Ultrahigh-resolution, whole-brain MAP-MRI ***in vivo*** using the NexGen 7T scanner

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Synopsis

Keywords: Microstructure, Diffusion Acquisition, diffusion propagator, cortical layers, in vivo diffusion acquisition, mean apparent propagator MRI, diffusion anisotropy

Motivation: To assess the potential of high-resolution diffusion propagator imaging in human subjects

Goal(s): To measure diffusion propagators with submillimeter spatial resolution and whole-brain coverage in healthy volunteers by leveraging the capabilities of the NexGen 7T MRI scanner

Approach: We designed an efficient protocol to acquire *in vivo* data with strong diffusion sensitization and high tissue sensitivity. We estimated the 3D net displacements of water molecules diffusing in tissue using mean apparent propagator (MAP) MRI.

Results: MAP-derived microstructural parameters revealed cortical laminar patterns in multiple brain regions. Variations in cortical diffusion anisotropy revealed laminar pattern discontinuities that may correlate with boundaries between cortical areas.

Impact: Ultrahigh resolution MAP-MRI could improve the neuroradiological assessment of cortical and subcortical gray matter and the early detection of neurodegenerative diseases. It could enable direct segmentation of cortical cytoarchitectonic domains and advance our ability to map connections between cortical layers.

Introduction

Diffusion MRI (dMRI) is uniquely suited to image tissue microstructure in both isotropic and anisotropic tissues. dMRI has excellent tissue contrast which can reveal cortical cytoarchitectonic features such as layers and areal boundaries at sufficiently high spatial resolutions[1]. Nevertheless, acquiring diffusion-weighted images (DWIs) in human subjects with whole-brain coverage, submillimeter resolution, and strong diffusion sensitization (i.e., large b- values) poses significant challenges, requiring a very high signal-to-noise ratio (SNR) and scan efficiency.

While some studies have acquired *in vivo* dMRI data at submillimeter resolution[2-4], these often suffer from limitations such as relatively low b-values, i.e., limited only to the diffusion tensor imaging (DTI)[5] regime; a limited number of gradient encodings, i.e., insufficient for high angular resolution diffusion imaging (HARDI)[6]; and long scan durations that are impractical for clinical use[2,3].

In this study, we utilize the advanced Impulse gradient system (Gmax=200mT/m, SR=900T/m/s) and ultra-high field strength of the NexGen 7T MRI scanner[7] to investigate the feasibility of directly measuring the probability density function of the 3D net displacements of water molecules (i.e., diffusion propagators) within submillimeter voxels across the entire brain. Our approach aims to evaluate the anatomical sensitivity and radiological potential of mean apparent propagator (MAP) MRI[8], which could provide unprecedented detail in mapping brain microstructure[1,9].

Methods

We scanned three healthy volunteers on the NexGen 7T scanner[7] using a 64-channel RF coil. We acquired dMRI data with 0.9mm isotropic resolution using single-shot spin-echo EPI (GRAPPAx3, MBx2, 0.75 partial Fourier, TE/TR=48.4ms/5500ms, BW/px=2175Hz, 207x207x137mm FOV). We acquired 279 DWIs with 10 b-shells (b_{max}=3,000s/mm^2) and multiple orientations per shell, including 48 DWIs with reversed blip encoding. The diffusion gradient pulse duration and separation of 7ms and 27ms, respectively. The total scan duration was 26 minutes. We also acquired a structural 0.75mm T_2-weighted turbo spin echo scan.

We processed[10] the DWIs using denoising[11], and corrections for Gibbs ringing artifacts[12], eddy current, EPI distortions, and subject motion, using the T2-weighted scan as a structural target for co-registration. We estimated the diffusion propagators by fitting the signals to a MAP-MRI series expansion truncated at order 4. We computed DTI and MAP-MRI microstructural parameters (including FA, RD, AD, PA, NG, RTAP, RTOP, RTPP) and estimated fiber orientation distribution functions (FODs)[13]. We segmented the brain tissues[14] directly from the MAP-MRI parameters and performed anatomically constrained tractography[15].

Results

DWIs acquired with b=3,000s/mm^2 had sufficient SNR for spatially accurate distortion correction and co-registration. *In vivo* MAP-MRI parameters showed excellent brain tissue contrast and revealed fine anatomical details in cortical and subcortical regions.

The RTAP contrast between gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), was comparable to that of a conventional MP-RAGE scan, allowing automatic brain tissue segmentation with FSL[14] (Fig. 1). The fine features of the internal capsule and the corona radiata can be best appreciated on the RTAP, FA, and especially in the PA-modulated DEC images (Fig. 2), while the boundaries of the deep brain structures such as the putamen, caudate, and thalamus are seen on RTPP, NG, and PA.

In vivo MAP parameters revealed cortical laminar patterns (Fig. 3) including deep layers 5-6 (FA - dark band, RTPP – bright band especially in primary sensory areas), mid-cortical layers 3-4 (FA, DEC – bright band), and superficial layers (bright NG and PA). Relatively high PA and NG values in the superficial layers were likely artifacts due to partial volume effects at the GM/CSF boundary, highlighting the need for precise co-registration of ultra- high-resolution, high-b DWIs.

Quantifying diffusion anisotropy using FODs at 0.9mm resolution provides detailed insights into cortical cytoarchitectonic features (Fig. 4). We observed a mix of neurites with radial and tangential orientations relative to the cortical surface in deep layers near the WM and a preponderance of radially oriented neurites in the mid-cortical layers. Whole-brain tractography performed with anatomical constraints derived from the MAP-based tissue segmentation (Fig. 1) clearly revealed crossing WM pathways (Fig. 4).

Discussion and Conclusion

This study bridges the scales from macroscopic to mesoscopic imaging. The excellent microstructural contrast in MAP parameters enables direct tissue segmentation and good discrimination of deep subcortical and fine cortical structures. Meanwhile, the use of high spatial and angular resolutions provides a comprehensive tissue characterization and can improve the accuracy of whole-brain tractography. These findings demonstrate the clinical feasibility of MAP-MRI[9] at fine scales, supporting the potential for detailed cortical mapping and quantitative connectivity analysis. The use of high- performance technology (NexGen 7T) to raise SNR, shorten TE, and achieve higher b-values in MAP-MRI acquisitions offers unprecedented sensitivity in studying live human cortical microstructure, promising new insights into brain structure and function.

Acknowledgements

This work was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the NIH BRAIN Initiative 5U24NS129949-02, 1U01EB026996-01.

References

1. Avram, A. V. et al. High-resolution cortical MAP-MRI reveals areal borders and laminar substructures observed with histological staining. NeuroImage 264, 119653 (2022). https://doi.org/10.1016/j.neuroimage.2022.119653

2. Heidemann, R. M., Anwander, A., Feiweier, T., Knösche, T. R. & Turner, R. k-space and q-space: Combining ultra-high spatial and angular resolution in diffusion imaging using ZOOPPA at 7T. NeuroImage 60, 967-978 (2012). https://doi.org/10.1016/j.neuroimage.2011.12.081

3. Wang, F. et al. In vivo human whole-brain Connectom diffusion MRI dataset at 760 µm isotropic resolution. Scientific Data 8, 122 (2021). https://doi.org/10.1038/s41597-021-00904-z

4. Setsompop, K. et al. Pushing the limits of in vivo diffusion MRI for the Human Connectome Project. NeuroImage 80, 220-233 (2013). https://doi.org/10.1016/j.neuroimage.2013.05.078

5. Basser, P. J., Mattiello, J. & LeBihan, D. MR diffusion tensor spectroscopy and imaging. Biophysical Journal 66, 259-267 (1994). https://doi.org/10.1016/S0006-3495(94)80775-1

6. Tuch, D. S. et al. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. Magnetic Resonance in Medicine 48, 577-582 (2002). https://doi.org/10.1002/mrm.10268

7. Feinberg, D. A. et al. Next-generation MRI scanner designed for ultra-high-resolution human brain imaging at 7 Tesla. Nature methods 20, 2048-2057 (2023).

8. Özarslan, E. et al. Mean apparent propagator (MAP) MRI: A novel diffusion imaging method for mapping tissue microstructure. NeuroImage 78, 16-32 (2013). https://doi.org/10.1016/j.neuroimage.2013.04.016

9. Avram, A. V. et al. Clinical feasibility of using mean apparent propagator (MAP) MRI to characterize brain tissue microstructure. NeuroImage 127, 422- 434 (2016). https://doi.org/10.1016/j.neuroimage.2015.11.027

10. Irfanoglu, M. O., Nayak, A., Jenkins, J. & Pierpaoli, C. in Program and proceedings of the ISMRM 25th annual meeting and exhibition, Honolulu, HI, USA.

11. Veraart, J. et al. Denoising of diffusion MRI using random matrix theory. NeuroImage 142, 394-406 (2016). https://doi.org/10.1016/j.neuroimage.2016.08.016

12. Kellner, E., Dhital, B., Kiselev, V. G. & Reisert, M. Gibbs-ringing artifact removal based on local subvoxel-shifts. Magnetic resonance in medicine 76, 1574-1581 (2016). https://doi.org/10.1002/mrm.26054

13. Tournier, J. D., Calamante, F., Gadian, D. G. & Connelly, A. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. NeuroImage 23, 1176-1185 (2004). https://doi.org/10.1016/j.neuroimage.2004.07.037

14. Zhang, Y., Brady, M. & Smith, S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE transactions on medical imaging 20, 45-57 (2001).

15. Smith, R. E., Tournier, J.-D., Calamante, F. & Connelly, A. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. Neuroimage 62, 1924-1938 (2012).

Figures

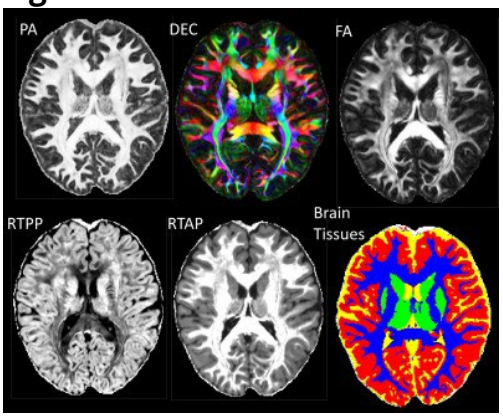

Figure 1: Microstructural parameters derived using MAP-MRI provide a comprehensive tissue microstructural characterization, revealing excellent contrast and good visualization of fine anatomical structures, and enabling direct segmentation of brain tissues. (PA - propagator anisotropy, FA - fractional anisotropy, RTPP - return-to-plane probability, RTAP - return-to-axis probability, DEC - FA-modulated direction encoded color)

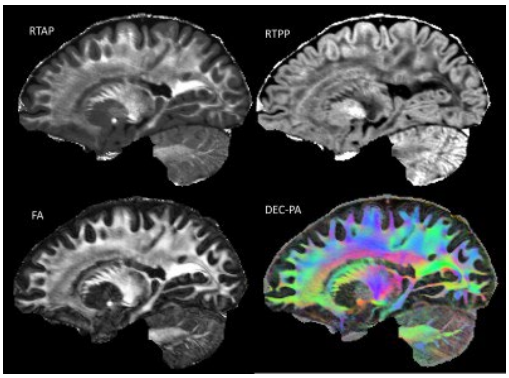

Figure 2: Sagittal images of MAP-derived parameters provide a good visualization of the internal capsule and the corona radiata. (FA - fractional anisotropy, RTPP - return-to-plane probability, RTAP - return-to-axis probability, DEC-PA - PA-modulated direction encoded color)

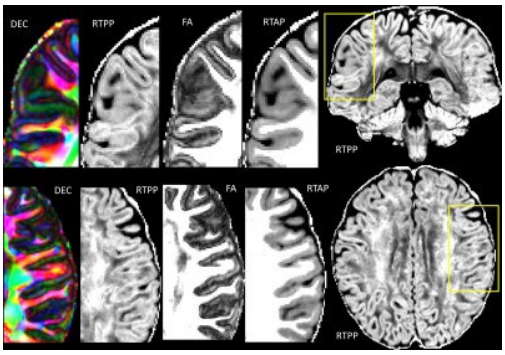

Figure 3: Characterization of cortical laminar patterns using several MAP-derived microstructural parameters in coronal (top) and axial (bottom) slices. (FA - fractional anisotropy, RTPP - return-to-plane probability, RTAP - return-to-axis probability, DEC - FA-modulated direction encoded color)

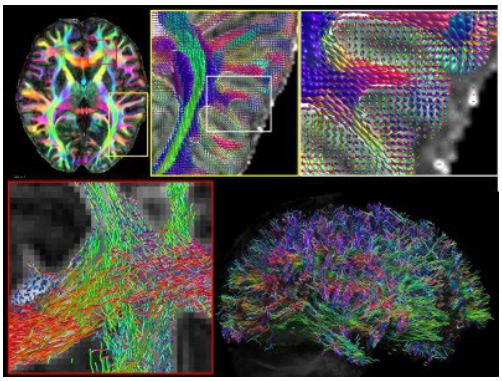

Figure 4: Fiber orientation distribution functions (FODs) in the live human brain (top row images) and anatomically constrained whole-brain fiber tractography (bottom images) derived from an *in vivo* MAP-MRI scan with 0.9mm spatial resolution acquired in 26 minutes.