3108

Assessing Diffusion Time Effects on Microstructural Comparment Estimates in Human White Matter using 7T dwSTEAM

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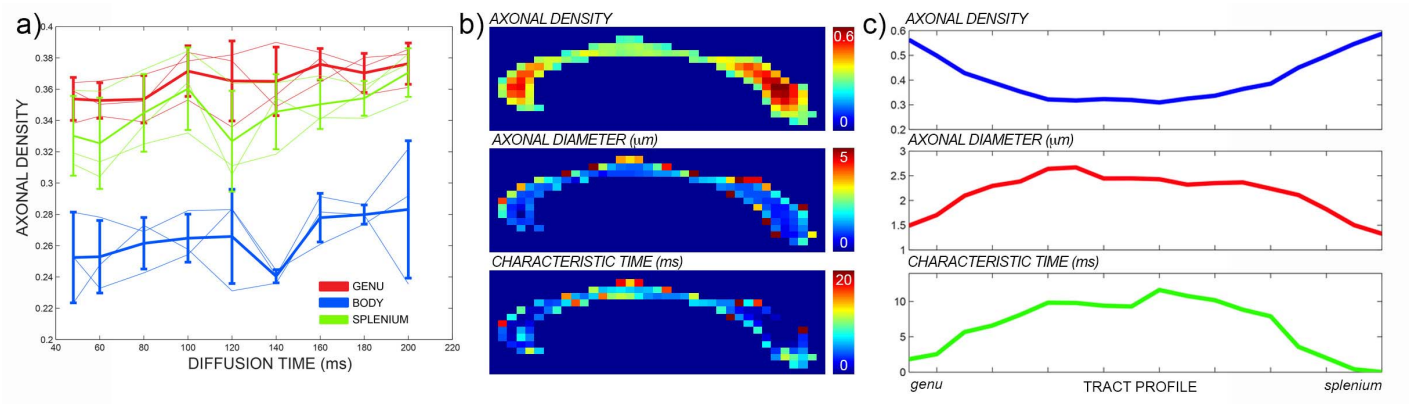
PURPOSE AND TARGET: The lack of specificity of diffusion tensor MRI is mainly its inadequacy to characterise more than one fibre population within a voxel and its implicit assumption of there being a single tissue compartment. This has motivated the search for more sophisticated approaches to model diffusion in complex tissue. Hybrid models like CHARMED [1] and NODDI [2], expressing the signal as a summation over intra- and extra-axonal compartments, have proven particularly useful in this context. These models tease apart the different contributions to diffusion anisotropy and provide more specific microstructural indices such as axonal density. These frameworks have been extended to characterize axonal diameters [3,4], providing the opportunity to non invasively map the distribution of axonal calibres within the brain, increasing the specificity of diffusion MRI even further. Axonal diameter methods seem to capture the relative trends for the diameter distribution in fibre tracts but the absolute diameter value is generally overestimated, which has been attributed to the fact that larger axons contribute quadratically more to the signal decay [4]. In addition, it has been shown [5,6] that the signal generated from the extra-axonal compartment, besides being the main contribution to the total signal, is inherently dependent on diffusion time, while all the models introduced to estimate axonal density and diameter disregard this dependency. The aims of this work are twofold: 1) to investigate the influence of diffusion time over a wide range in multi-compartment models using diffusion weighted (dw) STEAM at 7T; and 2) to modify current models to estimate axonal diameter distributions to take into account diffusion time effects for the extra-axonal compartment. The **target audience** for this work are basic scientists interested in the biophysics of the diffusion signal in white matter and in estimating microstructure compartment models.

METHODS: 5 healthy subjects were scanned using a dwSTEAM diffusion protocol at 7T with the following parameters: TE/TR=67/6200ms, δ=17ms, Δ= 48,60,80,100,120,140,160,180,195 ms, 4 shells of b-value 500, 1000, 2000 and 4000 s/mm^2, respectively, by using 1 (at maximum 70mT/m) or 2 (at effectively maximum 99 mT/m) simultaneous gradient axes. Since the focus of this study was the corpus callosum (CC), which is constituted by fibres homogeneously oriented along the L-R direction, the sampled gradient where oriented along 4 perpendicular and 1 parallel directions: [0 1 1], [0 -1 1], [0 1 0],[0 0 1] and [1 0 0]. An additional HARDI protocol (60 gradient orientations + 6 b0) was acquired to reconstruct the CC and recover local fibre orientation information. The resolution of all scans was 2 mm isotropic. After motion and distortion corrections [6], CHARMED maps were separately reconstructed for each diffusion time. Then, all the data were used to generate maps of the axonal diameter using a modified version of AxCaliber approach, where the axial elements of the extra-axonal tensor incorporated the dependency on the diffusion time suggested in [5]. This dependency was described by an additional parameter, that we call the characteristic time constant. As such, for each subject, 9 maps of the axonal density (one for each diffusion time) and single maps of the axonal diameter and correlation time were generated.

RESULTS AND DISCUSSION:

Fig. a) shows the plot of the axonal density at varying diffusion times for three locations in the CC (genu, body and splenium). To analyse the influence of the diffusion time on the estimates, a 2-way ANOVA was performed on the data, using location and diffusion time as factors. Both have a significant effect at $p<0.05$, while the interaction term is not significant. Reconstructing axonal diameter using the methods published in literature [3-4], i.e., without accounting for the dependency of the extra-axonal tensor on the diffusion time, returns maps of mean diameter ~20 µm (data not shown). Histologic measures on the CC show that the expected range for axonal diameter is 1-3 µm [7]. By accounting for the diffusion times in the extra-axonal compartment, the diameter estimates become compatible with histology, as reported in Fig. b). The characteristic time constant is of the order of 10 ms. In Fig. c) the smoothed profiles along the CC are reported for the axonal density, axonal diameter and characteristic time constant. The trends of high-low-high for the axonal density and low-high-low for the axonal diameter, as observed in histological measurements, are clearly respected. The characteristic time constant also shows a similar low-high-low trend, perhaps reflecting the difference in geometry, with the body characterised by a more inhomogeneous distribution of axonal sizes.



CONCLUSION:

The diffusion time has a significant effect on the estimates of the axonal density, thus caution is needed when comparing data obtained with different experimental protocols. When the dependency of the extra-axonal diffusion on the diffusion time, extensively documented in [5], is included in the estimation of axonal diameter maps, the magnitude of estimates gets closer to histology, while the relative trend along the CC is maintained.

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