

# Computational Modelling of Alzheimer's disease for Clinical Trials

**Neil Oxtoby, PhD**

UKRI Future Leaders Fellow

Progression Of Neurodegenerative Disease (POND) group

Centre for Medical Image Computing (CMIC)

Department of Computer Science, UCL



UK Research  
and Innovation

**EuroPOND**



**cmic**

Centre for Medical Image Computing

# My quest for Supermodels and Drugs

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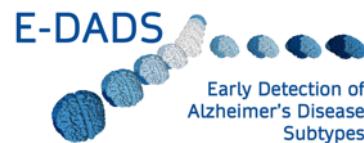
Centre for Medical Image Computing (CMIC)

Department of Computer Science, UCL



UK Research  
and Innovation

**EuroPOND**



**cmic**

Centre for Medical Image Computing

# Acknowledgements

**EuroPOND**



UK Research  
and Innovation

alzheimer's  
association®

Alzheimer's  
Research  
UK

The Power to Defeat Dementia

**EPSRC**

Engineering and Physical Sciences  
Research Council

**Magnims**



Magnetic Resonance Imaging in Multiple Sclerosis



**UCLiC**



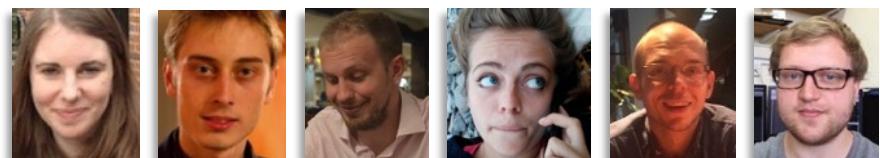
 THE MICHAEL J. FOX FOUNDATION  
FOR PARKINSON'S RESEARCH

  
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](http://pond.cs.ucl.ac.uk)
  - Alex Young, Danny Alexander, et al.
  - EuroPOND\*: [europond.eu](http://europond.eu)
- CMIC: [www.ucl.ac.uk/cmic](http://www.ucl.ac.uk/cmic)
- Links: COMBINE lab, DRC, MS@ION, HD, UCLiC, HDRUK, Lung Imaging

- 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?



- 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?



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

# Aducanumab?

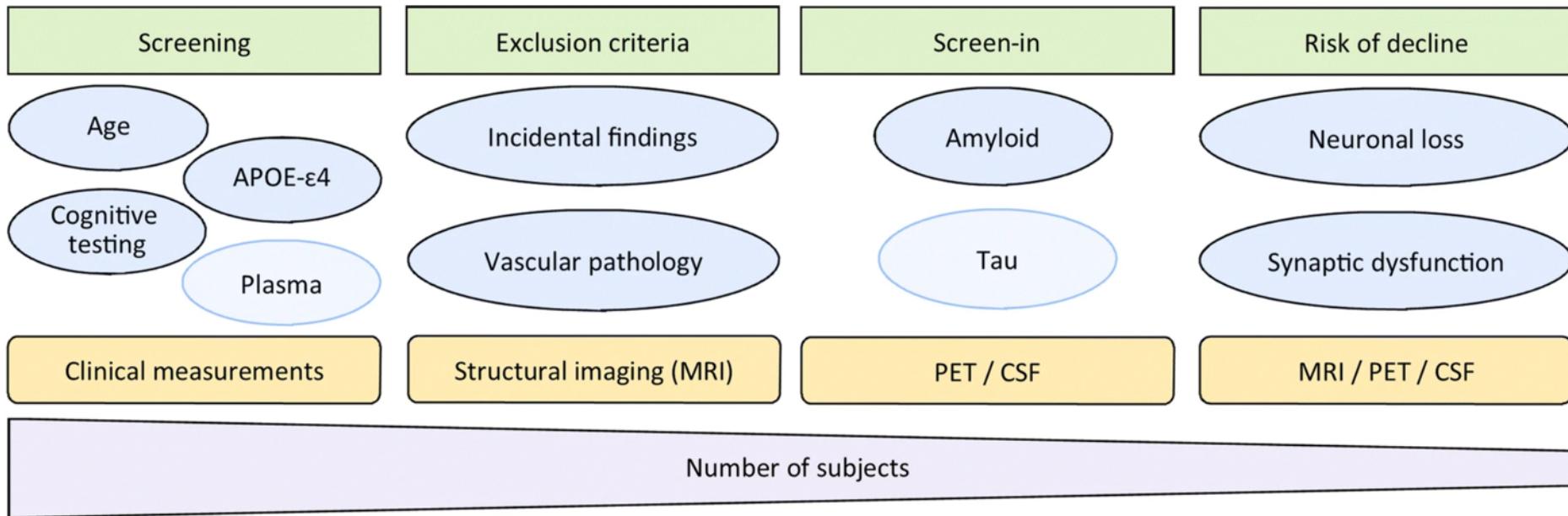
Relationship Status:  
**it's complicated**

- 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?

- Individual **variability**
  - **Age** of onset => unknown “disease time/stage”
  - **Progression**
- Overcoming Heterogeneity
  - Right people: individualized inclusion criteria
  - Right time: characterize earliest stages

- 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)

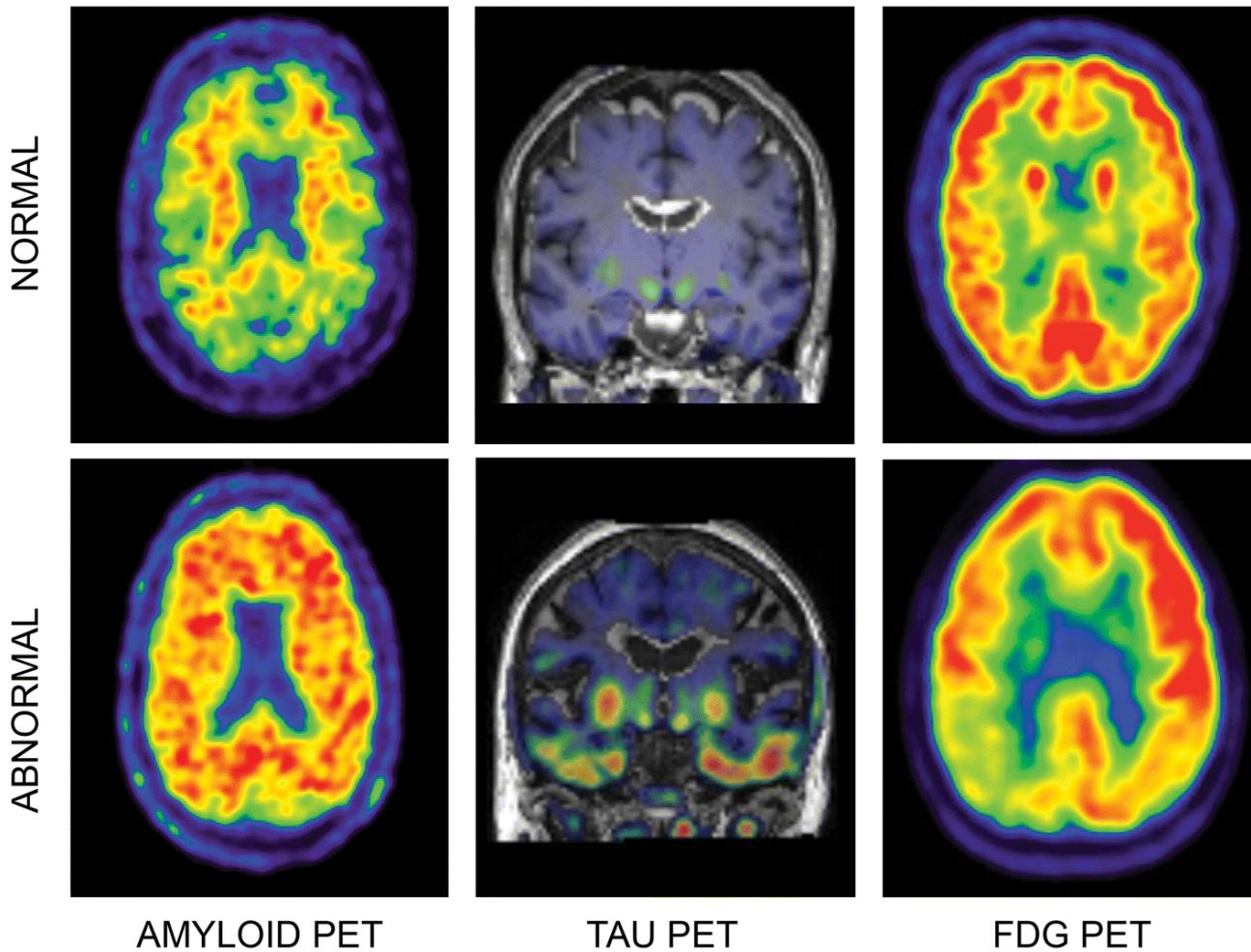
# What have trials done?



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

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

# What have trials done?

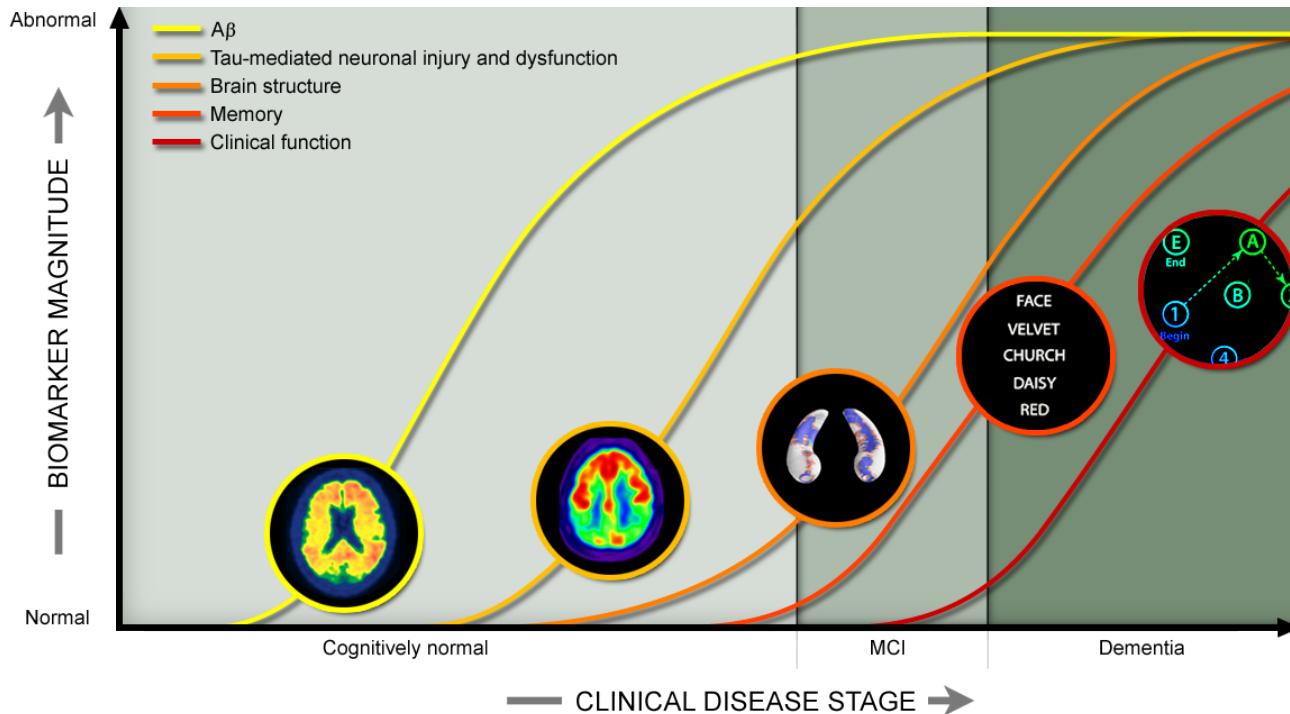


M. ten Kate et al., Alz. Res. Therapy (2018)

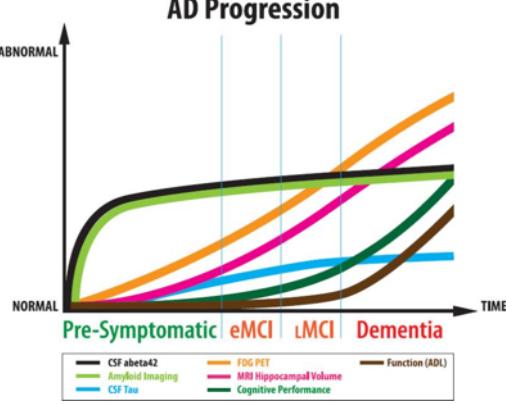
- Imaging: inclusion criteria (& endpoints)
  - Amyloid and volumetric imaging
- Alzheimer's Disease Neuroimaging Initiative
  - “discover, optimize, standardize, and validate clinical trial measures and biomarkers used in AD clinical research”  
[ADNI website, 2020]
- THE global benchmark
  - Protocols
  - 1800 papers



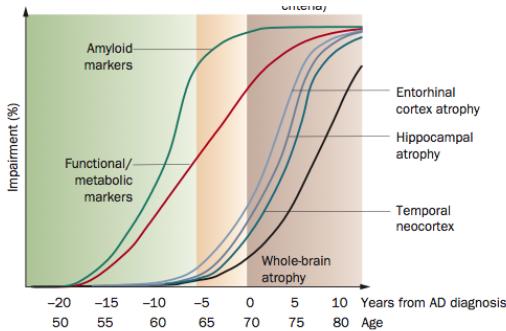
# AD Progression



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



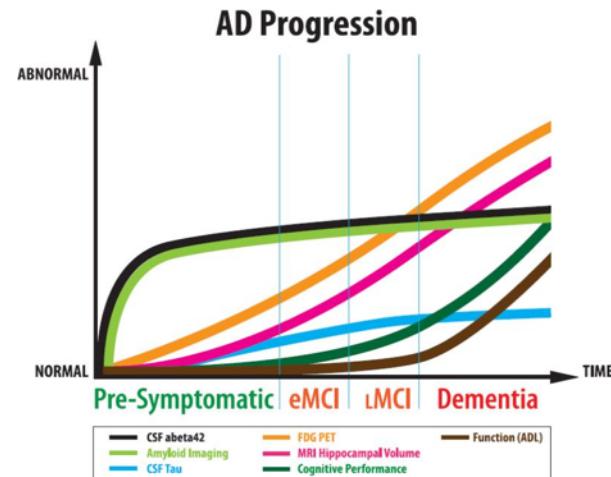
**Aisen et al.**  
**Alz. Dement.**  
 2010



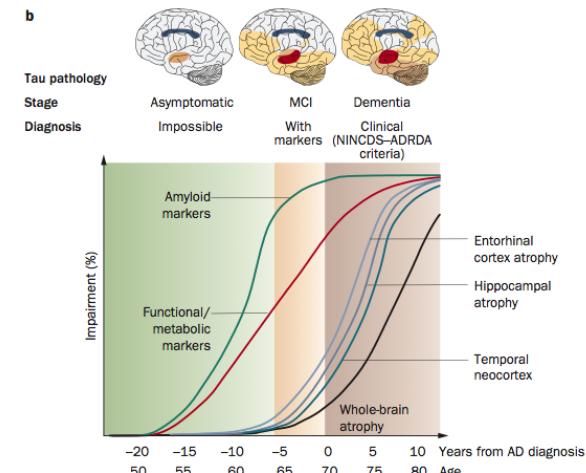
**Frisoni et al**  
**Nat. Rev.**  
**Neurol. 2010**

# Progression Modelling

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

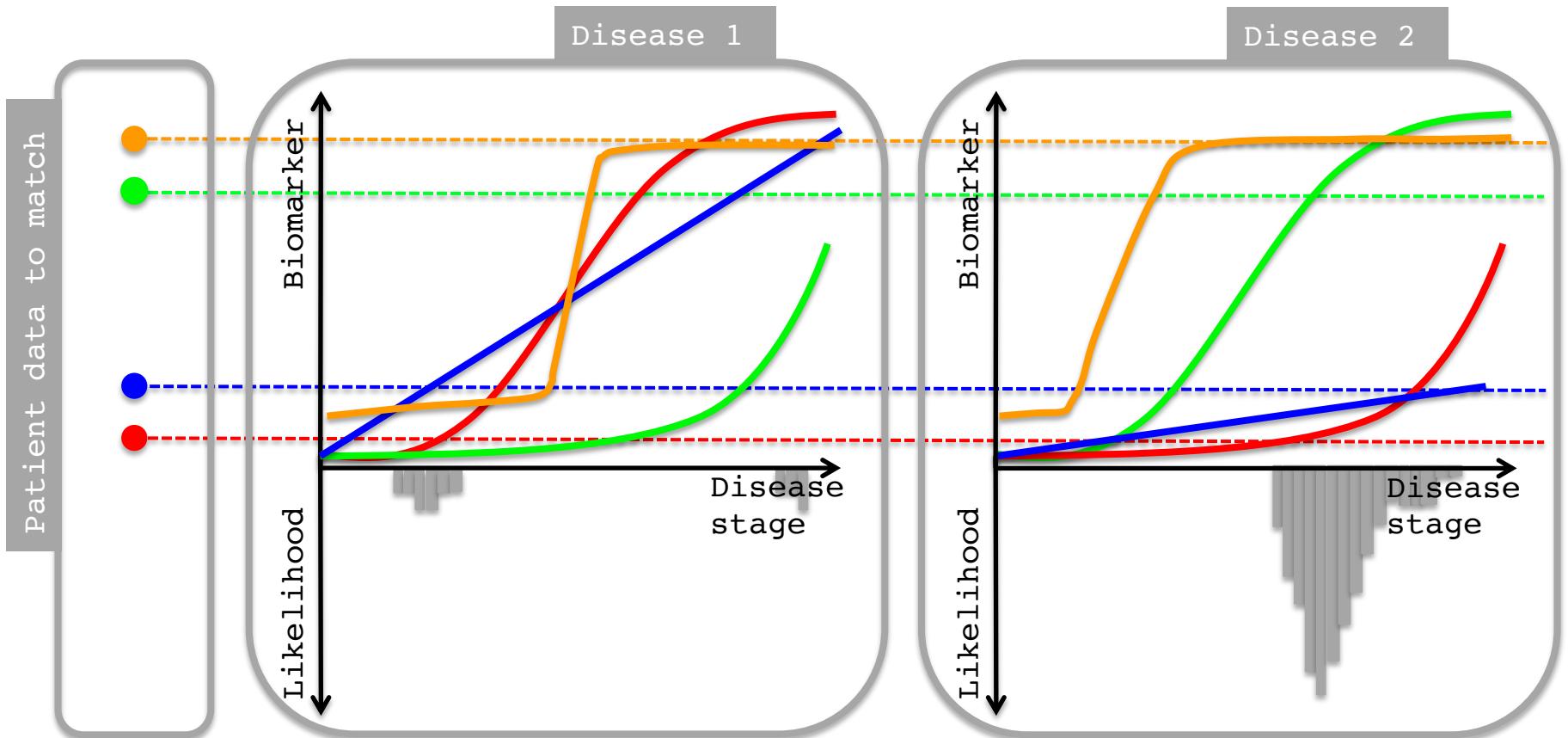


Aisen et al.  
Alz. Dement. 2010

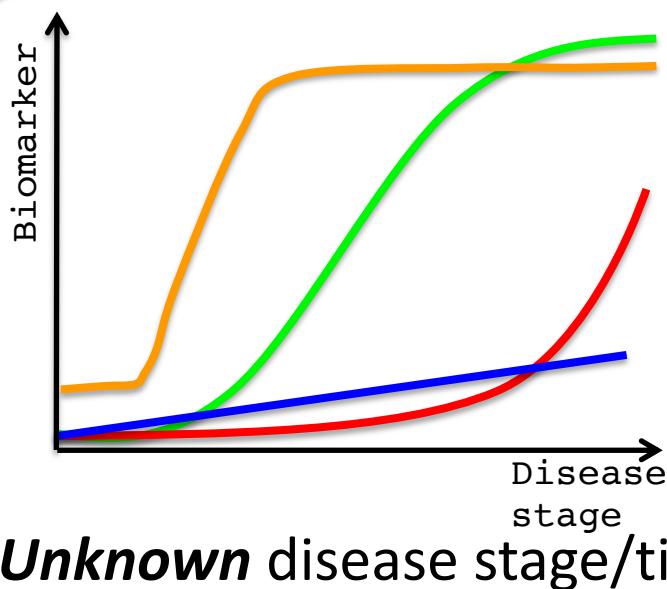


Frisoni et al. Nat.  
Rev. Neurol. 2010

# Diagnosis & Staging



# Traditional Models

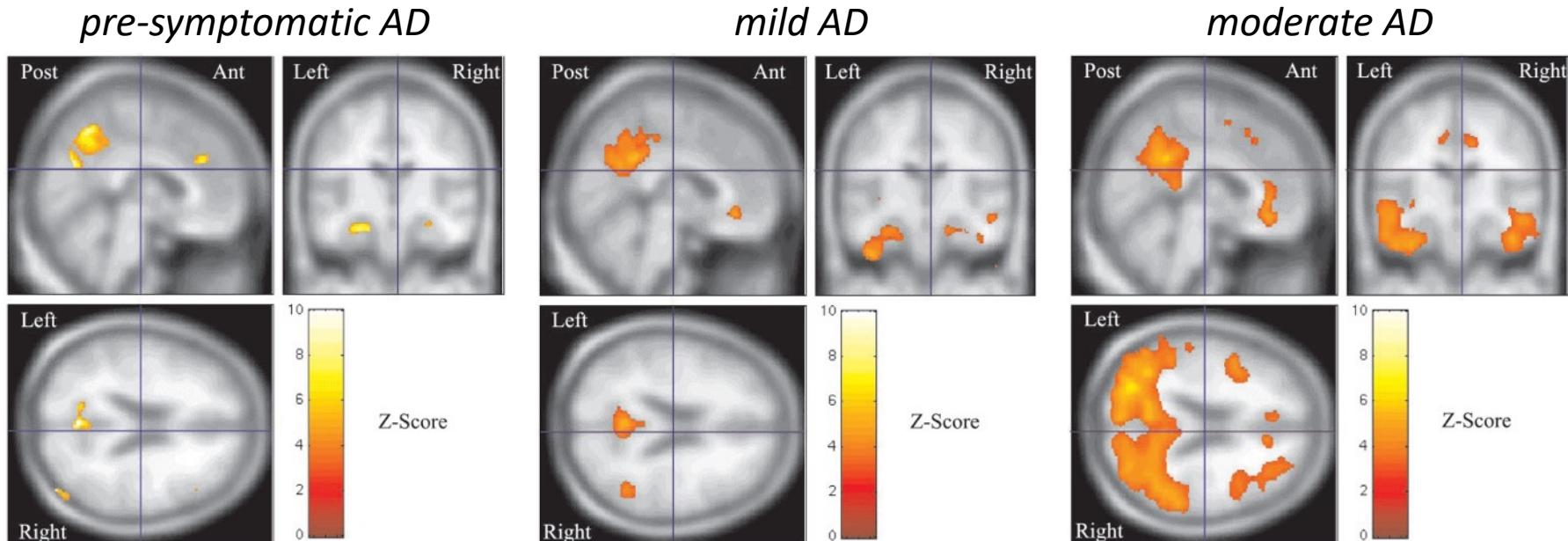


# Traditional Models

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

Scahill et al. PNAS 2002

- T1 MRI measures of neuronal atrophy

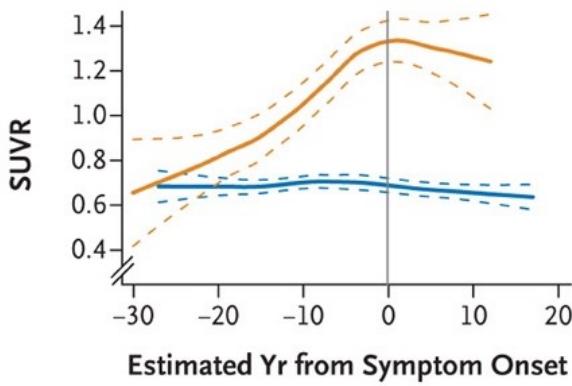


- Heritable diseases: estimable stage ( $\pm 5$  years)
  - *Autosomal dominant AD: familial age of onset*

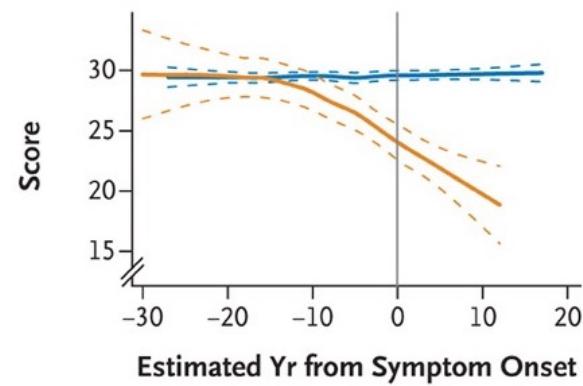
Bateman et al. NEJM 2012

- Imaging and clinical biomarkers

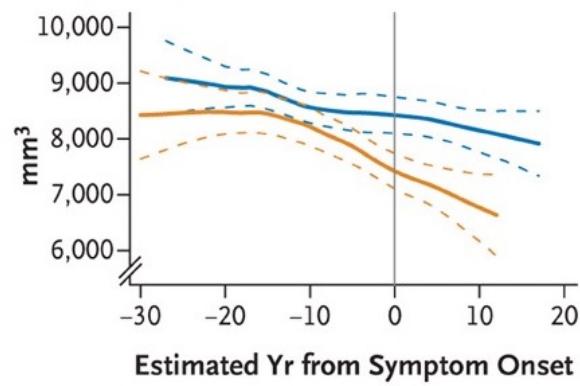
Amyloid PET  
(precuneus)



MMSE

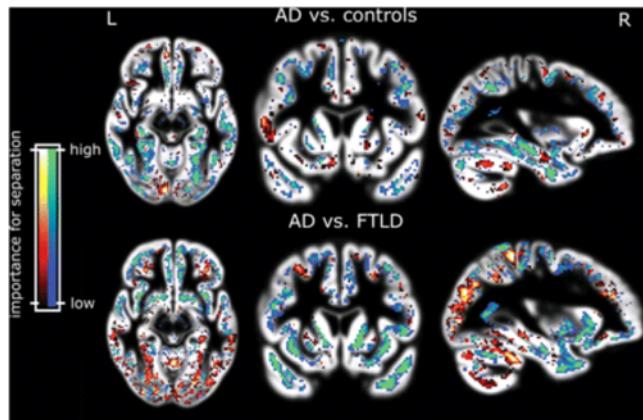


Hippocampus  
volume

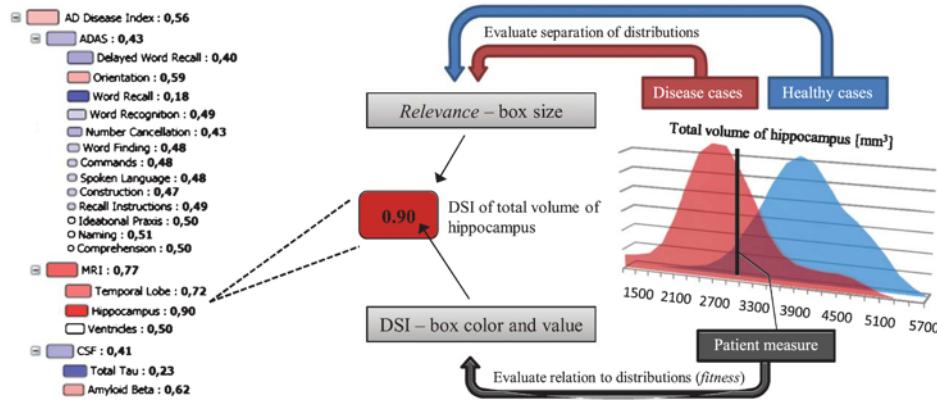


- Pattern recognition: **supervised learning**
  - Learn to classify patients from labelled data
  - Shown value of combining imaging and non-imaging data

## Classifying structural MRI in AD

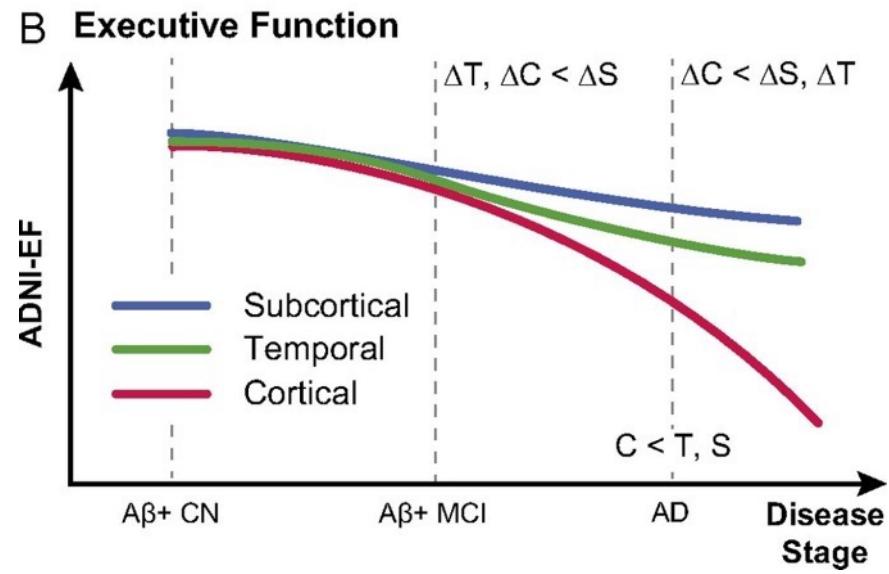
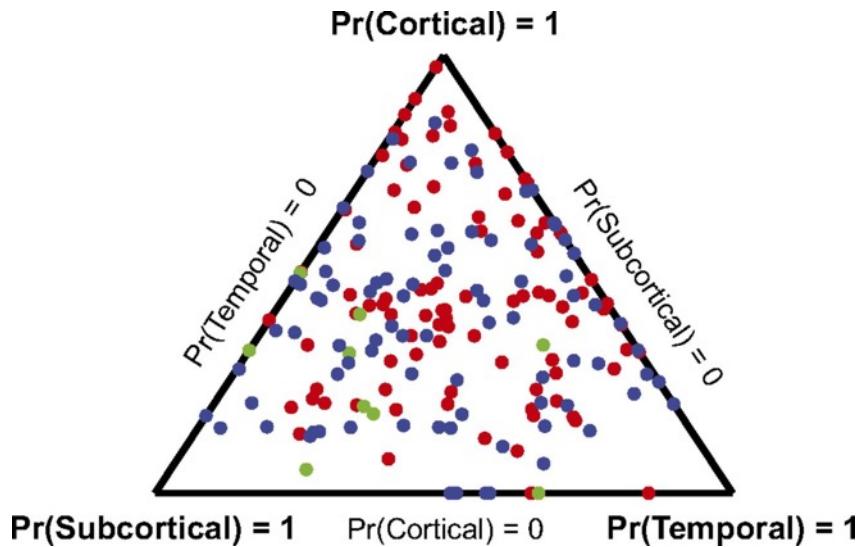


## Disease State Fingerprint for AD



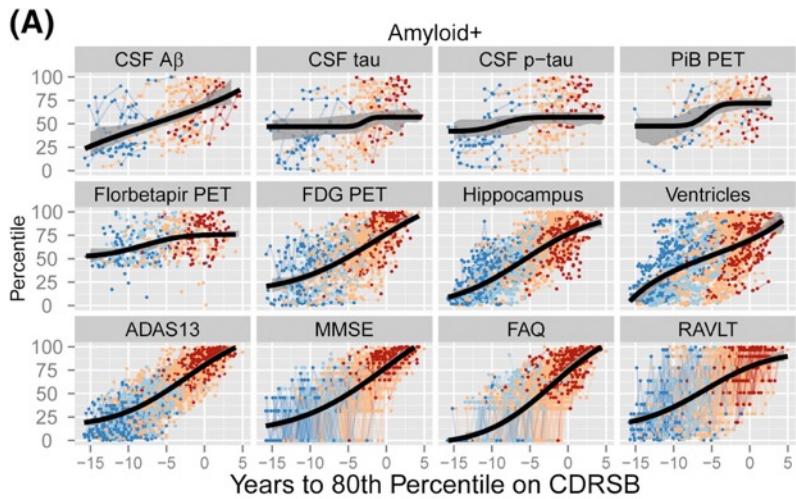
- Pattern discovery: **unsupervised** learning
  - Learn disease subtypes/stages automatically
  - Clustering

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



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

## Self-modelling regression

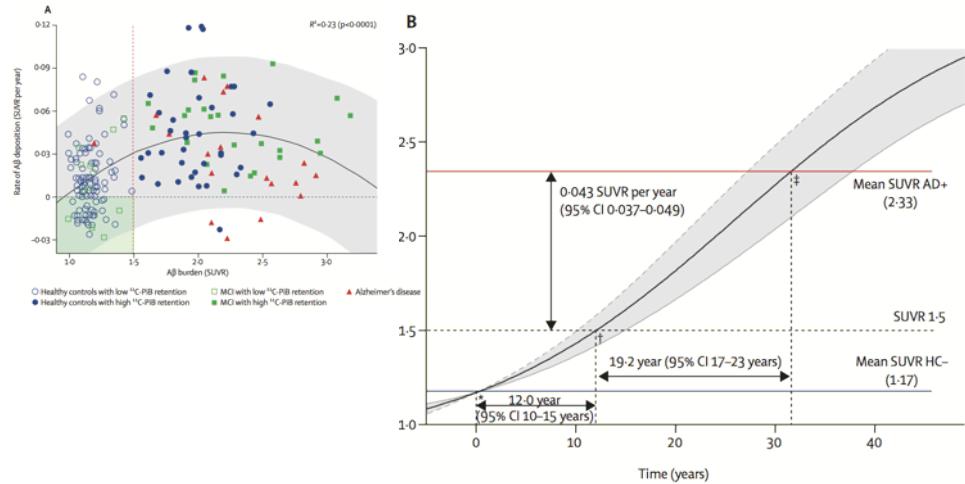


Donohue et al. Alz. Dem. 2014 (2017)

Jedynak et al. NIMG 2012; (2015;2019)

Lorenzi et al. NIMG 2017

## Differential Equation Models

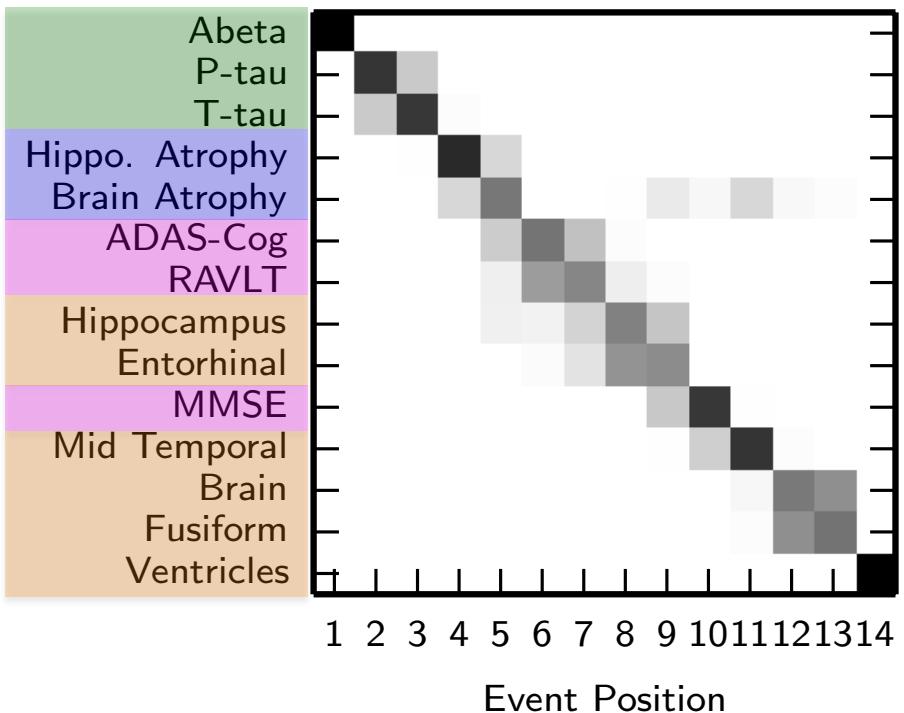


Villemagne et al. TLN 2013

Oxtoby et al. Brain 2018

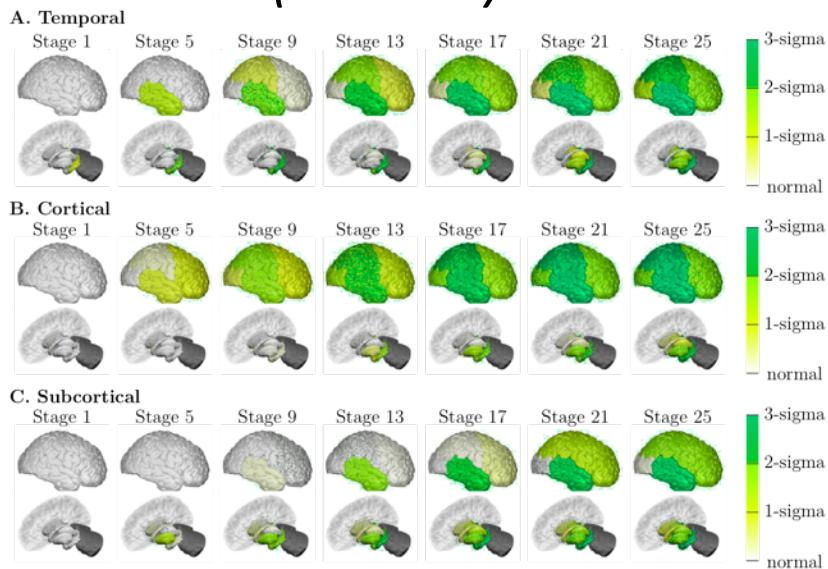
- **Unstructured data:** scalar biomarkers, phenomenological
  - Discrete: events

*Event-based model*



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

*Subtype & Stage Inference (SuStain)*



Young et al. Nat. Comms 2018

- **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

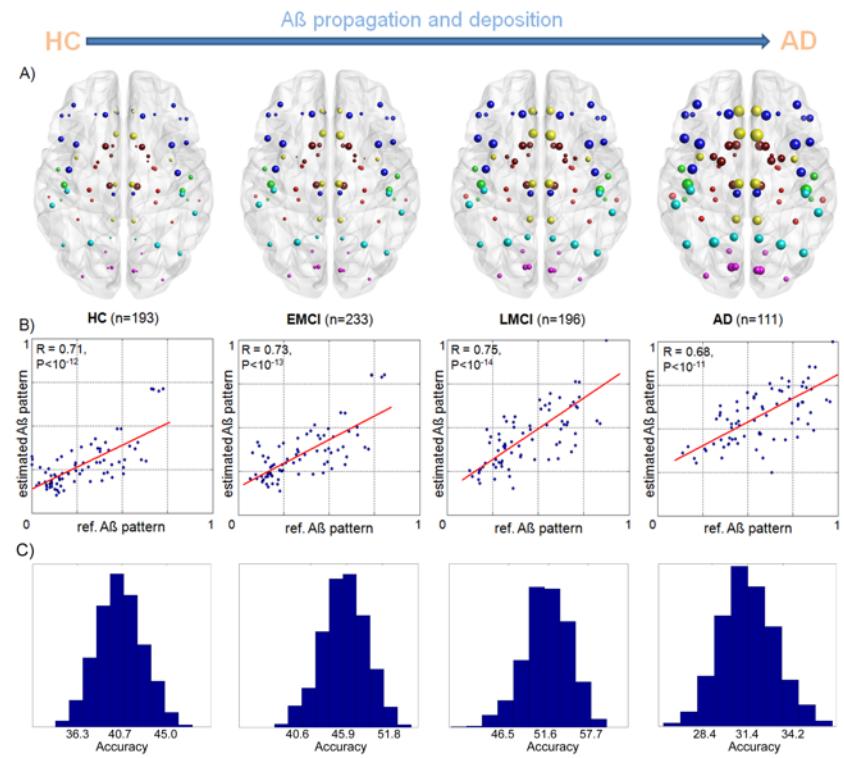
- Network propagation models:  
e.g. prion-like transmission

Iturria-Medina et al.

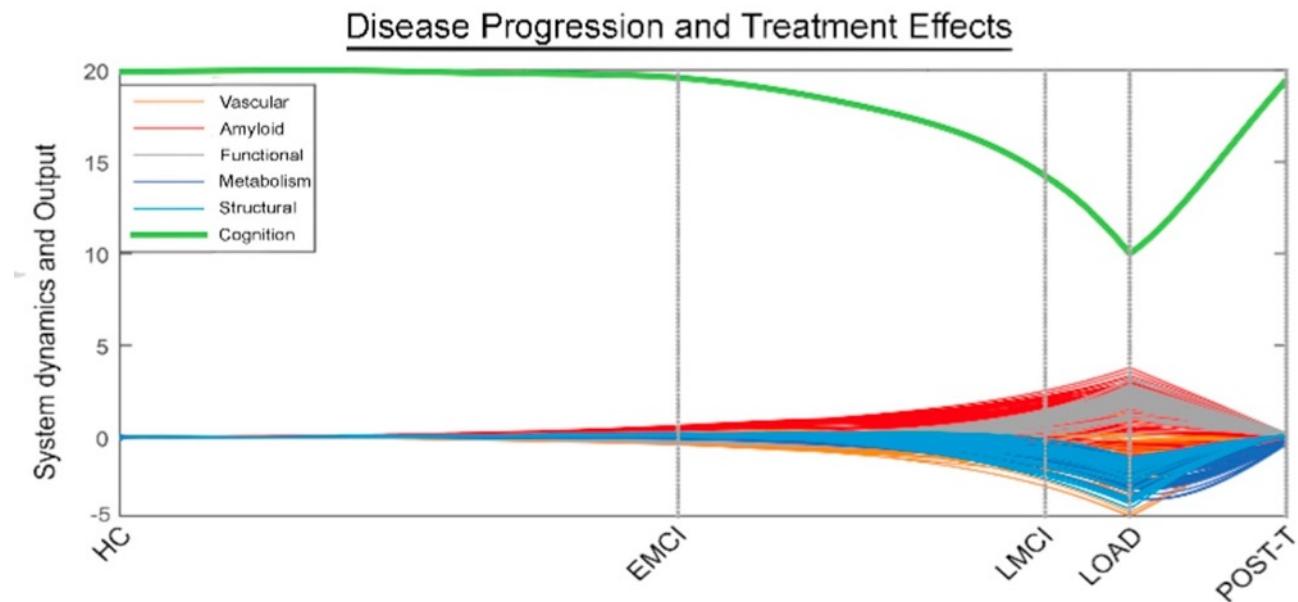
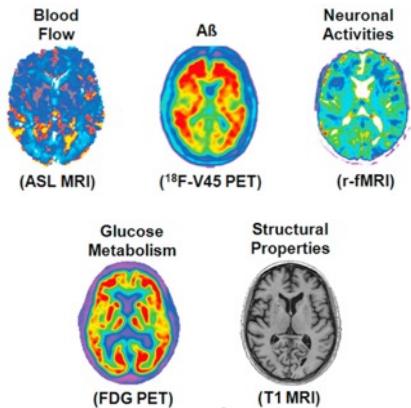
PLOS Comp. Biol. 2014; NIMG 2017

Raj et al. Neuron 2012

Garbarino et al. eLife 2019



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



# Next step

How can  
**computational modelling of AD progression**  
help clinical trials?

Example POND models...

- 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/ynimng](http://www.elsevier.com/locate/ynimng)



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

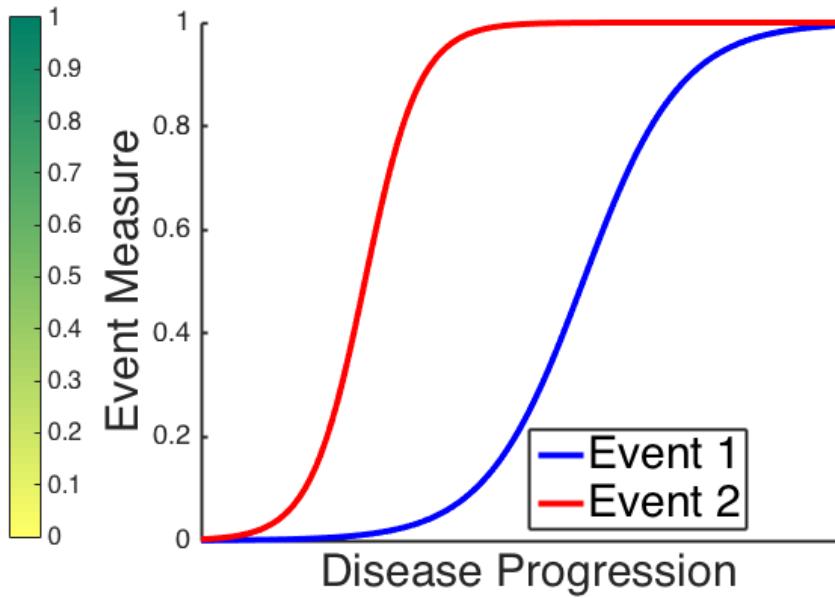
Hubert M. Fonteijn <sup>a,b,c,\*</sup>, Marc Modat <sup>a,d</sup>, Matthew J. Clarkson <sup>a,d,e</sup>, Josephine Barnes <sup>e</sup>,  
Manja Lehmann <sup>e</sup>, Nicola Z. Hobbs <sup>f</sup>, Rachael I. Scahill <sup>f,g</sup>, Sarah J. Tabrizi <sup>f,g</sup>, Sébastien Ourselin <sup>a,d,e</sup>,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



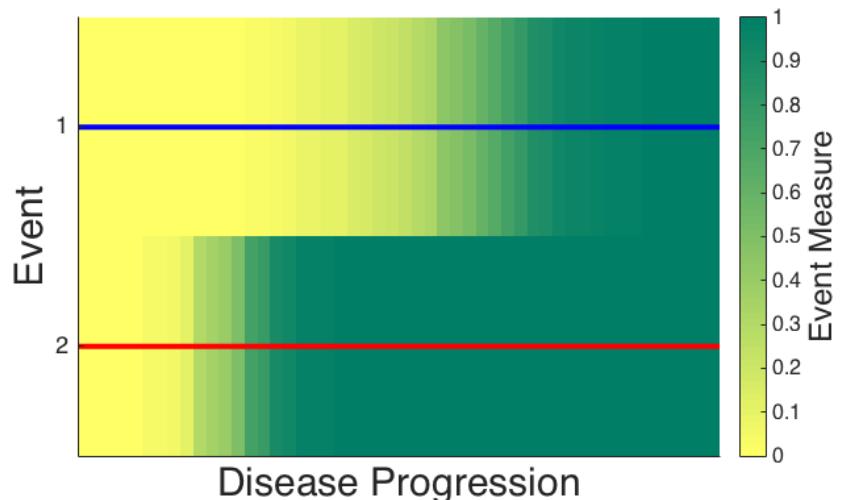
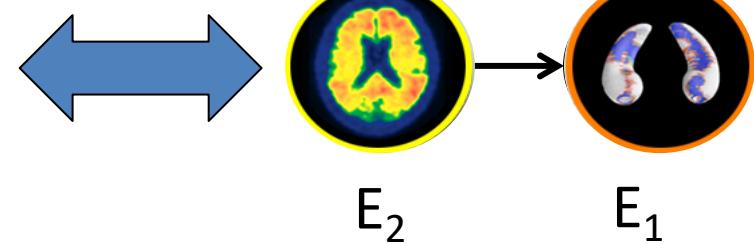
## A data-driven model of biomarker changes in sporadic Alzheimer's disease

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

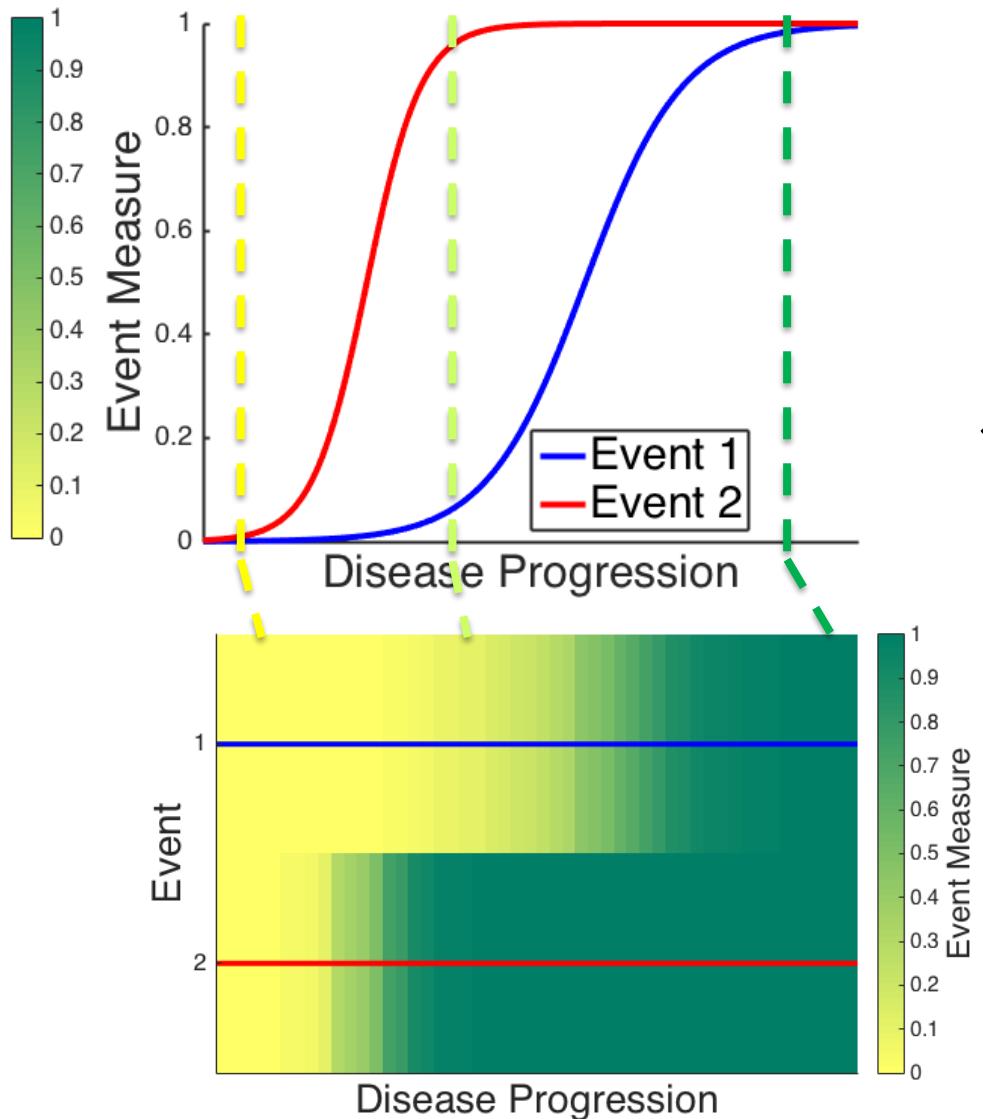
# Event-based Model



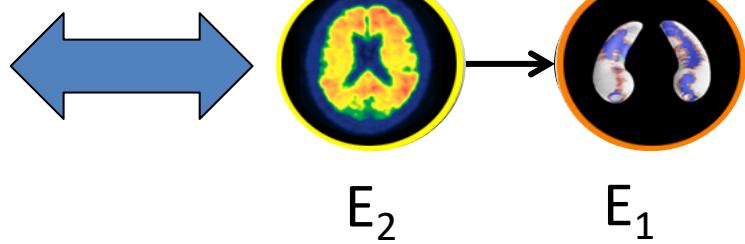
*After*  
Fonteijn et al.  
NeuroImage 2012



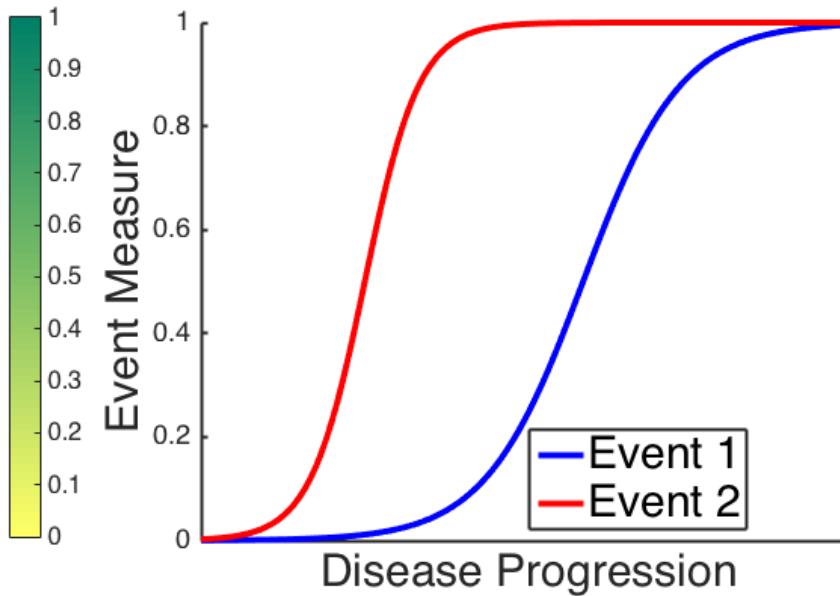
# Event-based Model



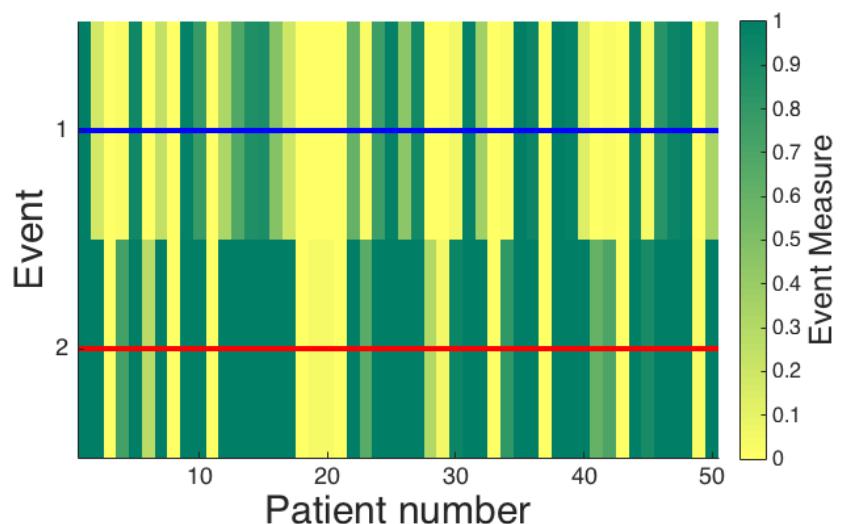
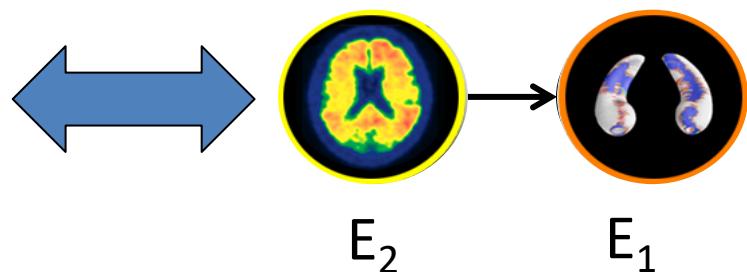
After  
Fonteijn et al.  
NeuroImage 2012



# Event-based Model

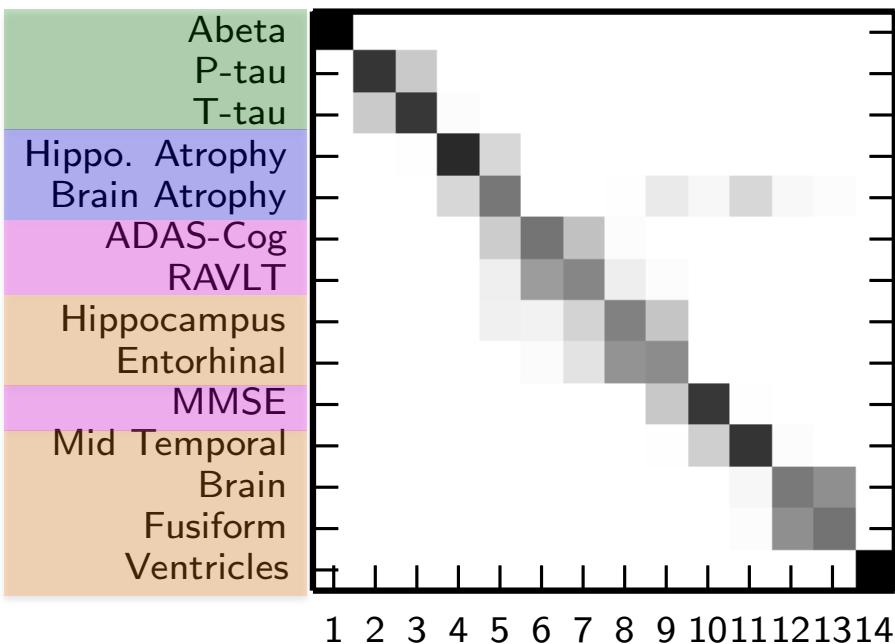
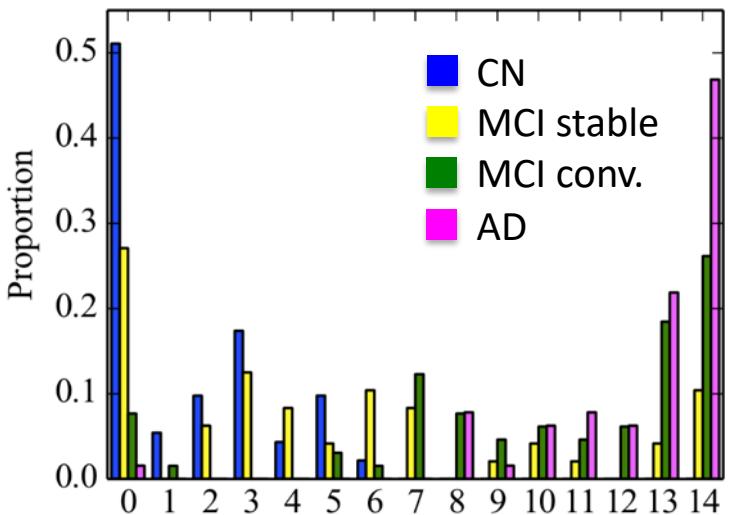


After  
Fonteijn et al.  
NeuroImage 2012



# Staging individuals

Young et al. Brain 2014



## Model Stages:

0

1-3

CSF

4-5

Rates of atrophy

6-8

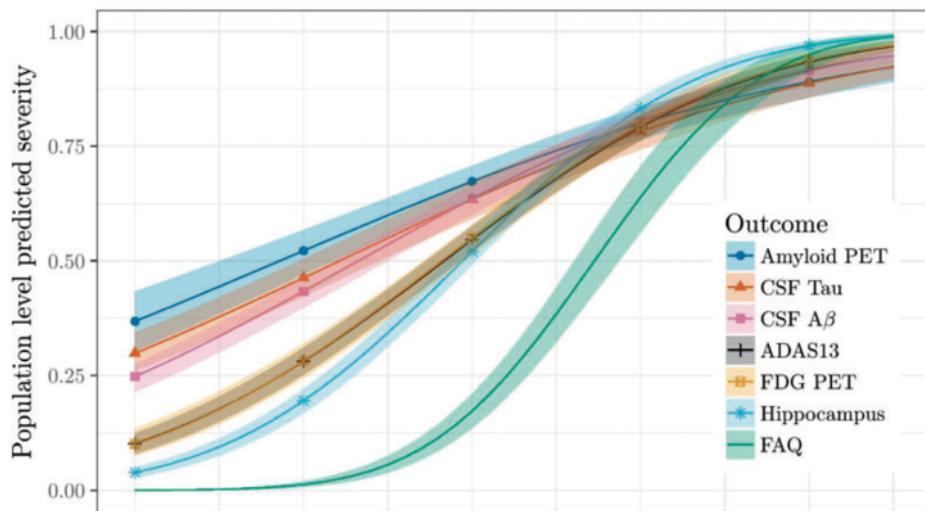
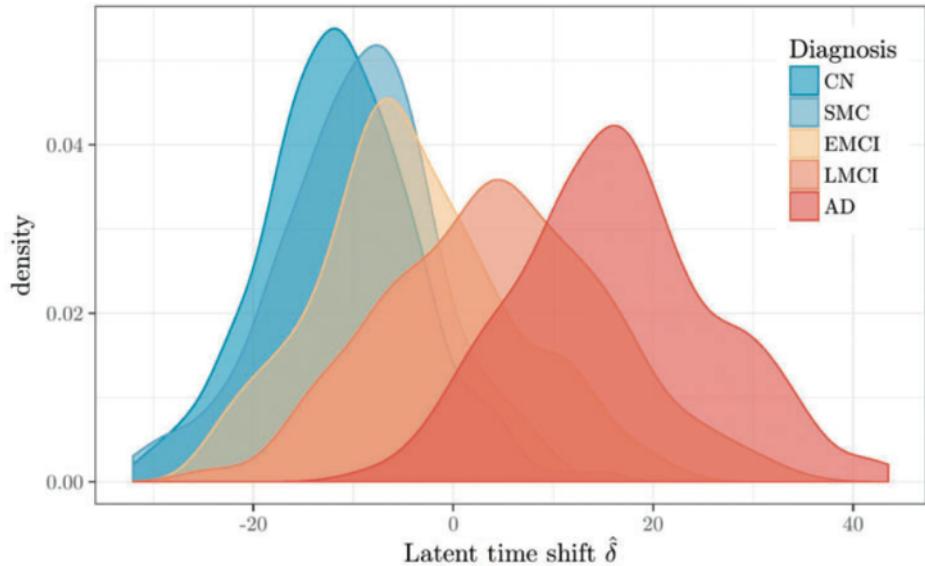
Cognitive test scores

9-14

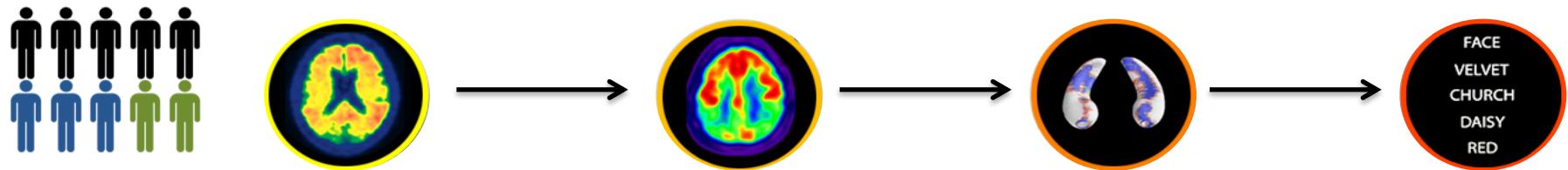
Brain volumes

# Staging individuals

Li et al. Stat Meth Med Res 2017



## Modification 1: Subtypes

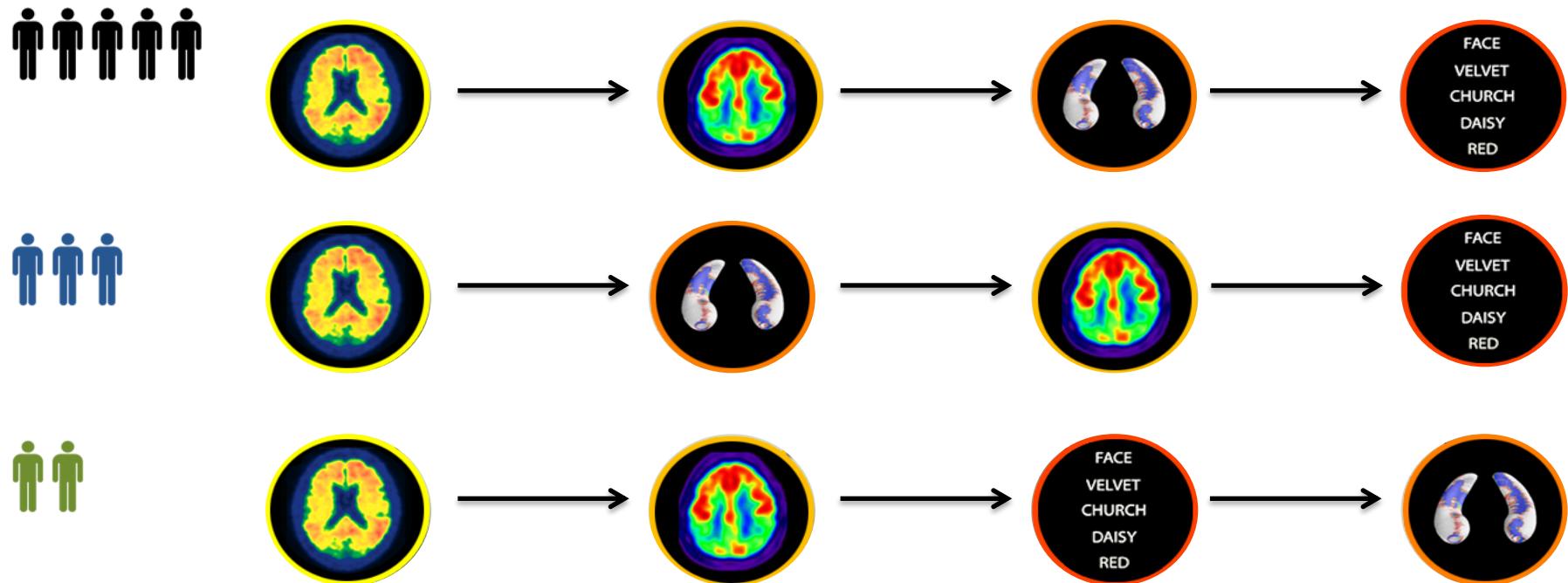


Adapted from ADNI website figure

# Heterogeneity & Subtypes

Young et al. IPMI 2015

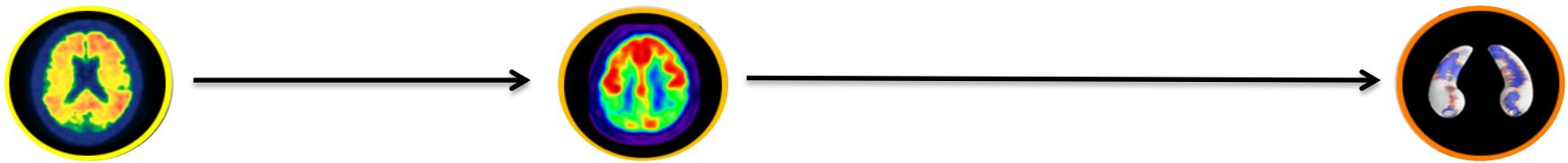
## Modification 1: Subtypes



Adapted from ADNI website figure

Young et al. Nature Comms. 2018

## Modification 2: Z-score events



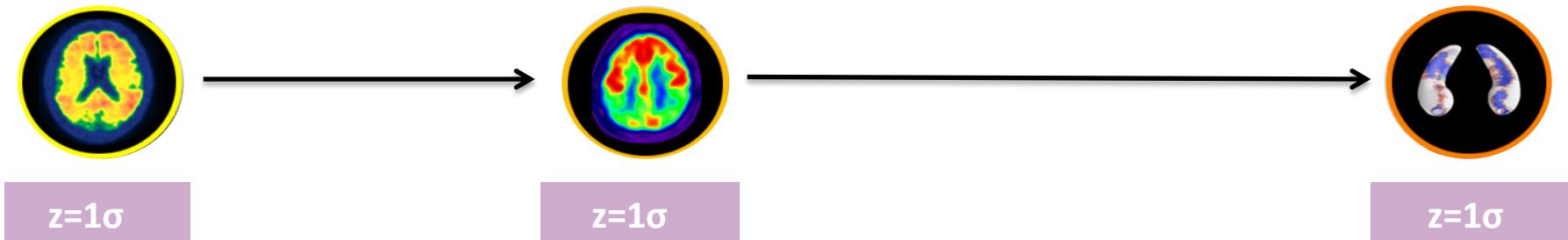
Adapted from ADNI website figure

# Heterogeneity & Subtypes



Young et al. Nature Comms. 2018

## Modification 2: Z-score events



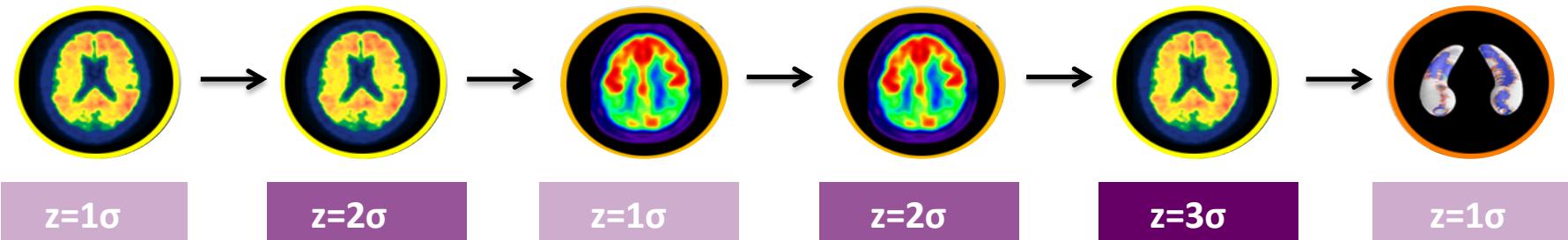
Adapted from ADNI website figure

# Heterogeneity & Subtypes



Young et al. Nature Comms. 2018

## Modification 2: Z-score events



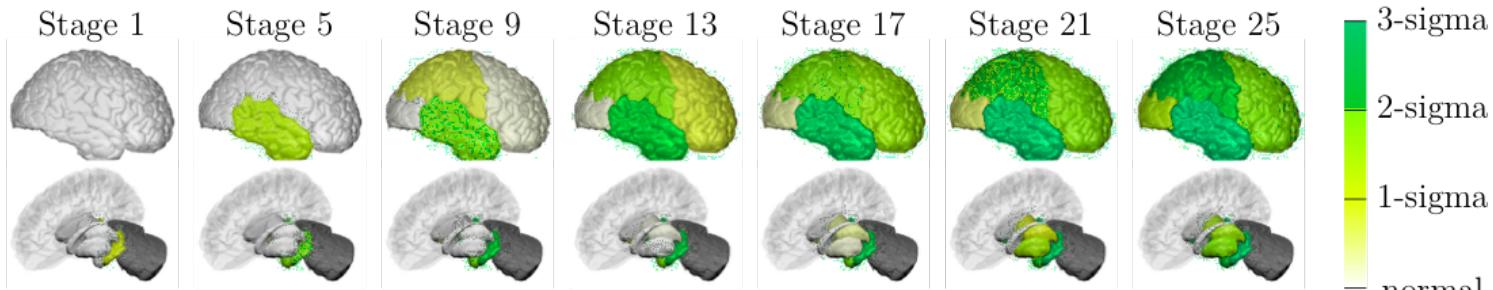
Adapted from ADNI website figure

# Heterogeneity & Subtypes

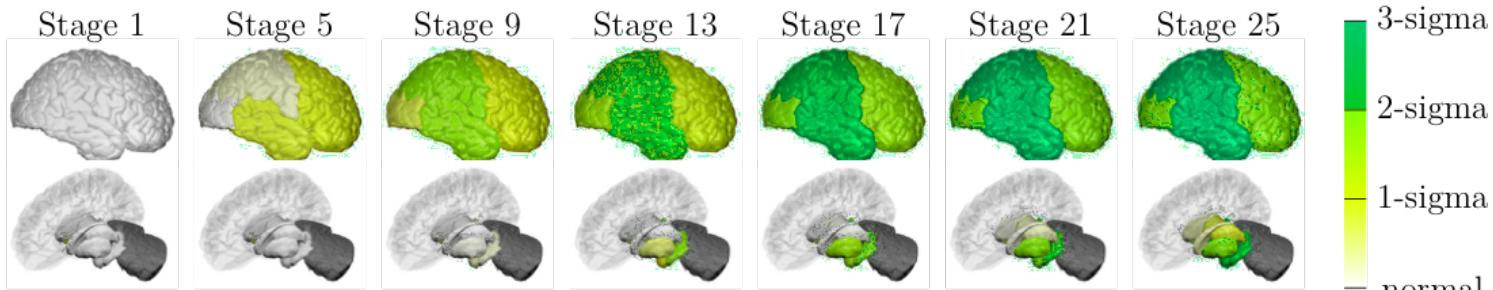


Young et al. Nature Comms. 2018

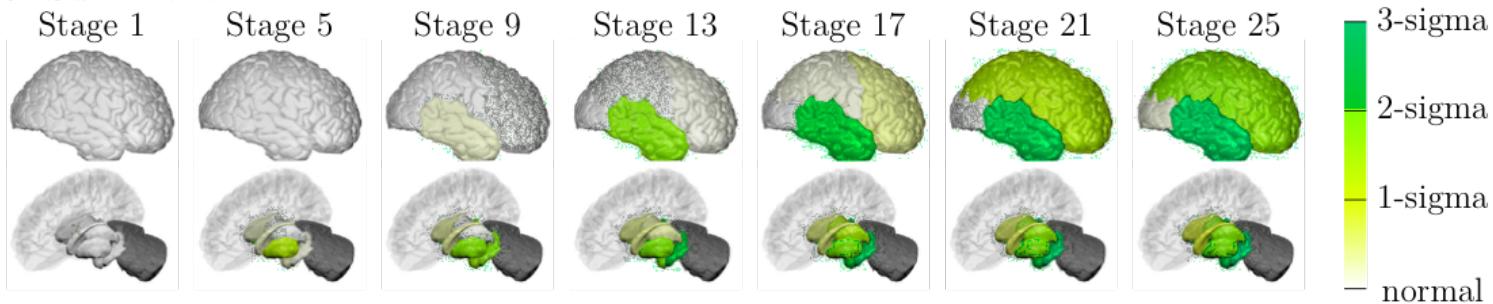
## A. Temporal



## B. Cortical



## C. Subcortical



The long game:  
Individualised models for precision staging and  
stratification

First step:  
*post hoc* analyses of completed trials



# MCI trial



The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 9, 2005

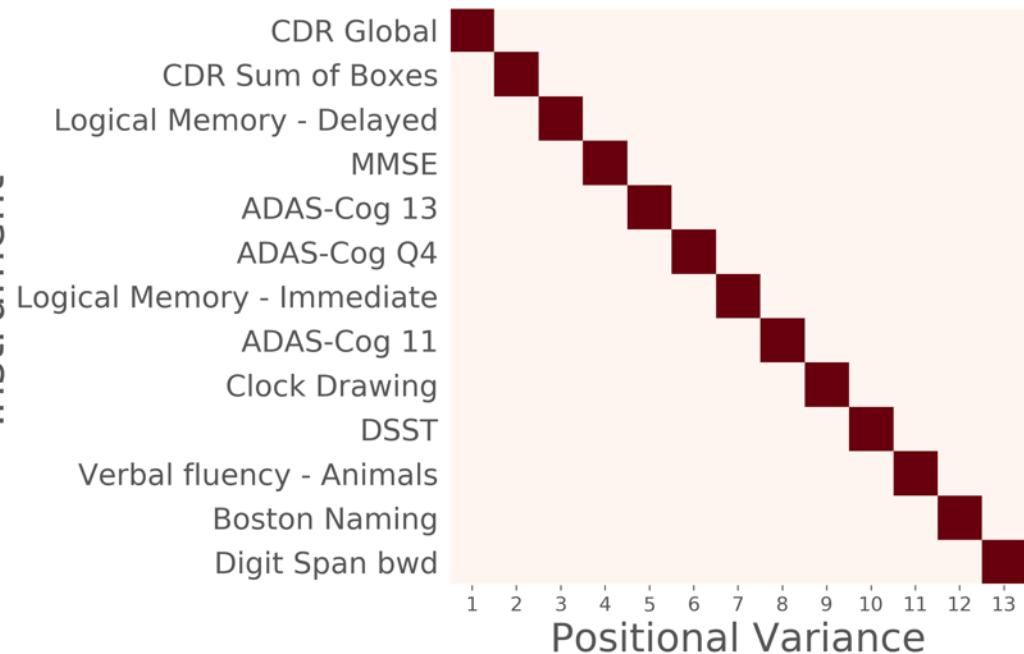
VOL. 352 NO. 23



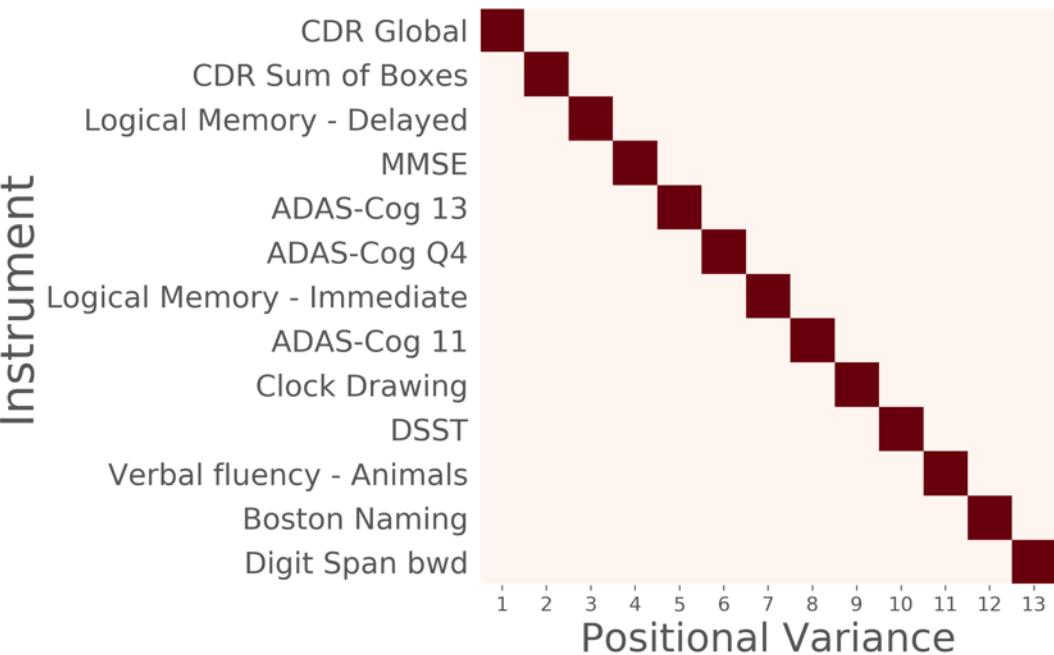
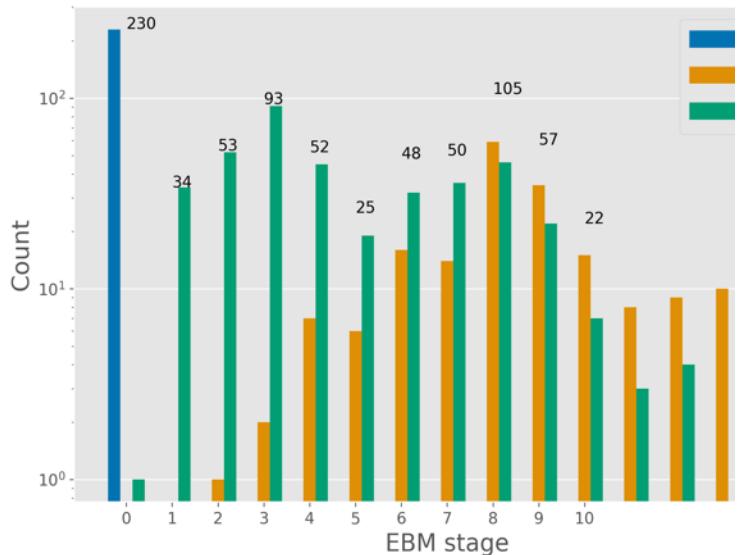
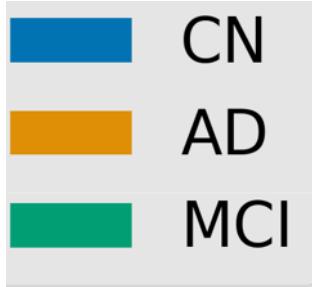
Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H.,  
David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D.,  
Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D.,  
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

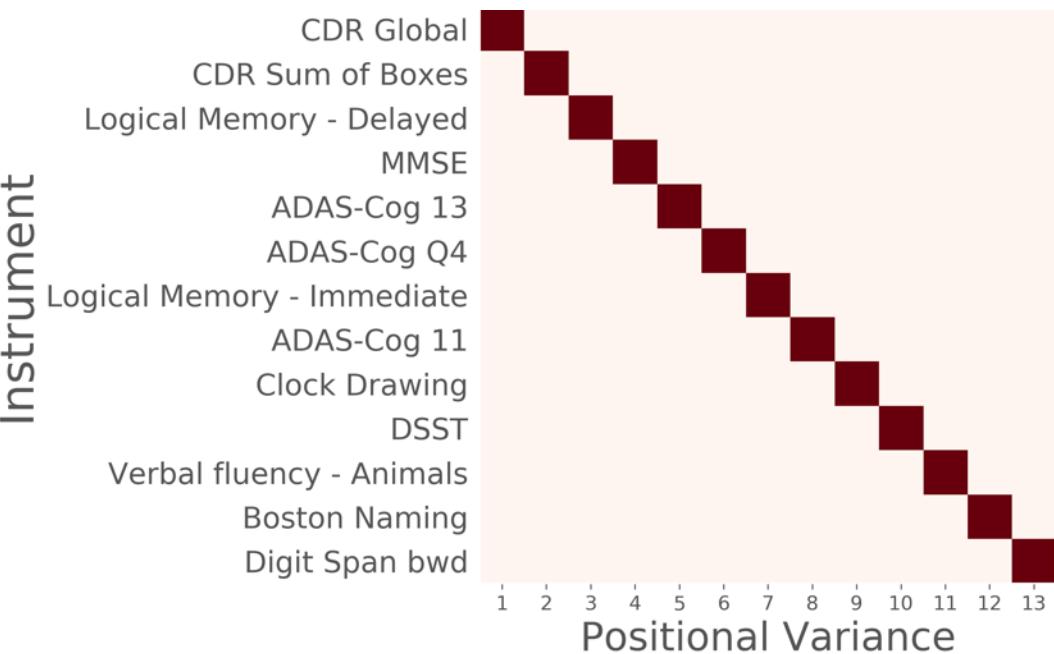
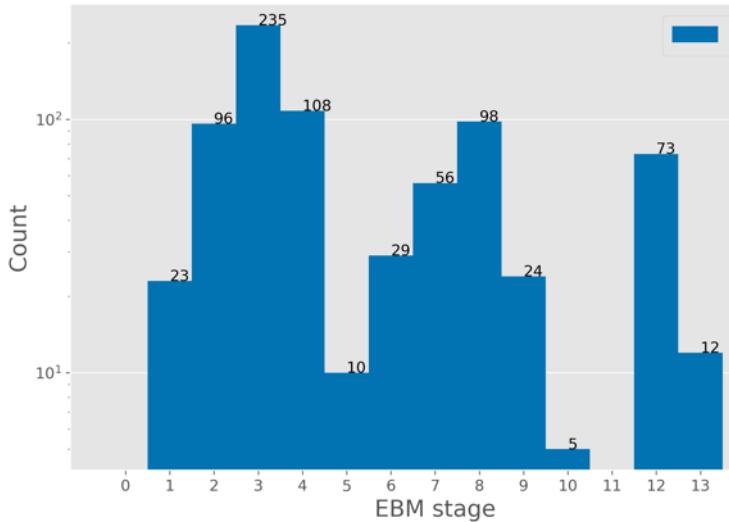




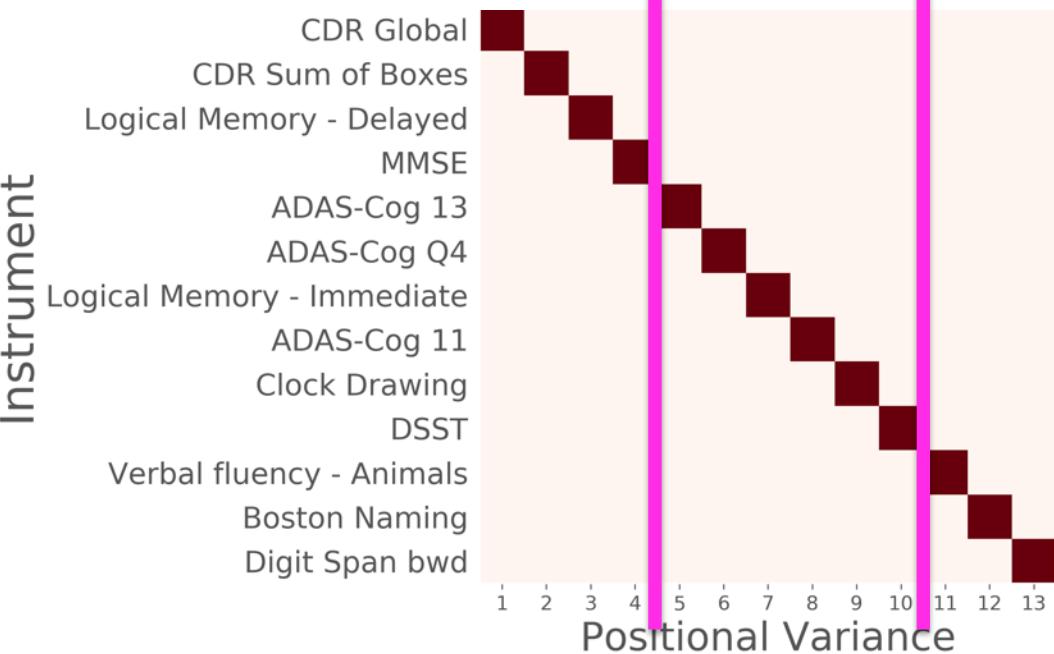
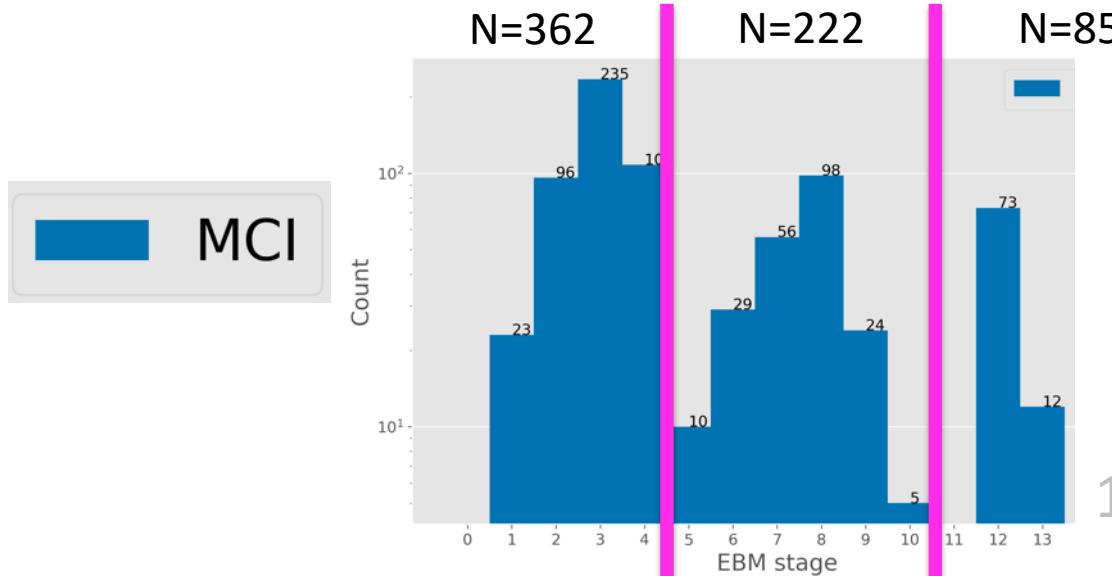
1. Build model (ADNI data)
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1. Build model (ADNI data)
2. Stage ADNI data (BL/SC)
3. Stratify
4. Analyse subgroups



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



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

Table 1. Group differences (Placebo – Treatment) in ADAS-Cog 13 between treatment and placebo (two-sample t test).

\* p < 0.05

	Instrument	Treatment	6mo	12mo	18mo	24mo	30mo	36mo
N=362	SS < 5	Donepezil	-0.14	-0.04	-0.11	-0.29	-0.60	0.32
		Vitamin E	-0.56	-0.71	-0.40	-0.51	-2.11	0.68
N=222	5 ≤ SS ≤ 10	Donepezil	-0.02	-0.77	0.55	-1.05	1.10	0.33
		Vitamin E	-0.51	-1.83	-0.50	0.47	-3.24	-1.48
N=85	SS > 10	Donepezil	1.92	3.71*	0.20	4.34	0.52	6.31*
		Vitamin E	2.81	1.97	1.16	-3.04	-0.24	0.09
	All	Donepezil	0.79	0.89	0.46	0.42	-0.45	1.12
		Vitamin E	-0.15	-0.64	-0.22	-0.56	-2.14	0.04

#### 4. Analyse subgroups

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**



# Supermodels for Trials



Join me in the quest for  
supermodels and drugs!

***2 Postdoc Vacancies (closing 25 May):***

**<http://pond.cs.ucl.ac.uk/vacancies>**

***PhD vacancy soon***