# Heterogeneity of human white matter development: diffusivity parameters decrease fastest in the center of white matter tracts, from 5 to 19 years of age

Shu-Wei Sun[1,2], Nirmalya Ghosh[1], Karen Tong[1], Barbara Holshouser[1], and Stephen Ashwal[1]
*[1]Loma Linda University, Loma Linda, CA, United States, [2]University of California, Riverside, CA, United States*

## Introduction

Recent studies have investigated brain maturation using multiple diffusion tensor imaging (DTI) parameters from childhood to adolescence and young adulthood [1-4]. Although different methods of DTI acquisition and data analysis are reported, there is general agreement that increased fractional isotropy (FA) and decreased mean diffusivity (MD) occur with maturation and vary regionally. In addition, gender and pubertal hormonal effects on DTI variables [5] have been observed as well as correlation of DTI parameters with psychological function [6].

In the current cross-sectional study, changes in DTI parameters taken from the center of white matter tracts were compared to parameters from the entire tract in a group of healthy children and adolescents. We hypothesized that changes with age in axial, radial and mean diffusivity (AD, RD, MD) values would be greatest in the center of white matter tracts suggesting greater myelin development and compactness compared to total white matter. These differences, which increase with maturation, could, in part, explain why shearing injuries after traumatic brain injury (TBI) tend to occur at the gray-white matter junctions (in addition to proposed gray/white matter biomechanical structural differences).

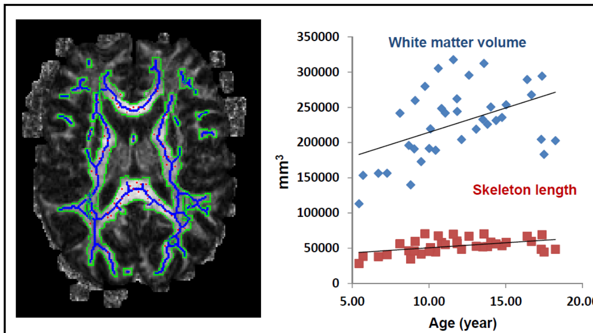


**Figure 1. White matter (green contours) and skeletons (blue) and their volume and length over time, respectively.** Both showed consistent age-related increases (2.5 and1.5 times, respectively).

## Materials and Methods

Data were acquired from 36 healthy children and adolescent controls (ages 5–19 yrs), enrolled in a larger IRB-approved study on pediatric TBI. DTI was collected using a Siemens 3T Trio scanner with B values of 0 and 1000 s/mm$^2$ in 30 diffusion encoding directions. Data were collected with the voxel size of 1mm x 1mm x 3mm (with 0.9 mm inter-slice gap) and interpolated to be isotropic 1mm x 1mm x 1mm using an in-house program written in Matlab. DTI indices including the fractional anisotropy (FA), axial, radial and mean diffusivities (AD, RD, MD) were quantified. A threshold of FA > 0.2 was used to segment the white matter area (green contours in Fig. 1). The center of tracts (i.e. medial-axes skeletons) was computed by morphological thinning of the white matter binary mask (blue lines in Fig. 1). We compared skeleton DTI parameters to that of total white matter which included the skeleton and remaining (i.e. entire) white matter. We calculated the slope for each DTI variable as a measurement of change of that variable per year.

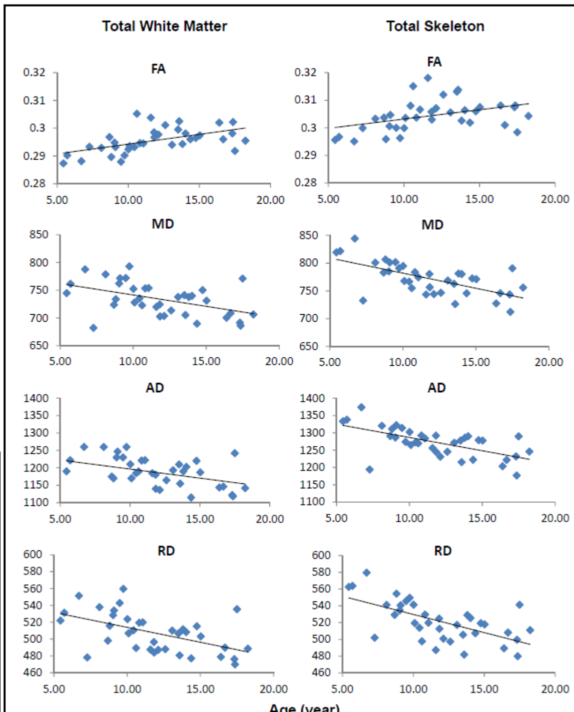


**Figure 2. Changes in DTI parameters of the entire white matter and of the center of the tracts (the skeleton) over age.**

## Results and Discussion

Total white matter volume increased ~ 2.5 times (100,000 mm$^3$ to 350,000mm$^3$) with maturation. Skeleton volume showed a similar trend but with a smaller increase (~1.5 times, from 30,000 to 75,000 mm$^3$) (Fig. 1), indicating that expansion of the white matter thickness is greater than tract lengthening.

Skeleton and total white matter age-related changes were observed for all DTI variables including increased FA; and decreased AD, RD and MD in agreement with the literature (Fig. 2). Also, as shown in Table 1, we observed that the magnitude of these changes (i.e. slope) was greater in the skeleton than in total white matter. Decreased RD and AD with maturation may be due to increased myelination or growth of neurofibrils, respectively, as well as changes in water content. Our data suggest that these changes are more prominent in the center of white matter tracts, compared to the remaining white matter surrounding the skeleton. Such findings of a more compact and mature myelin within the center of tracts, could affect the biomechanical properties, providing greater resistance to shearing injuries compared to the gray-white matter junction, after TBI.

| | Total white matter | | Skeleton | |
|---|---|---|---|---|
| | slope | $R^2$ | slope | $R^2$ |
| Size | 6915 | 0.22 | 1431 | 0.21 |
| FA | 0.0007 | 0.29 | 0.0007 | 0.17 |
| MD | -4.1 | 0.23 | -5.4 | 0.41 |
| AD | -5.2 | 0.16 | -7.7 | 0.38 |
| RD | -3.5 | 0.28 | -4.3 | 0.39 |

**Table 1. Linear regression analysis: Slope and $R^2$ of DTI changes over age.**

## Conclusion

Our findings suggest that white matter maturation is not homogeneous and that DTI parameters in the center of tracts suggest that myelin is more compact and developed. Whether these observations contribute to the distribution of shearing injuries after TBI requires further investigation.

## References:

1. Barnea-Goraly et al., Cereb. Cortex 2005; 15:1848–1854.
2. Bonekamp et al., Neuroimage 2007; 34: 733–742.
3. Giorgio et al., Neuroimage 2008;39:52–61.
4. Klingberg et al., Neuroreport 1999;10: 2817–2821.
5. Asato et al., Cereb Cortex. 2010 Sep;20(9):2122-31.
6. Tamnes et al., Hum Brain Mapp. 2010 Oct;31(10):1609-25.

**Acknowledgement:** NIH/NINDS: R01-NS0540001-01A1