Quantification of tissues' maturation in the infant brain with multi-parametric MRI

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Introduction

Post-mortem studies have highlighted that maturation proceeds with a specific spatio-temporal pattern across cerebral regions during early infancy and childhood. In white matter, myelination progresses in an infero-superior and caudorostral way, from central to peripheral regions [1]. In cortical grey matter, synaptogenesis and dendritic arborisation first take place in primary areas of sensorial systems [2]. MRI has recently enabled to study these processes non-invasively in babies, which offers the opportunity to correlate functional development with anatomical brain maturation [3]. Particularly, the early organisation and maturation of white matter bundles can be studied with Diffusion Tensor Imaging (DTI) [4], but the relationships between DTI indices and maturational processes are still debated particularly in the cortex [5]. Here we propose to use multi-parametric quantitative MRI to investigate these relationships in the developing brain of healthy infants. To do so, we compared DTI indices with T1 and T2 relaxation times, mapped with EPI sequences in a reasonable acquisition time.

Materials and Methods

MR acquisition The study was performed on 10 infants born at term (mean age: 12.1±3.3weeks, range: 5.9w-18w), under a protocol approved by the Institutional Ethical Committee. Infants were spontaneously asleep during MR imaging. Acquisitions were realized on a 3T MRI system (Siemens Tim Trio, Erlangen), equipped with a whole body gradient (40mT/m, 200T/m/s) and a 32-channel head coil. 50 interleaved axial slices covering the whole brain were imaged with a 1.8mm isotropic spatial resolution (FOV=23x23cm^2, matrix=128x128, slice thickness=1.8mm) with EPI single-shot spin-echo (SE) sequences. For ***DTI***, a DW-SE-EPI sequence was used with 30 orientations of diffusion gradients with b=700s.mm^{-2} (+b=0 volume): TE=72ms, TR=10s, parallel imaging GRAPPA factor 2, partial Fourier sampling factor 6/8, acquisition time 5min40s. For ***T1 mapping***, an inversion recovery (IR) SE-EPI sequence was used with 8 different values of inversion time (TI=250->1500ms each 250ms + TI=2000, 2500ms): TE=38ms, TR= TI+15s, partial Fourier sampling factor 5/8, acquisition time 2min11s. For ***T2 mapping***, a SE-EPI sequence was used with 8 different values of echo time (TE=50->260ms each 30ms): TR= 15.5s, parallel imaging GRAPPA factor 2, partial Fourier sampling factor 6/8, acquisition time 2min51s. For ***anatomical registration***, axial T2-weighted fast-spin-echo images were acquired with a high spatial resolution (1x1x1.1mm^3) in a short acquisition time (2min44s). The total acquisition time did not exceed 15min. Particular precautions were taken to minimize noise exposure, by using customized headphones, covering the magnet tunnel with a special noise protection foam, and decreasing the maximum slew rate factor of gradients in EPI sequences.

DTI post-processing Diffusion tensor parameters were estimated in each voxel using PTK/BrainVISA software [6]. Maps of fractional anisotropy (FA), longitudinal ($\lambda_{//}$) and transverse ($\lambda_{\perp}$) diffusivities and color-encoded directionality (RGB) were generated. 3D tractography was performed using regularized particle trajectories [7], from a whole-brain mask excluding voxels with low FA (<0.15) or high <D> (>2.10^{-3}mm^2.s^{-1}).

T1 and T2 mapping T1 and T2 maps were estimated using PTK software, by fitting the equations $S = \rho \cdot \left|1 - 2\exp\left(-TI/T_1\right)\right|$ and $S = \rho \cdot \exp\left(-TE/T_2\right)$ using their derivatives and employing a Levenberg-Marquardt (LM) optimizer. The maximum absolute and relative errors of the LM scheme were set to 0.0001, with a maximum number of iterations set to 500.

Regions of interest For quantification, we focused on 11 regions. First, we considered two compactly organized white matter bundles: the corpus callosum (CC), which is relatively immature, and the cortico-spinal tract (CST), which is relatively mature [8]. Regions of fiber selection and split were delineated to segment these specific tracts [8]: CC genu (CCg), body (CCb) and splenium (CCs); CST between the cerebral peduncles and the posterior limb of the internal capsule –plic (CST1), and between the plic and the low centrum semiovale (CST2). Second, regions of interest were manually drawn in the less organized frontal and parietal white matter (WMf, WMp), in the thalamus (THL) and in the cortex (CX: primary regions: central sulcus CXc and Heschl gyrus CXh; less mature frontal region CXf). Quantification of DTI, T1 and T2 indices was performed on average over the tracts and ROIs [8].

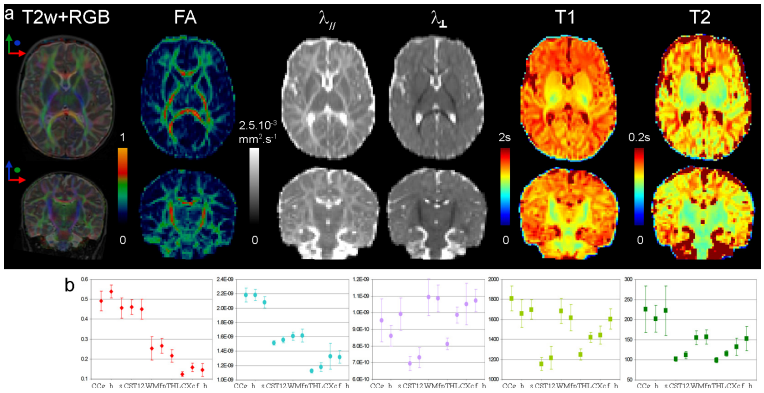

Figure 1: a: Quantification maps in a 9.7w-old infant, in axial and coronal views: DTI maps (RGB overlaid with T2w anatomy, FA, $\lambda_{//}$ and $\lambda_{\perp}$) and T1/T2 maps. b: Corresponding mean indices (FA, $\lambda_{//}$, $\lambda_{\perp}$, T1, T2) over the infant group (with standard deviations in plot bars) in the 11 regions.

R	FA	$\lambda_{//}$	$\lambda_{\perp}$	T1	T2
CCg	-0.12	0.18	0.17	0.09	0.40
CCb	**0.66**	-0.03	**-0.69**	-0.51	-0.51
CCs	0.47	-0.07	-0.40	-0.59	-0.19
CST1	**0.88**	0.57	**-0.89**	**-0.92**	**-0.77**
CST2	**0.74**	0.42	**-0.78**	**-0.87**	**-0.81**
WMf	-0.04	**-0.68**	-0.24	**-0.70**	**-0.70**
WMp	-0.05	-0.35	-0.18	-0.63	**-0.64**
THL	0.48	0.15	-0.56	**-0.82**	**-0.78**
CXc	-0.57	**-0.71**	-0.51	-0.24	-0.61
CXh	0.24	0.06	0.02	**-0.77**	-0.30
CXf	-0.01	0.16	0.16	-0.47	0.10

Table 1: Correlation coefficients between age and indices measured in the 11 regions (bold font: significant at p<0.05).

Results

Maps of high quality were obtained in all infants for DTI indices and T1/T2 relaxation times (Figure 1a). Three observations were performed through the index quantification over the 11 selected regions. **1)** Linear **age-related changes** were detected, at least for one index, in all regions except the corpus callosum genu and splenium, and the frontal cortex (Table 1). **2)** High **variability across brain regions** was observed (Figure 1b), making possible to segregate between these regions based on the different indices. The corpus callosum genu/splenium and the cortico-spinal tract present similar FA but different other indices. Cortical regions present similar $\lambda_{\perp}$ but different other indices. **3)** Specific **relationships between indices** were detected. Considering all regions and infants, FA was correlated with $\lambda_{//}$, $\lambda_{\perp}$ and T2 (R=0.79/-0.55/0.35) but not T1 (R=0.08); T1 was correlated with $\lambda_{//}$, $\lambda_{\perp}$ and T2 (R=0.59/0.63/0.79); T2 was correlated with FA, $\lambda_{//}$, $\lambda_{\perp}$ and T1 (R=0.35/0.77/0.44/0.79).

Discussion and Conclusion

This study presents a multi-parametric MRI approach to quantify cerebral tissues maturation in the infant brain. EPI sequences were used to map T1, T2 and DTI indices over the whole developing brain in a short acquisition time. Similar geometric distortions were observed in EPI images for T1/T2 mapping and DTI, which did not preclude the comparison of region location. Acquiring a further field map may help correcting these distortions. The quantified indices were in agreement with previous findings about the developing brain [8-10]. As previously described for T2* and DTI in the adult white matter [11], this study aimed at characterizing the significance of DTI, T1 and T2 indices, according to tissues, and their relationships with maturational processes. It is generally assumed that T1 and T2 rely on "spin-lattice" and "spin-spin" interactions respectively, and that DTI indices reflect water content and microscopic organisation. In the developing white matter, T1 and $\lambda_{\perp}$ may rely on axonal "pre-myelination", whereas T2 and FA rely on "true myelination" [8, 12]. FA detected early on in the cortex of premature newborns may reflect the radial orientation of dendritic arborisation [4]. Additional modelling may help to understand these physiological relationships. Our observations are partly in agreement with previous studies, and further regions of interest will be considered to confirm our results in a larger cohort of infants.

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