HOUSTON Methodist NEUROLOGICAL INSTITUTE

Neuroimaging: Serving Our Patients Integrally

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Faculty Disclosure

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research
General Electric Health	X	X	X
Eli Lilly	X		X
Avanir			X
Abbvie			X
ALS Association			X
Biogen			X
NIH (NIA)			X
Novartis			X

Found in the ASN Archives . . .

The American Society of Neuroimaging

1977-1997

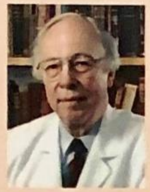
William H. Oldendorf, M.D.
1978-1979

William H. Oldendorf, M.D. 1925-1992

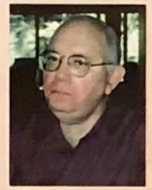
Dr. William H. Oldendorf was widely recognized as one of the original founders of the principles of computed tomography. Oldendorf's studies in the late 1950s and early 1960s were acknowledged by Sir Godfrey Hounsfield in his own work which led to the invention of the X-ray CT scanner and the Nobel Prize for medicine in 1979.

Oldendorf's work was invaluable to researchers in the field of neuroimaging, despite his inability to interest X-ray equipment manufacturers in his invention. In 1975, Oldendorf and Hounsfield were awarded the Albert and Mary Lasker Award for the conception of the principles which led to the development of computed tomography. Oldendorf's work has also been applied to the areas of PET and SPECT imaging.

Mazziotta, John C, and Robert C. Collins. William H. Oldendorf, 1925-1992. Ann Neurol 1993; 33:331.



William R. Kinkel, M.D.
1980-1981



Jack O. Greenberg, M.D.
1982-1984

William H. Stuart, M.D.
1985

Lawrence D. Jacobs, M.D.
1986-1988

A Word from the President

My most memorable experience involving the ASN was receiving the Oldendorf Award from Bill Oldendorf himself. The meeting was held in San Juan, and Bill and I flew there together from Los Angeles. Despite the fact that we were both members of the UCLA Neurology Department, we had hardly met before the trip because I was a resident and he was a senior faculty member running his research lab at the Wadsworth VA Hospital. After that meeting, we became close friends and I always trusted his advice, both in areas of imaging research, as well as in important professional decisions. He was a man for all seasons in the world of imaging and in neurology. I miss his good humor and quick wit and fondly remember the part the ASN played in initiating our friendship.

John C. Mazziotta, M.D., Ph.D.
President, American Society of Neuroimaging

1976 - Conception of ASN

Thirty neurologists attended the first Neurology Computed Tomography Symposium, organized by Dr. William Kinkel, in Buffalo, New York, September 24-25. One reason for calling this meeting was to implement the educational aspects of the American Academy of Neurology's Ad-Hoc Committee on Imaging. During the meeting, there was unanimous agreement that the group should organize under some name and continue to hold meetings. Dr. William Kinkel belonged to a group that stressed CT, while Dr. William Oldendorf and others stressed neuroimaging. As a compromise, the name *Society for Computerized Tomography and Neuroimaging* was chosen.

Leon D. Prockop, M.D.
1988-1990

William M. McKinney, M.D.
1990-1992

James F. Toole, M.D.
1992-1994

Joseph C. Masdeu, M.D., Ph.D.
1994-1996

John C. Mazziotta, M.D., Ph.D.
1996-1998

1977

- First meeting of new Society held in Hilton Head, South Carolina
- Executive Office located in Atlanta
- The Society was not restricted to neurologists - First Executive Committee included neuroradiologists and neurosurgeons - During this meeting, the main focus was on computerized tomography; however, the Society emphasized importance of educational courses and seminars which would provide members with cutting edge technology to better care for their patients
- Echo planar imaging

1978

- President William H. Oldendorf (1978-1979)
- Annual meeting held in Hilton Head, South Carolina
- During second annual meeting of the Society for Computerized Tomography and Neuroimaging (SCTN), the first examination by a national organization in the field of neuroimaging was given - Organized by Dr. William Kinkel, 100 physicians took the exam
- Neurosonology voted in by Board to be a part of the Society
- Number of CT scanners in the United States up to about 500

1979

- Annual meeting held in Ponte Vedra, Florida
- Professor Sokoloff was invited to speak at annual meeting in Jacksonville, Florida on Positron Emission Tomography (PET) Functional imaging of brain blood flow was also represented by Professor Niels Lassen
- Noninvasive cerebrovascular ultrasound examination
- Allan McLeod Cormack and Godfrey Newbold Hounsfield, developers of CT scanning, awarded the Nobel Prize
- Organizational meeting of the Ladies Auxiliary
- Real-time carotid ultrasound

1980

- President William R. Kinkel (1980-1981)
- Annual meeting held in Dorado, Puerto Rico
- During the Society's annual meeting in Puerto Rico, members were introduced to Nuclear Magnetic Resonance (NMR), later known as Magnetic Resonance Imaging (MRI)
- The Society's Executive Office was moved from Atlanta to Dent Neurological Institute in Buffalo
- Single photon emission computed tomography (SPECT) first reported

1981

- Annual meeting held in Dorado, Puerto Rico
- The Society's name changed to American Society of Neuroimaging (ASN)
- First William H. Oldendorf Essay Award was presented to John C. Mazziotta for his work with PET
- Dr. Martin Reivich was guest speaker at annual meeting
- Austrian Society of Neuroimaging was born in Vienna - Dr. William Kinkel represented American Society of Neuroimaging at this important event

1982

- President Jack O. Greenberg (1982-1984)
- TCD ultrasonography

1983

- Annual meeting held in Scottsdale, Arizona
- During seventh annual meeting, the Society's new name, American Society of Neuroimaging, was first used
- Magnetization transfer - First human studies
- Death of Felix Bloch, a developer of magnetic resonance imaging

1984

- Annual meeting held in Boca Raton, Florida
- First certification examination in Neurosonology was given
- Magnetic resonance imaging became commercially available

1985

- President William H. Stuart, M.D. (1985)
- Annual meeting held in Innisbrook, Florida
- Society continued interest in clinical applications of positron emission tomography (PET)
- SPECT was clinically used (Mid 1980's)

1986

- President Lawrence D. Jacobs (1986-1988)
- Annual meeting held in Clearwater Beach, Florida
- The William M. McKinney Research Award in Neurosonology was established
- Ultrastable lipid-coated microbubbles
- Functional neuroimaging - First animal studies
- Fast spin-echo pulse sequences - First human study

1997

- Annual meeting held in San Juan, Puerto Rico
- Society has rapidly grown from original thirty members to organization of nearly seven hundred members
- ASN is proud to celebrate its twentieth anniversary
  - First established neuroimaging society
  - First physician examinations for CT, MR, and Neurosonology
  - Multidisciplinary approach
  - *Journal of Neuroimaging*
  - Newsletter
  - Awards for outstanding research
  - Annual meetings
  - AMA membership with a seat in the House of Delegates
  - Major influence in: medical care, training, establishment of standards, examinations, reimbursement, medical legal issues
  - Executive office management

1996

- President John C. Mazziotta (1996-1998)
- Annual meeting held in Oakland, California
- American Medical Association recognized American Society of Neuroimaging as an official member and established seats in the House of Delegates
- Triple-headed or ring units introduced for SPECT

1995

- Annual meeting held in San Juan, Puerto Rico
- Linda J. Wilkerson became Executive Director
- Power Doppler ultrasound
- Brain disease deaths down 37 percent from 1979, according to CDC

1994

- President Joseph C. Masdeu (1994-1996)
- Annual meeting held in Beverly Hills, California
- 99m Technetium ECD introduced for study of seizures by SPECT

1993

- Annual meeting held in Orlando, Florida
- American Society of Neuroimaging was admitted to the Specialty and Service Society of the American Medical Association
- 20th anniversary of installation of first CT scanner in North America

1992

- President James F. Toole (1992-1994)
- Annual meeting held in San Francisco, California
- ASN and South-East European Society for Neurology and Psychiatry held a fourth joint meeting in Graz, Austria
- Diffusion-weighted MRI applied clinically
- Death of William H. Oldendorf, pioneer of CT scanning and leader in neuroimaging field

1991

- Annual meeting held in Orlando, Florida
- A third joint meeting was held between ASN and South East European Society for Neurology and Psychiatry in Salzburg, Austria

1990

- President William M. McKinney (1990-1992)
- Annual meeting held in San Diego, California
- A second joint meeting between ASN and South East European Society for Neurology and Psychiatry was held in Venice, Italy
- The *Journal of Neuroimaging* was founded as the official journal of American Society of Neuroimaging
- Biomagnetic imaging

1989

- Annual meeting held in Orlando, Florida
- Professor Helmut Lechner of Graz, Austria, sponsored joint meeting of South-East European Society for Neurology and Psychiatry in Salzburg, Austria
- SPECT was introduced at 10th annual meeting
- Proton spectroscopy
- Multi-modality imaging

1988

- President Leon D. Prockop (1988-1990)
- Annual meeting held in Tampa, Florida
- Dr. William Kinkel organized first certification exam in MRI

1987

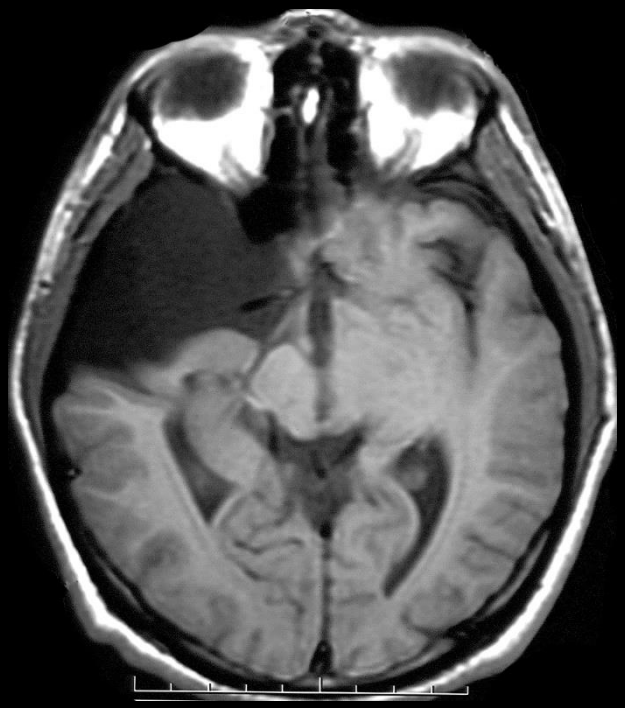
- Annual meeting held in Tampa, Florida
- First concurrent meeting with Stroke Society was held - Guests included Niels Lassen, John Sterling Meyer, Abass Alavi and Vladimir Hachinski - Professor Lassen discussed use of SPECT in the imaging of stroke
- Lawrence N. Bram was first recipient of McKinney Research Award
- Executive Office relocated to Minneapolis, Minnesota
- Magnetic resonance angiography

Presented by: Anne M. Watterson, Archivist; Michelle G. Flye, Archivist; The Dorothy Carpenter Medical Archives; The Archives Committee
Created by the Department of Biomedical Communications, Bowman Gray School of Medicine

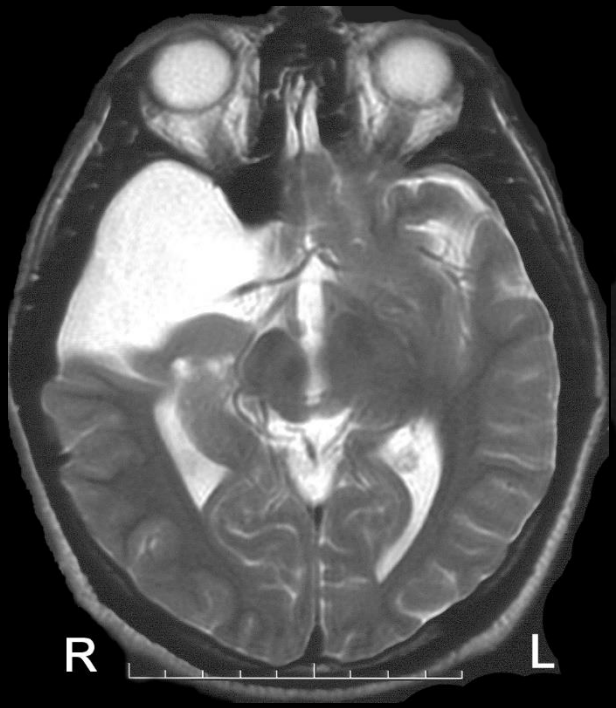
Twentieth Anniversary

28-y-o neurology resident with first headache of his life

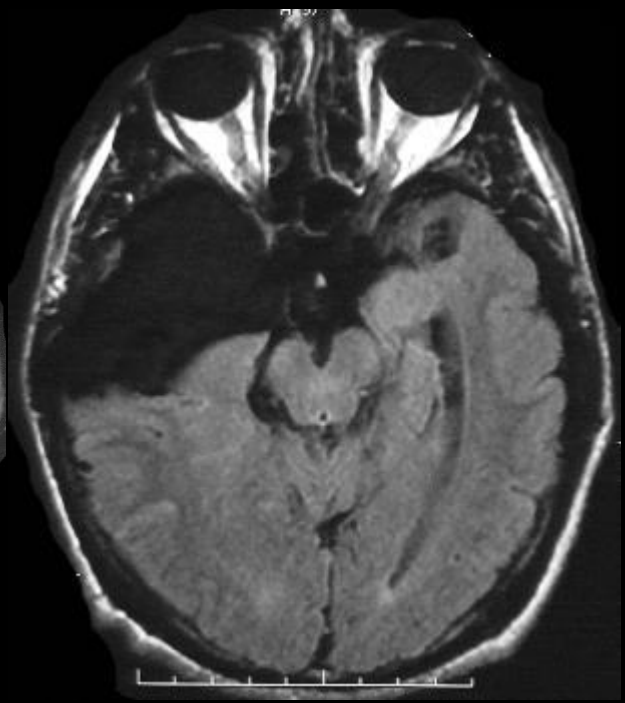
- Woke up at 6am with severe R retro-ocular pain
- Pain unabated 8 hours later, when MRI was performed



T1

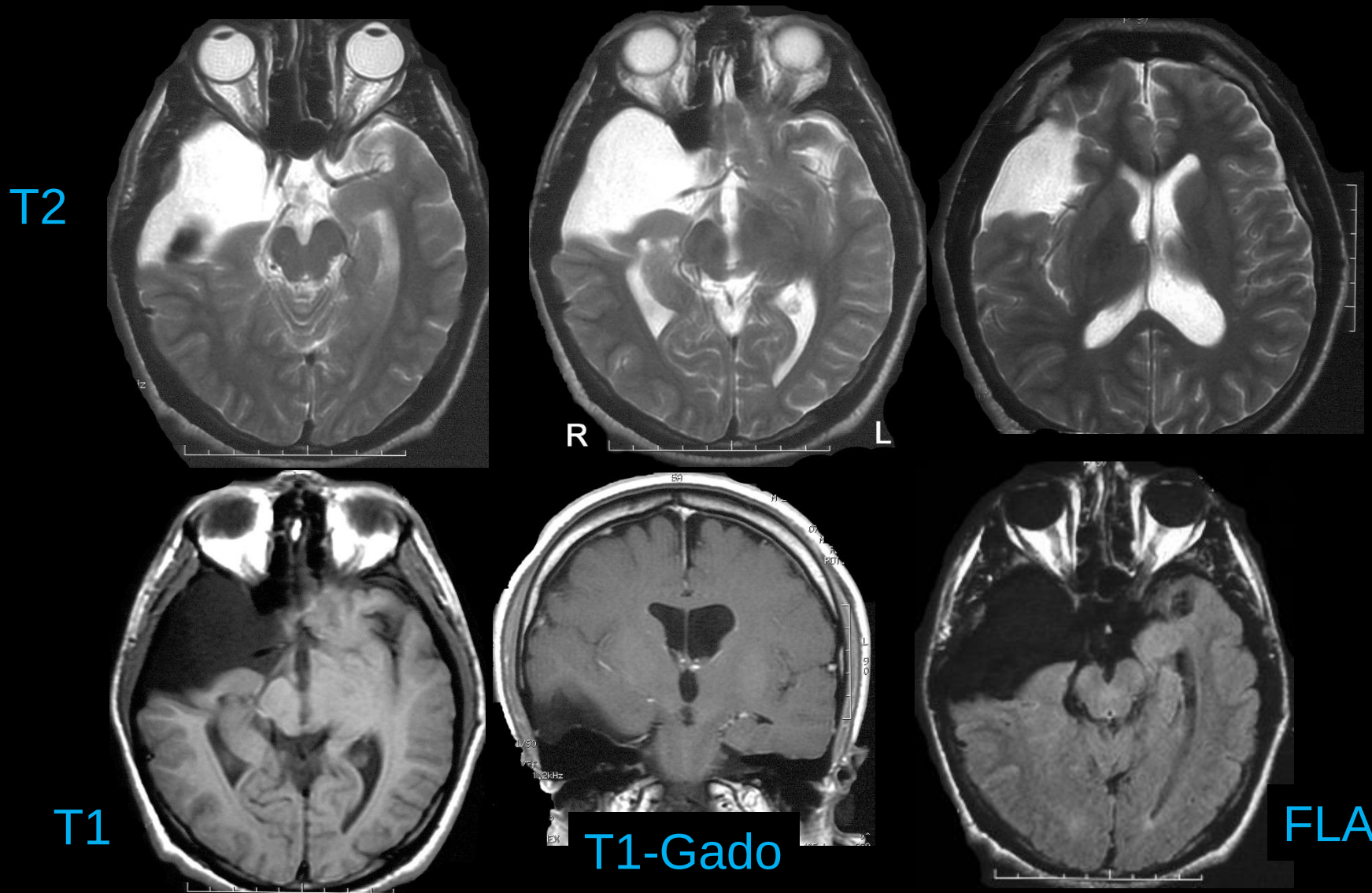


T2



FLAIR

28-y-o neurology resident with first headache of his life (R retro-ocular pain)

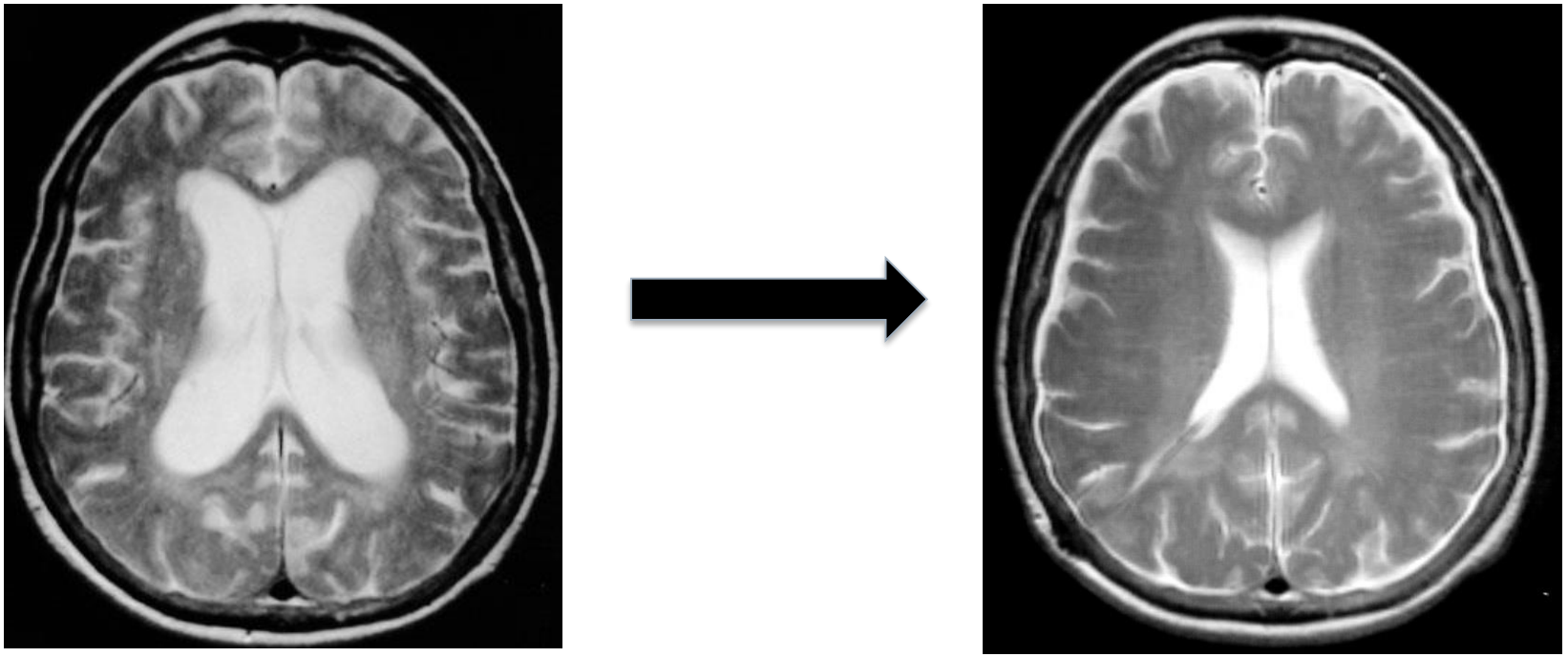


Neuroimaging: Key to Treatment

- 75-year-old
- Gait disorder
- Cognitive impairment

MRI: Hydrocephalus

- Treated with a ventriculo-peritoneal shunt



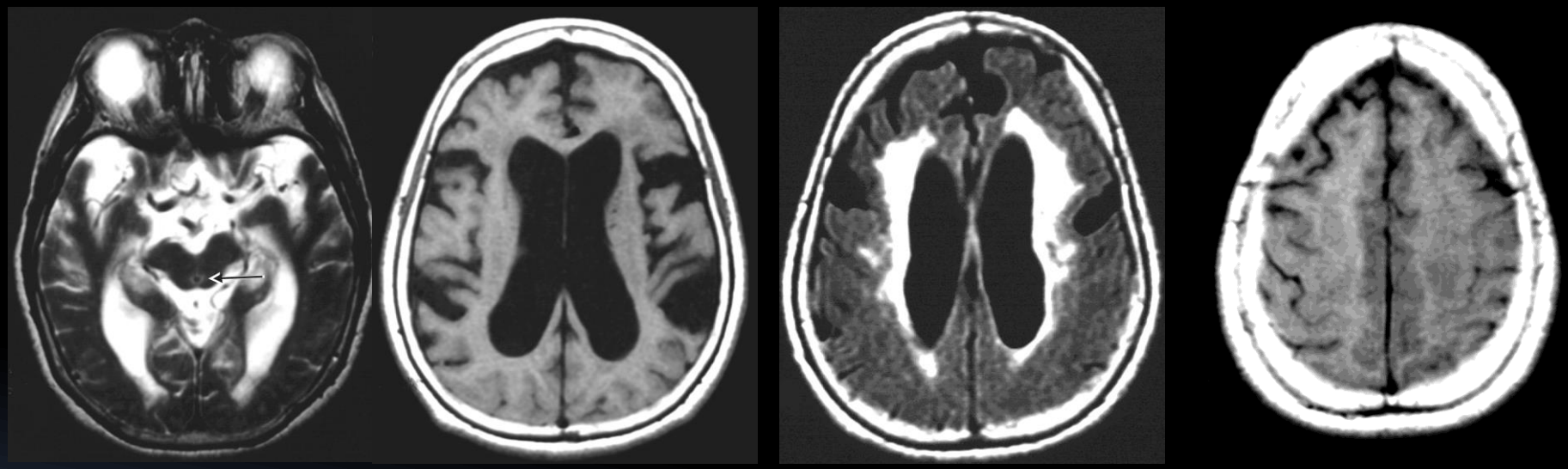
Before

After

Improved Gait and Cognition After Shunting

Symptomatic Hydrocephalus ?

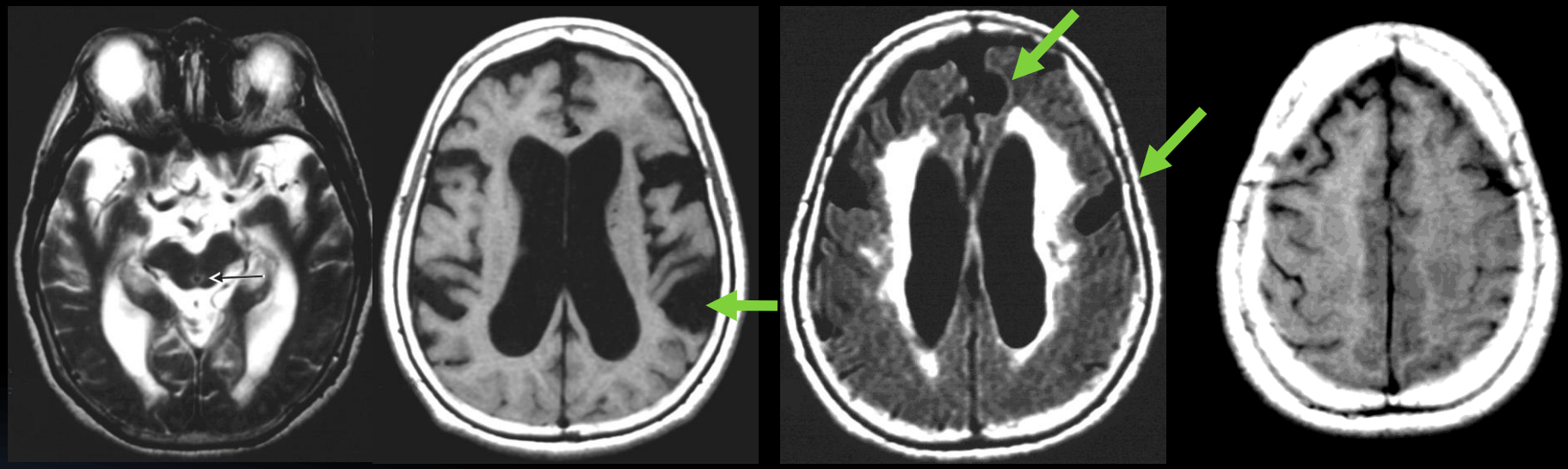
71-year-old woman unable to walk, incontinent and with impaired attention



Would you recommend a shunting procedure?

Hydrocephalus with Mega-Cisterns

71-year-old woman unable to walk, incontinent and with impaired attention. Did improve after shunting



Large basal, Sylvian cisterns → U-shaped sulci → Compressed high-convexity sulci

Holodny A et al. *J Neurosurg* 1998;89:742
Kitagaki H et al. *Am J Neuroradiol* 1998;19:1277
Tarnaris A et al . *J Neurosurg* 2009;110:837

Disproportionately Enlarged Subarachnoid Space Hydrocephalus (DESH)

ARTICLE IN PRESS

NeuroImage: Clinical xxx (xxxx) xxxx

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Automated detection of imaging features of disproportionately enlarged subarachnoid space hydrocephalus using machine learning methods

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[d] Department of Neurology, Mayo Clinic and Foundation, Jacksonville, FL, USA

ARTICLE INFO

Keywords:
Normal pressure ydrocephalus
Disproportionately enlarged subarachnoid hydrocephalus
Support vector machines
Computer-aided diagnosis
Tight high-convexity

ABSTRACT

Objective: Create an automated classifier for imaging characteristics of disproportionately enlarged subarachnoid space hydrocephalus (DESH), a neuroimaging phenotype of idiopathic normal pressure hydrocephalus (iNPH).

Methods: 1597 patients from the Mayo Clinic Study of Aging (MCSA) were reviewed for imaging characteristics of DESH. One core feature of DESH, the presence of tightened sulci in the high-convexities (THC), was used as a surrogate for the presence of DESH as the expert clinician-defined criterion on which the classifier was trained.

Alzheimer's (and other neurodegerative dementias) cannot yet be reversed with FDA-approved drugs

New treatment trials

Characteristic of Alzheimer's Disease: β-Amyloid Deposition in the Brain

- Not visible on MR
- Am
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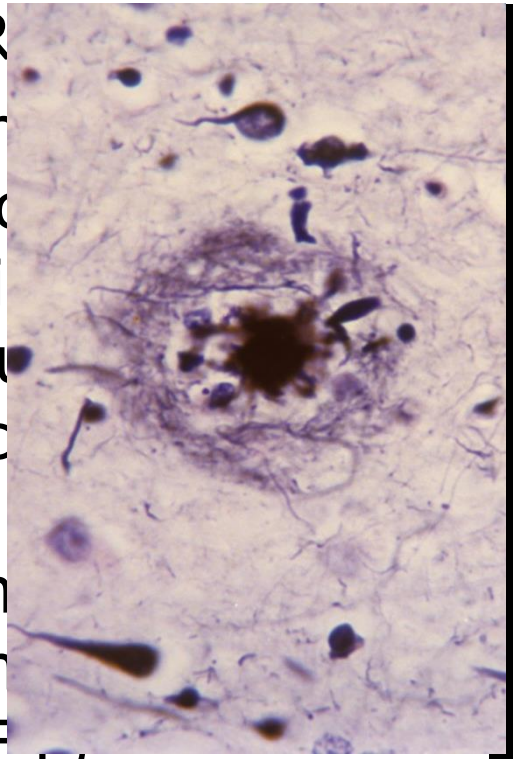
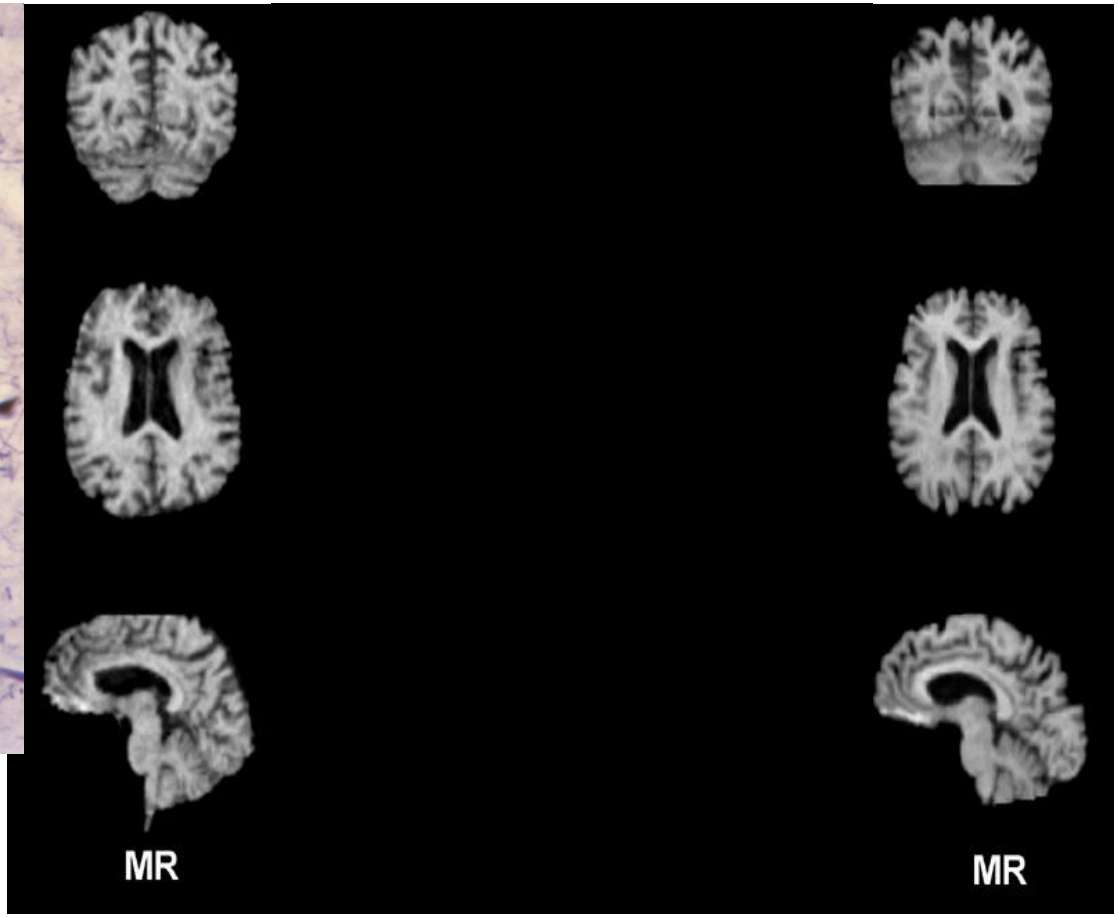


Patient with Alzheimer's Disease

Healthy Elderly

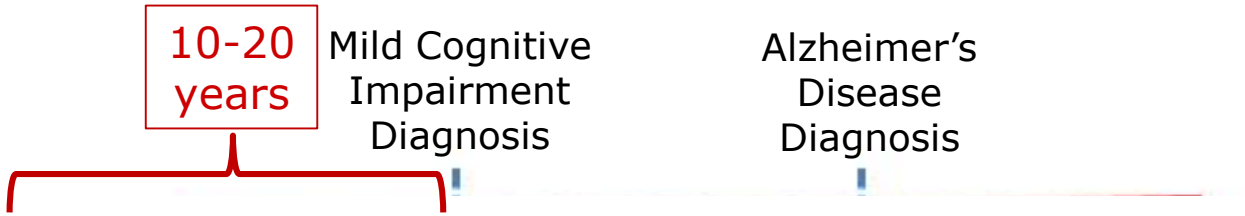


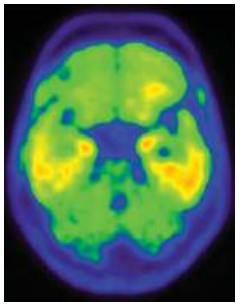
Klunk W. et al. *Ann Neurol* 2004;55:306

Neurodegeneration: An Evolving Process

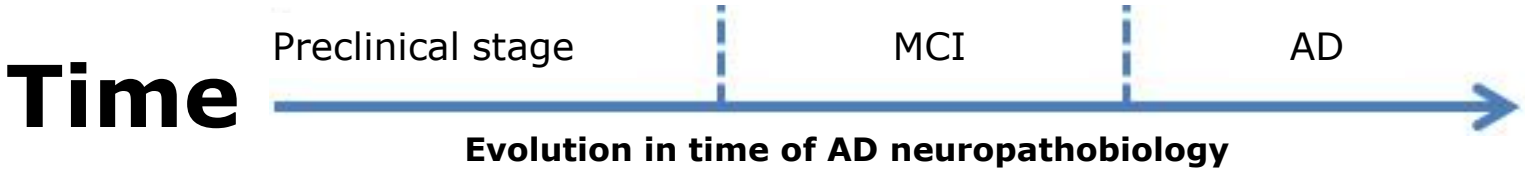
Personalized treatment requires defining the stage of each patient

Staging of AD: Imaging Findings





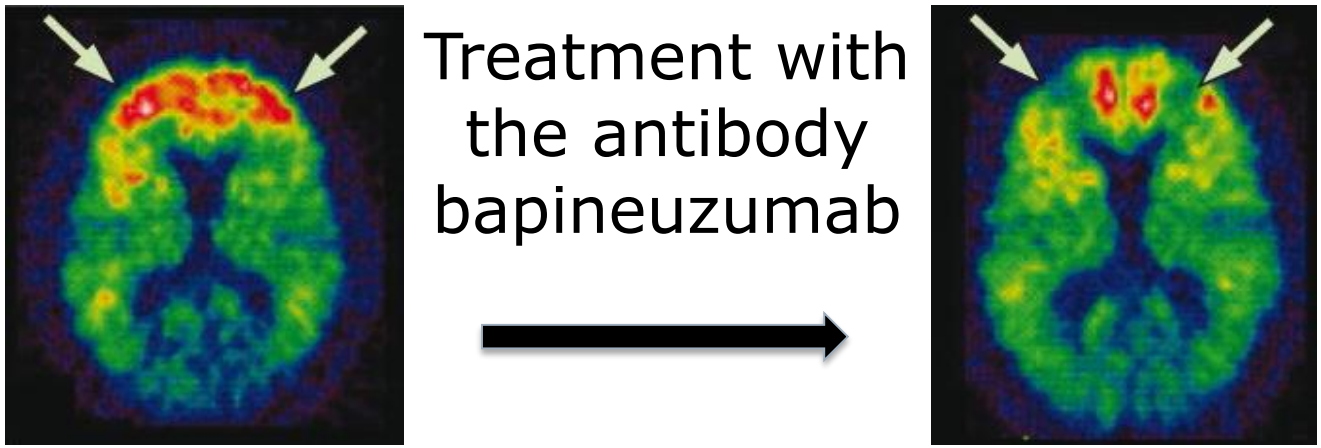
Tau imaging ^{18}F-T807 (2013)



Masdeu JC. *Curr Opin Neurol* 2012

Abnormal Brain Aβ Can Be Removed with Immunotherapy

- Antibody against deposited amyloid



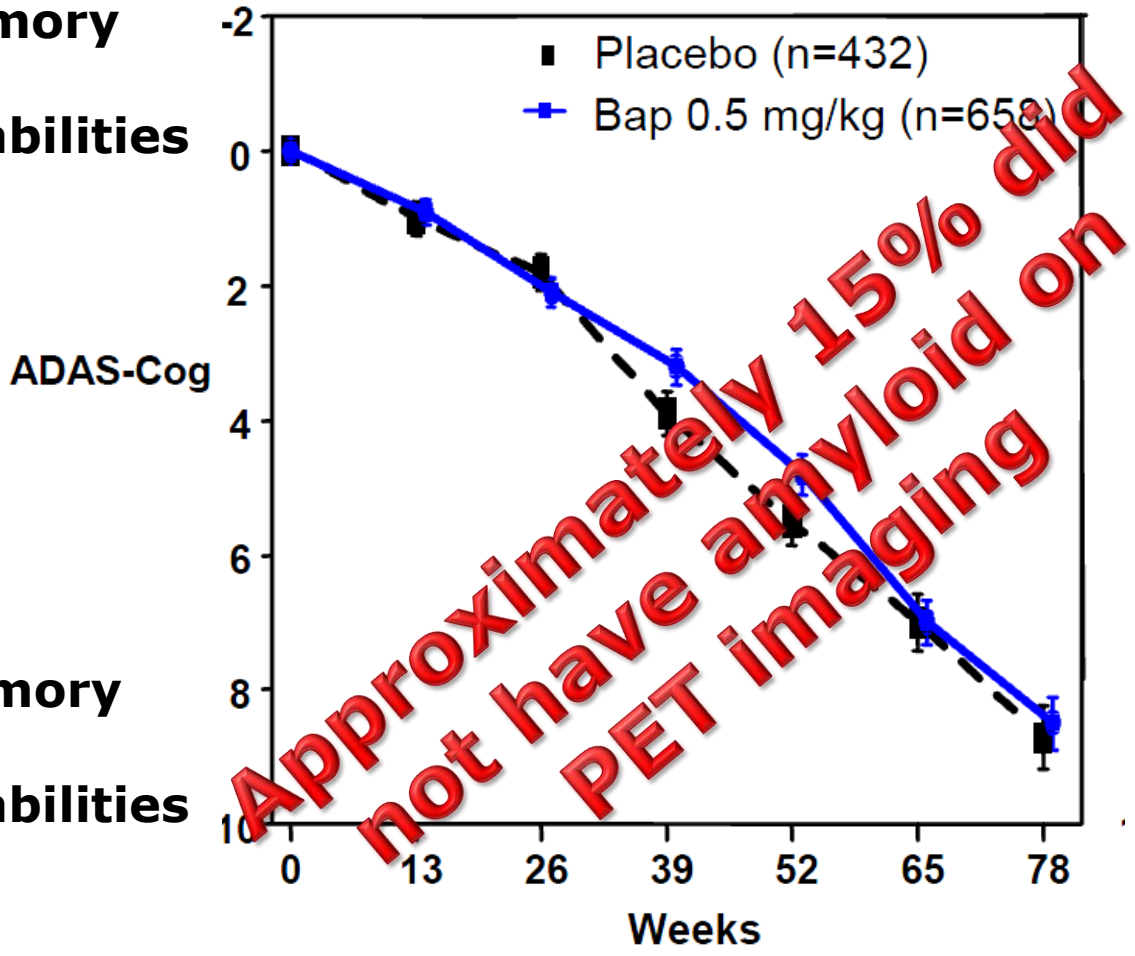
Before treatment

After treatment

Study of 2,452 patients with Alzheimer disease, funded by Janssen and Pfizer

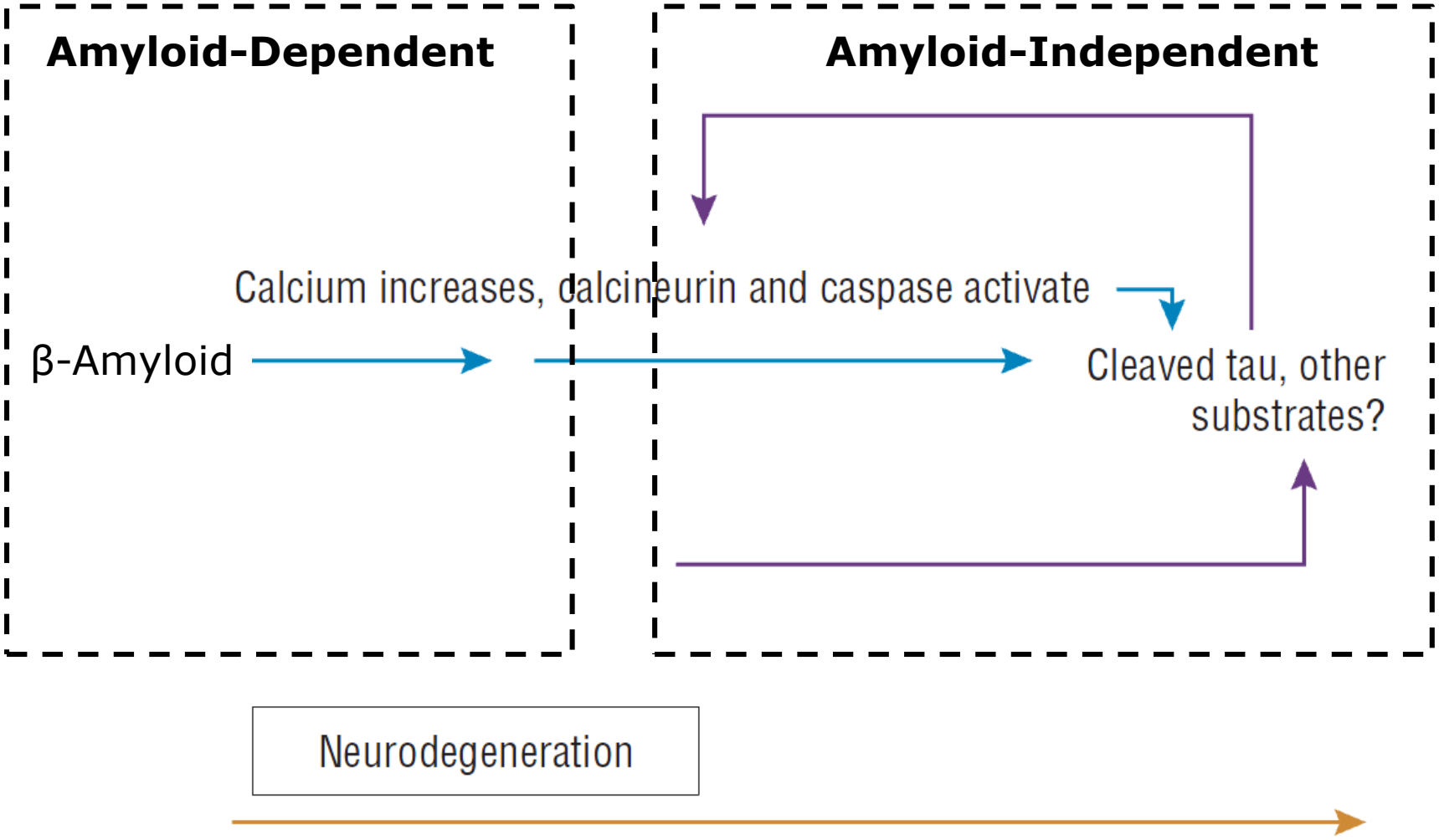
No Benefit on Cognition When Given at the AD-diagnosis Stage (But Did No Harm)

Better memory and other cognitive abilities



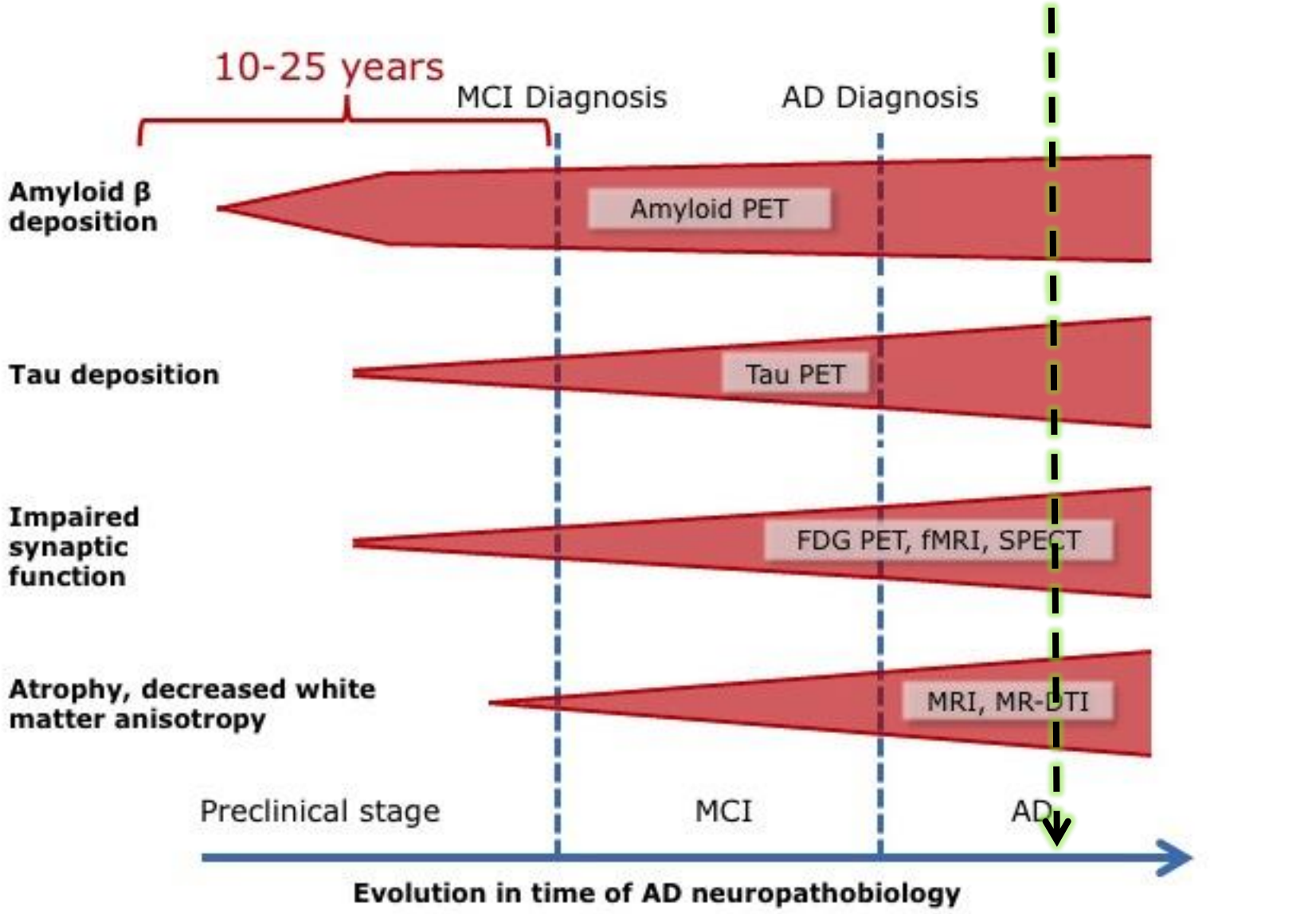
Worse memory and other cognitive abilities

Stages of AD



Hyman BT. *Arch Neurol* 2011:68;1062

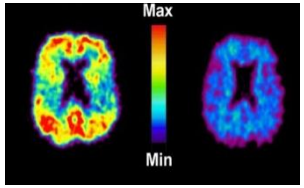
Immunotherapy



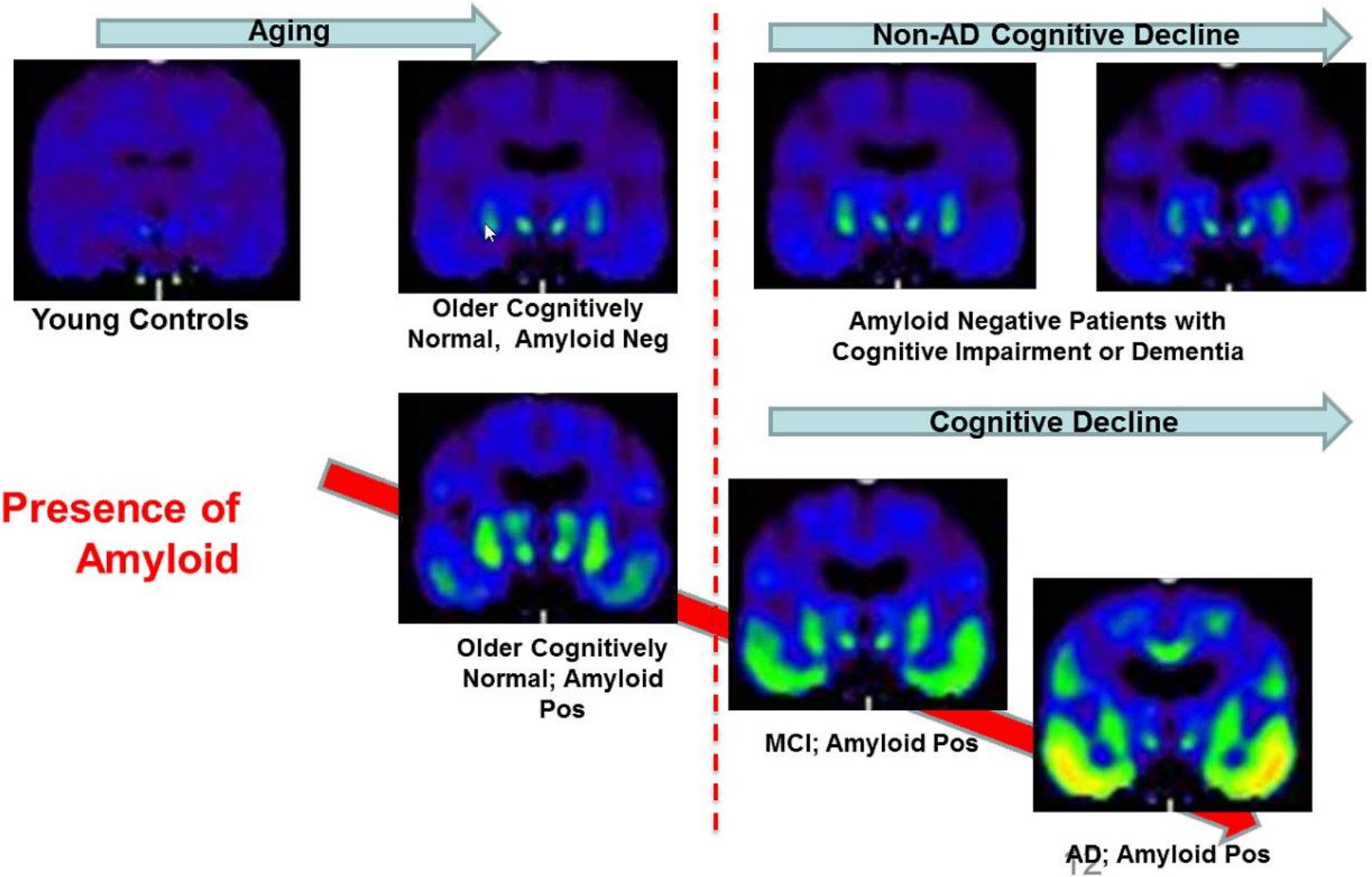
Masdeu JC. *Curr Opin Neurol* 2012;25:411

Clinical Trials At Houston Methodist on Anti-Amyloid Treatments

- For cognitive normal people at risk with an abnormal amyloid PET
  - Intravenous antibody (for people 65-85)
    - A4 Study: 6,763 screened, 4486 with PET; 1150 enrolled
    - APOE 4/4 genotype: Novartis Generation Study
- For mild cognitive impairment
  - Intravenous antibody (ages 50-85)
- PET tau load as an secondary end-point

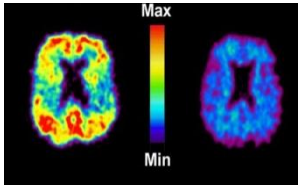


[^{18}F]AV-1451 Tau PET Imaging vs Age, Diagnosis and Amyloid Status in 124 Subjects



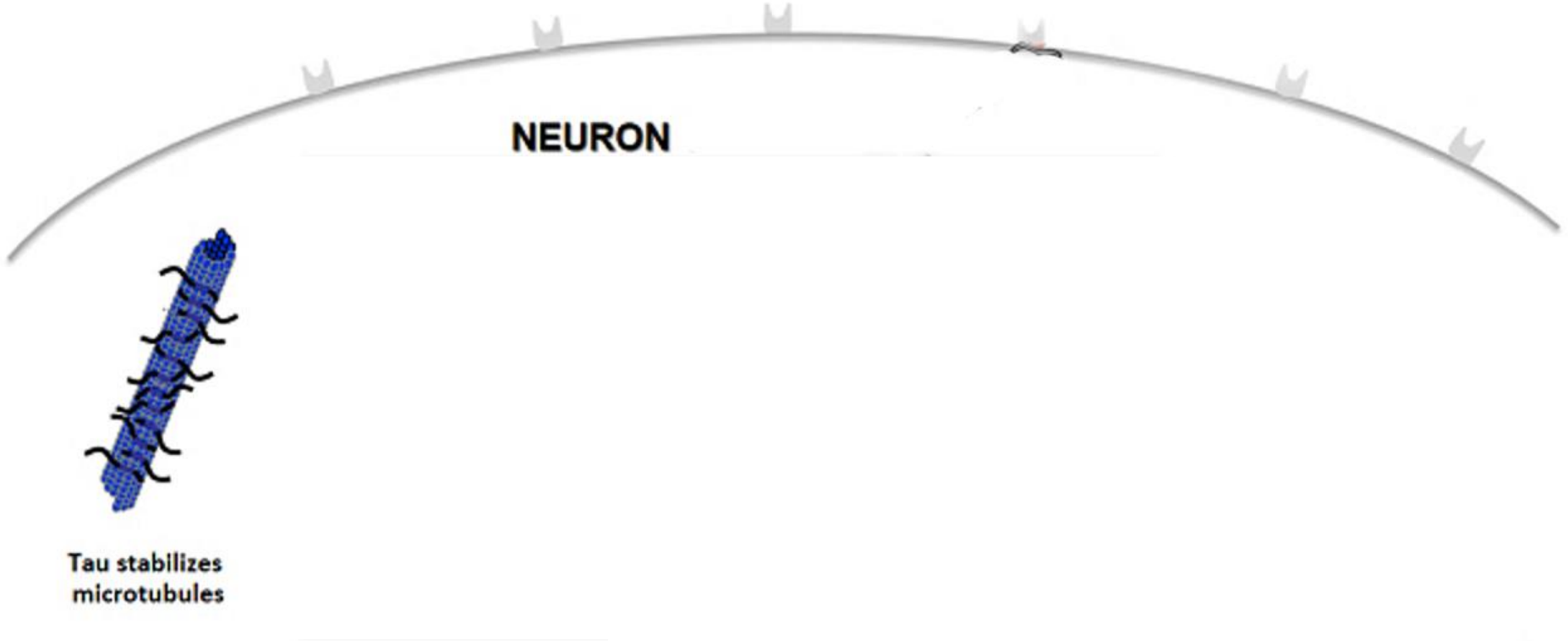
Role of beta-amyloid excess in Alzheimer's development

- It contributes to processes causing clinical cognitive impairment
- Beta-amyloid storage alone does not cause clinical cognitive impairment



Misfolded tau: Linked to neurodegeneration

Hyperphosphorylated, Misfolded Tau



Courtesy of Eli Lilly

Brain Metabolism Versus Brain Tau: Yin-Yang Relationship

Where Tau is High, Metabolism is Depressed

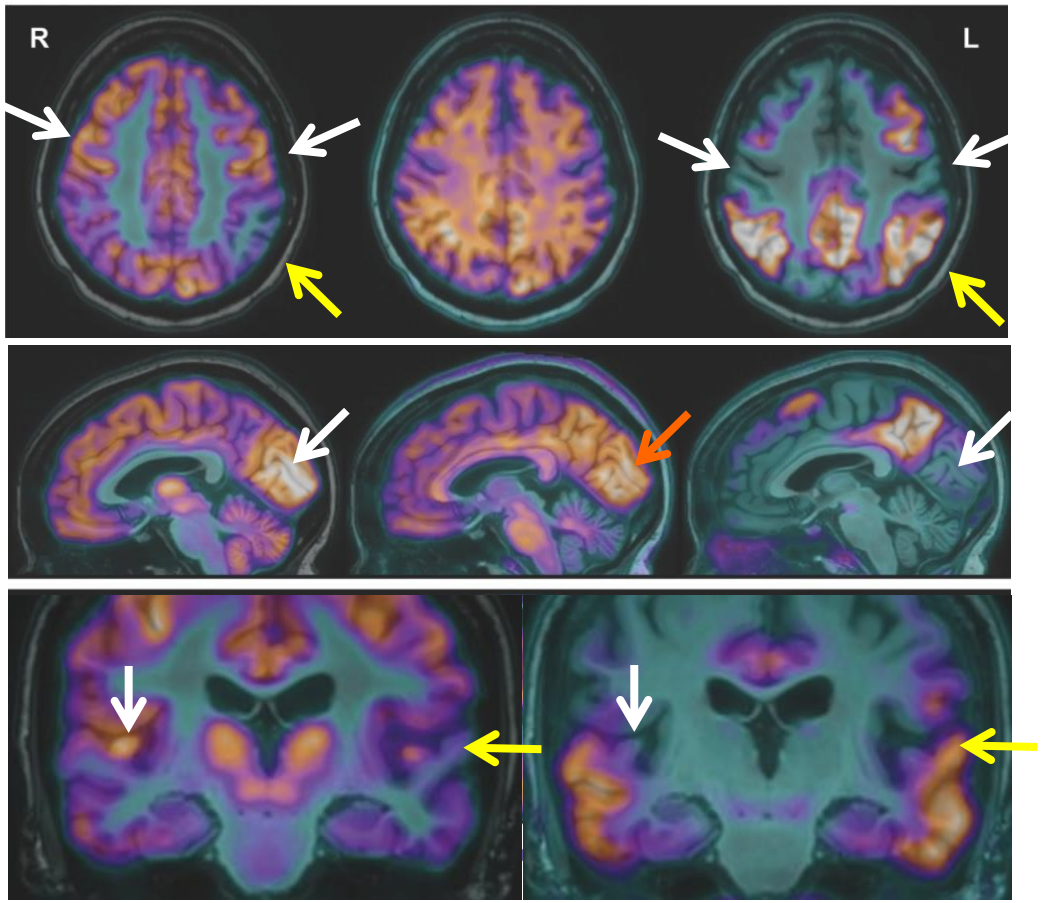
Logopenic Aphasia (Alzheimer disease)

- **Areas of normal metabolism**
- **Have no tau**

- **But areas with high amyloid**
- **May have normal metabolism**

- **Areas with high tau**
- **Have reduced metabolism**

Tau more closely linked to neurodegeneration than amyloid



Pascual et al. *Neurology* 2016;85:487

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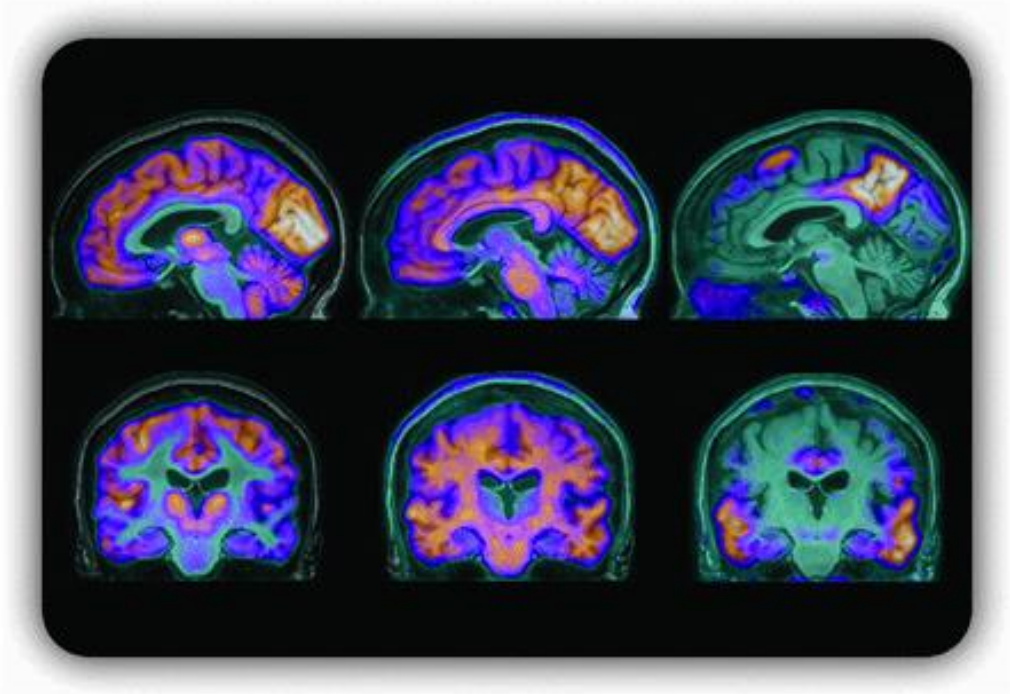
The Official Journal of the American Academy of Neurology

Feb 2, 2016 Issue

Cover image



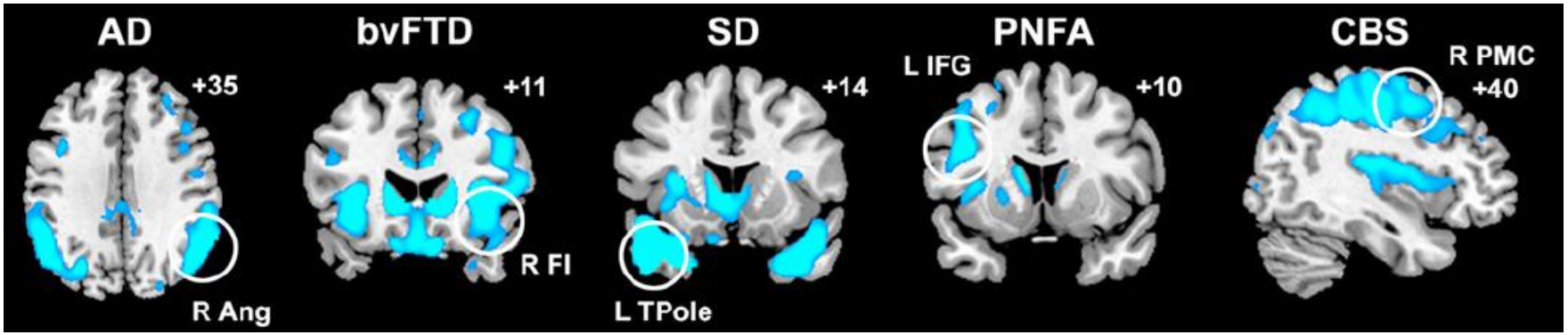
Cover image: Metabolism (^{18}F-FDG), amyloid (^{18}F-florbetapir), and tau (^{18}F-AV-1451) PET MRI in a patient with a logopenic variant of primary progressive aphasia. See page 487.

In Dementia, Tau Proteins Propagate in the Brain Like Prions *(Mad Cow Disease)*

Emerging evidence suggests that tau aggregates may undergo prion-like neuron-to-neuron transmission

Neuron-to-Neuron spread	
In cell culture	**In mice**
Kfoury *et al.* 2012	Lasagna-Reeves *et al.* 2012
Iba *et al.* 2013	De Calignon *et al.* 2012
	Lui *et al.* 2012
	Iba *et al.* 2013
	Ahmed *et al.* 2014
	Dujardin *et al.* 2014

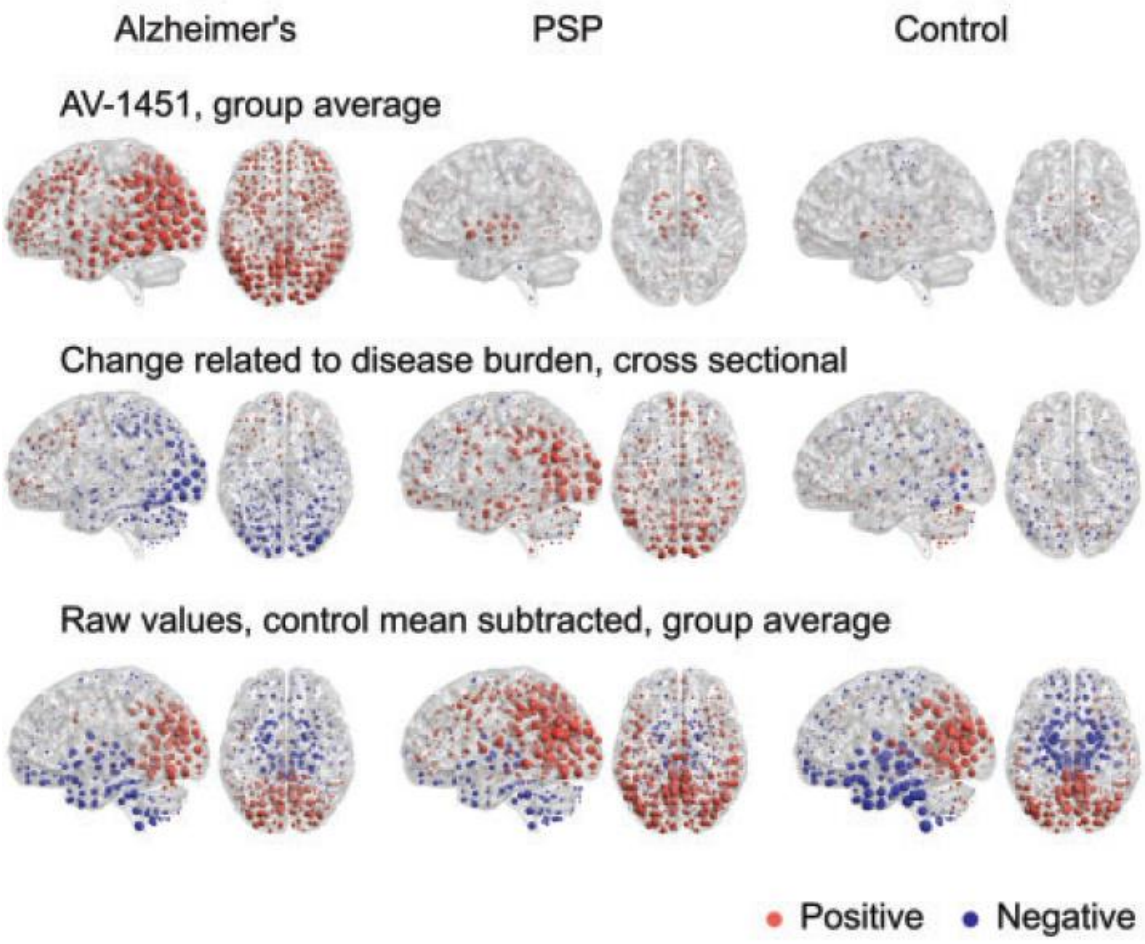
MRI atrophy patterns in human dementia suggest network involvement



Seeley *et al*. *Neuron* 2009

Pattern of tau distribution in patients with Alzheimer's disease seems to follow the Default-Mode Network

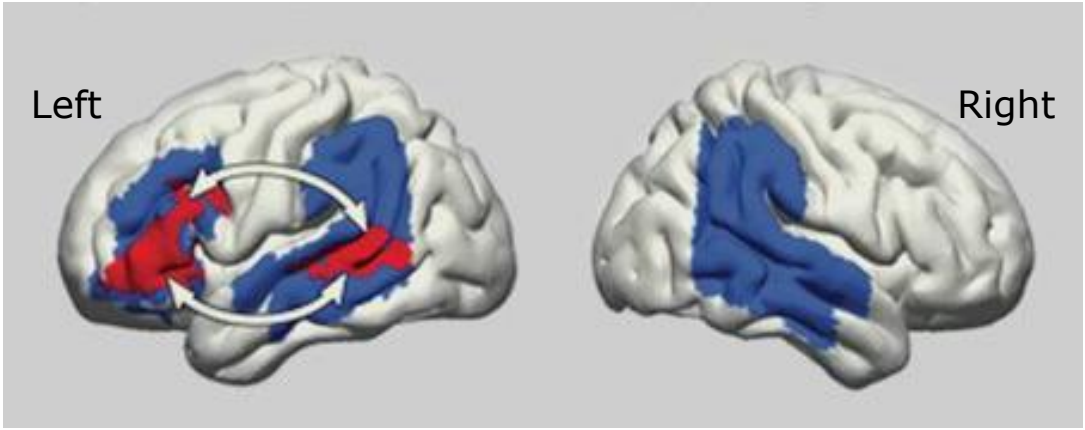
- However, tau spreading is difficult to image in Alzheimer's disease because of the **complexity of the default network**
- And the **effect of amyloid-β** on studies of MRI functional connectivity, like one recently published



Cope TE et al. Brain 2017

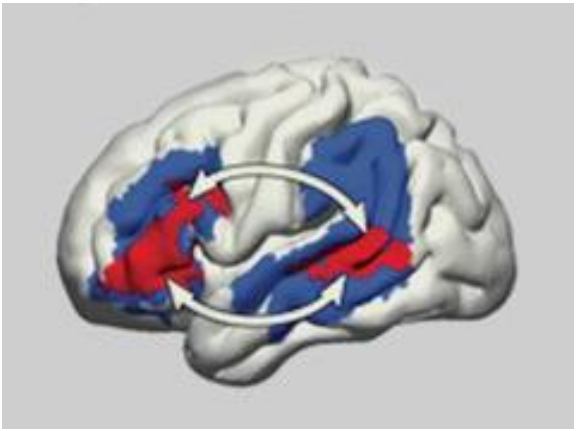
A simpler network to study prion-like propagation of tau: The syntactic network

- Syntactic network: Part of the language network

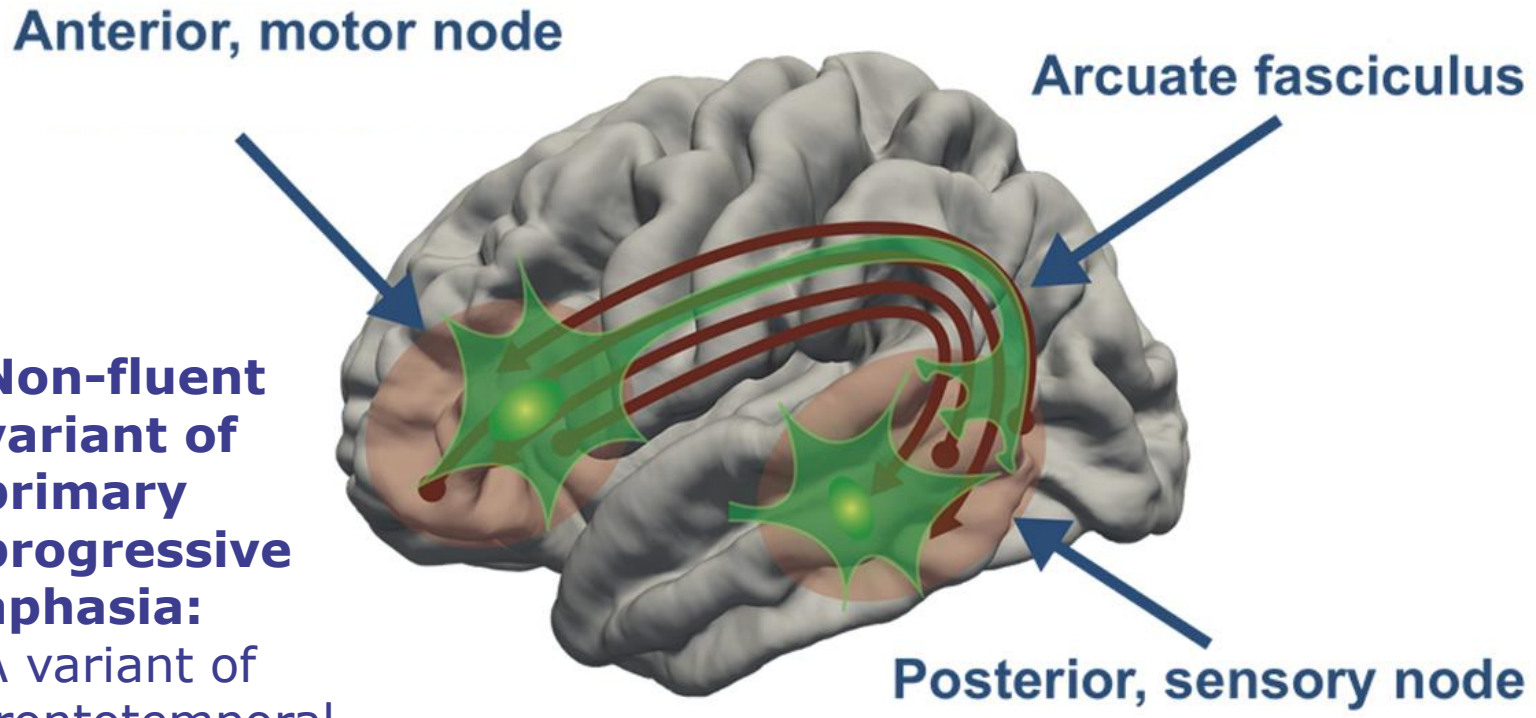


Shafto and Tyler, *Science* 2014

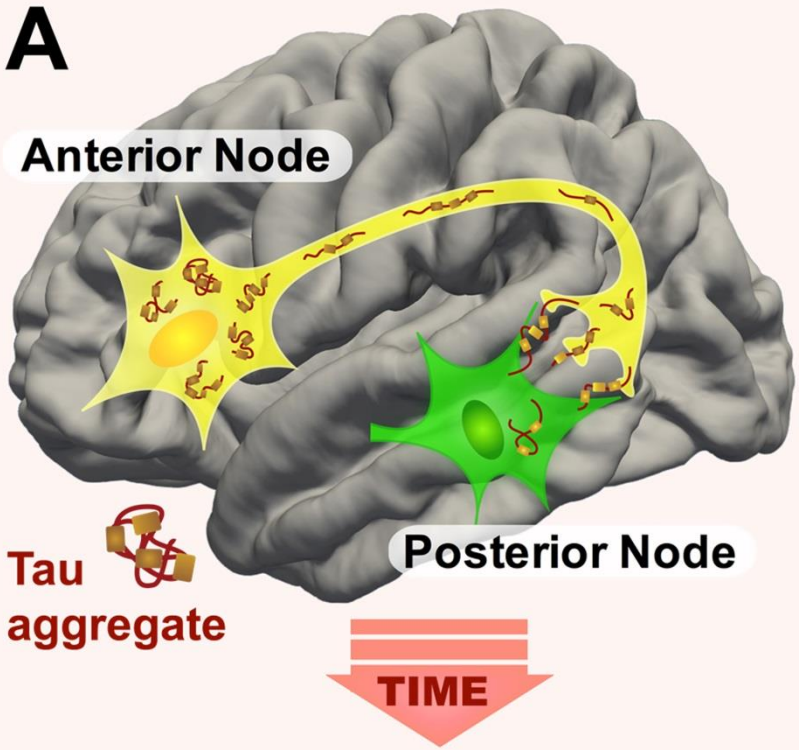
- Strongly left-lateralized network: inferior frontal and posterior middle temporal regions



Syntactic Network



Non-fluent variant of primary progressive aphasia:
A variant of frontotemporal dementia

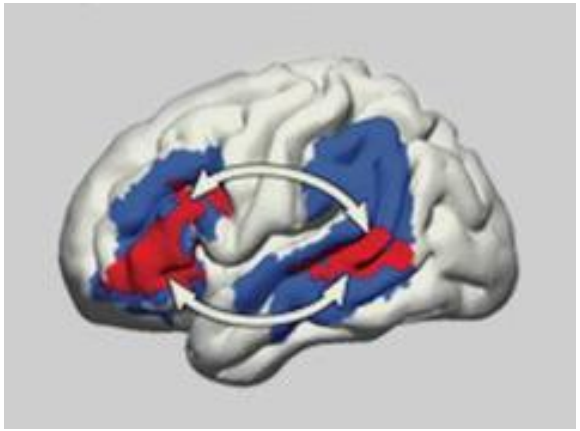


Prion-like Propagation of Tau *(Hypothetical in Humans)*

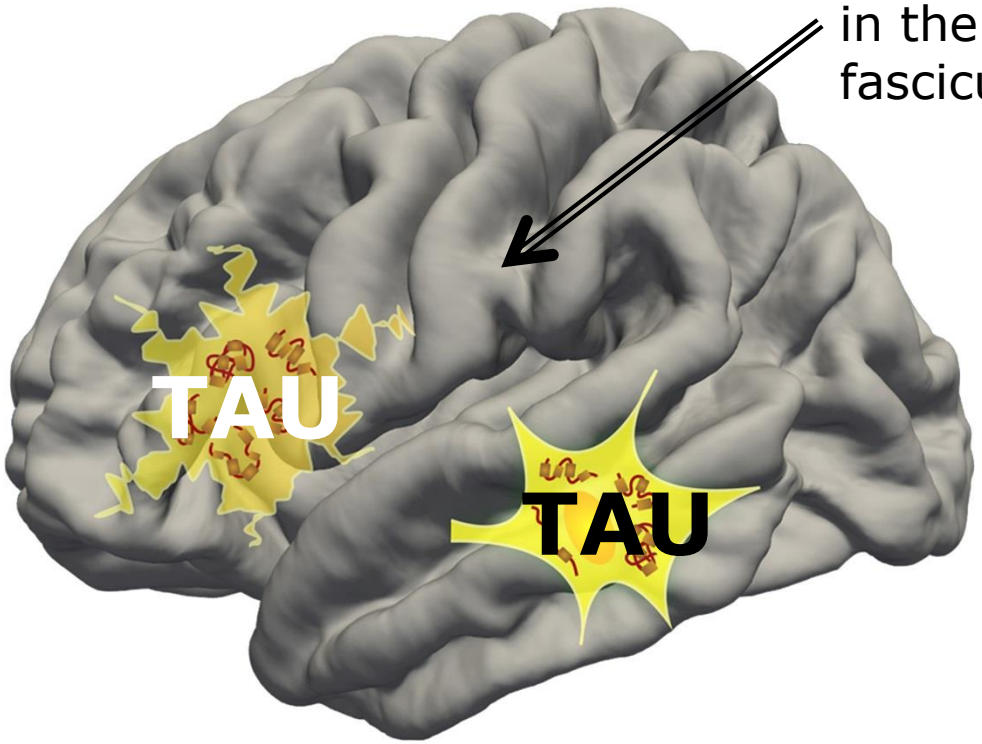
Stage A: Anterior node neuron still viable but containing tau aggregates
Posterior node neuron being infected

Stage B:

- Anterior node contains tau
- Posterior node neuron still viable but containing tau aggregates
- Arcuate fasciculus fibers lost

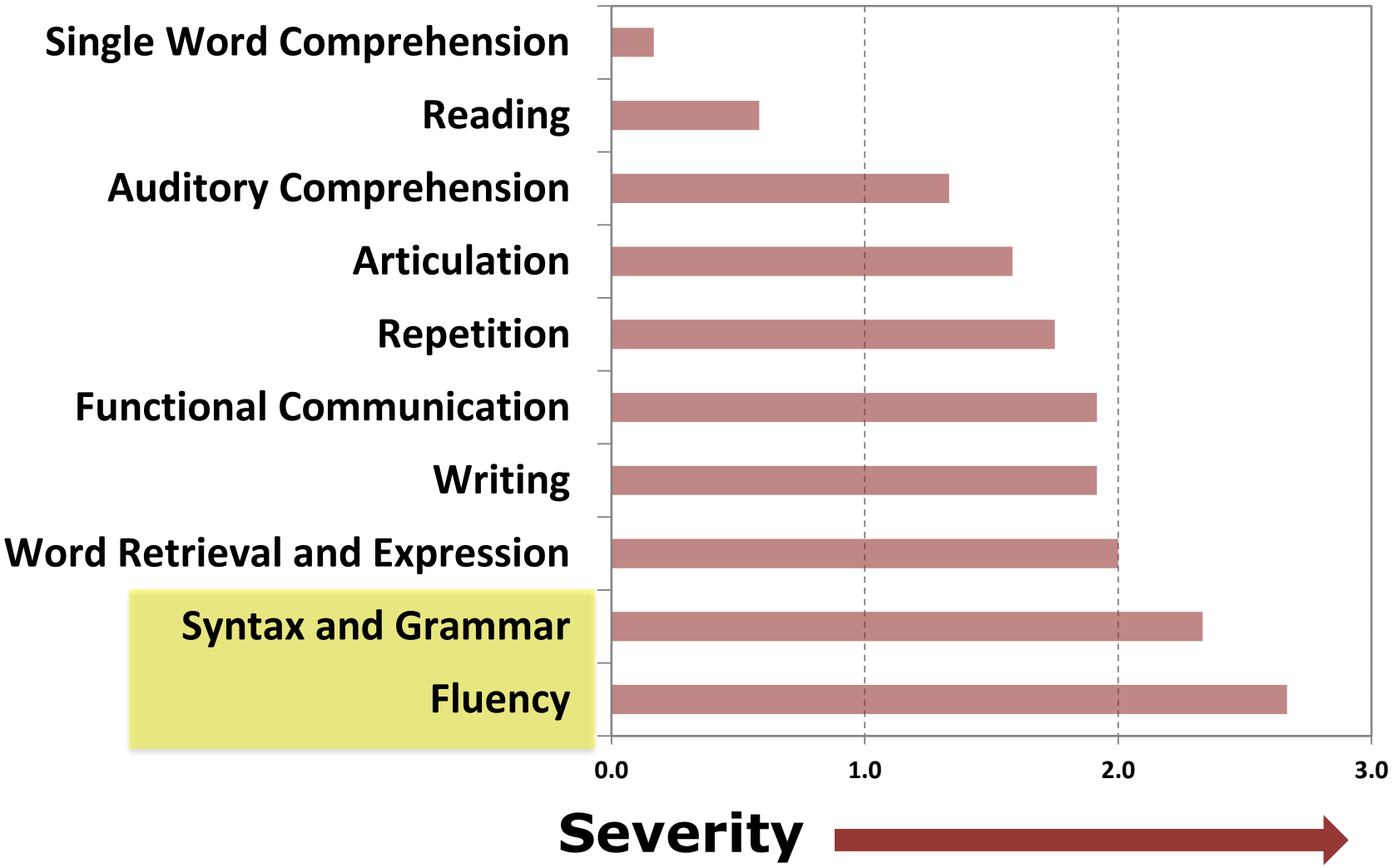


Syntactic Network in nfvPPA

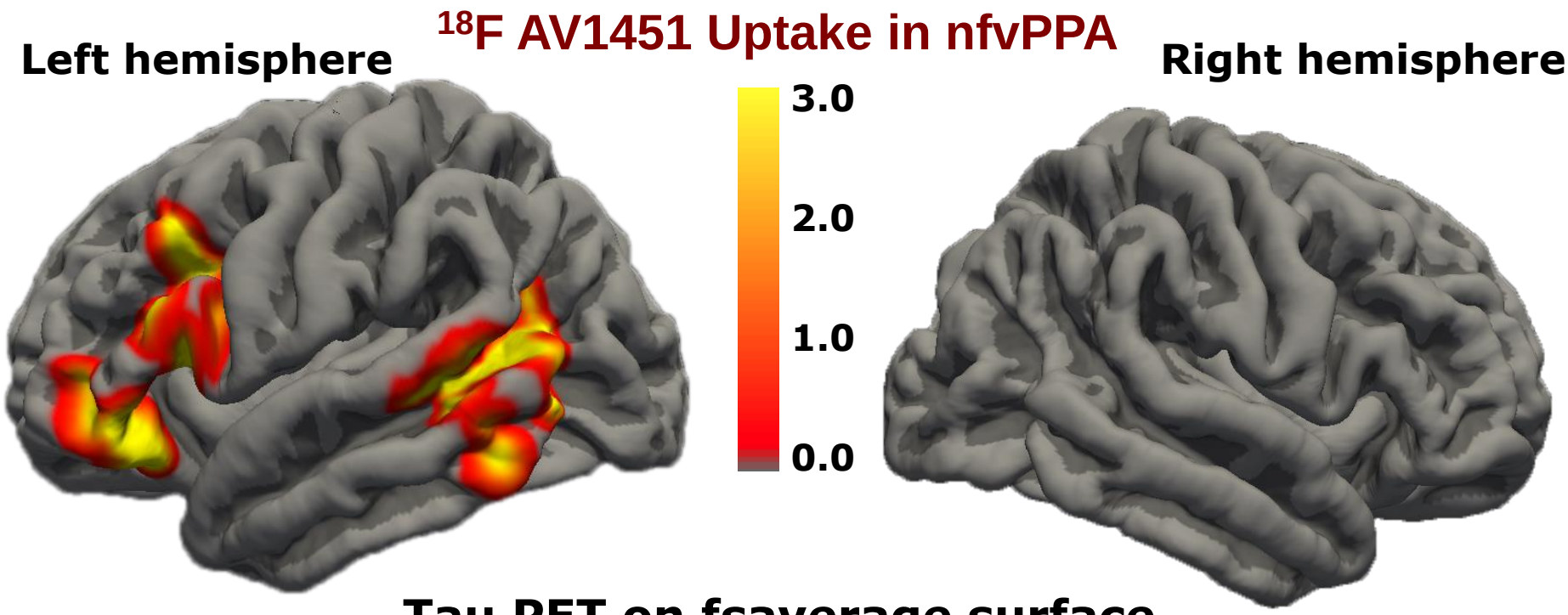


Non-fluent variant of primary progressive aphasia:
A variant of frontotemporal dementia

Fluency and syntax were most affected in nfvPPA patients, suggesting maximal involvement of the anterior node (Broca's area)



Tau deposition in non-fluent primary progressive aphasia occurred in **anterior** and **posterior nodes** of the **syntactic network**



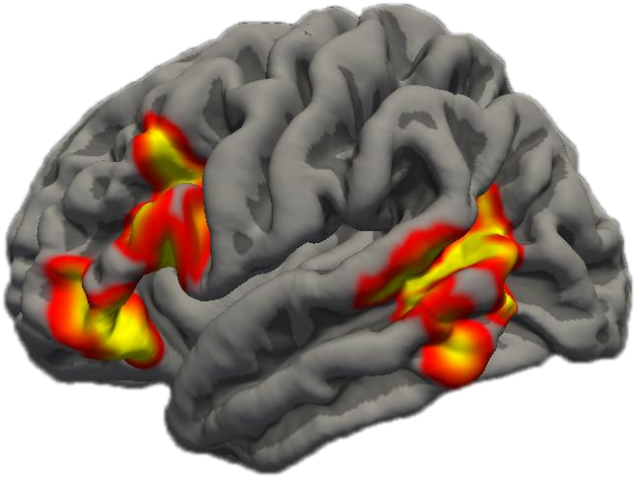
Tau PET on fsaverage surface

nfvPPA > Healthy Controls

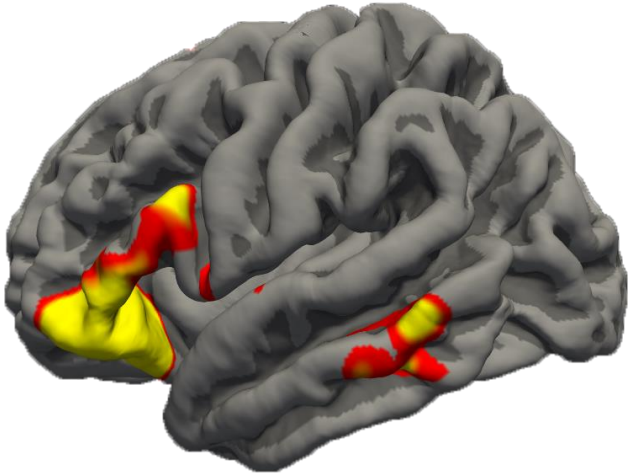
$p < 0.05$ FWE-corrected cluster-level

Tau was located in the two nodes of the syntactic network, maximally connected to each other as determined by fMRI

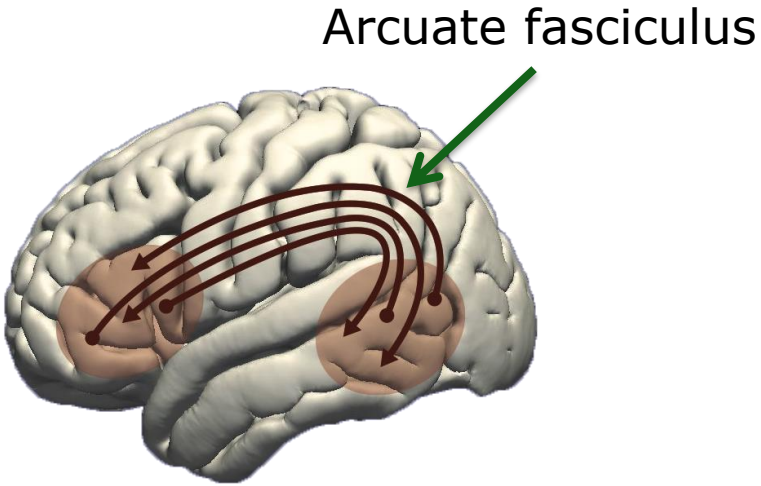
^{18}F AV1451 Uptake in nfvPPA



fMRI Connectivity Map in Healthy Controls



Next we studied the arcuate fasciculus, which connects both nodes



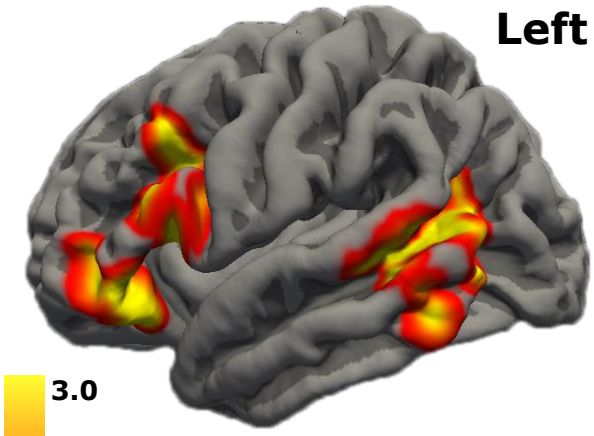
Tau deposits in anterior and posterior neuronal nodes of the syntactic network

These neuronal nodes are connected by the arcuate fasciculus, abnormal near the anterior node, where the disease begins

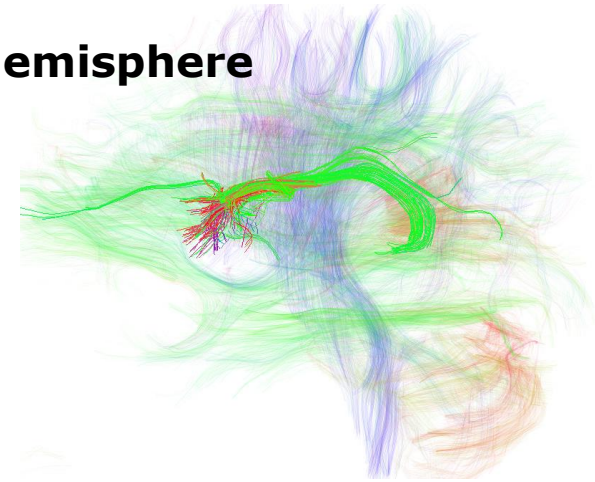
^{18}F-AV1451 Tau PET in Non-fluent Primary Progressive Aphasia (nfvPPA)

Arcuate Fasciculus Tractography

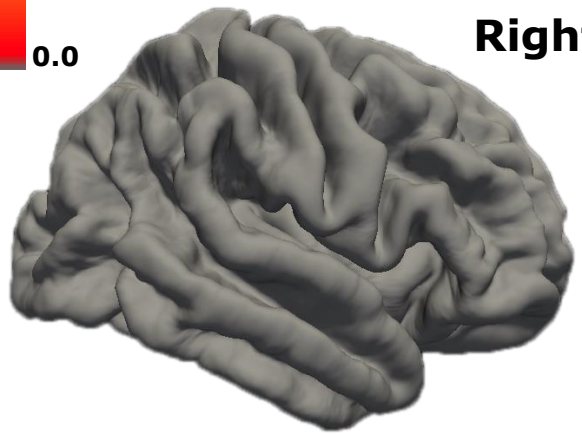
Fractional Anisotropy of Arcuate Fasciculus



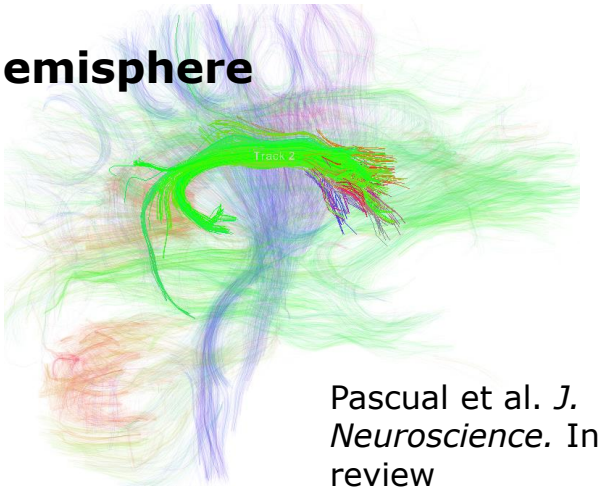
Left hemisphere

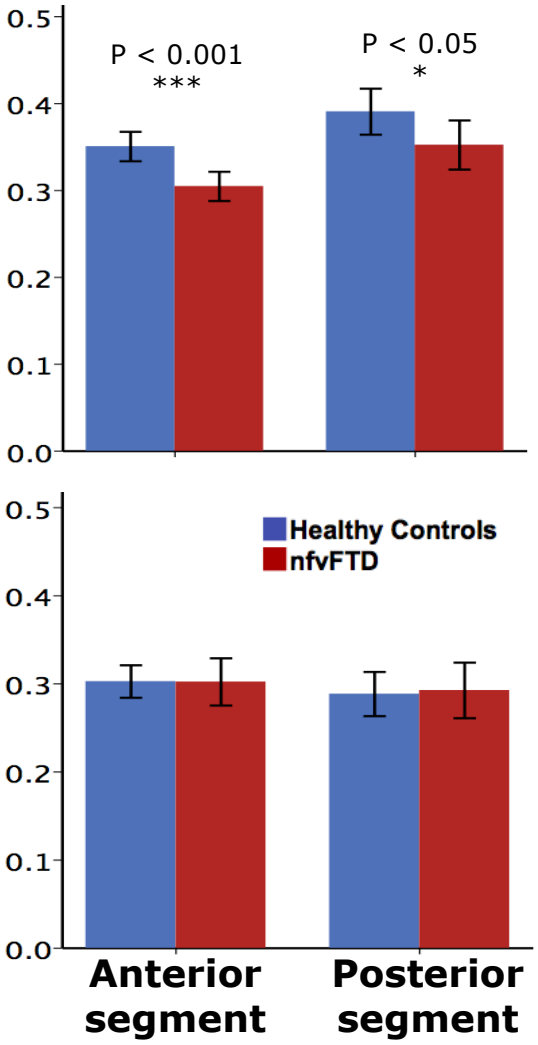


P < 0.05 FWE-corrected cluster-level



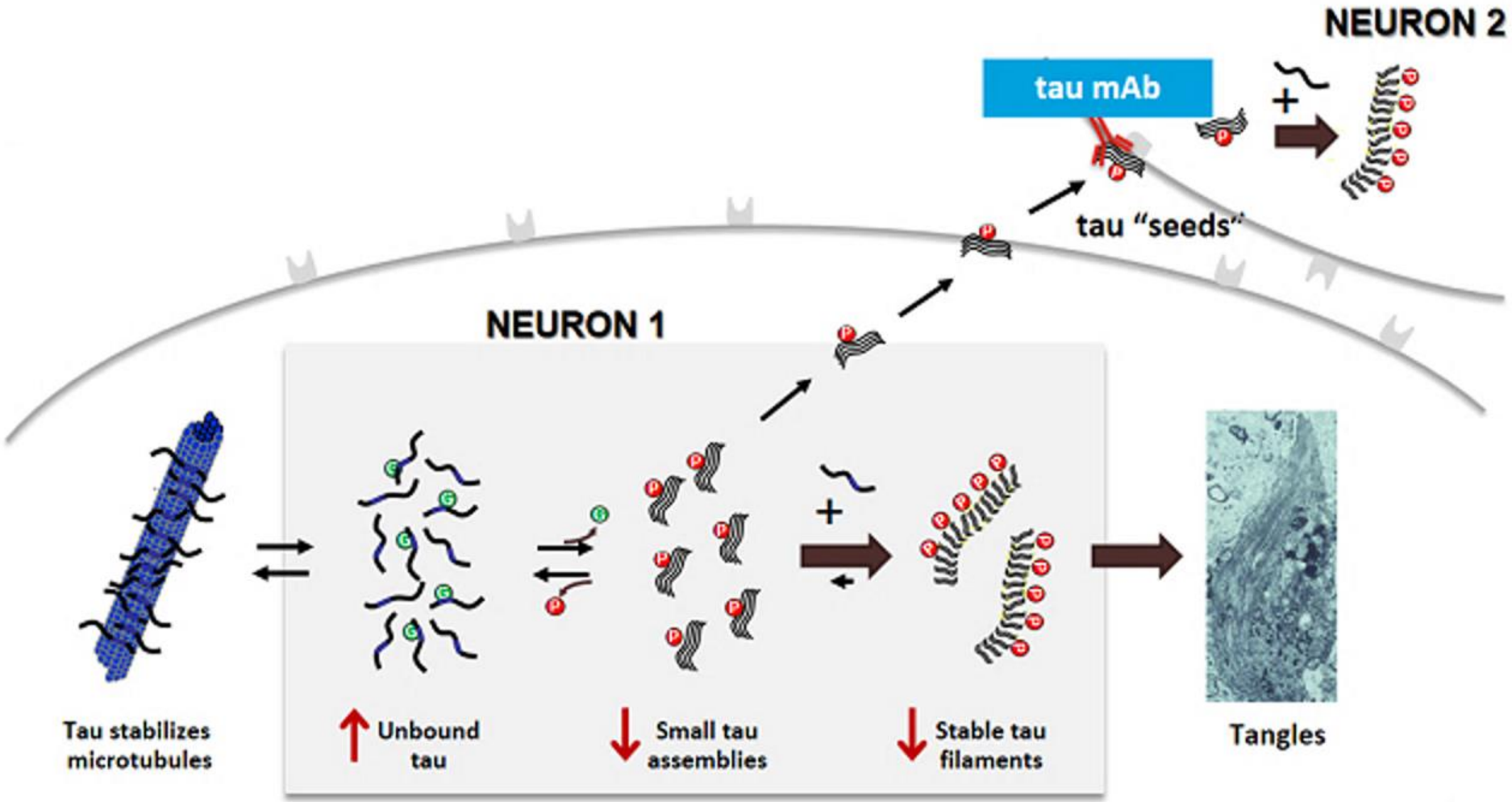
Right hemisphere





Pascual et al. *J. Neuroscience.* In review

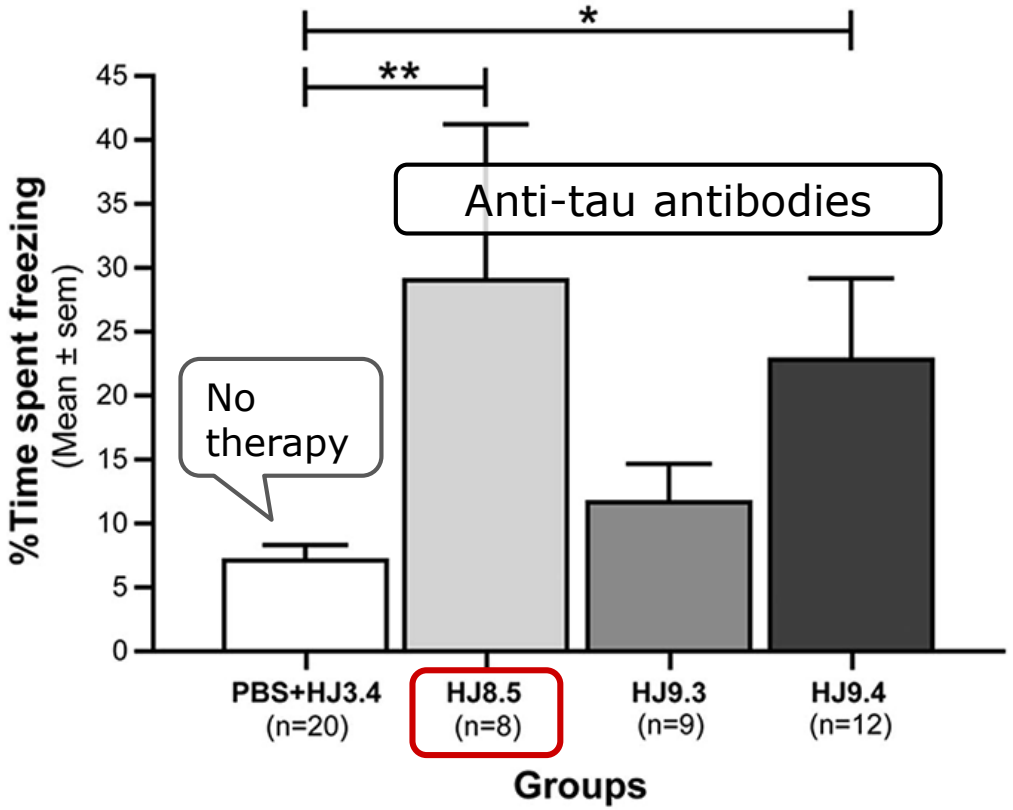
Antibodies Against Tau



Courtesy of Eli Lilly

Tau Immunotherapy

- P301S-tau transgenic mice
  - Antibody infusion into the lateral ventricle for 3 months

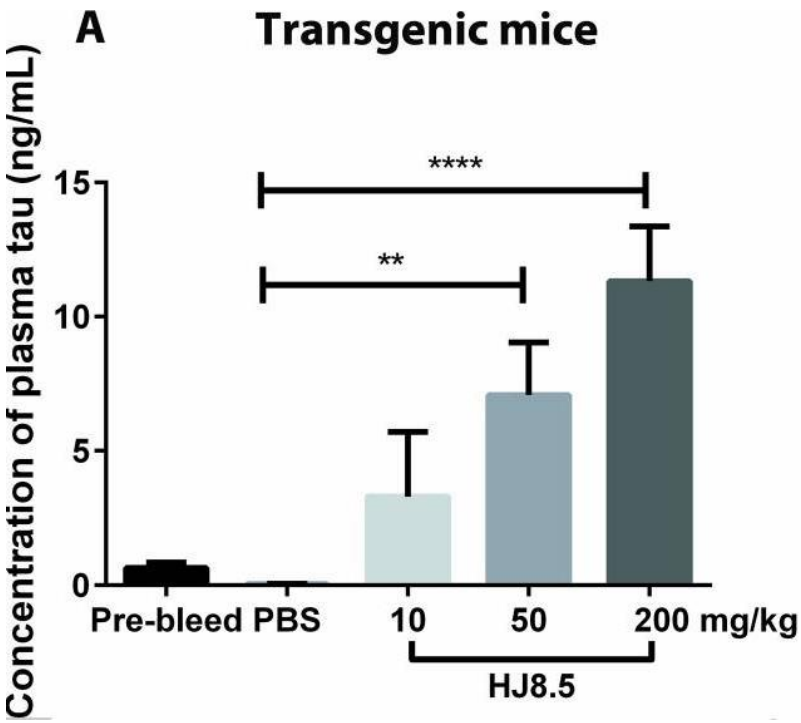


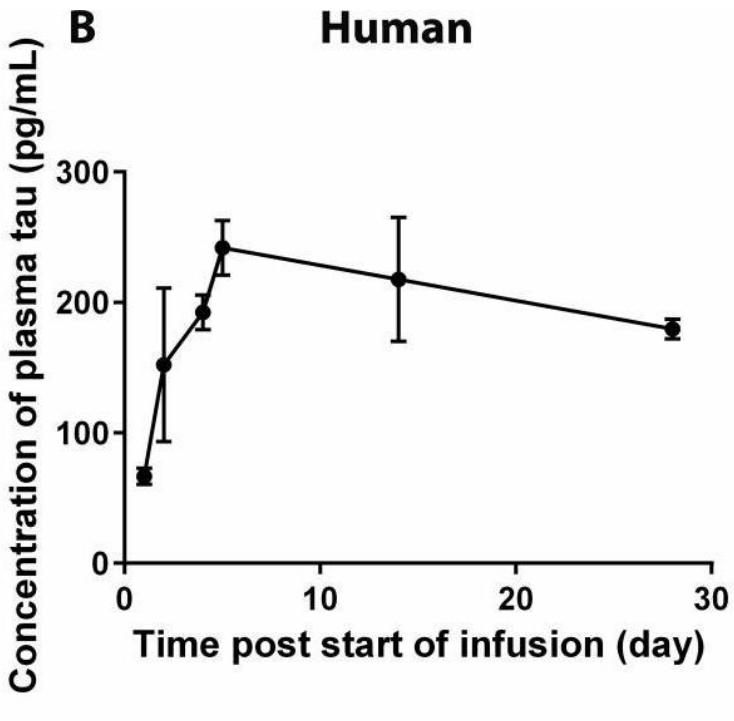
Contextual fear conditioning deficits in P301S tau transgenic mice are rescued by **HJ8.5**

Yanamandra K et al. *Neuron* 2013; 80:402

Tau Immunotherapy

Anti-tau antibody (HJ8.5) increases plasma tau in mice and patients with tauopathy

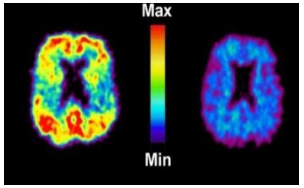




Yanamandra K et al. *Sci Transl Med* 2017;9(386)

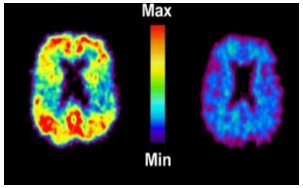
Anti-tau Treatment in Early AD (Aware Study, Abbvie)

- An antibody against tau (ABBV-8E12) is injected IV once/month
- People with early Alzheimer's disease
  - Age 55-85 years
  - Positive amyloid scan
  - Those having abnormal Aβ are randomized
    - Immunotherapy or placebo (75/25)
    - PET tau load as a secondary end-point



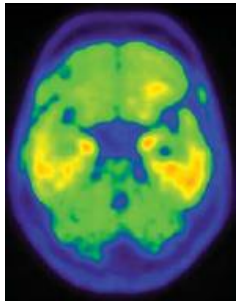
Anti-tau Treatment in Early AD (Tango Study, Biogen)

- An antibody against tau (BIIB092, three different doses) IV monthly
- People with early Alzheimer's disease
  - Age 50-80 years
  - CDR 0,5-1
  - Positive amyloid scan
  - Randomized
    - Immunotherapy or placebo (75/25)
    - PET tau load as a secondary end-point



Anti-tau Treatment in Early AD (Periscope Study, Eli Lilly)

- An antibody against tau (LY3303560, two different doses) IV monthly
- People with early Alzheimer's disease
  - Age 60-85 years
  - MMSE 28-20
  - Positive **tau** scan
  - Randomized
    - Immunotherapy or placebo (67/33)
    - PET tau load as a secondary end-point



Alzheimer's Disease: Towards Personalized Rx

- Therapies lowering brain amyloid
  - For preclinical stage (and MCI?)
    - Anti-β-amyloid antibodies
    - Anti-β-amyloid vaccines
- Therapies directed to misfolded tau
  - Mild cognitive impairment or early Alzheimer's disease (and potentially later stages)
    - Anti-tau antibodies
- Each directed to a specific patient at a specific stage of the disease

Training the Next Generation of Neuroimagers

Neuroimaging Fellowships: Training Neurologists to be Neuroimagers

Lawrence R. Wechsler, M.D.

UCNS Subspecialty in Neuroimaging

- In 2005, the *United Council of Neurological Subspecialties* approved the subspecialty of Neuroimaging
- Since then, only four programs have been accredited by the UCNS, only one at a classical academic medical center (SUNY Buffalo). The other three are:
  - NIH Intramural, Bethesda, MD
  - Winchester Neurology Associates, Winchester, VA
  - Dent Neurological Institute, Buffalo, NY

UCNS Subspecialty in Neuroimaging

- By contrast, there are more than 30 university-based Critical Care UCNS fellowship programs
- Yet, neurology residents finishing their clinical training are greatly interested in neuroimaging
- To try to understand better the difficulties Neurology chairs and program directors may have organizing neuroimaging fellowships, the AUPN posted a two-question survey in October 2012

AUPN 2012 Neuroimaging Survey

- Do you think you could organize a neuroimaging fellowship in your department?
  - Yes 14 (39 %)
  - No 22 (61 %)

- If not, why not?
  - Radiology would not like it (n= 8)
  - No faculty with training or interest (n=7)
  - Lack of funding (n=4)

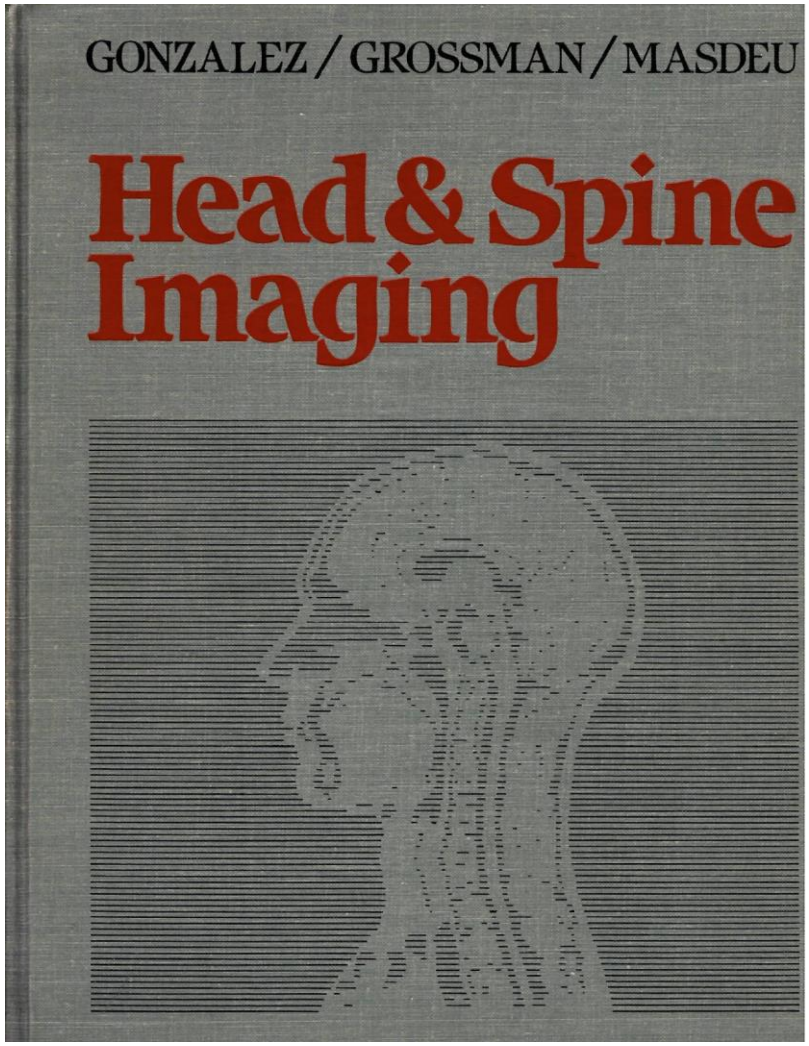
AUPN 2012 Neuroimaging Survey Solutions

- You don't need Radiology to start a fellowship

  If you like your radiologists, keep them out of the faculty until the time when Neuroimaging becomes an ACGME subspecialty

- prepare for and pass UCNS exam – lead fellowship program
- Fund fellowship from clinical income generated by instructor level trainee. Not the same as ACGME

1985



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PHYSICAL PRINCIPLES OF NUCLEAR MAGNETIC RESONANCE AND ITS APPLICATION TO IMAGING

Carl L. Kramer
Ferdinando S. Buonanno

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NUCLEAR MAGNETIC RESONANCE IMAGING IN NEUROLOGY

Ferdinando S. Buonanno
J. Philip Kistler
L. Dana DeWitt
Carl Kramer
Kenneth R. Davis

CLINICAL APPLICATIONS
NORMAL ANATOMY
TUMORS
VASCULAR DISORDERS
METABOLIC OR HEREDITARY DISEASES
INFECTION
DEGENERATIVE DISEASES
DEMYELINATIVE DISORDERS

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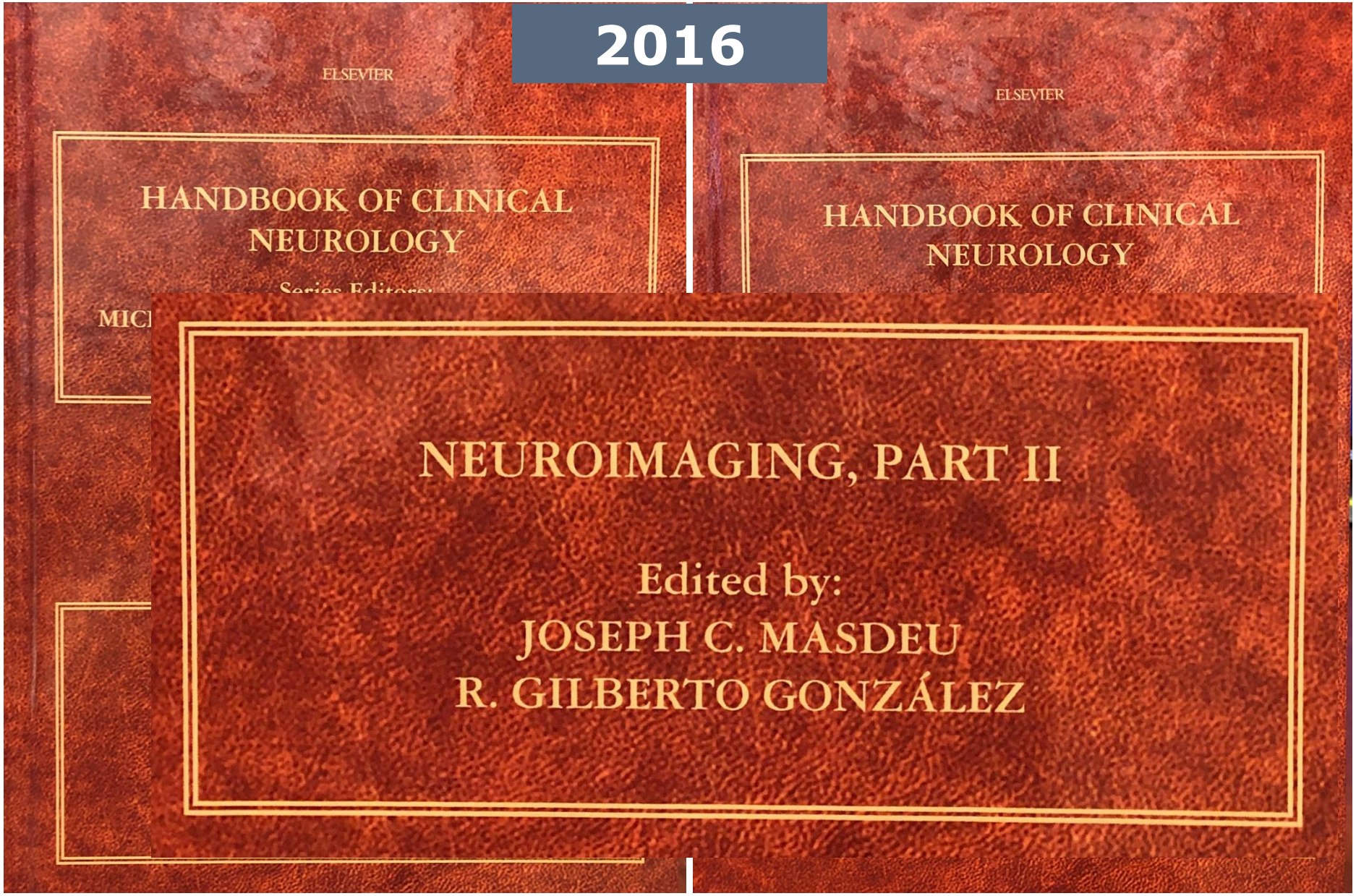
2016
ELSEVIER
HANDBOOK OF CLINICAL NEUROLOGY
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HANDBOOK OF CLINICAL NEUROLOGY
NEUROIMAGING, PART II
Edited by:
JOSEPH C. MASDEU
R. GILBERTO GONZÁLEZ

Imaging Subspecialties

- Radiology
  - Neuroradiology
- Neurology
  - Neuroimaging
    - ***Integrative Neuroimaging***
      - Integrated with patient care
      - Using all imaging modalities relevant to the clinical problem
      - Correlated with neuropath & outcome

Teaching Neuroimaging at Academic Departments

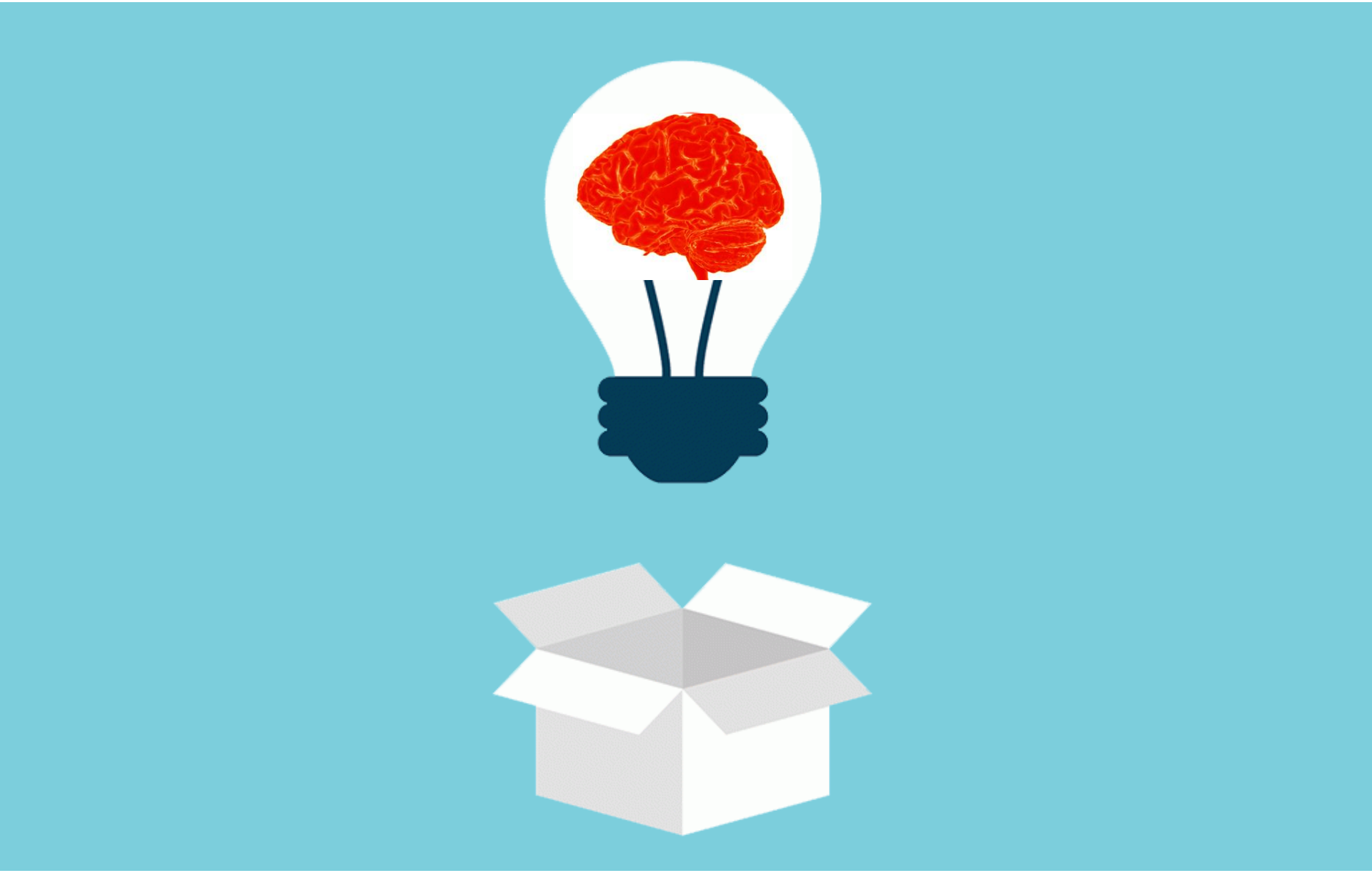
- Rotations through clinical services
  - Stroke
  - Neurosurgery, epilepsy
  - MS, neuroinflammation
  - Neurodegeneration
  - Peripheral neurology
  - Neuro-ophthalmology
  - ENT
- They can have an emphasis (e.g. stroke) with longer rotation

Neuroimaging Training Activities

- Become thoroughly familiar with the patient problem or be the treating neurologist
- Recommend imaging protocol
- Write/dictate formal report of the patient's images
  - Our fellows dictate about 28 per week
  - Reviewed and edited by faculty
- Follow up on the patient's course and imaging correlates (neuropath, etc)

1-Year Case Load in Fellowship

ACR Guideline: *500 MRI cases in the specialty area shall have been interpreted and reported in the past 36 months in a supervised situation. For neurologic MRI, at least 50 of the 500 cases shall have been MRA of the central nervous system*



Think outside the box

HMNI-HMRI Neuroimaging Lab