Multimodal imaging correlates of the Alzheimer-protective ApoE2 polymorphism

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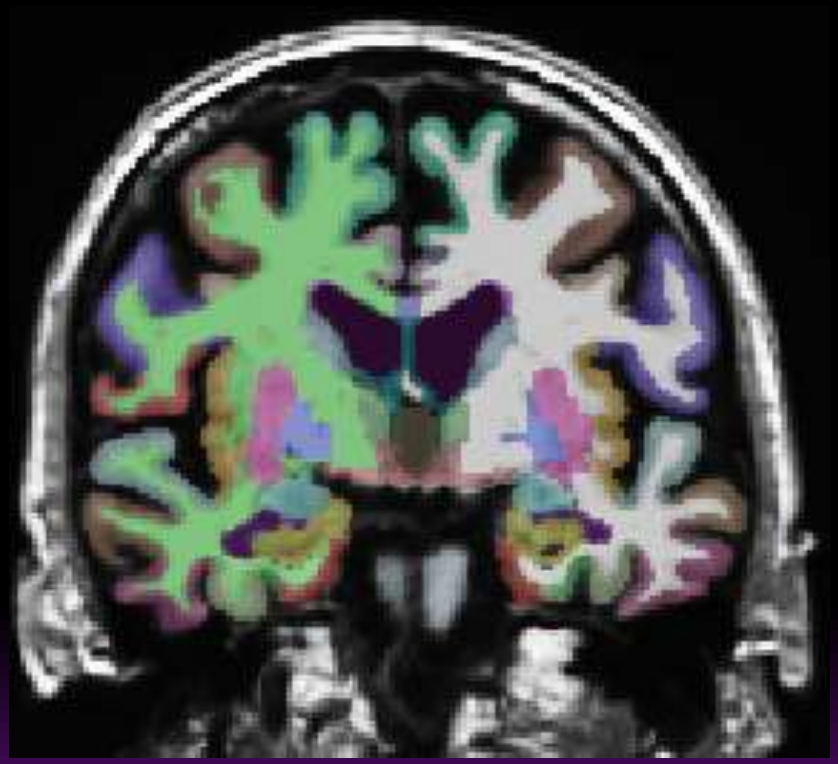
II. APOE2 in ADNI : MRI volumes, CSF



- N = 138 normals (27 ApoE2, 111 ApoE3)
- Alzheimer's Disease Neuroimaging Initiative (56-center cohort)
- 1.5 T MRI (baseline, 6 mo, 12 mo, 24 mo)
- Automated volumetry (Freesurfer)

II. APOE2 in ADNI : MRI volumes, CSF

Linear mixed-effects model (repeated measures):

$$V_{ij} = (B_0 + \beta_0) + \beta_1 \, ApoE2_i + (\beta_2 + \beta_3 \, ApoE2_i) \, t_{ij} + \text{covariates} + \varepsilon_{ij}$$

$$= \ldots \beta_1 \, ApoE2_i + \beta_2 \, t_{ij} + \beta_3 \, ApoE2_i * t_{ij} \ldots$$

β_1 = fixed effect of ApoE2 on hippocampal volume @ baseline
β_2 = effect of time on hippocampal volume (rate overall)
β_3 = time-ApoE2 interaction effect on hippo volume
(rate associated w ApoE2)

II. APOE2 in ADNI : MRI volumes, CSF

	Group	Estimated rate [95% CI]	Mean % change
Hippocampal volume (mm3/yr)	ApoE2	-33 [-66, 1]	-0.4%
	ApoE3	-81 [-96, -65]	-1.3%

The slower rate of hippocampal atrophy among ApoE2 normals is consistent with ApoE2 being protective against AD (p=0.01).

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II. APOE2 in ADNI : MRI volumes, Cog

Rate of change in:	Group	Estimated rate [95% CI]	Mean % change	p-value
Hippocampal volume(mm3/yr)	APOE2	-33 [-65, 0.4]	-0.5%	0.004
	APOE3	-86 [-102, -71]	-1.3%	
WMS-R delayed recall (units/yr)	APOE2	0.51 [0.06, 0.96]	+4.0%	0.23
	APOE3	0.21 [-.01, 0.42]	+1.6%	
ADAS-Cog (units/yr)	APOE2	-0.12 [-0.47, 0.23]	-2.1%	0.90
	APOE3	-0.09 [-0.25, 0.09]	-1.5%	

II. APOE2 in ADNI : CSF biomarkers

APOE2 carriers had:
34 pg/ml higher baseline levels of CSF Aβ
($p = 0.01$, 95% confidence interval: +7 to +60)
and
8 pg/ml lower levels of ptau
($p = 0.02$, 95% confidence interval: -14 to -1),
compared to APOE3/3 carriers.

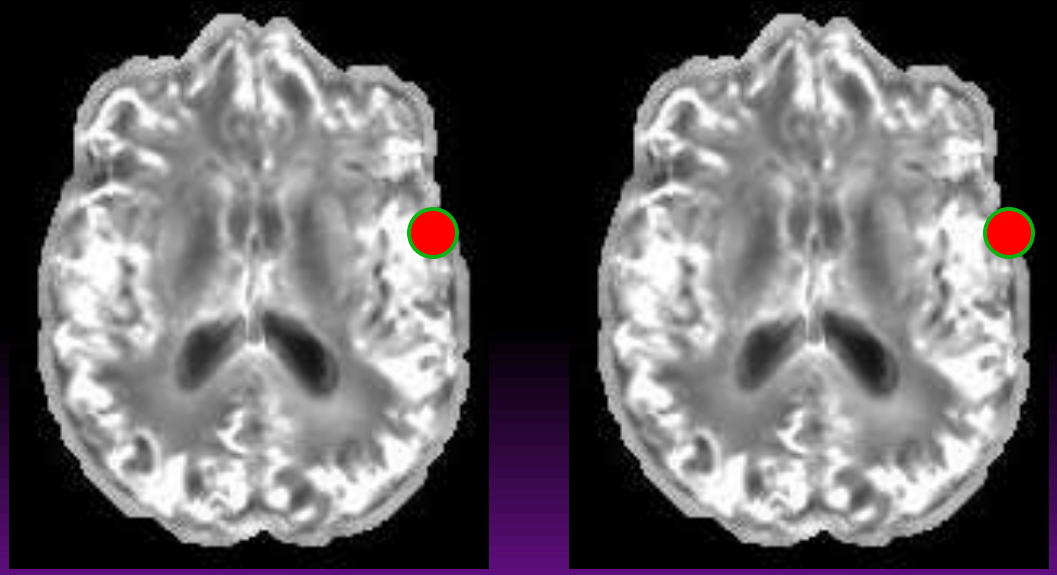
III. APOE2 at 4T: Morphometry

- 40 cognitively normal elderly individuals
  - ApoE3/3 = 20 (reference)
  - ApoE2/3 = 20 - protective

Age 50-90
MMSE 27-30, structured interview

III. APOE2 at 4T: Morphometry

- 4 Tesla MRI
- Deformation-based Morphometry (DBM)

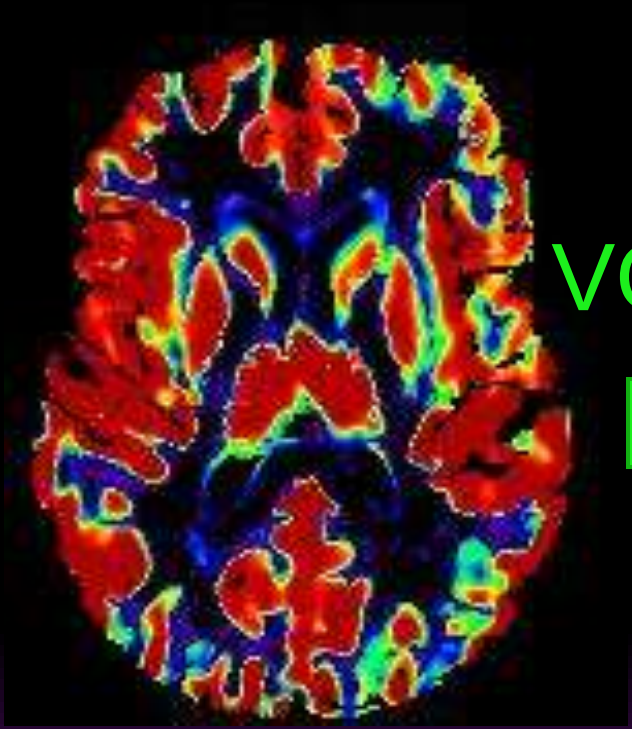


-**Goal**: compare homologous regions in different subjects

-**DBM**: determinant of the Jacobian matrix (measure of deformation to atlas)

-No morph differences (uncorrected p = 0.005)

III. APOE2 at 4T: Perfusion



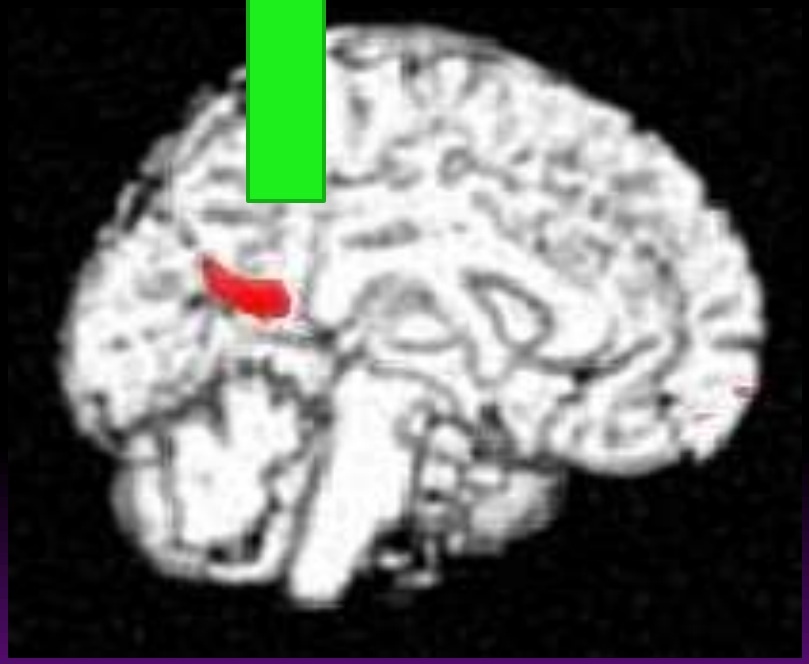
VOXEL

Continuous ASL (blood flow)

Gray template (derived from T1)

III. APOE2 at 4T: Perfusion

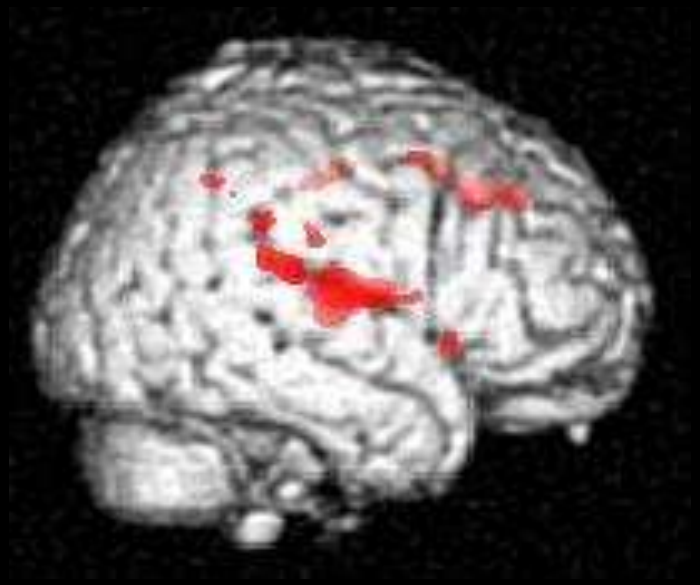
posterior cingulate / precuneus



ApoE2 (protective) carriers have increased CBF relative to ApoE3/3 (reference)

$P < 0.005$

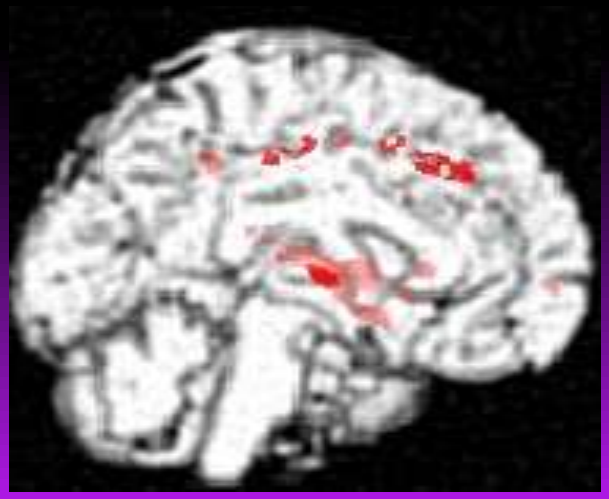
III. APOE2 at 4T: Perfusion



ApoE2 (protective) carriers have **<u>decreased</u>** CBF relative to ApoE3/3 (reference)

Insula
Anterior cingulate
Medial thalamus

$P < 0.005$



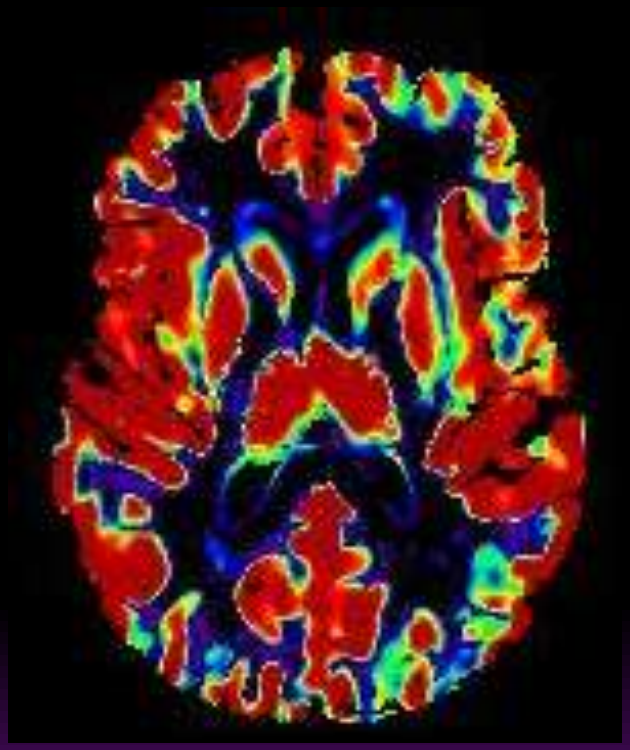
III. APOE2 at 4T: Perfusion

1. ASL-MRI detects CBF differences among normals with differing genetic risk for Alzheimer's disease. **Biomarker?**

2. ApoE2 (protective) carriers have increased posterior cingulate CBF, consistent with AD protection

Chiang G, Tosun D, et al. ASL-MRI Detects Perfusion Differences in Cognitively Normal ApoE2 and ApoE4 Carriers: a possible explanation for Alzheimer protection versus risk. Oral presentation at **ASNR** 48th annual meeting (Boston, MA).

III. APOE2 at 4T: Perfusion



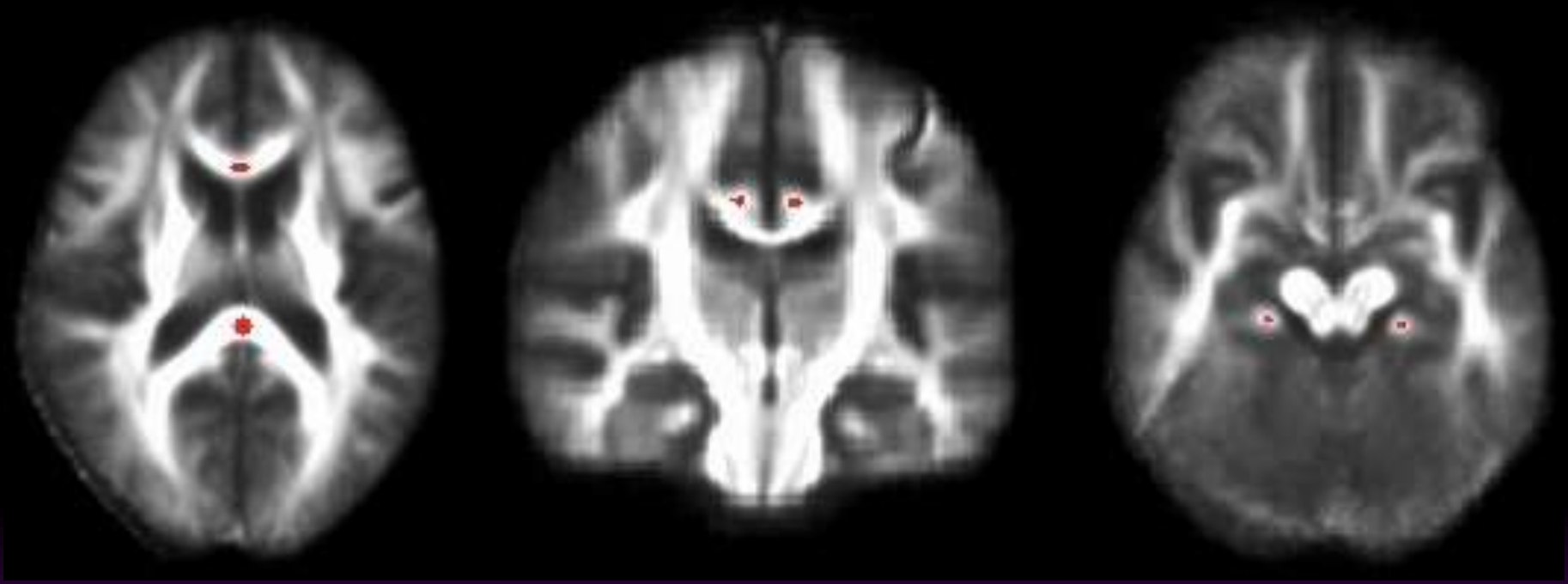
LIMITATIONS:

1. Small sample size.
2. Co-registration technique for voxel-based analysis.

* Correlation with neuropsychological assessment

* Other factors affect ASL (i.e. cerebrovascular disease, anti HTN therapy)

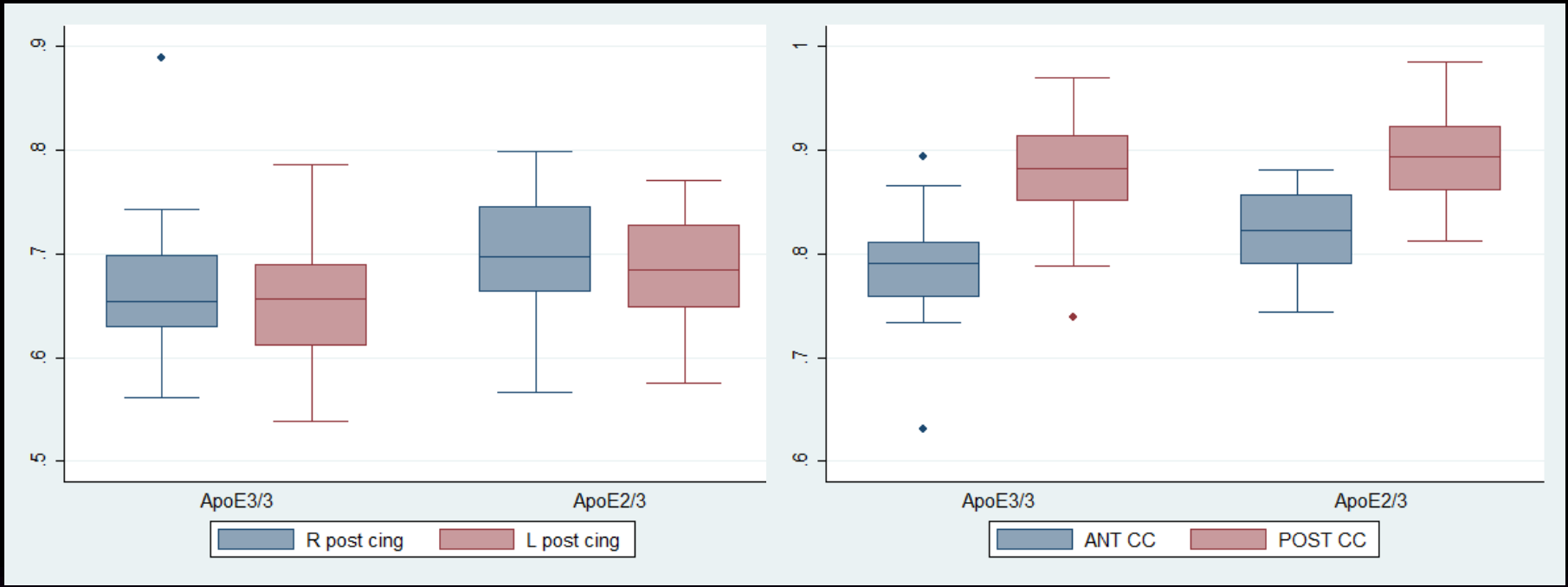
III. APOE2 at 4T: Diffusion Tensor Imaging



8 ROIs in native space (FSL): ACC, PCC, R/L anterior/posterior cingulate, R/L parahippocampal

Repeat measuremt after 3 months: ICC = 81-95%

III. APOE2 at 4T: Diffusion Tensor Imaging



APOE2 carriers had higher FA in the posterior cingulate (p = 0.02) and genu of the corpus callosum (p = 0.005) compared to APOE3/3.

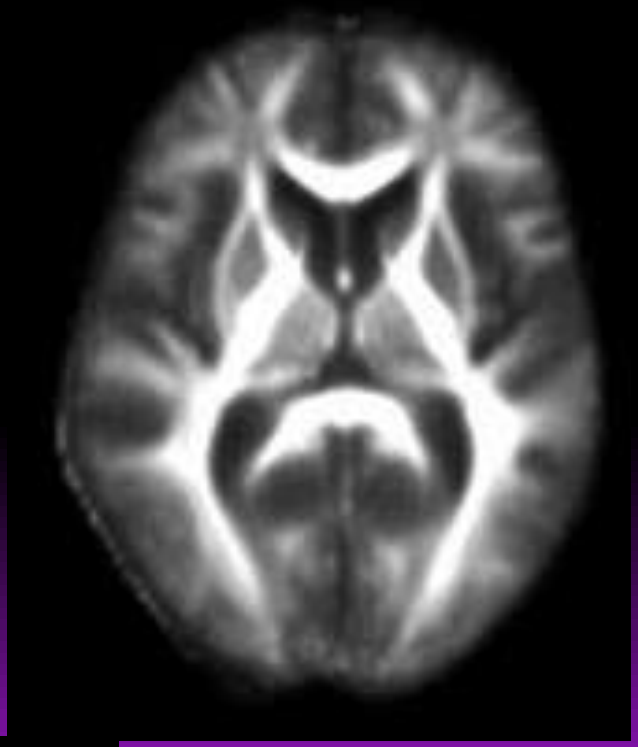
III. APOE2 at 4T: Diffusion Tensor Imaging

- APOE2 carriers had higher FA in the posterior cingulate ($p = 0.02$) and genu of the corpus callosum ($p = 0.005$) compared to APOE3/3.

- Same ROIs on eigenvalue maps:
  - Axial diffusivity λ_1
  - Radial diffusivity $(\lambda_2 + \lambda_3)/2$ – myelin (not axonal loss)

III. APOE2 at 4T: Diffusion Tensor Imaging

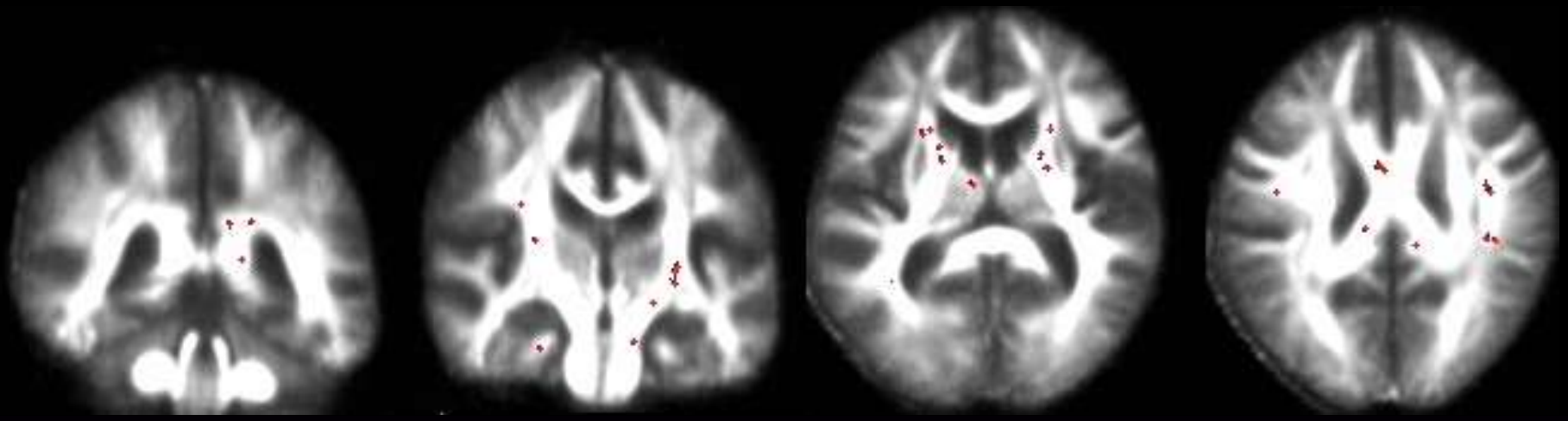
- Tract-Based Spatial Statistics



Projects FA values onto an alignment-invariant tract representation (skeleton)

III. APOE2 at 4T: Diffusion Tensor Imaging

- Tract-Based Spatial Statistics



APOE2 > APOE3/3 ($p = 0.005$)

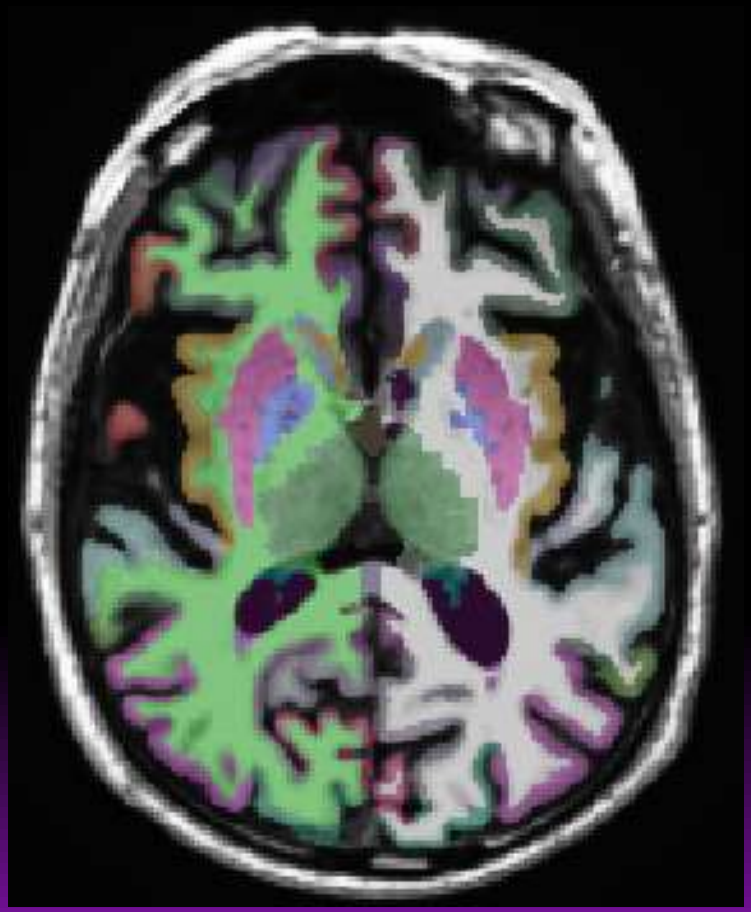
No regions APOE2 < APOE3/3 ($p = 0.005$)

III. APOE2 at 4T: Summary

- APOE2:
  -Slower hippocampal atrophy rates (ADNI)
  -Increased posterior cingulate perfusion
  -Increased FA (decreased radial diffusivity) in posterior cingulate and ACC
  -ALL consistent with Alzheimer's protection

*reflect AD pathology or APOE2 phenotype, how to relate modalities to each other?

IV. Other endeavors: Predicting risk for memory decline

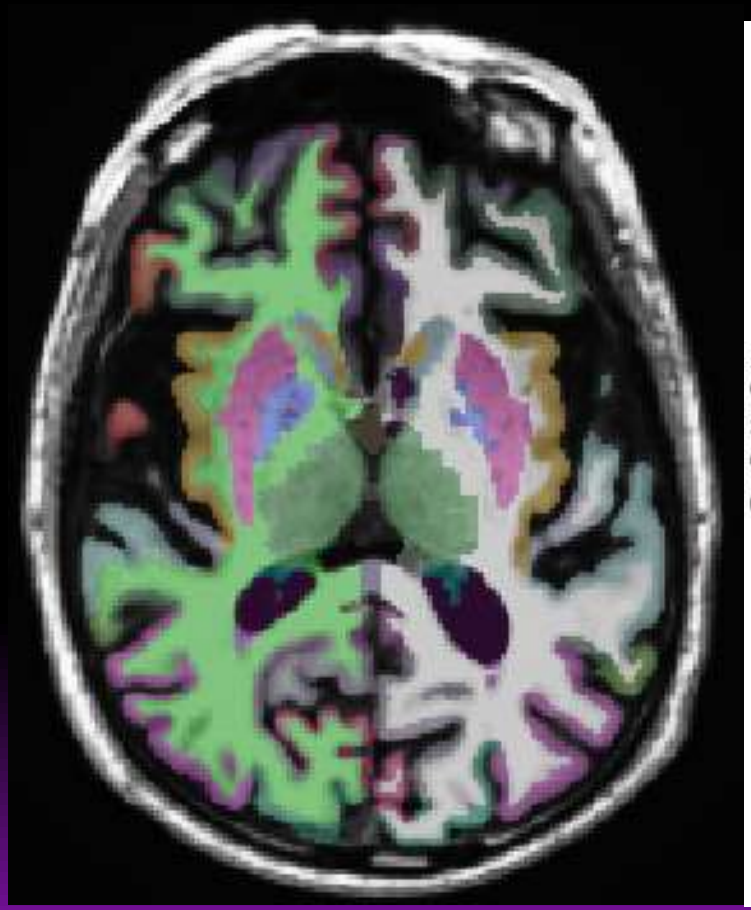


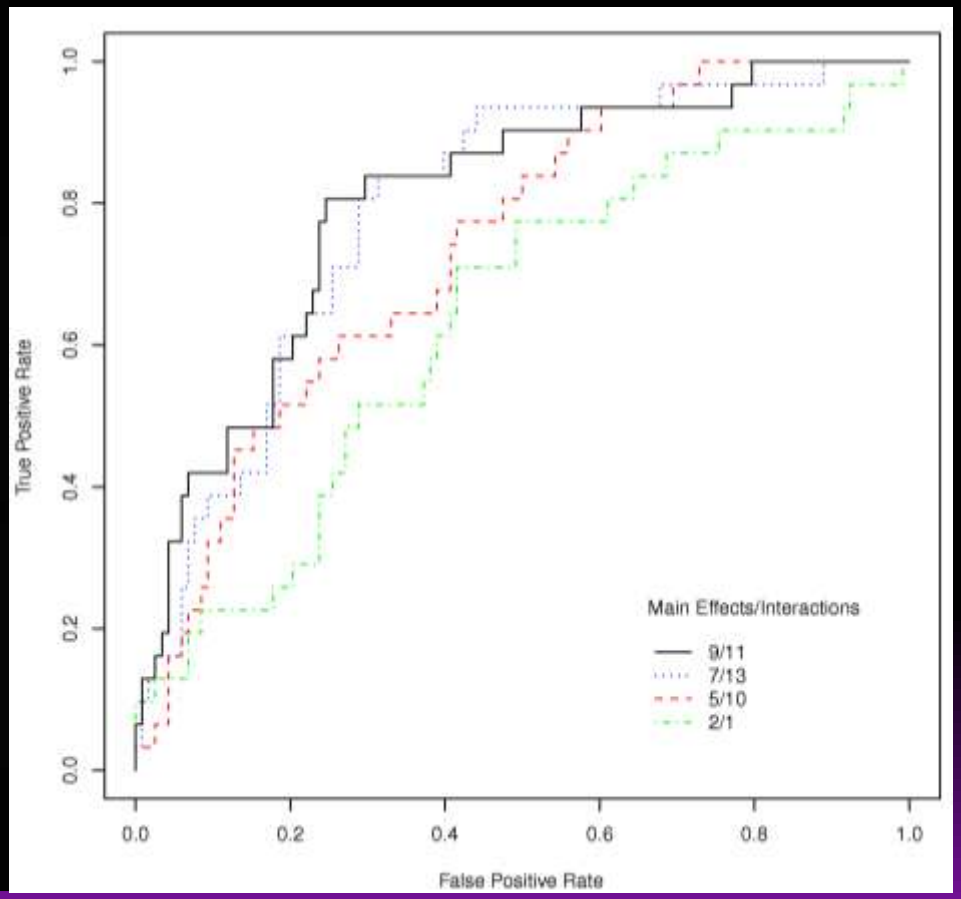
N = 150 ADNI normals

30 declined 1 SD below group mean (delayed verbal memory)

9 temporoparietal volumes predicted memory decline with **90% accuracy** (80% cross-validated)

IV. Other endeavors: Predicting risk for memory decline





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