

# Neuropsychological Profiles of Elderly Chinese People with Amnestic and Multiple-domain Mild Cognitive Impairment

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## Abstract

**Objective:** To compare profiles of neuropsychological impairment in elderly Chinese patients with amnestic, multiple-domain mild cognitive impairment and patients with normal ageing and mild Alzheimer's disease.

**Patients and Methods:** Patients with mild cognitive impairment were categorised into 2 groups: single-domain amnestic mild cognitive impairment ( $n = 54$ ) and multiple-domain amnestic mild cognitive impairment ( $n = 93$ ). The scores of neuropsychological tests of patients with mild cognitive impairment were compared with those of cognitively normal elderly controls ( $n = 78$ ) and patients with mild Alzheimer's disease ( $n = 85$ ).

**Results:** The 2 groups of patients with mild cognitive impairment had performances in the neuropsychological tests intermediate between the normal controls and patients with mild Alzheimer's disease. Patients in the multiple-domain amnestic mild cognitive impairment group had different profiles of cognitive impairment from those in the single-domain amnestic mild cognitive impairment group, but there was no significant difference in tests on episodic memory and category verbal fluency between the 2 groups.

**Conclusion:** Patients with mild cognitive impairment could be differentiated from cognitively normal controls, as well as from those with mild Alzheimer's disease, by neuropsychological measures.

*Key words:* Alzheimer disease, Cognition

## Introduction

Recently, the concept of mild cognitive impairment (MCI) has become increasingly popular. MCI is defined by subjective complaints of defective memory, abnormal memory functioning for age, normal performance of the activities of daily living, normal general cognitive functioning, and the absence of dementia.<sup>1</sup> The results of longitudinal studies on patients with MCI suggest that they 'convert' to Alzheimer's disease (AD) at a rate of 10% to 15% per year, whereas the conversion rate is 1% to 2% per year for the general elderly population.<sup>1</sup> This transitional state may be one of the optimum stages at which high-risk individuals can be identified for early intervention or preventive treatment. While there

is good agreement for the concept of MCI, there is considerable variability concerning the validity of MCI as a cohesive clinical entity, the applicability of the research-based concept in clinical practice, the homogeneity of cognitive deficits in MCI, and the prognosis.<sup>1,2</sup> Although researchers have focused on patients with MCI with relatively isolated memory deficits, increasing numbers of studies have shown that performance in cognitive domains other than memory may not be entirely normal.<sup>3-5</sup> Indeed, current studies suggest that there are 2 forms of MCI, one with predominant impairment of memory and the other with a wider range of cognitive impairments.<sup>1</sup> Population studies have shown that the patients with predominant memory impairment constitute a relatively small group compared with all individuals with a much broader form of mild cognitive deficit.<sup>6,7</sup>

Although the MCI syndrome is based on a neuropsychological pattern of impaired and non-impaired functions, there are still some discrepancies over how to classify these patients. The criteria for MCI subtypes proposed by Petersen do not specify the particular neuropsychological tests and their associated cut-off scores for case definition.<sup>1</sup> Detailed neuropsychological data can identify individuals experiencing mild or even unrecognised cognitive impairment in the primary care setting who are at a greater risk for developing AD. However, excessive reliance on neuropsychological data in the absence of the judgement of clinicians can lead to

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exaggerated inclusion of patients into the MCI cohort, and therefore affect the stability of the diagnosis and the reliability of the progression of the patients over time.<sup>8</sup>

In this study, the subscale of the Clinical Dementia Rating (CDR) was used to define single-domain and multiple-domain MCI in patients satisfying the criteria for questionable dementia. This operational criterion was chosen as it is more ecologically valid than batteries of neuropsychological tests for community-dwelling elderly patients who have a generally low level of literacy. Moreover, the collateral source-based clinical assessment has been proven to be sensitive to even mild interference in an individual's cognitive and functional capacity and it has been recommended for diagnosing MCI.<sup>1,3</sup> In Hong Kong, there has been a paucity of studies concerning clinical characterisation of elderly patients with different MCI subtypes. The aim of this study was to describe the pattern of neuropsychological deficits in patients with MCI by comparison with patients with mild AD and normal elderly people. Another aim was to test the applicability of the operational criteria of defining MCI subtypes based on the CDR in the community setting.

## Patients and Methods

### Patients

Patients were recruited from the local social centres and hostels for the elderly in Hong Kong between 2003 and 2005. All patients were active and ambulatory individuals who responded to poster announcements about research on cognitive functioning in elderly people placed in the social centres and residential homes. All patients were 60 years or older, and formal or informal caregivers were available to provide collateral information. The exclusion criteria included past history of a major psychiatric disorder apart from unipolar depression, evidence of degenerative neurological disorder, substance or alcohol abuse, regular use of psychotropic drugs or hospital admission 1 month before the study, and electroconvulsive treatment in the previous year. History of unipolar depression was not excluded because there is increasing evidence suggesting that late-life depression could be the prodromal phase of dementia. Those patients with significant depressive mood considered to affect functioning and motivation for assessment were excluded. Excluded patients included those with AD and a score of  $\geq 7$  for the Cornell Scale for Depression in Dementia, and the controls and patients with MCI with a diagnosis of major depressive episode according to the *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria. Patients with minor depressive symptoms that were not considered by the psychiatrists to have significantly affected the assessments were not excluded. The psychiatrists explained the procedure and obtained informed consent from the participants or their caregivers. This study was approved by the Joint CUHK-NTEC Clinical Research Ethics Committee of the Chinese University of Hong Kong.

Each patient was evaluated by a qualified psychiatrist to establish eligibility for inclusion in the study, a clinical

diagnosis, and an assessment of clinical staging using the CDR.<sup>9,10</sup> Patients with a global CDR score of 0 were recruited as cognitively normal controls (CDR 0 group). Patients with a global CDR score of 0.5, a score of at least 0.5 in the memory domain of CDR, and performance of at least 1 standard deviation [SD] below the mean of 10-minute delayed recall test of the age-matched cognitively healthy controls were recruited as the amnesic MCI group. The amnesic MCI group was further categorised into 2 groups: the amnesic single-domain MCI group (a-MCI) with impairment in memory subscale of the CDR only and the amnesic multiple-domain MCI group (md-MCI) with impairment in memory and one or more of the remaining domains of the CDR. Patients who met the National Institute of Neurological and Communicative Disorder and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADDA) criteria for probable or possible AD<sup>11</sup> and who had a global CDR score of 1 were recruited as dementia controls (CDR 1 group). The neuropsychological assessments were performed by trained raters who were blinded to the diagnostic categories of the subjects.

### Assessment Instruments

The CDR is used to determine the presence or absence of dementia and to stage its severity. CDR measures cognitive function in 6 categories: memory, orientation, judgment and problem solving, performance in community affairs, home and hobbies, and personal care. The global CDR score is derived by synthesising ratings in each of the 6 categories where a CDR score of 0 indicates no dementia and a score of 0.5, 1, 2, or 3 corresponds to questionable, mild, moderate, or severe dementia, respectively.

Global cognitive assessment was estimated using the Cantonese version of the Mini-Mental State Examination (CMMSE)<sup>12</sup> and the Chinese version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog).<sup>13</sup> To test for episodic memory, patients were also examined using a 10-minute delayed recall of a word list from the ADAS-Cog. Digit span and visual span tests were carried out to test attention and working memory. The Category Verbal Fluency Test (CVFT) was performed as a test for executive function. In the CVFT, patients were asked to generate exemplars in the categories of animals, fruit, and vegetables within 1 minute. Combined scores were then computed.<sup>14</sup>

### Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software (Version 11; SPSS, Chicago, IL, USA). The demographic data that were of a continuous nature and normally distributed were analysed using analysis of variance with post hoc Tukey test. Cognitive measures and demographic data that were continuous in nature and were not normally distributed were analysed using the Kruskal-Wallis test. Post hoc pairwise group comparisons were analysed using the Mann-Whitney *U* test. The significance level was set at  $p < 0.05$  and the significance level was adjusted to  $p < 0.01$  when multiple

comparisons were required. The chi-squared statistic was used to compare the frequencies of the categorical demographic data. Spearman correlation analyses were performed to assess the association between demographic data and cognitive test scores.

## Results

### Demographic Characteristics

310 patients were enrolled in the study; 78 in the CDR 0 group, 54 in the a-MCI group, 93 in the md-MCI group, and 85 in the CDR 1 group. The patients were predominantly women (84.8%).

The demographic characteristics of the patients are summarised in Table 1. The CDR 1 group was significantly older and had a lower level of education than the other 3 groups. There were no significant differences in age and

level of education between the CDR 0 and a-MCI groups or between the 2 MCI groups. Gender was grossly matched in the CDR 0 and 2 MCI groups, but the CDR 1 group had a significantly higher female to male ratio than the other 3 groups.

### Neuropsychological Profiles

The neuropsychological characteristics of the different groups are shown in Tables 2 and 3. The CMMSE, ADAS-Cog, delayed recall test, and CVFT scores of the 2 MCI groups were intermediate between those of CDR 0 and CDR 1 groups, with statistically significant inter-group differences. The CDR 1 group had significantly worse performance in all neuropsychological tests than the other 3 groups, except that there was no significant difference in the constructional praxis items of ADAS-Cog when compared with the md-MCI group.

Table 1. Demographic data and functional scores of the study participants.

	Clinical Dementia Rating 0 (n = 78)	Single-domain mild cognitive impairment (n = 54)	Multiple-domain mild cognitive impairment (n = 93)	Clinical Dementia Rating 1 (n = 85)	Differences between groups*
Age (years) [mean ± SD]	77.10 ± 5.12	79.28 ± 6.07	80.09 ± 6.52	84.45 ± 5.91	c, d, e, f < 0.05 <sup>†</sup>
Education (years) [mean ± SD]	4.15 ± 4.03	2.98 ± 3.96	2.08 ± 3.89	1.23 ± 3.35	c, d, e, f < 0.01 <sup>‡</sup>
Gender (%)					
Female	61 (78.2)	39 (72.2)	82 (88.2)	81 (95.3)	e, f < 0.01 <sup>§</sup>
Male	17 (21.8)	15 (27.8)	11 (11.8)	4 (4.7)	

Abbreviation: SD = standard deviation.

\* Comparisons: c = multiple-domain mild cognitive impairment vs Clinical Dementia Rating 1; d = Clinical Dementia Rating 0 vs multiple-domain mild cognitive impairment; e = single-domain mild cognitive impairment vs Clinical Dementia Rating 1; f = Clinical Dementia Rating 0 vs Clinical Dementia Rating 1.

<sup>†</sup> Analysis of variance and post hoc Tukey test.

<sup>‡</sup> Kruskal-Wallis and post-hoc Mann-Whitney U test.

<sup>§</sup> Chi-squared test.

Table 2. Neuropsychological test scores of the study participants.

	Clinical Dementia Rating 0		Single-domain mild cognitive impairment		Multiple-domain mild cognitive impairment		Clinical Dementia Rating 1		Differences between groups* (p < 0.01)
	Mean ± SD	Mean ± SD	z score	Mean ± SD	z score	Mean ± SD	z score		
Mini-Mental State Examination	27.23 ± 2.07	25.37 ± 3.04	-0.9	22.30 ± 3.05	-2.4 <sup>†</sup>	17.86 ± 3.16	-4.5 <sup>†</sup>	a, b, c, d, e, f	
Category Verbal Fluency Test score	37.80 ± 9.36	30.39 ± 8.00	-0.8	26.95 ± 7.26	-1.2 <sup>†</sup>	18.42 ± 6.50	-2.1 <sup>†</sup>	a, c, d, e, f	
Forward digit span	7.17 ± 1.54	7.15 ± 1.42	0	6.65 ± 1.34	-0.3	5.92 ± 1.46	-0.8	c, e, f	
Reverse digit span	3.05 ± 1.18	2.67 ± 1.15	-0.3	1.96 ± 1.13	-0.9	1.41 ± 1.28	-1.4 <sup>†</sup>	b, c, d, e, f	
Forward visual span	3.95 ± 0.97	3.77 ± 0.83	-0.2	3.43 ± 0.90	-0.5	2.99 ± 1.01	-1.0	c, d, e, f	
Reverse visual span	3.03 ± 0.90	2.83 ± 0.90	-0.2	2.14 ± 0.93	-1.0	1.65 ± 1.19	-1.5 <sup>†</sup>	b, c, d, e, f	

Abbreviation: SD = standard deviation.

\* Comparisons: a = Clinical Dementia Rating 0 vs single-domain mild cognitive impairment; b = single-domain mild cognitive impairment vs multiple-domain mild cognitive impairment; c = multiple-domain mild cognitive impairment vs Clinical Dementia Rating 1; d = Clinical Dementia Rating 0 vs multiple-domain mild cognitive impairment; e = single-domain mild cognitive impairment vs Clinical Dementia Rating 1; f = Clinical Dementia Rating 0 vs Clinical Dementia Rating 1.

<sup>†</sup> The absolute value of z score > 1, which represents the deviation from normal by more than 1 SD.

**Table 3. Alzheimer's Disease Assessment Scale-cognitive subscale scores of the study participants.**

	Clinical Dementia Rating 0	Single-domain mild cognitive impairment	z score	Multiple-domain mild cognitive impairment	z score	Clinical Dementia Rating 1	z score	Differences between groups* (p < 0.01)
	Mean ± SD	Mean ± SD		Mean ± SD		Mean ± SD		
Alzheimer's Disease Assessment Scale-cognitive subscale total	8.52 ± 3.84	13.99 ± 5.12	1.5 <sup>†</sup>	18.44 ± 6.65	2.6 <sup>†</sup>	27.13 ± 7.42	4.9 <sup>†</sup>	a, b, c, d, e, f
Alzheimer's Disease Assessment Scale-cognitive subscale word list immediate recall	3.87 ± 1.38	6.03 ± 1.24	1.6 <sup>†</sup>	6.32 ± 1.10	1.8 <sup>†</sup>	7.49 ± 1.09	2.6 <sup>†</sup>	a, c, d, e, f
Alzheimer's Disease Assessment Scale-cognitive subscale word list recognition	2.24 ± 1.91	3.42 ± 2.02	0.6	4.87 ± 3.00	1.4 <sup>†</sup>	7.23 ± 3.03	2.6 <sup>†</sup>	a, b, c, d, e, f
Alzheimer's Disease Assessment Scale-cognitive subscale word list delayed recall	6.27 ± 1.46	2.48 ± 1.49	-2.6 <sup>†</sup>	1.80 ± 1.52	-3.1 <sup>†</sup>	0.82 ± 1.29	-3.7 <sup>†</sup>	a, c, d, e, f
Naming objects and figures	0.23 ± 0.48	0.72 ± 0.81	1.0	0.73 ± 0.68	1.0	1.38 ± 0.74	2.4 <sup>†</sup>	a, c, d, e, f
Ideational praxis	0.12 ± 0.37	0.22 ± 0.46	0.3	0.48 ± 0.62	1.0	1.13 ± 0.97	2.8 <sup>†</sup>	b, c, d, e, f
Constructional praxis	0.69 ± 0.55	0.96 ± 0.93	0.5	1.39 ± 0.92	1.3 <sup>†</sup>	1.69 ± 1.02	1.8 <sup>†</sup>	b, d, e, f
Orientation	0.15 ± 0.46	0.76 ± 0.87	1.3 <sup>†</sup>	1.51 ± 1.45	3.0 <sup>†</sup>	2.75 ± 1.71	5.8 <sup>†</sup>	a, b, c, d, e, f
Remembering instructions	0.37 ± 0.49	0.70 ± 0.86	0.7	1.04 ± 1.09	1.4 <sup>†</sup>	1.66 ± 1.27	2.6 <sup>†</sup>	c, d, e, f
Following commands	0.63 ± 0.90	0.85 ± 0.94	0.3	1.45 ± 1.25	0.9	2.21 ± 1.37	1.8 <sup>†</sup>	b, c, d, e, f
Comprehension	0.13 ± 0.38	0.22 ± 0.50	0.2	0.39 ± 0.83	0.7	0.94 ± 1.20	2.1 <sup>†</sup>	c, e, f
Word finding	0.05 ± 0.28	0.07 ± 0.26	0	0.11 ± 0.34	0.2	0.33 ± 0.62	1.0	c, e, f
Spoken language	0.03 ± 0.23	0.02 ± 0.14	0	0.05 ± 0.23	0.1	0.29 ± 0.67	1.0	c, e, f

Abbreviation: SD = standard deviation.

\* Comparisons: a = Clinical Dementia Rating 0 vs single-domain mild cognitive impairment; b = single-domain mild cognitive impairment vs multiple-domain mild cognitive impairment; c = multiple-domain mild cognitive impairment vs Clinical Dementia Rating 1; d = Clinical Dementia Rating 0 vs multiple-domain mild cognitive impairment; e = single-domain mild cognitive impairment vs Clinical Dementia Rating 1; f = Clinical Dementia Rating 0 vs Clinical Dementia Rating 1.

<sup>†</sup> The absolute value of z score > 1, which represents the deviation from normal by more than 1 SD.

Patients in the a-MCI group performed on average 2.6 SD lower on the delayed recall test score, 1.6 SD higher on the error scores of word list immediate recall test, and 1.3 SD higher on the orientation items from the ADAS-Cog compared with the control group. Patients in the a-MCI group also had significantly worse performance in CVFT, word list recognition, and naming objects and figures items from the ADAS-Cog, but the deviation was ≤ 1 SD from normal.

Patients in the md-MCI group had worse performance than the control group in the CVFT, reverse digit span, forward and reverse visual span tests, and all the items of ADAS-Cog, except language ability. Compared with the control group, the largest decline from normal was observed for the delayed recall test (3.1 SD) and orientation items (3.0 SD). Beyond these tasks, impairment was also

seen on the word list immediate recall and recognition, constructional praxis items of ADAS-Cog and CVFT with deviation from normal by > 1 SD.

Patients in the a-MCI group had significantly better performance than those in the md-MCI group in global cognitive assessments (CMMSE and ADAS-Cog total scores). Patients in the md-MCI group gained significantly more error points than those in the a-MCI group in the word list recognition, ideational praxis, constructional praxis, and orientation items of the ADAS-Cog. Patients in the md-MCI group also had poorer performance in the reverse digit and visual span tests than those in the a-MCI group. However, there were no significant differences in the performance in the CVFT, word list immediate recall, and delayed recall tests between the 2 MCI groups.

**Table 4. Demographic correlates of neuropsychological test scores.**

	Clinical Dementia Rating 0	Single-domain mild cognitive impairment	Multiple-domain mild cognitive impairment	Clinical Dementia Rating 1
Education vs Chinese Mini-Mental State Examination score	NS	$r = 0.50$ $p < 0.001^*$	$r = 0.41$ $p < 0.001^*$	NS
Education vs forward digit span score	NS	$r = 0.40$ $p = 0.003^*$	NS	NS
Education vs reverse digit span score	NS	$r = 0.48$ $p < 0.001^*$	$r = 0.46$ $p < 0.001^*$	NS
Education vs forward visual span score	$r = 0.42$ $p < 0.001^*$	$r = 0.43$ $p = 0.001^*$	$r = 0.30$ $p = 0.005^*$	NS
Education vs reverse visual span score	$r = 0.35$ $p = 0.003^*$	$r = 0.47$ $p < 0.001^*$	$r = 0.35$ $p = 0.001^*$	$r = 0.30$ $p = 0.008^*$
Education vs Category Verbal Fluency Test score	NS	NS	NS	NS
Education vs Alzheimer's disease	$r = -0.35$	NS	$r = -0.53$	NS
Assessment Scale-cognitive subscale total score	$p = 0.003^*$		$p < 0.001^*$	
Education vs delayed recall test score	NS	NS	NS	NS
Age vs Chinese Mini-Mental State Examination score	NS	NS	NS	NS
Age vs forward digit span score	NS	NS	NS	NS
Age vs reverse digit span score	NS	NS	NS	NS
Age vs forward visual span score	NS	NS	NS	NS
Age vs reverse visual span score	NS	NS	NS	NS
Age vs Category Verbal Fluency Test score	NS	NS	$r = -0.32$ $p = 0.002^*$	NS
Age vs Alzheimer's Disease Assessment Scale-cognitive subscale total score	NS	NS	$r = 0.28$ $p = 0.007^*$	NS
Age vs delayed recall test score	NS	NS	NS	NS

Abbreviation: *NS* = not significant.

\* Statistical significance was set at  $p < 0.01$  in the subgroup correlation analyses.

Higher level of education was moderately associated with better performances in global cognitive assessment (MMSE and/or ADAS-Cog) and working memory assessment (digit and visual span) for patients with MCI and controls (Table 4). For patients with mild AD, higher level of education was only modestly associated with better performance in reverse visual span tests. Education was not associated with the performance in delayed recall test and CVFT in all groups. Age was modestly associated with the performance in ADAS-Cog ( $r = 0.28$ ,  $p = 0.007$ ) and CVFT ( $r = -0.32$ ,  $p = 0.002$ ) in the md-MCI group only. Gender was not associated with performances in neuropsychological tests in all groups.

## Discussion

It is known that MCI encompasses heterogeneous degrees of cognitive impairment. This study is the one of the few to

investigate the cognitive profiles in community-dwelling elderly Chinese people with amnesic MCI. The results confirm that patients with amnesic a-MCI have a different characterisation of cognitive deficits compared with those with amnesic md-MCI. Patients with these MCI subtypes can be distinguished from cognitively normal people and those with mild AD by global cognitive assessments, the delayed recall test, and the CVFT.

Similar to recruitment characteristics for MCI in the literature, these patients with a-MCI primarily had impairment in episodic memory, which was reflected in the immediate and delayed recall of the word list, while other cognitive domains were relatively intact. The other non-memory cognitive domains (CVFT and orientation) were not statistically normal but the impairments in these areas were not clinically significant. This finding is consistent with previous research by Royall et al who have shown that a significant portion of patients with MCI have comorbid executive

cognitive function.<sup>15</sup> As noted by other investigators, tests involving learning, attention, perceptual speed, category fluency, visuospatial ability, and executive function may be impaired in patients with MCI but these are far less prominent than the memory deficits.<sup>16-19</sup> Patients with md-MCI demonstrated mild impairment in multiple cognitive domains with predominantly memory impairment. They had impairment in visuospatial ability and working memory in addition to a more severe impairment in orientation compared with those with a-MCI. However, the degree of episodic memory impairment and category verbal fluency was similar in the 2 MCI groups. Thus, while they had memory deficits, the range of cognitive impairments suggests a more extensive pattern of cognitive deficits than would be expected in the a-MCI group.

These findings suggest that impairments in memory, orientation, and working memory are early signs of cognitive decline in elderly people with MCI. These cognitive deficits continue to deteriorate with increasing involvement of the non-memory domains such as attention and executive function. These authors propose that a-MCI and md-MCI are different stages in the cognitive spectrum spanning normal ageing to mild AD. Compared with results of the Alzheimer's Disease Cooperative Study,<sup>4</sup> the profile of cognitive impairments of these patients with md-MCI was similar to those with very mild AD (AD with CDR 0.5).<sup>4</sup> However, it was not possible to ascertain that these patients with md-MCI had mild AD in cross-sectional assessment and without neuropathological support. Prospective studies would be needed to detect the clinical course of this group of patients.

Higher education level was found to be associated with better performance in global cognitive and working memory tests in the control group and patients with MCI. The positive effect of education on performance in neuropsychological testing was less important in patients with AD. The lack of association between education and performance on the CVFT and delayed recall test in this study suggests that these 2 simple tests could be useful tools for screening MCI and early dementia in community-dwelling elderly people with different levels of literacy.

By studying cognitive profiles at different stages of cognitive decline, these results contribute new information towards a more comprehensive understanding of the development of the dementia process. The findings from this study are directly relevant to understanding the symptom profile and nosology of MCI. This could have a significant impact on the clinical characterisation of the MCI syndrome, inference about the aetiology, and possible clinical course of MCI. Large sample sizes and longer follow-up will be required to test the diagnostic validity of the clinical classification of MCI subtypes and its predictive ability for subsequent risk for dementia and the type of dementia.

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