Eurographics Workshop on Visual Computing for Biology and Medicine (2021)
S. Oeltze-Jafra, N. N. Smit, and B. Sommer (Editors)

# Interactive Multimodal Imaging Visualization for Multiple Sclerosis Lesion Analysis

S. Sugathan[1,2], H. Bartsch[1,2], F. Riemer[2], R. Grüner[2], K. Lawonn[3] and N. Smit[1,2]

[1] Department of Infomatics, University of Bergen, Norway, [2] Mohn Medical Imaging and Visualization Centre, Haukeland University Hospital, Norway
[3] Institute for Computer Science, University of Jena, Germany

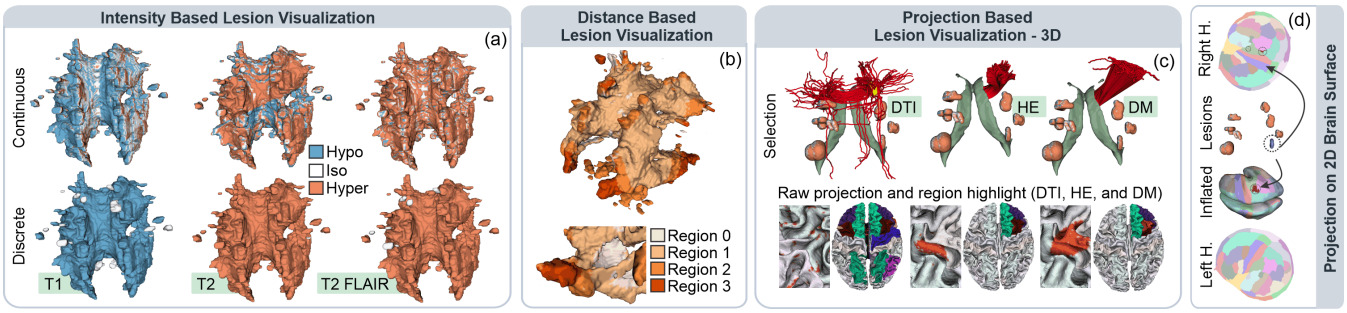


**Figure 1:** *(a) Discrete and continuous intensity difference visualization of multiple sclerosis lesions in T1, T2 and T2 FLAIR (Fluid-attenuated inversion recovery) images. (b) visualization of lesions to express relative distances to the cortical surface. (c) projecting and highlighting (second row) relevant regions based on user selection of lesions (first row). (d) projecting lesions on 2D unfolded brain surfaces.*

**Abstract**

*Multiple Sclerosis (MS) is a brain disease that is diagnosed and monitored extensively through MRI scans. One of the criteria is the appearance of so-called brain lesions. The lesions show up on MRI scans as regions with elevated or reduced contrast compared to the surrounding healthy tissue. Understanding the complex interplay of contrast, location and shape in images from multiple modalities from 2D MRI slices is challenging. Advanced visualization of appearance- and location-related features of lesions would help researchers in defining better disease characterization through MS research. Since a permanent cure is not possible in MS and medication-based disease modification is a common treatment path, providing better visualizations would strengthen research which investigates the effect of white matter lesions. Here we present an advanced visualization solution that supports analysis from multiple imaging modalities acquired in a clinical routine examination. The solution holds potential for enabling researchers to have a more intuitive perception of lesion features. As an example for enhancing the analytic possibilities, we demonstrate the benefits of lesion projection using both Diffusion Tensor Imaging (DTI) and gradient-based techniques. This approach enables users to assess brain structures across individuals as the atlas-based analysis provides 3D anchoring and labeling of regions across a series of brain scans from the same participant and across different participants. The projections on the brain surface also enable researchers to conduct detailed studies on the relationship between cognitive disabilities and location of lesions. This allows researchers to correlate lesions to Brodmann areas and related brain functions. We realize the solutions in a prototype application that supports both DTI and structural data. A qualitative evaluation demonstrates that our approach supports MS researchers by providing new opportunities for MS research.*

**CCS Concepts**

• ***Human-centered computing*** → ***Visualization application domains;***

## 1. Introduction

Multiple sclerosis (MS) is a neuro-degenerative disease of the central nervous system that leads to loss of neuronal functions in the grey and white matter of the brain and spinal cord [LBL07]. Using Magnetic Resonance Imaging (MRI) is one of the most common approaches for MS diagnosis, and it includes following diag-





DOI: 10.2312/vcbm.20211346

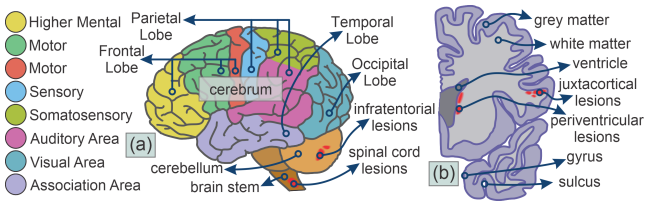


**Figure 2:** *An overview of the brain and potential MS lesion locations: (a) Different lobes of the human brain with labeled cortical functions. (b) Types of lesions based on their locations inside the brain.*

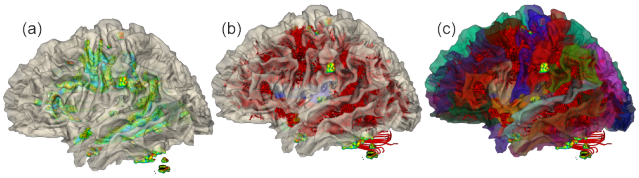


**Figure 3:** *3D rendering of brain data showing a rise in visual complexity as more data is added: (a) white matter surface and lesions (b) added stream tubes and (c) added parcellation information displayed in color.*

nostic criteria defined over multiple modalities. A common clinical practice in this context is the use of McDonald Criteria [TBB*18], which define a standard means of diagnosing MS. It is important to note that the criteria consider new lesions and their locations as a diagnostic tool. Figure 2 shows several possible locations (periventricular, juxtacortical, infratentorial or spinal cord) of MS lesions. In this work, we consider three commonly acquired structural modalities of MR images: T1, T2, and T2 FLAIR (fluid attenuation inversion recovery). These different modalities capture complementary image information.

For studying MS, researchers typically use slice views requiring lot of effort and knowledge. One reason for this is the orientation of the participant's brain in the image being dependent on its position in the scanner. This variability makes it impractical to rely on slice location to re-identify a lesion from a previous time point. It also involves repeated interactions to assess on the 2D image how close a particular lesion is to the cortical surface, given the convoluted folding structure of the cortical surface. An obvious and direct solution to limit the interpretation effort would be to consider rendering in 3D. However, due to the nature of lesions in MR imaging data, direct volume rendering is unlikely to succeed in effectively visualizing lesions. Direct volume rendering is not a suitable approach for MS lesion visualizations mainly due to factors such as magnetic field inhomogeneity, noise, obstructing anatomy, and patient-specific normal variations in anatomy. This is the reason why state-of-the-art MS visualizations still use 2D slices to render information. Considering the limitations of direct volume rendering, a good option is to consider using 3D surface data. To help understand the disease and support MS researchers, it is useful to harness the benefits of 3D surface visualizations. Realizing an interactive visualization setup is challenged by many factors such as lesion location, the folded surface anatomy of the human brain, and the lesion load. The degree of scene complexity induced by brain surface folds can be understood from Figure 2. Figure 3 shows how the complexity increases when we try to visualize more data. The outer white matter surface has some transparency applied to it, which allows us to see the lesions within. Figure 3(a) shows the white matter along with the lesions. Even though we can make lesions and brain surface distinguishable through coloring, it is still difficult to identify lesion proximity to the outer brain surface. The complexity further increases if we try to display fiber tracts or color-coded brain surface parcellations (distinct partitions in the brain based on organization and function), as shown in Figure 3(b) and (c). We face two problems in 3D due to nested objects rendered with different transparency levels. The first problem is occlusion that naturally happens, especially where there is a high lesion load. The second problem is the inherent difficulty in perceiving and differentiating lesions based on their depth from the brain surface.

To address these problems, we present a prototype tool with novel 3D lesion visualization features for improved understanding of MS lesions in 3D. The application performs interactive processing, filtering, voxel intensity based visualization of MS lesions, and most importantly, allows users to project lesions on the brain surface. By projecting lesions to the brain surface, we provide a new opportunity for MS researchers to study the probable effects of individual lesions on the brain. The area quantification can also help in researchers dealing with the inter- and intra-rater variability problem inherent to score based systems like EDSS (Expanded Disability Status Scale) [SS19], where the disability of a patient is quantified through manual cognitive tests. The projections would also allow researchers to further investigate potential impact of lesions on Brodmann areas to study the cognitive defect that a patient may experience. In our work, we emphasize visualizing single time point data while considering relevant spatial diagnostic criteria [BH18, TBB*18] for MS.

With this, we bring the following contributions to the literature:

- An interactive visualization for lesion characterization based on their intensities compared to surrounding normal tissue in multimodal MRI data.
- A novel solution for conveying lesion to brain surface distance information.
- Methods for visualizing and quantifying lesion projections on the brain surface (2D and 3D) applicable for both DTI and structural brain data.

## 2. Related Work

**3D visualization:** There is an extensive body of research that focuses on brain imaging data visualization, for example, in the context of neurosurgical planning [LSBP18, LBSP14, DPL*11]. Considerably less effort is put into visualization for multiple sclerosis in particular, especially in 3D. Understanding the nature/distribution of lesions in a fast and intuitive manner is not the only benefit of having lesion visualizations in 3D. In lesion research, 3D representations can reveal important characteristics [SHW*19] of the disease and even help in distinguishing between diseases [NWW*17]. With our tool, we aim to provide investigation support for disease mechanisms such as cognitive dysfunction and remyelina-

tion/demyelination while having location context in 3D space. Understanding the characteristics of lesions in 3D can be useful for both clinical and research purposes. The work by Louapre et al. [LGG*15] remains the closest literature among very few in this direction. They mapped colored lesions onto an inflated cortical surface based on 7T MRI data. In contrast to our approach, they only consider lesions within the cortex for mapping to the inflated brain surface and use a two-step method using a boundary-based registration. There are several existing tools that provide MS lesion information as textual data, and slice based overlay visualizations. The tool SepINRIA [Ser21] includes 3D support, but employs 3D only as a viewer that offers limited visualization and interaction options. As we are focussing on exploring the analytical possibilities of 3D visualizations, it becomes essential to have useful information as visualizations in 3D. Jönsson et al. [JBF*20] find 3D spatial views to be useful when linking with other interactive visualizations. In contrast to their approach, we make use of the brain surface as a canvas to render lesion-related visualizations. There are many scenarios where outer surface representation of organs can work as an effective medium for showing information about internal structures. In the context of visualization, the work by Lawonn et al. [LVPI18] provides good coverage of surface based illustrative rendering. One of our main goals is to project lesions to the brain surface in order to study potential lesion impact. For this, we are using gradients derived from structural MRI data. The gradients that we use are conceptually similar to the gradients in diffusion imaging. Vilanova et al. [VZKL06] demonstrated the use of 3D visualization for understanding the impact of MS lesions by using DTI data. They presented a coregistered visualization of DTI and MS lesion models by using streamtubes. To visualize the effect of MS lesion, they selectively displayed streamtubes in order to depict breaks in the neuronal tracts. In our case, we use streamtubes generated from DTI data to project lesions to the white matter surface. The work by Simon et al. [SZL*06] demonstrates fiber visualization as streamtubes, and uses 3D lesions to identify fibers at risk. In contrast to [SZL*06], we use the generated fiber tracts to provide visualizations on the brain surface. Besides projecting lesions to the surface, it is also useful to analyze the volume and location of a lesion inside the brain. In our work, we are focusing on bringing the advantages of 3D geometry, related computations and visualizations in a way that is useful to convey more information about MS lesions.

**Lesion voxel intensity:** Another important property of lesions worth studying is its image intensity when compared with the surrounding normal tissues. This intensity difference carries important information regarding the type and nature of the lesions. Studying lesion contrast is important in lesion research [KP20] and relates to certain pathological conditions [FPB*19]. The work by Simon et al. [SJS04] discussed several clinical correlations of T1-hypointense lesions in MS. Zhou et al. [ZSGZ10] described the analysis of T1-hyperintense lesions for diffusion tensor imaging data. Zimny et al. [ZNMBS15] conducted an elaborate review on intracranial lesions with hyperintensity in T1-weighted MR images. These studies show that characterizing lesions based on their intensity is a highly relevant aspect to consider when visualizing MS imaging data. While lesions can have different intensities, it is also possible that lesions have intensity inhomogeneities within. The work by Yao et al. [YBM*12] attempts to identify lesion inhomogeneities at the rim. Due to the relevance of understanding intensities at the lesion border, we also provide a continuous display of the voxel intensities computed at the lesion rim, besides visualizing the average lesion voxel intensity difference. From a visualization point of view, the work by Meyer et al. [MKC*16] performs voxel-based statistical analysis of stroke lesion impact and then plots them back on individual T1 slices as an overlay. In our case, we also provide the lesion mask as an overlay on the slices to help users relate their current observation on slices with our visualizations in 3D. The overlay supports interaction, where the users can select lesions on slice view in order to locate them in 3D view and vice versa. Rieder et al. [RSHP08] present visualization of inhomogeneous pathological tissue using 3D volume rendering. They use clipping planes, wherein they enhance the intensity inhomogeneities of the tissue for improved perception. In our case, considering the user requirements, we use a pathology surface mesh for visualizing intensity classifications.

Detection of lesions in MRI data is essential prior to performing any kind of quantification [MSP*02] or assessment over time. Lesion detection is a well-explored research space, and there are various methods out there to perform lesion segmentation. Once lesions are detected and segmented, it is typical to use basic visualization techniques for conveying useful clinical and/or statistical information about them. For instance, Ruggieri et al. [RFC*18] and Vellinga et al. [VGR*09] proposed statistical analysis of lesions followed by the use of probability maps to visualize them. Our application relies on a prior segmentation of the MS lesions, which can be achieved by any manual or automated techniques.

**Lesion location:** The location of lesions in white matter is one characteristic that influences the extent and nature of functional disability [CZT*03]. The work by Gaetano et al. [GMK*20] reports the correlation between white matter lesion and location and functional disability. From a research perspective, studying the spatial distribution of lesions is a relevant aspect [GBP*05], where we come up with an approach that supports easy localization of lesions. Many prior articles describe the importance of differentiating the lesion types and their location within the brain. In the work by Vellinga et al. [VGR*09], the clinical correlation of brain lesion distribution was studied in the context of multiple sclerosis. The work by Calabrese et al. [CBG*10] described different types of lesions and their cortical distribution. The distance of the lesion to the cortical surface [GPB*16] of the brain is also an important factor of clinical relevance which needs to be studied and visualized. Rieder et al. [RRRP08] introduce cylindrical cuts into the volume data for conveying tumor distance. In contrast, we encode distance coloring directly on the lesion mesh data, and also uses the mesh data for sampling fiber tracts instead of using spherical ROIs. The work by Beyer et al. [BHWB07] discuss visualization of superficial brain areas suitable for surgery planning again by making brain cuts, but the research interests in MS mainly motivate our approach of projecting lesions to the cortical surface instead. In the work by Geisseler et al. [GPB*16], the relevance of cortical lesions in MS is discussed. This motivates us to define a distance measurement mechanism in order to visualize lesions based on locations, such as juxtacortical or periventricular (around ventricles).

In summary, we can observe that a significant number of prior work has been done in the context of lesion visualization. In contrast to those visualizations, we focus on providing new visualizations for lesion analysis, and also reveal new information by exploiting the benefits of 3D.

## 3. Medical Background

This section covers the anatomical aspects of the human brain relevant to our research and other medical aspects related to MS pathology. A human brain comprises the cerebrum, cerebellum and the brain stem (Figure 2(a)). The ventricles (Figure 2(b)) inside the brain are responsible for the production and transportation of cerebrospinal fluid, which is useful for protecting the brain from cranial injuries. In our work, we focus only on MS lesions situated in the cerebrum and cerebellum regions, as we use datasets that only include the brain. The cerebrum is divided into two halves: the left and right hemispheres, which are connected to each other by the corpus callosum. Each hemisphere has four lobes: frontal, parietal, temporal and occipital. Each of those lobes can be again subdivided into areas related to specific cognitive functions, as shown in Figure 2(a). It is important to note that there exists a complex inter-relationship between different lobes in both hemispheres.

We can classify the central nervous system into two types of tissues (Figure 2(b)): gray matter and white matter. The gray matter appears in a pinkish gray color, and it is the area where the neural cell bodies, dendrites, axon terminals and nerve-synapses are present. The white matter comprises nerve cell axons protected by a fatty material known as myelin. 3D surface visualization tools can represent these tissues as 3D surfaces. The white matter surface envelops the edge between white matter and gray matter. The pial surface envelops the white matter surface whereas the inflated surface is an inflated version of the pial surface itself. Inflated brain surface views are mainly used to show the sulci areas of the brain to the user.

Myelin is a fatty matter that insulates the nerve cell axons inside the brain. The myelinated axons (distributed into bundles called tracts) in the white matter establish a connection between brain cells. In an MRI scan of an MS patient, we can observe lesions, which are areas of myelin loss. The different MRI sequences like T1, T2, T2 FLAIR, DTI etc. offer different ways of looking at the lesions and we get a unique image for each of those modalities. One can easily differentiate between T1 and T2 by looking at the ventricles. Typically, in T1-weighted images CSF (cerebrospinal fluid) appears dark whereas in T2, it appears brighter. The FLAIR sequence is similar to T2, but it is especially sensitive to the detection of inflammation. The difference in imaging parameters causes the inflammations in FLAIR to remain bright and the normal CSF to appear dark. This makes FLAIR sequence easier to use for differentiating a pathology and CSF. MS research also uses DTI, an MR imaging technique to study microstructural damage that is not visible using T1, T2 and FLAIR. With DTI data, we can get the structure and orientation of fiber bundles in deep white matter. In DTI tractography, users would typically get the information as tensors, which they visualize as fiber tracts inside the brain. The nature of DTI modality to provide context in regions (that otherwise show a uniform texture) is another reason why we consider DTI as a helpful modality. We can characterize the disease based on the appearance of MS lesions in different modalities. Typically, lesions appear dark (hypointense) in T1 (Figure. 4(c)) whereas T2 and T2 FLAIR image sequences show MS lesions as bright (hyperintense) spots (Figure. 4(a)) compared to normal surrounding tissue. These hyperintense lesions in T2 and T2 FLAIR are caused by both old and new inflammation. Other potential reasons for a bright lesion in these modalities are small vessel disease, which we do not consider in this study. Even though there exists a general expectation about the lesion contrast in different modalities, it is important to note that there are deviations. It is possible to have (partially) hyperintense lesions in T1 and there can be hypointense traces of lesions in T2. Lesions that appear hypointense compared to surrounding normal tissue are also possible in T2, but less common [WW04]. Another imaging technique involves injection of intravenous contrast agent and uses T1. If there are any MS inflammation areas in the brain, they will be contrast-enhanced. In this case, it is possible to observe different intensity profiles (hypo/iso/hyper intense). There is a state where the damage includes both myelin coating and the nerve cell itself. We would see this state in T1 as darker spots called black holes.

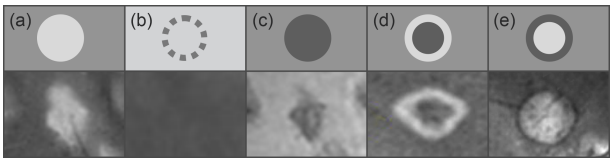


**Figure 4:** *Lesions in T1, T2 and T2 FLAIR sequences can have different voxel intensities when compared with normal surrounding tissue. Based on this, lesions can be broadly classified as (a) hyper-intense (b) iso-intense and (c) hypo-intense. Based on the intensity differences at the rim, lesions can have either (d) hyper-intense or (e) hypo-intense rims.*

Medication-based treatment is possible with MS and has shown a significant impact on new MRI activity. These medications help in disease modification by preventing appearance of new lesions and growth of existing lesions. Inspecting MRI slices helps in understanding the effectiveness of these medications, and we aim to provide useful visualizations to better understand the dissemination of lesions and their characteristics in 2D and 3D.

## 4. Requirement Analysis

Our collaborators and coauthors in this work include researchers from various backgrounds: medical visualization, medical imaging, computational neuroscience, and MRI physics. Based on discussion with our team, we identified several opportunities in terms of MS visualization. According to our collaborators, visualizing lesion subtypes based on intensity while aligning with standard diagnostic criteria would be useful for the neuroscience community because such visualizations enable easy localization of active or important lesions. Even though experts are good at reading MRI slices in 2D, it is difficult to form a mental picture of all lesion features, especially the intensity related ones. We identify these as situations where users appreciate having lesion visualization in 3D that provides a high-level overview. Besides lesion voxel intensity

information, we identify that end users need to solve the problem of depth perception when interpreting lesions in 3D. More specifically, a user should be able to locate white matter lesions and proximity to anatomical structures, e.g., ventricles or cortical surface, and this advocates for defining distance measurement mechanism inside the white matter. From requirement elicitation, we also found that it is essential for the target visualizations to provide support for multiple modalities. Identifying and differentiating lesions based on their dissemination in space is highly important, especially when there is a higher lesion load. For ease of interpretation of a 3D scene, and to reduce the cognitive load, users would like to have a filtering mechanism to filter lesions based on their properties. We also consider requirements for MS researchers who study cognitive disabilities in connection with MS lesions. We identify that lesion projection (and its quantification) on the brain surface as a potential approach that opens up the possibility of studying lesions while relating them with one or more cognitive disabilities. Here, it is important to recall that users usually define/interpret brain functions on the brain surface. One challenge in visualizing data on folded geometry such as the brain is self occlusion, where users require solutions with limited or no occlusion problems. For relating lesions to brain regions, users would rely on DTI as a primary modality, but if DTI is not available, alternate solutions should work as a fallback mechanism. Another requirement relates to interactive visualization support for lesions, resulting from a user's query on the brain surface. Here, the user would like to see all relevant lesions highlighted when the user selects a specific brain region.

Based on our literature study and collaborator input, we come to the following requirements:

R.1 Visualize spatial voxel intensity differences and compare across available modalities.
R.2 Develop a technique to visualize lesions based on their distance to standard brain regions.
R.3 Reduce cognitive load in 3D for easy localization of lesions.
R.4 Project lesion influence on standard brain regions and quantify the projected area. The user should also be able to find relevant lesions by querying the regions.
R.5 Filter lesions in 3D to focus only on lesions of interest.
R.6 Locate lesion projection quickly through occlusion-free visualization.

## 5. Interactive Presentation of MS Lesions

To address the requirements above, we propose a combination of visualization techniques (see Figure 1): (a) continuous and discrete lesion coloring based on intensities, (b) distance-based coloring for improved depth perception, (c) projecting lesions to the brain surface in 3D and (d) a 2D unfolded view. We integrate these functionalities into a prototype application which aims to enable deriving new insights from lesion data through interactive exploration. This section will explain the methods and techniques we used to present relevant lesion-related information along with our visualization design decisions.

### 5.1. Intensity-based Lesion Visualization

The intensity differences of lesions with respect to normal surrounding tissue can be one of the indicators of disease activity and thus important to visualize (R.1). Understanding the classification of a lesion by visual inspection of 2D slices is challenging for untrained image readers, because it involves inspecting several 2D slices before one can make out the overall intensity impression of a lesion. With an intensity visualization in 3D, we aim to show different lesion voxel intensity profiles as illustrated in Figure. 4. We provide these visualizations for T1, T2 and T2 FLAIR sequences in order to enable users to compare intensities across modalities. For visualizing different intensity classifications on the lesion surface, we use color as a visual channel because we only have three distinct classes, which can easily be discriminated. Pre-segmented lesion masks are used to generate a surface mesh for lesions. After generating the lesion surface, we separate them based on connectivity, and the intensity difference is color mapped on the lesion surface. We present two approaches (discrete and continuous) for mapping as some users want to understand the overall lesion voxel intensity difference per lesion, while others need a detailed impression of a lesion where they query intensity differences at every point on the lesion surface (rim). Our first approach uses a continuous coloring (Figure 1(a), first row) where every single point on the lesion rim gets a color based on the local intensity difference to cover the scenarios shown in Figure. 4(d) and 4(e). We can identify the rim differences by switching between continuous and discrete mapping. In the second approach, we use a discrete coloring method, where every disjoint lesion gets a single color to cover scenarios shown in Figure. 4(a), 4(b), and 4(c).

In continuous color mapping mode, every voxel on the surface of a lesion is assigned a color based on the intensity difference with the neighborhood voxels in healthy tissue. To avoid picking up neighboring lesions, we use an adaptive moving window computation to compute the intensity differences between lesion voxels and surrounding normal tissue voxels.

Considering the original T1 MRI data as $T$, and the lesion mask volume data as $M$, we compute a new volume $V$, where every voxel $V(i,j,k)$ is computed as:

$$V(i,j,k) = \frac{1}{N_l} \sum_{x=i-\lfloor \frac{m}{2} \rfloor}^{i+\lfloor \frac{m}{2} \rfloor} \sum_{y=j-\lfloor \frac{n}{2} \rfloor}^{j+\lfloor \frac{n}{2} \rfloor} \sum_{z=k-\lfloor \frac{p}{2} \rfloor}^{k+\lfloor \frac{p}{2} \rfloor} T(x,y,z)[M(x,y,z) \neq 0] - \frac{1}{N_h} \sum_{x=i-\lfloor \frac{m}{2} \rfloor}^{i+\lfloor \frac{m}{2} \rfloor} \sum_{y=j-\lfloor \frac{n}{2} \rfloor}^{j+\lfloor \frac{n}{2} \rfloor} \sum_{z=k-\lfloor \frac{p}{2} \rfloor}^{k+\lfloor \frac{p}{2} \rfloor} T(x,y,z)[M(x,y,z) \neq 1] \quad (1)$$

where $N_l$ and $N_h$ are the total number of lesion voxels and healthy tissue voxels, respectively. A 3D window of size $m \times n \times p$ is used to capture voxel intensity differences. As we are trying to capture the difference between the immediate surrounding normal tissue voxels and lesion voxels, we set $m = n = p = 3$. Keeping the window size minimal is intentional, as we don't want to include samples that are far away from the lesion surface. If the outer surrounding captured by the window includes another lesion, then these voxels are discarded from the computation (Equation 1).

After extracting a lesion surface mesh from the lesion mask data using the marching cubes algorithm [LC87], we probe the volume $V$ using the mesh. This process will associate intensity difference scalar values to the lesion mesh data. Finally, we process

the mesh data to apply suitable colors to depict different intensity based lesion classifications (hypo/iso/hyper). The color values that we use are colorblind-safe and selected from ColorBrewer [HB11]. For the purpose of coloring, we also employ a user-defined range $[-R_{iso}, R_{iso}]$, within which we classify a lesion as iso intense. For every vertex in mesh $M$, we assign one of the color values $(C_{hypo}, C_{iso}, C_{hyper})$:

$$M_i = \begin{cases} C_{hypo} & \text{if } S_i < -R_{iso} \\ C_{iso} & \text{if } -R_{iso} \leq S_i \leq R_{iso} \\ C_{hyper} & \text{if } S_i > R_{iso} \end{cases} \quad (2)$$

where $S_i$ indicates the intensity difference scalar value.

In discrete color mapping mode, the approach is similar but we assign every disjoint lesion a single color based on the average intensity difference between the whole lesion and its surrounding normal tissue.

#### 5.1.1. Interaction

To help users to establish a connection between existing observations or landmarks in 2D slices and our 3D visualizations, we have enabled lesion interaction in MPR (Multiplanar Reconstruction) slices that are basically image planes from volumetric data. We display three standard planes (axial, sagittal, and coronal) in the application, where the user can select lesion segmentations displayed on MPRs and have them highlighted in the 3D scene. It is also possible to query slices by interacting with the 3D lesions. To manage cognitive load and scene complexity (R.3), users can choose to see one or more other surfaces along with the lesions. The context can include ventricles, opacity-adjustable brain surfaces (pial or white), and volume data. Besides lesion color mapping, we also compute several statistical properties of lesion surfaces for enabling the users to filter lesions based on those properties. From the application user interface, one can choose a property listed in a combo box and use a slider to set display threshold for the selected property. The filter properties include voxel count, elongation, perimeter, spherical radius, spherical perimeter, flatness, and roundness of the lesion. Having this filtering feature can assist in reducing lesion clutter. This fulfils requirements R.3 and R.5 and allows users to focus only on lesions of interest, thus reducing cognitive load.

### 5.2. Distance-Based Lesion Visualization

Classifying lesions based on their distance to the cortical surface is another relevant clinical aspect (R.2). As mentioned earlier, researchers are interested in knowing if a lesion is close to the ventricles or outer white matter surface. Filtering lesions based on this using 2D slices becomes difficult and requires a brute force spatial search across multiple slices. In 3D, problems such as incorrect depth perception and occlusion occur due to high lesion load. Perception of depth becomes difficult due to the combination of complex surface anatomy with nested lesion surfaces. When we present all lesions in 3D, it becomes naturally difficult to identify them in terms of their proximity to context structures, e.g., ventricles and cortical surface. To overcome this difficulty in depth perception, we present distance information as a color mapping on every lesion to make them easily distinguishable. For this, we use a single-hue sequential color scheme from ColorBrewer [HB11]. Here, we assign a light color to lesion areas that are close to the ventricles, and the color gets darker gradually when moving towards the juxtacortical lesions. With the lesions color coded in this manner, it becomes easier to perceive the distance from standard anatomical structures. The distance-based visual mapping satisfies requirements R.2 and R.3 by reducing cognitive load for easy localization of lesions by their distance-based coloring.

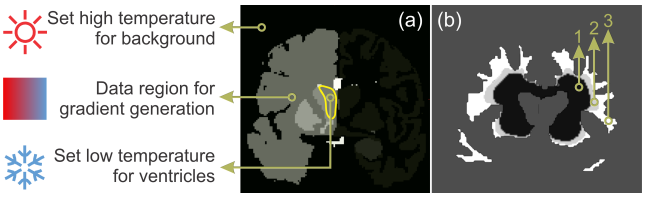


**Figure 5:** *For heat equation-based gradient computation, (a) segmentation data is used along with pre-defined temperature regions. (b) After gradient computation, the temperature gradient space is quantized into equally sized distance regions (1, 2 and 3).*

For realizing the requirement R.2, we propose to use a novel heat equation-based technique (https://github.com/mmiv-center/HeatEquation) which enables geodesic distance measurement between brain ventricles and the outer white matter surface. The technique involves simulation of a heat equation for generating temperature gradients in 3D, starting from brain ventricles to the white matter surface. To generate temperature data, we simulate the heat equation on structural MRI data, which is possible for any structural imaging modality. As part of initialization steps for temperature data generation, we set fixed temperatures -100 and +100 for the ventricles and the background (outside white matter) respectively. Figure 5 illustrates the regions where we initialize the temperatures. The heat equation simulation subsequently generates temperature data based on the pre-defined temperature regions. For lesion color coding based on distance, we quantize the resulting gradient region into several regions as shown in Figure 5(b).

### 5.3. Projection-Based Lesion Visualization

Projecting lesions to the surface of the brain, especially the juxtacortical lesions, is useful in deriving quantitative information relating to the number of brain regions potentially affected, and could be a basis for future studies correlating mappings with cognitive disabilities. The mapping or projection of lesions addresses requirement R.4. Projecting information on the brain surface is a well-known approach to manage cognitive load introduced by a 3D scene [KHC*12]. We present three user-adjustable mapping techniques to visualize lesion projection on the brain surface. The three techniques include DTI fiber tract-based projection, heat equation-based projection, and Danielsson distance map-based projection.

For doing a DTI-based projection, we make use of the fiber tracts. To generate fiber tracts from the DTI data, we make use of MRtrix3 [TSR*19], which is a suite of tools for image processing, analysis and visualization. Since this data does not contain MS lesions, we synthetically added the worst-case scenario of MS lesions (black holes) by refining masks in the MRtrix3 connectome generation pipeline. We use pre-processing to group the generated fiber tracts based on their intersection with a lesion. These fiber

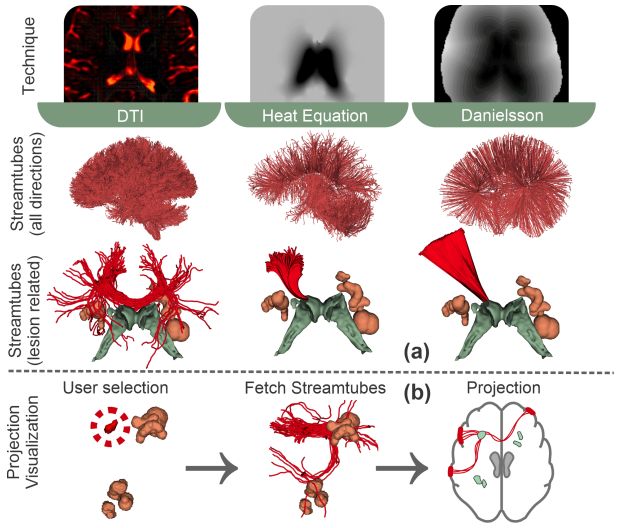


**Figure 6:** *Different approaches for projecting lesions. (a) generates streamtubes of different nature. Bottom row depicts streamtube bundles for an example lesion selection. (b) The application workflow allows the user to pick a lesion, visualize fiber bundle for the picked lesion, and see lesion projections on the brain surface.*

bundles are further processed to intersect with the brain surface to derive projection information. Figure 6(a) shows an illustration of different lesion projection techniques along with the application workflow.

For cases where DTI data is not available, our application can fall back to alternative projection techniques that use either a heat equation simulation or a distance map. The heat equation-based projection mimics heat transfer from the ventricles to the outer surface for generating 3D gradients, as described in the previous subsection. We use the Runge-Kutta-4 integration on the resulting temperature gradients to generate streamtubes originating from ventricles and headed towards the outer brain surface. Similar to the DTI-based approach, we only fetch those streamtubes that make contact with the lesions.

We also show lesion projection by using distance maps defined inside the white matter. We can incorporate any distance metric for creating the 3D map. We present an example using a Danielsson distance map [Dan80] to project lesions to the brain surface and we use the brain ventricles as a mask for calculating the distance map. As shown in Figure 6, the streamtubes generated from heat equation method seem to respect the shape of the anatomy more than Danielsson distance method.

For smaller lesions, we note that there are cases where an observer could easily miss spotting a lesion projection on the surface due to their smaller surface footprint. Such projections easily become occluded by the folded geometry of the brain surface. In addition, there are cases where lesion projections appear on multiple and opposite sides of the brain. Identifying all these patches would then require a lot of rotation interaction. To minimize the interaction needed and to avoid the risk of missing out a lesion patch due to occlusion, we propose to have a similar visualization on an unfolded brain surface, thus satisfying requirement R.6. As part of the unfolding, we perform a brain surface parametrization. There are two well-established algorithms that offer surface parametrization. The first method *Spectral Conformal Parametrization* (SCP) was introduced by Mullen et al. [MTAD08]. SCP yields a conformal, i.e., angle-preserving mapping of the brain surface to the 2D domain. In SCP, there is no need for a defined boundary. The second method *As-Rigid-As-Possible* (ARAP) developed by Liu et al. [LZX*08] reduces area distortion. This results in an unfolding that yields an area-preserving mapping in the 2D domain. As shown in Figure 7, ARAP does not introduce unnecessary distortions when compared to SCP. This allows us to preserve parcellation area and enables users to identify lesion impact without distortions. The closed brain surface mesh cannot be unfolded without introducing a hole. Thus, we added a hole by removing the corpus callosum region from both hemispheres. This removal is acceptable as users are interested in viewing the projections to other surface regions. By removing the unused region, we convert the original mesh to a disk topology that is suitable for unfolding.

#### 5.3.1. Interaction

In dual mode, we can either interact with the lesions in the left viewport or interact with the brain surface in the right viewport. Selecting a lesion with a mouse click will display the projection streamtubes and also highlights relevant brain regions along with the raw projection. Selecting a region on the brain will highlight the associated parcellation and relevant lesions in the left viewport. In addition, we have projection-based interactive filtering of lesions and regions. These interactions enable a user to define a required level of detail in terms of lesion and brain region relationship. Here, the primary motivation for establishing a two-way link is the fact that every brain parcellation can have contributions coming from multiple lesions and every lesion can influence multiple parcellations. Also, in 2D unfold mode, we support relating 2D parcellations to 3D inflated brain context using parcellation highlights.

## 6. Implementation

To showcase the proposed visualization design, we developed the MuScLeVis application (see Figure 8) in Python using the Visualization Toolkit (VTK) and the Insight Toolkit (ITK) libraries. We use a preprocessing pipeline to deal with computationally intensive tasks. One of the first steps in our pre-processing pipeline includes running FreeSurfer [Fis12] on the T1 data to generate high-quality brain surface files, tissue segmentation and parcellation label data. We also perform volume re-sampling on lesion masks to achieve a consistent dimension and voxel spacing across modalities. Based on the lesion mask, we do such re-sampling corrections on all available modalities to ease the computation at runtime. We extract lesion surfaces from the lesion mask data using a connected component analysis. The statistical properties of the lesions are computed using ITK. The lesion filtering mechanism reads these statistical data from a text file that follows the JavaScript Object Notation (JSON) encoding standard for structured data. For a smooth user experience, we also pre-compute lesion voxel intensity profiles for all available modalities and types (continuous and discrete). For distance-based coloring, we compute lesion colors per vertex by


**Figure 7:** *Comparison between SCP and ARAP shows that ARAP based surface unfolding introduces less surface deformation.*

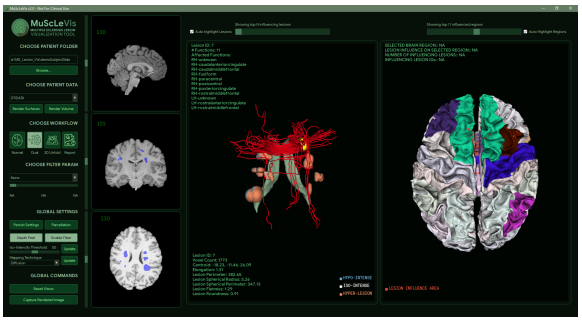


**Figure 8:** *The MuScLeVis prototype application for interactive analysis of lesions in 3D. The screenshot depicts the application's dual mode.*

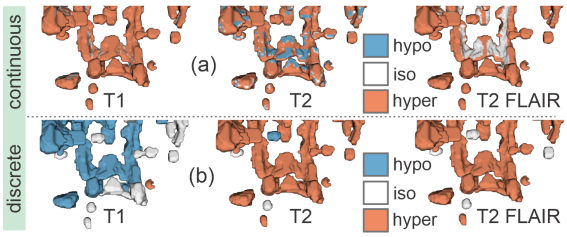


**Figure 9:** *Plotting the intensity difference ((a) continuous and (b) discrete) between lesion and surrounding normal tissue on the lesion surface itself is useful in understanding the behavior across modalities (T1, T2 and T2 FLAIR).*

sampling vertices on region quantization data. Recall that we derive region quantization from the temperature gradient data. To establish a two-way link between lesions and brain surface parcellations, we use the annotation data from FreeSurfer.

Overall, from an implementation perspective, we do most of the process intensive operations offline. Our application scales well to a range of systems from workstation to less powerful laptops due to these pre-computed data resources.

## 7. Results

We report the results using both structural and DTI datasets. For experimenting with structural data from multiple sequences and subjects, we use a publicly available MS Segmentation Challenge [CIK*18] dataset, which comprises T1, T2 and T2 FLAIR sequences from 15 subjects. This dataset includes a ground truth segmentation (binary mask data) of all lesions, based on manual delineation consensus from seven experts. For a DTI-based projection, we are using subject data 100307, which is openly available as part of the Human Connectome Project (https://db.humanconnectome.org/).

Our prototype application conveys the visualization results mainly through three different workflows: (1) Normal mode, (2) Dual mode and (3) 2D unfold mode. Besides this, we also provide a report mode, which basically offers support for exporting the render captures from other modes as a PDF document.

**normal mode:** We treat normal mode as an entry point to the application, and it provides options that enable visualization of intensity differences (R.1), visualization of distance information (R.2, R.3), and filtering of lesions (R.3, R.5). It comprises three standard orthogonal slice views, a standard volume renderer, and toolbox panels for invoking application features. In normal mode, we provide toggle group buttons for choosing both visualization type and modality of interest. Supported color-blind safe visualizations include continuous or discrete intensity (R.1) and distance coloring for the lesions (R.2 and R.3). Modality selection is only available for continuous and discrete intensity-based visualizations since distance-based coloring does not directly depend on voxel intensities information. We provide a color legend along with the visualization result to help identify the classifications, i.e., hypo-, iso- and hyper-intense. With the color mapped directly on the lesion surface, the user can switch between modalities to study the intensity difference profile of a lesion across modalities. We show an example of continuous lesion coloring done for all modalities in Figure 9.

The results from discrete mapping are useful in perceiving patterns depicted in Figure 4(a), 4(b), and 4(c). In contrast, continuous mapping is more useful in analysing patterns depicted in Figure 4(d) and 4(e). In the visualization shown in the first column of Figure 9, the application visualizes a significant lesion mass as hypo in discrete mode where the same mass gets visualized as hyper in continuous mode. This is because in discrete mode we are computing the average intensity difference between a whole lesion and its surroundings, whereas in continuous mode we compute a local intensity difference at every point on the surface of the lesion.

The distance-based coloring (Figure 10) of lesion is another useful feature that helps to locate lesions based on their proximity to standard brain anatomy, which is highly relevant for MS researchers. The use of a sequential coloring scheme gives a sense of which lesions are close to the outer surface and which ones are lying deep inside the brain, close to the ventricles. The results from our distance-based coloring helps in easy identification, counting, and analysis of such lesions while exploring and assessing their location profiles in 3D. Due to the complex nature of the brain surface combined with lesion structures that vary a lot between patients, it is otherwise difficult to assess such distances when viewing the nested surfaces in 2D slices or 3D reconstructions.

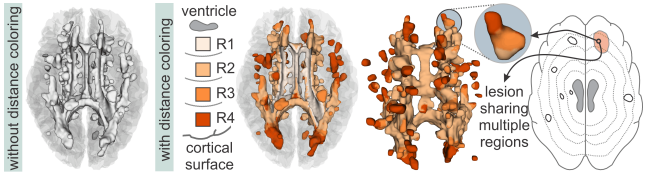


**Figure 10:** *Distance-based lesion visualization helps in better interpretation and localization of lesions in terms of proximity to standard anatomical structures.*

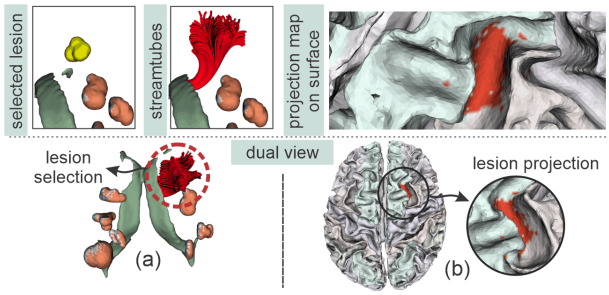


**Figure 11:** *A linked-view dual mode showing an example lesion projection using heat equation simulation. (a) For a selected lesion in the left viewport, (b) corresponding surface projection is displayed on the brain surface rendered in the right viewport.*

**dual mode:** The dual mode serves to fulfil requirement R.4 and offers two side-by-side views along with the standard orthogonal slice-views and the toolbox. Here, the key motivation for having separate visualization for lesions and brain surface is the nature of the workflow itself. There is a need to relate lesions to brain surface parcellations and vice versa. The reason for this is that every lesion can influence multiple surface parcellations and every parcellation can be influenced by multiple lesions. Our approach visually reveals these relationships with the help of a dual view and provides quantification of probable influence of a lesion by projecting it on the white matter surface. Besides revealing lesion influence as a visible patch on the surface, we also provide quantitative results as text overlays. When the user selects a lesion, besides overlaying lesion statistical features, we interactively display region related information associated with the selected lesion as shown in the first column of Table 1.

Figure 11 shows an example scenario where the user has made a lesion selection (showed inside a circle in the left renderer), and as a result, the surface rendering on the right gets updated with a lesion influence patch (red patch shown inside a circle in the right renderer). Users can optionally enable streamtubes for the selected lesion, highlighting the projection path followed to calculate surface projection. For operational convenience, we have also synchronized the camera of both renderers. When comparing different projection methods depicted in (Figure 12), we can say that DTI based projection follows on the underlying structural fiber tracts, whereas gradient based ones (heat equation and Danielsson distance) can help in the absence of DTI, and especially for lesions that are more closer to the cortical surface where DTI would exhibit a weak resolution.

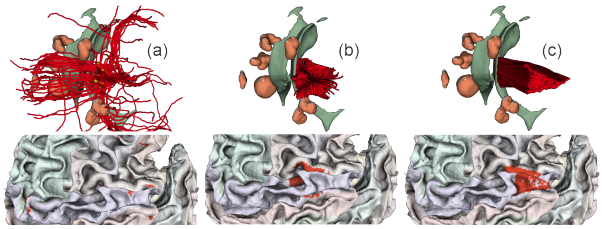


**Figure 12:** *Lesion projection results for different projection methods. (a) DTI, (b) Heat equation, and (c) Danielsson distance.*

Since we rely on the underlying real structural fiber tracts when using DTI data, the resulting projection (Figure 12(a)) will appear more spread across the brain surface, making related parcellations difficult to read through visual inspection. Depending on the location of the lesion, it is even possible that the lesion projection can appear at both hemispheres (Figure 13(a), 13(b), and 13(c)). This is due to the existence of corpus callosum that connects both hemispheres. As a result of the high projection spread, making sense of raw projection becomes difficult. For easy localization of parcellations, we allow users to have relevant parcellations highlighted along with projection patches. It is important to note that we highlight a parcellation, even if there exists a single fiber tract trace between a lesion and brain surface. Consequently, a lot of parcellations are highlighted as shown in Figure 13(c). We can interactively narrow down to the most relevant or top $n$ parcellation(s) using a slider. This way we can find the top region that links to the lesion through strong fiber connections. From the results in Figure 13(d), we can observe that the top region is the one lying close to the selected lesion, and can be interpreted as a region having higher strong fiber connections with the selected lesion.

Finding top $n$ lesions for a user selected parcellation is useful when the user interacts with the brain surface. By querying on the brain surface, depending on the projection method, the user can get linked lesions based on fiber connectivity or location. For brain surface interactions based on DTI, as shown in Figure 14(b), we identify linked lesions based on fiber tract connectivity, and highlight them in yellow. When we use a DTI-based projection, all lesions may not have the same relationship strength with the selected parcellation. From a user's perspective, it is useful to identify the most influential lesion. We achieve this by sorting lesions based on their connectivity strength with a specific brain region. To interactively visualize/highlight the most influential lesions or top $n$ lesions, the user can employ a slider. Figure 14(c) shows the results for different slider values that represent the number of lesions to display. It is also interesting to note here that the top lesion turns out to be the one that is proximal to the brain surface.

**2D unfold mode:** To address requirement R.6, the application can switch to a more abstract 2D unfold mode. Here, the central renderer comprises four viewports presented in a 2x2 layout. This arrangement of linked displays is common in radiology systems and familiar to the domain users of the software. Among the viewports, we dedicate the top row for displaying unfolded brain surfaces and the bottom row for 3D lesions and inflated brain surfaces. This workflow focuses on providing faster projection analysis at the

| Dual Left Viewport (shows region data for selected lesion) | Dual Right Viewport (shows lesion data for selected region) |
|---|---|
| Selected lesion ID: 15<br>Number of regions: 2<br>Connectivity based Proximal Regions:<br>RH-caudalanteriorcingulate<br>RH-caudalmiddlefrontal | Selected brain region: rostralmiddlefrontal<br>Lesion influence on selected region: 3.82%<br>Number of influencing lesions: 2<br>Influencing Lesion IDs: ['15', '17'] |

**Table 1:** *Dual mode data attributes in left and right viewports.*

cost of abstracting anatomical detail of the brain surface. This view reduces the risk of overlooking a lesion projection patch as the visualization provides a 2D abstract unfolded overview which can be inspected without interaction. As such, we do not require the user to rotate the brain surface to search lesion projection patches. Here, as shown in Figure 15, we visualize projection and parcellation information on a 2D unfolded plane and on the inflated white matter surface. In contrast to dual mode, 2D unfolded mode offers an occlusion free overview of lesion projection without requiring the user to perform an exhaustive search on a 3D surface.

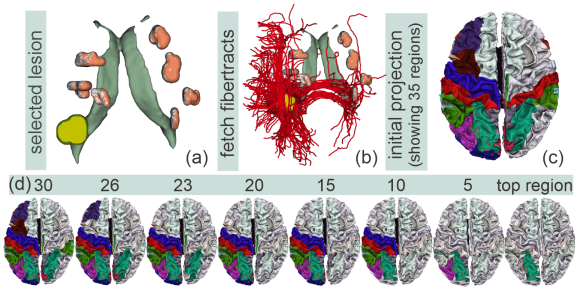


**Figure 13:** *Projection-based lesion visualization for DTI data. (a) For a selected lesion (b) relevant fiber tracts are fetched, and (c) followed to project on brain regions. (d) A slider can be used to find top n regions having strong fiber connectivity.*

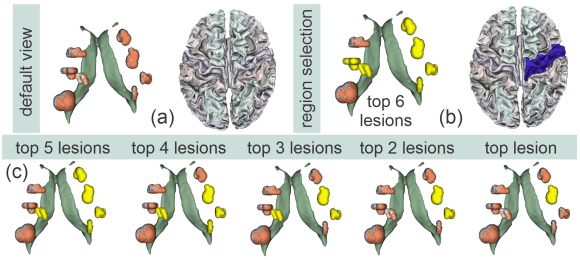


**Figure 14:** *Example demonstration of finding top n lesion(s) for a selected brain region using DTI data. (a) From the default dual view (b) user selects a region on the brain surface displayed in the right viewport highlighting (in yellow) 6 lesions in the left viewport. (c) Filtering out lesions based on fiber tract connectivity strength.*

## 8. Evaluation

In order to assess the utility and applicability of our MuScleVis prototype application, we performed a qualitative evaluation. Here, we discuss the evaluation setup and gathered feedback.

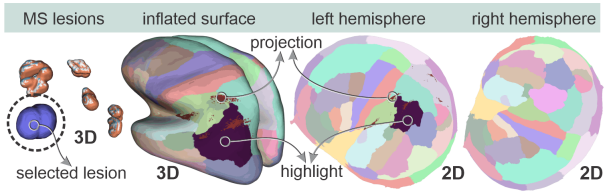


**Figure 15:** *Mapping of lesions to unfolded brain surfaces to enable easy localization. For a user-selected lesion (dark blue) a projection is visualized as a dark red patch over the colored parcellations.*

### 8.1. Evaluation Setup

We designed this user study mainly in order to understand the medical utility and potential of the prototype application. We have considered five experts having relevant knowledge and experience working as a neuroradiologist (Rad), neurologist (Neu) and brain imaging researchers (Res). We included mostly researcher participants, as they are the intended users and potentially stand to gain the most from this tool by exploring new visualizations in MS research. However, we have included few clinical participants (Rad and Neu) to understand more about the type of users who would find our work relevant and useful.

We showed the tool to individual participants, and enabled participants to explore the tool and ask questions. After the interactive session, we asked the participants to fill a questionnaire comprising 33 statements (Table 2). We structured the statements into five categories viz. General feedback (A1-A7), High-level features and user interface (B1-B5), Normal mode workflows (C1-C7), Dual mode workflows (D1-D11) and 2D unfold mode workflows (E1-E3). In order to avoid bias in responding to the statements, we phrased half of the questions negatively (indicated in Table 2 with an asterisk symbol). For ease of interpretation, we have inverted the scores on those statement responses in the table. For all the 33 statements, we recorded the response as agreement on a five-point Likert scale. In addition, we asked the participants for any additional feedback on the application or the evaluation via free-form text at the end of the questionnaire.

### 8.2. Evaluation Results

The user study gave us a general impression that the prototype application is more suited for a research setting than daily clinical use. This thought was generally consistent across all participants. One main reason for this could be the lack of fully automated MS lesion detection in current clinical practice. The participants also commented that the interactive visualizations especially in the dual mode is useful for research. The support for multimodal data, text and graphics overlays were considered useful in our application by all participants. The organization of the user interface was also appreciated by most participants.

Participant *Rad* is an experienced neuro-radiologist is quite familiar with making observations from 2D slices. Having less experience in using research tools, *Rad* gave a neutral score for statement A1. However, *Rad* appreciates the usefulness of the visualizations by providing good ratings. *Rad* also finds that the protocols

**Table 2:** *User response to 30 statements on a 5-point Likert-scale: 1: Strongly disagree, 2: Disagree, 3: Neither agree nor disagree, 4: Agree, 5: Strongly agree. Negatively phrased statements in the original form are indicated by a ⋆ and their scores are inverted for ease of interpretation.*

| | Statement | *Rad* | *Neu* | *Res1* | *Res2* | *Res3* |
|---|---|---|---|---|---|---|
| A1 | Improvement over existing MS lesion research tools/methods | 3 | 4 | 5 | 4 | 5 |
| A2 | Useful to researchers for studies related to MS | 4 | 4 | 5 | 4 | 4 |
| A3 | Useful to clinicians for patient communication ⋆ | 4 | 4 | 4 | 4 | 5 |
| A4 | Useful to clinicians for treatment planning ⋆ | 2 | 4 | 1 | 4 | 5 |
| A5 | Has potential to be possibly included as part of existing medical software ⋆ | 5 | 4 | 5 | 5 | 5 |
| A6 | More applicable to research rather than clinical practice | 4 | 3 | 4 | 4 | 3 |
| A7 | Exporting captured visualization results to PDF report is useful | 4 | 5 | 5 | 4 | 5 |
| B1 | User interface design is easy to understand | 4 | 4 | 5 | 5 | 5 |
| B2 | Separation of workflows into different modes is useful | 4 | 4 | 5 | 5 | 5 |
| B3 | Support for showing multiple sequences, such as T1, T2, and FLAIR data in the application is useful ⋆ | 5 | 4 | 5 | 5 | 5 |
| B4 | The lesion overlay displayed on top of the slice-based views are helpful ⋆ | 4 | 4 | 5 | 5 | 5 |
| B5 | The interaction speed is satisfactory ⋆ | 3 | 5 | 5 | 5 | 5 |
| C1 | Exploring lesions in 3D gives a better overview than slice-based exploration ⋆ | 2 | 5 | 5 | 5 | 5 |
| C2 | Filtering lesions based on their statistical properties is a useful feature ⋆ | 4 | 4 | 5 | 5 | 5 |
| C3 | Being able to add/remove structures from the 3D view helps me see what I am interested in | 4 | 5 | 5 | 4 | 5 |
| C4 | Making the surface more transparent helps me to locate lesions while having the surfaces as a reference | 4 | 3 | 5 | 5 | 5 |
| C5 | The overlay text display for providing lesion information dynamically based on mouse click is useful ⋆ | 4 | 4 | 5 | 4 | 5 |
| C6 | Having intensity classifications visualized on lesion surface in both continuous and discrete manner is a useful aspect for lesion research ⋆ | 4 | 5 | 5 | 4 | 5 |
| C7 | In 3D, the distance-based coloring of lesion helped in differentiating periventricular lesions from juxtacortical lesions | 4 | 5 | 5 | 4 | 5 |
| D1 | Separating lesion and brain surface while having the interactions synchronized is useful to manage complexity. | 4 | 4 | 4 | 4 | 5 |
| D2 | The display of stream tubes provides me a sense of direction for possible projections to the brain surface | 4 | 5 | 5 | 4 | 5 |
| D3 | The projection displayed on the brain surface upon clicking a lesion is useful ⋆ | 5 | 5 | 5 | 4 | 5 |
| D4 | Quantifying the projection area for every selected lesion is a useful feature for research ⋆ | 4 | 5 | 5 | 4 | 5 |
| D5 | The application allows me to relate lesions to parcellations and vice-versa ⋆ | 4 | 4 | 5 | 4 | 5 |
| D6 | For tiny lesions projected in dual mode, the surface mapping can be difficult to identify or even miss to identify on folded pial surface/white matter surface | 3 | 4 | 5 | 3 | 5 |
| D7 | By interacting with the brain surface, I was able to locate lesions that potentially influence the selected brain region | 4 | 5 | 5 | 4 | 5 |
| D8 | DTI fiber tract-based lesion projection is a useful feature ⋆ | 4 | 5 | 5 | 5 | 5 |
| D9 | It is useful to have alternate mapping methods when DTI data is not available ⋆ | 3 | 5 | 4 | 5 | 5 |
| D10 | For a selected lesion in dual mode, the provided slider tool for highlighting top N regions is helpful to get insight on the most relevant brain region(s) | 4 | 4 | 5 | 4 | 5 |
| D11 | For a selected parcellation in dual mode, the provided slider tool for highlighting top N lesions is helpful to get insight on the most relevant lesions ⋆ | 4 | 4 | 5 | 4 | 5 |
| E1 | It is useful to identify lesion impact when using the 2D unfolded view ⋆ | 2 | 5 | 5 | 4 | 3 |
| E2 | Linking 2D unfolded surfaces with 3D brain surfaces helps me to establish a good spatial awareness of how the unfolded view relates to regular anatomy | 3 | 5 | 5 | 4 | 5 |
| E3 | With the mapping displayed, I can see both parcellation boundaries as well as the patch that shows lesion projection ⋆ | 4 | 5 | 5 | 4 | 5 |

defined for 2D slices are good enough for him to get an overview of lesions. We see this statement as an indicator of the amount of experience and trust that practitioners have in using standard protocols for reading 2D slices. *Rad* also thinks that we cannot readily use the visualizations for treatment planning, mainly due to the lack of an established and approved scientific protocol. However, *Rad* appreciated the lesion projection visualization and prefers to have it on the folded brain geometry than the unfolded geometry. Considering the profile of *Rad*, we expected a few disagreements on statements regarding the use of some visualizations bypassing existing clinical protocols. This is also the reason we believe that MS researchers would be more keen to use and derive novel insights from these visualizations by conducting studies at a larger scale. As *Rad* agrees, novel findings would be possible if we employ this tool in a research setting.

Participant *Neu*, an experienced neurologist, found our tool useful in a clinical setting as well. Overall, *Neu* shared positive comments, and considers our tool a valuable contribution. Participants *Res1*, *Res2*, and *Res3* are quite familiar in brain research. Among the researchers, *Res1* is also a neurologist who thinks that the tools is not suited for treatment planning.

Overall, the evaluation results indicate that the users, including clinicians and researchers, believe that the tool has high potential for improving understanding of MS and gaining more insights boosting MS research. The feedback also informs us that quantifying risk is a useful feature in the application.

## 9. Discussion

The proposed techniques for intensity-based lesion coloring, comparison and surface projection are integrated in an application to enable analysis in linked 2D and 3D visual representations. Visualization of intensity difference on the lesion surface helps in easy comprehension of overall intensity of lesions in 3D. Having the visualizations on the lesion surface also serves as an easy way to compare the intensity profile of lesions across modalities. While the approach of projecting lesions using DTI fiber tracts receive more clinical acceptance as per the user study, we also demonstrate example distance-based approaches. This will make our application more applicable to standard clinical MR acquisition protocols. Interestingly, the approach of defining distance maps inside organs and using them for surface projection has got a wider scope. It is possible to deploy the same projection technique to other relevant hidden organs or internal structures in the body. The work by Smit et al. [SLK*17] is an example in the visualization domain that uses the distance-map based approach to visualize proximity on the surface. In our case, we show Danielsson distance as an example, which we can always replace with any standard distance metric. In contrast to distance maps, the usage of DTI or a heat equation based projection would represent the anatomy of the brain more

correctly. Also, it is important to note that instead of DTI, if we use non-standard techniques such as the heat equation or distance map to project lesions on the brain surface, the resulting streamtubes or resulting projections cannot represent any complex fiber associations inside the brain. For instance, a lesion interrupting the U-fiber (short association fibers) inside the brain can only be visualized when the application runs in DTI mode. However, it is important to note that the heat equation and other distance maps based projections are equally good or even better especially for lesions that are close to cortical gray matter. This is because in those areas, the nature of DTI would be more isotropic (may result in unreliable directions). Although we can use heat equation for the case of deeper lesions, we prefer it only as a fallback solution when DTI is not available. When DTI data is absent, distance based techniques can provide a decent estimate of proximity to standard brain regions, and the benefit of practical applicability in this case outweighs the limitations. Another practical limitation of our application is that it does not provide any lesion segmentation features. Automated lesion segmentation is a highly investigated topic, and this can be remedied by including existing segmentation modules in our pipeline. Finally, the application does not support simultaneously loading and comparing followup datasets, but we can always manually load individual time point data to understand the visualization differences.

## 10. Conclusion and Future Work

We present MuScLeVis, a prototype application designed for visualizing and analysing MS lesions in 3D, mainly for research purposes. The supported major features are distributed across three workflows. The normal workflow helps users to perform compare lesion voxel intensities in a continuous and discrete fashion. The 2D dual mode serves as a way for users to query both lesion and white matter surface for studying potential lesion influence. Finally, the 2D unfolded mode presents an abstraction from the anatomy of the white matter surface, which avoids occlusion and reduces the need for user interaction to get an overview of lesion impact. Overall, the primary purpose of the tool would be to gain a detailed understanding of the disease, supporting decision making relevant to choosing medication and improving data annotations. To a limited extent, the tool can also help in comparing followup scans through sequential data loading. Our evaluation with medical experts from diverse areas related to neuro-imaging reveals that our application has potential for both research and clinical purposes.

There are several avenues of future research for the work presented here. First, patient comparison would be an interesting area for further investigation, both between subjects, but also comparing lesions and their impact longitudinally. Including patient follow-up data would be beneficial from a clinical perspective. Here, matching data over multiple time points would be a challenging research question in itself due to brain atrophy, lesion load, as well as ageing-related changes. The visualizations developed from such temporal data would give more insights to understand disease progression. Adding more brain atlases would further increase the research potential for this application. Based on positive user responses, our work provides visualization support to empower researchers to derive further findings in MS studies.

## Acknowledgments

This work was partially funded by the Trond Mohn Foundation (grant number 811255 and 813558) and the Carl-Zeiss Foundation.

## References

[BH18] BOVE R. M., HAUSER S. L.: Diagnosing multiple sclerosis: art and science. *The Lancet Neurology 17*, 2 (2018), 109–111. doi:10.1016/S1474-4422(17)30461-1. 2

[BHWB07] BEYER J., HADWIGER M., WOLFSBERGER S., BÜHLER K.: High-quality multimodal volume rendering for preoperative planning of neurosurgical interventions. *IEEE Trans Vis Comput Graph 13*, 6 (2007), 1696–1703. doi:10.1109/TVCG.2007.70560. 3

[CBG*10] CALABRESE M., BATTAGLINI M., GIORGIO A., ATZORI M., BERNARDI V., MATTISI I., GALLO P., DE STEFANO N.: Imaging distribution and frequency of cortical lesions in patients with multiple sclerosis. *Neurology 75*, 14 (2010), 1234–1240. doi:10.1212/WNL.0b013e3181f5d4da. 3

[CIK*18] COMMOWICK O., ISTACE A., KAIN M., LAURENT B., LERAY F., SIMON M., ET AL.: Objective evaluation of multiple sclerosis lesion segmentation using a data management and processing infrastructure. *bioRxiv 8*, 1 (2018), 13650. doi:10.1038/s41598-018-31911-7. 8

[CZT*03] CHARIL A., ZIJDENBOS A. P., TAYLOR J., BOELMAN C., WORSLEY K. J., EVANS A. C., DAGHER A.: Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis. *NeuroImage 19*, 3 (2003), 532–544. doi:10.1016/S1053-8119(03)00117-4. 3

[Dan80] DANIELSSON P. E.: Euclidean distance mapping. *Comput graph image process 14*, 3 (1980), 227–248. doi:10.1016/0146-664X(80)90054-4. 7

[DPL*11] DIEPENBROCK S., PRASSNI J.-S., LINDEMANN F., BOTHE H.-W., ROPINSKI T.: Interactive Visualization Techniques for Neurosurgery Planning. In *Proc. of Eurographics* (2011), pp. 13–16. doi:10.2312/EG2011/med/013-016. 2

[Fis12] FISCHL B.: FreeSurfer. *NeuroImage 62*, 2 (2012), 774–781. doi:10.1016/j.neuroimage.2012.01.021. 7

[FPB*19] FILIPPI M., PREZIOSA P., BANWELL B. L., BARKHOF F., CICCARELLI O., DE STEFANO N., GEURTS J., ET AL.: Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. *Brain 142*, 7 (2019), 1858–1875. doi:10.1093/brain/awz144. 3

[GBP*05] GEURTS J. J., BÖ L., POUWELS P. J., CASTELIJNS J. A., POLMAN C. H., BARKHOF F.: Cortical lesions in multiple sclerosis: Combined postmortem MR imaging and histopathology. *AJNR Am J Neuroradiol 26*, 3 (2005), 572–577. 3

[GMK*20] GAETANO L., MAGNUSSON B., KINDALOVA P., TOMIC D., SILVA D., ALTERMATT A. E. A.: White matter lesion location correlates with disability in relapsing multiple sclerosis. *Mult Scler J 6*, 1 (2020), 2055217320906844. doi:10.1177/2055217320906844. 3

[GPB*16] GEISSELER O., PFLUGSHAUPT T., BEZZOLA L., REUTER K., WELLER D., SCHUKNECHT B., BRUGGER P., LINNEBANK M.: The relevance of cortical lesions in patients with multiple sclerosis. *BMC Neurol 16*, 1 (2016), 204. doi:10.1186/s12883-016-0718-9. 3

[HB11] HARROWER M., BREWER C. A.: *ColorBrewer.org: An Online Tool for Selecting Colour Schemes for Maps*. John Wiley & Sons, Ltd, 2011, ch. 3.8, pp. 261–268. doi:https://doi.org/10.1002/9780470979587.ch34. 6

[JBF*20] JÖNSSON D., BERGSTRÖM A., FORSELL C., SIMON R., ENGSTRÖM M., WALTER S., YNNERMAN A., HOTZ I.: VisualNeuro: A hypothesis formation and reasoning application for multi-variate brain

cohort study data. *Comput Graph Forum 39*, 6 (2020), 392–407. doi:10.1111/cgf.14045. 3

[KHC*12] KANG X., HERRON T. J., CATE A. D., YUND E. W., WOODS D. L.: Hemispherically-unified surface maps of human cerebral cortex: Reliability and hemispheric asymmetries. *PLoS ONE 7*, 9 (2012), 1–15. doi:10.1371/journal.pone.0045582. 6

[KP20] KUCHLING J., PAUL F.: Visualizing the central nervous system: Imaging tools for multiple sclerosis and neuromyelitis optica spectrum disorders. *Front Neurol 11* (2020), 450–471. doi:10.3389/fneur.2020.00450. 3

[LBL07] LASSMANN H., BRÜCK W., LUCCHINETTI C. F.: The immunopathology of multiple sclerosis: An overview. *Brain Pathol 17*, 2 (2007), 210–218. doi:10.1111/j.1750-3639.2007.00064.x. 1

[LBSP14] LAWONN K., BAER A., SAALFELD P., PREIM B.: Comparative evaluation of feature line techniques for shape depiction. In *Proc. of Vision, Modeling and Visualization* (Darmstadt, 08.-10. Oktober 2014), pp. 31–38. 2

[LC87] LORENSEN W. E., CLINE H. E.: Marching cubes: A high resolution 3D surface construction algorithm. *Proceedings of SIGGRAPH 21*, 4 (1987), 163–169. doi:10.1145/37401.37422. 5

[LGG*15] LOUAPRE C., GOVINDARAJAN S. T., GIANNÌ C., LANGKAMMER C., SLOANE J. A., KINKEL R. P., MAINERO C.: Beyond focal cortical lesions in MS: An in vivo quantitative and spatial imaging study at 7T. *Neurology 85*, 19 (2015), 1702–1709. doi:10.1212/WNL.0000000000002106. 3

[LSBP18] LAWONN K., SMIT N. N., BÜHLER K., PREIM B.: A survey on multimodal medical data visualization. *Comput Graph Forum 37*, 1 (2018), 413–438. doi:10.1111/cgf.13306. 2

[LVPI18] LAWONN K., VIOLA I., PREIM B., ISENBERG T.: A survey of surface-based illustrative rendering for visualization. *Comput Graph Forum 37*, 6 (2018), 205–234. doi:10.1111/cgf.13322. 3

[LZX*08] LIU L., ZHANG L., XU Y., GOTSMAN C., GORTLER S. J.: A local/global approach to mesh parameterization. *Comput Graph Forum 27*, 5 (2008), 1495–1504. doi:10.1111/j.1467-8659.2008.01290.x. 7

[MKC*16] MEYER S., KESSNER S. S., CHENG B., BÖNSTRUP M., SCHULZ R., HUMMEL F. C., ET AL.: Voxel-based lesion-symptom mapping of stroke lesions underlying somatosensory deficits. *Neuroimage Clin 10* (2016), 257–266. doi:10.1016/j.nicl.2015.12.005. 3

[MSP*02] MAKALE M., SOLOMON J., PATRONAS N. J., DANEK A., BUTMAN J. A., GRAFMAN J.: Quantification of brain lesions using interactive automated software. *Behavior Research Methods, Instruments, and Computers 34*, 1 (2002), 6–18. doi:10.3758/BF03195419. 3

[MTAD08] MULLEN P., TONG Y., ALLIEZ P., DESBRUN M.: Spectral conformal parameterization. *Comput Graph Forum 27*, 5 (2008), 1487–1494. doi:10.1111/j.1467-8659.2008.01289.x. 7

[NWW*17] NEWTON B. D., WRIGHT K., WINKLER M. D., BOVIS F., TAKAHASHI M., DIMITROV I. E., SORMANI M. P., PINHO M. C., OKUDA D. T.: Three-dimensional shape and surface features distinguish multiple sclerosis lesions from nonspecific white matter disease. *J. Neuroimaging 27*, 6 (2017), 613–619. doi:10.1111/jon.12449. 2

[RFC*18] RUGGIERI S., FANELLI F., CASTELLI L., PETSAS N., DE GIGLIO L., PROSPERINI L.: Lesion symptom map of cognitive–postural interference in multiple sclerosis. *Mult Scler J 24*, 5 (2018), 653–662. doi:10.1177/1352458517701313. 3

[RRRP08] RIEDER C., RITTER F., RASPE M., PEITGEN H.-O.: Interactive visualization of multimodal volume data for neurosurgical tumor treatment. *Comput Graph Forum 27*, 3 (2008), 1055–1062. doi:10.1111/j.1467-8659.2008.01242.x. 3

[RSHP08] RIEDER C., SCHWIER M., HAHN H. K., PEITGEN H. O.: High-quality multimodal volume visualization of intracerebral pathological tissue. In *Proc. of EG VCBM* (2008), pp. 167–175. doi:10.2312/VCBM/VCBM08/167-176. 3

[Ser21] SERMESANT M.: SepINRIA: A software to analyse multiple sclerosis brain MRI. https://www-sop.inria.fr/asclepios/software/SepINRIA/, 2021. [Online; accessed 31-March-2021]. 3

[SHW*19] SIVAKOLUNDU D. K., HANSEN M. R., WEST K. L., WANG Y., STANLEY T., WILSON A., ET AL.: Three-dimensional lesion phenotyping and physiologic characterization inform remyelination ability in multiple sclerosis. *J. Neuroimaging 29*, 5 (2019), 605–614. doi:10.1111/jon.12633. 2

[SJS04] SIMON J. H., JACOBS L., SIMONIAN N.: T1-hypointense lesions (T1 black holes) in mild-to-moderate disability relapsing multiple sclerosis. In *Early Indicators Early Treatments Neuroprotection in Multiple Sclerosis*. Springer, 2004, pp. 135–139. doi:10.1007/978-88-470-2117-4_14. 3

[SLK*17] SMIT N., LAWONN K., KRAIMA A., DERUITER M., SOKOOTI H., BRUCKNER S., EISEMANN E., VILANOVA A.: PelVis: Atlas-based surgical planning for oncological pelvic surgery. *IEEE Trans Vis Comput Graph 23*, 1 (2017), 741–750. doi:10.1109/TVCG.2016.2598826. 11

[SS19] SABA L., SURI J. S. (Eds.): *Neurological Disorders and Imaging Physics, Volume 1*. 2053-2563. IOP Publishing, 2019. doi:10.1088/2053-2563/ab1fdc. 2

[SZL*06] SIMON J. H., ZHANG S., LAIDLAW D. H., MILLER D. E., BROWN M., CORBOY J., BENNETT J.: Identification of fibers at risk for degeneration by diffusion tractography in patients at high risk for MS after a clinically isolated syndrome. *J Magn Reson Imaging 24*, 5 (2006), 983–988. doi:10.1002/jmri.20719. 3

[TBB*18] THOMPSON A. J., BANWELL B. L., BARKHOF F., CARROLL W. M., COETZEE T., COMI G. E. A.: Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology 17*, 2 (2018), 162–173. doi:10.1016/S1474-4422(17)30470-2. 2

[TSR*19] TOURNIER J. D., SMITH R., RAFFELT D., TABBARA R., DHOLLANDER T., PIETSCH M., CHRISTIAENS D., JEURISSEN B., YEH C. H., CONNELLY A.: MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *bioRxiv 202* (2019), 116137. doi:10.1101/551739. 6

[VGR*09] VELLINGA M. M., GEURTS J. J., ROSTRUP E., UITDEHAAG B. M., POLMAN C. H., BARKHOF F., VRENKEN H.: Clinical correlations of brain lesion distribution in multiple sclerosis. *J Magn Reson Imaging 29*, 4 (2009), 768–773. doi:10.1002/jmri.21679. 3

[VZKL06] VILANOVA A., ZHANG S., KINDLMANN G., LAIDLAW D.: *An introduction to visualization of diffusion tensor imaging and its applications*. Springer, Berlin, Heidelberg, 2006, pp. 121–153. doi:10.1007/3-540-31272-2_7. 3

[WW04] WHYTE A., WARAKAULLE D. R.: Differential diagnosis of intra-cranial lesions with high signal on T1 or low signal on T2-weighted MRI. *Clin Radiol 59*, 8 (2004), 764–765. doi:10.1016/s0009-9260(03)00268-x. 4

[YBM*12] YAO B., BAGNATO F., MATSUURA E., MERKLE H., VAN GELDEREN P., CANTOR F. K., DUYN J. H.: Chronic multiple sclerosis lesions: Characterization with high-field-strength MR imaging. *Radiology 262*, 1 (2012), 206–215. doi:10.1148/radiol.11110601. 3

[ZNMBS15] ZIMNY A., NESKA-MATUSZEWSKA M., BLADOWSKA J., SĄSIADEK M. J.: Intracranial lesions with low signal intensity on T2-weighted MR images - review of pathologies. *Pol J Radiol 80*, 1 (2015), 40–50. doi:10.12659/PJR.892146. 3

[ZSGZ10] ZHOU F. Q., SHIROISHI M., GONG H., ZEE C. S.: Multiple sclerosis: Hyperintense lesions in the brain on T1-weighted MR images assessed by diffusion tensor imaging. *J Magn Reson Imaging 31*, 4 (2010), 789–795. doi:10.1002/jmri.22103. 3