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ORIGINAL RESEARCH

Neurocognitive Features of Mild Cognitive Impairment and Distress Symptoms in Older Adults Without Major Depression

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Background: Two distinct symptom dimensions were identified in older adults who did not have major depressive disorder (MDD): a) a dimension associated with mild cognitive dysfunction, and b) a dimension related to distress symptoms of old age (DSOA). It is uncertain whether previous findings regarding the features of amnestic mild cognitive impairment (aMCI) remain valid when patients with MDD are excluded.

Methods: To examine the neurocognitive features of aMCI (n = 61) versus controls (n=59) and the objective cognitive characteristics of DSOA in participants without MDD. Neurocognition was evaluated utilizing the Cambridge Neurological Test Automated Battery (CANTAB) and memory tests.

Results: This research demonstrated that CANTAB tests may differentiate between aMCI and controls. The One Touch Stockings of Cambridge, probability solved on first choice (OTS_PSFC), Rapid Visual Information Processing, A prime (RVP_ A´), and the Motor Screening Task, mean latency, were identified as the significant discriminatory CANTAB tests. 37.6% of the variance in the severity of aMCI was predicted by OTS_PSFC, RVP_ A´, word list recognition scores, and education years. Psychosocial stressors (adverse childhood experiences, negative life events), subjective feelings of cognitive impairment, and RVP, the probability of false alarm, account for 40.0% of the DSOA score.

Discussion: When MDD is ruled out, aMCI is linked to deficits in attention, executive functions, and memory. Psychosocial stressors did not have a statistically significant impact on aMCI or its severity. Enhanced false alarm response bias coupled with heightened psychological stress (including subjective perceptions of cognitive decline) may contribute to an increase in DSOA among older adults.

Keywords: depression, mild cognitive impairment, adverse childhood experiences, stress, anxiety

Introduction

The geriatric population worldwide is expanding at a rapid rate. By 2050, it is expected to reach 22% of the total population, which implies a considerable increase from the current 11%.[1] Older age often leads to health problems, including mild cognitive impairment (MCI), a condition characterized by a subjective feeling of cognitive impairment and mild deterioration in memory functions. Nevertheless, other cognitive abilities and activities of daily living (ADL) are essentially unaffected.[2] It is estimated that around 10–15% of people with MCI may eventually develop Alzheimer's

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disease (AD), a figure approximately ten times higher than that of those without MCI.[3,4] aMCI has been linked to a range of behavioral and psychological symptoms, such as tension, anxiety, depressed mood, and sleep disturbances.[5,6] Additional research has established an association between mood disorders and cognitive deterioration among the elderly; in particular, depression may impair neurocognitive functions.[7–9]

The utilization of neuropsychological assessments, such as the Cambridge Neurological Test Automated Battery (CANTAB) and the Consortium to Establish a Registry for Alzheimer's Disease, neuropsychological battery (CERAD), is critical in the evaluation of MCI and AD. Determining cognitive decline with computerized neuropsychological testing, such as the CANTAB, is a practical and precise endeavor.[10] Cognitive deficits can be accurately predicted using CANTAB tests, specifically the Paired Associates Learning (PAL) task.[11] The PAL test consistently exhibits high sensitivity and specificity when differentiating clinically defined MCI from age-matched healthy controls. The application of Spatial Working Memory (SWM) to evaluate patients with MCI is further substantiated by a prior cohort study.[12] In a recent meta-analysis, the utility of CERAD cognitive tests in the diagnosis of MCI was demonstrated.[13] The study provided evidence that the CERAD is a benchmark instrument for assessing MCI. Several studies have discovered that cognitive assessments, including Word List Memory (WLM), Verbal Fluency Test (VFT), and Word List Recall (WLR), exhibit adequate efficacy in identifying MCI versus healthy controls.[14]

However, two significant challenges arise when attempting to evaluate MCI or aMCI. First, it remains uncertain whether previous findings regarding the neurocognitive characteristics of MCI in older adults remain valid when patients with major depression are excluded. An illustration of this can be observed in studies that used CANTAB tests to evaluate depression.[15,16] Furthermore, Beats and Sahakian[17] found a significant correlation between the number of depressive episodes encountered by patients with depression and the response latency of different CANTAB tests. Therefore, it is plausible that depressive symptoms influence the neurocognitive characteristics of MCI, making these assessments challenging to interpret in MCI studies that did not exclude depressed patients.

Furthermore, it is possible that the existing diagnostic criteria for aMCI are excessively lenient.[18] The question of whether aMCI is a representative sample or whether some individuals classified as aMCI may be part of the normal control sample is the subject of an ongoing debate.[14,18] Tran-Chi and Maes[19] identified two distinct dimensions among older adults who did not present with major depression in this regard. A) The first dimension, distress symptoms of old age (DSOA), comprises indications of anxiety, tension, and neuroticism; it is associated with negative life events and adverse childhood experiences (ACEs).[19] Furthermore, the subjective perception of cognitive impairment, as measured by the first item of Petersen's criteria,[20] is associated with DSOA, whereas there are no associations with objective indicators of cognitive decline.

b) The second dimension is a quantitative MCI (qMCI) score that represents the severity of objective cognitive decline. We calculated this score by extracting the first principal component from the Montreal Cognitive Assessment (MoCA), the Mini Mental State Examination (MMSE), and the modified Clinical Dementia Rating (CDR) scales.[21] Cluster analysis[19] has demonstrated that the diagnostic criteria for aMCI, as proposed by,[20] are excessively inclusive. This is because the aMCI group includes patients with DSOA who report subjective signs of cognitive impairment. Indeed, by eliminating these DSOA subjects, we[20] acquired a more homogeneous cohort of patients presenting with aMCI, which we designate as mild cognitive dysfunction (mCoDy) to differentiate it from the broader MCI category.

Consequently, after excluding individuals with severe depression and DSOA, the purpose of this study is to examine the neurocognitive characteristics of aMCI as well as the objective cognitive characteristics of DSOA. The study's specific objectives are to identify the neurocognitive CANTAB characteristics of aMCI that are not associated with major depression or DSOA and to determine whether DSOA is accompanied by any impairments in the CERAD or CANTAB tests.

Materials and Methods

Participants

This study enlisted participants ranging in age from 60 to 75 years. The study included 61 aMCI cases, referred to the King Chulalongkorn Memorial Hospital in Thailand, and 59 healthy controls. The same catchment area, Bangkok, Thailand, enlisted both the aMCI and control groups. At King Chulalongkorn Memorial Hospital, subjects with aMCI

were recruited at the Geriatric Clinic, the Cognitive Fitness Center unit, the Geriatric Psychiatry clinic, and the Neuroscience Center. Senior Red Cross volunteers, Health Check-up Clinics, neighborhood senior organizations, and healthy elderly caregivers of patients with aMCI who visited the Dementia Clinic comprised the control group. Patients who were diagnosed with aMCI met the Petersen criteria as outlined by Petersen.[20] These criteria include: a) experiencing subjective memory complaints, b) objective memory loss as assessed with an adjusted total MoCAscore < 24.4 (mean of normal controls adjusted for age and education years minus 1.5 standard deviations), c) maintaining essentially intact daily living activities (ADL), d) having a Clinical Dementia Rating (CDR) of 0.5; (e) near-normal general cognitive functions, and f) not meeting the criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised. This study did not make a diagnosis of multiple domain or single domain aMCI.

Individuals who were diagnosed with neurological disorders such as Parkinson's disease, stroke, epilepsy, or multiple sclerosis were ineligible to take part in the study. Patients who were diagnosed with neuropsychiatric disorders were also excluded from the study, including chronic fatigue syndrome, substance use disorders, major depression, schizophrenia, bipolar disorder, generalized anxiety and post-traumatic stress disorder, obsessive-compulsive disorder, and autism spectrum disorders. Participants who had medical conditions such as cancer, chronic obstructive pulmonary disease, chronic kidney disease, metabolic syndrome, chronic inflammatory bowel disease, or HIV infection were also precluded from the study. Individuals who were unable to communicate or speak, had vision impairment or blindness (even with corrective lenses), had hearing loss, were unable to sit stably due to physical conditions such as low back pain or chronic pain, or were unable to stand or walk were not permitted to participate.

Approved by the Institutional Review Board committee of the Faculty of Medicine Chulalongkorn University and the ethical committee of King Chulalongkorn Memorial Hospital (886/64), written informed consent was obtained from all subjects prior to their participation in the study.

Study Design

This study utilized a case-control design including 59 controls and 61 aMCI participants. To determine the required sample size, a power analysis was conducted, considering an effect size of 0.3, alpha of 0.05, power of 0.80, two groups, and four covariates. This power analysis revealed that a sample size of 90 participants would be sufficient to conduct an ANCOVA at a power of 0.8. To increase the power of our analysis and to account for potential dropouts, we included 30 more subjects, resulting in a final study sample size of 120 participants. Based on machine learning techniques performed on the same study group,[19] we found two different clinical dimensions within the group of older adults and an alternative more restrictive diagnosis of aMCI, namely mCoDy.[19] Using principal component analysis (PCA) performed on neurocognitive and stress-affective symptoms, we discovered two independent dimensions, namely the distress symptom of old age (DSOA) dimension, and a quantitative MCI (qMCI) dimension. These dimensions are shown in the Electronic Supplementary File (ESF), Table 1. The former was constructed as the first PC extracted from 6 ratings scales, namely the Perceived Stress Scale (PSS),[22] the State-Trait Anxiety Inventory (STAI),[23,24] the Thai Geriatric Depression Scale (TGDS),[25] the depression (HADS-D) and anxiety (HADS-A) subscale of the Hospital Anxiety and Depression Scale,[26] and the neuroticism trait score of Five Factor Model standardized psychometric pool of items (IPIP-NEO).[27] The qMCI (quantitative MCI) score was conceptualized as the first PC extracted from the total scores on the Montreal Cognitive Assessment (MoCA)[28] and Mini-Mental State Examination (MMSE) score[29] in a Thai version (developed by the Thai Cognitive Test Development Committee, 2002), as well as the modified Clinical Dementia Rating (CDR) score.[19,21] In addition, cluster analysis revealed a restricted sample of subjects with cognitive dysfunctions because this technique removed subjects with DSOA dimension symptoms from the aMCI sample.[19] As such a more restrictive aMCI subgroup was constructed (labeled mCoDy, mild cognitive dysfunction). Consequently, in the present study, we will show the results obtained on aMCI (n=61) as well as the more restricted sample mCoDy (n=52).

Assessments

The Mini International Neuropsychiatric Interview (M.I.N.I).[30] was used to make axis-1 DSM diagnoses. All participants underwent neuropsychological testing including the MMSE, MoCA, and CDR. In addition, we used the Cambridge Automated Neuropsychological Assessment Battery (CANTAB).[31] The CANTAB tests have a proven sensitivity in detecting

changes in neuropsychological performance. In the current study, we assessed key CANTAB tests[31] that are relevant to aMCI namely, Delayed Match to Sample (DMS), Motor Screening Task (MOT), One Touch Stockings of Cambridge (OTS), Paired Associates Learning (PAL), Pattern Recognition Memory (PRM), Reaction Time Task (RTI), Rapid Visual Information Processing (RVP) and Spatial Working Memory (SWM). In addition, we assessed three tests of the CERAD[32] in a Thai translation,[33] namely the Verbal Fluency Test (VFT), Word List Memory (WLM) and Word List Recall (WLR).

We conducted a structured interview to collect demographic and clinical data, the IPIP-NEO in a Thai translation,[27] the HADS in a Thai validated translation,[26] the Thai versions of the State-Trait Anxiety Inventory (STAI),[24] and the Perceived Stress Scale (PSS),[22] and the validated in a Thai version of the TGDS by Poungvarin and Committee.[34] In addition, we used the Adverse Childhood Experiences (ACEs) Questionnaire[35] in a Thai validated translation[36] to assess five ACE dimensions, namely emotional, physical and sexual abuse, and emotional and physical neglect. We also employed the Negative Event (Hassle) Scale[37] to assess negative life events (NLEs). The ASSIST was employed to exclude subjects with substance use, either tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants (including ecstasy), inhalants, sedatives, hallucinogens, opioids, or other drug use.

Statistical Analysis

All statistical analyses are conducted using version 29 of IBM SPSS for Windows. We used analysis of variance (ANOVA) to investigate between-group differences in scale variables, and contingency table analyses (X^2-tests) to examine associations between nominal variables. Adjusting for extraneous variables such as age, sex, and years of education, we used analysis of covariance to determine the associations between CANTAB test scores and aMCI/mCoDy compared to normal controls. To determine the best CANTAB test scores predicting aMCI/mCoDy (controls as the reference group), we utilized binary logistic regression analysis. We have accounted for potential confounding variables such as age, gender, and education in these analyses. We estimated the effect size using B (standard error, SE), Wald statistics with p-values, the Odds ratio with 95% confidence intervals (CI), the confusion matrix, and Nagelkerke pseudo-R square that was used as effect size estimate. We have employed multiple regression analysis to delineate the most significant predictors (primarily the CANTAB or CERAD test scores) on the qMCI or DSOA scores. We utilized a manual multiple regression technique in conjunction with an automated, stepwise approach, with p-values of 0.05 to enter and p=0.06 to remove. We computed standardized beta coefficients with t-statistics and p values, and essential model statistics including F values, df, and p-values. The total variance explained (R^2) was calculated and used to estimate the magnitude of the effect. We assessed the variance inflation factor (VIF) and tolerance to check potential (multi)collinearity issues. The White and modified Breusch-Pagan tests were utilized to assess heteroskedasticity. All analyses were two-tailed, and an alpha level of 0.05 signified statistical significance.

In addition, we utilized neural networks (SPSS, Windows version 29) to determine the optimal model for predicting the outcome variables, namely the aMCI or mCoDy diagnostic classes and controls as output variables. We employed multilayer perceptron neural network models with CANTAB test scores, age, gender, and level of education as input variables. In an automated feedforward network architecture with one or two hidden layers, up to six nodes were utilized. In a batch-style training session, a maximum of 250 epochs were used to train the models. The termination criterion was established based on the failure of successive steps to further reduce the error term. The error, relative error, and percentage of misclassifications were calculated, and the predictive precision of the models was estimated using the confusion matrix of the holdout sample. The importance chart depicts the significance and relative prominence of the input variables.

Using SmartPLS,[38] the causal relationships between CANTAB and CERAD variables, age, sex, and education (used as input variables), and DSOA versus qMCI symptom dimensions were evaluated. When the outer and inner models satisfied predetermined quality criteria, a comprehensive PLS analysis was performed. To determine the validity of the model, several criteria were examined. First, all loadings on the latent vectors must be greater than 0.66 at a $p < 0.001$ significance level. In addition, the Standardized Root Mean Square Residual (SRMR) should be less than 0.08 to indicate an adequate model fit. Furthermore, all latent vectors should demonstrate satisfactory composite reliability rho A values (> 0.7) with an average variance extracted (AVE) exceeding 0.50. Confirmatory Tetrad Analysis must verify that the factors have been specified adequately as reflective models. Using the Heterotrait-Monotrait ratio (HTMT) to evaluate discriminant validity should be sufficient (HTMT scores <0.9). The model's reproducibility was evaluated using the Q^2 predict values (PLSPredict).

Results

Socio-Demographic and Clinical Data

Table 1 shows the socio-demographic and clinical data of the aMCI group (n=61), and healthy controls (n=59). There were no significant differences in gender, BMI, and marital status between the groups. There was a minor difference in age between both groups and subjects in the aMCI group had a lower number of education years as compared with controls. In any case, we allowed for the effects of age, sex, and education in all multivariate analyses. The aMCI group exhibited significant lower scores on various neurocognitive tests, including the MoCA, MMSE, VFT, WLM, and WLR as compared with controls. There were no significant differences in IPIP-NEO neuroticism, HADS-A, HADS-D, STAI, ACEs neglect, total NLEs, and NLEs money+health scores among both study groups. The PSS and TGDS scores were higher in aMCI patients as compared with controls.

Table 1 Clinical Characteristics of Subjects with Amnestic Mild Cognitive Impairment (aMCI) and Healthy Controls (HC)

Variables	HC= 59	aMCI=61	F/X^2/ FET	df	*P*
Age (years)	66.75 (4.09)	68.72 (3.83)	7.36	1/119	0.00
Sex (male/female)	13/46	17/44	0.54	1/120	0.52
Education (years)	16.00 (2.82)	13.70 (4.46)	11.25	1/119	0.00
BMI (kg/m^2)	22.73 (2.88)	23.26 (3.50)	0.81	1/119	0.30
Marital status (S/M/D)	14/36/9	14/40/7	0.42	2	0.80[a]
Total MoCA	27.42 (1.57)	22.44 (1.62)	289.36	1/119	<0.001
Total MMSE	28.67 (1.23)	26.39 (2.27)	6.24	1/119	<0.001
Verbal Fluency test	24.03 (5.06)	20.67 (5.69)	11.38	1/119	0.001
Word List Memory	22.37 (4.37)	19.43 (4.03)	14.74	1/119	<0.001
Word List Recognition	7.00 (1.88)	5.36 (2.33)	17.80	1/119	<0.001
IPIP-NEO (neuroticism)	14.31 (4.63)	15.90 (5.13)	3.18	1/119	0.07
Perceived Stress scale	12.14 (6.38)	15.03 (5.59)	6.99	1/119	0.00
HADs anxiety	4.53 (2.49)	5.43 (3.12)	3.01	1/119	0.08
HADs depression	3.97 (3.63)	4.32 (3.77)	0.68	1/119	0.41
STAI	36.20 (7.41)	37.18 (8.81)	0.53	1/119	0.46
NLEs (health, money)	2.41(2.77)	3.22 (3.60)	1.90	1/118	0.17
NLEs (total)	15.89 (14.77)	14.91(12.94)	0.14	1/118	0.70
ACEs (neglect)	17.93(5.65)	19.67(6.23)	2.55	1/119	0.11
TGDS	4.10 (3.19)	6.18 (4.57)	8.27	1/119	0.00

Notes: All results are shown as means (SD). All results of analyses of variance (F), except [a]: χ^2 – test, analysis of contingency analyses.

Abbreviations: Kg, Kilogram; m^2, squared meter, Marital status; S, single; M, married; D, separated/divorced/widowed; MoCA, the Montreal Cognitive Assessment; MMSE, the Mini mental state examination; IPIP-NEO (neuroticism), The International Personality Item Pool-NEO; neuroticism domain, HADs anxiety, Hospital Anxiety and Depression scale_anxiety; HADs depression, Hospital Anxiety and Depression scale_depression; STAI, the State-Trait Anxiety Inventory; NLEs, negative life events; NLEs (total), negative life events total score; ACEs (neglect), adverse childhood experiences (neglect), TGDS, Thai Geriatric Depression Scale.

CANTAB Test Scores Predicting aMCI

We have employed binary logistic regression analysis using the key CANTAB tests as explanatory variables to predict aMCI (the dependent variable), while allowing for the effects of the variables age, sex, and education years. ESF, Table 2 Shows that there are only five key CANTAB tests that were significantly associated with aMCI, namely OTS_PSFC (Nagelkerke R^2 = 0.256), PRM_PCD (Nagelkerke R^2 = 0.206). RVP_A´ (Nagelkerke R^2 = 0.230), MOT_ML (Nagelkerke R^2 = 0.207). and MOT_SDL (Nagelkerke R^2 = 0.219). The clustered bar graphs in ESF, Figure 1 and ESF Figure 2 show the mean test scores of the 28 key CANTAB tests in aMCI and HC.

We have employed multivariable binary regression analysis to delineate the most important predictors of aMCI using the CANTAB tests scores, age, sex, and education. Table 2, regression #1 shows that OTS_PSFC, RVP_ A´ and male sex were the best predictors of aMCI (X^2=28.83, df=3, p<0.001, Nagelkerke=0.289, accuracy=66.1%). Allowing for the effects of the three CERAD tests, showed that OTS_PSFC, RVP_ A´, RVP_MDL and WLR best predicted aMCI versus healthy controls (X^2=41.24, df=4, p<0.001, Nagelkerke=0.408, accuracy=72.2%). We performed a third binary logistic regression using the restricted aMCI subgroup (namely the mCoDy group) as dependent variable. Table 2, regression #2 shows the outcome of this analysis; OTS_PSFC, RVP_ A´, MOT_ML and education best predicted mCoDy versus healthy controls (X^2=32.29, df=4, p<0.001, Nagelkerke=0.351, accuracy=71.1%).

Table 3 displays the outcomes of a neural network analysis (NN#1) that investigated the effects of input variables on the prediction of output variables (aMCI and healthy controls). Age, sex, education, and selected CANTAB test scores (those that were significant in ESF, Table 2, and those with p values < 0.12) were entered as input variables. In this NN#1 model, the concealed layer activation function was hyperbolic tangent, while the output layer activation function was softmax. The training consisted of two hidden layers, with three units in layer 1 and two in layer 2. Training substantially decreased the cross-entropy error, indicating enhanced trend generalization. The consistency of the percentage of incorrect predictions across training, testing, and holdout samples suggests that model overfitting is not present. In the holdout sample, the cross-validated precision of the model was sensitivity = 56.5% and specificity = 81.0%. ESF, Figure 3 depicts the importance chart with all input variables normalized importances. RVP_ A´, MOT_ML, PRM_PCD, and OTS_PSFC were identified as the most significant input variables by the NN#1 model, followed by DSM_PC4, education, RVP_PFA, and age.

Table 3, model NN#2 depicts a second neural network with the restricted group mCoDy and healthy controls as output variables and the selected CANTAB test scores, age, sex and education as input variables. As described above and in Tran-Chi and Maes,[19] this class derived from cluster analysis is a more restricted aMCI class because individuals with DSOA were excluded. In this model, the activation functions for the concealed layer and output layer were hyperbolic tangent and identity, respectively. The model was trained using a configuration with two hidden layers, with three units in the first hidden layer and two units in the second. The holdout sample's cross-validated precision was 82.1% accurate, with a sensitivity of 80.0% and a specificity of 83.3%. Figure 1 depicts the relevance chart displaying the normalized

Table 2 Binary Logistic Regression Analysis Results with Amnestic Mild Cognitive Impairment (aMCI) and mCoDy as Dependent Variables and Healthy Controls as Reference Group

Regression Number	Explanatory Variables	B	SE	Wald	P	OR	95% CI
aMCI	Male sex	1.254	0.543	5.34	0.021	3.501	1.210–10.147
	OTS_PSFC	−0.852	0.259	10.83	<0.001	0.426	0.257–0.708
	RVP_ A´	−0.713	0.229	9.66	0.002	0.490	0.312–0.768
mCoDy	OTS_PSFC	−0.694	0.266	6.83	0.009	0.500	0.297–0.841
	RVP_ A´	−0.576	0.260	4.89	0.027	0.562	0.337–0.937
	MOT_ML	0.514	0.248	4.29	0.038	1.672	1.028–2.719
	Education years	−0.153	0.067	5.23	0.022	0.858	0.753–0.978

Abbreviations: mCoDy, mild cognitive dysfunction (a subgroup of aMCI subjects); OTS_PSFC, One Touch Stockings of Cambridge; probability solved on first choice, RVP_A´, Rapid Visual Information Processing, A prime; MOT_ML, Motor Screening Task, mean latency.

Table 3 Results of Neural Network Analysis with Cambridge Neurological Test Automated Battery (CANTAB) Test Results as Input Data and Diagnosis, Healthy Control (HC) as Output Variables

	Models	NN#1	NN#2
Input layer	Number of units	13	13
Hidden layers	Number of hidden layers	2	2
	Activation function	Hyperbolic tangent	Hyperbolic tangent
	Number of units in hidden layer 1	3	3
	Number of units in hidden layer 2	2	2
Output layer	Output variables	aMCI and HC	mCoDy and HC
	Number of units	2	2
	Activation function	Softmax	Identity
Training	Error term	32.705 (cross entropy)	11.392 (sum of squares)
	% incorrect predictions	32.1%	28.6%
ROC curve	Area under the ROC curve	0.801	0.781
Testing	Error term	13.390 (cross entropy)	4.242 (sum of squares)
	% incorrect predictions	25.0%	30.4%
Holdout	% incorrect predictions	33.3%	17.9%
	Classification	Sensitivity=56.5%, specificity=81.3%	Sensitivity=80.0% specificity=83.3%

Abbreviations: aMCI, amnestic mild cognitive impairment; HC, healthy controls; mCoDy, mild cognitive dysfunction (a purer subgroup of aMCI subjects); ROC, receiver operating characteristics.

importances of the input variables. The model ascribed the greatest predictive power to OTS_PSFC, RVP_A´, DMS_PCS, and PRM_PCD, with education, MOT_ML, and PAL_FMAS trailing behind. RVP_PFA, sex, and age, on the other hand, demonstrated a very low predictive power for mCoDy.

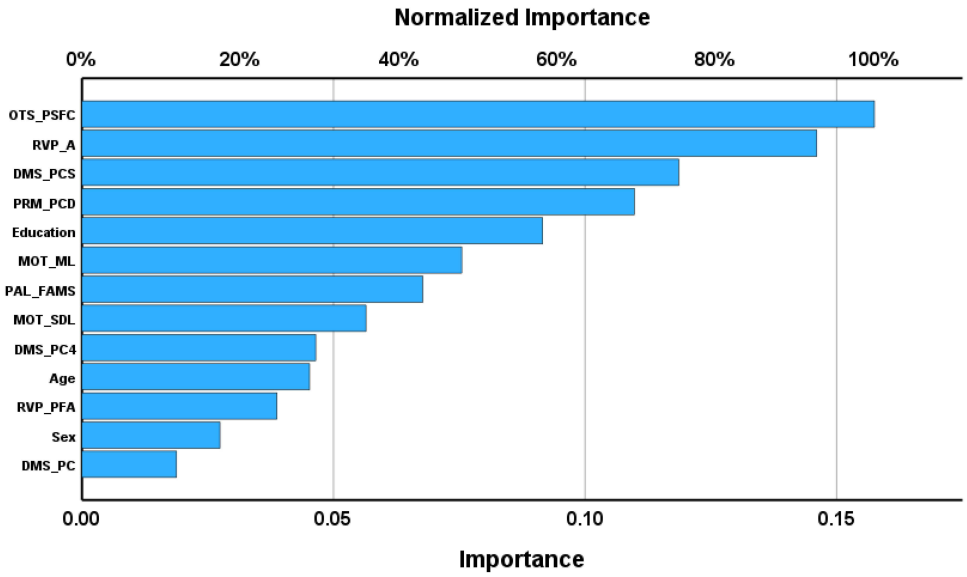

Figure 1 Results of neural network analysis with amnestic mild cognitive impairment and healthy controls as output variables and selected key Cambridge Neuropsychological Test Automated Battery (CANTAB) test scores as input variables.

Prediction of the qMCI and DSAO Latent Vector Scores by Cognitive Test Results

Table 4 shows the results of multiple regression analyses with the qMCI and DSOA scores as dependent variables and the key CANTAB tests (and VFT, WLM, and WLR in the case of mCoDy score; and Petersen item 1 in the case of the DSOA score) and age, sex, education, ACEs and NLEs variables as additional explanatory variables. Model #1 shows that 37.6% of the variance in the qMCI score was explained by OTS_PSFC, WLM, education and RVP_ A´ (all inversely associated). Figure 2 shows the partial regression of the qMCI score on the OTS_PSFC score. Model #2 shows an alternative model, after inclusion of the VFT test score, whereby 37.1% of the variance in qMCI is explained by OTS_PSFC, education, WLM, and VFT (all inversely associated). In both regression analyses, no significant effects of NLEs, ACEs, sex, or age could be established. Model #3 shows the outcome of the multivariate regression of the DSOA score on the significant predictors, namely NLE health+money, ACEs neglect, education, RVP_PFA and Petersen item 1 (all positively associated). Figure 3 shows the partial regression of the DSOA score on RVP_PFA score.

Results of PLS-Path Analysis

Figure 4 displays the PLS model after removing the non-significant input variables (eg, sex and age) and non-significant paths (eg, from DSOA to qMCI). The final outcome variables entered in the model were the DSOA and qMCI latent vectors. The former was extracted from HADS-A, HADS-D, PSS, STAI, TGDS, and neuroticism scores, and the latter

Table 4 Results of Multiple Regression Analyses with Quantitative Mild Cognitive Impairment (qMCI) and Distress Symptoms of Old Age (DSOA) Scores as Dependent Variables and Key Cambridge Neurological Test Automated Battery Test Scores as Independent Variables

Dependent variables	Explanatory Variables	Coefficients of input variables			Model statistics			
		β	t	p	R^2	F	df	p
qMCI	**Model 1**				0.376	16.58	4/110	<0.001
	OTS_PSFC	−0.299	−3.721	<0.001				
	WLR	−0.239	−3.211	0.002				
	Education years	−0.224	−3.171	0.002				
	RVP_ A´	−0.169	−2.056	0.042				
qMCI	**Model 2**				0.371	16.20	4/110	<0.001
	OTS_PSFC	−0.275	−3.41	<.001				
	Education years	−0.266	−3.36	0.001				
	WLM	−0.225	−2.82	0.006				
	VFT	−0.182	−2.28	0.025				
DSOA	**Model 3**				0.407	14.85	5/108	<0.001
	NLEs health+money	0.385	4.98	<0.001				
	Sum neglect	0.272	3.49	<0.001				
	Education years	0.297	3.75	<0.0001				
	RVP_PFA	0.191	2.45	0.016				
	Petersen item 1	0.190	2.42	0.017				

Abbreviations: OTS_ PSFC, One Touch Stockings of Cambridge, probability solved on first choice; RVP_A´, Rapid Visual Information Processing, A prime; RVP_PFA, Rapid Visual Information Processing, probability of false alarm; VFT, verbal fluency test, WLR: word list recognition; NLEs health +money, negative life events (health and money); Sum neglect, total neglect sum scores; Petersen item 1, subjective memory complaints.

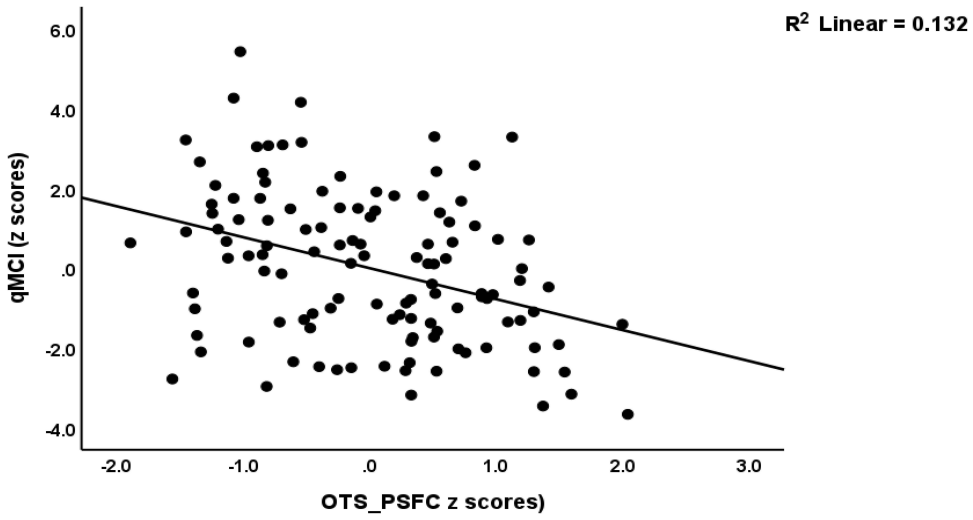

Figure 2 Partial regression of the quantitative mild cognitive impairment score (qMCI) on the One Touch Stockings of Cambridge (OTS), probability solved on first choice (OTS_PSFC) (adjusted for age, sex and education).

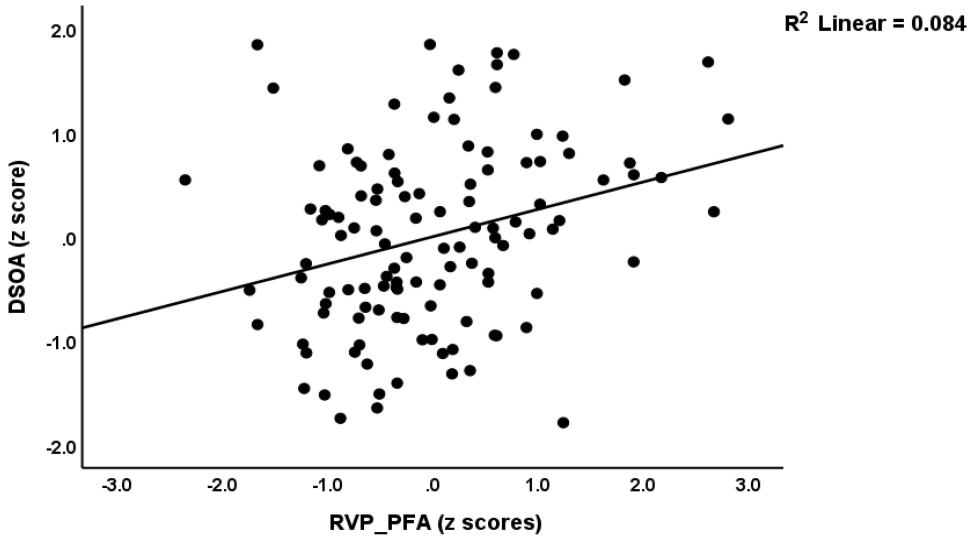

Figure 3 Partial regression of the distress symptoms of old age (DSOA) score on the Rapid Visual processing (RVP) probability of false alarm (PFA) score (adjusted for age, sex and education).

was extracted from the total MoCA and MMSE scores and CDR scores. Direct predictors were three CANTAB test scores (selection based on the abovementioned results of neural networks and multiple regression analysis and feature reduction), namely OTS_PSFC, RVP_ A´ and RVP_PFA, Petersen item 1 (entered as a dummy variable), education (years), NLEs health+money, and one latent vector extracted from VFT, WLM and WLR test scores (labelled "memory"). We also entered one formative model, namely a composite built using emotional abuse and neglect and physical neglect (labelled "ACEs"). Complete PLS analysis performed using 5.000 bootstrap samples showed that the construct reliability and convergence validities of the three reflective latent vectors were adequate with AVE values > 0.599 and rho_A > 0.7, while the SRMR of 0.054 indicated an adequate model fit. The outer loadings were all > 0.66 at $p<0.0001$. CTA showed that the three latent vectors were not mis-specified as reflective models. All Q^2 values exceeded zero, indicating replicability of the model. We found that 36.8% of the variance in the qMCI score was explained by the CERAD "memory" latent vector, education, OTS_PSFC and RVP_ A´. On the other hand, 42.4% of the variance in the

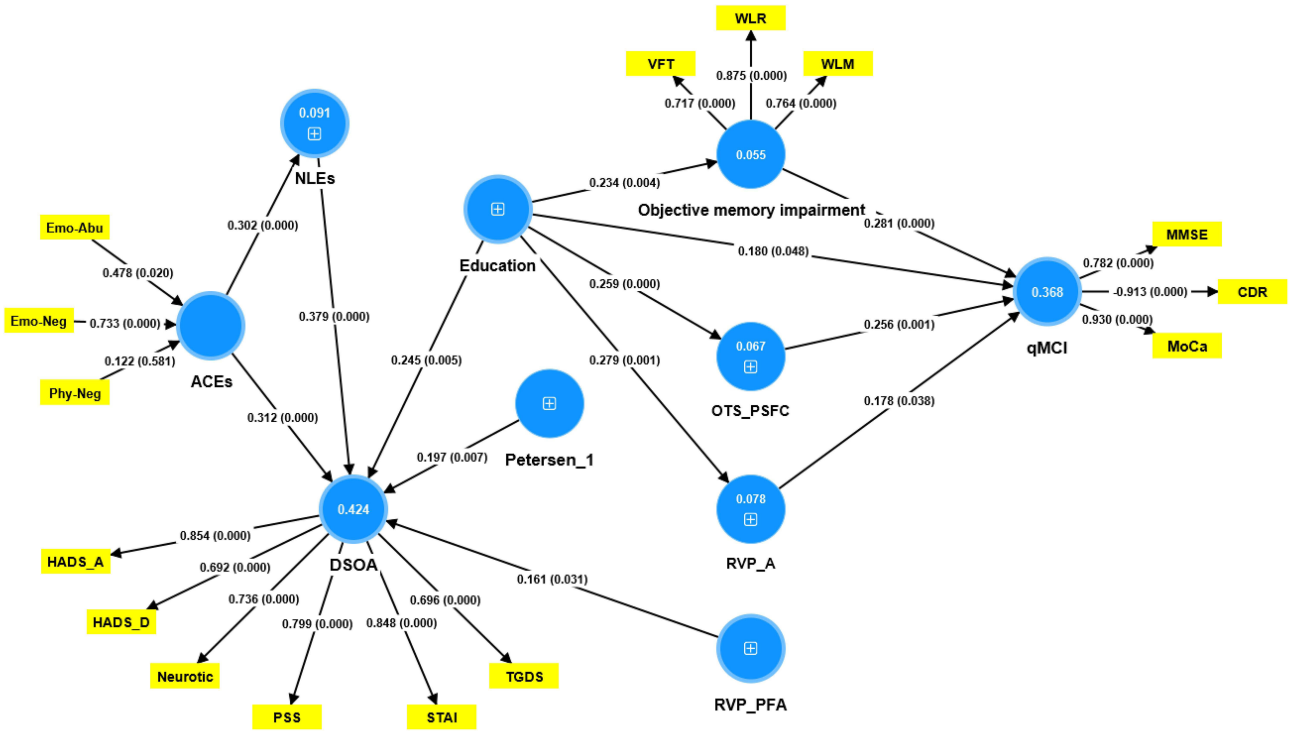

Figure 4 Results of partial least squares analysis. We entered two outcome variables, namely the quantitative mild cognitive impairment (qMCI) factor, and the distress symptoms of old age (DSOA) factor. Objective memory disorders were conceptualized as a factor extracted from three memory tests. Adverse childhood experiences (ACEs) were conceptualized as a factor extracted from three ACEs subtypes. All other predictors were entered as single indicators. The explained variance is shown as figures in blue circles. The outer model shows the loadings on the factors and p-values. Paths are shown as path coefficients with exact p values.

DSOA latent variable score was explained by ACEs, NLEs health+money, education, Petersen item 1, and the RVP_PFA score.

In this PLS model, there was no significant association between the DSOA and qMCI scores (p=0.577). There were no significant effects of "memory" (p=0.382), OTS_PSFC (p=0.318) and RVP_ A´ (p=0.901) or any of the other CANTAB tests on the DSOA factor score. There were no significant effects of NLEs health+money (p=0.169), ACEs (p=0.591) and RVP_PFA (p=0.485) on the qMCI latent variable score. Increasing education differently affected both dimensions, namely protecting against increasing qMCI, but contributing to increased DSOA scores.

Discussion

CANTAB Tests and aMCI or mCoDy

The first significant finding of this study is that RVP_ A´, RVP_MDL, OTS_PSFC, and MOT_ML were among the neuropsychological CANTAB tests that distinguished aMCI or the more restrictive group mCoDy from controls. Furthermore, neural network analysis demonstrated that PRM_PCD possessed some additional ability to differentiate aMCI.

Previous research showed that RVP_A´ scores were lower in multi-domain aMCI and AD patients compared to controls.[39] Several CANTAB tests, including RVP, differed significantly between MCI and control subjects, according to a prior systematic review.[40] The RVP test evaluates attention and psychomotor speed as well as the capacity to maintain visual attention and detect stimuli. The RVP_A´ key test assesses the subject's ability to identify target sequences by calculating the median response latency on trials in which the subject provided accurate responses. Conversely, RVP_MDL assesses the median response time, and both critical evaluations distinguish attention.[41]

In a prior investigation, Levy-Gigi and Kelemen[42] identified a notable disparity in the outcomes of OTS tests. Individuals with MCI exhibited a distinct pattern in the mean number of attempts at faultless solutions and the mean proportion of correct solutions compared to the control group. The OTS_PSFC test computes the aggregate count of evaluated trials in which the subject selects the accurate response on their initial attempt, encompassing all evaluated

trials.[41] The OTS test score may serve as an assessment tool for executive functions, encompassing problem-solving, working memory, mental flexibility, planning, strategic thinking, response inhibition in aMCI or AD.[31,42–44] It is noteworthy to mention that the frontal lobe of the brain is where executive functions are predominantly executed.[45]

Prior research[39] found that individuals with AD and multi-domain aMCI had significantly lower MOT_ML test scores than the control group. The MOT test results enable one to evaluate the reaction time, movement time, vigilance and sensorimotor deficit.[41] The MOT_ML test calculates the mean latency for a subject to correctly respond to the stimulus on the screen during the assessed trials.

PRM can predict the cognitive status of MCI patients, according to multiple investigations.[46,47] The PRM test evaluates visual pattern recognition memory in the context of a 2-choice forced discrimination paradigm; its design is intended to be sensitive to the medial lobe.

Numerous experimental studies have demonstrated the noteworthy efficacy of video-game training in ameliorating cognitive functions among individuals diagnosed with MCI. According to a study by Leelavanichkul and Hemrungrojn,[48] video games may improve executive functions and cognitive speed, as demonstrated by enhanced results on the OTS and PAL CANTAB tests. Furthermore, when applied to individuals with MCI, game-based neurofeedback demonstrated favorable outcomes, including enhanced attention and working memory, as evaluated by the SWM test.[49] However, the current study failed to identify any statistically significant variations in the measurement of SMW between subjects with aMCI and the control group, even though this test is frequently linked to MCI.[40]

Prediction of the Severity of MCI

The second main finding of this study was that the combined effects of OTS_PSFC, RVP_A´, WLM, WLR, VFT, and/or education predicted a quantitative score of mild cognitive dysfunction by a substantial margin (around 37% of the variance). As reviewed in the Introduction, earlier studies on cognitive functions in MCI focused primarily on the PAL test results.[50–52] However, the current research revealed the significance of executive functions (the OTS_PSFC test results) combined with episodic memory, semantic memory, verbal fluency, recognition memory, and working memory (PRM, RVP, VFT, WLM, and WLR test results) as predictors. Previously, Tran-Chi and Amrapala[53] demonstrated that RVP_MdL, SWM_Ber, and DMS_Cor account for 29.0% of the variance in a factor extracted from the MoCA and MMSE test scores and the diagnosis MCI (which is quite like the qMCI score that we utilized in the present study). This finding suggests that the RVP test is, in fact, the most replicable determinant of the severity of MCI.

Memory assessments, including those conducted by the CERAD, have been shown in a prior meta-analysis to be rather specific for MCI.[13] As previously demonstrated by Tunvirachaisakul et al,[14] the VFT, WLM, and WLR may in fact be effective at detecting MCI. By utilizing the CERAD-subtest scores, including those from the VFT, Modified Boston naming test, WLM, true recall, WLR, and constructional praxis, a noteworthy distinction was obtained between individuals with MCI and those who were asymptomatic, yielding an area under the ROC curve of 0.862 (95% CI = 0.816–0.908).[54] Prior research indicates that the CERAD total scores and various individual CERAD measures have the potential to effectively identify MCI.[55–58]

It is noteworthy that within our study sample, which excluded participants with major depression and BPSD, neither ACEs nor NLEs had a significant impact on aMCI, mCoDy, or the quantitative qMCI score. However, ACEs and NLEs significantly predicted DSOA. An increased risk of MCI has been linked to heightened psychological stressors, according to several studies.[59,60] In addition, negative social interactions may increase the risk of MCI and cognitive decline in older adults.[19,61] Furthermore, individuals with MCI may exhibit higher physical neglect scores compared to the control group.[62] However, after excluding patients with major depression, our study revealed that there are no such associations between the severity of aMCIs and ACEs or NLEs. Therefore, it is highly likely that the correlation between stressors and MCI can be attributed to the presence of depression; consequently, the association between MCI and psychological stressors found in previous studies may represent a spurious correlation.

The DSOA Score is Predicted by False Alarm

The third significant discovery of this study is that the DSOA score, which encompasses distress, emotional, and neuroticism scores, is influenced not only by ACEs and NLEs, but also by a subjective perception of cognitive

impairments and the RVP_PFA test scores. In this respect, it is interesting to note that a subjective cognitive decline, which is a feature of DSOA, has been linked to ACEs, such as sexual, physical, and psychological abuse.[63] The RVP_PFA test score is a particular cognitive predictor for DSOA that is not linked to MCI or the severity of MCI. RVP_PFA is calculated as the proportion of incorrect alarms in consecutive presentations compared to the total of incorrect alerts plus accurate rejections.[41] False alarms are crucial in signal detection theory.[64] Stressors have the tendency to alter response bias in highly anxious individuals.[65] Moreover, anxiety is linked to decreased ability to distinguish between hazardous and neutral stimuli when exposed to unclear threat cues[66] As such, the DSOA severity can be attributed to a combination of psychosocial stressors and false alarms in detecting distress and anxiety symptoms.

Limitations

There were certain limitations in the study. Conducting the study in a metropolitan area such as Bangkok may produce findings that are not applicable to elderly individuals residing in the rural regions of Thailand. The Bangkok region and the rural regions of Thailand exhibit substantial disparities in terms of education and socioeconomic status.

Conclusions

This study demonstrated that some CANTAB tests had the ability to differentiate between individuals with aMCI or the more specific category of mCoDy, and control subjects. The crucial CANTAB tests include RVP_A´, RVP_MDL, OTS_PSFC, MOT_ML, and PRM_PCD. The severity of MCI was primarily determined by a combination of two CANTAB tests (OTS_PSFC and RVP_A´) along with CERAD memory tests. The findings indicate that MCI, after removing major depression and DSOA, is linked to deficits in attention, executive functioning, and memory. Crucially, when we removed older adults with major depression, BPSD and DSOA from the analysis, we found no significant impact of psychosocial stressors on MCI or its severity. On the other hand, psychosocial stresses such as ACEs and NLEs, and the subjective perception of cognitive deficits are predictors of DSOA. Additionally, RVP_PFA suggests that false alarms can play a role in the development of DSOA, while there is no evidence of objective cognitive deterioration in the latter domain.

Subsequent investigations should reassess the connections between MCI or its severity and neurocognitive test outcomes, biomarkers, and AD onset. This should be done by eliminating patients with major depression and by accounting for DSOA. By doing this, researchers will be able to define the specific features of (a)MCI more clearly.

Data Sharing Statement

The corresponding author MM will provide the data file used in the present study upon receiving an appropriate request once the authors have fully utilized the data.

Ethical Approval and Consent to Participate

The research project (IRB no.886/64) received approval from the Institutional Review Board (IRB) at Chulalongkorn University's ethics board in Bangkok, Thailand. This approval is in accordance with the International Guidelines for the Protection of Human Research Participants, as mandated by the Declaration of Helsinki, The Belmont Report, CIOMS Guidelines, and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP). All participants signed the appropriate institutional informed consent forms before data collection. This study did not include any minors.

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This paper has been uploaded to Medrxiv as a preprint:https://www.medrxiv.org/content/10.1101/2023.12.05.23299448v1

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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