**Bundle-wise detection of white matter degeneration of the visual pathway via diffusion-weighted MRI**

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Diffusion-weighted MRI (dMRI) serves as a valuable non-invasive method for exploring the microstructural properties of brain tissue. However, its reliability diminishes in regions with intricate configurations, such as fiber crossings, challenging histopathological inference in neurodegenerative disorders. Prior work performed in rodents has validated advanced dMRI for analyzing bundle-wise quantitative metrics related to axonal density and their sensitivity to axonal degeneration in regions of crossing fibers (Rojas-Vite 2019). This study aims to assess the potential of advanced dMRI in detecting axonal degeneration in vivo. Patients with asymmetric glaucoma provide an opportunity to assess the validity of dMRI to individually assess fiber bundles in a region of crossing fibers (optic chiasm).

We scanned 25 control subjects and 25 patients with asymmetric glaucoma from the Instituto Mexicano de Oftalmología (IMO) using a 3T General Electric (GE) scanner. T1-weighted images were be obtained with resolution of 0.8x0.8x0.8 $mm^3$ Diffusion MRI were acquired with a multi-shot echo-planar imaging sequence with resolution of 1.7x1.7x1.7 $mm^3$ with 6 volumes with b=0 $s/mm^2$, and 16/32/64 volumes with unique directions for diffusion sensitization with b=500/1000/2000 $s/mm^2$.

Constrained Spherical Deconvolution (CSD) was used to perform tractography to delineate the optic nerves. Apparent fiber density (AFD) was extracted from tractography-aided regions of interest of the optic nerves and chiasm. Additionally, fractional anisotropy (FA) and mean diffusivity (MD), were obtained by fitting a diffusion tensor at each voxel in the optic nerves. The optic chiasm was also evaluated using the multi-resolution discrete search method (MRDS, Coronado-Leija et al., 2017). For voxels in the chiasm with more than one fiber population were analyzed by separating the tensors according to their corresponding optic nerves, reporting their FA and MD metrics separately for each. The average values of these diffusion metrics were compared between groups and between optic nerves and chiasms for patients with asymmetric glaucoma (i.e., most affected vs least affected).

AFD and tensor metrics of control subjects did not show asymmetries. The most affected optic nerves of patients with glaucoma showed a significant reduction of AFD and FA, and increased MD, as compared to their least affected nerves and were, in turn, statistically different from controls. Least affected nerves were also different from controls, albeit to a lesser degree.

The MRDS analysis revealed significant differences in both FA and MD, underscoring the potential of this method for characterizing white matter integrity in the context of axonal degeneration in regions of crossing fibers.

In conclusion, multi-tensor models provide valuable insights in regions of complex white matter configuration, such as the optic chiasm. The significant differences observed in FA and MD highlight the efficacy of this approach in characterizing white matter integrity in the context of axonal degeneration. Further investigations are warranted to explore the capacity of multi-tensor models in assessing other axonal crossings throughout the brain, potentially enhancing our understanding of neurodegenerative disorders.

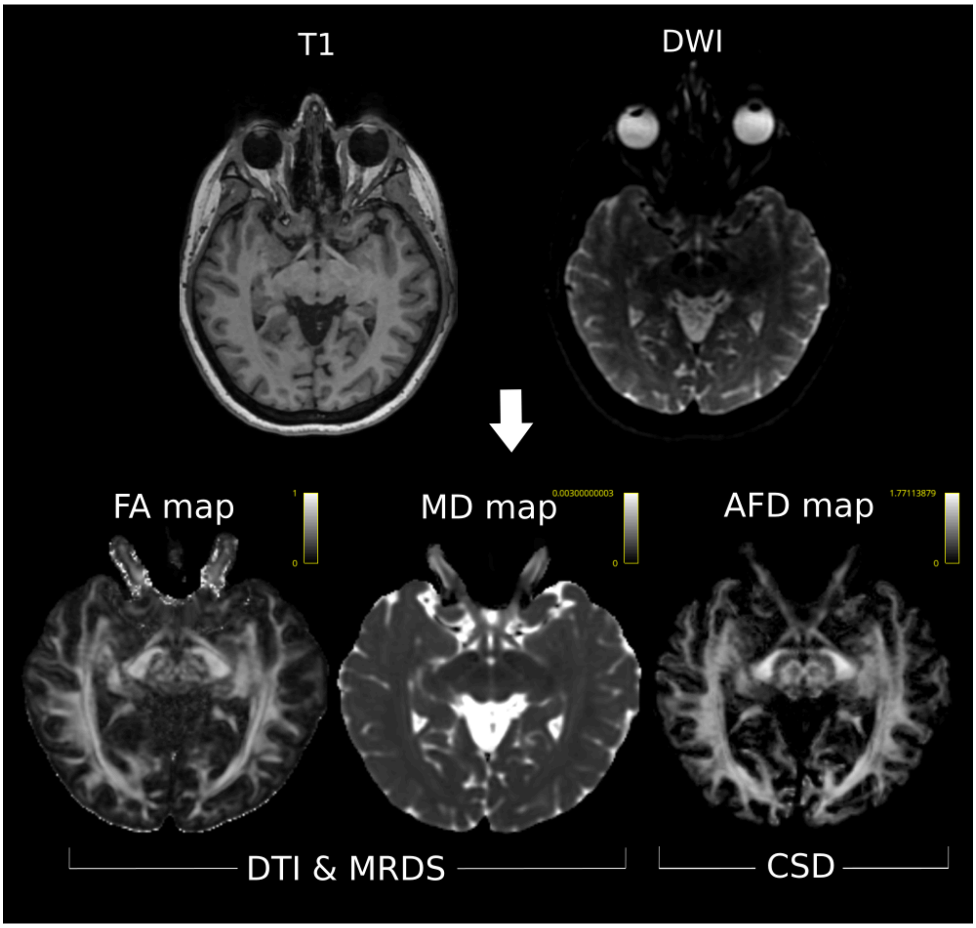


**Figure 1.** Acquisition of T1-weighted structural images and diffusion-weighted imaging (dMRI), from which quantitative maps of Fractional Anisotropy (FA) and Mean Diffusivity (MD) in optic nerves are derived using the Diffusion Tensor Imaging (DTI) model and the Multi-Resolution Discrete Search method (MRDS) in the optic chiasm. The quantitative map of Apparent Fibre Density (AFD) is derived from the use of Constrained Spherical Deconvolution.

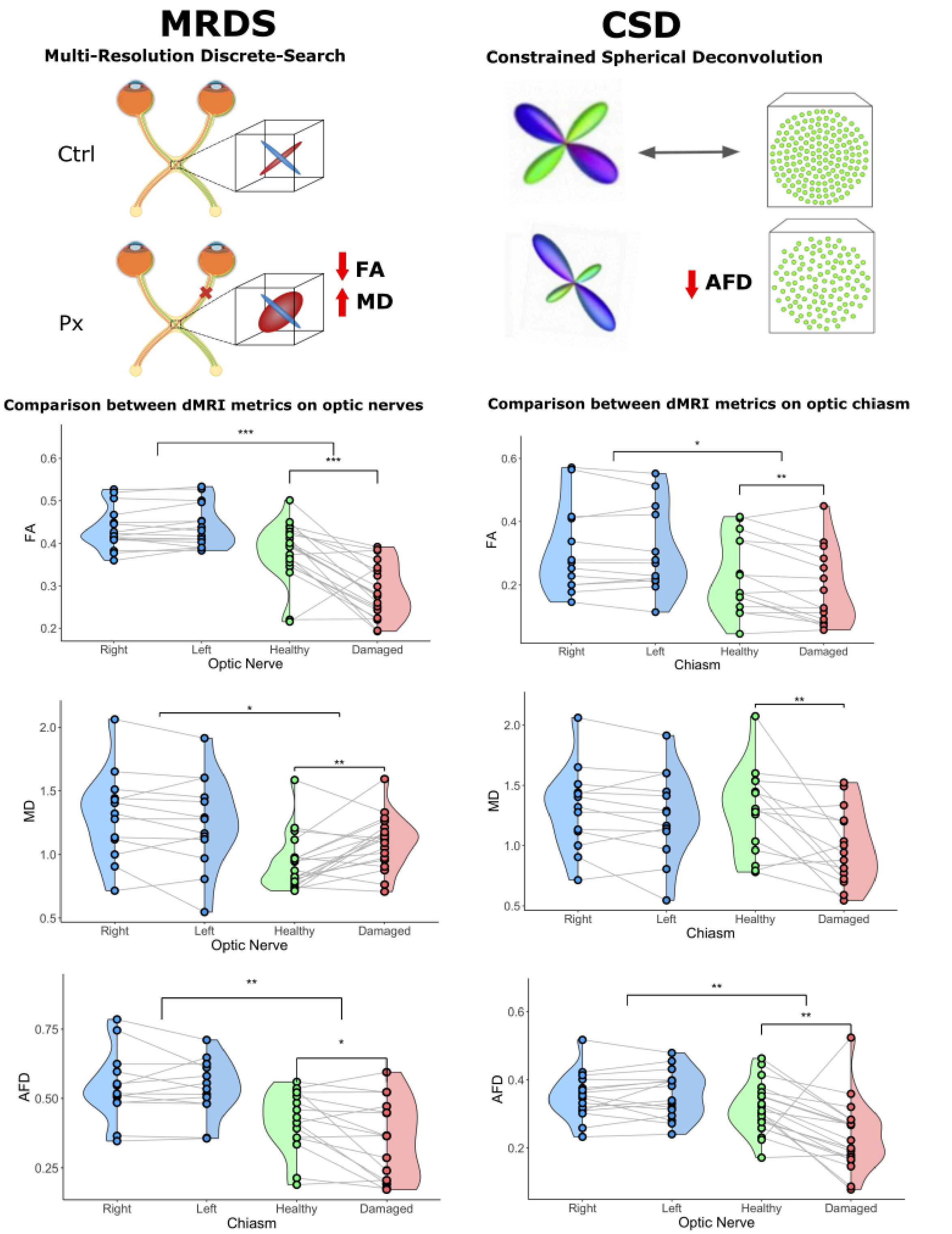


**Figure 2.** Comparison of metrics derived from MRDS and AFD between control subjects and patients. Significant alterations in these metrics are observed when comparing the control group to the patient group, and within the latter, when comparing the nerve affected by asymmetric glaucoma to the intact nerve.