Received: 31 August 2021 | Revised: 29 October 2021 | Accepted: 3 November 2021 | Published online: 23 December 2021

DOI: 10.1002/dad2.12269

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

White matter changes in empirically derived incident MCI subtypes in the Mayo Clinic Study of Aging

Mary M. Machulda[1] | **Emily S. Lundt**[2] | **Carly T. Mester**[2] | **Sabrina M. Albertson**[2] | **Sheelakumari Raghavan**[3] | **Robert I. Reid**[4] | **Christopher G. Schwarz**[3] | **Jonathan Graff-Radford**[5] | **Clifford R. Jack Jr.**[3] | **David S. Knopman**[5] | **Michelle M. Mielke**[5,6] | **Walter K. Kremers**[2] | **Ronald C. Petersen**[5] | **Mark W. Bondi**[7,8] | **Prashanthi Vemuri**[3]

[1] Division of Neurocognitive Disorders, Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota, USA

[2] Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

[3] Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[4] Department of Information Technology, Mayo Clinic, Rochester, Minnesota, USA

[5] Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

[6] Division of Epidemiology, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, USA

[7] Department of Psychiatry, University of California San Diego, School of Medicine, La Jolla, California, USA

[8] Veterans Affairs San Diego Healthcare System, San Diego, California, USA

Correspondence
Mary M. Machulda, Mayo Clinic, Department of Psychiatry and Psychology, 200 1st Street SW, Rochester, MN 59505, USA.
E-mail: machulda.mary@mayo.edu

Funding information
National Institutes of Health, Grant/Award Numbers: R01 AG49810, R37 AG011378, RO1 AG041851, R01 AG056366, R01 NS097495, U01 AG006786, R01 AG034676, P30 AG062677; Alexander Family Professorship of Alzheimer's Disease Research; The Elsie and Marvin Dekelboum Family Foundation; The GHR Foundation; The Robert Wood Johnson Foundation; the Mayo Foundation for Education and Research

Abstract

Introduction: The aim of this study was to examine white matter hyperintensities (WMH) and fractional anisotropy (FA) in empirically derived incident mild cognitive impairment (MCI) subtypes.

Methods: We evaluated 188 participants with incident MCI in the Mayo Clinic Study of Aging (MCSA) identified as having one of four cluster-derived subtypes: subtle cognitive impairment, amnestic, dysnomic, and dysexecutive. We used linear regression models to evaluate whole brain and regional WMH volumes. We examined fractional anisotropy (FA) on a subset of 63 participants with diffusion tensor imaging.

Results: Amnestic and dysexecutive subtypes had higher WMH volumes in differing patterns than cognitively unimpaired; the dysexecutive subtype had higher WMH than subtle cognitive impairment. There was widespread WM degeneration in long association and commissural fibers in the amnestic, dysnomic, and dysexecutive subtypes, and corpus callosum FA accounted for significant variability in global cognition.

Discussion: White matter changes likely contribute to cognitive symptoms in incident MCI.

KEYWORDS
cluster analysis, cognition, diffusion tensor imaging, fractional anisotropy, mild cognitive impairment, white matter hyperintensities

1 | INTRODUCTION

Cognitive impairment is a multifactorial process with cerebrovascular disease (CVD) being a significant contributor to the risk of dementia.[1] White matter hyperintensities (WMH), presumed to have a vascular etiology, are common in cognitively unimpaired (CU) older adults and those with amnestic and non-amnestic mild cognitive impairment (MCI).[2,3] Elevated WMH volumes are also associated with risk of incident MCI in community-based samples.[4-6] Although WMH can affect all cognitive domains, the most pronounced associations are typically with attention, processing speed, and aspects of executive function.[3,7–9] Recent work has also shown that early changes in white matter (WM) measured using diffusion tensor imaging (DTI) are a sensitive marker of WM degeneration,[10,11] are associated with incident MCI,[12] and predict future cognitive decline in prevalent MCI.[13]

Most studies of WM changes in MCI broadly use conventional criteria (i.e., ≤ 1.5 standard deviations [SD] below normal on one test within a domain)[5,6,14] or a Clinical Dementia Rating (CDR) rating of 0.5[4,15] to identify participants. Empirical methods for identifying cognitive subtypes of MCI have merit for diagnosing MCI because they do not rely on clinical judgement or prespecified cutpoints for cognitive impairment. We previously used cluster analysis and identified four subtypes of incident MCI in the Mayo Clinic Study of Aging (amnestic, dysnomic, dysexecutive, subtle cognitive impairment).[16] We also showed these MCI subtypes had patterns of cortical atrophy that corresponded to patterns of their cognitive impairment.[17]

Only one study to date has evaluated WM changes in empirically derived MCI subtypes, and this was on individuals with prevalent MCI.[18] Delano-Wood et al. identified three MCI subtypes in patients recruited from a geriatric neurology clinic: pure memory, memory/language, and executive/processing speed. The executive/processing speed group demonstrating significantly higher levels of WM pathology compared to the other subgroups. A limitation of studying individuals with prevalent MCI, however, is that length of time that clinical symptoms have been present varies, and therefore impairment in some cognitive domains may have progressed more for some individuals compared to others. No previous studies have examined WM changes (WMH or DTI alterations) in empirically derived subtypes of incident MCI.

Therefore, the aim of this study was to expand on our previous work by evaluating WM changes, as measured via WMH on fluid attenuated inversion recovery (FLAIR) and fractional anisotropy (FA), on DTI in the four subtypes of empirically derived incident MCI that we previously described from a population-based study.[16] We hypothesized that the dysexecutive MCI subtype would show more WM abnormalities on both FLAIR and DTI imaging than the other three MCI subtypes.

2 | METHODS

2.1 | Study sample

2.1.1 | Participants

The Mayo Clinic Study of Aging (MCSA) is a longitudinal population-based study of cognitive aging in Olmsted County, Minnesota.[19] Participants in this study represent a subset of those from our previous study in which we used agglomerative hierarchical clustering with Euclidean distance and Ward's linkage to identify neuropsychological subtypes of MCI based on performance on nine neuropsychological tests described below.[16] The MCI subtypes were named according to the cognitive domain with the most pronounced cognitive impairment: subtle cognitive impairment (very mild memory impairment; cognition features in this group were similar to that of the amnestic subset yet distinct from the other clusters with respect to level of cognitive performance and degree of functional impairment), amnestic (focal memory impairment), dysnomic (significant language impairment with mild to moderate impairment in memory, attention, and visuospatial domains), and dysexecutive (significant attention/executive impairment with mild impairment in memory, language, and visuospatial domains).

For the present study, MCI participants were included if they completed an MRI during the visit when they received an incident MCI diagnosis. Of our original sample of 506 MCI participants, 188 had usable imaging data. The current sample of 188 participants represents 37% (26/70) of the subtle cognitive impairment cluster, 43% (83/193) of the amnestic cluster, 36% (30/84) of the dysnomic cluster, and 31% (49/159) of the dysexecutive cluster. We also examined a subset of MCI participants with diffusion imaging: 12 subtle cognitive impairment, 23 amnestic, 8 dysnomic, and 20 dysexecutive.

2.1.2 | Standard protocol approval and patient consents

The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved these studies, which also followed Health Insurance Portability and Accountability Act (HIPAA) guidelines. Every participant provided written informed consent.

2.2 | Materials and procedure

2.2.1 | Evaluation

MCSA participants complete comprehensive evaluations approximately every 15 months, which include a physician examination, interview by a study coordinator, and neuropsychological testing.[19] The physician examination included medical history review, complete neurologic examination, and administration of the Short Test of Mental Status.[20] The study coordinator interview included collection of demographic information, medical history, and questions about memory to the participant using the Blessed Memory Test[21] and the informant using the CDR scale[22] and Functional Activities Questionnaire (FAQ).[23] Participants also completed the Beck Depression Inventory-2.[24]

Each participant underwent a detailed neuropsychological evaluation as described previously.[17,19] We evaluated four cognitive domains using nine tests: (1) memory (Auditory Verbal Learning Test [AVLT] Delayed Recall, Wechsler Memory Scale Revised [WMS-R] Logical Memory II & Visual Reproduction II), (2) language (Boston Naming Test, Category Fluency), (3) attention/executive (Trail Making Test B, WAIS-R Digit Symbol), and (4) visuospatial (Wechsler Adult Intelligence Scale Revised [WAIS-R] Picture Completion & Block Design). Global cognition z-scores were averaged over domain-specific z-scores and referenced to 3686 MCSA 2004–2012 cognitively unimpaired (CU) from the 50–89 cohort and weighted to the 2013 Olmsted County population by age and sex.

Procedure used to diagnose MCI included: (1) history from the participant and interview of a study partner to determine whether there has been a change in cognition; (2) objective scores more than −1.0 SD below the expected mean in one or more cognitive domains based on Mayo's Older American Normative Studies,[25,26] which were derived on a separate sample of individuals; (3) functionally intact; and (4) does not meet Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) criteria for dementia. These criteria are consistent with the recent practice guideline update summary on MCI based on review of the literature.[27] A final decision to diagnose CU or MCI was based on a consensus agreement among the study coordinator, examining physician, and neuropsychologist after taking into account education, prior occupation, and reviewing all other participant clinical information.[19] Raters were blinded to the previous diagnosis of the participant.

2.2.2 | Genetic characterization

Participants underwent a blood draw at their baseline visit. DNA extraction and apolipoprotein E (*APOE*) genotyping were performed using standard methods.[28] The *APOE* ε4 carriers included participants with one or two copies of the ε4 allele.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature that focused on white matter hyperintensities (WMH) and diffusion tensor imaging for evaluating brain changes in mild cognitive impairment (MCI) defined by conventional/internal consensus criteria and/or cluster analysis that was available on PubMed and Google Scholar. One study examined WMH in prevalent MCI subtypes derived from cluster analysis. No previous study has investigated white matter changes in empirically derived subtypes of incident MCI.
2. **Interpretation**: We found that amnestic and dysexecutive MCI had different patterns of elevated WMH, and amnestic, dysnomic, and dysexecutive subtypes have reduced fractional anisotropy in commissural and long association fibers.
3. **Future directions**: Future studies are needed to examine patterns of tau changes in incident MCI subtypes, ideally in conjunction with patterns of amyloid deposition. Further understanding of the brain changes underlying empirically derived incident MCI subtypes may aid with participant selection and assignment in future intervention studies.

2.2.3 | Indicator of systemic vascular health

We created a composite score of seven cardiovascular and metabolic conditions (CMC) as the summation of the presence/absence of the following conditions: hypertension, hyperlipidemia, cardiac arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke.[29]

2.2.4 | MRI

All magnetic resonance imaging (MRI) was obtained on 3T MRI systems (GE Healthcare). The acquisition and processing of MRI images are described by Graff-Radford et al.[30] The 3D magnetization-prepared rapid gradient echo (MPRAGE) and 2D FLAIR images were used to calculate WMH volume via a fully automated algorithm, updated from a previously described in-house semi-automated method.[31] Briefly, WMH were segmented on the native 2D FLAIR images via automated seed initialization based on location (spatial priors), intensity relative to the distribution of GM intensity values, and intensity relative to its local neighborhood. False-positive WMH segmentations were reduced by applying a WM mask derived from automated MPRAGE segmentation, and by using region-growing (lesion size). Total WMH volume

was calculated as cm3. The acquisition and processing of DTI data are described by Vemuri et al.[32]

2.3 | Statistical analyses

2.3.1 | WMH

Boxplots of WMH, as a percentage of total intracranial volume (TIV) to correct for head size, for CU and each MCI subtype were inspected for outliers and distributional properties. To compare WMH by group, we fit linear regression models on total WMH volume including group as a factor and adjusted for age, sex, and TIV given the known effect of these variables on WMH burden. The natural log transformation was applied to WMH volume and TIV to reduce skewness. Coefficients on the natural log scale are directly interpretable as approximate proportional differences.[33] To evaluate regional differences in WMH volume in the MCI subtypes, we selected lobar and deep gray/white regions of interest (ROIs) from the ADIR Lobar atlas (available as part of the Mayo Clinic Adult Lifespan Template, https://www.nitrc.org/projects/mcalt/). Separate linear regression models were fit on regional WMH (frontal, parietal, occipital, temporal, deep gray/white) following the previously described framework, including group as a factor, adjusting for age, sex, and TIV, and applying natural log transformations to volumes.

There were no adjustments for multiple comparisons to avoid making a priori assumptions about group differences. We did not want to strongly control the rate of false positive findings at the expense of false negatives. Because we show the actual *P* values, we allow the reader to calculate a Bonferroni type of adjustment, if desired.[34] Analyses were completed in R statistical software version 3.4.2 (https://www.r-project.org).

2.3.2 | DTI-FA

Tract-based spatial statistics (TBSS) was used to analyze the data.[35] The registered FA images were averaged to derive a mean FA, which was further skeletonized. The FA skeleton was then thresholded at 0.2 to include only WM and each participant's FA data was projected onto this skeleton. The differences in FA between each MCI subtype and CU were analyzed in a voxel-wise fashion using FSL randomise with 5000 permutations with age and sex as covariates. We report clusters that survive correction for family-wise error ($P < .05$) using labels from the Johns Hopkins University (JHU) "Eve" WM atlas.[36]

To supplement the voxel-based analyses, a regional analysis of FA in the corpus callosum (CC), the major interhemispheric WM connection, was also conducted. To quantify relative differences in WM damage, pairwise differences in covariate-adjusted group means were extracted from a linear regression model on FA adjusting for age, sex, and group.

To examine the clinical relevance of microvascular factors on cognition in incident MCI, a partial correlation coefficient was computed between CC FA and global *z*-score after adjusting for age, sex, WMH, and TIV and applying natural log transformations to volumes. The square of the partial correlation can be interpreted as the unique percentage contribution of CC FA to the total variation in global cognition.

3 | RESULTS

3.1 | Demographic characteristics and neuropsychological performance

The steps to derive the study samples are flowcharted (Figure S1 in supporting information). The current analysis includes individuals who completed imaging at the visit when incident MCI was diagnosed (n = 192), and 344 CU participants who were ≥ 70 at the time of their MRI with usable WMH data. Four participants failed WMH data quality control, leaving 188 with incident MCI. We compared the subset of 63 MCI participants with DTI to 100 CU participants with DTI.

Demographics and cognitive domain *z*-scores for the WMH (N = 188 MCI; N = 344 CU) and DTI (N = 63 MCI; N = 100 CU) samples are listed in Tables 1 and 2, respectively. Figure 1 shows box plots of cognitive domain *z*-scores for each MCI cluster for the original sample[16] and the WMH and DTI samples. We used analysis of variance for continuous variables and Pearson's Chi-squared test for categorical variables to determine whether the WMH and DTI samples differed significantly from the original sample of 506 participants used to derive the clusters.[16] For the WMH sample, there was a slightly higher number of males relative to our original sample (61% vs. 53% in original sample, $P = .048$). The WMH sample did not differ from the original sample on age, education, *APOE* ε4 genotype, or cognitive test *z*-scores. The mean age of the DTI sample was slightly younger than the original sample of 506 (80 vs. 82, $P = .01$), and the mean visuospatial domain z-score of the DTI sample was slightly higher than the original sample (−.65 vs. −1.01, $P = .008$), but other characteristics did not differ. For both the WMH and DTI cohorts, the frequency of *APOE* ε4 allele did not differ among the MCI subtypes ($P = .78$ and $P = .06$, respectively), but was greater for MCI subtypes compared to the CU group ($P < .001$ and $P = .03$, respectively). The MCI subtypes did not differ from CU by frequency of infarctions in either sample. Group-wise comparisons are provided in Tables 1 and 2.

3.2 | WMH volumes

Figure 2 plots TIV-adjusted WMH without adjustment for age or sex. Figure 3 provides demographically adjusted pairwise group differences from the models on total or regional WMH volumes. The amnestic (18% [0, 36] $P = .04$) and dysexecutive (30% [7, 52] $P = .01$) subtypes had significantly higher total WMH volumes compared to CU. The subtle cognitive impairment (−13% [−42, 16] $P = .39$) and dysnomic (6% [−22, 24= $P = .68$) clusters did not differ from CU. Additionally, the dysexecutive cluster had higher total WMH than the subtle cognitive impairment cluster (% WMH difference [95% confidence interval (CI)] *P*-value: 43%

TABLE 1 WMH sample demographic and cognitive characteristics

	CU n = 344	Subtle CI n = 26	Amnestic n = 83	Dysnomic n = 30	Dysexecutive n = 49	*P*-value
Demographics						
Age, years	78 (6)	80 (8)	80 (6)	84 (6)	83 (7)	< .001[†,‡,§]
Education, years	15 (3)	16 (3)	14 (3)	12 (3)	14 (3)	< .01[*,‡,§] < .001[†]
Males, no. (%)	185 (54%)	20 (77%)	47 (57%)	16 (53%)	32 (65%)	.02[*]
CDR Sum of Boxes	0.0 (0.3)	0.5 (0.6)	1.0 (0.9)	1.0 (1.0)	1.0 (1.1)	<.001[*,†,‡,§]
APOE ε4 carrier, no. (%)	81 (24%)	10 (38%)	31 (37%)	13 (43%)	22 (45%)	< .05[†,‡,§]
STMS	35 (2)	33 (2)	31 (3)	29 (3)	30 (3)	< .001[*,†,‡,§]
FAQ total score	0 (1)	1 (3)	2 (3)	1 (3)	3 (4)	< .01[*,†,§] < .001[‡]
BDI-II > 14, no. (%)	16 (5%)	3 (12%)	5 (6%)	2 (7%)	8 (16%)	.001[§]
CMC Index	2 (1)	2 (1)	3 (1)	3 (1)	3 (1)	.008[§]
Global z-score	−0.0 (0.9)	−0.3 (0.5)	−1.4 (0.4)	−2.9 (0.7)	−2.2 (0.7)	< .001[†,‡,§]
Memory z-score	0.1 (1.0)	−1.1 (1.1)	−1.8 (0.7)	−2.2 (0.7)	−1.1 (0.9)	< .001[*,†,‡,§]
Language z-score	−0.1 (0.9)	−0.1 (0.6)	−1.0 (0.7)	−3.3 (1.0)	−1.5 (0.7)	< .001[†,‡,§]
Attention z-score	−0.2 (1.0)	−0.1 (0.6)	−0.9 (0.8)	−2.1 (1.0)	−3.3 (0.7)	< .001[†,‡,§]
Visuospatial z-score	0.1 (0.9)	0.3 (0.8)	−0.6 (0.7)	−1.8 (0.9)	−1.2 (1.0)	< .001[†,‡,§]
Infarction, no. (%)	85 (25%)	5 (29%)	11 (32%)	2 (22%)	8 (35%)	.8

Notes: Values reported are of the form mean (standard deviation, SD) or count (percent) and subtypes were compared using linear model ANOVA or Pearson Chi-squared tests, respectively.
Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; BDI, Beck Depression Inventory; CDR, Clinical Dementia Rating scale; CI, cognitive impairment; CU, cognitively unimpaired; FAQ, Functional Activities Questionnaire; NS, not significant.; STMS, Short Test of Mental Status; Subtle CI, subtle cognitive impairment; WMH, white matter hyperintensity.
*Subtle CI versus CU.
†Amnestic versus CU.
‡Dysnomic versus CU.
§Dysexecutive versus CU.

[8, 77] $P = .02$). When examined by region and tested against CU, the amnestic subtype had higher WMH in the parietal (27% [2, 52] $P = .04$) and occipital (16% [2, 30] $P = .03$) lobes, while the dysexecutive subtype had higher WMH in the frontal (35% [8, 61] $P = .01$), parietal (33% [1, 65] $P = .04$), and deep grey/white (40% [11, 69] $P = .006$) regions (Figure 3).

3.3 | DTI

All MCI subtypes except subtle cognitive impairment had widespread decreased FA. Relative to CU, the amnestic cluster showed decreased FA in the anterior thalamic radiation (ATR), corticospinal tract (CST), forceps major/minor, inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (UF). The dysnomic cluster showed decreased FA in the forceps major/minor, and IFOF relative to CU. The dysexecutive subtype showed decreased FA in the ATR, CST, forceps major/minor, IFOF, ILF, and superior longitudinal fasciculus relative to CU and the subtle cognitive impairment subtype. The dysexecutive subtype also had the most severe bilateral involvement among all MCI subtypes (Figure 4).

In the complementary regional analysis amnestic, dysnomic, and dysexecutive subtypes had significantly lower FA of the CC than CU (% FA difference [95% CI] *P*-value: −3 [−4,−1] $P = .003$; −5 [−8,−2] $P < .001$; −5 [−7,−3= $P < .001$, respectively; Figure 2, Panel B). Additionally, among MCI subtypes CC FA explained 15% of the remaining variability in global cognition even after accounting for demographic and vascular features.

Clinical diagnoses for participants with a follow-up visit post-incident MCI diagnosis are given in Table S1 in supporting information for the WMH and DTI samples.

4 | DISCUSSION

The main findings of this study are: (1) the dysexecutive MCI subtype had increased WMH relative to CU and the subtle cognitive impairment subtype, had elevated WMH in frontal and parietal lobes as well as the deep gray/white matter region, and had the most widespread WM microstructural injury on DTI; (2) the amnestic MCI subtype had elevated parietal and occipital WMH and reduced FA relative to CU; (4) the dysnomic subtype did not have greater WMH but showed

TABLE 2 DTI sample demographic and cognitive characteristics

	CU n = 100	Subtle CI n = 12	Amnestic n = 23	Dysnomic n = 8	Dysexecutive n = 20	*P*-value*
Demographics						
Age, years	77 (6)	79 (9)	78 (7)	79 (5)	82 (8)	< .001§
Education, years	15 (3)	16 (2)	14 (2)	12 (3)	15 (3)	< .01‡ < .05*,†
Males, no. (%)	51 (51%)	10 (83%)	10 (43%)	5 (62%)	13 (65%)	.02*
CDR Sum of Boxes	0.0 (0.3)	0.5 (0.6)	1.0 (0.9)	1.0 (1.7)	1.0 (1.0)	< .001*,†,‡,§
*APOE ε*4 carrier, no. (%)	25 (26%)	4 (33%)	11 (48%)	3 (38%)	11 (55%)	.05† < .01§
STMS	36 (2)	34 (2)	32 (2)	29 (3)	30 (2)	< .001*,†,‡,§
FAQ total score	0 (1)	0 (0)	1 (1)	2 (3)	2 (3)	< .001‡,§ < .01†
BDI-II > 14, no. (%)	3 (3%)	0 (0%)	2 (9%)	1 (12%)	3 (15%)	< .05§
CMC Index	2 (1)	2 (1)	3 (1)	3 (1)	3 (1)	NS
Global z-score	0.0 (0.9)	−0.3 (0.7)	−1.3 (0.4)	−2.6 (0.5)	−2.1 (0.8)	< .001†,‡,§
Memory z-score	0.1 (1.0)	−1.3 (1.3)	−1.8 (0.8)	−2.0 (0.7)	−1.1 (0.9)	< .001*,†,‡,§
Language z-score	−0.0 (0.9)	−0.2 (0.7)	−1.1 (0.7)	−3.0 (0.7)	−1.4 (0.8)	< .001†,‡,§
Attention z-score	−0.1 (0.9)	0.1 (0.7)	−0.7 (0.7)	−1.9 (1.1)	−3.3 (0.6)	< .001†,‡,§
Visuospatial z-score	0.1 (1.0)	0.5 (1.0)	−0.6 (0.6)	−1.5 (0.8)	−1.1 (1.0)	< .001‡,§ < .01†
Infarction, no. (%)	24 (24%)	4 (33%)	8 (35%)	2 (25%)	7 (35%)	.8

Values reported are of the form mean (standard deviation, SD) or count (percent) and subtypes were compared using Linear Model ANOVA or Pearson Chi-squared tests, respectively.

Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; BDI, Beck Depression Inventory; CDR, Clinical Dementia Rating Scale; CI, cognitive impairment; CU, cognitively unimpaired; FAQ, Functional Activities Questionnaire; NS, not significant.; STMS, Short Test of Mental Status; Subtle CI, subtle cognitive impairment.

*Subtle CI versus CU.

†Amnestic versus CU.

‡Dysnomic versus CU.

§Dysexecutive versus CU.

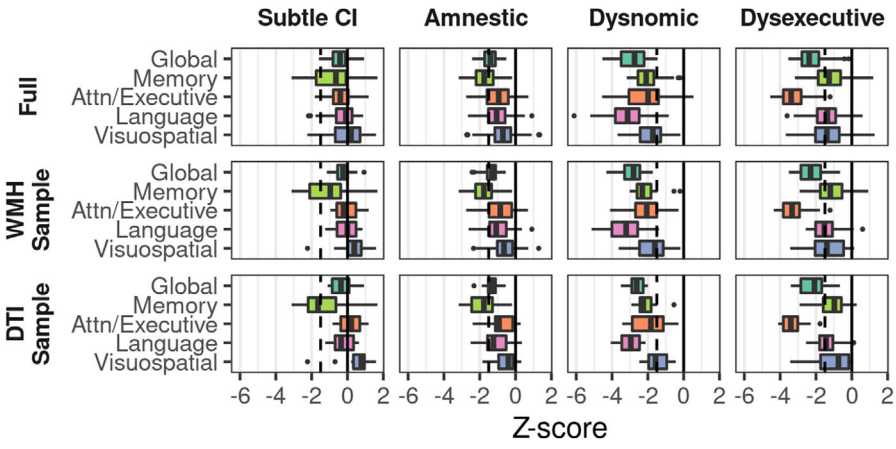

FIGURE 1 Box plots of cognitive domain scores for each mild cognitive impairment subtype in each cohort. CI, cognitive impairment; DTI, diffusion tensor imaging; WMH, white matter hyperintensity

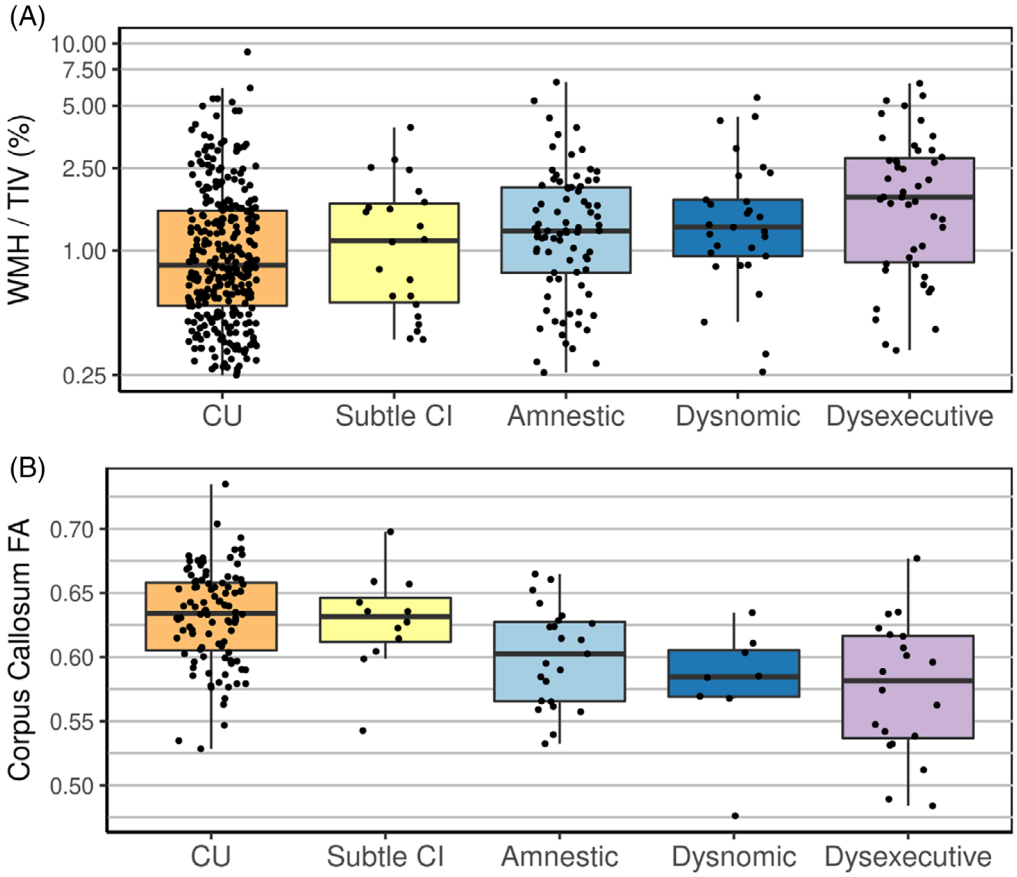

FIGURE 2 White matter hyperintensity (WMH) volume scaled by total intracranial volume (TIV) %, unadjusted for age and sex (A) and corpus callosum fractional anisotropy (FA) values for cognitively unimpaired (CU) and each mild cognitive impairment (MCI) subtype (B)

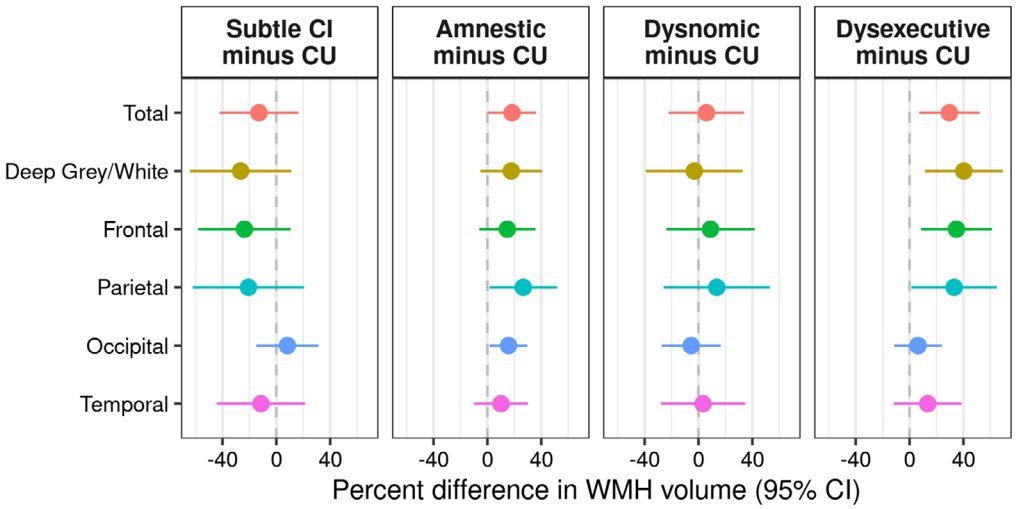

FIGURE 3 Differences in white matter hyperintensity (WMH) volume for each mild cognitive impairment (MCI) subtype relative to cognitively unimpaired (CU). The set of four points comprising the row labeled "Total" were estimated from a single linear regression model on total WMH volume controlling for age, sex, and total intracranial volume (TIV). Similarly, for the five regions listed, each set of four points for a given row is from a single regression. The x-axis shows the percent difference in WMH volume for each MCI subtype relative to CU

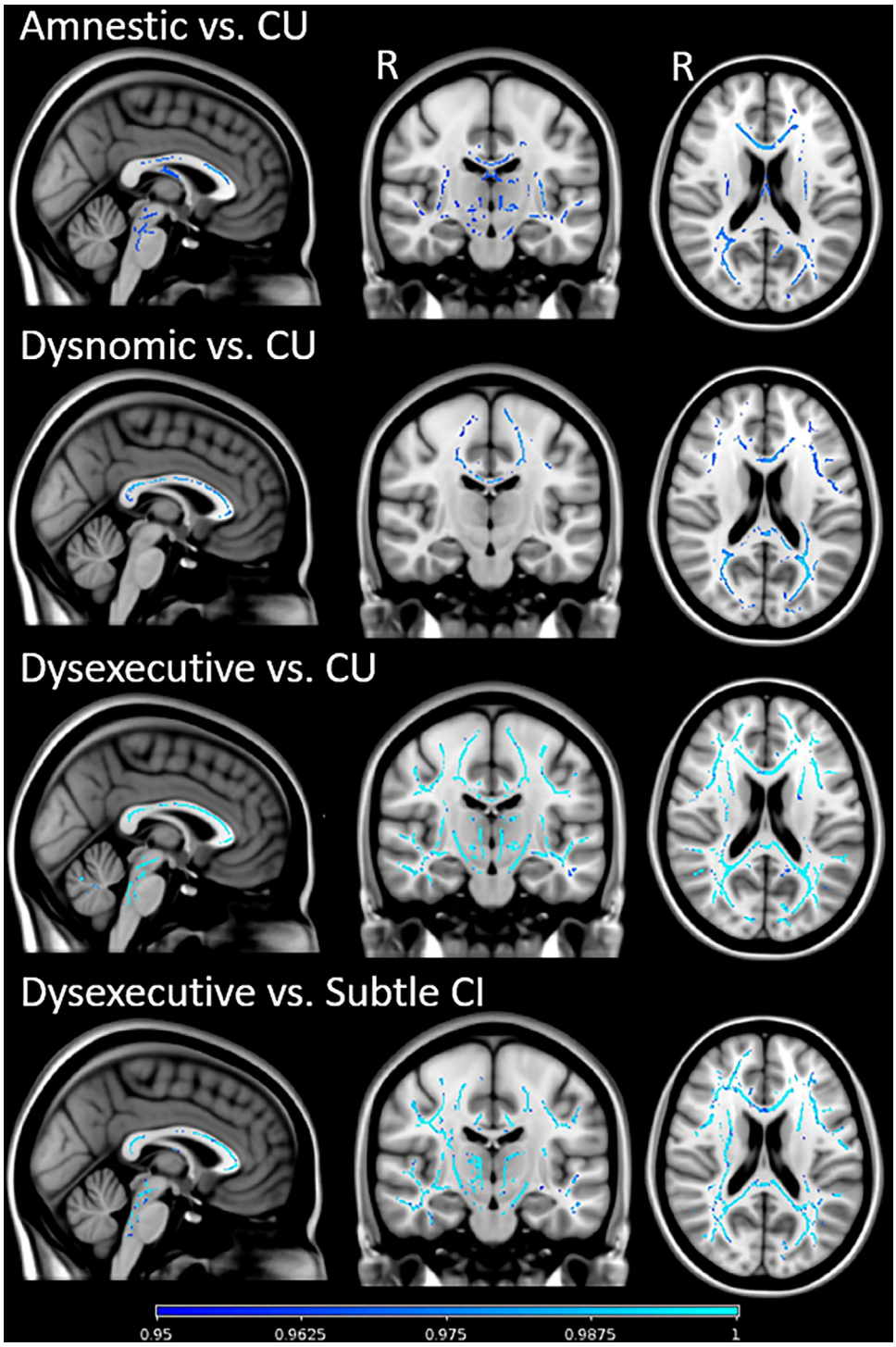

FIGURE 4 Tract-based spatial statistics fractional anisotropy (FA) maps showing the differences between cognitively unimpaired (CU) and each of the cluster derived incident mild cognitive impairment (MCI) subtypes, family-wise error (FWE) corrected, $P < .05$. The results are displayed with threshold free cluster enhancement (TFCE) randomization. The images were then viewed with a display threshold of 0.95-1, which corresponds to thresholding at FWE, $P < .05$. There were no significant FA changes in the subtle cognitive impairment subtype relative to CU

decreased FA in multiple WM tracts relative to CU; (5) voxel-level results confirmed the extent of CC damage in the amnestic, dysnomic, and dysexecutive subtypes; (6) the subtle cognitive impairment subtype did not differ from CU on WMH or FA; (7) CC FA accounted for significant variability in global cognition.

White matter health and executive function are strongly associated. Our results of elevated WMH in the dysexecutive subtype supports our hypothesis and are consistent with a recent meta-analysis showing that although there is an association between multiple cognitive domains and WMH in MCI, the largest effect sizes are in

attention/executive function and processing speed.[3] We did not expect elevated WMH in the amnestic subtype, especially given that this subtype's attention domain z-score was in the low normal range (median z = −.85). Conversely our dysnomic subtype, despite performing in the impaired range on the attention/executive function composite (median z = −2.1), did not have elevated WMH volume indicating that other pathologic brain changes are likely contributing to their impaired cognitive performance.

While deficits in processing speed and executive function are those most commonly associated with WM changes, previous studies on individuals with incident[6] and prevalent MCI[37] have reported an association between WMH volume and memory in addition to executive function. Our amnestic subtype differs from these other studies because we identified it via cluster analysis, and memory is the only impaired cognitive domain. The MCI participants in Boyle et al.[6] and Brugulat-Serrat et al.[38] were impaired in multiple cognitive domains so executive function deficits may have influenced memory performance. The study by Delano-Wood et al.[18] on empirically derived prevalent MCI subtypes did not find elevated WM lesion pathology in their pure memory group, whose memory performance (evaluated with the Consortium to Establish a Registry for Alzheimer's Disease 10-word list test) approximates our amnestic group in terms of level of memory impairment.

Previous studies that evaluated regional WMH in those at risk for AD and/or MCI have similarly found a posterior predilection for elevated WMH. For example, a study on participants from the Dominantly Inherited Alzheimer Network (DIAN) found elevated parietal and occipital WMH as early as 22 years before symptom onset.[39] Results from a community-based sample showed that cross-sectional parietal lobe WMH volume was associated with increased risk of AD dementia,[40] and increasing parietal WMH predicted progression to AD.[41] In a more recent study, amyloid-positive MCI participants had increased global, occipital, and temporal deep WMH compared to amyloid-negative CU participants whereas the MCI amyloid-negative participants did not differ from amyloid-negative CU.[42] It is possible that our amnestic subtype may follow a clinical trajectory consistent with an amnestic presentation of AD. Conversely, the dysexecutive subtype showed elevated WMH in frontal-subcortical (i.e., deep gray/white matter) and parietal regions. Elevated WMH in frontal and deep gray/white matter structures are thought to be associated with vascular disease[2] while the elevated parietal WMH in the dysexecutive subtype may be associated with Alzheimer's disease pathology,[40,41] although we could not confirm this in our study because the proportion of participants in the MCI subtype groups ranged from 33% to 65% for Pittsburgh compound B positron emission tomography (PET) and 0% to 15% for tau PET, too few for meaningful analysis.

We found widespread WM degeneration in the commissural and long association fibers of the amnestic, dysnomic, and dysexecutive subtypes. We also found that CC FA explained 15% of the variability in global cognition among MCI subtypes even after accounting for age, sex, WMH, and TIV, suggesting that the development of cognitive symptoms in MCI includes interhemispheric disconnection. The reduced FA in the dysnomic subtype without elevated WMH raises the possibility that these individuals may eventually develop WMH burden given previous reports showing that DTI-based measures of WM microstructural integrity occur earlier and predict the development of WMH.[11,43]

Several studies have evaluated whole brain WM changes in prevalent MCI compared to CU.[44–50] They found WM microstructural abnormalities in a number of areas, many of which overlap with our findings, including the anterior corona radiata,[50] superior longitudinal fasciculus,[48,49] cingulum,[44,46–49] forceps major,[44,50] anterior thalamic radiation,[45] posterior thalamic radiation,[44,50] superior/posterior thalamic peduncles,[49] uncinate fasciculus,[47,48] medial temporal region,[46] arcuate fibers at the temporal-parietal juncture,[49] cerebellum,[47] and brain stem.[47] Two studies also reported a predilection for posterior WM,[44,49] but we did not find a posterior anterior gradient in our MCI subtypes.

Several studies have also evaluated DTI changes in subjective cognitive impairment (SCI) or subjective cognitive decline (SCD), which are conceptualized as occurring earlier on the continuum from normal aging to dementia than our subtle cognitive impairment participants who were diagnosed with incident MCI for inclusion in our original cluster analysis.[16] One study did not find significant differences in DTI metrics SCD/SCI[46] whereas others have reported DTI changes in SCD/SCI that are intermediate between CU and MCI[44,50] or are more similar to amnestic MCI than CU.[51] We used rigorous methods to establish that our SCI subtype did not represent false positives[16] and also previously showed that this subtype has thinning in entorhinal and parahippocampal cortex,[17] so it is not clear why we did not see reduced DTI-FA.

Our findings extend previous research of WM changes in MCI by assessing WMH and DTI differences in empirically derived incident MCI cognitive phenotypes. A significant strength of this study is that we assessed WM changes just as participants are transitioning from CU to MCI, which differs from previous studies of WM changes in prevalent MCI in whom the WM pathology may have progressed more for some individuals than others. Hence, it is unlikely that our results are solely due to disease duration given that all imaging was performed at the first visit at which an MCI diagnosis was made. Weaknesses of the study include potential selection bias given the subset of individuals from our original sample who had imaging data at the same visit at which the diagnosis of incident MCI was made (imaging is offered to all participants regardless of diagnosis), a very limited number of participants with DTI data, participants who are largely of northern European descent, and lack of amyloid status.

In conclusion, we found that amnestic and dysexecutive incident MCI subtypes have different patterns of elevated WMH, and amnestic, dysnomic, and dysexecutive MCI subtypes have widespread WM degeneration in long association and commissural fibers. These results add to our understanding of underlying brain changes just as individuals are developing the cognitive symptoms of MCI and may aid in better prognosis and treatment strategies.

ACKNOWLEDGMENTS

The authors wish to thank the participants and staff at the Mayo Clinic Study of Aging. This research was made possible by the National Institutes of Health R01 AG49810, R37 AG011378, RO1 AG041851, R01

AG056366, R01 NS097495, U01 AG006786, R01 AG034676, P30 AG062677, Alexander Family Professorship of Alzheimer's Disease Research, The Elsie and Marvin Dekelboum Family Foundation, The GHR Foundation, The Robert Wood Johnson Foundation, and by the Mayo Foundation for Education and Research.

CONFLICTS OF INTEREST

Mary M. Machulda: receives funding from the NIH. Emily S. Lundt, Sabrina M. Albertson, Carly T. Mester, Sheelakumari Raghavan, and Robert I. Reid: no disclosures. Christopher G. Schwarz: receives funding from the NIH. Jonathan Graff-Radford: receives funding from the NIH. He serves as assistant editor for *Neurology*. Clifford R. Jack Jr: receives funding from the NIH. Has consulted for Biogen, served as a speaker for Eisai and serves on an independent data monitoring board for Roche but receives no personal compensation from any commercial entity. Michelle M. Mielke: receives funding from NIH and DOD. Has consulted for Biogen and Brain Protection Company. Walter K. Kremers: has had research funding from NIH, DOD, Biogen, AstraZeneca, and Roche. David S. Knopman: has served on a data safety monitoring board for the DIAN study. He serves on a data safety monitoring board for a tau therapeutic for Biogen, but receives no personal compensation. He is a site investigator in the Biogen aducanumab trials. He is an investigator in a clinical trials sponsored by Lilly Pharmaceuticals and the University of Southern California. He serves as a consultant for Samus Therapeutics, Third Rock, Roche, and Alzeca Biosciences but receives no personal compensation. He receives research support from the NIH. Ronald C. Petersen: consultant for Roche, Inc., Biogen, Inc., Eisai, Inc.; served on a DSMB for Genentech, Inc.; and receives funding from NIH. Mark W. Bondi: receives funding from the NIH. Receives royalties from Oxford University Press. Prashanthi Vemuri: Receives funding from the NIH.

AUTHOR CONTRIBUTIONS

Mary M. Machulda: full responsibility for the data, design and conceptualization of the study, data collection and has full access to all the data, analysis and interpretation of the data, conduct of the research, drafting the manuscript, revising the manuscript, study funding. Emily S. Lundt: design and conceptualization of the study, analysis and interpretation of the data, drafting the manuscript, revising the manuscript. Sabrina M. Albertson: design and conceptualization of the study, analysis and interpretation of the data, drafting the manuscript, revising the manuscript. Carly T. Mester: analysis and interpretation of the data, drafting the manuscript, revising the manuscript. Sheelakumari Raghavan: analysis of data, revising the manuscript. Robert I. Reid: analysis of data, revising the manuscript. Christopher G. Schwarz: analysis of data, revising the manuscript. Jonathan Graff-Radford: analysis of data, revising the manuscript. Clifford R. Jack Jr: data collection, study funding, revising the manuscript. Michelle M. Mielke: data collection, revising the manuscript. Walter K. Kremers: analysis and interpretation of the data, revising the manuscript. David S. Knopman: data collection, revising the manuscript. Ronald C. Petersen: data collection, analysis and interpretation of the data, study funding, revising the manuscript. Mark W. Bondi: study funding, revising the manuscript. Prashanthi Vemuri: design and conceptualization of the study, analysis and interpretation of the data, drafting the manuscript, study funding, revising the manuscript.

DATA AVAILABILITY STATEMENT

Data from this study are available upon reasonable request.

REFERENCES

1. Boyle PA, Yu L, Leurgans SE, et al. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. *Annals of Neurology*. 2019;85(1):114-124.
2. Alber J, Alladi S, Bae H-J, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): knowledge gaps and opportunities. *Alzheimer Dement Transl Res Clin Interv*. 2019;5:107-117.
3. Van Den Berg E, Geerlings MI, Biessels GJ, Nederkoorn PJ, Kloppenborg RP. White matter hyperintensities and cognition in mild cognitive impairment and Alzheimer's disease: a domain-specific meta-analysis. *J Alzheimers Dis*. 2018;63(2):515-527.
4. Silbert LC, Dodge HH, Perkins LG, et al. Trajectory of white matter hyperintensity burden preceding mild cognitive impairment. *Neurology*. 2012;79(8):741-747.
5. Ding D, Xiong Y, Zhao Q, et al. White matter hyperintensity predicts the risk of incident cognitive decline in community dwelling elderly. *J Alzheimer Dis*. 2018;61:1333-1341.
6. Boyle PA, Yu L, Fleischman DA, et al. White matter hyperintensities, incident mild cognitive impairment, and cognitive decline in old age. *Ann Clin Trans Neurol*. 2016;3(10):791-800.
7. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E. Presence and progression of white matter hyperintensities and cognition. *Neurology*. 2014;82(23):2127-2138.
8. Bolandzadeh N, Davis JC, Tam R, Handy TC, Liu-Ambrose T. The association between cognitive function and white matter lesion location in older adults: a systematic review. *BMC Neurol*. 2012;12(1):126.
9. Delano-Wood L, Abeles N, Sacco JM, Wierenga CE, Horne NR, Bozoki A. Regional white matter pathology in mild cognitive impairment. *Stroke*. 2008;39(3):794-799.
10. Maniega SM, Valdés Hernández MC, Clayden JD, et al. White matter hyperintensities and normal-appearing white matter integrity in the aging brain. *Neurobiol Aging*. 2015;36(2):909-918.
11. Maillard P, Carmichael O & Harvey D et al. FLAIR and Diffusion MRI Signals Are Independent Predictors of White Matter Hyperintensities. AJNR. 2013; 34(1): 54-61.
12. Power MC, Su D, Wu A, et al. Association of white matter microstructural integrity with cognition and dementia. *Neurobiol Aging*. 2019;83:63-72.
13. Raghavan S, Przybelski SA, Reid RI, et al. Reduced fractional anisotropy of the genu of the corpus callosum as a cerebrovascular disease marker and predictor of longitudinal cognition in MCI. *Neurobiol Aging*. 2020;96:176-183.
14. Debette Sté, Beiser A, Decarli C, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality. *Stroke*. 2010;41(4):600-606.
15. Smith EE, Egorova S, Blacker D, et al. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch Neurol*. 2008;65(1):94-100.
16. Machulda MM, Lundt ES, Albertson SM, et al. Neuropsychological subtypes of incident mild cognitive impairment in the Mayo Clinic Study of Aging. *Alzheimer Dement*. 2019;15:878-887.
17. Machulda MM, Lundt ES, Albertson SM, et al. Cortical atrophy patterns of incident MCI subtypes in the Mayo Clinic Study of Aging. *Alzheimer Dement*. 2020;16(7):1013-1022.

18. Delano-Wood L, Bondi MW, Sacco J, et al. Heterogeneity in mild cognitive impairment: differences in neuropsychological profile and associate white matter lesion pathology. *J Int Neuropsychol Soc*. 2009;15(6):906-914.
19. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology*. 2008;30(1):58-69.
20. Kokmen E. The short test of mental status. Correlations with standardized psychometric testing. *Arch Neurol*. 1991;48(7):725-728.
21. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. 1968;114:797-811.
22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412.2-2412-a.
23. Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982;37(3):323-329.
24. Beck AT, Steer RA, Brown GK. *Manual for Beck Depression Inventory-II (BDI-II)*. San Antonio, TX: The Psychological Corporation; 2006.
25. Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC. Neuropsychological tests' norms above age 55: cOWAT, BNT, MAE Token, WRAT-R Reading, AMNART, Stroop, TMT, and JLO. *Clin Neuropsychol*. 1996;10(3):262-278.
26. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's Older Americans Normative Studies: updated AVLT norms for ages 56 to 97. *Clin Neuropsychol*. 1992;6:83-104.
27. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment. *Neurology*. 2018;90(3):126-135.
28. Hixson Je, Vernier Dt. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with Hhal. *J Lipid Res*. 1990;31(3):545-548.
29. Vemuri P, Lesnick TG, Przybelski SA, et al. Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Annals of Neurology*. 2017;82(5):706-718.
30. Graff-Radford J, Aakre JA, Knopman DS, et al. Prevalence and heterogeneity of cerebrovascular disease imaging lesions. *Mayo Clinic Proc*. 2020;95(6):1195-1205.
31. Raz L, Jayachandran M, Tosakulwong N, et al. Thrombogenic microvesicles and white matter hyperintensities in postmenopausal women. *Neurology*. 2013;80(10):911.
32. Vemuri P, Lesnick TG, Przybelski SA, et al. Development of a cerebrovascular magnetic resonance imaging biomarker for cognitive aging. *Ann Neurol*. 2018;84(5):705-716.
33. Gelman A, Hill J. *Data Analysis using Regression and Multilevel/Hierarchical Models*. Cambridge, New York: Cambridge University Press; 2007.
34. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1(1):43-46.
35. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage*. 2006;31(4):1487-1505.
36. Oishi K, Faria A, Jiang H, et al. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. *NeuroImage*. 2009;46(2):486-499.
37. Smith EE, Salat DH, Jeng J, et al. Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology*. 2011;76(17):1492-1499.
38. Brugulat-Serrat A, Salvadó G, Sudre CH, et al. Patterns of white matter hyperintensities associated with cognition in middle-aged cognitively healthy individuals. *Brain Imaging Behav*. 2020;14(5):2012-2023.
39. Lee S, Viqar F & Zimmerman ME et al. White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. Ann Neurol. 2016; 79(6): 929-939.
40. Brickman AM, Provenzano FA, Muraskin J, et al. Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer disease in the community. *Arch Neurol*. 2012;69(12):1621-1627.
41. Brickman AM, Zahodne LB, Guzman VA, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiol Aging*. 2015;36(1):27-32.
42. Pålhaugen L, Sudre CH, Tecelao S, et al. Brain amyloid and vascular risk are related to distinct white matter hyperintensity patterns. *J Cereb Blood Flow Metab*. 2020;41(5):1162-1174.
43. Maillard P, Fletcher E, Lockhart SN, et al. White matter hyperintensities and their penumbra lie along a continuum of injury in the aging brain. *Stroke*. 2014;45(6):1721-1726.
44. Wen Q, Mustafi SM, Li J, et al. White matter alterations in early-stage Alzheimer's disease: a tract-specific study. *Alzheimers Dement (Amst)*. 2019;11:576-587.
45. Serra L, Cercignani M, Lenzi D, et al. Grey and white matter changes at different stages of Alzheimer's disease. *J Alzheimer Dis*. 2010;19:147-159.
46. Kiuchi K, Kitamura S, Taoka T, et al. Gray and white matter changes in subjective cognitive impairment, amnestic mild cognitive impairment and Alzheimer's disease: a voxel-based analysis study. *PLOS One*. 2014;9(8):e104007.
47. Liu Y, Spulber G, Lehtimäki KK, et al. Diffusion tensor imaging and Tract-Based Spatial Statistics in Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging*. 2011;32(9):1558-1571.
48. Lee S-H, Coutu J-P, Wilkens P, Yendiki A, Rosas HD, Salat DH. Tract-based analysis of white matter degeneration in Alzheimer's disease. *Neuroscience*. 2015;301:79-89.
49. Medina D, Detoledo-Morrell L, Urresta F, et al. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. *Neurobiol Aging*. 2006;27(5):663-672.
50. Brueggen K, Dyrba M, Cardenas-Blanco A, et al. Structural integrity in subjective cognitive decline, mild cognitive impairment and Alzheimer's disease based on multicenter diffusion tensor imaging. *J Neurol*. 2019;266(10):2465-2474.
51. Luo C, Li M, Qin R, et al. White matter microstructural damage as an early sign of subjective cognitive decline. *Front Aging Neurosci*. 2020;11(378). https://doi.org/10.3389/fnagi.2019.00378

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Machulda MM, Lundt ES, Mester CT, et al. White matter changes in empirically derived incident MCI subtypes in the Mayo Clinic Study of Aging. *Alzheimer's Dement*. 2021;13:e12269. https://doi.org/10.1002/dad2.12269