Title: CogState performance and associations with biomarkers in late-middle-aged people at risk for Alzheimer's disease

Running title: CogState performance and biomarker associations in midlife

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ABSTRACT

Background: CogState is a computerized cognitive battery spanning domains of memory, executive function, and speed and processing. CogState, designed to be robust to education level and efficient for repeated administration with minimal practice effects, holds potential for detecting early cognitive dysfunction in at-risk populations. This project aimed to provide convergent and construct validity for aspects of the CogState battery in a late-middle-aged cohort enriched for risk factors for Alzheimer's disease (AD) and to evaluate CogState performance against traditional neuropsychological tests of delayed memory.

Methods: 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+) completed a traditional paper-based neuropsychological battery and seven tests from the CogState battery approximately ten years post-baseline. A composite cognitive impairment index (CCII) was calculated using eight neuropsychological tests acquired longitudinally and estimated at age 65 to remove confounding effects of age. Early cognitive impairment status (n=70) was determined by consensus case review. A subset underwent cerebrospinal fluid (CSF) collection (n=73) and PET-PiB imaging (n=96). We examined relationships between CogState variables and demographic characteristics; relationships between CogState and scores on traditional paper-based neuropsychological tests as well as a composite cognitive impairment index; group differences between normal and cognitively impaired participants; and associations with previously acquired biomarkers for amyloid and tau (CSF total-tau/Aβ42 and global PET-PiB burden) and neural injury (CSF neurofilament light protein). In parallel we examined three traditional tests of delayed memory with demographics, cognitive status, and biomarkers.

Results: CogState variables were consistently related to age, but were relatively uncorrelated with other demographic variables examined. In contrast, traditional delayed memory tests were more highly influenced by demographic characteristics including sex, age, literacy, and education. With the exception of the One Back Test, CogState variables were statistically significantly related to most paper-based cognitive tests examined, and mapped onto the same cognitive domains. Cognitively impaired participants performed significantly worse compared to normal controls on all delayed memory and CogState tests except the One Back test. Greater CCII was associated with worse performance on all CogState tests. In this age range, cognitive performance on the CogState or delayed memory tests were not associated with biomarker levels with the exception of a mild relationship observed between One Card Learning test and CSF total-tau/Aβ42.

Conclusions: CogState is related to several cognitive measures (individual paper-based neuropsychological test scores, cognitive impairment status, and CCII) but was only mildly associated with biomarker levels in late-middle-aged adults. The congruent cognitive results suggest

the CogState tests employed may have utility as non-circular outcomes, which are less influenced by demographic variability, in longitudinal studies of people at risk for AD.

Key words: CogState, amyloid, cognitive impairment, preclinical Alzheimer's disease

1 INTRODUCTION

CogState is a computerized cognitive battery spanning domains of memory, executive function, and speed and 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 states of cognitive impairment and dementia (Hammers, et al., 2011; Lim, Jaeger, et al., 2013). CogState holds potential for detecting early cognitive dysfunction that may prove to be due to preclinical Alzheimer's disease (AD).

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 (Lim, et al., 2012; Maruff, et al., 2013). While some studies have found associations between CogState performance and biomarkers (Darby, et al., 2011; Lim, Ellis, et al., 2013; Lim, et al., 2014; Lim, Pietrzak, et al., 2015; Lim, Villemagne, et al., 2015; Mielke, et al., 2014; Thai, et al., 2015), other studies have failed to find such an association (Mielke, Machulda, Hagen, Christianson, et al., 2015; Mielke, et al., 2014). Thus far, there has been a primary focus on neuroimaging correlates of CogState, but there is a dearth of information on cerebrospinal fluid biomarkers.

These analyses build on previous work investigating CogState as a tool for detecting AD at various stages of the dementia spectrum and seek to provide convergent and construct validity for CogState in detecting pre-dementia cognitive deficits during late-midlife. First we explored relationships between CogState variables and demographic characteristics. To assess convergent validity, we examined relationships between CogState and scores on traditional paper-based neuropsychological tests as well as a composite cognitive impairment index estimated at age 65, the average age at which CogState was administered. To assess construct validity, cognitively impaired and normal controls were compared on CogState performance. Additional construct validity for AD pathology was investigated by examining whether biomarkers for amyloid and tau (CSF total-tau/Aβ42 and global PET-PiB burden) and neural injury (CSF neurofilament light protein) predicted CogState performance approximately four years later. To evaluate benefits of CogState over traditional neuropsychological tests, we also examined relationships of three traditional tests of delayed memory with demographics, MCI status, and biomarkers.

2 MATERIAL AND METHODS

2.1 Participants

The Wisconsin Registry for Alzheimer's Prevention (WRAP) is a longitudinally followed cohort designed to identify biological and lifestyle risk factors associated with development of dementia due

to Alzheimer's disease (Jonaitis, et al., 2013; Koscik, et al., 2014; Sager, Hermann, & La Rue, 2005). 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. The CogState was instituted in 2014 and administered regardless of the WRAP visit number (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 these analyses if they had completed at least one of the tests in the CogState battery, which consists of seven tests. Additionally, some participants were previously recruited for biomarker substudies. The University of Wisconsin Institutional Review Board approved all study procedures.

Of the 469 participants who had completed CogState, 10 met criteria for clinical MCI, another 60 exhibited more subtle deficits (which we termed psychometric MCI), and 6 were classified as having a non-MCI related cognitive impairment. The clinical MCI and psychometric MCI participants are grouped together into a cognitively impaired group and the remaining 393 unimpaired participants are considered cognitively normal (Table 1).

Table 1. Participant characteristics

Demographic	**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 (range 1-5)	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. APOE4=apolipoprotein E4 allele. WRAT=Wide Range Achievement Test. CES-D=Center for Epidemiological Studies Depression Scale.

2.2 WRAP battery: CogState, paper-based neuropsychological testing, and demographic data collection

CogState was administered on a laptop and included Continuous Paired Associate Learning (CPAL), Groton Maze timed chase test (GMCT), Groton Maze learning test (GML), Groton Maze learning

test delayed recall (GMR), One-card learning (OCL), One-back memory (ONB), and Two-back memory (TWOB). CPAL tests delayed visual memory through paired associate learning, GMCT tests speed of visual processing, GML tests executive function, GMR tests delayed recall, and OCL, ONB, and TWOB are tests of working memory. For CPAL, GML, and GMR, total number of errors were assed; 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). Not all participants completed the full CogState battery, with more incomplete data for tests administered at the end of the battery. Missing data and completion and integrity checks are summarized in Supplementary Table 1.

A comprehensive neuropsychological battery is performed at each WRAP visit. For this analysis, tests were selected that were primarily related to memory or executive function and included Rey Auditory Verbal Learning Test (RAVLT) total trials 1-5 and delayed recall; Wechsler Memory Scale-Revised (WMS-R) Logical Memory immediate and delayed recall; Brief Visuospatial Memory Test (BVMT) immediate and delayed recall; Boston Naming Test; Animal Naming; CFL fluency; Stroop color-word interference trial; Trail Making Test (TMT) Parts A and B; Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol, Letter Number, Digit Span forward, and Digit Span backward; and Mini Mental State Examination (MMSE).

A composite cognitive impairment index (CCII) was calculated using a set of eight cognitive measures: Trails A and B, WAIS Digit Span forward and backward, RAVLT total trials 1-5, RAVLT delayed recall, Boston Naming, and MMSE. Visits were excluded when fewer than four of these measurements were available. We applied the progression score model (Bilgel, Jedynak, Wong, Resnick, & Prince, 2015; Jedynak, et al., 2012) 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 and constrained the CCII scores to increase linearly with age within each individual. 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.

Supplementary Table 1. Completion, integrity, and missing data

CogState Test	**Completion Check**	**Integrity Check**	**Data missing**
CPAL	n=2 incomplete	N/A	n=3 missing
GMCT	N/A	N/A	n=0 missing

GML	n=0 incomplete	N/A	n=0 missing
GMR	n=3 incomplete	N/A	n=6 missing
OCL	n=0 incomplete	n=7 below level of chance	n=1 missing
ONB	n=0 incomplete	n=12 below level of chance	n=2 missing
TWOB	n=0 incomplete	n=2 below level of chance	n=4 missing

CPAL= Continuous Paired Associate Learning (CPAL); 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.

2.3 Biomarker collection

2.3.1 PET-PiB

Detailed methods for [C-11] PiB radiochemical synthesis, PiB-PET scanning, and distribution volume ratio map generation using the cerebellum as a reference region have been described previously (Johnson, et al., 2013). 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 (Berman, et al., 2015; Johnson, et al., 2013; Annie M. Racine, et al., 2014). 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 (Racine, et al., 2016; Sprecher, et al., 2015). N=91 participants underwent PiB-PET imaging approximately 4.1 years prior to CogState.

2.3.2 Cerebrospinal fluid

CSF was collected as described previously (Almeida, et al., 2015; Starks, et al., 2015). CSF $A\beta_{42}$ and total-tau (t-tau) were quantified with sandwich ELISAs (INNOTEST β-amyloid1-42, hTAU-Ag, respectively; Fujirebio Europe, Ghent, Belgium). CSF t-tau/$A\beta_{42}$ was calculated by dividing CSF t-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 prior to Cogstate.

CSF assays were performed in two batches. A subset of CSF samples (n=73 from the entire CSF database, not just from individuals who had also undergone CogState testing) was assayed in both batches so that reliability tests could be performed. Intraclass correlation coefficients (ICCs) for absolute agreement were high between batches for CSF t-tau/Aβ42 (ICC=.978) and NFL (.975) so batches were combined to obtain the maximal sample size, but interpretation of these variables should keep this limitation in mind.

2.4 Statistical analyses

2.4.1 Associations of CogState with demographics and traditional neuropsychological tests

For dichotomous characteristics (sex, parental family history of AD, and APOE4), 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; and depression as measured by the Center for Epidemiologic Studies Depression Scale), we performed Pearson correlations. For ordinal variables (computer familiarity as measured on a Cognitive Activities questionnaire) Spearman's rank-order correlations were performed. Relationships between traditional paper-based neuropsychological tests and CogState tests were evaluated with Pearson 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 (J. Cohen, 1992). Significance was inferred at a Bonferroni-corrected p-value for seven CogState tests ($p<.05/7=.007$)

Because we were interested in comparing performance of the CogState 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 (Backman, Jones, Berger, Laukka, & Small, 2005; Salmon & Bondi, 2009; Weintraub, Wicklund, & Salmon, 2012), 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, Logical Memory delayed, and BVMT delayed. Although there were only three delayed recall tests, we still evaluated significance at the threshold of $p<.007$.

2.4.2 ANCOVA comparing normal controls and participants with MCI

Cognitively impaired participants were compared to cognitively normal controls by ANCOVA controlling for age, literacy, sex, APOE4, family history of AD, and computer familiarity. Significance is inferred at $p<.007$ (Bonferroni-corrected p-value for seven CogState tests). Effect sizes by partial eta squared are reported. Small, medium, and large effect sizes for eta squared are .01, .06, and .14, respectively (Jacob Cohen, 1988).

We also compared cognitive groups on the select traditional neuropsychological tests identified in section 2.4.1.. However, it should be noted that performance on these tests were evaluated during consensus, particularly for determining whether MCI was an amnestic or non-amnestic variant; therefore, cognitive status and delayed recall scores are not unrelated. Thus, direct comparison of effect sizes for CogState and delayed recall tests by cognitive group is not possible.

2.4.3 Composite cognitive impairment index regression

In addition to examining individual neuropsychological tests, we investigated CCII, which takes advantage of longitudinally measured cognition, is associated with performance on CogState. We ran regression analysis with CogState as the dependent variable and CCII as the independent variable of interest, controlling for age at CogState testing, literacy, sex, APOE4, family history of AD, and computer familiarity. Significance was inferred at $p<.007$ (Bonferroni-corrected p-value for seven CogState tests). Variance inflation factors (VIF) and tolerance were assessed and deemed normal if tolerance is greater than .1 and VIF is 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 (Jacob Cohen, 1988). RAVLT delayed was included in the making of CCII so we only evaluated the relationships between Logical Memory delayed and BVMT delayed and CCII.

2.4.4 Biomarker associations

2.4.4.1. Biomarker normalization and dichotomization

To improve normality, CSF t-tau/Aβ42 and NFL were transformed using the natural log. 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 with the goal of capturing the hypothesized underlying binomial distribution.

A cut-off value for PiB positivity was determined using receiver operating characteristic (ROC) analysis in pROC R Statistical Package (Robin, et al., 2011) 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 (Johnson, et al., 2013; A. M. Racine, et al., 2014). 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 (Youden, 1950). A threshold of 1.19 was identified which corresponded to sensitivity of .938 and specificity of .917.

2.4.4.2. Associations between biomarkers and CogState

First, we performed Pearson correlations between CogState variables and three biomarkers of interest: CSF t-tau/Aβ42, CSF NFL, and global PiB burden. T-tests were performed to compare CogState performance between PiB+ and PiB- groups. Second, to investigate whether biomarkers are predictive of CogState performance, we ran multiple regressions with CogState scores as the dependent variable and biomarker as the independent variable of interest for biomarkers with significant or trending correlations with CogState. Comparable models with ANCOVA were

performed for PiB positivity. In addition to the covariates used in the CCII regression models, we additionally controlled for the interval from biomarker collection to CogState testing (CSF to CogState 44.3±13.5 months; PET-PiB to CogState 49.6±7.9 months). VIF and tolerance were again inspected.

We also analyzed the relationship between traditional neuropsychological tests and biomarkers using the same tests of delayed memory as section 2.4.3. and the same models as described for the CogState variables. Because we expected the relationship between cognitive performance and biomarkers to be mild, we evaluated significance at a more mild threshold of $p<.05$ for both CogState and delayed memory tests.

3 RESULTS

3.1 Associations of CogState with demographics and traditional neuropsychological tests

Participant characteristics are summarized in Table 1. Cognitively impaired and cognitively normal groups only differed on age at CogSate testing with the cognitively impaired group being slightly older (by about three years).

CogState scores did not differ significantly by APOE4 status or family history. CPAL ($p<.001$, Cohen's $d= 0.39$) and GMCT scores did differ by sex ($p=.004$, Cohen's $d=-0.27$) where females performed better on CPAL (fewer errors) and on GMCT (more moves per second). Older age was associated with worse performance on all CogState tests ($p<.001$, Pearson's r's = .165 to -.437) except ONB. Better GMCT performance correlated with more computer familiarity ($p<.001$, Spearman's rho=.224), more years of education, (Pearson's $r=.138$, $p=.003$), and better literacy (Pearson's $r=.192$, $p<.001$). More errors on Groton Maze delayed recall was associated with a higher depression score (Pearson's $r=.138$, $p=.003$). Higher accuracy on TWOB was correlated with better literacy (Pearson's $r=.159$, $p=.001$). Effect sizes for all associations with demographic and CogState variables were small except between age and GMCT (Pearson's $r=-.437$), which was moderate.

The three non-CogState delayed memory scores did not significantly differ by APOE4 or family history, but females performed better on RAVLT delayed ($p<.001$, Cohen's $d=-0.81$) and Logical Memory delayed ($p=.005$, Cohen's $d=-0.26$). All three delayed recall scores were significantly correlated with age (Pearson's r's=.-.138 to -.239, p's<.003), literacy (Pearson's r's=.194 to .324, p's<.001), and education (Pearson's r's=.139 to .232, p's<.003). Better performance on RAVLT delayed (Pearson's $r=.139$, $p=.003$) and Logical Memory delayed (Pearson's $r=.150$, $p=.001$) were also associated with more computer familiarity. 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.

Because the majority of neuropsychological test scores and CogState scores were significantly correlated, only tests exceeding the threshold for a moderate association (correlation coefficient >.3) are reported in the text. A correlation matrix is also provided as Table 2 with moderate correlations in bold. CPAL correlated with RAVLT total (r=-.487), RAVLT delayed (r=-.478), BVMT total (r=-.503), BVMT delayed (r=.476), and WMS-R Logical Memory delayed (r=-.335). GMCT correlated with RAVLT total (r=.332), RAVLT delayed (r=.305), Stroop (r=.412), TMT Part A (r=-.438), TMT Part B (r=-.420), BVMT total (r=.336), WMS-R Logical Memory immediate (r=.485), and Animal Naming (r=.366). GML correlated with BVMT total (r=-.344) and delay (r=-.371). GMR correlated with BVMT total (r=-.324) and delay (r=-.335). OCL correlated with RAVLT delay (r=.311). TWOB correlated with TMT Part B (r=-.360) and WAIS-R Digit Symbol (r=.303).

Table 2. Pearson correlations between traditional neuropsychological tests and CogState

Neuropsychological Test	**CPAL**	**GMCT**	**GML_**	**GMR**	**OCL**	**ONB**	**TWOB**
Memory							
RAVLT total trials 1-5	**-.483****	**.331****	-.265**	-.285**	.287**	0.087	.213**
RAVLT delayed	**-.473****	**.302****	-.252**	-.264**	**.305****	0.091	.225**
Logical Memory immediate	-.294**	.270**	-.245**	-.247**	.167**	0.016	.183**
Logical Memory delayed	**-.332****	.274**	-.279**	-.280*	.191**	-0.007	.163**
BVMT immediate	**-.500****	**.338****	**-.344****	**-.318****	.272**	0.064	.278***
BVMT delayed	**-.474****	.289**	**-.370****	-.327**	.237**	.099	.283**
Language							
Boston Naming	-.191**	.143*	-.205**	-.212**	0.082	0.009	.110
CFL fluency	-.113	.251**	-0.047	-0.035	0.086	0.057	.115
Animal Naming	-.287**	**.368****	-.198**	-.194**	.144*	0.019	.181**
Executive function							
Stroop color-word interference	-.211**	**.412****	-.172**	-.153*	.198**	.138*	.293**
TMT Part A	.241**	**-.438****	.227**	.212**	-.227**	-.124*	-.274**
TMT Part B	**.328****	**-.421****	.266**	.248**	-.292**	-.142*	**-.355****
WAIS-R Digit Symbol	-.238**	**.486****	-.161**	-.186**	.167**	.156*	**.301****
WAIS-R Letter Number	-.252**	.234**	-.204**	-.188**	.209**	0.086	.258**
WAIS-R Digit Span Forward	-.204**	.172**	-.165**	-.113	.183**	0.08	.250**
WAIS-R Digit Span Backward	-.243**	.182**	-.238**	-.256**	.179**	0.068	.227**
Global function							
MMSE	-.132*	.201**	-.194**	-.158*	.211**	.101	.165**

Pearson correlation coefficients are reported. *r<.01; *r<.001. RAVLT= Rey Auditory Verbal Learning Test; BVMT= Brief Visuospatial Memory Test; TMT=Trail Making Test; WAIS-R=Wechsler Adult Intelligence Scale-Revised; MMSE= Mini Mental State Exam; CPAL= Continuous Paired Associate Learning (CPAL); 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.

3.2 CogState performance by cognitive status

After controlling for risk factors and demographics, CogState performance differed between individuals who are cognitively impaired and cognitively normal controls for all CogState tests ($p<.007$, Table 3, Figure 1) except ONB. All effect sizes were small except GMR, which was moderate. Predictably, the three delayed memory tests were also significantly different between the cognitive groups ($p<.007$); effect sizes were large for RAVLT delayed and moderate for Logical Memory delayed and BVMT delayed. This was an expected finding since the non-CogState memory tests were considered when making the diagnosis.

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.

Table 3. CogState and traditional neuropsychological test performance by MCI status

CogState 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
RAVLT delayed	7.47 (3.5)	11.32 (2.5)	104.04	<.001	.187
Logical Memory delayed	20.63 (6.6)	27.63 (6.4)	55.26	<.001	.109
BVMT delayed	8.57 (2.2)	10.21 (1.7)	39.76	<.001	.081

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.

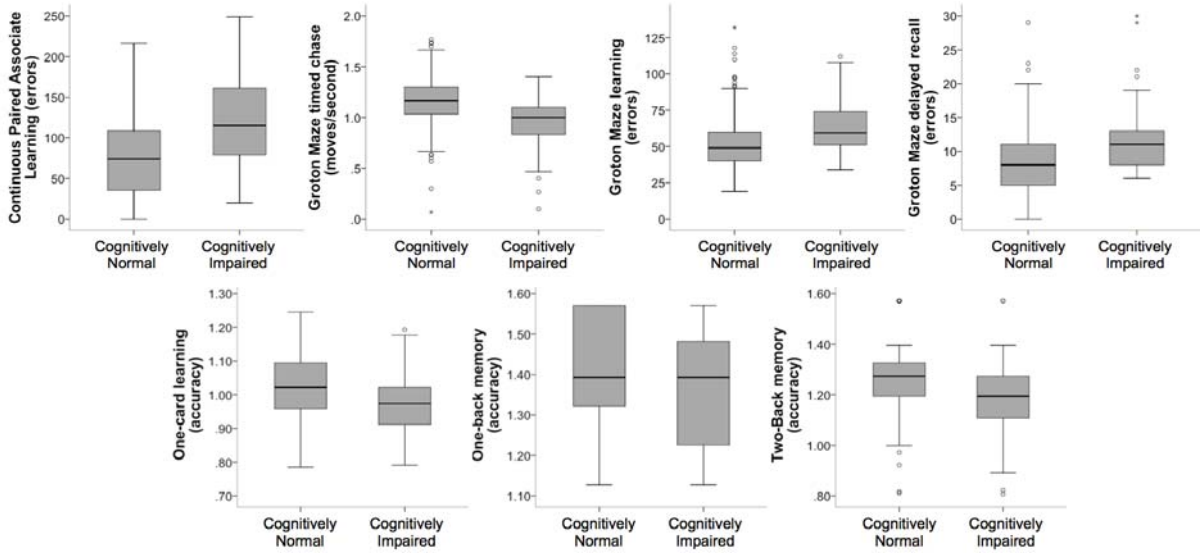

Figure 1. Comparison of Cognitively Normal and Cognitively Impaired groups on mean performance on CogState tests. Error bars represent 95% confidence intervals.

3.3 Association between CogState and Composite Cognitive Impairment Index

VIF and tolerance were in the normal range for all models. CCII significantly predicted performance on all CogState tests examined (p<.007, Table 4, Figure 2). Age at CogState testing (CPAL, GMCT, GML, OCL, TWOB) and sex (GML, GMR, TWOB) were common additional predictors of CogState performance (p<.05). Computer familiarity also significantly predicted GMCT only (p<.05). Logical memory delayed and BVMT delayed also significantly predicted CCII (p<.007, Table 4). Effect sizes were moderate for CPAL, GMR, Logical Memory delayed, and BVMT delayed; all others were small.

Table 4. CCII as a predictor of CogState performance

CogState Test	β-coefficient	T	p-value	f^2	R^2	R^2 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 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.

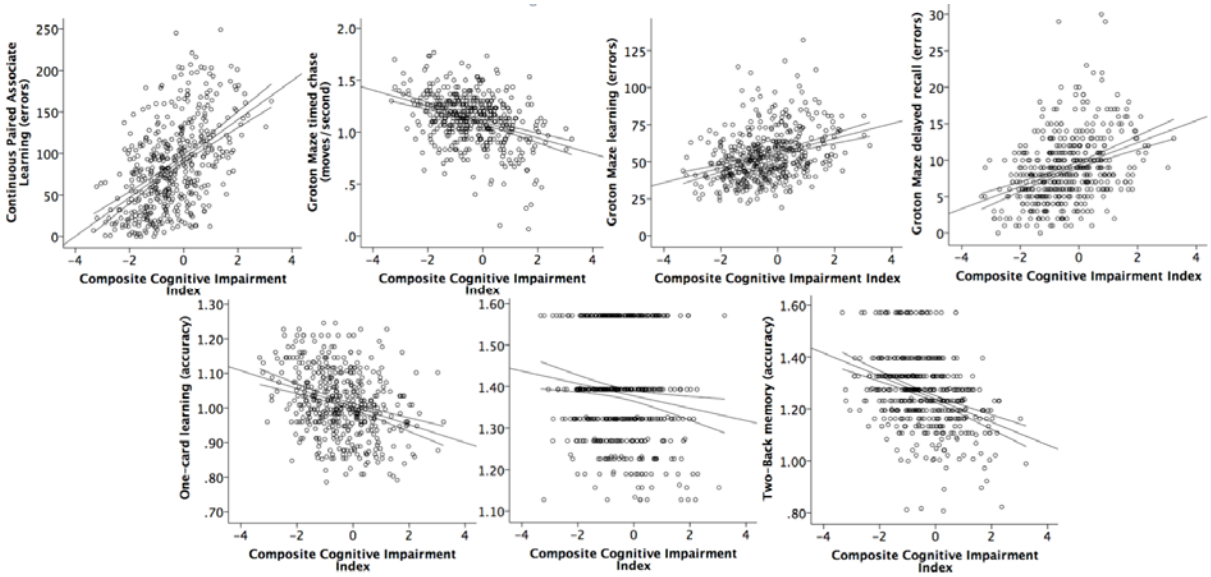

Figure 2. Relationships between CogState tests and a Composite Cognitive Impairment Index estimated at age 65. 95% confidence intervals for the regression line are displayed.

3.4 Biomarkers

Overall, biomarkers were not strongly associated with CogState scores. CSF NFL was correlated with CPAL (Pearson's r=.281, p=.022), GMCT (Pearson's r=.-.293, p=.014), and GML (Pearson's r=.261, p=.029). PiB burden (Pearson's r=-.250, p=.019) and CSF t-tau/Aβ42 (Pearson's r=-.265, =.029) were correlated with OCL. When the outlier was removed, the association between PiB burden and OCL became a trend (p=.060). Additional trends were observed between CSF t-tau/Aβ42 and GMR (Pearson's r=.229 p=.062); PiB positivity and GML (t=-.1842, p=.069); and PiB positivity and OCL (t=1.945, p=.055). When these correlations were investigated further in regression and ANCOVA models, CSF NFL, PiB burden, and PiB positivity were not predictive of CogState performance, but CSF t-tau/Aβ42 (Figure 3) was a significant predictor of OCL performance (β=-.057, t=-2.042, f^2=.0724, R^2=.144, R^2-change=.063, p=.046).

RAVLT delayed (Pearson's R=-.378, p=.001), Logical Memory delayed (Pearson's R=-.300, p=.012), and BVMT delayed (Pearson's R=-.257, p=.031) all correlated with CSF NFL. However, none of these relationships were significant in regression models controlling for other factors. There was a trend for CSF NFL predicting Logical Memory delayed (β=-4.861, t=-1.902, p=.062).

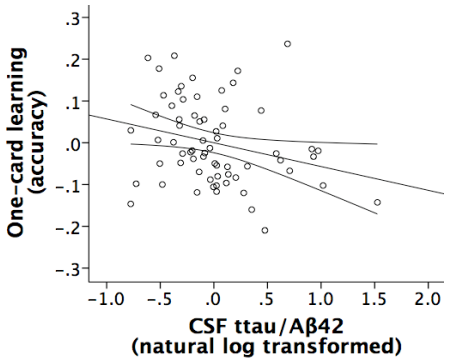

Figure 3. Partial regression plot of natural log-transformed CSF t-tau/$A\beta_{42}$ and One-card learning performance as measured by arcsine-corrected accuracy. 95% confidence intervals for the regression line are displayed.

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 (Snyder, et al., 2011; Wild, Howieson, Webbe, Seelye, & Kaye, 2008). Consequently, there has been a shift in interest to computer-administrated psychological batteries. CogState 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 (Fredrickson, et al., 2010; Zygouris & Tsolaki, 2015). Here we evaluated CogState performance at a single time point in relation to traditional neuropsychological tests, cognitive status, and biomarkers in a late-middle-aged sample from the WRAP cohort. We sought to provide convergent and construct validity for CogState during the earliest stages of potential AD and to provide a context for comparing CogState to traditional gold-standard tests of delayed memory.

Our results are consistent with previous studies of CogState showing weak to moderate relationships with demographic variables and traditional cognitive tests (Hammers, et al., 2012; Lim, et al., 2012; Mielke, Machulda, Hagen, Edwards, et al., 2015). 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 much more strongly associated with demographic characteristics, supporting the theory that CogState is more robust to education level compared to traditional paper-based neuropsychological tests.

4.1 Convergent validity

While the majority of CogState and paper-based tests were significantly correlated, only the correlation between CPAL and BVMT immediate—both tests of visual memory—passed the threshold for a large effect (r=-.5), but there were several other moderate associations. CPAL was also correlated with two tests of verbal memory, RAVLT and WMS-R Logical Memory. The Groton Maze tests combine skills of executive function, learning, and memory and correspondingly were correlated with traditional neuropsychological tests of memory (RAVLT, BVMT, WMS-R Logical Memory, Animal Naming) and executive function (Stroop, TMT). Interestingly, GMCT, which is generally considered a task to introduce subjects to the Groton Maze learning and delayed recall tasks, had the most associations with other neuropsychological tests of the three maze paradigms; GML and GMR were both only correlated with BVMT total and delay. Of the card tests, OCL, a visual memory test, was correlated with RAVLT delay; and TWOB, a test of working memory, was correlated with two executive functioning tasks, TMT Part B and WAIS-R Digit Symbol. 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 Alzheimer's Battery, 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 CogState test that did not differ between cognitively normal and cognitively impaired groups. Given the relative health and youthfulness 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 (Mielke, Machulda, Hagen, Edwards, et al., 2015). Its major function in the battery we selected was to serve as a warm up test for the more difficult TWB task. Our results suggest that ONB accuracy is less useful in the age range of our sample.

One of the earliest studies of CogState showed that patients with MCI declined within a one-year period on a CogState memory task (Continuous Learning Test) while decline was not detectable using routine memory tests (Maruff, et al., 2004). While we were not able to address decline in CogState performance across groups with only one time point for CogState, we did incorporate the extensive longitudinal data that has been collected in WRAP using traditional neuropsychological tests to create a composite of cognitive impairment. This type of cognitive impairment index could be a useful tool against which to measure novel tests of cognitive/clinical status and progression, like CogState. Both CogState and traditional delayed memory tests were associated with CCII. Effect sizes were moderate for CPAL, GMR, Logical Memory delayed, and BVMT delayed with the largest effect size observed for CPAL. Both GMR and CPAL test delayed recall using two different paradigms.

4.2 Convergent validity

With the exception ONB, cognitively impaired individuals differed significantly in their performance on CogState tests compared to cognitively normal controls. The difference was generally small, with the most marked difference observed for GMR. While the traditional delayed memory tests were large or moderate, these tests were available to the clinicians determining the consensus diagnosis so this finding is not particularly informative. It is interesting that the only CogState test to also have a moderate effect was the GMR, pointing to the emphasis on dysfunction in delayed memory for a diagnosis of cognitive impairment.

We did not find strong evidence for an association between CogState performance and biomarker levels with the exception of a mild relationship detected between higher levels of CSF total-tau/Aβ42 and 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 have evaluated intra-individual cognitive decline based on longitudinally acquired CogState testing rather than a single time point (Darby, et al., 2011; Lim, Ellis, et al., 2013; Lim, et al., 2014; Lim, Pietrzak, et al., 2015; Mielke, Machulda, Hagen, Christianson, et al., 2015). In contrast, a study with a single CogState evaluation did not find an association between CogState performance and amyloid PET (Mielke, et al., 2014). The latter study did, however, find relatively weak associations between CogState 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-occuring amyloid and tau pathology and one CogState test but none of the three traditional delayed memory tests, it remains unclear whether CogState at one time point would substantially improve inference about underling pathology beyond what is possible with traditional paper-based neuropsychological tests.

4.3 Limitations

The primary limitations of this study are that biomarkers were collected several years before CogState administration and that we do not yet have serial CogState testing, both of which constrain our ability to make stronger inferences about CogState and underlying pathology. Additionally, our study cohort was largely white and well educated, and so generalizability is restricted; it will be important to perform similar studies with CogState in more diverse populations. Longitudinal clinical outcomes will also be important for evaluating prognostic utility of CogState.

4.4 Conclusions

Overall this study provided convergent and construct validity for the use of CogState in evaluating cognitive function during late-middle-age. 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.

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7 REFERENCES

Almeida, R. P., Schultz, S. A., Austin, B. P., Boots, E. A., Dowling, N. M., Gleason, C. E., Bendlin, B. B., Sager, M. A., Hermann, B. P., Zetterberg, H., Carlsson, C. M., Johnson, S. C., Asthana, S., & Okonkwo, O. C. (2015). Effect of Cognitive Reserve on Age-Related Changes in Cerebrospinal Fluid Biomarkers of Alzheimer Disease. *JAMA neurology, 72*, 699-706.

Backman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology, 19*, 520-531.

Berman, S., Rivera, L., Clark, L., Racine, A., Carlsson, C., Bendlin, B., Bratzke, L., Rowley, H., Turski, P., Zetterberg, H., Blennow, K., Asthana, S., Johnson, S., & Wieben, O. (2015). Intracranial arterial 4D-Flow is associated with metrics of brain health and Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring.*

Bilgel, M., Jedynak, B., Wong, D. F., Resnick, S. M., & Prince, J. L. (2015). Temporal Trajectory and Progression Score Estimation from Voxelwise Longitudinal Imaging Measures: Application to Amyloid Imaging. *Inf Process Med Imaging, 24*, 424-436.

Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, New Jersey: L. In: Erlbaum.

Cohen, J. (1992). A power primer. *Psychol Bull, 112*, 155-159.

Darby, D. G., Brodtmann, A., Pietrzak, R. H., Fredrickson, J., Woodward, M., Villemagne, V. L., Fredrickson, A., Maruff, P., & Rowe, C. (2011). Episodic memory decline predicts cortical amyloid status in community-dwelling older adults. *Journal of Alzheimer's disease : JAD, 27*, 627-637.

Fredrickson, J., Maruff, P., Woodward, M., Moore, L., Fredrickson, A., Sach, J., & Darby, D. (2010). Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. *Neuroepidemiology, 34*, 65-75.

Hammers, D., Spurgeon, E., Ryan, K., Persad, C., Barbas, N., Heidebrink, J., Darby, D., & Giordani, B. (2012). Validity of a brief computerized cognitive screening test in dementia. *Journal of geriatric psychiatry and neurology, 25*, 89-99.

Hammers, D., Spurgeon, E., Ryan, K., Persad, C., Heidebrink, J., Barbas, N., Albin, R., Frey, K., Darby, D., & Giordani, B. (2011). Reliability of repeated cognitive assessment of dementia using a brief computerized battery. *Am J Alzheimers Dis Other Demen, 26*, 326-333.

Jedynak, B. M., Lang, A., Liu, B., Katz, E., Zhang, Y., Wyman, B. T., Raunig, D., Jedynak, C. P., Caffo, B., Prince, J. L., & Alzheimer's Disease Neuroimaging, I. (2012). A computational neurodegenerative disease progression score: method and results with the Alzheimer's disease Neuroimaging Initiative cohort. *NeuroImage, 63*, 1478-1486.

Johnson, S. C., Christian, B. T., Okonkwo, O. C., Oh, J. M., Harding, S., Xu, G., Hillmer, A. T., Wooten, D. W., Murali, D., Barnhart, T. E., Hall, L. T., Racine, A. M., Klunk, W. E., Mathis, C. A., Bendlin, B. B., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Hermann, B. P., Dowling, N. M., Asthana, S., & Sager, M. A. (2013). Amyloid burden and neural function in people at risk for Alzheimer's Disease. *Neurobiology of aging*.

Jonaitis, E., La Rue, A., Mueller, K. D., Koscik, R. L., Hermann, B., & Sager, M. A. (2013). Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease. *Psychology and aging, 28*, 1004-1014.

Koscik, R. L., La Rue, A., Jonaitis, E. M., Okonkwo, O. C., Johnson, S. C., Bendlin, B. B., Hermann, B. P., & Sager, M. A. (2014). Emergence of mild cognitive impairment in late middle-aged adults in the wisconsin registry for Alzheimer's prevention. *Dementia and geriatric cognitive disorders, 38*, 16-30.

Lim, Y. Y., Ellis, K. A., Harrington, K., Ames, D., Martins, R. N., Masters, C. L., Rowe, C., Savage, G., Szoeke, C., Darby, D., Maruff, P., & The Aibl Research, G. (2012). Use of the CogState Brief Battery in the assessment of Alzheimer's disease related cognitive impairment in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. *Journal of clinical and experimental neuropsychology, 34*, 345-358.

Lim, Y. Y., Ellis, K. A., Harrington, K., Pietrzak, R. H., Gale, J., Ames, D., Bush, A. I., Darby, D., Martins, R. N., Masters, C. L., Rowe, C. C., Savage, G., Szoeke, C., Villemagne, V. L., & Maruff, P. (2013). Cognitive decline in adults with amnestic mild cognitive impairment and high amyloid-beta: prodromal Alzheimer's disease? *Journal of Alzheimer's disease : JAD, 33*, 1167-1176.

Lim, Y. Y., Jaeger, J., Harrington, K., Ashwood, T., Ellis, K. A., Stoffler, A., Szoeke, C., Lachovitzki, R., Martins, R. N., Villemagne, V. L., Bush, A., Masters, C. L., Rowe, C. C., Ames, D., Darby, D., & Maruff, P. (2013). Three-month stability of the CogState brief battery in

healthy older adults, mild cognitive impairment, and Alzheimer's disease: results from the Australian Imaging, Biomarkers, and Lifestyle-rate of change substudy (AIBL-ROCS). *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, 28*, 320-330.

Lim, Y. Y., Maruff, P., Pietrzak, R. H., Ellis, K. A., Darby, D., Ames, D., Harrington, K., Martins, R. N., Masters, C. L., Szoeke, C., Savage, G., Villemagne, V. L., Rowe, C. C., & Group, A. R. (2014). Abeta and cognitive change: examining the preclinical and prodromal stages of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association, 10*, 743-751 e741.

Lim, Y. Y., Pietrzak, R. H., Bourgeat, P., Ames, D., Ellis, K. A., Rembach, A., Harrington, K., Salvado, O., Martins, R. N., Snyder, P. J., Masters, C. L., Rowe, C. C., Villemagne, V. L., & Maruff, P. (2015). Relationships between performance on the Cogstate Brief Battery, neurodegeneration, and Abeta accumulation in cognitively normal older adults and adults with MCI. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, 30*, 49-58.

Lim, Y. Y., Villemagne, V. L., Pietrzak, R. H., Ames, D., Ellis, K. A., Harrington, K., Snyder, P. J., Martins, R. N., Masters, C. L., Rowe, C. C., Maruff, P., Australian Imaging, B., & Lifestyle Research, G. (2015). APOE epsilon4 moderates amyloid-related memory decline in preclinical Alzheimer's disease. *Neurobiology of aging, 36*, 1239-1244.

Maruff, P., Collie, A., Darby, D., Weaver-Cargin, J., Masters, C., & Currie, J. (2004). Subtle memory decline over 12 months in mild cognitive impairment. *Dementia and geriatric cognitive disorders, 18*, 342-348.

Maruff, P., Lim, Y. Y., Darby, D., Ellis, K. A., Pietrzak, R. H., Snyder, P. J., Bush, A. I., Szoeke, C., Schembri, A., Ames, D., Masters, C. L., & Group, A. R. (2013). Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC Psychol, 1*, 30.

Mielke, M. M., Machulda, M. M., Hagen, C. E., Christianson, T. J., Roberts, R. O., Knopman, D. S., Vemuri, P., Lowe, V. J., Kremers, W. K., Jack, C. R., Jr., & Petersen, R. C. (2015). Influence of amyloid and APOE on cognitive performance in a late middle-aged cohort. *Alzheimer's & dementia : the journal of the Alzheimer's Association*.

Mielke, M. M., Machulda, M. M., Hagen, C. E., Edwards, K. K., Roberts, R. O., Pankratz, V. S., Knopman, D. S., Jack, C. R., Jr., & Petersen, R. C. (2015). Performance of the CogState computerized battery in the Mayo Clinic Study on Aging. *Alzheimer's & dementia : the journal of the Alzheimer's Association, 11*, 1367-1376.

Mielke, M. M., Weigand, S. D., Wiste, H. J., Vemuri, P., Machulda, M. M., Knopman, D. S., Lowe, V., Roberts, R. O., Kantarci, K., Rocca, W. A., Jack, C. R., Jr., & Petersen, R. C. (2014). Independent comparison of CogState computerized testing and a standard cognitive battery with neuroimaging. *Alzheimer's & dementia : the journal of the Alzheimer's Association, 10*, 779-789.

Racine, A. M., Adluru, N., Alexander, A. L., Christian, B. T., Okonkwo, O. C., Oh, J., Cleary, C. A., Birdsill, A., Hillmer, A. T., Murali, D., Barnhart, T. E., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Dowling, N. M., Asthana, S., Sager, M. A., Bendlin, B. B., & Johnson, S. C. (2014). Associations between white matter microstructure and amyloid burden in preclinical Alzheimer's disease: A multimodal imaging investigation. *NeuroImage. Clinical, 4*, 604-614.

Racine, A. M., Adluru, N., Alexander, A. L., Christian, B. T., Okonkwo, O. C., Oh, J., Cleary, C. A., Birdsill, A., Hillmer, A. T., Murali, D., Barnhart, T. E., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Dowling, N. M., Asthana, S., Sager, M. A., Bendlin, B. B., & Johnson, S. C.

(2014). Associations between white matter microstructure and amyloid burden in preclinical Alzheimer's disease: A multimodal imaging investigation. *NeuroImage: Clinical*.

Racine, A. M., Koscik, R. L., Nicholas, C. R., Clark, L. R., Okonkwo, O. C., Oh, J. M., Hillmer, A. T., Murali, D., Barnhart, T. E., Betthauser, T. J., Gallagher, C. L., Rowley, H. A., Dowling, N. M., Asthana, S., Bendlin, B. B., Blennow, K., Zetterberg, H., Carlsson, C. M., Christian, B. T., & Johnson, S. C. (2016). Cerebrospinal fluid ratios with Abeta42 predict preclinical brain beta-amyloid accumulation. *Alzheimers Dement (Amst), 2*, 27-38.

Robin, X., Turck, N., Hainard, A., Tiberti, N., Lisacek, F., Sanchez, J. C., & Muller, M. (2011). pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics, 12*, 77.

Sager, M. A., Hermann, B., & La Rue, A. (2005). Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. *Journal of geriatric psychiatry and neurology, 18*, 245-249.

Salmon, D. P., & Bondi, M. W. (2009). Neuropsychological assessment of dementia. *Annual review of psychology, 60*, 257-282.

Snyder, P. J., Jackson, C. E., Petersen, R. C., Khachaturian, A. S., Kaye, J., Albert, M. S., & Weintraub, S. (2011). Assessment of cognition in mild cognitive impairment: a comparative study. *Alzheimer's & dementia : the journal of the Alzheimer's Association, 7*, 338-355.

Sprecher, K. E., Bendlin, B. B., Racine, A. M., Okonkwo, O. C., Christian, B. T., Koscik, R. L., Sager, M. A., Asthana, S., Johnson, S. C., & Benca, R. M. (2015). Amyloid burden is associated with self-reported sleep in nondemented late middle-aged adults. *Neurobiology of aging, 36*, 2568-2576.

Starks, E. J., Patrick O'Grady, J., Hoscheidt, S. M., Racine, A. M., Carlsson, C. M., Zetterberg, H., Blennow, K., Okonkwo, O. C., Puglielli, L., Asthana, S., Dowling, N. M., Gleason, C. E., Anderson, R. M., Davenport-Sis, N. J., DeRungs, L. M., Sager, M. A., Johnson, S. C., & Bendlin, B. B. (2015). Insulin Resistance is Associated with Higher Cerebrospinal Fluid Tau Levels in Asymptomatic APOEvarepsilon4 Carriers. *Journal of Alzheimer's disease : JAD, 46*, 525-533.

Thai, C., Lim, Y. Y., Villemagne, V. L., Laws, S. M., Ames, D., Ellis, K. A., Rainey-Smith, S. R., Martins, R. N., Masters, C. L., Rowe, C. C., Maruff, P., Australian Imaging, B., & Lifestyle Research, G. (2015). Amyloid-Related Memory Decline in Preclinical Alzheimer's Disease Is Dependent on APOE epsilon4 and Is Detectable over 18-Months. *PloS one, 10*, e0139082.

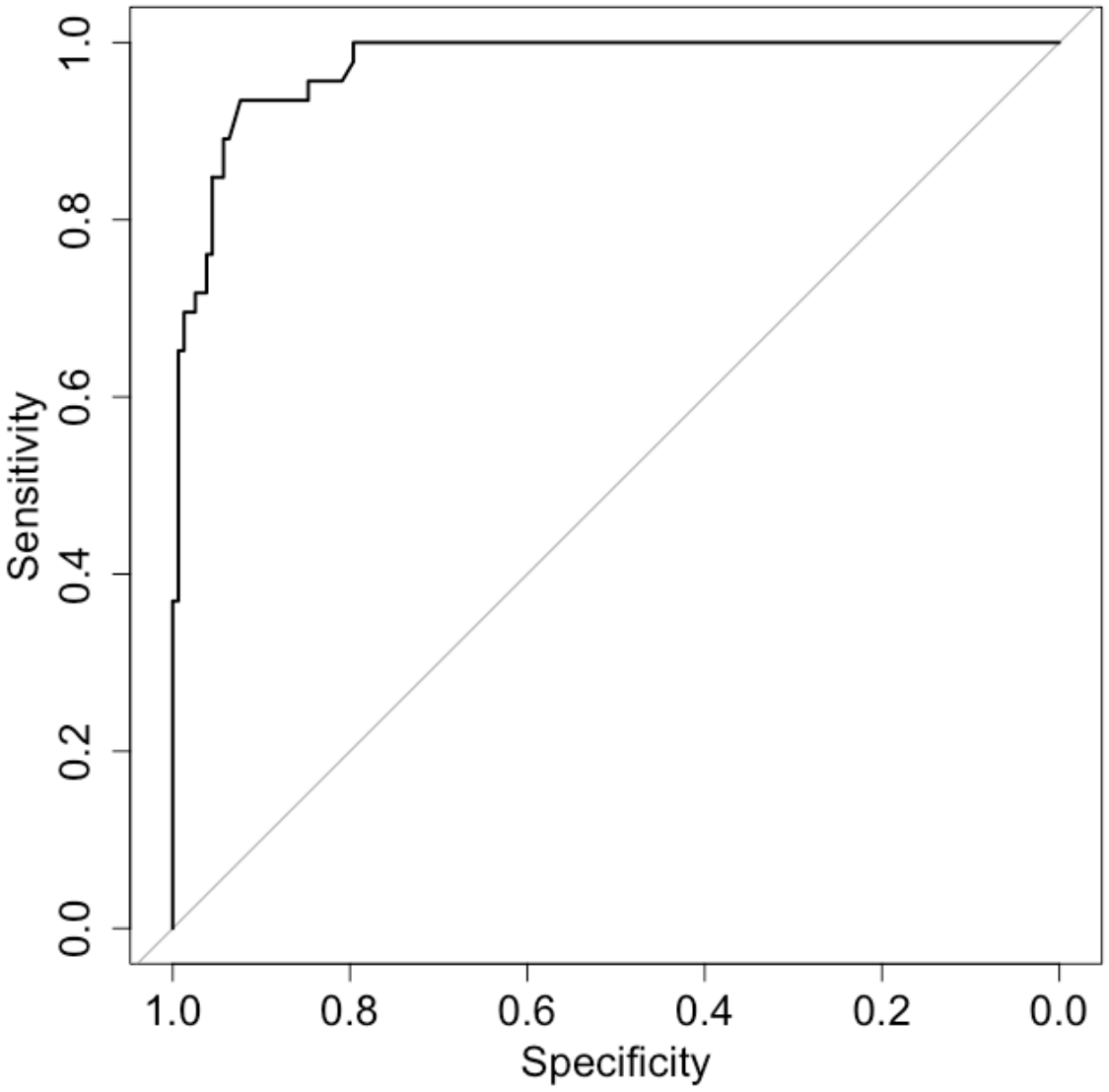
Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med, 2*, a006171.

Wild, K., Howieson, D., Webbe, F., Seelye, A., & Kaye, J. (2008). Status of computerized cognitive testing in aging: a systematic review. *Alzheimer's & dementia : the journal of the Alzheimer's Association, 4*, 428-437.

Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer, 3*, 32-35.

Zygouris, S., & Tsolaki, M. (2015). Computerized cognitive testing for older adults: a review. *Am J Alzheimers Dis Other Demen, 30*, 13-28.

8 SUPPLEMENTARY MATERIAL



Supplementary Figure 1. ROC Curve for PiB burden based on PiB visual ratings of positivity. Area under the curve=.974.