Data-driven Computational Modelling for Alzheimer's Disease Clinical Trials

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Progression **O**f **N**eurodegenerative **D**isease (POND) group
Centre for Medical Image Computing (CMIC)
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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 666992

Acknowledgements

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pond · UCL

EuroPOND · UK Research and Innovation · alzheimer's association · Alzheimer's Research UK – The Power to Defeat Dementia

EPSRC – Engineering and Physical Sciences Research Council

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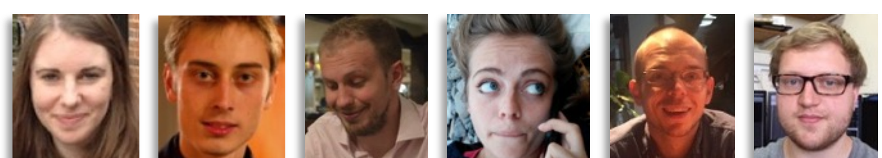
CHDI Foundation · wellcome · UCLIC

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Alzheimer's Society – United Against Dementia · WESTON BRAIN INSTITUTE · icometrix – IMAGING BIOMARKER EXPERTS

Collaboration for Leadership in Applied Health Research and Care North Thames

- POND: pond.cs.ucl.ac.uk
  - Alex Young, Danny Alexander, et al.
  - EuroPOND*: europond.eu
- CMIC: www.ucl.ac.uk/cmic
- EuroPOND: europond.eu



neiloxtoby.com

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The AD Challenge

- AD is a multifactorial, heterogeneous disease
- Putative therapies are not* reaching end-points in clinical trials
  - Individual variability? (wrong people)
  - Too late? (wrong time: damage done)
  - Insensitive end-points? (cognition)
  - Insufficient duration?
  - Comorbidities?

*Breaking news on next slide

Aducanumab?

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- Phase 3
  - March 2019: cancelled by futility analysis
  - October 2019: revived; regulatory filing in 2020
    - In consultation with the FDA
    - ✓ EMERGE study
      - Large dose arm
    - ✗ ENGAGE study

Aducanumab?

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ALZFORUM
NETWORKING FOR A CURE

‘Reports of My Death Are Greatly Exaggerated.’
Signed, Aducanumab

Aducanumab?

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Relationship Status:
it's complicated

The AD Challenge

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- AD is a multifactorial, heterogeneous disease

- Putative therapies are not* reaching end-points in clinical trials
  - **Individual variability**? (*right* people)
  - **Too late**? (*right* time)
  - **Insensitive end-points**? (*biomarkers*…)
  - Insufficient duration?
  - Comorbidities?

The AD Challenge

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- Individual **variability**
  - **Age** of onset => unknown "disease time/stage"
  - **Progression**

- Overcoming Heterogeneity
  - Right people: individualized inclusion criteria
  - Right time: characterize earliest stages

Take-home message

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- AD is a multifactorial, heterogeneous disease
- Requires commensurate tools
  – Quantitative assessments in asymptomatic phase
  – Individualised biomarker-based disease signatures

  – Mechanisms not well understood? (amyloid hypothesis)

AD Progression

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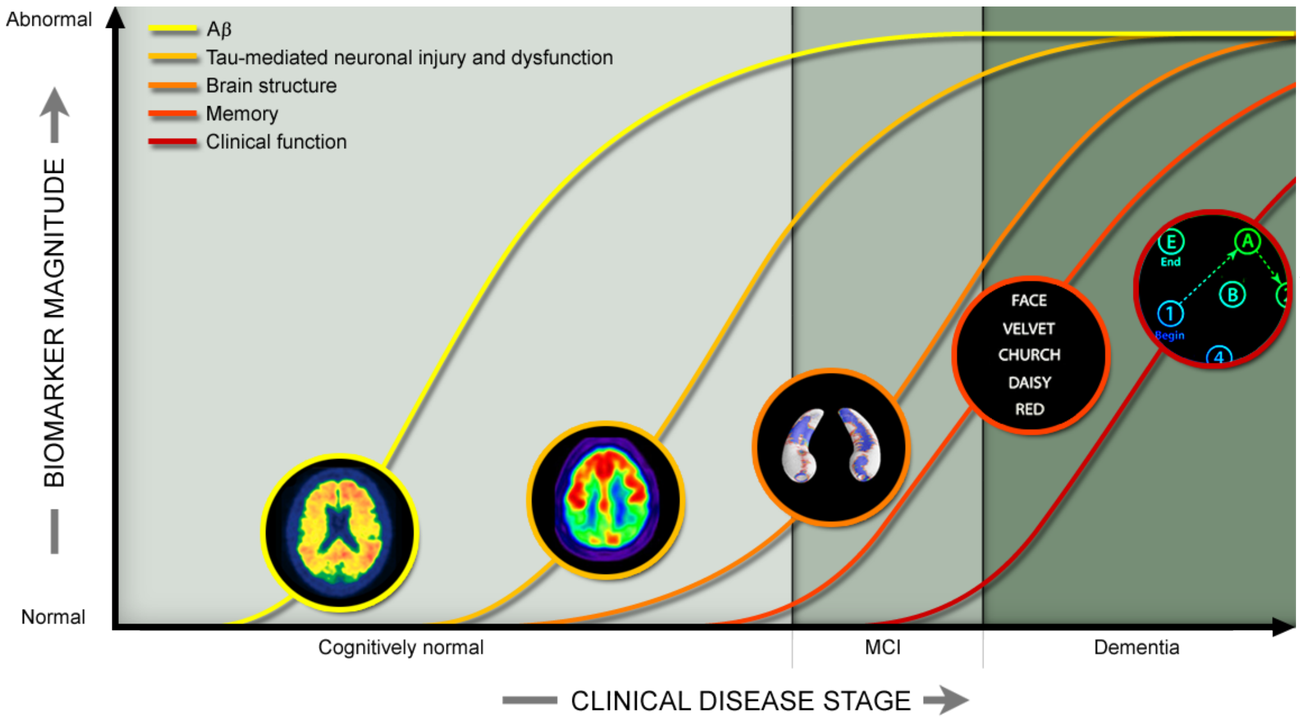
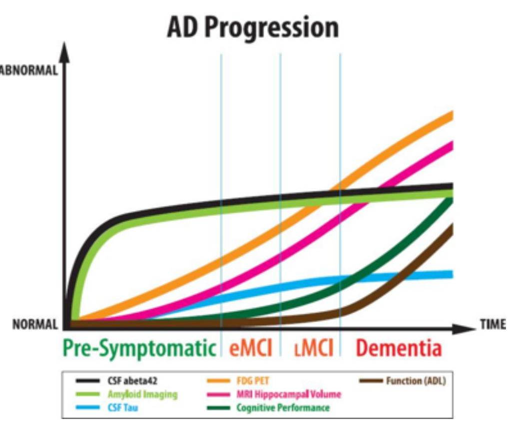
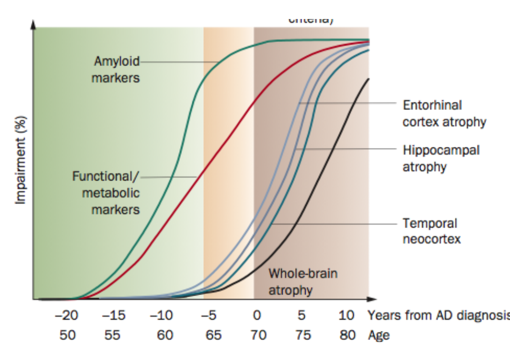


ADNI website: inspired by **Jack et al. Lancet Neurol. 2010, 2013.**



Aisen et al. Alz. Dement. 2010



Frisoni et al Nat. Rev. Neurol. 2010

Progression Modelling

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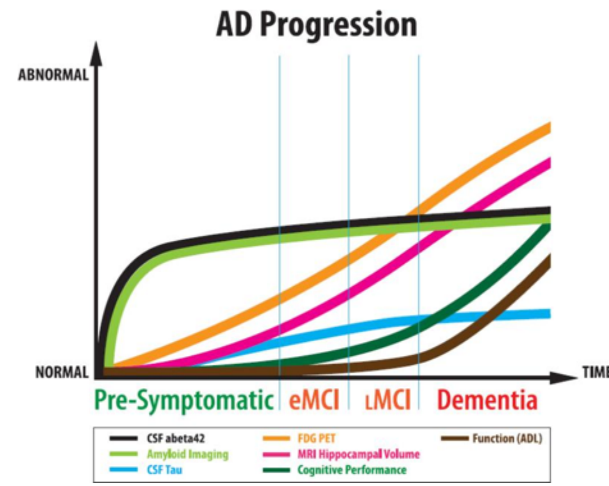
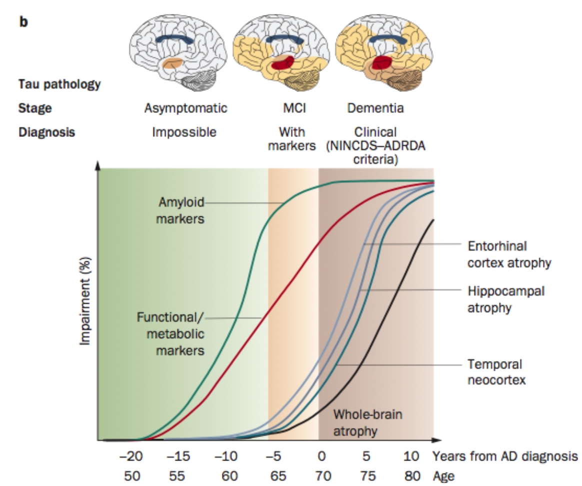
- Construct a quantitative **signature** of how a disease plays out over time
- Express in terms of symptoms, pathologies, biomarkers
- Uses: precision staging; diagnosis; prognosis



Aisen et al. Alz. Dement. 2010



Frisoni et al. Nat. Rev. Neurol. 2010

Diagnosis & Staging

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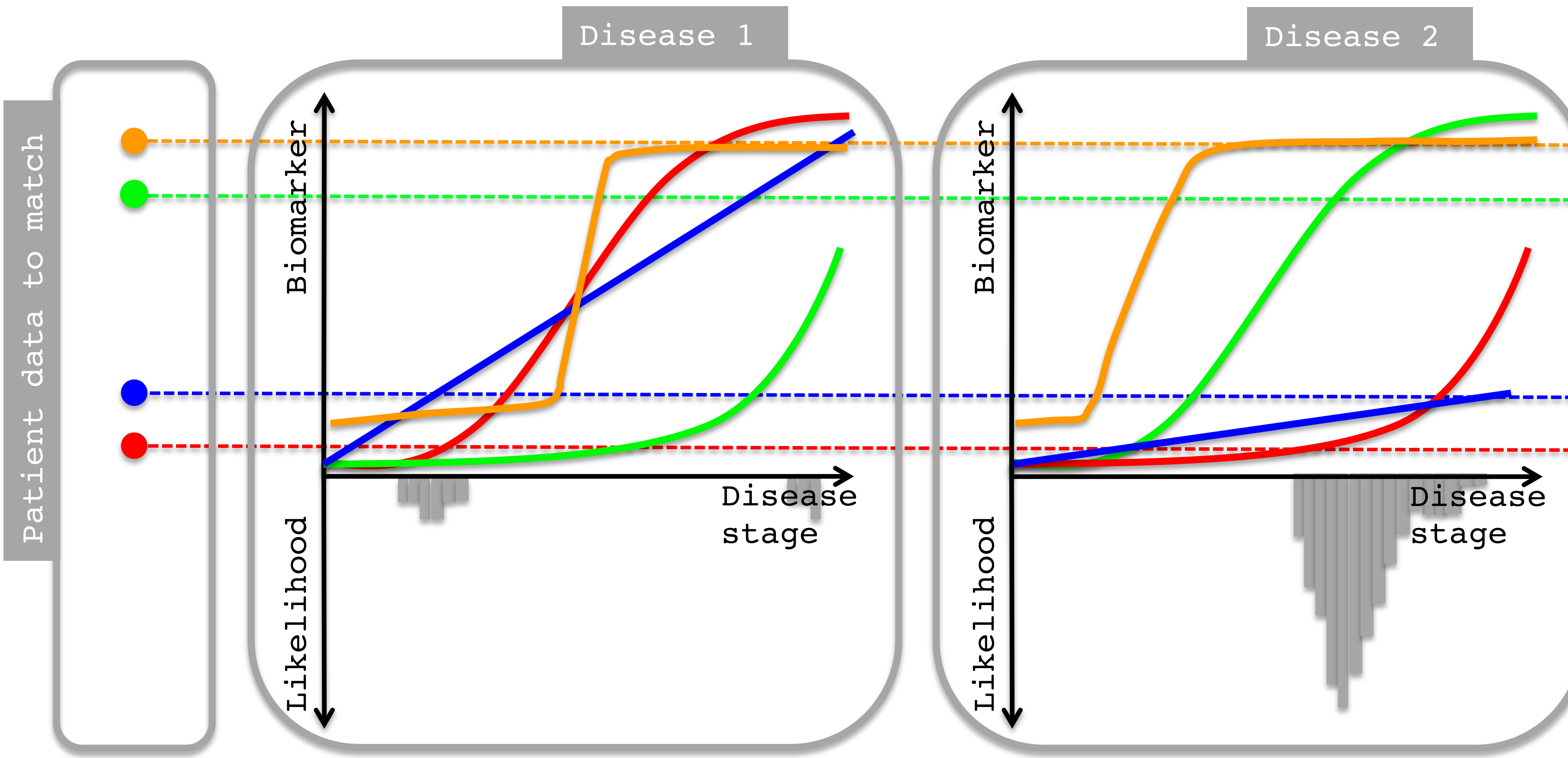

Traditional Models

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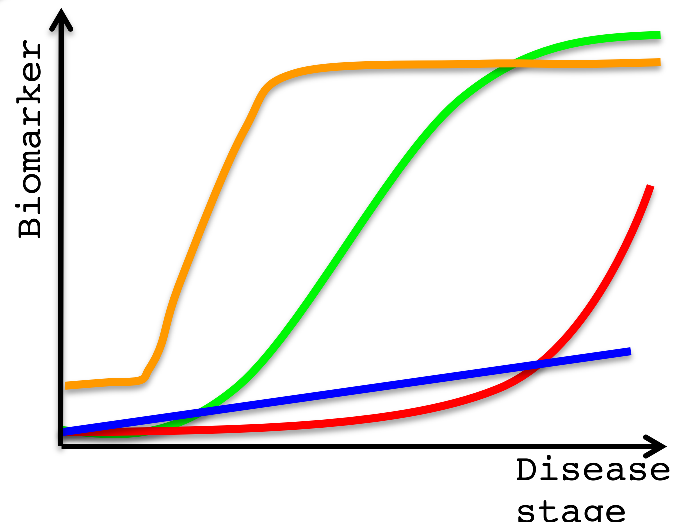

Unknown disease stage/time

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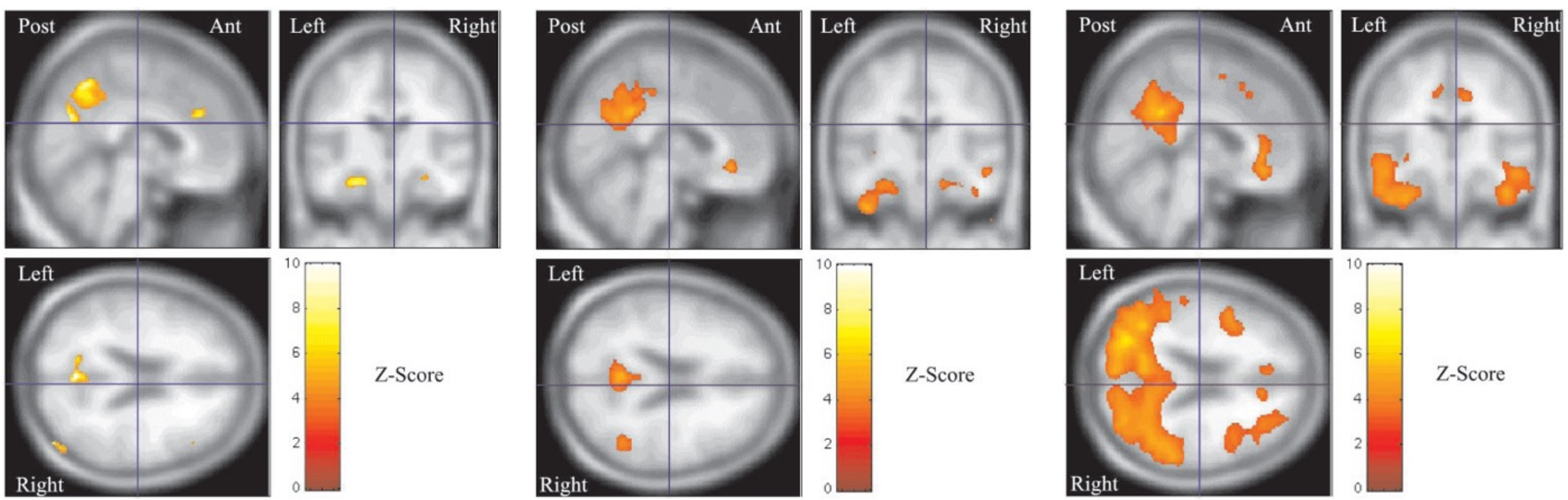
Traditional Models

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

Scahill et al. PNAS 2002

- T1 MRI measures of neuronal atrophy: subdivide using MMSE test

pre-symptomatic AD *mild AD* *moderate AD*



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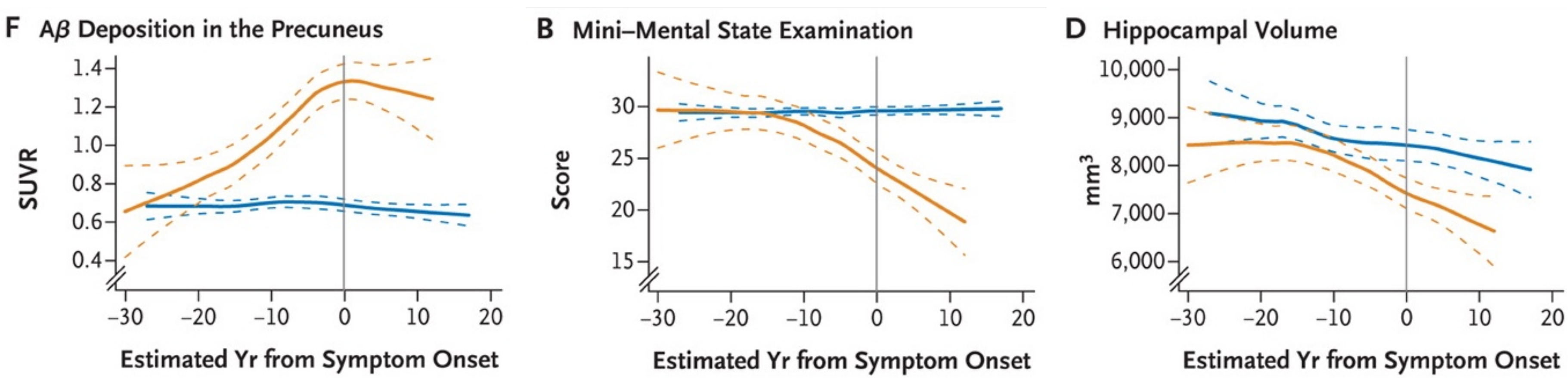
Traditional Models

- 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



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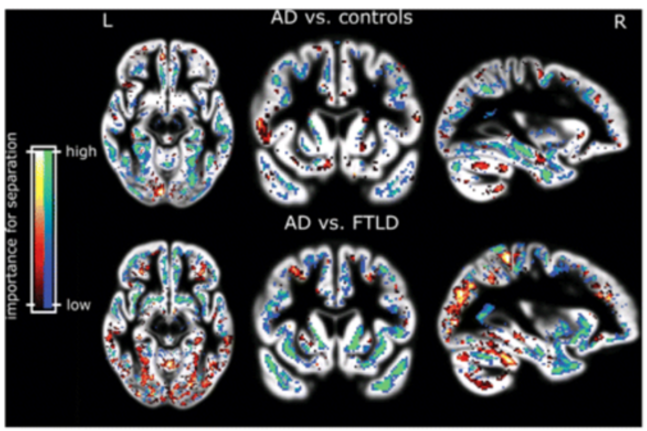
New Models 1

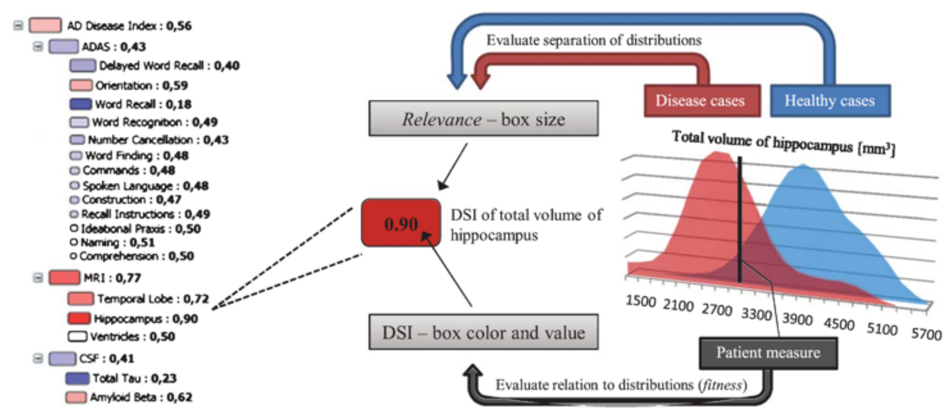
- Pattern recognition: supervised learning
  - Learn to classify patients from labelled data
  - Shown value of combining imaging and non-imaging data

Classifying structural MRI in AD



Klöppel et al. Brain 2008

Disease State Fingerprint for AD



Mattila et al. JAD 2011

pond

New Models 1

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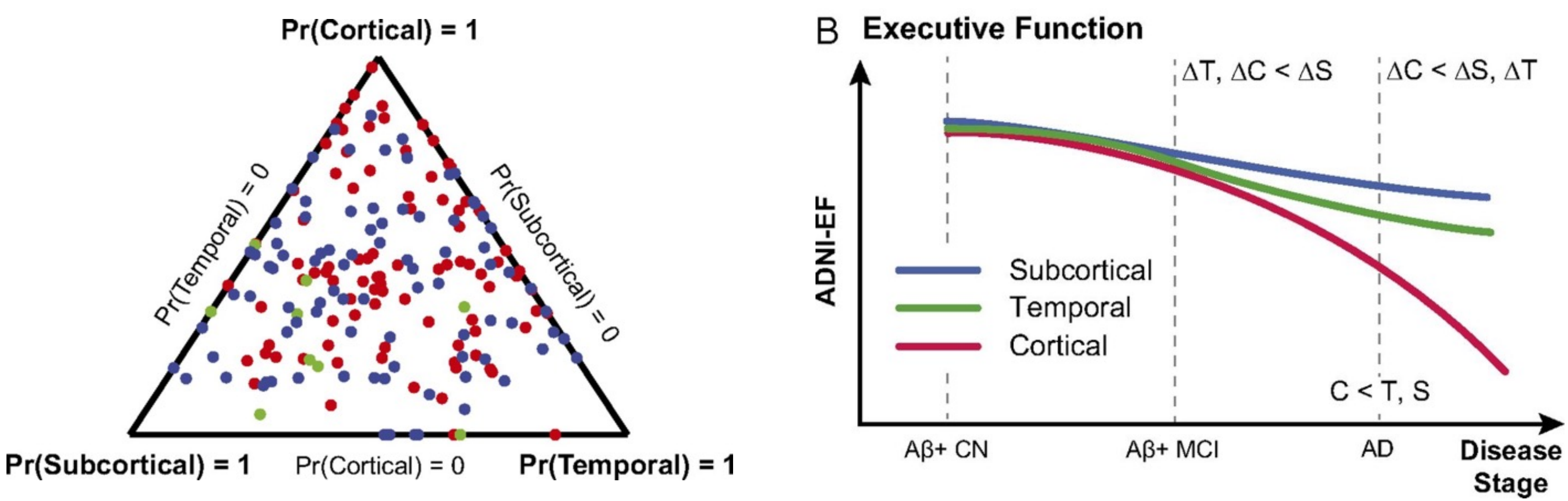
- Pattern discovery: unsupervised learning
  - Learn disease subtypes/stages automatically
  - Clustering

Clustering brain grey matter density to find atrophy "factors" in AD



Zhang et al. PNAS 2016

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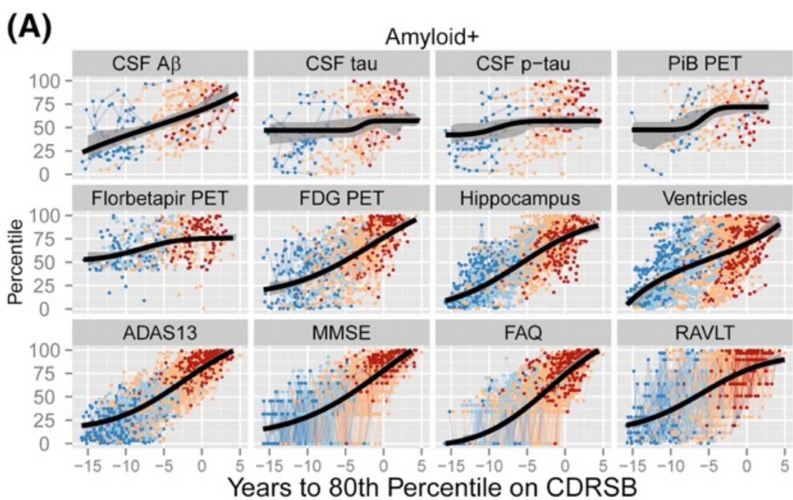
New Models 2

- **Generative** models
  - **Unstructured data**: scalar biomarkers, phenomenological

AD marker trajectories

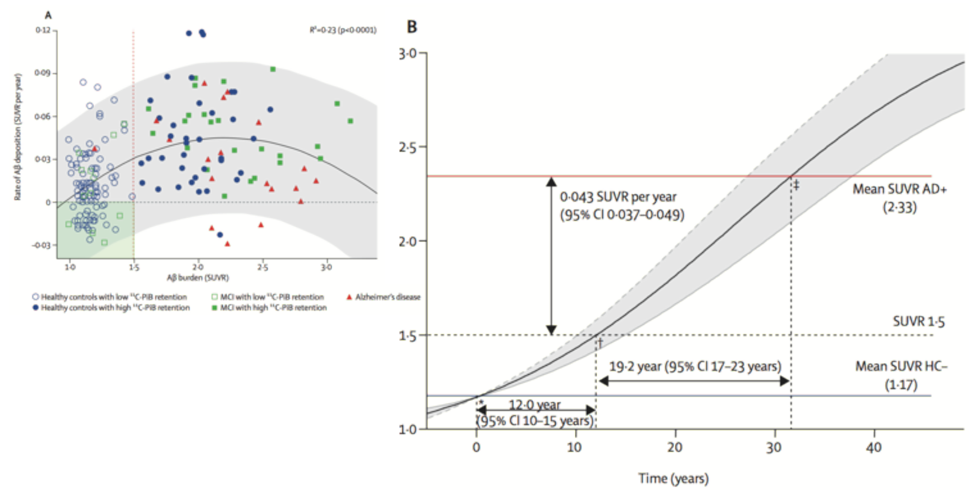
Self-modelling regression



Donohue et al. Alz. Dem. 2014

Related: **Jedynak et al. NeuroImage 2012**

Differential Equation Models



Villemagne et al. Lancet Neurol. 2013

Oxtoby et al. Brain 2018

New Models 2

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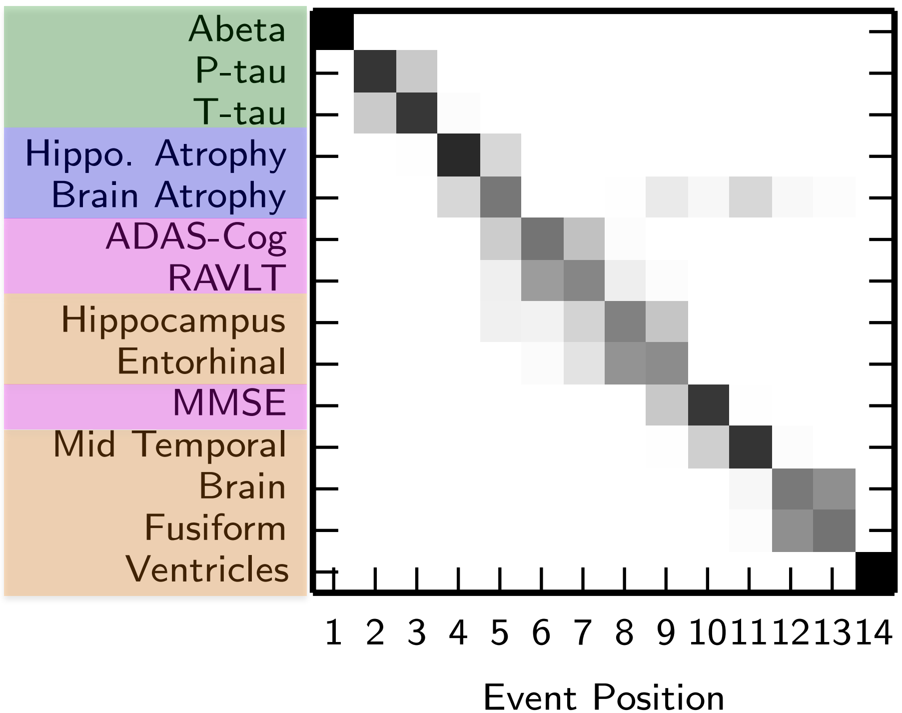
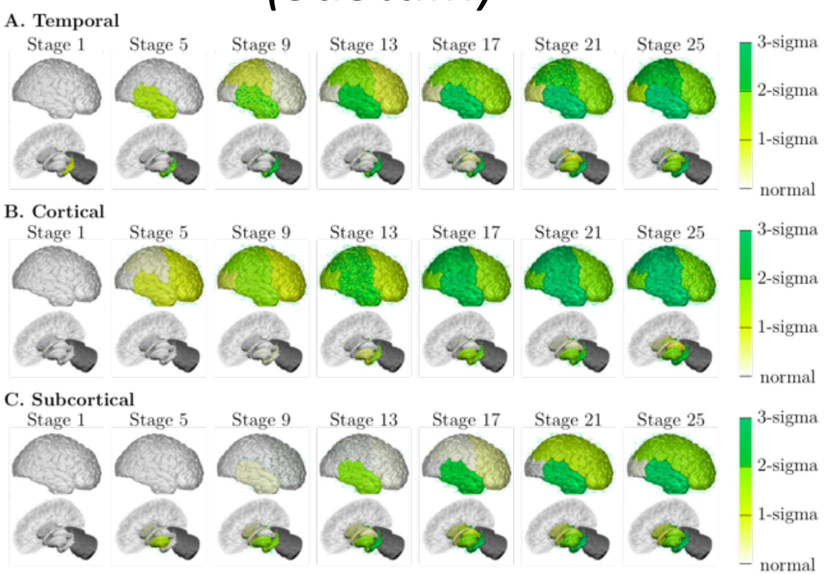
- **Generative** models
  - **Unstructured data**: scalar biomarkers, phenomenological

Event-based model



Fonteijn et al. NeuroImage 2012
Young et al. Brain 2014

Subtype & Stage Inference (SuStaIn)



Young et al. Nat. Comms 2018

New Models 2

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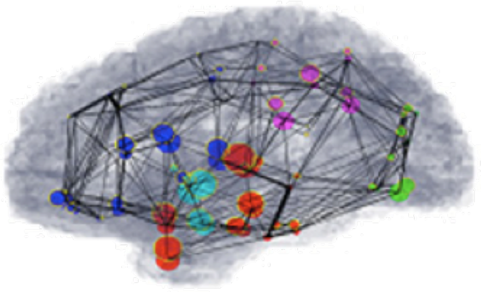
- **Generative** models
  - **Structured data**: spatial info. Images, connections
    - Spatiotemporal models: e.g. shape/image regression

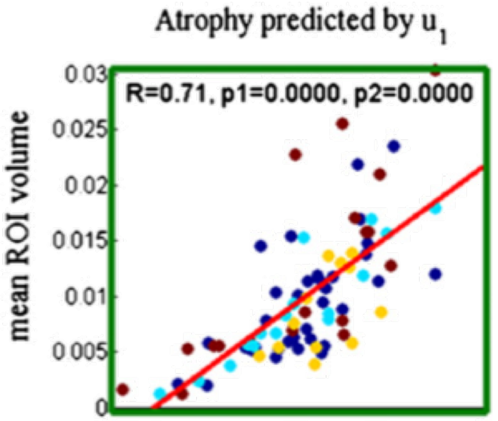
      Durrleman et al. IJCV 2013;
      Lorenzi et al. NeuroBiol Aging 2015

    - Network propagation models: e.g. prion-like transmission

      Raj et al. Neuron 2012;
      Iturria-Medina et al. PLOS Comp. Biol. 2014

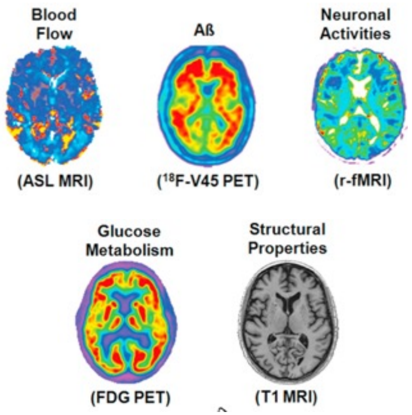


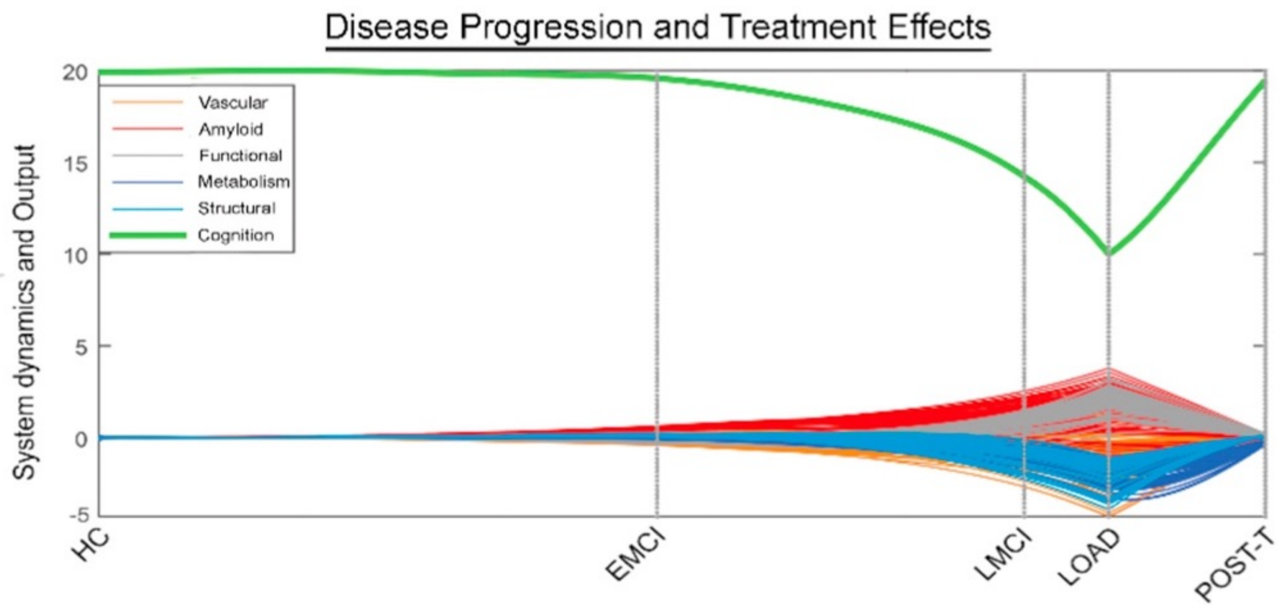
Connectivity predicts atrophy



New Models 3

- **Generative** models + *in silico* interventions
  - Image-based abnormality across the brain





Iturria-Medina et al. NeuroImage 2017,2018

Next step

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How can

computational modelling of AD progression

help clinical trials?

Example POND models…

Event-based Model

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

Data-driven: no prior knowledge of disease stage

NeuroImage 60 (2012) 1880–1889

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

ELSEVIER

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], Sebastien Ourselin [a,d,e], Nick C. Fox [e,g], Daniel C. Alexander [a,b]

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] Sebastien Ourselin,[1,2] Jonathan M. Schott[2,*] and Daniel C. Alexander[1,*]

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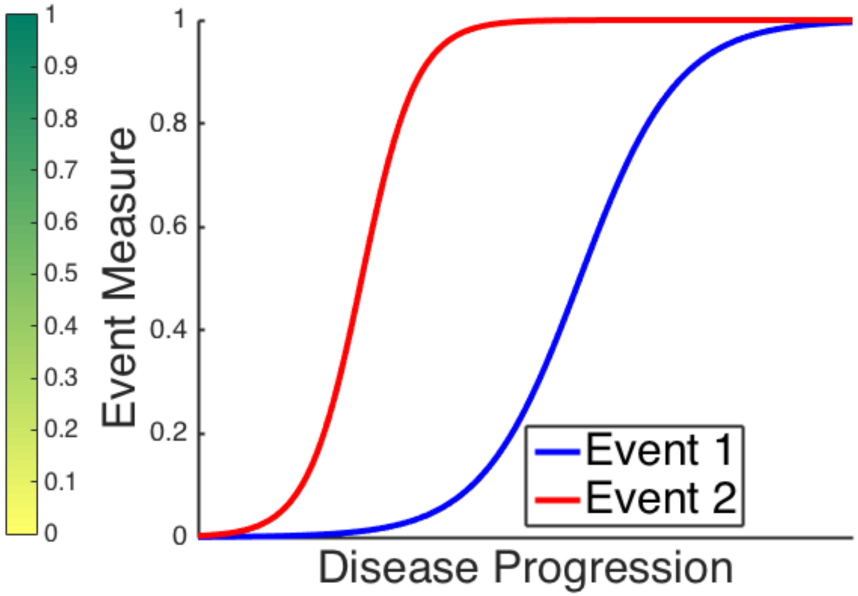
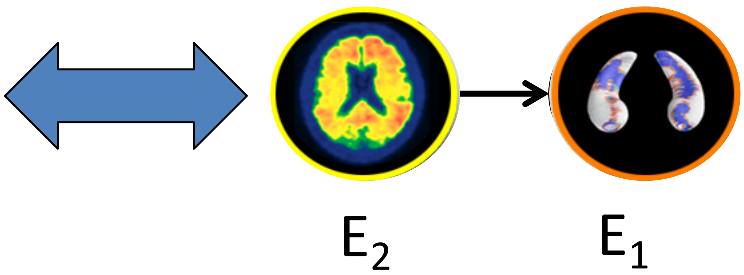
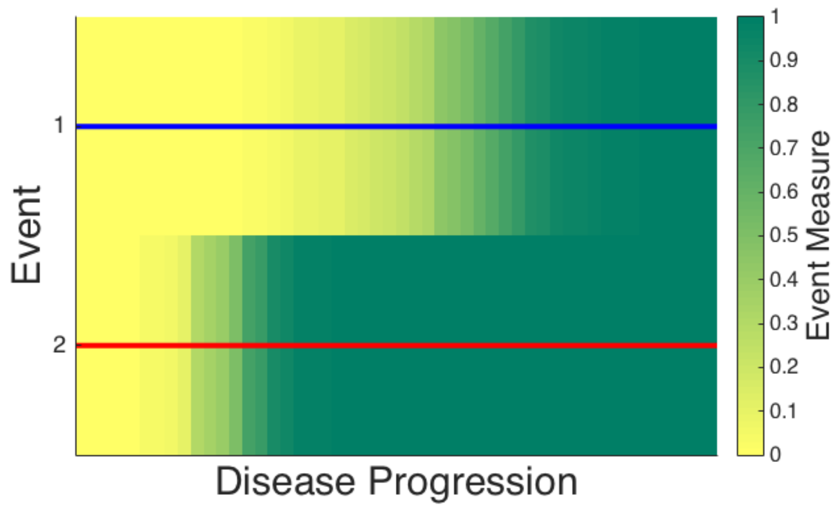
Event-based Model



After
Fonteijn et al. NeuroImage 2012





Event-based Model

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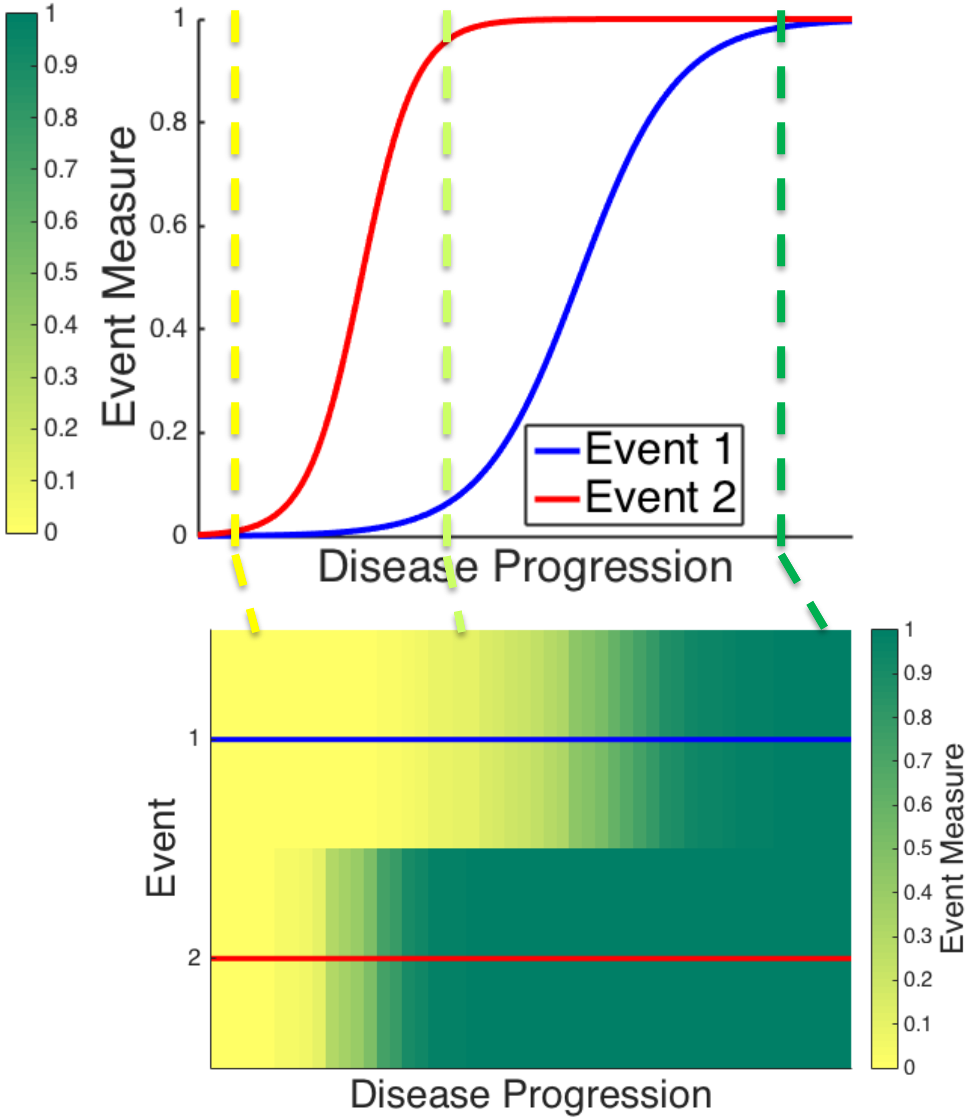

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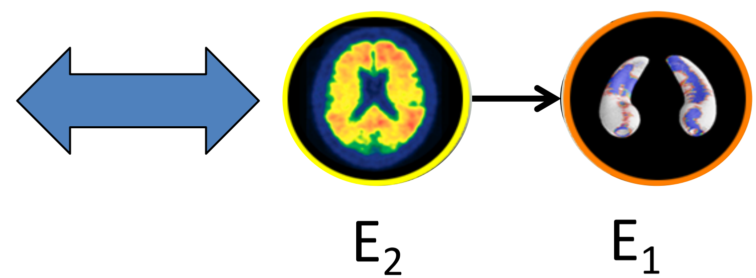

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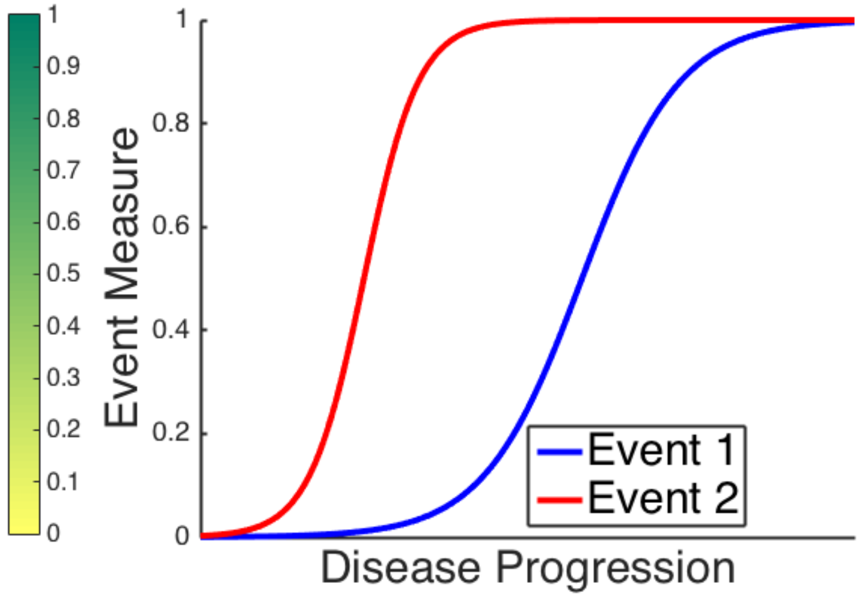

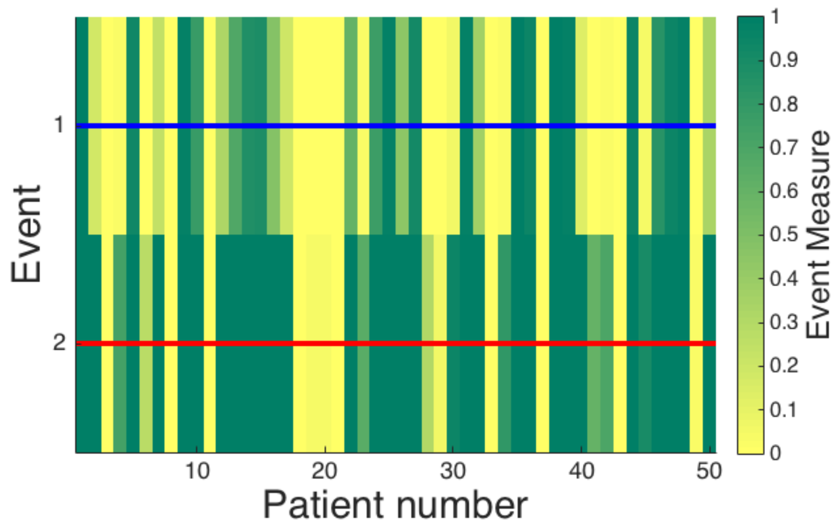

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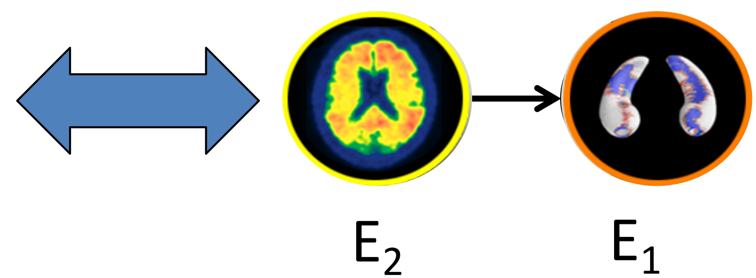

Staging individuals

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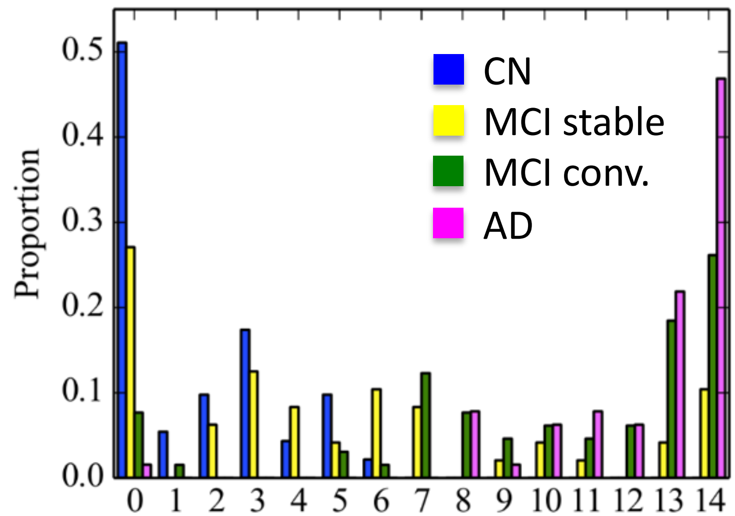
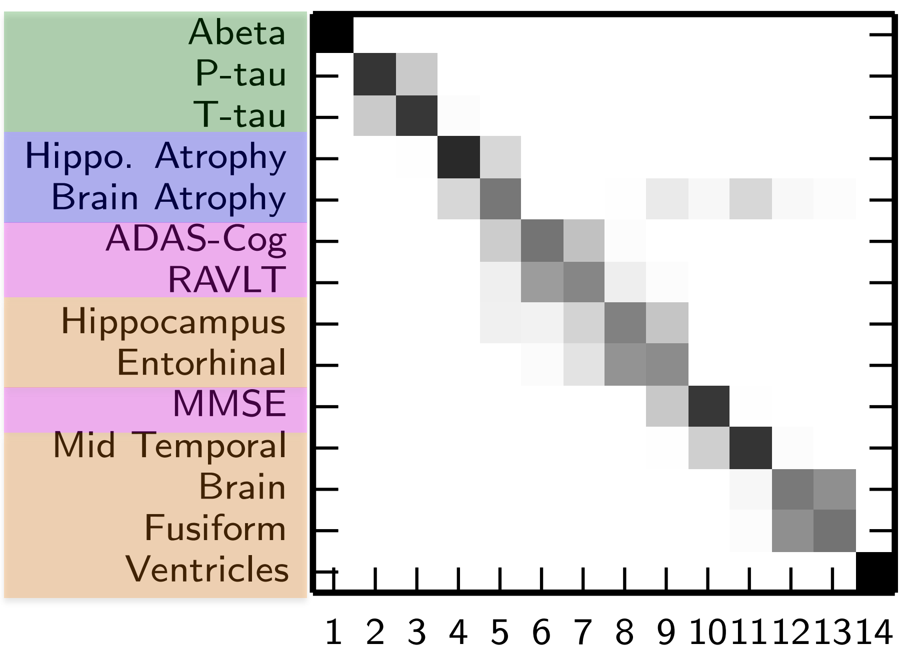
Young et al. Brain 2014





Model Stages:

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

Staging individuals

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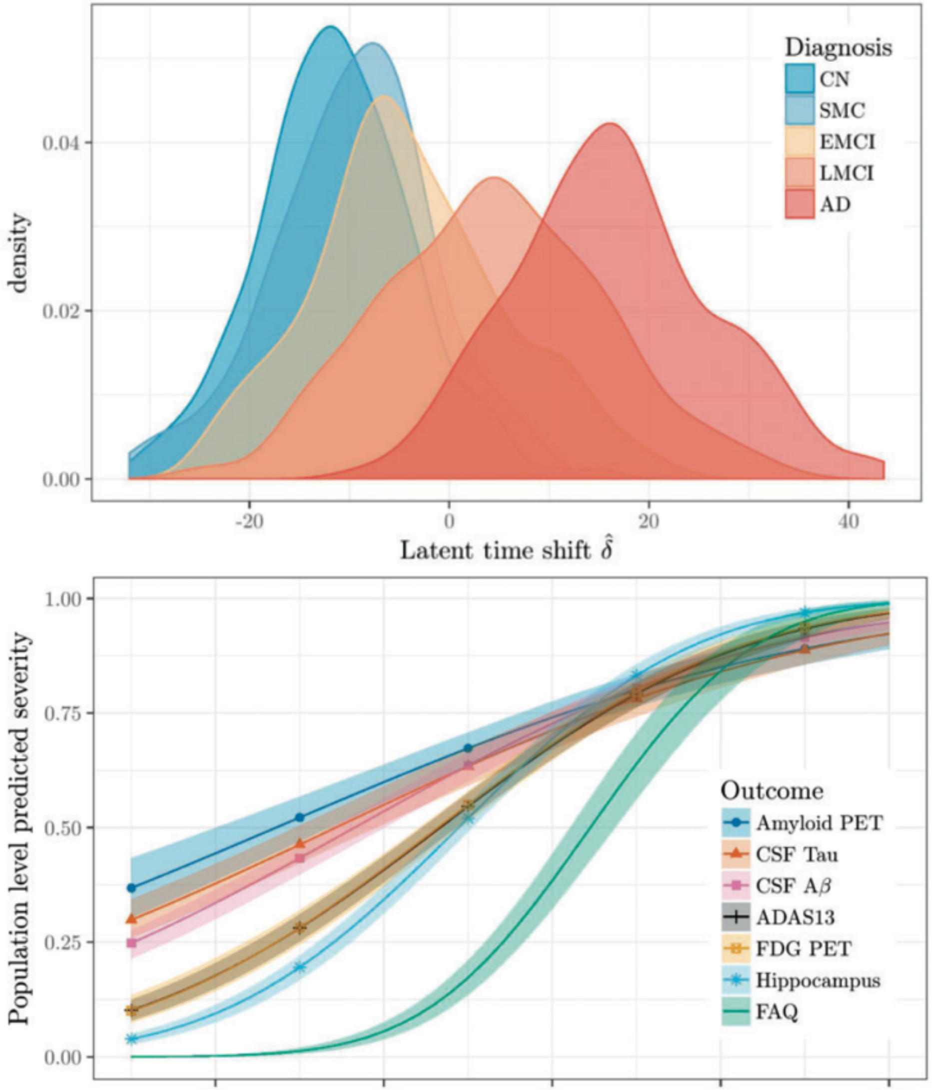
Li et al. Stat Meth Med Res 2017



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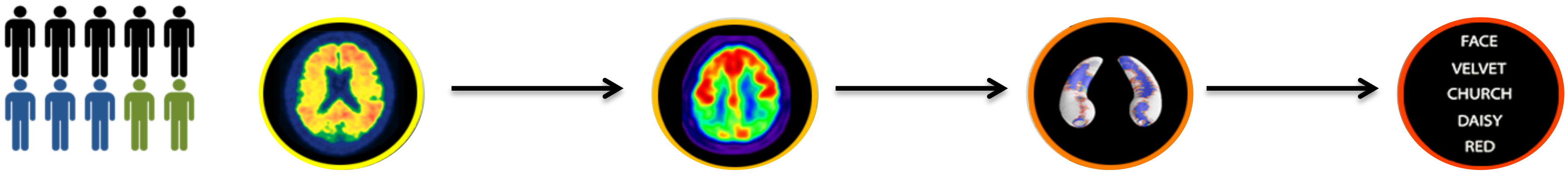
Young *et al.* IPMI 2015

Modification 1: Subtypes



Adapted from ADNI website figure

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Young *et al.* IPMI 2015

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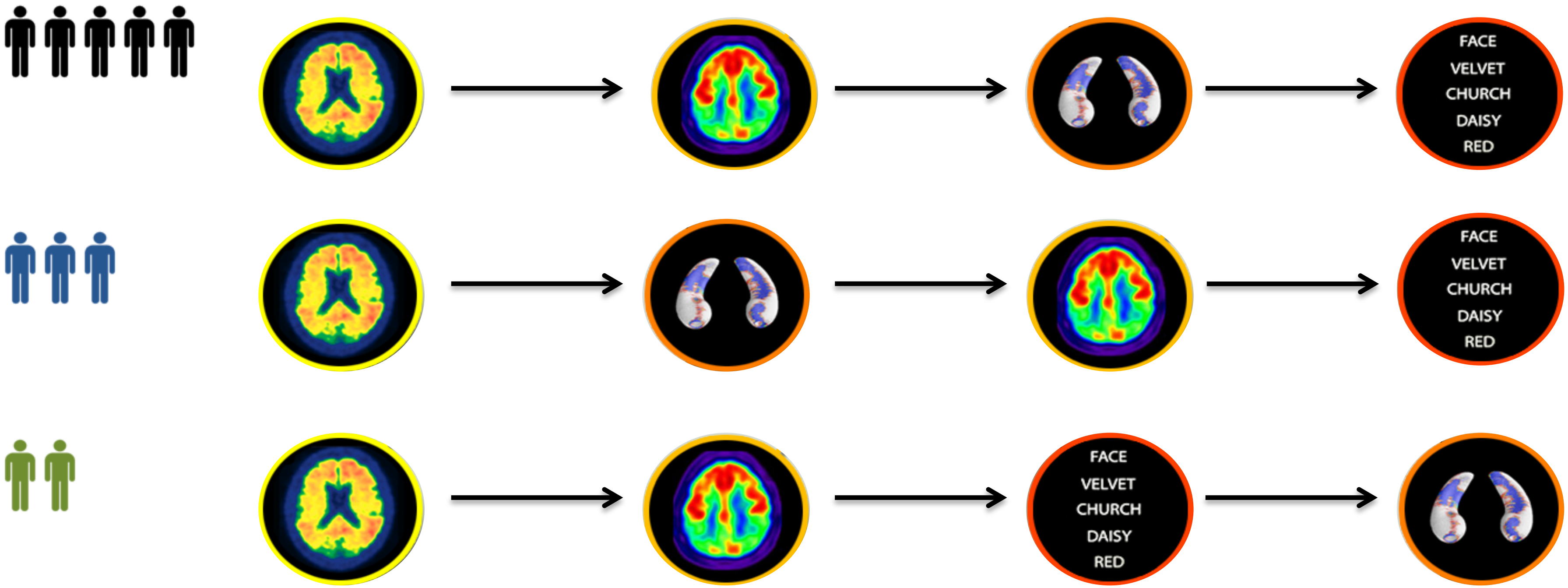

Adapted from ADNI website figure

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Young *et al.* Nature Comms. 2018

Modification 2: Z-score events

Adapted from ADNI website figure

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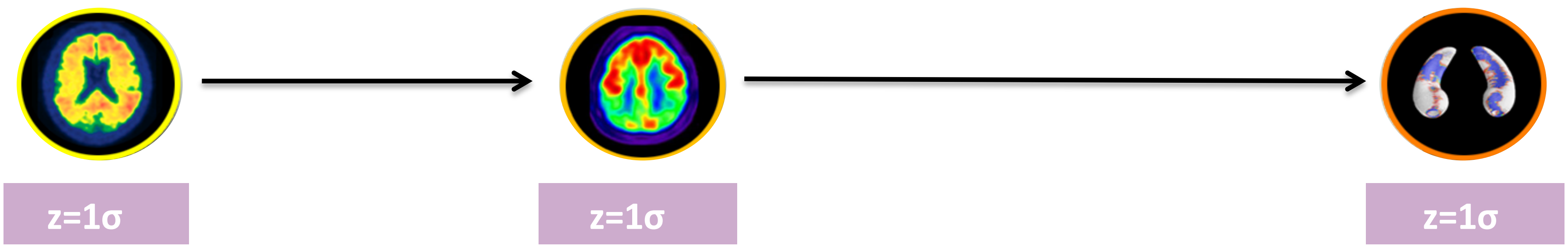
Young *et al.* Nature Comms. 2018

Modification 2: Z-score events



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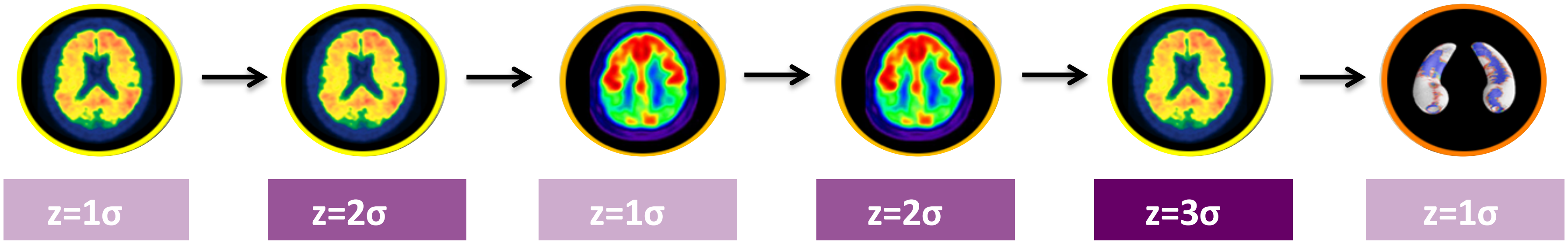
Modification 2: Z-score events



Adapted from ADNI website figure

Heterogeneity & Subtypes

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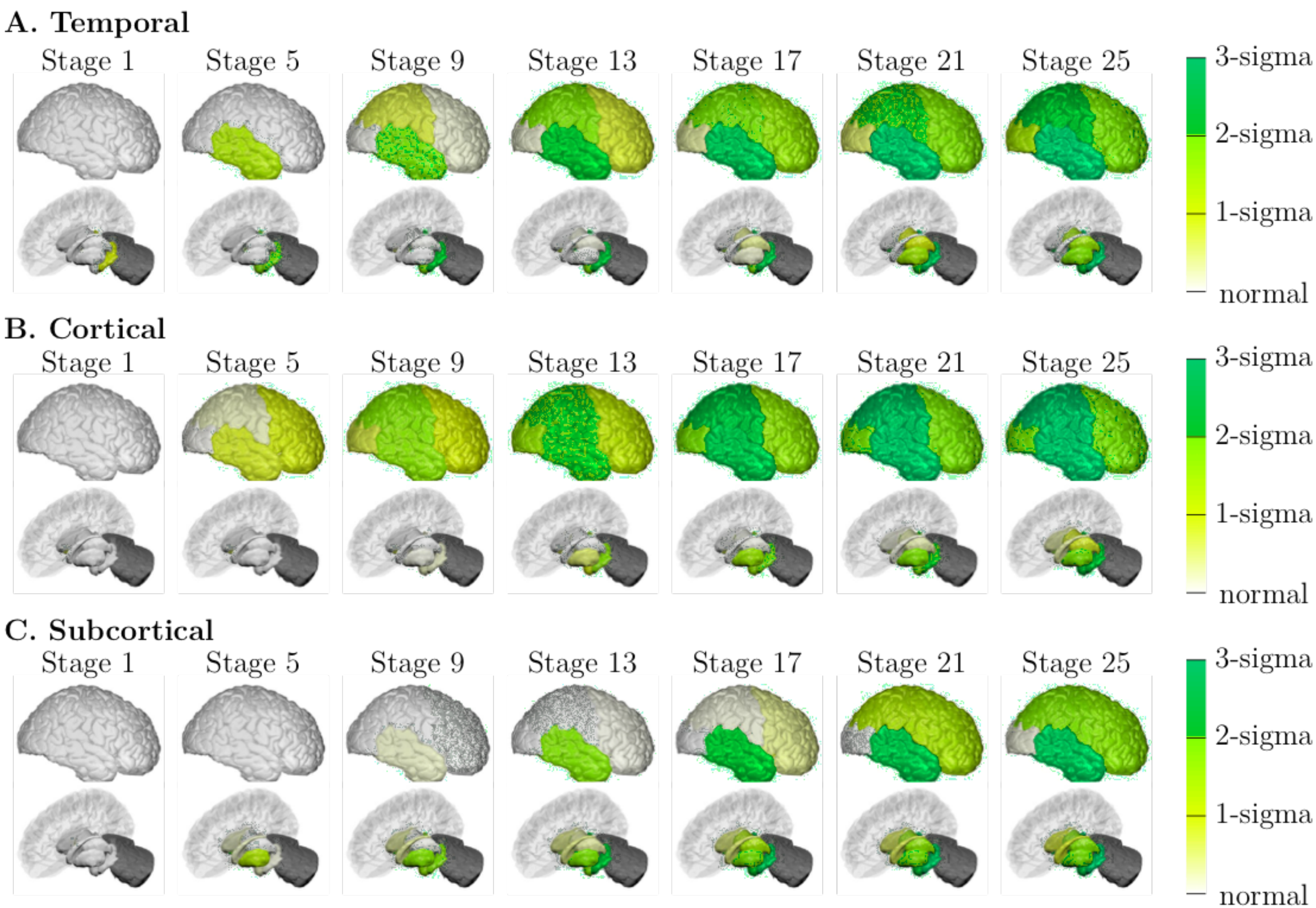
Young *et al.* Nature Comms. 2018



D^3PMs for Trials

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The long game:
Individualised models for precision staging and stratification

First step:
post hoc analyses of completed trials

D^3PM = Data Driven Disease Progression Model(ling)

UK Research and Innovation

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 9, 2005 VOL. 352 NO. 23

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

Table 2. Changes from Baseline in Cognitive and Functional Measures.*

Test	Change in Score from Baseline					
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
Cognitive and functional measures						
MMSE						
Donepezil	0.06±2.03†	−0.31±2.25‡	−0.52±2.46‡	−0.98±2.54‡	−1.47±3.04	−2.31±3.72
Vitamin E	−0.53±2.28	−0.54±2.28	−0.96±2.61	−1.21±2.78	−1.75±3.09	−2.20±3.64
Placebo	−0.36±2.02	−0.80±2.34	−1.02±2.61	−1.49±2.90	−1.77±3.24	−2.75±4.04
Activities of Daily Living Scale						
Donepezil	−0.21±3.43	−1.41±4.48	−1.78±5.02	−3.09±6.24	−4.44±7.39	−6.26±8.67
Vitamin E	−0.34±4.29	−1.08±4.90	−2.13±5.76	−2.84±6.16	−4.16±7.46	−5.63±8.75
Placebo	−1.06±4.54	−1.44±5.00	−2.34±6.02	−3.43±6.73	−5.00±8.05	−6.39±8.99
CDR sum of boxes						
Donepezil	0.05±0.66	0.25±0.92‡	0.51±1.18‡	0.87±1.55	1.19±1.69	1.60±2.09
Vitamin E	0.17±0.70	0.51±1.21	0.75±1.44	1.02±1.76	1.26±1.89	1.67±2.18
Placebo	0.14±0.86	0.40±1.28	0.72±1.55	0.97±1.76	1.26±2.15	1.64±2.55

D^3PMs for Trials

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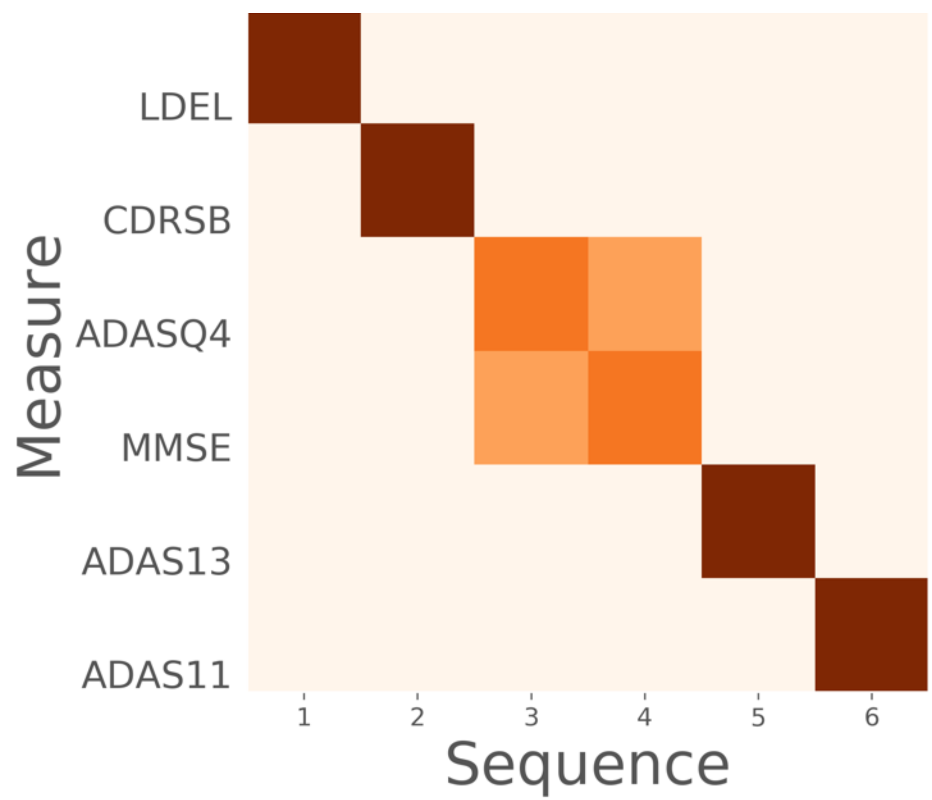

1. Build model (ADNI data)
2. Stage trial data (BL/SC)
3. Stratify
4. Analyse subgroups

UK Research and Innovation

D^{3}PMs for Trials

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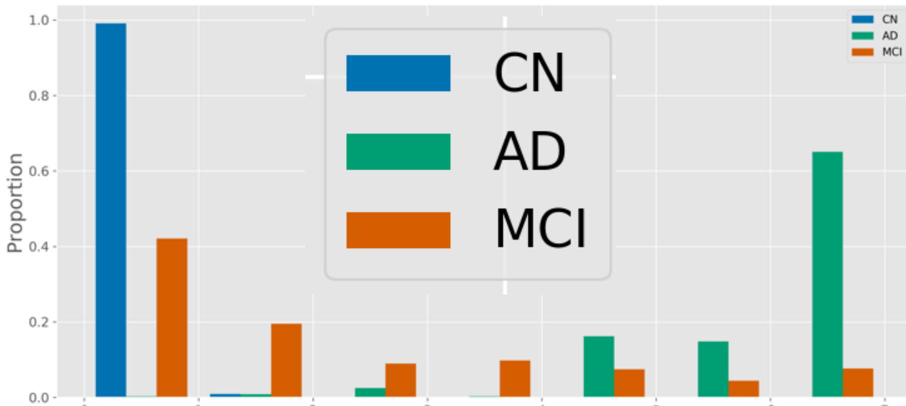

ɔnepezil for the Treatment
gnitive Impairment

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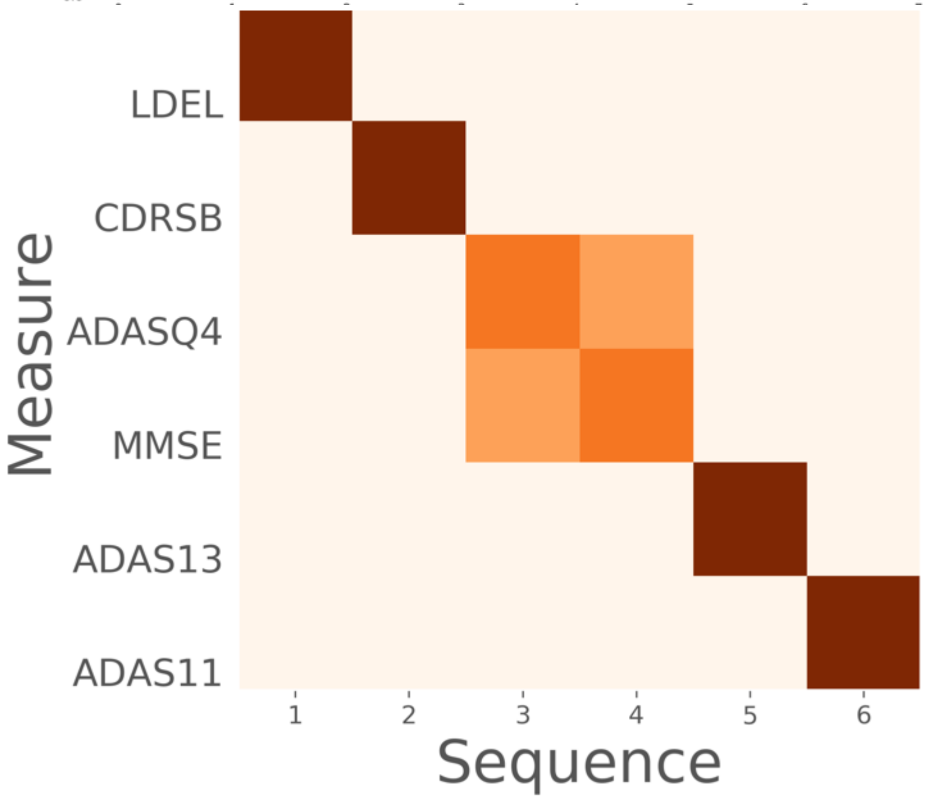
llan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D.,
l, M.D., for the Alzheimer's Disease Cooperative Study Group*



1. Build model (ADNI data)

UK Research and Innovation

FLF: D^3PMs for Trials

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Aims of my Future Leaders Fellowship:
"Individualised AI for Medicine"

- Models for individualised **prediction**
  - Precision staging & stratification: Right recruits/time
- Translate into **drug development tool**
- Models for disease **mechanisms**
- Role for **AI** (ML / DL) & novel biomarkers
  - Part of my training: future leader

Post doc position available in 2020

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