Three-Dimensional Analysis of the Geometry of Individual Multiple Sclerosis Lesions: Detection of Shape Changes Over Time Using Spherical Harmonics

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Purpose: To suggest a quantitative method for assessing the temporal changes in the geometry of individual multiple sclerosis (MS) lesions in follow-up studies of MS patients.

Materials and Methods: Computer simulated and in vivo magnetic resonance (MR) imaged MS lesions were studied. Ten in vivo MS lesions were identified from sets of axial MR images acquired from a patient scanned consecutively for 24 times during a one-year period. Each of the lesions was segmented and its three-dimensional surface approximated using spherical harmonics (SH). From the obtained SH polynomial coefficients, indices of shape were defined, and analysis of the temporal changes in each lesion’s geometry throughout the year was performed by determining the mean discrete total variation of the shape indices.

Results: The results demonstrate that most of the studied lesions undergo notable geometrical changes with time. These changes are not necessarily associated with similar changes in size/volume. Furthermore, it was found that indices corresponding to changes in lesion shape could be 1.4 to 8.0 times higher than those corresponding to changes in the lesion size/volume.

Conclusion: Quantitative three-dimensional shape analysis can serve as a new tool for monitoring MS lesion activity and study patterns of MS lesion evolution over time.

Key Words: MRI; multiple sclerosis; three-dimensional geometry; spherical harmonics; temporal analysis

THE GEOMETRY AND PATTERN of evolution of individual multiple sclerosis (MS) lesions reflect the complex pathologic chain of events that often culminate in the structural damage of axons and their myelin sheath. MS lesions present a considerable variability in shape and size between patients and even for the same patient. While the volumetric changes of MS lesions over time have been documented to some extent (1–3), almost no attention has been devoted to understanding the nature of changes in MS lesion shapes.

The advent of magnetic resonance imaging (MRI), with its digital representation of three-dimensional anatomy, and the development of image analysis and visualization tools allowing explicit three-dimensional depiction of lesions, provide powerful means to obtain morphologic description and associate pathogenic interpretations with the appearance of MS lesions. A further advantage offered by MRI is its ability to serve as a follow-up tool, allowing in vivo study of lesion evolution by tracking the temporal changes associated with the disease.

MS is an active and dynamic disease, presenting two kinds of lesions: active and chronic. Disease activity monitored by MRI was reported to be five to 10 times higher than the clinical neurologic changes (4–7). Moreover, MRI evidence suggests that disease activity can be identified in as many as 30% of patients who appear to be in clinical remission (8). As long as the lesions remain in the active stage, they are prone to change in size and shape over time.

Current methods for analyzing temporal changes in MS patients by brain MRI include counting the number of lesions and assessment of lesion load by measuring their area and/or volume. Similarly, by measuring the number and volume of new or active lesions, and the change in older lesions (9–11), an assessment of the disease activity can be obtained. The analysis of MS lesion shapes and their changes over time could lead to better understanding of the pathogenesis of MS. However, quantitative characterization of MS lesion geometry is a complicated task. Although most of the MS lesions present a rather spheroid or ellipsoid shape, in many cases, complex shapes can also be found (12).

Spherical harmonics (SH) have been used to quantitatively define and calculate different three-dimensional geometric features, including the surface of molecules (13) and MS lesions (14). The goal of the present study was to present a new approach, which utilizes SH, for analyzing the changes in MS lesions over time.
by quantitatively characterizing the lesion’s shapes and depicting patterns of shape evolution in individual lesions. It was not our intention to try to find the correlation between the changes in MS lesion shape over time and the clinical symptoms.

**MATERIALS AND METHODS**

**SH**

SH are orthonormal functions over the unit sphere utilized to describe complicated surfaces in three dimensions. These functions are defined by (15):

\[
Y_{l,m}(\theta, \phi) = \frac{2l+1}{4\pi} \frac{(l-m)!}{(l+m)!} P_l^m(\cos \theta) \exp(i m \phi) \quad (1)
\]

where \(Y_{l,m}(\theta, \phi)\) is the corresponding SH function defined in a spherical coordinate system \((R, \theta, \phi)\), \(P_l^m(\cos \theta)\) is the associated Legendre polynomial, the parameter \(l\) is zero or a positive integer, and the integer \(m\) can have only the values of \(-l, -(l-1), \ldots, 0, \ldots, (l-1), l\).

For a spherical coordinate system (i.e., \(R, \theta, \phi\)), the surface radii \(R\) can be discretely presented by:

\[
R(\theta, \phi) = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} r_{lm} Y_{l,m}(\theta, \phi) \quad (2)
\]

where \(r_{lm}\) are the amplitudes of the corresponding SH functions. Equation [2] can be represented as a multiple linear regression model. Thus, by using a least squares approximation, an MS lesion can be analytically described by calculating the corresponding \(r_{lm}\) coefficients (14).

**Characterization of Lesions’ Three-Dimensional Geometry Using SH**

Individual MS lesions extending into two or more image slices were localized. The characterization of the lesions’ three-dimensional geometry is based on the use of sets of MS lesion contours taken from segmented MR images. In order to obtain the same number of points in all traced contours, each of the contour lines was interpolated and resampled. Later, the points of each contour were rearranged in such a way that the first point on each contour was the most extreme point on the right-hand side. The rest of the points were then registered in a counterclockwise direction. The application and/or optimization procedures of the interpolation, and arrangement are explained with more details elsewhere (14). As only axial slices were acquired, in order to constrain the solution along the direction perpendicular to the axial plane, a sagittal and a coronal contour were added by applying the Akima interpolation method (16) to data points located on these planes and two additional points extrapolated from the contours center of gravity (14). These two contours were utilized by quantitatively characterizing the lesion’s shapes and depicting patterns of shape evolution in individual lesions. It was not our intention to try to find the correlation between the changes in MS lesion shape over time and the clinical symptoms.

### Table 1

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number of harmonics (N) used for the approximation</th>
<th>Number of time points in which the lesion appeared within one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>24</td>
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<td>3</td>
<td>18</td>
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<td>6</td>
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<td>24</td>
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<td>10</td>
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</tbody>
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together with the original axial contours to obtain the SH approximation of the lesion’s three-dimensional surface and its corresponding describing polynomial coefficients. The final sets of contours obtained for each lesion were arranged according to their respective spatial orientation, yielding a three-dimensional cluster of data points. Using this array of data points, the three-dimensional geometry and the corresponding SH polynomial representation of each individual lesion at all time points were estimated.

In order to allow a systematic analysis of the changes in the SH coefficients, each individual lesion has to be approximated using the same number of harmonics ($N$) at all time points. In a previous study (14), it was observed that the choice of $N$ must be set according to the ratio of lesion size to image resolution in order to avoid distortions in the estimated three-dimensional surface. In the current study, because of the change in size, MS

Figure 2. Three-dimensional reconstructions at 24 time points of in vivo MS lesion number 1 (reconstructed using $N = 2$). Note the significant changes in the lesion’s shape and size during the year of the study.

Figure 3. The temporal patterns for the shape indices corresponding to lesion number 1 during the year of the study. In this case the $MDTV$ value for $I_2$ was higher than for $I_0$. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
lesions did not extend into the same number of planes over time (the lesions analyzed here extended from two to seven slices). Therefore, \( N \) was selected to be the minimal number of axial slices in which the lesion extended at all time points.

Using the polynomial coefficients that describe the estimated surfaces, an analysis of the changes in the estimated MS lesions' size/volume and the changes for individual lesion shape was done. For the analysis, a space rotation invariant set of indices \( I_i \) was estimated using:

\[
I_i = \sum_{m=1}^{l} |r_{lm}|^2
\]  

Figure 4. Three-dimensional reconstructions of in vivo MS lesion number 5 (reconstructed using \( N = 3 \)). This lesion appeared in the set of images at time point number 7 (after 43 days). Note the rapid increase in its size, which peaked at day 64, and then the slow decrease in size that was associated with changes in the lesion's shape.
were $l = 0, 1, 2, \ldots$, the obtained $I_l$ indices were then normalized to the value of $I_0$ of the first time point in which the lesion appeared. The index $I_0$ comprises only $|r_0|^{2}$, which is the general average radius of the approximated surface. Thus, $I_0^{(1/2)}$ is proportional to the average radius of the shape and $I_0^{(3/2)}$ is proportional to the volume defined by the average radius. Hence, the changes in $I_0$ represent the oscillations in the shape’s size/volume. Unlike $I_0$, which expresses global changes, the $I_{l>0}$ indices express more local changes in the three-dimensional SH surface shape. As $l$ increases, the $I_l$ indices characterize more localized changes.

**Simulated Lesions**

Simulated lesions were required in order to understand the behavior of the SH-derived shape indices when specific geometric changes in the lesion geometry take place. The simulated lesions were chosen to be of spheroid or ellipsoid shapes because of their similarity to most of the real MS lesions. Three different simulations were carried out:

1. Changes in the SH coefficients by zooming a spheroid. A spheroid with a radius of 2 pixels was used in order to analyze the changes of the obtained SH coefficients. The spheroid was zoomed out by incrementing its radius by 0.5 pixels each time, up to a radius of 4.5 pixels.

2. Changes in the SH coefficients by zooming an ellipsoid. The analysis of the changes of the SH coefficients was also done by zooming an ellipsoid with a semi-axis length of $A = 2$ pixels, height semi-axis $B = 3$ pixels, and width semi-axis $C = 3.5$ pixels. Zooming was done by incrementing the semi-axes each time by 0.5 pixels.

3. Changes in the SH coefficients by enlarging only one of the ellipsoid’s semi-axes. The changes of the SH coefficients were analyzed for an ellipsoid with only one of its semi-axes increasing in length. An ellipsoid with a semi-axis length of $A = 4.5$ pixels, height semi-axis $B = 2.5$ pixels, and width semi-axis $C = 2$ pixels was used for the analysis. The width semi-axis was incremented each time by 0.5 pixels.

In the simulations, a discrete sampling of the analyzed three-dimensional surface points was taken and used to estimate the SH polynomial representations. As the simulations were done using spheroids and ellipsoids, the number of harmonics ($N$) used for the approximations was $N = 2$.

**In Vivo Data**

**Subject**

MRI brain images were obtained from a patient who completed a 12-month imaging study. The subject was a 38-year-old man suffering from relapsing-remitting MS. The patient was scanned 24 times, as follows: on a weekly basis for the first eight weeks, biweekly for the next 16 weeks, and then once monthly until the completion of one year.

**MRI Acquisition**

MR images were acquired on a 1.5-T Signa System (GE Medical Systems, Milwaukee, WI). The sets of images included proton density (PD) and $T_2$ images obtained using two interleaved dual-echo (TE = 30 and 80 msec) long TR (3000 msec) spin-echo sequences (VEMP = variable-echo multi-planar). Contiguous 3-mm thick axial sections covered the whole brain from the foramen magnum to the highest convexity with an in-plane voxel size of 0.94 mm × 0.94 mm (24-cm field of view [FOV]) with a 256 × 256 acquisition matrix. A variable receiver bandwidth technique was used to improve signal-to-noise ratio (SNR) in the second echo (2,17). Standard flow compensation was achieved using first-order gradient moment nulling. Spins were saturated in an 8-mm thick slab inferior to the imaging volume in slice-selective direction. Scan duration was kept at 11 minutes and 36 seconds using the half-Fourier technique.

**Image Alignment and Segmentation**

The MRI scans provided comprehensive volumetric coverage of the head. Therefore, it was not necessary to achieve precise repositioning of the patient in the MR scanner at subsequent examinations. Rather, images were aligned by applying the maximization of mutual information algorithm proposed by Viola and Wells (18). With this algorithm, the 23 subsequent sets of images were aligned to the set of images obtained at the first scan.

The segmentation of the images was automatically done from the aligned PD and $T_2$ images by applying a multistep procedure. In the first step, an outline of the intracranial cavity (ICC) was obtained for all studies (2,17). This ICC mask was used to define the region of interest containing the brain parenchyma and cerebrospinal fluid (CSF). Later, each pixel in the images was assigned to one of the following four categories: white matter, grey matter, CSF, or lesion. This procedure was performed by combining the self-adaptive expectation-maximization algorithm described by Wells et al (19) with a template driven segmentation (20,21), where anatomic knowledge is provided by non-linear projection of a brain model (template) onto the images of a patient’s brain. This technique has been shown to have high reproducibility and accuracy of lesion volume measurements with respect to the outlines provided by expert radiologists (22,23).

The preprocessing stage required the following times when using a Sun Ultra 80 workstation 450 MHz: registration of the images, 10 minutes for the operator to insert all the required variables and start running the program and 10 minutes of computer time per set of images, which includes all the images acquired at one time point (out of the 24) in this study; ICC mask, five minutes of operator time and 15 minutes of computer time per set of images; template driven segmentation, no operator time needed, and 40 minutes of computer time per set of images (including the analysis of both the PD and $T_2$ images). Computation for the SH approximation and estimation of the $I_l$ shape indices takes a few seconds per each temporal point on a PC Pentium II 399 MHz. As can be noted, the overall processing time
for one time point (including all images) is about one hour and 20 minutes, which may be considered reasonable for a clinical use.

**Analysis of the Changes in the Lesions’ Three-Dimensional Shape**

In the field of signal processing, the discrete total variation is used to measure the total amplitude of discrete signal oscillations (24). It is calculated by approximating the signal derivative by a finite difference over the sampling distance. In the present study, the mean discrete total variation (MDTV) was calculated and used to estimate the mean amplitude of the oscillations for the changes in the normalized $I_i$ indices by:

$$MDTV = \frac{\sum_{t=1}^{N} |I_i(t) - I_i(t+1)|}{N} \quad (4)$$

where $t$ is the time index and $N + 1$ is the total number of time points.

**RESULTS**

**Simulated Lesions**

The simulated lesions were approximated using the discrete sampling obtained from the original shapes (spheroid and ellipsoids). Figure 1a depicts the changes in the normalized $I_i$ indices for the zoomed spheroid. As expected, only the changes for $I_0$ were significant, representing the changes in size/volume of the spheroid. In this case, the indices for $I_1$ and $I_2$ were zero due to the symmetry of the shape.

The changes of the normalized $I_i$ indices for the zoomed ellipsoid depicted similar patterns as for the zoomed spheroid. However, due to the shape asymmetry, the obtained indices differed from zero for $I_0$ and $I_2$, indicating the direct dependence between the corresponding normalized $I_i$ indices and the ellipsoidal shape. These changes are presented in Figure 1b.

The changes of the normalized $I_i$ indices for an ellipsoid with only one of its semi-axes enlarging were also analyzed. These changes are depicted graphically in Figure 1c. In this case, the changes for $I_0$ and $I_2$ were both notable, indicating both changes in size and in the ellipsoid’s shape, while $I_1$ again remained zero.

**In Vivo Data**

From the sets of registered and segmented images, 10 individual white matter lesions were analyzed. According to the size of the identified lesions, four of the lesions (lesions 1–4) were approximated using $N = 2$, from which two appeared only during the scans performed at time points 21–24. Three lesions (lesions 5–7) were approximated using $N = 3$, from which one appeared only after the seventh scan. A value of $N = 4$ was used to approximate three additional lesions (lesions 8–10). The number of harmonics used to approximate the lesions and the number of time points in which they appeared are listed in Table 1. The graphical representation of the three-dimensional geometric changes over time for the normalized $I_i$ indices for four of the MS lesions are presented in Figures 2–9. The estimated MDTV values for the normalized $I_i$ indices of all the lesions are summarized in Table 2.

The three-dimensional reconstructions of lesion number 1, obtained using $N = 2$, at the 24 time points

<table>
<thead>
<tr>
<th>Lesion</th>
<th>$I_0$</th>
<th>$I_1$</th>
<th>$I_2$</th>
<th>$I_3$</th>
<th>$I_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32.3</td>
<td>23.1</td>
<td>46.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>16.9</td>
<td>3.6</td>
<td>10.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>37.9</td>
<td>8.7</td>
<td>7.8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>46.3</td>
<td>1.7</td>
<td>11.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>72.1</td>
<td>27.6</td>
<td>68.4</td>
<td>14.6</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>12.4</td>
<td>6.0</td>
<td>24.2</td>
<td>5.0</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>8.1</td>
<td>14.3</td>
<td>6.4</td>
<td>5.4</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>3.2</td>
<td>11.4</td>
<td>25.6</td>
<td>7.3</td>
<td>3.0</td>
</tr>
<tr>
<td>9</td>
<td>11.7</td>
<td>9.1</td>
<td>30.2</td>
<td>7.1</td>
<td>3.9</td>
</tr>
<tr>
<td>10</td>
<td>6.7</td>
<td>14.2</td>
<td>20.5</td>
<td>5.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Average ± SD</td>
<td>24.8 ± 22.1</td>
<td>12.0 ± 8.2</td>
<td>25.1 ± 19.5</td>
<td>7.5 ± 3.6</td>
<td>3.3 ± 0.4</td>
</tr>
</tbody>
</table>
Figure 6. The three-dimensional reconstructions at the 24 time points of in vivo MS lesion number 10 (reconstructed using N = 4). This lesion seems to engulf two overlapping lesions, one extending in the vertical direction and the other diagonal. Over time, the upper part of the lesion decreases, while the lower part presents smaller variations, causing larger changes in the lesion’s shape than in its size/volume.
are depicted in Figure 2. As can be noted, the lesion has been active throughout the year. Its size increased and decreased several times and its shape changed as well. These changes were quantitatively assessed by calculating the corresponding shape indices \( I_0, I_1, I_2 \) in this case) for each time point. Their values throughout the year are depicted graphically in Figure 3, and the changes were large and quite irregular. This is also indicated by the large \( MDTV \) values listed in Table 2 for this lesion.

In Figure 4, the three-dimensional reconstructions of lesion number 5 are depicted. This lesion was approximated using \( N = 3 \). The corresponding values of its shape indices are depicted in Figure 5. The lesion appeared about six weeks after the beginning of the study (detected on day 43). The size of this lesion increased tremendously, reaching a peak about three weeks later. This finding is also quantitatively indicated in Figure 5 by the large value of \( I_0 \) on day 64. Following this climax, the lesion started to shrink, initially at a rapid rate and then at a more moderate rate. The changes in size were associated with some changes in shape, as can be noted in Figures 4 and 5. The \( MDTV \) values for this lesion shape indices were relatively high (see Table 2).

The three-dimensional reconstructions of lesion number 10 are depicted in Figure 6. This lesion was approximated using \( N = 4 \) and it seems to engulf two overlapping lesions, one extending in a vertical direction and the second in a diagonal direction. Over time, the upper part of the lesion decreases, while the lower part has almost no variations. Accordingly, it can be noted in Table 2 that for this lesion, the \( MDTV \) values were higher for \( I_1 \) and \( I_2 \) than for \( I_0 \). This is also depicted graphically in Figure 7.

In an additional example, the geometric changes in lesion number 6 are shown in Figures 8 and 9. From the three-dimensional reconstructions of the lesion (depicted in Fig. 8) and the corresponding shape indices (depicted in Fig. 9), it can be noted that this lesion had little geometric activity for about nine months. Towards the end of the study, the lesion suddenly "erupted," markedly changing its shape and size.

A general analysis of the obtained \( MDTV \) values listed in Table 2 reveals that in four of the analyzed lesions (lesions 2–5), the \( MDTV \) values for \( I_0 \) were higher than for the other normalized \( I \) indices (i.e., \( I_1 - I_3 \)), indicating larger changes in the lesions’ size/volume than in the lesions’ shape. However, for the remaining six analyzed lesions, the \( MDTV \) for at least one of the normalized \( I \) indices that represent changes in shape (i.e., \( I_1 - I_3 \)) were higher than for \( I_0 \). The \( MDTV \) for \( I_2 \) were 1.4, 2.0, and 2.6 times higher than \( I_0 \) for lesions number 1, 6, and 9, respectively. For lesion number 7, the \( MDTV \) for \( I_1 \) was 1.8 times higher, while for lesion 8, the \( MDTV \) for \( I_1 - I_3 \) were 3.6, 8.0, and 2.3 times higher, respectively. Finally, for lesion number 10, the \( MDTV \) for \( I_1 - I_2 \) were 2.1 and 3.1 times higher than \( I_0 \), respectively.

**DISCUSSION**

In the present study, the implementation of a recently described method (14) that utilizes SH to approximate MS lesions’ three-dimensional surfaces from the lesions’ two-dimensional MRI contours for investigating time related changes in lesions is presented. Simulated and in vivo MS lesions were approximated using SH, and a space rotation invariant set of indices was used to analyze the temporal changes in the lesions’ size/volume and shape. The corresponding \( MDTV \) values for the normalized shape indices were then used to quantify the overall activity of each index throughout the year of the study. The approach presented here proposes and exemplifies a method to quantitatively assess the geometric activity of individual MS lesions over time. To the best of our knowledge, this is the first study that analyzes the temporal changes in the three-dimensional geometry of individual MS lesions.

In order to understand how the normalized \( I \) indices change under certain circumstances, three different simulations were carried out. From the analysis of the changes in the normalized \( I \) indices for these simulations, it can be concluded that the approach is sensitive to both changes in size and shape of simulated MS lesions. The changes in the \( I_0 \) indices corresponded to a symmetric growth, while an asymmetric growth was manifested by changes in the normalized \( I \) indices for higher values of \( I \) (see Fig. 1).

The results obtained from the analysis of the in vivo MS lesions show oscillating changes in size/volume and shape even within a short period of time. Figures 4 and 5, which correspond to lesion number 5, provide a clear example where a lesion grows substantially within a short period of time and the volumetric increase is accompanied by changes in shape. However, as can be observed, there were also cases (e.g., Fig. 7) in which changes in the lesions’ shape were larger than the changes in size/volume. Moreover, the analysis of the \( MDTV \) showed that the changes in shape, especially those represented by the \( MDTV \) for \( I_2 \) (related to ellipsoid shapes) are comparable to the changes in size/volume. By studying these lesions, it can be suggested that changes in shape are indicative of the lesion’s activity and that shape changes may be utilized as a tool for
exploration of characteristic patterns of lesion development.

It was not our goal to evaluate possible correlation between the changes in MS lesions' shape and the clinical parameters of the patient's disease course. The correlation with clinical relevance or outcome may require a much bigger scope of evaluation and setting, as the clinical symptoms can be potentially influenced by...
multiple factors such as the nature of the disease, the degree of inflammation, location of the lesion, consistency of brain tissues, time of imaging, etc. Therefore, clinical correlation may not be easily achieved with just temporal changes in the morphology alone. Nevertheless, it is expected that by systematically accumulating patterns of temporal changes of shape indices from a large population of patients, such correlation might be detected.

Because the analyzed data included only sets of contiguous 3-mm thick axial MR images, the choice of the appropriate number of harmonics (N) to be used for the approximations was limited. As mentioned above, N was selected to be the minimum number of axial slices into which the lesion was extended at all time points. This selection was made in order to prevent distortions in the reconstructed surface. Nevertheless, if the acquisition of the MR images is done using a better resolution (e.g., 1-mm isotropic sampling) it might be possible to use a higher N value and achieve better approximation for irregular MS lesions. On the other hand, thinner slice volume frequently decreases SNR and lesion contrast; thus, it may trade off lesion delineation for spatial resolution. However, it should also be noted that newer imaging techniques, such as Single Slab three-dimensional fast spin-echo (25), allow the acquisition of high isotropic resolution (e.g., 1 mm³) T2 images with adequate SNR. This technique has only recently started to be applied to the analysis of MS lesions. It can be expected that the combination of such new image acquisition techniques together with the method suggested here would improve the analysis of changes in even smaller MS lesions.

In summary, a method for studying temporal changes in individual MS lesion geometry is presented. The method provides a quantitative analysis for characterizing MS lesions size/volume and shape over time. The presented method may be applied for monitoring lesion’s activity and for a systematic study of lesion evolution in pursuit of characteristic mechanisms during the “life cycle” of MS lesions.

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