Towards Analysis of Growth Trajectory through Multi-modal Longitudinal MR Imaging

Neda Sadeghi[a,b], Marcel Prastawa[a,c], John H. Gilmore[d], Weili Lin[e], Guido Gerig[a,b,c]

[a] Scientific Computing and Imaging Institute, University of Utah, Salt Lake City, Utah 84112;
[b] Department of Biomedical Engineering, University of Utah, Salt Lake City, Utah 84112;
[c] School of Computing, University of Utah, Salt Lake City, Utah 84112;
[d] Department of Psychiatry, University of North Carolina, Chapel Hill, NC 27599;
[e] Department of Radiology, University of North Carolina, Chapel Hill, NC 27599

ABSTRACT

The human brain undergoes significant changes in the first few years after birth, but knowledge about this critical period of development is quite limited. Previous neuroimaging studies have been mostly focused on morphometric measures such as volume and shape, although tissue property measures related to the degree of myelination and axon density could also add valuable information to our understanding of brain maturation. Our goal is to complement brain growth analysis via morphometry with the study of longitudinal tissue property changes as reflected in patterns observed in multi-modal structural MRI and DTI. Our preliminary study includes eight healthy pediatric subjects with repeated scans at the age of two weeks, one year, and two years with T1, T2, PD, and DT MRI. Analysis is driven by the registration of multiple modalities and time points within and between subjects into a common coordinate frame, followed by image intensity normalization. Quantitative tractography with diffusion and structural image parameters serves for multi-variate tissue analysis. Different patterns of rapid changes were observed in the corpus callosum and the posterior and anterior internal capsule, structures known for distinctly different myelination growth. There are significant differences in central versus peripheral white matter, and also a wm/gm contrast flip in both T1 and T2 images but not diffusion parameters. We demonstrate that the combined longitudinal analysis of structural and diffusion MRI proves superior to individual modalities and might provide a better understanding of the trajectory of early neurodevelopment.

Keywords: Brain development, MRI, Diffusion tensor imaging, Longitudinal analysis, Growth trajectory

1. INTRODUCTION

The understanding of human brain development is both a significant scientific and clinical importance. Even though it has been suggested that the first two years of life is the period of rapid pace of maturation, most MRI studies of infants and young children have been focused on those born prematurely [1,2] or older children.[3,4] Characterization of the trajectory of early brain growth in healthy children is important as normative data to compare patterns of children at risk for mental illness, mental disorders, or brain diseases.

Most MRI studies that have been done so far have been focusing on morphometric measures such as volume [5–7] and shape.[8] These measurements provide important insight into understanding of brain growth, however measures related to the degree of myelination and axon density as is measured in MRI and DTI could provide additional insight about brain maturation. Also, in most previous studies on this age group studies have been done on measurements obtained from DTI or structural MRI,[5,9–12] there is relatively a few studies that have been done on joint analysis of MRI/DTI.[13] In this paper, we focus on the study of image intensity patterns in multi-modal MRI and DTI observed in longitudinal data of neonates, one year, and two year olds.

This paper is organized as follows: Section 2 describes a framework for intensity and spatial normalization scans of one subject across different modalities and different time points, and also across subjects. Then we talk about tractography which we use to define regions of interest. Section 3 summarizes results of structural and diffusion measurements of age-related changes on three different tracts from eight healthy subjects with repeated scans at approximately two-weeks, one year and two years old. The future work and limitation of our study is described in section 4.

2. FRAMEWORK FOR ANALYSIS OF MULTI-MODAL LONGITUDINAL DATA OF MULTIPLE SUBJECTS

In the present study, our goal is the analysis of spatio-temporal maturation of children undergoing normal growth. Image analysis of this age group presents multiple challenges including scale of developmental changes involved, contrast changes attributed to myelination, and high variability to name a few. Analysis of such data requires a method for identifying corresponding regions. We propose a registration framework that aims to map all the images into a common coordinate space and also within a common intensity range to allow us voxel by voxel or region by region analysis among different modalities, different ages, and different subjects. In this section, we first describe the co-registration and normalization of multi-modal longitudinal data followed by analysis of regions of interest defined by tractography.

2.1 Standardization of Multi-modal Longitudinal Data

Our registration and normalization framework is composed of the following steps: 1) A longitudinal multi-modal registration for each subject, 2) Registration of each subject to a common coordinate system, and 3) Intensity normalization.

2.1.1 Intrasubject Spatial Normalization

We first register scans of all modalities to T2W scan for each time point. We used the T2W as the template modality due to its similarity to the baseline image (B0) in DT imaging. In this step, each subjects T1W, PD, and B0 are affinely registered to the T2W scan of the same time point. This is followed by a nonlinear registration of the skull stripped B0 image to the T2W image using the method proposed by Rueckert et al.[14] The nonlinear registration method uses a 3D spline deformation model and normalized mutual information as the image match criterion to coregister images. Due to the distortions presented in the B0 image, nonlinear registration is a crucial step in mapping DTI to structural MR images for joint analysis.

We also perform a longitudinal registration for each subject using the baseline and follow up images. T2W scan of year-1 was selected as the template scan. Year-1 age was chosen as target age to minimize the degree of deformation that would be required from the other two age groups. Scans at 2-weeks and 2-years for a given subject are mapped to the corresponding T2W scan at 1-year. The longitudinal registration was carried out in two steps. A global transformation was first estimated using affine registration. Subsequently, using the result of the affine transformation as the starting point, a non-rigid registration step was carried out. Diagram of registration of multi-modal longitudinal data is shown in Figure 1

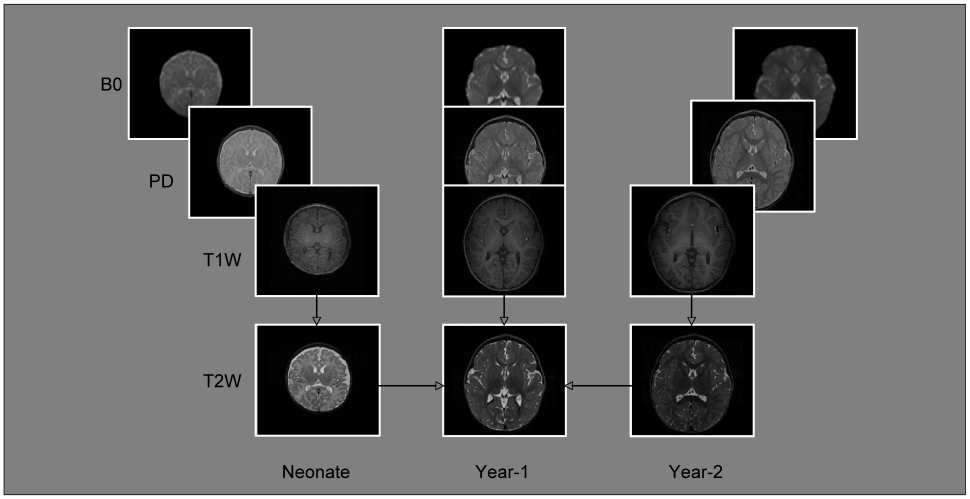

Figure 1. Intrasubject registration. First all modalities are registered to T2W of their respective time points. Second T2W of neonate and year-2 are registered to year-1 T2W.

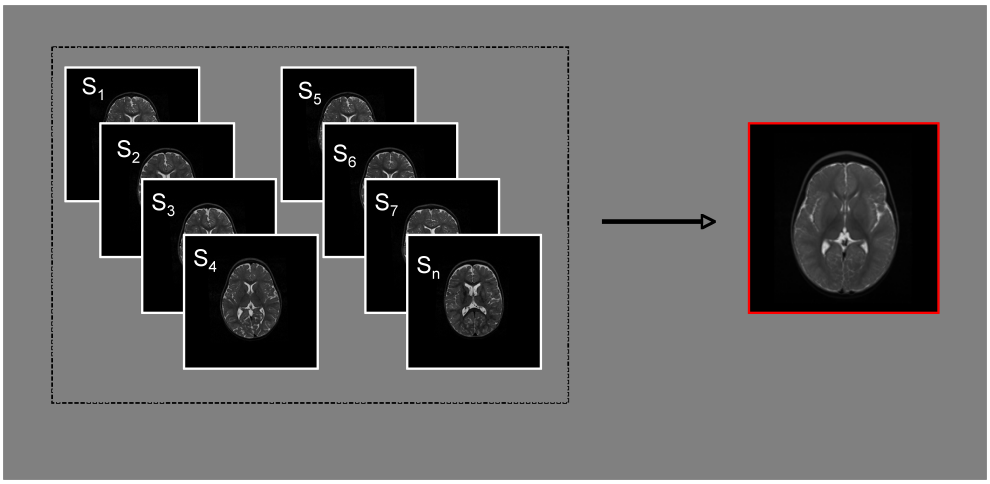

Figure 2. Unbiased atlas is created based on deformation of eight subjects' affined registered year-1 T2W scans

2.1.2 Intersubject Spatial Normalization

Comparison of structural and diffusion properties in multiple subjects requires a method for identifying corresponding regions of anatomy among subjects. We apply the atlas building procedure of Joshi et al.[15] to the set of T2W images at 1-year. This procedure was applied to the set of intensity adjusted T2W MR brain images of subjects at 1-year. As a preprocessing step, these images were aligned using an affine registration, and then using the atlas building tool we obtain an unbiased atlas based on our eight subjects as shown in Figure 2. This template construction framework produces invertible transformations between each subject and the atlas.

Based on the previous registration steps, we have a set of transformations between different modalities, between different age groups, and between each subject and the atlas. These transformations include series of linear and nonlinear transformations. We compose transformations into a single vector-field, and use this transformation to register each scan to the atlas.

Diffusion tensors were estimated for each subject time point from the diffusion weighted images using weighted least square tensor estimation. Each tensor is registered to the atlas using the cascaded transformations that was obtained by registering B0 to T2W. Tensors are resampled using finite strain reorientation and Riemannian interpolation. After all tensors are registered into atlas space, diffusion measurements such as fractional anisotropy (FA), mean diffusivity (MD), axial (AD) and radial diffusivity (RD) are calculated for each subject time point. Figure 3 shows registered multi-modal longitudinal scans of one subject.

2.1.3 Intensity Normalization

In order to obtain direct comparison of different scans, not only we need to have all the scans in the same coordinate system, but we also need to have scans of each modality normalized. T1W scans were normalized using mean intensity value of fatty tissue between the skull and the skin. This area was segmented using InsightSNAP (http://www.itksnap.org) on the atlas image, and applied to each subject. T2W scans were normalized with T2W values of ventricular CSF. The mean intensity values of these regions were then used as the normalization of T1W and T2W scans.

2.2 Analysis of Tract Properties

After spatial normalization of all structural and tensor images, corresponding values of different scans can be compared directly via voxel by voxel comparison, region of interest, or fiber tracts of interest. During neurodevelopment where understanding of myelination and pruning of axons is crucial to understanding of cognitive function, analysis of fiber tracts would be advantages. We use FibterTracking software (http://www.ia.unc.edu/dev) to extract fiber tracts from the tensor atlas. Tensor atlas was created by averaging transformed year-1 tensor images using the Log-Euclidean method.[16] The tensor atlas has an improved signal to noise (SNR) ratio that is

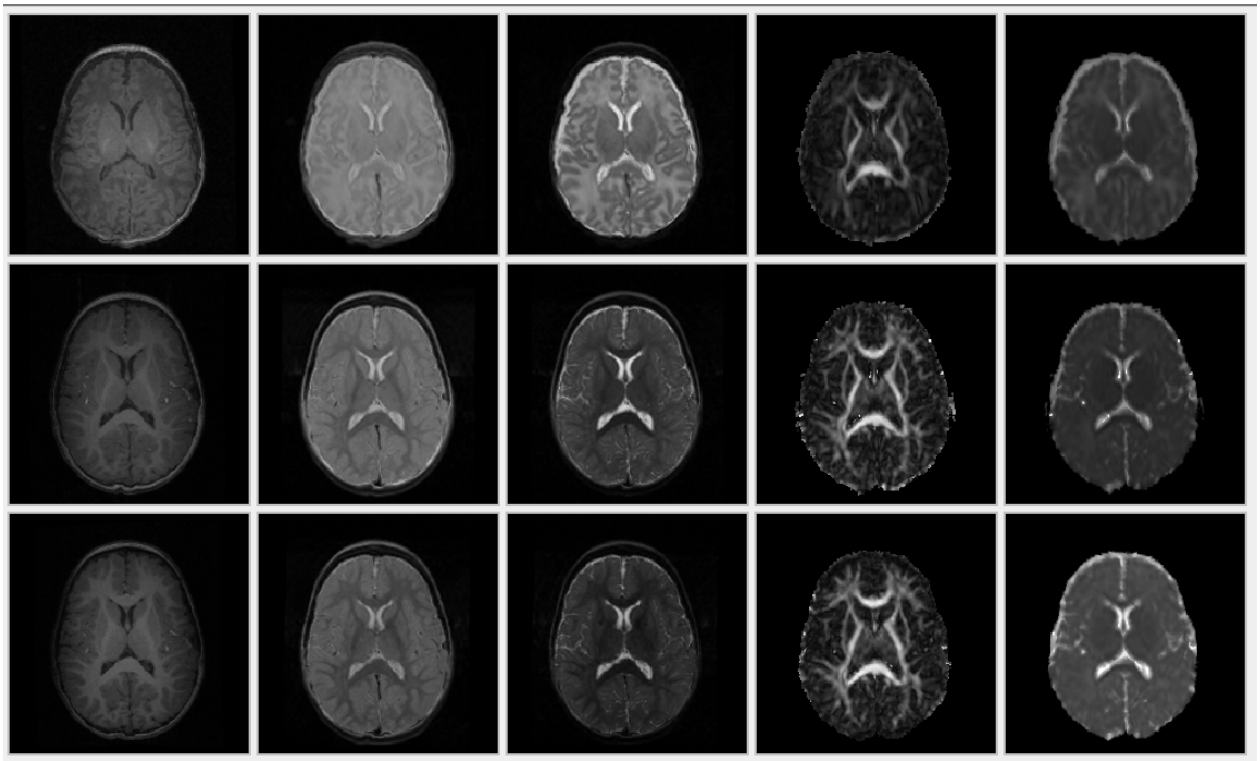

Figure 3. Axial view of co-registered multimodal MR data across age. Left to right: T1W, PD, T2W, FA, and MD. Top to bottom: Scans at approximately 2 weeks, 1 year, and 2 years.

used to create template fiber tracts. Also extracting fiber tracts in the atlas space ensures correspondence across subjects, and avoids the time consuming task of defining ROI to seed tractography on each scan. A streamline tractography algorithm using Runge-Kutta integration of the principal eigenvector field was used to extract the fiber tracts. Manual seeding and clustering of resulting tracts is used to input prior anatomical knowledge into the segmentation of fiber tracts. Extracted tracts were then mapped back into each subjects native space to obtain structural and diffusion properties for that subject. This results in a set of tracts in the atlas space with equivalent geometry but diffusion and structural values extracted from each subject. Corouge et. al, Jones et al., Maddah et al., and Lin et al. have proposed analysis of diffusion properties as a function sampled along arc length of fiber bundles.[17–20] We follow their proposed method in this work and also add structural measurements as a function sampled along arc length of fiber bundles.

3. ANALYSIS ON DTI/SMRI

Our preliminary study includes eight healthy pediatric subjects with repeated scans at the age of two weeks, one year, and two years. All the subjects received structural MRI scans on Siemens head-only 3T scanner with magnetization prepared rapid gradient echo T1-weighted, and turbo spin echo, dual-echo (proton density and T2 weighted) sequences. For DT I, a single-shot echo-planar spin-echo imaging sequence was used.

We used quantitative tractography for describing diffusion parameters such as FA, MD, axial (AD) and radial diffusivity (RD) along tracts of interest.[21] As an extension of the tool, we can add MRI measures of co-registered structural MR images for a multivariate analysis of diffusion and structural measures along tracts or within regions of interest. This is particularly interesting for the study of maturation and myelination of white matter tracts.

We extracted three fiber tracts: genu, splenium, and corticospinal tracts from tensor atlas via fiber tractography as is shown in Figure 4. The template tracts are then warped back to individual subject to compute scalar

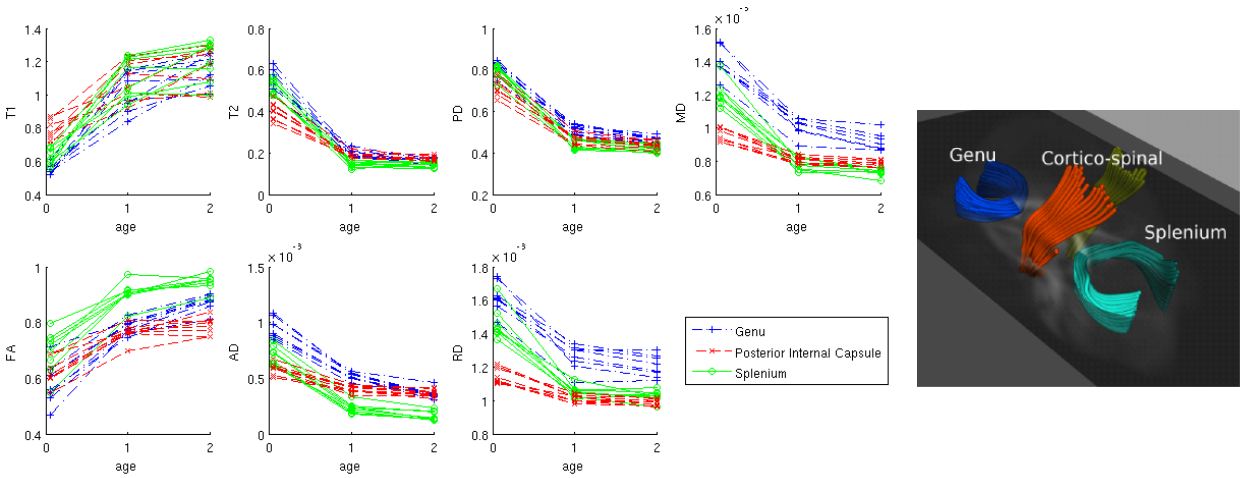

Figure 4. Left: Growth trajectories of regions of interest within fiber tracts of eight subjects. Right: Fiber tracts of interest.

invariant measures such as FA, MD, RD and AD, and also structural measures: T1W, T2W, and PD. Because geometry of individual fiber tracts are identical in the atlas space, the data from each subject is parametrized consistently. Tensor and structural measures are averaged at each cross-section along the bundle to produce a function of arc-length, except for fractional anisotropy where 80% quantile of each cross section is used to produce a function of arc length. We chose to use quantile rather than mean for FA values since FA doesn't have a gaussian distribution. For this study, the cross-sectional regions of interest were defined as follows: central regions of the genu and splenium fiber tracts were taken 3 mm on either side of the midsagittal plan. For the corticospinal tract, the cross-section of region of interest was defined such to contain posterior limb of internal capsule.

We analyzed changes of central regions of splenium and genu which are unmyelinated at birth, and posterior region of internal capsule which is myelianted at birth. Figure 4 shows growth trajectories of averages of cross-sections of regions of interest within a fiber tract, however, the values for fractional anisotropy (FA) are calculated by taking maximum of 80% quantile of cross sections. Different locations show different growth trajectories, however, the general trend is similar. FA and T1W increase as a function of age in contrast to T2W, PD, RD, and AD which decrease with age. Major changes of these measurements occurs between neonate and 1-years, followed by a slower rate of change from 1-year to 2-year, confirming previous findings in the literature.[22]

We also observed that the central regions of white matter tracts were more mature and organized than peripheral cortical regions; these central regions have low T2W, and higher FA and T1W. Figure 5 displays splenium tract on axial view of FA, T1W, and T2W images. As is shown in the images the central regions of splenium are more mature compared to peripheral regions, also the maturation of white matter as a function of age is from central to peripheral regions as is depicted in Figure 5. FA, T1W, and T2W show significant change between neonate and year-1, however, T1W shows a greater change between year-1 and year-2 compared to FA and T2W.

In this study we were also interested in finding differences in diffusion and structural properties that is attributed to myelination. Figure 6 shows an interesting finding obtained through quantitative analysis of regions of interest of specific tracts extracted through tractography[21] where increased FA is not always correlated with increased myelination. The FA values of myelinated posterior internal capsule is not higher than the unmyelinated central splenium contrary to the assumption that higher FA is linked to higher levels of myelination, similar finding was also reported by Gilmore et al.[13] The FA values appear to be more related to the structure and organization of fiber tracts than to the amount of myelin, and as a result studying FA alone can have misleading results. On the other hand, T2W values are better indicators of myelination even though it lacks structural information. Diffusion properties such as MD, AD, and RD can also provide more information about myelination. Our results

also show higher T1W and lower MD, RD, and AD values for myelinated regions. Using a joint multi-modal analysis of MRI and DTI provides a more complete understanding of neurodevelopment.

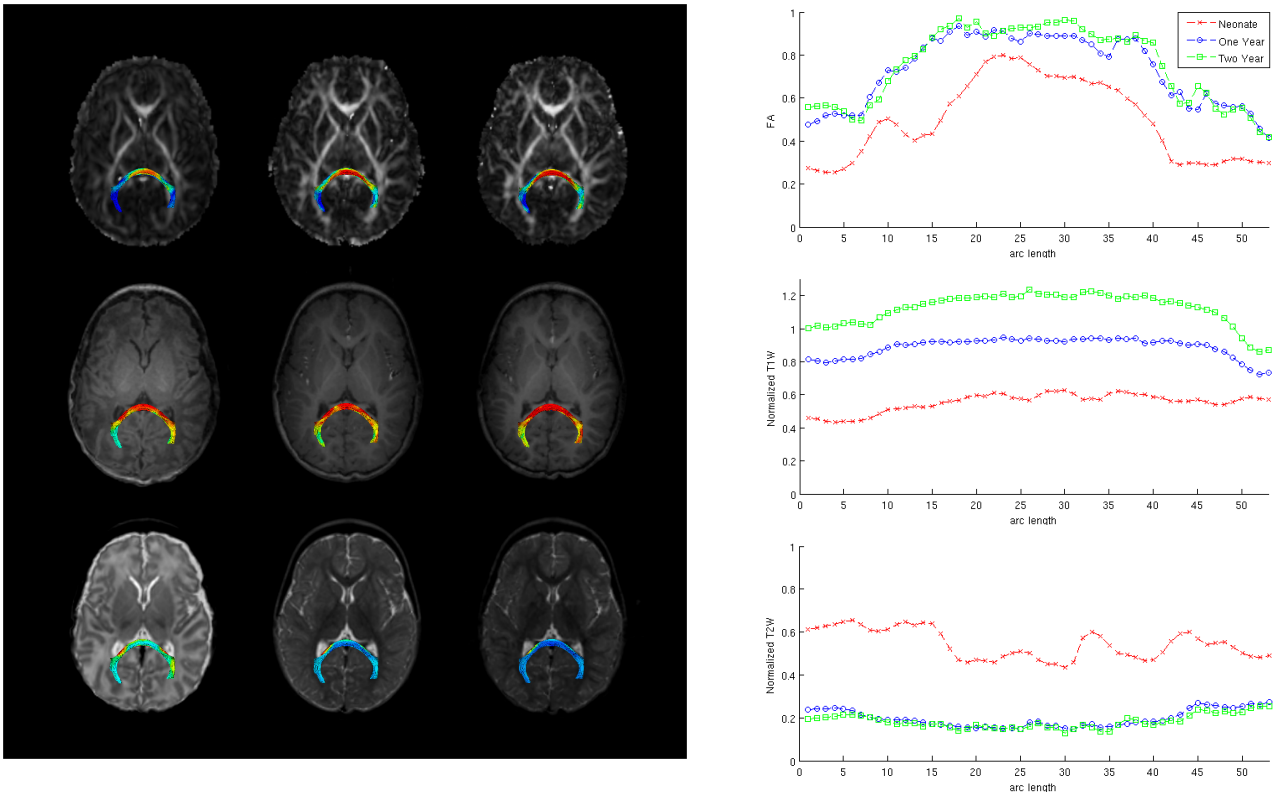

Figure 5. Left: Splenium tract overlaid on axial view of MR data across age. Top to bottom: FA, T1W, T2W, Left to right: scans at approximately 2 weeks, 1 year, and 2 years. Right: plots of FA, T1W, and T2W (top to bottom) as a function of arc-length for neonate, one year, and two years old. Horizontal axis is the location along the splenium tract from left to right.

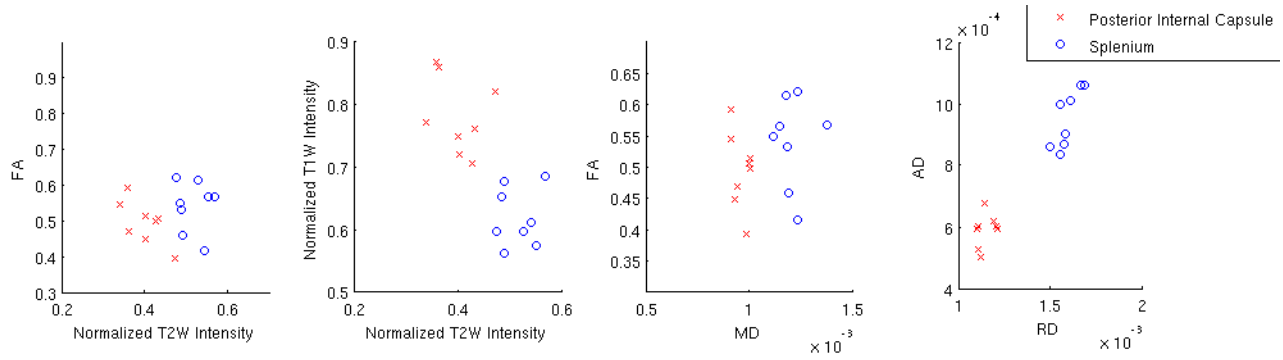

Figure 6. Left to right: Plot of FA vs T2W, T1W vs T2W, FA vs MD, and AD vs RD of unmyelinated central regions of splenium compared to myelinated regions of posterior internal capsule.

4. CONCLUSIONS

This work is in contrast to previous brain morphometry focuses on the analysis of brain tissue through intensity patterns of region of interest or fiber tracts of interest. We demonstrate that DTI alone is not sufficient to analyze tissue maturation and myelination, rather a multi-modal longitudinal analysis is needed for a better understanding of early brain development. A previous study by Gilmore et al.[23] arrived at similar conclusions, although it was restricted to infants of the same age group.

Our results suggest that we need a multi-modal framework with both structural imaging and diffusion imaging to better understand parameters related to tissue properties such as myelination, axon density changes and water density. Such a description will complement a characterization of brain morphometry changes and will potentially lead to an improved understanding of the trajectory of early brain maturation and changes thereof in disease. Our proposed registration and analysis framework for multi-modal MRI also includes spatial mappings that encode growth as spatial changes, and this information can be integrated in our framework for future work. Also we are planning to use longitudinal data analysis where we analyze continuous functions rather than discrete snap shots of data as we have done in this study. In the future we would like to analyze these multi-modal time curves and propose a normative model of tissue growth.

The are several limitation to our proposed framework. Our analysis relies on a spatial and intensity normalization of subjects. Registration of this age group is specially challenging due to the low contrast, high variability, and rapid growth of brain, and as a result, the registration is not perfect. Regions defined for intensity normalization were drawn manually on the atlas and mapped back to individual subjects. Any problem with spatial or intensity normalization will cause a problem in the quantitative analysis of fiber tracts. Also partial volume effect can cause differences in structural or diffusion measurements which do not reflect changes in myelination or axon density.

ACKNOWLEDGMENTS

Supported by NIH grants: BRP R01 NS055754 (GG) , 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).

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