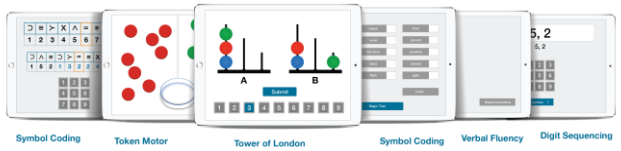
DETECTION OF EPISODIC MEMORY IMPAIRMENT IN MCI USING THE TABLET-BASED BRIEF ASSESSMENT OF COGNITION (BAC)

Sarah M. Karas, PsyD[1], Alexandra S. Atkins. PhD[1], Heather Stevens[1], Kathleen A. Welsh-Bohmer, PhD[2 1] VeraSci, Durham, NC, USA; [2] Departments of Psychiatry and Neurology, Duke University, Raleigh, NC, USA

BACKGROUND

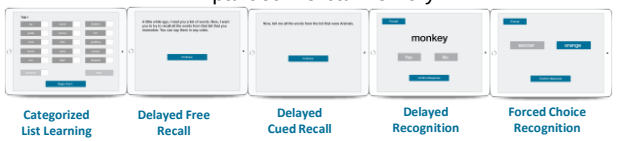
- For clinical trials targeting Mild Cognitive Impairment (MCI), selection of appropriate cognitive endpoints remains a challenge as the field moves into earlier stages of the disease process (1). In addition, recruitment for these trials requires streamlined methods for identifying and characterizing cognitive deficits in this non-demented population. The NIA-AA diagnostic criteria for MCI due to AD propose cognitive cut-off scores for MCI that fall 1 to 1.5 standard deviations below the age and education matched mean using culturally appropriate normative data (2, 3). While episodic memory impairment is often the hallmark of MCI due to AD, impairment may also be observed in executive function, attention, language, and visuospatial skills.
- The aim of the present work is to assess the utility of the tablet-based BAC to identify and quantify episodic memory and other deficits in MCI due to AD. The standard BAC battery (4) assesses Verbal Memory (5 trials of a List Learning Task), Working Memory (Digit Sequencing Task), Verbal Fluency (Phonemic and Semantic Fluency Tasks), Processing Speed (Symbol Coding Task), Motor Function (Token Motor Task), and Executive Functioning (Tower of London Task). In order to more effectively target cognitive impairment in MCI due to AD, the BAC testing platform has been enhanced to include: (1) An alternative Episodic Verbal Memory task utilizing semantically categorized 15-item word lists (4 trial learning) and including total learning as well delayed measures of Free Recall, Cued Recall, Yes/No Recognition and Forced Choice Recognition; (2) a self-administered, tablet-based test of Visuospatial Working Memory. Participants are required to tap sequences of objects that appear in various locations on a grid. At retrieval, participants are presented with a central probe and asked to tap the location the object originally appeared. Sequence length and grid size increase throughout the task. In part one, objects are probed in the order in which they were encoded; In part two, objects are probed in random order.

BAC Cognitive Measures

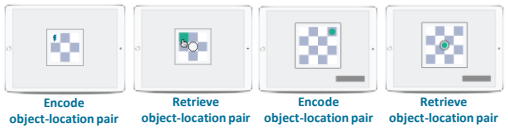


BAC Enhanced Measures

Expanded Verbal Memory



Visuospatial Working Memory



METHODOLOGICAL QUESTION

- Examine the utility of the tablet-based Brief Assessment of Cognition (BAC) to support detection and diagnosis of MCI due to AD by quantifying deficits in episodic memory and related cognitive domains.

METHODS

- Participants include 239 Healthy Older Controls (HC), and 36 participants with clinical diagnoses of MCI (amnestic type). Healthy Older Controls are participants over the age of 55 without cognitive decline as determined by MMSE scores of greater than or equal to 27 and CDR global scores of zero. Participants with clinical diagnoses of MCI due to AD were included if their MMSE scores were between 22-30 and CDR global scores were either 0.5 or 1 with Activities of Daily Living (ADLs) preserved.
- All participants completed BAC assessments in 6 individual cognitive domains: Episodic Verbal Memory (Categorized List Learning with delayed measures), Processing Speed, Working Memory, Verbal Fluency, Motor Function and Executive Function. Data were analyzed in SPSS statistical software. Group differences in age and education were assessed using independent t-tests. Group differences in performance of each measure were assessed using analysis of (ANCOVA) models that controlled for age, and education. Due to large differences in sample size between the two groups, homogeneity of variance on each measure was assessed using Levene's tests, and group by covariate interactions were examined to assess homogeneity of regression slopes. Finally, Z-scores were generated to describe demographically-corrected performance of the MCI group relative to a robust normative data set of 600 + healthy controls.

RESULTS

- The MCI group score distributions for the MMSE and CDR are displayed in Figures 1 and 2.
- The average age in years of the HC group was 69.33 (SD 8.72; range 55-89) and average years of education was 14.82 (SD 2.56; range 9-22). The average age in years of the MCI group was 74.14 (SD 8.45; range 58-90) and average years of education 16.89 (SD 2.72; range 12-23). Age and education differences were statistically significant between the HC and MCI groups (p=.002, p=.000, respectively).
- In order to control for these group differences, Age and Education were included as covariates in group comparisons of BAC performance. Despite large differences in sample size between groups, assumptions of homogeneity of variance and regression slopes was met for most measures. The exceptions to this were Verbal Memory Recognition, Forced Recognition and Cued Recall, all of which approached ceiling in the HC group, and Digit Sequencing. For these tests, performance differences between groups were confirmed using the Wilcoxon rank-sum test. In all cases, Wilcoxon rank-sum test findings concurred with results of the ANCOVA analysis.
- Robust differences were seen on all BAC Verbal Memory (Episodic Verbal Memory) measures including Total Learning, Delayed Recall, Cued Recall, Y/N Recognition, and Forced Choice Recognition with participants in the MCI group performing significantly worse than HCs each measure (p<.0001 for all). Significant differences ($p \leq .003$) were also observed in other cognitive domains for the MCI participants including Language (Verbal Fluency), Processing Speed (Symbol Coding Task), and Visuospatial Working Memory.
- The MCI group Z-scores for episodic memory measures fell 1 to 1.5 standard deviations below the mean, consistent with established criteria for clinically diagnosed MCI due to AD (Alberts et al., 2011).

Table 1. Study Group Characteristics

	HC (N=239)		MCI (N=36)		
	Mean	SD	Mean	SD	p
Age	69.33	8.72	74.14	8.45	.002
Education (years)	14.82	2.56	16.89	2.72	.000
Gender					
Females (%)	56.9		41.7		
Males (%)	43.1		58.3		

Figure 1.

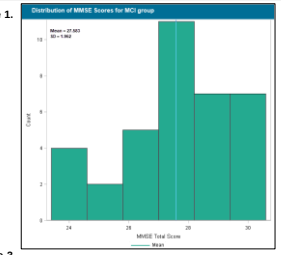


Figure 2.

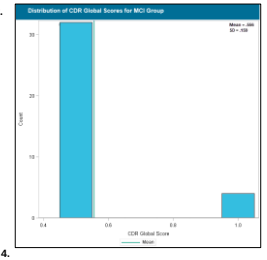


Figure 3.

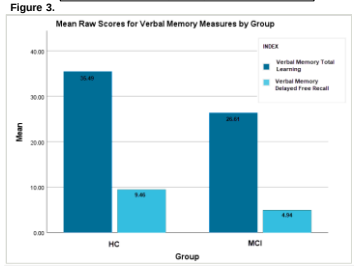
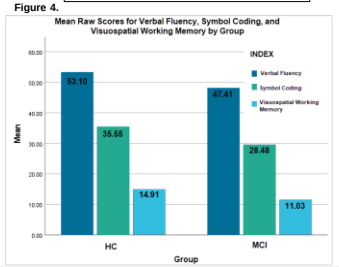


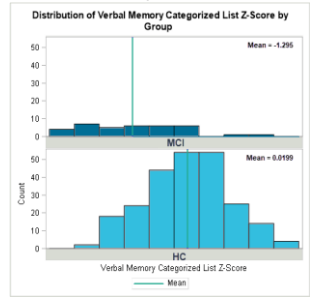
Figure 4.



CONCLUSIONS

- As Alzheimer's disease clinical trials move to earlier stages of the disease process, such as MCI or even the pre-clinical stages, cognitive endpoints need to be highly sensitive and have the ability to demonstrate improvement, not just worsening of cognition.
- Findings confirm the utility of the tablet-based BAC to assess objective episodic memory impairments in MCI due to AD and preclinical AD.
- The BAC is able to detect additional cognitive impairments that may be present in MCI due to AD, such as deficits in Language, Visuospatial Working Memory, and Processing Speed.
- While significant differences were observed between groups on many BAC measures, only verbal memory measures met the NIA-AA diagnostic cut-off of 1 to 1.5 standard deviations below the normative corrected mean. This finding is consistent with clinical characterization of the sample (MCI amnestic type).
- Taken together, results support use of the BAC for screening and evaluating individuals in a manner that is consistent with the established diagnostic criteria for MCI due to AD

Figure 5.



ACKNOWLEDGEMENTS

- This research was supported National Institutes of Health under NIMH 2R44 MH084240 (ASA) and NIA 1R44AG03191 (RSE).
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Table 2. BAC Descriptive Statistics and Statistical Analyses Results

	Healthy Older Controls (HC)			Mild Cognitive Impairment (MCI)			ANCOVA results adjusted for Age and Education			HC Z-Score	MCI Z-Score
	n	Mean Raw scores	SD	n	Mean Raw Scores	SD	Mean Square	F	Sig		
Verbal Memory (VM) – Total Learning	239	35.49	7.45	36	26.61	8.34	2390.982	47.326	.000	0.019	-1.298
VM - Delayed Free Recall	239	9.46	3.18	36	4.94	4.05	624.843	60.511	.000	0.019	-1.339
VM - Recognition	239	28.88	1.42	36	25.72	3.75	291.336	85.021	.000	--	--
VM - Forced Choice Rec	239	14.94	.22	36	14.27	1.40	12.067	41.947	.000	--	--
VM - Cued Recall	239	11.16	2.51	36	8.16	3.48	269.082	41.323	.000	0.040	-1.180
Verbal Fluency	239	53.10	13.22	34	47.41	13.01	1347.331	8.807	.003	0.152	-0.378
Symbol Coding	237	35.55	10.00	33	28.48	11.29	706.536	9.493	.002	0.235	-0.426
Visuospatial Working Memory	238	14.95	5.36	36	11.03	4.37	310.461	12.529	.000	0.160	-0.238
Digit Sequencing	238	20.50	3.96	36	19.50	4.91	52.453	3.196	.075	0.223	-0.460
Tower of London	237	16.29	3.38	35	15.22	2.93	23.710	2.210	.138	0.165	-0.246
Token Motor	235	60.77	25.54	35	64.05	21.63	1551.326	2.940	.088	0.104	0.395

REFERENCES

1. Kueper JK, Speechley M, Montero-Odasso M. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review. *J Alzheimers Dis*. 2018;63(2):423-444. doi:10.3233/JAD-170991
2. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005
3. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008
4. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res*. 2004;68(2-3):283-297. doi:10.1016/j.schres.2003.09.011

DISCLOSURES

- Kathleen Welsh-Bohmer is on the advisory boards of Biogen, Roche, Genentech, and contract support from VeraSci.
- Alexandra Atkins, Heather Stevens, and Sarah Karas are full-time employees of VeraSci.

VeraSci