Probing micro-structural information using the CHARMED model in the non-myelinated human newborn brain at 3T

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Introduction

Diffusion weighted imaging (DWI) has shown impressive advances over the last decades and is now an established protocol in clinical routines for probing, for example, brain tumors and stroke, as well as for tracking brain recovery processes or developmental disorders by assessing tissue microstructures information. Magnetic resonance, which is noninvasive, may be the only feasible technique to study structural and metabolic changes occurring during the delicate period of brain development. Indeed, many neurobiological disorders and disabilities originate from disruptions in structural and functional development, which motivates the need for a better understanding of brain development.

Diffusion tensor imaging (DTI), an application of DWI, already provides a unique insight into the cellular microstructure. However, the changes reported during brain development with DT-derived parameters (e.g. fractional anisotropy, FA, mean diffusivity, MD) cannot be directly related to physical cellular process such as the myelination stage or axonal density. Recently, Assaf et al. [1] proposed the composite hindered and restricted model of diffusion (CHARMED) based on a multi-shell q-ball acquisition to allow the modeling of the axonal microstructure. It models the diffusion within the axons as restricted and the extra-cellular diffusion as hindered, hence supporting the differentiation of the two compartments.

The CHARMED model may offer the possibility to track the potential axonal density changes during brain development. However, axons in newborn brains, due to lack of myelination, has higher membrane permeability than adult brains. This may lead to reduced restricted diffusion and difficulty in distinguishing the intra-cellular and extra-celluar compartments. We hypothesized that the major fiber tracts such as the corpus callosum (CC) or the corticospinal tracts (CST) present a sufficiently dense packing of axons to generate restricted diffusion. Therefore, the aim of this study was to examine the feasibility of a multi-shell q-ball acquisition in human newborns of 40 weeks gestational age at 3T.

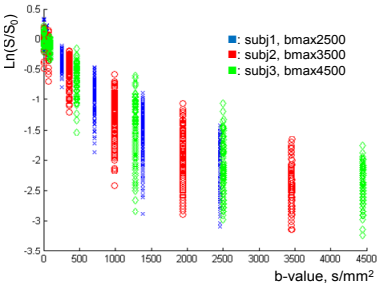

Figure 1: Natural logarithm of the signal decay with b-value in the three different subjects. Data are taken from 15 random voxels in the CC ROI. The data show two distinct diffusion regimes: situated below and above a b-value of 1500-2000 s/mm², respectively.

Table 1 : Fitting parameters (v_{IC}, D_{IC}, v_{iso} and fitting error)mean and standard deviation in the three ROIs (corpus callosum, CC, left and right corticospinal tract, l-CST and r-CST, respectively), for the three CHARMED acquisitions (maximum b-value : 2500, 3500, 4500 s/mm²).

		bmax2500	bmax3500	bmax4500
CC	v_{IC}	0.26 ± 0.19	0.21 ± 0.16	0.19 ± 0.15
	D_{IC}	0.88 ± 0.35	0.52 ± 0.2	0.29 ± 0.11
	v_{iso}	0.44 ± 0.25	0.54 ± 0.18	0.6 ± 0.13
	error	-305.6 ± 7.2	-301.7 ± 4.9	-296.9 ± 2.7
r-CST	v_{IC}	0.18 ± 0.11	0.14 ± 0.09	0.13 ± 0.05
	D_{IC}	0.93 ± 0.20	0.56 ± 0.11	0.30 ± 0.05
	v_{iso}	0.31 ± 0.17	0.45 ± 0.12	0.54 ± 0.07
	error	-303.5 ± 3.1	-300.5 ± 3.7	-296.1 ± 1.6
l-CST	v_{IC}	0.19 ± 0.15	0.14 ± 0.09	0.13 ± 0.07
	D_{IC}	0.88 ± 0.25	0.56 ± 0.11	0.30 ± 0.06
	v_{iso}	0.33 ± 0.20	0.46 ± 0.12	0.55 ± 0.08
	error	-303.7 ± 5.2	-300.4 ± 3.7	-296.2 ± 2.2
Vent	v_{IC}	0.75 ± 0.38	0.75 ± 0.39	0.76 ± 0.40
	D_{IC}	0.03 ± 0.38	0.03 ± 0.06	0.01 ± 0.03
	v_{iso}	0.90 ± 0.07	0.90 ± 0.05	0.89 ± 0.04
	error	-306.2 ± 16.0	-306.2 ± 19.5	-298.6 ± 16.1

Materials and Methods

Subjects: 3 human newborns born at term were scanned at term (40 weeks gestational age); the protocol was approved by the local ethical committee. During the MR examination the newborns were spontaneously asleep. Special "mini-muffs" were put on their ears to reduce noise exposure.

Data acquisition: Experiments were performed on a 3T Trio Tim System (Siemens Medical Solutions, Erlangen, Germany) operating with the Syngo VB15 software. Data were acquired using a 32-channel head coil.

Three different CHARMED protocols - with a maximum b-value (bmax) of 2500, 3500 and 4500 s/mm^2, respectively -were tested (one on each newborn). The data were acquired using a double refocusing spin echo echo-planar imaging (SE-EPI) pulse sequence combined with parallel imaging [2]. The common acquisition parameters were: spatial resolution 2×2×2 mm^3 (FOV = 16×16cm^2, matrix = 80×80), parallel imaging GRAPPA factor 2 and 44 axial slices. The diffusion scheme was composed of 66 DW images including 3 reference images without diffusion gradients (b_0 images). The remaining 63 non-collinear directions were split in 5 shells with the following orientations and b-values: 1st shell 6 directions 0.02·bmax; 2nd shell 9 directions 0.1·bmax; 3rd shell 12 directions 0.28·bmax; 4th shell 16 directions 0.55·bmax; 5th shell 20 directions 1.0·bmax [1]. The TE and TR were: 95/5800, 108/6200 and 118.2/6700 ms for the protocols with bmax set to 2500, 3500 and 4500 s/mm^2, respectively. The total acquisition time was 8 min.

Data analysis: Three regions of interest (ROIs; corpus callosum, CC, left and right corticospinal tract, l-CST and r-CST), were drawn on thresholded FA maps (FA>0.3), which were computed after a conventional DTI reconstruction based on the first three shells of each measurements with maximum b-value of 1500 s/mm^2, which is comparable to conventional acquisition.

The ROIs were then fitted on a voxel-wise basis with a CHARMED model with an additional CSF compartment to model CSF contamination. The parallel diffusivity of the extra-cellular compartment is identical to the intra-cellular diffusivity (D_{IC}). perpendicular diffusivity is set to $(1-v_{IC})\cdot D_{IC}$ via a tortuosity model [3]. The minimization algorithm started with a grid search, which sets the initial parameters for a subsequent maximum-likelihood gradient-descent algorithm [4]. The model has 3 free parameters: the intra-axonal volume fraction (v_{IC}); the intra-axonal diffusivity (D_{IC}); a CSF compartment (v_{iso}) with a free diffusivity (D_{iso}) fixed at 3×10^{-5} mm^2/s. The mean axonal diameter was set to 1 µm.

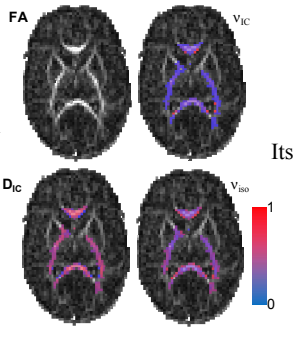

Figure 2: Axial slice of FA maps acquired in human newborn., overlaid with colormap representing intra-axonal volume fraction (v_{IC}), the intra-axonal diffusivity (D_{IC}) and the CSF volume fraction (v_{iso}). (ITK-SNap)

Results and Discussion

The two lowest bmax acquisitions show a good image quality. The same was true for the bmax 4500 s/mm^2 data-set, except for the last shell, which shows a low SNR. The signal decay in the white-matter ROIs was multi-exponential (**Fig.1**), demonstrating restricted diffusion. This result supports the choice of using a compartmented model such as CHARMED to analyze the DW images. The fitting error was in the same range over the three acquisitions and ROIs, with a trend to decrease at higher bmax (Table 1). More interestingly, v_{IC} was significantly higher in the CC than in the CST and much lower than previously reported in adults [1]. The v_{iso} map shows large values, which may be explained by partial volume effects with the ventricles next to the ROIs (Fig 2).

This preliminary study suggests that despite the lack of myelin at this age, the CHARMED acquisition protocol is feasible in the human newborn brain as well as that water experienced restricted diffusion in the CC and CST at a b-value > 2000 s/mm^2.

References: [1] Assaf et al, NeuroImage 2005 **[2]** Clayeden et al, IPMI 2009 **[3]** G. Stanisz et al, MRM 97 **[4]** Alexander et al, NeuroImage 2010

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