Prediction of future development of MCI patients based on cognitive function

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Mild Cognitive Impairment (MCI) refers to a transitional stage between normal aging and dementia. The purpose of this study was to predict the development of MCI patients based on cognitive function. 222 MCI patients were studied at baseline and at a follow-up of 2 years. Using discriminant analysis, they were predicted into four diagnostic groups: Improved, Stable MCI, Dementia of the Alzheimer's Type (AD) and Other Dementia. Using four tests - Rey-Osterrieth Complex Figure Test recall, Auditory-Verbal Learning Test recall, TMTB time and Digit Symbol – overall 62.6% of cases were correctly classified after cross-validation. The rate of prediction in this study was 1.8 times better than chance, which is better than reported in most other studies. The model did best for the AD group with 80% of cases correctly classified. However, most cases in the Other Dementia group were also classified as AD.

The concept of Mild Cognitive Impairment (MCI) refers to persons who exhibit some form of cognitive deficits without being demented (Palmer, Fratiglioni & Winblad, 2003). The condition is not as yet an established diagnosis but is rather a concept under development, and there have been different criteria for it in use (Ritchie & Touchon, 2000). However, the cognitive impairment in question has usually been thought of in terms of memory deficits and the condition has often been considered to be a progressively degenerative phase to Dementia of the Alzheimer's Type (AD) (Petersen, 2004). The rationale of MCI research has been to make early interventions for AD possible, which is important because available treatments work better in early stages of dementia (Brucoli and Loverstone, 2004; Modrego, 2006). To do this, more information is needed about which MCI patients will progress to AD.

Studies show that the condition also covers other cognitive functions than episodic memory, and progression to other forms of dementia than AD is known to be possible (Petersen, 2004). It can also be a stable condition for many years and many patients even seem to recover from it (Palmer et al., 2003; Winblad et al., 2004). Table 1 shows the variation across studies in patients that improve, remain stable at the MCI diagnosis or develop dementia. The variation is partly due to different definitions of MCI (Palmer et al., 2003).

Table 1. Status at Follow-Up in Studies Examining the Evolution of MCI Patients (Palmer et al., 2003)

Status at Follow-Up	Frequencies
Improved	15-44%
Stable MCI	11-76%
Demented	9-80%

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Petersen el al.'s (1999) first proposed definition of MCI focused on memory impairment. This definition soon became very influential. Later, Petersen et al. (2001a) revised the criteria and suggested a classification of three MCI subtypes based on the number of impaired cognitive functions and whether or not memory deficits are involved. They also speculated about the likely progression of the different subtypes. The first subtype was called amnestic MCI and is made up of patients with an isolated memory impairment. This subtype corresponds to the original definition of MCI. Those patients were thought to be most likely to progress to AD. The second subtype consists of patients with impairments in more than one cognitive function, with or without memory. Those patients could develop AD, but Vascular Dementia (VAD) was also thought to be possible. Finally, the third subtype consists of patients with impairment in a single cognitive function other than memory. Those patients could develop other forms of dementia such as Lewy Body Dementia or Frontotemporal Dementia, even thought AD or VAD was also considered to be likely candidates. Thus, this model suggests many possible cognitive deficits in preclinical AD. Other forms of aetiology than dementia are also thought to be possible. For example, in a later version of this model, Petersen (2004) notes that depression may sometimes be the cause of the MCI subtypes with memory deficits. However, improvement or MCI as a stable condition was not covered by this model.

Previous studies have investigated the possibility of predicting the conversion of MCI patients to dementia using cognitive function, and the results seem promising. In a systematic review of articles on the subject published between 1991 and 2001, Brucoli and Loverstone (2004) found that cognitive function was the single most important factor in predicting the future development of MCI patients, and they concluded that even very simple assessments of cognitive function with MMSE (Mini Mental State Examination) or just a few simple questions may result in successful prediction. Petersen et al. (2001b) reached the same conclusion in another independent review.

Are measures of cognitive function enough to predict AD? According to Modrego (2006) there is not enough evidence to recommend specific techniques for prediction. The author recommended using a combination of comprehensive neuropsychological assessments, genotype and neuroradiological techniques. Bäckman et al. (2004) encourage future research to combine cognitive indicators of AD with other types of markers.

How accurate are the predictions? In a review of studies investigating this issue, Modrego (2006) found that prediction of the development of MCI patients to AD using neuropsychological assessments have a sensitivity and specificity of up to 70%. Chong and Sahadevan (2005) found measures in the same range in another review. The best result was reached with delayed word-list recall with a sensitivity of 75-80% and a specificity of 80%. However, there seems to be some variability across studies. In a study of 49 MCI patients, Griffith et al. (2006) successfully predicted cases at two years follow-up to either AD converters or MCI nonconverters with 76.9% sensitivity and 88.9% specificity using only assessments of cognitive function. In another study predicting the development of MCI patients into AD converters or nonconverters (Artero, Tierny, Touchon & Ritchie, 2003), a model was created with a sensitivity of 73% and specificity of 99%. The differences across studies could, in part, be explained by variation in study design, time to follow-up and inclusion criteria.

It seems that measures of many different cognitive functions can be used to predict which MCI patients will develop AD. In their review, Chong and Sahadevan (2005) found that episodic memory, semantic memory, attention processing and mental speed can successfully

be used for this purpose. Other studies have given support to other cognitive functions as predictors of AD, such as executive function (Albert, Moss, Tanzi & Jones 2001; Griffith et al., 2006; Tabert et al., 2006) and visual spatial function (Amieva et al., 2004; Artero et al., 2003; Barbeau et al., 2004; Blackwell et al., 2004; Griffith et al., 2006). In a study comparing amnestic MCI patients with MCI patients that also had other deficits, Storandt, Grant, Miller and Morris (2006) reached the conclusion that AD can begin with impairment in a cognitive function other than memory. In another study, Kramer et al. (2006) found that most MCI patients may have deficits in several cognitive functions. For that reason, they argued that MCI patients should be examined using comprehensive neuropsychological assessments even when they themselves are only reporting memory decline. However, measures of episodic memory seem to be the most consistent predictors (Aggarawall, Wilson, Beck, Bienias & Bennett, 2005; Bäckman, Jones, Berger, Laukka, & Small, 2004; Bäckman, Small & Fratiglioni, 2001; Ivanoiu et al., 2005; Petersen et al. 2001b; Tabert et al., 2006), followed by executive function deficits (Bäckman et al, 2004; Tabert et al, 2006). Tabert et al. (2006) have suggested that episodic memory is first affected, but as AD progresses in its preclinical stage, other cognitive functions are impaired before the disease is finally possible to diagnose. The idea is that the amnestic single domain subtype of MCI suggested by Petersen et al. (2001a) is followed by the multiple domain subtype.

Most studies to this date have focused on the conversion of MCI patients to AD. Little is known about those who improve, remain stable or develop dementia other than AD. However, a preclinical phase to Vascular Dementia (VAD) has been reported in a few studies. Using MMSE as well as psychometric tests, deficits in episodic memory have been identified in these patients 3 year before the onset of dementia. (Jones, Jonsson Laukka, Small, Fratiglione & Bäckman, 2004; Jonsson Laukka, Jones, Small, Fratiglioni & Bäckman, 2004). Even more interesting, there were no preclinical diferences in terms of cognitive function between patients with VAD and AD in these studies. Using MMSE, Stirling Meyer, Xu, Thornby, Chowdhury and Quach (2002) have also identified a preclinical phase to some VAD subtypes (those caused by subcortical microvascular disease) that mimic the preclinical phase to AD. This phase was marked by poor performance at memory subtests.

The purpose of this study was to predict the future development of MCI patients using measures of cognitive function. A clinical sample of MCI patients from the Karolinska University Hospital at Huddinge in Stockholm was studied at baseline and at follow-up. Most previous studies have focused on the conversion of MCI patients to AD. In this study patients converting to other forms of dementia were also included, as well as patients that remained stable or improved.

Patients and methods

Study sample

260 patients were taken from the memory clinic (sub division of the Geriatric clinic) at the Karolinska University Hospital, Huddinge. There were three inclusion criteria in this study:

- First, that the patient had been examined and diagnosed at two or more occasions
- Second, that the patient's first diagnosis was MCI.
- Third, that the patient had been assessed by a clinical neuropsychologist at the time for the first diagnosis.

The patients fitting all of the above criteria were taken from the journal data base called GEDOC. At follow-up, all patients were diagnosed a second time, which resulted in four diagnostic groups: Improved (i. e. patients no longer fitting the criteria of MCI used at the clinic, see below), Stable MCI (i.e. patients retaining the MCI diagnosis), AD (i.e. patients that converted from MCI to AD) and Other Dementia (i.e. patients that converted to Vascular Dementia (n = 12), Dementia Not Otherwise Specified (DNOS) (n = 11), or Lewy Body Dementia (n =1), total n = 24). Because only one case had the diagnosis Lewy Body Dementia, it was dropped from further analysing. Some patients had visited the clinic several times and the data from their latest visit were used in this study as follow-up data.

There was a variation in terms of time interval between the neuropsychological assessment and the date of the first diagnosis. As the maximum time interval, 3 months was set and as a result of this, 26 cases were dropped from further analysing. Also, 6 months was set as minimum time to follow-up. As a result, 12 cases were dropped from further analysing. A total sum of 35 cases were dropped (3 cases were dropped because of both too long time to follow-up, and too long time between date of first diagnosis and neuropsychological assessment).

Procedure

The patients were mainly referred to the clinic from physicians in general practice or occupational physicians (Wahlund, Pihlstrand & Eriksdotter Jönhagen, 2003). They had visited the clinic between the years of 1990 to 2005. Procedures for examination of patients at the clinic have been described elsewhere (Wahlund et al., 2003). They include neuropsychological testing, physical and psychiatric evaluations, CT or MRI scans, EEG as well as cerebral SPECT, lumbar puncture, blood analyses, neuropsychiatric, linguistic and occupational therapeutic examinations. This procedure takes 4 days.

Diagnosis was set at a meeting with clinicians present from the different professions involved in the examination of the patient. Diagnosis of AD and other forms of dementia was made according to DSM-IV (APA, 1994). The diagnostic criteria for MCI at the clinic were as follows (Wahlund et al., 2003):

- Subjective complaints about memory
- Objective signs of decline in any cognitive function (below 1, 5 SD as compared to age norms on neuropsychological tests).
- Activities of daily living intact.
- Non-demented according to criteria from DSM-IV (APA, 1994)/ICD-10 (WHO, 1992).

Tests of Cognitive functions

The tests used in this study included Arithmetic, Block Design, Digit Span Forwards and Backwards (maximum number of digits), Digit Symbol, Information and Similarities from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), Logical Memory, free and cued recall, from the Wechsler memory Scale-Revised (WMS-R) (Wechsler & Stone, 1973), Auditory Verbal Learning Test (AVLT), learning trails 1-5 (total sum) and delayed recall (Rey, 1959), Rey-Osterrieth complex Figure Test (RO) copying and immediate recall (Lezak, 1995), Trail Making Test (TMT) A and B, number of correct connections and time (seconds) (Reitan & Wolfson, 1993), 12-word list (Äldrecentrums ordlista, d') (Bäckman & Forsell, 1994), Verbal Fluency Test (FAS) (Fernaeus & Almkvist, 1998) and Figure Classification (SRB2) (number of correct replies minus the number of wrong replies divided by 4) (Andersson, Berg, Lawenius & Svanborg, 1978).

Data handling
Frequencies of missing data were studied for cases and test variables. All variables had missing values, and variables with a frequency of missing values more than 32% were rejected. These were Logical Memory free recall and cued recall, FAS, Arithmetic and SRB2. 67% of cases had missing data in one or more variables. 2 cases had more than 60% missing data and were therefore eliminated. After this, a total sum of 9% of data was missing.

After cases had been removed, 222 patients remained. In the Other Dementia group, 19 cases had DNOS and 9 had VAD. Demographic data (age, gender, and education), time to follow-up and scores at MMSE for the four groups, are shown in Table 2. The test results at baseline for the four diagnostic groups on each test are listed in Table 3. Possible group differences were investigated using one-way ANOVA and Pearson's Chi-square.

The data was examined in order to detect outliers. Univariate outliers were defined as cases with values in any variable +/- 3SD from the sample mean. Multivariate outliers were detected using Mahalanobi's distance (Tabachnick & Fidell, 2007). The χ^2 value corresponding to a significance level of 0.001 and the number of variables (15) as degrees of freedom, was used as criterion. Thus, any observation with a Mahalanobi's distance exceeding 37.7 was considered to be a multivariate outlier. A number of outliers were identified. Their data were compared to the original data in their journal records to make sure they were not due to data entry error. If so, they were corrected. Of the remaining outliers, one had low values on both TMTB time and correct, which was thought to indicate that the patient had given up the test prematurely. The value on TMTB time was therefore adjusted by dividing it by the number of correct connections and then multiplying it with 24. This would be the value for this case if the patient had finished the test. The value of this case at TMTB correct was deleted and treated as missing data. The rest of the outliers were thought to be genuine observations and were therefore retained.

Of the remaining variables, two were positively skewed and were therefore transformed to better accommodate the assumption of normal distribution demanded in discriminant analysis. These variables were TMTA time and TMTB time, and they were inverted (renamed TMTA time $^{-1}$ and TMTB time^{-1}).

Multicollinearity was studied in the whole sample using collinearity diagnostics (Hair, Anderson, Tatham, & Black, 1998). As the critical value for the condition index, 30 was chosen and 0.6 was set as the critical value for variance proportions. No multicollinearity was detected. Finally, replacement values were imputed for missing data using regression for the four diagnostic groups.

Table 2. Demographic Characteristics (Sex, Age and Education), MMSE and Time to Follow-Up (mean and SD) for the Four Diagnostic Groups and the Whole Sample

	Diagnosis of Cases at Follow-Up					
	Improved	Stable MCI	AD	Other Dementia	Total	Sig.
N	49	75	79	19	222	
female/male	33/16	38/37	60/19	12/7	143/79	0.012
Age (y)	60.8 ± 8.6	64.1 ± 9.8	68.1 ± 9.1	68.8 ± 10.6	65.2 ± 9.8	0.000
Education (y)	12.0 ± 4.1	10.7 ± 3.8	11.1 ± 3.7	9.5 ± 3.9	11.1 ± 3.8	0.104
MMSE	28.4 ± 1.9	27.1 ± 2.1	26.6 ± 2.7	25.6 ± 2.9	27.0 ± 2.5	0.000
Time to Follow-Up (m)	22.0 ± 17.5	26.9 ± 20.7	21.6 ± 17.2	22.4 ± 16.0	23.5 ± 18.5	0.295

Table 3. Neuropsychological Test Results (mean and SD) for the Four Diagnostic Groups and the Whole Sample

Neuropsychological Tests	Diagnosis of Cases at Follow-Up: Improved	Stable MCI	AD	Other Dementia	Total	Sig.
Learning and episodic memory						
Äldrecentrums Ordlista, d'	2.9 ± 1.2	2.8 ± 1.0	2.2 ± 1.0	2.0 ± 1.3	2.5 ± 1.1	0.001
AVLT recall	9.5 ± 3.0	6.9 ± 3.0	4.4 ± 3.9	2.8 ± 3.1	6.4 ± 4.0	0.000
AVLT learning	41.8 ± 11.8	36.8 ± 10.7	31.2 ± 10.8	25.0 ± 7.0	35.3 ± 11.8	0.000
RO recall	16.3 ± 7.4	14.8 ± 6.0	7.6 ± 6.3	6.7 ± 6.3	12.3 ± 7.6	0.000
Visuospatial functions						
RO copy	32.4 ± 2.5	31.0 ± 5.0	30.3 ± 5.7	30.3 ± 5.8	31.0 ± 4.9	0.135
Block Design	25.8 ± 10.3	21.5 ± 8.6	17.7 ± 8.3	20.0 ± 11.0	21.0 ± 9.6	0.000
Language						
Information	20.9 ± 4.1	19.8 ± 4.6	17.7 ± 5.3	16.0 ± 7.2	18.9 ± 5.3	0.000
Similarities	19.9 ± 5.7	17.9 ± 5.7	16.5 ± 6.4	13.5 ± 9.0	17.5 ± 6.4	0.002
Speed and attention						
TMTA time	53.7 ± 41.9	63.4 ± 34.8	67.9 ± 50.7	91.3 ± 86.1	65.2 ± 48.6	0.042
TMTA correct	23.9 ± 0.6	23.6 ± 1.7	23.8 ± 1.1	23.3 ± 1.6	23.7 ± 1.3	0.488
TMTB time	112.6 ± 59.4	152.4 ± 79.4	168.8 ± 92.4	211.7 ± 122.2	153.0 ± 87.3	0.000
TMTB correct	23.2 ± 2.4	21.3 ± 5.5	20.7 ± 5.7	18.9 ± 6.0	21.4 ± 5.2	0.021
Digit Symbol	37.0 ± 9.2	31.2 ± 12.0	32.3 ± 10.7	30.4 ± 13.2	33.0 ± 11.2	0.074
Digit Span backwards	4.7 ± 1.2	4.2 ± 1.3	4.4 ± 1.3	4.2 ± 2.0	4.4 ± 1.4	0.248
Digit Span forwards	5.8 ± 1.3	5.6 ± 1.8	6.0 ± 1.2	5.7 ± 1.5	5.8 ± 1.5	0.432

Analysis

Data was analyzed using discriminant analysis. This method creates a number of discriminant functions by combining the independent variables and assigning them coefficients in order to create maximum separation between the groups of the dependent variable. Cases are predicted to groups by calculating discriminant scores for each case on every discriminant function. The group mean of discriminant scores for a discriminant function is known as the group centroid. Overfitting is avoided by using cross-validation, e. g. by using one part of the sample to estimate the functions and the other part to validate the result. The functions can be interpreted by studying the coefficients of the independent variables. The greater the absolute value of the coefficient, the greater is that independent variable's contribution to the function. In this way it can be determined what cognitive domain the discriminant function is expressing. However, since the coefficients are considered to be unstable, it is usually recommended that the interpretation is made using the structure loadings, i. e. the correlations between independent variables and functions. Interpretation using structure loadings is analogous to the interpretation of factors in factor analysis (Hair et al., 1998).

The contribution of the independent variables to the analysis across all significant functions can be determined by calculating their composite potency indices. This is done in two steps. First, each function's relative contribution to the analysis is calculated by dividing the function's eigenvalue with the sum of the eigenvalues of the significant functions. Second, the squared factor loadings for each independent variable are multiplied by the relative contribution of the respective function. This is the potency index for that independent variable in that function. The products are then summarized for each independent variable. This sum is called the composite potency index for the independent variable, and by comparing the composite potency indices of the independent variables, their order of importance to the analysis can be established. It is important to note that the potency index can only be used to determine the relative importance of the independent variables and it has no absolute meaning (Hair et al., 1998).

Box's test was also performed. This is a statistical test for the equality of the covariance matrices of the independent variables, i. e. it examines if the variance of the independent variables is equal across the groups of the dependent variable. Equality of covariance matrices is an assumption of discriminant analysis (Hair et al., 1998). Little's MCAR test examines if data is missing completely at random or not, i. e. if there is a pattern in the missing data relating to observed or unobserved data in the sample (Little & Rubin, 1987). This test was also performed on the sample.

Results

Stepwise discriminant analysis was performed using the 15 test variables as predictors of membership in the four diagnostic groups. The stepwise analysis was based on reduction of Wilks' □ and picked out 4 variables in the following order: AVLT recall, RO recall, TMTB time^{-1} and Digit Symbol.

The discriminant analysis resulted in two significant discriminant functions (Wilks' □ = 0.915, □^{2}(6, N = 222) = 19.3, Sig. = 0.004) based on the 4 tests. The first function had an eigenvalue of 0.871 and accounted for 90.4 % of the variance in the solution. The second function had an eigenvalue of 0.091 and accounted for 9.5 % of the variance in the solution. Structure loadings and standardized canonical discriminant function coefficients are listed in

Table 4. Group centroids are listed in Table 5. The dispersion of cases for the four diagnostic groups on the two functions is shown in Figure 1.

Using the two functions with prior probabilities calculated from group size, 64.4% of all cases were correctly classified. After cross-validation a total of 62.6 % were correctly classified. Cross-validated classification results for the four diagnostic groups are shown in table 6.

A misclassification analysis was carried out using independent t-tests, comparing the correctly and incorrectly classified cases for all groups on test performance. The results are listed in Table 7. Also, the potency index for each test used in the discriminant analysis was calculated, and the results are listed in Table 8.

Box's test of equality of covariance matrices proved significant (Box's M = 77.317, F(30, 19417) = 2.452, Sig. = 0.000), suggesting unequal distribution of variance across the four diagnostic groups. For that reason, the discriminant analysis was run once more using separate matrices for the four diagnostic groups. This did not change the results in any way except slightly lowering the rate of prediction for the Improved and AD groups, and slightly raising it for the Stable MCI and Other Dementia group. The overall rate of prediction remained the same.

Little's MCAR test was also performed and proved significant (χ^2(723, N = 222) = 945.6, Sig. = 0.000), suggesting that data in the sample was not missing completely at random. Using independent t-tests and Pearson's Chi-square, cases with and without missing data were compared in demographic variables (age, education, and sex), MMSE and time to follow-up. The results are listed in Table 9.

Finally, the cases used in the analysis were compared to the removed cases in terms of demographic characteristics (age, education and sex), MMSE and time to follow-up. This was done using independent t-tests and Pearson's Chi-square. There were significantly more women in the retained sample (χ^2(1, N=260) = 3.998, Sig. = 0.046), but no other differences were detected.

Table 4. Standardized Coefficients and Structure Loadings

Neuropsychological Tests	Standardized Coefficients		Structure Loadings	
	Function 1	Function 2	Function 1	Function 2
AVLT recall	0.66	0.48	0.73*	0.42
RO recall	0.58	-0.73	0.72*	-0.36
Digit Symbol	-0.45	0.73	0.19	0.67*
TMTB time^{-1}	0.54	0.10	0.35	0.43

Note * = Largest absolute correlation between each variable and any discriminant function. TMTB time^{-1} had its greatest loading in the third nonsignificant discriminant function.

Table 5. Functions at Centroids of the Four Diagnostic Groups

Group	Function 1	Function 2
Improved	1.2	0.36
Stable MCI	0.51	-0.36
AD	-0.92	0.18
Other Dementia	-1.3	-0.25

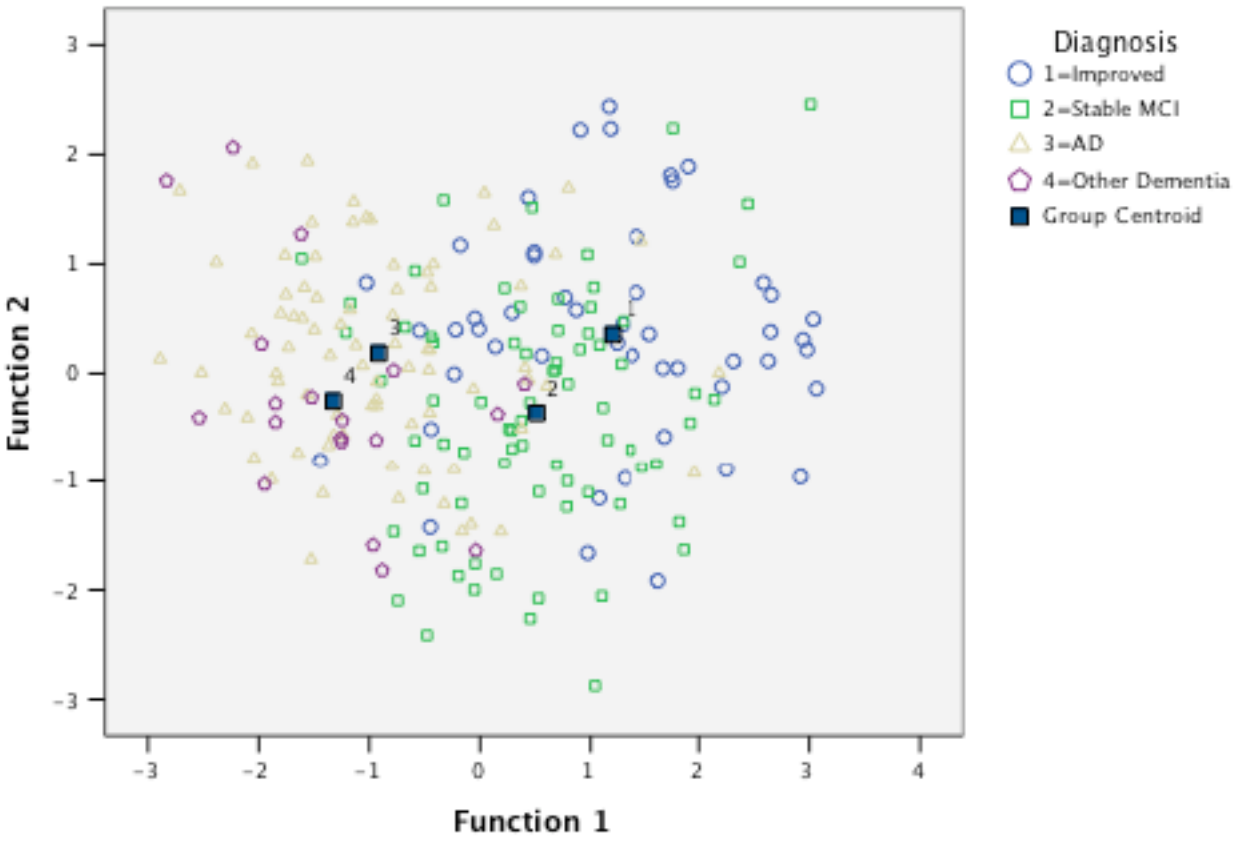

Figure 1. Group Centroids and Dispersion of Cases for the Four Diagnostic Groups on the Two Discriminant Functions

Table 6. Cross-Validated Classification Results (number/%)

	Predicted Group Membership				
Actual Group Membership	Improved	Stable MCI	AD	Other Dementia	Total
Improved	27/55%	13/27%	9/18 %	0/0.0%	49/100%
Stable MCI	13/17%	49/65%	13/17%	0/0.0%	75/100%
AD	4/5%	12/15%	63/80%	0/0.0%	79/100%
Other Dementia	0/0.0%	3/16%	16/84.0%	0/0.0%	19/100%

Table 7. Comparison of Correctly Classified and Misclassified Cases on Test Performance (mean and SD)

	Correctly Classified	Misclassified	Sig.
Improved			
RO recall	18.3 ± 6.7	13.4 ± 7.4	0.020
AVLT recall	10.9 ± 2.3	7.0 ± 2.3	0.000
TMTB time^{-1}	0.013 ± 0.004	0.007 ± 0.003	0.000
Digit Symbol	42.1 ± 5.0	30.1 ± 7.6	0.000
Stable MCI			
RO recall	16.5 ± 4.5	11.2 ± 6.1	0.000
AVLT recall	6.4 ± 2.6	8.0 ± 3.2	0.012
TMTB time^{-1}	0.008 ± 0.003	0.01 ± 0.006	0.038
Digit Symbol	28.6 ± 9.5	35.5 ± 11.7	0.008
AD			
RO recall	5.7 ± 3.8	14.1 ± 6.9	0.000
AVLT recall	3.4 ± 2.8	8.2 ± 3.7	0.000
TMTB time^{-1}	0.007 ± 0.003	0.007 ± 0.003	0.313
Digit Symbol	32.2 ± 9.3	29.7 ± 10.9	0.359

Table 8. Composite Potency Indices for the four Tests

Neuropsychological Tests	Composite Potency index
AVLT recall	0.500
RO recall	0.482
TMTB time^{-1}	0.128
Digit Symbol	0.075

Table 9. Demographic Characteristics (Sex, Age and Education), MMSE and Time to Follow-Up (mean and SD) for Cases With and Without Missing Data

	With Missing data	Without Missing Data	Sig.
N	149	73	
female/male	96/53	47/26	0.995
Age (y)	66.3 ± 10.0	62.9 ± 9.1	0.014
Education (y)	10.7 ± 3.7	11.8 ± 4.0	0.053
MMSE	26.5 ± 2.7	28.2 ±1.5	0.000
Time to Follow-Up (m)	23.0 ± 18.8	24.6 ± 17.9	0.534

Discussion

This study investigated the prediction of MCI patients at a mean follow-up of 2 years using baseline testing of cognitive function. A model was created that successfully predicted 62.6% of all patients using four tests: AVLT recall, RO recall, TMTB time^{-1} and Digit Symbol. They were combined in two significant discriminant functions. The model did best at predicting the AD group (80% correctly classified), and somewhat worse for the Improved and Stable MCI groups (55% and 65% correctly classified). However, none of the cases in the Other Dementia group were classified as such. Instead, most of them (84%) were classified as AD.

Even though the prediction in this study was successful, the overall rate of prediction (62.6%) was not as good as reported in other studies. For example, in a review of studies, Modrego (2006) concluded that in studies of prediction of MCI patients to AD, baseline cognitive testing reaches sensitivity and specificity levels of up to 70%. Chong and Sahadevan (2005) also found rates of prediction in the same range. One explanation for this discrepancy is that the studies mentioned by Modrego as well as Chong and Sahadevan had only focused on AD converters and non converters. Thus, they had only discriminated between two groups, which is an easier task than discriminating between four groups as in this study. In the former case, the probability of successful prediction by mere chance is 50%, given that the groups are of equal size. A rate of prediction of 70% is only 1.4 times better than this. If the groups are of unequal size, the largest group sets the criterion with which the rate of prediction is to be compared (maximum chance criterion) (Hair et al., 1998). In this study, the largest group was AD, with 35.5% of all cases. The number of successfully predicted cases was 62.6% which is 1.8 times better than the maximum chance criterion of 35.5%. If the number of groups and their sizes are taken into account, the predictive success of this study is therefore better than in most other studies.

There are different definitions of MCI in use, which is a problem when studies are to be compared (Ritchie and Touchon, 2000). For example, in some studies, the only cognitive impairment relevant to the MCI diagnosis is memory (Carr, Gray, Baty & Morris, 2000). In this study, impairment in any cognitive function could have led to an MCI diagnosis. It is also possible that differences in design could account for differences across studies. It should also be mentioned that diagnostics is itself not perfect and the reliability of clinical criteria for AD is not 100% (Modrego, 2006). This affects the rate of prediction using measures of cognitive functions, making perfect prediction undesirable. This is because a perfect prediction would mean that the model suffered the same faults as the diagnostics.

As already mentioned this study differs from previous ones in that it included other dementia than AD and separated the nonconverters into two groups: Stable MCI and Improved. By doing this, a model more relevant to clinical practice was achieved. Because not all MCI patients develop AD, clinicians need to know how to predict other developments as well. It is unclear what the term nonconverters used in many studies refers to, making it difficult to interpret. Does that group consist of patients that have improved from MCI or retained the diagnosis, or both?

The first function is best described using AVLT recall and RO recall, because of the magnitude of these tests' loadings (0.73 and 0.72 respectively) in this function and the huge gap between them and the other two tests (see Table 4). The usefulness of AVLT recall and word-list recall in predicting dementia has been confirmed in other studies (Andersson et al., 2006; Artero et al., 2003; Chong & Sahadevan, 2005; Estevez-Gonzalez, Kulisevsky, Boltes,

Otermin & Garcia-Sanchez, 2003). There are also results from other studies indicating that MCI patients have a reduced performance at RO recall (Kasai, M. et al, 2006). The two tests are primarily associated with episodic memory (Alladi, Arnold, Nestor, & Hodges, 2006), and the first function should therefore be an expression of that cognitive domain. Their contribution to the discriminant scores was positive, as indicated by the positive standardized canonical discriminant function coefficients. By studying the group centroids (see Table 5), we can see that a poor performance at these tests would be a risk factor for dementia.

The second function is more difficult to make sense of. There is a discrepancy between coefficients and loadings in terms of size. Since structure loadings are considered to be more stable they should be used for interpretation (Hair et al., 1998). Digit Symbol have the highest loading (0.67) and there is a gap between this test and the others, indicating that this is the most important one. Digit Symbol is known to be sensitive to dementia (Lezak, 1995). However, as a rule of thumb, all tests with a loading of 0.33 or more are interpretable (Tabachnick & Fidell, 2007). Since all tests have interpretable loadings, and the differences between them are small, this function should express something that all tests have in common. (The possible exception would be RO recall with a loading of -0.36, which barely qualifies as interpretable.) They do all involve motor skills and perception, but it is unlikely that these functions would be involved in separating the diagnostic groups. Digit Symbol and TMTB time^{-1} are measures of attention and speed (Nordlund et al., 2005). Attention is also involved in memory tests (Nilsson et al., 2006). Thus, the second function could express that cognitive domain. However, attention is an executive function (Nordlund et al., 2005; Nyman & Bartfai, 2000), and other sorts of executive functions are also involved in the performance at the tests. Performance at memory tests is dependent not only of retention of information, but also of encoding and retrieving it. These processes can involve executive functions, such as strategic elaboration of the material being learned and guided searching at time of recall (Buckner, 2004). Since all tests had a contribution to the second discriminant function it would be best to give it a broad interpretation. It is therefore thought to express executive function.

There seems to be differences in group centroids for the second function, separating the Improved group from the Stable MCI and Other Dementia groups. AD patients seem to be somewhere in between. All tests are positively associated with this function, except RO recall. The most intelligible conclusion is that the Improved group is characterized by a better executive functioning than the others. The negative contribution of RO recall to the discriminant scores, as indicated by the negative standardized canonical discriminant function coefficient, is difficult to understand. Since its loading is low, it is ignored in order to make sense of this function. It is important to note that since the interpretation of this function is less than obvious, it should not be taken too gravely. It is also important to note that the second function only accounted for 9.5 % of the variance in the solution and is therefore of far less importance than the first one.

Another way to interpret the results of discriminant analysis is by calculating the composite potency indices of the tests (Hair et al., 1998). As Table 8 clearly shows, AVLT recall and RO recall had the greatest contribution to the discriminant solution. This also indicates the importance of measures of episodic memory in separating the diagnostic groups. Interestingly, the potency index of TMTB time^{-1} (0.128) was greater than for Digit Symbol (0.075), even though its contribution to the significant discriminant functions was modest. This test is also known to be sensitive to dementia (Lezak, 1995)

Both the interpretation of functions and potency indices stress the importance of episodic memory in predicting the development of MCI patients and thus confirm findings from previous studies (Tabert et al., 2006). The model also includes something else, here thought to be executive function. This also confirms findings from other studies (Albert et al., 2001). The results are in line with the model suggested by Petersen (2001a), which supposes MCI subtypes with possible progression to AD characterized by dysfunction in several cognitive functions, with or without memory.

The importance of episodic memory in this study may not be very surprising since all patients at baseline had subjective memory complaints, and the institution where they had been examined was a memory clinic. However, this fact makes the finding of a second dimension even more interesting and raises the question of the relationship between memory and executive function in these patients. It has been suggested elsewhere (Buckner, 2004), that even though deficits in executive function among the elderly may not be limited to memory tasks, those deficits could be an important reason why the elderly experience problems in the memory domain. The present results suggest that deficits in terms of executive function could at least play a part in the performance of MCI patients at memory tasks.

The present result shows that the tests used in this study can be used not only to differentiate between dementia and non dementia, but also to predict patients that will improve and those that will retain the MCI diagnosis at two years follow-up. This is a very interesting result. Even more interesting is the fact that this is done using the same dimensions for all groups, primarily episodic memory. The result raises the question of the nature of the improved patients and those that retain the MCI diagnosis. It seems that the MCI diagnosis of patients in the Improved group is only temporary. A possible explanation for this could be that these patients suffer from depression at baseline and have recovered at follow-up. Depression is known to affect episodic memory functioning. However, depression is also known to have a negative effect at executive function (Nyman & Bartfai, 2000). Since the patients in the Improved group had a better executive functioning relative to patients in the other groups, it could be argued that depression would be an unlikely cause of their condition. Patients in the Stable MCI group are known to progress to AD in due time (Modrego, 2006). This means that the difference between the Stable MCI and AD groups is a matter of how severely affected they are from the disease at baseline. As Modrego (2006) points out, the prediction in regard to these two groups is best to be thought of as risk of early/late conversion to dementia.

The Other Dementia group proved especially difficult to predict using measures of cognitive function alone, and most patients from this group were instead predicted into the AD group (84% of Other Dementia patients). It is important to note, that even tough most cases belonging to the Other Dementia group were not classified as such, they were recognized as patients with dementia. These results are line with the findings by Jones et al. (2004), Johansson Laukka et al. (2004) and Stirling Meyer et al. (2002) that have identified a preclinical phase of VAD that was difficult to distinguish from AD.

Since an important goal of MCI research is to make early interventions for AD patients possible, the difficulty in separating the different forms of dementia poses a great problem. For this reason, an important goal of future research should be to develop specific predictors for the different kinds of dementia. It is possible that this cannot be done using only measures of cognitive function, and combinations with other markers should be considered. Genetic, social, biochemical markers and neuroradiological techniques have been suggested elsewhere

as interesting candidates to combine with measures of cognitive function (Bäckman et al., 2004; Modrego, 2006).

In general, false positives were a problem for all groups in the analysis to about the same extent (on average, only 62% of cases predicted to any group actually belonged to it). To investigate this further, a misclassification analysis was carried out. The results are listed in Table 7. There were significant differences at all tests between correctly classified and misclassified cases for both the Improved and Stable MCI groups. It is interesting that as many as 18% of cases belonging to the Improved group were predicted to the AD group due to their performance at baseline. Since patients in this group performed better at measures of executive function than cases belonging to the other groups, it is likely that other measures of this function could improve predictions of these cases. Cases in the Stable MCI group were misclassified into the Improved and AD groups to the same extent. Apparently there was a great variation in this group in terms of performance at baseline, making it difficult to predict. Misclassified cases belonging to the AD group performed better than correctly classified cases at the episodic memory tests only: RO recall and AVLT recall. It is likely that the misclassified cases had a more rapid decline in episodic memory than the correctly classified cases.

There were a number of limitations to this study. First, the interpretation of the results for the group Other Dementia is problematic because it consists of two different diagnoses: DNOS and Vascular Dementia. The prediction may have been better if they were separated. However, they had too few cases to make separate groups and the alternative would have been not to include them in the analysis at all. It was thought to be better to include them in this fashion. Furthermore, the discriminant analysis cannot give the characteristics of any group in itself. It can only tell in what ways the groups differ from one another (Hair et al., 1998). By not including the Other Dementia group, the characterization of the other groups would therefore have suffered. It is also worth mentioning that heterogeneity is not unique for the Other Dementia group. All groups in this sample except AD are likely to consist of different subgroups. For example, the Stable MCI group may consist of patients that will improve or develop AD in due time, as well as chronic MCI patients (Wahlund et al, 2003).

Another problem was the fact that assessment of cognitive function was used setting diagnosis at two occasions, first at baseline and then at follow-up. This could render the prediction circulatory. However, not on any occasion was assessment of cognitive function the only ground for diagnosis. This makes the assessments less influential and increases the predicative value.

The patient data used in this study was taken from a database called GEDOC. Unfortunately, not all patients visiting the clinic get their data stored in this database. If the patients that do get their data stored are not a random sample of the patients visiting the clinic, this would be a problem. This issue has not been possible to investigate further. However, the percentage of patients in the diagnostic groups is in accordance with previous studies (Table 1), indicating that there are no major deviations from other samples. The fact that the patients were taken from a clinical population must also be taken into consideration. It is a well known fact that the development of MCI patients takes a different course in samples based on patients from a clinical setting than in population based samples. For example, the rate of progression differs and is more accelerated in samples based on patients from memory clinics. This is because people that have visited a memory clinic are a subgroup of impaired people that have noticed their difficulties and sought help for it (Palmer et al., 2003). This obviously affects the

external validity of the findings. Since this study is based on cases from a clinical setting, conclusions from it should primarily be applied to patients from memory clinics.

There were significant differences between the diagnostic groups in terms of age and sex (see Table 2). This could in part have accounted for the prediction. Decline of episodic memory and executive function is involved in normal aging (Bäckman et al., 2004; Nilsson, 2003). It is doubtful though, that the age gap in question is large enough to have had a considerable effect on the results. Some studies have shown gender related differences in terms of episodic memory (Nilsson, 2003). However, these differences are in favour of women and could not explain the severity of impairment in the AD group - that had the largest proportion of women - in this study.

A few cases had to be removed from the analysis. Since there were no significant differences between the removed and retained cases other than in terms of sex, it is not likely that this could have produced a bias in the results.

A problem of statistical nature is the presence of heterogeneity in this material. Box's M proved significant, indicating unequal variation across the four diagnostic groups. However, this test is known to be overly sensitive, and the conclusions drawn from this should therefore be made carefully. The large sample in this study should also be taken into consideration, making the analysis robust to this problem. Also, the discriminant analysis was run once more using separate matrices, but with only minor changes in the results. This indicates that the problem was not severe. By studying the dispersion of cases on the two discriminant functions (Figure 1), it seems that the Other Dementia group had less variation than the other groups. It is not obvious that the difference is large enough to influence the results of the discriminant analysis, but in combination with the relatively small size of this group to the other ones in the sample, it could be a problem and in part explain the failure of prediction to this group (Tabachnick & Fidell, 2007).

Little's MCAR test was performed and proved significant, suggesting that data in this sample was not missing completely at random. That is, there is a pattern to the missingness of data (Hair et al., 1998). This is not a surprise. When assessing patients in a clinical setting, neuropsychologists may not treat all patients in the same way. Rather, the psychologists select tests based on their clinical judgment and the patients' performance on other tests. For example, some tests may be considered difficult and will therefore not be administered to patients that seem unable to manage them. This interpretation is supported by the comparisons made in Table 9 between patients with and without missing data. Patients with missing data had significantly lower scores on MMSE and were significantly older. Furthermore, the patients had visited the clinic between 1990 and 2005, and it is likely that procedures have not been constant during that time interval.

Since a lot of data was missing, imputation using regression was performed on the sample. There are disadvantages to this procedure. Most importantly, it may lead to an underestimation of variance for the four groups as well as making the data too consistent across variables (Tabachnick & Fidell, 2007). However, missing data had to be dealt with in some way, and using regression is a better choice than omitting cases (Tabachnick & Fidell, 2007). It is worth noting that Digit Symbol did not separate the four diagnostic groups at a level of significance of 0.05 using one-way ANOVA (Table 3). However, this test proved important in the discriminant analysis after imputation for missing values using regression. Since imputation using regression reduce bias compared to other methods of handling

missing data, it is likely that the result after imputation is a better estimate of the true state of facts.

In conclusion, the present model managed to predict the development of MCI patients with greater success than what is common in other studies. By predicting patients to four different groups - Improved, Stable MCI, AD and Other Dementia - it also differs from other studies and produced a result more relevant to clinical practice. It is interesting that the prediction was done using primarily one dimension, episodic memory. Like other studies, the present results also indicate that there is a second dimension important to the prediction of development of MCI patients, here thought to be executive function. The prediction was most successful for the AD group (80% of cases correctly classified). However, different kinds of dementia proved difficult to separate and future research should focus on finding specific predictors for different kinds of dementia.

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