Monthly at-home computerized cognitive testing to detect diminished practice effects in preclinical Alzheimer's disease

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Background

- A major challenge for Alzheimer's disease (AD) secondary prevention trials is the long and subtle course of cognitive decline observed in individuals with preclinical AD.
- Computerized testing has the potential to capture subtle cognitive change more rapidly, by enabling standardized administration and data analyses allowing for remote, unsupervised, and more frequent assessments.
- The higher frequency assessments afforded through the use of computerized testing enable the study of practice effects (PE) that can occur with repeated assessments in older adults, and which previously has been shown to provide a meaningful cognitive marker in preclinical AD.[1-3]

Objectives

To investigate **A)** whether monthly assessments of a computerized cognitive composite (C3) could aid in the detection of differences in practice effects (PE) in clinically unimpaired (CU) older adults, and whether diminished PE would be associated with **B)** AD neuroimaging biomarkers and **C)** cognitive decline observed on standard annual in-clinic testing.

Methods

Participants and procedures

- **N=114 CU individuals (age 77.1±4.9, 61% female, MMSE 29±1.3**) from the Harvard Aging Brain Study (HABS) completed the **self-administered C3 monthly at-home** on an iPad for up to one year (11.7±2.8 months follow-up).
- At baseline, participants had undergone **PIB-PET imaging** (1.25±1.05 years within at-home baseline) and **Flortaucipir PET imaging** (n=109, 0.56±0.4 years within at-home baseline) and in-clinic **Preclinical Alzheimer's Cognitive Composite - 5 (PACC5)** testing.
- A subsample (n=72, age 78.1±5.2, 59% female, MMSE 29±1.3) also had one year follow-up in-clinic PACC5 testing available.

Computerized Cognitive Composite (C3)

- C3 includes the Face Name Associative Memory Exam (**FNAME**), the Behavioral Pattern Separation Task-Object version (**BPSO**), and the Cogstate Brief Battery including the One Card Learning task (**OCL**).[4,5]
- The FNAME, BPSO and OCL accuracy z-scores are combined into a **C3 z-score**.[5]

Statistical analyses

- Linear mixed models (LMM) to investigate C3 performance over time (months) adjusting for age, sex, and years of education, and to extract individual covariate-adjusted C3 slopes over the first 3 months.
- Correlations to investigate associations between 3-month C3 slopes (covariate-adjusted) and 1) global amyloid burden (DVR); (2) tau deposition in the entorhinal cortex and inferior-temporal lobe (SUVr, partial-volume corrected); and 3) change on the PACC5 over one year.
- Receiver Operating Curve (ROC) analyses to examine how accurately 3-month C3 slopes could identify individuals who would show more than 0.10 standard deviation (SD) annual decline on the PACC5.[6]

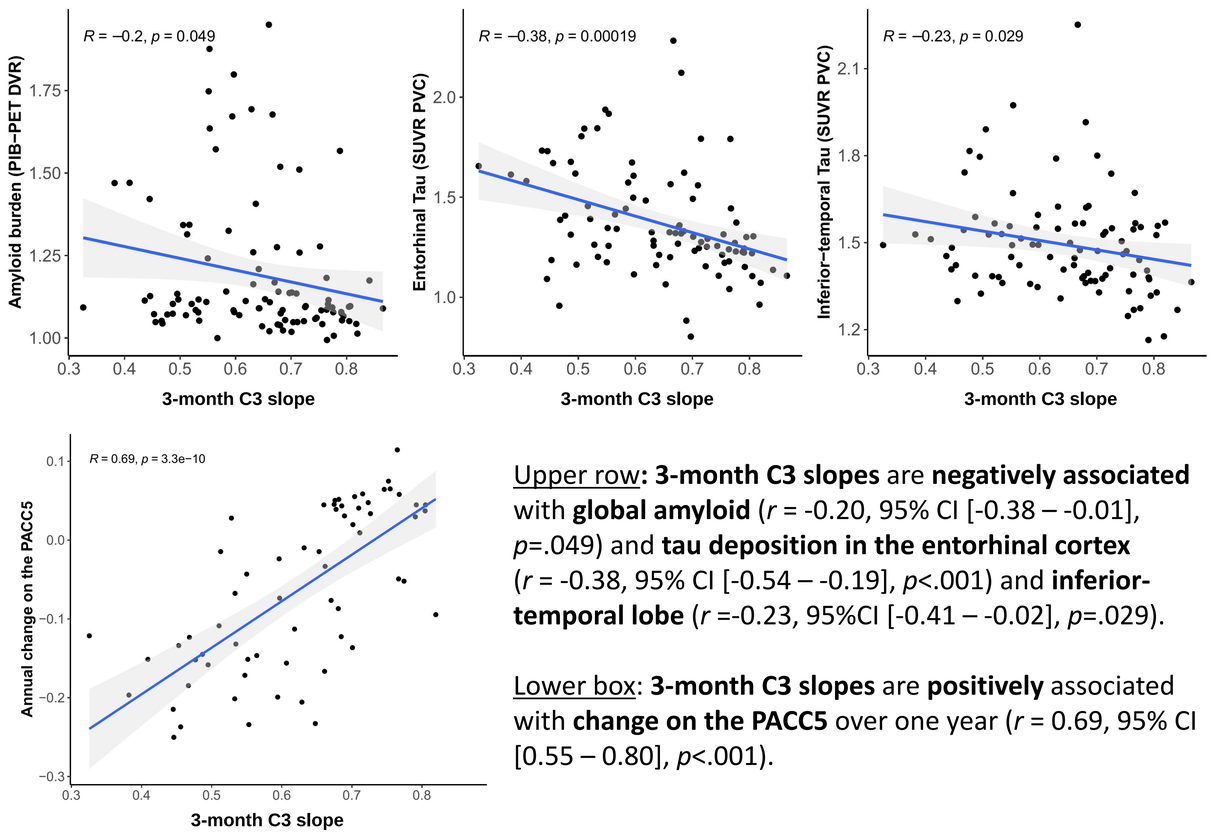
A. Individuals showed improved performance on all C3 measures. In general, effect-sizes over 3 months were greater than those over 12 months, suggesting stronger practice over initial repeated exposures.

TABLE 1. STANDARDIZED TIME ESTIMATES OBTAINED FROM LMM

	Monthly change over 12 months			Monthly change over first 3 months		
	Time	95% CI	P-Value	Time	95% CI	P-Value
C3	0.226	0.207 – 0.245	<0.001	0.665	0.566 – 0.763	<0.001
BPSO	0.073	0.061 – 0.085	<0.001	0.210	0.148 – 0.271	<0.001
FNAME	0.098	0.088 – 0.108	<0.001	0.378	0.328 – 0.429	<0.001
OCL	0.051	0.041 – 0.060	<0.001	0.074	0.021 – 0.127	0.006

*Time estimates obtained from LMM adjusting for age, sex and years of education. All scores are z-transformed to facilitate comparisons across measures and follow-up durations. C3 = z-score combining BPSO + FNAME + OCL scores.

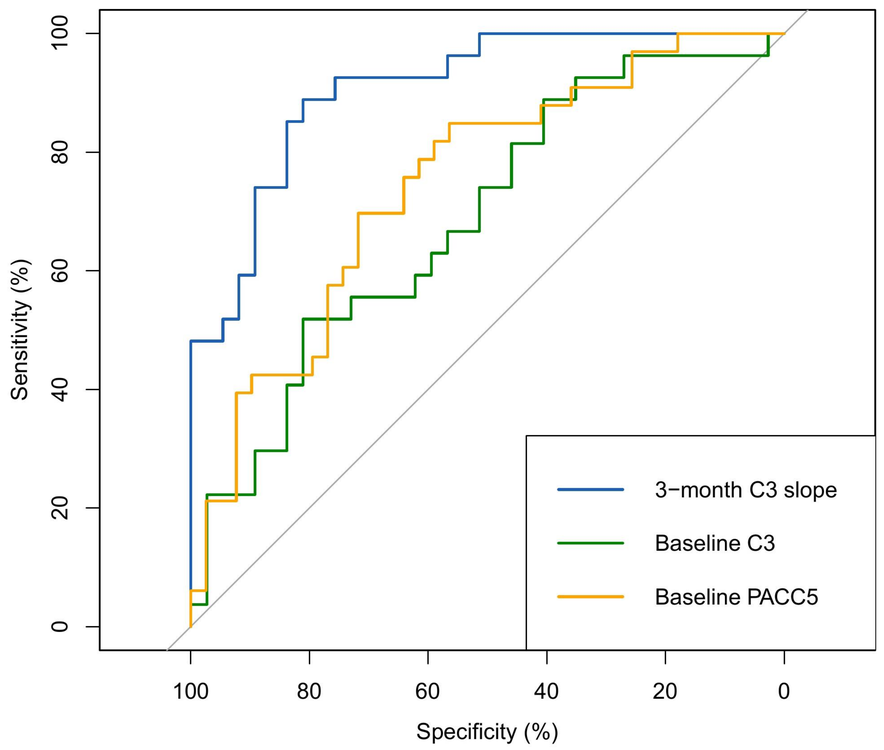
B. Lower 3-month C3 slopes are associated with greater AD biomarker burden and annual cognitive decline.



Upper row: **3-month C3 slopes** are **negatively associated** with **global amyloid** (r = -0.20, 95% CI [-0.38 – -0.01], p=.049) and **tau deposition in the entorhinal cortex** (r = -0.38, 95% CI [-0.54 – -0.19], p<.001) and **inferior-temporal lobe** (r =-0.23, 95%CI [-0.41 – -0.02], p=.029).

Lower box: **3-month C3 slopes** are **positively** associated with **change on the PACC5** over one year (r = 0.69, 95% CI [0.55 – 0.80], p<.001).

C. 3-month C3 slopes exhibit good discriminative ability to identify > 0.10 SD annual decline on the PACC5.



3-month C3 slopes (AUC= 90.8%, optimal cut-off: 0.7), performed better than **baseline C3** (AUC=68.6%, p<.001) and **baseline PACC5** (AUC=74.5%, p=.02) scores.

Conclusion

A. Overall, CU adults show practice effects (PE) on monthly repeated computerized testing, and PE are strongest over initial repeated exposures (i.e., over the first 3 months).

B. However, diminished PE over 3 months are associated with greater AD biomarker burden and cognitive decline over one year.

C. Characterizing PE on the C3 over 3 months could provide a valuable marker to identify individuals who will show more than 0.10 SD annual decline on the PACC5.

Our findings imply that remote computerized testing using monthly retest paradigms can provide rapid detection of diminished PE indicative of future cognitive decline in preclinical AD. This could accelerate clinical trial recruitment and screening as well as the detection of treatment effects.

References: [1]Duff et al. Archives of Clinical Neuropsychology (2007) - [2]Jutten et al. Alzheimer's & Dementia DADM (2020) – [3] Samaroo et al. Alzheimer's & Dementia DADM (2021) [4]Rentz et al. Journal of Prevention of Alzheimer's Disease (2016) - [5]Papp et al. Journal of Prevention of Alzheimer's Disease (2021) – [6] Petersen et al. Annals of Neurology (2021).

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