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Validity of a Brief Computerized Cognitive Screening Test in Dementia

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Abstract

Background: While preliminary evidence supports the criterion validity of the CogState computerized brief battery in mild cognitive impairment (MCI) and Alzheimer disease (AD), definitive validation studies examining a wider range of dementia-related disorders relative to conventional neuropsychological techniques are necessary. Methods: Participants satisfying clinical consensus criteria for dementia (AD, n = 37; frontotemporal dementia, n = 7; and dementia with Lewy bodies, n = 5), MCI (n = 16), and the healthy controls (n = 22) were administered a battery of brief neuropsychological and select computerized (CogState) cognitive tests. The battery, administered through the University of Michigan Alzheimer's Disease Research Center, included measures of processing speed, attention, working memory, and learning. Results: CogState and standard neuropsychological task scores were significantly lower for dementia participants than that of the nondementia groups ($P < .05$), with a single CogState test distinguishing control from MCI participants, but minimal differentiation existing between dementias using the CogState. Correlations were modest between conventional and computerized test scores, covering matching domains and mostly reflecting the multidimensional nature of cognitive paradigms. Conclusions: Results support the clinical validity of this brief computerized screening battery when used in established dementias, but not to differentiate between various dementias, and suggest that the select CogState battery's effectiveness in identifying MCI from controls was not as strong as identifying specific dementias.

Keywords

neuropsychological testing, cognitive decline, dementia

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Introduction

The use of neuropsychological batteries has become routine in the assessment of suspected dementia and mild cognitive impairment (MCI) to identify impairment in comparison to normative data. In addition, neuropsychological tests are often used to characterize relative impairments in terms of specific cognitive domains or cognitive changes over time in order to facilitate diagnostic and management decisions.[1,2] Particularly when retest intervals are short or testing constraints limit available testing time or resources, the use of relatively brief cognitive assessment techniques has advantages for decision making about the presence, magnitude, and progression of cognitive impairment, as well as for monitoring progress during treatment. In cases where impairment or change is demonstrated by brief batteries, more extensive neuropsychological evaluation or other targeted assessments may be appropriate.

The computerized CogState brief battery used in the current study consisted of 4 brief subtests designed to assess simple psychomotor reaction time, attention, working memory, and new learning. Construct validation recently has been reported for these specific subtests in a range of neurological conditions including traumatic brain injury, schizophrenia, and AIDS-dementia complex,[3] and in MCI and Alzheimer disease (AD)[4,5]; however, criterion validity has not been previously

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reported in MCI and AD in comparison with other neurodegenerative dementias. The current study evaluated the ability of this CogState brief battery to differentiate AD, frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB) as representative of dementing syndromes, as well as MCI as a possible prodromal dementia syndrome.

There were 2 aims of the current study. First, the criterion validity was evaluated by establishing the nature of the performance on the CogState brief battery in various dementias (AD, FTD, and DLB) and MCI in comparison to healthy controls (HCs). The hypothesis was that there would be qualitative and quantitative differences in the nature of performance in these different dementias groups and that performance deficits in the MCI group would be less than those associated with any of the dementias. In addition, the construct validity of the CogState brief battery, via the use of convergent and divergent evidence, was investigated in comparison to conventional neuropsychological tests with established validity in corresponding domains.[3,4] The hypothesis was that the respective CogState subtests would be correlated with validated neuropsychological tests of the same construct; for example, the simple reaction time task was anticipated to correlate most closely with a psychomotor processing speed task, the choice reaction time task was anticipated to correlate most closely with visual attention tasks, the one-back memory task was anticipated to correlate most closely with working memory and attention tasks, and the single-card learning task was anticipated to correlate most closely with visual learning and attention tasks. For these analyses, the recommendations of Cohen[6] and Zakzanis[7] were followed with conclusions based on the interpretation of effect sizes and their confidence intervals (CIs) in addition to statistical significance.

Method

Sample and Design

The 87 participants in this study (aged 52-88 years) represent a convenience sample of successively enrolled participants who completed the CogState testing during enrollment in the longitudinal cohort of the University of Michigan Alzheimer's Disease Research Center (MADRC). Of the 114 participants initially enrolled, 27 were unable to successfully complete the CogState for reasons including confusion, fatigue, or hesitation on using a computer. The MADRC participants were recruited from the Cognitive Disorders Clinic in the Department of Neurology, the Neuropsychology Section at the University of Michigan, or from the community via a multitude of other avenues, including newspaper advertisements, community outreach programs, the MADRC Web site, or word of mouth from a University clinic or the community. Following a neurological and physical health screening examination, in order to exclude individuals with a history of stroke, traumatic brain injury (TBI), and intellectual disability, volunteers were enrolled in the MADRC and underwent neuropsychological testing by a trained technician. The longitudinal cohort study was approved by the Institutional Human Use Review Board of the University of Michigan Health System; all enrolled participants were required to have a study partner with a durable power of attorney for health care. Both participants and study partners were consented and in circumstances where informed consent was limited because of diminished functioning/capacity, informed consent was provided by a legal guardian and assent was obtained from the participant.

Diagnosis of the participants was carried out at a consensus meeting consisting of at least 1 neuropsychologist and 2 neurologists, as well as other MADRC support staff. Normal controls were in good health and demonstrated a normal neurological examination, had no history of central nervous system disease, and had no memory-related complaints or cognitive impairments on neuropsychological testing. Participants were diagnosed using the uniform data set (UDS) criteria of the National Alzheimer's Coordinating Center,[8] which defined MCI according to the revised criteria published by Petersen,[9] probable AD according to (National Institute of Neurological and Communicative Disorders and Stroke –Alzheimer's Disease and Related Disorders Association) criteria (prior to April 2011),[10] and FTD[11] and DLB (consistent with McKeith and Neary criteria)[12] by consensus criteria.

CogState Brief Battery

Computerized testing was performed using selected tests from a CogState brief battery in the current study. This battery has been described in detail elsewhere.[3] The CogState subtests chosen for this battery were selected based on their use in prior CogState analyses,[3,4] as well as on their capacity to optimally measure change and reduce ceiling/floor effects. For example, on straightforward subtests like simple and choice reaction time, accuracy measures were not selected because notable ceiling effects exist for those tasks (most participants were 100% accurate), whereas for more challenging subtasks (working memory and new learning), accuracy measures better represented performance. All CogState subtests were presented on a personal computer and completed by all participants under the supervision of a trained research assistant. For each task, the instructions were provided on the computer screen, with the aid of an animated icon and graphic keyboard display, indicating the proper key/keys for the participants to select for their responses. Stimuli were displayed on the computer screen and responses were indicated using the computer keyboard. For each task, research assistants also provided the participant with a brief introduction to the task, reiterating the icon introduction. The timing of tasks and collection of response data were under the control of the software program. After the instructions were presented to the participant, a short set of practice trials was provided, followed by the actual CogState task. No verbal feedback was provided by the administrator during the task administration; but after a series of incorrect responses, the icon instructions and graphic keyboard reappeared on the computer screen while the task continued. The tasks used, the domains they assess, and the main outcome measures as defined by the test developer[13-15] are summarized in Table 1.

In each task, a playing card was presented facedown in the center of the screen on a green background. After an interval

Table 1. Description of Cognitive Outcome Measures

Task	Abbreviation	Domain	Main Outcome Measure
CogState battery			
Detection	DET	Psychomotor function	Mean of the log 10 transformed reaction times
Identification	IDN	Visual attention	Mean of the log 10 transformed reaction times
One back accuracy	OBK	Working memory and attention	Arcsine transformed correct responses/total responses
One card learning	OCL	Visual learning and attention	Arcsine transformed correct responses/total responses
Neuropsychological tests			
Trail Making Test parts A and B	TMT-A and TMT-B	Visual scanning and processing	Time in seconds of B-A
Digit Symbol subtest of WAIS-R	DSYM	Processing speed	Number correctly identified in 90 seconds minus number incorrectly identified
Benton Visual Form Discrimination test	BVFD	Attention and visual discrimination	Number correctly discriminated from list of choices
Logical Memory	LM-IR	Auditory verbal memory	Initial recall
Visual Reproduction	VR-IR	Visual memory	Initial recall
Digit Span from WMS-R	DS-F and DS-B	Working memory	Total score on DS forward and DS backward subtests
Wisconsin Card Sorting Test	WCST	Executive functioning	Number of correct responses

Abbreviations: DET, detection task; IDN, identification task; OBK, one back task; OCL, one card learning task; DSYM, Digit Symbol test; BVFD, Benton Visual Form Discrimination test; LM, logical memory; VR, visual reproduction; IR, initial recall; DS, digit span; F, forward; B, backward; WCST, Wisconsin Card Sorting Test; TMT B-A, trail making test part A subtracted from part B.

that varied randomly between 2.5 and 3.5 seconds, the card turned faceup and participants were required to respond "Yes" or "No" based on simple questions that varied for each task. The Yes response was indicated by a keyboard "K" key and No by a "D" key, respectively, for right-handed individuals and reversed for left-handed participants. The keys immediately surrounding the K and D keys were also sensitive to selection in order to accommodate for poor aim or motor control. Visual feedback differentiated correct and incorrect responses, with the cards after correct responses turning over to the right side and after incorrect responses turning over to the left and auditory feedback providing different sounds after correct and incorrect responses. Anticipatory responses occurring before the card turned faceup (and within 100 milliseconds of it turning faceup) triggered a distinctive error sound. Each task is described below.

The detection task (DET) is a simple reaction time task that measures the psychomotor function. In this task, the participant was required to press the Yes key as quickly as possible when the central card turned faceup (constituting 1 trial). Correct responses following an anticipatory response were ignored.

The identification task (IDN) is a choice reaction time task that measures the visual attention. This task is presented similarly to the DET task, with instructions indicating the participant should respond Yes if the faceup card is red, or No if not red.

The one back task (OBK) is a task that assesses working memory and attention. This task was similar in presentation to the IDN task, with instructions indicating the participant should respond Yes if the faceup card was exactly the same as the immediately previous card, or No if it was not the same as the previous card.

The one card learning (OCL) task is a continuous visual recognition learning task that assesses visual recognition memory and attention. This task is similar in presentation to the OBK task, with instructions indicating the participant should respond Yes if the faceup card had appeared in the current task previously, and No if it had not yet appeared. There were 6 different randomly selected cards that repeated and 42 trials without resampling for postanticipatory correct trials.

Standard Neuropsychological Test Battery

As part of their participation in the MADRC longitudinal cohort, all participants are administered a battery of neuropsychological tests, including measures specified by the UDS.[8] The battery assesses a broad range of cognitive functions within a short time frame and also includes the Mini-Mental State Examination (MMSE[16]) and the Geriatric Depression Scale (GDS[17]). For the current study, neuropsychological tests (Table 1) were selected that cover similar cognitive domains as those reported to be assessed by the CogState battery, with the exception that tests utilizing verbal stimuli were included as representative of well-established working memory (digit span [DS]) and memory tests (this is in contrast to the prior validity study[3] that reported the use of nonverbal comparator tests only). Specific domains were assessed as follows: the trail making test ([TMT] seconds to completion for trails test part B minus seconds for trails test part A was used as a dependent variable to reduce the influence of simple motor speed)[18] and the digit symbol (DSYM) subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS-R[19]) were used for information processing and executive ability, the Benton Visual Form Discrimination (BFVD[20]) test was used as a test of attention and visual discrimination, the logical memory (LM), and visual reproduction (VR) subtests from the Wechsler Memory Scale-III (WMS-III[21]) assessed verbal and visual learning, and the DS from the Wechsler Memory Scale—Revised (WMS-R[22]) and the Wisconsin Card sorting test (WCST[23]) utilized working memory and executive functioning. The specific neuropsychological test outcome measures are those that

Table 2. Summary of Demographic Characteristics of Each Group Studied[a]

Measure	HC	MCI	AD	FTD	DLB	Overall	*F* or χ^2	*P* Value
n	22	16	37	7	5	87		
Age[b]	67.7 (9.1)	73.7 (6.3)	72.0 (8.8)	61.6 (6.7)	73.0 (6.9)	70.5 (8.7)	3.77	<.05
Gender (% male)[c]	45.5	41.2	61.5	100	85.7	58.7	10.91	<.05
Right-handed (%)	86.4	100	92.3	100	100	93.5	4.08	.40
Years of education	14.8 (0.4)	14.6 (0.6)	14.6 (0.5)	14.3 (0.5)	14.6 (0.5)	14.6 (0.5)	1.35	.26
% CI[d]	0	18.7	83.3	57.1	80.0	47.1	41.72	<.001
MMSE[e]	29.1 (0.8)	26.7 (2.4)	22.9 (3.8)	22.4 (3.6)	22.6 (4.1)	25.0 (4.1)	17.37	<.001
GDS[f]	1.6 (2.1)	1.8 (2.2)	1.9 (2.5)	4.5 (1.7)	5.7 (4.6)	2.2 (2.6)	4.49	<.01

Abbreviations: HC, healthy controls; MCI, mild cognitive impairment; AD, Alzheimer disease; FTD, fronto-temporal dementia; DLB, dementia with Lewy bodies; % CI, percent of population taking cholinesterase inhibitors; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale (short-form, cutoff 5/15).
[a] Values represent the mean (standard deviation) unless otherwise noted.
[b] FTD group being significantly younger than the MCI, DLB, and AD groups, and controls being younger than the MCI group, $P < .05$.
[c] FTD and DLB groups having significantly more males than all other groups, $P < .05$.
[d] AD, FTD, and DLB groups being prescribed cholinesterase inhibitors at a significantly higher rate than controls or MCI, $P < .001$.
[e] AD, FTD, and DLB groups having significantly lower MMSE scores than controls or MCI, $P < .001$, and MCI having lower scores than controls, $P < .05$.
[f] FTD and DLB groups having significantly higher GDS scores than the MCI, DLB, and AD groups, $P < .01$.

have been described in neuropsychological compendia (see Table 1).[1,2,24]

Procedure

Participants practiced the CogState battery prior to the neuropsychological battery to become familiarized with the use of a computer and then underwent the CogState test session battery following the completion of neuropsychological testing. Assessments were conducted in a quiet room with no distractions using a desktop computer running Windows XP. The entire testing process took approximately 3 to 4 hours to complete, in addition to 30 minutes with administrative staff and 30 minutes with a neurologist. Participants were oriented to the testing process, administered the MMSE and the GDS, then given the CogState practice session, which lasted approximately 20 to 25 minutes. The order of the neuropsychological battery was as follows: WMS-III LM IR and VR IR, WCST, BVFD, WMS-R DS, TMT A and B, and WAIS-R DSYM; measures of manual dexterity, delayed memory, verbal fluency, reading, naming, and mobility were administered as part of the UDS battery but not included in the analyses. The CogState (test session) was then readministered, approximately 2 hours after the practice session. Participants were provided with breaks at their leisure, and most participants took taking a single break in the middle of the neuropsychological battery.

Data Analysis

Outcome measure. For each computerized task, speed and accuracy measures were computed and evaluated as previously reported,[3,13,25] though based on previous explanation the reaction time was used as the dependent variable for the detection and identification subtests and accuracy was used for the OBK and OCL tasks. The speed measure was computed as the mean of the distribution of base 10 logarithmic transformed reaction times, and the accuracy as the arcsine transformed proportion of correct responses (correct responses divided by total responses). These transformations aim to normalize the data distributions for parametric analyses. In addition, test scores that failed to meet test completion criteria ($\geq$75% trials completed) were excluded; a total of 27 participants from the sample (1 HC, 4 MCI, 15 AD, 3 FTD, and 4 DLB) were excluded from the study due to poor completion rate during testing.

The criterion validity for each CogState task was established by (i) determining the nature of significant differences of each CogState task for each clinical group relative to the control group using analysis of variance (ANOVA or analysis of covariance [ANCOVA], if necessary) followed by planned comparisons; (ii) expressing the magnitude of the difference between groups as an effect size using Cohen *d*[6,7] together with their 95% CIs,[26] and (iii) computing the nonoverlap statistic (non-OL%) for each difference. The non-OL% statistic reflects the extent to which data distributions of the clinical and control groups do not overlap, hence, for the current study, the non-OL% reflects the proportion of the clinical group whose performance was not shared by the control group with larger values indicating a better classification.[7] Duplicate analyses were performed for the standard neuropsychological tests.

The construct validity of each CogState task was determined by the extent to which performance on each task correlated with performance on the comparator neuropsychological tests. Pearson product—moment correlations were computed between the CogState measures and the neuropsychological tests for the HCs, due to the desire to both avoid spurious associations via mixing patients and controls. Correlations were then expressed as measures of effect size.[6,7] Statistical results were generated using the Social Sciences and Statistical Package for Windows (version 17).

Results

Of the 87 participants who could successfully complete the CogState assessment (age 70.5 $\pm$ 8.7 years), there were 22

Table 3. Results of Analyses of Variance Evaluating Between Disease Group (HC, MCI, AD, FTD, and DLB) Effects by Task After Controlling for Age and Education

	df (groups)	*df* (error)	Mean Square	*F*	*P*
DET	4	81	0.05	2.82	<.05
IDN	4	81	0.2	6.03	<.01
OBK	4	81	0.41	5.73	<.01
OCL	4	81	0.10	6.54	<.01

Abbreviations: HC, healthy controls (n = 22); MCI, mild cognitive impairment (n = 16); AD, Alzheimer disease (n = 37); FTD, fronto-temporal dementia (n = 7); DLB, dementia with Lewy bodies (n = 5); DET, detection task; IDN, identification task; OBK, one back task; OCL, one card learning task.

healthy volunteers (HC), 16 MCI, 37 probable AD, 7 FTD, and 5 DLB based on consensus diagnosis. Demographics of these participants are shown in Table 2. There was a significant difference in age between groups, with the FTD group being younger than the MCI, DLB, and AD groups, and controls being younger than the MCI group. There were more males in the FTD and DLB groups. Most participants were right-handed and caucasian in all groups, and there was no difference in the overall years of educational attainment. Significant differences existed for MMSE scores between HC and MCI groups, and all dementia groups had significantly lower MMSE scores than either the HC or MCI groups. The FTD and DLB groups also possessed higher GDS depression scores than HC, MCI, and AD groups. A higher percentage of patients from the dementia groups were prescribed cholinesterase inhibitors at the time of testing than both the HC and MCI groups, though no differences existed between dementia groups. Although 18.7% of MCI participants were prescribed cholinesterase inhibitors, this difference was not statistically significant from HC individuals (0%; $P = .06$).

Criterion Validity

Given the significant differences in age and mental status between diagnostic groups, these demographic variables were used as covariates in the following analyses. The ANCOVAs across clinical groups were significant for each CogState main outcome variable after covarying for age and mental status, the details of which are shown in Table 3. Planned comparisons are presented in Table 4, showing the mean performance (and variability) from the CogState tasks in each of the clinical groups in comparison to the HCs. Table 4 also shows the diagnostic group raw (back transformed) means and range of scores (in milliseconds or percentage for speed and accuracy, respectively) across the different measures (using 95% CIs). There were significant differences between the HC and all dementia groups (AD, FTD, and DLB) on all speed (DET and IDN) and accuracy (OBK and OCL) outcome measures. The HC and MCI groups were statistically different on the OBK accuracy task at the $P = .05$ level, but not on the other CogState subtests. As observed in Table 4, for the control group, the average speed of performance on DET ranged from 300 to 360 milliseconds and for IDN, the average group performance speed ranged from 500 to 600 milliseconds. The accuracy of performance on OBK ranged from 91% to 98% and the accuracy of performance on OCL ranged from 64% to 71%. For the dementia groups, the speed of performance on the DET and IDN decreased by a range of 30 to 600 milliseconds for each task, and the accuracy of performance on the OBK and OCL decreased by a range of 44% to 66% and 19% to 35%, respectively. The non-OL% statistic (Table 4) ranged from 97% (OBK for the DLB group) to 47% (DET and IDN for AD group), with most non-OL% statistics falling between 59% and 82%.

To allow direct comparison between measures within clinical groups, the difference in mean performance between each clinical group and the HC group was expressed as a measure of effect size (Cohen *d*; Figure 1). The data in Figure 1 reflect a graphical representation of the effect sizes listed for each analysis in Table 4. Figure 1 indicates that the MCI group showed similar results to the HC group for DET and IDN speed of performance but was less accurate on the OBK accuracy of performance measure ($d = -0.7$) and displayed a low-to-modest effect size for OCL accuracy of performance ($d = -0.3$). Each of the dementia groups showed moderate or large differences from HCs for most speed measures and relatively larger accuracy of performance differences. The AD group showed a large effect size for all performance measures, particularly for OBK ($d = -2.1$) and OCL ($d = -1.6$) accuracy of performance. The FTD group showed a similar profile in the AD group with marked differences from controls on OBK and OCL accuracy ($d = -1.5$ and -1.9, respectively). The DLB group was the slowest on DET and IDN speed measures ($d = 2.1$ and 2.2 for DET and IDN, respectively) and also consistently performed much worse on both accuracy measures ($d = -3.7$ and -2.96 for OBK and OCL, respectively).

Similar ANOVA analyses as listed in Tables 3 and 4 were performed for the neuropsychological tests to facilitate effect size comparisons between the computerized and standard neuropsychological batteries. Analyses across clinical groups were significant for each standard neuropsychological main outcome variable (see Table 5). Planned comparisons are also presented in Table 6, showing the mean performance (and variability) for the standard tasks in each of the clinical groups in comparison to the HCs. Briefly, consistent with the CogState analyses, there were significant differences between the HC and all dementia groups (AD, FTD, and DLB) on all standard neuropsychological measures. Each of the dementia groups showed moderate-to-large effect sizes relative to controls, ranging from $d = -1.0$ to -3.6, with the largest effect sizes for the AD group being related to memory tasks ($d = -2.8$ for LM-IR and $d = -2.6$ for VR-IR), the largest effect sizes for the FTD group being related to auditory memory ($d = -2.3$ for LM-IR) and visual scanning and processing ($d = 2.0$ for TMT B-A), and the largest effect sizes for the DLB group being related to visual memory ($d = -2.9$ for VR-IR) and processing speed

Table 4. Group Means and Statistical Significance for Comparison of Each Patient Group with the Control Group on the CogState Tasks on Planned Comparison Tests[a]

		Transformed Data					Back Transformed Data					
Clinical Group	Task	Mean (SD) Clinical Group	Mean (SD), Controls (n = 22)	*P*	*d*	Non-OL%	Mean Clinical Group	Lower 95% CI	Upper 95% CI	Mean Control Group	Lower 95% CI	Upper 95% CI
MCI (n = 16)	DET	2.51 (.06)	2.52 (.09)	.80	−0.1	8	324	303	345	331	303	362
	IDN	2.75 (.07)	2.74 (.08)	.78	0.1	8	562	521	606	550	507	595
	OBK	1.06 (.30)	1.25 (.23)	.05	−0.7	43	87	80	93	95	91	98
	OCL	0.70 (.14)	0.74 (.10)	.29	−0.3	21	64	59	69	67	64	71
AD (n = 37)	DET	2.67 (.23)	2.52 (.09)	<.01	0.8	47	468	404	542	331	303	362
	IDN	2.83 (.12)	2.74 (.08)	<.01	0.8	47	676	626	730	550	507	595
	OBK	0.62 (.33)	1.25 (.23)	<.01	−2.1	82	58	50	65	95	91	98
	OCL	0.55 (.13)	0.74 (.10)	<.01	−1.6	73	52	49	55	67	64	71
FTD (n = 7)	DET	2.65 (.18)	2.52 (.09)	<.05	1.1	59	447	332	601	331	303	362
	IDN	2.86 (.12)	2.74 (.08)	<.01	1.3	65	724	595	883	550	507	595
	OBK	0.81 (.47)	1.25 (.23)	<.01	−1.5	71	72	46	91	95	91	98
	OCL	0.55 (.09)	0.74 (.10)	<.01	−1.9	79	52	47	58	67	64	71
DLB (n = 5)	DET	2.80 (.26)	2.52 (.09)	<.05	2.1	79	631	398	1000	331	303	362
	IDN	2.94 (.14)	2.74 (.08)	<.01	2.2	82	871	680	1116	550	507	595
	OBK	0.41 (.21)	1.25 (.23)	<.01	−3.7	97	40	25	54	95	91	98
	OCL	0.42 (.16)	0.74 (.10)	<.01	−2.9	91	41	29	52	67	64	71

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer disease; FTD, fronto-temporal dementia; DLB, dementia with Lewy bodies; DET, detection task; IDN, identification task; OBK, one back task; OCL, one card learning task; *d*, measure of effect size; non-OL%, nonoverlap percentage statistic; CI, confidence interval.

[a] Back transformed units for DET and IDN are milliseconds, and percentage correct responses for OBK and OCL tasks.

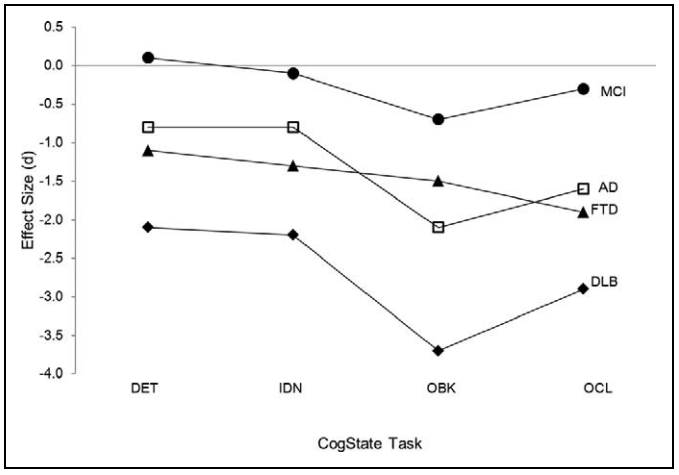

Figure 1. Effect sizes (*d*) for the magnitude of the cognitive impairment on the CogState outcome measures for mild cognitive impairment (MCI), Alzheimer disease (AD), frontotemporal dementia (FTD,) and dementia with Lewy bodies (DLB) clinical groups in comparison to the performance of the controls.

Table 5. Results of Analyses of Variance Evaluating Between Disease Group (HC, MCI, AD, FTD, and DLB) Effects by Neuropsychological Task

	df (Groups)	*df* (Error)	Mean Square	*F*	*P*
LM-IR	4	83	3426.88	28.91	<.01
VR-IR	4	79	5149.07	19.51	<.01
TMT B-A	4	83	75154.46	14.57	<.01
WCST	4	80	1152.67	11.62	<.01
DS-F	4	80	19.74	3.95	<.01
DS-B	4	80	40.73	10.90	<.01
DSYM	4	73	2735.15	20.25	<.01
BVFD	4	73	138.29	9.37	<.01

Abbreviations: HC, healthy controls (n = 22); MCI, mild cognitive impairment (n = 16); AD, Alzheimer disease (n = 37); FTD, fronto-temporal dementia (n = 7); DLB, dementia with Lewy bodies (n = 5); DET, detection task; IDN, identification task; OBK, one back task; OCL, one card learning task; LM, logical memory; VR, visual reproduction; IR, initial recall; TMT B-A, trail making test part A subtracted from part B; WCST, Wisconsin Card Sorting Test; DS, digit span; F, forward; B, backward; DSYM, digit symbol test; BVFD, Benton Visual Form Discrimination test.

($d = -3.6$ for DSYM). The non-OL% statistic ranged from 95% (DSYM for the DLB group) to 55% (DS-F for the AD group and VR-IR/BVFD for the FTD group), with most non-OL% statistics falling between 68% and 92%. The HC and MCI groups were statistically different on the memory tasks (LM-IR and VR-IR) and the processing speed task (DSYM) but not for the other neuropsychological variables. Effect sizes for these analyses were $d = -1.0$ for LM-IR, $d = -0.6$ for VR-IR, and $d = -0.7$ for DSYM, and the non-OL% statistic ranged from 43% to 59% for these tasks but from 8% to 43% for all nonsignificant MCI analyses.

Construct Validity

The results of the correlations between the computerized and neuropsychological tasks in the HC group are presented in

Table 6. Group Means and Statistical Significance for Comparison of Each Patient Group With the Control Group on the Neuropsycholol gical Tasks on Planned Comparison Tests

		Transformed Data				
Clinical Group	Task	Mean (SD) Clinical Group	Mean (SD) Controls (n = 22)	*P*	*d*	Non-OL%
MCI (n = 16)	LM-IR	30.65 (11.61)	43.00 (10.28)	<.01	−1.1	59
	VR-IR	58.12 (20.79)	69.05 (13.05)	<.05	−0.6	38
	TMT B-A	76.17 (60.25)	42.04 (23.50)	.14	0.7	43
	WCST	40.59 (10.08)	46.14 (6.79)	.09	−0.6	38
	DS-F	8.11 (1.80)	8.90 (1.77)	.28	−0.4	27
	DS-B	6.18 (1.91)	7.32 (2.06)	.07	−0.6	38
	DSYM	41.25 (10.60)	49.00 (11.06)	<.05	−0.7	43
	BVFD	29.86 (2.33)	30.10 (2.05)	.86	−0.1	8
AD (n = 37)	LM-IR	13.85 (10.48)	43.00 (10.28)	<.01	−2.8	91
	VR-IR	35.09 (13.03)	69.05 (13.05)	<.01	−2.6	90
	TMT B-A	176.55 (90.31)	42.04 (23.50)	<.01	2.0	81
	WCST	29.38 (11.44)	46.14 (6.79)	<.01	−1.8	77
	DS-F	6.69 (2.61)	8.90 (1.77)	<.01	−1.0	55
	DS-B	4.18 (1.96)	7.32 (2.06)	<.01	−1.6	73
	DSYM	23.52 (11.52)	49.00 (11.06)	<.01	−2.3	85
	BVFD	26.55 (4.27)	30.10 (2.05)	<.01	−1.1	59
FTD (n = 7)	LM-IR	18.80 (10.91)	43.00 (10.28)	<.01	−2.3	85
	VR-IR	48.20 (28.15)	69.05 (13.05)	<.05	−1.0	55
	TMT B-A	172.12 (86.40)	42.04 (23.50)	<.01	2.1	81
	WCST	35.33 (8.69)	46.14 (6.79)	<.05	−1.4	68
	DS-F	6.33 (2.42)	8.90 (1.77)	<.05	−1.2	62
	DS-B	4.00 (1.90)	7.32 (2.06)	<.01	−1.7	75
	DSYM	31.29 (15.16)	49.00 (11.06)	<.01	−1.3	65
	BVFD	25.17 (7.00)	30.10 (2.05)	<.01	−1.0	55
DLB (n = 5)	LM-IR	16.50 (12.32)	43.00 (10.28)	<.01	−2.3	85
	VR-IR	27.50 (15.61)	69.05 (13.05)	<.01	−2.9	92
	TMT B-A	147.00 (83.29)	42.04 (23.50)	<.01	1.7	75
	WCST	26.83 (11.35)	46.14 (6.79)	<.01	−2.1	81
	DS-F	6.33 (2.34)	8.90 (1.77)	<.05	−1.2	62
	DS-B	4.17 (1.17)	7.32 (2.06)	<.01	−1.9	81
	DSYM	14.20 (7.73)	49.00 (11.06)	<.01	−3.6	96
	BVFD	19.25 (5.56)	30.10 (2.05)	<.01	−2.6	89

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer disease; FTD, fronto-temporal dementia; DLB, dementia with Lewy bodies; DET, detection task; IDN, identification task; OBK, one back task; OCL, one card learning task; LM, logical memory; VR, visual reproduction; IR, initial recall; TMT B-A, trail making test part A subtracted from part B; WCST, Wisconsin Card Sorting Test; DS, digit span; F, forward; B, backward; DSYM, digit symbol test; BVFD, Benton Visual Form Discrimination test; *d*, measure of effect size; non-OL%, nonoverlap percentage statistic.

Table 7. Pearson Product—Moment Correlations Between Each CogState Performance Measure and the Neuropsychological Measures in the Healthy Control Group[a]

	DSYM	BVFD	LM-IR	VR-IR	DS-F	DS-B	WCST	TMT B-A
DET	.27	.15	.25	.50[b]	.19	.08	.20	.41
IDN	.29	.38	.03	.45[b]	.15	.28	.24	.23
OBK	.52[b]	.49[b]	.09	.47[b]	.06	.36	.11	.31
OCL	.03	.10	.07	.04	.07	.30	.20	.13

Abbreviations: DET, detection task; IDN, identification task; OBK, one back task; OCL, one card learning task; DSYM, digit symbol test; BVFD, Benton Visual Form Discrimination test; LM, logical memory; VR, visual reproduction; IR, initial recall; DS, digit span; F, forward; B, backward; WCST, Wisconsin Card Sorting Test; TMT B-A, trail making test part A subtracted from part B.

[a] Correlation coefficients are expressed as absolute values.

[b] $P < .05$.

Table 7. Significance testing used 2-tailed analyses. The equivalent effect sizes are plotted in Figure 2. Performance on the DET and IDN speed of performance measures showed significant correlations with the VR-IR variable ($d = 1.15$ and 1.01, respectively), and modest associations were observed between the DET and TMT B-A ($d = 0.9$) and IDN and BVFD

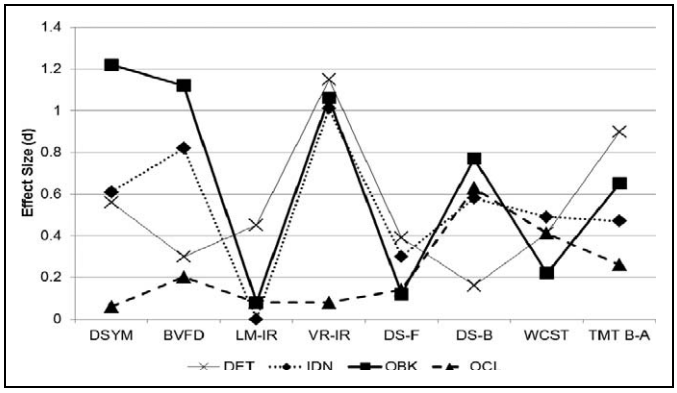

Figure 2. Healthy control group effect sizes (*d*) for comparison between computerized and conventional tests (primary outcome measures). DET indicates detection task; IDN, identification task; OBK, one back task; OCL, one card learning task; DSYM, digit symbol test; BVFD, Benton Visual Form Discrimination test; LM, logical memory; VR, Visual Reproduction; IR, initial recall; DS, digit span; F, forward; B, backward; WCST, Wisconsin Card Sorting Test; TMT B-A, trail making test part A subtracted from part B.

($d = 0.82$) variables, respectively. The OBK accuracy performance measure displayed significant correlations with DSYM, BVFD, and VR-IR performance ($d = 1.22$, 1.12, and 1.06, respectively), as well as a modest association with the DS-B variable ($d = 0.77$) but not the verbal memory subtest ($d = 0.08$). The OCL accuracy showed low-to-moderate effect sizes with performance on the DS-B and WCST tests ($d = 0.63$ and 0.41, respectively).

Discussion

For the first time, this study evaluates the criterion validity of this selected battery of CogState computerized subtests in AD, FTD, and DLB. Construct validity of the computerized battery in HCs was also assessed. The ability of a neuropsychological test to detect reduced cognitive functioning is an important aspect of criterion validity when the test is proposed as a measure of abnormality for a specific condition. In the present study, the criterion validity of the psychological paradigms measured by the CogState brief battery was investigated by evaluating the nature of performance for reaction time (DET and IDN) and accuracy (OBK and OCL) outcome measures in patients with MCI, AD, FTD, and DLB compared to HCs. Prior work has reported impairment in both MCI and AD[4,5] but has not been characterized in comparison to other types of dementia. The present study used well-characterized patients recruited from an ADRC using consensus criteria and well-defined and standardized procedures for diagnosis.

Compared to the control group, significant differences were seen in performance on the CogState for each of the dementia clinical groups (AD, FTD, and DLB) compared to HCs, with qualitatively similar but quantitatively more minor differences also seen in the MCI group relative to controls. The nature of the discrepancies in each of the dementia groups was similar, with relatively mild effect sizes in speed measures of performance (DET and IDN) and larger effect sizes across all groups for the accuracy measures (OBK and OCL). This pattern was also seen in 2 prior studies in patients with AD, as well as in MCI groups where the only notable differences were in measures of performance accuracy.[4,5] The magnitude of effect sizes for the FTD and AD groups was very similar, while the DLB group was both much slower and less accurate. Fluctuating cognition with significant deficits and variability in processing speed are characteristic of Parkinsonism and DLB, which may in part relate to the deficits in cholinergic neurotransmission.[27,28] As no differences in the proportion of participants prescribed cholinesterase inhibitors were noted among dementia groups, medication effects do not appear to contribute to differences in cholinergic neurotransmission.

When comparing the CogState tasks to the standard neuropsychological measures, the CogState subtests displayed smaller, but still significant, effect sizes and non-OL% statistics across the various dementia groups. None of the tasks (CogState or standard), however, were as effective at discriminating poor performance in MCI as compared with dementia. For performance comparisons among the MCI participants relative to controls, only 1 of 4 analyses for the CogState variables was significant (OBK) compared to 3 of 8 analyses for the standard neuropsychological tasks; none of the measures displayed comparable non-OL% statistics relative to the dementia groups. For the standard measures, 2 of the 3 significant analyses were related to reduced memory, which is consistent with the diagnostic criteria for MCI[9]; whereas for the CogState tasks, only the analysis related to working memory/attention subtest was significant.

Overall, the results of the present study suggested that the tasks in the CogState brief battery identified differences in performance in a similar fashion to the standard neuropsychological measures across a range of clinical presentations including the various dementia syndromes, although with somewhat smaller effect sizes noted across groups. The nature and magnitude of these differences on the CogState between clinical groups and controls were also similar to that reported in mild TBI (mTBI) groups and in patients with chronic schizophrenia (when compared to appropriately matched control groups[3]). These results support the contention that although the paradigms of the computerized battery appear to be sensitive at identifying reduced performances in clinically impaired groups, a given profile of worse cognitive performance on the computerized performance measures cannot be used to differentiate among different etiologies of dementia, at least when using this very short computerized screening battery. This may remain as a limitation of the brevity of a 20- to 25-minute computerized battery whereby clinically significant differentiating features are more easily observed utilizing focused test measures. Alternatively, there may be similarities in the nature of the cognitive dysfunction seen in these conditions (AD, FTD, DLB, mTBI, and schizophrenia) when at particular stages of their progression, with presumed involvement of subcortical and cortical neuronal systems leading to similar computerized test profiles. In support of this notion, other studies using the

same computerized tasks[29] have displayed reduced performance predominantly in processing speed performance after acute concussion, with a relative insensitivity of accuracy performance measures, and differential decline in learning accuracy in older adults at risk of prodromal AD pathology.[30]

The potential clinical significance of the cognitive performances reported in the current study can be better appreciated by the non-OL% statistic, which gives the percentage of the patients in the clinical group whose scores do not overlap with those of the control group.[7] A non-OL% statistic of 55%, for example, indicates that it would be difficult to differentiate individual cases of MCI from controls on the basis of any one of the outcome measures of the CogState battery alone, which is consistent with previous research,[4,5] and suggests that additional assessment is likely required to aid in differential diagnosis. On the other hand, nearly all (97%) of the patients with DLB could be differentiated from the HCs on the basis of their OBK accuracy scores (with a non-OL% of 98% regarded as required for diagnostic certainty and 93% a good clinical marker[7]). The nonoverlap in performance scores between the control group and the AD and FTD groups for the accuracy performance measures was also moderate to high, with 71% to 82% of patients in these groups having differentiable accuracy performance scores on OBK and/or OCL tasks. Consequently, although the computerized measures are not able to differentiate between the dementia groups evaluated in this study, they are likely to be able to discriminate a large proportion of impaired patients from within a general population. The brevity, decreased need for highly skilled psychometrists, user-friendly nature of this battery, and the reported stability over time and sensitivity to decline in healthy older people would suggest it could have a role in screening for existing dementia.[15,31-33] Also, while the CogState was not as effective at discriminating MCI from controls as compared with dementia cases from controls, it was generally comparable to the discriminating ability of the standard neuropsychological tasks (that are typically used in a clinical setting to identify MCI). However, given that decline is frequently observed in patients with MCI,[9] the reliability[34] and ease of use of the CogState battery suggest that it still may possess a role in tracking cognitive change over time for patients with MCI.

To evaluate the construct validity using convergent and divergent methods in the current study, associations between the computerized and comparator neuropsychological tests were considered statistically significant if their *P* value was less than .05. Overall, our hypothesis that the respective CogState subtests would be correlated with validated neuropsychological tests of the same construct was not supported. The observed correlations between performance on the computerized tasks and comparator neuropsychological tests were somewhat unexpected in that highest correlations were not observed within analogous domains, which is in contrast with previous findings confirming construct validity.[3] Rather, our results were consistent with the contribution of multiple and different cognitive operations to each task,[1,2] with none of the tasks used here, including the computerized tasks, dependent upon only a single operationally defined neuropsychological domain construct. In our study, for example, a measure of visual memory (VR-IR) was the only significant correlation to performance on the CogState reaction time subtests (DET and IDN), suggesting that rapid detection, identification, and learning of stimuli relied heavily on basic visual processing. While the nonsignificant association of the OCL performance with DS-B and WCST performance could be related to similar learning constructs, it could also be related to a broader coverage of cognitive domains such as working memory. However, in partial support of construct validity, the strongest associations for the computerized measure of working memory (OBK) were for the conventional measures of visual attention (DSYM and BVFD) and memory (VR-IR); a broad consideration of the associations between the computerized working memory (OBK) and conventional tasks appears to support prior reported patterns of association consistent with theoretically derived models (OBK associated with neuropsychological tasks dependent upon memory, processing speed, and visual attention).

There are several important limitations of the current study. In particular, the number of participants in the current HC group was small, and smaller sample size may contribute to type II errors or false negatives, where real correlations are not observed. Spurious results may also be a function of small sample sizes, consequently it is important that future studies be undertaken with greater number of participants to expand the generalizability to our current results. Similarly, the number of patients in the FTD and DLB groups was also small, possibly resulting in our sample not necessarily being representative to the FTD and DLB populations in general. For example, the high rates of males in our sample of FTD and DLB populations are larger than that reported in other studies.[35,36] Because of the smaller sample sizes for these diagnostic groups, it is necessary to temper our study's conclusions when generalizing to larger FTD and DLB populations. Larger studies will be required to confirm and extend these findings. While the age of the FTD participants were younger than the other dementia groups, this is consistent with a younger age of onset of FTD relative to AD.[27]

The MMSE mean score of the MCI group was intermediate between those of the HC and AD groups, which is concordant with expectations that MCI includes patients with cognitive impairment that may be prodromal to AD and other dementias, although research suggests that less than 50% of patients with MCI eventually develop AD.[9] Alternatively, the FTD group is likely to be quite advanced in disease progression, based on their comparable MMSE scores relative to the AD group[35]; studies of patients with higher MMSE values, suggesting they are in earlier stages of FTD, may find different patterns and magnitudes of reduced cognitive functioning on the computerized battery used in the current study. In addition, future research tailoring the specific CogState subtests used, such as incorporating the Groton Maze Learning Test[37] subtest for a measure of executive functioning, may be helpful to differentiate FTD from other clinical groups. While it has previously been suggested that the CogState battery would be good as a

measure of change,[31,34] whether or not the CogState is useful for single assessment differentiation of such early FTD patients awaits further study.

In conclusion, the current study supported the criterion validity of the CogState brief battery for discriminating dementia clinical groups when compared to HCs and indicated that consistent with prior research, the CogState's effectiveness at discriminating MCI from controls was not as strong as when identifying dementia. The present study also presented evidence supporting the sensitivity, but not specificity at discriminating between dementia diagnoses, of the battery for these conditions on a single assessment. Lastly, support for the construct validity of the CogState battery used at present was weaker than previous studies, suggesting that few to none of the tasks were dependent upon only a single operationally defined neuropsychological domain construct. Future studies should evaluate the nature and magnitude of reduced cognitive functioning detectable using this battery in earlier stages of FTD and DLB, and whether the battery is useful for wider community screening programs for the detection of existing dementia or MCI.

Authors' Note

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Declaration of Conflicting Interests

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