White Matter Maturation Profiles Through Early Childhood Predict General Cognitive Ability

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Target Audience: Developmental neuroscientists.

Introduction: Infancy and early childhood is a dynamic, yet vulnerable, period of brain development. In response to a complex cascade of environmental and genetic influences, the brain structurally and functionally matures alongside evolving cognitive ability. An important neurodevelopmental process during this post-natal period is the maturation of the myelinated white matter, which facilitates rapid and coordinated communication across the brain's networks and systems. Though prior brain imaging studies in children (4 years of age and above), adolescents, and adults have consistently linked white matter development with cognitive maturation and intelligence[1], few studies have examined how these processes are related throughout early development (birth to 4 years of age). Here we sought to determine how profiles of white matter myelination across the first 5 years of life are related to cognitive ability. Using a longitudinal study design, we examined and compared developmental myelination trajectories in children stratified by cognitive ability as assessed by the Mullen Scales of Early Learning[2]. We found that children with above average ability have initially slower, but prolonged early development compared to average and below-average ability children, even when controlling for socioeconomic status, gestation, and birth weight. These results provide new insight into the early neuroanatomical correlates of cognitive ability, and stresses the need for longitudinal perspectives for investigating typical or atypical cognitive maturation.

Purpose: To investigate how cognitive ability is related to, or predicted by, profiles of white matter maturation throughout early childhood (birth to 5 years of age).

Methods: *MRI Acquisition:* Whole-brain myelin water fraction (MWF) datasets were acquired using mcDESPOT[3] from 126 (53 female) healthy and typically-developing children, 98 to 1814 days of age (3 months to 5 years), corrected to a 40-week gestation. All were scanned at least twice; 39 scanned at least 3x; 15 scanned at least 4x; and 4 scanned 5x. The mean inter-scan interval was 280 days (~9 months). *Cognitive Assessment:* Within one week of MRI, all children were assessed using the Mullen Scales of Early Learning[2], which provides age-normalized scores for fine and gross motor control, visual reception, and expressive and receptive language for children up to 5 years, 9 months of age. In addition to the individual domain scores, the Mullen Scales provides an overall composite score (the Early Learning Composite, ELC, expressed as a standard score with mean=100 and standard deviation of 15) derived from the sum of the fine motor, visual reception, and expressive and receptive language age-normalized T-scores. On the basis of their ELC, children were divided into one of three groups: above-average (n=38, ELC=121±5.2), average (n=54, ELC=99±6.5), and below average (n=34, ELC=79±5.4). There were no significant group differences in male:female ratio or racial composition, mean age, gestation duration, birth weight, or maternal SES. *Image Analysis:* Following non-linear co-registration of all datasets to a common template, mean Gompertz growth curves[4] were calculated for whole-brain white matter (WM), as well as frontal, temporal, occipital, parietal, cerebellar, and corpus callosal WM, using non-linear mixed-effects regression[5]. Growth model parameters were then compared.

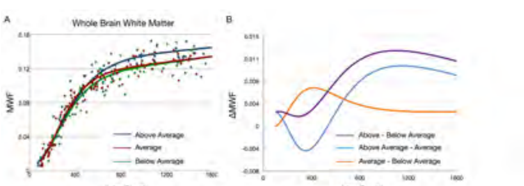

Figure 1: Comparison of Whole-Brain White Matter MWF development. (A) Reconstructed continuous growth models for mean whole-brain white matter calculated using the longitudinal data from the above average (blue), average (red), and below average (green) ELC children. Individual data points represent the mean values calculated from each individual child's data. The results show a trend seen in all other investigated brain regions, with overall development in the above average children > average > below average. Differences in development are more clearly visualized by examining the ΔMWF curves **(B)**, which show an early delay in myelination onset and prolonged myelination in the above average children, resulting in an overall increase in MWF in later childhood.

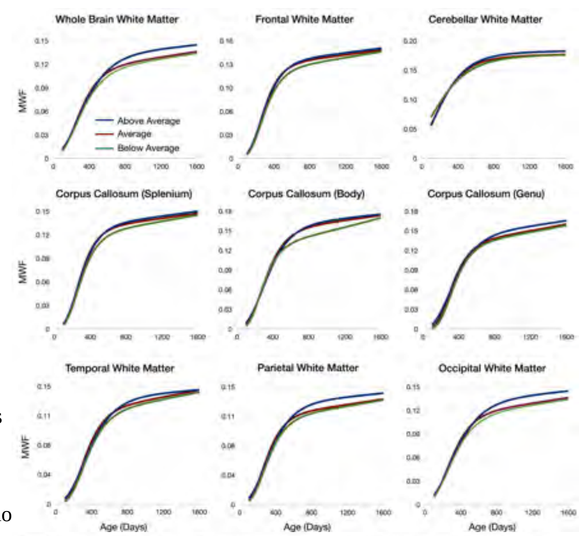

Figure 2: Comparison of MWF development. Reconstructed continuous growth models for different brain regions for the above average (blue), average (red), and below average (green) ELC children.

Results & Discussion: We found above-average, average and below-average children had significantly different MWF development in each of the brain regions investigated (Fig. 1a and 2). In all regions, the above-average group displayed greater MWF values by 3 years of age compared to the average and below-average groups. Examining whole-brain WM, plots of group MWF difference (ΔMWF) (Fig. 1b) highlight the different developmental trajectories associated with each group. Results suggest the above-average children have initially slower, but prolonged, WM maturation through the first two years of life. This trajectory yields a maximal MWF difference by ~3 years of age. In contrast, the average group showed increased early development relative to belo average children with these groups appearing to normalize with age. While prior studies have examined WM development with respect to cognition and learning (Nagy et al., 2004; Fields, 2008), this is the first study to examine this critical process throughout early childhood. Prior investigations of WM volume *and* cortical thickness have shown cortical thinning is spatially and temporally concomitant with brain volume growth, with the authors suggesting thinning may be driven by increased myelination of neural fibers in the lower cortical layers. A current model of development posits that more gradual rates of development yield increased cortical volumes, particularly in areas important to intelligence[6]. Our results provide new support for these developmental models.

References: 1. Nagy Z, et al. J Cogn Neurosci. 2004 :1227–33. 2. Mullen EM. Mullen scales of early learning. 1995. 3. Deoni SCL, et al. Magn Reson Med. 2008 :1372–87. 4. Dean DC, et al. Brain Struct Funct. 2014. 5. Lindstrom MJ, Bates DM. Biometrics. 1990. 6. Clancy B, Darlington RB, Finlay BL. Developmental Science. Blackwell Publishers Ltd; 2000:57–66.