Asymmetry of White Matter Pathways in the Human Brain: Fetal, Neonatal, and Toddler Stages

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TARGET AUDIENCE

Neuroradiologists and neuroscientists interested in brain development.

PURPOSE

The left and right sides of the human brain contribute asymmetrically to different kinds of information processing. Recent studies suggest that left-right differentiation of structure and function enhances the functional capacity of the brain (e.g. Halpern et al., 2005), and therefore studying the developmental emergence of the brain asymmetry will provide key information on the functional capability of the human brain. We aimed to describe and quantify emerging asymmetry of a major migration-related pathway (ganglionic eminence) and white matter pathways including limbic (cingulum, fornix) and association pathways (inferior longitudinal fasciculus [ILF], inferior fronto-occipital fasciculus [IFOF], and arcuate fasciculus [AF]) in fetal, newborn, and children younger than 3 years old, using high angular resolution diffusion imaging (HARDI) tractography.

METHODS

We included in this study *ex vivo* fetal and postnatal brains along with living postnatal baby brains, which allowed us to see detailed brain pathways starting from an early fetal period (15 gestational weeks [GW]). Human fetal brain specimens of 17GW and 20 GW were imaged using a 4.7T Bruker MR system. Additionally, premature newborns (30GW, 34GW), term-birth newborns (40 GW), toddlers (2 years old) were imaged *in vivo* using a 3T Siemens MR system. A 3D diffusion-weighted spin-echo echo-planar imaging (EPI) sequence (60 diffusion-weighted and 1 non-diffusion-weighted measurements), TR/TE 1000/40 ms, with b = 8,000 (for *ex vivo*) and b = 1,000 (for *in vivo*), ∂/Δ= 12.0/24.2 ms was performed. Spatial resolution ranged from 400 x 500 x 550 µm to 2 x 2 x 2 mm depending on the brain size. Tractography pathways were reconstructed by Diffusion Toolkit using a streamline algorithm with an angle threshold of 40°. Pathways were segmented in each subject, using TrackVis. Volume and diffusion properties [fractional anisotropy (FA) and apparent diffusion coefficient (ADC)] were obtained on the identified tracts to explore emerging asymmetry.

RESULTS

The ganglionic eminence (GE) pathway was very thick at 15GW, and contained several branching pathways in the most anterior and posterior parts of the GE pathway that entered into the cerebral mantle (**Fig. 1, white arrowheads at 15GW**). The thickness of the GE pathway gradually decreased by 22GW, but it was still a coherent, dense bundle having the branching pathways (**white arrowheads**). At 30GW and 34GW, the GE pathway became significantly thinner and sparse.

The fornix was the thickest at and before 21GW, and became thinner at later developmental stages, but the change in the thickness was not as obvious as in the GE pathway. The cingulum was smooth and thin at and before 21GW, having very short branches in both anterior and posterior regions (**Fig. 1, yellow arrowheads at 15GW**). The branching pathways became longer and more obvious at later stages (**yellow arrowheads**). The main body of the cingulum was not extended into ventral brain regions before 40GW, but pathways were observed extending to the medial, inferior frontal regions and parahippocampal regions at and after 40GW (**Fig. 1, blue arrowheads**).

The ILF was dense at 21GW and 30GW. Both the ILF and IFOF became significantly longer during development. The AF was hardly identifiable before 30GW, and it became evident by tractography at 30GW. Until 34GW, the AF was sparse and short, and did not have obvious branches from the main body of the tract. At 40GW, short branching pathways from the main body of the tract became identifiable (**Fig. 1, red arrowheads;** the arrowheads are not shown in later stages for a visualization purpose), and they became longer at later developmental stages. The main body of the AF continuously became thicker by 3Y.

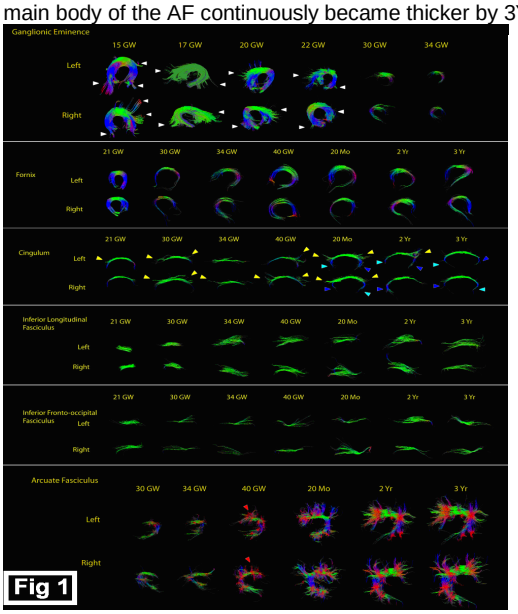

Fig 1

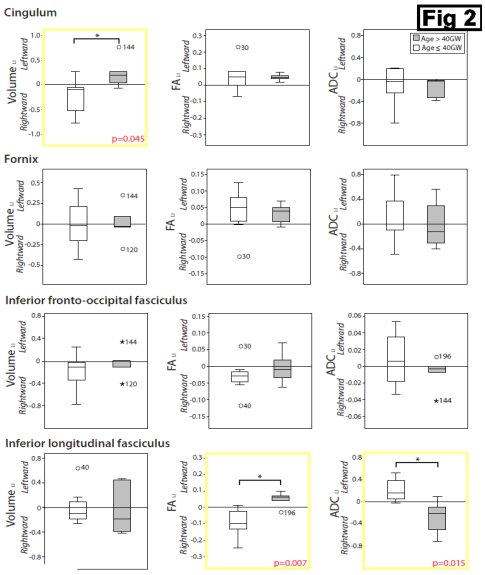

Fig 2

Age-related development of laterality was not observed in the ganglionic eminence, cingulum, and fornix. Among the studied cortico-cortical association pathways (ILF, IFOF, and AF), only the ILF showed the age-related development of laterality in the FA and ADC values: laterality indices (LIs) for these values were positively correlated with the age.

Furthermore, LIs for FA and ADC values started to deviate from symmetry around 40 GW. The ILF showed a significant leftward asymmetry in FA in brains aged >40 GW, and a significant rightward asymmetry in ADC in brains aged >40 GW (**Fig. 2**).

We finally tested correlations of the LIs of volume, FA, and ADC for all the identified pathways. The age-related two LIs (FA and ADC for ILF) were inversely correlated. During myelination process, it has been reported that FA increases and ADC decreases, and FA and ADC are inversely correlated.

DISCUSSION and CONCLUSION:

Our results suggest that the ILF compared to the IFOF and AF develops laterality during the very early developmental stage before 3 years old. Leftward dominant myelination may proceed in ILF during the early developmental stage, and the development of the IFOF and AF may proceed differentially from that of the ILF.