Preliminary results on the clinical relevance of multiple sclerosis lesion distribution independent of lesion volume

F. Sheikhzadeh[1,2], and R. Tam[2,3]
[1]Biomedical Engineering Program, University of British Columbia, Vancouver, BC, Canada, [2]MS/MRI Research Group, University of British Columbia, Vancouver, BC, Canada, [3]Department of Radiology, University of British Columbia, Vancouver, BC, Canada

Introduction

Previous MRI studies that have used multiple sclerosis (MS) lesions to compute surrogate biomarkers have largely focused on global or regional lesion volume and their correlation to measures of clinical disability, the most common being the Kurtzke Expanded Disability Status Scale (EDSS). The correlation between lesion volume and EDSS is generally weak, especially in T2-weighted imaging studies [1]. In this study we investigate whether a mathematical measure of the 3D spatial distribution of lesion voxels can reveal clinical significance that is independent of lesion volume. Our hypothesis is that for any two given patients with similar lesion loads, the one with greater distribution would tend to have greater disability.

Methods

MRI acquisition: The T2w and PDw MRIs of 24 patients (EDSS range = 1.5 – 8.0, mean = 5.0, SD = 2.2) from a selected scanning site of an MS clinical trial were used. The scans were acquired in the axial orientation, using the two most inferior points on the boundary of the corpus callosum to define the slice angle, on a Philips Achieva 3T scanner with a dual-echo sequence with TE1=15.0ms, TE2=75.0ms and TR=2700.0ms. The image dimensions were 256 × 256 × 50 with voxel size 0.937mm × 0.937mm × 3.0mm. **Data preparation:** For each patient, the white matter lesions were delineated on each T2/PDw pair using a semi-automatic method [2]. Binary images were obtained in which lesion voxels have the value of 1 and all other voxels have value 0. **Measuring lesion distribution:** To quantify the distribution of lesion voxels for each patient, we computed the variance of the 3D Euclidean distance between each lesion voxel and a fixed reference point. We tried several reference points and found the center point of the brain defined on the largest slice, but projected onto the most inferior slice, to yield the strongest results. Figure 1 shows the position of different reference points that were tried. **Analysis:** The results were analyzed to see if there is a statistically significant relationship between lesion distribution and EDSS and determine whether distribution has the potential to provide information that is additional to and independent from lesion volume. First, we computed Pearson's and Spearman's correlations to investigate the relationships between lesion distribution, EDSS, and total lesion volume. Since we have three variables, we used regression analysis to investigate whether there is a potentially meaningful relationship between lesion distribution and EDSS, independent of total lesion volume. Linear regression analysis assumes that the dependent variable is a linear combination of the other variables, and it helps us understand how the typical value of the dependent variable (EDSS) changes when either one of the independent variables (lesion distribution or total lesion volume) is varied, while the other independent variable is held fixed [3]. In addition, to examine the relationship between distribution and EDSS while adjusting for volume, we ran two multiple regressions: one predicting EDSS using only volume as the predictive variable and a second regression using both volume and distribution as the predictive variables. After constructing regression models, the statistical significance of the estimated parameters were checked by an F-test of the overall fit.

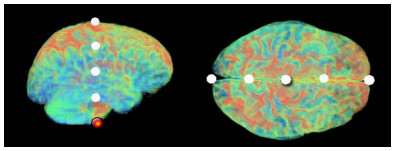

Figure 1. Different reference points were tried for distribution measurement. The red point (the center point on the largest slice projected onto the most inferior slice) was the best reference point in our measurements.

Results and observations

Table 1 contains the correlation coefficients and p-values that relate EDSS, lesion distribution, and total lesion volume. The results illustrate that the EDSS values are significantly correlated with both total lesion volume ($p < 0.05$) and lesion distribution ($p < 0.01$), with the distribution correlations being higher than the volume correlations. In addition, volume and distribution are not correlated ($p > 0.05$) which means these variables are independent for this data set. The F-values and p-values from the regression analysis are shown in Table 2. The results indicate that the EDSS has a significant linear relationship ($p < 0.05$) with total lesion volume. More interestingly, Table 2 shows that adding distribution to the regression model is statistically significant ($p<0.001$), meaning that EDSS and distribution are significantly related even after adjusting for volume. The same results can be observed in Figure 2; the left graph illustrates the approximate linear relationship between EDSS and distribution and the right graph summarizes the relationships between EDSS, volume and distribution, and shows that for the same volume range, EDSS generally increases with lesion distribution.

Table 1. Correlation values (rho) investigating EDSS, distribution, and volume relationships.

Correlation values		Volume & EDSS	Distribution & EDSS	Distribution & Volume
Pearson	rho	0.4824	0.5770	0.1288
	p-value	**0.0170**	**0.0032**	**0.5488**
Spearman	rho	0.4553	0.5735	0.3026
	p-value	**0.0254**	**0.0034**	**0.1505**

Table 2.F-values and p-values of the overall fit in regression models

Regression models	F-value	p- value
Regression of EDSS on volume	6.6724	0.0170
Significance of adding distribution to the model	11.3749	0.0004
Regression of EDSS on volume and distribution	10.5969	0.0007

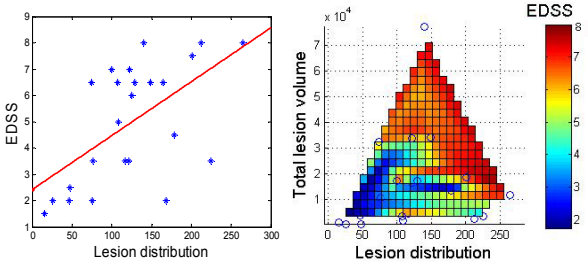

Figure 2. EDSS vs distribution and volume; Left: approximate linear relationship between EDSS and distribution. Right: EDSS values are shown using a range of colors (dark blue and brown correspond to 2 and 8). For the same volume range, EDSS increases as lesion distribution increases.

Conclusions

In this study we computed the spatial distribution of lesion voxels in the MRI scans of 24 MS patients using a measure based on the variance of distances. Comparing these values to EDSS we have found that there is a potentially meaningful correlation between patient disability and lesion distribution. In this data set, we observed that the distribution values provide new information about the severity of MS that is independent from and potentially more sensitive than total lesion volume. From these preliminary results we can conclude that measures of lesion distribution hold some promise as surrogate biomarkers for monitoring MS progression. Further work on larger patient samples is needed to confirm these findings.

References

1. Barkhof F, Multiple Sclerosis, Vol 5, 1999, 283- 286. **2.** McAusland J et al., IEEE Trans on Biomed Eng., 2010, 57(11), 2689-2698.**3.** van Belle G et al, Biostatistics, John Wiley and Sons, 2004, 442.