# Digital cognitive assessments discriminate early tau pathology in cognitively unimpaired older adults

**Karra D. Harrington[1], Casey R. Vanderlip[1], Charles O'Connor[2], Pam Ventola[1], Paul Maruff[2], the A4 study group**

1. *Cogstate Ltd, New Haven CT*
2. *Cogstate Ltd, Melbourne Australia*

## Background

- With the shift towards earlier intervention in Alzheimer's disease (AD), there is a need for scalable approaches to identify AD pathology in older adults prior to the onset of symptomatic disease.
- Digital cognitive assessments (DCA) represent highly scalable, cost-effective, and low burden tools, that have demonstrated sensitivity to subtle cognitive dysfunction associated with abnormal AD biomarkers in cognitively unimpaired older adults [1,2].
- Consequently, such assessments may provide a useful approach for identifying individuals who are more likely to have AD pathology for advancement into biomarker-based screening for preclinical AD trials.

### Aim

- Here we examine how information from two validated memory composite scores from the Cogstate C3 battery, the Learning/Working Memory (LWM) and C3 Memory (C3mem), improve discriminability of abnormal AD biomarkers beyond demographic risk factors.

## Method

### Sample

- Participants were drawn from the screening for the A4 and LEARN studies, and all were clinically normal (Clinical Dementia Rating = 0) and cognitively unimpaired (Mini Mental State Examination >25 and Logical Memory Delayed Recall = 6-18).
- Included participants completed the Cogstate C3 battery at screening visit one and had plasma pTau217 (n= 1563), amyloid PET (n=4486), or tau PET (n=441) data available.

### Measures

- The LWM composite was computed from the performance on the Cogstate One Card Learning (OCL) and One Back (ONB) tests, standardized using age matched normative data.
- The C3mem composite was computed from performance on the Cogstate OCL, Behavioral Pattern Separation Object Test (BPSO) and the Face-Name Associative Memory Exam (FNAME), also standardized using age matched normative data.
- Abnormal plasma ptau217 and amyloid PET levels were defined according to the cut scores used for the A4 trial[3].
- Abnormal tau PET was defined as SUVr >1.1052 on an early tau VOI consisting of uptake in parahippocampal, fusiform, and inferior temporal regions[4].

## Results

### Analyses

- Logistic regression models compared age and sex alone with age, sex, and either LWM or C3mem for prediction of abnormal status for each of the biomarkers.
- Model discrimination was assessed using stratified five-fold cross-validated AUCs.
- Incremental predictive value was evaluated using change in AUC (ΔAUC) relative to the age-and-sex model.
- 95% confidence intervals (CI) for AUCs and ΔAUCs estimated using 5,000 paired stratified bootstrap resamples of the out-of-fold predictions.

### Table 1: Sample Characteristics

**Plasma pTau217**

| Characteristic | Overall (n=1563) | Biomarker negative (n=1184) | Biomarker positive (n=379) |
|---|---|---|---|
| Age, years | 71.45 (4.70) | 70.84 (4.46) | 73.36 (4.93) |
| Sex: Female | 934/1,563 (59.8%) | 702/1,184 (59.3%) | 232/379 (61.2%) |
| Education, years | 16.61 (2.75) | 16.66 (2.72) | 16.45 (2.85) |
| LWM | -0.17 (0.81) | -0.10 (0.79) | -0.37 (0.86) |
| C3 Memory | -0.28 (0.66) | -0.24 (0.64) | -0.40 (0.68) |

**Amyloid PET**

| Characteristic | Overall (n=4486) | Biomarker negative (n=3163) | Biomarker positive (n=1323) |
|---|---|---|---|
| Age, years | 71.29 (4.67) | 70.95 (4.53) | 72.10 (4.89) |
| Sex: Female | 2,663/4,486 (59.4%) | 1,885/3,163 (59.6%) | 778/1,323 (58.8%) |
| Education, years | 16.58 (2.84) | 16.60 (2.85) | 16.54 (2.81) |
| LWM | -0.13 (0.81) | -0.08 (0.79) | -0.24 (0.84) |
| C3 Memory | -0.25 (0.65) | -0.21 (0.64) | -0.32 (0.67) |

**Tau PET**

| Characteristic | Overall (n=441) | Biomarker negative (n=381) | Biomarker positive (n=60) |
|---|---|---|---|
| Age, years | 71.85 (4.85) | 71.66 (4.78) | 73.04 (5.18) |
| Sex: Female | 254/441 (57.6%) | 217/381 (57.0%) | 37/60 (61.7%) |
| Education, years | 16.22 (2.83) | 16.22 (2.83) | 16.23 (2.85) |
| LWM | -0.25 (0.82) | -0.18 (0.82) | -0.66 (0.74) |
| C3 Memory | -0.33 (0.66) | -0.28 (0.63) | -0.68 (0.74) |

### Table 2: Model Outcomes

| Outcome | Added predictor | M1 AUC | M1 CI low | M1 CI high | M2 AUC | M2 CI low | M2 CI high | ΔAUC | Δ CI low | Δ CI high |
|---|---|---|---|---|---|---|---|---|---|---|
| Plasma pTau217 | LWM | 0.651 | 0.620 | 0.682 | 0.658 | 0.627 | 0.688 | 0.006 | -0.007 | 0.019 |
| Plasma pTau217 | C3 Memory | 0.649 | 0.616 | 0.681 | 0.648 | 0.615 | 0.679 | -0.001 | -0.010 | 0.008 |
| Amyloid PET | LWM | 0.567 | 0.549 | 0.586 | 0.577 | 0.559 | 0.596 | 0.010 | 0.000 | 0.020 |
| Amyloid PET | C3 Memory | 0.566 | 0.547 | 0.585 | 0.568 | 0.549 | 0.588 | 0.002 | -0.007 | 0.011 |
| Tau PET | LWM | 0.518 | 0.431 | 0.601 | 0.644 | 0.570 | 0.718 | 0.127 | 0.037 | 0.219 |
| Tau PET | C3 Memory | 0.522 | 0.437 | 0.609 | 0.636 | 0.553 | 0.716 | 0.114 | 0.008 | 0.219 |

M1 = Model 1, demographics only, M2 = Model 2, demographics + DCA

## Results

- There was limited evidence for demographics alone to discriminate abnormal status for pTau217, amyloid PET or early-tau VOI.
- Addition of the LWM composite to the model improved discriminability of abnormal early-tau VOI, with AUC increasing from 0.518 to 0.644 (ΔAUC= 0.127, 95% CI 0.037 to 0.219).
- Addition of the C3mem composite improved discriminability of abnormal early-tau VOI, with the AUC increasing from 0.522 to 0.636 (ΔAUC= 0.114, 95% CI 0.008 to 0.219).
- For ptau217 and amyloid PET, improvement in AUCs with the addition of each composite were small and the ΔAUC confidence intervals included zero for both LWM and C3 memory, indicating there was no clear improvement in discrimination over and above demographics only.

## Conclusion

- In clinically normal and cognitively unimpaired older adults, the LWM and C3mem composites each improved discrimination for abnormal tau PET over and above demographics alone.
- In contrast, LWM and C3mem provided limited additional discrimination of abnormal plasma ptau217 or amyloid PET beyond demographics.
- These results demonstrate the utility of digital memory composite scores for identifying individuals who are more likely to have early-stage tau accumulation associated with AD.
- DCAs, such as LWM and C3mem, may therefore offer a low-burden and scalable approach to screen for enrichment of tau pathology in preclinical AD trials.

## References

1. Harrington, K. D. et al. Amyloid β-associated cognitive decline in the absence of clinical disease progression and systemic illness. 1–9 (2017) doi:10.1016/j.dadm.2017.05.006.
2. Papp, K. V. et al. Change in Digital Cognitive Test Performance between Solanezumab and Placebo Groups in Preclinical Alzheimer's Disease: Secondary Analyses from the A4 Study. J. Prev. Alzheimer's Dis. 11, 846–856 (2024).
3. Sperling, R. A. et al. Trial of Solanezumab in Preclinical Alzheimer's Disease. N. Engl. J. Med. 389, 1096–1107 (2023).
4. Kotari, V. et al. Early tau detection in flortaucipir images: validation in autopsy-confirmed data and implications for disease progression. Alzheimer's Res. Ther. 15, 41 (2023).

## Disclosures

All authors are employees of Cogstate.

**Presented at CTAD 2026, Boston**