

Rapid Progressors in Alzheimer's Disease: Differences in Cognitive Domain Decline

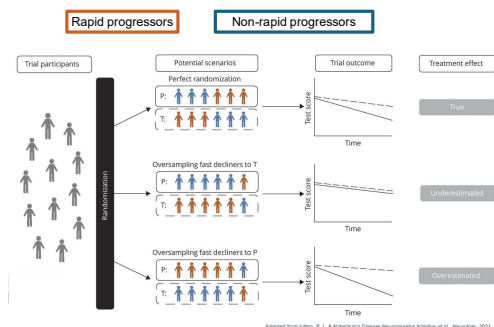
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BACKGROUND & RATIONALE

- Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by **cognitive, mood, and behavioral changes**, as well as impaired **activities of daily living**.
- Rapid progressors (RP) are patients that exhibit accelerated decline, leading to a greater difficulties for patients, families, and healthcare systems.
- Early identification of RPs could facilitate **targeted interventions and personalized care**.
- It is possible that changes in specific cognitive domains (**complex attention, executive function, language, learning & memory, perceptual motor function, and social cognition**) may differ between RPs and non-RPs.



This study explores whether **early change trajectories and changes in specific cognitive domains** can differentiate RPs, from non-RPs at **clinically intervenable timepoints**.



COHORT CHARACTERISTICS

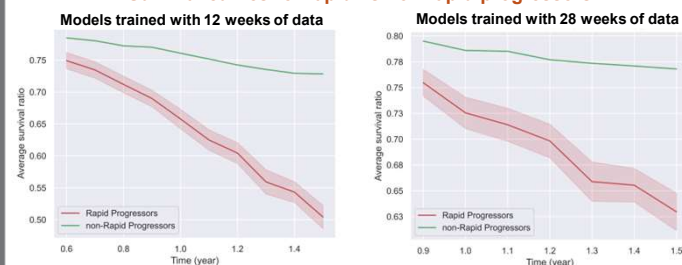
	Pooled (N = 1603)	Rapid Progressor (CDR) (N = 150, 9.4%)
Age at baseline (years, mean (± SD))	73.0 (±7.8)	72.5 (±7.2)
Age of symptom onset (years)	68.6 (±8.0)	68.5 (±7.5)
Sex		
Female	929 (58.0%)	82 (54.7%)
Male	674 (42.0%)	68 (45.3%)
Ethnicity		
Hispanic or Latino	124 (7.7%)	8 (5.3%)
Not Hispanic or Latino	1163 (72.6%)	142 (94.7%)
Race		
White	1299 (81.0%)	126 (84.0%)
Black or African American	27 (1.7%)	4 (2.7%)
Asian	203 (12.7%)	13 (8.7%)
American Indian or Alaska Native	1 (0.06%)	0 (0.0%)
Multiple/Unknown	4 (0.2%)	7 (4.7%)
Baseline Conditions		
Measures of neurocognitive and/or functional impairment (mean (± SD))		
ADAS-Cog14**	30.9 (±9.5)	36.6 (±9.4)
ADCS-ADL*	64.9 (±10.4)	60.6 (±10.9)
CDR-SB	4.2 (±2.1)	4.7 (±1.7)
MMSE**	22.2 (±2.7)	21.1 (±2.7)
vMRI (mean (± SD))		
Whole brain volume (cm ³)	990.7 (±106.1)	984.5 (±107.0)
Ventricular volume (cm ³)*	48.6 (±22.6)	55.4 (±23.0)
Left entorhinal cortex volume (mm ³)	1037.1 (±553.7)	994.2 (±493.2)
Right entorhinal cortex volume (mm ³)	986.2 (±535.1)	935.4 (±500.4)
Left hippocampus volume (mm ³)	2412.6 (±781.5)	2331.5 (±762.9)
Right hippocampus volume (mm ³)	2496.0 (±820.4)	2392.4 (±822.8)

** p < 0.001, * p < 0.01



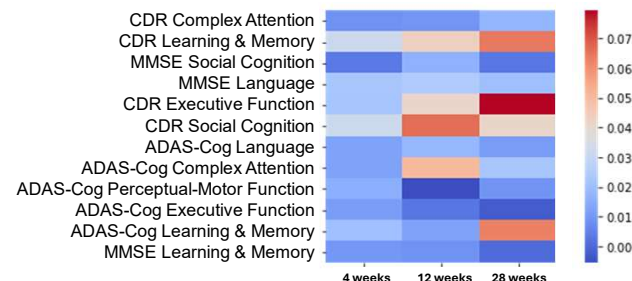
RESULTS

Survival curves for rapid vs non-rapid progressors



Probability separation based on CDR score change. Models trained with CDR-based features and adjusted for age, sex, education, and ApoE status. Shaded regions indicate 95% CIs.

Differential cognitive domain contributions to RP classification



Feature importance derived from permutation models trained at each timepoint. Higher values indicate greater contribution to RP discrimination.



METHODS

Definition

- Rapid progressors were defined as the top 10% of individuals with greatest CDR-SB decline over 80 weeks.

Data Source

- Cohort (n = 1603) derived from placebo-arm data of 3 EXPEDITION trials.

Models

- Trained deep survival models at four time points (4, 12, 28, and 80 weeks) to predict time-dependent probability of RP classification at 80 weeks.

Metrics

- Model performance assessed with AUROC and AUPRCs and compared with Cox proportional hazards models.
- Feature importance was used to identify domains contributing to risk discrimination.



DISCUSSION & CONCLUSIONS

- Early **domain-specific decline** (learning & memory and executive function) contributes to RP differentiation
- Survival models show consistent early separation at **clinically intervenable timepoints**
- Findings support the need for **tailored approaches to clinical trials** for this AD phenotype



Early Identification of RPs may enable more efficient trial design and targeted interventions.



FUTURE DIRECTIONS



- Investigate the relationship between **neuroanatomical changes and cognitive domain decline** in RPs v. nRPs



- Develop prediction models to identify potential factors (e.g., more **malignant forms of tau**) that underly rapid progression



- Inform randomized clinical trial design, patient stratification, and targeted drug development specific to RPs