

Decoding Heterogeneity in A4: Explainable ML Identifies Solanezumab-Responsive Subgroups in Preclinical AD

Jan Sedway¹, Bessi Qorri¹, Mike Tsay¹, Christian Cumbaa¹, Paul Leonchyk¹, Larry Alphs¹, Luca Pani^{2,3}, Joseph Geraci^{4,5}

¹ NetraMark Corp., Toronto ON, Canada; ² Miller School of Medicine, University of Miami, FL USA; ³ University of Modena and Reggio Emilia, Modena, Italy; ⁴ Department of Pathology and Molecular Medicine, Queen's University, Kingston ON, Canada; ⁵ Arthur C. Clarke Centre for Human Imagination, School of Physical Sciences, University of California San Diego, CA USA

KEY FINDINGS

- Explainable AI uncovered clinically interpretable responder subgroups within a negative Phase 3 trial
- Responders demonstrated greater regional brain reserve (right amygdala / right superior temporal cortex) and stronger baseline psychomotor speed / attention
- Subgroups showed large treatment effects (Cohen's d up to 1.52) with minimal placebo-associated benefit
- Suggests anti-amyloid efficacy may depend on preserved network integrity

RESEARCH QUESTION

To test whether a novel machine learning method can surface patient subpopulations with differential response within a negative Alzheimer's disease trial and to deconstruct those populations into explainable and unexplainable subgroups.

METHODS

Dataset:

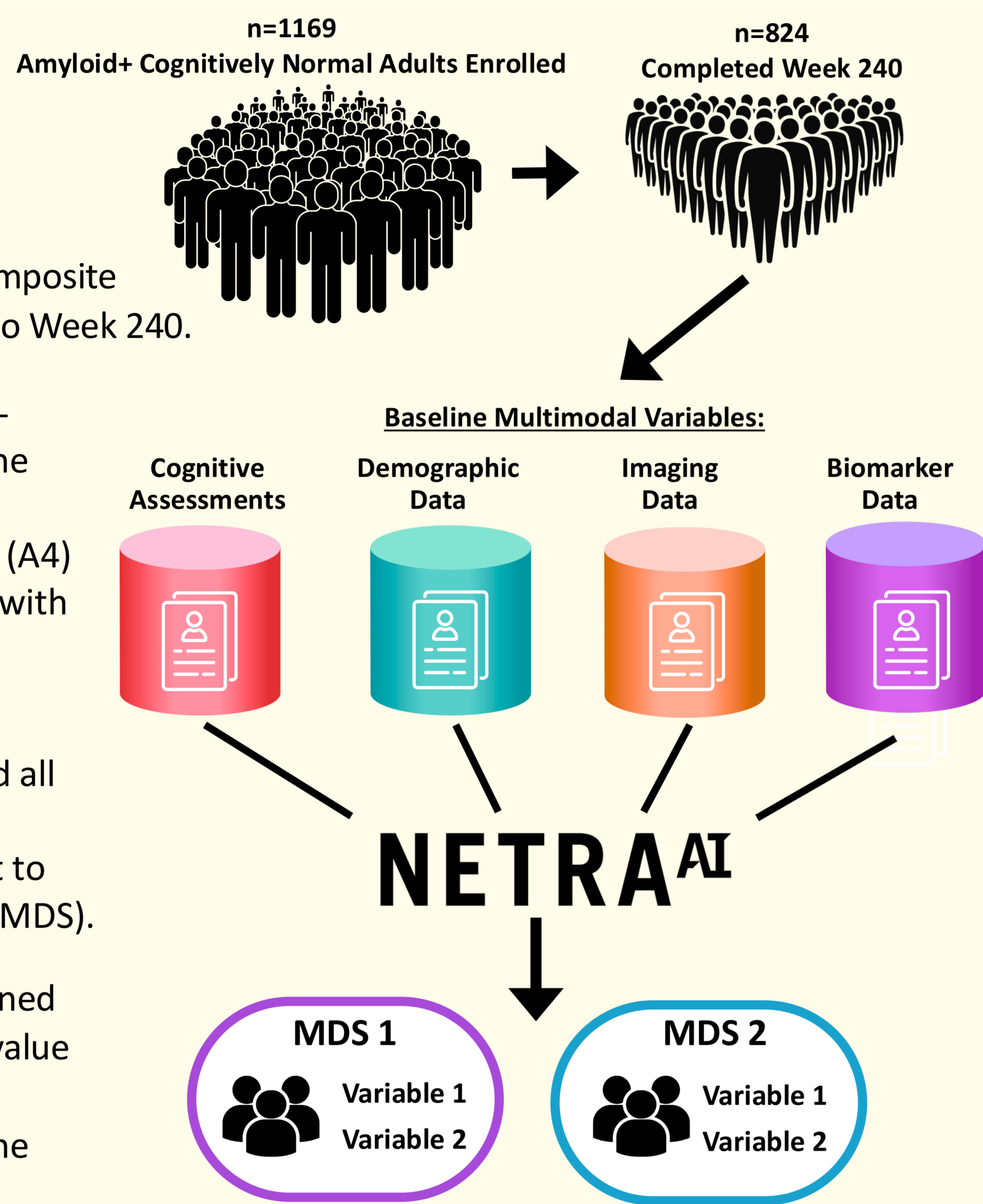
A4 randomized trial comparing sola and placebo.

Primary endpoint: Preclinical Alzheimer's Cognitive Composite (PACC) score change from Baseline to Week 240.

An explainable, dynamical-systems-based AI platform was applied to the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) dataset to identify subpopulations with differential placebo or treatment response.

The platform, NetraAI, incorporated all available **baseline multimodal variables** within the analytic cohort to identify model-derived subgroups (MDS).

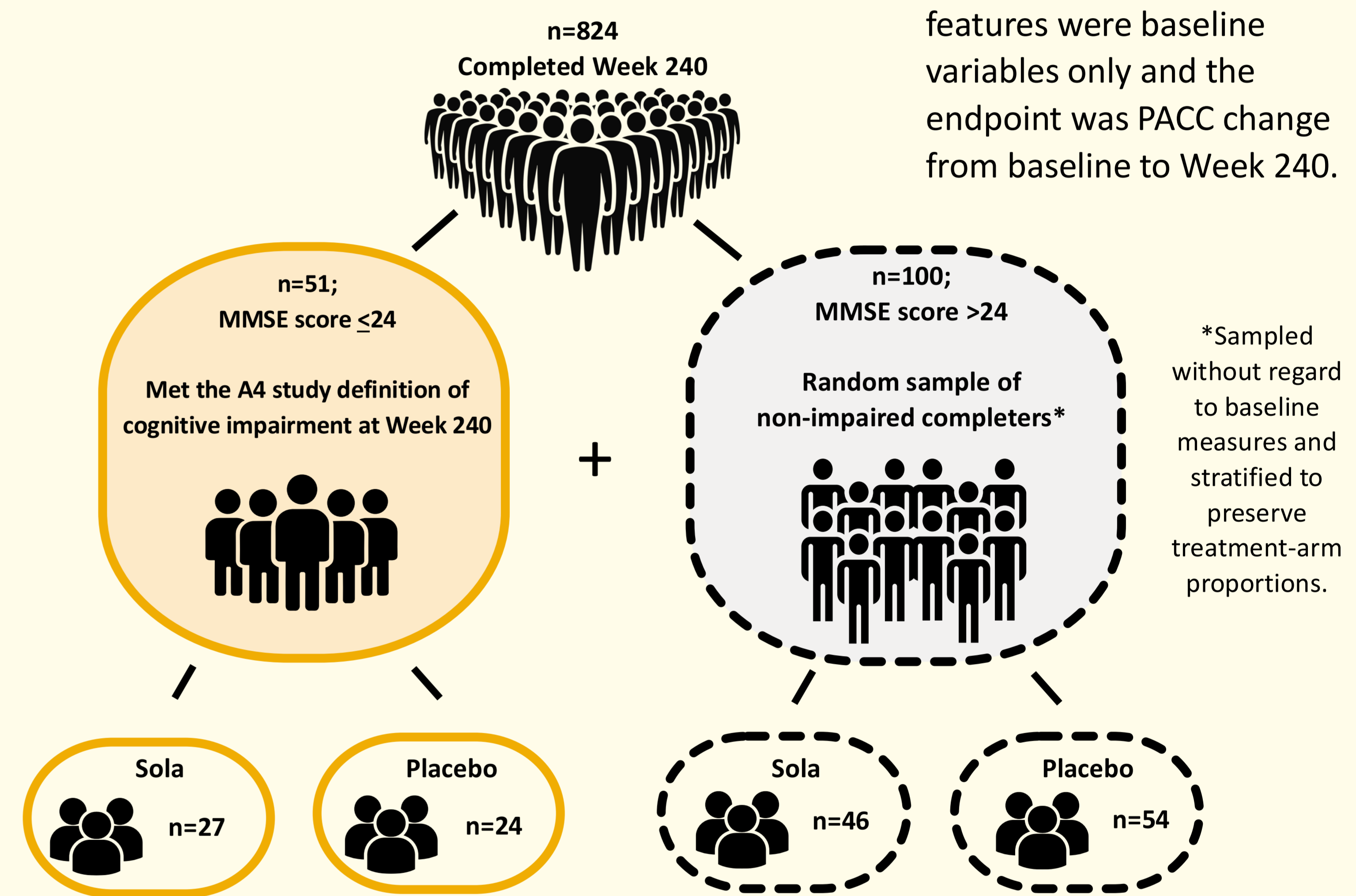
MDS are explainable subgroups defined by 2-4 baseline variables and their value ranges, associated with differential treatment vs placebo response on the primary endpoint.



Analytic Cohort: (enriched case-cohort sample)

Among Week 240 completers (N=824), we included all participants who met the A4 study definition of cognitive impairment at Week 240 (n=51; MMSE score ≤ 24), plus a random sample of non-impaired completers (n=100).

This enrichment was used to increase representation of decliners for exploratory subgroup discovery; MDS features were baseline variables only and the endpoint was PACC change from baseline to Week 240.



RESULTS

NetraAI Results:

2 subpopulations with greater regional brain volume and stronger baseline psychomotor speed and attention demonstrated less decline with sola at Week 240. Specifically:

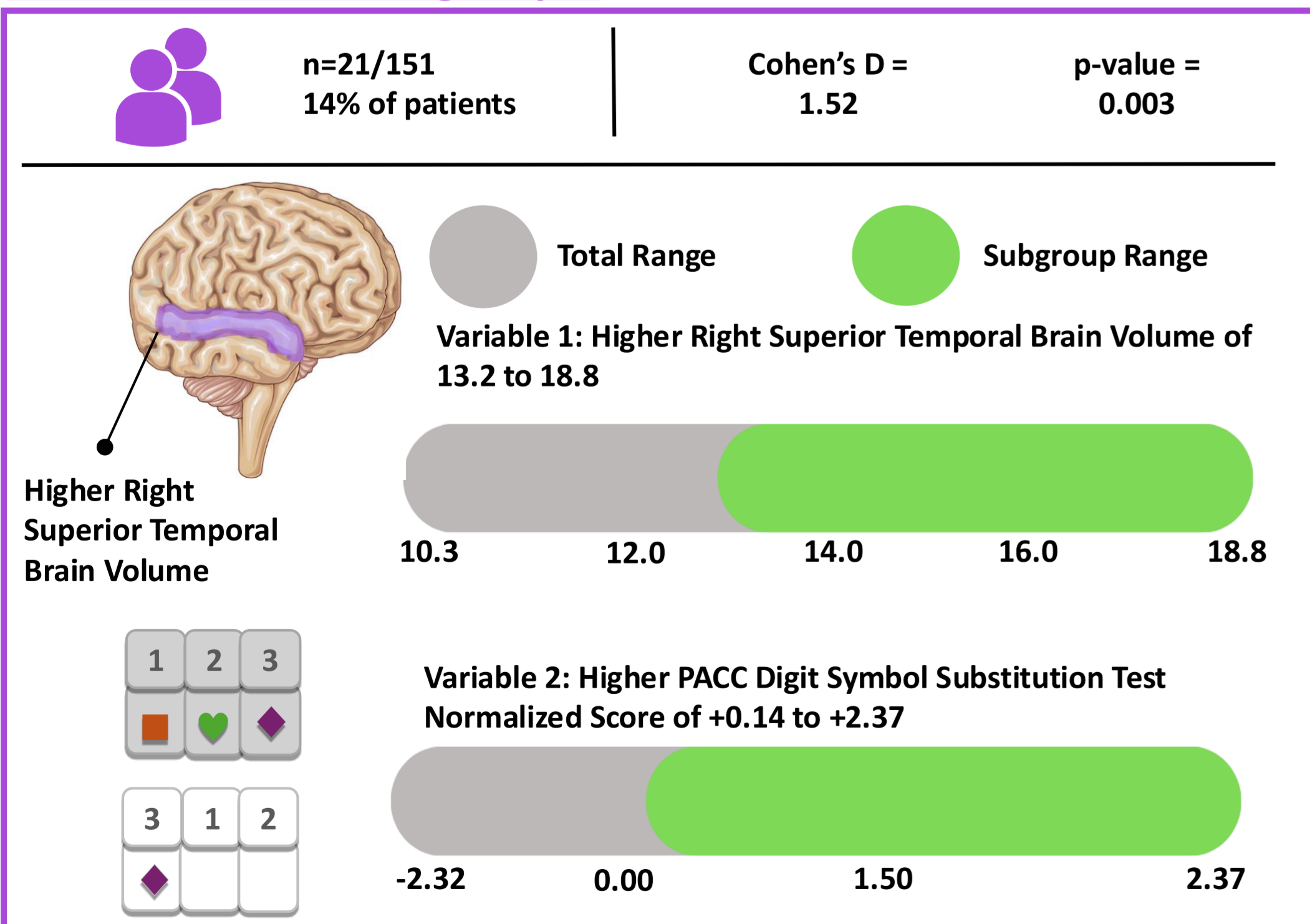
- Higher baseline volume in areas responsible for recognizing, interpreting, and responding to emotional and social information (right amygdala or right superior temporal cortex) and
- Higher baseline scores on the PACC Digit Symbol Substitution Test (DSST), indicating better memory, processing speed, and attention.

Original A4 trial: No significant benefit (Cohen's D = ~0, p=0.26). Explainable AI identified two subgroups with significant treatment effect.

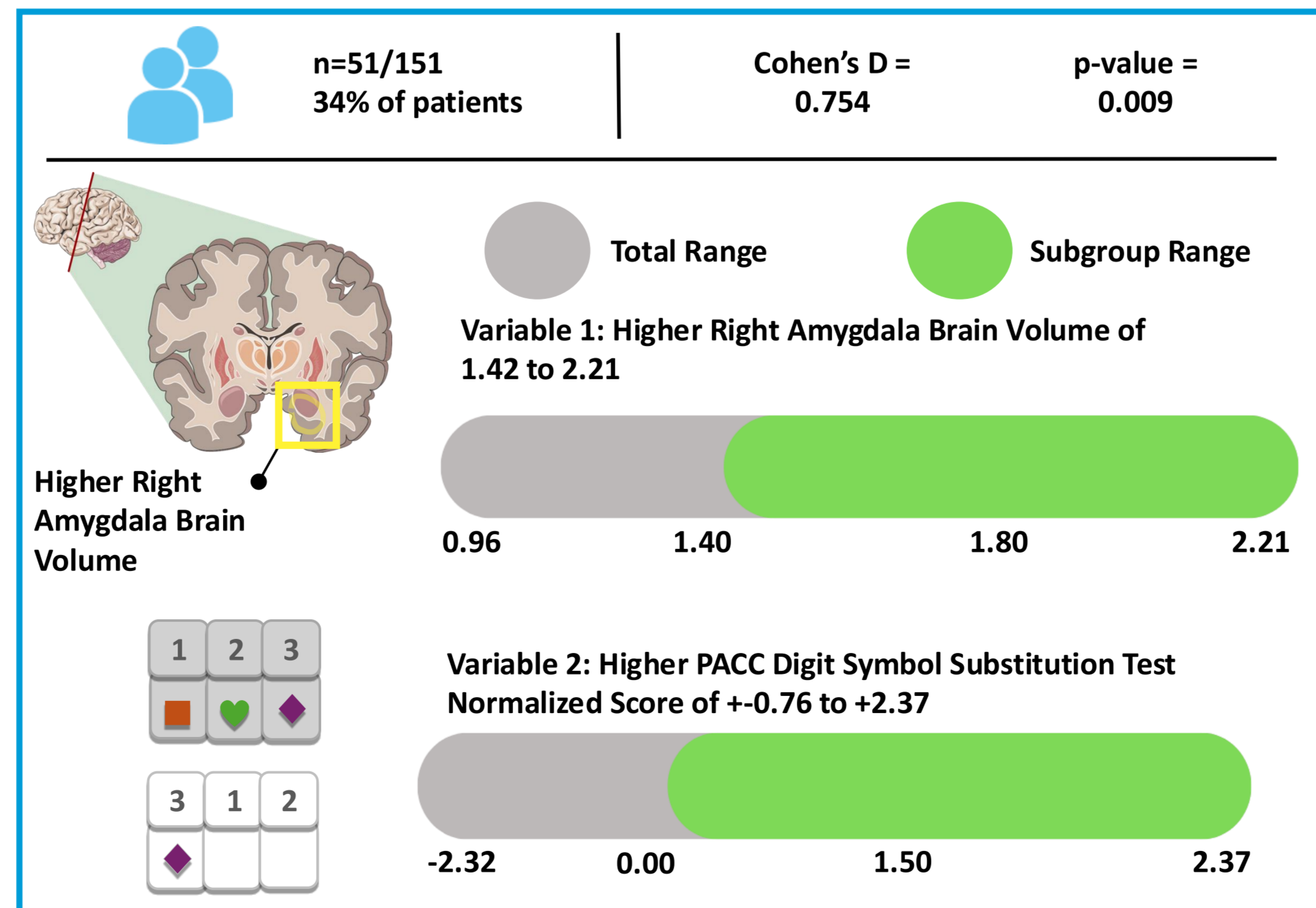
General dataset characteristics:

Analytic dataset mirrored total dataset trend of overall better response to placebo versus sola but showed more decline in both groups. At Week 240, PACC decline for placebo was 1.80 points vs. 1.13 points in the total dataset and the PACC decline for sola was 2.19 points vs. 1.43 points in total dataset.

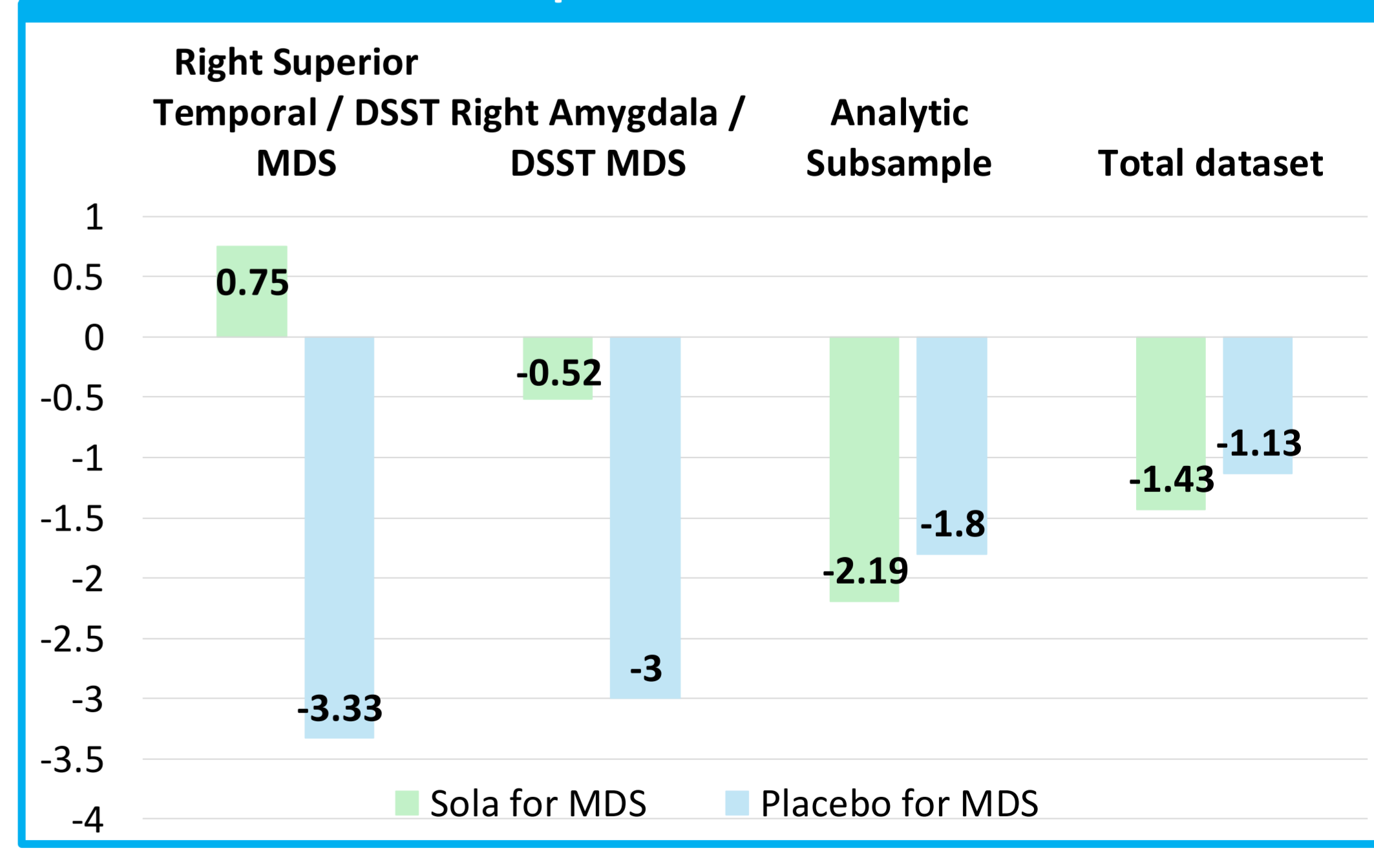
Model-Derived Subgroup 1



Model-Derived Subgroup 2



PACC Score Change : Comparison of Two MDSs versus Subsample and Total Dataset



*Negative values indicate decline, positive values indicate improvement

INTERPRETATION

Explainable AI revealed biologically coherent responder profiles characterized by superior baseline limbic and temporal network structure and stronger baseline cognitive performance. This suggests that treatment response in preclinical AD may require preserved neural reserve. Failure of overall trials may mask meaningful subgroup benefit.

LIMITATIONS

Small subgroup sizes, independent replication required, exploratory analysis, no multiplicity correction

CONCLUSIONS

- 1) Brain reserve, preserved cognition may enrich for anti-amyloid response;
- 2) Approach supports precision enrichment in future preclinical AD trials, demonstrates potential of explainable AI in therapeutic development.



DISCLOSURES
Dr. Joseph Geraci is the founder of NetraMark and is a significant shareholder of NetraMark Holdings, which is a publicly traded company. Luca Pani, Jan Sedway, Christian Cumbaa, Bessi Qorri, Mike Tsay, Paul Leonchyk and Larry Alphs are employed by NetraMark. Dr. Luca Pani's Disclosures (past 3 years): Luca Pani is/has been a consultant or advisory board member for AbbVie, USA; BCG, Switzerland; Boehringer Ingelheim International GmbH, Germany; GH Research, Ireland; Immunogen, USA; Johnson & Johnson USA; LB Pharmaceuticals, USA; Magdalena BioSciences, USA; Sanofi-Aventis-Genzyme, France and USA; Lundbeck, Denmark and Italy; Napo-Pharma, USA and EU; NetraMark, Canada; Pfizer Global, USA; Reimada Therapeutics, USA; Takeda, USA and owns shares/options from ADance Germany; Adapt UK, Eneta USA, NetraMark Canada, and Reimada, USA.