Frontotemporal Degeneration: New Tools for Early Diagnosis and Monitoring Set the Stage For Treatment Trials

June 10, 2011

Bradford C. Dickerson, M.D.
Associate Professor of Neurology, Harvard Medical School
Director, MGH/Harvard Frontotemporal Disorders Unit
Massachusetts General Hospital
mghftdunit@partners.org

Outline

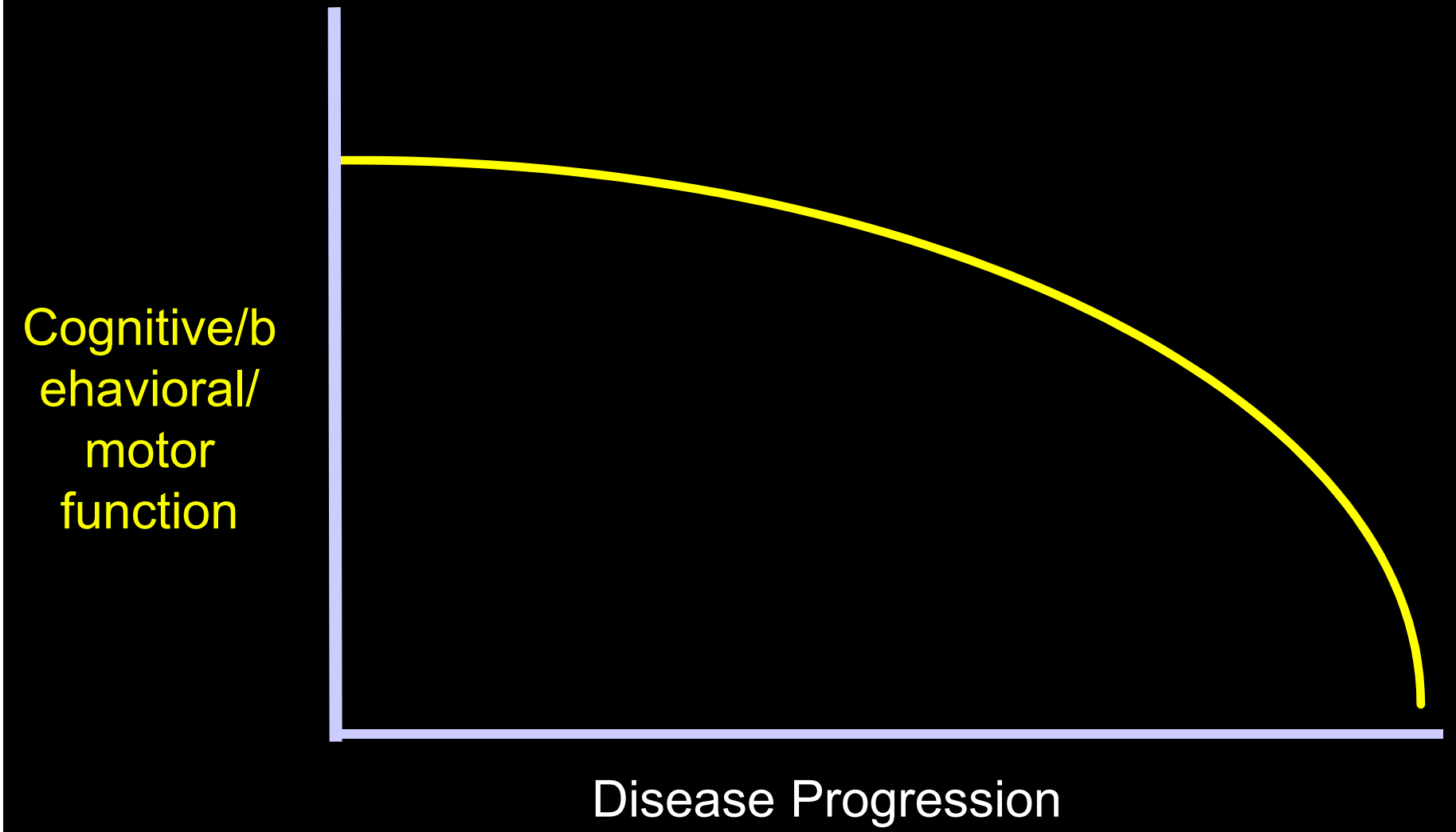
- General concepts in neurodegenerative diseases
- FTD
  - Clinical
  - Imaging
  - Pathology
  - Genetics
  - Treatment

Neurodegenerative diseases

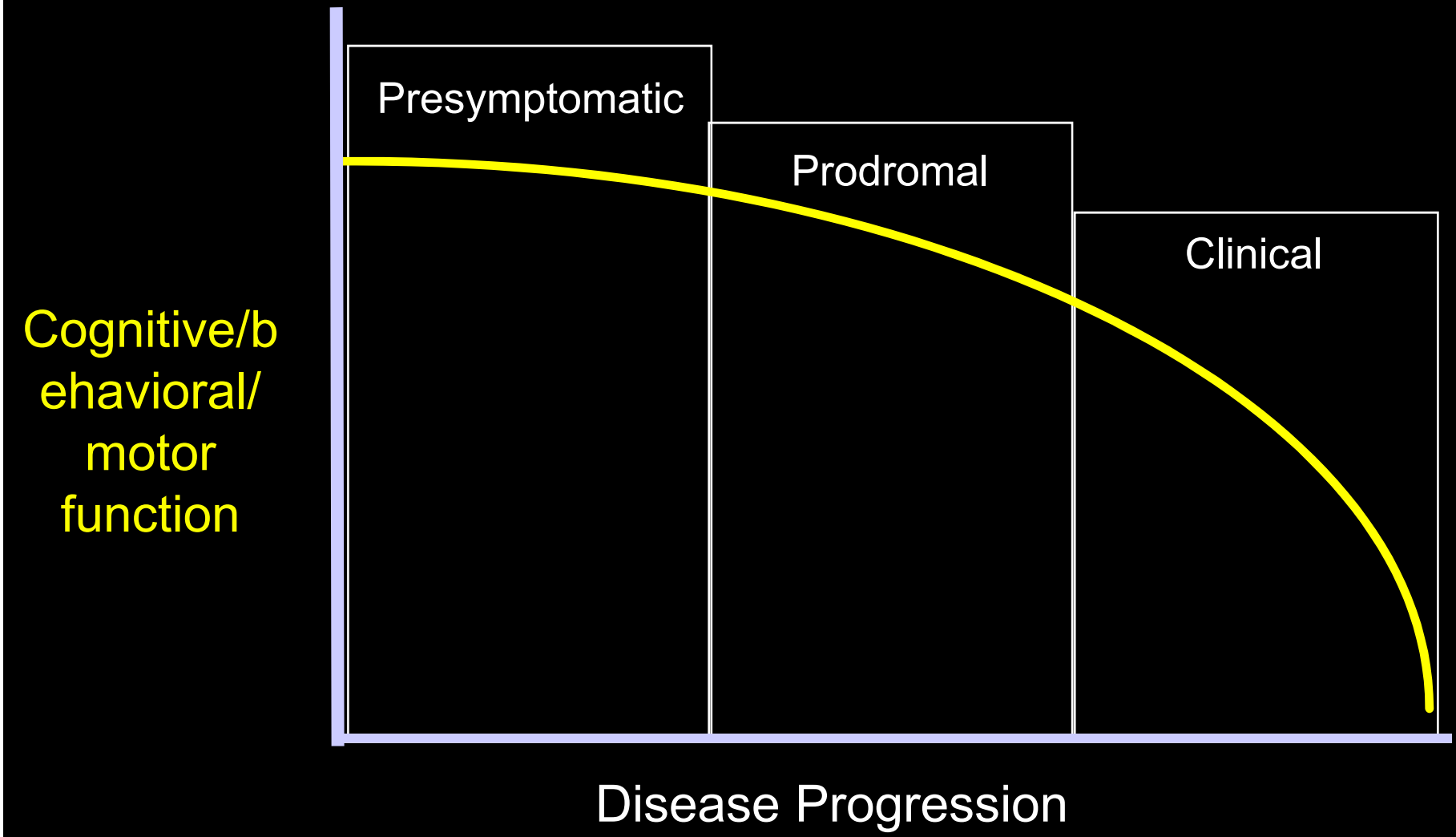
- Frontotemporal dementia/primary progressive aphasia

- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- Alzheimer's disease
- Parkinson's disease
- Dementia with Lewy bodies (DLB)
- ALS (Lou Gehrig's disease)
- Huntington's disease
- Many others

Progression of neurodegenerative diseases



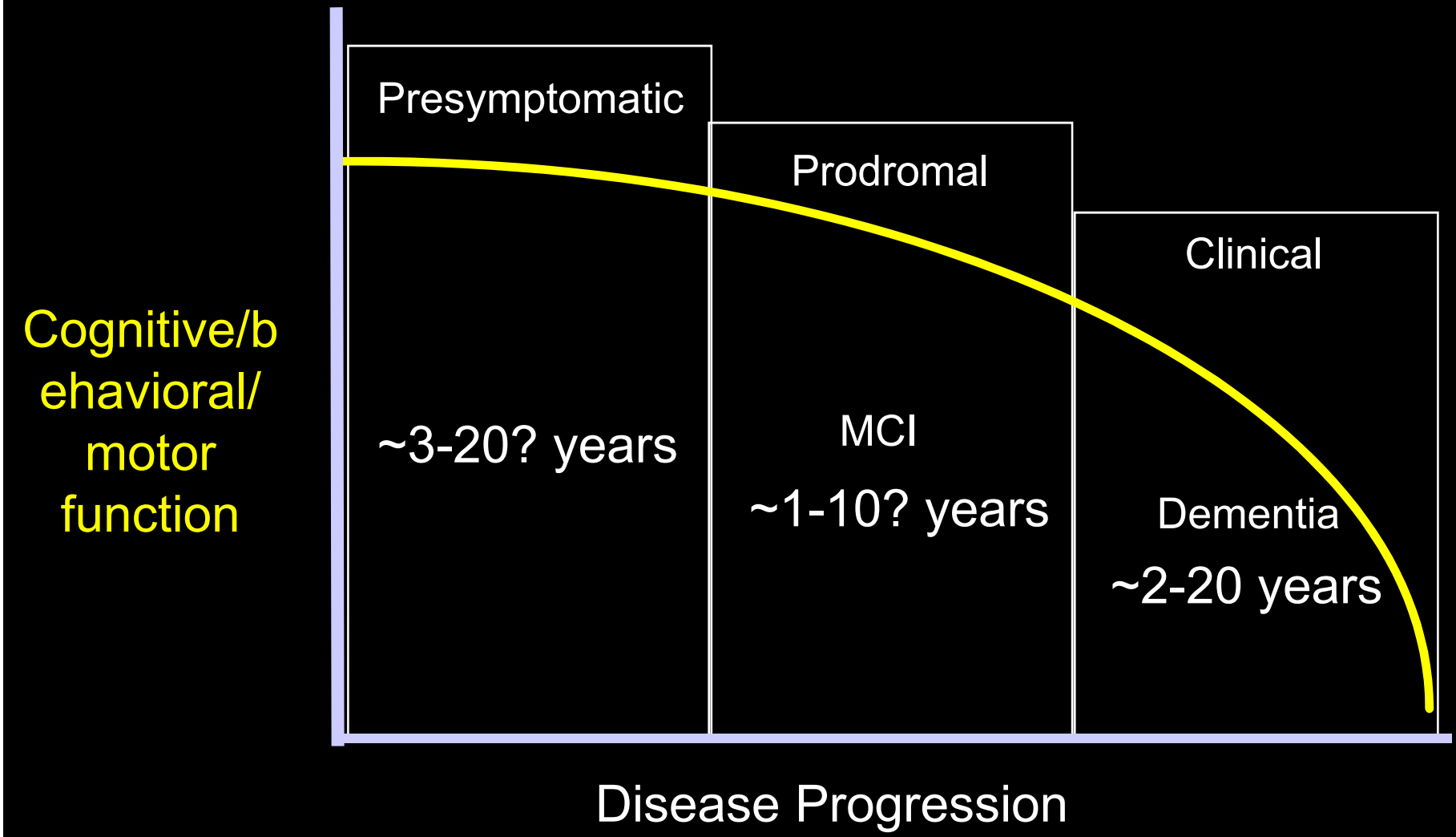
Progression of neurodegenerative diseases



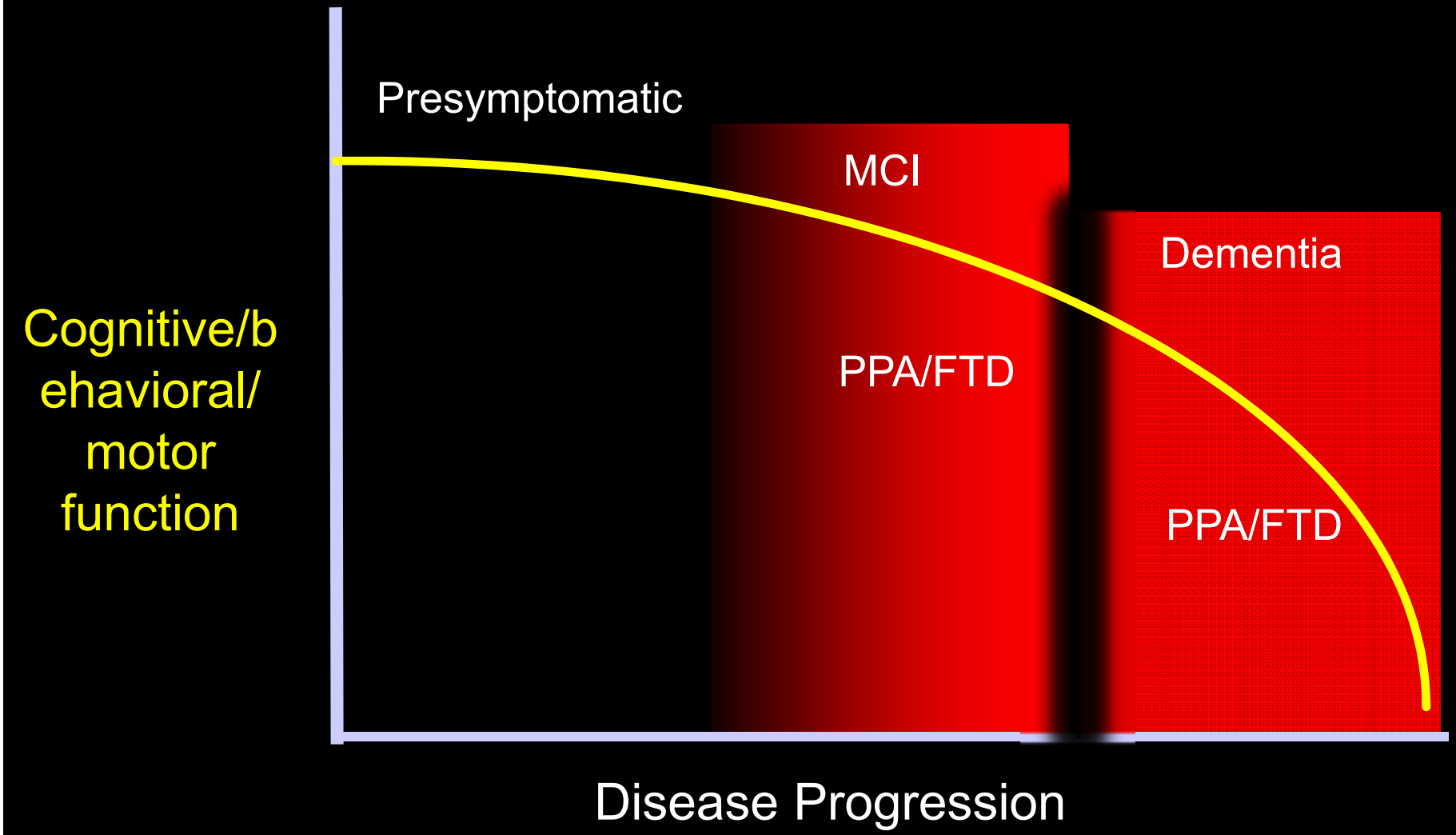
A word on dementia

- Dementia
  - Acquired loss of multiple cognitive abilities that is significant enough to interfere with typical social or occupational activities
  - In the past has been part of the diagnostic criteria for most of these disorders
    - Patient must have “dementia” to receive diagnosis
  - Some patients who ultimately turn out to have one of these illnesses may have symptoms long before they would fit the typical definition of “dementia”
  - In the Alzheimer community, this prodrome is often referred to as mild cognitive impairment (MCI)

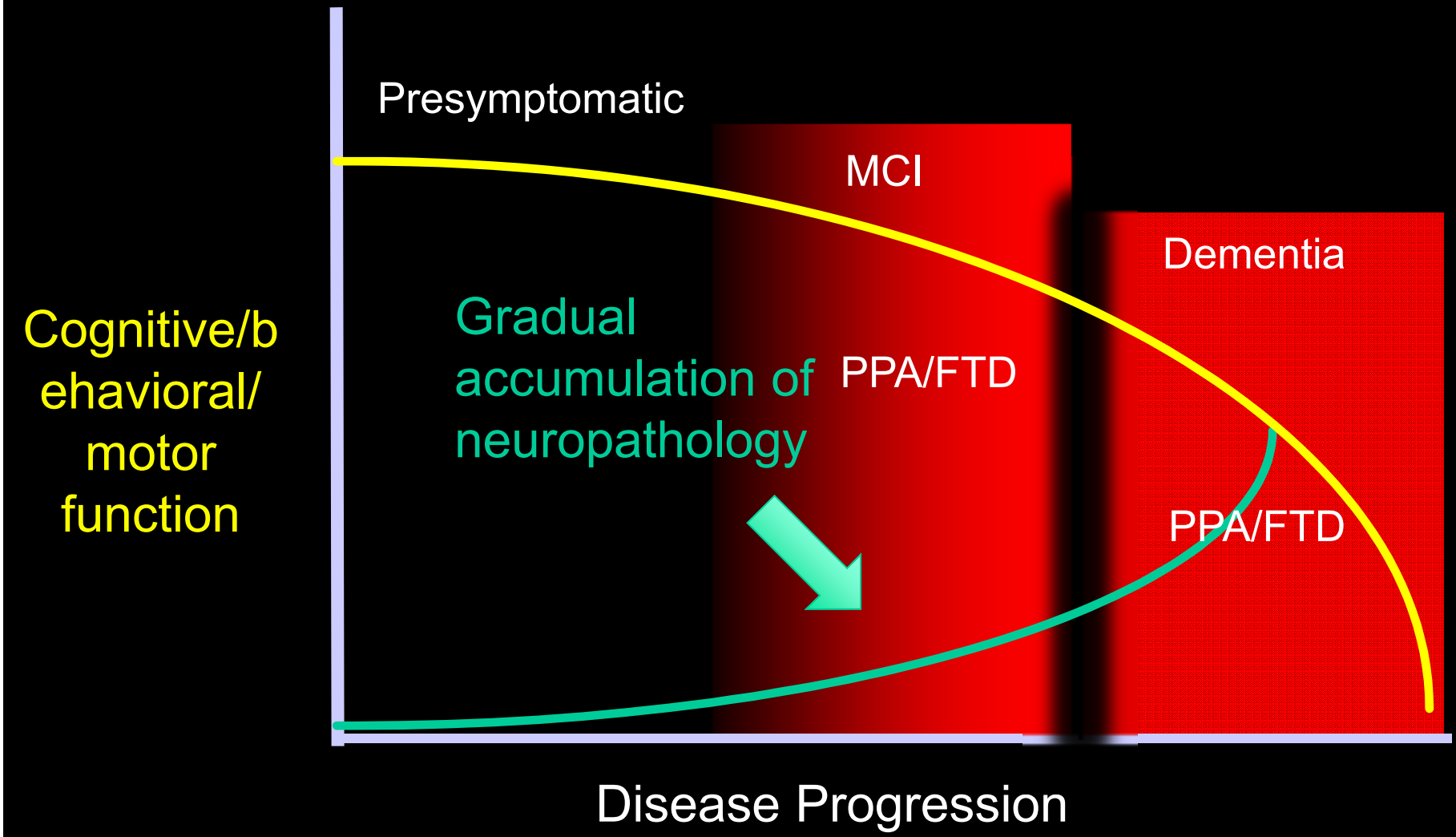
Progression of neurodegenerative diseases



Progression of neurodegenerative diseases



Progression of neurodegenerative diseases

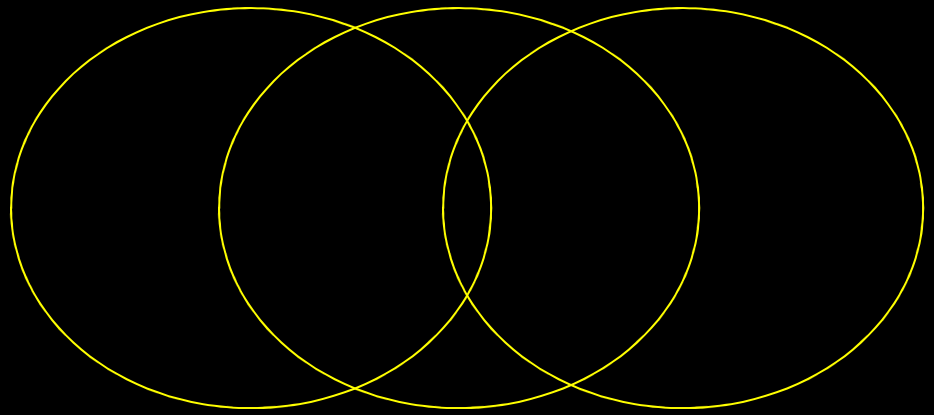


FTD: Brief history

- Dr. Arnold Pick, 1892, 4 case descriptions
  - 71 year old with gradual behavioral decline followed by speech and language deterioration
  - At autopsy, brain showed focal frontal and temporal lobar atrophy
- Dr. Alois Alzheimer, 1911, pathologic description
  - Neuronal swelling & deposits within neurons (Pick bodies): “Pick’s disease”
- Little work until 1980s
- 1982: Dr. Marsel Mesulam coins term “PPA”
- 1980s and 1990s: Early studies of other aspects of clinical and pathologic features of FTD
- 1994: First diagnostic criteria for FTD (Lund-Manchester)
- 1998: First “consensus” diagnostic criteria for FTD (Neary)
- 2000s: More new discoveries than in past 100 years
- 2002: AFTD was founded
- 2010: 7th International Conference on FTD

Complexity of FTD

- Medical professionals are often bewildered by the wide array of terminology and the complexity of relationships

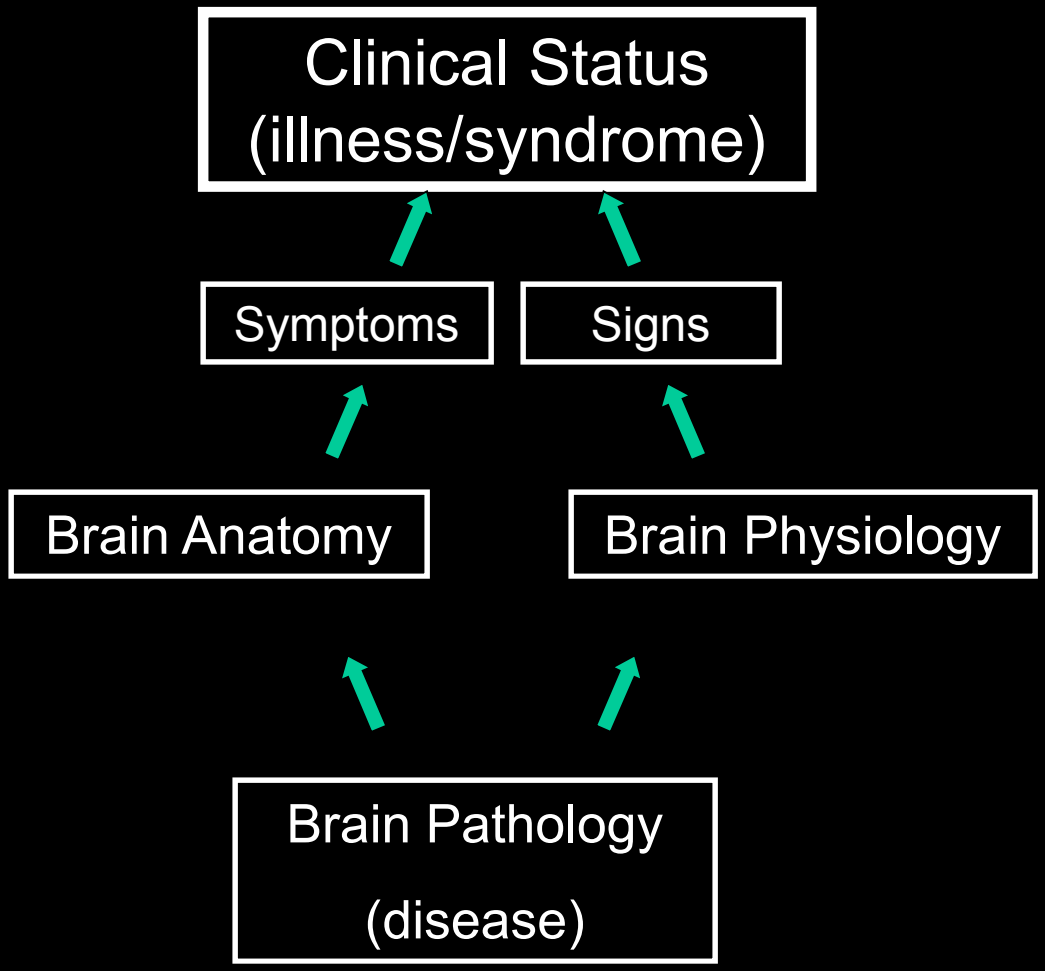


- Multiple classification systems
- --major recent advancements in classifying clinical problems as well as pathology

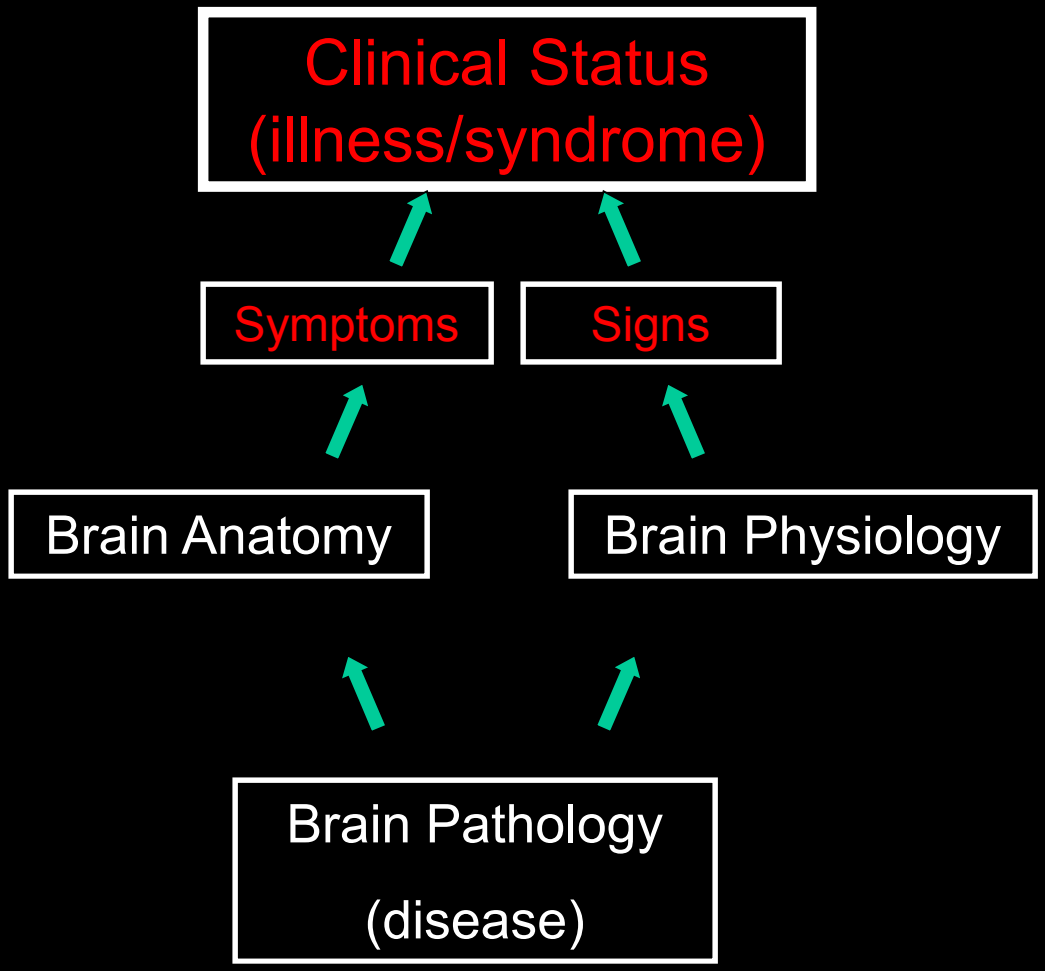
How common is FTD?

- ~3rd most common neurodegenerative dementia
  - After AD and DLB
  - 5 - 15% of dementias
- Estimated to affect 250,000 Americans
  - Similar to ALS (Lou Gehrig's)
- Typically early onset, often 50s – 60s
  - Most common early onset dementia
- Cases have been reported with onset as young as 20s, as old as 80s (MGH FTD Unit: 27 – 86)

Understanding FTD



Understanding FTD



Clinical

- New diagnostic criteria
  - PPA “Gorno-Tempini criteria 2011”
  - bvFTD “Rascovsky criteria 2011”
- New scales and tests for diagnosis and monitoring
  - PASS
- New multicenter collaborative efforts for working together to develop better understanding of the “natural history” and biomarkers of FTD
  - NACC FTD Module
  - Neuroimaging Initiative in FTD

Behavioral variant(s) of FTD

- Revised international diagnostic criteria, 2010-11
  - Disinhibition
    - Socially inappropriate behavior
    - Impulsive
  - Apathy
    - Loss of interest, drive, motivation
  - Loss of sympathy/empathy
    - Diminished response to others' feelings
    - Diminished personal warmth/social connection
  - Repetitive/compulsive/ritualistic behavior
    - Often for no particular purpose
  - Change in eating/drinking/etc behavior
    - Change in preferences
    - Excessive intake

Behavioral variant(s) of FTD

- Possible bvFTD
  - Fulfill criteria on previous page
  - No major memory deficit initially; often executive dysfunction
  - Not better explained by a primary psychiatric disorder
- Probable bvFTD
  - Above plus typical imaging abnormalities on MRI or PET
- International study to provide pathologic validation
  - 16 centers (7 US, 2 Canada, 1 South America, England, Italy, Netherlands, France, Germany, Australia)
  - 406 pathologic cases of FTLD
  - Old criteria: 53% of cases met clinical criteria
  - New criteria: 76% of cases met probable, 86% possible

Language variant(s) of FTD

- Progressive aphasias (PPA)
  - Non-fluent/agrammatic variant
    - Reduced ability to produce speech/language
    - Grammar
    - “Apraxia of speech”
  - Semantic variant
    - Reduced ability to understand language
    - Difficulty understanding single words
  - Logopenic variant
    - Word finding difficulty, halting speech, difficulty repeating, variable speech ability

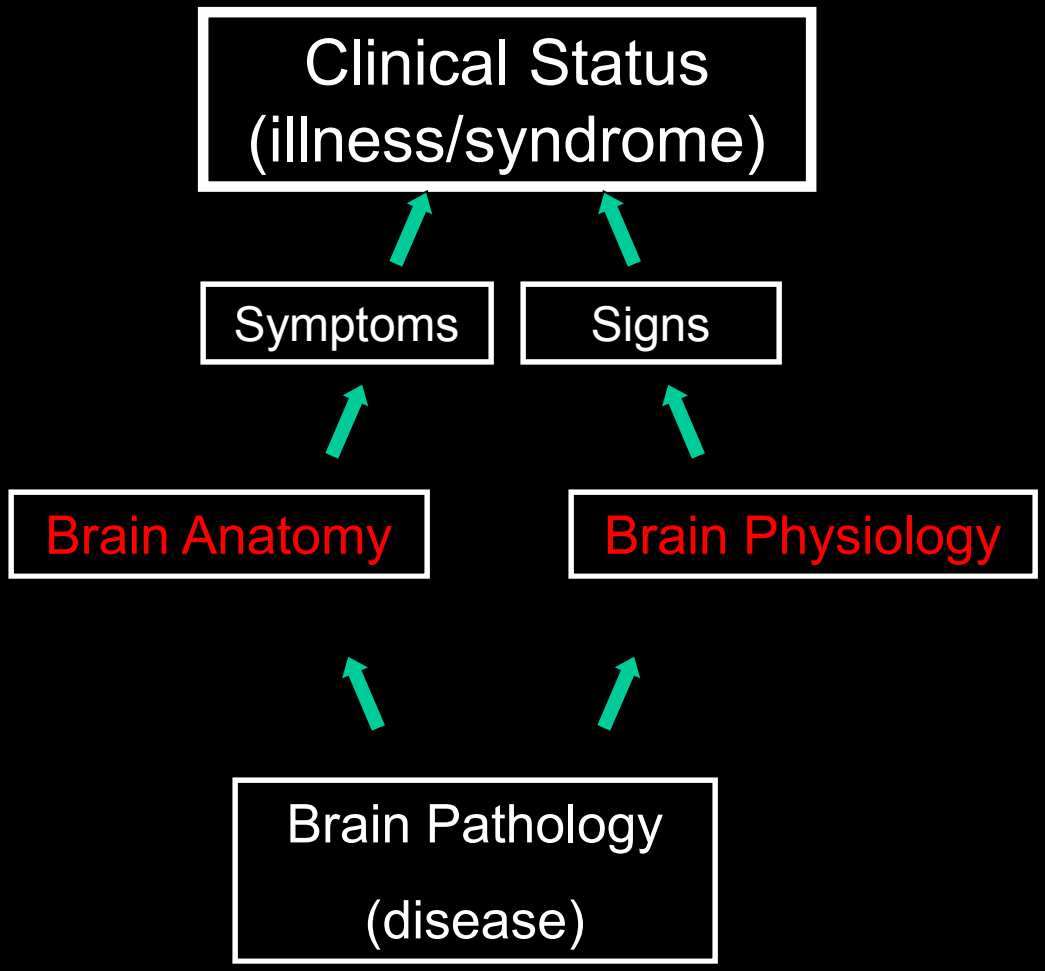
Progression of PPA/FTD

- Usually, though not always, starts out distinctly as one of these variants
- Progresses to involve other domains
- Depending on the type and location of changes in the brain, changes in movement may also occur (major topic of 2010 FTD conference)
  - Incoordination
  - Slowing, stiffness
  - Changes in walking/falls
  - Changes in eye movements
  - Impaired swallowing
  - Survival is 2 – 20+ years after onset of symptoms
  - Average is 7-8 years (new findings coming out)
    - Depends on how early diagnosis is made

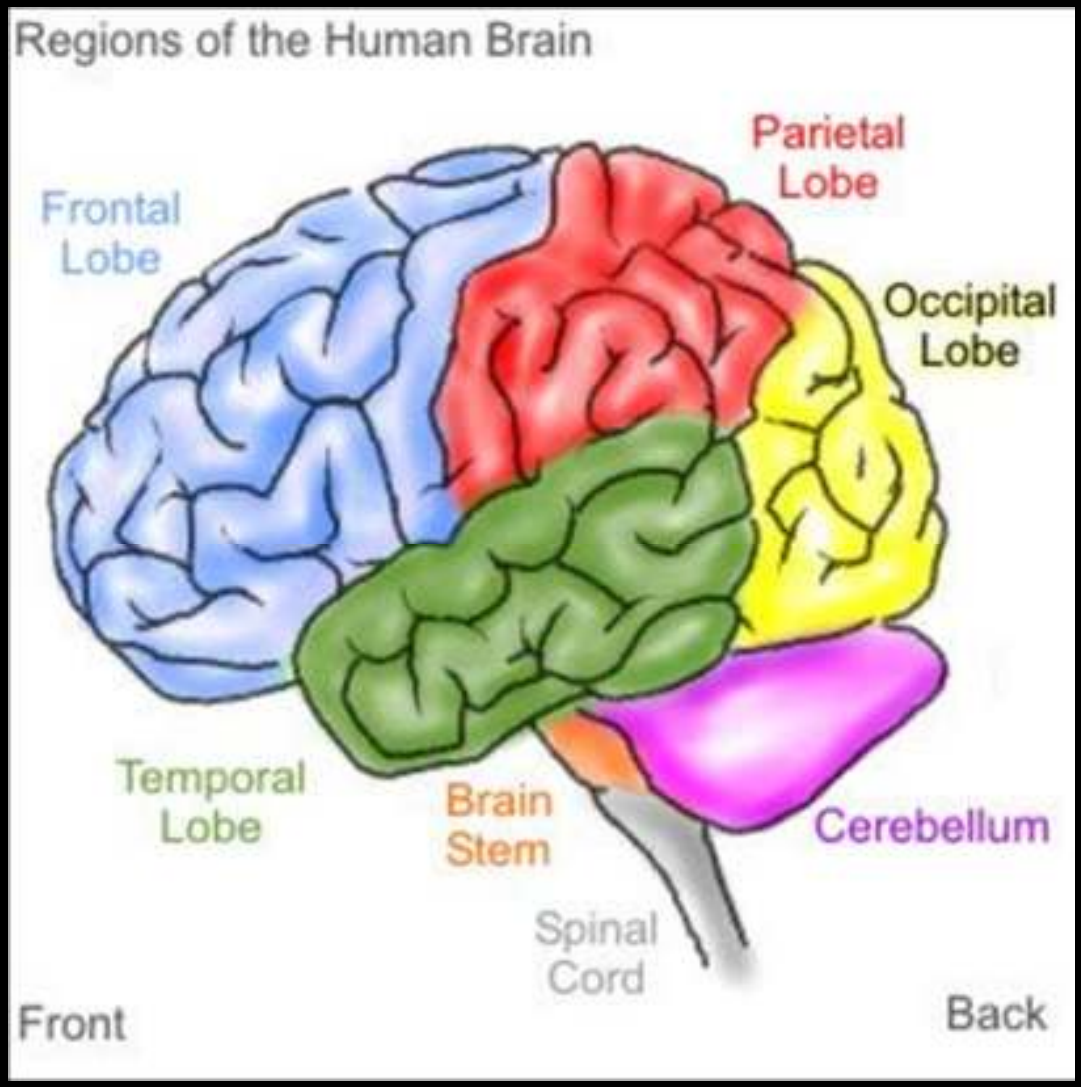
FTD: Current treatment

- Medicines to slow disease progression: still in the distance (but multiple medicines being tested for related conditions may possibly provide benefit)
- Medicines to treat symptoms
  - Nothing is yet proven
  - Clinical trials are in progress and being planned
    - memantine; initial studies demonstrate safety and tolerability
  - Existing medicines may be helpful for managing various symptoms
    - Antidepressants, antiseizure medicines, others
- Comprehensive interdisciplinary team approach
  - Neurologist, psychiatrist, neuropsychologist, social worker
  - Speech therapist for PPA
  - Occupational/physical/cognitive therapist
  - AFTD/Alzheimer's Association/other organizations

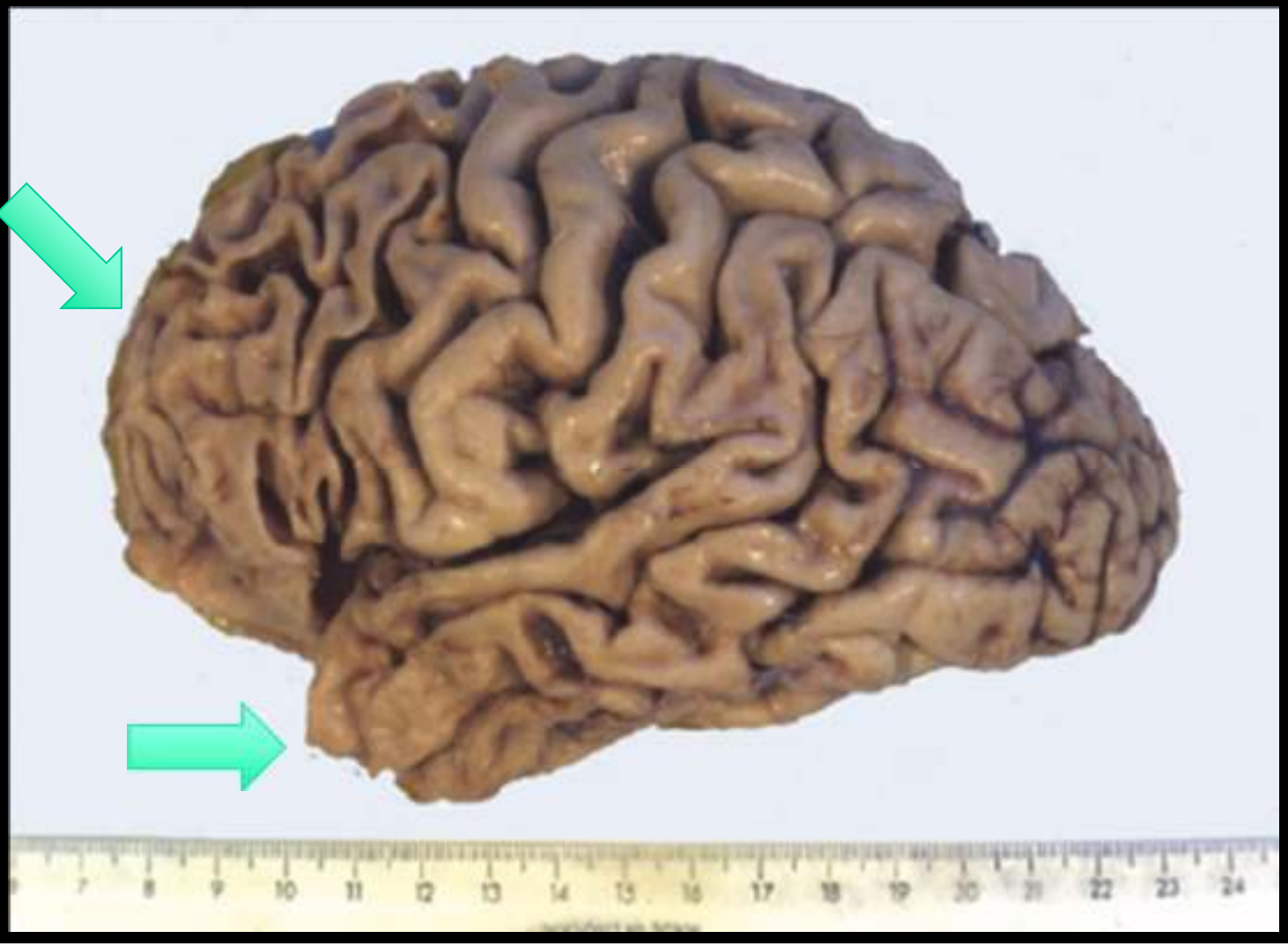
Understanding FTD

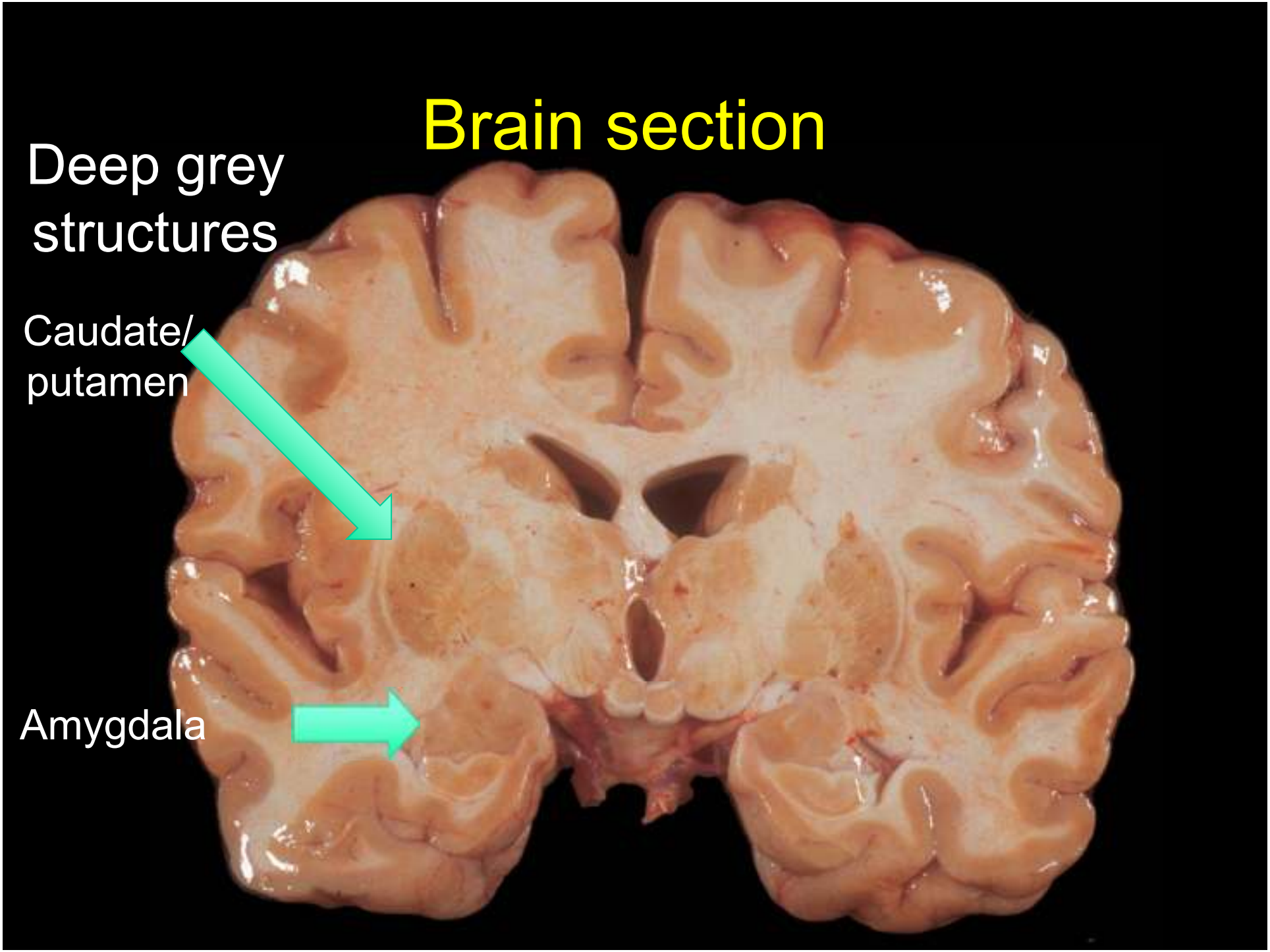


Brain regions



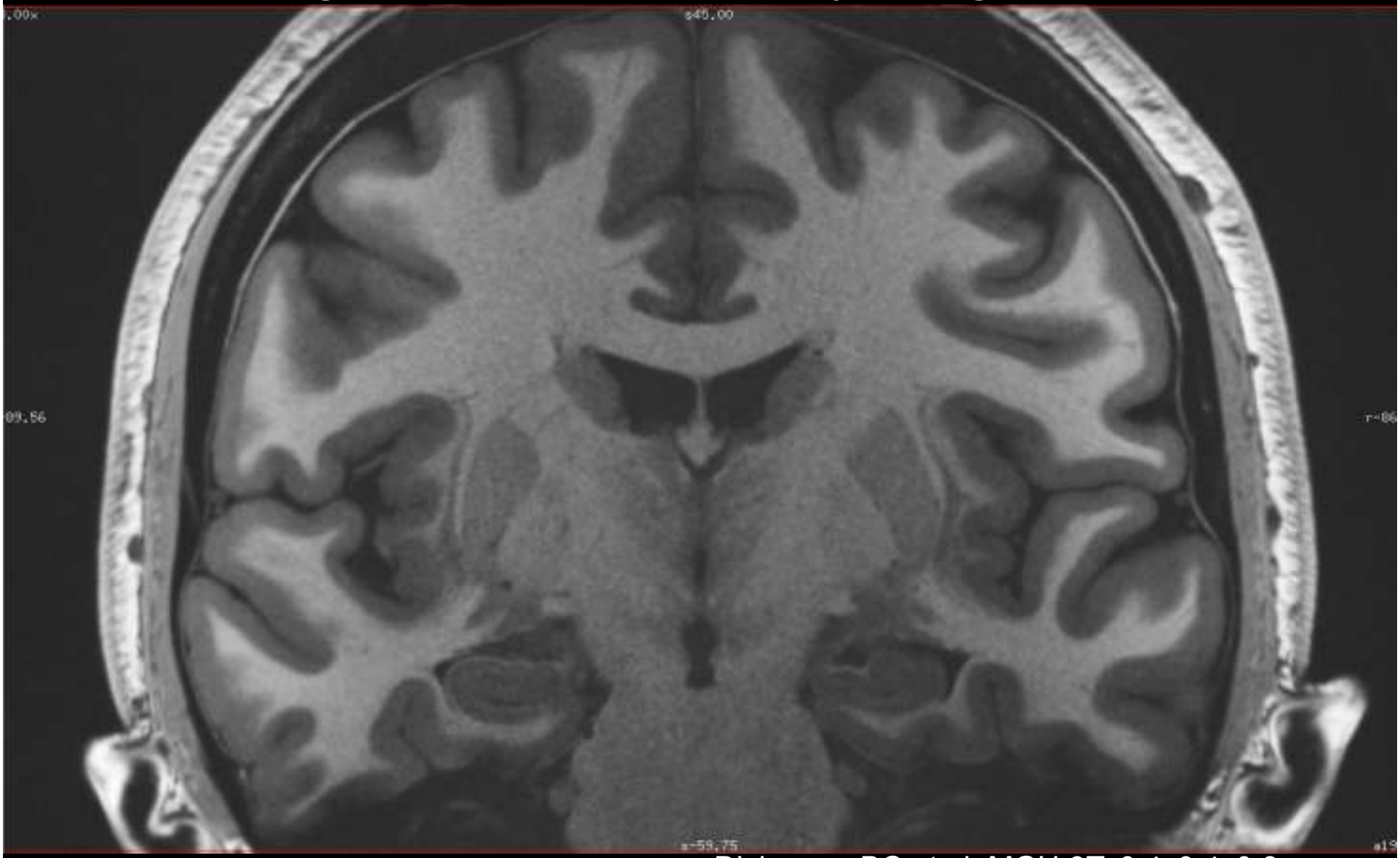
Frontotemporal dementia




Brain section
Deep grey structures
Caudate/ putamen
Amygdala

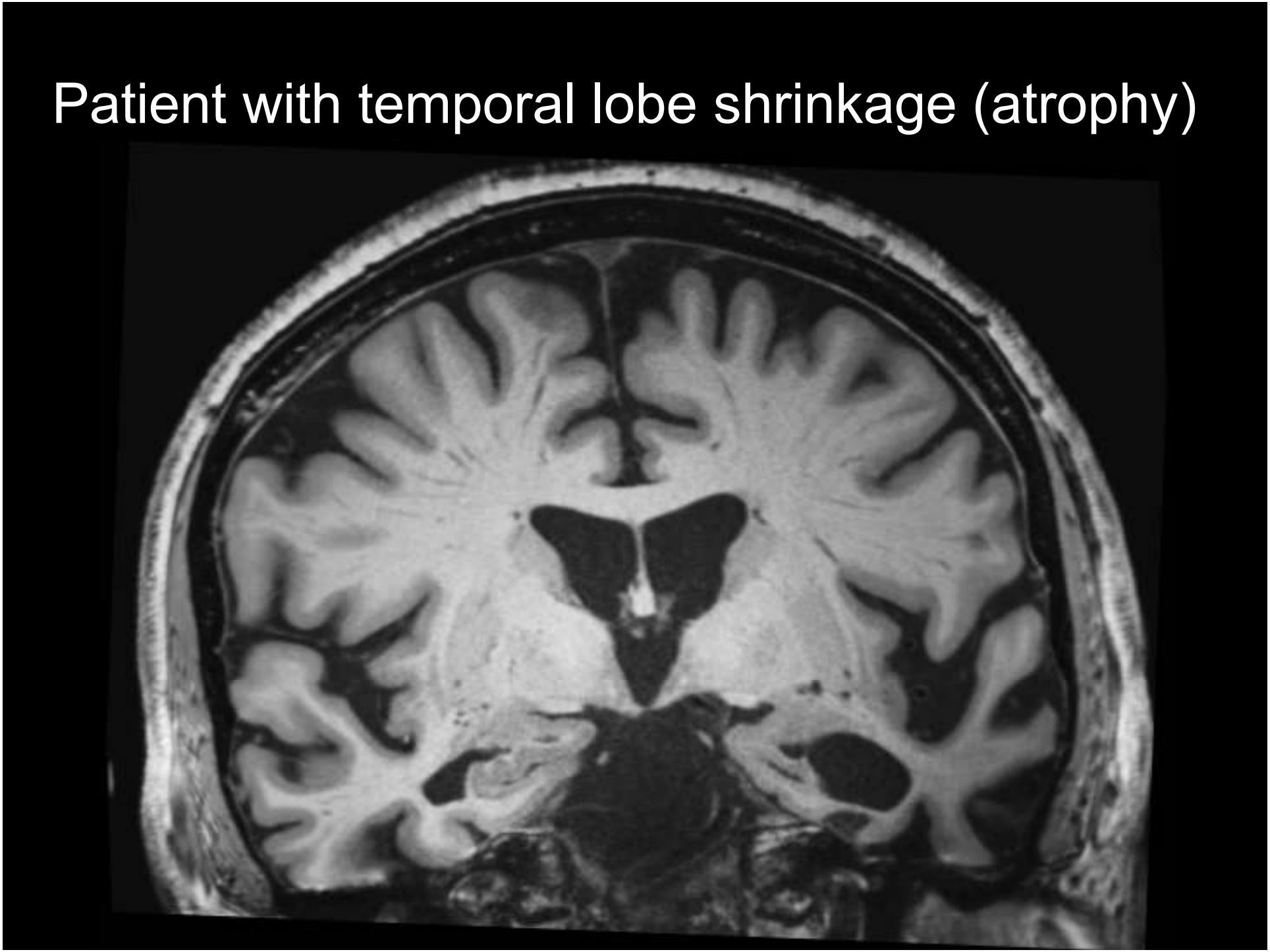
Brain Imaging

High resolution MRI: young adult

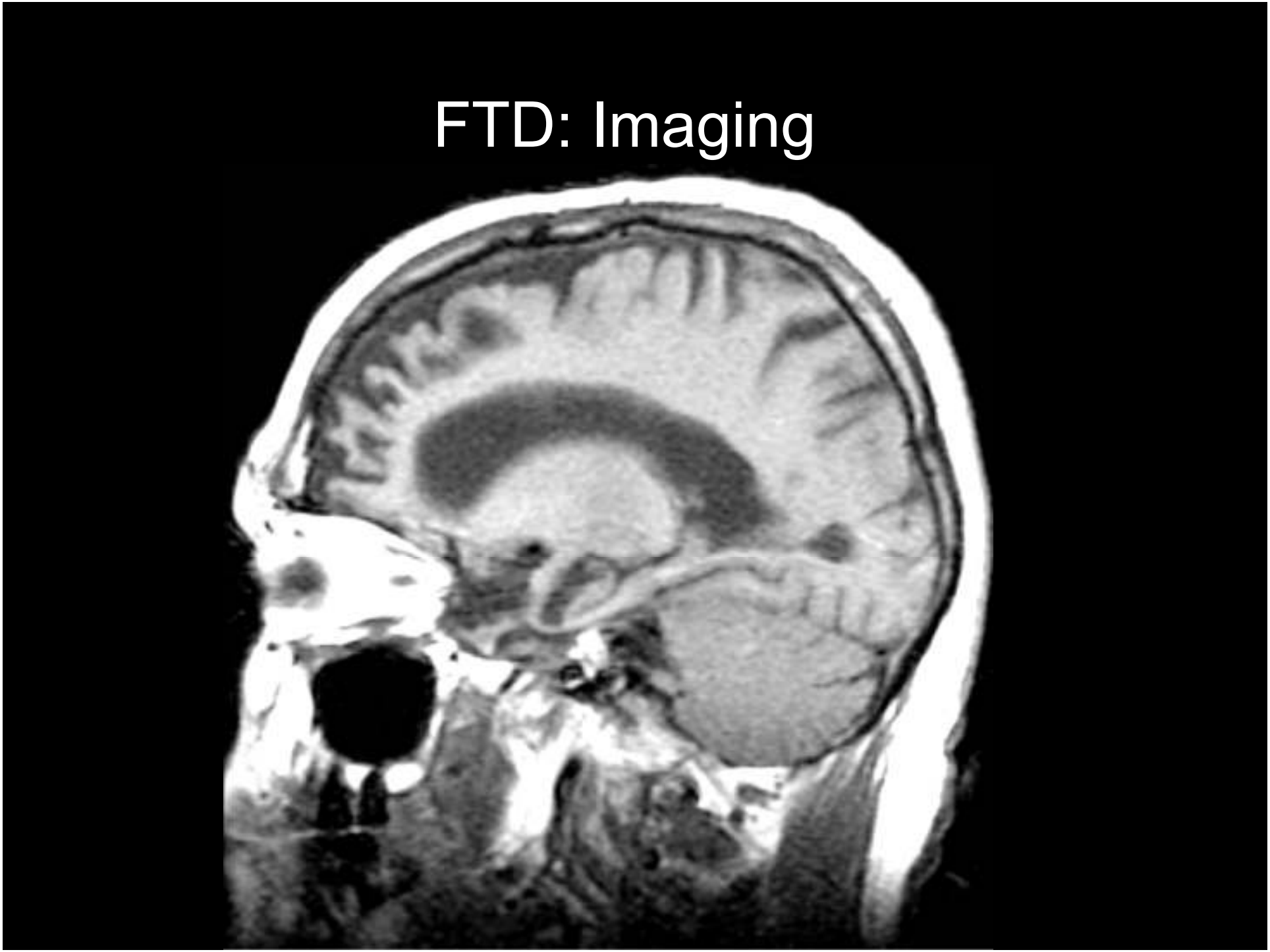


Dickerson BC et al, MGH 3T, 0.4x0.4x0.8mm

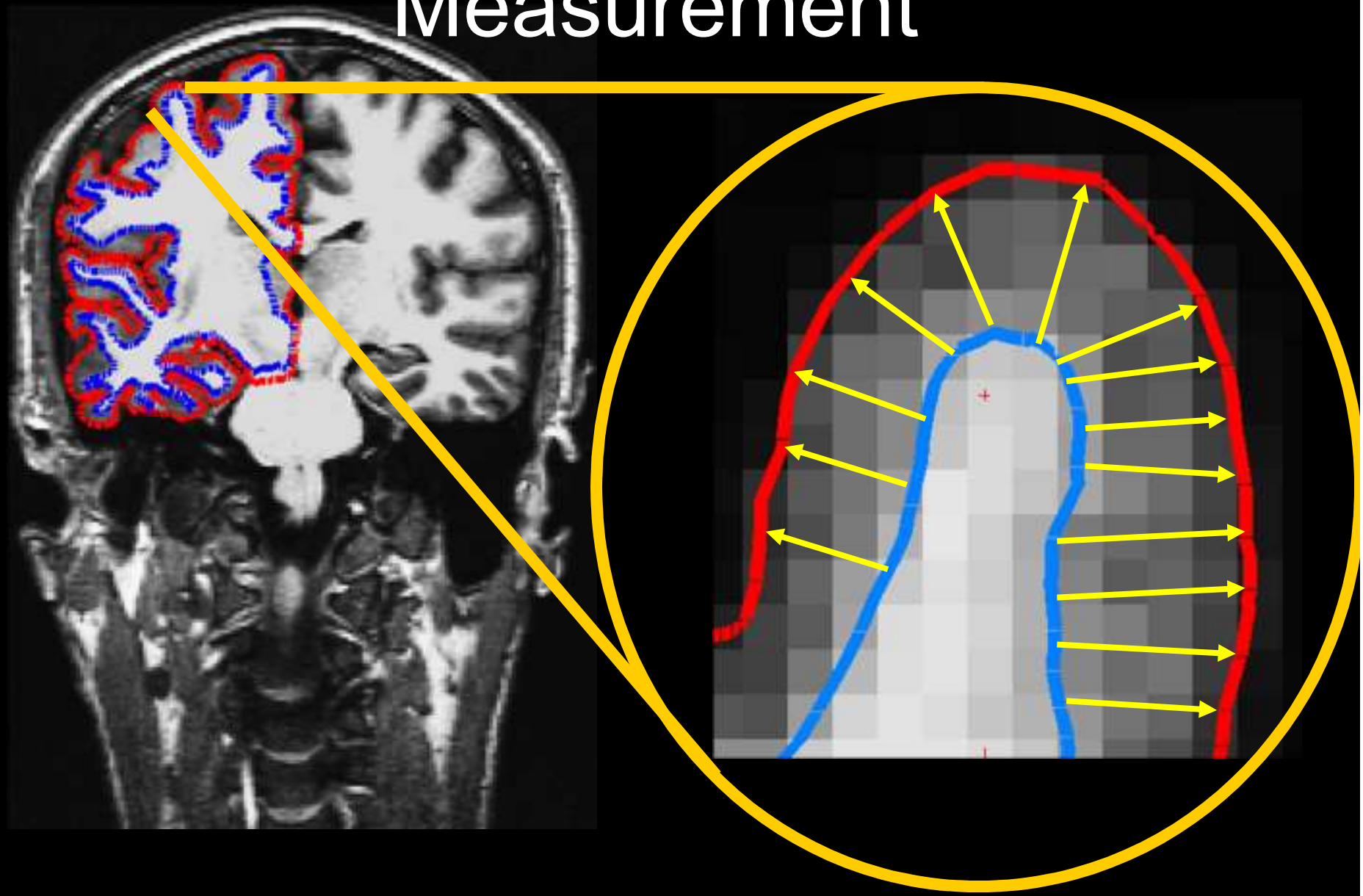
Patient with temporal lobe shrinkage (atrophy)



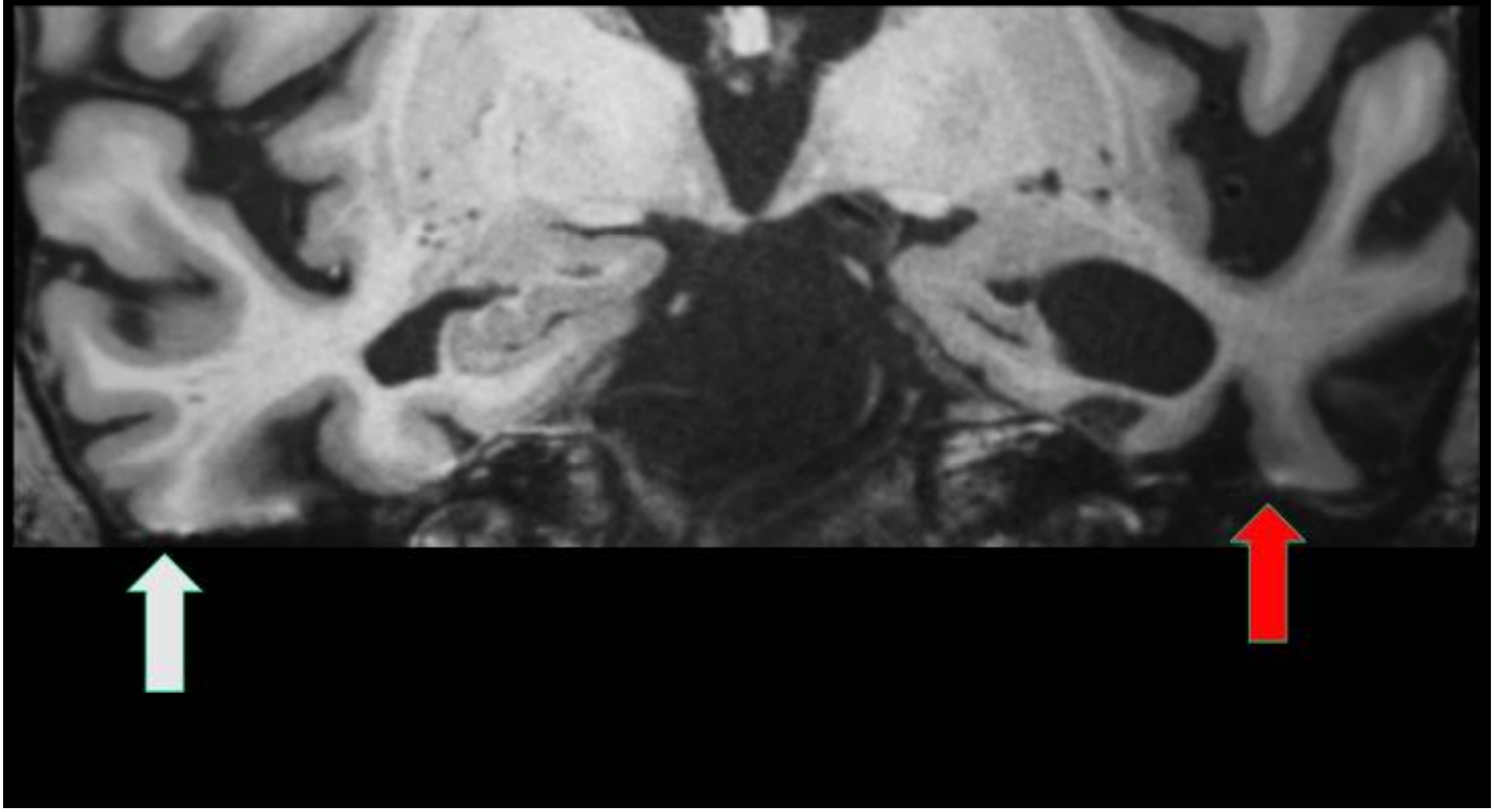
FTD: Imaging



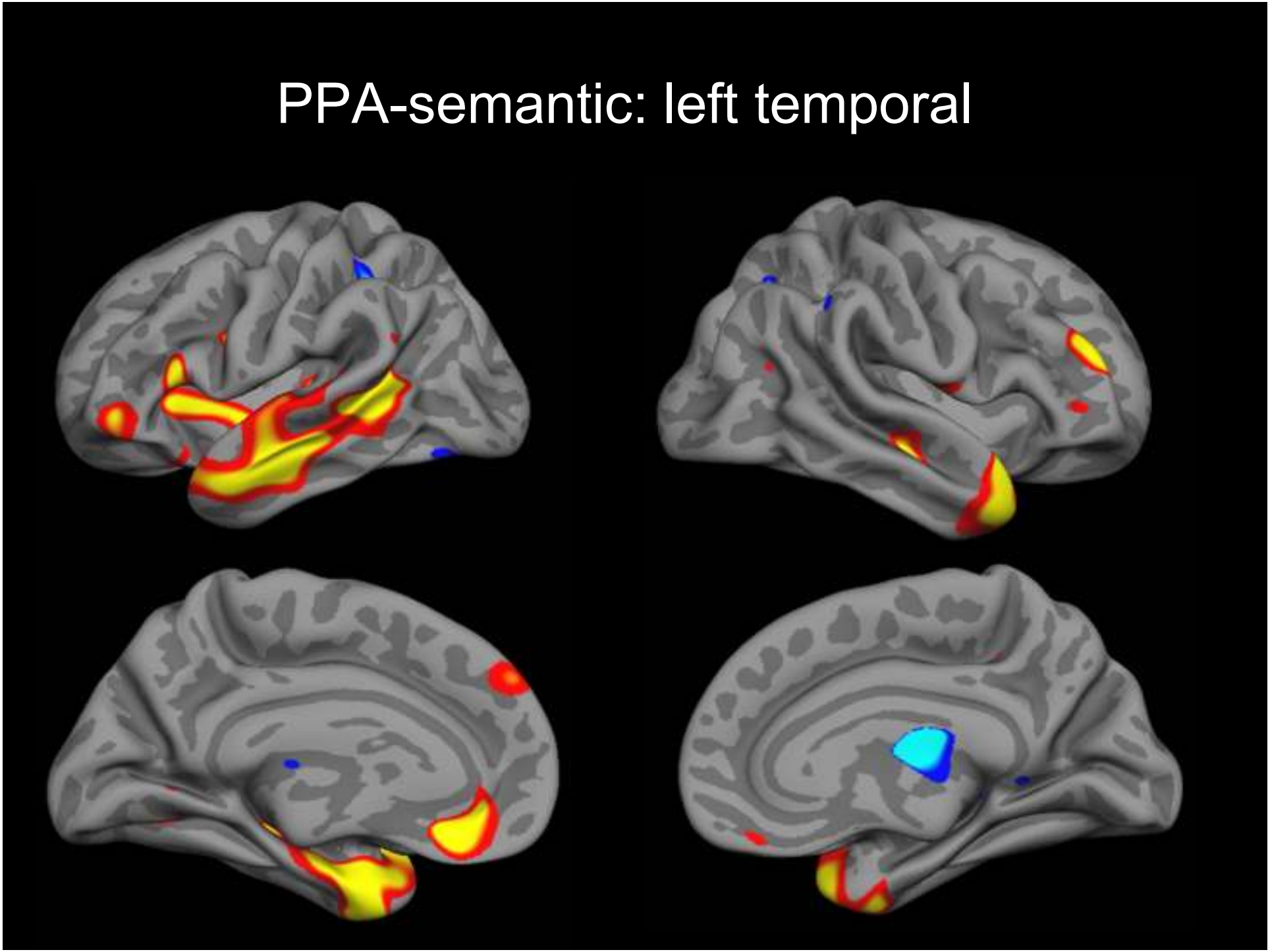
Cortical Thickness Measurement

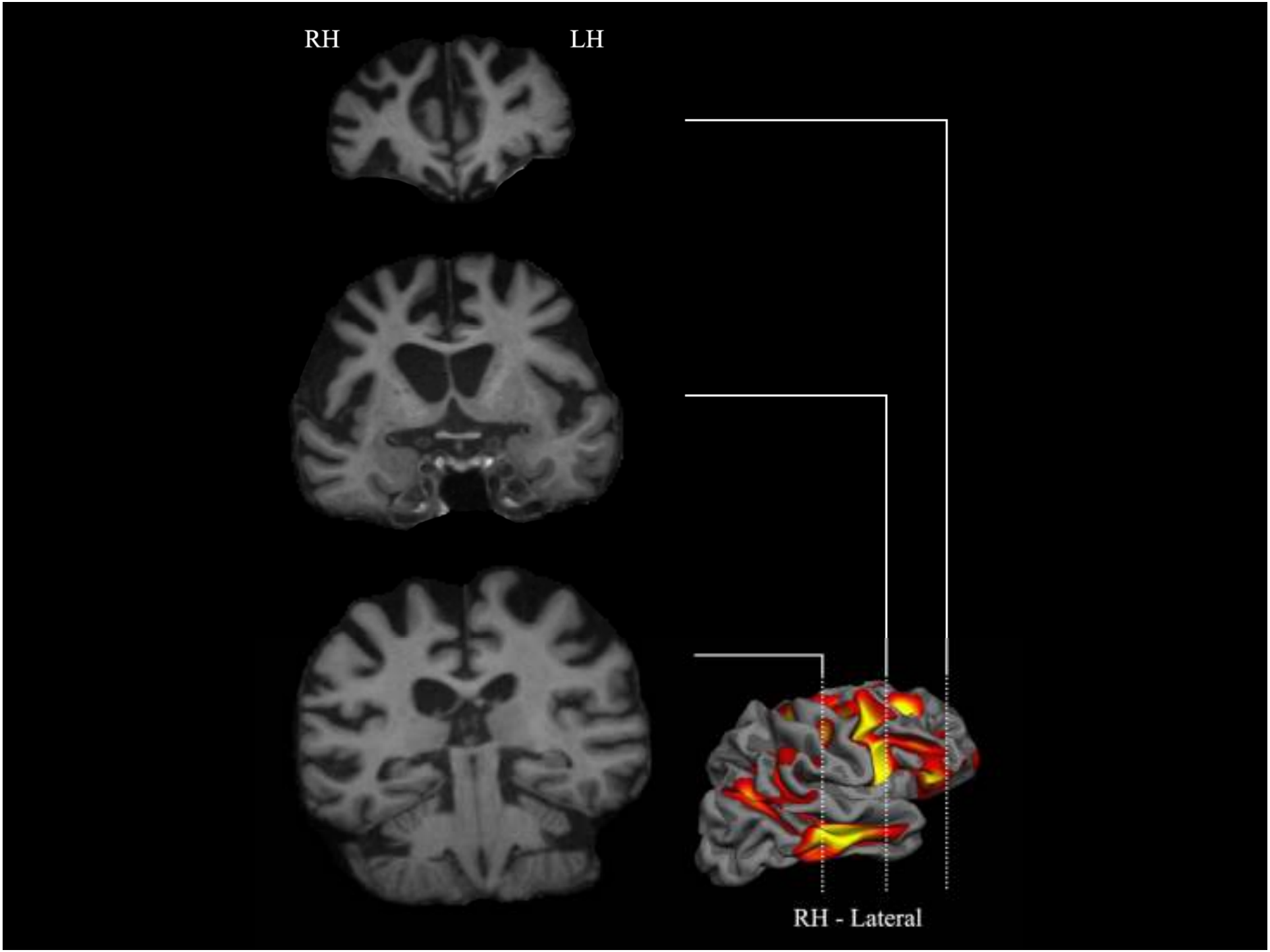


Patient with temporal lobe shrinkage (atrophy)

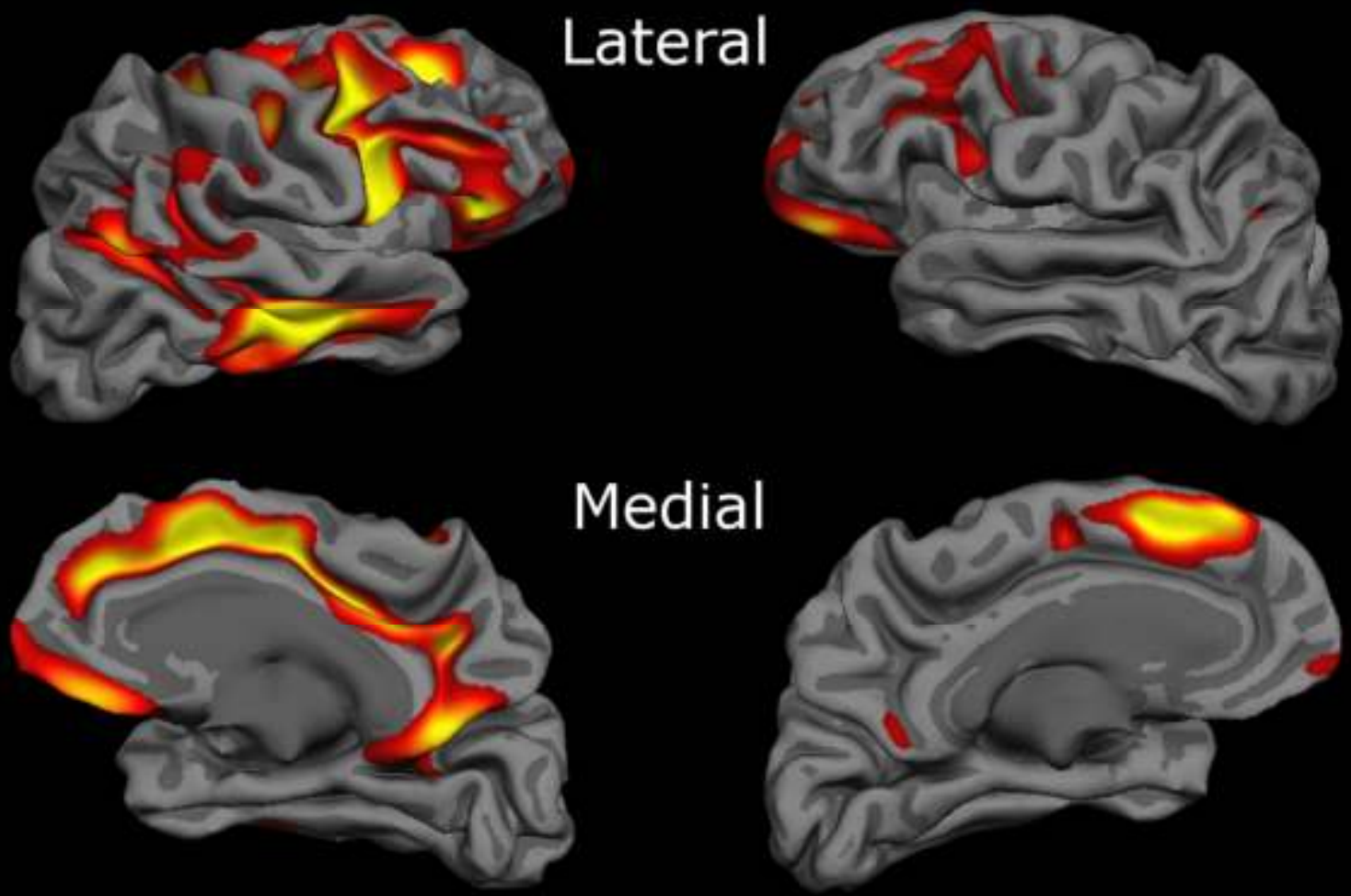


PPA-semantic: left temporal

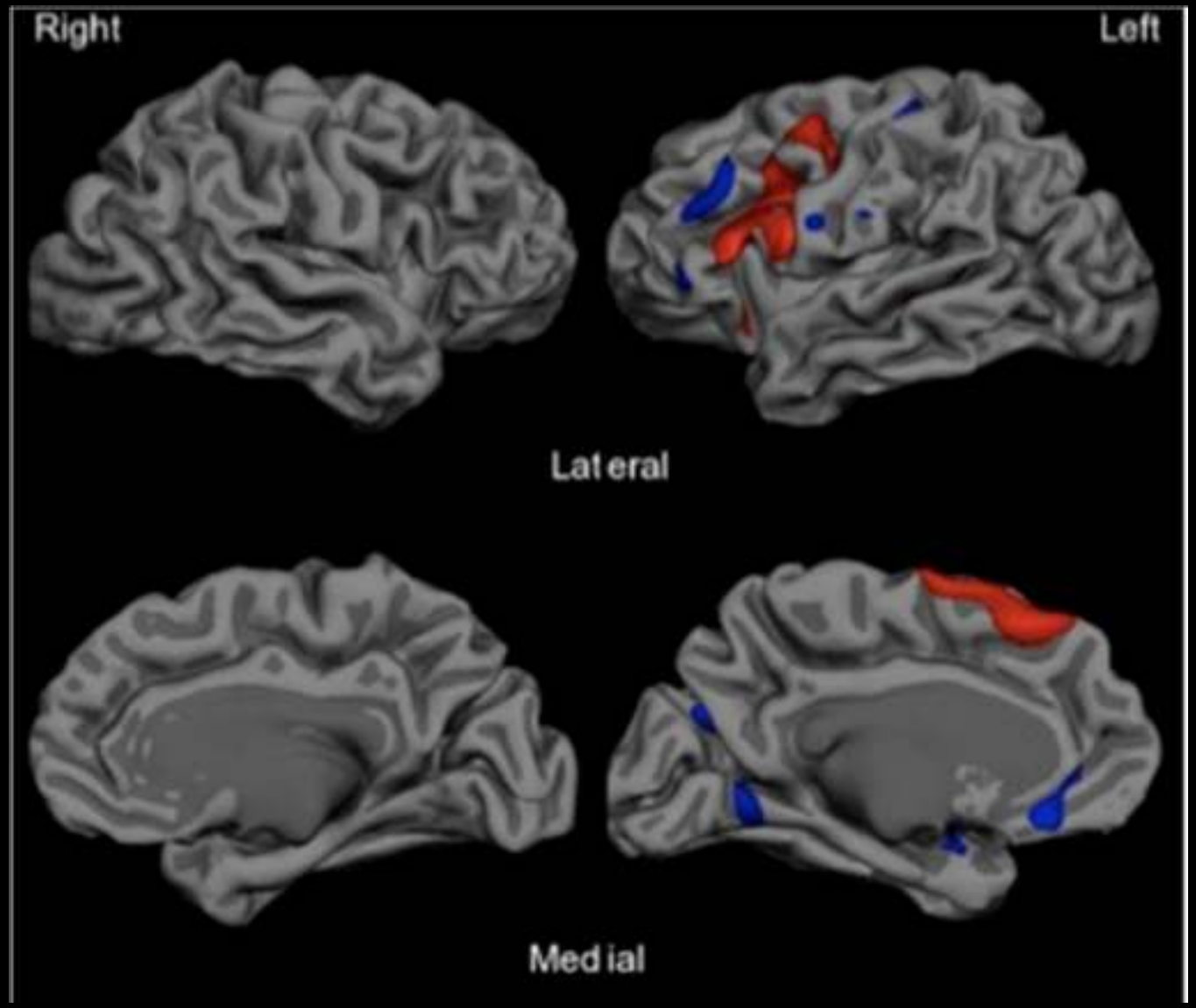



RH
LH
RH - Lateral

Behavioral variant: right frontal and temporal

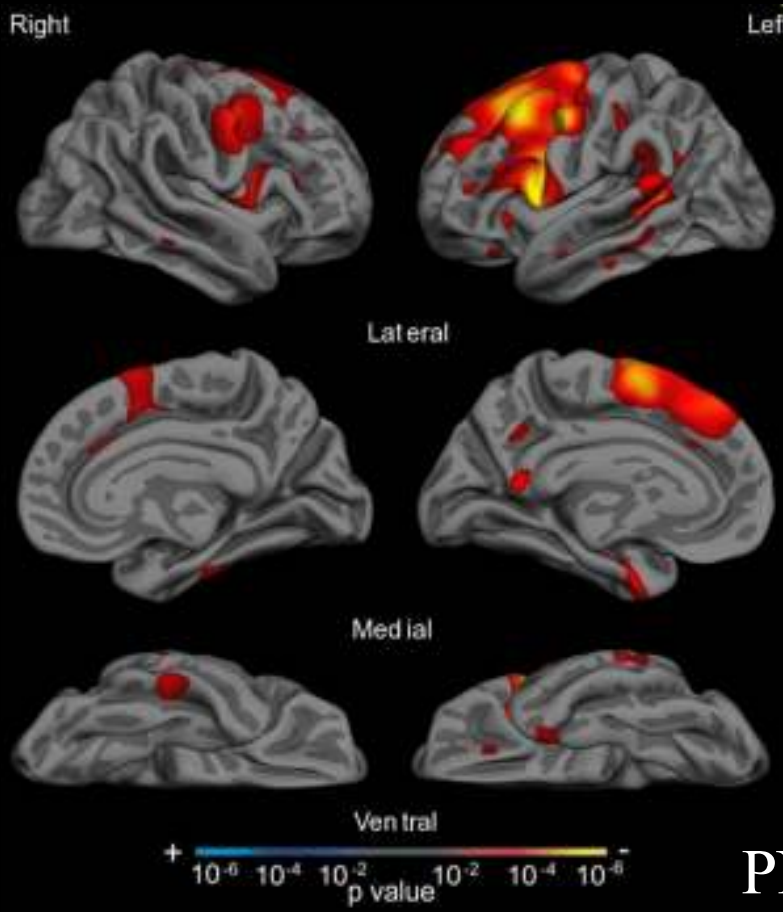


PPA-Non-fluent: Left frontal



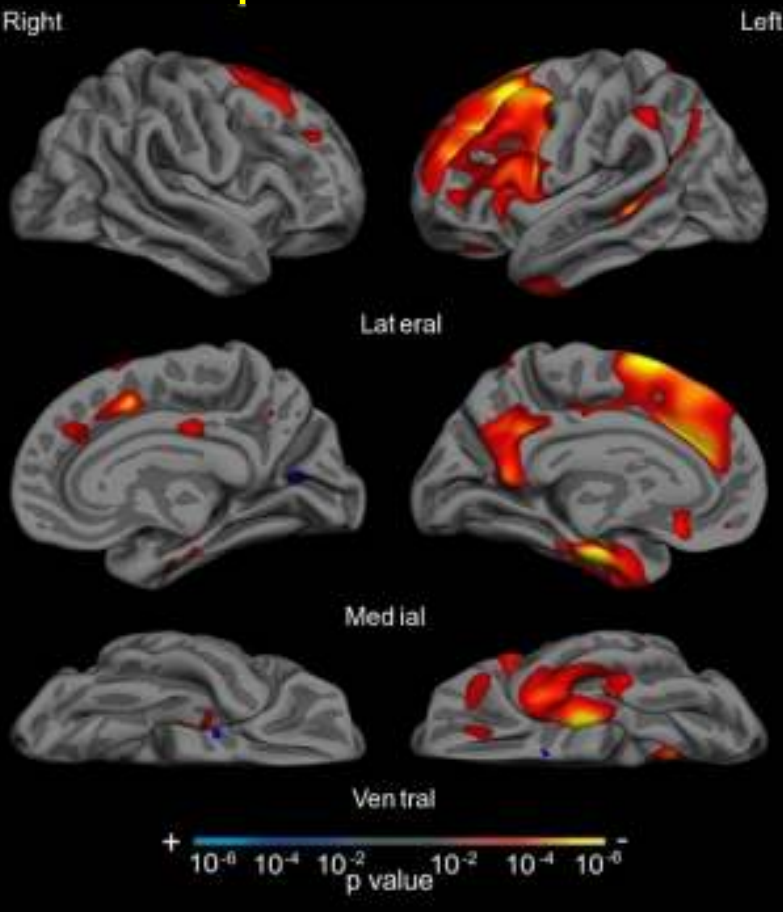
PPA subtypes:

Consistency across samples



MGH

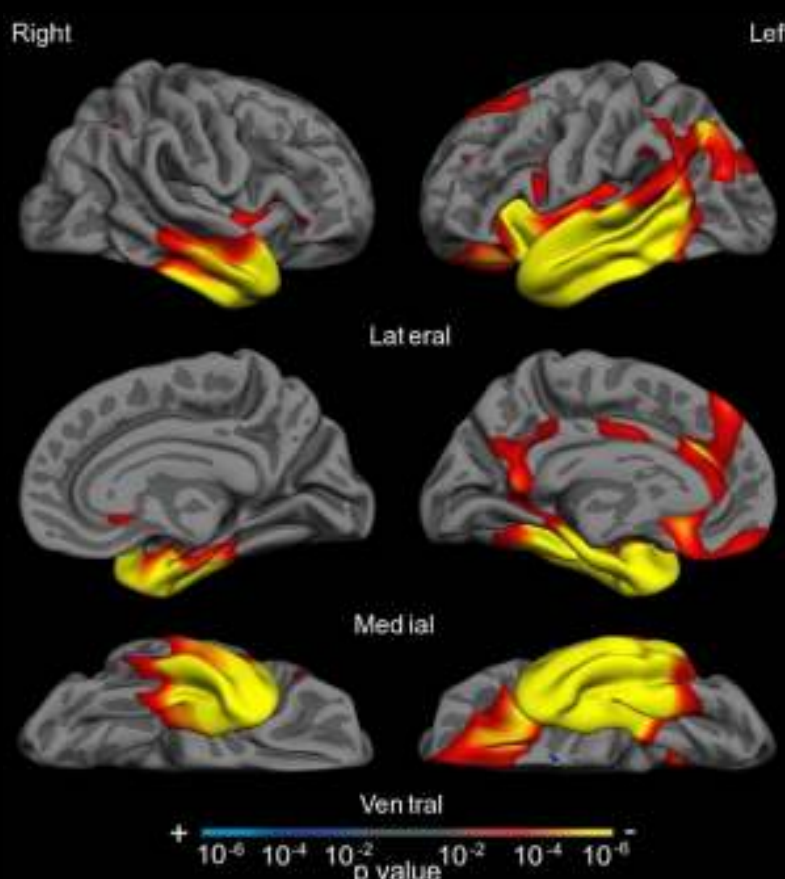
PNFA/
Nonfluent/
Agrammatic



Northwestern

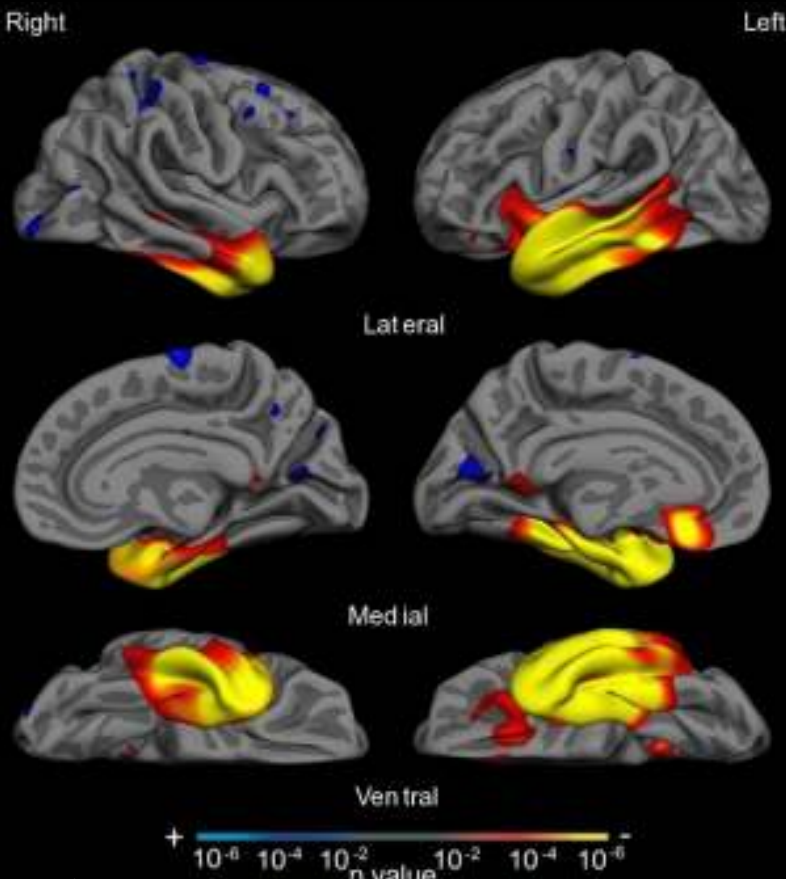
PPA subtypes:

Consistency across samples



MGH

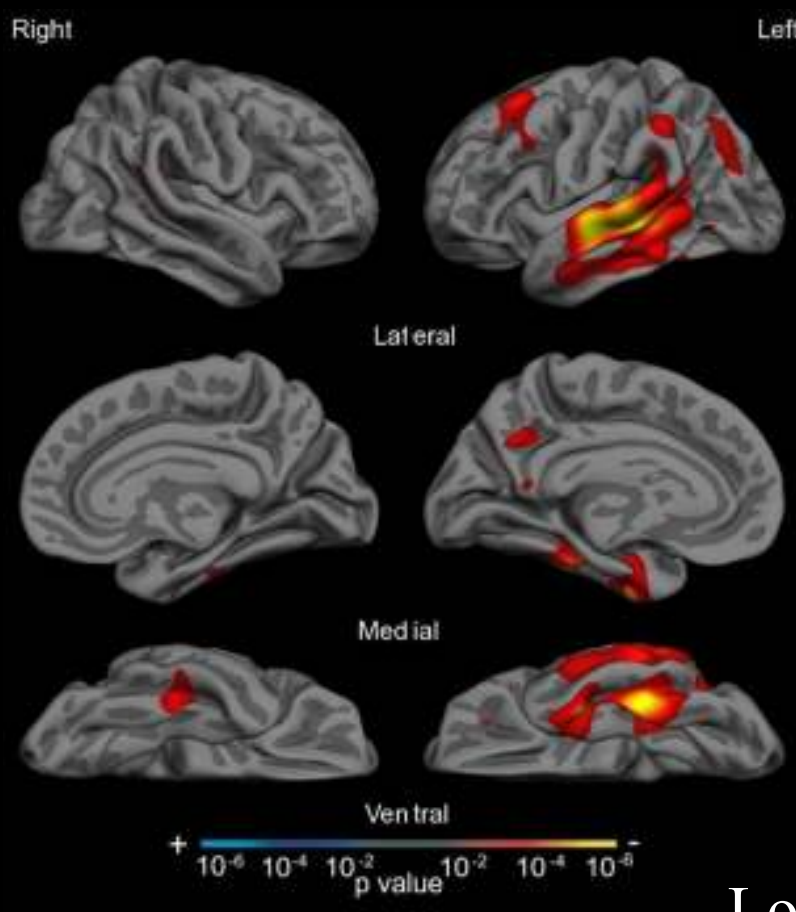
Semantic



Northwestern

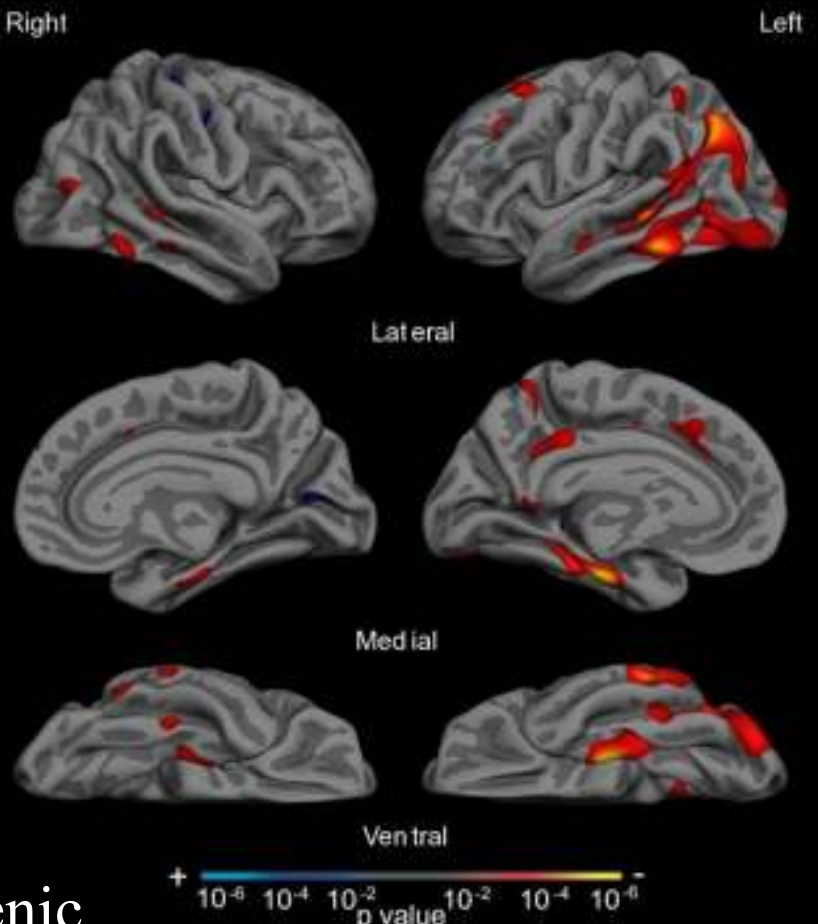
PPA subtypes:

Consistency across samples



MGH

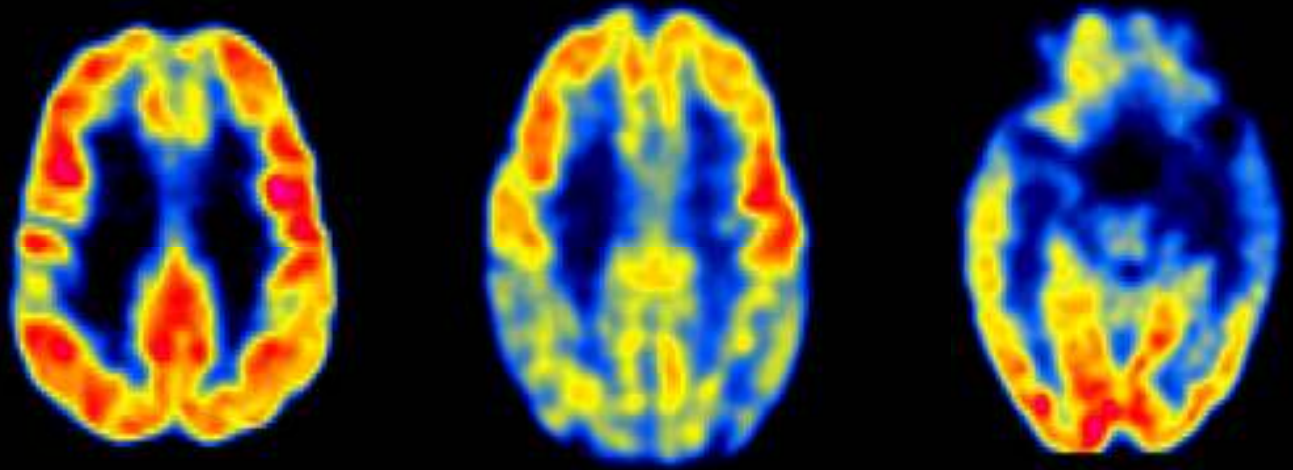
Logopenic



Northwestern

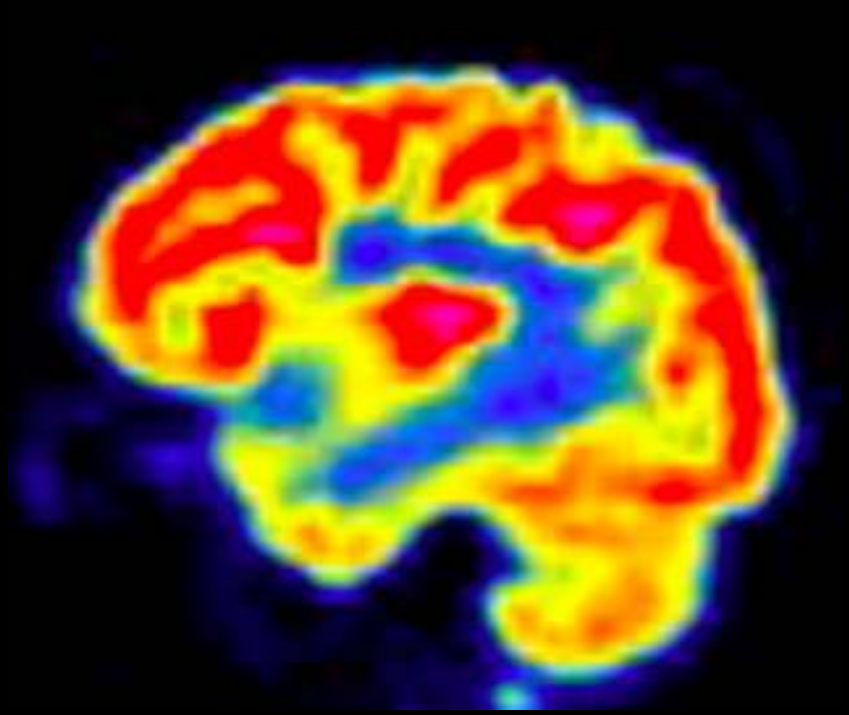
FDG-PET: glucose metabolism

- major use in clinical dementia:
  AD vs. FTD

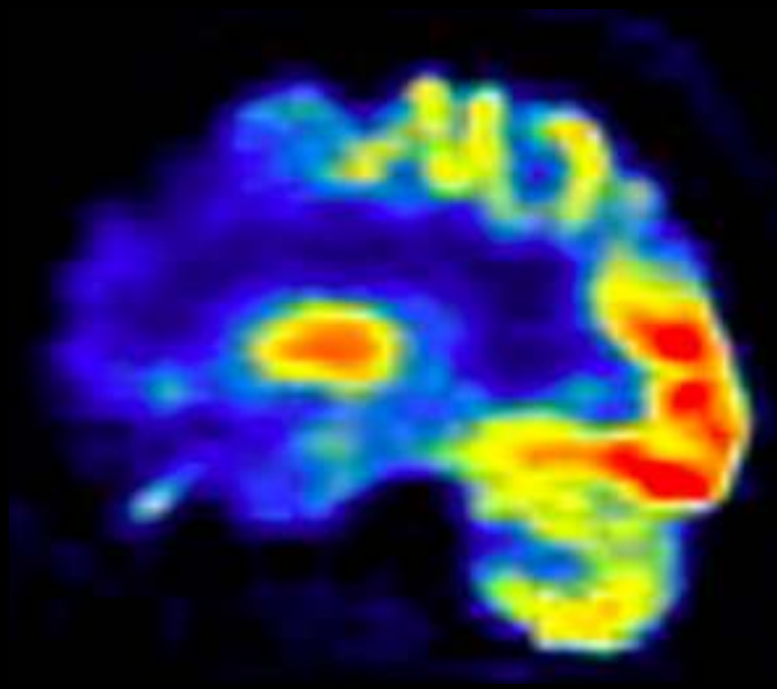


Normal Aging Alzheimer's FTD

PET scans

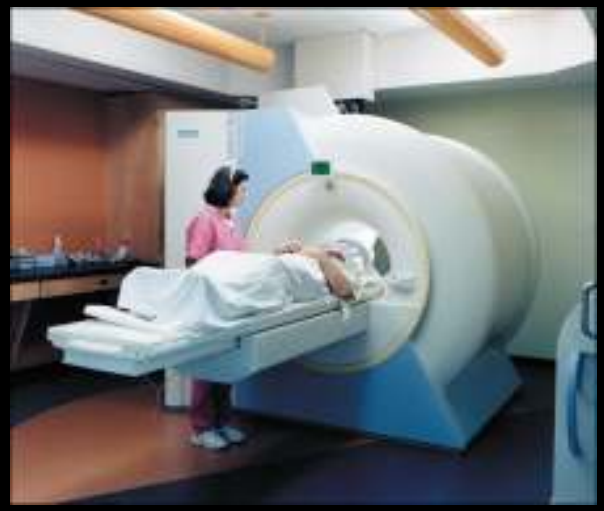


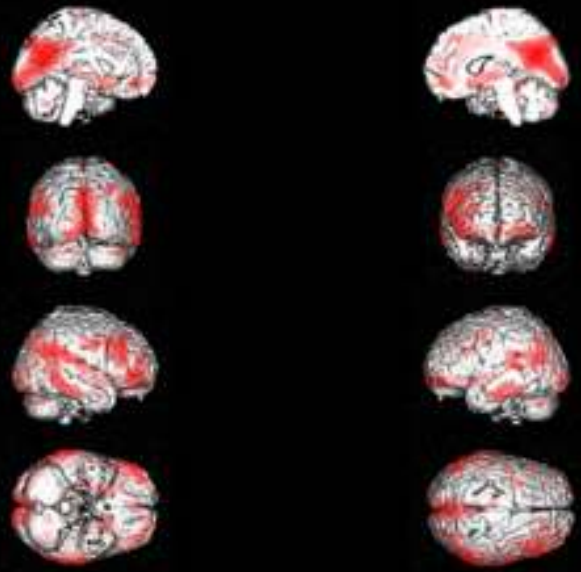
Mild

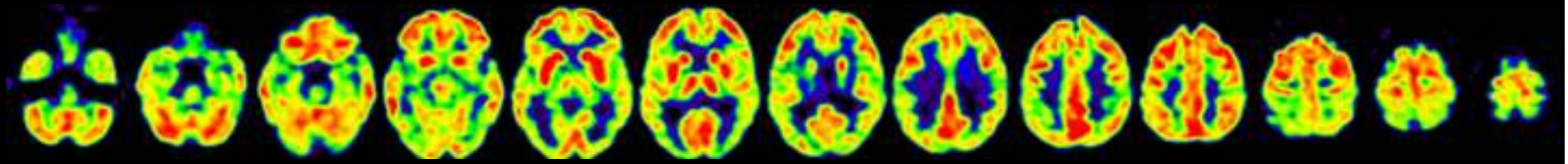


Severe

Combined MR-PET







First dementia patient scanned on this system, the first of its type in the world

Imaging and other biomarkers

- Earlier diagnosis
- More confident diagnosis
- Can be used as “inclusion criteria” for trials

- Prediction

- Monitoring amount of change over time
- Can be used as “outcome measures” in trials

- Need to compare MRI and PET to see whether the are redundant, complementary, etc

Alzheimer's disease neuroimaging initiative

- 60 centers in U.S.
- 200 healthy older adults, 400 people with MCI, 200 people with Alzheimer's dementia
- MRI, PET, spinal fluid, cognitive testing
- 3 year study
- Recently funded for an additional 5 years

- Very valuable information about progression over time and about biomarkers being used by many pharmaceutical companies to plan trials

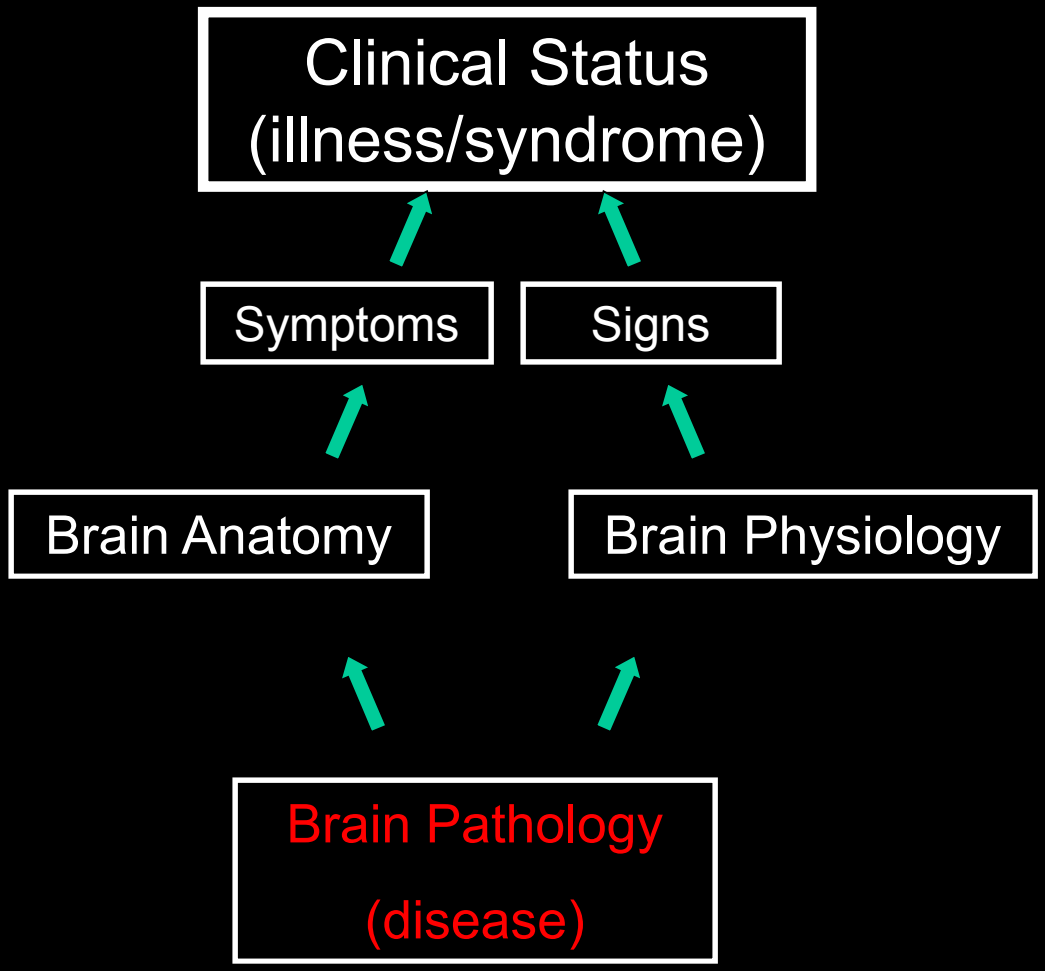
- ADNIs in Europe, Japan, Australia, other countries

Neuroimaging Initiative in Frontotemporal Degeneration

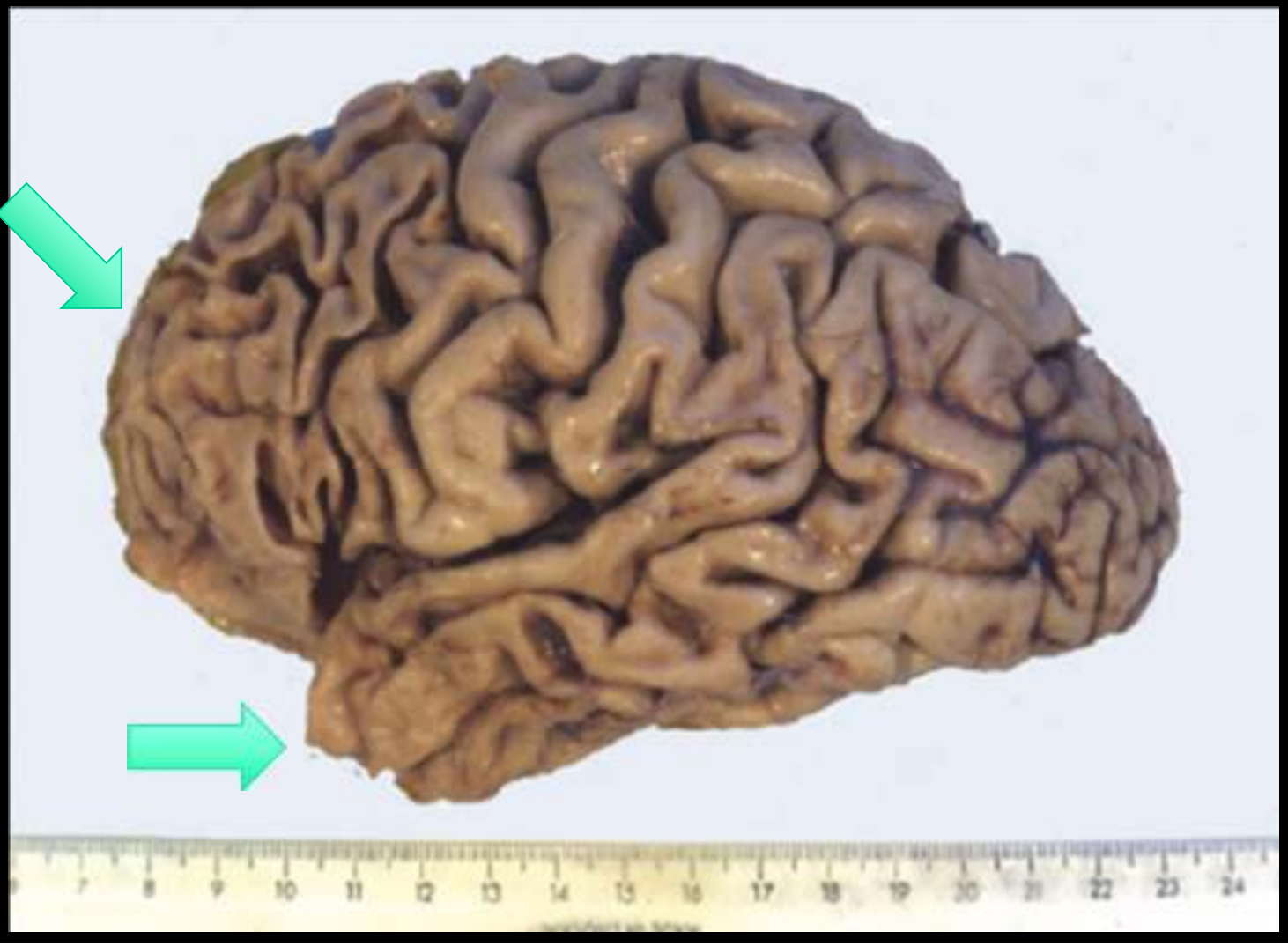
- 3 centers in U.S. (UCSF, Mayo, MGH/Harvard)
- 75 healthy older adults, 120 people with various forms of FTD
- MRI, PET, spinal fluid, cognitive testing
- 2 year study
- In discussion with federal government and other centers to supplement study with additional centers

- Will likely provide similarly valuable information to that of ADNI

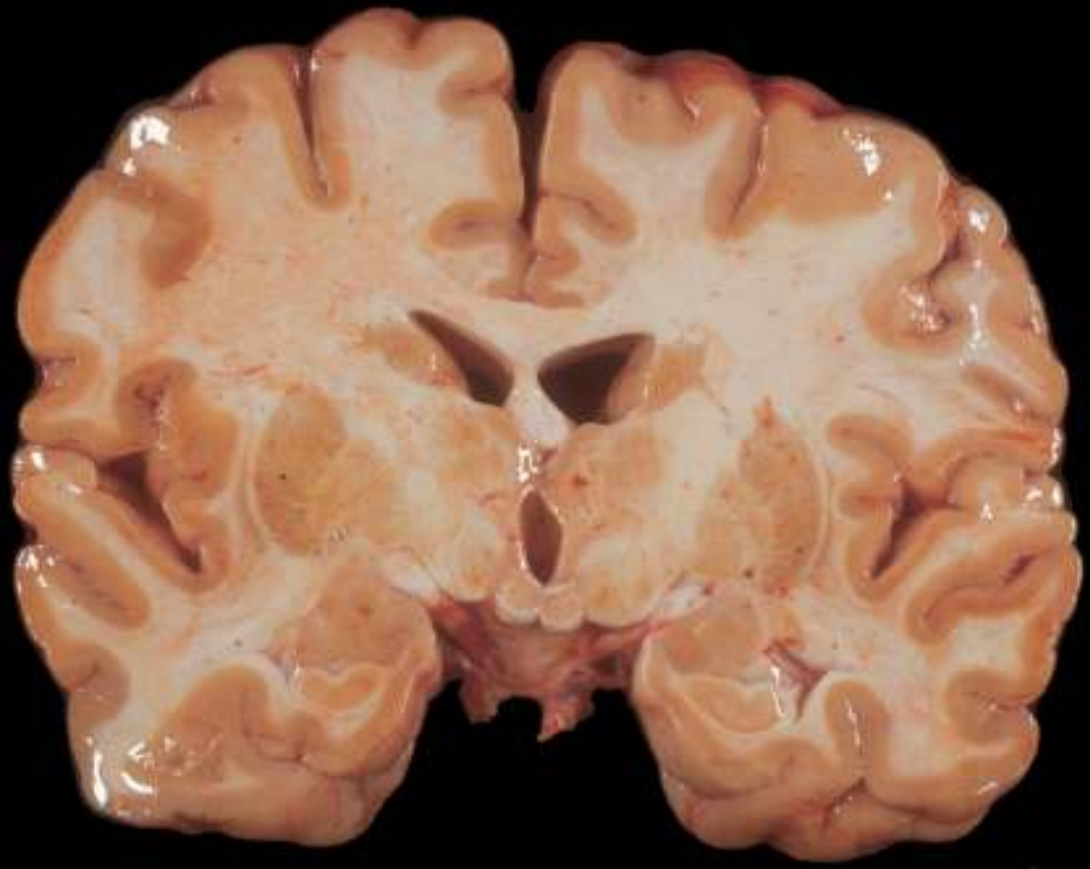
Understanding FTD



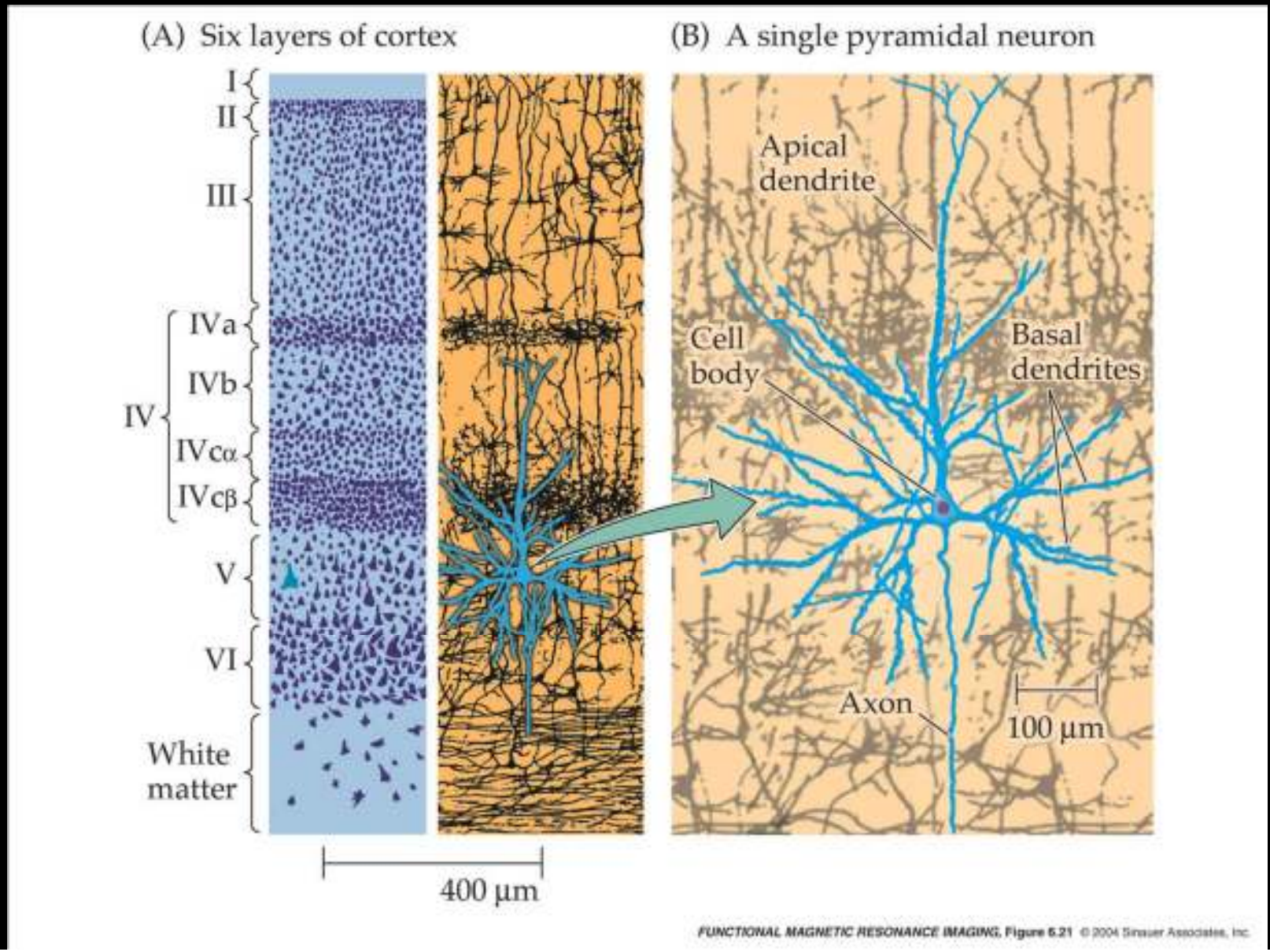
Frontotemporal dementia



Microscopic investigation



Cerebral cortex

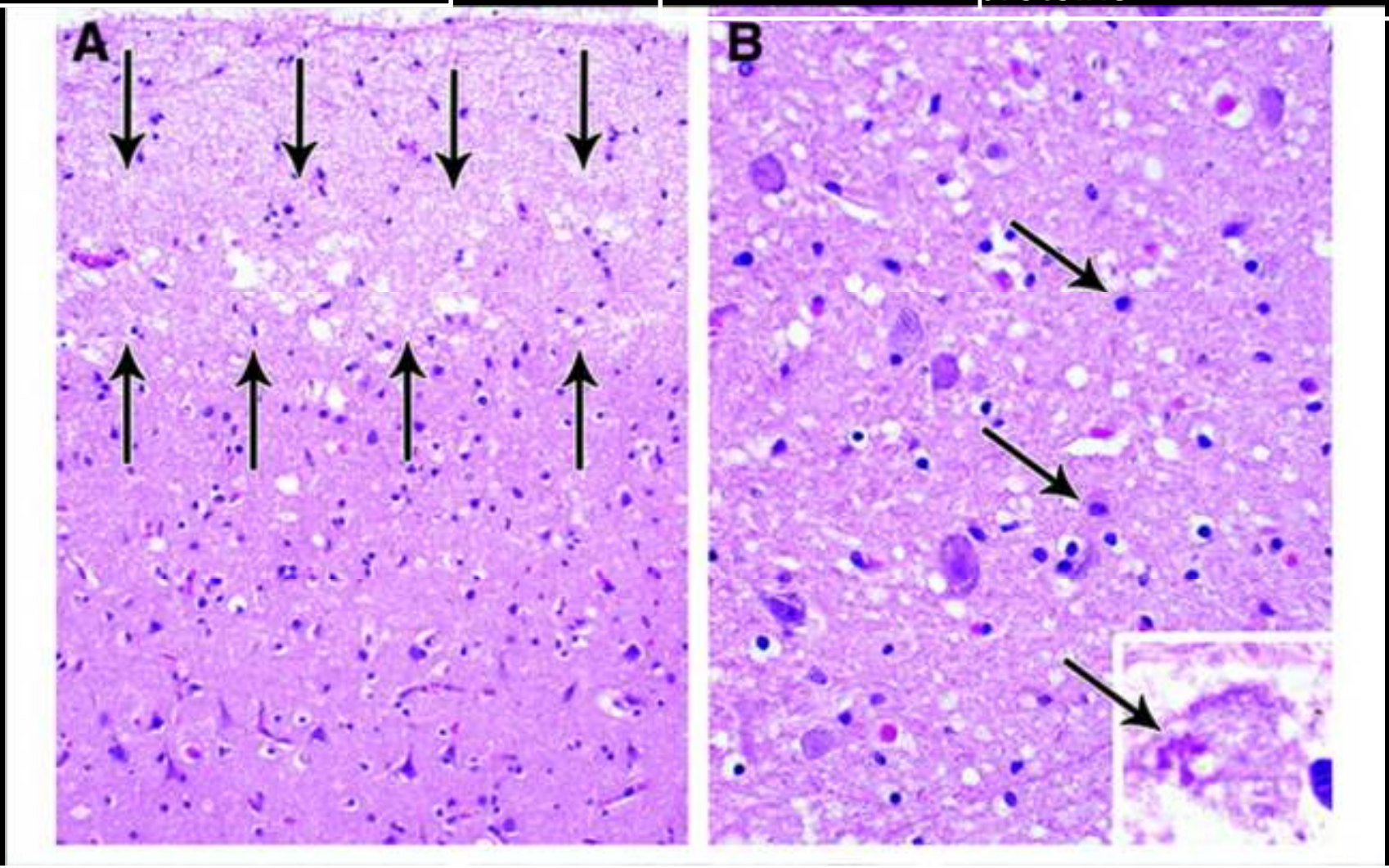


FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 6.21 © 2004 Sinauer Associates, Inc.

Neuropathology

Loss of brain cells & conections

Accumulation of abnormal forms of proteins



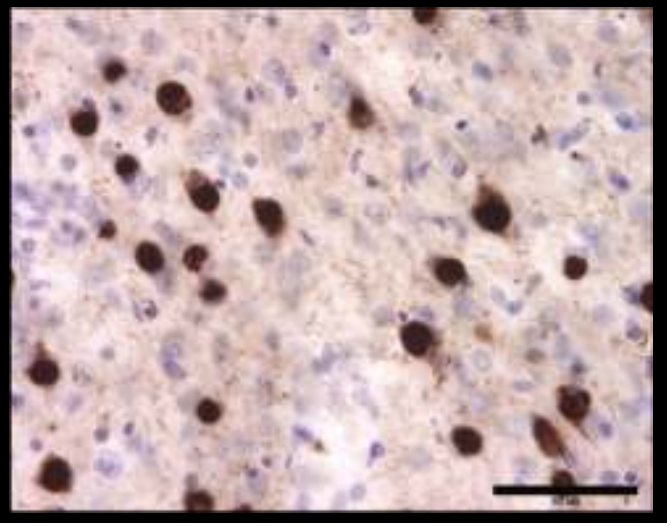
FTD: Pathology

- Where
  - Frontotemporal cortex
  - Subcortical nuclei and brainstem
- What
  - Major types of proteins in FTD
    - Tau
      - Pick body (Pick's disease)
      - Note that tau is abnormal in a number of diseases, including AD, FTD, CBD, PSP, and others; different types of abnormalities are present
    - TDP-43 (2006)
    - FUS (2009)
    - Other
  - AD (amyloid), PD/DLB (synuclein)

FTD: Pathology

- These are normal proteins in brain cells
  - perform important functions
- They become twisted and tangled
- Clump within cells, clogging machinery, damaging cell
- For some reason, this only occurs in particular types of cells in certain brain regions

Sometimes, this is because of a single genetic mutation (1998; 2006); most of the time, it's not



Surrogate measures of pathology in living people

- Goal # 1: Rule out AD pathology
  - Spinal fluid (amyloid and tau)
  - (Amyloid PET imaging)

- Goal #2: Detect FTD pathology
  - Working on tau PET imaging
  - Spinal fluid for measures of tau, TDP-43, etc
  - Blood?

FTD: Genetics

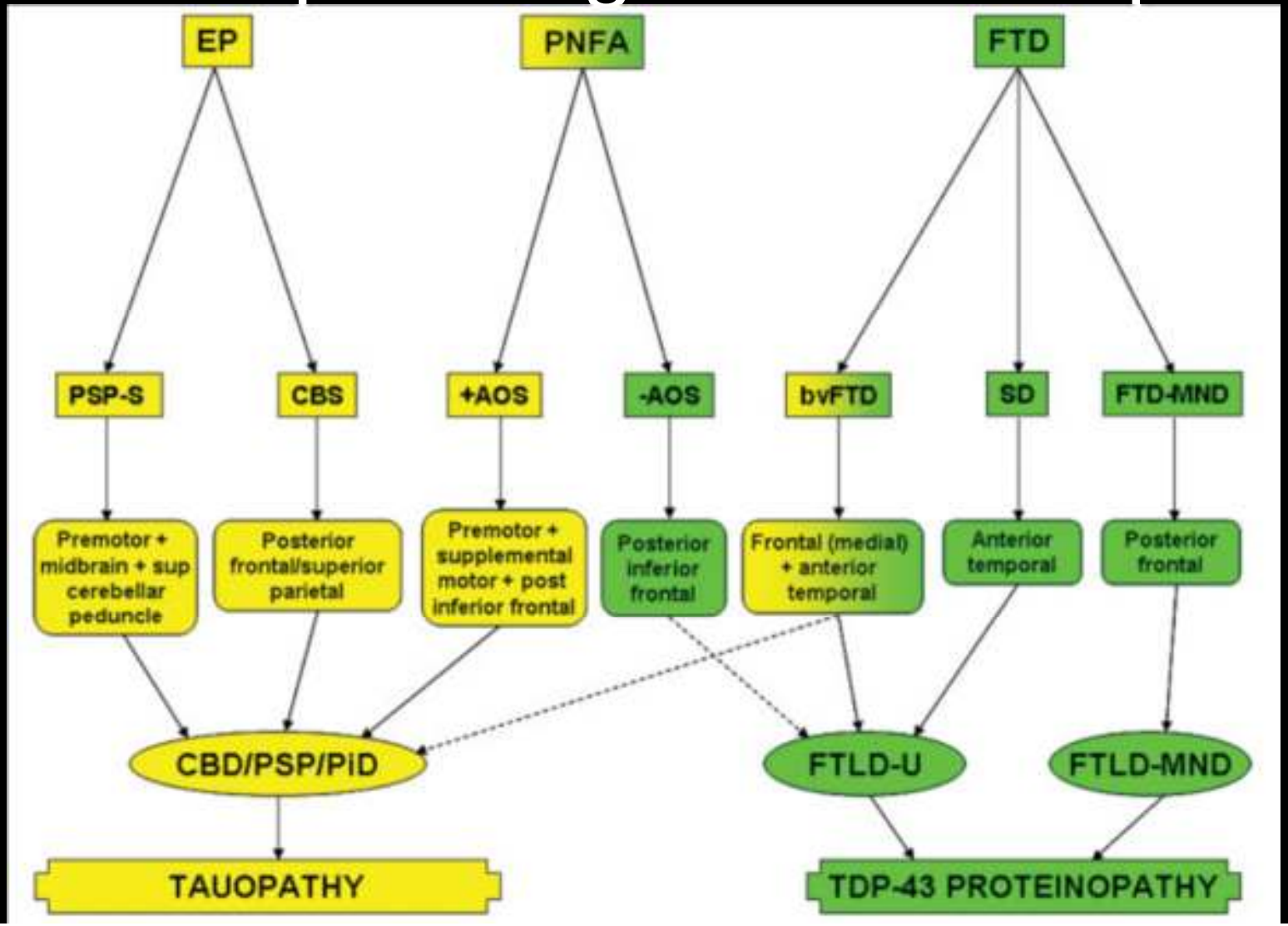
- Up to 1/3 or more of FTLD cases may be inherited
  - Tau/MAPT mutations
    - Now known to be linked to other clinical diagnoses, including classic FTD, MND, CBD, PSP
  - Progranulin (PRGN)
    - Now known to be linked to other clinical diagnoses
  - FUS
    - Linked to MND
  - Still more to be found

FTD: Links between neurodegenerative diseases

- Frontotemporal dementia
  - Tau, TDP-43

- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- (Alzheimer's disease)
- (Parkinson's disease)
- Dementia with Lewy bodies (DLB)
- ALS (Lou Gehrig's disease)
- Huntington's disease
- Many others

Complex probabilistic clinicopathologic relationships



FTD: Very active research

- Internationally cooperative groups of clinicians, scientists, others
- Governmental organizations: more responsive
- Pharmaceutical companies: more interested

- Moving toward more effective treatment
  - Genetics & pathology: molecules & animal models
  - Imaging/blood/CSF markers: Earlier & more accurate diagnosis, monitoring
  - Clinical: Better diagnosis, monitoring
  - Social: Better resources, support, education
  - Infrastructure for clinical trials
    - Current trial of memantine (Namenda)

Frontotemporal Dementia: The Next Therapeutic Frontier

Friday, March 25th and Saturday, March 26th 2011

Cleveland Clinic Lou Ruvo Center for Brain Health • Las Vegas, NV

An academic-industry conference focused on drug development for FTD and related disorders associated with tau or TDP-43 pathology. Topics include:

- preclinical models relevant to FTD and roles in drug development
- orphan drug development and FTD
- novel collaborative mechanisms

MGH Frontotemporal Disorders Unit

- Our mission to provide clinical care
  - To provide comprehensive diagnostic evaluation of patients suspected of having frontotemporal dementia or related disorders, involving a multidisciplinary team of clinicians
  - To provide comprehensive treatment and continuity care with the goal of managing symptoms and maximizing overall function in daily life using a variety of approaches
  - To provide social support and assist in connecting patients and families with community resources
  - To provide genetic counseling for patients and families
  - To provide autopsy services for pathologic diagnosis

MGH Frontotemporal Disorders Unit

- Our Research Mission
  - To develop better methods for assessing the presence and severity of symptoms in daily life
  - To develop better instruments to objectively measure performance on tests of language, social and emotional behavior, and cognition
  - To enhance advanced imaging techniques for measuring brain structure and function

  - Improve accuracy of early diagnosis
  - Enable prediction of types and rates of progression
  - Monitor progression with an eye toward markers to measure effects of potential therapies
  - Identify rehabilitative strategies to try to improve daily function

MGH Frontotemporal Disorders Unit

- New programs
  - We have been getting more heavily involved in education and training

  - Fellowship training program
  - To train clinician-researchers as specialists in this field, or with specialized skills in the field
    - Speech pathology: Daisy Sapolsky
    - Neurology: Dr. Kimi Domoto-Reilly, Dr. Josh Shulman
    - Psychiatry: Dr. Stephane Poulin
    - Internal Medicine: Dr. Luce Pellerin
    - Psychology: Dr. Belen Pascual, Dr. Kristen Lindquist, Dr. Mimi Castelo

  - Neurology residents, Medical students, graduate students, undergraduates, high school students

Thanks to

MGH FTD Unit

Daisy Sapolsky, MS, CCC-SLP
Aly Negreira, BS
Mike Brickhouse, BS
Mark Hollenbeck, BS
Belen Pascual, PhD
Kimi Domoto-Reilly, MD
Scott McGinnis, MD
Kristen Lindquist, PhD
Diane Lucente
Ayana Cole

MGHFTDUnit@partners.org

Collaborators

David Caplan, MD, PhD
Brad Hyman, MD, PhD
John Growdon, MD
Deborah Blacker, MD
Bruce Fischl, PhD
Matthew Frosch, MD, PhD
Janet Sherman, PhD
Mimi Castelo, PhD
Keith Johnson, MD
Lisa Feldman-Barrett, PhD
Kalo Tanev, MD
Kirk Daffner, MD
Mick Alexander, MD
Sandy Weintraub, PhD
Marsel Mesulam, MD

Support

NIA: R01-AG29411 (BCD), R21-AG029840 (BCD)
Alzheimer's Association (BCD),
NIA: P01-AG04953, NCRR: P41-RR14075
Mental Illness and Neuroscience Discovery (MIND) Institute

bradd@nmr.mgh.harvard.edu http://www.dickersonlab.org