

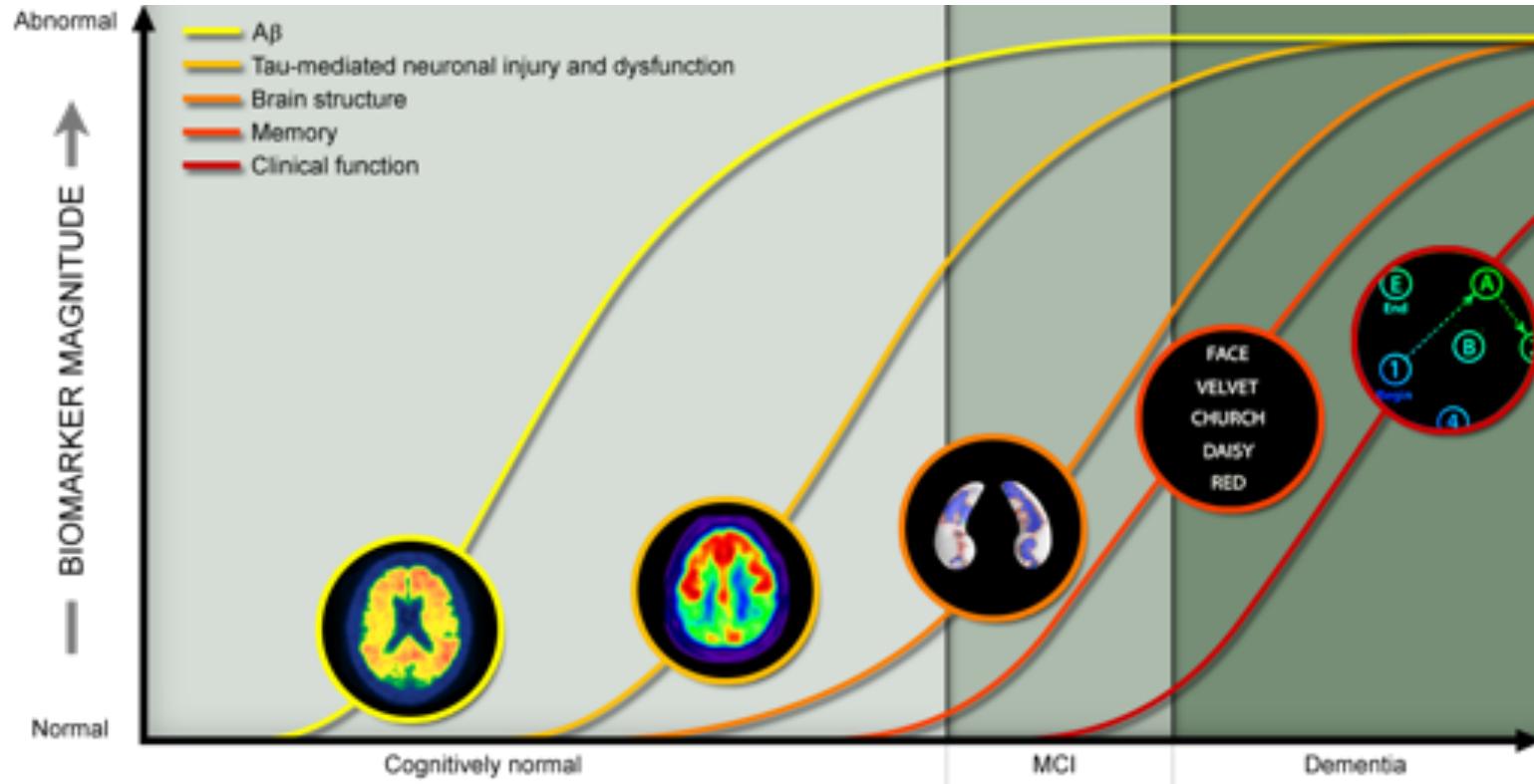
Introduction to Data-Driven Disease Progression Modelling

The word "pond" in a large, blue, sans-serif font. The letters have a slight shadow or glow effect, and they are set against a light blue circular background.

Neil Oxtoby

Progression Of Neurodegenerative Disease (POND) group
Centre for Medical Image Computing (CMIC)
Department of Computer Science, UCL

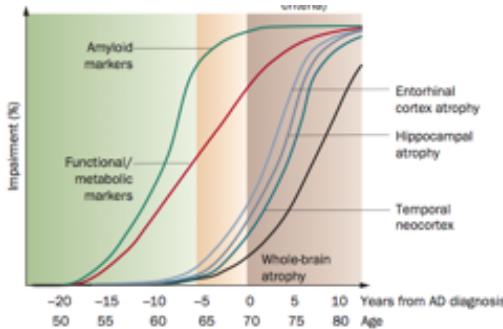
Disease Progression



ADNI website:
inspired by
Jack et al.
Lancet Neurol.
2010, 2013.



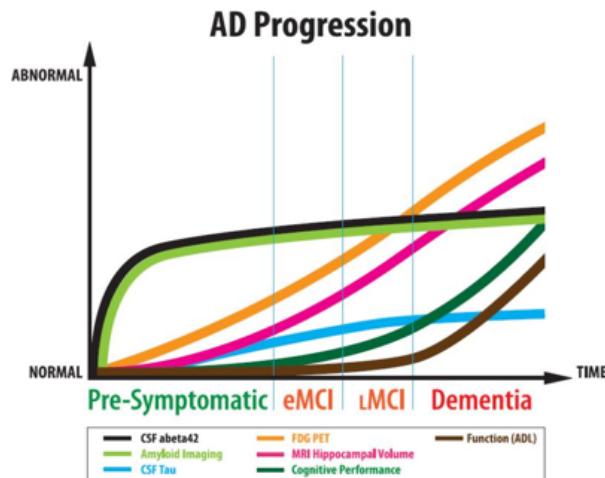
Aisen et al.
Alz. Dement.
2010



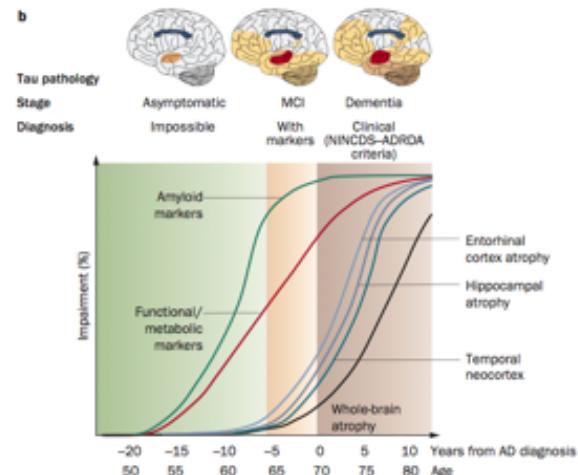
Frisoni et al
Nat. Rev.
Neurol. 2010

Progression Modelling

- Construct a picture of how a disease plays out over time
- Express in terms of symptoms, pathologies and/or **biomarkers**
- Reconstruction ideally exploits cross-sectional data



Aisen et al.
Alz. Dement. 2010

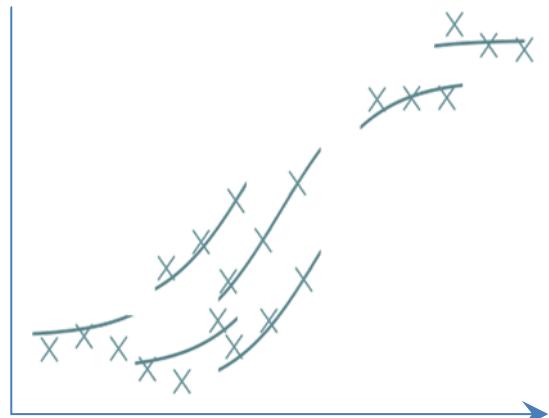
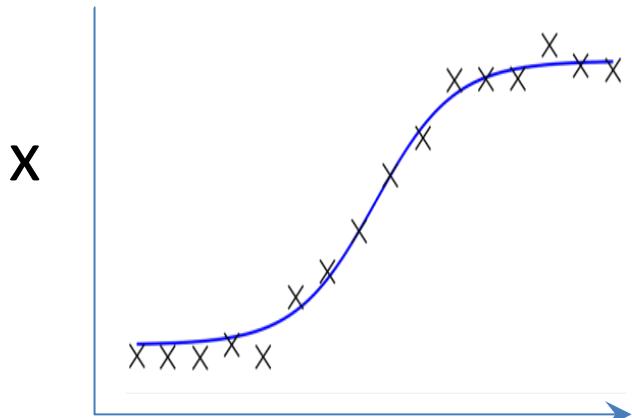


Frisoni et al. Nat.
Rev. Neurol. 2010

What we want



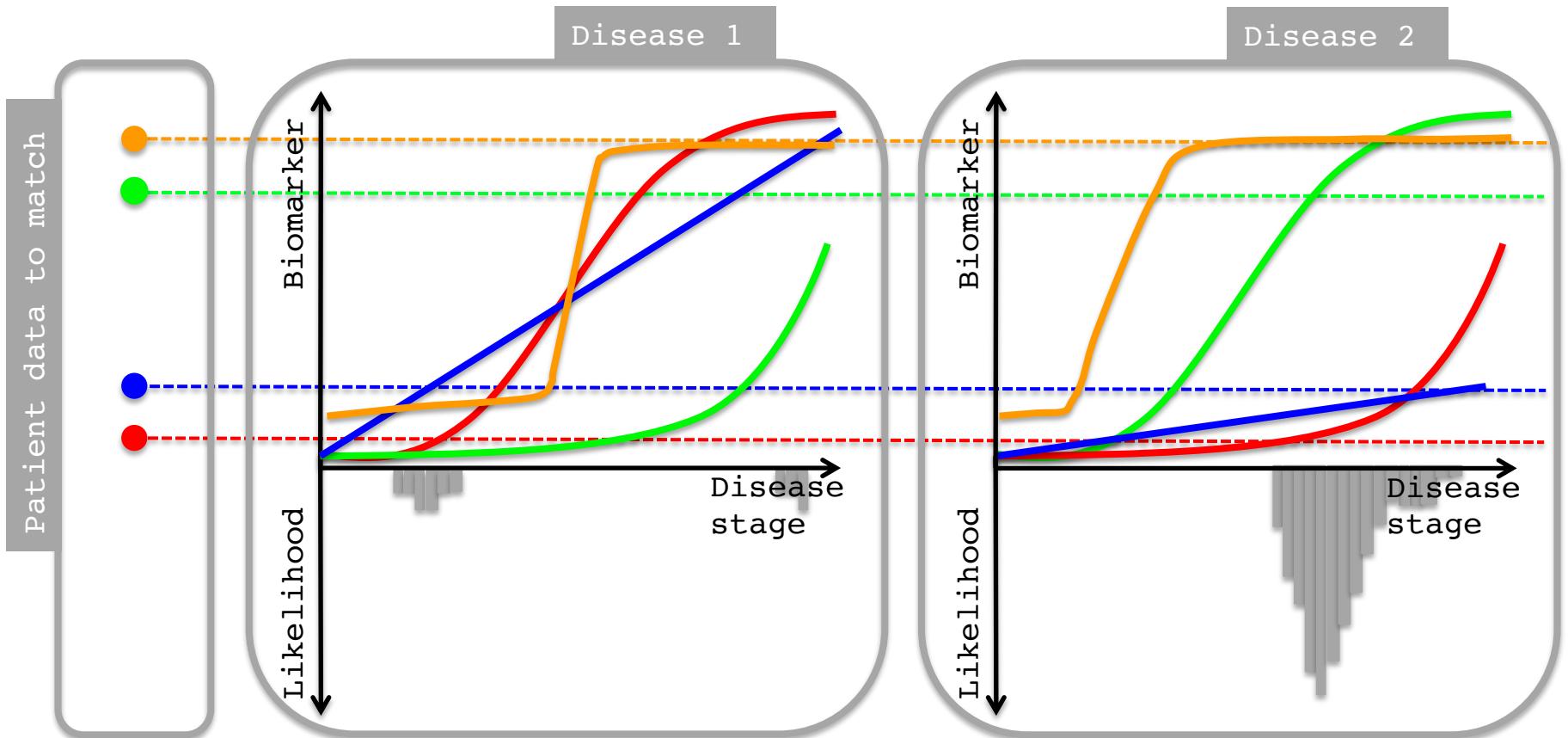
What we have



What's involved?

- Machine Learning, Estimation
 - Latent variable regression
 - Clustering, mixture modelling
 - Optimisation, Regularisation
 - Likelihoods
 - Bayesian statistics

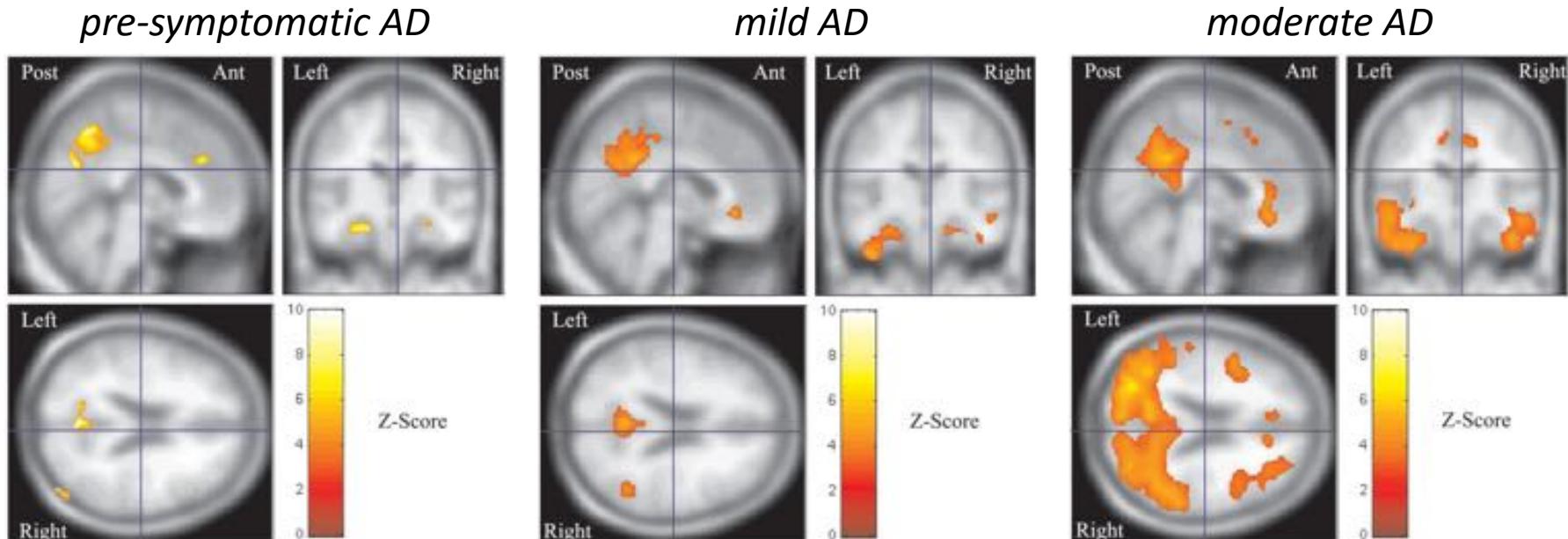
Diagnosis & Staging



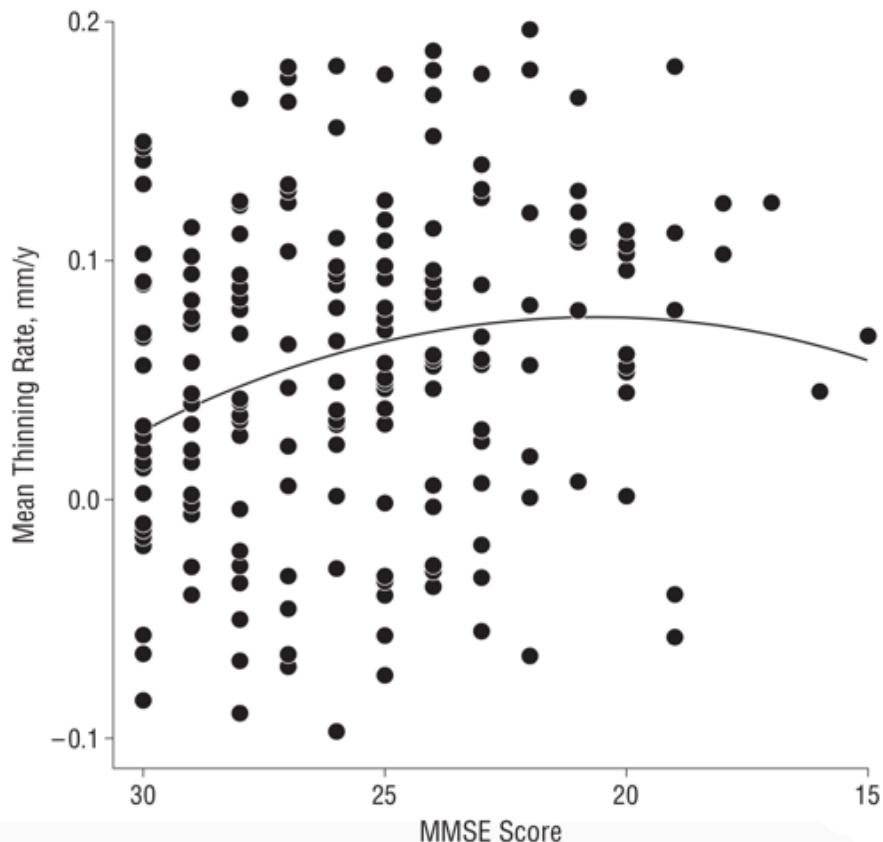
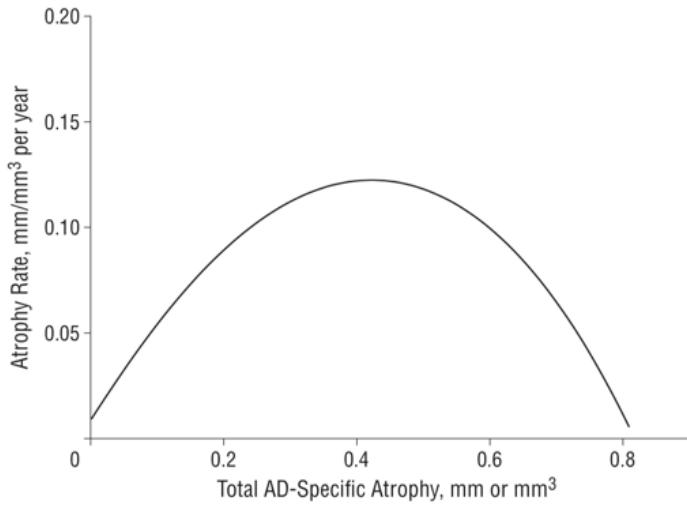
- Regress biomarker against pre-specified disease stage
 - Clinical groups: Normal / Prodromal / Symptomatic

Scahill et al. PNAS 2002

- T1 MRI measures neuronal atrophy: subdivide using MMSE test



- Regress biomarker against disease severity
 - Clinical groups: Normal / Prodromal / Symptomatic
 - Cognition:
 - MMSE (Sabuncu 2011)
 - ADAS-Cog (Yang 2011)
 - Hippocampal atrophy

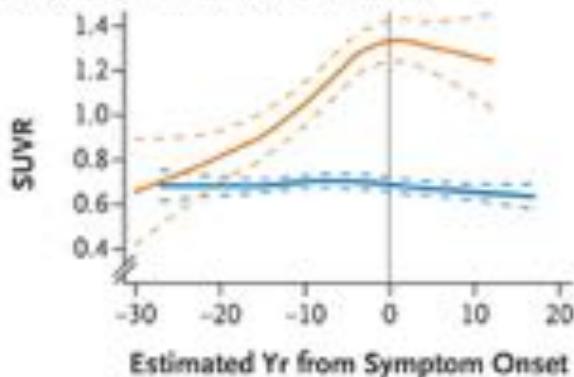


- Regress biomarker against pre-specified disease stage
 - Inherited diseases: familial age of onset

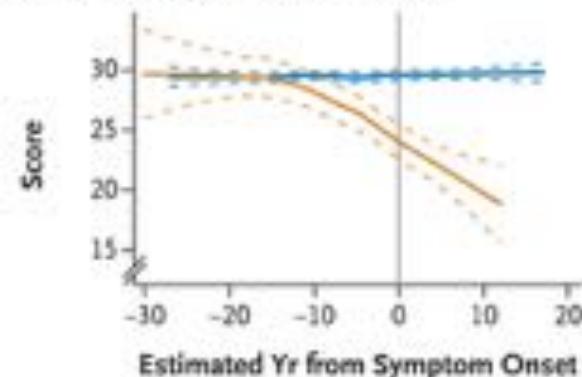
Bateman et al. NEJM 2012

- Parental age of symptom onset in dominantly-inherited AD

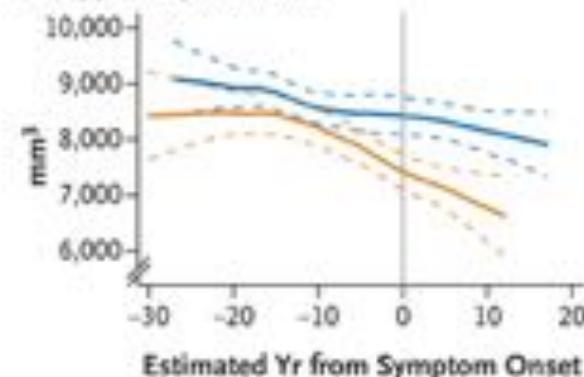
F A_β Deposition in the Precuneus



B Mini-Mental State Examination

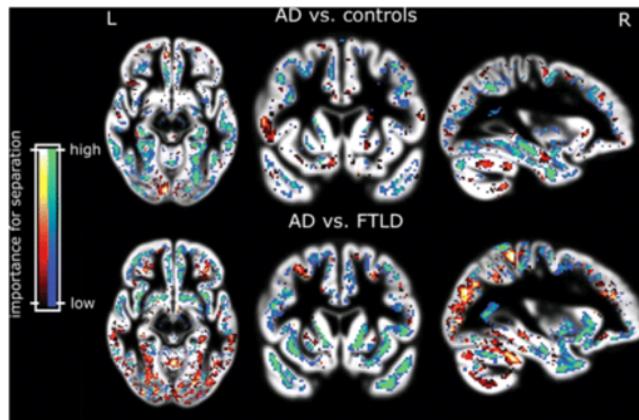


D Hippocampal Volume



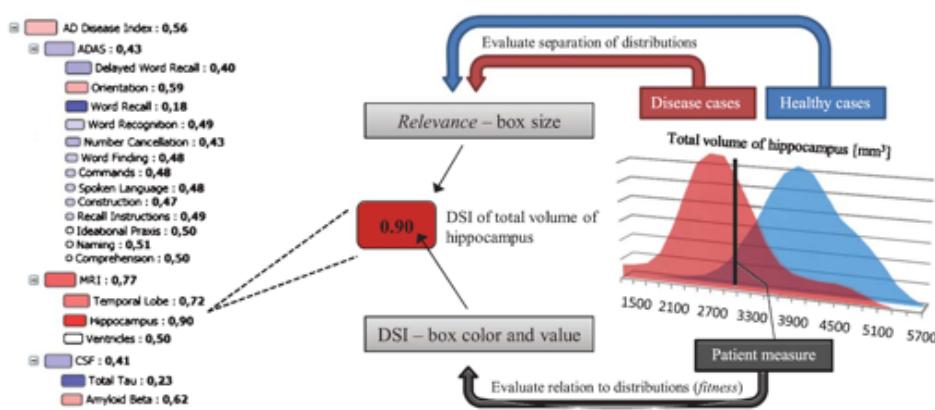
- Pattern recognition: supervised learning
 - Learn to classify patients from labelled data
 - Shown value of combining imaging and non-imaging data

Classifying structural MRI in AD



Klöppel et al. Brain 2008

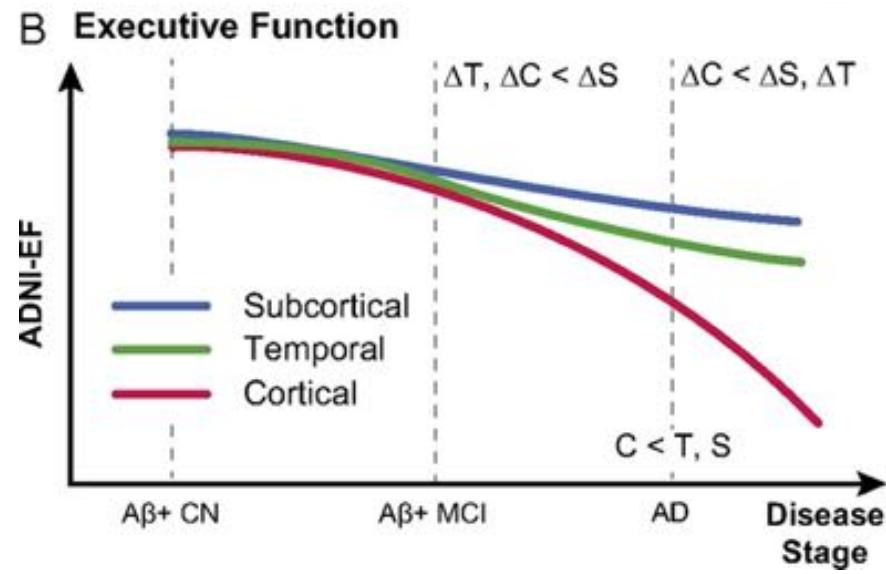
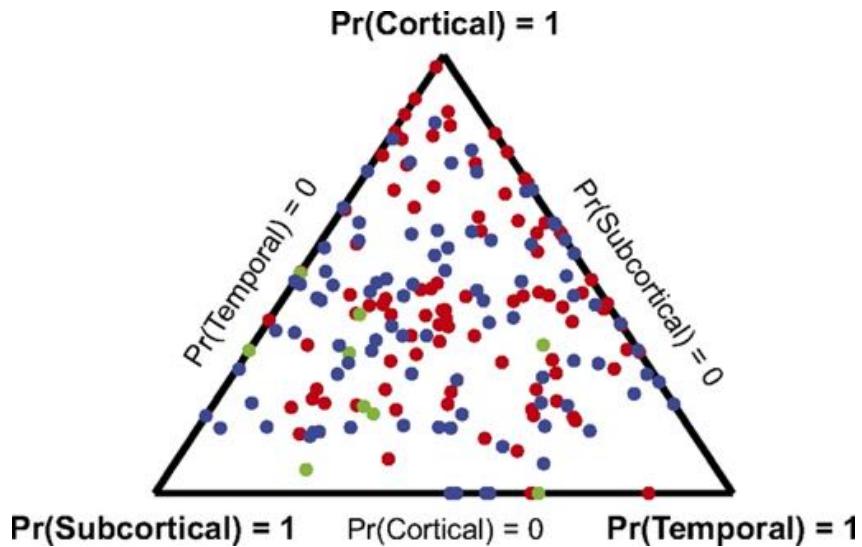
Disease State Fingerprint for AD



Mattila et al. JAD 2011

- Pattern discovery: unsupervised learning
 - Learn disease subtypes/stages automatically
 - Clustering

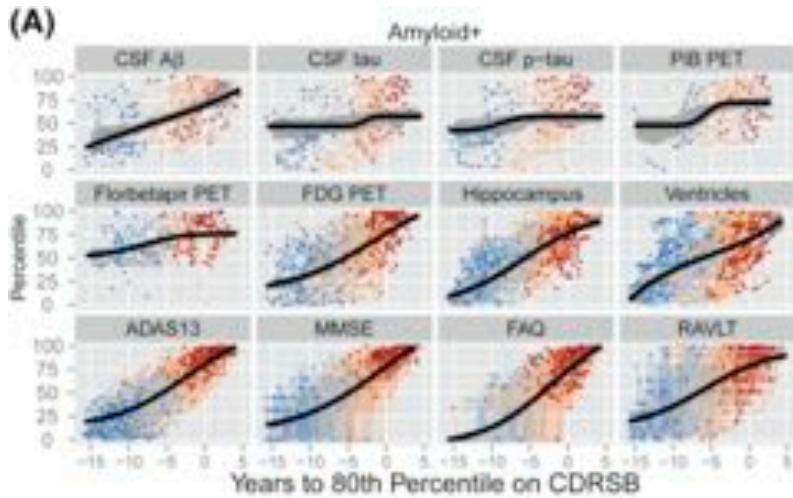
Clustering brain grey matter density to find atrophy “factors” in AD



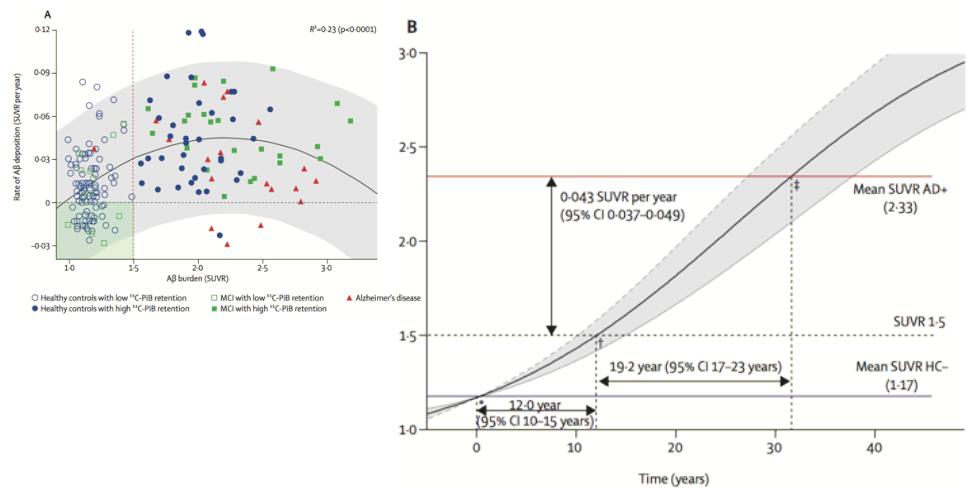
- Generative models
 - **Unstructured data:** scalar biomarkers, phenomenological
 - Structured data: images, connections

AD marker trajectories

Self-modelling regression



Differential Equation Models

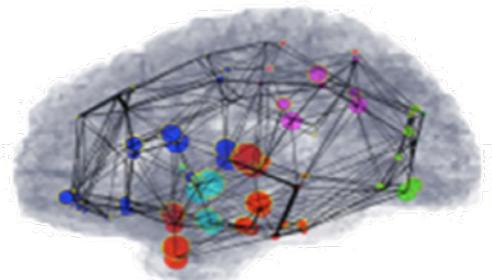


Donohue et al. Alz. Dem. 2014

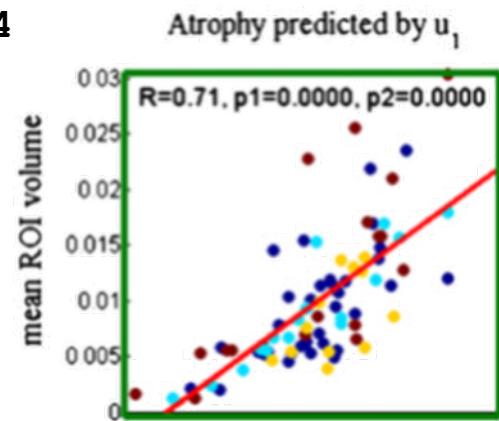
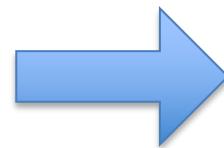
Related: Jedynak et al. NeuroImage 2012

Villemaigne et al.
Lancet Neurol. 2014

- Generative models
 - Unstructured data: scalar biomarkers, phenomenological
 - **Structured data:** spatial info. — images, brain connectivity
 - Spatiotemporal models: e.g. shape/image regression
Durrleman et al. IJCV 2013;
Lorenzi et al. NeuroBiol Aging 2015; etc.
 - Network propagation models: e.g. prion-like transmission, diffusion
Raj et al. Neuron 2012;
Iturria-Medina et al. PLOS Comp. Biol. 2014



Connectivity
predicts atrophy



Event-based Model

NeuroImage 60 (2012) 1880–1889



Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimng

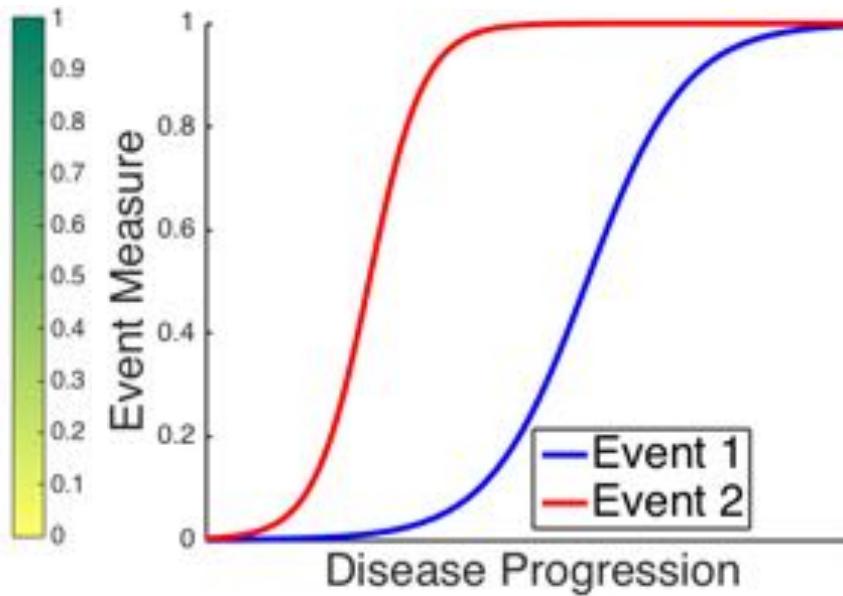
An event-based model for disease progression and its application in familial Alzheimer's disease and Huntington's disease

Hubert M. Fonteijn ^{a,b,c,*}, Marc Modat ^{a,d}, Matthew J. Clarkson ^{a,d,e}, Josephine Barnes ^e,
Manja Lehmann ^e, Nicola Z. Hobbs ^f, Rachael I. Scahill ^f, Sarah J. Tabrizi ^{f,g}, Sébastien Ourselin ^{a,d,e},
Nick C. Fox ^{e,g}, Daniel C. Alexander ^{a,b}

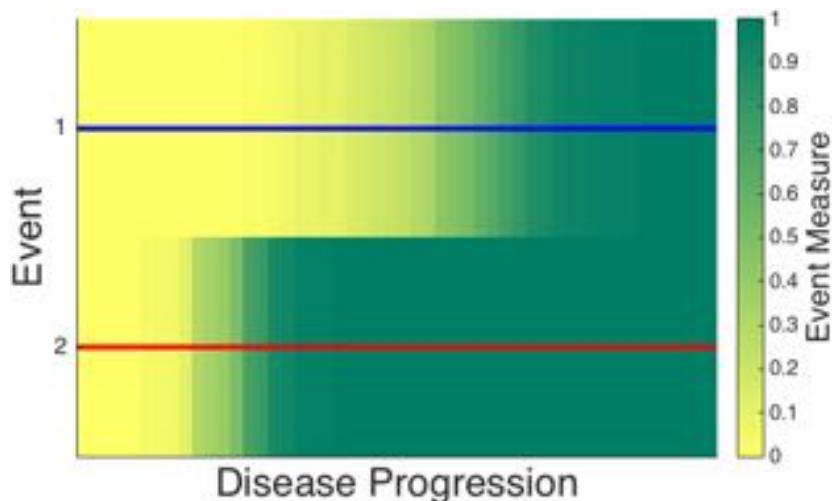
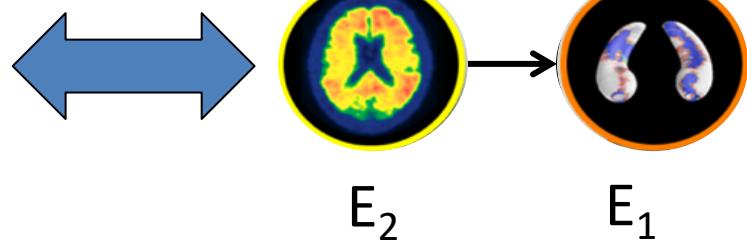
- Estimates the order of the “events” from a cross-sectional (or short-term longitudinal) data set

Data-driven: no prior knowledge of disease stage

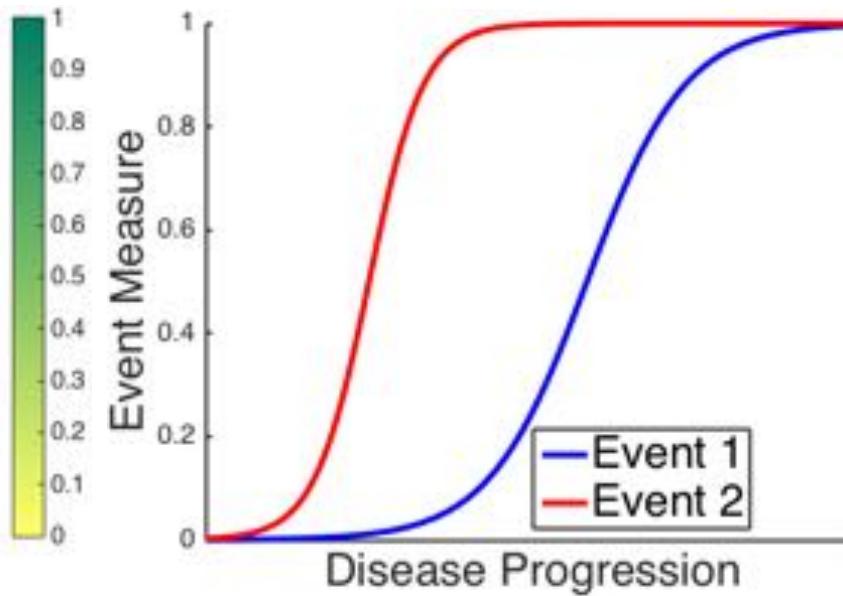
Event-based Model



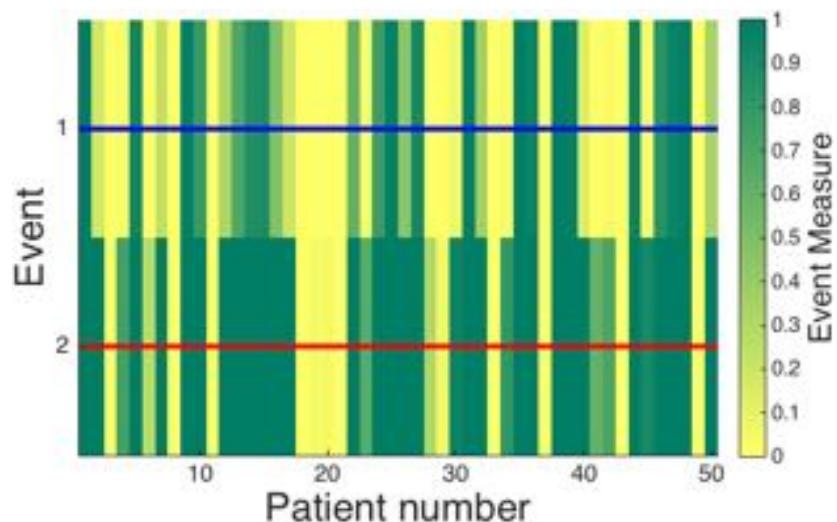
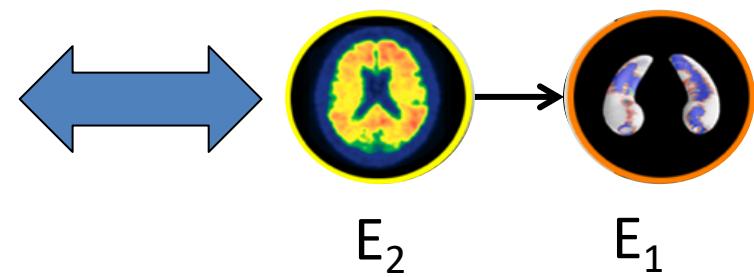
After
Fonteijn et al.
NeuroImage 2012



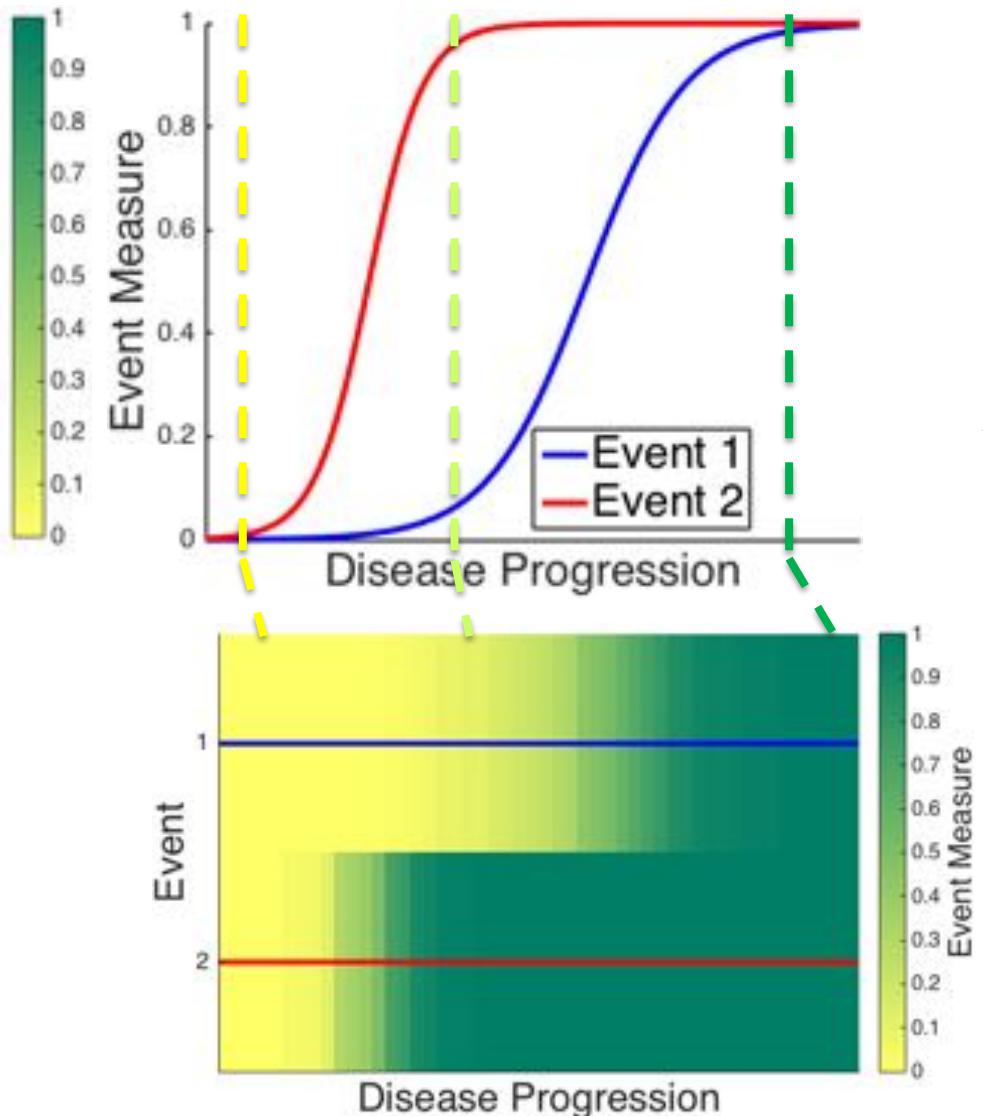
Event-based Model



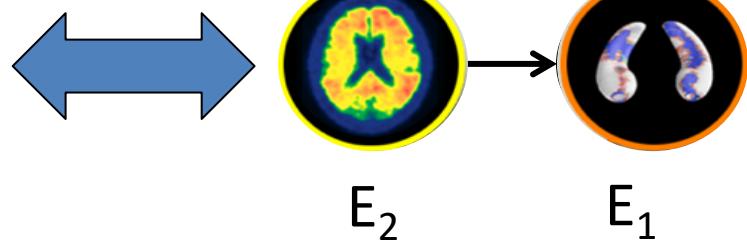
After
Fonteijn et al.
NeuroImage 2012



Event-based Model



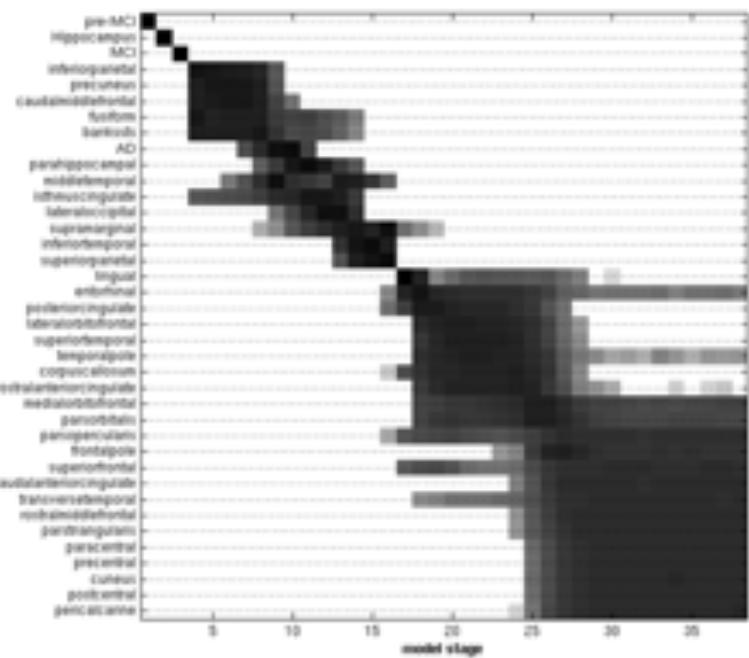
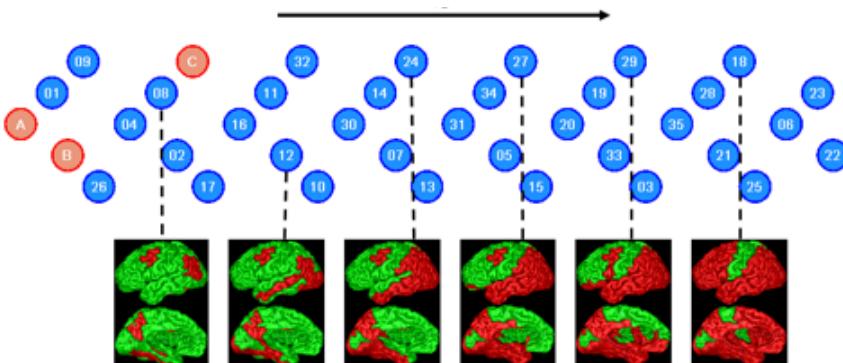
After
Fonteijn et al.
NeuroImage 2012



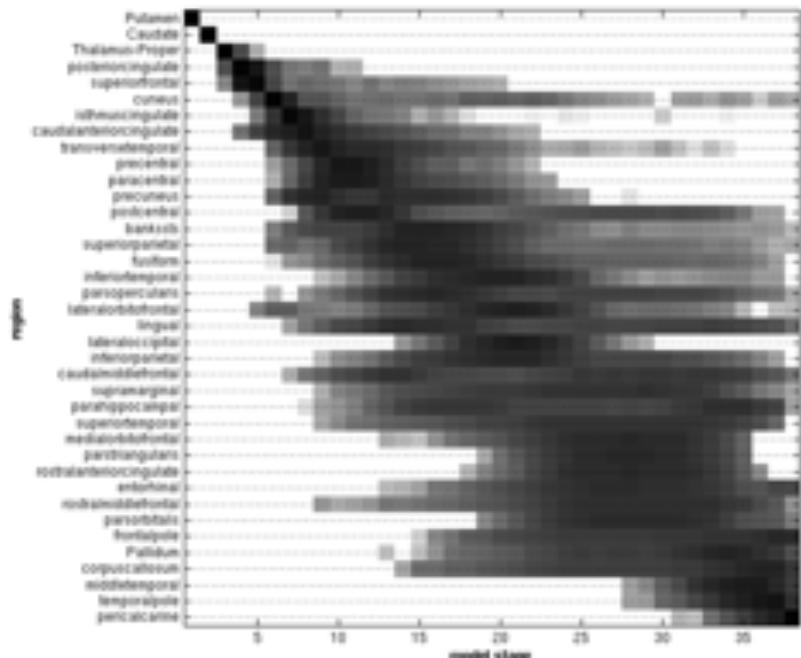
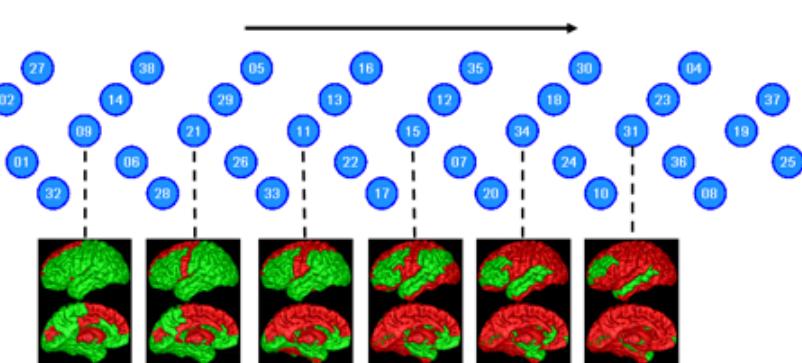
Event-based Model

Fonteijn *et al.* NeuroImage 2012

Familial Alzheimer's progression



Huntington's progression



doi:10.1093/brain/awu176

Brain 2014; 137; 2564–2577 | 2564

BRAIN
A JOURNAL OF NEUROLOGY

A data-driven model of biomarker changes in sporadic Alzheimer's disease

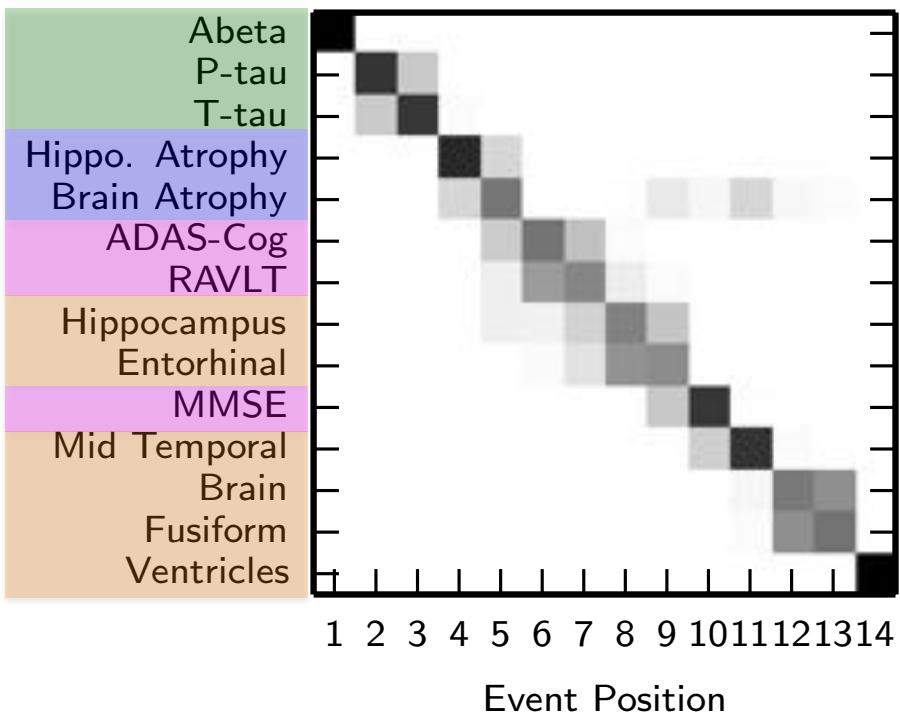
Alexandra L. Young,¹ Neil P. Oxtoby,¹ Pankaj Daga,¹ David M. Cash,^{1,2} on behalf of the Alzheimer's Disease Neuroimaging Initiative,[†] Nick C. Fox,² Sébastien Ourselin,^{1,2} Jonathan M. Schott^{2,*} and Daniel C. Alexander^{1,*}

¹ Centre for Medical Image Computing, Department of Computer Science, University College London, Gower Street, London, WC1E 6BT, UK

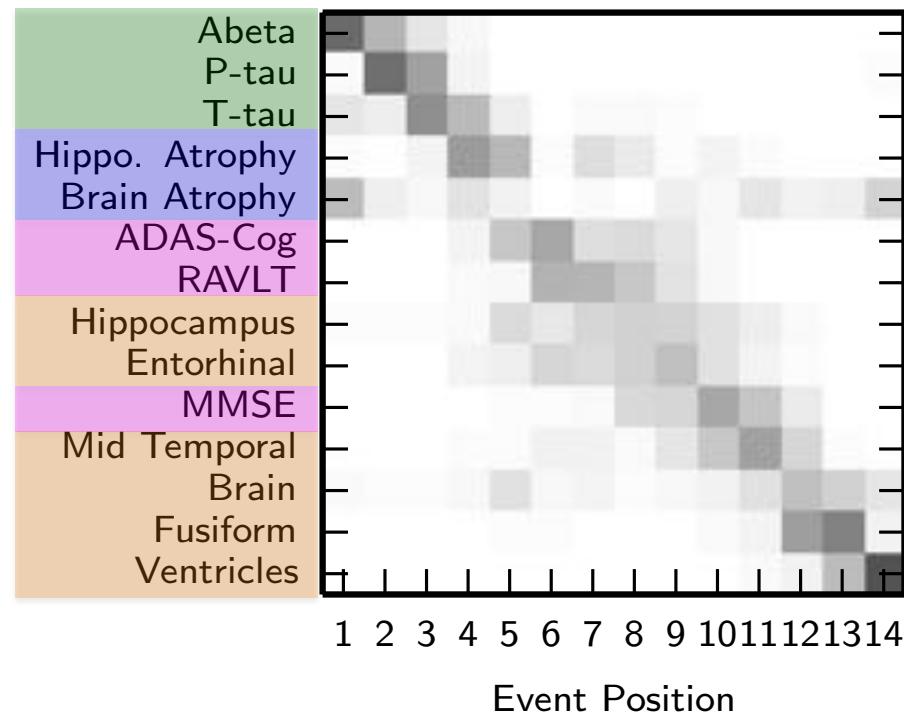
² Dementia Research Centre, UCL Institute of Neurology, University College London, 8-11 Queen Square, London, WC1N 3AR, UK

ApoE4-positive subjects: ordering supports hypothetical models

Event Sequence

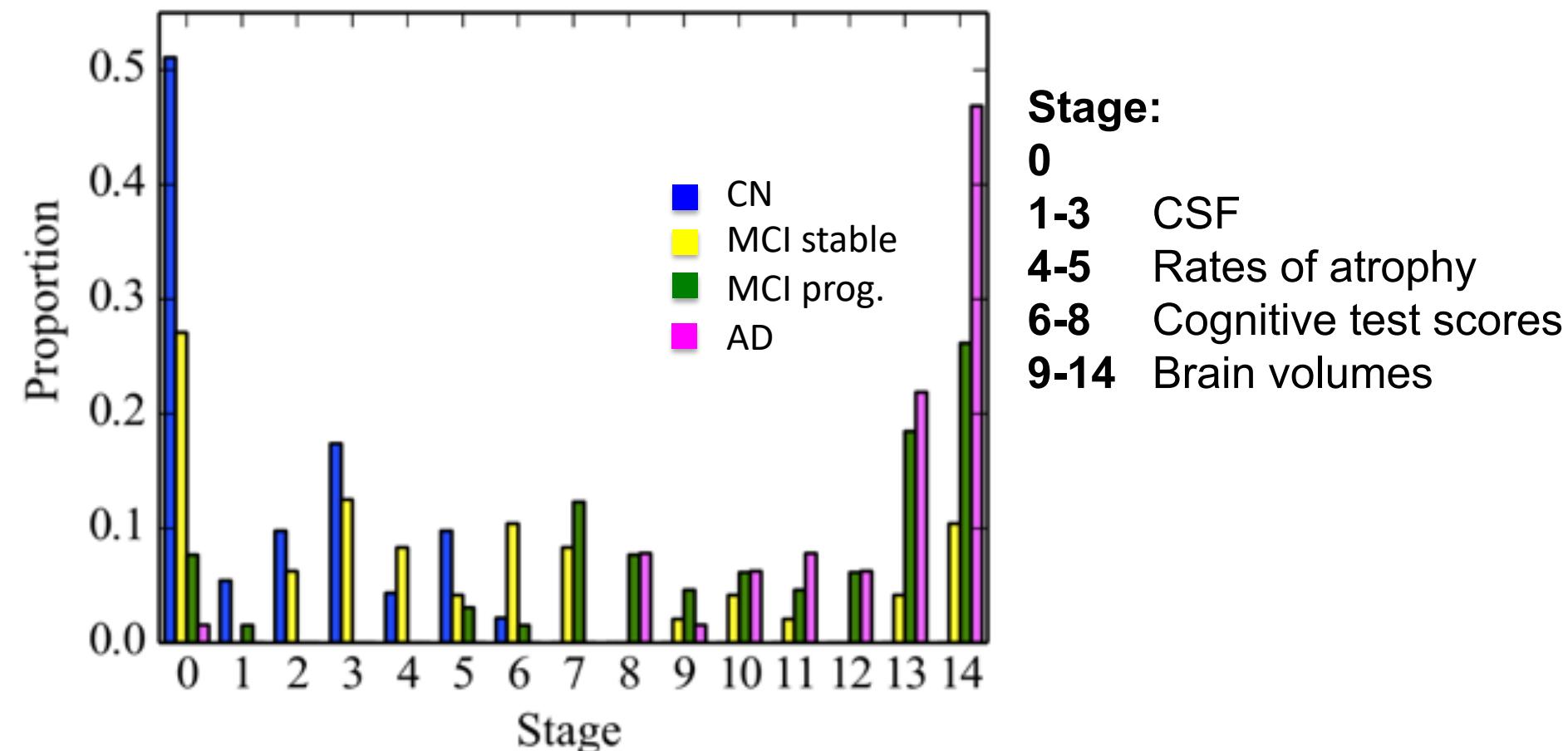


Cross Validation

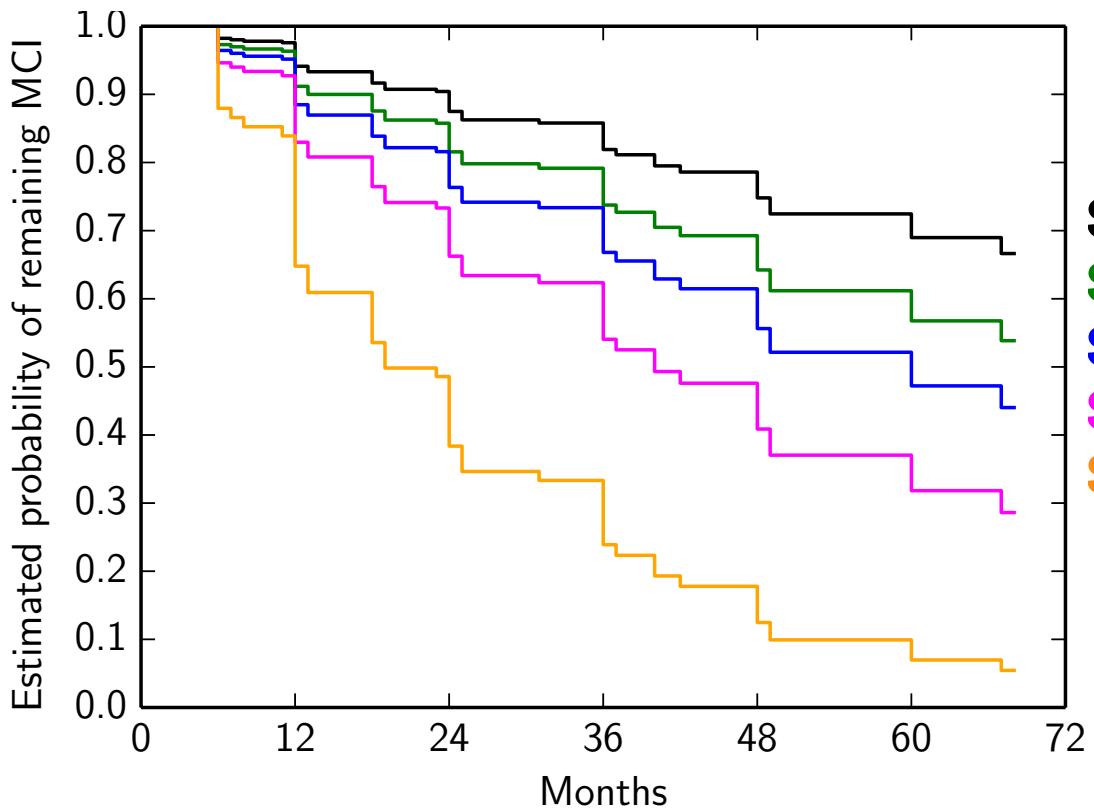


EBM: ADNI staging

Young et al. Brain 2014



Cox Proportional Hazards Model

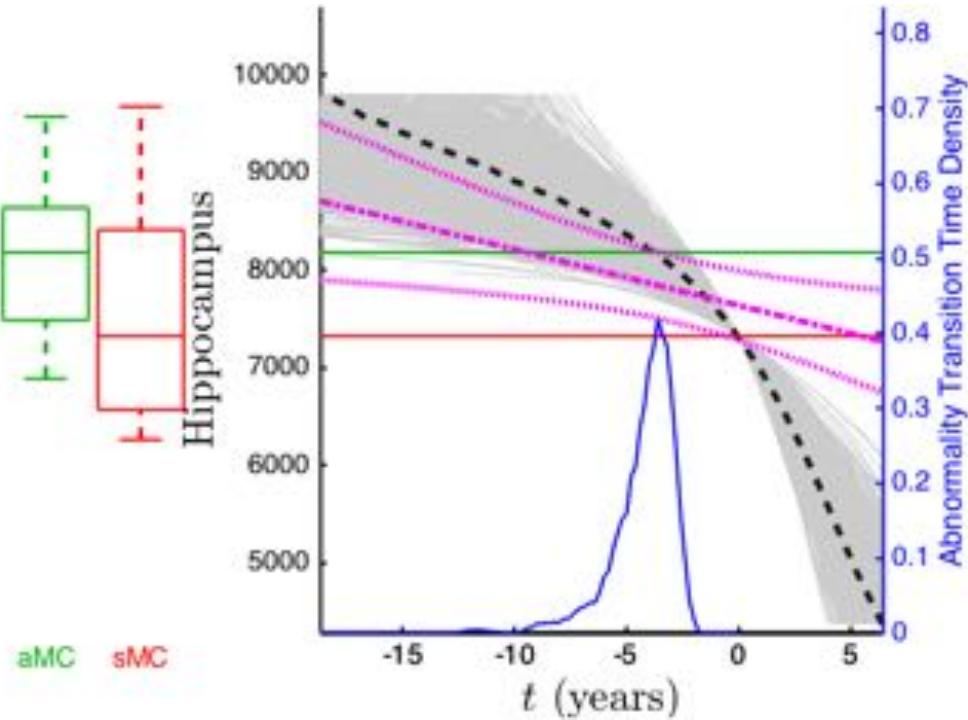
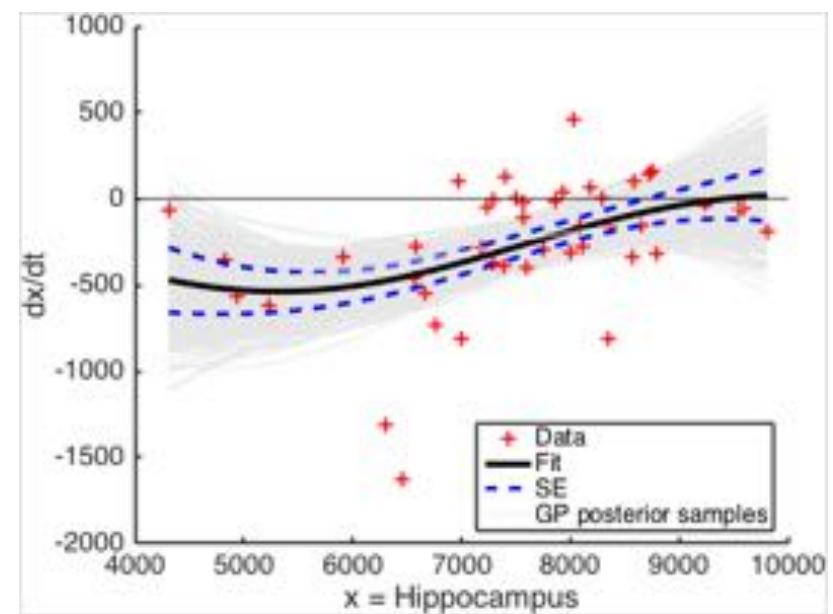


- Stage 0**
- Stage 1-3 CSF**
- Stage 4-5 Rates of atrophy**
- Stage 6-8 Cognitive test scores**
- Stage 9-14 Brain volumes**

77% accuracy
Converters vs. Non-converters
3-5 year follow up

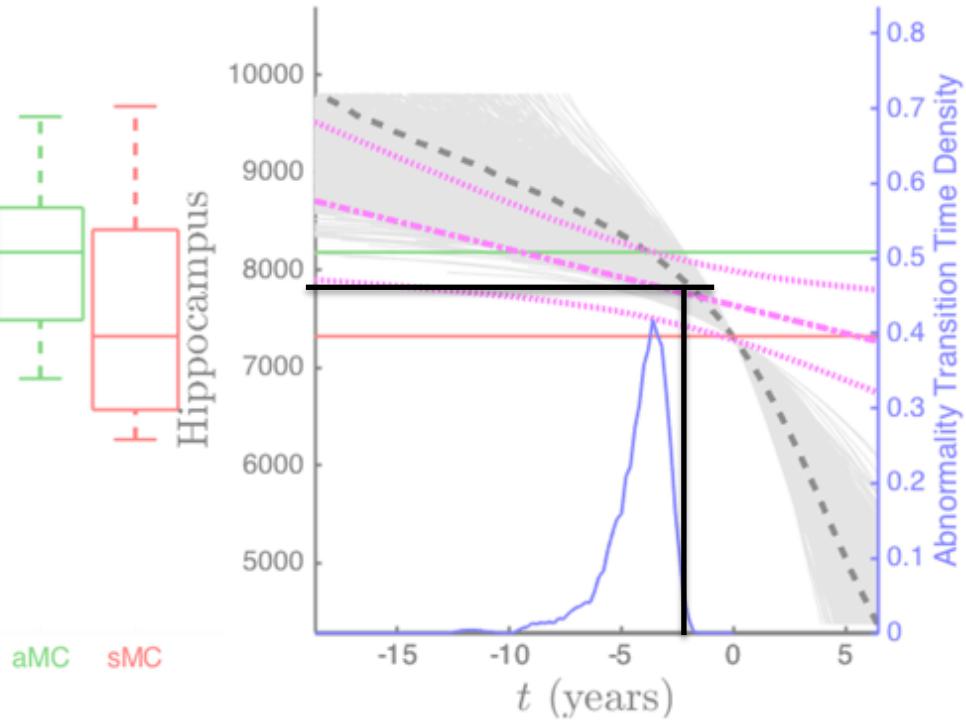
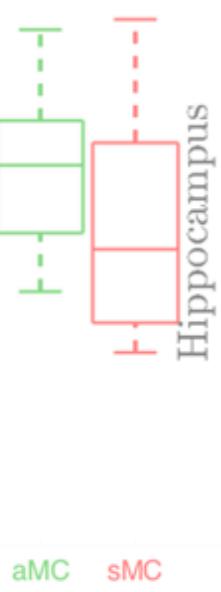
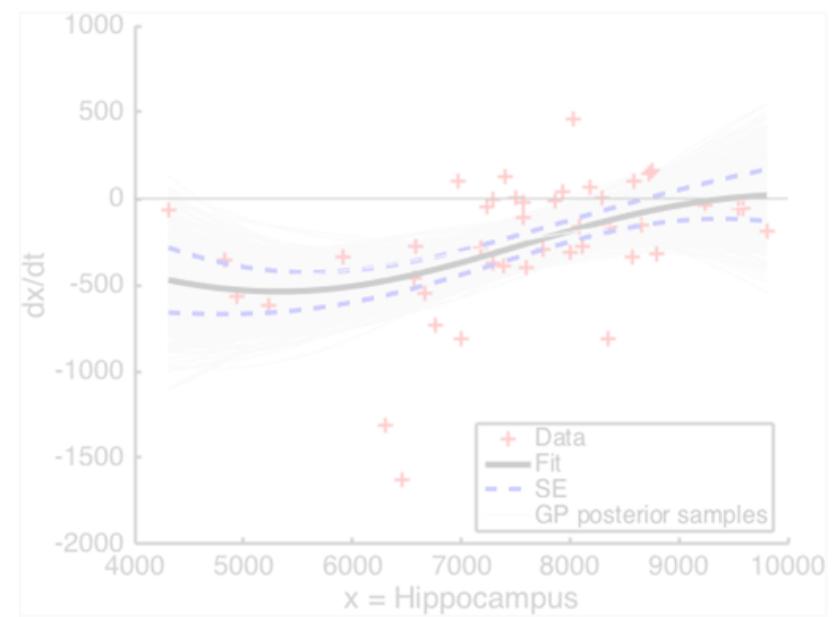
Trajectories from rates of change

Oxtoby et al. Brain 2018



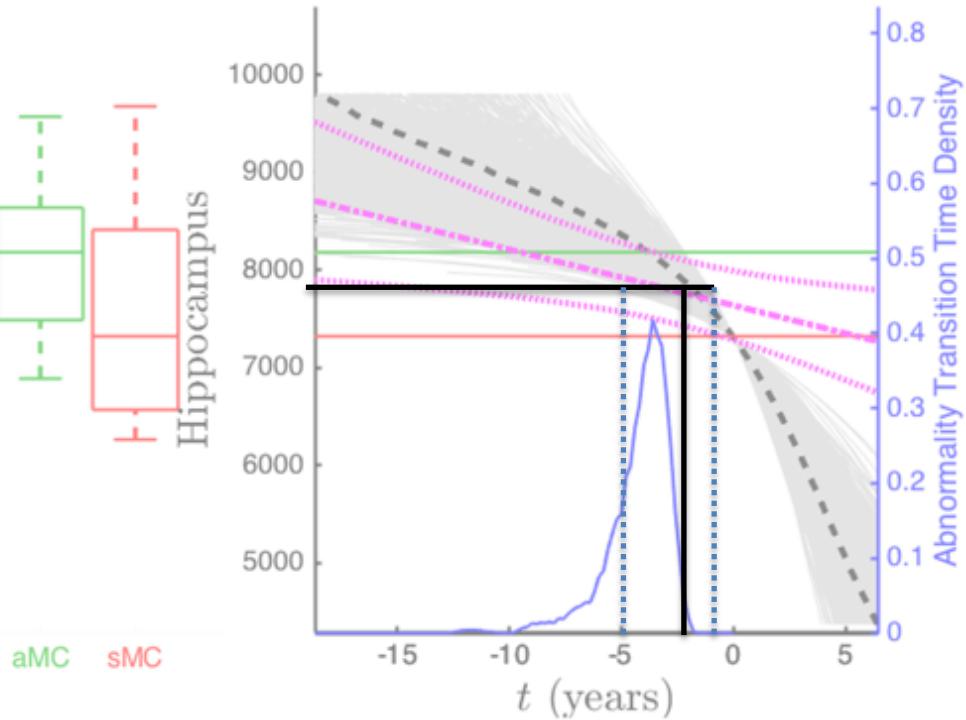
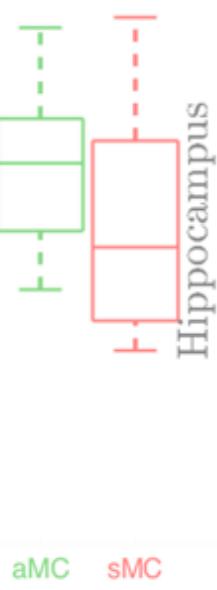
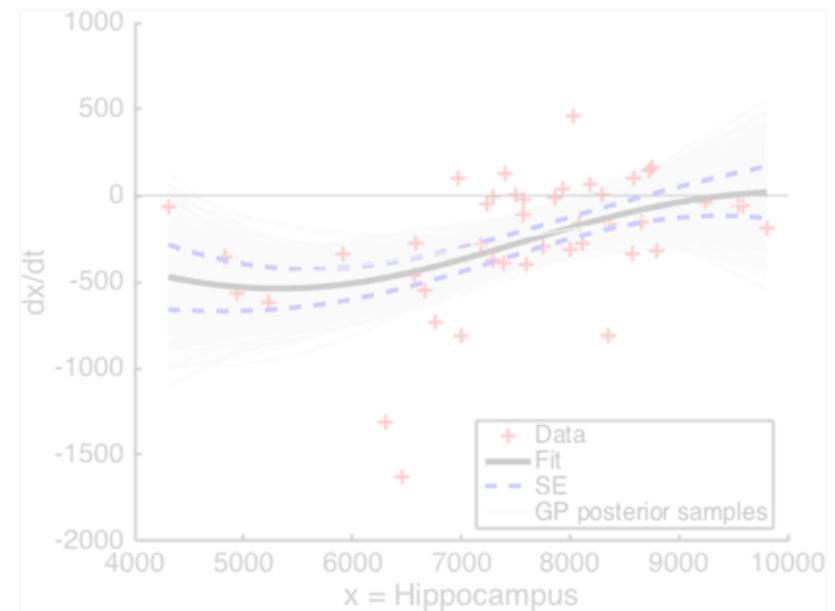
Trajectories from rates of change

Oxtoby et al. Brain 2018



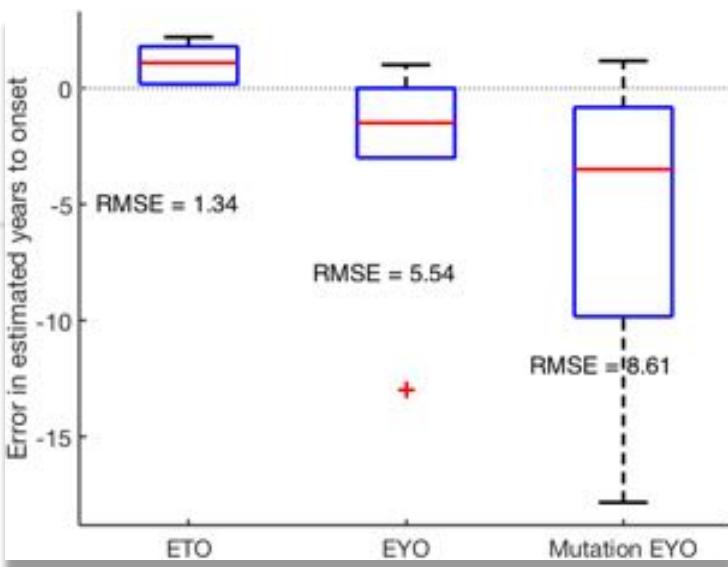
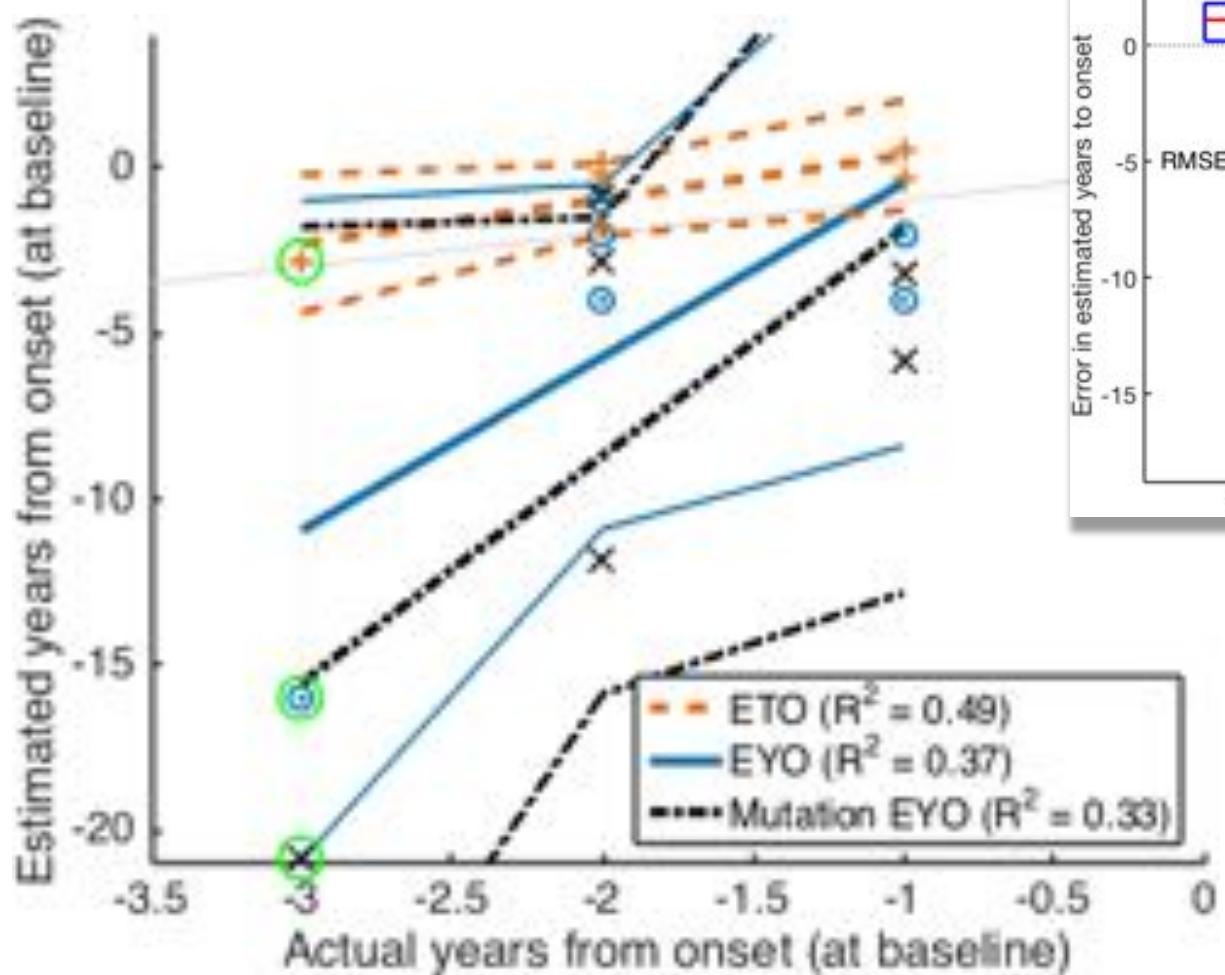
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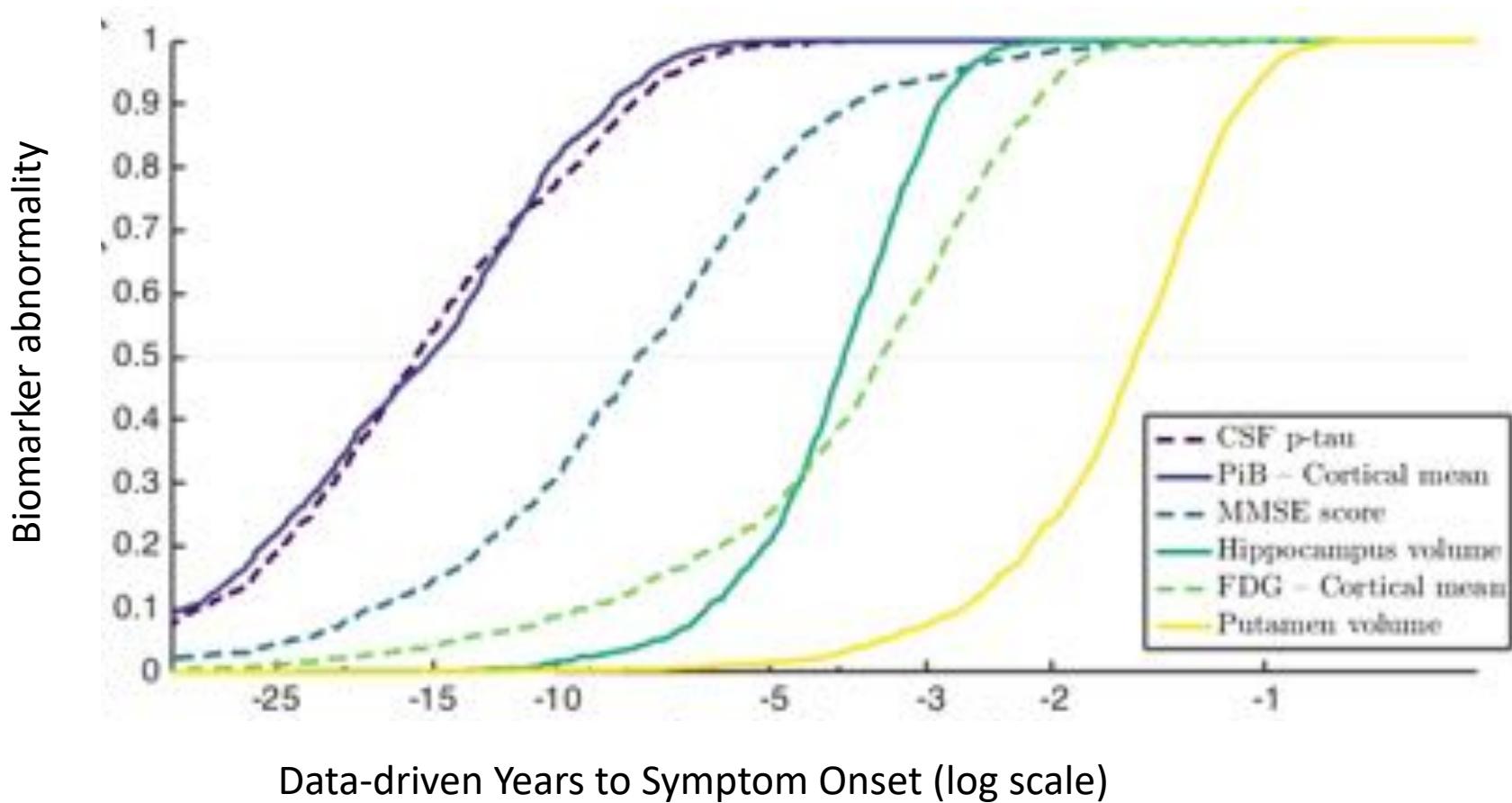
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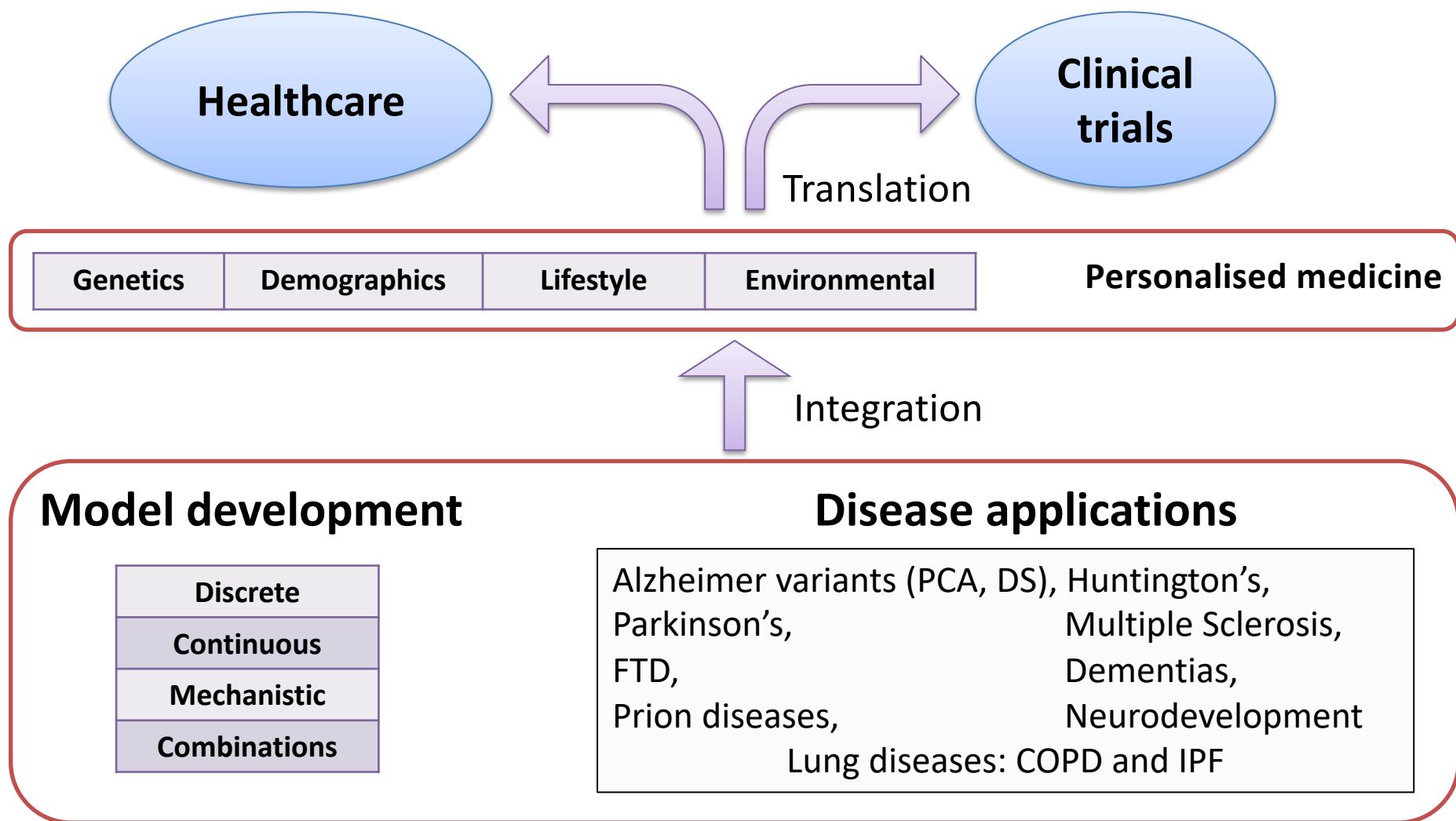


Trajectories from rates of change

Oxtoby et al. Brain 2018



What we are PONDering:





Now and Next



What I am PONDering:

Individualised AI for Medicine

UK Research and Innovation
Future Leaders Fellowship