Relating the structural and functional maturation of visual and auditory white matter pathways with diffusion imaging and event-related potentials in infants

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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]. Diffusion tensor imaging (DTI) provides quantitative markers of the tissues microstructure that reflect various mechanisms of structural maturation in the healthy infant brain[2]. Since fiber myelination drastically accelerates the speed of information transfer between brain regions (i.e. the speed of electrical impulses passing through axons)[3], DTI parameters are also expected to reflect the functional efficiency of brain networks during infancy, particularly transverse diffusivity ($\lambda\perp$) which might be the best DTI marker of myelination[4-6]. Our aim was to evaluate, in infants, the relationships between the structural maturation of white matter bundles and the maturation of corresponding functional responses assessed with high density EEG. This study may be of particular interest for researchers specialized in brain development and diffusion imaging, as well as for pediatricians and clinicians.

Purpose: A previous study[5] demonstrated that the conduction speed of visual information between the stimulus presentation and its early perception in the visual cortex was related more to the optic radiations maturation than to the infants' age. In this study, we tested this relationship by considering two different responses to lateralized stimuli for both the visual and auditory modalities: 1) the early lateralized responses (measured in occipital and temporal regions resp. in the hemisphere contralateral to the stimulus presentation), conducted by projection bundles (optic and acoustic radiations resp.), 2) the inter-hemispheric transfer of responses (from the contra- to the ipsilateral hemisphere), conducted by associative corpus callosum fibers (connecting occipital and temporal regions resp.). We investigated whether inter-individual differences in the conduction speed of ERP functional responses can be explained by differences in $\lambda\perp$ measured in the corresponding tracts, while taking into account the infants' age.

Methods: *Subjects:* 15 healthy infants aged between 6 and 22 weeks were tested in MRI and EEG experimental protocols within a few days (<1 week) of delay. EEG data were reliably recorded for 13 infants for the visual experiment, 12 for the auditory experiment. *Assessing structural maturation with DTI:* 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. After the acquisition of the b=0 volume, diffusion gradients were applied along 30 orientations with b=700s.mm^{-2} (acquisition time: 5min40s). After correction for motion artifacts[7] with Connectomist software[8], probabilistic tractography was performed based on a 2-crossing-fiber diffusion model[9] with FSL software[10]. Using individual seed regions, we identified 6 tracts in each infant's brain: left and right optic and acoustic radiations, callosal fibers connecting occipital and temporal regions. $\lambda\perp$ was quantified on average over each tract by taking into account fiber density[11]. *Assessing functional maturation with ERP:* Infants were presented with lateralized stimuli over many trials (for visual experiment: a face picture at left or right visual hemifield; for auditory experiment: a syllable at left or right ear), while recording continuous EEG with a geodesic 128-electrode net (EGI®). For both the visual and auditory experiments, ERP responses were computed by averaging non-artifacted trials, and we determined the latency of the first positive peak (P1) in the contralateral hemisphere, and the transfer latency between contra- and ipsilateral P1. For each of the four responses (visual and auditory P1 and P1 transfer), conduction speed was computed from the latency to take into account inter-individual differences in brain size and thus in bundles length. *Relationships between structural and functional maturation:* Linear models were used to explain inter-individual differences in conduction speeds according to age and microstructural measures ($\lambda\perp$) of the corresponding tracts. Averaged values over left and right hemispheres were considered since tractography cannot dissociate left->right vs right->left callosal fibers.

Results: All tracts were successively reconstructed, with a coherent organization of visual and auditory callosal fibers within the splenium (Fig1a). $\lambda\perp$ showed significant decreases with age in all tracts ($r \leq -0.61$, $p<0.01$). For both the visual and auditory functional experiments, lateralized ERP responses were observed: first in the contralateral hemisphere, then in the ipsilateral hemisphere (transfers were identified in all but one subject) (Fig1b). Conduction speeds showed significant increases with age, except for the transfer of auditory responses (Tab1). Linear models showed that speeds for the visual P1 and transfer responses were better explained by the maturation of corresponding tracts ($\lambda\perp$ in the optic radiations and visual callosal fibers resp.) than by age (Tab 1, Fig1c). On the contrary, speeds for auditory P1 and transfer responses were not reliably explained neither by the tract maturation nor by age (Tab1).

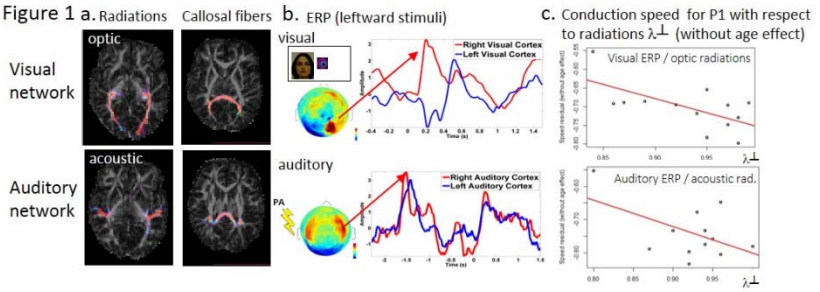

Table 1.	Model: speed = a . age + c	Model: speed = a . age + b . λ + c		
Speed			age	λ
Visual P1	R2 = 0.51, F = 11.9, p = 0.005	R2 = 0.64 , F = 9.24, p = 0.005	t = 1.57 , p = 0.14	t = -1.92 , p = 0.08
Visual transfer	R2 = 0.53, F = 11.49 , p = 0.007	R2 = 0.69 , F = 10.15 , p = 0.005	t = 0.88 , p = 0.40	t = -2.15, p = 0.06
Auditory P1	R2 = 0.3 , F = 4.254 , p = 0.06	R2 = 0.41, F= 3.16 , p = 0.09	t = 0.68 , p = 0.51	t = -1.32 , p = 0.22
Auditory transfer	R2 = 0.12 , F = 1.3 , p = 0.28	R2 = 0.13, F= 0.6 , p = 0.57	t = 0.35 , p = 0.73	t = -0.21 , p = 0.84

Discussion and conclusion: We investigated anatomo-functional relationships within the developing visual and auditory networks, by using, in the same infants, diffusion imaging to assess the structural maturation of white matter pathways on one hand, and ERP experiments to assess the functional maturation of brain responses on the other hand. In addition to the age effect patterns observed in structural and functional indices separately, we evaluated whether the speeds associated with visual or auditory P1 and inter-hemispheric transfer could be explained by the maturation of white matter tracts (i.e. optic and acoustic radiations and interhemispheric callosal fibres) conducting the functional information between involved cerebral regions. The observation of different results for the visual and auditory networks might be related to their asynchronous maturation: the maturation of visual network is particularly intense during the first post-natal weeks, while the maturation of auditory network is protracted over a longer time period. Moreover, earlier maturation of projection pathways than callosal pathways might explain the observed differences between the speeds for P1 and for transfer of auditory responses. Therefore, evaluating infants along a larger age range may help in identifying the time periods across development at which the networks structural maturation would allow quantification of their functional maturation. Considering larger cohorts of infants might also help in increasing the statistical significance of results. One other possibility is that stronger ipsilateral connections in the auditory network may mask the callosal transfer and subsequently its maturational impact on functional efficiency of the interhemispheric transfer of the auditory responses. Such correlation study may help to understand whether functional development might be "predicted" from early structural MRI, when functional studies cannot be easily implemented.

References: [1] Yakovlev and Lecours, 1967. [2] Dubois et al, Neuroscience 2014. [3] Song et al, NeuroImage 2003. [4] Song et al, NeuroImage 2005. [5] Dubois et al, J Neurosci 2008. [6] Baumann and Pham-Dinh, Physiol Rev 2001 [7] Dubois et al, Magn Reson Imaging 2014. [8] Duclap et al, Proceedings ESMRMB 2012. [9] Behrens et al, NeuroImage 2007. [10] http://fsl.fmrib.ox.ac.uk/fsl [11] Hua et al, NeuroImage 2008.