Computerized cognitive testing battery identifies mild cognitive impairment and mild dementia even in the presence of depressive symptoms

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Abstract

Cognitive and depressive symptoms co-occur, complicating detection of mild cognitive impairment (MCI) and early dementia. In this study, discriminant validity of a novel computerized cognitive battery for MCI detection was evaluated after covariation for depressive symptom severity. In addition to the computerized battery, participants at two sites received the 30-item self-administered Geriatric Depression Scale (GDS; n = 72); those at two other centers received the observer-administered Cornell Scale for Depression in Dementia (CSDD; n = 88). In both cohorts, a Global Cognitive Score and memory, executive function, visual spatial, and verbal index scores discriminated among cognitively healthy, MCI, and mild dementia groups after covariation for GDS or CSDD, respectively ($p < 0.05$). Thus, the computerized battery for detection of mild impairment is robust to comorbid depressive symptoms, supporting its clinical utility in identifying neurodegenerative disease even in elderly with depression.

Key words: mild cognitive impairment, depression, dementia, cognitive assessment, computerized battery

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Introduction

Depression represents a major challenge to the clinical diagnosis of mild cognitive impairment (MCI) and early dementia, as it is widespread in older individuals and also a common comorbidity of both conditions. A recent population-based longitudinal study[1] found that while only 7.2 percent of older individuals exhibited depressive symptoms within the previous month, 20.1 percent of individuals with MCI[2] and 32.3 percent of those with dementia had such symptoms. Furthermore, from onset of cognitive symptoms, 26.3 percent of individuals with MCI and 43.6 percent of individuals with dementia showed depressive symptoms.

The co-occurrence of cognitive and depressive symptoms in older people creates a formidable problem for

cognitive assessment.[3] For a given assessment tool, it must be determined whether discriminant validity is significantly affected by depression.[4] As paper-based neuropsychological tests are subject to interpretation bias,[5] the discriminant validity of such tests may be compromised by the influence of depressive symptoms. In contrast, the greater objectivity of computerized cognitive assessment may make such testing more robust to the impact of depressive symptoms. Thus, the current study evaluates the ability of a novel computerized cognitive battery[6-8] to detect MCI after adjustment for severity of depressive symptoms.

The brief computerized tests utilized in the present study were recently shown to detect MCI better than paper-based neuropsychological tests that tap comparable cognitive domains.[6] However, the ability of the computerized tests to detect MCI and early dementia following adjustment for depressive symptoms has not been investigated. Discriminant validity in MCI robust to depressive symptoms would make the computerized cognitive testing battery a valuable tool for clinicians faced with the challenge of identifying cognitive impairment in the presence of depressive symptoms. To minimize the likelihood that results obtained would be specific to a particular depression scale or a particular cohort, the discriminant validity of the computerized tests is examined in two separate cohorts, one given a popular self-report depression scale and another evaluated with a supervisor-administered depression scale.

Methods

Participants

Participants were examined at three tertiary care memory clinics (Bloomfield Centre for Research in Aging, McGill-Jewish General Hospital, Montreal, Canada; Memory Disorders Clinic, Shaare Zedek Medical Center, Jerusalem, Israel; Alzheimer's Disease Research Center, State University of New York, Brooklyn, NY); and one assisted living facility (Ramat Tamir Home for the Aged, Jerusalem, Israel). Participants were diagnosed by consensus of evaluation teams led by dementia experts at each of the sites and were diagnosed prior to computerized testing with MCI, mild Alzheimer's disease (AD), or as cognitively healthy. Diagnosis of MCI was according to the following criteria for 'MCI-amnestic'[9]: 1) a complaint of defective memory, 2) normal activities of daily living, 3) a memory deficit documented on mental status evaluation and supported by abnormalities on neuropsychological testing, and 4) absence of dementia. Diagnosis of AD was according to the *Diagnostic and Statistical Manual, 4th ed. (DSM IV)*. Cognitively healthy elderly had no memory complaint or demonstrated normal performance on objective paper-based neuropsychological tests (e.g., Rey Auditory Verbal Learning Test, Clock-Drawing Test). To maximize the generalizability of the results, depressive symptoms were measured with two different scales in two separate cohorts; the choice of depression scale was based on that most familiar to the staff at each center. Participants at McGill-Jewish General Hospital and State University of New York (N = 72) received the 30-item self-administered Geriatric Depression Scale (GDS).[10] In contrast, participants at Shaare Zedek Medical Center and Ramat Tamir Home for the Aged (N = 88) received the observer-administered Cornell Scale for Depression in Dementia (CSDD).[11] Institutional Review Board approval was obtained at each site, and informed consent was obtained from all participants.

In view of the clinical distinction between depression of AD and major depressive disorder (MDD),[12-14] participants with a history of MDD (i.e., DSM IV Axis I) were excluded from all diagnostic groups. Aside from participants with evidence of AD, participants with neurological or psychiatric disease were excluded from all groups. Colorblind participants were also excluded. Participants were also excluded if they had previously been tested with the computerized battery or if the battery was unavailable in participants' most comfortable spoken ("primary") language.

Demographic and clinical characteristics are presented in Table 1, separately for those who received the GDS (range: 0 to 24) and for those who received the CSDD (range: 0 to 13). Note severity of cognitive function for each diagnostic group as indexed by the Mini-Mental State Examination (MMSE).[15] More than a quarter of participants across GDS and CSDD groups were depressed,[16,17] and prevalence of depression increased with greater severity of dementia (Kendall's Tau-c = 0.208, $p < 0.001$) (Table 2).

Procedure

All participants completed tests from the Mindstreams® (NeuroTrax Corp., NY) Global Assessment Battery (formerly "Mild Impairment Battery") designed to detect mild impairment.[6] In brief, Mindstreams consists of custom software installed on the local testing computer that serves as a platform for interactive cognitive tests that produce precise accuracy and reaction time (millisecond timescale) data. Web-based administrative features allow for secure entry and storage of patient demographic data. Once tests are run on the local computer, data are automatically uploaded to a central server,

Table 1. Demographic and clinical characteristics for participants who received Mindstreams and either the 30-item Geriatric Depression Scale (GDS) or the Cornell Scale for Depression in Dementia (CSDD)

Characteristic		GDS (N = 72)	CSDD (N = 88)
Age, mean years (SD)		74.9 (6.9)	78.4 (8.8)
Education, mean years (SD)		12.1 (3.2)	13.7 (3.6)
Gender, percent female		50.0	67.0
Computer experience, percent no		76.4	54.5
Handedness, percent left-handed		6.9	4.6
Expert consensus diagnosis, percent	Cognitively healthy	30.6	50.0
	MCI	40.3	36.4
	Mild AD	29.2	13.6
MMSE, score out of 30 (SD)	Cognitively healthy	28.1 (1.8)	28.4 (1.4)
	MCI	27.4 (2.1)	26.6 (1.8)
	Mild AD	23.4 (3.5)	24.6 (3.6)

SD, standard deviation; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.

where calculation of outcome parameters from raw single-trial data and report generation occur.

The complete Global Assessment Battery (administration time: approximately 45 minutes) samples a wide range of cognitive domains, including memory (verbal and nonverbal), executive function, visual spatial skills, verbal fluency, attention, information processing, and motor skills (Table 3).[6] Outcome parameters varied with each test, as in Table 3. Given the speed-accuracy tradeoff,[18] a performance index ([accuracy/reaction time]*100) was computed for timed Mindstreams tests in an attempt to capture performance both in terms of accuracy and reaction time (RT). All participants completed the paper-based MMSE and either the GDS or the CSDD prior to Mindstreams testing. Tests were always run in the same fixed order.

Following are brief descriptions of the tests that comprise the Mindstreams Global Assessment Battery:

- **Verbal Memory:** Ten pairs of words are presented, followed by a recognition test in which one member (the target) of a previously presented pair appears together with a list of four candidates for the other member of the pair. There are four immediate repetitions and one delayed repetition after 10 minutes.

- **Nonverbal Memory:** Eight pictures of simple geometric objects are presented, followed by a recognition test in which four versions of each object are presented, each oriented in a different direction. There are four immediate repetitions and one delayed repetition after 10 minutes.

- **Go-NoGo:** Timed continuous performance test during which responses are made to large colored stimuli that are any color but red.

- **Problem Solving:** Puzzle completion test that increases in difficulty; the best geometric form to complete a pattern must be identified.

Table 2. Relationship between severity of depression as measured by the 30-item Geriatric Depression Scale (GDS) or the Cornell Scale for Depression in Dementia (CSDD) and severity of dementia as determined by expert consensus diagnosis

		Severity of dementia			
		No cognitive impairment	MCI	Mild AD	Total
Severity of depression*	No depression	58	41	18	117
	Mild depression	6	17	13	36
	Moderate depression	2	3	2	7
	Total	66	61	33	160
	Percent depressed	12.1	32.8	45.5	26.9

*Classification was as follows: No depression, 30-item GDS 0 to 9, CSDD 0 to 7; Mild depression, 30-item GDS 10 to 19, CSDD 8 to 12; Moderate depression, 30-item GDS 20+, CSDD 13+.

- **Stroop:** Timed test of response inhibition and set shifting modified from the well-established paper-based test.[19] In the first phase, participants choose the letter-color of a general word. In the next phase (termed the Choice Reaction Time test), the task is to choose the color named by a word presented in white letter-color. In the final (Stroop interference) phase, participants choose the letter-color of a word that names a different color.

- **Verbal Function:** In the rhyming portion, participants must choose the word that rhymes with a picture shown on the screen; in the naming portion, the word that names the picture must be selected.

- **Visual Spatial Imagery:** Computer-generated scenes containing a red pillar are presented. Participants must select the view of the scene from the vantage point of the red pillar.

- **Staged Information Processing Speed:** Timed test requiring a binary decision based on the solution of simple arithmetic problems with three levels of information processing load and three rates of presentation.

- **Finger Tapping:** Participants must tap on the mouse button with their dominant hand.

- **Catch Game:** A novel test of motor planning requiring hand-eye coordination and rapid responses that requires participants to "catch" a "falling object" by moving a "paddle" horizontally so that it can be positioned directly in the path of the falling object.

Outcome parameters and index scores

Mindstreams data were uploaded to the NeuroTrax central server, where automatic data processing occurred, during which aggregate outcome parameters were computed from raw single-trial data.[6] Outcome parameters were calculated using custom software blind to diagnosis or testing site. To minimize differences in age and education and to permit averaging performance across different types of outcome parameters (e.g., accuracy, RT), each outcome parameter was normalized and fit to an IQ-style scale (mean: 100, SD 15) in an age- and education-specific fashion. Normative data consisted of test data for individuals with an expert consensus diagnosis of cognitively healthy in controlled research studies at eight clinical sites. The normative group consisted of male and female ambulatory and institutionalized elderly, both with and without prior computer experience. Data for each outcome parameter was normalized according to two stratifications of age (50 to 70 years, greater than 70 years) and education (12 or fewer years, greater than 12 years) to give a distribution with a mean

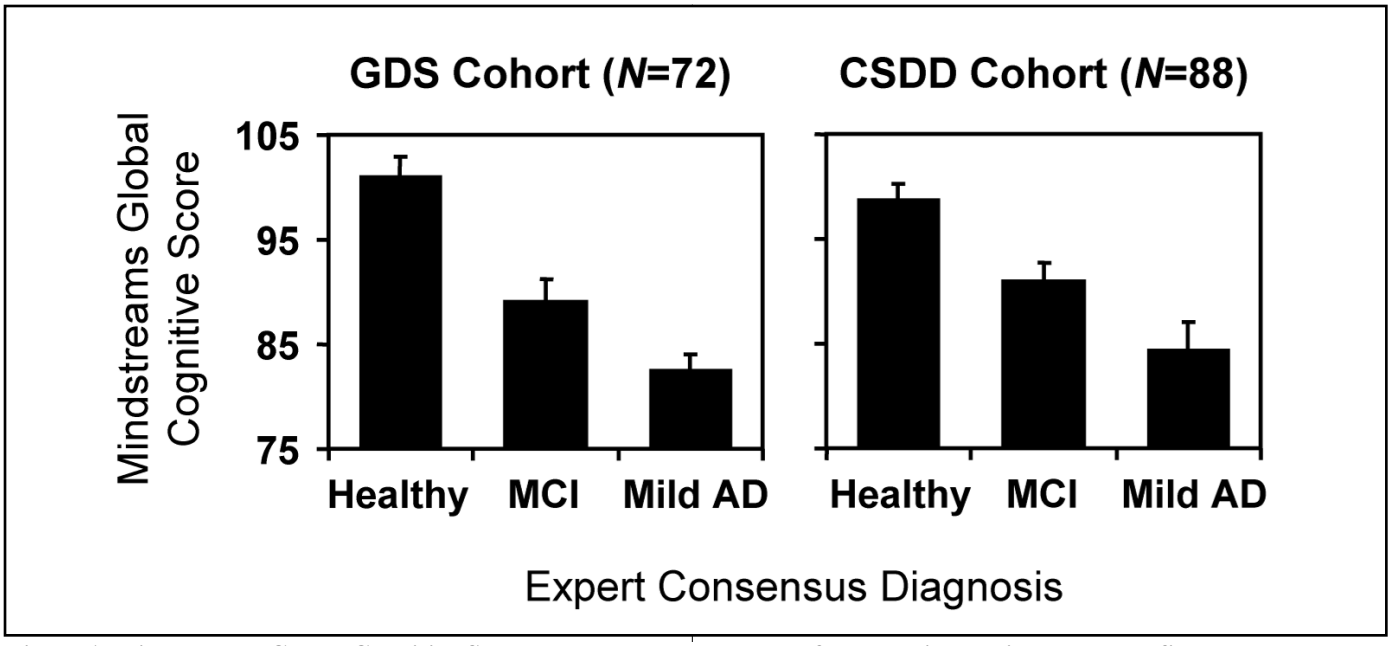

Figure 1. Mindstreams Global Cognitive Score (mean + standard error) for each diagnostic group as defined by expert consensus diagnosis. The score was able to discriminate among groups following covariation for depression scale score both in the cohort receiving the 30-item Geriatric Depression Scale (GDS, left; $F[2,62] = 15.066$, $p < 0.001$) and in the cohort receiving the Cornell Scale for Depression in Dementia (CSDD, right; $F[2,77] = 12.783$, $p < 0.001$).

of 100 and a standard deviation of 15 (i.e., an IQ-style scale). The normative sample for this study was comprised of 213 individuals stratified as follows: 50 to 70 years of age and 12 or fewer years of education, N = 40; 50 to 70 years of age and greater than 12 years of education, N = 70; greater than 70 years of age and 12 or fewer years of education, N = 39; greater than 70 years of age and greater than 12 years of education, N = 64. Normalized subsets of outcome parameters were averaged to produce six index scores[8,20] as follows:

- **Memory:** mean accuracies for learning and delayed recognition phases of Verbal and Nonverbal Memory tests;
- **Executive function:** performance indices for Stroop test and Go-NoGo test, mean weighted accuracy for Catch Game;
- **Visual spatial:** mean accuracy for Visual Spatial Imagery test;
- **Verbal:** weighted accuracy for Verbal Rhyming test (part of Verbal Function test);
- **Attention:** mean reaction times for Go-NoGo and choice reaction time (Stroop, second phase) tests, mean standard deviation of reaction time for Go-NoGo test, mean reaction time for a low-load stage of Staged Information Processing Speed test, mean accuracy for a medium-load stage of Staged Information Processing Speed test; and
- **Motor skills:** mean time until first move for Catch Game, mean inter-tap interval and standard deviation of inter-tap interval for Finger Tapping test.

A Global Cognitive Score (GCS) was computed as the average of the six index scores.

Statistical analyses

Between-group comparison was assessed using univariate analysis of covariance (ANCOVA) with depression scale score (i.e., GDS or CSDD) as a covariate. Analyses were performed separately for GDS and CSDD cohorts. Two-tailed statistics were used throughout, and $p < 0.05$ was considered significant. To ensure statistical validity, an interaction term was included in the ANCOVA when significant at $p < 0.10$. As automatic quality control algorithms[6] rendered test data reflecting questionable effort (e.g., too many trials with no response, too many trials with too quick a response) invalid, a minimum of 7 data points per diagnostic group

Table 3. Validity of Mindstreams tests in discriminating among elderly who were cognitively healthy, those with mild cognitive impairment (MCI), and those with mild Alzheimer's disease (AD) following covariation for depression scale score in Geriatric Depression Scale (GDS) and Cornell Scale for Depression in Dementia (CSDD) cohorts by analysis of covariance (ANCOVA) using weighted least squares

Cognitive domain	Mindstreams test (outcome parameter)	GDS cohort (N = 72)		CSDD cohort (N = 88)	
		Diagnosis p-value	GDS p-value	Diagnosis p-value	CSDD p-value
Memory	Verbal Memory (accuracy, all repetition trials)	< 0.001*†‡	0.802	< 0.001*‡	0.297
	Verbal Memory (accuracy, delayed recognition)	< 0.001*†‡	0.706	< 0.001*‡	0.651
	Nonverbal Memory (accuracy, all repetition trials)	< 0.001*†‡	0.366	< 0.001*†‡	0.682
	Nonverbal Memory (accuracy, delayed recognition)	< 0.001*†	0.279	0.003*†	0.521
Executive function	Go-NoGo (performance index)	< 0.001*†‡	0.571	0.052	0.751
	Stroop Interference (performance index)	< 0.001*‡	0.004	–	–
	Catch Game (accuracy)	< 0.001*‡	0.722	< 0.001*‡	0.230
Visual spatial	Visual Spatial Imagery (accuracy)	0.001*†	0.819	0.022†	0.392
Verbal	Verbal Function (accuracy, rhyming)	< 0.001*†	0.832	< 0.001*†‡	0.680
Attention	Go-NoGo (RT)	< 0.001*‡	0.542	0.397	0.366
	Go-NoGo (standard deviation of RT)	0.001*†	0.122	0.032	0.188
	Choice Reaction Time (RT)	0.001*‡	0.650	0.033*	0.555
	Staged Information Processing Speed, low load, medium speed (RT)	0.002*‡	0.447	–	–
Motor skills	Finger Tapping (inter-tap interval)	0.441	0.001	0.071	0.016
	Finger Tapping (standard deviation of inter-tap interval)	0.080†	0.177	0.019	0.044
	Catch Game (time to first move)	<0.001*‡	0.382	<0.001*‡	0.226

RT, reaction time; Results of pairwise contrasts using Least Significant Difference (LSD): * Cognitively healthy performed better than mild AD; † Cognitively healthy performed better than MCI; ‡ MCI performed better than mild AD.

Table 4. Validity of Mindstreams tests in discriminating among elderly who were cognitively healthy, those with mild cognitive impairment (MCI), and those with mild Alzheimer's disease (AD) following covariation for depression scale score in Geriatric Depression Scale (GDS) and Cornell Scale for Depression in Dementia (CSDD) cohorts by analysis of covariance (ANCOVA) using weighted least squares

Mindstreams summary measure	GDS cohort (N = 72)		CSDD cohort (N = 88)	
	Diagnosis p-value	GDS p-value	Diagnosis p-value	CSDD p-value
Memory	< 0.001*†‡	0.298	<0.001*†‡	0.913
Executive function	< 0.001*†‡	0.469	< 0.001*†‡	0.249
Visual spatial	0.001*†	0.819	0.022†	0.392
Verbal	< 0.001*†	0.832	< 0.001*†‡	0.680
Attention	< 0.001*‡	0.244	0.415*†	0.210
Motor skills	0.002*‡	0.031	0.741*	0.016
Global cognitive score	< 0.001*†‡	0.781	< 0.001*†‡	0.926

RT, reaction time; Results of pairwise contrasts using Least Significant Difference (LSD): * Cognitively healthy performed better than mild AD; † Cognitively healthy performed better than MCI; ‡ MCI performed better than mild AD.

was deemed acceptable for statistical analysis. All statistics were computed with SPSS statistical software (SPSS, Chicago, IL).

Because substantial heterogeneity of variance was observed between the diagnostic groups for some outcome measures, the ANCOVA analyses employed a weighted least squares procedure. The weights were the estimated error variances in linear regression analyses of the outcome measure on the depression score run separately for each of the three diagnostic groups. Results obtained with this procedure generally agreed with those of the original analyses, and variances were homogeneous for all outcome measures (Levene's Test, p's > 0.05).

Given the small sample sizes in this study, validity of the pairwise comparisons between diagnostic groups was confirmed using a nonparametric procedure. For each outcome measure Y, an adjusted outcome measure Y_{new} was computed using the formula $Y_{new} = Y - ßX$, where X is the depression score and ß is the coefficient of the regression score obtained in the ANCOVA analysis. Pairwise comparisons between the diagnostic groups were then computed on the adjusted outcome measure using the Wilcoxon-Mann-Whitney rank test. Good agreement was obtained between these results and those of the ANCOVA analyses.

Results

Mindstreams outcome parameters assessing multiple cognitive domains discriminated among MCI, mild AD, and cognitively healthy participants following covariation for depression scale score in both GDS and CSDD cohorts. With inclusion of depression scale score as a covariate, the vast majority of Mindstreams outcome parameters significantly ($p < 0.05$) distinguished among participants on the basis of cognitive diagnosis (Table 3). Mindstreams index scores showed similarly robust discriminant validity following covariation (Table 4). Indeed memory, executive function, visual spatial, and

verbal index scores showed consistently robust discriminant validity in both GDS and CSDD cohorts, with only attention and motor index scores giving equivocal results. Further, in both cohorts, the GCS (Figure 1) showed ability to discriminate among all pairs of diagnostic groups following covariation for depression scale score (Table 4). Hence, severity of depressive symptoms did not affect the ability of the Mindstreams tests to detect cognitive impairment due to early neurodegenerative disease.

For both GDS and CSDD cohorts, severity of depressive symptoms was unrelated to Mindstreams outcome parameter performance across cognitive domains shown to be compromised in early dementia. Depression scale score did not significantly affect performance ($p > 0.05$) for the vast majority of Mindstreams outcome parameters (Table 3). In both cohorts, Mindstreams index score performance was unrelated to severity of depressive symptoms for all cognitive domains but motor skills (Table 4), where greater severity of depressive symptoms was associated with psychomotor slowing. Severity of depressive symptoms was also unrelated to overall performance on the battery, as reflected by the GCS.

Discussion

The present study demonstrates that despite the increased prevalence of depression with greater cognitive impairment,[1] a novel set of computerized cognitive tests can detect MCI and mild dementia after covarying for depressive symptom severity. Indeed, in two separate cohorts using different depression scales, robust discriminant validity was found for memory, executive function, visual spatial, and verbal function—the cognitive domains shown to be most sensitive to early dementia.[6,21-24] Further, Mindstreams performance in all but one cognitive domain (i.e., motor skills) was found to be unaffected by depressive symptom severity. These results both confirm the validity of this brief battery of tests and underscore their utility in helping clinicians identify cognitive impairment due to neurodegeneration even in the presence of comborbid depressive symptoms.

The co-occurrence of dementia and depression and the considerable overlap in symptoms (e.g., memory complaint, diminished emotional reactivity, loss of interest, apathy)[12,13] complicate the clinical problem of arriving at an accurate diagnosis. As demonstrated by the current results, the present set of computerized tests can assist the clinician in identifying cognitive impairment indicative of MCI or mild dementia over a range of severity of depressive symptoms. Only motor skills performance was influenced by depression symptom severity, and this finding is consistent with a considerable body of evidence demonstrating a slowing of gross and fine motor ability in depression.[25]

The present study was limited to participants within a circumscribed range of cognitive impairment and depression severity as those with moderate to severe dementia and those with MDD were excluded. Nonetheless, these results are generalizable for individuals with MCI or mild dementia and comorbid depressive symptoms. A strength of the study was inclusion of separate cohorts tested with two different depression scales validated for use in the elderly. This, coupled with the heterogeneity of the study sample, which included both ambulatory and institutionalized participants, supports the generalizability of the results.

In conclusion, the present study demonstrates that the validity of a novel battery of computerized cognitive tests in detecting MCI and mild dementia is unaffected by depression. That similar results were found in two separate cohorts using two different depression scales suggests that the lack of influence of depression on these tests is generalizable. Future work will extend the current findings to longitudinal studies and to additional populations with more severe depression.

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