Top-down and bottom-up multimodal computational models of Alzheimer's disease progression

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Progression Of Neurodegenerative Disease

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cmic
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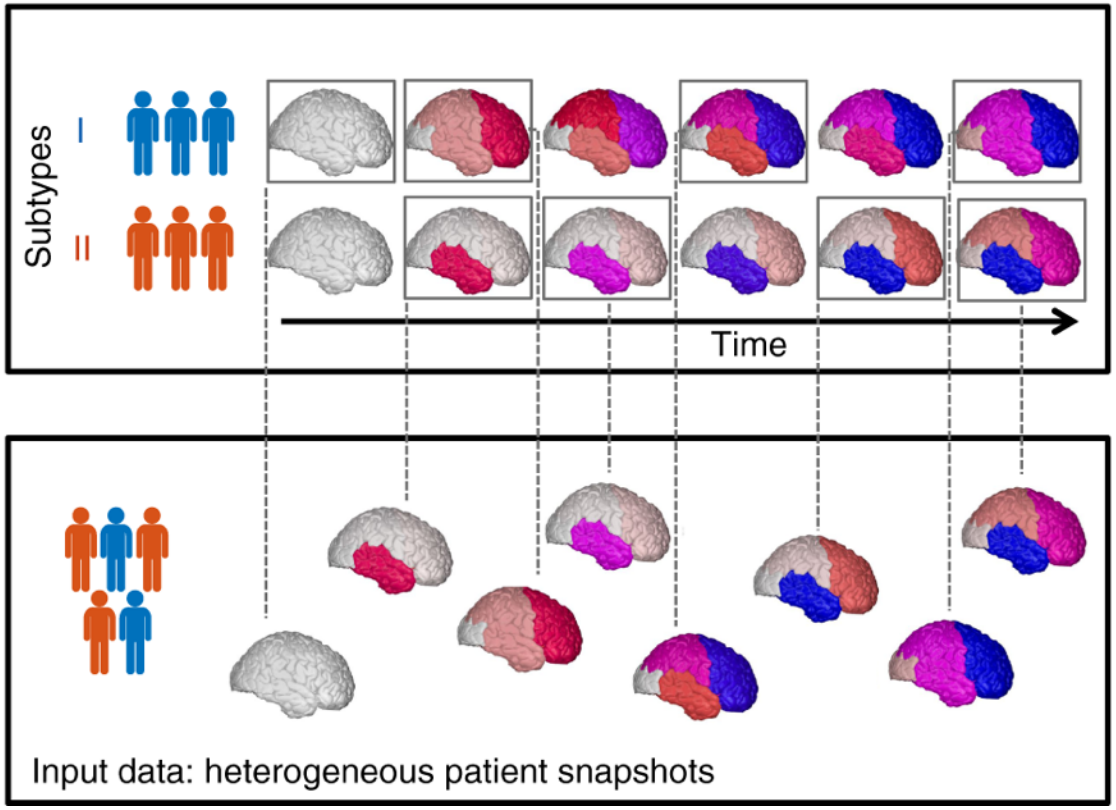
Why am I here?

Data-driven disease progression modelling

Fusing snippets of multimodal data
into quantitative signatures of progression

- Top-down (phenomenology,
  James Rowe: precision phenotype)
- Bottom-up (mechanistic)



Young *et al.* Nature Comms. 2018

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Neuroimaging *lean*:

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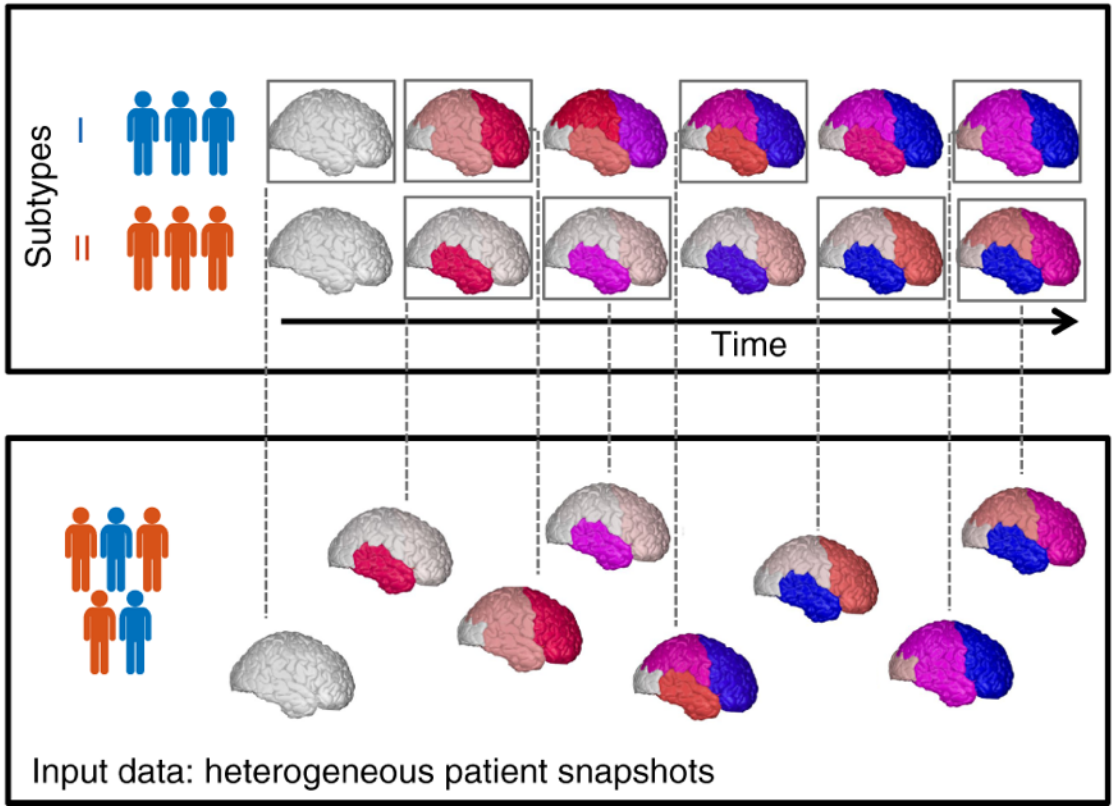
Heidi Johansen-Berg's talk

Clinical impact:

DRC
DEMENTIA RESEARCH CENTRE



Young *et al.* Nature Comms. 2018

Understanding complex systems
(brain diseases)

Top-down approaches

✓ Phenomenology: *in vivo* + clinical

✓ Amenable to data-driven…

× Mechanistic insight

Reverse engineering

Bottom-up approaches

× Requires postmortem

× Data-driven?

✓ Mechanistic insight

Forward engineering

What do we know about Alzheimer's?

- *Defined* by postmortem histopathology
  - Braak staging
- Clinical syndrome: memory ***etc.***
- *Looooong* pre-symptomatic period: decades of pathology
  - Rare familial/inherited forms
  - Risk factors: genetics, etc.
- Heterogeneity in syndrome, onset, progression, and pathology!
  - Can probe pathology *in vivo* (PET, MRI)

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: *Craig Ritchie's talk*)
  - Too late? (*wrong* time: prevention vs cure)
  - Individual variability? (*wrong* people)
  - Insufficient duration?
  - Insensitive end-points? (biology/biomarkers vs clinical benefit: *Craig Ritchie's talk*)
  - Amyloid hypothesis "wrong"? (*wrong* biology / comorbidities / multitarget strategies)

  (Salloway, CTAD 2019; Aisen, CTAD 2019)

- What has/can be done about it?

O'Connor et al. ART 2020
Oxtoby et al. medRxiv 2021

Top-down models

The Journey to
Data-driven disease progression modelling

The Journey to Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

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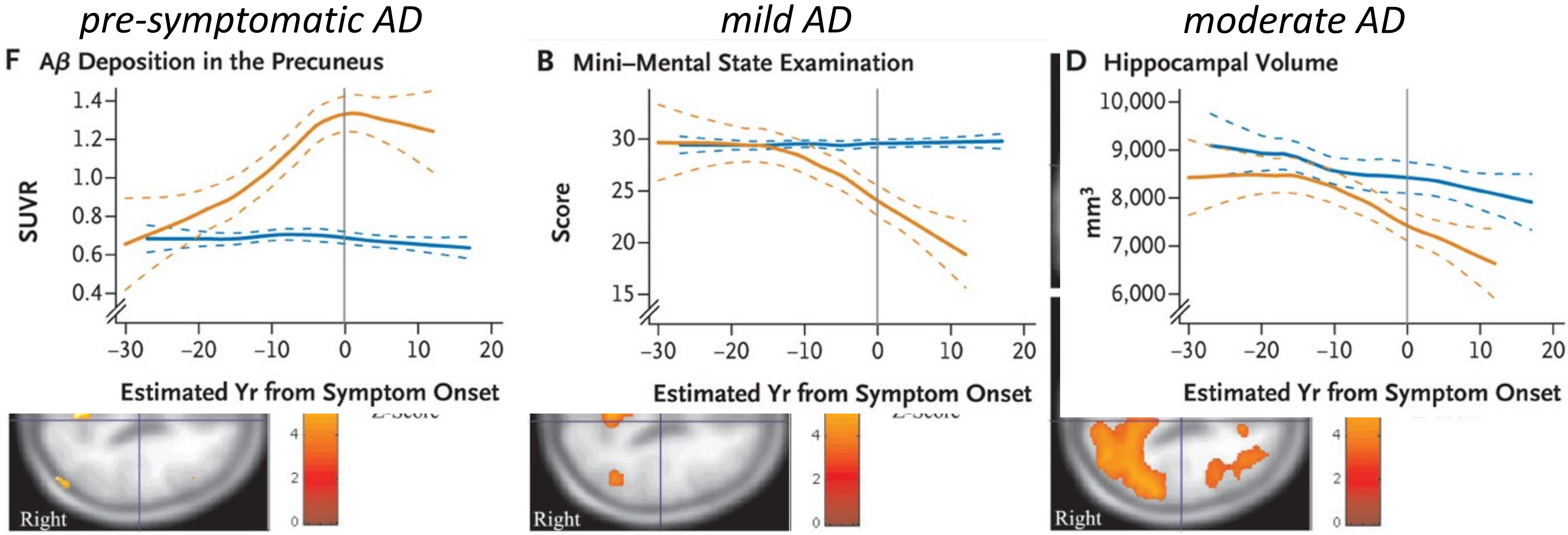
- Regression

Bateman et al. NEJM 2012
Scahill et al. PNAS 2002

- Parental age of symptom onset in dominantly-inherited AD
- T1 MRI measures of temporal atrophy: subdivided using MMSE test



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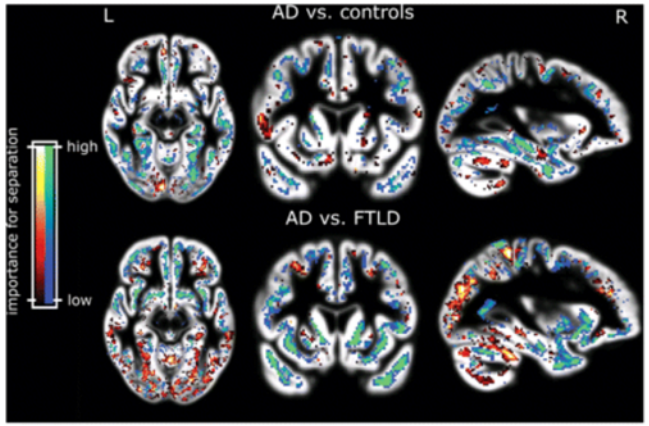
- Pattern recognition (supervised ML)

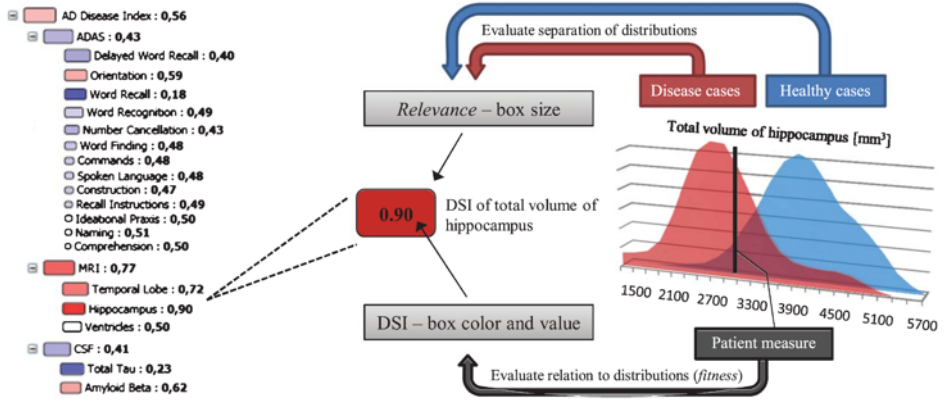
See also Zoe Kourtzi's talk

Classifying structural MRI in AD



Klöppel et al. Brain 2008

Disease State Fingerprint for AD



Mattila et al. JAD 2011

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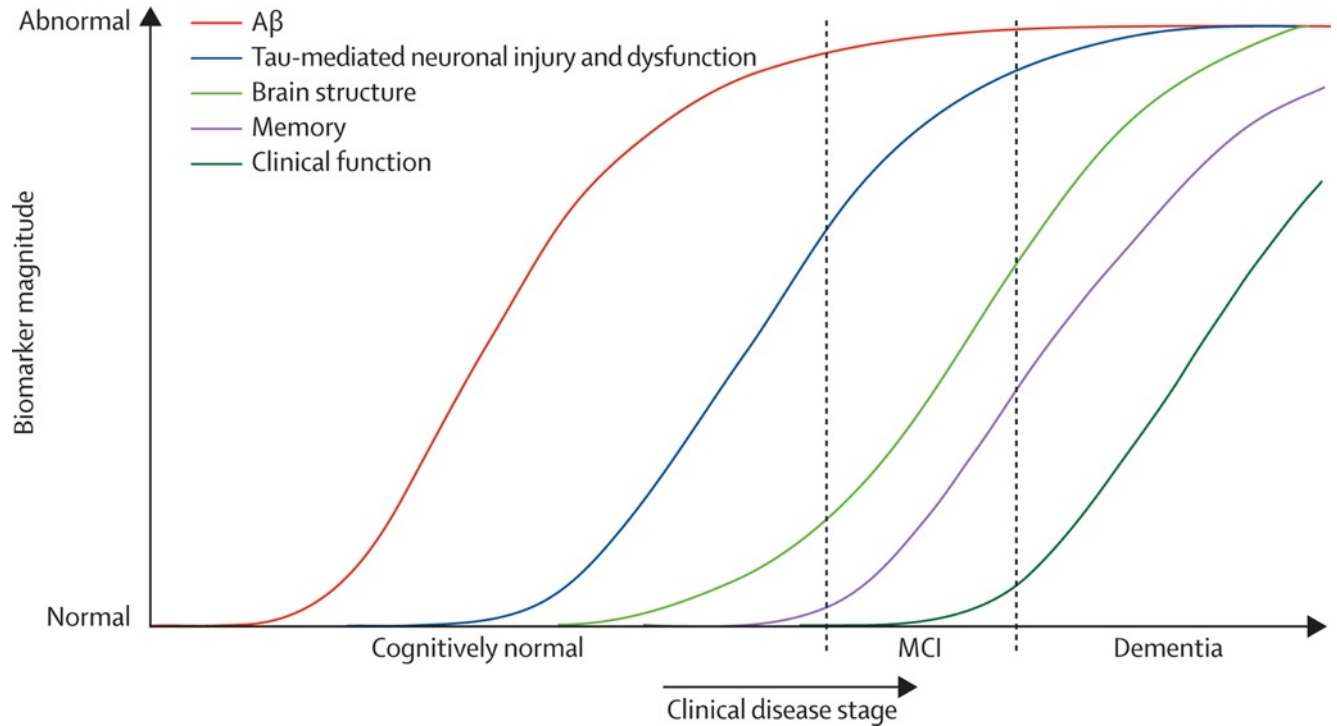

Jack et al. TLN 2010

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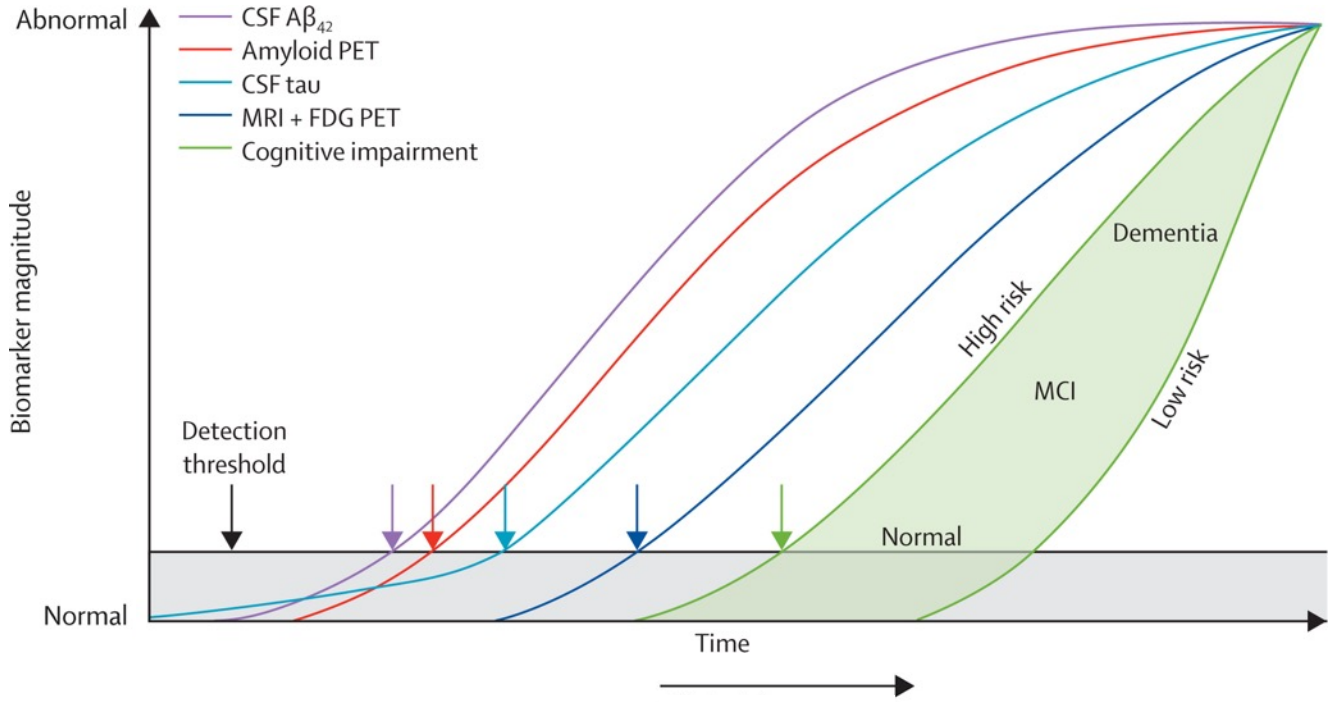

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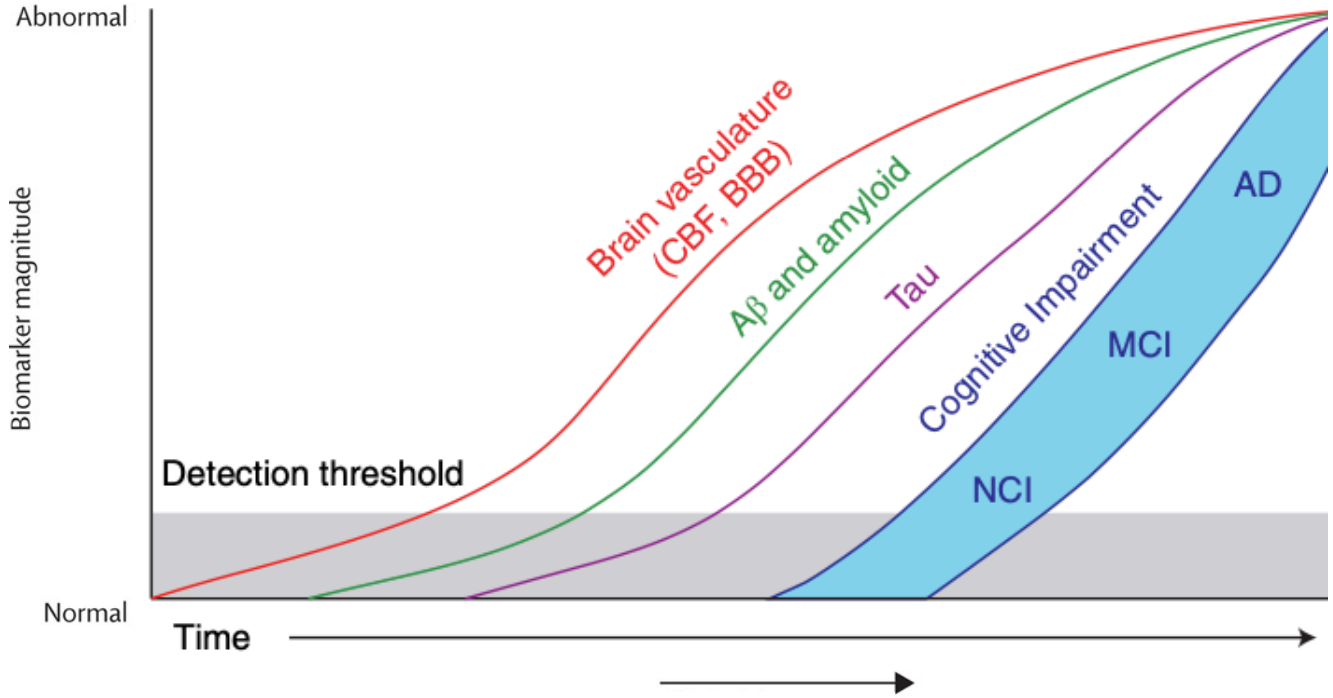

Sweeney et al. Nat Comms 2018

Laura Parkes' talk

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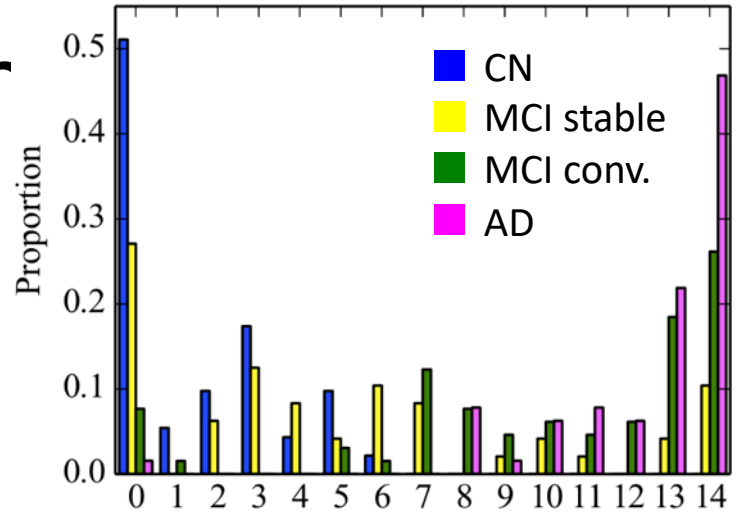
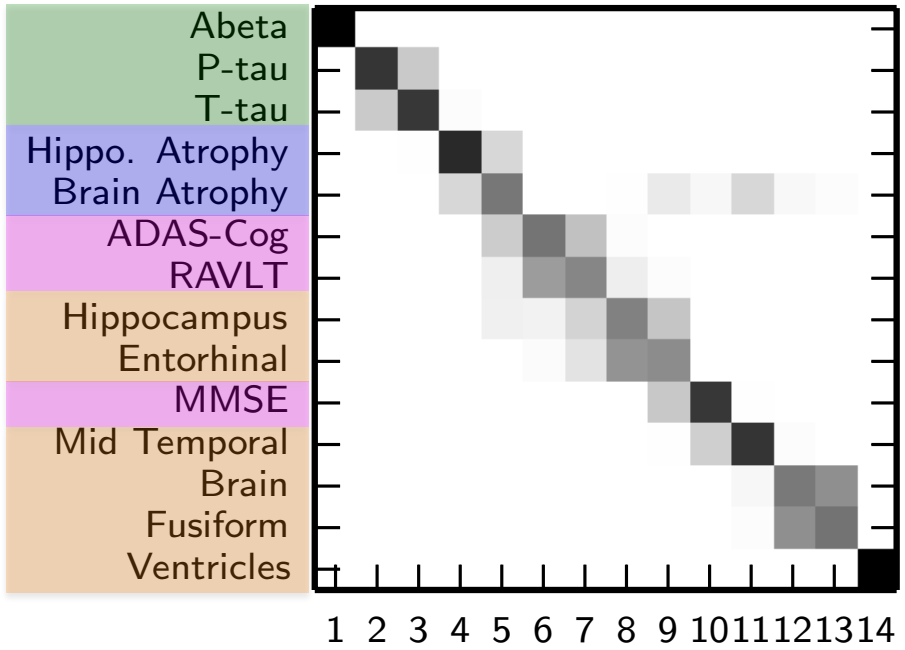
- Pseudo-time methods:
  - discrete (EBM sequencing)



Event-based model



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

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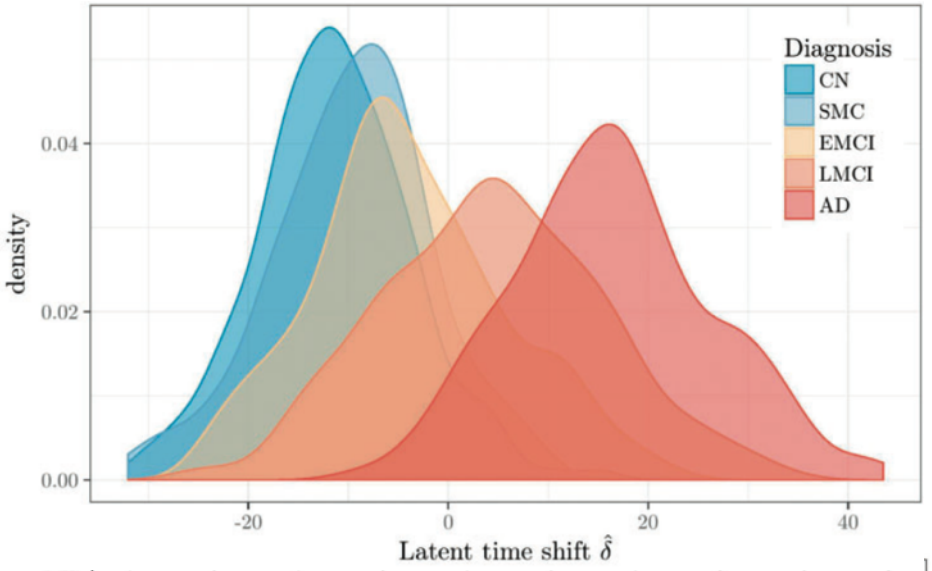

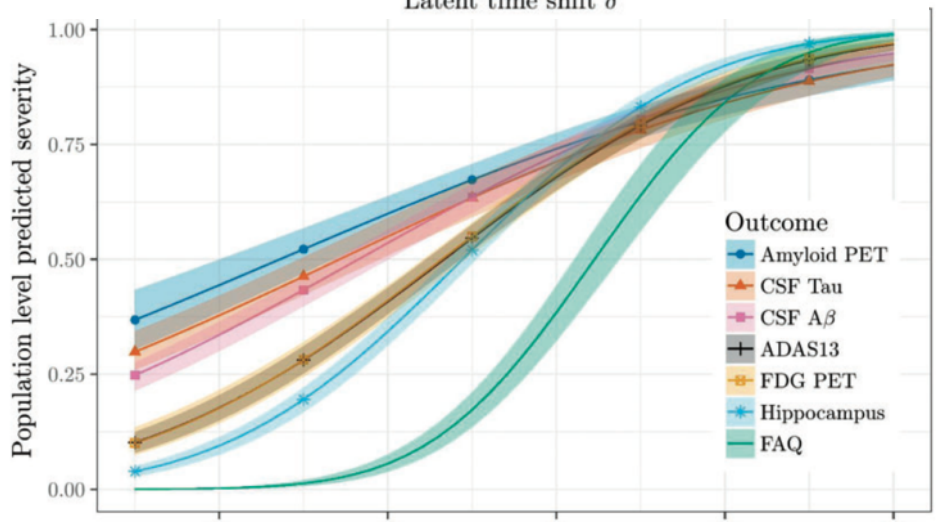

Li et al. Stat Meth Med Res 2017
Leoutsakos et al. JPAD 2016
Lorenzi et al. NIMG 2017

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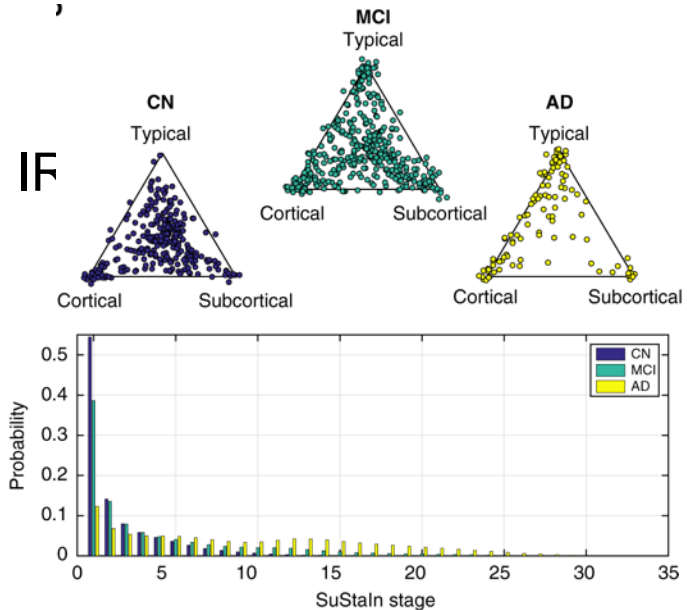
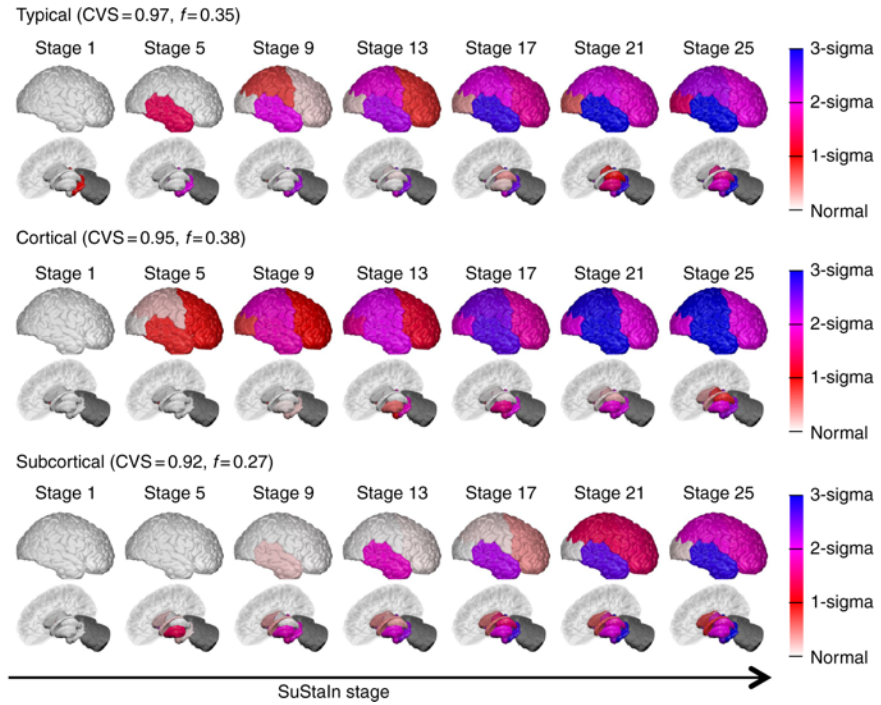
- Pseudo-time + Clustering



Subtype & Stage Inference (SuStaIn)



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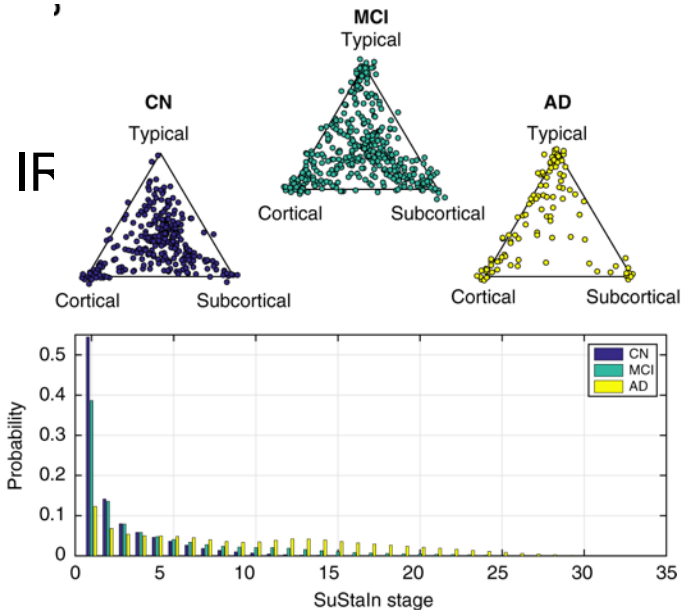
- *tau PET:*

Vogel et al. medRxiv 2020



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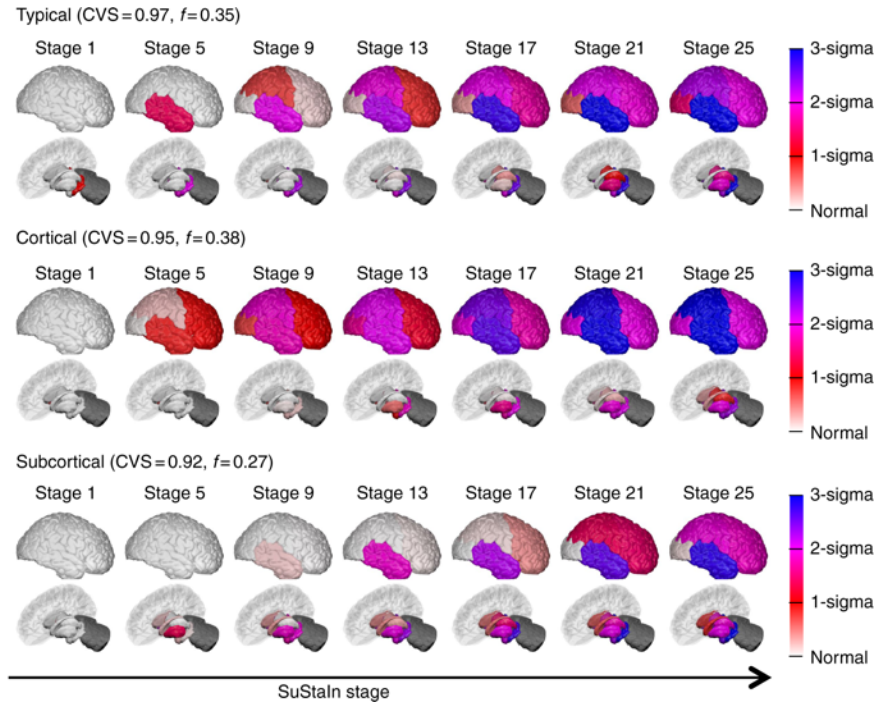


Young et al. Nat. Comms 2018

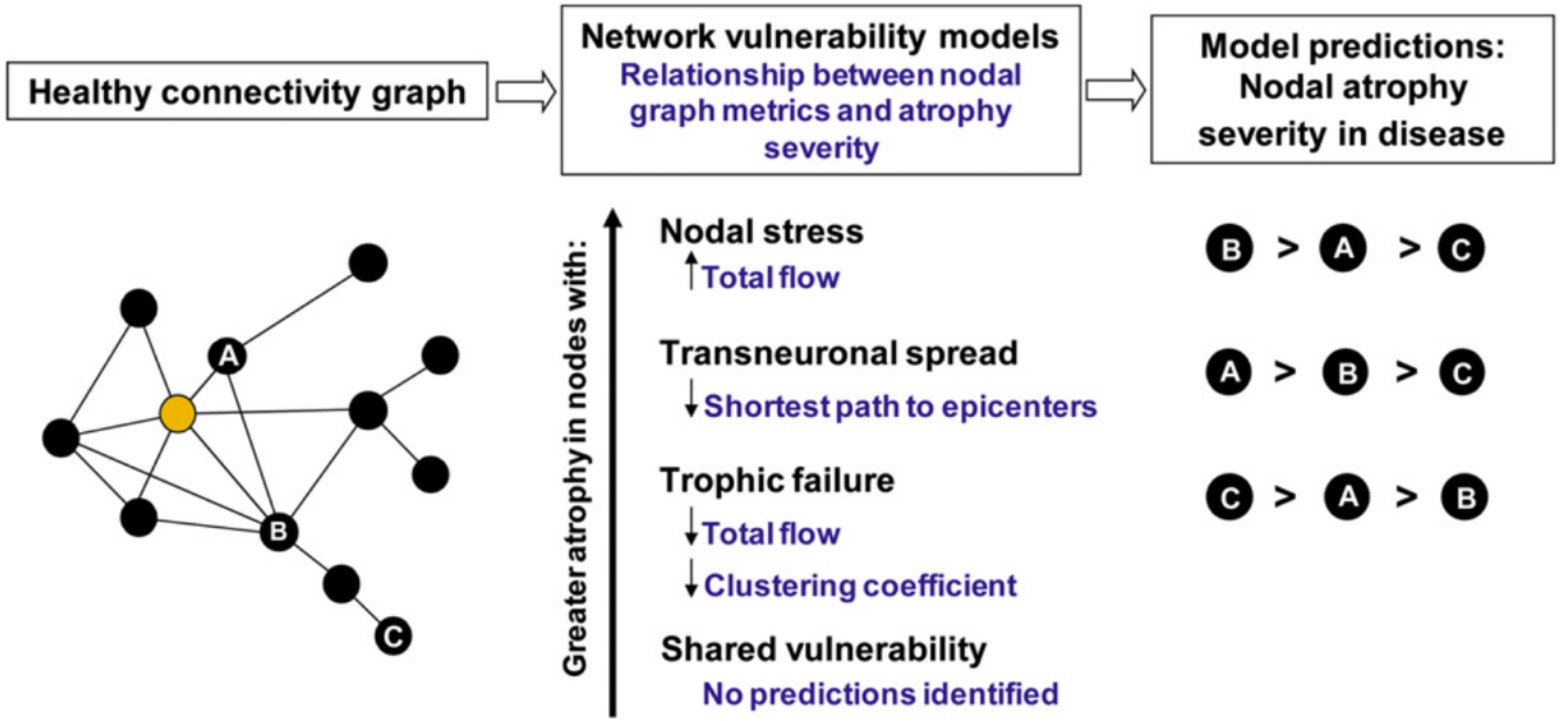
What about disease *mechanisms*?

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

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`**



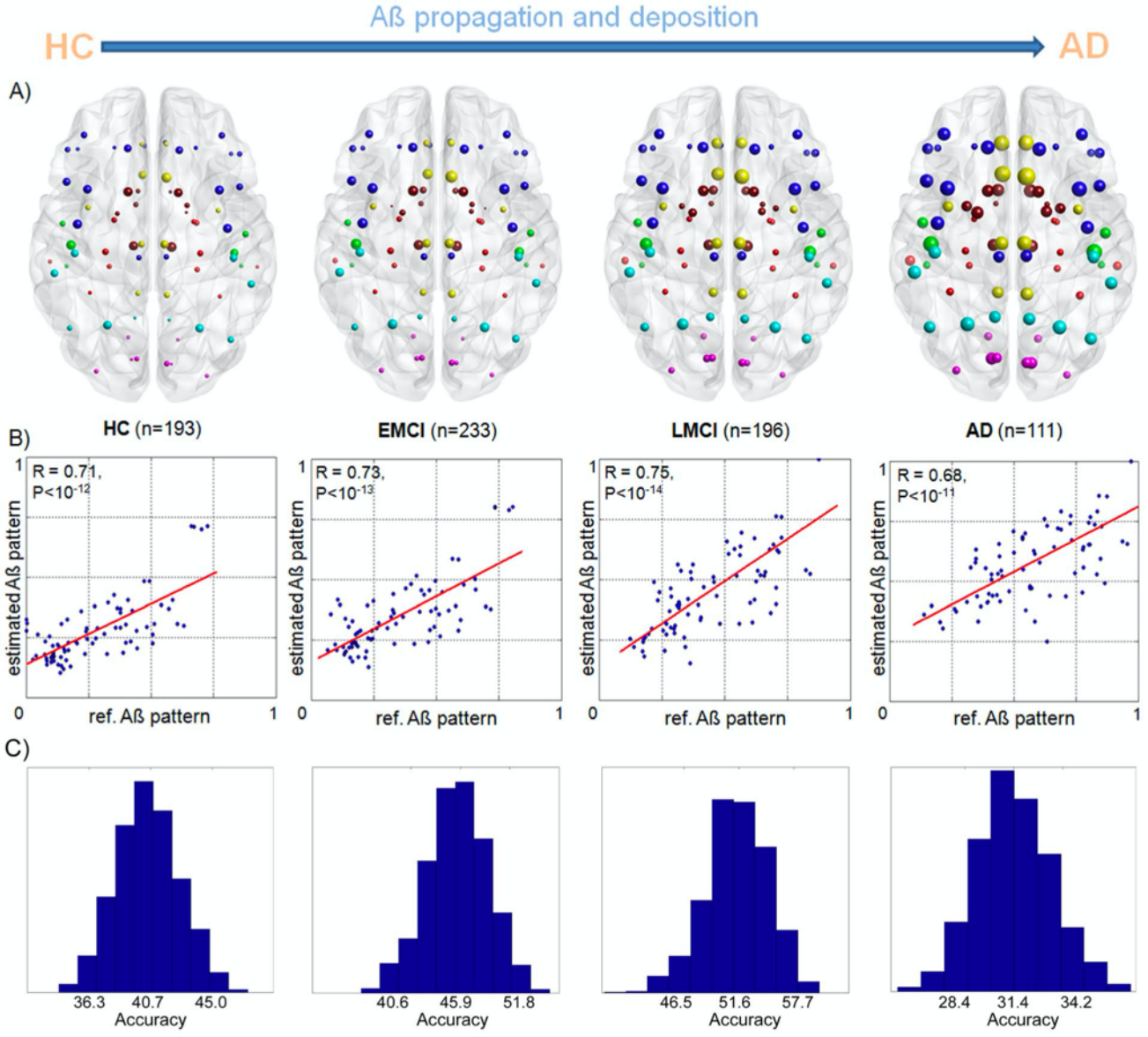
Bottom-up models

2009–2012 Hypotheses of 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

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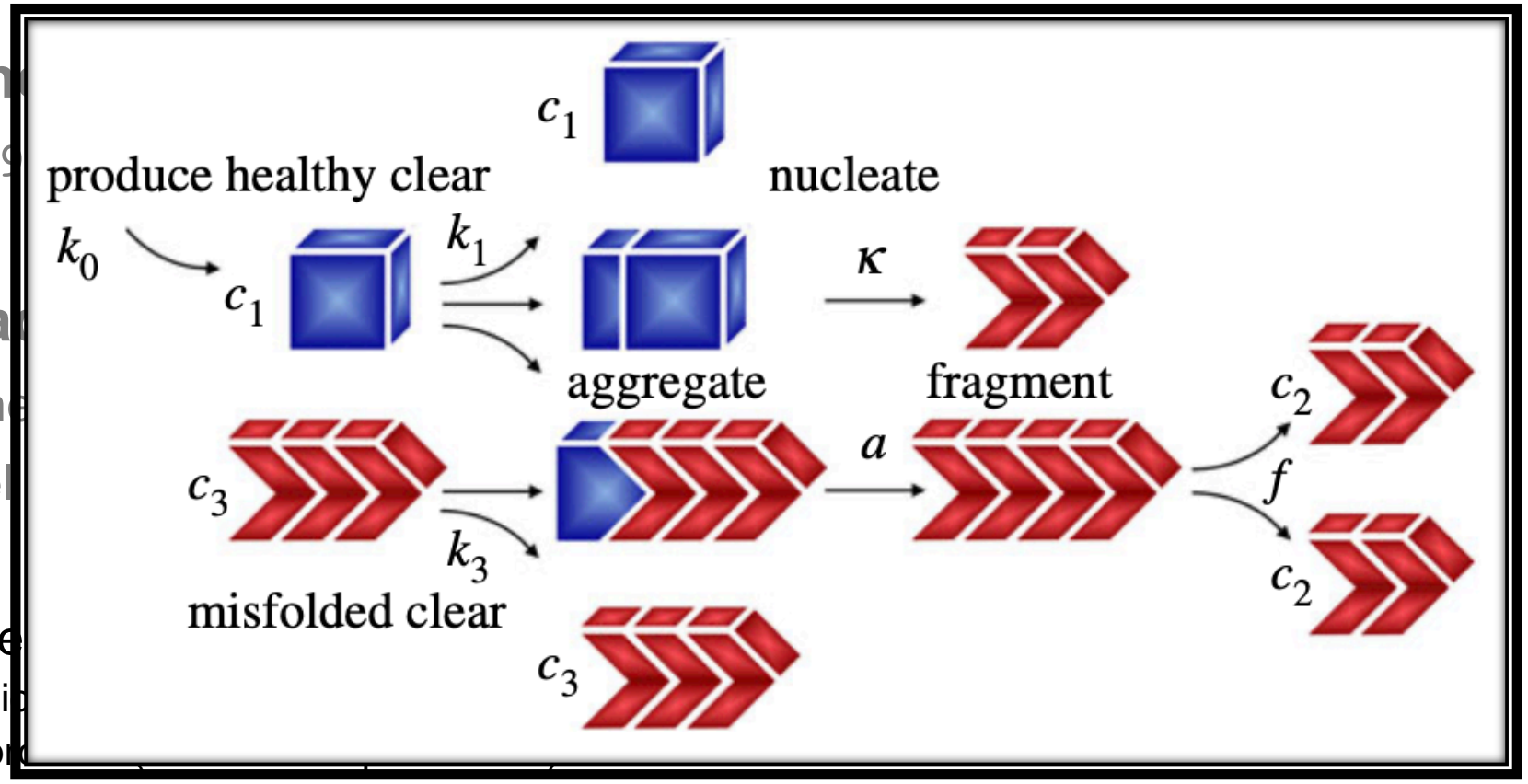
- **2018–19: Physics (**Network Spre
  - Fisher-Kolmogorov = reaction-diffusi
  - Heterodimer = normal & abnormal pr
  - Smoluchowski = stat. physics workhorse (+ size of protein aggregates)

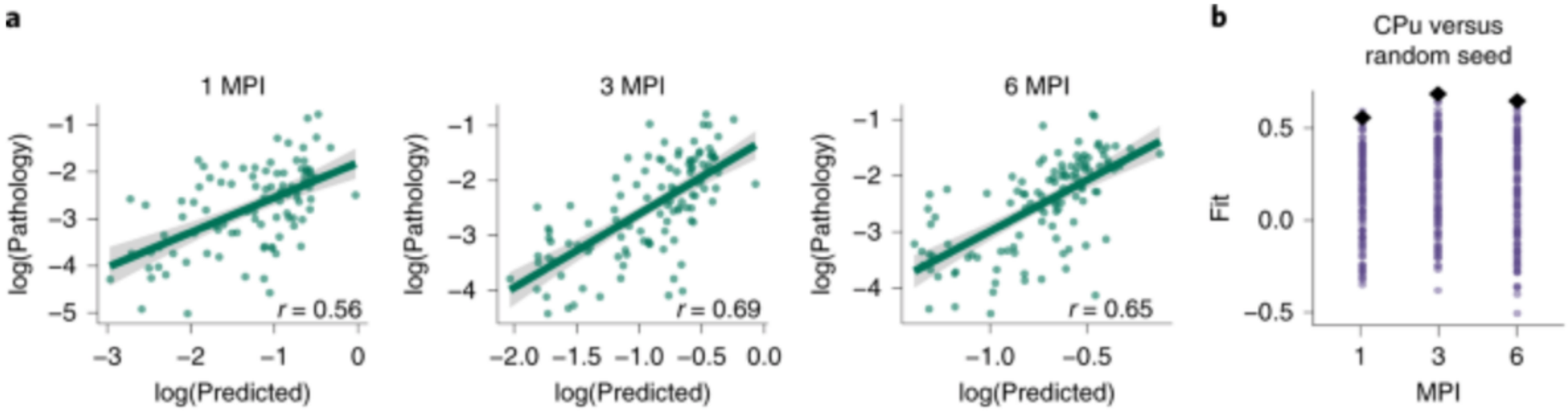


Weickenmeier et al. Phys Rev Lett 2018
Fornari et al. J.R.Soc. Interface 2019

Mouse models

- Network diffusion + selective vulnerability

Fig. 4: Network diffusion model based on anatomical connectivity explains pathological α-synuclein spread.



Henderson et al. Nature Neuroscience 2019

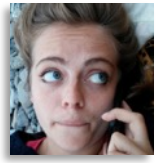
Recap

- Whirlwind tour of Data-Driven Disease Progression Modelling

Take Home (At Home?) Message:

Physics-based computational models are improving our understanding and clinical management of neurodegenerative diseases at multiple scales

Related work from the UCL POND group



- **Sara Garbarino** (former PDRA), w/ Marco Lorenzi
  - Topological progression profiles in Aging, AD, MS (`eLife 2019` + IPMI)

- **Anna Schroder** (PhD student)
  - False positive/negative connections in tractography

- **Isaac Llorente** (PhD student), Marc Busche (UK DRI @ UCL)
  - Neuroscience-informed Physics-based models (across scales)
    - *Paul Matthews' Conceptual Challenge 4 (mechanisms)*

- **Hanyi Chen** (senior PDRA), Andre Altmann
  - E-DADS project: early detection (with COMBINE lab at UCL)
    - *Paul Matthews' Conceptual Challenge 1 (distinguish early)*

- **Neil Oxtoby** (UKRI Future Leaders Fellowship), Cameron Shand…
  - Individualised AI/ML/modelling for Medicine (Alzheimer's; Clinical Trials; Mechanisms)

The Alzheimer's Disease Progression Of Longitudinal Evolution Challenge

Predictive modelling challenge for Alzheimer's disease

tadpole.grand-challenge.org

TADPOLE SHARE: tadpole-share.github.io

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Progression Of Neurodegenerative Disease

EuroPOND

ADNI

Alzheimer's Society
United Against Dementia

alzheimer's association

Alzheimer's Research UK
The Power to Defeat Dementia

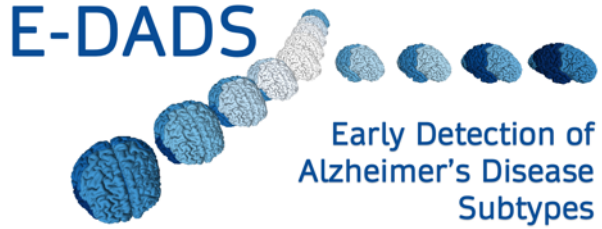
Marinescu et al. arχiv:1805.03909
arχiv:2002.03419

Acknowledgements

- UCL POND pond.cs.ucl.ac.uk
  Prof. Danny Alexander, et al.

- EuroPOND europond.eu

- E-DADS e-dads.github.io



- Collaborators, Data providers, Volunteers (patients & families)

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