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## Associations Between Performance on an Abbreviated CogState Battery, Other Measures of Cognitive Function, and Biomarkers in People at Risk for Alzheimer's Disease

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## **Associations between performance on an abbreviated CogState battery, other measures of cognitive function, and biomarkers in people at risk for Alzheimer's disease**

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## Abstract

It is not known whether computerized cognitive assessments, like the CogState battery, are sensitive to preclinical cognitive changes or pathology in people at risk for Alzheimer's disease (AD). In 469 late middle-aged participants from the Wisconsin Registry for Alzheimer's Prevention (mean age 63.8±7 years at testing; 67% female; 39% APOE4+), we examined relationships between a CogState abbreviated battery (CAB) of seven tests and demographic characteristics, traditional paper-based neuropsychological tests as well as a composite cognitive impairment index, cognitive impairment status (determined by consensus review); and biomarkers for amyloid and tau (CSF phosphorylated-tau/Aβ<sub>42</sub> and global PET-PiB burden) and neural injury (CSF neurofilament light protein). CSF and PET-PiB were collected in n=71 and n=91 participants, respectively, approximately four years prior to CAB testing. For comparison, we examined three traditional tests of delayed memory in parallel. Similar to studies in older samples, the CAB was less influenced by demographic factors than traditional tests. CAB tests were generally correlated with most paper-based cognitive tests examined and mapped onto the same cognitive domains. Greater composite cognitive impairment index was associated with worse performance on all CAB tests. Cognitively impaired participants performed significantly worse compared to normal controls on all but one CAB test. Poorer One Card Learning test performance was associated with higher levels of CSF phosphorylated-tau/Aβ<sub>42</sub>. These results support the use of the CogState battery as measures of early cognitive impairment in studies of people at risk for AD.

## Keywords

Amyloid; cognitive impairment; cerebrospinal fluid; biomarkers

## Key words not in MeSH database

CogState; preclinical Alzheimer's disease; computerized cognitive testing; neural injury

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## 1 INTRODUCTION

CogState is a computerized cognitive battery spanning domains of memory, executive function, and speed of processing. It has been shown to have acceptable stability and test-retest reliability with minimal practice effects at short test-retest intervals in groups of healthy controls and patients at various stages of cognitive impairment and dementia [1, 2]. Computerized testing, such as the CogState battery, may hold potential for detecting early cognitive dysfunction associated with preclinical Alzheimer's disease (AD)[3].

Previous studies have demonstrated differences between healthy controls, Mild Cognitive Impairment (MCI), and AD, with the most pronounced impairments in the latter two groups

on CogState tests of learning and memory [4, 5]. The vast majority of studies investigating biomarker correlates of the CogState have focused on neuroimaging biomarkers, with a particular focus on PET amyloid imaging. The majority [3, 6–11] but not all [12] have found an association with amyloid. One study also found an association with hippocampal volume and glucose metabolism [12]. Of note, the majority of published studies that have examined biomarkers and the CogState battery have been performed on two cohorts, the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) and the Mayo Clinic Study on Aging. The present study adds the largest long-term study of healthy relatives of persons with Alzheimer's disease, the Wisconsin Registry for Alzheimer's Prevention (WRAP), to the cohorts simultaneously investigating biomarkers and the CogState battery. Additionally, there is a dearth of information in the current scientific literature on the association between the CogState battery and potentially informative cerebrospinal fluid (CSF) biomarkers for Alzheimer's pathology and neural injury. This is an important gap to fill as recent work suggests that CSF biomarkers become abnormal in the earliest stages of AD, before changes in amyloid positron emission tomography are apparent [13, 14].

The present study investigated whether CogState is sensitive to pre-dementia cognitive dysfunction and early accumulation of AD pathology during late-midlife. First we explored relationships between CogState tests and demographic characteristics. Next, we examined relationships between CogState tests and three measures of cognitive function: individual scores on traditional paper-based neuropsychological tests, a composite cognitive impairment index, and cognitive status (cognitively impaired vs. cognitively normal). Finally, we investigated sensitivity to underlying AD pathology by examining whether biomarkers for amyloid and tau (CSF phosphorylated-tau/A $\beta$ <sub>42</sub> and global PET-PiB burden) and neural injury (CSF neurofilament light protein) predicted CogState performance approximately four years later. We hypothesized that performance on the CogState battery would be relatively robust to demographic variability but would be associated with cognitive functioning as well as biomarkers for AD pathology. Additionally, to evaluate whether the CogState battery may be more robust to demographics and more associated with disease outcomes compared to traditional neuropsychological tests, we also examined relationships of three traditional tests of delayed memory with demographics, cognitive function, and biomarkers and provide effect sizes for comparison between the cognitive measures. By examining relationships between the CogState battery and multiple measures of early cognitive dysfunction as well as biomarkers for amyloid and neural injury in an at-risk cohort, this study investigated whether the CogState battery is sensitive to early cognitive and pathological changes suggestive of incipient AD.

## 2 MATERIALS AND METHODS

### 2.1 Participants

WRAP is a longitudinally followed cohort designed to identify biological and lifestyle risk factors associated with development of dementia due to Alzheimer's disease [15–17]. The WRAP study consists of 1,545 participants (mean age=53.6±6.6 years at first cognitive assessment), of which 72.4% have a parental family history of dementia due to Alzheimer's disease. In 2014, the CogState was added to the assessment protocol for each visit; data used

in this paper represents first CogState for each person, although the overall WRAP visit number varies from 2 to 5 (3.2% of participants were administered the CogState at visit 2, 19.8% at visit 3, 24.5% at visit 4, and 52.5% at visit 5). Participants were selected for the current analyses if they had completed at least one of the seven CogState tests that have been added to the WRAP battery. The University of Wisconsin Institutional Review Board approved all study procedures, informed consent was obtained for all participants, and the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Cognitive status was determined via consensus review conference by a panel of experts in cognitive aging and dementia, including clinical neuropsychologists, physicians, and nurse practitioners for the same WRAP visit that CogState was administered. The consensus panel reviews cognitive performance as well as additional information in the participant's chart (e.g., medical history, social history, informant reports) to determine final cognitive status. A cut-off of 1.5 standard deviations below a robust normative sample (e.g., low-risk WRAP participants who remained normal throughout the study; [17, 18]) was used to define impairment on cognitive measures. A diagnosis of clinical MCI was based on the NIA-AA criteria [19, 20] including subjective cognitive decline, objective impairment in one or more cognitive domains, and preservation of functional abilities. The construct of early MCI was developed to identify cognitive decline expected to precede a clinical MCI diagnosis, and identifies individuals who exhibit lower than expected performance on neuropsychological measures (e.g., 1.5 SD below demographically-corrected robust norms), but do not necessarily report subjective cognitive decline. Of the 469 participants who were administered the abbreviated CogState battery, 10 met criteria for clinical MCI, another 60 exhibited subtle deficits indicative of early MCI, and 6 were classified as having a cognitive impairment primarily due to depression rather than MCI. The clinical MCI and early MCI participants were grouped together into a cognitively impaired group and the remaining 393 unimpaired participants were considered cognitively normal (Table 1). The 6 individuals with potential non-MCI cognitive impairment were included in the total sample but in neither the cognitively impaired nor normal groups. None of the cognitively impaired participants had dementia.

## 2.2 Measures of cognition

**2.2.1 CogState**—Select tests from the CogState battery were administered on a laptop to participants after completing the non-computerized assessments. This CogState abbreviated battery (CAB) included a test of delayed visual memory through paired associate learning (Continuous Paired Associate Learning, CPAL), speed of visual processing (Groton Maze timed chase test, GMCT), executive function (Groton Maze learning test, GML), delayed recall (Groton Maze learning test delayed recall, GMR), and working memory (One-card learning, OCL; One-back memory, ONB; and Two-back memory, TWOB). For CPAL, GML, and GMR, total number of errors was assessed; for GMCT moves per second was assessed; and for the three card tasks (OCL, ONB, and TWOB) accuracy was assessed using the arcsine proportion to correct for normality. Data were only included that passed criteria for completion and integrity. To be considered “complete,” at least 75% of all responses needed to be observed for the card tasks (OCL, ONB, TWOB), all 28 steps of the maze path

needed to be completed for the Groton Maze tasks (GML, GMR), and all rounds needed to be completed for CPAL; there is no completion check for GMCT. Integrity checks were completed for the three card tasks only and were satisfied if the proportion correct was above chance (at least 50% correct). 99.4–100% of participants passed completion checks for each of the seven tests and 97.5–99.6% passed the integrity checks for each of the three card tasks. Selection of test outcomes, transformations to correct for normality, and tests of completion and integrity were performed per the recommendations from the CogState manual [21]. Additionally, not all participants finished the full CAB, with more missing data for tests administered at the end of the battery. All participants finished at least one test and 98.7% finished all seven tests. Non-completion of the CAB was due to fatigue, frustration, or technical difficulties. Missing data and checks for completion and integrity are summarized in Supplementary Table 1.

**2.2.2 Traditional neuropsychological battery**—A comprehensive neuropsychological battery was performed at each WRAP visit. For this analysis, non-computer tests were selected that measure memory, language, executive function, or global cognitive function. These included Rey Auditory Verbal Learning Test (RAVLT [22]) total trials 1–5 and delayed recall; Wechsler Memory Scale-Revised (WMS-R [23]) Logical Memory I and II (immediate and delayed recall, respectively); Brief Visuospatial Memory Test-Revised (BVRT-R [24]) immediate and delayed recall; Boston Naming Test–2<sup>nd</sup> Edition (BNT [25]); Animal Naming [26]; Controlled Oral Word Association Test phonemic fluency (CFL [27]); Stroop Neuropsychological Screening Test color-word interference trial (Stroop [28]); Trail Making Test (TMT [29]) Parts A and B; Wechsler Adult Intelligence Scale-Revised (WAIS-R [30]) Digit Symbol; Wechsler Adult Intelligence Scale-Third Edition (WAIS-III [31]) Letter Number Sequencing and Digit Span subtests; and Mini Mental State Examination (MMSE [32]).

**2.2.3 Composite cognitive impairment index**—A composite cognitive impairment index (CCII) was calculated using a set of eight cognitive measures: TMT A and B, WAIS-III Digit Span forward and backward, RAVLT total trials 1–5 and delayed recall trial, BNT, and MMSE. Visits were excluded when fewer than four of these measurements were available. We applied the progression score model [33–35] to align individuals along a linear cognitive trajectory based on their longitudinal cognitive measure profiles, adjusting for inter-individual differences in rates of change. The composite cognitive impairment index computed using this method is an individualized summary of the eight cognitive measures, with higher values indicating lower cognitive performance in all measures. Different from previous approaches, we accounted for correlations among cognitive measures. To remove confounding effects of age at entry into WRAP, a composite was estimated at age 65 based on an approximate expression for the time derivative of the CCII.

## 2.3 Biomarker collection

Some WRAP participants were recruited for biomarker substudies which do not necessarily correspond to a specific WRAP visit. We examined PET and CSF biomarker data, which were collected independently and up to several years prior to the CogState.

**2.3.1 PET-PiB**—Detailed methods for [C-11] PiB radiochemical synthesis, PiB-PET scanning with a 70 minute dynamic acquisition, and distribution volume ratio map generation using the Logan method and the cerebellum as a reference region have been described previously [36]. PiB-PET images were registered to a T1-weighted anatomical scan collected on a GE 3.0 Tesla MR750 (Waukesha, WI) using an 8 channel head coil [36, 37]. A composite measurement of global amyloid derived from eight bilateral ROIs (angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus) was calculated as described previously [38, 39]. N=91 participants underwent PiB-PET imaging approximately 4.1 years (SD 0.66, range 2.0–5.3) prior to CAB testing.

**2.3.2 Cerebrospinal fluid**—CSF was collected as described previously [40, 41]. CSF A $\beta_{42}$  and phosphorylated-tau (p-tau) were quantified with sandwich ELISAs (INNOTEST  $\beta$ -amyloid1–42 and Phospho-Tau[181P], respectively; Fujirebio Europe, Ghent, Belgium). CSF p-tau/A $\beta_{42}$  was calculated by dividing CSF p-tau by CSF A $\beta_{42}$ . CSF neurofilament light protein (NFL) was measured with a sandwich ELISA method as described by the manufacturer (NF-light ELISA kit, UmanDiagnostics AB, Umeå, Sweden). N=70 participants underwent baseline lumbar puncture approximately 3.7 years (SD 1.11, range 1.17–5.33) prior to CAB testing.

CSF assays were performed in two batches. We corrected for batch differences using simple linear regression (SLR) on a subset of CSF samples (n=96 from the entire CSF database, not just from individuals who had also undergone CogState testing) that were assayed in both batches. SLR was also used to test whether batch corrections were necessary using null hypothesis tests of a slope of 1 and an intercept of 0. If there was insufficient evidence to suggest that any of these hypotheses should be rejected, raw values from both batches were used; otherwise, predictions were made with SLR on CSF values from batch 2 as if they had been tested in batch 1. All analyses for CSF batch corrections were performed using R version 3.2.3 using the base “lm” function.

## 2.4 Statistical analyses

Significance was inferred at a Bonferroni-corrected p-value for seven CogState tests ( $p < .05/7 = .007$ ) unless otherwise stated.

**2.4.1 Correlations between CAB, demographics, and traditional neuropsychological tests**—For dichotomous characteristics (sex, parental family history of AD, and APOE4 carriage), t-tests were performed on the seven CogState variables. For continuous variables (total years of education; literacy as measured by baseline Wide Range Achievement Test reading raw score; age at testing; depression as measured by the Center for Epidemiologic Studies Depression Scale; and traditional paper-based neuropsychological tests) and ordinal variables (e.g., computer familiarity as measured on a Cognitive Activities questionnaire), we performed Spearman rank-order correlations. Cohen’s d were calculated for t-tests and effect sizes of .2, .5, and .8 are interpreted as small, medium, and large, respectively. Correlation coefficients of .1, .3, and .5 are interpreted as small, medium, and large effect sizes, respectively [42].



To determine whether CAB is more robust to education and other demographic characteristics compared to traditional paper-based tests, we also examined correlations between demographics and select traditional neuropsychological tests. Numerous studies have identified delayed episodic memory as one of the earliest cognitive domains to become impaired in AD [43–45], likely during the preclinical timeframe; therefore, to reduce the number of multiple comparisons, we selected three tests of delayed memory from our neuropsychological battery: RAVLT delayed recall, Logical Memory delayed recall, and BVMT-R delayed recall. For the analyses described here and as follows, these three delayed recall tests served to provide context for interpreting the CAB findings compared to more traditional neuropsychological testing formats.

**2.4.2 ANCOVA comparing cognitive groups on CAB performance**—Scores on the CAB of cognitively impaired participants were compared to cognitively normal controls by ANCOVA controlling for age, literacy, sex, APOE4 positivity, family history of AD, and computer familiarity. Effect sizes by partial eta squared are reported. Small, medium, and large effect sizes for eta squared are .01, .06, and .14, respectively [46]. We did not compare cognitive groups on the select traditional neuropsychological tests identified in section 2.4.1 because these tests were evaluated during diagnostic consensus conference.

**2.4.3 Associations between the individual cognitive tests and composite cognitive impairment index**—In addition to examining individual neuropsychological tests, we investigated whether CCII, which takes advantage of longitudinally measured cognition up to (and including) the visit at which the CAB was administered, is associated with performance on the CAB. We ran regression analysis for each of the seven CogState tests, with the CAB test as the dependent variable and CCII as the independent variable of interest, controlling for age at CAB testing, literacy, sex, APOE4, family history of AD, and computer familiarity. Variance inflation factors (VIF) and tolerance were assessed and deemed normal if tolerance was greater than .1 and VIF was less than 10. Cohen's  $f^2$  for hierarchical regression,  $R^2$ , and  $R^2$ -change (the change in  $R^2$  after adding CCII to the model) are reported. Cohen's  $f^2$  of 0.02, 0.15, and 0.35 are considered small, medium, and large, respectively [46]. For comparison, parallel models were run for the three traditional delayed recall tests except RAVLT delayed which was used to calculate CCII.

#### **2.4.4 Cognition and biomarker associations**

**2.4.4.1. Biomarker normalization and dichotomization:** Although PiB burden was skewed to the right, traditional transformations were ineffective at improving normality. Instead, we chose to examine PiB burden untransformed (with and without an outlier) as a continuous variable and as a dichotomous variable (i.e., PiB positive vs. PiB negative) with the goal of capturing the hypothesized underlying binomial distribution [47]. A cut-off value for PiB positivity was determined using receiver operating characteristic (ROC) analysis in pROC R Statistical Package [48] bootstrapping 2000 times with replacement and stratification of sample. We used expert visual ratings of PiB positive or negative that have been described previously as the diagnostic groups [36, 37]. Supplementary Figure 1 depicts the ROC plot with an area under the curve of .974. A threshold was determined using Youden's Index which identifies the PiB burden value that maximizes both sensitivity and

specificity [49]. A threshold of 1.19 was identified which corresponded to sensitivity of .938 and specificity of .917.

**2.4.4.2. Cognition and biomarkers associations:** We performed Spearman correlations between CAB variables and three biomarkers of interest: CSF p-tau/A $\beta$ <sub>42</sub>, CSF NFL, and global PiB burden (with and without an outlier). T-tests were performed to compare CogState performance between PiB+ and PiB- groups. Furthermore, we investigated promising correlations (significant or trending) through multiple regressions with CAB scores as the dependent variable and biomarker as the independent variable of interest. In addition to the covariates used in the CCII regression models, we additionally controlled for the interval from biomarker collection to CAB testing (CSF to CAB 44.3 $\pm$ 13.5 months; PET-PiB to CAB 49.6 $\pm$ 7.9 months) because the biomarker assessments were conducted at various time points prior to administration of the CAB. Comparable models with ANCOVA were performed for PiB positivity. VIF and tolerance were again inspected. Because we expected smaller effect sizes, we optimized statistical power by not adjusting for multiple comparisons in these cognition/biomarker analyses (i.e.,  $p < .05$  was considered significant). For comparison, we also analyzed the relationships between the three traditional neuropsychological tests (see 2.4.1) and biomarkers.

### 3 RESULTS

Participant characteristics are summarized in Table 1.

#### 3.1 Correlations between the CAB, demographics, and traditional neuropsychological tests

None of the seven CAB scores or traditional delayed memory scores differed significantly by APOE4 status or family history. Females performed better on CPAL (fewer errors;  $p < .001$ , Cohen's  $d = 0.39$ ) and on GMCT (more moves per second;  $p = .004$ , Cohen's  $d = -0.27$ ), similar to traditional verbal memory tests [RAVLT delayed ( $p < .001$ , Cohen's  $d = -0.81$ ) and Logical Memory delayed ( $p = .005$ , Cohen's  $d = -0.26$ )]. Spearman rank-order correlation coefficients are reported in Table 2 for age, education, literacy, depression, and computer familiarity. Effect sizes for all associations with demographic and CAB variables were small except between age and GMCT and age and TWOB, which were both moderate. A large effect size was observed for sex on RAVLT delayed and a moderate effect size was observed for literacy on Logical Memory delayed. All other effect sizes were small.

The majority of neuropsychological test scores and CAB scores were significantly correlated. A correlation matrix is provided as Table 3 with moderate correlations in bold. Within CogState correlations are reported in Supplementary Table 2.

#### 3.2 CAB performance by cognitive status

After controlling for risk factors and demographics, CAB performance differed between individuals who were cognitively impaired and cognitively normal controls for all CAB tests ( $p < .007$ , Table 4, Figure 1) except ONB. All effect sizes were small except GMR, which was moderate. There were several other significant ( $p < .05$ ) predictors in the CogState models.

Age and literacy were significant predictors of CogState performance in every model except ONB. Sex was a significant predictor for CPAL, GML, and GMR. APOE4 was a significant predictor of CPAL and GML. Computer familiarity was significantly associated with GMCT and family history was significantly associated with OCL.

### 3.3 Associations between individual cognitive tests and composite cognitive impairment index

VIF and tolerance were in the normal range for all models. CCII significantly predicted performance on all CAB tests ( $p < .007$ , Table 5, Figure 2). Age at CAB testing (CPAL, GMCT, GML, OCL, TWOB) and sex (GML, GMR, TWOB) were common additional predictors of CAB performance ( $p < .05$ ). Computer familiarity also significantly predicted GMCT only ( $p < .05$ ). Logical memory delayed and BVMT-R delayed also significantly predicted CCII ( $p < .007$ , Table 5). Effect sizes were moderate for CPAL, GMR, Logical Memory delayed, and BVMT-R delayed; all others were small.

### 3.4 Associations between cognition and biomarkers

Based on null hypothesis testing,  $p$ -tau/ $A\beta_{42}$  but not NFL required batch correction. Overall, biomarkers were not strongly associated with the CAB or delayed recall scores in the subset with CSF ( $n=70$ ) or PiB ( $n=91$ ), with significant and trending associations only present for the CSF biomarkers. Spearman correlations are reported in Table 6. When significant or trending correlations were investigated further in regression and ANCOVA models, only CSF  $p$ -tau/ $A\beta_{42}$  (Figure 3) was a significant predictor of OCL performance ( $\beta = -1.13$ ,  $t = -3.09$ ,  $f^2 = .162$ ,  $R^2 = .203$ ,  $R^2$ -change = .129,  $p = .003$ ).

## 4 DISCUSSION

Computer-based psychological batteries offer several advantages over traditional psychological (often paper-and-pencil-based) tests including reduced testing time and administrative training, standardization of test administration, accurate measures of response latencies, and reduced risk of human error [50, 51]. Consequently, there has been a shift in interest to computer-administrated psychological batteries. The CogState battery is one such computerized battery that has been shown to have good accuracy, efficiency, and stability for repeated assessment, as well as demonstrated sensitivity to cognitive impairment and cognitive change [52, 53]. Here we evaluated performance on an abbreviated CogState battery at a single time point in relation to demographics characteristics, traditional neuropsychological tests, cognitive status, a composite cognitive score, and biomarkers in a late-middle-aged sample from the WRAP cohort. We also sought to provide a context for assessing the sensitivity of the select CogState tests by examining traditional gold-standard tests of delayed memory in parallel. Our findings that select CogState tests were associated with several measures of early cognitive impairment and a CSF biomarker for AD pathology support the use of the CogState battery as a neuropsychological testing tool during the preclinical timeframe.

Our results are consistent with previous studies of CogState showing generally weak relationships with demographic variables and weak to moderate associations with traditional

neuropsychological tests [5, 11, 54]. Associations with demographic characteristics were generally small, with the most consistent relationships observed with age and sex. GMCT was most affected by demographic characteristics like computer familiarity, education, and literacy. Traditional delayed memory tests were more strongly and consistently associated with demographic characteristics (e.g., all three tests were significantly correlated with age, education, and literacy) than CogState measures, supporting the theory that the CogState battery is more robust to education level compared to traditional paper-based neuropsychological tests.

The majority of the CAB and traditional tests were significantly correlated, and moderate correlation coefficients were generally observed between tests of comparable cognitive domains. CPAL was moderately correlated with almost all traditional tests of memory examined. The Groton Maze tests combine skills of executive function, learning, and memory and correspondingly were moderately correlated with traditional neuropsychological tests of memory (RAVLT, BVMT) and executive function (Stroop, TMT, WAIS-R Digit Symbol), as well as Animal Naming. Interestingly, GMCT, which is generally considered a task to introduce subjects to the Groton Maze learning and delayed recall tasks, had the most frequent associations with other neuropsychological tests of the three maze paradigms; GML and GMR were both only moderately correlated with BVMT-R immediate and delayed recall. Of the card tests, OCL, a visual memory test, was moderately correlated with RAVLT delayed recall and TMT Part B; and TWOB, a test of working memory, was moderately correlated with three executive functioning tasks: Stroop, TMT Parts A and B, and WAIS-R Digit Symbol. Moderate correlations between CogState and traditional neuropsychological tests, therefore, were generally consistent with the domains they are expected to probe.

Curiously, although ONB is included in CogState's recommended Alzheimer's Battery [4], it was the most weakly correlated with any traditional neuropsychological tests, often not reaching even liberal thresholds for statistical significance (i.e.,  $p < .05$ ). Performance on ONB was also the only CAB test that did not differ between cognitively normal and cognitively impaired groups. Given the relative health and younger age of our sample, we suspect this test was too easy for our participants and resulted in a marked ceiling effect. Indeed, participants only made on average two errors on ONB with one-fourth of the sample making zero errors and 93% of participants making five or fewer errors. This contrasts with the other two card tasks: an average of five errors were made on TWOB with only 7% making zero errors, and an average of 26 errors were made on OCL and no participants made fewer than 10 errors. Others have found differences between diagnostic groups on ONB test using reaction time instead of accuracy, which could be less prone to ceiling effects and may be more applicable in cohorts without clinical dementia [11]. Its major function in the battery we selected was to serve as a warm up test for the more difficult TWOB task. Our results suggest that ONB accuracy is less useful in late middle-age.

One of the earliest studies of the CogState battery showed that 15 patients with MCI declined within a one-year period on a CogState memory task (Continuous Learning Test) compared to age, education, IQ, and gender matched controls; while decline was not detectable using routine memory tests in either group [55]. While we were not able to

address decline in CogState performance across groups with only one time point of CAB administration, we did incorporate the extensive longitudinal data that has been collected in WRAP using traditional neuropsychological tests to create a composite of cognitive impairment. Unlike simple z-score composites, the CCII adjusts for inter-individual differences in rates of change, removes confounding effects of age at study entry, and accounts for correlations among cognitive measures. This type of cognitive impairment index could be a useful tool against which to measure novel tests of cognitive/clinical status and progression, like the CogState battery. Both the CAB and traditional delayed memory tests were associated with CCII. Effect sizes were moderate for CPAL, GMR, Logical Memory delayed, and BVMT-R delayed with the largest effect size observed for CPAL. Since GMR, CPAL, Logical Memory delayed recall, and BVMT-R delayed recall all measure delayed memory, it would seem that this cognitive domain is either driving the CCII calculation or that delayed recall tests—either computerized or not—are the most sensitive to early cognitive decline, as measured by this unique composite cognitive impairment index.

With the exception of ONB, cognitively impaired individuals performed significantly worse on the CAB tests compared to cognitively normal controls. The difference was generally small, with the most marked difference observed for GMR, a tests of delayed memory, suggesting that GMR is most sensitive to early cognitive dysfunction among the CAB variables.

After correcting for covariates, only CSF p-tau/A $\beta$ <sub>42</sub> was associated with worse performance on OCL test, which uses a pattern separation paradigm to measure visual memory. Most previous studies that have found an association between biomarkers and CogState tests have evaluated intra-individual cognitive decline based on longitudinally acquired CogState testing rather than a single time point [3, 6–8, 56]. In contrast, a study with a single CogState battery evaluation did not find an association between CogState test performance and amyloid PET [12]. The latter study did, however, find relatively weak associations between CogState test performance and FDG-PET hypometabolism and smaller hippocampal volumes, suggesting that a single time point could still be informative of underlying pathology. While we were able to detect a relationship between a CSF measure of co-occurring amyloid and tau pathology and one CogState test but none of the three traditional delayed memory tests, it remains unclear whether CogState tests at one time point would substantially improve inference about underlying pathology beyond what is possible with traditional paper-based neuropsychological tests.

#### 4.1 Limitations

The primary limitations of this study are that biomarkers were collected several years before CAB administration and that we do not yet have serial CAB testing, both of which constrain our ability to make stronger inferences about the CogState battery and underlying pathology. The correlational analyses between the CAB and traditional tests may have also been affected by the number of times of previous administration on the pencil-and-paper tests which are known to have practice effects [57, 58]. Due to testing duration considerations, we only selected two of the four CogState card tasks; while the selected tasks utilize the

cognitive domains of primary interest to this study (learning and memory), this may limit the comparability to other studies which used all four card tasks. It is also worth noting again the smaller samples sizes in the biomarkers analyses; it is possible that we lacked sufficient power to detect important associations between these cognitive tests and underlying pathology; indeed, although most correlations between p-tau/A $\beta$ <sub>42</sub> and the CAB tests were considered not significant, all were in the expected direction. Additionally, our study cohort was largely Caucasian and well educated, and so generalizability is restricted. This homogeneity may have also reduced our ability to detect demographic correlates of the CAB. It will be important to perform similar studies with CogState in more diverse populations. Longitudinal clinical outcomes will be important for evaluating prognostic utility of the CAB.

## 4.2 Conclusions

Overall this study provided support for the use of the CAB in evaluating cognitive function during late-middle-age. The present study is unique in that the WRAP participants are younger and cognitively healthier than the typical clinical MCI groups that have been investigated in prior studies; the population is also enriched for higher risk of developing MCI and dementia due to parental history of AD. Although prior studies provide evidence that the CogState battery can differentiate between healthy controls and clinical MCI in older age, this study suggests that it is also sensitive to decline in early MCI, before clinical symptoms and multiple objective cognitive impairments are apparent. It further provides evidence for an association between one CogState test in particular (OCL) and an important pathological marker for preclinical AD, CSF p-tau/A $\beta$ <sub>42</sub>. However, it also suggests that CogState at a single time point may not substantially improve preclinical AD detection over traditional neuropsychological tests. Still, its administration offers several advantages over paper-based tests, which make it desirable for large, longitudinal studies with demographic variability. Future directions will focus on longitudinally collected CogState data in the WRAP cohort and examination of a greater array of biomarkers.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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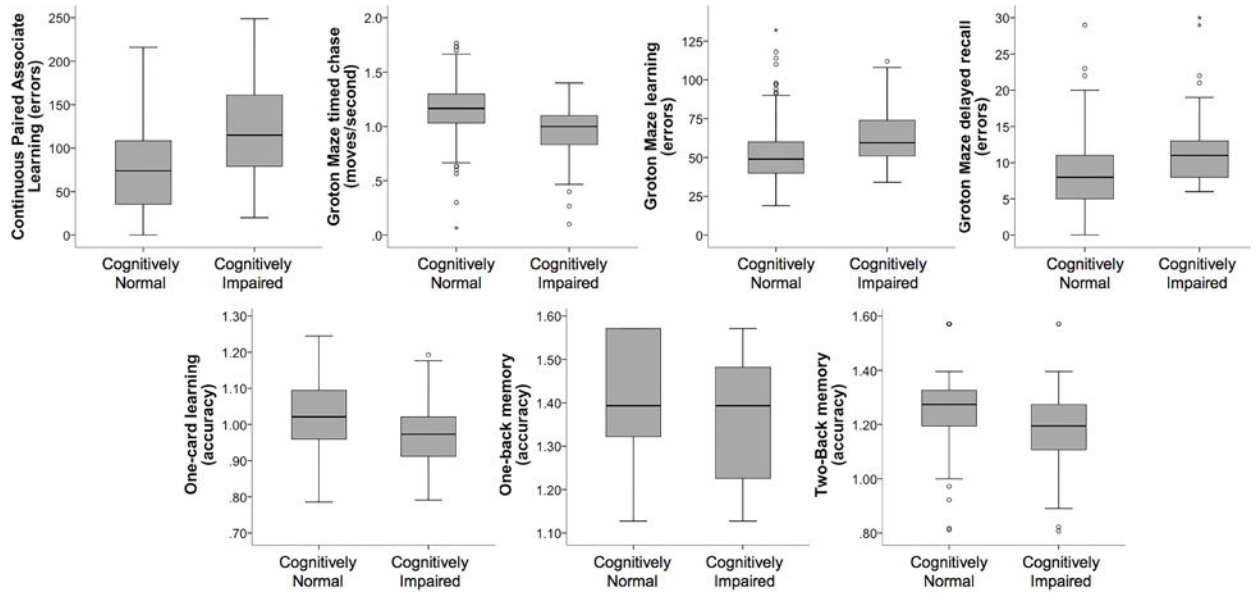
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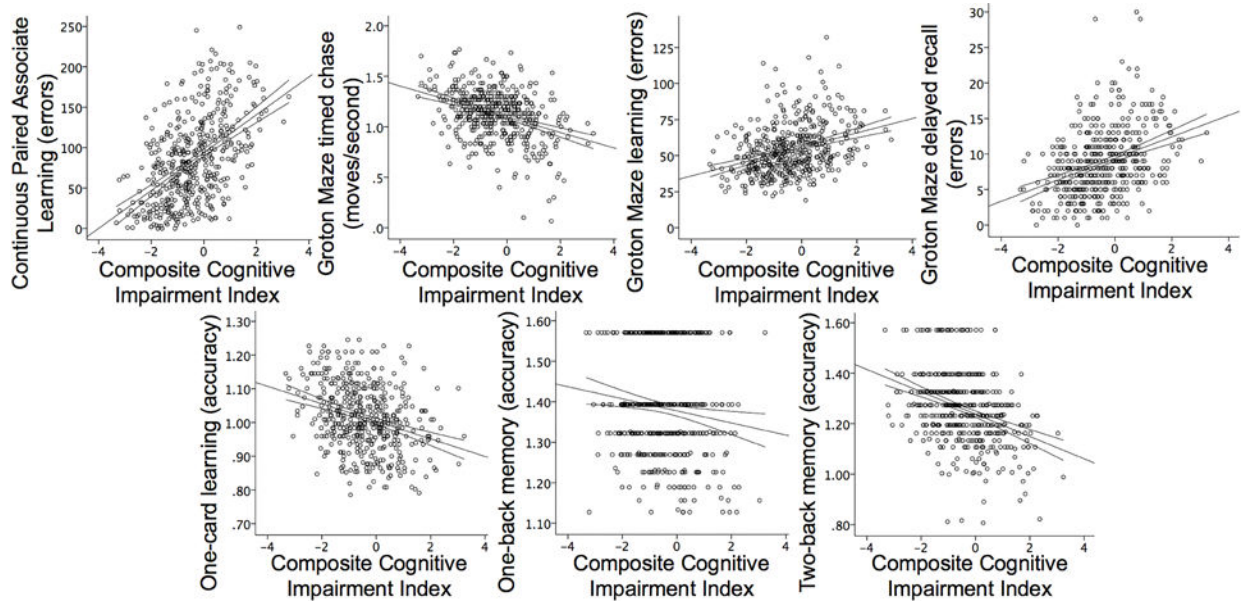


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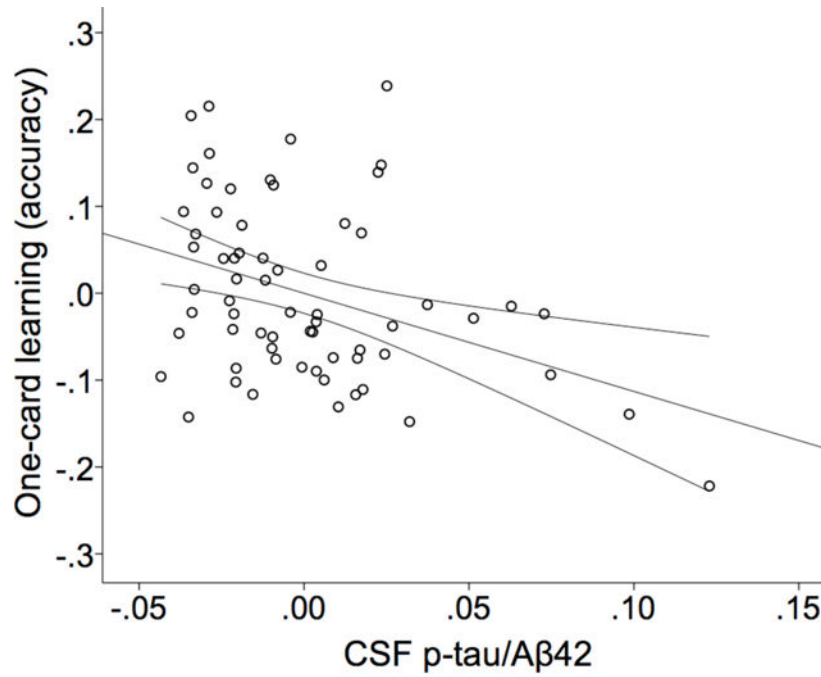
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**Figure 1.** Boxplots depicting comparison of Cognitively Normal and Cognitively Impaired groups on mean performance on CogState tests. Accuracy was transformed using the arcsine proportion to correct for normality.



**Figure 2.** Relationships between CogState tests and a composite cognitive impairment index estimated at age 65. 95% confidence intervals for the regression line are displayed. Accuracy was transformed using the arcsine proportion to correct for normality.



**Figure 3.**

Partial regression plot of CSF p-tau/Aβ<sub>42</sub> and One-card learning performance as measured by arcsine-corrected accuracy. 95% confidence interval for the regression line is displayed.  $R^2=.139$ .

**Table 1**

## Participant characteristics

Sample characteristic	Total Sample (N=469)	Cognitively Impaired (n=70)	Cognitively Normal (n=393)	p-value*
Age at CogState (years)	64.81 (6.6)	66.26 (6.1)	63.39 (6.6)	.001
Sex (% female)	67.0%	57.1%	68.4%	.064
APOE4+	39.0%	37.1%	38.7%	.808
Family History of AD	74.4%	67.1%	75.6%	.137
Education (years)	16.50 (2.6)	16.40 (2.9)	16.53 (2.6)	.703
WRAT reading standard score**	106.35 (9.2)	105.17 (11.2)	106.57 (8.8)	.242
WRAT reading raw score**	51.17 (4.4)	50.41 (5.4)	51.31 (4.2)	.189
Depression (CES-D)	6.21 (6.6)	6.30 (5.8)	5.93 (6.1)	.634
Computer familiarity***	4.74 (0.7)	4.56 (1.0)	4.77 (0.7)	.097

Values are Mean (SD) unless otherwise indicated.

\* P-value is for chi square or t-test comparing Cognitively Impaired and Cognitively Normal groups.

\*\* WRAT reading standard scores in addition to raw scores are reported for easier interpretation, but raw scores were used in all statistical models to main consistency with other variables which were not standardized for age and sex. Computer familiarity was measured on a 1–5 scale where “1” corresponds to using a personal computer “once a year or less” and “5” corresponds to using a personal computer “every day or about every day.” APOE4=apolipoprotein E4 allele. WRAT=Wide Range Achievement Test. CES-D=Center for Epidemiological Studies Depression Scale.

**Table 2**

Spearman rank-order correlations between demographic characteristics and CogState and traditional delayed recall tests

Cognitive Test	Age at CogState (years)	Education (years)	WRATreading raw score	Depression (CES-D)	Computer familiarity
CPAL errors	.234 **	-.023	-.122 *	.034	-.004
GMCT moves/sec	<b>-.452</b> **	.126 **	.140 **	-.073	.224 **
GML errors	.286 **	-.048	-.113 *	.059	-.026
GMR errors	.174 **	-.035	-.103 *	.110 *	-.036
OCL accuracy	-.233 **	-.013	.090	-.026	-.002
ONB accuracy	-.085	-.001	-.023	-.110 *	-.017
TWOB accuracy	<b>-.315</b> **	.090	.156 **	-.017	.050
RAVLT delayed	-.244 **	.152 **	.244 **	-.052	.139 **
Logical Memory delayed	-.141 **	.232 **	<b>.343</b> **	-.107 *	.150 **
BVMT-R delayed	-.243 **	.160 **	.197 **	-.065	-.058

Spearman correlation coefficients are reported.

\* p<.05;

\*\* p<.007. Moderate correlations (>.3) are bolded. CPAL= Continuous Paired Associate Learning; GMCT=Groton Maze timed chase test; GML= Groton Maze learning test; GMR=Groton Maze learning test delayed recall; OCL=One-card learning; ONB=One-back memory; TWOB=Two-back memory. RAVLT= Rey Auditory Verbal Learning Test; BVMT= Brief Visuospatial Memory Test. Accuracy was transformed using the arcsine proportion to correct for normality.

**Table 3**  
Spearman rank-order correlations between traditional neuropsychological tests and CogState

Neuropsychological Test	CPAL	GMCT	GML	GMR	OCL	ONB	TWOB
<b>Memory</b>							
RAVLT total trials 1-5	-.478**	.301**	-.270**	-.266**	.279**	.095*	.197**
RAVLT delayed	-.477**	.278**	-.249**	-.247**	.319**	.112*	.205**
Logical Memory immediate	-.298**	.238**	-.255**	-.236**	.186**	.010	.188**
Logical Memory delayed	-.332**	.245**	-.291**	-.257**	.204**	.000	.181**
BVMT-R immediate	-.486**	.314**	-.347**	-.317**	.279**	.075	.296**
BVMT-R delayed	-.453**	.266**	-.378**	-.340**	.246**	.116*	.292**
<b>Language</b>							
Boston Naming	-.160**	.110*	-.158**	-.198**	.084	-.006	.107*
CFL fluency	-.119*	.236**	-.068	-.057	.093*	.082	.136**
Animal Naming	-.285**	.386**	-.166**	-.192**	.141**	.053	.215**
<b>Executive function</b>							
Stroop color-word interference	-.183**	.427**	-.161**	-.140**	.193**	.134**	.313**
TMT Part A	.241**	-.475**	.194**	.177**	-.207**	-.102*	-.324**
TMT Part B	.298**	-.448**	.252**	.206**	-.316**	-.127*	-.406**
WAIS-R Digit-Symbol	-.239**	.499**	-.177**	-.176**	.172**	.159**	.336**
WAIS-III Letter Number	-.233**	.251**	-.203**	-.166**	.182**	.091	.273**
WAIS-III Digit Span Forward	-.192**	.168**	-.187**	-.121*	.168**	.081	.245**
WAIS-III Digit Span Backward	-.219**	.177**	-.227**	-.256**	.147**	.064	.231**
<b>Global cognitive function</b>							
MMSE	-.115*	.184**	-.145**	-.125*	.201**	.077	.199**

Spearman correlation coefficients are reported.

\* p<.05;



\*\* p<.007. Moderate correlations (>.3) are bolded. RAVLT= Rey Auditory Verbal Learning Test; BVMT= Brief Visuospatial Memory Test; WAIS=Wechsler Adult Intelligence Scale (-R=Revised); MMSE= Mini Mental State Exam; CPAL= Continuous Paired Associate Learning; GMCT=Groton Maze timed chase test; GML= Groton Maze learning test; GMR=Groton Maze learning test delayed recall; OCL=One-card learning; ONB=One-back memory; TWOB=Two-back memory.

**Table 4**

CogState performance by cognitive status

Cognitive Test	Cognitively Impaired (n=70)	Cognitively Normal (n=393)	F	p-value	Partial eta-squared
CPAL errors	116.29 (.53)	77.55 (50.3)	22.15	<.001	.048
GMCT moves/sec	0.96 (.26)	1.16 (.22)	26.47	<.001	.055
GML errors	62.72 (17)	51.75 (16.3)	18.19	<.001	.039
GMR errors	11.68 (5.1)	8.17 (4.4)	30.38	<.001	.065
OCL accuracy	0.97 (.09)	1.02 (.09)	9.58	.002	.021
ONB accuracy	1.37 (.14)	1.39 (.13)	0.31	.576	.001
TWOB accuracy	1.18 (.15)	1.27 (.13)	16.59	<.001	.036

CPAL= Continuous Paired Associate Learning; GMCT=Groton Maze timed chase test; GML= Groton Maze learning test; GMR=Groton Maze learning test delayed recall; OCL=One-card learning; ONB=One-back memory; TWOB=Two-back memory. Accuracy was transformed using the arcsine proportion to correct for normality.

**Table 5**

CCII as a predictor of CogState and traditional neuropsychological test performance

Cognitive Test	$\beta$ -coefficient	T	p-value	$f^2$	R <sup>2</sup>	R <sup>2</sup> change
CPAL errors	22.201	10.864	<.001	0.2644	.304	.184
GMCT moves/sec	-.041	-4.546	<.001	0.0459	.324	.031
GML errors	4.823	6.835	<.001	0.0985	.198	.082
GMR errors	1.765	9.045	<.001	0.1846	.209	.145
OCL accuracy	-.023	-5.515	<.001	0.0682	.135	.059
ONB accuracy	-.017	-2.730	.007	0.0690	.030	.017
TWOB accuracy	-.039	-6.697	<.001	0.0996	.197	.080
Logical Memory delayed	-2.37	-8.798	<.001	0.1693	.291	.120
BVMT-R delayed	-.652	-8.769	<.001	0.1680	.256	.125

CPAL= Continuous Paired Associate Learning; GMCT=Groton Maze timed chase test; GML= Groton Maze learning test; GMR=Groton Maze learning test delayed recall; OCL=One-card learning; ONB=One-back memory; TWOB=Two-back memory; RAVLT= Rey Auditory Verbal Learning Test; BVMT= Brief Visuospatial Memory Test. Accuracy was transformed using the arcsine proportion to correct for normality.

**Table 6**

Biomarker correlations with CogState and traditional neuropsychological tests

Cognitive Test	Biomarker			
	PiB burden	PiB burden (outlier removed)	CSF p-tau/A $\beta$ <sub>42</sub>	CSF NFL
CPAL errors	-.002	-.023	.203	<b>.305</b>
GMCT moves/sec	-.083	-.089	-.102	<b>-.296</b>
GML errors	.030	.006	.118	<i>.219</i>
GMR errors	.057	.035	.165	<i>.217</i>
OCL accuracy	-.141	-.115	<b>-.347</b>	<i>-.204</i>
ONB accuracy	.072	.111	-.018	-.148
TWOB accuracy	-.120	-.121	-.007	-.069
RAVLT delayed	.120	.105	<i>-.235</i>	<b>-.378</b>
Logical Memory delayed	-.053	-.026	-.199	<b>-.300</b>
BVMT-R delayed	-.121	-.100	-.192	<b>-.257</b>

Spearman correlation coefficients are reported. Significant ( $p < .05$ ) results are bolded. Trends ( $p < .1$ ) are italicized. Accuracy was transformed using the arcsine proportion to correct for normality.