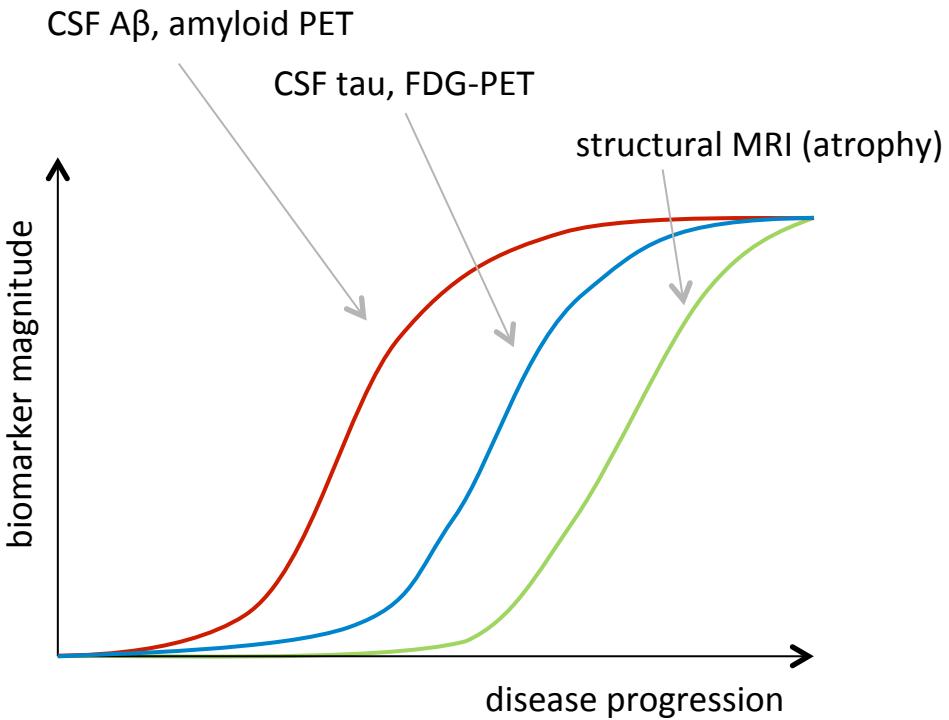


# Dementia Diagnosis using MRI Cortical Thickness, Shape, Texture, and Volumetry

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- 1) Dept. of Computer Science, University of Copenhagen, Denmark
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- 3) DTU Compute, Technical University of Denmark, Denmark

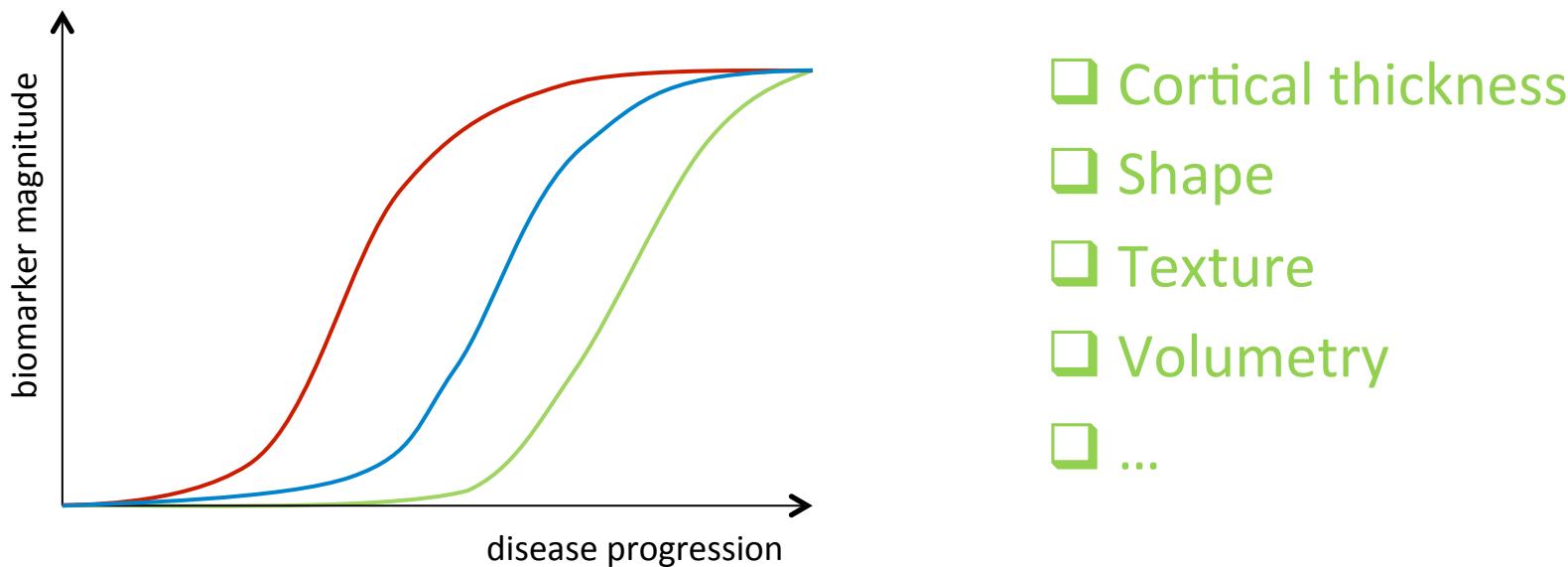
# Structural MRI in AD biomarker context [1]



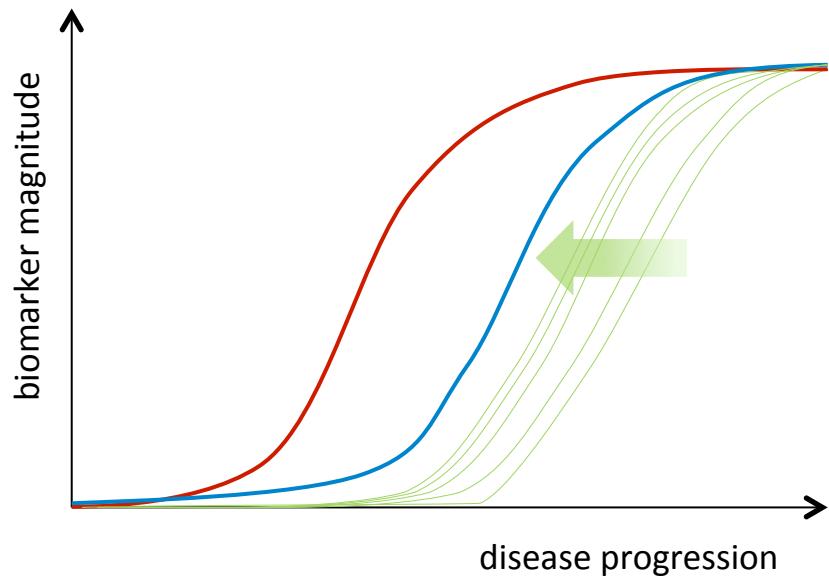
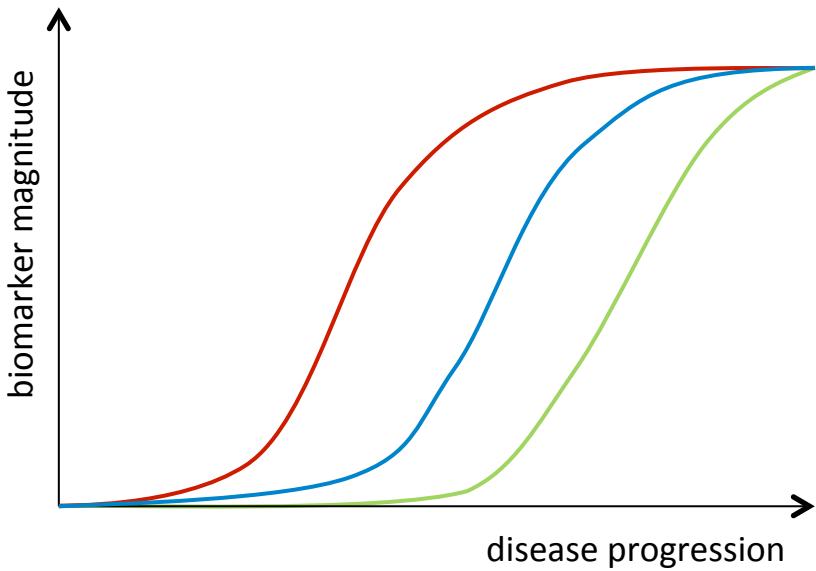
[1] Jack Jr, CR, et al. (2010): Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurology.

# Different structural MRI biomarkers

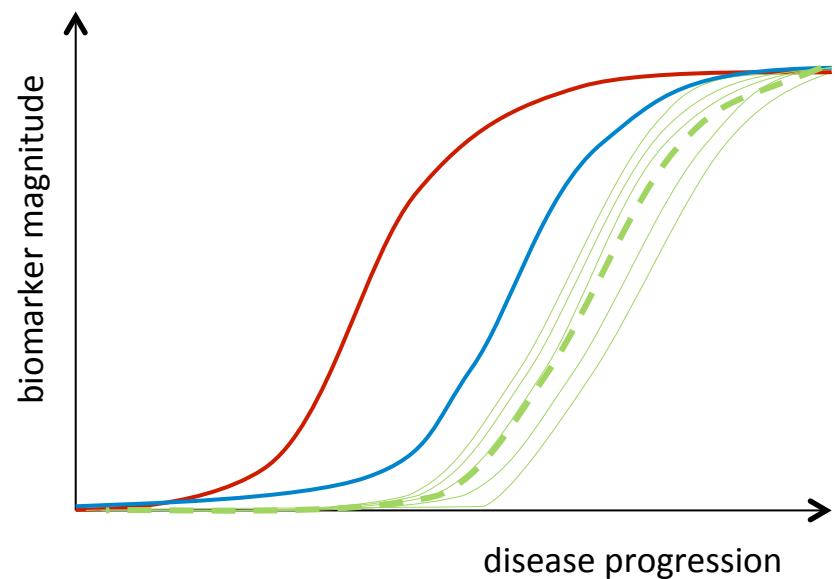
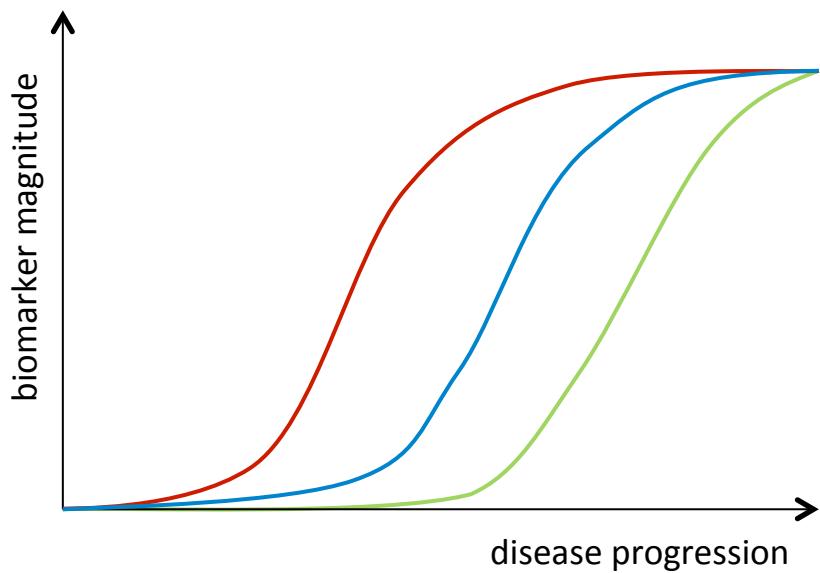
- not all are atrophy based



Some are sensitive to earlier stages of AD than, e.g., volume is



# Combining may broaden the dynamic range of structural MRI



# Data

		n	Age, years (mean±std)	Male (%)	MRI field strength (1.5-T/3-T)
[2] ADNI	Total	504	75.3±6.5	57.9	504/0
	NC	169	76.0±5.1	50.9	169/0
	MCI	234	74.8±7.0	66.5	234/0
	AD	101	75.3±7.4	50.5	101/0
[3] HHP	Total	40	74.1±7.4	47.5	40/0
	NC	12	76.9±6.2	41.7	12/0
	MCI	11	70.9±6.8	54.6	11/0
	AD	17	74.2±8.6	47.1	17/0
[4] AIBL	Total	145	75.4±7.4	44.6	1/144
	NC	88	75.2±7.2	47.7	1/87
	MCI	29	77.5±7.1	51.7	0/29
	AD	28	73.6±8.1	35.7	0/28
CADdementia train	Total	30	65.2±7.0	43.3	0/30
	NC	12	62.3±6.3	25.0	0/12
	MCI	9	68.0±8.5	44.4	0/9
	AD	9	66.1±5.2	66.7	0/9
CADDementia test	Total	354	65.1±7.8	60.2	0/354

[2] Wyman, B.T., et al. (2013): Standardization of analysis sets for reporting results from ADNI MRI data. *Alzheimer's & Dementia*.

[3] Frisoni, G.B., Jack , C.R. (2014): Harmonization of magnetic resonance-based manual hippocampal segmentation: a mandatory step for wide clinical use. *Alzheimer's & Dementia*.

[4] Ellis, K.A., et al. (2009): The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. *International Psychogeriatrics*.

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☐ age difference

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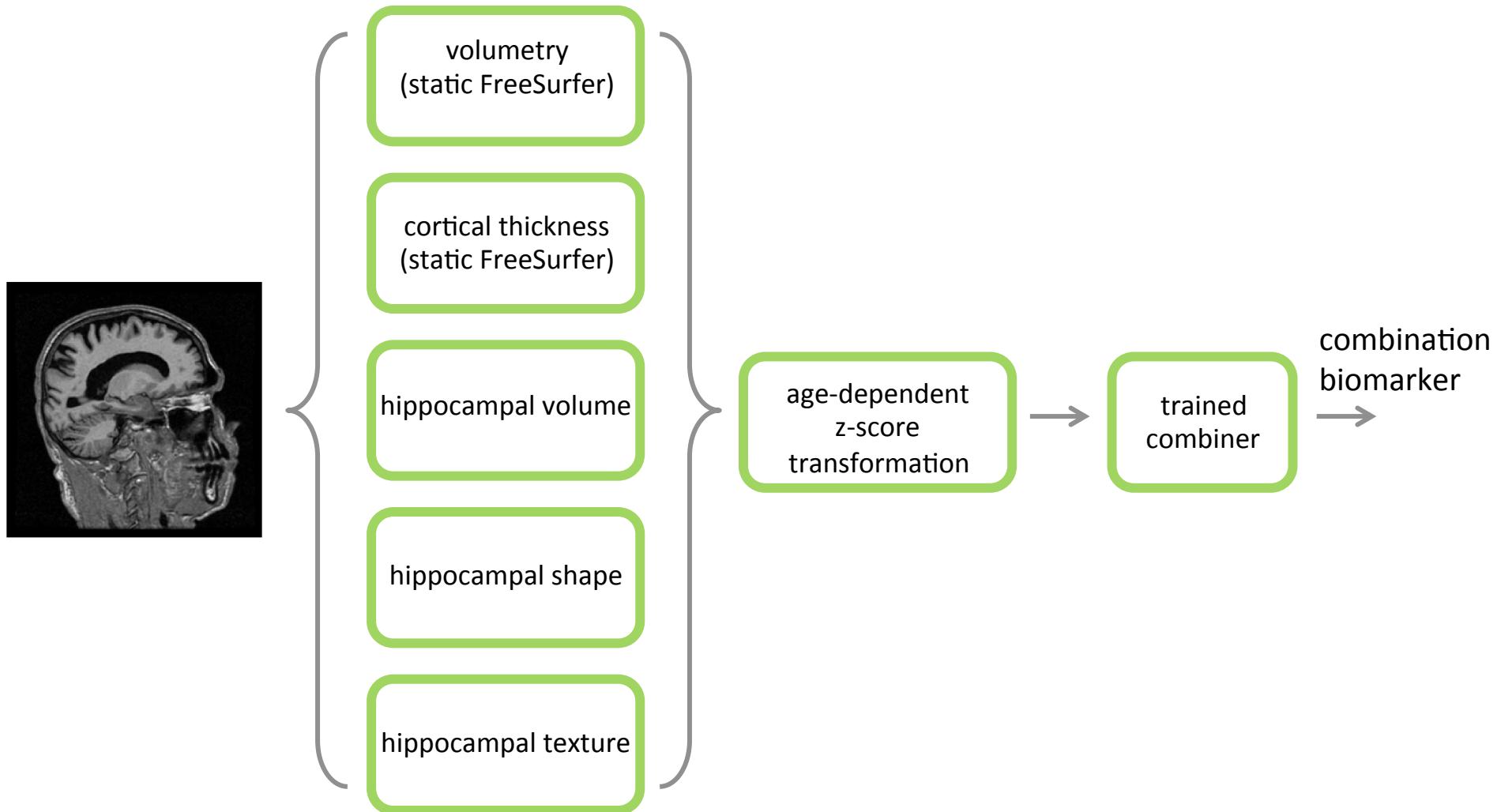
- age difference
- field strength difference

[2] Wyman, B.T., et al. (2013): Standardization of analysis sets for reporting results from ADNI MRI data. *Alzheimer's & Dementia*.

[3] Frisoni, G.B., Jack , C.R. (2014): Harmonization of magnetic resonance-based manual hippocampal segmentation: a mandatory step for wide clinical use. *Alzheimer's & Dementia*.

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# Method overview



# FreeSurfer volumetry and cortical thickness measurements

- Static FreeSurfer version 5.1.0 using default parameters
- Volumetry [5]
  - Seven measurements: amygdala, caudate nucleus, hippocampus, pallidum, putamen, ventricular, whole brain
  - Bilateral ROIs joined
  - All measurements divided by intra-cranial volume (ICV)
- Cortical thickness measurements [6]
  - five measurements: frontal, occipital, parietal, and temporal lobe, and the cingulate gyrus (by joining ROIs from the Desikan-Killiany atlas)
  - left and right hemispheres joined

[5] Fischl, B., et al. (2002): Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*.

[6] Fischl, B., Dale, A.M. (2000): Measuring the thickness of the human cerebral cortex from magnetic resonance images. *PNAS*.

# Hippocampal volume [7]

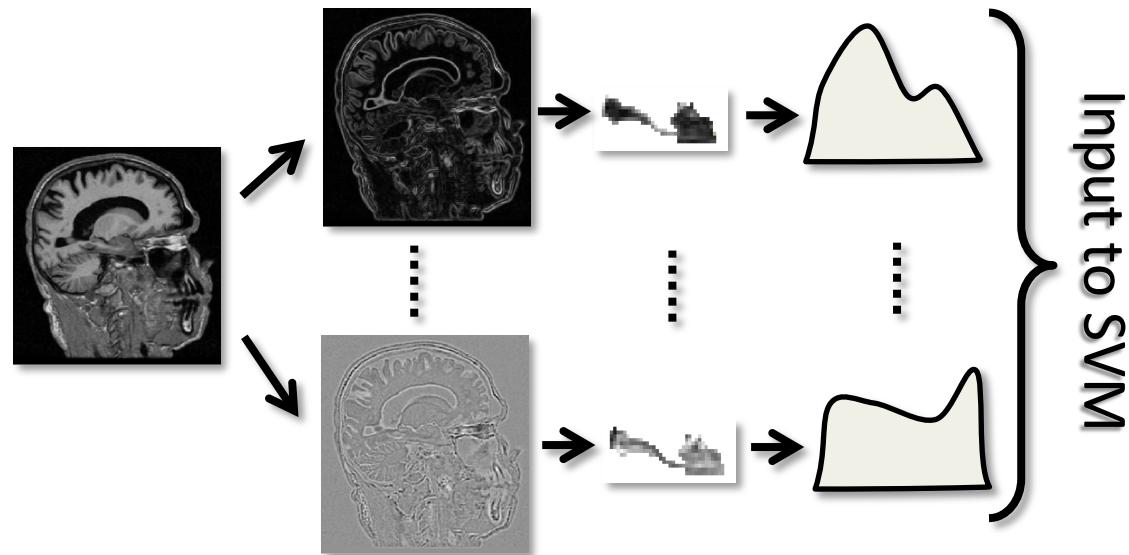
- Multi-atlas, affine-registration, non-local patch-based segmentation method
  - 40 segmentations from HHP in atlas (all used during pre-selection, only 9 most similar used in final segmentation)
- A subset of 15 HHP segmentations used to optimize parameters (according to Dice's coefficient)
  - Number of atlases after pre-selection
  - Cubic patch size
  - Search volume
- Bilateral volume computed from individually segmented left and right hippocampus and divided by ICV

# Hippocampal shape

- Shape descriptor:
  - Each hippocampus represented by 30 uniformly distributed surface landmarks
  - All data (represented as landmarks) aligned using generalized Procrustes alignment followed by PCA (retaining 90 % variance)
- Shape classifier: naive Bayes
- Left and right shape score computed separately

# Hippocampal texture [8,9]

- Texture descriptor: adaptively binned marginal filter response histograms from rotation-invariant, multi-scale Gaussian-derivative-based filter bank [10] (7 base filters, 4 scales)
- Texture classifier: SVM with RBF kernel on concatenated histograms



[8] Sørensen, L., et al. (2012): Hippocampal texture provides volume-independent information for Alzheimer's disease diagnosis. AAIC 2012.

[9] Sørensen, L., et al. (2013): Hippocampal texture predicts conversion from MCI to AD. AAIC 2013.

[10] Sørensen, L., et al. (2012): Texture-Based Analysis of COPD: A Data-Driven Approach. IEEE Transactions on Medical Imaging.

# Need for standardization of individual MRI biomarkers

- Training data (ADNI and AIBL) from subjects 10 years older than subjects in the CADDementia data!
- Individual MRI biomarkers not in same units.

# Age-dependent z-score transformation

- Training data (ADNI and AIBL) from subjects 10 years older than the CADDementia data!
- Individual MRI biomarkers not in same units.
- Transformation:

$$z = (x - \mu_{\text{age}})/\sigma_{\text{age}}$$

z-score transformed  
biomarker

individual biomarker

age-dependent weighted  
mean

age-dependent weighted  
standard deviation

The diagram illustrates the components of the z-score transformation equation. It shows the formula  $z = (x - \mu_{\text{age}})/\sigma_{\text{age}}$ . To the left of the equation, there is a blue arrow pointing to the variable  $z$ , labeled "z-score transformed biomarker". Below the equation, there is a blue arrow pointing to the variable  $x$ , labeled "individual biomarker". To the right of the equation, there are two blue arrows: one pointing to  $\mu_{\text{age}}$  labeled "age-dependent weighted mean" and another pointing to  $\sigma_{\text{age}}$  labeled "age-dependent weighted standard deviation".

# Age-dependent z-score transformation

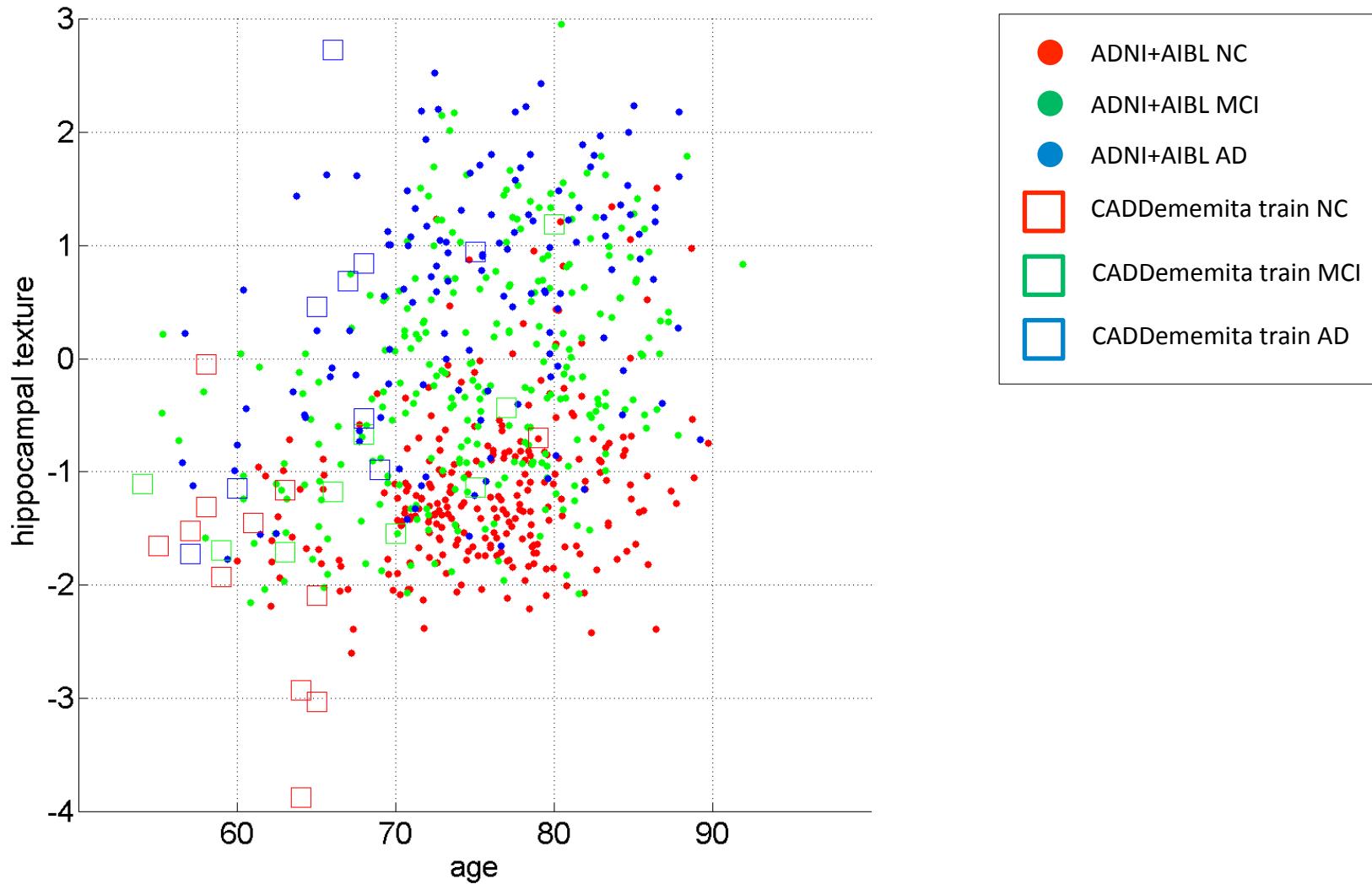
- Training data (ADNI and AIBL) from subjects 10 years older than the CADDementia data!
- Individual MRI biomarkers not in same units.
- Transformation:

$$z = (x - \mu_{\text{age}})/\sigma_{\text{age}}$$

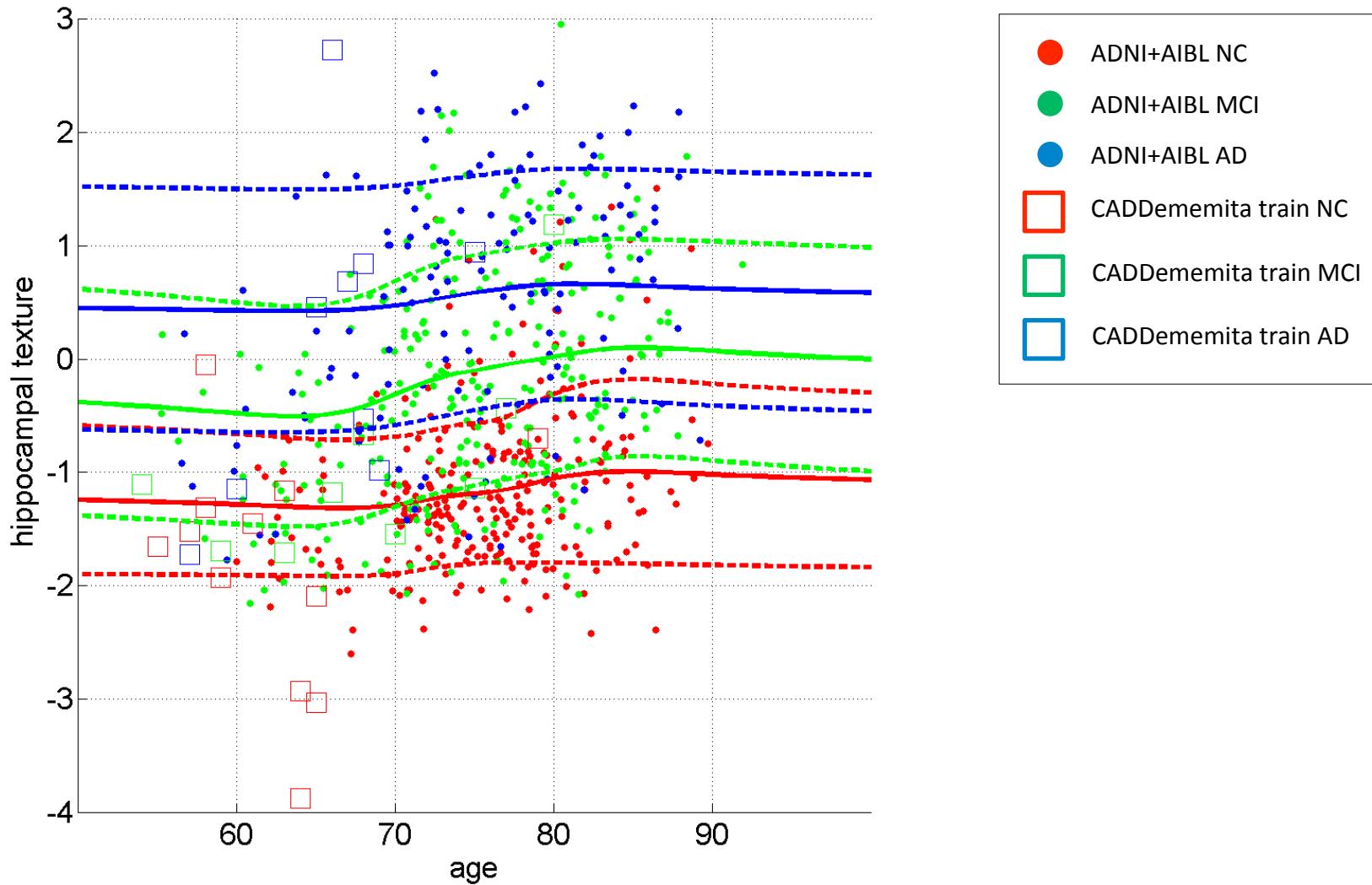
- Applied within each diagnostic group, resulting in a tripling of the original  $N$  features (or biomarkers)

$$\{z_{\text{NC}}^{(i)}, z_{\text{MCI}}^{(i)}, z_{\text{AD}}^{(i)}\}_{i=1\dots N}$$

# Example: age vs. hippocampal texture



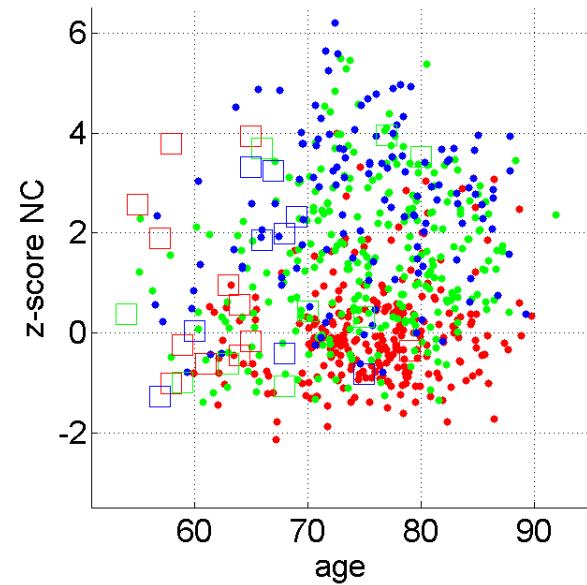
# Example: kernel density estimate



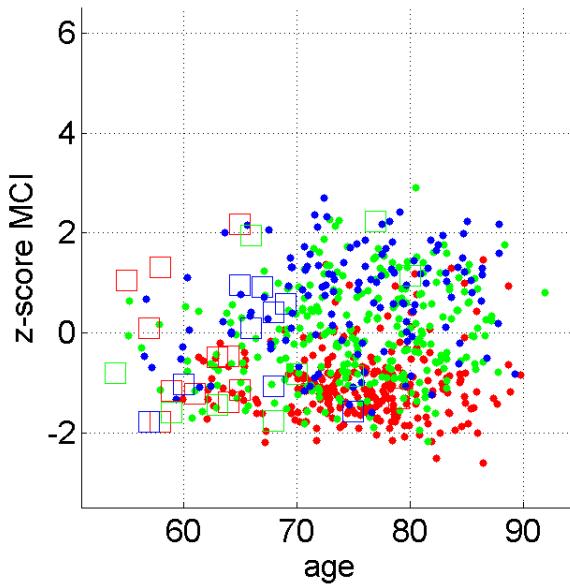
# Example: hippocampal texture z-

## scores

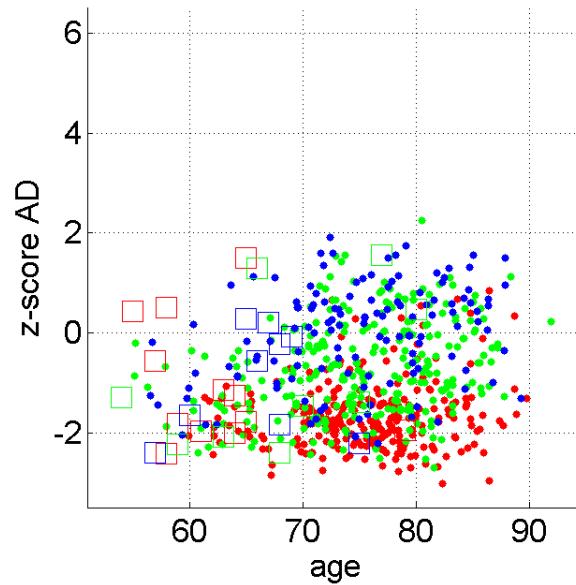
"NC transformation"



"MCI transformation"



"AD transformation"



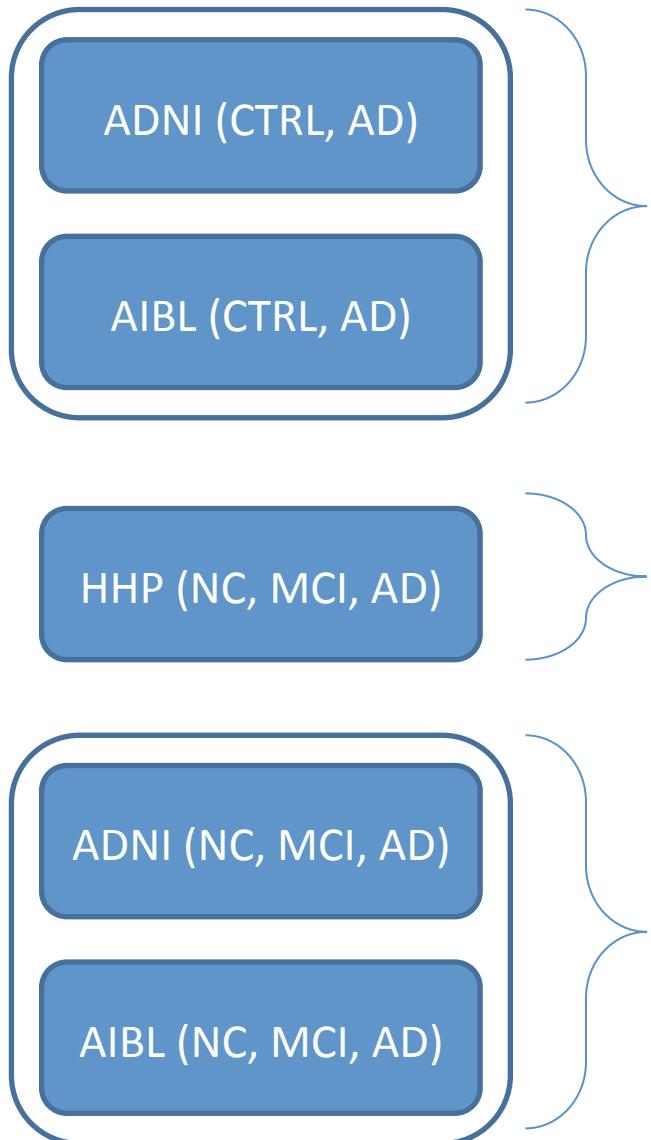
# Combining individual MRI biomarkers

- Regularized linear discriminant analysis (LDA) [11] with individual (z-score transformed) biomarkers as features.
- Regularization parameter determined using cross-validation performance on the training data.
- LDA applied using the Shark C++ machine learning library [12].

[11] Guo, Y., et al. (2007): Regularized linear discriminant analysis and its application in microarrays. *Biostatistics*.

[12] Igel, C., et al. (2008): Shark. *Journal of Machine Learning Research*.

# Training overview



## Hippocampal texture

- Filter scales selected from experience
- Adaptive binning
- SVM (RBF and regularization parameter)

## Hippocampal shape

- Descriptor parameters selected from experience
- Naive Bayes

## Hippocampal volume

- Number of atlases after pre-selection
- Cubic patch size
- Search volume size

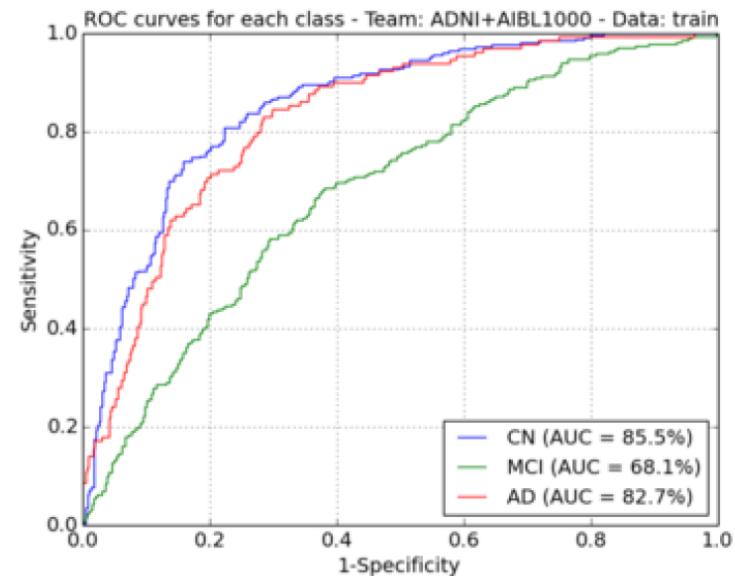
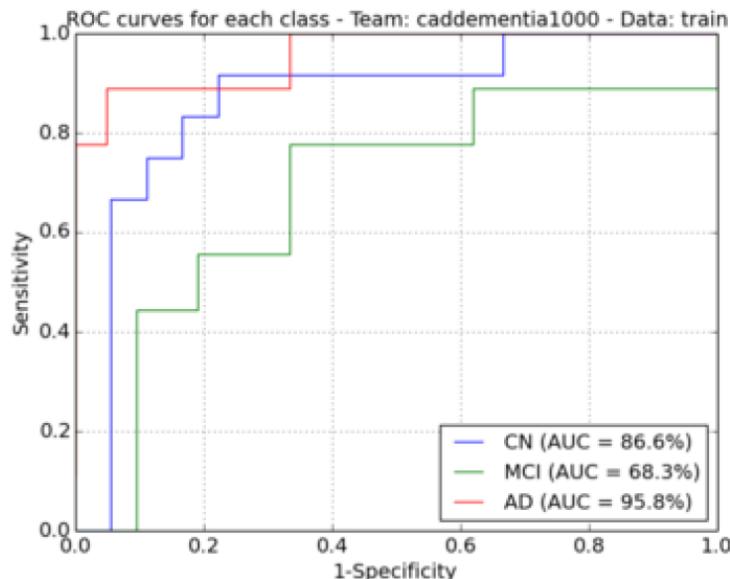
## Combination biomarker

- Age-dependent z-score transformation
- LDA

# Results: ROC analysis<sup>1</sup>

	AUC			
	Total	NC	MCI	AD
CADDementia train	83.2	86.6	68.3	95.8
ADNI+AIBL*	78.4	85.5	68.1	82.7

\* scores obtained by 10-fold cross-validation stratified by cohort and diagnostic group



<sup>1</sup> results are computed using the Python scripts supplied by CADDementia (<http://caddementia.grand-challenge.org/evaluation/>)

# Results: classification<sup>1</sup>

	CA	True positive fraction		
		NC	MCI	AD
CADDementia train	73.3	91.7	44.4	77.8
ADNI+AIBL*	62.2	79.8	53.2	45.7

\* scores obtained by 10-fold cross-validation stratified by cohort and diagnostic group

## Confusion matrices

CADDementia train				ADNI+AIBL			
	NC	MCI	AD		NC	MCI	AD
NC	11	3	0	NC	205	74	13
MCI	1	5	2	MCI	48	140	57
AD	0	1	7	AD	4	49	59

<sup>1</sup> results are computed using the Python scripts supplied by CADDementia (<http://cadementia.grand-challenge.org/evaluation/>)

# Optimizing priors (using CADDementia train)

- Optimal priors:  $P(\text{NC}) = 1/8$ ,  $P(\text{MCI}) = 3/8$ ,  $P(\text{AD}) = 1/2$

CADDementia train (equal priors)			
	NC	MCI	AD
NC	11	4	0
MCI	1	4	2
AD	0	1	7

CA = 73.3 %



CADDementia train (optim. priors)			
	NC	MCI	AD
NC	9	1	0
MCI	3	7	1
AD	0	1	8

CA = 80.0 %

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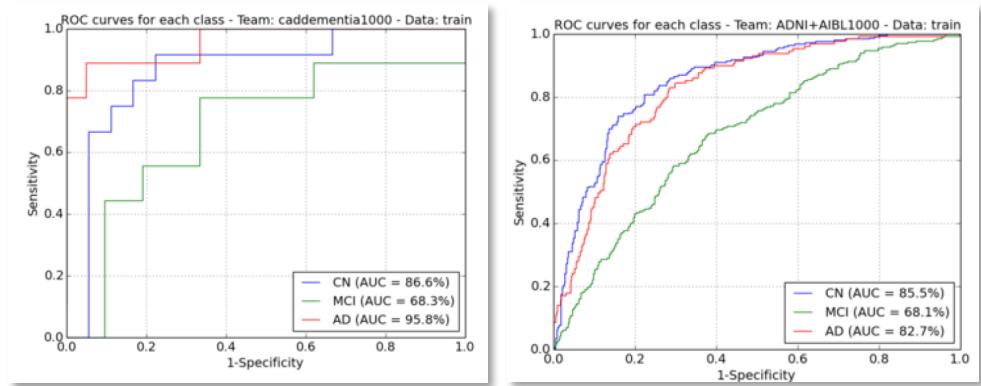
CA = 80.0 %

- Also had a balancing effect on the CADDementia test set<sup>2</sup>
  - Equal priors: 204 NC, 63 MCI, 87 AD
  - Optimized priors: 133 NC, 110 MCI, 111 AD

<sup>2</sup> We should expect approximately equally many subjects in each of the diagnostic groups (<http://cadementia.grand-challenge.org/about/>)

# Conclusions

- Fairly consistent results on ADNI+AIBL and CADDementia train



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- Optimizing priors for CADDementia train had a balancing effect on CADDementia test
- Combining a range of structural MRI biomarkers is a promising approach

	NC	MCI	AD
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MCI	3	7	1
AD	0	1	8

CA = 80.0 %

# Conclusions

- Fairly consistent results on ADNI+AIBL and CADDementia train
- Optimizing priors for CADDementia train had a balancing effect on CADDementia test
- Combining a range of structural MRI biomarkers is a promising approach
- However, still problems discriminating MCI from NC and AD

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# Conclusions

- Fairly consistent results on ADNI+AIBL and CADDementia train
- Optimizing priors for CADDementia train had a balancing effect on CADDementia test
- Combining a range of structural MRI biomarkers is a promising approach
- However, still problems discriminating MCI from NC and AD
  - Would probably need combination with other non-structural MRI biomarkers

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