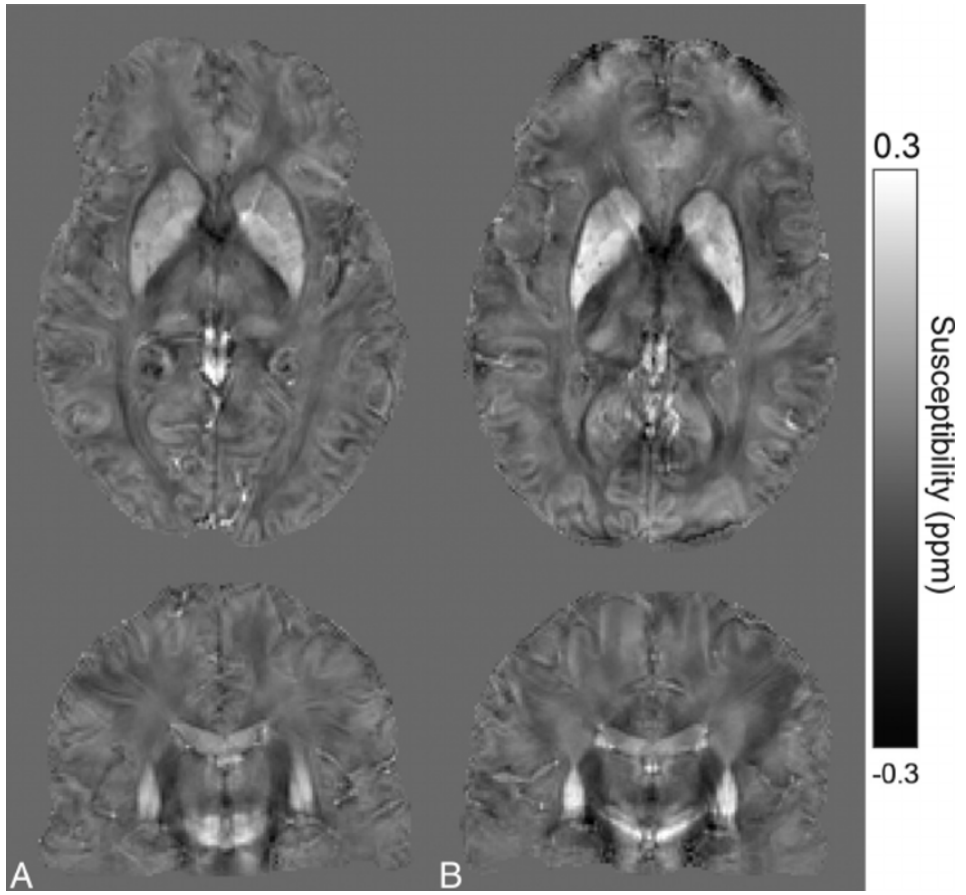

QSM for iron

Neuroimaging in AD: other modalities and contrast mechanisms

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Radiology

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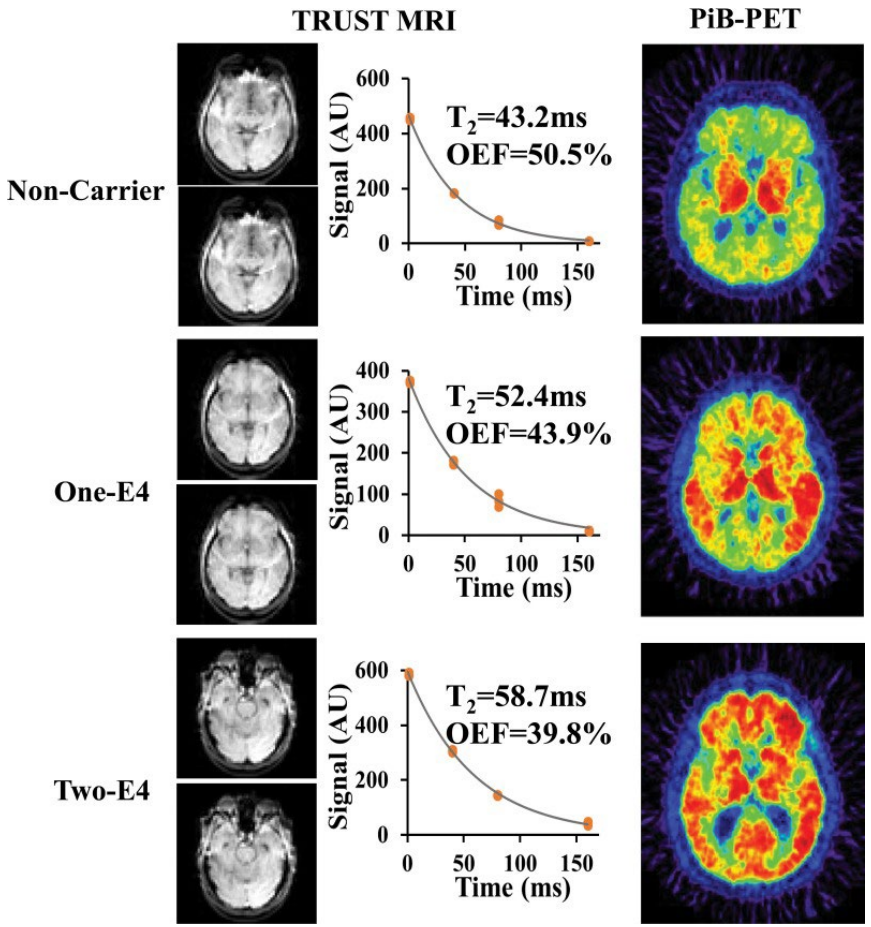

OEF for oxygen extraction

L. Zhou, Brain Health Imaging Institute (BHII)

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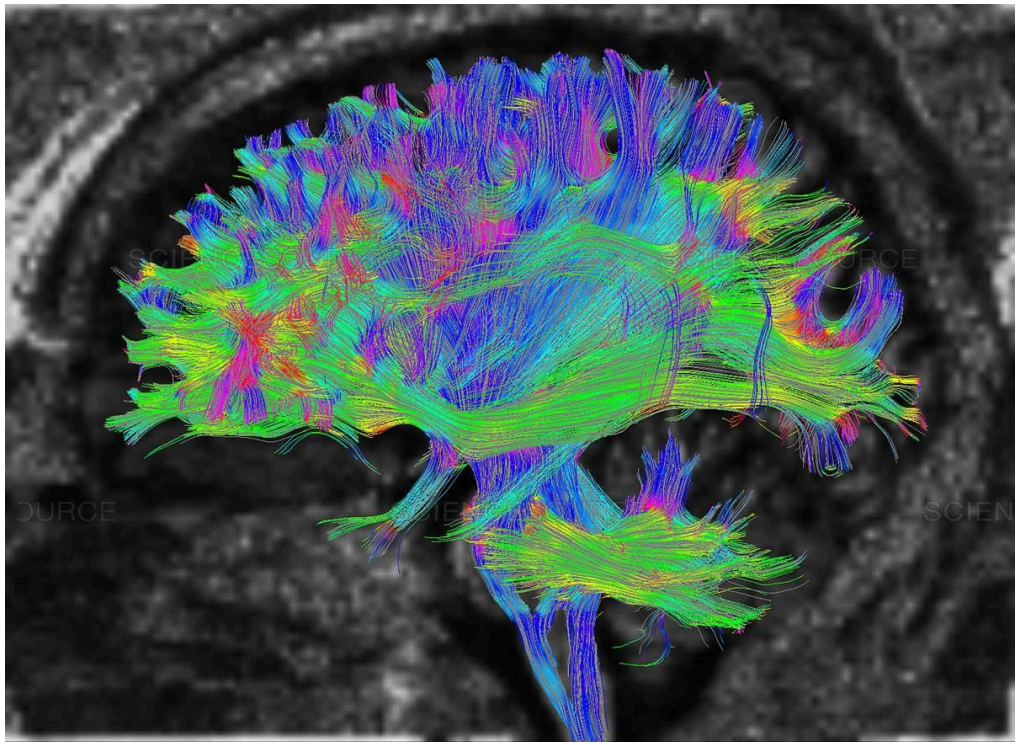

DTI fiber tractography

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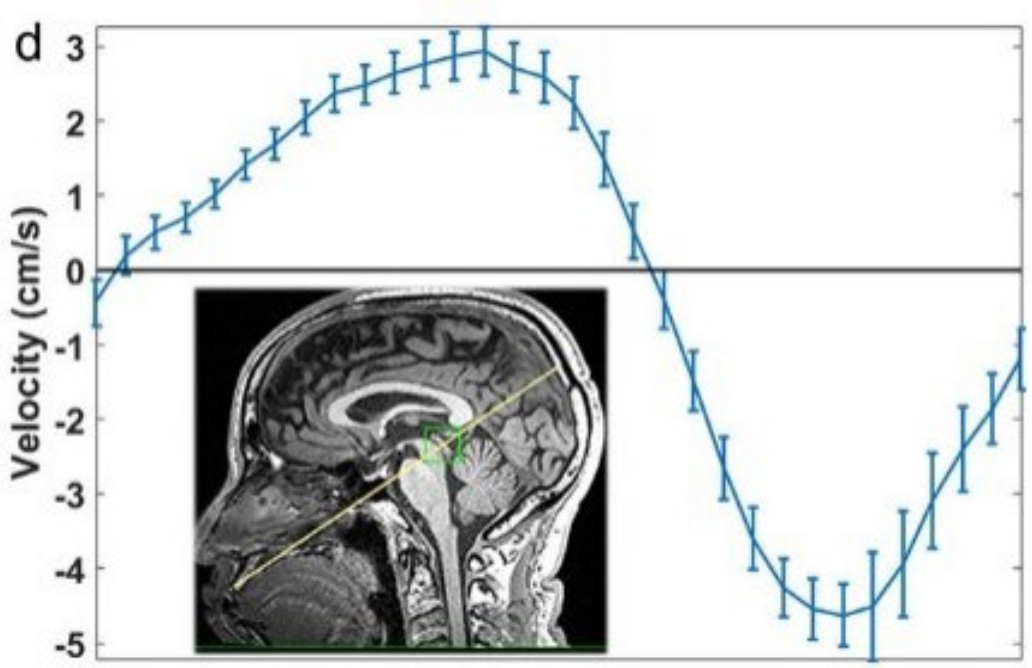

PC-MRI for CSF flow in aqueduct

L. Zhou, Brain Health Imaging Institute (BHII)

Neuroimaging in AD: other modalities and contrast mechanisms

Weill Cornell Medicine
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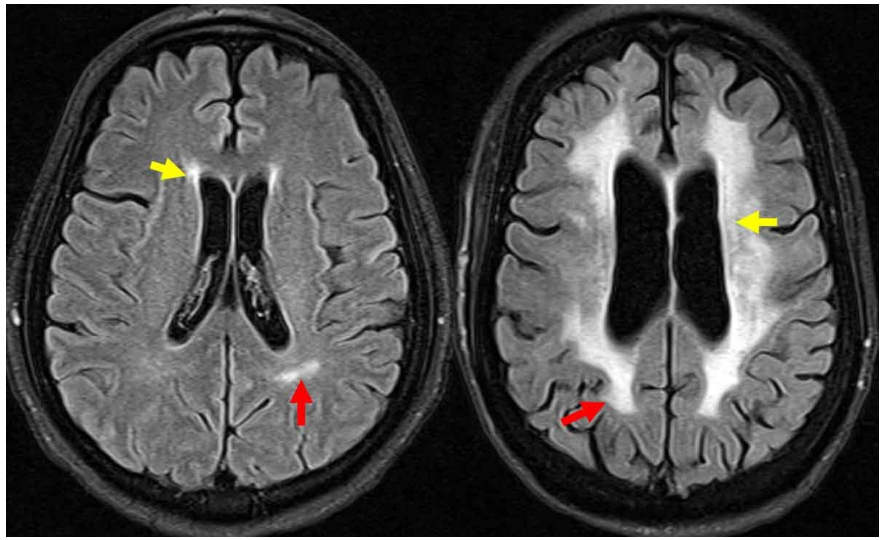

FLAIR for WMH

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Neuroimaging in AD: other modalities and contrast mechanisms

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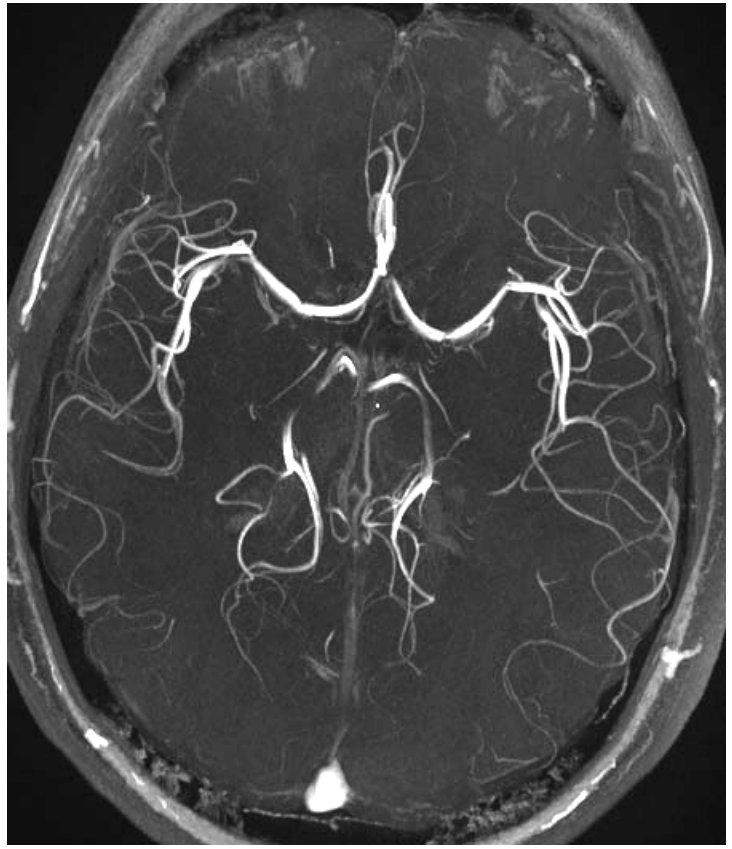

MRA for vasculature info

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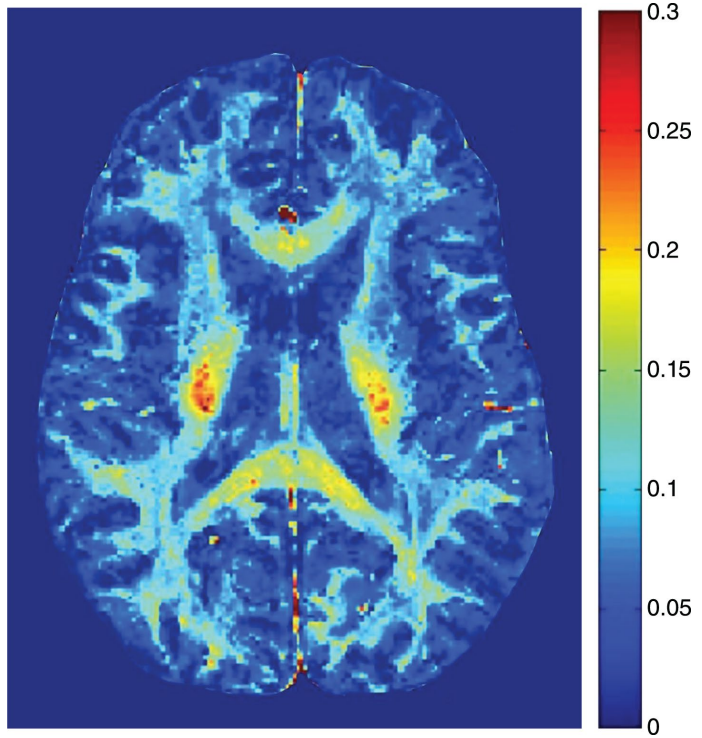

MWI

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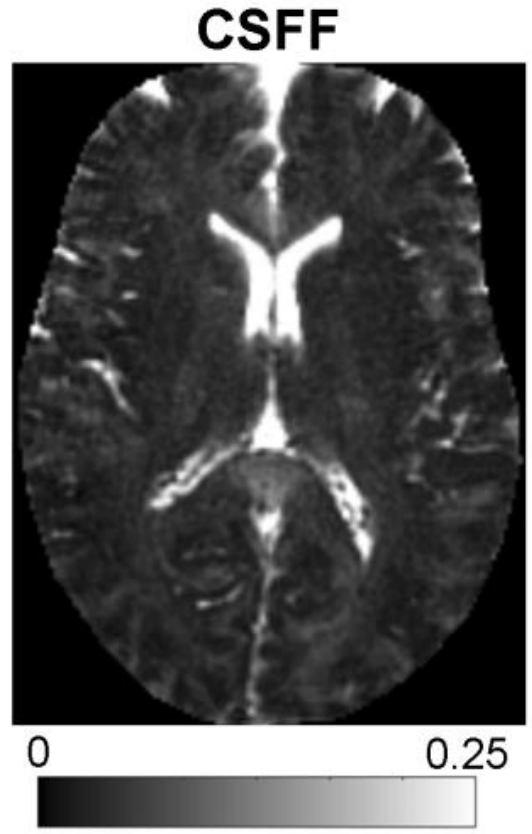

Parenchymal CSF fraction

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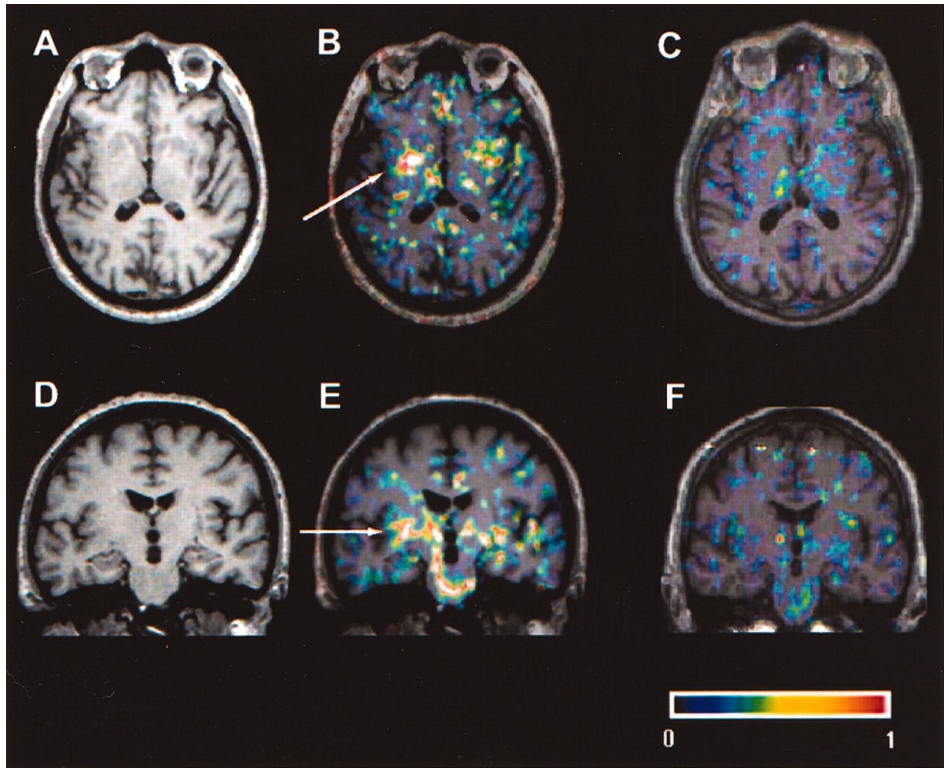

PK11195 PET for microglia activation

L. Zhou, Brain Health Imaging Institute (BHII)

Neuroimaging in AD: other modalities and contrast mechanisms

Weill Cornell Medicine
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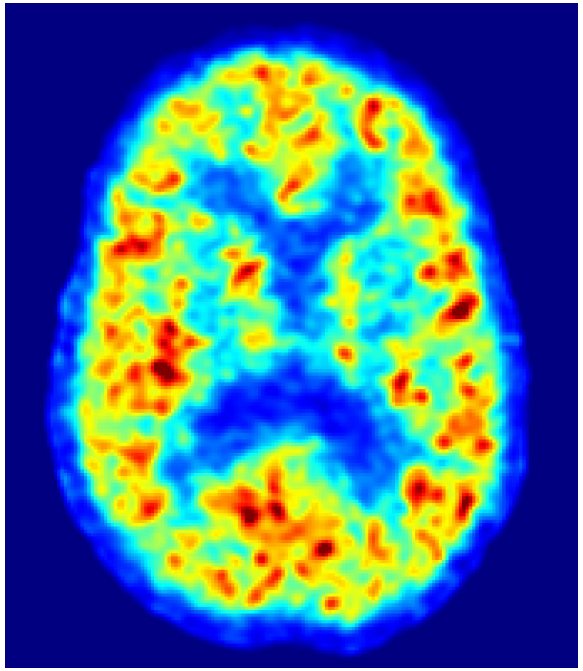


Butanol PET for blood perfusion

L. Zhou, Brain Health Imaging Institute (BHII)

Weill Cornell Medicine
Radiology

V. Engineering Applications in Modeling Alzheimer's Disease

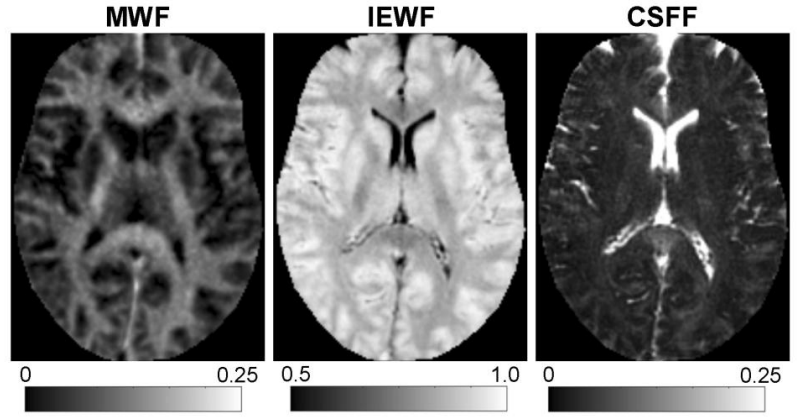
L. Zhou, Brain Health Imaging Institute (BHII)

Engineering application in AD: model based approaches

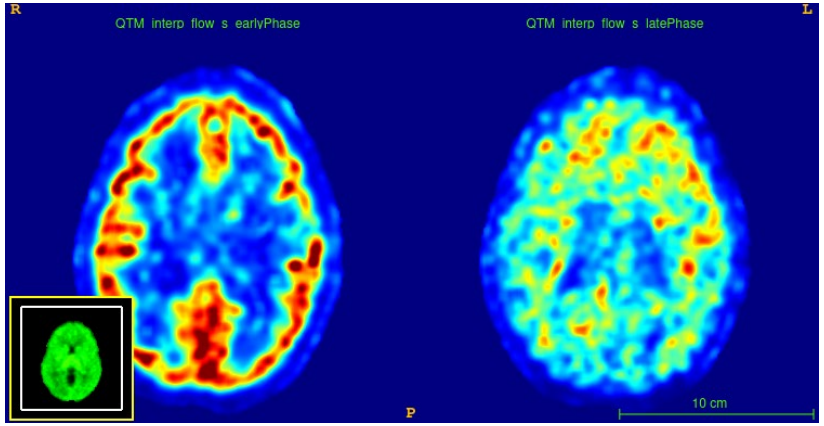
Weill Cornell Medicine
Radiology

- ❑ Biophysical modeling:
  - MRI signal decomposition: CSF fraction (CSFF, PMID: 37396667):
  - Tracer velocity from spatiotemporal data (QTM, PMID: 33210310):
- ❑ Kinetic modeling:
  - 1 tissue compartmental model:
  - 2 tissue compartmental model:
- ❑ Computational fluid dynamics:
  - Navier-Stokes equation for flow in vascular space (PMID: 31640500):
  - Transport equation for tracer (https://doi.org/10.3390/fluids4040196) :
  - Fick's law of diffusion:
  - Darcy's law for tissue permeability:
- ❑ Biomechanical modeling:
  - Brain atrophy progression. (PMID: 34600936)

$$S(TE) = A_{IEW}e^{-TE/T2_{IEW}} + A_{CSF}e^{-TE/T2_{CSF}} + A_{MW}e^{-TE/T2_{MW}}$$



$$\boldsymbol{u}, D = \text{argmin}_{\boldsymbol{u}, D} \sum_{t=1}^{N_t - 1} \| \partial_t c + \nabla \cdot c\boldsymbol{u} - \nabla \cdot D \nabla c \|_2^2 + \lambda \left\| \nabla u \right\|_1 + \mu \left\| \nabla D \right\|_1$$



42y, F, CN, A-, T-

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Engineering application in AD: model based approaches

Weill Cornell Medicine
Radiology

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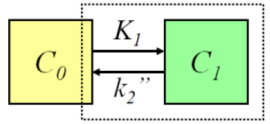
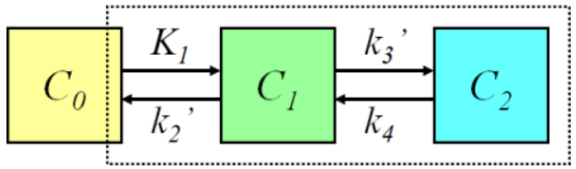


$$\frac{dC_1(t)}{dt} = K_1 C_0(t) - k_2 C_1(t)$$

  - 2 tissue compartmental model:



$$\frac{dC_1(t)}{dt} = K_1 C_0(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

- ❑ Computational fluid dynamics:
  - Navier-Stokes equation for flow in vascular space (PMID: 31640500):
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Engineering application in AD: model based approaches

Weill Cornell Medicine
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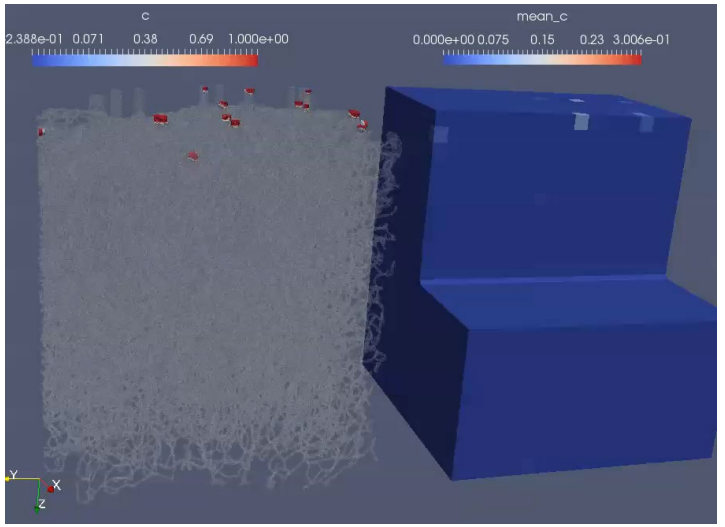
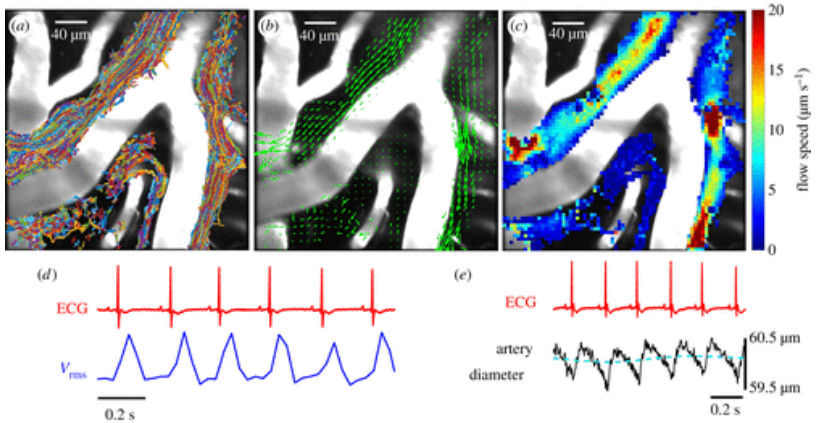
  - Fick's law of diffusion: $\frac{\partial \varphi}{\partial t} = D\Delta\varphi$
  - Darcy's law for tissue permeability: $q = -\frac{k}{\mu L}\Delta p$
- ❑ Biomechanical modeling:
  - Brain atrophy progression. (PMID: 34600936)



$$\rho_b(\boldsymbol{u}\cdot\nabla)\boldsymbol{u} = -\nabla p + \mu\nabla\cdot\nabla\boldsymbol{u},\ \forall \boldsymbol{r}\in\Omega_v,$$

$$\rho_b\nabla\cdot\boldsymbol{u} = 0,\ \forall \boldsymbol{r}\in\Omega_v,$$

$$-\nabla\bullet c(\boldsymbol{r},t)\boldsymbol{u}(\boldsymbol{r}) + \nabla\bullet D(\boldsymbol{r})\nabla c(\boldsymbol{r},t) = \partial_t c(\boldsymbol{r},t).$$



L. Zhou, Brain Health Imaging Institute (BHII)

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Radiology

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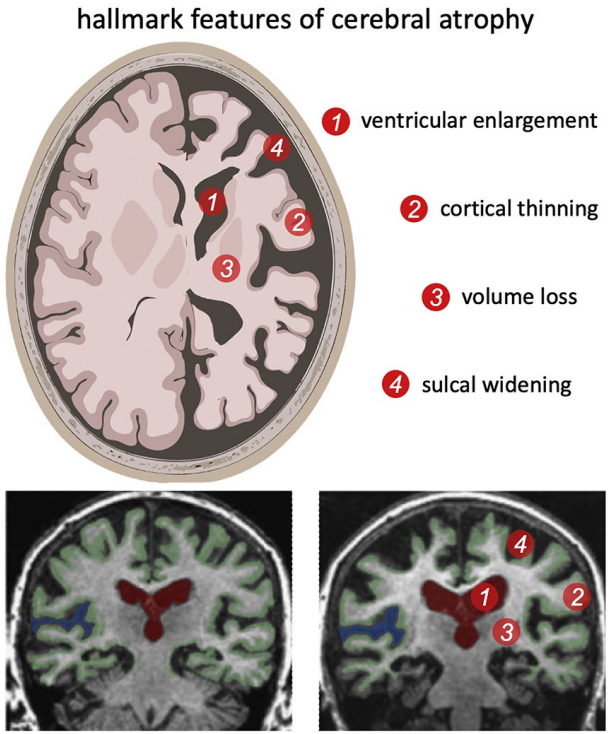
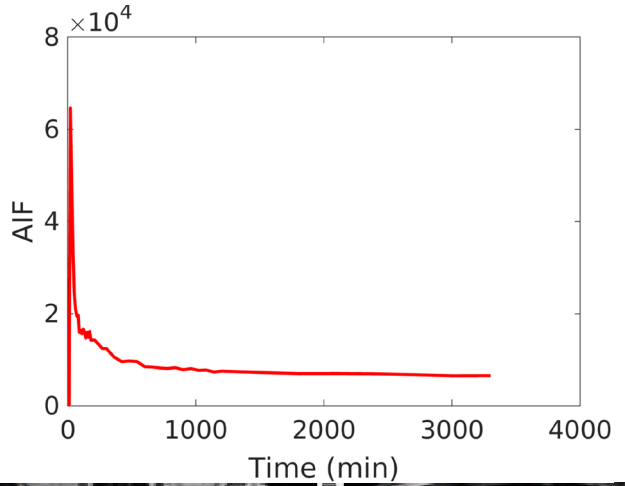
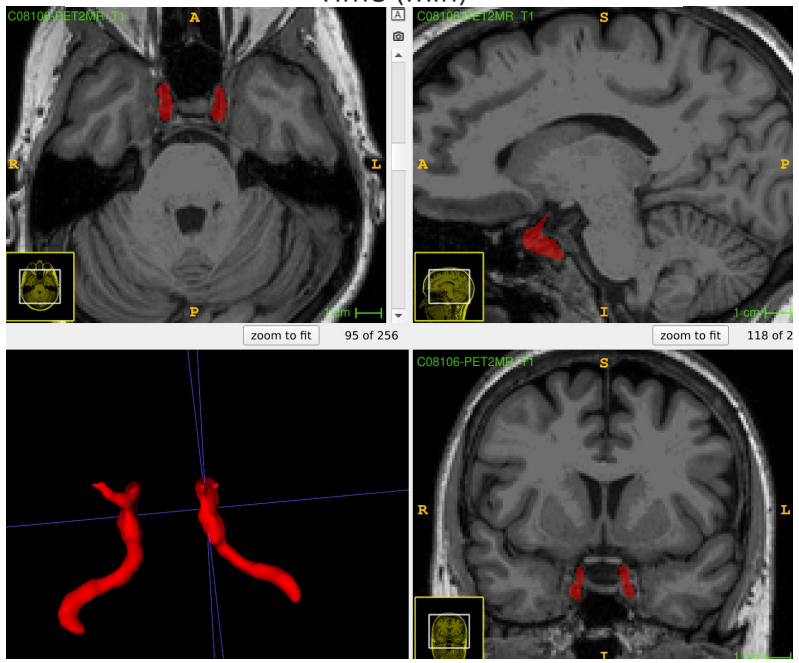


Engineering application in AD: data driven approach

Weill Cornell Medicine
Radiology

- ❑ Unsupervised machine learning (small sample)
  - K means: clustering, group separation
  - Hierarchical clustering: tree structure clustering
  - ICA: temporal characteristic extraction
  - PCA: spatial features extraction
- ❑ Supervised machine learning (large sample)
  - SVM, random forest: group separation
  - Linear regression: relationship between variables
  - Logistic regression: classification
  - KNN: multiple class
  - Random forests: medical diagnosis
  - CNN: lesion segmentation, new contrast mechanism mapping (PMID: 36692103)





L. Zhou, Brain Health Imaging Institute (BHII)

Engineering application in AD: data driven approach

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Radiology

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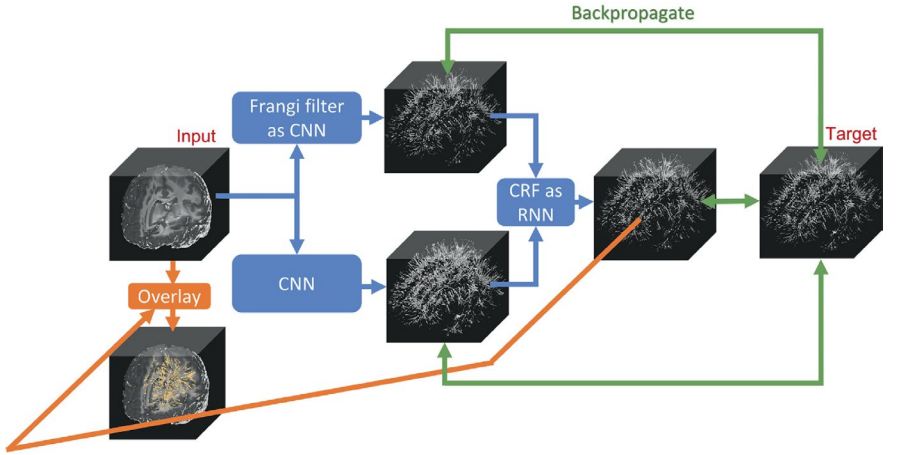
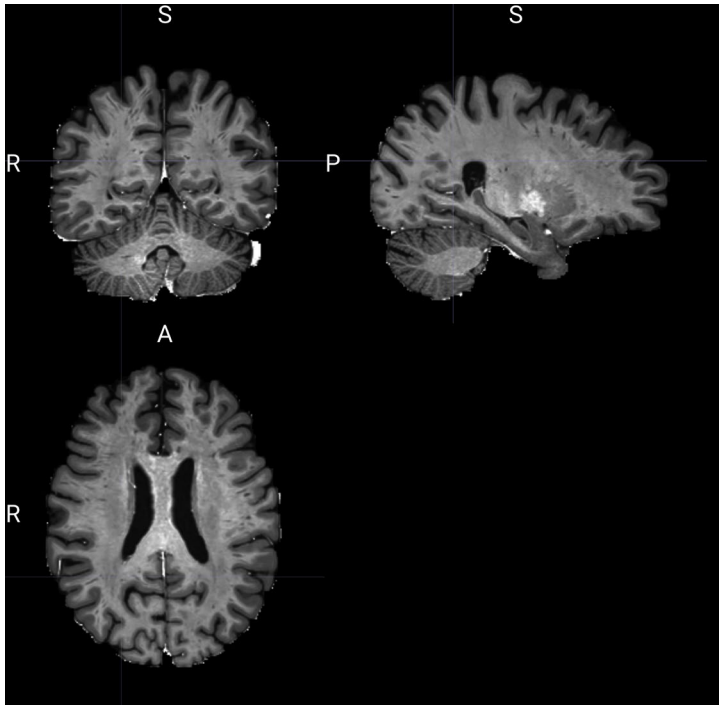
  - Random forests: medical diagnosis
  - CNN: lesion segmentation, new contrast mechanism mapping (PMID: 36692103)





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VI. Challenges and Opportunities

Challenges and Opportunities in AD research

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❑ Challenges

- **Understanding**: While progress has been made, the exact mechanisms and progression of Alzheimer's remain not fully understood.
- **Diagnostic capabilities**: Early diagnosis remains a challenge. Many cases are identified only after significant brain damage has occurred.
- **Interdisciplinary collaboration**: Combining knowledge from neurology, biology, radiology, pharmacology, engineering, informatics, and other fields can foster innovation.

❑ Opportunities

- **Technological advancements**: New tools, especially in neuroimaging and data analysis, can revolutionize the way we study and diagnose AD.
- **Data-Driven Research/pharmacotherapeutic development**: Leveraging big data and advanced machine learning methods can uncover patterns and insights previously undetected.

Summary

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I. Introduction to Alzheimer's Disease (AD): **was identified around 120 years ago, now prevail all over the world.**

II. Clinical Overview: **has multiple stages and progress at different speed from patient to patient.**

III. Pathological Basis: **Amyloid, tau, and neurodegeneration (A/T/N).**

IV. Neuroimaging in AD: **structural, functional, and multiple contrast MRI, PET for amyloid, tau and metabolism.**

V. Engineering Applications in AD: **model based and data driven approaches help to develop more contrast and diagnostic tools.**

VI. Challenges and Opportunities: **Mechanism is still not fully understood, new tools/engineering approaches could be helpful.**

Brain Health Imaging Institute (BHII)

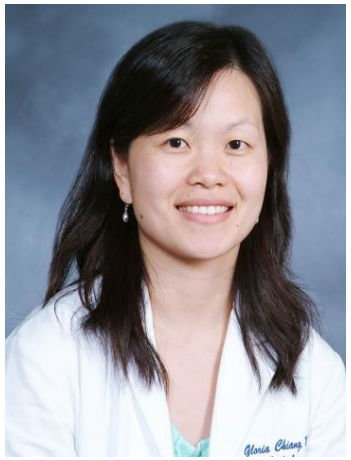
BHII Mission

The Brain Health Imaging Institute (BHII) of the Weil Cornell Medicine (WCM) Department of Radiology was founded in 2019. The BHII is a neurodegeneration research-dedicated organization focused on improving understanding of the contributions of aging, gender, and genetics to neurodegenerative processes, and developing treatments for Alzheimer's disease (AD).

BHII Scientific Objectives

BHII research objectives include development and use of advanced medical imaging and biomarker technology to improve the early and specific diagnosis and mechanistic treatment of brain neurodegenerative diseases. This includes diseases marked by AD spectrum pathology (senile amyloid plaque, neurofibrillary tangle, Lewy body, and TDP43) as well as brain impairments due to environmental and biological exposures. The latter include: traumatic brain injury (TBI), COVID-19, sleep apnea, hypertension, oral bacterial dysbiosis, lipid metabolism disorders, fatty liver disease, and genetics.

Dr. Mony J. de Leon
Director



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