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Featured Article

Operationalizing mild cognitive impairment criteria in small vessel disease: the VMCI-Tuscany Study

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Abstract

Background: Mild cognitive impairment (MCI) prodromic of vascular dementia is expected to have a multidomain profile.

Methods: In a sample of cerebral small vessel disease (SVD) patients, we assessed MCI subtypes distributions according to different operationalization of Winblad criteria and compared the neuroimaging features of single versus multidomain MCI. We applied three MCI diagnostic scenarios in which the cutoffs for objective impairment and the number of considered neuropsychological tests varied.

Results: Passing from a liberal to more conservative diagnostic scenarios, of 153 patients, 5% were no longer classified as MCI, amnestic multidomain frequency decreased, and nonamnestic single domain increased. Considering neuroimaging features, severe medial temporal lobe atrophy was more frequent in multidomain compared with single domain.

Conclusions: Operationalizing MCI criteria changes the relative frequency of MCI subtypes. Nonamnestic single domain MCI may be a previously nonrecognized type of MCI associated with SVD.

Keywords: Cerebrovascular disease; Vascular dementia; Mild cognitive impairment; Neuropsychology; Cognitive aging

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1. Background

Mild cognitive impairment (MCI) is an intermediate state between normal cognitive status and dementia; it is considered a risk factor for dementia and has become a focus of several clinical and intervention trials. MCI is generally defined with the aid of neuropsychological tests providing evidence for object impairment with intact global cognitive functioning and activities of daily living. The criteria and the operationalization of MCI have been subjected to much debate as there is no real agreement regarding neuropsychological tests, the number and/or type of cognitive domains to be assessed, and the proper use of neuropsychological cut scores [1]. The lack of a universal operational definition of MCI resulted in divergent outcomes in terms of prevalence and progression rates across studies [2].

In 2003, a multidisciplinary and international experts group proposed specific recommendations for MCI diagnostic criteria [3]. The definition of MCI according to Winblad et al.'s criteria includes four clinical subtypes: amnestic MCI (A-MCI, single or multiple domain) and non-amnestic MCI (NA-MCI, single or multiple domain). It has been hypothesized that different MCI subtypes subtend different etiologies [4,5]; amnestic MCI, either single or multiple domain, was considered to have a degenerative etiology, whereas multiple domain MCI, either amnestic or not, a vascular etiology.

Subcortical ischemic vascular disease caused by small vessel disease (SVD) has been shown to be closely associated with cognitive impairment [6,7], particularly with deficits in attention and executive function, and slowing of motor performance and information processing [8–10]. The clinical spectrum of vascular cognitive impairment (VCI) ranges from MCI to dementia [6] and a recent proposal of diagnostic criteria for vascular MCI highlights the need of an objective evidence of decline using validated measures of cognitive functions and giving equal importance to several cognitive domains [11].

We aimed to study the effects of operationalizing Winblad et al.'s clinical consensus criteria on the MCI subtypes distributions in a sample of nondemented patients with cerebral SVD. We hypothesized that the frequency of MCI and its subtypes may be influenced by the operationalization of criteria. For example, using less restrictive criteria could increase the frequency of multidomain subtype that is, however, expected to be prominent in a sample of patients with cerebrovascular disease. The second aim was to compare the neuroimaging features across different MCI subtypes.

2. Methods

The vascular MCI (VMCI)-Tuscany study is an ongoing multicenter, prospective, observational study aimed at evaluating predictors of the transition from VMCI (defined by the presence of moderate-to-severe white matter lesions) to dementia [12]. The study methodology has been reported elsewhere [12]. To be included, outpatients, referred from neurologic or geriatric units, had to be classified as affected by MCI with SVD according to the following inclusion criteria: (1) MCI defined according to Winblad et al.'s criteria [3] and (2) evidence on magnetic resonance imaging (MRI) of moderate-to-severe degrees of white matter hyperintensities (WMH) according to the modified version of the Fazekas scale [13]. The degree of WMH severity was rated on fluid attenuated inversion recovery sequences taking into account only deep and subcortical white matter lesions. The modified Fazekas scale is a visual scale based on a categorization into three severity classes: grade 1 (mild WMH) = single lesions $<$10 mm, areas of "grouped" lesions $<$20 mm in any diameter; grade 2 (moderate WMH) = single lesions between 10 and 20 mm, areas of "grouped" lesions $>$20 mm in any diameter, no more than "connecting bridges" between individual lesions; and grade 3 (severe WMH) = single lesions or confluent areas of hyperintensity $\geq$20 mm in any diameter. According to the study protocol, each patient underwent an extensive clinical and neuropsychological assessment and an MRI examination [12]. The study was approved by local ethics committees, and each patient gave a written informed consent.

We developed a neuropsychological test battery thought to be specific for MCI due to SVD to allow automation and standardization of the scoring procedures and to obtain a cognitive profile for each patient. The development and psychometric properties of the VMCI-Tuscany neuropsychological battery were detailed in a methodological article [14]. For the construction of the VMCI-Tuscany neuropsychological battery, tests were selected among those recommended for VCI [15] and having recent and robust norms based on healthy Italian adult samples [16]. We took primarily into consideration the protocols proposed by the National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network consensus conference on harmonization standards for VCI [15] and selected the tests that had received validation, correction, and evaluation norms based on healthy Italian adult samples. The review of Italian neuropsychological normative studies started from the work of Bianchi and Dai Prà [16], and proceeded with the analysis of the original papers. Most of these studies applied the equivalent scores (ES) methodology proposed by Capitani and Laiacona [17]. ES methodology is a nonparametric norming method based on percentiles and independent from the distribution form. ES is an ordinal 5-point scale (ranging from 0 to 4). The main characteristic of ES methodology is to fix the outer tolerance limit of the left queue of the adjusted scores so that it is possible to assess, with a known risk of error ($<$5%), the cutoff splitting the bottom 5% of the population and representing pathologic performance (ES = 0). On the other end of the scale, ES = 4 indicates an optimal performance ($\geq$median), while the limits for ES = 1, 2, and 3 are established portioning the distribution of adjusted scores between the 5th and the 50th centiles into equal intervals. ES = 1 indicates a borderline

performance (an adjusted score between the outer and inner confidence limits for the 5th centile of the normal population), whereas ES = 2, 3 represent normal performances. ES methodology allows to convert age and education-adjusted scores into comparable ones having the same unit of measure and to compare the performances from the various tests so as to obtain a cognitive profile of the impaired and preserved functions.

The VMCI-Tuscany neuropsychological battery includes two global cognitive functioning tests and other nine tests which cover a wide range of cognitive abilities (Table 1). ES methodology was available for all the tests included in the battery except for the symbol digit modalities test.

Trail making test (TMT, part A and B) administration had a time limit: if patients did not complete the task in 5 minutes, the examiner stopped the administration and scored 300 seconds. In this case, raw scores were not adjusted for age and education while an ES = 0 was assigned. The administration of TMT-B had two preliminary restrictions: the completion of the TMT-A in <300 seconds and the knowledge of the correct order of the alphabet letters.

Data collected were entered into a database on a specifically developed Web site (www.vmci-tuscany.it). Raw scores were automatically adjusted for demographic variables using regression equations extracted by normative studies and then transformed into ES.

The diagnosis of MCI according to the Winblad et al.'s criteria [3] requires specific prerequisites: (1) patients or caregivers complaints about cognitive deficits and (2) no or minimal disability in activities of daily living (no impairment at all on activities of daily living scale [28] and no impairment or only one item compromised on instrumental activities of daily living scale [29]; Fig. 1). In our operationalization of MCI diagnostic algorithm, prerequisites' definition was maintained and we worked on the definition of the objective cognitive impairment and the classification of cognitive domains.

Table 1
The VMCI-Tuscany neuropsychological battery

Cognitive domain	ES	Test
Global mental functioning		Mini mental state examination (MMSE) [18]
		Montreal cognitive assessment battery (MoCA) [19]
Memory	*	Rey auditory-verbal learning test (RAVL) [20] (immediate recall)
	*	Rey auditory-verbal learning test (RAVL) [20] (delayed recall)
	*	Short story [21]
	*	Rey-Osterrieth complex figure (ROCF) (recall) [22]
Attention and executive functions	*	Trail making test, part A [23]
	*	Visual search [24]
		Symbol digit modalities test (SDMT) [25]
	*	Color word Stroop test [26]
	*	Trail making test, part B [23]
Language	*	Phonemic verbal fluency [27]
	*	Semantic verbal fluency [27]
Constructional praxis	*	Rey-Osterrieth complex figure (ROCF) (copy) [22]

*Equivalent score methodology available.

The Winblad et al.'s MCI diagnostic algorithm requires the three following hierarchical steps: (1) definition of objective cognitive impairment; (2) definition of an objective impairment in memory; and (3) definition of an objective cognitive impairment in cognitive domains other than memory (Fig. 1). For each of the three steps, we defined: (1) how much each score had to be below the mean to be considered impaired and (2) how many scores were impaired. We built three possible scenarios: (1) at least one score borderline (ES = 1; corresponding to our inclusion criterion); (2) at least two scores borderline; and (3) at least one score frankly impaired (ES = 0 or an adjusted score lower than the 5th centile of the normal population; Fig. 1). To this purpose, we used the 12 scores deriving from the 9 neuropsychological tests (Table 1): the immediate and delayed recalls of the Rey auditory-verbal learning test were used as two different scores, as well as the copy and the delayed reproduction of the Rey-Osterrieth complex figure, and the part A and B of the trail making test. As stated before, ES methodology was not available for the symbol digit modalities test and its performance was classified as "abnormal" when the adjusted score was below the 5th centile of the normal population (ES = 0) or "normal" when the adjusted score was above the 5th centile (no ES was assigned).

An additional issue was the definition of cognitive domains. In a previous methodological article on psychometric properties of the VMCI-Tuscany neuropsychological battery, a confirmatory factor analysis showed a good fit of the four theoretically assumed dimensions to empirical data [14]. Based on those findings, we considered four cognitive domains: memory (assessed by four cognitive scores), attention/executive functions (five cognitive scores), language (two cognitive scores), and constructional praxis (one cognitive score; Table 1). In scenario 2, considering constructional praxis domain, that is assessed in our battery by only one score, we applied the restricted criterion "at least one score impaired."

The MRI baseline scans were centrally revised at the NEUROFARBA Department, University of Florence. Visual assessment of neuroimaging was performed by an experienced neurologist (A.P.) who was blind to clinical details and MCI classification. After the central MRI revision, of the 200 patients enrolled in the baseline VMCI-Tuscany cohort, 47 were excluded because of the evidence of WMH of only mild degree (modified Fazekas scale = 1). The neuroimaging variables used in the present study were: (1) WMH (modified Fazekas scale) [13], lacunar infarcts (total number in the entire brain) [30], global cortical

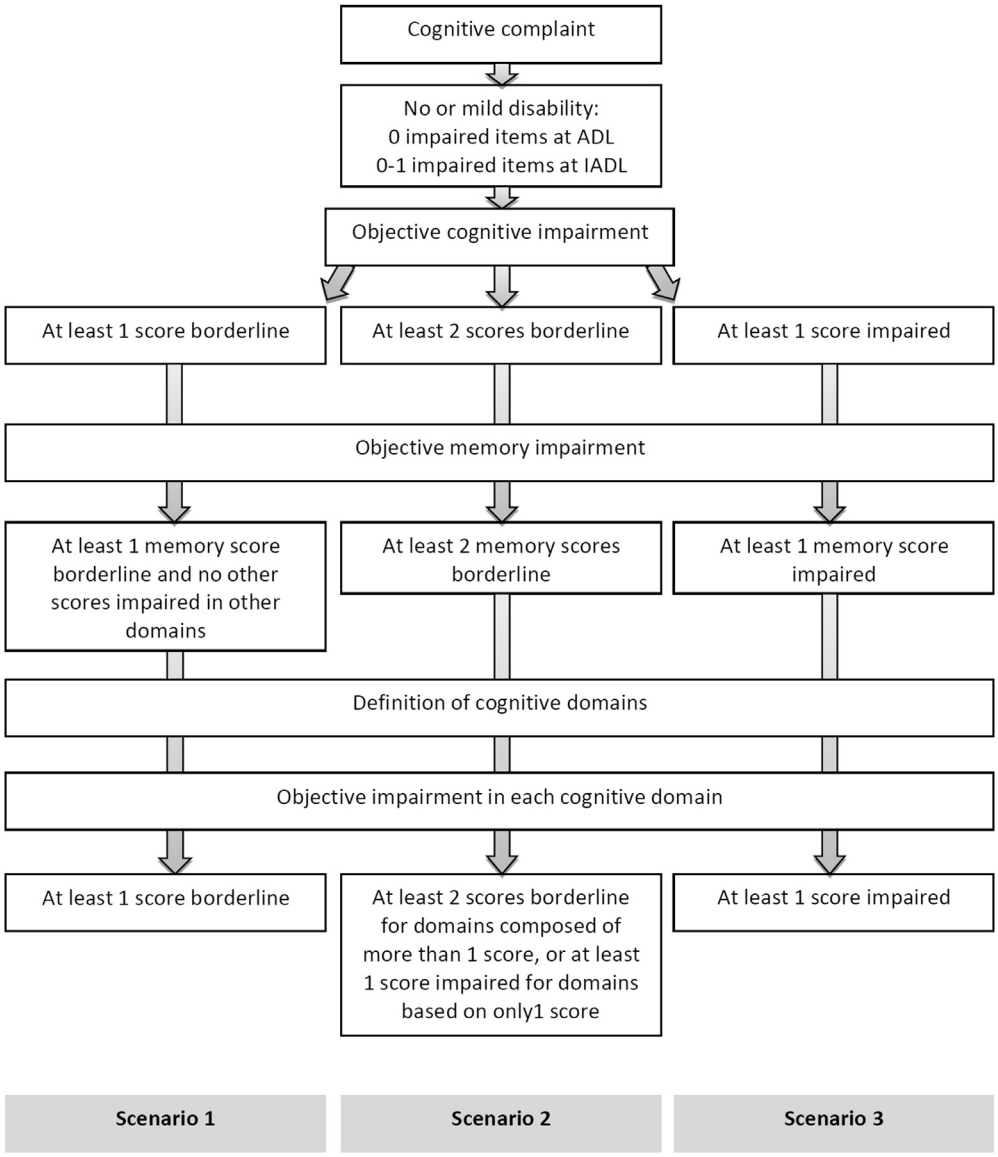

Fig. 1. Operationalization of the MCI diagnostic algorithm according to three possible scenarios. Abbreviations: MCI, mild cognitive impairment; ADL, Activities of Daily Living; IADL, Instrumental Activities of Dailiy Living.

atrophy (Pasquier visual scale) [31], and medial temporal lobe atrophy (MTA) (Scheltens scale) [32]. Forty randomly selected scans were scored twice for the determination of the intrarater reliability, which was good (weighted Cohen's κ: MWH = 0.91; lacunar infarcts = 0.82; global cortical atrophy = 0.62; and MTA = 0.86).

2.1. Statistical analysis

Correlations across neuropsychological tests (Pearson's *r*) and the Cronbach's α coefficients were used to verify the internal consistency of cognitive domains.

Descriptive statistics were used to show frequency distributions of MCI subtypes across the three scenarios. To show the overlapping of distributions of MCI subtypes in all scenarios, 95% confidence intervals (CI) for percentages were calculated by Wilson score method with a correction for continuity [33].

Descriptive statistics were also used to show means and standard deviations (SD) of mini mental state examination (MMSE) scores for each MCI subgroup, and univariate analysis of variance was applied to verify significant differences in MMSE scores distributions across MCI subgroups within all scenarios.

Univariate statistical analyses (Pearson's χ^2 test) were used to compare single and multiple domain MCI groups in terms of neuroimaging variables (WMH, lacunar infarcts, global cortical atrophy, and MTA) in the whole sample of patients classified as MCI according to scenario 1. Descriptive statistics were used to verify frequency distributions of neuroimaging variables in MCI subtypes in both scenarios 1 and 3 (95% CI for percentages calculated

by Wilson score method with a correction for continuity). For statistical analysis, lacunar infarcts were coded as absent or present, mean MTA of the bilateral scores was calculated and dichotomized (MTA score 0–2.5, MTA score ≥3), and global cortical atrophy scores were dichotomized (global cortical atrophy score 0–2, global cortical atrophy score 3).

3. Results

Of the 153 enrolled patients, 84 (55%) were males, and the mean (±SD) age and years of education were 74.7 ± 6.9 and 7.9 ± 4.2, respectively. Mean age and education level were not significantly different among MCI subtypes in any of the three scenarios (data not shown). Concerning vascular risk factors distributions, of the 153 patients, 125 (82%) had hypertension, 91 (60%) had hypercholesterolemia, 22 (14%) had diabetes, 67 (44%) reported smoking habits, 57 (37%) had history of stroke, and 46 (30%) consumed alcohol.

As shown in Table 2, across neuropsychological tests of the same cognitive domain, all Pearson's correlation coefficients resulted statistically significant and Cronbach's α were >0.650 showing a good internal consistency of each domain. No measure of internal consistency could be calculated for the constructional praxis domain (assessed by only the immediate copy of the Rey-Osterrieth complex figure). Nevertheless, this test resulted significantly although moderately correlated with the delayed reproduction of the Rey-Osterrieth complex figure ($r = 0.217$, $P < .01$), the TMT-A ($r = 0.201$, $P < .05$), and the phonemic verbal fluency ($r = 0.162$, $P < .05$).

Table 2
Internal consistency of cognitive domains

	Memory (Cronbach's α = 0.671)		
Cognitive domain	RAVL (immediate)	RAVL (delayed)	Short story
RAVL (delayed)	0.678**		
Short story	0.337**	0.352**	
ROCF (recall)	0.289**	0.191*	0.225**

	Attention and executive functions (Cronbach's α = 0.761)			
Cognitive domain	TMT-A	Visual search	SDMT	Stroop test
Visual search	0.509**			
SDMT	0.515**	0.388**		
Stroop test	0.287**	0.362**	0.255**	
TMT-B	0.553**	0.446**	0.513**	0.415**

	Language (Cronbach's α = 0.651)
	Semantic fluency
Phonemic fluency	0.331**

Abbreviations: RAVL, Rey auditory-verbal learning test; ROCF, Rey-Osterrieth complex figure; TMT-A, trail making test part A; SDMT, symbol digit modalities test; TMT-B, trail making test part B.
*Pearson's *r* coefficient significant at $P < .05$.
**Pearson's *r* coefficient significant at $P < .01$.

Percentage distributions of subjects categorized according to different ES values for all the 12 cognitive scores used in the operationalization of MCI diagnostic criteria are shown in the Online Supplemental Table. Percentages of patients with at least a borderline performance were approximately 50% for all tests included in the memory domain except the short story test that resulted sparsely impaired. In the attention/executive domain, percentages of patients with at least a borderline performance were between 40% and 60% in all tests. The Rey-Osterrieth complex figure resulted the most difficult test for the patients (66% with abnormal performances and 3% with borderline performances), whereas language tests resulted normal in approximately two-third of our sample.

The application of the three scenarios led to the following distributions of MCI subtypes (Fig. 2).

3.1. Scenario 1 (at least one score borderline)

This was the inclusion MCI criteria in our study, and consequently all the 153 enrolled patients were classified as MCI. The A-MCI type prevailed (78%; 95% CI, 70–84) and 86% of patients resulted to be of the multiple domain type (72% A-MCI; 95% CI, 64–79; 14% NA-MCI; 95% CI, 9–21).

3.2. Scenario 2 (at least two scores borderline)

Applying this intermediate criterion, of the 153 enrolled patients, 3 (2%) resulted cognitively normal. For further four MCI patients, we were not able to define the MCI subtype because they had two scores borderline but only one in the memory domain. All these seven patients fell into the A-MCI group (three single domain and four multiple domain) in scenario 1.

Passing from scenario 1 to scenario 2, of the 153 MCI patients, 119 were classified in the same subtypes, 20 moved from the A-MCI multiple domain group to the other subtypes (11 NA-MCI multiple domain, 7 NA-MCI single domain, and 2 A-MCI single domain), and 7 moved within NA-MCI from multiple to single domain group.

3.3. Scenario 3 (at least one score impaired)

Applying this restricted criterion, of the 153 enrolled patients, 7 (5%) resulted cognitively normal, 59% (95% CI, 50–67) were A-MCI and 73% resulted to be of multiple domain type (53% A-MCI; 95% CI, 44–61; 20% NA-MCI; 95% CI, 14–28).

The distribution of MCI subtypes was almost the same for both the intermediate and restricted criterion. Passing from scenario 2 to scenario 3, of the 146 MCI patients, 9 moved from the A-MCI multiple domain group to other subtypes (4 NA-MCI multiple domain, 4 NA-MCI single domain, and 1 A-MCI single domain).

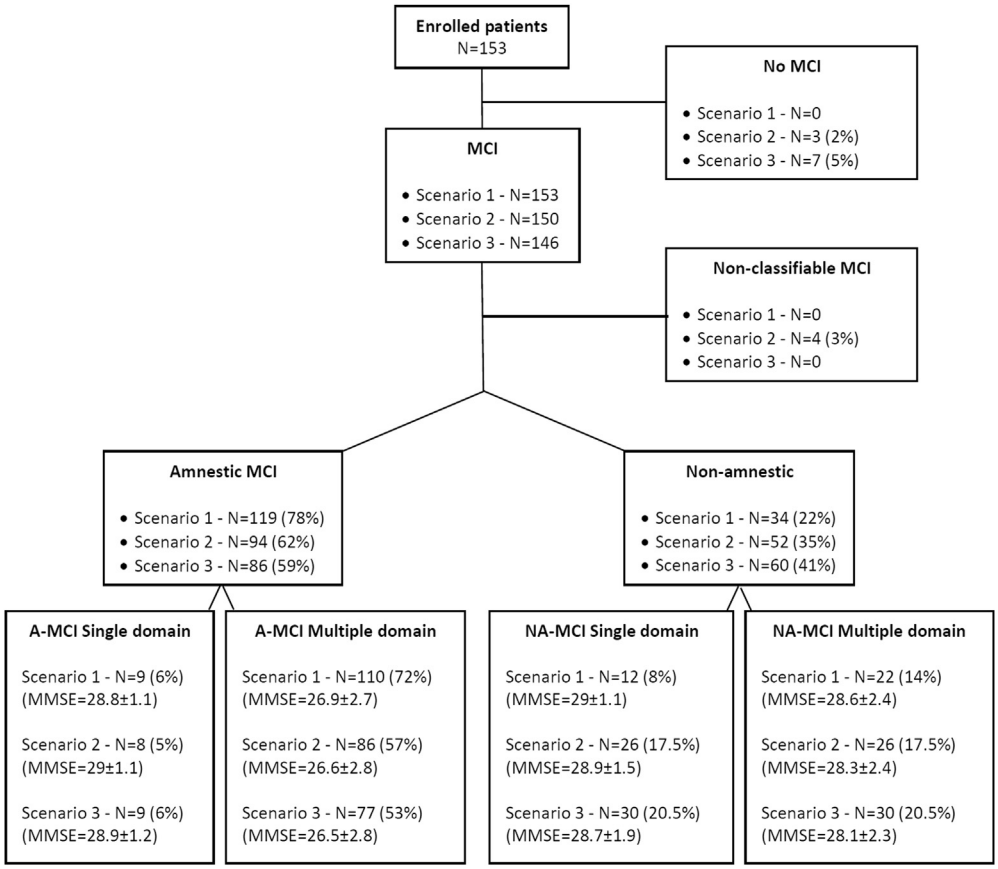

Fig. 2. Distributions of MCI subtypes according to three possible scenarios. Definitions of scenarios are as follows: Scenario 1: at least one test borderline; Scenario 2: at least two tests borderline; and Scenario 3: at least one test impaired. Percentages refer to the total number of MCI patients in each scenario. Abbreviations: MCI, mild cognitive impairment; A-MCI, amnestic mild cognitive impairment; NA-MCI, nonamnestic mild cognitive impairment; MMSE, mini mental state examination.

In comparison to scenario 1, applying scenarios 2 and 3 produced a decrease in percentages of multiple domain A-MCI (from 86% to 77% and 73%, respectively) and an increase in percentages of single domain NA-MCI (from 8% to 18% and 20%, respectively). Ninety-five percent CI for percentages of MCI subtypes in all scenarios are shown in Fig. 3 using a forest plot. The 95% CI distribution of percentages of diagnoses made according to scenarios 1 and 3 for the subtypes A-MCI multiple domain and NA-MCI single domain were not overlapping.

Mean MMSE scores and SD for each MCI subgroup are shown in Fig. 2. In all scenarios, significant differences in MMSE scores distributions were found across MCI subgroups (scenario 1: $F = 5.49$, $P < .01$; scenario 2: $F = 8.43$, $P < .01$; and scenario 3: $F = 8.04$, $P < .01$). The mean MMSE scores of A-MCI multiple domain group always resulted lower compared with the other MCI subtypes, and post hoc tests (Bonferroni) showed significant differences between A-MCI multiple domain group and NA-MCI groups, either single or multiple domain, in all scenarios (data not shown).

3.4. Neuroimaging characterization of single and multiple domain MCI

Of the 153 enrolled patients, 82 (54%) had a severe degree of WMH, 103 (67%) at least one lacunar infarct, 28 (18%) a severe degree of global cortical atrophy, and 94 (61%) a mean MTA score ≥ 3.

Using Pearson's χ^2 test, only MTA showed a statistically significant association with multiple domain MCI (68% vs. 38% multiple vs. single domain MCI; $\chi^2 = 6.82$, $P = .009$). Global cortical atrophy (20% vs. 10% multiple vs. single domain), WMH (55% vs. 43%), and lacunar infarcts (68% vs. 67%) were not significantly associated with single or multiple domain MCI.

The 95% CI distribution of percentages of neuroimaging variables were largely overlapping between scenarios 1 and 3 for all MCI subtypes (data not shown). Comparing neuroimaging variables that could characterize those MCI subtypes whose distributions of diagnoses differed between the scenarios, the A-MCI multiple domain group resulted always in high percentages of both lacunar infarcts (66% vs. 69%, scenario 1 vs. 3) and mean MTA score ≥ 3 (70% vs.

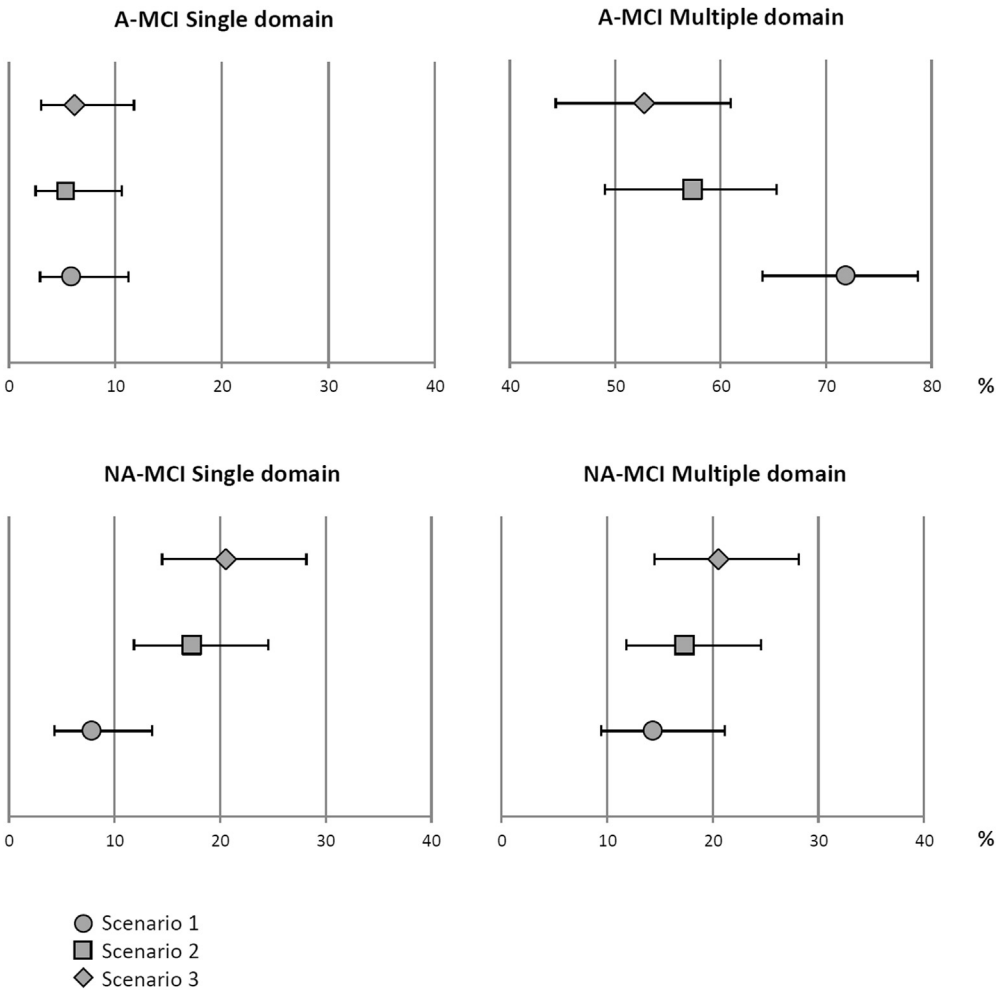

Fig. 3. Ninety-five percent confidence intervals of percentage distributions of MCI subtypes in three scenarios. Abbreviations: MCI, mild cognitive impairment; A-MCI, amnestic mild cognitive impairment; NA-MCI, nonamnestic mild cognitive impairment.

68%, scenario 1 vs. 3), whereas the NA-MCI single domain group showed high percentages of lacunar infarcts (73% vs. 73%, scenario 1 vs. 3; Fig. 4).

4. Discussion

This study represents the first attempt to assess the effect of the operationalization of MCI consensus criteria in terms of subtypes distribution in a sample of patients with SVD. We found that the application of differently operationalized criteria led to minimal changes in the total number of patients diagnosed as MCI but to more marked differences in the frequency of MCI subtypes. Most of our patients were classified as multiple-domain A-MCI in line with the Winblad et al.'s hypothesis. However, about one-fifth showed a single-domain profile. Finally, in comparison with single-domain MCI patients, multiple-domain patients showed higher frequency of severe MTA.

Multiple-domain MCI was highly prevalent in our sample across all scenarios and this is in line with the hypothesis that MCI subtypes characterized by impairment in nonmemory domains, such as executive function and visuospatial skills, may have a vascular etiology [5,34–36].

The fact that when using more restrictive criteria to diagnose MCI, a certain number of our patients were diagnosed with single NA domain MCI supports the hypothesis that MCI patients with SVD might have specific patterns of cognitive impairments in domains other than memory [34,35]. This would expand the clinical spectrum of vascular MCI.

Recent studies have examined empirically derived subtypes of MCI based on patterns of neuropsychological deficits in clinic- and community-based samples and most of them had identified homogenous subgroups that were consistent across studies and could reflect a common etiology (e.g., memory impaired group, multidomain amnestic group, and dysexecutive group) [1,34,36]. In particular, Delano-Wood *et al.* [34] found significantly greater levels of white matter changes burden on neuroimaging in their empirically derived dysexecutive MCI subgroup, consistently with the hypothesis of the association of cerebrovascular lesions with this pattern of deficits.

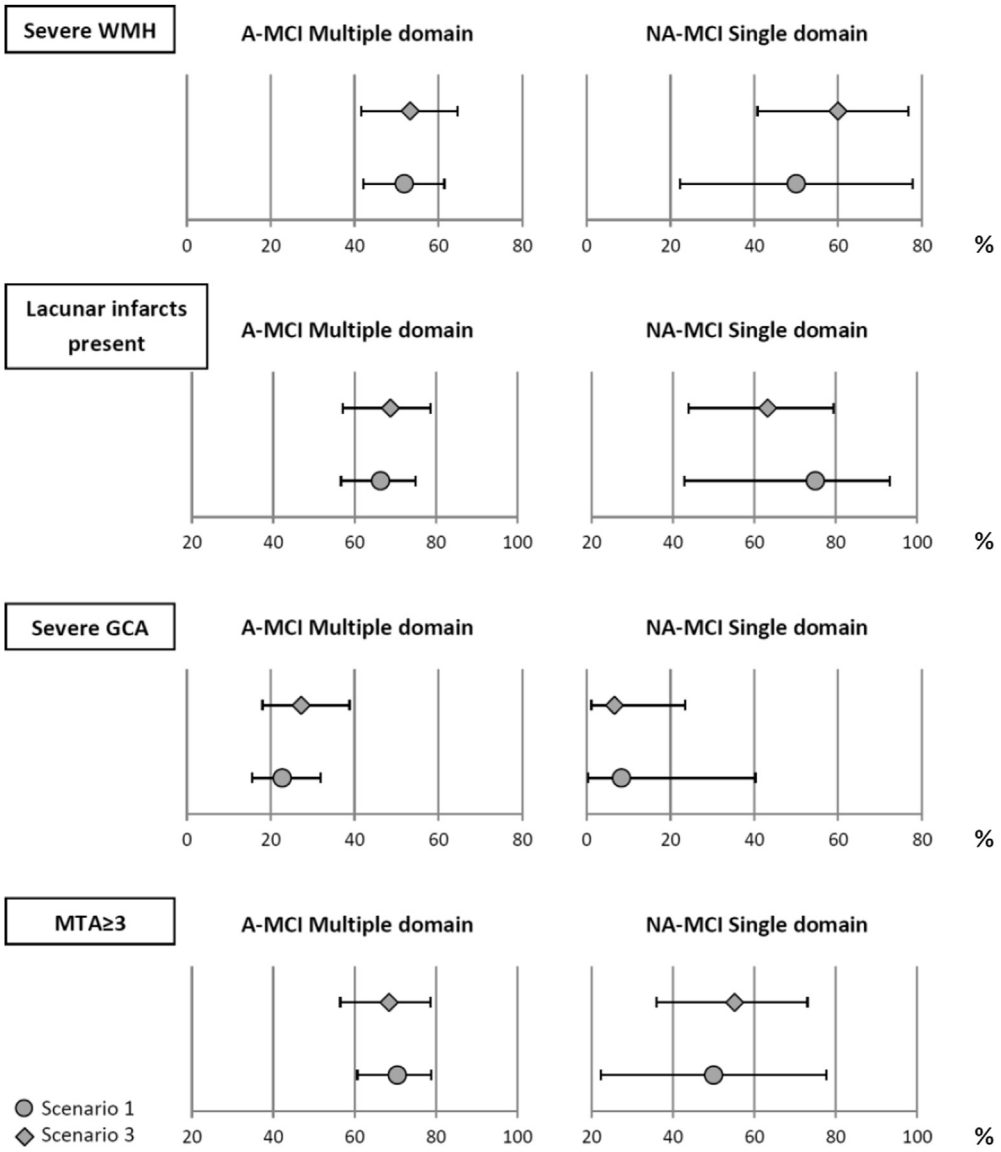

Fig. 4. Ninety-five percent confidence intervals of percentage distributions of neuroimaging variables in A-MCI multiple domain and NA-MCI single domain subtypes between scenarios 1 and 3. Abbreviations: WMH, white matter hyperintensities; A-MCI, amnestic mild cognitive impairment; NA-MCI, nonamnestic mild cognitive impairment; GCA, global cortical atrophy; MTA, medial temporal lobe atrophy.

Most of our patients fell in the A-MCI group across different scenarios. This is likely a result of the fact that in Winblad et al.'s criteria for MCI memory deficits are hierarchically prevailing over other cognitive domains in the diagnostic algorithm. As a result, patients with mild memory deficits and severe deficits in other domains are nonetheless classified as amnestic. Taking into account the mentioned aspect and applying the three different scenarios, we had to decide how to classify those patients with borderline performances in memory domain and frankly abnormal performances in other cognitive domains. We decided to classify as A-MCI only those patients who had at least one memory score borderline and no frankly impaired scores in other cognitive domains; otherwise patients were assigned to NA-MCI. For MCI subtyping, it seems advisable to take into account the overall neuropsychological profile of patients without attributing to memory a prominent role. This is in line with the recent proposal of redefinition of VMCI diagnostic criteria which, according to a comprehensive and neuropsychological approach, excludes the prevailing position of memory impairment and gives equal importance to other cognitive domains [11].

Previous reports are conflicting on the nature and extent of brain changes associated with MCI subtypes [37]. According to Winblad et al.'s criteria, VMCI should be characterized by a multidomain profile [5]. However, between one-sixth and one-fourth of our patients were

classified as single domain. To test whether this latter group differed in neuroimaging terms from the multidomain group, for example for an overrepresentation of degenerative aspects, we compared MRI findings and found that instead neurodegenerative features, such as MTA, were more prevalent in the multidomain group, particularly in the A-MCI multi domain. On the other hand, the main neuroimaging characteristics emerged in the NA-MCI single domain group was the presence of lacunar infarcts.

Limitations of our study need to be considered. The main limitation is that each cognitive domain included a different number of tests and scores. Theoretically, having more cognitive scores increases the likelihood of finding a deficit in that specific domain. The memory impairment was evaluated taking into account four cognitive scores, whereas the attention/executive impairment was based on five scores and this difference is likely to influence the decrease in proportion of A-MCI, and the resulting increase of NA-MCI, when using more restrictive criteria. Distribution of cognitive performances confirmed that attention-executive dysfunction was one of the prominent features, but impairments in memory and high-level visuoconstructional abilities were also observed in our sample despite the lower number of available scores.

Another consequence of different number of tests and scores is that language and constructional praxis impairments might have been underestimated in comparison with memory and attention/executive functions deficits. To verify the impact of different number of tests and scores in each cognitive domain on MCI subtypes distributions, we explored also an operationalization based on three cognitive domains: memory and executive functions (as described mentioned), and a third "mixed" cognitive domain that pooled the two language tests and the constructional praxis test. Applying this three-domain strategy, distributions of MCI subtypes according to three possible scenarios were basically the same of our original analysis. In all scenarios, only one patient, classified as NA-MCI multiple domain in the four-domain analysis, moved to the NA-MCI single domain group in the three-domain analysis. Also, 95% CI for percentages of MCI subtypes in all scenarios remained the same. Furthermore, our results showed a good internal consistency of cognitive domains in the four-domain approach. We therefore decided to use the model confirmed also in the previous methodological article on the psychometric properties of the VMCI-Tuscany neuropsychological battery [14].

A second limitation is the use of the number of impaired cognitive scores, as opposed to that of an overall summary score, for the determination of cognitive impairment. A recent study found that summary scores, such as averaging of *z*-scores and item response theory score, provided a more accurate determination of the prevalence of cognitive impairment in a very large sample of 461 patients and 724 controls [38]. Although the use of the number of impaired cognitive scores has been demonstrated to be less sensitive than summary scores, the relatively small sample in our study did not allow the use of such sophisticated methods; that, however, will have to be implemented in further studies on the optimization of operationalization of criterion of mild cognitive impairment.

A third limitation is that the multiple-domain MCI group was notably larger than the single-domain MCI group and this reduced the statistical power of comparative analyses.

Another possible limitation may be the lack of cerebrospinal fluid biomarkers and positron emission tomography assessments of markers of Alzheimer disease to better define the etiology of our sample. This, however, reflects the current situation in most centers. On the other hand, the lack of an association between cerebrovascular burden and MCI subtypes may be due also to the quantification of WMH according to a visual rating scale, rather than a more objective and metric methodology. Therefore, we cannot be completely sure that our sample was composed of patients with pure vascular MCI. Yet, this patient sample likely represents what is encountered in clinical practice. At the end of the ongoing follow-up, data will be available concerning the incidence of dementia and its subtypes and their possible association with baseline neuropsychological patterns of deficits. Finally, it is important to note that our results and conclusions refer to a sample of patients with MCI and SVD and not to the global MCI population.

Cognitive profiling of MCI subtypes is important from the clinical, research, and epidemiologic points of view. In this sense, the hierarchical approach used in the Winblad et al.'s criteria, based on the presence or absence of memory deficits, could not be optimal to identify other specific patterns of cognitive impairment, particularly in patients with cerebrovascular diseases thought to have domains other than memory mainly affected. A more comprehensive evaluation of the cognitive profile, based on several hierarchically equivalent cognitive domains, should guide the classification, and future studies in this regard are warranted.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2015.02.010.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using standard databases (e.g., PubMed). The topic is in expansion, and relevant articles related to the debate on best criteria for MCI diagnosis and their operationalization are appropriately cited.
2. Interpretation: Our findings suggest that the hierarchical approach used in current MCI criteria could not be optimal to identify specific patterns of cognitive impairment in patients with cerebrovascular diseases who have domains other than memory mainly affected.
3. Future directions: Our study provides a framework for further studies on operationalization of criteria for MCI in patients with cerebrovascular disease: (1) studies on MCI diagnostic criteria based on a comprehensive cognitive evaluation without a hierarchical approach; (2) studies on comparisons between clinically and empirically derived subtypes of MCI based on patterns of neuropsychological deficits; and (3) studies on the reliability of different MCI diagnostic approaches on the progression to dementia and its subtypes.

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