Exploring the early organization and maturation of linguistic pathways in the human infant brain

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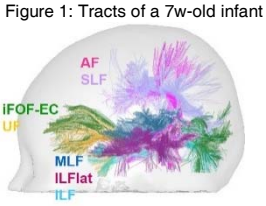
Target audience: White matter myelination is a complex and long-lasting process which occurs during normal brain development at different times and speeds depending on bundles and underlying networks[1]. It can be explored non-invasively in babies using diffusion tensor imaging (DTI), which provides quantitative structural markers reflecting various maturational mechanisms. Since fiber myelination drastically accelerates the speed of information transfer between brain regions, DTI parameters are also expected to reflect the functional efficiency of brain networks during infancy[2]. We focused here on the developing language network to demonstrate how different pathways assumed to support different functional processing, can be distinguished according to their microstructure and maturation based on DTI parameters. This study may be of particular interest for researchers specialized in imaging of brain development, and for pediatricians.

Figure 1: Tracts of a 7w-old infant



Purpose: Infants listening to speech activate perisylvian regions from the preterm period on[3]. To understand how these temporal and frontal regions collaborate during the first stages of language acquisition, we investigated the development of the main white matter bundles connecting these regions in the infant's brain. Using diffusion imaging, the main bundles of the language network were dissected [4,5]: for dorsal pathway (assumed to support phonological processing), the arcuate and superior longitudinal fascicles (AF and SLF); for ventral pathway (assumed to support semantic processing), the inferior fronto-occipital fasciculus / extreme capsule (iFOF-EC), the middle (MLF) and inferior (ILF) longitudinal fascicles and lateral branches (ILFlat) and the uncinate fasciculus (UF). The maturation asynchrony between these bundles was further evaluated over the first post-natal weeks using original analyses of DTI parameters.

Methods: Acquisition: 21 healthy 6 to 22 week-old infants and 17 young adults were studied under a protocol approved by the regional ethical committee. Acquisitions were performed during spontaneous sleep on a 3T MRI system (Tim Trio, Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil. A diffusion-weighted (DW) spin-echo single-shot EPI sequence was used: 1.8mm isotropic spatial resolution, GRAPPA acceleration factor 2, TE = 72ms, TR = 10s/14s for 50/70 slices in infants and adults resp. After the acquisition of the b=0 volume, diffusion gradients were applied along 30 orientations with b=700s.mm^{-2} (acquisition time: 5min40s). Post-processing: DW images were processed using Connectomist software[6]. After correction for motion artifacts[7], whole-brain tractography was performed using an analytical Q-ball model[8] and a streamline-based algorithm with regularization[9], particularly adapted to reconstruct immature bundles despite low anisotropy[10]. Bundles were dissected using regions of interest and of exclusion delineated manually for each subject using Anatomist software[11]. Since DTI parameters provide complementary information on both the white matter organization and maturation[12], fractional anisotropy FA, longitudinal $\lambda_{//}$ and transverse $\lambda_{\perp}$ diffusivities were quantified over the tracts, and analyzed jointly in both the infant and adult groups. Because these parameters vary across bundles even at the mature stage[13], parameters in infants were further divided by the corresponding median over the adult group ("normalized parameters": nFA, $n\lambda_{//}$ and $n\lambda_{\perp}$). Statistical analyses: To explore whether linguisitic bundles may be grouped into classes, hierarchical clustering was performed using Euclidean distances and average linkage approach (implemented in Python with NumPy and StatsModels[14]): 1) based on FA, $\lambda_{//}$ and $\lambda_{\perp}$ over the adult group to examine similarities in microstructural properties, 2) based on nFA, $n\lambda_{//}$ and $n\lambda_{\perp}$ over the infant group to consider similarities in maturational properties. ANOVAs with Tukey analyses were also conducted on each parameter to highlight the effect of resulting classes, after computing the average over all bundles of each class. We finally focused on age-related changes in $n\lambda_{\perp}$ to investigate differences in maturational patterns across pathways.

Figure 2

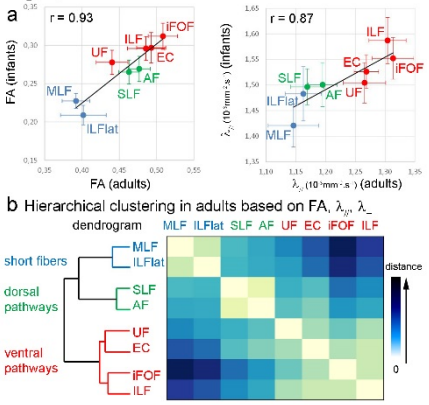
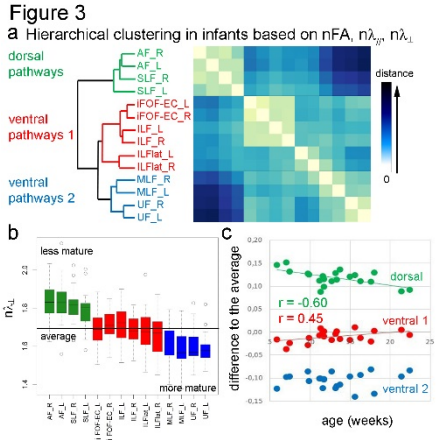


Figure 3



Results: Bundles were reconstructed in all infants (Fig1) and adults, showing similar trajectories. Although DTI values were extremely different in infants and adults, the FA and $\lambda_{//}$ medians across bundles were strongly correlated between groups (Fig2a). The trend was not significant for $\lambda_{\perp}$, suggesting that this parameter in infants is affected by the differences in maturation levels across bundles, and thus is more sensitive to maturational changes than FA and $\lambda_{//}$. In the ***adult group***, the hierarchical clustering on FA, $\lambda_{//}$ and $\lambda_{\perp}$ demonstrated three ***"microstructural classes"*** (Fig2b): 1) short-distance fibers (MLF and ILFlat), 2) dorsal pathways (AF and SLF), and 3) ventral pathways (UF, iFOF-EC, ILF). ANOVAs with Tukey analyses confirmed the similar segregation in infants, particularly in terms of FA and $\lambda_{//}$. In the ***infant group***, the hierarchical clustering on the normalized values (nFA, $n\lambda_{//}$ and $n\lambda_{\perp}$) demonstrated three ***"maturational classes"*** (Fig3a): 1) dorsal pathways (AF and SLF), and two classes of ventral bundles: 2) iFOF-EC, ILF, ILFlat; 3) MLF, UF. The results were similar when only $n\lambda_{\perp}$ was considered. ANOVAs with Tukey analyses confirmed the classification particularly in terms of $n\lambda_{\perp}$. Dorsal bundles actually displayed the highest $n\lambda_{\perp}$ (Fig3b), meaning a delayed maturation compared with ventral bundles. Furthermore, age-related decreases in $n\lambda_{\perp}$ were observed in the three classes, but the patterns of maturation differed. With increasing age, the dorsal and ventral classes got closer to the average over all bundles (Fig3c). Indeed, the difference in $n\lambda_{\perp}$ between the dorsal and ventral classes significantly decreased with age, demonstrating that the maturation of dorsal pathways caught up the maturation of ventral pathways during the first post-natal weeks.

Discussion: Using diffusion imaging, tractography and DTI parameters, we demonstrated structural similarities between infants and adults in the organization and microstructure of the bundles of the language network. Especially, a segregation between dorsal and ventral pathway was clearly seen at both ages. According to normalized transverse diffusivity, we further highlighted the developmental calendar of these bundles. The ventral pathway starts maturing before the dorsal pathway, confirming a previous study[15]. Nevertheless the maturation of dorsal pathway catches up during the first post-natal months. This fast development, highlighted with brain structural markers, might be related to the language progresses at this age and in particular the development of speech cross-modal representations.

References: [1] Yakovlev and Lecours, 1967. [2] Dubois et al, J Neurosci 2008. [3] Mahmoudzadeh et al, PNAS 2013. [4] Catani and Thiebaut de Schotten, Cortex 2008. [5] Turken and Dronkers, Front Syst Neurosci 2011. [6] Duclap et al, Proceedings ESMRMB 2012. [7] Dubois et al, Magn Reson Imaging 2014. [8] Descoteaux et al, Magn Reson Med 2007. [9] Perrin et al, Inf Process Med Imaging 2005. [10] Dubois et al, Hum Brain Mapp 2008. [11] Rivière et al, Proceedings OHBM 2000. [12] Dubois et al, Neuroscience 2014. [13] Kulikova et al, Brain Struct Funct 2014. [14] Seabold and Perktold, Proceedings of Python in Science Conference 2010. [15] Brauer et al, Brain Lang 2013.