@NeilOxtoby
neiloxtoby.com
n.oxtoby@ucl.ac.uk

UCL

Data-driven Disease Progression Modelling: thinking outside the black box

Neil P. Oxtoby

Principal Research Fellow (research track Assoc. Prof.)
UCL Centre for Medical Image Computing

pond
Progression Of Neurodegenerative Disease

Data Science Lead, DEMON Network
demondementia.com

cmic
Centre for Medical Image Computing

Douglas CIC Lecture Series, 28 Feb 2024

Today (Tonight)

- Background & Motivation: Alzheimer’s disease (+ others)
  - Lack of a well-defined and consistent “disease time” axis

- Data-driven Disease Progression Modelling
  - Math + Human Insight + ML + “Big” Data

This talk is based on two papers

2017

CURRENT OPINION

Imaging plus X: multimodal models of neurodegenerative disease

Neil P. Oxtoby and Daniel C. Alexander, for the EuroPOND consortium

2024

nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]

nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]

Definition of "Data-driven disease progression model":

- Constructs a quantitative timeline of disease
- Directly informed by measured data

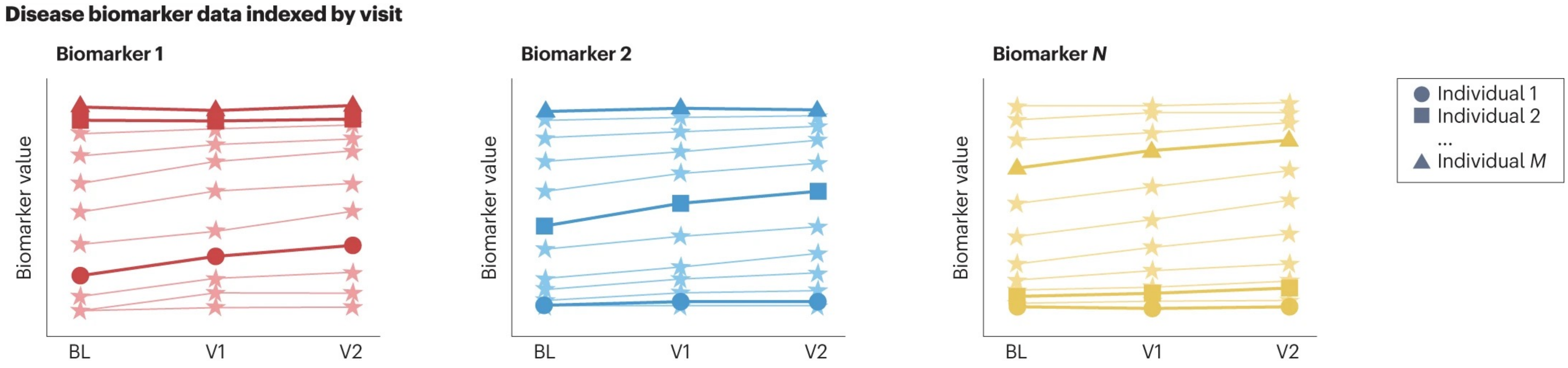
- Construct a quantitative timeline of disease.

- Directly informed by measured data

nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]



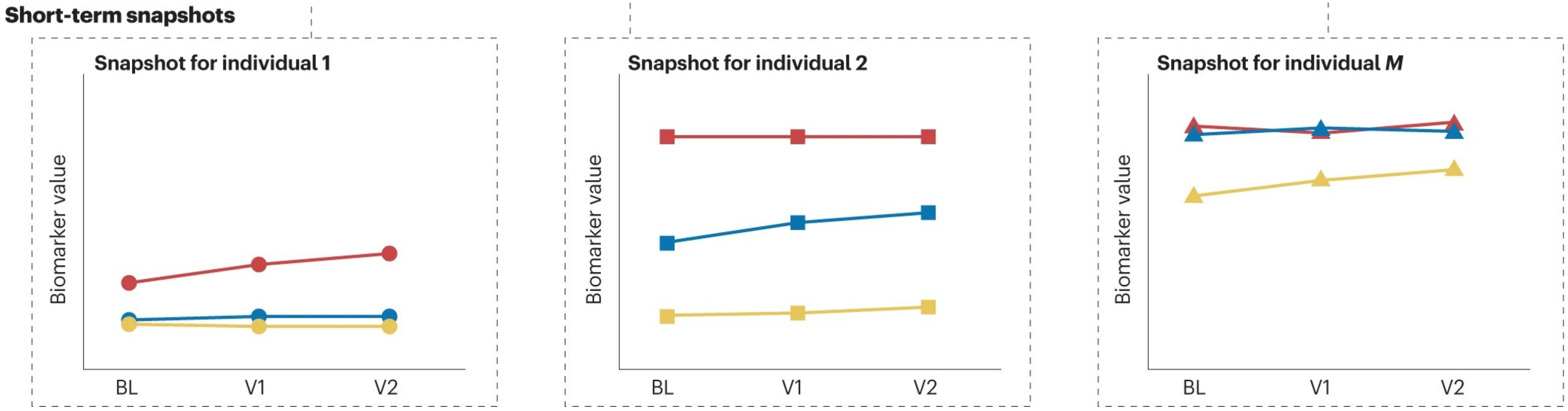
• Construct a quantitative timeline of disease.

• Directly informed by measured data

nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]



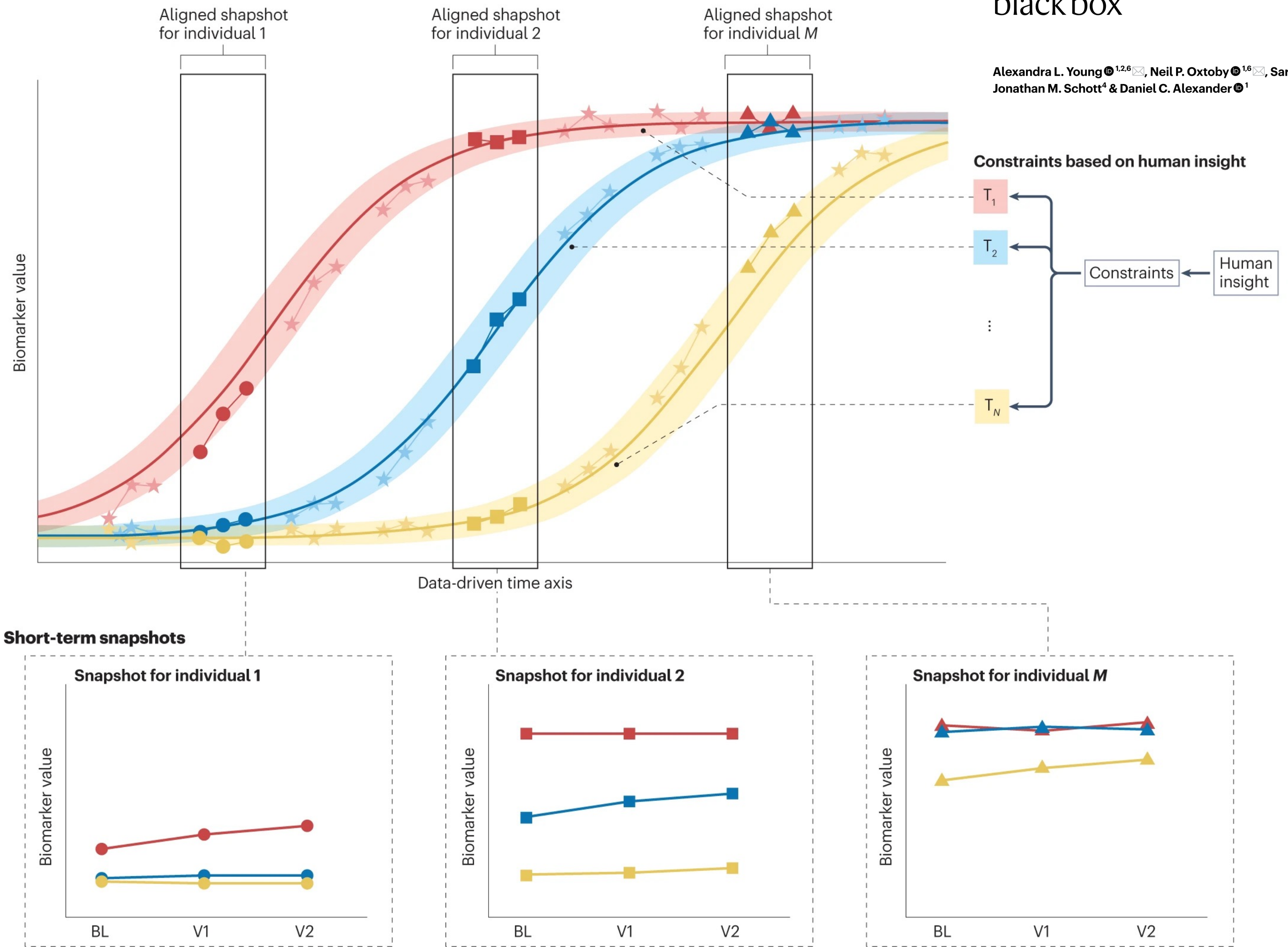
- Construct a quantitative timeline of disease.
- Directly informed by measured data

nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6] ✉, Neil P. Oxtoby[1,6] ✉, Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]

Data-driven disease progression modelling reconstructs long-term disease timelines



nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]

Taxonomy:

- Phenomenological
- Pathophysiological, a.k.a., Mechanistic

nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]

Taxonomy:

- “Top-down”: Phenomenological
- “Bottom-Up”: Pathophysiological, a.k.a., Mechanistic

Davenport et al., J R Soc Interface 2022

What do we know about Alzheimer’s?

- <u>Defined</u> by *post mortem* histopathology
  - Braak staging

- Clinical syndrome: memory ***<u>etc</u>.***

- *Loooooong* pre-symptomatic period: decades of pathology
  - Virtually impossible to identify future patients
    - Risk factors: genetics, etc.
    - Rare familial/inherited forms

- Heterogeneity in syndrome, onset, progression, and pathology!
  - **Imaging** can probe pathology *in vivo* (PET, MRI)

What do we know about Alzheimer's?

- Defined by *post mortem* histopathology
  - Braak staging
- Clinical syndrome: memory ***etc.***
- *Looooong* pre-symptomatic period: decades of pathology
  - Virtually impossible to identify future patients
    - Risk factors: genetics, etc.
    - Rare familial/inherited forms
- Heterogeneity in syndrome, onset, progression, and pathology!
  - **Imaging** can probe pathology *in vivo* (PET, MRI)

Treatments for Alzheimer’s?

Treatments for Alzheimer's?

- Amyloid cascade hypothesis **`(Hardy/Higgins 1992; Selkoe/Hardy 2016)`**
  - \+ Plenty of supporting evidence
  - – Anti-amyloid therapies: sketchy efficacy in large clinical trials

Treatments for Alzheimer's?

- Amyloid cascade hypothesis **(Hardy/Higgins 1992; Selkoe/Hardy 2016)**
  + Plenty of supporting evidence
  – Anti-amyloid therapies: sketchy efficacy in large clinical trials

- Why are clinical trials "failing"? (hundreds since 2003)
  - Too late? (*wrong* time: prevention vs cure)

O'Connor et al. Alz Res Ther 2020
Oxtoby et al. Frontiers 2022

Treatments for Alzheimer's?

- Amyloid cascade hypothesis **(Hardy/Higgins 1992; Selkoe/Hardy 2016)**
  - \+ Plenty of supporting evidence
  - – Anti-amyloid therapies: sketchy efficacy in large clinical trials

- Why are clinical trials "failing"? (hundreds since 2003)
  - Too late? (*wrong* time: prevention vs cure)
  - Individual variability? (*wrong* people)

O'Connor et al. Alz Res Ther 2020
Oxtoby et al. Frontiers 2022

Treatments for Alzheimer's?

- Amyloid cascade hypothesis **(Hardy/Higgins 1992; Selkoe/Hardy 2016)**
  + Plenty of supporting evidence
  – Anti-amyloid therapies: sketchy efficacy in large clinical trials

- Why are clinical trials "failing"? (hundreds since 2003)
  - Too late? (*wrong* time: prevention vs cure)
  - Individual variability? (*wrong* people)
  - Insufficient duration?

O'Connor et al. Alz Res Ther 2020
Oxtoby et al. Frontiers 2022

Treatments for Alzheimer's?

- Amyloid cascade hypothesis **(Hardy/Higgins 1992; Selkoe/Hardy 2016)**
  + Plenty of supporting evidence
  – Anti-amyloid therapies: sketchy efficacy in large clinical trials

- Why are clinical trials "failing"? (hundreds since 2003)
  - Too late? (*wrong* time: prevention vs cure)
  - Individual variability? (*wrong* people)
  - Insufficient duration?
  - Insensitive end-points? (biology/biomarkers vs clinical benefit)

O'Connor et al. Alz Res Ther 2020
Oxtoby et al. Frontiers 2022

Treatments for Alzheimer’s?

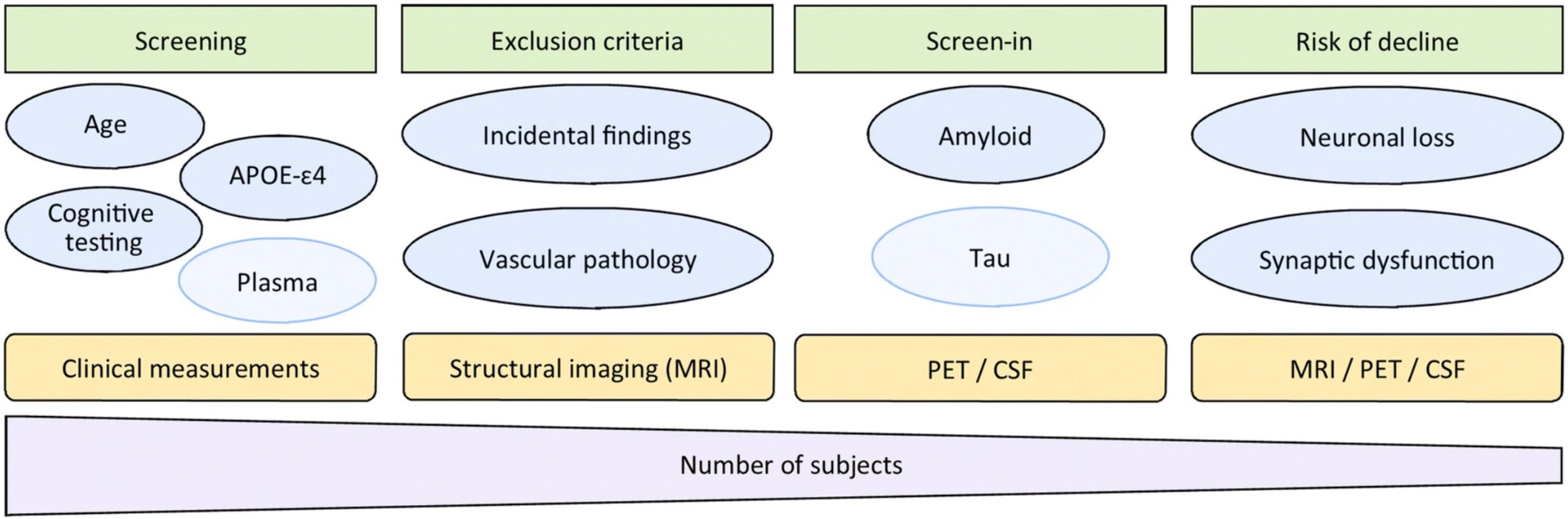
- Amyloid cascade hypothesis **(Hardy/Higgins 1992; Selkoe/Hardy 2016)**
  + Plenty of supporting evidence
  – Anti-amyloid therapies: sketchy efficacy in large clinical trials

- Why are clinical trials “failing”? (hundreds since 2003)
  - Too late? (*wrong* time: prevention vs cure)
  - Individual variability? (*wrong* people)
  - Insufficient duration?
  - Insensitive end-points? (biology/biomarkers vs clinical benefit)
  - Wrong target? (*wrong* biology / comorbidities / multitarget strategies)

  (Salloway, CTAD 2019; Aisen, CTAD 2019)

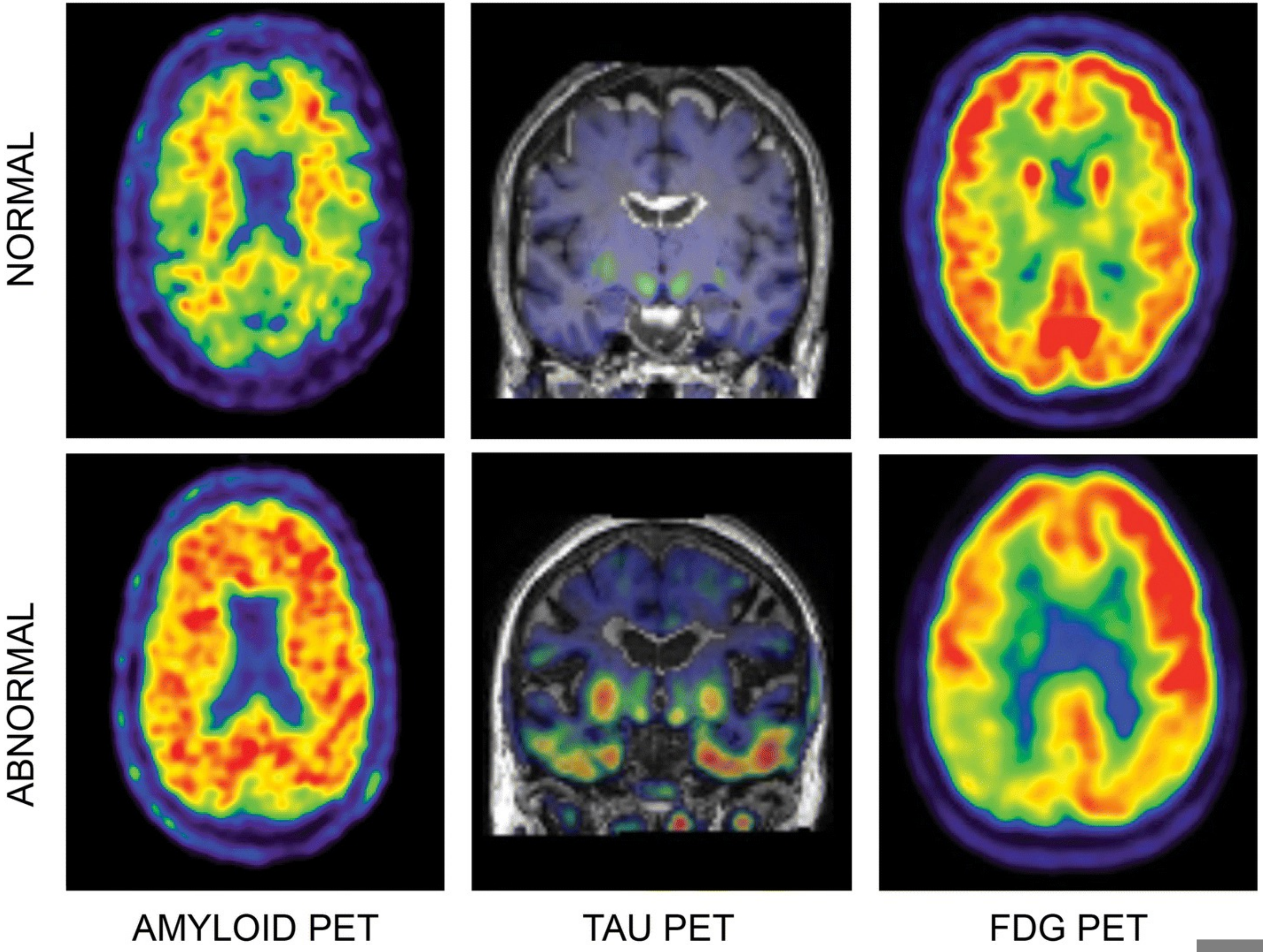
O’Connor et al. Alz Res Ther 2020
Oxtoby et al. Frontiers 2022

What have clinical trials done?



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

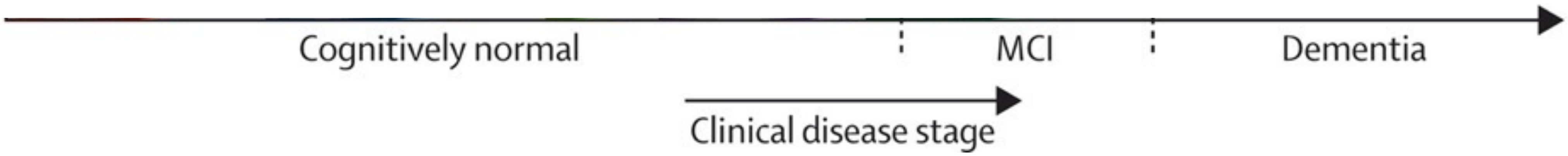
See also: D. Cash et al., Alz Res Ther (2014)



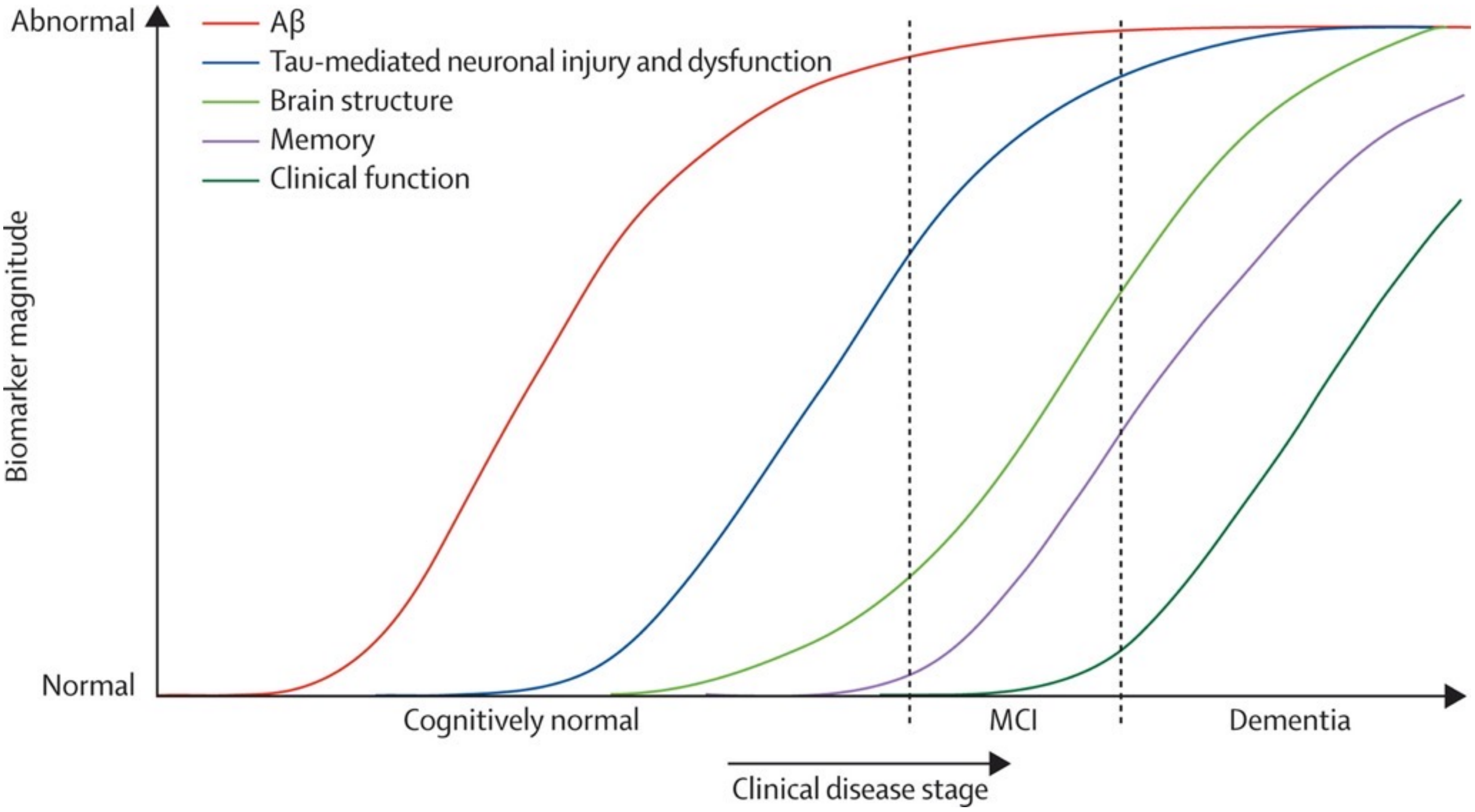
What have clinical trials done?

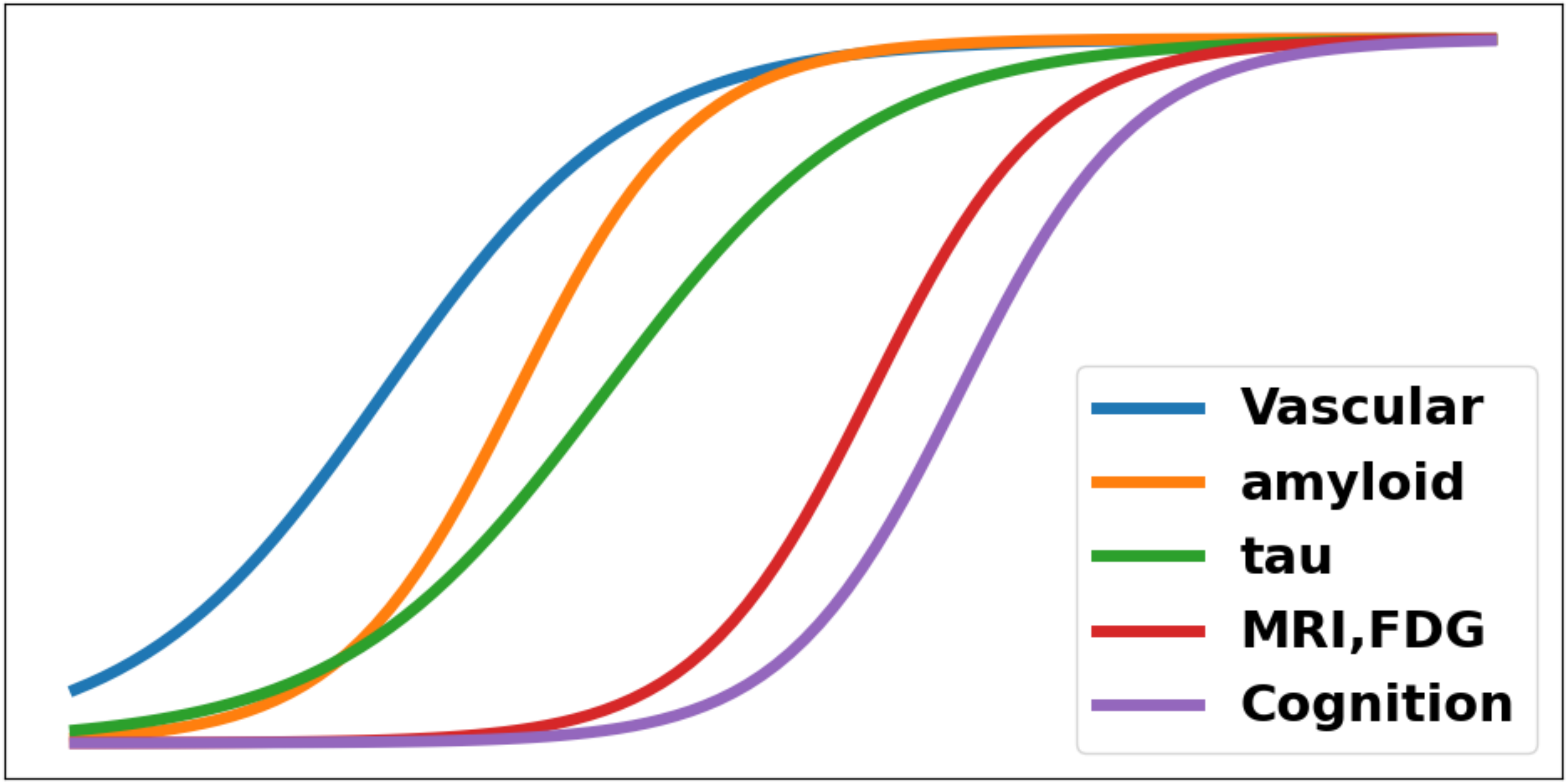
M. ten Kate et al., Alz Res Ther (2018)

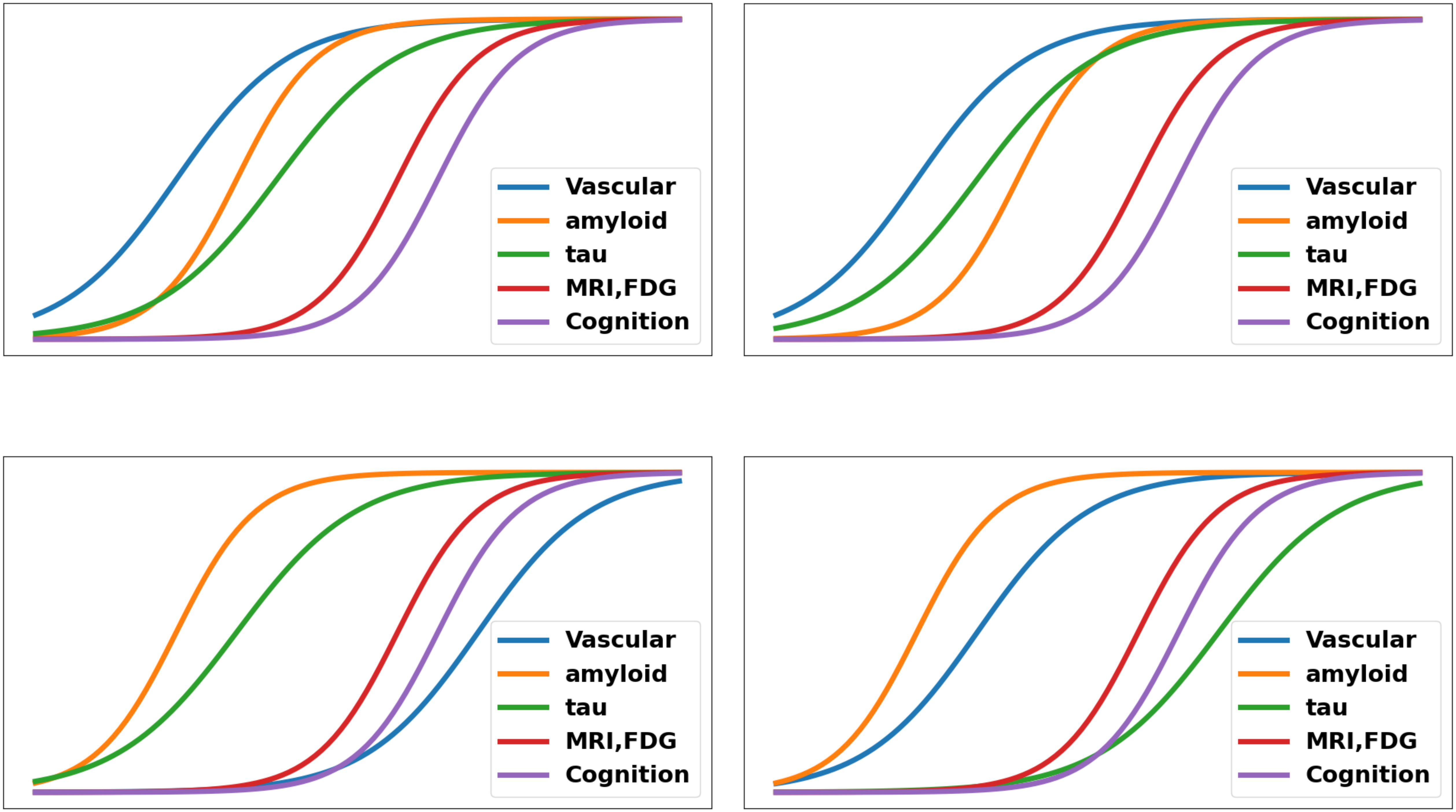
C.R. Jack Jnr et al., The Lancet Neurol (2010)



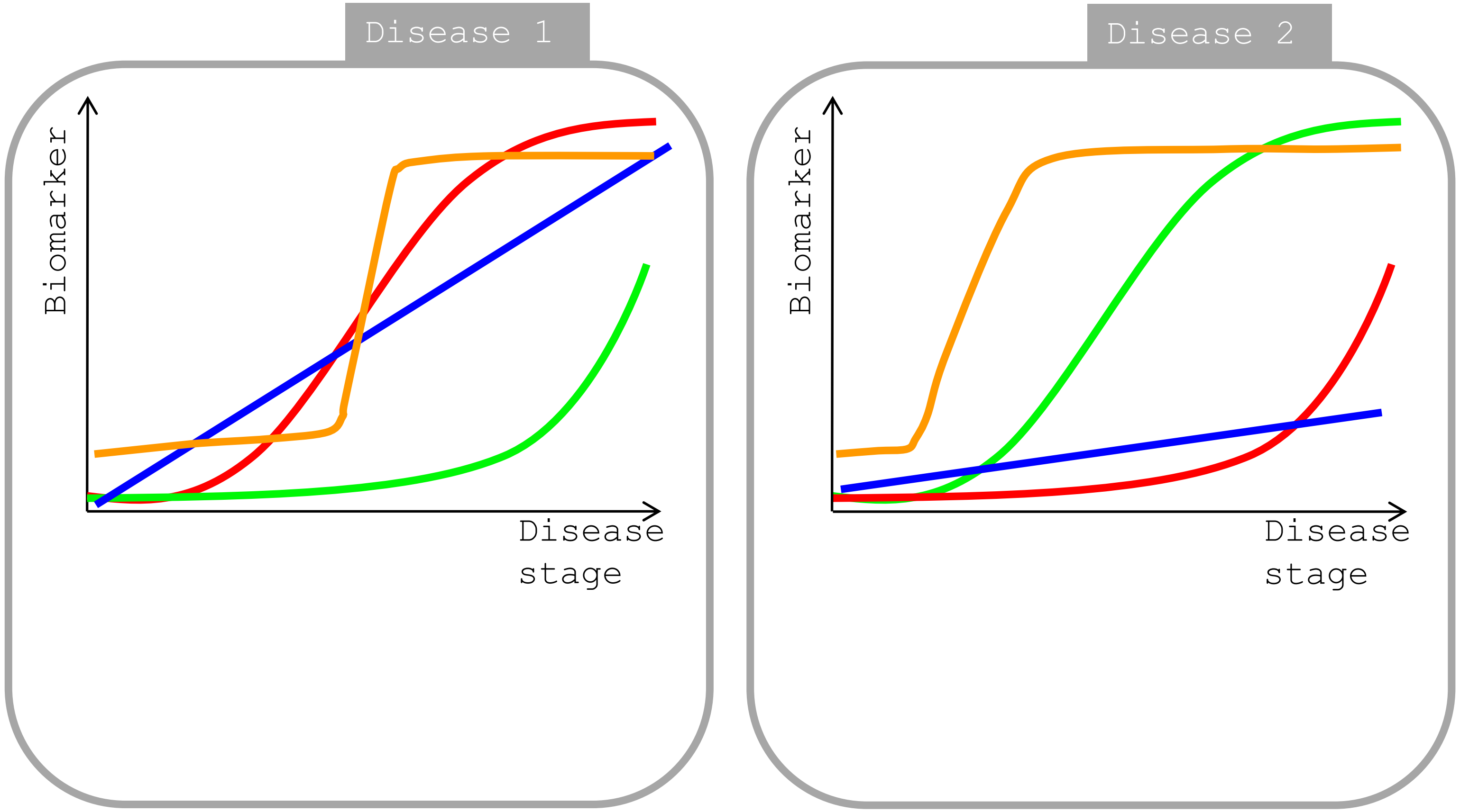
C.R. Jack Jnr et al., The Lancet Neurol (2010)



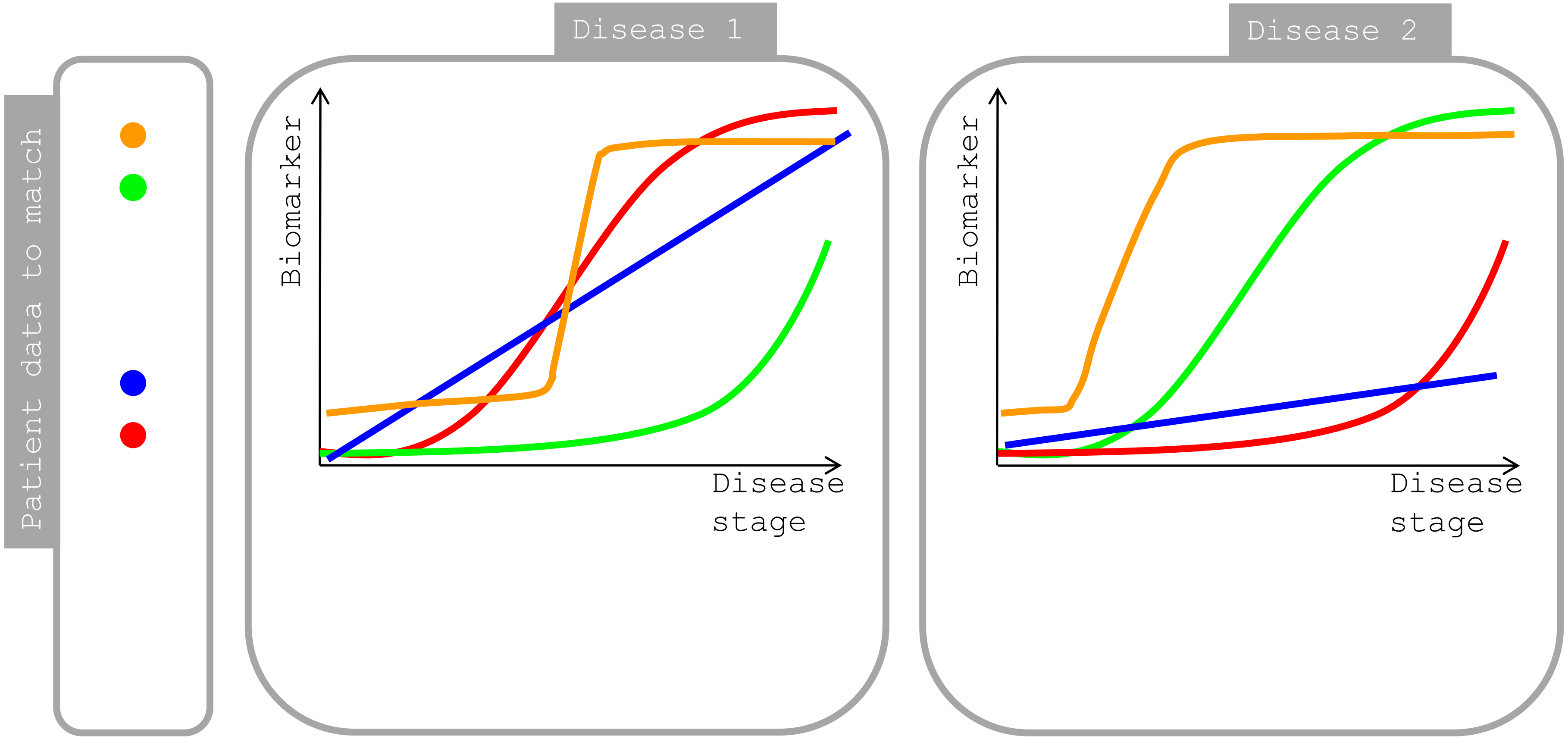

Vascular
amyloid
tau
MRI,FDG
Cognition


Vascular
amyloid
tau
MRI,FDG
Cognition
Vascular
amyloid
tau
MRI,FDG
Cognition
Vascular
amyloid
tau
MRI,FDG
Cognition
Vascular
amyloid
tau
MRI,FDG
Cognition

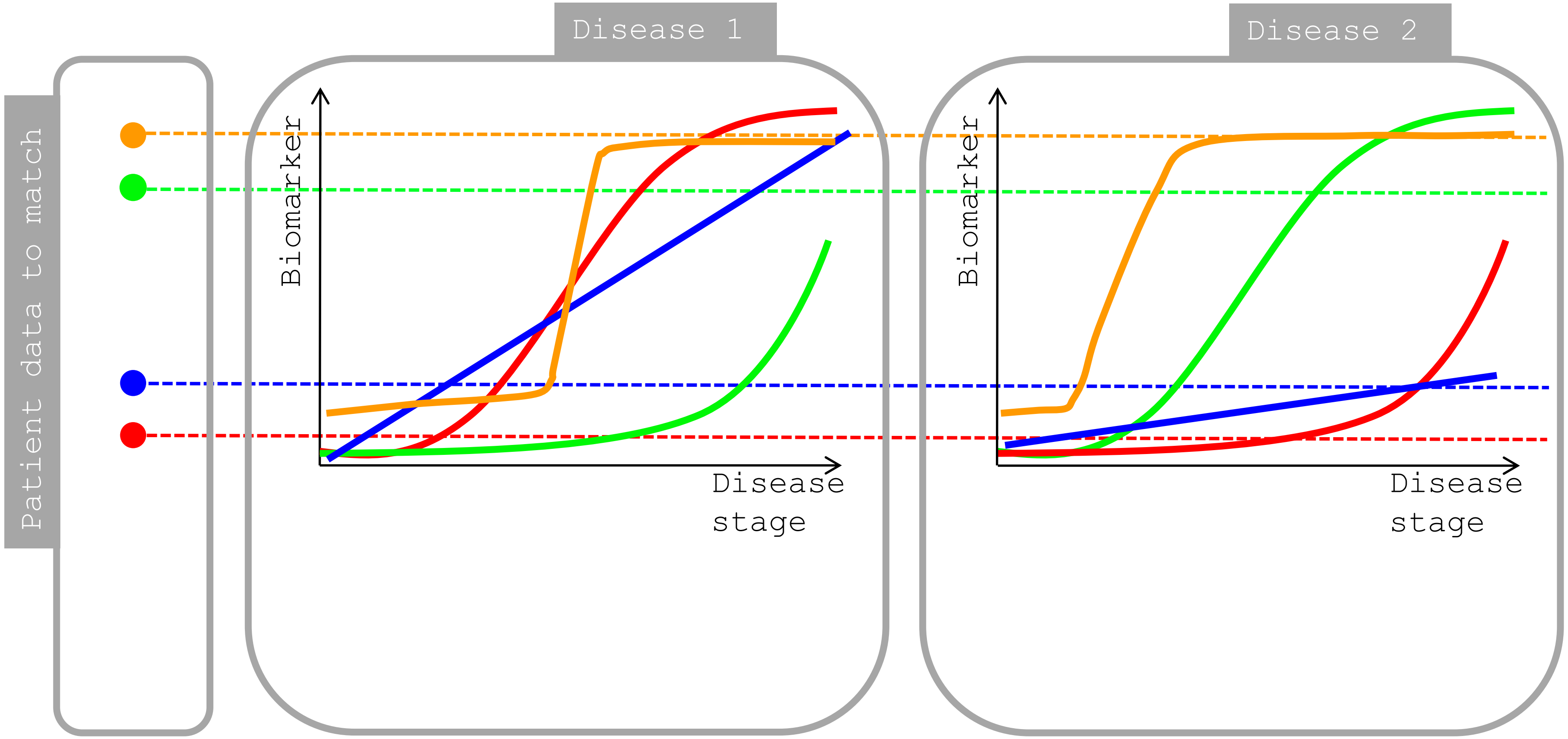
Quantitative utility of data-driven models



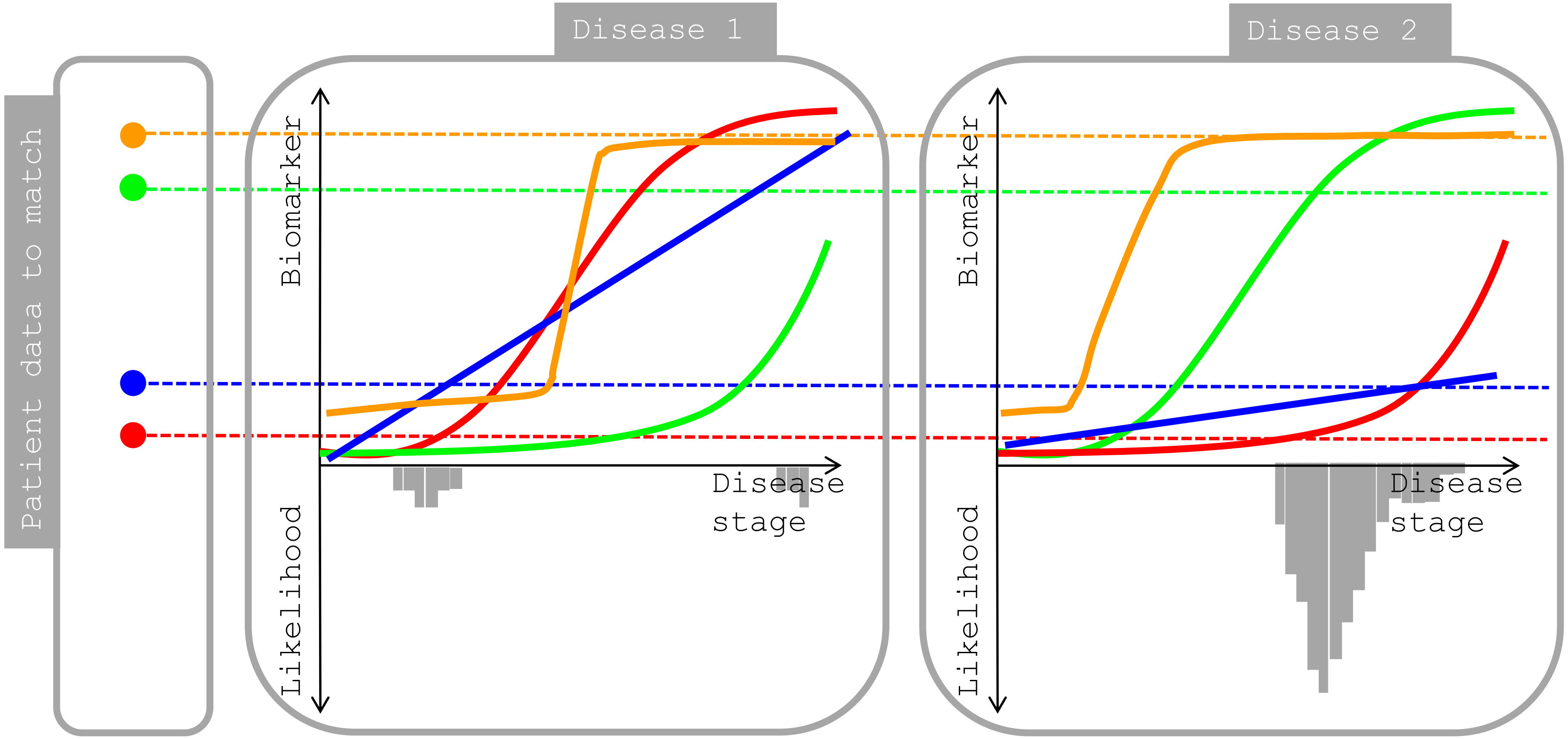
Quantitative utility of data-driven models



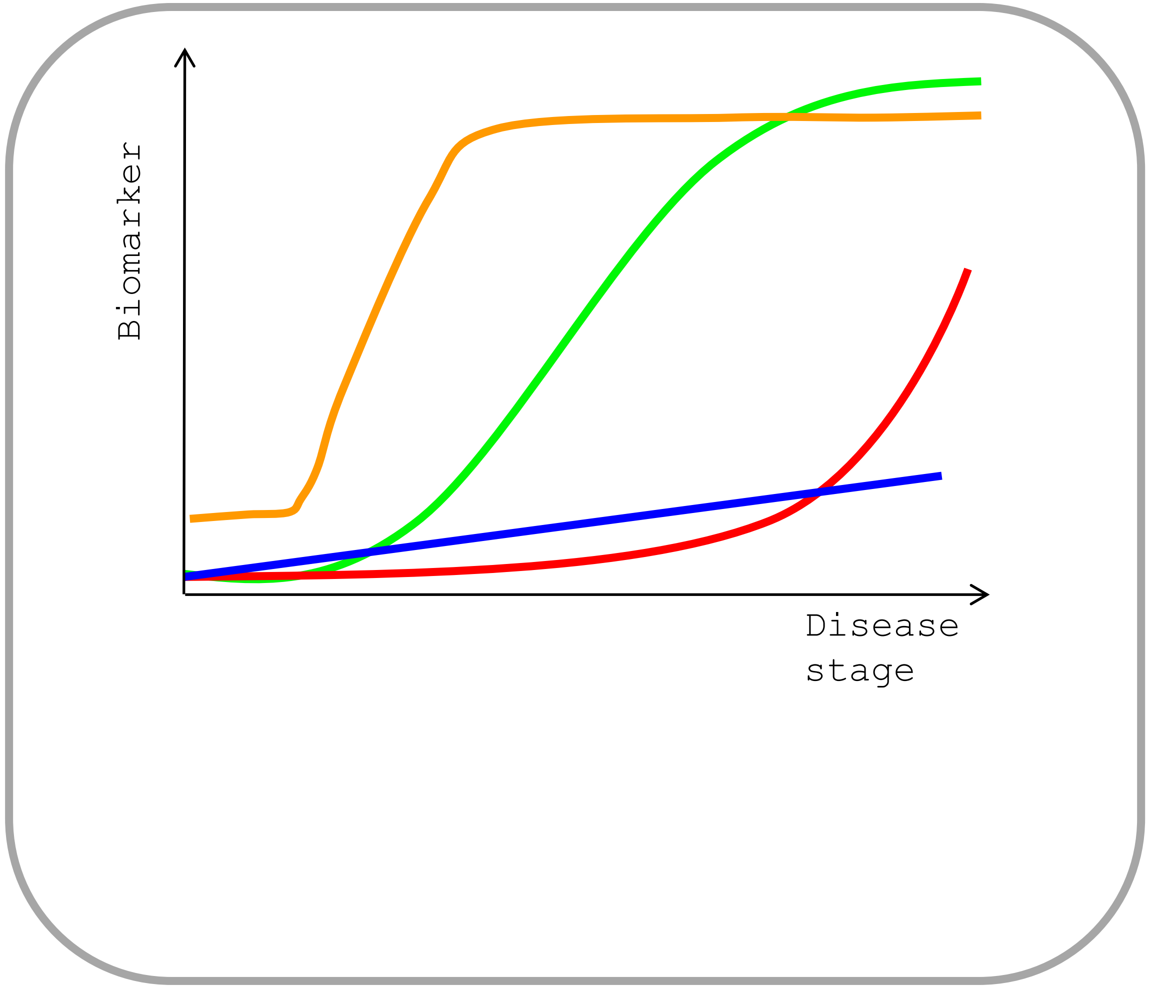
Quantitative utility of data-driven models



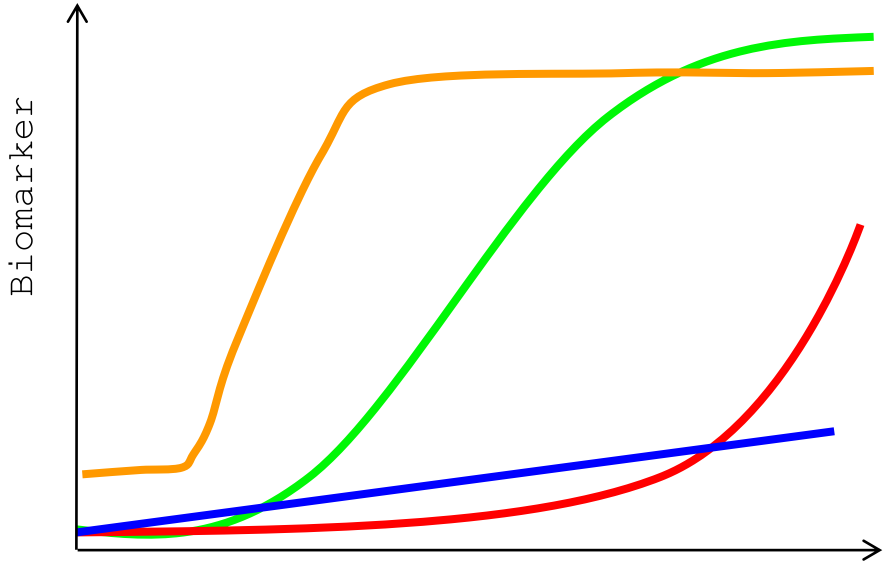
Quantitative utility of data-driven models



Traditional models



Traditional models



Unknown disease stage/time

The Journey to
Data-driven disease progression modelling

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

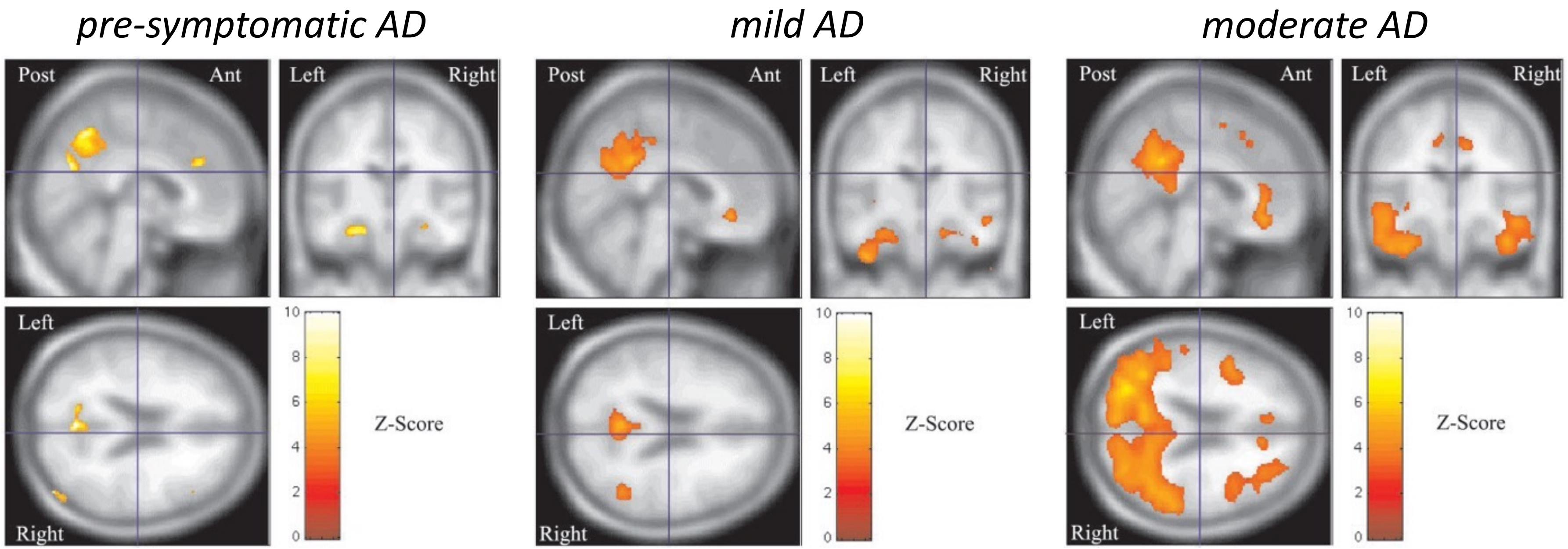
The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression

Scahill et al. PNAS 2002

- T1 MRI measures of neuronal atrophy: MMSE “clock”



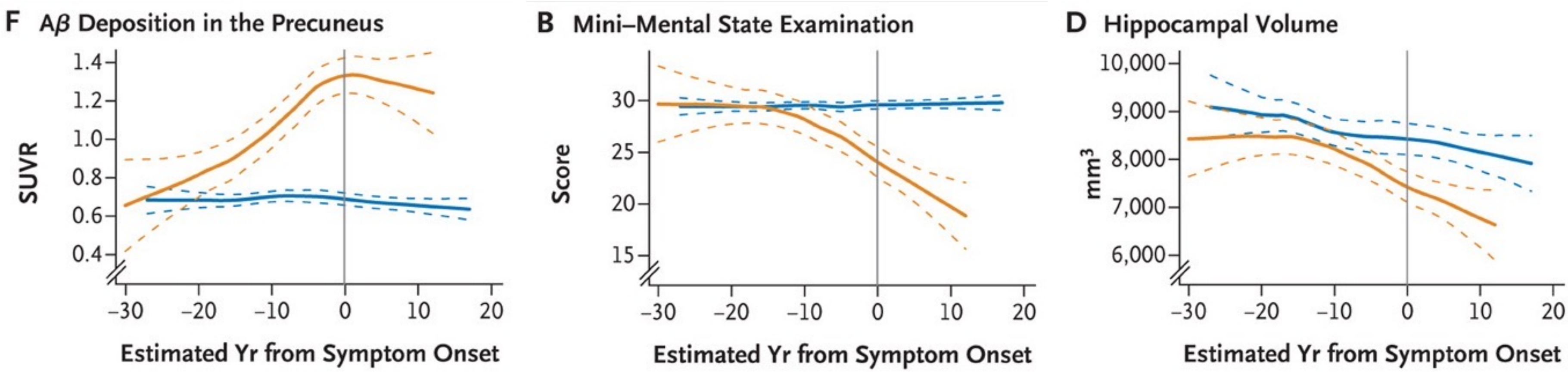
The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression

Bateman et al. NEJM 2012

- Parental age of symptom onset in dominantly-inherited AD

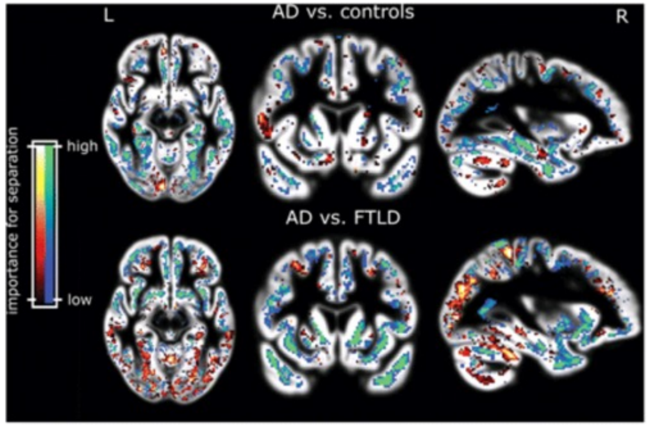


The Journey to Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression
- Pattern recognition (supervised ML)

Classifying structural MRI in AD



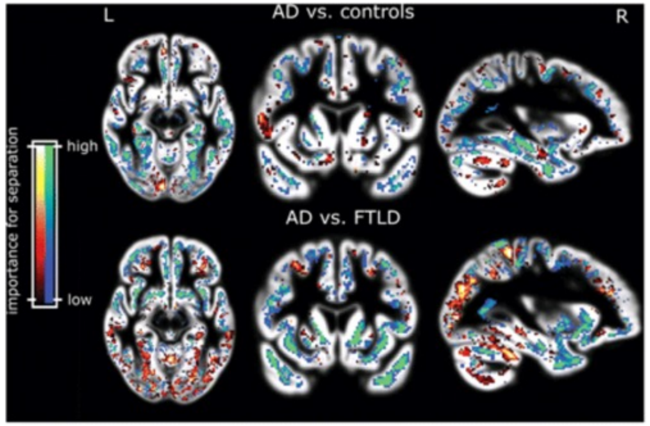
Klöppel et al. Brain 2008

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

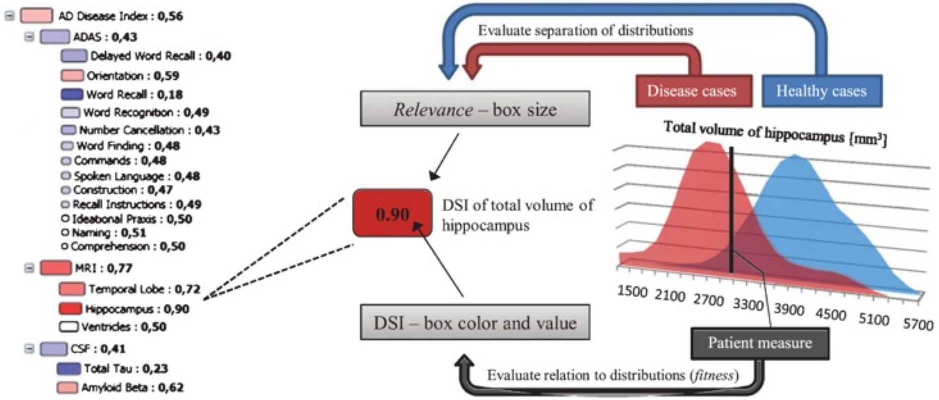
- Regression
- Pattern recognition (supervised ML)

Classifying structural MRI in AD



Klöppel et al. Brain 2008

Disease State Fingerprint for AD



Mattila et al. JAD 2011

The Journey to Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

2004 Alzheimer's Disease Neuroimaging Initiative

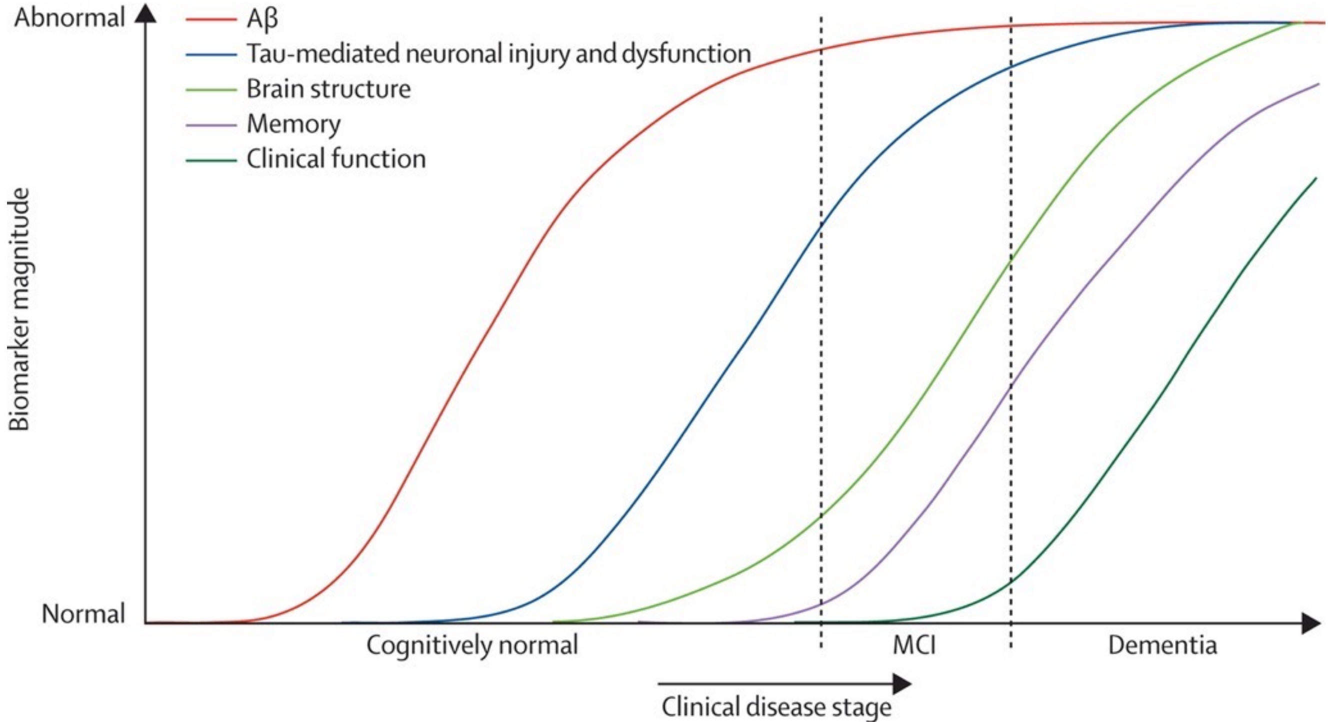
The Journey to Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

2004 Alzheimer's Disease Neuroimaging Initiative

2010 Hypothetical Models of Alzheimer's progression



Jack et al. TLN 2010

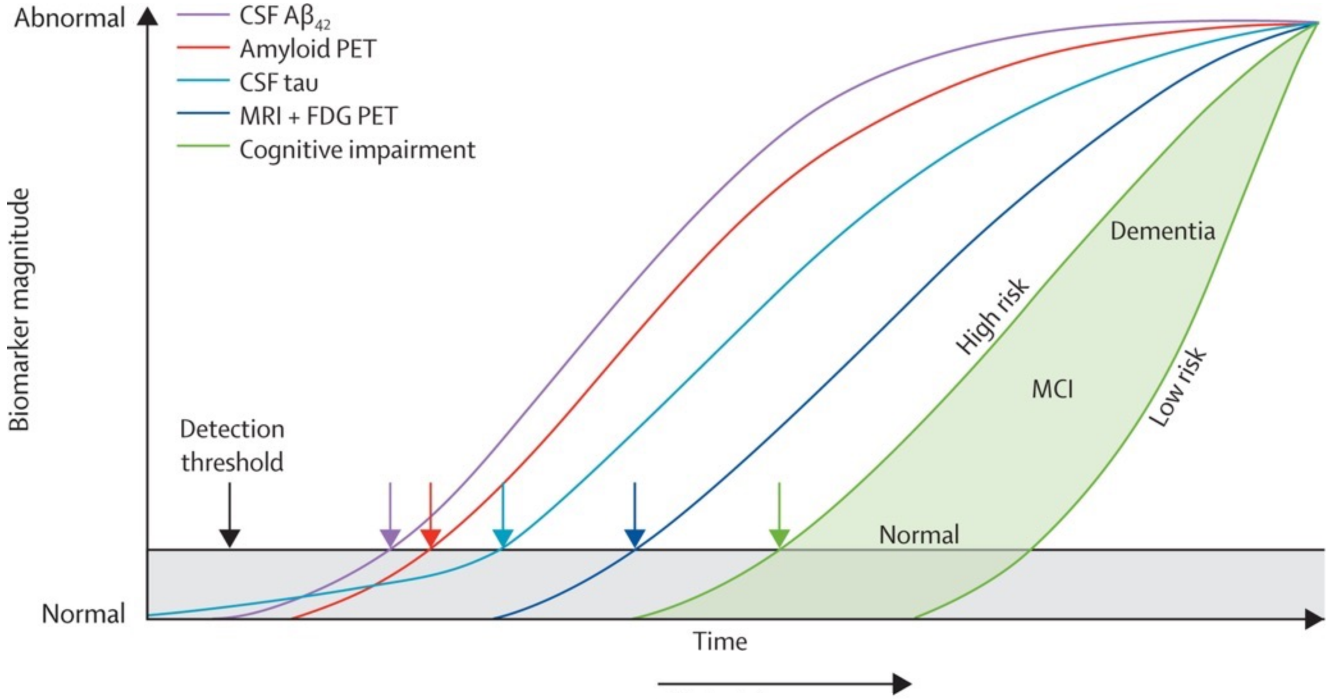
The Journey to Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

2004 Alzheimer's Disease Neuroimaging Initiative

2010 Hypothetical Models of Alzheimer's progression (updated 2013)



Jack et al. TLN 2013

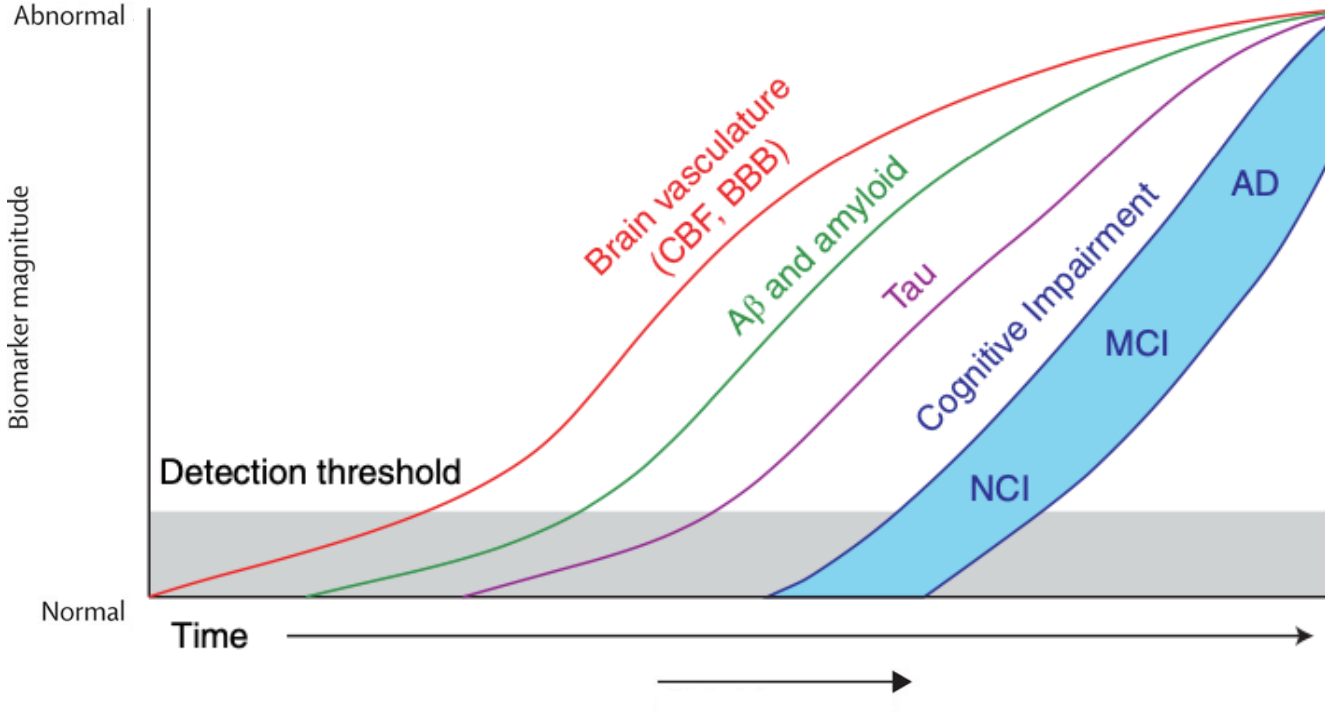
The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

2004 Alzheimer's Disease Neuroimaging Initiative

2010 Hypothetical Models of Alzheimer's progression (updated 2018)



Sweeney et al. Nat Comms 2018

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

2004 Alzheimer’s Disease Neuroimaging Initiative

2010 Hypothetical Models of Alzheimer’s progression

2011 Data-Driven Disease Progression Modelling

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

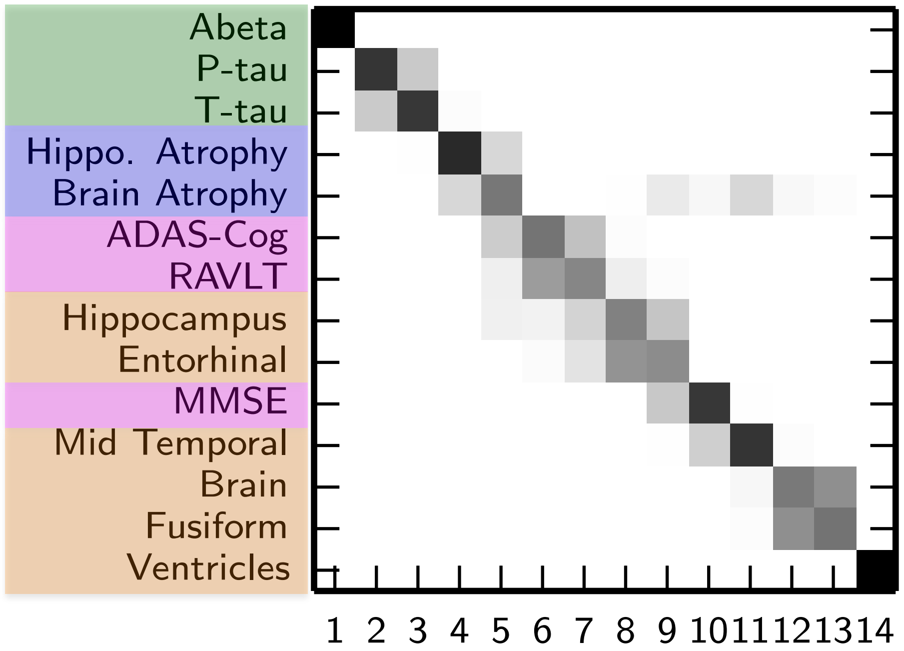
2004 Alzheimer's Disease Neuroimaging Initiative

2010 Hypothetical Models of Alzheimer's progression

2011 Data-Driven Disease Progression Modelling

- Pseudo-time methods:
    - discrete (EBM sequencing)

Event-based model



Fonteijn et al. IPMI 2011, NeuroImage 2012
Young et al. Brain 2014

The Journey to

Data-driven disease progression

2002–2008 Traditional: stage == symptoms

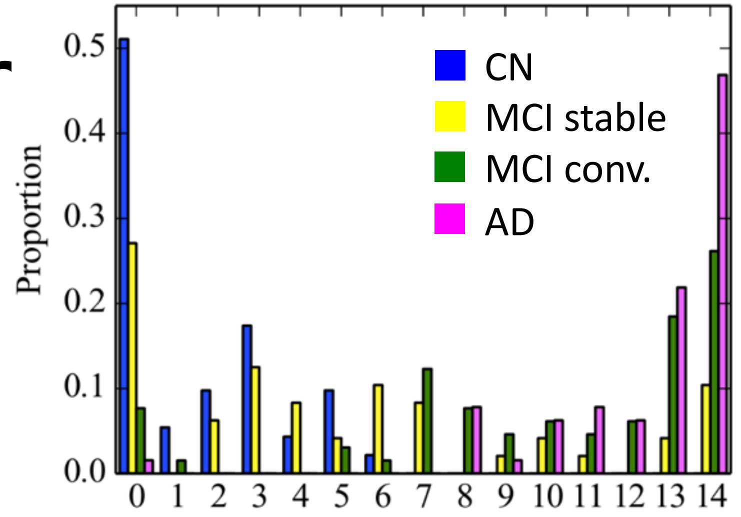
- Regression, Pattern recognition (supervised ML)

2004 Alzheimer’s Disease Neuroimaging Initiative

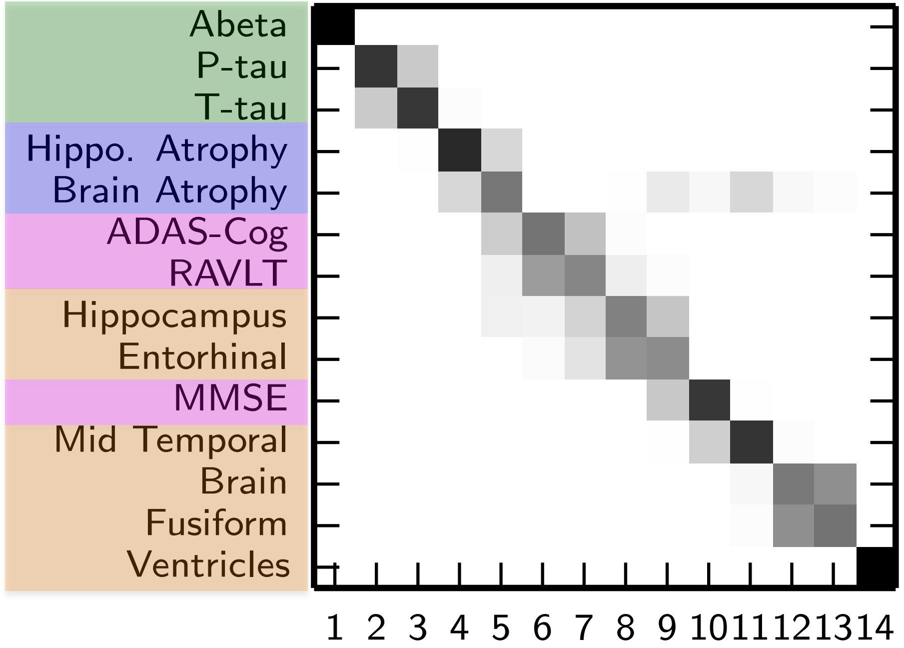
2010 Hypothetical Models of Alzheimer’s progression

2011 Data-Driven Disease Progression Modelling

- Pseudo-time methods:
    - discrete (EBM sequencing)



Event-based model



Fonteijn et al. IPMI 2011, NeuroImage 2012
Young et al. Brain 2014

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

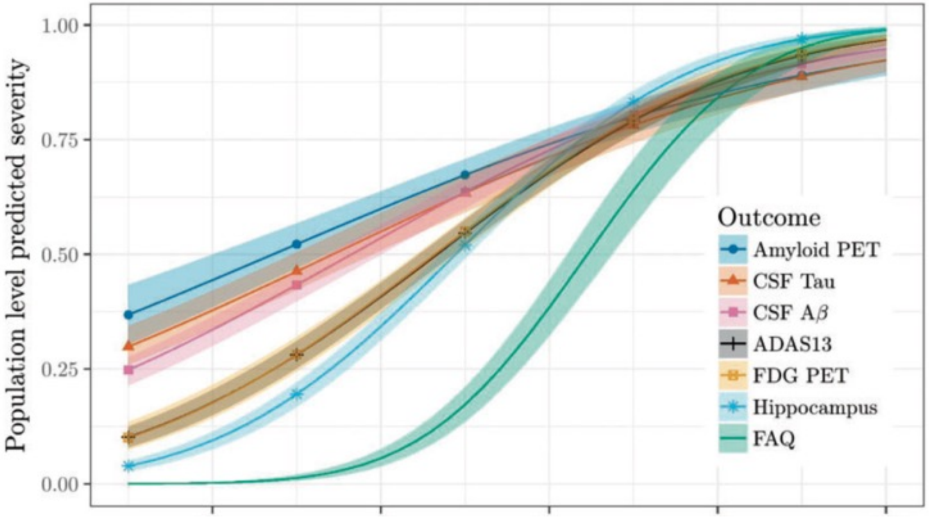
2004 Alzheimer's Disease Neuroimaging Initiative

2010 Hypothetical Models of Alzheimer's progression

2011 Data-Driven Disease Progression Modelling

- Pseudo-time methods:
  - discrete (EBM sequencing)
  - continuous (latent-time: LTJMM, IRT, GPPM)

Li et al. Stat Meth Med Res 2017 (2014)
Leoutsakos et al. JPAD 2016
Schiratti et al. MICCAI 2015, JMLR 2017
Lorenzi et al. NIMG 2017



The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

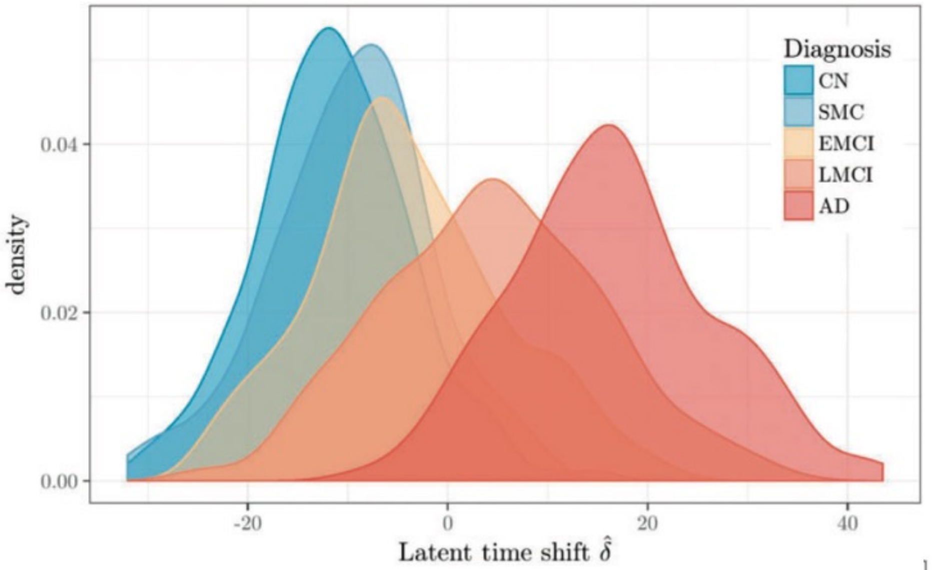
- Regression, Pattern recognition (supervised ML)

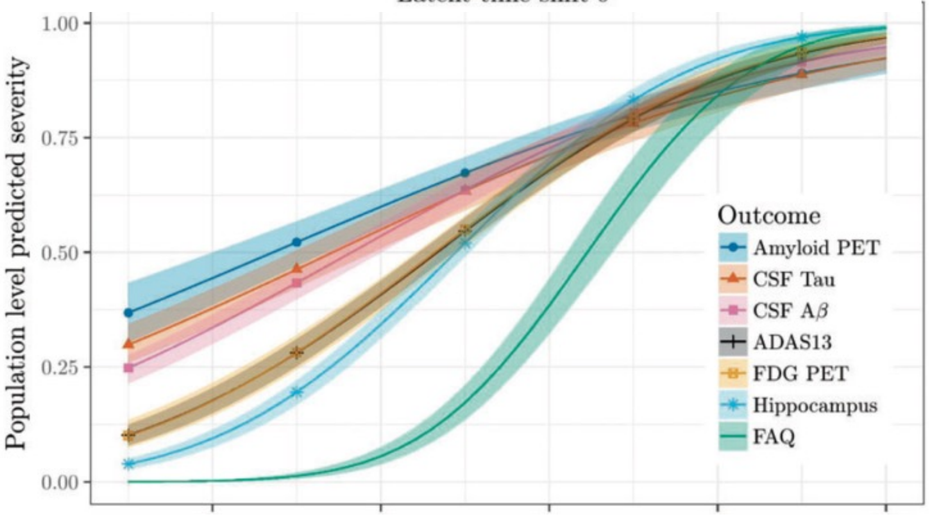
2004 Alzheimer's Disease Neuroimaging Initiative

2010 Hypothetical Models of Alzheimer's progres

2011 Data-Driven Disease Progression Modelling

- Pseudo-time methods:
  - discrete (EBM sequencing)
  - continuous (latent-time: LTJMM, IRT, GPPM)





Li et al. Stat Meth Med Res 2017 (2014)
Leoutsakos et al. JPAD 2016
Schiratti et al. MICCAI 2015, JMLR 2017
Lorenzi et al. NIMG 2017

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

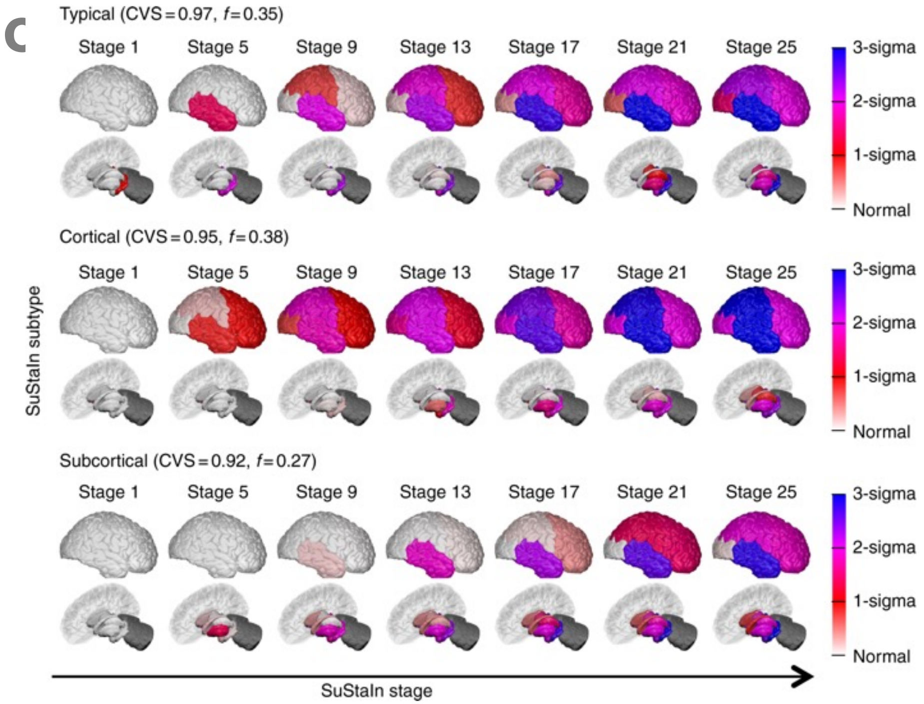
2004 Alzheimer's Disease Neuroimaging Initiative

2010 Hypothetical Models of Alzheimer's progressic

2011 Data-Driven Disease Progression Modelling

- Pseudo-time methods:
  - discrete (EBM sequencing)
  - continuous (latent-time: LTJMM, IRT, GPPM)
- Pseudo-time + Clustering

Subtype & Stage Inference (SuStaIn)



Young et al. Nat. Comms 2018

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

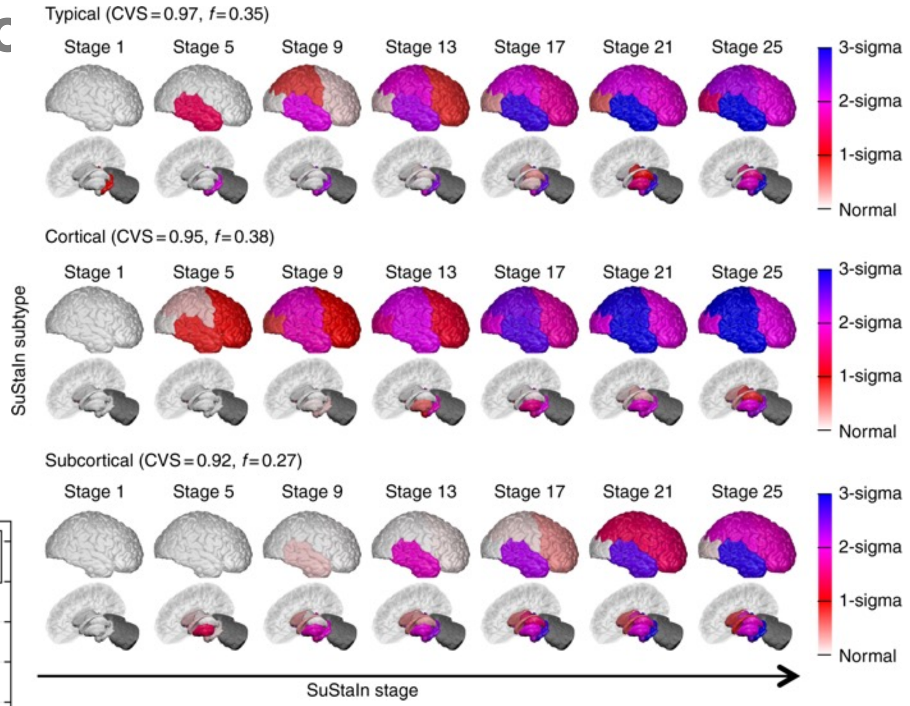
2004 Alzheimer's Disease Neuroimaging Initiative

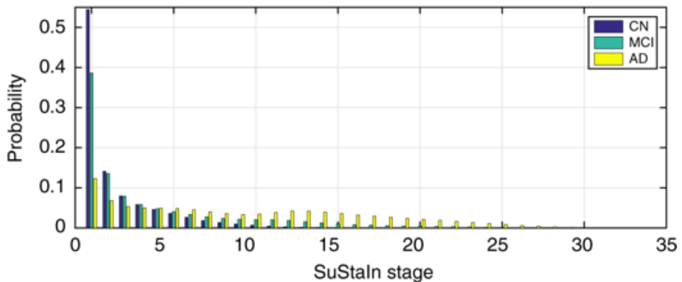
2010 Hypothetical Models of Alzheimer's progressic

2011 Data-Driven Disease Progression Modelling

- Pseudo-time methods:
  - discrete (EBM sequencing)
  - continuous (latent-time: LTJMM, IRT, GPPM)
- Pseudo-time + Clustering

Subtype & Stage Inference (SuStaIn)





Young et al. Nat. Comms 2018

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

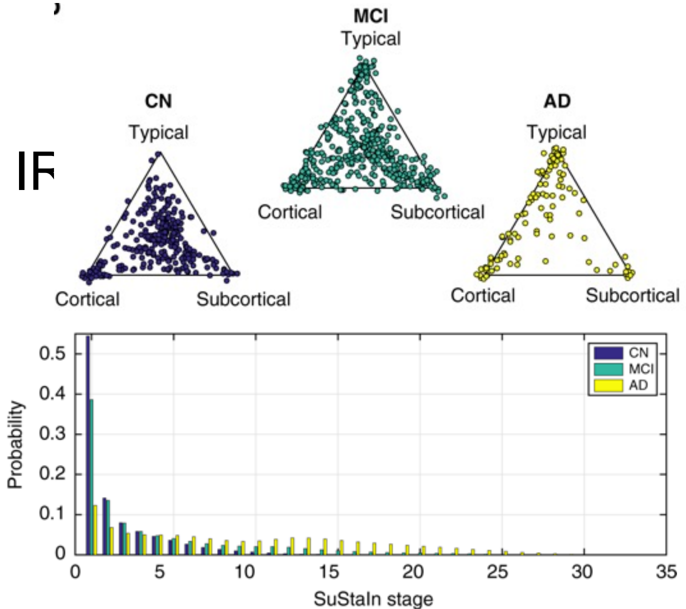
2004 Alzheimer’s Disease Neuroimaging Initiative

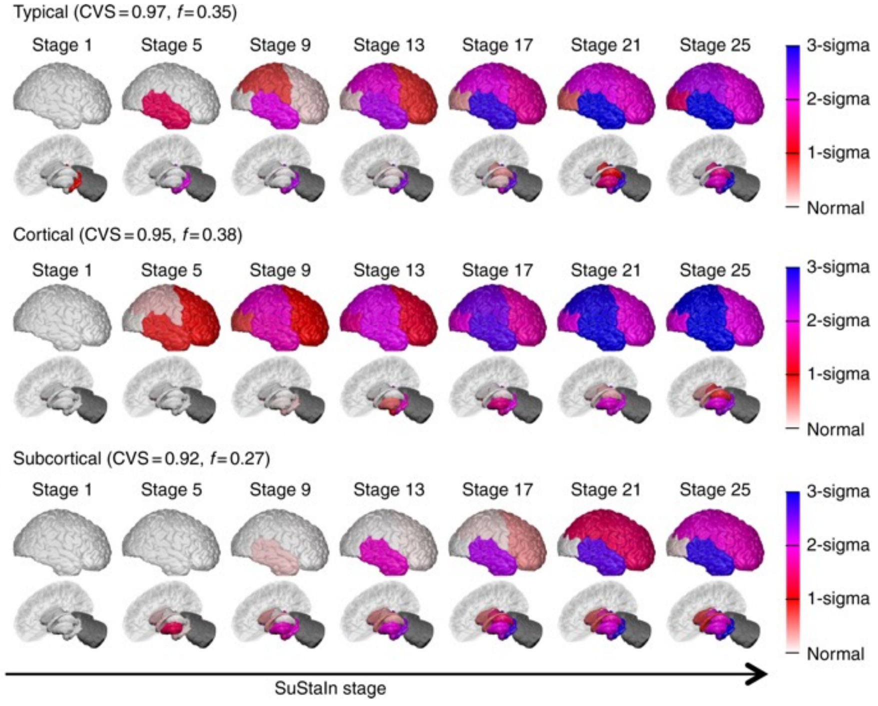
2010 Hypothetical Models of Alzheimer’s progressic

2011 Data-Driven Disease Progression Modelling

- Pseudo-time methods:
    - discrete (EBM sequencing)
    - continuous (latent-time: LTJMM, IF
- Pseudo-time + Clustering

Subtype & Stage Inference (SuStaIn)





Young et al. Nat. Comms 2018

The Journey to
Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression, Pattern recognition (supervised ML)

2004 Alzheimer's Disease Neuroimaging Initiative

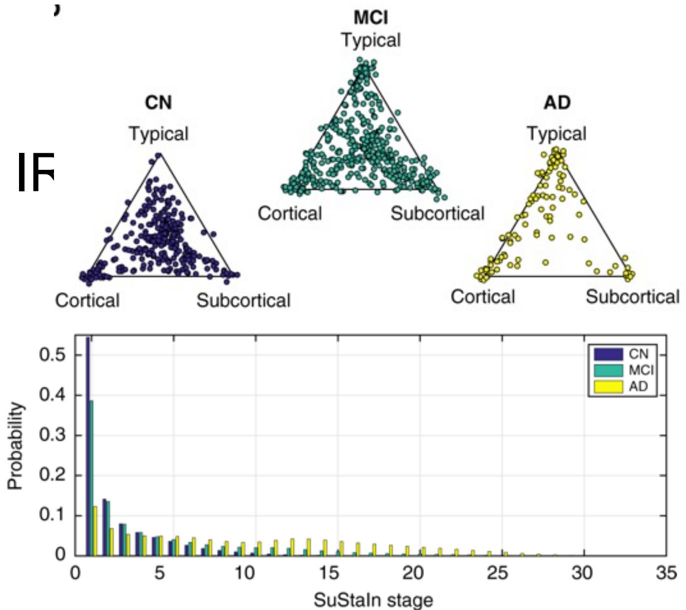
2010 Hypothetical Models of Alzheimer's progressic

2011 Data-Driven Disease Progression Modelling

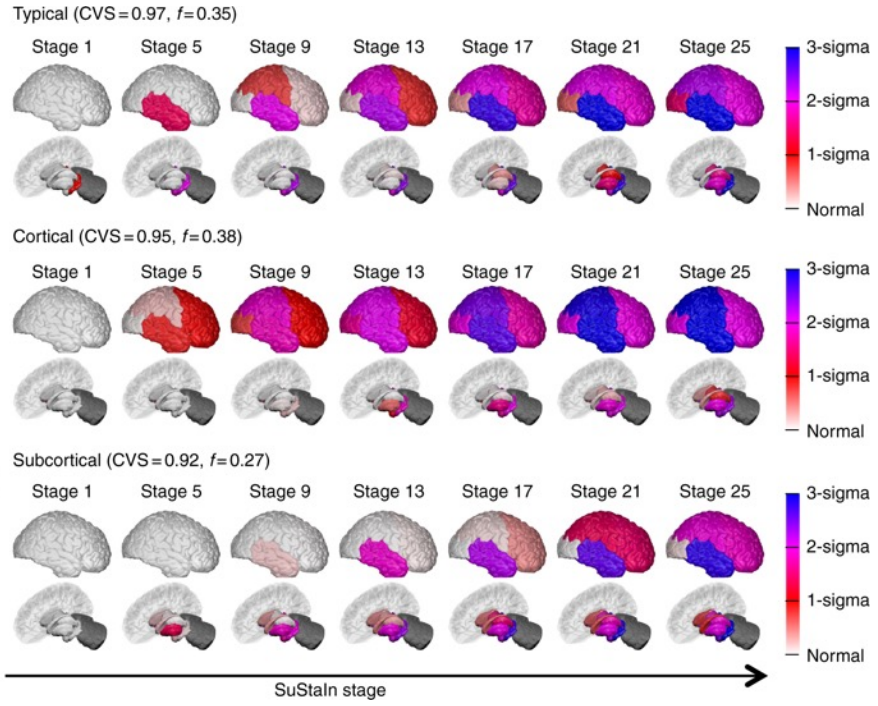
- Pseudo-time methods:
  - discrete (EBM sequencing)
  - continuous (latent-time: LTJMM, IF
- Pseudo-time + Clustering

- *tau PET:* **`Vogel+ Nat Med 2021`**
- *Amyloid+tau:*

`Aksman bioRxiv 2020, Brain 2023`



Subtype & Stage Inference (SuStaIn)



`Young et al. Nat. Comms 2018`

Data-driven disease progression models

So far:

Phenomenological models

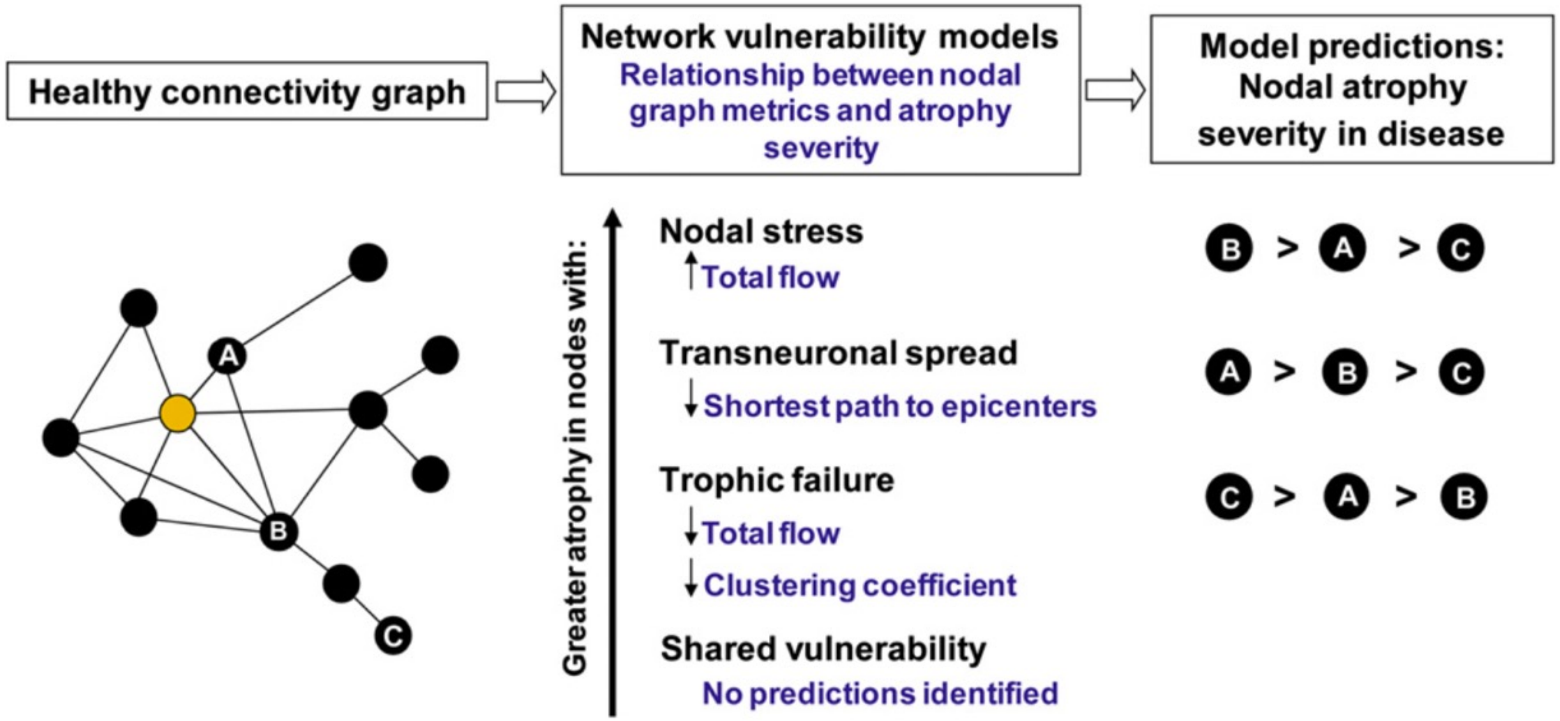
What about disease *mechanisms*?

Can we understand/explain
“Top-down” observations of pathology, using
“Bottom-up” models of mechanism/physiology?

Bottom-up models

2009–2012 Hypotheses of neurodegeneration due to pathogens

- Selective vulnerability / Wear-and-tear / Network / Use-it-or-lose-it
- **`Seeley et al. Neuron 2009, Zhou et al. Neuron 2012`**



Bottom-up models

2009–2012 Hypotheses of neurodegeneration

- Seeley et al. Neuron 2009, Zhou et al. 2012

2012– Protein (prion) Spreading Models

- **2012**: Network diffusion model (heat eq)
- **2014**: Epidemic Spreading Model

Raj et al. Neuron 2012

Iturria-Medina+ PLOS Comp. Biol. 2014

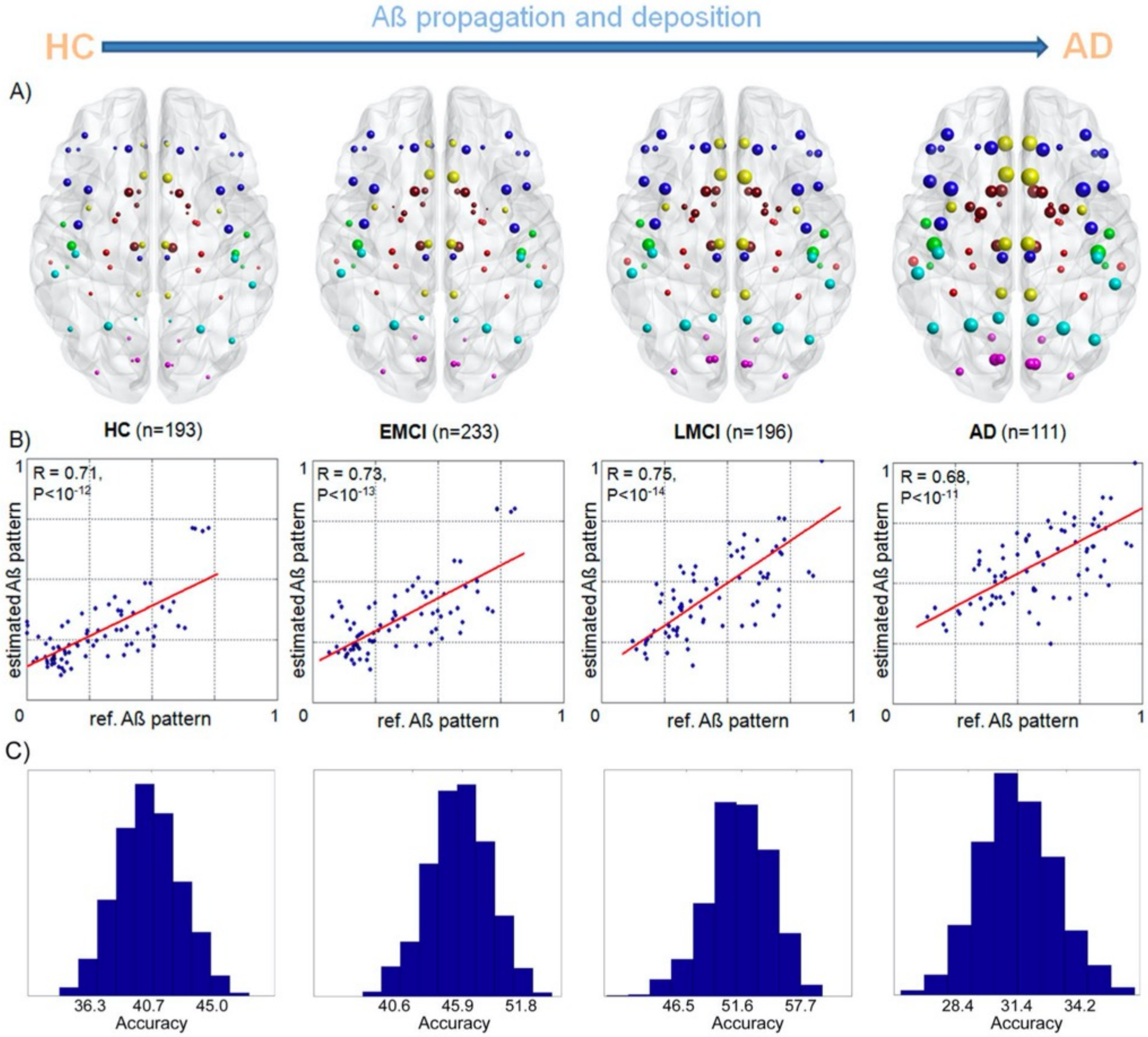
Bottom-up models

2009–2012 Hypotheses of neurodege

- Seeley et al. Neuron 2009, Zhou et

2012– Protein (prion) Spreading Mod

- **2012**: Network diffusion model (heat eq)
- **2014**: Epidemic Spreading Model



Raj et al. Neuron 2012

Iturria-Medina+ PLOS Comp. Biol. 2014

Bottom-up models

2009–2012 Hypotheses of neurodegeneration

- Seeley et al. Neuron 2009, **Zhou et al. 2012**

2012– Protein (prion) Spreading Models

- **2012**: Network diffusion model (heat eq)
- **2014**: Epidemic Spreading Model

Multiphysics of Prionlike Diseases: Progression and Atrophy

Johannes Weickenmeier, Ellen Kuhl, and Alain Goriely
Phys. Rev. Lett. **121**, 158101 – Published 12 October 2018

Physics See Focus story: A Physical Model for Neurodegenerative Disease

- **2018–19: Physics (**Network Spreading + misfolding kinetics)
  - Fisher-Kolmogorov = reaction-diffusion eq. (no mechanistic insight)
  - Heterodimer = normal & abnormal proteins (+ clearance/production)
  - Smoluchowski = stat. physics workhorse (+ size of protein aggregates)

Weickenmeier et al. Phys Rev Lett 2018
Fornari et al. J.R.Soc. Interface 2019

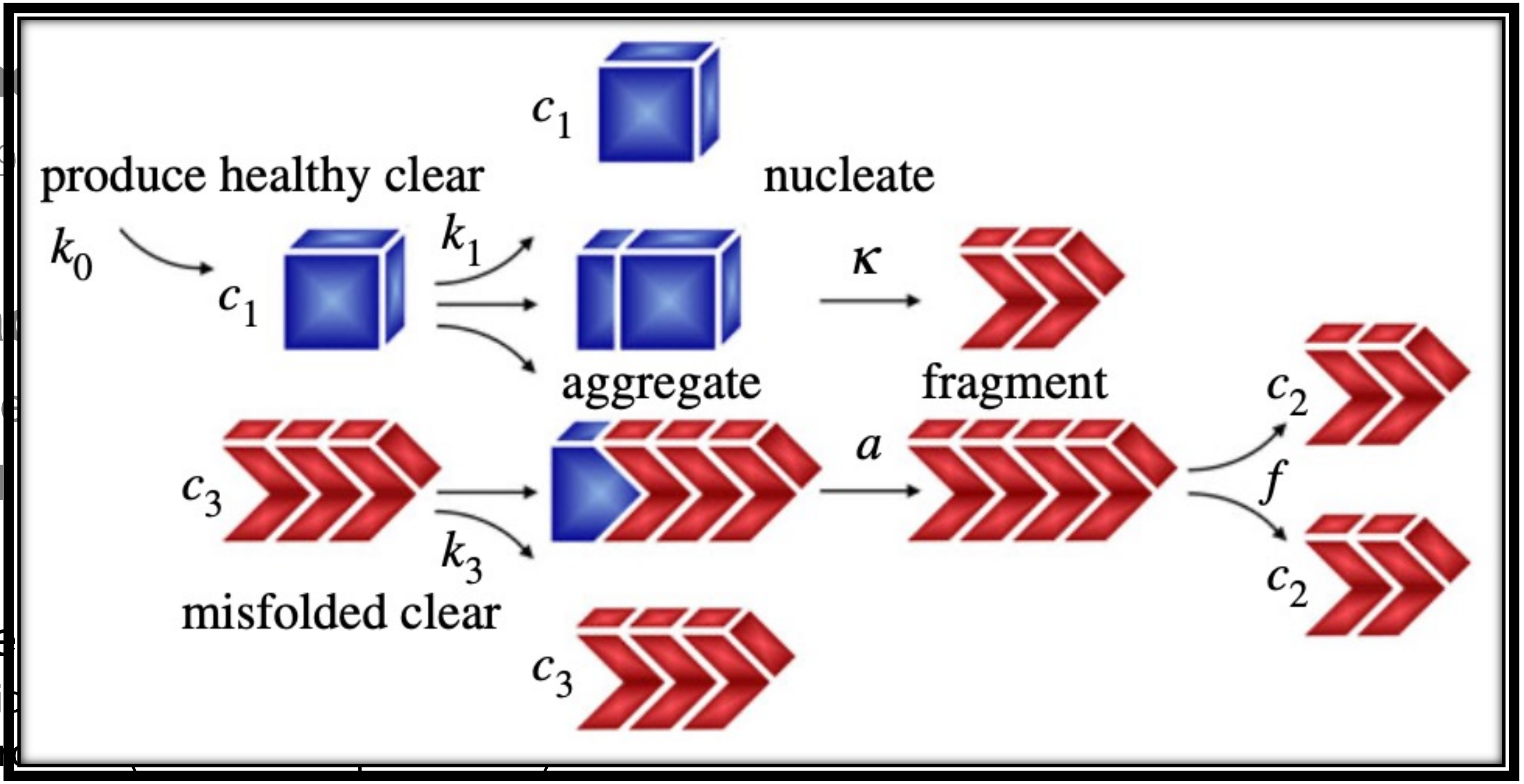
Bottom-up models

2009–2012 Hypotheses of n

- Seeley et al. Neuron 2009

2012– Protein (prion) Sprea

- **2012**: Network diffusion model (he
- **2014**: Epidemic Spreading Model



- **2018–19: Physics (**Network Spre
  - Fisher-Kolmogorov = reaction-diffusi
  - Heterodimer = normal & abnormal pr
  - Smoluchowski = stat. physics workhorse (+ size of protein aggregates)

Weickenmeier et al. Phys Rev Lett 2018
Fornari et al. J.R.Soc. Interface 2019

2023

tau *Production* vs *Transport*

In Alzheimer's

THE PREPRINT SERVER FOR BIOLOGY

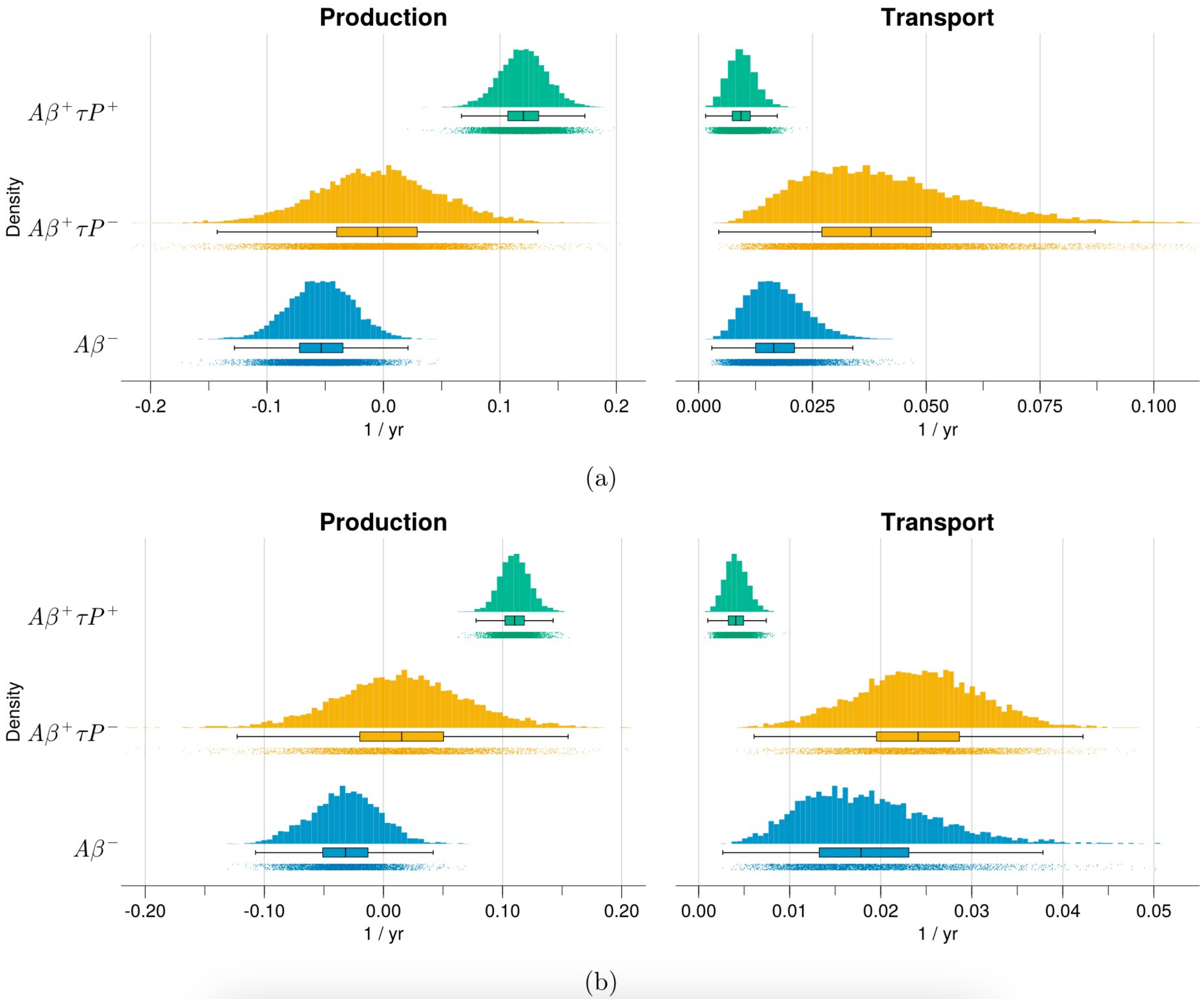
New Results

Follow this preprint

Personalised Regional Modelling Predicts Tau Progression in the Human Brain

Pavanjit Chaggar, Jacob Vogel, Alexa Pichet Binette, Travis B. Thompson, Olof Strandberg, Niklas Mattsson-Carlgren, Linda Karlsson, Erik Stomrud, Saad Jbabdi, Stefano Magon, Gregory Klein, the Alzheimer's Disease Neuroimaging Initiative, Oskar Hansson, Alain Goriely

doi: https://doi.org/10.1101/2023.09.28.559911

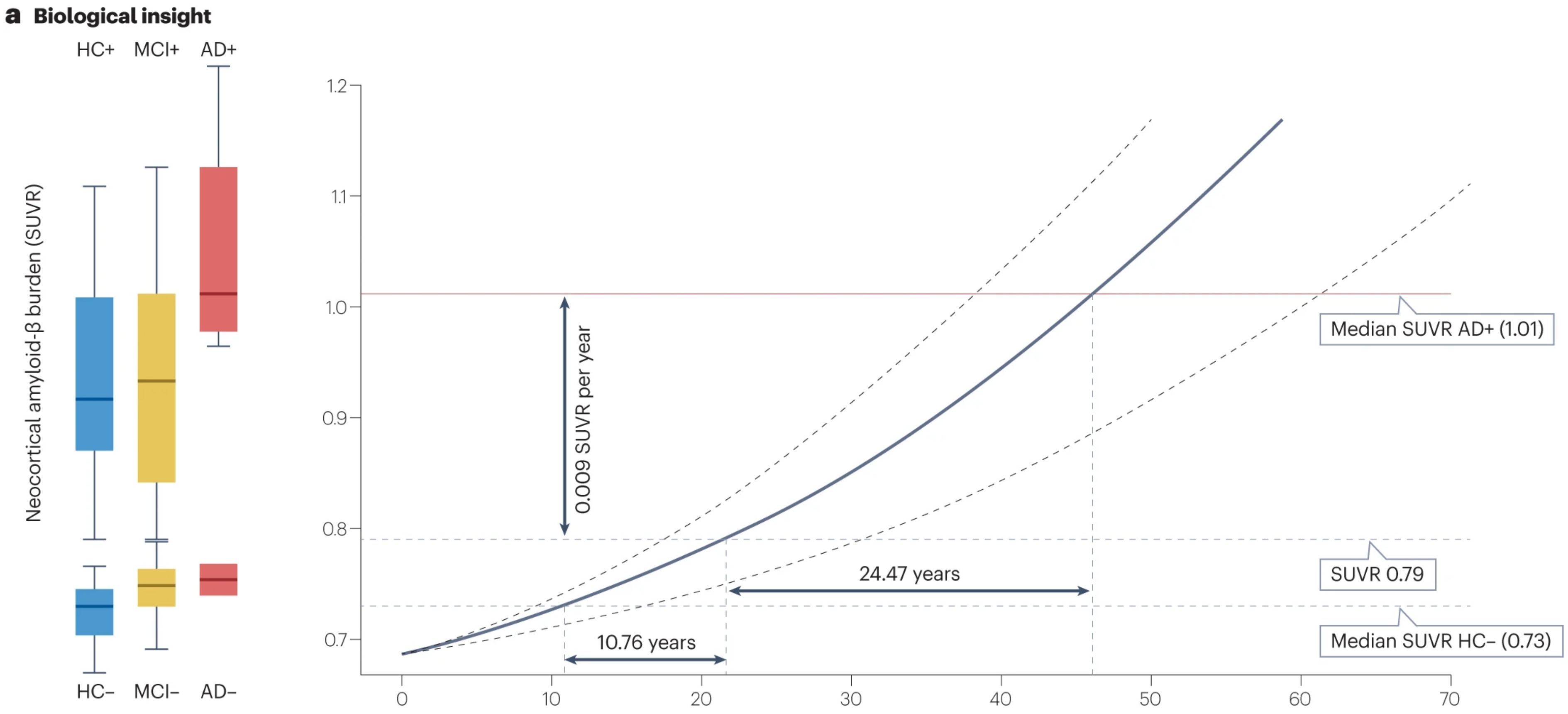


Applications

nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]



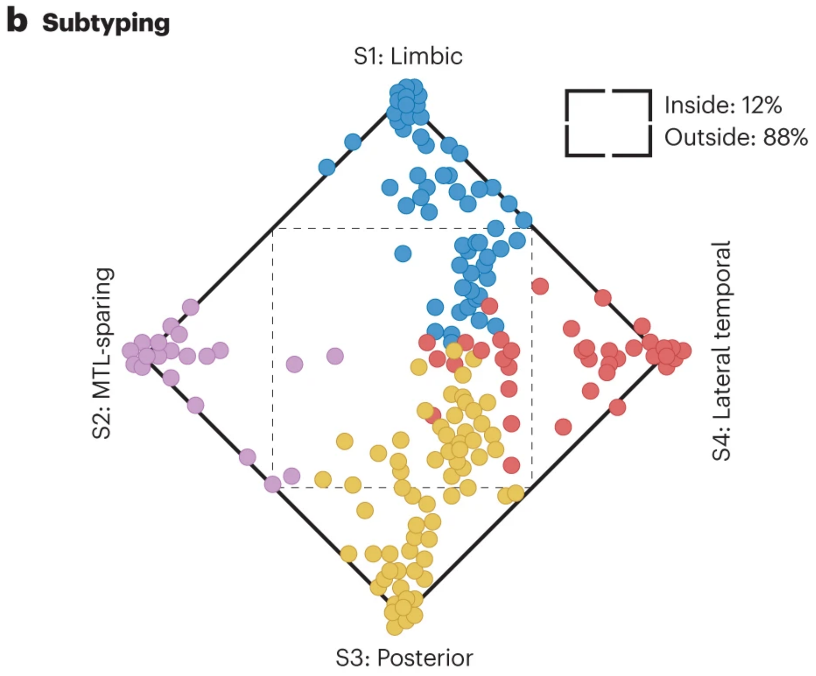
Villemagne et al. The Lancet Neurol 2013

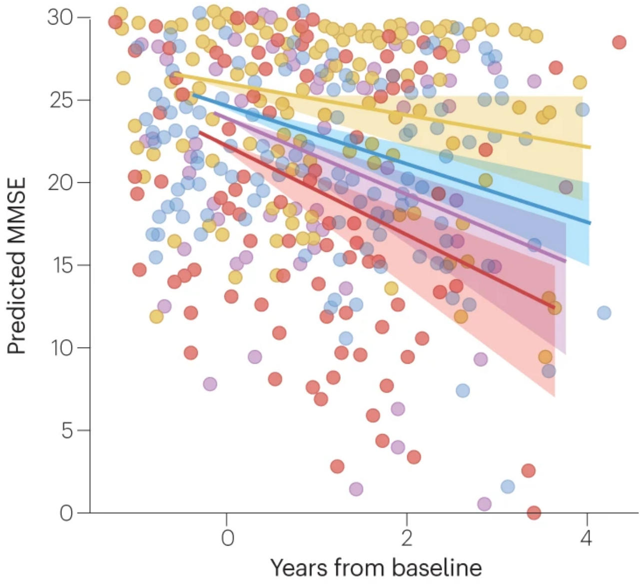
Applications

nature reviews neuroscience

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]





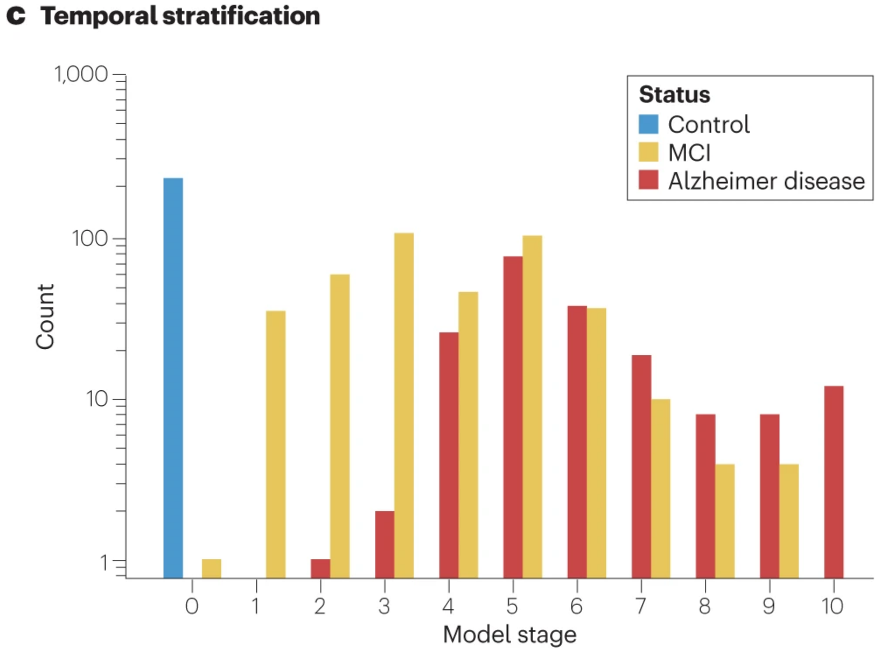
Vogel et al. Nat Med 2021

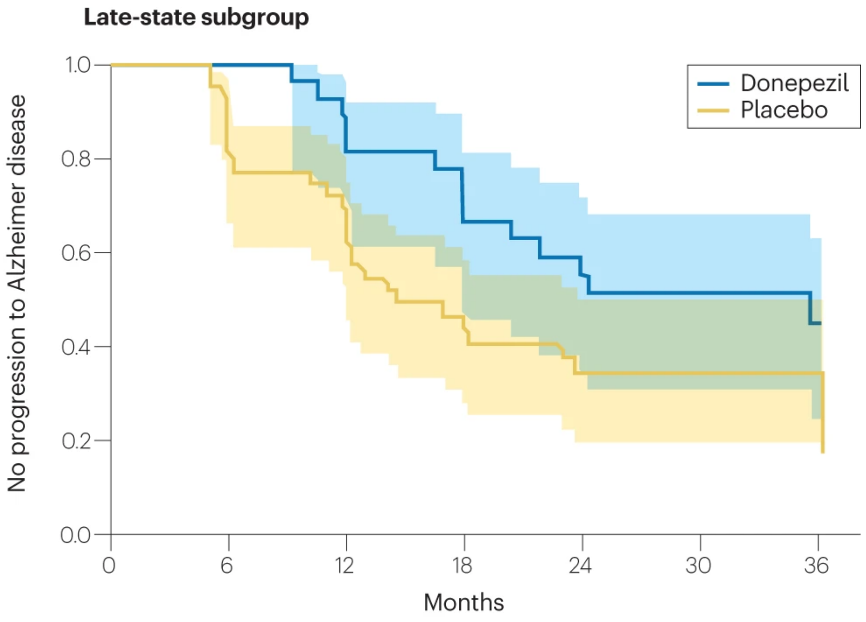
nature reviews neuroscience

Applications

Data-driven modelling of neurodegenerative disease progression: thinking outside the black box

Alexandra L. Young[1,2,6], Neil P. Oxtoby[1,6], Sara Garbarino[3], Nick C. Fox[4], Frederik Barkhof[1,5], Jonathan M. Schott[4] & Daniel C. Alexander[1]





Oxtoby et al. Frontiers AI 2022

Recap

Data-Driven Disease Progression Modelling

- Goes beyond “black box” approaches: “human insight + ML”
- Aids disease understanding at multiple scales
- Can support clinical decision making

Interested in Data-Driven Disease Progression Modelling?

https://disease-progression-modelling.github.io

Contributors

Igor Koval

Post-doc @ Paris Brain Institute & Inria

Neil Oxtoby

Senior Research Fellow @ UCL, UK

Sara Garbarino

Postdoctoral research fellow @ UNIGE, Genova

Marco Lorenzi

Researcher @Inria Sophia Antipolis, Université Côte d'Azur, France

Vikram Venkatraghavan

Postdoctoral researcher @ Alzheimer Center, Amsterdam UMC

Interested in Data-Driven Disease Progression Modelling?

https://disease-progression-modelling.github.io

Disease Progression Modelling

Search this book...

Disease Progression Modelling

MODELS

Introduction to DPM

Event Based Model

Disease Course Mapping

GP Progression Model

NOTEBOOKS

Overview

Disease Course Sequencing with the Event Based Model

Disease Course Mapping with Leaspy

GP Progression Model

CONFERENCES

Conferences

MICCAI 2021

ISBI 2021

Disease Progression Modelling

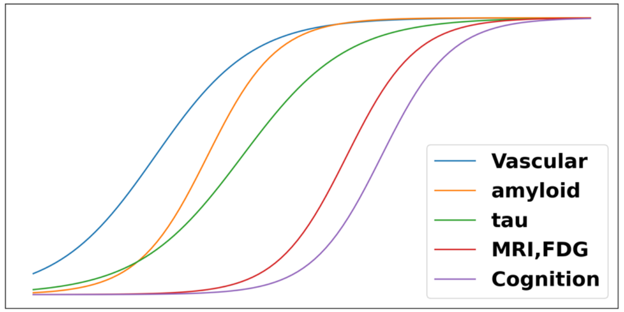
Contents

Disease Progression Modelling in a nutshell

Site content

The **Disease Progression Modelling** community unites medics with researchers and engineers across the physical and life sciences to tackle some of the biggest challenges of 21st-century medicine by harnessing the power of mathematics, computer science, and data.

—This website aims to serve as a portal for Disease Progression Modelling



The Alzheimer's Disease Progression Of Longitudinal Evolution Challenge

TADPOLE

Predictive modelling challenge for Alzheimer's disease

tadpole.grand-challenge.org

TADPOLE SHARE: tadpole-share.github.io

Marinescu et al. arχiv:1805.03909
MELBA Vol 1, 2021:19

pond
Progression Of Neurodegenerative Disease

EuroPOND

ADNI

Alzheimer's Society United Against Dementia

alzheimer's association

Alzheimer's Research UK The Power to Defeat Dementia

Acknowledgements

- UCL POND ucl-pond.github.io
  Prof. Danny Alexander, Alexandra Young, et al.
- EuroPOND europond.eu
- E-DADS e-dads.github.io
- Collaborators, Data providers, Volunteers (patients & families)

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

@NeilOxtoby
neiloxtoby.com
n.oxtoby@ucl.ac.uk

UCL

Thank you

Data-driven Disease Progression Modelling: thinking outside the black box

Neil P. Oxtoby

Principal Research Fellow (research track Assoc. Prof.)
UCL Centre for Medical Image Computing

pond
Progression Of Neurodegenerative Disease

Data Science Lead, DEMON Network
demondementia.com

cmic
Centre for Medical Image Computing

Douglas CIC Lecture Series, 28 Feb 2024