Examining the Relationships between Cortical Maturation and White Matter Myelination throughout Early Childhood

Elise Croteau-Chonka[1], Justin Remer[2], Jonathan O'Muircheartaigh[3], Holly Dirks[2], Doug Dean III[4], and Sean Deoni[2]
[1]*Advanced Baby Imaging Lab, Brown University, Providence, Rhode Island, United States,* [2]*Advanced Baby Imaging Lab, Brown University, Rhode Island, United States,* [3]*King's College London, England, United Kingdom,* [4]*Waisman Center, University of Wisconsin-Madison, Wisconsin, United States*

Target Audience: Pediatric Imaging Neuroscientists, Neuroimaging Scientists

Introduction: Two important neurodevelopmental processes that occur throughout infancy and early childhood are the maturation of the myelinated white matter and cortical development (including changes in thickness, surface area, gyrification, and volume). In a magnetic resonance (MR) image of a 2 year-old brain, white matter tracts are well defined and there exists a clear boundary between gray and white matter. At earlier ages, however, the gray/white matter demarcation is increasingly difficult to outline[1]. This raises concerns about whether contrast-based measures of cortical development, such as cortical thickness[2], are accurately defining the cortex or if they instead represent adjacent white matter maturation.

Objective: Prior MR imaging studies in children have investigated white matter development independently of cortical thickness, with few elucidating the dynamic relationship between these related processes. Moreover, few studies have investigated these processes in young children under 5 years of age. Here, we attempt to address this gap by examining the relationship(s) between myelination and cortical development in children between 1 and 6 years of age.

Materials/Methods: *MRI Acquisition:* Longitudinal myelin water fraction (MWF) data was successfully acquired from 140 (60 female) healthy and typically-developing children 363 to 2198 days (corrected to a 40 week gestation) on a Siemens Tim Trio scanner with a 12-channel head RF coil array. A total of 184 imaging datasets were acquired during natural (non-sedated) sleep or while watching a movie. *Image Analysis:* Myelin Content: From the MWF data (mcDESPOT[3]), voxelwise estimates of myelin content were made by fitting a three-pool tissue model. Cortical Thickness: The Freesurfer analysis pipeline[2] was used to delineate the cortical ribbon, and demarcate the cortex into 34 regions / hemisphere. For each cortical region, mean thickness was measured, as well as mean MWF in the directly adjacent white matter. We then examined the relationship between cortical thickness and adjacent white matter MWF (Fig. 1). To remove the effect of age from these relationships, quadratic (cortical thickness) and logarithmic (MWF) curves were fit to the data, and these models were then subtracted from the individual measures. The resultant residuals were then plotted against each other.

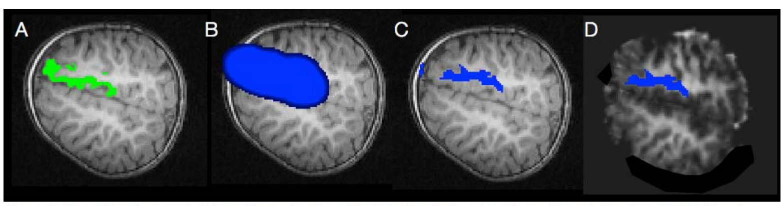

Figure 1. Generation of adjacent white matter masks. Freesurfer-derived cortical regions (a) were blurred with a 5mm FWHM Gaussian kernel (b), and then gray matter and brain portions were removed (c). The final mask was then superimposed on to the co-registered MWF image (d) and mean adjacent MWF calculated.

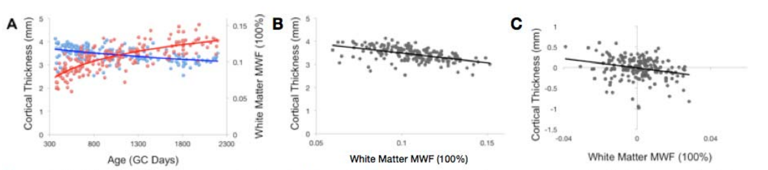

Figure 2. (a) Plot of cortical thickness and adjacent white matter MWF as a function of age across our cohort in left superior frontal gyrus. (b) Relationship between cortical thickness vs. adjacent white matter MWF. (c) Relationship between cortical thickness vs. adjacent white matter MWF after removing the age trend.

Results/Discussion: From 1 to 6 years of age, mean cortical thickness follows a decreasing quadratic trajectory, while adjacent white matter and cortical myelination logarithmically increase with age (Fig 2a). Plotting these data against each other (Fig. 2b), we observe strong and significant relationships between these processes. Removing the effects of age, however, reduces the trend (Fig. 2c). A statistically significant ($p < 0.05$ corrected for multiple comparisons) negative relationship was found in at least one hemisphere in 3 out of 7 examined bilateral regions, with increased white matter myelination predicting reduced cortical thickness. A statistically significant ($p < 0.05$ corrected for multiple comparisons) negative relationship was found in at least one hemisphere in 5 out of 7 bilateral regions, with increased cortical myelination predicting reduced cortical thickness. However, despite the observed significant relationships, the magnitude of the correlation is at most 0.2, suggesting that this relationship is explaining at most 20% of the variance in the data. This suggests that these two measures are not just proxies for one another, but rather represent more independent processes.

Conclusions: In this work we sought to elucidate the relationship between cortical development and adjacent white matter maturation through measures of cortical thickness and white matter MWF in a large cohort of typically-developing children. We have shown that the maturation profiles of these processes in different brain regions of interest can be characterized using quadratic and logarithmic fits. In particular, the cortical thickness trajectory observed in these brain regions could be a precursor to non-linear behavior that has been seen in children and young adults. Overall, this work suggests that measures of cortical thickness based on MR image contrast are not mistakenly representing adjacent white matter maturation. There is still, however, much to be elucidated about what other factors are influencing cortical development. It is also possible that cortical development and white matter maturation are linked instead with a temporal offset. It is unclear how we would begin to investigate the existence of such an offset, but we can rely on the knowledge that the results presented here provide the first insight into early neural network development, suggesting that the white matter maturation is closely linked to changes in cortical structure within similar networks.

References: 1. Deoni SCL, et al. Neuroimage. 2012;63(3):1038–53. 2. Fischl B. FreeSurfer. Neuroimage. 2012 Aug 15;62(2):774–81. 3. Deoni SCL, et al. Magn Reson Med. 2008 Dec;60(6):1372–87.