

Data-driven disease progression models for
Computational Neurology

*Progression-aware subtyping and its
application to clinical trials
in Alzheimer's disease*

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Nagoya Computational Neurology Journal Club
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The gist

- Context: Alzheimer's disease heterogeneity
 - Lack of a well-defined and consistent “disease time” axis
- Data-driven Disease Progression Modelling
 - Math + Human Insight + ML + Data
 - data-driven disease phenomenology and mechanisms
- Examples

Who is “POND”?

POND P.I.s

Neil Oxtoby

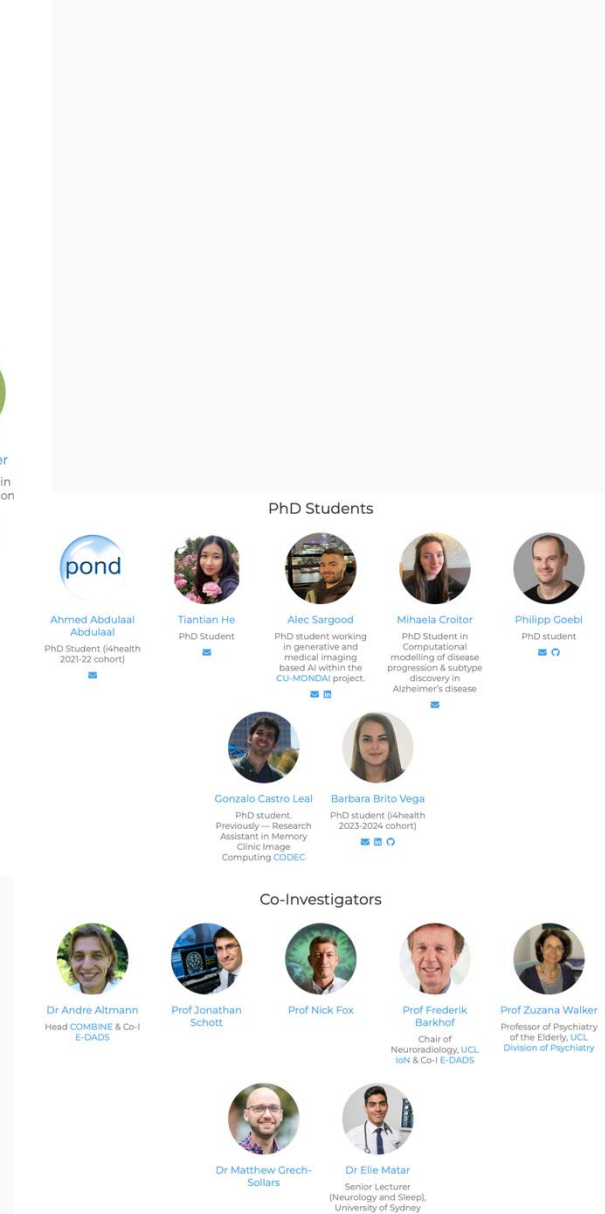
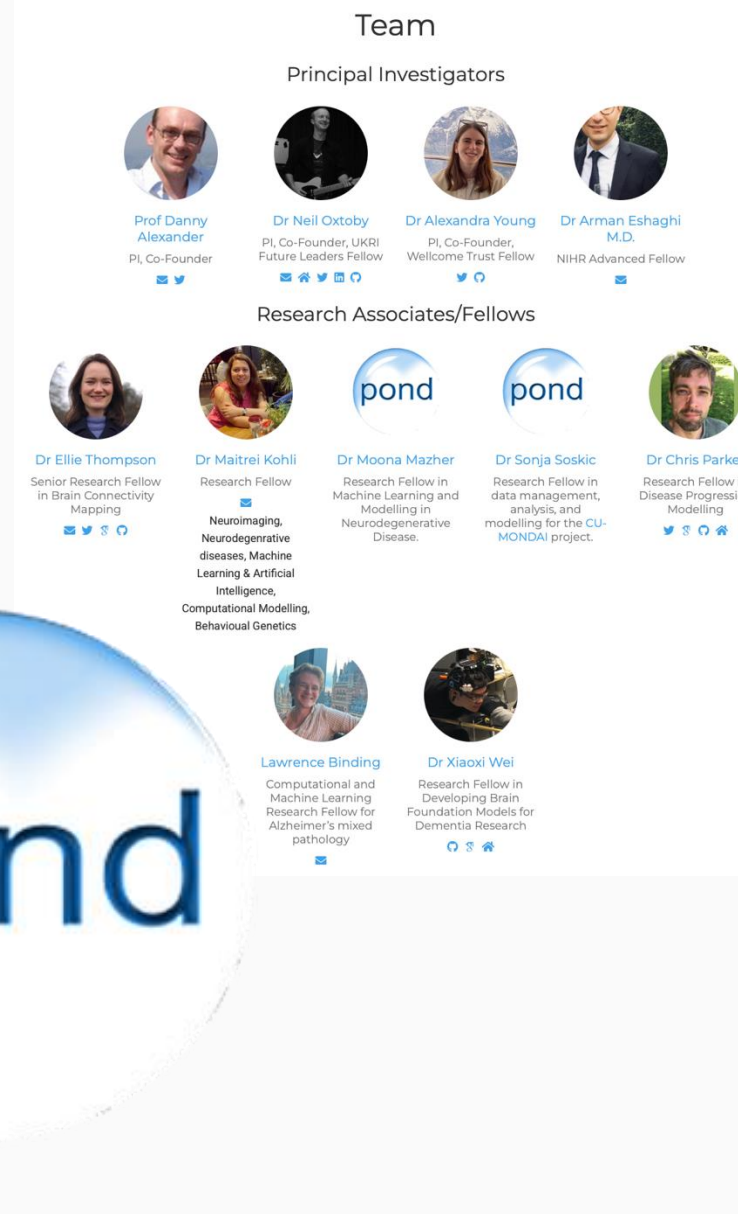
Danny Alexander

Alexandra Young

Key collaborators

DRC, IoN

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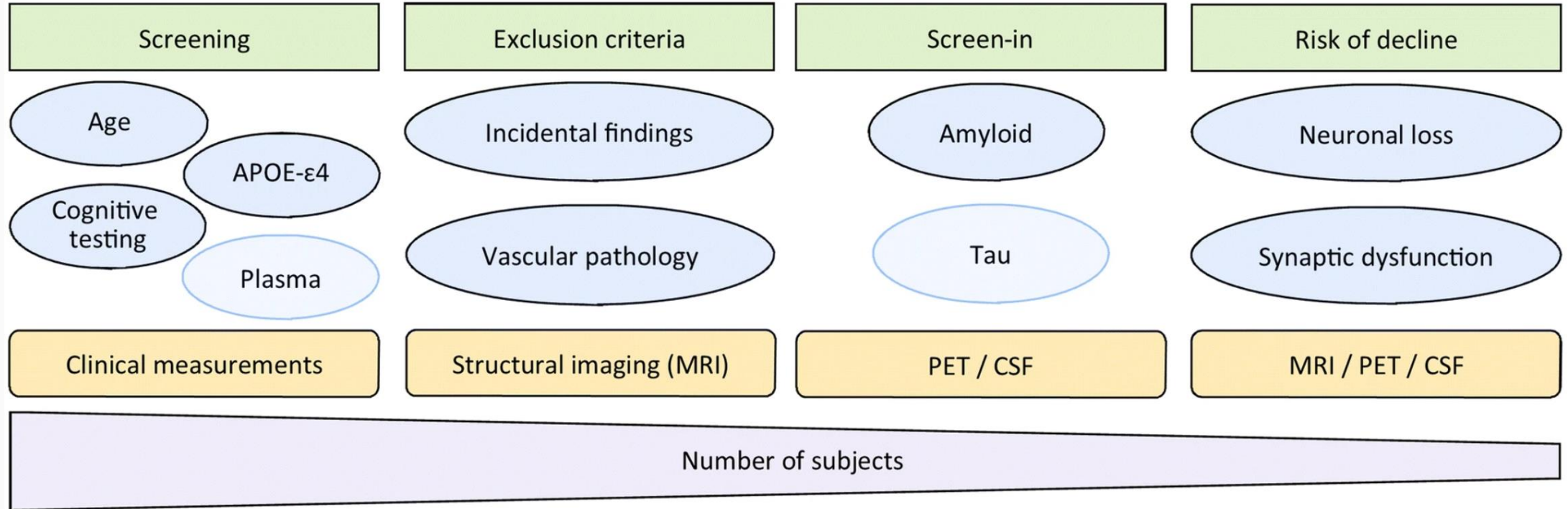


What do we know about Alzheimer's?

- Defined by *post mortem* histopathology
 - Braak staging
- Clinical syndrome: memory **etc.**
- *Looooong* pre-symptomatic period: decades of pathology
 - Near 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)



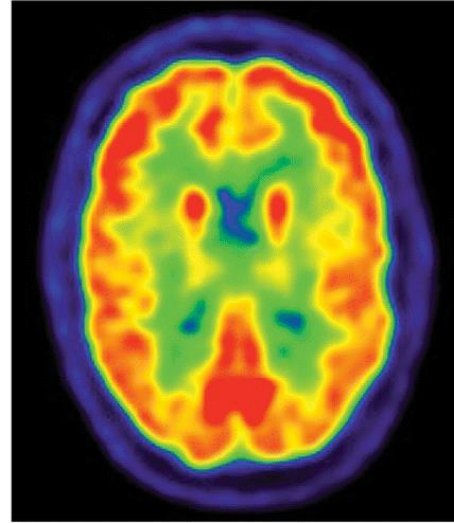
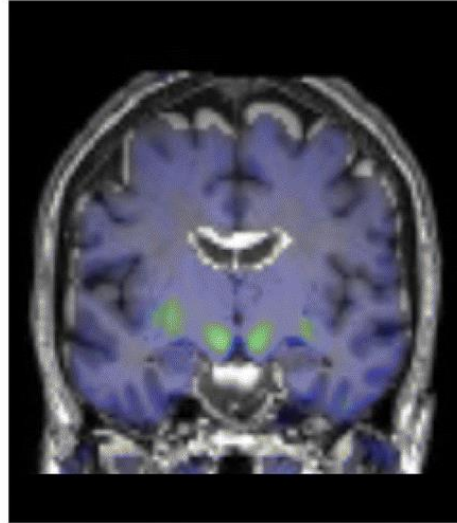
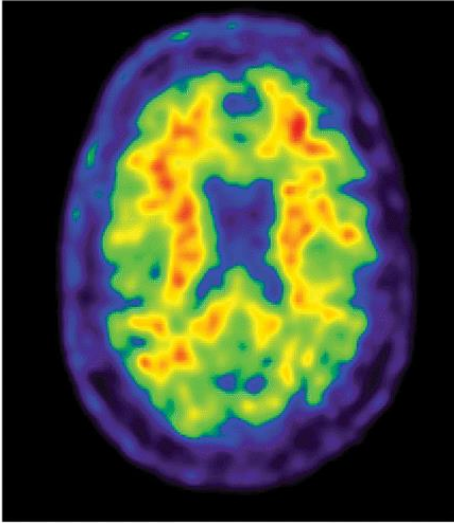
What have clinical trials done?



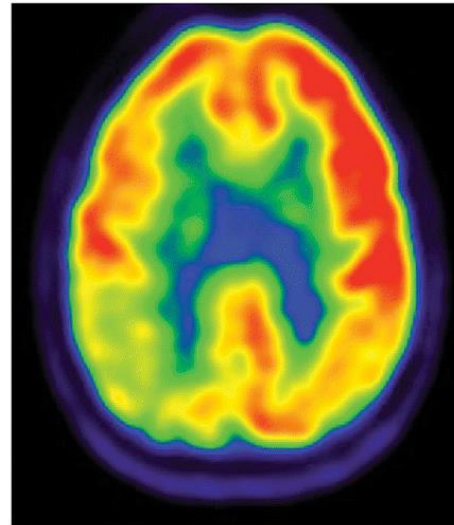
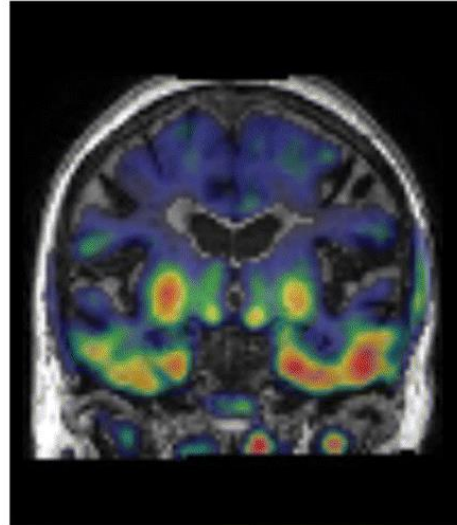
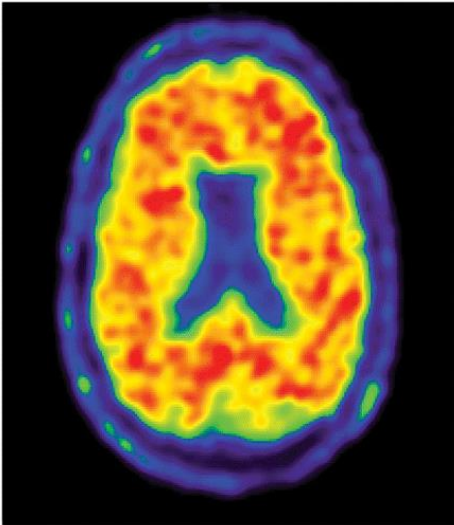
M. ten Kate et al., Alz Res Ther (2018)

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

NORMAL



ABNORMAL



AMYLOID PET

TAU PET

FDG PET

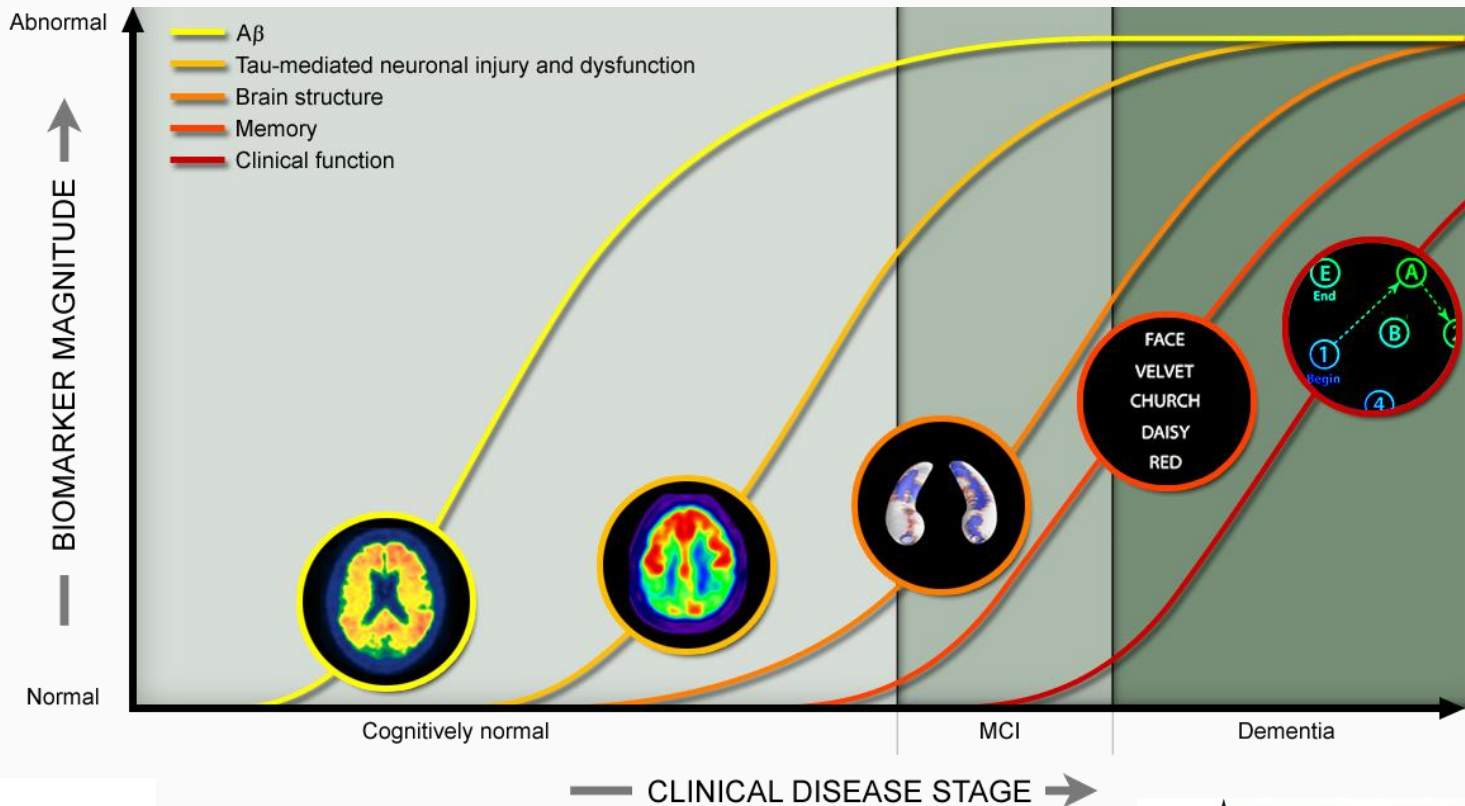
What have
clinical
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done?

Treatments for Alzheimer's?

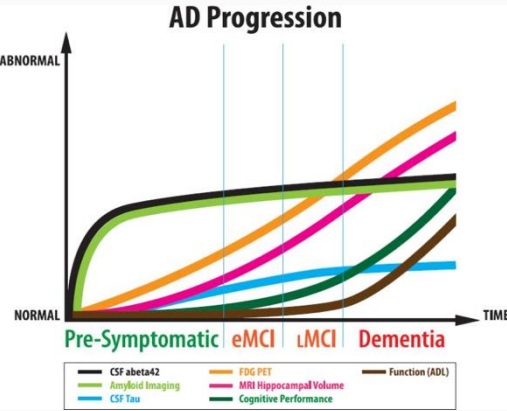
- Amyloid cascade hypothesis (**Hardy/Higgins 1992; Selkoe/Hardy 2016**)
 - + Plenty of supporting evidence
 - Anti-amyloid therapies: sketchy efficacy in large clinical trials
- Why are clinical trials “failing”? (hundreds since 2003)
 - Too late? (*wrong* time: prevention vs cure)
 - Individual variability? (*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**)

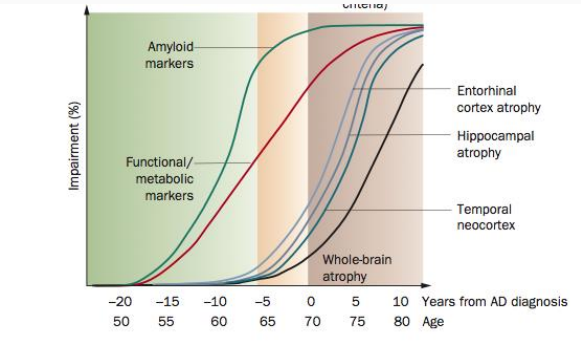
Background: Progression Modelling



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



Aisen et al.
Alz. Dement.
2010



Frisoni et al
Nat. Rev.
Neurol. 2010



Goals of Progression Modelling

- Quantitative signature of how a disease plays out over time
- Directly informed by measured data
 - medical imaging
 - also symptoms, pathologies
- Utility
 - precision stratification
 - diagnosis
 - prognosis

Data-driven Disease Progression Modelling

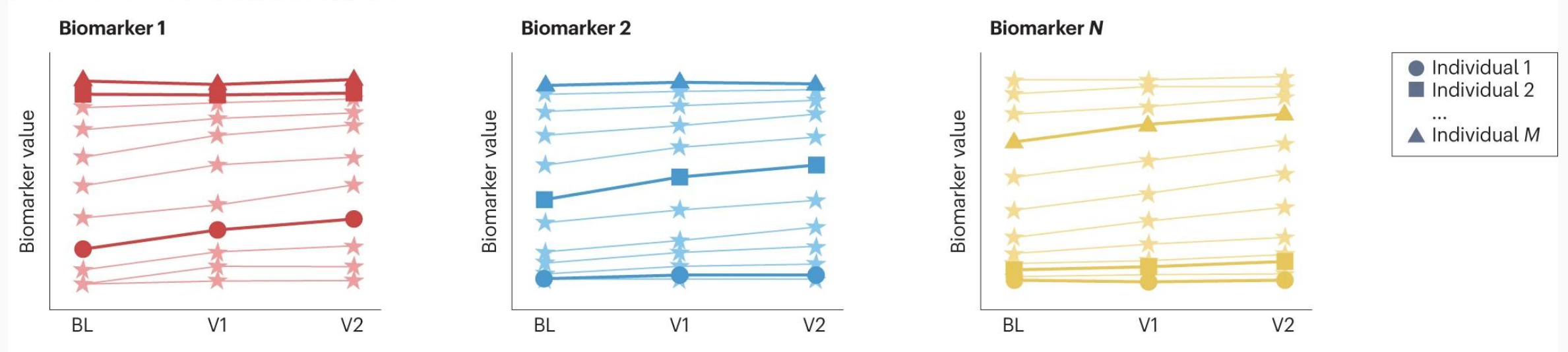
nature reviews neuroscience

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. Fox⁴, Frederik Barkhof ^{1,5}, Jonathan M. Schott⁴ & Daniel C. Alexander ¹

Data-driven Disease Progression Modelling

Disease biomarker data indexed by visit



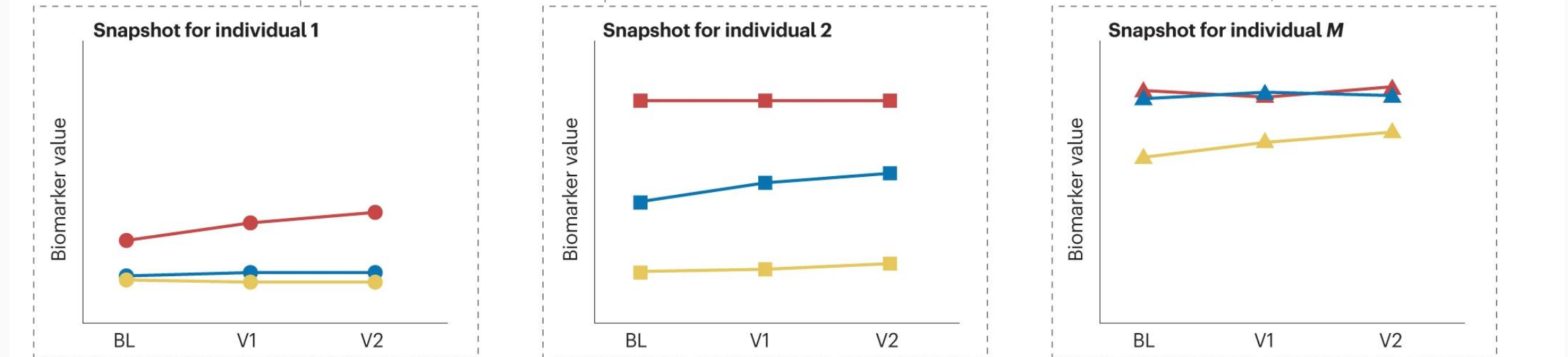
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Data-driven Disease Progression Modelling

Short-term snapshots

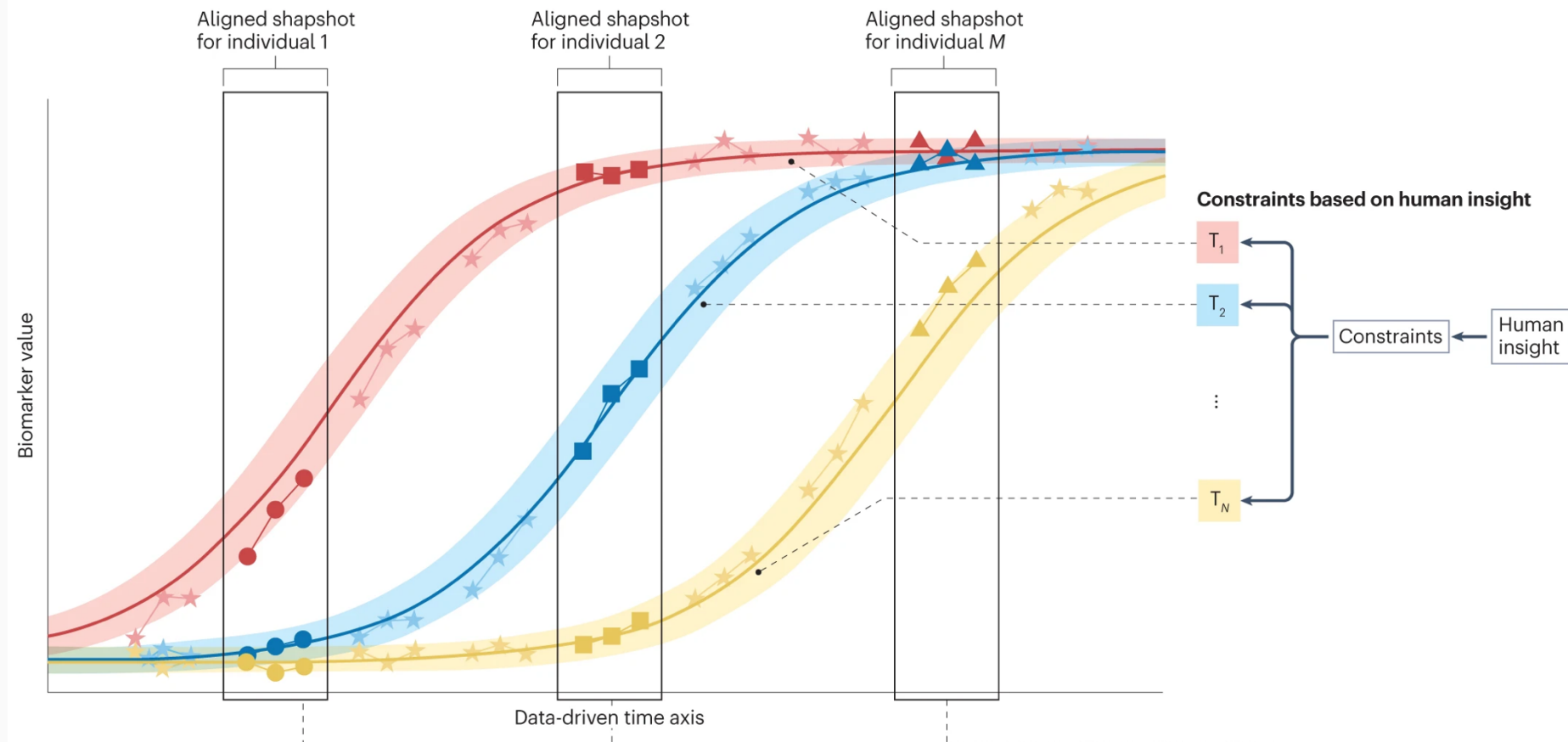


nature reviews neuroscience

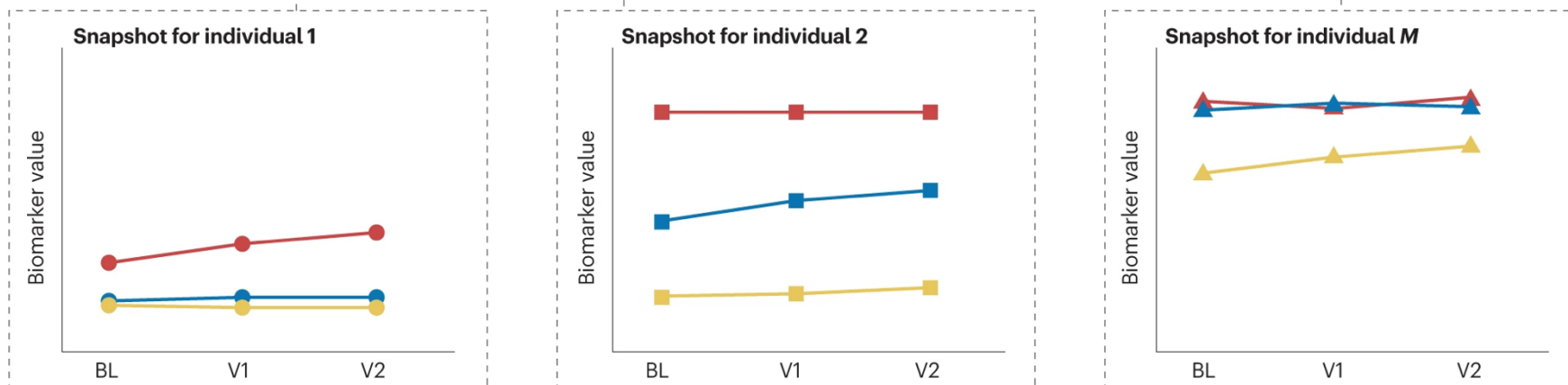
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Data-driven disease progression modelling reconstructs long-term disease timelines



Short-term snapshots



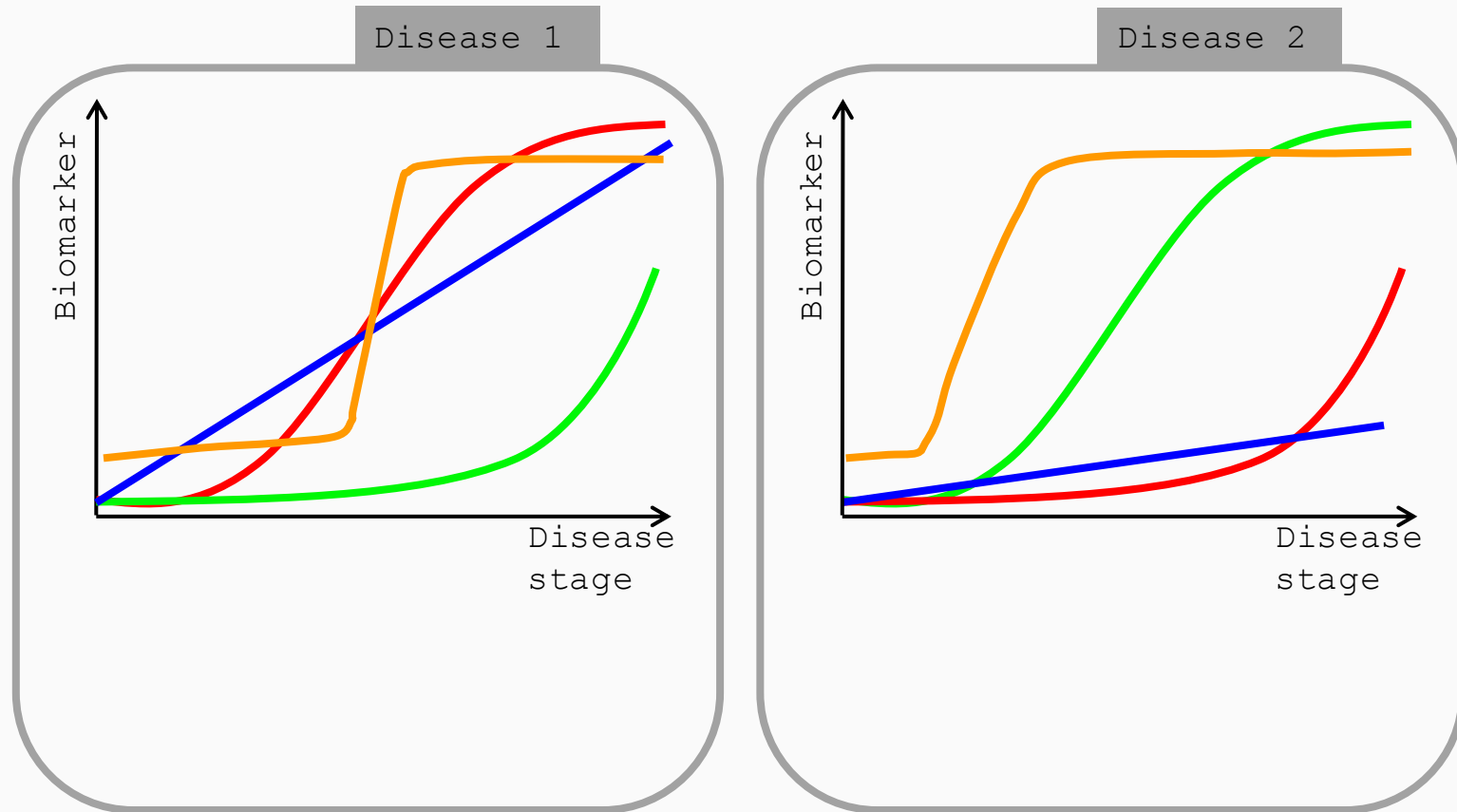
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Taxonomy:

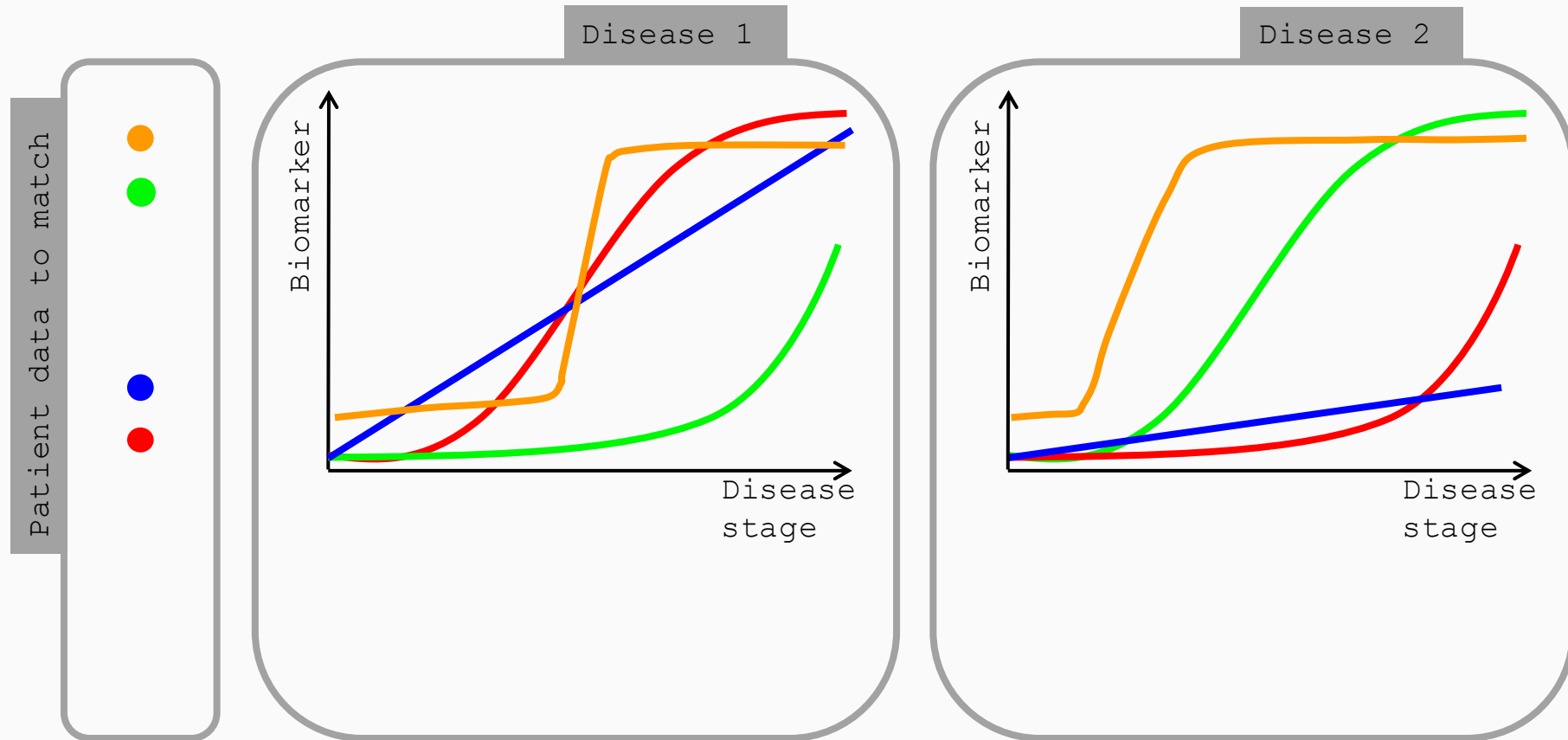
- Phenomenological
- Pathophysiological, a.k.a., Mechanistic

What are these in silico models good for?
e.g., Differential Diagnosis and Precision Staging



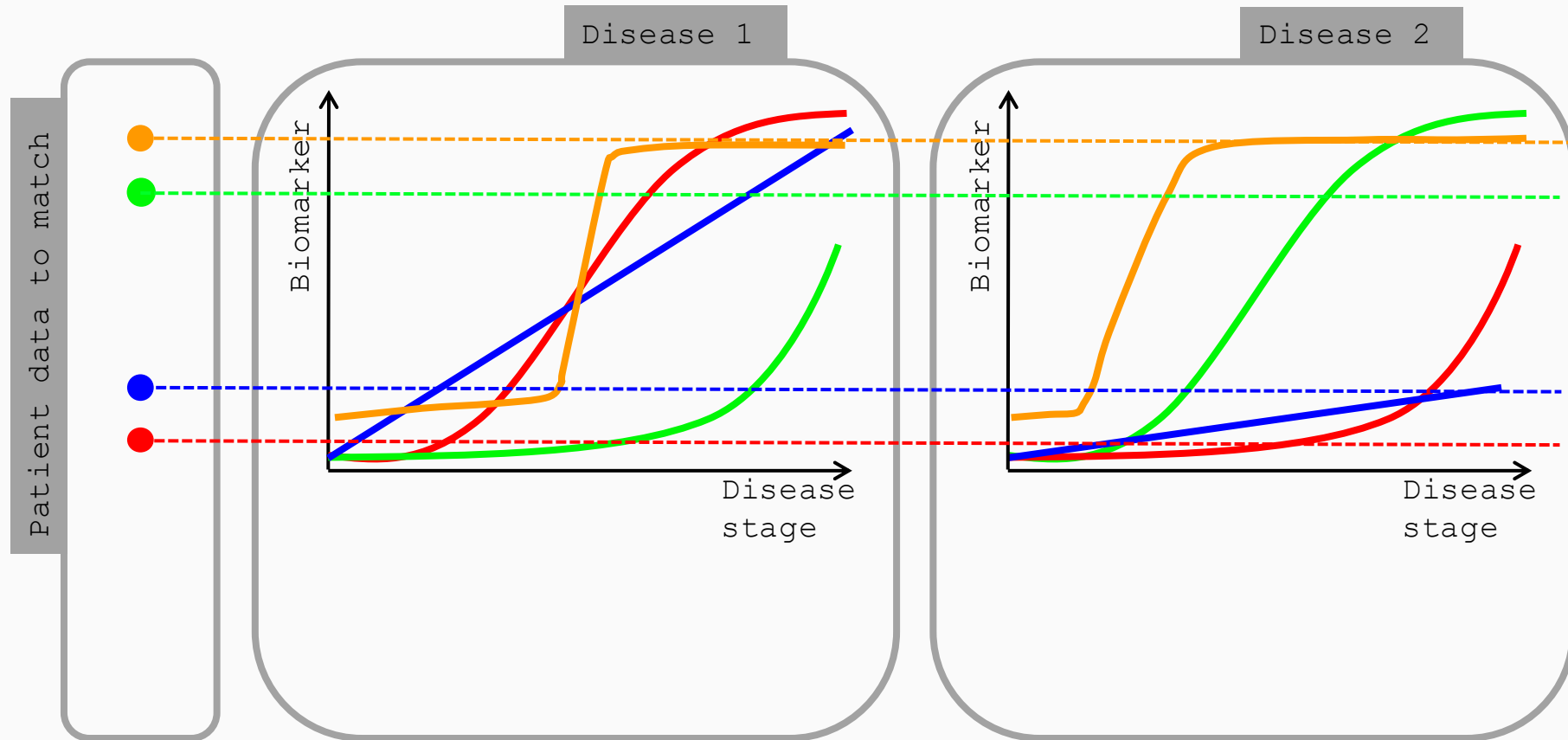
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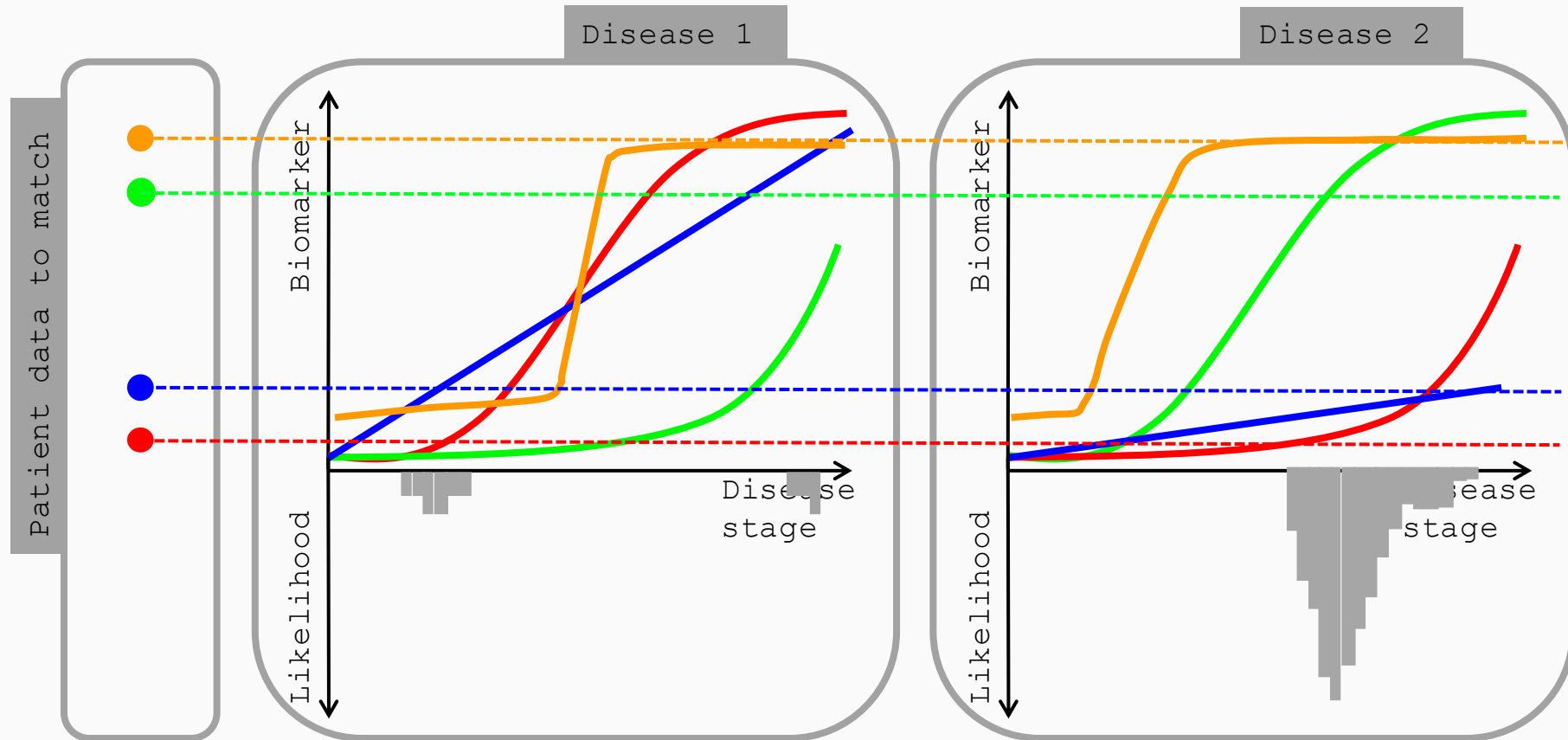
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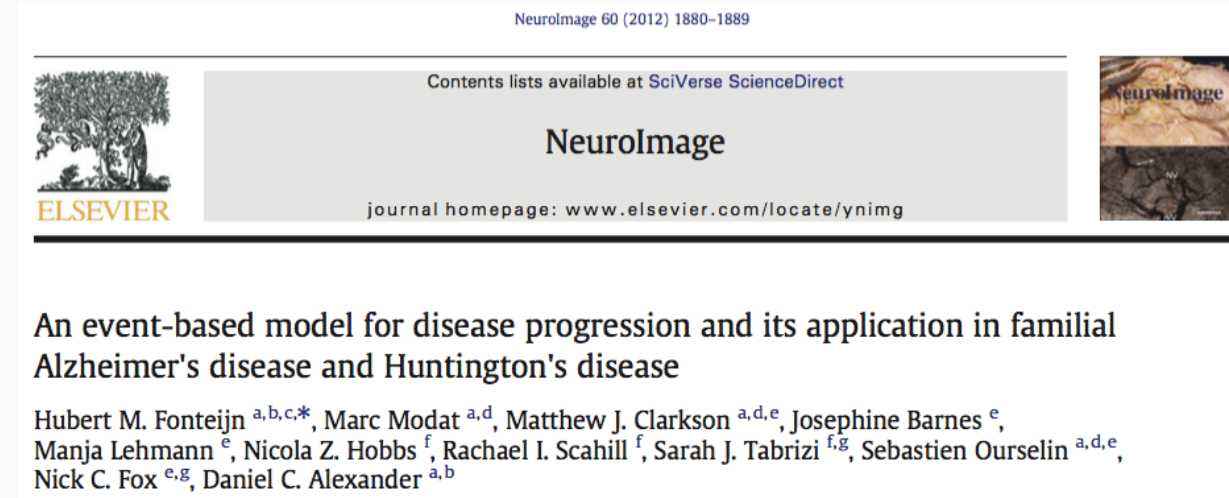


What are these in silico models good for?

e.g., Differential Diagnosis and Precision Staging



The Event-Based Model

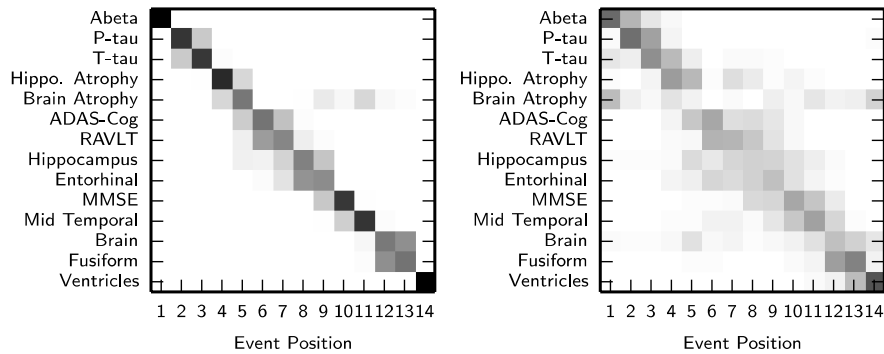


- Estimates order of “events” from a cross-sectional (or short-term longitudinal) data set
- Fine-grained staging tool for clinical decision support

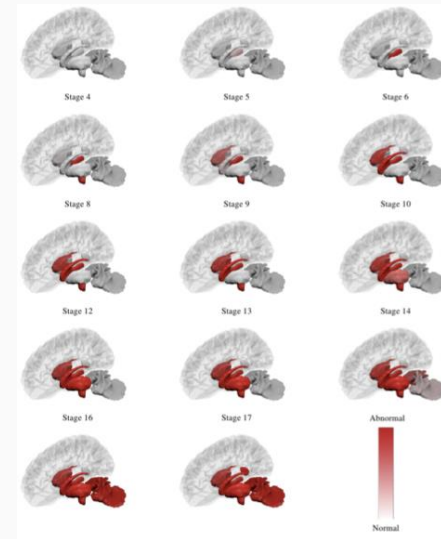
Data-driven: no prior knowledge of disease stage



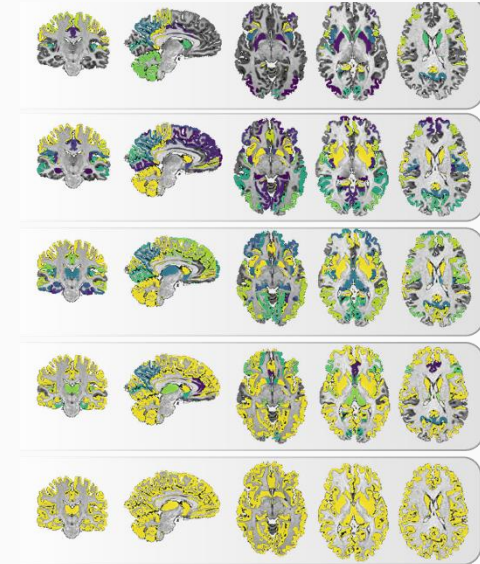
Our EBM of neurological diseases



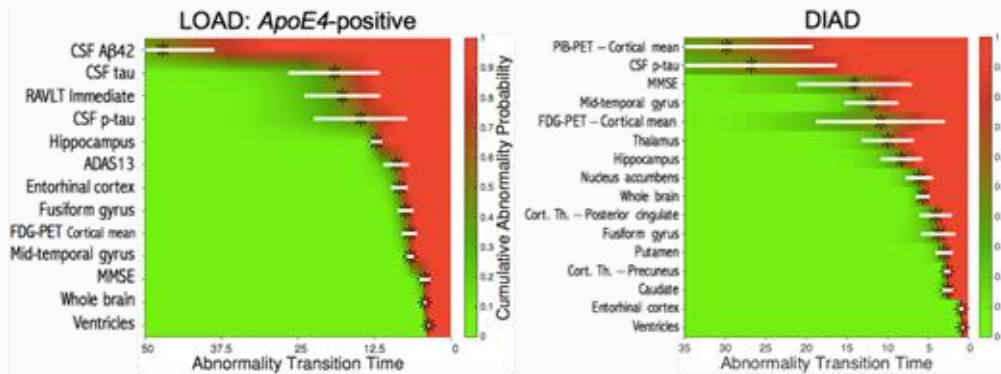
Sporadic AD
(Young, Brain 2014)



Huntington's
(Wijeratne ACTN 2018)

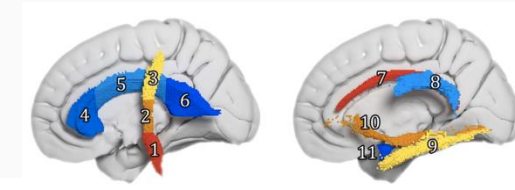
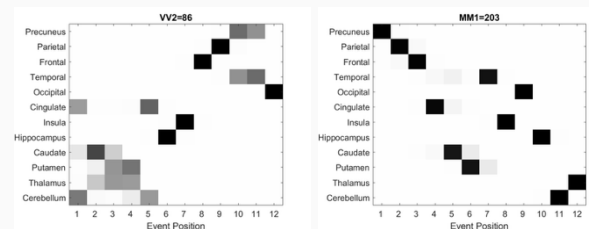


Multiple Sclerosis
(Eshaghi, Brain 2018)

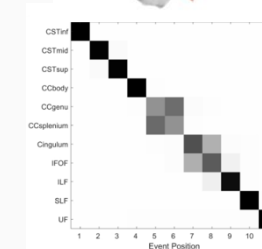


Familial vs Sporadic AD
(Oxtoby, Brain 2018)

Prion Diseases
(Pascuzzo 2018)



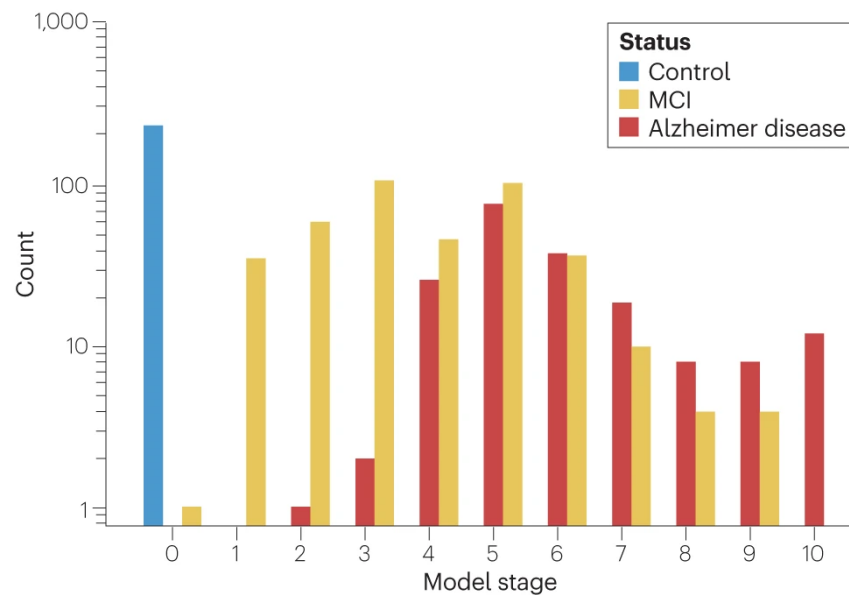
Motor Neuron Disease (ALS)
(Gabel 2019)



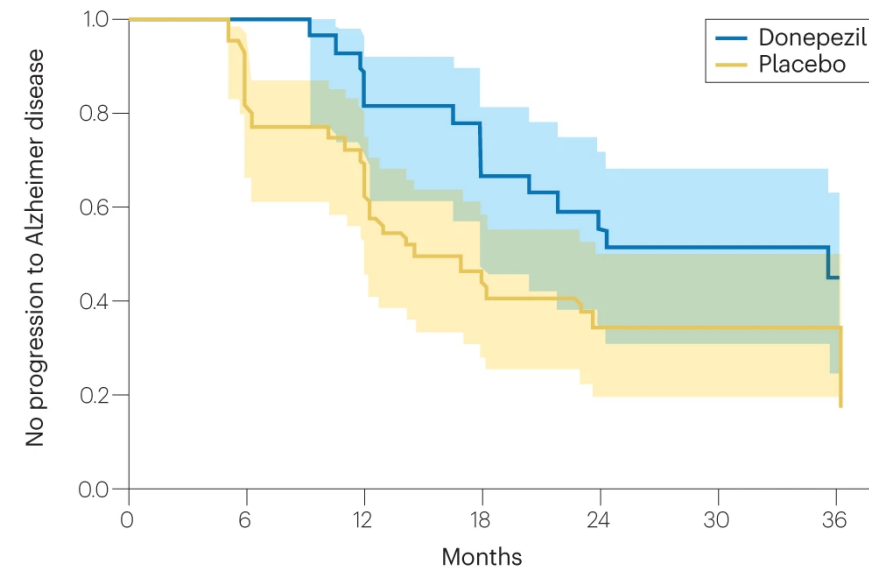
EBM applied to a clinical trial



C Temporal stratification



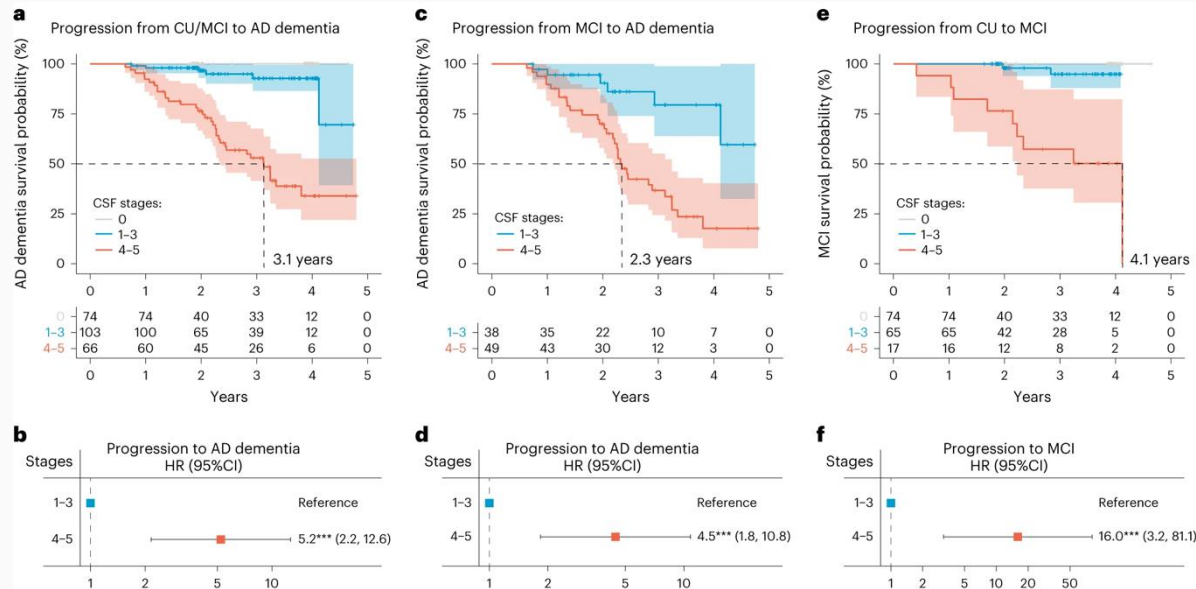
Late-stage subgroup



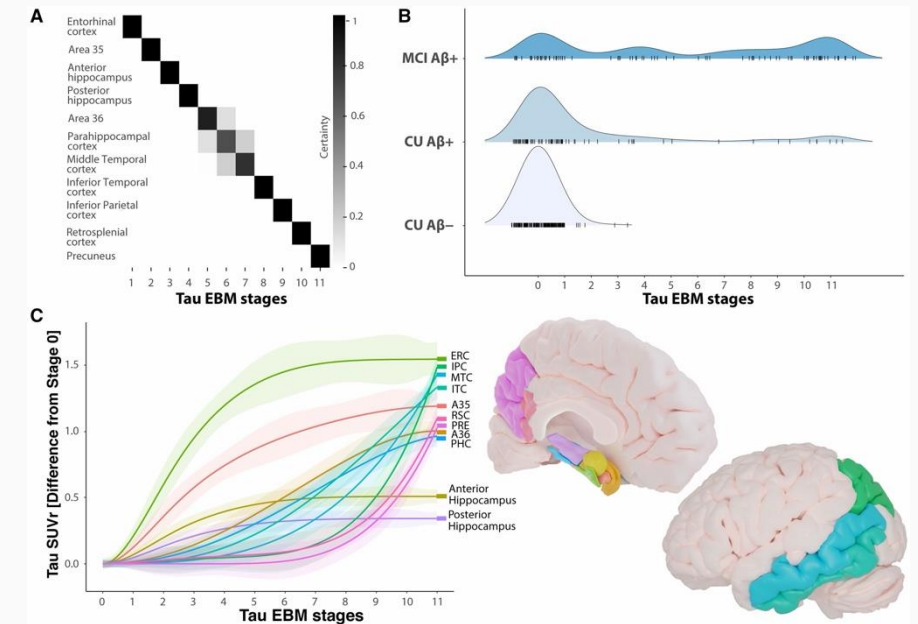
Oxtoby et al. Frontiers AI 2022

Examples of EBM in the wild

Salvado, Nature Aging 2024
EBM predicts future diagnosis

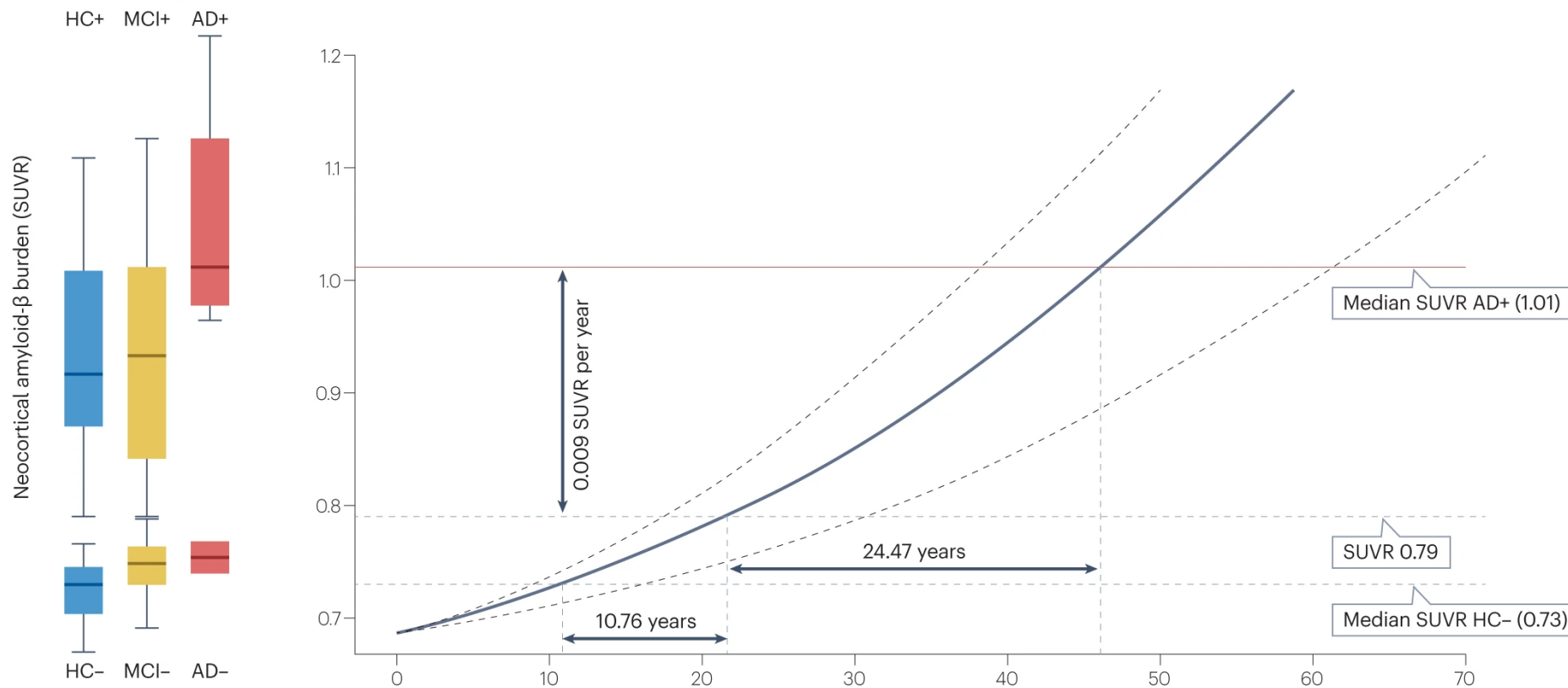


Berron, Brain 2021
tau spread in early Alzheimer's



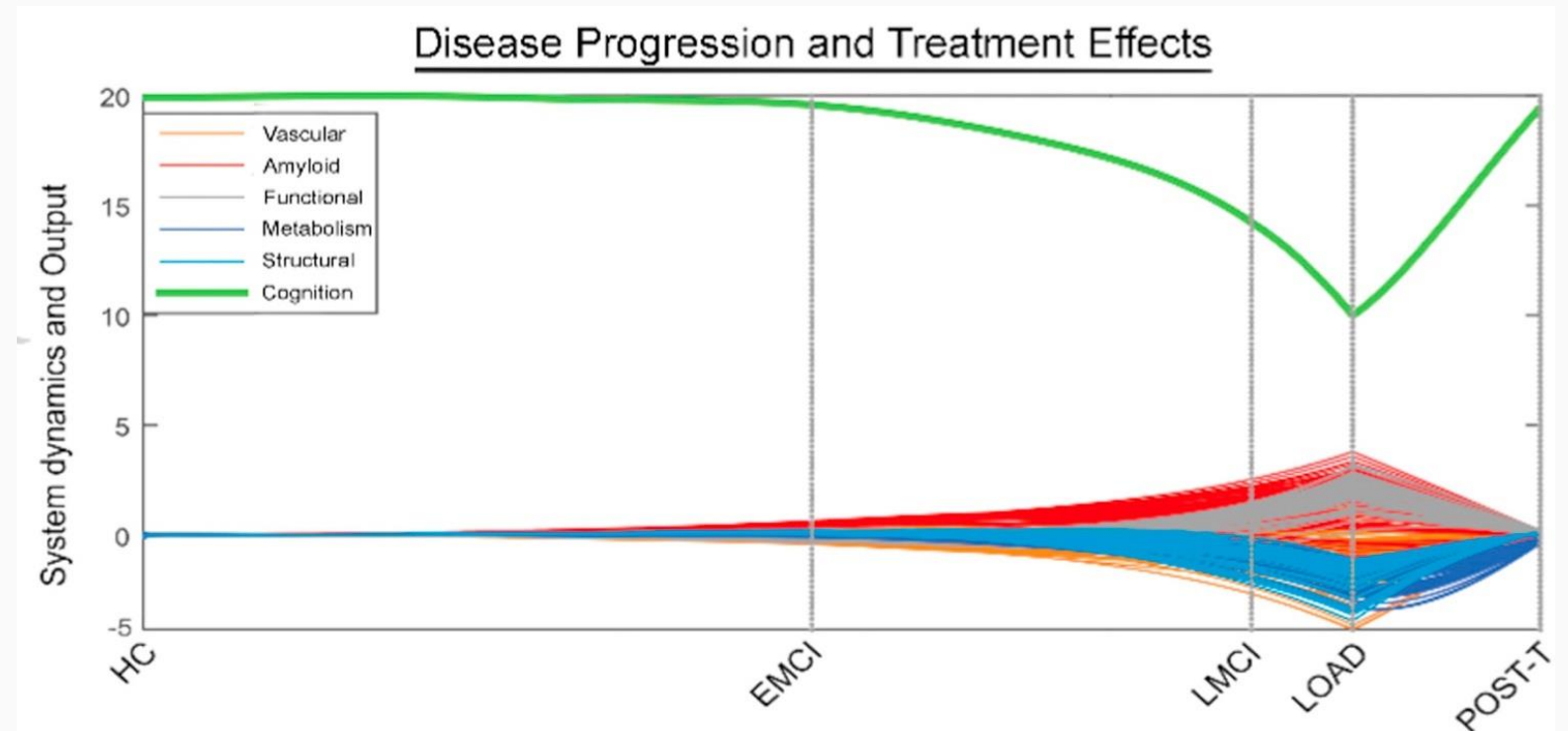
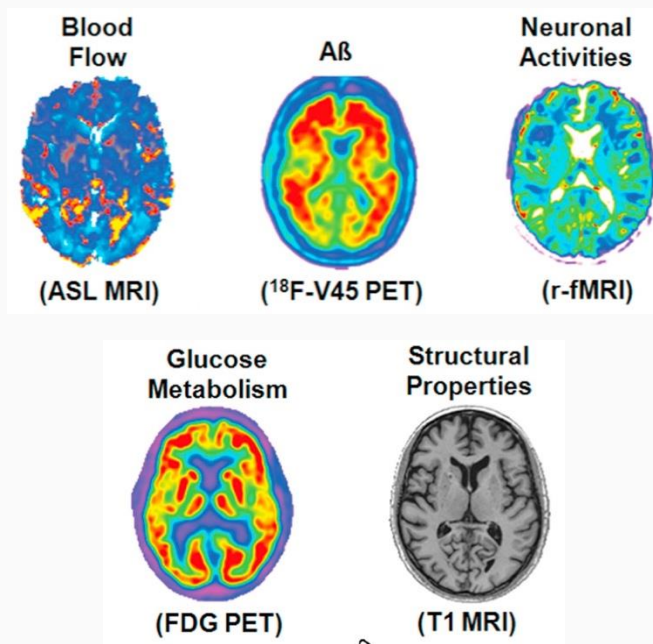
Other models: 25 years for amyloid to accumulate

a Biological insight



Other models: *in silico* interventions

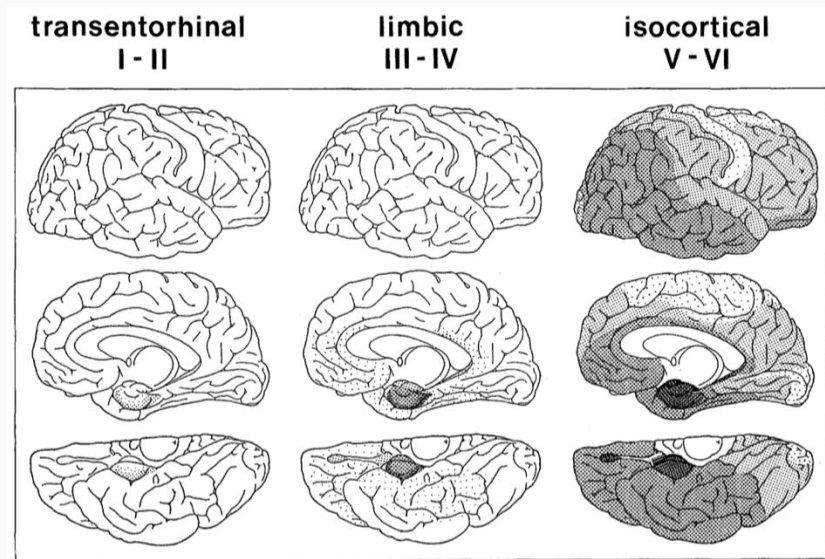
- **Generative** models + *in silico* interventions
 - Image-based abnormality across the brain



But what if disease progression is heterogeneous?

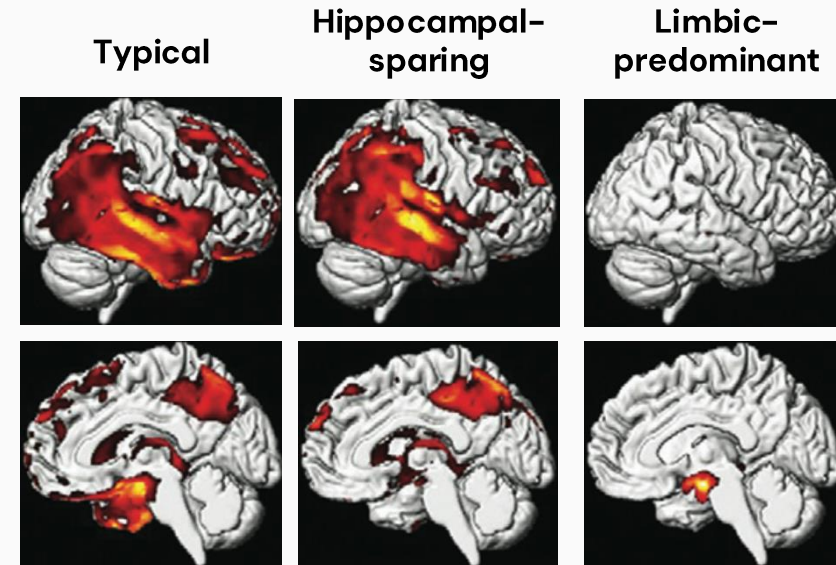
Disease progression & heterogeneity

Temporal progression stages



Braak and Braak 1991

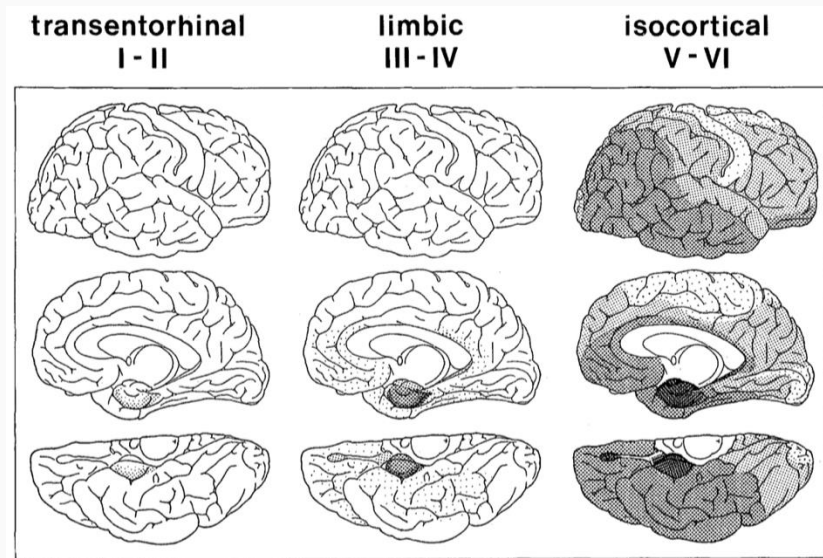
Subtype heterogeneity



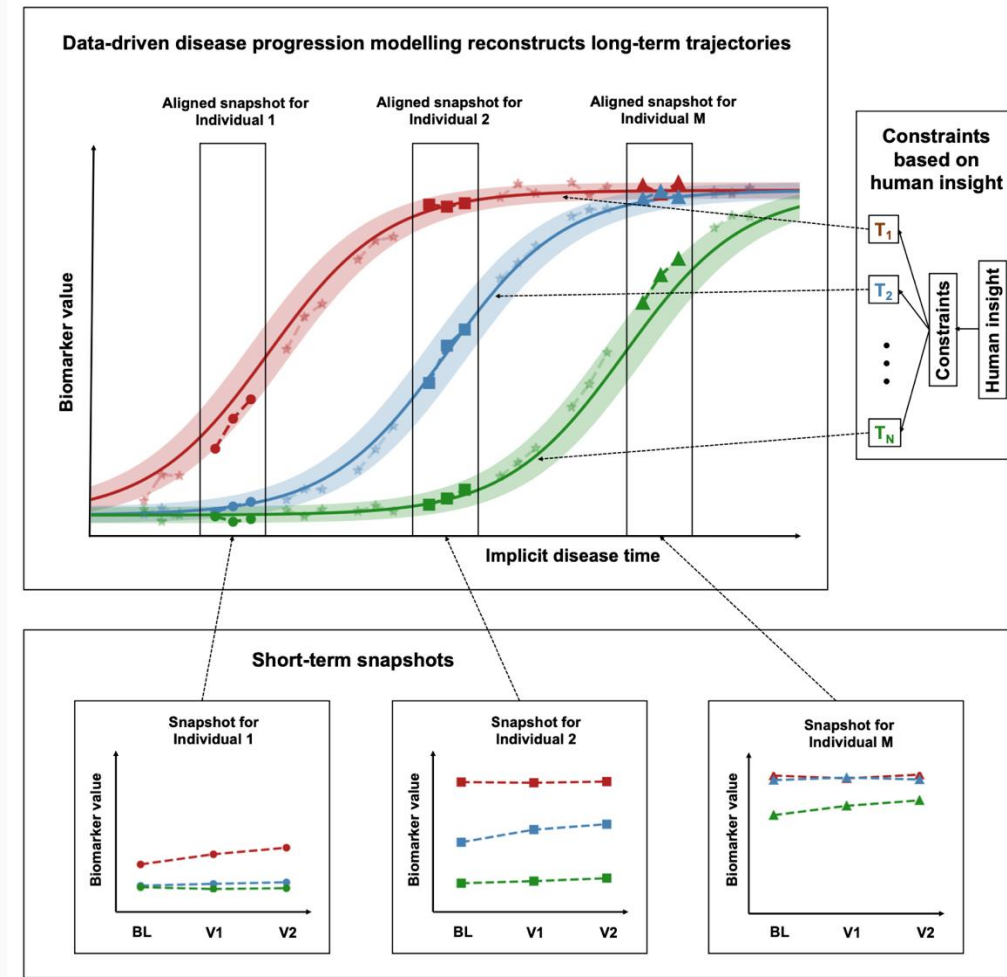
Murray et al. 2011; Whitwell et al. 2012

Data-driven disease progression models

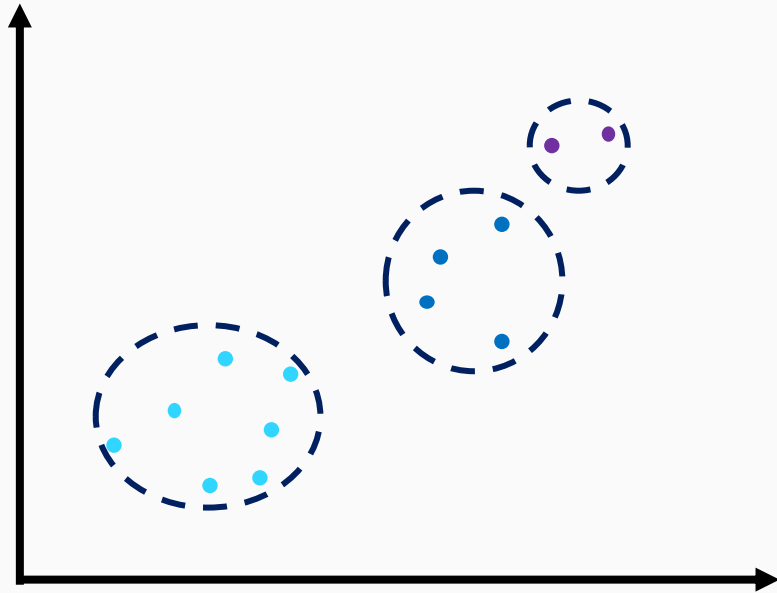
Temporal progression stages



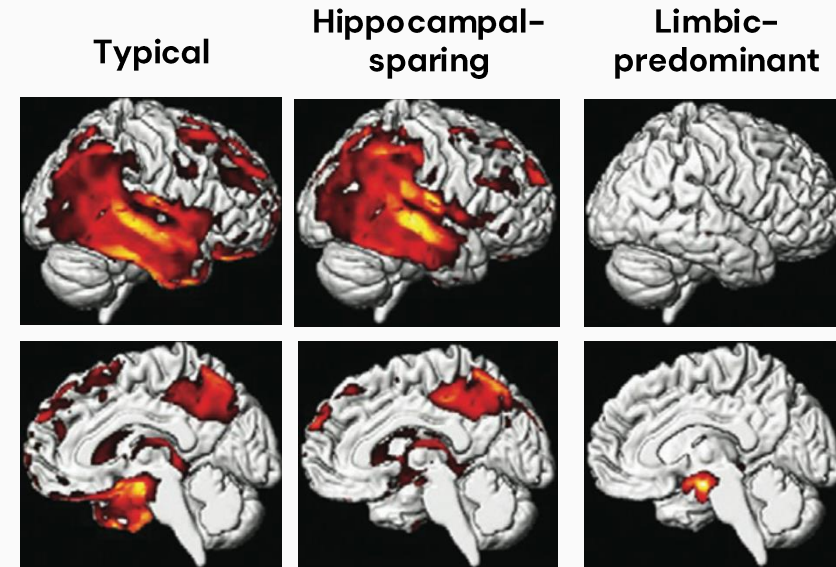
Braak and Braak 1991



Clustering



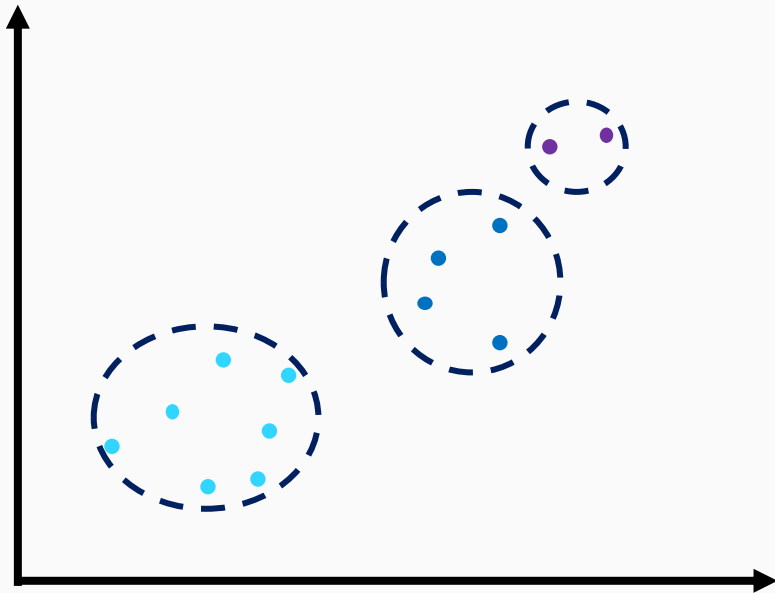
Subtype heterogeneity



Murray et al. 2011; Whitwell et al. 2012

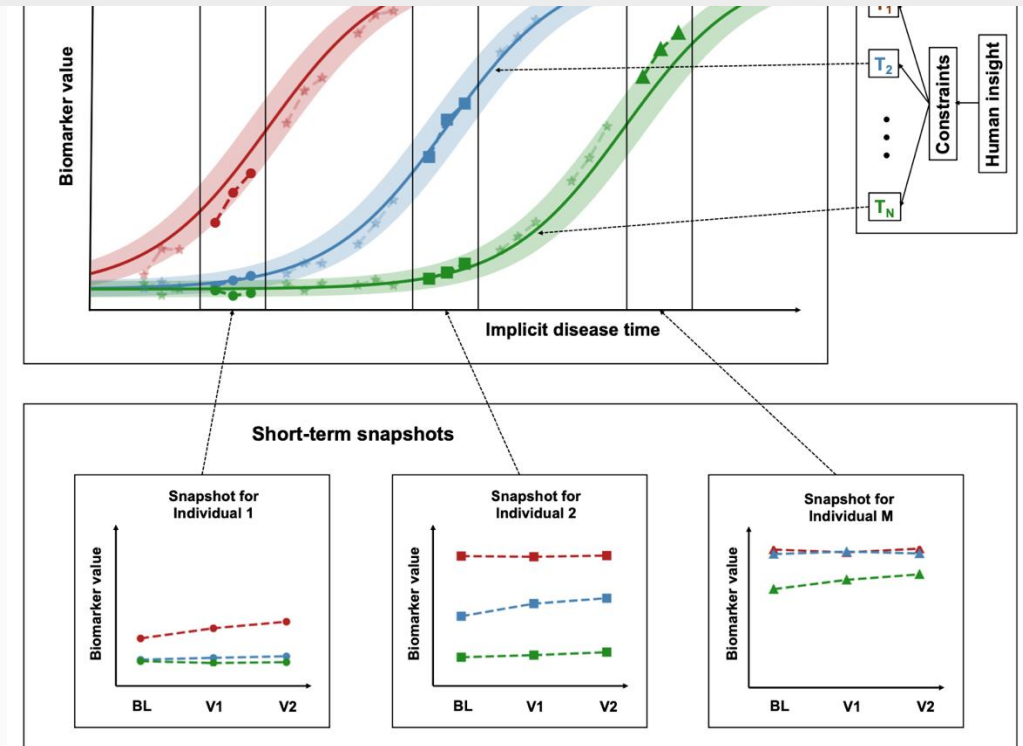
Each has limitations

Clustering: no stages
Assumes a common stage



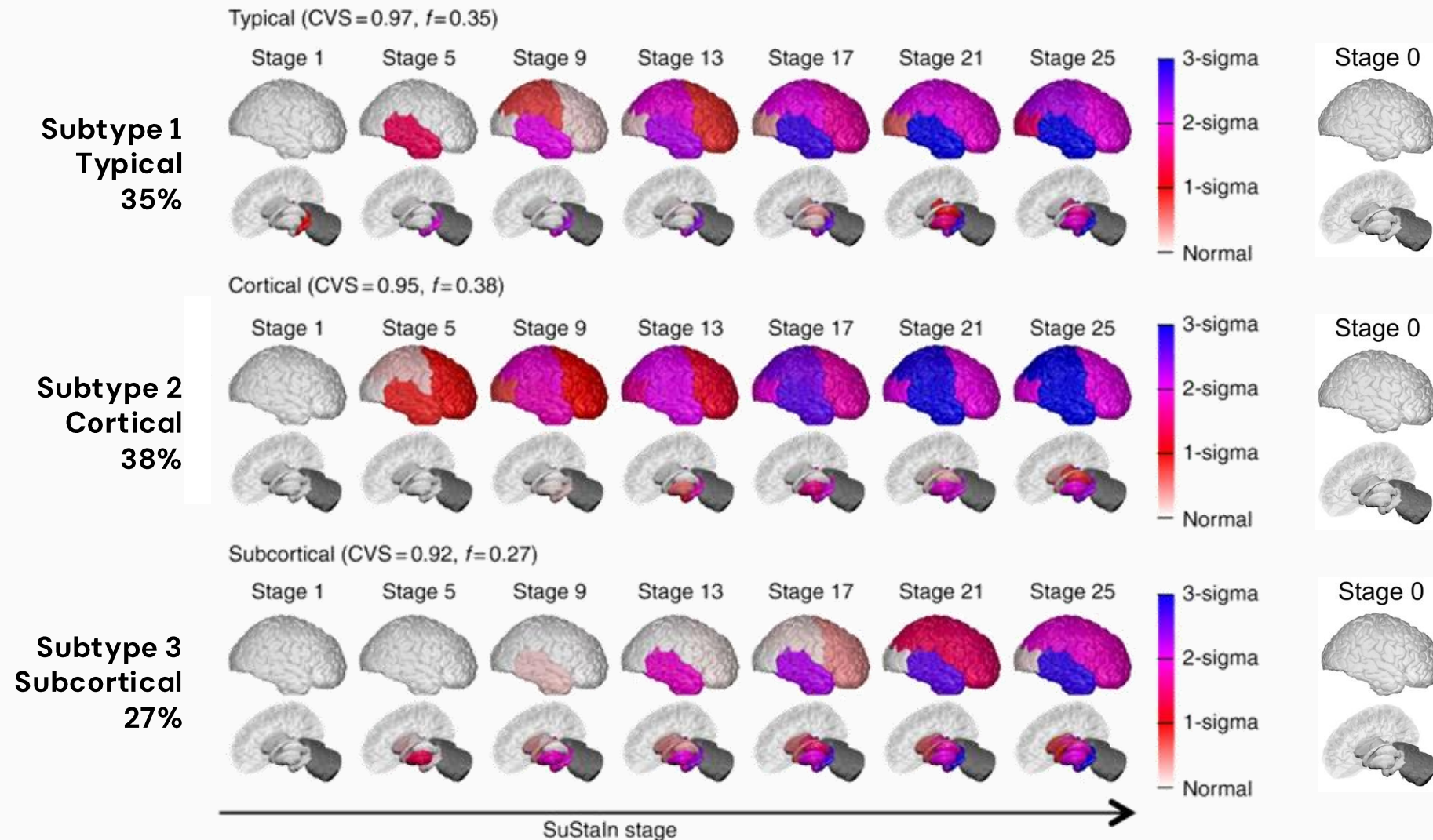
Data-driven disease progression modelling reconstructs long-term trajectories

Disease progression modelling: no subtypes
Assumes a common progression pattern



SuStain: Subtype and Stage Inference

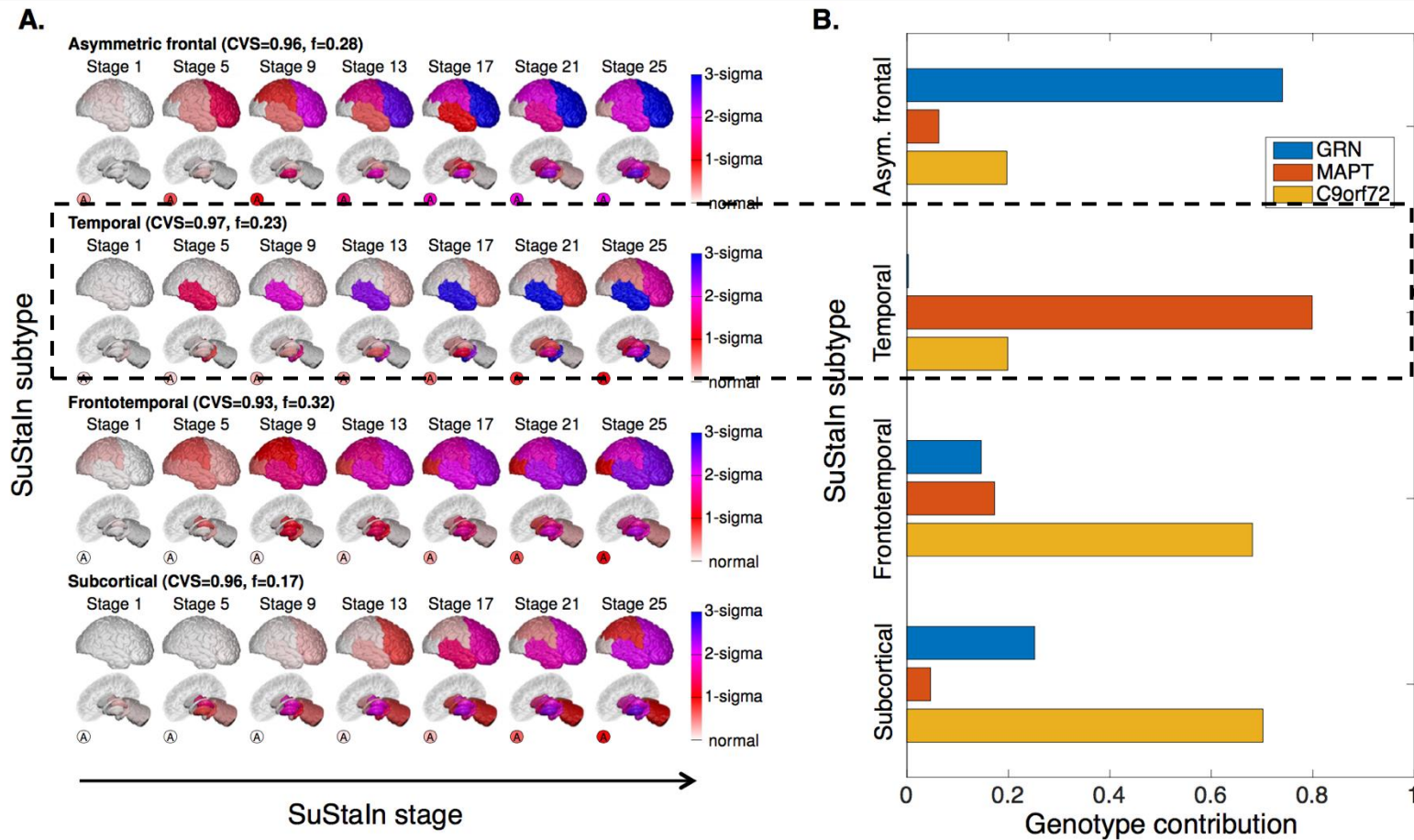
Alzheimer's disease atrophy



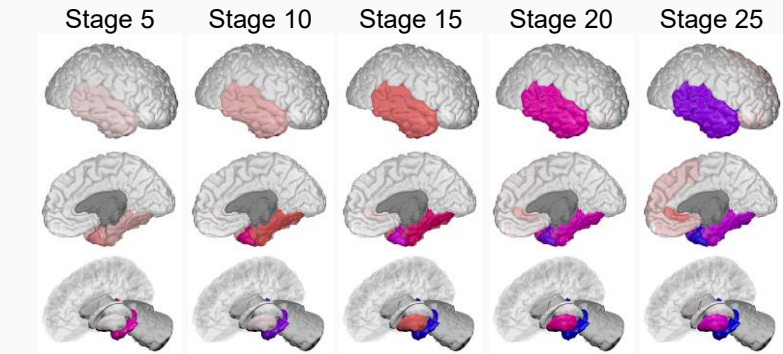


SuStaln: Subtype and Stage Inference

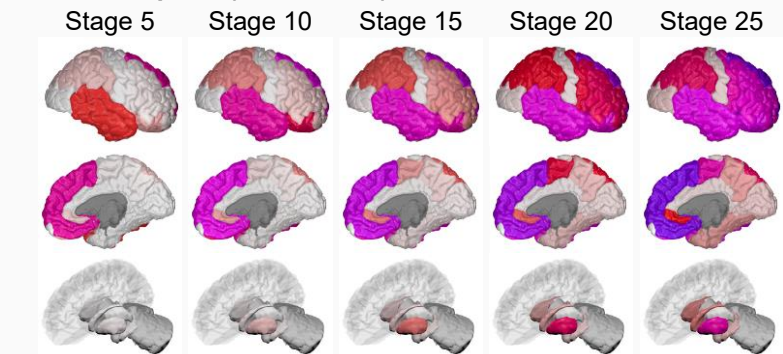
Genetic FTD atrophy: image-based SuStaln predicts genotypes



Temporal (68%; IVS10+16, R406W)



Frontotemporal (32%; P301L)



Young et al, Neurology 2021



Our SuStain studies

- **Young, Nature Communications 2018:** Alzheimer's and genetic FTD
- **Young, Neurology 2021:** MAPT-FTD
- **Young, AJRCCM 2019 (*Blue Journal*) :** Lung disease (COPD)
- **Eshaghi, Nature Communications 2021:** Multiple Sclerosis treatment response
- **Young and Vogel, Brain 2023:** TDP-43 postmortem
- **Taylor, Brain 2024:** Primary Progressive Aphasia
- **Shawa, Brain Communications 2025:** Parkinson's disease

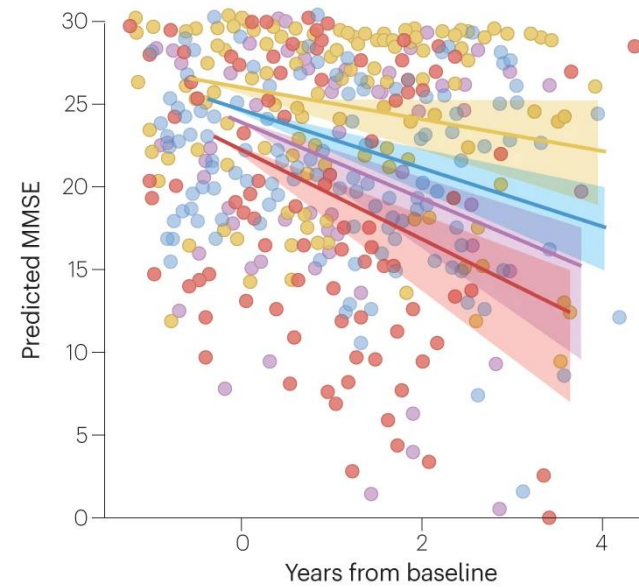
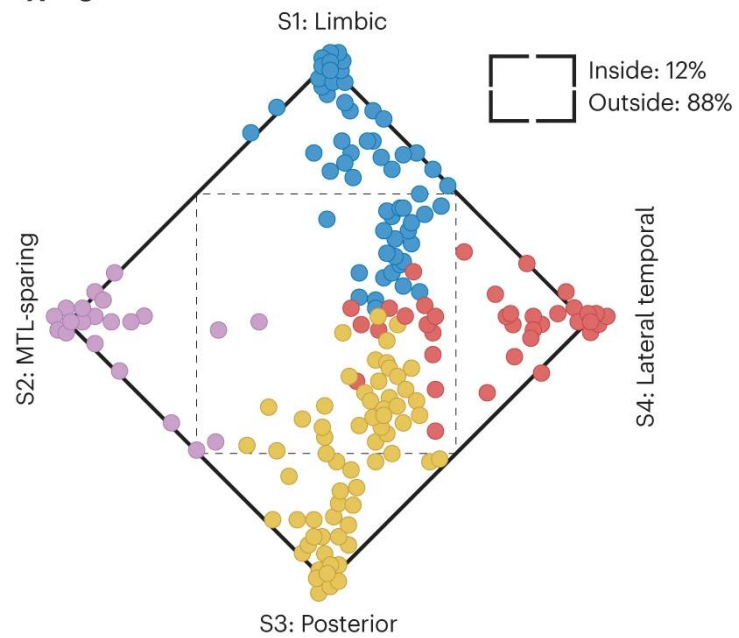
Methodological:

- **Young, Frontiers in AI 2021:** Scored (Ordinal) events model
- **Estarellas, Brain Communications 2024:** Missing data
- **Binding, AAIC 2025:** "AddiPath" co-pathology modelling



SuStaln in the wild

b Subtyping



Vogel et al. Nat Med 2021

SuStain in the wild

github.com/ucl-pond/pysustain

- **Vogel, Nat Med 2021:** tau PET subtypes of Alzheimer's disease predict clinical phenotype & decline
- **Li, Frontiers in Public Health 2021:** Knee Osteoarthritis
- **Chen, Nature Mental Health 2023:** Major depressive disorder
- **Jiang, Nature Mental Health 2023:** Schizophrenia
- **Xiao, Brain 2023:** Epilepsy
- **Mastenbroek, Nature Communications 2024:** alpha-synuclein postmortem
- **Sakato, Brain 2024:** Parkinson's disease

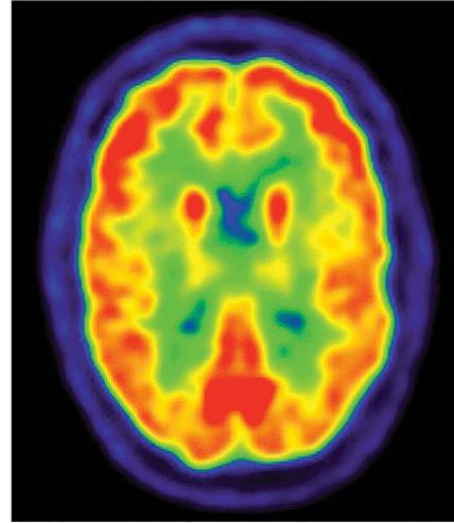
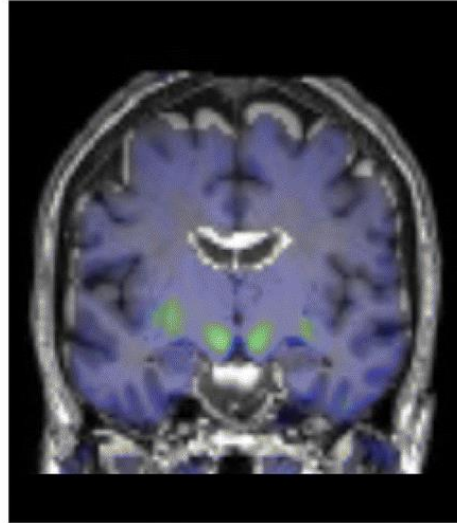
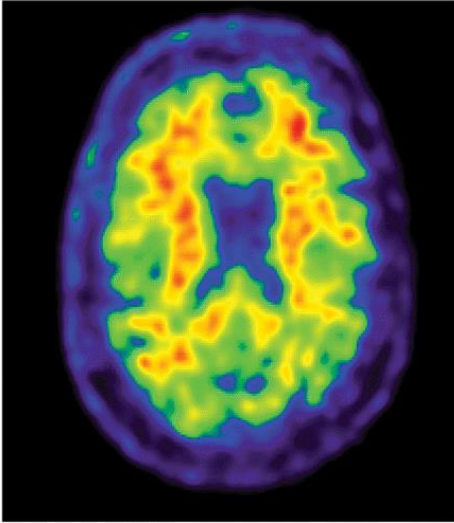
Methodological:

- **de Jong, ISBI 2026:** Mixed event types, e.g., Ordinal + Continuous + Binary
- *...more coming*

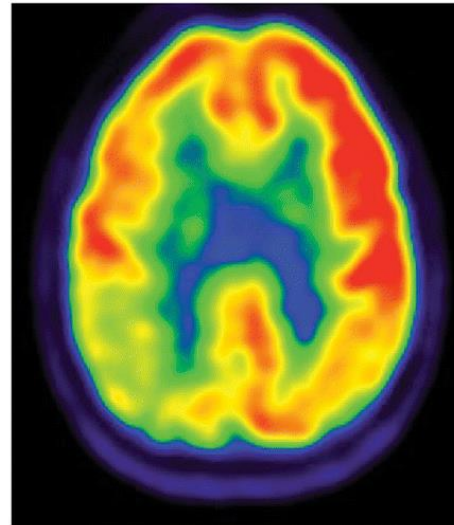
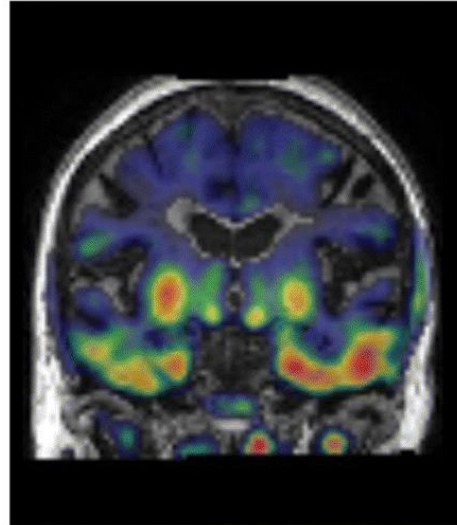
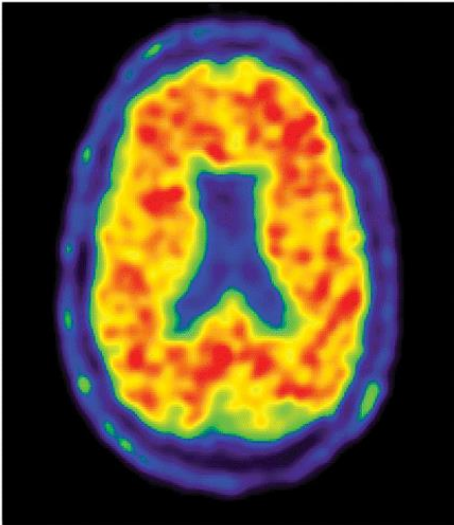


Clinical trial enrichment using SuStaln

NORMAL



ABNORMAL



AMYLOID PET

TAU PET

FDG PET

What have
clinical
trials
done?

Background

Clinical trial enrichment 101

Assume that a drug works, then find the:

Right people (treatment **responders**)

at the

Right time (placebo **decliners**)

Background

Clinical trial enrichment 101

Assume that a drug works, then find the:

Right people (treatment **responders**)
at the

Right time (placebo **decliners**)

Outcomes:

Smaller trial population

=> less exposure to side-effects

=> save time and ¥ £ \$ €

Targeted/personalised/precision medicine...can limit prescriptions

Background

Clinical trial enrichment 101

Ultimately, enrichment aims to increase statistical power by:

1. Increasing sensitivity/specificity
e.g., patients who definitely have the disease
2. Finding high-risk patients
e.g., patients having more severe disease
3. Finding patients likely to respond
e.g., patients with the right biology

Background

Clinical trial enrichment 101

Ultimately, enrichment aims to increase statistical power by:

1. Increasing sensitivity/specificity

e.g., amyloid-positive, no vascular pathology

2. Finding high-risk patients

e.g., MCI converters

3. Finding patients likely to respond

e.g., APOe4-negative???

Background

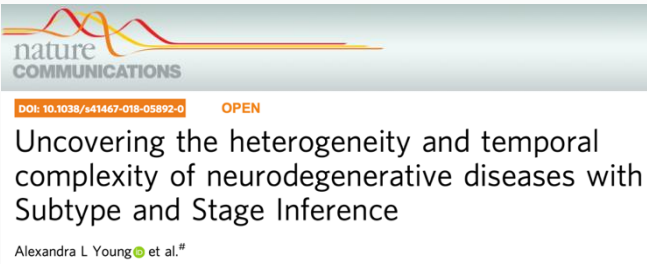
Clinical trial enrichment 101

Ultimately, enrichment aims to increase statistical power by:

1. Increasing sensitivity/specificity == **Practical** enrichment
e.g., amyloid-positive, no vascular pathology
2. Finding high-risk patients == **Prognostic** enrichment
e.g., MCI converters
3. Finding patients likely to respond == **Predictive** enrichment
e.g., APOe4-negative???

Background

SuStaln enrichment 101

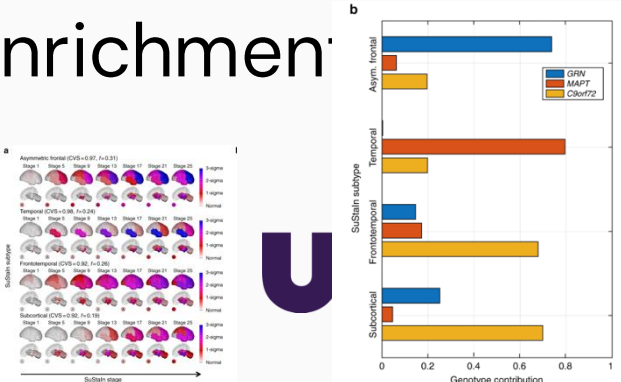
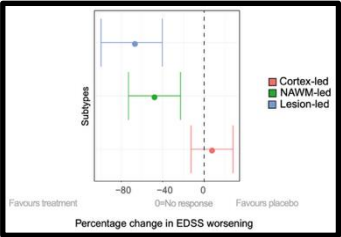
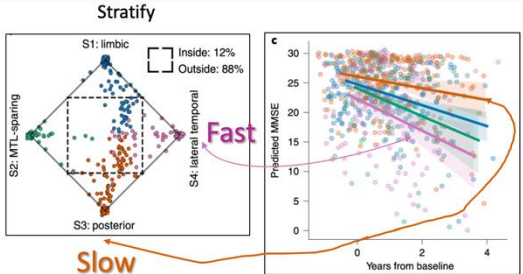


Ultimately, enrichment aims to increase statistical power by:

✓ Increasing sensitivity/specificity == Practical enrichment

✓ Finding high-risk patients == Prognostic enrichment

? Finding patients likely to respond == Predictive enrichment



SuStain for Clinical Trials

1. TOMMORROW (pioglitazone): **via Vivli.org**
 - CN, N=3391
 - Endpoint: MCI Dx

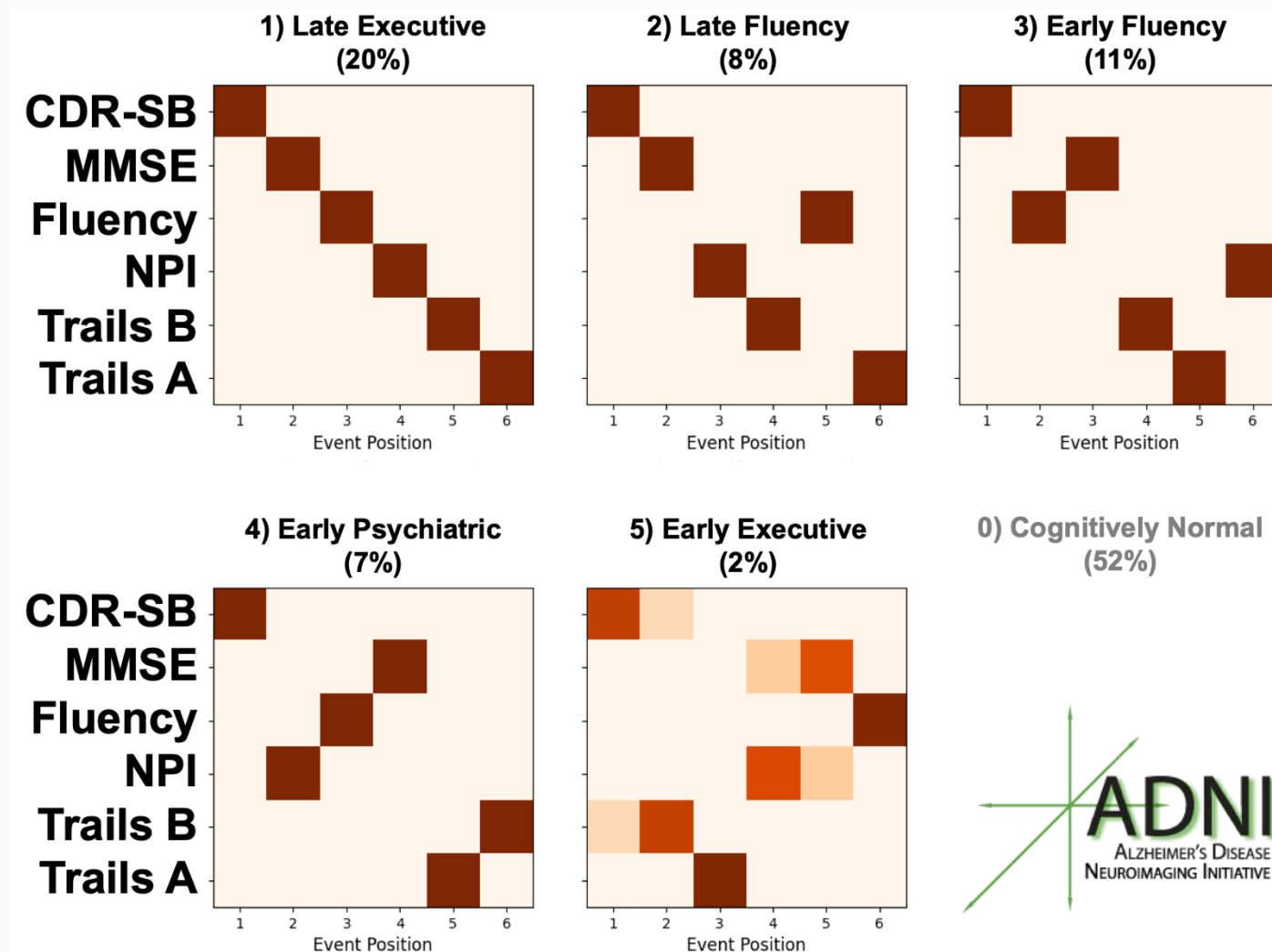
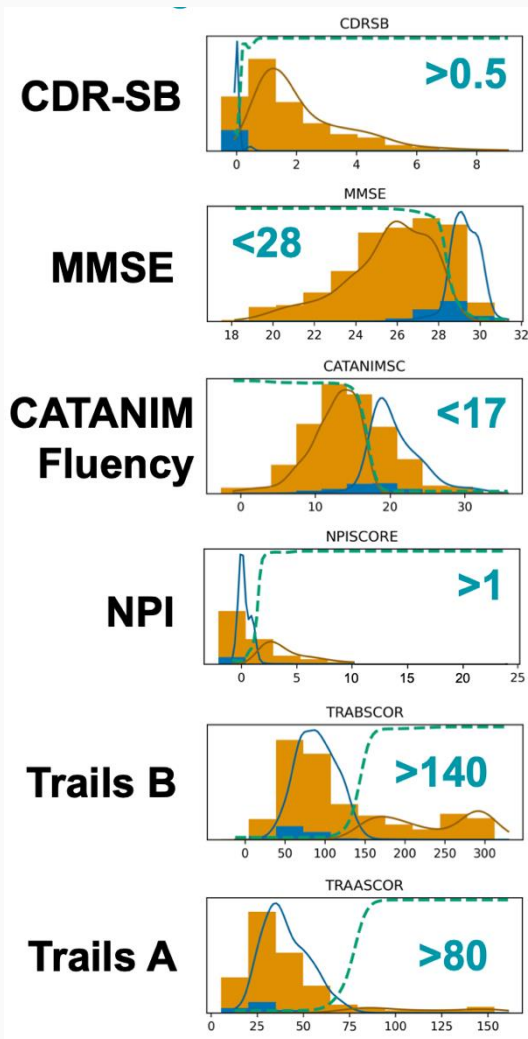
2. ENGAGE / EMERGE (aducanumab): **direct collab w/ Biogen**
 - MCI/AD: N=1563 / 1532
 - Endpoint: CDR

3. A4 (solanezumab): **open data**
 - CN: N=1179
 - Endpoint: PACC



SuStaln for Clinical Trials 1: TOMMORROW

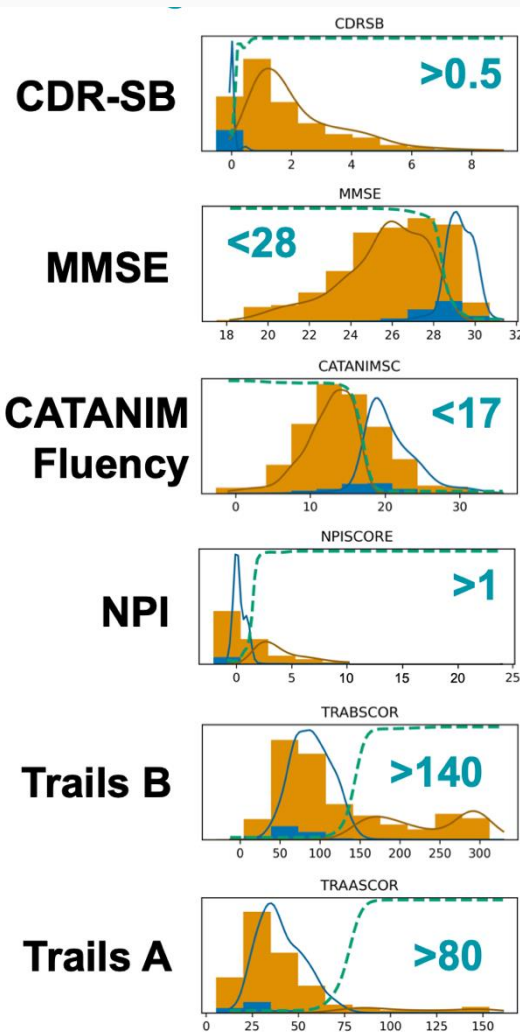
- SuStaln inputs: Cog test scores
- Trained model





SuStain for Clinical Trials 1: TOMMORROW

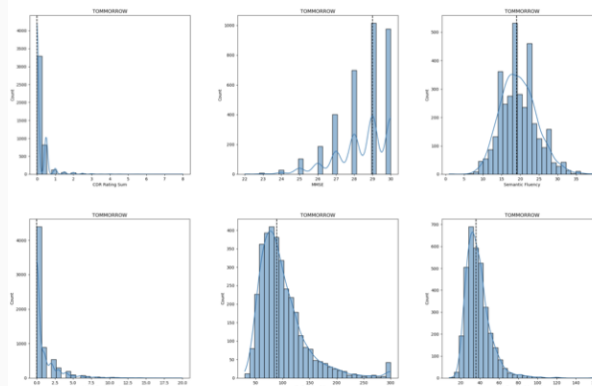
- TOMMORROW stratification: subtype-specific demographics & survival



Subtype vs Subtype (ANOVA, χ^2 ; $p < 0.01$)

$p < 0.01$	ST1	ST2	ST3	ST4	ST5
Age	74.6	74.8	73.8	74.2	76.4
Female	54%	56%	57%	45%	40%
Education	15.2	13.5	16.0	14.5	13.6

- 52% cognitively normal (Stage Zero)
- Subtle abnormality in cognitive domains



1) Late Executive (20%)

2) Late Fluency (8%)

3) Early Fluency (11%)

4) Early Psychiatric (7%)

5) Early Executive (2%)

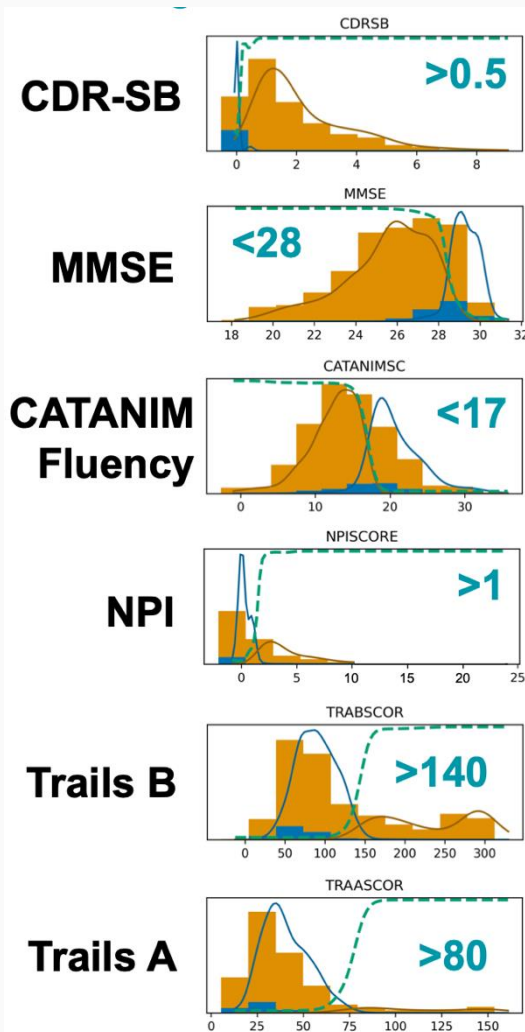
0) Stage Zero (52%)

288	282	87	22	6
47	172	55	4	1
226	20	88	27	1
151	92		7	
23	16	7	9	
1	2	3	4	5
Stage				

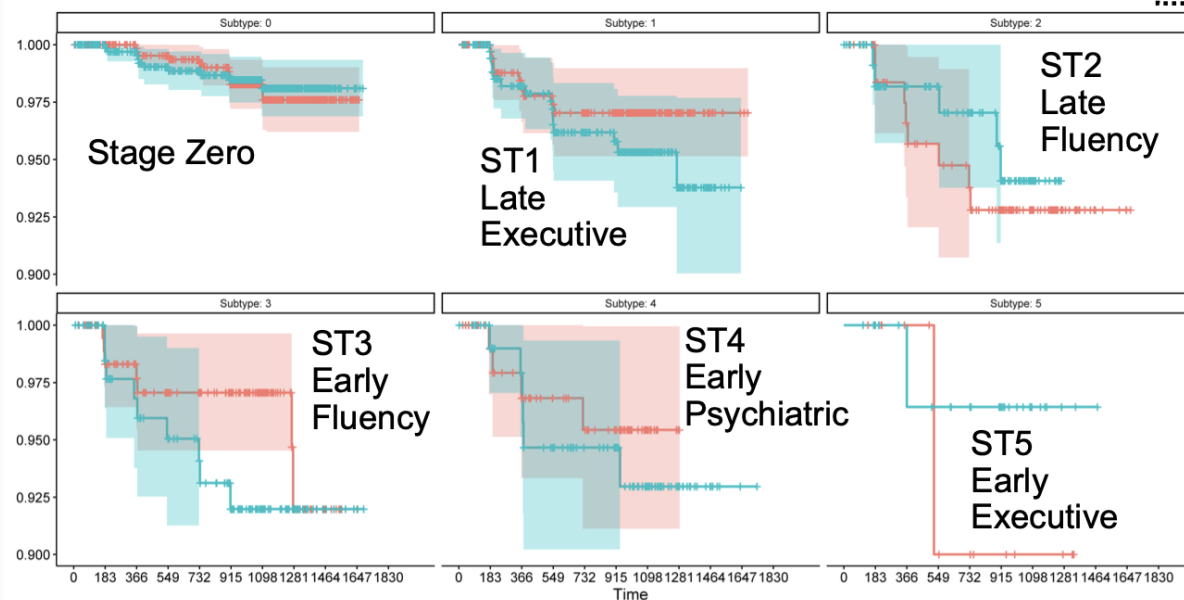
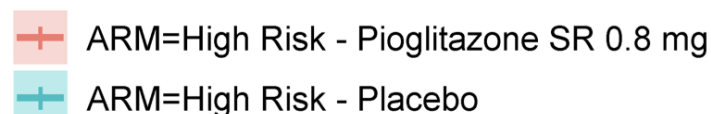


SuStain for Clinical Trials 1: TOMMORROW

- TOMMORROW stratification: subtype-specific demographics & survival

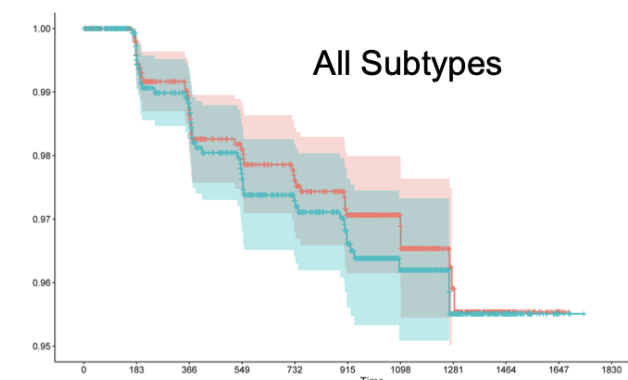


Survival: High Risk



Subtype vs Subtype (ANOVA, χ^2 ; $p < 0.01$)

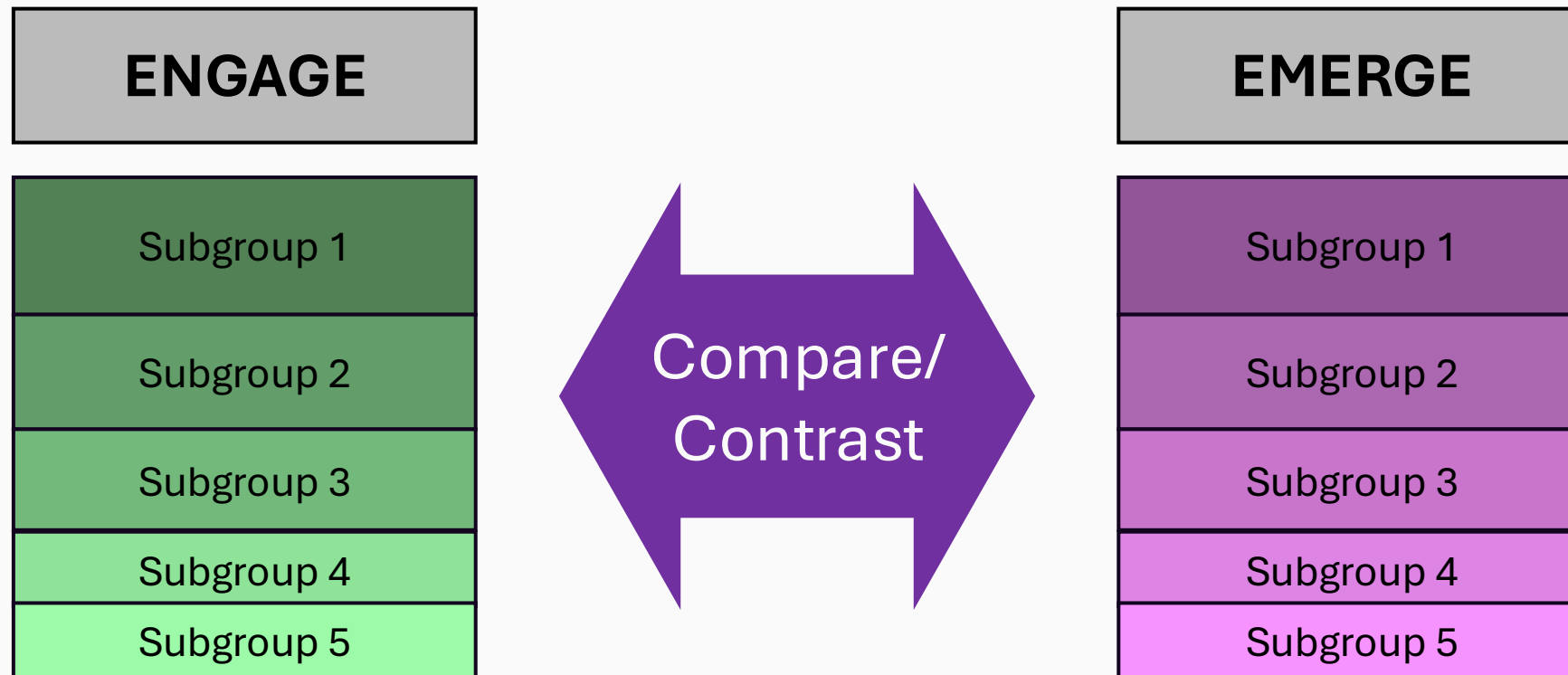
$p < 0.01$	ST1	ST2	ST3	ST4	ST5
Age	74.6	74.8	73.8	74.2	76.4
Female	54%	56%	57%	45%	40%
Education	15.2	13.5	16.0	14.5	13.6



SuStaln for Clinical Trials 2: ENGAGE / EMERGE



- SuStaln inputs: regional brain volumes (FreeSurfer 7)
- Only baseline data available



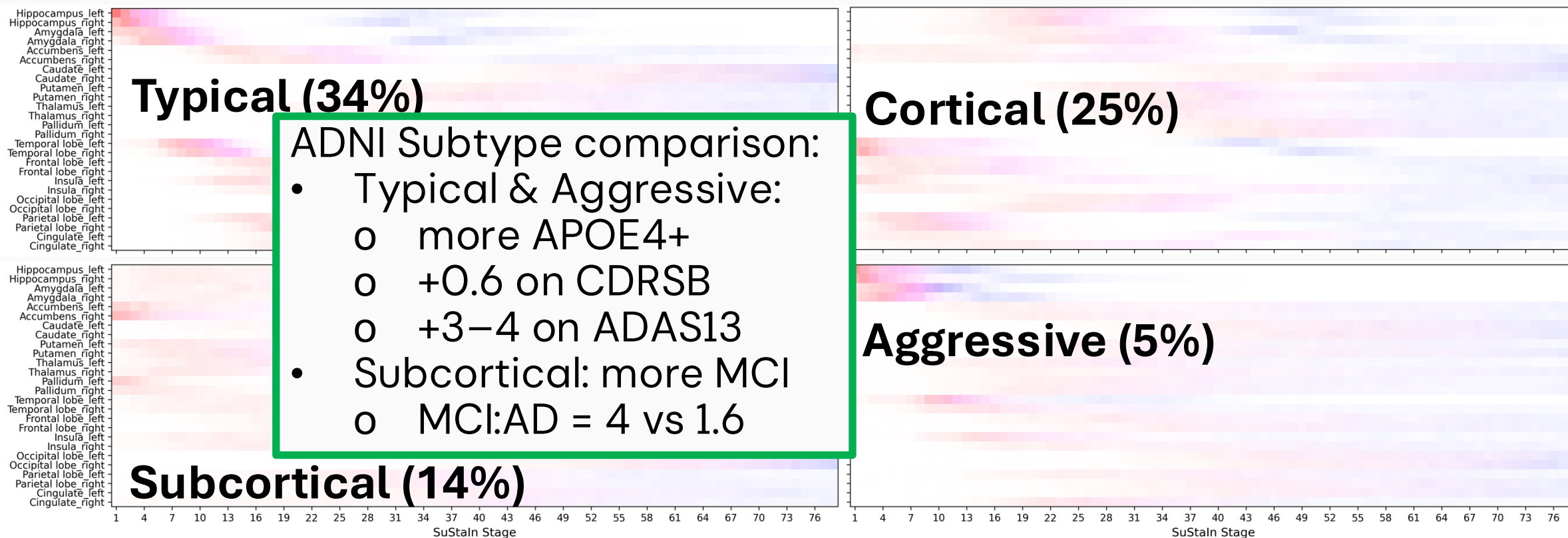
SuStain for Clinical Trials 2: ENGAGE / EMERGE



- Trained model: 4 atrophy subtypes



Stage Zero (Minimal Atrophy; 21%)





SuStaln for Clinical Trials 2: ENGAGE / EMERGE

SuStaln stratification: ENGAGE vs EMERGE*

- Between trials: within subgroup **proportion imbalance**

ENGAGE had fewer Stage Zero, more Typical.

Subgroup	ENGAGE	EMERGE	$\chi^2 = 13.7$ $\text{dof} = 4$ $p = 0.008$
Stage Zero	7.3%	10.7%	
Typical	47.3%	43.5%	
Cortical	32.7%	31.7%	
Subcortical	6.7%	7.2%	
Aggressive	6.1%	6.9%	



SuStaln for Clinical Trials 2: ENGAGE / EMERGE

SuStaln stratification: ENGAGE vs EMERGE*

- Between trials: within subgroup **clinical imbalance**

	Typical			Cortical			Subcortical		
	ENGAGE	EMERGE*	<i>p</i>	ENGAGE	EMERGE*	<i>p</i>	ENGAGE	EMERGE*	<i>p</i>
N	738 (47%)	671 (44%)		510 (33%)	488 (32%)		104 (7%)	111 (7%)	
Age	70.3	71.5	0.001						
CDRSB	2.5 (1.0)	2.6 (1.0)	0.07						
ADL-MCI	43	42	0.05						
ADAS13				22.8 (6.7)	22.2 (6.9)	0.09			
Females							43%	30%	0.05

SuStaln for Clinical Trials 2: ENGAGE / EMERGE



SuStaln stratification: ENGAGE vs EMERGE*

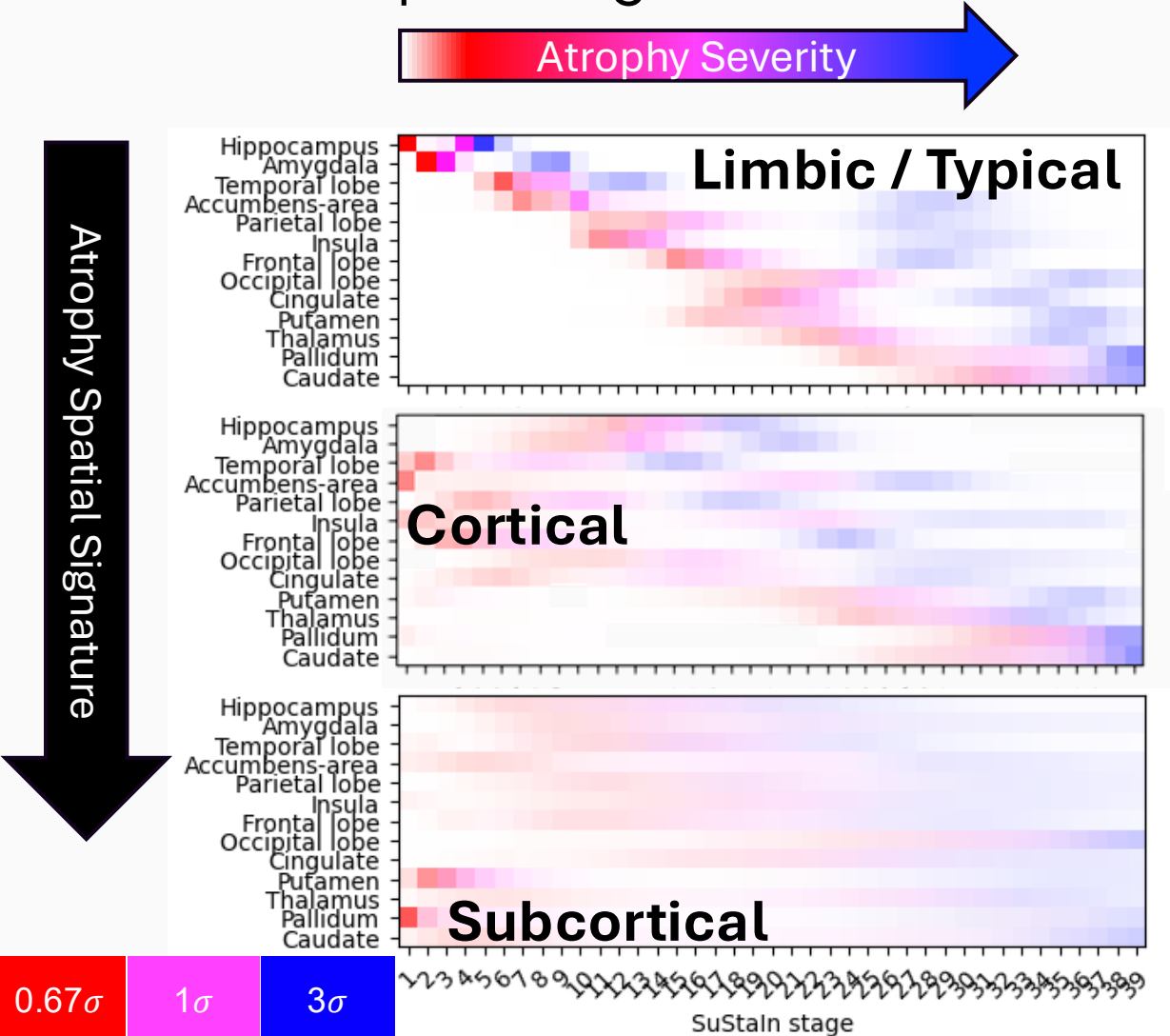
- Between trials: within subgroup imbalance

Take Home:

- SuStaln suggests ENGAGE participants may have higher treatment resilience:
 - younger (possibly earlier onset)
 - more females
 - more advanced atrophy stages (fewer Stage 0, more Typical subtype)

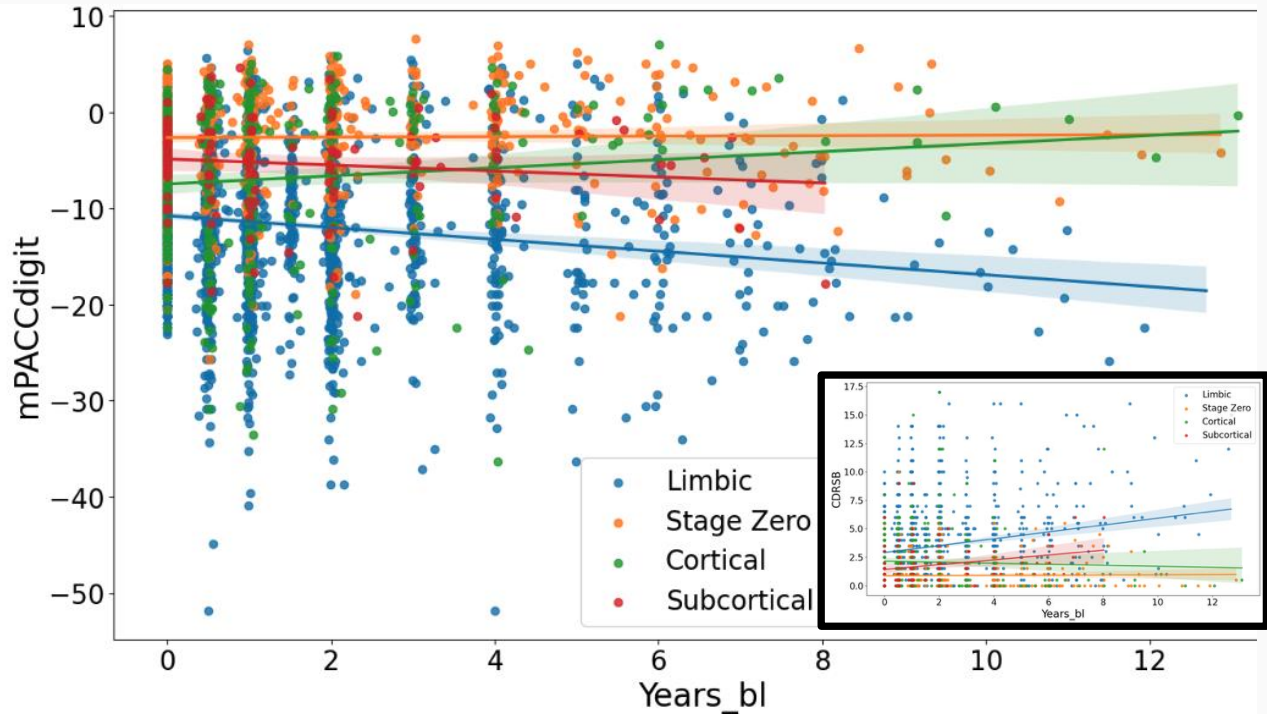
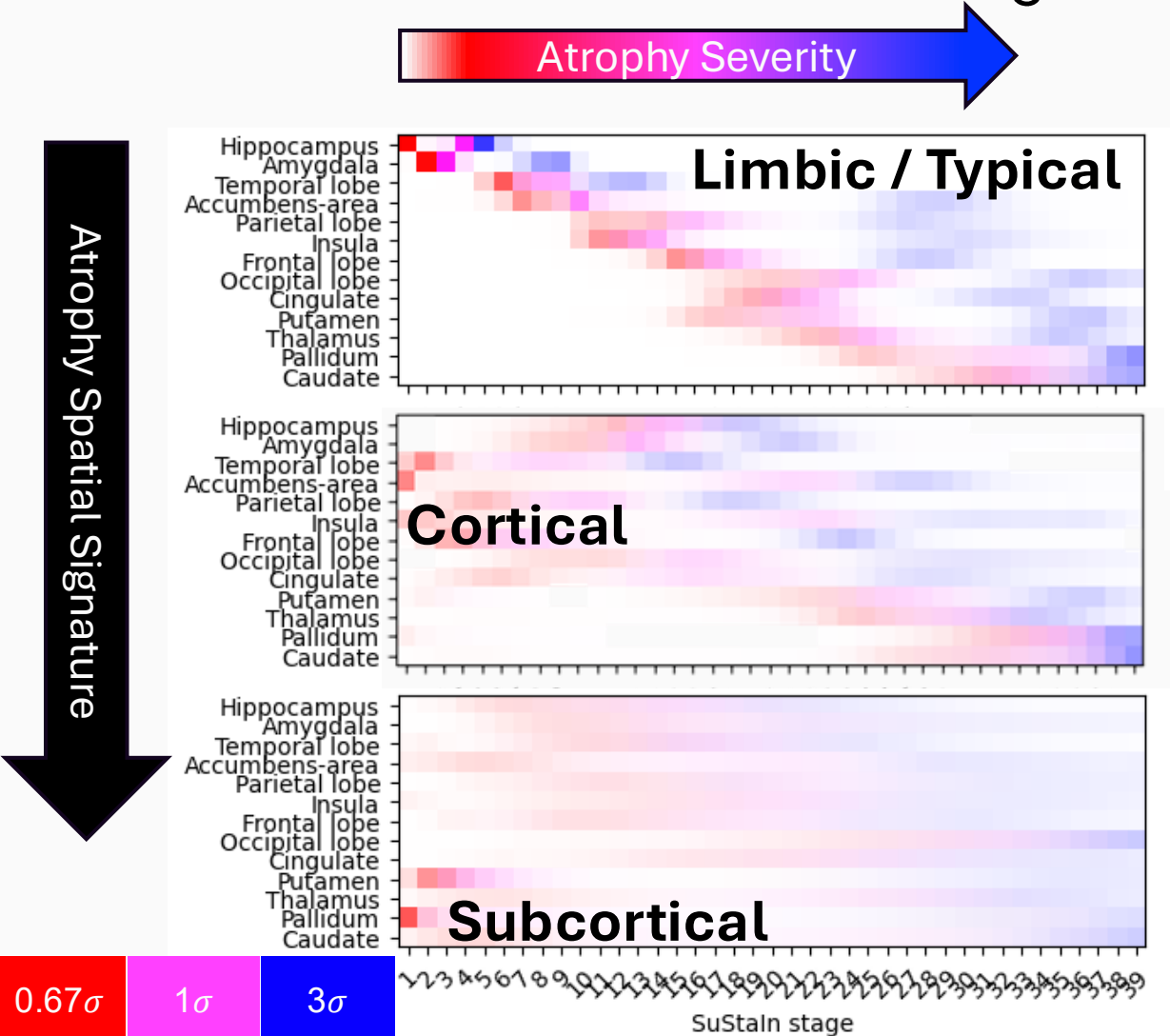
SuStaln for Clinical Trials 3: A4

- SuStaln inputs: regional brain volumes (FreeSurfer 7)



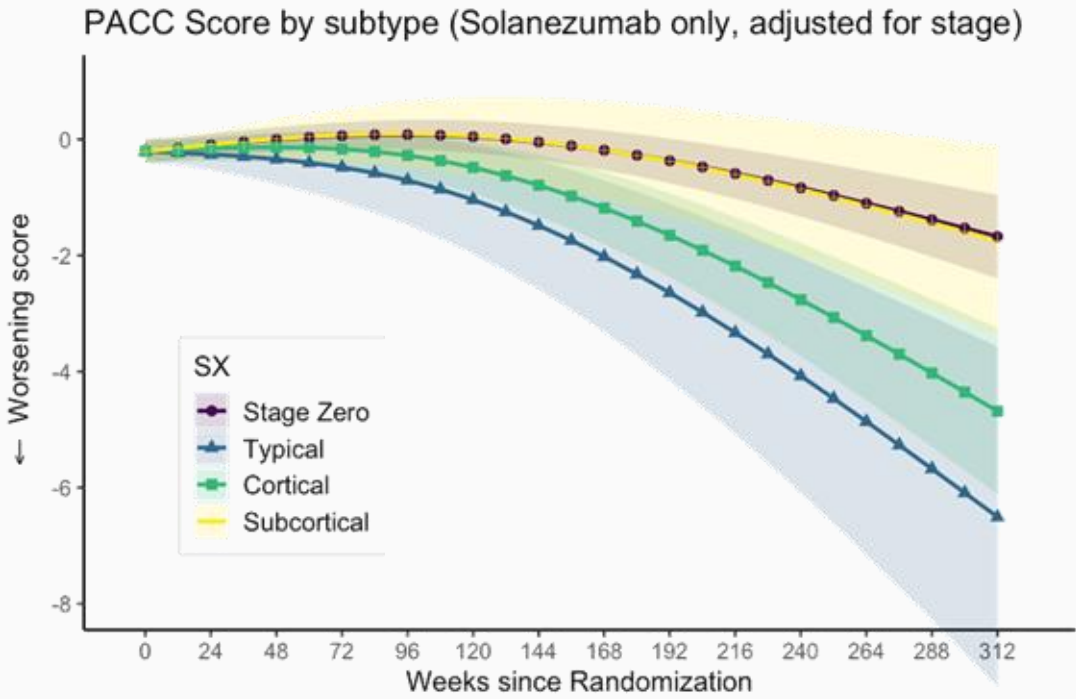
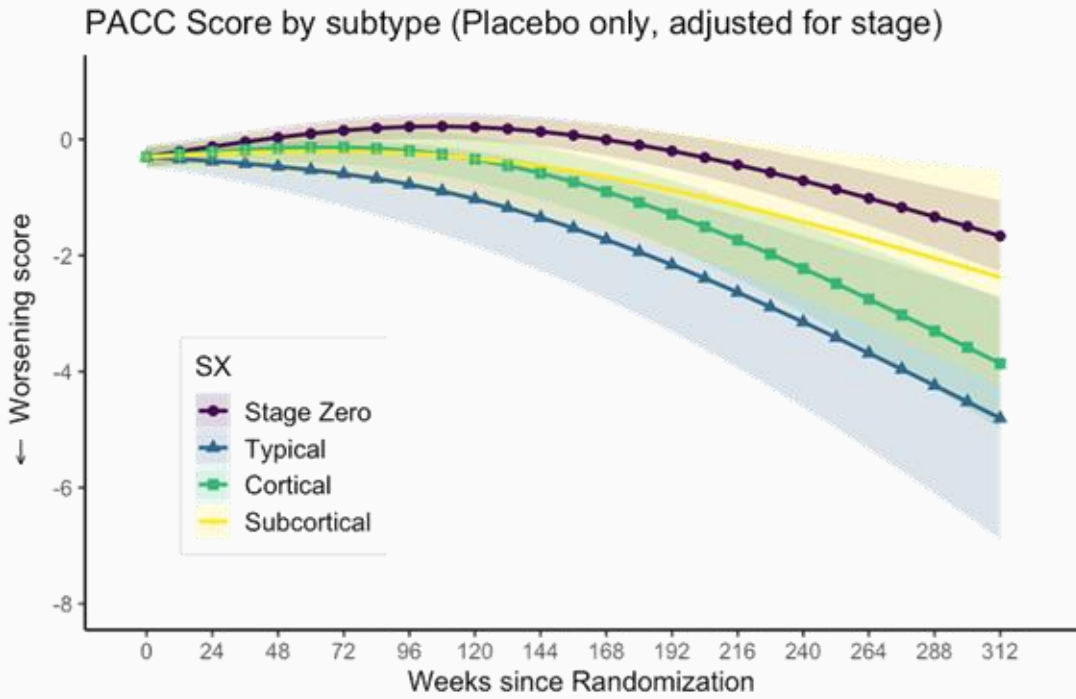
SuStain for Clinical Trials 3: A4

- SuStain stratification: subtle cognitive differences



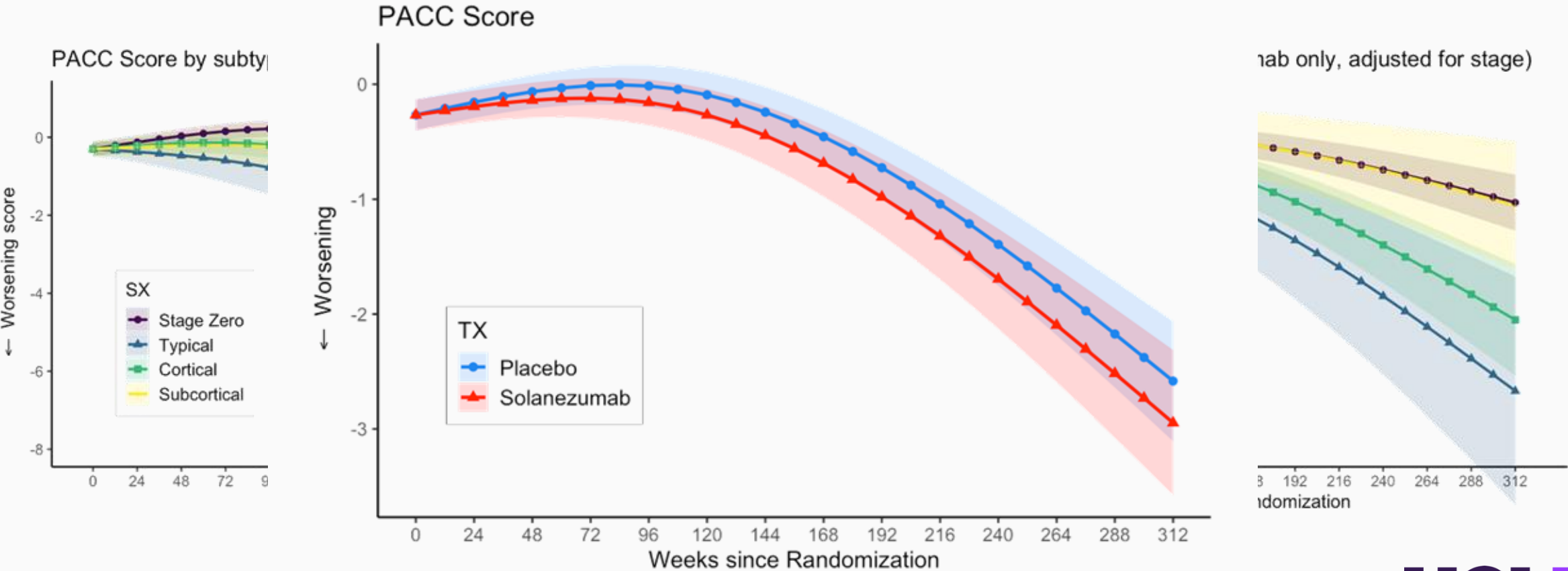
SuStaln for Clinical Trials 3: A4

- SuStaln stratification of A4 trial



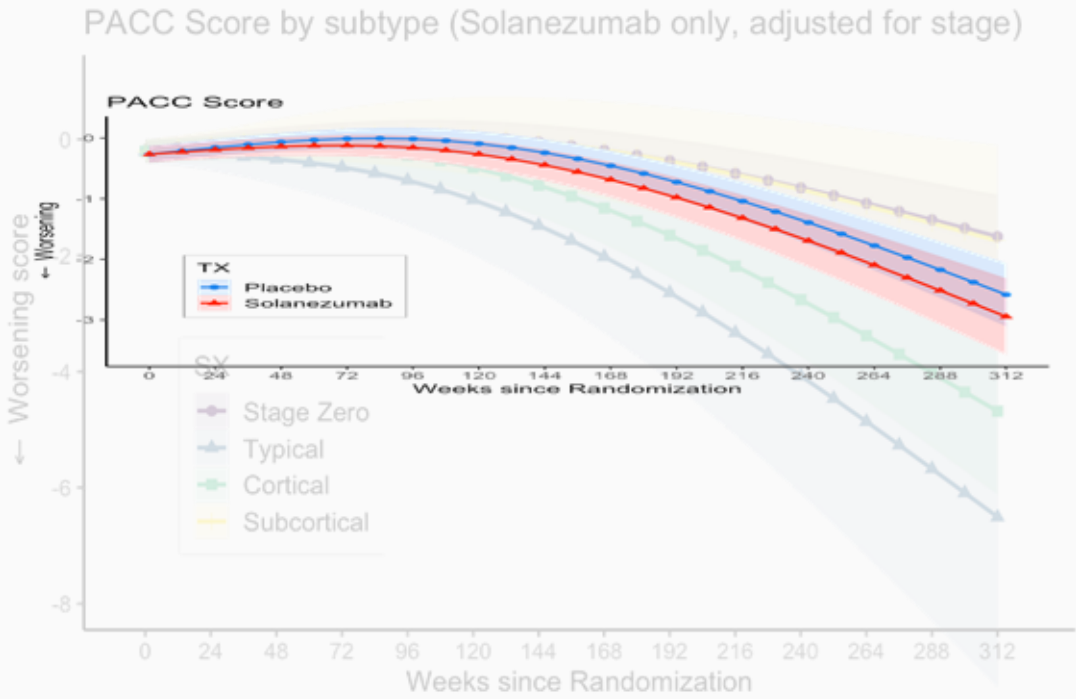
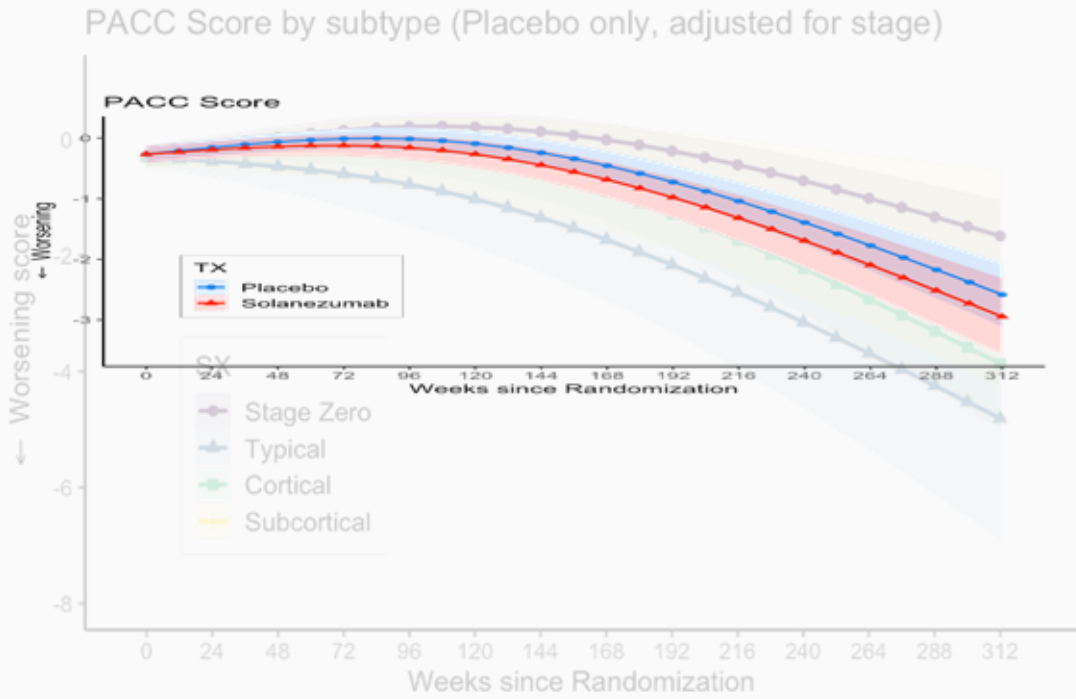
SuStaln for Clinical Trials 3: A4

- SuStaln stratification of A4 trial



SuStaln for Clinical Trials 3: A4

- SuStaln stratification of A4 trial



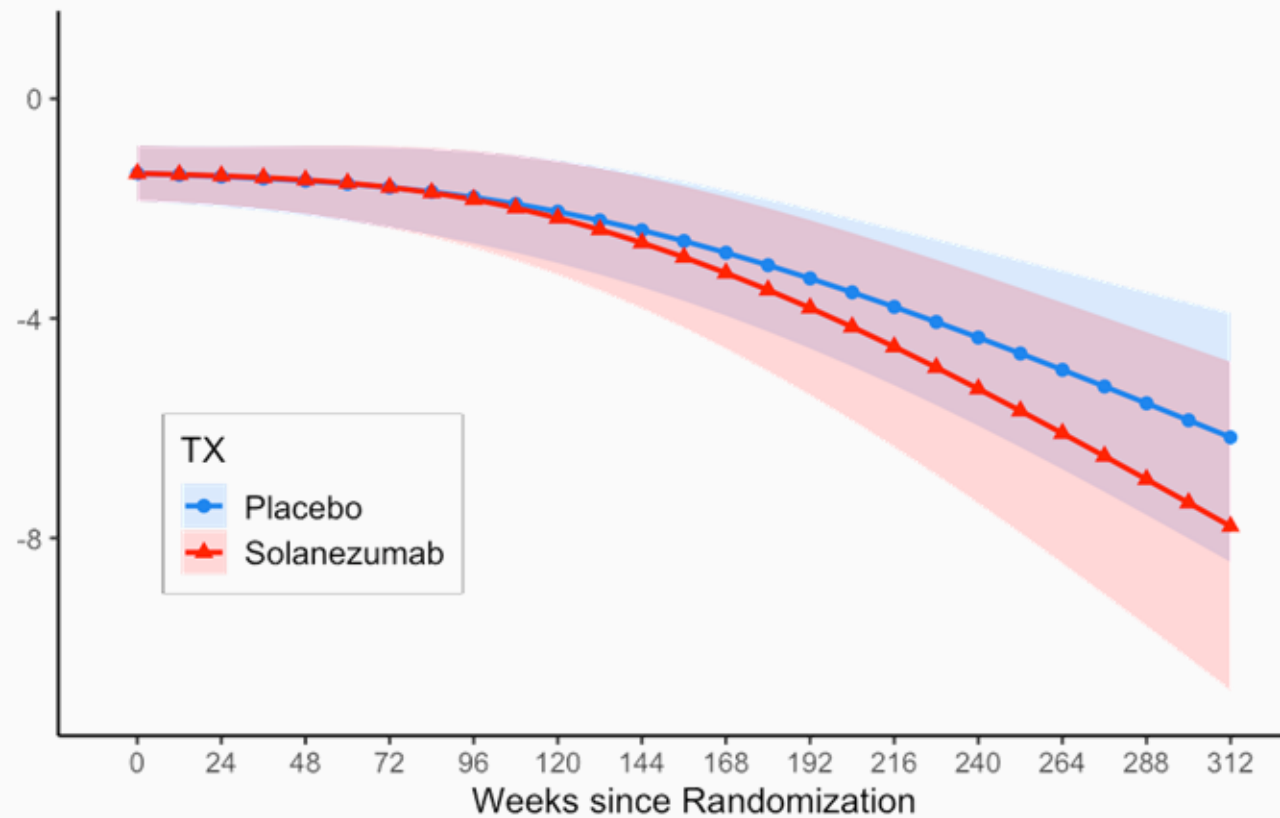
SuStaln for Clinical Trials 3: A4

- SuStaln stratification of A4 trial



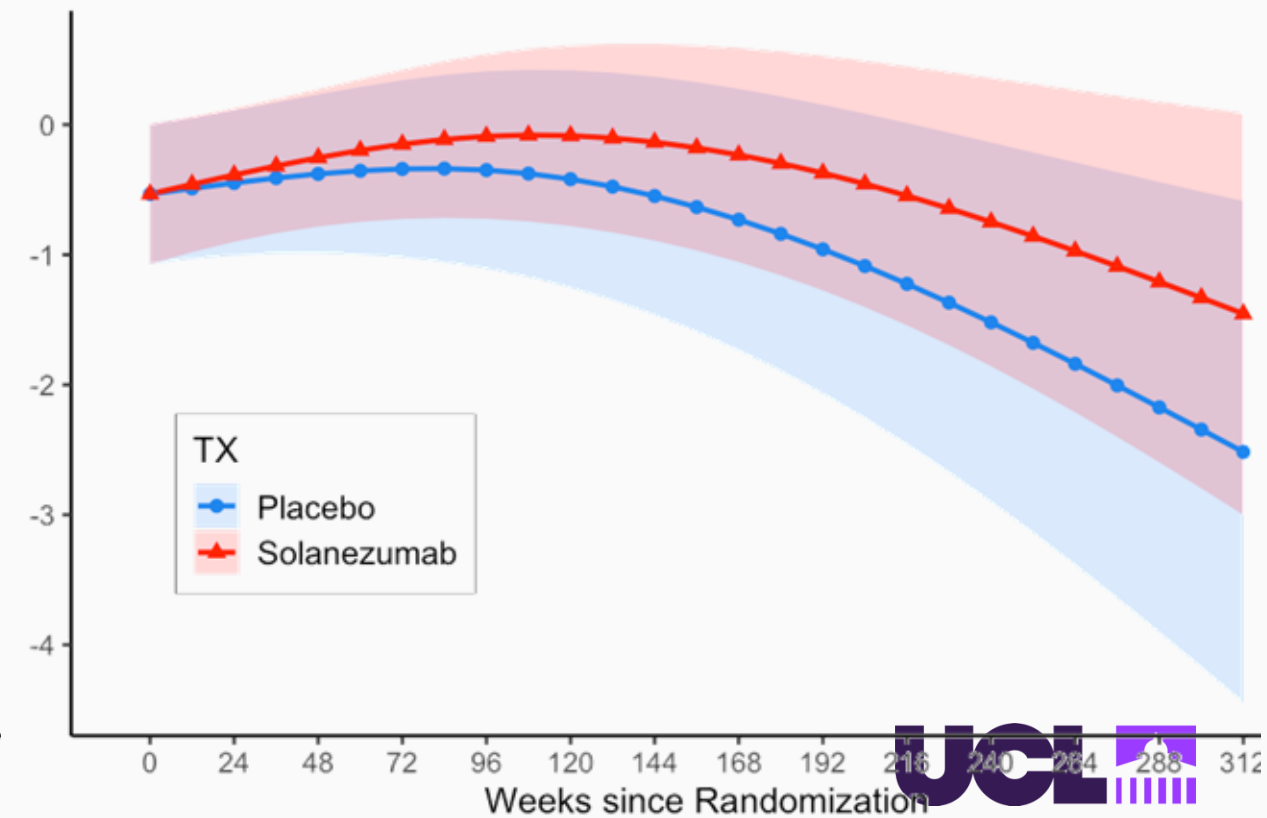
N=105 (9%)

PACC Score: Typical subtype



N=89 (7%)

PACC Score: Subcortical subtype



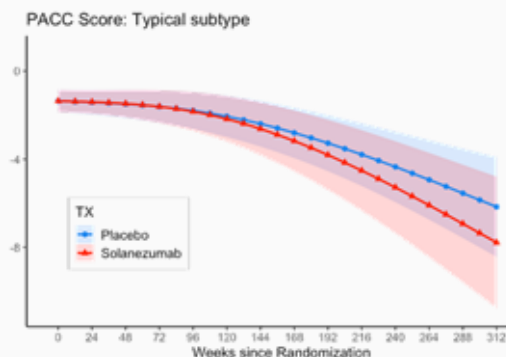
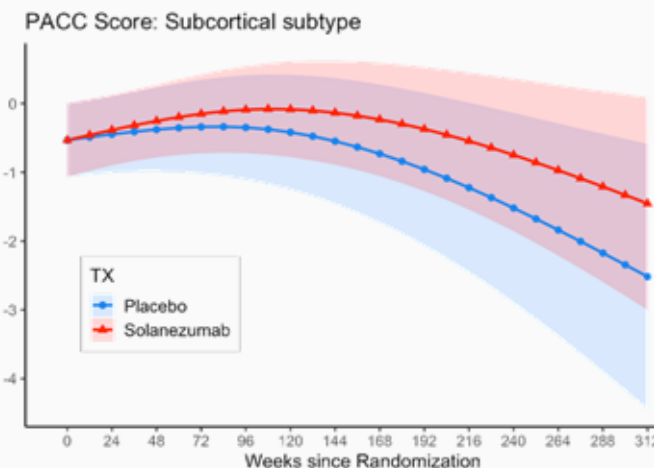
SuStaln for Clinical Trials 3: A4

- SuStaln stratification of A4 trial



Take home:

- A4 trial *post hoc* subgroup analysis
 - Subcortical (7%) apparently responsive to Sola
 - Predictive enrichment
 - Typical/Limbic (9%) (and Cortical, 25%) decline fastest
 - Prognostic enrichment



ADDI Data Challenge



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Alzheimer's Trials Data Discovery Challenge

Powered by the AD Data Initiative and Vivli, and supported by Alzheimer's Research UK

The Alzheimer's Trials Data Discovery Challenge will award \$75,000 in prizes to teams that can unlock discoveries from the new Integrated Alzheimer's Disease Clinical Trial Dataset – a fully harmonized dataset featuring decades of placebo-arm data from 11 trials, ready for analysis on Vivli's secure, cloud-based research environments.

This challenge opened July 10, 2026, and is currently open.

[SUBMIT YOUR LETTER OF INTENT](#) 



Future Work: Next-Gen SuStaln

- Variational EBM => voxel-level (**Wijeratne, et al.**)
- Temporal EBM (**Wijeratne, et al.**)
- T-SuStaln (**Aksman/Wijeratne, et al.**)
- Co-pathology (**Young/Binding, et al.**)
- *Deep Learning variants* (**Castro Leal, et al.; Binding, et al.**)
 - e.g., hierarchical (~ mixed model style)
for personalised subtyping and staging

pySuStaln: github.com/ucl-pond/pySuStaln



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master pySuStaln / notebooks / SuStaln tutorial using simulated data.ipynb Go to file ...

ayoung11 Added workshop notebook and data and updated existing tutorial notebook Latest commit 13e924a on 22 Oct History

1 contributor

Executable File 1.14 MB Download

SuStaln tutorial using simulated data

Written by Alex Young in April 2020, last updated in October 2022. Please email alexandra.young@kcl.ac.uk with any questions.

This tutorial demonstrates how to run Subtype and Stage Inference (SuStaln) using simulated data. SuStaln is an unsupervised learning algorithm that identifies subgroups of individuals with distinct biomarker progression patterns. See [Young et al. Nature Communications 2018](#) for more details.

SuStaln is a generalisable algorithm in which you can choose how to model the progression of biomarkers within a subtype. In this tutorial I use the linear z-score model I used in [Young et al. 2018](#), but it is possible to use other models of biomarker evolution, such as the event-based model.

For a demonstration of the 'event-based'/mixture modelling version of SuStaln (i.e. MixtureSustaln), see `simrun.py`, available in the `/sim` subdirectory of the `pySuStaln` package.

YouTube

Search

Subtype and Stage Inference Tutorial

With Alex Young, Peter Wijeratne, Neil Oxtoby, Leon Aksman,
Mar Estarellas Garcia and Jake Vogel

<https://github.com/ucl-pond/pySuStaln>

0:00 / 2:10

Aksman and Wijeratne *et al.*, SoftwareX 2021



POND 2026 / WORKSHOP

Progression Of Neurodegenerative Disease

DATE

Nov 12th–13th, 2026

VENUE

Inria Center
at University Côte d'Azur
Sophia Antipolis, France



43.6937, 7.27

POND 2026 is the latest scientific meeting in the series of “POND modelling” meetings.

ORGANISING COMMITTEE

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Acknowledgements



ucl-pond.github.io

- UCL POND research group
- SuStaln inventors: Alexandra Young, Danny Alexander
- SuStaln developers: Alexandra Young, Leon Aksman, Peter Wijeratne, ...
- For more info:
 - <https://github.com/ucl-pond/pySuStaln>
 - <https://pondmodels.net>

Interested in Data-Driven Disease Progression Modelling?

Home

PONDModels.net is a home for data-driven disease progression modelling.

Upcoming meetings/events:

- POND 2026 — Mar/Apr (TBC) 2026 in Nice, France.

Previous meetings/events:

- [POND 2024](#) — Sep 2024 in London, UK.
- [POND 2022](#) — Jul 2022 in London, UK.
- [Compage 2020](#) — Sep 2020 at the ICM Centre for Neuroinformatics in Paris, France. (online due to CoViD-19).
Co-organised by the [ARAMIS Lab](#), Inria and Fraunhofer SCAI.
- POND 2018 — Feb 2018 at Campus Biotech in Geneva, Switzerland.
- POND 2016 — Feb 2016 at the Wellcome Collection in London, UK.

Resources:

- Where POND modelling began: [UCL POND](#), part of the [UCL Hawkes Institute](#) (formerly the [Centre for Medical Image Computing](#))
- A review article:
[Data-driven modelling of neurodegenerative disease progression: thinking outside the black box](#)
- Hands-on Guide (including software URLs) for people who would like to learn:
[Data-Driven Disease Progression Modeling](#), a chapter in "Machine Learning for Brain Disorders" assembled by Olivier Colliot.
- Tutorials and example code:
[disease-progression-modelling.github.io](#)
- [EuroPOND](#) — a Horizon 2020 consortium that organised POND workshops 2016–2020
- [E-DADS](#) — an EU JPND consortium that followed EuroPOND

<https://pondmodels.net>



pond.cs.ucl.ac.uk