

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

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ABSTRACT

Background: Clinical subtypes of mild cognitive impairment (MCI) may represent different underlying aetiologies.

Methods: This European, multicentre, memory clinic based study (DESCRIPA) of non-demented subjects 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.

Results: Severity of MTA differed between MCI subtypes ($p < 0.001$), increasing from a mean of 0.8 (SD 0.7) in subjective complaints ($n = 77$) to 1.3 (0.8) in non-amnesic MCI ($n = 93$), and from 1.4 (0.9) in single domain amnesic MCI ($n = 70$) to 1.7 (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 of age. Severity of WMH did not differ between MCI subtypes ($p = 0.21$). However, the combination of MTA and WMH differed between MCI subtypes ($p = 0.02$)

Conclusion: 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 the underlying cause. In non-amnesic MCI, the relatively higher prevalence of MTA in combination with WMH may suggest a different pathophysiological origin.

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).^{1–3} However, not all subjects with MCI will develop AD—some will remain stable or even improve over time while others will develop other types of dementia.^{4–6} 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 (amnesic versus non-amnesic) and the number of cognitive domains affected (single versus multiple).⁵ The amnesic 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.^{5–7} Preliminary studies have shown that

MCI subtypes may indeed represent different disorders.^{7–9}

Several studies have investigated underlying brain pathology in MCI subtypes, using MRI. In all studies, subjects with single domain or multiple domain amnesic MCI were characterised by medial temporal lobe atrophy (MTA). MTA on MRI is a sensitive diagnostic marker for AD.^{9–12} The presence of MTA in amnesic MCI has been shown to be predictive of AD.^{6–13–14} In non-amnesic MCI, conflicting findings have been reported. One study reported MTA to be present in non-amnesic MCI³ while another study did not find this.¹⁵ White matter hyperintensities (WMH) were more common in non-amnesic MCI compared with amnesic MCI¹⁶ although this was not found in another study.¹⁷ WMH, which are generally viewed as evidence of small vessel disease, are commonly observed on MRI across the cognitive spectrum.^{17–22} 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.²³

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 hypothesised 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.²⁴

METHODS

Study design

Subjects were selected from the DESCRIPA study (www.descripa.eu), a multicentre study of the European Alzheimer's Disease Consortium, aiming to develop clinical criteria and screening guidelines for AD in the pre-dementia stage. A detailed outline of the DESCRIPA study has been described earlier.²⁵ Inclusion criteria were: age 55 years or

older, new referral for the evaluation of cognitive complaints and 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 tumour, 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 centres 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)²⁶ or 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 (SD)): 25 (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 with the rest of the cohort. There were no differences with respect to age, level of education and 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.

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,²⁷ 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 mm Hg or diastolic blood pressure >90 mm Hg, a history of hypertension or use of antihypertensive medication), a history of diabetes mellitus, hyperlipidaemia and atherosclerosis (a history of ischaemic heart disease, carotid stenosis, cerebrovascular incident or transient ischaemic attack in the past).

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.

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 SD 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 (six centres),²⁸ the word list of the Consortium to Establish a Registry for AD (CERAD) neuropsychological battery (three centres)²⁹ and the Selective Reminding Test (one centre).³⁰ The tests to assess language were 1 min verbal fluency for animals (nine centres) and 1 min verbal fluency for fruits, animals or car trades (one centre).³¹ The test to assess executive function and attention was the Trail Making Test part A and B (all centres).³² The tests to assess visuoconstruction were the copy subtest of the Rey-Osterrieth complex figure (six centres),³³ the copy of the CERAD figures (three centres)²⁹ or the copy of figures from the Mental Deterioration Battery (one centre).³⁴

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.⁵ 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.

MRI acquisition

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

Visual rating of MTA and WMH

MTA was rated on coronal T1 weighted images using a 5 point visual rating scale,¹² ranging from 0 (no atrophy) to 4 (severe atrophy) based on the height of the hippocampal formation and the surrounding CSF spaces. In the analysis, the average score of left and right was used, as well as the dichotomised score (MTA ≥ 2 = atrophy). The degree of WMH severity was rated on the axial FLAIR images using the Age Related White Matter Changes scale (ARWMC).³⁵ 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 the 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 test set of 20 MR scans scored twice (weighted $\kappa = 0.95$).

Table 1 Baseline characteristics in the total sample and according to the 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				
Demographics									
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 (%))*	126 (48)	27 (45)	27 (35)	34 (58)	28 (41)	0.11	–		
Vascular risk factors									
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	–		
MRI									
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	–		

Values are expressed as mean (SD) unless stated otherwise. ANOVA or logistic regression models for dichotomous outcome variables with age, sex and centre of origin as covariates were performed. Bonferroni correction was used to correct for multiple comparisons.

*ApoE genotype was available for 265 subjects: 60 subjective, 77 non-amnestic, 59 amnestic single domain and 69 amnestic multiple domain. Only significant differences are reported.

MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination (0–30); MTA, medial temporal lobe atrophy; WMH, white matter hyperintensities (0–30), MTA present: score ≥ 2 ; WMH moderate: score > 5 .

APOE

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

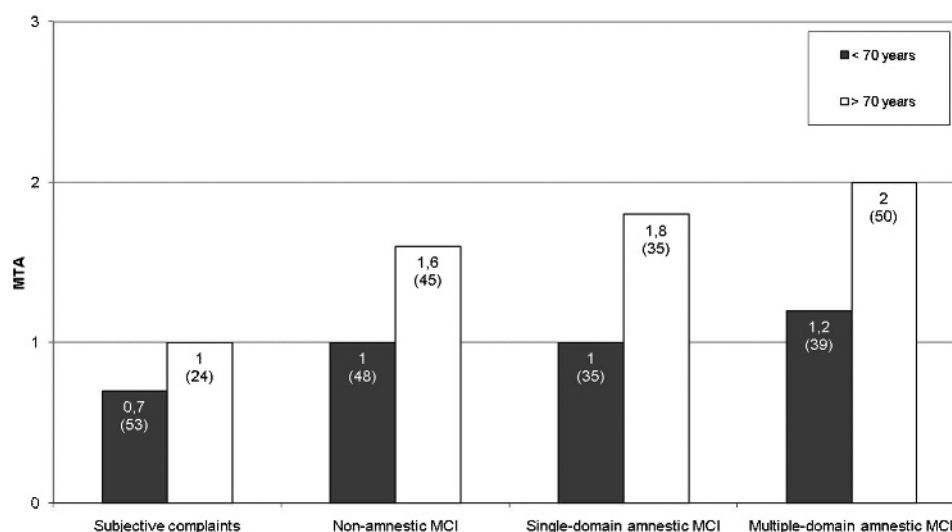
Statistics

SPSS for Windows, V.12.0 (Chicago, Illinois, USA) was used for data analysis. Characteristics of subjects in the present study sample were compared with characteristics of excluded subjects without MRI and missing neuropsychological data using Student's t tests or χ^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 pairwise 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; and (4) MTA and WMH present. The difference in distribution of subjects over the MTA–WMH

Figure 1 Bar chart showing the severity of medial temporal lobe atrophy (MTA) in each mild cognitive impairment (MCI) subtype by age group (<70 vs ≥ 70 years). Numbers indicate mean MTA score (and number of subjects).



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groups across MCI subtypes was assessed using multinomial logistic regression analysis with MTA-WMH group as the dependent variable and MCI subtype as a predictor, adjusting for age.

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 ($p = 0.027$) and 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 ($p < 0.001$). Pairwise 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 with subjects with multiple domain amnesic MCI ($p = 0.006$). The presence of MTA ≥ 2 increased from 14% of subjects with subjective complaints to 38% of subjects with non-amnesic MCI, to 44% in subjects with single domain amnesic MCI and to 55% in subjects with multiple domain amnesic 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).

The association between the MTA score and MCI subtype was modified by age, as indicated by a significant interaction between age (dichotomised 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 ($p = 0.02$) (fig 1).

No significant interaction between MCI subtype and age group in association with WMH was present ($p = 0.19$), nor

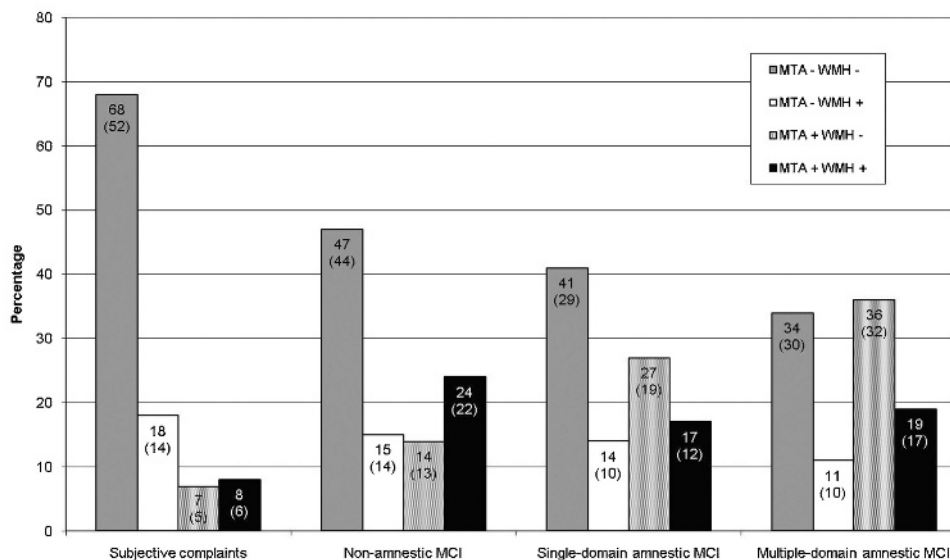
were there any interactions for gender or level of education and MCI subtype in association with severity of MTA ($p = 0.53$ and $p = 0.70$) or WMH ($p = 0.74$ and $p = 0.31$).

The distribution of four MRI categories, based on the dichotomised scores of MTA (0–1 vs ≥ 2) and WMH (0–5 vs ≥ 6), over the MCI subtypes is shown in fig 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 $R^2 = 0.30$). Pairwise 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 with 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 with multiple domain amnesic MCI ($p = 0.002$). Finally, the proportion of subjects without any MRI abnormality compared with isolated MTA was greater in subjective complaints compared with 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.

DISCUSSION

We have provided 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 with subjects with subjective complaints. This is in keeping with previous studies demonstrating atrophy of the medial temporal lobe in subjects with amnesic MCI^{36, 37} and may be associated with an increased risk of development of AD.^{6, 14} 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

Figure 2 Bar chart showing the distribution of MRI subgroups, based on the presence of medial temporal lobe atrophy (MTA) and white matter hyperintensities (WMH), within the mild cognitive impairment (MCI) subtypes. Numbers indicate percentage of subjects (and number of subjects) within each MCI subtype.



clinical AD,^{7,38} 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.³ 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.¹⁵ Two other studies showed focal atrophy of the medial temporal lobe, including the hippocampus, in subjects with amnesic MCI in contrast with subjects with multiple domain MCI, which was associated with a more diffuse pattern of cortical atrophy.^{39,40} It is difficult to compare our results directly, as 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,⁴¹ and that in subjects with MCI the risk for developing dementia over a 10 year interval is strongly dependent on age.⁴²

WMH have been reported to be associated with executive function in MCI⁴³ and control subjects.⁴⁴ Therefore, we hypothesised 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.¹⁷ Also, the prevalence of vascular risk factors did not differ across the MCI subtypes. This is in contrast with the study of Mariani *et al* who reported a higher frequency of vascular risk factors and white matter hyperintensities on MRI in their single non-memory MCI group.¹⁶ 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 led to an under-representation of subjects with significant small vessel disease. Furthermore, the absence of controls subjects did not allow us to compare the prevalence of WMH with a normal population.

Although MCI subtypes were similar with regard to WMH severity, differences between combined involvement of MTA and WMH were observed (fig 2). To our knowledge, this has not been investigated before. The higher prevalence of MTA in the amnesic MCI subtypes compared with 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: seven (58%) subjects with isolated MTA were APOE-e4 carrier compared with four (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.^{45,46} In our study, the majority of subjects categorised 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 centre in the analyses. Among the strengths of this study is the large sample size of MCI subjects with available MRI scans. All scans were analysed 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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