MAPPING THE AXON DIAMETER INDEX IN THE CORPUS CALLOSUM IS CLINICALLY FEASIBLE

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Introduction

We propose a novel diffusion weighted imaging (DWI) protocol that achieves high-resolution *in-vivo* axon diameter estimates in the corpus callosum (CC) in only 35 minutes of scan time. Diffusion tensor imaging (DTI) has proven valuable in the investigation of diseases in the central nervous system, despite the fact that DTI derived parameters lack specificity to the underlying microstructure changes. Alternatives methods can directly infer microscopic features of biological tissue such as axon diameter and density [1,2], but need hours of data acquisition and have hardware requirements that cannot be met by current clinical MRI systems. Recently, the feasibility of estimating an index of axon diameter in vivo using a clinical 3T system has been demonstrated by Alexander et al's ActiveAx technique [3], following the development of a computational framework [4]. However, the proposed DWI protocol still requires more than 1h of scan time to achieve acceptable accuracy in the parameter estimates, which is usually too long to be used in clinical practice. It has recently been demonstrated that the efficacy of axon measurements can be improved in structures such as the CC if the known single fibre (SF) orientation is taken into consideration [5]. In this study we introduce a novel imaging protocol that allows high quality high resolution microstructure imaging of the CC in a clinically acceptable scan time of 35 minutes, obtained by combining (i) an improved SF DWI signal model that accounts for T2 decay in the tissue and (ii) an optimized imaging strategy. We validate our approach in a scan/rescan pilot study of 5 healthy volunteers.

Methods

Study design: We recruited 5 healthy volunteers to be scanned on a Philips Achieva 3TX scanner. All subjects were recalled for a second scan on a separate occasion to assess the intra-subject reproducibility of the experiment.

Protocol optimisation: We use the SF protocol optimization framework [5] with an additional T2 decay factor that accounts for the varying signal loss in the DWI due to different echo times (TE). For the protocol optimization we assumed a T2 relaxation time of 70ms for white matter (WM) in the CC. We allowed a maximum gradient strength of 87mT/m, which is achievable by combining perpendicular 62mT/m, gradients. We also acquired a standard DTI acquisition (max b=800s/mm^2, 1 b=0, 16 uniformly distributed directions). The full protocol is given in Table 1.

	δ	Δ	G	TE
1b0	0	0	0	23
1b0 + 5$\parallel$	8	22	78	46
1b0 + 14$\perp$	13	20	87	54
1b0 + 7$\perp$	22	56	48	96
1b0 + 26$\perp$	23	29	87	73
1b0 + 20$\perp$	27	50	63	93
1b0 + 11$\perp$	35	42	81	93
1b0 + 16 DTI	b=800 s/mm^2			47
	scan time =35 min			

Table 1: *Diffusion parameters of the optimised SF protocol for a total of N=108 acquisition ($\parallel$/$\perp$=number of gradient direction acquired parallel/perpendicular to major WM direction, G=gradient strength in mT/m, δ=gradient duration, Δ =diffusion time (all in ms))*

Data acquisition: We acquired the DWI protocol for 10 sagittal slices with high in-plane resolution and centered on the mid-sagittal plane of the CC, perpendicular to the dominant fibre direction of the CC. Acquisition parameters were: voxel size: 1x1x4mm^3, FOV=96x96mm^2, TR=6000ms, 2 averages, using an outer-volume suppressed ZOOM acquisition [6] to avoid fold-over artifacts.

Model fitting: We fitted a single axon diameter model according to [5], based on the minimal model of white matter diffusion [4] (zeppelin-cylinder-ball in the model taxonomy of [7]) with an additional T2 relaxation factor. We computed the posterior distributions of the model parameters using an MCMC method on a voxel-by-voxel basis. We used mean of the posterior distribution of the axon diameter, *d*, as the axon diameter index and the volume fraction, *f*, of the restricted compartment to generate maps of mean *d* and the axonal density index $\rho = f/\pi d^2$. We also fitted the diffusion tensor to the 16-direction DTI data and derive maps of FA and the principal eigenvector ***v1***. All fitting was performed using the open-source Camino toolkit [8] (camino.org.uk).

Data analysis: In each subject we defined the mid-sagittal slice of the CC by manually segmenting the CC and excluded voxels where either FA<0.5 or ***v1*** deviated more than 10 degrees from the dominant CC fibre direction. We divided each CC in 10 regions along the anterior-posterior baseline similar to [9].

Results and Discussion

Figure 1 shows an example of the obtained *d* and ρ maps and the CC subdivision. Figure 2 shows plots of *d* and ρ over the CC subdivisions for each subject. Figure 3 shows the axon diameter index and standard deviation over all subjects in each CC region for scan and rescan experiments. In all subjects we find the highest values of *d* (12.5-13.5μm) in regions B1-I and smaller values between 9-11.5μm for *d* in the anterior genu (G1-G2) and splenium regions (S1-S3). Similarly we find the highest axonal density in genu and splenium and low density in the mid-body regions. These trends are in excellent agreement with studies of post-mortem CC, which report highest number of large fibres between B1 and I [9] and low fibre density [10] compared to genu and splenium. The high estimates of *d* compared to reported post-mortem values can be explained by the shrinkage of axons due to histological preparation. Also the limited gradient strength available on the clinical MRI system makes the experiment insensitive to small fibres, as shown e.g. by [11]. Therefore we can postulate that differences between CC regions in our experiment are mainly driven by the presence of larger fibres.

Scan/rescan reproducibility: Figure 2 and 3 show good agreement between *d* and ρ values in all regions consistently in all subjects. We find the variability of *d* to be less than 10% between scan and rescan in each subject, with the largest relative difference found in the genu and splenium (6±5% variation) and lowest in the mid-body (<3±2%). As seen in Figure 3, inter-subject variability is below 0.8μm in *d* and 0.01μm^{-2} in ρ in both scan and rescan experiments. Standard deviation is lowest in the mid-body (0.3μm) measurement and larger in genu and splenium regions (>0.7μm). Similarly, in ρ we observe low variability in the mid-body (0.001-0.002μm^{-2}) and higher intra-subject variability in the posterior part of the CC, particularly in the splenium (0.005-0.01μm^{-2}).

Conclusion:

We have proposed a novel DWI protocol for measuring axon diameter and density in the CC in vivo. We have demonstrated that our microstructure estimates agree with reported post-mortem evaluation of the CC fibre density distribution. Further, we showed good inter- and intra-subject reproducibility. The scan time of the protocol is short enough to be easily incorporated into clinical studies. In future work, we are planning to use this approach in subjects with known altered microstructure of the CC.

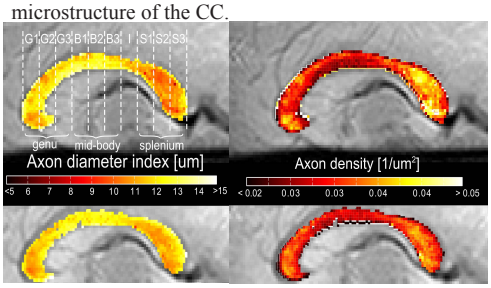

Figure 1: *Scan and rescan maps of d and ρ for one representative subject. The CC subdivision scheme is illustrated on the the first map (G=genu,B=mid-body,I=isthmus,S=splenium.)*

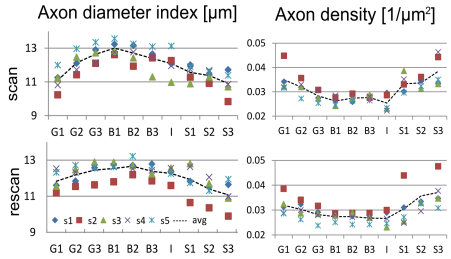

Figure 2: *Estimates of d and ρ in each CC region for each subject (upper row: scan, lower row: rescan). Dashed lines present the average over all 5 subjects.*

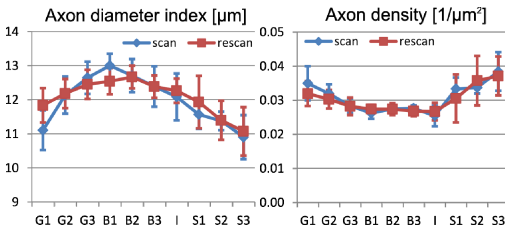

Figure 3: *Average d and ρ measurements over all subjects for scan and rescan experiment.Bars represent the standard deviation over all subjects for each CC region.*

References: [1] Stanisz, MRM (1997) [2] Barazany, Brain (2009) [3] Alexander, Neuroimage (2010) [4] Alexander, MRM (2008) [5] Schneider, MICCAI (2010) [6] Wilm, NMR in Biomed (2009) [7] Panagiotaki, Neuroimage (2011) [8] Cook, ISMRM (2006) [9] Aboitiz, Brain Research (1992) [10] Highley, Brain (1999) [11] Lätt, TMI (2007)

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