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CANS-MCI Statistical Validity and Sensitivity

The initial validation studies of the CANS-MCI were published in 2005 in a major peer-reviewed journal (Tornatore et al, 2005). Those studies concluded that the CANS-MCI is "a reliable, valid screening tool to determine whether more intensive testing for early cognitive impairment is warranted".[1] The concurrent validity and confirmatory factor analyses in those studies established the tests as worthy of expensive sensitivity/specificity studies (carried out with over $900,000 in funding from the National Institute on Aging). Three such studies are discussed below, two evaluating the first-administration use of the CANS-MCI (one of those became an ongoing longitudinal study) and one evaluating the one-year follow-up of those subjects. These studies confirmed of validity of the CANS-MCI and resulted in the expansion of clinical use in primary care.

To determine the ability of the CANS-MCI to accurately test for mild cognitive impairment (MCI), the CANS-MCI test battery was used to predict which people, when given a full, independent neuropsychological exam, would be classified as having MCI.[2] Although the CANS-MCI only costs a small fraction of the amount for the full neuropsychological exam, it predicted almost exactly which people would be classified as normal and which would be classified as MCI.

Logistic regression models were used to predict MCI (or normal) as determined by the full neuropsychological exam. Because education can affect scores on measures of cognitive impairment, the sample was separated into individuals with a high school degree or less (N=26) and those with education beyond high school (N=57). Gender and age were included in the model. Receiver operating characteristic (ROC) analyses were performed to calculate the sensitivity (the proportion of persons who have MCI that are defined as having MCI) and specificity (proportion of persons who have normal cognitive functioning that are defined as having normal functioning) of the CANS-MCI.

The CANS-MCI has excellent sensitivity and specificity (100% and 100%) in classifying those in the first subset (with an education up to a high school degree). For those in the second subset (13+ years of education), the CANS-MCI statistical sensitivity and specificity were a bit lower (100% and 85%); but still excellent—with an area under the curve of .96.

Table 1: CANS-MCI ROC Analyses[2]

Education	Area Under the Curve	% Sensitivity	% Specificity
Less Than 13 Years	1.0	100	100
13 or More Years	.96	100	84.8

The analyses above were then performed using factor scores on the 74 subjects who returned a year later.[3] Despite small numbers of subjects to date, these data indicate that the overall probability that a full neuropsychological evaluation will indicate MCI can be effectively predicted with the CANS-MCI. The algorithms correctly classified 85% of participants with a high school degree or less (Chi-square = 11.7; Nagelkerke pseudo-R2 =.63) and 80% of those with at least some college (Chi-square = 31.4; Nagelkerke pseudo-R2 =.59) indicating a good fit of the data to the model (Table 3). The CANS-MCI has good levels of sensitivity and specificity in classifying those with an education up to a high school degree. The optimum sensitivity and specificity for those with 13+ years of education is lower but still excellent.

Table 3: CANS-MCI Logistic Regression Analyses (1-year follow-up)[3]

Education	$\chi 2$	Nagelkerke R2	Predicted Classification % Correct
Less Than 13 Years	11.7	.63	85.0
13 or More Years	31.4	.59	79.6

Table 4: CANS-MCI ROC Curve Analyses

Education	Area Under Curve	% Sensitivity	% Specificity
Less Than 13 Years	.917	92.9	83.3
13 or More Years	.888	83.9	73.9

ROC curve analyses on the two educational levels revealed cut-points leading to sensitivities/specificities of .93/.83 (<=12 yrs) and .84/.74 (13+ yrs). Areas under the curve were high: .917 for <= 12 yrs education and .888 for 13+ yrs (Table 4).

The results are impressive given that: 1) this study used a community sample of people living independently, with a lower incidence of MCI than the clinical samples often used; 2) the CANS-MCI screens for the differentiation of normal functioning from MCI which is more difficult to detect than the differentiation between normal functioning and diagnosable AD, used to measure the sensitivity and specificity of some other instruments; and 3) all of the tests within the CANS-MCI, unlike other brief screening devices, are designed to be used longitudinally, comparing each person to his or her own previous performance. This allows for even higher onset detection accuracy and more timely recommendations concerning extensive neuropsychological and/or imaging evaluations, even in those people whose high cognitive reserve results in scores that are declining but still well above average.

When decline is detected, we recommend that a more extensive (and expensive) evaluation of the physician's choosing be undertaken before a full treatment plan is implemented. We do not specify the recommended tests (or give any diagnoses or recommendations for FDA-approved drugs such as Aricept, Exelon, Razadyne, or Namenda). The most frequent follow-up procedures to the CANS-MCI reported by doctors in the United States are:

- Further interviews with the patient and their family to assess day-to-day functional abilities.
- SPECT and PET imaging scans.
- Laboratory tests for possible reversible causes of dementia (e.g. thyroid function, folate, B12).

In a study by Celeste de Jager at Oxford (2010)[4] comparing the utility and sensitivity of the CANS-MCI to traditional cognitive screening tools for MCI, the CANS-MCI and MoCA revealed highly significant differences between normal controls and MCI ($p<.0001$), while the MMSE discrimination between groups was much less significant ($p<.05$). Specificity and sensitivity of the tests was assessed using ROC curve analysis. The ACE-R and MoCA total scores showed similar and very high sensitivity (90%) but lower specificity (67%). The CANS-MCI revealed similarly high sensitivity (89%), and good specificity (73%) overall. The MMSE showed the lowest sensitivity (80%) and specificity (60%) in discrimination of the groups.

In addition, our on-going validation research finds good agreement between the CANS-MCI measures and the results of well-known "gold standard" cognitive tests.[5] As an example of this, an optimal cognitive screen would be expected to detect all of the patients considered demented by the Dementia Rating Scale (DRS2) and the majority of those judged to be MCI by the Wechsler Immediate Memory (WMS1) and Wechsler Delayed Memory (WMS2). By those criteria, the CANS-MCI Memory factor alone appears as sensitive to dementia and MCI as full neuropsychological examination, while the full three factor CANS-MCI results (median time=34 min.) may be even more sensitive than a conventional full neuropsychological examination (typically completed in 2.5 hours).[5]

Table 5: CANS-MCI and Neuropsych. Exam vs. cognitive "gold standards" (n=169)

	Neuropsych Examination	**CANS-MCI Memory alone**	**CANS-MCI All 3 Factors**
DRS2 Impairment (Memory or Initiation)	89%	93%	100%
Wechsler Impairment (WMS1 or WMS2)	79%	80%	95%

Unpublished data have been collected at the University of Kentucky (Frederick A Schmitt, PhD, Co-director of the Memory Disorders Clinic and Co-director of the Biostatistics and Data Management Core at the Alzheimer's Disease Research Center, University of Kentucky Medical Center).[6,7] This is a definitive study, because it is independent, longitudinal and compares the CANS-MCI to both full neuropsychological evaluations and to imaging. Eventually there will be comparisons to autopsy data as well. The CANS-MCI in general, and particularly the Memory factor, looks extremely good at discriminating the normal from the MCI groups the ADRC created through extensive evaluations. In the first 48 cases analyzed, the CANS-MCI memory factor score (CANS-MEM) and executive functioning factor score (CANS-EXEC) showed significant declines in subjects who had initially tested as completely normal according to Uniform Data Set (UDS) criteria and numerous research oriented cognitive instruments but subsequently showed declines in research cognitive testing, but would not be officially classified as MCI or demented by UDS criteria. The CANS-MCI fluency factor score (CANS-FLU) did not show such changes, consistent with the understanding that fluency in general is less sensitive to the earliest MCI/AD changes.[6]

In more recent imaging studies, a subset of the Kentucky subjects (N=21), were also assessed with volumetric MRI, revealing that CANS-MEM was positively related to hippocampal brain volume (right hippocampus: $r=.43$, $p<.05$; left hippocampus: $r=.38$, $p<.08$)[7]. These provocative findings from the Kentucky data set indicate that the CANS-MEM and CANS-EXEC are sensitive to early cognitive changes which are "pre-clinical" in nature, occurring before any formal diagnosis of MCI or dementia is likely to occur, while the hippocampal imaging results suggest that CANS-MEM differences reflect differences in brain volume.

A 2008 article by Wild *et al*[8] documents the establishment of reliability and validity as well as the superior usability of the CANS-MCI, compared to other computerized tests. The CANS-MCI uses friendly interactions, a geriatric-tested display size, and a single finger touch method to avoid the reliability problems when using a small tablet (as well as the anxiety aroused when many seniors are asked to use a keyboard, stylus or mouse). The CANS-MCI offers the fewest possible administration and scoring errors for physicians and eliminates the need for staff training in test administration or scoring.

References

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8. Wild K, Howieson D, Webbe F, Seelye A, Kaye J. Status of computerized cognitive testing in aging: a systematic review. Alzheimers & Dementia.; 4(6):428–437, 2008. *Each test battery was rated on the availability of normative data, level of evidence for test validity & reliability, comprehensiveness and usability. The article gave Screen's test battery the top overall score and special mention for user-friendliness with elderly patients.*