

Use of a novel technology for presenting screening measures to detect mild cognitive impairment in elderly patients

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Disclosures

Drs Wright and LaPlaca are co-inventors of the DETECT Technology. After the completion of this study, a patent was filed and is pending. A new company, Zenda Technologies, was created to further develop and market the DETECT device. Dr Wright, Dr LaPlaca and Mr Brumfield are not employees of the company, but do retain financial interest.

SUMMARY

Background: Available screening tools for mild cognitive impairment (MCI), often a precursor to Alzheimer's disease, are insensitive or not feasible for administration in a busy primary care setting. Display Enhanced TEsting for Cognitive impairment and Traumatic brain injury (DETECT™) addresses these issues by creating an immersive environment for the brief administration of neuropsychological (NP) measures. **Objective:** The aim of this study was to determine if the DETECT™ cognitive subtests can identify MCI patients as accurately as standard pen and paper NP tests. **Methods:** Twenty patients with MCI recruited from a memory disorders clinic and 20 age-matched controls were given both a full battery of NP tests (standard NP) and the DETECT™ screen. Logistic regression models were used to determine whether individual tests were predictive of group membership (MCI or control). Demographic variables including age, race, education and gender were adjusted as covariates. Selection methods were used to identify subset models that exhibited maximum discrimination between MCI patients and controls for both testing methods. **Results:** Both the standard NP model (C-index = 0.836) and the DETECT™ model (C-index = 0.865) showed very good discrimination and were not significantly different ($p = 0.7323$). **Conclusion:** The DETECT™ system shows good agreement with standard NP tests and is capable of identifying elderly patients with cognitive impairment.

What's known

Alzheimer's disease (AD) is a growing health issue in the world. MCI is a precursor to AD that provides a window into early diagnosis and interventions. Modalities for early detection are being developed, but barriers still exist.

What's new

DETECT™ is a novel tool developed to measure cognitive impairment and reduce many of the barriers to widespread screening in the primary care setting.

Introduction

In the 1990s, the term mild cognitive impairment (MCI) was introduced to denote an intermediate stage between normal ageing and dementia (1). Criteria for the amnesic subtype of MCI, as proposed by Petersen et al., include a subjective memory complaint, an objective memory impairment detected via clinical examination, normal general cognitive functioning in other areas, and intact activities of daily living. Other subtypes of MCI have since been identified to refer to impairment in a single non-memory domain such as executive functioning or language (2–4). Studies have found that patients with MCI commonly progress to dementia, most often Alzheimer's disease (AD), with rates of progression typically ranging from 16% to 18% a year (4,5). The risk for vascular dementia, the second most common cause of dementia, is also associated with preclinical

MCI (6). The global burden of AD is striking with over 26.6 million persons worldwide currently affected (7). By 2050, the burden is expected to quadruple (8). The number of persons with MCI is estimated to be double or triple this figure (9). As a result, research has increasingly focused on the importance of the early detection of MCI to test and to implement therapies that may be neuroprotective, thus improving quality of life for both the affected individual and their significant others (10).

Mild cognitive impairment can be difficult to detect because of the often subtle cognitive manifestations and the relative intactness, by definition, of activities of daily living such as driving and medication management. Available screening instruments such as the Mini Mental State Examination offer the benefits of brevity in a busy clinical practice and can often detect cases of frank dementia, but they may miss patients with MCI (11–14). On the other hand,

detailed neuropsychological (NP) assessment can identify patients with MCI, but the measures can take up to several hours to administer by a skilled technician, and the results must be scored and then interpreted by an appropriately trained professional such as a Clinical Neuropsychologist. As a result, the entire process can be quite costly. Computerised NP testing is now available and has some advantages over traditional pen and paper testing (e.g. reaction time measurements, objective test batteries). However, most of the current systems require close monitoring by staff and require a distraction free environment to ensure reliability.

As a potential solution to the above challenges, the Display Enhanced TEsting for Cognitive impairment and Traumatic brain injury (DETECT™) was developed to administer a brief battery of cognitive assessment tasks in an immersive environment (Figure 1). The advantages of the system include a shortened battery of tests (7–10 min to complete) that examine multiple domains including information processing speed and episodic and working memory and an automated scoring algorithm (objective and independent of an examiner), all in an environment free from external distractions. The testing does not require operator oversight or input, making the device more feasible in a busy clinical setting.

The objective of the current pilot study was to determine if the DETECT™ cognitive measures can identify patients MCI as well as standard NP tests. The measures were adapted from NP tests of simple and complex attention, episodic memory and working memory. We hypothesised that abilities including information processing speed and memory as measured by the DETECT™ subtests would be especially vulnerable in older individuals with MCI.



Figure 1 DETECT heads up display device

Methods

Study design

This was a prospective, cross-sectional, case-controlled study comparing the accuracy of the DETECT™ device and standard NP tests in a group of patients with known MCI. Demographically matched normal controls were also used for comparison. MCI was determined by a full assessment in a Cognitive Neurology Program and included NP testing, assessment of activities of daily living, neurological examination and select adjunctive tests (imaging, blood work, etc., when medically indicated). This assessment and subsequent diagnosis was considered the 'gold standard'. The study was approved by the Emory Institutional Review Board.

Participants

Study participants were identified from an existing registry of patients over 65 years old who were evaluated in the Cognitive Neurology Program in the Wesley Woods Center on Aging at Emory University School of Medicine, Atlanta, GA, USA. The registry included a list of geriatric patients who had agreed to be contacted for research purposes. Over 80% of the patients participated in this registry. All patients in the current study had been examined by experienced neurologists in the Memory Disorders Clinics, and they had received workups for treatable causes of cognitive impairment including screening blood tests and brain imaging. Patients who were diagnosed as having MCI were contacted for participation with the following exclusionary criteria: histories of neurological illnesses (e.g. Parkinson's disease, large vessel strokes, traumatic brain injury resulting in loss of consciousness), psychiatric disturbances (e.g. major depression, psychosis), and substance abuse. Healthy controls were matched for age, socio-economic status and education level. These were often family members or spouses of the patients with MCI.

Study protocol

Both the DETECT™ and NP tests were administered by a psychometrician at the Wesley Woods Geriatric Clinic. Scoring of the DETECT™ device was automated (values generated by the computer autoscoring – reaction time, number correct, number of errors and number of misses). A clinical neuropsychologist supervised scoring of the NP tests.

Description of DETECT™

The hardware creates a unique immersive environment. The components include an ultra-mobile touch-screen computer; a heads-up-display; passive

noise reduction headphones with audio inputs; and a hand-held input unit with two buttons ('Yes' and 'No').

The DETECT™ software consists of a series of tests described below (Figure 2) that evaluate information processing speed, episodic memory and working memory. Three tests used in clinical and experimental research settings were abstracted, modified and computerised for display on a virtual reality screen: (i) simple and complex choice reaction time test (15), (ii) selective reminding memory test (16), and (iii) N-back working memory test (17–19). Individual items were designed to be answered with binomial 'Yes' or 'No' responses. Performance was scored based on response type (correct, incorrect and missing) and response time (to the hundredth of a second). The

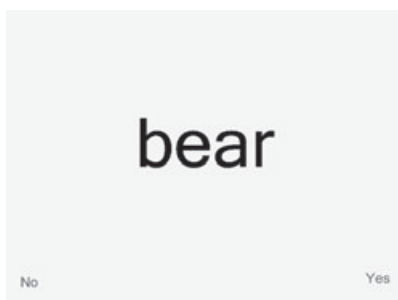
test items were presented for 2-s intervals. If no response was logged within 2 s, the next item was presented. This ensured a shortened battery, while challenging the patient to respond quickly, thereby evaluating potentially slow information processing speed as an indicator of cognitive difficulty.

We previously evaluated the immersive quality of the system in 42 normal college-age students (20). Group 1 completed NP tests using the DETECT™ system in a quiet environment. This same group was then required to retake the test in an artificially induced external noisy environment (~75 dB of fluctuating noise, equivalent to an average football game crowd). Group 2 took the same test in the noisy environment first, and then completed the second round of tests in the quiet environment. There were no



Test 1: Simple and complex attention (information processing) -

Subjects respond to a stimulus with 1 to 3 characteristics: shape, color, and internal line orientation. In the Simple Attention condition, they are asked to respond to a stimulus that has only one characteristic (e.g., a circle). In the complex attention condition, they respond to a stimulus with three features (e.g., a blue circle with vertical lines), and they must ignore other similar stimuli that may vary by only one characteristic, (e.g., blue square with vertical lines).



Test 2: Selective reminding (episodic memory) -

Subjects are asked to remember a list of 12 words. At the end of the trial, they are shown 24 words (12 original and 12 distractors) and are asked to determine whether each word was or was not presented. On subsequent trials, they see only the words they did not correctly identify as having been on the previous list. They are then shown 24 words (the original words and 12 new distractors), and recognition memory is again evaluated. Delayed recognition memory is assessed at the completion of the detect measures.



Test 3: N-Back task (working memory) -

Test 3 contains 9 blocks on a 3 X 3 grid. Subjects are required to remember the location of a block that flashes on the grid. In the first series, N-Back 1, subjects indicate whether a subsequent flash is in the same position as the flash before it (Yes), or in a different location (No). The recognition process is continual, so that each response depends on remembering the location of the block on the previous trial. In the second series, N-Back 2, subjects are required to remember the location of a block that was presented two trials ago. In similar fashion, the correct selection is a continuous process that depends on remembering the location of the block presented two trials previously.

Figure 2 DETECT software: sample screen shots

significant differences in participants' test scores or response times when taking the tests in the quiet vs. noisy environments, demonstrating the feasibility of using the device in a distraction filled setting.

Description of the NP tests

Performance on paper and pencil NP tests was compared with the DETECT™ system in terms of the ability to correctly classify individuals as having or not having MCI. The tests required 60 min to administer. The measures (and their associated abilities) included the paced auditory serial addition test (working memory; 21–23), controlled word association test – timed phonemic and category verbal fluency (language/semantic memory; 24,25), trails A and B (timed visuomotor processing speed and set shifting; 26), the six trial version of the verbal selective reminding test (episodic memory; 16).

Statistical methods

This study tested two diagnostic modes of screening for MCI. Of particular interest was determining which tests in the DETECT™ battery were predictive of MCI. Every eligible patient received the DETECT™ test (the experimental diagnostic mode) and the standard NP tests within the same session.

Outcome measures from all three DETECT™ tests and the paper and pencil tests were summarised and used as predictors of MCI status in univariate logistic regression models. For the DETECT tests, these measures included overall accuracy and response times for the simple and complex attention conditions and for the N-back 1 and N-back 2 conditions. For the selective reminding test, these included the total number of hits and false alarms as well as reaction times for both the immediate and delayed recall conditions. For the paper and pencil tests, outcome measures included total correct responses (Paced Auditory Serial Addition Task, letter and category fluency), completion times (trails A and B), short and long-term retrieval of words (selective reminding), and the number of completed categories. Each univariate model was evaluated using the following statistical criteria:

- The Concordance Index (C-index) – analogous to the area under the receiver operating characteristic curve, this exhibits the degree of discrimination associated with the variable, i.e., how well the variable is able to separate patients with MCI and controls. This measure varies between 0.5 and 1.0. The closer a value is to 1.0 the better the discrimination of the variable. This approach incorporates the whole spectrum of diagnosis probabilities and presents an overall measure of discrimination that

is more informative than simple measures of sensitivity and specificity, which are based on a single probability cut-off.

- Classification statistics – patients were classified as MCI if the probability of impairment was greater than 50%. For instance, a patient whose predicted probability of being an MCI patient is 0.46 is classified as a control patient while a predicted probability of 0.63 would necessitate an MCI classification.
- Wald statistics – indicates whether the association between the predictor and designation of MCI is statistically significant.

To determine the best set of predictive variables, a model-building algorithm called stepwise selection was employed for both the DETECT battery and the NP testing predictors, separately. The C-index was collected for each of the models that were chosen by the algorithms.

The accuracy of a test was treated as a continuous variable. Differences in continuous variables across groups were compared using a two-sample *t*-test. χ^2 tests were used to assess group differences with respect to categorical outcomes. All tests were evaluated at the 0.05 alpha level.

Results

The two groups, MCI and non-MCI, consisted of 20 persons each. The groups were similar in terms of their demographic characteristics (see Table 1). The DETECT test overall showed excellent discrimination between MCI and controls (see Figure 3).

For both the simple and complex attention and selective reminding tests, the cognitively impaired group performed significantly worse than the control group (Table 2). For the simple attention test, the response time was 0.4 s slower for the MCI vs. the control group ($p = 0.008$). Response time was 0.3 s

Table 1 Equivalence of matching characteristics

Matching factor	Non-MCI patients <i>n</i> = 20	MCI patients <i>n</i> = 20	p-Value
Patient age in years (SD)	85.1 (12.6)	82.3 (10.3)	0.45
Education in years (SD)	15.3 (3.5)	15.3 (3.2)	1.00
Non-Caucasian race (%)	1 (5.0)	3 (15.0)	0.29
Female (%)	8 (40.0)	10 (50.0)	0.53

MCI, mild cognitive impairment; SD, standard deviation.

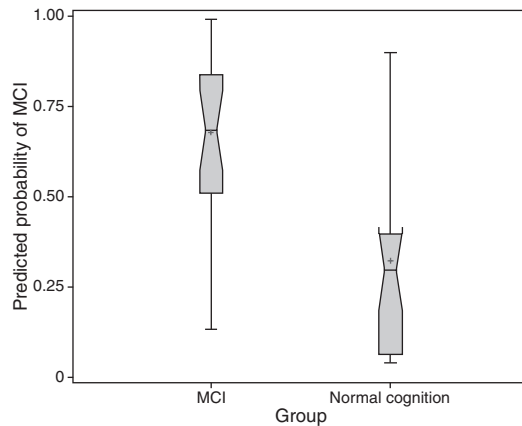


Figure 3 Box plot

slower for the MCI vs. the controls on the complex attention test ($p = 0.043$). The MCI group also was less accurate in performing both the simple attention (86% vs. 94%, $p = 0.009$) and the complex attention tests (78% vs. 89%, $p = 0.012$). For the selective reminding test, the MCI group had significantly poorer recognition memory than the control group (75% vs. 88%, $p = 0.003$), and their mean reaction times were 0.4 s longer ($p < 0.001$).

For the N-back test (Table 3), the MCI group was less accurate and had slower response times. In the first round of the 1-back test, the MCI group made more errors (10.1 vs. 6.2, $p = 0.003$) and took more time (2.1 vs. 1.7 s, $p = 0.051$). Similarly, in the second round, the MCI group made more errors (10.5 vs. 6.1, $p < 0.001$) and took more time (2.3 vs. 1.7, $p = 0.003$). For the first round of the 2-back test, the MCI group made a higher mean number of errors (10.7 vs. 8.1, $p = 0.042$) and was slower (2.4 vs. 1.8, $p = 0.02$). In the second round of the 2-back test, the mean errors were again higher for the MCI group (11.4 vs. 8.2, $p = 0.022$) but the response time did not statistically differ (2.4 vs. 2.0, $p = 0.14$).

In addition to the overall summary measures (Table 4), several individual items from the DETECT battery and NP testing were found to be significantly associated with presence of MCI via univariate logistic regression analysis. From the NP testing, both the long-term retrieval (C-index = 0.836, $p = 0.003$) and the long-term storage (C-index = 0.833, $p = 0.002$) measures of the paper and pencil selective reminding test were associated with MCI. From the DETECT battery, the item with the best discrimination was accuracy in performing Round 1 of the N-back-1 test (C-index = 0.836, $p = 0.009$). For selected items from both modalities, see Tables 4 and 5.

Multivariable analysis

Model fitting strategies were performed separately for both administration modes (paper-and-pencil tests and DETECT™) to identify the set of predictors that best discriminated MCI and non-MCI patients. For the paper and pencil tests, all of the individual items were highly correlated, and the most discriminant model was the univariate model measuring long-term retrieval on the selective reminding test, which had a C-index of 0.836. For the DETECT™ items, the most discriminating model had two predictors – accuracy on the complex attention test ($p = 0.066$) and Round 2 accuracy of the N-back 1 test ($p = 0.014$). The C-index was 0.865. The C-index values from the two modes were not statistically different ($p = 0.73$).

Discussion

DETECT™ was comparable to NP testing in discriminating normal controls from MCI patients. This is an important finding given the advantages of the DETECT™ system and its potential role for early screening.

Screening for MCI in the primary healthcare setting is extremely challenging. Traditional cognitive

Table 2 Performance of MCI patients vs. controls on the DETECT attention and memory tests

	Non-MCI controls <i>n</i> = 20	MCI subjects <i>n</i> = 20	<i>p</i> -Value
Simple attention accuracy rate (mean ± SE)	94% (1.6)	86% (2.7)	0.009
Simple attention response time in seconds (mean ± SE)	1.1 (0.10)	1.5 (0.10)	0.008
Complex attention accuracy	89% (2.1)	78% (3.4)	0.012
Complex attention response time time in seconds	0.9 (0.09)	1.2 (0.09)	0.043
Selective reminding accuracy	88% (1.8)	75% (3.5)	0.003
Selective reminding response time in seconds	0.9 (0.04)	1.3 (0.08)	< 0.001

DETECT, Display Enhanced Testing for Cognitive impairment and Traumatic brain injury; MCI, mild cognitive impairment; SE, standard error.

Table 3 Performance of MCI patients vs. controls on the N-back test

	Non-MCI controls	MCI patients	p-Value
N-back 1 (Round 1)	<i>n</i> = 15	<i>n</i> = 16	
Number of errors (SE)	6.2 (0.9)	10.1 (0.8)	0.0030
Response time (SE)	1.7 (0.1)	2.1 (0.2)	0.0507
N-back 1 (Round 2)	<i>n</i> = 19	<i>n</i> = 20	
Number of errors (SE)	6.1 (1.0)	10.5 (0.7)	0.0008
Response time (SE)	1.7 (0.1)	2.3 (0.1)	0.0028
N-back 2 (Round 1)	<i>n</i> = 18	<i>n</i> = 17	
Number of errors (SE)	8.1 (0.9)	10.7 (0.9)	0.0419
Response time (SE)	1.8 (0.2)	2.4 (0.1)	0.0201
N-back 2 (Round 2)	<i>n</i> = 18	<i>n</i> = 20	
Number of errors (SE)	8.2 (1.1)	11.4 (0.7)	0.0217
Response time (SE)	2.0 (0.2)	2.4 (0.1)	0.1407

MCI, mild cognitive impairment; SE, standard error.

Table 4 Selected (univariate) items from both the paper test and DETECT™ modes

DETECT TEST MODE	Predictor variable	C-index	p-Value	Classification rate (%)
DETECT Test 1	SIMPLE2 Accuracy	0.763	0.025	31/40 (0.73)
	SIMPLE3 Accuracy	0.714	0.023	28/40 (0.70)
DETECT Test 2	Round of Completion	0.713	0.29	28/40 (0.70)
	First Round Accuracy	0.771	0.025	27/40 (0.68)
	Fifth Round Accuracy	0.776	0.14	27/40 (0.68)
DETECT Test 3	Overall Accuracy	0.790	0.014	30/40 (0.75)
	1Back Round 1 Accuracy	0.817	0.026	21/31 (0.68)
	1Back Round 2 Accuracy	0.836	0.009	30/39 (0.77)
	2Back Round 1 Accuracy	0.742	0.073	23/35 (0.66)
	2Back Round 2 Accuracy	0.778	0.067	26/38 (0.68)

DETECT, Display Enhanced TEsting for Cognitive impairment and Traumatic brain injury.

testing is not feasible because of the time, training and facilities required for administration. A number of screening tools have emerged to help identify potentially impaired patients. However, no tool currently available has been able to overcome all of the challenges required for rapid screening in an office setting. Tools such as the Mini Mental Status Examination have not correlated well with early MCI and are usually only accurate at the extremes of the disease (normal or very impaired). The Mini-Cog (clock test and three answer survey) has recently been studied and appears better than the Mini Mental Status Examination (27). However, both of these screens still require clinician administration and should be performed in a distraction free environment to assure reliability. Other computerised NP tests have been developed that have the advantage of autoscoring and measuring response time (a potentially important factor in

MCI). Most of the tests still require a substantial amount of time to complete (up to 30 min) and should be performed in a distraction free environment. Although the requirement limitations of each specific test (e.g. expert examiner, distraction free environment, time to administer, etc.) may be perceived as minor, the reality is that they are significant enough to reduce the feasibility of NP testing in a primary care setting.

Other screening and diagnostic tools including brain imaging and serum markers are being developed. Imaging techniques such as MRI show great promise for detecting amyloid plaques, but are very expensive and unlikely to be a primary screening mechanism. Serum markers have the potential for early detection, but none are currently available for use. Moreover, these ancillary tests are indirect measures of disease and only NP testing can provide functional information.

Table 5 Discrimination of individual items from NP test

Predictor variable	C-index	p-Value	Classification rate (%)
Verbal selective reminding (memory)			
Total recall	0.830	0.006	33/40 (0.83)
Long-term retrieval	0.836	0.002	33/40 (0.83)
Short-term retrieval	0.828	0.004	29/40 (0.73)
Long-term storage	0.833	0.002	31/40 (0.78)
Consistent long-term retrieval	0.831	0.009	32/40 (0.80)
Random long-term retrieval	0.745	0.025	27/40 (0.68)
Delayed recall	0.866	0.002	29/40 (0.73)
Paced auditory serial edition (working memory)			
PASAT Series 1	0.735	0.066	28/40 (0.70)
PASAT Series 2	0.703	0.087	25/40 (0.63)
PASAT Series 3	0.684	0.13	25/40 (0.63)
PASAT Series 4	0.620	0.83	26/40 (0.65)
PASAT total score	0.725	0.11	29/40 (0.73)
Trails test A and B (visuomotor processing speed and set shifting)			
Trails A and B total time	0.710	0.074	27/40 (0.68)
Trails A and B total errors	0.728	0.051	27/40 (0.68)
Controlled word association test (verbal fluency, executive cognitive dysfunction)			
COWA correct responses	0.669	0.43	23/40 (0.58)
COWA number of perseverative	0.639	0.77	22/40 (0.55)
COWA number of non-perseverative	0.641	0.83	23/40 (0.58)
COWA, controlled oral word association test.; PASAT, paced auditory serial addition task.			

Why screen for MCI? There is currently no cure for AD. However, there are numerous reasons to detect MCI as early as possible. Experts agree that the key to treatment and future research is early diagnosis. Several pharmacological agents currently available on the market can delay symptom onset as much as 3 years in selected patients (28). Importantly, there is evidence that the earlier these drugs are initiated, the better the response and more effective the treatment (10,28,29). In addition, when drugs are found that halt the disease – early testing will be critical.

Another reason for early identification is to inform the patient and family. A slow age-associated decline in cognitive function is expected and not considered pathological. Small lapses in memory (forgetting names, tasks, etc.) raise the concern in patients as to whether they may have Alzheimer's or other pathological conditions. A tool that can track an individual's natural course of cognitive function could

provide significant peace of mind. On the other hand, early identification of a pathological level of cognitive decline could herald significant disease onset and provide patients and their families the information necessary to better prepare for the future and to alter the living environment to enhance safety (setting up daily medication reminders, frequent monitoring, etc.). However, for the tool to be useful, it must be feasible for clinicians to use in the primary care setting and widely available for follow-up visits. The DETECT system may be able to overcome previous testing limitations.

There are several caveats regarding this study. First, DETECT™ is a screening tool for MCI, not a diagnostic test. Poor performance on this tool is simply a warning that a person is potentially experiencing more than normal age-related cognitive changes. The formal diagnosis of MCI requires additional follow-up including feedback from family members concerning their impression of the patient's cognitive functioning, as well as workups for treatable causes (e.g. screening blood tests, brain imaging) and a comprehensive NP assessment to verify the cognitive findings and rule out possible causes (e.g. depression, poor effort). Population based studies have demonstrated that approximately 40% of persons who are diagnosed as having MCI revert to 'normal' 1 year later (30,31). As a result, caution must be exercised when explaining the results to the patient and family. As a result of the cross-sectional nature of our study, we are unable to determine the test–retest reliability of measurements.

Limitations

This was a small pilot study to determine how well the DETECT™ MCI battery is compared with the classical NP testing. Despite the small sample size – 40 subjects (20 control/20 MCI), we were able to show significant correlation.

Using a population of known patients MCI demonstrated high sensitivity. However, the testing characteristics (sensitivity and specificity) will be different in a population with a lower prevalence rate of the disease. Moreover, the demographics of our test population were not representative of the general population and may not be generalisable. We acknowledge these limitations and have started a study that includes a more diverse group of patients in a geriatrics setting (age 65 and older) and in whom the diagnosis of MCI/dementia is unknown.

Future studies are planned to address both the test–retest validity and the impact of the 'learning effect'. Several different versions (word sets and images) have been developed specifically to reduce

the learning effect and provide a valid method for serial testing. However, at the time of this publication, these have not undergone rigorous evaluation.

Conclusion

The study demonstrates good correlation of the DETECT™ system with a classical battery of NP tests in the setting of known MCI and control patients. The DETECT™ test has overcome many of the limitations of current MCI screening and may be a feasible way to conduct screening in the primary care setting.

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Author contributions

DWW, MP, FG, conceived and designed the study, participated in study operations, assisted with data interpretation, and contributed significantly to manuscript preparation. JRB, TR and MLD assisted with study development and conduct, and participated in manuscript preparation. PK performed data analysis, assisted in data interpretation, and contributed significantly to manuscript preparation.

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