Strategy for Detecting Neuronal Fibers at Risk for Neurodegeneration In Earliest MS by Streamtube Tractography at 3T

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Background: While demyelination is central to the onset of MS, focal inflammatory MS lesions are also characterized by axonal injury, including transections[1]. As a result, the study of axonal injury has become an important new area of MS research, and axonal injury is now considered an important contributor to irreversible injury, disability and possibly conversion to progressive stages of disease. In advanced stages of MS, there is direct evidence for significant neuronal loss for example in corpus callosum [2]. In early MS, there is circumstantial evidence for neuronal tract injury due to focal, inflammatory demyelinating lesions associated with a clinically isolated syndrome (CIS) based on neuronal tract (Wallerian) degeneration patterns in corticospinal tract [3] and across the corpus callosum (transcallosal bands) [4]. The presence of such axonal injury is supported by an informative case study where confocal microscopy revealed empty myelin cylinders in spinal cord of an MS patient with a distant subacute brainstem lesion [5].

Purpose: We report an MRI strategy to detect "at-risk" neuronal fibers in the corpus callosum related to distant focal demyelinating lesions. This strategy is necessary since a priori assumptions about the anatomical location of lesions relative to fiber tracts is often misleading.

Methods: We conducted a prospective longitudinal study including 18 CIS patients with an MRI (at least 2 characteristic T2-lesions) placing them at high risk for the development of MS [6] . MRI acquisition was at 3T and included 3mm thick non-gapped proton density/T2 series and sagittal fast spin echo (FSE) T2-weighted imaging with 3mm non-gapped slices. A diffusion tensor imaging sequence is run in the axial plane with sets of diffusion tensor images acquired by echo-planar technique using a slice thickness of 5.1 mm and each series shifted from the prior series by 1.7 mm inferiorly, in 25 gradient directions with maximal b-value of 1000. Lesions are segmented by in-house semi-automated segmentation routines based on the FSE image data. A mutual information algorithm was used to determine the optimal 12 DOF affine transformation registering T2 axial with B0 diffusion data. This transformation was then applied to the segmented T2 data. A set of streamtubes [7] is generated by seeding from within the lesions. Each streamtube follows the fastest direction of diffusion until it transcends the dataset boundary, hits a region of low linear anisotropy, or curves excessively. The redness on the streamtubes represents linear anisotropy. Cerebrospinal fluid in the ventricles is represented by a blue surface, and lesions are shown as yellow surfaces.

Results: Case CIS 2 is shown as a representative example. This individual presented with unilateral optic neuritis, and had a positive MRI. Structural images suggest lesions potentially related to corpus callosum . The streamtube tractography suggests lesions intersecting numerous fiber pathways, and provides (best viewed in 3D-not shown) the explicit pathways that are potentially affected by lesion. Further culling to fibers that intersect corpus callosum shows a large potential volume of involvement. Unedited initial runs contain assignment errors, for example some fibers running anterior-posterior. These can be removed through further culling using objective template driven criteria or based on expert review of the images in 3D. The sagittal fiber-at-risk map shows that the distribution of the at-risk fibers does not correspond to the limited areas of abnormal appearing white matter conventionally determined by T2-hyperintensity.

Discussion and Conclusion: Our streamtube strategy was devised to allow us to interrogate voxels–at-risk by quantitative MRI techniques. Using our methodology risk is assessed based on connection via fiber tracts to typical focal MS lesions. Our ultimate goal is to test the hypothesis that focal inflammation results in Wallerian degeneration that can be explicitly assayed over time in vivo. Initial attempts to relate focal MS lesions to corresponding regions in callosum have been unsatisfactory to date, as fiber tracts from corpus callosum curve in 3D space, and lesions such as those located lateral to the mid-sagittal corpus callosum previously assumed to lie in transcallosal tracts often do not intersect the fibers of interest. Using the tractography strategy outlined here, we can explicitly determine the locations of voxels in corpus callosum that are most likely to be injured by secondary degeneration, and we can follow these at-risk locations prospectively in longitudinal MRI studies. In addition, the tractography approach provides a unique perspective into early MS pathology allowing us to visualize the full extent of potentially injured fibers from multiple lesions. This strategy is applicable to any neuronal tract that can be imaged with high quality diffusion tensor and structural MRI.

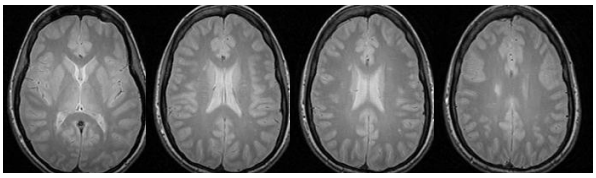

Fig. 1 FSE images through the region of corpus callosum.

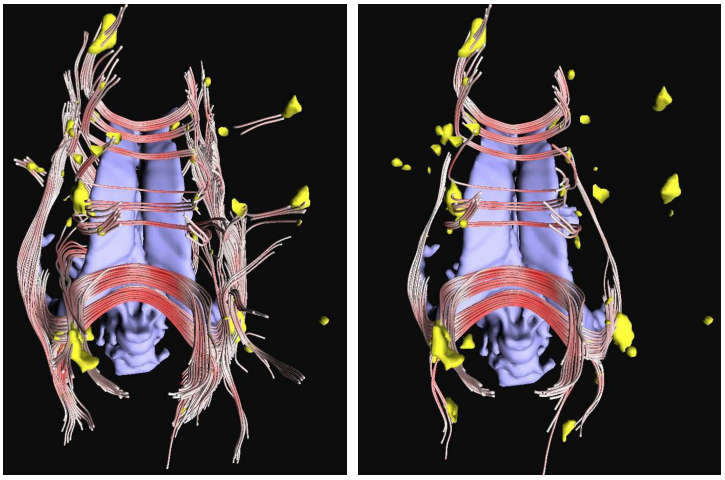

Fig. 2 . Left-Streamtube map culled to fibers intersecting lesions. Right-Streamtube map with additional culling to fibers passing through corpus callosum and intersecting lesion.

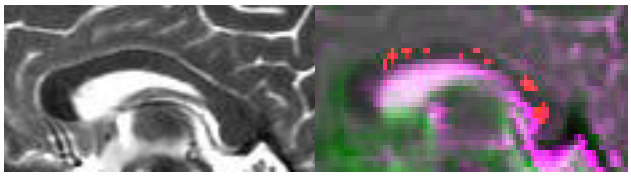

Fig. 3. Left- T2W image showing few focal T2-hyperintensities. Right-Sagittal fiber map showing in red the location of fibers in the midline corpus callosum that "connect to" the focal MS lesions.

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This work is supported in part by a grant from the National Multiple Sclerosis Society RG 3307-A-1(Neuronal Tract Degeneration in Early MS), NSF (CCR-0086065), and GE Medical Systems (3T Diffusion Imaging).