3774

High Resolution *Ex Vivo* Diffusion Tensor Distribution MRI of Neural Tissue

Kulam Najmudeen Magdoom[1,2,3], Michal E. Komlosh[1,2,3], Saleem Kadharbatcha[1,3], Dario Gasbarra[4], and Peter J. Basser[2,3]

[1]The Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF) Inc.,, Bethesda, MD, United States, [2]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Healt, Bethesda, MD, United States, [3]Center for Neuroscience and Regenerative Medicine, Uniformed Services University of Health Sciences, Bethesda, MD, United States, [4]University of Helsinki, Helsinki, Finland

Synopsis

Neural tissue microstructure plays a key role in developmental, physiological, and pathophysiological processes. Diffusion tensor distribution (DTD) MRI is a promising approach to resolve sub-voxel microstructural features using multiple diffusion encodings. In this study, we have applied a novel DTD framework and pulse sequence to investigate its capabilities in revealing neural tissue microstructure. We present high resolution data acquired using an excised visual cortex and cervical spinal cord of a macaque monkey. The results show DTD MRI untangles size, shape and orientation heterogeneity within a voxel and parcellates tissue consistent with histological findings.

Introduction

In the continuing quest to characterize it at ever finer length scales, we use a novel diffusion tensor distribution (DTD) paradigm to probe microstructural features much smaller than the nominal MRI voxel size. The DTD is a normal tensor variate distribution whose samples are constrained to be positive definite (CNTVD) characterized by a mean and covariance tensor. We estimate this DTD using Monte Carlo signal inversion combined with parsimonious model selection framework that exploits a hierarchy of symmetries of mean and covariance tensors. High resolution multiple pulsed field gradient (mPFG) MRI measurements were performed using excised visual cortex and spinal cord from perfusion-fixed macaque monkey brain to investigate the capabilities of DTD MRI in revealing neural tissue microstructural and architectural features using strong gradients not typically available in clinical MRI scanners.

Methods

Assuming Gaussian diffusion in microscopic water pools within a voxel, the signal model is given by[1],

$$S(b_{ij}) = S_0 \left(\overline{e^{-b_{ij}D_{ij}}} + \varepsilon \right)$$

where the overbar denotes averaging over the DTD, b_{ij}, D_{ij} are the b-tensor and diffusion tensor respectively, and ε is the offset parameter used to model the so called dot-compartment thought exist at large b-values[2]. The above signal model, estimated using Monte Carlo method by drawing samples from CNTVD, is fitted to DWIs acquired with rank-1 and rank-2 b-tensors to estimate the mean and covariance tensor of CNTVD[3].

From the microscopic diffusion tensors sampled from the estimated CNVTD, microscopic fractional anisotropy (μFA) and micro-orientation distribution function (μODF) is calculated based on the non-commutativity of the FA and ODF operator as shown below,

$$\mu FA = \overline{FA(D_{ij})} \neq FA(\overline{D_{ij}}), \mu ODF = \overline{ODF(D_{ij})} \neq ODF(\overline{D_{ij}})$$

We also quantify the size (V_{size}) and shape (V_{shape}) heterogeneity of micro-diffusion tensors within a voxel as the normalized median absolute deviation of their average trace and FA-weighted skewness of the eigenvalues, respectively. The orientation heterogeneity (V_{orient}) is quantified as the extent of dispersion of the eigenvectors of the micro-diffusion tensors around the mean eigenvector[3]. These metrics are normalized between 0 and 1 and increase with the increasing amount of heterogeneity within the voxel. In addition, the distribution of apparent diffusion coefficient (ADC) is obtained from the histogram of average trace of micro-diffusion tensors whose moments are measured and mapped.

The diffusion measurements encoded with rank-1 and rank-2 b-tensors were acquired using a novel double PFG pulse sequence in a single spin echo with the two independent trapezoidal gradients sandwiched between the 180º RF pulse to reduce echo time. MRI data was acquired on a 7T system (Bruker Biospin) capable of up to 1,500 mT/m gradient strength and 8,700 T/m/s slew rate. The visual cortex specimen was imaged at 100 μm × 100 μm × 250 μm spatial resolution using 6-shot 3D EPI with the following parameters: Δ/δ = 10/3.5 ms, TR/TE = 1200/25 ms and 4 averages. The spinal cord was imaged at 125 μm × 125 μm × 1 mm spatial resolution using 2-shot 3D EPI with the following parameters: Δ/δ = 20/5 ms, TR/TE = 1000/60 ms and 4 averages. A total of 217 different b-tensors were sampled with b-values ranging from 0 - 6,000 s/mm² for the visual cortex and 0 - 12,000 s/mm² for the spinal cord. The DWIs were denoised[4], and registered using the FSL software[5] before fitting the model.

Results and Discussion

DTD derived stains obtained from a section of the visual cortex along with its overall location in the macaque brain is shown in Figure 1. The white matter tract adjacent to the cortex, on either side of the inferior occipital sulcus (ios), despite having similar FA values were distinguished in the ADC skewness map. Microscopic anisotropy was detected in the cortex shown by elevated µFA (~ 0.6) which may be due to high shape and orientation heterogeneity resulting from heterogeneously shaped neuronal soma and penetrating white matter tracts. The µODF shown in Figure 2 provides evidence of crossing and splaying of white matter fibers as they penetrate the cortex.

DTD derived stains obtained in cervical spinal cord are shown in Figure 3. In the gray matter, the intermediate zone (iz) exhibited high size heterogeneity while shape and orientation heterogeneity were zero thus indicating a spherical emulsion type DTD in this region. Microscopic anisotropy was detected in gray and peripheral white matter as shown by elevated µFA in this region with concomitant increase in shape and orientation heterogeneity. The µODFs shown in Figure 4 show the fibers start splaying as they penetrate the gray matter with increased presence of orthogonal lateral fibers.

Conclusion

In this study, we present DTD measured in neural tissue demonstrating that our experimental design and signal inversion framework in capturing the heterogeneity. New heterogeneity stains may one day be useful in assessing disease, normal and abnormal developmental processes, degeneration and trauma in the brain and other soft tissues.

Acknowledgements

References

1. Jian, B., Vemuri, B. C., Ozarslan, E., Carney, P. R. & Mareci, T. H. A novel tensor distribution model for the diffusion-weighted MR signal. Neuroimage 37, 164–76 (2007).

2. Bretthorst, G. L. Characterizing Water Diffusion In Fixed Baboon Brain. in AIP Conference Proceedings vol. 735 3–15 (AIP, 2004).

3. Magdoom, K. N., Pajevic, S., Dario, G. & Basser, P. J. A new framework for MR diffusion tensor distribution. Sci. Rep. 11, 2766 (2021).

4. Veraart, J. et al. Denoising of diffusion MRI using random matrix theory. Neuroimage 142, 394–406 (2016).

5. Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W. & Smith, S. M. FSL. Neuroimage 62, 782–790 (2012).

6. Saleem, K. S. & Logothetis, N. K. A combined MRI and histology atlas of the rhesus monkey brain in stereotaxic coordinates. (Elsevier/Academic Press, 2012).

Figures
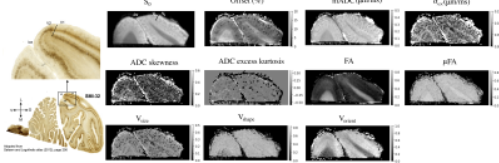
DTD derived stains obtained in an excised visual cortex of a macaque monkey showing microscopic anisotropy and heterogeneity. Approximate location in the macaque brain from which 10 mm x 5 mm x 5 mm piece was dissected for MR imaging shown using SMI-32 stained sections (highlights pyramidal neurons and their processes) in Saleem and Logothetis macaque brain atlas [6] in the left most column. The V1 and V2 areas of the visual cortex and inferior occipital sulcus (ios) are highlighted for reference.
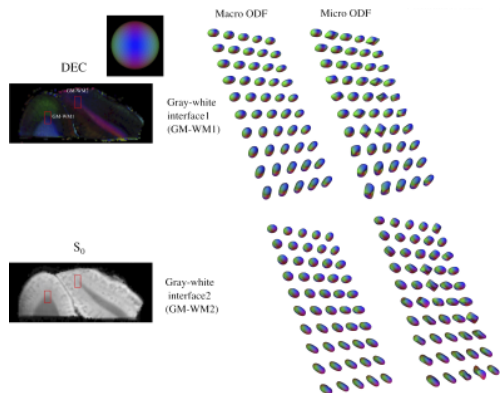
Orientation dispersion observed in macaque visual cortex shown by comparing the macro and micro ODFs. Two regions of interest (ROIs) at gray-white matter interface regions are highlighted in the direction-encoded color (DEC) map, showing the principal direction of the mean diffusion tensor, and S_0 map.
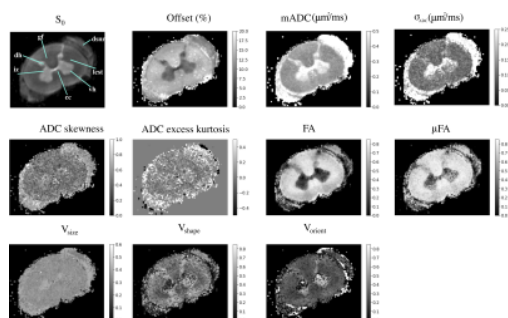
DTD derived stains obtained in a excised cervical spinal cord of macaque monkey showing microscopic anisotropy and heterogeneity.The following regions of interest in the spinal cord are highlighted in the non-diffusion weighted image (S_0): iz – intermediate zone, dh - dorsal horn, gf - gracile fasciculus, dsnr - dorsal spinal nerve root, lcst - lateral corticospinal tract, vh - ventral horn and cc - central canal.
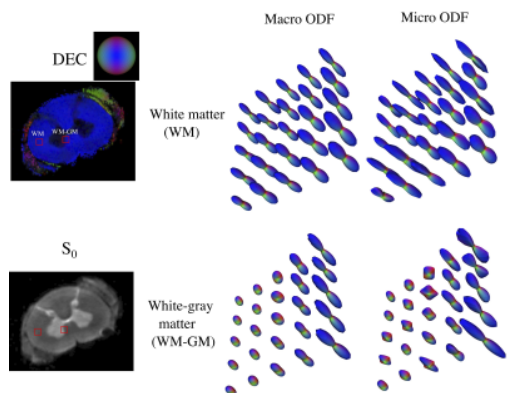
Orientation dispersion observed in macaque cervical spinal cord shown by comparing the macro and micro ODFs. Two regions of interest (ROIs) one in white matter (WM) and gray-white matter (GM-WM) interface regions are highlighted in the direction encoded color (DEC) map, showing the principal direction of the mean diffusion tensor, and S_0 map.