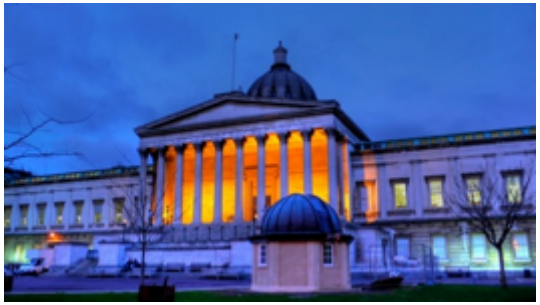
Images and Genes:
From AD to MS



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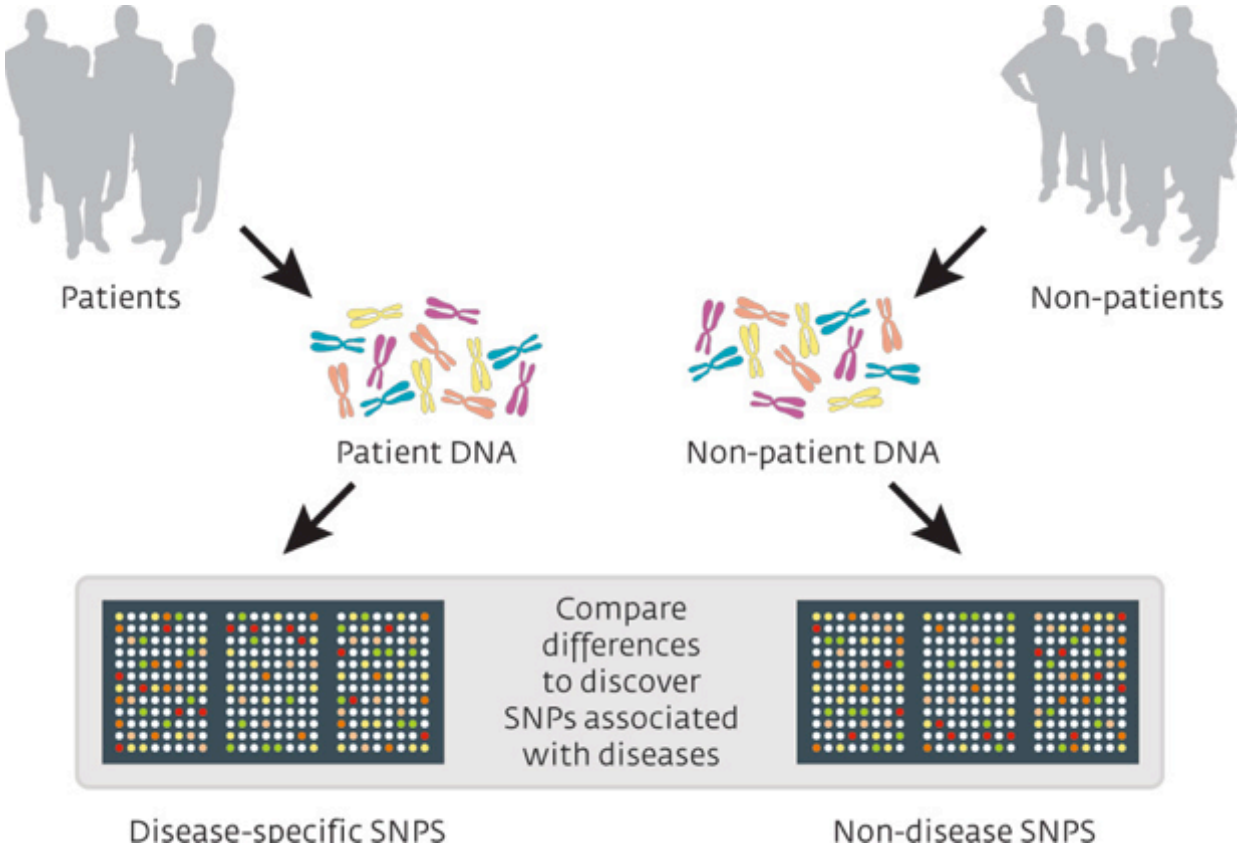
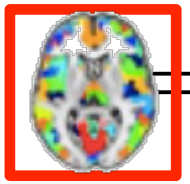
London, January 31st 2018

Genome-wide Association Study (GWAS)

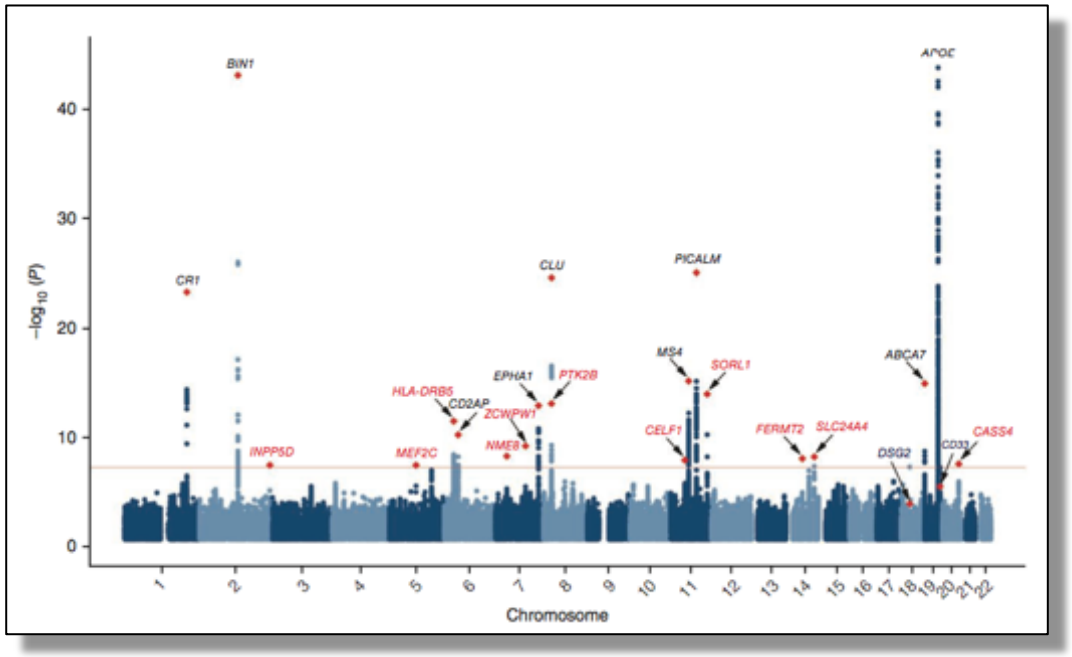
- Single Nucleotide Polymorphisms (SNPs)
- ~ 1 million genetic markers measured (~0.001%)
- Sample acquisition cheap (£30 per participant)



Genome-wide Association Study (GWAS)

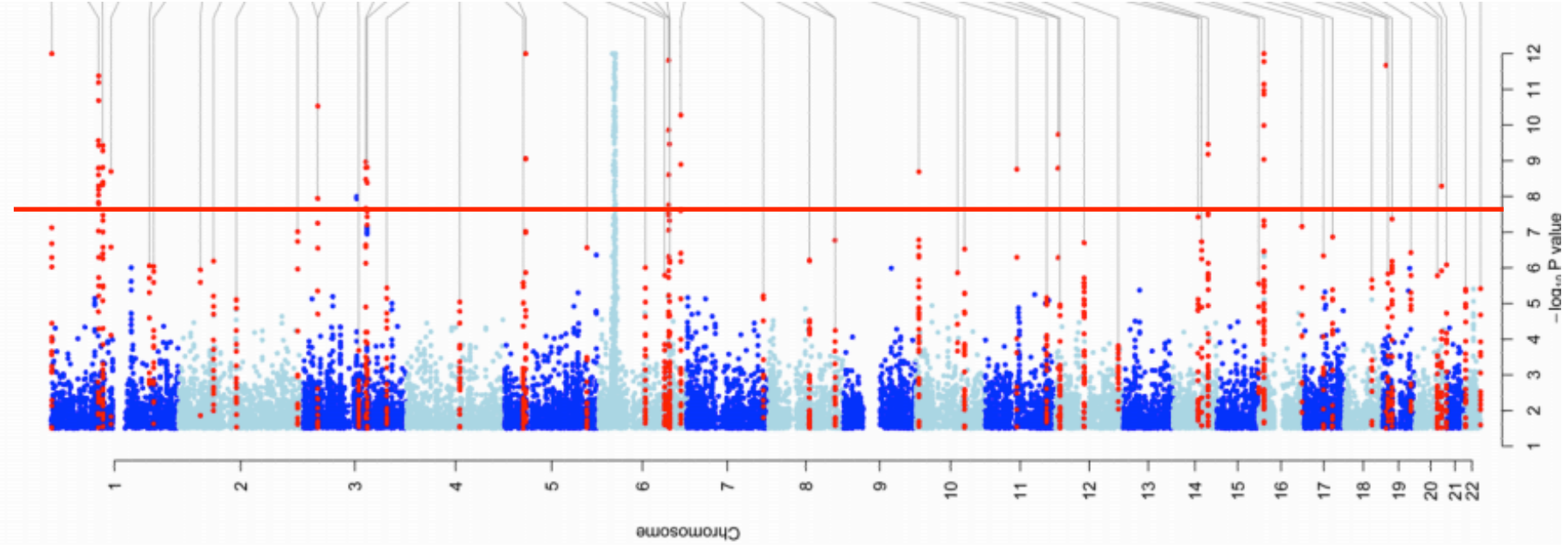


$$= \beta_0 + \beta_1 \times \mathrm{SNP} + \sum_{i=2}^{N} \beta_i x_i + \epsilon$$



- Mass univariate testing
- P<5x10^{-8} is ‘genome-wide significant’

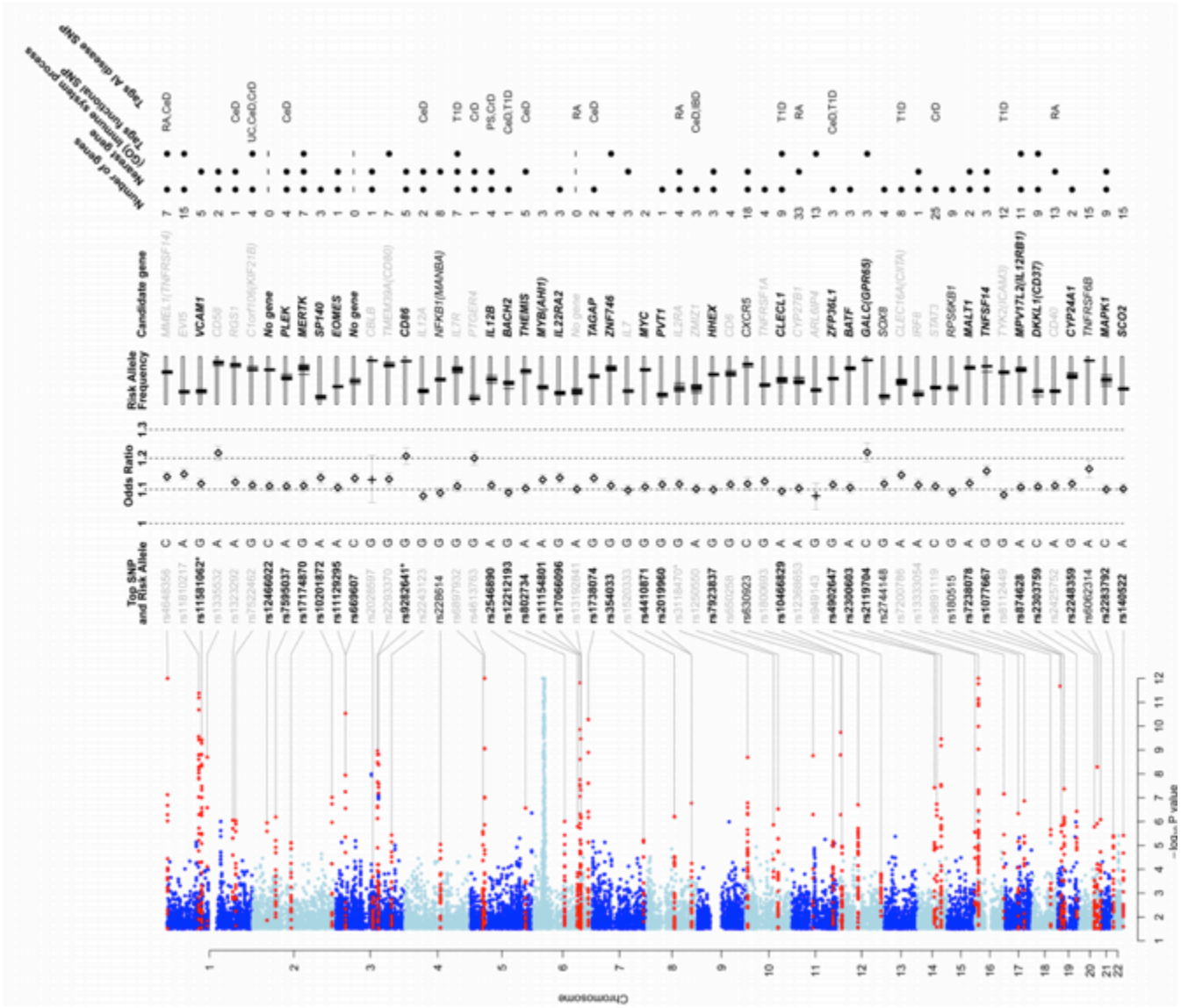
Genome-wide Association Study (GWAS)



2011: ~10,000 cases
~17,000 controls

doi:10.1038/nature10251

Genome-wide Association Study (GWAS)



2011: ~10,000 cases ~17,000 controls

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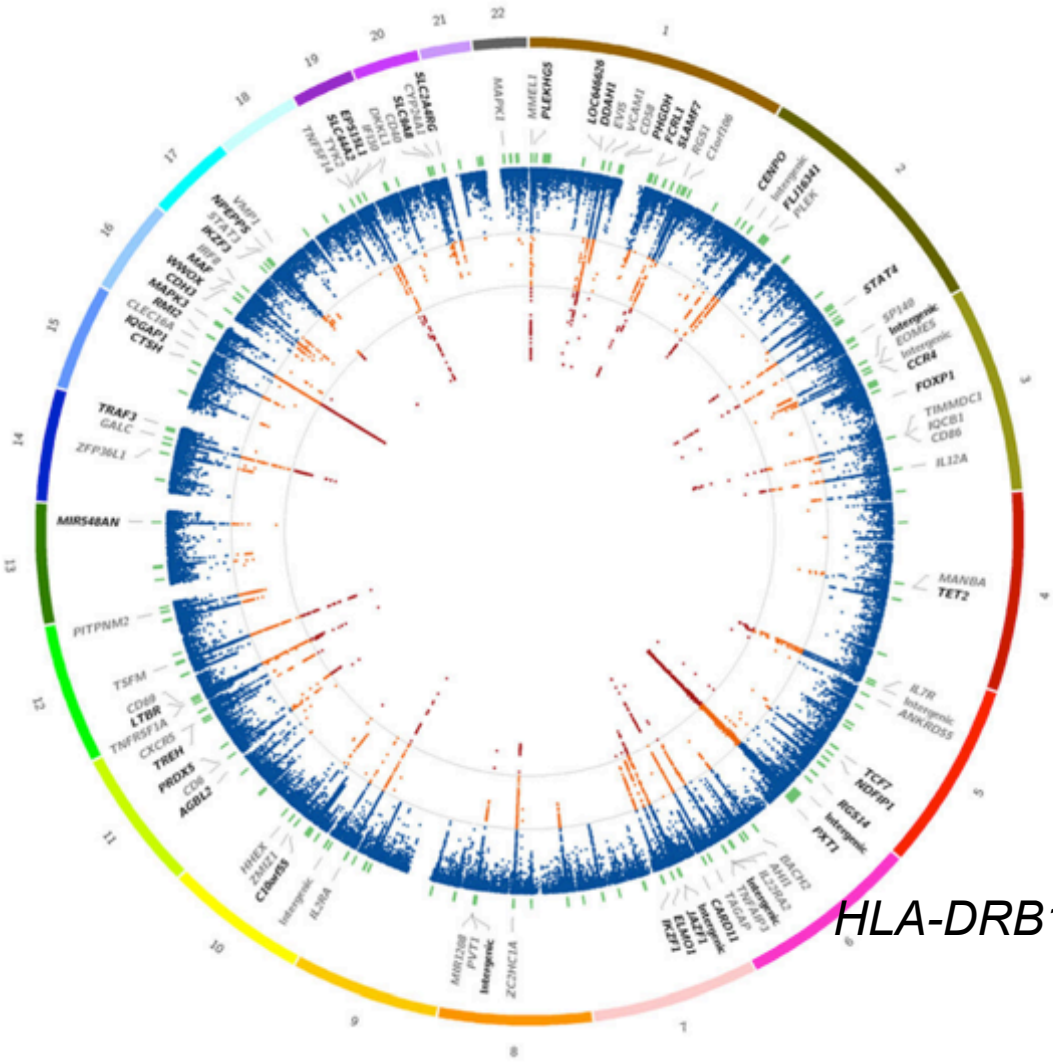
Genome-wide Association Study (GWAS)



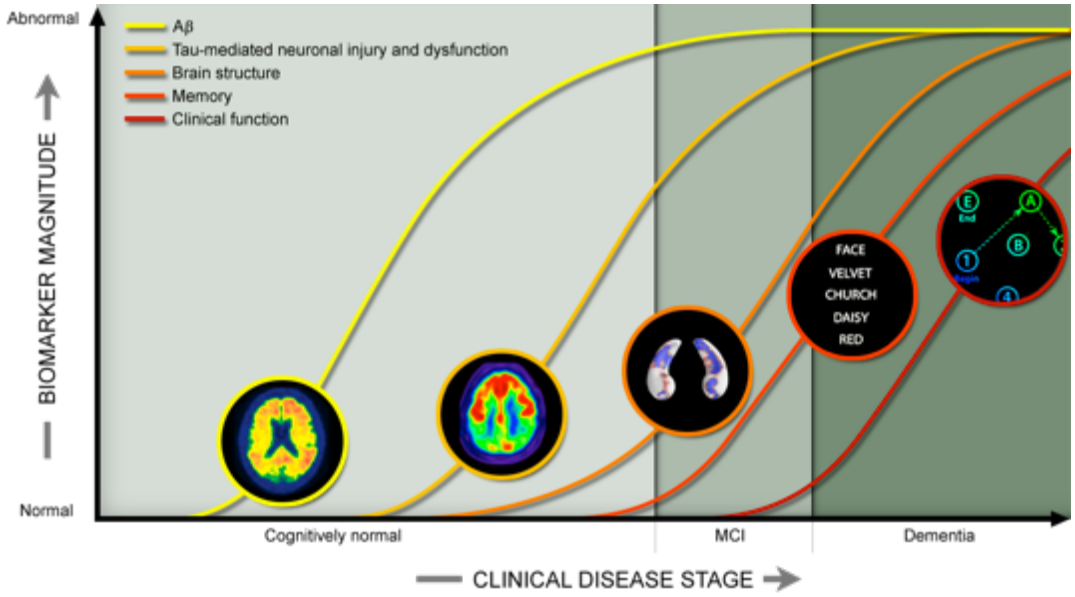
*HLA-DRB1*1501*

2013: ~15,000 cases
~24,000 controls

doi:10.1038/ng.2770

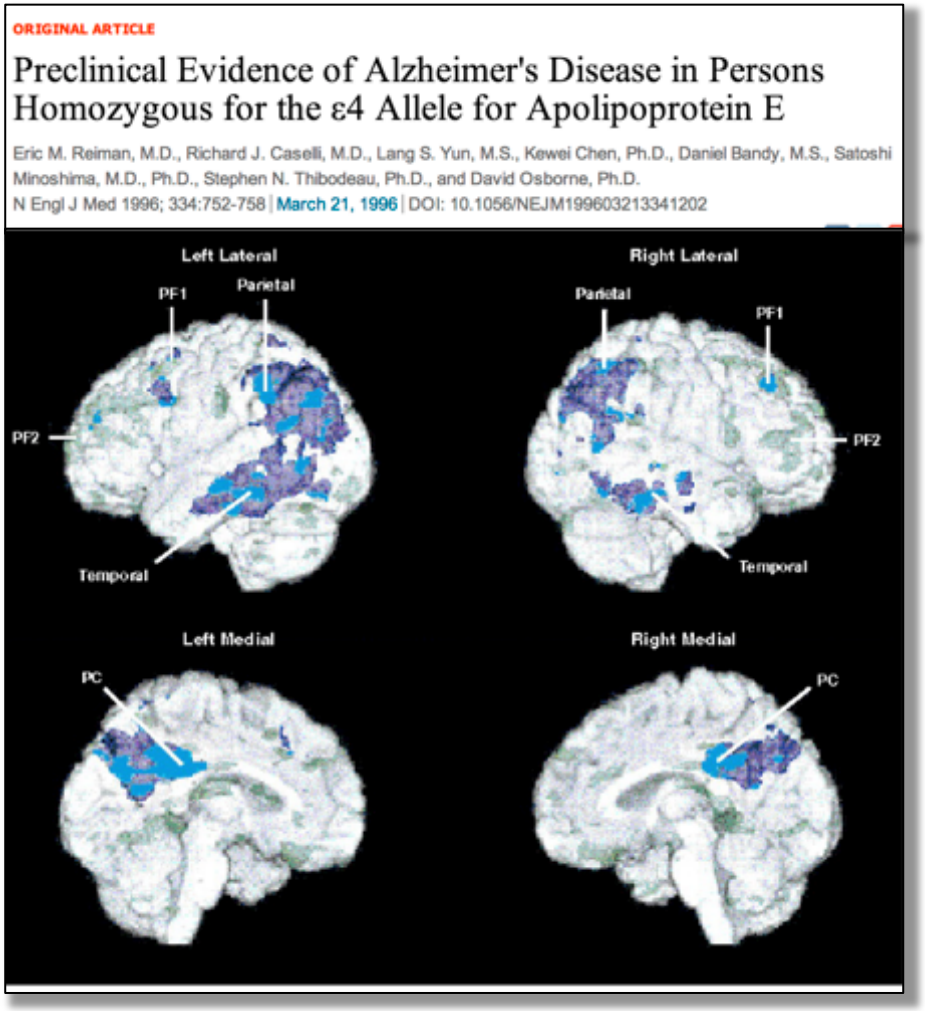
Why Imaging Genetics?

- Imaging genetics uses imaging phenotypes in genetic studies
- Imaging phenotypes are ‘closer’ to the disorder than diagnoses
  - Often diagnoses are ‘mixed bags’
  - Allows us to study how the disorder develops



Early Imaging Genetics Example

- APOE-e4 is a strong risk factor for AD
- Reiman et *al.* (1996) studied glucose metabolism
- APOE-e4 homozygotes showed reduced meta-bolism in typical AD regions



Example ir

UCL

Imaging
Multiple

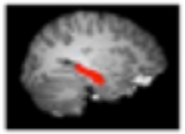
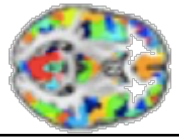
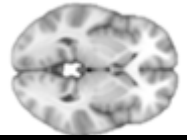
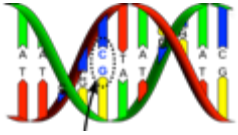
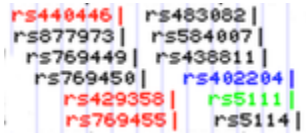
Stefan Dirk Roosendaal,

2015

Table 1
Relations between MS susceptibility genes and brain MR imaging

Study, Year	Patients (CIS/RR/SP/PP)	HC	MR Imaging	Most Important Findings
Baranzini et al,[30] 2009	987 (100/659/137/72)[a]	883	T2LL, BV	GWA; T2LL and BV associated with multiple (non-HLA) SNPs, not with HLA-DRB1*1501
Gourraud et al,[38] 2013	484 (76/343/45/20)	—	LPM	GWA; 31 SNPs associated with lesion pattern
Healy et al,[87] 2010	532 (17/351/123/37)[b]	776	T2LL, BV	HLA B44 associated with higher BV and lower T2LL
Hooper-van Veen et al,[36] 2003	492 (-/221/172/99)[c]	228	T1BH, T2LL, BV	No associations interleukin-1 polymorphism with MR imaging
Hooper-van Veen et al,[88] 2006	489 (-/220/175/440)[d]	180	T1BH, T2LL, BV	Change in T1BH associated with CD28, IFNGR2, IL1B-511
Horakova et al,[34] 2011	205 (CIS only)	—	T2LL, T1Gad, BV	HLA-DRB1*1501 associated with higher T1Gad, not with BV
Jensen et al,[89] 2010	1006 (RR and SP[e])	—	BV (ICR)	No associations 7 susceptibility SNPs with BV
Kalincik et al,[33] 2013	179 (CIS only)	—	T2LL, BV	No associations 16 susceptibility SNPs with T2LL and BV
Karrenbauer et al,[32] 2013	100 (-/79/19/2)	—	T2LL, T1BH, lesion location	No associations HLA-DRB1*15 or *04 with MR imaging
Okuda et al,[24] 2009	505 (88/352/46/14)	—	T2LL, T1Gad, MRS	Higher T2LL and lower NAA in NAWM in HLA-DRB1*1501 + patients
Qiu et al,[70] 2011	252 (-/119/117/16)	—	T2SC	No associations HLA-DRB1 alleles and number/location SC lesions
Sepulcre et al,[37] 2008	50 (15/28/3/4)	—	T2LL, BV, LPM	No association HLA-DR2 status with lesion distribution and BV
Schreiber et al,[28] 2002	71 (21/40/10)	—	T2LL	No associations HLA with T2LL
Sombekke et al,[27] 2009	150 (-/88/32/30)	—	T2LL, T2SC	HLA-DRB1*1501 not associated with T2LL
Sombekke et al,[29] 2011	208 (-/126/42/40)	—	T2LL, LPM	MHC II region SNP associated with lesion distribution
Van der Walt et al,[90] 2011	978 (-/639/339/-)[f]	—	BV (ICR)	No associations HLA-DRB1 alleles with BV
Zivadinov et al,[25,91] 2003; 2009	100 (-/71/16/13)	122	T2LL, T1BH, BV	B7 associated with higher T2LL and T1BH; DRB1*12 with higher T1BH and lower BV
Zivadinov et al,[26] 2007	41 (-/27/7/7)	—	T2LL, T1BH, BV	Multiple HLA alleles associated with MR imaging (eg, HLA-DRB1*1501 associated with lower BV and higher T1BH)

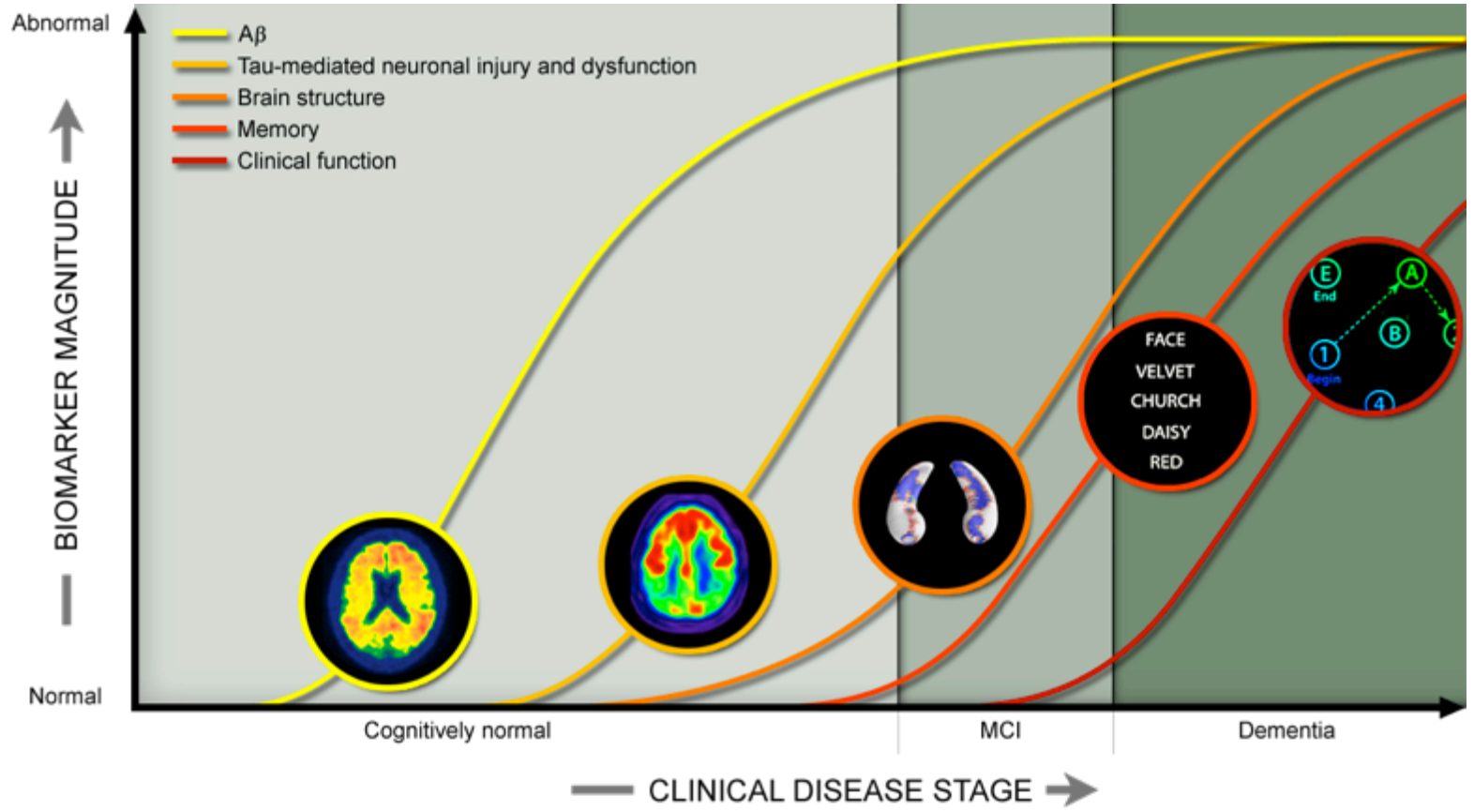
Imaging Genetics 'Menu'

	Candidate ROI 	Many ROIs 	Voxelwise 
Candidate SNP 			[Filippini et al. 2009] 29,812 voxels 1 SNP
Candidate Gene	[Joyner et al. 2011] 4 ROIs, 11 SNPs		
Genome-wide Gene			[Hilbar et al. 2011] 31,622 voxels 18,044 Genes
Genome-wide SNP 	[Stein et al. 2012] 1 ROI, 1.1 mio SNPs [Potkin et al. 2009] 1 ROI, 317,503 SNPs		[Stein et al. 2010] 31,622 voxels 448,293 SNPs

Multimodal Imaging Genetics

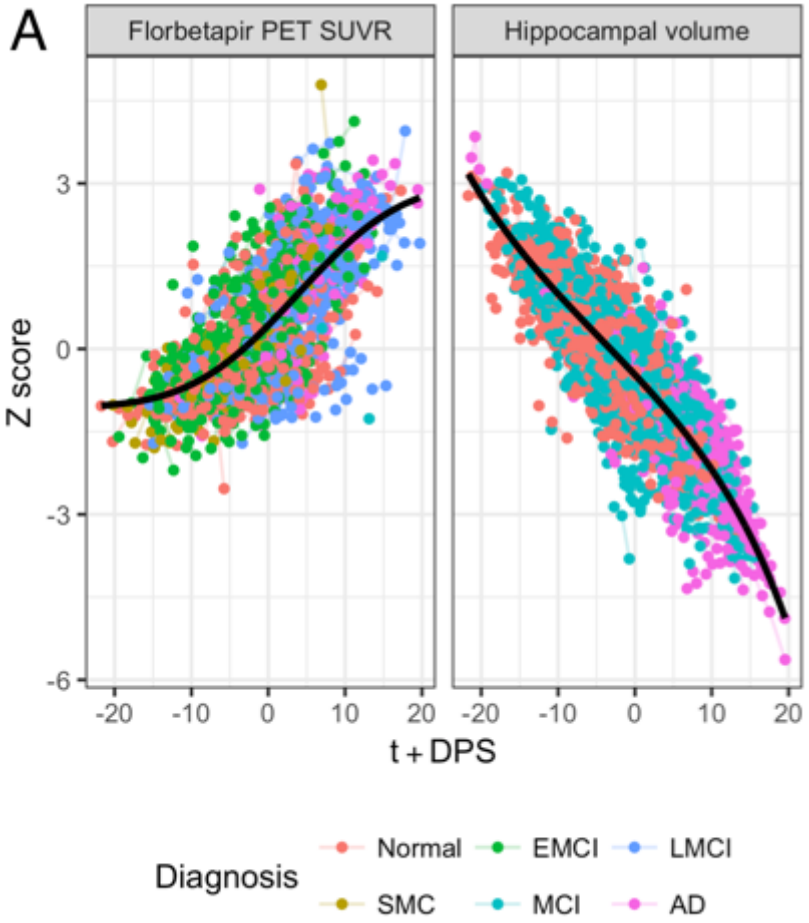
Marzia Scelsi

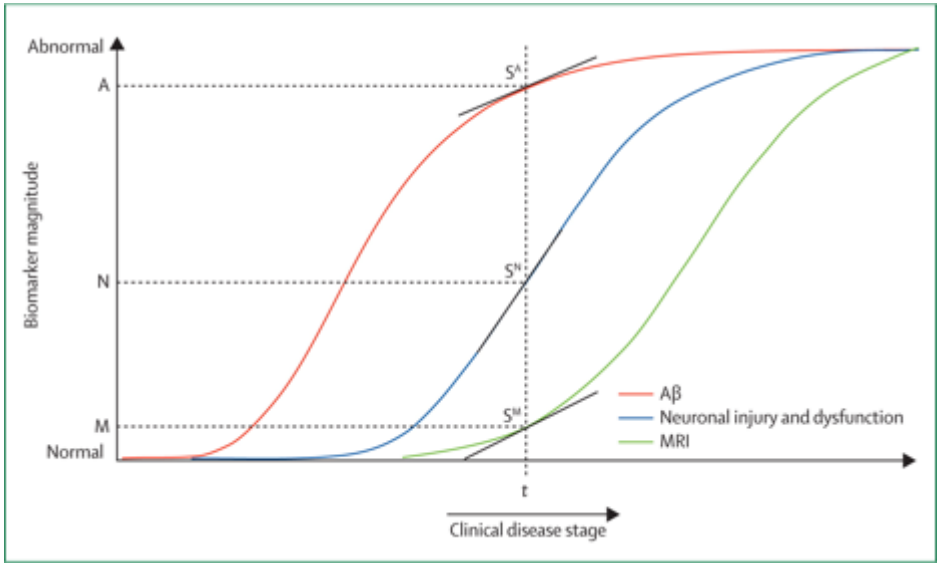
- One (imaging) biomarker may be noisy
- Considering multiple markers may improve robustness



Disease progression modelling

🙂 agreement with theoretical models



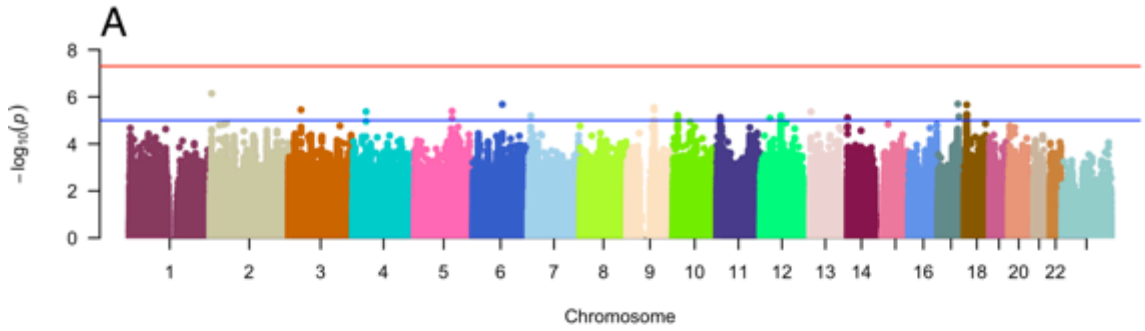


Jack et al., Lancet Neur., 2010

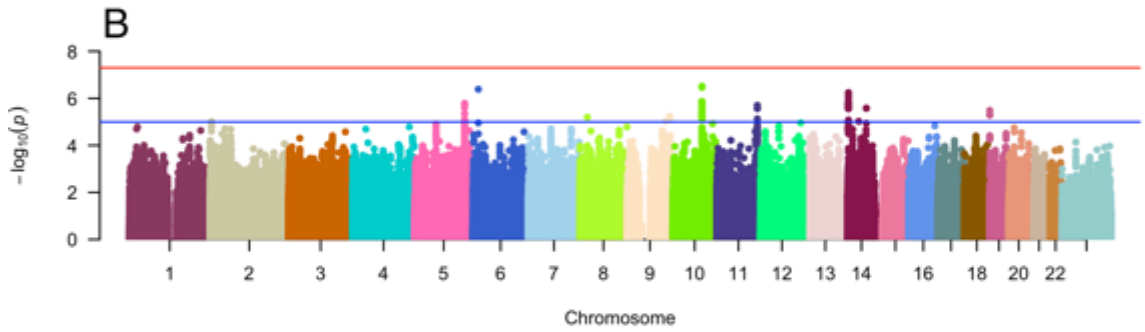
Scelsi et al. *Brain* (in revision)

Genome-wide association tests

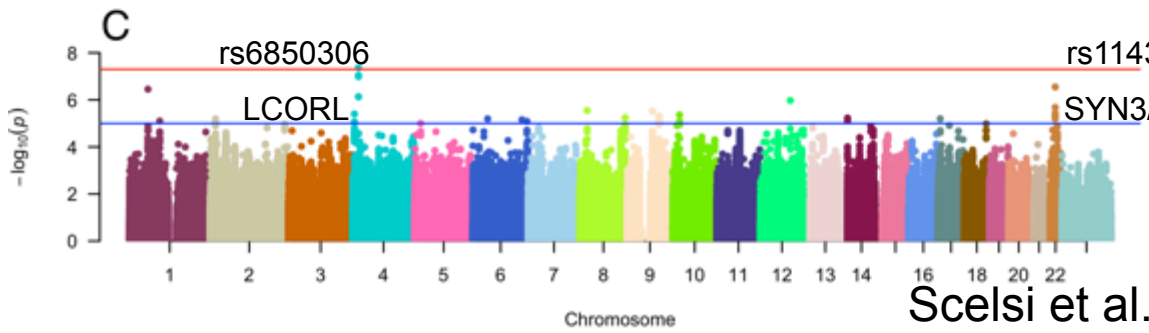
Hippocampal volume



Cortical amyloid

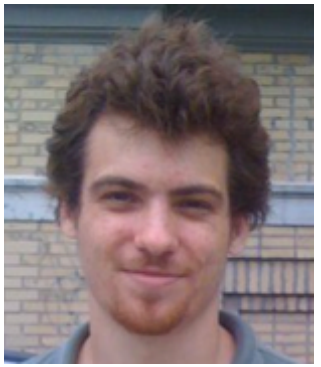


DPS



Scelsi et al. *Brain* (in revision)

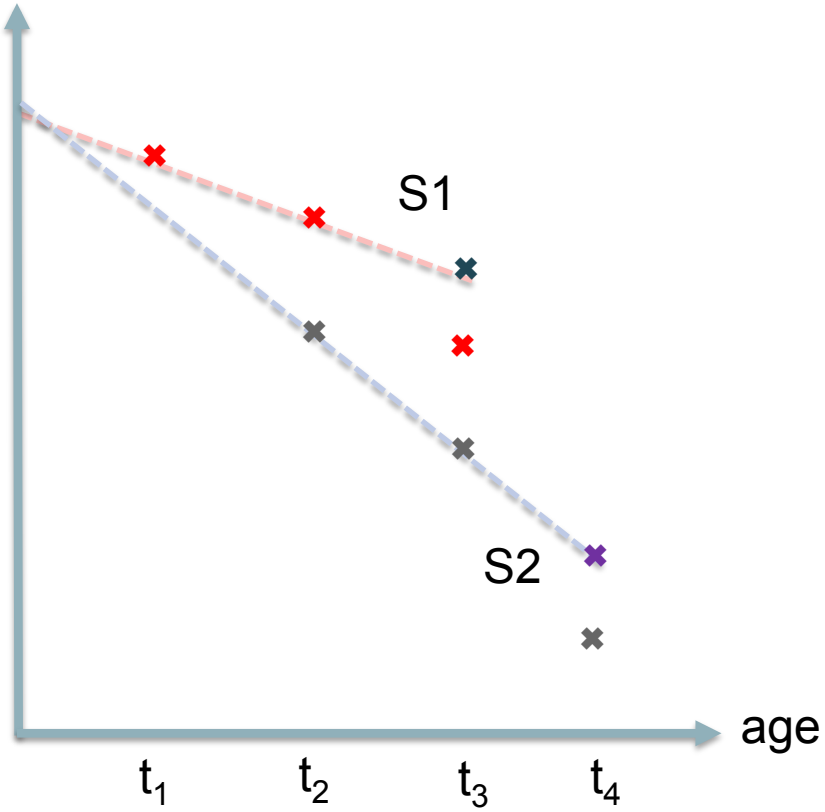
Bayesian Multi-task Learning



Leon Aksman

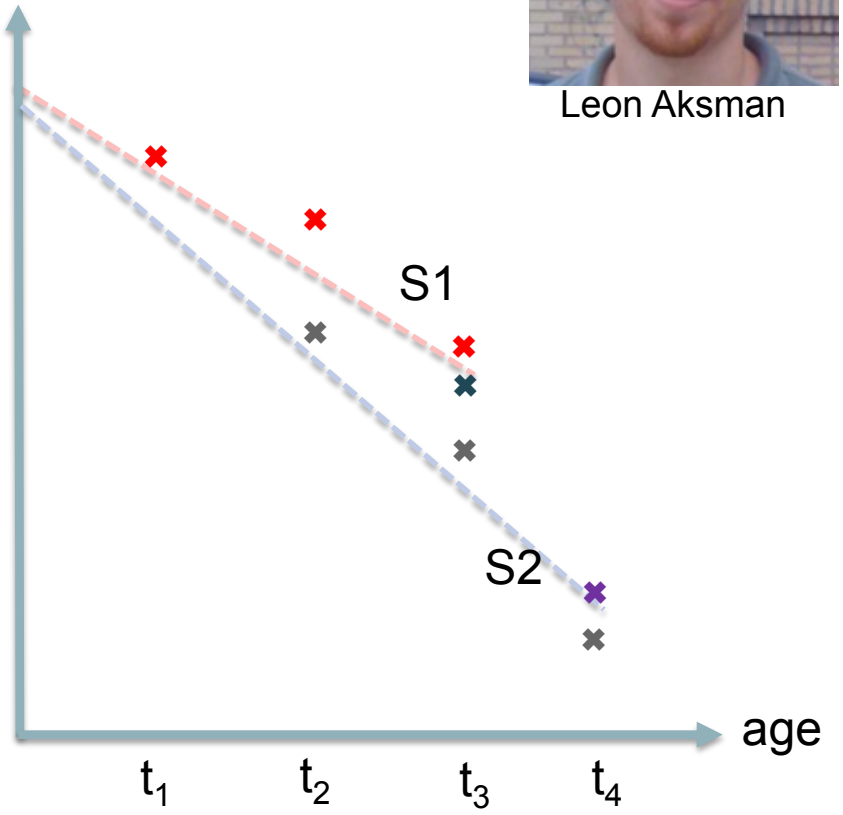
Independent

hippo volume

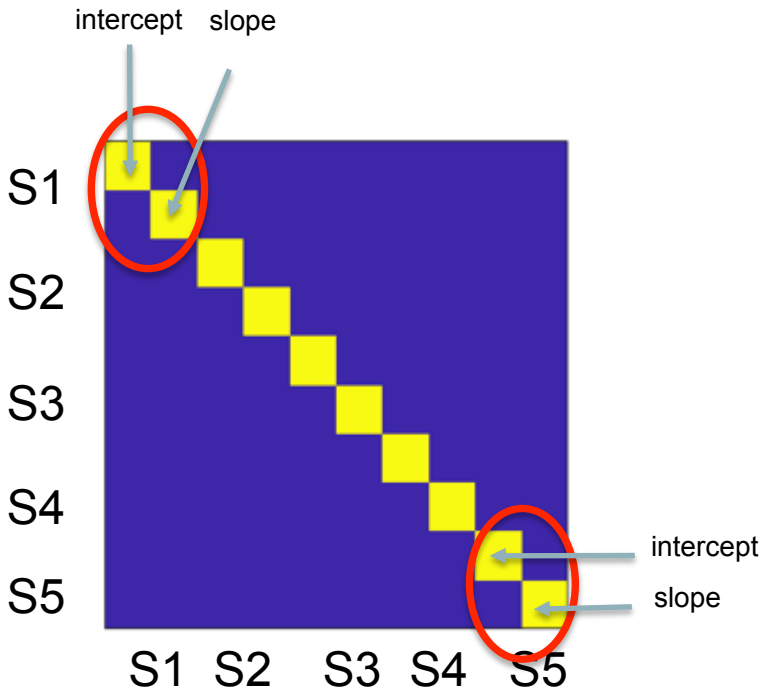


Coupled

hippo volume



Prior covariance: independent

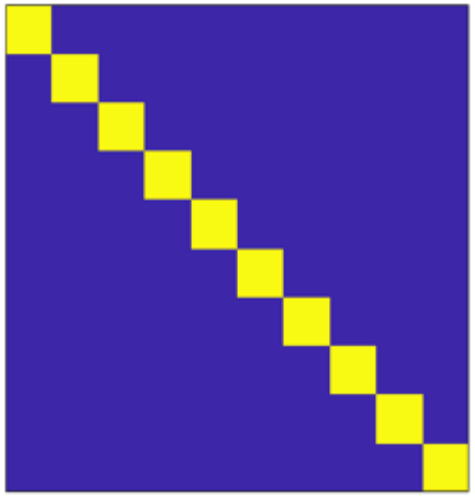
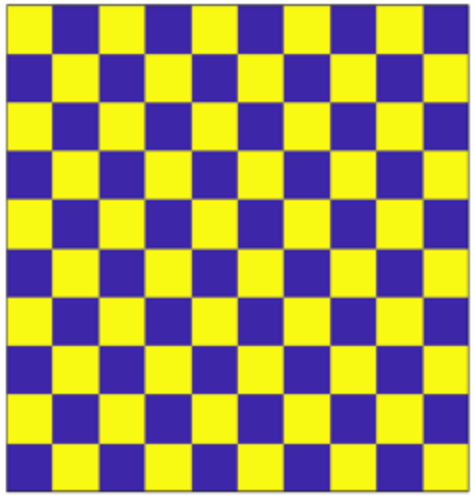
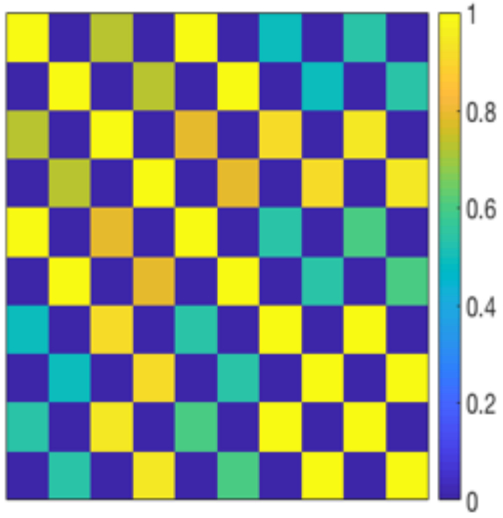


Flexible prior covariance

Fully independent

Fully coupled

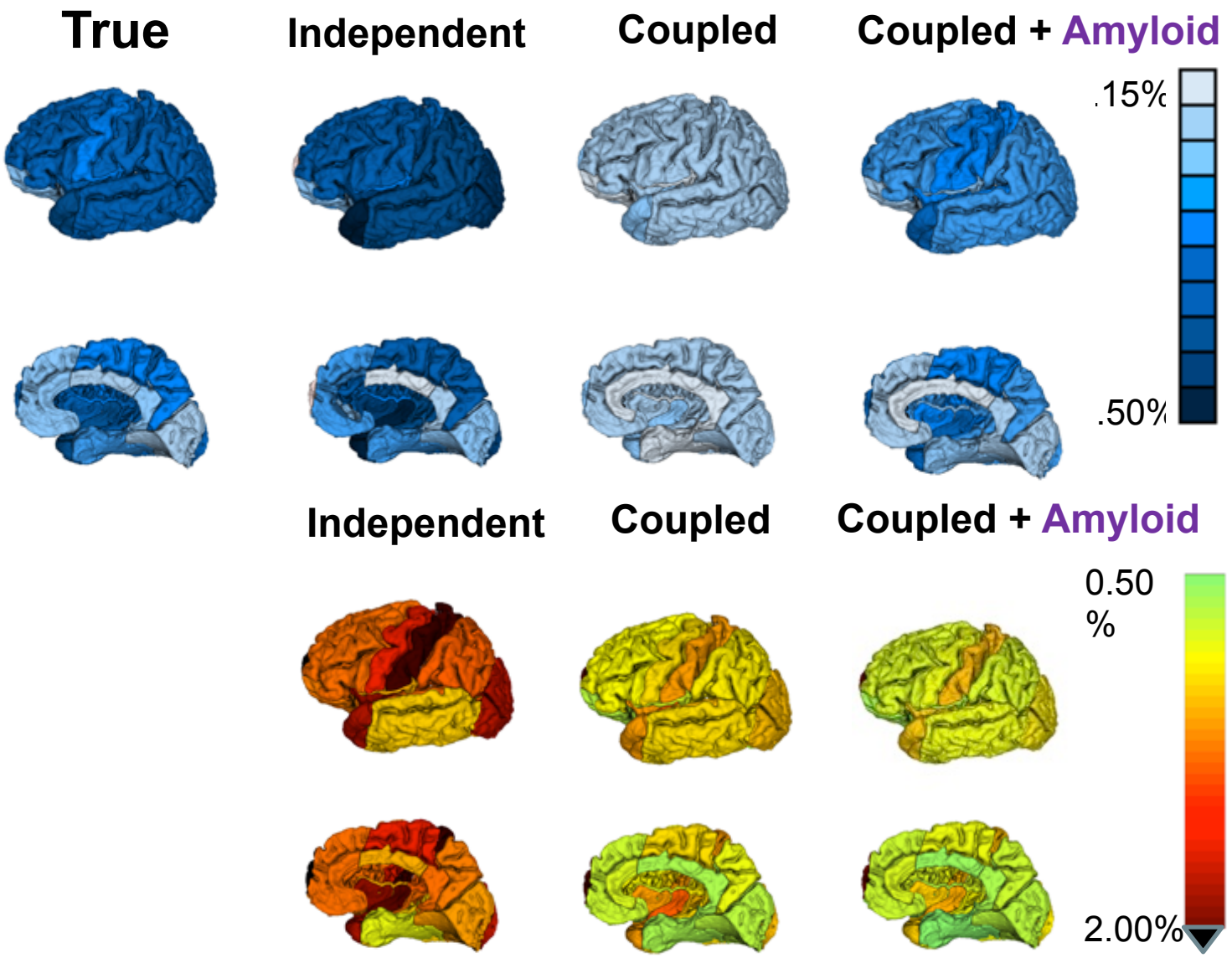
Biomarker coupled

α_1  $+ \alpha_2$  $+ \alpha_3$ 

α's are learned from data (Bayesian machine learning)

ADNI Dataset

- Smaller prediction errors with coupled
- Further improvement by coupling subjects' trajectories based on amyloid load (PET SUVR)

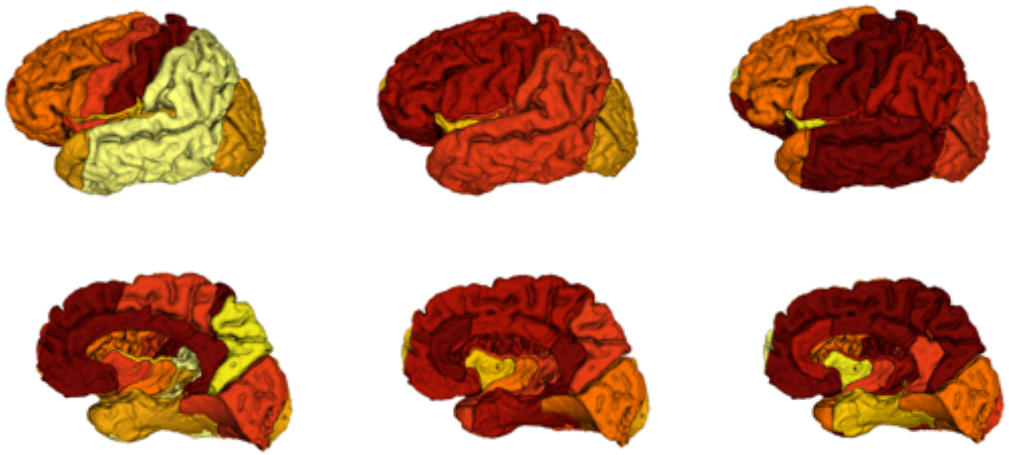


ADNI Dataset

- We can look at group differences in trajectories (intercepts, slopes) across subjects
- Coupled models: less significant intercept differences, more significant slope differences
- These are more plausible models: neurodegeneration initiates from a similar level in developed adults

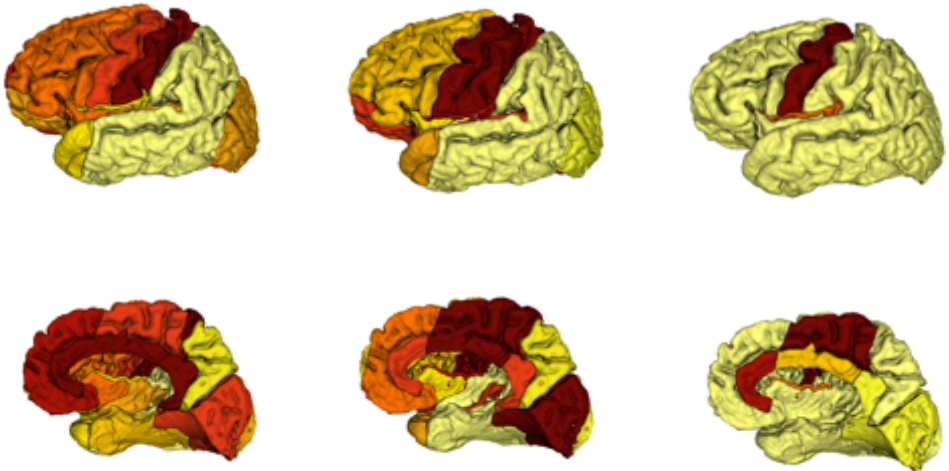
Intercept Group Differences

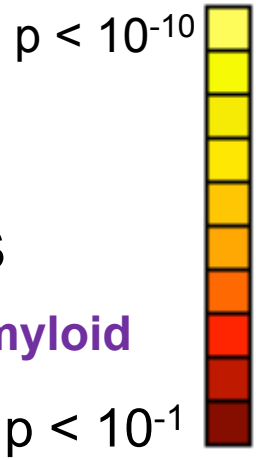
Independent **Coupled** **Coupled + Amyloid**



Slope Group Differences

Independent **Coupled** **Coupled + Amyloid**



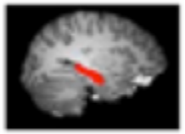
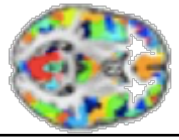
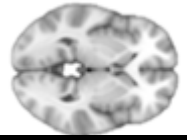
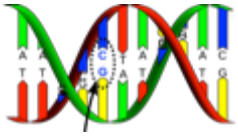


Application to MS?

- Currently exploring other kernels
  - APOE-e4 kernel
  - Polygenic kernel

- In MS?
  - Longitudinal (imaging) biomarker
  - Genetic information from genotyping

Imaging Genetics "Menu"

	Candidate ROI 	Many ROIs 	Voxelwise 
Candidate SNP 			[Filippini et al. 2009] 29,812 voxels 1 SNP
Candidate Gene	[Joyner et al. 2011] 4 ROIs, 11 SNPs		
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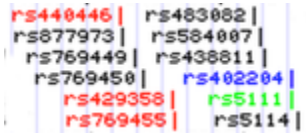
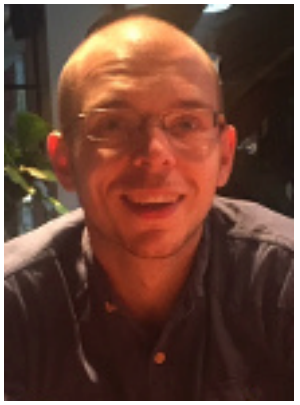
Genome-wide SNP 	[Stein et al. 2012] 1 ROI, 1.1 mio SNPs [Potkin et al. 2009] 1 ROI, 317,503 SNPs		[Stein et al. 2010] 31,622 voxels 448,293 SNPs

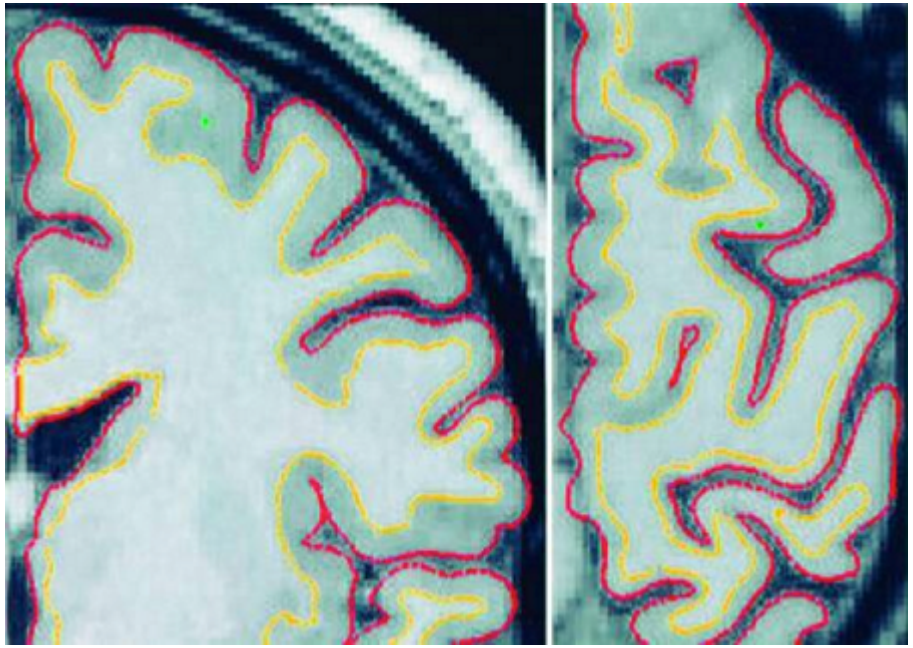
Cortical Thickness

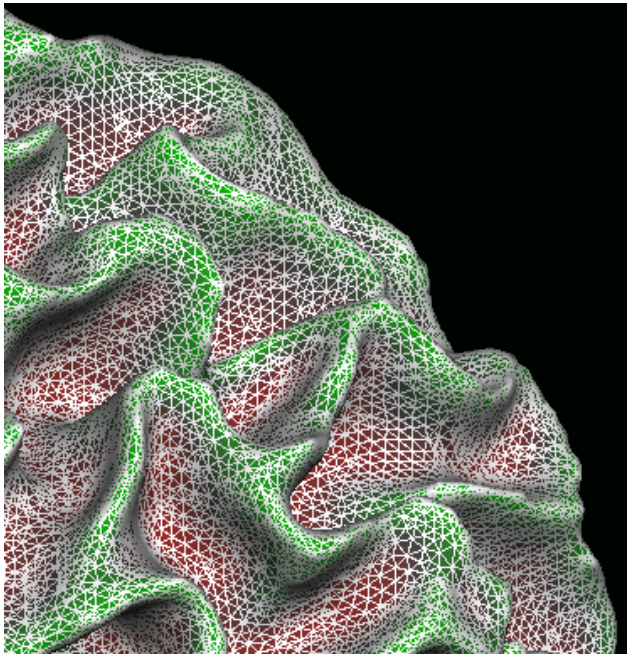


Marco Lorenzi

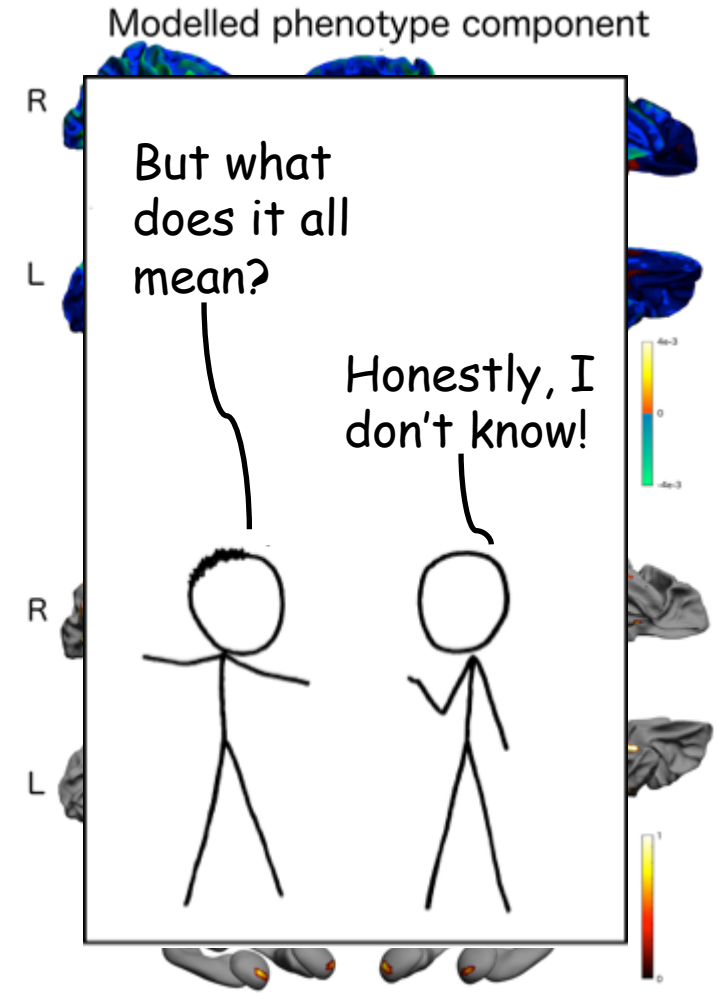
Genetics of cortical thickness in AD

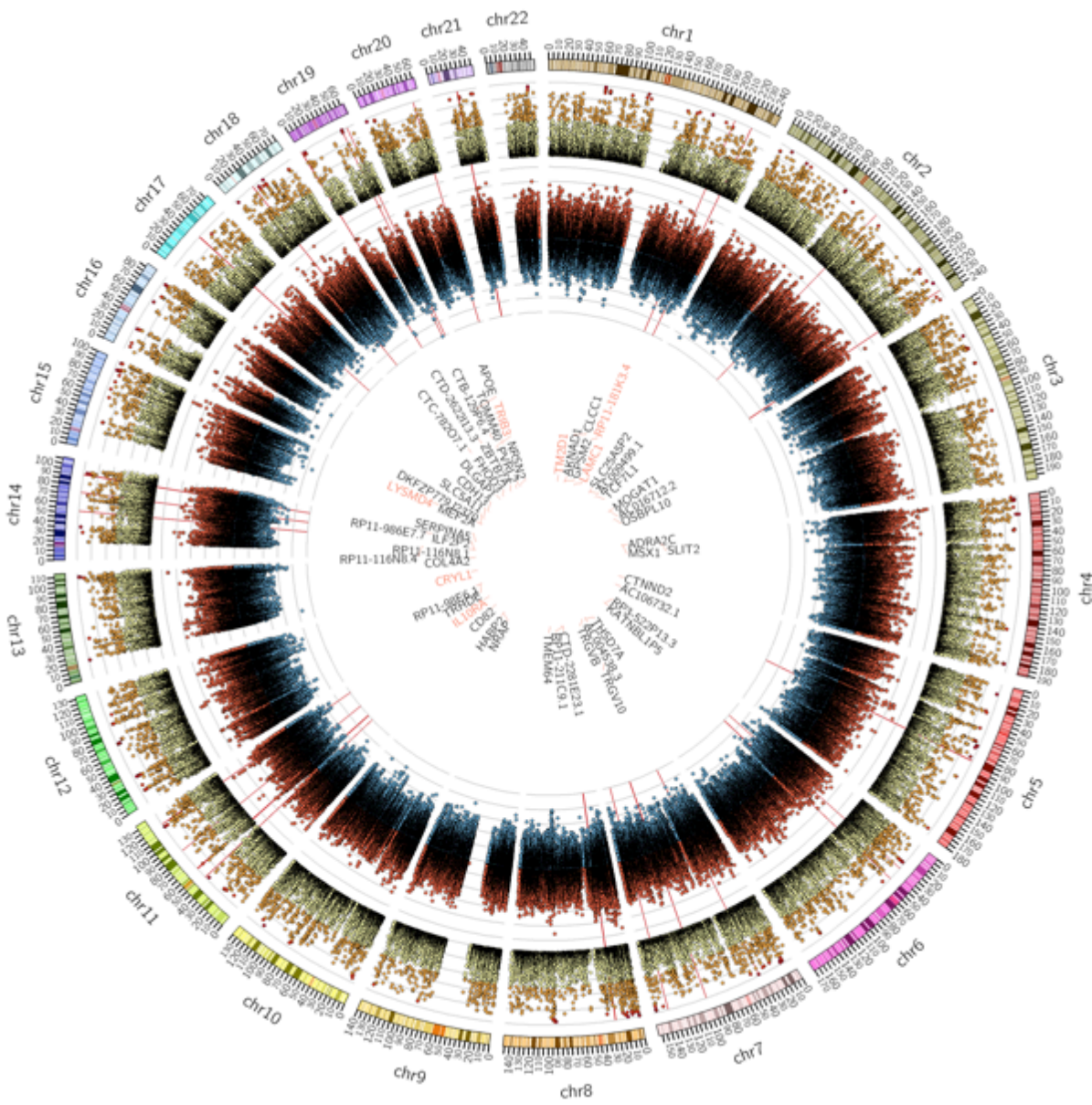
- Loss of gray matter in AD
- Cortical thickness derived from structural T1 weighted MRI scans





Results – Component 1





Lorenzi*,Altmann*, et al. *PNAS* (in revision)

Acknowledgements

Centre for Medical Image Computing

TRANSLATIONAL IMAGING GROUP

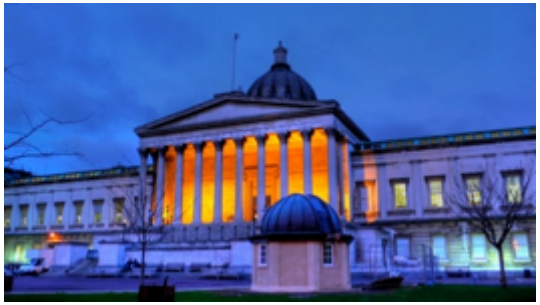
DEMENTIA RESEARCH CENTRE

eMedLab

informatics mathematics

Marco Lorenzi

Images and Genes:
From AD to MS



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London, January 31st 2018