Clustering analysis of human infant brain maturation based on multi-parametric MR images

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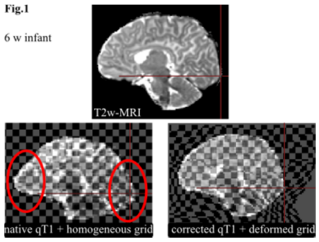
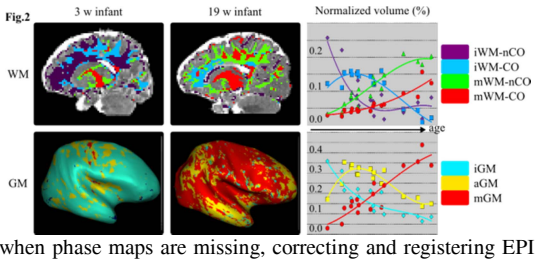
Target audience: During the first post-natal months, dendritic development and myelination are intense in the brain grey and white matters. This restricts water movement in the infant's cerebral tissues and thus consequently affects MR parameters, which can be thus used to follow maturation [1]. The rare post-mortem studies have reported asynchronous maturation within the white matter and the cortical regions [2]. Thanks to the latest advances in echo-planar imaging (EPI), quantitative mappings related to T1- and T2-relaxometries (qT1 and qT2 resp.) as well as diffusion tensor imaging (DTI) can now be acquired in infants within a limited scan duration thus providing information on cerebral brain tissues organization and maturation non-invasively [3]. Here, we took advantage of the complementarity of these quantitative imaging modalities to propose a novel approach to classify infant's cerebral tissues according to their structural organization and their degree of maturation. This work may interest researchers specialized in brain development imaging, in neuroanatomy and pediatricians.

Purpose: Previous works have shown that qT1, qT2 and DTI parameters including longitudinal diffusion ($\lambda_{//}$), transverse diffusion ($\lambda_{\perp}$) and fractional anisotropy imaging (FA) can be used to differentiate the developing gray matter (GM) and the white matter (WM) myelinating fascicles [1,4]. All these MRI quantitative parameters are indeed sensitive to changes induced by maturation. Since their maturational sensitivity differs in regards to their biophysical mechanisms, combining these parameters may better highlight the maturation asynchrony across WM bundles than univariate analyses [5]. Here we proposed to perform clustering analyses [6] on these MRI parameters to study the whole brain maturation without a priori on spatial localization for regions of interest.

Methods: Acquisition: The database included 17 sets of images obtained in spontaneously asleep healthy infants, aged from 3 to 21 weeks (corrected ages), under a protocol approved by the Institutional Ethical Committee. Spin-echo EPI sequences (1.8mm isotropic) were acquired in less than 11min on a 3T MRI Trio system using a 32-channels head coil (Siemens HealthCare, Erlangen, Germany). For DTI, 30 diffusion gradient orientations were used at b=700s.mm^{-2}. For qT1 and qT2, 8 inversion and 8 echo times were used respectively. MRI parameters (qT1, qt2, FA, $\lambda_{//}$ and $\lambda_{\perp}$) were estimated in each voxel using the Connectomist and Relaxometrist toolboxes [7]. For each subject, anatomical T2w-MRI were also acquired. Distortion correction and multimodal image registration: To be able to reliably compare the parameter maps, the first step was to correct geometrical distortions due to the use of EPI read echotrains. The common approach to correct these distortions consists of using concomitant fieldmap calibration. Because of limited acquisition time, this map was not acquired. We thus proposed to correct distortions by directly registering qT1, qT2 and DTI maps with the subject's T2w-MRI. A global rigid transformation based on mutual information (MI) was first estimated between the brains semi-automatically extracted from the images. An elastic deformation, based on cubic B-splines and using MI as a similarity criterion, was then estimated to locally improve the correction [8]. For DTI maps, deformations estimated on $\lambda_{//}$ maps were applied to $\lambda_{\perp}$ and FA maps. Clustering analysis: To classify tissues according to their different microstructural properties and their degree of maturation, a clustering analysis was performed from the registered MRI data using Gaussian Mixture Modeling based on an Expectation-Maximization algorithm and using all brains together (i.e. 5 data x 17 infants). The CSF was previously automatically removed from the data using a histogram analysis. For this experiment, the number of classes was a required input parameter. We hypothesized that characterizing the developing tissues would require at least 7 classes in infants: immature GM (iGM), averagely mature GM (aGM), mature GM (mGM), immature WM non-compactly organized (iWM-nCO), immature WM compactly organized (iWM-CO), mature WM non-compactly organized (mWM-nCO), and mature WM compactly organized (mWM-CO). To validate this hypothesis, we expected to find known results 2 (first mature WM and GM regions should be around the central sulcus). In addition, normalized volumes (defined as the volume of each class divided by the whole brain volume) were plotted as a function of age assuming that the volumes of immature classes should decrease with age while the reverse is expected for the more mature classes. To validate the clustering, we computed Dice indices between the GM and WM resulting from the clustering analysis and what was obtained through a semi-automatic segmentation obtained from T2w-MRI [9], for 4 infants with a regularly-spaced age (3w, 6w, 13 w and 19 w).





Results: This study is a proof of concept to use EPI-based quantitative imaging methods to non-invasively study human brain maturation within a reasonable acquisition time in healthy infants. Even when phase maps are missing, correcting and registering EPI sequences towards an undistorted T2w-MRI is possible using an estimation of linear and non-linear transformations. Further tests are needed to quantify this registration improvement. The clustering analysis provided partitions of brain tissues in good agreement with post-mortem studies [2]. Results interpretation is currently investigated to sort cerebral regions regarding their maturation degree to correlate these microstructural-based results with functional activities. Dice indices highlighted that some voxels were misclassified in the GM or in the WM, suggesting that performing clustering analyses on GM and on WM separately would refine the results. Unfortunately, anatomical segmentations cannot be easily obtained during the first post-natal year due to the poor and heterogeneous tissue contrast on T1w and T2w-MRI, and manual corrections are required to reliably segment the maturing GM and WM. Different number of classes will also be tested. Finally, the robustness and information value of the DTI, qT1 and qT2 parameters combination will be considered to evaluate their pertinence for the developing brain exploration.

Discussion: This study is a proof of concept to use EPI-based quantitative imaging methods to non-invasively study human brain maturation within a reasonable acquisition time in healthy infants. Even when phase maps are missing, correcting and registering EPI sequences towards an undistorted T2w-MRI is possible using an estimation of linear and non-linear transformations. Further tests are needed to quantify this registration improvement. The clustering analysis provided partitions of brain tissues in good agreement with post-mortem studies [2]. Results interpretation is currently investigated to sort cerebral regions regarding their maturation degree to correlate these microstructural-based results with functional activities. Dice indices highlighted that some voxels were misclassified in the GM or in the WM, suggesting that performing clustering analyses on GM and on WM separately would refine the results. Unfortunately, anatomical segmentations cannot be easily obtained during the first post-natal year due to the poor and heterogeneous tissue contrast on T1w and T2w-MRI, and manual corrections are required to reliably segment the maturing GM and WM. Different number of classes will also be tested. Finally, the robustness and information value of the DTI, qT1 and qT2 parameters combination will be considered to evaluate their pertinence for the developing brain exploration.

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