Neuroimaging in the Diagnosis of Dementia
Laura Eisenmenger, M.D.
University of Wisconsin, Madison
leisenmenger@uwhealth.org

Learning Objectives
✓ Role of imaging in dementia
✓ Imaging tools: from structure to function
✓ Future areas of imaging development

UW Alzheimer’s Disease Research Center
Drs. Asthana, Johnson, Carlsson, Bendlin, Rowley...
Alzheimer’s Disease

• The most common form of dementia
  ~ 70% of all dementia cases

• 2 main forms:
  • Early onset / familial (~ 1% of cases)
    • Symptoms develop before age 60
    • Highly linked to 3 genes on chromosomes 1, 14, 21
  • Late onset / sporadic (~ 99% of cases)
    • Symptoms usually develop after age 70
    • Linked to genetic risk factor apolipoprotein E4
Alzheimer’s Disease

Prevalence: increases with aging

Years

Prevalence, %

65-74 75-84 85+
Alzheimer’s Disease

Alarming statistics:
• 50M people worldwide with dementia
• Nearly 10 million new cases every year
• $818B annual global cost of care
• New case every 4 seconds
• 6th leading cause of death
• Only leading cause of death whose prevalence continues to grow
• 78M ‘Baby Boomers’ > 65 in 2011
• 82M will have dementia in 2030, 152M in 2050
• ¼ of humans will develop Alzheimer’s
Alzheimer’s Disease Prevention

Asymptomatic, Middle-Aged, At-Risk

Normal

Mild Cognitive Impairment

Alzheimer’s Disease

Brain Changes

CSF biomarkers

Neuroimaging

Cognitive measures

Comatose Function

Time

Courtesy of Cindy Carlsson, MD
Alzheimer’s Disease

Clinical diagnostic criteria

• Memory loss + dysfunction in other cognitive domains
• Gradually progressive decline from previous cognitive abilities
• Affects daily function
• No disturbance of consciousness
• Absence of systemic disorders that could account for deficits in memory and cognition
Mild Cognitive Impairment

- Clinical diagnostic criteria
  - Memory loss on cognitive testing
  - Memory complaint
  - Daily function NOT affected
Traditional Risk Factors of Alzheimer’s Disease

- Age
- Genetic risks (APO e4)
- Family history of AD
- Down syndrome
- Head trauma with loss of consciousness
- Low educational level
Role of Imaging in Dementia

• **Identify treatable causes / exclude alternate diagnoses**
  • Metabolic
  • Infectious
  • Neoplastic
  • Hydrocephalus
  • Post-traumatic --- etc.

• **Refine likely substrate(s) for dementia**
  • Vascular – micro and macrovascular
  • Degenerative – identify regional patterns
CONCLUSION: Overall, neuroimaging confirmed, clarified, or contradicted the initial clinical diagnosis in more than 80% of patients, whereas fewer than 20% had abnormal/not diagnostic patterns. Imaging suggested a complex dementia etiology in 21% of cases clinically thought to be caused by a single process, whereas 46% of complex clinical differential diagnoses appeared to reflect a single causal pattern. Further work is needed to determine whether refinement of clinical diagnoses using specialized neuroimaging improves clinical decision-making and patient outcomes. J Am Geriatr Soc 58:1453–1458, 2010.
53 F Memory loss, personality changes

Meningioma
86 F Mild Cognitive Impairment

Normal Pressure Hydrocephalus (NPH)

T2 FLAIR
73 M with memory loss

Wernicke’s Disease - Thiamine Deficiency
85 M with dementia, ataxia, startle

PRION Disease (Creutzfeldt-Jakob)
Clinical Cases - Approach

- **Imaging tools**
  - Volumetric T1 & T2 FLAIR
  - DWI / DTI
  - T2* / Susceptibility
  - Perfusion
  - Spectroscopy
  - PET – various ligands

- **Imaging analysis**
  - Gray vs white matter involvement
  - Regions affected
  - Exclude non-degenerative causes
  - Diagnosis and prognosis

Vesalius’ *De Humani Corporis Fabrica* (1543)
"OK, Mrs. Dunn. We'll slide you in there, scan your brain, and see if we can find out why you've been having these spells of claustrophobia."
MRI Magnet

- All MRI systems rely on a main magnetic field to produce a signal.
- The main magnetic field is abbreviated as $B_0$ and referred to as B zero or B “nought.”
- There are primarily three types of magnets used in the clinic:
  - Super Conducting Magnets (0.5T and up)
  - Permanent Magnets (up to 0.3T)
  - Resistive and Electromagnets (up to 0.6T)
MRI Signal

- Utilize magnetic properties of hydrogen
- When there is no main magnetic field ($B_0$), the orientation of hydrogen atoms are random
- In the presence of a $B_0$ field, hydrogen nuclei orient in the direction of the $B_0$ field

$M_0 = \text{Magnetic Moment}$

$M_0 = 0$

$M_0 = \uparrow$
T1-weighted

- **T1**: time constant for regrowth of longitudinal magnetization ($M_z$)
  - Long T1 equals dark signal
  - Short T1 equals bright signal
- **Gadolinium (Gd)** contrast agents shorten the T1 of tissue

**Equation:**

$$M_z = M_0 (1 - e^{-t/T1})$$

**Symbols:**

- $B_o$ – Main Magnetic Field
- $M_z$ – Magnetization in z direction
- $M_0$ – Net Magnetization
- $T1$ – Spin-lattice relaxation
Volumetric T1

• T1-weighted images have excellent gray-white matter contrast

• Volumetric imaging acquires isometric voxels

• These features are essential in dementia imaging
Total Cranial Volume: Gender and Age

Framingham data: N=2266 MRI’s, adults 34-97 yrs

DeCarli, C et al Neurobiol Aging 2005; 26:491–510
Grey Matter Involvement in AD

Frisoni et al. Brain 2007; 130: 720-730
73 M Mild Cognitive Impairment

Medial temporal atrophy: Risk for progression to AD

Prominent perivascular spaces: incidental
Mild Cognitive Impairment

Age 61

Age 64

Normal appearance
Serial Imaging

Progressive L > R hippocampal & cortical atrophy

Age 64

Age 69

Age 72
Automated Regional Atrophy Quantification in Dementia

Automated atlas-based 3D-T1 segmentation

Brewer et al. AJNR 2009; 30:578-580
Clinical Alzheimer’s Disease - age 72

Bilateral hippocampal atrophy < 1%
### Clinical Alzheimer’s Disease - age 72

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<thead>
<tr>
<th>Structure</th>
<th>Total Volume (cm³)</th>
<th>Percentile</th>
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<td>Whole Brain</td>
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**Subcortical Structures**

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<td>Ventral Diencephalon</td>
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### Cortical Brain Regions

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<td>Fusiform</td>
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<td>Hippocampus</td>
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*NeuroQuant® Triage Brain Atrophy Report*
81 F Clinical Dementia
Frontotemporal Dementia
81 F Clinical Dementia
Progressive Supranuclear Palsy

“Hummingbird Sign” – Progressive Supranuclear Palsy

See Kato et al J Neurol Sci 2003; 210: 57-60
T2-weighted

\[ M_{xy} = M_0 \ e^{-t/T_2} \]

- \( B_0 \) – Main Magnetic Field
- \( M_{xy} \) – Magnetization in transverse plane
- \( M_0 \) – Net Magnetization
- \( T_2 \) – Spin-spin relaxation time

• T2: time constant for decay (dephasing) of transverse magnetization (\( M^{xy} \))
  • Long T2 equals bright signal
  • Short T2 equals dark signal
• Sensitive to fluid collections
Volumetric T2 FLAIR

• T2 imaging emphasizes parenchymal abnormalities
• Commonly see white matter hyperintensities with age
• Marker of vascular disease?
White Matter Hyperintensity
Risk Factors: Stroke Risk Profile

Stroke Risk Profile Predicts White Matter Hyperintensity Volume
The Framingham Study

Tom Jeerakathil, MD; Philip A. Wolf, MD; Alexa Beiser, PhD; Joseph Massaro, PhD;
Sudha Seshadri, MD; Ralph B. D’Agostino, PhD; Charles DeCarli, MD

Background and Purpose—Previous studies of cardiovascular risk factors and white matter hyperintensity (WMH) on brain MRI have been limited by the failure to exclude symptomatic cerebrovascular disease and dementia or by the use of semiquantitative rather than quantitative methods to measure WMH volume (WMHV). We examined the relationship between Framingham Stroke Risk Profile (FSRP) and WMHV measured quantitatively in a stroke and dementia-free subset of the Framingham Offspring Cohort.

Methods—Brain MRI was performed in 1814 members of the Framingham Offspring Cohort. Pixel-based quantitative measures of WMHV corrected for head size were obtained using a semiautomated algorithm. WMHV was not normally distributed and therefore was log-transformed (LWMHV). The FSRP and its component risk factors measured a mean of 7.5 years before MRI were related to both continuous measures of LWMHV and to the presence of large volumes of LWMHV (LWMHV-large). All analyses were adjusted for age and sex.

Results—FSRP was strongly associated with LWMHV and LWMHV-large. Age, smoking, history of cardiovascular disease, hypertension, and left ventricular hypertrophy by electrocardiogram were all significantly related to LWMHV or LWMHV-large.

Conclusions—FSRP and several cardiovascular risk factors were related to both WMHV measured continuously and to a categorical designation of large volumes of WMH. These findings provide strong evidence of a vascular basis for WMH. (Stroke. 2004;35:1857-1861.)
"Relax, honey—change is good."
WMH volume versus age

Framingham Study Data

N=1330, stroke-free and dementia-free

Atwood et al. Stroke 2004;35:1609-1613
White Matter Segmentation – T2 FLAIR

Microscopic Pathology of Aging White Matter

Myelin pallor
Fibrosis
Hyalinosis

H&E

Courtesy of S. Salamat, MD, PhD – UW Madison
White Matter Grading Scale

Wahlund

1
2
3

Bronge and Wahlund  Br J Radiol 2007; 80: S115-20
White Matter Grading Scales: Useful???

LADIS Leukoaraiosis And DISability Study
618 independently living elderly

WMH assessment vs Disability
- Fazekas
- Scheltens
- ARWMC
- Volume

➢ Volumes more sensitive than visual scales
➢ No correlation # lesions, lesion type
➢ Scales: ceiling effects, not discriminant

Van Straaten et al. Stroke 2006; 37:836-840
Are all WMHs the same?

- Deep white matter/subcortical: chronic small vessel ischemic
- Periventricular: relates to a combination of demyelination, ependymitis granularis, and subependymal gliosis, less closely tied with ischemia
Are all WMHs the same?

• Multiple types of pathology are bright on T2
  • Ischemia / gliosis
  • Damage to small blood vessel walls
  • Breaches of the barrier between the cerebrospinal fluid and the brain
  • Loss and deformation of the myelin sheath
CADASIL Syndrome:
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Multiple Sclerosis
Susac Syndrome
Levamisole Toxicity
Contribution of Vascular Disease to Dementia

Traditional

Revised

Mechanisms of Vascular Cognitive Impairment

- Cerebral small vessel disease (SVD)
- Cerebral amyloid angiopathy (CAA)
- Large artery occlusion (multiple or strategic)
- Hypoperfusion
- Multiple infarcts
- Strategic infarcts
- Microinfarcts
- Enlarged perivascular spaces
- Secondary loss of white and grey matter (atrophy)
- WML
- Lacune
- Lobar hemorrhage
- Deep hemorrhage
- Microbleeds
Cerebral Amyloid

85 F  Alzheimer’s Disease

Medial temporal atrophy >> white matter changes
T2* / Susceptibility

- Susceptibility differences lead to local magnetic field inhomogeneity
- Results in faster T2* relaxation and signal loss
- Increases with field strength
85 F Mixed AD + Vascular Dementia
Cerebral Amyloid Angiopathy

Epidemiology
- Important cause of ischemia and hemorrhage in the elderly
- Sporadic or familial
- M = F
- Age Dependent
  - 2%: ages 65-74
  - 8%: ages 75-84
  - 12%: ages >85
- CAA incidence of 80-90% in Alzheimer’s Disease

MRI Findings
- Leukoencephalopathy
- Small cortical infarcts
- Lobar/subarachnoid hemorrhage
- Superficial siderosis
- Microbleeds

Haacke et al  AJNR 2007; 28: 316
ARIA  Amyloid-Related Imaging Abnormalities

Multi-focal white matter involvement (FLAIR)

Leptomeningeal involvement (FLAIR)

Microhemorrhage

Gyral swelling (FLAIR)

Amyloid Trials ➔ Vasogenic Edema and Microbleeds

 Courtesy Jerry Barakos, MD
Amyloid β Angiitis – T1 CUBE Black Blood MRI + C

Inflammatory Amyloid Angiopathy

Leptomeningeal enhancement
Arterial wall enhancement
Parenchymal enhancement
Vasogenic edema
Extensive Microhemorrhages
Amyloid β Angiitis  
(Inflammatory Amyloid Angiopathy)

- Ranges from frank vasculitis to perivascular inflammation
- Autoimmune response to vascular amyloid β deposits (APO-E gene frequently expressed similar to AD)
- Responds to steroids, immunosuppressive therapy
Amyloid β Angiitis (Inflammatory Amyloid Angiopathy)

- Ranges from frank vasculitis to perivascular inflammation.
- Autoimmune response to vascular amyloid β deposits (APO-E gene frequently expressed similar to AD).
- Responds to steroids, immunosuppressive therapy.
Cerebral Amyloid Angiopathy
Hypertensive Microhemorrhages
Iatrogenic Microhemorrhages
Emboli
Diffuse axonal injury
Cerebral blood flow

AD patients have decreased blood flow
Perfusion Imaging

• Imaging the passage of fluid through the circulatory system

• Usually referring to the delivery of blood to a capillary bed in tissue

• Some techniques use contrast
Arterial Spin Labeling
76M with Alzheimer’s Disease
Morphology (FLAIR) vs Physiology (ASL Perfusion)

3D T2 FLAIR Reconstructions
76M with Alzheimer’s Disease

Morphology (FLAIR) vs Physiology (ASL Perfusion)

ASL CBF - quantitative
Normal White Matter Perfusion

47 normal adults
ECD SPECT
Periventricular perfusion

Holland et al Stroke 2008; 39:1127-1133
4D Flow MRI

• Phase contrast MRI method with a blood flow vector and temporal component

• Enables both volumetric angiographic and quantitative assessment of blood flow velocities in a single acquisition

• Wall shear stress, pulsatility, pressure gradients, vessel area measurements
Macrovascular disease

- Neuron loss $\rightarrow$ decreased metabolism
- Decreased vessel compliance (e.g. increased pulsatility index)

Macrovascular disease

- Pulse wave velocity (PWV) gold standard noninvasive biomarker for arterial stiffness
- Carotid-femoral PWV associated with deposition of Aβ in nondemented individual

\[ PWV = \frac{\Delta d}{\Delta t} \]

- High speeds:
  - high blood pressure
  - arterial stiffness
- Low speeds:
  - low blood pressure
  - elastic arteries
Assessment of other brain compartments

Multiple compartments (e.g. 4D flow probes arteries, ignores tissue)

- arterial pressure (fast velocities)
  - tissue (small displacements)
  - CSF (slow velocities)

Need for multi-scale characterization
- Intracranial PWV
- Strain mapping
- Intracranial pressure
**DWI/DTI**

- Diffusion-weighted MRI (DWI) uses differences in the diffusion of water molecules
- Molecular diffusion in tissues is not free
- Water molecule diffusion patterns reveal microscopic details about tissue architecture
- Diffusion tensor imaging (DTI) can be used to map white matter tractography
Tractography in Degenerative Disorders

Mod from Catani by Ciccarelli  Lancet Neurol 2008; 7:715-727
Fractional Anisotropy: AD vs VaD

Transcallosal prefrontal FA + Fazekas score = 87.5% accuracy

fMRI Resting Connectivity - Lost with AD

ICA group comparison (voxel-wise)

Healthy elderly controls

Mild cognitive impairment

Alzheimer’s disease

Courtesy of Dr. Walter Koch
Munich, Germany
The Aging Brain: Gross Anatomy

Courtesy of Josh Medow, MD – UW Madison
Alzheimer’s Disease: Pathology

Plaques
Amyloid-β protein

Tangles
Phosphorylated tau protein

Modified from Small, G. Lancet Neurol 2008; 7: 161–72
Symptoms of AD correlate with selective amyloid PET binding

Posterior Cingulate Gyrus
Functions: memory and self reflection

UW-Madison, Sterling Johnson PhD
Florbetapir-PET vs Amyloid Pathology*

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<th>79 y</th>
<th>+ AD</th>
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*(p< 0.001)
**Neurofibrillary tangles**

- **Ghost tangles**

**Candidate Tau Agents**

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*Saint-Aubert Molecular Neurodegeneration 2017*
PET Agents in Alzheimer’s Disease

**Tau**
- [18F]THK5317

**Glucose**
- [18F]FDG

**Amyloid**
- [11C]PIB

74 M – prodromal AD (MMSE 27)

74 F – advanced AD (MMSE 23)

Saint-Aubert, Molecular Neurodegeneration 2017
Cerebrospinal Fluid (CSF) Biomarkers of AD

CSF Tau and Aβ42, pg/mL

0 200 400 600 800 1000

Time

CSF Tau

CSF Aβ42

Asymptomatic → MCI → Clinical AD

Neuronal degeneration

Courtesy of Cindy Carlsson, MD
Combined Multi-Biomarker Diagnosis: MRI, PET, and CSF t-tau/Aβ42 in AD

Hpc volume
Hpc + t-tau/A42
Hpc + t-tau/A42 + retrosplenial thickness
Hpc volume

Walhovd...Brewer et al AJNR 2010; 31:347–54
Dementia: Risk Factors

Fixed
- Age
- Family history
- Apo ε4 status (Head trauma)

Modifiable
- Cardiovascular
  - Hypertension
  - Diabetes
  - Lipids
- Lifestyle
  - Diet / Alcohol
  - Education
  - Activity
  - Exercise
  - Games
Dementia Imaging: Summary

• Clinical spectrum
  • Multifactorial causes / differential diagnosis
  • Alzheimer’s: Pre clinical → MCI → Dementia

• Imaging and biomarkers
  • Structural patterns concerning for AD
    • Hippocampal / mesial temporal atrophy
  • Functional imaging supportive of AD
    • PET agents, perfusion patterns

• Research and treatment directions
• Can I still eat chocolate?

- 90 elderly with MCI
- Flavanols x 2 months:
  - Cognitive tests ↑
  - Insulin resistance ↓
  - Blood pressure ↓

Desideri, G et al Hypertension 2012;60:794-801
Supported by a grant from Mars, Inc.

Hot Cocoa May Boost Seniors' Brain Power

Published: Aug 13, 2012

By Kristina Fiore, Staff Writer, MedPage Today

Cocoa flavanols have shown some benefits for the heart, but they may also be good for cognitive function in older people, researchers found.

In a double-blind study, elderly patients with mild cognitive impairment who consumed high or moderate levels of cocoa flavanols for 2 months had significant improvements on certain cognitive assessment tests compared with those who took in only small amounts, Giovannitissa Desideri, PhD, of the University of L'Aquila in Italy, and colleagues reported online in Hypertension.

*Although additional confirmatory studies

http://www.medpagetoday.com/Cardiology/Dementia/34179
Can I still eat chocolate? **YES!**

- 90 elderly with MCI
- Flavanols x 2 months:
  - Cognitive tests: ↑
  - Insulin resistance: ↓
  - Blood pressure: ↓

Desideri, G et al. *Hypertension* 2012;60:794-801

Supported by a grant from Mars, Inc.

[MedPage Today](http://www.medpagetoday.com/Cardiology/Dementia/34179)
Thank you
Neuroimaging in the Diagnosis of Dementia
Laura Eisenmenger, M.D.
University of Wisconsin, Madison
leisenmenger@uwhealth.org

Learning Objectives
✓ Role of imaging in dementia
✓ Imaging tools: from structure to function
✓ Future areas of imaging development

UW Alzheimer’s Disease Research Center
Drs. Asthana, Johnson, Carlsson, Bendlin, Rowley...