Montreal Cognitive Assessment in Assessing Clinical Severity and White Matter Hyperintensity in Alzheimer's Disease with Normal Control Comparison

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Abstract-

Purpose: Use Taiwanese version of the Montreal Cognitive Assessment (MoCA) in evaluating patients in different stages of Alzheimer's disease (AD) and correlate with white matter change.

Methods: Ninety-seven normal controls (NC), 52 very-mild AD (clinical dementia rating [CDR] = 0.5), 48 mild AD (CDR = 1) and 38 moderate AD (CDR = 2) patients were enrolled for the MoCA, Mini-Mental State Examination (MMSE) and the Cognitive Assessment Screening Instrument (CASI). White matter hyperintensities (WMHs) on brain MRI were visually rated and classified as deep or periventricular WMHs.

Results: In NC group, education ($\beta = 0.326$, $p < 0.01$) but not age ($\beta = -0.183$, $p = 0.069$), was significantly related to MoCA score. However, while we added two points to the AD patients with less than 6 years education, the effects of education disappeared as compared with those of 7 years of education. For all educational levels, the cutoff value of MoCA for very-mild AD was 22/23 (sensitivity = 82.7%, specificity = 87.6%). No significant differences were found in the areas under the curves that differentiated NC from the patients with AD for MoCA and MMSE (differences = 0.008, $p = 0.490$), or for MoCA and CASI (differences = 0.023, $p = 0.082$). Total WMHs, frontal deep and periventricular WMHs were inversely correlated with the attention and delayed-recall subdomain.

Conclusion: The MoCA is a good clinical tool for screening very-mild stage AD if the educational effects are carefully considered. The correlation between the executive subdomains with the frontal WMHs also makes it a useful tool for detecting subtle WMHs.

Key words: Montreal Cognitive Assessment, Alzheimer's disease, white matter hyperintensities, Cognitive Ability Screening Instrument, Mini-Mental State Examination

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INTRODUCTION

The Montreal Cognitive Assessment (MoCA) is a cognitive battery for screening patients with early cognitive impairment which was validated in 2005 [1]. The MoCA is a rapid and sensitive tool for detecting mild cognitive impairment [1,2]. In contrast with the Mini-Mental State Examination (MMSE) [3], MoCA scores are adjusted to compensate for educational differences between subjects. In the initial study, the cutoff value between normal controls (NC) and mild cognitive impairment was 25/26 [1].

Several additional studies explored the utility of the MoCA for evaluating cognitive performance in patients with subcortical dementia arising from Parkinson's disease [4], Huntington's disease [5] and small vessel diseases [6]. The MoCA was more sensitive than the MMSE for detecting early cognitive deficits in patients with Parkinson's disease [7]. In addition, the MoCA was better than the MMSE for capturing memory, language, executive, and visuospatial deficits in Huntington's disease [5] with anatomical pathologies in the caudate nuclei and connected cortical regions. Furthermore, the functional capacity scale scores were also correlated more highly with MoCA scores than with MMSE scores [5]. Using an optimal cutoff of 21/22, the MoCA has been shown to help differentiate between controls and patients with small vessel diseases and lacunas and white matter damage [6].

Although pathological studies suggest that white matter hyperintensities (WMHs) may be ischemic in origin and are caused by consistent or variable hypoperfusion, there is emerging evidence that they may also reflect the vascular deposition of beta-amyloid, particularly when they are distributed in the posterior brain regions in patients with Alzheimer's disease (AD) [8]. Patients with AD manipulate information at a slower speed, implying the coexistence of subcortical dysregulation [9]. In recent studies focusing on AD patients, we determined that WMHs should not be dismissed as incidental findings, because there is a close inter-relationship with vascular risk factors [10] and poor cognitive performance [11].

Based on a literature review that usage of the MoCA is a sensitive screening battery for cortical and subcortical dementia [5-7], the aim of this study was to investigate whether that also applies to different staging of AD with variable WMHs. The optimal cutoff points for the MoCA in very-mild AD were determined and compared with the MMSE and cognitive assessment screen instrument (CASI) for their screening ability. The executive and non-executive subdomains derived from the MoCA were also calculated and correlated with the visually rated WMH score.

MATERIAL AND METHODS

Subjects

The Department of Neurology at Kaohsiung Chang Gung Memorial Hospital recruited 97 NC and 138 AD patients for this study. The clinical diagnosis of AD was based on the National Institute of Neurological and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), and the Diagnostic and Statistical Manual of Mental disorders, 4th edition (American Psychiatric Association, 1994) [12]. Each AD patient underwent an extensive medical examination during the initial visit, including a standard medical history, physical and neurologic examination, and a brain magnetic resonance imaging (MRI) scan. We defined patients with a clinical dementia rating (CDR) [13] score of 0.5 as very-mild AD, 1 as mild AD, and 2 as moderate AD.

The exclusion criteria included: (1) history of clinical stroke, (2) modified Hachinski ischemic score > 4; [14] (3) abnormal liver function test results (reference: aspartate aminotransferases < 40 and alanine aminotransferase < 56); and (4) low vitamin B12 levels (reference: 185 pg/ml).

The NC were come from our normative database during routine examinations. None of the NC had a history of neuropsychological disorders, and all had normal complete blood counts, electrolyte panels, renal function tests and liver function tests. The CASI scores for all NC were within the reference limit for Taiwan, [15] and all of the NC had a CDR score of zero. The Human Ethics

Committee of Chang Gung Memorial Hospital approved this study.

MoCA Taiwan version

The MoCA Taiwan version was downloaded from the website (www.mocatest.org) and administered according to the instructions of Nasreddine et al [1]. The MoCA assesses 7 subdomains: visuospatial/execution, naming, attention, language, abstraction, delayed-recall and orientation. The executive subdomains include visuospatial-execution, abstraction, attention and orientation, while the remaining 3 were categorized as non-executive subdomain in this study. One point was added for the subjects who had received 12 years or less of education. The MoCA Taiwan version differs from the English version in the following: (1) In the visuospatial test, English alphabet letters are substituted with 甲, 乙, 丙, and 丁, which are common serial words in Chinese. (2) In the attention test, English alphabet letters are substituted with numbers. (3) In the language test, the patients were instructed to generate the word within the semantic category of fruit instead of the phonemic category in the English version. Two additional batteries were administered at the same visit for comparison with the following orders: MMSE [2], MoCA and CASI [16].

Assessment of white matter changes

MRI was performed using a 3.0T scanner (Excite, GE Medical System, Milwaukee, WI) equipped with echo-planar capability. Axial fluid-attenuated inversion recovery (FLAIR) image sequences were as follows: 8000/100/2000/1[TR/TE/TI/NEX]; FOV, 240 mm; matrix, 320×256; and section thickness 5 mm.

The FLAIR sequences were rated visually for the presence of WMHs using the visual assessment scale developed by Ylikoski et al [17]. WMHs were classified as deep white matter hyperintensities (DWMHs) and periventricular white matter hyperintensities (PWMHs) in each of 4 areas (i.e., frontal horns, ventricular body, trigones and occipital horns [11]). Total DWMH and PWMH scores ranged from 0 to 24. The total WMH score was the sum of the DWMH and PWMH scores, and ranged from 0 to 48. One rater (Chang Y-T), who was blind to the clinical data, conducted all WMH scoring. In a sub-sample of 40 subjects from the study population, the intra-rater coefficient for WMH score ranged from 0.81 to 0.89.

Statistical analysis

The chi-square test was used to examine differences in categorical variables between groups. The Student's t test was used to examine gender effects in the MoCA, MMSE, and CASI, and to examine differences in the MoCA scores of patients with high and low WMH scores. For the purpose of analysis, patients with WMH scores above the mean were considered to have high scores, and those with scores below the mean were considered to have low scores. Linear regression analysis and one-way analysis of variance (ANOVA) with a post-hoc Tukey test were used to determine whether age and educational level contributed significantly to the variance in control MoCA scores, and to compare total and subdomain MoCA scores among patients with very mild, mild or moderate AD with the NC. Partial Pearson correlation analysis was used to examine the relationship between WMHs and the total and MoCA subdomain scores adjusted for the effects of age and education. We calculated the area under the curve (AUC) of the receiver-operator curves (ROC) as a measure of predictive value of the test (sensitivity, specificity, positive predictive values and negative predictive value were measured at threshold scores). Diagnostic accuracy was also assessed by calculating the sensitivity and specificity for the threshold that yielded the highest Youden index [Youden index = sensitivity - (1 - specificity)]. The biggest slope from the ROC curve was used to determine the cutoff values of the MoCA between the NC, and patients with very mild, mild and moderate dementia using either the original scoring system [1] or our educational adjustment system (for 0-6 years of education: +2 points to the raw score; 7-12 years of education: according to Nasreddine et al [1]). Statistical analysis was performed using the Statistical Package for Social Sciences (version 13 for Windows, SPSS Inc., Chicago, IL). Results were considered statistically significant if $p < 0.01$.

RESULTS

Demographic data of the study participants

The demographic data and cognitive test results of the participants are shown in Table 1. Among the 138 AD patients, 52 had CDR 0.5 (very-mild AD), 48 had CDR 1 (mild AD) and 38 had CDR 2 (moderate AD). The average age of the NCs was significantly lower than those with AD ($F = 33.420$, $p < 0.01$). In addition, there was a significant difference in age between the very-mild and moderate AD patients ($p = 0.03$). Significantly more NC had more than 12 years of education compared to the patients with AD ($F = 31.222$, $p < 0.01$), and significantly more males than females in the NC and moderate dementia group ($\chi^2 = 17.110$, $p < 0.01$). Not surprisingly, the patients with AD had significantly lower MMSE and MoCA total scores and subdomain scores than the NC (all $p < 0.01$). Patients with moderate dementia had significantly lower scores in the naming, attention and orientation subdomains as compared with the mild dementia group ($p < 0.01$).

Effect of gender, age and education on MoCA score

Because the age, gender and level of education were different between the NC and those with AD, we first examined the effect of these 3 demographic characteristics on MoCA score in the NC. There was no significant difference between males and females in the MoCA total scores (males, 25.9±3.0 vs. females, 25.2±3.7, $p = 0.34$). Both age ($r = -0.298$, $p < 0.01$) and educational level ($r = 0.395$, $p < 0.01$) were significantly correlated with MoCA total score. After entering both factors into the linear regression model, the effect of age disappeared ($\beta = -0.183$, $p = 0.069$), while the effect of educational level ($\beta = 0.326$, $p < 0.01$) was still present.

We therefore divided the NC into 3 educational groups: Group 1, 0-6 years of education; Group 2, 7-12 years; and Group 3, > 12 years. In MoCA total scores, there were significant group-group differences among the 3 educational groups ($F = 7.34$, $p < 0.01$). With the post hoc test, a significant difference was only found between group 1 and 2 ($p < 0.01$), but not between group 2 and 3 ($p = 0.583$).

Based on the above findings, a compensatory scoring system was created by adding one more point (i.e. +2 to the original raw score) to those with an educational level of less than 6 years, and comparisons made with those having an educational level of more than 6 years.

Table 1. Demographic data and the scores of normal controls and patients with Alzheimer's disease

	Normal control	Very mild dementia	Mild dementia	Moderate dementia
Clinical dementia rating (case numbers)	0 (n = 97)	0.5 (n = 52)	1 (n = 48)	2 (n = 38)
Age (years)	64.5 ± 8.2 (50-88)	72.6±8.6 (53-92) [a]	76.5±9.8(51-92) [a]	78 ± 8.3 (58-95) [ab]
Gender (male/female)	59/38	23/29 [a]	23/25 [a]	32/6 [bc]
Education (years)	10.9 ± 3.4 (0-19)	7.1±5.2(0-18) [a]	6.2±5.2(0-16) [a]	3.5 ± 4.0 (0-12) [abc]
Mini-Mental Status Examination (30)	28.1 ± 2.0 (19-30)	22.8±3.2(15-29) [a]	16.3±3.9(4-23) [ab]	9.1 ± 3.1 (3-16) [abc]
Cognitive assessment screening instrument (100)	92.7 ± 5.5 (71-100)	79±11.6(54-99) [a]	53.8±16.0(16-80) [ab]	25.2 ± 14.8 (1-63) [abc]
Montreal cognitive assessment	25.7 ± 3.3 (15-30)	17.3±5.1(7-29) [a]	9.1±3.7(2-18) [ab]	3.8 ± 2.1 (1-13) [abc]
Visuospatial-Executive (5)	4.1 ± 1.2 (2-5)	2.5±1.8(0-5) [a]	0.9±1.1(0-4) [ab]	0.3±0.7(0-3) [ab]
Naming (3)	2.7 ± 0.7 (0-3)	1.8±1.2(0-3) [a]	1.0±1.2(0-3) [ab]	0.2±0.5(0-2) [abc]
Attention (6)	5.5 ± 0.7 (2-6)	4.5±1.3(1-6) [a]	2.7±1.5(0-6) [ab]	1±0.8(0-3) [abc]
Language (3)	2.2 ± 0.8 (1-3)	1.1±1.0(0-3) [a]	0.5±0.7(0-3) [ab]	0.2±0.5(0-2) [ab]
Abstraction (2)	1.3 ± 0.6 (0-2)	0.6±0.8(0-3) [a]	0.3±0.4(0-1) [ab]	0.1±0.2(0-1) [ab]
Delayed- recall (5)	3.2 ± 1.6 (0-5)	0.9±1.4(0-5) [a]	0.1±0.4(0-2) [ab]	0.1±0.2(0-1) [ab]
Orientation (6)	5.8 ± 0.5 (4-6)	5.2±1.1(2-6) [a]	2.8±1.3(0-6) [ab]	1.1±0.8(0-3) [abc]

Values are expressed as mean±standard deviation (range); number in parentheses following the task name = the maximum possible score. Scoring of Montreal cognitive assessment according to Nasreddine *et al* [1]. [a] = $p < 0.01$ vs. controls. [b] = $p < 0.01$ vs. very mild dementia. [c] = $p < 0.01$ vs. mild dementia.

The statistical differences then disappeared (p = 0.252) between the two educational groups. A comparison in the NC between the two educational groups showed significant differences in the total scores, visuospatial/executive, naming, abstraction and orientation, while there was no difference in the attention, language, and delayed-recall scores (Table 2).

Comparison of NC and patients with AD divided by the two educational groups

Based on the educational effects found in the NC, the comparison of the NC and the patients with AD was based on the two educational groups (i.e. 0-6 years and > 6 years) using the original scoring system [1] (Table 2). There were significantly lower scores in the total and subdomain MoCA scores in those with advanced stage AD. The only exception was the abstraction score, which was not different between the mild and moderate dementia patients (p = 0.179).

Cutoff value of MoCA for detecting dementia severity

A summary of the MoCA cutoff scores for the two educational groups, as well as their respective sensitivity, specificity positive and negative predictive values, are listed in Table 3. For all educational levels, a cutoff

Table 2. Montreal cognitive assessment scores in normal controls (NCs) and Alzheimer's disease (AD) patients based on educational level

Education level (years)	0 - 6 (n = 104)				> 6 (n = 131)			
	NC (n = 16)	Very-mild (n = 30)	Mild (n = 26)	Moderate (n = 32)	NC (n = 81)	Very mild (n = 22)	Mild (n = 22)	Moderate (n = 6)
Total score (30)	23.1±3.8	14.9±4.3 [a]	7.5±3.5 [ab]	3.6±2.1 [abc]	26.2±2.9*	19.2±4.5 [a]	11.2±2.6 [ab]	4.7±2.2 [abc]
Visuospatial-Executive (5)	3.3±1.4	1.5±1.6 [a]	0.7±1.0 [a]	0.3±0.6 [ab]	4.3±1.1*	3.7±1.2	1.1±1.1 [ab]	0.5±0.8 [ab]
Naming (3)	2.2±1.0	1.3±1.2 [a]	0.4±0.7 [ab]	0.1±0.4 [ab]	2.8±0.6*	2.4±0.9	1.6±1.1 [ab]	0.7±0.8 [abc]
Attention (6)	5.2±1.1	4.0±1.3 [a]	2.1±1.5 [ab]	0.9±0.7 abc	5.6±0.9	4.9±1.2	3.3±1.5 [ab]	1.5±1.0 [abc]
Language (3)	1.9±0.9	1.1±1.0 [a]	0.4±0.8 [ab]	0.3±0.5 [ab]	2.3±0.8	1.2±1.1 [a]	0.5±0.7 [ab]	0±0 [ab]
Abstraction (2)	0.8±0.5	0.2±0.4 [a]	0.1±0.3 [a]	0.1±0.2 [a]	1.4±0.6*	0.8±0.7	0.4±0.5 [ab]	0±0 [ab]
Delayed- recall (5)	2.9±2.0	0.9±1.4 [a]	0.1±0.3 [ab]	0.1±0.2 [ab]	3.3±1.5	0.3±0.8 [a]	0.2±0.5 [a]	0±0 [a]
Orientation (6)	5.4±0.6	5.1±1.2	2.6±1.4 [ab]	1.0±0.8 [abc]	5.9±0.4*	5.1±1.3 [a]	3.2±1.0 [ab]	1.2±1.0 [abc]

Values are expressed as mean±standard deviation.

Number in parentheses following the task name = the maximum possible score

Scoring according to Nasreddine et al [1].

Very-mild AD indicated clinical dementia rating (CDR)=0.5, mild AD with CDR=1, moderate AD with CDR=2

* = $p < 0.01$ between 2 NC groups, a = $p < 0.01$ vs. educational matched controls, b = $p < 0.01$ vs. very-mild dementia, c = $p < 0.01$ vs. mild dementia.

Table 3. Cutoff value of the MoCA for very-mild Alzheimer's dementia

Group	Cutoff value	Sensitivity	Specificity	PPV	NPV
All educational levels	21/22	0.77	0.88	0.85	0.87
	22/23	0.83	0.88	0.81	0.89
	23/24	0.87	0.76	0.80	0.92
Education < 6 years	16/17	0.70	1.00	1.00	0.53
	17/18	0.80	0.94	1.00	0.64
	18/19	0.83	0.81	0.97	0.73
Education > 7 years	21/22	0.59	0.93	0.85	0.88
	22/23	0.64	0.93	0.79	0.90
	23/24	0.73	0.83	0.76	0.91

MoCA = Montreal Cognitive Assessment; PPV = positive predictive value ; NPV = negative predictive value

value of 22/23 achieved a higher specificity, whereas 23/24 was used for a higher sensitivity in detecting very-mild AD.

The ROC curves of the two educational group were further plotted for cutoff values of dementia severity. For those with 0-6 years of education, the optimal cutoff value of the MoCA between NC and those with very-mild dementia was 17/18 (sensitivity = 93.8%, specificity = 92.0%). There was significant difference between very mild, mild and moderate AD in the MoCA total scores (very mild, 14.9±4.3 [range of scores: 7-26]; mild, 7.5±3.5 [ranges: 2-18]; moderate, 3.6±2.1 [ranges: 1-11] , all $p < 0.01$).

For those with more than 6 years of education, the optimal cutoff value of the MoCA between NC and those with very-mild dementia was 22/23 (sensitivity = 92.6%, specificity = 84.0%). There was significant difference between very mild, mild and moderate AD in the MoCA total scores (very mild, 19.2±4.5 [range of scores: 12-29]; mild, 11.2±2.6 [ranges: 6-18]; moderate, 4.7±2.2 [ranges: 1-7], all $p < 0.01$).

Comparison of AUC in the MoCA, MMSE and CASI for screening dementia

ROC analysis was used to evaluate the potential of MoCA scores to discriminate between NC and patients with very-mild AD, as compared to the CASI and MMSE. The cutoff value between NC and those with very-mild AD was 26/27 for the MMSE (sensitivity = 94.2%, specificity = 83.5%), and 93.3/93.4 for the CASI (sensitivity = 86.5%; specificity = 57.7%). There was no significant difference between the AUC differentiating the NC from those with AD in the MoCA and MMSE (AUC differences=0.008, p=0.490), or for the MoCA and CASI (AUC differences=0.023, p=0.082; Figure 1).

Using the MoCA to assess the WMHs in the patients with AD

The total WMH score in those with very-mild dementia (10.2±8.4) was different from that of those with mild (14.1±8.1, p = 0.046) but not moderate (13.1 ±7.7, p = 0.56) dementia. The DWMH and PWMH scores in those with very-mild (DWMH 3.1±4.0; PWMH 7.1±5.1), mild (DWMH 3.1±4.0, p = 0.531; PWMH 10.0±5.4, p =0.016) and moderate AD (DWMH: 3.7±2.9, p = 0.447; PWMH: 9.4±5.3, p = 0.034) were calculated. The mean age was significant lower in very mild dementia than moderate dementia. After we controlled the age, we do correlation between three dementia groups with DWMH, DWMH and total WMH, there were no any significant correlation (all $p > 0.05$).

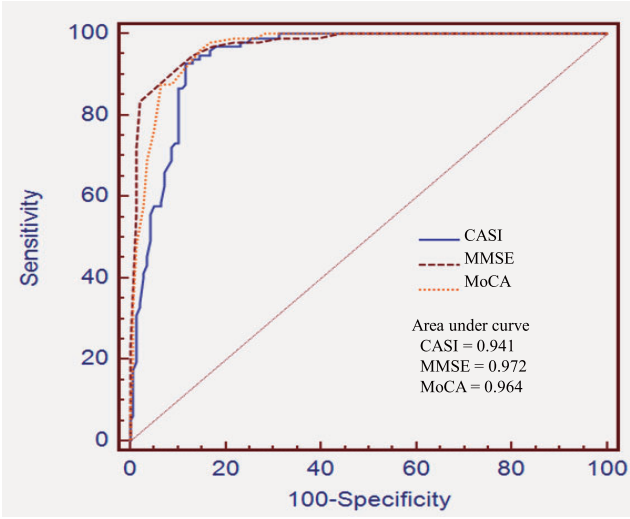

Figure 1. Receiver operating characteristic curves for the cognitive assessment screening instrument (CASI), Mini-Mental Status Examination (MMSE) and Montreal cognitive assessment (MoCA) for the detection of Alzheimer's disease.

We also determined the mean WMH scores (mean = 1.48), PWMH scores (mean = 1.51), and DWMH scores (mean = 1.43) and divided the patients into high or low WMH groups. For MoCA total score, there was no significant difference between patients with high and low WMH scores of any type (WMH: p = 0.094, PWMH: p = 0.224, DWMH: p = 0.060).

The unadjusted correlations between the executive and non-executive domains of the MoCA with WMH scores are presented in Table 4. The total number of WMHs, frontal DWMHs and PWMHs were inversely correlated with the attention and delayed-recall subdomains. After entering age and education serially into the linear regression model, there were only significance dif-

Table 4. Correlation of white matter hyperintensities to MoCA scores of 138 Alzheimer's disease patients

	MoCA executive subdomains					MoCA nonexecutive subdomains			
	Total score	Visuospatial-executive	Attention	Abstraction	Orientation	Total score	Naming	Language	Delayed recall
Total PWMHs	-0.196	-0.159	-0.219	-0.073	-0.114	-0.246*	--0.163	-0.180	-0.222*
Frontal horn	-0.245*	-0.211	-0.261*	-0.108	-0.142	-0.303*	-0.225	-0.139	-0.286*
Ventricular body	-0.170	-0.154	-0.187	-0.046	-0.121	-0.206	-0.116	-0.165	-0.176
Occipital horn	-0.096	-0.037	-0.130	-0.014	-0.014	-0.104	0.023	-0.130	-0.140
Trigone area	-0.067	-0.060	-0.073	-0.058	-0.047	-0.132	-0.210	-0.139	-0.048
Total DWMHs	-0.174	-0.098	-0.233*	-0.061	-0.052	-0.168	-0.114	-0.070	-0.179
Frontal horn	-0.291*	-0.123	-0.318*	-0.134	-0.179	-0.218	-0.172	-0.100	-0.223*
Ventricular body	-0.073	-0.085	-0.126	-0.046	0.025	-0.116	-0.082	-0.039	-0.092
Occipital horn	-0.001	0.000	-0.054	0.083	0.055	0.016	0.125	-0.013	-0.012
Trigone area	0.053	0.005	-0.007	0.038	0.096	-0.049	-0.101	0.007	-0.106
Total WMHs	-0.205	-0.148	-0.247*	-0.075	-0.098	-0.235*	-0.158	-0.149	-0.225*

Abbreviations: MoCA = Montreal cognitive assessment, SD = standard deviation, PWMHs = periventricular white matter hyperintensities, DWMHs = deep white matter hyperintensities. Total scores indicate summation of PWMH and DWMH scores. * = $p < 0.01$.

ferences in the frontal PWMHs (β= -0.264, p = 0.006) and DWMHs (β= -0.255, p = 0.009) for prediction of the executive subdomain of the MoCA.

DISCUSSION

Based on a hospital cohort, we explored the clinical value of the MoCA in assessing clinical severity and WMHs in patents with AD. There were four major findings. First, while age and educational level both conferred effects on the MoCA score, the influence was most strongly affected by educational level [18]. Even when adding a one point adjustment according to Nasreddine et al [1] to those with less than 12 years of education, the NC who had less than 6 years of education were still underestimated for their cognitive performances. As such, our findings suggest adding one more point (i.e. +2 to the raw score) to those having less than 6 years of education in order to compensate for the educational effects. Second, our findings suggest that that the MoCA has good sensitivity and specificity for discriminating NC from very-mild dementia, and that it reflects different AD clinical severities. Third, the AUC of the MoCA for detecting very-mild dementia was similar to that of the MMSE or CASI. Lastly, while the WMHs were different in those with very-mild, mild or moderate AD, the executive subdomains of the MoCA were correlated with frontal PWMHs and DWMHs after adjusting for the effects of age and education.

In the original MoCA scoring system [1], a one-point adjustment was made to the scores of subjects with less than 12 years of education. The results from our NC suggest that this adjustment is only effective for those with 7 to 12 years of education, as the MoCA total score was not different from those with more than 12 years of education. However, this system did not adequately adjust the scores of the NC with 0-6 years of education, as their adjusted scores were still significantly lower than those with 7 or more years of education. Most validation studies of the MoCA [1,18] indicate education, but not age or gender, is the only factor that influences MoCA performance which is the rationale for the original one-point correction [1,18]. However, most subjects enrolled into validation studies [1,18] were part of highly educated populations with a mean educational level of 12 years. Recently, one normative population based study [19] pointed out that even with the educational adjustments, the majority (62%) of participants still scored below the

published cutoff point (i.e. 26). This is also true from studies in Chinese [20], English [21] and Portuguese [22] speaking populations.

Our study indicates that a MoCA cutoff value of 22/23 is optimal for detecting very-mild AD patients. Taking the effect of education into consideration, the MoCA could still differentiate patients with very-mild AD from the NC with fair sensitivity and specificity. Studies from Beijing [23], Hong Kong [6], Japan [24], Korea [25] and Taiwan [20] have published the normative Asian data. While the educational levels and the optimal cutoff values from Japanese [24] (mean = 12.1, SD = 3.0; 24/25) for AD and Beijing [23] (male mean = 13.7, female = 11.4; 26/27) for mild cognitive impairment populations were more similar to the original Western study [23,24] in the educational level and cutoff values, the educational levels and the optimal cutoff values from the Korean [25] (mean = 7.9, SD = 3.7; 19/20) and Taiwanese study [20] (mean = 8.4, SD = 4.9; 21/22) were closer to our study. Cross-cultural analysis [4,6,7,22-26] suggests that although factors such as educational level, age and regional differences are all important, the average educational level appears to be most critical.

One previous Taiwan study [20] indicated that frontal and memory subdomains declined first in MoCA subdomains and followed by language and visual-spatial. Compared with our results, one American study [27] investigated the relationship between the seven subdomains of the MoCA and found that orientation, language and Visuospatial/Executive is a relatively good discriminator for patients with cognitive impairment but the naming and delayed recall score was not correlated with cognitive impairment. They thought animal picture naming is poor discriminator because of a ceiling effect (the item is 'too easy'), and 5-word recall is a poor discriminator because of a floor effect (the item is 'too hard'). This may be related to the cultural differences between English speakers and Chinese speakers. The educational level also influenced the subdomain scores in our NC, and the visuospatial-executive, abstraction, orientation and naming subdomains were particularly involved. While the casual-relationship of education to the former three subdomains are not fully understood, we noticed that the animals (i.e., lion, rhinoceros, and camel) listed in the naming tests were more difficult for illiterate respondents than the common objects used in the MMSE test, as these animals are not native to Taiwan.

The MoCA was designed to screen patients who present with mild cognitive complaints and are within the normal range of the MMSE [1]. This was fully established in our AD patients as we found compatible AUC between the MoCA and MMSE or CASI. Three AD studies [1,24,25] explored the sensitivity, specificity, and correlations between the MMSE and MoCA, and found high correlations between them with similar sensitivities and specificities in screening AD. The previous studies [1,6,20,23-25] revealed the cutoff value in AD was lower than mild cognitive function impairment without investigated different severity of dementia. In our study, MoCA provide good discrimination in different dementia stage. As the MoCA requires less administration time than the CASI, the similar discriminatory power of these two measures means that the MoCA can effectively be used instead of the CASI in screening very mild AD. This could be considered the major strength of this psychometric battery if educational effects have been carefully considered.

Despite controversy, the MoCA has still been found to have better discriminative abilities compared with the MMSE in mild cognitive impairment [20], white matter disease [6] and Parkinson's disease [7]. While controlling for the effects of age and education, we found that the MoCA executive subdomains were associated with periventricular and deep frontal WMHs. This could be considered as another strength of the MoCA, as our previous studies [28] failed to find a correlation between the MMSE or CASI with WMHs in AD patients. This is consistent with a recent report in which the MoCA was found to be useful for detecting small vascular disease-related cognitive deficits [6]. However, as we did not find a difference in MoCA scores between the high and low WMH group, this may be due to the fact that AD is basically a gray matter disease and white matter load might only play a minor role in cognitive performance [29].

There are a few limitations to this study. First, it is a cross-sectional study based on a hospital cohort, and the

results of this study need to be corroborated by further community-based studies. Second, it is worthy pointing out that although significant, the correlation coefficients between the MoCA subdomains with the WMHs were not particularly high. The results should be interpreted with care and careful consideration of the regression model for the effects of age and education. Third, as the NC were significantly different from our AD patients in age and educational level, the cutoff value for very-mild AD should be based on two educational levels. However, as the comparison with the published literature was compatible, the cutoff value here is still highly valid.

In conclusion, although educational level is a well known and important determent for the MoCA, a careful interpretation of the scores is still necessary especially in those with an educational level below 6 years. We provided the optimal cutoff values based on the educational level to facilitate the screening of very-mild AD. Although the screening ability of the MoCA for AD was not superior to the MMSE or CASI, the relationship between the executive subdomains of the MoCA to frontal WMHs still suggests that it is a valuable tool for detecting the subcortical changes in AD.

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