

# Study of the Development of Major Cerebral Fiber Bundles and its Lateralization from Birth to Adulthood using Quantitative Diffusion Tensor Tractography (DTT)

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**Introduction:** In humans, much of the axonal organization is established by birth but axonal wiring and pruning processes as well as myelination in white matter tracts are known to extend to the postnatal periods and continues till adulthood (1). Postmortem studies of the young population are very limited. Even with postmortem samples there are no reliable histology-based techniques that can quantitatively assess the axonal architecture of the entire fiber tracts. Conventional magnetic resonance imaging (MRI) has provided an opportunity to visualize the progression of myelination in white matter tracts throughout infancy and childhood non-invasively (2). However, conventional MRI is unable to delineate individual white matter fiber tracts. Diffusion tensor imaging (DTI) allows us to estimate dominant fiber orientation at each pixel. The popular region of interest (ROI) – based morphometric DTI method is limited to 2 dimensions that do not reflect the whole fiber bundle; however diffusion tensor tractography (DTT) offers an overall view of individual fiber bundle in 3 dimensional spaces. The aim of our study was to compare axonal growth with age among major fiber bundles and also to detect cerebral laterality in terms of anatomy, if any.

**Materials and Methods:** Conventional MRI and DTI were performed on normal human brain (n = 45) with age group ranging from 10 days to 38 years. All of the subjects included in this study were right-handed. Healthy volunteers were recruited from the community who had come for routine brain screening with no neurological symptoms. Small babies formed the controls in project relating to hypoxic ischemic encephalopathy.

**Imaging protocol:** MRI data was acquired on a 1.5-T GE MRI scanner using quadrature transmit–receive head coil. The MRI protocol included T2, T1, T2-fluid attenuated inversion recovery (FLAIR), and DTI. DTI was acquired by using a single-shot echo planar dual spin-echo sequence with ramp sampling. The b-factor was set to 0 and 1,000 s/mm<sup>2</sup>; TR, 8 s; TE, 100 ms; and NEX, 8. In total, 32 to 36 axial sections (depending upon head size) were acquired with a slice thickness of 3 mm, no inter-slice gap, FOV of 240 mm. The diffusion tensor encoding used was a dodecahedral scheme with 10 uniformly distributed directions. Tracking has been done using FACT Algorithm (3). The software enables to select region of interest (ROI) from the plane orthogonal to the orientation of fiber bundle associated with the thickest part of the fiber bundle. The interface incorporates a number of plug-in for the operations of add/delete selected fibers, morphological trimming operations, adding fibers from another ROI and gathering statistics on the obtained fiber volume or parts of it. The free hand ROIs were placed on mid sagittal T2 image on corpus callosum (CC) at the level of massa intermedia. Free hand ROIs for both right and left superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), fornix (Fx), and cingulum (CNG) were placed on those coronal images where the thickness of respective fiber bundle was maximum.

**Statistical analysis:** To study the exact relationship between age and FA of the fiber bundles, linear, quadratic, cubic, log-linear, growth and exponential models were applied. R<sup>2</sup> statistics was used to determine the best fit model. The left-right asymmetry in the anisotropy of CNG, Fx, SLF, and ILF and its temporal dependence were assessed by using the sign test on the difference of FA {FA (right fiber bundle) – FA (left fiber bundle)}. p value < 0.05 was considered to be significant.

**Results:** Quadratic model was considered to examine the trends in FA in all fiber bundles with increasing age [Fig. 1(A-E)]. FA was highest in CC followed by ILF, CNG, SLF, and Fx (Fig. 2). The highest increase in FA was observed upto the age of 15 years in CC and ILF; and upto the age of 20-25 years in SLF, CNG and Fx (Fig. 2). As can be seen from Figure B, C, D, and E, the FA values were observed to be higher in the left fiber bundles of each tract compared with the right fiber bundles at all ages. The FA value of the left CNG (p = 0.004, sign test) as well as left SLF (p = 0.024, sign test) was observed to be significantly greater than that of the right CNG and right SLF, respectively. Figure 3 shows the 3D projection of different fiber bundles on mid sagittal plane at different ages. In Fig. 3, red, green, and blue represent left-to-right, anterior-to-posterior, and superior-to-inferior directions, respectively.

**Discussion:** It is known that sensorimotor intelligence develop first during childhood. Subsequently, the child learns to integrate visuospatial information that is associated with SLF. Based on relaxation-based measurements of pediatric and adolescent populations (4–17 years old), Paus et al. reported that the SLF is one of the slowest maturing white matter tracts and related the findings to the extensive use of language during this period (4). It has been reported that cingulate cortex is involved in many higher-level cognitive functions that develops during the later stages of childhood (5). In our study lag of SLF and CNG maturation compared to CC and ILF reflects late emergence of visuospatial and higher-level cognitive functions during the normal process of brain development.

In addition we observed significantly high FA values in left CNG and left SLF compared to their contralateral fiber bundles at all age that suggest cerebral laterality. It has been postulated in postmortem anatomical studies on macaque monkey that the SLF connects several important language areas (6). Recent DTI-based 3D tract reconstruction results have also confirmed that SLF is closely associated with Broca's area, Wernicke's area, and supramarginal gyrus (7). All of our subjects were right handed. The vast majority of right-handers demonstrate left-hemisphere language localization. A large number of lesion studies have confirmed the functional localization of language to the left hemisphere in 99% of right-handers (8). This study demonstrates the normal development of the white matter fiber bundles as well as cerebral lateralization by using quantitative DTT that may be useful for assessing brain maturation in patients with developmental anomalies associated with cerebral white matter.

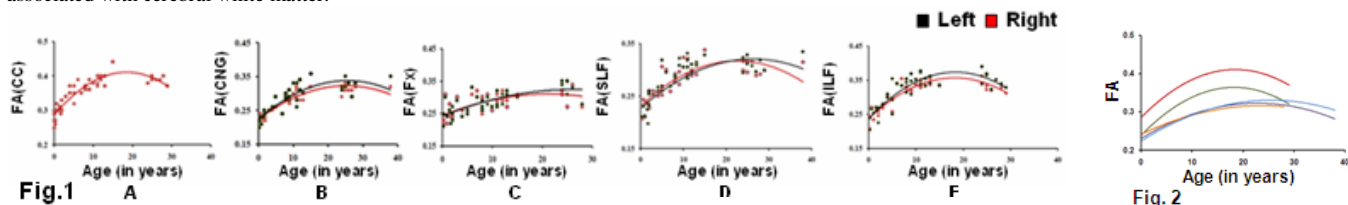


Fig.1

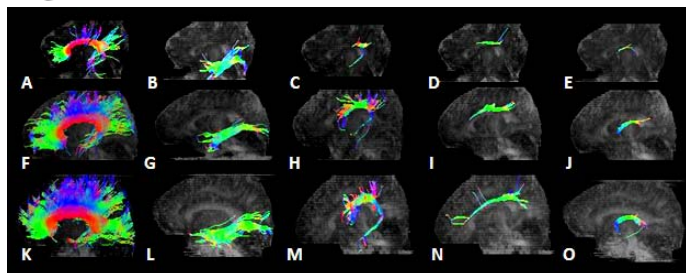


Fig. 3

**Fig.1:** Relationship between FA in different fiber bundle [(A) CC; (B) CNG; (C) Fx; (D) SLF; and (E) ILF] and age using quadratic regression model. **Fig. 2:** Comparison between FA and age among different fiber bundles using quadratic fit (Red-CC, green- ILF, blue-cingulum, purple-SLF, Orange-Fx).

**Fig.3:** Projection of different fiber bundles of left hemisphere on mid sagittal plane at different age: (A-E) 1 month, (F-J) 4 years, (K-O) 25 years shows normal pattern of fiber bundles in human brain. **Note:** (A,F,K) CC; (B,G,L) ILF; (C,H,M) SLF; (D,I,N) CNG; and (E,J,O) Fx.

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