Topic: Validation of a computerized Hong Kong – Vigilance and Memory Test (HK-VMT) to Detect Early Cognitive Impairment in Healthy Older Adults.

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Disclosure of Interest

The authors report no conflict of interest.

Ethics Approval

The study had obtained approvals from the Institutional Ethics Committees of The Chinese University of Hong Kong.

ABSTRACT

Objectives: Hong Kong – Vigilance and Memory Test (HK-VMT) is developed to distinguish early cognitive impairment in the pre-symptomatic phase from normal cognitive ageing in older adults. The objectives were to validate HK-VMT to differentiate mild cognitive impairment (MCI) and healthy control (HC), and to explore the cut-off scores for different educational levels.

Method: A total of 606 older adults underwent the HK-VMT and conventional cognitive tests. HK-VMT is a 15 minutes cognitive battery that assesses episodic memory, attention, and visuospatial ability. The HK-VMT total is the sum of accuracy of all subtests with a range of 0 to 40. Differences in socio-demographic and clinical characteristics between groups were explored. Receiver operating characteristic (ROC) analyses were used to compare HK-VMT and Cantonese Mini Mental State Examination (CMMSE). A sample of 50 participants repeated the HK-VMT in 1 month to evaluate test-retest reliability.

Results: ROC analysis of Area Under Curve (AUC) demonstrated that HK-VMT (AUC 0.793) was comparable to CMMSE (AUC 0.748) in differentiating MCI from HC in a matched sample. A cutoff at 21/22 was chosen yielding a sensitivity of 86.1% and a specificity of 75.3% for differentiating MCI and HC. Test-retest reliability of HK-VMT total was 0.71 ($p<.001$) in a month time.

Conclusion: HK-VMT has demonstrated satisfactory validity in detecting cognitive impairment with good test-retest reliability in local older adults. It also performed favourably in the highly educated group when compared to CMMSE.

Keywords: Computerized Neurocognitive Test, Dementia, Mild Cognitive Impairment, Early detection, Highly educated older adults

INTRODUCTION

People are living longer than ever, but they also spent more time with the disability of disease as they aged. Findings from the Global disease of burdens study 2016 indicated that the disability-adjusted life-years (DALYs) for non-communicable diseases (NCDs) is on the rise. In particular, DALYs for Alzheimer's Diseases (AD) and other dementia has increased 37% since 2006 (GBD 2016 DALYs and HALE Collaborators, 2017). It is believed that early identification of neurodegenerative disorders in old age could reduce the costs on healthcare and burdens on caregivers.

Evidence showed that neurodegenerative pathology begins more than a decade prior to onset of cognitive decline (Beason-Held et al., 2013). Theoretically, detecting cognitive deficits as early as in pre-symptomatic phase when early intervention or treatment could be most effective. However, early identification of cognitive impairment in pre-symptomatic phase is difficult. Conventional tests have long been criticized for their utility to detect subtle and early signs of cognitive impairment, as performance is often moderated by education and age (O'Bryant et al., 2008). They often suffer from ceiling effects that could mask early signs of cognitive impairment in healthy older adults. With better education opportunity and medical advances, it will be even more difficult to distinguish cognitive impairments from normal cognitive aging in the future. Furthermore, recent study reported a steeper decline and a higher morbidity in dementia progression in highly educated older adults (Ardila, Ostrosky-Solis, Rosselli, & Gomez, 2000). Therefore, there is rising need for a computerized cognitive test with good precision to capture early and subtle signs of cognitive impairment which would probably have been missed by conventional testing.

Currently, a number of computerized tests have been developed to screen cognitive impairments in older population, such as CANS-MCI, CANTAB, MCIS, Mindstreams, Cogstate, and CoCoSc (Dwolatzky et al., 2004; Tornatore, Hill, Laboff, & McGann, 2005; Trenkle, Shankle, & Azen, 2007; Troyer et al., 2014; Wong, Fong, Mok, Leung, & Tong, 2017). However, each has their limitations. For instance, delayed recall in episodic memory was not assessed in a web-based screening tools targeting middle-aged and older adults (Troyer et al., 2014), while response time was missing in another local computerized cognitive test (Wong et al., 2017). Most importantly, many of them are written in English, with some even require sign-up fee for non-validate assessment which can be expensive ("Cambridge Brain Sciences" ; "Lumosity Brain Games & Brain Training"). There is also a great variability in case definition that based on established criteria for mild cognitive impairment (MCI) in the Caucasian older population, target population, means of administration, and domains tested, which make comparisons on the capability of computerized cognitive tests difficult (Wild, Howieson, Webbe, Seelye, & Kaye, 2008). The selection of an appropriate cognitive test, thus, should consider brevity, domains tested, purpose of testing and language used (Wild et al., 2008).

To address the limitations, Hong Kong – Vigilance and Memory Test (HK-VMT) is a Chinese cognitive test battery that is developed to measure cognitive performance in healthy Chinese older adults in Hong Kong. It assesses episodic memory, attention, and visuospatial ability, that were known to have substantial decline in normal cognitive aging (Johnson, Storandt, Morris, & Galvin, 2009; Luo & Craik, 2008). Yet, it should be reminded that the development of HK-VMT is never meant to replace other cognitive tests that developed in Western countries. It isto provide an alternative to improve detection of cognitive impairments in healthy older adults, so to identify targets for early interventions specifically designed for the

Chinese older population. The study aimed at validating HK-VMT to differentiate MCI and HC in a local healthy older population, and to explore the optimal cut-off score for detecting cognitive impairment in different educational levels.

MATERIALS AND METHODS

Participants and Procedures

A total of 606 community dwelling older Chinese adults, 97 MCI and 509 HC, aged 60 years or above were recruited from March 2012 and November 2013 in elderly activity centers across Hong Kong. Case definition of MCI followed a combined clinical and cognitive criteria suitable for local older population (Lam et al., 2010). The criteria of amnestic MCI include: (1) presence of subjective memory complaints; (2) objective memory impairment in delayed recall score of 1.5 standard deviation (SD) below age and educational matched individuals with CDR 0; (3) relatively intact activities of daily living; and (4) absence of clinical dementia with a CDR of less than 1. Older adults possible non-amnestic MCI would also be recruited with the following criteria: (1) objective memory impairment in delayed recall score above -1.5 SD cut-off; (2) impaired global cognition or other cognitive function as indicated by 1.5 SD below adjusted age and educational cut-offs; (3) 2 or more domains other than memory in CDR larger than 0 (Morris, 1997).

They completed both the Hong Kong – Vigilance and Memory Test (HK-VMT) and selected conventional cognitive tests, including Cantonese version of the mini-mental state examination (CMMSE) , Category Verbal Fluency Test (CVFT), and 10 word list delayed recall extracting from the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) (H. F. Chiu et al., 1997; H. F. Chiu, Lee, H. C., Chung, W. S., & Kwong, P. K., 1994; Chu et al., 2000). Exclusion criteria were clinical dementia with a CDR rating larger than or equal to 1 (Morris, 1997), any conditions known to affect cognitive performance including but not limited to severe hearing and visual impairments, psychotic disorders and traumatic brain injury, and being institutionalized. CDR is a semi-structured interview used to quantify the severity of symptoms of dementia. It is used to assess cognitive functioning in 6 domains: i) memory, ii) orientation, iii) judgment and problem solving, iv) community affairs, v) home and hobbies, and vi) personal care. Each of these components is rated based on a 5-stage rating system: 0 = no cognitive impairment, 0.5 = very mild dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia. In addition to domain ratings, a global CDR rating results from a combination of all components assessed. Any suspected case of dementia would be discussed and referred to the team psychiatrist for diagnosis. Participants were explained the aim and the purpose of the study. They were also fully informed of the need to re-test in a month time. Informed consent was obtained before testing. No monetary incentives was given to participants in this study. Information regarding socio-demographic data, physical health status, and cognitive performance was collected. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. It is done in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975.

HK-VMT ran in the same fixed order for all participants. A well-trained researcher was present for facilitating test administration throughout the assessment. Practice trial was given to all participants before test initiation. Participants responded on a touch screen laptop directly. A performance report on score and reaction time was automatically generated by the program for each subtest. The average completion time of HK-VMT was 14.29+/-1.85 minutes. There was no significant difference in the completion time between MCI and HC groups (t=1.697, p=.090).

Hong Kong – Vigilance and Memory Test (HK-VMT)

The HK-VMT is a standalone Chinese computerized cognitive program installed on a touch screen computer. It comprised of three newly developed subtests, including 16-word list learning, attention tests, and delayed matching test. The subtests were administered in fixed order for all participants. Test order and outcome parameters for each subtest are presented in Table 1.

16 Word List Learning and free delayed recall

Sixteen words were presented to the participants over 3 acquisition trials. Then, without additional presentation, participants were asked to free recall the sixteen words after 10-minute delayed interval. It measures average immediate free recall and 10 minutes delayed free recall. The sequence of word recall and number of incorrect responses were also recorded automatically.

Attention Tests

This test comprises four blocks of 10 trials. In each trial, five arrows lined up horizontally in the middle of the screen with the target stimuli underscored (for example, → ← <u>→</u> → ←). Two response buttons (a left and a right arrow) were showed under the five stimuli. For the first block, participants were instructed to focus on the middle arrow and tap on the right arrow button continuously for ten times. For the second block, they were instructed to tap the left arrow button for ten times. For the third block, they were instructed to tap according the direction of the middle arrow (either right or left). For the last block, they were required to tap depending on the location and the direction of the underscored target stimuli (for example, →̲ ← → → ←.). The tests required visual scanning, hand-eye coordination, discrimination and giving responses.

Delayed matching test

Participants were instructed to memorize a 2D target object presented on screen. After 5-seconds delay, they were instructed to identify previous target object from four rotated or identical alternatives arranged randomly in a 2 by 2 grid format. The test required mental rotation, working memory, discrimination and making choices.

Other covariates

Physical burden was evaluated using the Cumulative Illness Rating Scale (CIRS) (Parmelee, Thuras, Katz, & Lawton, 1995). Medical diseases are categorized according to major bodily systems: (1) cardiovascular; (2) respiratory; (3) gastrointestinal; (4) genitourinary; (5) musculoskeletal-integumentary; (6) neuropsychiatric illness; and (7) endocrine systems. Illness burden for each system is rated according to a scoring scheme from 0 to 4: 0=No impairment to organs/system; 1=Mild impairment (No interference normal activity; treatment required; prognosis excellent); 2=Moderate impairment (Interference normal activity; treatment required; prognosis good); 3=Severe impairment (Disability; urgent treatment required; prognosis guarded); 4=Extremely severe impairment (Life threatening; treatment is emergent or of no avail; grave prognosis). The total score is the sum of all bodily system scores ranging from 0 to 52. Higher score represents increasing severity of impairment and urgency of medical intervention. Other socio-demographics including age, years of completed education (i.e., years of school)[1], gender (Female/Male), marital status (Married/ Not married), and family history of dementia (Yes/No) were also obtained.

STATISTICAL ANALYSES

For all subtests, accuracy was calculated based on the proportion of number of corrected responses out of total responses [i.e., Accuracy = (No. of corrected responses ÷ total responses) x 10)]. For subtest involving processing speed, total response time was taken. Performance index (PI) was derived from accuracy divided by the total response time. A HK-VMT total score was the sum of accuracy of four subtests ranging from 0 to 40. In this study, high level of education referred to those with 7 or more years of completed education, while those with less than or equal to 6 years of education was categorized as having low level of education.

Between-group differences on sociodemographic and cognitive characteristics was determined by the use of independent sample t-test. One month test-retest reliability was estimated using the intra-class correlation coefficient (ICC) (Portney, 2000). Pearson correlation was performed on CMMSE and all computerized subtest scores to evaluate the concurrent validity. Receiver operating characteristics (ROC) was used to compare and evaluated the ability of CMMSE and HK-VMT to differentiate MCI from HC. All statistical analyses were conducted using IBM SPSS Statistics 22. The significance level was set to $p<0.05$.

RESULTS

A total of 606 older adults, including 97 MCI and 509 HC, completed both the HK-VMT and conventional cognitive tests. Sociodemographic and cognitive characteristics between MCI and

[1] I In Hong Kong, primary and secondary education each consists of 6 years.

HC were presented in Table 2. Individuals with MCI were significantly older, less educated and poorer in physical health than the HC group. They also performed significantly worse than HC group across all conventional cognitive tests.

Table 3 showed the logistic regression analysis assessed the influence of sociodemographic characteristics on the association between the HK-VMT score and diagnosis of MCI. After adjustment on differences in age, education, physical health and computer experience, binary logistic regression revealed an association between the HK-VMT score and the diagnosis of MCI (OR=0.670, p<.001, 95% CI=0.612-0.734). The non-adjusted odd ratios (OR=0.671, p<.001, 95% CI=0.622-0.725) is similar to the adjusted one, indicating no or small confounding effect from the sociodemographic characteristics on the HK-VMT score in differentiating MCI and HC.

Discriminant Validity of HK-VMT

Discriminant validity was established on a matched sample of 174 older adults extracted from the entire sample. The sub-sample consisted of 87 MCI and 87 HC matched on age, gender and educational level. There were no group differences in CIRS score (t=-1.61, p=0.109) and the proportion of individuals with computer experience is significant (x^2=4.38, p=0.036). CMMSE score (t=6.61, p<.001) and HK-VMT score (t=7.65, p<.001) were significantly lower in MCI than in HC.

The result of ROC analyses of the area under curve (AUC) for CMMSE and HK-VMT were presented in Table 4. Figure 1 displayed the AUC for CMMSE and HK-VMT of 0.748 and 0.793 respectively. Moderate correlations were observed between the HK-VMT and CMMSE (r=0.53, p<0.001). Table 5 displayed the linear regression that showed an association between HK-VMT score and CMMSE score with adjustment on age, education, physical health and computer experience (B=0.132, $p<.001$, 95% CI=0.101-0.164). Large effect size was observed for the HK-VMT total score with a Cohen's d value of 1.18.

Optimal cut-off for HK-VMT

Different cut-off points of HK-VMT was established for the entire sample as well as for different educational levels. On comparing different HK-VMT scores, a cutoff of 21/22 was chosen for the entire sample yielding a sensitivity of 86.1% and a specificity of 75.3% for differentiating MCI and HC. For individuals with less than 6 years of completed education, a HK-VMT score less than 22 yielded a sensitivity of 71.1% and a specificity of 87.3% for MCI. For those with more than 6 years of completed education, a HK-VMT score less than 25 yielded a sensitivity of 71.4% and a specificity of 76.5% for MCI.

Test-retest reliability of HK-VMT

Table 6 displayed the test-retest reliability of HK-VMT was evaluated in a sub-sample of 50 older adults selected from the HCs at an interval of one month. Moderate correlation in HK-VMT was observed between the two time-points ($r=0.71$, $p<.001$). The strongest correlation was observed in 16-word list learning. For sub-tests also measuring processing speed, moderate correlations were also observed in response time across the two time-points.

DISCUSSION

In this study, we first established the discriminant validity in a sub-sample that were matched on age, gender and education. Performance of HK-VMT was also assessed in individuals with low and high education. Optimal cut-off was then determined for the entire sample as well as for each educational subgroup. Overall results from this study indicated that HK-VMT is both valid and reliable in differentiating MCI and HC with a considerable effect size. Our ROC analyses showed that the AUC of HK-VMT in the matched sample in differentiating MCI was 0.793, and yielding a high sensitivity of 86.1% and a good specificity of 75.3% at a cut-off of 22 or less regardless of the educational level. When entire sample is considered, our results showed that HK-VMT has an AUC of 0.874 that is higher than that of CMMSE (AUC=0.818) and is comparable to that of "Mindstreams" (AUC=0.859). In addition, all individual outcome parameters in HK-VMT significantly discriminated MCI from HC. Moderate correlation was also found between CMMSE and HK-VMT demonstrating good concurrent validity. Regression results indicated that HK-VMT was significantly associated with the diagnosis of MCI and CMMSE score with socio-demographic differences and computer experience adjusted.

The test-retest reliability of 0.71 for the HK-VMT total provides evidence for stability over time, despite the reliability in some of the individual task pairs were relatively low. The test scores and response time were still correlated significantly in all parameters concerned. There was no abnormal deviation observed in all pairs between the two time-points. Additionally, an alternate form of word list learning test was used during re-test with good reliability of 0.81 and 0.79 in immediate recall and delayed recall respectively. This suggested that the use of an alternate form was also consistent in assessing verbal memory without learning effect from using same word list. Therefore, HK-VMT demonstrated an acceptable reliability with a one-month interval in this study.

Furthermore, the higher AUC of HK-VMT yielded in the highly educated group supports its use in older people with high level of education. In Hong Kong, the proportion of older adults with 6 or more years of completed education has increased 2.9% since 2011. For those aged 60 years or above, older adults with 6 or more years of completed education has increased 6.6%, while those with less than 6 years of completed education has declined 6.6% since 2011 (The Hong Kong Census and Statistics Department, 2016). The proportion of the highly educated older adults will continue to increase as the population aged. The HK-VMT is a timely development for screening cognitive impairment in this group.

When considering the performance of individual sub-tests, lower performance was observed in attention tests, which is consistent with previous findings using other standardized computerized cognitive tests (Dwolatzky et al., 2004). The AUC of attention accuracy parameters in HK-VMT was low relative to that of other sub-tests in HK-VMT. Ceiling effect with an accuracy over 95% was observed in attention tests. It is not surprising given that the test was administered to a healthy and highly educated sample containing 84% of HC. This limitation could be due to non-specificity or inadequacy of attention accuracy parameter as a measurement of cognitive impairments. In our attention tests, the accuracy parameter might only reflect the level of test difficulty. Therefore, we integrated accuracy and response time to a single performance index. It is believed that the performance index is a more stable and sensitive parameters than the use of either parameter alone, because the tradeoff between accuracy and response time is more capable in capturing inter-individual differences in a sample of high resemblance (Thorne, 2006). Future longitudinal study is needed to explore if changes in attention test over time might be better associated with cognitive impairments.

There are some limitations of the study. First, the study was limited by oversampling individuals with high level of education at 64%. In Hong Kong, older population with 6 years or more completed education constituted 40% of those aged 60 years or older (The Hong Kong Census and Statistics Department, 2016). The results could not be generalized to the general older population. Although validity of the test was established with a sample matched on age, gender and education, caution must be paid when interpreting scores from those with lower education due to convenient sampling in this study.

On the other hand, several strengths must be addressed. First, the validation procedure was carried out in a sample of MCI that matched with a HC based on age, gender and education. The two groups were not differed in their physical health and computer experiences. Second, unlike studies using loosely defined criteria for MCI cases, our case definition of MCI is in consensus with clinical definition of MCI used in the local older population. This provided a strong clinical foundation for future researches when looking for conversion rate of dementia in this sample. Third, given that HK-VMT has been administered in over 600 older adults aged 60 years or above without any difficulty in understanding test instruction reported, suggesting the interface is simple and easy to use. Besides, it has also demonstrated good usability as the completion time was not significantly differed between MCI and HC group. All these have demonstrated a potential feasibility of further development into a self-administered version.

CONCLUSION

The result suggested that HK-VMT is valid and reliable instrument for differentiating MCI and HC in healthy older population as well as in the highly educated group. It is helpful in detecting cognitive deficits that may be subtle in the early stage, and thus, to facilitate in designing interventions specifically for this group. Future studies are encourage to evaluate if HK-VMT was able to predict progress from MCI to dementia.

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Tables

Table 1 List of subtests in the HK-VMT and their outcome parameters.

Order	HK-VTM sub-tests	Cognitive Domains Tested	Outcome Parameters	
			*Accuracy (Range)	Response Time
1	16 word list learning	Episodic Memory	✓ (0-10)	
2	Attention tests	Attention	✓ (0-10)	✓
3	Delayed matching test	Visuospatial ability	✓ (0-10)	✓
4	10-mins delayed recall	Episodic Memory	✓ (0-10)	

* Accuracy = (Number of corrected responses ÷ Total responses) x 10

Table 2 Sample characteristics of mild cognitive impairment (MCI) and Healthy control (NC)

	All (N=606)	MCI (N=97)	HC (N=509)	t-test/x^2 test
Characteristics	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Age	69.5 (6.6)	73.4 (7.0)	68.8 (6.3)	<.001
Education years	9.2 (5.0)	6.2 (5.1)	9.8 (4.8)	<.001
CIRS	4.4 (2.6)	5.8 (3.0)	4.2 (2.4)	<.001
Female, %	53.3	45.4	54.8	0.087
Computer experience, %	41.1	16.5	45.8	<.001
CMMSE	28.3 (1.9)	26.0 (2.4)	28.7 (1.4)	<.001
CVFT	43.9 (9.8)	35.2 (8.2)	45.5 (9.2)	<.001
10 word list delayed recall	6.4 (1.9)	3.6. (1.5)	6.9 (1.5)	<.001

Table 3. Association (OR and 95% CI) in HK-VMT with the diagnosis of MCI in non-demented elderly people (N=606).

	Unadjusted Model				Adjusted Model			
			95% C.I. for EXP(B)				95% C.I. for EXP(B)	
	Sig.	Exp (B)	Lower	Upper	Sig.	Exp (B)	Lower	Upper
Age	-	-	-	-	0.531	0.986	0.943	1.030
Years of Education	-	-	-	-	0.782	0.991	0.931	1.055
CIRS Score	-	-	-	-	<.001	1.211	1.090	1.346
Computer Experience	-	-	-	-	0.987	1.006	0.481	2.106
HK-VMT Total	<.001	0.671	0.622	0.725	<.001	0.670	0.612	0.734

Table 4. Comparison of ROC analyses measuring the ability of HK-VMT and CMMSE to differentiate MCI and HC in a matched sample.

Cognitive Tests	MCI (N=87)		HC (N=87)		All (N=174)	
(Range)	Mean	SD	Mean	SD	AUC	p-value
CMMSE (0-30)	26.1	2.3	28.1	1.6	0.748	<.001
HK-VMT (0-40)	19.6	4.2	24.6	4.3	0.793	<.001

Note: SD = Standard deviation; AUC = Area under curve

Table 5. Linear regression on the association between HK-VMT and CMMSE with adjustment on age, education, physical health and computer experience.

			95% C.I. for B	
	Sig.	B	Lower	Upper
Age	0.710	-0.004	-0.026	0.018
Years of Education	<.001	0.123	0.095	0.151
CIRS Score	0.107	-0.042	-0.092	0.009
Computer Experience	0.635	0.000	-0.001	0.002
HK-VMT Total	<.001	0.132	0.101	0.164

Dependent variable: CMMSE

Table 6. Test-retest reliability of HK-VMT

	Test 1	Test 2	Paired t-test	
Cognitive tests	Mean (SD)	Mean (SD)	r	p-value
HK-VMT	25.2 (4.8)	26.5 (4.5)	0.71	<.001
16 word list learning				
Immediate recall, Acc	4.9 (1.4)	5.1 (1.3)	0.81	<.001
Delayed recall, Acc	4.6 (2.0)	4.9 (1.7)	0.79	<.001
Delayed matching				
Acc	6.0 (2.2)	6.6 (2.3)	0.30	0.04
RT, ms	31550.8 (19825.7)	29870.2 (17990.7)	0.72	<.001
PI	0.2 (0.1)	0.3 (0.2)	0.33	0.020
Attention				
Acc (0-10)	9.7 (0.4)	9.9 (0.1)	0.34	0.017
RT, ms	65161.3 (37495.6)	56900.4 (21054.5)	0.78	<.001
PI	3.1 (1.1)	3.1 (0.8)	0.81	<.001

Note: Acc = Accuracy; RT = Response time; ms = milliseconds; PI = Performance Index; SD = Standard deviation; ICC = Intra-class correlation

Figure 1. ROC curves for CMMSE and HK-VMT