Development of Cerebellar Connectivity in Fetal Human Brains Revealed by Diffusion Tractography

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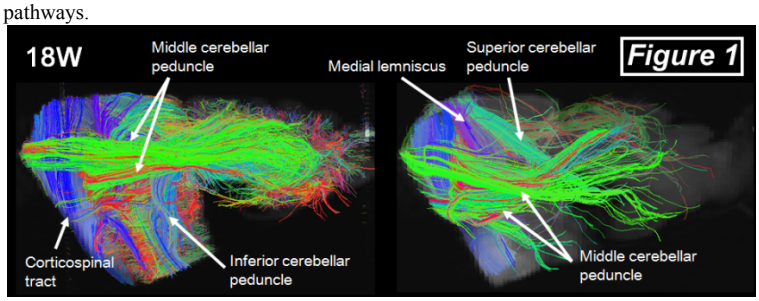
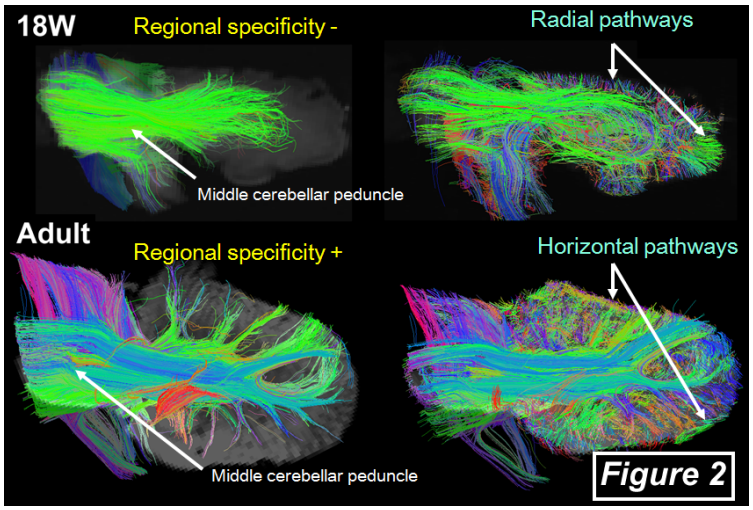
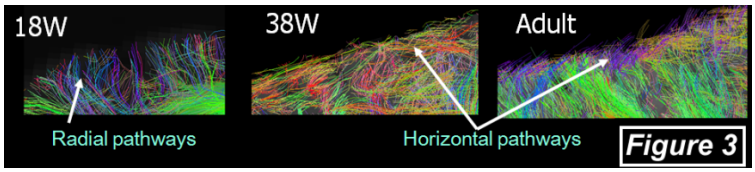
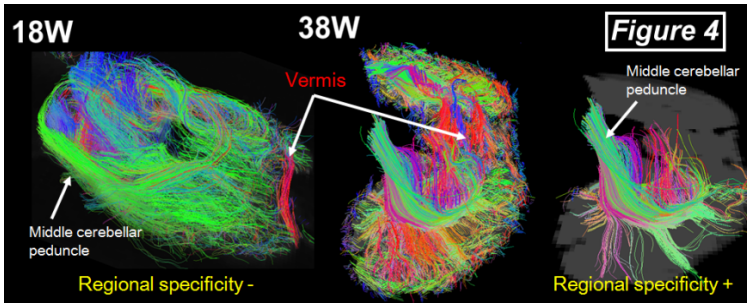
Introduction: The developmental time-course of the cerebellum is unique compared to the cerebrum **[1]**, and the cerebellum plays crucial roles not only in motor functions but also in higher cognitive functions in humans **[2]**. However, our understanding of the human cerebellum development has not advanced at the same level as our understanding of the cerebral development, because it is especially difficult to image 3-dimensional cerebellar connectivity using diffusion tractography due to the following reasons: 1) there are many narrow folia and therefore detecting tractography pathways in one folium are easily contaminated with a neighboring folium, and 2) there are many crossing axonal pathways in the cerebellum. High-angular resolution diffusion imaging (HARDI) has been proposed as an alternative to diffusion tensor imaging (DTI) for improved resolution of crossing fiber pathways **[3]**, and is effective for delineating the structural changes that occur in developing fetal (preterm) brains **[4, 5]**. Here, we applied HARDI tractography to intact postmortem fetal cerebellums to explore the 3-dimensional development of cerebellum pathways.









Methods: We used human fetal cerebellum specimens of post-gestational week (W)18, W22, W31, W38, as well as adult cerebellum specimens (two samples for each time point), using a 4.7T Bruker Biospec system. We performed a 3D diffusion-weighted spin-echo echo-planar imaging (EPI) sequence (61 measurements), TR/TE 1000/40 ms, with b = 8,000, small/large delta = 12.0/24.2 ms, spatial resolution 320 x 380 x 380 µm for W18-22, 425 x 425 x 500 µm for W31 and W38, and 600 x 730 x 760 µm for adult. The color-coding of fibers is based on a standard RGB code (Blue: dorsal-ventral, Red: right-left, Green: anterior-posterior).

Results:

Tractography at W18-W22: Superior, middle, inferior cerebellar peduncles were already imaged along with the corticospinal tract and the medial lemniscus at these stages (**Fig. 1**). Although main tracts of the cerebellar peduncles already developed, there was not obvious regional specificity at these stages (**Fig. 2 upper left**). The cerebellar cortex contained abundant radial pathways (**Fig. 2 upper right, Fig. 3**) but not horizontal pathways observed in later stages. An immature form of the cerebellar vermis was imaged (**Fig. 4**).

Tractography at W31- W38: Horizontal pathways were emerging in the cerebellar cortex increasing their densities (**Fig. 3**). The cerebellar vermis contained an increased number of pathways (**Fig. 4**). Regional specificity gradually became evident at these stages.

Tractography in the adult: Cerebellar peduncles were clearly imaged with regional specificity (**Fig. 2**). The upper half of the middle cerebellar peduncle at the level of pons projected to lower cerebellar hemisphere (blue in **Fig. 2 lower left**), and the lower half of the middle cerebellar peduncle at the level of pons projected to upper cerebellar hemisphere (green in **Fig. 2 lower left**), which was not clear at 18W (**Fig. 2 upper left**). Horizontal pathways further increased the densities in the cerebellar cortex (**Fig. 3**).

Conclusion: Our results show the usefulness of HARDI tractography to image developing cerebellar connectivity. We observed regression of radial organization in the cerebellar cortex and the emergence of regional specificity of cerebellar peduncles that were similar to our previous observations on the development of cerebral cortex **[6].**

References: **[1]** Volpe, 2008; **[2]** Schmahmann et al., 2006; **[3]** Tuch et al. 2003. Neuron, 40, 885-895. **[4]** Takahashi et al. 2010a. Neuroimage 49, 1231-1240. **[5]** Takahashi et al. 2010b. Cerebral Cortex (published online, DOI: 10.1093/cercor/bhq084). **[6]** Takahashi et al. 2010c. ISMRM 2010 abstract.