ALZHEIMER'S ASSOCIATION

AAIC 23

ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®

JULY 16-20 > AMSTERDAM, NETHERLANDS, AND ONLINE

ISTAART Neuroimaging PIA
THE BASICS OF NEUROIMAGING SEMINAR SERIES

ISTAART Neuroimaging PIA

The Basics of Neuroimaging Series

BASICS OF NEUROIMAGING

STRUCTURAL MRI

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GOALS

By the end of this session, you should be able to:

- Identify the common structural MRI sequences and how they are used in dementia research
- Outline the basic preprocessing steps needed for structural MRI data and how to look for issues in the data and processing
- Differentiate the numerous applications of registration using structural MRI

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NEUROIMAGING DATA ANALYSIS: A BLUEPRINT FOR STRUCTURAL MRI

1. Data acquisition	**Aim**: obtain good quality and consistent data	**Different sequences (T1w, T2w, FLAIR) provide complimentary information** Trade-offs often necessary (e.g. time vs resolution). Optimize protocol for research aim.
2. Data preprocessing	**Aim**: Reduce noise and prepare data for further analyses	**Bias correction: remove intensity inhomogeneity** **Brain extraction: remove non-brain tissue** **Registration: within-subject, align to template** Requires careful checking.
3. Single-subject analysis	**Aim**: Obtain measure of interest for each subject (often an image)	**Brain/regional volumes, GM/WM concentration, cortical thickness, White Matter Hyperintensities, longitudinal change between scans**
4. Group-level analysis	**Aim**: Compare single-subject results across groups	**Comparisons between groups** **Associations of volumes with other clinical data** **Voxel/Vertex-wise analysis** **Consider data harmonization if multiple cohorts**
5. Statistical inference	**Aim**: test reliability of results and generalizability to the general population	Common step across modalities

Blueprint courtesy Ludovica Griffanti, University of Oxford

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What can we measure with structural MRI?

1. Data acquisition → 2. Data preprocessing → 3. Single-subject analysis → 4. Group-level analysis → 5. Statistical inference

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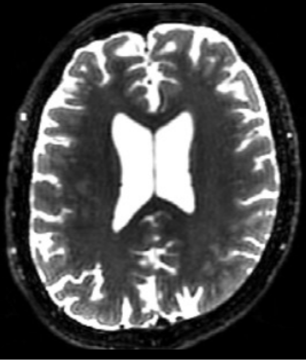
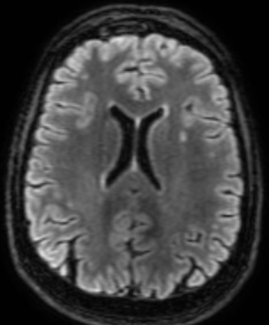
MRI SEQUENCES AND WEIGHTINGS

T1-Weighted

T2-Weighted

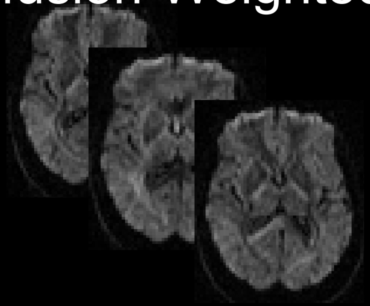


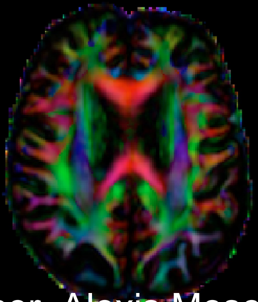
T2-FLAIR



Arterial Spin Labeling (ASL)

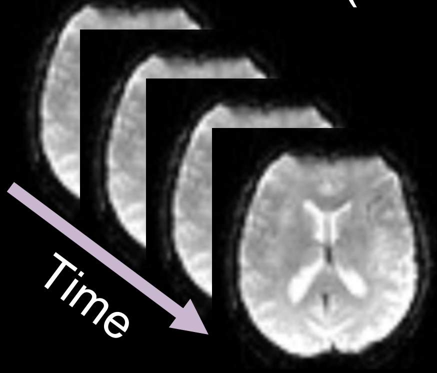
Diffusion-Weighted Imaging (DWI)





April 21 webinar

Functional-MRI (fMRI)



April 26 webinar

Slide courtesy Tobey Betthauser, Alexis Moscoso

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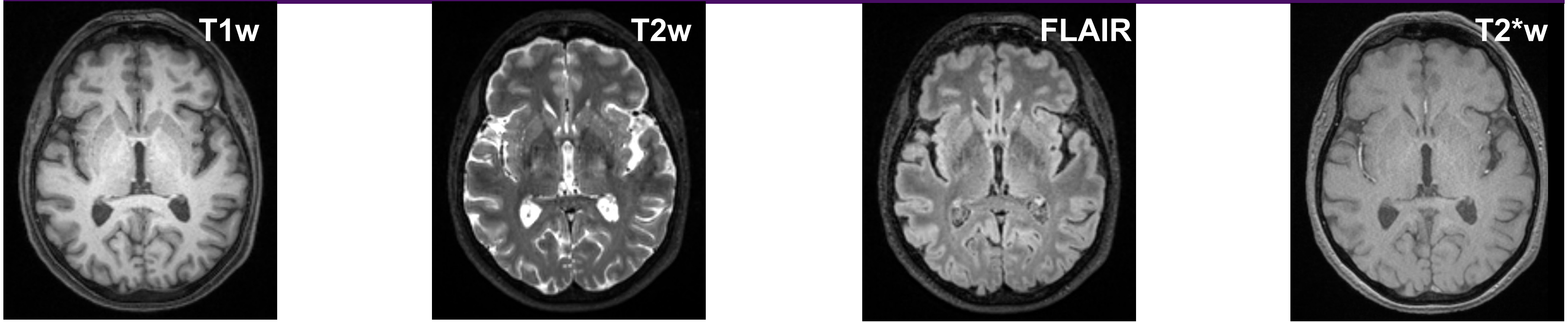
Structural MRI scans



- The MRI scanner can be tuned in different ways (**pulse sequences**), resulting in different contrasts
- Structural MRI sequences are sensitive to (or **weighted** by) one of three fundamental properties: **T1, T2, and T2* relaxation times**.
  - *Intensities are NOT quantitative measures of T1, T2, T2*.*
- **FLAIR** (FLuid Attenuated Inversion Recovery) is a T2 weighted sequence where we suppress CSF signal, so bright CSF voxels become dark

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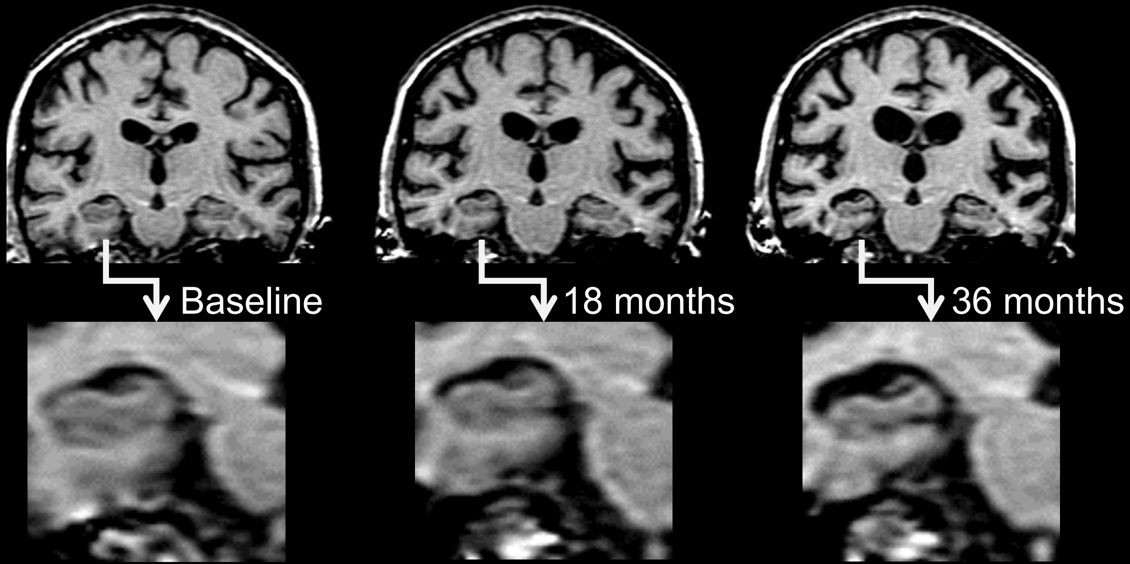
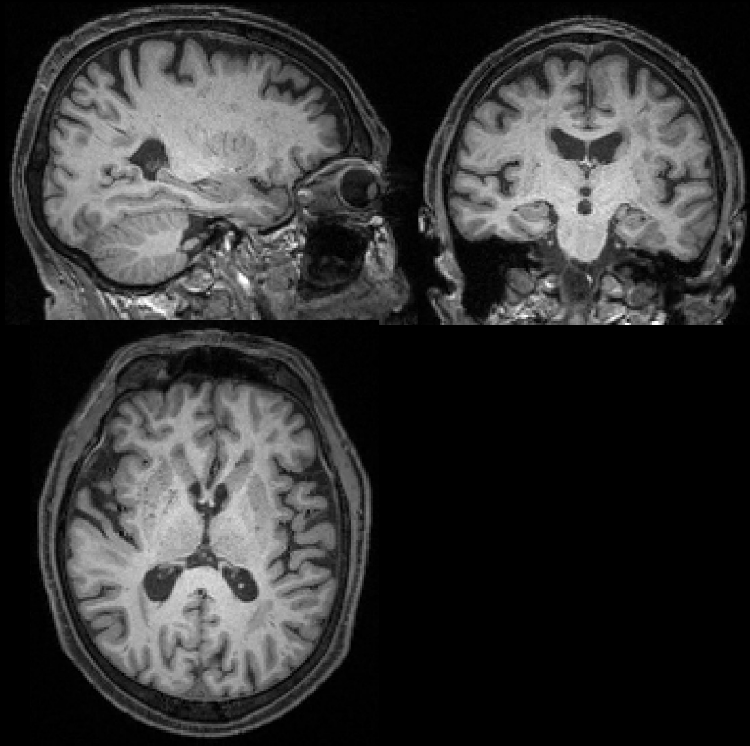
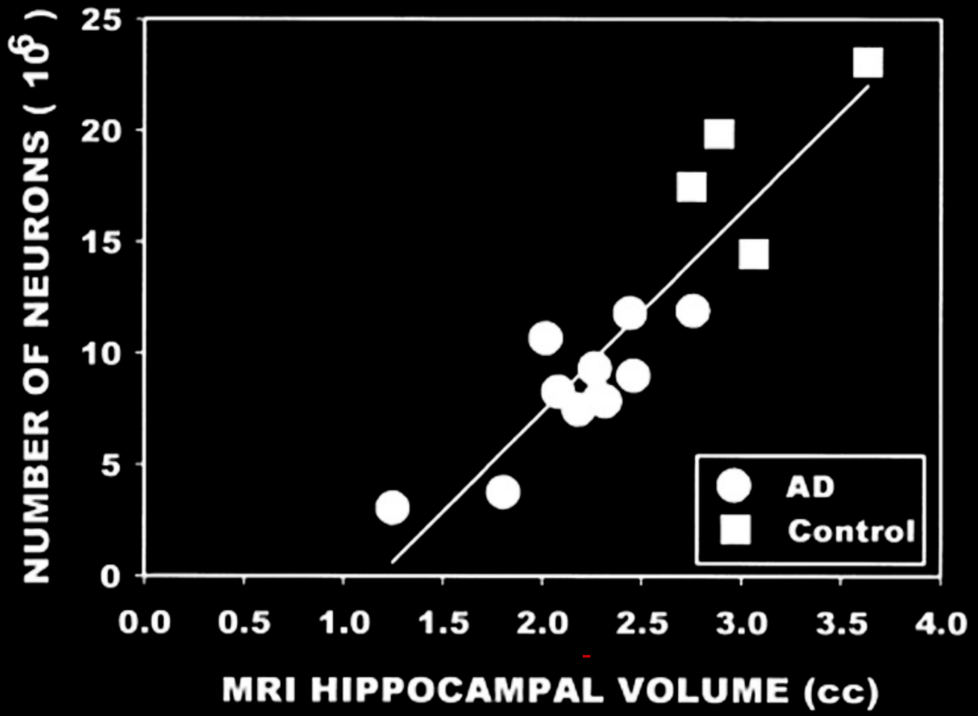
T1-weighted MRI

- High-resolution (~1 mm) information about **neuroanatomy** and **neurodegeneration**
- Can be acquired in any orientation in ~4-6 minutes
- Good contrast between different tissues (GM, WM, CSF)





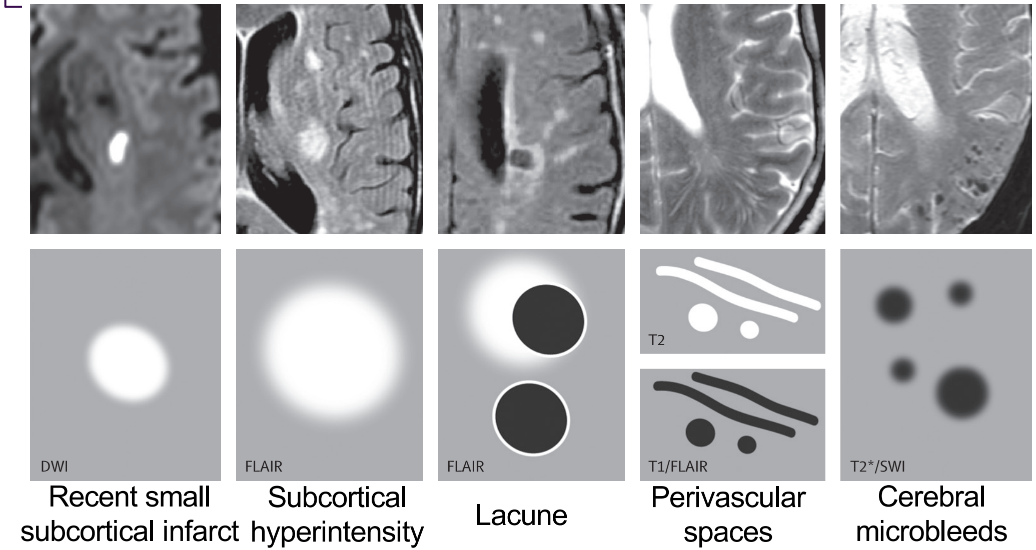
Atrophy on MRI relates to loss of neurons



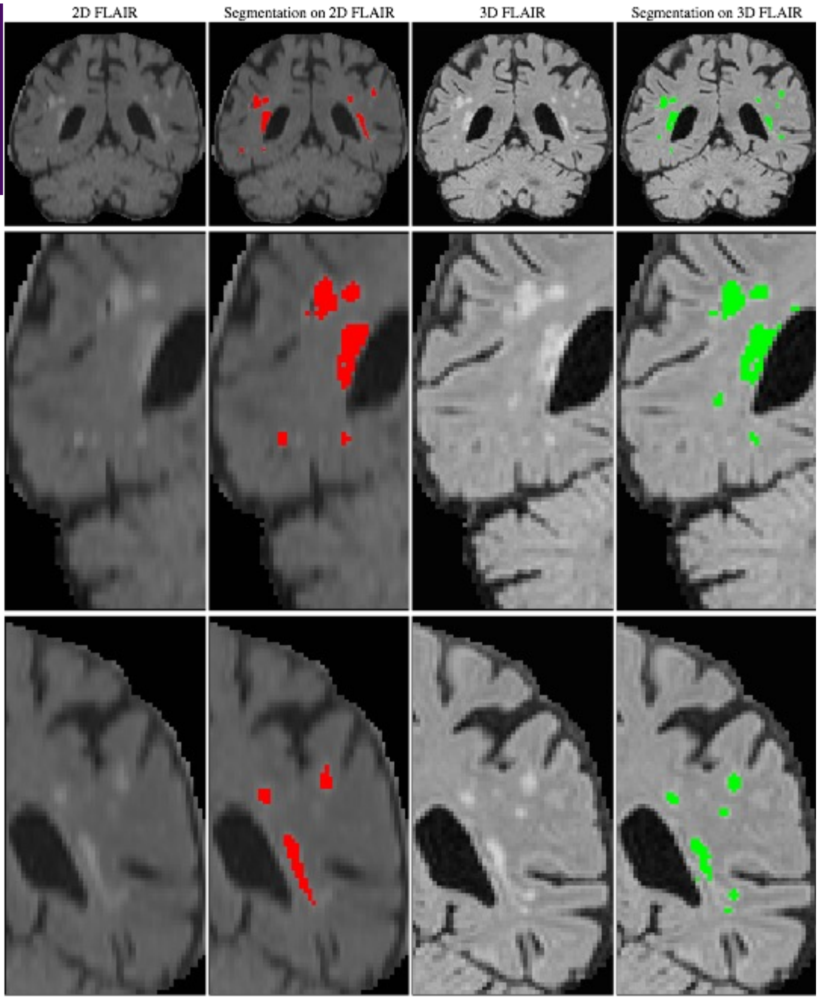
Bobinski M et al. **The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease**. *Neurosci* 95(3): 721-725. (1999)

T2, T2*, FLAIR

- Best sequence for detecting white matter hyperintensities (WMH) and other vascular-related damage
- Provide complimentary information to T1
- Clinical versions of these scans tend to have good in-plane resolution (≤1 mm) but thick slices (thick slabs of 3-5 mm)
- Newer versions of these scans have similar resolution to T1 scans



Wardlaw Lancet Neurol 2013; 12: 822–38



Images courtesy Carole Sudre, UCL

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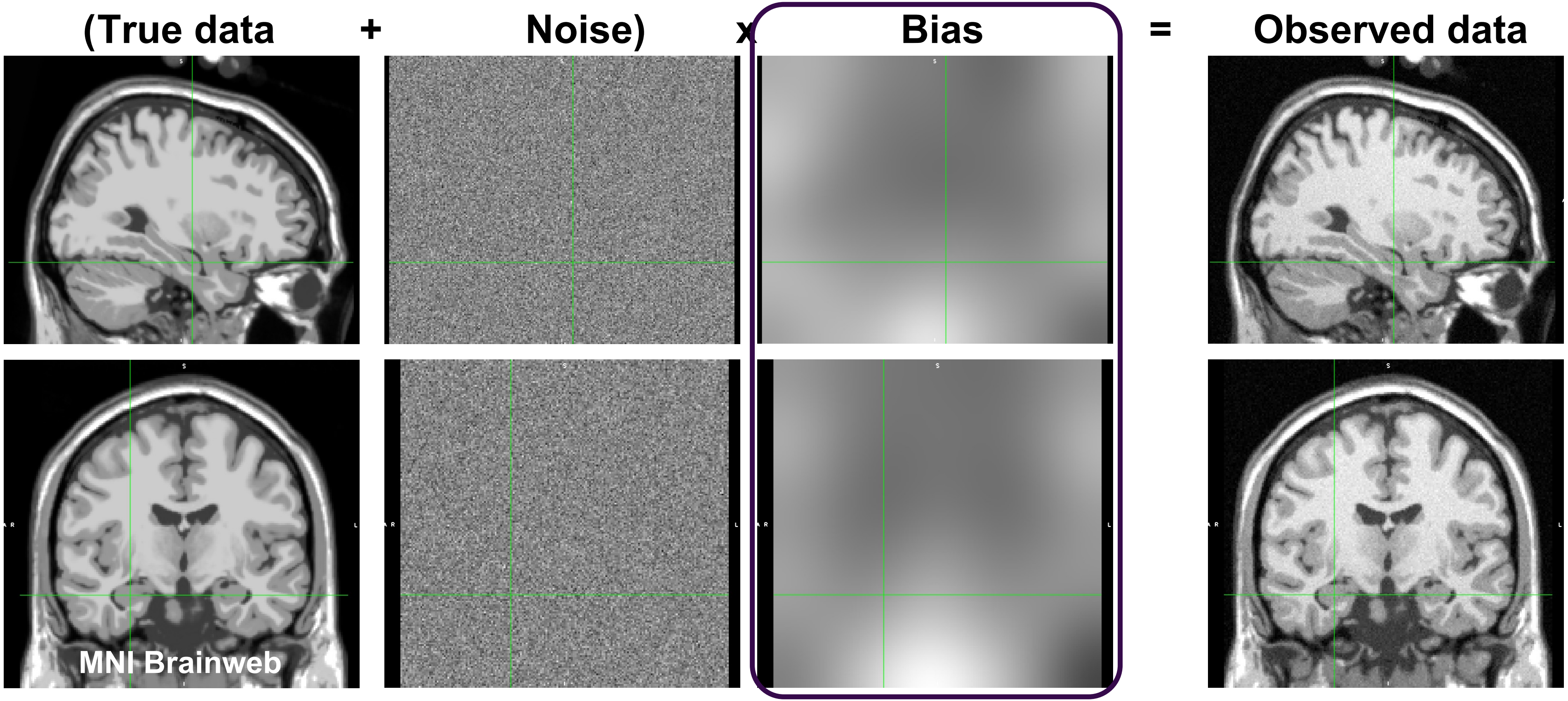
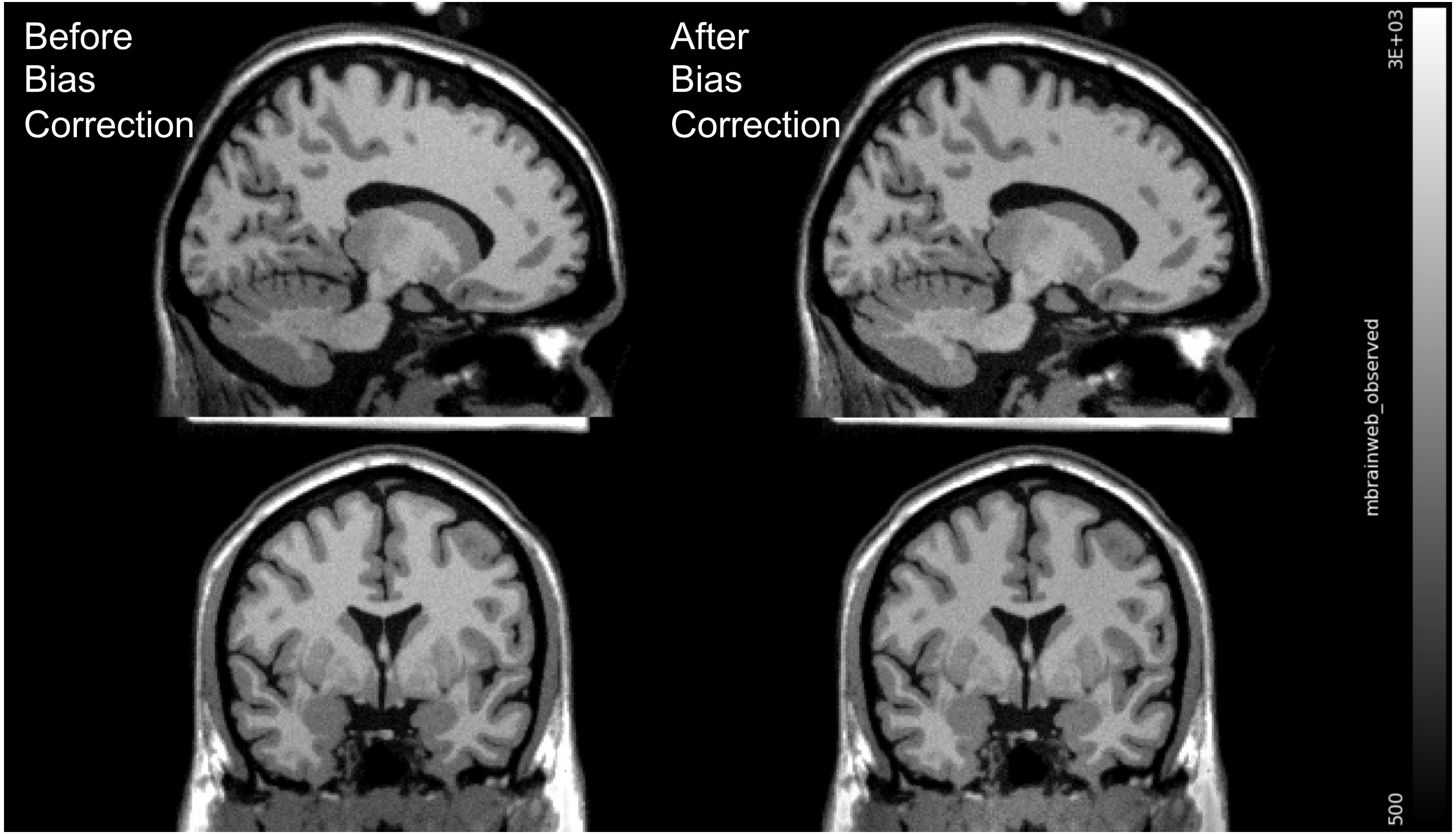
What are the key processing steps?

1. Data acquisition
2. Data preprocessing
3. Single-subject analysis
4. Group-level analysis
5. Statistical inference

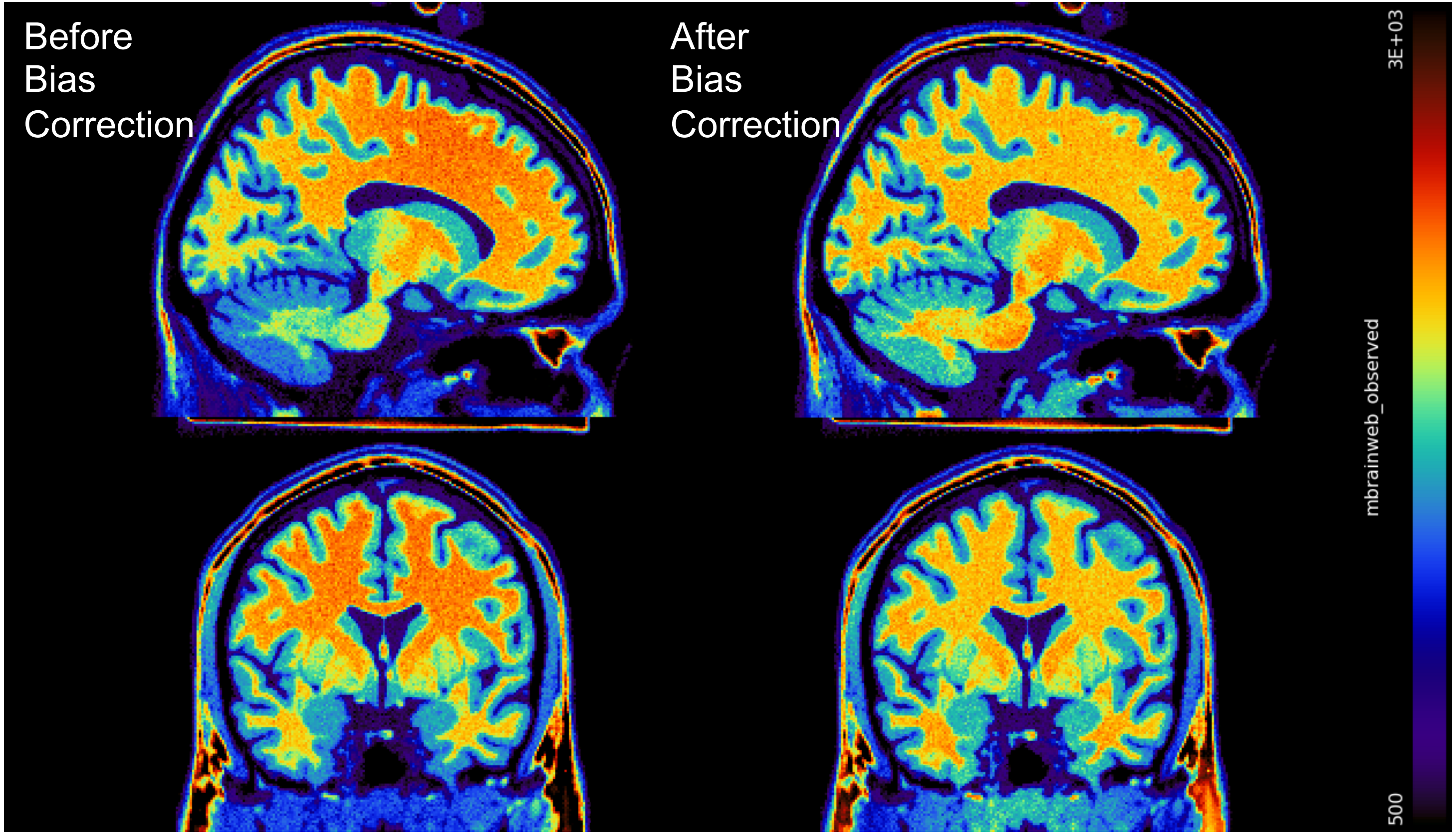
Bias Correction



Bias correction: Has it worked?

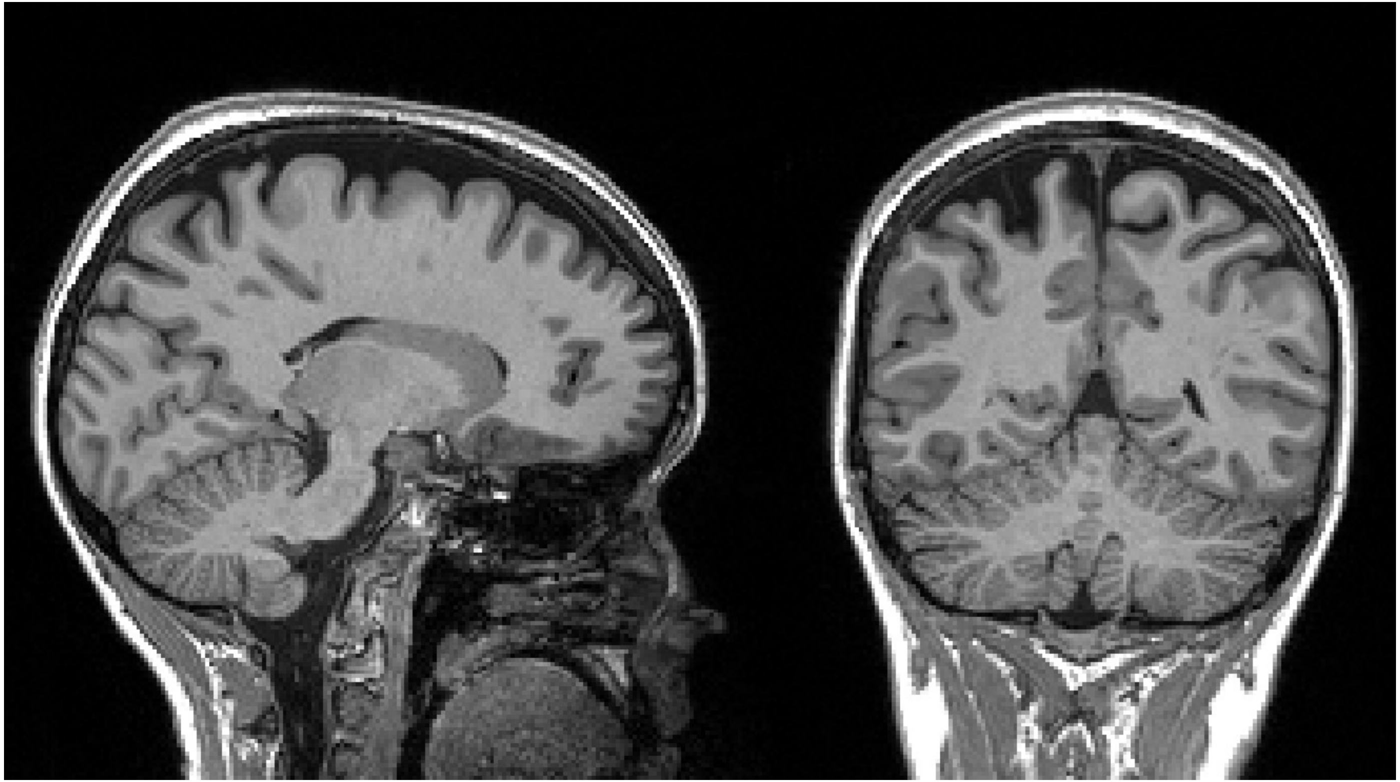


Bias correction: Did it work?



Tissue segmentation

- Assigns voxels to one of three main tissue classes
  - Grey matter (GM)
  - White matter (WM)
  - Cerebrospinal fluid (CSF)
- "Soft" segmentation - each voxel contains the probability that it belongs to a class



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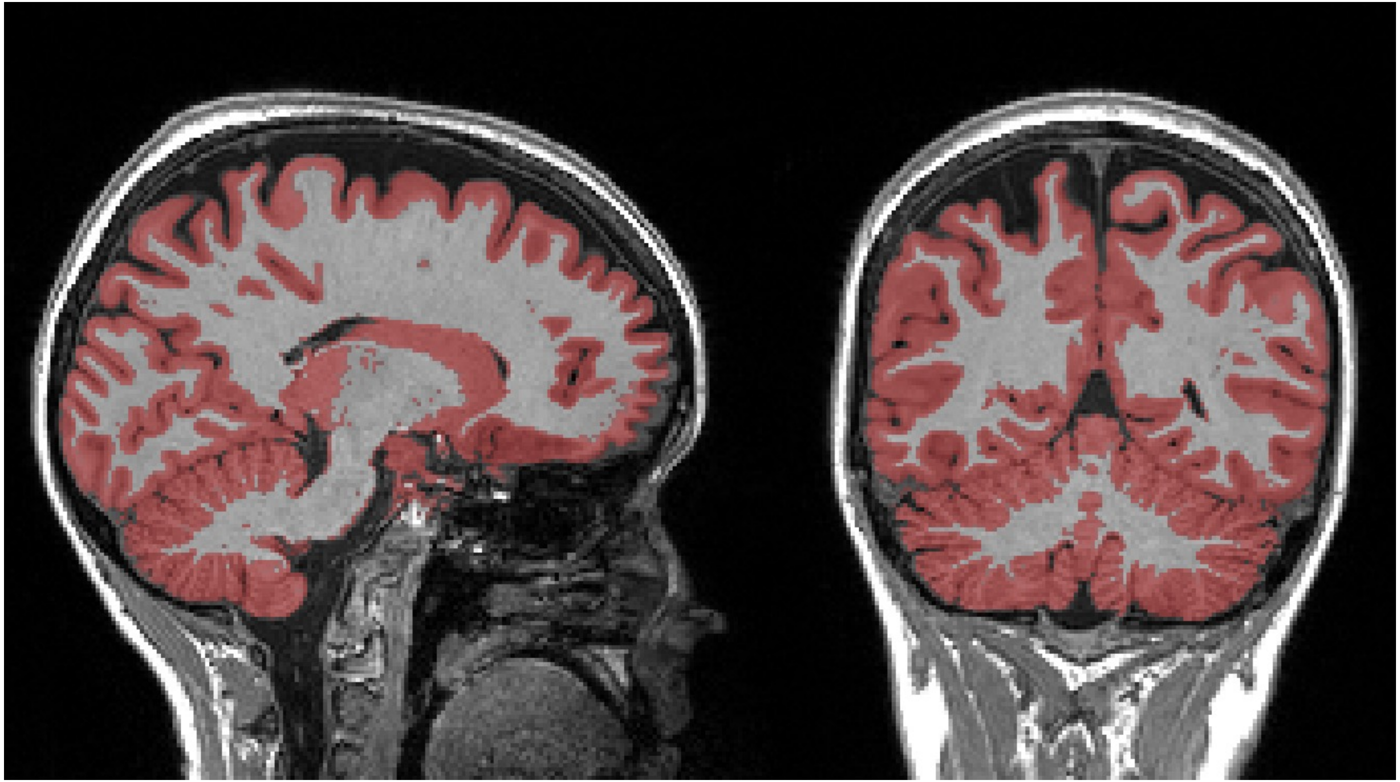

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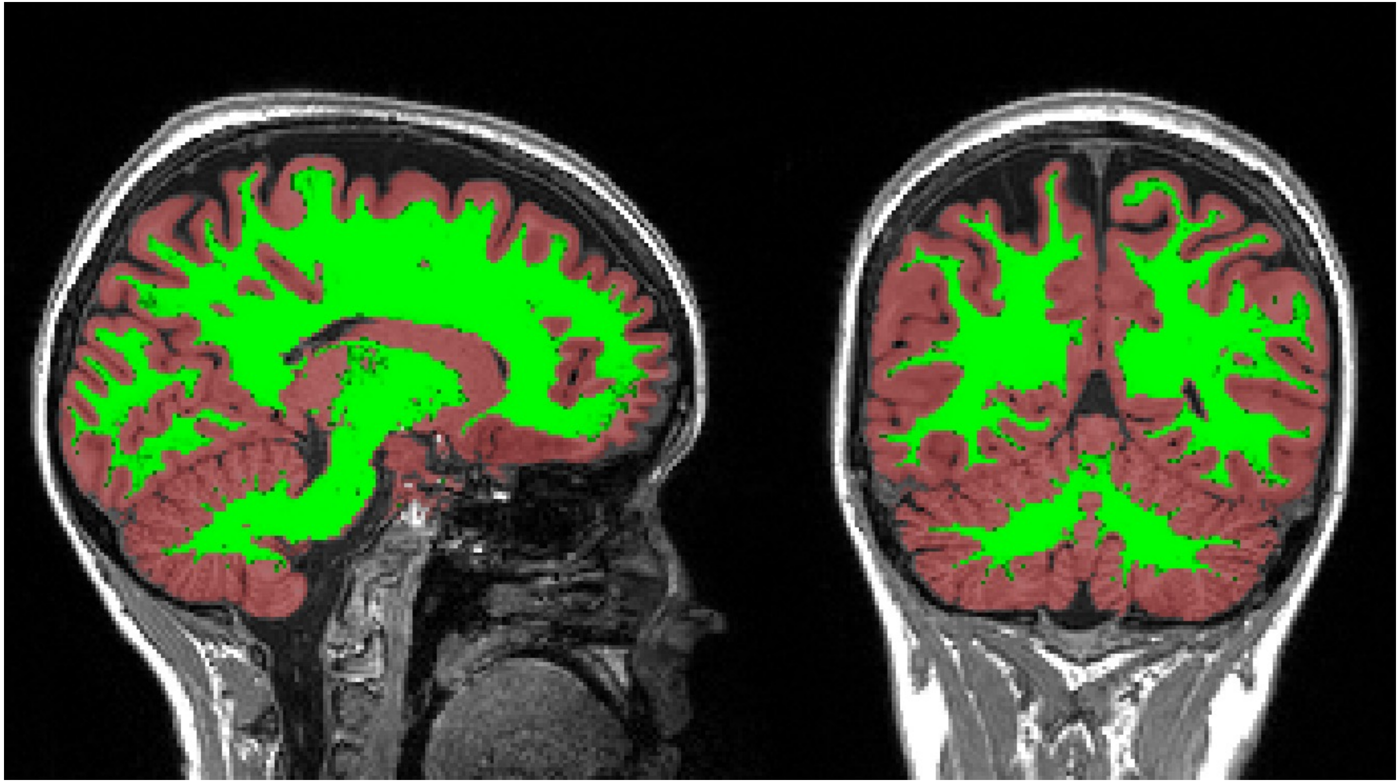

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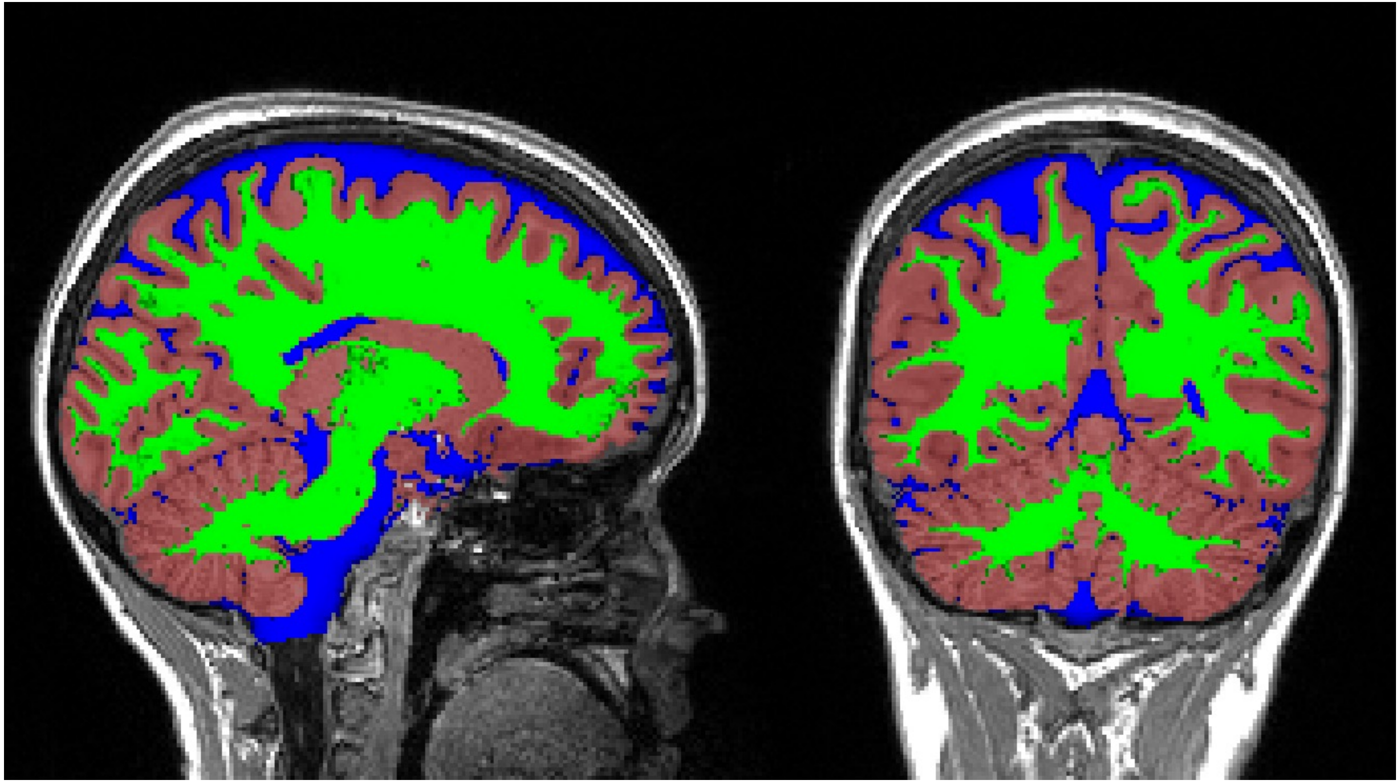

Tissue segmentation: Did it work?

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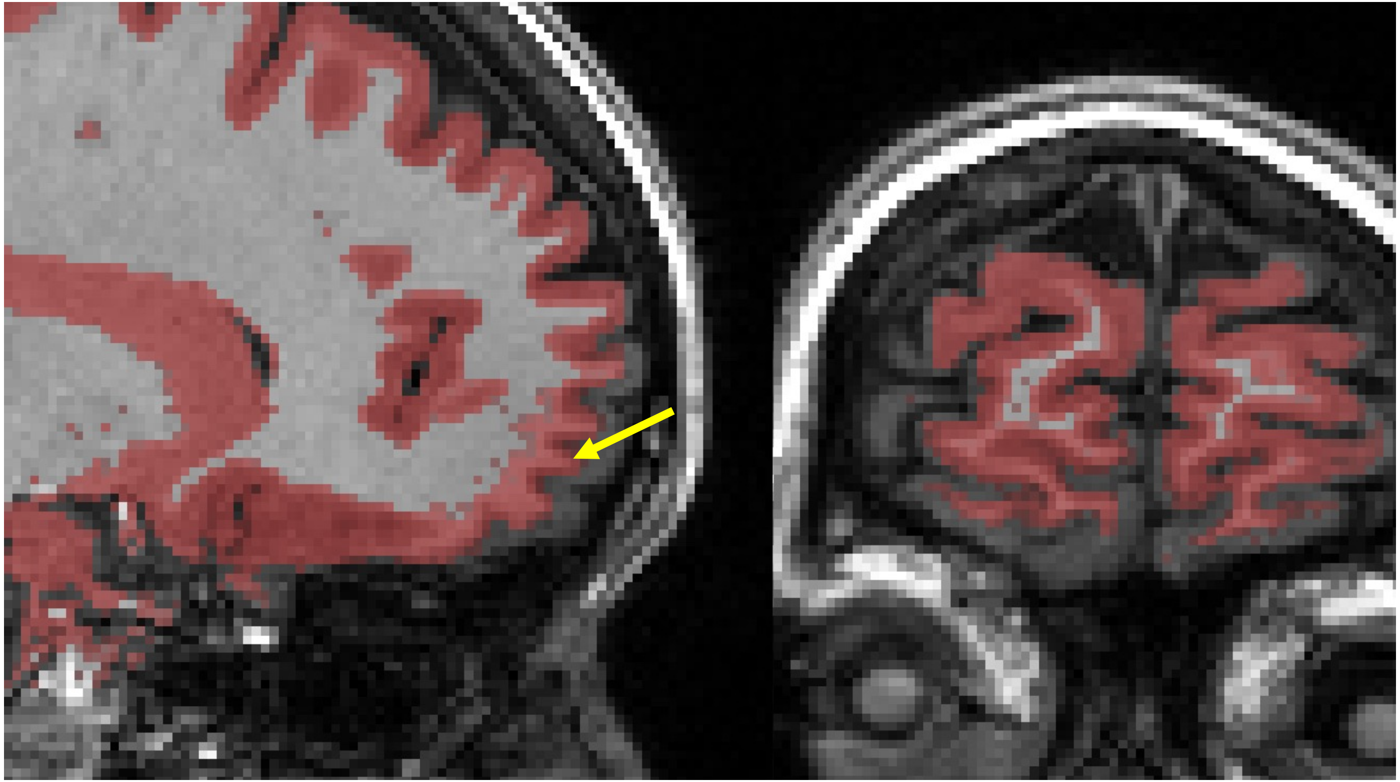
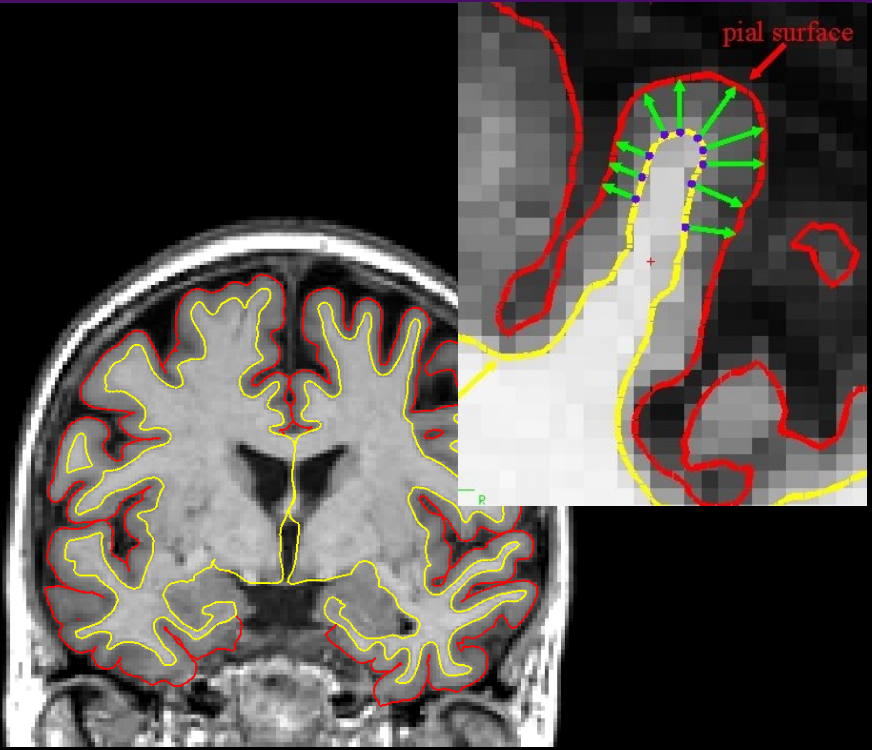
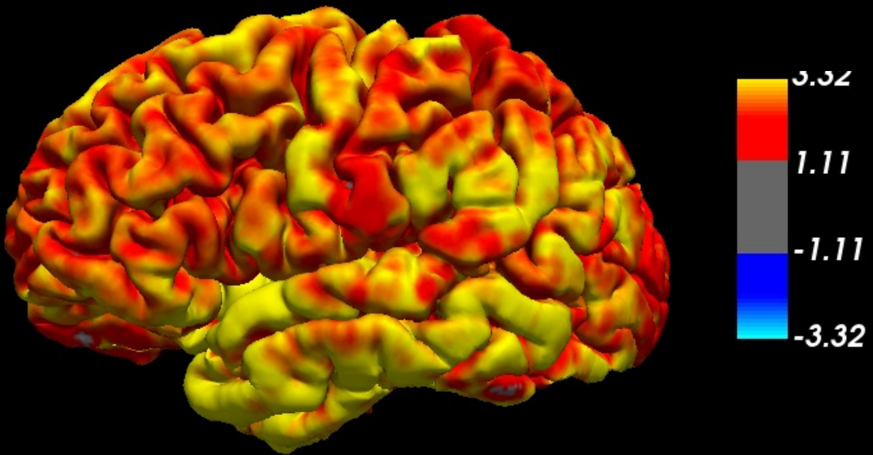
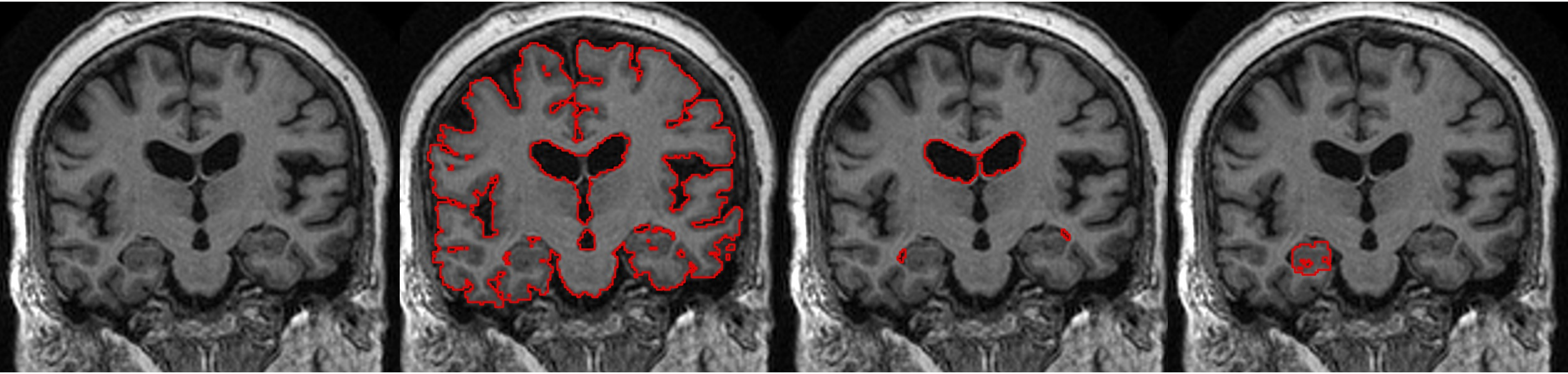


Cortical Thickness





Regional segmentation



Brain parcellation

- Rather than tissue types, assign voxels to anatomically defined structures in the brain
- Based on a single atlas or multiple subjects from a template database
- Helpful for regional statistics, both in T1 and multimodal studies
- Difficult to check each region in each image, look for obvious failures, volume outliers

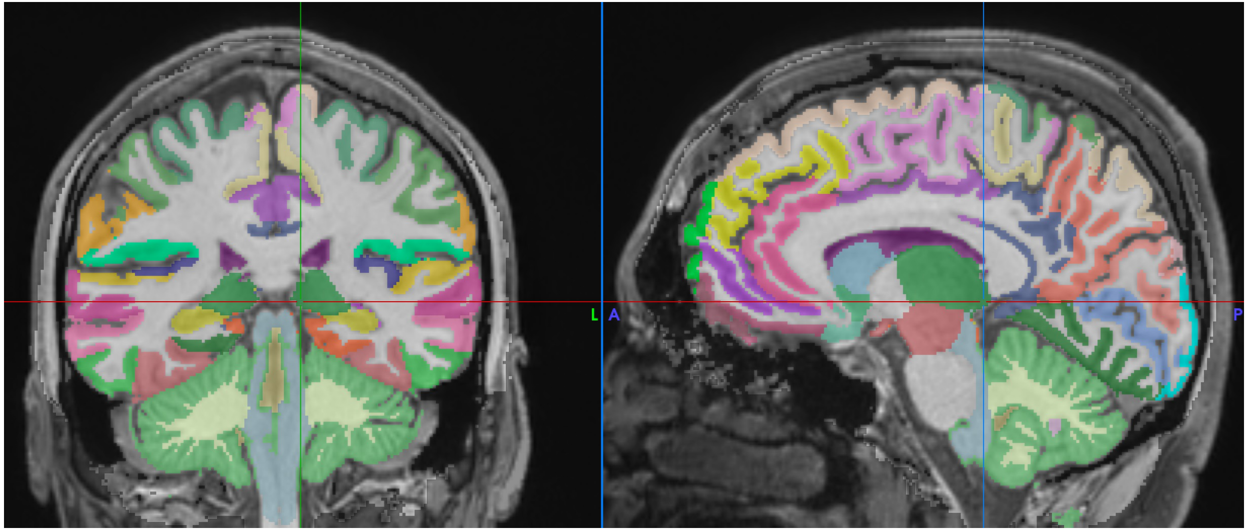


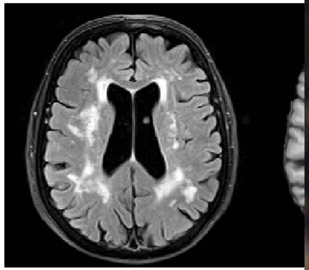
IMAGE REGISTRATION

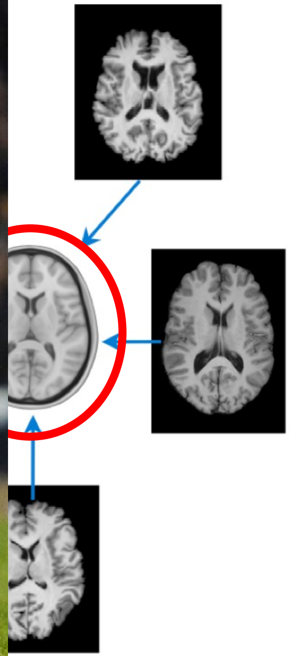
1. Data acquisition → 2. Data preprocessing → 3. Single-subject analysis → 4. Group-level analysis → 5. Statistical inference

INTRODUCTION TO IMAGE REGISTRATION

Within-subject &

n-subjects

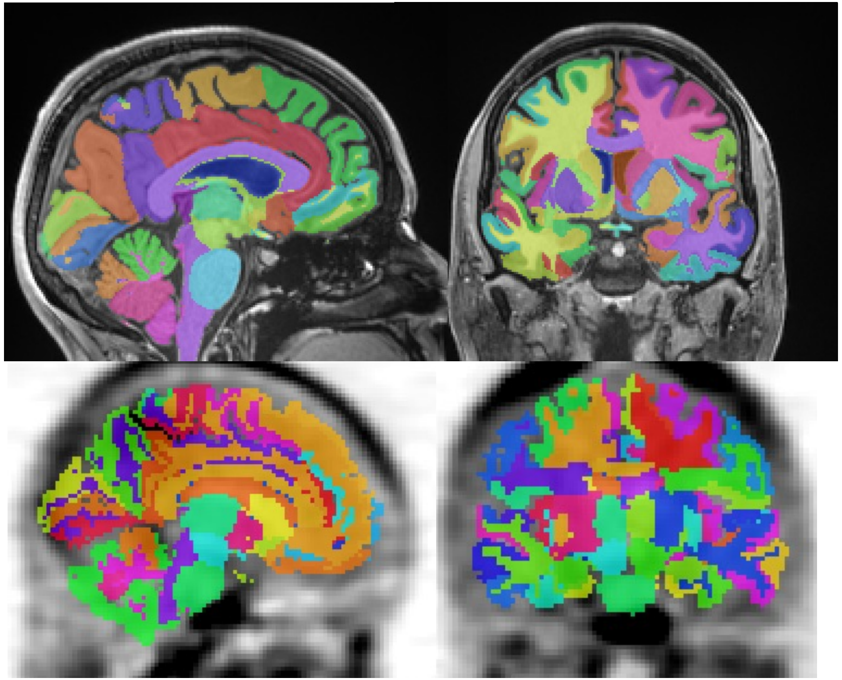




andard space =
"average brain" used as reference

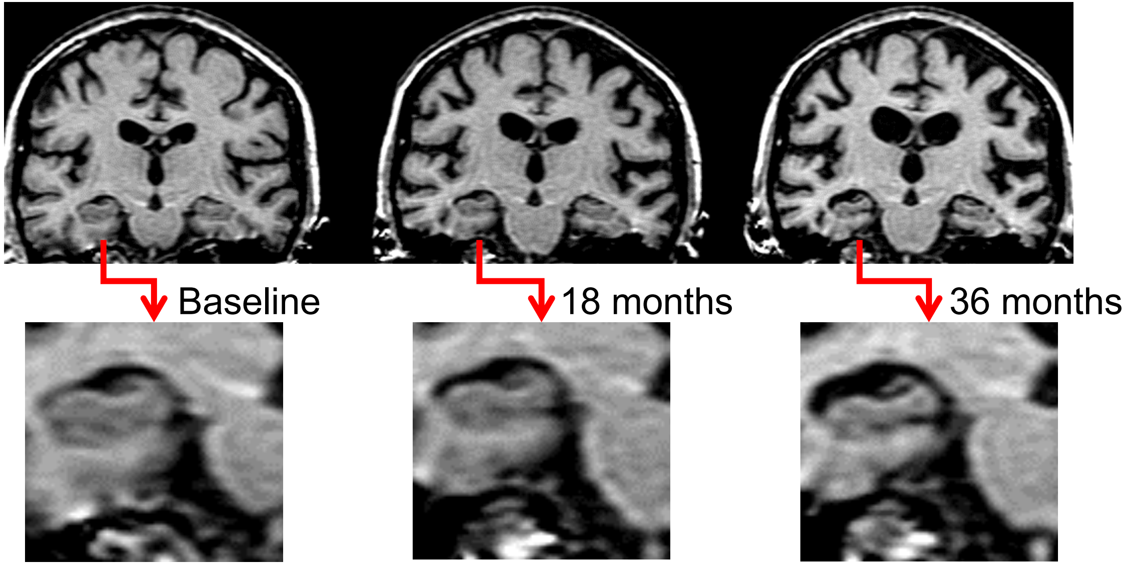
Co-registration: Within subject, within session

- Structural T1 provides high-resolution anatomical context for other lower resolution modalities (fMRI, DWI, PET)
- Regions of interest (ROIs) defined on the structural T1 scan can be transferred to co-registered images
- Tissue properties from segmentation can also provide some information on partial volume effect (mixture of different tissues)



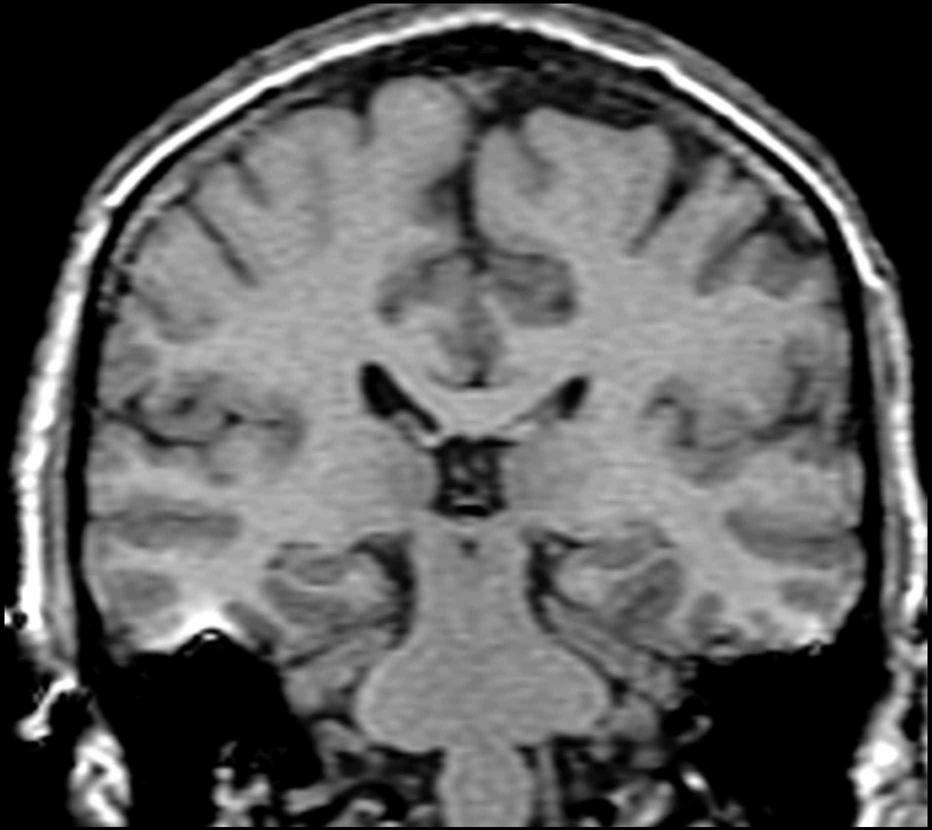
Longitudinal registration: within subject, between sessions

- Register baseline T1 with follow-up scans and measure differences
- More sensitive to disease-related atrophy than cross-sectional measures
- Abnormal rates of atrophy can be detected with scan intervals as small as six months apart (though longer intervals tend to be more reliable)
- Be careful! Check that changes in the images result from disease-related effects, not changes in acquisition (different parameters, movement)



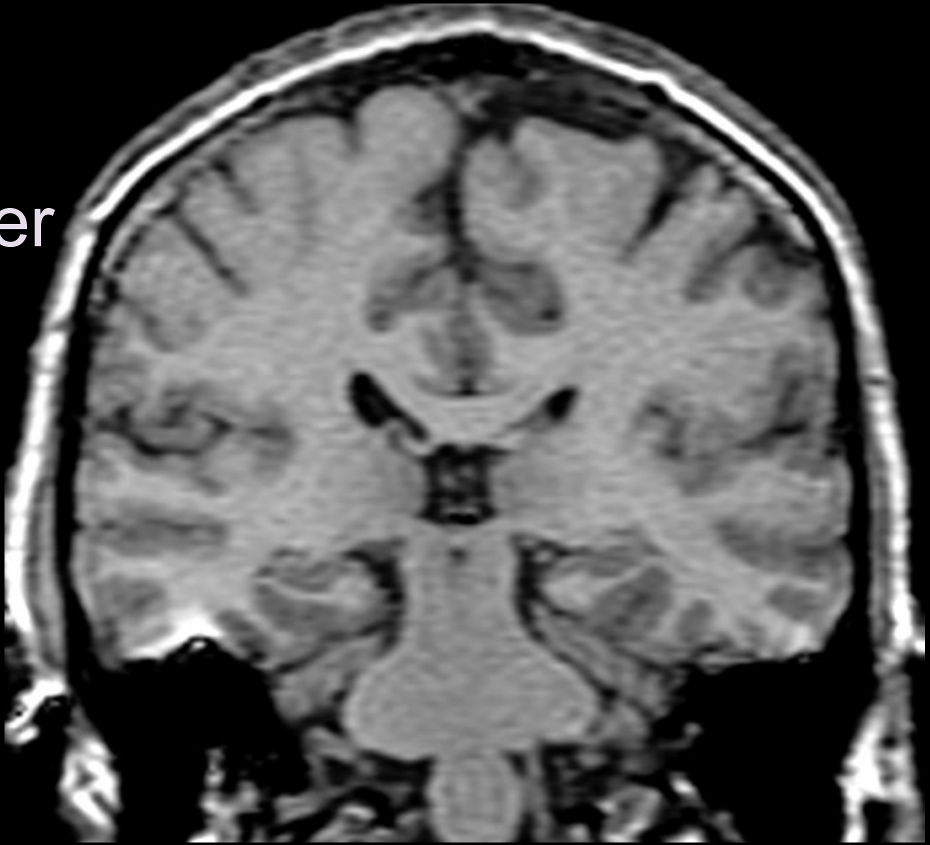
MCI

Scan 1



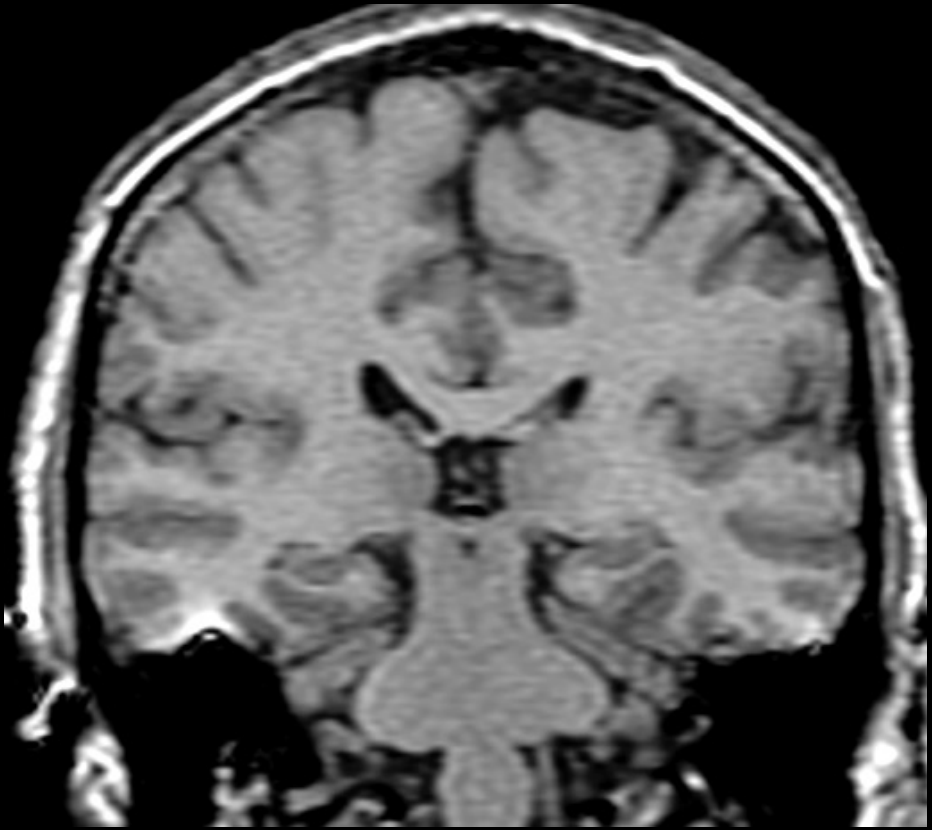
MCI

Scan 2
1 year later



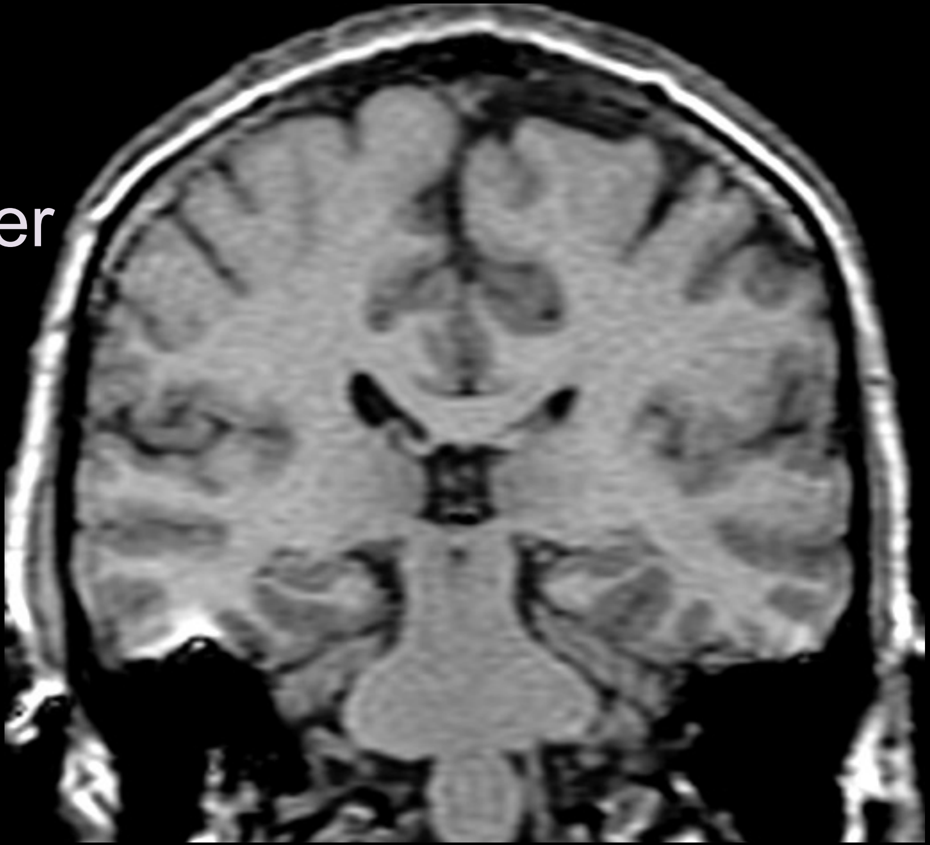
MCI

Scan 1



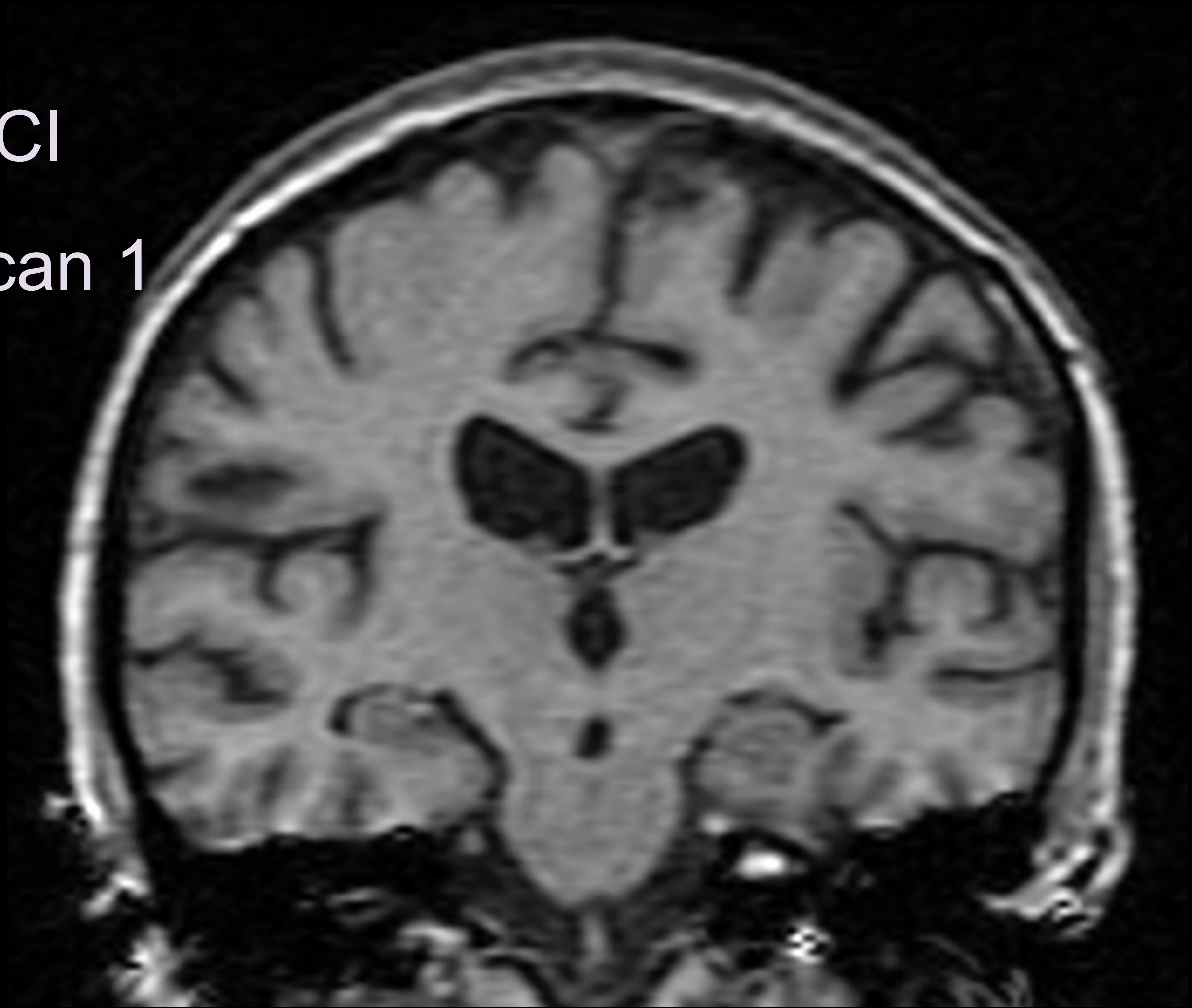
MCI

Scan 2
1 year later



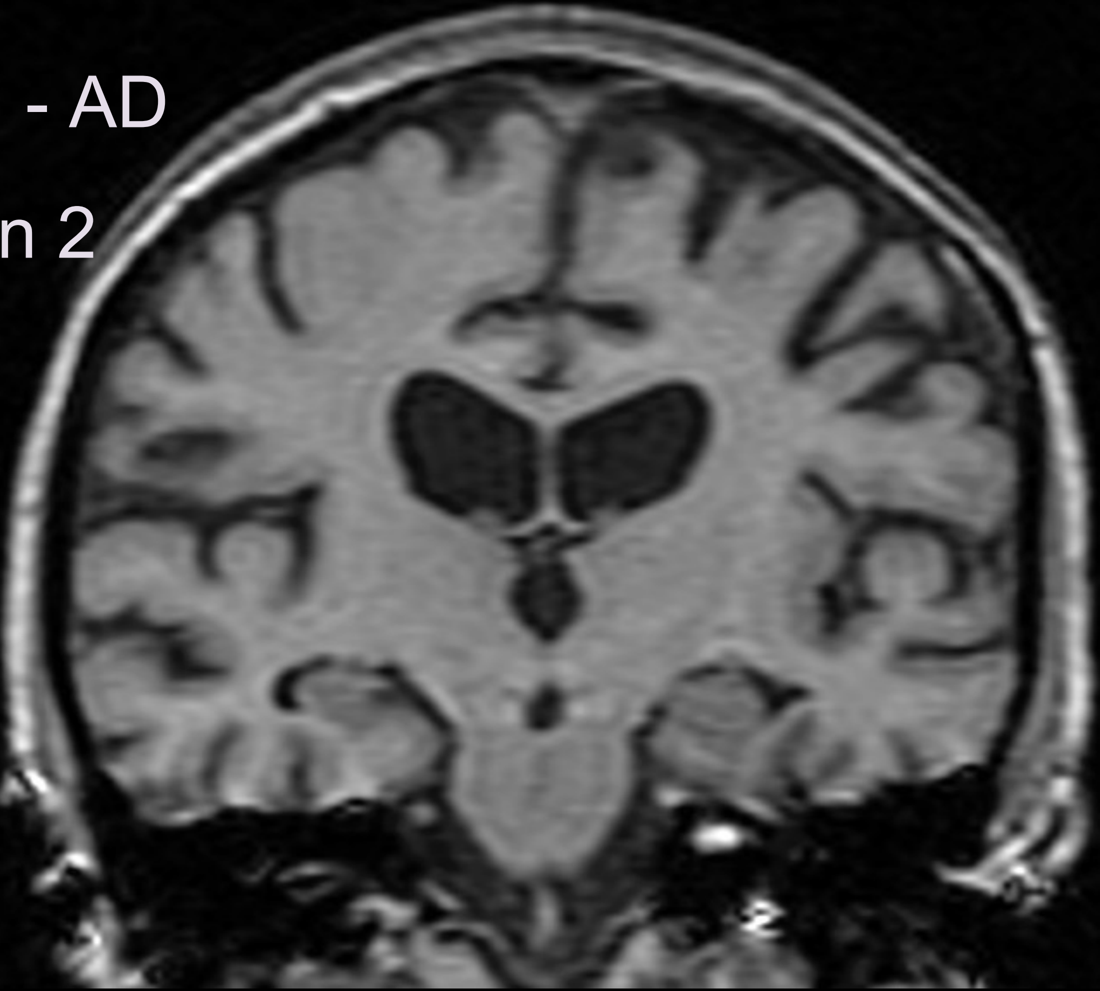
MCI

Scan 1



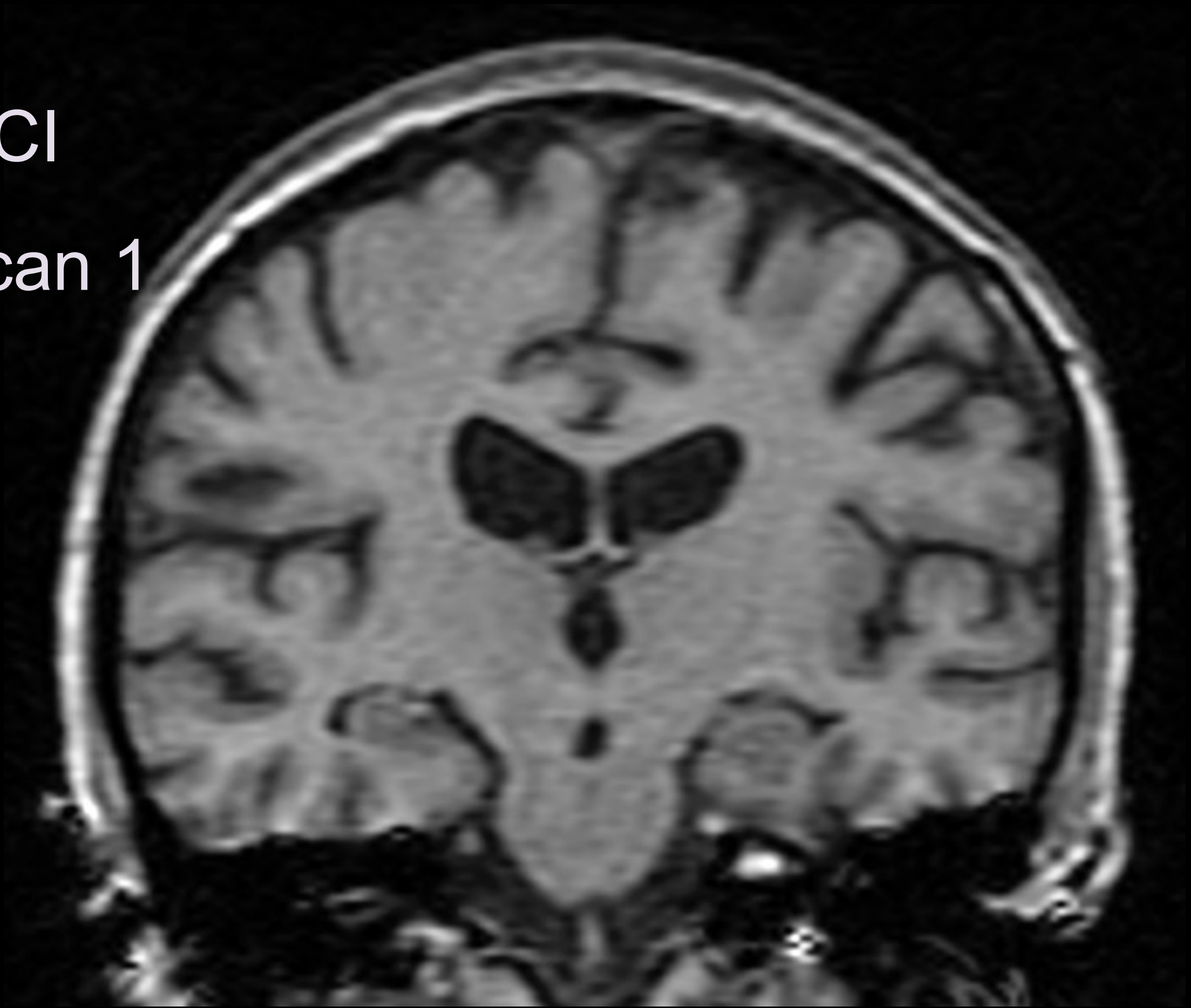
MCI - AD

Scan 2



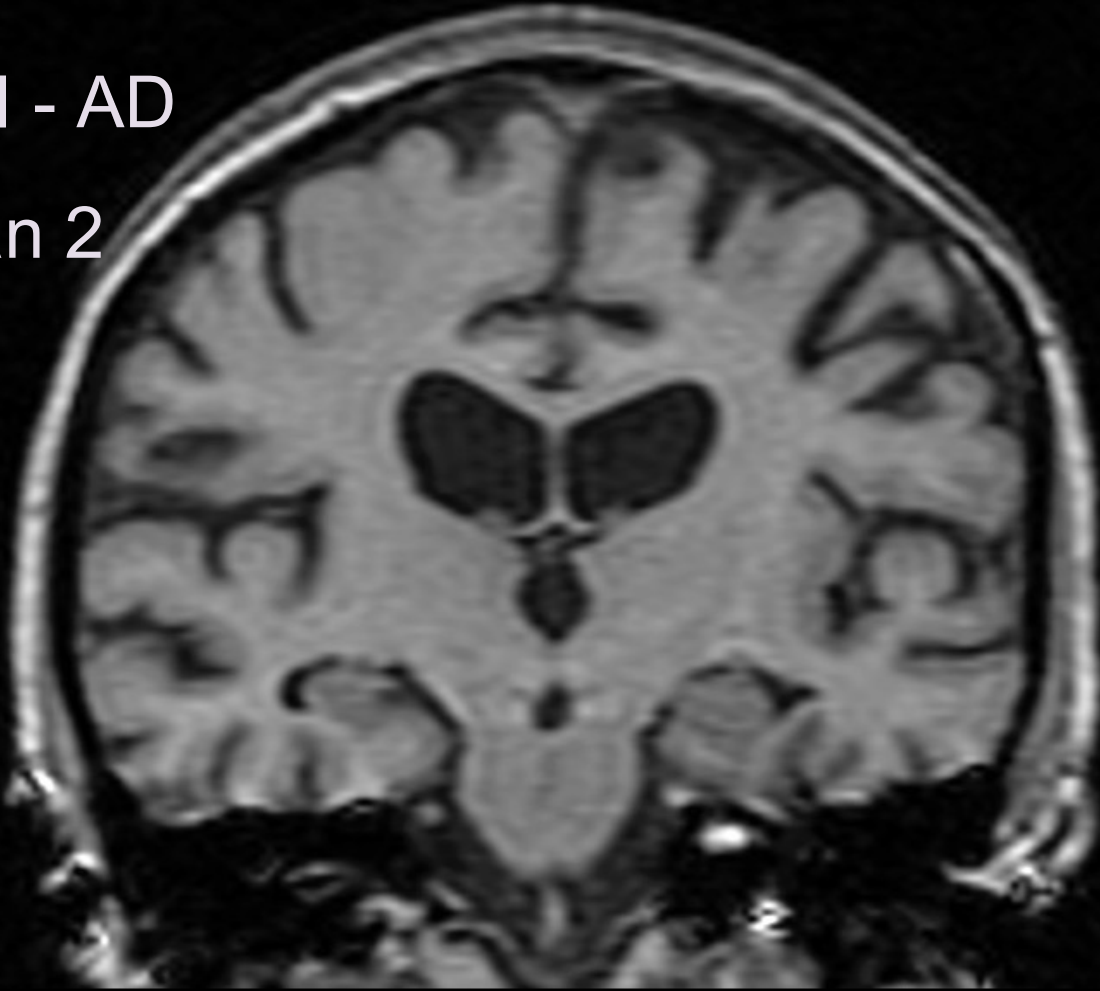
MCI

Scan 1



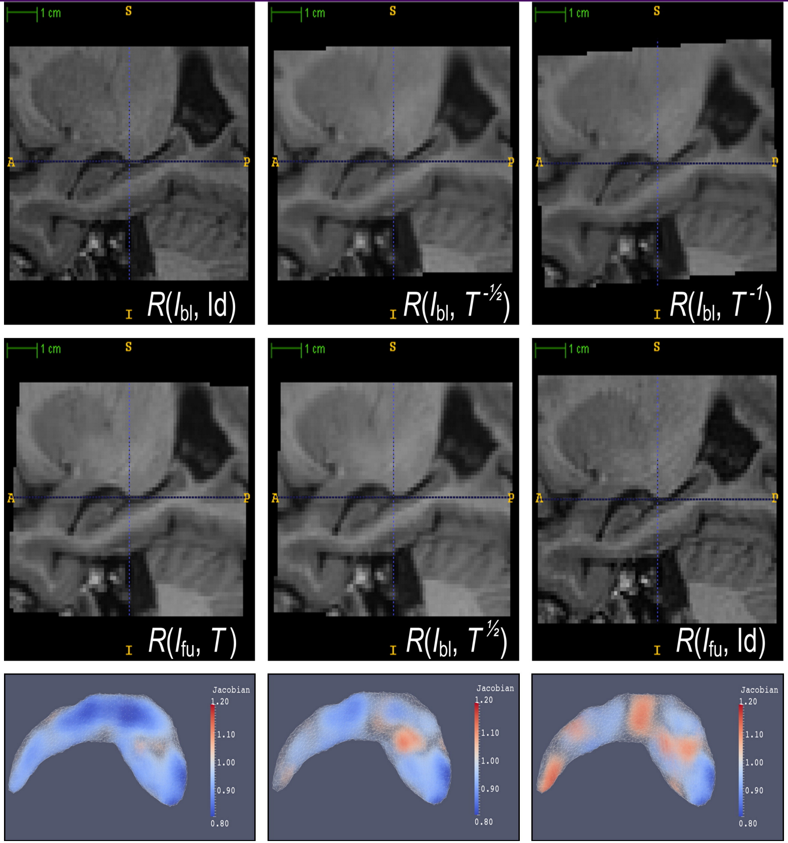
MCI - AD

Scan 2



Longitudinal Registration: Treat all images equally

- Registering all follow-up images to baseline means that these images undergo more processing than the baseline scan
- This creates an asymmetry that results in biased measurements of atrophy
- Be sure to use a pipeline that treats all images equally, often creating a “halfway” or “midpoint” space between all timepoints so that all images are treated equally

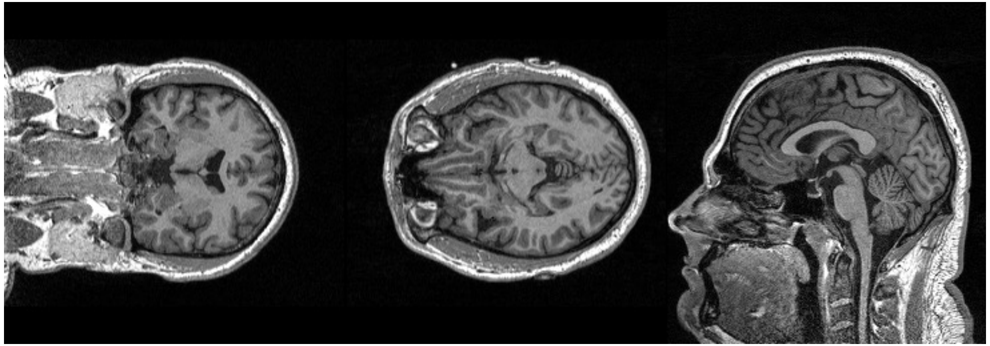


Yushkevich P.A *et al.* (2010). *NeuroImage*, *50*(2), 434–445.

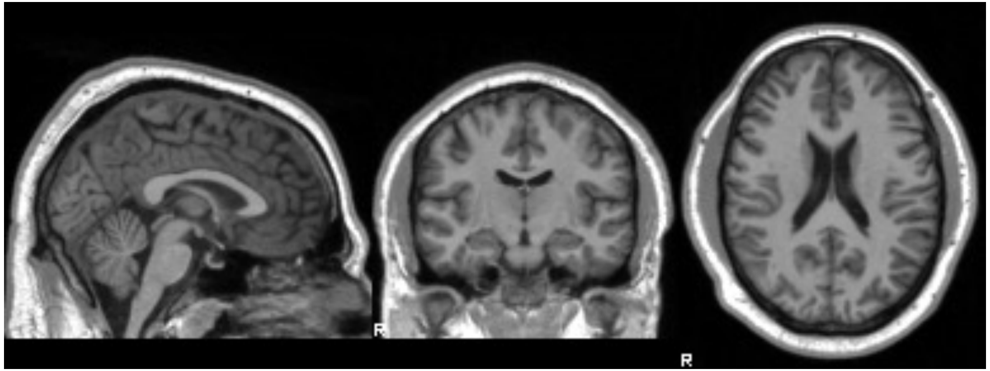
Spatial Normalization: Between-subject

- Warping an individual scan(s) to a population atlas or template.
- After spatial normalization, the same anatomy is in the same area of the image
- The anatomy of every individual is unique, so it is not possible to exactly align images
- Spatially normalizing atlases are based on young, healthy adults to different populations (AD, Down's syndrome, older individuals) can result in greater error and bias

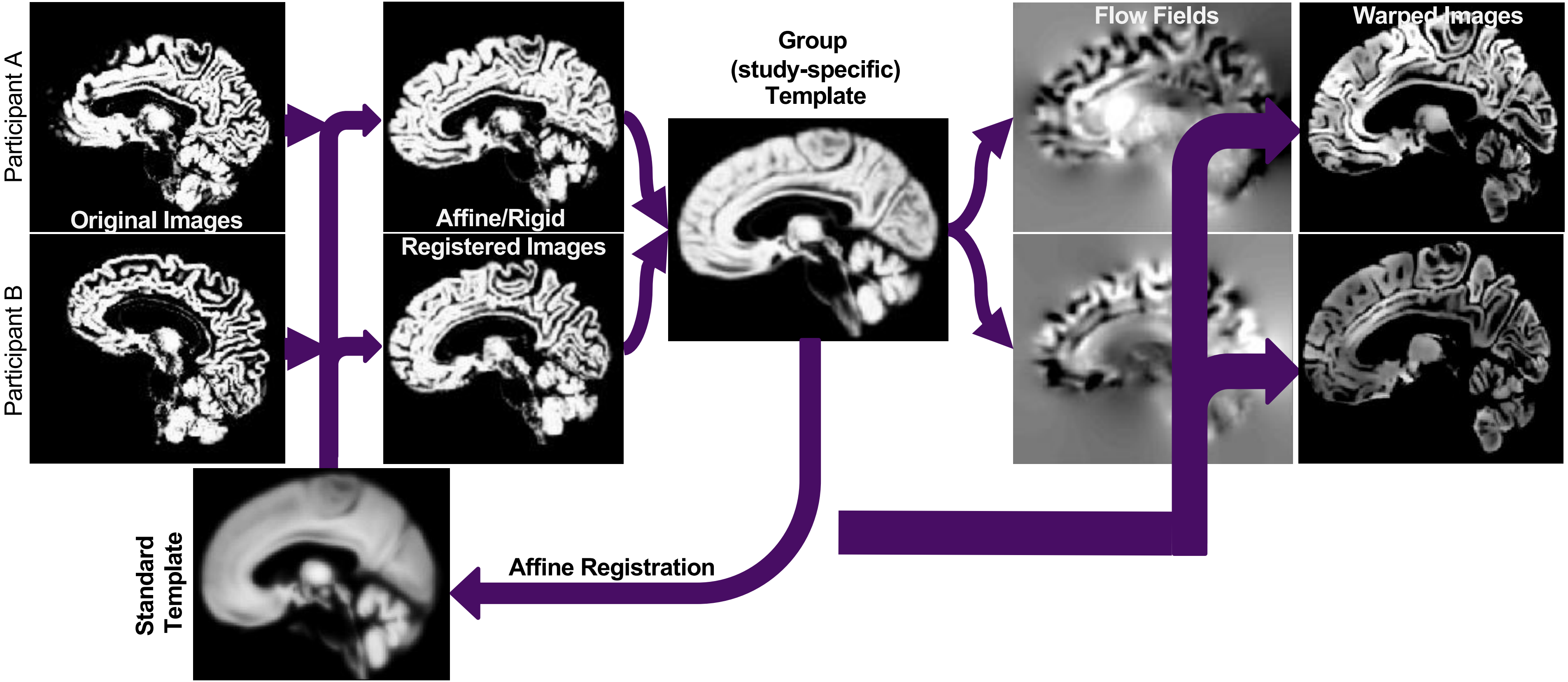
342 Participants - Original



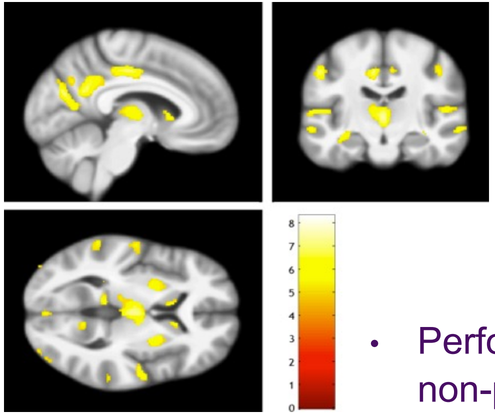
342 Participants - Registered

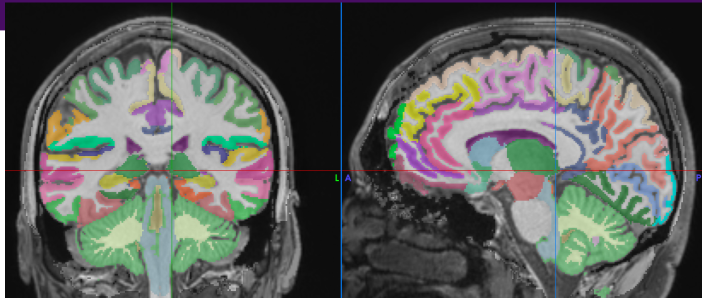


Creating a study-specific template to reduce errors in spatial normalisation



Regional versus voxel/vertex analysis





VOXEL/VERTEX LEVEL

- Perform statistical tests (t-test, F-test, non-parametric) on each voxel/vertex
- Localizes changes to a very high resolution
- Not constrained by anatomical definitions
- Corrections needed for multiple comparisons to control for false positives – reduces sensitivity

REGIONAL LEVEL

- Conventional stats on volume
- Hard segmentation

  Volume = voxel volume * (# voxels)
- Soft segmentation

  Volume = voxel volume * Σ p(x)
- Averaging over region reduces noise, increase SNR
- Volume differences more interpretable
- Can be performed in native or standard space

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What have we learned about dementia from structural MRI?

Please see "Structural and Vascular Imaging" webinars at https://training.alz.org/Research-Webinars

1. Data acquisition → 2. Data preprocessing → 3. Single-subject analysis → 4. Group-level analysis → 5. Statistical inference

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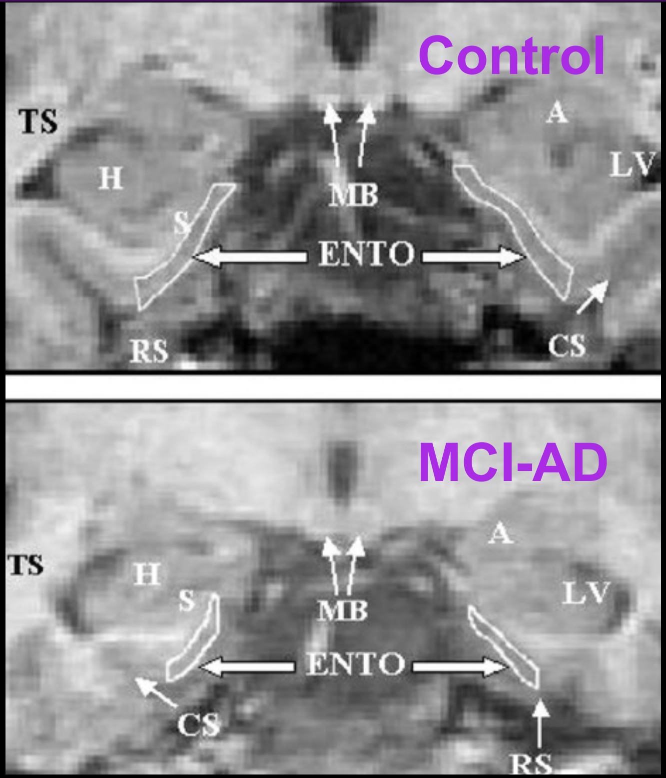
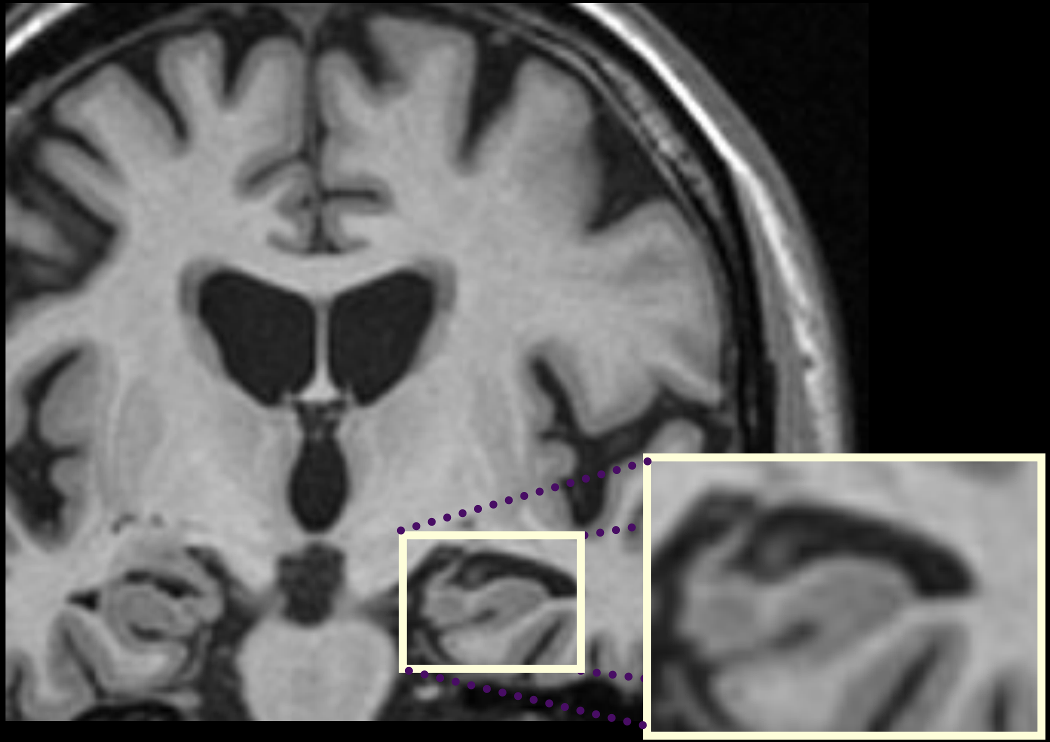
Entorhinal Cortex and hippocampus are some of the earliest sites of atrophy in AD





Devanand *et al* **Neurology** 2007

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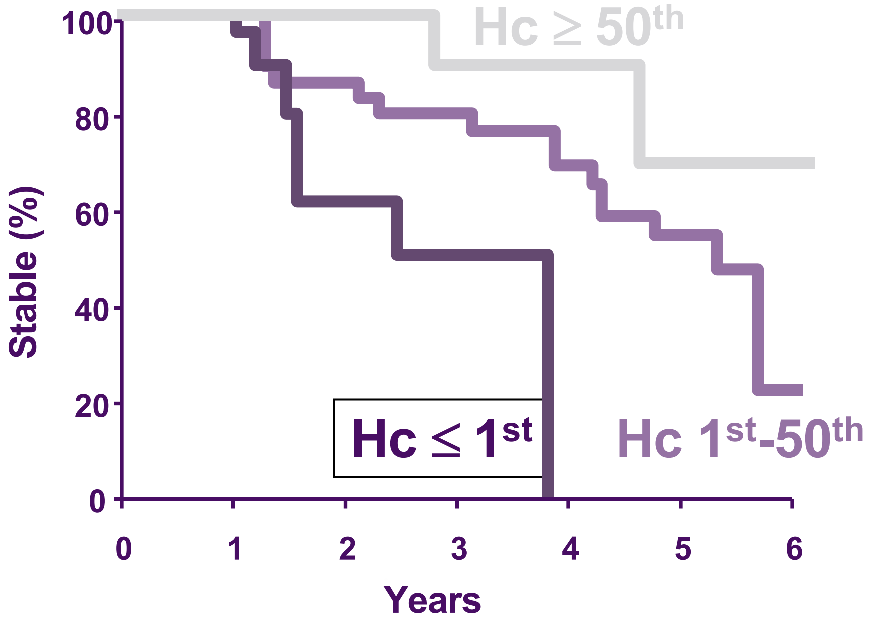
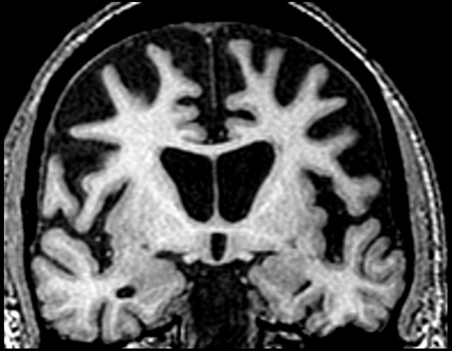
Hippocampal atrophy as a predictor for future decline



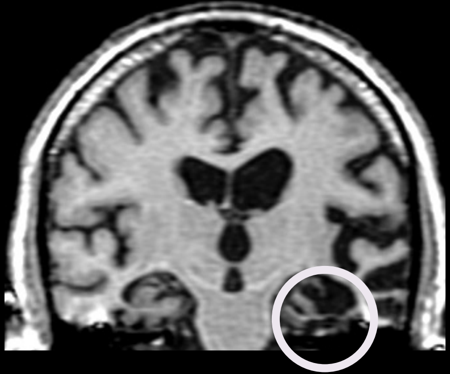
- A marker for AD
- A risk factor for progression MCI → AD

Jack *et al* **Neurology**: '97, '99; De Leon **AJNR** '93 etc; Apostolova **Arch Neurol** '06; De Carli **Arch Neurol** '07

Focal atrophy patterns helpful for differential diagnosis



Frontotemporal dementia



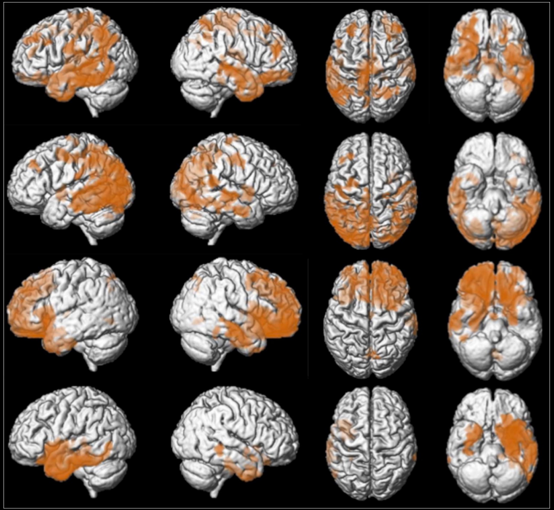
Semantic dementia: Ubi +ve, tau -ve

Alzheimer's Disease

Posterior Cortical Atrophy

Frontotemporal Dementia

Semantic Dementia



Adapted from Hedderish, et al., *European Radiology*, 2020

Neary *Lancet Neurol* 2005; Chan *Ann Neurol* 2001

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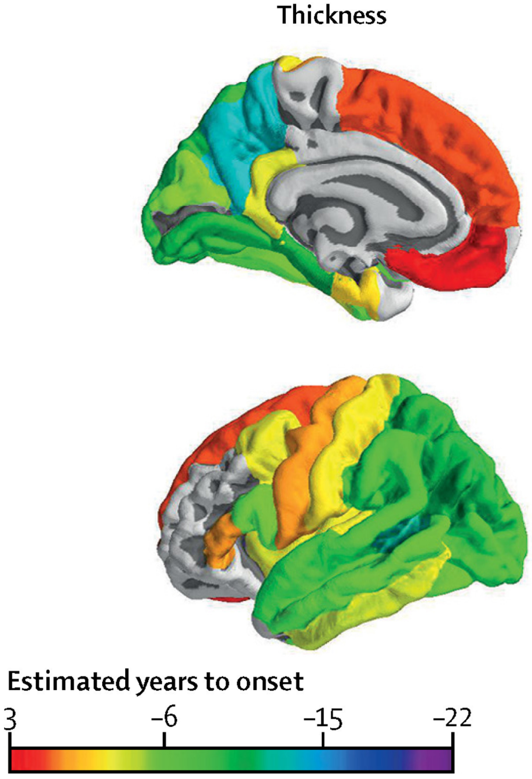
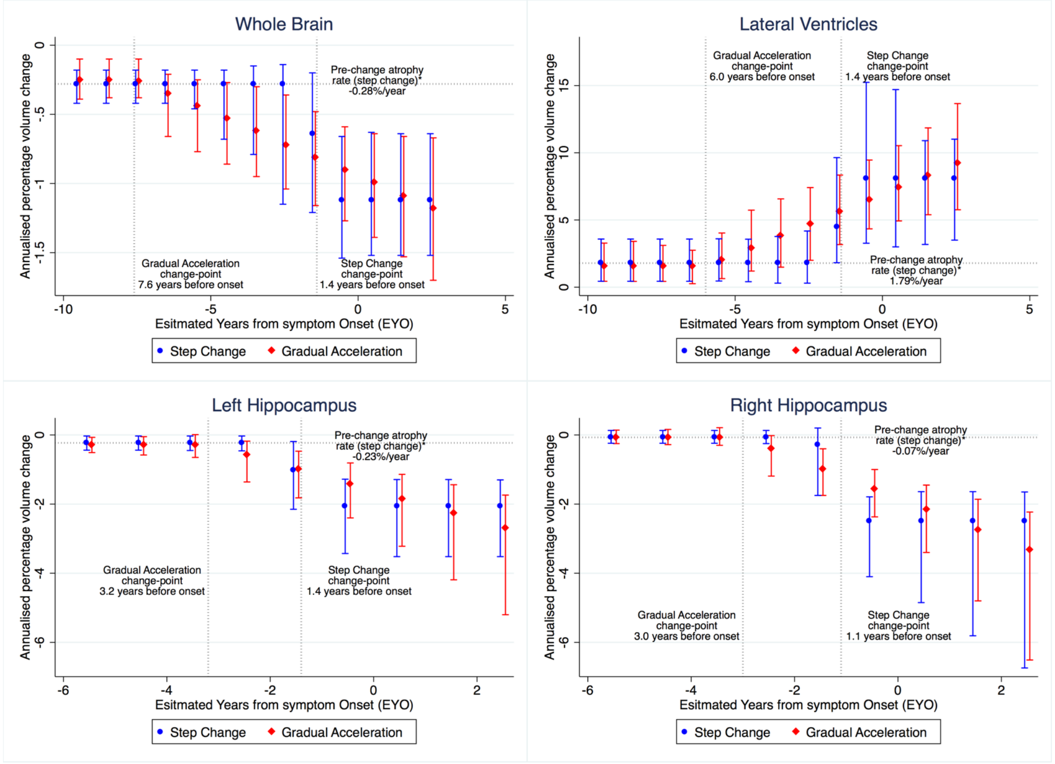
Longitudinal MRI detects atrophy before onset of symptoms



Gordon et al, *Lancet Neurol.* 17(3):241-250, 2018



Kinnunen et al, *Alz & Dem.* 14(1):43-53, 2018

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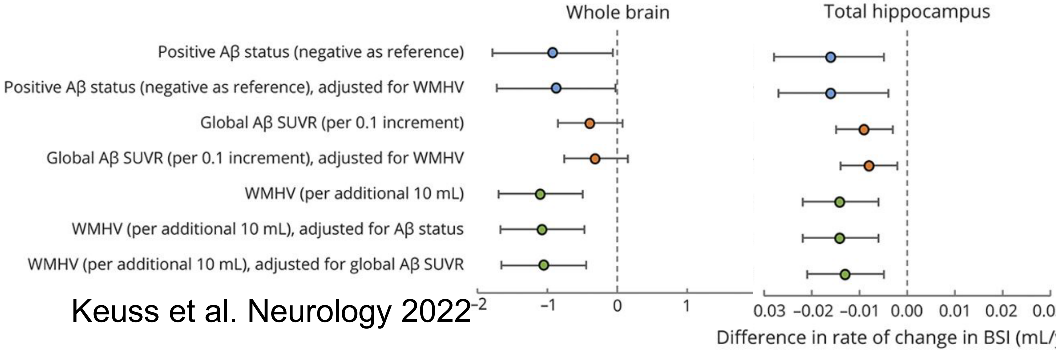
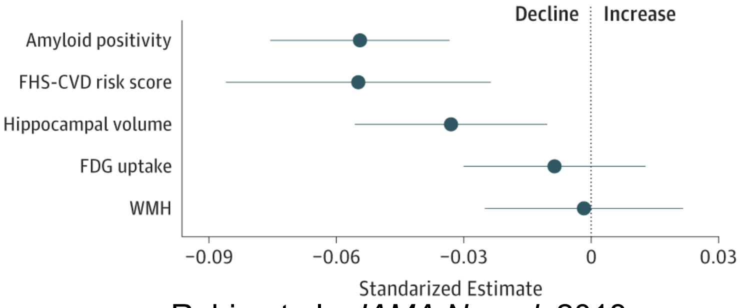
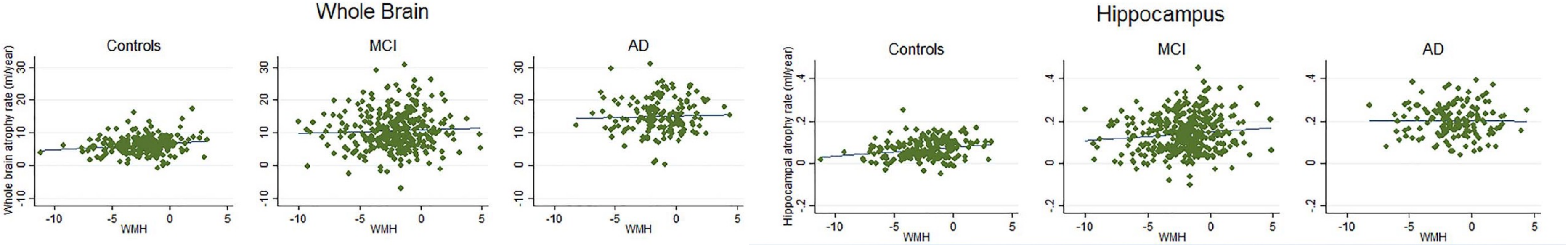
Vascular contributions to AD



Keuss et al. Neurology 2022



Rabin et al., *JAMA Neurol*, 2018



Barnes Neurobiology Aging 2013
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POP QUIZ!

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QUESTION 1

The earliest structure in the brain where atrophy can be detected is:

a) Cerebellum
b) Hippocampus
c) Posterior Cingulate
d) Entorhinal Cortex
e) Fusiform Gyrus

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QUESTION 2

The process of bias correction involves:

a) Removing a slowly varying intensity inhomogeneity caused by small imperfections in the magnetic field
b) Removes noise and differences across scanners
c) Correct for systematic changes when comparing scans between different scanners

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QUESTION 3

Which one of these statements is true about spatial normalization?

a) It is important to get all of the image to line up exactly
b) Study-specific templates that are representative of the participants in the study reduces potential errors
c) Affine registrations are sufficient for spatial normalization.

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The Basics of Neuroimaging Series

THANK YOU!

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