Building an ex vivo MRI Atlas of the Earliest Brain Regions Affected by Alzheimer's Disease Pathology

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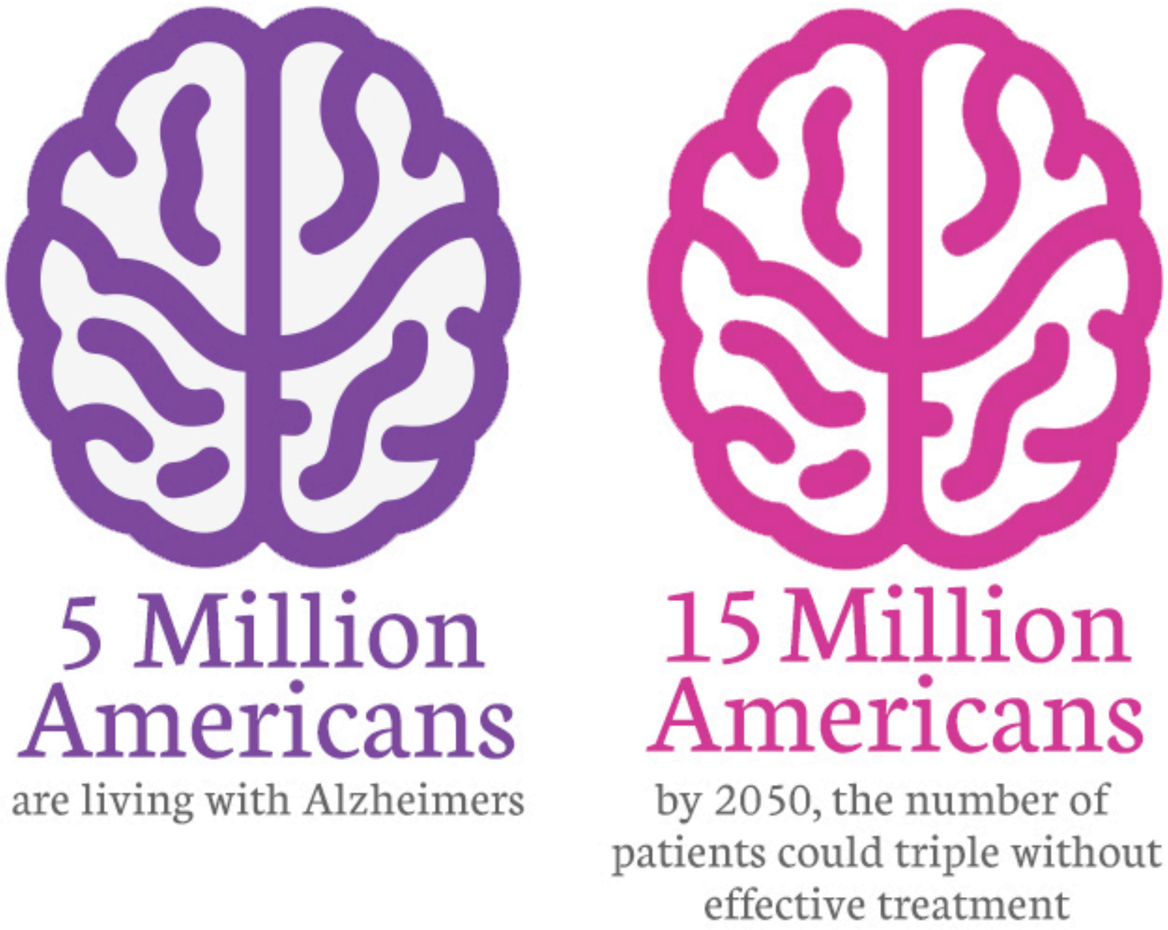
Alzheimer's Disease (AD)

- Most common cause of dementia among older adults (60-80%)
- Decline in memory, language, and logical thinking



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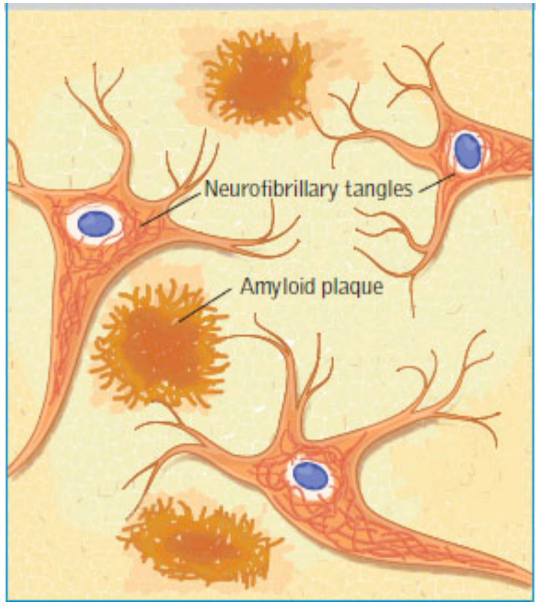
https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet
https://www.docpanel.com/blog/post/alzheimers-disease-and-benefit-radiology-second-opinion

Neuropathology of Alzheimer's Disease

- Changes in the brain begin a decade or more before memory and other cognitive problems appear

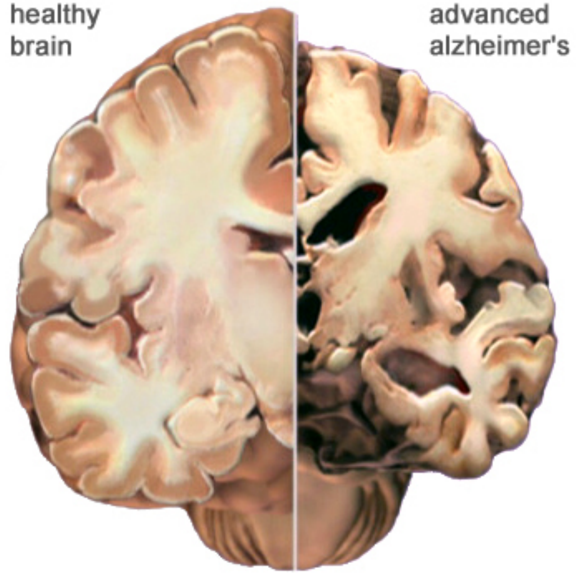


Amyloid plaques
extracellular deposits of beta amyloid- Aβ

?

?

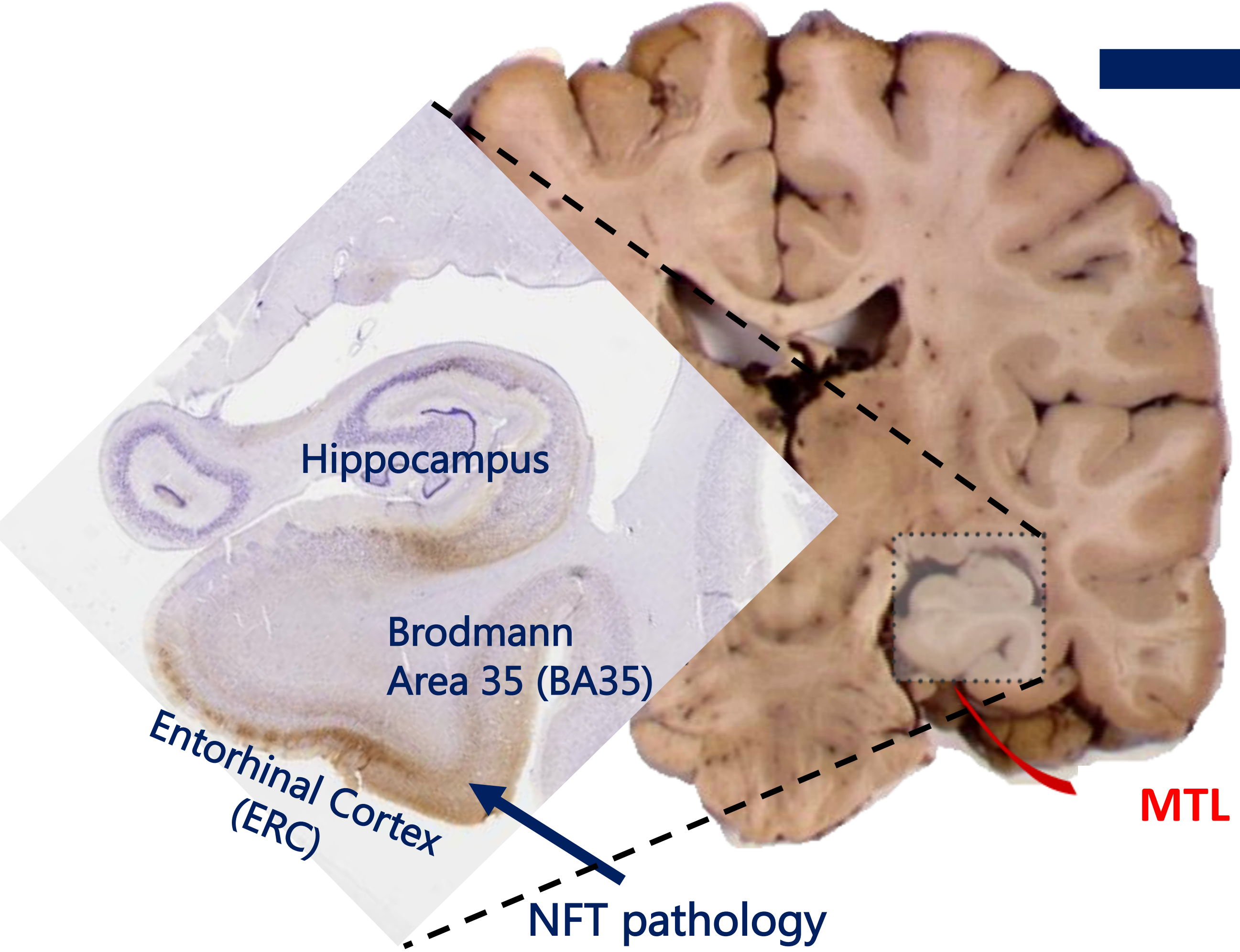
Neurofibrillary Tangles
intracellular accumulation of tau protein



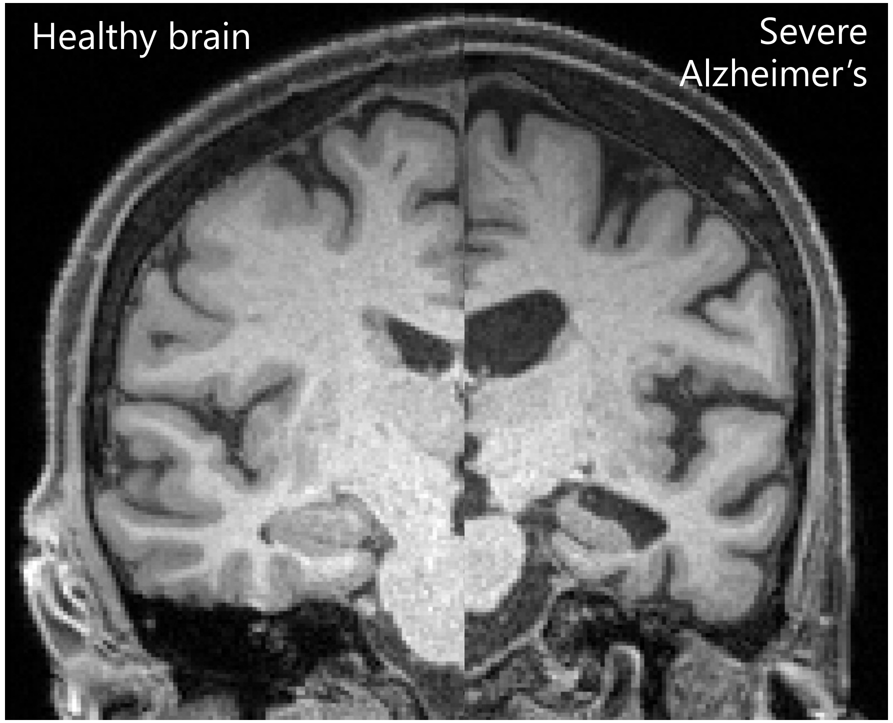
Neurodegeneration
Shrinkage of the cortex

Jin J. Alzheimer Disease. *JAMA.* 2015;313(14):1488. doi:10.1001/jama.2015.2852

Earliest Neurofibrillary Tangle (NFT) pathology occurs in the Medial Temporal Lobe (MTL)



in vivo **biomarker:** volumetric changes in structural MRI (sMRI)

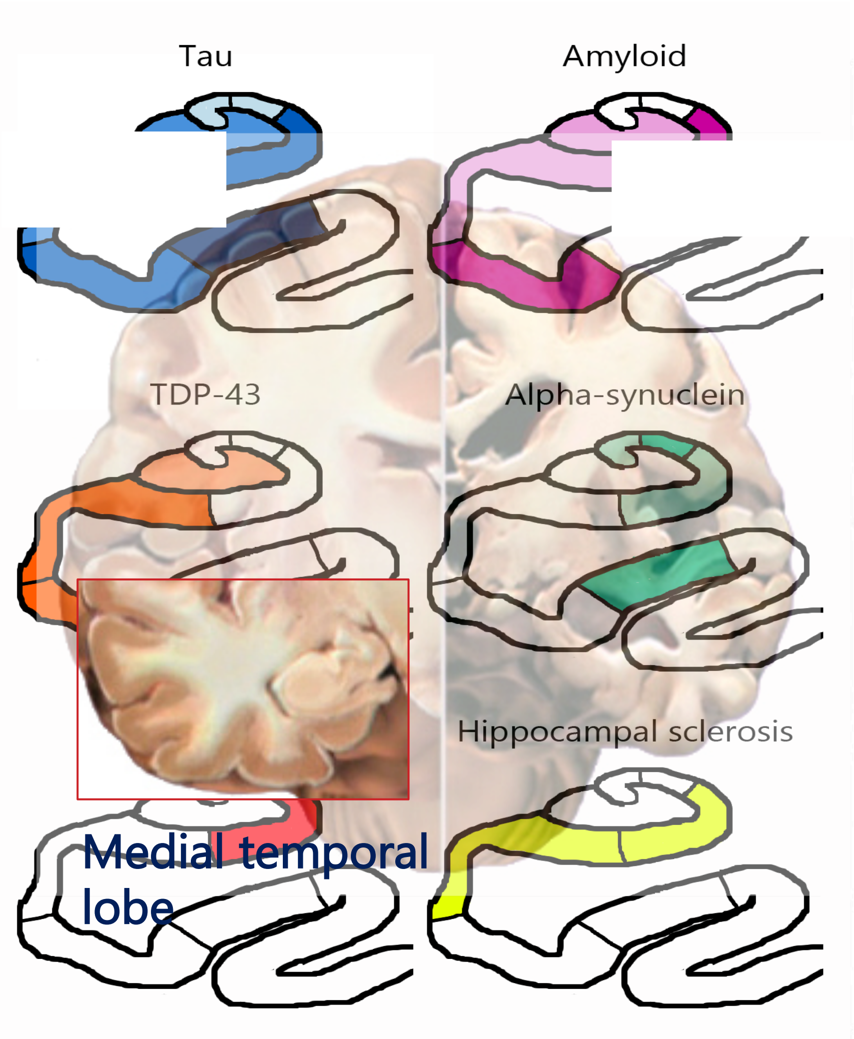


Focusing on the MTL for better biomarkers

- NFT pathology follows a characteristic pattern of spread

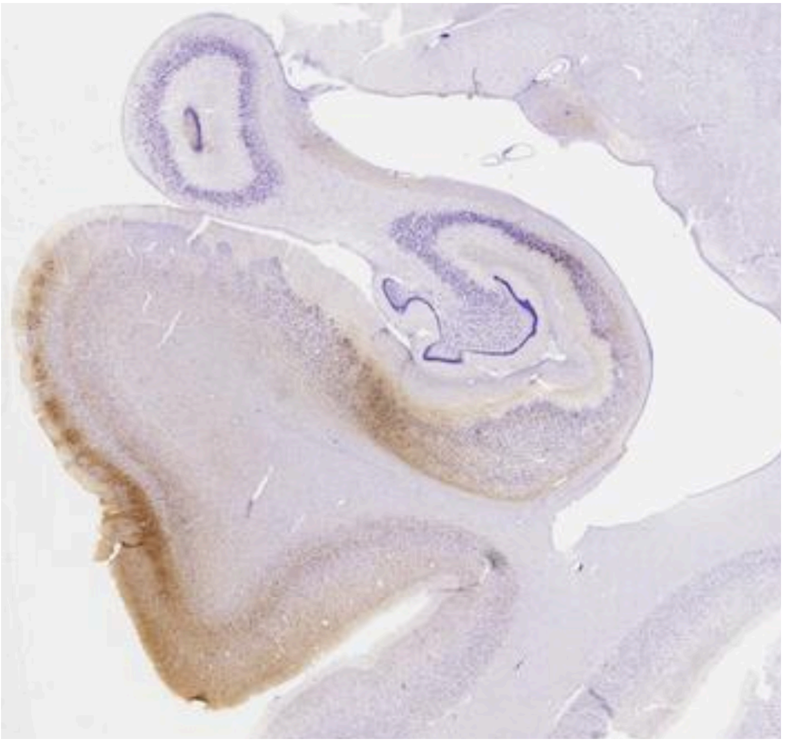
- MTL also affected by other commonly co-morbid pathologies

Need to identify and obtain structural measurements from AD-specific regions

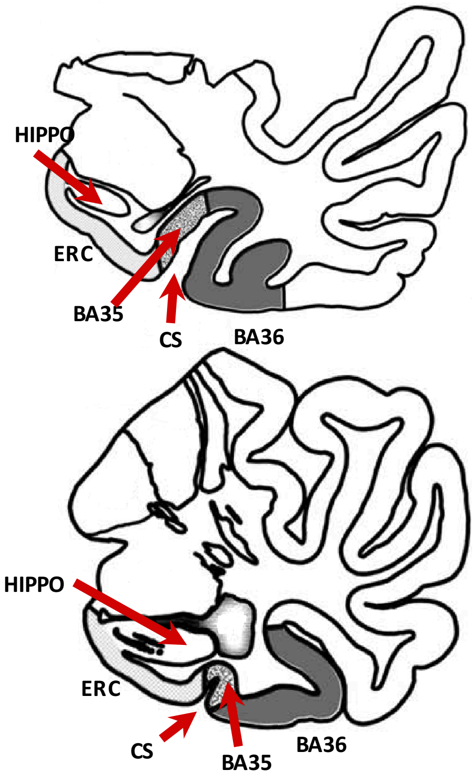


Darker colors indicate regions that are affected earlier

Challenges in existing MTL morphometry studies in MRI



2D nature of histology (based on one or two sections)



Anatomical variability

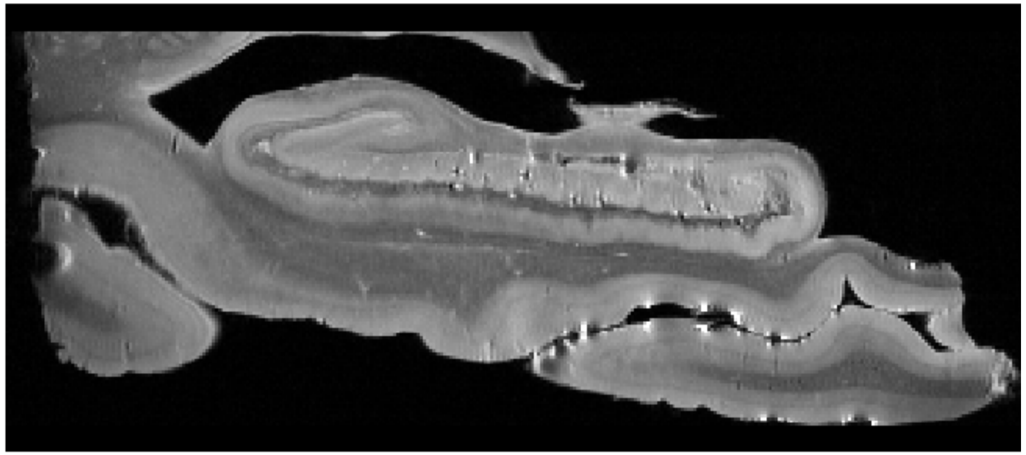
T1-weighted, 3 Tesla
whole-brain 1 x 1 x 1 mm^3

in vivo studies are limited by low-resolution of images

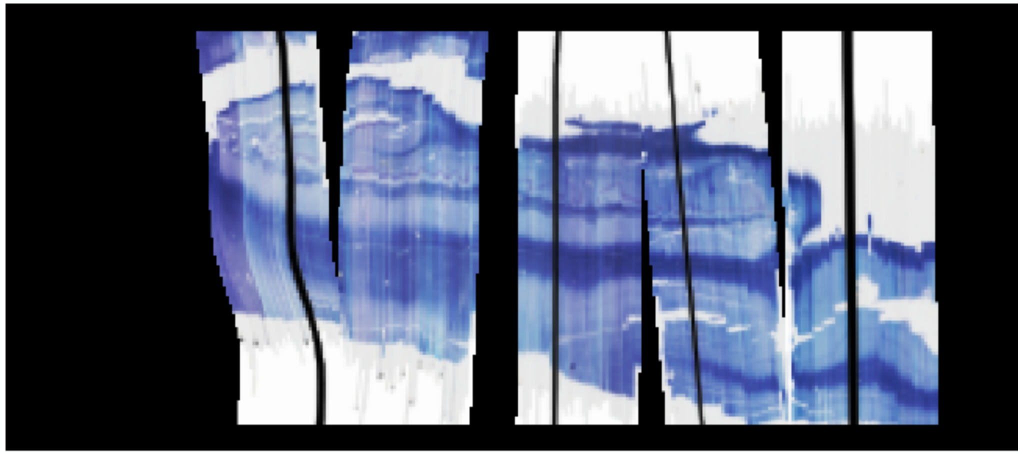
Guiding Hypothesis

Ex vivo imaging combined with **serial histopathology** provides a direct link between MRI measures of MTL structure and the underlying pathology.

In vivo MRI biomarkers defined over **MTL regions where structural changes correlate most strongly with AD-specific pathology,** would be **more sensitive** to disease progression during preclinical AD.

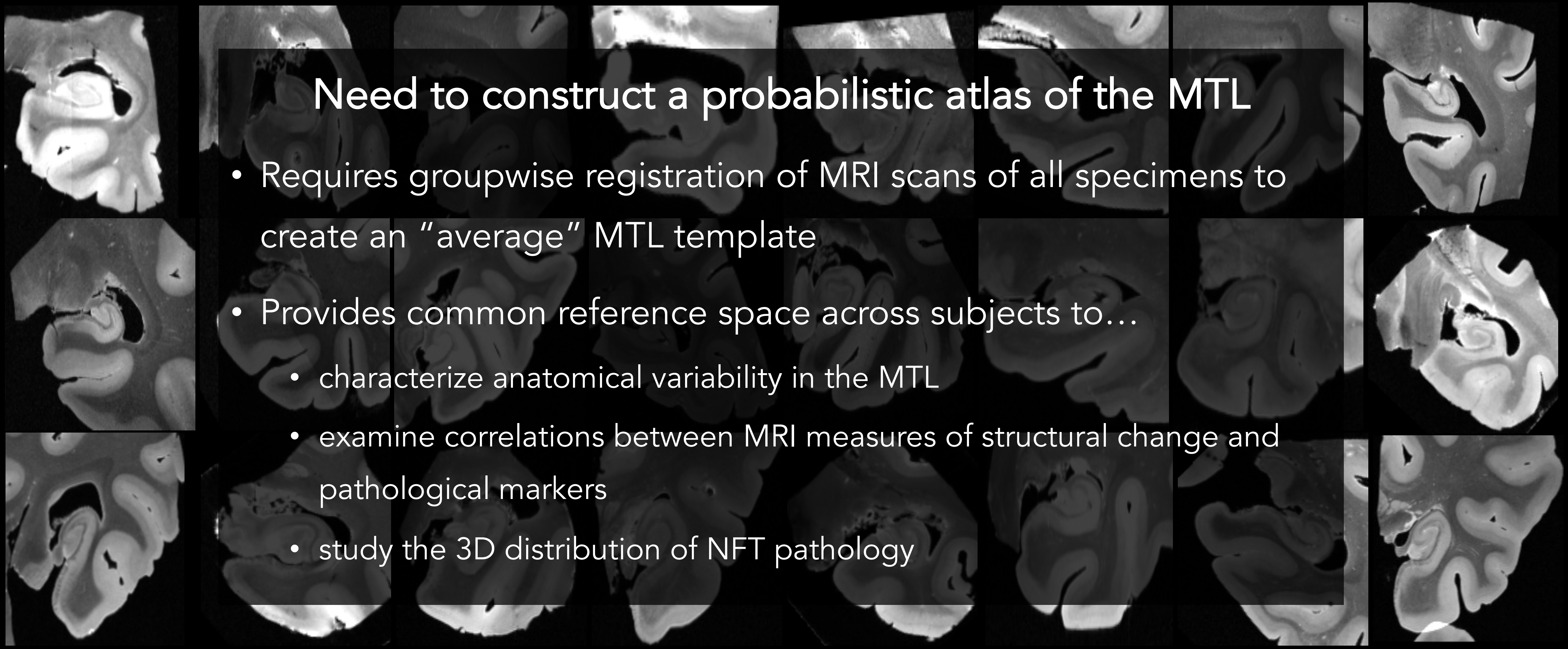


ex vivo MRI



Reconstructed histology

Adler, Wisse et al. "Characterizing the human hippocampus in aging and Alzheimer's Disease suing a computational atlas derived from ex vivo MRI ad histology" (2018)

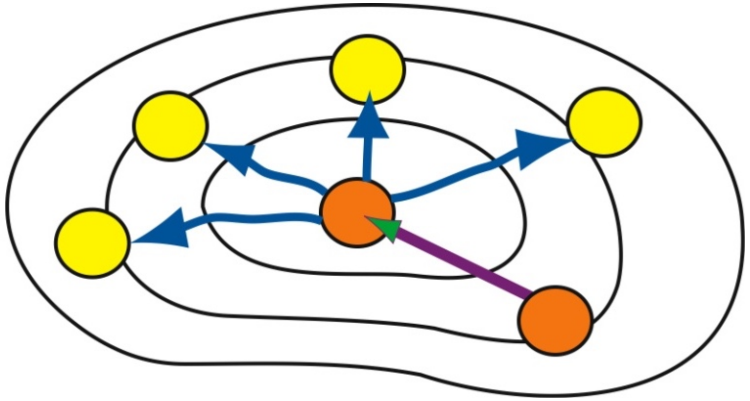


Need to construct a probabilistic atlas of the MTL

- Requires groupwise registration of MRI scans of all specimens to create an "average" MTL template
- Provides common reference space across subjects to…
  - characterize anatomical variability in the MTL
  - examine correlations between MRI measures of structural change and pathological markers
  - study the 3D distribution of NFT pathology

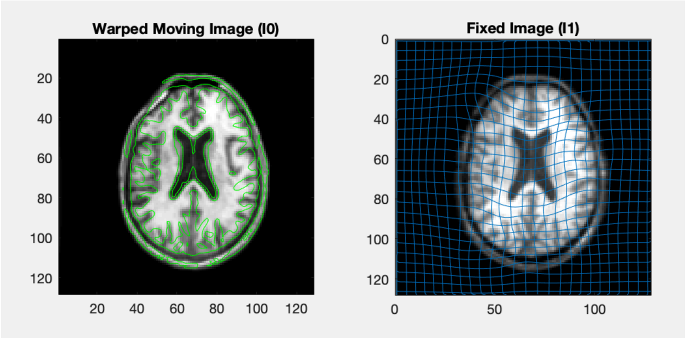
- **9.4T**, T2-weighted MRI of **24 MTL autopsy** specimens (0.2 x 0.2 x 0.2 mm^3 resolution)
- 21 specimens had **semi-quantitative pathological rating**

The conventional approach is to build an unbiased population template using iterative deformable registration and image averaging

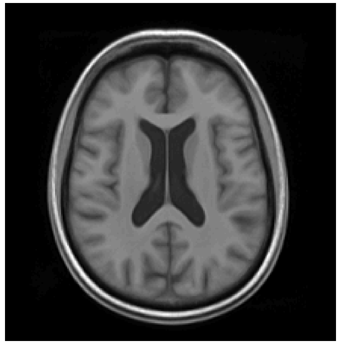


Algorithm 1 Atlas construction framework

Input : N volume inputs
Output: Template atlas volume
for $k = 1$ to max_iters **do**
  Fix images I_i^k, compute the optimal template $\hat{I}^k = \frac{1}{N}\sum_{i=1}^{N} I_i^k$
  for $i = 1$ to N **do** {loop over the images}
    Fix the template $\hat{I}^k$, solve pairwise-matching problem between I_i^k and $\hat{I}^k$
    Update the image with optimal velocity field
  end for
end for

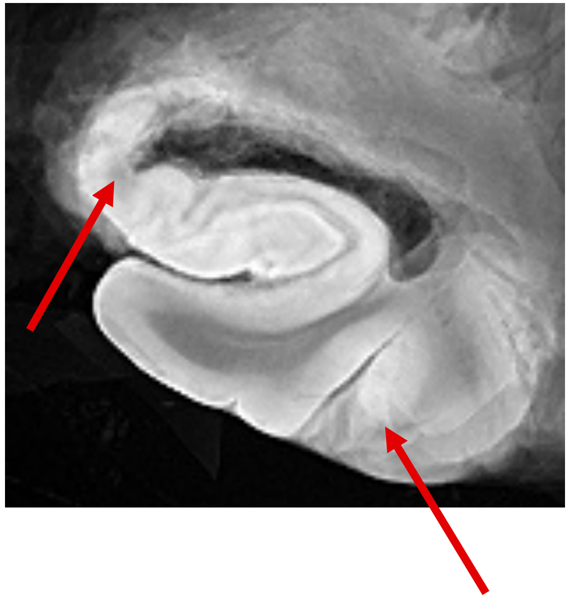


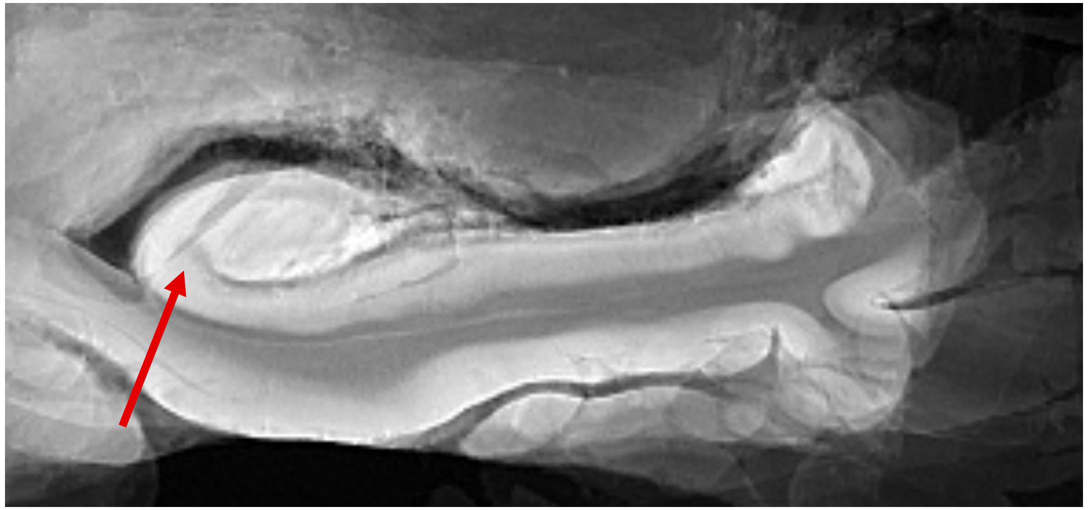
Deformable registration



Template from n=20 scans

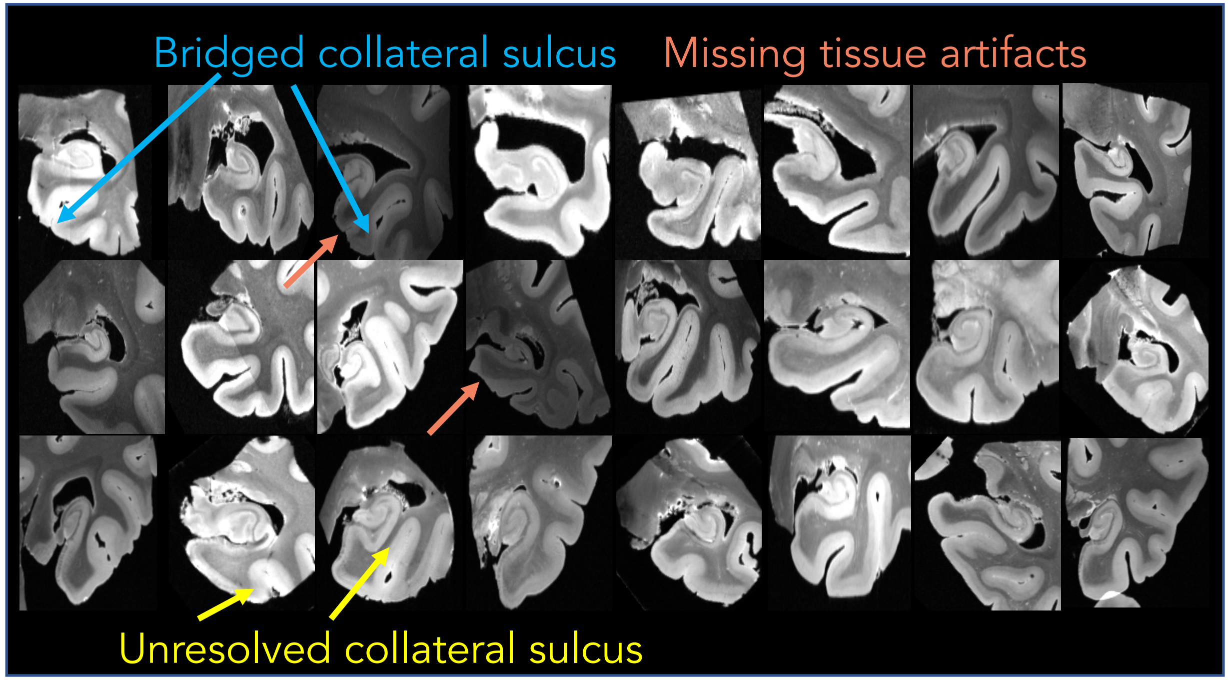
In ex vivo MRI, the unbiased population template approach does not do a good job of capturing complex anatomical details





A shape + intensity approach to building an ex vivo atlas

- Requires segmentations of MTL to guide registration
- Interslice-interpolation used to facilitate manual segmentation
- Challenges:
  - Unresolved sulcal folds
  - Image artifacts



Ravikumar et al. "Facilitating manual segmentation of 3D datasets using contour and intensity guided interpolation"(ISBI 2019)

A shape + intensity approach to building an ex vivo atlas

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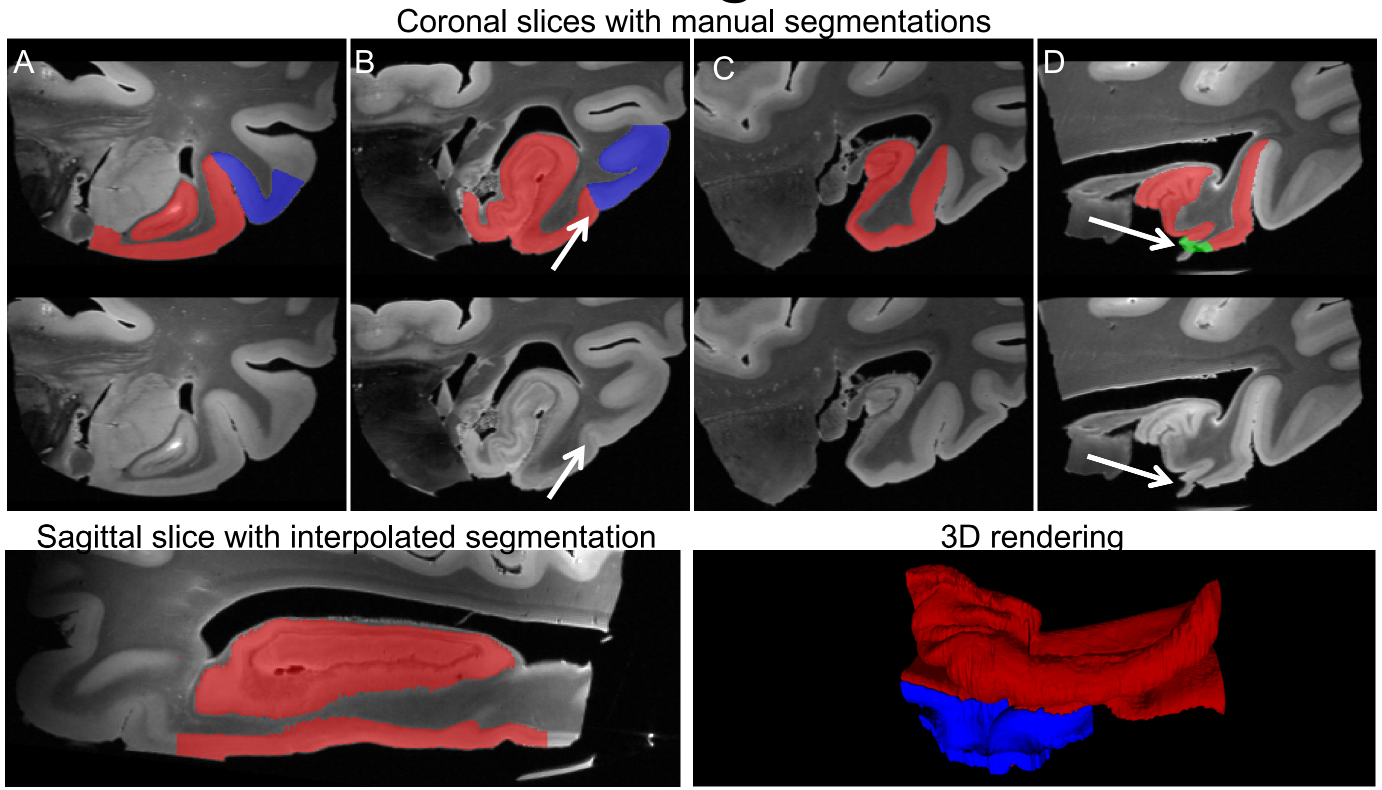
- Interslice-interpolation used to facilitate manual segmentation
- Challenges:
  - Unresolved sulcal folds

  - Explicit labelling to enforce a separation (blue)

  - Image artifacts

  - Explicit label to mask out affected regions from intensity-based registration (green)



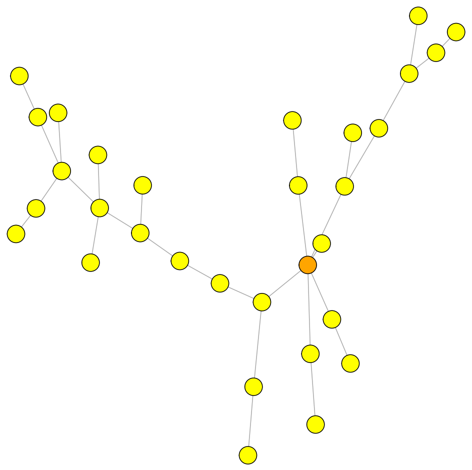
Ravikumar et al. "Facilitating manual segmentation of 3D datasets using contour and intensity guided interpolation"(ISBI 2019)

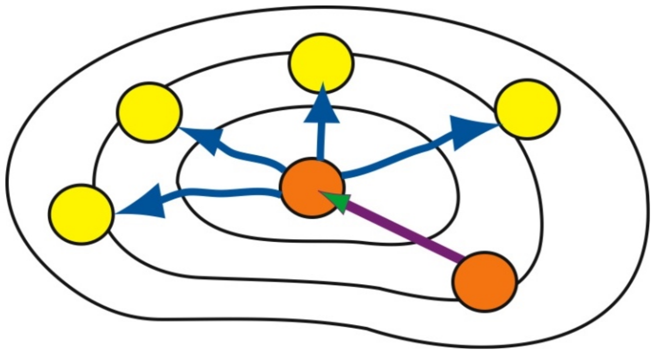
The shape + intensity approach to building an ex vivo atlas of the MTL consists of three stages

1. Shape Matching

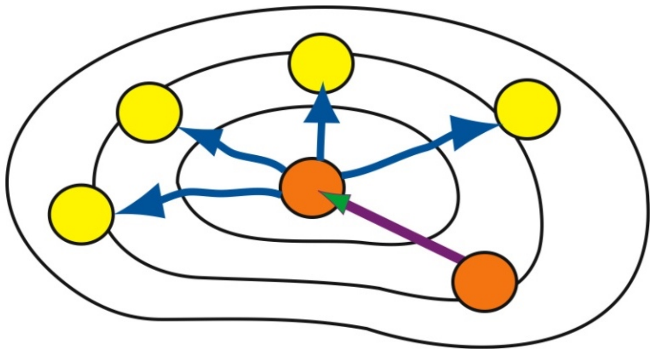
2. Shape Averaging

3. Groupwise Intensity Registration





(in shape space)



(in image space)

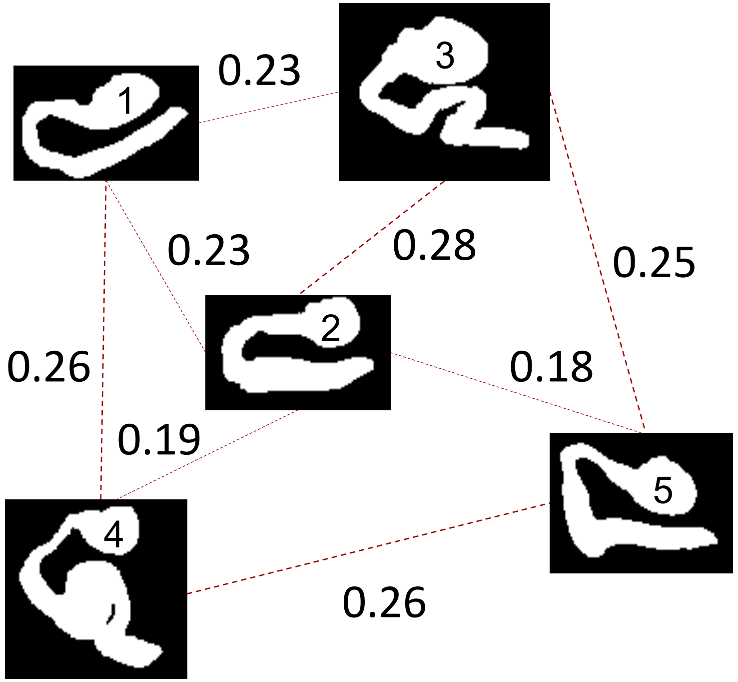
Uses a graph-based approach to shape matching

1. Shape Matching → 2. Shape Averaging → 3. Groupwise Intensity Registration

- A complete graph is constructed from all shapes
- Edges weighted by shape dissimilarity

$$\eta_{ij} = 1 - \frac{1}{2}\mathrm{GDSC}(\mathbf{S}_\mathrm{i}, \mathbf{S}_\mathrm{j} \circ \mathrm{A}^{\mathrm{rough}}_{\mathrm{i}\to\mathrm{j}} \circ \phi^{\mathrm{rough}}_{\mathrm{i}\to\mathrm{j}})$$

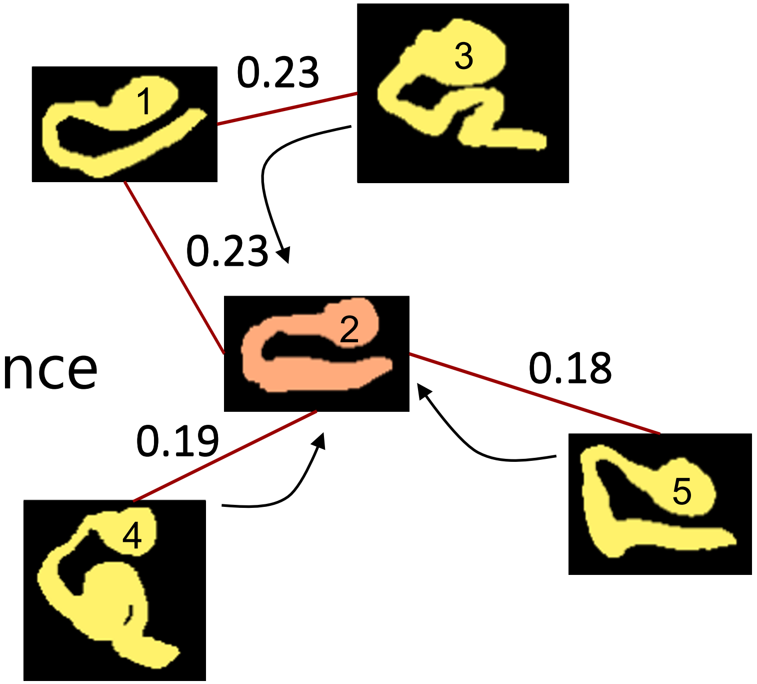
$$- \frac{1}{2}\mathrm{GDSC}(\mathbf{S}_\mathrm{i} \circ \mathrm{A}^{\mathrm{rough}}_{\mathrm{j}\to\mathrm{i}} \circ \phi^{\mathrm{rough}}_{\mathrm{j}\to\mathrm{i}}, \mathbf{S}_\mathrm{j})$$



Use a graph-based approach to shape matching

1. Shape Matching → 2. Shape Averaging → 3. Groupwise Intensity Registration

- A minimum spanning tree (MST) is formed on this graph
- The root of the tree is identified
- All shapes are deformed to the root shape using the sequence of deformable registrations following the MST paths



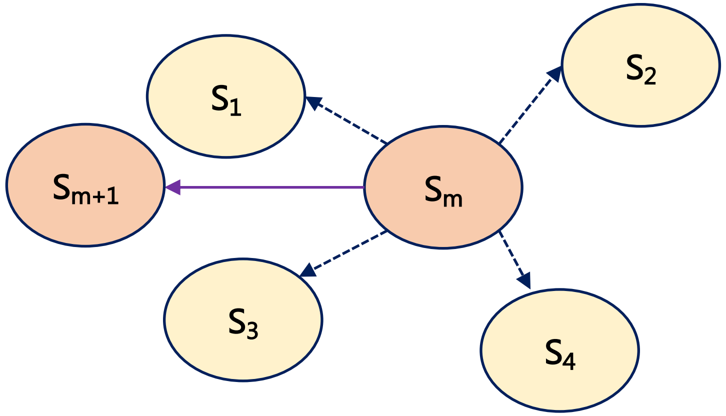
Shape averaging using the geodesic shooting framework

1. Shape Matching → 2. Shape Averaging → 3. Groupwise Intensity Registration

- Transformation represented by initial momentum (geodesic shooting)

Compute diffeomorphic transformation to match average shape, S_m to subject space, S_j

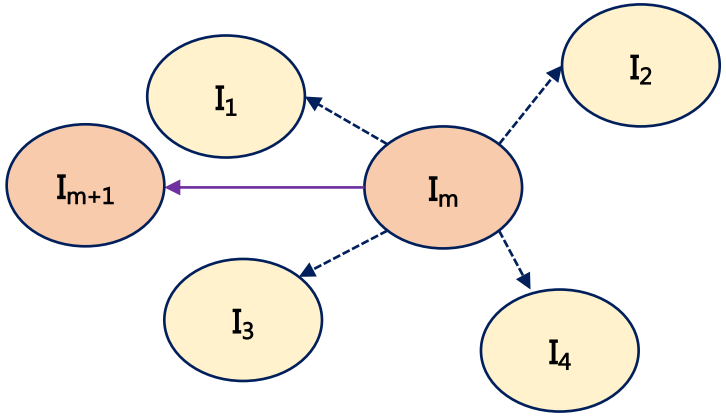
Apply geodesic shooting in direction of average initial momenta to update S_m



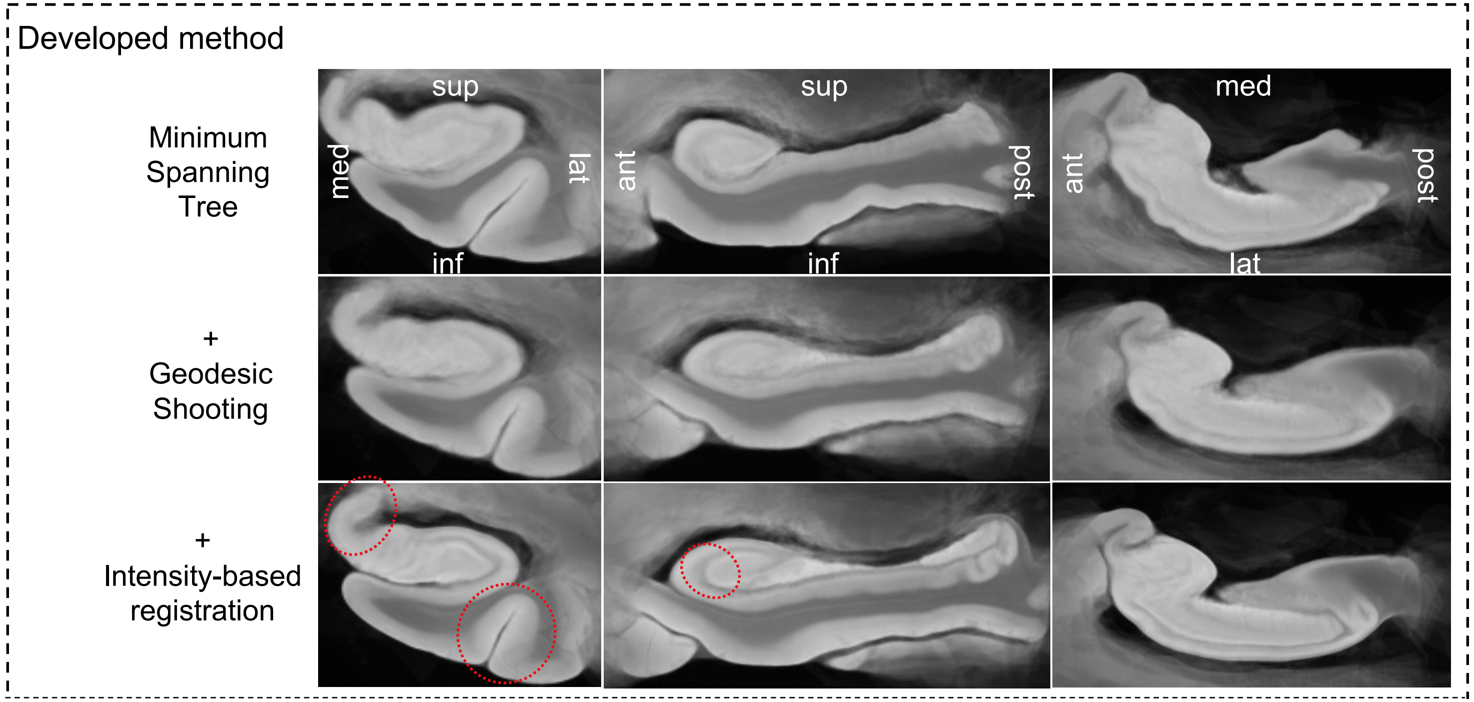
Compute unbiased population template after applying initialization transformations from 'Stage 2'

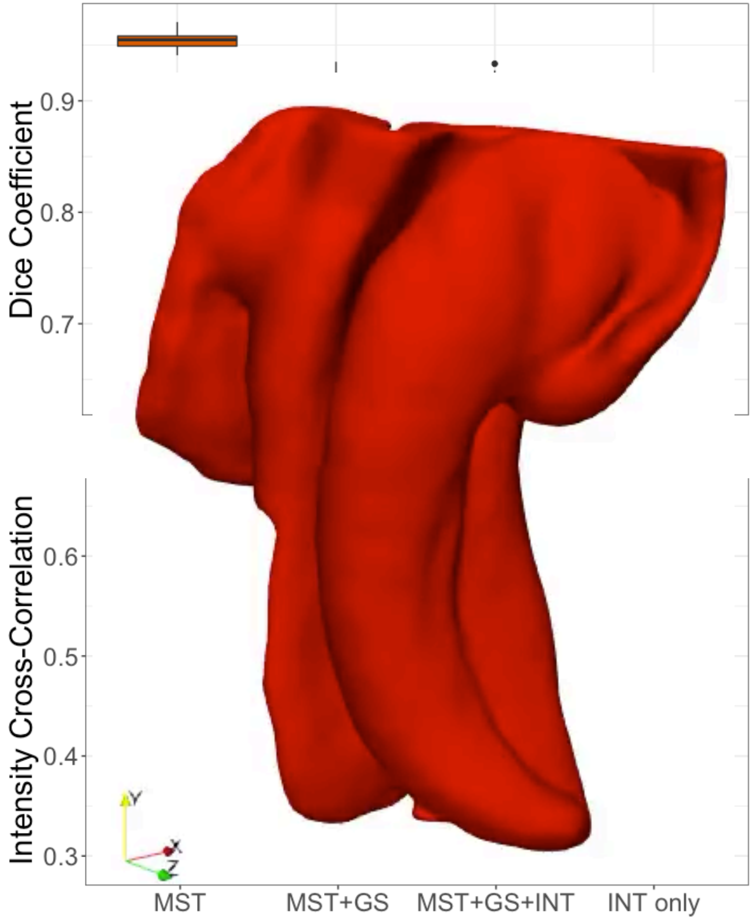
1. Shape Matching → 2. Shape Averaging → **3. Groupwise Intensity Registration**

- Unbiased population template construction algorithm is applied to MR images deformed into the space of the shape average
- Shape matching and averaging serve as initialization to intensity-based registration

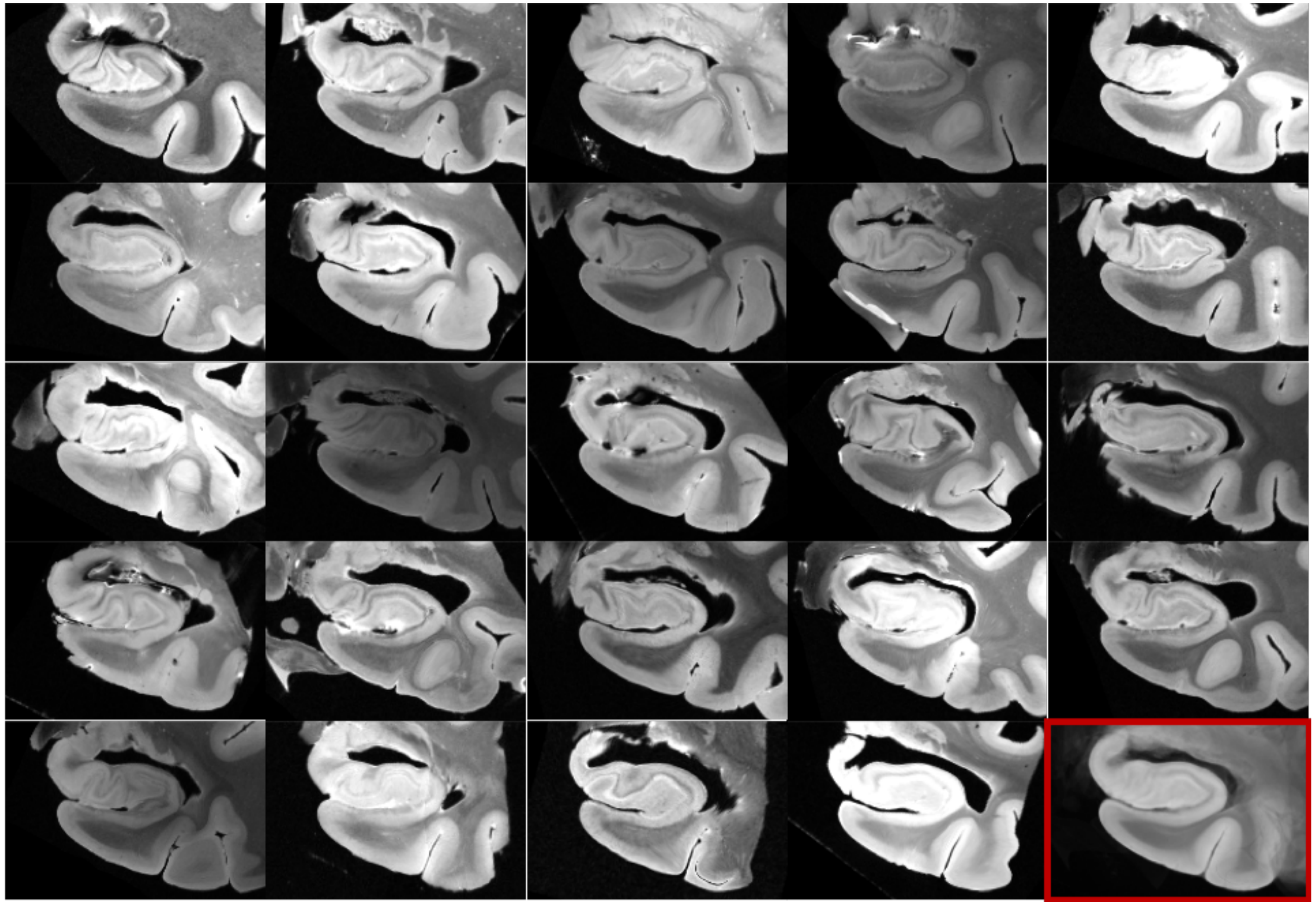


Evaluation of atlas quality by approach and stage





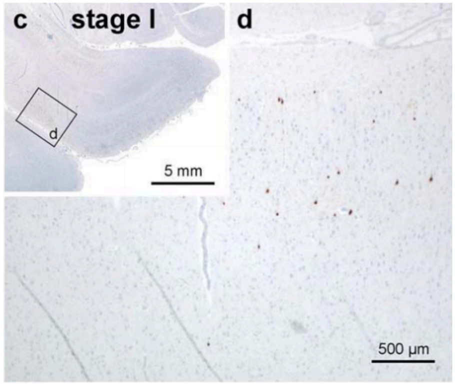
Individual specimens warped into atlas space look similar to each other



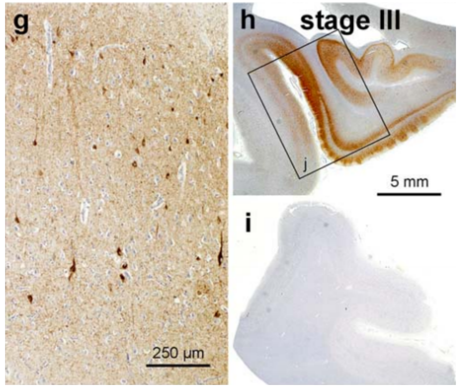
Association of cortical thickness with severity of tau pathology in the MTL

Subject	Tau ERC	Tau DG	Tau CA	Average Tau
A	3	2	3	**2.67**
B	1	2	0.5	**1.67**
C	2	2	3	**2.33**
⋮	⋮	⋮	⋮	⋮

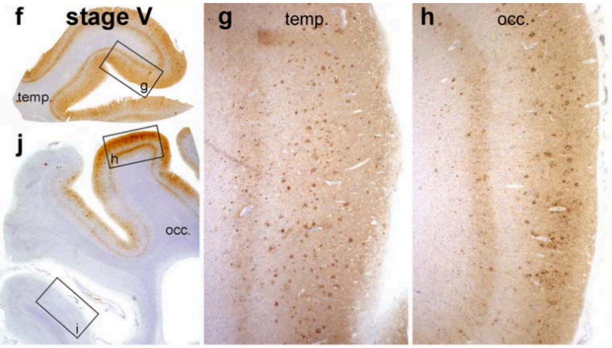
Semi-quantitative measures of tau pathology



1 – Stage I or II

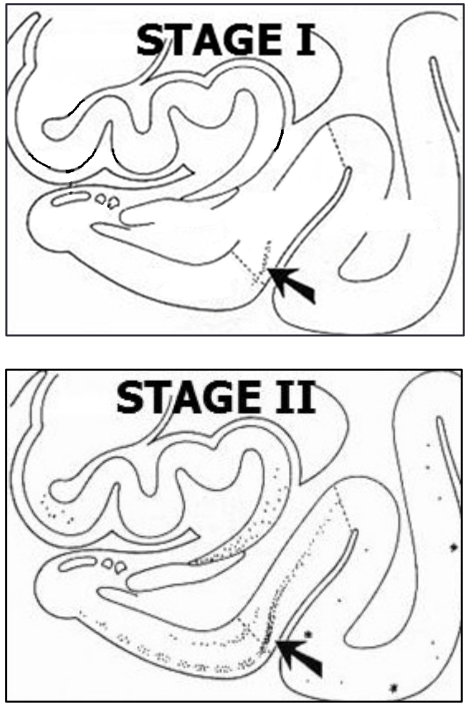


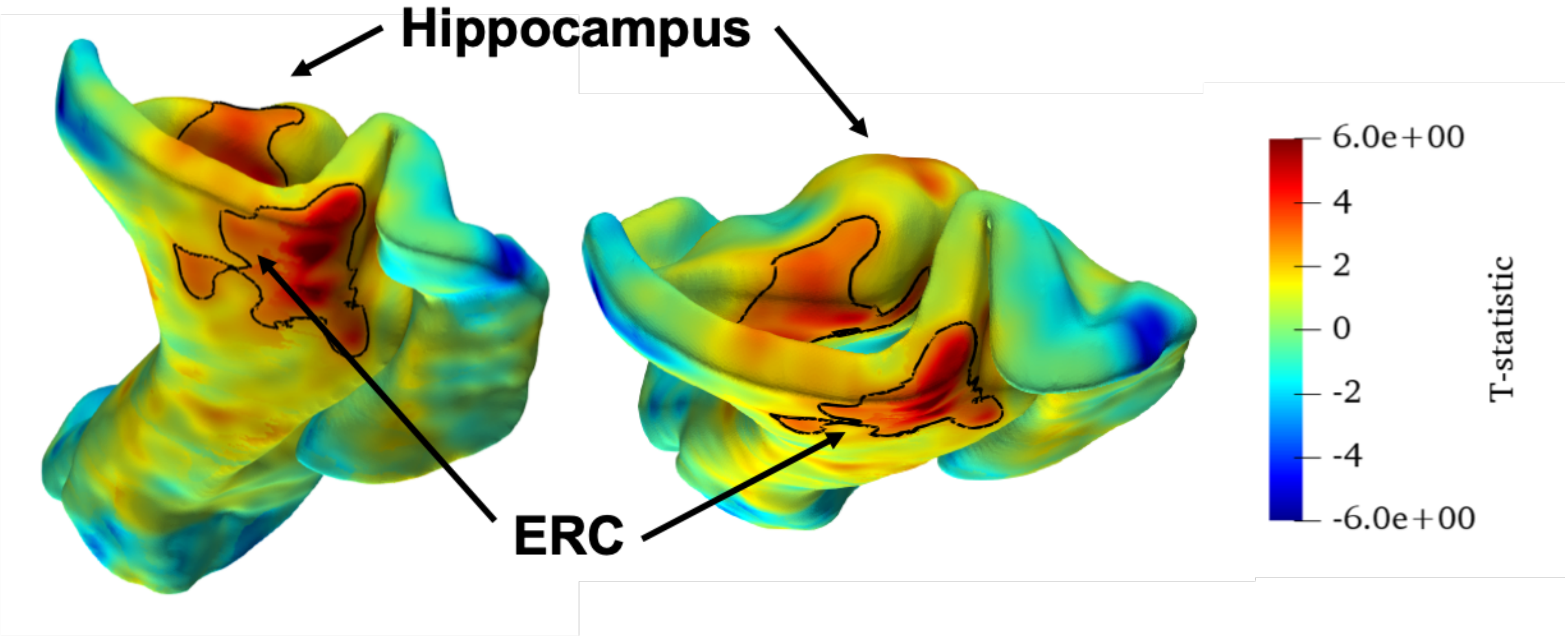
2 – Stage III or IV



3 – Stage V or VI

Association of cortical thickness with severity of tau pathology in the MTL





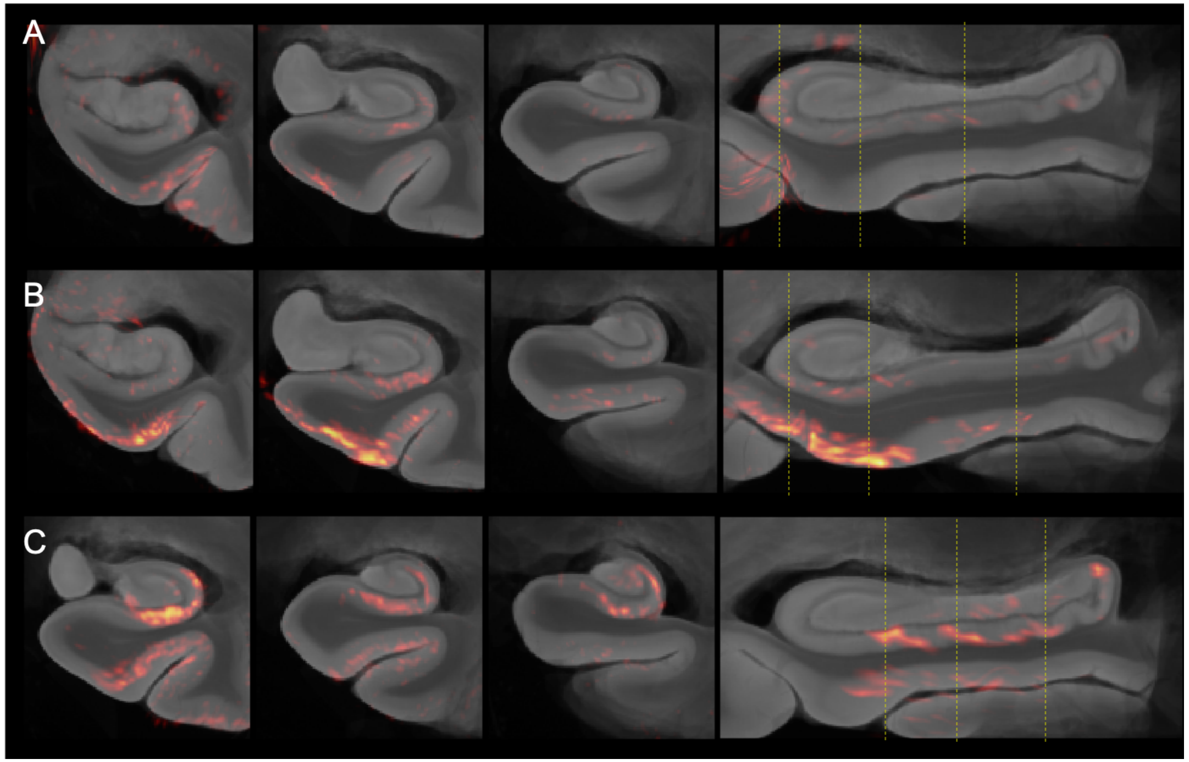
Antero-inferior view *Anterior view*

Black lines outline clusters with significant correlation, $p < 0.05$

Model: Thickness = (MTL Tau) * b1 + (Age) * b2 + (MTL TDP43) * b3 + Error

Towards more quantitative pathology measurements

- Weakly supervised learning used to quantify tau pathology in serial histology images
- Corresponding ex vivo MRI and histology images registered to allow <u>visualization of tau density "heat maps" in atlas space</u>
- Details in "3D Mapping of Tau Neurofibrillary Tangle Pathology in the Human Medial Temporal Lobe" Yushkevich et al. (ISBI 2020)



Summary

- Ex vivo imaging allows us to directly correlate MTL structural change with the underlying pathology
- Customized shape and intensity based registration pipeline used to construct ex vivo atlas of the MTL
- Can be used to define regional "hot spots" where AD pathology correlates most strongly with MTL structural change

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Thanks for your attention!

Questions?