# Measuring the lesion load of multiple sclerosis patients within the corticospinal tract

Jan Klein[a], Katrin Hanken[b], Jasna Koceva[a], Helmut Hildebrandt[b,c], and Horst K. Hahn[a]

[a]Fraunhofer MEVIS, Center for Medical Image Computing, Bremen, Germany
[b]Clinical Center Bremen-Ost, Department of Neurology, Bremen, Germany
[c]University of Oldenburg, Institute for Psychology, Oldenburg, Germany

## ABSTRACT

In this paper we present a framework for reliable determination of the lesion load within the corticospinal tract (CST) of multiple sclerosis patients. The basis constitutes a probabilistic fiber tracking approach which checks possible parameter intervals on the fly using an anatomical brain atlas. By exploiting the range of those intervals, the algorithm is able to resolve fiber crossings and to determine the CST in its full entity although it can use a simple diffusion tensor model. Another advantage is its short running time, tracking the CST takes less than a minute. For segmenting the lesions we developed a semi-automatic approach. First, a trained classifier is applied to multimodal MRI data (T1/FLAIR) where the spectrum of lesions has been determined in advance by a clustering algorithm. This leads to an automatic detection of the lesions which can be manually corrected afterwards using a threshold-based approach. For evaluation we scanned 46 MS patients and 16 healthy controls. Fiber tracking has been performed using our novel fiber tracking and a standard deflection based algorithm. Regression analysis of the old and new version of the algorithm showed a highly significant superiority of the new algorithm for disease duration. Additionally, a low correlation between old and new approach supports the observation that standard DTI fiber tracking is not always able to track and quantify the CST reliably.

**Keywords:** diffusion imaging, global fiber tracking

## 1. INTRODUCTION

Multiple sclerosis (MS) is an auto-immune system mediated chronic disease which leads to demyelination of axons in the brain and spinal cord and also to neurodegeneration of neurons in the cortex. The location of MS lesions is a promising biomarker for predicting the progression of clinical impairment.[1] Initial studies have indicated that certain areas like the inferior fronto-occipital fasciculus or the corticospinal tract (CST) can show a significant correlation with the rate of progression.[1–3] However, the automatic determination of lesion locations is still a difficult problem. On the one hand, the segmentation is complex due to the variability in size, shape and location of the lesions.[4] On the other hand, the determination of the lesion load within certain fiber bundles is difficult due to the uncertainty of fiber tracking and the dependence on user interaction for drawing regions of interest which are used for seeding or filtering.[5,6] In this paper we focus on the CST, a large bundle which originates in the precentral gyrus and terminates in the spinal cord. The anatomy of this bundle is well-understood and several landmarks like the internal capsule and the cerebral peduncle allow for verifying the quality of the tracking results.

## 2. METHODS

### 2.1 Patients and image acquisition

All 46 MS patients were participants in an ongoing prospective, non-interventional study on MRI parameters characterising progression of MS. The inclusion criteria were age of 18-65 years, diagnosis of relapsing-remitting (RRMS) or secondary progressive MS according to the McDonald criteria 2001 and EDSS 0-6.5. We also investigated 14 healthy controls for comparison. Magnetic resonance images of the brain were obtained at 3.0T

Further author information: (Send correspondence to Jan Klein)
Jan Klein: E-mail: jan.klein@mevis.fraunhofer.de, Telephone: 49 421 218 59239

(Siemens Skyra, Erlangen, Germany). Diffusion MRI images were obtained using 64 non-collinear orientations in the axial plane (image resolution 2x2x2 mm, 55 slices, TR = 7600, TE = 90, number of excitations (NEX) =1, b-value=1000, scanning time $\sim$ 9 minutes). T1-weighted images (TR=1900, TE=2.43) and FLAIR-weighted images (TR=5000, TE= 388) used for the lesion segmentation were obtained by an isotropic resolution of 1x1x1mm3.

### 2.2 Interactive segmentation of the precentral gyrus

Our fiber tracking algorithms utilizes the whole precentral gyrus as a seed volume for reconstructing the CST. For that purpose, we developed a method where the precentral gyrus can be segmented interactively in 3D on a skull stripped brain. Skull stripping is performed on T1-weighted image data using a watershed transformation. For the interactive segmentation, markers are placed within the precentral gyrus. For each marker a sphere with a certain radius is determined. The resulting mask is used for masking the FA map which is finally used for a watershed-transformation.

### 2.3 Reliable reconstruction of the corticospinal tract

The basis of our local, adaptive fiber tracking algorithm is an advection-diffusion based algorithm.[7] In addition to the basic algorithm, it adapts its control parameters to specific regions of the white matter atlas "JHU-MNI-ss atlas", which is often called "Eve Atlas".[8,9] The atlas is based on the T1-MRI data of 152 healthy volunteers and consists of 176 regions.

For each tracking position, the corresponding atlas region is determined. If the tracking is reaching a new region, the parameters are randomly changed from predefined intervals, and thus, the reconstruction is locally adapted. The selection is done randomly in order to avoid missing fibers resulting from discrete samplings. Afterwards, it is tested if one of the stopping criteria is reached and if the tracking process should be aborted. If the fibers are determined for all seed points, the tracking process is repeated until a predefined fiber density is reached or the number of iterations exceeds a predefined threshold (we used 500 as maximum). We adapted the following control parameters:

- $\alpha \in 0,1$ which interpolates between streamline ($\alpha = 1$) and deflection-based tracking ($\alpha = 0$)
- window length (mm): length of a window where parameters like curvature and FA are averaged. The averaged values are used for comparing with the minimal allowed FA or the maximal allowed curvature instead of comparing the current values directly. As a consequence, local outliers do not immediately stop the tracking process.
- minimal FA value.
- maximal curvature.
- step width (mm): the step width between two consecutive fiber points.

Finally, the fibers may be filtered with include and exclude ROIs.

### 2.4 Lesion segmentation

Our lesion segmentation comprises of two steps. In the first step, an automatic segmentation is performed, while in the second step the user has the possibility to manually correct the segmentation result interactively by the help of a threshold-based approach. The automatic segmentation step consists of three main steps of which the first two are applied per a slice and the third is applied to the whole data set. An overview of the algorithm is given in Figure 1. The aim of the first step is to identify the intensity spectrum of the MS lesions within the T1-FLAIR space, i.e., to find the range of T1/FLAIR values which are typical for the lesions. To achieve this goal, two generally known facts are used. The former is that in the FLAIR images the lesion are brighter than the white matter and the gray matter. The latter is that in the T1 images MS lesions are darker than the white matter, while similar to the gray matter. Using the average values of the white and the gray matter in the T1-FLAIR space, the region within the T1-FLAIR space which is typical for the MS lesions is defined. In order

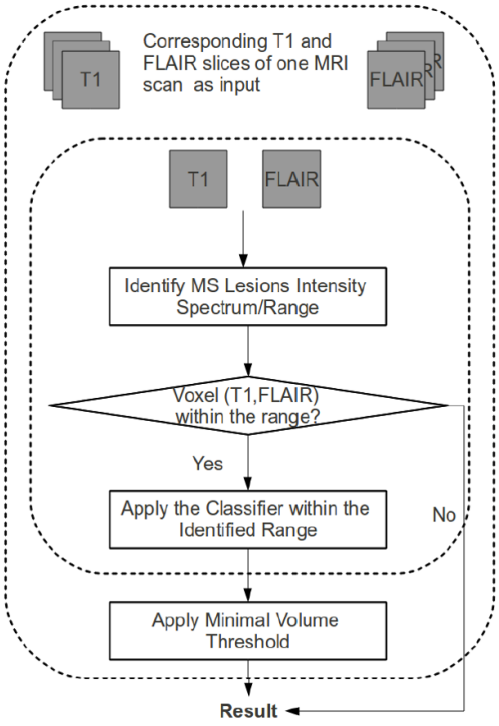


Figure 1. Schematic overview of segmentation algorithm.

to compute the average values of the white and the gray matter, the k-medians clustering algorithm is used to segment such brain tissue.

However, the defined region still contains T1/FLAIR pairs of values which are not typical for the lesions. The aim of the latter step of the algorithm is to determine which of the T1/ FLAIR pairs, which are included in the region, are typical for the MS lesions and which are not. For this purpose, a classifier within the defined T1-FLAIR intensity spectrum is employed. The classifier is trained to learn to make difference between a (T1, FLAIR) pair which is a MS lesion characteristic, and one which is not. The classifier is in the form of a decision tree, and is built using the C4.5 algorithm. A training data set for building the classifier is created based on a provided ground truth. A data set of several brain MRI scans which contains T1 and FLAIR images as well as a segmentation of the MS lesions performed by radiologists is used. The last step of the algorithm is performed on the intermediate segmentation result for the whole MRI scan which is obtained by applying the previous steps. The aim of this step is to handle with voxels which are labeled as MS lesions but are false positives. Most of those voxels are successfully removed by thresholding the intermediate MS segmentation result based on the lesions volume.

### 2.5 Quantification

In order to quantify the lesion load within the CST, we voxelized all tracked fibers into an image which is used afterwards for masking the FA image. Finally, this masked image is used for the quantification. Overall, the lesion load in CST, the average FA in CST, the average FA in lesions of CST and the volume of CST can be derived.

## 3. RESULTS

All of our algorithms have been implemented in MeVisLab[10] using C++. The computations have been performed on an Intel Core i7-2600 with 3.40GHz and 32GB main memory. The tracking and filtering process of the CST of one hemisphere took around 30 seconds. The most time consuming part is the filtering which is done after each iteration, i.e., if fibers have been tracked for all seed points. Fig. 3 and Fig. 4 demonstrate that the fibers end in

| *m*, *gt* | Accuracy | Error rate | Sensitivity | Specificity |
|---|---|---|---|---|
| 1,1 | 0.999 | 0.0004 | 0.31 | 0.999 |
| 1,2 | 0.99 | 0.0002 | 0.45 | 0.99 |
| 1,3 | 0.99 | 0.0002 | 0.79 | 0.99 |
| 2,1 | 0.99 | 0.0005 | 0.2 | 0.99 |
| 2,2 | 0.99 | 0.0003 | 0.24 | 0.99 |
| 2,3 | 0.99 | 0.0003 | 0.54 | 0.99 |

Figure 2. Results for accuracy, error rate, sensitivity and specificity have been computed for two representative MRI scans. $m$ denotes the $m$-th MRI scan and $gt$ the number of the corresponding ground truth ($gt$=1: radiologist 1, $gt$=2: radiologist 2, $gt$=3: logical and between the two radiologists ground truths).

the precentral gyrus. Furthermore, it can be seen that no false fibers belonging to the corona radiata have been computed. This has been achieved by using seed points only in the precentral gyrus and not in the capsula interna or in the brain stem as it can be found in oftentimes in literature. For evaluating the proposed segmentation method, it has been applied to the MRI scans from the MICCAI 2008 MS segmentation challenge where manual segmentations of two radiologists have been given. We computed several metrics including accuracy, error rate, sensitivity and specificity. Results for two representative MRI scans can be found in Figure 2.

The accuracy always has a high value, almost one, and the error rate is always close to zero. This is due to the high value of true negative lesion voxels. Due to the same reasons, the value of the specicity metric is also close to one, meaning that the method has high capability to identify non-lesions. The methods sensitivity, i.e., the capability to identify MS lesions, has the highest values for $gt = 3$, which is the logical and between the two radiologists ground truths. This is, as expected due to the classier being trained according to that ground truth.

We have performed a regression analysis of the patients. Inclusion variable was the age. The lesion load within the CST (old and new fiber tracking algorithm) has been used as a group for forward regression. The lesion load within the CST is used in the model when using the duration of the disease as dependent variable. The model describes 74 percent of the variance of the duration of the disease (R=0.74, F=12.117, $p \leq 0.001$).

## 4. DISCUSSION AND CONCLUSIONS

We have shown that a reliable tracking of the corticospinal tract is possible if adapting the control parameters of the algorithm to the local regions. To the best of our knowledge, this is the first fiber tracking algorithm which adapts its parameters locally using a white matter atlas. Crossing fibers of the corticospinal tract and the superior longitudinal fascicle can easily be determined by our approach if increasing the step width in the corresponding region. Fibers with a high curvature, e.g., fibers of the corticospinal tract ending in "face area" of the precentral gyrus can be computed if increasing the allowed curvature. Note that this parameter adaption can be done fully automatically.

The segmentation method proposed has some strength compared to some other already developed methods. A positive characteristic of the proposed method is that it does not make use of a-prior knowledge which is in form of an atlas, as many algorithms do. In this manner, the additional challenges that are imposed by the atlas based methods, besides the segmentation itself, are avoided. Actually, the prior knowledge used by the method is in the form of manually segmented MRI images, which is easier to be provided and employed. The method performs the segmentation using a classifier. The main difference between the classifier employed here, and the classifiers which are used in some other methods is the range of the intensity values on which it works. In the proposed method, the classifier works within the identified MS lesions region within the T1-FLAIR space, instead of handling the whole range of intensity values. The main benefit of this approach is that all voxels which are primarily typical for the WM, but also appear as lesions, are directly labeled as non-lesions. In this manner we eliminated one of the most frequent problem in many other methods, the number of FP lesions, similar to the WM, is reduced. Regression analysis of the old and new version of the algorithm showed a highly significant superiority of the new algorithm for disease duration. In addition, a low correlation with the results achieved by standard fiber tracking suggests that standard DTI fiber tracking is not always able to track and quantify the CST reliably.

In the upcoming month, all patients and healthy volunteers will be scanned again and we will examine whether our approach is also powerful for detecting differences over time. For that purpose, the use of high-quality registration algorithms will constitute the basis for a thorough analysis.

## Acknowledgements

This work has been supported by Novartis Pharma GmbH, Roonstr. 25, 90429 Nuremberg. However, Novartis is not responsible for its content. Additionally, we would like to thank Volker Diehl and Jochen Hirsch for acquiring the MRI data.

## REFERENCES

1. B. Bodini, M. Cercignani, A. Toosy, N. D. Stefano, D. H. Miller, A. J. Thompson, and O. Ciccarelli, "A novel approach with skeletonised mtr measures tract-specific microstructural changes in early primary-progressive ms," *Human Brain Mapping* **35**(2), pp. 723–733, 2014.
2. A. Giorgio, M. Battaglini, M. Rocca, A. De Leucio, M. Absinta, R. van Schijndel, A. Rovira, M. Tintor, D. Chard, O. Ciccarelli, C. Enzinger, C. Gasperini, J. Frederiksen, M. Filippi, F. Barkhof, N. De Stefano, and M. S. Group, "Location of brain lesions predicts conversion of clinically isolated syndromes to multiple sclerosis," *Neurology* **80**(3), pp. 234–241, 2013.
3. A. Charil, A. P. Zijdenbos, J. Taylor, C. Boelman, K. J. Worsley, A. C. Evans, and A. Dagher, "Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis: application to 452 patient data sets," *NeuroImage* **19**(3), pp. 532 – 544, 2003.
4. D. Garca-Lorenzo, S. Francis, S. Narayanan, D. L. Arnold, and D. L. Collins, "Review of automatic segmentation methods of multiple sclerosis white matter lesions on conventional magnetic resonance imaging," *Medical Image Analysis* **17**(1), pp. 1 – 18, 2013.
5. M. Bucci, M. L. Mandelli, J. I. Berman, B. Amirbekian, C. Nguyen, M. S. Berger, and R. G. Henry, "Quantifying diffusion MRI tractography of the corticospinal tract in brain tumors with deterministic and probabilistic methods," *NeuroImage: Clinical* **3**(0), pp. 361 – 368, 2013.
6. M. Wilson, C. Tench, P. Morgan, and L. Blumhardt, "Pyramidal tract mapping by diffusion tensor magnetic resonance imaging in multiple sclerosis: improving correlations with disability," *J Neurol Neurosurg Psychiatry* **74**, pp. 203–207, 2003.
7. S. Barbieri, M. H. Bauer, J. Klein, C. Nimsky, and H. K. Hahn, "Segmentation of fiber tracts based on an accuracy analysis on diffusion tensor software phantoms," *NeuroImage* **55**(2), pp. 532 – 544, 2011.
8. S. Mori, K. Oishi, H. Jiang, L. Jiang, X. Li, K. Akhter, K. Hua, A. V. Faria, A. Mahmood, R. Woods, A. W. Toga, G. B. Pike, P. R. Neto, A. Evans, J. Zhang, H. Huang, M. I. Miller, P. van Zijl, and J. Mazziotta, "Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template," *NeuroImage* **40**(2), pp. 570 – 582, 2008.
9. K. Oishi, K. Zilles, K. Amunts, A. Faria, H. Jiang, X. Li, K. Akhter, K. Hua, R. Woods, A. W. Toga, G. B. Pike, P. Rosa, A. Evans, J. Zhang, H. Huang, M. I. Miller, P. C. M. Van, J. Mazziotta, and S. Mori, "Human brain white matter atlas: Identification and assignment of common anatomical structures in superficial white matter," *Neuroimage* **43**, pp. 447–457, 2008.
10. MeVisLab 2.7, "Homepage at: http://www.mevislab.de.," 2015.

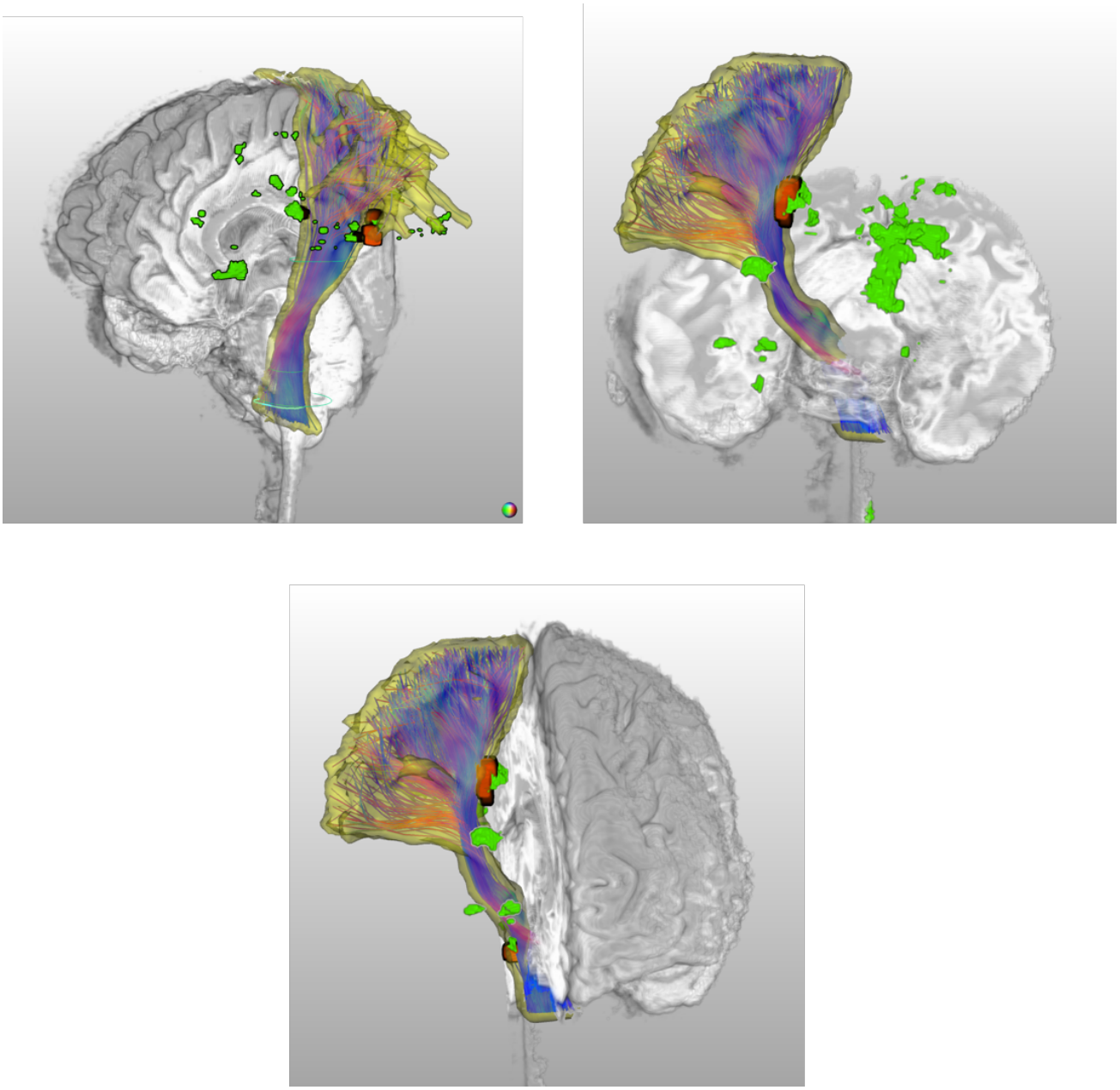

Figure 3. Example data where the right CST has been tracked using our novel approach. As one can see, the full CST including lateral fibers ending in the face area are shown. Segmented lesions are highlighted in green, lesions inside the CST are colored in orange (note that for visualization purposes, lesions inside the CST have been increased in size using a morphological dilation.

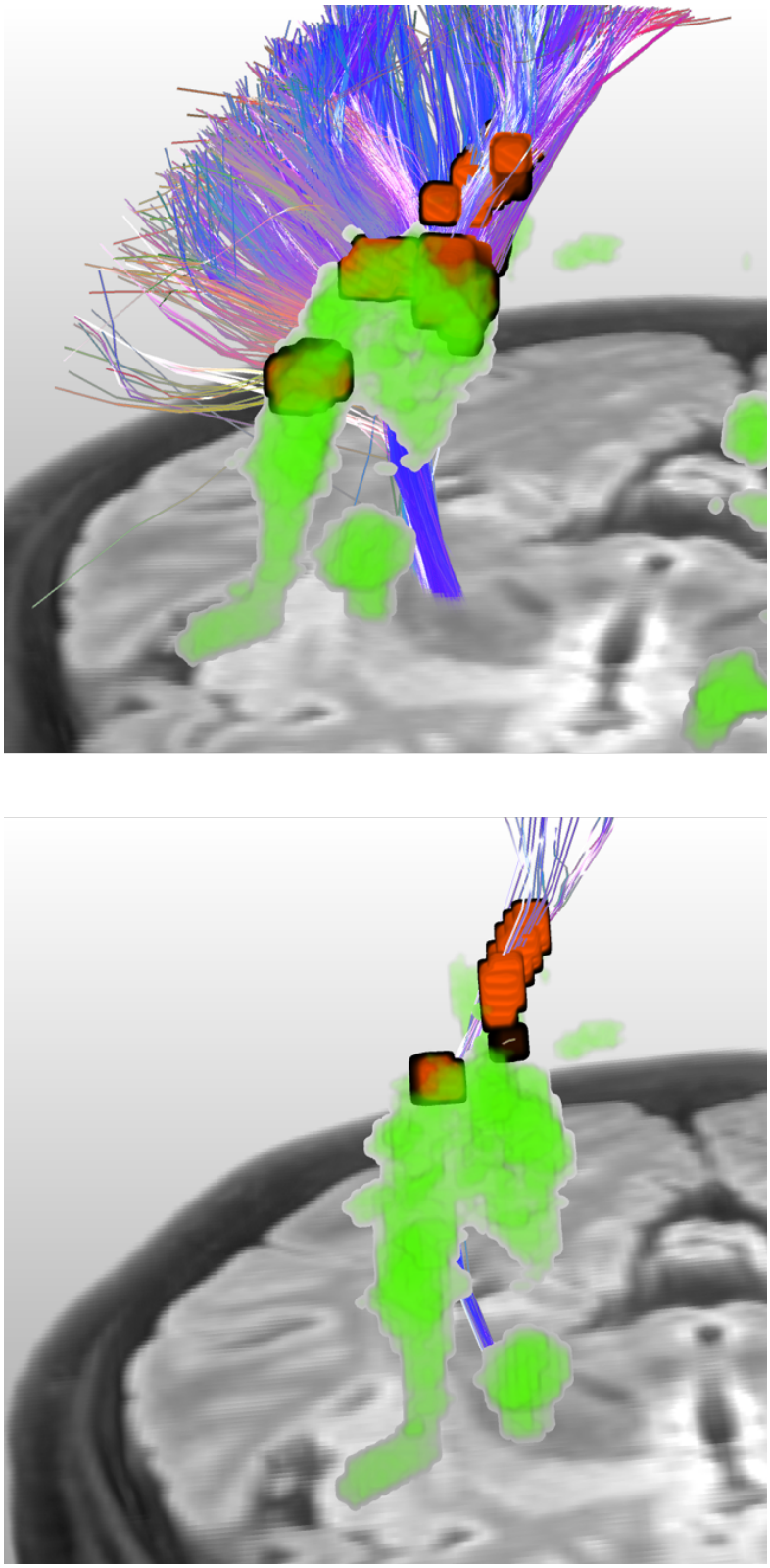

Figure 4. Upper image: CST tracked by our new approach, lower image: the standard deflection fiber tracking is only able to compute small parts of the CST and, as a consequence, the lesions are only partially determined within the CST.