

# Remote assessment of cognition with the unsupervised version of the Cogstate Brief Battery: Association of composite endpoints with Alzheimer's disease biomarkers

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## Background

- With recent approval of disease modifying therapies for early symptomatic Alzheimer's disease (AD), interest has grown in secondary prevention trials (defined as the presence of AD pathology in clinically normal individuals).
- However, it takes screening massive numbers of people to identify cognitively normal people with biomarker evidence of AD.
- Cognitive assessment can be made efficient through use of internet-based registries, which can be linked to clinical trials for potential therapies, but understanding of the relationship between performance on assessments and AD biomarkers is needed.
- The Cogstate Brief Battery (CBB), a compilation of 4 cognitive tests, has been optimized for unsupervised, remote use in registries.
- To determine the utility of validity of data collected from remote administration of the CBB, data from cognitively unimpaired (CU) middle aged adults with various AD risk factors, enrolled in a registry, were investigated for relationships with in-clinic performance on standardized neuropsychological assessments and with AD biomarkers obtained from cerebral spinal fluid (CSF) sampling.

## Methods

- Adults (40-70 years) enrolled in The Healthy Brain Project <https://www.healthybrainproject.org.au> (HBP) were invited to participate in biomarker assessments if they had completed 80% of HBP assessments, provided a saliva sample, indicated they were able to attend a major metropolitan hospital. Exclusion criteria were active infection/skin rash, uncontrolled headaches, immunodeficiency, uncontrolled epilepsy or blood clotting abnormalities.
- 82 adults assessed clinically as cognitively unimpaired (CU) completed unsupervised CBB assessments, followed by in-clinic assessment of AD biomarkers and cognition.
- CBB tests ([www.cogstate.com](http://www.cogstate.com)) included Detection (DET; psychomotor-function), Identification (IDN; attention), One Card Learning (OCL; learning) and One Back (OBK; working memory). Performance on the DET and IDN was defined using speed (msec) of correct answer. Performance on the OCL and OBK tests was measured using accuracy (proportion of correct responses). Scores were standardised using mean and SD of the HBP sample.
- The validated Learning/Working Memory composite and Psychomotor/Attention composite from Cognigram™ were derived from these 4 tests by averaging scores of the component tests.
- To determine whether inclusion of speed in learning (e.g., OCL) and working memory (e.g., OBK) added sensitivity when compared to the validated CBB composite performance measures, two novel composites were also computed. The OCL speed/accuracy composite combined standardized data for speed and accuracy of performance on the OCL test alone. The OCL-OBK speed/accuracy composite combined speed and accuracy data from the OCL and OBK tests.
- In-clinic assessments included the International Shopping List, Logical Memory, Digit Symbol Substitution Test, Mini Mental Status Examination, and FAS to provide a Preclinical Alzheimer's Cognitive Composite (PACC) score.
- CSF concentrations of amyloid beta 42 (Aβ1-42), total tau (t-tau), and tau phosphorylated at threonine 181 (p-tau181) were measured by immunoassay (Roche Elecsys®) and CSF concentrations of neurofilament light chain protein (NfL) were measured using ELISA (UmanDiagnostics, Umeå, Sweden). Aβ+ was classified when CSF Aβ42 levels < 1000, in accord with standardised cut-scores provided by Roche.
- Associations with CSF Aβ<sub>42</sub>, t-tau, p-tau<sub>181</sub>, NfL and PACC were determined for each CBB composite using a series of linear regressions, with age, sex and estimated intelligence as covariates.

## Results

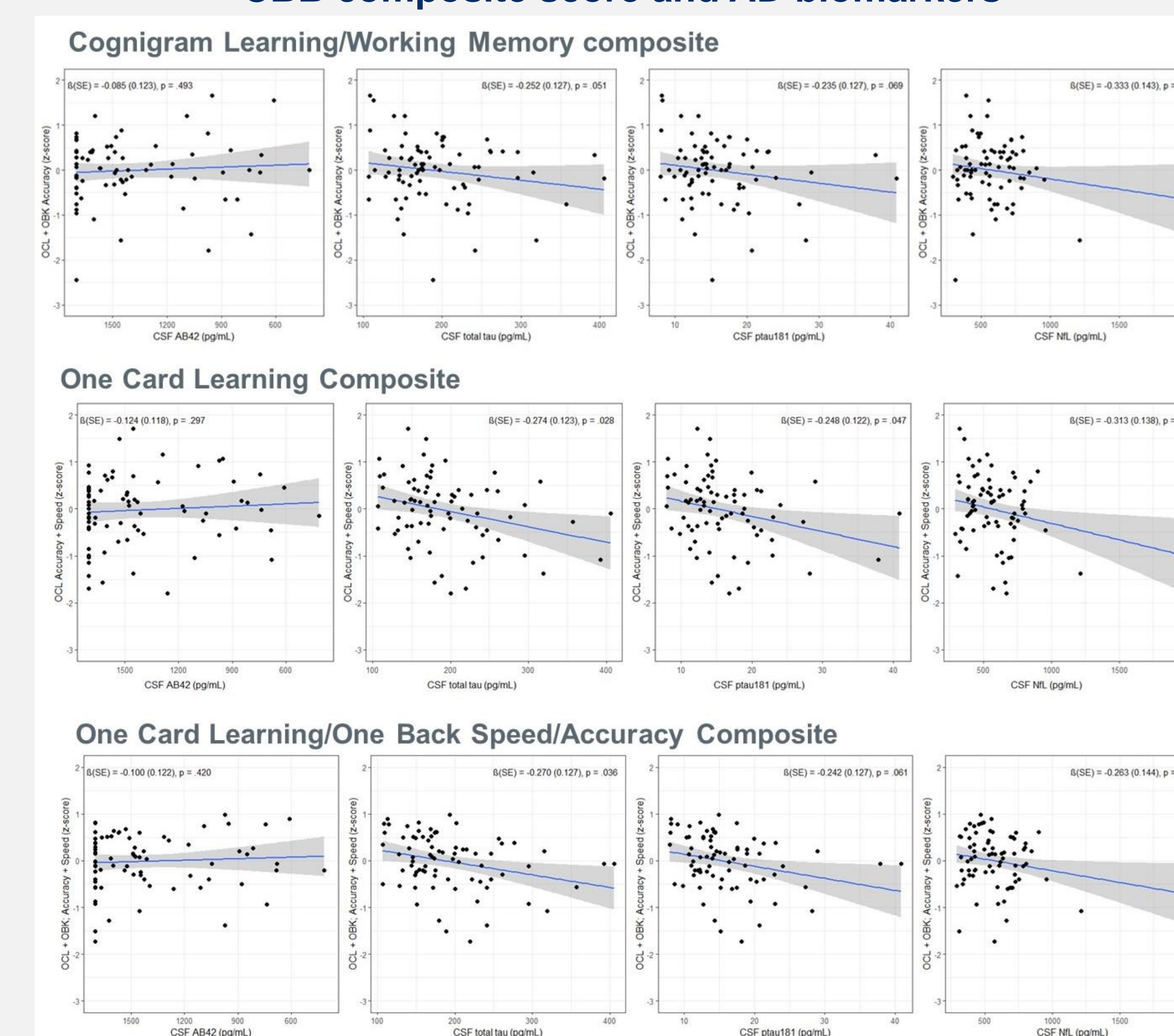
- Enrolled participants had mean age of 58.4 years and were predominantly female and of white race; 13 were amyloid positive (Table)
- The Cognigram Learning/Working memory composite, the OCL speed/accuracy composite, and the OCL-OBK speed/accuracy composite were associated with PACC scores ( $\beta$ (SE) 0.31-0.39 (0.13-0.14),  $p$  0.02-0.005) and with t-tau, p-tau181, and NfL levels. Magnitude of relationships were similar across composites (Figure)
- No cognitive composite was associated with CSF Aβ<sub>42</sub>
- Performance on the Psychomotor/Attention composite was unrelated to AD biomarkers or PACC scores

Table 1: Demographic and cognitive characteristics (N = 82)

Characteristic	% or Mean (SD)
Age (yrs)	58 (6.7)
Female	67%
Education (yrs)	16 (3.5)
Family History of Dementia	79%
APOE e4 carrier	38%
Amyloid positive	17% (13/76)
Time between online and biomarker assessments (yrs)	0.4 (0.9)
Estimated IQ	114.3 (5.5)
MMSE	28.8 (1.2)
CDR Sum of Boxes	0.04 (0.16)
ISLT Total Recall	24.89 (3.67)
ISLT Delayed Recall	8.90 (2.05)

\*amyloid positive was defined by CSF Aβ<sub>42</sub> levels < 1000, in accordance with standardized cut-offs

Figure 1: Nature and strength of relationships between each CBB composite score and AD biomarkers



## Methodologic Considerations

- Small sample size of young, healthy participants (few amyloid positive cases) limit power to detect associations between CBB tests and AD biomarkers
- Sensitive biomarkers to the earliest pathologic changes in AD (such as pTau217) were not available, limiting ability to detect associations between performance and AD biomarkers in participants who were still cognitively normal

## Conclusions

- In CU middle-aged adults, unsupervised performance on CBB composites containing learning and working memory measures, but not psychomotor speed or attention, were associated with in-clinic neuropsychological outcomes and AD biomarkers. For efficiency, assessment could be reduced to 2 tests (One Card Learning and One Back) when looking for impairment related to AD
- The addition of performance speed to accuracy did not add substantively to the sensitivity of composite score of learning and working memory.
- Remote measurement of cognition can validly assess aspects of learning and working memory disrupted by early AD processes such as increases in tau and could be useful for identification of individuals with early disease.

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