Tractography-Based Mapping of Spatial Patterns in Early Childhood White Matter Maturation

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Introduction

Early childhood is characterized by exceptionally rapid and spatially heterogeneous development of cerebral white matter. Generally, white-matter maturation occurs rapidly within the first ~2 years (Gilmore, 2018). Spatially, postmortem studies have revealed that myelination generally progresses from sensory to motor regions, from projection to associative areas, and from posterior to anterior regions (Kinney, 1988).

Diffusion tensor imaging (DTI) is a powerful tool for characterizing white matter development non-invasively. By utilizing the tensor model as the signal representation, it provides indices such as fractional anisotropy (FA) and radial diffusivity (RD), which reflect axonal organization and myelination, and the principal diffusion direction (V1) that can be integrated with tractography to reconstruct white matter pathways. Integrating tensor-derived metrics with tractography allows direct assessment of maturation along selected white-matter tracts.

Although many prior DTI studies have examined white-matter development, few have conducted comparisons with functional relevance, and the developmental differences between superficial white matter (SWM) and deep white matter (DWM) in early childhood remain unexamined. To bridge this gap, we adopt a tractography-based approach to compare two pairs of representative structures. Functionally, we contrast thalamus-to-superior frontal (motor decision) and thalamus-to-precentral (motor execution) pathways (Johansen-Berg, 2004). Anatomically, we compare SWM, composed of short-range association fibers (SAFs), with DWM, which is dominated by long-range fibers. By examining their developmental trajectories, our study provides new insights into the spatial patterns of white-matter maturation during early childhood.

Method

Data. With written consent and IRB approval, diffusion MRI data were acquired from 70 children aged 0-5 years (1-60 months, distribution in Figure 1a) at West China Second Hospital. Scans were performed on a 3-Tesla Siemens MAGNETOM Skyra using a product 2D simultaneous multi-slice (SMS) pulsed gradient spin echo (PGSE) single-shot echo planar imaging (EPI) sequence at $0.9 \times 0.9 \times 3$ mm^3 resolution, with 2 b=0 volumes and 64 b=1000 s/mm^2 DWI volumes (echo time = 93 ms, repetition time = 4300 ms, SMS factor = 2, GRAPPA factor = 2, partial Fourier factor = 0.875).

Processing. (Figure 1b) All diffusion MRI data were corrected for eddy current-induced distortions and up-sampled to 0.9 mm isotropic resolution using bicubic interpolation. The diffusion tensor model was fitted using MRtrix3 "dwi2tensor" with the weighted least squares option, and maturation indices (i.e., fractional anisotropy (FA) and radial diffusivity (RD)) were derived using MRtrix3 "tensor2metric". The mean DWI image was calculated and co-registered to the age-appropriate T1-weighted image in an atlas constructed based on the BCP dataset (Chen, 2022) using ANTs "SyN" registration, or FSL "fnirt" for cases where ANTs failed. Volumetric segmentation and cortical parcellation from the atlas were then transformed to each subject's native space to obtain the corresponding parcels.

Tractography. (Figure 1c) Whole-brain tractography was performed using the Fiber Assignment by Continuous Tracking (FACT) algorithm, with FA-modulated V1 as input, implemented in MRtrix3 "tckgen". Anatomically-constrained tractography (ACT) was applied based on tissue segmentation, ensuring that streamlines originate and terminate at the gray-white matter interface for greater biological accuracy. The connectivity matrix was then constructed using the native parcels with MRtrix3 "tck2connectome".

Tract Dissection. (Figure 1d) The thalamus-to-superior frontal (motor decision) and thalamus-to-precentral (motor execution) tracts were extracted by selecting streamlines with endpoints in both the thalamus and the respective gyrus. Short-range Association Fibers (SAFs) were defined as tracts connecting adjacent gyri (Zheng, 2025).

Statistics. FA and RD were sampled along the motor decision and motor execution tracts. The mean value was computed for each streamline, and these per-streamline means were then averaged across all streamlines within each tract. Superficial white matter (SWM) voxels were defined as those traversed by ⩾20 SAF streamlines (out of 1 million total streamlines in the whole-brain tractogram). Deep white matter (DWM) was defined as regions contained no SAFs. Mean FA and RD were calculated within the volumetric SWM and DWM regions. Developmental trajectories of each metric versus age were modeled using generalized additive models (GAMs) with penalized splines, and piecewise linear regression was applied to estimate trajectory breakpoints.

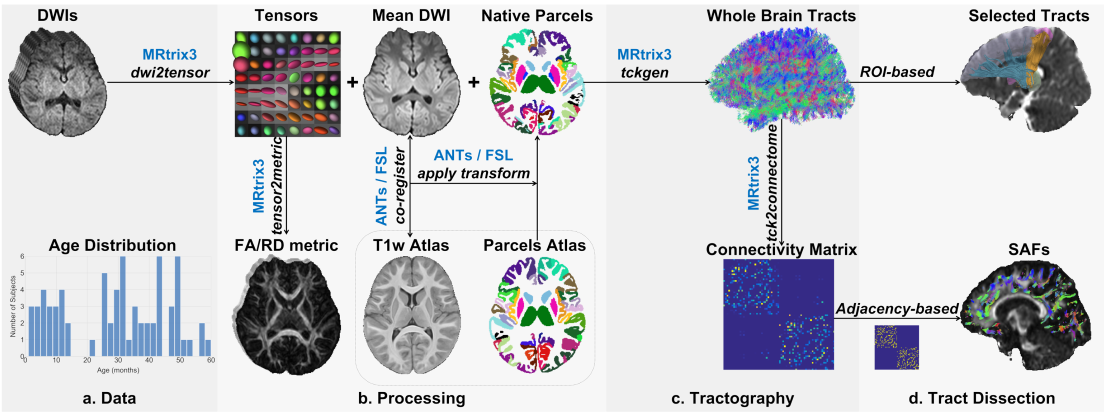

Figure 1. Research Pipeline. Diffusion MRI data from 70 children aged 1-60 months were used (a). The diffusion data were co-registered to a BCP-based atlas for parcellation and were used to fit the diffusion tensor model to derive maturation index and aid tractography (b). Anatomically-constrained tractography was performed to generate a whole-brain tratogram and a connectivity matrix (c). Two types of tracts were selected: the thalamus-to-superior frontal tract and the thalamus-to-precentral tract, were selected based on ROI-inclusion criteria, and short-range association fibers were identified as streamlines connecting adjacent gyri (d).

Results

The gross morphology of white-matter bundles was consistent across subjects of different ages (Figure 2a-b), suggesting that these bundles are established prenatally. Age-related increases in FA and decreases in RD were observed in the motor decision and motor execution tracts, as well as within SWM and DWM, consistent with progressive maturation (Gilmore, 2018). Most regions (except SWM) exhibited a biphasic developmental trajectory, characterized by rapid early change followed by slower development, consistent with prior reports (Gilmore, 2018) (Figure 2c).

Functionally, (Figure 2c, i, ii), the motor decision and motor execution tracts showed nearly parallel developmental trajectories, suggesting coordinated development. The motor decision tract exhibited lower FA and higher RD than the motor execution tract, consistent with a higher-order functional profile. The decision tract's rapid maturation phase was slightly longer than that of the execution tract, implying greater dependence on postnatal experience and learning.

Anatomically, (Figure 2c, iii, iv), SWM showed lower FA, higher RD, and slower changes compared with DWM, consistent with later myelination of SAFs. It may reflect early prioritization of long-range fibers that support fundamental sensorimotor and survival-related functions over SAFs that support high-level cortico-cortical communications.

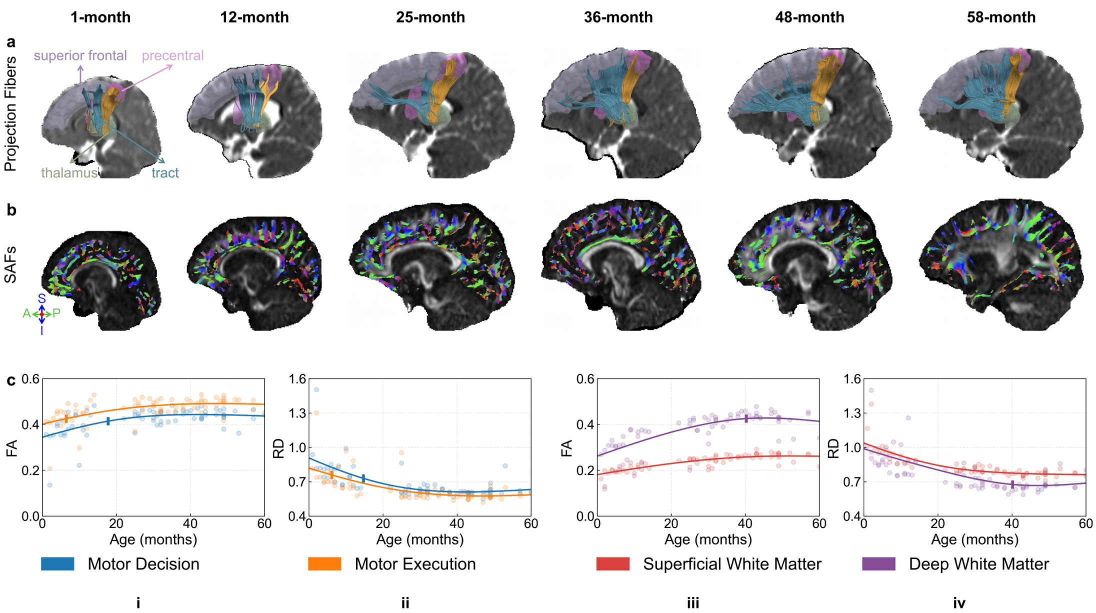

Figure 2. Visualization and developmental trajectories of examined tracts. (a-b) Illustrative thalamus-to-superior frontal (motor decision) and thalamus-to-precentral (motor execution) tracts, together with the ROIs used for selec, overlaid on radial diffusivity (RD) map (a) as well as short-range association fibers (SAFs) intersecting the plane overlaid on fractional anisotropy (FA) map (b) are shown for representative subject at 1, 12, 25, 36, 48 and 58-month-old. **(c)** Development trajectory for FA and RD versus age for each structure (different colors) are shown, with short vertical ticks indicate ages at which the ragte of development shifts.

Conclusions

This tractography-based study compared two representative pairs of structures: motor decision versus motor execution tracts, as well as SWM versus DWM. We found coordinated development between the motor decision and execution tracts, and earlier, faster maturation of DWM relative to SWM. These results provide new insights into the spatial patterns of white-matter maturation during early childhood.

Reference

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