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# Spatial mapping of structural and connectional imaging data for the developing human brain with diffusion tensor imaging

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ABSTRACT

During human brain development from fetal stage to adulthood, the white matter (WM) tracts undergo dramatic changes. Diffusion tensor imaging (DTI), a widely used magnetic resonance imaging (MRI) modality, offers insight into the dynamic changes of WM fibers as these fibers can be noninvasively traced and three-dimensionally (3D) reconstructed with DTI tractography. The DTI and conventional T1 weighted MRI images also provide sufficient cortical anatomical details for mapping the cortical regions of interests (ROIs). In this paper, we described basic concepts and methods of DTI techniques that can be used to trace major WM tracts noninvasively from fetal brain of 14 postconceptional weeks (pcw) to adult brain. We applied these techniques to acquire DTI data and trace, reconstruct and visualize major WM tracts during development. After categorizing major WM fiber bundles into five unique functional tract groups, namely limbic, brain stem, projection, commissural and association tracts, we revealed formation and maturation of these 3D reconstructed WM tracts of the developing human brain. The structural and connectional imaging data offered by DTI provides the anatomical backbone of transcriptional atlas of the developing human brain.



## 1. Introduction

Human brain development is a complex and fascinating biological process. Starting as a simple tubular structure, the human brain undergoes a series of cellular and molecular processes underlying both microstructural and macrostructural changes during development. These cellular and molecular processes are precisely modulated by differential gene expressions [e.g. 1–4]. Understanding dynamics of neuroanatomy is complementary to establishing transcriptional atlas of the developing brain. Histology has been a dominant modality and remains to be an important method to study the detailed neural structures of developing brains [5–10]. Diffusion tensor imaging (DTI) [11], based on diffusion magnetic resonance imaging, has been effective to delineate the macrostructure and microstructure of developing brains. Compared to histology, DTI is noninvasive, three-dimensional (3D) and requires much less time to characterize the entire brain anatomy with the modern scanners. DTI based tractography can be used to effectively trace the major white matter (WM) tracts noninvasively. Structural and connectional data from DTI, therefore, can serve as the anatomical backbone for the transcriptional atlas of the developing brain.

Dramatic morphological changes of human brain take place during its development from early fetal stage to adulthood. The brain WM can be categorized into five tract groups based on their functions, namely, limbic, brain stem, projection, commissural and association tracts. In the prenatal early fetal stage such as 14 postconceptional weeks (pcw), most of traced major tracts with DTI tractography are brain stem and limbic tracts [12–15]. The 3D morphology of these traced WM tracts provides complementary information to the knowledge of WM obtained from histology at this age [e.g. 16,17]. More WM tracts in different tract groups can be appreciated with DTI tractography during fetal development until birth [12,13,18–20]. At birth, except the superior longitudinal fasciculus in the association tract group [e.g. 21], most other major WM tracts including short association tracts are well

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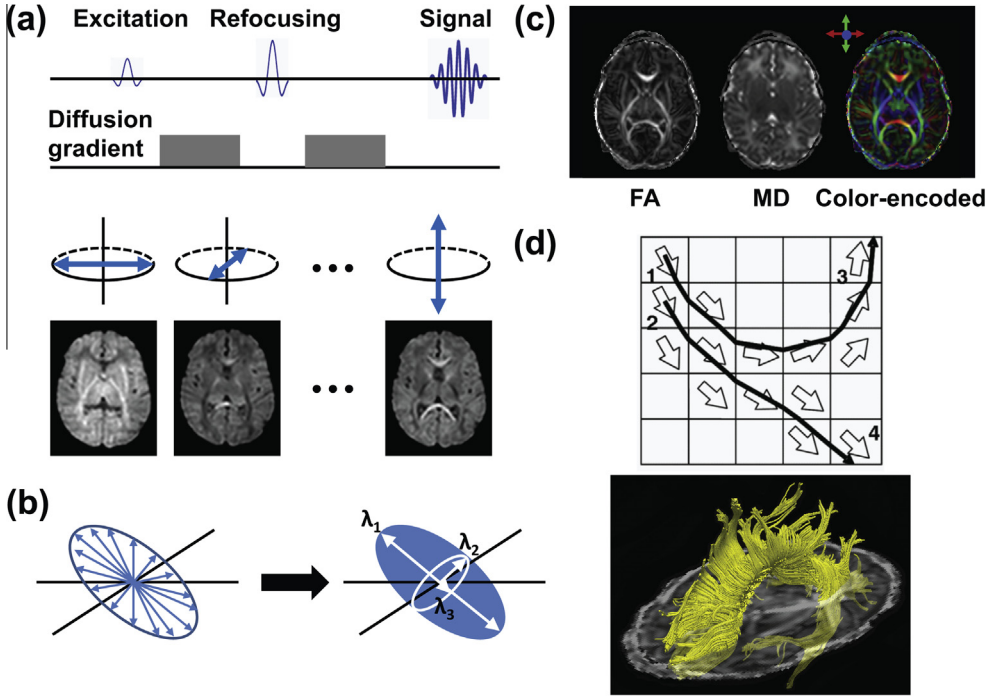


**Fig. 1.** (a) Typical Stejskal–Tanner diffusion sequence with the DWIs of a 37 pcw subject along the left–right, anterior–posterior, and inferior–superior directions. (b) Tensor fitting with the diffusion weighted image and diagonalization into the three eigenvalues and eigenvectors. (c) DTI-derived contrast maps with fractional anisotropy (FA), mean diffusivity, and color-encoded map from left to right. The red, green and blue color encodes orientation along left–right, anterior–posterior and inferior–superior, respectively. (d) DTI tractography with top panel showing the FACT algorithm and bottom panel presenting the traced corpus callosum using FACT.

developed [18,22] although many of them are not well myelinated. Postnatal WM development is associated with myelination, continuous maturation of part of the association fibers and elimination of another part of the short and unmyelinated fibers [23–28].

In this paper, we used DTI techniques to acquire data and trace, reconstruct and visualize major WM fibers of human brain during development from 14 pcw in the early fetal stage to adulthood. Qualitative morphological instead of quantitative microstructural changes (e.g. myelination or integrity enhancement characterized by measurement of DTI-derived metrics) of WM fibers were the focus of this study. After categorizing major WM fiber bundles into five tract groups, namely association, brain stem, projection, limbic and commissural tracts, we revealed formation and maturation of these 3D reconstructed WM tracts of the developing human brain by directly demonstrating the 3D morphological dynamics of these tracts. Below, we first described DTI techniques including concepts, acquisition method, tensor fitting and tractography protocols. We then showed 3D-reconstructed major WM tracts in each of the five categories for the developing brains from prenatal fetal stage to adulthood. The method of delineating 11 cortical regions of interests (ROIs) used for gene profiling and segmented from the cortical surface reconstructed with MRI data was also described. The advantages and limitations of the presented methods, specifically those related to DTI tractography, were discussed in the end.

## 2. Material and methods

### 2.1. DTI concepts and principles

DTI [11] is based on diffusion magnetic resonance imaging (MRI). MRI measures signals from $^1$H (proton) nuclei which are magnetic spins in the magnetic field. In DTI studies, we can assume the signals are dominated by water protons. Diffusion magnetic resonance imaging measures water diffusion noninvasively by using the phase difference to detect water motion. Modern MR scanners are usually equipped with three orthogonal gradient systems in the $X$, $Y$ and $Z$ direction. They can also be used to measure diffusion. This function of the gradient systems is emphasized in Fig. 1a. A typical diffusion sequence [29] is featured with a pair of diffusion gradients placed on either side of the refocusing pulse, shown as Fig. 1a. The frequency of the water proton spin ($\omega$) and the magnetic field $B_0$ have a simple relationship: $\omega = \gamma B_0$. By adding the gradient, the equation is changed to $\omega = \gamma(B_0 + \boldsymbol{G}(\boldsymbol{x})\cdot\boldsymbol{x})$ where $\boldsymbol{G}(\boldsymbol{x})$ is the gradient strength and $\boldsymbol{x}$ is the spatial location. After the first gradient, spins at different locations $\boldsymbol{x}$ have different frequencies and go out of phase as they "see" the different magnetic field strength ($B_0 + \boldsymbol{G}(\boldsymbol{x})\cdot\boldsymbol{x}$). With the second gradient, only the spin that does not move between two gradient lobes has perfect refocusing. Refocusing results in a strong signal which is bright in the acquired diffusion weighted images (DWI) (Fig. 1a). By combining the $X$, $Y$ and $Z$ gradients, we can apply the gradient along arbitrary directions. The blue arrows in Fig. 1a indicate the gradient directions. In human brain WM, water protons tend to move along the axons rather than perpendicular to them. When the diffusion gradient direction aligns with a specific axonal direction, the signal loss is displayed as dark intensities in the images. For example, the first gradient is applied along the horizontal direction ($X$ direction) which is parallel to the axonal directions of the corpus callosum around midline of this axial brain image. Thus the corpus callosum area around the midline is dark in the correspondent diffusion weighted image. The amount of signal loss for those spins with movement is dependent on several parameters, the gradient strength $G$, the interval of the two gradients $\Delta$ and gradient duration $\delta$. This can be described with the following equation:

$$\ln(S/S_0) = -\gamma^2 G^2 \delta^2 (\Delta - \delta/3) D \quad (1)$$

where $D$ is diffusion coefficient, $S$ and $S_0$ are the diffusion sensitized signal and non-diffusion signal. The complicated term $\gamma^2 G^2 \delta^2 (\Delta - \delta/3)$ can be simplified as a scalar $b$. Thus Eq. (1) can be simplified as $\ln(S/S_0) = -bD$.