Creating a child brain connectivity atlas for reliable bundle identification in developmental studies

Sofya Kulikova[1], Jessica Dubois[2], Pamela Guevara[3], Jean-François Mangin[4], Catherine Chiron[5], Nicole Chemaly[5], Silvia Napuri[6], Cyril Poupon[7], and Lucie Hertz-Pannier[1]

[1]INSERM UMR1129, CEA/Neurospin/UNIACT, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [2]INSERM UMR992, CEA/Neurospin/UNICOG, Université Paris Sud, Paris, France, [3]University of Concepción/Departamento de Ingeniería Eléctrica, Chile, [4]CEA/Neurospin/UNATI, Gif-sur-Yvette, France, [5]INSERM UMR1129, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [6]Pediatric Department, CHU Hôpital Sud, Rennes, France, [7]CEA/Neurospin/UNIRS, Gif-sur-Yvette, France

Target audience: This work would be of interest to neuroscientists and clinicians interested in brain development, for example in studies of normal or pathological maturation of the brain white matter within distinct bundles.

Introduction: Diffusion imaging offers a unique tool for *in vivo* visualization of the white matter bundles using 3D tractography techniques. Normal and abnormal brain regional maturation can be studied in reconstructed bundles using different MRI parameters that quantitatively reflect various maturation processes[1]. However, tractography datasets are extremely complex and extracting individual bundles from such datasets is still a challenging task. To reliably extract bundles and overcome drawbacks of using regions of interest (ROI), either defined manually in individual subjects or based on atlases, fiber-clustering techniques, that take into account fiber shape and localization variabilities, have been recently proposed for automatic bundles identification[2], based on an atlas of main bundles. However, this atlas was generated for adults hindering its application to children as fiber shapes and lengths change during development.

Purpose: Because reliable bundle identification in children requires dedicated atlases, we describe here the creation of the first atlas of this kind in preschool children.

Methods: *Subjects and Data Acquisition:* Seventeen children (47±20 months, 17 to 81 months) with unilateral focal epilepsy were considered: 9 subjects with normal MRI (cryptogenic epilepsy) and 8 with tiny focal lesions at different locations. It was not possible to include healthy children, as it is exceptional to have them spontaneously asleep for the whole acquisition time (50min) at the considered age range. Diffusion data was acquired under sedation on a 3T system with a 32-channel head coil using a DW-SE-EPI sequence: 2mm isotropic resolution, 60 orientations of diffusion gradients, b = 1500s/mm^2 (+ 3b = 0), TE = 92ms, TR = 11s, GRAPPA reduction factor 2. Anatomical T1w images were acquired using a 3-D MP RAGE sequence with 1mm isotropic resolution. *Post-treatment of the data*: Diffusion-weighted images were corrected for motion and eddy currents artifacts[3] and co-registered with the T1w images using affine transformations. Streamline-based regularized 3D tractography[4] was performed according to a 6-order analytical Q-ball model[5]. All data was pre- and post-processed using Connectomist software[6]. *Atlas creation*: Atlas was created using a strategy similar to Guevara et al.[2], with the following steps: a) creation of an age-specific anatomical T1 template (**Fig.1**). T1w images from the cryptogenic children were non-linearly registered to a T1w template for 48-month children[7] and averaged; b) hierarchical intra-subject fiber clustering in each individual subject[8]. Each cluster centroid minimizes the sum of the symmetrized mean closest point distances[2,8] to the fibers within that cluster; c) inter-subject clustering of the clusters obtained in all subjects. Among the resulting clusters only those were kept that included centroids from at least half of the subjects; d) manual selection and labeling of the inter-subject clusters (**Fig.2**); e) adapting classification thresholds for bundle labeling in new subjects using a leave-5-out strategy. The thresholds were selected as the values giving the maximum ratio between correctly selected clusters and false positives. *Atlas application*: Bundle identification in a new subject starts with an intra-subject fiber clustering and the calculated cluster centroids are transformed to the template space using affine transformations. Each centroid of the new subject is then labeled by the closest centroid of the atlas, assuming that the distance between them does not exceed the classification threshold.

Results and Discussion: The generated atlas included 8 white matter bundles, each containing several cluster centroids, as shown in **Fig.2**. As 9 out of 17 children (53%) had normal-appearing MRI images, and the rest 8 subjects had only tiny lesions differently distributed over the brain, it is unlikely that lesion-affected clusters were included in the atlas. Classification thresholds identified for these bundles were close to those reported in the adult atlas[2]; however, applying adult atlas to the same children data failed to detect any of the bundles, stressing out that it was important to create atlas and its anatomical template from children data. Indeed, our children atlas allowed automatic identification of all considered white matter bundles in all subjects (**Fig.3A**), except for arcuate fasciculus (missing in one subject), and fronto-occipital fasciculus (not detected in 2 subjects). The shapes of the reconstructed bundles were highly variable across the subjects, but not depending on age. Nevertheless artefacts were observed in some individual reconstructions: in certain subjects, reconstructed cortico-spinal tract also included fibers from spino-thalamic tract and reconstructed arcuate fasciculus included fibers from the extreme capsule. This suggests that using more shape-sensitive distance measures for fiber clustering may further improve the quality of bundle reconstruction. Nevertheless, even at the current stage evaluation of the fractional anisotropy (FA) across the reconstructed bundles was able to capture age-related increases with different slopes across the bundles (**Fig.3B**), showing the relevance of this approach for studies on white matter regional maturation.

Conclusions: Although still in progress, this atlas demonstrated its potentials for automatic bundles identification in preschool children. It thus opens the way to studies of normal and abnormal brain regional development. Furthermore, it may be also used to analyze white matter microstructural properties when it is not possible to perform reliable tractography (e.g. in case of white matter diseases, like demyelination) by projecting the atlas to the subject data.

References: 1. Kulikova et al. (Brain Struct Funct, 2014); 2. Guevara et al. (NeuroImage, 2012); 3. Dubois et al. (Magn Reson Imaging, 2014); 4. Perrin et al. (Inf Process Med Imaging Proc Conf, 2005); 5. Descoteaux et al. (Magn Reson Med, 2007); 6. Duclap et al. (ESMRMB 2012, #842); 7. Dean et al. (NeuroImage, 2014); 8. Guevara et al. (NeuroImage, 2011).

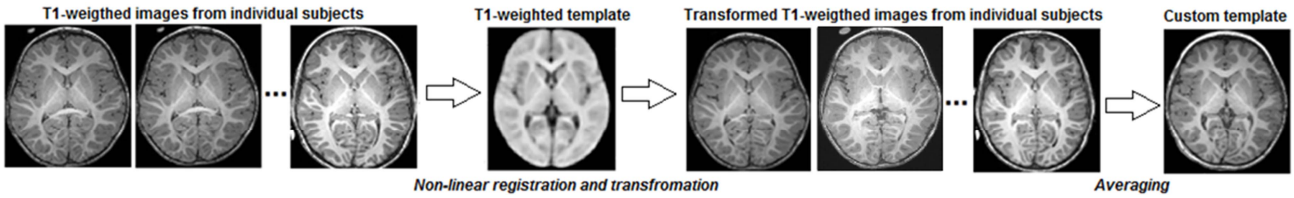

Fig.1 Creation of an age-specific anatomical template

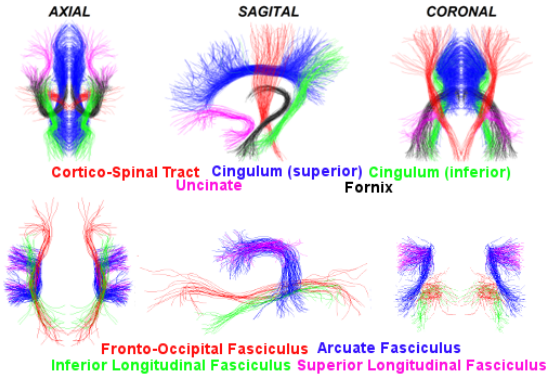

Fig.2 White matter bundles of the atlas

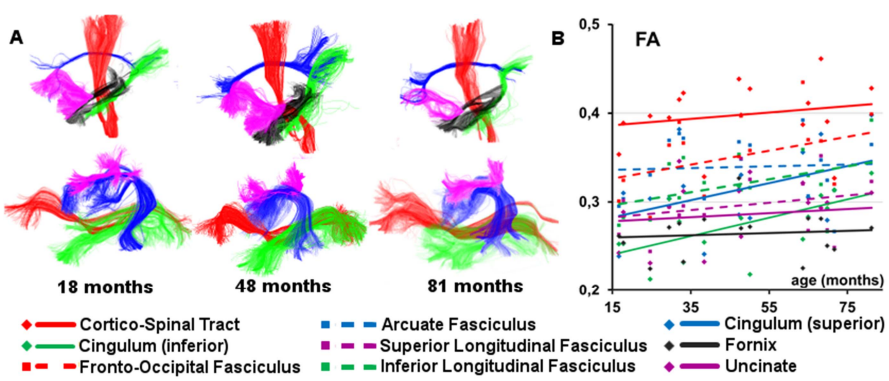

Fig.3 A) Identified bundles in selected subjects. B) Age-related changes in FA across the identified bundles.