Investigation of Longitudinal Neurodevelopment using Quantitative MRI

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Introduction: Human brain development is characterized by rapid, nonlinear growth throughout the first years of life[1]. Of particular importance is the elaboration of myelinated white matter that is essential for the establishment of efficient brain communication pathways and necessary for higher-ordered brain function[2]. Moreover, abnormal white matter development is believed to be associated with the emergence of many neurodevelopmental disorders[2]. Thus, improved understanding of healthy white matter maturation during infancy and early childhood, and its association with developing behavior, is central to provide insight into the processes underlying typical and atypical development.

Objective: We present longitudinal developmental trajectories of quantitative T_1, T_2, and myelin water fraction (VF_M). Longitudinal trajectories were fit to growth curves using non-linear mixed effects modeling, providing a description of neurodevelopment; longitudinal brain changes were hypothesized to relate to changes in cognitive ability.

Materials/Methods: *MRI Acquisition:* Longitudinal mcDESPOT data was successfully acquired from 103 healthy children (total of 260 imaging datasets) between the ages of 3 months and 5.5 years of age on a Siemens Tim Trio scanner during non-sedated sleep or while watching a movie. Three-pool mcDESPOT post-processing[3] was used to calculate quantitative T_1, T_2, and VF_M maps, which were subsequently aligned to a study template using a developed longitudinal image registration pipeline. Non-linear mixed effects modeling[4] was performed to characterize regional T_1, T_2, and VF_M trajectories from 28 regions of interest and provide subject-specific parameters of growth. Relationships between changes in quantitative MRI parameters and normalized indices of cognitive change (difference between final and initial Mullens Scales for Early Learning scores[5]) as well as their interactions with mean age were tested with a general linear model while controlling for the mean age and age difference between measurements.

Results: Longitudinal trajectories reveal a monotonically decreasing shape for both T_1 and T_2, while VF_M is sigmoidal. Mixed modeling provides parameters of fixed and random effects, allowing the characterization of population and individual growth, respectively (Fig 1a). Changes in T_1, T_2, and VF_M showed significant ($p<0.05$, corrected for multiple comparisons using FDR) relationships with changes in cognitive ability (gross and fine motor, visual reception, expressive and receptive language) in most of the examined regions (Fig 1b).

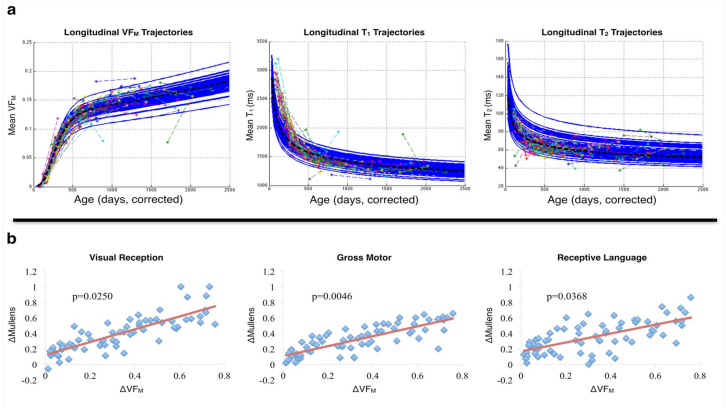

Fig 1: **a)** Developmental trajectories of VF_M, T_1, and T_2 for the body of the corpus callosum. Points with dashed lines represent individual measurements, blue lines correspond to subject-specific trajectories, and black dashed line describes the population trend. **b)** Illustrative correlations between changes in cognitive assessment scores (Mullens) and changes in VF_M. Significant ($p<0.05$) correlations suggest concomitant structure-function development.

Discussion: The observed changes in T_1, T_2, and VF_M reflect the progressive development of myelinated white matter, while changes in T_1 and T_2 are also influenced by decreasing water content. Mixed effects modeling provides an advantageous framework to investigate brain development due to its ability to account for repeated measurements from the same individual and provide indices of growth that describe the overall population and individual. Significant relationships between changes in MRI parameter and scores of behavior/cognitive ability suggest that these quantitative metrics may provide a structural marker of emerging cognitive function.

Conclusions: In this work we have sought to characterize longitudinal changes of T_1, T_2, and VF_M in a large cohort of typically developing children. We have shown that these longitudinal trajectories can be characterized using non-linear mixed effects modeling techniques, providing a unique description of early neurodevelopment. Moreover, combining quantitative MRI measures with age-appropriate scores of cognition and behavior revealed significant relationships between maturing structural and functional networks. This presented work provides an important step for understanding the typical patterns of normative white matter maturation and its relationship to emerging cognition; as well as providing a foundation for future studies examining atypical brain development.

References: [1]Giedd JN & Rapoport JL. Structural MRI of Pediatric Brain Development: What have we learned and were are we going? *Neuron.* 2010;**67**:728-734 [2]Fields RD. White matter in learning, cognition and psychiatric disorders. *Trends Neurosci*. 2008;**31**:361-370. [3]Deoni SCL, et al. One Component? Two Components? Three? The effects of including a non-exchanging 'free' water component in mcDESPOT *MRM.* 2012;**70**:147-154. [4]Lindstrom MJ & Bates DM. Nonlinear mixed effects models for repeated measures data. 1990;**46**:673-687. [5]Mullen E. Mullen scales of early learning. American Guidance Services Inc. 1995.