Textural Characterisation on Regions of Interest: A Useful Tool for the Study of Small Vessel Disease

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Abstract

We propose a framework for investigating the properties of apparently normal tissues on brain structural magnetic resonance images of patients with small vessel disease (SVD). It involves the extraction of textural features in regions of interest (ROIs) obtained from an anatomically-relevant template, combined with a statistical analysis that considers the relative distribution of SVD markers (e.g. microbleeds, perivascular spaces and white matter hyperintensities) with respect to the ROIs' textural characteristics in arterial territories derived from another template. We apply this approach to data from 42 patients from a study of mild stroke to investigate whether or not normal tissues in different brain regions are homogeneous regardless of the presence of specific SVD markers and varieties in the manifestations of the pathology (stroke lesion in different arterial territories). Our results suggest that this is not the case: that normal tissues are heterogeneous and that local variations (represented by the entropy) are associated with SVD markers, in agreement with clinical reports.

1 Introduction

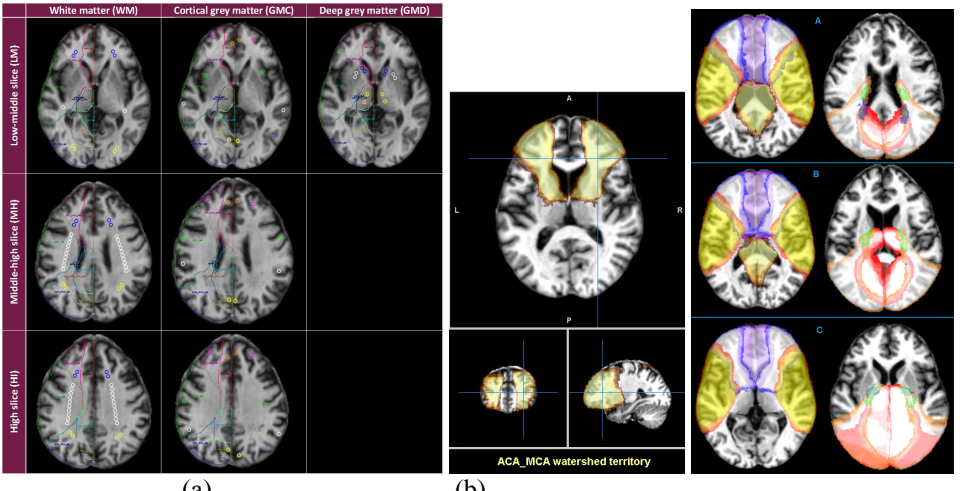
Stroke is the second largest cause of death worldwide and the commonest cause of disability in adulthood[1]. The lifetime risk of stroke in middle-aged men is 1 in 6, and even higher for women[2]. Magnetic Resonance Imaging (MRI) has become essential in

the study of stroke not only for examining infarct lesions but also for determining the presence of coexisting white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS) and brain microbleeds (BMB) that are part of the same diffuse small vessel disease (SVD) spectrum. These SVD features have been, for years, the focus of attention, whilst the apparently "normal" tissues have mainly been relegated to study atrophy. We developed a template and a framework that uses texture analysis to study normal tissues in brain MRI scans of stroke patients. Textural features contain information about the spatial distribution of intensity variations on an image and are independent of tone and invariant under monotonic grey-tone transformations. As clinical images are not quantitative, having a large dependency on non-normalised intensities, we hypothesised that texture analysis could be useful in studying tissue properties from these types of images and designed several experiments to determine whether normal tissues in different brain regions are or not homogeneous regardless of the presence of specific SVD markers and varieties in the manifestations of the pathology (stroke lesion in different arterial territories).

2 Methods

2.1 Template design

We created a Region of Interest (ROI) template relevant for the study of stroke and SVD (Figure 1(a)), and mapped on it the brain arterial territories obtained from a probabilistic template of brain arterial territories [3] (Figure 1(b and c)).



(a) (b) (c)

Figure 1: Templates (a) Object map of the ROIs and arterial territories on a fast spoiled gradient echo (flip angle 12°) (fspgr12) (b) Example of a probabilistic map of arterial territory; (c) Representative slices of the probabilistic map of all arterial territories, including watershed regions, on a T1-weighted image.

The ROIs are circular, cover approximately 12 mm^2 in-plane and are placed on three representative axial slices of the brain. Each ROI, with a volume ranging from 45 to 50 mm^3, is enumerated so as to provide information on specific locations. The criteria for selecting each slice are as follows: the base (i.e. low-to-middle) (LM) slice includes the basal ganglia (caudate nuclei heads and lentiform nuclei) and thalami, as well as third ventricle and horns of the lateral ventricles. In the LM there are 10 ROIs (5 per hemisphere) in the white matter (WM), 12 in the cortical grey matter (GMC) and 12 in the deep grey matter (GMD). The middle-to-high (i.e. top) (MH) slice does not show the basal ganglia, but the body of the lateral ventricles. On it, the centrum semiovale is largely present. The slice at the top of the brain (i.e. high, HI) is the first or second slice after the lateral ventricles are not visible at all, showing a clear patch of white matter centrally on each hemisphere (Figure 1(a)). Both in the MH and HI there are 28 ROIs in the WM and 12 in the GM. The template consists of a set of seven Analyze object maps (i.e. *.obj files): one for each slice and tissue type, as Figure 1(a) shows. These object maps can be uploaded into the ROI tool of Analyze 11.0™ (AnalyzeDirect Inc, Mayo Clinic) and semi-automatically re-assigned to any image to avoid noise, partial volume effects, artefacts, WMH, perivascular spaces, mineral depositions, lacunes and ischaemic or haemorrhagic lesions.

2.2 Textural features

From the 14 textural features described by Haralick and colleagues in [4], we used: contrast, correlation, homogeneity and entropy as they have a more intuitive meaning for our purpose, and computed them from grey-level co-occurrence matrices (GLCMs) [4] calculated using the function 'graycomatrix' from MATLAB R2014a. For each ROI, each textural feature (e.g. contrast, entropy, etc.) was calculated 4 times (i.e. using 4 GLCMs). Each of these 4 GLCMs used a different orientation (0º, 45º, 90º and 135º), all with distance 1 and size 8x8. The final value for the textural feature on a ROI was obtained averaging the values obtained from these 4 GLCMs.

We also determined the sum, mean and standard deviation of the intensities on each ROI and expressed them in relation to the maximum intensity value in the tissue type for the specific subject: (mean/max tissue intensity) x 100%. To determine the adjacent contrast between grey matter (GM) and white matter (WM) on the same arterial territory and slice, we calculate the mean GM_WMcontrast (C) as: C = (WMmean -GMmean) / (WMmean + GMmean).

2.3 Hypotheses framework

We created the following hypotheses framework to study the texture of the normal tissues (i.e. GM and WM) in their relationship to SVD markers:

	To test the inter-hemispheric balance of the texture in normal tissues
1	HI WM ROIs that correspond to the radiations of the corpus callosum, have low entropy high mean intensity and small SD in all patients, balanced in left and right hemispheres
2	The average contrast C between cortical GM (GMC) and WM should be similar in the HI, LM and MH ROIs between themselves, and between hemispheres for each patient

	To test the spatial relationship between the texture of normal tissues and the infarcted region
3	Hemisphere of the infarct and location per arterial territories are not associated with ROIs intensity and entropy values
	To test the association between the texture of normal tissues and age
4	Entropy values for the WM regions (HI, LM, MH) should be all similar per subject, and will depend on the WMH load and patient's age
5	Entropy values for the GMC regions (HI, LM, MH) should be all similar per subject, and will not depend on the WMH load or patient's age
6	The mean contrast between GM and WM is associated with WMH load and patient's age
	To test the association between texture of normal tissues and SVD markers
7	Entropy values of all ROIs are associated with the number of microbleeds and EPVS
8	Intensity and entropy values of all WM ROIs are similar on each patient, and the same stands for all GMC ROIs, but not for GMD ROIs

Table 1: Hypotheses framework

3 Experiments and Results

3.1 Datasets

We used imaging data from 42 individuals that presented to a hospital with mild to moderate stroke symptoms, mean age ± SD=64.9±10.0 years, and consented to participate on a study of stroke. From the 42 patients, 19 (45.2%) had a stroke type identified as lacunar. The MRI data were acquired on a 1.5T GE Signa Horizon HDxt clinical scanner operating in research mode with an 8-channel phased-array head coil. We used axial fluid-attenuated inversion recovery (FLAIR; TR/TE/TI=9000/153/2200, 24x24 cm FoV, 384×224 acquisition matrix, 28 x 5 mm slices, 1 mm slice gap) and prepared fast spoiled gradient echo (fspgr; TR/TE=8.2/3.1 ms, 12° flip angle, 24x24 cm FoV, 256×192 acquisition matrix, 42 x 4 mm slices). We also used WMH volume measurements and microbleeds and PVS visual ratings determined previously as described in [5]. Images were not pre-processed before ROI extraction or texture analyses.

Mann Whitney U tests were used to determine the significance in differences between 2 independent variables (i.e. textures in WM and GM), Kruskal-Wallis H test was used when the test involved k independent variables. When related variables were examined (i.e. WM on different ROIs or ROIs from the same patient) Wilcoxon's and Friedman's tests were used. Associations were determined using univariate linear regression. All analyses were carried out in IBM SPSS 20 and MATLAB R2014a.

3.2 Results

The median SVD marker characteristics in the group were: 5 (IQR 3, 6) microbleeds, 4 (IQR 3, 7) EPVS and WMH volume of 18.4 ml (IQR 10.2 ml, 42.1 ml) per patient. The results corresponding to the hypothesis framework are summed up in Table 2.

Hypothesis no.	Stats. test	Results in FLAIR	Results in fspgr12	Meaning of the result / implications
1	Wilcoxon's	p=0.98 (variance and norm. intensities), p=0.97 (norm. intensity means), p=0.20 (entropy)	p=0.26 (variance and norm. intensities), p=0.52 (norm. intensity means), p=0.16 (entropy)	HI WM normalised intensities, their variations and entropies were balanced in both cerebral hemispheres.
2	Kruskal Wallis H	**p=0.04** (LM slice) p=0.23 (MH slice) p=0.29 (HI slice)	**p=0.01** (LM slice) **p=0.001** (MH slice) **p=0.001** (HI slice)	WM/GM contrast was not balanced between hemispheres across different slices.
3	Mann Whitney U	p=0.15-0.88 (LM intens.) p=0.12-1.00 (MH intens.) p=0.09-0.93 (HI intens.) p=**0.01**-0.66 (LM entro.) p=**0.03**-0.97 (MH entro.) p=0.11-0.91 (HI entro.)	p=**0.03**-0.79 (LM intens.) p=0.11-0.92 (MH intens.) p=0.06-1.00 (HI intens.) p=**0.02**-0.94 (LM entro.) p=0.12-0.93 (MH entro.) p=0.09-0.82 (HI entro.)	Overall the hemisphere of the stroke lesion and location per arterial territories was not associated with ROI normalised intensity and entropy values, apart from a very select few associations
4	Friedman's test and univar. linear regression	p=0.06 to 0.77 (all WM ROIs, LM, MH, HI); median WM entropy associated with age (**p=0.02**) and WMH volume (**p=0.001**).	p=0.56 to 0.91 (all WM ROIs, LM, MH, HI); median WM entropy not associated with age (p=0.61) or WMH volume (p=0.21)	WM entropy values were balanced in both fspgr12 and FLAIR. The association of WM entropy values with age and with WMH volume varies with MRI sequence: present in FLAIR but not in fspgr12.
5	Friedman's test and univar. linear regression	p=0.21 to 0.27 (GMC LM, MH, HI), **p=0.04** (all GMC ROIs); median GMC entropy not associated with age (p=0.31) or WMH volume (p=0.06).	**p=0.01** (LM), p=0.07 to 0.97 (all GMC ROIs, MH, HI); Median GMC entropy not associated with age (p=0.22) and neither with WMH volume (p=0.20).	GMC entropy values were balanced in some regions depending on the MRI sequence. No association was observed between GMC entropy values and age or WMH volume regardless of MRI sequence used.
6	Univar. linear regression	p=0.33 to 0.81 median contrast across slices	p=0.16 to 0.24 median contrast across slices	GM/WM contrast was not found to be associated with age or WMH volume.

7	Univar. linear regression and Mann Whitney U	WM entropy: p=**0.02** (EPVS), p=**0.04** (BMB). GMC entropy: p=0.52 (EPVS), p=**0.02** (BMB). GMD entropy: p=0.28 (EPVS), p=0.13 (BMB).	All: p=0.21 to 0.81 (EPVS), p=0.25 to 0.97 (BMB)	GMD entropy was not found to be associated with EPVS or brain microbleeds (BMB). WM and GMC entropies could be associated with EPVS or brain microbleeds in FLAIR.
8	Friedman's	**p<0.001** (all WM, GMC, GMD ROI norm. intensities), **p=0.04** (all GMC ROI entropies), p=0.21 to 0.75 (all WM, GMD ROI entropies).	**p<0.001** (all WM, GMC, GMD ROI norm. intensities), p=0.07 to 0.91 (all WM, GMC, GMD ROI entropies).	Normalised intensity values for all ROIs per patient were not balanced. ROI entropy values per patient per tissue type were balanced almost in all slices in both MRI sequences.

Table 2: Results from the texture analysis on individual ROIs on normal-appearing tissue

4 Discussion and Conclusion

Clinical manifestations of MRI-defined SVD are generally moderate and heterogeneous, with post-mortem studies confirming the existence of WM disease also heterogeneous in terms of histopathology [6]. Damage to the tissue has been found to range from slight disentanglement of the matrix to varying degrees of myelin and axonal loss. Our results also suggest that normal tissues are heterogeneous and that local signal intensity variations (represented by the entropy) could be associated with SVD markers. We did not correct for multiple comparisons because our objective was only to develop an approach to explore the usefulness of texture for characterising normal tissues, encouraged by previous reports of the applicability of texture analysis in tumour characterisation [7,8]. Overall the location of the infarct (i.e. hemisphere and, more precisely, arterial territory) was not found to be associated with normal tissue textural data (intensity, entropy). However, in some cases sample sizes were very small (e.g., only 3 stroke lesions in left PCA territory) so further research is needed to confirm these findings. It will be recommended to reproduce this study in larger sample sizes for further examining the associations between tissue textural data (especially from FLAIR scans) and SVD markers.

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