Shades of white: diffusion properties of T1- and FLAIR-defined white matter signal abnormalities differ in stages from cognitively normal to dementia

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Abstract

The underlying pathology of white matter signal abnormalities (WMSAs) is heterogeneous and may vary dependent on the magnetic resonance imaging contrast used to define them. We investigated differences in white matter diffusivity as an indicator for white matter integrity underlying WMSA based on T1-weighted and fluid-attenuated inversion recovery (FLAIR) imaging contrast. In addition, we investigated which white matter region of interest (ROI) could predict clinical diagnosis best using diffusion metrics. One hundred three older individuals with varying cognitive impairment levels were included and underwent neuroimaging. Diffusion metrics were extracted from WMSA areas based on T1 and FLAIR contrast and from their overlapping areas, the border surrounding the WMSA and the normal-appearing white matter (NAWM). Regional diffusivity differences were calculated with linear mixed effects models. Multinomial logistic regression determined which ROI diffusion values classified individuals best into clinically defined diagnostic groups. T1-based WMSA showed lower white matter integrity compared to FLAIR WMSA-defined regions. Diffusion values of NAWM predicted diagnostic group best compared to other ROIs. To conclude, T1- or FLAIR-defined WMSA provides distinct information on the underlying white matter integrity associated with cognitive decline. Importantly, not the “diseased” but the NAWM is a potentially sensitive indicator for cognitive brain health status.

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1. Introduction

White matter signal abnormalities (WMSAs) are a common observation on magnetic resonance imaging (MRI) scans in older individuals as well as patients with dementia. WMSA appear dark (i.e., hypointense) on T1-weighted images and bright (i.e., hyperintense) on fluid-attenuated inversion recovery (FLAIR) images, showing a generally larger volume on FLAIR images compared with T1-weighted images. Their prevalence and severity increase with age and are associated with cognitive dysfunction and an increased risk of Alzheimer’s disease (AD) [Abe et al., 2002; Burns et al., 2005; DeCarli et al., 1995; de Leeuw et al., 2001; Erten-Lyons et al., 2013].

While the underlying pathology of WMSA is still not fully understood, they are considered to be an important proxy for vascular-associated brain tissue damage [Benedictus et al., 2014; Salat, 2014; Wardlaw et al., 2013a,b]. Meta-analysis of 19 studies correlating postmortem observations of WMSA with pathology data revealed that the suspected pathogenic mechanisms are heterogeneous, including ischemia/hypoxia, hypoperfusion and altered cerebrovascular autoregulation, blood-brain barrier leakage, inflammation, degeneration, and amyloid angiopathy [Erten-Lyons et al., 2013; Gouw et al., 2008, 2011].
The wide range of potential etiologies underlying WMSA reflects the currently accepted idea that WMSA have a more global effect on white matter integrity, reaching beyond the WMSA itself. Variability in microstructural changes in the normal-appearing white matter (NAWM) have been shown to be associated with various neuropsychological measures (Vernooij et al., 2009), suggesting that changes in NAWM integrity based on diffusion tensor imaging (DTI) may be more closely associated with early symptomatology and related early pathology in neuronal tissue cognitive decline than WMSA load (Altamura et al., 2016). The Rotterdam study showed that WMSA may impact the health of the NAWM, showing a relationship between WMSA burden and microstructural white matter changes in the NAWM, as measured with DTI (Vernooij et al., 2008). In this study, the relation between regional decreases in fractional anisotropy (FA) and age was nearly completely explained by white matter atrophy or white matter lesions. Interestingly, Leritz et al. applied a similar approach but defined the WMSA using T1 contrast and reported that WMSA do not fully explain the association between age and microstructural white matter changes in the NAWM. The latter authors suggested that the differences in the amount of explained variance by WMSA may be dependent on the MRI contrast on which WMSAs are defined (Leritz et al., 2014).

This could suggest that WMSA identified on either T1 or FLAIR images reflect different neural markers or represent similar pathologies but have a different sensitivity to the severity of the pathology. Studies in multiple sclerosis (MS) patients, showed that the T1 sequence is more specific for atrophy (Sailer et al., 2001) and that T1 WMSA are histologically correlated with axonal loss and demyelination (Bitsch et al., 2001). However, log-transformed WMSA volumes determined on FLAIR images are on average 1.14 times higher than those on T1-weighted images, but both volumes are highly correlated in both aging and MS (Coutu et al., 2016) (Klisterner et al., 2016).

WMSA are also important for the clinical outcome of patients, as large WMSA have been linked to dementia (Prins and Scheltens, 2015). But distinguishing cognitively healthy individuals from those with incipient to mild cognitive impairment (MCI) based on WMSA is more challenging. Studies correlating the WMSA burden with cognition have shown both negative and positive associations as well as no associations (Bombois et al., 2007; Burns et al., 2005; Debette et al., 2007; de Mendonca et al., 2005; Jacobs et al., 2012; Smith et al., 2000; Tullberg et al., 2004; ). DTI may be a more promising technique to identify subgroups early on in the disease as it is more sensitive to microstructural changes. Variability in microstructural properties in the NAWM has been shown to be associated with various neuropsychological measures in the general population (Vernooij et al., 2009) and in patients with dementia (Altamura et al., 2016). This suggests that NAWM integrity measures based on DTI may be more closely associated with early symptomatology and related early pathology in neuronal tissue than WMSA load. The NAWM may indeed contain valuable predictive information for pathology, as changes in the DTI properties of the penumbra of WMSA have been shown to predict future formation of WMSA (Amlien and Fjell, 2014; Maillard et al., 2013).

It is the aim of this study to investigate whether the microstructural properties of white matter tissue measured with DTI within WMSA, differs between those identified on T1-weighted images, from those identified on FLAIR images in memory-clinic patients, which received a clinical diagnoses of AD, MCI, subjective cognitive decline (SCD), and in normal controls. Furthermore, based on the previously discussed literature, we expect that the white matter integrity in the NAWM and the border surrounding the WMSA will be higher compared to the integrity in the FLAIR- or T1-defined regions. Finally, to test the hypothesis that the discrimination of diagnostic groups by DTI measures may be dependent on the choice of the region of interest (ROI), we also investigated the probability of diffusion values in these different ROIs to distinguish groups based on clinical diagnoses. The results of this study can provide more insight into the difference in white matter integrity of WMSA defined on T1 versus FLAIR in neurodegenerative disorders and can contribute in tailoring more sensitive biomarkers based on DTI data.

2. Materials and methods

2.1. Participants

A total of 85 patients (SCD, n = 26), MCI patients (n = 43) and patients with AD (n = 16) were recruited at the memory clinic of Maastricht University Medical Center. In addition, 18 healthy participants without signs or complaints of cognitive impairment were recruited via advertisements from the general population to serve as cognitively normal controls (CN). All patients underwent a standard diagnostic workup, including clinical history taking, medical and neurological examination, blood draw for clinical chemistry, functional evaluation using the Clinical Dementia Rating scale (Hughes et al., 1982), rating scales for depression and neuropsychiatric symptoms, a neuropsychological test battery and neuroimaging. The diagnoses were made by a senior staff member (F.R.J. Verheij) using the core clinical criteria for MCI and AD (Albert et al., 2011; McKhann et al., 2011). Criteria for SCD diagnosis included the self-reported presence of subjective cognitive complaints but absence of impairment in any of the measured cognitive domains (normal scores on age-, gender-, and education-adjusted performance [within 1.5 SD of the mean] on the standardized cognitive tests). Controls were required to have a clinical dementia rating of 0, no cognitive complaints and no evidence of cognitive deficits on testing. For all healthy controls, general demographic data, educational level, medical history, and neuropsychological-testing data were recorded. Exclusion criteria for all participants were age <51 years, macrovascular abnormalities, large cerebral infarction, hemorrhage, a history of psychoactive medication use, abuse of alcohol or drugs, past or present psychiatric or neurological disorders (i.e., Parkinson’s disease, epilepsy, stroke, multiple sclerosis, brain surgery, brain trauma, electroconvulsive therapy, heart disease or brain infections), presence of depressive symptoms as indicated by the Hamilton Depression Rating Scale (Hamilton, 1960) (HDRS17; score ≥17), or contraindications for scanning. An experienced neuroradiologist reviewed the magnetic resonance images to ensure that none of the participants had radiological findings consistent with pathology in our exclusion criteria. This study was carried out in accordance with the rules and regulations of institutional research and ethics committees of the Maastricht University Medical Center, and written informed consent was obtained from all participants before participation.

2.2. MRI acquisition

All participants were scanned on a single MRI system (Philips Achieva 3.0 T) using an 8-channel head coil. T1-weighted images were acquired with repetition time (TR) = 8.2 ms, echo time (TE) = 3.7 ms, flip angle = 8°, number of slices = 180 (sagittal), matrix size = 240 × 240, and voxel size = 1.0 mm isotropic. The T2-weighted images were collected with TR = 2500 ms, TE = 100 ms, flip angle = 90°, number of slices = 48 (axial, no slice gap), matrix size = 512 × 512, and voxel size = 0.5 × 0.5 × 3.0 mm. The FLAIR images were acquired with TR = 11000 ms, TE = 125 ms, inversion time (TI) = 2800 ms, flip angle = 90°, number of slices = 48 (axial, no slice gap), matrix size = 512 × 512, and voxel size = 0.5 × 0.5 × 3.0 mm. The field of view across the various sequences was kept constant to improve registration and anatomical
localization. The diffusion-weighted images were acquired with TR = 8250 ms, TE = 80 ms, number of slices = 70 (axial), 61 directions with b value = 1000 (s/mm²), one b = 0 scan, matrix size = 128 × 128, and voxel size = 2.0 × 2.0 × 2.0 mm.

2.3. WMSA on T2- and FLAIR-weighted images

WMSA were identified using a semiautomated method (in-house developed software package GIANT) (Jacobs et al., 2014). First, the FLAIR and T2 scans were corrected for intensity non-uniformities (Sled et al., 1998), followed by a coregistration of the T2 scans with the corresponding FLAIR scans using FMRIB’s linear image registration tool from the FMRIB’s Software Library (FSL) version 5.0.4 (www.fmribo.ox.ac.uk/fsl). The axial FLAIR- and T2-weighted images were displayed side by side allowing for visual inspection and easy identification of WMSA, while they were traced manually. These manual WMSA traces served as input to train the segmentation algorithm. The actual segmentation was then performed semiautomatically by identifying each WMSA region in each slice of the simultaneously displayed FLAIR- and T2-weighted images to provide a seed point to initiate a region-growing algorithm. Manual corrections were performed slice-by-slice where necessary by a single-trained rater W.M. Freeze, who performed excellent (intra class correlation >0.98 [Shrout and Fleiss, 1979]) when compared to an experienced neuroradiologist on 2 independent data sets. Intrarater variabilities were computed for a subset (n = 10) (intra class correlation >0.99).

2.4. WMSA on T1-weighted images

Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite (version 5.1), which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale and Sereno, 1993; Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999a,b, 2004a, 2004b; Jovicich et al., 2009; Segonne et al., 2004). The T1 hypointensities were labeled using a probabilistic procedure subsequently extended to label WMSA (Fischl et al., 2002). All images were visually checked after processing and if necessary, we edited voxels where the algorithm overestimated or underestimated the gray/white matter boundaries or where the brain areas were erroneously excluded during skull stripping.

2.5. Diffusion-weighted analyses

The DTI data were processed with the freely available MR diffusion toolbox Explore-DTI version 4.8.3 (www.exploredti.com) (Leemans and Jones, 2009). In brief, the diffusion-weighted data were corrected for motion- and eddy current-induced distortions, incorporating the B-matrix rotation to preserve the diffusion gradient orientation information correctly (Leemans and Jones, 2009). This was done in 1 step together with the correction for echo-planar imaging and susceptibility distortions, using the T1 data as the undistorted template to unwarp the diffusion data using rigid transformations (Irfanoglu et al., 2012). The diffusion tensor was estimated from the aforementioned data (in isotropic T1 space) using “RESTORE”, a robust nonlinear least-squares method (Chang et al., 2005). From this diffusion tensor, the DTI metrics FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AxD) were derived. Diffusion images were thresholded at individual level of FA > 0.20 to minimize a bias due to partial volume effects of voxels located on the border of white matter and cerebral spinal fluid or on the border of white and gray matter (Jones et al., 2013).

To extract DTI metrics from the WMSA data, the T1 data were coregistered linearly to each individual’s FLAIR-weighted scan data by using FMRIB’s linear image registration tool from FSL version 5.0.4. Using the derived warp field, the DTI data were subsequently warped to the FLAIR data. All warping was done using affine transformations. The same procedure was applied to the FreeSurfer data to warp the T1-weighted hypointensities to the FLAIR data. All registrations were checked visually to ensure correctness. DTI metrics were then extracted from the WMSA determined on the FLAIR images, T1-weighted images, and the overlapping voxels of the FLAIR- and T1-based WMSA, FLAIR not T1, and T1 not FLAIR (see Fig. 1). In addition, a border zone surrounding the union of T1 and FLAIR were also evaluated.

Fig. 1. Distribution and overlap of T1 and FLAIR WMSA for 3 representative cases. The yellow regions denote the areas of overlap of T1 and FLAIR WMRS. Red is T1 not FLAIR, and green is FLAIR not T1 WMSA. T1 WMSA were warped to FLAIR space and superimposed on the FLAIR image and FLAIR WMRS. Abbreviations: FLAIR, fluid-attenuated inversion recovery; WMSA, white matter signal abnormalities. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
FLAIR WMSA (T1 U FLAIR) was determined by dilating this region of WMSA by 1 voxel. Voxels located in the ventricles were excluded from this border zone. The remaining white matter (i.e., white matter tissue map of FreeSurfer excluding the union of T1 and FLAIR WMSA and its dilated border) was labeled as NAWM, and DTI metrics were also extracted from this region. This resulted in diffusion metrics extracted from 7 regions: the FLAIR-defined WMSA, FLAIR not T1 (FLnotT1), T1 not FLAIR (T1notFL), T1-defined WMSA, the overlap between T1- and FLAIR-defined WMSA, the border of WMSA, and the NAWM. In this context, the WMSA as defined in T1 or FLAIR or a subset thereof is referred to as a ROI.

2.6. ICV estimation

WMSA volumes were adjusted for Intracranial volume (ICV) by means of the scaling factor generated by FSL-SIENAX, which correlates well with manual estimations (Keihaninejad et al., 2010).

2.7. Neuropsychological assessment

The Mini Mental State Examination (Folstein et al., 1975) was used as a general cognitive screening. Neuropsychological testing for specific cognitive domains included the verbal 15-word learning test for measuring episodic memory (Dutch version of Rey auditory verbal memory learning test delayed word free recall [number of correctly reproduced words 20 minutes after the last learning trial] and cued retrieval presenting 15 new and 15 old words). The verbal semantic fluency test measuring language (Van der Elst et al., 2005) (number of correctly named animals within 1 minute) and the Stroop color-word test as a measure of executive functioning (time to read Stroop color-word test card 3) (Klein et al., 1997; Van der Elst et al., 2006b,c). The letter digit substitution test was used for assessment of information-processing speed (van der Elst et al., 2006a).

2.8. Downstream topographical markers

Medial temporal lobe atrophy (MTA) score was assessed blinded using a qualitative visual rating scale (Scheltens et al., 1992). Coronal T1-weighted images were rated on using a 5-point scale ranging from 0 (no atrophy) to 4 (severe atrophy) based on the height of the hippocampal formation and surrounding cerebrospinal spaces. Participants given a MTA score of 2 or higher (both hemispheres summed) were considered as positive for AD risk (Clerx et al., 2013; Korf et al., 2004). In the control group, 6 of 18 (33%) scored 2 or higher (5 persons had an MTA score of 2 and 1 person had a score of 3). All (100%) MCI and AD patients had an MTA sum score of 2 or higher (n = 16 with 2 and n = 20 with 3, n = 13 with 4, n = 10 with >5). At the time of the inclusion, we followed the clinical core criteria of Albert et al. (2011), and these criteria suggested that the patients included in this study (amyloid pathology unknown, presence of neurodegeneration) have an intermediate probability to have cognitive deficits due to AD pathology (Albert et al., 2011). Of the SCD patients, 14 of 26 (54%) had MTA sum score of 2 or higher (n = 9 score 2, n = 1 score 3, n = 3 score 4, n = 1 score 5). Applying age-dependent MTA cutoffs as recently suggested in the literature (Ferreina et al., 2015; Rhodius-Meester et al., 2017) would still classify 95% of our cognitively impaired patients as having a higher likelihood of having AD pathology (2 of 18 CN, 13 of 26 SCD, 42 of 43 MCI, and 14 of 16 AD patients would be above the cutoff).

We would like to note that the research criteria for preclinical and prodromal AD have recently changed and indicate that MTA scale-derived topographical biomarker evidence are associated with increased likelihood to progress to AD in the context of elevated levels of amyloid pathology (Dubois et al., 2016). Unfortunately, we did not have amyloid pathology data available.

2.9. Statistical analysis

Statistical analyses were conducted in R version 3.2.4 (Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, http://www.R-project.org/) and Stata 13 (Stata Corp, College Station TX, USA).

One-way analyses of variance with post hoc t-tests were performed to assess group differences for continuous variables. Fisher’s exact tests were used to test for differences in proportions between groups for categorical variables. All pairwise t-tests were corrected for multiple comparisons using the Bonferroni method.

To investigate whether the diffusivity values differed depending on the different ROIs, we conducted linear mixed effects analyses with a random intercept for each participant using the restricted estimated maximum likelihood method for parameter estimation within the LME4 package (Bates, Maechler & Bolker, 2015). This approach allowed us to control for interdependency from the multiple measurements (ROIs) per participant. Age, sex, education level, diagnosis, and ICV-adjusted WMSA volume were used as covariates for the total group analyses. These models were repeated adding the scores on the HDRS (total) as a covariate. As the results were similar, we opted to provide the results without HDRS in the model, as this allowed to include all participants (n = 17 missing values on the HDRS).

To investigate whether the DTI differences between ROIs were dependent on the diagnostic status of participants, we added the interaction term “ROI by diagnosis” to the linear mixed effect model. Probability values were obtained by a parametric bootstrap test and a Kenward-Roger modification of F-tests for linear mixed effects models (Halekoh and Højsgaard, 2014; Kenward and Roger, 1997). Bonferroni correction was used to account for multiple comparisons (20 comparisons).

To investigate the ability of the diffusion values underlying the ROIs to predict diagnostic group belongingness, we applied multinomial logistic regression using the maximum likelihood method for parameter estimation, with diagnosis as outcome measure, and DTI metric in the ROI as predictor of interest. Age, sex, education level, and ICV-adjusted WMSA volume were added to the model as covariates. For each ROI, we ran a different model. Model fit, using the Nagelkerke R² and Akaiki information criterion (AIC), was evaluated for each model. As the models are non-nested, likelihood ratio testing was not possible; hence, we used the weighted delta Akaiki information criterion with finite sample size correction (ΔAICc), which accounts for finite sample size, to compare the performance of the various models in combination with the evidence ratio (Burnham et al., 2011).

3. Results

3.1. Group demographics and cognitive testing results

Demographic and cognitive group characteristics are shown in Table 1. There were significant differences between the 4 groups for age (F(3,99) = 12.79, p < 0.0001), Mini Mental State Examination (F(3,99) = 18.41, p < 0.0001) and HDRS (F(3,82) = 8.36, p < 0.0001). As expected, there were also significant group differences in cognitive performance on the verbal-learning test total and delayed score (F(3,99) = 31.04, p < 0.001; F(3,99) = 32.54, p < 0.001, respectively), letter digit substitution test (F(3,92) = 11.20, p < 0.001, [CN-AD]), fluency (F(3,95) = 11.31 p < 0.001, and Stroop card 3 time (F(3,95) = 6.7, p < 0.01). There were no significant group differences in education. WMSA volumes differed between diagnostic groups for FLAIR.
Table 1

Characteristics of the SCD, aMCI, AD, and control participants

|                          | Controls (n = 18) | SCD (n = 26) | aMCI (n = 43) | AD (n = 16) | F-test or Fisher’s exact |
|--------------------------|------------------|--------------|--------------|-------------|-------------------------|
| Age (y)                  | 64.6 (3.4)       | 64.5 (8.8)   | 66.8 (4.5)   | 76.9 (6.9)  | 12.79***                 |
| Gender (%) female         | 0                | 27           | 21           | 62.5        | 0.01*                    |
| Education level           | 4.4 (1.5)        | 4.2 (2.3)    | 3.6 (1.9)    | 3.6 (2.5)   | 0.89                     |
| MMSE                     | 28.9 (10)        | 28.7 (12.2)  | 27.6 (2.3)   | 24.6 (2.5)  | 18.41***                 |
| Total WLT (words)        | 37.5 (7.6)       | 42 (7.6)     | 27.7 (9.8)   | 20.6 (5.5)  | 31.04***                 |
| WLT delayed recall (words)| 8.6 (3.4)       | 8.8 (2.9)    | 3.7 (2.7)    | 2.1 (3.9)   | 32.54***                 |
| Stroop card 3 (sec)      | 108.1 (19.7)     | 116.4 (32.4) | 134.8 (52.0) | 182.4 (68.7) | 6.74***                  |
| Fluency animals (number) | 23.2 (5.3)       | 19.8 (3.9)   | 18.4 (5.4)   | 12.6 (3.0)  | 11.31***                 |
| Hamilton Depression Rate Scale total (score) | 0.6 (1.2) | 7.1 (4.5) | 3.9 (2.7) | 5.8 (3.4) | 7.66*** |
| Temporal medial atrophy sum score | 1.1 (0.9) | 1.5 (1.6) | 2.5 (1.5) | 3.1 (1.45) | 12.01*** |
| Hippocampal volumea      | 0.51 (0.03)      | 0.46 (0.06)  | 0.445 (0.07) | 0.384 (0.06) | 11.57*** |
| FA values in the FLAIR WMSA (mm3) | 7178 (3274) | 10,930 (13,317) | 12,510 (11,752) | 20,650 (13,677) | 4.08 CN |
| T1 WMSA (mm3)a           | 3578 (2607)      | 7732 (11,591)| 6645 (8475)  | 13,280 (10,757) | 3.38 CN |
| T1 FA not FLAIR (mm3)    | 5382 (1856)      | 6168 (4978)  | 8070 (5263)  | 10,687 (5563) | 4.34 b |
| T1 FLAIR not T1 (mm3)    | 1797 (1293)      | 7734 (11,573)| 5290 (7084)  | 13,284 (10,715) | 5.60 CN |
| T1 Overlap (mm3)         | 1795 (1881)      | 4758 (8807)  | 4439 (7144)  | 9962 (8574)  | 3.73 CN |
| Border zone (mm3)a       | 17,305 (5579)    | 17,391 (11,248)| 22,594 (11,442) | 28,249 (13,418) | 4.24 CN |
| Normal-appearing white matter (mm3)a | 503998 (45,237) | 470551 (63,802) | 481866 (72,204) | 410725 (64,648) | 6.52 b |

Note: Independent t-tests (Bonferroni corrected for multiple comparisons) were used for post hoc group differences for the continuous variables; a standardized 8-point scale was used to indicate educational level (range 1 = primary school to 8 = university).

*p < 0.05; **p < 0.01; ***p < 0.001.

Key: AD, Alzheimer’s disease; aMCI, amnestic mild cognitive impairment; CN, cognitively normal controls; FE, Fisher’s exact test with CN excluded (p value = 0.00027) with CN included; FLAIR, fluid-attenuated inversion recovery; MMSE, Mini Mental State Examination; MCI, mild cognitive impairment; mv, number of missing values; SCD, subjective cognitive decline; WLT, Verbal Learning Test, WMSA, white matter signal abnormalities.

Supplemental Tables 1 and 2 include the diffusion values per group are listed in Supplementary Tables 4a and 4b.

3.2. Diffusion characteristics

3.2.1. Diffusion properties are different across ROIs

The adjusted threshold for significance after correction for multiple comparisons was p < 0.0025. The linear mixed effect analyses across the entire sample showed higher mean FA values in the NAWM compared to the T1, T1notFL, Overlap, FlnotT1, and FLAIR-defined WMSA (p < 0.0005). No significant differences were found in FA values between the Border zone and NAWM (p = 0.61) and between FLAIR and FlnotT1 (p = 0.023). FLAIR-based WMSA FA values were significantly higher than T1-based WMSA FA values (p < 0.0005). The FA values in the Overlap region were lower than the FA values in the FLAIR-defined WMSA and the Border zone (p < 0.0005) but not the T1-defined WMSA (uncorrected p = 0.014). For the MD, AxD, and RD values, the WMSA values were lower than the T1-defined WMSA, Overlap, FLAIR, and the Border zone values (p < 0.0005), and the Overlap lies between diffusion values in the FLAIR- and T1-defined WMSA and different from both (p < 0.0001). Mean MD in FLAIR-defined WMSA was lower compared to T1-defined WMSA, Overlap, and higher than the Border (p < 0.0005) (see Fig. 2 and Table 2 for the FA and MD results; the results for AxD and RD are provided in the Supplemental Tables 1 and 2).

Adding the interaction term “ROI by diagnosis” to the model showed that the FA differences between the NAWM and T1-defined WMSA (T1 and T1notFL), FLAIR-defined WMSA (FLAIR and FlnotT1), or Overlap were larger for CN than for the SCD, MCI, or AD group (p < 0.0005). The difference between the FA of the Border zone and the NAWM and FLAIR compared to FlnotT1 was not different across the 4 groups. Interaction effects with the NAWM as reference region are listed in Table 2, while the interactions with other ROIs as reference region are provided in the Supplemental Data Tables 1 and 2. These interactions revealed effects in the same direction. No group differences were observed for the comparison between FA values in T1-defined WMSA, T1notFL, and the Overlap region. For the MD metric, we observed only a significant interaction effect when comparing the MD values of the NAWM with those of the T1-based WMSA, indicating that the difference in MD values between these 2 regions was larger for CNs than for MCI and AD patients (p < 0.0005 after multiple comparison correction for results see Table 2). The interaction effects for the axial and RD are provided in the Supplemental Data (Table 2 supplemental).

3.3. Predicting clinical diagnosis group based on diffusion values from the different ROIs

As the interaction “ROI by diagnosis” in the previous analyses showed mainly significant associations for the FA values, we performed the multinomial logistic regression models on the FA values to investigate the potential of using FA values to predict diagnosis. These models showed that the FA values in every ROI were able to predict the difference between CN and SCD. A 0.1 unit increase in the FA of the NAWM was associated with 7.27 log odds decrease in
being SCD compared to CN. Interestingly, the FA log odds values of SCD are in similar ranges as the AD patients in the Overlap, NAWM, and Border zone (see Supplemental Table 3). The ability to correctly differentiate CN from the other patients groups was only significant for FA values in the NAWM and the Border zone (see Supplemental Table 3), showing that as the FA value increases with 0.1 unit in the NAWM or the Border zone, the log odds to be MCI compared to control decreased with 3.28 or 2.29, respectively. For the AD group, these log odds are even higher (a decrease of 7.58 vs. 4.55, respectively). These results do not change when using NAWM volume (controlled for ICV) instead of WMSA volume as a covariate (data not shown).

Fig. 3 shows the expected probability of belonging to a specific diagnostic group at certain FA values in each ROI. The plots showed that for NAWM and the Border zone, higher FA values were more strongly associated with the CN group, whereas lower FA values were associated with the AD group. The MCI group showed higher probabilities in the midrange FA values. As the NAWM and the Border zone were able to differentiate all diagnostic groups, we compared the Nagelkerke $R^2$, the $\Delta AICc$, and the evidence ratio to determine the best model. A lower AIC indicates a better model, whereas the $\Delta AICc$ compares the relative merit of each model (Supplemental Table 3). The $\Delta AICc$ of NAWM and Border zone 10.60, between the Border zone and the FLAIR 15.45, between the FLAIR and the T1 11.41, and between the T1 and Overlap 8.97, and T1 not FL versus T1 8.9 indicating a higher likelihood of information loss when comparing to the next best model, whereas between FLnotT1 and FLAIR, the $\Delta AICc$ of 1.6 indicates that the models are relatively equal in merit. The evidence ratio of weighted AICs indicated $4.6 \times 10^5$ times stronger evidence for the NAWM model relative to the FLAIR model and 201.1 times stronger relative to the Border zone.

4. Discussion

In this study, we aimed to investigate differences in microstructural properties of T1- and FLAIR-defined WMSA in a total of 103 participants within the range of cognitively healthy to AD dementia. Previous work suggested that the pathology underlying WMSA may differ in type or severity, depending on the type of MRI contrast that is used to define WMSA (Bitsch et al., 2001; Leritz et al., 2014; Sailer et al., 2001). Our results add important information to the existing literature by showing that first, the diffusion properties underlying T1-defined WMSA are more abnormal than those defined on the FLAIR images, additionally T1notFL voxels are different from general T1 voxels, while FLnotT1 are not different from general FLAIR, suggesting that these 2 MRI contrasts provide different information regarding the underlying pathology. Second, even though most ROIs showed differences in all DTI metrics across the entire group, an interaction effect with diagnosis was only
Table 2
Mixed effects models examining the diffusion metrics between the ROIs across the entire sample

| Fractional anisotropy | Estimate | t-value | p value* |
|-----------------------|----------|---------|----------|
| Effect of ROI         |          |         |          |
| NAWM vs. Border       | 0.005    | -1.41   | <0.158   |
| NAWM vs. FLAIR        | -0.026   | -7.13   | <0.0005* |
| NAWM vs. Overlap      | -0.034   | -9.42   | <0.0005* |
| NAWM vs. FLAIR        | -0.081   | -22.13  | <0.0005* |
| NAWM vs. T1           | -0.071   | -17.30  | <0.0005* |
| NAWM vs. T1notFL      | -0.046   | -12.71  | <0.0005* |
| FLAIR vs. Overlap     | -0.061   | -8.11   | <0.0005* |
| FLAIR vs. T1          | -0.036   | -9.91   | <0.0005* |
| FLAIR vs. T1notFL     | -0.012   | -3.28   | 0.0014   |
| FLAIR vs. flonotT1    | 0.0084   | 2.29    | 0.023    |
| T1 vs. T1notFL        | 0.0243   | 6.63    | <0.0005* |
| T1 vs. flonotT1       | 0.0448   | 12.21   | <0.0005* |
| T1 vs. Border         | -0.076   | 20.755  | <0.0005* |
| Overlap vs. Border    | -0.086   | -22.6   | <0.0005* |
| Overlap vs. flonotT1  | 0.055    | 15.00   | <0.0005* |
| Overlap vs. flonotFL  | 0.034    | 9.43    | <0.0005* |
| Overlap vs. T1        | -0.010   | -2.79   | 0.0062   |

Interaction effect ROI: group

| Mean diffusivity      | Estimate (1e-5) | t-value | p value* |
|-----------------------|-----------------|---------|----------|
| NAWM-T1-CN vs. SCD    | 0.083           | 8.57    | <0.0005* |
| NAWM-FLAIR-CN vs. SCD | 0.042           | 4.38    | <0.0005* |
| NAWM-Border-CN vs. SCD | 0.012         | 1.29    | 0.21     |
| NAWM-Overlap-CN vs. SCD | 0.094          | 7.98    | <0.0005* |
| NAWM-FlonotT1-CN vs. SCD | 0.034      | 3.54    | 0.012    |
| NAWM-Overlap-CN vs. SCD | 0.092          | 9.53    | <0.0005* |
| NAWM-T1-CN vs. MCI    | 0.059           | 6.65    | <0.0005* |
| NAWM-FLAIR-CN vs. MCI | 0.003           | 3.46    | <0.0005* |
| NAWM-Border-CN vs. MCI | 0.009          | 1.06    | 0.289    |
| NAWM-Overlap-CN vs. MCI | 0.067          | 7.46    | <0.0005* |
| NAWM-FlonotT1-CN vs. MCI | 0.024        | 2.72    | 0.14     |
| NAWM-T1notFL-CN vs. MCI | 0.057         | 6.47    | <0.0005* |
| NAWM-T1-CN vs. AD     | 0.095           | 8.64    | <0.0005* |
| NAWM-FLAIR-CN vs. AD  | 0.045           | 4.10    | <0.0005* |
| NAWM-Border-CN vs. AD  | 0.012           | 1.08    | 0.289    |
| NAWM-Overlap-CN vs. AD | 0.108           | 9.82    | <0.0005* |
| NAWM-FlonotT1-CN vs. AD | 0.097         | 3.65    | 0.0068   |
| NAWM-FlonotT1-CN vs. AD | 0.039         | 9.00    | <0.0005* |

Mean diffusivity

| Mean diffusivity      | Estimate (1e-5) | t-value | p value* |
|-----------------------|-----------------|---------|----------|
| NAWM-FLAIR-CN vs. AD  | -1.5            | -3.84   | 0.70     |
| NAWM-Overlap-CN vs. AD | -1.27           | -3.18   | 0.001*   |
| NAWM-T1notFL-CN vs. AD | -4.59           | -10.19  | <0.0005***|
| NAWM-FlonotT1-CN vs. AD | -1.90           | 0.42    | 0.67     |

Note: Mixed effects model using random intercept for each subject. Models were corrected for age (centered at mean), gender (reference was female), education, and intracranial volume (both centered at mean). Threshold of significance after Bonferroni correction for 20 comparisons: *p < 0.0025, **p < 0.0005, ***p < 0.0005.

Key: AD, Alzheimer’s disease; CN, cognitively normal controls; FLAIR, fluid-attenuated inversion recovery; NAWM, normal-appearing white matter; ROI, region of interest; SCD, subjective cognitive decline.

* Kenward-Rogers approximation of p values.

observed in the FA values. This may suggest that the FA metric may be more sensitive to subtle differences in white matter health compared to the MD. Third, diffusion values from the NAWM can predict group adherence of individuals of varying cognitive impairment with higher probabilities than the other white matter ROIs. Even though T1-weighted WMSA were characterized by the most abnormal diffusion values, they also provide the lowest classification accuracy. These results illustrate a need for a better understanding of what the underlying pathology for WMSA may constitute and how it can be detected and defined in various MRI sequences.

WMSA can be defined on both T1- and FLAIR-weighted images, although aging and Alzheimer’s research has mainly focused on FLAIR-weighted WMSA. The considerable heterogeneity in pathology within WMSA and between WMSA and the penumbra of the WMSA areas, suggests that not all WMSA reflect the same degree or type of white matter damage (Gouw et al., 2008, 2011; Maillard et al., 2011, 2014; Viswanathan, 2014). Our study shows that T1 and FLAIR signal abnormalities are highly localized phenomena as most, but not all, T1-defined WMSA are localized within the FLAIR-defined WMSA. While volumes of T1-defined WMSA correlated highly with the FLAIR-defined WMSA, T1 WMSA was characterized by more aberrant diffusion values compared to the FLAIR-defined WMSA. We did not observe a different pattern with regard to the various diffusion metrics across the ROIs for all groups, but rather observed differences in the magnitude of the diffusion values, which may indicate that T1-defined WMSA, reflect more severe rather than different pathology compared to FLAIR-defined WMSA.

Postmortem neuropathology combined with high-field MRI determined that myelin is a dominant source of MRI contrast in T1 maps (Stuber et al., 2014). In addition in MS, T1 lesions are thought to be a combination of permanent demyelination and loss of tissue matrix (Kistler et al., 2016). The reported high correlation of T1- and T2-weighted WMSA volumes in the latter study (r = 0.94) is very similar to those computed from a subsample of the Alzheimer’s Disease Neuroimaging Initiative population (r = 0.96) (Couto et al., 2016) and our findings (r = 0.89) and suggest that even though the volumes are similar, the tissue integrity is more severely affected in T1-defined WMSA compared to the FLAIR ones. It is important to note that the pathology and symptomatology underlying MS is different than that in AD, though neuroinflammatory responses can be a component of this signal, as neuroinflammation also plays an important role in disease progression of AD (Calsolaro and Edison, 2016).

As for FLAIR, a recent series of 134 premortem MRI scans and subsequent autopsy observed that FLAIR sequence-identified WMSA overestimated demyelination in the periventricular and perivascular regions but underestimated it in the deep WM during normal brain aging (Haller et al., 2013). This is possibly due to
Fig. 3. Predicted probability of group adherence as a function of diffusion by group for each region of interest. Note: (top left) the predicted probability of belonging to the CN groups (green) is higher for higher values of fractional anisotropy, while for values in the midrange (0.40) the probability of belonging in the MCI (blue) group is higher. For sub 0.35 values of fractional anisotropy, the probability belonging in the AD (red) group increases sharply. The association of diffusion and all groups is significant for NAWM (top left) and Border zone (top right), but not for FLAIR not T1, FLAIR, T1 not FLAIR, T1 and Overlap where only CN versus SCD (orange) is significantly different (lower 5). Abbreviations: AD, Alzheimer’s disease; CN, cognitively normal controls; FLAIR, fluid-attenuated inversion recovery; MCI, mild cognitive impairment; NAWM, normal-appearing white matter; SCD, subjective cognitive decline; WMSA, white matter signal abnormalities. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
increased blood-brain barrier permeability in the perivascular and periventricular areas leading to a higher high local water concentration. Maillard et al. (2014) reported normalizing FLAIR signal over time in stagnant WMSA, possibly due to a resolving inflammation. FLAIR WMSA could therefore be a mix of white matter damage, peri-inflammatory processes as well as proxies of increased vascular and blood-brain barrier permeability (Young et al., 2008), whereas T1 WMWSA would involve areas with more severe demyelinating damage. It may therefore be speculated that T1 WMWSA, especially outside the FLAIR boundaries, reflect more consolidated WMWSA.

We found that the NAWM is negatively affected in patients; this is consistent with literature (Maillard et al., 2014; Maniega et al., 2013; Topakian et al., 2010). A new intriguing finding is that the difference in FA values between the NAWM and the other ROIs seems to be related to the diagnosis, while there was no such clear association for MD. We did not find overall or group differences between the NAWM and the Border zone. While the Border zone has the highest probability of capturing voxels of the penumbra as they are closest to the WMWSA, the average signal could be influenced by including voxels of the NAWM. The interpretation of the underlying biology is speculative, and care should be taken not to interpret the findings beyond what can reasonably be deducted from the tensor model. Any small nonproportional change in any of the eigenvectors could hypothetically result in a large change in FA especially when the magnitude of the vectors is small. Very early stages of deteriorating cellular health and its resulting minute microstructural changes could possibly introduce a reduction in anisotropy that would be more apparent in the FA but much less so in MD, RD, or AxD. This may explain why the FA values in Overlap and T1 not FLAIR and T1-defined WMWSA are in the same range for all diagnostic groups, including the healthy controls, while showing a clear difference in the distribution of the MD values between healthy controls and patients excluding the T1 not FLAIR group. Possible underlying biological processes can be neurofibrillary loss, glial damage, increased fluid in the extracellular and perivascular space, but more work is needed to better understand the relation between biology and diffusion.

Even though the diffusion values for T1-defined WMWSA were the most aberrant, the diffusion properties of the NAWM show promise as a predictor for diagnostic adherence. The fact that the mean FA in NAWM was a better predictor of group adherence than the mean FA in the Border zone, suggests that more variance can be found in the NAWM that is not adjacent to any WMWSA. These results are not conclusive as the groups are small, and there are confounders that the current data available do not allow us to adequately control for. Despite these limitations, the results of the multinominal logistic regression are consistent with previous studies showing that subtle white matter alterations can occur in the NAWM in clinically healthy older individuals (Firbank et al., 2003; Maillard et al., 2014; Maniega et al., 2015; Vernooij et al., 2009). Our results now show similar findings in a memory-clinic population. Replication in larger populations will be needed to reach more definitive conclusions.

Notably, we included SCD individuals in our sample to have a broad range of individuals and spanning the entire range from healthy aging to AD dementia. Interestingly, the diffusion values of the SCD group in our sample behaved quite similarly as the AD group. Studies including individuals with SCD reported higher volumes of temporal WMWSA, lower hippocampal volume, and more amyloid-β compared to controls (Amariglio et al., 2015; Schultz et al., 2015; Stewart et al., 2008; van der Flier et al., 2004). Inconsistent findings have been reported regarding alterations in the microstructural properties of white matter in SCD individuals. So far, the few studies performed within SCD, observed either local lower FA and higher MD values in medial temporal lobe regions in SCD individuals compared to controls (Ryu et al., 2017; Wang et al., 2012) or no differences between both groups (Kiuchi et al., 2014; Wang et al., 2012). One study reported that DTI was a better predictor for the progression of SCD to AD than cerebral spinal fluid markers (Selnes et al., 2013). These inconsistencies may be related to the criteria used to define SCD (Jessen et al., 2014) or the recruitment strategy (Perrotin et al., 2017). We adopted a broad definition of SCD, allowing everybody entering the outpatient memory clinic presenting with complaints but no objective memory deficits (Cognitive tests within 1.5 SD of mean corrected for age, education, and sex) and no clear medical reason underlying these deficits into the study. Therefore, this group of subjective memory complaints represents a heterogeneous group in terms of the underlying etiology of their complaints. We did not have information on amyloid burden or genetic risk factors in these individuals, but 53% of the MTA scores of the SCD group were 2 or higher, indicative for ongoing neurodegenerative processes, potentially AD related. Furthermore, correcting for the level of depressive symptoms, which was higher in SCD individuals, did not change our results, suggesting that mood was most likely not driving these relationships.

There are some limitations to this study. As this study population was acquired in a clinical setting, the spatial resolution of the FLAIR sequence was based on commonly used clinical parameters. By warping all images to FLAIR resolution, we may have lost some information. Replication of these results using high-resolution isotropic FLAIR sequence could provide more detailed information. Furthermore, the used DTI sequence does not take into account the effects of crossing and kissing fibers, more complex models using multi shell acquisition schemes could be considered for future studies. The results were derived using 2 separate software packages (GIANT and FreeSurfer) to extract FLAIR and T1 WMWSA. Although GIANT is designed to closely interact with FreeSurfer, this could possibly induce a bias. As we did not collect amyloid or tau data on these individuals, we cannot totally rule out that some of our cognitively normal participants are in a preclinical AD stage and cannot fully guarantee that the cognitive impairment in the MCI and AD groups was due to Alzheimer pathology. We also did not incorporate other measures of vascular health, such as blood pressure, cholesterol, or diabetes, as these were not available for all participants. Cardiovascular risk factors have been shown to be linked independently to WMWSA and DTI metrics (Jacobs et al., 2013), and therefore may relate differently to T1- or FLAIR-defined WMWSA. Even though, our results survived stringent multiple comparisons corrections, the sample size is moderate and replication in larger cohorts is needed.

5. Conclusions

The underlying pathology of WMWSA is heterogeneous, and our study showed that different MRI contrasts used to identify WMWSA can provide more information about the underlying WM integrity. T1- and FLAIR-defined WMWSA are microstructurally different, potentially reflecting differences in the type or severity of white matter pathology in individuals with cognitive decline and in healthy older adults. Diffusion values of the NAWM have potential for use as an early and sensitive indicator for brain health decline in AD. Further investigation is warranted, especially in SCD individuals and in larger longitudinal samples.

Disclosure statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.03.029.

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