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Temporal texture and shape analysis for quantification and monitoring of lesion load in multiple sclerosis

Purpose:

- Multiple Sclerosis (MS) is a chronic idiopathic disease that results in multiple areas of inflammatory demyelination within the central nervous system. Within individuals the clinical manifestations are unpredictable, particularly with regard to the development of disability.

- MRI is used in MS to detect disease onset and monitor activity and progression [1].

- Texture and shape features quantify macroscopic lesions and also the macroscopic abnormalities that may be undetectable using conventional measures of lesion volume and number. Texture analysis is used widely in MRI enabling disease characterization and quantification of disease distribution [2].

- New multi-scale amplitude-modulation and frequency-modulation (AM-FM) models have been used in a variety of applications including image reconstruction, image retrieval and video processing [3]. More recently, this method was employed in the characterization of carotid plaque in ultrasound images [4].

- This work explores the potential of texture, shape and AM-FM analysis in serial brain MRI to quantify and monitor lesion load in MS, as well as to facilitate understanding of the underlying pathophysiological mechanisms.

Methods and Materials:

A. Study Group and MRI Acquisition

Thirty six subjects (16 males, 20 females), aged 33.9±10.4 (mean±SD), with a clinical isolated syndrome (CIS) of MS and MRI detectable brain lesions underwent MRI brain scans twice in 12 months. The data were collected retrospectively. No registration algorithm was implemented, but standardized planning procedures were followed. All subjects remained untreated between the baseline and the follow-up MRI. Following the MRI, the patients were clinically examined by an experienced neurologist and were given a score in the expanded disability status scale (EDSS) score. Additionally, 10 healthy (4 males, 6 females), age-matched (mean±SD: 30.8±7.6) volunteers were scanned for image texture analysis on normal brain white matter (BWM). The images used for analysis were obtained using a T2-weighted turbo spin echo pulse sequence (TR=4408ms, TE=100ms, echo spacing=10.8ms).

B. Delineation of Regions of Interest

All detectable lesions were identified and manually segmented by an experienced neurologist and confirmed by a radiologist. Similar regions of interests (ROIs) were delineated to define normal appearing white matter (NAWM), as well regions of homogeneous high (cerebrospinal fluid) and low (air in the sinuses) signal intensities. Normal BWM areas, cerebrospinal fluid and air in the sinuses were also arbitrary segmented for the ten healthy subjects.

C. Interscan Intensity Normalization

To reduce the variability introduced by different gain settings and facilitate image comparability, a normalization algorithm [5] was used to adjust signal intensity distributions of each follow-up scan to match those of the corresponding baseline image. Global signal characteristics were first determined by quantifying the average high (cerebrospinal fluid) and low (air in the sinuses) intensity values in the original baseline and follow-up images. The histogram of the original follow-up image was then stretched and shifted to match the grey scale levels of the baseline image, thus producing a normalized image (**Figure 1**). A small reproducibility study concerning 5 scans was undertaken to confirm that the normalization procedure does not affect detectability and lesion visual perception.

D. Texture and Shape Analysis

The following statistical and texture features [6], as well as shape parameters, were extracted from segmented lesions and delineated NAWM and normal BWM regions.

(i) Statistical Features (SF): 1) standard deviation (σ),

(ii) Spatial Gray Level Dependence Matrices (SGLDM): 1) Contrast, 2) Sum of squares: variance, 3) Inverse difference moment, 4) Sum average, 5) Sum variance, 6) Sum entropy, 7) Entropy, 8) Difference variance, and 9) Difference entropy. Each feature was computed using a distance of one pixel and

(iii) 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.

E. AM-FM Analysis

A multi-scale AM-FM representation of digital non-stationary images was considered [7], and two AM-FM features were computed from the segmented regions: The instantaneous amplitude (IA) and the instantaneous frequency (IF). The IA models average intensity variations, and the IF provides information at a pixel level related with orientation variations, or structures in an image region. The two AM-FM features were computed at different frequency scales, considering only horizontal oriented filters of the three-scale filter bank used:

(i) Low frequencies (11.3 to 32 pixels wavelengths),

(ii) Medium frequencies (5.7 to 16 pixels wavelengths) and

(iii) High frequencies (2.8 to 8 pixels wavelengths).

F. Statistics

As data were not normally distributed, non-parametric tests were employed to test statistical significance. The Wilcoxon signed-rank and the Mann-Whitney rank-sum tests were used for dependent and independent samples respectively. Significant (S) or non-significant (NS) difference is given with a 95% confidence level.

Results:

- **Figure 1** shows a follow-up MR image, along with its histogram distribution, before and after normalization.

- **Figure 2** depicts the drawn ROIs enclosing the same lesion on the MRI scans of the same subject acquired at 0 and 12 months, along with their corresponding histogram distributions. The median and inter-quartile range (IQR) of the lesions at 0 and 12 months were 108 and 9.6 vs 99 and 11.8 respectively.

- **Table I** presents the statistical analysis for the shape features of all the lesions detected at the MRI scans acquired at 0 and 12 months. It is shown that there was a slight increase in the median and IQR of the number of lesions, total lesion area and total lesion volume per subject between 0 and 12 months, as well as for the major axis length (median=49 and IQR=86 vs median=83 and IQR=87), equivalence diameter (median=38 and IQR=63 vs median=63 and IQR=72) and perimeter (median=131 and IQR=219 vs median=189 and IQR=236).

- **Table II** presents the shape feature statistical analysis summed up for all lesions and for all subjects between the baseline and follow-up acquisitions. Significant differences were found for the eccentricity ($p=0.04$) and the minor axis length ($p=0.04$) between the MRI scans acquired at 0 and 12 months.

- **Table III** presents the median and IQR values for the texture features extracted from normal BWM tissue, NAWM, as well as from all lesions detected at 0 and 12 months. The statistical analysis performed showed that most of the features present a significant difference ($p<0.05$) between: i) normal BWM tissue and lesions at 0 months, ii) normal BWM tissue and lesions at 12 months. No significant differences were found for the features studied between the lesions detected at 0 and 12 months, whilst certain texture features differed significantly between NAWM and healthy white matter.

- **Table IV** presents the cases for which the studied AM-FM features (i.e. IA and IF) show statically significant differences. When data are summed-up, it appears that, mostly, intensity amplitude can differentiate between normal BWM and lesions, NAWM and lesions, and also between normal BWM and

NAWM. The extracted features fail, however, to pick-up any differences between lesions at 0 and 12 months.

TABLE I

EDSS VALUES AND SHAPE FEATURES FOR THE LESIONS DETECTED FOR EACH SUBJECT AT 0 AND 12 MONTHS. THE MANN-WHITNEY RANK-SUM TEST SHOWS THE NUMBER OF SIGNIFICANTLY DIFFERENT (S) AND NON-SIGNIFICANTLY DIFFERENT (NS) FEATURES BETWEEN 0 AND 12 MONTHS

	EDSS	NrL		MAL [mm]			EQD [mm]			PER [mm]			AL [mm^2]			VL [mm^3]	
		0	12	0	12	S/NS	0	12	S/NS	0	12	S/NS	0	12	S/NS	0	12
Nr. of S and NS						7/29			6/30			7/29			5/31		
Min	1.0	4	2	13	5		10	4		33	4		26	16		115	80
Max	8.5	15	14	236	253		173	173		654	659		454	448		2268	2241
Med	2	6,5	8	49	83		38	63		131	189		56	60		256	300
IQR	1	5.5	6	86	87		63	72		219	236		39	95		188	475

EDDS: Expanded disability status scale, IQR: Inter quartile range. NrL: Number of lesions per subject, MAL: Major axis length, EQD: Equivalence diameter, PER: Perimeter, AL: Total lesion area per subject, VL: Total lesion volume per subject.

TABLE II

SHAPE FEATURE STATISTICAL ANALYSIS FOR ALL LESIONS AND FOR ALL SUBJECTS BETWEEN BASELINE AND FOLLOW-UP STUDIES. THE WILCOXON SIGNED-RANK TEST SHOWS SIGNIFICANCE AT $P<0.05$

Features	0 vs 12 months
Area	NS (0.45)
Volume	NS (0.86)
Perimeter	NS (0.92)
Eccentricity	S (0.04)
Equivalence Diameter	NS (0.10)
Major Axis Length	NS (0.08)
Minor Axis Length	S (0.04)

TABLE III

MEDIAN (IQR) VALUES OF TEXTURE FEATURES FOR ALL LESIONS IDENTIFIED AT 0 AND 12 MONTHS. THE MAN WHITNEY RANK-SUM TEST SHOWS SIGNIFICANCE AT $P<0.05$

Texture Feature	Normal BWM tissue	Lesions at 0 months	Lesions at 12 months	BWM vs 0	BWM vs 12	0 vs 12	BWM vs NAWM
Stand. Dev.	4.1(0.8)	23(9.3)	22(7.8)	S	S	NS	NS
Median	70(6.8)	66(16)	56(21)	NS	S	NS	S
Contrast	14(4.5)	195(11)	142(12)	S	S	NS	NS
SOSV	16(6.3)	549(53)	487(35)	S	S	NS	NS
Entropy	4.8(0.4)	5.0(0.2)	5.2(0.6)	NS	NS	NS	S
IDM	0.3(0.04)	0.12(0.03)	0.11(0.03)	S	S	NS	S
Sum Aver.	142(14)	138(36)	122(52)	NS	NS	NS	S
Sum Var.	52(21)	2016(2152)	1794(1280)	S	S	NS	S
DV	5(1.5)	68(39)	52(40)	S	S	NS	NS
DE	2.1(0.2)	2.9(0.2)	2.8(0.3)	S	S	NS	NS

SOSV: Sum of squares variance, IDM: Inverse difference moment, DV: Difference variance, DE: Difference entropy, IQR: Inter quartile range

TABLE IV

COMPARISON OF THE CALCULATED IA AND IF (IA/IF) VALUES BASED ON THE MANN WHITNEY RANK SUM TEST AT $p<0.05$. TABLE PRESENTS RESULTS FOR LOW (L), MEDIUM (M) AND HIGH (H) FREQUENCIES. (-) DENOTES NON-SIGNIFICANCE

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		NAWM		Lesions	
		0 months	12 months	0 months	12 months
Normal BWM		LIA/- MIA/- HIA/-	LIA/LIF MIA/- HIA/-	LIA/LIF MIA/MIF HIA/-	LIA/LIF MIA/MIF HIA/-
NAWM	0 months		-/LIF -/- -/-	LIA/- MIA/- -/HIF	LIA/- MIA/- -/-
	12 months			LIA/LIF MIA/- -/-	LIA/LIF MIA/- -/HIF
Lesions	0 months				-/- MIA/- -/-

Conclusions:

- The majority of the examined texture and shape features differed significantly between segmented lesions, independently of the MRI acquisition time-point, and healthy BWM, revealing their discrimination potential.

- Texture features, along with new AM-FM features, also succeeded in distinguishing NAWM from MRI-detectable lesions and, to a lesser degree, from normal BWM, suggesting that they could possibly assist in pinpointing disease manifestation and in accurate disease monitoring.

- No significant correlation was seen between changes in shape and texture parameters, suggesting that alterations in tissue structure proceed MRI-detectable macroscopic changes.

- The observed changes probably reflect the underlying pathophysiological processes which result in different intensity patterns.

- No significant variation in lesion texture was resolved between serial scans, warranting the need for retrospectively studying the performance of the extracted features on an individual lesion basis in order to assess their potential as surrogate markers for temporal monitoring of lesion load in MS.

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