PAPER

The Goteborg MCI study: mild cognitive impairment is a heterogeneous condition

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Background: Mild cognitive impairment (MCI) has been considered a transitional state between normal aging and dementia, characterised by memory impairment but normal general cognitive functioning. Recently other cognitive deficits have been reported. This has led to a modification of MCI criteria.
Objective: To examine which neuropsychological tests most clearly distinguish MCI subjects from normal controls.
Methods: 112 consecutive MCI subjects and 35 controls were included in the study. The diagnosis of MCI was based on an objective history of cognitive decline and a neuropsychiatric examination, comprising instruments STEP, I-Flex, MMSE, and CDR. Participants were examined with 21 neuropsychological tests in the cognitive domains speed/attention, memory and learning, visuospatial function, language, and executive function.
Results: Controls were significantly older. No differences were found in education or general intellectual capacity. Controls performed significantly better than MCI on tests within all five cognitive domains. The clearest differences were seen on language tests, followed by executive function, and learning and memory. Only two subjects (1.8%) were purely amnestic; 17% showed no impairment compared with controls, with a cut off of 1.5 SD below age mean. These subjects were better educated and performed significantly better on measures of general cognitive capacity.
Conclusions: The results illustrate the heterogeneity of MCI, with a significant degree of impairment in all five cognitive domains. When examined with a comprehensive neuropsychological battery, very few subjects had an isolated memory impairment.

With symptomatic treatment now available for Alzheimer's disease and other dementia disorders, interest in the identification of the disease in its earliest manifestations has increased. Through the years there have been many attempts to describe and conceptualise the spectrum of conditions in the borderland between normal aging and cognitive decline associated with disease: benign senescent forgetfulness,[1] age consistent memory impairment,[2] aging associated cognitive decline (AACD),[3] and age related cognitive decline.[4] When subjects with objectively confirmed cognitive decline were shown to be at increased risk for Alzheimer's disease and other dementia disorders, interest in cognitive decline as a possible preliminary stage of dementia increased. Concepts such as age associated memory impairment (AAMI)[5] and mild cognitive impairment (MCI)[6] emerged as targets for studies. In particular, MCI has attracted a great deal of attention and has become a topic of considerable research.

MCI is conceptualised as a boundary or transitional state between normal aging and dementia. It is not an established diagnosis but a concept for which different criteria have been proposed, and also modified over time. Consequently, various studies have used the term MCI but not the criteria originally proposed.[7] In most studies MCI is defined as memory impairment, with other cognitive domains relatively spared.[6 8–10] According to a number of studies, individuals with a subjective and objective memory impairment but normal general cognitive functioning convert to Alzheimer's disease at a rate of 10–15% a year.[6 10–14] Although the focus of these studies has been the preliminary stages of Alzheimer's disease, and thus memory impairment, other cognitive impairment has occasionally been reported—for example naming deficits,[6] impaired concept formation,[11] and executive impairment.[11 15] It has even been suggested that the risk of dementia is significantly increased when other cognitive impairments are present. According to one study,[16] subjects with memory impairment alone were very uncommon and rarely progressed to dementia. MCI criteria were modified in accordance with these findings in a manner which makes it possible to designate subjects to either of three subgroups: group I, amnestic; group II, multiple domains slightly impaired; and group III, single non-memory domain impaired.[17]

Cognitive impairment is also a characteristic of cerebrovascular disease.[18–20] Although some study results suggest that subjects with vascular cognitive impairment are at a high risk of progression to dementia,[18 21] little is still known about the conversion rate from vascular impairment to dementia.

Thus, when examining subjects with subjective cognitive impairment, the increasing heterogeneity of the MCI concept calls for a comprehensive neuropsychological assessment.

The objective of this study was to examine which neuropsychological tests most clearly distinguish subjects with clinically defined MCI from healthy controls.

Abbreviations: AACD, aging associated cognitive decline; AAMI, aging associated memory impairment; AAN, American Academy of Neurology; ASLD, assessment of subtle language disorders; CDR, clinical dementia rating; GDS, global deterioration scale; I-Flex, short form of the executive interview (EXIT) test; MCI, mild cognitive impairment; MMSE, mini-mental state examination; PaSMO, parallel serial mental operations; PCA, principal components analysis; RAVLT, Rey auditory verbal learning test; RCF, Rey complex figure test; STEP, stepwise comparative status analysis; VOSP, visual object and space perception; WCST, Wisconsin card sorting test; WLM, Wechsler's logical memory test

METHODS

Subjects and diagnostic procedure

Between January 2000 and October 2002, 190 consecutive subjects at our memory clinic were included, together with 35 healthy controls, in the Goteborg MCI study. The majority (about 75%) of the subjects were referred to our clinic by their general practitioners or by a specialist. About 25% came on their own initiative; they experienced cognitive problems and contacted our clinic for an examination. The distribution of diagnoses was as follows: MCI 59%, mild Alzheimer's disease 23%, mild vascular dementia 13%, and ''other'' 5%. Subjects with depression or other psychiatric disorders were excluded. The diagnosis of MCI was made by means of a history and checklists for cognitive assessment: stepwise comparative status analysis (STEP),[22] cognitive variables 13–20 (memory disturbance; disorientation; reduced abstract thinking; visuospatial disturbance; poverty of language; sensory aphasia; visual agnosia; apraxia) for basic cognitive symptoms; I-Flex, which is a short form of the executive interview (EXIT)[23] (items: number–letter task; word fluency; anomalous sentence repetition; interference task; Luria hand sequences; counting task) for executive symptoms; and mini-mental state examination (MMSE)[24] and clinical dementia rating (CDR)[25] as global measures of functioning. The information for the CDR was gathered from both the subject and an informant. For inclusion, subjective and objective (verified by an informant) anamnestic proof of progressive cognitive impairment for more than six months was required. A positive outcome on STEP, I-Flex, MMSE, or CDR was also required. Subjects without a positive outcome on the checklists were not included, as their cognitive impairment was considered too mild; neither were subjects with more than two positive outcomes on STEP or a score below 25 on the MMSE, or both, as they were considered to fulfil criteria for dementia.

Of the 190 subjects included in the study, 112 fulfilled the criteria for a clinical diagnosis of MCI, and thus the data presented are based on those.

The healthy controls were mainly recruited from senior citizen organisations and through information meetings on dementia. A few controls were spouses of subjects in the study.

Inclusion criteria for controls were that they should be physically and mentally healthy and not experiencing or exhibiting any cognitive impairment. All controls were thoroughly interviewed about their somatic and mental health by a research nurse before inclusion in the study.

Parts of the data and the test battery have been presented before as a poster at the 31st Annual Meeting of the International Neuropsychological Society in Honolulu, Hawaii, February 2003.[26]

Neuropsychological assessment instruments

Following recommendations by the American Academy of Neurology (AAN),[27] our neuropsychological examination comprised *speed and attention*, *learning and episodic memory*, *visuospatial*, *language*, and *executive functions*. Within each cognitive domain several aspects of function were assessed in order to obtain as complete a picture as possible of the cognitive status of the subjects.

Speed and attention

The digit symbol test from Wechsler's adult intelligence scale–revised (WAIS-R)[28] and trail making A and B[29] are some of the most frequently used tests for assessing speed and attention. ''Digit span''[28] is a test of attention span.

Table 1 Means and significance levels for the test battery

Test	Controls	MCI	*t*	p Value	Adj p value	η^2
Speed and attention						
Digit symbol	47.7 (10.2), n=35	39.1 (11.1), n=112	4.07	0.0004	0.003	0.10
Trail making A	37.3 (12.5), n=35	46.7 (18.2), n=112	3.42	0.001	0.004	0.07
Trail making B	86.9 (28.1), n=35	115.0 (57.7), n=111	2.83	0.005	0.050	0.05
Digit span	13.7 (3.1), n=35	13.0 (3.3), n=112	1.14	NS	NS	
Memory and learning						
RAVLT delayed recall	9.1 (3.1), n=35	6.6 (3.9), n=112	3.43	0.0008	0.004	0.12
Logical memory delayed recall	23.2 (5.4), n=25	17.9 (8.8), n=70	3.50	0.001	0.005	0.15
Rey complex figure delayed recall	15.4 (5.8), n=35	12.3 (7.7), n=112	2.56	0.013	NS	
Face recognition	28.2 (2.1), n=35	27.7 (2.5), n=111	0.99	NS	NS	
Visuospatial function						
VOSP silhouettes	22.1 (3.1), n=35	19.1 (4.5), n=112	3.58	0.0004	0.003	0.08
Rey complex figure copy	32.1 (3.1), n=35	29.8 (5.4), n=112	2.31	0.022	NS	
Block design	28.4 (7.1), n=35	26.8 (8.9), n=112	0.97	NS	NS	
Language						
Token test	20.7 (1.3), n=35	18.6 (3.2), n=110	4.73	0.0004	0.003	0.20
ASLD repetition	22.1 (4.3), n=31	17.3 (6.9), n=86	4.48	0.0004	0.003	0.19
Boston naming test	55.2 (2.8), n=35	51.6 (6.0), n=109	4.20	0.0004	0.003	0.17
Similarities	21.7 (2.9), n=35	19.9 (4.5), n=112	2.13	0.035	NS	
FAS word fluency	46.3 (14.0), n=35	39.3 (13.3), n=112	2.69	0.008	NS	
Executive function						
PaSMO	65.8 (25.0), n=33	88.8 (41.7), n=109	3.58	0.0004	0.003	0.08
Dual task my	92.0 (10.1), n=35	89.8 (12.6), n=100	0.82	NS	NS	
WCST-CV64 correct	42.6 (10.2), n=26	37.5 (13.6), n=63	1.47	NS	NS	
Stroop	26.1 (7.1), n=24	33.8 (10.9), n=45	2.30	0.025	NS	
Picture word test	95.7 (18.0), n=18	116.7 (31.9), n=67	3.06	0.003	0.005	0.10
Weighted average (PCA)	1.66 (2.15), n=35	−0.76 (3.11), n=112	4.88	0.0004		0.21

Values are mean (SD).
Adj, adjusted; ASLD, assessment of subtle language disorders; FAS, verbal fluency test (number of words beginning with F, A, S); MCI, mild cognitive impairment; PaSMO, parallel serial mental operations; PCA, principal components analysis; RAVLT, Rey auditory verbal learning rest; VOSP, visual object and space perception; WCST-CV, Wisconsin card sorting test – computer version.

Learning and episodic memory

The Rey auditory verbal learning test (RAVLT) is a well validated word recall test,[30] and Wechsler's logical memory test (WLM)[31] is a frequently used episodic memory test. The Rey complex figure (RCF) recall is used for examining several cognitive disorders.[32] ''Face recognition'' is a measure of non-verbal recognition.[33]

Visuospatial functions

The visual object and space perception (VOSP) silhouettes subtest has been used to distinguish mild Alzheimer's disease from normal aging.[34] The Rey complex figure copy test[32] is used for examining various different cognitive disorders and also as a dementia screening instrument.[34] ''Block design'' is a subtest of WAIS-R.[28]

Language

The token test, subtest V, is a test of syntax comprehension shown to be sensitive for mild Alzheimer's disease.[35] Assessment of subtle language disorders (ASLD) repetition is a test constructed to assess higher order language.[36] It consists of 10 sentences of increasing length which the subject is asked to repeat verbatim.[37] The Boston naming test[38] has been shown to be sensitive for both mild Alzheimer's disease and vascular dementia.[39] ''Similarities'' is another WAIS-R subtest, and is considered to assess verbal abstraction.[28] Word fluency FAS (the number of words initiated by the letters F, A, and S) is often used when assessing possible dementia.[40]

Executive functions

In parallel serial mental operations (PaSMO), the subject is asked to rattle off the alphabet, stating the number of the letter after each letter—that is, A-1-B-2-C-3...; a measure of mental control. The task is presented in Lezak (1995).[37] ''Dual task'' is a test of divided attention in which the subject is asked to draw crosses in boxes on a sheet of paper while simultaneously repeating series of digits.[41] The Wisconsin card sorting test (WCST) is a well documented executive test, and also employed when assessing dementia.[42] We used the computerised short version (-CV64). The Stroop test, Victoria version, is a short form of this executive test.[43] The picture word test (PWT) is a version of Stroop, with pictures with words written in them instead of coloured words.

Neuropsychological assessment procedure

The tests were administered in a standardised sequence and the testing was divided into two sessions of one to two hours. Verbal tests were varied with non-verbal in each session. The test sequence was also decided on the consideration of risk of contamination on the memory tests. Hence, no test with content that could affect performance on a memory test was administered between immediate and delayed recall. Six psychologists performed the testing and data collection. The test battery was slightly modified during the course of the study, which resulted in missing data on a few tests for some MCI subjects and controls.

Statistical analysis

Several variables were found to be skewed and were rescaled as appropriate to approximate normality before being entered in the statistical calculations. The data are presented as mean (SD) of the raw data. Group comparisons were made with the *t* test and the Mann–Whitney U test (SPSS). Corrections for multiple comparisons were made by the Bonferroni Holm method.[44] In order to illustrate the magnitude of the difference between controls and MCI, standardised *z* scores are presented for tests with significant differences between the groups.

As an index of effect size we report eta squared (η^2), which can vary between 0 and 1. When η^2 is more than 0.15, effects are ''large'' in magnitude, and when η^2 is more than 0.06 but less than 0.15 the effects are ''medium.''

Principal components analysis (PCA) was carried out using SIMCA-P 9.0 software.[45] The significance of the model was determined by cross validation—that is, by creating a model on the basis of part of the database and testing its validity on the remaining data. PCA offers a statistically meaningful summary of the constituent neuropsychological tests, and assigns a useful composite score to each subject which expresses the general level of neuropsychological performance.

RESULTS

Demographic data

Data from 112 consecutive MCI subjects and 35 healthy controls were analysed.

Controls were slightly older (67 (5.5) years) than MCI (64 (8.2) years) and had a greater proportion of women, though this was not significant. Controls also had a slightly higher mean MMSE score than MCI, at 29.3 (1.1) *v* 28.5 (1.5). There was no difference in years of education or general intellectual capacity, as assessed with Raven's coloured matrices[46] (controls, 32.0 (2.7); MCI, 31.6 (3.3)). Twenty MCI subjects had a CDR score of 0.0 and 92 a score of 0.5. Forty three subjects had a global deterioration scale (GDS)[47] score of 2 (= very mild cognitive impairment, minimal clinically objective evidence of cognitive decline) and 69 a score of 3 (= mild cognitive impairment, clinically objective evidence of cognitive decline).

Neuropsychological data

Table 1 shows that controls performed significantly better than the MCI group on 11 tests, after correction for multiple comparisons. Examination of the effect sizes for each of these 11 significant group differences showed that one (trail making B) was trivial. In all, then, 10 group differences with acceptable effect sizes were recorded (*z* scores in brackets). These tests were two tests of *speed and attention*: digit symbol (−0.85) and trail making A (−0.75); two tests of *memory and learning*: RAVLT (−0.80) and logical memory (−1.0) delayed

Table 2 Proportion of subjects with results 1.5 SD below controls

Cognitive domain	Proportion of MCI 1.5 SD below controls
Speed and attention	40.2%
Learning and memory	48.2%
Visuospatial function	42.0%
Language	57.1%
Executive function	52.7%

MCI, mild cognitive impairment.

Table 3 Classification according to mild cognitive impairment (MCI) criteria

Subgroup	Proportion of MCI
No impairment	17.0%
I – amnestic	1.8%
II – multiple domains impaired	64.2%
III – single non-memory domain impaired	17.0%

Table 4 Fifteen controls compared with 19 cases of mild cognitive impairment (MCI) with no impairment on the Mann–Whitney U test

Variable	Controls	No impairment	Mann–Whitney U test	p Value
Age (years)	60.4 (3.5), n=15	59.7 (7.2), n=19	100.5	NS
Education (years)	10.8 (2.6), n=15	14.5 (2.7), n=19	47.0	0.002
Raven's coloured matrices	32.0 (2.9), n=14	34.0 (2.1), n=17	68.0	0.040
Block design	28.9 (8.0), n=15	34.9 (8.5), n=19	75.0	0.034
Similarities	20.5 (3.0), n=15	23.6 (1.8), n=19	59.0	0.006

Values are mean (SD).

recall; one test of *visuospatial function*: VOSP silhouettes (−0.97); three *language* tests: token test (−1.62), Boston naming test (−1.29), and ASLD repetition (−1.11); and two tests of *executive function*: PaSMO (−0.95) and PWT (−1.17). However, on two executive tests (WCST-64 and Stroop), the number of subjects was considerably smaller than on the other tests, which could in part explain the lack of statistical significance, though there were differences in mean scores.

Principal component analysis on the results from the neuropsychological battery yielded one significant component accounting for 42% of the variance. All tests contributed to form this dimension, because the 95% confidence intervals for each variable's loading did not overlap with zero. Table 1 shows that the mean composite PCA scores of the MCI group were significantly lower than those observed for controls.

The tests that differentiated between MCI and controls covered all cognitive domains. In order to determine the distribution of impairment over the domains, we identified subjects with impairment on at least one test within each domain. We began our post-hoc analysis by setting a cut off at 1.5 standard deviations below the mean of controls for each test, to establish a level of ''impaired function for age and education,'' the proposed criteria for MCI.[17] The cognitive domains with the largest proportion of impairment were language and executive function, followed by learning and memory (table 2).

We further calculated the proportion impaired on one or more tests in just one domain, then in two, three, and four domains, and finally those with impairment in all five domains. We found that the subjects were evenly distributed, with approximately the same proportions in all five groups, 18.4% showing impairment in only one domain, and 16.1% in all five domains. We also found that a roughly equal proportion of subjects (17.0%) had no impairment with the present cut off.

As only 18.4% showed impairment in one domain, we examined the proportion of purely amnestic MCI. Every subject was classified according to subgroup, as shown in table 3.

Subgroup I turned out to be very small, consisting only of two subjects (1.8%). Seventeen per cent did not show any impairment compared with normal controls. The vast majority (81.2%) belonged to subgroups II and III; this indicates that most MCI subject were impaired in domains other than memory.

When the 17% ''no impairment'' were compared with 15 age matched controls, they were better educated and scored significantly higher on tests considered to measure general cognitive capacity, as seen in table 4.

DISCUSSION

Our objective was to determine which neuropsychological tests most clearly distinguish MCI subjects from normal controls. Of 21 tests, 10 tests, covering five cognitive domains, distinguished between the groups, which implies that the MCI group is heterogeneous. The MCI subjects showed a significant degree of impairment in all cognitive domains. Consequently, the traditional, purely amnestic MCI was very rare, constituting only 1.8%. Approximately one of six MCI subjects had no impairment when compared with normal controls. However, these subjects had higher education and performed significantly better on tests of general cognitive capacity.

The MCI group in our study was younger and scored higher on MMSE than MCI subjects in most comparable studies.[6 8 10 48–51] Nevertheless, they were significantly impaired on various cognitive tests—tests assessing very specific functions: spatial perception, language comprehension, naming, and episodic memory. Impairment on these tasks has been shown in several studies to be associated with Alzheimer's disease.[34 35 39] Impairment was also seen on tests of speed and attention and executive function, which are considered to be associated, though not specifically, with white matter changes and vascular dementia.[52] Of four WAIS-R subtests only digit symbol differentiated between the groups. On the other three (digit span, block design, and similarities) hardly any difference was seen. These results indicate that intelligence tests are not well suited for the detection of symptoms of MCI; measuring IQ seems of less interest than examining the specific functions typically impaired in dementia—a conclusion that is in agreement with previous reports.[6 53]

At first glance, the proportion of impairment in each cognitive domain may appear to be simply related to the number of tests. However, when only those tests which significantly distinguished between controls and MCI are taken into account, there is no such relation. Thus our data illustrate the heterogeneity of MCI—the high frequency of cognitive impairments other than memory. From our data, MCI does not typically manifest episodic memory impairment alone. Our neuropsychological examination was very extensive, which could in part explain why our results differ from those of other studies on MCI. There are, however, some previous studies[16 54] which found that few subjects with MCI had memory loss as the sole feature.

One of six MCI subjects (17%) did not show any impairment when the cut off point was set 1.5 standard deviations below the mean of controls. We need to consider possible explanations for this. Table 4 shows that this group had more education and outperformed controls on measures of general cognitive capacity. These results lead us to the ''cognitive reserve''[55] hypothesis. This argues that individuals with high IQs and superior education run a lower risk of being affected by dementia, as they have a cognitive reserve capacity and are able to compensate effectively for cognitive loss in the preliminary stages of dementia. This hypothesis is in agreement with our clinical impression. Although they had deteriorated subjectively and anamnestically, these subjects showed no marked deficits when tested, even though they performed well below their general capacity on some tests. These findings raise the question, already posed by others,[56] of whether MCI criteria should be based only on age means,

or whether an individual assessment of premorbid capacity should be done. We see this as a very important issue to address in the near future.

Another possible explanation for the ''no impairment'' group could be the poor ecological validity of many neuropsychological tests. In our experience, this is a particular problem where memory testing is concerned. Some MCI subjects showed pronounced memory problems in their day to day lives but had no deficits when tested. One possible explanation for this is that the problems the subjects experienced primarily were of prospective memory capacity[57] and consequently were not identified with episodic memory tests.

A third possible explanation is that some subjects experienced cognitive impairment because of stress or other psychosocial causes.

In published reports there is no agreement over what each individual test measures—for example, what test should be classified under which cognitive domain. Thus objections could be raised to our definitions of tests and cognitive domains, and in the end to our conclusions. We have, however, to the best of our ability searched the literature and chosen the descriptions, definitions, and concepts that best meet our clinical experience. Digit span, for example, is labelled both as a memory test[9 10] and an attention test.[8 37]. The ASLD repetition test is also described both as a memory test[37] and as a language test.[36] Our decision to label neither as a memory test was based on our clinical experience. Also, the overall picture would not change even if we had labelled both as memory tests—the pure memory loss group would still have been very small, consisting of five subjects (4.5%).

In relation to the increasing costs of dementia disorders, and possible treatment options for MCI on their way, the urge for more exact and reliable diagnostic procedures for these disorders is obvious. Others[58] have already raised the issue of the present MCI criteria, and called for more precise guidelines as to what neuropsychological instruments should be used when assessing different subtypes of MCI. The tests in our neuropsychological battery that most clearly distinguished between normal controls and MCI subjects are tests associated with both Alzheimer's disease and vascular dementia symptoms. Hence we believe that those tests make a clinically useful contribution in the detection of MCI in the broader sense of the concept.

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