University of Thessaly
Medical School

Master in Science

Methodology of Biomedical Research, Biostatistics and Clinical Bioinformatics

Assessment of MoCA, Rey, Trails A tests for the characterization of MCI in PD screening using covariate information

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September 2015

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ABSTRACT

The concept of mild cognitive impairment (MCI) in the general population has received increased attention over recent years, and is associated with risk of progression to Alzheimer's disease. Within Parkinson's disease (PD), MCI (PD-MCI) is recognized to be relatively common, with certain subtypes predicting progression to Parkinson's disease dementia (PDD). Considering the importance of this emerging entity, new diagnostic criteria have recently been proposed. Early recognition and accurate classification of PD-MCI could offer opportunities for novel therapeutic interventions.

The object of this study was to evaluate the efficacy of MoCA, Rey and Trails A for the detection of MCI in PD patients and whether additional diagnostic value is achieved by combining the measures.

A convenience sample of patients (n=334 after exclusions) were examined at the New Zealand Brain Research Institute (NZBRI). Subjects were administered the MoCA, TMT-Part A, RCFT Copy and RCFT Recall and classified in three categories: (a) Confirmed MCI (n=17), (b) Final Probable MCI (n=226) and (c) Final Possible MCI (n=91), based on their performance on the standardized neuropsychological tests.

Primary outcomes using receiver operating characteristic (ROC) curve analyses showed that the combination of the MoCA, RCFT Copy and RCFT Recall produced good discrimination of the Confirmed MCI (n=17) vs. Possible MCI (n=91) (area under the curve [AUC]: 86.1%) , even better for the Confirmed MCI (n=17) vs. non-MCI (n=337) (AUC: 93.9%) and excellent discrimination of the Confirmed MCI (n=17) vs. Probable HC (n=226) (AUC: 97.2%). The TMT Part A produced non-significant results in all 3 analyses. Moreover, the results demonstrated that combining the MoCA with the RCFT Copy and RCFT Recall provided better discrimination of MCI than the using single measures. Thus, researchers and clinicians should consider adding the RCFT as an adjunct test to the more routinely used MoCA when screening for cognitive impairment, given that its copy and the immediate recall trial can be completed in less than 10 minutes. The models were validated using a leave-one-out analysis cross-validation technique.

GLOSSARY

AUC area under the curve; CI confidence interval; MMSE MiniMental State Examination; MoCA Montreal Cognitive Assessment; MCI; Mild Cognitive Impairment; NPV negative predictive value; PPV positive predictive value; PD Parkinson disease; PD-D Parkinson disease with dementia; PD-MCI Parkinson disease with mild cognitive impairment; Rey RCFT Rey Complex Figure Test; ROC receiver operating characteristic; Trails A TMT Trail Making Tests Part A .

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease affecting over 4 million people over age 50 years and it is expected to double over the next 2 decades. [1]

Diagnosing Parkinson's disease can be difficult, especially in its early stages. Even as the disease progresses, symptoms may be difficult to assess and may mirror other disorders.

Cognitive impairment is common in Parkinson's disease, even in the earliest disease stages and can range from mild impairment (PD-MCI) to florid dementia. 30% to 40% of PD patients eventually suffer from dementia. (Aarsland, et al., 2001) Neuropsychology testing has shown evidence of cognitive impairment in over 20% of patients who are diagnosed with Parkinson's disease [2][3]and over 80% of PD patients will develop dementia over an 8 year period. [4] Dementia doubles the mortality risk of PD and increases nursing home placement. [5][6]. Abnormalities that are shown in neuropsychological tests in non-demented PD patients may predict the development of dementia, although the types of abnormalities are plenty. [7] [8][9][10]

Within years, the concept of mild cognitive impairment (MCI) has changed from global cognitive measure to a cognitive syndrome with both clinical and research diagnostic criteria. [11][12]-[14] Mild cognitive impairment was first introduced in Alzheimer's disease (AD)[11] but has been extended to other neurodegenerative disorders, like PD.[15]

In general, mild cognitive impairment (MCI) refers to cognitive decline that is not normal for age, like basic activities of daily living, thus not severe enough to conclude dementia. [11] MCI does not necessarily progresses to a dementia, but its construct implies that may lead from normal cognition to dementia, with MCI representing a transitional or prodromal state. [12]

Despite the high frequency of cognitive impairment in PD, there is no accurate screening tool to identify cognitive impairment in these patients.[16] Identification of the early stages of MCI in PD patients is important, because it predicts future cognitive decline, including development of PD dementia (PDD), [17]-[20] and worsening of health-related quality of life.[21]

Tests such as the Mini-Mental State Examination (MMSE) [22] are insensitive to the cognitive impairments in PD. [23]

 The Montreal Cognitive Assessment (MoCA) [24] was developed as a short screening tool for mild cognitive impairment (MCI). It is similar to the MMSE, but is more sensitive in identifying MCI in general population. The MoCA includes tests of the cognitive domains of executive and visuospatial function, memory, language and attention, which are affected in early PD. [3][8] A lot of studies have tried to use the concept of MCI in PD to define this population and a lot more will be conducted in

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order to fulfill the necessity of detecting cognitive impairment in PD that does not meet criteria for dementia. [18][20]

One longitudinal study between patients who became demented during follow-up and people who remained non-demented, showed that the most significant predictors to indicate that individuals will develop dementia are the tests of speeded processing of visuospatial information. [25]. Therefore, tests like the Rey Complex Figure Test (RCFT) and the Trail Making Test Part A (TMT Part A) were also included in the study with the MoCA test. The RCFT is a neuropsychological assessment that measures both visuospatial abilities and memory and Part A of the TMT a neuropsychological test of visual attention and speed of processing.

METHODS

Participants

This study was conducted at Christchurch, New Zealand. Six hundred and nine (609) people ≤65 were recruited through newspaper advertisement, public seminars made to community groups in the Canterbury region and the New Zealand Brain Research Institute (NZBRI) database. Of the 609 volunteers only 387 remained in the study. Exclusion criteria included: (1) aged 85 years or older; (2) previous or current medical complications (i.e., multiple sclerosis, Parkinson's disease, major coronary disease, stroke, cancer); (3) developmental disorders (i.e., learning disability, Autistic spectrum disorder); (4) major psychiatric conditions (i.e., schizophrenia, bipolar); or (5) current medications (i.e., antidepressants, benzodiazepines) that are likely to affect cognitive functioning.

After the final classification, 17 participants were classified as Confirmed MCI, 226 as Final Probable MCI and 91 as Final Possible MCI.

Standard protocol approvals, registrations, and patient consents.

The study was approved by the Upper South Ethics Committee of the New Zealand Ministry of Health and informed consent was provided by all participants with additional consent from a significant other when required

Neuropsychological evaluation

A neuropsychological battery was completed by all 334 participants. . Neuropsychological tests were conducted on 2 sessions with a fixed order that balanced verbal and nonverbal materials with breaks to avoid fatigue, using three postgraduate psychology students including the author, trained in administering the neuropsychological tests.

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Statistical Analyses

The R program version 3.2.2 was used for group comparisons and ROC curve analyses.

The primary ROC curve analyses tested the diagnostic performance of each individual screening measure, namely the MoCA, RCFT Copy, RCFT Recall, and TMT Part A, across pairs of groups. For the analyses relevant to MCI diagnosis in the general elderly population the Possible MCI and the Probable HC were treated as a single non-MCI group (n=317) and compared with the Confirmed MCI group (n=17). To specify performance detecting MCI from normal cognition, the Confirmed MCI group (n=17) was compared with the Probable HC group (n=226). In order to diagnose MCI from individuals with some cognitive impairments but not sufficient for a diagnosis of MCI, the Confirmed MCI group (n=17) was compared with the Possible MCI group (n=91).

Binary logistic regression was performed for each of the three groups listed above. The analysis was conducted to examine whether diagnostic utility was achieved by combining the measures. In addition with the four screening measures, demographic data like sex, age and educational-adjusted scores were also used.

Cross validation techniques were used to evaluate the model. The results of 10-fold cross validation and leave-one-out analysis cross-validation techniques were compared in order to determine which technique best evaluates the predictive ability of the model.

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RESULTS

1. <u>Confirmed MCI vs. non-MCI (Possible MCI and Probable HC combined) (n=17 vs n=337)</u>

When discriminating patients with MCI from patients without MCI, the diagnostic utility of the different screening tests, namely MoCA, RCFT Copy and RCFT Recall, produced high AUCs, but in this instance the RCFT Recall appeared to perform better than all 3 other measures (Table 1). The optimal cut-off point, sensitivity, specificity, PPV and NPV for each screening instrument are listed in Table 1. The AUC for the RCFT Recall was significantly higher than that shown by the MoCA (AUC difference = 8.2%, p <0.05), however the RCFT Copy (AUC difference = 10.8%, p = 0.055 (>0.05)) was marginally significant. The AUC for TMT Part A was significantly inferior compared to the MoCA, RCFT Copy and RCFT Recall A (AUC difference of 26.1% for the MoCA, p < 0.001; AUC difference of 23.5% for the RCFT copy, p < 0.01; and AUC difference of 34.3% for the RCFT recall, p < 0.001). The AUC difference between the MoCA and RCFT Copy was not statistically significant (AUC difference = 2.6%, p = 0.58(>0.05)).

Combination of the MoCA, RCFT Copy and RCFT Recall approached perfect separation between patients with and without MCI and were significantly superior in this regard compared to the AUC for the MoCA (AUC difference = 11.0%; p < 0.001) and the RCFT Copy (AUC difference = 13.6%; p < 0.001). The AUCs for the combined model and the RCFT Recall were similar. However, the difference failed to reach significance (AUC difference = 2.8%; p = 0.22(>0.05)), although sensitivity and PPV were increased by the combination model compared to the RCFT Recall. The TMT Part A was not statistically significant (p =0.55>0.05). The AUCs of each test are illustrated in Figure 1-1 and of the combination model in Figure 1-2.

Table 1-1. Diagnostic Performance of MoCA, RCFT Recall, RCFT Copy, TMT Part A

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC(95% CI)	p-value
MoCA	<26	88.23	67.5	12.7	99	0.829(0.748, 0.909)	<0.001
RCFT Recall	<-1.10	82.4	86.1	20	98.8	0.911(0.848, 0.973)	<0.001
RCFT Copy	<-0.82	70.6	78.5	15	98	0.803(0.685, 0.920)	<0.001
TMT Part A	<1.03	88.2	33.9	16.47	98.79	0.568(0.437, 0.698)	0.347
Combined Model	—	94.1	89.6	32	99.64	0.939(0.870,1.000)	<0.001

MoCA = Montreal Cognitive Assessment; RCFT = Rey Complex Figure Test; TMT = Trail Making Test; Combined model = MoCA + RCFT Copy + RCFT Recall; cut-off = the value that produced the highest Youden index; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve; CI = confidence interval.

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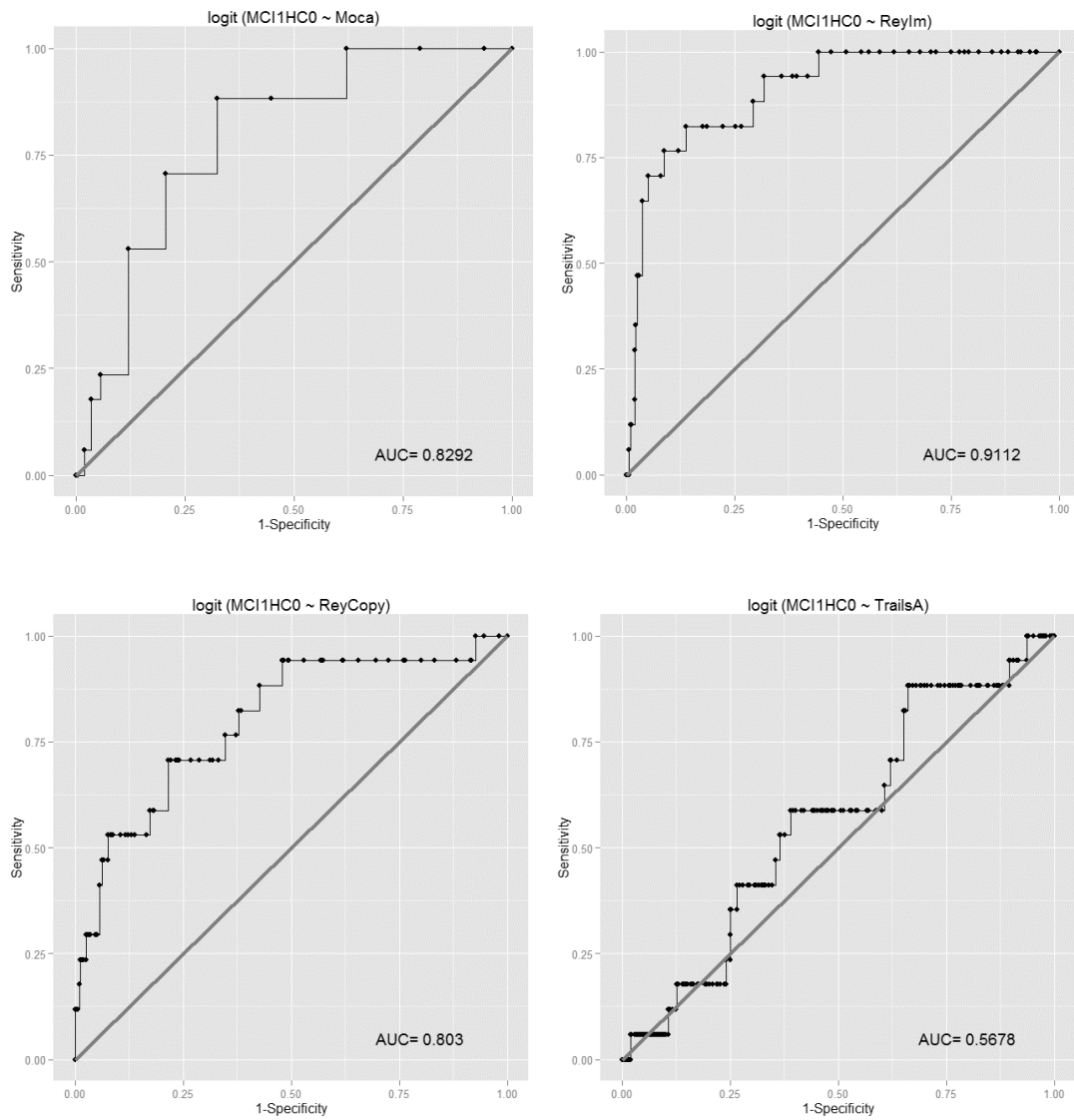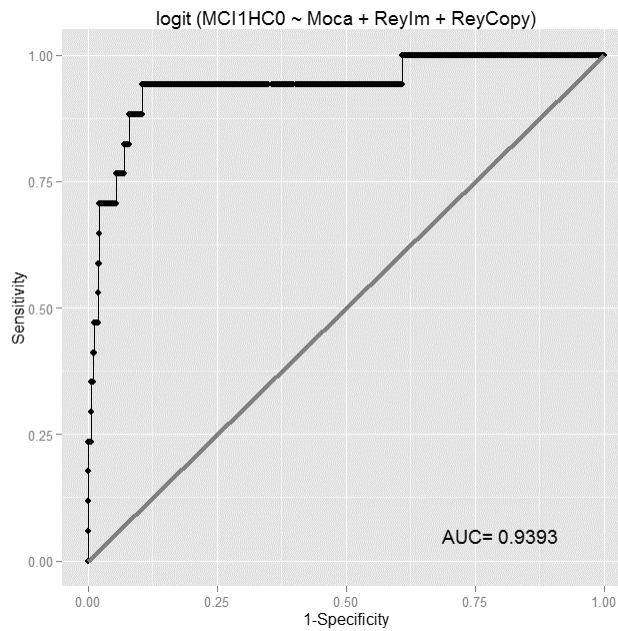**Figure 1-1. ROC curves for MoCA, RCFT Recall, RCFT Copy, TMT Part A**

logit (MCI1HC0 ~ Moca)
AUC= 0.8292

logit (MCI1HC0 ~ ReyIm)
AUC= 0.9112

logit (MCI1HC0 ~ ReyCopy)
AUC= 0.803

logit (MCI1HC0 ~ TrailsA)
AUC= 0.5678

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Figure 1-2. ROC curves for the combined model (Moca + RCFT Recall + RCFT Copy) to detect Confirmed MCI vs. Non-MCI

logit (MCI1HC0 ~ Moca + ReyIm + ReyCopy)

AUC= 0.9393

1.2 Cross-validation

As shown in Table 1-2 leave-one-out cross validation technique performs better from 10-fold cross validation since the difference between observed (Delta[1]) and predicted value (Delta[2]) with the leave-one-out technique (dif.= 5.21_x10^{-6}) is less than the difference of the 10-fold cross validation (dif.= 1.5_x10^{-4}).

($Error_i = y_i - f_{i,}$ $_i$= observed value, f_i= predicted value)

Table 1-2. Performance of 10-fold cross validation and leave one out cross validation technique

Cross-validation technique	Delta[1]	Delta[2]	Difference
10-fold cross-validation	0.03057016	0.03041945	1.5_x10^{-4}
Leave-one-out cross-validation	0.03156990	0.03156469	5.21_x10^{-6}

Delta[1]= observed value; Delta[2]= predicted value

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2. Confirmed MCI (n=17) vs. Possible MCI (n=91)

Both the MoCA and RCFT Recall produced statistically significant results when discriminating Confirmed from Possible MCI. The optimal cut-off point, sensitivity and specificity, PPV and NPV for each screening instrument are listed in Table 2. The AUC for the RCFT Recall (AUC: 0.78, $p<0.01$) was higher from the AUC for the MoCA (AUC: 0.743, $p<0.01$) with a difference of 3.7% ($p=0.61>0.05$). Although the TMT Part A was not statistically significant ($p>0.05$), the AUC between the TMT Part A and the MoCA (AUC difference of 20%, $p<0.01$) and the RCFT Recall (AUC difference of 23.7%, $p<0.01$) was significant higher, while the AUC difference between the RCFT Copy and the MoCA (AUC difference of 13.6%, $p=0.10>0.05$) and the RCFT Recall (AUC difference of 17.3%, $p=0.11>0.05$) did not reach significance. The RCFT Copy and the TMT Part A produced non-significant AUCs ($p=0.1$, $p=0.54$ respectively).

The optimal combination was produced by the inclusion of MoCA, RCFT Copy and RCFT Recall. The combination of these tests again produced significantly higher AUC than the MoCA (AUC difference of 11.8%; $p<0.05$) and the RCFT Copy (AUC difference of 25.4%, $p<0.001$). The difference failed to reach significance when compared to the RCFT Recall (AUC difference of 8.1%; $p=0.09>0.05$). The AUCs of each test are illustrated in Figure 2-1 and of the combination model in Figure 2-2.

Table 2. Diagnostic Performance of MoCA, RCFT Recall, RCFT Copy, TMT Part A

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC(95% CI)	p-value
MoCA	<26	88.24	53.8	22.05	95	0.743(0.634, 0.851)	<0.01
RCFT Recall	<-1.5	70.6	82.4	32.43	92.95	0.780(0.653, 0.906)	<0.01
RCFT Copy	<-1.53	52.94	73.6	25.71	89.04	0.607(0.441, 0.851)	0.1
TMT Part A	<1.03	88.24	31.86	10.34	82.27	0.457(0.409, 0.676)	0.578
Combined Model	—	70.6	92.3	63.15	94.38	0.861(0.745,0.976)	<0.001

MoCA = Montreal Cognitive Assessment; RCFT = Rey Complex Figure Test; TMT = Trail Making Test; Combined model = MoCA + RCFT Copy + RCFT Recall; cut-off = the value that produced the highest Youden index; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve; CI = confidence interval.

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Figure 2-1. ROC curves for MoCA, RCFT Recall, RCFT Copy to detect Confirmed MCI vs Possible MCI
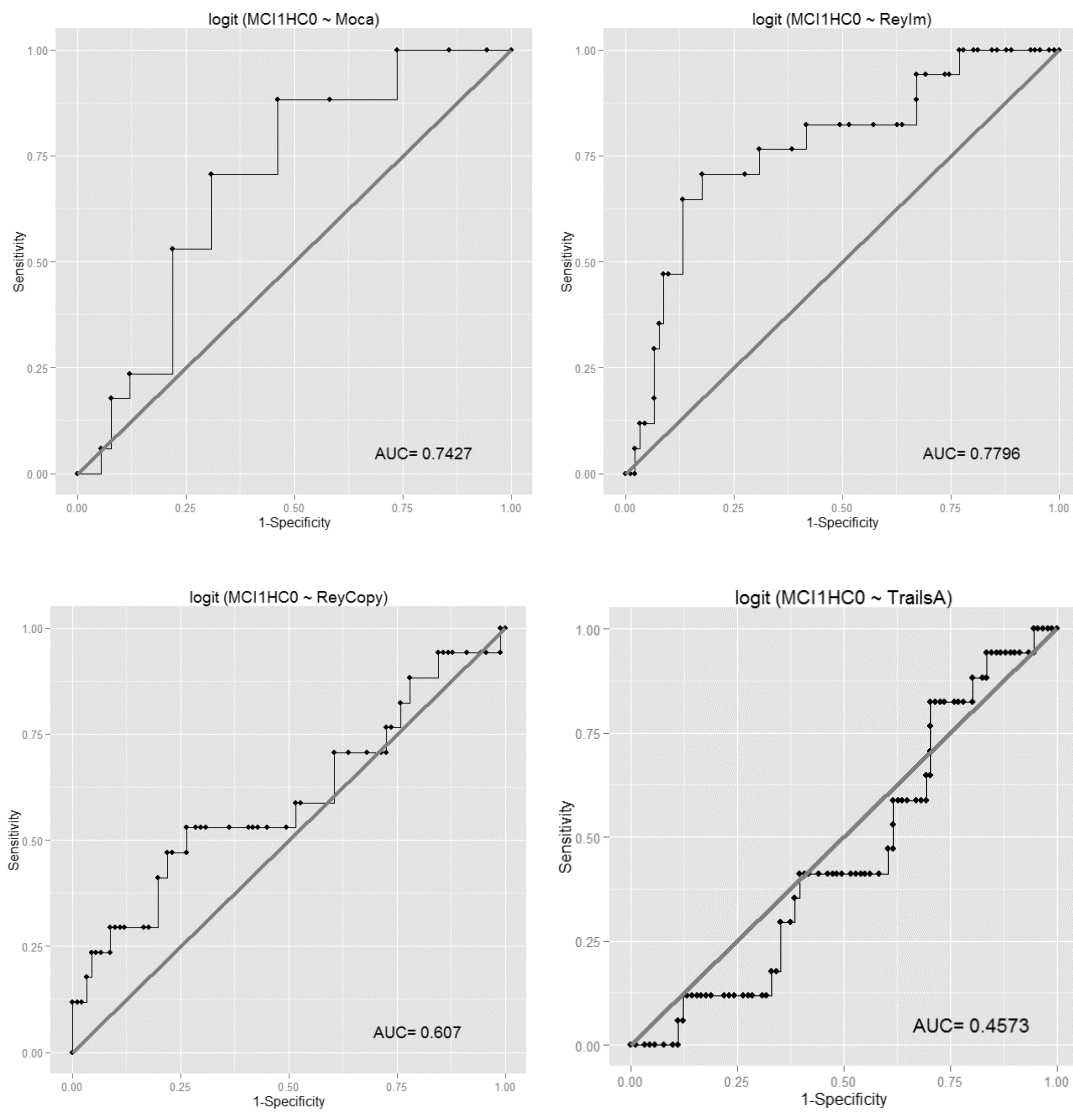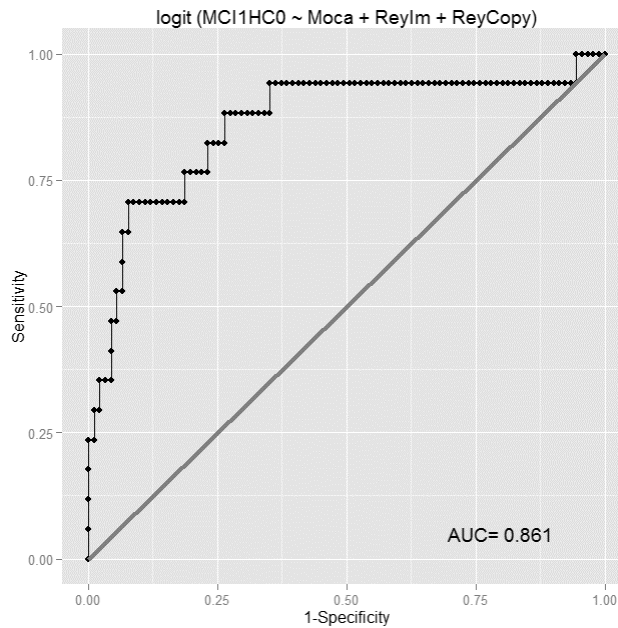
Figure 2-2. ROC curves for the combined model (Moca + RCFT Recall + RCFT Copy) to detect Confirmed MCI vs Possible MCI

2.2 Cross-validation

Once again, (Table 2-2), the Error of leave-one-out cross validation technique (dif.= 6.01_x10^{-5}) is smaller from 10-fold cross validation (dif.= 6.53_x10^{-4}). Thus, leave-one-out cross validation technique evaluates better the predictive ability of the logistic regression.

($Error_i = y_i - f_{i,}$ $_i$= observed value, f_i= predicted value)

Table 2-2. Performance of 10-fold cross validation and leave one out cross validation technique

Cross-validation technique	Delta[1]	Delta[2]	Difference
10-fold cross-validation	0.09769609	0.09704344	6.53_x10^{-4}
Leave-one-out cross-validation	0.09838890	0.09832875	6.01_x10^{-5}

Delta[1]= observed value; Delta[2]= predicted value

3. Confirmed MCI (n=17) vs. Probable HC (n=226)

In order to differentiate the Confirmed MCI from the Probable HC the tests that produced higher AUCs were the MoCA, RCFT Copy and RCFT Recall and they were superior to the TMT Part A (Figure 3-1). The AUC of the RCFT Recall was significantly higher than that shown by the MoCA (AUC difference of 10.0%, p<0.01) but it did not reach significance between the RCFT Copy (AUC difference of 1.8%, p=0.07). Once again, The TMT Part A was not statistically significant (p =0.246>0.05).

The combination model which was consisted of the MoCA, RCFT Copy and the RCFT Recall, performed better than the individual screening measures (Figure 3-2). In fact, it produced excellent AUC, sensitivity, specificity, PPV and NPV (Table 3). The combined model was significantly superior to the MoCA (AUC difference of 10.8%, p<0.001) and the RCFT Copy (AUC difference of 9.0%, p<0.01). The combination model now produced an AUC difference that approached significance for the RCFT Recall (AUC difference of 0.74%, p =0.67(>0.05)).

Table 3. Diagnostic Performance of MoCA, RCFT Recall, RCFT Copy, TMT Part A

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC(95% CI)	p-value
MoCA	<26	88.23	73	14.42	98.56	0.864(0.788, 0.939)	<0.001
RCFT Recall	<-0.8	82.35	97.34	70	98.65	0.964(0.924, 1.000)	<0.001
RCFT Copy	<-0.8	70.58	94.24	48	97.7	0.882(0.773, 0.991)	<0.001
TMT Part A	<1.03	88.2	34.7	35	98.52	0.578(0.441, 0.715)	0.246
Combined Model	—	94.1	100	94.1	99.55	0.972(0.916,1.000)	<0.001

MoCA = Montreal Cognitive Assessment; RCFT = Rey Complex Figure Test; TMT = Trail Making Test; Combined model = MoCA + RCFT Copy + RCFT Recall; cut-off = the value that produced the highest Youden index; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve; CI = confidence interval.

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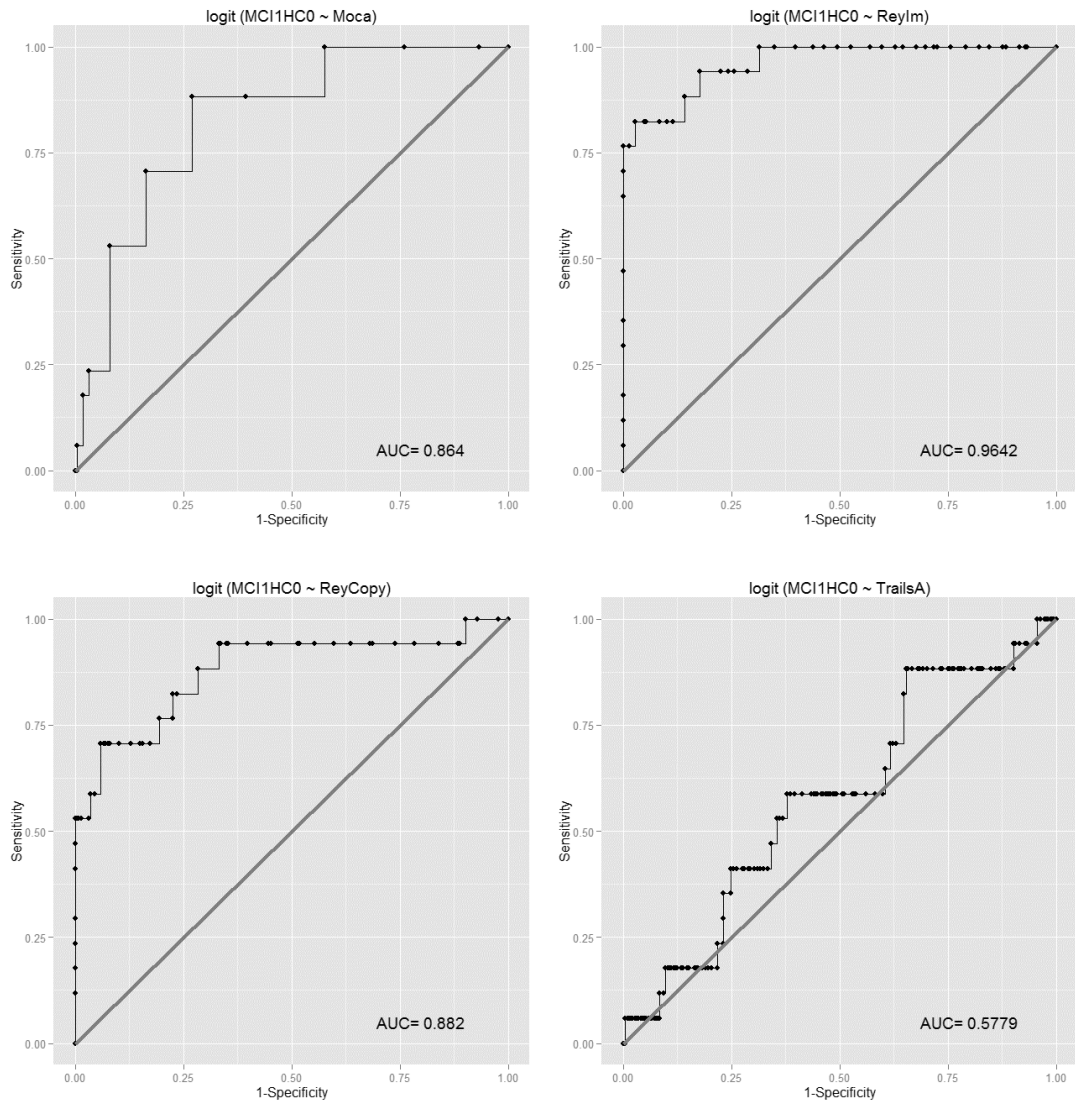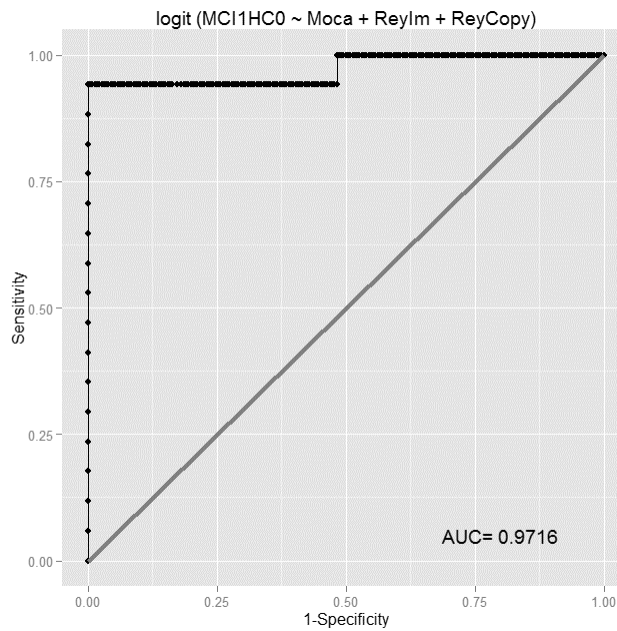**Figure 3-1. ROC curves for MoCA, RCFT Recall, RCFT Copy, TMT Part A model to detect Confirmed MCI vs Probable HC**

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Figure 3-2. ROC curves the combined model (Moca + RCFT Recall + RCFT Copy) to detect Confirmed MCI vs Probable HC

logit (MCI1HC0 ~ Moca + ReyIm + ReyCopy)

AUC= 0.9716

3.2 Cross-validation

Like the previous comparisons, 10-fold cross-validation is not the best way to evaluate the predictive value of the model. The difference between observed and predicted value (dif.= 8.72_x10^{-5}) is bigger from the difference of the leave-one-out cross validation technique (dif.= 3.14_x10^{-6}). Leave-one-out cross validation technique shows good predictive ability and is the appropriate technique to assess the accuracy and validity of the statistical model.

($Error_i = y_i - f_{i,}$ $_i$= observed value, f_i= predicted value)

Table 3-2. Performance of 10-fold cross validation and leave one out cross validation technique

Cross-validation technique	Delta[1]	Delta[2]	Difference
10-fold cross-validation	0.01030491	0.01021768	8.72_x10^{-5}
Leave-one-out cross-validation	0.01003743	0.01003429	3.14_x10^{-6}

Delta[1]= observed value; Delta[2]= predicted value

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DISCUSSION

The current study provides evidence that the combination of the MoCA, RCFT Copy an RCFT Recall produces good discrimination of the patients with MCI from patients without MCI. In fact, the combination of these tests performed better than using each test individually. ROC Curve analyses for the discrimination of the Confirmed vs. the Possible cases showed that the combined model (MoCA, RCFT Copy an RCFT Recall) again exhibited better relative to each individual test, although the AUC difference that approached significance for the RCFT Recall suggested that an increased sample size might confirm the benefit of the combination model for this discrimination. Importantly, for the last analyses, the combination model showed excellent AUC, sensitivity, specificity, PPV and NPV. Consistent with the Confirmed MCI vs. non-MCI and the Confirmed MCI vs. the Possible MCI comparisons, the AUC for the Confirmed MCI vs. Probable HC produced by the combination model was excellent. The TMT Part A produced non-significant AUC, in all three analyses, which indicates that it is a poor diagnostic marker. Therefore, researchers and clinicians should consider adding the RCFT as an adjunct test to the more routinely used MoCA when screening for cognitive impairment, given that its copy and the immediate recall trial can be completed in less than 10 minutes.

The primary limitation of the current study is that not everyone's cognitive status was confirmed by comprehensive neuropsychological assessment. This may have caused some classification errors. Larger sample sizes of MCI and Possible MCI might have prevented the elucidation of statically significant effects, since there was a clear imbalance of sample size between the three cognitive classes. Thus, future studies should require larger sample sizes.

ACKNOWLEDGMENT

APPENDIX

```r
## convert xlsx file to txt file

library(xlsx)

file <- read.xlsx("excelfile.xlsx",sheetIndex=1)

colnames(file) <- c("ID","MCI1HC0","Sex","Age","Educ","Moca","ReyIm","ReyCopy","TrailsA")

write.table(file,"txtxfile.txt")

mydata <- read.table("txtfile.txt",header=T)


## view the first six rows of the data

head(mydata)


## logistic regression model for each of the tests (MoCA, RCFT Recall, RCFT Copy, TMT PartA)
## F is a binary factor
## x_i are continuous predictors (i=1,…,4)
## y_i is the response variable of the models

library(MASS)

y_i <- glm(F ~x_i, data = mydata, family = "binomial")

summary(y_i)


##  logistic regression for the combined model (fit model)

Test <- glm(F ~x_1 + x_2 + x_3, data = mydata, family = "binomial")

summary(Test)


## creation of ROC Curves

library(pROC)

library(ROCR)

library(Deducer)

rocplot(y_i)


##  AUC, 95% CI AUC for each test and the combined model

prob=predict(y_i ,type=c("response"))

mydata$prob=prob

library(pROC)

roc_i<- roc(F ~ prob, data = mydata)
```

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auc(y_i)

ci.auc(y_i)

optimal cut-off point graphically for each test and the combined model

library(Epi)

bestpointtest<-ROC(form=F~ y_i, data=mydata)

optimal cut-off point numerically for each test and the combined model

opt <- which.max(rowSums(bestpointtest$res[, c("sens", "spec")]))

bestpointtestreslr.eta[opt]

Sens, Spec, PPV, NPV for each test and the combined model

coords(y_i, bestpointtestreslr.eta[opt], "threshold", ret=c("sensitivity","specificity","ppv","npv"))

Tests between curves

roc_1, roc_2 the two ROC curves to compare

roc.test(roc_1, roc_2)

crossvalidation

library(boot)

10-fold CV for the combined models

val.10.fold<- cv.glm(data = mydata, glmfit= Test, K = 10)

val.10.fold

val.10.fold$delta

leave-one-out CV for the combined models

val.all.fold<- cv.glm(data = mydata, glmfit= Test, K = nrow(mydata))

val.all.fold

val.all.fold$delta

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