Computational Modelling of Alzheimer's disease for Clinical Trials

Neil Oxtoby, PhD
UKRI Future Leaders Fellow
Progression **O**f **N**eurodegenerative **D**isease (POND) group
Centre for Medical Image Computing (CMIC)
Department of Computer Science, UCL

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 666992

My quest for Supermodels and Drugs

Neil Oxtoby, PhD
UKRI Future Leaders Fellow
Progression **O**f **N**eurodegenerative **D**isease (POND) group
Centre for Medical Image Computing (CMIC)
Department of Computer Science, UCL

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 666992

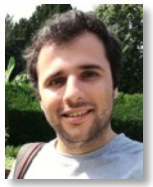
Acknowledgements

n.oxtoby@ucl.ac.uk

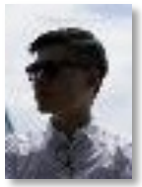


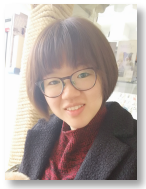




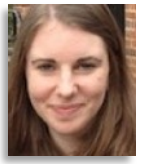



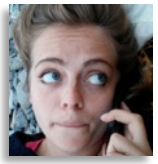
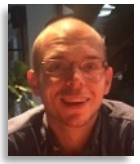






- POND: pond.cs.ucl.ac.uk
  - Alex Young, Danny Alexander, et al.
  - EuroPOND*: europond.eu
- CMIC: www.ucl.ac.uk/cmic
- Links: COMBINE lab, DRC, MS@ION, HD, UCLIC, HDRUK, Lung Imaging, Cole Miners




*This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 666992

The AD Challenge

n.oxtoby@ucl.ac.uk

- 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?

*Caveat on next slide

Aducanumab?

n.oxtoby@ucl.ac.uk

- 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?

n.oxtoby@ucl.ac.uk
UCL

ALZFORUM
NETWORKING FOR A CURE

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

Aducanumab?

n.oxtoby@ucl.ac.uk

The AD Challenge

n.oxtoby@ucl.ac.uk
UCL

- 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

n.oxtoby@ucl.ac.uk

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

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

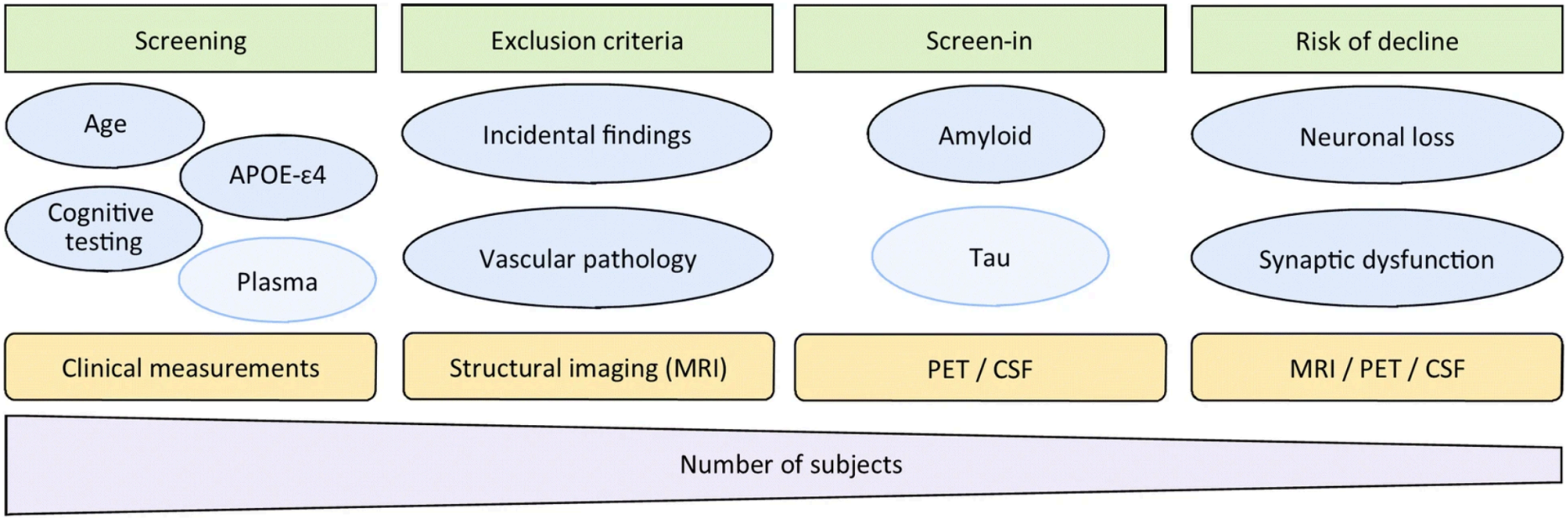
Take-home message

n.oxtoby@ucl.ac.uk

- 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)

Existing work

n.oxtoby@ucl.ac.uk

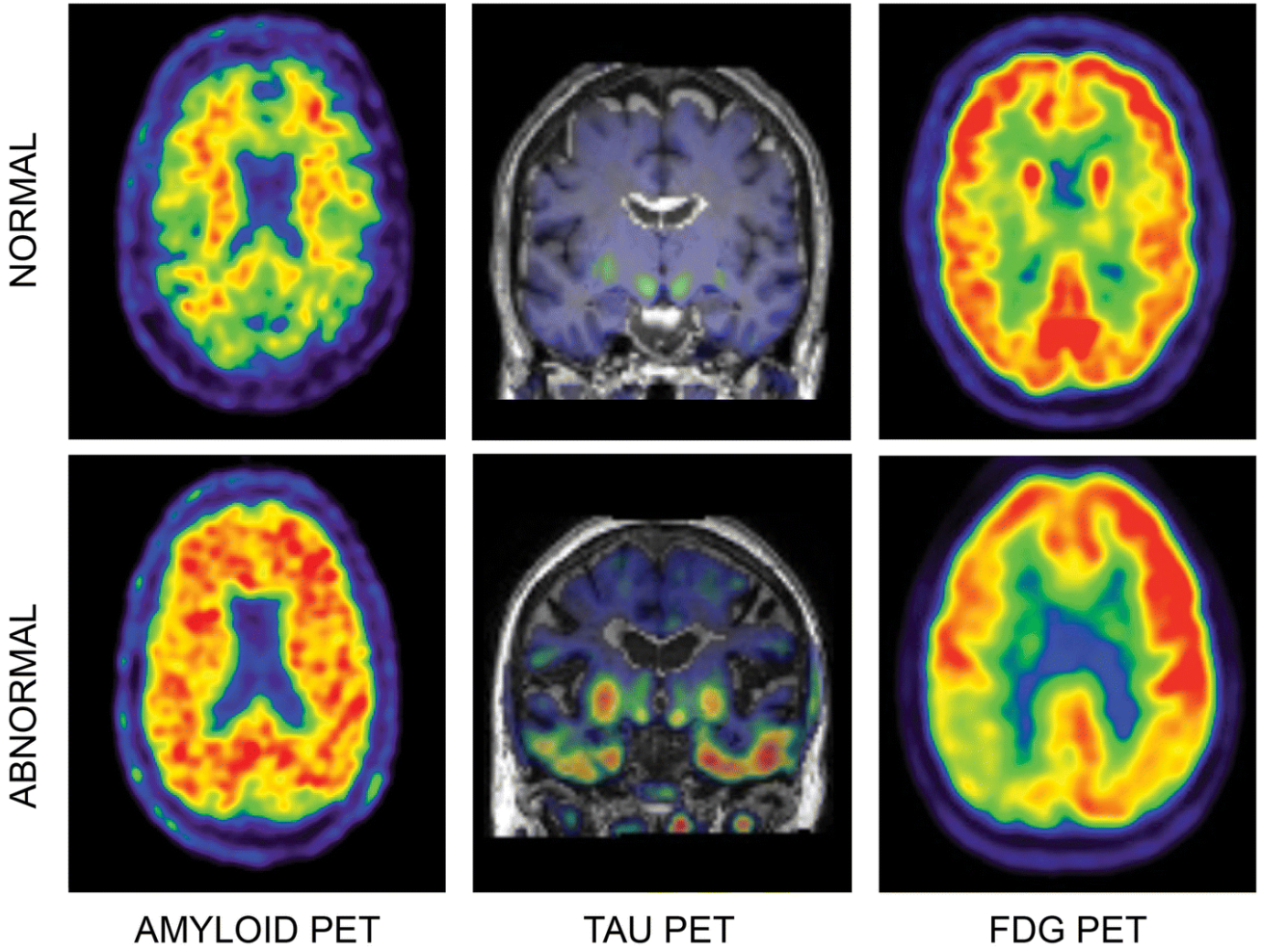


M. ten Kate et al., Alz. Res. Therapy (2018)

See also: **D. Cash et al., Alz. Res. Therapy (2014)**

Existing work

n.oxtoby@ucl.ac.uk
UCL



M. ten Kate et al., Alz. Res. Therapy (2018)

Existing work

n.oxtoby@ucl.ac.uk
UCL

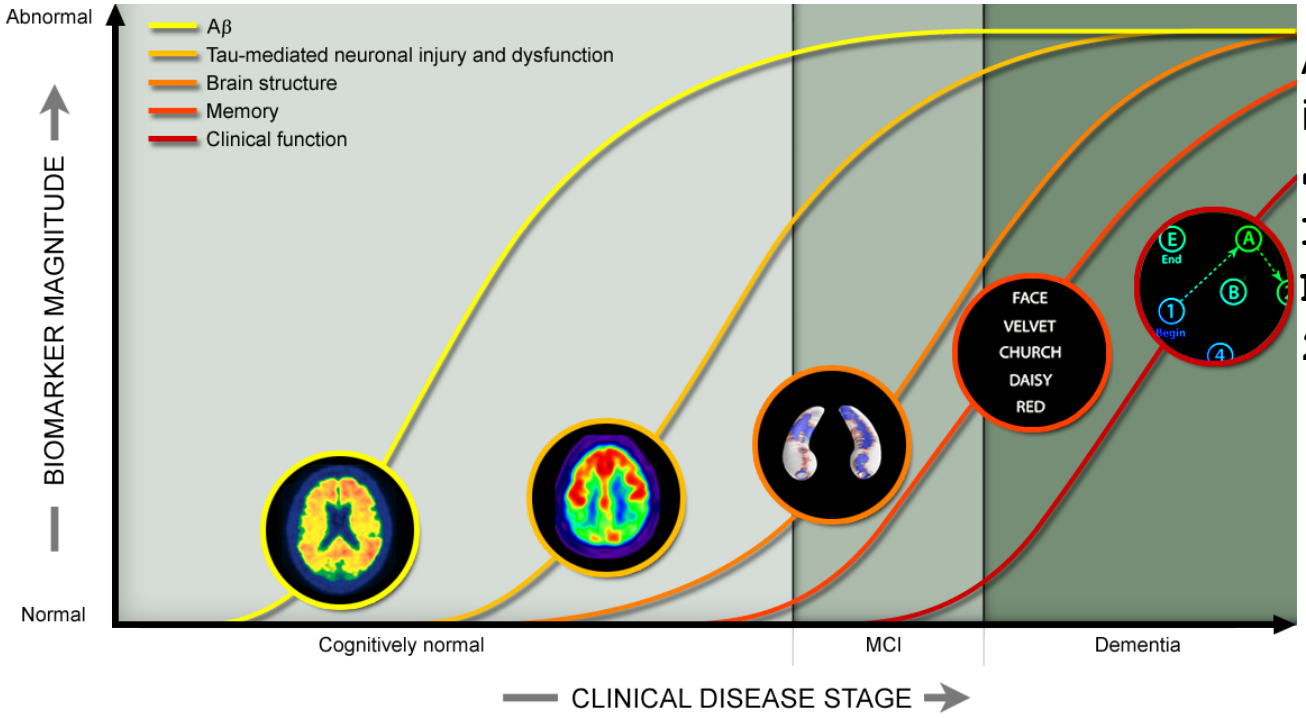
- Imaging: inclusion criteria (& endpoints)
  - Amyloid and volumetric imaging

- Alzheimer's Disease Neuroimaging Initiative
  - "discover, optimize, standardize, and validate clinical trial measures and biomarkers used in AD clinical research"

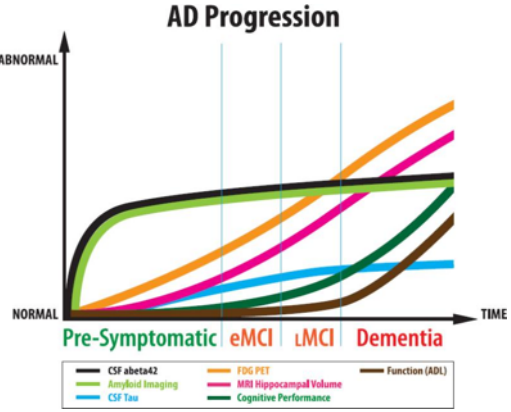
    [ADNI website, 2020]
- THE global benchmark
  - Protocols
  - 1800 papers

AD Progression

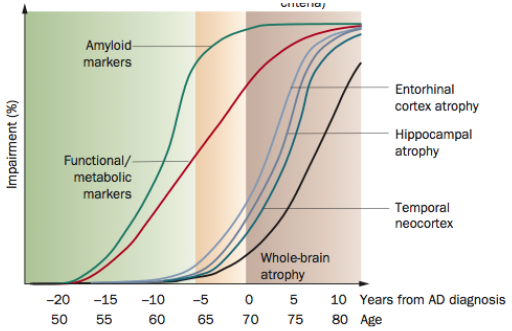
n.oxtoby@ucl.ac.uk



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



Aisen et al. Alz. Dement. 2010

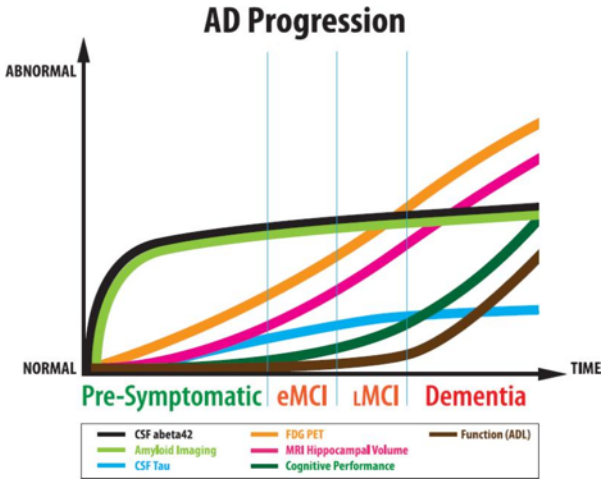


Frisoni et al Nat. Rev. Neurol. 2010

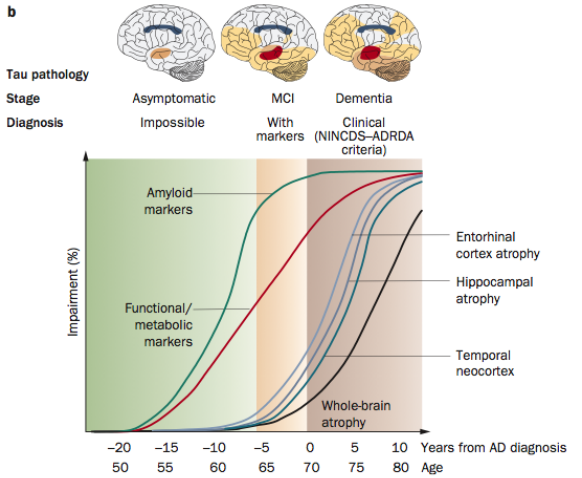
Progression Modelling

n.oxtoby@ucl.ac.uk

- Quantitative **signature** of how a disease plays out over time
- Biomarker based: also symptoms, pathologies
- Utility: precision staging; diagnosis; prognosis



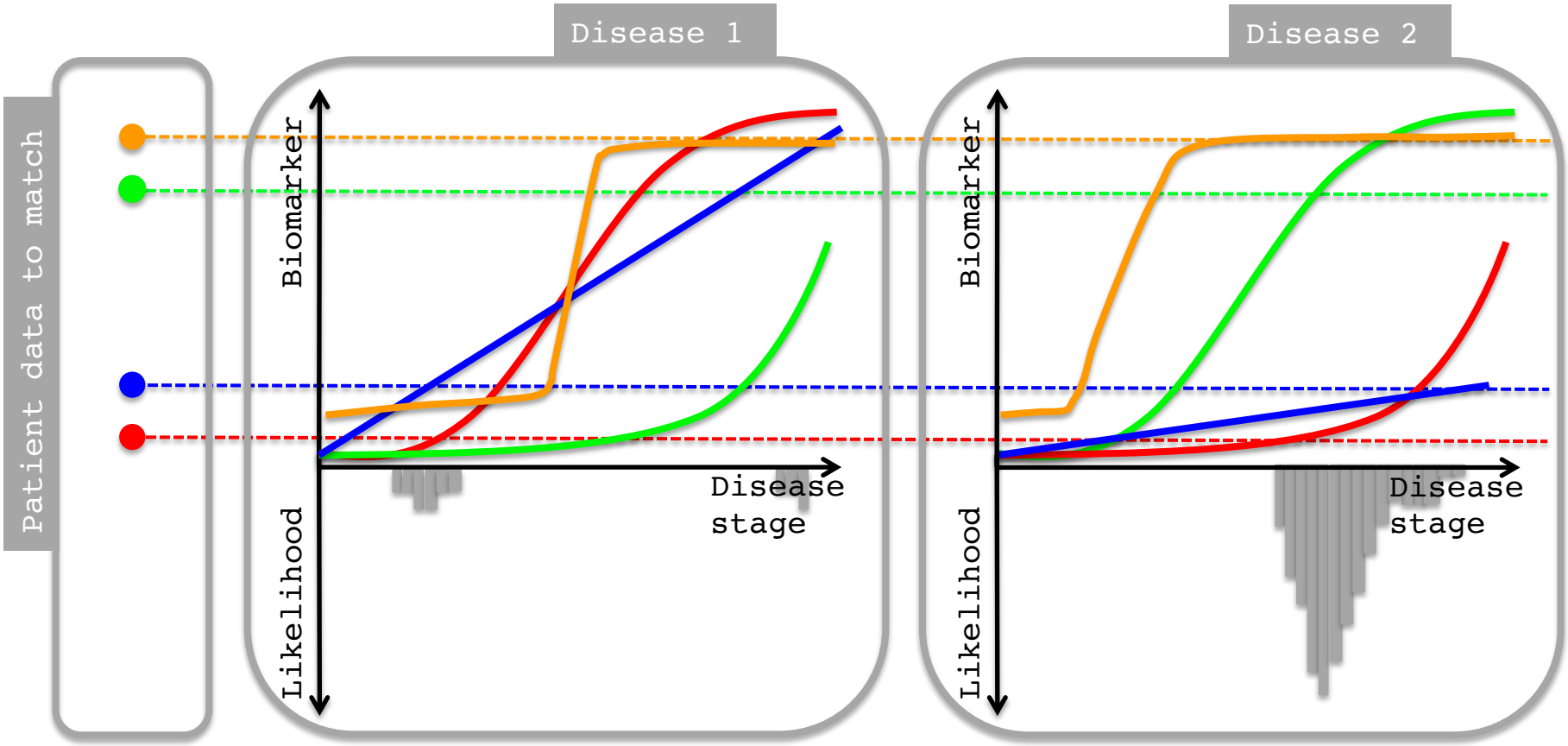
Aisen et al. Alz. Dement. 2010



Frisoni et al. Nat. Rev. Neurol. 2010

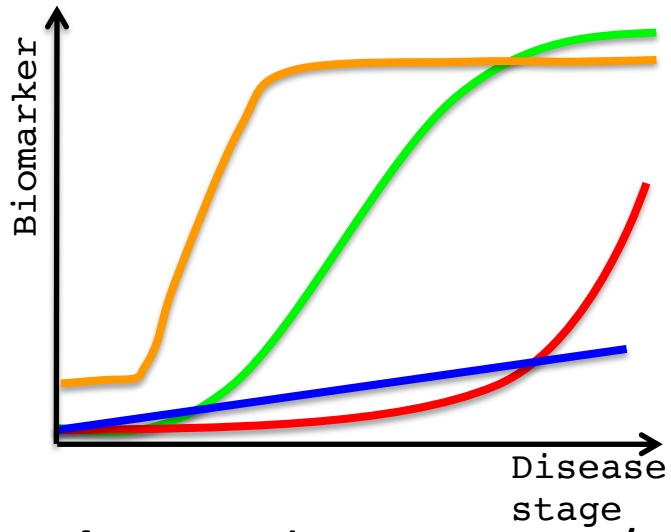
Diagnosis & Staging

n.oxtoby@ucl.ac.uk



Traditional Models

n.oxtoby@ucl.ac.uk



Unknown disease stage/time

Traditional Models

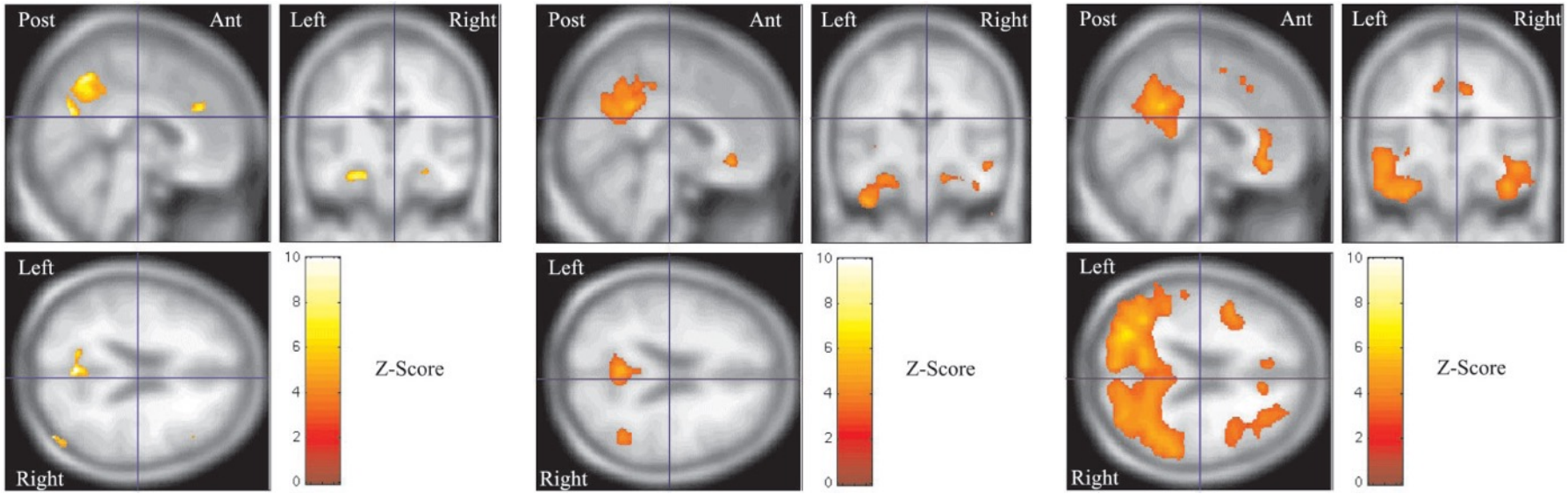
n.oxtoby@ucl.ac.uk

- Disease stage = symptoms (e.g. MMSE scores)
  - Crude group differences

Scahill et al. PNAS 2002

- T1 MRI measures of neuronal atrophy

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



n.oxtoby@ucl.ac.uk

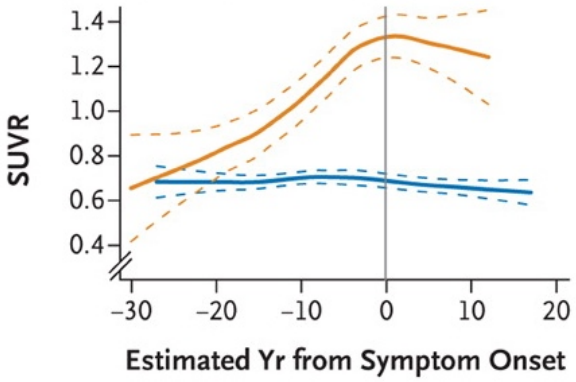
Traditional Models

- Heritable diseases: estimable stage (± 5 years)
  - *Autosomal dominant AD: familial age of onset*

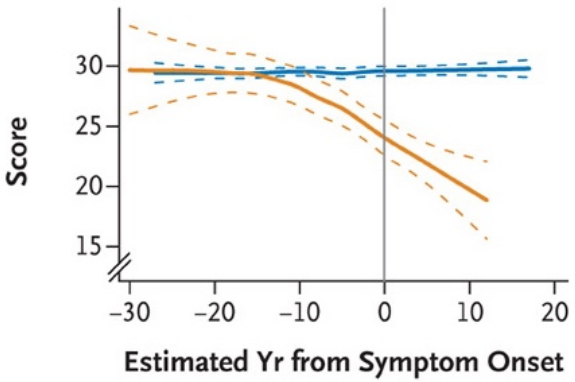
Bateman et al. NEJM 2012

- Imaging and clinical biomarkers

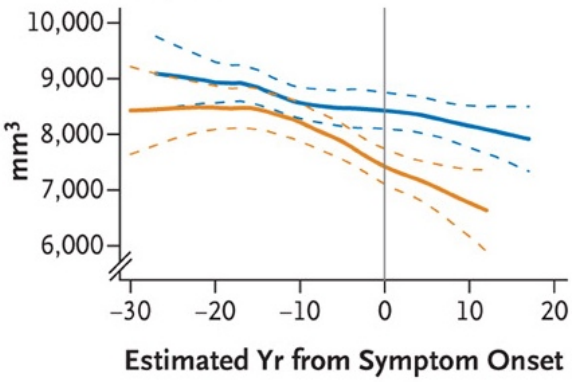
Amyloid PET (precuneus)



MMSE



Hippocampus volume

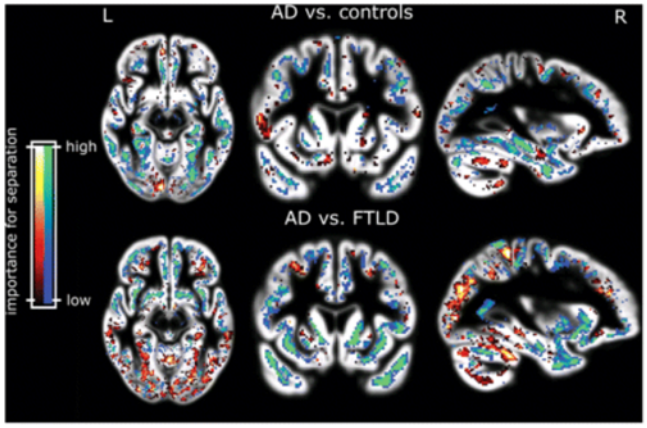


n.oxtoby@ucl.ac.uk

Machine Learning

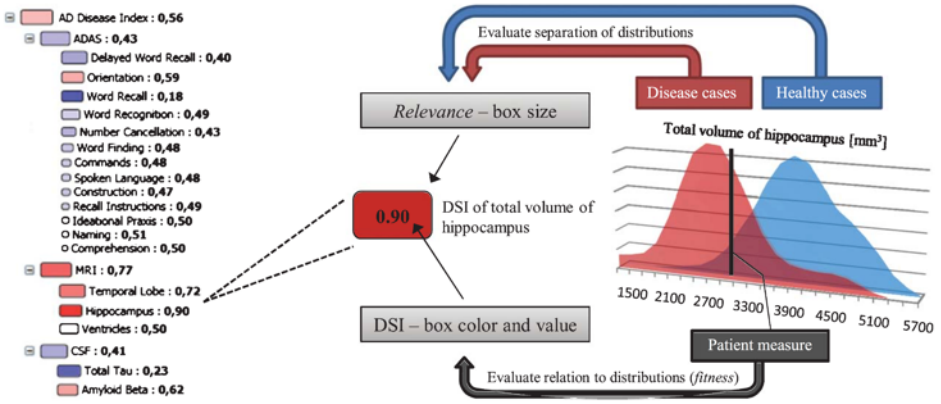
- Pattern recognition: **supervised** learning
  - Learn to classify patients from labelled data
  - Shown value of combining imaging and non-imaging data

Classifying structural MRI in AD



Klöppel et al. Brain 2008

Disease State Fingerprint for AD



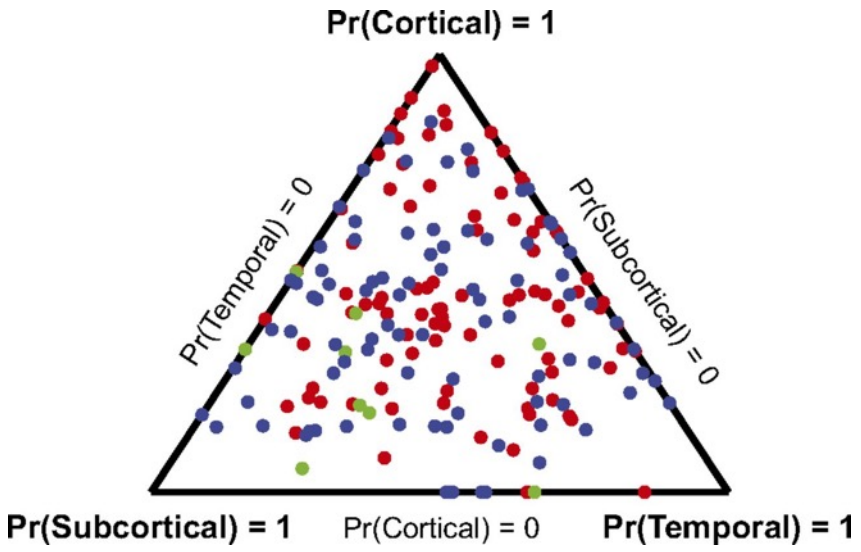
Mattila et al. JAD 2011

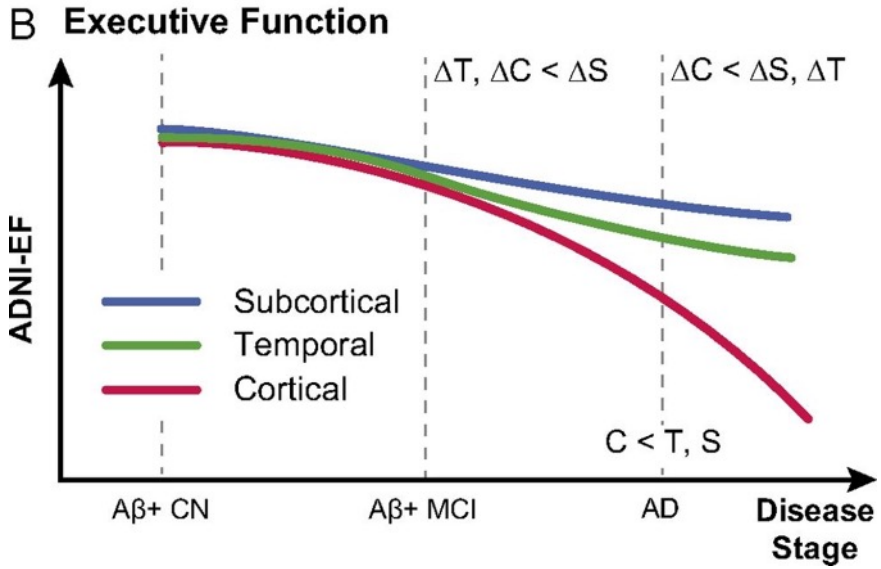
Machine Learning

n.oxtoby@ucl.ac.uk
UCL

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

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





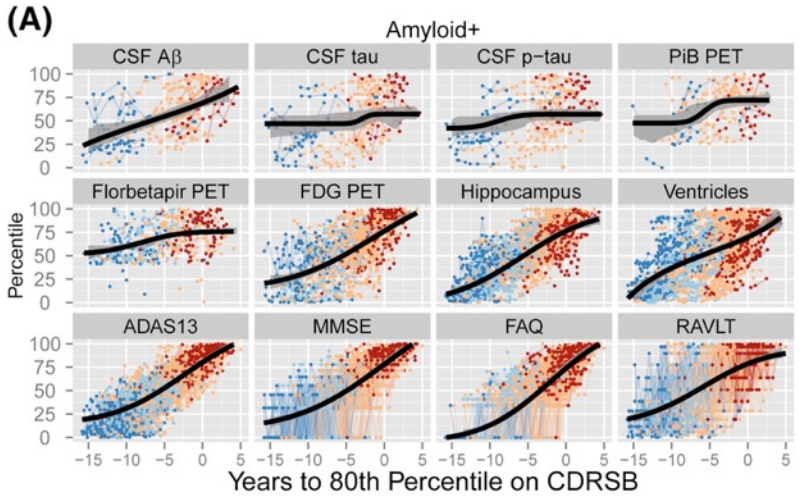
Zhang et al. PNAS 2016

Generative Models 1

n.oxtoby@ucl.ac.uk

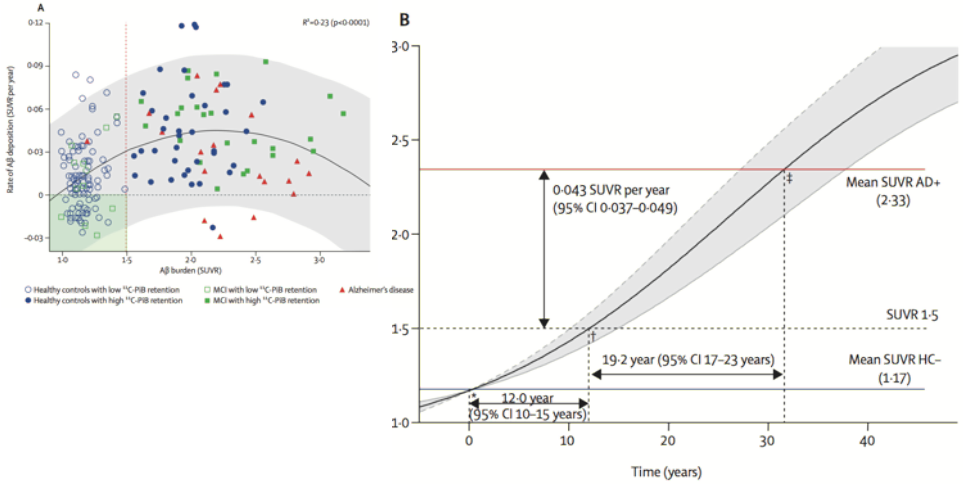
- **Unstructured data**: scalar biomarkers, phenomenological
  - Continuous: biomarker trajectories

Self-modelling regression



Donohue et al. Alz. Dem. 2014 (2017)
Jedynak et al. NIMG 2012; (2015;2019)
Lorenzi et al. NIMG 2017

Differential Equation Models



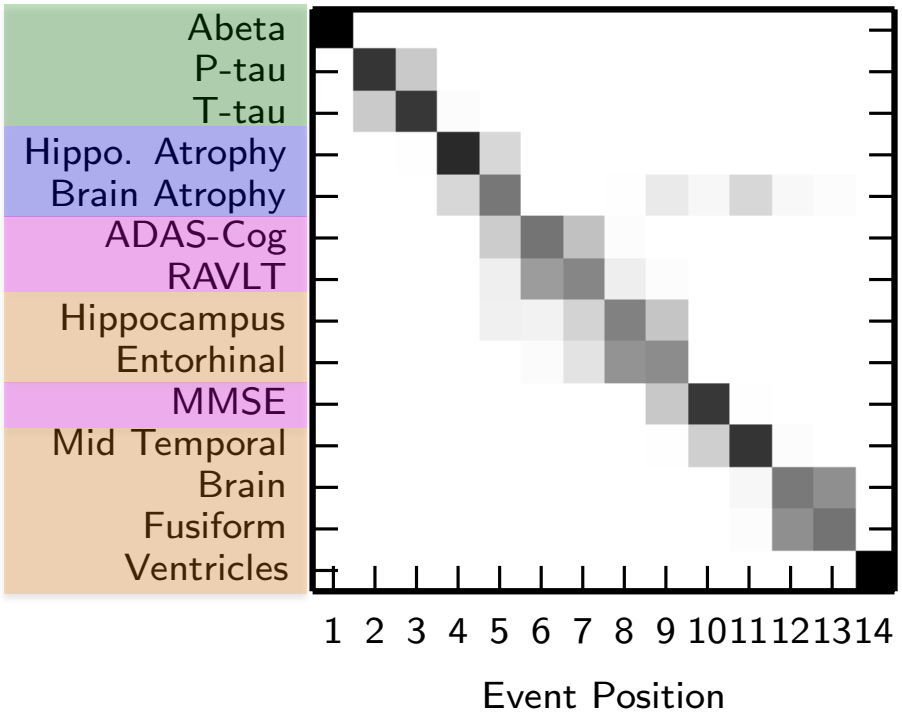
Villemagne et al. TLN 2013
Oxtoby et al. Brain 2018

Generative Models 1

n.oxtoby@ucl.ac.uk

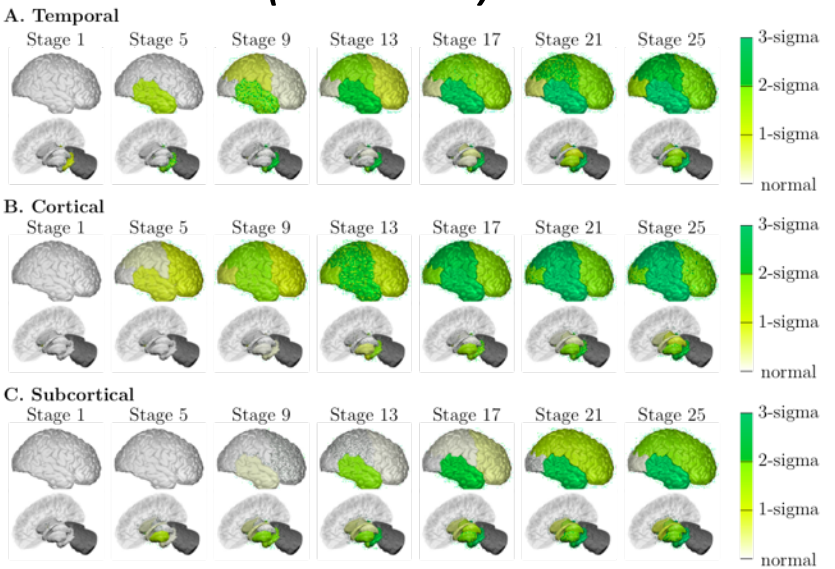
- **Unstructured data**: scalar biomarkers, phenomenological
  - Discrete: events

Event-based model



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

Subtype & Stage Inference (SuStaIn)



Young et al. Nat. Comms 2018

Generative Models 2

n.oxtoby@ucl.ac.uk

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

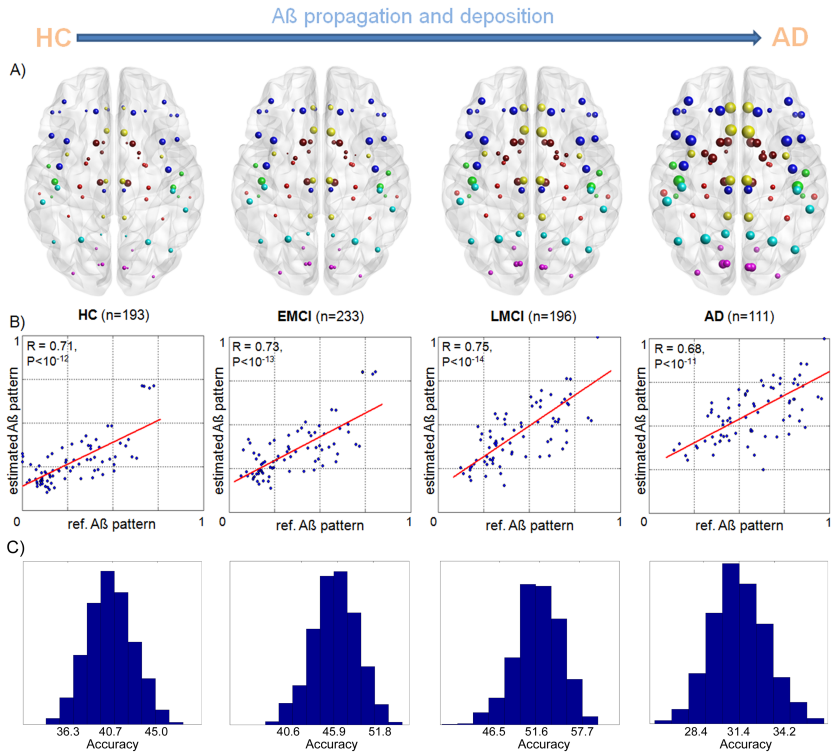
    Durrleman et al. IJCV 2013
    Lorenzi et al. NeuroBiol Aging 2015
    Schiratti et al., IPMI 2015; JMLR 2017

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

Iturria-Medina et al.
PLOS Comp. Biol. 2014; NIMG 2017

Raj et al. Neuron 2012

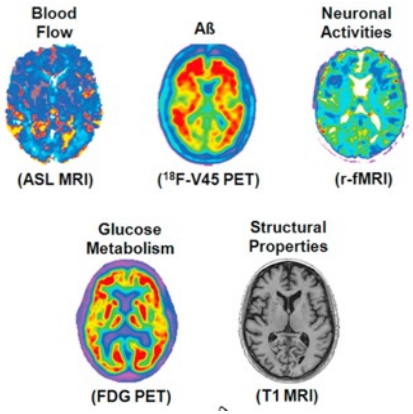
Garbarino et al. eLife 2019

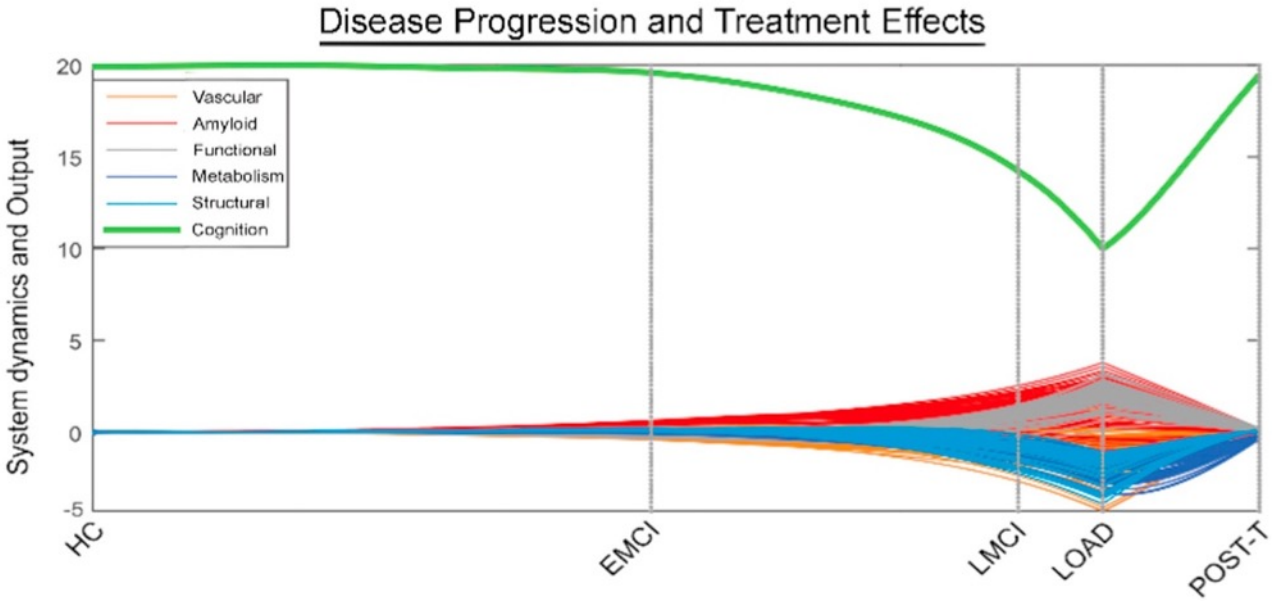


Generative Models 3

n.oxtoby@ucl.ac.uk

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





Iturria-Medina et al. NeuroImage 2017,2018

Next step

n.oxtoby@ucl.ac.uk
UCL

How can

computational modelling of AD progression

help clinical trials?

Example POND models…

Event-based Model

n.oxtoby@ucl.ac.uk

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

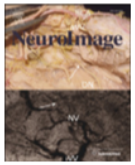
Data-driven: no prior knowledge of disease stage

NeuroImage 60 (2012) 1880–1889

Contents lists available at SciVerse ScienceDirect

NeuroImage

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



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

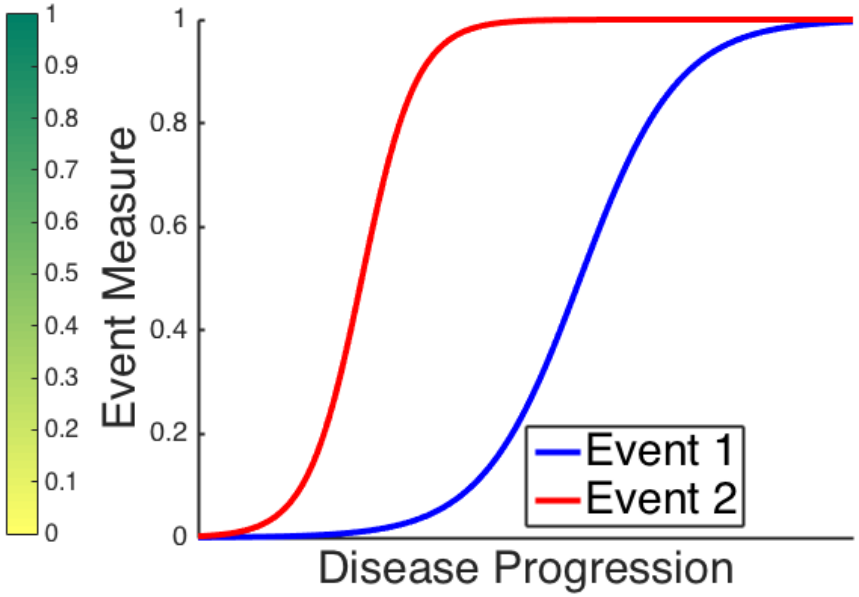
BRAIN
A JOURNAL OF NEUROLOGY

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

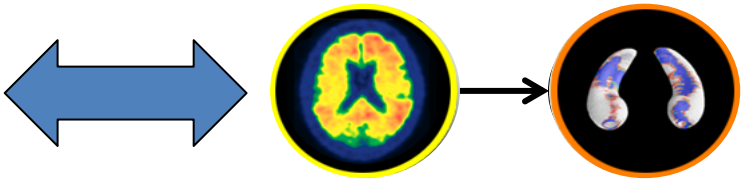
Alexandra L. Young,[1] Neil P. Oxtoby,[1] Pankaj Daga,[1] David M. Cash,[1,2] on behalf of the Alzheimer's Disease Neuroimaging Initiative,[†] Nick C. Fox,[2] Sebastien Ourselin,[1,2] Jonathan M. Schott[2,*] and Daniel C. Alexander[1,*]

Event-based Model

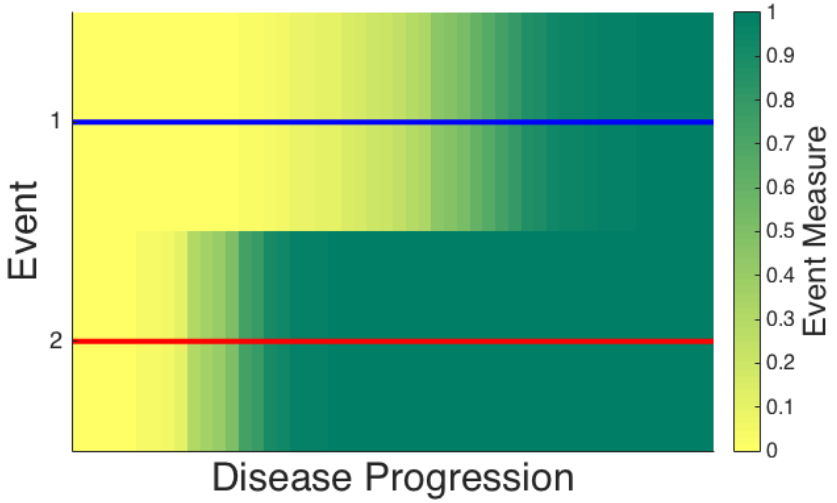
n.oxtoby@ucl.ac.uk



After
Fonteijn et al. NeuroImage 2012

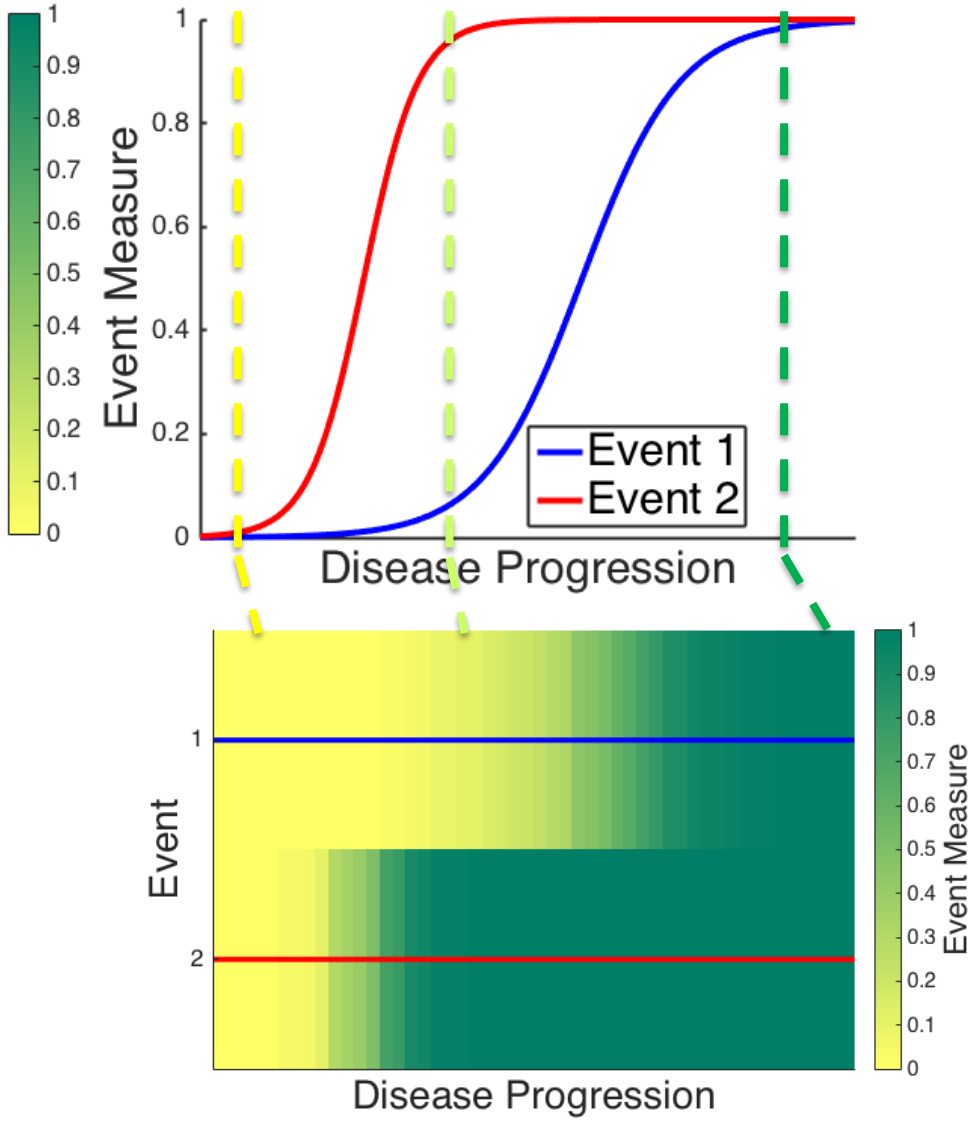


E_2 E_1

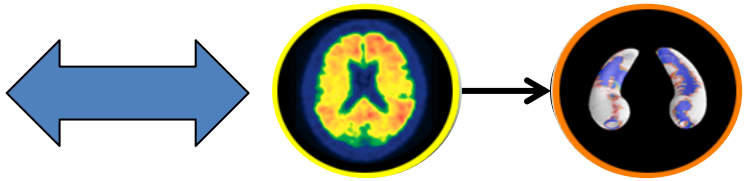


Event-based Model

n.oxtoby@ucl.ac.uk



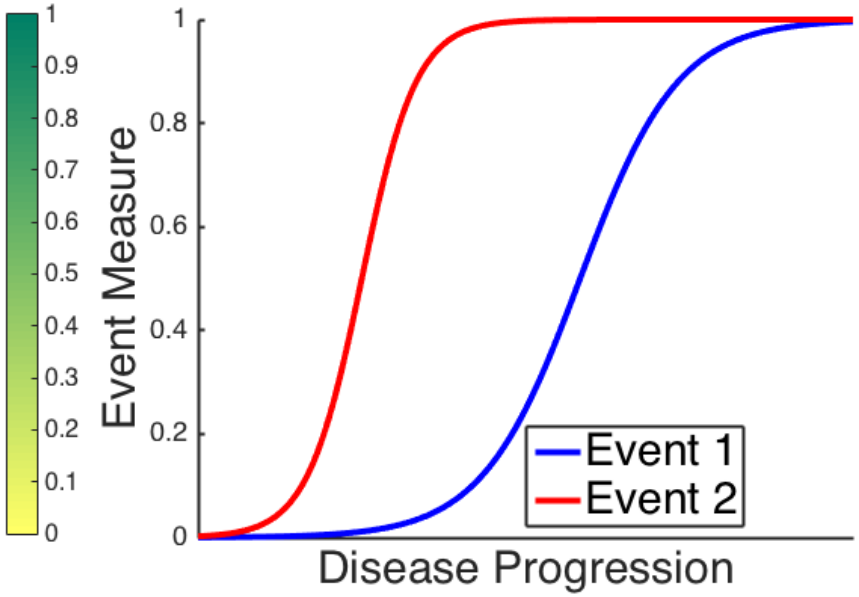
After
Fonteijn et al. NeuroImage 2012



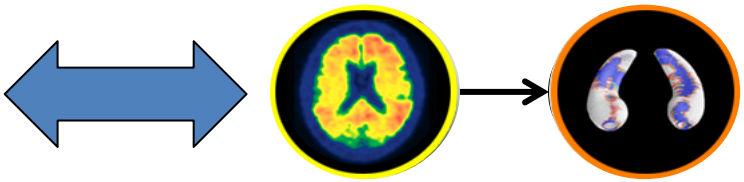
E_2 E_1

Event-based Model

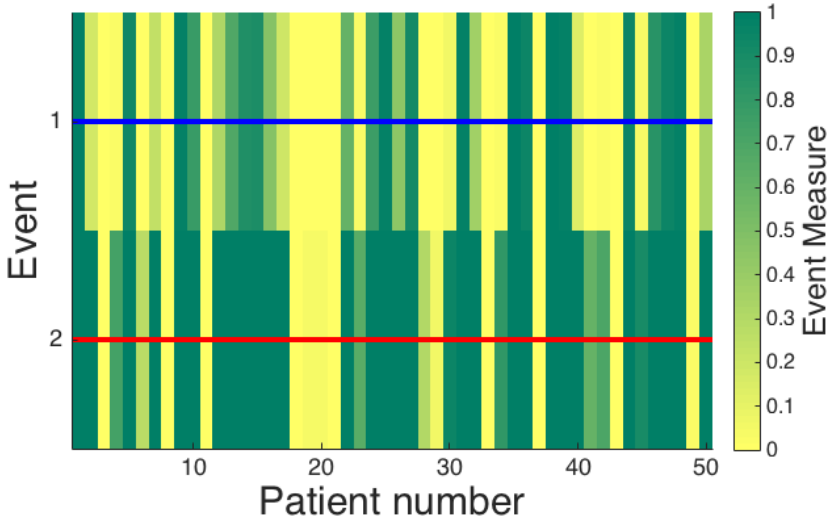
n.oxtoby@ucl.ac.uk



After
Fonteijn et al. NeuroImage 2012



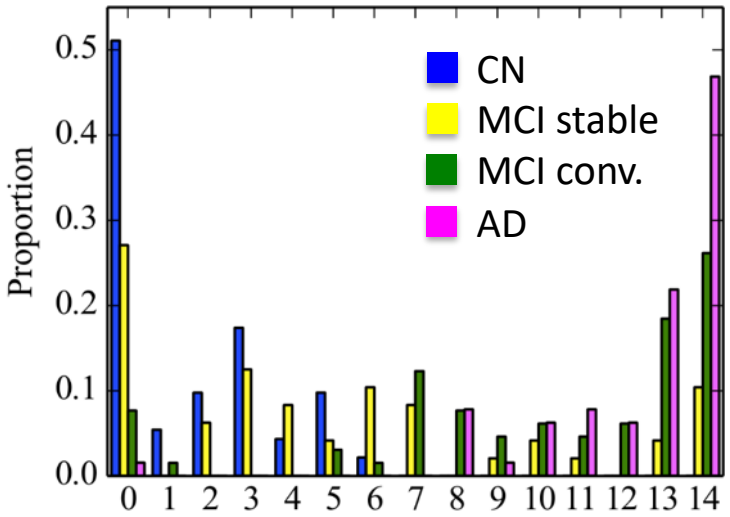
E_2 E_1

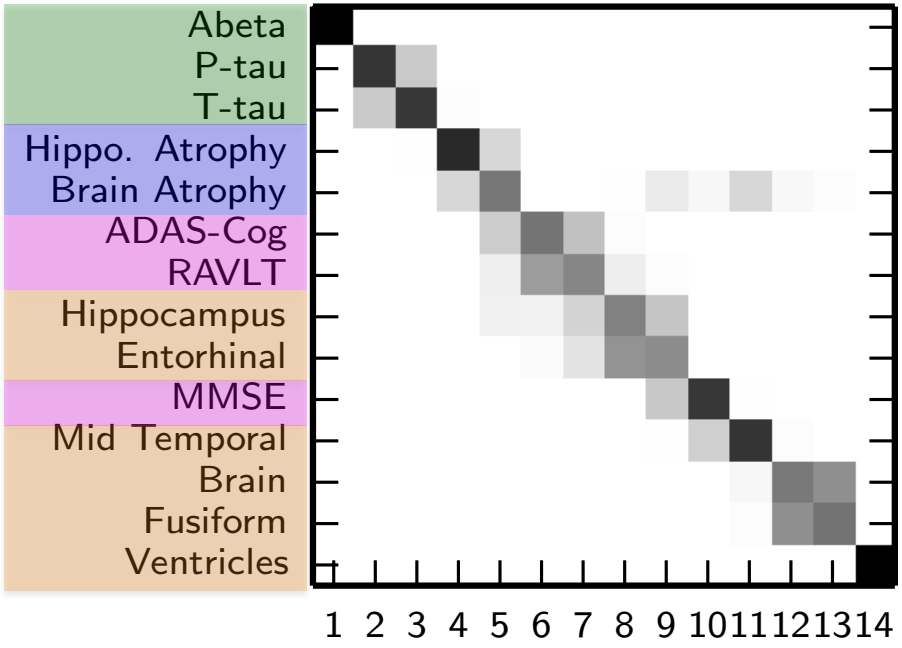


Staging individuals

n.oxtoby@ucl.ac.uk

Young et al. Brain 2014





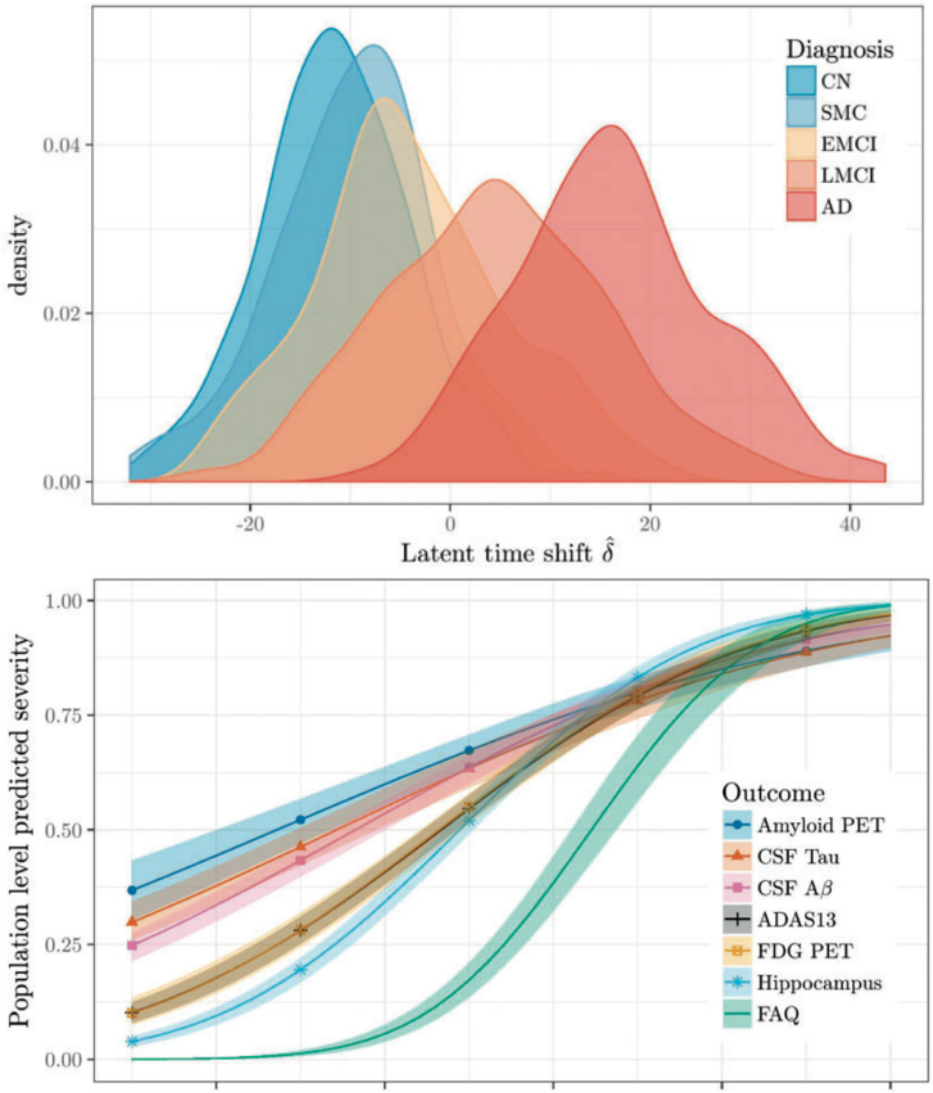
Model Stages:

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

Staging individuals

n.oxtoby@ucl.ac.uk

Li et al. Stat Meth Med Res 2017

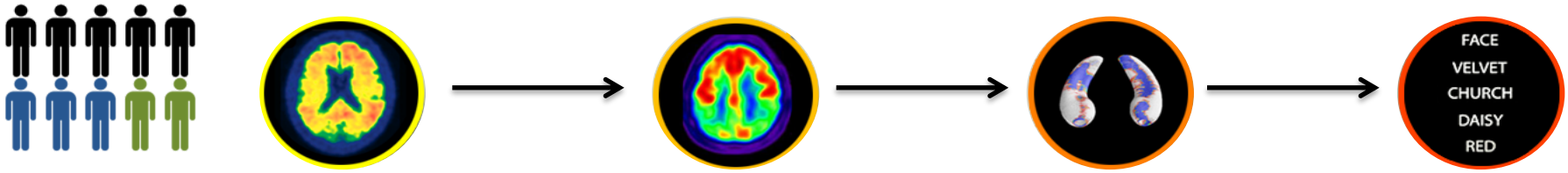


Heterogeneity & Subtypes

n.oxtoby@ucl.ac.uk

Young *et al.* IPMI 2015

Modification 1: Subtypes



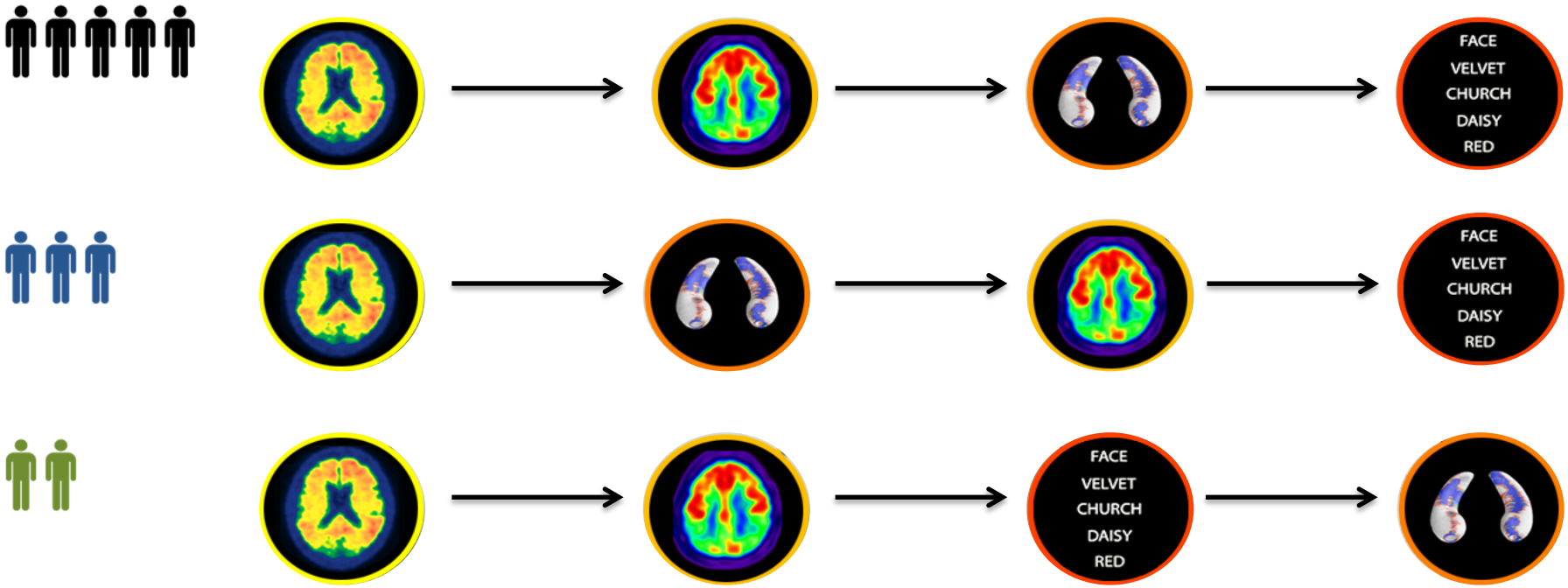
Adapted from ADNI website figure

Heterogeneity & Subtypes

n.oxtoby@ucl.ac.uk
UCL

Young *et al.* IPMI 2015

Modification 1: Subtypes



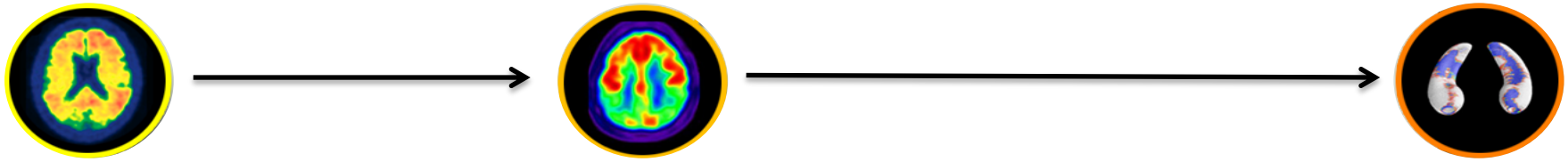
Adapted from ADNI website figure

Heterogeneity & Subtypes

n.oxtoby@ucl.ac.uk
UCL

Young *et al.* Nature Comms. 2018

Modification 2: Z-score events



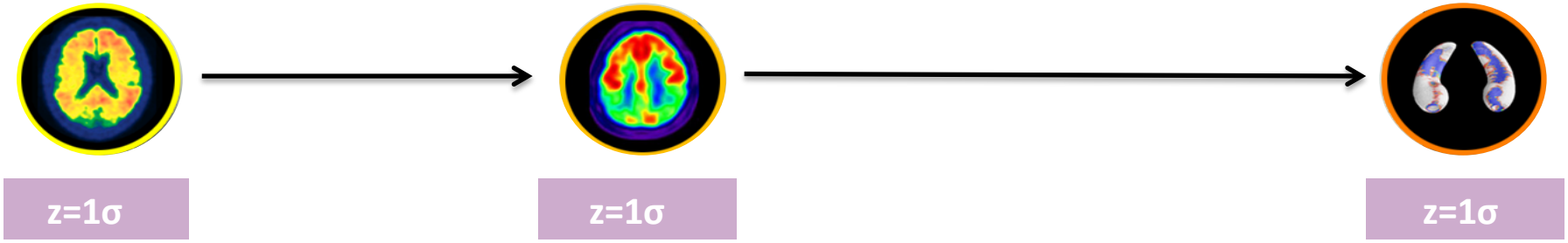
Adapted from ADNI website figure

Heterogeneity & Subtypes

n.oxtoby@ucl.ac.uk

Young *et al.* Nature Comms. 2018

Modification 2: Z-score events



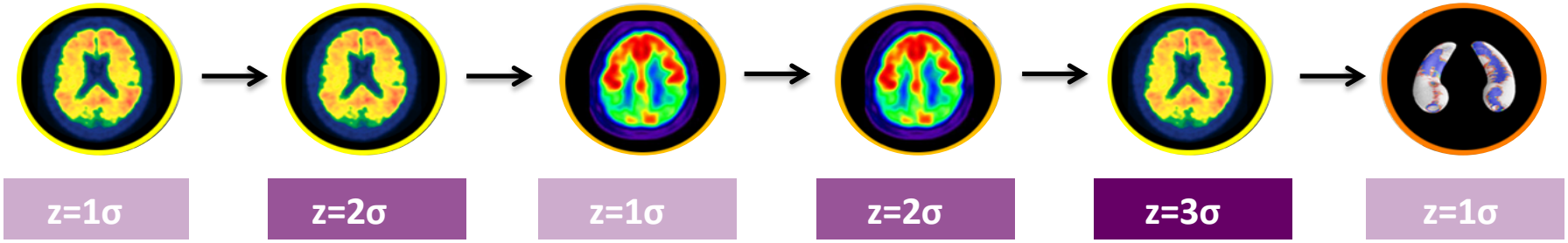
Adapted from ADNI website figure

Heterogeneity & Subtypes

n.oxtoby@ucl.ac.uk
UCL

Young *et al.* Nature Comms. 2018

Modification 2: Z-score events

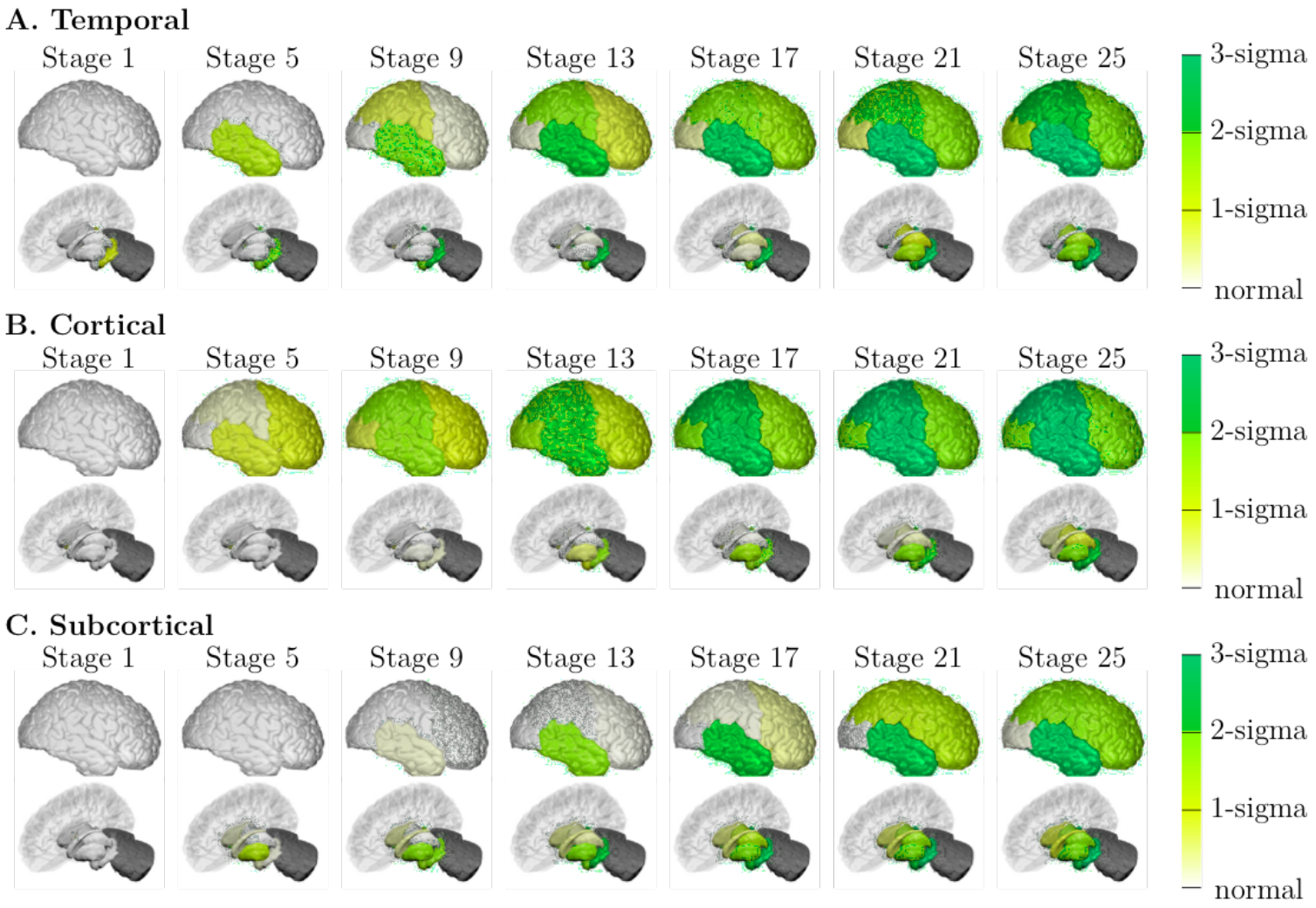


Adapted from ADNI website figure

Heterogeneity & Subtypes

n.oxtoby@ucl.ac.uk

Young *et al.* Nature Comms. 2018



Models for Trials

n.oxtoby@ucl.ac.uk

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

Models for Trials

n.oxtoby@ucl.ac.uk

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

UK Research and Innovation

Models for Trials

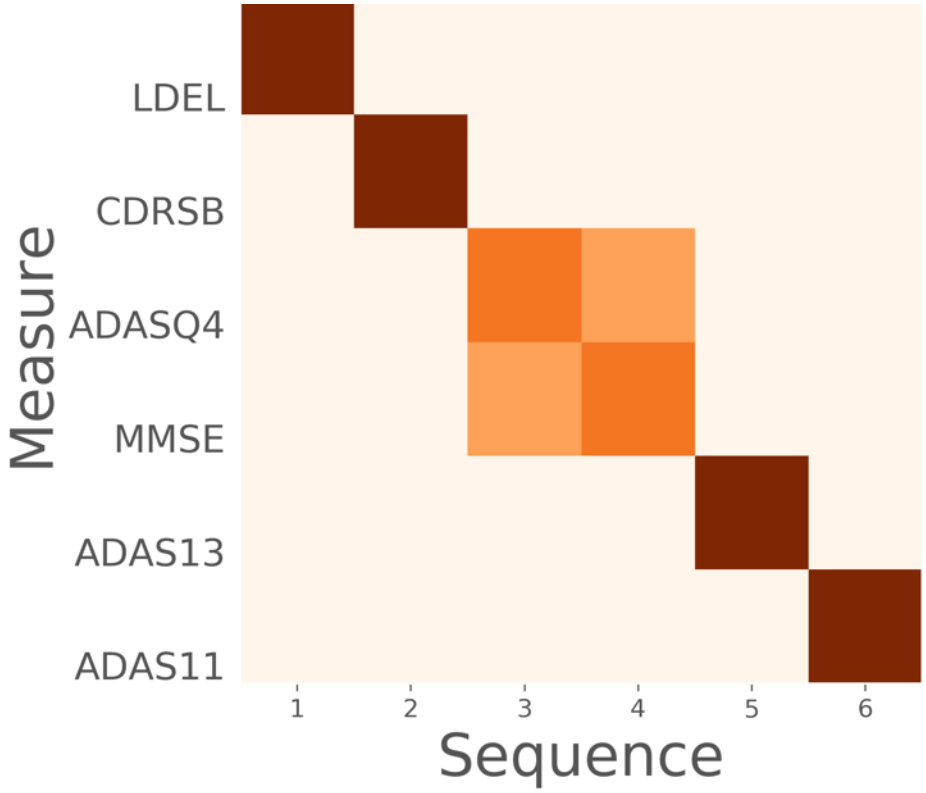
n.oxtoby@ucl.ac.uk
UCL

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

ALZHEIMER'S DISEASE COOPERATIVE STUDY

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*

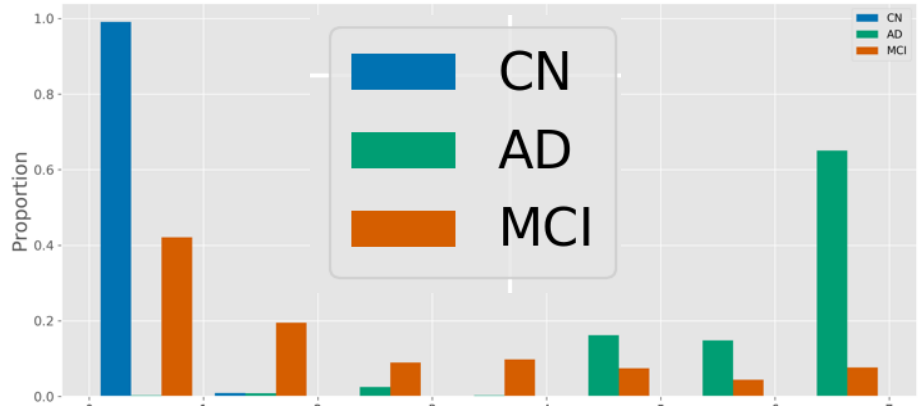


1. Build model (ADNI data)
2. Stage trial data (BL/SC)
3. Stratify
4. Analyse subgroups

pond
UK Research and Innovation

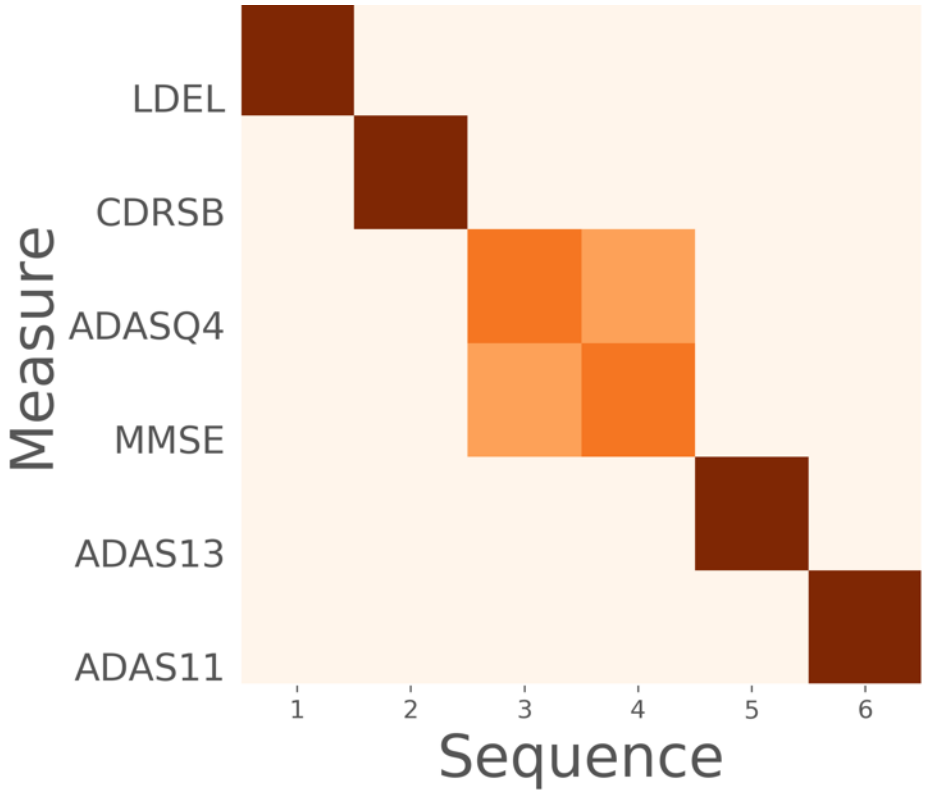
Models for Trials

n.oxtoby@ucl.ac.uk
UCL



onepezil for the Treatment
gnitive Impairment

G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H.,
D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D.,
lan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D.,
, M.D., for the Alzheimer's Disease Cooperative Study Group*



1. Build model (ADNI data)

UK Research and Innovation

FLF: New Models for Trials

n.oxtoby@ucl.ac.uk

Aims of my Future Leaders Fellowship:
"I AIM: 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

UK Research and Innovation

Supermodels for Trials

n.oxtoby@ucl.ac.uk

Join me in the quest for supermodels and drugs!

Vacancies: Post doc and PhD opening soon

UK Research and Innovation