ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE
DELLA RICERCA

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

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

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:
Salvadori, E., Poggesi, A., Valenti, R., Pracucci, G., Pescini, F., Pasi, M., et al. (2016). Operationalizing mild cognitive impairment criteria in small vessel disease: The VMCI-Tuscany Study. ALZHEIMER'S & DEMENTIA, 12(4), 407-418 [10.1016/j.jalz.2015.02.010].

Availability:
This version is available at: https://hdl.handle.net/11585/567580 since: 2016-11-15

Published:
DOI: http://doi.org/10.1016/j.jalz.2015.02.010

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (https://cris.unibo.it/).
When citing, please refer to the published version.

(Article begins on next page)

12 October 2024

This is the final peer-reviewed accepted manuscript of:

Salvadori, Emilia, Anna Poggesi, Raffaella Valenti, Giovanni Pracucci, Francesca Pescini, Marco Pasi, Serena Nannucci, Sandro Marini, Alessandra Del Bene, Laura Ciolli, Andrea Ginestroni, Stefano Diciotti, Giovanni Orlandi, Ilaria Di Donato, Nicola De Stefano, Mirco Cosottini, Alberto Chiti, Antonio Federico, Maria Teresa Dotti, Ubaldo Bonuccelli, Domenico Inzitari, and Leonardo Pantoni. "Operationalizing Mild Cognitive Impairment Criteria in Small Vessel Disease: The VMCI-Tuscany Study." *Alzheimer's & Dementia* 12, no. 4 (2016): 407-18.

The final published version is available online at:

https://doi.org/10.1016/j.jalz.2015.02.010

Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (https://cris.unibo.it/)

When citing, please refer to the published version.

Operationalizing MCI criteria in small vessel disease: the VMCI-Tuscany Study

E. Salvadori, PhD,[a] A. Poggesi, PhD,[a] R. Valenti, MD,[a] G. Pracucci, MD,[a] F. Pescini, PhD,[b] M. Pasi, MD,[a] S. Nannucci, MD,[a] S. Marini, MD,[a] A. Del Bene, PhD,[a] L. Ciolli, PhD,[a] A. Ginestroni, PhD,[c] S. Diciotti, PhD,[d] G. Orlandi, MD,[e] I. Di Donato, MD,[f] N. De Stefano, MD,[f] M. Cosottini, MD,[g] A. Chiti, MD,[e] A. Federico, MD,[f] M. Teresa Dotti, MD,[f] U. Bonuccelli, MD,[e] D. Inzitari, MD,[a] L. Pantoni, PhD,[b]* on behalf of the VMCI-Tuscany Study Group

[a] NEUROFARBA Department, Neuroscience Section, University of Florence, Florence, Italy
[b] Stroke Unit and Neurology, Azienda Ospedaliero Universitaria Careggi, Florence, Italy
[c] 'Mario Serio' Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy
[d] Department of Electrical, Electronic, and Information Engineering 'Guglielmo Marconi', University of Bologna, Cesena, Italy
[e] Department of Neurosciences, University of Pisa, Pisa, Italy
[f] Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy
[g] Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

***Corresponding author**:
Leonardo Pantoni, MD, PhD
Stroke Unit and Neurology,
Azienda Ospedaliero Universitaria Careggi
Largo Brambilla 3, 50134 Firenze, Italy
Phone: #39-055-7945519
Fax: #39-055-4298461
e-mail: pantoni@unifi.it

Authors' disclosures:
Salvadori, Poggesi, Valenti, Pracucci, Pescini, Pasi, Nannucci, Marini, Del Bene, Ciolli, Ginestroni, Diciotti, Orlandi, Di Donato, Cosottini, Chiti, Federico, Dotti, Bonuccelli reports no disclosures.
De Stefano has served on scientific advisory boards and steering committees of clinical trials for Merck Serono S.A., Teva and Novartis Pharma AG, and has received support for congress participation or speaker honoraria from Biogen Idec, Merck Serono S.A., Bayer-Schering AG, Teva, Sanofi-Aventis and Novartis Pharma AG. He received grants from the Italian MS Society, outside the submitted work.
Inzitari serves as a member in the Editorial Board of Stroke, and is Associate Editor of Neurological Sciences Journals. He has received grants for research by Bayer Italy, and fees for conferences by Boheringer Italy and Bayer Italy.
Pantoni serves on the editorial boards of Acta Neurologica Scandinavica and Cerebrovascular Diseases, and as Vascular Cognitive Impairment Section Editor for Stroke.

Abstract

Background. Mild cognitive impairment (MCI) prodromic of vascular dementia is expected to have a multi-domain 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 multi-domain MCI. We applied 3 MCI diagnostic scenarios in which the cut-offs for objective impairment and the number of considered neuropsychological tests varied.

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

Conclusions. Operationalizing MCI criteria changes the relative frequency of MCI subtypes. Non-amnestic single domain MCI may be a previously non-recognized type of MCI associated with SVD.

Key Words: cerebrovascular disease, vascular dementia, mild cognitive impairment, neuropsychology, cognitive aging

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, while 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 non-demented 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 multi-domain 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-Tuscany Study is an ongoing multicenter, prospective, observational study aimed at evaluating predictors of the transition from vascular MCI (defined by the presence of moderate-severe white matter lesions) to dementia (12). The study methodology has been reported elsewhere (12). To be included, out-patients, 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 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 (FLAIR) sequences taking into account only deep and subcortical white matter lesions. The modified Fazekas scale is a visual scale based on a categorization into 3 severity classes: grade 1 (mild WMH) = single lesions below 10 mm, areas of 'grouped' lesions smaller than 20 mm in any diameter; grade 2 (moderate WMH) = single lesions between 10 and 20 mm, areas of 'grouped' lesions more than 20 mm

in any diameter, no more than 'connecting bridges' between individual lesions; grade 3 (severe WMH) = single lesions or confluent areas of hyperintensity 20 mm or more 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 paper (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 (NINDS) and the Canadian Stroke Network (CSN) 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 non-parametric 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 cut-off splitting the bottom 5% of the population and representing pathological performance (ES=0). On the other end of the scale, ES=4 indicates

an optimal performance (≥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), while 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 2 global cognitive functioning tests and other 9 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 less than 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 1 item compromised on Instrumental Activities of Daily Living scale (29)) (figure 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.

The Winblad et al.'s MCI diagnostic algorithm requires the 3 following hierarchical steps: 1) definition of objective cognitive impairment; 2) definition of an objective impairment in memory; 3) definition of an objective cognitive impairment in cognitive domains other than memory (figure 1). For each of the 3 steps, we defined: i) how much each score had to be below the mean to be considered impaired; and ii) how many scores were impaired. We built 3 possible scenarios: 1) at least one score borderline (ES=1) (corresponding to our inclusion criterion); 2) at least two scores borderline; 3) at least one score frankly impaired (ES=0 or an adjusted score lower than the 5th centile of the normal population) (figure 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 (none ES was assigned).

An additional issue was the definition of cognitive domains. In a previous methodological paper 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 4 cognitive

domains: memory (assessed by 4 cognitive scores), attention/executive functions (5 cognitive scores), language (2 cognitive scores), constructional praxis (1 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 1 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 (AP) who was blind to clinical details and MCI classification. After the central MRI revision, out 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 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 intra-rater reliability, which was good (weighted Cohen's kappa: MWH=0.91; lacunar infarcts=0.82; global cortical atrophy=0.62; 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 3 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 (ANOVA) was applied to verify significant differences in MMSE scores distributions across MCI subgroups within all scenarios.

Univariate statistical analyses (Pearson's chi-squared 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

Out 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, out of the 153 patients: 125 (82%) had hypertension, 91 (60%) hypercholesterolemia, 22 (14%) diabetes, 67 (44%) reported smoking habits, 57 (37%) had history of stroke, and 46 (30%) alcohol consumption.

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 >.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=.217, p<.01), the TMT-A (r=.201, p<.05), and the phonemic verbal fluency (r=.162, p<.05).

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), while language tests resulted normal in approximately two-third of our sample.

The application of the 3 scenarios led to the following distributions of MCI subtypes (figure 2).

Scenario 1 (at least 1 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).

Scenario 2 (at least 2 scores borderline)

Applying this intermediate criterion, out of the 153 enrolled patients, 3 (2%) resulted cognitively normal. For further 4 MCI patients we were not able to define the MCI subtype

because they had 2 scores borderline but only one in the memory domain. All these 7 patients fell into the A-MCI group (3 single domain, and 4 multiple domain) in scenario 1.

Passing from scenario 1 to scenario 2, out 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.

Scenario 3 (at least 1 score impaired)

Applying this restricted criterion, out 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, out 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).

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 figure 3 using a Forest Plot. The 95% CI distribution of percentages of diagnoses made according to scenario 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 figure 2. In all scenarios, significant differences in MMSE scores distributions were found across MCI subgroups (scenario 1: $F=5.49$, $p<.01$; scenario 2: $F=8.43$, $p<.01$; scenario 3: $F=8.04$, $p<.01$).

The mean MMSE scores of A-MCI multiple domain group always resulted lower compared to 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).

Neuroimaging characterization of single and multiple domain MCI

Out 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 chi-squared test, only MTA showed a statistically significant association with multiple domain MCI (68% vs. 38% multiple vs. single domain MCI; χ^2=6.82, p=0.009). 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. 68% scenario 1 vs. 3), while the NA-MCI single domain group showed high percentages of lacunar infarcts (73% vs. 73% scenario 1 vs. 3) (Figure 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 non-memory 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 amount of our patients was 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, multi-domain amnestic group, and dysexecutive group) (1, 34, 36). In particular, Delano-Wood and colleagues 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 (34).

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 above aspect and applying the 3 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 1 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 vascular MCI 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, vascular MCI should be characterized by a multi-domain 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 multi-domain group, for example for an over-representation of degenerative aspects, we compared MRI findings and found that instead neurodegenerative features, such as MTA, were more prevalent in the multi-domain 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 4 cognitive scores, while the attention/executive impairment was based on 5 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 visuo-constructional 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 to 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 above), and a third 'mixed' cognitive domain that pooled the two language tests and the constructional praxis test. Applying this 3-domain strategy, distributions of MCI subtypes according to 3 possible scenarios was basically the same of our original analysis. In all scenarios, only one patient, classified as NA-MCI multiple domain in the 4-domain analysis, moved to the NA-MCI single domain group in the 3-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 4-domain approach. We therefore decided to use the model confirmed also in the previous methodological paper 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). Despite 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 epidemiological 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.

References

1. Bondi MW, Smith GE. Mild cognitive impairment: a concept and diagnostic entity in need of input from neuropsychology. J Int Neuropsychol Soc 2014;20:129-34.

2. Christa Maree Stephan B, Minett T, Pagett E, Siervo M, Brayne C, McKeith IG. Diagnosing Mild Cognitive Impairment (MCI) in clinical trials: a systematic review. BMJ Open 2013;3. doi: 10.1136/bmjopen-2012-001909.

3. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment - beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240-6.

4. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985-92.

5. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet 2006;367:1262-70.

6. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. Lancet Neurol 2003;2:89-98.

7. Pantoni L, Poggesi A, Inzitari D. The relation between white-matter lesions and cognition. Curr Opin Neurol 2007;20:390-7.

8. Sachdev PS, Brodaty H, Looi JC. Vascular dementia: diagnosis, management and possible prevention. Med J Aust 1999;170:81-5.

9. Lamar M, Price CC, Giovannetti T, Swenson R, Libon DJ. The dysexecutive syndrome associated with ischaemic vascular disease and related subcortical neuropathology: a Boston process approach. Behav Neurol 2010;22:53-62.

10. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010;9:689-701.

11. Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic Criteria for Vascular Cognitive Disorders: A VASCOG Statement. Alzheimer Dis Assoc Disord 2014;28:206-18.

12. Poggesi A, Salvadori E, Pantoni L, Pracucci G, Cesari F, Chiti A, et al. Risk and Determinants of Dementia in Patients with Mild Cognitive Impairment and Brain Subcortical Vascular Changes: A Study of Clinical, Neuroimaging, and Biological Markers-The VMCI-Tuscany Study: Rationale, Design, and Methodology. Int J Alzheimers Dis 2012;608013. doi: 10.1155/2012/608013.

13. Pantoni L, Basile AM, Pracucci G, Asplund K, Bogousslavsky J, Chabriat H, et al. Impact of age-related cerebral white matter changes on the transition to disability -- the LADIS study: rationale, design and methodology. Neuroepidemiology 2005;24:51-62.

14. Salvadori E, Poggesi A, Pracucci G, Inzitari D, Pantoni L. Development and Psychometric Properties of a Neuropsychological Battery for Mild Cognitive Impairment with Small Vessel Disease: The VMCI-Tuscany Study. J Alzheimers Dis. 2014. doi: 10.3233/JAD-141449.

15. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37:2220-41.

16. Bianchi A, Dai Prà M. Twenty years after Spinnler and Tognoni: new instruments in the Italian neuropsychologist's toolbox. Neurol Sci 2008;29:209-17.

17. Capitani E, Laiacona M. Composite neuropsychological batteries and demographic correction: standardization based on equivalent scores, with a review of published data. The Italian Group for the Neuropsychological Study of Ageing. J. Clin Exp Neuropsychol 1997;19:795-809.

18. Measso G, Cavarzeran F, Zappala G, Lebowitz B, Crook TC, Pirozzolo FJ, et al. The Mini Examination: normative study of an Italian random sample. Developmental Neuropsych 1993;9:77-85.

19. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-9.

20. Carlesimo GA, Caltagirone C, Gainotti G. The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The group for the Standardization of the Mental Deterioration Battery. Eur Neurol 1996;36:378-84.

21. Novelli G, Papagno C, Capitani E, Laiacona M, Cappa SF, Vallar G. Tre test clinici di memoria a lungo termine. Archivio di Psicologia, Neurologia e Psichiatria 1986:47:278-96.

22. Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A. Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurological Sciences 2002;22:443-7.

23. Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail making test: normative values from 287 normal adult controls. Italian Journal of Neurological Sciences 1996;17:305-9.

24. Della Sala S, Laiacona M, Spinnler H, Ubezio C. A cancellation test: its reliability in assessing attentional deficit in Alzheimer's disease. Psych Med 1992;22:885–901.

25. Nocentini U, Giordano A, Di Vincenzo S, Panella M, Pasqualetti P. The Symbol Digit Modalities Test - Oral version: Italian normative data. Funct Neurol 2006;21:93-6.

26. Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A. Una versione abbreviata del test di Stroop. Dati normativi nella popolazione italiana. Nuova Rivista di Neurologia 2002;12:111-5.

27. Novelli G, Papagno C, Capitani E, Laiacona M, Vallar G. Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normali. Archivio di Psicologia, Neurologia e Psichiatria 1986;47:477-506.

28. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. JAMA 1963;185:914-9.

29. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-86.

30. Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. Stroke 2008;39:1414-20.

31. Pasquier F, Leys D, Weerts JG, Mounier-Vehier F, Barkhof F, Scheltens P. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. Eur Neurol 1996;36:268-72.

32. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992;55:967-72.

33. Newcombe R. Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods. Statistics in Medicine 1998;17:857-72.

34. Delano-Wood L, Bondi MW, Sacco J, Abeles N, Jak AJ, Libon DJ, et al. Heterogeneity in mild cognitive impairment: Differences in neuropsychological profile and associated white matter lesion pathology. J Int Neuropsychol Soc 2009;15:906–14.

35. Rasquin SM, Lodder J, Visser PJ, Lousberg R, Verhey FR. Predictive accuracy of MCI subtypes for Alzheimer's disease and vascular dementia in subjects with mild cognitive impairment: a 2-year follow-up study. Dement Geriatr Cogn Disord 2005;19:113-9.

36. Clark LR, Delano-Wood L, Libon DJ, McDonald CR, Nation DA, Bangen KJ, et al. Are empirically-derived subtypes of mild cognitive impairment consistent with conventional subtypes? J Int Neuropsychol Soc 2013;19:635-45.

37. Jak AJ, Bangen KJ, Wierenga CE, Delano-Wood L, Corey-Bloom J, Bondi MW. Contributions of neuropsychology and neuroimaging to understanding clinical subtypes of mild cognitive impairment. Int Rev Neurobiol 2009;84:81-103.

38. Godefroy O, Gibbons L, Diouf M, Nyenhuis D, Roussel M, Black S, et al. Validation of an integrated method for determining cognitive ability: Implications for routine assessments and clinical trials. Cortex 2014;54:51-62.

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

Table 2. Internal consistency of cognitive domains.

Memory (Cronbach's α=.671)			
	RAVL (immediate)	*RAVL (delayed)*	*Short story*
RAVL (delayed)	.678**		
Short story	.337**	.352**	
ROCF (recall)	.289**	.191*	.225**

Attention and Executive functions (Cronbach's α=.761)				
	TMT-A	*Visual search*	*SDMT*	*Stroop Test*
Visual search	.509**			
SDMT	.515**	.388**		
Stroop Test	.287**	.362**	.255**	
TMT-B	.553**	.446**	.513**	.415**

Language (Cronbach's α=.651)	
	Semantic fluency
Phonemic fluency	.331**

* Pearson's *r* coefficient significant at *p*<.05

** Pearson's *r* coefficient significant at *p*<.01

RAVL: Rey Auditory-Verbal Learning Test; ROCF: Rey–Osterrieth Complex Figure; TMT-A: Trail Making Test Part A; TMT-B: Trail Making Test Part B; SDMT: Symbol Digit Modalities Test

Figure 1. Operationalization of the MCI diagnostic algorithm according to 3 possible scenarios.

Figure 2. Distributions of MCI subtypes according to 3 possible scenarios.

Figure legend:

Definitions of scenarios:

- Scenario 1: *at least 1 test borderline*.
- Scenario 2: *at least 2 tests borderline*.
- Scenario 3: *at least 1 test impaired*.

Percentages refer to the total number of MCI patients in each scenario

Figure 3. Ninety-five percent confidence intervals of percentages distributions of MCI subtypes in 3 scenarios.

Figure 4. Ninety-five percent confidence intervals of percentages distributions of neuroimaging variables in A-MCI multiple domain and NA-MCI single domain subtypes between scenarios 1 and 3.

Acknowledgements: we wish to thank Dr. David Libon (Department of Neurology, Drexel University College of Medicine, Philadelphia, PA) for useful comments and criticism on this paper.

Funding Sources: the VMCI-Tuscany study is funded by Tuscany region. Emilia Salvadori is currently supported by a project funded by Tuscany region and Health Ministry (Bando Ricerca Finalizzata 2010, Grant number: RF-2010-2321706, ClinicalTrials.gov Identifier: NCT02033850, PI Leonardo Pantoni).

Appendix. List of participating centers and personnel in the VMCI-Tuscany.

University of Florence: (Coordinating Center): Domenico Inzitari (Study coordinator), Rosanna Abbate, Maria Boddi, Francesca Cesari, Laura Ciolli, Mirella Coppo, Alessandra Del Bene, Stefano Diciotti, Andrea Ginestroni, Betti Giusti, Anna Maria Gori, Sandro Marini, Mario Mascalchi, Serena Nannucci, Leonardo Pantoni, Marco Pasi, Francesca Pescini, Anna Poggesi, Giovanni Pracucci, Emilia Salvadori, Raffaella Valenti

University of Pisa: Ubaldo Bonuccelli, Paolo Cecchi, Alberto Chiti, Mirco Cosottini, Giovanni Orlandi, Cristina Pagni, Gabriele Siciliano, Gloria Tognoni

University of Siena: Antonio Federico, Nicola De Stefano, Ilaria Di Donato, Maria Teresa Dotti, Patrizia Formichi, Claudia Gambetti, Antonio Giorgio, Francesca Rossi, Laura Stromillo, Enza Zicari

Tuscany Region: Arezzo (Paolo Zolo, Alessandro Tiezzi); Empoli (Elisabetta Bertini, Stefania Brotini, Leonello Guidi, Maria Lombardi, Stefania Mugnai, Antonella Notarelli); Florence (Laura Bracco, Massimo Cadelo, Renzo Cisbani, Luciano Gabbani, Guido Gori, Lorella Lambertucci, Luca Massacesi, Enrico Mossello, Marco Paganini, Maristella Piccininni, Francesco Pinto, Claudia Pozzi, Sandro Sorbi, Gaetano Zaccara); Grosseto (Tiziano Borgogni, Mario Mancuso, Roberto Marconi); Lucca (Monica Mazzoni, Marco Vista); Livorno (Giuseppe Meucci, Giovanna Bellini); Massa Carrara (Luciano Gabrielli); Pisa (Cristina Frittelli, Renato Galli, Gianna Gambaccini); Pistoia (Stefano Bartolini, Carlo Biagini, Veronica Caleri, Paola Vanni); Prato (Donatella Calvani, Carla Giorgi, Stefano Magnolfi, Pasquale Palumbo, Carlo Valente); Siena (Alessandro Rossi, Rossana Tassi, Stefania Boschi); Viareggio (Filippo Baldacci)