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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 A The A4 Study

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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 <u>SuStaln</u>
- SuStaIn: Subtype 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:

Detect heterogeneity in A4 Make model-based predictions

- $A^4 = \underline{A}$ nti- \underline{A} myloid treatment in \underline{A} symptomatic \underline{A} lzheimer'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

https://doi.org/10.1101/2023.02.07.23285572

Our study: Experiment

Screening

A4 Trial: ~4 years



Results: trained model (3 subtypes)

The A4 Study • 33/34/33% split NOW IS THE TIME • z=1Typical (N=170) • Frontal lobe Temporal lobe Parietal lobe Occipital lobe Typical - 80 38 12 14 7 6 5 5 Cingulate Accumbens Cortical -53 29 24 18 20 8 2 2 5 2 2 Amygdala Caudate Subcortical -47 35 21 20 12 Entorhinal Hippocampus Pallidum 10 11 12 13 14 15 16 17 18 19 20 21 22 8 9 Putamen Thalamus Stage Subcortical (N=174) $p \le 0.05$ $p \le 0.001$ Frontal lobe 25 Temporal lobe p ≤ 1e-4 p ≤ 0.05 Parietal lobe 10 Occipital lobe -≤ 0.01 Cingulate p ≤ 0.001 Accumbens 20 Amygdala Caudate Entorhinal Hippocampus CFI (Total) Pallidum Putamen PACC Thalamus 0 Cortical (N=179) 10 Frontal lobe Temporal lobe Parietal lobe -5 Occipital lobe Cingulate Accumbens Amygdala Caudate Entorhinal -10Hippocampus · Pallidum Putamen Subtype Zero Typical Cortical Subcortical Subtype Zero Typical Cortical Thalamus

1 3 5 7 9 11 13 15 17 19 21 23 25

SuStaln Stage

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



3

Results: forecasting model



Thanks

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

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