Characterizing Anatomical Variability And Alzheimer's Disease Related Cortical Thinning in the Medial Temporal Lobe

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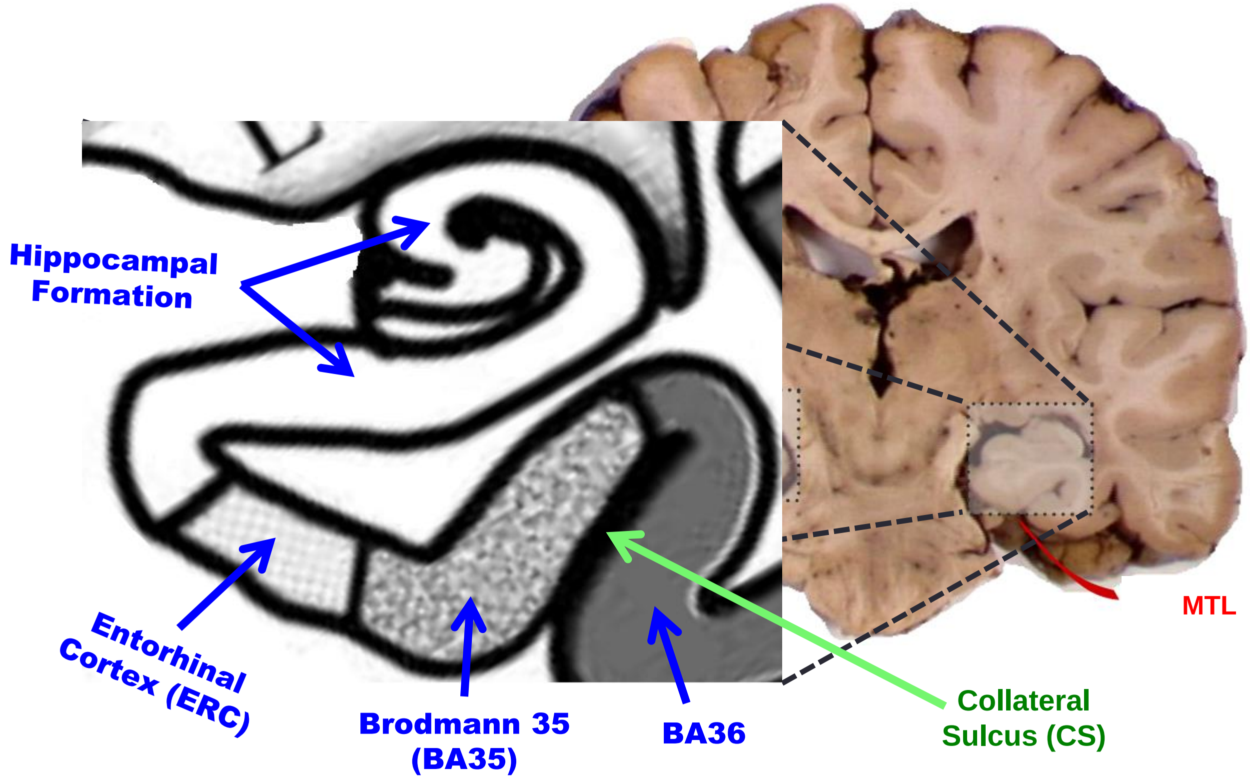
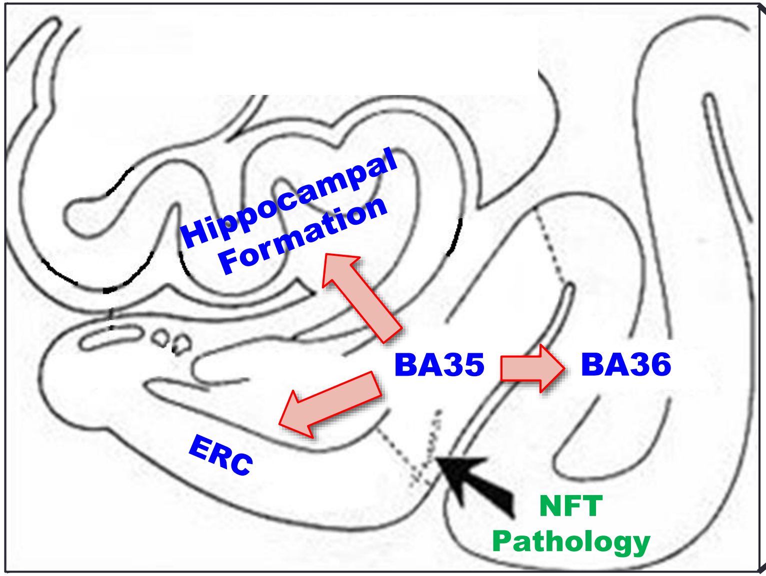
Subregions of the medial temporal lobe (MTL)

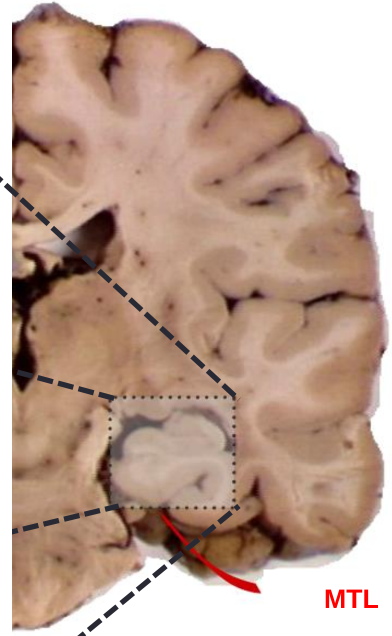


- BA35 and BA36 are subregions of the perirhinal cortex (PRC)

Early neurofibrillary tangle pathology (NFT) and related cell/synapse loss of Alzheimer' disease begin in the medial temporal lobe (MTL)

Stages of Neurofibrillary Tangle Pathology
[Braak & Braak 1991,95]



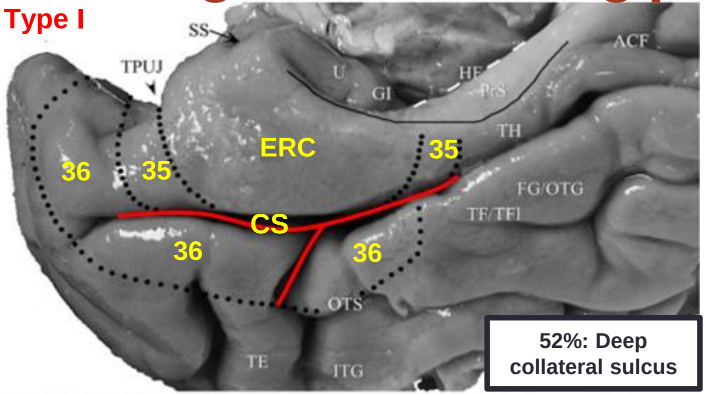


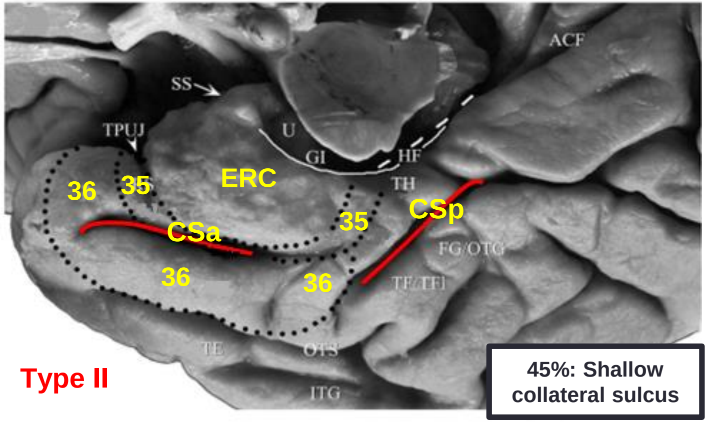
- Structural measurement of the MTL substructures are promising biomarkers of AD.

Figure adapted from Braak and Braak, Neurobiol Aging, 1995

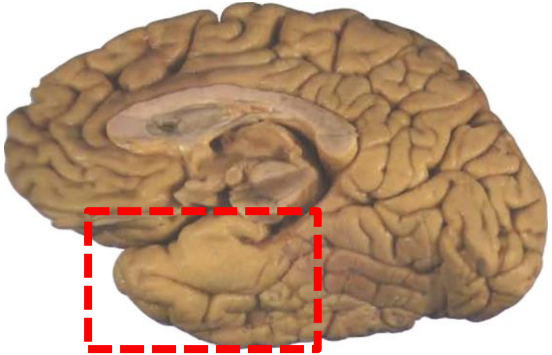
Hard to quantify due to the existence of discrete anatomical variants, defined by the folding and branching patterns of the CS

Type I





Type II

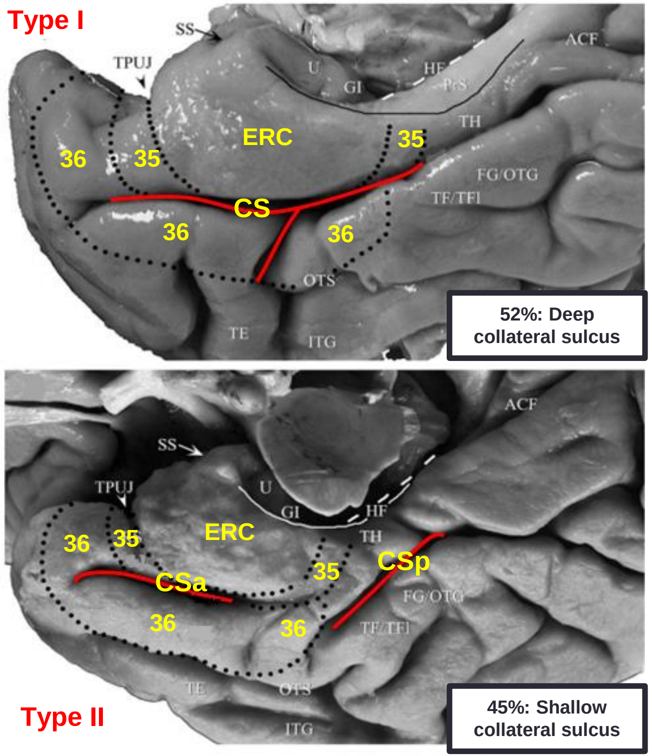


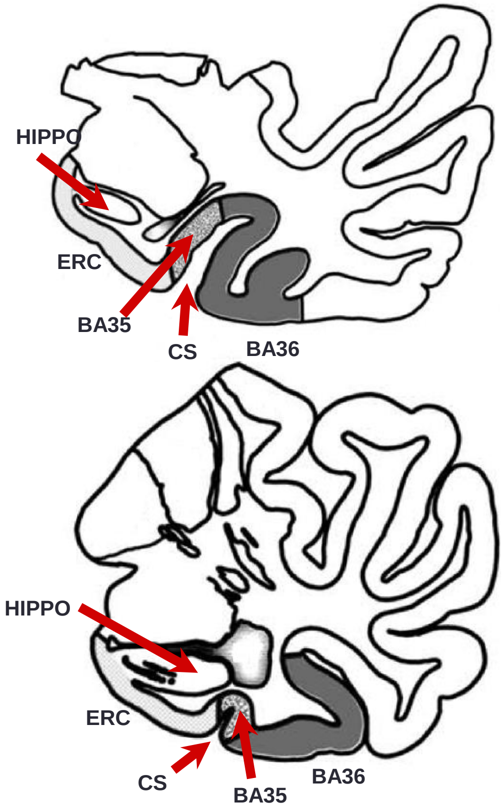
Angevine et al., The Human Brain in Photographs and Diagrams

CS: Collateral Sulcus; CSa/p: anterior/posterior CS

Ding et al., *Human Brain Mapping*,2010

Borders and extents of BA35 and BA36 depend on the depth of CS





- Failing to account for the anatomical variability in the analysis degrades our ability to reliably localize and accurately quantify brain regions in individual subjects.

Outline/Aims

- Automatic segmentation pipeline to segment ERC, BA35/36 from structural MRI
    - Apply to both T1-weighted and T2-weighted MRI
- The multi-template thickness analysis pipeline
    - To extract regional thickness of these structures
    - Establish anatomical meaningful correspondence between subjects
- Characterizing anatomical variability and Alzheimer's disease related cortical thinning
    - Apply the proposed pipeline to a large dataset of the baseline T1-weighted MRI scans from Alzheimer's Disease Neuroimaging Initiative (ADNI)

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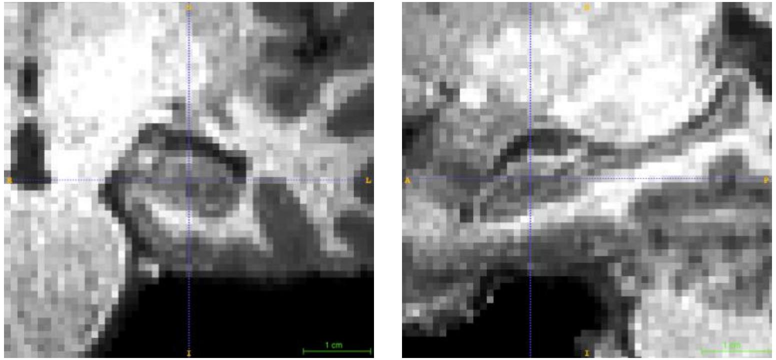
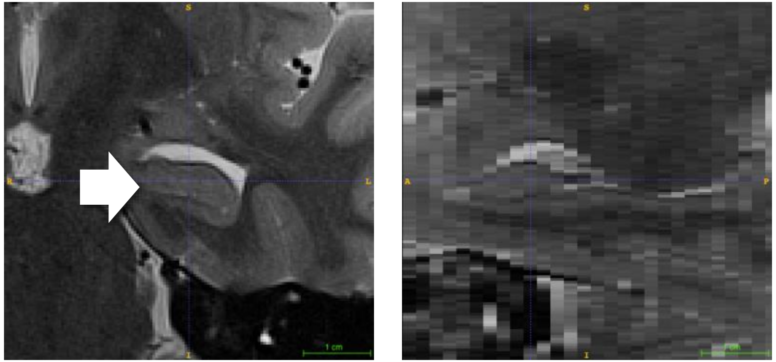
ASHS: A multi-atlas segmentation pipeline optimized for MTL substructure segmentation in T2-weighted MRI

3 Tesla T1-weighted MRI $(1.0 \times 1.0 \times 1.0 \text{mm}^3)$



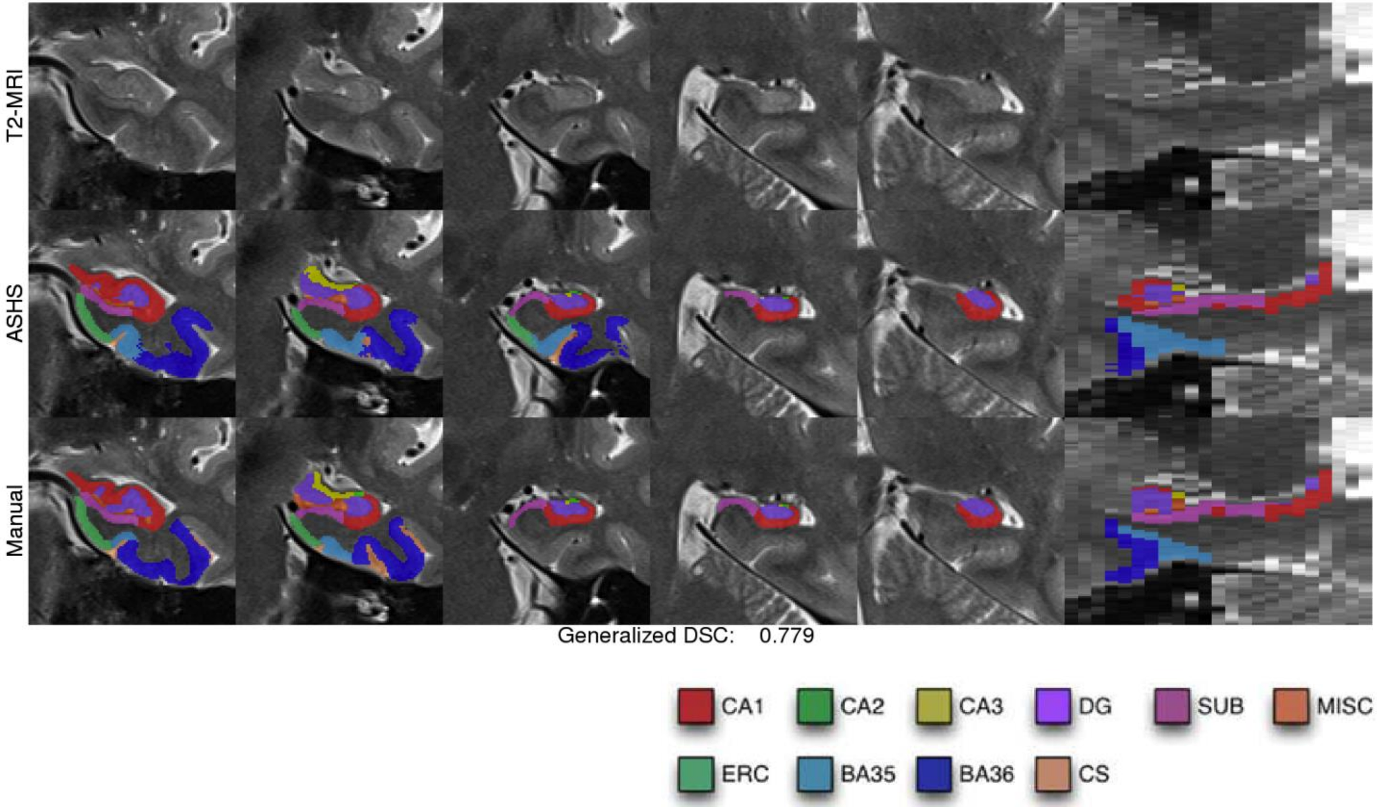
3 Tesla T2-weighted MRI $(0.4 \times 0.4 \times 2.0 \text{mm}^3)$



- **Segmenting a new subject**
  - **Inputs:**
    - High-resolution T2w MRI
    - 1 mm^3 isotropic T1w MRI
  - **Algorithms:**
    - ANTS deformable registration[2]
    - Joint label fusion[3]
    - Corrective learning[4]
  - **Output:**
    - Segmentation of hippocampal subfields and MTL cortex in the space of the T2w MRI
- **Atlas set: 29 subjects (15 controls, 14 MCI)**
  - High-resolution T2w MRI
  - 1 mm^3 isotropic T1w MRI
  - Manual segmentation in the T2w MRI space

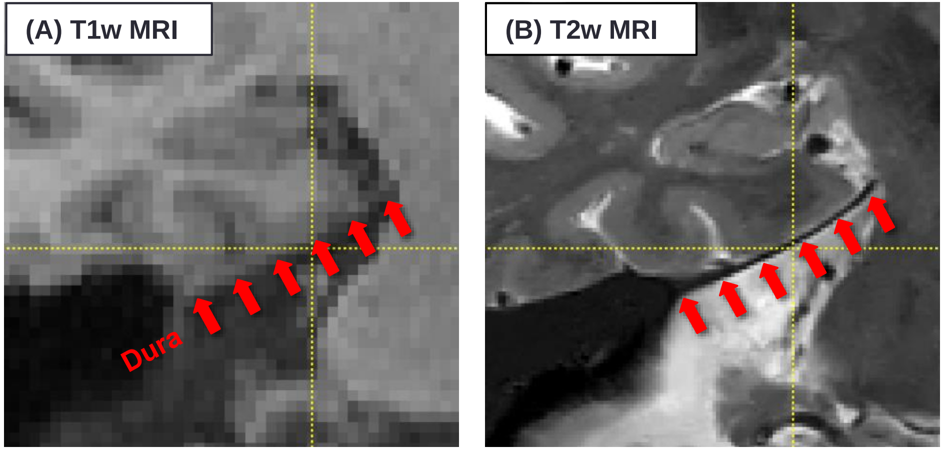
[1]: Yushkevich et al., *Human Brain Mapping*, 2016; [2]: Avants et al., *MedIA*, 2006; [3]: Wang et al., *Pattern Anal Mach Intell*, 2012; [4]: Wang et al., *Neuroimage*, 2011

ASHS can reliably segment MTL substructures

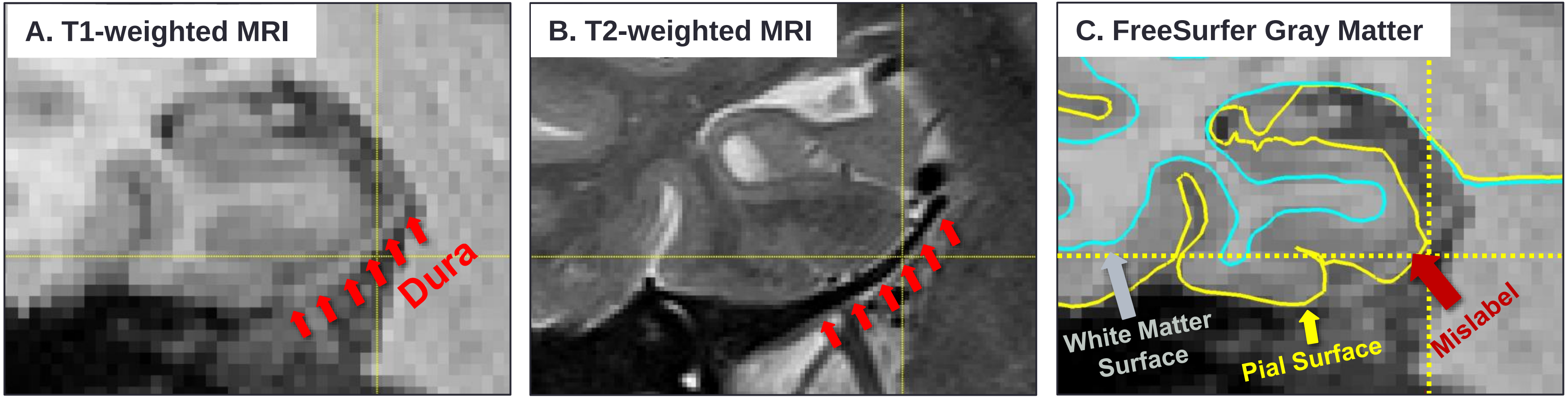


ASHS-T1: From T2-weighted to T1-weighted MRI

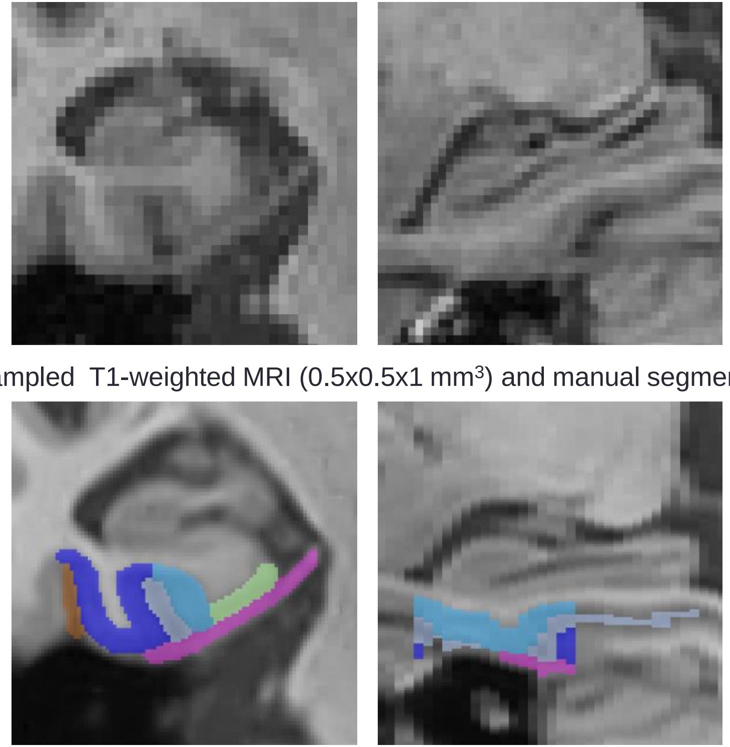
- **Motivation: T1w MRI is the most commonly acquired MRI modality**
  - Although T1w MRI does not provide enough contrast to visualize hippocampal subfields, the MTL cortex can be reliably segmented in T1w MRI.
  - More than 1000 T1w MRI scans of subjects at different stages of AD are available in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database
  - Large sample size allows us to the characterize cortical thinning patterns of anatomical variant
- **Difficulty: Dura has similar intensity as gray matter in T1-weighted MRI**



The dura is segmented as gray matter by FreeSurfer[1]



ASHS-T1[1]**:** A multi-atlas segmentation pipeline optimized for MTL substructure segmentation **in T1-weighted MRI**



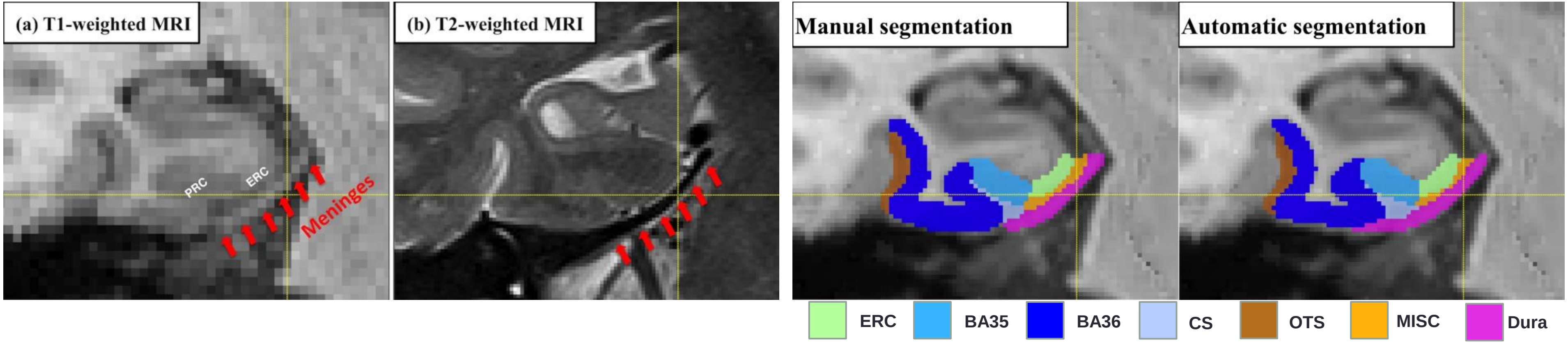
3 Tesla T1-weighted MRI (1.0 x 1.0 x 1.0 mm^3)

Upsampled T1-weighted MRI (0.5x0.5x1 mm^3) and manual segmentations

- **Atlas set: 29 subjects (15 controls, 14 MCI)**
  - 1 mm^3 isotropic T1w MRI
  - Manual segmentation in the upsampled 0.5x0.5x1 mm^3 T1w MRI space
- **Segmenting a new subject**
  - **Inputs:**
    - 1 mm^3 isotropic T1w MRI
  - **Algorithms:**
    - ANTS deformable registration[2]
    - Joint label fusion[3]
    - Corrective learning[4]
  - **Output:**
    - Segmentation of the MTL cortex in the space of the upsampled T1w MRI

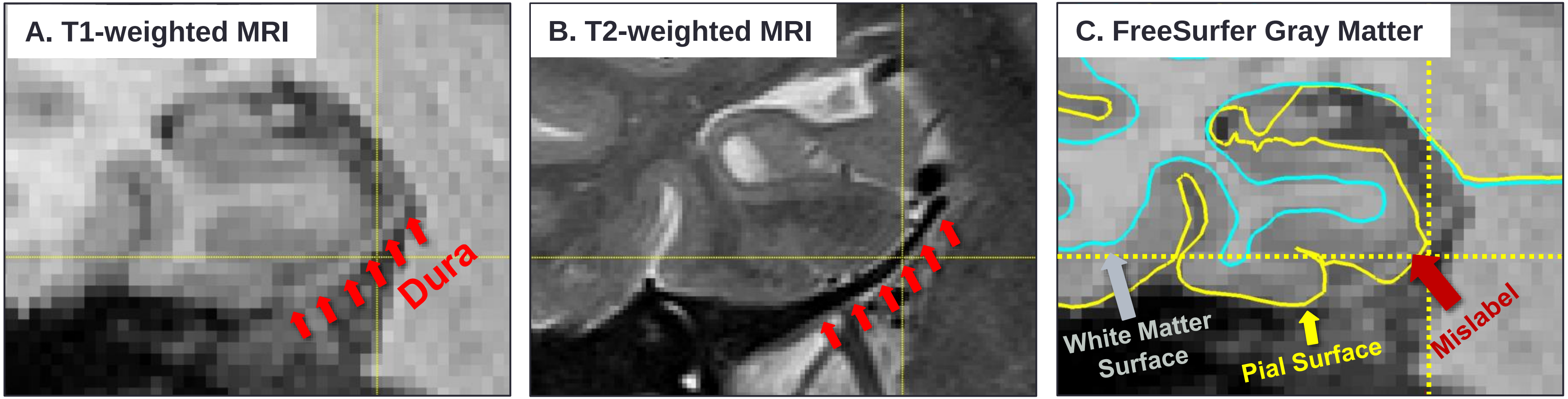
[1]: Xie et al., MICCAI 2016; [2]: Avants et al., *MedIA*, 2006; [3]: Wang et al., *Pattern Anal Mach Intell*, 2012; [4]: Wang et al., *Neuroimage*, 2011

Segmentation accuracy is comparable to that in T2w MRI



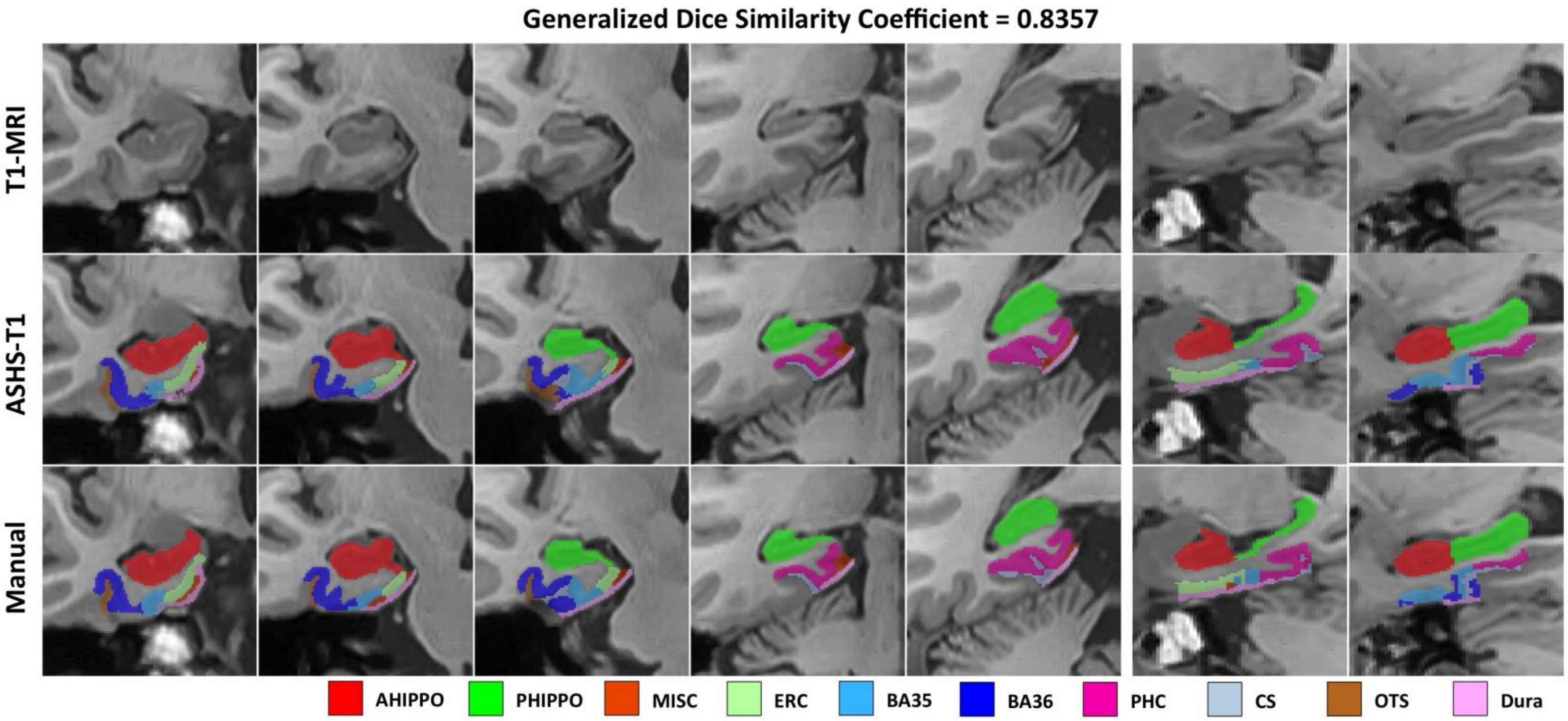
Dice coefficients between automatic and manual segmentations in SR-T1w and T2w MRI				
Modality	**ERC**	**BA35**	**BA36**	**Dura**
T1w MRI	0.76 (0.03)	0.70 (0.06)	0.78 (0.04)	0.75 (0.05)

Dura mater is often labeled as gray matter by FreeSurfer[1]



% of dura voxels in manual segmentation labeled as			
Method	**Dura**	**Gray Matter**	**Other**
FreeSurfer[1]	N/A	62.4 (10.5)	37.6 (10.5)

Extended to segment the anterior/posterior hippocampus and parahippcampal gyrus and it is publicly available



https://sites.google.com/view/ashs-dox/

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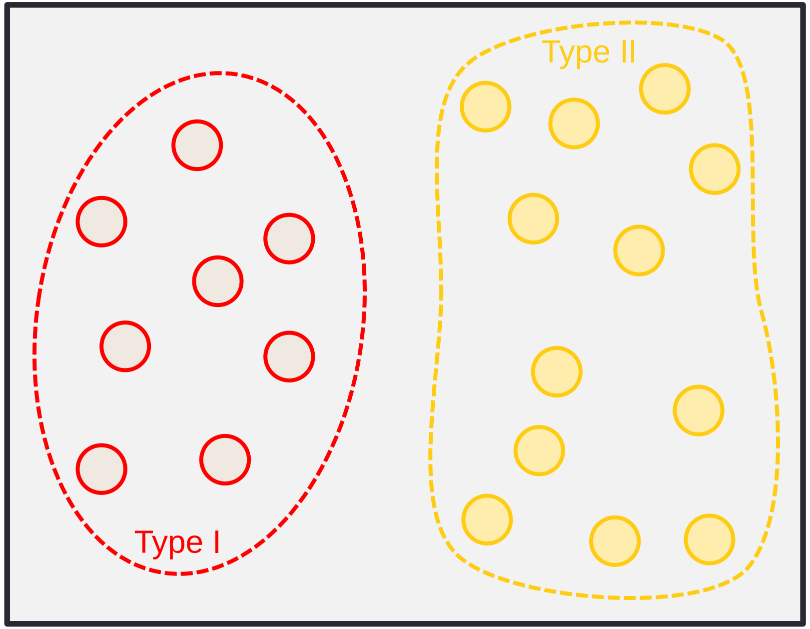
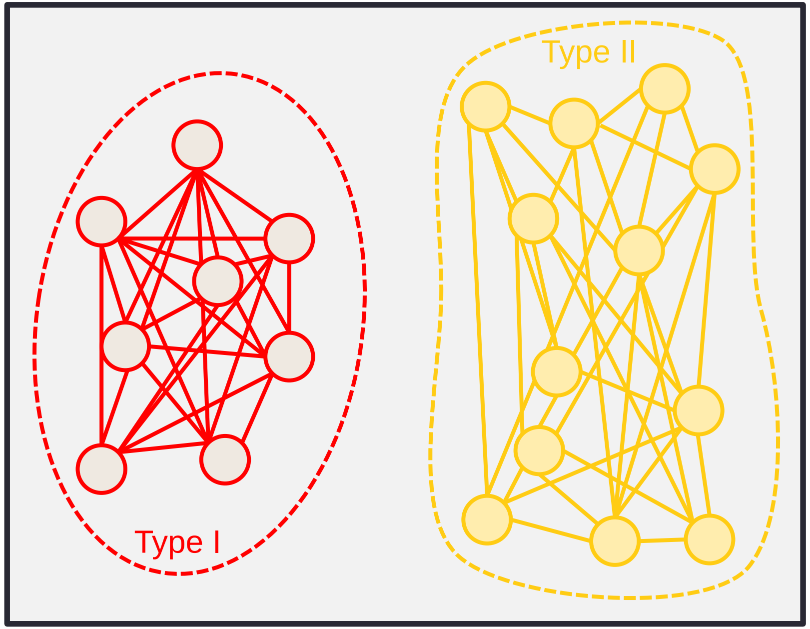
Build template for each variant from the atlas set using graph-based groupwise registration[1]



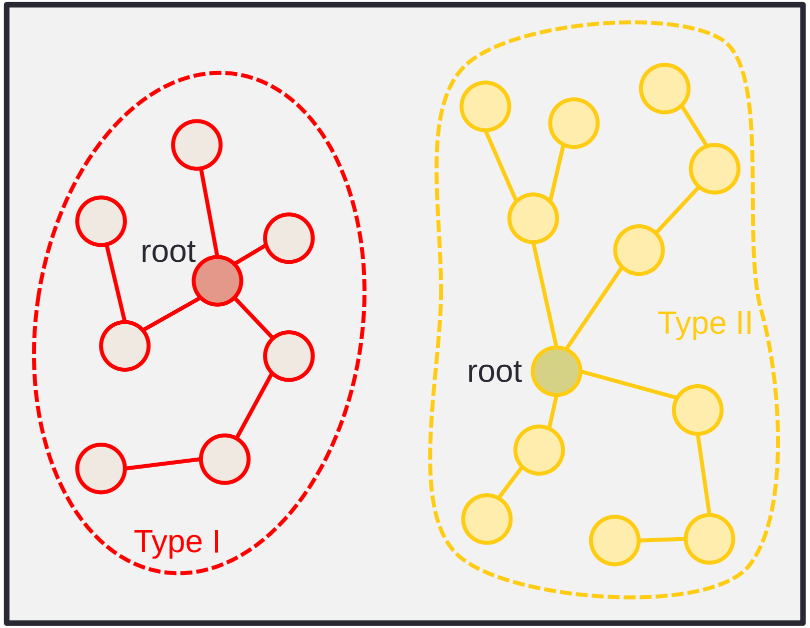
- Manual segmentations from the right side were flipped, yielding 58 samples
- Subtype of each manual segmentation was manually assigned

Build template for each variant from the atlas set using graph-based groupwise registration[1]



- Pairwise highly regularized coarse registrations were performed within each subtype
- Edge weight was set to the GDSC of BA35, BA36 and CS after registration

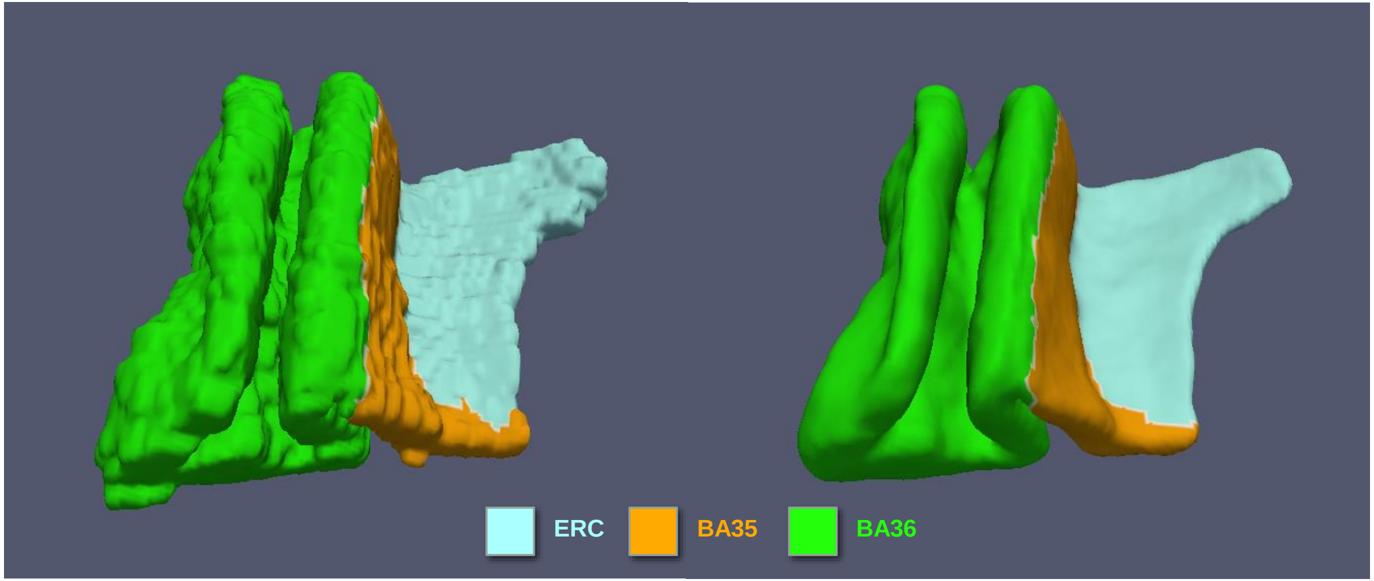
Build template for each variant from the atlas set using graph-based groupwise registration[1]



- Minimum spanning tree[2] was build for each subtype
- The sample that is closest to all the other samples was identified as the "root"

[1]Wu et al., NeuroImage 2011; [2]Prim Bell Syst Tech J 1957

Drawback: the template is very similar to the “root”



“Root”

Template derived from graph-based registration

Shape correction and model shape variability using pointset geodesic shooting

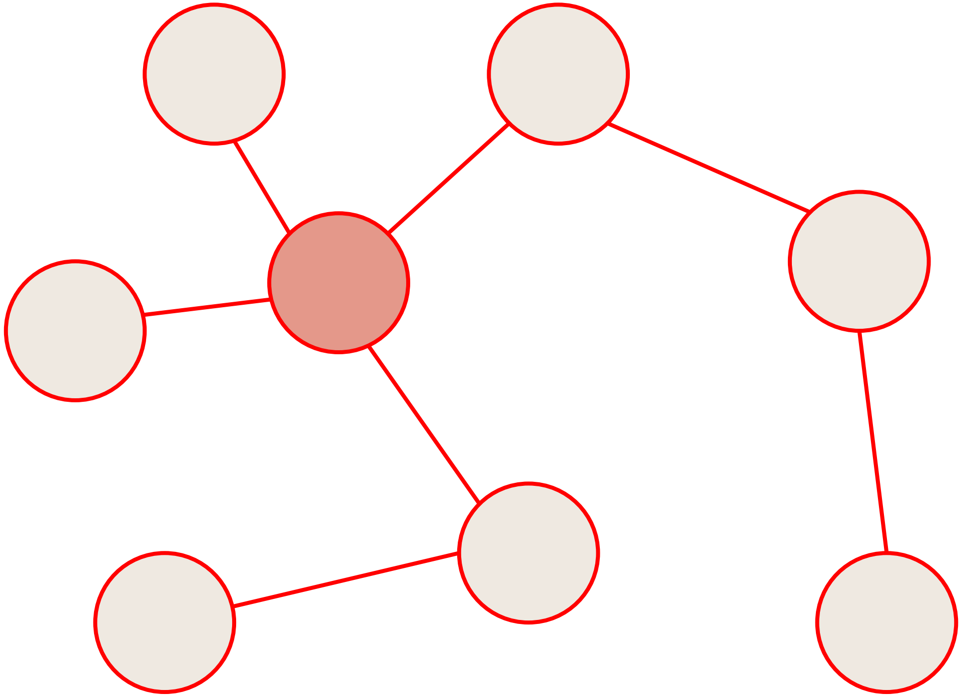
- **Nice properties of large deformable diffeomorphic metric mapping (LDDMM) via geodesic shooting[1,2,3]**

  - The deformation field between template and the target subject can be compactly represented by the initial momentum
  - The space of initial momentum provides a linear representation of the high-dimensional non-linear diffeomorphic transformation space, which is important for statistical analysis of shape variability

https://www.youtube.com/watch?v=jurwTuCJn7s

[1]Allassonniere et al. *EMMCVPR '05 Proc* 2005; [2]Vaillant et al. Neuroimage 2004; [3]Miller and Younes J Math Imaging 2006

Shape correction via pointset geodesic shooting[1]



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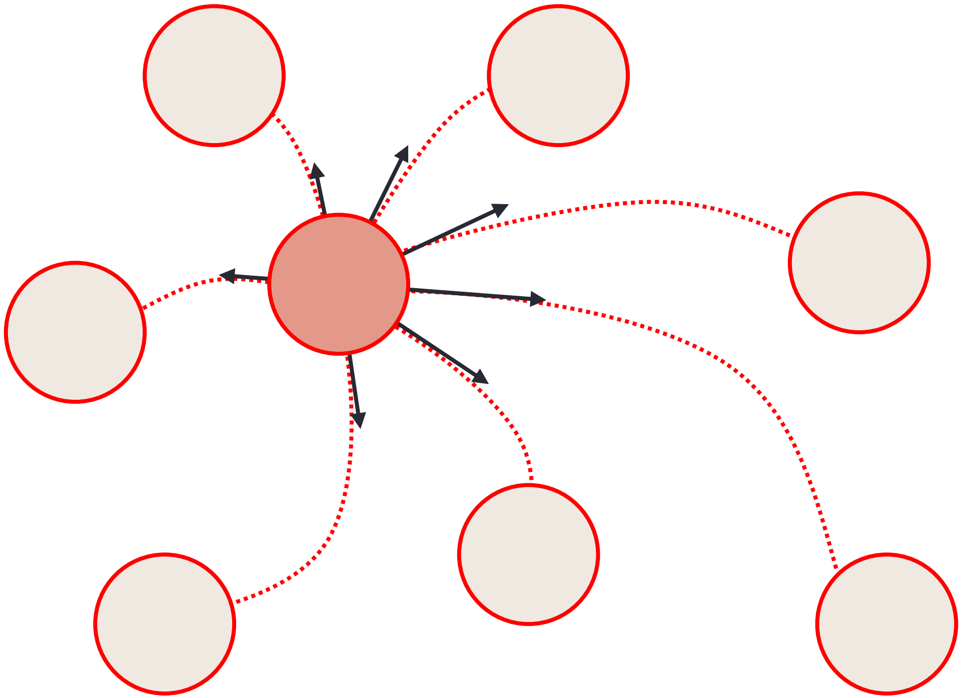

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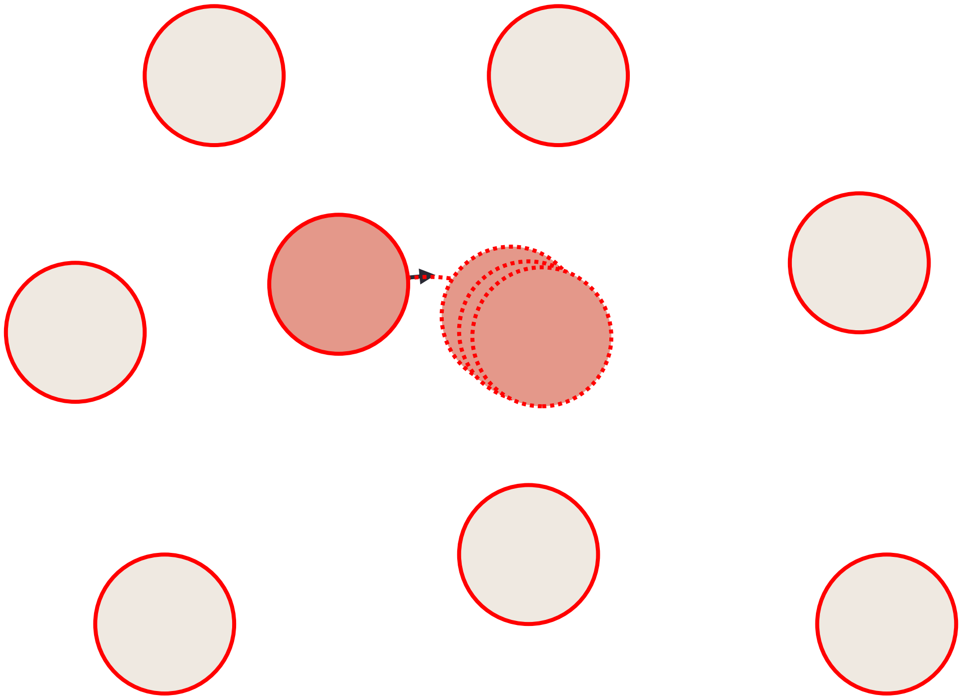

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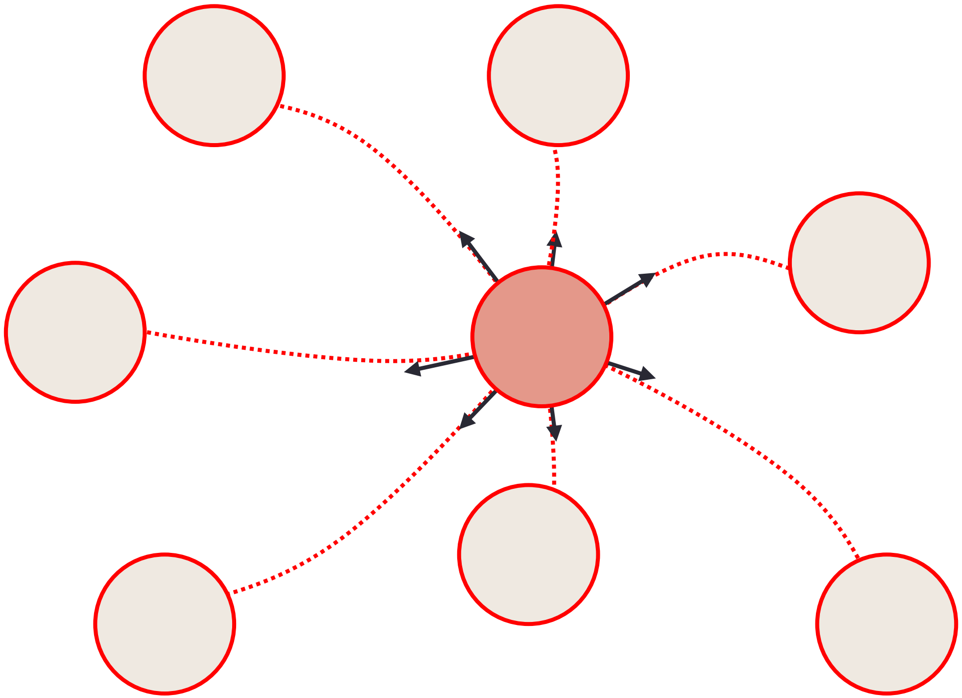
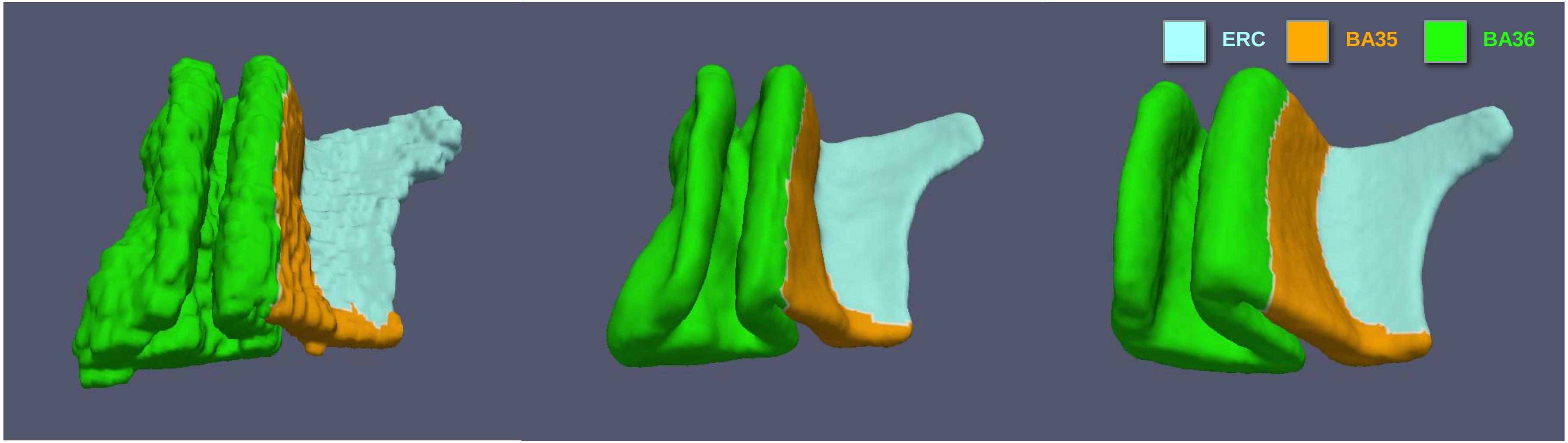


The corrected template does seem to represent the mean shape

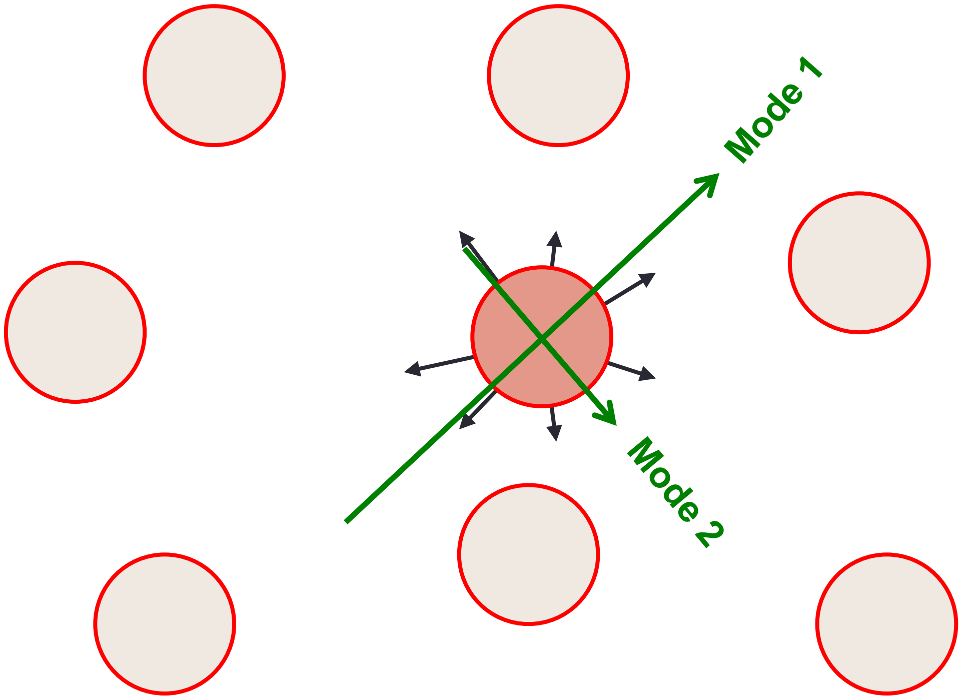


"Root"

Template derived from graph-based registration

Shape corrected template

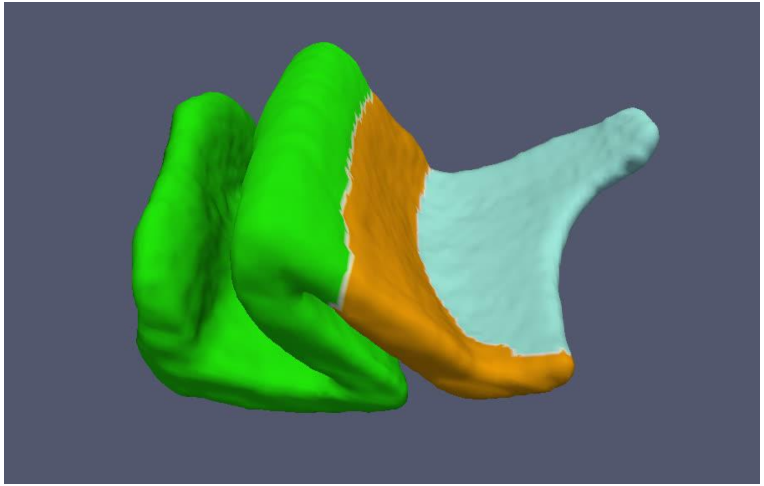
Principal component analysis on the initial momenta[1]



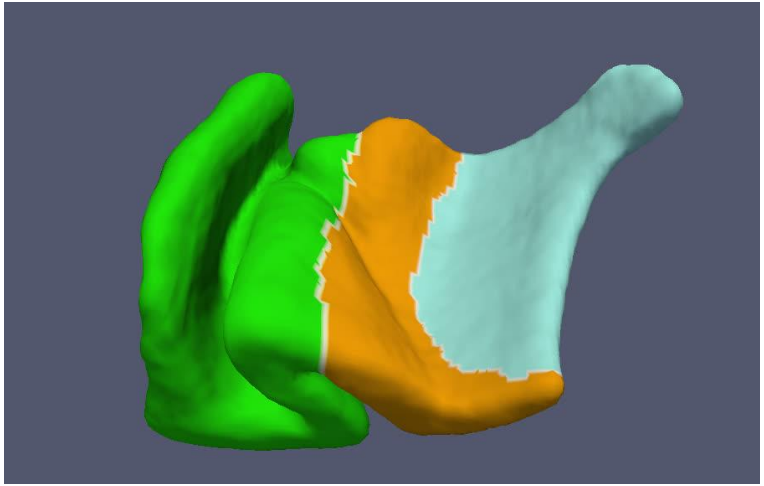
[1]Vaillant et al. Neuroimage 2004

Principal modes capture expected variability – T1 Atlas

Variant with continuous CS



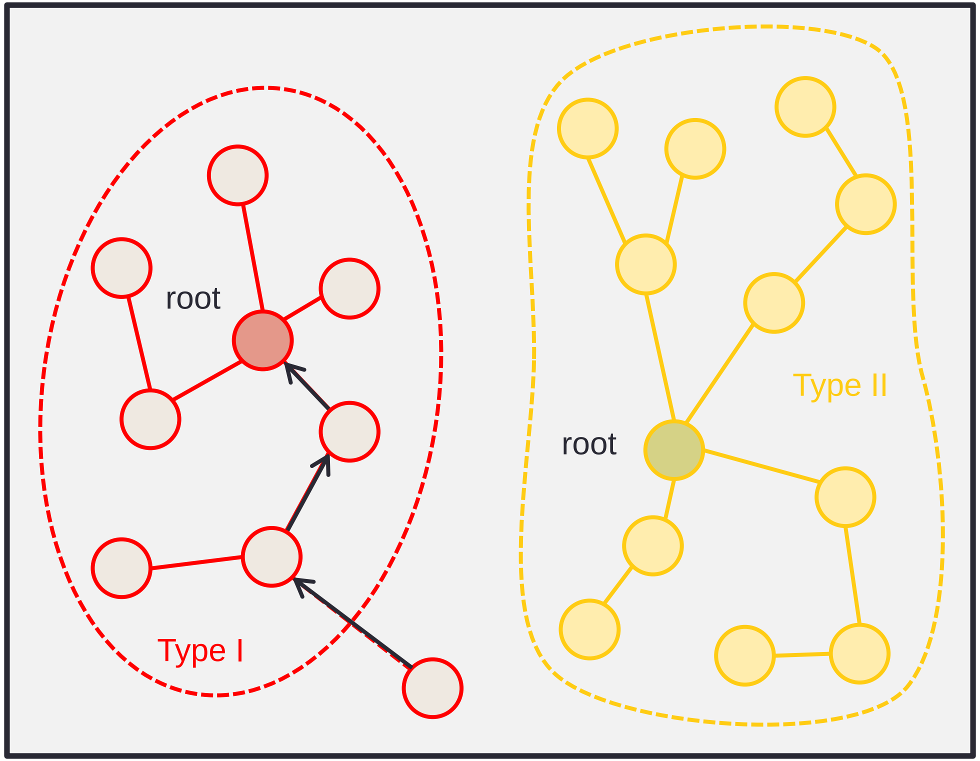
Variant with discontinuous CS



- **Shape analysis using the manual segmentations of the T1 atlas**

Fit the template to a new automatic segmentation along the minimum spanning tree

- Automatic segmentation using ASHS-T1
- Register to all the manual segmentations in the atlas set
- Pick the most similar 6 atlases and perform a weighted vote to decide the variant membership of the new sample
- Connect the sample with the most similar manual segmentation in its group
- Warp the template to the target sample



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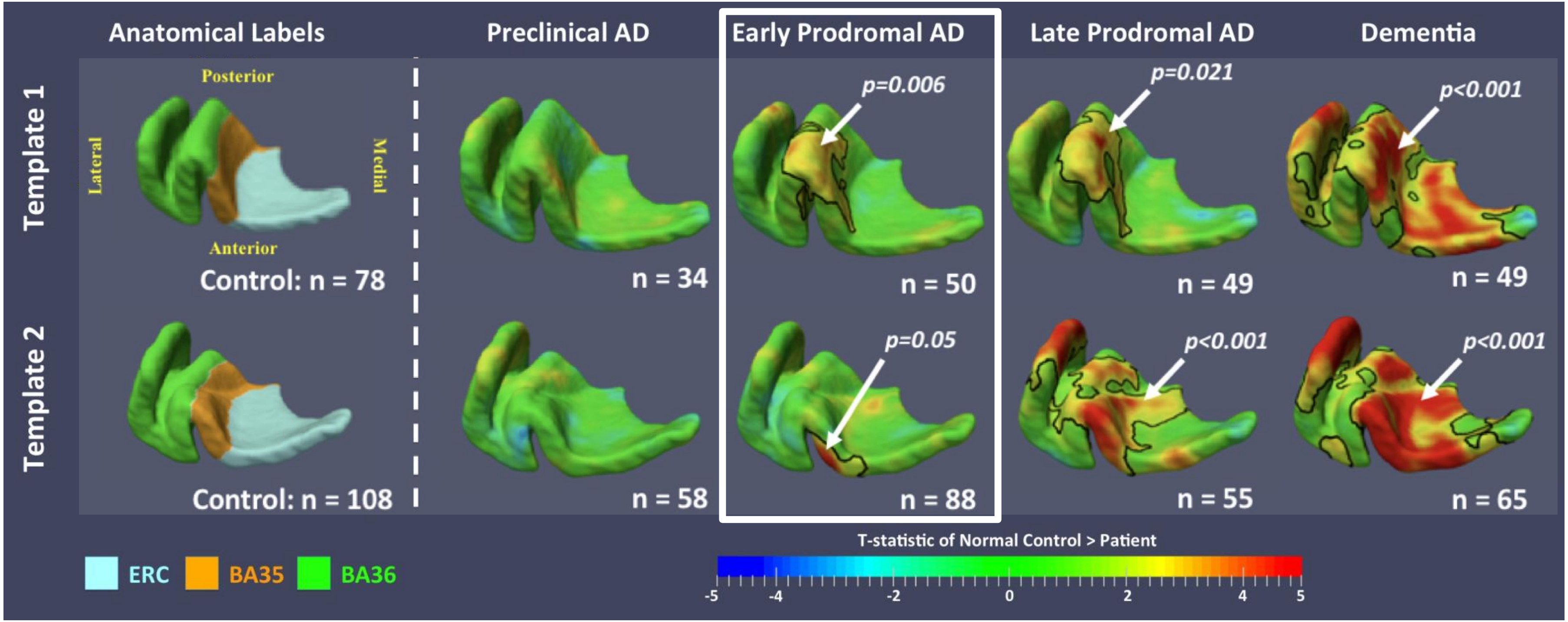
Applied to baseline T1-weighted MRI scans from ADNI

	Control	Preclinical AD	Early Prodromal AD	Late Prodromal AD	Dementia
N	180	94	139	109	81
Age (yrs)	72.0 (6.0)	74.5 (5.7) ***	73.0 (6.9)	71.7 (6.8)	74.9 (7.8) ***
Gender (M/F)	94 / 86	32 / 62 **	80 / 59	57 / 52	47 / 34
Education (yrs)	16.9 (2.4)	16.1 (2.7) *	15.7 (2.9) ***	16.6 (2.6)	15.4 (2.6) **
MMSE	29.0 (1.3)	29.0 (1.1)	28.0 (1.7) ***	27.2 (1.9) ***	23.2 (2.1) ***

Abbreviations: AD = Alzheimer's disease; MMSE = mini-mental state examination.

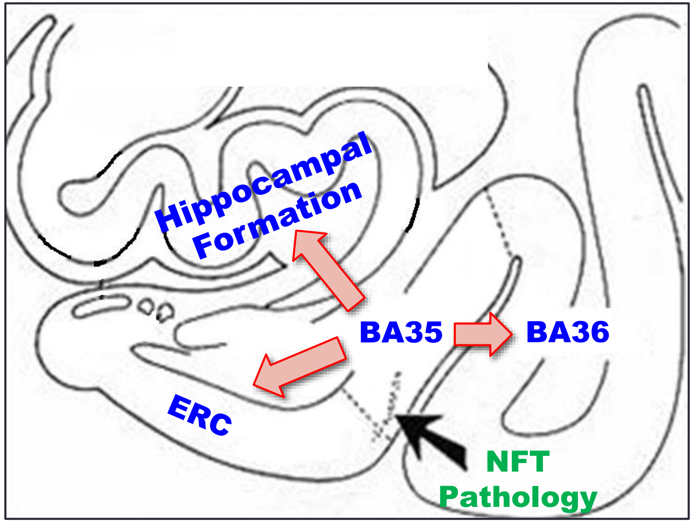
AD-related cortical thinning – ADNI cross-sectional dataset

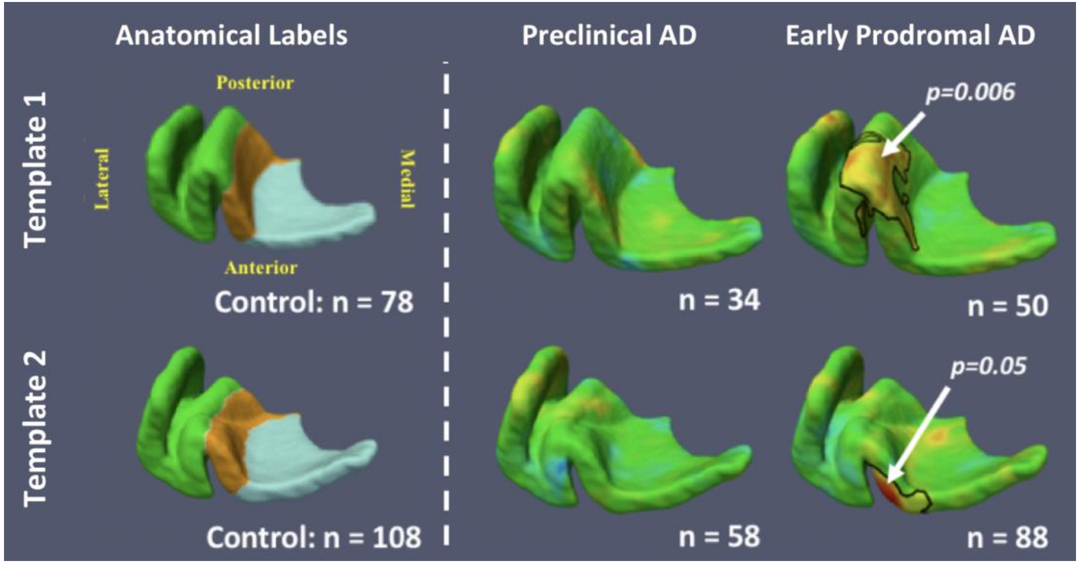


t-statistical maps of the contrast between amyloid-negative cognitively normal adults and the other 4 groups (preclinical AD, early and late Prodromal AD, dementia) of both variant-templates, with age and education as covariates. Only results of the right hemisphere are shown. The patterns are similar on the left side.

Early neurofibrillary tangle pathology (NFT) and related cell/synapse loss begin in the medial temporal lobe (MTL)

Stages of Neurofibrillary Tangle Pathology [Braak & Braak 1991,95]

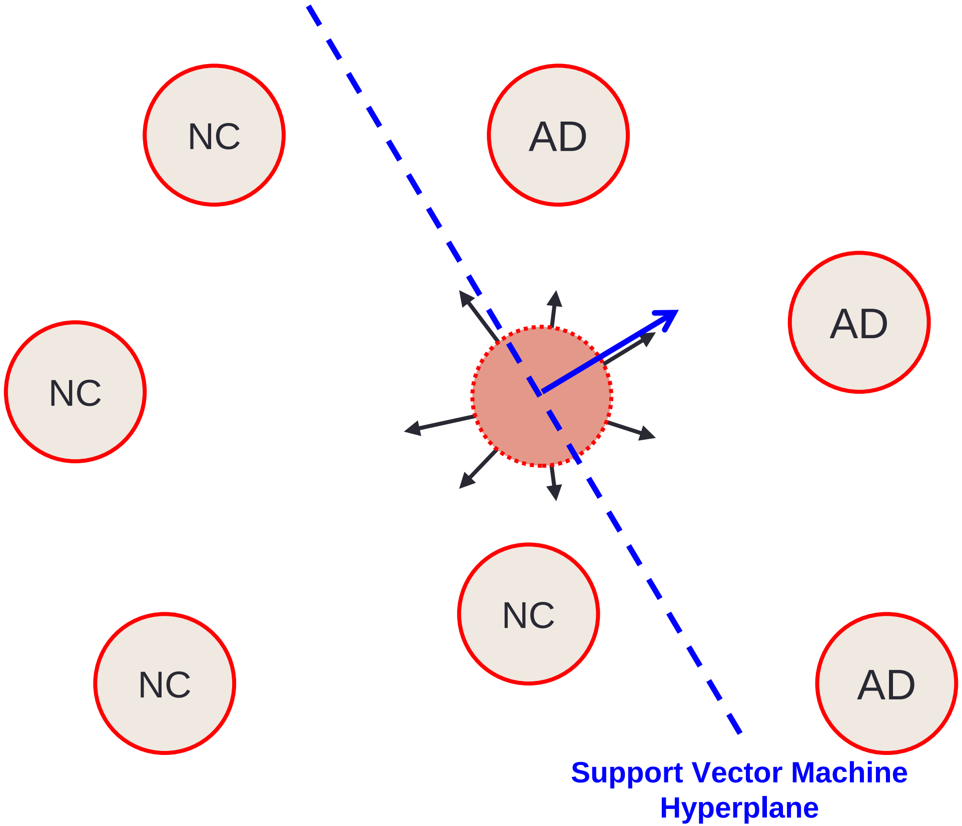




- Being able to replicate findings from pathology studies supports the utility of structural measurement of MTL cortex in tracking early Alzheimer's disease progression

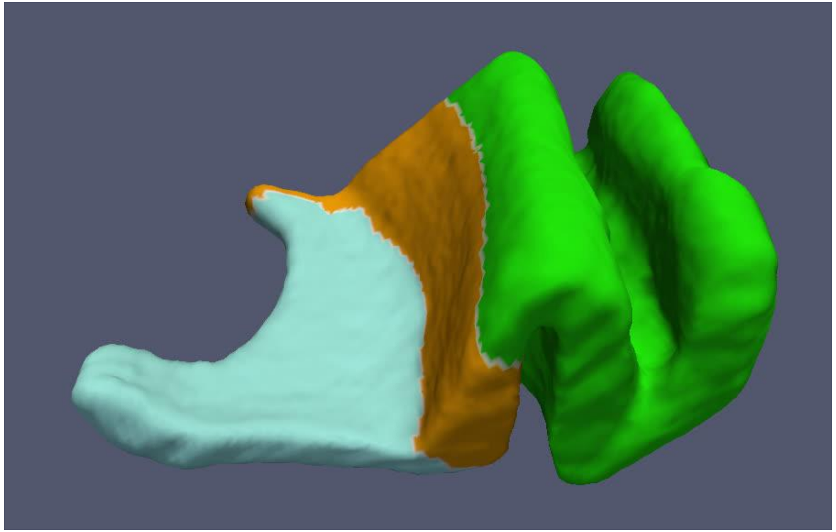
Figure adapted from Braak and Braak, Neurobiol Aging, 1995

Classification using the initial momenta



Effect of AD on MTL shape – ADNI Dataset

Variant with continuous CS



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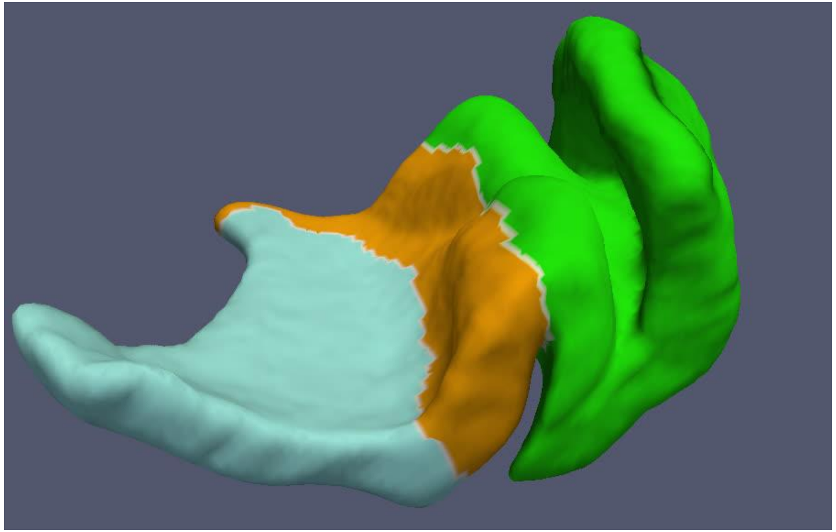

- AD is associated with decrease in overall size of the MTL, cortical thinning and widening of the CS
- These shape features may provide complementary information in identifying disease groups

Summary

- The first automatic segmentation pipeline of MTL cortex using T1-weight MRI that explicitly accounts for the confound of the dura mater[1]
- A novel multi-template analysis pipeline to quantify shape variability of anatomical variants of the MTL
- Progression of cortical thinning that is consistent with known progression of NFT pathology within the MTL cortex related to AD
- Proposed method may have important utility in the early detection and monitoring of AD and the findings in this study may help us better understand the effect of AD on the shape of MTL substructures

THANK YOU!

- **Link to ASHS and ASHS-T1 software**

  https://sites.google.com/view/ashs-dox/

- **Publicly available atlas sets for T1w and T2w MRI**

  https://www.nitrc.org/projects/ashs/

- **Acknowledgements**

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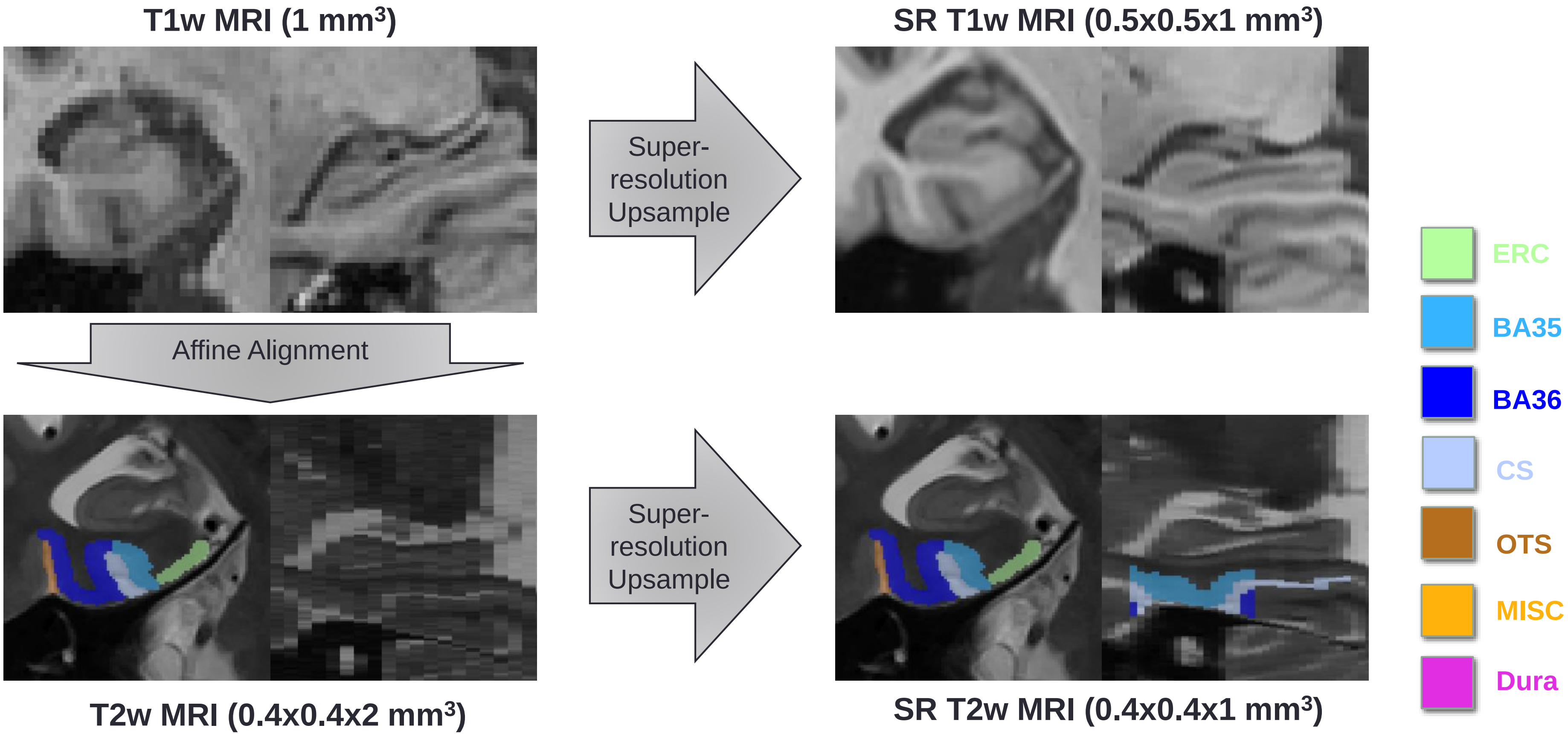
SCAN US!

T1 Atlas: derived from manual segmentation in T2 space



OTS = occipitotemporal sulcus; MISC = miscellaneous; SR = super-resolution

Xie et al., MICCAI 2016

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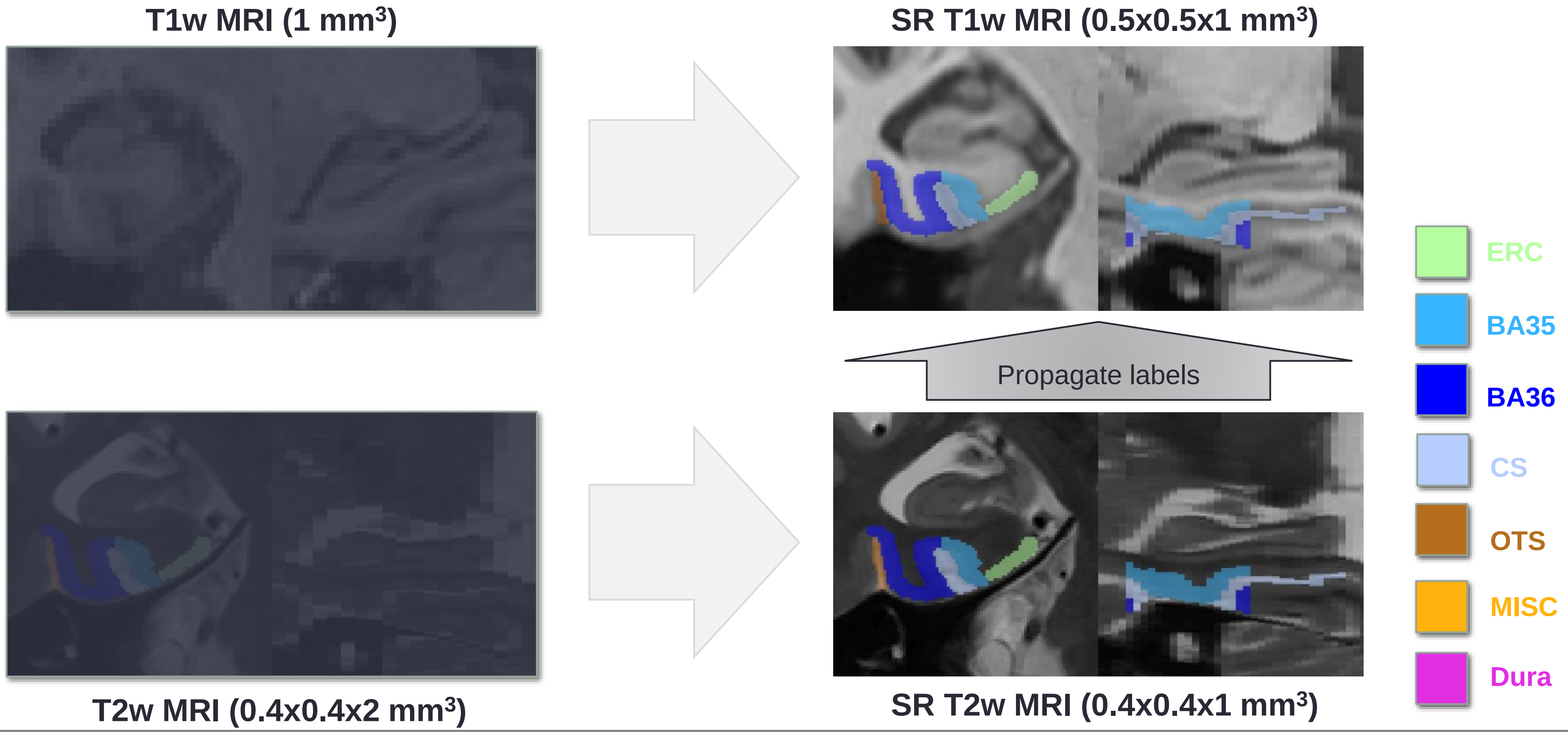

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