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## **White matter hyperintensities and medial temporal lobe atrophy in clinical subtypes of mild cognitive impairment: the DESCRIPA study.**

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**Abstract**

Clinical subtypes of mild cognitive impairment (MCI) may represent different underlying aetiologies. In a European, multi-center, memory-clinic based study (DESCRIPA) of non-demented subjects we investigated whether MCI subtypes have different brain correlates on MRI and whether the relation between subtypes and brain pathology is modified by age. Using visual rating scales medial temporal lobe atrophy (MTA) (0-4) and white matter hyperintensities (WMH) (0-30) were assessed. Severity of MTA differed between MCI subtypes ( $p < 0.001$ ), increasing from (mean  $\pm$  standard deviation)  $0.8 \pm 0.7$  in subjective complaints ( $n=77$ ), to  $1.3 \pm 0.8$  in non-amnesic MCI ( $n=93$ ),  $1.4 \pm 0.9$  in single-domain amnesic MCI ( $n=70$ ) and  $1.7 \pm 0.9$  in multiple-domain amnesic MCI ( $n=89$ ). The association between MCI subtype and MTA was modified by age, and mainly present in subjects  $>70$  years. Severity of WMH didn't differ between MCI subtypes ( $p=0.21$ ). However, the combination of MTA and WMH differed between MCI subtypes ( $p=0.02$ ). We conclude that MCI subtypes may have different brain substrates, especially in older subjects. Isolated MTA was mainly associated with amnesic MCI subtypes, suggesting AD as underlying cause. In non-amnesic MCI the relatively higher prevalence of MTA in combination with WMH may suggest a different pathophysiological origin.

**Keywords:**

Mild cognitive impairment

Subtypes

MRI

Medial temporal lobe atrophy

White matter hyperintensities

Age

## 1. Introduction

Mild cognitive impairment (MCI) refers to cognitive decline in non-demented subjects and is considered to be a risk state for Alzheimer's disease (AD).<sup>1-3</sup> However, not all subjects with MCI will develop AD, some will remain stable or even improve over time, whilst others will develop other types of dementia.<sup>4-6</sup> Clinical subtypes of MCI have been suggested, that are assumed to represent different underlying aetiologies. These subtypes are based on the cognitive domains in which the impairment occurs (amnestic versus non-amnestic), and the number of cognitive domains affected (single versus multiple).<sup>5</sup> The amnestic type of MCI is regarded as a prodromal form of AD, whereas the subtypes with impairment in non-memory domains are assumed to represent prodromal stages of other types of dementia, such as vascular dementia or dementia with Lewy bodies.<sup>5,7</sup> Preliminary studies have shown that MCI subtypes may indeed represent different disorders.<sup>7,8</sup>

Several studies have investigated underlying brain pathology in MCI subtypes, using MRI. In all studies, subjects with single-domain or multiple domain amnestic MCI were characterized by medial temporal lobe atrophy (MTA). Atrophy of the medial temporal lobe (MTA) on MRI is a sensitive diagnostic marker for AD.<sup>9-12</sup> The presence of MTA in amnestic MCI has been shown to be predictive of AD.<sup>6,13,14</sup> In non-amnestic MCI, conflicting findings have been reported. One study reported MTA to be present in non-amnestic MCI,<sup>3</sup> while another study did not find this.<sup>15</sup> White matter hyperintensities (WMH) were more common in non-amnestic MCI compared to amnestic MCI,<sup>16</sup> although this was not found in another study.<sup>17</sup> WMH, which are generally viewed as evidence of small vessel disease, are commonly observed on MRI across the cognitive spectrum.<sup>17-22</sup> No studies have yet investigated the interaction between MTA and WML in subtypes of MCI. This interaction might be of interest as WML and MTA may have an additive effect on cognitive function.<sup>23</sup>

In order to provide further support for the idea that the subclassification of MCI may differentiate between various underlying aetiologies, we investigated the **presence** of MTA and WMH, and their **combination**, across MCI subtypes. Subjects were classified into four groups: 1: subjective complaints, 2: non-amnesic MCI, 3: single-domain amnesic MCI, and 4: multiple-domain amnesic MCI, based on neuropsychological test performance. We hypothesized that MTA would be mainly associated with amnesic MCI, whereas WMH might be more involved in non-amnesic MCI. We also investigated whether the prevalence of MTA and WMH in MCI subtypes was dependent on age, educational level and sex, because population-based studies have shown that older age, female sex and low educational level are associated with an increased risk for dementia.<sup>24</sup>

## **2. Methods**

### *2.1 Study design*

Subjects were selected from the DESCRIPA study ([www.descripa.eu](http://www.descripa.eu)), a multi-center study of the European Alzheimer's Disease Consortium, aiming to develop clinical criteria and screening guidelines for AD in the predementia stage. **A detailed outline of the DESCRIPA study has been described earlier.**<sup>25</sup> Inclusion criteria were: age 55 years or older, new referral for the evaluation of cognitive complaints, no diagnosis of dementia. Exclusion criteria were: any somatic, psychiatric, or neurological disorder that may have caused the cognitive impairment such as a cerebrovascular accident or strategic infarction with an acute onset of the cognitive impairment, neurodegenerative diseases such as Parkinson's disease, severe head trauma, brain tumor, a history of alcohol abuse, and severe depression. The study closely followed regular clinical practice or was performed as part of a research project. For the present study subjects were selected from 10 centers in which MRI scanning was part of clinical

practice or a research project (n=512). MRI was available for 351 (69%) subjects. Reasons for no MRI included: contra-indication for MRI, patient refusal, poor quality of MRI scan, and avoidance of waiting lists for MRI assessment. Subjects with and without MRI did not differ with respect to demographic characteristics, score on the Mini-Mental State Examination (MMSE),<sup>26</sup> and prevalence of vascular risk factors.

Twenty-two subjects who could not be classified as one of the MCI subtypes, because of missing data for one or more neuropsychological tests, were excluded. These subjects scored lower on MMSE (mean  $\pm$  SD):  $25 \pm 4$  ( $t = -5.0$ ,  $df = 346$ ,  $p < 0.001$ , MMSE scores were missing for one of these 22 subjects and for two subjects of the final sample), and a lower prevalence of hyperlipidaemia (14%;  $\chi^2 = 4.8$ ,  $df = 1$ ,  $p = 0.03$ ), compared to the rest of the cohort. There were no differences with respect to age, level of education and the prevalence of other risk factors. The final study sample consisted of 329 subjects. The study was approved by the local Medical Ethics Committee in each centre.

## *2.2 Baseline clinical assessment*

All subjects underwent a standard battery of examinations, including a clinical history, medical and neurological examination, laboratory tests, functional evaluation using the Clinical Dementia Rating scale (CDR),<sup>27</sup> rating scales for depression and neuropsychiatric symptoms, a neuropsychological test-battery (see below), and neuroimaging. General cognition was assessed using the MMSE. The following vascular risk factors were included in the analyses: hypertension (systolic blood pressure  $>140$  mmHg or diastolic blood pressure  $> 90$  mmHg or a history of hypertension or use of antihypertensive medication), a history of diabetes mellitus, hyperlipidaemia, and atherosclerosis (a history of ischemic heart disease or carotid stenosis or cerebrovascular incident or transient ischemic attack in the past).

### *2.3 Neuropsychological examination*

In each centre a battery of neuropsychological tests was performed to assess cognitive performance in the domains of memory, language, executive function and attention, and visuoconstruction. The tests used to assess each domain could vary between centres. Raw scores were converted to age, education, and gender corrected z-scores according to locally collected normative data or published normative data and these z-scores were used for further analysis.

### *2.4 Definition of MCI subtypes*

Subjects were classified into four MCI subtypes on the basis of the performance on tests in the cognitive domains of memory, language, executive function and attention, and visuoconstruction as described below. Subjects without impairment in any domain were classified as subjective complaints, subjects with impairment in one or more non-memory domains as non-amnesic MCI, subjects with isolated impairment in the memory domain as single-domain amnesic MCI, and subjects with impairment in the memory domain and at least one other domain as multiple-domain amnesic MCI. Impairment was defined as a z-score of -1.5 or lower, which equals a score of 1.5 standard deviation below the average score of healthy control subjects after correction for age, sex, and education.

Due to variability in the neuropsychological test protocol, the tests used to define MCI subtypes varied between centres. We selected in each centre one test for each domain, that was identical or similar to tests used in other centres. The tests to assess memory were the learning measure and delayed recall measure of the Rey Auditory Verbal Learning Test (6 centres),<sup>28</sup> the word list of the Consortium to Establish a Registry for AD (CERAD) neuropsychological battery (3 centres)<sup>29</sup> and the Selective Reminding Test (1 centre).<sup>30</sup> The tests to assess language were 1-

minute verbal fluency for animals (9 centres), and 1-minute verbal fluency for fruits, animals or car trades (1 centre).<sup>31</sup> The test to assess executive function and attention was the Trail Making Test part A and B (TMT A and B, all centers).<sup>32</sup> The tests to assess visuoconstruction were the copy subtest of the Rey-Osterrieth complex figure (6 centres)<sup>33</sup> the copy of the CERAD figures (3 centres)<sup>29</sup> or the copy of figures from the Mental Deterioration Battery (MDB) (1 centre).<sup>34</sup>

Thirty-two subjects classified as non-amnesic MCI (34% of all subjects in this subgroup) had impairments in more than one non-memory domain, and could be considered to have multiple-domain non-amnesic MCI.<sup>5</sup> Post-hoc analyses showed no statistically significant differences with regard to MRI characteristics between subjects with single-, and multiple-domain non-amnesic MCI, and therefore we analysed the data of subjects with non-amnesic MCI as a single group.

### *2.5 MRI acquisition*

All subjects were studied by MRI within  $0.1 \pm 0.2$  (mean  $\pm$  SD) years of the baseline clinical assessment. At each site subjects were scanned according to the routine MRI protocol, consequently the scanners and protocols at different sites varied. All scanning was performed at 1.0 or 1.5T and included a 3D T1-weighted gradient-echo sequence and a fast fluid attenuated inversion recovery (FLAIR) sequence. MRI data were collected and analysed centrally. Sagittal 3D T1-weighted images were reformatted in a plane perpendicular to the long axis of the (left) hippocampus (at a slice thickness of 2mm).

### *2.6 Visual rating of MTA and WMH*

MTA was rated on coronal T1-weighted images using a five point visual rating scale,<sup>12</sup> ranging from 0 (no atrophy) to 4 (severe atrophy) based on the height of the hippocampal formation and



the surrounding cerebrospinal fluid spaces. In the analysis, the average score of left and right was used, as well as the dichotomized score ( $MTA \geq 2$  = atrophy). The degree of WMH severity was rated on the axial FLAIR images using the Age-Related White Matter Changes scale (ARWMC).<sup>35</sup> Here, we used the total degree of WMH (range 0-30) by adding the region-specific scores of both hemispheres, and a dichotomised score (at the population mean WMH score:  $ARWMC > 5$  = moderate WMH). All visual ratings were carried out centrally by a single rater (LvdP) who was blinded to clinical information. The intra-rater agreement for the MTA scale was good (kappa 0.68) as well as the intra-rater agreement for the ARWMC scale as determined on a testset of 20 MR scans scored twice (weighted kappa: 0.95).

## APOE

APOE genotype was determined in a subset of subjects ( $n=265$ , 81%) on genomic DNA extracted from EDTA anticoagulated blood using the polymerase chain reaction technique. Subjects with data on APOE genotype had a higher score on the MMSE compared to subjects with data on APOE genotype (28.1 vs. 27.5,  $p=0.05$ ) while age, years of education, gender, systolic bloodpressure, severity of MTA and WMH, and scores on the cognitive tests did not differ between the groups.

## 2.7 Statistics

SPSS for Windows, version 12.0 (Chicago, IL) was used for data analysis. Characteristics of subjects in the present study sample were compared to characteristics of excluded subjects without MRI and missing neuropsychological data using Student's t-tests or  $\chi^2$ -tests when appropriate. Subsequently, group differences between the MCI subtypes were assessed using analysis of variance (ANOVA), or logistic regression models for dichotomous outcome variables. Age and sex were used as covariates, and centre of origin as a categorical covariate.

Bonferroni correction was used to adjust for multiple comparisons in the post-hoc pair-wise comparisons. MTA and WMH scores were used both in their continuous as well as dichotomised form (as described in the visual rating section above). Interactions between MCI subtype and age (dichotomised at 70 years), gender and level of education were tested for severity of MTA and WMH (as continuous variables).

Finally, using both dichotomised MRI measures we computed a new MTA-WMH categorical variable, yielding four groups: 1: MTA and WMH absent; 2: MTA absent, WMH present; 3: MTA present, WMH absent; 4: MTA and WMH present. The difference in distribution of subjects over the MTA-WMH groups across MCI subtypes was assessed using multinomial logistic regression analysis with MTA-WMH group as dependent variable and MCI subtype as a predictor, adjusting for age.

### 3. Results

Table 1 shows the baseline characteristics for the total study sample and for the four MCI subtypes. Age ( $p < 0.0001$ ), sex ( $\chi^2 = 36.1$ ,  $df = 13$ ,  $p = 0.028$ ), years of education ( $p = 0.027$ ), MMSE scores ( $F_p < 0.0001$ ), were significantly different between the groups. There were no differences in APOE genotype or the prevalence of vascular risk factors across the MCI subtypes.

Severity of MTA, as reflected by the continuous MTA score, differed across the MCI subtypes ( $p < 0.001$ ). Pair-wise comparisons showed that subjects with subjective complaints had less severe MTA than subjects with non-amnesic MCI ( $p = 0.047$ ), single-domain amnesic MCI ( $p = 0.005$ ), and multiple-domain amnesic MCI ( $p < 0.0001$ ), and that subjects with non-amnesic

MCI had less severe MTA compared to subjects with multiple-domain amnestic MCI ( $p = 0.006$ ). The presence of medial temporal lobe atrophy ( $MTA \geq 2$ ), increased from 14% of subjects with subjective complaints, to 38% of subjects with non-amnestic MCI, 44% in subjects with single-domain amnestic MCI and 55% in subjects with multiple-domain amnestic MCI (post-hoc pairwise comparisons: subjective complaints versus all other subtypes ( $p < 0.01$ )). In contrast, the total ARWMC score, and the proportion of subjects with at least moderate WMH (ARWMC score  $> 5$ ), did not differ across the MCI subtypes.

Correction of the analyses for level of education and vascular risk factors did not essentially change the results (data not shown).

**Table 1** Baseline characteristics in total sample and according to four MCI subtypes

	Total sample (n=329)	Subjective complaints (n=77)	Non-amnestic MCI (n=93)	Amnestic MCI		Overall p-value	Group comparisons
		Group 1	Group 2	Group 3	Group 4		
<b>Demographics</b>							
Age, years	69 (8)	66 (7)	70 (8)	69 (8)	71 (8)	<0.0001	1 < 2,4
Sex, n (%) female	188 (57)	39 (51)	64 (69)	31 (44)	54 (61)	0.003	2 > 3
Education, years	10 (4)	11 (4)	8 (4)	12 (4)	9 (4)	0.03	2 < 3
MMSE	28 (2)	28 (2)	28 (2)	28 (2)	27 (2)	<0.0001	1,2,3 > 4
ApoE4 genotype, n(%) <sup>1</sup>	126 (48%)	27 (45)	27 (35)	34 (58)	28 (41)	0.11	-
<b>Vascular risk factors</b>							
Hypertension, n (%)	216 (66)	48 (63)	62 (67)	45 (65)	61 (69)	0.95	-
Diabetes Mellitus, n (%)	38 (12)	7 (9)	12 (13)	4 (6)	15 (17)	0.28	-
Hyperlipidaemia, n (%)	122 (38)	21 (28)	36 (40)	27 (40)	38 (44)	0.30	-
Atherosclerosis, n (%)	45 (15)	8 (11)	13 (15)	12 (18)	12 (15)	0.45	-
<b>MRI</b>							
MTA score	1.3 (0.9)	0.8 (0.7)	1.3 (0.8)	1.4 (0.9)	1.7 (0.9)	<0.0001	1 < 2,3,4; 2 < 4
MTA present, n (%)	126 (38)	11 (14)	35 (38)	31 (44)	49 (55)	<0.001	1 < 2,3, 4
WMH	4.8 (4.9)	3.8 (3.5)	5.3 (5.0)	4.5 (4.5)	5.3 (5.9)	0.21	-
Moderate WMH, n (%)	105 (32)	20 (26)	36 (34)	22 (31)	27 (30)	0.16	-

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Legend to table 1.

Values are expressed as mean (standard deviation) unless stated otherwise. ANOVA's or logistic regression models for dichotomous outcome variables with age, sex and center of origin as covariates were performed. Bonferonni correction was used to correct for multiple comparisons. Abbreviations: MMSE: Mini-Mental State Examination (0-30); MTA: medial temporal lobe atrophy; WMH: white matter hyperintensities (0-30), MTA present: score  $\geq 2$ ; WMH moderate: score  $>5$ . 1. ApoE genotype was available for 265 subjects: 60 subjective, 77 non-amnesic, 59 amnesic single-domain, 69 amnesic multiple domain. Only significant differences are reported in the table.



The association between the MTA score and MCI subtype was modified by age, as indicated by a significant interaction between age (dichotomized at 70 years) and subtype ( $p = 0.03$ ). If age was used as a continuous variable, the effect of age on MTA was also statistically significant. Post-hoc analysis showed that in older subjects MTA score was strongly associated with MCI subtype ( $p < 0.0001$ ), in contrast with a weaker association in younger subjects ( $p = 0.02$ , Figure 1).

No significant interaction between MCI subtype and age group in association with WMH was present ( $p = 0.19$ ), nor were there any interactions for gender or level of education and MCI subtype in association with severity of MTA ( $p = 0.53$  and  $p = 0.70$ ) or WMH ( $p = 0.74$  and  $p = 0.31$ ).

The distribution of four MRI categories, based on the dichotomized scores of MTA (0-1 versus  $\geq 2$ ) and WMH (0-5 versus  $\geq 6$ ), over the MCI subtypes is shown in Figure 2. A multinomial logistic regression model, adjusted for age, showed that the distribution of subjects over the four MRI categories differed between the four MCI subtypes (overall:  $\chi^2 = 25.7$  df = 9,  $p = 0.002$ , Nagelkerke's  $R^2 = 0.30$ ). Pair-wise comparisons showed that the distribution of subjects over the four MRI categories differed between subjects with subjective complaints and the amnesic MCI subtypes ( $p = 0.023$  for single-domain amnesic MCI and  $p = 0.002$  for multiple-domain amnesic MCI) and between non-amnesic MCI and multiple-domain amnesic MCI ( $p = 0.015$ ). In more detail: in multiple-domain amnesic MCI a greater proportion of subjects had isolated MTA, versus MTA in combination with WMH compared to subjects with non-amnesic MCI ( $p = 0.011$ ). Subjects with subjective complaints had a greater proportion of subjects with isolated WMH versus isolated MTA compared to multiple-domain amnesic MCI ( $p = 0.002$ ). Finally, the proportion of subjects without any MRI abnormality compared to

isolated MTA was greater in subjective complaints compared to both types of amnesic MCI ( $p = 0.004$  and  $p < 0.0001$  respectively), and in non-amnesic MCI versus multiple-domain amnesic MCI ( $p = 0.003$ ). Other pairwise comparisons were not statistically significant.

#### 4. Discussion

We provide evidence that the clinical subtypes of MCI, based on neuropsychological profiles, may have different brain substrates. Both single- and multiple-domain amnesic MCI were associated with more severe MTA in comparison to subjects with subjective complaints. This is in keeping with previous studies demonstrating atrophy of the medial temporal lobe in subjects with amnesic MCI<sup>36 37</sup> and may be associated with an increased risk of development of AD.<sup>6 14</sup> However, MTA was not restricted to amnesic MCI, as a substantial part of subjects with non-amnesic MCI showed MTA as well. This is in line with previous longitudinal studies that have shown that a proportion of subjects with non-amnesic MCI progresses to clinical AD,<sup>7 37</sup> and another MRI study, using voxel-based morphometry, showing varying involvement of the medial temporal lobe in the non-amnesic (single and multiple-domain) MCI subtypes.<sup>3</sup> Alternatively, MTA in non-amnesic MCI may have a different aetiology and relate to vascular causes.

Our findings are in keeping with a study demonstrating that subjects with amnesic MCI had a higher prevalence of MTA than subjects with non-amnesic MCI.<sup>15</sup> Two other studies showed focal atrophy of the medial temporal lobe, including the hippocampus, in subjects with amnesic MCI in contrast to subjects with multiple-domain MCI, which was associated with a more diffuse pattern of cortical atrophy.<sup>39 40</sup> It is difficult to compare our results directly, since these studies used different MRI techniques. In addition, the multiple-domain MCI subtype in these studies included both subjects with impairment in multiple non-memory domains and in



both memory and non-memory domains. Our study suggests that the classification of subjects with and without memory impairment into one subtype may result in a heterogeneous group.

The differences in MTA observed across the MCI subtypes were largely attributable to subjects aged over 70 years, suggesting that the concept of MCI subtypes may be less useful in younger subjects. Our observation may be explained by the fact that the prevalence of dementia strongly increases with age,<sup>41</sup> and that in subjects with MCI the risk for developing dementia over a 10-year interval is strongly dependent on age.<sup>42</sup>

WMH have been reported to be associated with executive function in MCI<sup>43</sup> and control subjects.<sup>44</sup> Therefore we hypothesized that WMH might be associated with non-amnesic MCI. However, we could not demonstrate a direct association between the severity of WMH and any of the MCI subtypes, in keeping with a recent study.<sup>17</sup> The prevalence of vascular risk factors did not differ across the MCI subtypes also. In contrast the study of Mariani et al did report a higher frequency of vascular risk factors and white matter hyperintensities on MRI in their single non-memory MCI group.<sup>16</sup> The fact that in our study subjects were recruited from memory clinics and that subjects with a history of stroke were excluded from the study, may have lead to an under-representation of subjects with significant small vessel disease in the present cohort. Furthermore, the absence of controls subjects did not allow us to compare the prevalence of WMH to a normal population.

Although MCI subtypes were similar with regard to WMH severity, differences between combined involvement of MTA and WMH were observed (Figure 2). To our knowledge this has not been investigated before. The higher prevalence of MTA in the amnesic MCI subtypes compared to the other subtypes was mainly because isolated MTA was more common in

amnesic MCI. This suggests that AD may be the underlying cause in most amnesic MCI patients with MTA. In non-amnesic MCI isolated MTA was relatively rare as most subjects with MTA also had WMH. As the APOE-e4 allele is a risk factor for AD, we post-hoc investigated whether the relation of APOE-4 with MTA was different for subjects with isolated MTA and subjects with MTA and WMH. In the whole sample, the proportion of APOE e4 carriers in the group with isolated MTA was higher 29 (53%) than that in the group with combined MTA and WMH 16 (33%,  $p = 0.05$ ). This effect was also present in subjects with non-amnesic MCI: 7 (58%) of subjects with isolated MTA were APOE-e4 carrier versus 4 (17%) for subjects with MTA and WMH ( $p = 0.03$ ) This suggests that in subjects with MTA and WMH, MTA may have a different pathophysiological background, in which AD pathology is possibly less relevant. The group of subjects with subjective complaints has received relatively little attention in previous studies so far, and the clinical outcome of these subjects still remains unclear.<sup>45 46</sup> In our study the majority of subjects categorized as subjective complaints showed no or few abnormalities on MRI, suggesting that these subjects are in the earliest stages of a neurodegenerative disease or that other factors underlie the complaints.

The cross-sectional design of our study limits interpretation about causal mechanisms underlying MRI measures and MCI subtypes. Another limitation may be the fact that neuropsychological test batteries differed across the various sites, although this difference may in part be accounted for by correcting for center in the analyses. Among the strengths of this study is the large sample size of MCI subjects with available MRI scans. All scans were analyzed centrally, which reduced the variability of MRI measures to a large extent. Another strength of this study is its clinical setting, which makes the results relevant for clinical practice.

In conclusion, these data provide evidence that the clinical subtypes of MCI, based on neuropsychological profiles, may have different brain substrates, especially in older subjects.

However, the observed differences were small and clearly an overlap of MRI profiles between the MCI subtypes existed. Further longitudinal analysis is needed to reveal the clinical outcome of MCI subtypes in relation to MRI measures, which is important with respect to preventive and possible early therapeutic interventions in MCI.

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## Figure Legends

### Figure 1

Barchart showing the severity of MTA in each MCI subtype by age group (< 70 versus  $\geq$  70 years). Numbers indicate mean MTA score, and (number of subjects).

### Figure 2

Barchart showing the distribution of MRI subgroups, based on the presence of MTA and WMH, within the MCI subtypes. Numbers indicate percentage of subjects (and number of subjects) within each MCI subtype.

Figure 1

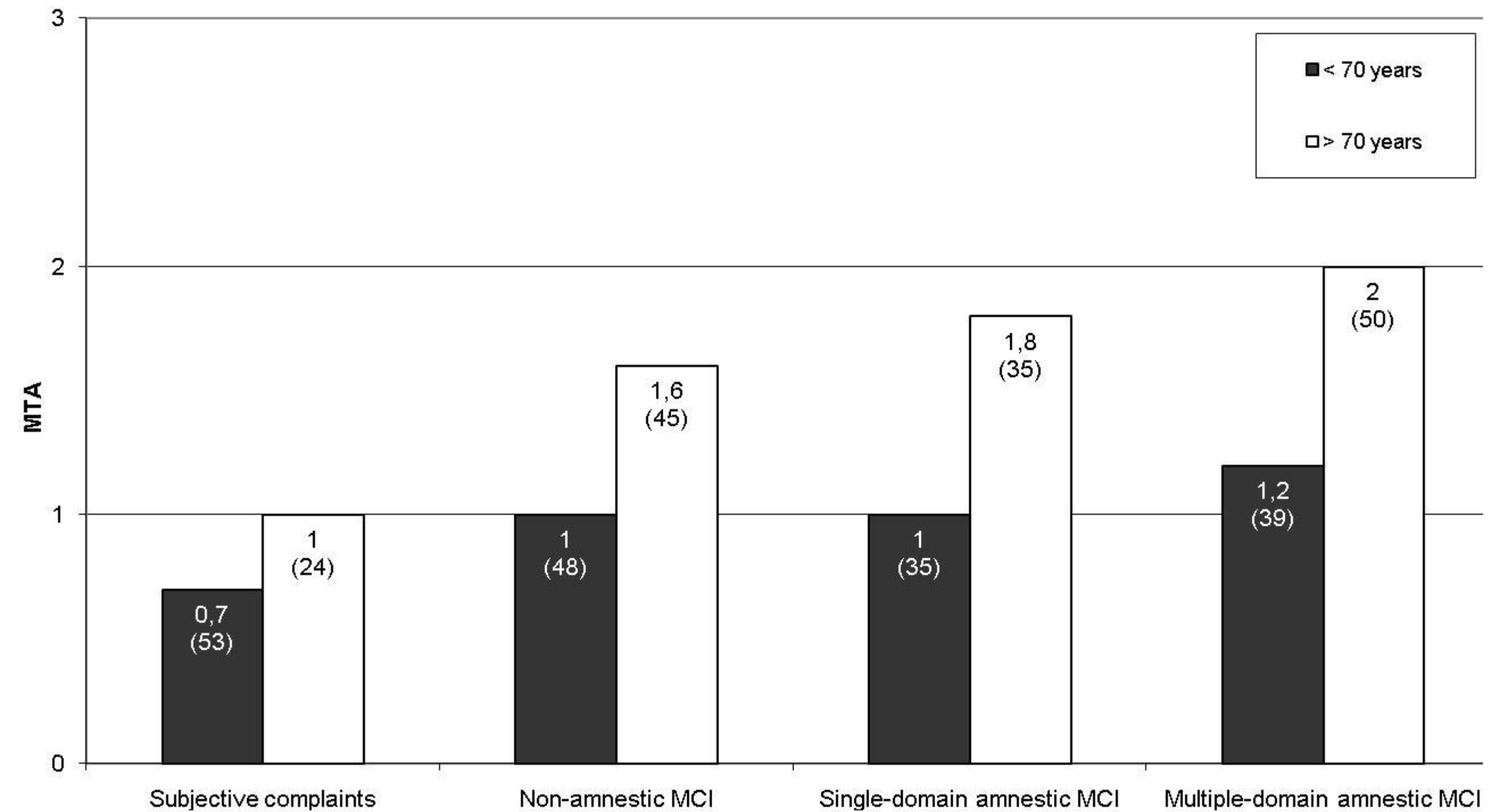


Figure 2

