Rapid progressors in Alzheimer's Disease: Using neuroimaging to predict cognitive decline

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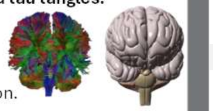
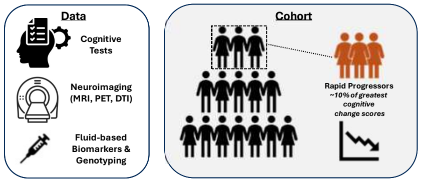
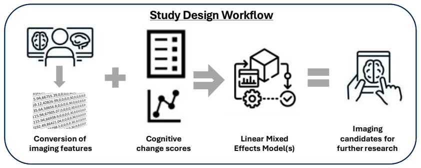
BACKGROUND & RATIONALE

- Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by **cognitive decline, cortical atrophy,** and the buildup of **amyloid plaques and tau tangles.**
- **Diffusion tensor imaging (DTI)** can be used to detect degradation of white matter in the brain as an early indicator of disease progression.



- Variability in disease progression impedes **effective identification of** and **treatment development for** patient subgroups who rapidly progress (**rapid progressors, RPs**).
- RPs may demonstrate **different microstructural changes than non-RPs.**


Data
Cognitive Tests
Neuroimaging (MRI, PET, DTI)
Fluid-based Biomarkers & Genotyping
Cohort
Rapid Progressors
~10% of greatest cognitive change scores


Study Design Workflow
Conversion of imaging features
Cognitive change scores
Linear Mixed Effects Model(s)
Imaging candidates for further research

This study explores whether changes in specific white-matter pathways predict cognitive score changes between rapidly progressing (RP) and traditionally progressing (nRP) patients.

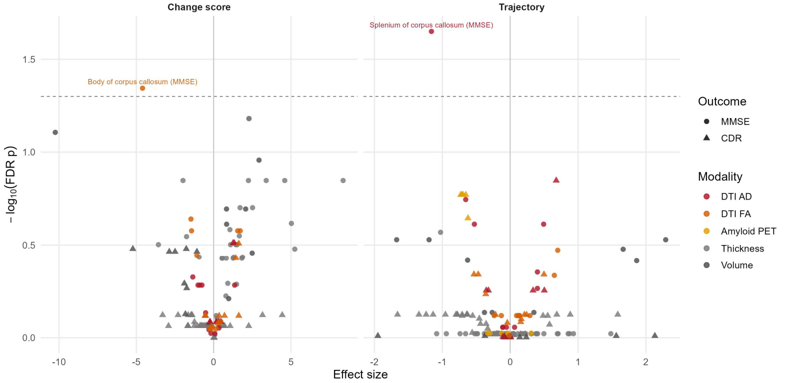
COHORT CHARACTERISTICS

	Non-Rapid Progressor (N = 90, 83.3%)	Rapid Progressor (N = 18, 16.7 %)
Age at baseline mean (± SD)	67.7 (±10.3)	72.1 (±9.2)
Sex		
Female	43 (47.8%)	9 (50.0%)
Male	47 (52.2%)	9 (50.0%)
Ethnicity		
Hispanic or Latino	48 (53.3%)	14 (77.8%)
Not Hispanic or Latino	42 (46.7%)	4 (22.2%)
Race		
White	70 (77.8%)	16 (88.9%)
Black or African American	20 (22.2%)	2 (11.1%)
Baseline Conditions & Other Imaging Metrics		
Measures of neurocognitive and/or functional impairment mean (± SD)		
CDR-SB	2.8 (± 2.1)	3.9 (± 3.4)
MMSE	24.5 (± 4.2)	22.3 (± 5.3)
PET SUVR		
Amyloid Global*	1.01 (0.96-1.06)	1.34 (1.23-1.44)
Tau Medial Temporal*	1.12 (1.02-1.19)	1.82 (1.66-1.97)
vMRI (cm^3), mean (± SD)		
Whole brain volume	1354.7 (± 132.1)	1395.9 (± 60.4)
Ventricular volume	26.7 (± 17.7)	35.8 (± 13.7)
Left entorhinal cortex volume**	3.16 (± 0.43)	2.72 (± 0.54)
Right entorhinal cortex volume***	3.31 (± 0.53)	2.73 (± 0.55)
Left hippocampus volume**	2.92 (± 0.48)	3.44 (± 0.19)
Right hippocampus volume**	2.94 (± 0.46)	3.21 (± 0.11)

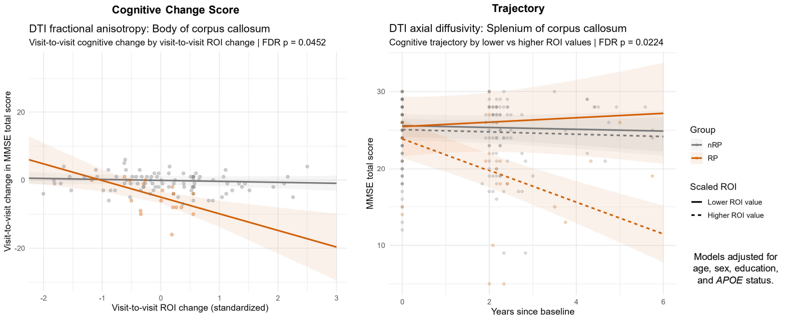
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

RESULTS

nRP v. RP Model Associations by ROI & Cognitive Outcome



Clinical interpretation of cognitive change scores and trajectories by ROI



Models adjusted for age, sex, education, and *APOE* status.

METHODS

Definition

- Rapid progressors were defined as the top ~10% of individuals exhibiting the greatest decline in CDR-SB & MMSE over 18-24 months.

Data Source

- Diagnosed AD subjects with ≥2 visit & MRI scans (n = 108) from the Health and Aging Brain Study-Health Disparities (HABS-HD) Cohort

Analyses

- Linear mixed-effects models tested whether visit-level imaging values moderated longitudinal cognitive change between groups.
- Between-visit cognitive change was modeled as a function of ROI change, group, and their interaction.

Metrics

- ROIs were z-scored before modeling. Covariates included age, sex, education, *APOE* status, and total brain volume.
- P-values were FDR corrected within each ROI set and cognitive outcome.

DISCUSSION

1. Identified two white matter measures that demonstrate **significant associations** with cognitive decline in RPs.
2. Exploratory results suggest that changes in white matter microstructural integrity **may contribute** to rapid progression

The identified regions should be interpreted as potential candidates for further study

FUTURE DIRECTIONS

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

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