Restriction Spectrum Imaging (RSI): A new method for resolving complex tissue microstructures in diffusion MRI

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INTRODUCTION

Diffusion tensor imaging (DTI)[1] is a powerful non-invasive technique for studying brain tissue microstructure *in vivo*. However, a well-known limitation of DTI is the inability to characterize diffusion in complex tissue microstructures. Recently, model-based deconvolution techniques have become increasingly popular for resolving multiple fiber orientations in heterogeneous fiber populations[2]. However, these methods rely on the assumption that the tissue is composed of fibers with identical water restriction properties (i.e. morphology and size scale). Here, we propose a new model-based analysis approach for multiple b-value acquisitions called Restriction Spectrum Imaging (RSI). RSI relaxes the assumption above and models the tissue using a spectrum of both oriented and non-oriented tissue components with different water restriction scales.

METHODS

Data Acquisition: An excised adult male Sprague-Dawley rat brain was immersed for 4 weeks in a 4°C 1mM GdDTPA solution and positioned in a sealed plastic tube filled with Fomblin liquid. Scanning was performed using a 4.7T Bruker scanner equipped with a 3 cm solenoid receiver coil. Pulse-sequence parameters: TR/TE = 650/49 msec, Δ/δ = 23/12 msec, 515 q-space directions, $|G|_{max}$ = 380 mTm^{-1}, matrix = 64x64x128, 265 µm isotropic voxels, b-max ~32,000 mm^2/sec. However, for this study only 123 q-space directions were used with a max b-value of 10,000. Myelin stained histological sections were obtained and registered to the MRI data as described previously[3].

RSI Signal Model: For simplicity, we use an axisymmetric tensor model to characterize restricted water, but the method can easily be extended with a non-Gaussian form for the restricted water[4] without loss of generality. Using the axisymmetric tensor model, the RSI signal model can be written:

$$\frac{S(\mathbf{q}_i)}{S_0} = \int_{\lambda_\perp}\int_{\mathbf{x}} R(\mathbf{q}_i, \lambda_\perp, \mathbf{x}) f(\mathbf{x}) d\mathbf{x} d\lambda_\perp + \exp(-b_i\lambda_0) + n_i \, ,$$

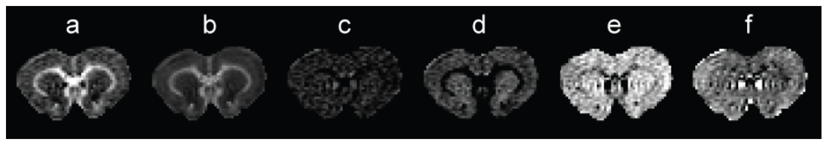

Fig. 1 *RSI restriction maps showing the volume fraction of spins at different restriction scales (from left to right in sec/mm^2). (a) $\lambda_\perp = 1\times10^{-5}$, (b) $\lambda_\perp = 2.4\times10^{-5}$, (c) $\lambda_\perp = 5.8\times10^{-5}$, (d) $\lambda_\perp = 1.4\times10^{-4}$, (e) $\lambda_\perp = \lambda_\parallel$ (tissue isotropic), and (f) $\lambda_0 = 2\lambda_\parallel$ (free water). Images (a-d) have oriented structure, while (e,f) are isotropic.*

where $S(\mathbf{q}_i)$ is the signal measured during the *i*-th diffusion wavevector $\mathbf{q}_i$, S_0 is the signal measured with no diffusion weighting, $R(\mathbf{q}_i, \lambda_\perp, \mathbf{x}_j) = \exp(-b_i\lambda_\perp)\cdot\exp(-b_i((\lambda_\parallel - \lambda_\perp)(\mathbf{r}_i\cdot\mathbf{x}_j)^2)$ is the signal response with perpendicular and parallel diffusivities $\lambda_\perp$ and $\lambda_\parallel$, respectively, $b_i = \tau|\mathbf{q}_i|^2$ is the b-value, τ is the mixing time, $\mathbf{r}_i = \mathbf{q}_i\cdot|\mathbf{q}_i|^{-1}$ is the measurement direction, $f(\mathbf{x})$ is the (fiber) orientation along $\mathbf{x}$, λ_0 is the "free" water diffusivity, and n is measurement noise. Note, that while the parallel diffusivity is fixed across all tissue components, the perpendicular (i.e. restricted) diffusivity is allowed to vary.

Linear Estimation: To fit the model above, we discretize the signal equation using P restriction scales $\lambda_\perp = \{\lambda_1, \lambda_2, ..., \lambda_P\}$ and use a spherical harmonic (SH) parameterization for the fiber orientation function $f(\mathbf{x}) = \sum_{k=1}^{K}\beta_k Y_k(\mathbf{x})$. This leads to a simple linear model of the normalized signal $\mathbf{S} = [\mathbf{R}(\lambda_1) \quad \mathbf{R}(\lambda_2) \quad \cdots \quad \mathbf{R}(\lambda_P) \quad e^{-\mathbf{b}\lambda_0}]\boldsymbol{\beta} + \mathbf{n}$, where the *ik*-th element of the matrix $\mathbf{R}(\lambda_j)$ is $\mathbf{R}_{ik}(\lambda_j) = \int R(\mathbf{q}_i, \lambda_j, \mathbf{x})Y_k(\mathbf{x})d\mathbf{x}$ and the parameter vector $\boldsymbol{\beta}$ has $(K\times P)+1$ elements. Here, we use a maximum SH order of 4 (thus $K = 15$), set $\lambda_\parallel = 3.4\times10^{-4}$ sec/mm^2 (which was estimated from the data), $\lambda_0 = 2\lambda_\parallel$, and use 5 restriction scales for $\lambda_\perp$ (P = 5). Maximum a posteriori estimates of the parameters $\boldsymbol{\beta}$ were obtained using Tikhonov regularization.

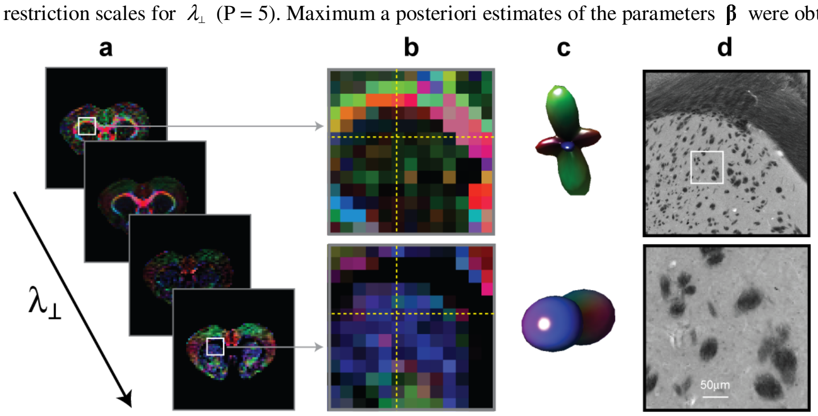

Fig. 2 *RSI direction maps for the oriented diffusion components. (a) RGB colormaps indicating the primary fiber direction (FOD maximum) at each restriction scale. (b) close-up sections of the striatum for the highest (top) and lowest (bottom) restriction levels. (c) 3D fiber-orientation distributions (FODs) for the voxel highlighted in (b) with the FOD corresponding to the highest restriction scale on top and the lowest restriction scale on bottom. (d) histological section images showing the corresponding myeloarchitecture in this region.*

RESULTS

RSI "restriction maps" showing the volume fraction of spins experiencing various restriction scales are shown in **Fig. 1** for a coronal slice through the genu of the corpus callosum. Maps were obtained using the 0-th order SH estimates, normalized to sum to 1. The first 4 images (a-d) correspond to oriented diffusion, while the last 2 images (e,f) correspond to isotropic diffusion. Note, highly restricted spins are predominantly located in white matter (a,b), while less restricted spins are mainly seen in gray matter (d). Also, note the separation between the tissue isotropic (e) and free water spins (f). Fiber orientation distributions (FODs) at each restriction scale can also be estimated with RSI using the higher order SH. An example of this is shown in **Fig. 2** using the same restriction scales as in **Fig.1** (a-d). FOD reconstructions are shown for a single voxel in the striatum (c) along with corresponding myelin stain images showing the striated myeloarchitecture in this region (d). Note that the fiber orientation is dependent on the restriction scale with mainly mediolateral and anterioposterior directionality for the highest restriction scale (top row) and rostro-caudal (through-plane) orientation for the lowest restriction scale (bottom row). This may potentially reflect separated spin diffusion in and around striatal gray and white matter compartments.

DISSUSION

Restriction spectrum imaging (RSI), presented here, is a new model-based analysis strategy for multiple b-value acquisitions designed to differentiate tissue components with dissimilar morphologies and size scales on the basis of their water restriction characteristics. Both volume fraction and orientation information can be extracted for each restriction scale using simple linear estimation methods. As such, RSI provides a new computationally efficient framework for studying complex neuroarchitectures in the brain and may allow for improved *in vivo* characterization of neuromorphology in healthy and pathological tissue.

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