# Spatial Dispersion of Lesions as a Surrogate Biomarker for Disability in Multiple Sclerosis

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## Abstract

*Many previous studies in multiple sclerosis (MS) have focused on the relationship between white matter lesion volume and clinical parameters, but few have investigated the independent contribution of the spatial dispersion of lesions to patient disability. In this study, we examine the ability of four different measures of lesion dispersion including one connectedness-based measure (compactness), one region-based measure (ratio of lesion convex hull to brain volume) and two distance-based measures (Euclidean distance from a fixed point and pair-wise Euclidean distances) to act as potential surrogate markers of disability. We use a set of T2-weighted and proton density-weighted MRIs of 24 MS patients, collected from a single selected scanning site participating in an MS clinical trial. For each patient, clinical status is available in the form of expanded disability status scale (EDSS) a standard measure of disability in MS. We segment all white matter lesions in each scan with a semi-automatic method to produce binary images of lesion voxels, quantify their spatial dispersion using the defined measures, then perform a statistical analysis to compare the dispersion values to EDSS and total lesion volume. We use linear and rank correlations to investigate the relationships between lesion dispersion, EDSS, and total lesion volume, and regression analysis to investigate whether there is a potentially meaningful relationship between lesion dispersion and EDSS, independent of total lesion volume. Our results show that one distance based measure, Euclidean distance from a fixed point, correlates with EDSS more strongly than total lesion volume ($r = 0.57$ vs. $r = 0.47$ for Pearson correlation), and has predictive value that is at least partly independent of lesion volume. The results suggest that for any two given patients with similar lesion loads, the one with greater dispersion would tend to have greater disability, but further experiments with larger data sets are required to confirm these findings.*

## 1. Introduction

Measurement of the total white matter lesion volume on magnetic resonance images (MRIs) is a widely used outcome measure for monitoring the pathological state and progression of multiple sclerosis (MS) [9]. However, previous studies have shown that the relationship between lesion volume and patient disability is generally weak, especially in T2-weighted (T2w) imaging studies [1]. Specifically, the cross-sectional correlation between T2w lesion volume and the Extended Disability Status Scale (EDSS), which is the most frequently used clinical measure in MS [10], typically ranges between 0.15 to 0.4 with some studies reporting values as high as 0.6 [1]. A number of factors are known to affect the strength of this correlation, including the lack of pathological specificity of T2w imaging, neuroplasticity which helps the brain adapt to local injury, and limitations of the EDSS [2]. In addition to having a limited predictive value, the focus on global lesion volume has left other lesion variables under-explored. In this study we investigate whether mathematical measures of the 3D spatial dispersion of lesion voxels can reveal clinical significance that is independent of lesion volume. A number of studies have explored the contribution of lesion location (*e.g.*, [5, 12]) to

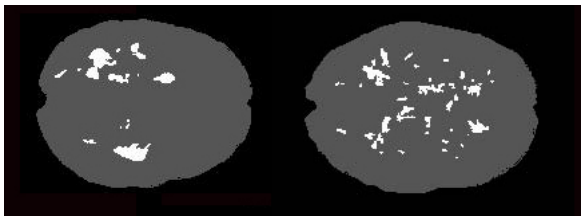


Figure 1: White matter lesions, transverse view; left: a patient with the total lesion volume of 3071 $mm^3$ and EDSS of 3.5, right: a patient with the total lesion volume of 2957 $mm^3$ voxels and EDSS of 6.5. This example illustrates our hypothesis that for any two given patients with similar lesion loads, the one with greater dispersion would tend to have greater disability.

MS disability, most commonly done using a lesion probability map that is sometimes referred to as representing "distribution" [3, 6], but there has been minimal work done to quantify the spatial extent of MS lesions and its contribution to disability while controlling for volume as a variable. We use the term "dispersion" rather than "distribution" to define spatial extent in order to distinguish our work from studies on lesion location. Our hypothesis is that for any two given patients with similar lesion loads, the one with greater dispersion would tend to have greater disability due to a greater global impact on the brain, thereby reducing its capacity to adapt. Figure 1 presents a motivating example, and shows the projection of all lesion voxels onto the largest transverse slice of the brain scans of two patients in our data set. These patients have approximately the same total lesion volume ($\sim$3000 $mm^3$), but different spatial dispersion. The EDSS value for the patient with more distributed lesions is higher (6.5 vs. 3.5). Exploring such relationships can improve the understanding of MS and potentially lead to the discovery of novel surrogate biomarkers for clinical use. In this paper, we investigate four different measures of lesion dispersion. The first, termed compactness, quantifies the connectedness between the lesion voxels without incorporating distances. The second measure is the volume ratio of the convex hull of the lesion voxels to the brain volume. The convex hull approximates the region impacted by the lesions and in most cases includes normal-appearing tissue. The third measure uses the mean, variance, entropy and skewness of the distribution of the Euclidean distances of the lesion voxels from a fixed reference point. The last method also uses the mean, variance, entropy and skewness of a set of Euclidean distances, but computed as pair-wise distances between the lesion voxels rather than from a fixed reference point. After computing each measure for our patient samples, we perform a statistical analysis to determine the strength of its relationship to the patients' disability, and compare the contribution of the dispersion to that of lesion volume. To the best of our knowledge, this is the first study on the relationship between spatial lesion dispersion and MS disability.

## 2. Methods

### 2.1. Data

We use T2w and proton density-weighted (PDw) MRIs of 24 patients from a selected scanning site of an MS clinical trial. The scans were acquired in the axial orientation on a Philips Achieva 3T scanner with a dual-echo sequence with TE1 = 15.0 ms, TE2 = 75.0 ms and TR = 2700.0 ms. The original image dimensions are $256 \times 256 \times 50$ with voxel size $0.937\,\text{mm} \times 0.937\,\text{mm} \times 3.0\,\text{mm}$. The white matter lesions are delineated on each T2/PDw pair using a semi-automatic method [8] to produce binary images in which the lesion voxels have the value of 1. The 3.0 mm slices of the binary images are divided into 1.0 mm slices to account for voxel anisotropy in the lesion dispersion measurements, resulting in images with dimensions of $256 \times 256 \times 150$. For each patient, clinical status is available in the form of an EDSS score, which is defined on a scale from 0 to 10, where 0 represents a normal neurological exam, and 10 represents death due to MS. The score is based upon testing and examination of functional systems of the patients by a qualified neurologist. The patient sample is a mix of RRMS (13) and SPMS (11) patients with well-distributed EDSS values that have a mean of 5.0, standard deviation of 2.2, and range of 1.5 – 8.0.

### 2.2. Lesion dispersion measures

**Compactness.** Developed by Bribiesca [4] to quantify the connectedness of shapes composed of cubic voxels, compactness is mathematically defined as follows:

$$C = \frac{n - A/6}{n - (\sqrt[3]{n})^2} \tag{1}$$

where $A$ corresponds to the total area of the externally visible faces of the solid and $n$ is the total number of voxels. Intuitively, as a shape becomes less compact, there are fewer connections between voxels, and $A$ increases, causing $C_d$ to decrease. The main advantages of compactness are: its ease of computation for voxel data; and having a range between 0 and 1, thereby removing the need for any external normalization factor. Its main limitation is that distances between voxels are not modeled.

**Ratio of convex hull volume to brain volume.** For each patient, we compute the convex hull that contains all of the lesion voxels. Then we use the volume ratio of the lesion convex hull to the brain as a measurement of lesion dispersion. The rationale for this measure is that using the lesions to form a convex hull defines a region that is more likely to be impacted by the visible damage than the areas outside of

the convex hull. The brain volume acts as a normalization factor. This measure is the only one among the four in this study that is region-based.

**Euclidean distance from a fixed reference point.** To quantify the lesion dispersion using distance, we compute the mean, variance, entropy and skewness of the distribution of the 3D Euclidean distance between each lesion voxel and a fixed reference point. The mean and variance are computed from the distances directly, whereas the entropy and skewness are computed from a histrogram of the distances. We have tested a number of different reference points for our measurement, including the centroid of the brain, several extremal points, and points in-between. We observe that the results are dependent on the location of the reference point, and that the center point of the brain defined on the largest slice, but projected onto the most inferior slice, yields the strongest correlation to EDSS. In order to account for natural variations in brain size among different patients, we apply principle components analysis to the brain voxels to compute the anterior-posterior, left-right and superior-inferior axes for each patient. The maximum extent along each direction is then used to normalize the lesion distances along the same direction. Mathematically speaking, we use Equation 2 to compute the normalized distance beween the $i$th lesion voxel and the reference point $r$:

$$d_{ir} = \sqrt{(\frac{x_i - x_r}{x_b})^2 + (\frac{y_i - y_r}{y_b})^2 + (\frac{z_i - z_r}{z_b})^2}. \quad (2)$$

where $(x_i, y_i, z_i)$ are the coordinates of the lesion voxel, $(x_r, y_r, z_r)$ are the coordinates of the reference point, and $x_b$, $y_b$, and $z_b$ are the maximum brain extents in the anterior-posterior, left-right and superior-inferior directions respectively.

**Pair-wise Euclidean distances analysis.** To have a distance-based measure that is independent of any reference points, we compute the pair-wise Euclidean distances of lesion voxels in each patient. We measure the mean, variance, entropy and skewness of the distribution of the pair-wise distances. The mean and variance are computed from the distances directly, whereas the entropy and skewness are computed from a histogram of the distances. Similarly to the fixed-point method, the distances are normalized to the brain extents of each patient.

### 2.3. Statistical analysis

We analyze the results to investigate if there is a statistically significant relationship between lesion dispersion and EDSS and determine whether such dispersion has the potential to provide information that is additional to and independent from lesion volume. First, we compute Pearson and Spearman correlations to investigate the relationships between lesion dispersion, EDSS, and total lesion volume (normalized by intradural volume computed using a method

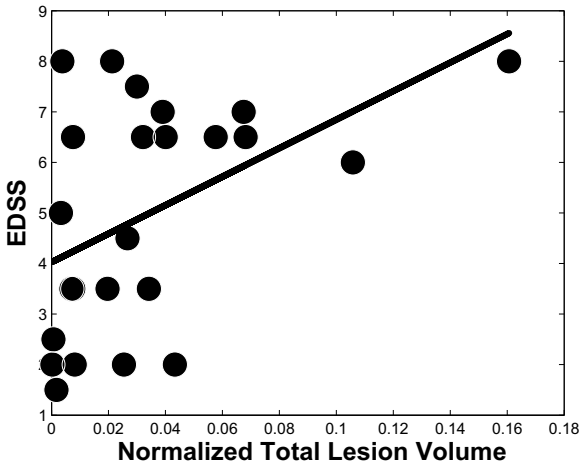



Figure 2: Relation between total lesion volume (normalized by intradural volume) and EDSS.

based on [7]). The Pearson method assumes a linear relationship, whereas the Spearman method is a rank correlation that does not assume any particular type of relationship. The $p$-values of both correlations are computed to test for statistical significance. For this study we make a general assumption of linearity, therefore any discussion of correlation can be taken to mean Pearson correlation unless otherwise specified, and the Spearman values are provided primarily for completeness. Since we have three variables, in the next step, we use regression analysis to investigate whether there is a potentially meaningful relationship between lesion dispersion 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 dispersion or total lesion volume) is varied, while the other independent variable is held fixed [11]. We compute two multiple regressions: one predicting EDSS using only volume as the predictive variable and a second regression using both volume and dispersion as the predictive variables. After constructing regression models, the statistical significance of the estimated parameters is checked by an F-test of the overall fit.

## 3. Results

### 3.1. Total lesion volume normalized by intradural volume

To establish a baseline of clinical significance, we first analyze the total lesion volume, normalized by intradural volume to minimize the influence of head size. This mea-

Table 1: Correlation values in the sample of 24 patients (13 RRMS, 11 SPMS), between EDSS and normalized total lesion volume (V), compactness (C), ratio of lesion convex hull (RCH) to brain volume, mean, variance, skewness and entropy of the distribution of Euclidean distances from a fixed point (MED, VED, SHED, EHED), mean, variance, skewness and entropy of pair-wise Euclidean distances between lesion voxels (MPWED, VPWED, SHPWED, EHPWED). The statistically significant correlations ($p < 0.05$) are in bold.

| Measures | correlation with EEDS | | correlation with V | | Significance of adding the measure to the linear regression of E on V |
|---|---|---|---|---|---|
| | Pearson | Spearman | Pearson | Spearman | |
| **V** | **r = 0.47**<br>**p = 0.02** | **r = 0.44**<br>**p = 0.02** | - | - | - |
| C | **r = 0.45**<br>**p = 0.02** | r = 0.35<br>p = 0.08 | **r = 0.71**<br>**p = 7×10$^{-5}$** | **r = 0.82**<br>**p = 2×10$^{-6}$** | p = 0.45 |
| RCH | **r = 0.49**<br>**p = 0.01** | **r = 0.44**<br>**p = 0.02** | **r = 0.77**<br>**p = 9×10$^{-6}$** | **r = 0.81**<br>**p = 2×10$^{-6}$** | p = 0.29 |
| MED | r = 0.001<br>p = 0.99 | r = 0.005<br>p = 0.98 | r = 0.26<br>p = 0.20 | r = −0.09<br>p = 0.64 | r = 0.64 |
| **VED** | **r = 0.57**<br>**p = 0.003** | **r = 0.57**<br>**p = 0.003** | r = 0.11<br>p = 0.59 | r = 0.25<br>p = 0.23 | **p = 0.0004** |
| SHED | **r = -0.48**<br>**p = 0.01** | r = −0.38<br>p = 0.06 | **r = -0.42**<br>**p = 0.04** | r = −0.33<br>p = 0.11 | p = 0.06 |
| **EHED** | **r = 0.54**<br>**p = 0.006** | **r = 0.39**<br>**p = 0.05** | **r = 0.44**<br>**p = 0.02** | **r = 0.58**<br>**p = 0.02** | **p = 0.02** |
| **MPWED** | **r = 0.47**<br>**p = 0.01** | **r = 0.52**<br>**p = 0.008** | **r = 0.44**<br>**p = 0.02** | **r = 0.50**<br>**p = 0.01** | p = 0.08 |
| VPWED | r = −0.28<br>p = 0.17 | r = −0.20<br>p = 0.33 | r = −0.32<br>p = 0.12 | **r = -0.43**<br>**p = 0.03** | p = 0.57 |
| SHPWED | r = −0.29<br>p = 0.15 | r = −0.25<br>p = 0.22 | r = −0.31<br>p = 0.14 | **r = -0.65**<br>**p = 7×10$^{-4}$** | p = 0.50 |
| **EHPWED** | **r = -0.45**<br>**p = 0.02** | **r = -0.40**<br>**p = 0.04** | **r = -0.62**<br>**p = 0.001** | **r = -0.75**<br>**p = 2×10$^{-5}$** | p = 0.31 |

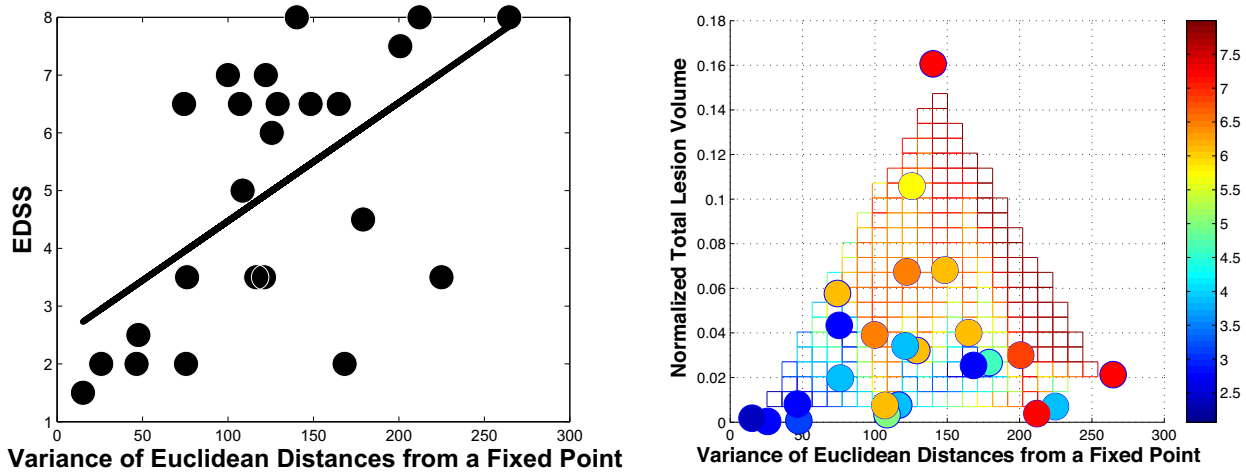
sure has a mean of 0.03, standard deviation of 0.03, and range of $2.8\times10^{-4}$ – 0.14. Figure 2 shows the relation between total lesion volume and EDSS. Each point represents a patient in this graph and the line is the best fit to the data given by the linear regression of EDSS on total lesion volume. The Pearson and Spearman correlations between EDSS and volume are 0.47 ($p = 0.02$) and 0.44 ($p = 0.02$), which are within the range of published values [1]. The results indicate that the EDSS has a significant linear relationship ($p < 0.05$) with volume.

### 3.2. Compactness

To quantify the strength of the relationships between compactness, EDSS and lesion volume, we calculate the correlations between compactness and EDSS ($r = 0.45$, $p = 0.02$), and compactness and total lesion volume ($r = 0.71$, $p = 7.3\times10^{-5}$). Detailed results are provided in Table 1. The Pearson correlation between EDSS and compactness is significant and comparable to that between EDSS and volume, and shows that patients with lower compactness (*i.e.*, more disconnectedness) tend to have more disability. However, the correlation between compactness and volume is high, and statistically significant, which means that in terms of a linear relationship, these two variables seem to be strongly dependent. Adding compactness to the linear regression model of EDSS on volume is not statistically significant ($p = 0.51$). Therefore, there does not seem to be a linear relationship between compactness and EDSS that is independent of volume.

### 3.3. Ratio of convex hull (RCH) volume to brain volume

As shown in Table 1, the ratio of lesion convex hull volume to brain volume is correlated with EDSS ($r = 0.49$, $p = 0.01$), but again, like compactness, the correlation between total lesion volume and RCH is strong ($r = 0.79$, $p = 3\times10^{-6}$). As a result, even though the correlation between RCH and EDSS is significant, adding RCH to the lin-




(a) (b)

Figure 3: Relationship between lesion volume, variance of Euclidean distances from a fixed point (VED), and EDSS; a) approximate linear relationship between EDSS and VED. b) EDSS values are shown using a range of colors (dark blue and brown correspond to 2 and 8, respectively). For the same volume range, EDSS generally increases as VED increases.

ear regression model of EDSS on volume is not ($p = 0.29$), and we cannot conclude that RCH is informative about MS disability independent of total lesion volume.

### 3.4. Euclidean distance (ED) from a fixed reference point

Table 1 contains the correlation coefficients and $p$-values that relate EDSS to the mean and variance of Euclidean distance (VED and MED), skewness and entropy of the histogram of Euclidean distance (SHED and EHED) and total lesion volume (V). The results show that the EDSS values are significantly correlated with VED ($r = 0.57$, $p = 0.003$) and EHED ($r = 0.54$, $p = 0.006$), with both correlations being higher than the volume-EDSS correlation ($r = 0.47$, $p = 0.02$). In addition, V and VED are not correlated ($p = 0.59$) which means these variables are independent for this data set. However, EHED is correlated with V ($p = 0.02$). More interestingly, the $p$-values from the regression analysis show that adding VED to the regression model of EDSS on V is statistically significant ($p = 0.0004$), meaning that EDSS and VED are significantly related even after adjusting for V. The same observation can be made for EHED since adding it to the regression model is statistically significant ($p = 0.02$). The left graph in Figure 3 illustrates the approximate linear relationship between EDSS and variance of Euclidean distances (VED) and the right diagram shows the relationship between EDSS, volume and VED values using a range of colors (from dark blue, which corresponds to 1.5, to brown, which corresponds to 8). The color of each point represents the EDSS score of that patient. For improved visualization of the overall trends, we interpolate the EDSS values and display them as a color grid in the background. The right graph shows that for the same volume range, EDSS generally increases with lesion dispersion.

### 3.5. Pair-wise Euclidean distances (PWED)

Table 1 contains the correlation coefficients and p-values that relate EDSS to the mean and variance of pair-wise Euclidean distances (MPWED and VPWED), skewness and entropy of the histogram of the pair-wise Euclidean distances (SHPWED and EHPWED) and total lesion volume (V). The EDSS values are correlated with MPWED ($r = 0.47$, $p = 0.01$) and EHPWED ($r = -0.45$, $p = 0.02$). The MPWED-EDSS correlation is comparable to the volume-EDSS correlation. However, volume is correlated to MPWED ($r = 0.44$, $p = 0.02$), and adding MPWED to the linear regression model of EDSS on volume is not statistically significant ($p = 0.08$), which means this variable is not independent of volume for this data set.

## 4. Discussion and conclusion

In this study we computed the spatial dispersion of lesions in the MRI scans of 24 MS patients using different measures. Comparing these values to EDSS and total lesion volume, we have found that there is a potentially meaningful correlation between patient disability and distance-based measurements of lesion dispersion. For quantifying

lesion dispersion, we used one connectedness-based measure (compactness), one region-based measure (ratio of lesion convex hull to brain volume) and two distance-based measures (Euclidean distance from a fixed point and pairwise Euclidean distances). In this data set, we observed that for describing lesion dispersion in MS patients the distance factor plays a more important role compared to connectedness and convex region size. In particular, the variance of Euclidean distance from a fixed point provides new information about the severity of MS that is independent from and potentially more sensitive than total lesion volume.

The two distance-based measures that we tested have several components each, which may raise the concern of a statistical chance finding resulting from multiple comparisons. If we apply Bonferroni correction to the 3rd and 4th approaches which have 4 related tests each, we obtain a new significance value of $(0.05/4 = 0.0125)$. Our most promising result (variance of distances from a fixed point) yielded a $p$-value of 0.0004, which is well below the corrected threshold. From these preliminary results we can conclude that distance-based measures of lesion dispersion hold some promise as surrogate markers of MS disability. Further work on larger patient samples is needed to confirm these findings.

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