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# Longitudinal regression analysis of spatial–temporal growth patterns of geometrical diffusion measures in early postnatal brain development with diffusion tensor imaging

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ABSTRACT

Although diffusion tensor imaging (DTI) has provided substantial insights into early brain development, most DTI studies based on fractional anisotropy (*FA*) and mean diffusivity (*MD*) may not capitalize on the information derived from the three principal diffusivities (e.g. eigenvalues). In this study, we explored the spatial and temporal evolution of white matter structures during early brain development using two geometrical diffusion measures, namely, linear (*Cl*) and planar (*Cp*) diffusion anisotropies, from 71 longitudinal datasets acquired from 29 healthy, full-term pediatric subjects. The growth trajectories were estimated with generalized estimating equations (GEE) using linear fitting with logarithm of age (days). The presence of the white matter structures in *Cl* and *Cp* was observed in neonates, suggesting that both the cylindrical and fanning or crossing structures in various white matter regions may already have been formed at birth. Moreover, we found that both *Cl* and *Cp* evolved in a temporally nonlinear and spatially inhomogeneous manner. The growth velocities of *Cl* in central white matter were significantly higher when compared to peripheral, or more laterally located, white matter: central growth velocity $Cl = 0.0465 \pm 0.0273/\log(\text{days})$, versus peripheral growth velocity $Cl = 0.0198 \pm 0.0127/\log(\text{days})$, $p < 10^{-6}$. In contrast, the growth velocities of *Cp* in central white matter were significantly lower than that in peripheral white matter: central growth velocity $Cp = 0.0014 \pm 0.0058/\log(\text{days})$, versus peripheral growth velocity $Cp = 0.0289 \pm 0.0101/\log(\text{days})$, $p < 10^{-6}$. Depending on the underlying white matter site which is analyzed, our findings suggest that ongoing physiologic and microstructural changes in the developing brain may exert different effects on the temporal evolution of these two geometrical diffusion measures. Thus, future studies utilizing DTI with correlative histological analysis in the study of early brain development are warranted.



## Introduction

Quantitative analysis of brain growth in the early postnatal period provides a critical tool in the understanding of normal brain development. In addition, the creation of a voxel-based, rather than ROI-based, digital atlas for the spatiotemporal maturation patterns of human brain affords valuable information in the identification of normal brain developmental features as well as abnormal brain developmental patterns in pediatric patients. Diffusion tensor imaging (DTI) (Basser and Pierpaoli, 1996; Le Bihan et al., 1986) enables a quantitative, non-invasive examination of brain maturation processes utilizing a set of water diffusion related parameters, including fractional anistropy (*FA*), mean (*MD*), axial (*AD*), and radial (*RD*) diffusivities. *FA* is a reflection of water diffusion anisotropy due to the differences among diffusitivities along the three principal directions. As a result of the presence of orderly arranged myelin sheaths within white matter fiber tracts, *FA* values are usually higher in white matter structures when compared to sourounding brain regions. *MD* is an averaged measure of local water diffusivty. In addition, *AD* and *RD* may permit the discrimination between the water diffusivities parallel and perpendicular to the long axis of white matter fiber tracts, with implications for axonal and myelin integrity, respectively, as previously suggested by Song et al. (Song et al., 2003).

Over the past decade, substantial insights toward brain development from prenatal to adolescent stages have been gained with DTI (Cascio et al., 2007; Hüppi and Dubois, 2006; Mukherjee and McKinstry, 2006; Neil et al., 2002). Mckinstry et al. and Gupta et

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al. have imaged the developing human fetal cortex, showing radially oriented major eigenvectors in the cortical plate and subplate (Gupta et al., 2005; McKinstry et al., 2002). In this study, the temporal changes in *FA* demonstrated an initial increase up to 27 weeks gestational age (GA), peaking at 26–28 weeks GA, followed by a gradual decrease in FA through 36 weeks GA. In early postnatal brain development, increased *FA* and decreased *MD* were observed within white matter with advancing age. Neonates demonstrated significantly lower anistropy values and significantly higher MD when compared with adults (Neil et al., 1998; Zhai et al., 2003). Zhai et al. further demonstrated that neonates had consistently higher *FA* and lower *MD* values in the central white matter areas when compared to the peripheral white matter regions. Furthermore, this central–peripheral variation became smaller in adults when compared to neonates (Zhai et al., 2003). In preterm newborns, from 28 to 43 GA weeks, Berman et al. found significant correlation between all tract-specific DTI parameters and age (Berman et al., 2005). Notably, motor tracts had higher *FA* and lower *MD* values than sensory pathways (Berman et al., 2005). In addition, Dubios et al. performed correlation studies between ROI-based DTI parameters and age (Dubois et al., 2006). By examinging 7 pediatric volunteers and 23 pediatric patients (age range: 0–54 months), Hermoye and collegues observed three phases of *FA* and *MD* changes in the early postnatal period, consisting of a rapid change within the first 12 months, a slow maturation from 12 to 24 months, and a steady state following 24 months (Hermoye et al., 2006). In a study by Huang et al. with human fetal, newborn and pediatric brains, the white matter developmental pattern was identified as limbic fiber tract developement preceeding association fiber tracts, and commisural and projection fiber tracts forming from anterior to posterior regions of the brain (Huang et al., 2006). More recently, Gao et al. also demonstrated a significant elevation in *FA* and a signficant reduction in *MD*, *AD* and *RD* in a cross-sectional study consisting of three age groups, neonates, 1-year-olds and 2-year-olds (Gao et al., 2009).

Statistical regression analysis has been applied to quantify the growth trajectories of DTI parameters in early brain development. With selective ROIs, it has been demonstrated that the changes in DTI, including the principal diffusivities represented via the three eigenvalues, follow a non-linear pattern as shown in the studies by Mukhejee et al. (Mukherjee et al., 2001, 2002) and Schneider et al. (Schneider et al., 2004). Later, in subjects 5 to 30 years of age, the non-linear developmental pattern was detected in a tractography based developmental study (Lebel et al., 2008). In a more recent study by Faria et al., a statistical atlas based linear fitting was performed in the voxel level between *FA* and *MD* with the logarithm of age. Investigators found that after two years of life, *FA* still increases and diffusivities still decrease linearly with the logarithm of age (Faria et al., 2010).

Current DTI based early brain developmental studies do not exploit information readily available through the three principal diffusivities (e.g. eigenvalues). Most of the *FA* or *MD* based work falls short in revealing specific microstructural changes of white matter during early brain development, since the composite DTI indices like *FA* or *MD* can not distinguish between different effects exerted by the myelination process on the three eigenvalues. To address this limitation, the hypothesis that *AD* and *RD* may reflect water diffusivities parallel and perpedicular to, respectively, the principle fiber direction (Song et al., 2003), has been applied to early brain development. Gao et al. have found that only RD but not AD showed significant changes from 1 to 2 years of age (Gao et al., 2009). Physiologic and microstructural alterations which may serve as the underpinnings of DTI parameters during early brain development are numerous, and include expansion and growth of the axon cylinders, axonal membrane permeability fluxes, the cellular proliferation of "myelinating glia", and thickness and compaction of the myelin sheath (Wimberger et al., 1995).

This *AD*/*RD* hypothesis originated in a dysmyelination mouse model (Song et al., 2003) and assumed a cylindrical shape of white matter fiber bundles. It has been suggested that central white matter contains relatively compact cylinidrical structures, while peripheral white matter has more structurally complex fiber systems, including fiber crossings and fannings (Wiegell et al., 2000). Previous studies demonstrated that the geometrical diffusion parameters such as linear anistropy *Cl* (the trace normalized difference between the primary and second eigenvalues) and planar anisotropy *Cp* (the traced normalized difference between the secondary and tertertiary eigenvalues) can be utilized to more accurately model different white matter microstructures (Wiegell et al., 2000; Zhang et al., 2006). To date, the geometrical aspects of white matter maturation has not yet been explored in early brain development. Given the changing microstructural landscape within developing white matter, we hypothesized that the temporal evolution of linear (*Cl*) and planar (*Cp*) anistropies may show different characteristics between central and peripheral white matter regions.

In this study, we recruited only healthy, full term infants. Imaging was performed without the use of sedation, in order to control for confounding variables, such as drug effects, and to simulate as closely as possible, natural conditions in order to serve as a representative window into normal brain development.[1] We followed a longitudinal experimental design to minimize the bias which accrues from sporadic across-subject time-invariant factors, and accordingly, we adopted generalized estimate equations (GEE) based longitudinal regression in combination with model selection for soundness in statistical analysis. The spatial and temporal growth patterns of these two geometrical diffusion measures, *Cl* and *Cp*, were evaluated on a voxel basis. Furthermore, the growth velocites of *Cl* and *Cp* between some central and peripheral white matter regions were compared to address the proposed hypothesis.

## Materials and methods

### *Subjects*

Our study was approved by the institutional review board. A total of 29 healthy full-term subjects (17M and 12F) during the first four years of age were recruited and written informed constents were obtained from their parents before image acquisition. The subjects were drawn from a larger study at our institution focused on the investigation of early brain development. A total of 71 datasets with 25 neonates (age $0.07 \pm 0.07$ years, 14M and 11F), 16 1-year-olds (age $1.05 \pm 0.05$ years, 9M and 7F), 23 2-year-olds (age $2.03 \pm 0.07$ years, 14M and 9F), and 7 4-year-olds (age $4.15 \pm 0.16$ years, 4M and 3F) were included in this study. Each subject was scanned at least twice (Fig. 1). None of the subjects were sedated during the imaging session. Instead, efforts were made to ensure that the subjects sleep comfortably inside the MR scanner. All subjects were fed and calmed to sleep on a warm blanket with proper ear protection.

### *Image acquisition and data preprocessing*

All images were acquired on a 3T Allegra head only MR system (Siemens Medical Inc., Erlangen, Germany) with a maximal gradient strength of 40 mT/m and a maximal slew rate of 400 mT/(m·ms). A single shot double refocused EPI DTI sequence (TR/TE = 5400/73 ms)

[1] As pointed out in Mukherjee and McKinstry (2006), pretermity and sedation are two major limitations to numerous current brain developmental studies.