Post hoc data-driven subgroup analysis of the A4 Study: spatiotemporal atrophy predicts differential treatment response to solanezumab

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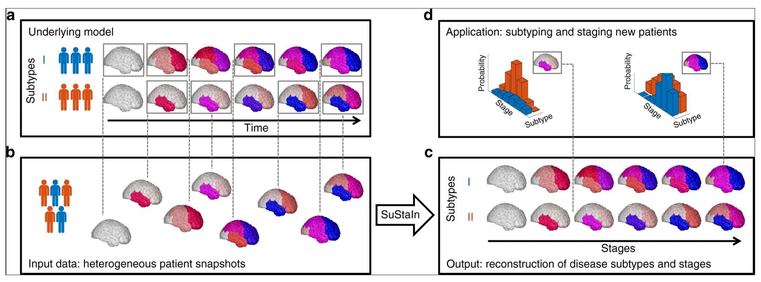
Background

- The A4 Study was a Phase 3 secondary prevention trial of solanezumab in preclinical Alzheimer's[1]
- Subtype & Stage Inference[2] (SuStaIn) is a biomarker clustering algorithm that uniquely disentangles severity from subtype, e.g., finding subtypes of AD progression having unique spatial profiles of atrophy.
- Hypothesis: spatial atrophy may have trial enrichment capabilities

Experimental Design

1. *post hoc* subgroup analysis of A4 trial
2. Subgroups are data-driven: SuStaIn ***model of AD atrophy subtypes*** using T1w MRI from ADNI

Disease Progression Modelling



SuStaIn[2] (Subtype and Stage Inference algorithm) finds one or more temporal progression patterns from cross-sectional data, uncovering disease progression subtypes

Methods

Computational Model of AD atrophy

Software: pySuStaIn[3]

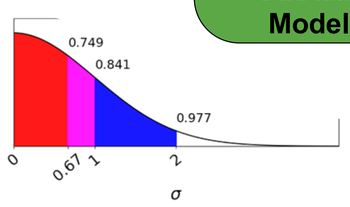
Training Data:

- 3T T1w MRI => FreeSurfer 7.1.1 => 13x2 ROI volumes
- **N = 1505** Cases: Aβ+
  - 190 CN, 951 MCI, 364 AD
- 435 Controls: Aβ− CN
  - Covariate adjustment (age, sex, education, intracranial volume)
  - z-scoring

3T MRI + FreeSurfer 7.1.1 → Covariate adjustment, z-scoring → Cross-validation to select model → Trained SuStaIn Model

Model hyperparameters:

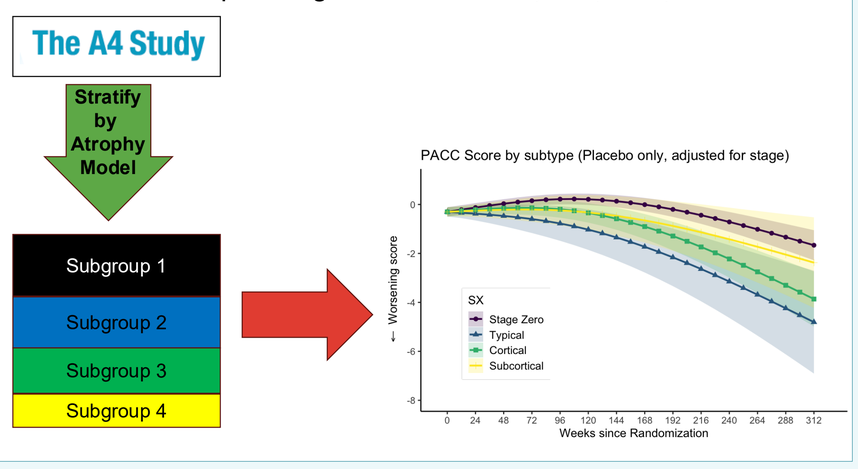
- Atrophy events: z = 0.67, 1, 2
- Number of subtypes determined by 10-fold cross-validation



Test Data: A4 trial (N = 1167)

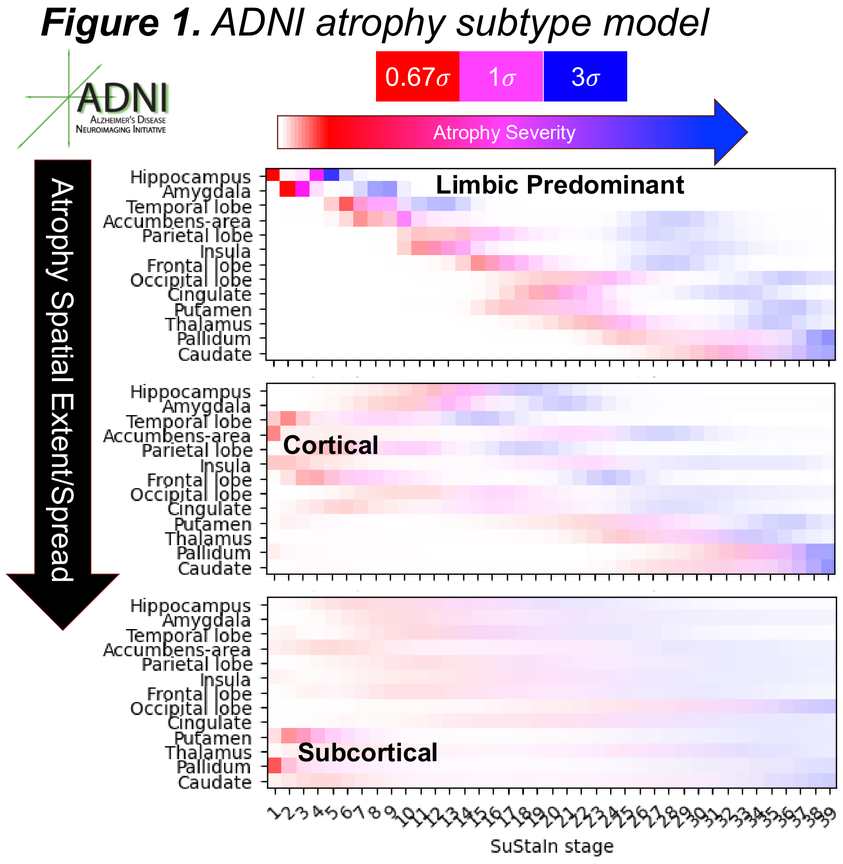
SAP: A4 primary analysis, stratified by SuStaIn subtype

- Natural cubic spline regression[4]: PACC, CFI, ADL, CDR-SB



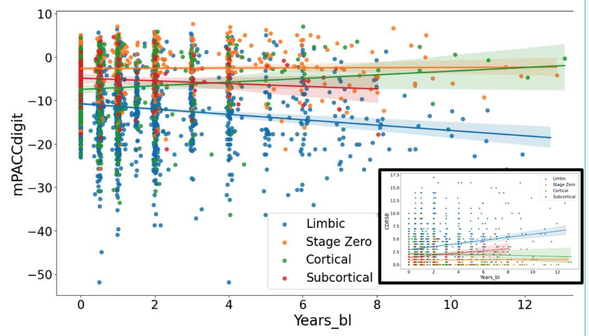
Result 1: Computational Model of AD Atrophy Subtypes

Figure 1. *ADNI atrophy subtype model*



- 3 atrophy subtypes:
  Limbic (48%)
  Cortical (24%)
  Subcortical (4%)
- 1 minimal atrophy subgroup:
  Stage Zero (25%)
  - all z-scores < 0.67

DX	Stage Zero 379 (26%)	Limbic 725 (50%)	Cortical 308 (21%)	Subcortical 26 (2%)
A+ CN (13%)	**69 (30%)**	19 (4%)	32 (11%)	4 (12%)
MCI (63%)	291 (65%)	428 (58%)	**213 (70%)**	**18 (72%)**
AD (24%)	19 (5%)	**278 (37%)**	63 (19%)	4 (15%)
Age	73 ± 7	74 ± 7	71 ± 10	73 ± 7
Edu	16 ± 3	.	.	.



Result 2: A4 trial outcomes by subgroup *Sx*

Figure 2A. *Sx: A4 vs ADNI*

Similar distribution of Sx between A4 and ADNI

DX	Stage Zero	Limbic	Cortical	Subcortical
A+ CN A4	669 (58%)	165 (14%)	280 (24%)	32 (3%)
A+ CN ADNI	69 (56%)	19 (15%)	32 (26%)	4 (3%)
Age A4 Age ADNI	72 ± 5 74 ± 6	74 ± 5 74 ± 5	72 ± 5 75 ± 6	72 ± 5 76 ± 2
Edu A4 Edu ADNI	16 ± 3 16 ± 2	16 ± 3 16 ± 3	17 ± 3 17 ± 3	16 ± 3 17 ± 3

$\chi^2 = 0.37$
dof = 3
p = 0.95

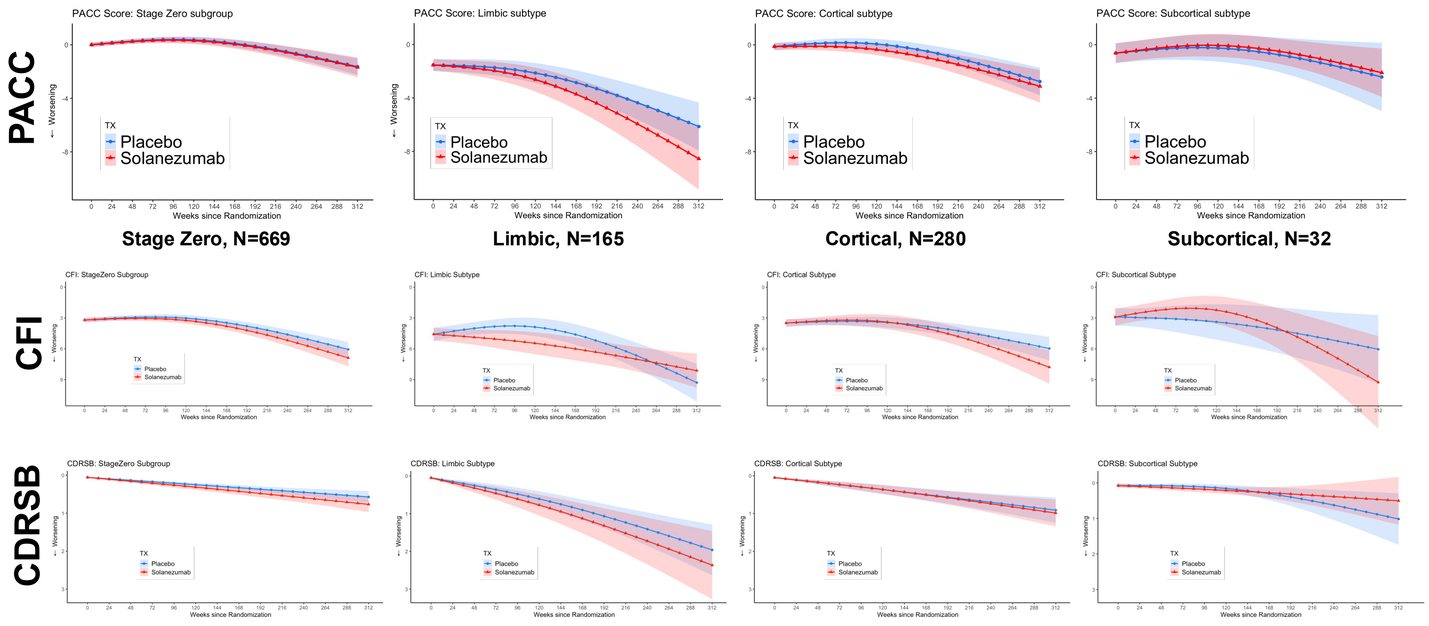
Figure 2B. *A4: Sx by Tx*

Placebo and Sola arms were balanced by Sx

Subgroup	Placebo	Sola
Stage Zero	57% N=331	60% N=338
Limbic	15% N=85	14% N=80
Cortical	26% N=150	23% N=130
Subcortical	3% N=16	3% N=16

$\chi^2 = 1.4$
dof = 3
p = 0.7

Figure 3. *Trial outcomes*



Conclusions

- **MRI-based data-driven atrophy subtypes model** identifies clinical heterogeneity:
  - Limbic subtype showed more aggressive decline
  - Subcortical subtype showed mild decline
  - Cortical subtype: no decline
- **Model-based stratification of A4** Phase 3 trial of solanezumab **suggests that:**
  - Arms were balanced by subtype
  - Subcortical subtype trended towards positive treatment efficacy (PACC, CDRSB)
- **Heterogeneity could confound trials if not accounted for in design, but disease progression modelling could help mitigate this in future trials.**

References

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[3] L.M. Aksman & P.A. Wijeratne, et al., SoftwareX 16, 100811 (2021); DOI: 10.1016/j.softx.2021.100811
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