High-Angular Resolution Diffusion Tractography of Emerging Cerebellar Pathways from Newborns to Young Adults

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TARGET AUDIENCE: Neuroradiologists and neuroscientists interested in brain development.

PURPOSE: We aimed to describe the evolution of the cerebellar pathways of the superior (SCP), middle (MCP), inferior peduncles (ICP) and the deep nuclei (DN) in developing human subjects ranging from newborn to adult, using high angular resolution diffusion imaging (HARDI) tractography. The ICP primarily contains fibers from/to the inferior olivary (IO) nucleus related to proprioceptive sensory and motor vestibular inputs and outputs for balance and posture maintenance. The MCP contains two dissociated pathways: 1) pathways from the rostral pons to the inferior cerebellum (MCP-1) attributed with a sensory-motor function and 2) pathways from the caudal pons to the superior cerebellum (MCP-2) attributed with a higher cognitive function. The SCP pathways are the primarily output pathways from the cerebellum. The DN integrate afferent information from the middle and inferior peduncles and from the cerebellar cortex producing the efferent fibers of the SCP.

METHODS:

***<u>Imaging</u>*:** For 60 apparently healthy individuals, aged 30GW to 28Y, we performed T1-weighted MPRAGE imaging, T2-weighted turbo spin-echo imaging, and an isotropic 3D diffusion-weighted spin-echo echo-planar imaging. Thirty diffusion-weighted measurements (b = 1,000 sec/mm^2) and five non-diffusion-weighted measurements (b= 0 sec/mm^2) were acquired on a 3T Siemens MR system with TR= 10 sec; TE= 88 msec; small delta= 12.0 ms; large delta= 24.2 ms; field of view= 22 x 22 cm; slice thickness= 2.0 mm; matrix size= 128 x 128, iPAT= 2.

<u>Diffusion Data Reconstruction for Tractography:</u> DiffusionToolkit and TrackVis (trackvis.org) were used to reconstruct and visualize tractography pathways. A streamline algorithm with a 45° angle threshold was applied for the fiber reconstruction using all HARDI-detected local maxima.

***<u>Tract Delineation and Quantification</u>*:** A coordinate-based tractography atlas was used to guide ROI placement in order to delineate the pathways of interest. Fractional anisotropy (FA), apparent diffusion coefficient (ADC), number, length, and volume of tracts per pathway were quantified in each subject. Pathways were color-coded as described in **Fig. 1**.

RESULTS: Examples of cerebellar tracks in developing brains are provided in **Figs. 1 & 2**, and sample quantitative growth curves are provided in **Figs. 3 & 4**.

1. Number and volume of all studied pathways increased progressively with age with an initial plateau varying across pathways (DN at 2Y, MCP-2 at 3Y, MCP-1 at 5Y, ICP at 6Y, SCP at 8Y) (chi-square test, $p < 0.05$) (for MCP, **Fig. 3A**).

2. The MCP volume normalized by the total cerebellar volume was shown to exponentially decrease with age and reach a plateau by age 5 years (**Fig. 3B**).

3. MCP-1 and MCP-2 pathways were distinctly identifiable starting from the earliest ages, and the volume of MCP-1 was consistently greater than the volume of MCP-2 (2-way ANOVA, $p < 0.05$).

4. Mean ADC for all studied pathways decreased in the first 5 years post-term then plateaued, while mean FA increased until adult ages (chi-square test, $p < 0.05$).

DISCUSSION and CONCLUSION: Given the nature of diffusion imaging, the absence of diffusion tractography pathways is not directly inferred to the non-existence of axonal fibers. However, the absence of tractography pathways is likely to indicate lower myelination and lower density of axons, suggesting lower maturity of the pathways. Interestingly, the ICP, involving primary sensorimotor functions appears to begin maturing later, although complete more rapidly, than the SCP, MCP, and DN pathways. This may suggest that the output pathways from the DN to the IO nucleus may play a role in the maturation of IO neurons and therefore axons which compose the ICP. The dissociated maturation patterns of the two MCP pathways suggest that although there are pathways related to higher cognitive functions, primary motor functions are dominant in the cerebellum, consistent with previous studies. Initial high normalized MCP volume may be another indication of early MCP maturation relative to the other areas of the cerebellum. We hope that this work may represent an initial step towards the creation of a reference atlas for the developing cerebellar tracts as viewed by diffusion tractography.

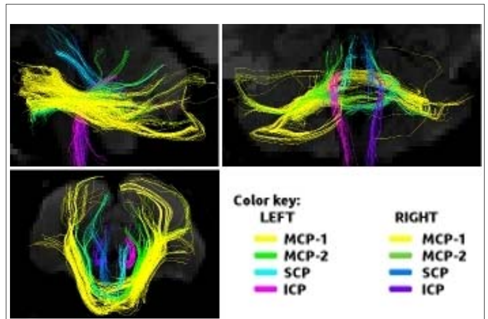

Fig 1: Cerebellar Peduncular Tracks at 6Y.

Fig 2: Cerebellar Tracks at several ages.

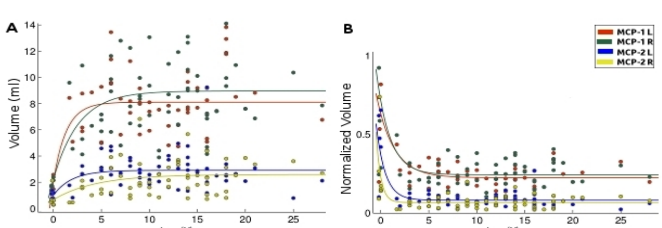

Fig 3: Absolute (A) and Normalized Volume (B) of MCP Tracks.

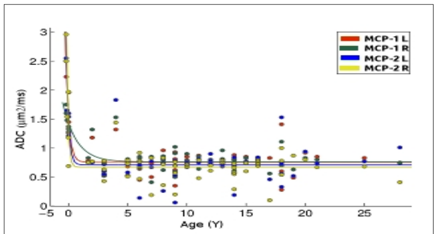

Fig 4: Mean ADC for MCP Tracks.