Sensitivity of individual and composite test scores from the Cogstate Brief Battery to mild cognitive impairment and dementia due to Alzheimer's disease.

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Background

The Cogstate Brief Battery (CBB) is a computerized cognitive test battery found to be sensitive to AD-related changes in cognition (decline and improvement) in both clinical studies and in clinical trials. In studies of AD related cognitive impairment, there has been variability between studies in estimates of the sensitivity and specificity of CBB tests. This could be because optimization of the CBB for detection of cognitive may have acted to limit sensitivity to cognitive impairment. This could reflect use of a) small or idiosyncratic normative samples b) restriction of outcome measures to those optimized for clinical trials or c) validation of rules to detect impairment in highly studied and enriched samples such as the Australian Imaging, Biomarker and Lifestyle (AIBL) sample. Here, new normative (cognitively unimpaired, CU) and AD dementia data sets were developed for older adults naive to the CBB, whose unimpaired cognitive status or clinical dementia rating was confirmed independently and whose CBB performance was supervised and complete. From these data, estimates of sensitivity and specificity for individual and composite CBB performance measures were computed.

Methods

Data for the CU group was drawn from the first screening visit of a sample of 5001 older adults (65 and 85 yrs) recruited for the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study. To qualify for CBB assessment, participants had to be classified as CU based on a Mini Mental Status Exam (MMSE) score of ≥ 25 and a Global Clinical Dementia Rating (CDR) Score of 0. Exclusion criteria included diagnosis of cognitive impairment or dementia, use of AD medications, significant anxiety or depression, history of cerebral vascular disease and unstable medical conditions.

Table 1: Demographic and clinical characteristics of the CU adults from A4 and adults with AD from the ADAMANT study used in this analyses.

	CU (N=4871)	CDR 0.5 (N=103)	CDR > 0.5 (N=81)
Age yrs (mean SD))	71.37 (4.69)	71.71 (7.50)	72.11 (8.23)
Female N (%)	2868 (58.9%)	49 (47.6%)	52 (64.2%)
Education <13 yrs N(%)	499 (10.3%)	56 (55.4%)	47 (59.5%)
MMSE Median (Q1, Q3)	29 (28, 30)	24 (22, 25)	23 (21, 24)

Data for the AD group was drawn from the first CBB attempt of 194 individuals undergoing assessment for enrolment in the ADAMANT study. Participants met criteria for probable AD (NIA-AA), MMSE total score ≥20 and ≤26, a brain MRI consistent with the diagnosis of AD and evidence of the AD pathophysiological process. Stable therapy with acetylcholinesterase inhibitors or memantine for >3 months before screening was required. Exclusion occurred when a CNS disorder other than AD could cause dementia, comorbidities such as recent cancer, recent myocardial infarction, poorly controlled diabetes, poorly controlled congestive heart failure, severe renal insufficiency, relevant psychiatric illness, epilepsy, chronic liver disease, chronic infectious disease (hepatitis B, hepatitis C, HIV or syphilis); uncorrected hypothyroidism or B12 hypovitaminosis.

Data analyses

Participants completed the (CBB) (www.cogstate.com) consisting of Detection test (DET, psychomotor function), Identification Test (IDN, Attention), One card Learning Test (OCL, Learning and Memory) and One Back Test (OBK, working memory). Outcome measures were speed (msec of correct responses) and accuracy (proportion of correct responses) for each test. CU and AD data were standardized using means and SDs of the CU sample. Theoretical composite scores were computed by averaging scores of component tests (Figure 1). Statistically derived composite scores were computed using logistic regression, factor analyses and linear discriminate analyses (LDA) of all outcomes to check if precision was improved through statistical weighting of scores.

Results

For each outcome, receiver operating characteristics (ROC) analyses were undertaken, with the area under the curve (AUC) and its associated 95% confidence interval computed to compare and rank sensitivity of individual and composite CBB measures. The results of this analyses are summarised on Figure 1.

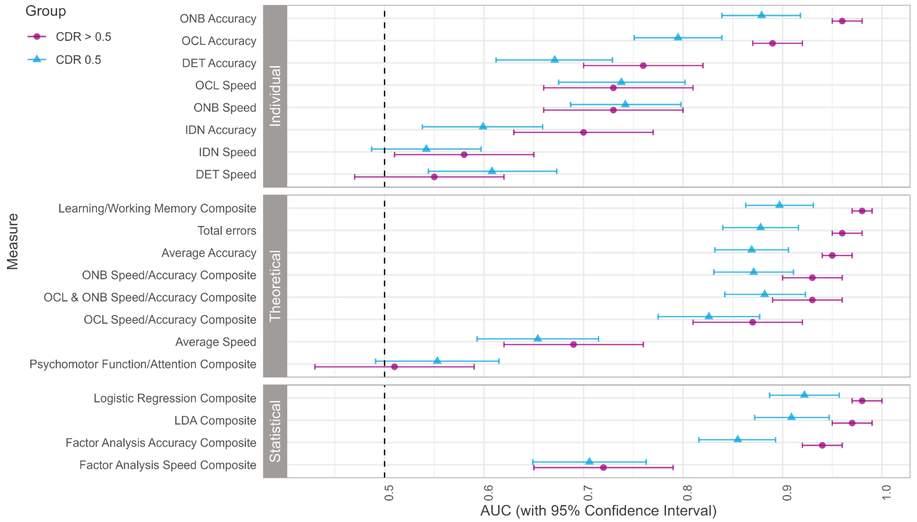

Figure 1: Comparison of AUC (+/-95% CIs) for classification of cognitive impairment in MCI (purple) or AD dementia (blue) for each individual and composite CBB outcome measure

Second Glass's Δ was calculated to provide scale-free effect sizes reflecting magnitudes of impairment in mean performance in AD groups. Statistical significance of differences was determined using a series of Welch's t-tests. Estimates of sensitivity were also computed for each outcome for each clinical group with impairment defined as performance </=-1SD from CU adults (Table 2).

Table 2: Magnitude of group impairment, and sensitivity (given 1-specificity = 13%) for each individual and composite CBB outcome in MCI and AD dementia group.

CBB Outcome	CU Vs MCI				CU Vs AD dementia			
	Glass' s Δ	t*	1 SD threshold		Glass' s Δ	t*	1 SD threshold	
			Crit	Sens			Crit	Sens
Individual Measures								
ONB Accuracy	2.73	22.64*	1.22	0.90	2.05	14.93*	1.22	0.74
OCL Accuracy	1.46	22.14*	0.92	0.77	1.09	12.27*	0.92	0.55
DET Accuracy	1.26	7.49*	1.37	0.59	0.82	5.61*	1.37	0.50
OCL Speed	1.40	5.25*	3.16	0.60	1.37	6.28*	3.16	0.57
ONB Speed	1.07	5.88*	3.05	0.58	1.09	8.17*	3.05	0.52
IDN Accuracy	1.04	6.41*	1.28	0.56	0.56	4.32*	1.28	0.39
IDN Speed	0.32	2.13	2.86	0.28	0.11	1.01	2.86	0.17
DET Speed	0.06	0.35	2.50	0.30	0.39	3.02*	2.50	0.32
Theoretically Derived Composites								
Learning/Working Memory	2.74	28.76*	1.10	0.96	2.05	17.41*	1.10	0.79
Total errors	3.04	18.06*	42.40	0.93	2.07	13.23*	42.40	0.77
Average Accuracy	2.65	19.81*	1.25	0.89	1.85	14.57*	1.25	0.74
ONB Speed/Accuracy Comp	2.54	16.88*	-0.75	0.86	2.10	13.66*	-0.75	0.77
OCL & ONB Speed/Accuracy	2.71	15.67*	-0.61	0.86	2.28	14.34*	-0.61	0.78
OCL Speed/Accuracy Comp	2.08	11.14*	-0.69	0.79	1.79	10.96*	-0.69	0.68
Average Speed	0.84	4.64*	2.93	0.51	0.67	4.70*	2.93	0.40
Psychomotor Function/Attention	0.13	0.77	2.77	0.27	0.19	1.53	2.61	0.26
Statistically Derived Composites								
Logistic Regression	3.25	25.01*	-4.03	0.98	2.65	18.21*	-4.03	0.87
LDA	3.47	20.49*	0.86	0.95	2.83	15.79*	0.86	0.83
Factor Analysis Accuracy	2.55	18.16*	-1.12	0.86	1.76	13.64*	-1.12	0.72
Factor Analysis Speed	0.97	5.40*	0.99	0.54	0.88	6.66*	0.99	0.50

Note. Crit = Criterion value on CBB test or composite, Sensitivity is defined using a criterion of 1 SD below normative mean (85% specificity) * = statistically significant

Conclusion

The results of the study show that MCI and AD groups, naive to the CBB show the greatest impairment on the OCL and OBK tests alone, and in composite measures. These same individual and composite outcome measures provide the greatest sensitivity to cognitive impairment in early AD. Sensitivity is not improved by statistically weighted combination of scores from the OCL, OBK tests or from combination of these tests with measures of response speed. Together these data provide a strong basis for development of normative data, and composite outcomes for use of the CBB in clinical decision-making contexts.