Neuroimaging for non-imagers

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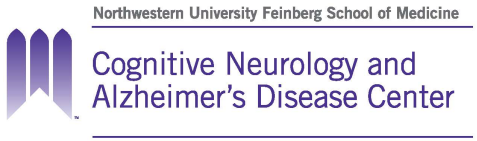
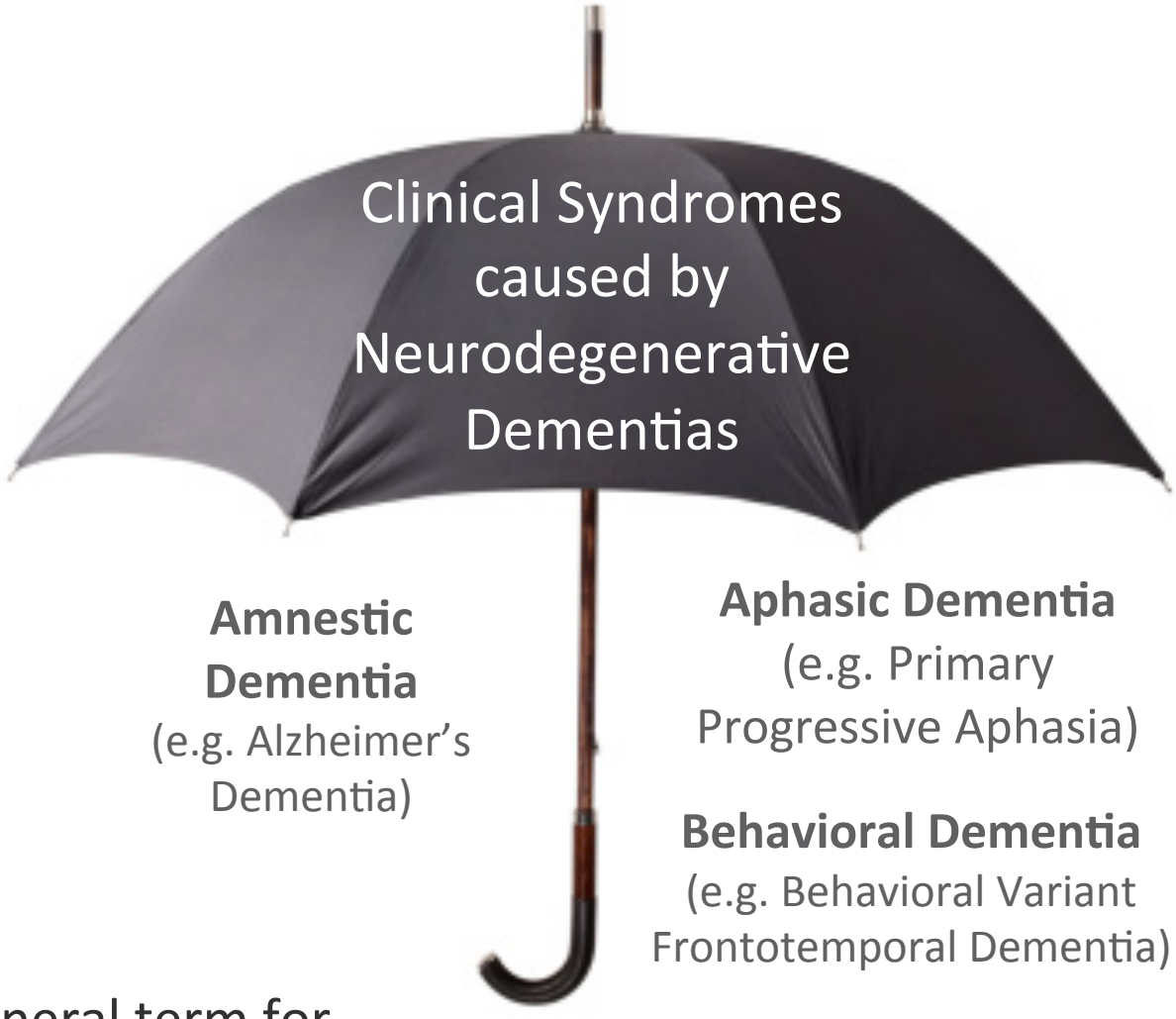


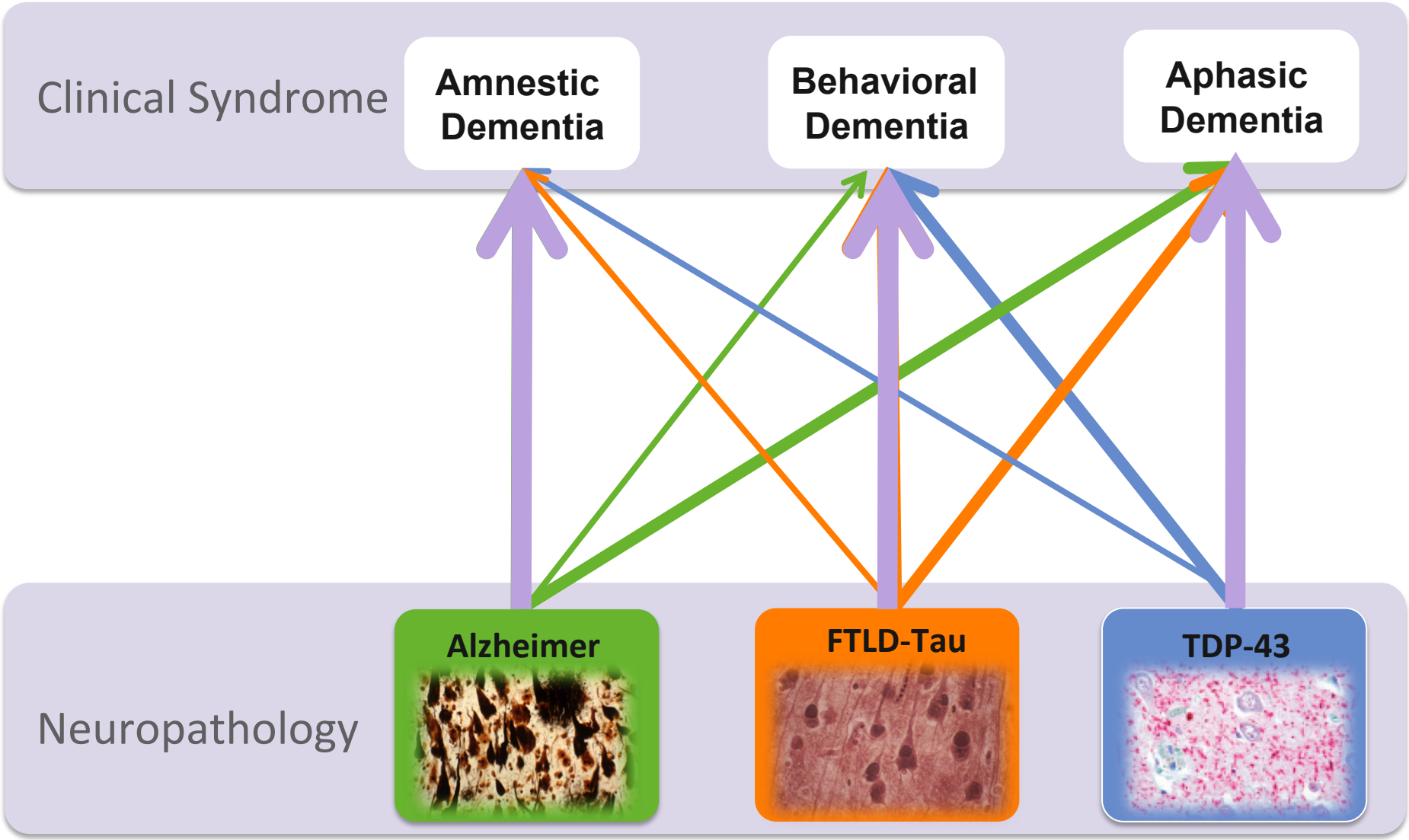
Dementia phenotypes



Dementia: A general term for…

1) The loss of memory or other thinking skills
2) Significantly interferes with daily life (work, school, family)

Heterogeneity of Dementia



Pathology Pictures courtesy of E.Bigio & Hatanpaa, K 2008 J Neuropath

Brain Basics: White versus Gray Matter

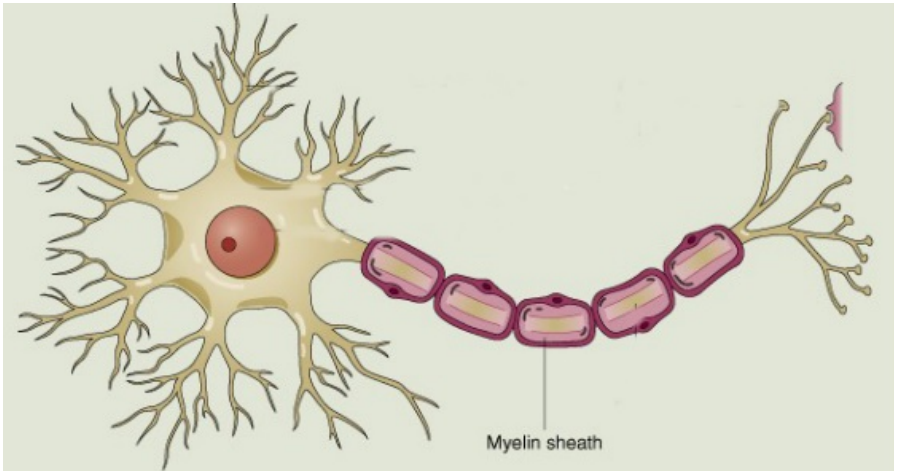
There are a hundred billion **neurons** (cells) in the human brain, all of which are in use.

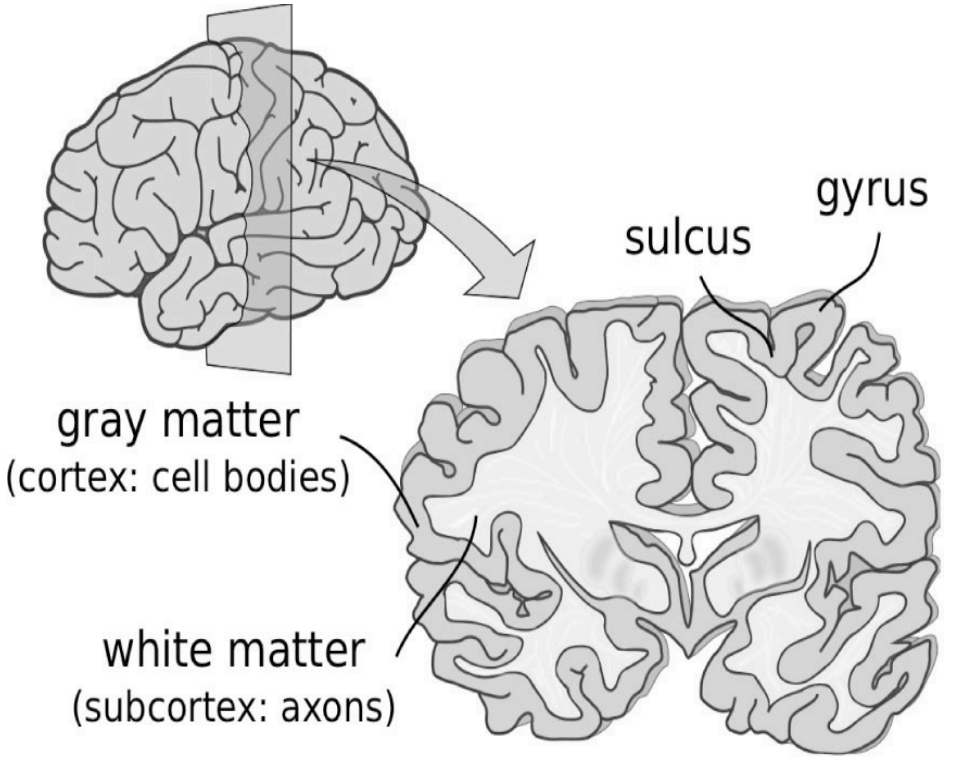
Each neuron communicates with many other neurons to form circuits and share information.

The myelinated axons of neurons are able to transfer information more rapidly

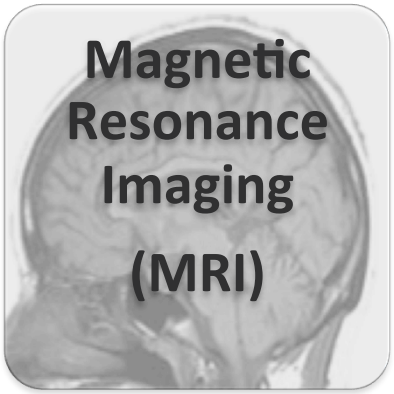
As a result of myelination, the large axon fiber tracts in the brain appear white, and are known as **white matter**

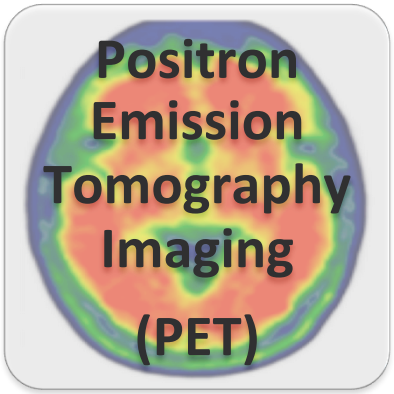
Just as highways connect cities filled with people, white matter tracts connect regions of cortex filled with neuronal cell bodies, known as **gray matter**





Neuroimaging Techniques

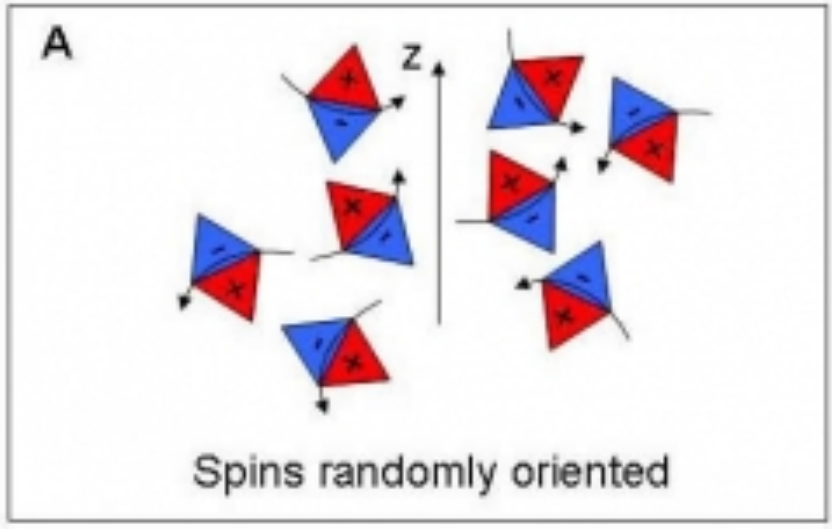




- What does it do?
- How does it do this?
- Pros/Cons:
- How is this method used in dementia research or in the clinic?

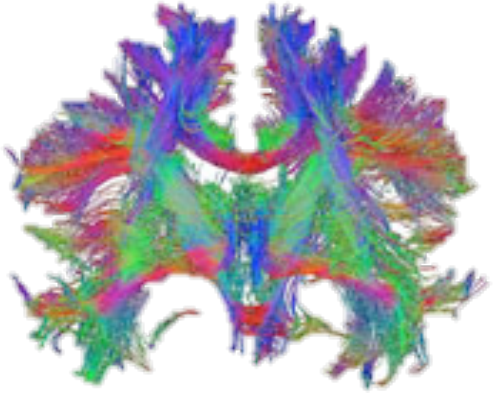
Magnetic Resonance Imaging (MRI)

- What does it do?
  - Technique that uses a magnets, radio waves, and a computer to create 3D images of organs and structures inside the body
- How does it do this?
  - **Magnetic Field:** Orients most of the protons (Hydrogen) in water in the same direction
  - **Radio-frequency pulse:** Flips the orientation of the protons momentarily
  - **Relaxation:** of protons to their prior orientation which emits a radiofrequency signal that is measured by sensors to create images
- Pros/Cons:
  - no radiation (noninvasive), relatively good resolution, relatively fast
  - expensive (research rate: $500+, clinical $$$+, machine $1.5 million+), exclusion criteria (e.g., pacemakers) may be problematic for elderly

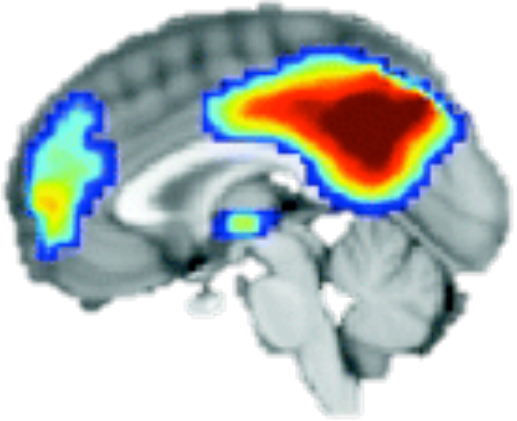


MRI Imaging Modalities

Brain structure

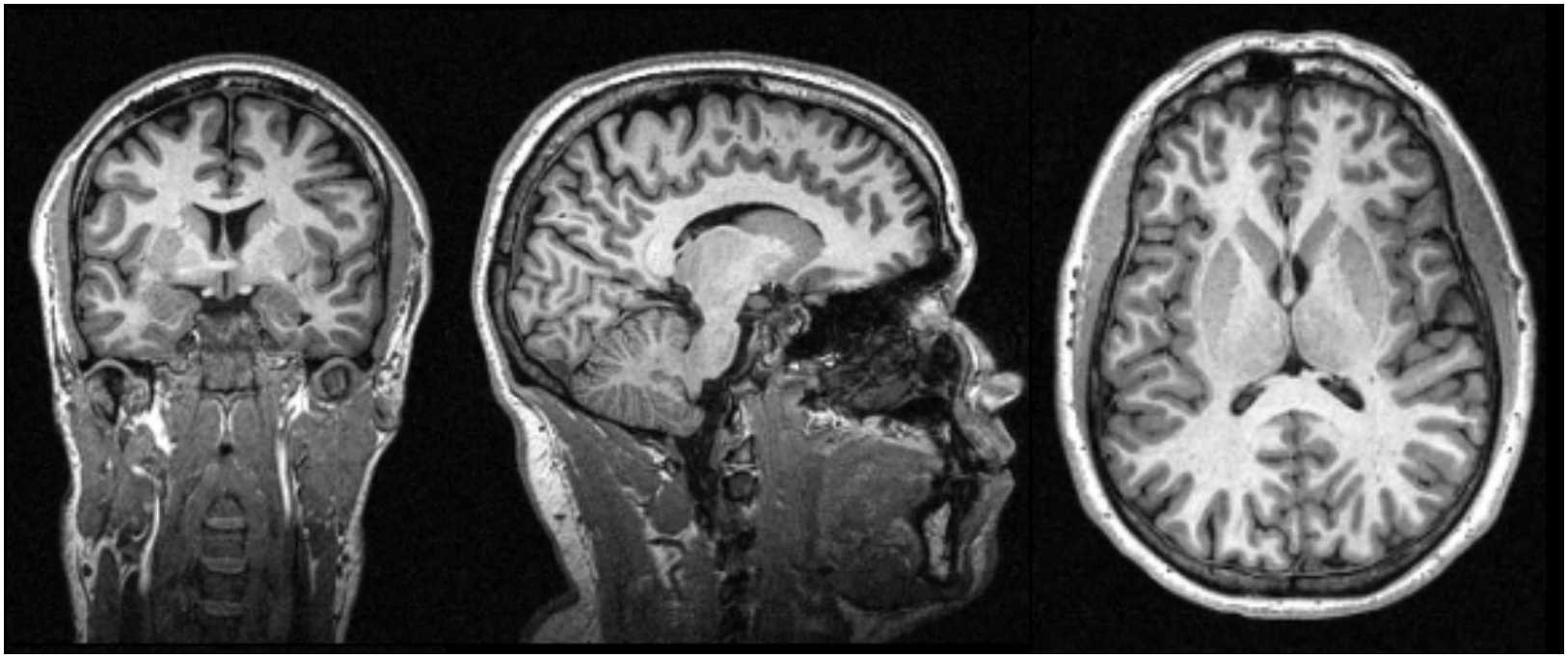


Axonal Pathways



Functional Activity/Connectivity

Structural MRI



In **structural MRI**, we measure the density of protons to make an image of different tissue types, allowing us to see white matter, gray matter, cerebrospinal fluid, skull, etc.

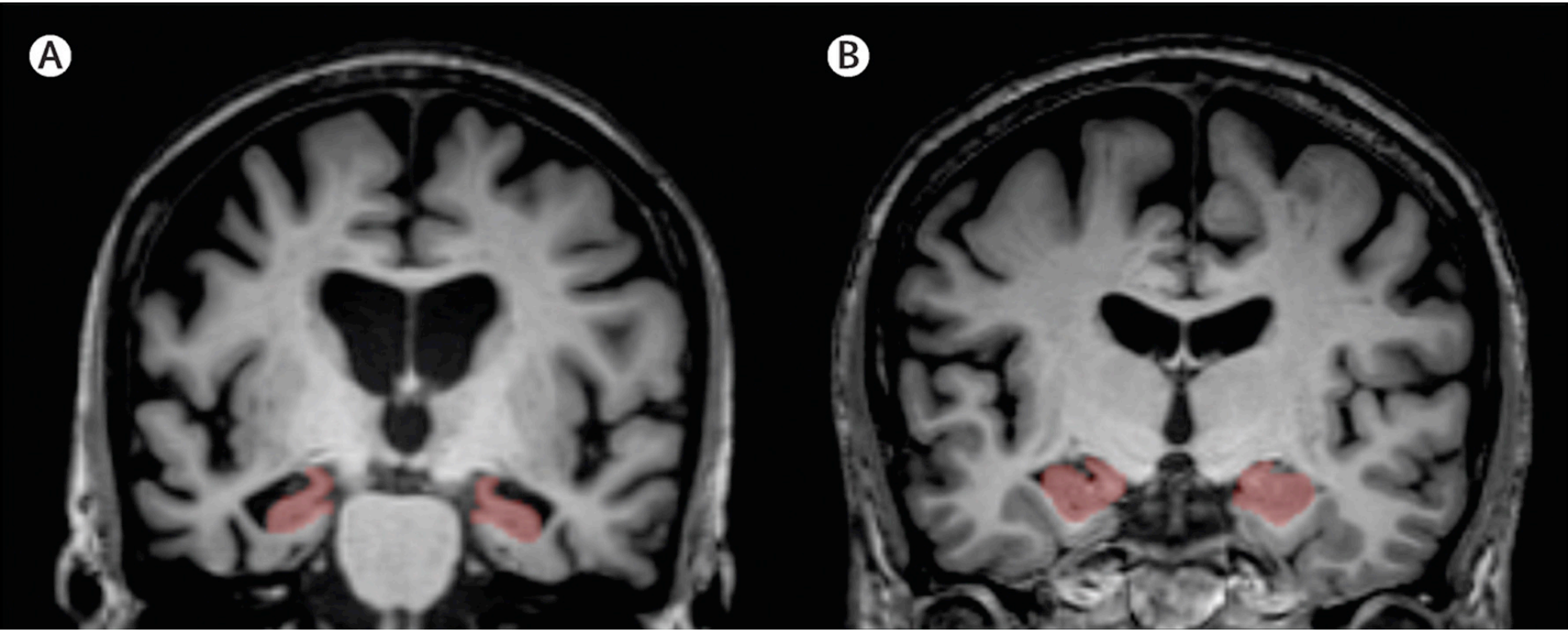
We can also use this to see where patients have lesions (from stroke, neurodegeneration, etc.).

Slides adapted with permission from R. Hurley

Structural MRI: How is it used?

Assist with the differential diagnosis

- Rule out other causes of dementia (e.g. tumors, stroke, etc.)
- Support the clinical diagnosis of dementia (e.g. hippocampal atrophy)
  - Note: There are no agreed upon standardized values that would establish the significance of a specific amount of shrinkage at the individual level

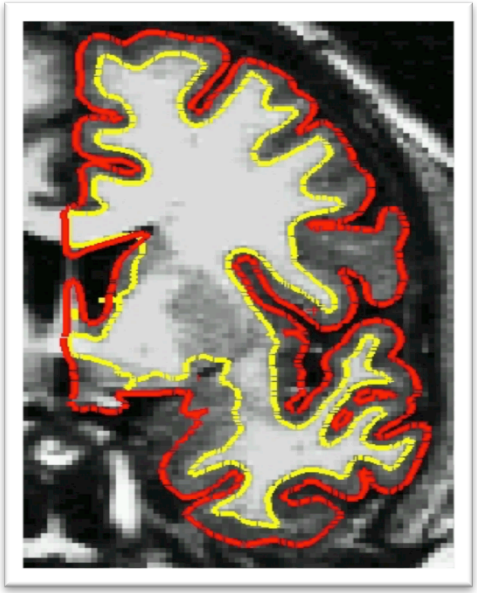


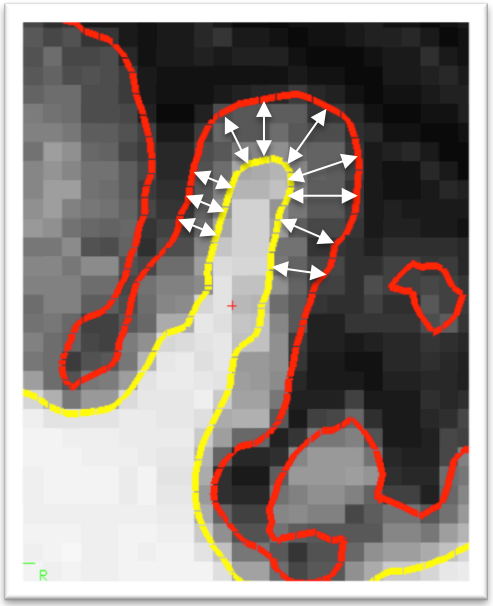
Individual with Alzheimer Dementia

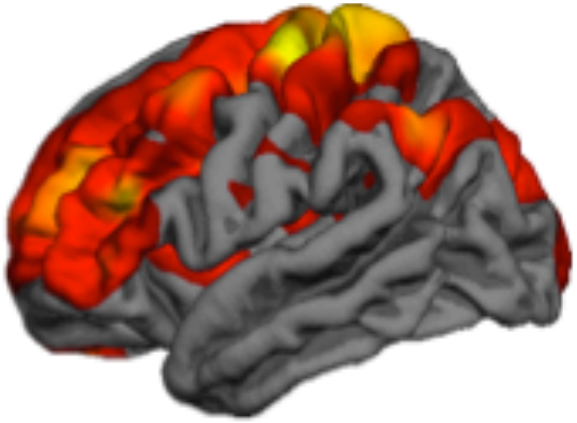
Cognitively Healthy Individual

Teipel et al 2015

Quantitative analysis of MR data with FreeSurfer







Structural MRI patterns in different dementia syndromes

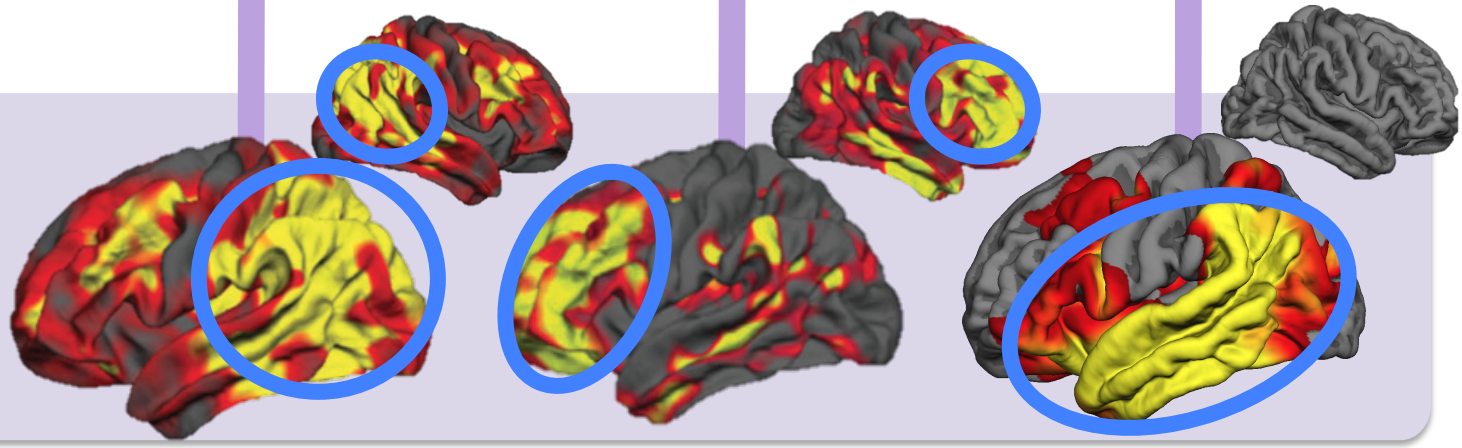
Clinical Syndrome

Amnestic Dementia

Behavioral Dementia

Aphasic Dementia

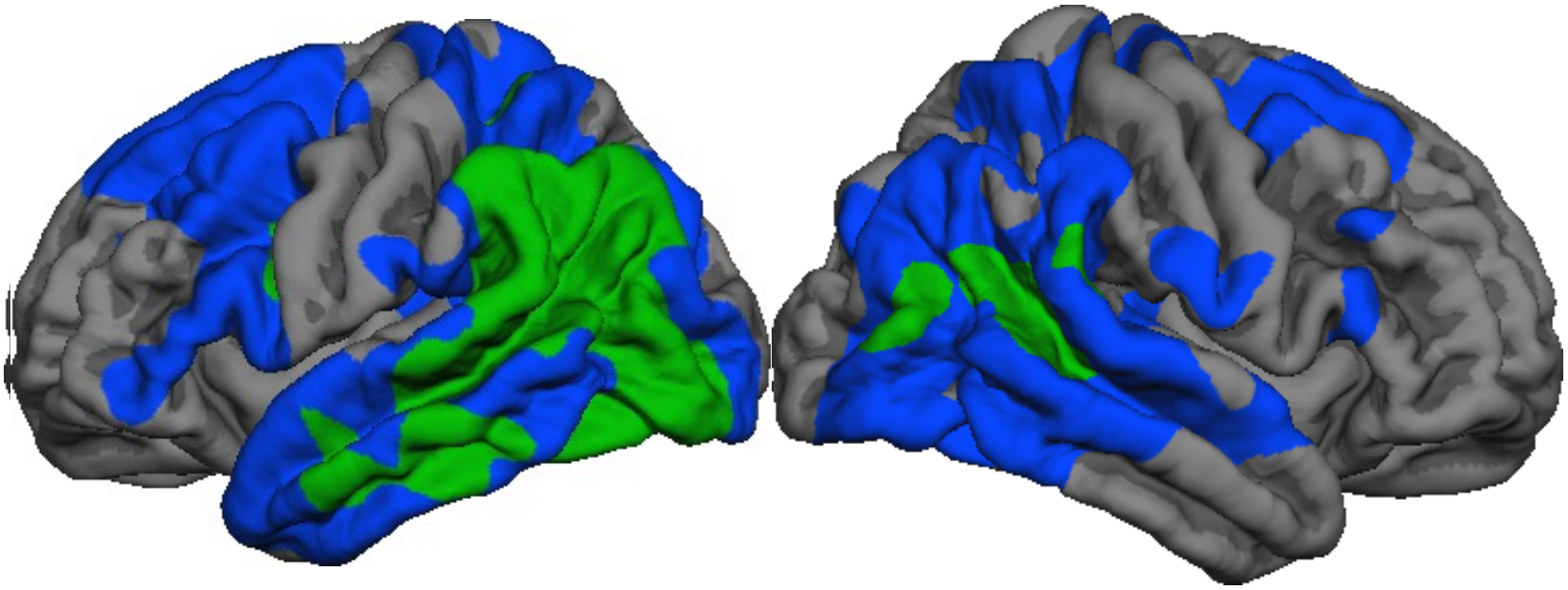
Structural MRI



Images from: Du 2007; Mesulam 2009

Structural MRI: How is it used?

Determine the Neurobiologic Changes Over Time

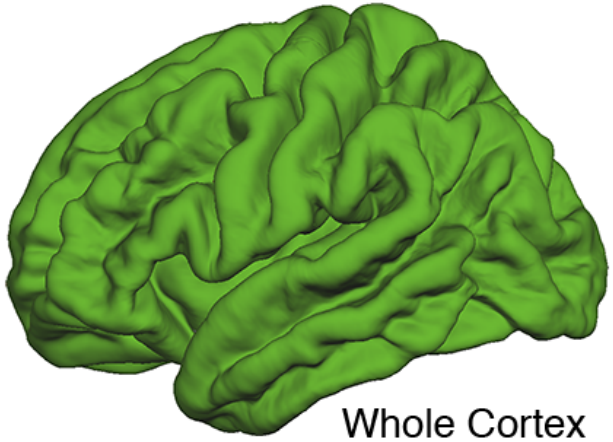


Rogalski et al Neurology 2011, Rogalski et al J Neuroscience 2011

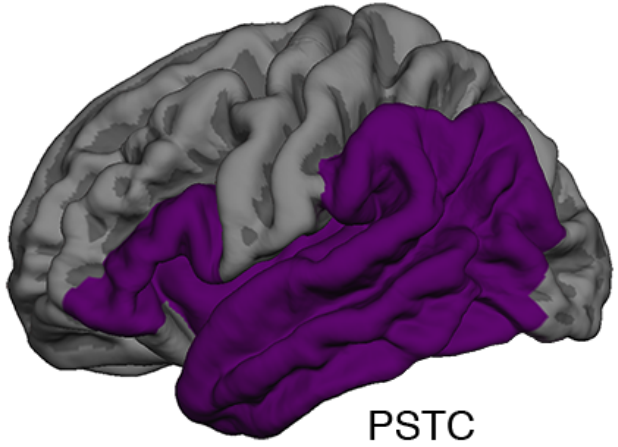
Structural MRI: How is it used?

Clinical trials outcome measures

of participants needed for a clinical trial = 10



25 individuals



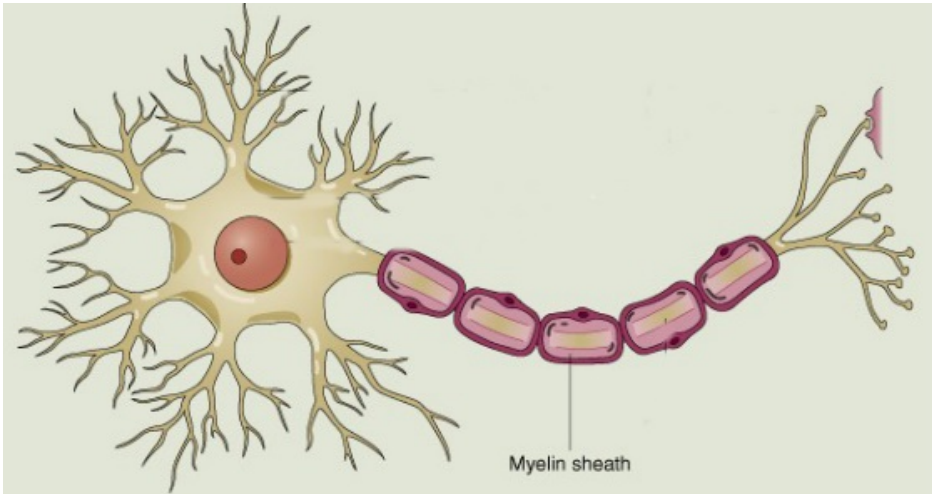
21 individuals

Rogalski et al, 2014, Neurology

Diffusion Tensor Imaging (DTI)

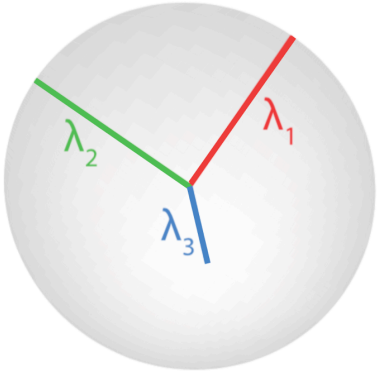
What is it?

- Identifies the unique directional movement (diffusion) of water along neural tracts.
- Can provide in vivo quantification of macro- and micro-structural alterations in the white matter of the brain

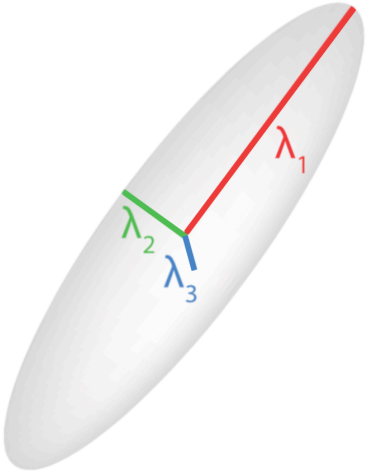


How does it do this?

- Diffusion is measured in multiple directions to generate a 3D image
- Quantitative metrics are used to characterize the diffusion
  - Fractional anisotropy (FA):
    - common quantitative measure
    - [range: 0 to 1],
    - characterizes the longitudinal directional diffusion.



Isotropic



Anisotropic

Functional Imaging Modalities

Functional MRI (fMRI)

- **What is it? What does it do?**
  - Detect changes in local cerebral blood volume, cerebral blow flow and oxygenation levels during neural activity
- **How does it do this?**
  - Blood flows to "active" brain regions and brings oxygen to the hard-working brain cells.
  - Deoxygenated (used) blood is more magnetic than oxygenated blood.
  - By tracking variations in blood flow, functional MRI can detect activity in the brain.
    - BOLD (blood oxygen level dependent) signal, which goes up when a region of the brain is active
- Pros/Cons:
  - Noninvasive; Reveals participating brain regions
  - BOLD signals is relatively slow compared to neural activity (peak 5 sec after neural activity)
  - An indirect measure of brain function: we are measuring blood flow

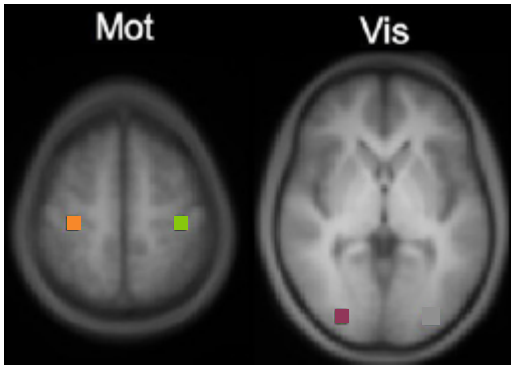
Types of fMRI: Resting State fMRI

What is it?

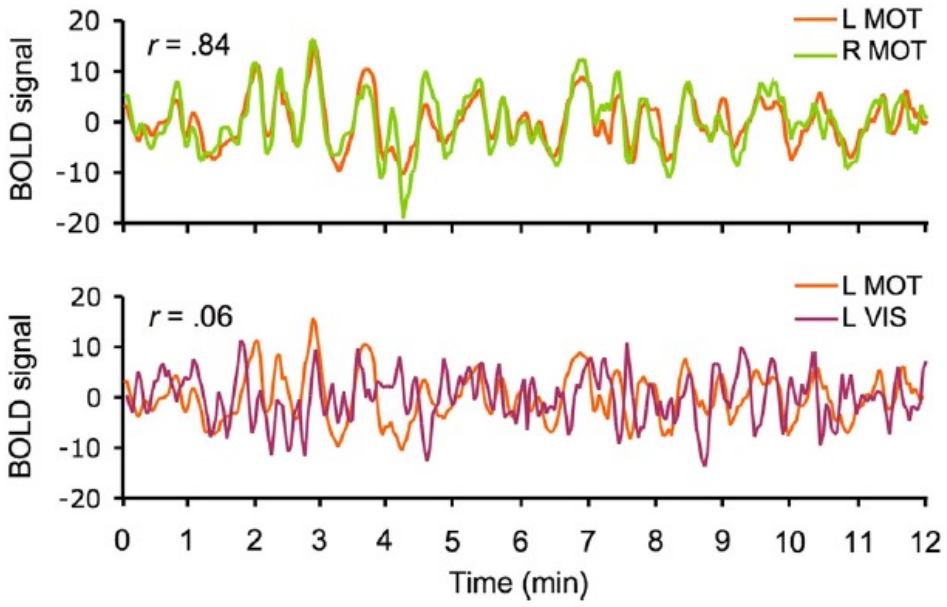
- fMRI scan acquired while an individual is doing "nothing"

How does it work?

- Communication between brain regions causes their fMRI signals to fluctuate together
- Functional Connectivity analysis measures how closely these signals fluctuate together

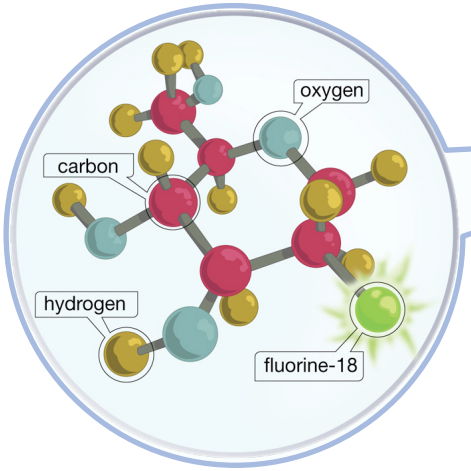


Seed regions in:
1) left motor cortex,
2) right motor cortex
3) left visual cortex

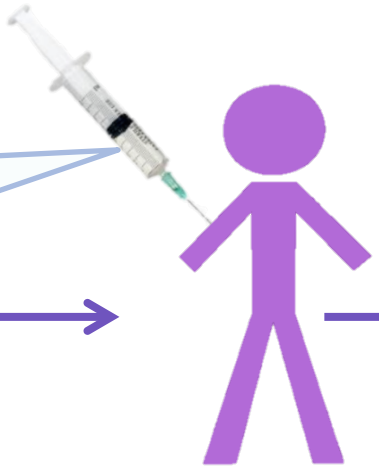


Van Dijk et al. 2010 J Neurophysiol; Yeo 2011

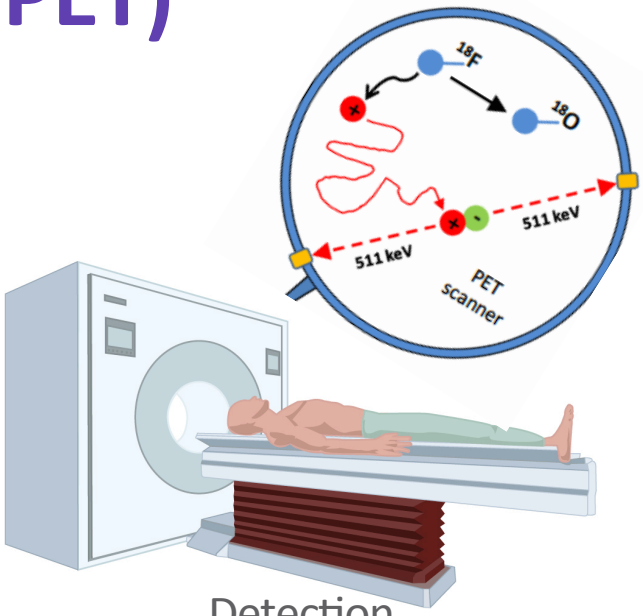
Positron Emission Tomography (PET)



Modified glucose molecule

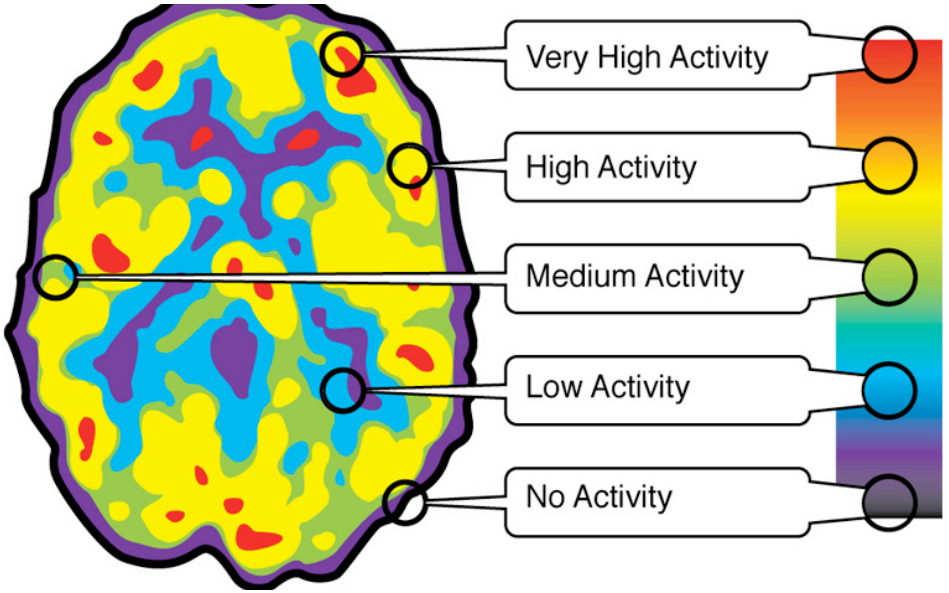


Injection



Detection

Image construction



Cartoon PET Image

Images adapted from: http://learn.genetics.utah.edu/content/addiction/brainimaging/

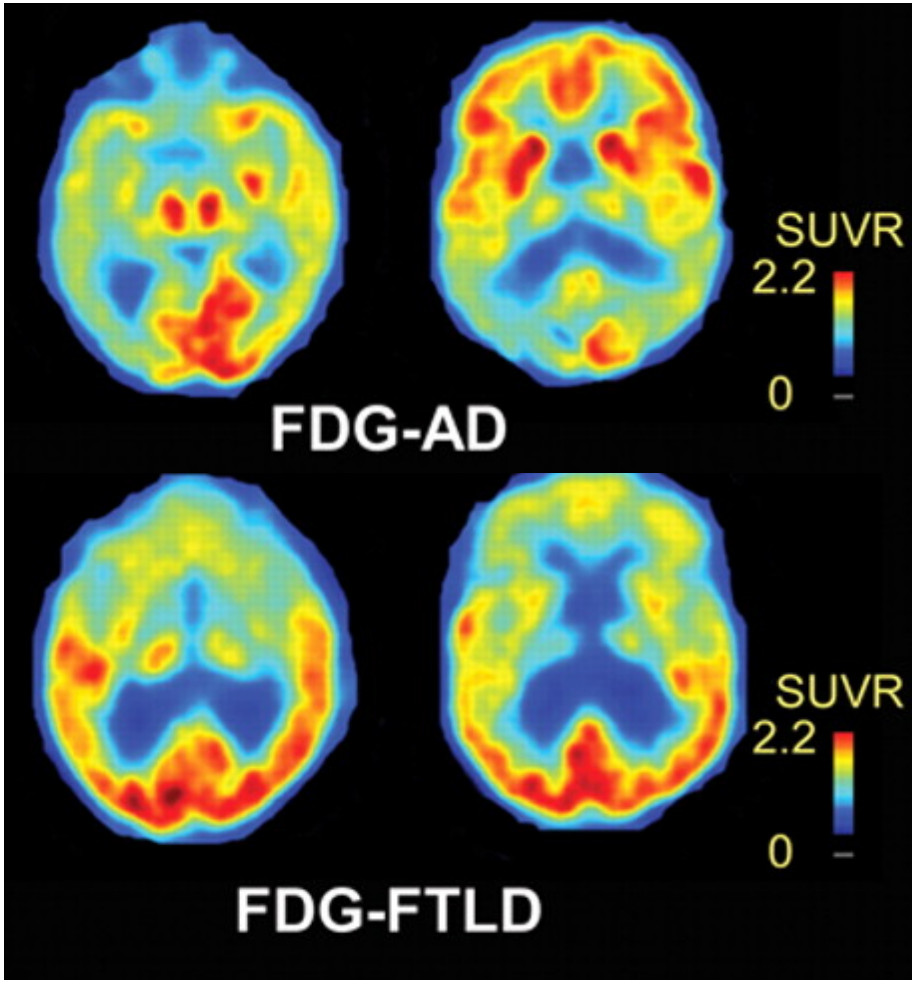
Fluorodeoxyglucose-PET: FDG-PET

What is it? What does it show?

- Functional imaging technique
- Measures glucose metabolism
- When neurons are active, glucose increases in that area

How does it compare to other imaging techniques?

- Pros: In neurodegenerative disease reduced metabolic brain activity may precede MRI atrophy
- Cons: Cost: $$$ (higher than structural MRI; Requires a Cyclotron (particle accelerator); Spatial resolution: worse than structural MRI

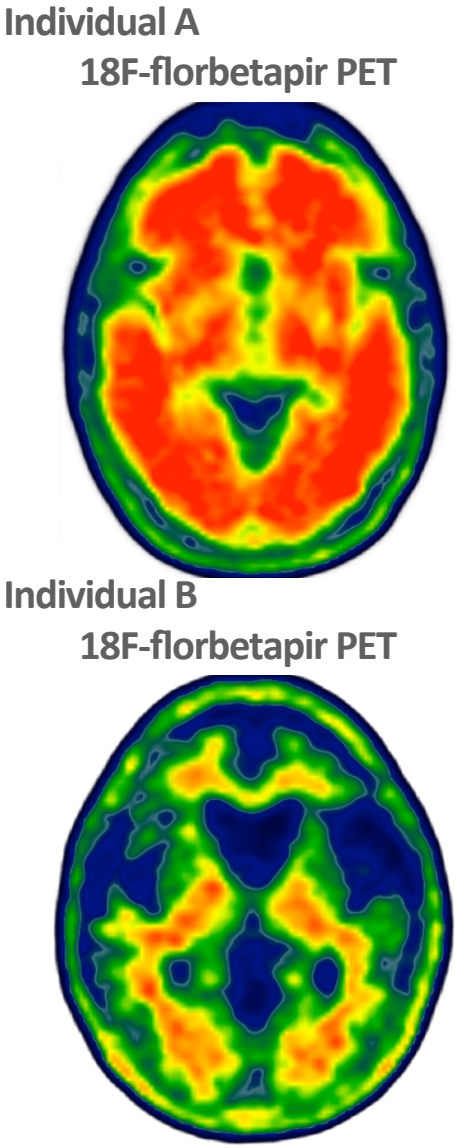


G.D. Rabinovici et al. Neurology 2011;77:2034-2042

Amyloid PET Imaging

What does it do?

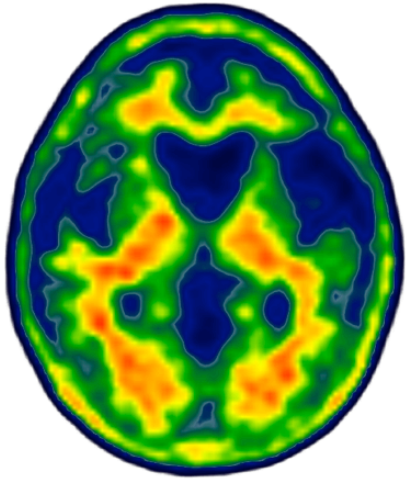
- Ligand that binds to beta amyloid
  - Multiple FDA approved tracers
- Potential Uses:
  - Support differential diagnosis
    - Note: A positive amyloid PET scan in itself is not definitive for Alzheimer's disease
  - Identifying at-risk individuals / Early detection tool
  - Improve understanding of AD pathophysiology
  - Increasingly used in clinical trials as a screening or outcome measure (e.g., A4)
- Challenges:
  - Expensive, insurance coverage is problematic



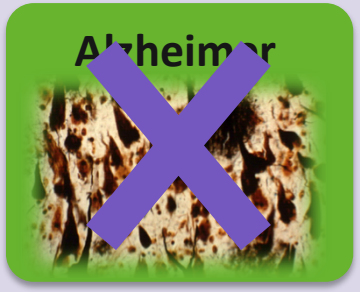
Amyloid PET Imaging: Clinical Potential

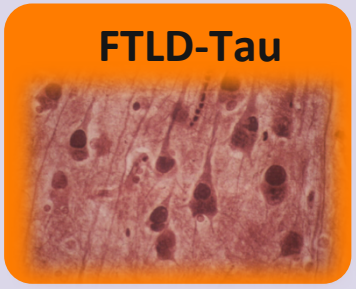
Clinical Syndrome

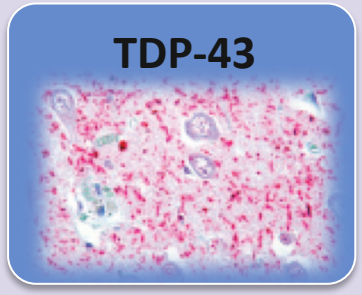
Aphasic Dementia



Neuropathology

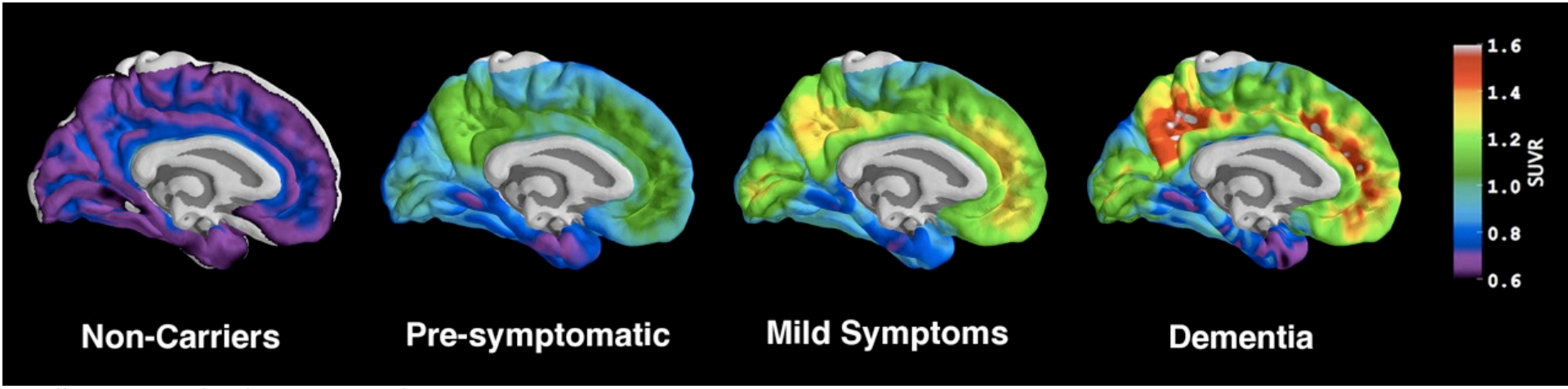






Pathology Pictures courtesy of E.Bigio & Hatanpaa, K 2008 J Neuropath

Amyloid PET Imaging: Research Findings

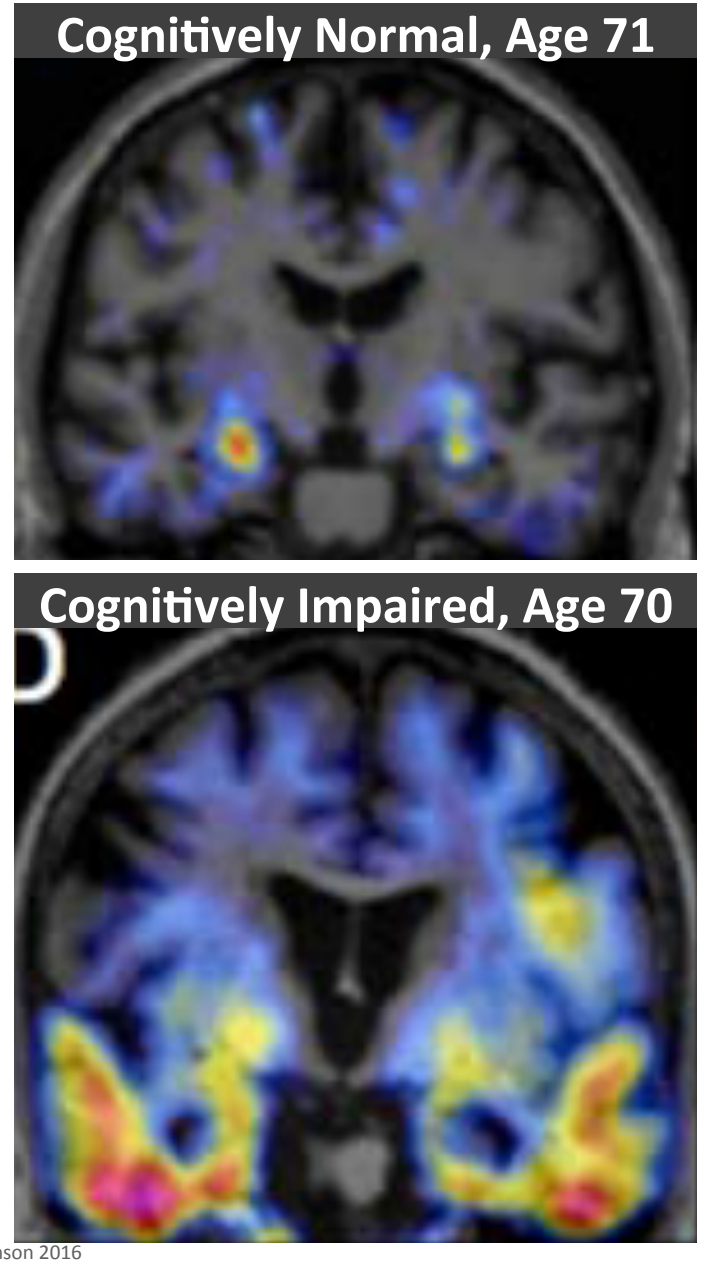


http://www.alzforum.org/news/conference-coverage/expanding-network-dian-starts-showing-longitudinal-data

Brain β amyloid pathology is present 20 years before a person is diagnosed with dementia

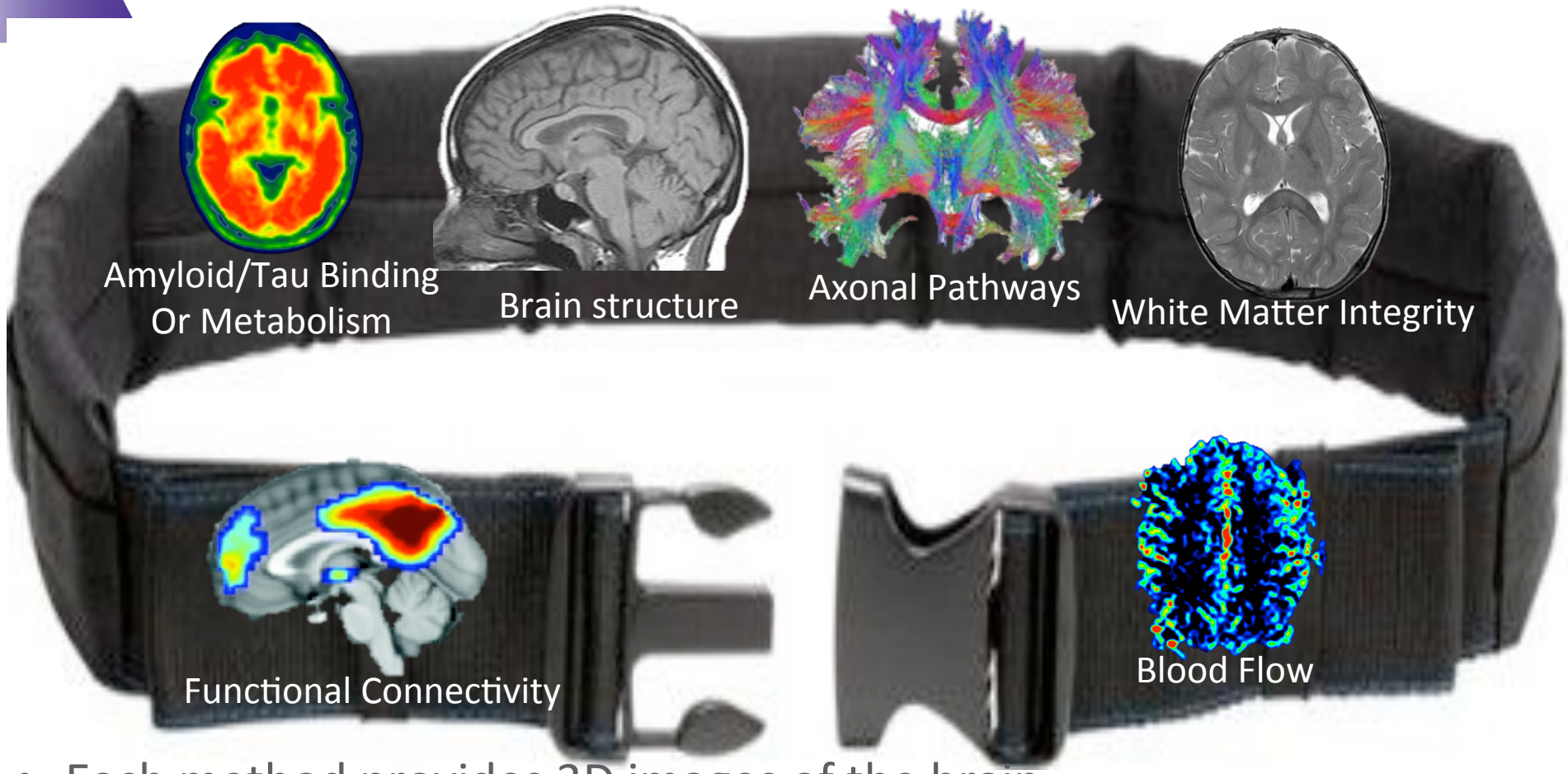
Tau PET Imaging

- What does it do?
  - Experimental ligands for imaging tau (e.g. tangles)
  - Newer than amyloid PET
- Potential Uses:
  - Tracking disease progression
  - Biomarker
  - An outcome measure for clinical trials
- Next Generation of tracers:
  - Ideally the tracer would distinguish among different tauopathies



Johnson 2016

Imaging tool belt



- Each method provides 3D images of the brain
- Some provide information about ***brain structure*** while others provide information about ***brain function*** or ***pathology***
- Combining methodologies may provide a richer understanding of a particular scientific question