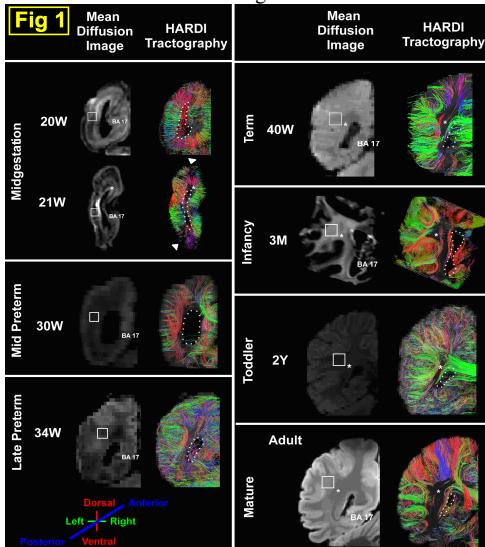


# Defining the Structural Basis of the Radial Coherence of Diffusion Tractography in the Human Fetal Telencephalon: Insights from Neuroanatomic Correlations

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**Introduction:** High angular resolution diffusion imaging (HARDI) tractography of the human fetal brain demonstrates transient radial coherence of the telencephalic wall that extends perpendicular from the lateral ventricle to the pial surface (Takahashi et al., 2011). The objective of this study was to define the neuroanatomic basis of this radial coherence through a correlative HARDI- and postmortem immunohistochemical analyses.

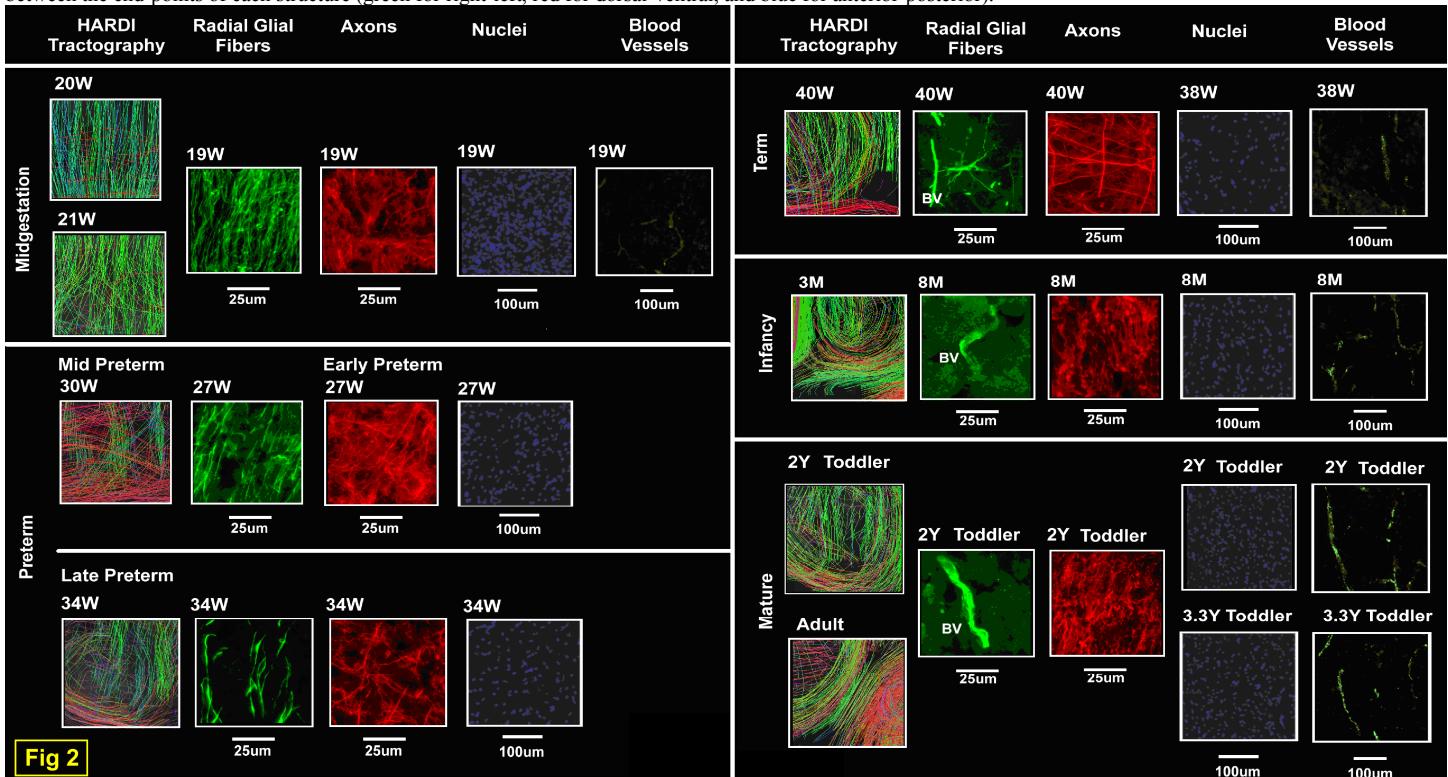


**Methods:** We performed HARDI on a total of 11 human brain specimens (5 at autopsy and 6 in living patients) in the following age brackets: preterm (n=5), full-term (n=2), infancy (n=1), toddler (n=1), and adult (n=2) at a 4.7T Bruker and 3T Siemens MR Systems. We performed a 3D diffusion-weighted spin-echo echo-planar imaging (EPI) sequence (61 measurements), with  $b = 1,000$  to 8,000, small/large delta = 12.0/24.2 ms, TR/TE 1000/40 ms, spatial resolution 315x450x500  $\mu\text{m}$  to 2x2x2 mm, depending on brain sizes. Diffusion Toolkit and TrackVis were used for reconstructing and visualizing tractography. Applying immunomarkers to radial glial fibers (vimentin), axons (SMI 312), blood vessels (CD31), and DAPI staining for white matter nuclei from 18 cases (19 gestational weeks to 3 postnatal years), we compared each of their developmental profiles to HARDI tractography.

**Results:** At midgestation, radial coherence by HARDI corresponded with the presence of radial glial fibers and chains of migrating neuroblasts. In the mid preterm period (30-31 weeks), the transition from HARDI-defined radial coherence to cortico-cortical coherence began, simultaneously with the transformation of radial glial fibers to white matter astrocytes. By term (37-41 weeks), both radial coherence and radial glial fibers had essentially disappeared. While many axonal processes were radial in the white matter over the second half of gestation, others were equally oriented in the tangential and oblique directions, consistent with the time-frame in which elongating axons "search" in multiple directions for their final targets. The radial pattern of blood vessels persisted from midgestation onward.

**Conclusions:** These data suggest that HARDI-determined radial coherence in the fetal white matter from approximately 20 to 30 weeks reflects radial glial fibers, radially oriented chains of migrating neuroblasts, and a subset of radially oriented, immature axons in combination. This study provides important baseline for the interpretation of radial coherence in the preterm brain, as tractography becomes more routine in the clinical assessment of preterm infants at risk for encephalopathy of prematurity and radial glial fiber injury.

**Fig. 1.** HARDI images (right) with the comparable mean diffusion image (left) at term, infancy, toddler, and adult time points at the level of the atrium of the occipital lobe. The asterisks indicate the location where emerging axonal pathways run anterior to posterior through the tissue plane. The boundary of the lateral ventricle is shown with a dotted white line. The square represents the tissue sample in the central white matter illustrated in Figures 2 and 3, but rotated 90°. BA, Brodmann Area; M, postnatal months; W, weeks. The color-coding of tractography connections is based on a standard red-green-blue (RGB) code which was applied to the vector between the end-points of each structure (green for right-left, red for dorsal-ventral, and blue for anterior-posterior).



**Fig. 2.** Composite image of HARDI data (left) and tissue data (middle and right) at midgestation and in the preterm period at the central site of the occipital white matter indicated by squares in Figure 3, but rotated 90°. All images are oriented with the pial surface towards the top of the page. HARDI images were magnified images of white rectangles in Figure 3, using a standard option of TrackVis software. BV: blood vessel.

**Reference:** Takahashi et al. Emerging cerebral connectivity in the human fetal brain: An MR tractography study. Cerebral Cortex 2011. doi: 10.1093/cercor/bhr126.