A NEW FRAMEWORK FOR ANALYZING WHITE MATTER MATURATION IN EARLY BRAIN DEVELOPMENT

Marcel Prastawa[1]*, Neda Sadeghi*[1]*, John H. Gilmore*[2]*, Weili Lin*[3]*, Guido Gerig*[1] *

[1] Scientific Computing and Imaging Institute
University of Utah
Salt Lake City, Utah 84112

Department of [2]Psychiatry and [3]Radiology
University of North Carolina
Chapel Hill, NC 27599

ABSTRACT

The trajectory of early brain development is marked by rapid growth presented by volume but also by tissue property changes. Capturing regional characteristics of axonal structuring and myelination via neuroimaging requires analysis of longitudinal image data with multiple modalities. Complementary to earlier studies of volume and cortical folding analysis, this paper focuses on white matter tissue changes as seen in multimodal MRI and DTI. We propose a new framework for analyzing early maturation in white matter that generates a normative spatiotemporal model and provides 3D maps of absolute and relative indices of maturation. The method, using a continuous model of intensity changes using modified Legendre polynomials, has been applied to a multimodal dataset (T1W, T2W, PD, DTI) with 8 subjects that have been scanned at approximately 2 weeks, 1 year, and 2 years. We demonstrate that spatial maturation maps generated from different modalities capture different properties of white matter growth which might lead to a better understanding of the underlying neurobiology.

***Index Terms*—** Brain development, MRI, Diffusion tensor imaging, Longitudinal analysis, Growth trajectory

1. INTRODUCTION

The understanding of human brain development is of significant scientific and clinical importance as relatively little is known about the quantitative trajectory and pattern of early growth. Characterization of early brain growth in healthy children is important to generate normative data to be compared to children at risk for mental disorders or brain diseases. This might lead to structural phenotypes of growth patterns in disease and eventually to early detection and diagnosis.

Previous neuroimaging studies have been mostly focused on morphometric measures such as volume [1, 2, 3] and shape, e.g. cortical folding [4]. Diffusion imaging provides information about the early brain development trajectory that might complement structural image information. Seminal work by Dubois et al. [5, 6] explored changes of diffusion measurements (FA, MD) as a function of age and presented a model for maturation stage which inspired methodology as presented in this paper. This might lead to a normative model of tissue growth that could eventually characterize maturation changes presented in disease.

Our main goal is to complement brain growth analysis based on morphometry [1] with the study of longitudinal tissue property changes as reflected in patterns observed in multi-modal structural MRI and DTI. Such patterns of appearance in imaging are the major features discussed in radiology textbooks [7]. To our knowledge, this is the first joint MRI/DTI analysis of brain maturation. We propose a new framework for analyzing maturation of white matter to create white matter maturation maps. In contrast to previous works that analyzes discrete values through time, we propose a longitudinal data analysis where we analyze continuous functions rather than discrete snap shots of data.

2. ANALYSIS FRAMEWORK

Our goal is the analysis of spatio-temporal patterns that are observed in the multimodal MR data of children undergoing normal growth. This analysis generates imaging markers that can isolate interesting features in early brain development. We assume that we have repeated measurements of multiple subjects at different stages of development, with no missing data. Co-registered multimodal MR data scanned at approximately 2 weeks, 1 year, and 2 years are shown in Fig. 1.

We propose a framework that is composed of the following steps: 1) Averaging of temporal curves to create normative data, 2) an absolute measurement of maturation using growth rates at each location, 3) spatial clustering of average growth curves to find distinct patterns of growth, and 4) a relative measurement of maturation within white matter.

2.1. Averaging of Multimodal Growth Curves

To measure the relative maturation index of white matter in normal subjects, we first create a model for the average non-

*Supported by NIH grants: MH070890 (JHG), Conte Center MH064065 (JHG, GG), National Alliance for Medical Image Computing (NA-MIC) U54 EB005149 (GG), and Autism Center of Excellence R01 HD055741-01 (GG).

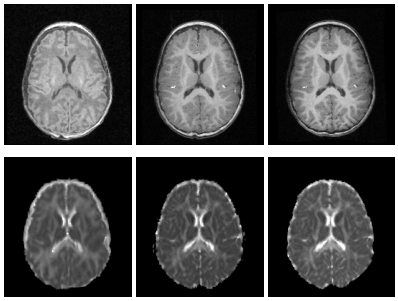

Fig. 1. Axial view of a co-registered multimodal MR data across age. Top: T1-weighted scans. Bottom: Axial diffusivity from DT-MRI (λ_1). Left to right: Scans at approximately 2 weeks, 1 year, and 2 years.

linear growth in the observed multimodal data. We perform a least squares fit within each modality to a modified Legendre polynomial basis, using the following three basis functions for the three observations:

$$\begin{aligned} L_1(t) &= 1 \\ L_2(t) &= \sqrt{3}(2t-1) \\ L_3(t) &= \sqrt{5}(6t^2-6t+1) \end{aligned} \quad (1)$$

These basis functions are orthonormal in the $[0,1]$ domain, where $\int_0^1 L_i(t)L_i(t)dt = 1$ and $\int_0^1 L_i(t)L_j(t)dt = 0$ for $i \neq j$. This results in a simplification of algebraic operations on the curves since dot products and norms are reduced to Euclidean operations on the vector of basis coefficients.

Given a set of m intensity values $y_1, y_2, ..., y_m$ taken at m time points $t_1, t_2, ..., t_m$ at a particular location x, we estimate the polynomial coefficients $\beta = (\beta_1, \beta_2, \beta_3)$ that minimizes the squared error measure:

$$\sum_{j=1}^{m}(y_j - \sum_{k=1}^{3}\beta_k L_k(t_j))^2 \quad (2)$$

Therefore, each location x is represented by one curve $f_x^{(c)}(t) = \sum_{k=1}^{3}\beta_k L_k(t)$ for each modality c that represents the average defined in the least squares sense. Fig. 2 illustrates an example of least squares fitting using the modified Legendre polynomial basis.

2.2. Absolute Measure of Maturation

We measure the absolute growth as the total changes in time at each location. Given a set of smooth functions represented by the β coefficients at each location, we can measure the growth rate as the squared magnitude of the derivatives in time (Fig. 3). Specifically, we measure the total growth rate for a set of multimodal observations as follows:

$$GR = \sum_{c\in C}||\frac{d}{dt}f^{(c)}(t)||^2 = \sum_{c\in C}\int_0^1(\frac{d}{dt}f^{(c)}(t))^2dt \quad (3)$$

where C represents a subset of the modalities in our datasets.

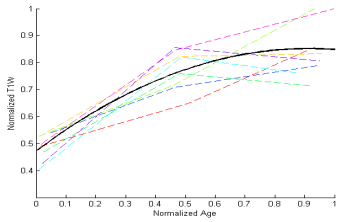

Fig. 2. Curve averaging through least squares fit with modified Legendre polynomial basis functions. Dashed colored curves: Growth trajectories of a white matter voxel of different subjects. Black curve: Average curve that minimizes the squared error.

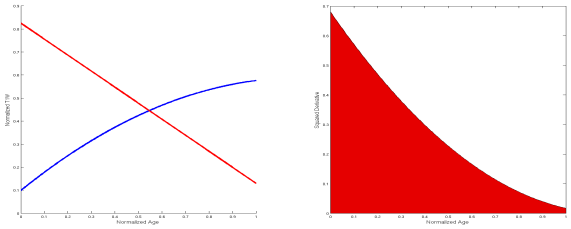

Fig. 3. Growth rate as a measure of maturation. Left: Average T1 growth trajectory of a white matter region (blue) with derivative (red). Right: Squared derivative of the trajectory, where growth rate is measured as the area under the curve.

2.3. Data Driven Spatial Clustering

We are interested in isolating spatial regions with distinct patterns of growth represented by the average curves described in section 2.1. The patterns are represented by a feature vector formed by the β coefficients for all modalities (i.e., for M modalities we have vectors of length $3M$).

We assume that the feature vectors can be represented using mixtures of Gaussian distributions; we use the Dirichlet Process Mixture Models (DPMM) [8] to automatically determine the number of clusters, and estimate the representative parameters[1]. This is a data driven approach to extract the unknown patterns that are present in the data. Fig. 4 shows the mean curves of three different clusters for all modalities (T1, T2, PD, axial diffusion, and radial diffusion). Within the same modality, the clusters seem to have similar patterns of changes (e.g., increase in T1, and decrease in T2 and in axial diffusivity). However, different regions at different stages of development appear to be shifted in time relative to the matured region.

2.4. Relative Measure of Maturation

The data driven approach described in the previous subsection highlighted the fact that region in white matter appear to undergo similar growth patterns, but different locations may be at different stages of growth. We propose to use this

[1] http://www.kyb.tuebingen.mpg.de/bs/people/dilan/dpcode/

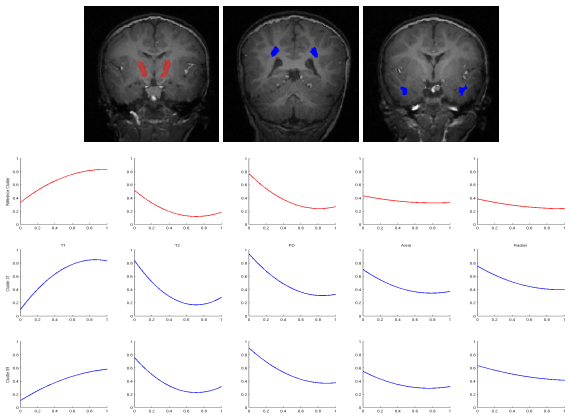

Fig. 4. Multimodal growth trajectories of three different clusters (shown in top row). Patterns for a reference cluster that represents matured white matter regions are shown in red. Patterns for two white matter regions (cluster 37 and 59) that undergo later maturation are shown in blue. Patterns per modality seems to be similar, but shifted in time.

observation to design a *relative measure of maturation* as the amount of shift (in time) required to transform a curve to a reference curve. This reference curve is assumed to be a representation of a region that has already matured. the relative maturation at each location is then calculated as the time shift between the curve at each voxel and the reference curve:

$$TS = \underset{s}{\operatorname{argmin}} \sum_{c \in C} ||f^{(c)}(t+s) - g^{(c)}(t)||^2 \qquad (4)$$

where $||f-g||^2 = \int_0^1 (f(t)-g(t))^2 dt$. Parameter s is the amount of shift, C is a subset of modalities, $f^{(c)}$ is the curve of interest, and $g^{(c)}$ is a reference curve. We use the known early myelination region of the internal capsule as a reference for calculating relative maturation state of the rest of white matter. The time shift can be calculated for different subsets of the observed modalities, yielding an estimate of the amount of energy needed to transform a curve to the reference curve. Fig. 5 shows a curve shifted to match the reference curve. We treat the curve being shifted to be extended infinitely and find the shift transform that would yield the best match in the $[0, 1]$ time window.

3. ANALYSIS OF WHITE MATTER MATURATION IN EARLY BRAIN DEVELOPMENT

3.1. Data Description and Preprocessing

Our preliminary study includes eight healthy pediatric subjects with repeated scans at the age of two weeks, one year, and two years. Images acquired include T1W, T2W, PD, and diffusion tensor images. We apply the unbiased atlas building procedure [9] to the set of T2W images at 1-year to obtain spatial mappings between each subject. Scans of other

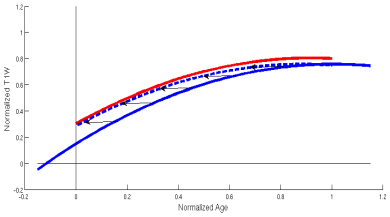

Fig. 5. Time shifting for matching a reference curve. Red: T1 growth trajectory of a white matter region with early maturation. Dashed blue: Original growth trajectory of a white matter cluster (extended). Solid blue: Shifted growth trajectory.

modalities and at different time points within each subject are registered using linear transformations followed by nonlinear registration [10]. Tensor maps are calculated for each DTI scan, and each tensor map is registered to the atlas using transformations between the baseline (B0) and T2W images. Tensors are resampled using finite strain reorientation and Riemannian interpolation. Diffusion measurements such as axial (λ_1) and radial ($\lambda_2 + \lambda_3$) diffusivity are calculated for each scan. The T1W, T2W, and PD intensities were normalized to ensure comparison across subjects and time points. T1W scans were normalized using high intensity of fatty tissue between the skull and the skin, which was segmented using InsightSNAP[2]. T2W and PD scans were normalized using values within ventricular CSF.

3.2. Results

We show the characterization of white matter maturation using the absolute growth rate (GR) measure and the relative time shift (TS) measure. The top row of Fig. 6 illustrates the growth rates (section 2.2) inferred from all structural modalities ($C = \{T1, T2, PD\}$), as well as all diffusion modalities ($C = \{\lambda_1, \lambda_2 + \lambda_3\}$). Areas with low (internal capsule, e.g.) and high growth rates (deep white matter in anterior and posterior regions, temporal lobe) are depicted at locations as expected from radiological knowledge [7]. The bottom row of Fig. 6 displays the timing of maturation as measured by calculating time shift of growth trajectories relative to a template 2.4. As shown, the structural and diffusion modalities capture different properties of growth. Structural TS values show gradual changes in white matter in regions that undergo myelination, while diffusion TS values highlight differences between central and peripheral white matter regions which might indicate degree of structuring.

Our results show white matter maturation presenting asynchronous contrast changes in multiple modalities, which might reflect different characteristics of complex axonal maturation such as axon elimination and myelination [7]. Our study confirms that basic brain functions such as motor and

[2]http://www.itksnap.org

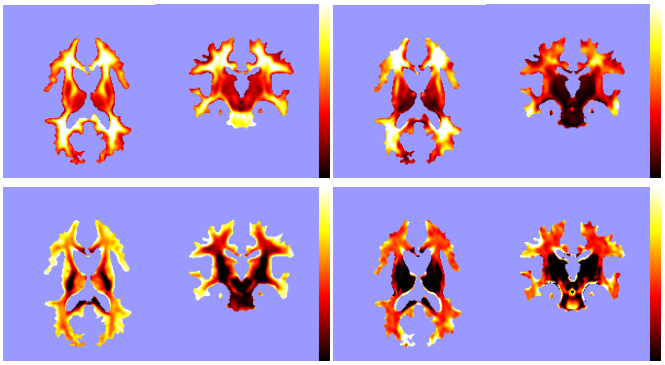

Fig. 6. **Top**: Axial and coronal views of growth rates (GR) map which shows absolute speed of maturation. GR maps computed using structural modalities (T1, T2, PD) is shown on left, while GR maps computed using diffusion modalities (axial and radial diffusion) is shown on right. Darker regions mark low GR and bright regions high GR. **Bottom**: Time shift (TS) maps which show relative timing of maturation, which was computed using structural modelities (left) and diffusion modalities (right). Darker regions mark areas which have similar pattern to early myelination, whereas bright regions indicate later maturation.

sensory processes undergo maturation earlier. We also observe that central regions of white matter tracts were more mature and organized than peripheral cortical regions, confirming [11]. The earlier maturation of the posterior versus anterior internal capsule is clearly visible, and the significantly later maturation of temporal lobes relative to other white matter areas is depicted as well.

4. CONCLUSIONS

We have proposed a new framework for analysis of normal brain growth using patterns of temporal change in multimodal data. This approach provides the basis for measuring maturation using an absolute measure of the rate of change (GR) and a relative measure computed as the amount of energy to map growth curves to a reference curve (TS). The resulting maturation maps for white matter shows that the different MR modalities capture different properties of the complex maturation process in early brain development, which will be explored in our future developments.

The normative spatiotemporal trajectories, along with the maturation measures (GR and TS), can be applied for analysis of subjects at risk for mental illness or cognitive deficits. This might highlight the relationship between growth trajectory and cognitive development.

This research represents work in progress towards analysis of tissue property changes which complements the parallel effort of volume changes [1]. Our analysis framework is currently limited to studies with repeated time scans and no missing data. We assume that the data can be co-registered across time points and modalities, which showed encouraging results for this study but needs further validation. We also plan to extend the simplified measures of growth rate and time shift to include more complex models of growth.

5. REFERENCES

[1] R. C. Knickmeyer, S. Gouttard, C. Kang, D. Evans, K. Wilber, J. K. Smith, R. M. Hamer, W. Lin, G. Gerig, and J. H. Gilmore, "A structural MRI study of human brain development from birth to 2 years," *J. Neurosci.*, vol. 28, pp. 12176–12182, Nov 2008.

[2] P. S. Hüppi, "Neuroimaging of brain development–discovering the origins of neuropsychiatric disorders?," *Pediatr. Res.*, vol. 64, pp. 325, Oct 2008.

[3] M. Murgasova, L. Dyet, D. Edwards, M. Rutherford, J. Hajnal, and D. Rueckert, "Segmentation of brain MRI in young children," *Acad Radiol*, vol. 14, pp. 1350–1366, Nov 2007.

[4] H. Xue, L. Srinivasan, S. Jiang, M. Rutherford, A. D. Edwards, D. Rueckert, and J. V. Hajnal, "Automatic cortical segmentation in the developing brain," *IPMI*, vol. 20, pp. 257–269, 2007.

[5] J. Dubois, L. Hertz-Pannier, G. Dehaene-Lambertz, Y. Cointepas, and D. Le Bihan, "Assessment of the early organization and maturation of infants' cerebral white matter fiber bundles," *NeuroImage*, vol. 30, no. 4, pp. 1121 – 1132, 2006.

[6] J. Dubois, G. Dehaene-Lambertz, M. Perrin, J. F. Mangin, Y. Cointepas, E. Duchesnay, D. Le Bihan, and L. Hertz-Pannier, "Asynchrony of the early maturation of white matter bundles in healthy infants," *Hum Brain Mapp*, vol. 29, pp. 14–27, Jan 2008.

[7] Mary Rutherford, Ed., *MRI of the Neonatal Brain*, W.B. Saunders, 2002.

[8] Carl Rasmussen, "The infinite gaussian mixture model," *Advances in (NIPS)*, vol. 12, pp. 554–560, 2000.

[9] S. Joshi, B. Davis, M. Jomier, and G. Gerig, "Unbiased diffeomorphic atlas construction for computational anatomy," *NeuroImage*, vol. 23, pp. S151–S160, 2004.

[10] D. Rueckert, LI Sonoda, C. Hayes, D.L.G. Hill, M.O. Leach, and D.J. Hawkes, "Nonrigid registration using free-form deformations," *IEEE Trans Med Imag*, vol. 18, no. 8, pp. 712–721, 1999.

[11] W. Gao, W. Lin, Y. Chen, G. Gerig, J.K. Smith, V. Jewells, and J.H. Gilmore, "Temporal and Spatial Development of Axonal Maturation and Myelination of White Matter in the Developing Brain," *AJNR*, vol. 30, no. 29, Feb 2009.