

Exploratory Machine Learning Analysis of Functional and Cognitive Indicators of Subtle 12-Month Clinical Change in Cognitively Normal Older Adults

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Background

- Early detection of decline in cognitively normal (CN) older adults is important for dementia prevention. However, conventional screening tools may be insufficiently sensitive to subtle short-term changes. We therefore examined whether baseline cognitive and functional profiles are associated with 12-month changes in Clinical Dementia Rating–Sum of Boxes (CDR–SB) among CN individuals.

Objective

- To identify baseline cognitive and functional indicators associated with subtle 12-month changes in Clinical Dementia Rating–Sum of Boxes (CDR–SB) among cognitively normal older adults using machine learning.

Methods

- Participants: 374 cognitively normal (CN) older adults from the Alzheimer’s Disease Neuroimaging Initiative (ADNI), with baseline CDR–SB = 0 and MMSE ≥ 24.
- Outcome: Maximum 12-month change in CDR–SB was categorized as No Change, Mild Change (+ 0.5), or Severe Change (≥ + 1.0).
- Predictors: Baseline cognitive scores, Functional Activities Questionnaire (FAQ), demographics, and APOE ε 4 status.
- Analysis: Kruskal–Wallis, chi-square, and post-hoc tests were used for group comparisons. Logistic regression with 20 imputed datasets and class-weighted random forest with SHAP were used to identify baseline indicators.

Participants

- 374 cognitively normal older adults, grouped by their 12-month change in Clinical Dementia Rating–Sum of Boxes (CDR–SB):



Progression (Mild + Severe) was uncommon over 12 months, reflecting the preclinical setting.

Baseline Group Differences

Variables	NC (n=354)	MC (n= 10)	SC (n= 10)
AGE (year)	74 (71, 78)	71 (70, 75)	73 (71, 77)
Education (year)	16 (15, 18)	16 (14, 18)	16 (13, 16)
APOE4_yes (%)	28.2	30.0	20.0
FAQ	0 (0, 0)	0 (0, 1)	0 (0, 0)
MMSE	29 (29, 30)	29 (28, 29)	29 (28, 29)
ADAS_Cog13	9 (6, 12)	8 (5, 11)	13 (10, 15)
TRABSCOR	71 (55, 91)	82 (53, 105)	106 (87, 125)
DIGITSCOR	46 (41, 53)	43 (40, 46)	38 (34, 41)
mPACC_trailsB	0.3 (-1.5, 1.9)	-0.2 (-1.2, 0.6)	-1.5 (-3.3, -0.6)
mPACC_digit	0.3 (-1.6, 1.8)	-0.2 (-1.1, 0.9)	-1.8 (-3.1, -1.0)

APOE4; Apolipoprotein E epsilon 4 allele, FAQ; Functional Activities Questionnaire, MMSE; Mini-Mental State Examination , ADAS - Cog; Alzheimer’s Disease Assessment Scale - Cognitive Subscale, TRABSCOR = TMT; Trail Making Test, DIGITSCOR = DSST; Digit Symbol Substitution Test, mPACC; Modified Preclinical Alzheimer’s Cognitive Composite.

Adjusted Logistic Regression

- For logistic regression, the three groups were collapsed into two, and the outcome was defined as the presence vs. absence of 12-month CDR–SB decline (Mild + Severe combined as "decline")

Marker	OR	95% CI	p
FAQ	1.76	1.06–2.93	0.029
DIGITSCOR	0.95	0.89–1.00	0.049
TRABSCOR	1.01	1.00–1.02	0.052
ADAS_Cog13	1.09	0.98–1.22	0.114
mPACC_trailsB	0.86	0.70–1.04	0.116
mPACC_digit	0.89	0.75–1.07	0.222

Each marker modeled separately, adjusted for age, gender, education and APOE4. FAQ and DIGITSCOR were independent indicators of progression (p < 0.05).

Random Forest Performance

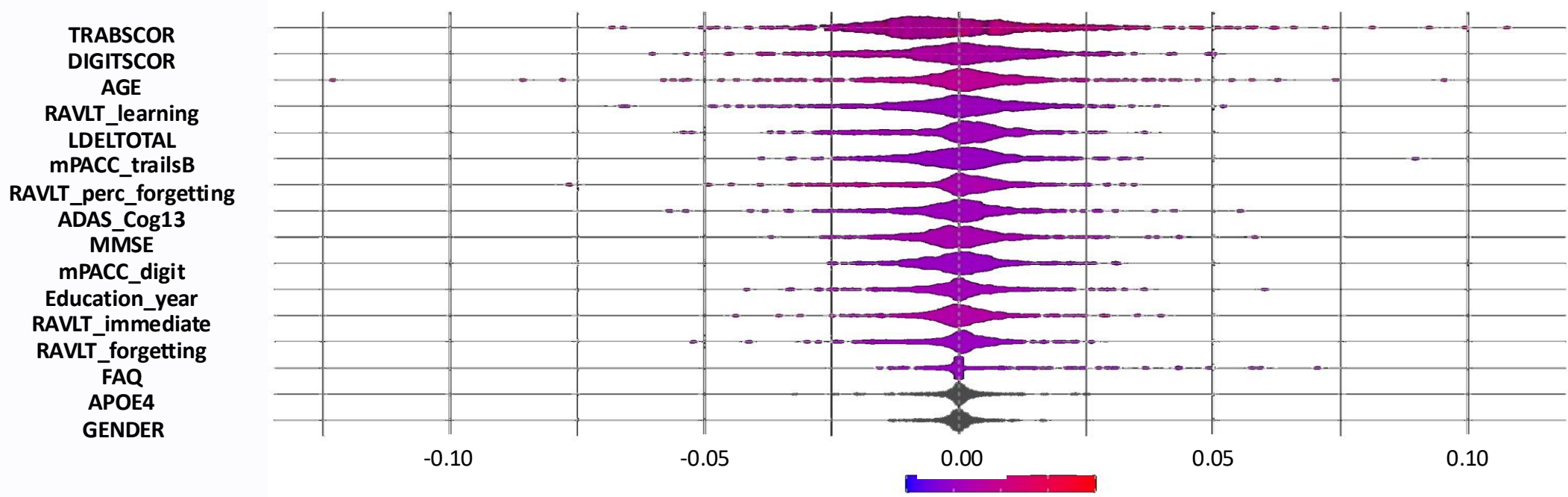
- In this study, predicting progression from baseline data was difficult — discrimination was only marginally above chance.

ROC-AUC (pooled)	0.538
PR-AUC (low prevalence)	0.14
Brier score	0.053
Calibration slope	≈ 1.0

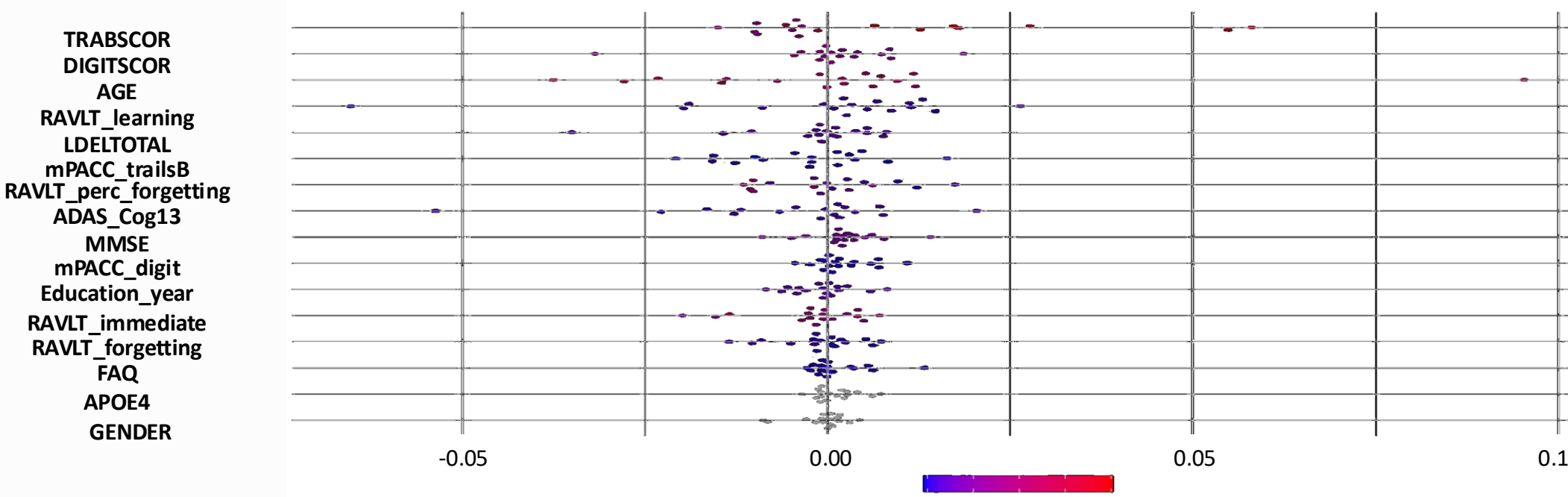
multiple imputation with 20 imputed datasets

Feature Contributions — SHAP Analysis (Random Forest)

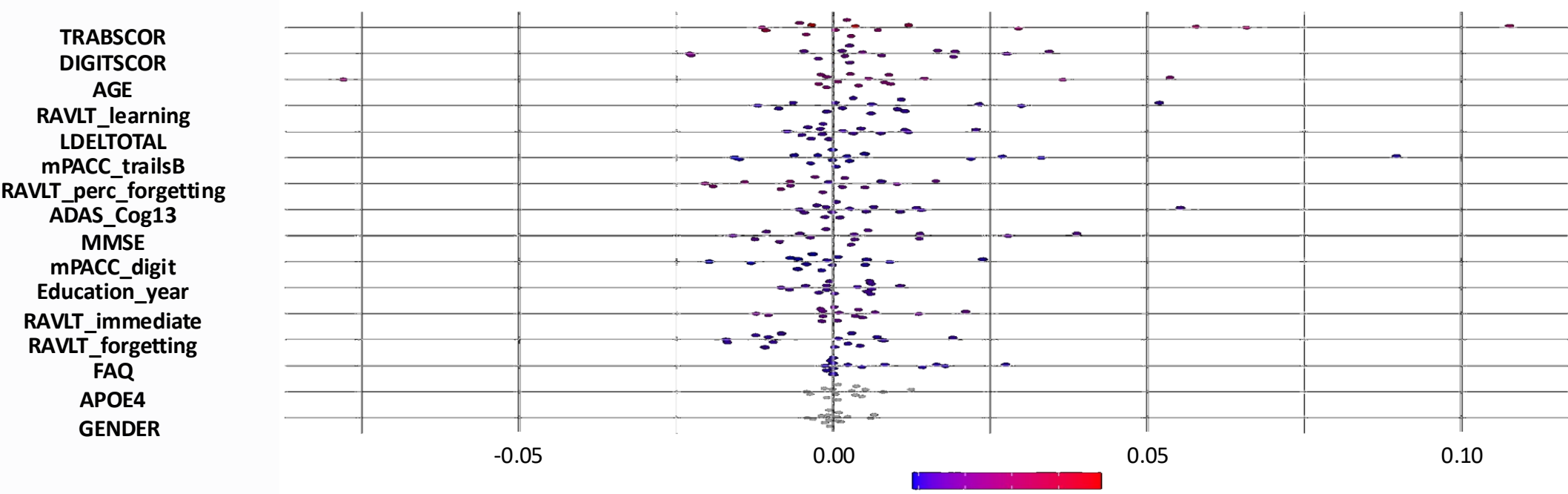
All progression vs. No Change



Mild Change only



Severe Change only



Features ranked by mean |SHAP|. Overall: TRABSCOR, DIGITSCOR, age & learning dominate. Mild Change: FAQ & DIGITSCOR more influential. Severe Change: broader cognitive contributions. (TRABSCOR = TMT-B · DIGITSCOR = DSST · LDELTOTAL = Logical Memory · grey = factor variables.)

Conclusions

- Baseline single-timepoint cognitive measures, including mPACC, showed limited ability to capture subtle 12-month CDR–SB changes in cognitively normal adults, partly due to the small number of progressors. Functional change (FAQ) and processing speed (DSST) showed the most consistent associations with subsequent clinical change. Repeated, time-course measures may be needed for preclinical monitoring and should be validated in larger biomarker-defined cohorts.**

References

1. Jack CR Jr, et al. NIA-AA Research Framework. *Alzheimers Dement*. 2018;14(4):535–562. 2. Sperling RA, et al. Toward defining the preclinical stages of Alzheimer’s disease. *Alzheimers Dement*. 2011;7(3):280–292. 3. van Dyck CH, et al. Lecanemab in early Alzheimer’s disease. *N Engl J Med*. 2023;388(1):9–21. 4. Sims JR, et al. Donanemab in early symptomatic AD. *JAMA*. 2023;330(6):512–527. 5. Donohue MC, et al. The Preclinical Alzheimer Cognitive Composite. *JAMA Neurol*. 2014;71(8):961–970. 6. Petersen RC, et al. ADNI: clinical characterization. *Neurology*. 2010;74(3):201–209.

Disclosure of Conflicts of Interest

Presenting author: Kouki Tomida (employee of Theoria Technologies, Inc.).No other conflicts to disclose.
Data obtained from the ADNI database (adni.loni.usc.edu) under its data-use agreement.