High-field neurite orientation dispersion and density imaging of sheep brain development

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Target audience: Brain development, diffusion imaging (DTI and NODDI).

Introduction: Diffusion tensor imaging (DTI) has been widely used to study rodent brain development as well as animal models of perinatal brain injury [1]. Nevertheless, generally two main disadvantages limit previous studies: first, rodent brain is non-gyrified which makes comparison with human brain difficult and second, the parameters derived from DTI (diffusivities: mean: MD, parallel: $D_{//}$ and orthogonal: $D_{\perp}$ as well as fractional anisotropy: FA) are sensitive to, but non-specific to, the tissue's microstructure. For instance, anisotropy can be modulated by the degree of myelination, axonal density, axon diameter distribution, orientation coherence and cell membrane permeability. Recently, the neurite orientation dispersion and density imaging (NODDI [2]), a new practical diffusion MRI technique for estimating the microstructural complexity of neurites (*i.e.* dendrites and axons) has been successfully used *in-vivo* on clinical MRI scanners [2]. From this model, one can estimate the intra-neurite volume fraction (f_{icvf}), the extra neurite-volume fraction (f_{ecvf}), the cerebrospinal volume fraction (f_{iso}) and a new index called orientation dispersion index (ODI) to model the dispersion/fanning of the axonal fibers or dendrites. In this work, to fulfil the weaknesses previously mentioned, we aimed to study *ex-vivo* brain development of a gyrencephalic species (sheep brain) at different gestational ages by using DWI acquisition at 9.4T fitted with the NODDI model.

Material and Methods: Fetal sheep brains were collected at 50, 90 and 110 days of gestation (term = 145d, 1 brain/age). MR experiments were performed on an actively-shielded 9.4T/31cm magnet (Agilent) equipped with 12-cm gradient coils (400mT/m, 120µs) with 3 different birdcage coils of 1, 2.5 and 3.5 mm diameter as a function of the gestational age. A multi-b-value shell protocol was acquired using a spin-echo sequence with the following parameters: FOV = 30×30 mm^2 (d110), 22×22 mm^2 (d90) and 10×10 mm^2 (d50), matrix size = 128×64, 12 slices (d50) and 20 slices (d90 and d110) of 0.6 mm thickness in the axial plane, 4 averages with TE/TR = 45/3000 ms. A total of 96 DWI were acquired, 15 of them as b_0 reference images. The remaining 81 were separated in 3 shells with the following distribution (# of directions/b-value in s/mm^2): 21/1750, 30/3400 and 30/5100. All 81 directions were non-collinear and were uniformly distributed in each shell. The total acquisition time was 20h. Acquired data were fitted using the NODDI toolbox [2]. NODDI estimates were measured in the cortical grey matter (GM) and white matter (WM).

Results: In both GM and WM from d50 to d110, f_{iso} decreased (drastically from d50 to d90) corresponding to the decrease of cerebral water content during brain development. In GM from d50 to d110, $D_{//}$ was reduced while f_{ecvf} and ODI increased. FA and f_{icvf} increased from d50 to d90 then decreased from d90 to d110 whereas $D_{\perp}$ followed opposite pattern. In WM, reduction of $D_{\perp}$ was observed from d50 to d90 to reach a plateau. From d50 to d110, FA, f_{ecvf} and f_{icvf} increased gradually whereas ODI decreased in the same time. Finally, a decrease then an increase of $D_{//}$ was observed from d50 to d90 and from d90 to d110, respectively.

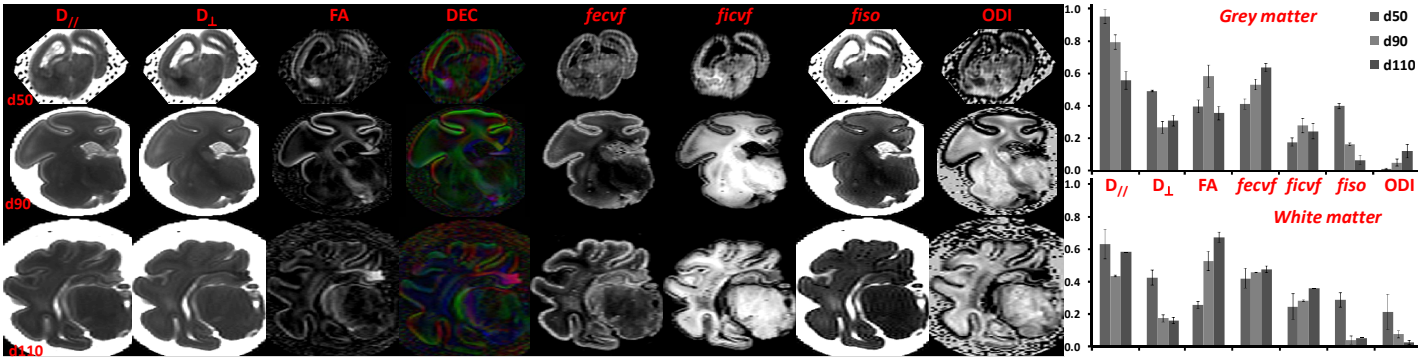

Figure 1: typical DTI derived maps: diffusivity ($D_{//}$ and $D_{\perp}$), FA and color maps as well as NODDI derived maps, f_{ecvf}, f_{icvf}, f_{iso} and ODI maps of d50, d90 and d110 sheep brain. Right panel, mean values±SD of these parameters in cortical grey matter and white matter.

Discussion and conclusion: **In this study we show for the first time feasibility of NODDI *ex-vivo* on the sheep brain at 9.4T.** The NODDI isotropic volume fraction parameter reflects clearly the decrease of cerebral water content during development whereas intra- and extra-cellular volume fractions increase with the development of pre-myelinating micro-structure. In GM, the increase in FA from d50 to d90 coincides with active neuronal migration along the radial glial scaffolding, whereas the decrease from d90 to d110 coincides with the phase of neocortical maturation with transformation of the radial glia into the more complex astrocytic neuropil (e.g. arborization of basal dendrites of cortical neurons) [3,4]. Dendritic arborization leads to larger fanning of the cortical fibers as depicted by ODI values. In the WM, setting up of pre-myelinating oligodendrocytes leads to FA increase (reduction of $D_{//}$ and augmentation of $D_{\perp}$) as well as ODI decrease reflecting fiber compaction during development. In conclusion, NODDI modeling leads to more specific markers of the tissue's microstructure development and will be of high interest to study models of perinatal brain injury as well as in clinical practice.

References: [1] van de Looij Y Cur Opin in Neur 2014 [2] Zhang H Neuroimage 2012 [3] Mc Kinstry RC Cereb Cortex 2002 [4] Sizonenko SV Cereb Cortex 2007

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