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ORIGINAL ARTICLE

Quantitative texture analysis of brain white matter lesions derived from T2-weighted MR images in MS patients with clinically isolated syndrome

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KEYWORDS
MRI;
Multiple sclerosis;
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Summary
Introduction: This study investigates the application of texture analysis methods on brain T2-white matter lesions detected with magnetic resonance imaging (MRI) for the prognosis of future disability in subjects diagnosed with clinical isolated syndrome (CIS) of multiple sclerosis (MS).
Methods: Brain lesions and normal appearing white matter (NAWM) from 38 symptomatic untreated subjects diagnosed with CIS as well as normal white matter (NWM) from 20 healthy volunteers, were manually segmented, by an experienced MS neurologist, on transverse T2-weighted images obtained from serial brain MR imaging scans (0 and 6—12 months). Additional clinical information in the form of the Expanded Disability Status Scale (EDSS), a scale from 0 to 10, which provides a way of quantifying disability in MS and monitoring the changes over time in the level of disability, were also provided. Shape and most importantly different texture features including GLCM and laws were then extracted for all above regions, after image intensity normalization.
Results: The findings showed that: (i) there were significant differences for the texture futures extracted between the NAWM and lesions at 0 month and between NAWM and lesions at 6—12 months. However, no significant differences were found for all texture features extracted when comparing lesions temporally at 0 and 6—12 months with the exception of contrast (gray level difference statistics-GLDS) and difference entropy (spatial gray level dependence matrix-SGLDM); (ii) significant differences were found between NWM and NAWM for most of the texture features investigated in this study; (iii) there were significant differences found for the lesion

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texture features at 0 month for those with EDSS $\leq$ 2 versus those with EDSS > 2 (mean, median, inverse difference moment and sum average) and for the lesion texture features at 6—12 months with EDSS > 2 and EDSS $\leq$ 2 for the texture features (mean, median, entropy and sum average). It should be noted that whilst there were no differences in entropy at time 0 between the two groups, significant change was observed at 6—12 months, relating the corresponding features to the follow-up and disability (EDSS) progression. For the NAWM, significant differences were found between 0 month and 6—12 months with EDSS $\leq$ 2 (contrast, inverse difference moment), for 6—12 months for EDSS > 2 and 0 month with EDSS > 2 (difference entropy) and for 6—12 months for EDSS > 2 and EDSS $\leq$ 2 (sum average); (iv) there was no significant difference for NAWM and the lesion texture features (for both 0 and 6—12 months) for subjects with no change in EDSS score versus subjects with increased EDSS score from 2 to 5 years.

Conclusions: The findings of this study provide evidence that texture features of T2 MRI brain white matter lesions may have an additional potential role in the clinical evaluation of MRI images in MS and perhaps may provide some prognostic evidence in relation to future disability of patients. However, a larger scale study is needed to establish the application in clinical practice and for computing shape and texture features that may provide information for better and earlier differentiation between normal brain tissue and MS lesions.

Introduction

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system, with complex pathophysiology, including inflammation, demyelination, axonal degeneration, and neuronal loss. Within individuals, the clinical manifestations are unpredictable, particularly with regard to the development of disability [1,2]. Diagnostic evaluation of MS can be very difficult and is thus performed by a neurologist specialized in treating MS. The MS evaluation is generally based on conventional magnetic resonance imaging (MRI), following the McDonald criteria [3,4]. It is furthermore based on clinical signs and symptoms. The development of modern imaging techniques for the early detection of brain inflammation and the characterization of tissue-specific injury is an important objective in MS research. A better understanding of disease pathogenesis can also form the basis for the further development of new and more effective therapies. Recent MRI studies have shown that brain and focal lesion volume measures as well as magnetization transfer ratio and diffusion weighted imaging-derived parameters can provide new information in diagnosing MS [5,6]. Texture feature analysis can provide information regarding the underlying tonal and structural properties of image regions. It can be used to analyze macroscopic lesions and other macroscopic changes in the MS brains that go beyond the conventional measures of lesion volume and number [1]. These lesions might usually be undetectable using conventional measures of lesion volume and number [1,6]. Texture feature analysis is also used widely in neuro MRI to enable disease characterization and quantification. Therefore, texture features may provide needed information for disease evaluation.

Several studies have documented that texture features can be used in the assessment of MS lesions for:

- differentiating between lesions for normal white matter (NWM) and normal appearing white matter (NAWM);
- monitoring the progression of the disease over longitudinal scans [6—17], and this paper aims to provide additional information to support these.

MRI-based texture analysis was shown to be effective in classifying MS lesions from NWM and NAWM, with an accuracy of 96—100% [7]. In [10], texture features were used for differentiating between normal and abnormal tissue, and for image segmentation, while differences in texture between normal and diseased spinal cord in MS subjects were found in [13]. Active and non-active lesions were differentiated in [14], whereas in [15], texture analysis was used to discriminate between MS lesions, NAWM and NWM from healthy controls. In [18], hemispherical differences for MS were found with texture analysis, while in [19], correlation between texture features of T2-weighted MRI images and histological changes of postmortem MS brains were investigated.

The primary objective of this study was to investigate the use of texture features analysis to detect significant differences between NWM, NAWM, and lesions as well as to achieve better discrimination between the different tissues. Significant differences between NWM and NAWM may be critical to the early diagnosis of the disease, whilst better tissue discrimination may be valuable as a prognostic factor in the assessment of the natural evolution of the disease. Since some form of quantitative MRI analysis is used in MS clinical trials, we hypothesise that there is a close relationship between the change in the extracted features, the clinical status and the rate of development of disability. The patient's images acquired at the initial stages of the disease (0 month) as well as after 6—12 months (6—12 months), are analyzed and the corresponding texture feature findings are correlated with disability assessments for ground truth, interrelating the Expanded Disability Status Scale (EDSS) scores [20], with standard shape intensity and texture features. EDSS is a scale from 0 to 10, which provides a way of quantifying disability in MS and monitoring the changes over time in the level of disability.

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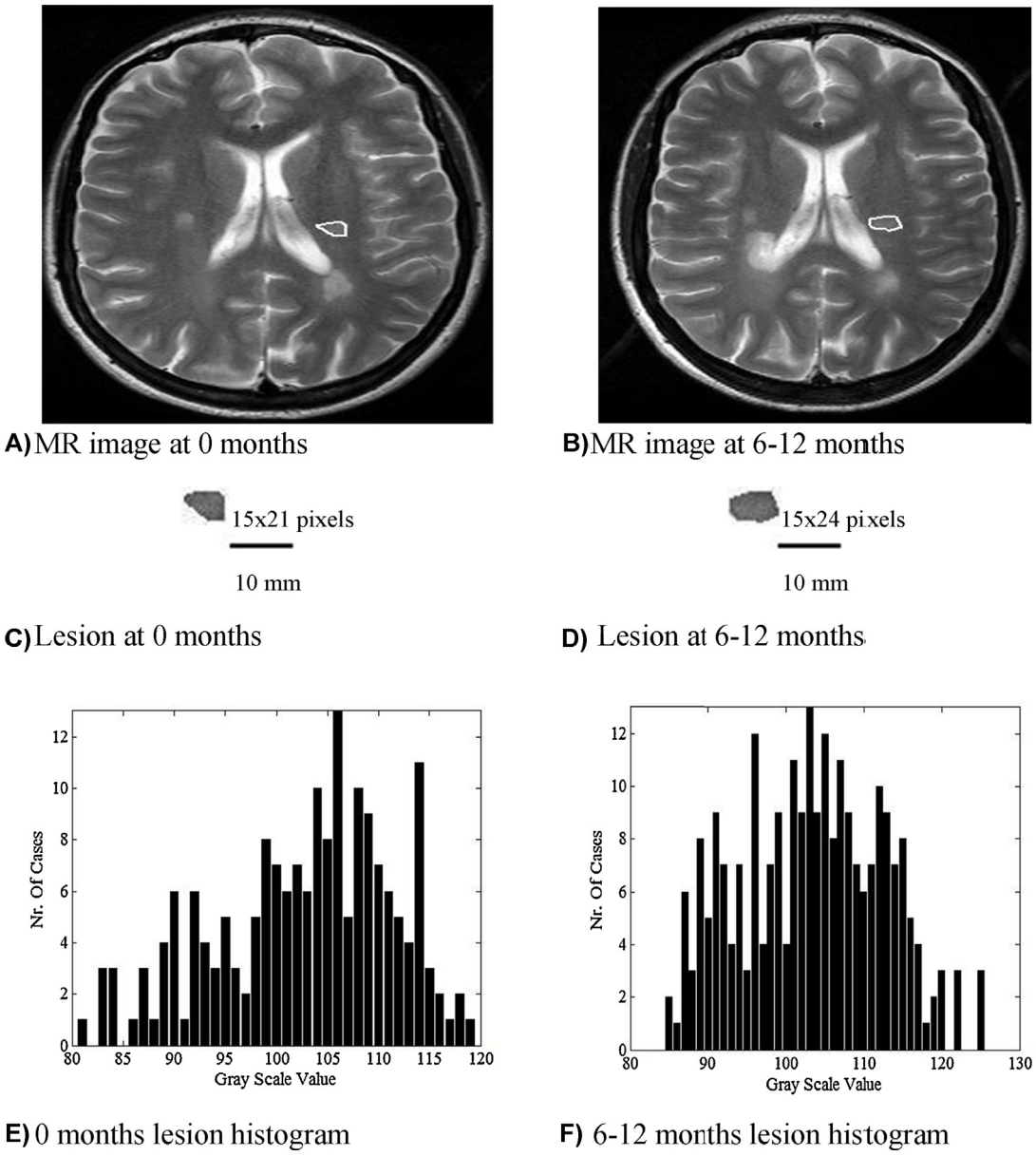

Figure 1 A. ROIs drawn on MR images of the brain obtained from a 32-year-old female MS patient with an EDSS = 3 (measured in two years after initial examination) at A: 0 and B: 6—12 months. C and D. Magnified segmented lesions from A and B that are acquired at a pixel resolution of 2.226 pixels per mm. The bar below the lesions shows the size of 10 mm. E and F. Histograms of the ROIs, for the texture feature mean, at 0 and 6—12 months respectively. The image intensity median and inter-quartile range (IQR) of the segmented lesions at 0 and 6—12 months were 108 and 9.6 vs. 99 and 11.8 respectively.

Preliminary findings of this study, for the texture analysis of NAWM in MS subjects, were also published in [16,17]. It should be noted that the same problem was also investigated in a recent study published by our group using multi-scale Amplitude Modulation-Frequency Modulation (AM-FM) analysis [17]. The motivation of this study was to investigate the usefulness of classical texture analysis, which is more comprehensive and easily understood by the clinicians.

Materials and methods

Texture feature analysis can be used to identify different tissues and changes thereof — this can be seen at the example presented in Fig. 1. Fig. 1 shows two transaxial T2-weighted MR images at the same level of the brain acquired from the same female patient at the age of 32, with an EDSS [20] equal to 3. The image in Fig. 1A corresponds to the initial diagnosis of a CIS. A second MR scan acquired within the time framework of 6—12 months later is shown in Fig. 1B. The two delineated ROIs corresponding to the same MS plaque are also depicted. Fig. 1C shows the magnified segmented lesions from Fig. 1A and B (original images were acquired at a sampling rate of 2.226 pixels per mm). To maintain physical perspective, the bar below the lesions shows the corresponding physical size of 10 mm. Fig. 1D and F show the lesions histograms for the texture feature mean, at 0 and

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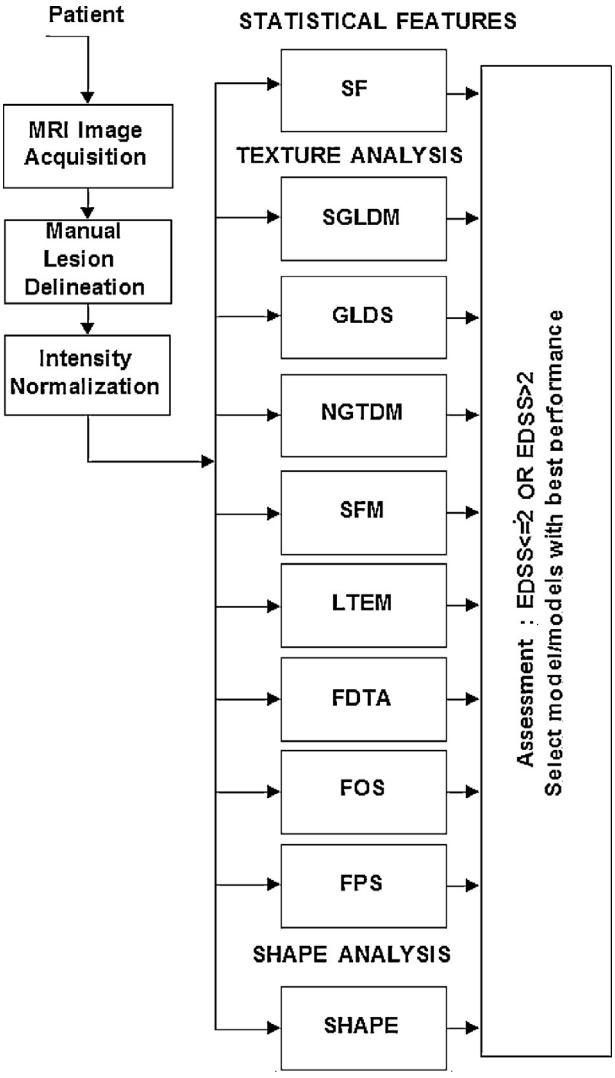

Figure 2 MRI image analysis system diagram. MRI: magnetic resonance imaging; SF: statistical features; SGLDM: spatial gray dependence matrix; GLDS: gray level dependence matrix; NGTDM: neighborhood gray tone difference matrix; SFM: statistical feature matrix; LTEM: laws texture energy; FDTA: fractal dimension texture analysis; FPS: Fourier power spectrum; shape: shape parameters; EDSS: expanded disability status scale.

6—12 months respectively. The median and inter-quartile range (IQR) for the mean intensity of the lesions at 0 and 6—12 months were 108 and 9.6 vs. 99 and 11.8 respectively. In what follows, texture analysis refers to the image processing of the extracted ROIs.

The system diagram presented in Fig. 2 illustrates the process followed in the MRI lesion analysis. The different steps for texture analysis of the extracted ROIs are analyzed herein below.

Study group and MRI acquisition

Thirty-eight subjects (17 males, and 21 females), aged 34.1 ± 10.5 (mean age ± standard deviation) with a suggestive CIS and MRI-detectable brain lesions were scanned twice at 1.5 T MRI in an interval of 6—12 months. The transverse MR images used for analysis were obtained using a T2-weighted turbo spin echo pulse sequence (repetition time = 4408 ms, echo time = 100 ms, echo spacing = 10.8 ms). The reconstructed image had a slice thickness of 5 mm and a field of view of 230 mm with a pixel resolution of 2.226 pixels per mm. Standardized planning procedures were applied during each MRI examination. The MR images were acquired using a 1.5T whole body Philips ACS NT MR imager (Philips Medical Systems, Best, the Netherlands). A built-in quadrature radiofrequency (RF) body coil and a quadrature RF head coil were used for proton excitation and signal detection respectively. It is noted that CIS is a single episode of neurological symptoms that need treatment with various outcomes depending on the severity of symptoms and the residual symptoms after treatment. The repeat MRI scans at 6—12 months were not related to determining the outcome of the CIS but rather to depicting new T2 lesions which are correlated with increased probability of transformation of CIS to clinically definite MS. The mean time difference between the first and the second MRI exam was about 8.5 months, a time period adequate for the depiction of new MRI-visible lesions.

Initial clinical evaluation was made by an experienced MS neurologist (co-author, M. Pantziaris) who referred the 38 subjects for a baseline MRI upon diagnosis (time 0) and clinically followed all subjects for over five years. At the initial scan, the stage of the disease was evaluated using the EDSS score [20]. All subjects were also given an EDSS test two years after initial diagnosis to quantify disability and then again in five years. This gave starting EDSS scores with a mean of 2.2 and a standard deviation of 0.9. The number of subjects with EDSS $\leq$ 2, and EDSS > 2, two years after the first examination were 23 and 15 respectively. In five years time, the EDSS score gave a mean value of 2.85 and a standard deviation of 1.5. The number of subjects with EDSS $\leq$ 2, and EDSS > 2, five years after the first examination were 15 and 23 respectively. An EDSS score of 2.0 was selected as a cut-off point because above this point neurological signs demonstrate the onset of accumulating disability. As a result, any patient having an EDSS score below 2.0 two or five years after the initial MRI scan can be regarded as having a rather benign course of the disease. It is noted that EDSS at baseline (time 0) was not used since our study focuses on texture analysis of T2 brain MR images and future disability progression, as measured at 2 and 5 years after the initial (time 0) MRI scan. It is also known that the initial (presenting) EDSS is not strongly associated with future disability. Furthermore, to the best of our knowledge, there are few studies that correlate lesion texture to neuropathology/histology sections [6—11], but EDSS is the only instrument evaluating the clinical impact of lesion features (number, texture, etc.).

Additionally, brain imaging from 20 healthy, age-matched (mean ± SD: 30.8 ± 7.6) volunteers (8 males, and 12 females) were carried out to allow segmentation and analysis of brain NWM. The subjects were referred for the MRI scans to Ayios Therissos Medical Diagnostic Center (co-author, I. Seimenis), at the same time period as the patients.

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Inter-scan intensity normalization

In a recent study [21], where six different inter-scan normalization techniques for MRI were compared, it was shown that a normalization method based on histogram normalization proposed in [22], in which the original histogram of the whole image is stretched and shifted in order to cover a wider dynamic range, yields better results than the other methods tested. The original image histogram was stretched, and shifted using [21,22] in order to cover all the gray scale levels in the image as follows:

$$f(x,y) = \frac{g_{GWM} - g_{BWM}}{g_{\max} - g_{\min}}.(g(x,y) - g_{\min}) + g_{BWM} \quad (1)$$

where $g(x,y)$ denotes the original image gray scale value at x and y, and $g_{\max}$ and $g_{\min}$ represents the maximum and the minimum gray scale values in the original image respectively. The g_{BWM}, represents the manual selection of the black-white matter (which is the darkest image area in the original image) and g_{GWM} represents the gray-white matter (which is the brightest image area in the image which is the brain) selected from slices of the whole MRI, as described in the following section. The output image is represented with $f(x,y)$.

Manual delineations and visual perception

All MRI-detectable brain lesions were identified and segmented by an experienced MS neurologist and confirmed by a radiologist. Only well-defined areas of hyperintensity on T2-weighted MR images were considered as MS plaques. The neurologist manually delineated the brain lesions by selecting consecutive points at the visually defined borders between the lesions and the adjacent NAWM on the acquired transverse T2-weighted sections. Similar regions corresponding to NAWM were manually delineated contralaterally to the detected MS lesions with extra caution to avoid contamination from dirty white matter areas. The manual delineations were performed using a graphical user interface implemented in MATLAB® developed by our group. For each brain MRI scan of MS subjects, 10 discrete round regions of interest (ROIs) with an approximate radius of 25 pixels were also drawn in brain white matter, usually on the contralateral to the lesion side, to represent NAWM. Every effort was made to avoid white matter areas with subtle, patchy and diffuse abnormal signal intensities. Finally, the neurologist manually segmented cerebrovascular fluid (CSF) areas as well as areas with air (sinuses) from all MS brain scans. Similarly, ROIs representing NWM, CSF and air from the sinuses, of the same size as the NAWM and lesions, were arbitrarily segmented from the brain scans of the 20 healthy subjects. Manual segmentation by the MS expert was performed in a blinded manner (without knowledge of the MRI-subject time-point relationships), without the possibility of identifying the subject, the time-point of the exam or the clinical findings. The selected points and delineations are the regions used for texture analysis.

Feature extraction: shape and texture

Shape features and texture features were extracted from all MS lesions detected and segmented as well as from all the segmented ROIs from the healthy brain areas. The texture features were normalized with respect to ROI's under investigation size. The overall shape and texture features for each subject were then estimated by averaging the corresponding values for all lesions for each subject. The following features were extracted:

- shape parameters: (1) x-coordinate maximum length, (2) y-coordinate maximum length, (3) area, (4) perimeter, (5) perimeter^2/area, (6) eccentricity, (7) equivalence diameter, (8) major axis length, (9) minor axis length, (10) centroid, (11) convex area, and (12) orientation;
- statistical features [16,23]: (a) mean, (b) variance, (c) median value, (d) skewness, (e) kurtosis, (f) energy and (g) entropy;
- spatial gray level dependence matrices (SGLDM) as proposed by Haralick et al. [23]: (a) angular second moment (ASM), (b) contrast, (c) correlation, (d) sum of squares variance (SOSV), (e) inverse difference moment (IDM), (f) sum average (SA), (g) sum variance (SV), (h) sum entropy (SE), (i) entropy, (j) difference variance (DV), (k) difference entropy (DE), and (l) information measures of correlation (IMC). For a chosen distance d (in this work d = 1 was used) and for angles $\theta = 0^0$, 45^0, 90^0, and 135^0, we computed four values for each of the above texture measures. Each feature was computed using a distance of one pixel. Then for each feature the mean values and the range of values were computed, and were used as two different feature sets;
- gray level difference statistics (GLDS) [24]: (a) homogeneity, (b) contrast, (c) energy, (d) entropy, and (e) mean. The above features were calculated for displacements $\delta = (0,1), (1,1)(1,0), (1,-1)$, where $\delta \equiv (\Delta x, \Delta y)$, and their mean values were taken;
- neighborhood gray tone difference matrix (NGTDM) [25]: (a) coarseness, (b) contrast, (c) busyness, (d) complexity, and (e) strength;
- statistical feature matrix (SFM) [26]: (a) coarseness, (b) contrast, (c) periodicity, and (d) roughness;
- laws texture energy measures (LTEM) [26]: LL-texture energy from LL kernel, EE-texture energy from EE kernel, SS-texture energy from SS kernel, LE-average texture energy from LE and EL kernels, ES-average texture energy from ES and SE kernels, and LS-average texture energy from LS and SL kernels;
- fractal dimension texture analysis (FDTA) [26]: the Hurst coefficients for dimensions 4, 3 and 2 were computed;
- Fourier power spectrum (FPS) [26]: (a) radial sum, and (b) angular sum.

Statistical analysis

The Mann-Whitney rank sum test (for independent samples of different sizes) [27] was used in order to identify if there were significant differences (S) or not (NS) between the extracted texture features at $P < 0.05$. The median values over the segmented components (NWM, NAWM, and

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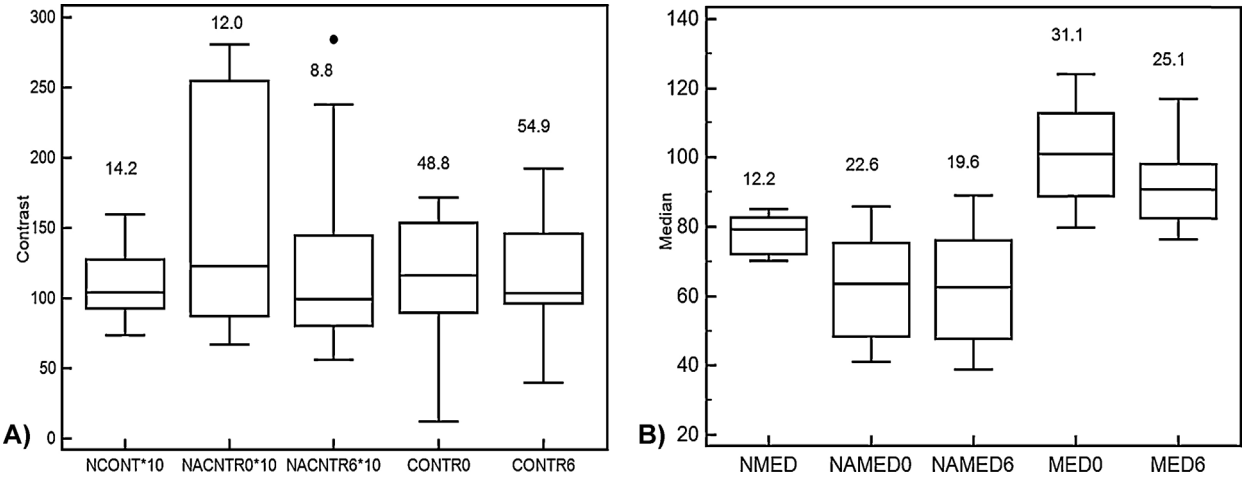

Figure 3 Box plots for the median ± inter-quartile range (IQR) values for texture features A contrast and B median from NWM (NCONT, NMED), NAWM at 0 month (NACONTR0, NAMED0) and 6—12 months (NACONTR6, NAMED6), and MS lesions at 0 months (CONTR0, MED0) and 6—12 months (CONTR6, MED6) respectively. IQR values are shown above the box plots. In each plot, we display the median, lower, and upper quartiles and confidence interval around the median. Straight lines connect the nearest observations within 1.5 of the IQR of the lower and upper quartiles. The features NCONT, NACONTR0 and NACONTR6 were multiplied by the factor of 10 for better visualization.

MS lesions) were used for investigating the relationships between the 0 and the 6—12 months intervals. Similarly, for comparing independent samples from equal populations, the Wilcoxon rank sum test was used [28].

For independent samples of different sizes, the Mann-Whitney rank sum test was used for detecting texture feature differences between NWM, NAWM, and MS lesions for subjects with an EDSS ≤ 2 and EDSS > 2, computed at two years and five years after the initial MRI examination. Box plots were used to compare the texture features between the NAWM, and MS lesions both at 0 and 6—12 months.

Results

We present in Fig. 3 box plots of the contrast (CNTR0, CONTR6, of GLDS features group) and median (MED0, MED6 of Statistical Features group) features extracted from lesions at 0 and 6—12 months compared with the NAWM (NACONTR, NAMED) and normal tissue (NCONT, NMED) in Fig. 3A and B respectively for all subjects investigated ($n = 38$). They show clearly the increased values of MS lesions at 0 and 6—12 months compared to NWM (note that NCONT, NACONTR0 and NACONT6 were multiplied by 10 for better visualization).

There are also significant differences in the box plots of Fig. 3 (see also Table 4). From the plots of Fig. 3A and B, one can see a difference between the contrast ($P = 0.23$) and the median value of lesions ($P = 0.11$) at 0 or 6—12 months (although not significantly different) and the contrast of the NAWM at 0 and 6—12 months ($P = 0.01$) as well as with the normal tissue (NWM) ($P = 0.001$, $P = 0.007$ for 0 and 6—12 months respectively).

Fig. 4 shows box plots of the lesion features mean (Mean0_1, Mean0_2, $P = 0.025$) and median (Median0_1, Median0_2, $P = 0.035$) from the statistical features group and Sum Average (SA0_1, SA0_2, $P = 0.04$) from the SGLDM features group, for 0 months for EDSS ≤ 2 (_1) ($n = 23$) and EDSS > 2 (_2) ($n = 15$) (EDSS measured at 2 years).

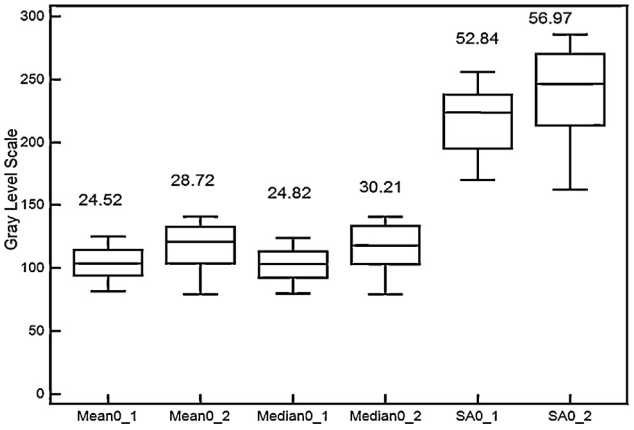

Figure 4 Box plots for the median ± inter-quartile range (IQR) values for texture features mean, median and sum average (from SGLDM feature group), from MS lesions at 0 months for EDSS ≤ 2 ($n = 23$) and EDSS > 2 ($n = 15$) corresponding to feature notation _1, and _2 respectively (see also Table 1). EDSS was measured in 2 years after initial examination. See Fig. 3 for the box plot description.

Shape feature analysis

Table 1 tabulates the disease duration (DD) for each subject in months, the EDSS score measured after two and five years of the initial examination, the number of lesions at 0 and 6—12 months, and the average of their corresponding shape features. It is interesting to note that the median of the number of lesions (IQR) at 0 and 6—12 months were 7.5 (4.5) vs. 8 (5.3) whereas as there was a corresponding non-significant increase in median area (IQR) (45 (58) vs. 48

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Table 1 Shape features for each subject ($n = 38$) for lesions at 0 (0) and 6—12 (6—12) months and statistical analysis based on the Mann-Whitney rank sum test are shown with S and NS features that are and are not significantly different at 0 months and 6—12 months at $P < 0.05$ respectively.

A/A	DD	EDSS	NrL		AL [mm^2]			VL [mm^3]			PER [mm]			EQD [mm]			MAL [mm]		
			0	6—12	0	6—12	S/NS	0	6—12	S/NS	0	6—12	S/NS	0	6—12	S/NS	0	6—12	S/NS
1	54	1.0 (1.0)	6	4	79	65	NS	397	327	NS	123	69	NS	36	20	NS	43	26	NS
2	52	1.0 (2.5)	5	9	57	51	NS	283	253	NS	112	204	NS	33	61	NS	45	80	NS
3	26	1.0 (2.0)	9	9	11	19	NS	56	95	NS	64	66	NS	22	22	NS	26	27	NS
4	21	1.0 (1.0)	5	8	15	10	NS	76	51	NS	36	39	NS	11	12	NS	10	10	NS
5	24	1.0 (1.0)	7	6	11	19	S	56	95	S	35	47	NS	11	13	NS	14	19	NS
6	23	1.0 (1.0)	7	6	7	10	NS	37	49	NS	44	70	NS	15	24	NS	18	30	NS
7	24	1.0 (1.0)	10	13	9	9	NS	46	49	NS	25	26	NS	8	8	NS	9	9	NS
8	64	1.0 (2.0)	8	6	23	18	NS	117	90	NS	25	26	S	7	8	S	6	7	S
9	71	1.5 (1.5)	8	8	231	140	NS	115	701	NS	390	305	NS	104	83	NS	140	109	NS
10	67	1.5 (2.5)	6	8	48	63	NS	238	313	NS	91	165	NS	26	48	NS	35	65	NS
11	43	2.0 (2.0)	6	2	49	16	NS	243	80	NS	84	12	NS	23	4	NS	32	5	NS
12	40	2.0 (2.5)	6	7	60	51	NS	298	256	NS	83	174	NS	26	50	NS	29	61	NS
13	23	2.0 (2.0)	4	4	40	35	NS	201	174	NS	55	60	NS	16	18	NS	22	24	NS
14	22	2.0 (2.0)	10	9	28	40	S	138	201	S	106	128	NS	33	40	S	42	49	NS
15	55	2.0 (3.0)	5	6	40	30	NS	198	150	NS	71	77	NS	21	23	NS	29	31	NS
16	67	2.0 (2.0)	13	12	133	191	NS	664	957	NS	542	659	S	152	172	NS	211	253	S
17	55	2.0 (2.5)	7	6	8	11	S	39	56	S	29	37	NS	10	13	NS	8	11	NS
18	19	2.0 (2.5)	12	9	24	19	NS	118	93	NS	126	88	NS	40	29	S	34	24	NS
19	18	2.0 (2.0)	16	17	9	15	NS	43	73	NS	36	46	NS	11	14	NS	15	19	NS
20	22	2.0 (2.0)	3	4	10	15	NS	51	73	NS	49	62	NS	17	21	NS	14	18	NS
21	15	2.0 (3.0)	6	5	81	59	NS	403	295	NS	80	133	S	23	39	NS	19	34	NS
22	17	2.0 (2.0)	9	13	29	43	S	147	217	S	119	197	NS	37	59	NS	49	77	S
23	22	2.0 (2.5)	12	13	112	129	NS	330	357	NS	130	145	NS	145	167	NS	200	32	NS
24	51	2.0 (2.5)	8	7	26	31	NS	128	154	NS	286	321	NS	85	95	NS	107	117	NS
25	67	2.5 (5.0)	4	3	40	27	NS	200	133	NS	61	44	NS	16	11	NS	23	19	NS
26	32	2.5 (3.0)	12	14	54	61	NS	269	306	NS	171	235	NS	51	68	NS	64	90	NS
27	57	2.5 (3.0)	4	14	27	135	NS	134	675	NS	33	474	NS	10	106	NS	13	131	NS
28	52	2.5 (4.5)	9	8	109	121	NS	146	222	NS	221	297	NS	36	45	S	90	178	NS

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Table 1 (*Continued*)

A/A	DD	EDSS	NrL		AL [mm^2]			VL [mm^3]			PER [mm]			EQD [mm]			MAL [mm]		
			0	6—12	0	6—12	S/NS	0	6—12	S/NS	0	6—12	S/NS	0	6—12	S/NS	0	6—12	S/NS
29	30	3.0 (2.5)	14	15	98	110	NS	510	540	NS	398	410	NS	111	124	NS	117	125	NS
30	74	3.0 (3.0)	12	12	72	64	NS	360	321	NS	237	232	NS	69	64	NS	85	86	NS
31	77	3.0 (4.0)	7	7	454	448	S	2268	2241	S	654	624	S	173	166	S	236	220	S
32	84	3.0 (3.0)	9	8	73	229	S	364	1146	S	246	526	S	70	141	S	95	198	S
33	71	3.0 (4.0)	6	6	31	27	NS	156	134	NS	74	94	NS	22	27	NS	26	37	NS
34	24	3.0 (4.5)	13	13	108	113	NS	540	566	NS	417	434	NS	124	126	NS	155	162	NS
35	35	3.0 (5.0)	15	13	94	120	NS	470	599	NS	337	342	NS	98	102	S	124	125	S
36	47	3.0 (5.0)	6	8	79	59	NS	393	293	NS	139	119	NS	40	34	NS	53	46	NS
37	65	3.5 (5.0)	13	10	40	42	NS	199	212	NS	307	291	S	86	82	NS	119	112	NS
38	66	3.5 (8.5)	12	11	165	212	NS	827	1062	NS	468	654	NS	123	173	NS	176	236	NS
	Min	1.0 (1.0)	3	2	7.4	5.4		37	27		5	4		7	4		9.4	47	
	Max	3.5 (8.5)	16	17	423	451		2116	2256		654	659		173	173		236	253	
	Med	2.0 (2.5)	7.5	8	45	48		223	238		88	123		33	39		49	83	
	IQR	1.3 (1.6)	4.5	5.3	58	96		291	482		190	193		58	63		86	87	
	Aver	2.1 (2.8)	8.2	8.6	67	80		335	397		155	188		49	56		63	75	
	std	0.9 (1.5)	3.4	3.5	78	91		391	456		158	185		44	50		60	68	

DD: disease duration for each subject in months; M: month; EDDS: expanded disability status scale measured after 2 and 5 (in parentheses) years of the initial examination; NrL: number of lesions; AL: total lesion area per subject; VL: total lesion volume per subject; PER: perimeter at 0 and 6—12 months; EQD: equivalence diameter; MAL: major axis length; Med: median; IQR: inter-quartile range; Aver: average; std: standard deviation.

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Table 2 Shape feature statistical analysis for all subjects ($n = 38$), for lesions at 0 and 6–12 months. Wilcoxon rank sum test shows with S and NS the features, that are (S) and are not significantly different (NS) at $P < 0.05$ respectively. P-values are shown in parentheses.

Shape feature	Lesion 0 vs. lesions 6–12
Area	NS (0.45)
Volume	NS (0.86)
Perimeter	NS (0.92)
Eccentricity	S (0.04)
Equivalence diameter	NS (0.14)
Major axis length	S (0.04)
Minor axis length	S (0.02)
Centroid	NS (0.27)
Convex area	S (0.01)
Orientation	NS (0.96)

(96) in mm^2) and median perimeter (IQR) (88 (190) vs. 123 (193) in mm) and a significant increase in median major axis length (IQR) (49 (86) vs. 83 (87) in mm) (as shown also in Table 2).

Table 2 presents statistical comparisons for the shape features for all lesions and for all subjects at 0 and 6–12 months based on the Wilcoxon rank sum test. It is shown that:

- significant differences were found for the eccentricity ($P = 0.04$), the major axis length ($P = 0.04$), the minor axis length ($P = 0.02$) and the convex area ($P = 0.01$) between the shape features at 0 and 6–12 months respectively;
- it is noted that the area ($P = 0.45$) and volume ($P = 0.86$) showed no significance difference.

Texture feature analysis

Table 3 presents the SF median (IQR) values for texture features for the NWM and NAWM and MS lesions at 0 and 6–12 months. Selected features are presented that showed significant difference using the Mann-Whitney rank sum test at 0 vs. 6–12 months as demonstrated also in Table 4. Table 4 shows the results for the statistical analysis between the NWM, and NAWM and lesions at 0 and 6–12 months. The Mann-Whitney rank sum test was used and shows with (S) significantly and (NS) non-significantly different features at $P < 0.05$. It is shown that:

- for NAWM tissue and lesions at 0 month all texture features were significantly different as expected;
- for NAWM tissue and lesions at 6–12 months almost all features were significantly different with the exception of standard deviation and median (from the statistical features group);
- for lesions at 0 and 6–12 months, only difference entropy (SGLDM), contrast (GLDS) and periodicity (SFM) were significantly different;
- features median (statistical features), IDM (SGLDM), contrast (GLDS), and entropy (GLDS) showed significant difference between NWM and NAWM at 0.

Texture feature analysis based on the EDSS score

Table 5 presents the statistical texture features comparisons for brain lesions and NAWM recorded at 0 and 6–12 months between subjects with an EDSS score lower than or equal to 2 (≤ 2) and subjects with an EDSS score greater than 2 (> 2) estimated in two and five years from initial diagnosis respectively, based on the Mann-Whitney rank sum test. It is noted that for each comparison different features gave significant difference based on the Mann-Whitney test for both EDSS at 2 and 5 years. It is shown that:

- only skewness (statistical features group) could be used to differentiate between NAWM at 0 month and EDSS ≤ 2 versus EDSS > 2, and NAWM at 0 month versus 6–12 months for EDSS ≤ 2 for both two and five years respectively (−/−) (see also Table 5);
- mean and median (statistical features group) could be used to differentiate between, lesions at 0 month for EDSS ≤ 2 versus EDSS > 2, and lesions at 6–12 months for EDSS ≤ 2 versus EDSS > 2 for both two and five years respectively (−/−);
- there was no significant difference for NAWM and the lesion texture features (for both at 0 and 6–12 months) for subjects with no change in EDSS score ($n = 17$) versus subjects with increased EDSS score ($n = 20$) from 2 to 5 years (see also Table 1 for details about the EDSS score at 2 and 5 years for each subject. One subject had a slight decrease in EDSS score). Moreover, Spearman's correlation analysis showed only a few features that had moderate correlation (with significant difference at $P < 0.05$) with no change vs. increased EDSS score. For example for lesions at 6–12 months, only feature SGLDM – Information Measure of Correlation (IMOC) gave a Spearman's correlation coefficient of 0.31 (and a P value of 0.01).

Results analysis

The presented analysis is based on the manually segmented MS lesions and NAWM areas from the MRI scans of 38 subjects with CIS, in an attempt to quantify pathological changes that occur in MS. The population sample used in our study represents more than 50% of CIS cases diagnosed in the Cypriot population within the time span of two years. All subjects were scanned twice with an interval of 6–12 months and were followed up for more than five years.

The results showed that:

- there was not a significant difference between the shape features extracted from the lesions at 0 and 6–12 months respectively with the exception of eccentricity, convex area, major and minor axis length (see Table 2);
- there was a significant difference between most of the texture features extracted from the NWM and NAWM and the corresponding texture features extracted from the lesions at 0 and 6–12 months (with the exception of standard deviation (SF feature group) and median (SF feature group) at 6–12 months). Moreover, there was no significant difference between features extracted from the lesions at 0 and 6–12 months with the exception of contrast (GLDS feature group) and DE (SGLDM feature group),

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Table 3 Texture features median (±IQR) values for NWM and NAWM and lesions at 0 and 6–12 months. Selected features are tabulated that showed significant difference using the Mann-Whitney rank sum test at 0 vs. 6–12 months as demonstrated in Table 4.

Feature	Texture				
	NWM	NAWM 0	NAWM 6–12	Lesion 0	Lesions 6–12
Statistical features					
Standard deviation	5.7 (3.2)	4.5 (1.1)	4.2 (1.1)	17 (5)	18 (6.6)
Median	80 (8.1)	65 (22)	66 (19)	107 (31)	101 (25)
Spatial gray level dependence matrix (SGLDM) mean values					
SOSV	25 (14)	20 (10)	18 (9)	391 (250)	346 (231)
IDM	0.3 (0.05)	0.3 (0.09)	0.3 (0.1)	0.15 (0.02)	0.15 (0.02)
Sum average	162 (17)	131 (40)	133 (40)	212 (50)	212 (50)
Sum variance	83 (39)	62 (30)	65 (30)	1305 (850)	1340 (820)
Difference variance	6.4 (39)	5.5 (4.4)	4.5 (3.0)	33 (18)	32 (18)
Difference entropy	2.2 (0.3)	2.1 (0.3)	2.0 (0.4)	2.7 (1.2)	2.7 (0.2)
Gray level difference statistics (GLDS)					
Contrast	18 (15)	15 (12)	12 (9)	90 (48)	85 (44)
Entropy	5.2 (0.3)	4.7 (0.4)	4.7 (0.5)	5.4 (0.9)	5.4 (1.1)
Neighbourhood gray tone difference matrix (NGTDM)					
Coarseness	7.8 (0.8)	7.7 (2.3)	8.7 (2.3)	12.3 (8.6)	15.1 (10.5)
Complexity	277 (111)	260 (227)	250 (200)	4064 (3014)	3748 (3767)
Statistical feature matrix (SFM)					
Periodicity	0.4 (0.03)	0.42 (0.08)	0.45 (0.08)	0.6 (0.01)	0.7 (0.01)
Roughness	0.68 (0.03)	2.64 (0.11)	2.6 (0.14)	2.3 (0.1)	2.3 (0.1)
Laws texture energy measures (LTEM)					
LL	7140 (903)	6086 (3667)	5413 (4455)	36619 (1978)	40376 (1711)
SS	40 (52)	112 (51)	100 (45)	177 (50)	158 (38)
Fractal dimension analysis (FDTA)					
H1	0.3 (0.01)	0.27 (0.07)	0.31 (0.09)	0.5 (0.001)	05 (0.1)
H2	0.2 (0.01)	0.17 (0.02)	0.17 (0.04)	0.3 (0.2)	0.3 (0.1)
Fourier power spectrum (FPS)					
Radial sum	873 (250)	618 (243)	647 (301)	1586 (1048)	1330 (909)

NWM: normal white matter; NAWM 0, NAWM 6–12: normal appearing white matter at 0 and 6–12 months respectively; lesion 0, lesions 6–12: lesions at 0 and 6–12 months respectively; LL: texture energy from LL kernel; SS: texture energy from SS kernel.

(see also Table 4), signifying the potential to aid in disease diagnosis;

- there were mostly non-significant differences based on the EDSS score between lesions at 0 month and lesions at 6–12 months for EDSS ≤ 2 and EDSS > 2 (see Table 5);
- for each comparison different features gave significant difference based on the Mann-Whitney test for both EDSS at 2 and 5 years (see Table 5).

Table 2 showed that the shape features eccentricity, major and minor axis length, and convex area are statistically different between the same lesions detected and segmented at 0 and 6–12 months. These shape features may therefore prove to have some value as markers for the longitudinal monitoring of these lesions. In [2] it was shown that new lesions and increase in disease volume is very weakly associated ($\rho = 0.13$–0.23) with increase in disability (EDSS). On the other hand, a simple correlation of the onset and progression of lesions in relation to the EDSS is extremely unlikely as documented in [9].

Table 3 showed that some of the texture features are sensitive to the onset of the MS disease. It was shown that texture features such as standard deviation (SF feature group), contrast (GLDS feature group), SOSV, SV, DV, DE, increase with the onset of the disease when compared with their corresponding NAWM tissue values, whereas with the onset of the disease to 6–12 months they decrease when compared with the NWM (see also Fig. 3).

Table 4 shows that there are features that can be used to distinguish between NWM, NAWM and lesions at 0 and 6–12 months.

From Table 5, one can see that there are some texture features that can be possibly used to differentiate between subjects with mild (EDSS ≤ 2) and advanced (EDSS > 2) MS disease states and also that there are features that have differences not present at the baseline and which may be used for following the progression of disability. Table 5 (left part), showed that the SGLDM features DE, contrast, SV, entropy and mean can be used to differentiate NAWM in advanced disease cases of subjects with EDSS > 2

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Table 4 Statistical analysis between the NWM, and NAWM and lesions at 0 and 6—12 months. The Mann-Whitney rank sum test was used and shows with (S) significantly and (NS) non-significantly different features at $P < 0.05$.

Feature	Texture							
	NWM vs. NAWM 0	NWM vs. NAWM 6—12	NWM vs. lesion 0	NWM vs. lesions 6—12	NAWM 0 vs. NAWM 6—12	NAWM 0 vs. lesions 0	NAWM 6 vs. lesions 6—12	Lesion 0 vs. lesions 6—12
Statistical features								
Standard deviation	NS	S	S	S	NS	S	NS	NS
Median	S	S	S	S	NS	S	NS	NS
Spatial gray level dependence matrix (SGLDM) mean values								
Contrast	NS	S	S	S	NS	S	S	NS
Correlation	NS	S	S	S	S	S	S	NS
IDM	S	S	S	S	S	S	S	NS
Sum variance	NS	NS	S	S	NS	S	S	NS
DV	NS	S	S	S	S	S	S	NS
DE	NS	S	S	S	S	S	S	S
Gray level difference statistics (GLDS)								
Contrast	S	S	S	S	S	S	S	S
Entropy	S	S	NS	S	NS	S	S	NS
Neighbourhood gray tone difference matrix (NGTDM)								
Coarseness	NS	S	S	S	S	S	S	NS
Contrast	NS	S	S	S	S	S	S	S
Statistical feature matrix (SFM)								
Periodicity	NS	S	S	S	S	S	S	S
Roughness	NS	S	NS	S	S	S	S	NS
Laws texture energy measures (LTEM)								
LL	NS	NS	NS	S	NS	S	S	NS
SS	NS	NS	NS	S	NS	S	S	NS
Fractal dimension analysis (FDTA)								
H1	NS	S	NS	S	S	S	S	NS

NWM: normal white matter; NAWM 0, NAWM 6—12: normal appearing white matter at 0 and 6—12 months respectively; lesion 0, lesions 6—12: lesions at 0 and 6—12 months respectively; SOSV: sum of squares variance; IDM: inverse difference moment; DV: difference variance; DE: difference entropy.

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Table 5 Comparison of the texture features between subjects with EDSS ≤ 2 and EDSS > 2, measured in two and in five years after initial diagnosis (shown separated with '/'). The Mann-Whitney rank sum test was used at $P < 0.05$. Significant difference is depicted with S with the P-values shown in parentheses. Only the features that showed significant difference are shown out of 61 different texture features.

		NAWM			Lesions		
		Feature	0 month	6—12 months	Feature	0 month	6—12 months
	EDSS		> 2	≤ 2		> 2	≤ 2
0 month	≤ 2	Skewness-FOS	S (0.03)/S (0.03)	S (0.03)/S (0.01)	Mean-FOS	S (0.03)/S (0.04)	—
		Contrast-SGLDMm	—	S (0.03)/—	Median-FOS	S (0.03)/S (0.03)	—
		IDM-SGLDMm	—/S (0.03)	S (0.04)/S (0.04)	IDM-SGLDMm	S (0.01)/S (0.04)	—
		Sum entropy-SGLDMm	S (0.03)/—	—	Sum average-SGLDMm	S (0.04)/—	—
		Bussynes-NGTDM	S (0.04)/S (0.04)	—	IMOC-SGLDMm	S (0.006)/S (0.04)	—
		Complexity-NGTDM	S (0.01)/—	—	ASM-GLDS	S (0.02)/S (0.03)	—
		Strength-NGTDM	S (0.03)/—	—	Mean-GLDS	S (0.04)/—	—
		Periodicity-SFM	—	S (0.04)/—	Contrast-NGTDM	S (0.04)/S (0.04)	—
		Roughness-SFM	—	S (0.04)/S (0.04)	Hurst coefficients 3-FDTA	—/S (0.02)	—
		LE and EL-TEM	S (0.04)/S (0.04)	—		—	—
		LS and SL-TEM	S (0.04)/S (0.04)	—		—	
6—12 months	> 2	Sum average-SGLDMm	—/S (0.03)	S (0.03)/—	Mean-FOS	—	S (0.02)/S (0.05)
		Difference entropy-SGLDMm	S (0.02)/S (0.05)	—	Median-FOS	—	S (0.02)/S (0.04)
		Contrast-SGLDMr	S (0.04)/—	—	Sum average-SGLDMm	—	S (0.02)/S (0.06)
		Sum variance-SGLDMr	S (0.01)/—	—	Entropy-SGLDMm	—	S (0.03)/S (0.04)
		IDM-SGLDMr	—	—/S (0.04)	IMOC-SGLDMm	—	S (0.01)/S (0.04)
		Entropy-SGLDMr	S (0.04)/—	—	ASM-GLDS	—	—/S (0.04)
		Mean-GLDS	S (0.04)/S (0.03)	—	IDM-SGLDMr	—	—/S (0.01)
		Coarseness-NGTDM		—/S (0.04)	Sum entropy-SGLDMm	—	—/S (0.01)
		Contrast-NGTDM	S (0.04)/S (0.04)	—	Radial sum-FDS	—	—/S (0.01)

NAWM: normal appearing white matter; IDM: inverse difference moment; SA: sum average; IMOC: information measures of correlation; ASM: angular second moment; LE and EL: average texture energy from LE and EL kernels: LS and SL: average texture energy from LS and SL kernels.

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between 0 and 6—12 months intervals. The features skewness (SF), contrast (SGLDM), IDM (SGLDM), periodicity (SFM) and roughness (SFM) can be used to differentiate NAWM at mild disease cases (EDSS $\leq$ 2) between subjects at 0 and 6—12 months. Finally, the texture feature SA, IDM and coarseness can be used to differentiate NAWM between mild (EDSS $\leq$ 2) and advanced (EDSS > 2) disease cases for subjects at 6—12 months. From the results of Table 5 (right part), the features mean, median, IDM, SA, IMOC, ASM, contrast and Hurts coefficients for 0 month and the features mean, median, SA, entropy and IMOC for 6—12 months gave significant differences between the two cases (EDSS $\leq$ 2 versus EDSS > 2). Those features may be used therefore to reliably differentiate lesions associated with mild and advanced cases of the disease.

To the best of our knowledge, only a handful of other studies [29,30] were carried out for differentiating between the aforementioned two disability scores investigating a smaller set of different features. Several studies were carried out for differentiating and classifying NWM, and or NAWM, and lesions, as these are summarized below.

Discussion

The primary objective of this study is to evaluate different texture features that can be used to predict MS brain lesions that at a later stage are associated with advanced clinical disability. In addition, the use of texture features analysis to detect significant differences between NWM, NAWM, and MS lesions as well as for better tissue discrimination between them is also investigated. Texture features were extracted and investigated based on statistical measures, and univariate statistical analysis.

Various studies have been performed in order to establish a relationship between the various gray levels and texture features [9—14]. In [7], MRI texture analysis based on statistical, autoregressive model, and wavelet-derived texture analysis was performed on 29 MS subjects. The classification accuracy between MS lesions, NAWM and plaques NWM, was 96—100%. In [10], the authors showed that texture features can reveal discriminant features for differentiating between normal and abnormal tissue, and for image segmentation. The differentiation between active and non-active brain lesions in MS subjects from brain MRI was investigated in [14], where active lesions were identified without frequent gadolinium injections, using run length analysis criteria.

Likewise in [15], texture analysis was performed, using linear discriminant analysis, on MR images of MS subjects and normal controls and a combined set of texture features were explored in order to better discriminate tissues between MS lesions, NAWM and NWM. The results demonstrated that compared with GLCM-based features, the combined set of texture features were better at discriminating MS lesions and NWM, equally good at discriminating MS lesions and NAWM and at all three tissue types, but less effective in classification between NAWM and NWM. The classification accuracy in tissue discrimination between MS lesions and NAWM was over 90%.

In [18], it was shown that several hemispherical differences for primary progressive MS and relapsing remitting MS sclerosis can be found with texture analysis. Most recently, Zhang et al. [19] hypothesized correlation between texture features of T2-weighted MRI images and histological changes of postmortem MS brains. They found that tissues with more significant myelin and axonal pathology are associated with greater texture heterogeneity showing that texture analysis on routine clinical MR images may be a potential measure of tissue integrity and thus MS disease activity and progression.

In [31], quantitative parameters anisotropy and laminarity were derived from 3D texture analysis. Differences in NWM texture associated with gender and changes of NWM texture with age were studied on healthy subjects. The study demonstrated that the texture anisotropy analysis of anatomical MRI brain datasets provides quantitative information, which may help to better understand the gender-related differences and NWM alterations with brain maturation and aging.

In [29], 23 normal controls and 73 subjects with either a CIS (38 subjects) or clinically definite MS (CDMS, with 35 subjects) were scanned and texture parameters were extracted. The texture parameters were compared between the groups and correlated with clinical measures of disability in the MS subjects to investigate any association with disease severity. The study showed that no significant differences were found between the texture parameters from controls and CIS subjects; but that several parameters differ between MS subjects and the two other groups, particularly in the gray matter, but also in the NAWM. There were also correlations found between some of the parameters and the clinical scores obtained from the subjects. The EDSS and timed walk test correlate with gray matter texture measures, while the Paced Auditory Serial Addition Test 3 score, a cognitive measure, correlates with NAWM texture. The study highlighted potential for texture analysis measures in classifying central nervous system demyelinating diseases that warrants further investigation; and the results added evidence to the idea that widespread, but subtle, damage occurs to NAWM in MS, and that this occurs in both white matter and gray matter.

The work in [9] showed that histograms could characterize changes between MS lesions and NAWM. It was also shown that texture features and histograms might be used in discriminating between segmented areas of normal and abnormal tissue. In [13], significant differences in texture were also found between normal and MS subjects in the spinal cord as well as a significant correlation between texture features and disability. The increase of these texture features suggests that the lesions texture in MS subjects is less homogeneous and more complex than the corresponding healthy tissue (NWM) in normal subjects [13]. This loss in homogeneity may be a result of some pathological processes, including demyelination, gliosis, inflammation, axonal loss, or changes in water content and leading to a less uniform MR signal intensity.

Findings presented in Table 4 corroborate the findings in [9] showing that texture features increase with the onset of the MS disease when compared to normal tissue (see Table 4). In Table 4 we showed using statistical analysis, that there was a significant difference between NWM and NAWM for some features. These findings may prove quite useful for propelling the research for early diagnosis and treatment of MS.

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In most previous studies [29,32,33] assessment of MS lesions nature and corresponding differential diagnosis was performed by visual evaluation of the lesion's features such as size, site and morphology. Only in [13] has an attempt been first made to assess the lesion's texture by computer methods. Such analysis may be of value since pixel values, pixel interrelations, and lesion texture may be more accurately analyzed by computer methods than they can be visually estimated. According to the findings of the present study, there exist significant differences in the values of the textural features extracted between 0 and 6–12 months.

Recently MRI studies using magnetization transfer imaging and, specifically, the magnetization transfer ratio (MTR) can quantify demyelination severity, because MTR is reduced in WM lesions [34] with milder decreases also observed in NAWM and gray matter [35,36]. Tozer et al. [29] estimated GLCM textural features extracted from magnetization transfer MRI acquired from 23 healthy controls as well as from 32 subjects with relapsing remitting MS, 3 subjects with secondary progressive MS, and 38 subjects with CIS, and investigated the relationship between textural features and the EDSS. While the authors found no differences between the features extracted from controls and subjects with CIS, several features differed between subjects with MS and the 2 other groups, especially in gray matter (but also in NAWM). Disability scores also correlated well with GLCM textural features extracted from NAWM regions. Texture feature abnormalities in MS suggested there might be tissue damage beyond classic white matter lesions and that these features show potential for quantifying the severity of demyelination. In [37], the damage to the uncinated fasciculus and inferior longitudinal fasciculus in 16 patients with progressive supranuclear palsy (PSP) was evaluated using diffusion tensor tract-specific analysis. It was found that patients with PSP and Richardson syndrome had significantly different clusters of reduced gray matter when compared to the healthy control subjects, and thus demonstrated impairment of the uncinated fasciculus and inferior longitudinal fasciculus. Finally, in a more recent study [38], alterations in brain white matter in photosensitive epilepsy (PSE) were studied in 24 subjects by applying tract-based spatial statistics analysis. It was shown that the corpus callosum of the PSE patients was abnormal and had significantly lower fractional anisotropy values when compared with the control subjects.

In the presented study with the evaluation of a much more extensive set of texture features the correlation of disability scores with the different features is more pronounced with the presence of features that may enable the classification of patients with scores EDSS $\geq$ 2 (see also Table 5). We have shown in a recent study [39] performed by our group that a classification score of 69% was achieved when using the SVM classifier for classifying MS lesions and NAWM.

Furthermore, the texture features shown in Table 4 might encode meaningful interpretations regarding the clinical context of MS, lesions and NAWM. The median value is an index that intuitively shows the brightness of each ROI. As can be seen from Table 3, MS lesions are brighter than NWM. Another important textural feature is contrast, which is a measure of local variation between pixel intensities. MS regions had higher contrast values than NWM regions. Inverse different moment (IDM) is related to lesions homogeneity [23]. In NWM, IDM had higher values than in MS regions, implying that NWM were smoother and more homogeneous. From another perspective, MS lesions attained lower entropy and sum of average values than NWM ROIs, indicating that the degree of randomness of pixel intensities or textural roughness in MS regions was lower. Conclusively, MS regions exhibit lower signal intensity, higher contrast, less homogeneous and rougher as compared to NWM. These findings are in agreement with observations by Mathias et al. [13] regarding MS lesions. The latter were found with increased entropy and decreased angular second moment, implying that MS lesion texture was rough and of low homogeneity. This loss of homogeneity in MS may be attributed to a number of processes such gliosis, inflammation, demyelination and changes in water content that may disrupt MR signal intensity uniformity [13].

Limitations of the texture analysis method

The limitations of this study are similar with the ones presented in a recent study performed by our group where Amplitude Modulation-Frequency Modulation features were extracted from NWM, NAWM and lesions [17] and here below presented in detail. The MRI images in this study were intensity normalized based on the method proposed in [21]. This was done in order to reduce the effects of image intensity variation between images obtained at different time-points. The variation in intensity can have a significant impact when trying to compare between different images and texture and also when trying to generate global tissue models for tissue classification [14]. The normalization process proposed in this study uses prior knowledge of the high and low intensity values of the brain, so that the new intensity histogram of the lesion has its maximum peak close to its average gray scale value [12]. More specifically, the influence of different MRI acquisition protocols and four gray level intensity normalization methods on the discrimination power on the texture analysis of two classes of samples were investigated in [12]. MRI image may suffer from artifacts of different origin, such as image thermal noise, image background nonuniformity form magnetic field in homogeneities, and no standardization of image gray scale intensity. High image quality and minimization of these artifacts are important for performing quantitative analysis. The intensity normalization method firstly proposed in [22] and then later applied in [12,20] was used in this study. The proposed normalization method allows the scanner sensitivity variations and variations due to repeatability studies to be largely corrected and thereby facilitating meaningful comparisons between MRI data sets obtained at different times and/or different subjects. By normalizing the histogram of the whole-brain we introduced an automatic procedure with little sensitivity to pathological or morphological changes between the different image data sets. The method does not depend on knowledge of the scanner calibration and thus can be used on retrospective data.

T2-weighted MR imaging is very sensitive to tissue abnormalities in human brain, and many histopathological features in MS, such as edema, gliosis, demyelination and remyelination are depicted as hyperintensity lesions. It is not sensitive, however, to discrete tissue damage in NAWM.

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Since the assessment of NAWM may provide more information concerning disease burden and evolution, the intention here was to characterize NAWM by using texture features.

The fact that ROI-specific findings were summed up per subject is a limitation of the current study since statistical results may have been distorted to some extent (either by masking differences via averaging out subtle changes or by enhancing small differences through outlier overweighting). More than two time-points for imaging data acquisition would be needed to allow drawing of reliable conclusions regarding the existence or not of temporal resolving power of the features computed. In addition, the interval between the examined time-points can be considered relatively small with respect to disease evolution in CIS. Although a standardized procedure was followed for brain MRI planning purposes, image registration between serial scans was not implemented to ensure maximum compatibility regarding lesion detection and segmentation. Regarding texture analysis, the correspondence between texture features and histological parameters remains a matter of debate since MRI image voxel resolution is much lower than the resolution in histological structures [10]. In addition, texture features analysis presented in this study is dependent [10] on:

- MR acquisition parameters;
- the quality assessment of the MRI device used;
- the methods of image reconstruction and processing.

Another limitation is that by computing the average values in texture features per subject somehow the individual lesions variability is diminished and that inter correlation between texture analysis results derived from T2-weighted images and other MRI findings may provide further insight in the pathophysiology of the disease and offer valuable information towards the development of prognostic disability measures. It is noted that no multiple comparison testing was carried out and this is a limitation of the study. On the other hand, a relatively small number of statistical tests was carried out and thus we think that multiple testing correction wouldn't affect the results.

Conclusion

The results of this study indicate that several texture features of T2 MRI brain white matter lesions can be used to differentiate between brain lesions NWM, and NAWM, that lead to minimal (EDSS ≤ 2) and mild clinical signs (EDSS > 2). They may furthermore, have an additional potential role in the clinical evaluation of MRI images in MS and perhaps may provide some prognostic evidence in relation to future disability of patients. However, a larger scale study is needed to establish the application in clinical practice and for computing shape and texture features that may provide information for better and earlier differentiation between normal brain tissue and MS lesions.

Further future directions including improvements in the measurement and preprocessing of the image by applying image normalization and validation of the results in a larger number of subjects have also been discussed in [17].

In conclusion, we believe that the proposed methodology in this study can provide a new and better clinical method for the early diagnosis and monitoring of quantitative disease progression and of the effectiveness of various treatment protocols in multiple sclerosis. Texture analysis will likely play in the future a supportive rather than a comprehensive role in the future of medical image interpretation. The robustness of texture analysis makes it particularly attractive for monitoring disease progression or treatment response with time, as demonstrated with MS.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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