UCL CENTRE FOR MEDICAL IMAGE COMPUTING
DEPARTMENT OF COMPUTER SCIENCE

# Data-Driven Disease Progression Modelling for Research (and Healthcare?)

**Neil Oxtoby**

**UKRI Future Leaders Fellow**
**POND group: Progression Of Neurodegenerative Disease**

UK Research and Innovation

pond
Progression Of Neurodegenerative Disease

cmic
Centre for Medical Image Computing

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# My quest for supermodels and drugs

Neil Oxtoby

# Today's menu

Alzheimer's Disease

*Heterogeneity*

**D**isease
**P**rogression
**M**odelling

*Pseudo-time*

DPM & Clinical Trials

*Enrichment*

# Alzheimer's Disease

- *Defined* by post mortem histopathology
- Clinical syndrome: memory ***etc.***
- *Looooong* pre-symptomatic period: decades of pathology
- Heterogeneity in syndrome, onset, progression, and pathology!

# Treatments for Alzheimer's?

- Amyloid cascade hypothesis (Hardy/Higgins 1992; Selkoe/Hardy 2016)

+ Plenty of supporting evidence
– Anti-amyloid therapies not proving efficacious in large clinical trials

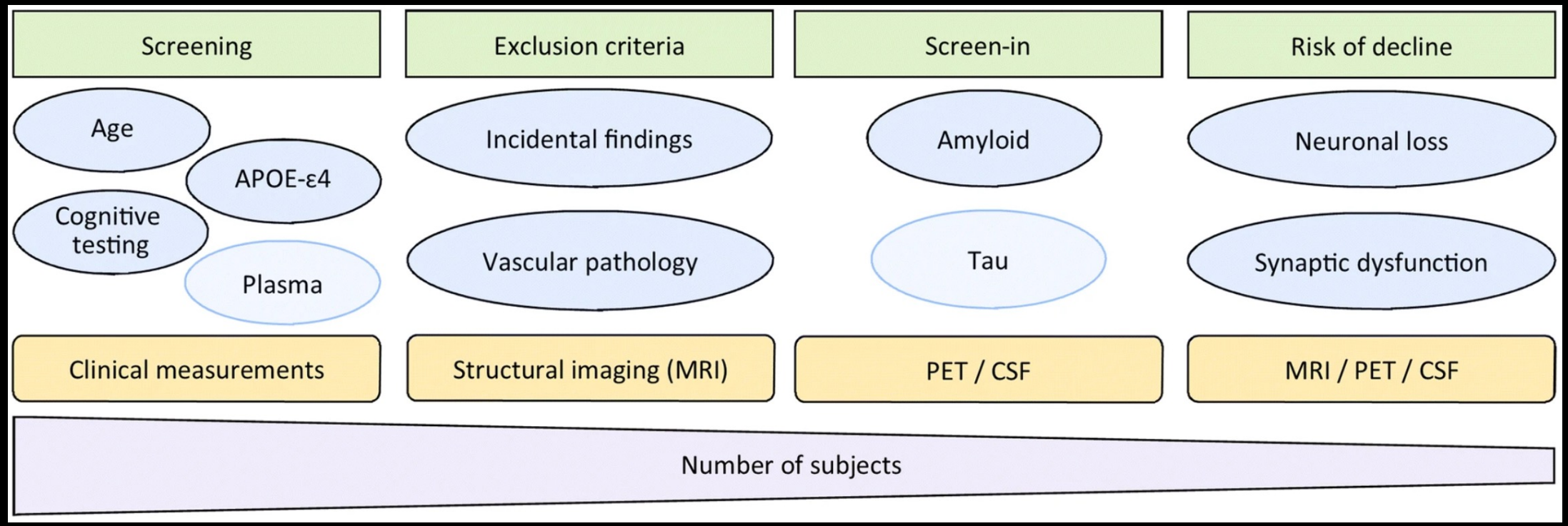
- Why are clinical trials "failing"? (hundreds since 2003)

➢ Wrong time? (too late: prevention vs cure)
➢ Wrong people? (subgroups)
➢ Insufficient duration?
➢ Insensitive end-points? (biology/biomarkers vs clinical benefit)
➢ Amyloid hypothesis "wrong"? (*wrong* biology / comorbidities / multitarget strategies)

(Salloway, CTAD 2019; Aisen, CTAD 2019; + many at CTAD 2021/22)

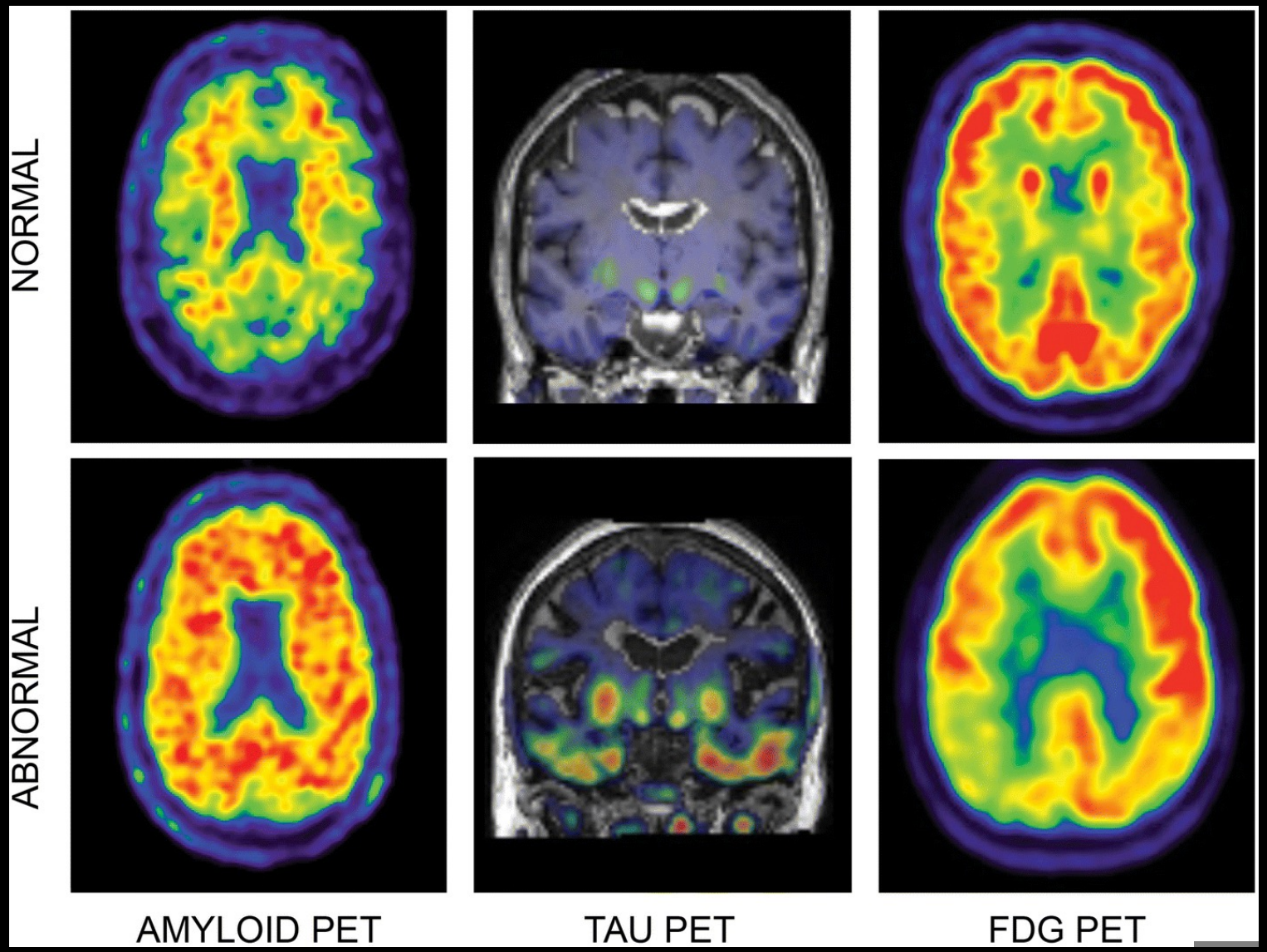
O'Connor et al. Alz Res Ther 2020
Oxtoby et al. medRxiv 2021; Frontiers 2022

# What have clinical trials done?




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

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

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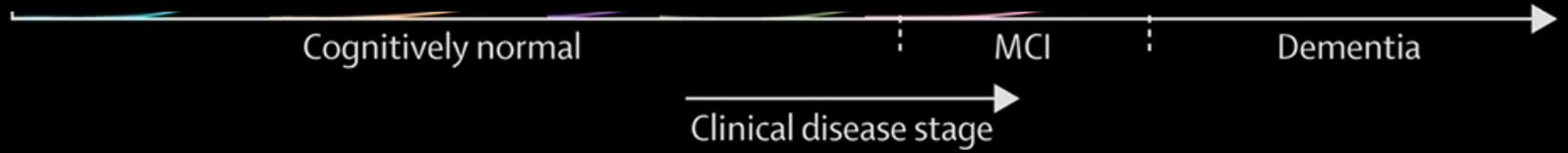
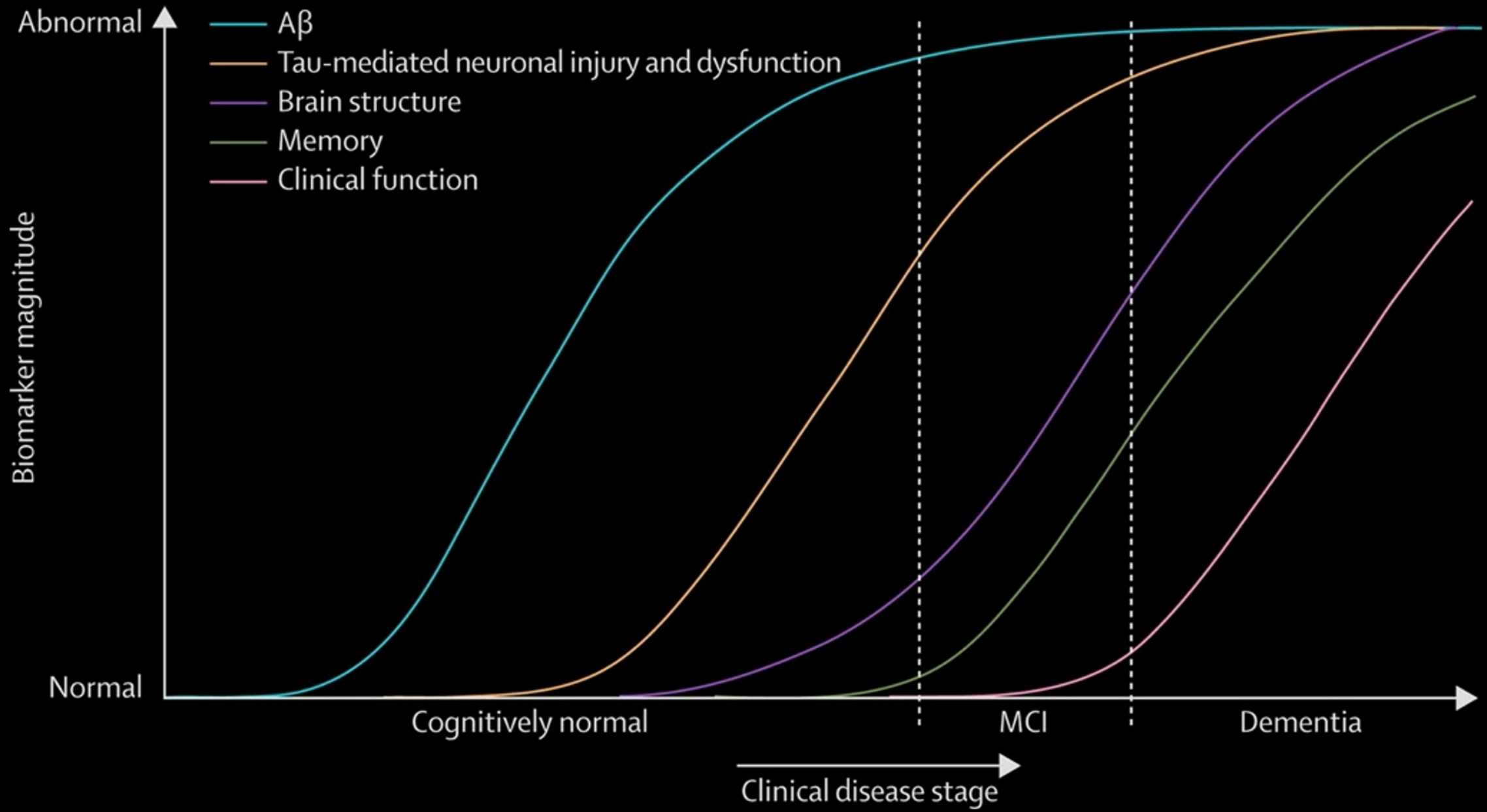
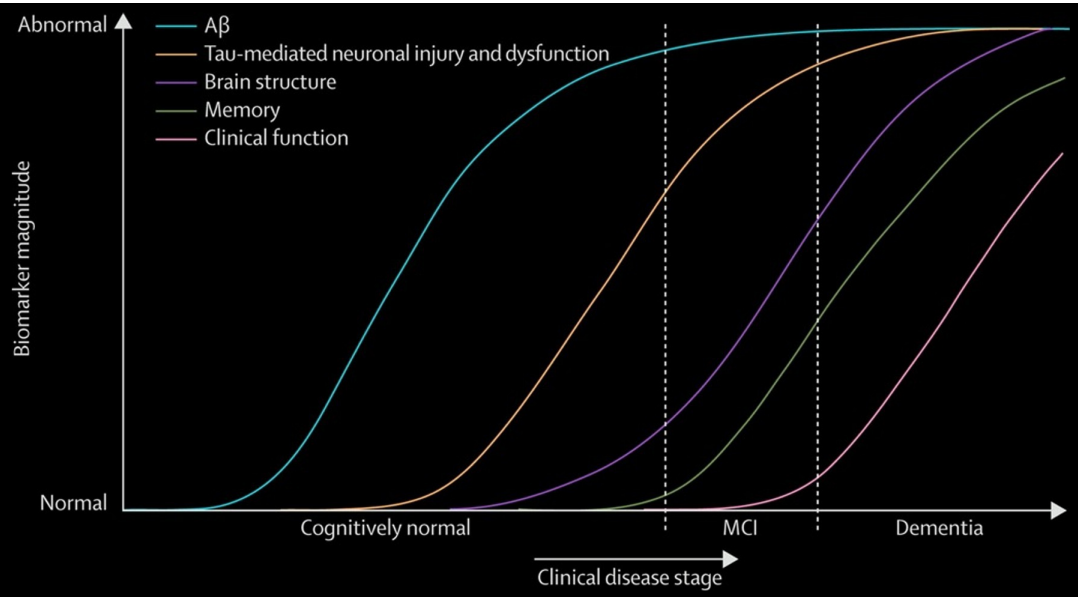

Cognitively normal
MCI
Dementia
Clinical disease stage


Abnormal
Aβ
Tau-mediated neuronal injury and dysfunction
Brain structure
Memory
Clinical function
Biomarker magnitude
Normal
Cognitively normal
MCI
Dementia
Clinical disease stage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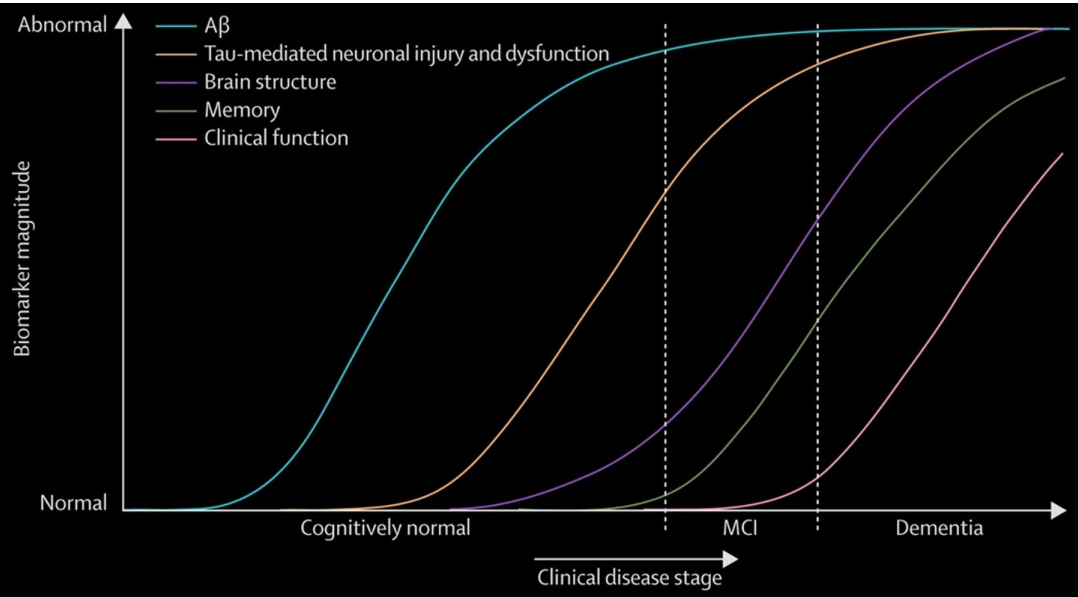
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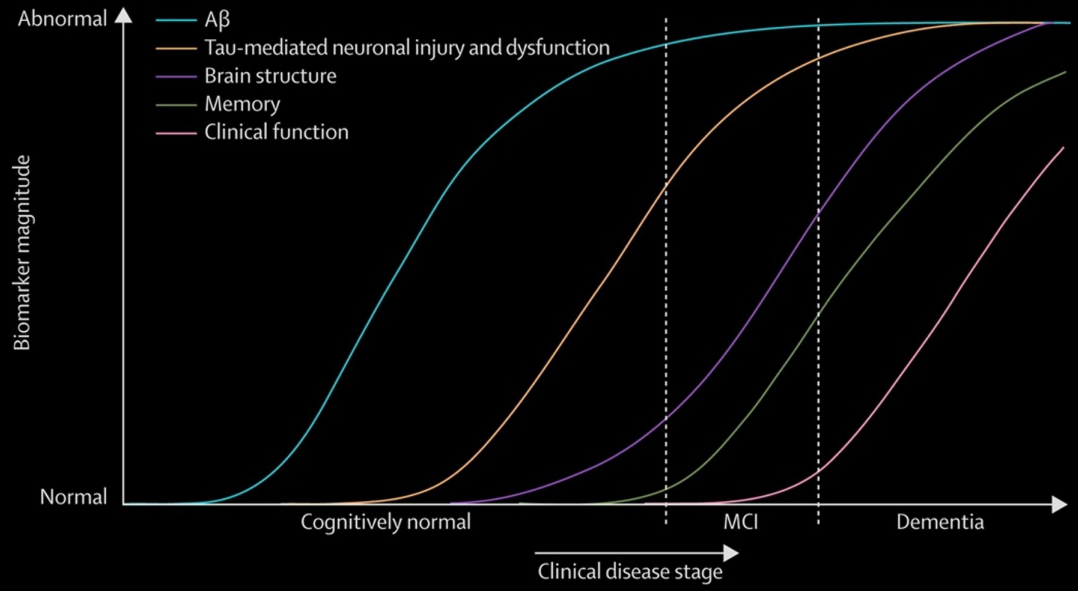
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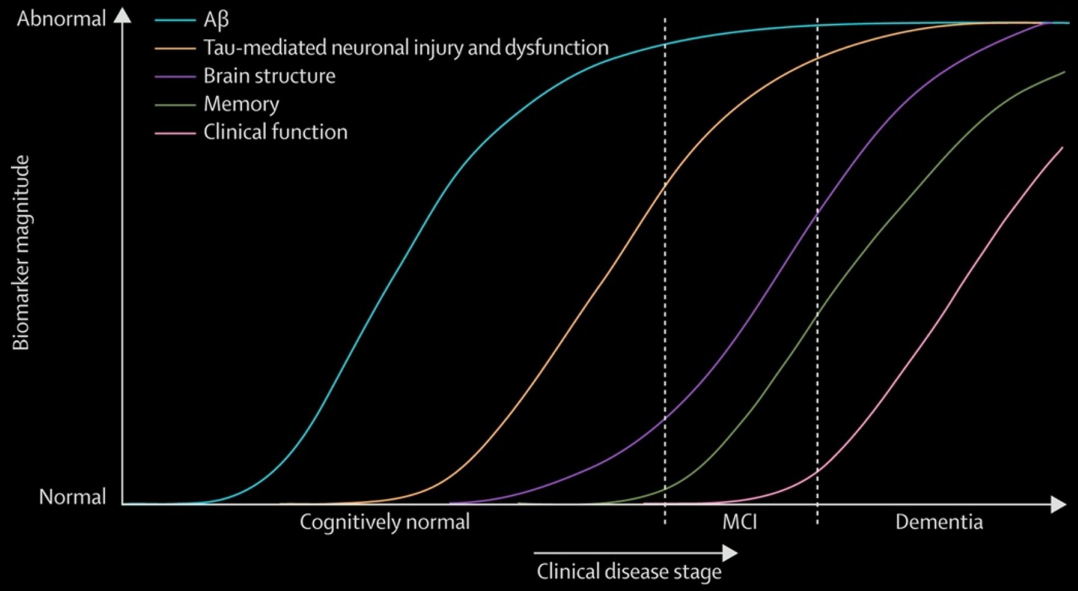
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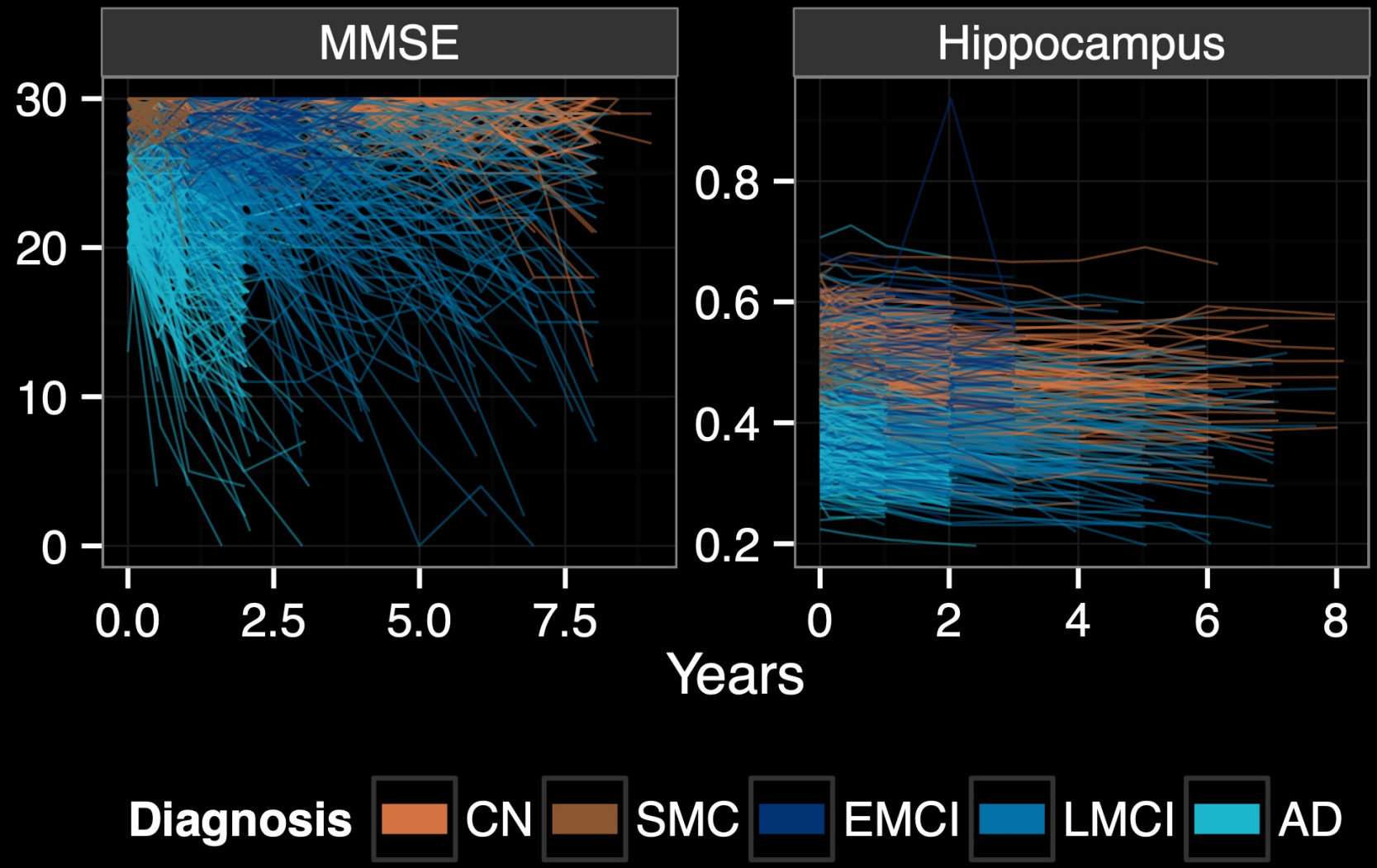
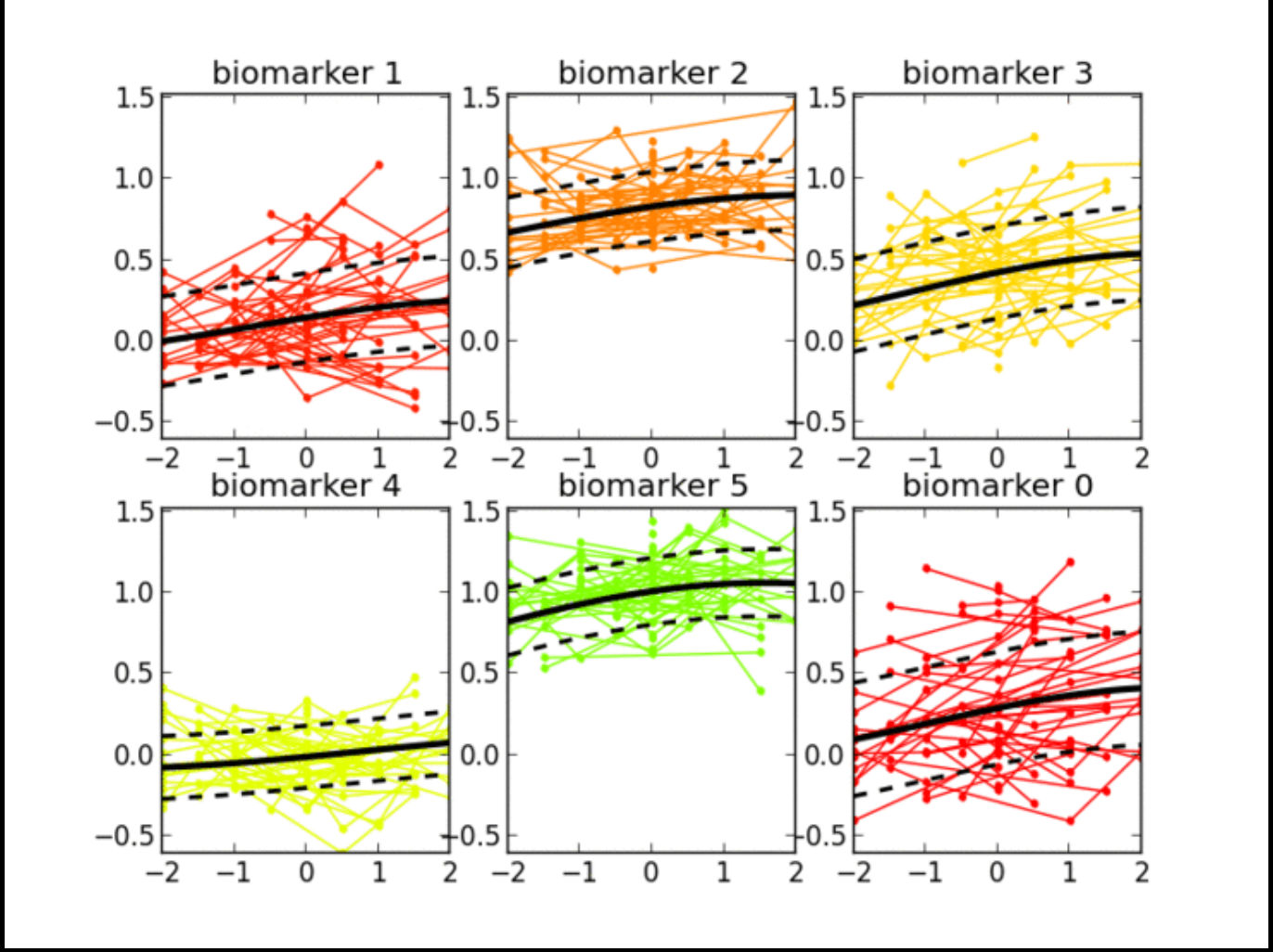
# *Sporadic* AD, natural history: no time zero!




Credit:
Mike Donohue, USC

Alzheimer's Disease Neuroimaging Initiative (adni-info.org)

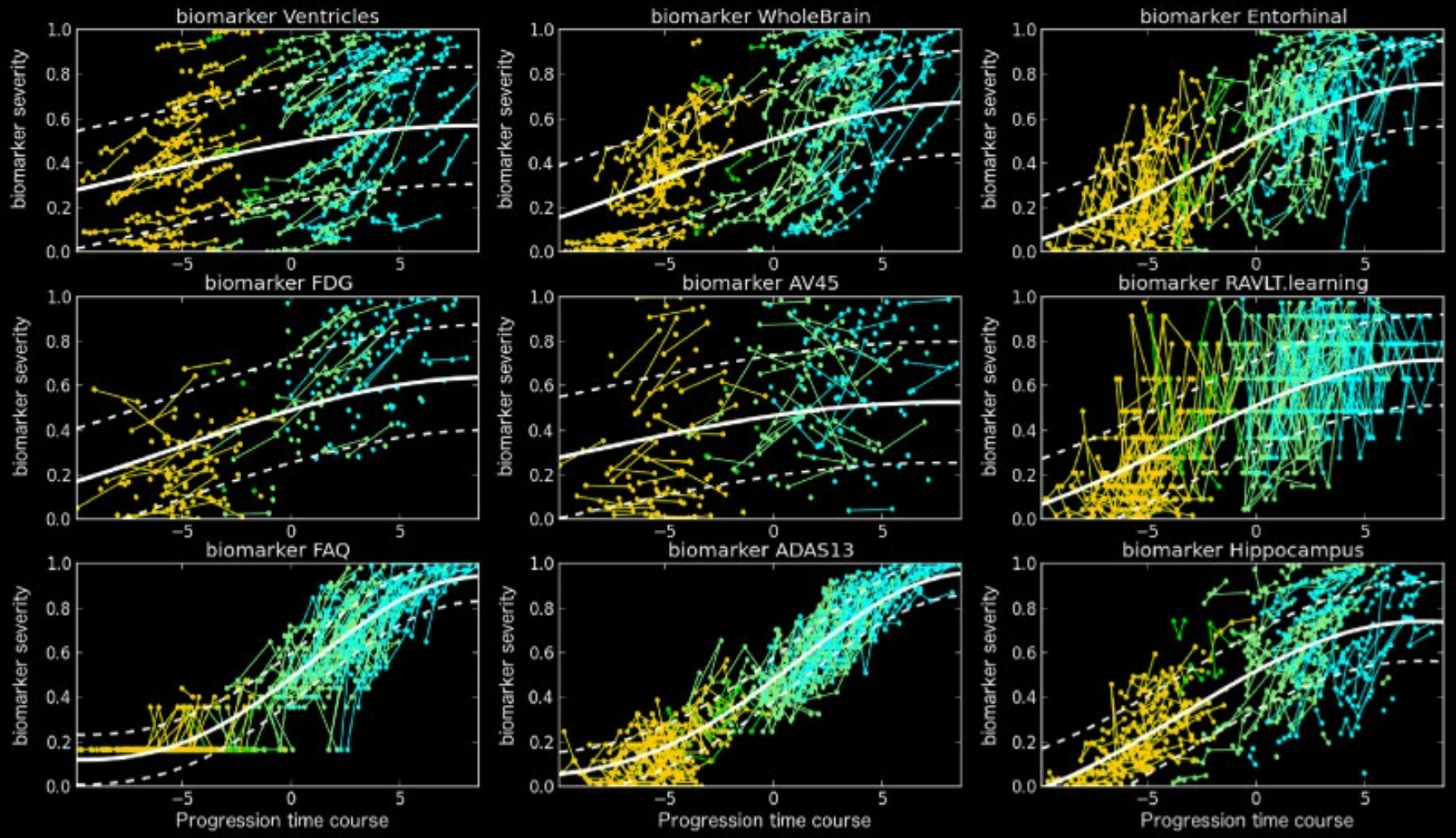
# Data-driven Disease Progression Modelling




Lorenzi et al,
NeuroImage 2017

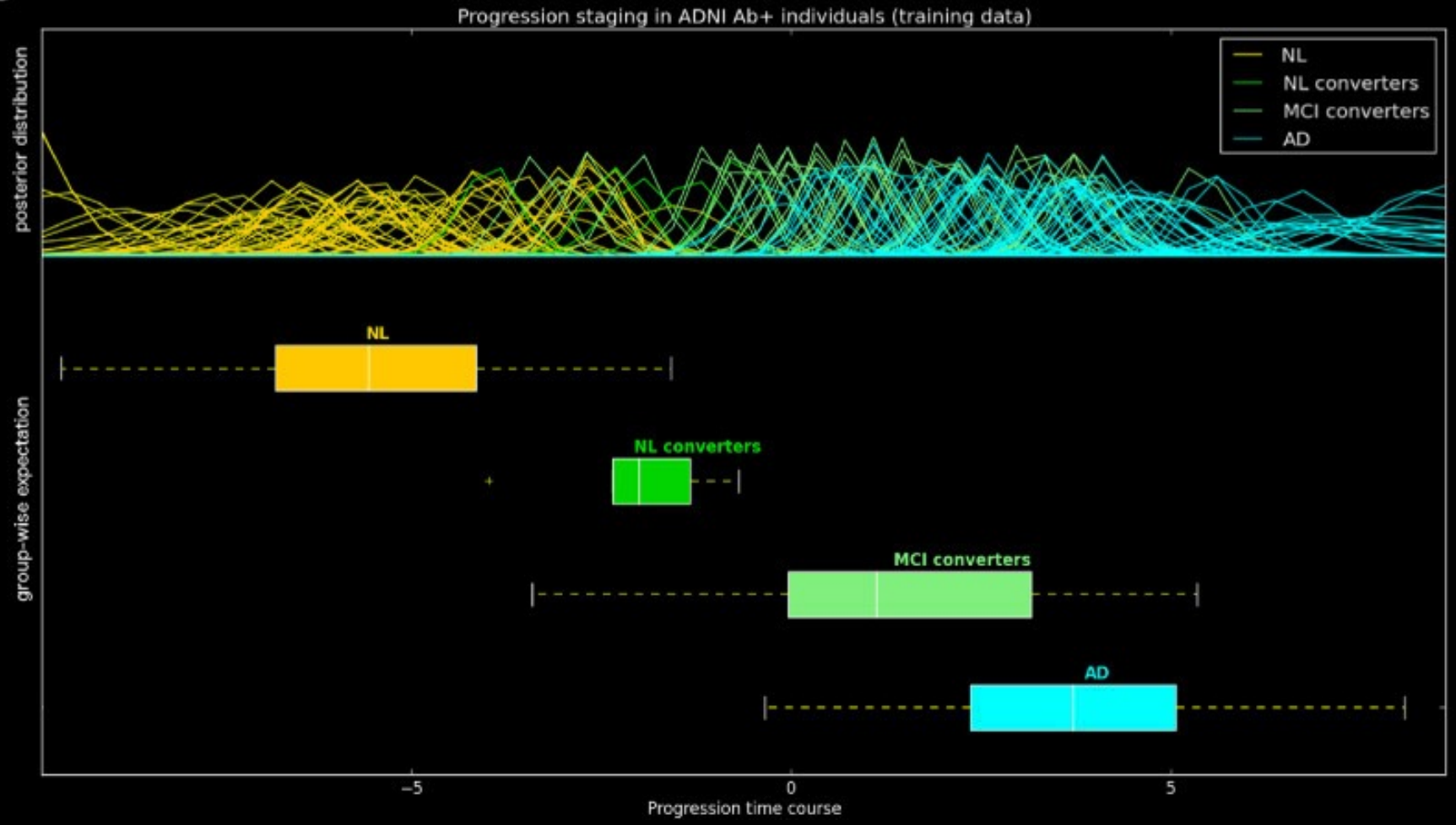
# Data-driven Disease Progression Modelling

A




Lorenzi et al, NeuroImage 2017

# Data-driven Disease Progression Modelling




Lorenzi et al, NeuroImage 2017

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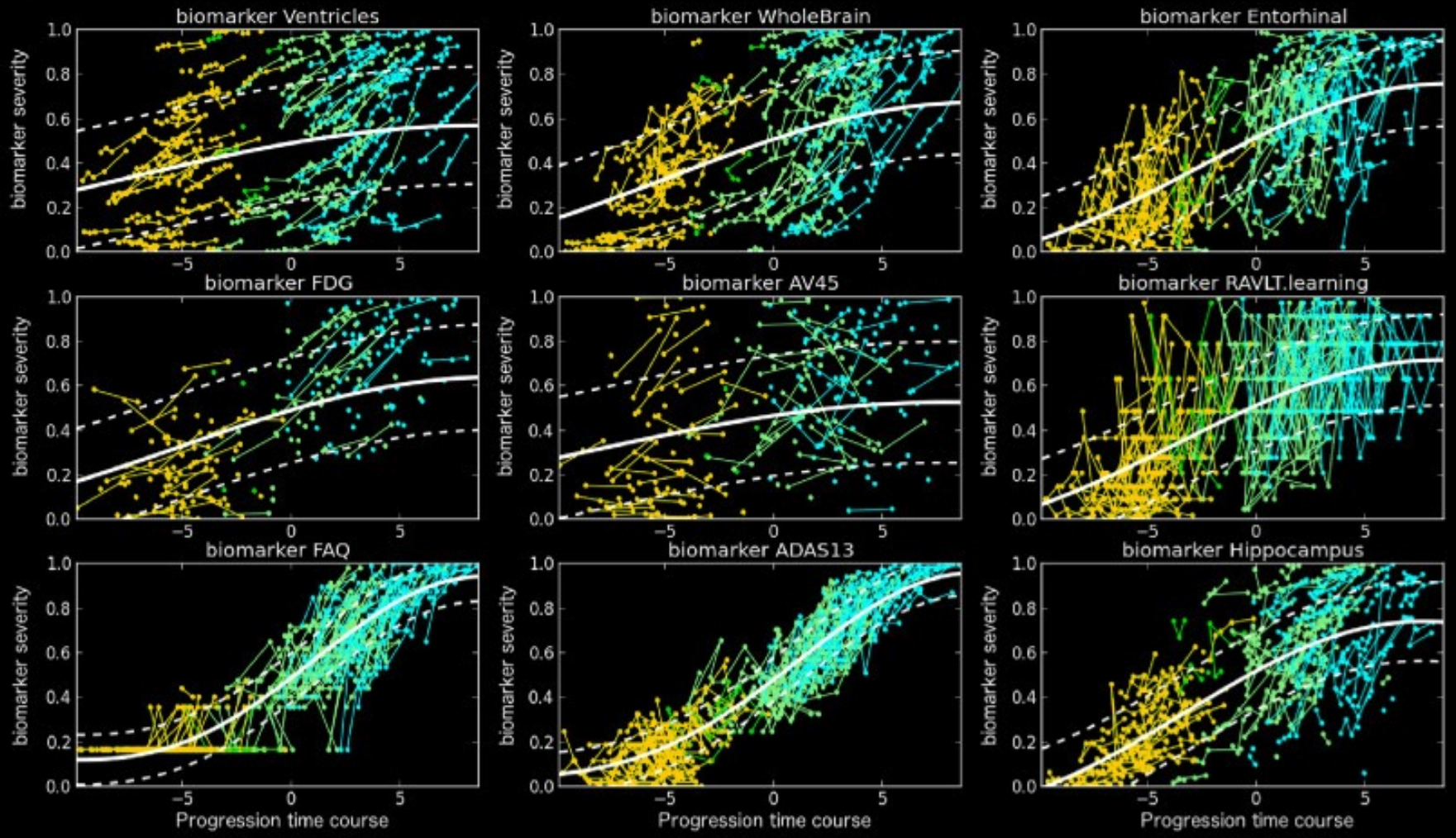


Lorenzi et al, NeuroImage 2017

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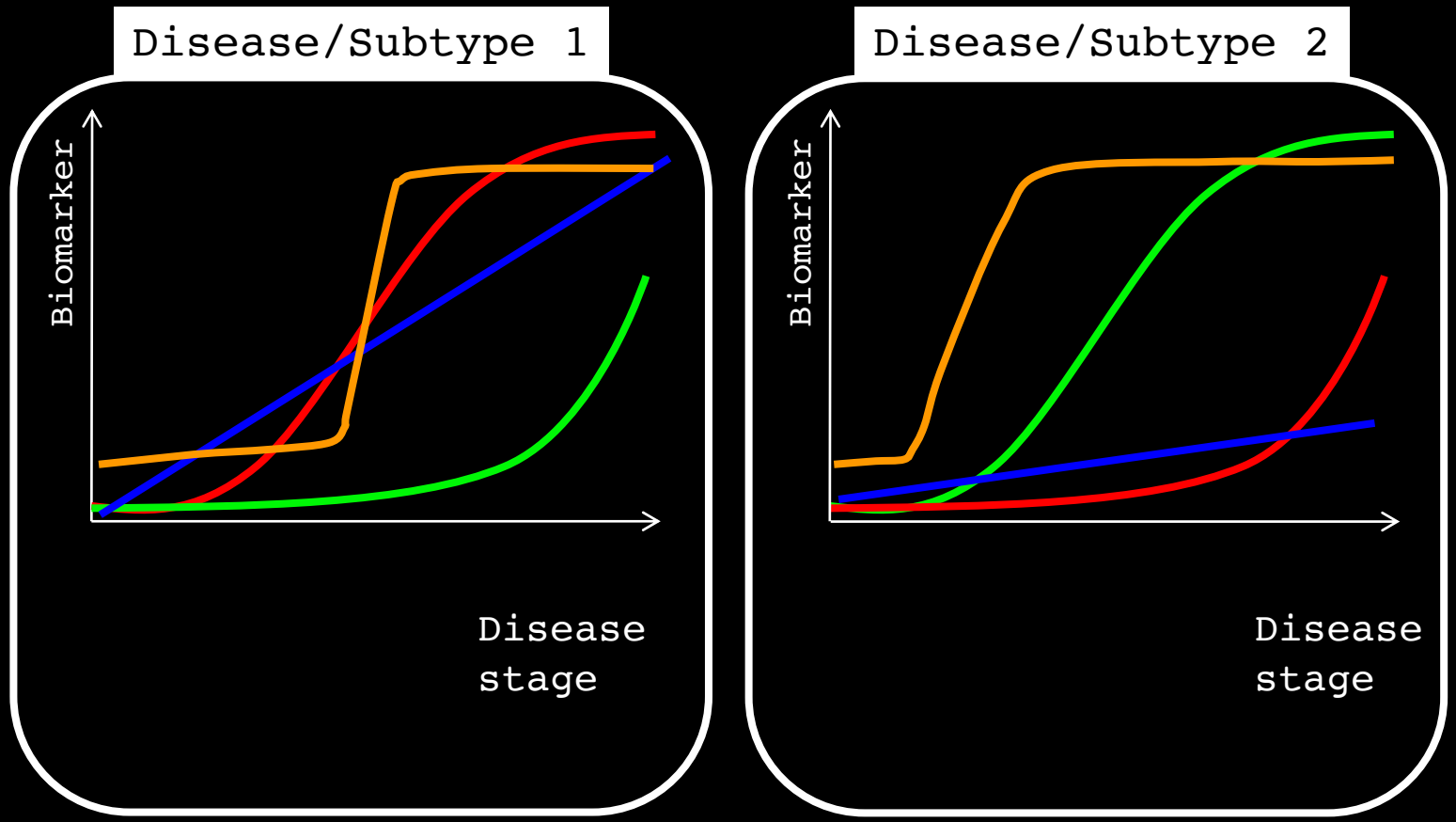

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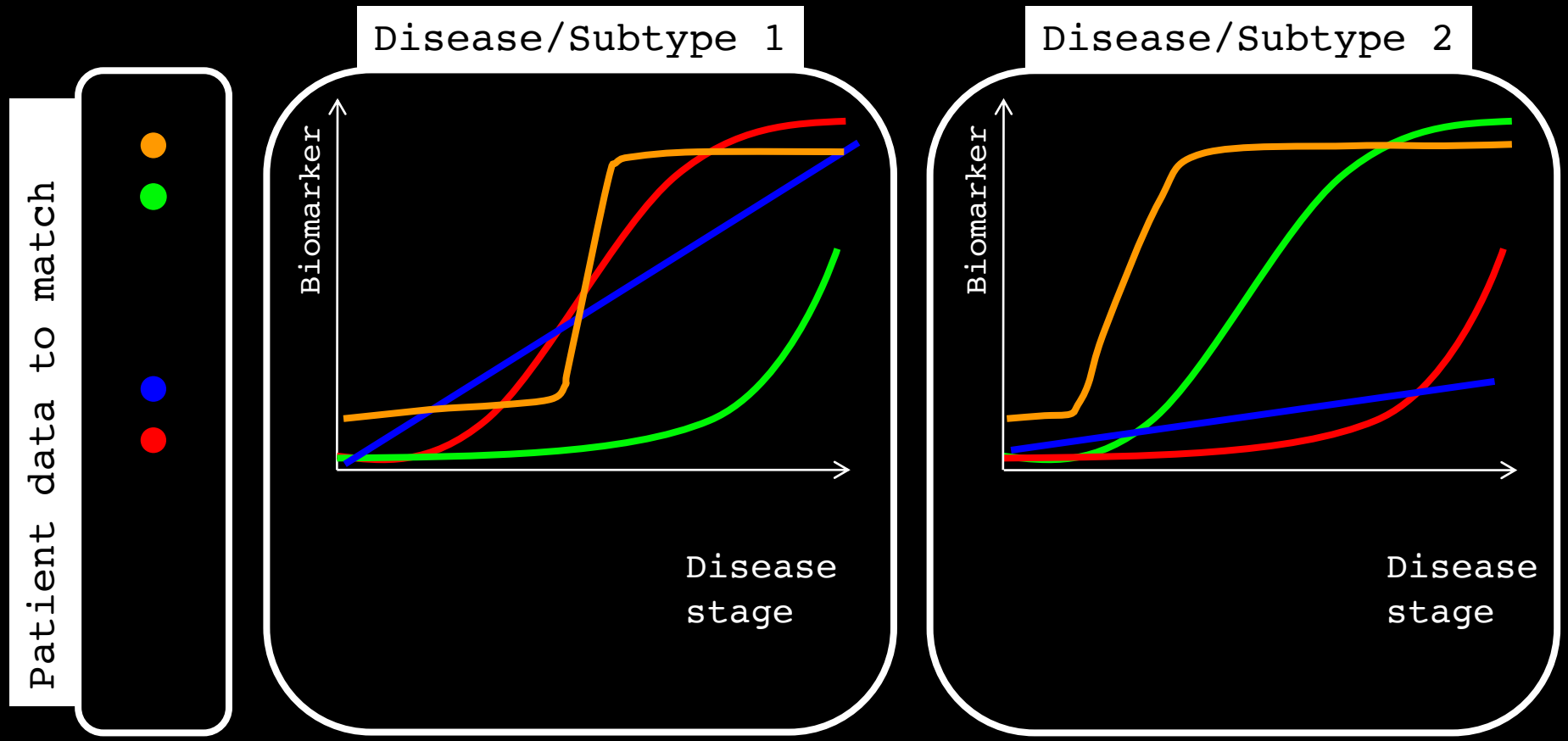

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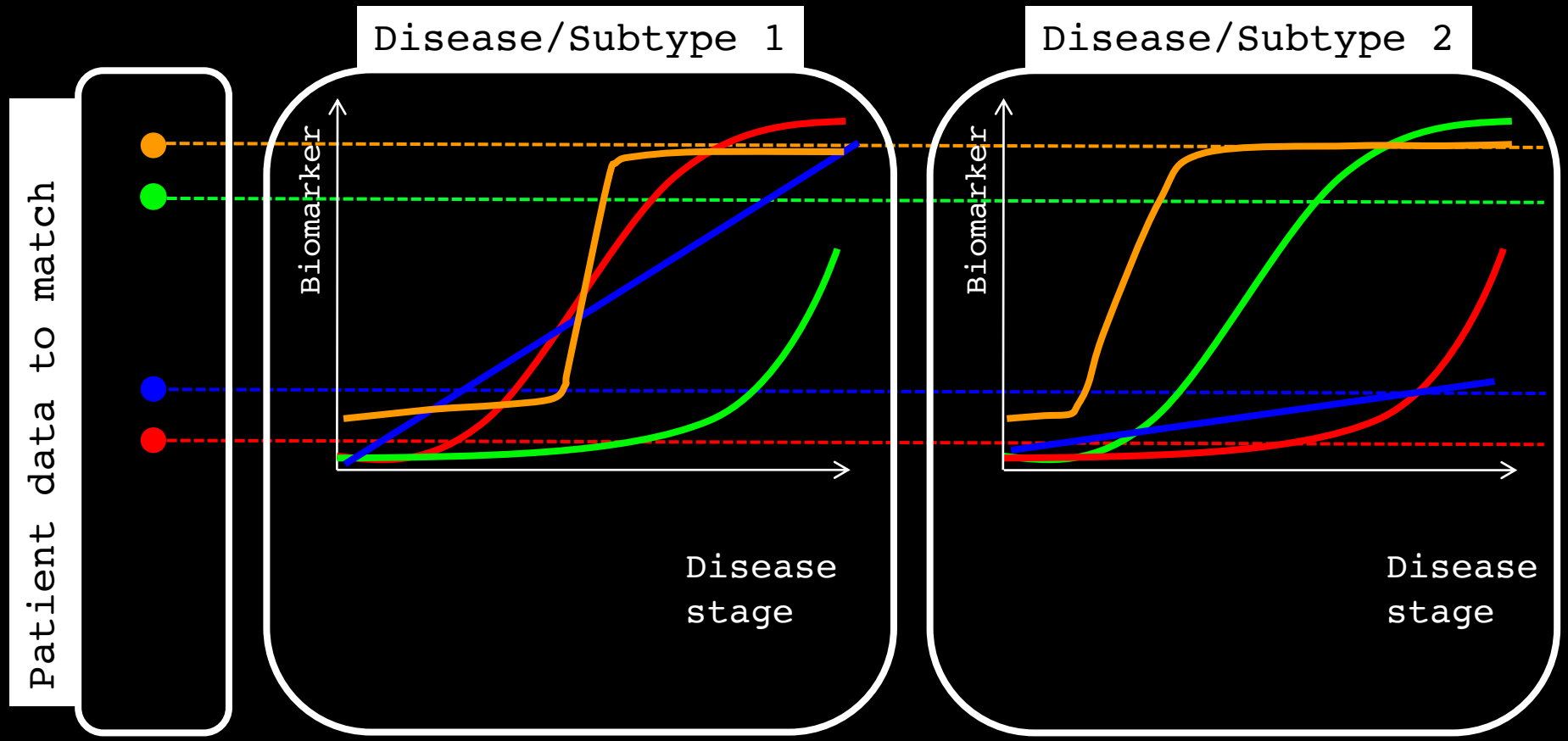

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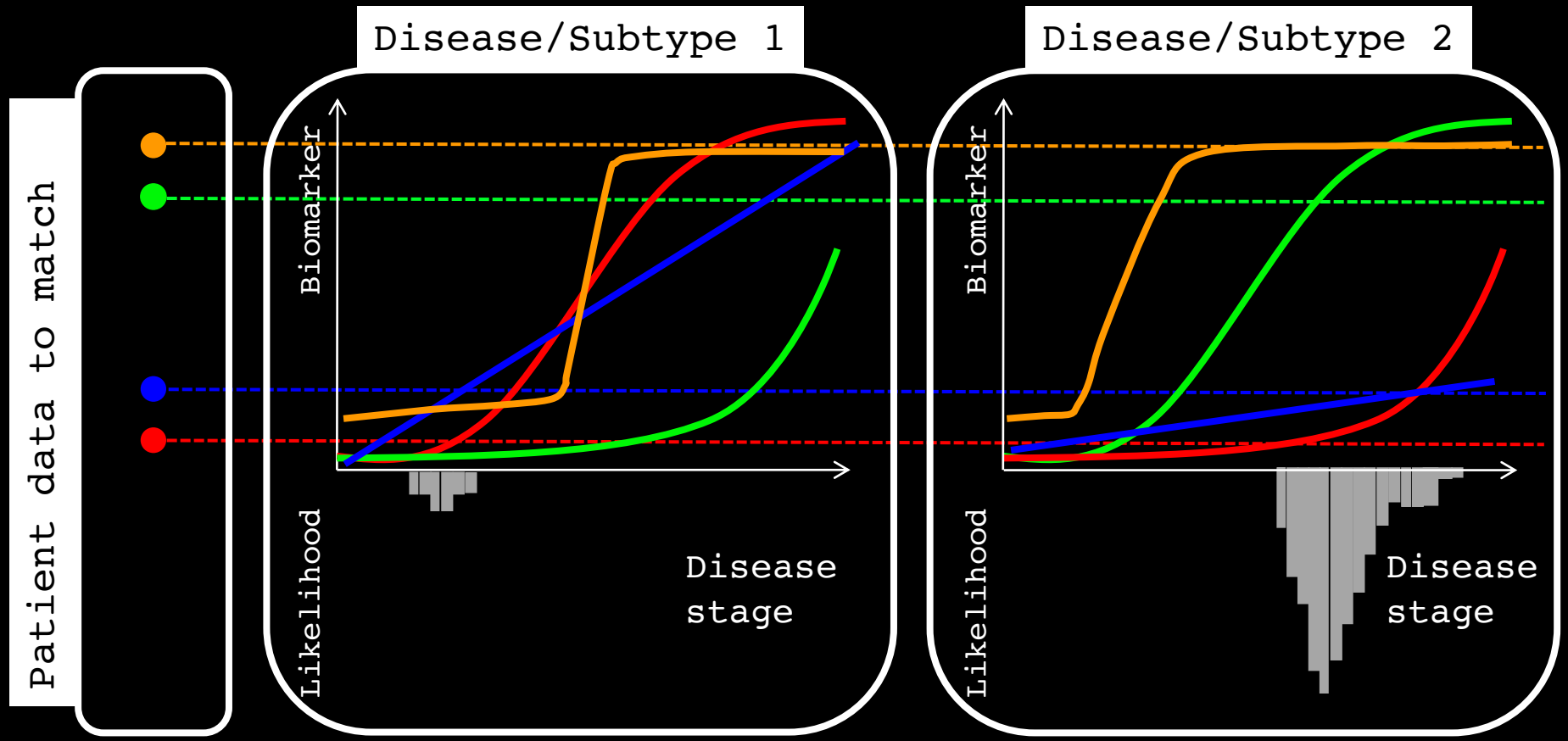

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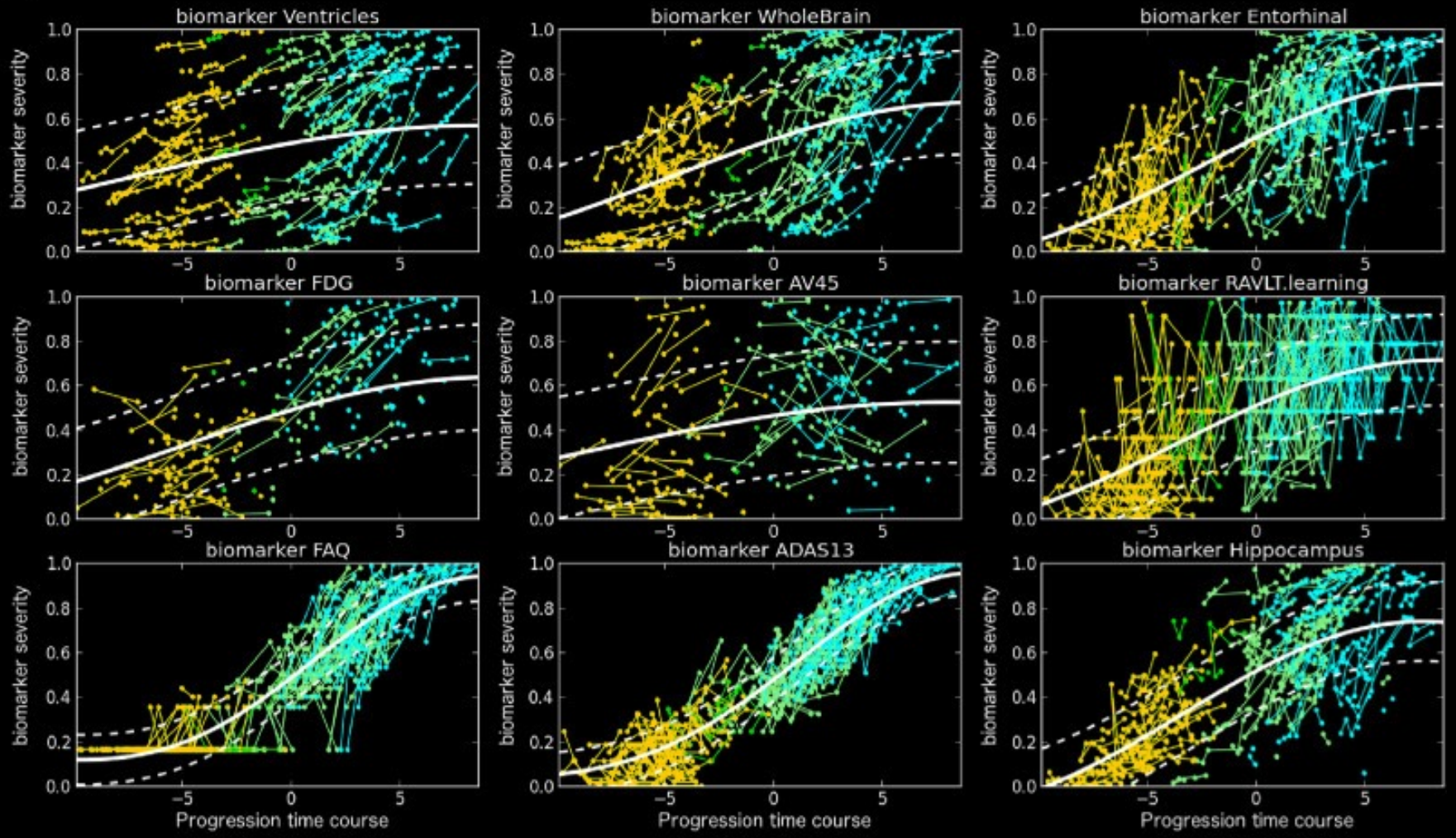



Lorenzi et al, NeuroImage 2017

# Disease Progression Modelling + Clustering

- Discrete: Subtype and Stage Inference

  Young at al., Nature Communications 2018

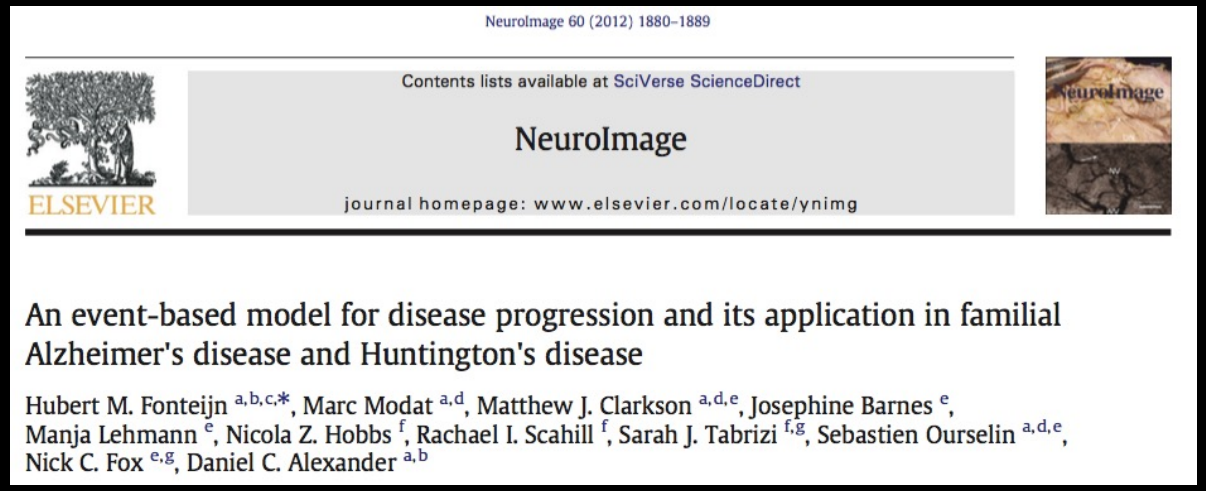
- Continuous: LT-NLME + GMM

  Poulet & Durrleman, IPMI 2019

# Event-based model

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

**Data-driven**: no prior knowledge of disease stage



NeuroImage 60 (2012) 1880–1889

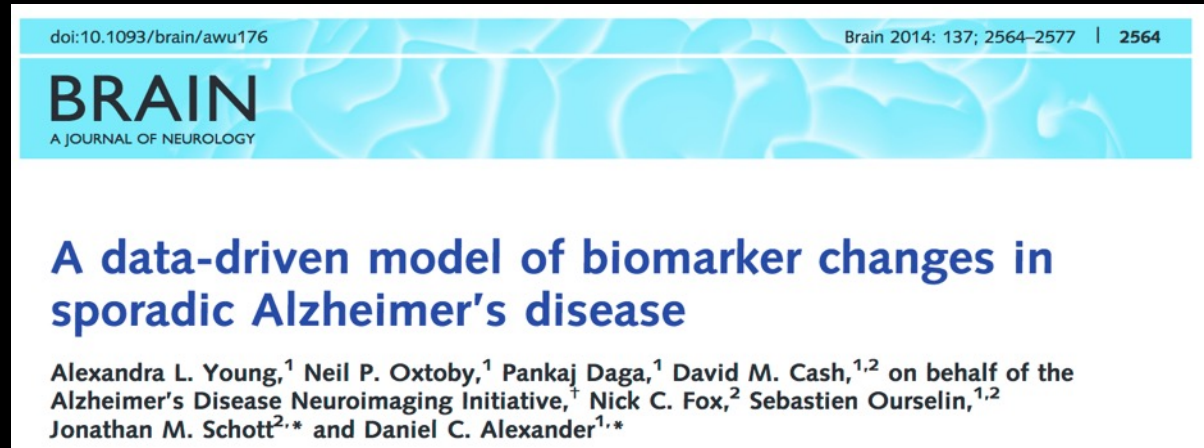
Contents lists available at SciVerse ScienceDirect

NeuroImage

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

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

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



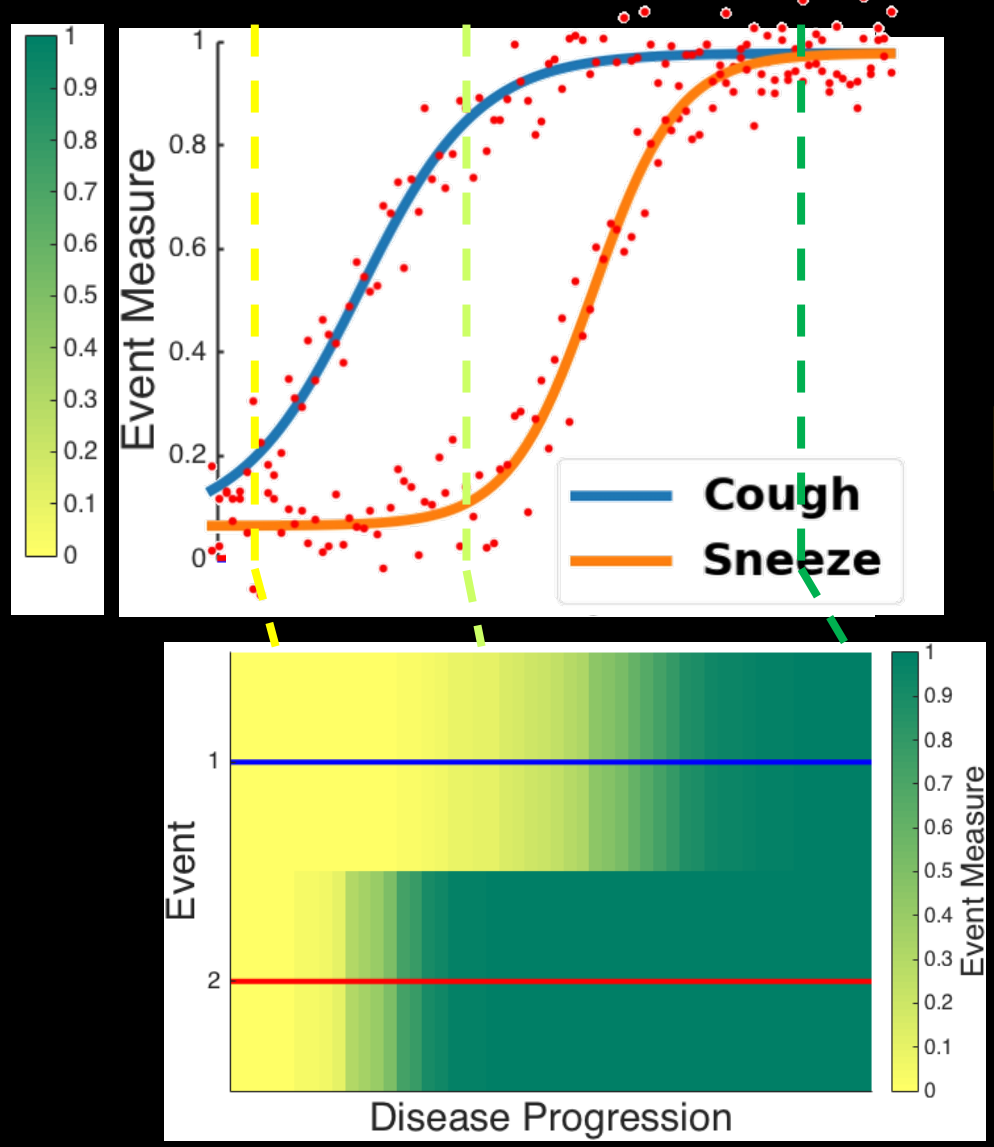
doi:10.1093/brain/awu176 Brain 2014: 137; 2564–2577 | 2564

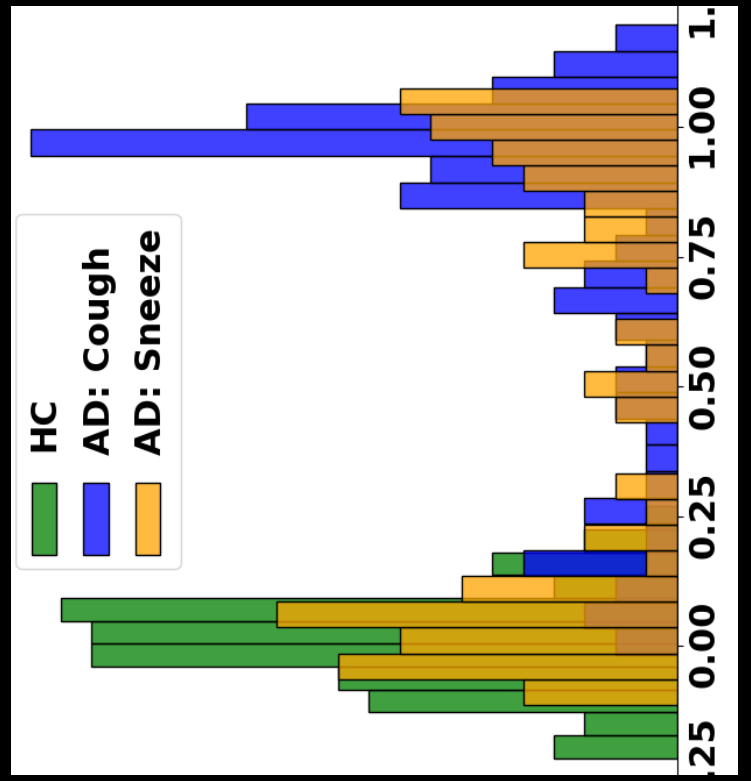
BRAIN
A JOURNAL OF NEUROLOGY

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

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

# Event based model



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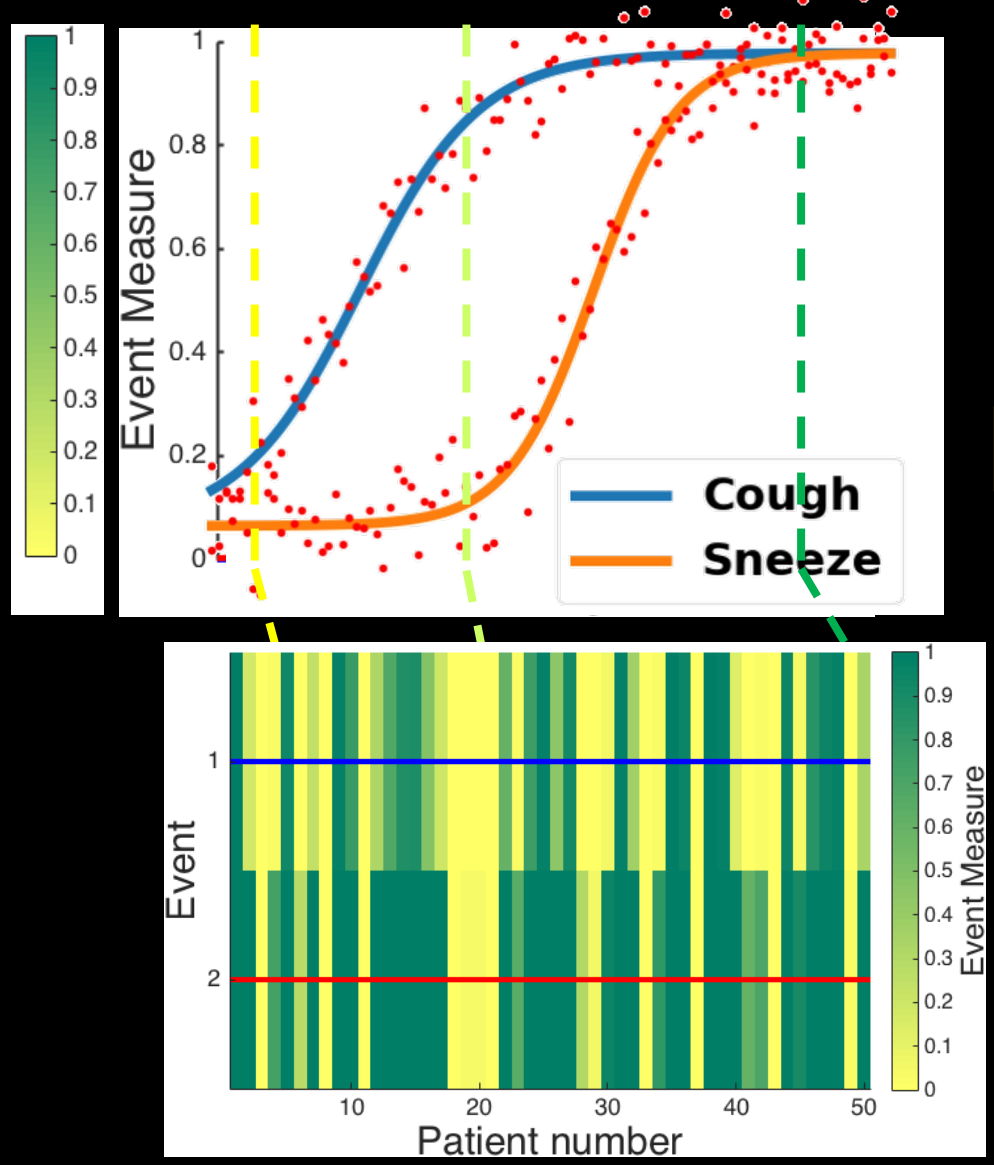
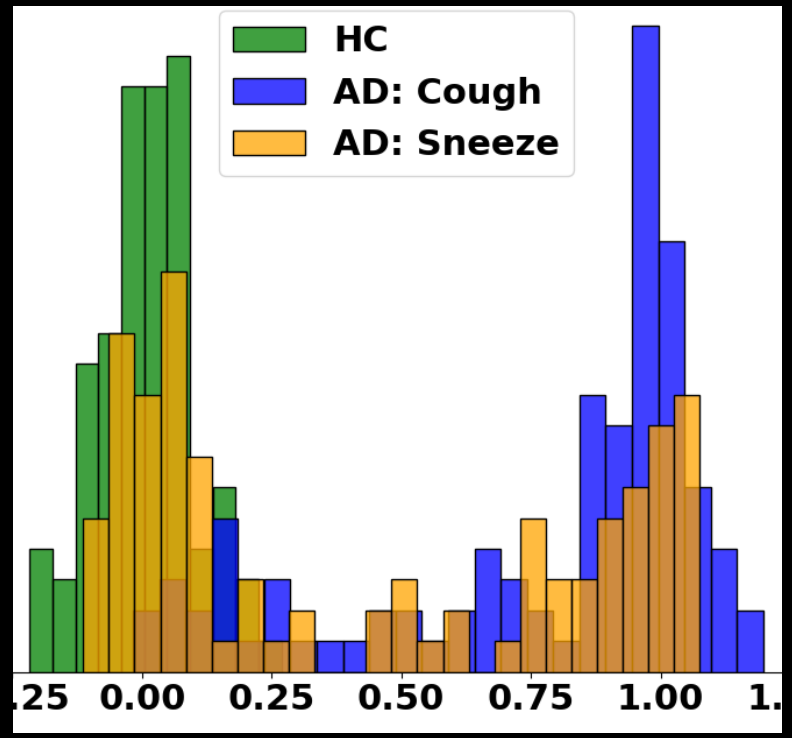
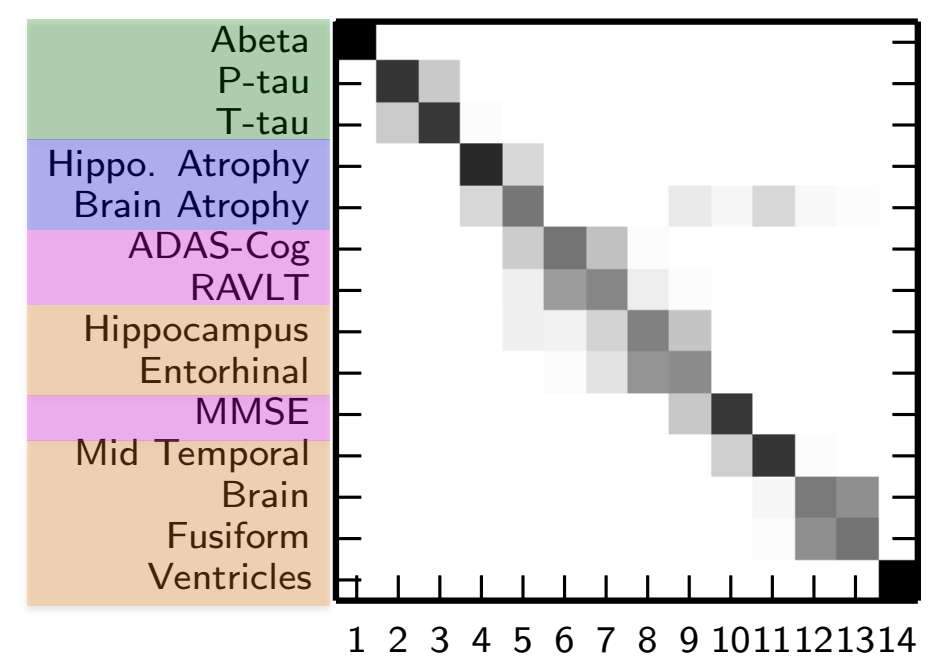


# Event based model of Alzheimer's disease progression

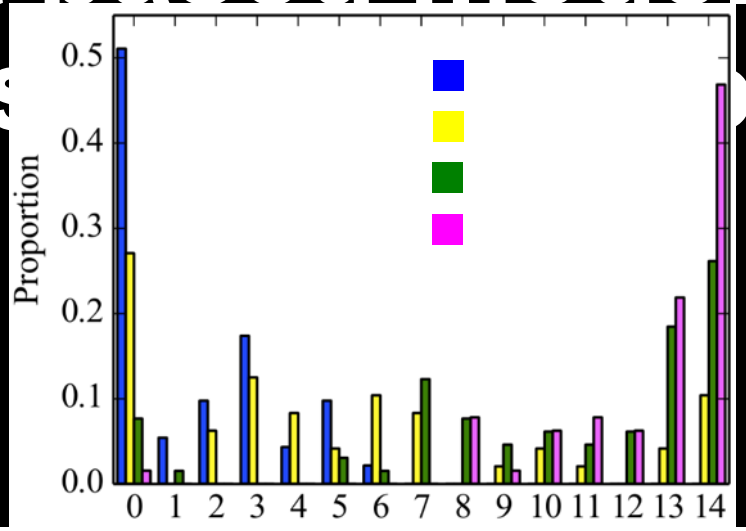


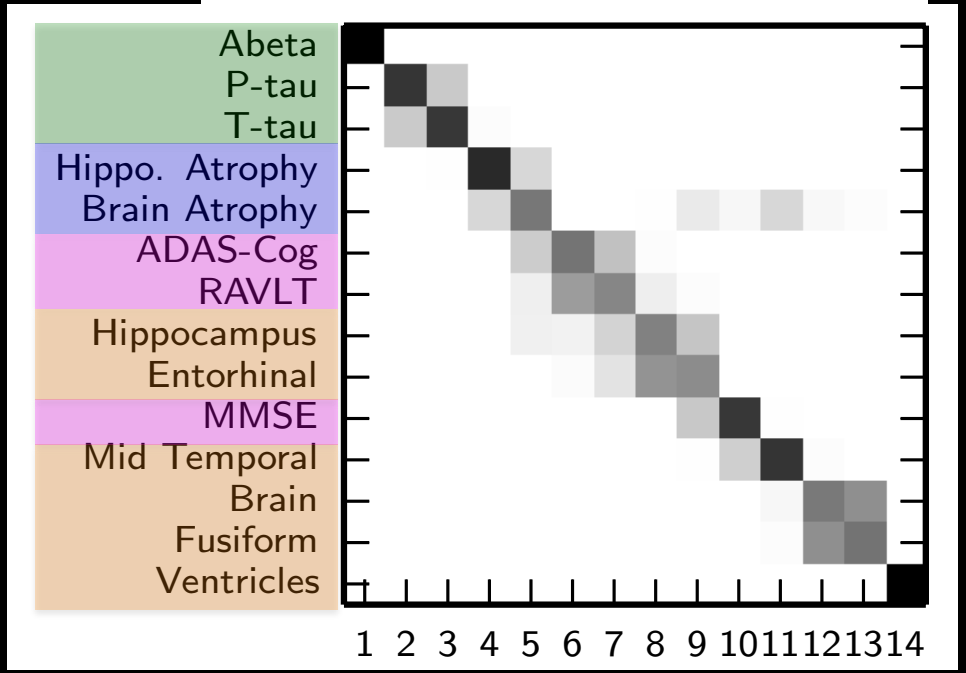

**Model Stages:**

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

Young et al, Brain 2014

# Event based model of Alzheimer's diseas on

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Young et al, Brain 2014

# Event based model in Alzheimer's disease progression: CSF vs PET

Research

JAMA Neurology | Original Investigation

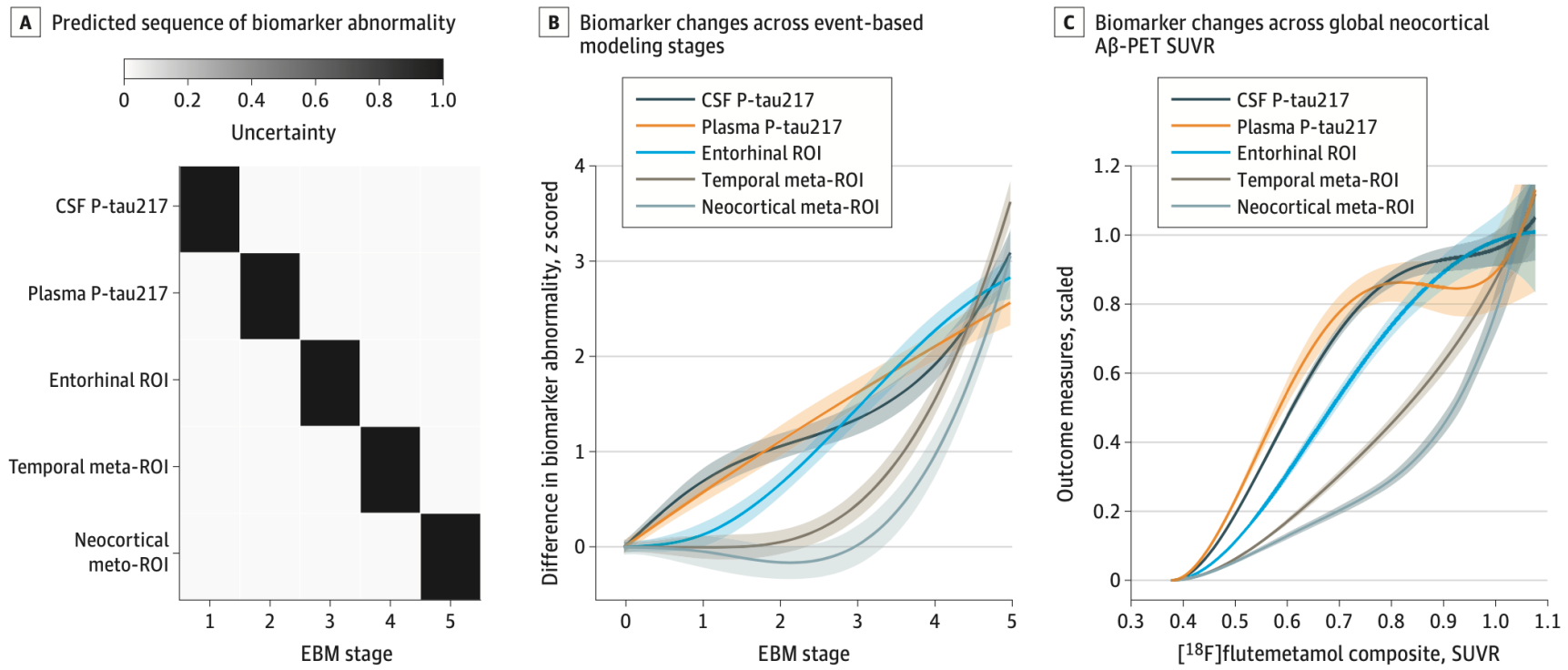
## Associations of Plasma Phospho-Tau217 Levels With Tau Positron Emission Tomography in Early Alzheimer Disease

Shorena Janelidze, PhD; David Berron, PhD; Ruben Smith, MD, PhD; Olof Strandberg, PhD; Nicholas K. Proctor, BS; Jeffrey L. Dage, PhD; Erik Stomrud, MD, PhD; Sebastian Palmqvist, MD, PhD; Niklas Mattsson-Carlgren, MD, PhD; Oskar Hansson, MD, PhD

Janelidze et al, JAMA Neurol 2021

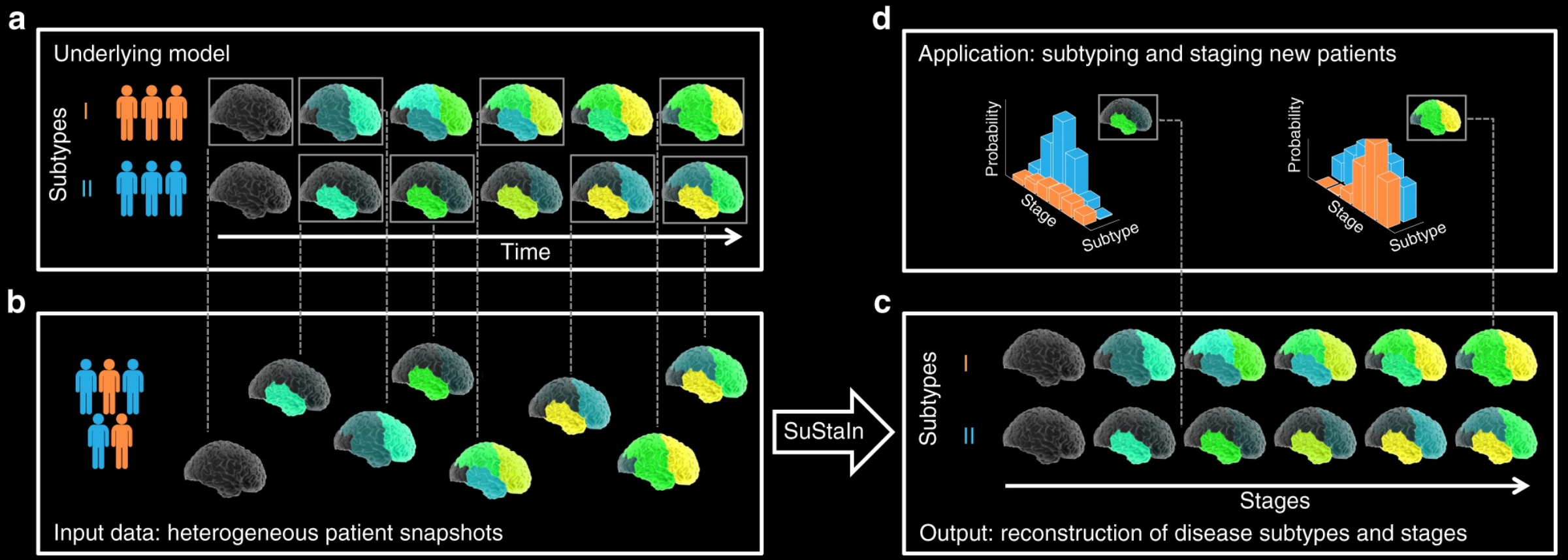
# Event based model in Alzheimer's disease progression: CSF vs PET

Figure 3. Order of Change in Plasma Tau Phosphorylated at Threonine 217 (P-tau217), Cerebrospinal Fluid (CSF) P-tau217, and Tau–Positron Emission Tomography (PET) Abnormality



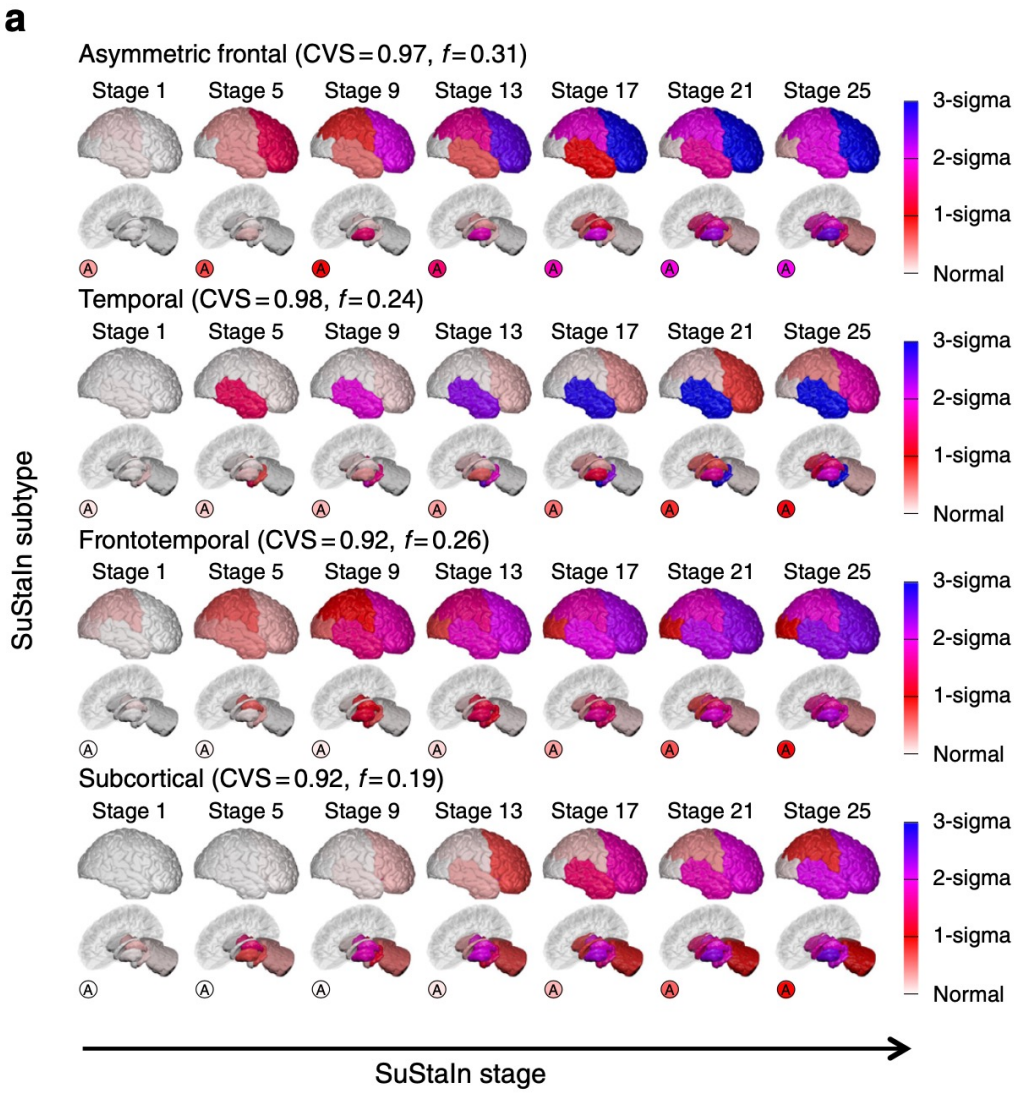

Janelidze et al, JAMA Neurol 2021

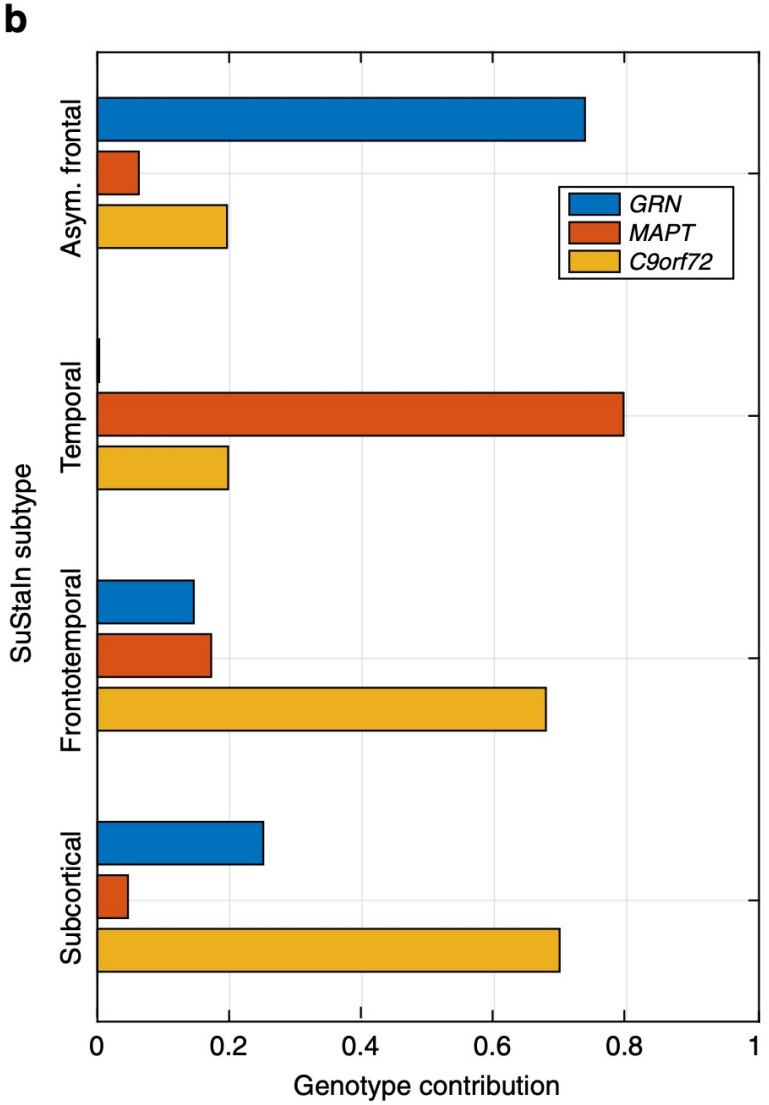
# Subtype and Stage Inference (DPM + clustering)




Young et al, Nat Commun 2018

# Subtype and Stage Inference – Genetic FTD

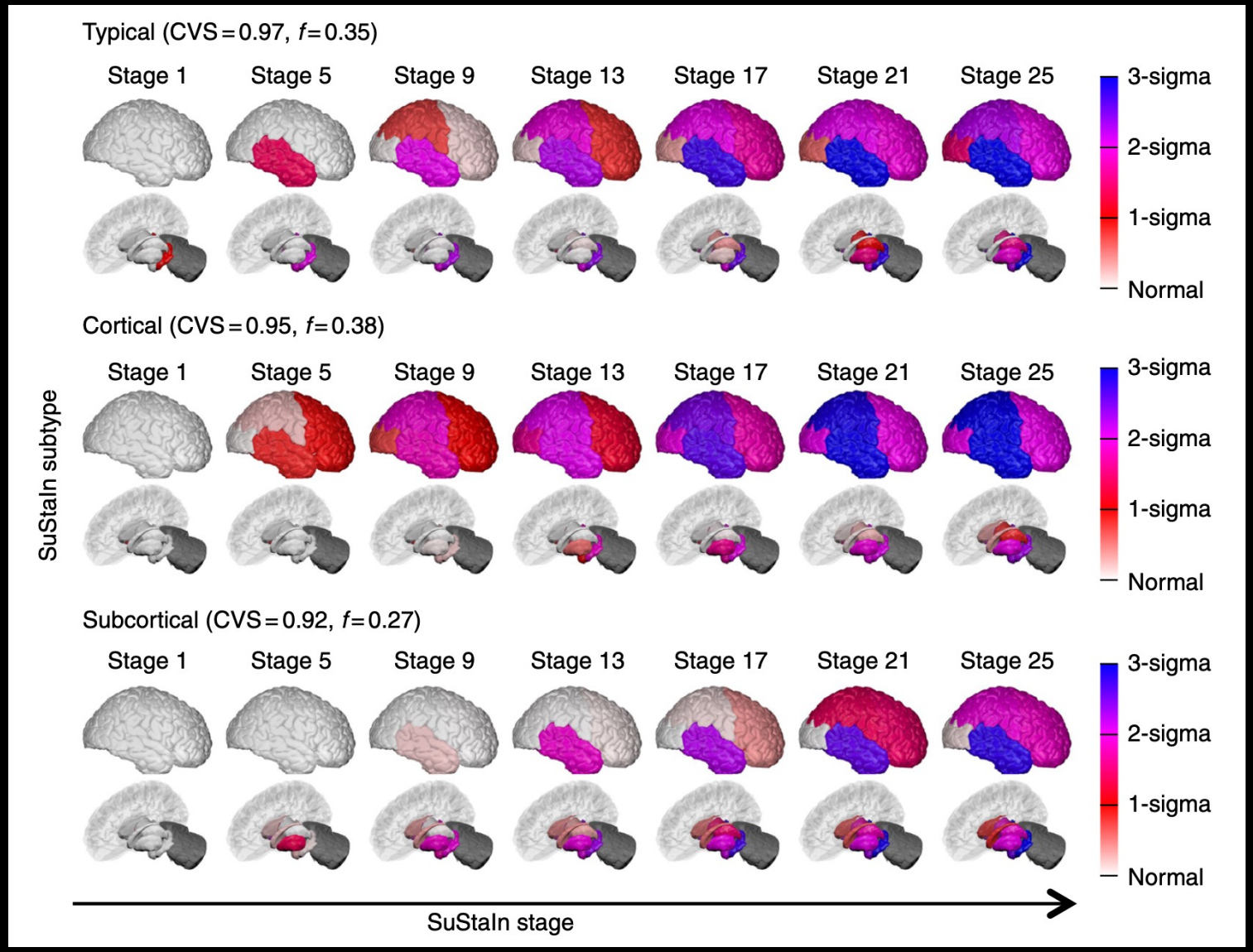



GENFI
GENETIC FTD INITIATIVE

Young et al,
Nat Commun 2018

# Subtype and Stage Inference – sporadic AD




ADNI
Alzheimer's Disease Neuroimaging Initiative

Young et al,
Nat Commun 2018

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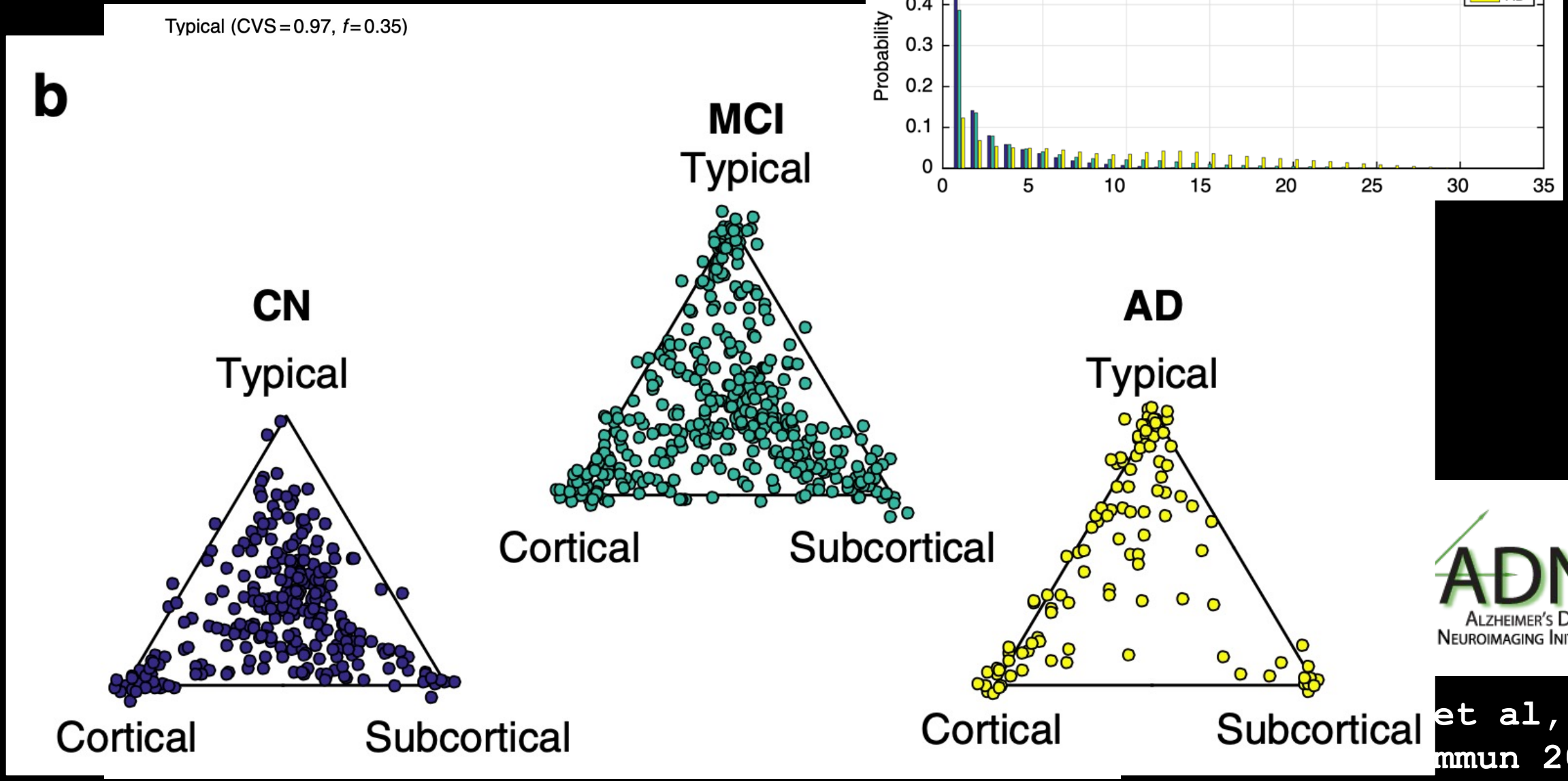


ADNI
Alzheimer's Disease Neuroimaging Initiative

et al,
mmun 2018

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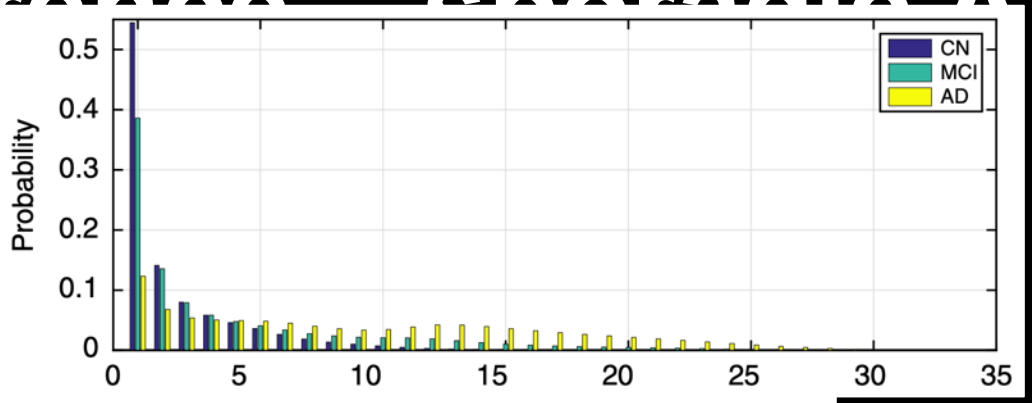


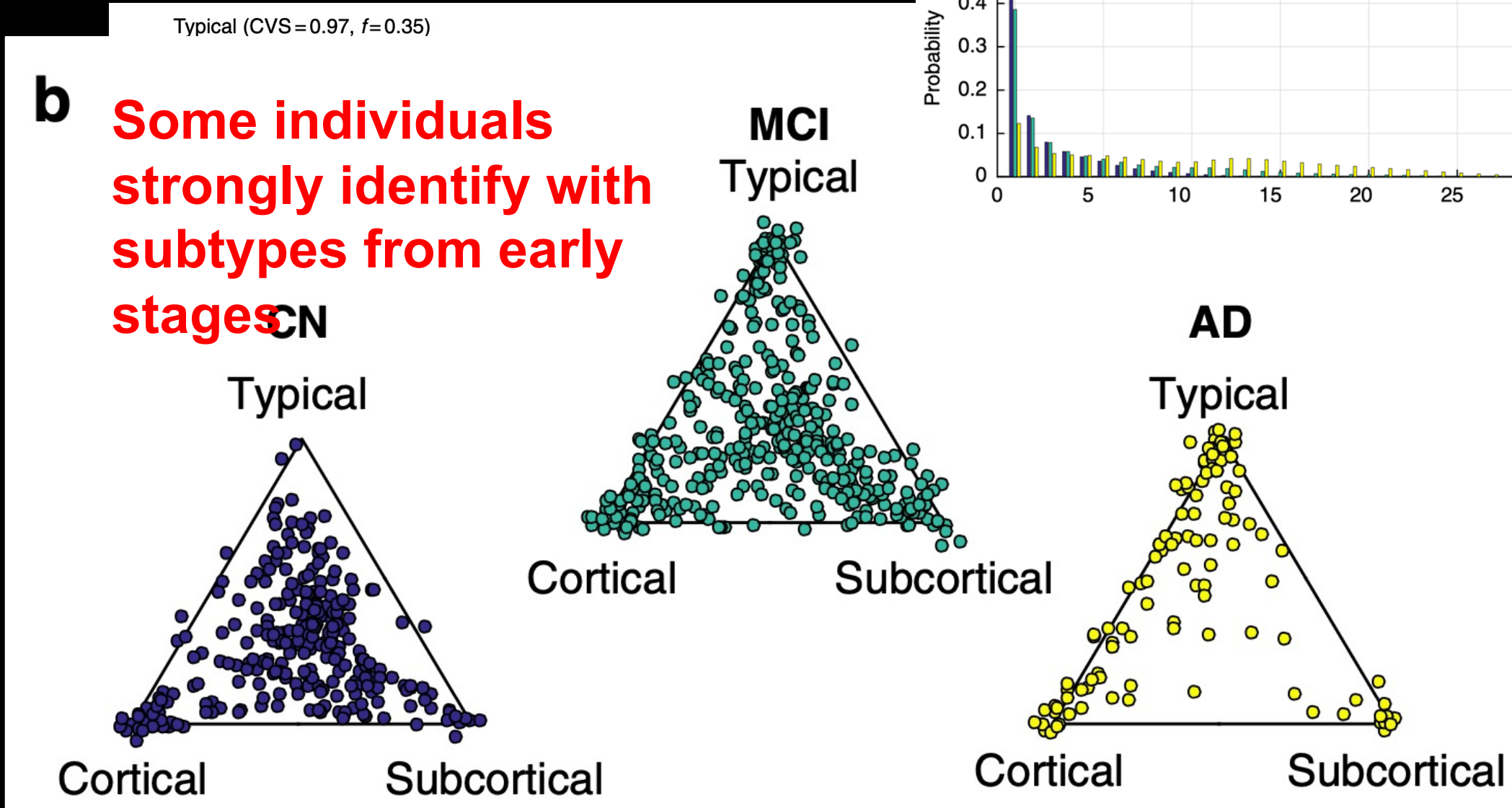


et al,
mmun 2018

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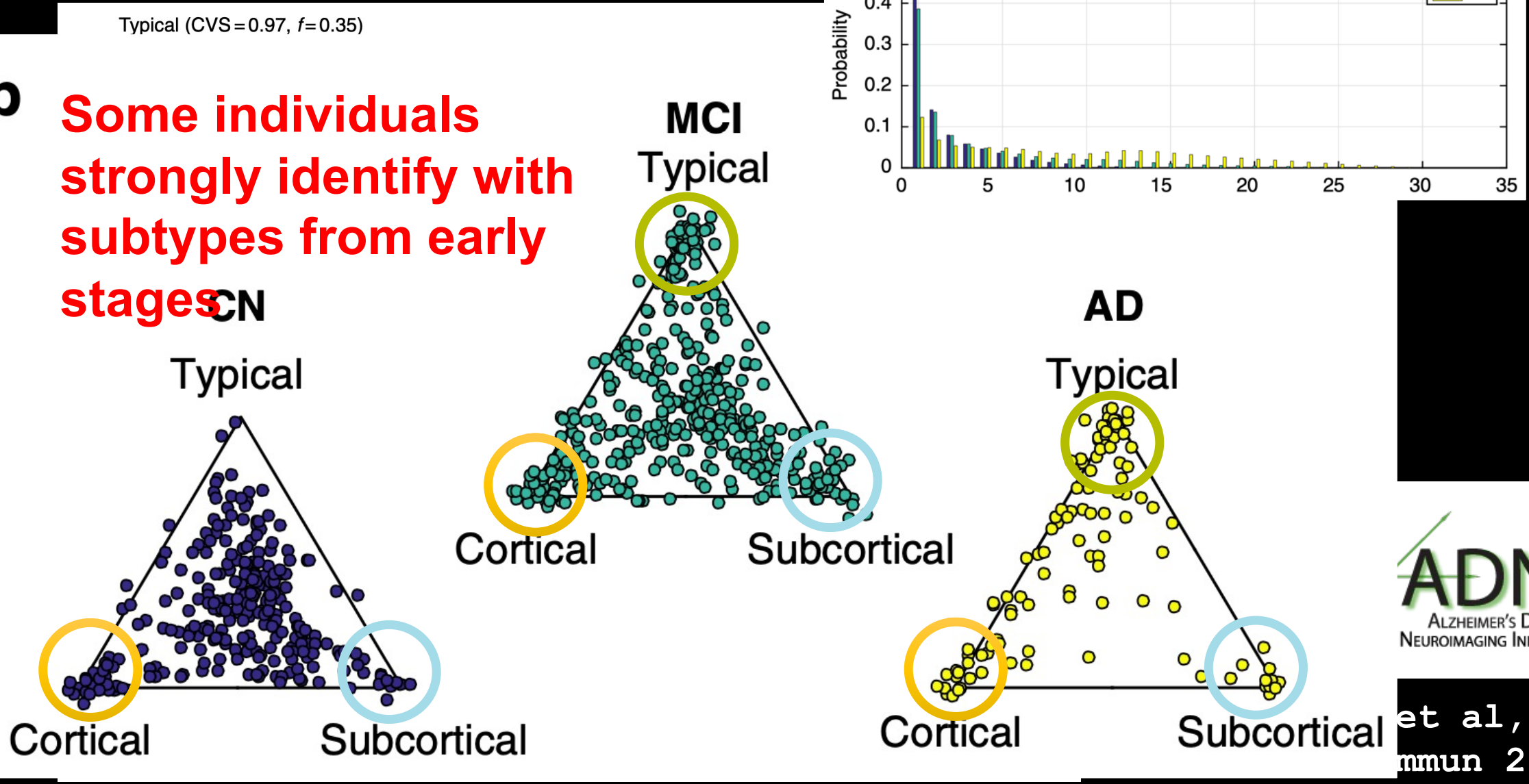



ADNI
Alzheimer's Disease Neuroimaging Initiative

et al,
mmun 2018

# Subtype and Stage Inference – further reading

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01309-6

## Four distinct trajectories of tau deposition identified in Alzheimer's disease

Jacob W. Vogel[1]✉, Alexandra L. Young[2], Neil P. Oxtoby[3,4], Ruben Smith[5,6], Rik Ossenkoppele[5,7], Olof T. Strandberg[5], Renaud La Joie[8], Leon M. Aksman[3,9], Michel J. Grothe[10,11], Yasser Iturria-Medina[1], the Alzheimer's Disease Neuroimaging Initiative*, Michael J. Pontecorvo[12], Michael D. Devous[12], Gil D. Rabinovici[8,13], Daniel C. Alexander[3,4], Chul Hyoung Lyoo[14], Alan C. Evans[1] and Oskar Hansson[5,15]✉

`github.com/ucl-pond/pySuStaIn`

nature COMMUNICATIONS

https://doi.org/10.1038/s41467-021-22265-2 OPEN

## Identifying multiple sclerosis subtypes using unsupervised machine learning and MRI data

Arman Eshaghi[1,2]✉, Alexandra L. Young[2,3], Peter A. Wijeratne[2], Ferran Prados[1,2,4], Douglas L. Arnold[5], Sridar Narayanan[5], Charles R. G. Guttmann[6], Frederik Barkhof[1,2,7,8], Daniel C. Alexander[2], Alan J. Thompson[1], Declan Chard[1,9,10] & Olga Ciccarelli[1,9,10]

nature COMMUNICATIONS

DOI: 10.1038/s41467-018-05892-0 OPEN

## Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference

Alexandra L Young et al.#

# Applications of DPM in Clinical trials in Alzheimer's disease

# Applications of DPM in Clinical trials in Alzheimer's disease


Jerry Maguire,
Sony Pictures 1996

# Applications of DPM in Clinical trials in Alzheimer's disease

- Event-based model

  `Oxtoby et al., Frontiers 2022`

- Subtype and Stage Inference

  `Shand et al., AD/PD 2022`

# MCI clinical trial of Donepezil (& vitamin E)

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

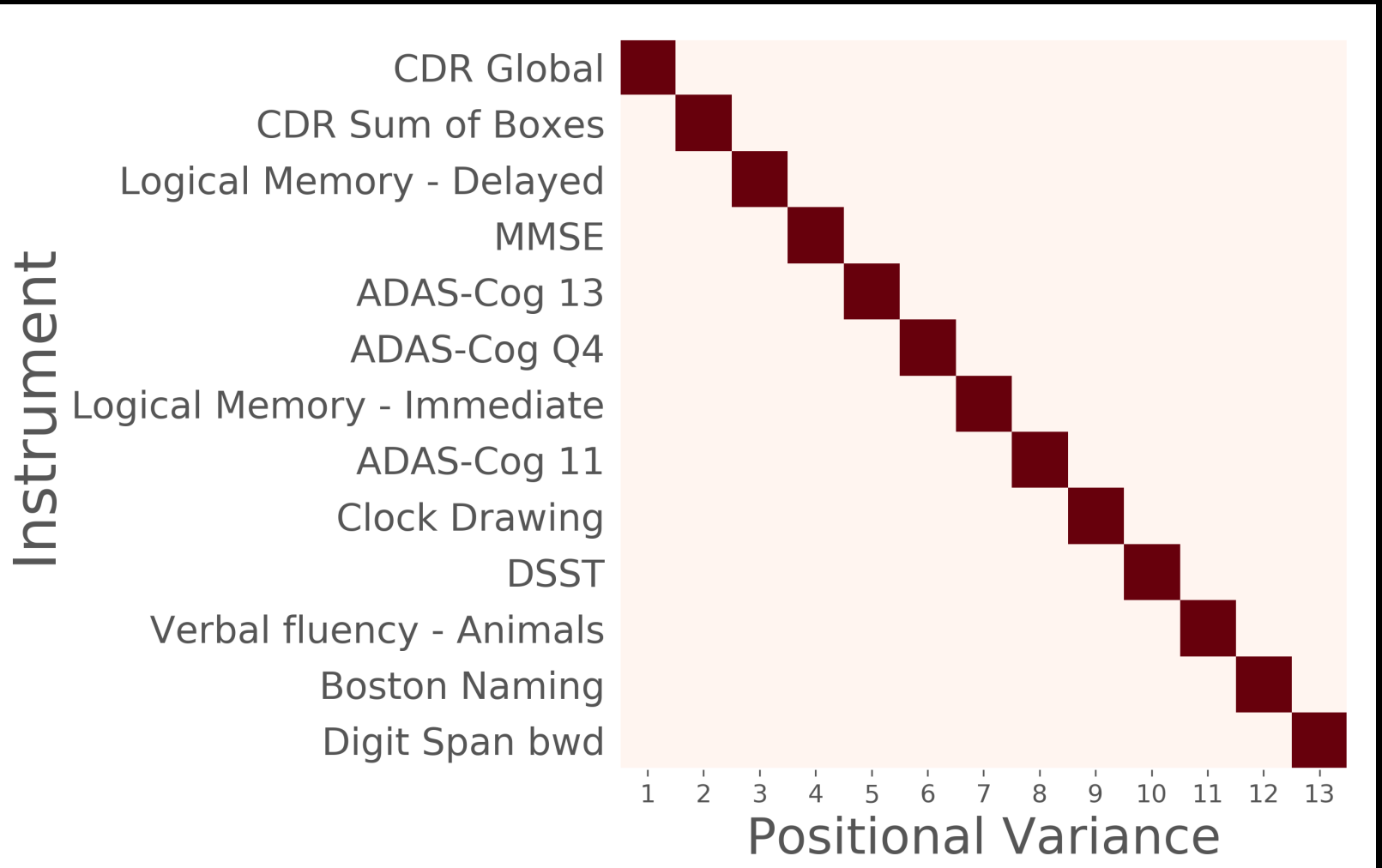
Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

ALZHEIMER'S DISEASE ADCS COOPERATIVE STUDY

Experiments:

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

# MCI clinical trial of Donepezil (& vitamin E)

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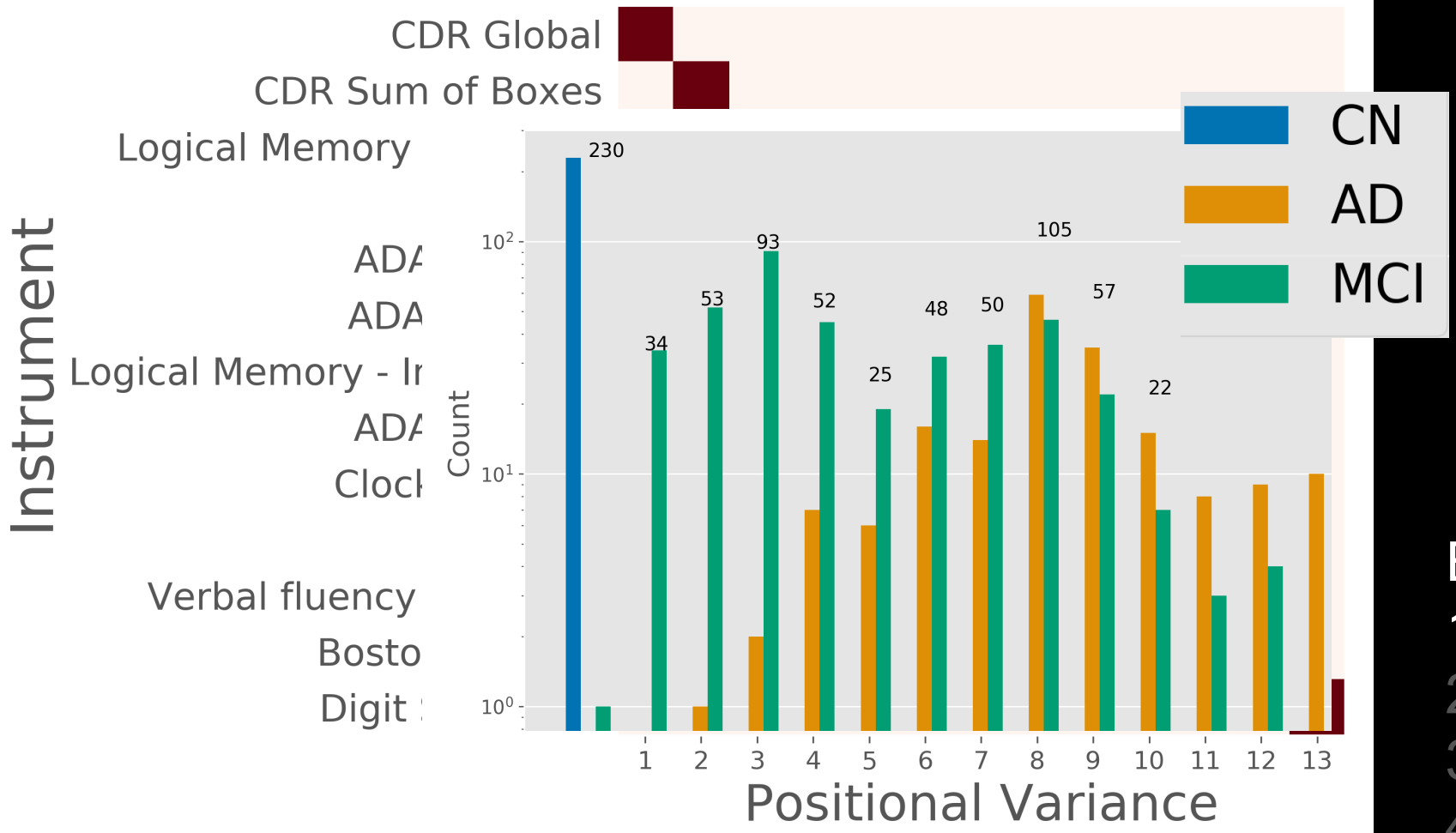


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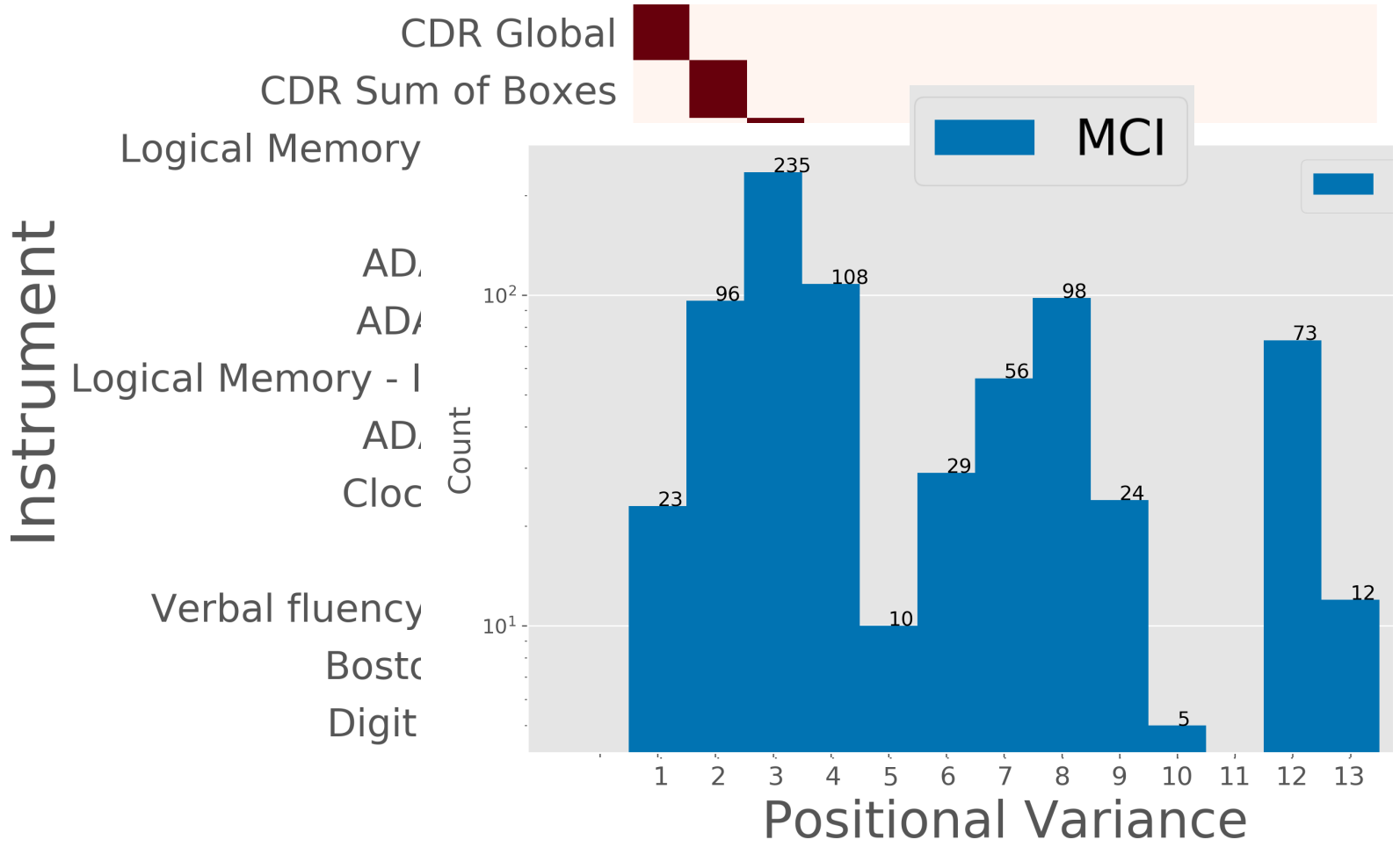
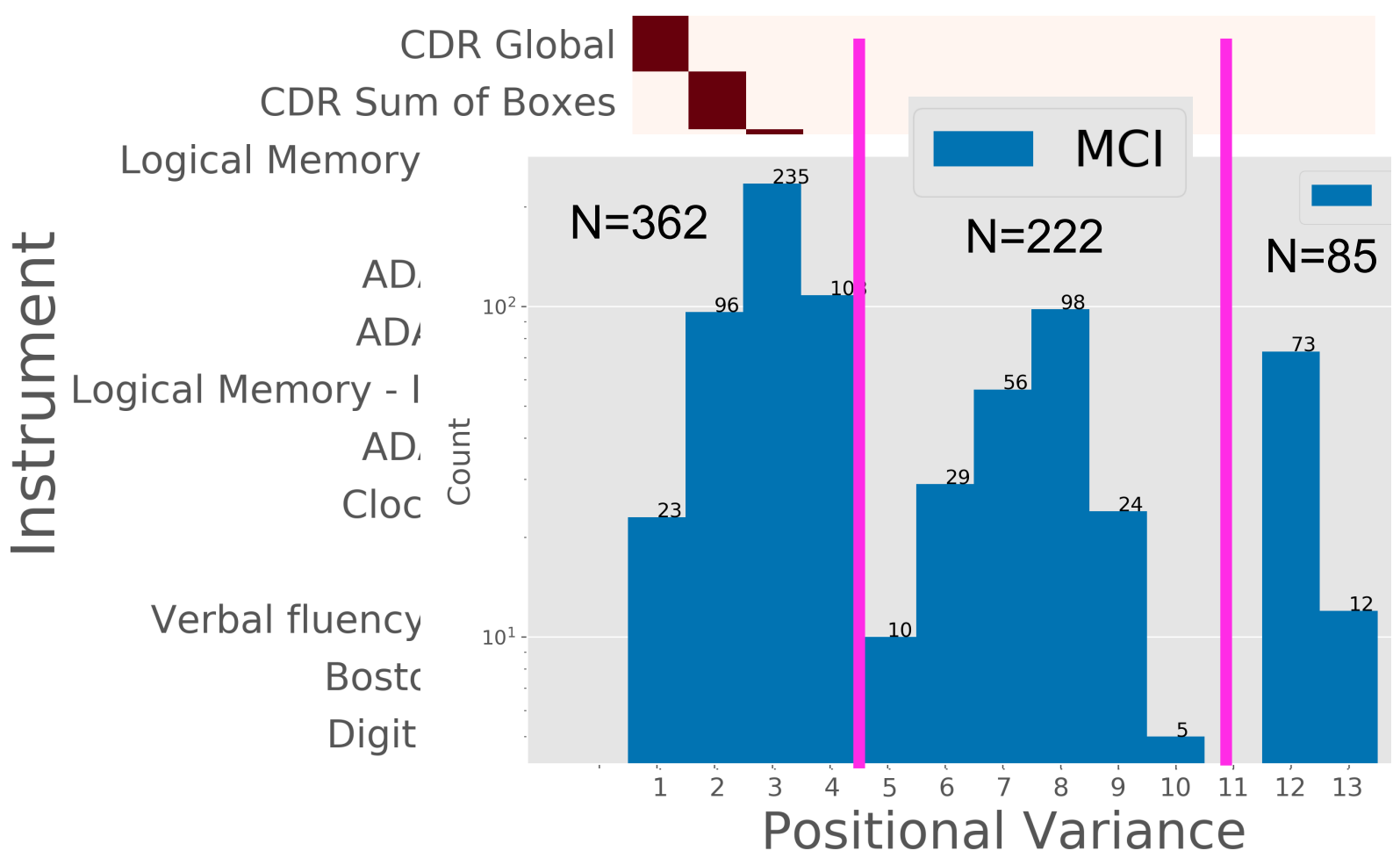
# MCI clinical trial of Donepezil (& vitamin E)




Experiments:

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

# MCI clinical trial of Donepezil (& vitamin E)

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# MCI clinical trial of Donepezil (& vitamin E)

N=362

N=222

N=85

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 |
|---|---|---|---|---|---|---|---|
| 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 |
| 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 |
| 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 |

Experiments:

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# FYN trial of ADZ0530

Experiments:

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

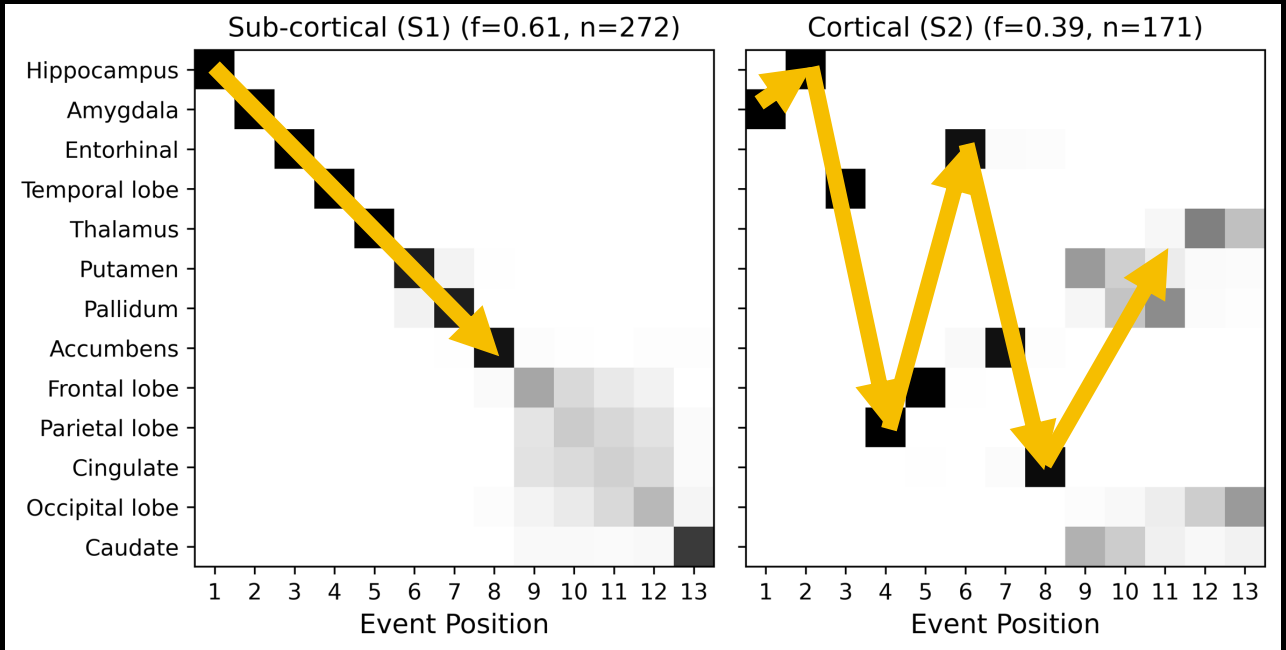


***Figure 1*: Positional variance diagrams showing disease progression event sequence (intensity indicates sequence positional density)**

# FYN trial of ADZ0530

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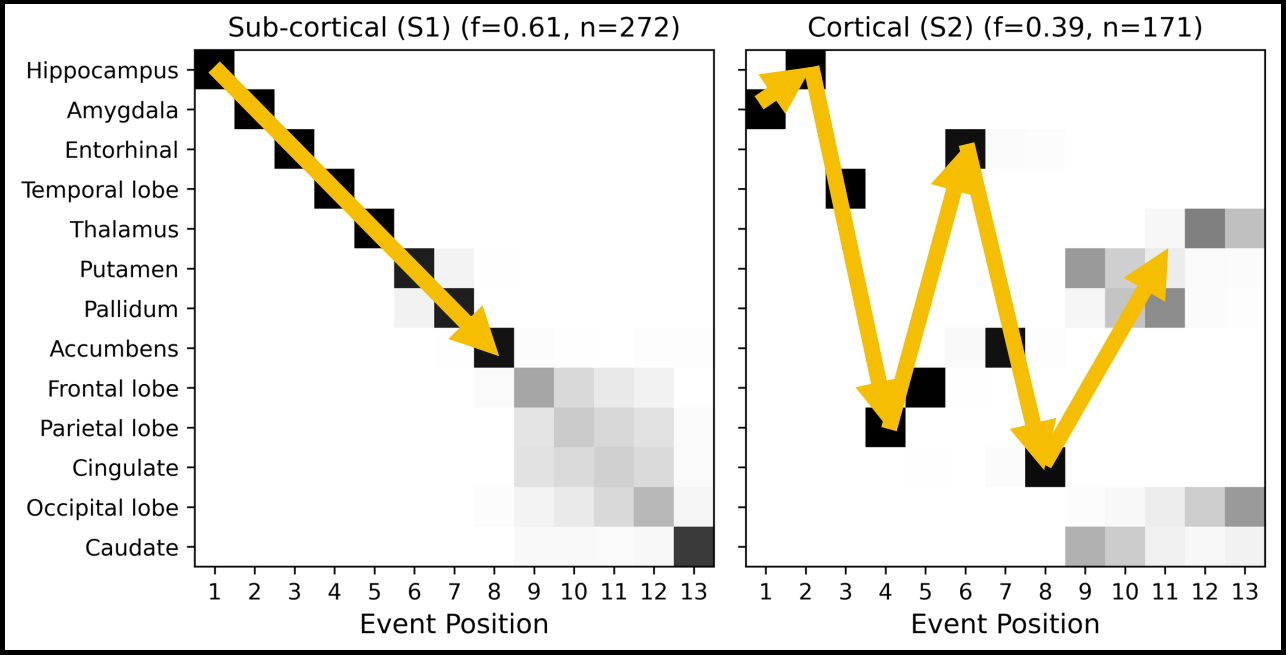


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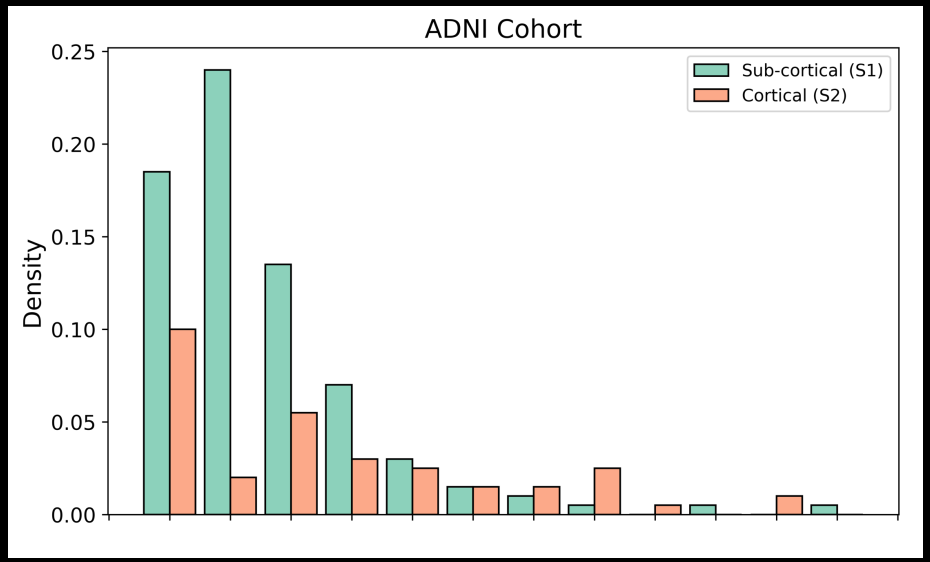


***Figure 2*: Disease stage histogram in ADNI (top) and FYN (bottom)**

# FYN trial of ADZ0530

Experiments:

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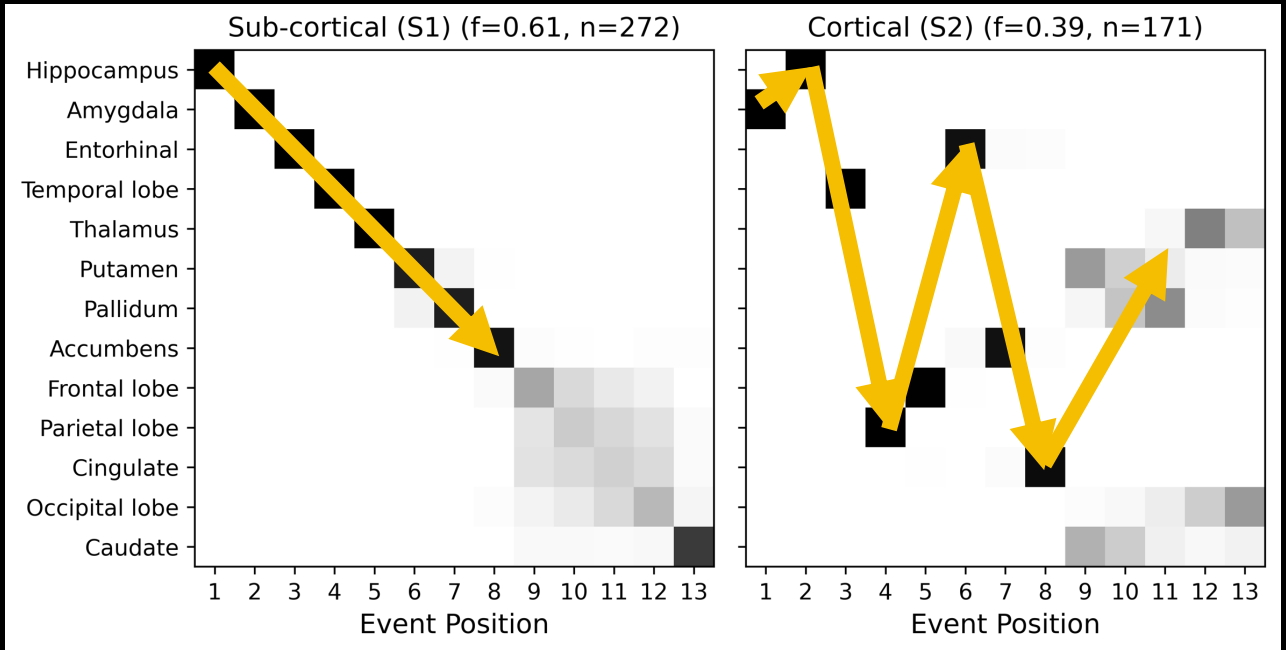
4. Analyse subgroups

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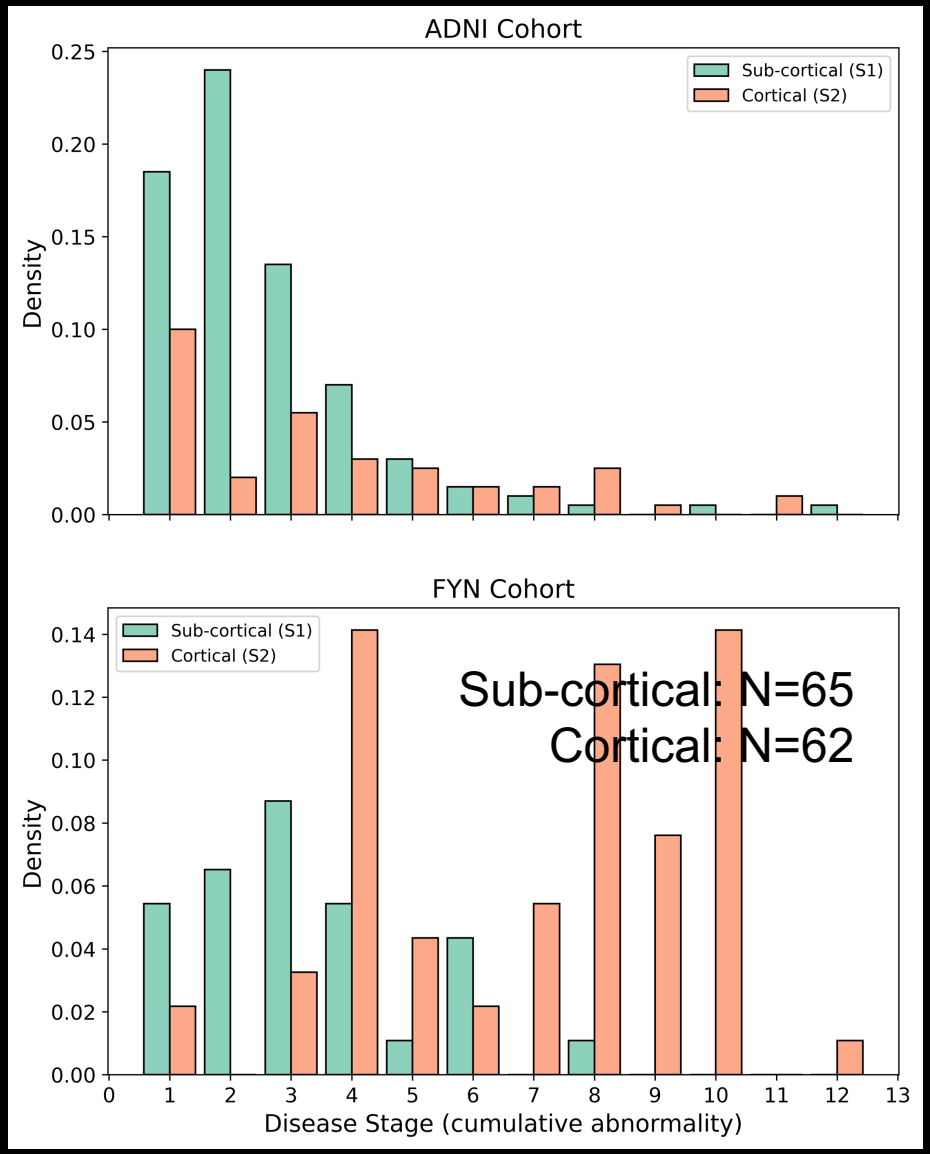


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# FYN trial of ADZ0530

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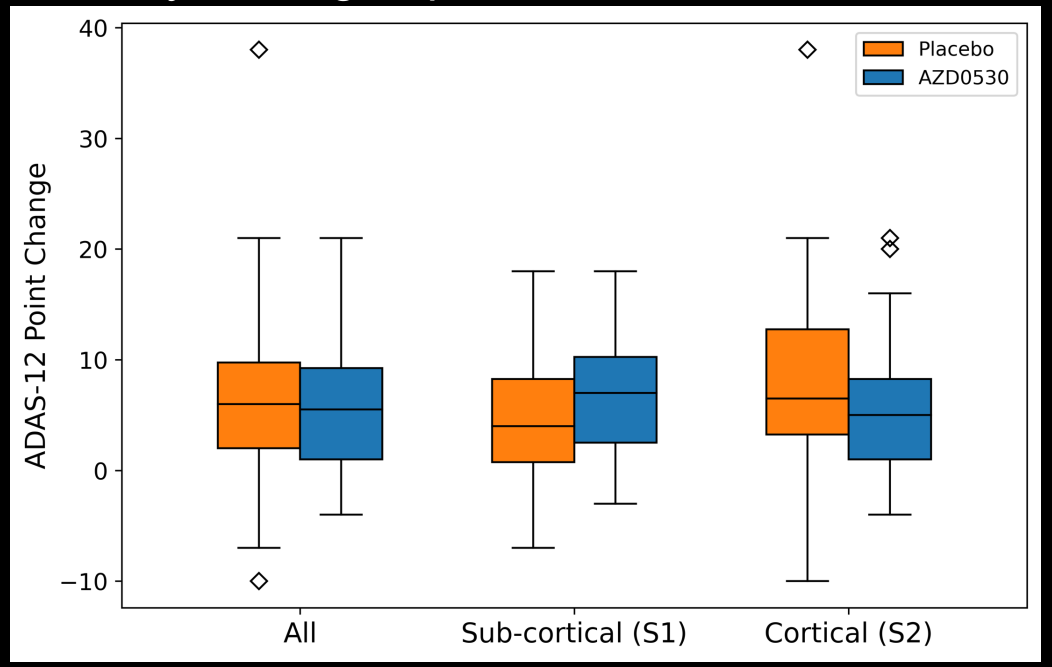


***Figure 3*: Change in ADAS-Cog 12 scores across 52-week period for whole cohort and two subtypes, separated by trial arm (greater point increase = greater cognitive decline)**

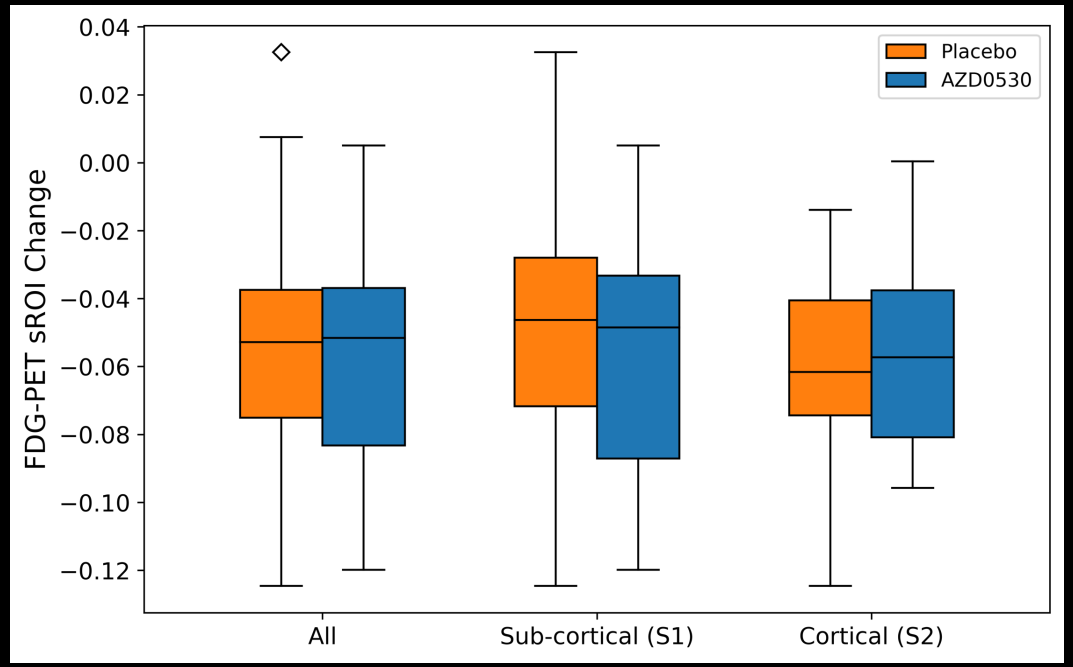


***Figure 4*: Change in FDG-PET sROI across 52-week period for whole cohort and two subtypes, separated by trial arm (greater sROI decrease = greater neurodegeneration)**

# FYN trial of ADZ0530

Experiments:

1. Build model (ADNI data)
2. Subtype & Stage trial data (BL/SC)
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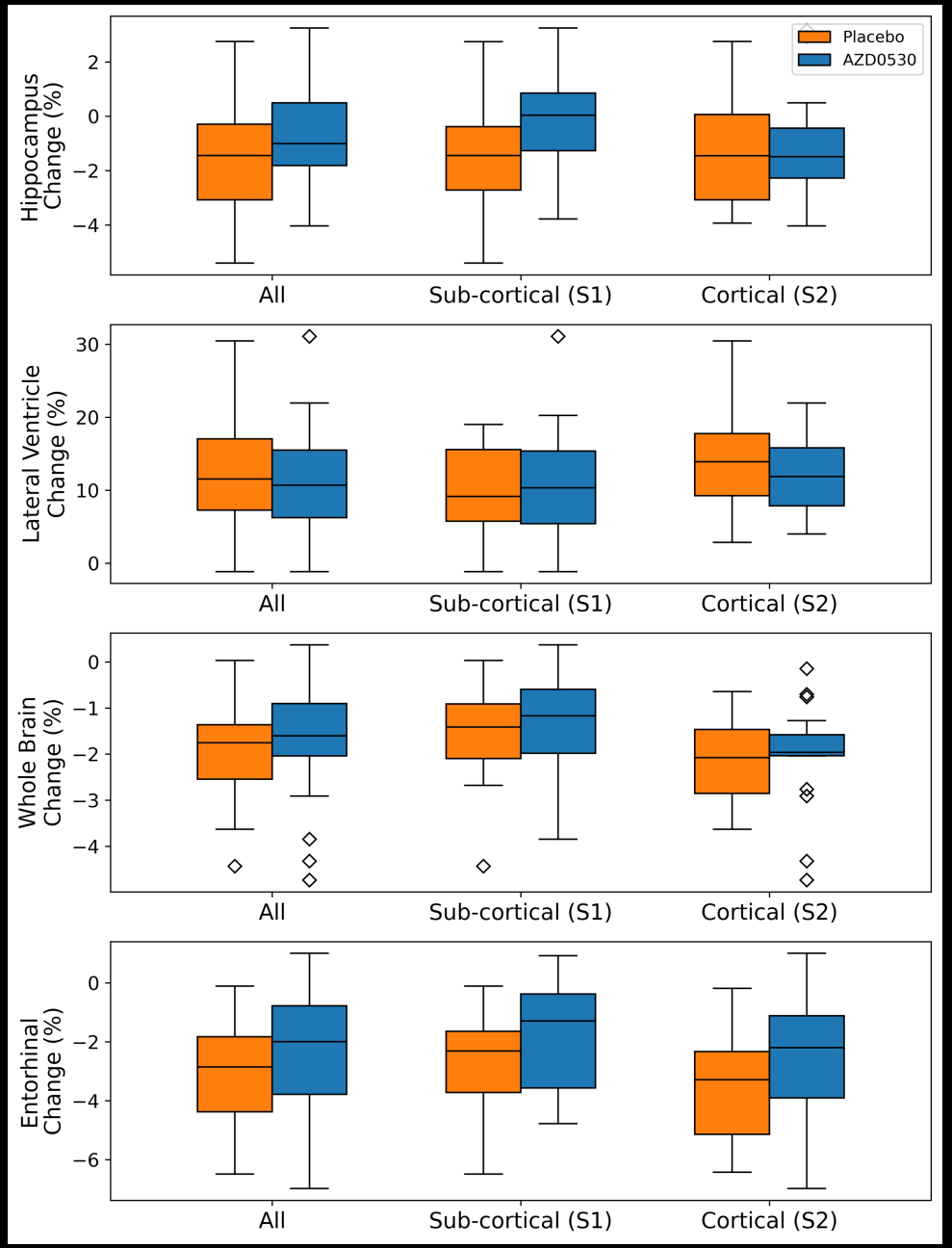


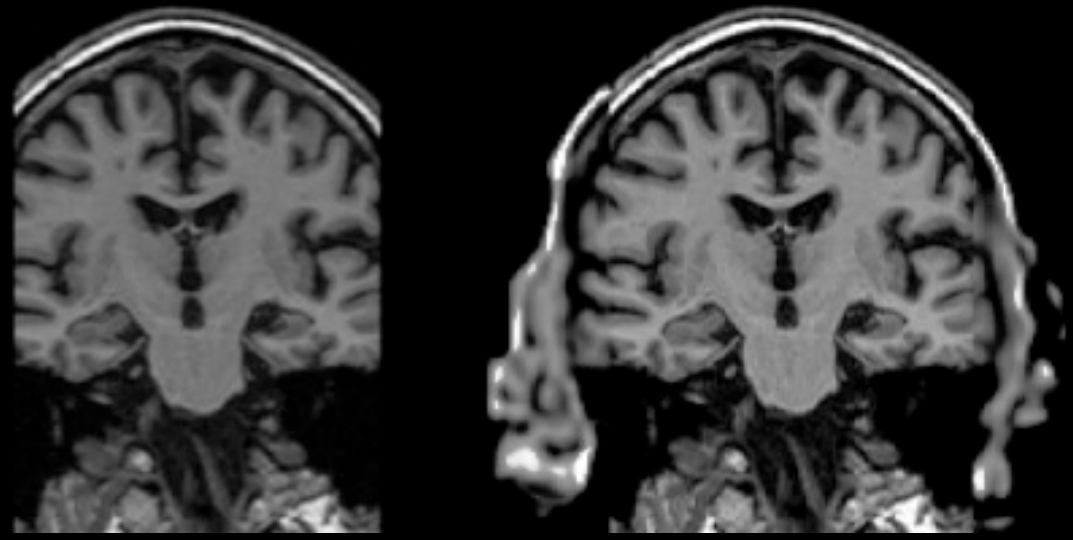

***Figure 5*: Percentage change in regional volumes across 52-week period for whole cohort and two subtypes, separated by trial arm**

# Take home messages

- Alzheimer's disease is a heterogeneous mystery
- Disease Progression Modelling can help to unravel the mystery
- DPM produces quantitative templates of AD progression that can enrich clinical trials to find *the right patients at the right time*

# Healthcare?

- Local memory clinic in England
- T2w MRI used for routine care
- T1w MRI cropped!



UCL CENTRE FOR MEDICAL IMAGE COMPUTING
DEPARTMENT OF COMPUTER SCIENCE

# My quest for supermodels and drugs

Neil Oxtoby

**Thanks to all research participants, their families, and my colleagues, in particular those in POND developing supermodels.**