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UCL

Heterogeneity in Preclinical Alzheimer's Disease Trial Cohort Identified by Image-based Data-Driven Disease Progression Modelling, a.k.a.

Subtype and Stage Inference

in



Cameron Shand, Pawel Markiewicz, David Cash, Daniel Alexander,
Michael Donohue, Frederik Barkhof, **Neil Oxtoby**

UCL Centre for Medical Image Computing
UCL Queen Square Institute of Neurology
USC Keck School of Medicine
Amsterdam University Medical Center

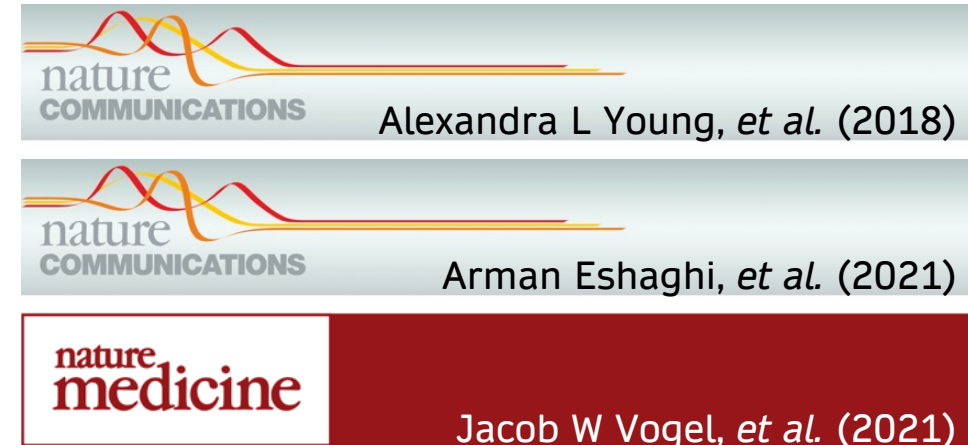


Disclosures: Some of us (or our spouses) benefit either financially or academically from interactions with pharmaceutical and related companies.



Heterogeneity vs Clinical Trials

- Detect heterogeneity at screening?
 - Syndrome is too simplistic, especially for prodromal/mild trials
 - Extremely low trial success rates, despite imaging/biomarker screening
- Spatiotemporal subtypes of pathology discovered from observational data using **SuStaln**
- SuStaln: **Sub**type and **Stage Inference**
 - *Clustering that is not confounded by disease stage/severity*
 - Individualised, fine-grained, quantitative inference



Young et al., 2018 *Nature Communications*

This work

- **Aims:**
 - 1) **Detect heterogeneity in A4**
 - 2) **Make model-based predictions**
 - A⁴ = Anti-Amyloid treatment in Asymptomatic Alzheimer's
 - Solanezumab (Eli Lilly)
- **Experimental Setup:**
 - Model trained on A4: Screening T1w MRI (cross-sectional)
 - N=1240 amyloid-positive, cognitively normal, elderly
 - Predictions for A4: model-based stratification of ADNI (longitudinal)
 - N=731 (5 MCI) matching A4 inclusion criteria

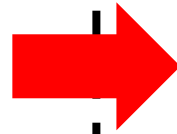
Our study: Experiment

Screening

Train SuStaln (sc)



Stratify ADNI (bl)

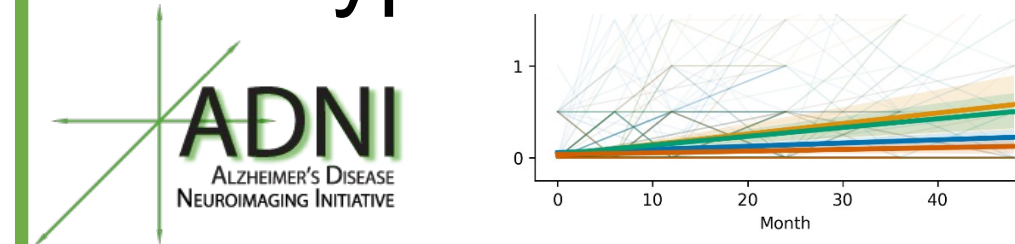


A4 Trial: ~4 years

Forecasts for A4



Subtype outcomes



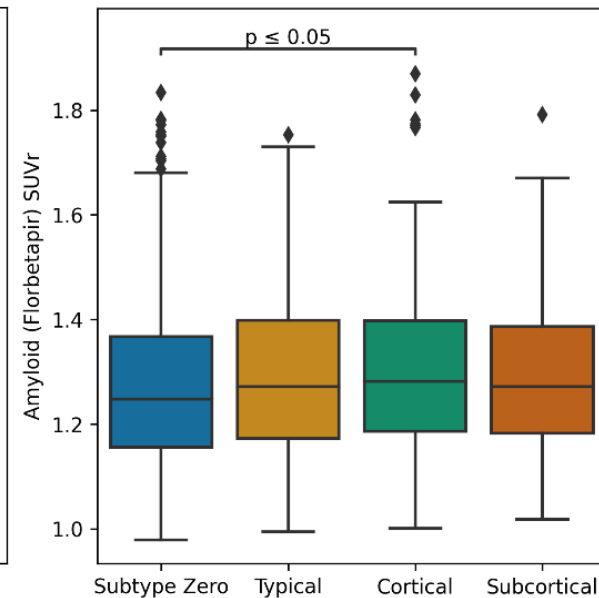
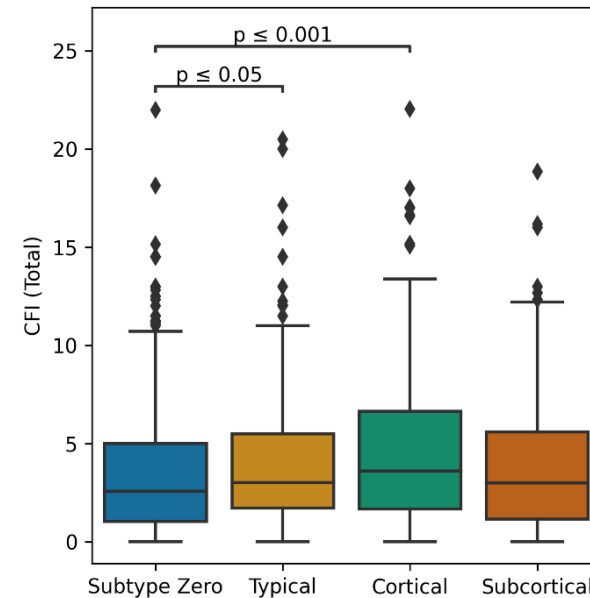
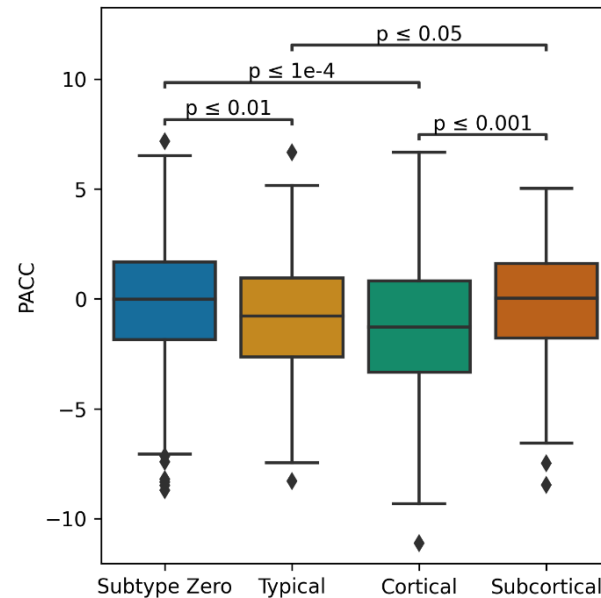
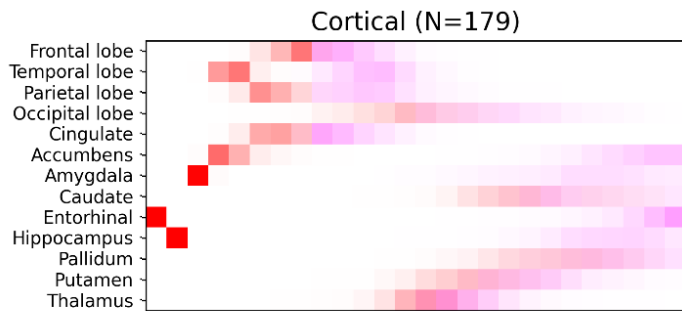
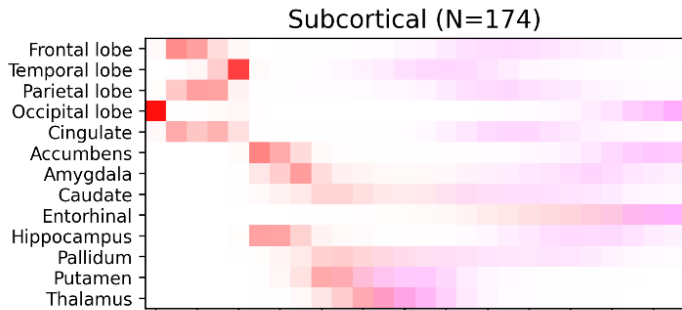
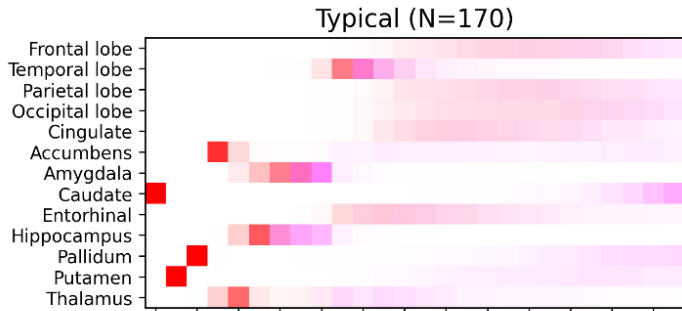
Results: trained model (3 subtypes)



z=1 2

- 523 (42%) subtype-able
- 33/34/33% split
- Subtle differences at screening: PACC, CFI, Florbetapir SUVR
- No differences in demographics, genetics

Typical	80	38	12	14	7	6	5	5	1	2													
Cortical	53	29	24	18	20	8	5	7	4	2	2		2					2	3				
Subcortical	47	35	21	20	12	12	4	7	4	2	1	2	2		2		1			1		1	
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22



Thanks








- A4: releasing screening data
- ADNI: eternally grateful
- Co-authors

medRxiv



BMJ Yale

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