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Original Article

Artificial Intelligence of Neuropsychological Tests for the Prediction and Verification of Decline in Gait Parameters in Patients with Mild Cognitive Impairment

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SUMMARY

Background: Mild cognitive impairment (MCI) is considered a transitional state between normal aging and very early dementia. Increasing evidence reveals gait and cognition are inter-related in older adults with MCI. Therefore, it is important to find reliable biomarkers for these MCI patients, which can be utilized as an indicator for early detection and intervention.
Methods: The deterioration of cognitive function will affect the patient's walking ability; thus, we conduct a two-stage study with comprehensive neuropsychological testing and a portable device for gait analysis at the beginning and repeated gait analysis six months later to evaluate gait deterioration. By machine learning using neuropsychological testing scores as the input feature parameters, a classification model capable of predicting the gait performance of MCI patients can be obtained.
Results: Machine learning is capable of predicting several gait features of the MCI patients, such as reduction in walking speed (with up to 81.82% accuracy), increase in the time of the timed up and go (TUG) test (with up to 66.67% accuracy), and reduction in vertical jump height (with up to 69.23% accuracy) based on the predictive neuropsychological testing scores.
Conclusion: Overall, the neuropsychological testing is predictive of gait decline, especially of walking speed, followed by vertical jump height in MCI patients. Therefore, the highest correlation among gait parameters in MCI patients could be the walking speed.

1. Introduction

Mild cognitive impairment (MCI) is considered a transitional state between normal aging and very early dementia. Although a small percentage of patients will return to normal cognitive function from MCI, most of them are likely to degenerate into a high-risk group of dementia patients.[1] The deterioration of cognitive function will also be affected by the patient's walking performance.[2] In recent years, many studies have mentioned that gait is an important indicator of overall health and longevity in the elderly community.[3,4] Gait is no longer regarded purely as athletic behavior. There is also a complex relationship between gait and cognition.[5] In the case of normal aging, gait and cognitive ability may decline at the same time, but it is not known exactly how gait declines with age.[3] Hence, in this study, we used formal neuropsychological testing as a predicting biomarker for future gait parameter decline, including walking and jump. Here jump performance is included in the study due to the fact that the ability to jump is a multi-joint movement requiring complex motor coordination, involving muscle strength and power, speed and amplitude of the lower limb movements. The vertical jump has been shown to be a good predictor of functional capacity and risk of falling.[6] To the best of our knowledge, no research to-date is published on the interaction among cognitive function, walking ability and simple vertical jump in the elderly.

With the advancement of medical technology, more and more studies have utilized gait sensors in gait analysis systems to obtain accurate gait parameters, such as pace, rhythm, variability, asymmetry and posture control.[7,8] Some studies have reviewed the use of gait sensors in the assessment of neurological diseases, but gait studies have not yet led to changes in clinical practice. This is perhaps because most studies mainly compare the differences between pathological and healthy gait, such as gait distinguished between Parkinson's disease (PD) patients and healthy subjects.[9] However, it is more important to assess the severity or prognosis of neurological diseases.[10] In this study, machine learning was used to predict patients' future gait performance via neuropsychological testing, with the purpose of assisting medical experts to understand that patients' gait performance may deteriorate in the future, as well as to provide appropriate diagnosis and treatment. The diagnosis of different types of MCI, including MCI due to Alzheimer's disease (AD), PD and cerebrovascular disease, were based on previously published consensus criteria.[11–15]

2. Patients and methods

2.1. Proposed approach

A constructed block diagram of a machine learning system, built

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for the classification of future gait functions of MCI patients, is shown in Figure 1. The gait and neuropsychological tests of MCI patients began in April 2018, and gait tests were performed again, six months later. All patients provided informed consent, and the study was granted ethical approval by the MacKay Memorial Hospital Institutional Review Board. Participants tested were MCI patients, with MCI diagnosed according to Petersen's MCI diagnostic criteria.[16] The criteria for MCI are: 1) cognitive complaint; 2) cognitive decline not normal for age; 3) no dementia, and 4) essentially normal functional activities.

Using a BTS G-WALK wearable device[17,18] for gait evaluation, three tests were conducted in this study: a simple test of walking in a 5.5 m long straight line, atimed up and go (TUG) test, and a vertical jump test. It is noteworthy that some participants may have knee injuries and cannot jump, whereas others have missing data attributed to misuse of the measuring instrument. Hence, the missing data points were predicted by applying support-vector regression (SVR). Next, the data were normalized, and principal component analysis (PCA) was utilized to reduce and extract features, as well as to reduce noise. Finally, a support-vector machine (SVM) model was created to predict if future gait would decline.

According to relevant studies, walking speed during comfortable gait will remain stable until the age of 60. After 60 years of age, the comfortable walking speed will drop by about 15% every 10 years. The speed of fast gait will peak at the age of 20, and then drop by about 20% every 10 years.[19,20] Therefore, walking speed, TUG test time, and height of the in-situ jump test were used as targets for each respective test in this study. To compare changes in gait parameters, the data of the first test was subtracted from the data of the second test, and the result was divided by the data of the first test. Based on the aforementioned relevant studies,[19,20] it was decided that patients participating in the study, who would exhibit a 5% degraded gait performance over six months, were to be classified as the decline group, while the remaining patients would be the unchanged group.

2.2. Participants

This was a prospective study, and consecutive series of patients with MCI were enrolled from April 2018 to July 2018. Patients were studied at the neurological department of the MacKay Memorial Hospital (Taiwan). Diagnoses were assigned during routine assessments in the study by reviewing clinical, neuropsychological, brain imaging data, and biochemical tests. The study involved a face-to-face interview with a trained research assistant. The time limit for each interview was 90 minutes, to avoid fatigue. The participants' condition was as follows:

1. Age exceeds 30 years.
2. Clinically accurate compliance with MCI diagnostic criteria.
3. Without dementia (for those who have received more than six years of education, the mini-mental state examination (MMSE) must be higher than 23 points; for those who have less than six years of education, the MMSE must be higher than 13 points).
4. Aconsent form should be signed.

Exclusion conditions:

1. Participants meet the diagnostic criteria for dementia (CDR $\geq$ 1.0).
2. Recent major medical illness or surgery that may affect gait performance.
3. Recently used (within three months) drugs that may affect cognitive function.
4. Acute medical illness or surgery that may be severe enough to affect cognitive function.
5. Unable to walk more than 12 m without assistance.

All the exclusion criteria were judged by the clinical physician. Figure 2 shows the flow chart for the screening and grouping process of the participants in this study.

2.3. Wearable sensors and portable system

In this study, the BTS G-WALK gait analysis system was utilized to record the gait parameters. The sensor measures 70 mm $\times$ 40 mm $\times$ 18 mm and weighs approximately 37 g. It can be attached behind the waist, as shown in Figure 3. BTS G-WALK is a wireless inertial sensor with a triaxial accelerometer (dynamic range $\pm$2, $\pm$4, $\pm$8, $\pm$16 g and bandwidth from 4 to 1000 Hz); and a 16 bit triaxial gyroscope (dynamic range $\pm$250, $\pm$500, $\pm$1000, $\pm$2000 °/sec and bandwidth from 4 to 8000 Hz; and a 13 bit triaxial magnetometer (dynamic range $\pm$1200 μT and bandwidth up to 100 Hz). It evaluates the participant's walking ability and transmits data to a computer through Bluetooth wireless transmission.

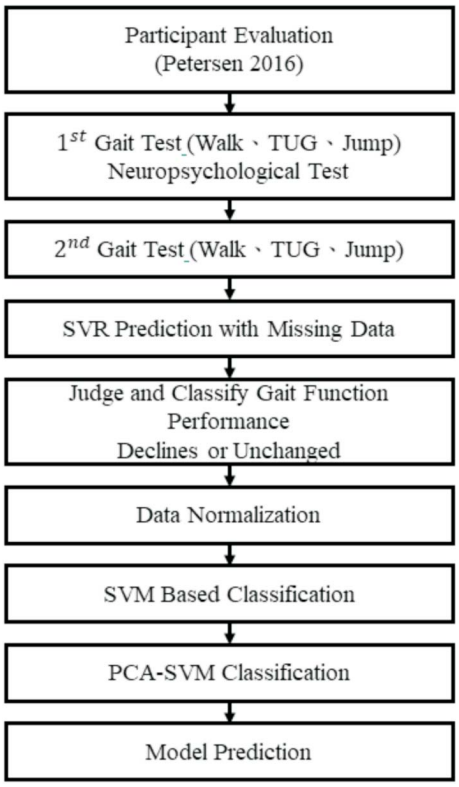

Figure 1. Block diagram of the proposed methodology. PCA, principal component analysis; SVM, support-vector machine; SVR, support-vector regression; TUG, timed up and go.

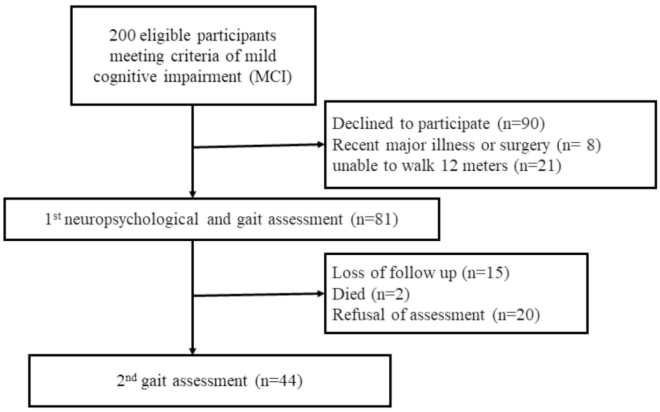

Figure 2. Screening and grouping process of the participants in the study.

Figure 3. A BTS G-WALK sensor.

2.4. Gait test

1. Walk test: Participants walked 5.5 m to record gait performance, at their normal walking speed.
2. Timed up and go (TUG): Participants first sat on a chair with a backrest and no armrests. When they heard the start signal, they arose and walked for 3 m. Subsequently, they turned around and walked back to the chair to sit down.
3. Jump test: Participants started in an upright position with their hands on the outside of their thigh. They squatted slightly and subsequently attempted to jump up as high as they could.

2.5. Neuropsychological test

The neuropsychological test focuses on attention and working memory, executive function, memory, visuospatial function, and language.[21] The test areas are shown in Table 1.

2.6. Data analysis

A MATLAB package was used to perform SVR, in order to address missing data problem. Subsequently, PCA and SVM were employed to build a classification model.

2.6.1. SVR with missing data

By mapping the training data to a high-dimensional feature space, SVR aims to obtain an optimal hyperplane that can predict the data accurately and minimize the distance of all data to this plane. Suppose we have a set $\{x_i, y_i\}$, $i = 1, \ldots, n$, $x_i \in R^n$, $y_i \in R$, where x_i is the input value, and y_i is the corresponding target output value. The following is a regression hyperplane of SVR:

$$f(\mathrm{x}) = \mathrm{w} \cdot \varphi(x) + b \tag{1}$$

where, w is the weight vector, b is an adjustable factor, φ is the mapping function, and $\varphi(x_i)$ indicates that x_i is mapped to a high-dimensional space by the function φ.[22] Mapping the indivisible data to a high-dimensional feature space can facilitate the classification of data in the high-dimensional space.

The mapping function is typically linear, but it can be replaced by a kernel function, $\mathrm{k}(x_i, x_j) = (\varphi(x_i) \cdot \varphi(x_j))$, to simplify the complicated calculation in a high-dimensional space. In this study, in addition to a linear function, a radial basis function (RBF) of $\mathrm{k}(x_i, x_j) = \exp(-\gamma |x_i - x_j|^2)$ and polynomial function of $\mathrm{k}(x_i, x_j) = [(x_i^T x_j) + 1]^d$ are also used to solve the missing data problem and fill in the data from SVR prediction subsequently.[23–25]

2.6.2. Data normalization

Before applying the SVR prediction model, data min-max normalization was performed to avoid numerical size differences that may affect the overall performance and cause misjudgment.[26–28] Normalization scales the input feature values to be within [0, 1] or [–1, 1] and does not change the distribution of the original dataset. Thus, the dataset is consistent in format. In this study, the 36 neuropsychological test scores in Table 2 are used as the input feature parameters for the SVR prediction model. By applying data normalization these neuropsychological scores are scaled within [0, 1] or [–1, 1] for better prediction performance. Consequently, the neuropsychological scores of every participant are entered into a dataset: $X \in R^{n \times p}$, where n is the number of features (= 36 in this study), and p is the number of participants. After min–max normalization, the data in X' are within [–1, 1] using the following transformation:

$$x' = -1 + \frac{2(x - x_{\min})}{x_{\max} - x_{\min}} \tag{2}$$

where, $x_{\min}$ is the minimum and $x_{\max}$ is the maximum value of the feature x in dataset X. It is also noted that for the subsequent SVM classification model, these normalized neuropsychological test scores are still the input feature parameters for classifying each patient into groups with or without gait decline.

2.6.3. PCA

PCA is applied in this study to reduce the dimension of the dataset while preserving the most important principal components (PCs), by transforming the normalized data into a new coordinate system using orthogonal transformation.[29,30,31] The first few PCs can be selected to reduce the data dimension and provide the SVM with a lower dimension for predictive classification; hence, the training model can accelerate the calculation and improve accuracy. More specifically, a dataset: $X \in R^{n \times p}$ can be transformed into a new

Table 1
Neuropsychological tests.

Cognitive Domain	Neuropsychological Test
General Cognitive Test	MMSE
	CDR
Attention and working memory	Trail Making Test: Trail A
	Digits Forwards/Backwards
Executive function	Animal Category Fluency Test
	Trail Making Test: Trail B
Memory	Taylor Figure: Recall
	CVLT-SF
Visuospatial function	Taylor Figure: Copy
	Judgment of line orientation
Language	Boston Naming Test
	Story Telling

CDR, clinical dementia rating; CVLT-SF, California verbal language test-II short form; MMSE, mini-mental state examination.

Table 2
Neuropsychological test scores.

Test	Score	Test	Score
MMSE-total	25.64 ± 3.44	Trail A Making Test-Time(s)	23.3 ± 15.0
MMSE-orientation	9.34 ± 1.41	Trail A Making Test-Number	6.75 ± 1.1
MMSE-memory	4.05 ± 1.12	Trail B Making Test-Time(s)	63.33 ± 38.45
MMSE-calculation	4.05 ± 1.14	Trail B Making Test-Number	12.11 ± 3.01
MMSE-language	4.55 ± 0.7	Taylor Figure-Copy Time(s)	242.93 ± 138.76
MMSE-emotion actions	3.66 ± 0.57	Taylor Figure-Copy	30.26 ± 7.05
CDR	0.5	Taylor Figure-Recall Time(s)	151.39 ± 135.81
CDR-SB	1.78 ± 1.1	Taylor Figure-Recall	13.41 ± 9.01
CVLT-SF-1	3.41 ± 1.34	Animal Category Fluency Test	12.66 ± 3.87
CVLT-SF-2	4.57 ± 1.48	Boston Naming	21.93 ± 5.54
CVLT-SF-3	5.32 ± 1.86	Test(Self-report)-People	2.36 ± 0.99
CVLT-SF-4	6.11 ± 1.51	Test(Self-report)-Place	0.7 ± 0.85
CVLT-SF-delay	5.75 ± 2.02	Test(Self-report)-Object	6 ± 3.94
CVLT-SF-recall delay	4.75 ± 2.29	Test(Self-report)-Thing	4.05 ± 1.45
CVLT-SF-recall prompt	3.95 ± 2.79	Test(Prompt)-People	2.93 ± 0.33
Judgment of line orientation	13.41 ± 3.35	Test(Prompt)-Place	1.36 ± 0.57
Digits forwards	7.5 ± 1.37	Test(Prompt)-Object	7.77 ± 3.91
Digits backwards	4.05 ± 1.45	Boston Naming Test(Prompt)-Thing	4.55 ± 1.84

CDR, clinical dementia rating; CVLT-SF, California verbal language test-II short form; MMSE, mini-mental state examination.

coordinate system: $X' = V(X - \bar{X}) \in R^{k\times p}$, where $k \leq n$ is the number of principal components chosen. Note that $\bar{X}$ is the mean dataset of X and the transformation matrix $V \in R^{k\times n}$ stores the first k eigenvectors (corresponding to the first k largest eigenvalues) of the covariance matrix of $(X - \bar{X})$ in its row vectors.

2.6.4. SVM

The SVM theory is the same as that of SVR, in which the training data are mapped to a high-dimensional feature space. The difference is that we wish to obtain an optimal hyperplane that can distinguish the data into two different sets.[30] As the margin of the two sets on this plane becomes larger, the classification performance improves. Herein, we will compare the results using different kernel functions.

2.6.5. ROC AUC

AUC is the area under the ROC (Receiver Operating Characteristics) curve.[32] ROC curve is a plot of true positive rate (TPR) versus false positive rate (FPR), defined as follows:

$$TPR = \frac{TP}{TP + FN} \tag{3}$$

$$FPR = \frac{FP}{FP + TN} \tag{4}$$

at different classification thresholds, as shown in Figure 4. AUC measures the quality of a model's predictions irrespective of what classification threshold is. The closer of the AUC value to 1, the better the quality and confidence of the model's prediction.

3. Results

After the first neuropsychological test and theset of three gait tests, neuropsychological test scores and gait characteristics of 81 patients who participated in the study were obtained. The results of the psychological test scores are shown in Table 2, where the values are mean averages with ± standard deviation.

Participants (n = 81) were aged between 34 and 89 years (median 70, interquartile range 63 to 78.5); 55.6% were male (n = 45). After six months, a further 37 participants could not complete the the second gait test, including loss of follow up (n = 15), died (n = 2), and refusal of assessment for any reason (n = 20). Consequently, a total of 44 patients underwent a second set of three gait tests.

Data for the speed of the walk test and jump height test from some of the participants are missing; therefore, other gait features are utilized to predict the missing data via SVR. After the missing data are predicted, the training of the classification prediction model can begin. In some participants who are unable to jump due to poor mobility in their knees, the height of their jump was noted as zero.

In the first gait test, among the 44 patients, one participant's walking speed and another participant's height in the jump test were missing. The results of using SVR to predict the missing data of the two patients in the study, utilizing data from the other patients, are shown in Table 3. Each RMSE (root-mean-square error), MAE (mean absolute error), and their corresponding kernel functions are displayed sequentially.

Next, SVR must be utilized again to account for missing values in the second gait test, where the speeds from seven participants' walking tests were lost. The data from the other patients are used and the results of using SVR to predict missing data for the seven participants are shown in Table 3.

3.1. Walking speed test

The speed from the first walk test was compared with that from the second test. The 44 participants were divided into two groups based on the participants' walking speed. There were 8 participants whose walking speed was less in the second test, and 36 participants whose walking speed was maintained.

Next, the scores were obtained from the neuropsychological

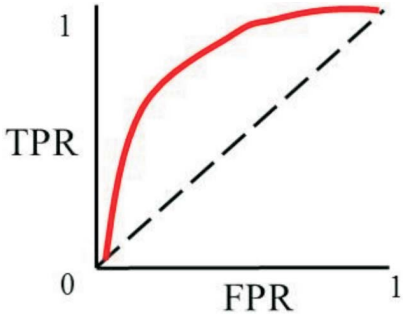

Figure 4. ROC curve. ROC, receiver operating characteristics.

Table 3
Prediction of the missing data.

Speed prediction of the first walk test							
Five examples of walk speed (m/s)	1.11	0.67	0.94	1.02	0.81		
Predictive results	0.7833						
RMSE	0.1364						
MAE	0.1077						
Kernel function	RBF						
Height prediction of the first jump test							
Five examples of jump height (cm)	16.8	0	1.2	8.3	15		
Predictive results	9.3967						
RMSE	4.7743						
MAE	3.5715						
Kernel function	Linear						
Speed prediction of the second walk test							
Five examples of walk speed (m/s)	1.26	1.06	0.86	0.49	1.01		
Predictive results	0.9091	1.0076	0.9945	1.0504	1.028	0.933	0.9939
RMSE	0.2312	0.2312	0.2312	0.2312	0.1633	0.1914	0.1914
MAE	0.1593	0.1593	0.1593	0.1593	0.1372	0.1636	0.1636
Kernel function	RBF	RBF	RBF	RBF	RBF	RBF	RBF

MAE, mean absolute error; RBF, radial basis function; RMSE, root mean square error.

test; the SVM model was trained, and PCA-SVM classification models were built. The results are shown in Table 4.

From Table 4, we can see that the highest prediction result accuracy for the SVM is 84.62%, which is for the polynomial SVM classification model; however, its ROC AUC is 0.6364, which is not a desirable value. When the PCA extracts the gait feature, the accuracy of the polynomial kernel function is as high as 92.31%. Its ROC AUC is the same, at 0.6364. Here, the linear PCA-SVM classification model was considered to be better, with an accuracy of 81.82%. The ROC AUC from the original SVM is 0.6667, and the accuracy after using the PCA model was unchanged at 81.82%, while the ROC AUC was significantly improved to 0.9167. In addition, the number of feature selections is significantly reduced, and better prediction results can be obtained.

3.2. TUG test

In this case, 15 participants' time from the TUG test increased, while the remaining 29 participants' time did not change significantly. The classification results obtained are shown in Table 5.

The polynomial SVM classifier has the highest prediction accuracy of 77.78%, but with a poor ROC AUC of only 0.5556. When PCA extracts the gait features, the accuracy of the PCA-SVM classification model with polynomial kernel function deteriorates. On the contrary, the accuracy of linear kernel function remains unchanged in PCA-SVM, but the ROC AUC is increased to 0.8333. Therefore, in this case, the linear PCA-SVM classification model is the best solution. In addition, the number of feature selections is significantly reduced, and better prediction results can be obtained.

Table 4
Prediction results of walking speed.

Classifier model	Kernel function	Number of features	Accuracy	ROC AUC
SVM	Linear	36	81.82%	0.6667
	RBF	36	81.82%	0.5556
	Polynomial	36	84.62%	0.6364
PCA-SVM	Linear	1	81.82%	0.9167
	RBF	1	81.82%	0.7222
	Polynomial	7	92.31%	0.6364

AUC, area under the ROC curve; PCA, principal component analysis; SVM, support-vector machine; RBF, radial basis function; ROC, receiver operating characteristics.

3.3. Height of vertical jump test

A total of 14 participants in the group showed reduced values of height in the vertical jump test. The remaining participants maintained their jump height. The classification results are presented in Table 6.

From the SVM classifier, we can see that the highest prediction accuracy is 70.00%, which is for the polynomial kernel function, while the ROC AUC for this is poor, at only 0.619. When the PCA extracts the gait features, the accuracy of the polynomial kernel function is unchanged, and the ROC AUC is not improved significantly. In the SVM classification model, the accuracy of the RBF kernel function is 69.23%, and its ROC AUC is 0.7778. In the PCA-SVM

Table 5
Prediction results of the TUG test.

Classifier model	Kernel function	Number of features	Accuracy	ROC AUC
SVM	Linear	36	66.67%	0.6111
	RBF	36	69.23%	0.6111
	Polynomial	36	77.78%	0.5556
PCA-SVM	Linear	16	66.67%	0.8333
	RBF	1	69.23%	0.6389
	Polynomial	1	66.67%	0.8333

AUC, area under the ROC curve; PCA, principal component analysis; SVM, support-vector machine; RBF, radial basis function; ROC, receiver operating characteristics.

Table 6
Prediction results of jump height.

Classifier model	Kernel function	Number of features	Accuracy	ROC AUC
SVM	Linear	36	66.67%	0.7222
	RBF	36	69.23%	0.7778
	Polynomial	36	70.00%	0.619
PCA-SVM	Linear	8	66.67%	0.7222
	RBF	3	69.23%	0.7778
	Polynomial	2	70.00%	0.6667

AUC, area under the ROC curve; PCA, principal component analysis; SVM, support-vector machine; RBF, radial basis function; ROC, receiver operating characteristics.

classification model, although the accuracy and ROC AUC are unchanged, the number of feature selections is significantly reduced. Therefore, it can be said that the PCA-SVM classification model of the RBF kernel function is better in comparison with the other models.

4. Discussion

Machine learning is capable of predicting several factors, such as reduction in walking speed (with up to 81.82% accuracy and ROC AUC 0.9167); increase in the time of the TUG test (with up to 66.67% accuracy and ROC AUC 0.8333); and reduction in vertical jump height (with up to 69.23% accuracy and ROC AUC 0.7778). Overall, neuropsychological tests are predictive of gait decline, especially walking speed, in MCI patients. Therefore, the highest correlation among gait parameters in MCI patients could be walking speed, and then followed by vertical jump height. Most studies have explored the gait of PD rather than the gait of MCI and there are different types of MCI. It needs to be considered together with other neurological diseases. Therefore, this study included patients with MCI caused by PD, AD, etc. There were many studies comparing the differences between pathological gait and healthy gait. The strength of our study is to investigate the gait parameters in different types of MCI patients. The decline of gait parameters in MCI patients can be predicted by neuropsychological tests via machine learning.

Several limitations must be addressed. First, the small sample size may limit the strength of the study. This is attributable to the study involving the combination of detailed neuropsychological and gait assessments. Second, selection bias may occur in this hospital-based study and high loss follow-up rate. Third, several known important factors affecting gait and jump performance, such as body mass index, medical conditions, medication information, and others, were not included in this study. Finally, all participants are still in the course of disease progression after the first visit, and their gait parameters may change in the future. A more extended period of observational study is warranted, using machine learning and gait parameters, to predict the decline in gait and jump performance. If more gait parameters and more participants with MCI are included, the amount of machine learning data can be increased, which would improve the accuracy of the prediction model.

5. Conclusion

This study included patients with MCI caused by PD, AD, etc. To explore the gait changes in MCI patients, we used machine learning to predict the possible reduction in walking speed, increase in the time of the TUG test and reduction in jump height through comprehensive neuropsychological tests. The neuropsychological testing is predictive of gait decline in MCI patients, especially in walking speeds.

Acknowledgments.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was reviewed and approved by the MacKay Memorial Hospital Institutional Review Board (number 18MMHIS 005e and 18MMHIS152).

Conflict of interest

Pei-Hao Chen, Chieh-Wen Lien, Wen-Chun Wu, Lu-Shan Lee, Jin-Siang Shaw declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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