Title: Comparison Between an Empirically Derived and a Standard Classification of Amnestic Mild Cognitive Impairment from a Sample of Adults with Subjective Cognitive Complains

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Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Abstract

Objective: The aim of this study is to compare an empirically derived classification of amnestic mild cognitive impairment (aMCI) from a sample of adults with subjective cognitive complaints by using cluster analysis of their performance on the California Verbal Learning Test (CVLT) with a classification of aMCI based on standard clinical criteria. Method: Three hundred ninety-one individuals aged 48 years and older were diagnosed as aMCI or healthy controls. Cluster analysis of the CVLT performance was conducted, followed by logistic regression analysis. Results: A two-cluster solution performed on the CVLT measures correctly classified 98.0% of the aMCI patients and 73.4% of the healthy controls diagnosed by using standard aMCI criteria. Discussion: The empirically derived classification of aMCI is consistent with the classification based on standard criteria; however, standard criteria should also be considered to prevent false positives.

Keywords

cognitive impairment, diagnosis, early detection, subjective cognitive complaints, verbal memory

Introduction

Amnestic mild cognitive impairment (aMCI) is a diagnostic entity used to describe individuals who suffer from cognitive impairment that is not severe enough to constitute dementia and that is characterized by notable impairment of episodic memory (single-domain aMCI) or episodic memory and other cognitive domains (multiple-domain aMCI). Individuals with aMCI are likely to progress to Alzheimer's disease (AD) and probably represent prodromal forms of AD (Gauthier et al., 2006; Petersen et al., 2009; Winblad et al., 2004). Early identification of such individuals is one of the most important challenges facing researchers in the field (Ritchie & Ritchie, 2012). Informant-based confirmation of subjective cognitive complaints (Juncos-Rabadán et al., 2014) is one of the clinical criteria that is essential for the diagnosis of aMCI, together with poorer performance in memory and other cognitive domains, functional activities mainly preserved or minimally impaired, and non-fulfilment of diagnostic criteria for dementia (Albert et al., 2011). Clinical diagnosis based on conventional criteria of individuals with aMCI usually considers these cognitive scores together with functional measures and a negative diagnosis of dementia.

Some authors have recently proposed the use of cluster analysis techniques to examine how individuals are grouped together on the basis of patterns of performance of different measures with no requirements for fulfilling predetermined criteria (Clark et al., 2013; Libon et al., 2010, 2011). Empirically derived methods have been shown to be useful in determining MCI subtypes (Damian et al., 2013; Delano-Wood et al., 2009), and can be also useful in predicting the usefulness of intervention strategies (Lewis et al., 2005). Edmonds and colleagues (Edmonds et al., 2015) performed cluster analysis on neuropsychological data from 825 MCI diagnosed as aMCI with clinical standard criteria and identified a large subgroup (34% who did not differ from a normal control group in terms of cognition or imaging measures despite their MCI diagnosis. They found that the statistical method of classifying MCI based on neuropsychological test scores resulted in a significant improvement in the specificity but at the cost of some modest decline in sensitivity as 10.7% of individuals in the cluster-derived normal group progressed to dementia over time. The authors concluded that the conventional diagnosis of MCI might be highly susceptible to false positive (FP) diagnostic errors whereas the statistical method of classifying MCI based on neuropsychological test scores resulted in a significant improvement in the specificity of the diagnosis. The data-driven diagnosis of MCI may be an important method from the practice and research perspectives because it can improve diagnosis accuracy avoiding FP errors and enhances better clinical decision making.

The present study aimed to evaluate the data-driven diagnosis of aMCI by cluster analysis of the California Verbal Learning Test (CVLT) performance in a sample of individuals attending primary care centers with subjective cognitive complaints. A previous study based on a two-stage cluster analysis revealed four reliable subtypes of efficiency in memory that were differentiated by their performance of the CVLT (Campos-Magdaleno, Facal, Juncos-Rabadán, Braña, & Pereiro, 2014) that assesses, via presentation of a 16-word list, several aspects of verbal episodic memory such as short/long delayed free and cued recall and recognition (Delis, Kramer, Kaplan, & Ober, 1987; Ribeiro, Guerreiro, & De Mendonça, 2007). Subtypes 1 and 4 represented opposing patterns of performance, and the performance of Subtypes 2 and 3 was intermediate. Subtype 1 performed best and Subtype 4 performed worst across all clustering variables grouped in two main factors: general verbal learning which represented general capacity to recall and learn words, including short and delayed recall and semantic strategies, and Inaccurate Memory which represented recall intrusions and recognition errors. Subtype 1 comprised the youngest participants and participants who had attained the highest level of education, read the most frequently, and who attained the highest scores for general cognitive performance. Subtype 4 showed the opposite demographic and cognitive characteristics. In this study, the objective was to compare an empirically derived classification of aMCI based on the CVLT clusters described by Campos-Magdaleno et al. (2014) with the standard aMCI classification based on clinical criteria (Albert et al., 2011; Gauthier et al., 2006) from a sample of adults with subjective cognitive complaints.

Method

Participants

All participants were volunteers over 47 years old who were attending primary care centers with subjective cognitive complaints and who were participating in a larger longitudinal study on cognitive decline (Juncos-Rabadán et al., 2012). The study met with the approval of the Research Ethics Committee of the Xunta de Galicia (Spain) and was conducted in accordance with the provisions of the Declaration of Helsinki, as revised in Seoul 2008. All volunteers were required to sign an approved informed consent form and were subjected to extensive clinical and neuropsychological evaluation. Exclusionary criteria included the following: prior diagnosis of psychiatric disturbances (according to Diagnostic and Statistical Manual of Mental Disorders [4th ed.; DSM-IV; American Psychiatric Association, 1994] criteria), neurological disease, including probable AD or other types of dementia (according to Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association and DSM-IV criteria), type 2 diabetes, sensorial or motor disturbances, undergoing chemotherapy and previous brain damage.

The final sample of participants comprised 391 individuals, 293 of whom were classified as healthy controls (HC; 74.9%) and 98 (25.1%) of whom were diagnosed with aMCI. The HC group comprised participants who performed the cognitive and memory tests according to the standard age and education norms. Clinical diagnosis of aMCI followed the core criteria outlined by Petersen and colleagues (Gauthier et al., 2006; Petersen et al., 2009) and updated by Albert et al. (2011): (a) informant-corroborated memory complaints assessed by the Subjective Memory Complaints Questionnaire (SMCQ; Benedet & Seisdedos, 1996); (b) performance of 1.5 SDs below age norms on the Spanish version of the Verbal Paired Associates–Immediate (VPA1) and Verbal Paired Associates–Delayed (VPA2) tests, from the Wechsler Memory Scale–Third Edition (WMS-III; Wechsler, 1999); (c) no significant or minimal impact on activities of daily living assessed by the Lawton and Brody Index (Lawton & Brody, 1969); and (d) not demented according the NINCDS-ADRDA and DSM-IV (American Psychiatric Association,

1994) criteria. The aMCI group included patients with multiple-domain and single-domain aMCI (mdaMCI and sdaMCI, respectively). The patients with mdaMCI scored 1.5 SDs below age- and education-related norms on at least two cognitive subscales of the Cambridge Cognitive Examination–Revised (CAMCOG-R), which assesses deterioration in specific domains such as language, attention-calculation, praxis, perception, and executive functioning (Roth, Huppert, Mountjoy, & Tym, 1999). Their general cognitive functioning was therefore around 1.5 SDs below age- and education-related norms in the Spanish version of the Mini-Mental State Examination (MMSE; Lobo et al., 1999). Patients with sdaMCI scored 1.5 SDs below age norms in the memory tests and maintained normal general cognition, as measured by MMSE and the CAMCOG-R subtests. For the purposes of the present study, we have included the two subtypes into only one group that is the aMCI group. Non-amnestic MCI patients have been excluded from the study. Demographic and neuropsychological variables of the two groups are shown in Table 1.

INSERT TABLE 1 ABOUT HERE

Measures and Procedure

Participants were referred to us by professionals in the collaborating health centers and attended several sessions of neuropsychological evaluation conducted by expert psychologists. The Spanish version of the CVLT (Benedet & Alejandre, 1998) was administrated as part of a more comprehensive assessment in which the following cognitive instruments pertinent to the purposes of this study were also applied: a short version of the SMCQ (Benedet & Seisdedos, 1996), which comprised seven items each scored on a Likert-type scale from 1 to 5 (maximum 35), one copy of which was completed by the patients and another by an informant; the Spanish version of the MMSE (Lobo et al., 1999); the Spanish version of the CAMCOG-R (Roth et al., 1999); and the Logical Memory-Immediate (LM1) and LM-Delayed (LM2) and VPA1 and VPA2 of the WMS (Wechsler, 1999). The following demographic variables were obtained from an ad hoc questionnaire administered to the participants during an interview: age, total number of years of formal schooling, and reading habits. The latter variable evaluated the frequency of reading during the last 3 years as frequent (at least twice a week) and infrequent (less than twice a week).

Statistical analyses

Cross-tabulation was performed to determine how participants were distributed in each of the four clusters identified in the previous study (Campos-Magdaleno et al., 2014). A chi-square test was used to assess the global significance, and corrected standardized residuals (Haberman, 1973) were used to determine the specific associated categories. The healthy control participants were significantly concentrated in Clusters 1 and 2, whereas participants with aMCI were almost exclusively included in Clusters 3 and 4 (Table 2). We therefore decided to combine Clusters 1 and 2 in one cluster and Clusters 3 and 4 in another. A significant and close association was obtained for the distribution of these two clusters, $\chi 2(1, 391) = 151.323$; $p < .001$; Cramer's V = .622, and the standardized residuals were higher than those corresponding to the four-cluster solution (Table 2).

INSERT TABLE 2 ABOUT HERE

Multivariate logistic regression analysis was then applied to assess the predictive value of the two-cluster variable for discriminating between healthy controls and aMCI patients. Clinical diagnosis of aMCI and healthy controls was considered as a dependent variable. Taking into account that previous classification of participants in the four clusters was significantly related to other variables such as age, gender, years of education, and frequency of reading and general cognitive performance (measured by MMSE and CAMCOG-R; Campos-Magdaleno et al., 2014), we decided to use these variables as predictors together with the two-cluster variable.

Results

Multivariate logistic regression analysis revealed that the best model included only the cluster variable as a predictor. This model accounted for 54% (Nagelkerke's R2) of the variance (B = 4.88; Estandard Error = 0.727; Wald's $\chi 2 = 45.20$; $p < 0.001$; odds ratio = 132.30; 95% confidence interval [31.85, 549.58]) and correctly classified 98.0% of aMCI patients (sensitivity) and 73.4% of controls (specificity). The model had a positive predictive value of 55.2 and a negative predictive value of 99.1 (conventional positive likelihood ratio = 3.68; conventional negative likelihood ratio = 0.03). Figure 1 shows the profiles (Z scores) of the CVLT variables (List A5 [LA5], short delay free recall [SDFR] and short delay cued recall [SDCR], long delay free recall [LDFR] and long delay cued recall [LDCR], semantic clustering, free recall intrusions [FRIs] and cued recall intrusions [CRIs] and FPs) for the aMCI patients and the healthy controls included in Cluster 2 and for the healthy controls included in Cluster 1. The Z scores for the aMCI patients included in Cluster 2 were around 1.5 SDs below the mean values for the variables of recall efficiency LA5, SDFR, SDCR, LDFR and LDCR, and the Z scores were around 1.5 SDs above the mean values for two of the three error measures, CRIs and FPs.

INSERT FIGURE 1 ABOUT HERE

Discussion

The purpose of this study was to compare an empirically derived classification of aMCI from a sample of adults with subjective cognitive complaints based on clusters that describe patterns of memory deficits measured by the CVLT with a classification based on standard criteria. The two-cluster solution revealed that cluster analysis of the performance on the CVLT may correctly identify individuals classified as aMCI according to standard criteria. This solution concentrates 98% of the aMCI sufferers diagnosed by use of the standard criteria (Albert et al., 2011; Gauthier et al., 2006; Petersen et al., 2009) in Cluster 2. These were those individuals who performed worst on the CVLT variables included in the general verbal learning factor (LA5, SDFR and SDCR, LDFR and LDCR, and semantic clustering variables) and who produced the highest number of errors (FRIs and CRIs and FPs in recognition). The Z scores for this group (Figure 1) were around 1.5 SDs below the mean values for the critical measures short and long delay free and cued recall, corresponding to the typical range of scores of 1 to 1.5 SDs below the mean proposed for clinical diagnosis of aMCI (Albert et al., 2011). The two-cluster solution based on the performance on the CVLT may successfully classify participants with subjective memory complaints as aMCI sufferers. However, this solution grouped only 73.4% (specificity) of the healthy control participants (diagnosed by standard criteria) in Cluster 1, and 26.6% of these participants were included in Cluster 2 together with the aMCI sufferers. This 26.6% represents healthy control participants who scored around 0.5 SD below the mean and who do not meet the standard criterion of aMCI. We found that the cluster-based method attained a very good level in sensitivity but at the cost of some decline in specificity, whereas the study by Edmonds et al. (2015) obtained the opposite pattern. Although the two studies are not comparable in the sample and in the used neuropsychological measures, the results from both indicate that although cluster analysis based on patterns of performance on the different neuropsychological measures is a sensitive procedure (Clark et al., 2013), it must be complemented with clinical or standard criteria to prevent FP diagnoses. In our case, the high sensitivity of the cluster solution in identifying aMCI in a sample of adults with subjective cognitive complaints suggests the potential for the CVLT as an important diagnosis instrument, in spite of the relatively lengthy of this test. This indicates that although cluster analysis based on patterns of performance on the different memory measures provided by the CVLT is a sensitive procedure (Clark et al., 2013), it must be complemented with clinical or standard criteria to prevent FP diagnoses. The cluster solution might be used for clinical and research purposes because it provides not only a diagnosis but also a learning and memory profile of the aMCI with respect to the general verbal learning factor (LA5, SDFR and SDCR, LDFR and LDCR, and semantic clustering variables) and the inaccurate memory factor (FRIs and CRIs and FPs in recognition). The cluster solution could be applied to other samples for diagnosis of disorders in the aforementioned factors. However, we believe that further research comparing clustering methodology and standard criteria is needed to test consistency of resulting MCI types (Libon et al., 2010), to know a more complete aMCI profile on recall and learning (Libon et al., 2011) and to have the best effective diagnosis methods for clinical practice.

In conclusion, the empirically derived classification of aMCI based on cluster subtypes of the CVLT is consistent with the classification based on standard criteria among adults with subjective cognitive complaints; however, use of predetermined criteria (such as the standard recommendation of a prespecified cutoff of 1 to 1.5 SDs below the means on the memory measures according to normative data for age and education) is also necessary to determine whether these individuals are actually suffering from aMCI.

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Table 1. Description of the study groups by the demographic and neuropsychological variables initially used to diagnose the participants.

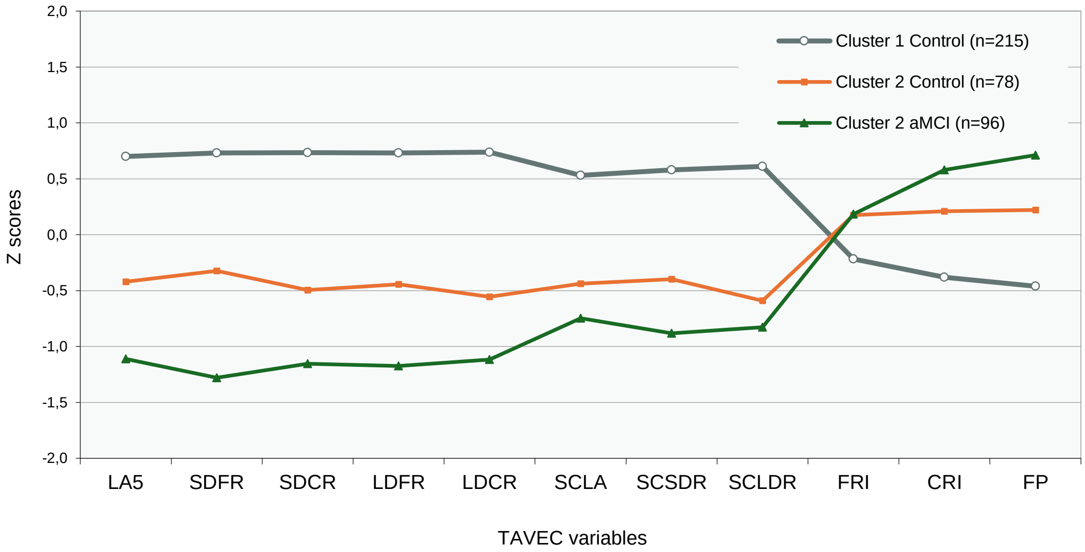
	Amnesic MCI		Control	
	$\overline{X}$	95% *CI*	$\overline{X}$	95% *CI*
Age**	69.89	68.10-71.68	65.38	64.35-66.41
Years of education**	9.49	8.64-10.34	9.93	9.39-10.46
SMCQ**	17.03	16.04-18.01	15.54	15.00-16.07
WMS-III, LM1**	15.09	13.73-16.45	22.14	21.33-22.94
WMS-III, LM2**	10.24	8.80-11.68	18.23	17.34-19.12
WMS-III, VPA1**	6.92	5.89-7.96	14.57	13.77-15.38
WMS-III, VPA2**	1.90	1.53-2.26	4.66	4.34-4.99
CAMCOG-R**	78.97	77.02-80.92	88.31	87.43-89.19
MMSE**	25.76	25.28-26.24	28.07	27.89-28.25
	%	95% *CI*	%	95% *CI*
Gender*	58.0 women	48.2-67.8	70.0 women	64.7-75.2
Reading frequency*	55.0 frequent 20.0 infrequent	45.1-64.9 12.0-28.0	58.0 frequent 12.3 infrequent	52.3-63.7 8.5-16.1
Cluster**	98.0 belong to cluster 2	95.1-100.0	73.4 belong to cluster 1	68.3-78.5

Note. SMCQ = Subjective Memory Complaints Questionnaire (Informant); WMS-III = Wechsler Memory Scale, LM1 = Logical Memory-Immediate, LM2 = Logical Memory-Delayed, VPA1= Verbal Paired Associates-Immediate, VPA2 = Verbal Paired Associates-Delayed; CAMCOG-R = Cambridge Cognitive Examination-Revised; MMSE = Mini Mental State Examination; CI = Confidence Interval. * = p<.05; ** = p<.001.

Table 2. Cross-tables results (n and adjusted residuals *e*) from the 4 cluster solution obtained in Campos-Magdaleno et al. (2014) and from the 2 cluster solution used in this study.

		Healthy Control		Amnestic MCI	
		n	*e*	*n*	*e*
Cluster number (4 clusters solution)	1	**156**	8.9	2	-8.9
	2	**59**	4.8	0	-4.8
	3	69	-5.5	**52**	5.5
	4	9	-10.5	**44**	10.5
Cluster number (2 clusters solution)	1	**215**	12.3	2	-12.3
	2	78	-12.3	**96**	12.3
Total		293		98	

Figure 1. Profiles for the CVLT variables corresponding to the healthy control participants included in Cluster 1 and to the aMCI sufferers and the healthy control participants included in Cluster 2.



Note. Variables: LA5 = List A5; SDFR = short delay free recall; SDCR = short delay cued recall; LDFR = long delay free recall; LDCR = long delay cued recall; SCLA = semantic clustering list A; SCSDR = semantic clustering short delay recall; SCLDR = semantic clustering long delay recall; FRI = free recall intrusion (errors); CRI = cued recall intrusion (errors); FP = false positive (errors). TAVEC = CVLT = California Verbal Learning Test; aMCI = amnestic mild cognitive impairment.