Painting of historical Bulfinch building at MGH by patient with FTD

The Promise and Pitfalls of Imaging Biomarkers in the Diagnostic Evaluation of Research Participants with MCI

17th Annual MCI Symposium Jan 19, 2019

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MGH FTD Unit, ADRC & Center for Translational Brain Mapping

Disclosures

Data Safety Monitoring Board:

Merck

Consulting:

Lilly, Biogen, Wave LifeSciences, Piramal

Med Learning Group, Haymarket Media, Catamount

Best Doctors.com, GrandRounds.com

Royalties:

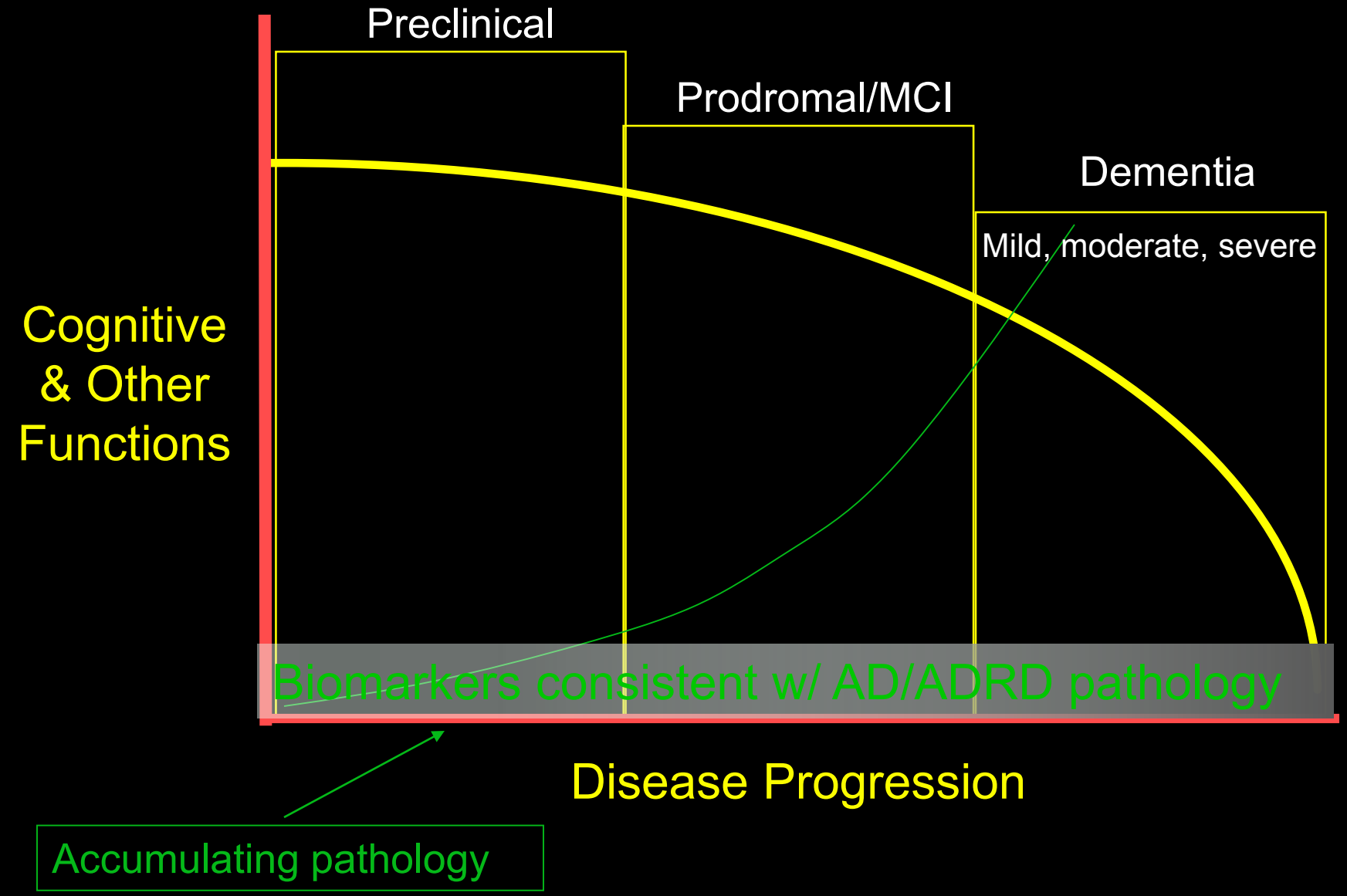
Oxford University Press (*Dementia: Comprehensive Principles and Practice*, 2014)

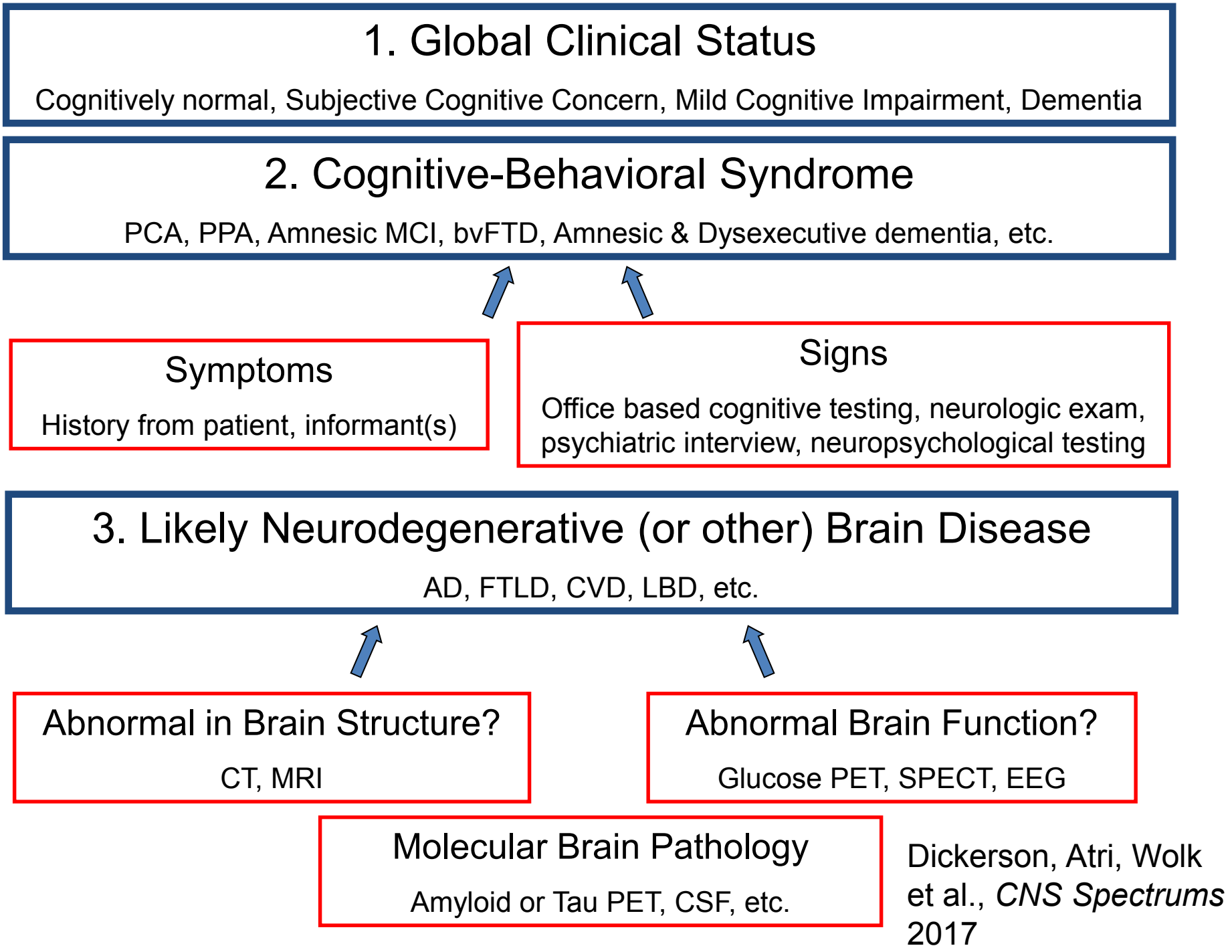
Cambridge University Press (*Hodges' Frontotemporal Dementia*, 2016)

Editorial Board:

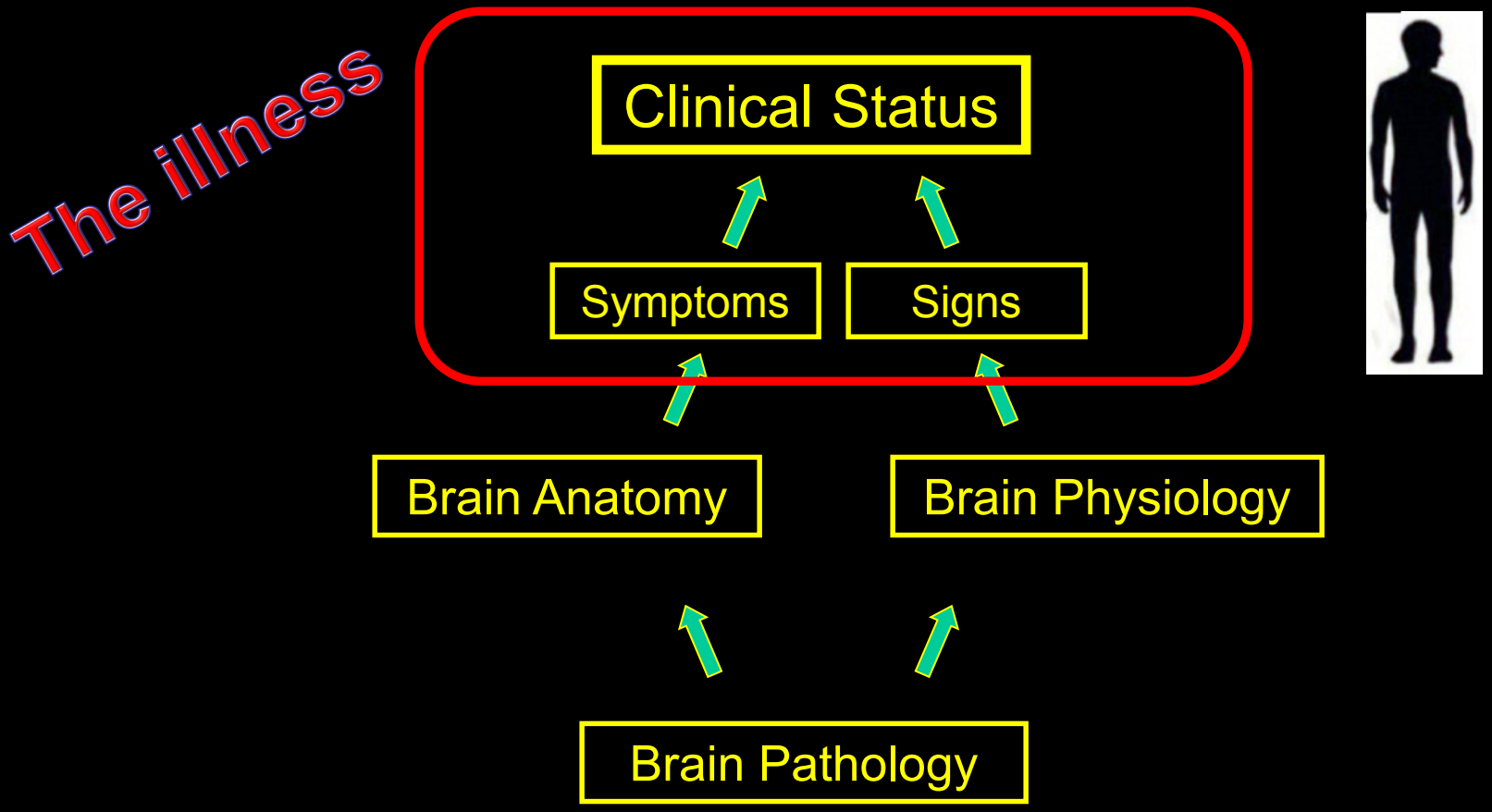
Neuroimage: Clinical; Cortex; Alzheimer's & Dementia; Hippocampus; Neurodegenerative Disease Management

The continuum of neurodegenerative dementias




1. Global Clinical Status
Cognitively normal, Subjective Cognitive Concern, Mild Cognitive Impairment, Dementia
2. Cognitive-Behavioral Syndrome
PCA, PPA, Amnesic MCI, bvFTD, Amnesic & Dysexecutive dementia, etc.
Symptoms
History from patient, informant(s)
Signs
Office based cognitive testing, neurologic exam, psychiatric interview, neuropsychological testing
3. Likely Neurodegenerative (or other) Brain Disease
AD, FTLD, CVD, LBD, etc.
Abnormal in Brain Structure?
CT, MRI
Abnormal Brain Function?
Glucose PET, SPECT, EEG
Molecular Brain Pathology
Amyloid or Tau PET, CSF, etc.
Dickerson, Atri, Wolk et al., *CNS Spectrums* 2017

Approach to diagnosis



The forgetful attorney

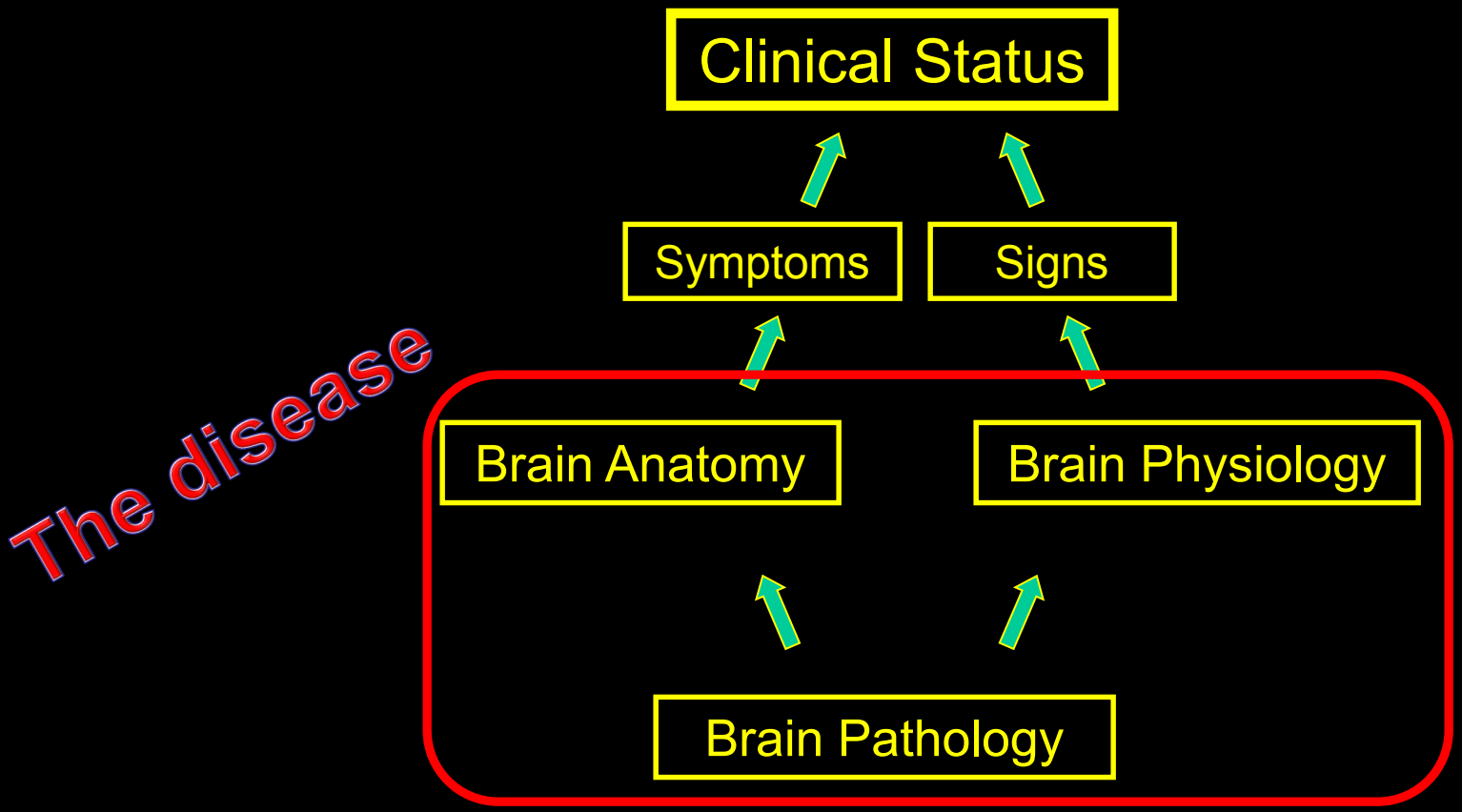
- 72 year old man, retired tax attorney
- Gradually increasing forgetfulness over past 2 years
  - Did not remember the "whole evening" of Superbowl party the next week; frequently argues with family about memory lapses
- Does family taxes but takes longer, serves on local housing community board, plays golf
- Wife/daughter prompted clinic visit

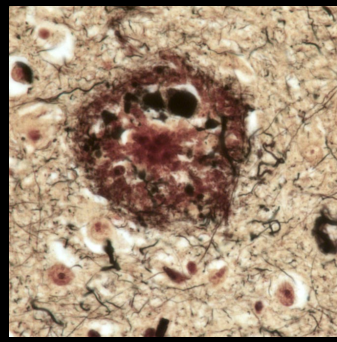
- Office visit & neuropsychological testing revealed poor learning of word list (5-7-8-9-10), difficulty with free recall (4), relatively preserved recognition (13/16 with 2 false positives); otherwise intact

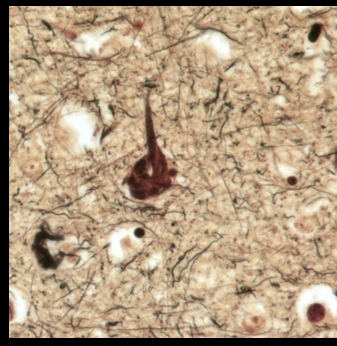
MCI, memory predominant (amnestic MCI)

Progressive Amnestic Syndrome

Approach to diagnosis





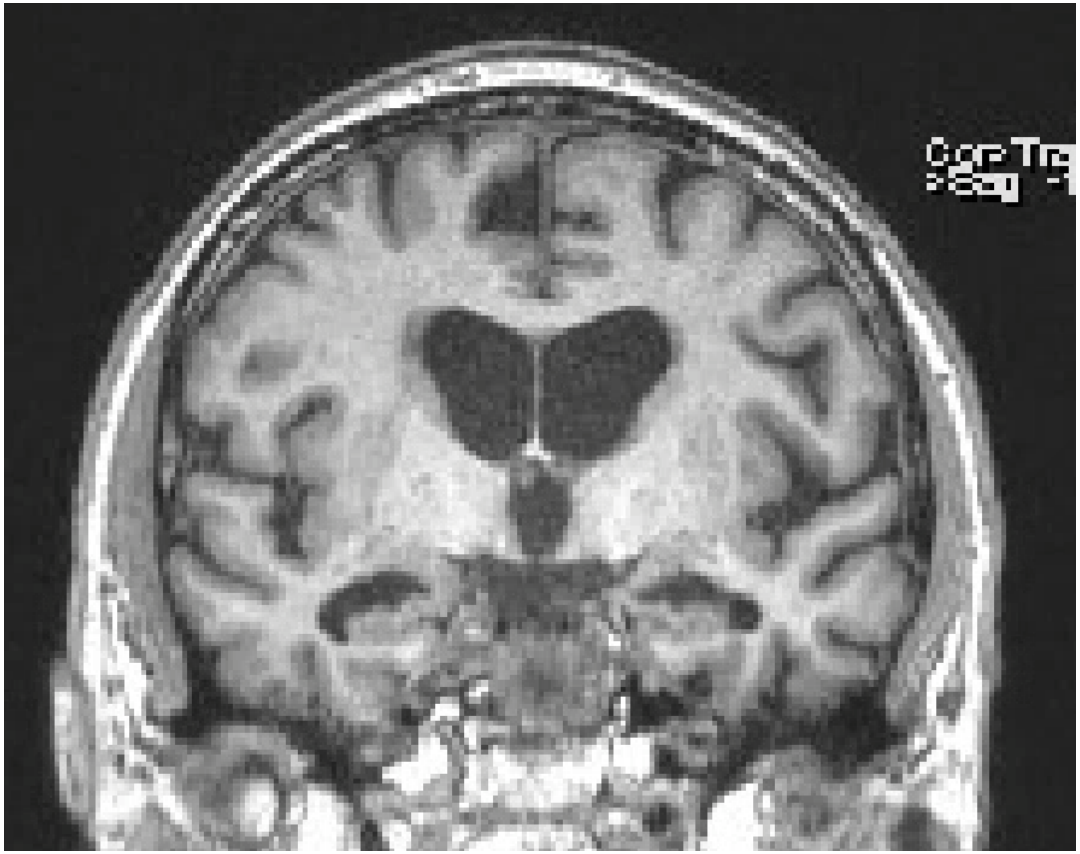


The spectrum of etiologies for MCI & dementia

- Alzheimer's disease
- Cerebrovascular disease
- Lewy Body Disease
- Frontotemporal Lobar Degeneration
  - Tauopathies
  - TDP43 proteinopathies
- Hippocampal sclerosis
- Argyrophilic grain disease
- etc

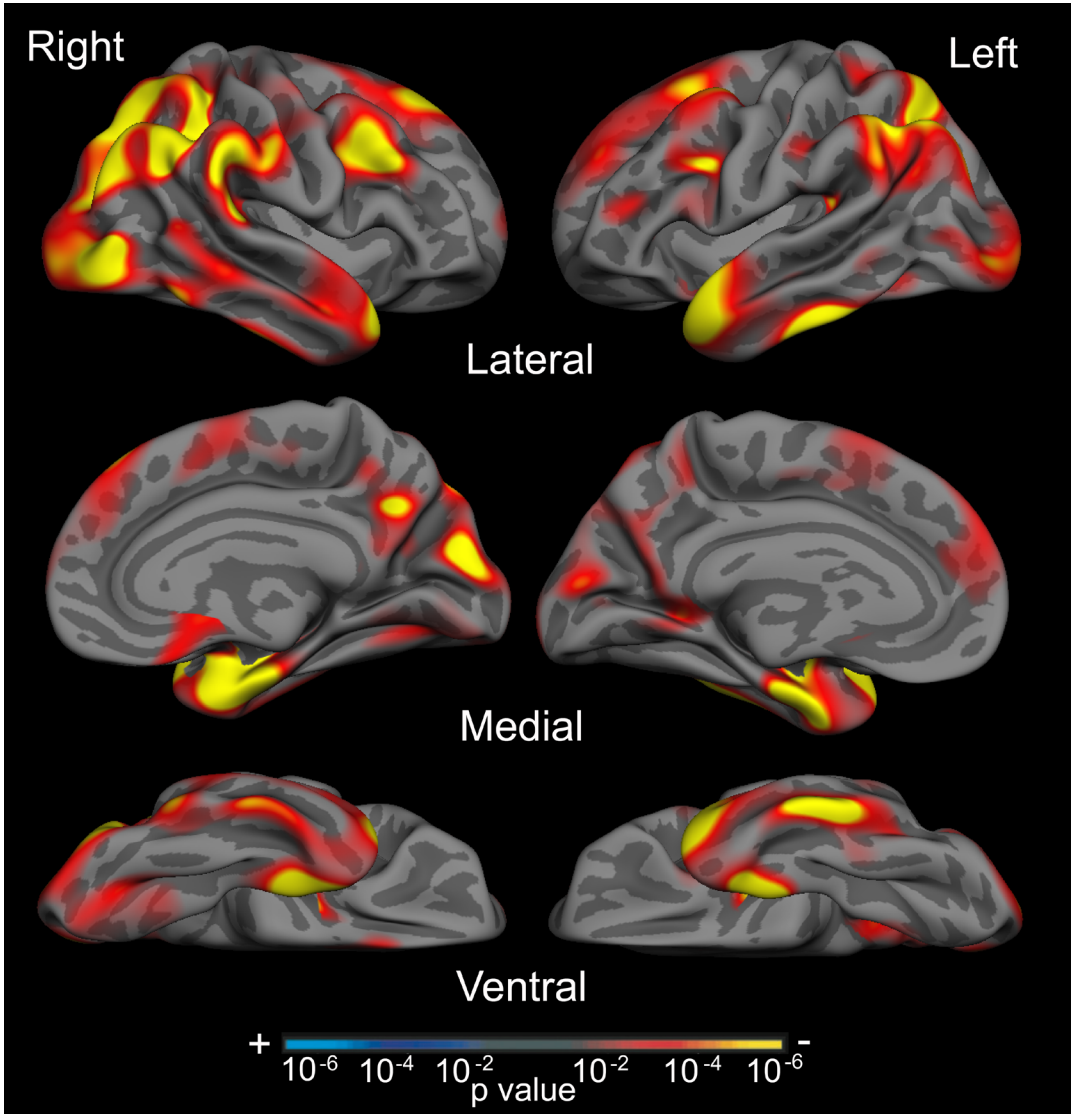
- Medical
  - Neoplasm
  - Trauma/anoxia
  - NPH
  - Toxins
  - Infections
  - Neurologic illness
  - Organ failure

Hippocampal/MTL atrophy in typical aMCI: likely etiology AD



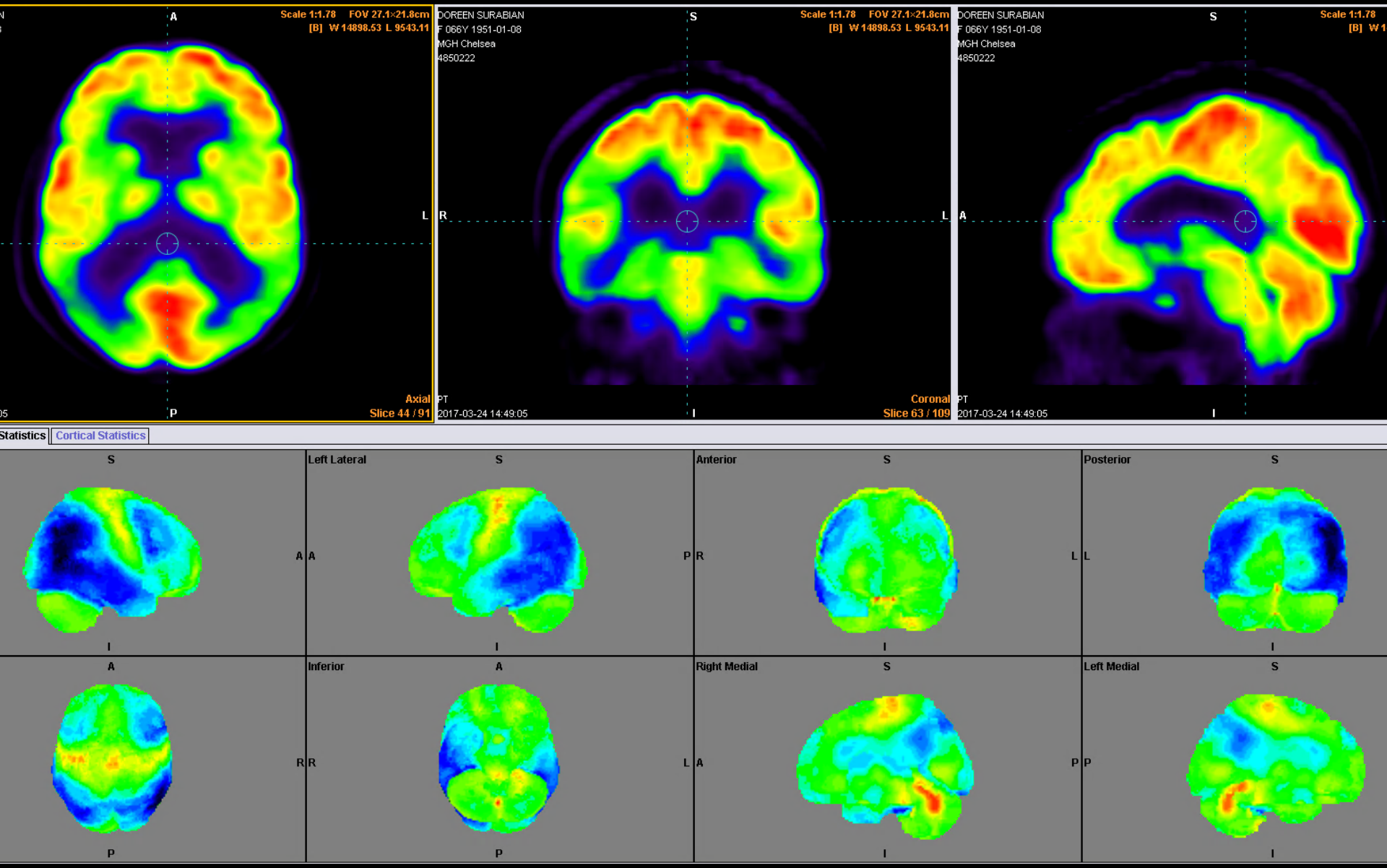
ALZHEIMER DISEASE NEUROPATHOLOGIC CHANGE [ADNC]:
Thal stage 5 of 5 for amyloid deposition Braak and Braak tangle stage: V of VI.
CERAD age related plaque score: Abundant
NIA-Alzheimer association score: A3B3C3
High probability of cognitive impairment due to Alzheimer Disease

The cortical signature of AD-related atrophy (MRI)



Dickerson BC, et al., Cerebral Cortex, 2009

FDG-PET: AD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Coronal
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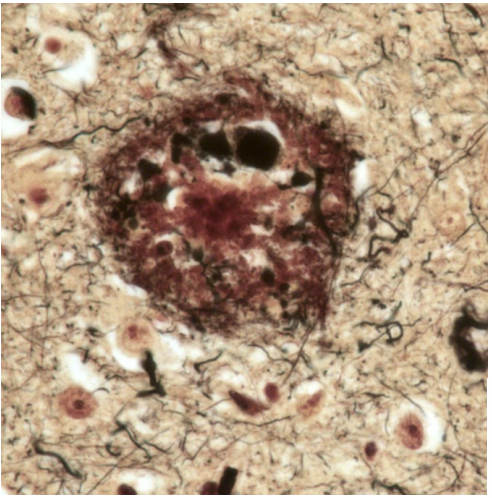
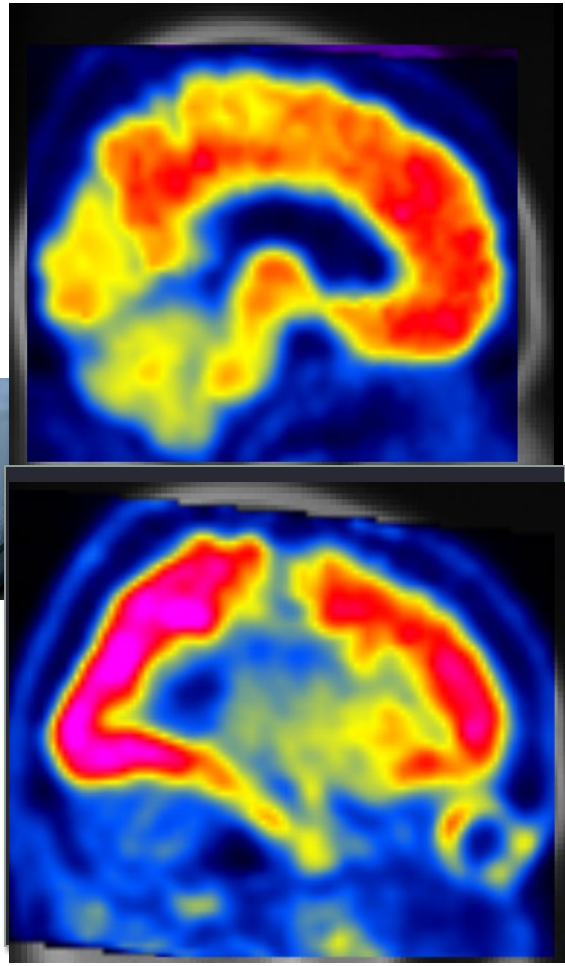
Statistics
Cortical Statistics
Left Lateral
Anterior
Posterior
Inferior
Right Medial
Left Medial

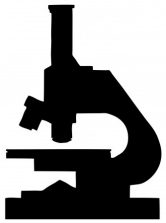
In vivo biomarkers of AD molecular pathology

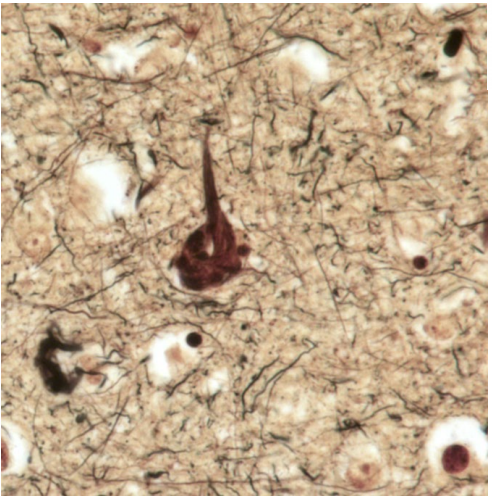


Microscopic amyloid plaque

Amyloid PET

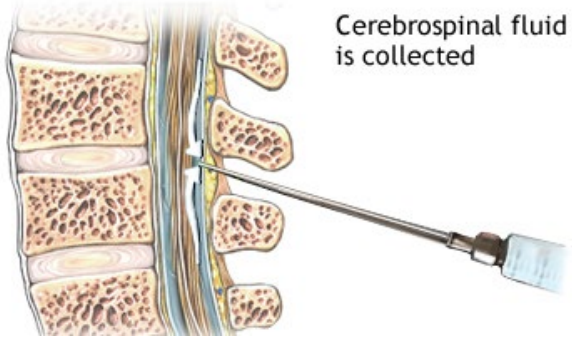




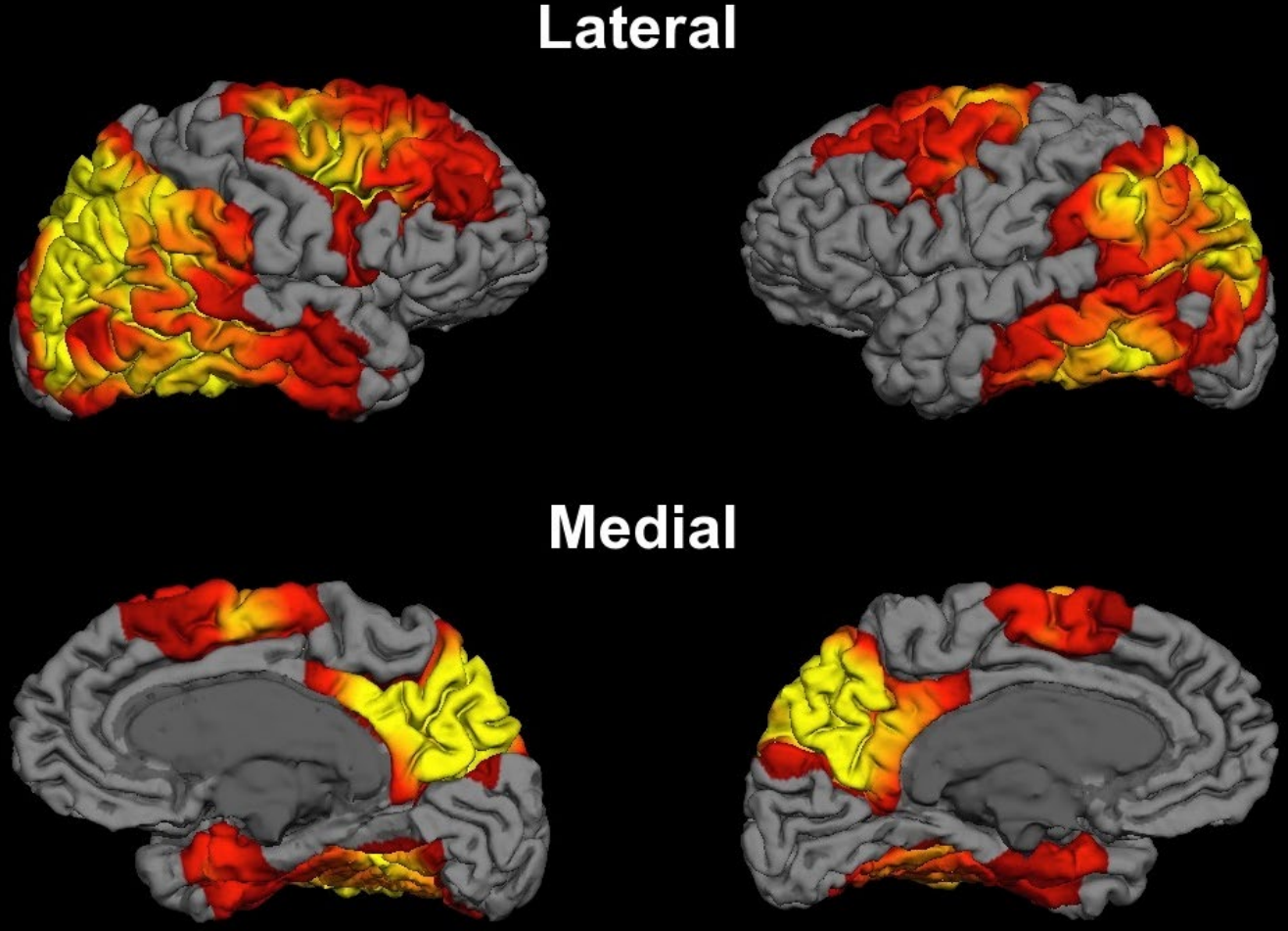


Microscopic tau tangle

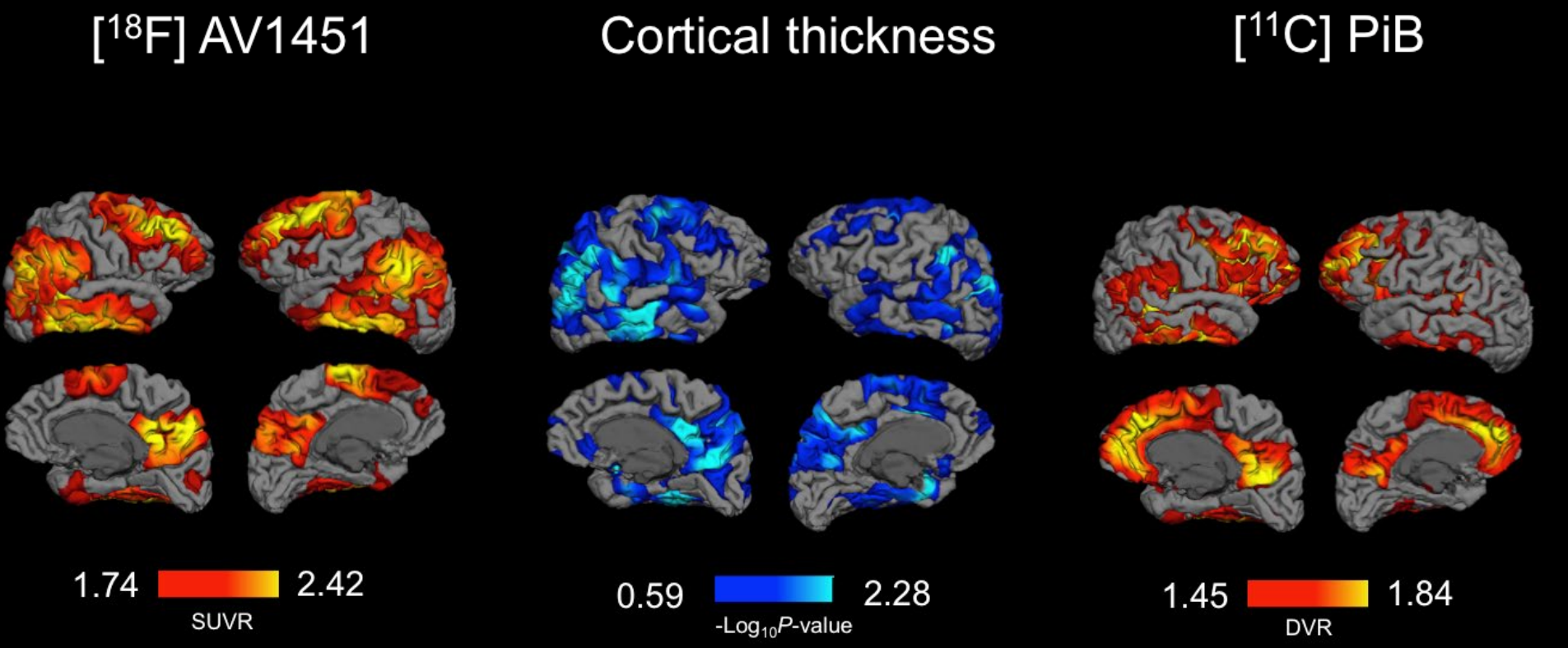
Tau PET



[^{18}F] AV1451 localizes congruently with expected tau pathology in AD dementia



60 year-old with typical amnesic AD dementia



Xia & Dickerson et al, JAMA Neurology 2017

Major clinical phenotypes of AD

a. **Memory:** (most common; referred to as typical): The deficits should include impairment in learning and recall of recently learned information along with deficits in other cognitive domains

b. **Language:** The most prominent deficits are in word-finding; deficits in other cognitive domains should be present (Primary progressive aphasia)

c. **Visuospatial**: The most prominent deficits are in spatial orientation, visual object recognition (e.g., faces), reading/writing (Posterior cortical atrophy)

d. **Executive function**: The most prominent deficits are impaired reasoning, judgment, and problem solving

e. Personality (social-emotional): Frontal variant AD

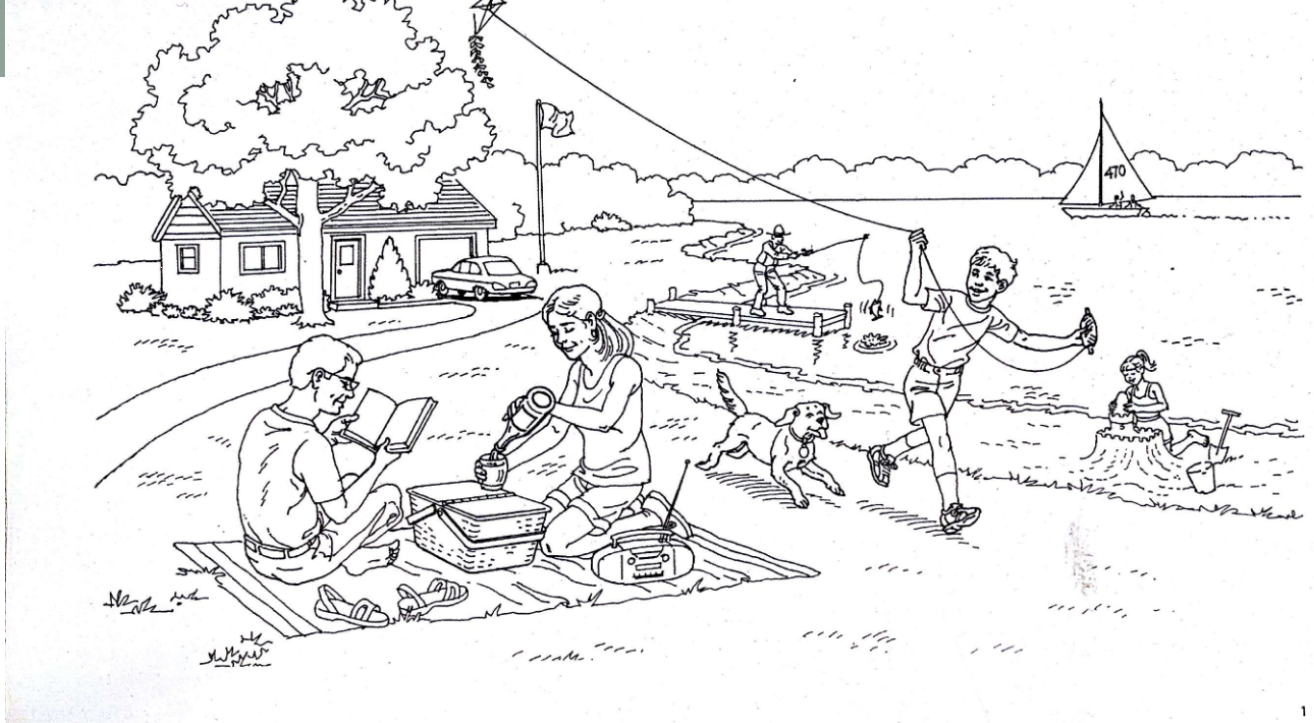
f. **Motor:** (Corticobasal syndrome)

   a. Atypical are much more common in young-onset (<65)

The stuttering engineer

- Retired engineer, age 70, with 4 year history of progressive language and word-finding difficulties
- Difficulty naming common objects; could think of the object and describe it, but was unable to name it; made errors pronouncing words
- Patient noted decline in ability to keep up with understanding conversations in groups and remembering conversations but denied difficulties with other aspects of memory, visuospatial skills, executive function, math skills
- Very independent in daily function

MCI, language predominant (non-amnestic)
Primary Progressive Aphasia, logopenic variant



Age 70

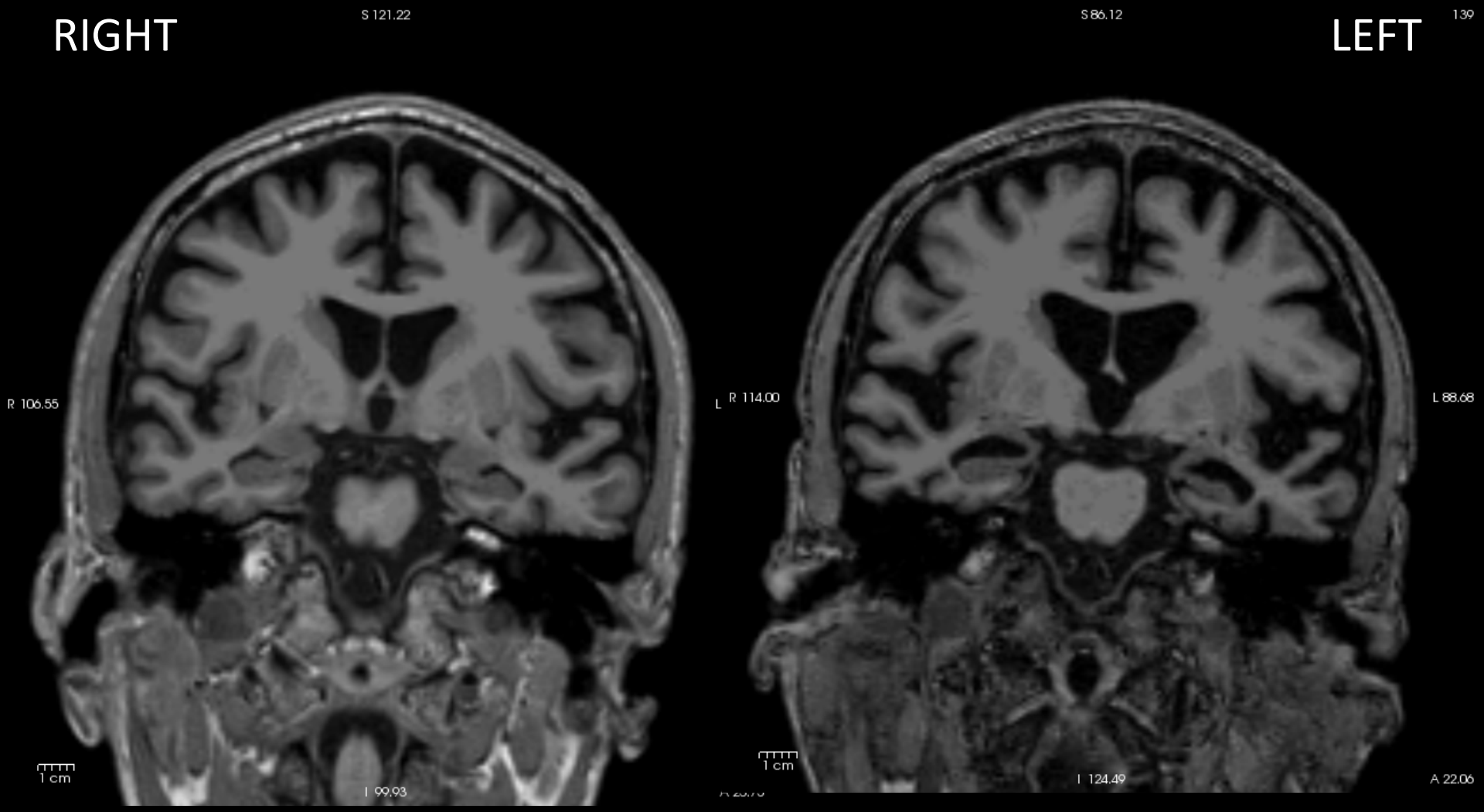
- Looks like a family is uh has a hou- uh I think it's a house or a friend's place on the leck-lake. And the kids are having a good time. They're gonna have a picnic. Uh, and uh they have somebody who is uh finishing-fishing. The kids are playing, uh, uh one is working uh is playing the girls, playing with-with uh uh putting together a sand castle. Uh the boy is- uh has a uh kite. Uh some friends are in the boat, in the so-saiboat-sail-sailboat. And they- I think they are sort of waking…the wave.

Age 75-76

- Minimal intelligible content due to high frequency of phonemic parahpasias and neologisms, occasional short phrases are recognizable
- By age 76, fewer recognizable words/phrases

Age 70

Age 75


RIGHT
S 121.22
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139
L 88.68
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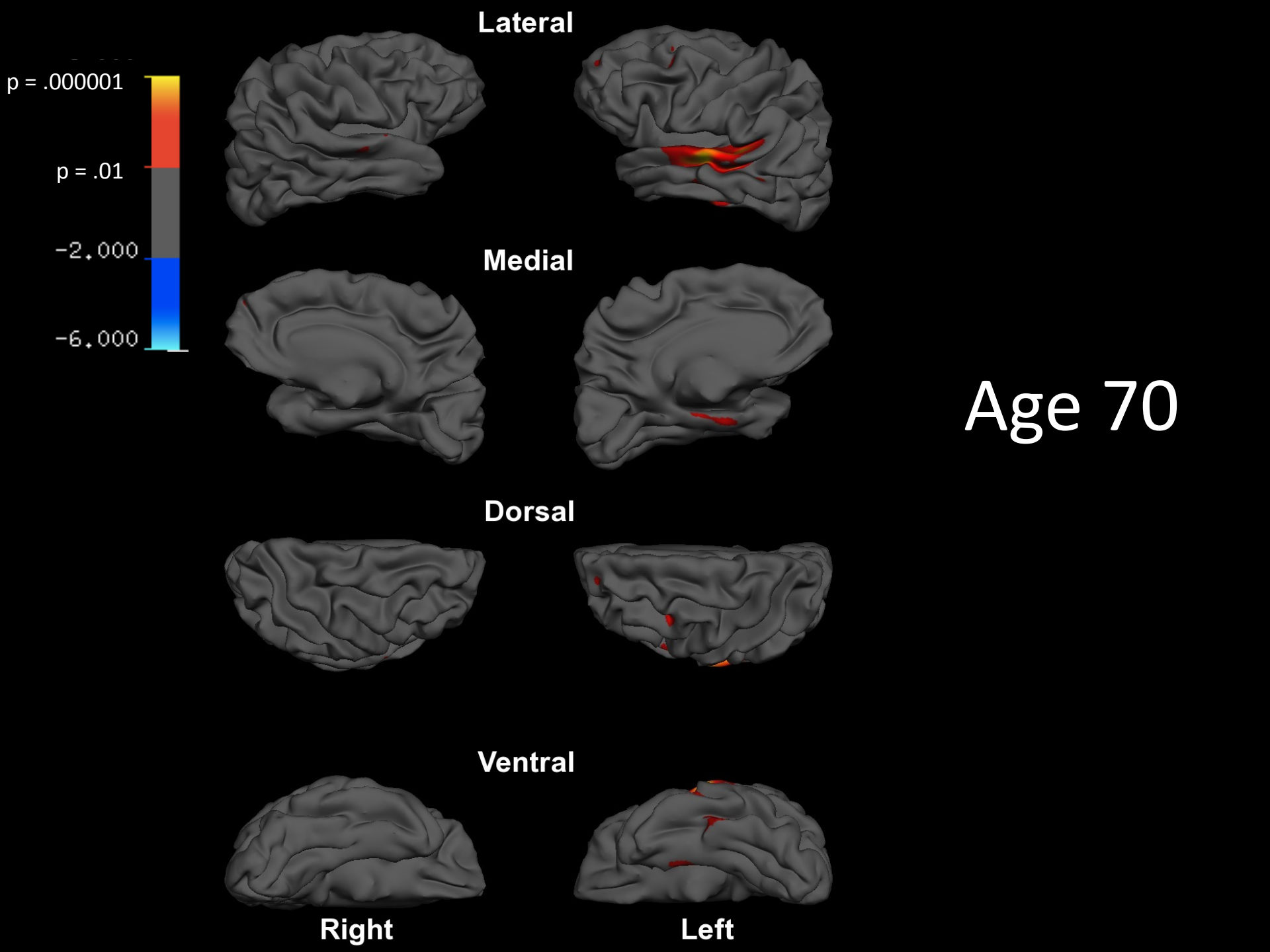
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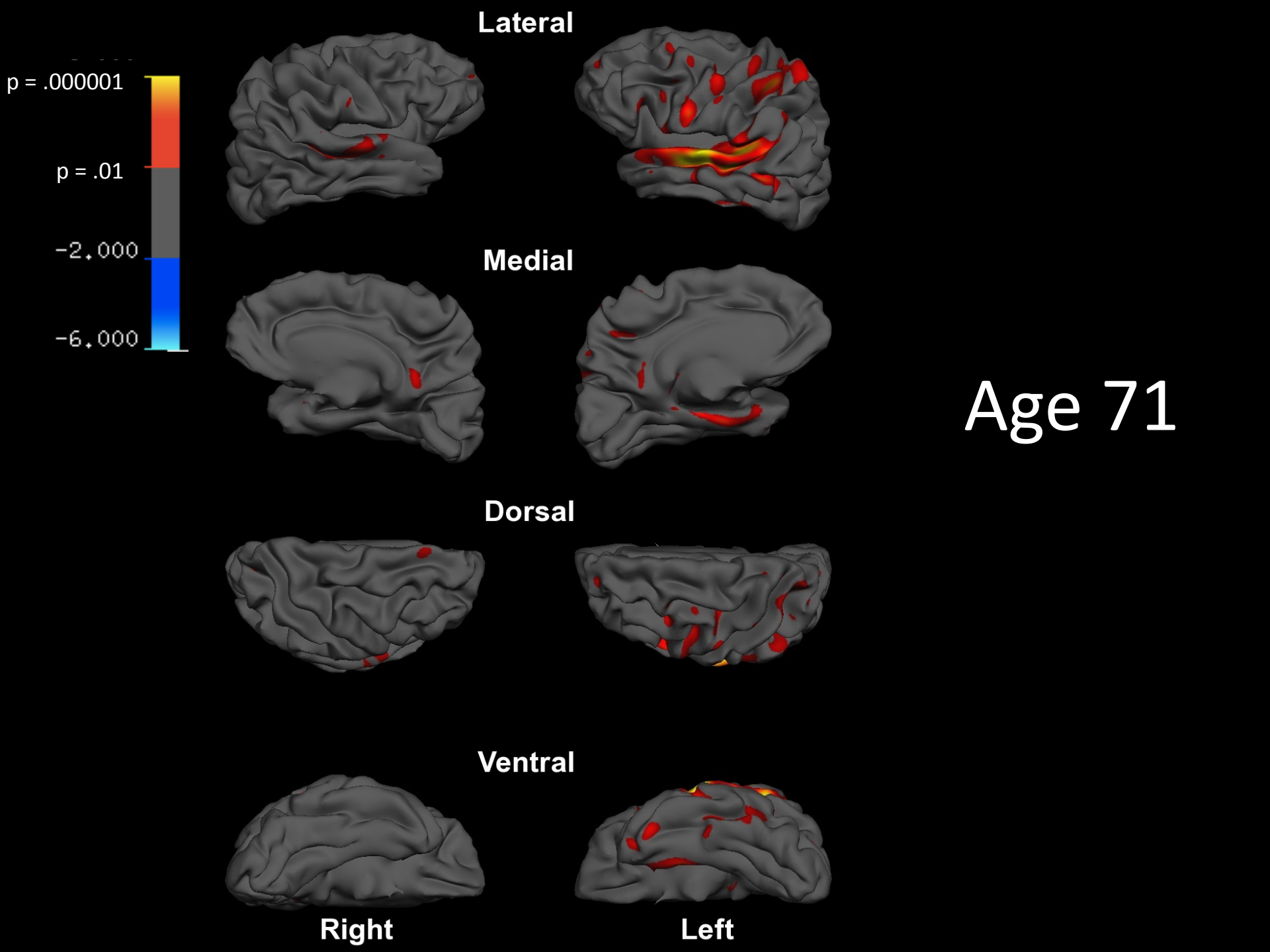
Age 70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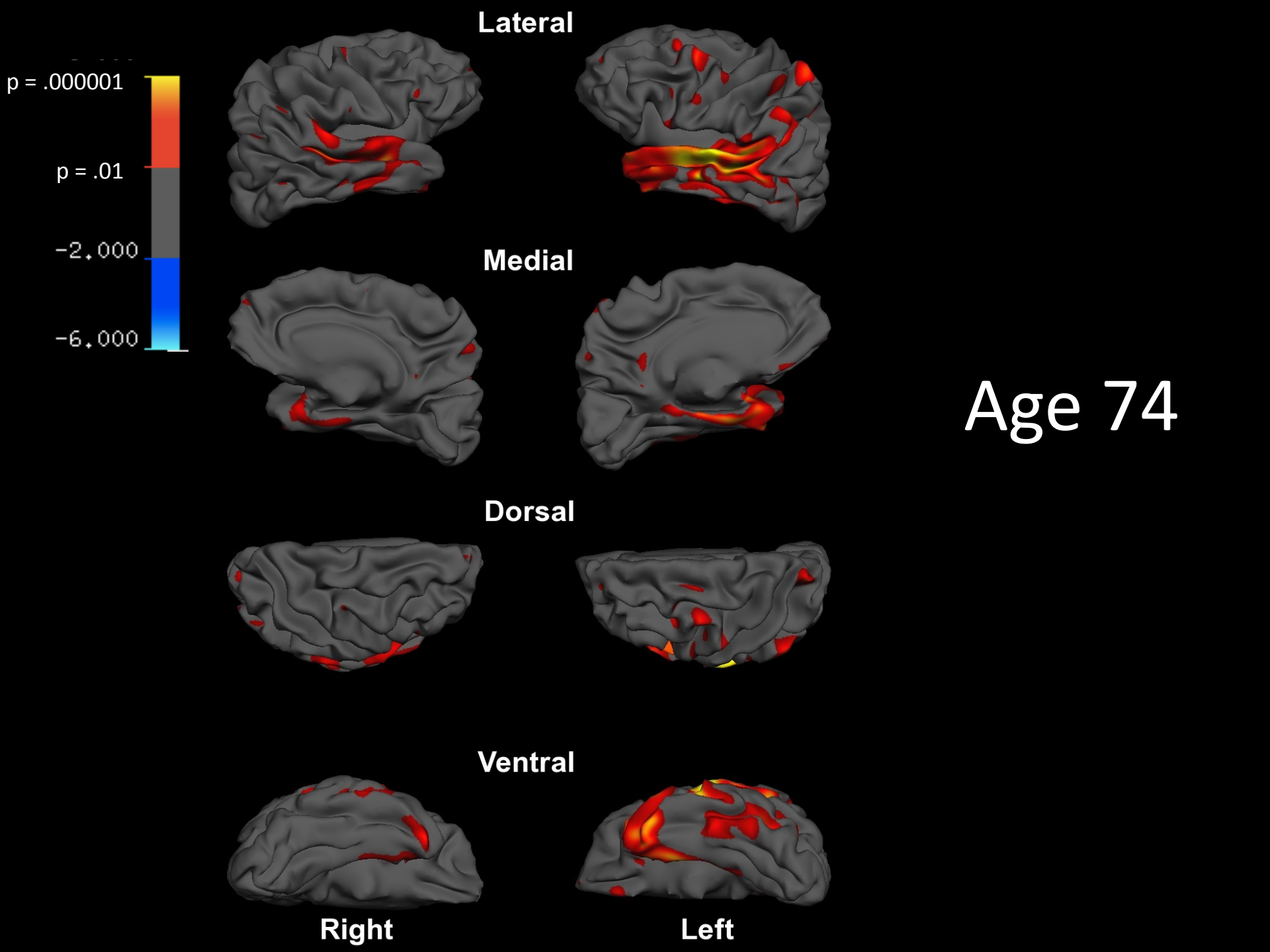
Age 71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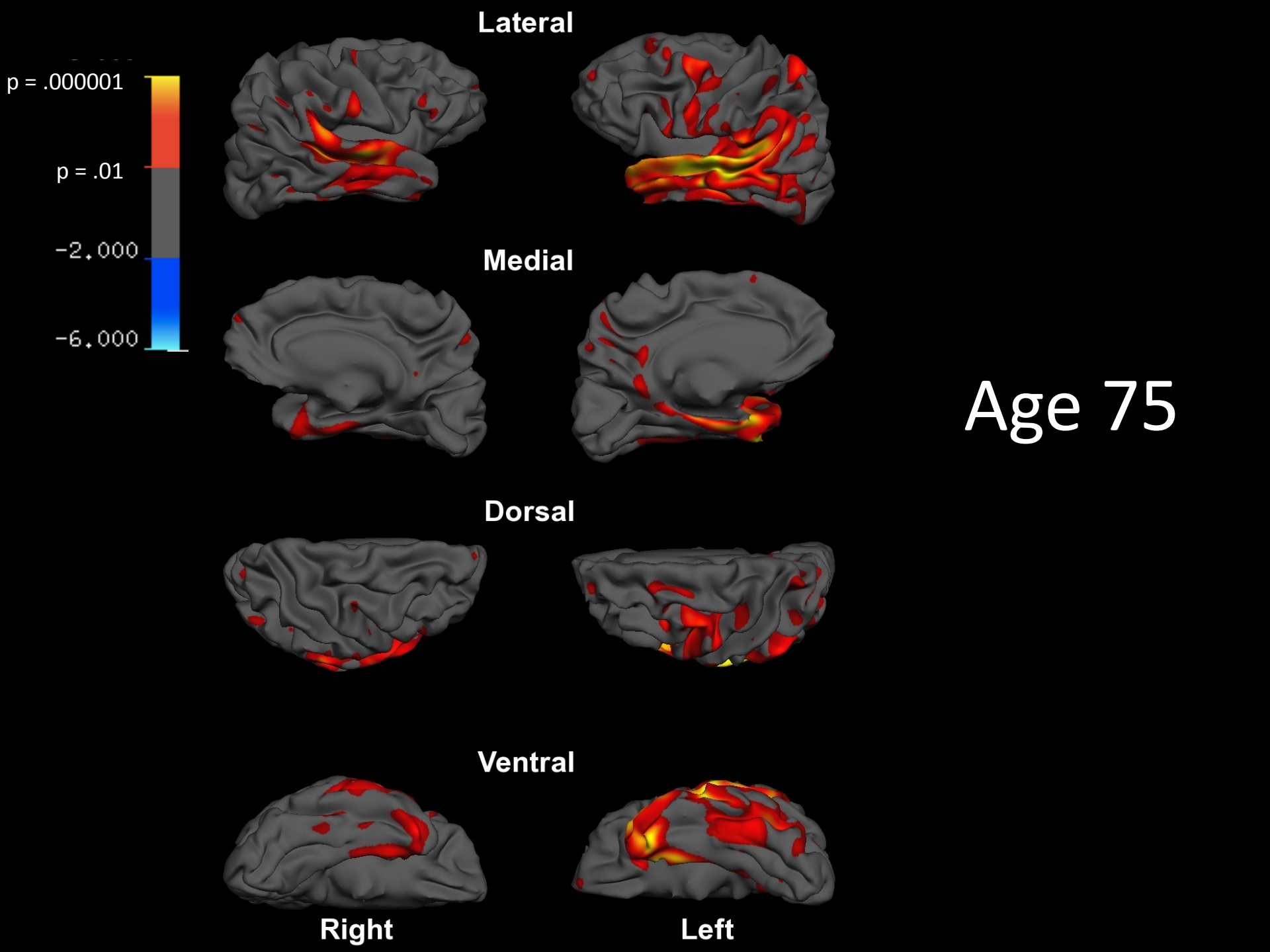
Age 74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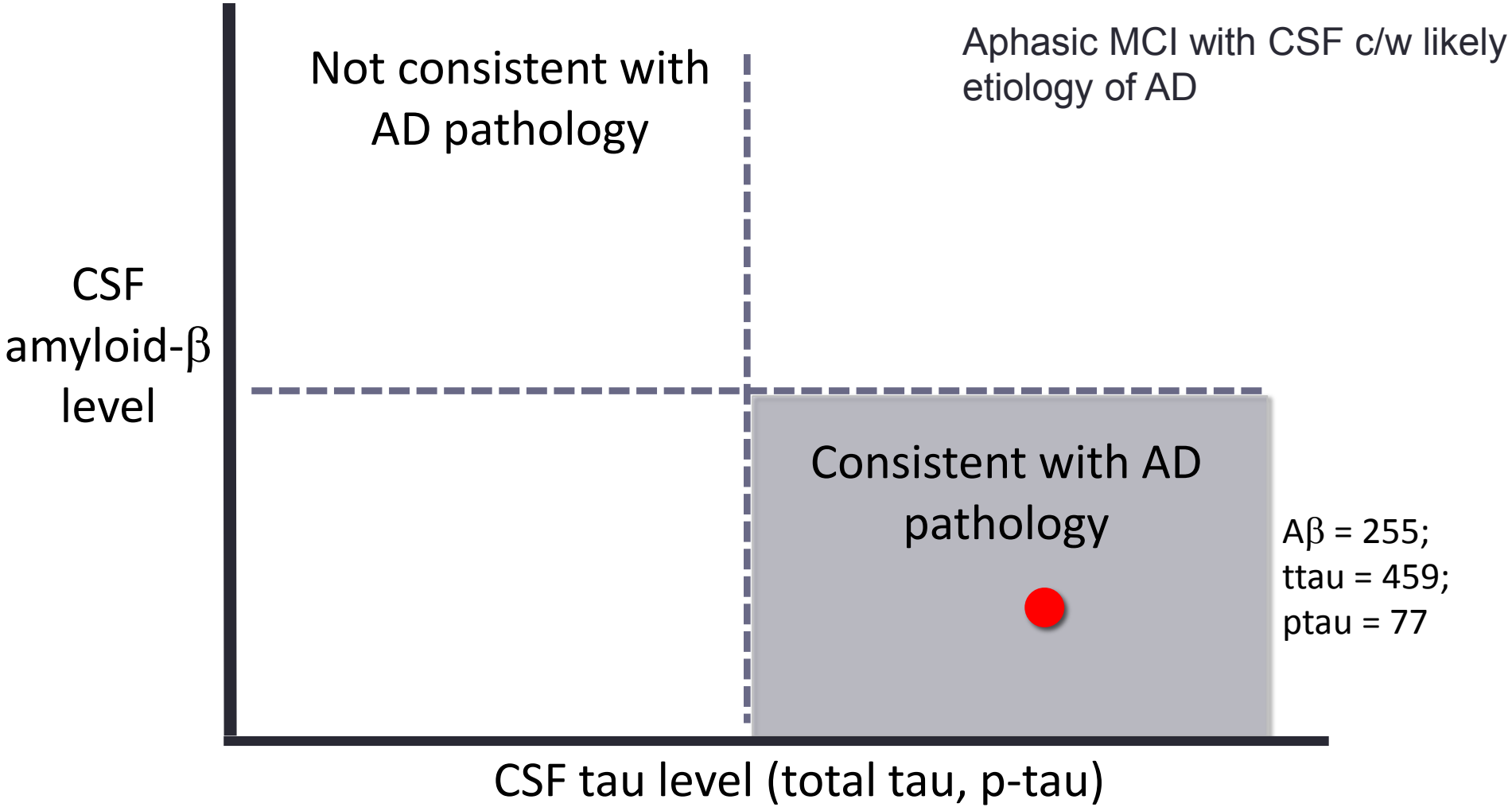
Age 75



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CERAD age related plaque score: Abundant
NIA-Alzheimer association score: A3B3C3
High probability of cognitive impairment due to Alzheimer Disease

The teacher who forgot words

- A 70 year-old retired teacher developed progressive word-finding difficulties, followed by confusion about the meaning of words when other people spoke to her. For example, during a recent family event, she did not understand what the word “punchbowl” meant.

- She had a good memory for recent events of her life, recounting multiple stories (at times to an excessive extent during history-taking, requiring redirection) and an excellent sense of direction.

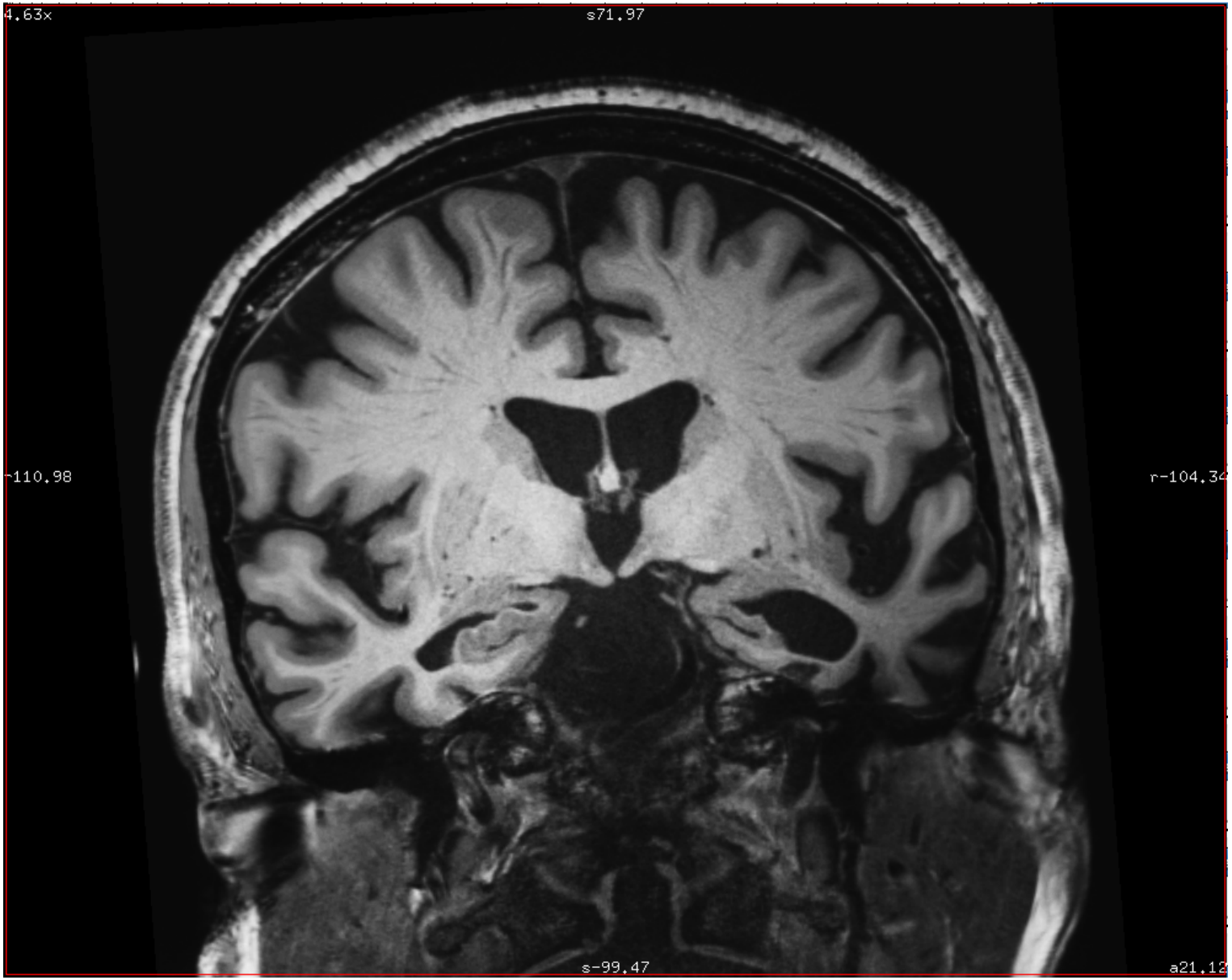
- She was still fully independent in her daily life. She had been widowed 10 years previously, living alone since. She was able to perform all IADLs independently, including managing her money, paying bills, driving, and volunteering in the community (visiting senior centers to play piano and attending regular practices of a community choir).

- Exam showed anomia with single word comprehension problems and surface dyslexia, otherwise preserved cognition

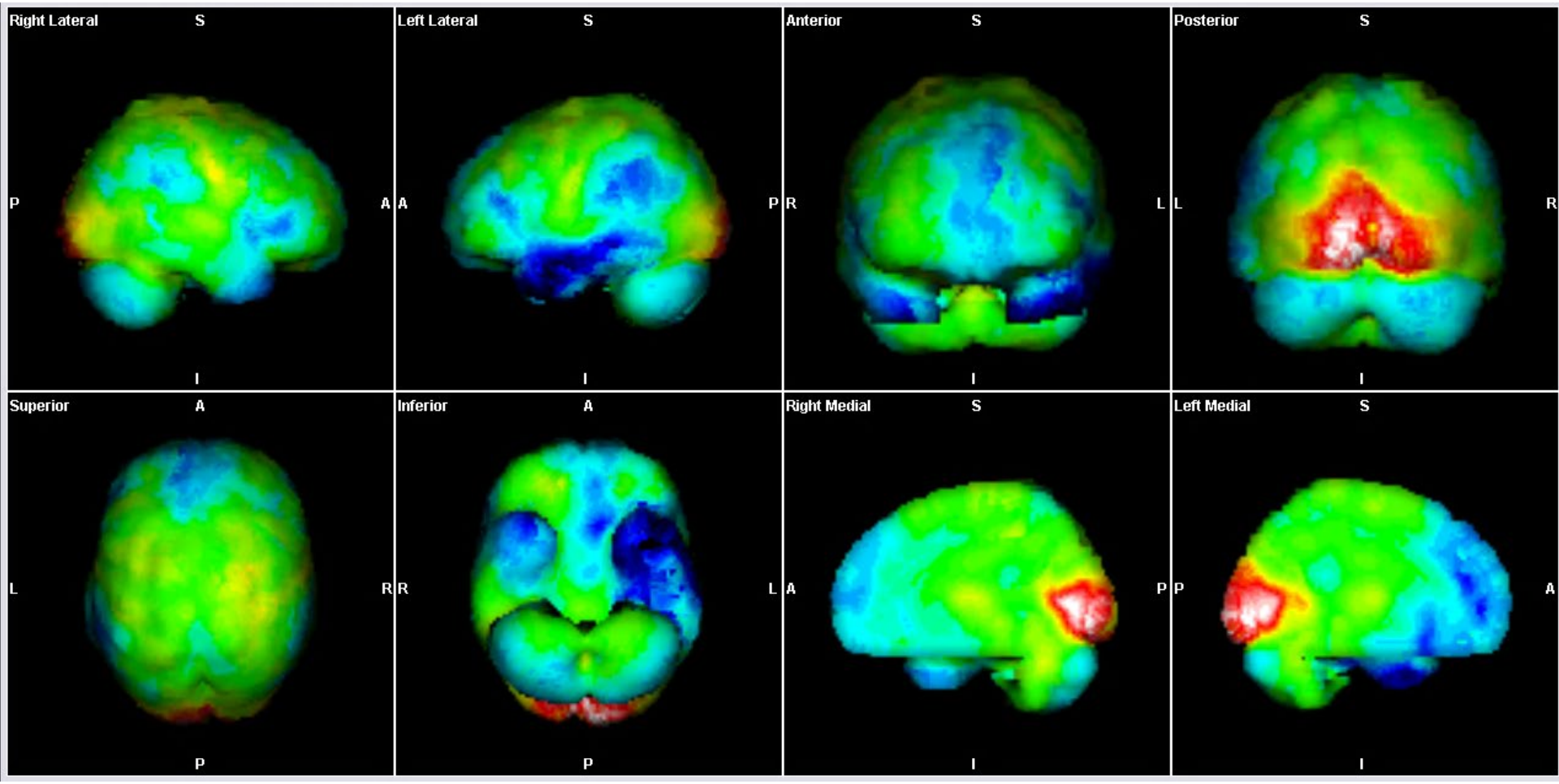
MCI, language predominant (non-amnestic)
Primary Progressive Aphasia, semantic variant

Mesulam, Dickerson, et al., NEJM 2017

MRI



FDG PET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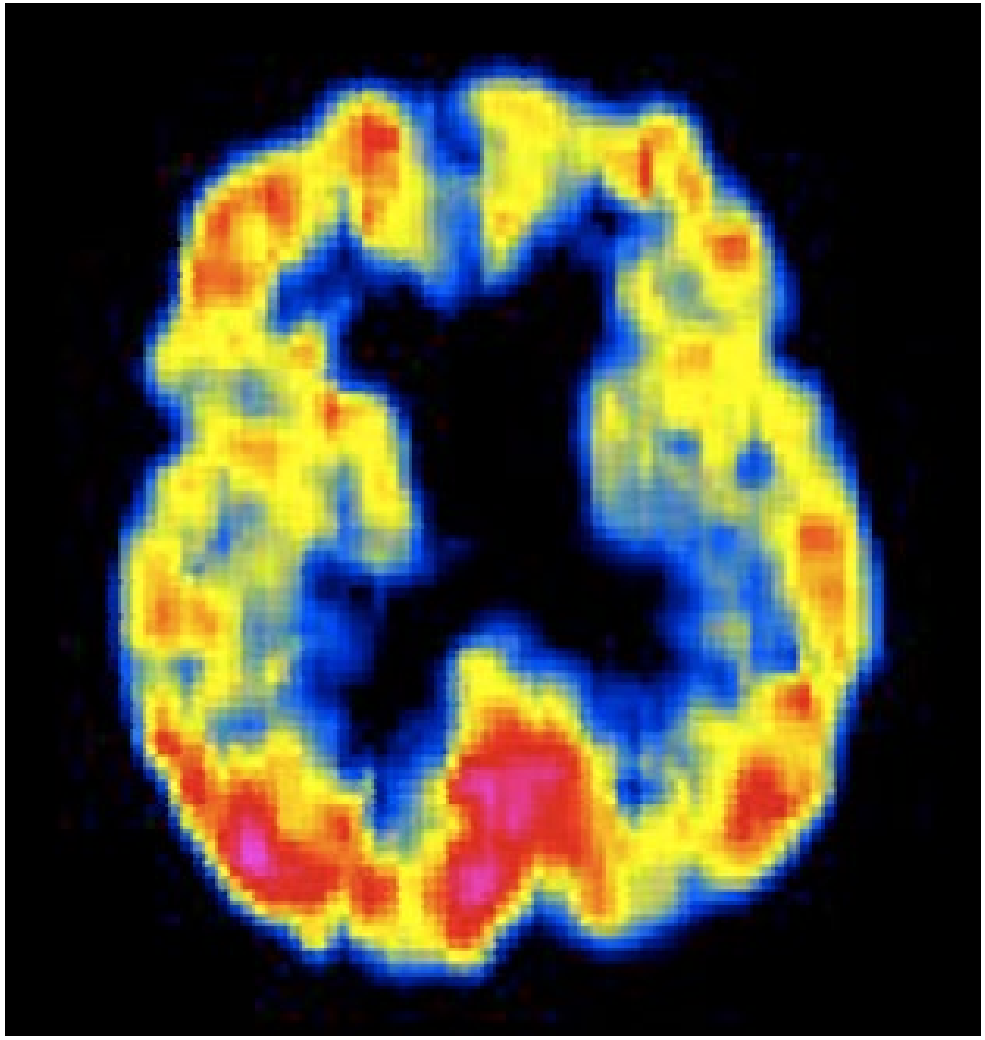
Amyloid PET



Mesulam, Dickerson, et al., NEJM 2017

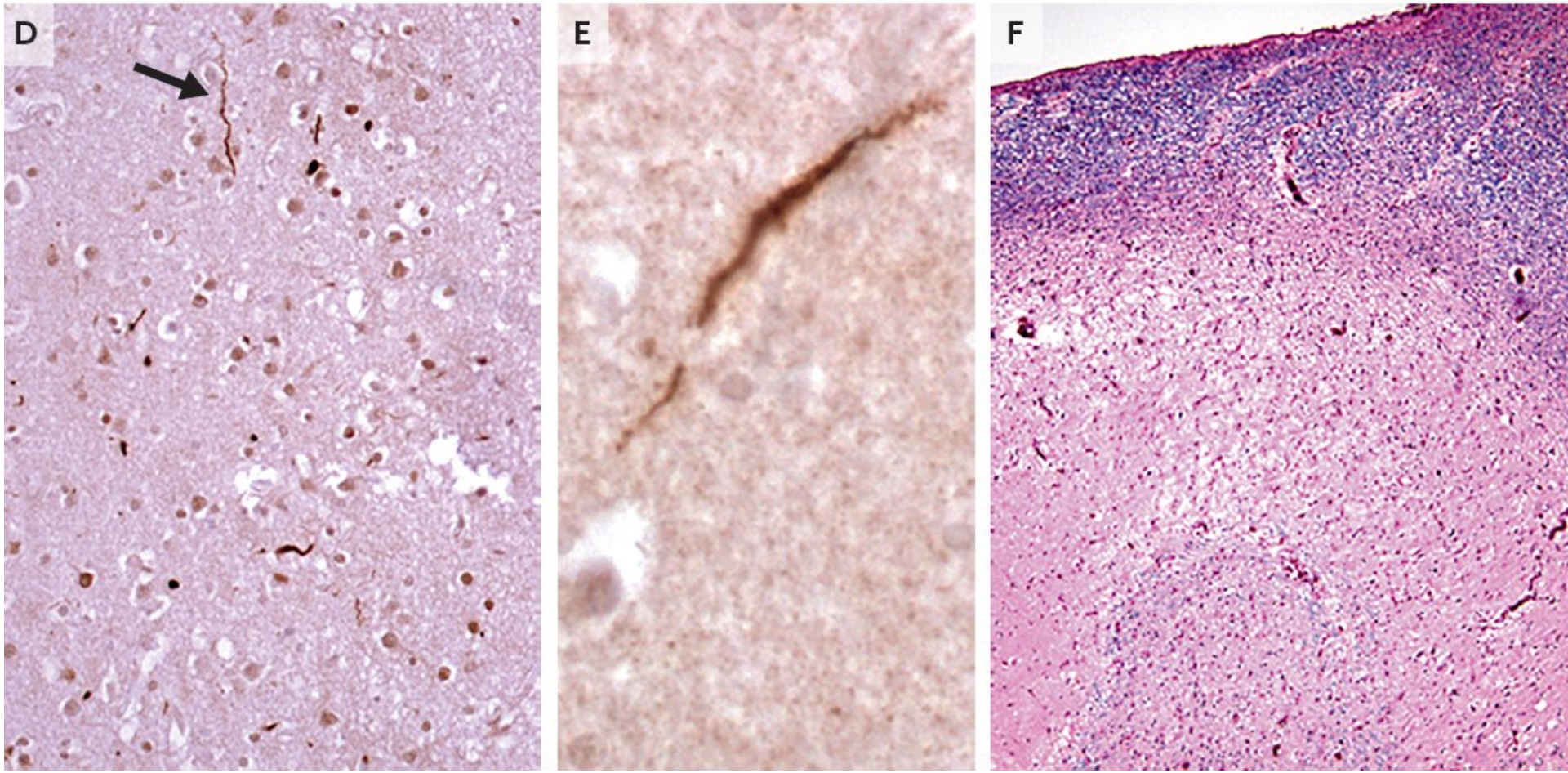
Likely etiology?

- Alzheimer's disease
- Cerebrovascular disease
- Lewy Body Disease
- Frontotemporal Lobar Degeneration
  - Tauopathies
  - TDP43 proteinopathies
- Hippocampal sclerosis
- Argyrophilic grain disease
- etc

- Medical
  - Neoplasm
  - Trauma/anoxia
  - NPH
  - Toxins
  - Infections
  - Neurologic illness
  - Organ failure

Mesulam, Dickerson, et al., NEJM 2017

FTLD-TDP43 type C with concomitant mild AD pathology (likely contributing minimally; Thal 4/5, Braak II/VI, A3B1C1)



Mesulam, Dickerson, et al., NEJM 2017

The professor who got lost

- 78y F former English professor with gradual visual/spatial symptoms
  - Started to notice she hadn't seen something she should have, missing turns while driving or walking. Led to decision to stop driving; otherwise intact IADLs
  - Unsure of where things are; looks for purse at least 5 times a day
  - Difficulty recognizing familiar people by their face, even including her son, but recognizes them from voice, gait (prosopagnosia)
  - Change in ability to carry out other visual tasks
    - Map reading
    - Finding letters on keyboard: "no tactile memory"
    - Writing a check - remembering what to put where
  - Neurologic exam and cognitive testing: Impaired visual and constructional ability with simultanagnosia and prosopagnosia, otherwise intact

MCI, visual predominant (non-amnestic)
Progressive Visuospatial Syndrome (Posterior Cortical Atrophy syndrome)

Conclusions

MCI encompasses a spectrum of amnestic and non-amnestic phenotypes, some of which can be considered as specific clinical syndromes (e.g., svPPA, lvPPA, PCA)

primary progressive memory loss?

The MCI clinical syndrome is predictive of imaging and biomarker findings (localization and prediction of lesions)

Biomarkers predict facets of neuropathology that they measure, but need to be contextualized with prior probability based on clinical syndrome and other biomarkers

We always have to keep in mind the possibility of dual pathologies

Thank you!

MGH FTD Unit & Center for Translational Brain Mapping

Affiliated with the Mass ADRC and Martinos Center for Biomedical Imaging

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