Developing Connectivity in Human Fetal Brains: Emerging Regional Variations

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Introduction: Examination of the three-dimensional axonal pathways in the developing brain is key to understanding the formation of cerebral connectivity. By tracing fiber pathways throughout the entire brain, diffusion tractography provides information that cannot be achieved by conventional anatomical MR imaging or histology. However, standard diffusion tractography (based on diffusion tensor imaging, or DTI) tends to terminate in brain areas with low water diffusivity, indexed by low diffusion fractional anisotropy (FA), which can be caused by crossing fibers as well as fibers with less myelin. For this reason, DTI tractography is not effective for delineating the structural changes that occur in the developing brain, where the process of myelination is incomplete, and where crossing fibers exist in greater numbers than in the adult brain [Innocenti & Price 2005]. Using high-angular resolution imaging (HARDI) tractography, we imaged development of cerebral fiber pathways in human fetal specimens ranged from 18 to 33 post-gestational weeks.

Methods: We performed scans on human fetal brain specimens of post-gestational week 18 (18 W), 20 W, 22 W, 24 W, 31 W, and 33W. We scanned two samples for each timepoint. Brains were removed from the cranium and fixed in 4% paraformaldehyde containing 1 mM gadolinium (Gd-DTPA) MRI contrast agent for at least 1 week to reduce the T1 relaxation time while ensuring that enough T2 -weighted signal remained. For MR image acquisition, the brains were placed in the Fomblin solution (Fomblin Profludropolyether; Ausimont, Thorofare, NJ). We used 4.7T Bruker Biospec MR system. The pulse sequence used for image acquisition was a 3D diffusion-weighted spin-echo echo-planar imaging (EPI) sequence, TR/TE 1000/40 ms, with an imaging matrix of 112 x 112 x 112 pixels. Spatial resolution was around 550 x 550 x 550 μm, but varied slightly depending on the brain size. We performed high angular resolution imaging (Tuch et al., 2003). Briefly, we acquired 61 diffusion-weighted measurements, corresponding to a cubic lattice in Q-space with b = 8,000, with small delta = 12.0 ms, large delta = 24.2 ms. The total acquisition time was 2 hours for each experiment. Diffusion Toolkit and TrackVis (http://trackvis.org) were used for reconstructing and visualizing tractography.

Figure 1

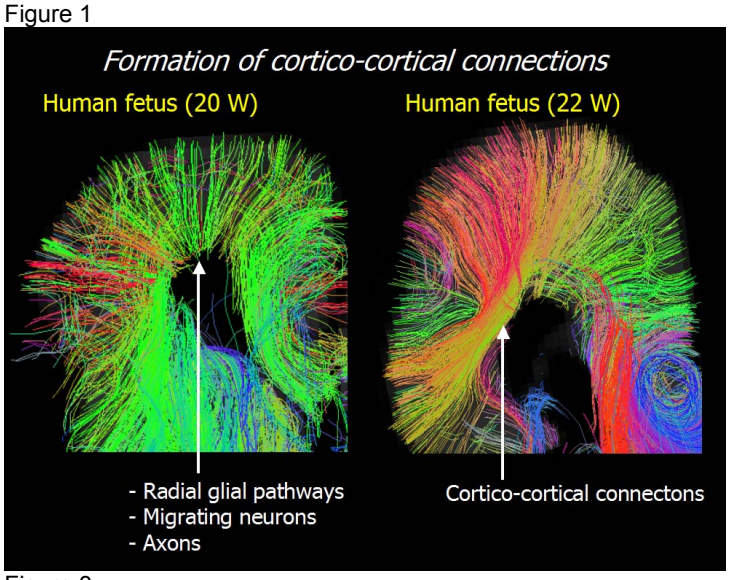


Figure 2

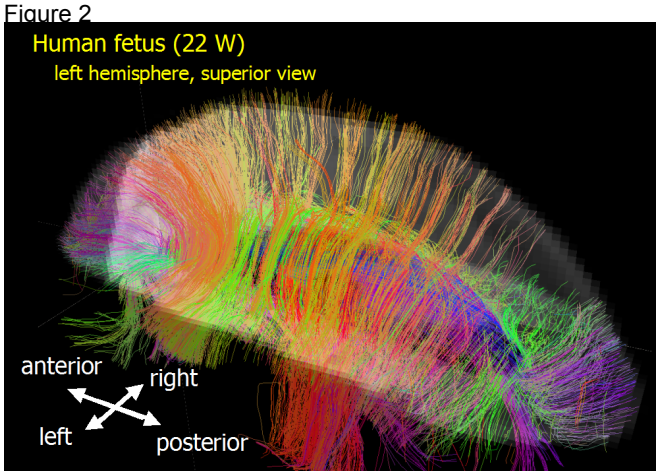
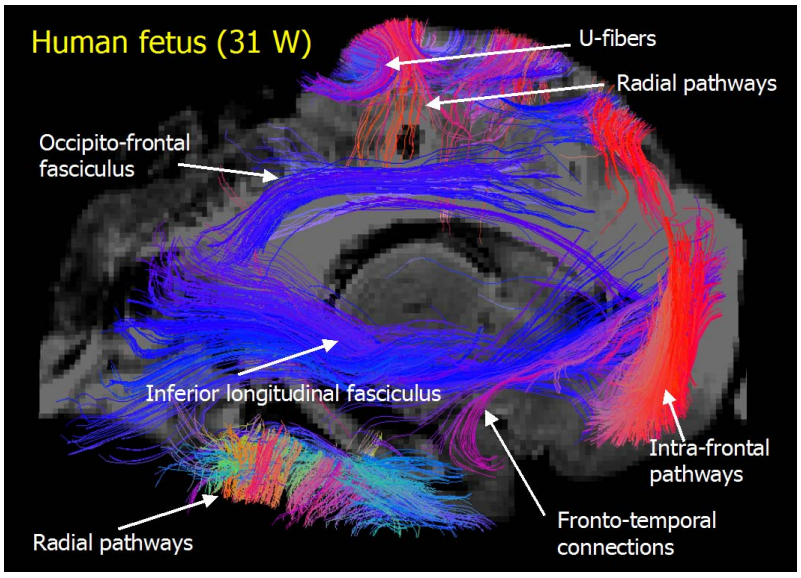


Figure 3



Results & Conclusions

18W and 20W: Dominant radial pathways from the ventricular margin to the brain surface were found across most of the brain areas (Fig.1 left). At these stages, the radial pathways contain radial glial pathways, migrating neurons, and axons from those neurons [Rakic 2009]. We also observed intracortical horizontal short pathways that may reflect forming horizontal interneuron connections. Projection pathways were already observed at these stages.

22W and 24 W: Coherent intrahemispheric cortico-cortical connections were emerging in specific regions in the brain. Although radial pathways still remained, they were less dominant (Fig.1 right). One parasagittal group of intrahemispheric cortico-cortical connections formed a coherent structure in the anterior-posterior direction (predominantly orange fibers in Fig. 2).

31W and 33W: Coherent groups of short- and long-range intrahemisphere association pathways were emerging (Fig. 3). Coincident with gyrification, subcortical U-fibers emerged. Radial pathways from the ventricular margin to the brain surface were further reduced at these ages, and showed regional variability being more pronounced in the temporal regions.

These results demonstrate that HARDI tractography can detect radial migration and emerging connectivity during fetal development. In addition a more homogeneous cerebral mantel gives rise to one with more regional variation suggesting emerging regional specification and connectivity. Therefore, HARDI tractography has the potential to map morphological changes in unmyelinated low FA areas critical to fetal growth and development and provides a new tool for evaluating emerging connectivity.

References

Innocenti GM and Price DJ. Exuberance in the development of cortical networks. Nat Rev Neurosci. 2005.
Tuch DS, Reese TG, Wiegell MR, Wedeen VJ. Diffusion MRI of complex neural architecture. Neuron 2003.
Rakic P Evolution of the neocortex: a perspective from developmental biology. Nat Rev Neurosci. 2009.