Is Myelin Content Associated with Early Language Development in Healthy Toddlers?

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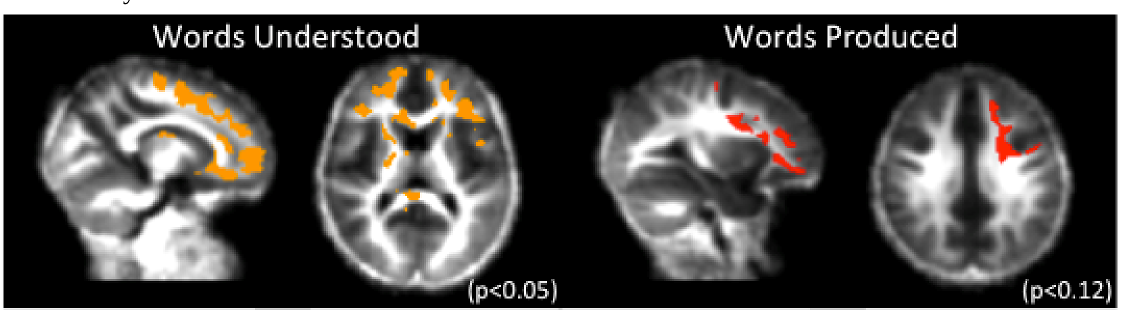
Introduction: Language acquisition and production are complex cognitive tasks, requiring the coordinated recruitment of, and messaging between disparate cortical and deep brain regions. Facilitating this synchronized brain messaging are the myelinated white matter pathways connecting these regions. The development of these pathways, therefore, is an important process of neurodevelopment, and atypical myelination may lead to reduced brain "connectivity" and functional impairment. Delayed language acquisition in infants, for example, is an early clinical indicator of later language impairment [1], and may be a precursor to developmental disorders, such as autism [2,3]. As the elaboration of the myelinated white matter is believed to spatially and temporally coincide with evolving behavioral and cognitive functioning, it may be hypothesized that delayed language acquisition may result from delayed or abnormal myelination in the language sub-serving brain networks. In this work, we sought to test this hypothesis by investigating the relationship between myelin content and language acquisition and production in toddlers.

Methods: *Image Acquisition:* A surrogate measure of myelin content, termed the myelin water fraction (MWF), was measured using a multi-component relaxometry technique (mcDESPOT) [4], which derives the MWF using a three-pool model fit to a combination of T_1-*weighted* SPRG and T_2/T_1-*weighted* bSSFP imaging data, with additional correction for B_0 and B_1 magnetic field inhomogeneities [5]. For this pilot study, data from 9 infants (10 to 16 months of age; mean ± SD = 12.4 ±1.9; corrected to 40 week gestation; 7 male) was acquired during natural sleep on a 3T Siemens scanner with a 12-channel head coil. Imaging parameters: 1.8 mm isotropic voxels (17 cm × 17 cm × 14.4 cm sagittal FOV), SPGR: TE/TR = 5.9 ms/12 ms; flip angles = {2, 3, 4, 5, 7, 9, 11, 14} degrees, IR-SPGR: matched to SPGR with half the resolution in the slice direction; TI of 600 ms and 900 ms, bSSFP: TE/TR = 5.1 ms/10.2 ms; flip angles = {9, 14, 20, 27, 34, 41, 56, 70} degrees. Two sets of bSSFP data are acquired with phase-cycling increments of 0 and 180° [6].

Language Assessment: Language was assessed using the MacArthur-Bates Child Development Inventory (CDI) Words and Gestures parent report [7]. Briefly, parents are presented with a vocabulary list of 396 words and asked to identify words understood (receptive language) and words understood and spoken (expressive language) by the child. We used age-normalized percentile scores of Words Understood and Words Produced as measures of receptive and expressive language, respectively, to correlate with MWF estimates.

Image analysis: Following acquisition and processing, voxel-wise MWF maps were non-linearly aligned to a study specific T_1-weighted template in approximate MNI space [5,6] and smoothed using a 3mm Gaussian kernel. Statistical analysis (correlation) was performed at each voxel to identify regions in which a significant relationship existed between MWF and the Words Understood and Words Produced CDI scores. A general linear model was used [8], modeling the relationship of language score on myelin content, including age as a covariate of no interest. Significance was defined as $p < 0.05$ cluster corrected for multiple comparisons.

Results: Significant *positive* correlation between MWF and Words Understood (i.e., greater MWF predicted higher receptive language score) was found in frontal cortical white matter, corpus callosum and internal capsule. A *trend* towards a *positive* correlation between MWF and Words Produced ($p < 0.12$ corrected) was found in the left frontal cortical white matter, consistent with Broca's area. No negative correlations of myelin content and CDI scores were found.



Discussion & Conclusion: In this pilot work, we sought to assess possible structure-function relationships linking myelination and language development in a small group of toddlers. We found that language understanding was correlated with brain regions responsible for general understanding and learning; while language production was more specifically linked to Broca's area, although only at *trend* levels. These results indicate that myelination may be implicated in language acquisition during key developmental stages. Further analysis, including additional infants over an expanded age-range, and using additional assessments (for example, the Mullen Scales of Early Learning [9]) may improve the spatial-specificity of these early findings, as well as the predictive ability.

References: [1] Ellis EM & Thal DJ, Perspect Lang Learn & Ed 2008; 15(3):93-100, [2] Miniscalco C et al, Dev Med & Child Neurol 2006; 48:361-366, [3] Buschmann A et al, Dev Med & Child Neurol 2008; 50:223-229, [4] Deoni SCL et al, MRM 2008; 60:1372–1387, [5] Deoni SCL, Proc. Advanced White Matter Imaging, Iceland, 2011 (2012); p. A10, [6] Deoni SCL, et al, NeuroImage 2012; 63(3):1038–1053, [7] Fenson L et al, Paul H. Brookes Publishing Co. 2007, [8] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/, [9] Mullen E, T.O.T.A.L. Child, Inc. 1995