MRI Core
WW ADNI
Vancouver 2012

Bret Borowski - Mayo

Matt Bernstein - Mayo

Jeff Gunter – Mayo

Clifford Jack - Mayo

David Jones - Mayo

Kejal Kantarci - Mayo

Denise Reyes – Mayo

Matt Senjem – Mayo

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Chad Ward – Mayo

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Nick Fox – UCL

Norbert Schuff – UCSF/VA

Paul Thompson – UCLA

ADNI GO/2 MRI 3T Protocol

CORE

- 3D T1 volume un - & 2x accelerated (MPRAGE on Siemens and Phillips, IR SPGR on GE) – morphmetry
- FLAIR –cerebro vascular disease grading
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Accelerated vs. Non-Accelerated (ADNI)

Tensor-based Morphometry (TBM) numerical summaries

and 3-dimensional maps of cumulative brain atrophy

Chris Ching, Xue Hua, Derrek Hibar, Paul Thompson

Laboratory of Neuro Imaging

March 2012

EMCI – no difference accel vs un accel, TBM rates

We found no significant difference between numerical summaries derived from accelerated and non-accelerated scans at 6 and 12 months, using the TBM method (p>.38, R>.69).

6mo

Cumulative Atrophy	2 tail paired t-test p-value	correlation coef.
Stat ROI	0.78	0.69
Temporal ROI	0.51	0.74
Temporal GM ROI	0.44	0.74

12mo

Cumulative Atrophy	2 tail paired t-test p-value	correlation coef.
Stat ROI	0.75	0.77
Temporal ROI	0.41	0.70
Temporal GM ROI	0.39	0.70

6 and 12 month n80's - EMCI

6mo

	Accel Stat ROI	NonAccel Stat ROI	Accel Temporal ROI	NonAccel Temporal ROI	Accel Temporal GM ROI	NonAccel Temporal GM ROI
% Tissue atrophy	0.64	0.62	0.30	0.27	0.35	0.30
Std	0.85	0.80	0.64	0.61	0.80	0.77
N80 [CI]	441 [252,1401]	419 [272, 782]	1127 [540, 3922]	1280 [630, 4742]	1342 [613, 5119]	1637 [727, 6664]

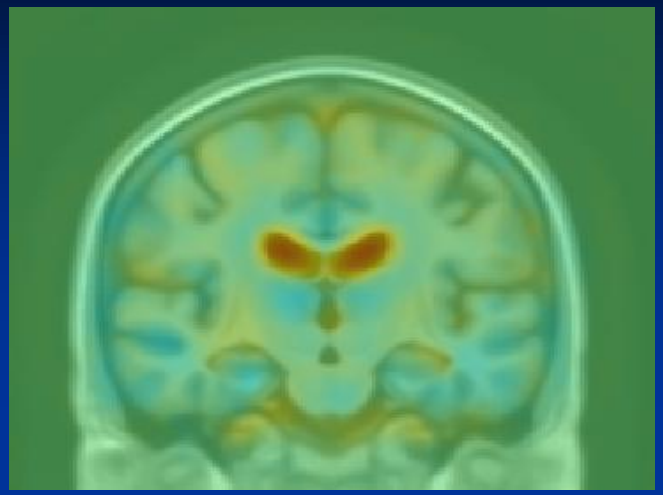
12mo

	Accel Stat ROI	NonAccel Stat ROI	Accel Temporal ROI	NonAccel Temporal ROI	Accel Temporal GM ROI	NonAccel Temporal GM ROI
% Tissue atrophy	1.10	1.08	0.55	0.49	0.62	0.55
Std	0.87	0.97	0.67	0.64	0.82	0.83
N80 [CI]	157 [107, 267]	201 [128, 465]	382 [224, 856]	421 [250, 818]	435 [245, 1006]	556 [306, 1319]

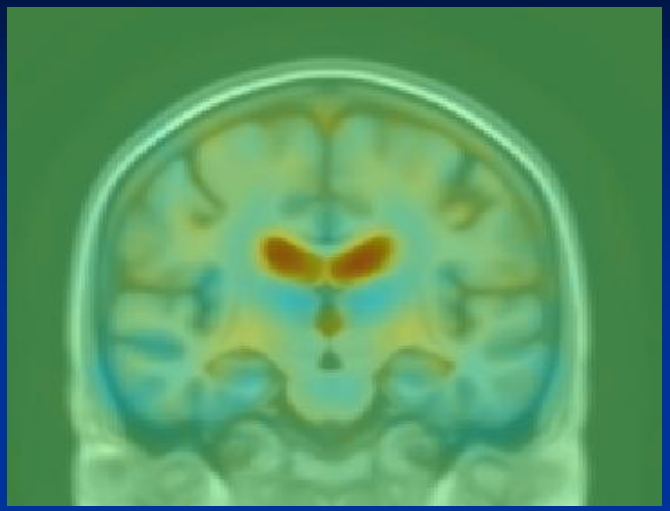
Accelerated scans provide lower n80's (except for 6mo Stat ROI), but given the wide spread of the confidence intervals, this difference is not significant.

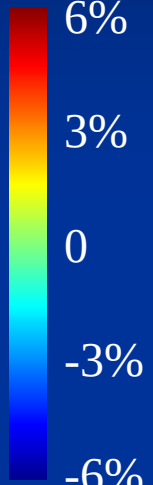
Average maps of cumulative brain atrophy - EMCI

6mo Accelerated

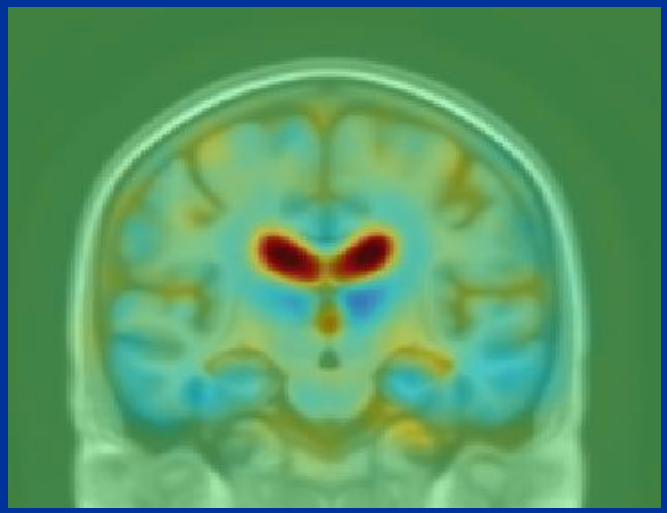


6mo Non-Accelerated

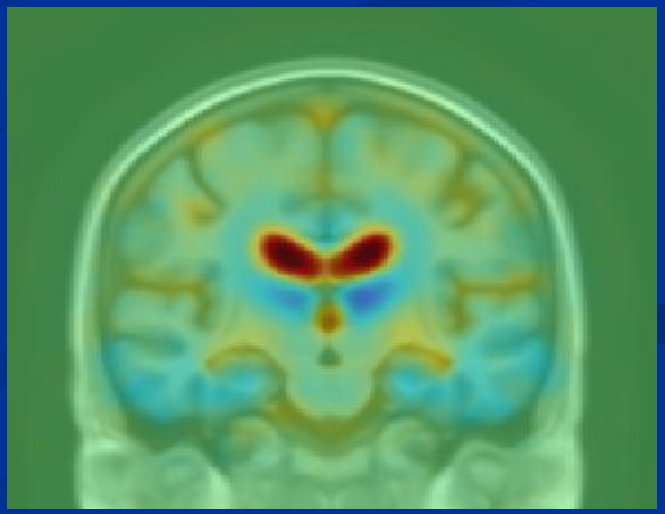




12mo Accelerated



12mo Non-Accelerated

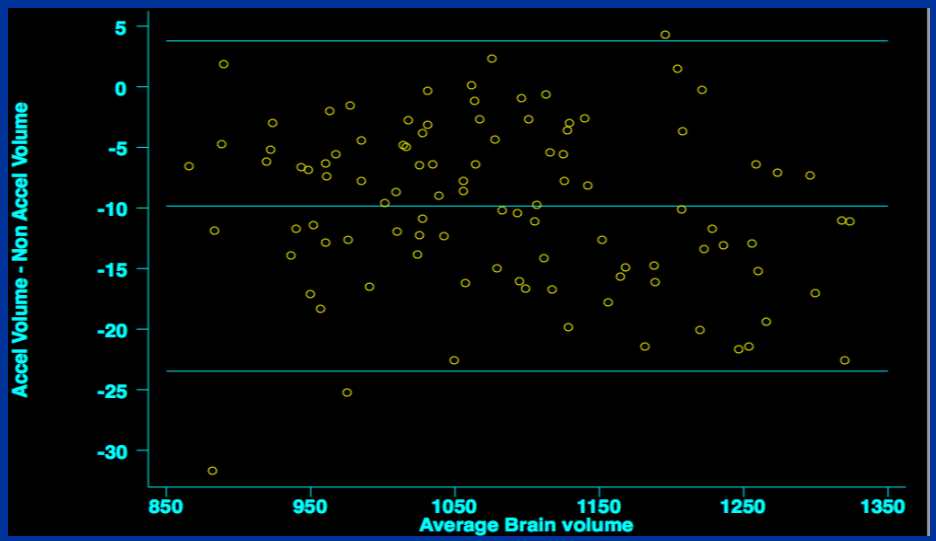


ADNI-GO and ADNI-2 results

University College London
Dementia Research Centre
Institute of Neurology
12 April 2012

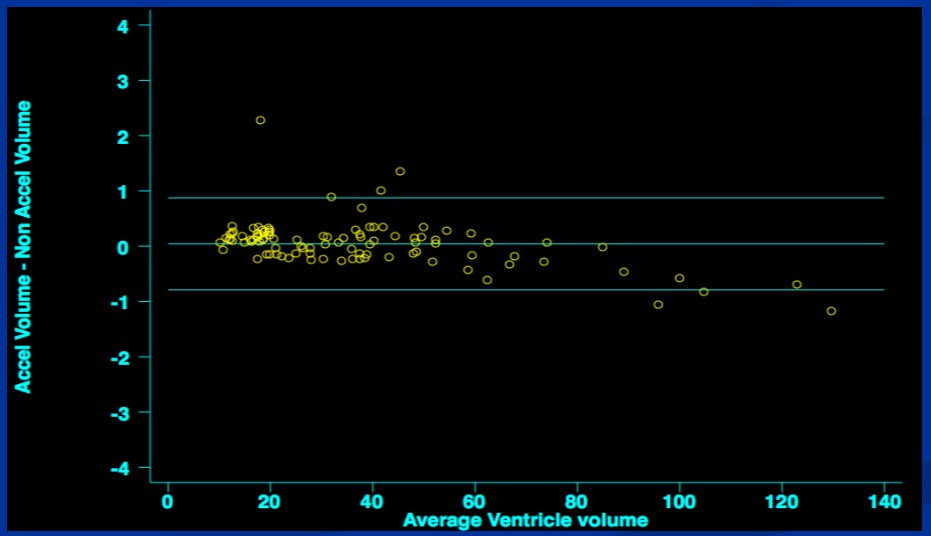
Cross sectional Accelerated vs. Non-accelerated for ADNIGO EMCI subjects

	n	Brain (ml) Accelerated	Brain (ml) Non-Accel.	Pairwise p val	Ventricles (ml) Accelerated	Ventricles (ml) Non-Accel.	Pairwise p val
Screening	58	1088 ± 123	1097 ± 126	< 0.001	36.5 ± 25.4	36.5 ± 25.6	0.39
Month 6	35	1068 ± 110	1078 ± 111	< 0.001	36.8 ± 24.5	36.9 ± 24.8	0.56
Month 12	7	1115 ± 117	1123 ± 118	0.01	40.1 ± 21.9	40.1 ± 22.0	0.46



Brain volume:

- Consistently lower brain volume (~1%) in accelerated scans compared to non-accelerated
- Largest difference (> 30 mL): accelerated scan was considered very borderline by DRC due to motion.



Ventricle volume:

- No significant differences between accelerated and non-accelerated scan.

Longitudinal Accelerated vs. Non-accelerated for ADNIGO EMCI subjects

	n	Brain KN-BSI (% of baseline) Accelerated	Brain KN-BSI (% of baseline) Non-accel	p val	VBSI (mL) Accelerated	VBSI (mL) Non-Accel	p val
Month 6	32	1.037 ± 1.261%	0.892 ± 1.396%	0.86	0.83 ± 1.56	0.80 ± 1.52	0.79
Month 12	6	0.369 ± 0.772%	0.618 ± 0.633%	0.10	0.98 ± 1.45	1.03 ± 1.53	0.30

BBSI and VBSI calculated from EMCI subjects in ADNI-GO
Note: excludes subjects where there is no screening and only 1 x scan for each protocol per visit, hence slightly lower numbers than cross sectional

ADNI 2 and ADNI GO STAND-scores

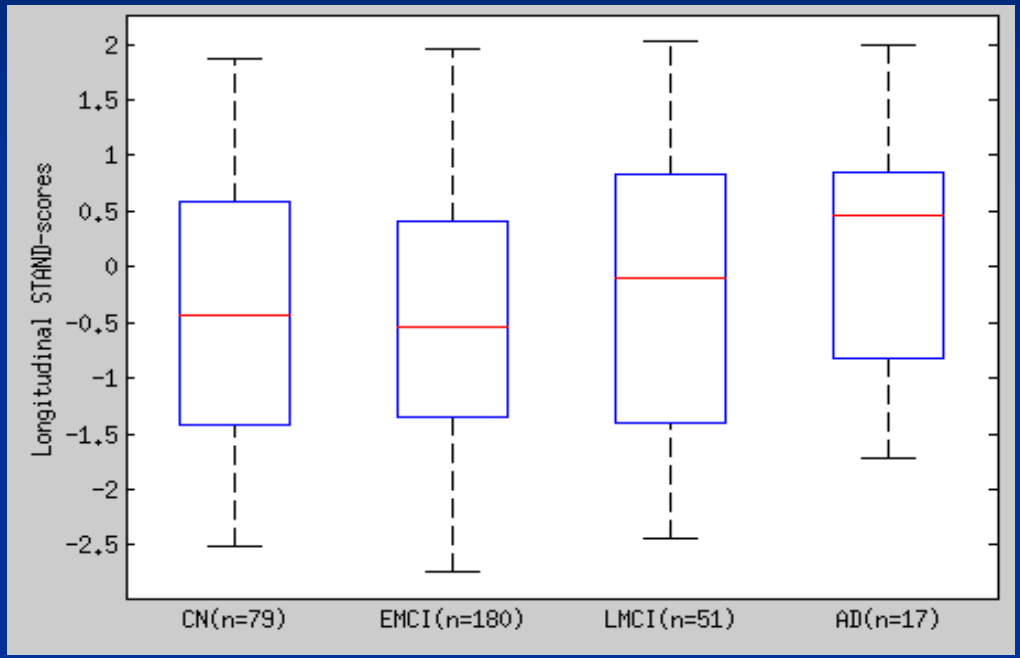
Prashanthi Vemuri, Matthew Senjem, Jeffrey Gunter, Clifford Jack

MAYO CLINIC ROCHESTER

TBM-SyN & Longitudinal STAND-scores

1) "TBM-SyN": Unbiased, intra-subject longitudinal nonlinear registration
   - Annualized log of Jacobian determinant from Symmetric Normalization (SyN) [Avants et al. Med Image Anal, 2008].
   - ROI level summary statistics, e.g. mean annualized change in each ROI.
2) "Longitudinal-STAND": Machine learning method for high classification accuracy & selecting ROIs for power calculations
   - Application of SVM to TBM-SyN ROI data
   - Independent data set for training and ROI selection, from Mayo Clinic Study of Aging: 51 CN (PIB –ve) and 51 AD subjects

Longitudinal STAND-scores in ADNI GO and ADNI-2 3 T subjects

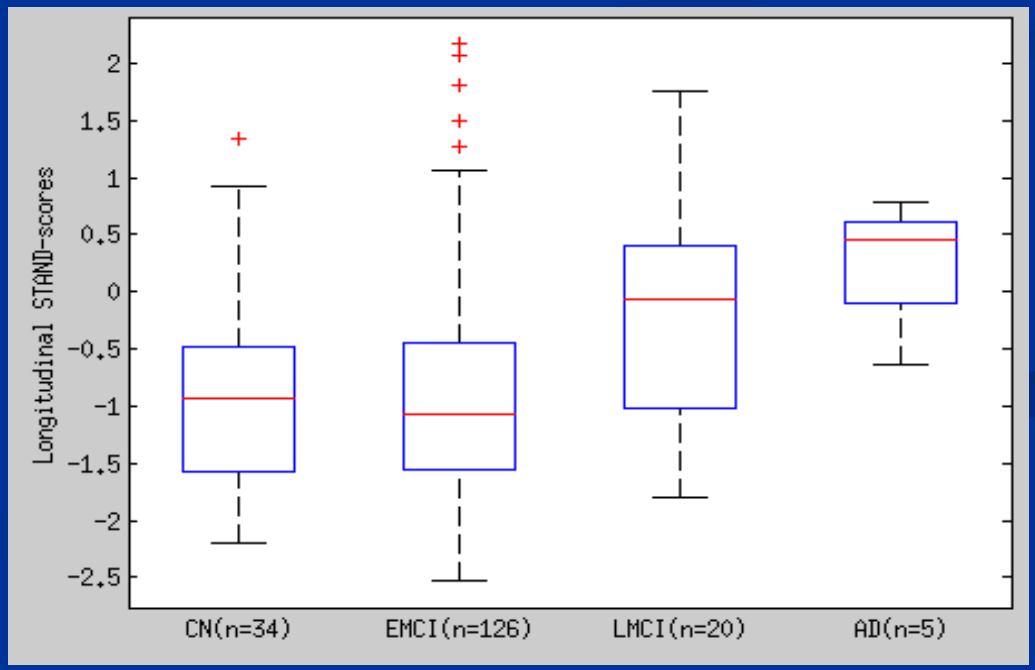


3 Month Estimates:

AUC and 95 % CI separation for AD and CN =0.635 [0.48 0.79]

6 Month Estimates:

AUC and 95 % CI separation for AD and CN =0.86 [0.65 1.0]



Sample Size Estimates based on TBM-SyN in selected ROIs:

	CN	EMCI	LMCI	AD
3 mo.	359 (227, 655) N = 79	427 (296, 665) N = 180	230 (136, 475) N = 51	188 (75, 720) N = 17
6 mo.	244 (124, 587) N = 34	431 (281, 761) N = 126	86 (48, 170) N = 20	* N = 5
12 mo.	* N = 1	133 N = 61		

Table 1. Sample size with bootstrap 95% CI to detect 25% reduction in atrophy rate with 80% power and alpha = 0.05

* Too few subjects

sMRI - summary

- Some evidence that accelerated sMRI is equivalent to non accelerated. But evidence is not uniform ➔ further study, esp cross vendor
- A reasonable atrophy signal is seen at 3 months in CN, EMCI, LMCI and AD
- Sample sizes for EMCI at 3 and 6 months ~ 400s, and ~ 150 – 200 at 12 months

ADNI GO/2 MRI 3T Protocol

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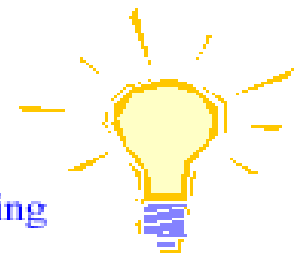
Analysis of Vascular Factors in ADNI II

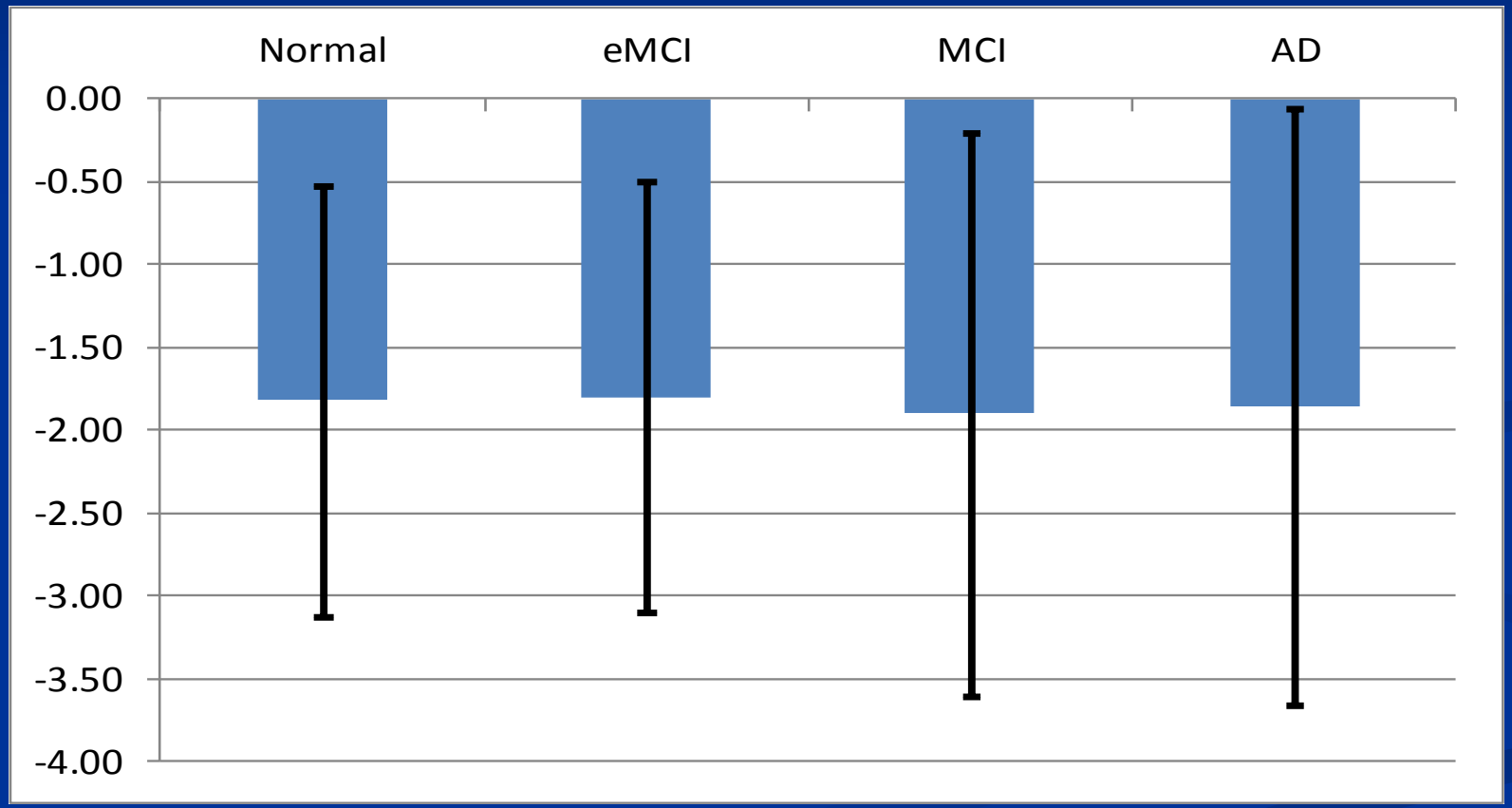
Charles DeCarli, Chris Swartz, Baljeet Singh, Oliver Martinez, Evan Fletcher, Jing He, Owen Carmichael

IDeA Lab

Imaging of Dementia and Aging

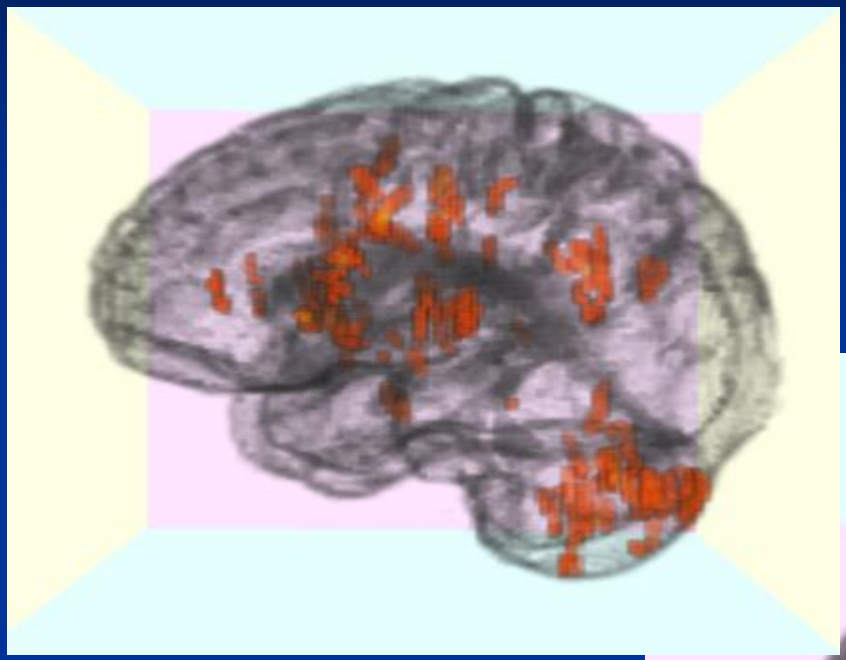


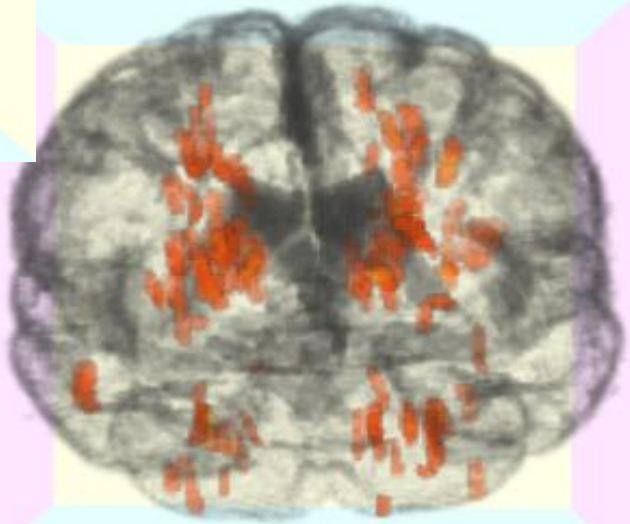
Differences in WMH* at basline

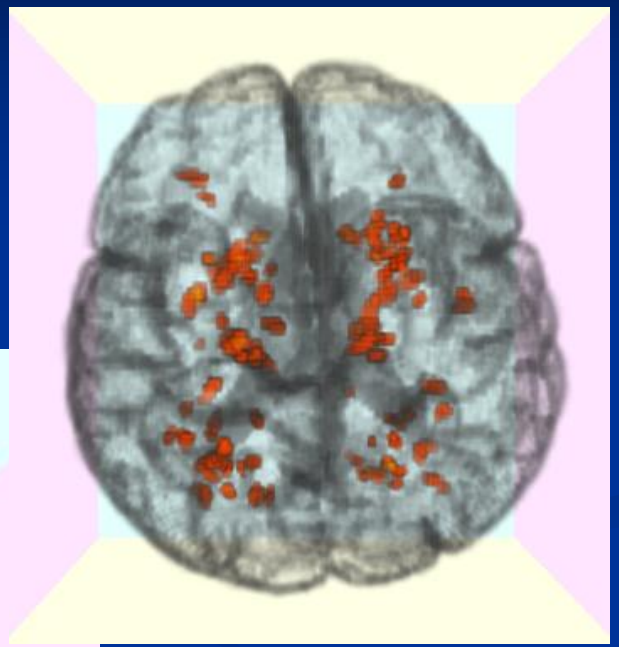


* Log normalized volumes as percentage of TCV

MR Infarct Distribution







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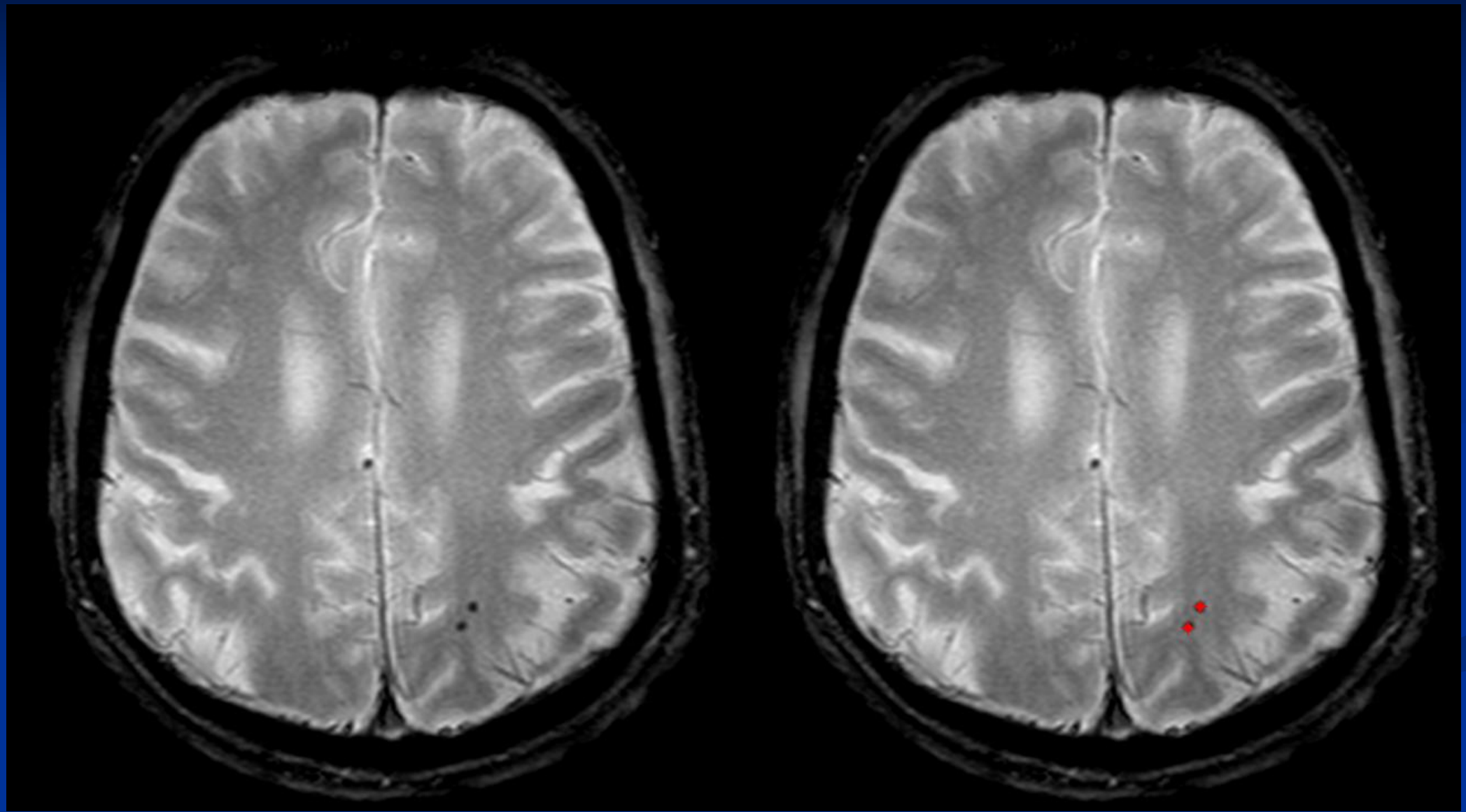
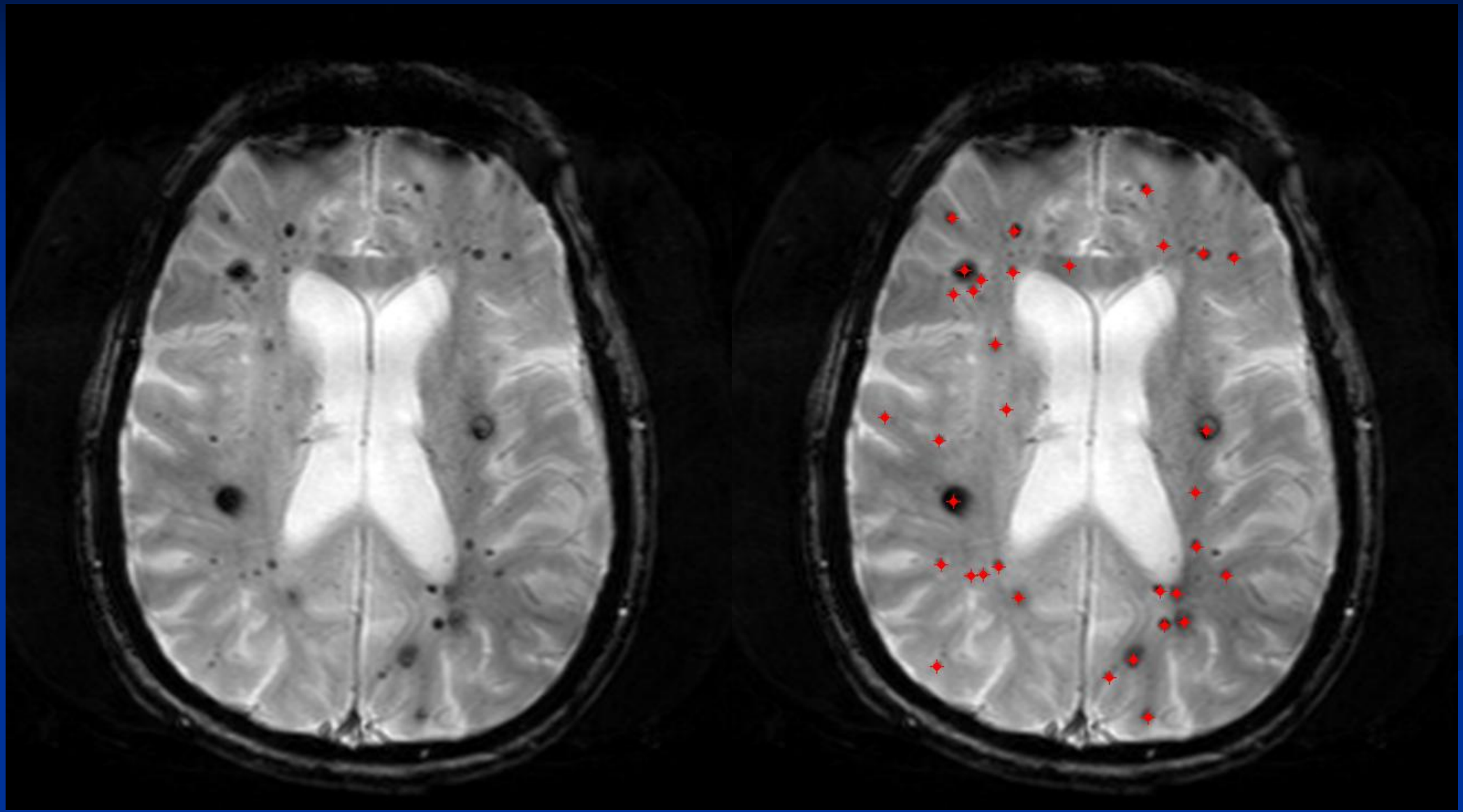
ARIA-H Marking SW application – J Gunter

- Spatial registration and display of all volumes in subject time series
- Each MCH is tracked as an individual entity over time
- Definite vs possible at each time point
- x,y,x coordinates of each
- Marking done first by trained image analysts, all positive findings verified by MD

Few MCH



305 MCH (EMCI)



summary

- prevalence of one or more definite microhemorrhages 25%
- increasing with age (0.22; $p<0.001$) and Aβ load (florbetapir) (0.16; $p<0.001$)
- prevalence of superficial siderosis 1%
- topographic densities highest in the occipital lobes and lowest in the frontal lobes and deep/infratentorial
- APOE ε4 and ε2 carriers had greater numbers of microhemorrhages compared to ε3 homozygotes
- greater number of microhemorrhages at baseline were associated with a higher incidence of subsequent microhemorrhages (rank correlation =0.43; $P<0.001$)

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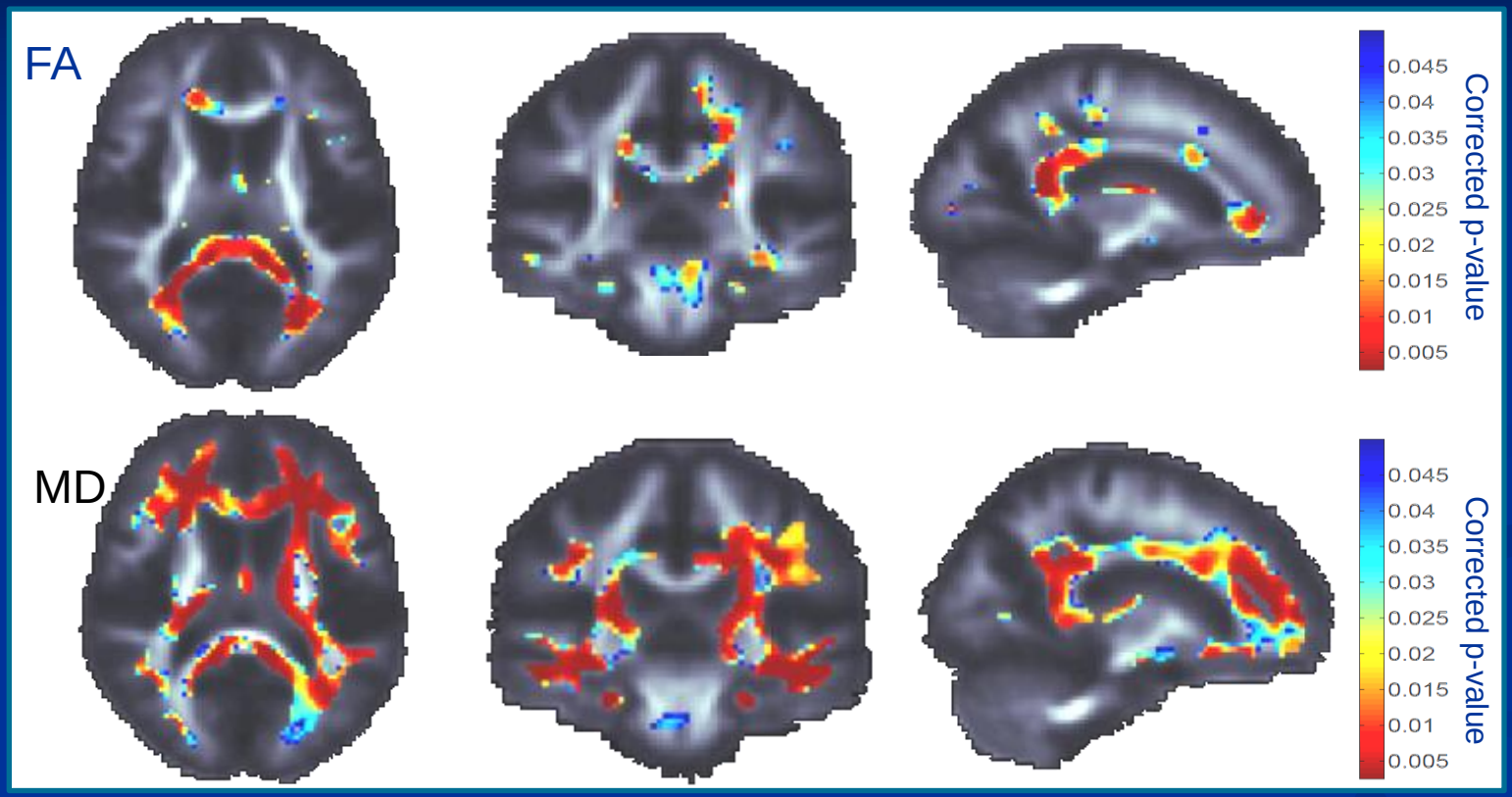
ADNI-2 – Diffusion Imaging Year 1

Talia Nir, Neda Jahanshad, Paul Thompson
(Thompson lab, UCLA)

Cross Sectional Differences
AD (N=15) vs Controls (N=29)

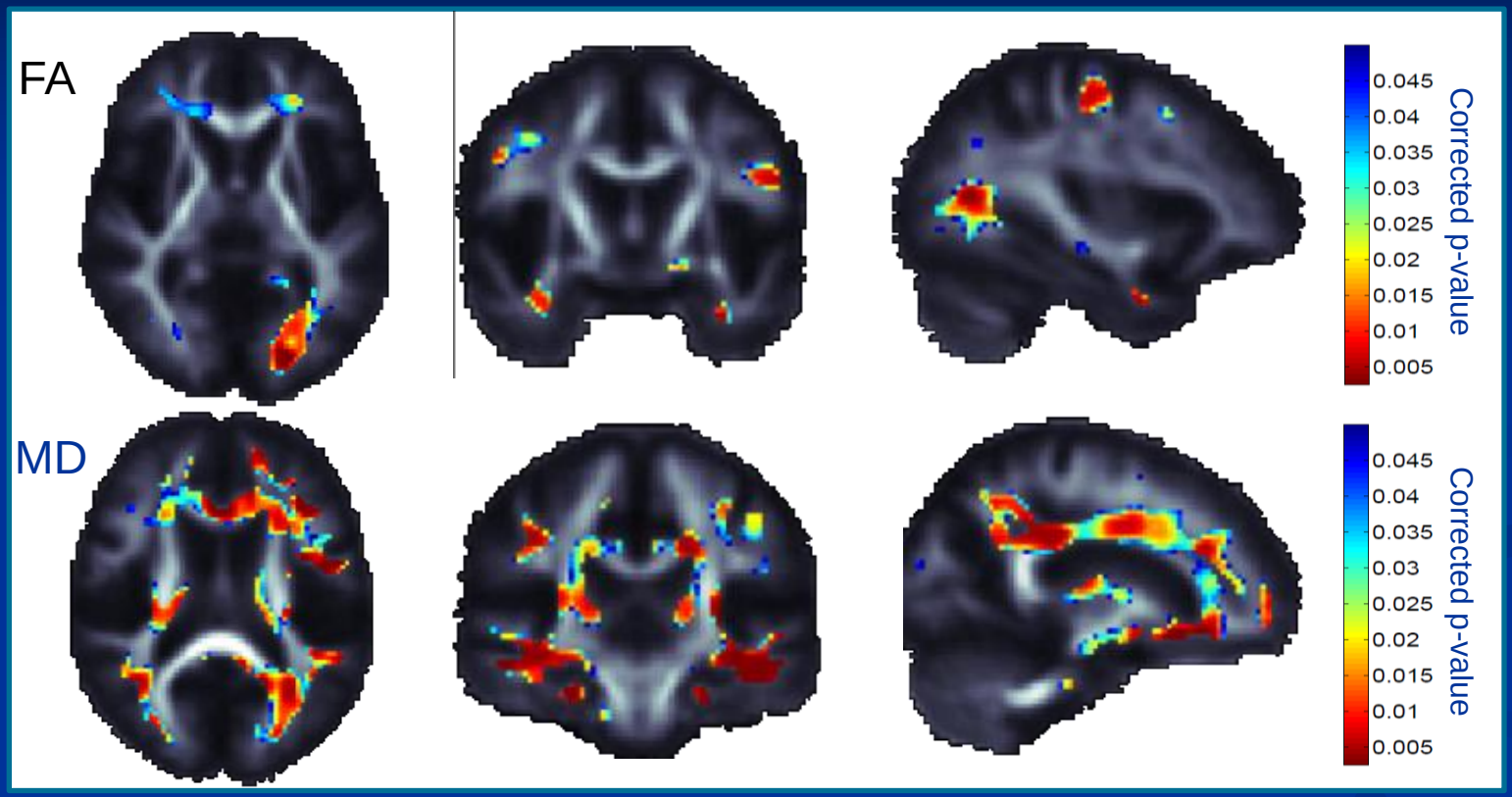
FA

MD



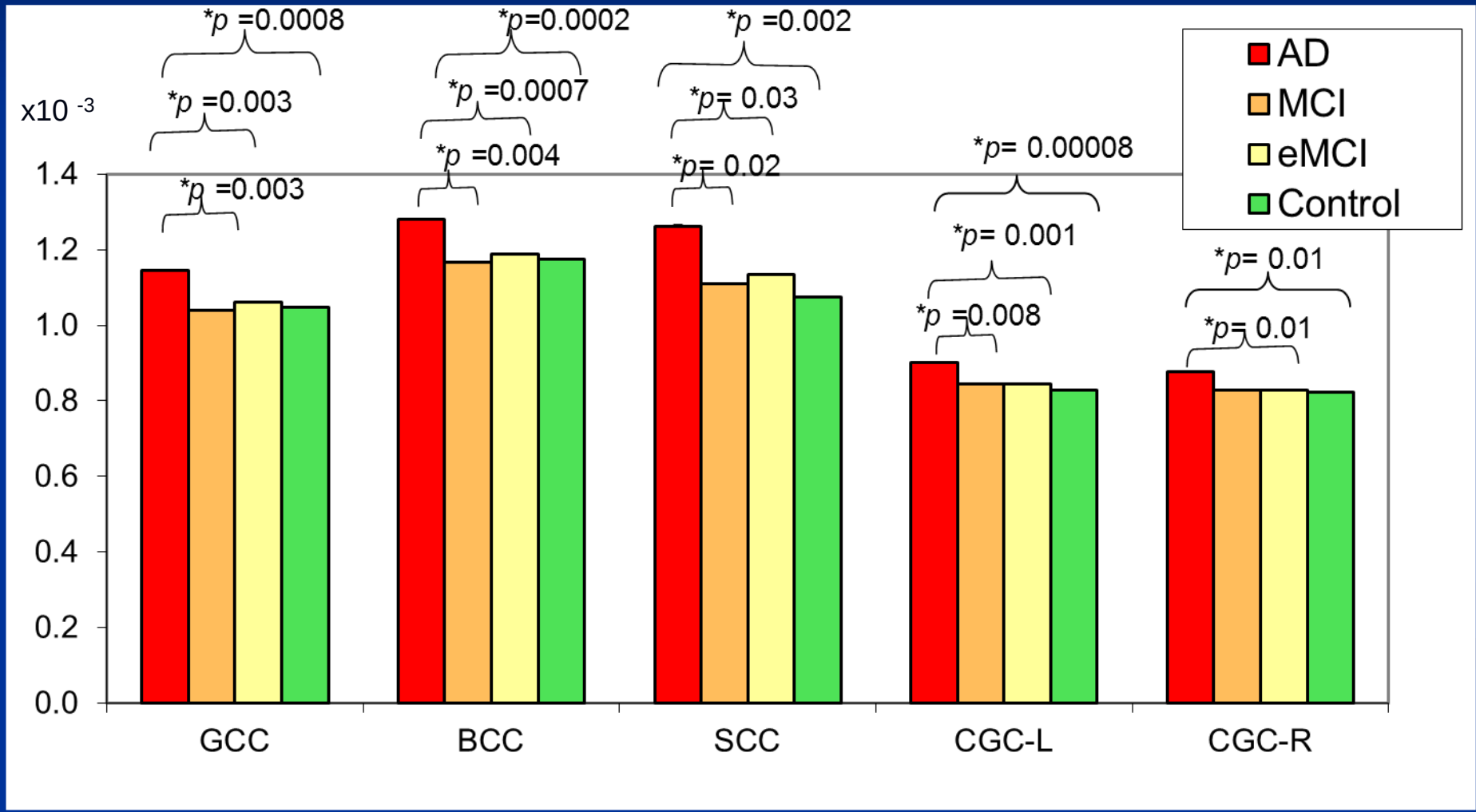
Regions of significant difference (corrected p<0.05) between AD and normal elderly groups after controlling for sex and age. As expected, the AD group has lower FA and higher MD than controls throughout the WM. Type I errors controlled using the searchlight false discovery rate (sFDR) method (Langers et al., 2007).

Cross Sectional Differences
AD (N=15) vs eMCI (N=57 early MCI)

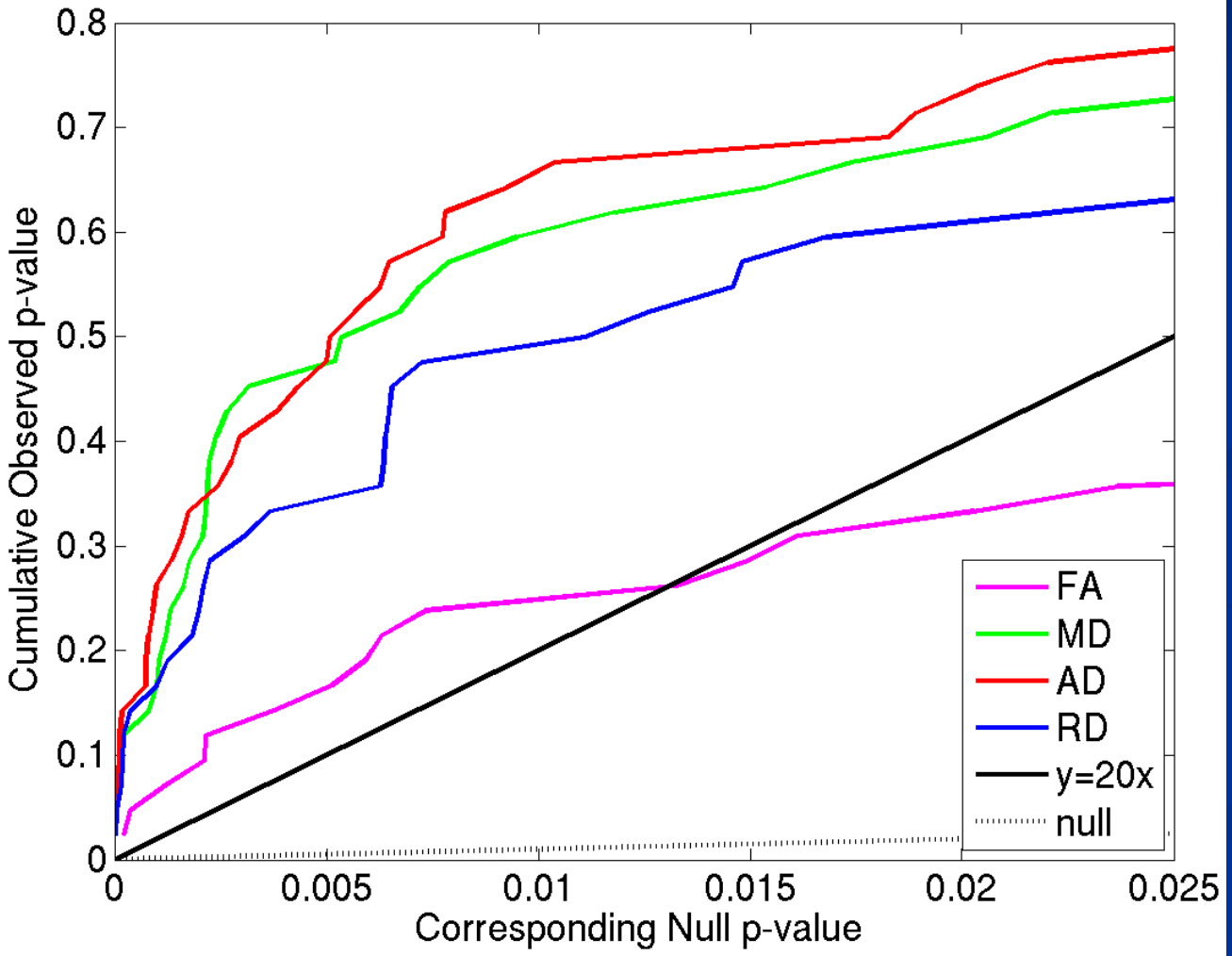


Regions of significant difference (corrected p< .05) between AD and eMCI groups after controlling for sex and age. As predicted, the AD group has lower FA and higher MD than eMCI throughout. Type I errors controlled using the searchlight false discovery rate (sFDR) method (Langers et al., 2007).

Regional differences in Average MD



Which DTI-derived measures best discriminate AD vs Controls?



- Cumulative distribution plot of all 42 ROI p-values obtained when comparing AD to controls
- Diffusivity measures other than FA are more powerful for discriminating AD vs. controls
- Particularly MD and **axial diffusivity,** suggesting more axonal damage

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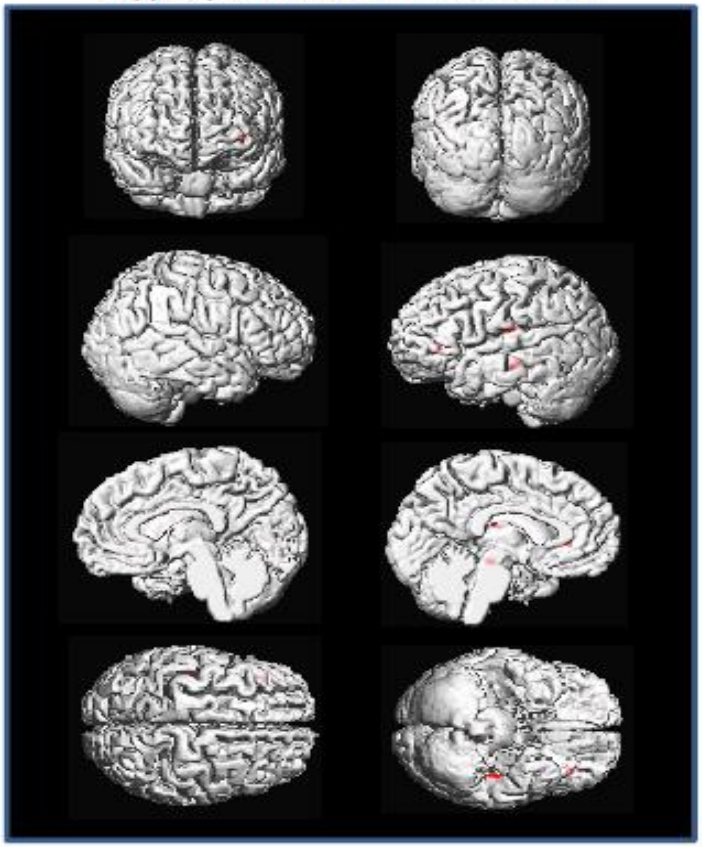
ADNI2
Arterial Spin Labeling (ASL) Perfusion MRI
Preliminary Results April 2012

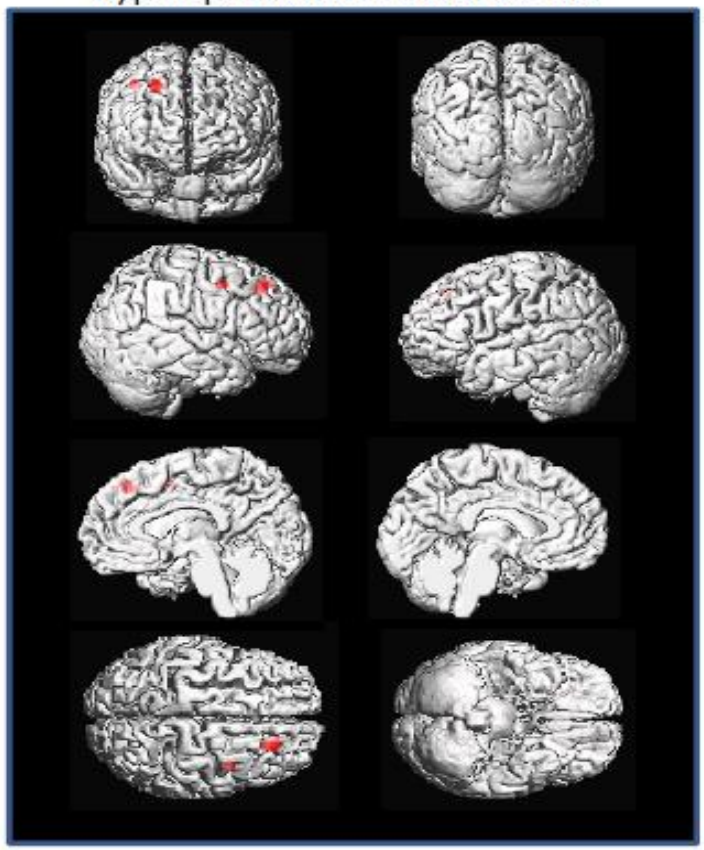
Miriam Hartig, Yu Zhang, Daniel Cuneo, Derek Flenniken, Diana Truran, Duygu Tosun, Norbert Schuff
SFVAMC/UCSF Lab

Baseline - Regional CBF Differences Between MCI and Control

Hypo-perfusion in MCI vs. CN



Hyper-perfusion in MCI vs. CN



Regions of significant differences between MCI and CN after controlling for sex, age and global mean CBF.
[smooth = 8mm]
Highlighted are regions with uncorrected $p < 0.001$ and cluster size > 20 voxels.

Baseline - Regional CBF Differences Between EMCI and Control

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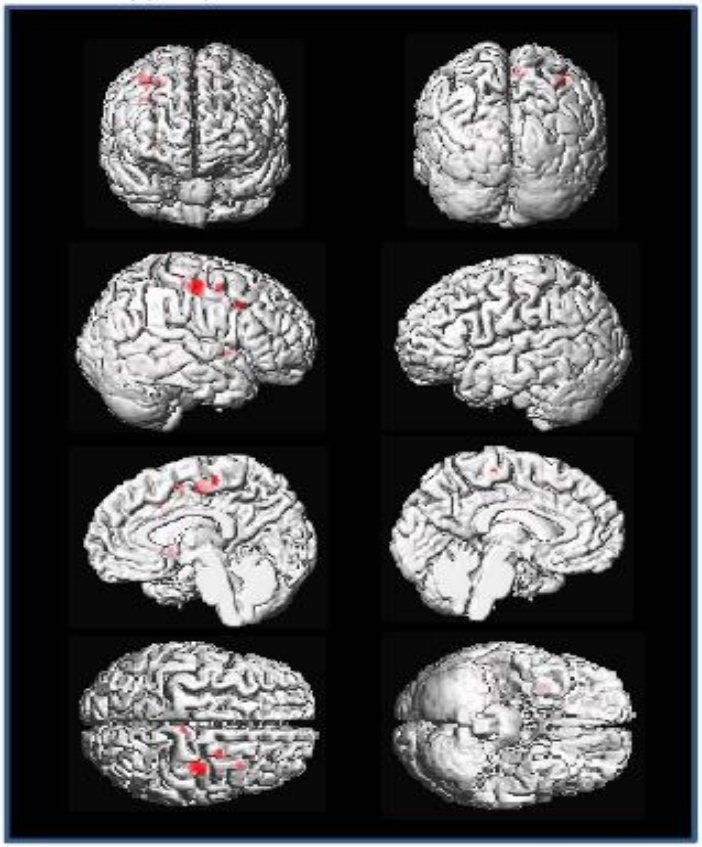
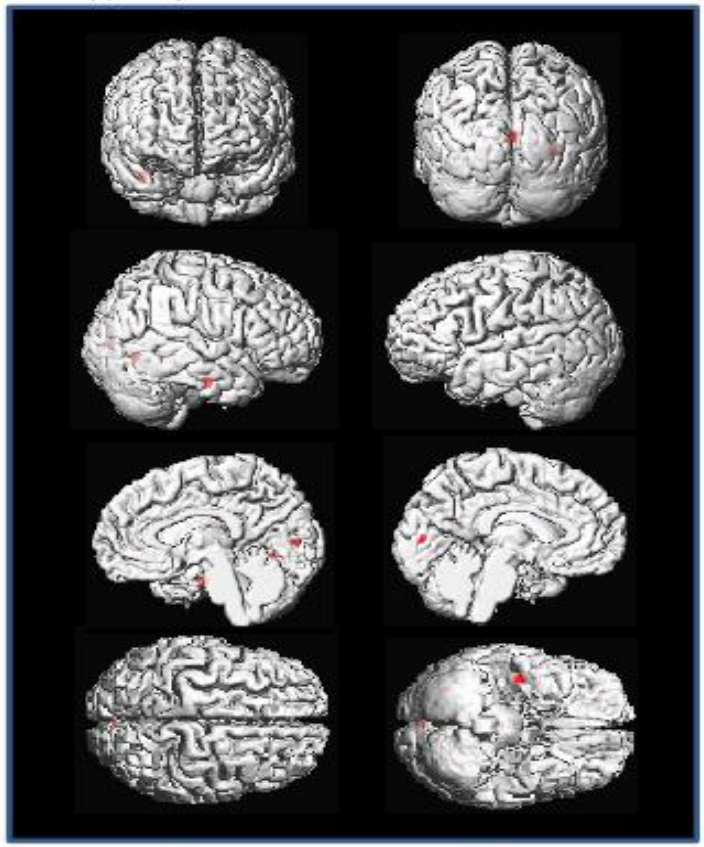


Hyper-perfusion in EMCI vs. CN



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[smooth = 8mm]
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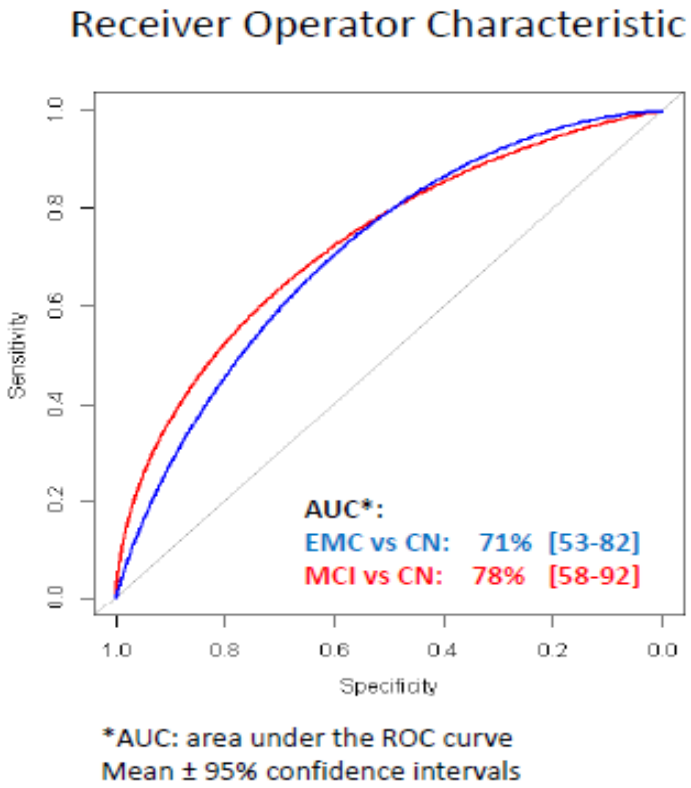
Group Classification



*AUC: area under the ROC curve
Mean ± 95% confidence intervals

Group classification using CBF from 50 regions

- 4-fold cross-validation
- LASSO regularization

Main cortical regions contributing:

- Cuneus
- Middle Frontal
- Temporal Transverse

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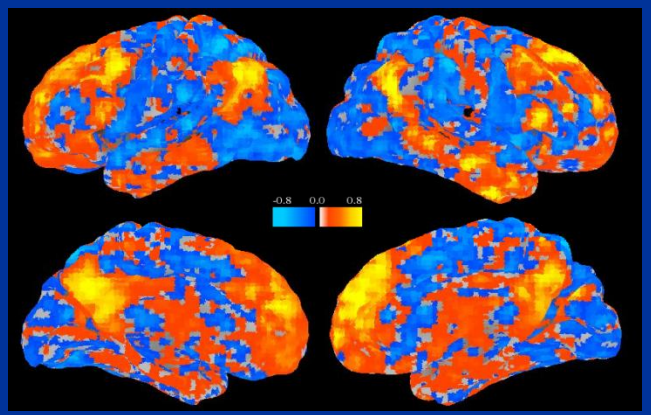
TF-fMRI Metrics

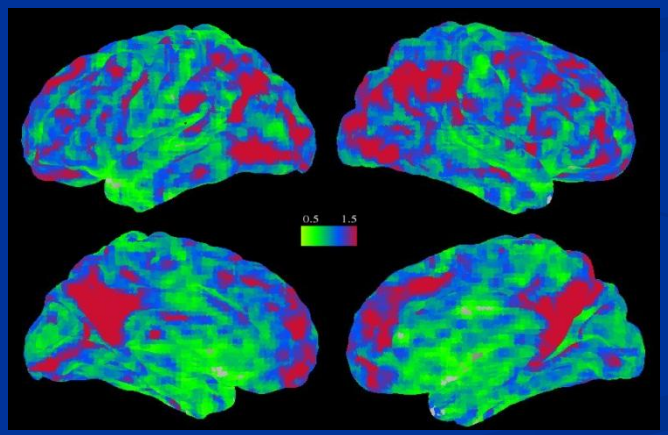
Functional atlas from 892 Mayo Clinic Study of Aging CN

- Functional Atlas extraction of ROI to Brain FC
- Functional Atlas extraction of ReHo
- Functional Atlas FC Matrix

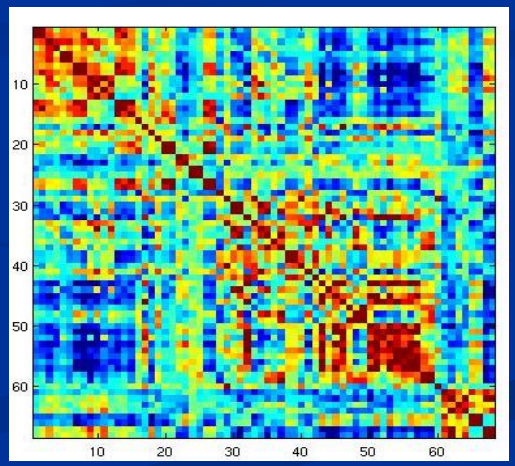
ADNI Control Subject



ROI to Brain



ReHo



FC Matrix

Classification ADNI CN vs EMCI

- **Feature Selection: aDMN ROI to Brain FC**
  - 2 Features Selected
    - **aDMN to right salience network***
    - **aDMN to right superior temporal***
- **Feature Selection: ReHo**
  - 2 Features Selected
    - Right dDMN medial ROI
    - Left deep gray ROI
- **Feature Selection: FC Matrix**
  - 5 Features Selected
    - Right attention to right parietal operculum
    - Right dDMN lateral ROI to right tDMN
    - **Right deep gray to left dorsal visual stream***
    - Right posterior limbic to right face
    - Right posterior limbic to right anterior limbic
- **Combined Features Cross Validation**
  - 4 Fold CV Accuracy Rate [95% CI] =**72.2% [72.1,72.4]**

*CN vs EMCI discriminant features with significant across group ANOVA (i.e. CN,EMCI,MCI,AD).

Summary

- TF-fMRI is complex - different ways to analyze the data, different metrics can be extracted from each analysis method, the individual features can be combined in many ways
- relationships between some fMRI metrics and disease severity appear non-linear, not monotonic
- there is evidence for a TF-fMRI signal separating CN from EMCI
- More work to be done to identify optimal ways to analyze data in clinical trial context - single value metrics as outcome measures