New insights into γ-stretched exponential Anomalous-Diffusion imaging experiments

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Purpose. The departure from purely mono-exponential decay of the Pulsed Field Gradient signal S(b)=S(0)exp(-bD) as a function of the b-value observed in biological tissues, prompted the search for alternative models to characterize non-Gaussian dynamics of water diffusion. Several approaches have been proposed in the last years[1]. In this study we investigated the so-called anomalous diffusion (AD) stretched exponential γ-imaging model[2,3] which is based on fitting the stretched function $S(b)=S(0)\exp(-(bD)^{\gamma})$ to PFG data obtained by varying the gradient strength g. Although γ is not a tensor, it is possible to use a "first order approximation approach in which γ is projected along the DTI main directions of diffusion[3]. As a consequence, invariant indices, such as the mean γ (Mγ) and the γ anisotropy (Aγ) can be obtained[3]. The biophysical origin of the contrast observed in Mγ maps is related to water multi-compartmentalization and to internal gradients (G_i) generated at the interface between tissues characterized by different magnetic susceptibility (Δχ), as recently suggested[4,5]. As a consequence, Mγ in heterogeneous tissues provides different and additional microstructural information when compared to those obtainable by using conventional diffusion tensor imaging (DTI) methods. Recent in vitro results[4,5] suggested that the main directions of anomalous diffusion could be different from those of conventional DTI. The aim of the present study was to overcome the "first order approximation" approach proposed in[3] to obtain Mγ values in the intrinsic γ reference frame, together with the main direction of γ in the stretched exponential γ-imaging model reference frame. Toward this goal we examined a fixed mouse brain at 7T by performing conventional DTI and variable gradient strength γ-imaging experiments, and assessing the correspondence between T_2* (which quantifies G_i), DTI parameters, DTI main directions, stretched exponential γ-imaging parameters (by using the approximated[3] and the new processing method), γ-imaging main directions (by using a new processing method) in various anatomical regions and in the whole mouse brain.

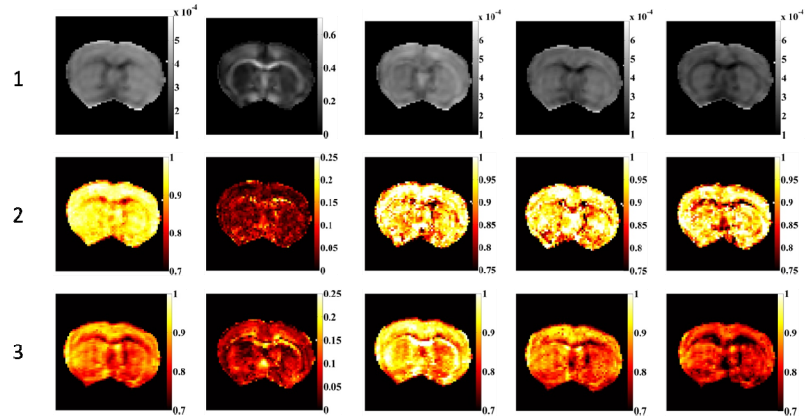

Fig.1

Methods. *Theory.* In this work, we assumed the tensorial nature of anomalous diffusion as reasonable. In analogy with the conventional DTI, we hypothesized that it is possible to identify a specific reference frame defined by the main directions of the anomalous diffusion. Indeed, in a three dimensional space it is always possible to decompose the motion into its projections along three main axes. Thanks to the property of the Fourier Transform, by considering a generic direction of **b**, it is possible to write: $S(b)\propto\Pi_{i=1,2,3}\ \exp[-A_i(b_i^*)^{\gamma_i}]$ [1], where A_i is a generalization of the diffusion constant, b_i^* is the projection of **b** along the i-th main direction of the anomalous diffusion, $[\boldsymbol{\eta_i}]_{i=1,2,3}$: $b_i^*=\mathbf{b}\cdot\boldsymbol{\eta}_i$, and γ_i is the γ stretching exponential parameter measured along the direction $\boldsymbol{\eta}_i$. The main difference of the method proposed here compared to that reported in [3], is that $[\boldsymbol{\eta_i}]_{i=1,2,3}$ is not assumed to be the DTI reference frame, $[\boldsymbol{\varepsilon_i}]_{i=1,2,3}$, but an unknown reference frame that has to be extracted from a fitting of relation [1] to the experimental PFG data. The corresponding three γ values can be used to extract invariant indices, such as the $M\gamma=1/3\sum_{i=1,2,3}\gamma_i$ and the $A\gamma=\{3/2[\sum_{i=1,2,3}(\gamma_i-M\gamma)^2]/(\sum_{i=1,2,3}\gamma_i^2)\}^{1/2}$, similar to the conventional MD and FA. *Experiments:* One mouse brain fixed in paraformaldehyde and stored in PBS was used to ensure long acquisition time and sufficiently high SNR and CNR. All the experiments were performed on an NMR scanner operating at 7.0T (Biospin, Bruker). An imaging version of pulse gradient stimulated echo (PGSTE) sequence with TE/TR = 25.77/4000 ms, diffusion gradient pulse delay Δ= 40ms, diffusion gradient pulse duration δ= 2ms, number of average NA = 14; sixteen axial slice with thickness STH= 0.750mm, FOV=6cm, an in plane resolution of about 470μm, and 11 values of b, ranging from 100 to 9000s/mm^2, along 30 no-coplanar directions plus five b=0s/mm^2 images was acquired to perform the conventional DTI processing and the new AD processing proposed here in all slices. Moreover T_2*-weighted images were acquired (TE=3 to 30 ms/TR=1500ms to obtain T_2*-maps. The reconstruction of conventional MD and FA maps were computed using b-values <2500s/mm^2, while Mγ and FAγ maps were computed using all the b-values. All the processing procedures were performed using MATLAB®.

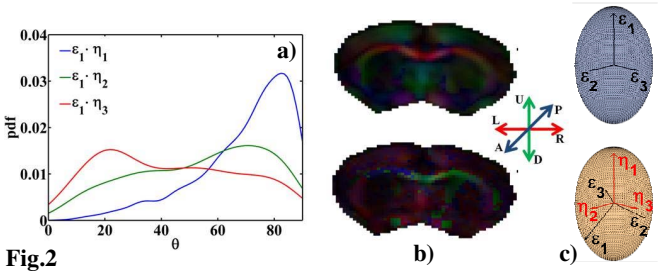

Fig.2

Results. A significant negative correlation was found between $M\gamma$ and T_2* in all anatomical mouse brain regions. **Fig.1** shows MD (**1-a**), FA (**1-b**), the three diffusion tensor eigenvalues λ_1(**1c**), λ_2(**1d**) and λ_3(**1e**) maps obtained from conventional DTI; Mγ (**2a**), FAγ (**2b**), γ_1 (**2c**), γ_2 (**2d**) and γ_3 (**2e**) maps obtained from the approximated approach[3]; and Mγ (**3a**), FAγ (**3b**), γ_1 (**3c**), γ_2 (**3d**) and γ_3 (**3e**) maps obtained from the new approach described here for the first time. **Fig.2a** shows the pdf of the angle between the first eigenvector of the diffusion tensor ($\boldsymbol{\varepsilon_1}$) and the three vector $\boldsymbol{\eta_1}$, $\boldsymbol{\eta_2}$ and $\boldsymbol{\eta_3}$ derived within the new γ stretching exponential framework for the whole brain. **Fig.2b** shows the color maps of the main diffusion direction $\boldsymbol{\varepsilon_1}$ (upper image) and the main anomalous diffusion direction $\boldsymbol{\eta_1}$ (lower image). **Fig.2c** shows the reference frames $[\boldsymbol{\varepsilon_i}]_{i=1,2,3}$ (upper image) and $[\boldsymbol{\eta_i}]_{i=1,2,3}$ (lower image).

Discussion. The AD maps reported in lines 2 and 3 of **Fig.1** show a different image contrast compared to that of conventional DTI maps displayed in line 1. Specifically, the map shown in line 3a provides a better discrimination between different anatomical brain regions, in agreement with previous results[1,3], while the map in line 3b may provide microstructural information about the brain tissue. Moreover, the AD maps shown in row 3 of Fig.1, obtained with the new approach described here, exhibit a higher image quality and a better contrast to noise ratio compared to the maps obtained using the approximated AD approach[3]. Results shown in **Fig.2** suggest that $\boldsymbol{\eta_1}$ is about perpendicular to $\boldsymbol{\varepsilon_1}$, in agreement with recent observations[6]. On the other hand, $\boldsymbol{\eta_2}$ and $\boldsymbol{\eta_3}$ seem to lie approximately along the same direction of $\boldsymbol{\varepsilon_3}$ and $\boldsymbol{\varepsilon_2}$, respectively**.** The reason of the difference between the $\boldsymbol{\eta_1}$, $\boldsymbol{\eta_2}$, $\boldsymbol{\eta_3}$ and the $\boldsymbol{\varepsilon_1}$, $\boldsymbol{\varepsilon_2}$, $\boldsymbol{\varepsilon_3}$ reference frames is probably due to the concomitant dependence of γ on both water multi-compartmentalization and internal gradients. However further experiments must be performed in controlled phantoms to explain the different orientation of γ compared to the DTI reference frame.

Conclusion. We have extended previous work in the field of non-Gaussian diffusion methods. Specifically, our results highlight aspects of anomalous diffusion γ-imaging that may be exploited to obtain microstructural information complementary to those of the DTI..

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