

# Computational Modelling of Alzheimer's disease for Clinical Trials

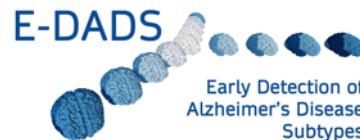
Neil Oxtoby, PhD

UKRI Future Leaders Fellow

Progression Of Neurodegenerative Disease (POND) group

Centre for Medical Image Computing (CMIC)

Department of Computer Science, UCL



# My quest for Supermodels and Drugs

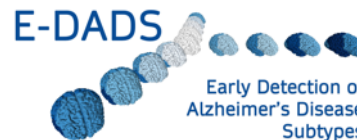
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# Acknowledgements

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## EuroPOND



UK Research and Innovation



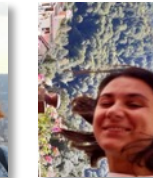
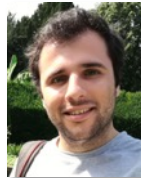
Alzheimer's Research UK  
The Power to Defeat Dementia

## EPSRC

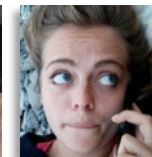
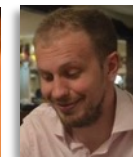
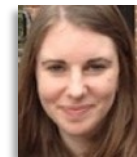
Engineering and Physical Sciences Research Council



## UCLiC



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/cmhc](http://www.ucl.ac.uk/cmhc)

- Links: COMBINE lab, DRC, MS@ION, HD, UCLiC, HDRUK, Lung Imaging

[neiloxtooby.com](http://neiloxtooby.com)

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

- 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





- 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
    - X ENGAGE study



# Aducanumab?

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



# Aducanumab?

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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



# Take-home message

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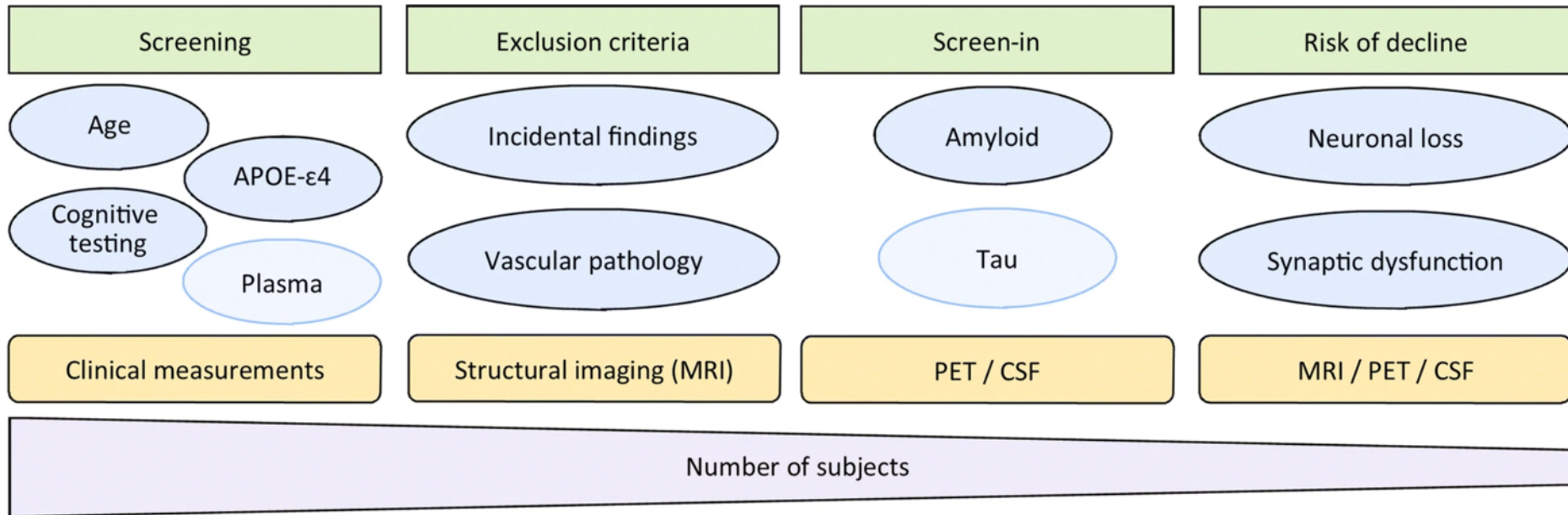


- AD is a multifactorial, heterogeneous disease
- Requires commensurate tools
  - Quantitative assessments in asymptomatic phase
  - Individualised biomarker-based disease signatures
  - Mechanisms not well understood?  
(amyloid hypothesis)



# What have trials done?

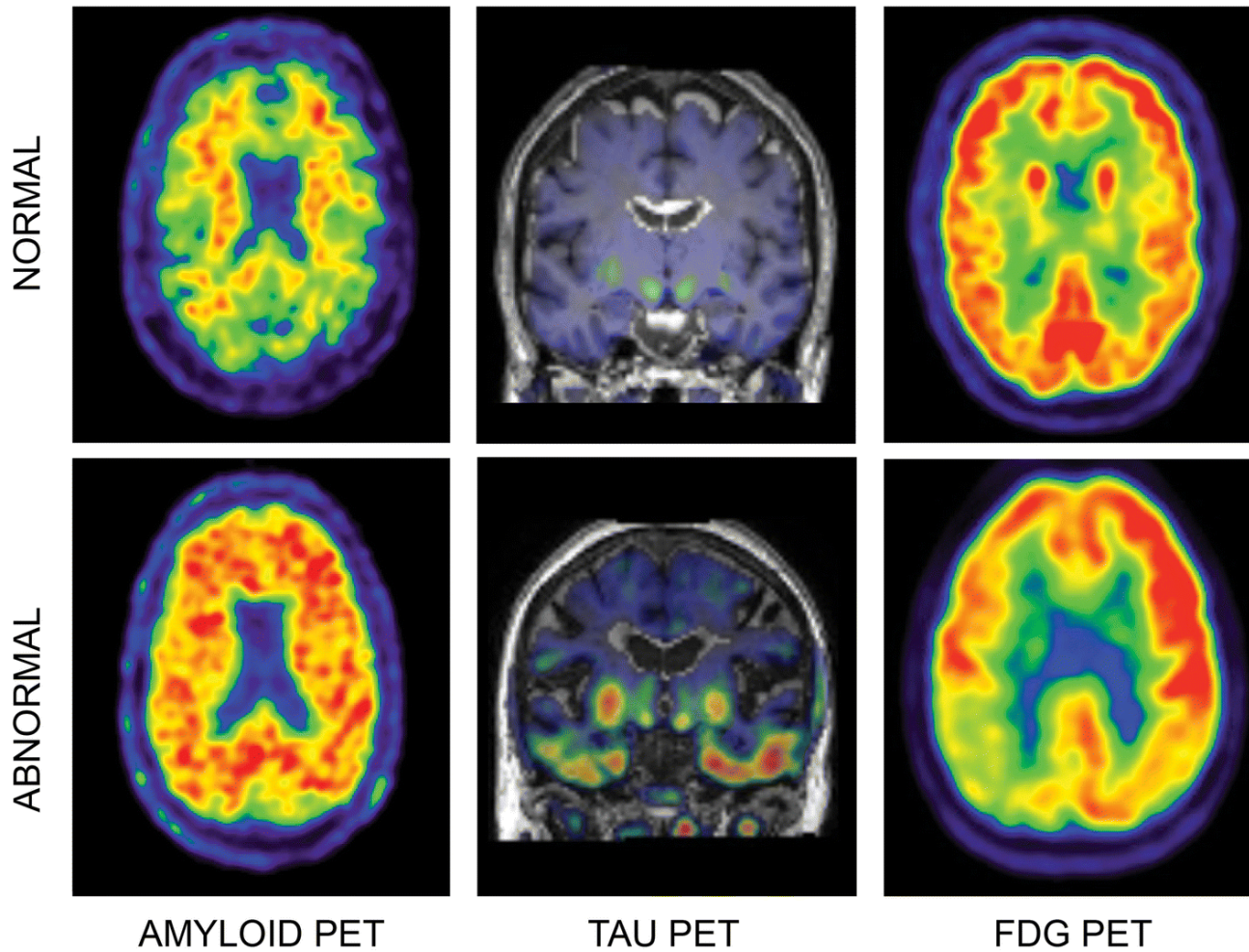
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M. ten Kate et al., Alz. Res. Therapy (2018)

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

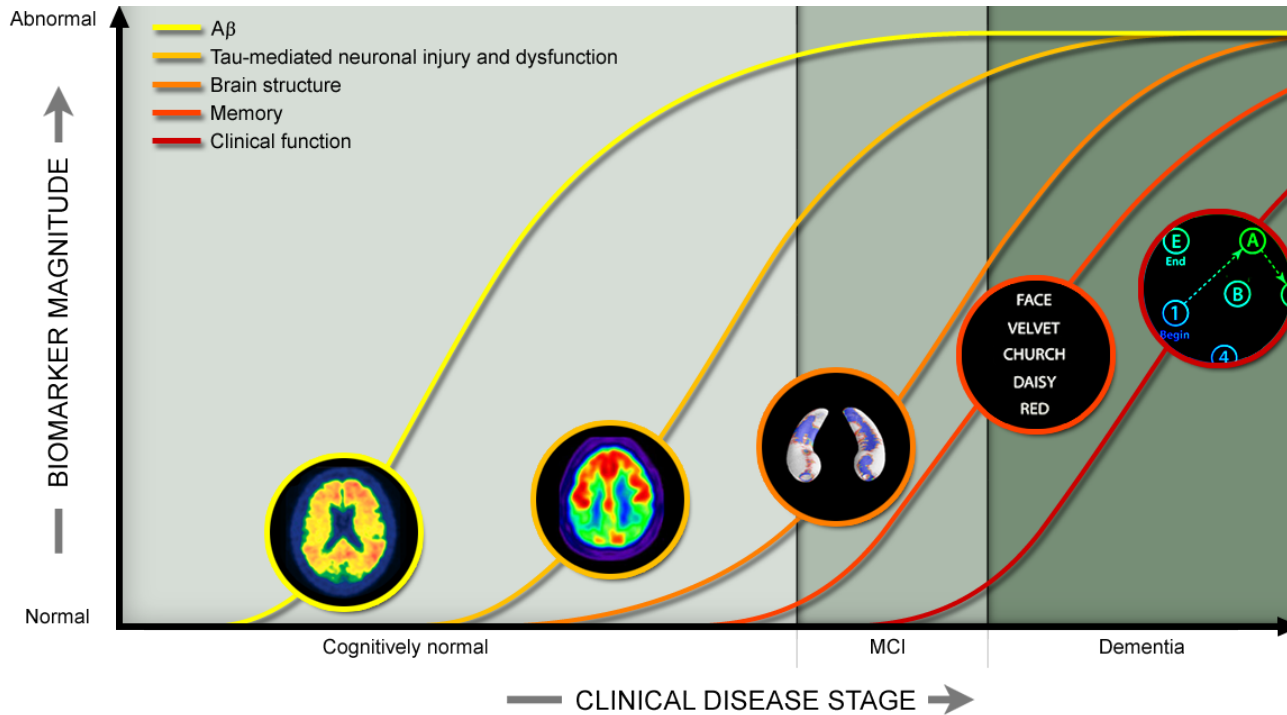




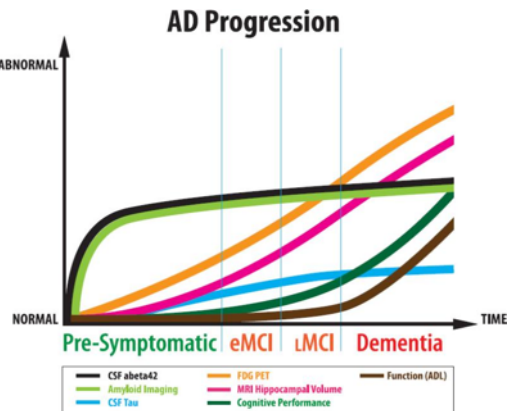
M. ten Kate et al., *Alz. Res. Therapy* (2018)

- 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

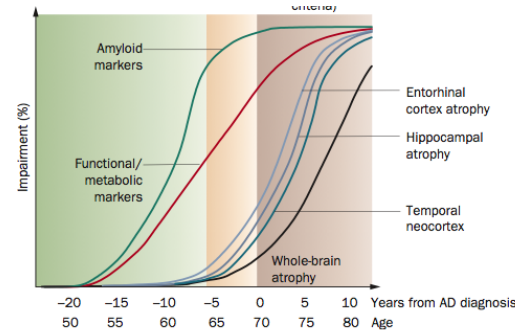




ADNI website:  
inspired by  
**Jack et al.**  
**Lancet**  
**Neurol.**  
2010, 2013.

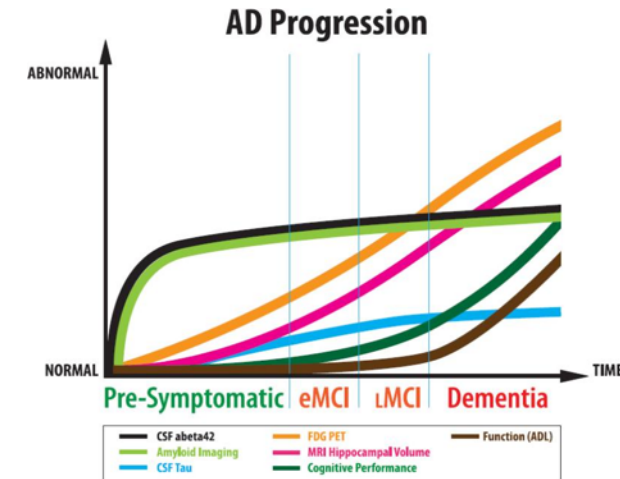


**Aisen et al.**  
**Alz. Dement.**  
2010

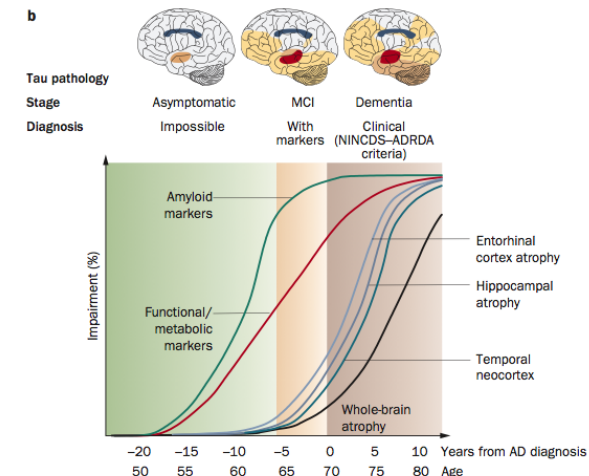


**Frisoni et al**  
**Nat. Rev.**  
**Neurol.** 2010

- 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

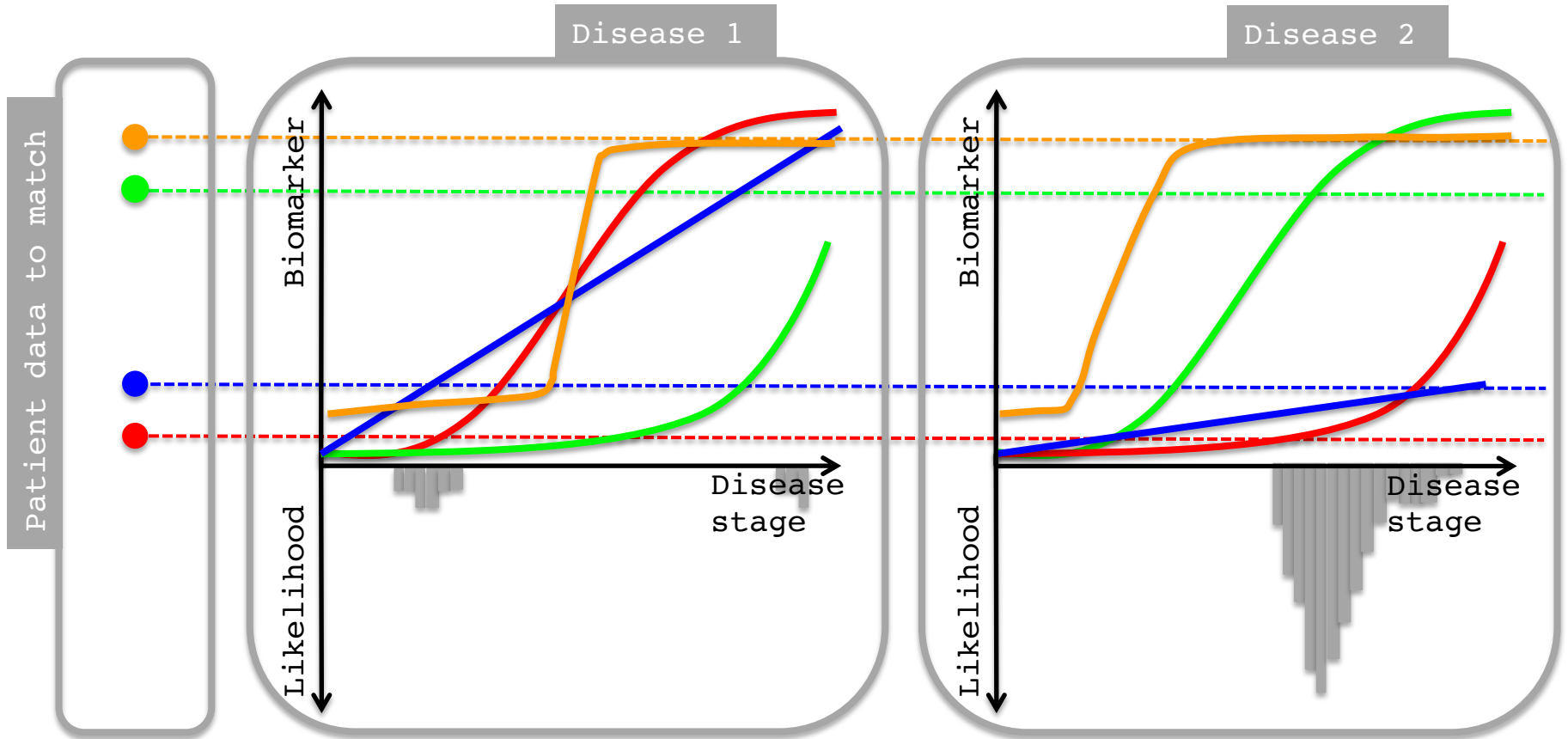


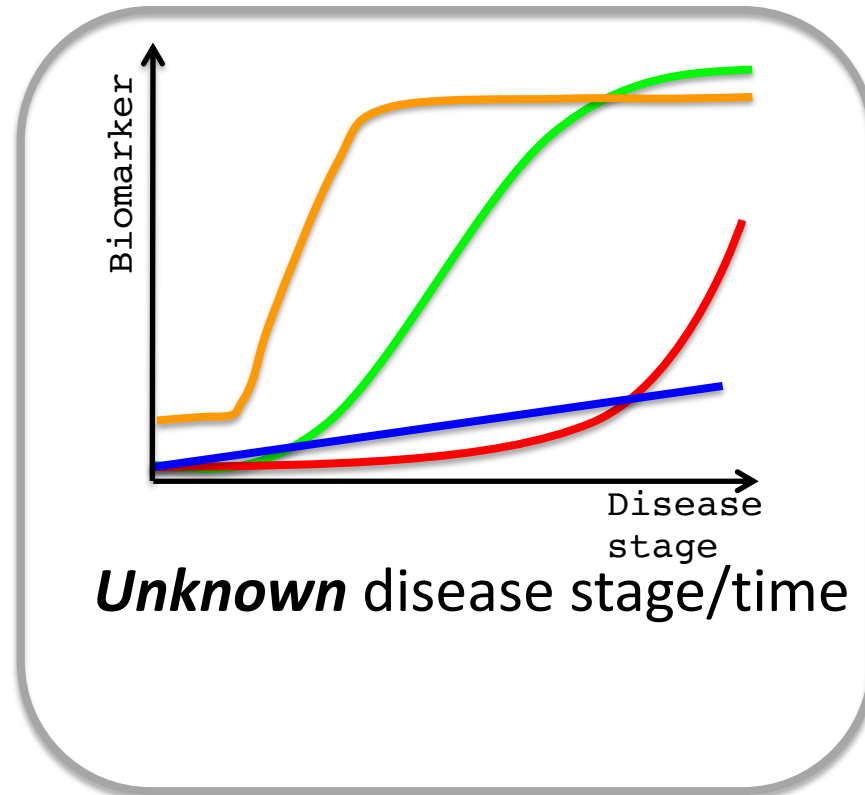
Frisoni et al. Nat.  
Rev. Neurol. 2010



# Diagnosis & Staging

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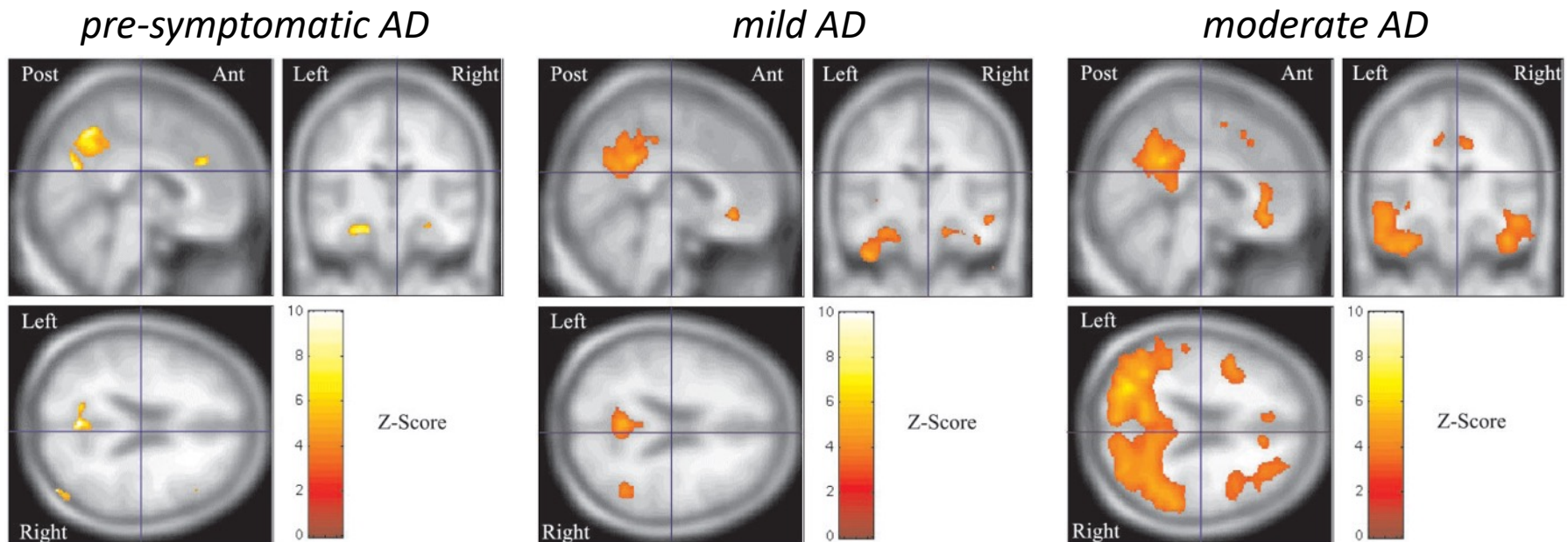




- Disease stage = symptoms (e.g. MMSE scores)
  - Crude group differences

Scahill et al. PNAS 2002

- T1 MRI measures of neuronal atrophy



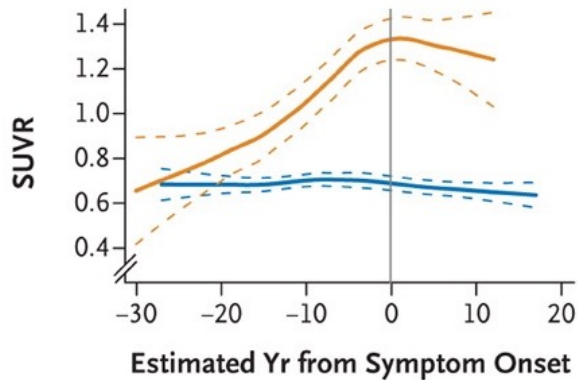


- Heritable diseases: estimable stage ( $\pm 5$  years)
  - *Autosomal dominant AD: familial age of onset*

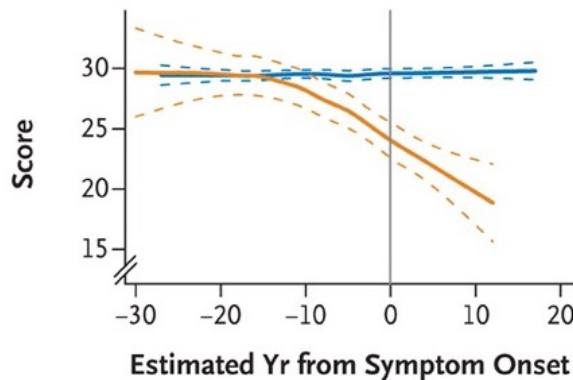
Bateman et al. NEJM 2012

- Imaging and clinical biomarkers

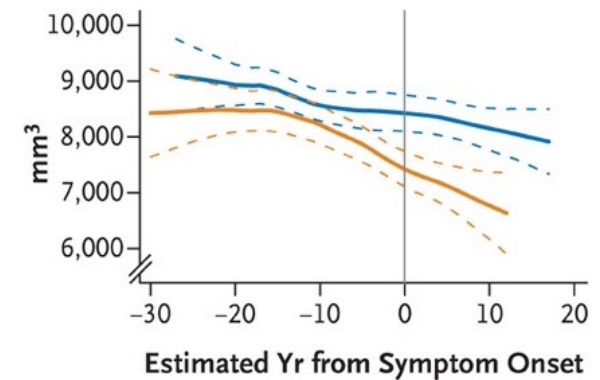
Amyloid PET  
(precuneus)



MMSE



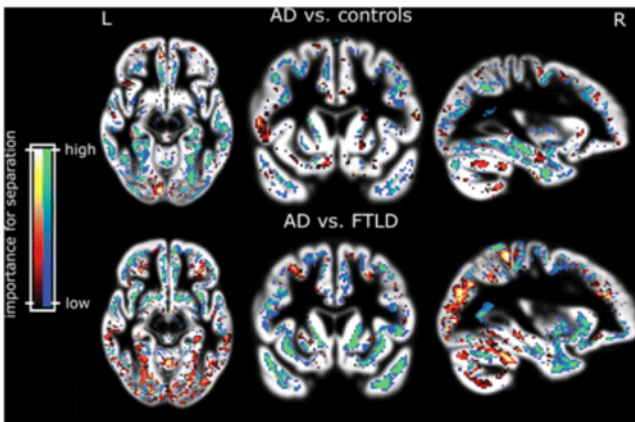
Hippocampus  
volume



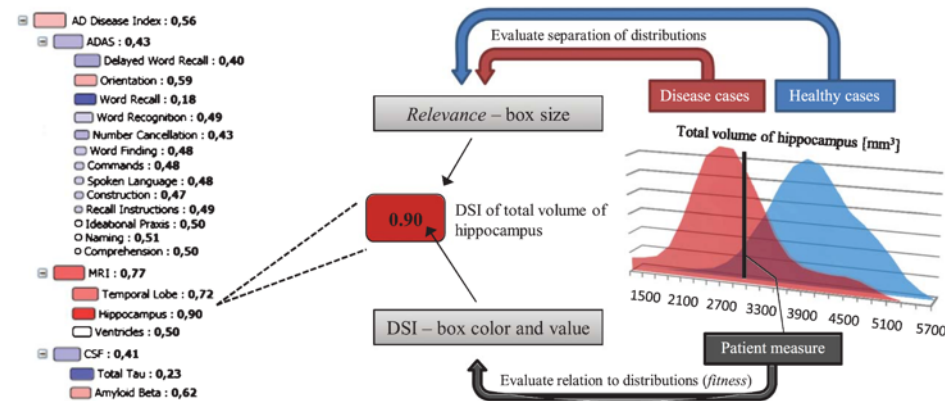
- Pattern recognition: **supervised** learning
  - Learn to classify patients from labelled data
  - Shown value of combining imaging and non-imaging data

## Classifying structural MRI in AD

## Disease State Fingerprint for AD



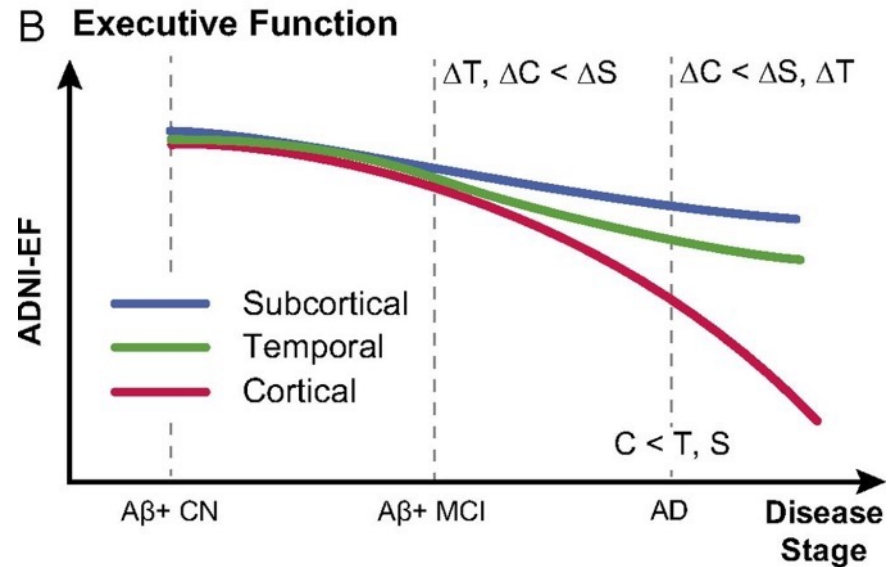
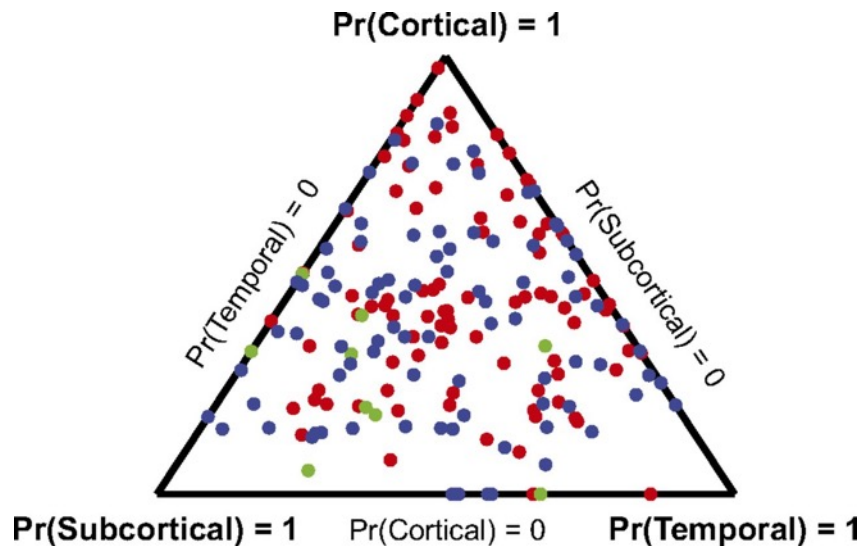
Klöppel et al. Brain 2008



Mattila et al. JAD 2011

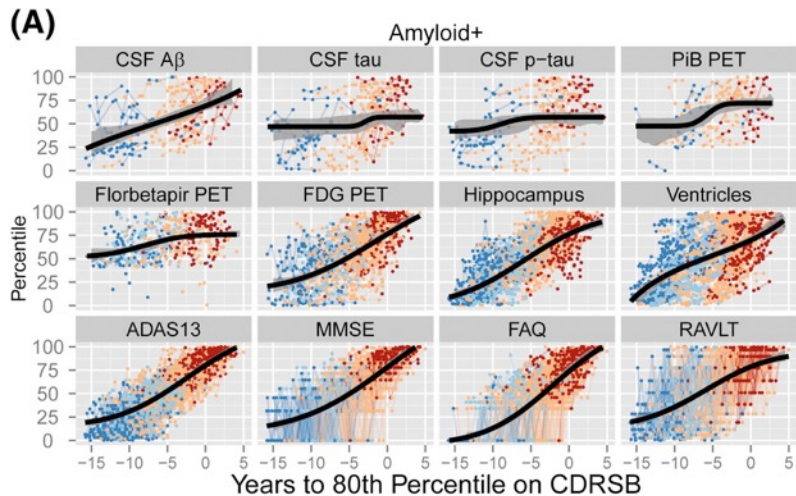
- Pattern discovery: **unsupervised** learning
  - Learn disease subtypes/stages automatically
  - Clustering

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

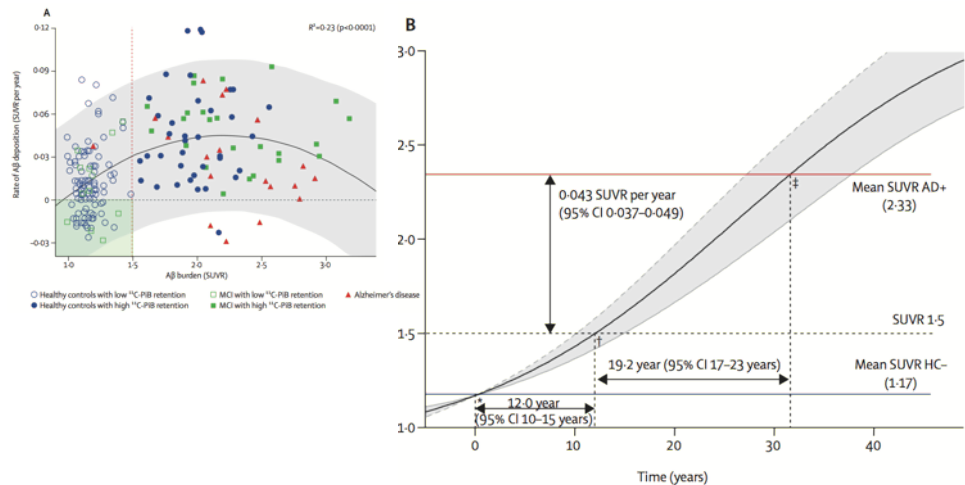


- **Unstructured data:** scalar biomarkers, phenomenological
  - Continuous: biomarker trajectories

## Self-modelling regression



## Differential Equation Models

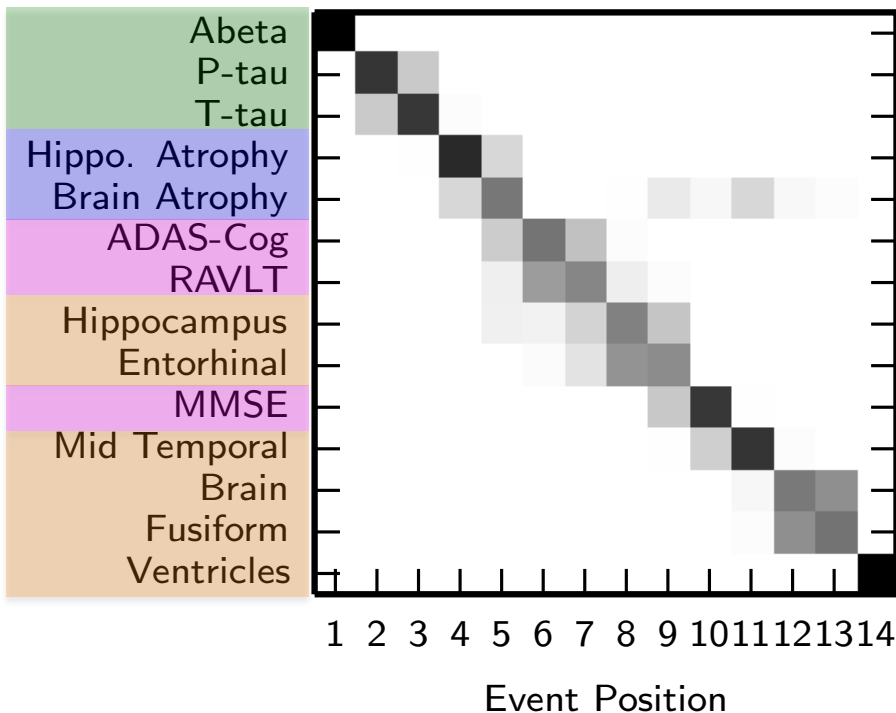


Donohue et al. *Alz. Dem.* 2014 (2017)  
 Jedynak et al. *NIMG* 2012; (2015;2019)  
 Lorenzi et al. *NIMG* 2017

Villemagne et al. *TLN* 2013  
 Oxtooby et al. *Brain* 2018

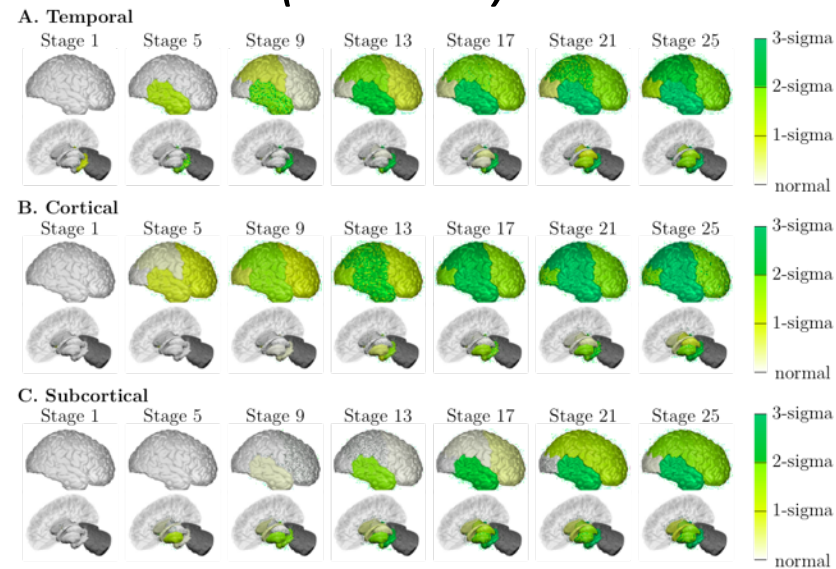
- **Unstructured data:** scalar biomarkers, phenomenological
  - Discrete: events

## Event-based model



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

## Subtype & Stage Inference (SuStaln)



Young et al. Nat. Comms 2018

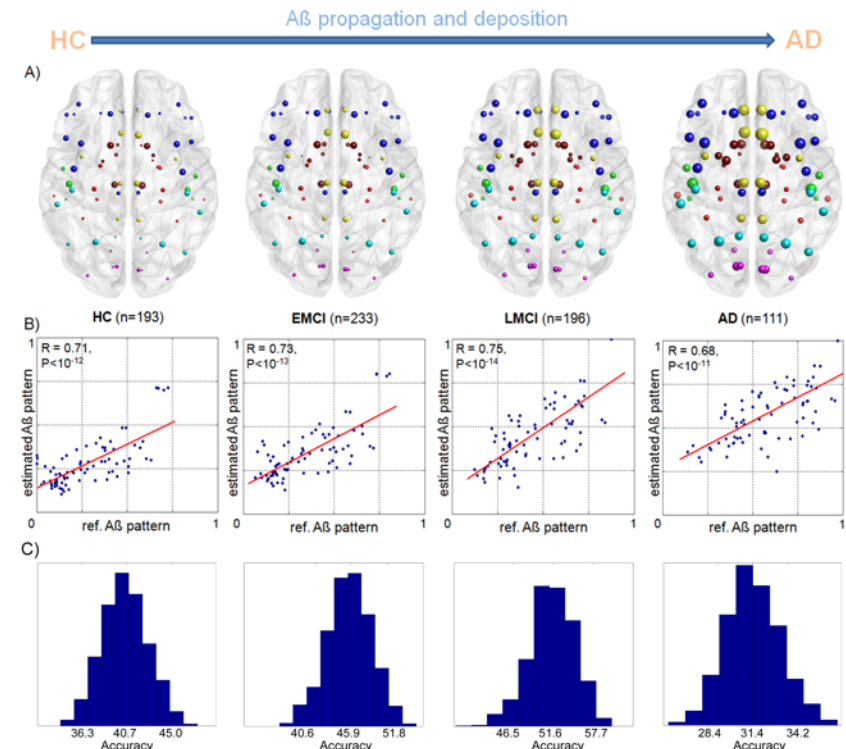


- **Structured data:** spatial info. Images, connections
  - Spatiotemporal models: e.g. shape/image regression  
 Durrleman et al. IJCV 2013  
 Lorenzi et al. NeuroBiol Aging 2015  
 Schiratti et al., IPMI 2015; JMLR 2017
  - Network propagation models:  
 e.g. prion-like transmission

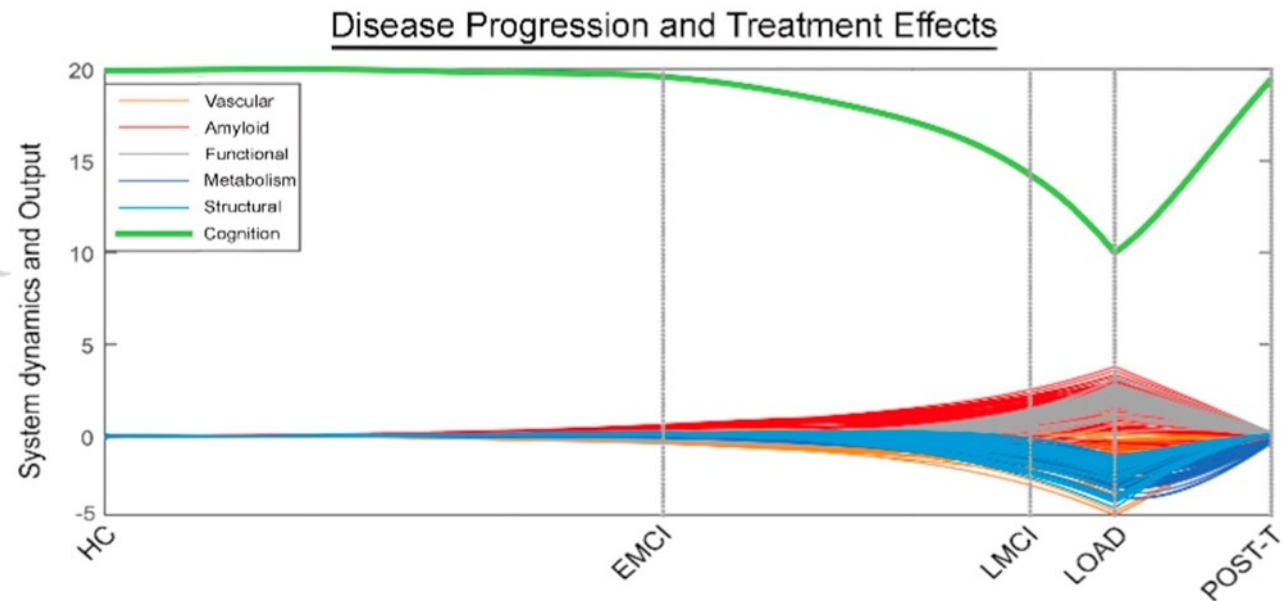
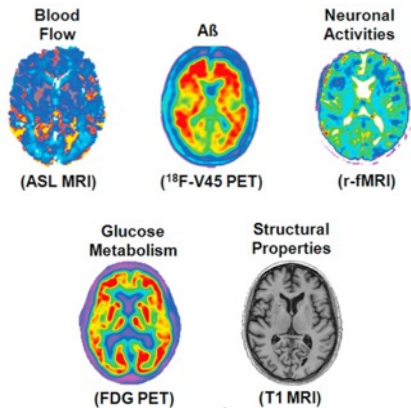
Iturria-Medina et al.  
 PLOS Comp. Biol. 2014; NIMG 2017

Raj et al. Neuron 2012

Garbarino et al. eLife 2019



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







# Next step

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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

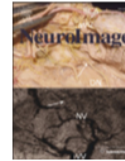


ELSEVIER

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: [www.elsevier.com/locate/ynimg](http://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<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</sup>, Sarah J. Tabrizi<sup>f,g</sup>, Sebastien Ourselin<sup>a,d,e</sup>, Nick C. Fox<sup>e,g</sup>, Daniel C. Alexander<sup>a,b</sup>

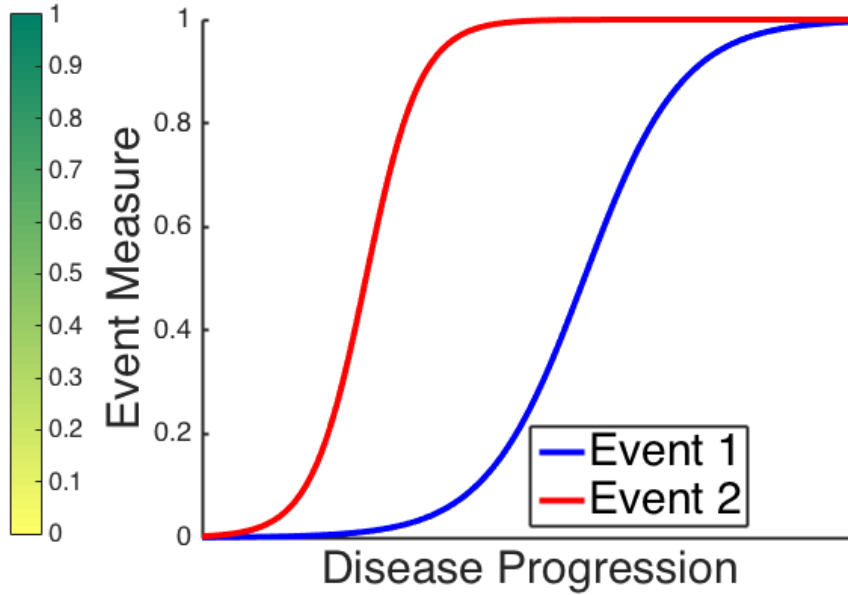
doi:10.1093/brain/awu176

Brain 2014; 137; 2564–2577 | 2564

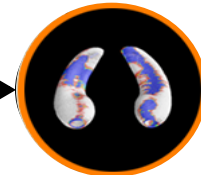
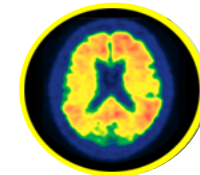
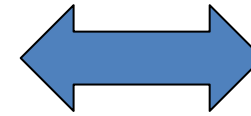
**BRAIN**  
A JOURNAL OF NEUROLOGY

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

Alexandra L. Young,<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>1</sup> Nick C. Fox,<sup>2</sup> Sebastien Ourselin,<sup>1,2</sup> Jonathan M. Schott<sup>2,\*</sup> and Daniel C. Alexander<sup>1,\*</sup>

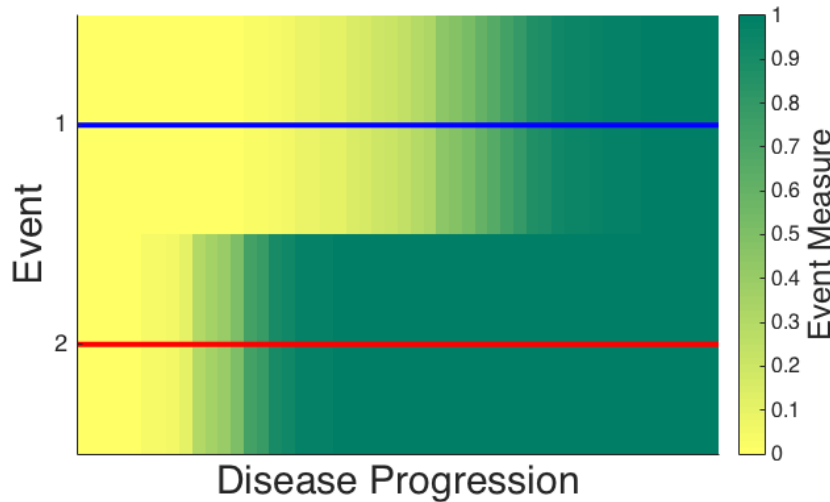


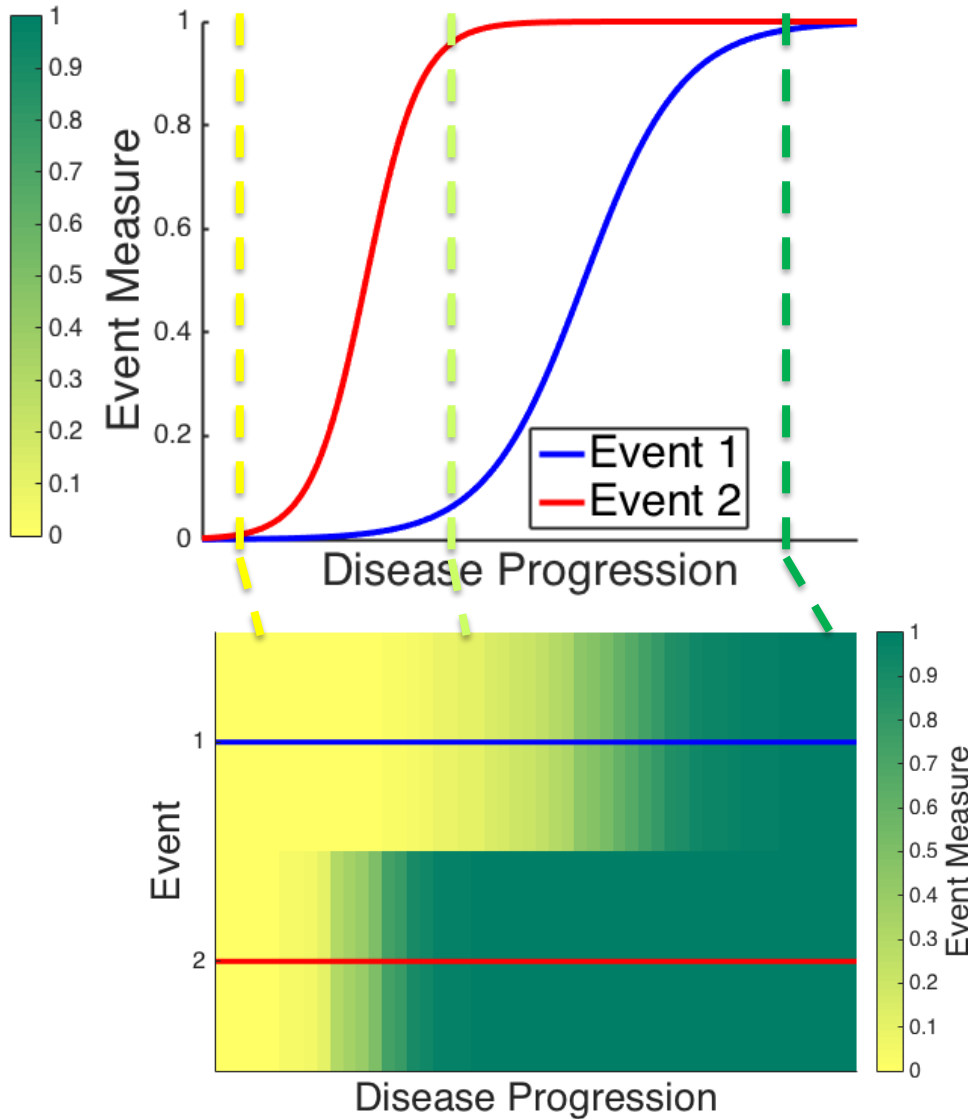
After  
Fonteijn et al.  
NeuroImage 2012



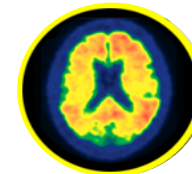
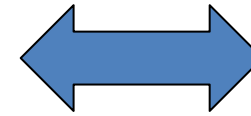
$E_2$

$E_1$

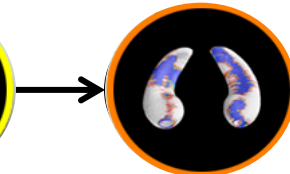




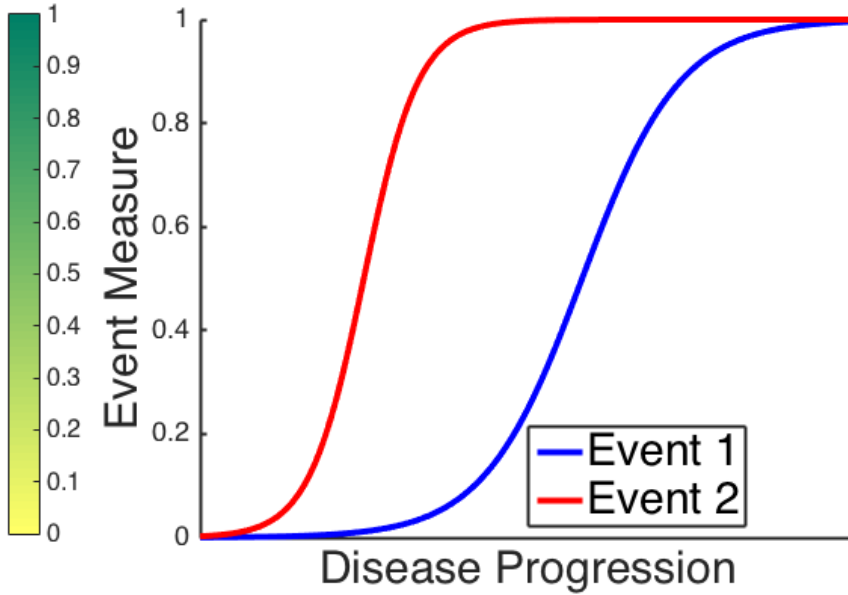
After  
Fonteijn et al.  
NeuroImage 2012



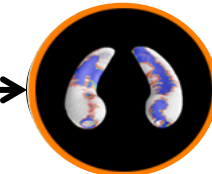
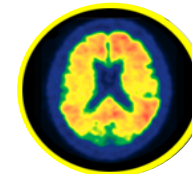
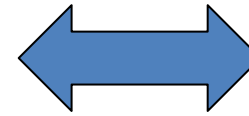
$E_2$



$E_1$

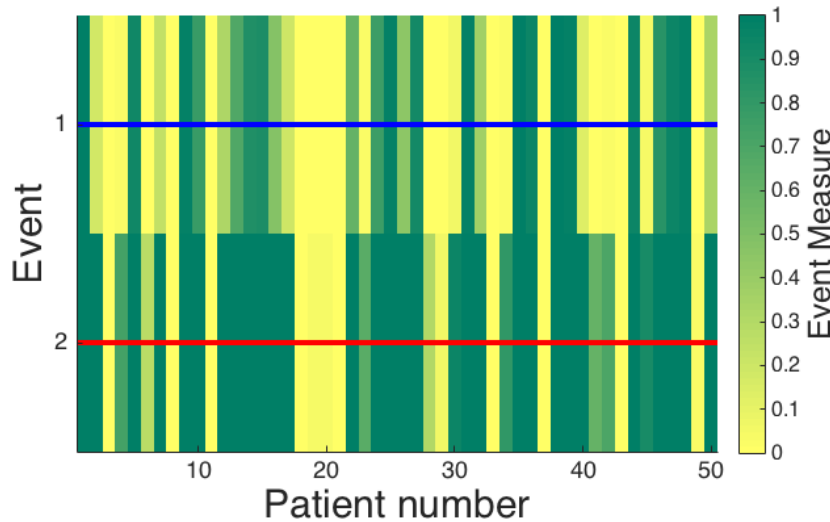


After  
Fonteijn et al.  
NeuroImage 2012

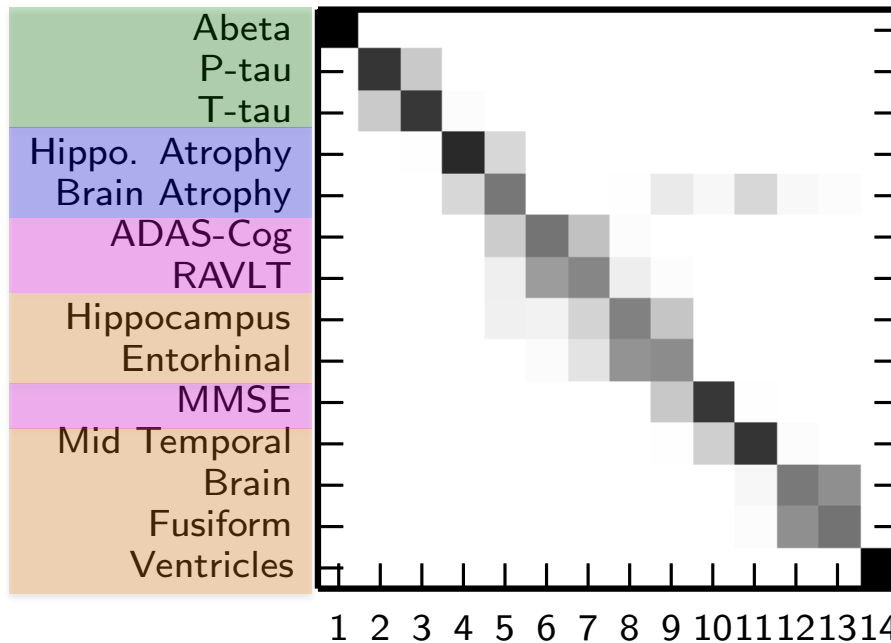
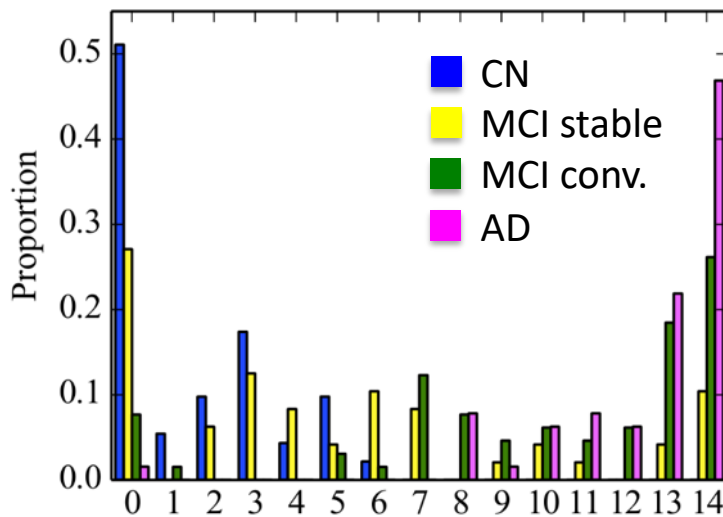


$E_2$

$E_1$



Young et al. Brain 2014



**Model Stages:**

0

1-3

CSF

4-5

Rates of atrophy

6-8

Cognitive test scores

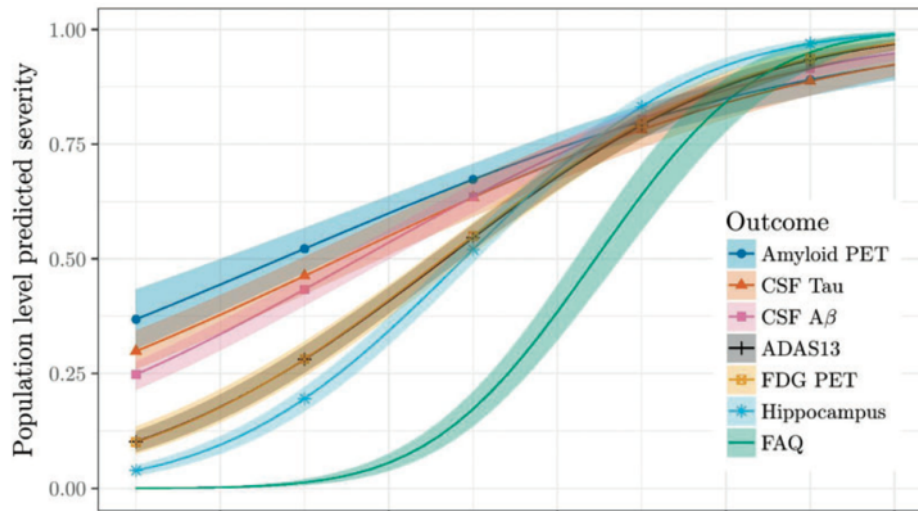
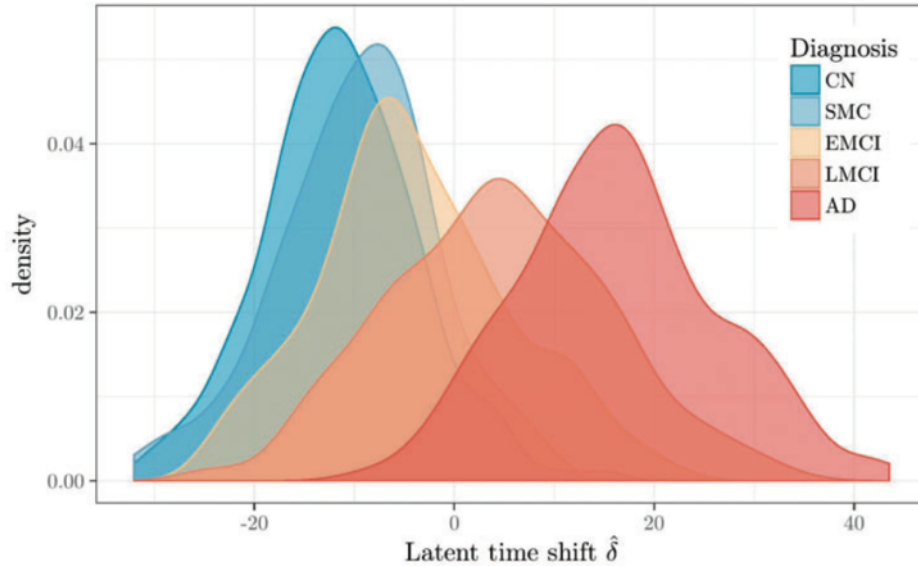
9-14

Brain volumes



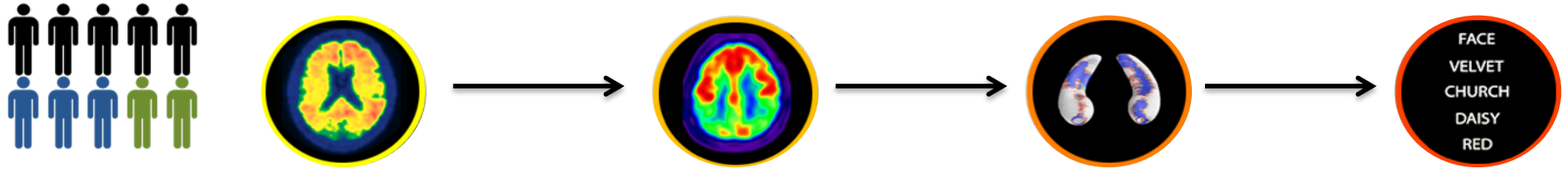
# Staging individuals

Li et al. Stat Meth Med Res 2017

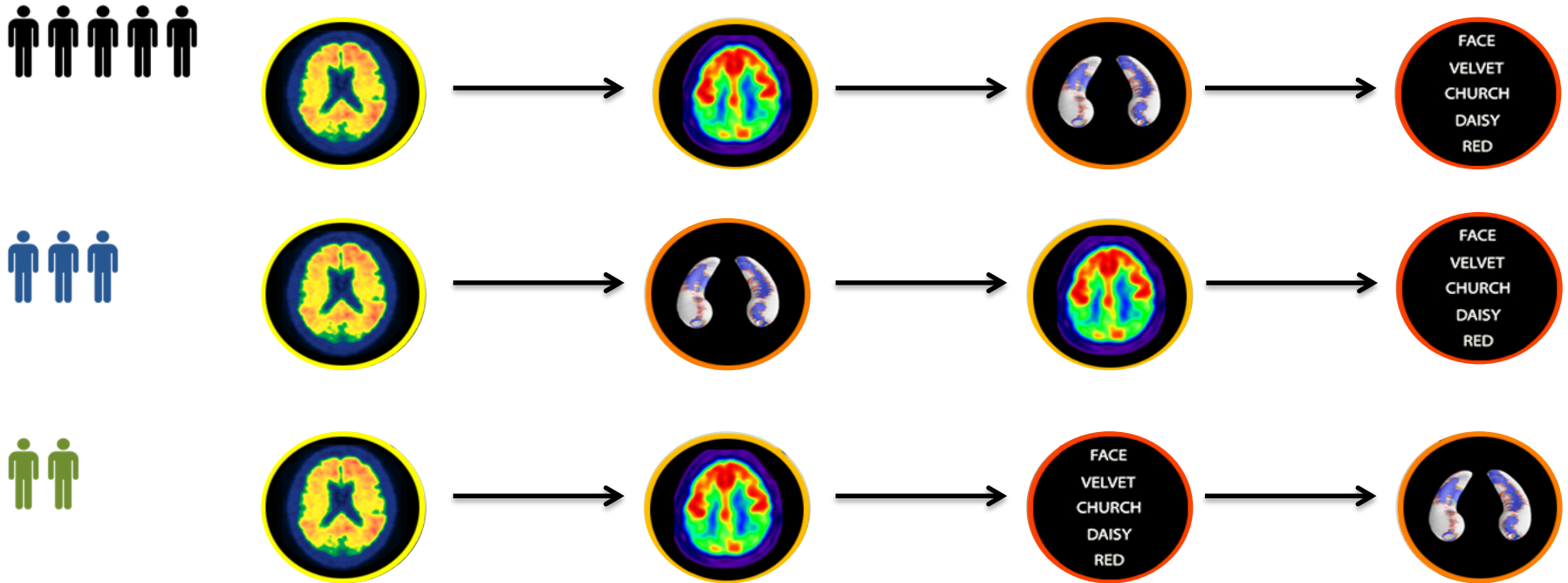




## Modification 1: Subtypes



## Modification 1: Subtypes



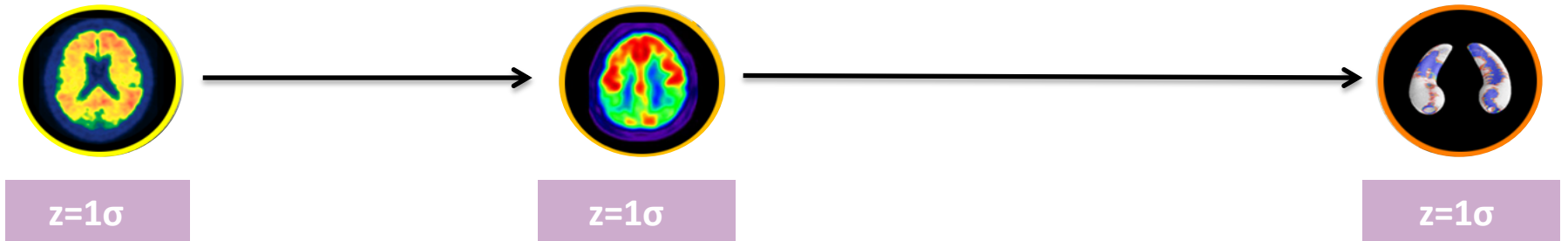


## Modification 2: Z-score events

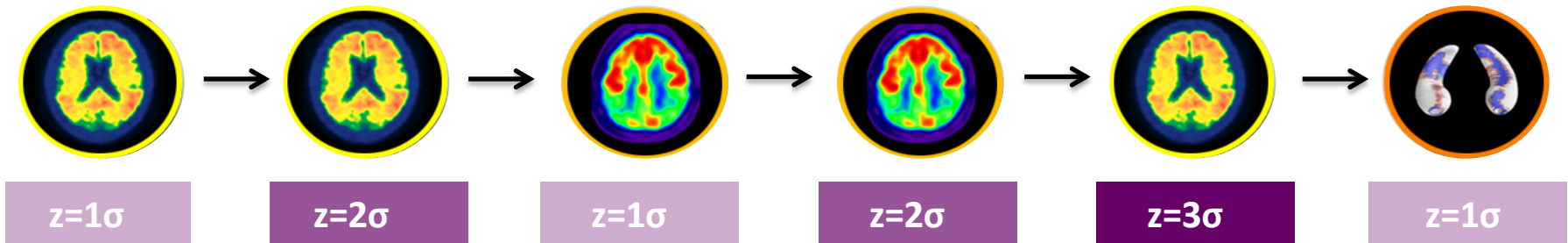




## Modification 2: Z-score events

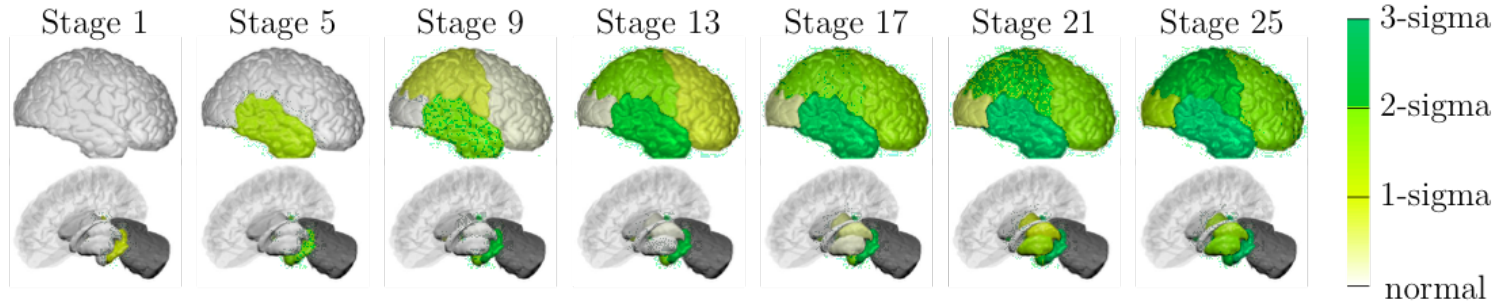


## Modification 2: Z-score events

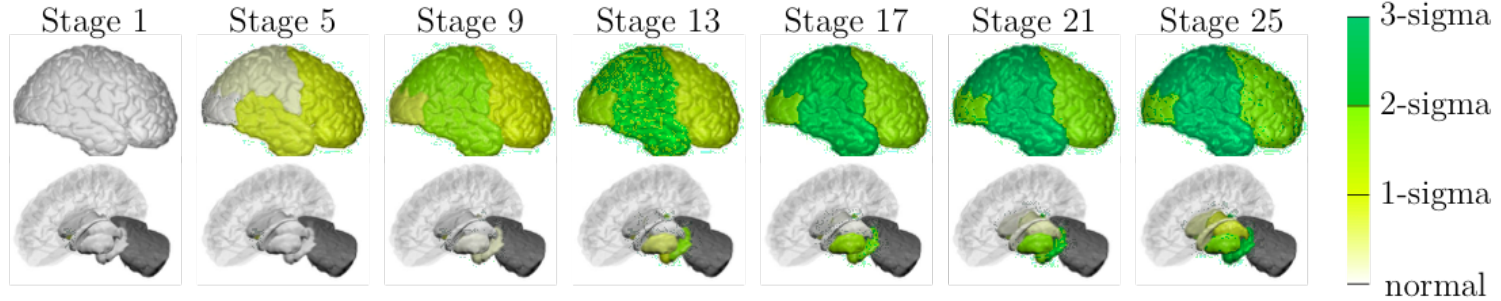


Young *et al.* Nature Comms. 2018

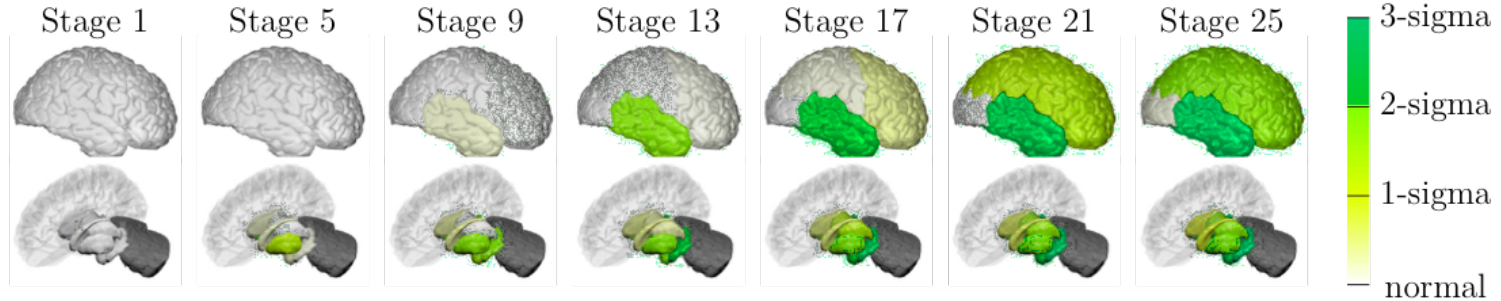
## A. Temporal



## B. Cortical



## C. Subcortical



The long game:  
Individualised models for precision staging and  
stratification

First step:  
*post hoc* analyses of completed trials





# MCI trial

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The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2005 VOL. 352 NO. 23

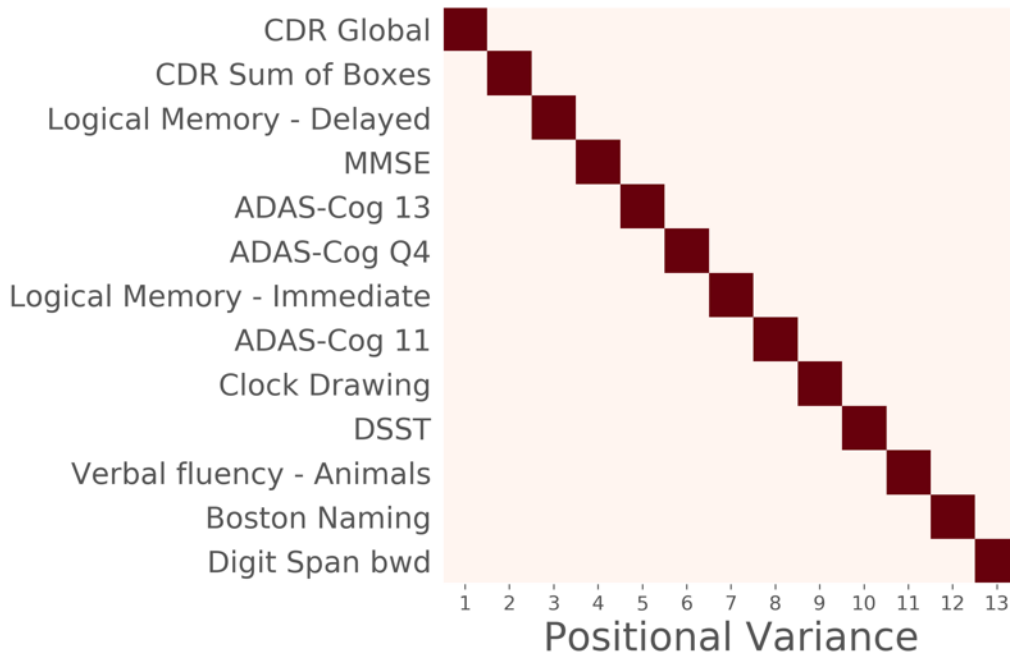
## Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

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\*

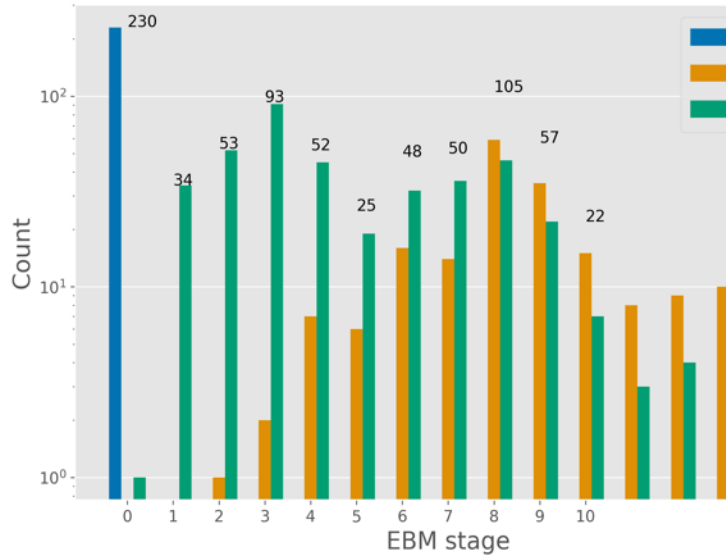
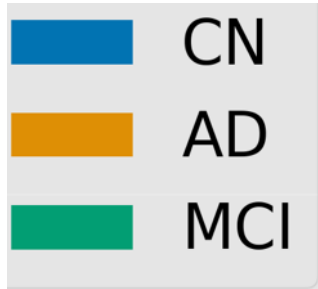


1. Build model (ADNI data)
2. Stage trial data (BL/SC)
3. Stratify
4. Analyse subgroups

Instrument

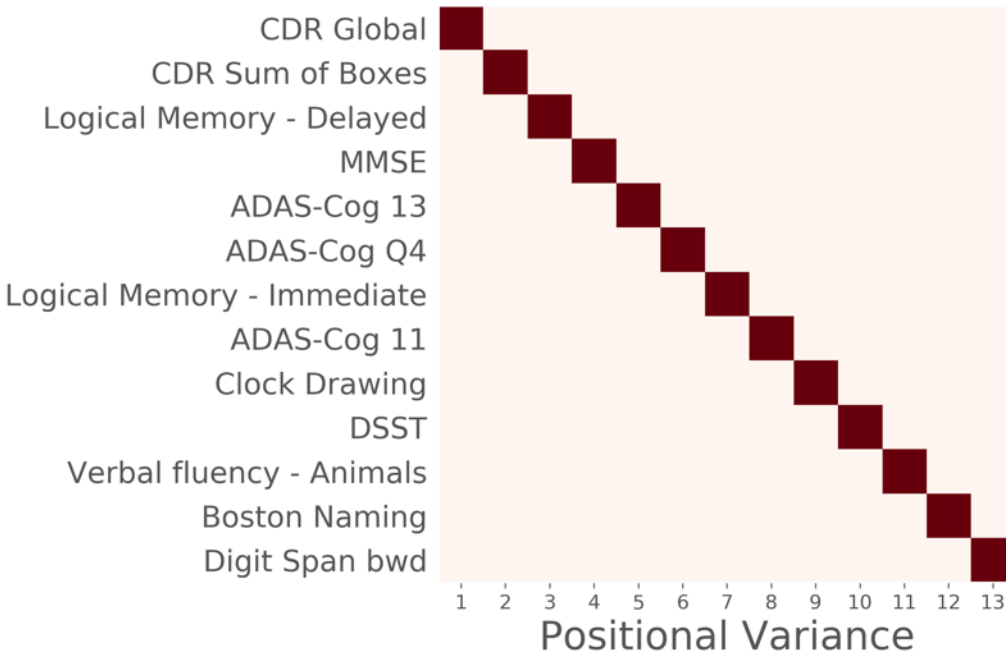


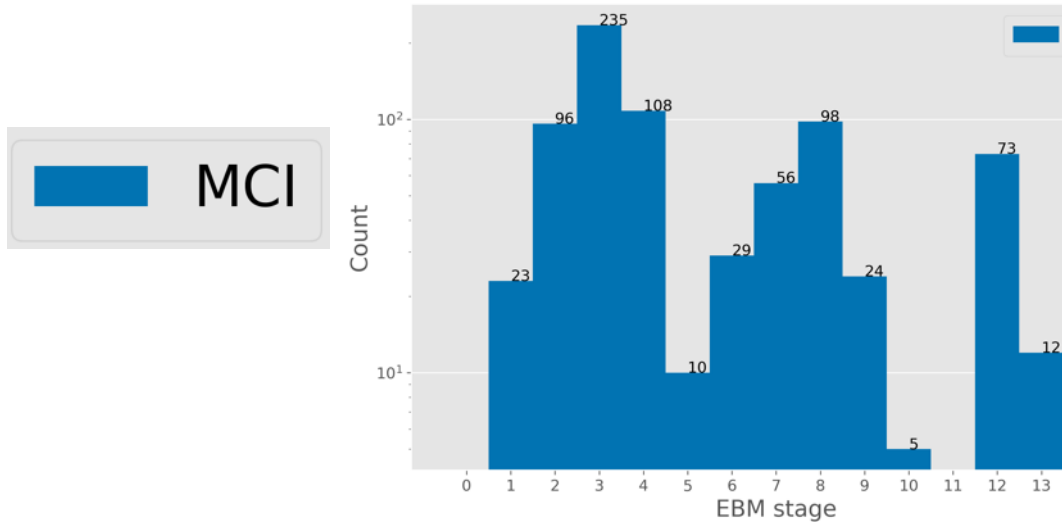
1. Build model (ADNI data)
2. Stage trial data (BL/SC)
3. Stratify
4. Analyse subgroups



1. Build model (ADNI data)
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Instrument



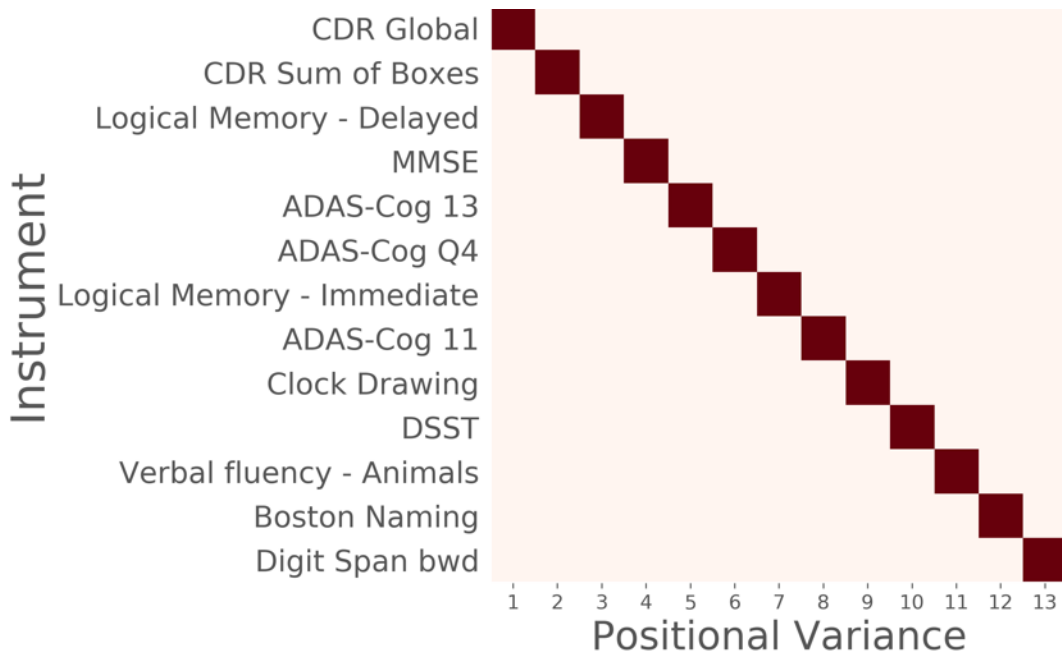


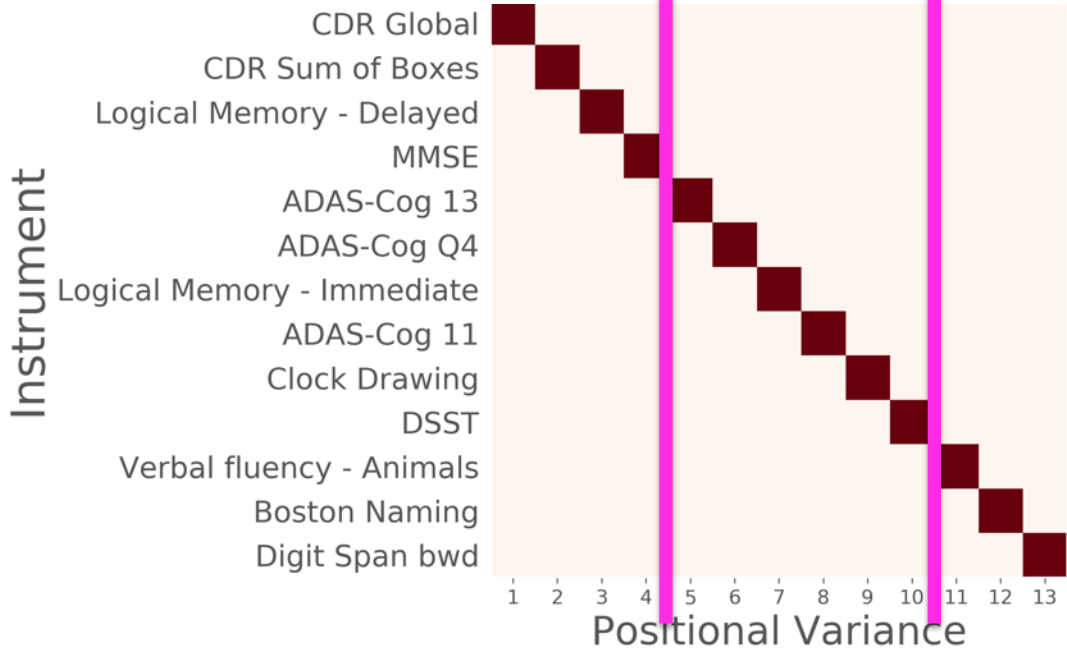
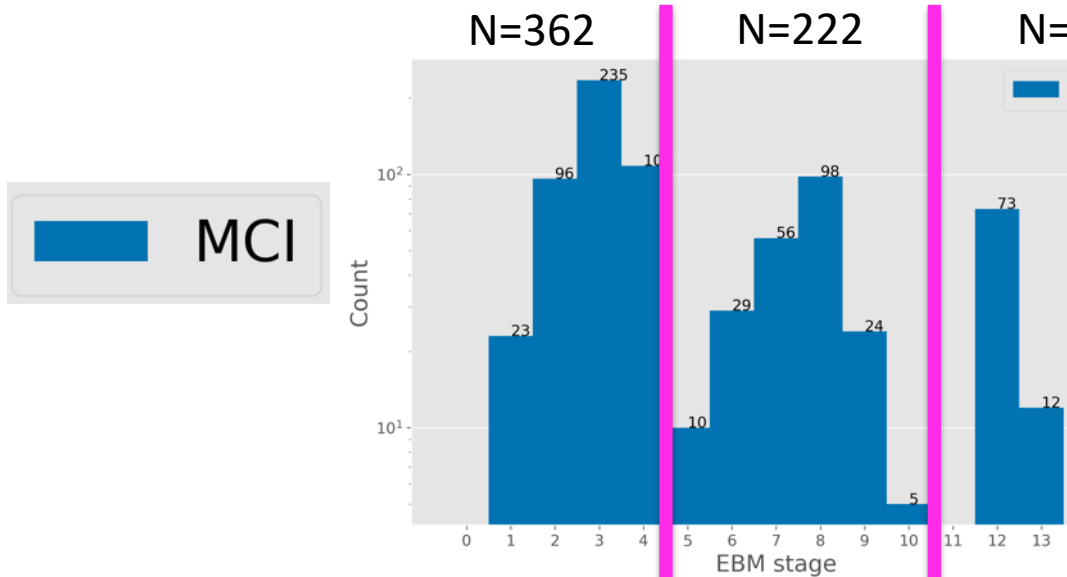
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Table 1. Group differences (Placebo – Treatment) in ADAS-Cog 13 between treatment and placebo (two-sample t test).

\*  $p < 0.05$

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	<b>3.71*</b>	0.20	4.34	0.52	<b>6.31*</b>
		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







**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***

