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Directional sensitivity of anomalous diffusion in human brain assessed by tensorial fractional motion model

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ABSTRACT

Anisotropic diffusion in the nervous system is most commonly modeled by apparent diffusion tensor, which is based on regular diffusion theory. However, the departure of diffusion-induced signal attenuation from a mono-exponential form implies that there is anomalous diffusion. Recently, a novel diffusion NMR theory based on the fractional motion (FM) model, which is an anomalous diffusion model, has been proposed. While the FM model has been applied to both healthy subjects and tumor patients, its anisotropy in the nervous system remains elusive. In this study, this issue was addressed by measuring the FM-related parameters in 12 non-collinear directions. A metric to quantify the directional deviation was derived. Furthermore, the FM-related parameters were modeled as tensors and analyzed in analogy with the conventional diffusion tensor imaging (DTI). Experimental results, which were obtained for 15 healthy subjects at 3T, exhibited pronounced anisotropy of the FM-related parameters, although the effects were smaller than the apparent diffusion coefficient (ADC). The tensorial nature for α, which is the Noah exponent in the FM model, showed behavior similar to the ADC, especially the principal eigenvector for α aligned with the dominant white matter fiber directions. The Hurst exponent H in the FM model, however, showed no correlation with the major fiber directions. The anisotropy of the FM model may provide complementary information to DTI and may have potential for tractography and detecting brain abnormalities.

1. Introduction

Diffusion MRI (dMRI) is a powerful and non-invasive tool for the detection of diffusion processes of water molecules in vivo. It has been observed via dMRI that the diffusion process in the nervous system is directionally dependent [1,2]. This directional dependence (i.e., anisotropy) mainly occurs due to the dense packing of axons and the inherent axonal membranes that hinder water diffusion perpendicular to the long axis of the fibers relative to the preferential parallel direction [3]. Measurements of the anisotropy of water diffusion at the micron level within a tissue provide an indirect measure of the underlying microstructure [4].

Conventional dMRI regards diffusion in biological tissues as a regular diffusion process and thus relates the signal attenuation to the apparent diffusion coefficient (ADC) in the mono-exponential form, $S/S_0 = \exp(-b \cdot \mathrm{ADC})$. The b-value characterizes the applied magnetic field gradient sequence. To describe the orientation dependence of regular diffusion, a three-dimensional Gaussian ellipsoid model of molecular displacements is often used, which contains a symmetric effective or apparent diffusion tensor (ADT) of water, D, in place of a scalar ADC [5]. Based on this concept, diffusion tensor imaging (DTI) was developed [6,7]. Metrics such as the mean diffusivity (MD) and the degree of anisotropy (fractional anisotropy, FA), which are derived from DTI, provide information about underlying microstructures.

As mentioned above, DTI is based on the regular diffusion model. However, numerous experiments have shown that in biological tissues, the observed dMRI signal decay curve deviates from the mono-exponential form, especially over an extended b factor range [8]. Additionally, the observed diffusion-time dependence of the MR signal reflects the non-Gaussian nature of diffusion [9]. To address this issue, several mathematical models have been developed to provide an optimal agreement between the experimental data and the proposed fitting curves, including the bi-exponential model [10,11], the stretched

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exponential model [12], the statistical model [13] and the kurtosis model [14]. In addition, several physics-motivated dMRI models have been proposed based on different theories of various anomalous diffusion processes [15–20]. These models have been extended to describe the anisotropy in anomalous diffusion [21–26]. Another limitation of DTI is that the tensor model is too simple, meaning that many features of the microstructure can affect its indices. Therefore, more descriptive models of tissues have been proposed [27–33], and the diffusion-time dependence has also been used [9,15,34,35] to probe the microstructure.

Recently, a novel dMRI theory, which is based on the fractional motion (FM) model, was proposed. The FM model is regarded in the biophysics community to be an appropriate model for describing the complex diffusion process in biological systems [36–40], and it is a promising candidate to describe the diffusion process in brain tissue. The FM model assumes that the diffusion process is α-stable, H-self-similar and has stationary increments [41]. The symbol α denotes the Noah exponent that quantifies the fluctuations of the random process. The increments have a Gaussian distribution when $\alpha=2$, whereas they have a Levy distribution when $0<\alpha<2$. H is the Hurst exponent that describes the self-similarity property of molecular trajectories. The increments of the process are negatively correlated and exhibit short-range dependence (short memory, anti-persistence) when the memory parameter $\mu=H-1/\alpha<0$. In this case, the diffusion process follows a subdiffusive pattern [38].

The FM-based dMRI theory has been applied to both healthy volunteers and brain tumor patients [20,42,43]. Results have shown that the FM-related parameters showed remarkable contrast between gray matter, white matter and cerebrospinal fluid [20], and they improved differentiation between low- and high-grade brain tumors over ADC [42,43]. However, in previous FM-based dMRI studies, diffusion gradients were only applied in three directions at most, and the anisotropy was neglected [20,42,43]. The directional sensitivity of the FM model in biological tissues remains elusive. In this study, the FM-related parameters were obtained in 12 non-collinear directions, and their directional deviations were assessed quantitatively. Furthermore, the FM-related parameters were expressed as tensors analogous with ADT to investigate their directionality.

2. Material and methods

2.1. Subjects

Fifteen healthy subjects (seven males and eight females; mean age, 24.1 ± 1.4 years) participated in this study. This study was approved by the local institutional review board, and informed consent was obtained from all participants.

2.2. Image acquisition

MR imaging was performed on a 3T whole body MRI scanner (MR750, GE Healthcare, Milwaukee, Wisconsin) equipped with an 8-channel head coil in the Center for MRI Research at Peking University, Beijing, China. All dMRI images were obtained using the Stejskal-Tanner diffusion gradient [44] with the single-shot spin-echo echo-planar-imaging technique. The diffusion gradients were applied successively in 12 non-collinear directions to detect the effects of diffusion anisotropy. These directions were along radial lines in q-space, which was approximately evenly distributed on a sphere. In each direction, after an image was acquired without diffusion sensitization ($b=0$ s/mm^2), 24 non-zero b-values ranging from 158 to 3548 s/mm^2 were produced by varying the diffusion gradient amplitude (G_0) and the separation time (Δ). $G_0$was set at 14.70, 18.70, 23.79, 30.27, 38.51 and 49.00 mT/m, and Δ was set at 28.500, 34.400, 41.500 and 50.000 ms. Both were chosen to be approximately evenly spaced on a log axis. The gradient duration (δ) was kept constant (22 ms). The other parameters of this diffusion sequence were as follows: TR/TE = 4500 ms/110 ms; acceleration factor = 2; field-of-view (FOV) = 24 cm × 24 cm; matrix size = 80 × 80; slice thickness = 3 mm; number of slices = 35; and number of excitations = 2. In addition, a sagittal 3D fast spin echo T_1-weighted image (TR/TE = 600 ms/12 ms, echo train length = 24, 1 mm isotropic voxel resolution) was acquired as an anatomical reference for each subject.

2.3. Image analysis

Prior to image analysis, acquired images were corrected for eddy current distortions and head motions using FSL [45]. To obtain the anomalous diffusion parameters α and H, the images were analyzed under the FM-based dMRI theory framework [20] in which the diffusion-induced signal decay is formulated as

$$S/S_0 = \exp\left(-\eta D_{\alpha,H}\gamma^{\alpha}G_0^{\alpha}\Delta^{\alpha+\alpha H}\right) \tag{1}$$

where $D_{\alpha,H}$ is the generalized diffusion coefficient of anomalous diffusion and γ is the gyromagnetic ratio. In Eq. (1), η is a dimensionless number, which can be calculated using the form [20]:

$$\eta = \frac{1}{(1+\mu)^{\alpha}}\left[\int_0^{\delta/\Delta}\left|\left(\frac{\delta}{\Delta}+1-u\right)^{1+\mu}-(1-u)^{1+\mu}-\left(\frac{\delta}{\Delta}-u\right)^{1+\mu}\right|^{\alpha}du + \int_{\delta/\Delta}^{1}\left|\left(\frac{\delta}{\Delta}+1-u\right)^{1+\mu}-(1-u)^{1+\mu}\right|^{\alpha}du + \int_1^{1+\delta/\Delta}\left(\frac{\delta}{\Delta}+1-u\right)^{\alpha+\alpha\mu}du\right] \tag{2}$$

where $\mu=H-1/\alpha$ is the memory parameter mentioned above. The signal attenuation at each voxel was fitted separately to Eq. (1) along each direction. In addition, both ADC and the stretching parameter γ of the stretched exponential model were calculated as references. ADC maps were calculated using the images acquired at b-values of 0 and 1084 s/mm^2, which is the closest to the conventional 1000 s/mm^2 b value in this acquisition. The stretched exponential model ($S(b)/S_0=\exp(-(b\cdot DDC)^{\gamma})$) was fitted to all b-values [12]. All fitting procedures were performed using the trust-region-reflective nonlinear fitting algorithm in Matlab (The Mathworks, Inc., Natick, MA).

To investigate the directional deviation obtained from multiple diffusion gradient orientations, a generalized FA, termed gFA, was introduced as the sample standard deviation dividing the root mean square:

$$gFA(V) = \sqrt{\frac{N}{N-1}\frac{\sum_{i=1}^{N}(V_i-\overline{V})^2}{\sum_{i=1}^{N}V_i^2}} \tag{3}$$

where N is the number of sampling directions, V_i is the parameter in the i-th direction, and $\overline{V}$ is the directionally averaged parameter. The gFA maps were calculated for ADC, γ, α and H.

Although gFA quantifies the directional deviation for the parameter, its value depends on the set of sampling directions, i.e., the diffusion gradient directions used in the experiment. This effect can only be eliminated with enough chosen directions to sample the space uniformly. Therefore, the tensorial approach proposed by Hall and Barrick, which is independent of the sampling directions, was adopted [22]. Analogous to the ADT, this approach generalized the stretched exponential model to include directional dependence and assumed that its parameters are well-described by Gaussian ellipsoids [22]. Following this approach, the FM-related parameters α and H can be expressed as symmetric and positive definite tensors. In particular, α and H along the direction $\hat{\mathbf{n}}=(n_x,n_y,n_z)^T$ are related to the respective tensors ($\mathbf{A}$ and $\mathbf{H}$) in the following equations:

$$\alpha(\hat{\mathbf{n}}) = \hat{\mathbf{n}}^T\cdot\mathbf{A}\cdot\hat{\mathbf{n}} \tag{4}$$