T1/T2-weighted ratio in multiple sclerosis: A longitudinal study with clinical associations

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ABSTRACT
Background: T1-w/T2-w ratio has been proposed as a clinically feasible MRI biomarker to assess tissue integrity in multiple sclerosis. However, no data is available in the earliest stages of the disease and longitudinal studies analysing clinical associations are scarce.

Objective: To describe longitudinal changes in T1-w/T2-w in patients with clinically isolated syndrome (CIS) and multiple sclerosis, and to investigate their clinical associations.

Methods: T1-w/T2-w images were generated and the mean value obtained in the corresponding lesion, normal-appearing grey (NAGM) and white matter (NAWM) masks. By co-registering baseline to follow-up MRI, evolved lesions were assessed; and by placing the mask of new lesions to the baseline study, the pre-lesional tissue integrity was measured.

Results: We included 171 CIS patients and 22 established multiple sclerosis patients. In CIS, evolved lesions showed significant T1-w/T2-w increases compared to baseline (+7.6%, P < 0.001). T1-w/T2-w values in new lesions were lower than in pre-lesional tissue (-28.2%, P < 0.001), and pre-lesional tissue was already lower than baseline NAWM (-7.8%, P < 0.001). In CIS at baseline, higher NAGM T1-w/T2-w was associated with multiple sclerosis diagnosis, and longitudinal decreases in NAGM and NAWM T1-w/T2-w were associated with disease activity. In established multiple sclerosis, T1-w/T2-w was inversely correlated with clinical disability and disease duration.

Conclusion: A decrease in T1-w/T2-w ratio precedes lesion formation. In CIS, higher T1-w/T2-w was associated with multiple sclerosis diagnosis. In established multiple sclerosis, lower T1-w/T2-w values were associated with clinical disability. The possible differential impact of chronic inflammation, iron deposition and demyelination should be considered to interpret these findings.

1. Introduction

Magnetic resonance imaging (MRI) is the most important paraclinical tool in diagnosing and monitoring multiple sclerosis (MS), and a key surrogate endpoint in clinical trials. However, pathophysiological research has shown that conventional MRI has limited sensitivity to the microstructural changes, both at the lesonal level and the normal-appearing grey (NAGM) and white matter (NAWM) (Filippi et al., 2019). In clinical routine, new T2-weighted (w) lesions and contrast-enhancing lesions are commonly used for monitoring subclinical disease activity and evaluating the effectiveness of pharmaceutical treatments (Wattjes et al., 2015). However, at least at individual level, these sequences have poor correlation with clinical findings. Several novel MRI techniques have been developed to probe MS related cerebral changes in a more specific and quantitative manner. Magnetization transfer imaging, diffusion tensor imaging, and myelin-water imaging have been described as more specific techniques to unravel the diversity of microstructural tissue changes not visible with conventional MRI. Nevertheless, these techniques have limitations, such as longer acquisition times, poor spatial resolution, lack of harmonization or the need for expertise in image post-processing (Enzinger et al., 2015).

The ratio of T1-w and T2-w image intensities (T1-w/T2-w) from...
standard MRI protocols was initially described as a biomarker of cortical myelin content (Glasser and Van Essen, 2011; Glasser et al., 2014; Shams et al., 2019) although further studies have established T1-w/T2-w as a measure of microstructural integrity (Righart et al., 2017; Arshad et al., 2017; Uddin et al., 2019; Pareto et al., 2020). Two works showed the application of the T1-w/T2-w ratio in cortical pathology in MS (Righart et al., 2017; Nakamura et al., 2017). Both studies have demonstrated an association between reduced T1-w/T2-w values and tissue damage. Furthermore, two other studies have found reduced T1-w/T2-w ratios in the NAWM of MS patients compared to healthy controls (Beer et al., 2016; Cooper et al., 2019). Taking it all into consideration, both low myelin content and/or loss of microstructural integrity may explain most of these findings. However, longitudinal studies with clinical associations are scarce and few data is available in the earliest stages of the disease.

In this study, we set out to assess, in patients with clinically isolated syndrome (CIS) and in a cohort of relapsing remitting MS patients treated with disease modifying drugs, baseline and longitudinal changes in T1-w/T2-w ratio in NAGM and NAWM with clinical associations. We also aimed to investigate the dynamics of T1-w/T2-w ratio in focal lesional tissue to gauge the microstructural changes underlying lesion formation and evolution.

2. Subjects/Materials and methods

2.1. Patients and clinical assessments

We analyzed two cohorts described as CIS cohort and MS cohort. First, we assessed previously acquired data from a prospective cohort of patients with CIS (CIS cohort) who underwent brain MRI for diagnosis and for monitoring disease evolution (Tintore et al., 2015). CIS was defined as an episode suggestive of CNS inflammatory demyelination (Donald et al., 2001). At baseline, the demographic data, previous history of neurological abnormalities, the CIS topography, and disability according to the Expanded Disability Status Scale (EDSS) score were recorded. The patients were evaluated on a regular basis (every 3 to 6 months) to assess both the EDSS score and the occurrence of relapses. A lumbar puncture to assess the presence of IgG oligoclonal bands (OB) was performed within the first 3 months of disease onset. Baseline MRI was obtained within the first 3 to 5 months after the onset of symptoms and the second, at 12 months after clinical onset. After excluding alternative diagnosis, all CIS patients were analyzed, regardless of the presence or absence of brain lesions that met criteria for MS at first relapse (e.g. CIS that are already clinically definite MS patients at baseline, and also isolated myelitis or optic neuritis with a normal brain MRI). Fulfillment of McDonald 2017 diagnostic criteria was assessed at baseline (Thompson et al., 2018). From this first cohort, the clinical data used (EDSS and relapses) were analyzed up to 3 years of follow-up. In the second cohort (MS cohort), which consisted of established relapsing remitting MS patients starting on disease-modifying treatment, a baseline brain MRI was acquired at treatment onset, and a follow-up brain MRI 12 months afterwards. In the MS cohort, baseline and 1-year follow-up clinical data was retrospectively collected, including EDSS and MS relapses.

The study was approved by the local ethical committee and a written informed consent was signed by the participating patients.

2.2. MRI acquisition

All patients from the CIS cohort and the MS cohort underwent brain MRI at baseline and follow-up on the same 3 T magnet (Tim Trio; Siemens, Erlangen, Germany) with a 12-channel phased array head coil. The MRI protocol included the following sequences: 1) sagittal T1-w 3D MPRAGE (TR = 2,300 ms, TE = 2.98 ms, TI = 900 ms, voxel size = 1.0 × 1.0 × 1.2 mm³), 2) transverse proton density (PD)- and T2-w fast spinecho (TR = 3,080 ms/TE = 21–91 ms, voxel size = 0.78 × 0.78 × 3.0 mm³), and 3) transverse fast FLAIR (TR = 9,000 ms, TE = 87 ms, TI = 2,500 ms, flip angle = 120°, voxel size = 0.49 × 0.49 × 3.0 mm³).

2.3. MRI qualitative analysis

To define any MRI abnormalities, to fulfill McDonald 2017 diagnostic criteria and to exclude alternative diagnosis, all MRI scans were analyzed by an expert neuroradiologist. This analysis included the number and location of hyperintense lesions on T2-FLAIR scans, the presence of gadolinium-enhancing lesions and the number of new T2-w lesions. A normal brain MRI was defined as displaying no WM abnormalities ≥ 3 mm suggestive of MS (Filippi et al., 2019).

2.4. Processing of the T1-w/T2-w ratio imaging data

T1-w/T2-w images were generated as proposed by Ganzetti et al., (Ganzetti et al., 2014) with the MRTool - Multimodal Mapping extension (v. 1.2, Swiss Federal Institute of Technology, Zurich, Switzerland, http://www.fil.ion.ucl.ac.uk/spm/ext) for Statistical Parametric Mapping (SPM) 12 (University College London, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The processing includes Intensity Non-Uniformity correction and rigid registration of the T2-w images to the T1-w images, with linear calibration of image intensity modes using non-brain tissue masks (eye and temporalis muscle from both the T1-w and T2-w images). The output includes: 1) a normalized, scaled and unbiased T1-w and T1-w/T2-w ratio image, and 2) a normalized unbiased T1-w image, which can be used for tissue segmentation (to allow the evaluation of regional values in T1-w/T2-w in the same space). For an overview of the entire processing pipeline see Fig. 1.

2.5. Brain tissue segmentation and T1-w/T2-w for NAWM and NAGM

Tissue segmentation into GM, WM, and CSF was achieved using the segment tool implemented in SPM12. This procedure was applied to the normalized T1-w image. Lesion masks were subtracted from the WM and GM masks to create NAWM and NAGM masks. Only voxels with a WM or GM probability higher than 0.7 in T1-w were used to define the NAGM and NAWM masks. Mean intensity values on the T1-w/T2-w images were obtained for the NAGM and NAWM masks in each subject. An additional analysis was performed to generate separate masks for deep and cortical GM. Deep GM was segmented with FIRST, (Patenaeud et al., 2011) the corresponding mask was created and removed from the NAGM, generating, as a result, the cortical GM masks.

3. Generation of lesion masks and T1-w/T2-w for lesional tissue

3.1. Baseline, follow-up and evolved lesion masks

Baseline and follow-up WM lesion masks were obtained with the Lesion Segmentation Tool (LST) toolbox version 1.2.3. for SPM12, using T2-FLAIR and T1-w images in all cohorts and the corresponding volumes, calculated. In the CIS cohort and the MS cohort, baseline MRI and lesion mask were co-registered to the follow-up MRI scan to create a mask of the evolved lesional tissue, regardless of their appearance on follow-up scans (see Fig. 2).

3.2. New lesions and pre-lesional tissue masks

In the CIS cohort, new T2-w lesions visually detected by a trained technician on follow-up MRI and were annotated on T2-proton density (PD) images by using the semiautomatic tool included in Jim 5.0 (http://www.xinapse.com/home.php). New lesion masks were later revised and confirmed by an expert neuroradiologist. For technical reasons, new lesion masks were only available for 52 out of 59 patients with new lesions. T2-FLAIR images and masks for new lesions were then co-registered to baseline MRI scans using SPM12 (first to follow-up and then to individual T1-w scans to allow for easy visualization).
baseline MPRAGE images) to create a mask of baseline pre-lesional tissue (see Fig. 2).

3.3. T1-w/T2-w Ratio in lesion masks

Since the normalized T1-w/T2-w image from MRTool and the lesion masks were in the native space and differ topographically across the brain, we added an extra step to analyze the corresponding lesion topography. On one side, the raw T1-w images and their corresponding lesion masks, and, on the other side, the calibrated and unbiased T1-w and T1-w/T2-w images, all were registered to the MNI152 T1-w 1 mm brain template from the Montreal Neurological Institute. Mean intensity values on the T1-w/T2-w images were obtained for all lesion masks. An additional exploratory analysis was performed, assessing separately T1-w and T2-w signal intensity at baseline and follow-up lesion masks to analyze whether the numerator or denominator was the main driver of the changes observed.

3.4. Statistical analysis

Statistical analysis was performed by using IBM SPSS Statistics 26 for Mac (IBM, Armonk, USA). Kolmogorov-Smirnov test was used to assess normality. Unpaired parametric data using unpaired t-test and unpaired non-parametric data using independent-samples Mann-Whitney U test. Paired analyses were compared with paired t-test for parametric data and related samples Wilcoxon signed rank test for non-parametric data. For multigroup comparisons, repeated measures analysis of variance (ANOVA) was performed to compare T1-w/T2-w values between masks and times, followed by Bonferroni multiple comparisons to identify between which masks and times the differences occur.

In the CIS cohort, to evaluate differences between patients with or without suggestive MS diagnosis at CIS onset (abnormal MRI, positive OB and 2017 McDonald criteria fulfillment) and with or without inflammatory disease (new lesions and new relapses) in T1-w/T2-w values, we performed a general linear model with adjustment for age and sex. Bivariate correlations were analyzed with Pearson correlation for parametric data and Spearman’s rank correlation coefficient for non-parametric data. Partial correlations were assessed using covariates of interest (age and sex). A two-tailed \( P < 0.05 \) was considered statistically significant.

4. Data availability

Requests for access to the data reported in this article will be
considered by the corresponding author.

5. Results

5.1. Demographic, clinical and radiological characteristics

A total of 171 CIS patients and 22 treated MS patients were included in the study. All clinical, demographic and MRI data is summarized in Table 1.

5.2. T1-w/T2-w In NAGM, NAWM and lesional tissue

In the entire CIS cohort with valid data at baseline and follow-up (168 patients), no significant longitudinal T1-w/T2-w changes in NAGM (0.96 ± 0.08 vs 0.97 ± 0.08, P = 0.64) and NAWM (1.52 ± 0.16 vs 1.53 ± 0.16, P = 0.69) were observed. In the subgroup of patients with abnormal MRI at baseline (117 patients), T1-w/T2-w in baseline lesional tissue was lower compared to T1-w/T2-w ratio in baseline NAWM (0.85 ± 0.1 vs 1.52 ± 0.15, P < 0.001) and NAGM (0.85 ± 0.1 vs 0.97 ± 0.08, P < 0.001). T1-w/T2-w ratio in evolved lesional tissue was significantly higher (+7.6%) than baseline lesional tissue (0.91 ± 0.15 vs 0.85 ± 0.1, P < 0.001). In the subgroup of patients with new lesions (52 patients), T1-w/T2-w in new lesions tissue was lower than in pre-lesional tissue (-28.2%, 1.02 ± 0.24 vs 1.42 ± 0.24, P < 0.001) (Fig. 3). Interestingly, T1-w/T2-w in pre-lesional tissue was significantly lower than baseline NAWM (-7.8%, 1.42 ± 0.25 vs 1.54 ± 0.18, P < 0.001) (Fig. 3) but higher than baseline lesional tissue (+65.1%, 1.42 ± 0.25 vs 0.86 ± 0.1, P < 0.001) (Fig. 3).

T1-w/T2-w values were higher in deep GM as compared to cortical GM, both at baseline (cortical GM: 0.96 ± 0.08 vs deep GM 0.99 ± 0.09, P < 0.001) and over follow-up (cortical GM: 0.97 ± 0.08 vs deep GM 0.99 ± 0.09, P < 0.001) (Fig. 3).

5.3. T1-w/T2-w And clinical outcomes

In the CIS cohort at baseline, a higher NAGM T1-w/T2-w ratio was observed in patients with an abnormal brain MRI, positive OB and fulfilment of 2017 McDonald criteria. In NAWM, only a trend for a higher T1-w/T2-w was observed in patients fulfilling 2017 McDonald criteria (Table 2). Over follow-up, larger decreases in T1-w/T2-w values in both NAGM and NAWM were observed in patients fulfilling 2017 McDonald criteria, presence of OB, and an abnormal brain MRI at baseline, although these differences did not reach statistical significance.
significance. Patients presenting disease activity during the follow-up (new T2-w lesions at 12 months MRI, new relapses one and three years after CIS) showed a decrease in T1-w/T2-w values in NAGM and NAWM, while in stable patients an increase in T1-w/T2-w values was observed (Table 2). For cortical and deep GM, these same associations are demonstrated in Supplementary Table 1. Longitudinal changes in T1-w/T2-w values in lesional tissue were not associated with clinical activity during the follow-up (data not shown). After age and sex adjustment, no significant correlations were observed between baseline EDSS and baseline T1-w/T2-w values in NAGM and NAWM (r = 0.015, P = 0.87), NAWM (r = 0.032, P = 0.74) or baseline lesional tissue (r = 0.094, P = 0.32).

In the MS cohort, after adjusting for age and sex, disease duration and baseline EDSS were inversely correlated with baseline T1-w/T2-w in NAGM (disease duration: r = -0.557, P = 0.031; and; baseline EDSS: r = -0.505, P = 0.044) and NAWM (disease duration: r = -0.522, P = 0.046; baseline EDSS: r = -0.517, P = 0.049).

Partial correlations between T1-w/T2-w at the different compartments and clinical variables (EDSS, disease duration and lesion volume) are presented as supplementary data (Supplementary Table 2), for both cohorts and time-points.

6. Discussion

In this study, we investigated changes in T1-w/T2-w within NAGM, NAWM, and focal lesional tissue in CIS and MS patients. To the best of our knowledge, this is the first study to investigate longitudinal associations with clinical outcomes concerning T1-w/T2-w at all tissue levels. In CIS patients, we found that T1-w/T2-w changes occurring in lesions seem to indicate tissue damage and recovery and that alterations in T1-w/T2-w precede lesion formation. In NAGM and NAWM, discordant associations have been found in the CIS cohort: higher baseline T1-w/T2-w values were associated with a diagnosis of MS but, in contrast, longitudinal decreases were associated with worse outcomes. In established MS, lower T1-w/T2-w ratio in NAGM and NAWM was associated with longer disease duration and higher EDSS and remained unchanged after one year of therapy.

![Fig. 3. T1-w/T2-w mean values in different tissues and time points in the CIS cohort. Multigroup comparisons with repeated measures analysis of variance (ANOVA), followed by Bonferroni multiple comparisons. All masks in this graph showed a statistically significant difference among them (P < 0.001). NAWM = normal-appearing white matter.](image-url)
These results suggest that changes in NAWM of patients with MS occur before lesions become evident on conventional MRI scans. Comparable findings have been identified in previous studies with other methods, such as MRI frequency shifts using susceptibility-weighted imaging (Wiggermann et al., 2013); magnetization transfer ratio (MTR) (Filippi et al., 1998; Goodkin et al., 1998; Pike et al., 2000) and proton MR spectroscopy (Tartaglia et al., 2002).

We have found unexpected associations in NAGM and NAWM in CIS patients: higher baseline T1-w/T2-w values were associated with a diagnosis of MS but, conversely, longitudinal decreases were associated with concurrent disease activity. Hypercellular content state could justify the unexpected higher T1/T2 ratio (Blystad et al., 2016; Thaler et al., 2017) in pathological CIS patients, decreasing with inflammation resolution. These findings also show the low specificity of this marker. Two studies (Richart et al., 2017; Nakamura et al., 2017) demonstrated correlations between reduced values and tissue damage, although in different topographies and pathological substrates: in demyelinated cortex correlating with myelin density, and in cortical NAGM correlating with dendrite density. Still on histological validation at the cortical level, despite a good sensitivity to detect cortical demyelination, a modest T1-w/T2-w ratio specificity was demonstrated in a recent work (Zheng et al., 2022). In addition to the cerebral cortex, in two other studies focusing on different subcortical regions, (Arshad et al., 2017; Uddin et al., 2019) T1-w/T2-w ratio has been suggested as a general measure of microstructure, which may be more affected by axonal diameter/density than myelin density. These studies used myelin water fraction (MWF) as a validated measure of myelin density, (Laule et al., 2006) showing low concordance between T1-w/T2-w and MWF measurements in cerebral WM and subcortical GM structures. On this basis, these works have suggested that T1-w/T2-w and MWFs appear to be sensitized to different subcortical microstructural properties. Recently, (Pareto et al., 2020) our group demonstrated moderate correlation between MTR and T1-w/T2-w in NAGM, and strong correlation in NAWM and lesions. This study suggests again that, besides myelin integrity, other factors may be playing a role in T1-w/T2-w measures.

More recently, three different articles also showed higher T1-w/T2-w values in different CNS regions in other disorders: Parkinson disease (Du et al., 2019), Huntington disease (Rowley et al., 2018) and in Alzheimer’s patients (Pelkmans et al., 2019). Such differences clearly suggest that T1-w/T2-w is not just measuring myelin, and that other factors such as iron content, microglia activation and amyloid deposition may be playing a role. Certainly, in MS and very early CIS patients, other processes such as edema resolution, inflammation, iron uptake and removal, and axonal/dendrite diameter and density may influence these values.

In the MS cohort, T1-w/T2-w values were inversely correlated with disease duration and EDSS. Previous non-longitudinal studies showed different results concerning clinical associations between T1-w/T2-w and EDSS. In line with our results, T1-w/T2-w values in NAWM were inversely correlated with EDSS in a study of 244 MS patients (Beer et al., 2016). In contrast, another work did not show any significant associations between T1-w/T2-w and EDSS, although the sample size was much smaller (26 patients) (Granberg et al., 2017, 2018). A recent longitudinal work (Cooper et al., 2021) in CIS and early MS patients showed that T1-w/T2-w in NAWM is associated with increasing lesion volume and disease activity in the first 2 years of disease after first clinical presentation.

Concerning T1-w/T2-w values in cortical and deep GM, ferritin iron has a strong effect on decreasing T2-w signal, but only a weak effect on increasing T1-w signal, (Vymazal et al., 1995) leading to an slight increase in T1-w/T2-w. This could explain the higher T1-w/T2-w in deep GM compared to cortical GM, as the basal ganglia have been shown to accumulate iron.

Compared to previous studies, we could highlight some positive aspects of ours, namely the first complete T1-w/T2-w brain tissue analysis of a large CIS cohort with prospective clinical and radiological evaluation. Concerning our methodology, some limitations should be noted. We did not include healthy controls for comparison. Although T1-w/T2-w has usually been applied to high resolution 3D T1-w and 3D T2-w sequences, we used 2D T2-w sequences with 3 mm slice thickness, which may have introduced a partial volume effect in our T1-w/T2-w. Cerebral atrophy may also influence tissue segmentation, inducing partial volume effects. However, the short duration of disease in the CIS cohort could mitigate this effect, due to minor atrophy observed in this phase. Another limitation is the lack of B1 - residual correction of the T1-w/T2-w maps, something that is not yet widely available, but means that it might be wise to regress measures of head size (i.e. all head tissues, not just brain size in the subject’s own physical space) and body mass index (BMI) out of any statistical analyses as covariates of no interest. We have considered age and sex. But it would be very interesting to investigate the role of BMI in future studies. An additional assessment that might be included is the cortical lesional tissue, using MRI sequences as double inversion recovery and phase sensitive inversion recovery, to evaluate T1-w/T2-w in cortical lesion GM. Nevertheless, the total cortical lesion volume is much lower than the total volume of cortical NAGM, thus we may not expect a change in the mean value.

In conclusion, no longitudinal changes in T1-w/T2-w values in NAGM and NAWM were observed over 1 year in both cohorts. In CIS patients, T1-w/T2-w changes occurring in lesional tissue seem to indicate tissue damage and recovery with alterations in T1-w/T2-w ratio predating lesion formation. This finding can be adressed in future studies, with potential clinical applications in predicting the appearance of new lesions. In NAWM and NAGM, higher baseline T1-w/T2-w values in CIS patients were associated with baseline MS diagnosis, whereas longitudinal decreases in T1w/T2w ratio were associated with concurrent disease activity. In established MS, lower T1-w/T2-w was associated with worse clinical outcomes and disease duration. The differential impact of chronic inflammation, iron deposition and demyelination should be considered to interpret all these findings. Future research should take confounding effects such as iron and inflammation into account, through multimodal MRI acquisitions and post-mortem studies, to quantify T1-w/T2-w in healthy and pathological tissue.

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J. Sastre-Garriga: over the last 12 months, J. Sastre-Garriga has engaged in consulting and/or participating as speaker/chair in events organized by Merck, Bayer, Celgene, Sanofi and Biogen, is director of Revista de Neurología and editor for controversies of the Multiple Sclerosis Journal.

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A. Ravira serves on scientific advisory boards for Novartis, Sanofi-Genzyme, Icometrix, SyntheticMR, Bayer, Biogen and OLEA Medical, and has received speaker honoraria from Bayer, Sanofi-Genzyme, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche and Biogen.

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Howell, O.W., Rundle, J.L., Garg, A., Komada, M., Brophy, P.J., Reynolds, R., 2010. A prospective study of MRI markers of neuroaxonal pathology in early multiple sclerosis. Brain 133 (7), 1874–1887. https://doi.org/10.1093/brain/awp111.

Barkhof, F., Broch, W., de Groot, C.J.A., Bergers, E., Hulshof, S., Geurts, J., Polman, C.H., van der Valk, P., 2003. Remyelinated lesions in multiple sclerosis. Arch. Neurol. 60 (3), 369–373. https://doi.org/10.1001/archneur.60.3.369.

McDonald, W.I., Compston, A., Edan, G., Goodkin, D., Hartung, H.P., Lublin, F.D., et al., 2015. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—establishing disease progression and monitoring patients. Nat. Rev. Neurol. 11, 597–606.

Enzinger, C., Barkhof, F., Ciccarelli, O., Filippi, M., Kappos, L., Rocca, M.A., Ropele, S., Rovira, A., Schneider, T., de Stefano, N., Verroken, H., Wheeler-Kingshott, C., Wuerfel, J., Fazekas, F., 2015. Nonconventional MRI and microstructural cerebral changes in multiple sclerosis. Nat. Rev. Neurol. 11 (12), 676–686.

Glasser, M.F., Van Essen, D.C., 2011. Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MR. J. Neurosci. 31 (32), 11597–11616.

Glasser, M.F., Goyal, M.S., Preus, T.M., Raichle, M.E., Van Essen, D.C., 2014. Trends and properties of human cerebral cortex: Correlations with cortical myelin content. Neuroimage 93, 165–175.

Shams, Z., Norris, D.G., Marques, J.P., Lundberg, P., 2019. A comparison of in vivo MRI based cortical myelin mapping using T1w/T2w and R1 mapping at 3T. PloS One 14 (7), e0218099. https://doi.org/10.1371/journal.pone.0218099.

Righart, R., Biberacher, V., Jonkman, I.E., Elsner, S., Schmidt, P., Buck, D., Berthele, A., Kirschke, J.S., Zimmer, C., Hemmer, B., Jeuille, J.G., Mühlau, M., 2017. Cortical pathology in multiple sclerosis detected by the T1/T2-weighted ratio from routine magnetic resonance imaging. Ann. Neurol. 82 (4), 519–529.

Arshad, M., Stanley, J.A., Raz, N., 2017. Test-retest reliability and concurrent validity of in vivo myelin content indices: Myelin water fraction and calibrated T 1 w/T 2 w image ratio. Hum. Brain Mapp. 38 (4), 1780–1790.

Uddin, M.N., Figley, T.D., Solar, K.G., Shati, A.S., Figley, C.R., 2019. Comparisons between multi-component myelin water fraction, T1w/T2w ratio, and diffusion tensor imaging measures in healthy human brain structures. Sci. Rep. 9 (1) https://doi.org/10.1038/s41598-019-43199-x.

Pareto, D., García-Vidal, A., Martín, M., Auquier, C., Montalban, X., Tintore, M., Sastre-Garriga, J., Ravira, J., 2020. Ratio of T1-weighted to T2-weighted signal intensity as a measure of tissue integrity: comparison with magnetization transfer ratio in patients with multiple sclerosis. Am. J. Neuroradiol. 41 (3), 461–463.

Nakamura, K., Chen, J.T., Oonoda, D., Fox, R.J., Trapp, B.D., 2017. T1/T2-weighted ratio differs in demyelinated cortex in multiple sclerosis. Ann. Neurol. 82 (4), 635–639.

Beer, A., Biberacher, V., Schmidt, P., Righart, R., Buck, D., Berthele, A., Kirschke, J., Zineh, C., Hemmer, B., Mühlau, M., 2016. Tissue damage within normal appearing white matter in early multiple sclerosis: assessment by the ratio of T1- and T2-weighted MR image intensity. J. Neurol. 263 (8), 1495–1502.

Cooper G, Finke C, Chien C et al. Standardization of T1w/T2w Ratio Improves Detection of Tissue Damage in Multiple Sclerosis. Front Neurol. 10, Epub ahead of print 9 April 2019. DOI: 10.3389/fneur.2019.00334.

Tintore, M., Ravira, A., Río, J., Otero-Romo, S., Arrambide, G., Tur, C., Comabella, M., Nos, C., Aretxaga, M.L., Negroto, L., Galán, L., Vidal-Jordana, A., Castiijllo, J., Palavra, F., Simon, E., Mitjana, R., Auquier, C., Sastre-Garriga, J., Montalban, X., 2015. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 138 (7), 1863–1874.

McDonald, W.L., Compton, A., Edan, G., Goodkin, D., Hartung, H.P., Lublin, F.D., McFarland, H.F., Pady, D.W., Polman, C.H., Reingold, S.C., Sandberg-Wollheim, M., Sibley, W., Thompson A., Van Den Noort, S., Weiskenherz, B.Y., Wolinsky, J.S., 2001. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. Neurol. Ann. 50 (1), 121–127.

Thompson A.J., Banwell, B.L., Barkhof, F., Carroll, W.W., Coetzee, T., Cor, M., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., Fujihara, K., Galeta, S.L., Hartung, H.P., Kappos, L., Lublin, F.D., Marrie, R.A., Miller, A.E., Mill, D.H., Montalban, X., Mowry, E.M., Sorensen, P.S., Tintore, M., Traboulsee, A.L., Trojano, M., Uitdehaag, B.M.J., Vukusic, S., Waubant, E., Weiskenherz, B.G., Reingold, S.C., Cohen, J.A., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.

Filippi, M., Preziosi P, Banwell Bl, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain 2019; 142: 1885–1875.

Ganzetti M, Wenderoth N, Mantini D. Whole brain myelin mapping using T1- and T2-weighted MRI imaging data. Front Hum Neurosci. 8. Epub ahead of print 2 September 2014. DOI: 10.3389/fnhum.2014.00671.

Patenauade, B., Smith, S.M., Kennedy, D.J., Jenkinson, M., 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56 (3), 907–922.

Bitch, A., Kuhlmann, T., Stadelmann, C., Lassmann, H., Lucchinetti, C., Brück, W., 2001. A longitudinal MRI study of histopathologically defined hypointense multiple sclerosis lesion. Ann. Neurol. 49 (6), 793–796.

Barkhof, F., Bruck, W., de Groot, C.J.A., Bergers, E., Hulshof, S., Geurts, J., Polman, C.H., van der Valk, P., 2003. Remyelinated lesions in multiple sclerosis. Arch. Neurol. 60 (8), 1073. https://doi.org/10.1001/archneur.60.8.1073.

Laule, C., Leung, E., Li, D.R., Traboulsee, A.L., Pady, D.W., Mackay, A.L., Moore, G.R.W., 2006. Myelin water imaging in multiple sclerosis: quantitative correlations with histopathology. Mult. Scler. J. 12 (6), 747–753.

Kutzelnigg A, Lucchinetti CF, Stadelmann C et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 2005; 128: 2705–2712.

Howell, D.W., Rundle, J.L., Garg, A., Komada, M., Brophy, P.J., Reynolds, R., 2010. Activated microglia mediate axonal disruption that contributes to axonal injury in multiple sclerosis. J. Neuropathol. Exp. Neurol. 69 (10), 1017–1033.

Granberg T, Fan Q, Trebash CA, et al. In vivo characterization of cortical and white matter pathological changes in multiple sclerosis. Brain 2017; 140: 2912–2926.
Lucchinetti C, Brck W, Parisi J, et al. Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. Ann Neurol 2000; 47: 707–717.

Thaler, C., Faizy, T.D., Kumar, D., Sedlack, J., Broocks, G., Groser, M., Stellmann, J.-P., Heesen, C., Fiehler, J., Siemonsen, S., Cercignani, M., 2016. Heterogeneity of multiple sclerosis lesions in multislice myelin water imaging. PLoS One 11 (3), e0151496. https://doi.org/10.1371/journal.pone.0151496.

Goldschmidt, T., Antel, J., König, P.K., Bruck, W., Kublmann, T., 2009. Remyelination capacity of the MS brain decreases with disease chronicity. Neurology 72 (22), 1914–1921.

Wiggermann, V., Hernandez Torres, E., Varasou, I.M., Moore, G.R.W., Laule, C., Mackay, A.L., Li, D.K.B., Traboulsee, A., Rauscher, A., 2013. Magnetic resonance frequency shifts during acute MS lesion formation. Neurology 81 (3), 211–218.

Filippi, M., Rocca, M.A., Martin, G., Horsfield, M.A., Comi, G., 1998. Magnetization transfer changes in the normal appearing white matter precede the appearance of enhancing lesions in patients with multiple sclerosis. Ann. Neurol. 43 (6), 809–814.

Goodkin, D.E., Rooney, W.D., Sloan, R., Bacchetti, P., Gee, L., Vermathen, M., Waubant, E., Abundo, M., Majumdar, S., Nelson, S., Weiner, M.W., 1998. A serial study of new MS lesions and the white matter from which they arise. Neurology 51 (6), 1689–1697.

Pike, G.B., De Stefano, N., Narayanan, S., Worsley, K.J., Pelletier, D., Francis, G.S., Antel, J.P., Arnold, D.L., 2000. Multiple sclerosis: magnetization transfer MR imaging of white matter before lesion appearance on T2-weighted images. Radiology 215 (3), 824–830.

Tartaglia, M.C., Narayanan, S., De Stefano, N., Arnaoutelis, R., Antel, S.B., Francis, S.J., Santos, A.C., Lapierre, Y., Arnold, D.L., 2002. Choline is increased in pre-lesional normal appearing white matter in multiple sclerosis. J. Neurol. 249 (10), 1382-1390.