Anomalous diffusion stretched exponential γ-imaging model provides new information on spinal cord microstructure

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PURPOSE. The additional information provided by non-Gaussian diffusion approaches may improve the sensitivity and specificity of the conventional Diffusion Tensor Imaging (DTI) investigations. Among these, the stretched exponential γ-imaging model which is based on fitting the stretched function $S(b)=S(0)\exp(-(bD)^{\gamma})$ to pulse field gradient (PFG) data obtained by varying the gradient strength g, provided interesting results in mouse and human brain[1-2]. Recently, we proposed a strategy to obtain γ stretching parameters independently of the directions chosen for the measurement by obtaining maps of scalar invariants such as the mean value of γ (Mγ) and its anisotropy (Aγ)[3]. Successively, we clarified the physical origin of the γ parameter suggesting that it can be explained in the framework of the Anomalous Diffusion (AD) theoretical model of Continuous Time Random Walk (CTRW)[4-6] and we named it the anomalous diffusion (AD) stretched exponential γ-imaging model. In this context, γ quantifies water AD effects due to both water multi-compartmentalization and magnetic susceptibility differences (Δχ) at the interface between different compartments[3-6]. In this work we applied AD stretched exponential γ-imaging model to investigate cervical sections of a fixed mouse spinal cord. In order to highlight the new additional information provided by AD approach we compared AD images with results obtained by using conventional DTI and relaxometry and histological data. **METHOD.** C57 BL6 mouse spinal cord was fixed in glutaraldehyde/paraformaldehyde 4%/2% and stored in PBS. All measurements were performed on a Bruker 9.4T Avance system, operating with a micro-imaging probe (10mm internal diameter bore) and equipped with a gradient unit characterized by a maximum gradient strength of 1200 mT/m. The slice package was centered in the cervical portion of the spinal cord, with slices thickness ST=0.7 mm, field of view FOV=4.2x4.2 mm^2, matrix=128x128 pixels, and in-plane spatial resolution 33x33 μm^2. An imaging version of pulsed gradient stimulated echo sequence (PGSTE) was used for both the γ-imaging (TR/TE=3000/17ms, Δ/δ=40/2 ms) and the conventional DTI (TR/TE=3000/12ms, Δ/δ = 40/2 ms) protocols. The γ-imaging was performed along 3 orthogonal directions with 10 b-values ranging from 100 to 4000 s/mm^2 while the DTI was performed along 6 non collinear directions, with b = 700 s/mm^2. T_2^* maps were obtained by using TR=1000 ms and 13 values of TE from 2 to 40 ms. In every case NS=16. The expression $S(q)=S(0)e^{-A(4\pi^2)^{\gamma}q^{2\gamma}\Delta}$, where $q=\sqrt{\frac{b}{4\pi^2(\Delta-\delta/3)}}$, was fitted to the PGSTE signal decay in each voxel. Parametric maps of $M\gamma=(\sum_{i=1,2,3}\gamma_i)/3$, $A\gamma=\sqrt{3\sum_{i=1,2,3}(\gamma_i-M_\gamma)^2/2\sum_{i=1,2,3}\gamma_i^2}$, γ_{par} and γ_{ortho} that are the stretching exponents, respectively computed in the direction parallel and orthogonal to the main fibers direction (which in this case coincides with the $\overrightarrow{B_0}$ field direction), were obtained together with mean diffusivity (MD), fractional anisotropy (FA) and T_2^* maps. Mean ± SD were obtained for each aforementioned parameter in specific spinal cord regions identified in three cervical slice by using histological reference images[7,8]. Homogeneity of variances was tested by using Levene's test. Pairwise comparisons were made using a Welch ANOVA. Games-Howell corrections were performed to correct for multiple testing. Relationship between pairs of parameters were assessed with linear correlation analysis (Pearson's r coefficient). P-values <0.05 were considered statistically significant.

Fig.1

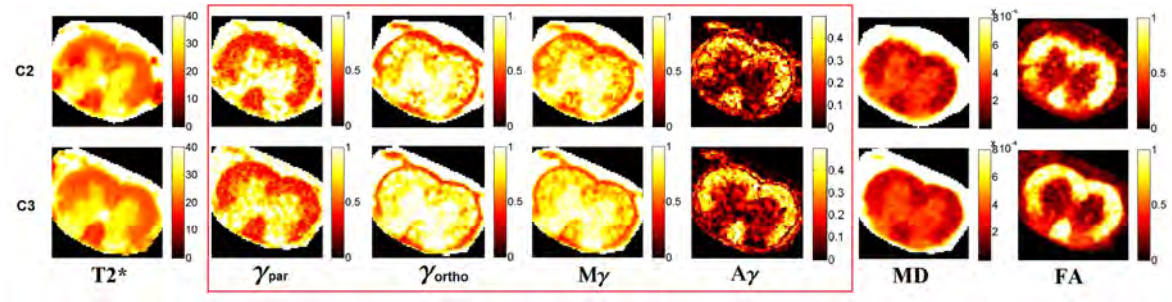
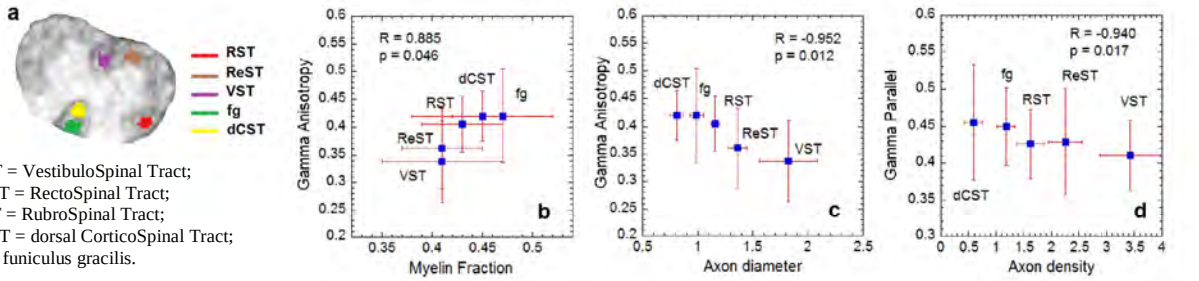


Fig.2



VST = VestibuloSpinal Tract;
ReST = RectoSpinal Tract;
RST = RubroSpinal Tract;
dCST = dorsal CorticoSpinal Tract;
fg = funiculus gracilis.

RESULTS. Parametric maps of C2 and C3 cervical slices, are shown in **Fig.1**, where the AD maps are highlighted in the red box. Please note the enhancement at the interface between the spinal cord and the PBS medium surrounding it in the Mγ and Aγ maps due to Δχ . The cervical nerves are well-defined only in AD maps. According to previous results[9], in white matter (WM) tract, γ along fibers direction is significantly lower compared to that across fibers ($\gamma_{par}=(0.45\pm0.08)$; $\gamma_{ortho}=(0.82\pm0.12)$). By considering the spinal cord sub-regions depicted in **Fig.2a**, differently from T_2^*, MD and FA maps, Aγ significantly discriminates (p=0.02) between VST and RST regions. On the other hand, only FA significantly discriminates between ReST and fg, and dCST and fg regions, while, unlike FA and MD, Aγ significantly discriminates between VST and dCST (p=0.001), VST and fg (p=0.01), ReST and dCST (p=0.02). Moreover, unlike FA and MD, γ_{ortho} discriminates between RST and ReST (p=0.009) and between RST and fg (p=0.027). Differently from FA and according to T2*, Aγ shows a positive correlation with the myelin fraction (p=0.046, **Fig.2b**) and, unlike FA and T_2^*, a negative correlation was found between Aγ and the axon diameters (p=0.012, **Fig.2c**). On the other hand, unlike FA and MD and according with T_2^*, γ_{par} exhibits a negative correlation (p=0.017, **Fig.2d**) with the axon density and a positive correlation with axons diameter (R=0.9084, p=0.0328). Finally, Mγ shows a significant positive correlation with T_2^* in the gray matter (R=0.5829 p<0.0001). **DISCUSSION.** Aγ and γ_{par} in WM tract showed significant correlations with histological measurements that cannot be found, when the conventional DTI parameters are considered. In particular, the correlation between Aγ and myelin fraction is in agreement with recent results highlighted by Yablonskiy[10] that underline the existence of high anisotropy and Δχ variation along WM fibers due to the presence of specific anisotropic rearrangement of fatty acids constituting myelin sheaths. This characteristic of myelinated fibers can be experimentally detected by AD γ parameters, due to their dependence on both water multi-compartmentalization and Δχ at the interface between different compartments[5]. In this context, AD γ-imaging allows to go beyond the resolution of conventional DTI. **CONCLUSION.** Our results in fixed spinal cord confirm previous AD results obtained in phantoms[4,5], in excised human tissue[6] and in human brain[3]. Moreover, differently from previous works, the peculiar anisotropic structure of spinal cord investigated at high magnetic field (9.4 T) highlights new potential of AD analysis. Specifically, AD γ-imaging is able to detect microstructural information of WM tract in spinal cord more specific and complementary to those provided by DTI.

REFERENCES. [1]Hall MG, Barrick TR. NMR Biomed 2012;25:286–294. [2]Ingo C, et al. 2014;71(2):617-627. [3]De Santis S, et al. Magn Reson Med 2011;65:1043-1052. [4]Palombo M, et al. J Chem Phys 2011;135:034504. [5]Palombo M, et al. J Magn Reson 2012;216:28-36. [6]Capuani S, et al. Magn Reson Imaging 2013;31:359-365. [7]Ong H H, et al. Neuroimage 2008;40:1619-32. [8]Ong H H, Wehrli FW. NeuroImage 2010;51:1360-66. [9]GadElkarim J et al. IEEE J EMERG SEL TOP CIRC SYST, 2013;3:432-441.[10]Yablonskiy DA and Sukstanskii AL, Magn Reson Med 2014;71:1956–1958.