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Validity of a novel computerized cognitive battery for mild cognitive impairment

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Abstract

Background: The NeuroTrax *Mindstreams* computerized cognitive assessment system was designed for widespread clinical and research use in detecting mild cognitive impairment (MCI). However, the capability of *Mindstreams* tests to discriminate elderly with MCI from those who are cognitively healthy has yet to be evaluated. Moreover, the comparability between these tests and traditional neuropsychological tests in detecting MCI has not been examined.

Methods: A 2-center study was designed to assess discriminant validity of tests in the *Mindstreams* Mild Impairment Battery. Participants were 30 individuals diagnosed with MCI, 29 with mild Alzheimer's disease (AD), and 39 healthy elderly. Testing was with the *Mindstreams* battery and traditional neuropsychological tests. Receiver operating characteristic (ROC) analysis was used to examine the ability of *Mindstreams* and traditional measures to discriminate those with MCI from cognitively healthy elderly. Between-group comparisons were made (Mann-Whitney U test) between MCI and healthy elderly and between MCI and mild AD groups.

Results: *Mindstreams* outcome parameters across multiple cognitive domains significantly discriminated among MCI and healthy elderly with considerable effect sizes ($p < 0.05$). Measures of memory, executive function, visual spatial skills, and verbal fluency discriminated best, and discriminability was at least comparable to that of traditional neuropsychological tests in these domains.

Conclusions: *Mindstreams* tests are effective in detecting MCI, providing a comprehensive profile of cognitive function. Further, the enhanced precision and ease of use of these computerized tests make the NeuroTrax system a valuable clinical tool in the identification of elderly at high risk for dementia.

Background

Mild cognitive impairment (MCI) is the term applied to a condition in which elderly individuals who have a subjective cognitive complaint have objective memory impairment in the absence of functional disability [1-3]. Its importance arises from the observation that it often constitutes the clinical state between normal cognition and dementia in the elderly [4]. Approximately 12-15% of MCI subjects per year convert to clinical dementia with functional disability [4,5]. For this reason, much interest has centered on the development of standardized techniques for quantification of cognitive deficits in MCI and potential therapeutic interventions for treatment of these high-risk individuals [6].

While memory impairment is the hallmark of MCI [3], multiple cognitive domains are compromised in the majority of MCI individuals [7-9], as in those with mild Alzheimer's disease (AD). Therefore, sufficiently broad and sensitive instruments are key in the effective diagnosis of these two groups. While traditional neuropsychological tests have been shown to discriminate among individuals with MCI and cognitively healthy elderly [10-12], there is no standard, comprehensive neuropsychological battery that is suitable for the screening and follow-up of mild impairments in routine clinical care. Moreover, while paper-based neuropsychological batteries have been applied in research settings, they are generally impractical for widespread clinical use due to high cost and extended administration time.

Computerized cognitive testing has the potential to effectively address the limitations posed by traditional paper-based measures. Technical innovations for accurate measurement of reaction time as well as frequency of errors enhance overall sensitivity, and on-line adjustment of level of difficulty may minimize ceiling or floor effects. Standardized batteries with alternate forms allow for accurate follow-up of patients over time. A computerized testing session can be of shorter duration and is less expensive than a paper-based session. Further, computerized testing can be made widely available via the Internet and easily

administered so that high quality testing is on hand to supplement clinical evaluation in routine patient care settings. Indeed computerized tests have been developed to assist researchers and psychologists in screening for cognitive dysfunction [13,14]. We chose to evaluate *Mindstreams*TM (NeuroTrax Corp, NY), a new commercially available computerized testing system for comprehensive clinical assessment of cognitive impairment, designed primarily for use in the elderly. Specifically, we examine the ability of *Mindstreams* tests to discriminate individuals with MCI from among cognitively healthy elderly. The present study is the first to assess discriminant validity of the computerized tests as compared with that of traditional neuropsychological tests.

Methods

Participants

Participants were 98 elderly individuals assessed at two 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). Participants were diagnosed by consensus of evaluation teams led by dementia experts at each of the sites and were diagnosed with mild cognitive impairment (MCI), mild Alzheimer's disease (AD), or as cognitively healthy. Diagnosis of MCI followed Petersen et al. [15] and included the following features: (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. These criteria define the subtype of MCI known as 'MCI-amnesic' [3]. Diagnosis of mild AD was according to the *Diagnostic and Statistical Manual, 4th ed. (DSM IV)*. Healthy elderly had no cognitive complaints and were volunteers for research testing. Each diagnostic group was taken to be representative of a distinct population defined by the criteria outlined above. Ethics Committee approval in compliance with the Declaration of Helsinki was obtained at both testing sites, and informed consent was obtained from all participants.

Table 1: Demographic and clinical characteristics for each of the three diagnostic groups.

Characteristic	Healthy Elderly N = 39	MCI N = 30	Mild AD N = 29
Age, mean years (SD)	73.41 (8.00)	77.15 (6.43)	80.55 (4.91)
Education, mean years (SD)	14.95 (3.50)	13.07 (2.86)	11.31 (2.85)
Gender, N female	26	13	16
Computer Experience, N no	10	24	28
Handedness, N left-handed	0	1	2
MMSE, mean score (SD)	29.03 (1.11)	27.63 (1.54)	24.17 (3.25)
ADAS-cog, mean score (SD)	8.01 (3.58)	14.06 (5.23)	23.51 (8.33)

SD: standard deviation

Participants were excluded if there was a prior history of major psychiatric disorder, major depression, or any neurological disorder. All participants were native English speakers. Demographic and clinical characteristics for each diagnostic group are presented in Table 1. The MCI group was older ($t_{67} = 2.091$, $p = 0.040$) and had fewer years of education ($t_{67} = 2.391$, $p = 0.020$) relative to the healthy elderly group. Conversely, the MCI group was younger ($t_{57} = 2.276$, $p = 0.027$) and more highly educated ($t_{67} = 2.359$, $p = 0.022$) than the mild AD group. The MCI and healthy elderly groups were comparable in terms of gender and handedness (gender: $\chi^2[1, N = 69] = 3.757$, $p = 0.053$; handedness: $\chi^2[1, N = 69] = 1.319$, $p = 0.251$) as were the MCI and mild AD groups (gender: $\chi^2[1, N = 59] = 0.827$, $p = 0.363$; handedness: $\chi^2[1, N = 59] = 0.388$, $p = 0.533$). Fewer MCI participants had prior computer experience relative to the healthy elderly group ($\chi^2[1, N = 69] = 20.046$, $p = 0.000$), but more participants with MCI had computer experience relative to those with mild AD ($\chi^2[1, N = 59] = 3.863$, $p = 0.049$). Between-site differences across diagnostic groups were found for years of education ($t_{96} = 4.315$, $p = 0.000$), gender ($\chi^2[1, N = 98] = 7.936$, $p = 0.005$), and computer experience ($\chi^2[1, N = 98] = 12.001$, $p = 0.001$), but not for age ($t_{96} = 0.250$, $p = 0.802$) or handedness ($\chi^2[1, N = 98] = 0.140$, $p = 0.709$). Consistent with the expert consensus diagnoses, MCI participants performed more poorly than healthy elderly on the Mini-Mental State Examination (MMSE [16]; $U = 279$, $p = 0.000$) and on the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog [17]; $U = 190.500$, $p = 0.000$), but the MCI group performed better than the mild AD group on these measures (MMSE: $U = 570.500$, $p = 0.000$; ADAS-cog: $U = 588.000$, $p = 0.000$).

Procedure

All participants were administered the MMSE and the ADAS-cog and completed the *Mindstreams*[™] (NeuroTrax Corp., NY) battery designed to detect mild cognitive impairment (the "Mild Impairment Battery"). Participants at the McGill-Jewish General Hospital site (20 with MCI, 15 healthy elderly, and 19 with mild AD) underwent a neuropsychological battery in addition, comprising standardized tests of memory, executive function, visual spatial skills, and verbal fluency. Memory tests included the Logical Memory subtest of the Wechsler Memory Scale, 3rd Edition (WMS-III) and the Rey Auditory Verbal Learning Test (RAVLT), Version 1. Tests of executive function included the Clock Drawing Test, the Trail Making Test (Part A), the Digit Symbol subtest of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III), and the Mental Control subtest of the WMS-III. Visual spatial skills were assessed with the Block Design subtest of the WAIS-III. Tests of verbal fluency included the Boston Naming test, the Controlled Oral Word Association (COWA) test, and the Similarities subscale of the WAIS-

III. Paper-based tests at both sites and *Mindstreams* tests at the Shaare Zedek site and were administered by research assistants blind to diagnosis. *Mindstreams* tests at the McGill-Jewish General Hospital site were administered by a research assistant aware of the diagnoses, but uninformed in their determination. Notably, research assistants at both sites were trained not to assist participants during actual testing, but rather to ensure that they sufficiently understood the instructions prior to each *Mindstreams* test. Paper-based tests were administered first, followed by the *Mindstreams* Mild Impairment Battery. Both *Mindstreams* and paper-based tests were administered in English.

Mindstreams Computerized Cognitive Testing

A detailed treatment of the NeuroTrax system, including the computerized tests, data processing, and usability considerations appears in a supplementary document (Additional File 1). In brief, *Mindstreams* consists of custom software that resides on the local testing computer and serves as a platform for interactive cognitive tests that produce precise accuracy and reaction time (millisecond timescale) data. Tests are adaptive, in that the level of difficulty is adjusted accordingly depending upon performance. This feature increases sensitivity and minimizes the prevalence of ceiling effects. Feedback is provided in the practice sessions that precede each test, but not during the actual tests. 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, where calculation of outcome parameters from raw single-trial data and report generation occur.

The *Mindstreams* Mild Impairment Battery (administration time: 45 minutes) samples a wide range of cognitive domains, including memory (verbal and non-verbal), executive function, visual spatial skills, verbal fluency, attention, information processing, and motor skills (see Table 2). The tests that comprise this battery were designed for use with the elderly. All responses were made with the mouse or with the number pad on the keyboard (intuitively similar to the telephone keypad). Participants were familiarized with these input devices at the beginning of the battery, and practice sessions prior to the individual tests prepared them for the specific types of responses required for each test. Outcome parameters varied with each test, as in Table 2. Given the speed-accuracy tradeoff, (e.g., [18]) a performance index (computed as $[\text{accuracy}/\text{reaction time}] * 100$) was computed for timed *Mindstreams* tests in an attempt to capture performance both in terms of accuracy and reaction time (RT). Tests were run in the same fixed order for all participants.

Table 2: Validity of Mindstreams tests in discriminating participants with mild cognitive impairment (MCI; N = 30) from cognitively healthy elderly (N = 39).

Cognitive Domain	Mindstreams Test (outcome parameter)	AUC	SE	Asymptotic Significance	95% CI
MEMORY	Verbal Memory (accuracy, first repetition trial)	0.779	0.057	0.000	0.668–0.890
	Verbal Memory (accuracy, second repetition trial)	0.838	0.05	0.000	0.741–0.936
	Verbal Memory (accuracy, third repetition trial)	0.752	0.063	0.000	0.629–0.876
	Verbal Memory Accuracy (accuracy, final repetition trial)	0.783	0.062	0.000	0.662–0.904
	Verbal Memory (accuracy, all repetition trials)	0.859	0.048	0.000	0.765–0.953
	Verbal Memory (accuracy, delayed recognition)	0.771	0.061	0.000	0.651–0.890
	Non-Verbal Memory (accuracy, first repetition trial)	0.654	0.067	0.033	0.522–0.786
	Non-Verbal Memory (accuracy, second repetition trial)	0.698	0.069	0.006	0.563–0.833
	Non-Verbal Memory (accuracy, third repetition trial)	0.712	0.065	0.003	0.585–0.839
	Non-Verbal Memory Accuracy (accuracy, final repetition trial)	0.773	0.061	0.000	0.654–0.892
	Non-Verbal Memory (accuracy, all repetition trials)	0.756	0.063	0.000	0.633–0.879
	Non-Verbal Memory (accuracy, delayed recognition)	0.728	0.065	0.002	0.601–0.854
EXECUTIVE FUNCTION	Go-NoGo (accuracy)	0.736	0.065	0.001	0.608–0.863
	Go-NoGo (performance index)	0.810	0.056	0.000	0.701–0.920
	Problem Solving (accuracy)	0.768	0.059	0.000	0.653–0.884
	Stroop Interference (performance index)	0.703	0.077	0.023	0.551–0.854
	Catch Game (accuracy)	0.696	0.075	0.016	0.548–0.843
VISUAL SPATIAL	Visual Spatial Imagery (accuracy)	0.765	0.060	0.000	0.648–0.881
VERBAL	Verbal Function (accuracy, naming)	0.716	0.067	0.005	0.584–0.848
	Verbal Function (accuracy, rhyming)	0.824	0.051	0.000	0.724–0.923
ATTENTION	Go-NoGo (RT)	0.771	0.063	0.000	0.648–0.893
	Go-NoGo (standard deviation of RT)	0.706	0.066	0.006	0.576–0.835
	Choice Reaction Time (performance index)	0.490	0.084	0.894	0.326–0.653
INFORMATION PROCESSING	Staged Information Processing, Low Load (performance index)	0.579	0.083	0.345	0.416–0.743
	Staged Information Processing, Medium Load (performance index)	0.783	0.070	0.001	0.646–0.920
	Staged Information Processing, High Load (performance index)	0.688	0.088	0.037	0.515–0.860
MOTOR SKILLS	Finger Tapping (inter-tap interval)	0.595	0.076	0.215	0.446–0.744
	Finger Tapping (standard deviation of inter-tap interval)	0.625	0.080	0.101	0.469–0.782
	Catch Game (time to first move)	0.521	0.082	0.797	0.360–0.682

Mindstreams outcome parameters with insufficient data (<13 data points per group) due to failed practice sessions (see Methods) were excluded. AUC = area under the curve SE = standard error CI = confidence interval RT = reaction time

Following are brief descriptions of the Mindstreams tests included in the Mild Impairment 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. Participants must indicate which word of the four alternatives was paired with the target when presented previously. Four consecutive repetitions of the recognition test are administered

during the 'learning' phase. An additional recognition test is administered following a delay of approximately 10 minutes.

Non-Verbal 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. Participants are required to remember the orientations of the originally presented objects. Four consecutive repetitions of the recognition test are administered

during the 'learning' phase of the test. An additional recognition test is administered following a delay of approximately 10 minutes.

Go-NoGo test

A series of large colored stimuli are presented at pseudo-random intervals. Participants are instructed to respond as quickly as possible by pressing a mouse button if the color of the stimulus is any color except red, for which no response is to be made.

Problem Solving

Pictorial puzzles of gradually increasing difficulty are presented. Each puzzle consists of a 2 × 2 array containing three black-and-white geometric forms with a certain spatial relationship among them and a missing form. Participants must choose the best fit for the fourth (missing) form from among six possible alternatives.

Mindstreams Stroop test

The Stroop is a well-established test of response inhibition [19]. The *Mindstreams* Stroop test consists of three phases. Participants are presented with a pair of large colored squares, one on the left and the other on the right side of the screen. In each phase, participants are instructed to choose as quickly as possible which of the two squares is a particular color by pressing either the left or right mouse button, depending upon which of the two squares is the correct color. First, participants are presented with a general word in colored letters. In the next phase (termed the Choice Reaction Time test), participants are presented with a word that names a color in white letters. In the final phase (the Stroop phase), participants are presented with a word that names a color, but the letters of the word are in a color other than that named by the word. The instructions for the final phase are to choose the color of the letters, and not the color named by the word.

Verbal Function

Pictures of common objects of low and high familiarity are presented. Participants are instructed to select the name of the picture from four choices. In a related test, participants are instructed to select the word that best rhymes with the name of the picture.

Visual Spatial Imagery

Computer-generated scenes containing a red pillar are presented. Participants are instructed to imagine viewing the scene from the vantage point of the red pillar. Four alternative views of the scene are presented as choices.

Staged Information Processing test

This test comprises three levels of information processing load: single digits, two-digit arithmetic problems (e.g., 5-1), and three-digit arithmetic problems (e.g., 3+2-1). For

each of the three levels, stimuli are presented at three different fixed rates, incrementally increasing as testing continues. Participants are instructed to respond as quickly as possible by pressing the left mouse button if the digit or result is less than or equal to 4 and the right mouse button if it is greater than 4.

Finger Tapping

Participants are instructed to tap on the mouse button for 12 seconds with their dominant hand. This task is repeated twice.

Catch Game

The Catch game is a novel motor screen that assesses cognitive domains distinct from those in other *Mindstreams* tests. Participants must "catch" a rectangular white object falling vertically from the top of the screen before it reaches the bottom of the screen. Mouse button presses move a rectangular green "paddle" horizontally so that it can be positioned directly in the path of the falling object. The test requires hand-eye coordination, scanning and rapid responses.

Data Analysis

Mindstreams data were uploaded to the NeuroTrax central server, where automatic data processing occurred, during which aggregate outcome parameters were computed from the raw single-trial data (Additional File 1). Outcome parameters were calculated using custom software that was blind to diagnosis or testing site, and results were relayed to each of the sites for review and analysis. Outcome parameters were computed for each test only when performance on the preceding practice session exceeded a predetermined minimum accuracy. The actual test was not given when practice session performance was below this cutpoint. Given this source of 'missing' data, a minimum of 13 data points was deemed acceptable for inclusion of a group in statistical analyses.

All statistics were computed with SPSS statistical software (SPSS, Chicago, IL). Two-tailed statistics were used throughout, and $p < 0.05$ was considered significant. Receiver operating characteristic (ROC) analysis was used to evaluate the ability of *Mindstreams* outcome parameters and traditional neuropsychological tests to discriminate participants with MCI from cognitively healthy elderly. Area under the curve (AUC), an index of effect size, was the primary result of the ROC analysis. For each measure, the AUC indicated the probability that a randomly selected individual with MCI would perform more poorly than a randomly selected cognitively healthy individual. An AUC of 0.50 indicated no better than chance discriminability, and an AUC of 1.00 indicated perfect discriminability. If the 95% confidence interval around an AUC included 0.50, the measure was unable to discriminate

among MCI and healthy elderly at a significance level of $p < 0.05$. Separate between-group comparisons were made on *Mindstreams* outcome parameters between MCI and cognitively healthy and between MCI and mild AD. Given heterogeneous variances across these pairs of groups for numerous outcome parameters (Brown-Forsythe test, $p > 0.05$), the non-parametric Mann-Whitney U was used to make the comparisons.

Results

Discriminant Validity of Mindstreams Outcome

Parameters: Effect Sizes

Results of an ROC analysis measuring the ability of *Mindstreams* outcome parameters to discriminate MCI from cognitively healthy elderly are presented in Table 2, subdivided by cognitive domain. All *Mindstreams* memory outcome parameters discriminated significantly, with a maximum AUC of 0.859 for mean accuracy across all recognition test repetitions in the 'learning' phase of the Verbal Memory test. Similarly, all executive function outcome parameters discriminated significantly, with a maximum AUC of 0.810 for the Go-NoGo performance index. All outcome parameters measuring visual spatial skills and verbal fluency discriminated significantly, with a maximum AUC of 0.824 for accuracy on the rhyming portion of the Verbal Function test. Significant discriminability was found for attention outcome parameters from the Go-NoGo test, with an AUC of 0.771 for Go-NoGo RT and 0.706 for Go-NoGo standard deviation of RT. The Choice Reaction Time performance index did not discriminate significantly among MCI and cognitively healthy elderly. Medium- (AUC = 0.783) and high-load (AUC = 0.688) information processing outcome parameters discriminated significantly, but the low-load parameter did not. All motor skills outcome parameters did not discriminate significantly.

Effect Sizes of Mindstreams Outcome Parameters Relative to Traditional Neuropsychological Tests

Table 3 presents ROC analysis results for the subset of MCI and healthy elderly participants who received a battery of standardized neuropsychological tests in addition to *Mindstreams* testing. For each cognitive domain, the ability of *Mindstreams* outcome parameters to discriminate MCI from cognitively healthy elderly was compared with paper-based neuropsychological tests designed to tap the same domain. Outcome parameters measuring attention, information processing, and motor skills were excluded from this analysis for lack of corresponding traditional tests in these cognitive domains.

As above (Table 2), the *Mindstreams* memory outcome parameter that best discriminated MCI from cognitively healthy elderly was accuracy across the 'learning' phase of the Verbal Memory test (AUC = 0.894; Table 3); the best

traditional memory test was the WMS-III Logical Memory II subtest (AUC = 0.885). Also as above, the *Mindstreams* executive function outcome parameter that discriminated best was the Go-NoGo performance index (AUC = 0.840); the best traditional executive function test was the WAIS-III Digit Symbol subtest (AUC = 0.729; Figure 1A). The *Mindstreams* visual spatial outcome parameter discriminated significantly (AUC = 0.778), but the corresponding WAIS-III Block Design subtest did not (Figure 1B). The *Mindstreams* verbal outcome parameter that discriminated best was accuracy on the naming portion of the Verbal Function test (AUC = 0.837); the best traditional verbal test was the COWA FS test (AUC = 0.768).

Discriminant Validity of Mindstreams Outcome

Parameters: Group Differences

Mindstreams outcome parameters discriminated MCI from cognitively healthy and from mild AD (e.g., Figure 2). Descriptive statistics for outcome parameters in each cognitive domain are presented in Table 4, subdivided by diagnostic group. The results of two Mann-Whitney U tests are shown for each parameter, one comparing MCI and healthy elderly participants and the other comparing MCI and mild AD participants. Results for the MCI/healthy elderly comparison are similar to those in Table 2. For cognitive domains with sufficient data for conclusive results, significant differences between MCI and mild AD participants were found for memory, visual spatial, and verbal outcome parameters. Results were mixed for attention outcome parameters, such that timed Go-NoGo parameters did not significantly discriminate among MCI and mild AD, but the performance index from the Choice Reaction Time test did.

Discussion

Cognitive assessment is essential to the effective care and treatment of the elderly. Given that the number of elderly is predicted to increase steeply as the baby boomer generation ages [20], there is an urgent need for standardized cognitive assessment tools that deliver high quality information and are practical for routine clinical use. Traditional paper-based neuropsychological testing is seriously limited by the formidable cost in time and money. We therefore evaluated a novel computerized cognitive testing system, the *Mindstreams* system (NeuroTrax Corp., NY), which was designed for widespread clinical application in the detection of MCI and mild dementia.

The present study evaluated the discriminant validity of *Mindstreams* tests in distinguishing individuals with MCI from healthy elderly. Outcome parameters across multiple cognitive domains significantly discriminated among MCI and healthy elderly with considerable effect sizes (Table 2). Particularly strong results were obtained for outcome parameters assessing memory, executive

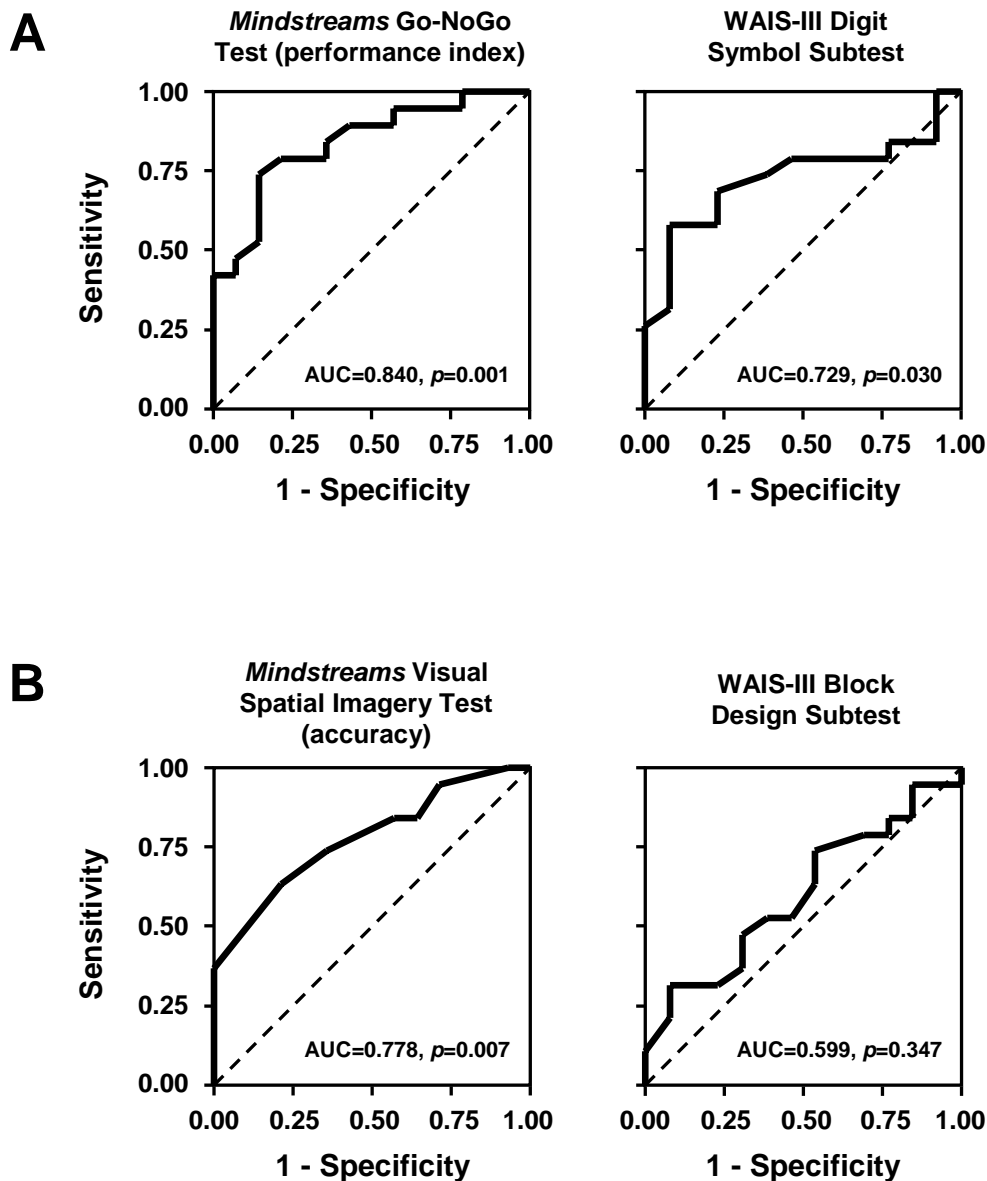


Figure 1

Discriminant Validity of Executive Function and Visual Spatial Tests. Receiver operating characteristic (ROC) curves demonstrating the ability of *Mindstreams* tests to discriminate individuals with mild cognitive impairment (MCI) from among cognitively healthy elderly as compared to traditional neuropsychological tests (MCI: $N = 20$; Healthy Elderly: $N = 15$). In (A), discriminability of the *Mindstreams* Go-NoGo performance index is compared with that of the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III) Digit Symbol subtest. In (B), discriminability of accuracy on the *Mindstreams* Visual Spatial Imagery test is compared with that of the WAIS-III Block Design subtest. Discriminant validity of the *Mindstreams* tests was better than traditional paper-based tests designed to tap similar cognitive domains. AUC=area under the curve.

Table 3: Validity of Mindstreams tests in discriminating mild cognitive impairment (MCI; N = 20) from cognitively healthy elderly (N = 15) as compared with traditional paper-based tests of the same cognitive domains.

Cognitive Domain	Mindstreams Test (outcome parameter)	AUC	SE	Asymptotic Significance	95% CI	Traditional Measure	AUC	SE	Asymptotic Significance	95% CI
MEMORY	Verbal Memory (accuracy, first repetition trial)	0.848	0.066	0.001	0.719–0.977	WMS-III Logical Memory I	0.800	0.076	0.003	0.650–0.950
	Verbal Memory (accuracy, second repetition trial)	0.831	0.071	0.001	0.692–0.971	WMS-III Logical Memory II	0.885	0.055	0.000	0.778–0.992
	Verbal Memory (accuracy, third repetition trial)	0.720	0.089	0.031	0.547–0.894	RAVLT Immediate Recall A	0.632	0.096	0.188	0.443–0.820
	Verbal Memory Accuracy (accuracy, final repetition trial)	0.752	0.086	0.014	0.583–0.920	RAVLT Total	0.833	0.068	0.001	0.701–0.966
	Verbal Memory (accuracy, all repetition trials)	0.894	0.056	0.000	0.785–1.000	RAVLT Immediate Recall B	0.688	0.091	0.06	0.510–0.866
	Verbal Memory (accuracy, delayed recognition)	0.748	0.085	0.015	0.582–0.914	RAVLT Short Term Retention	0.874	0.062	0.000	0.752–0.995
	Non-Verbal Memory (accuracy, first repetition trial)	0.654	0.097	0.127	0.464–0.844	RAVLT Delayed Recall	0.846	0.073	0.001	0.702–0.990
	Non-Verbal Memory (accuracy, second repetition trial)	0.681	0.095	0.074	0.494–0.867	RAVLT Recognition	0.823	0.073	0.001	0.680–0.965
	Non-Verbal Memory (accuracy, third repetition trial)	0.642	0.097	0.160	0.453–0.831					
	Non-Verbal Memory Accuracy (accuracy, final repetition trial)	0.686	0.093	0.066	0.505–0.867					
	Non-Verbal Memory (accuracy, all repetition trials)	0.719	0.090	0.030	0.542–0.897					
	Non-Verbal Memory (accuracy, delayed recognition)	0.684	0.094	0.069	0.499–0.869					
EXECUTIVE FUNCTION	Go-NoGo (accuracy)	0.742	0.088	0.019	0.570–0.915	Clock Drawing	0.680	0.092	0.072	0.499–0.861
	Go-NoGo (performance index)	0.840	0.069	0.001	0.705–0.976	Trail Making Test A	0.660	0.092	0.11	0.479–0.841
	Problem Solving (accuracy)	0.685	0.098	0.077	0.492–0.877	WAIS-III Digit Symbol	0.729	0.091	0.03	0.550–0.908
					WMS-III Mental Control	0.706	0.092	0.05	0.525–0.888	
VISUAL SPATIAL	Visual Spatial Imagery (accuracy)	0.778	0.079	0.007	0.622–0.934	WAIS-III Block Design	0.599	0.102	0.347	0.400–0.798
VERBAL	Verbal Function (accuracy, naming)	0.777	0.085	0.009	0.610–0.944	Boston Naming Test	0.747	0.082	0.014	0.585–0.908
	Verbal Function (accuracy, rhyming)	0.837	0.070	0.001	0.700–0.973	COWA FS	0.768	0.081	0.008	0.609–0.928
						COWA A	0.739	0.086	0.018	0.570–0.907
						COWA Animals	0.711	0.088	0.037	0.538–0.883
					WAIS-III Similarities	0.553	0.11	0.618	0.337–0.768	

Mindstreams outcome parameters with insufficient data (<13 data points per group) due to failed practice sessions (see Methods) were excluded. AUC = area under the curve WMS-III = Wechsler Memory Scale, 3rd edition SE = standard error RAVLT = Rey Auditory Verbal Learning Test, Version I CI = confidence interval WAIS-III = Wechsler Adult Intelligence Scale, 3rd Edition RT = reaction time COWA = Controlled Oral Word Association

function, visual spatial skills, and verbal function. Further, effect sizes of the computerized tests in these domains were at least comparable to neuropsychological tests designed to assess the same domains (Table 3; Figure 1). Results were mixed for Mindstreams attention and information processing outcome parameters, and those assess-

ing motor skills did not discriminate among MCI and healthy elderly (Table 2).

The current findings are consistent with those of studies designed to identify traditional neuropsychological tests that predict conversion to dementia. Many such studies have found standard tests of verbal- and non-verbal

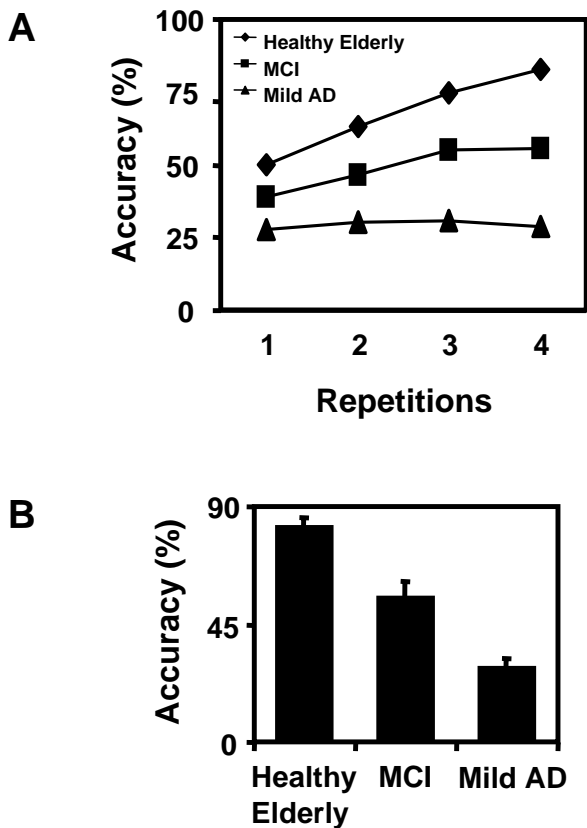


Figure 2
 Discriminant Validity of Non-Verbal Memory Test. During the 'learning phase' of the *Mindstreams* Non-Verbal Memory test, four consecutive repetitions of a recognition test were administered. In (A), mean accuracy is shown across repetitions for cognitively healthy elderly (diamonds), mild cognitive impairment (MCI; squares), and mild Alzheimer's disease (AD; triangles) participants. (B) depicts mean performance (+ standard error) for each of the diagnostic groups on the final repetition trial. MCI participants are discriminable from healthy elderly and from those with mild AD (see Table 4).

memory and executive function to be excellent predictors [10,11,21-23]. Others have found verbal fluency to be a good predictor [24,25], and a recent report by Mapstone et al. [12] suggests that visual spatial impairment may also predict conversion to dementia. Hence every cognitive domain with strong discriminant validity for *Mindstreams* outcome parameters in MCI has been associated with prediction of conversion to dementia in studies of traditional tests.

Computerized tests other than *Mindstreams* have been employed to discriminate MCI from cognitively healthy elderly. Indeed the paired associates learning (PAL) test of the Cambridge Neuropsychological Test Automated Battery (CANTAB) has been shown sensitive to cognitive decline [26]. While demonstrating the general utility of computerized cognitive testing, the CANTAB-PAL is limited in scope, difficult to use, and requires specialized equipment. A brief set of three tests developed by CogState Ltd. and administered serially four times in 3 hours has recently been shown to discriminate among MCI and cognitively healthy elderly on the basis of learning performance [7]. However, the CogState tests fail to provide a comprehensive cognitive profile, consisting exclusively of reaction time tests. Finally, MicroCog [27], a multi-domain computerized battery, showed good discriminability among participants with mild dementia and cognitively healthy elderly in an initial validity study [28]. However, MicroCog has not been widely used clinically, likely because it tests only selected cognitive domains and must be administered by a trained psychologist [29].

It is important to note that the results reported in the present study are preliminary. Population based studies with longitudinal follow-up, pathological confirmation of diagnosis, and comparison with a wider array of traditional tests are required to fully establish the validity of the *Mindstreams* tests in MCI detection. Further, given the between-group differences in age and years of education in the present study, future studies must collect normative data on *Mindstreams* tests so that performance can be standardized according to age and years of education. Given the between-group difference in computer experience in the present study, subsequent studies will collect more detailed information on participants' facility with the computer in general and with each of the *Mindstreams* tests in particular. However, the absence of between-group differences on *Mindstreams* motor skills tests in the current study, those most dependent upon facility with the computer, suggests that differential computer experience did not confound the results. Finally, future work might incorporate test data in the event of a failed practice session. As such data was labeled 'missing' in the present study, the reported results likely underestimate the true discriminant validity of the *Mindstreams* tests.

An important limitation imposed upon the present study and all studies of MCI arises from lack of consensus regarding the clinical definition of MCI [30,31]. Our MCI participants were selected according to the standard definition in the field [4], but these criteria for 'MCI-amnesic' [3] require only memory impairment. Consistent with the present results, individuals classified as 'MCI-amnesic' are often impaired in other cognitive domains [7-9]. A more clinically valid classification of this pre-dementia

Table 4: Discriminant validity of Mindstreams computerized tests: summary statistics and group differences (Mann-Whitney U).

Cognitive Domain	Mindstreams Test (outcome parameter)	Healthy Elderly N = 39	MCI N = 30	Mild AD N = 29	MCI / Healthy Elderly p-value	MCI / Mild AD p-value
MEMORY	Verbal Memory (accuracy, first repetition trial)	71.35 (18.88)	48.21 (22.94)	24.00 (20.41)	0.000	0.000
	Verbal Memory (accuracy, second repetition trial)	87.37 (13.09)	60.71 (25.08)	23.60 (23.96)	0.000	0.000
	Verbal Memory (accuracy, third repetition trial)	94.47 (7.60)	71.43 (29.9)	20.80 (22.16)	0.000	0.000
	Verbal Memory Accuracy (accuracy, final repetition trial)	97.37 (5.54)	73.21 (29.07)	22.00 (23.8)	0.000	0.000
	Verbal Memory (accuracy, all repetition trials)	88.08 (8.51)	63.68 (24.13)	22.76 (21.72)	0.000	0.000
	Verbal Memory (accuracy, delayed recognition)	87.30 (12.17)	62.50 (30.26)	18.40 (19.30)	0.000	0.000
	Non-Verbal Memory (accuracy, first repetition trial)	49.92 (21.25)	38.71 (15.61)	27.96 (16.35)	0.027	0.017
	Non-Verbal Memory (accuracy, second repetition trial)	63.11 (20.63)	46.68 (25.91)	30.13 (13.95)	0.006	0.014
	Non-Verbal Memory (accuracy, third repetition trial)	74.89 (23.65)	55.18 (27.44)	30.74 (17.98)	0.003	0.002
	Non-Verbal Memory Accuracy (accuracy, final repetition trial)	82.84 (18.19)	55.64 (28.36)	28.92 (15.33)	0.000	0.000
	Non-Verbal Memory (accuracy, all repetition trials)	67.79 (17.17)	49.21 (20.36)	28.96 (11.24)	0.000	0.000
	Non-Verbal Memory (accuracy, delayed recognition)	74.92 (21.92)	55.14 (25.00)	37.68 (17.65)	0.002	0.012
EXECUTIVE FUNCTION	Go-NoGo (accuracy)	94.28 (6.59)	84.89 (18.93)	81.90 (14.19)	0.001	0.238
	Go-NoGo (performance index)	20.55 (2.63)	16.47 (3.75)	13.68 (4.77)	0.000	0.036
	Problem Solving (accuracy)	73.45 (15.27)	61.36 (13.09)	55.00 (15.62)	0.000	0.161
	Stroop Interference (performance index)	11.70 (6.40)	7.16 (5.38)	---	0.023	---
	Catch Game (accuracy)	59.67 (14.91)	46.24 (19.80)	---	0.016	---
VISUAL SPATIAL	Visual Spatial Imagery (accuracy)	60.16 (15.61)	44.37 (15.53)	35.56 (15.43)	0.000	0.015
VERBAL	Verbal Function (accuracy, naming)	92.33 (8.79)	83.22 (14.05)	66.96 (18.37)	0.004	0.002
	Verbal Function (accuracy, rhyming)	80.38 (16.97)	52.21 (29.36)	37.79 (22.79)	0.000	0.02
ATTENTION	Go-NoGo (RT)	464.39 (56.66)	556.04 (102.82)	666.38 (243.81)	0.000	0.244
	Go-NoGo (standard deviation of RT)	119.17 (46.40)	171.96 (89.02)	242.81 (160.75)	0.006	0.149
	Choice Reaction Time (performance index)	15.84 (3.84)	15.52 (5.51)	9.34 (4.41)	0.894	0.004
INFORMATION PROCESSING	Staged Information Processing, Low Load (performance index)	15.21 (1.91)	14.52 (2.28)	---	0.345	---
	Staged Information Processing, Medium Load (performance index)	8.83 (1.55)	7.04 (1.75)	---	0.001	---
	Staged Information Processing, High Load (performance index)	5.55 (1.16)	4.71 (1.51)	---	0.037	---
MOTOR SKILLS	Finger Tapping (inter-tap interval)	221.10 (42.71)	242.83 (64.88)	279.00 (66.09)	0.215	0.055
	Finger Tapping (standard deviation of inter-tap interval)	38.38 (28.82)	58.35 (49.46)	66.62 (78.09)	0.101	0.888
	Catch Game (time to first move)	774.91 (158.10)	783.14 (169.16)	---	0.797	---

Summary statistics presented as mean (standard deviation). Accuracies are given as percent correct. Timed outcome parameters are given in milliseconds. '---' indicates insufficient data (<13 data points per group) due to failed practice sessions (see Methods). MCI = mild cognitive impairment AD = Alzheimer's disease RT = reaction time

state may be Aging-Associated Cognitive Decline (AACD; [32]), which has clearly defined diagnostic criteria and requires impairment in multiple cognitive domains [30,31]. Indeed AACD has recently been validated as a predictor of conversion to dementia [33,34].

Computerized testing has been criticized relative to paper-based testing in terms of technical limitations and appropriateness for clinical use [35]. Perhaps the most pervasive technical limitation is measurement error that varies depending upon the refresh rate of the monitor, the sam-

pling rate of the input device, operating system activities, and the data acquisition software. Mindstreams, which runs under Microsoft Windows, utilizes the DirectX library to minimize imprecision due to operating system activities and data acquisition software to sub-millisecond levels. The remaining sources of error are hardware-dependent and typically result in imprecision on the order of less than 20 milliseconds, still far better than human measurement error. Computerized assessment has also been criticized on the grounds that testing is not customizable for the individual participant. While paper-

based tests are indeed more flexible, the inherent lack of uniformity confounds the valid comparison of test results across participants. Further, *Mindstreams* testing batteries can be customized to suit specific clinical needs. Batteries can be constructed to include only relevant tests, and stimulus presentation parameters can be altered as appropriate for a particular clinical population.

We found *Mindstreams* tests straightforward to administer and easy for even the mild AD participants to learn. Administration time for the comprehensive testing battery used in this study (45 minutes) was appropriate, and participants were pleased with the positive feedback that the system provided throughout the session. The automatic uploading and scoring of the data streamlined the entire data collection process, and, in our view, these features may lead to widespread adoption of computerized cognitive testing.

The present study is evaluative in that it serves to guide future studies in determining the optimal set of *Mindstreams* tests and outcome parameters for differentiating among various patient groups. For example, not all information processing outcome parameters discriminated equally among MCI and cognitively healthy elderly (Table 2). It appears that the level of difficulty associated with the 2-digit arithmetic (i.e., medium load) portion of the Information Processing test discriminated best, while that associated with the single digit (i.e., low load) portion of the test was ineffectual in discriminating. This suggests that level of difficulty is an important consideration in selecting the *Mindstreams* parameters that best discriminate among groups. Similarly, the mixed pattern of results for attention outcome parameters (i.e., Choice Reaction Time did not discriminate, but Go-NoGo timed outcome parameters did discriminate; Table 2) can be accounted for by inter-task differences in level of difficulty. These observations may guide both clinical research on existing *Mindstreams* tests and future test development.

Conclusions

The present preliminary study demonstrates the ability of *Mindstreams* computerized cognitive tests to discriminate individuals with MCI from cognitively healthy elderly. *Mindstreams* measures of memory, executive function, visual spatial skills, and verbal fluency discriminated best, and discriminability was at least comparable to that of traditional neuropsychological tests in these domains. Our findings and experience with the NeuroTrax system underscore the utility of this novel clinical tool in the diagnosis of MCI and mild dementia in circumstances where full neuropsychological evaluation is unavailable or impractical. Guided by the present results, further work is necessary to examine the suitability of *Mindstreams* tests

for additional clinical and non-clinical validation cohorts and for longitudinal use.

Competing Interests

T Dwolatzky: None Declared

V Whitehead: None Declared

GM Doniger: Employee of NeuroTrax Corp.

ES Simon: Employee of NeuroTrax Corp.

A Schweiger: Consultant for NeuroTrax Corp.

D Jaffe: Consultant for NeuroTrax Corp.

H Chertkow: None Declared

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Authors' Contributions

TD and HC contributed to study design and oversaw data collection at each of the two sites. Data analysis was performed by GMD and VW, guided by contributions from DJ, ES, AS and HC. Manuscript preparation was handled primarily by GMD and ES, with contributions from HC, AS, and TD. All authors read and approved the final manuscript.

Additional material

Additional File 1

Mindstreams Cognitive Health Assessment, Version 2.1 (May 2003). A detailed treatment of the NeuroTrax system, including the computerized tests, data processing, and usability considerations.

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