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Detection of MCI in the clinic: evaluation of the sensitivity and specificity of a computerised test battery, the Hopkins Verbal Learning Test and the MMSE

CELESTE A. DE JAGER[1], ANNE-CLAIRE M. C. SCHRIJNEMAEKERS[2], THURZA E. M. HONEY[1], MARC M. BUDGE[3]

[1]Oxford Project to Investigate Memory and Ageing (OPTIMA), Department of Physiology, Anatomy and Genetics, University of Oxford, UK
[2]Stichting Revalidatie Limburg, Hoensbroeck Revalidatiecentrum, afdeling Niet-Aangeboren Hersenletsel, Hoensbroek, The Netherlands
[3]Department of Geriatric Medicine, Australian National University Medical School, Canberra, Australia

Address correspondence to: C. A. de Jager. Tel. (+44) 1865 231460/231270; Fax: (+44) 1865 231154.
Email: celeste.de-jager@dpag.ox.ac.uk

Abstract

Introduction: the sensitive detection of mild cognitive impairment (MCI) in older adults is an important problem that requires objective assessment. We evaluated whether the computerised cognitive test battery, CogState, was as sensitive to MCI as two well-validated 'paper-and-pencil' tests, the Hopkins Verbal Learning Test (HVLT) and the Mini-Mental Status Examination (MMSE).
Methods: these tests were administered with a subjective memory questionnaire and an 'Activities of Daily Living' scale to 21 individuals with MCI and 98 cognitively healthy controls matched for sex, education and IQ levels. The sensitivity and specificity of the tests and their discrimination between groups were determined.
Results: the HVLT had a maximum discrimination between controls and MCI cases of 90%, compared with 86% for CogState and 65% for the MMSE. Only CogState showed correlations with subjective memory complaints (SMC) and activities of daily living for the whole cohort when controlled for age, sex and years of education. Logistic regression analyses showed that diagnosis (control:MCI) was predicted by HVLT and a CogState ratio score. Age was a significant predictor of HVLT performance, while age and SMC predicted CogState performance. The computerised test battery was well tolerated by older adults, but presentation speed was a limiting factor for some participants.
Conclusions: overall, we conclude that the HVLT has better sensitivity for the detection of MCI in older adults than the CogState, but that CogState may enable the identification of cognitive deficits above and beyond impairments in memory.

Keywords: *mild cognitive impairment, memory, computerised tests, older adults, HVLT, CogState, Alzheimer's disease, elderly*

Introduction

The prevalence of Alzheimer's disease (AD) is on the rise [1], and evidence is accruing for the existence of a detectable pre-clinical phase of AD [2–4], a syndrome captured under the title of mild cognitive impairment (MCI). Whilst debate remains as to the optimal way to detect and diagnose the early, pre-clinical phases of dementia in the clinic, it is likely that any treatments available to treat the symptoms or slow progression of AD will be more efficacious in these early stages [5]. Although episodic memory deficits are the most common, initial precursor to AD [2, 4, 6–9], there are recent suggestions that other subtle cognitive deficits may manifest prior to [8, 9], or concurrent with [7, 9], memory impairment.

At present, an abundance of tests for the screening of dementia and cognitive impairment exists, but not all have been validated for their accuracy of diagnosis [5]. Furthermore, different tests have differing merits, are relevant for different forms of dementia and suit various stages of decline [5]. Paper-and-pencil tests such as word list recall and paragraph recall have been shown to be sensitive to MCI and very early cognitive impairment in older adults [10, 11]. The

Hopkins Verbal Learning Test (HVLT) has been validated [12] and had very good accuracy for AD diagnosis when compared with the Mini-Mental Status Examination (MMSE) [13].

Computerised neuropsychological test batteries have been reported to be more sensitive than paper-and-pencil tests for the detection of MCI and cognitive decline that may progress to AD or other dementias [14]. CogState is a multitask computerised battery with tests in the domains of attention, processing speed, memory and executive function. Repeated testing on the same day discriminated between those with early MCI and controls [14] with a similar magnitude of diminished performance observed with the CANTAB Paired Associates Learning test [15, 16]. Consequently, we aimed to determine the sensitivity and specificity of CogState for MCI and to compare its performance with that of the HVLT and MMSE with our Foresight Challenge cohort of community-dwelling older adults. We also aimed to determine whether subjective assessments of memory impairment (SMC) and activities of daily living (ADL) were associated with performance on the CogState. This study may help clinicians to decide whether to change from using paper-and-pencil tests in the clinic to computerised batteries, which may be self-administered by more competent patients, and therefore save clinician time.

Methods

Cohort

Foresight Challenge cohort

A total of 119 subjects who were initially recruited as healthy, community-dwelling volunteers over 60 years of age without significant progressive, subjective memory complaints (SMC) were included in this study [4]. Volunteers were assessed at baseline by clinical examination and dementia screening tests as previously described. Cognitive scores were all in the normal range on the CAMCOG [17], and MMSE. Ethical approval was granted by the Central Oxford Research Ethics Committee. Informed consent was obtained from all participants.

After 4 years of follow-up, subjects were diagnosed as having amnestic MCI if they scored 1.5 SD from the norm on at least one of five episodic memory tests at visit 4, did not have dementia, were still functioning independently in the community [18] and had normal general cognition (i.e. MMSE > 24). Memory tests included CERAD 10-word list recall [19], the Rivermead paragraph recall [20], the Placing Test [21], CANTAB spatial recognition and Paired Associates Learning. The HVLT was not used for MCI classification. A total of 21 subjects were classified with MCI and 98 as controls. Testing with CogState, MMSE and HVLT for this study was done 1 year after classification. SMC was not used as a criterion for MCI, but rather in the analysis of predictors of performance. The sensitivity of SMC to MCI diagnosis has not been shown to be sufficiently high, meaning that subtle impairment will go undetected if those with no SMC are left out of MCI studies [18].

Assessment measures

(i) Subjective memory assessment derived from four questions on the CAMDEX [17].

(ii) ADL, an abbreviated version of the Cambridge activities if daily living (ADL) scale, from the Cambridge Behavioural Inventory (CBI) [6]. The ADL scale was answered by study participants, as people with early cognitive impairment might not necessarily have an informant who would know about their memory performance at home. Questions related to memory, orientation and attention in daily living and everyday skills. Questions on self-care and feeding were omitted, being inappropriate for independently living participants.

(iii) The MMSE [22].

(iv) HVLT (HVLT-revised) with a delayed recall component [12]. The HVLT consists of a 12-item word list, comprising four words from each of three well-known semantic categories. A total recall score and a learning index are calculated. After 20 min, delayed recall of the word list is tested. Then, for yes/no recognition, from a list of 24 words, 12 original and 12 distracters, a 'discrimination index' is calculated as (true positives − false positives). The test takes about 10 min to administer in total.

(v) CogState.com is accessible on the Internet and takes ∼20 min to complete. Demographic information may be entered before starting the test. The test battery is based on a pack of playing cards with two keys on the keyboard used for responses. The eight tests in the battery include Simple Reaction Time for sustained attention and processing speed, Congruent Reaction Time and Choice Reaction Time for attention, processing speed and decision making. One-back task for working memory, Monitoring task for visual tracking and attention and Matching, Incidental Learning and Paired Associative Learning tasks for episodic memory. For analyses, the CogState subtest scores were computed into overall scores for accuracy, speed and an accuracy:speed ratio.

(vi) An assessment questionnaire on reactions to CogState, asking about card playing, computer use, test difficulty and fatigue level (Table 1).

The entire testing session took between 1 h and 1 h 15 min and was administered by three psychologists. Participants were supervised through a practice session on CogState, (to maximise good performance), followed by the test battery, with minimal supervision/assistance.

Statistics

Independent means tests were used to compare demographic factors and performance between control and MCI groups

Table 1. Demographics comparing control and MCI groups

	Control ($n = 98$) Mean (SD)	MCI ($n = 21$) Mean (SD)	Significance (P-value) Two-tailed
GDS (0–16)	4.38 (3.62)	4.71 (4.41)	0.714
Age (65.85–91.65)	77.18 (5.9)	81.95 (5.40)	0.001**
NartIQ (92–131)	118.96 (9.65)	119.29 (6.39)	0.882
ADL (0–104)	7.15 (6.95)	7.48 (5.82)	0.844
SMC (0–4)	1.23 (1.00)	1.76 (1.04)	0.032*
Handedness (chi-square)			0.226
Gender (chi-square)			0.777
Education, primary (1) secondary (2) tertiary (3)	2.50 (0.65)	2.38 (0.740)	0.457
Fatigue, no (0) mild (1) severe (2)	0.47 (0.56)	0.57 (0.68)	0.489
Medication, none (0) <5 (1) >5 (2)	0.90 (0.57)	1.06 (0.54)	0.299
Alcohol, none (0) rare (1) social (2) frequent (3)	1.67 (0.89)	1.43 (0.68)	0.239
Smoking, none (0) occasional (1) regular (2) often (3)	0.11 (0.47)	0.00 (0.00)	0.021*
Do you play cardgames? never (1) rarely (2) now and then (3) regularly (4) every week (5)	2.01 (1.24)	2.81 (1.29)	0.505
Have you used a keyboard before? never (1) rarely (2) now and then (3) regularly (4) every week (5)	3.09 (1.51)	3.20 (1.36)	0.756
Does the fact that it is a computerised test, rather than a 'pencil-and-paper' test make any difference to you? More difficult (1) slightly more (2) the same (3) slightly easier (4) easier (5)	2.83 (1.08)	2.67 (1.35)	0.557
Is CogState more difficult than previous computer tests? More difficult (1) slightly more difficult (2) the same (3) slightly easier (4) easier (5)	2.82 (1.20)	2.57 (1.47)	0.477
How stressful is CogState? very (1) quite (2) moderately (3) slightly (4) not (5)	4.01 (1.09)	3.67 (1.16)	0.196
Are you tired from doing the tests? Extremely tired (1) quite tired (2) moderately tired (3) a little tired (4) not tired (5)	4.15 (0.95)	4.05 (0.81)	0.632

** $P < 0.01$ level (two-tailed test) significance.
* $P < 0.05$ level (two-tailed test) significance.

on the CogState, MMSE and HVLT. Spearman's correlations were determined between the CogState and HVLT. The HVLT total recall score was used for correlations, as it was more sensitive to MCI than the learning and discrimination indices, and even the delayed recall score. Receiver operating characteristic (ROC) curve analyses allowed calculation of the optimal sensitivity (to correctly detect cases) and optimal specificity (to correctly detect controls) using different cut-off scores of the cognitive tests. This analysis was performed for accuracy measures, followed by accuracy to speed ratios to determine whether the latter measures were more sensitive to diagnosis. Pearson's partial correlations were determined for ADL and SMC with the CogState subtests and combined accuracy, accuracy/speed ratio and speed scores as well as with the HVLT and MMSE. Backward logistic regression was used to establish the best predictors for performance on the CogState, HVLT and MMSE and for diagnosis.

Results

Demographics

The MCI group was older and had more SMCs than the control group, which had a higher proportion of smokers (Table 1). There were no differences between the groups in gender ratio, level of education, NART IQ, ADL scores, handedness, fatigue level, alcohol intake and number of medications taken or the perceived user-friendliness of CogState.

Independent means tests

Performance on the CogState accuracy (86.38 ± 6.2 vs. 76.79±7.74), speed (23.35 ± 0.53 vs. 23.80 ± 0.76) and ratio (3.70 ± 0.31 vs. 3.23 ± 0.38) measures was significantly different between control and MCI groups ($P < 0.01$).

Performance on the HVLT (28.30 ± 4.21 vs. 21.10 ± 4.30) and MMSE (28.92 ± 1.29 vs. 27.81 ± 1.99) was significantly different between control and MCI groups ($P < 0.01$).

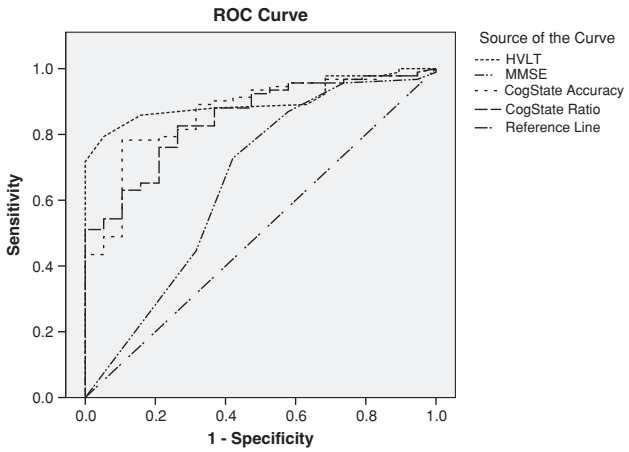
Spearman's correlations with the HVLT

The CogState accuracy ($r = 0.392$, $P < 0.01$), speed ($r = -0.201$, $P < 0.05$) and accuracy:speed ratio ($r = 0.373$, $P < 0.01$) scores correlated significantly with the HVLT.

ROC curves for sensitivity and specificity of tests for diagnosis (Figure 1)

ROC curves produced areas under the curve (AUC) for accuracy and accuracy:speed ratios for CogState as well as for the HVLT and MMSE accuracy. The HVLT had the highest AUC (90%). AUCs for CogState accuracy (86%) and accuracy:speed ratio (84%) were significant, while the MMSE had 65% AUC.

Optimum sensitivity and specificity of CogState for diagnosis (control, MCI) were determined from the ROC curve analysis using the most appropriate cut-off scores for discriminating between controls and those with MCI. The CogState accuracy score was slightly better than the accuracy:speed ratio for discriminating between the two groups, with the accuracy score identifying controls with a specificity of 90%



TEST	AUC	Optimum cut-off	Sensitivity	Specificity
CogState Accuracy	86%	82.86	78%	90%
CogState Ratio	84%	3.54	76%	79%
HVLT	90%	25.5	79%	95%
MMSE	65%	28.5	44%	69%

Figure 1. ROC curve showing the sensitivity and 1-specificity of the HVLT and MMSE for MCI vs. control classification as compared with CogState accuracy and accuracy:speed ratio scores.

and MCI with a sensitivity of 78%. However, the HVLT outperformed both of these tasks in terms of specificity (95%) and sensitivity (79%) (Figure 1). The MMSE had reasonable specificity (69%), but poor sensitivity (44%).

Cognitive performance and associations with ADL and SMC

CogState subtest accuracy:speed ratios, the combined accuracy, ratio and speed scores and the HVLT and MMSE were tested for Pearson's partial product correlation coefficient with ADL and SMC scores for the whole cohort with age, sex and education entered as covariates. A number of CogState ratios including SRT, Congruent and Choice RT, Monitoring and Matching showed associations with SMC and ADL, but the MMSE and HVLT did not. When the subtests were combined into an overall accuracy, speed and accuracy:speed ratio score, only the association with SMC remained, while those with ADL were no longer significant ('. . .please see the Table 3, Appendix 1 in the supplementary data available at Age and Ageing online').

Predictive factors for performance on the cognitive tests

Backward regression analyses were carried out to establish the best predictive factors for performance on each of the tests, with the CogState, HVLT and MMSE as dependent variables, and age, years of further education, gender, ADL and SMC as independent variables. Age and SMC were shown to be the best predictors for performance on CogState accuracy, speed and accuracy:speed ratio measures (Table 2), and age was the best predictor of HVLT performance. Diagnosis (Control vs. MCI) was predicted by both HVLT and CogState accuracy:speed ratio with the same independent variables entered.

Table 2. Backward logistic regression analyses showing significantly predictive factors for performance on the tests, and factors/tests significantly predictive of diagnosis

Tests	Dependent variables: factors/demographics	*B*-value	*T*-value	*P*-value
CogState accuracy	Age	−0.438	−5.187	0.000
	SMC	−0.208	−2.464	0.015
CogState ratio	Age	−0.414	−4.911	0.000
	SMC	−0.243	−2.875	0.005
CogState speed	Age	0.197	2.155	0.033
	SMC	0.289	3.158	0.002
HVLT	Age	−0.280	−3.150	0.002
Diagnosis	HVLT	−0.422	−5.039	0.000
	CogState ratio	−0.467	−3.794	0.000

Independent variables entered into analyses: age, education (years of further education), gender, activities of daily living (ADL) and subjective memory complaints (SMC).

User-friendliness of CogState

Independent means tests revealed no significant differences between groups (control, MCI) regarding individual's perceptions of the user-friendliness of CogState (Table 1). CogState was developed to be self-administered. However, our observations were that the older subjects in the cohort needed some verbal instruction. Some participants could not keep up with the speed of the test battery, particularly in the paired associative learning tasks and therefore scored errors for not responding rather than for incorrect responses.

Discussion

We aimed to determine whether a novel computerised neuropsychological test battery had better sensitivity and specificity than two well-validated assessment measures, the HVLT and MMSE, to inform clinicians about the potential for early detection of MCI in older adults. Significant differences between control and MCI groups were shown on all cognitive tests. However, the HVLT had the highest sensitivity and specificity for discriminating between MCI cases and cognitively normal controls. This reaffirms the evidence for episodic memory impairment being the most common initial symptom of MCI, a frequent prodrome to AD [2, 23–25]. The HVLT has a cued recall element in its design, which introduces a learning strategy that is of benefit to cognitively healthy older subjects and those with MCI who remain stable or improve over time, but not to those with MCI who decline [26]. The three categories of words in each list also help with

initial encoding. Thus, the HVLT is similar to the ideal type of the episodic memory test for prodromal AD proposed by Du Bois *et al.* [3].

The CogState correlated significantly with the HVLT, demonstrating that it is a robust assessment scale. It had acceptable sensitivity and specificity, almost matching that of the HVLT. CogState accuracy measures showed greater associations with the HVLT than CogState speed measures, as would be expected. One of the strengths of computerised testing is the ability to record very accurate reaction times. The sensitivity of these measures was effectively demonstrated in the comparison between controls and those with MCI, where the mean differences between speed measures for the two groups were highly significant. In complex tests of working memory, monitoring and learning, the mean group differences were approximately twice the differences between reaction times on simple processing speed tasks (data not shown for subtests). This suggests that information-processing mechanisms are slower in people with MCI than in healthy, older adults. This degree of separation between those with very early cognitive impairment and those without suggests that reaction times could prove useful as an outcome measure for clinical trials of cognitive enhancing treatment [27]. However, differences between speeds of response are a less clear predictor of group assignment (MCI vs. control), as speed declines with age.

The unlimited equivalent forms of the CogState tests confer the advantage of minimal learning effects with serial assessment. However, the HVLT has six well-correlated alternative versions which give it these same advantages [28]. Significant practice effects between the first and second administration of CogState were shown by Collie *et al.* [27]. This suggests that pre-study training is important in reducing confounding practice effects, before doing serial assessments [29].

CogState showed correlations with SMC and ADL, not demonstrated with the HVLT and MMSE, indicating that CogState may be detecting more functional deficits than the HVLT and MMSE. One could infer from this correlation that SMC reflect one's overall sense of cognitive decline rather than a specific deficit in memory function. As MCI progresses, impairments are evident not only in episodic memory but also in a range of cognitive domains. This is thought to reflect the spreading pathology of disease from the medial temporal lobes to areas affecting attention, working memory and executive function [30]. As a result, a more global assessment such as the CogState might be preferable to domain-specific tests like the HVLT, for detection of disease progression and differential diagnosis of MCI types (amnestic, nonamnestic) that may progress to different types of dementia.

If one accepts that detecting MCI (as a prodromal form of dementia) is important as an appropriate time for intervention with novel disease modifying agents, then quick appraisals of cognition, using the HVLT or the CogState in geriatric psychology and clinical settings could be most appropriate. As maintenance of cognitive health becomes more important, these assessment tools may also prove useful for prospective evaluation of the risk of future cognitive impairment. Future research could test the predictive value of CogState for conversion from amnestic MCI to AD, and compare this with progression of non-amnestic MCI.

Key points

- The HVLT had better sensitivity to MCI than CogState and the MMSE and would thus be an ideal tool in the clinic for early detection of cognitive impairment.
- Computerised testing was well tolerated by older adults, although the speed of the programme was too fast for some people to respond to in time.
- Although both CogState and the HVLT have alternate versions suitable for repeat testing, the ability of computers to record reaction times may be of particular use.

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Conflicts of interest

There were no conflicts of interest associated with this study. The authors have no interest in CogState other than researching its use as a cognitive assessment tool.

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Supplementary data

Supplementary data are available at *Age and Ageing* online.

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