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Examining the relationships between cortical maturation and white matter myelination throughout early childhood

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ABSTRACT

Cortical development and white matter myelination are hallmark processes of infant and child neurodevelopment, and play a central role in the evolution of cognitive and behavioral functioning. Non-invasive magnetic resonance imaging (MRI) has been used to independently track these microstructural and morphological changes *in vivo*, however few studies have investigated the relationship between them despite their concurrency in the developing brain. Further, because measures of cortical morphology rely on underlying gray–white matter tissue contrast, which itself is a function of white matter myelination, it is unclear if contrast-based measures of cortical development accurately reflect cortical architecture, or if they merely represent adjacent white matter maturation. This may be particularly true in young children, in whom brain structure is rapidly maturing. Here for the first time, we investigate the dynamic relationship between cortical and white matter development across early childhood, from 1 to 6 years. We present measurements of cortical thickness with respect to cortical and adjacent myelin water fraction (MWF) in 33 bilateral cortical regions. Significant results in only 14 of 66 (21%) cortical regions suggest that cortical thickness measures are not heavily driven by changes in adjacent white matter, and that brain imaging studies of cortical and white matter maturation reflect distinct, but complimentary, neurodevelopmental processes.

Introduction

Two important neurodevelopmental processes that occur throughout infancy and early childhood are the maturation of myelinated white matter and the development of the cerebral cortex. The formation of the lipid bilayer myelin sheath around neuronal axons (myelination) is essential for the rapid brain messaging required for higher order behavioral and cognitive functioning. Brain disconnectivity resulting from aberrant or insufficient development of the myelin sheath may underlie a number of neuropsychiatric disorders, including autism and attention deficit hyperactivity disorder (Belmonte et al., 2004; Krain and Castellanos, 2006; Konrad and Eickhoff, 2010; Xiao et al., 2014). Measures of cortical development, including changes in thickness, surface area, gyrification, volume, and gray matter myelination, have also been investigated in the context of developmental and psychiatric disorders (Courchesne et al., 2007; Hazlett et al., 2012), and in relation to cognitive performance (Shaw et al., 2007, 2012).

Advances in magnetic resonance imaging (MRI) have allowed for the *in vivo* investigation of myelination and cortical maturation both across development and in association with cognitive and behavioral development. Multicomponent relaxometry (MCR) techniques, such as mcDESPOT (multicomponent driven equilibrium single pulse observation of T_1 and T_2) (Deoni et al., 2008), enable the visualization and quantification of a surrogate measure of myelin content, termed the myelin water fraction (MWF). MCR decomposes the measured MRI signal into the contributions of signal signatures associated with differing microanatomical water compartments. In the brain, three distinct water pools are commonly observed, corresponding to the free intra- and extra-axonal water, the CSF water, and the water trapped between lipid bilayers of the myelin sheath (MacKay et al., 2006). Quantification of the myelin-associated signal, the MWF, is a useful metric for tracking white matter maturation (Deoni et al., 2012; Dean et al., 2015) and its

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relationship to cognitive development (O'Muircheartaigh et al., 2013, 2014; Deoni et al., 2014) in the developing brain.

Most commonly measured through Freesurfer segmentation (Fischl, 2012) of the cortical ribbon from a T_1-weighted MR image, cortical thickness is an oft used metric for tracking synaptic density and cortical maturation. While Freesurfer analysis is not formally recommended for use in children under 4 years of age, it has been utilized in investigations of cortical development in infants and toddlers as young as 12 months (Lowe et al., 2012; Travis et al., 2014). Accurate and reproducible delineation of cortical gray matter from underlying and adjacent white matter is a prerequisite for calculating cortical thickness. In ours (Deoni et al., 2015), and others (Lyall et al., 2014) experience, inaccuracies in cortical segmentation can be attributed to insufficient gray–white matter contrast in children under 12 months.

While myelination and cortical development do not occur independently, with both processes occurring symbiotically during the development of neural systems, few studies have sought to investigate the relationship between them. Further, since accurate cortical thickness measures necessitate strong gray–white matter image contrast, which itself is a function of white matter myelination, it is unclear if measures of cortical thickness in early childhood reflect cortical architecture or adjacent white matter maturation. In this work, we aim to directly examine the relationships between cortical thickness and white matter myelination in a large cohort of 134 typically-developing children between 1 and 6 years of age. We measured cortical thickness and calculated the MWF within directly adjacent white matter in 33 bilateral cortical regions. Our results show that cortical thickness changes are not fully explained by MWF changes alone, suggesting that Freesurfer cortical thickness values and MWF are measuring distinct and complementary processes of neurodevelopment.

Materials and methods

Study design and participants

Data from 134 (58 female) healthy and typically-developing children approximately 1 to 6 years of age (363 to 2198 days corrected to a 40-week gestation) were used in this study. These children were recruited as part of an ongoing longitudinal investigation of white matter maturation in relation to behavioral development in infancy and early childhood (Deoni et al., 2012). Full demographic information is provided in Table 1. A total of 177 scans were performed, with 36 children scanned at least twice and 7 children scanned three times. The average time between repeat scans was approximately one year (Fig. 1). Inclusion criteria consisted of: birth between 37 and 42 weeks gestation; no abnormalities present on fetal ultrasound; no delivery complications (*i.e.* no visits to the neonatal intensive care unit); APGAR score of 8 or higher; no *in utero* exposure to illicit drugs or alcohol; no pregnancy complications (*i.e.* preeclampsia); no familial history of learning disability, behavioral or psychiatric disorder; and no reported neurological events or disorders in the infant such as head trauma or epilepsy. Child, sibling, and parent medical histories were collected as a supplement to parental interviews conducted at the time of study enrollment. Written informed consent was obtained from the parent(s) or legal guardian of each participating child, and all experimentation was performed under the approval of the Brown University Institutional Review Board.

Table 1
Participant demographic information.

Gender	Male (n)	76
	Female (n)	58
Racial background	Caucasian (n)	89
	African American (n)	11
	Asian (n)	2
	Mixed Race (n)	18
	Unknown (n)	16
Ethnic background	Hispanic (n)	28
	Non-Hispanic (n)	10
	Unknown (n)	96
Mean age (days)	1044 ± 523	
Age range (days)	363–2198	
Mean gestation (weeks)	39 ± 1.4	
Mean birth weight (lbs)	6.9 ± 1.0	
Mean maternal SES	5.9 ± 1.1	

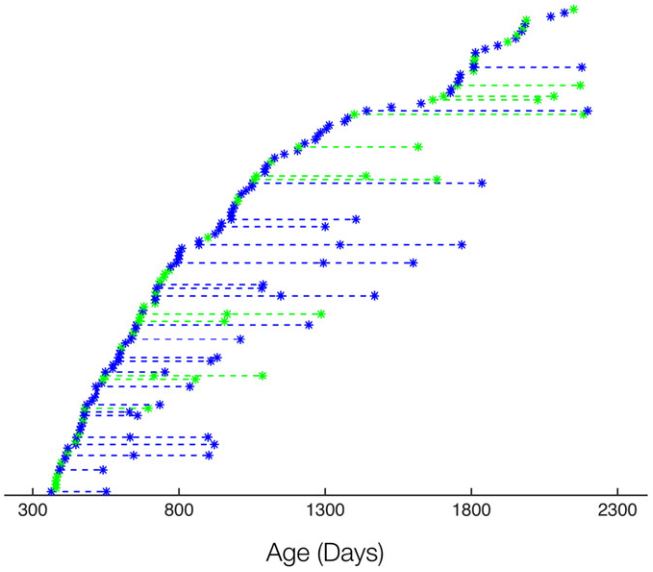

Fig. 1. Age distribution (corrected to a 40-week gestation) of study cohort with females in green and males in blue. Individual scans are denoted by an asterisk, with dashed lines connecting repeated measurements from the same child.

Image acquisition

To measure MWF, whole-brain mcDESPOT data were acquired using age-optimized imaging protocols described previously (Deoni et al., 2012) and summarized in Table 2. All imaging was performed on a 3T Siemens Tim Trio scanner with a 12-channel head RF coil array. The data set for each child includes 8 T_1-weighted spoiled gradient echo (SPGR) images, 2 inversion-prepared SPGR images (IR-SPGR), and 2 sets of T_1/T_2-weighted steady-state free precession (bSSFP) images, each acquired with a differing radio-frequency phase-cycling pattern (Deoni, 2011). High resolution volumetric T_1-weighted MP-RAGE data were also acquired for cortical morphometry analysis.

Children under the age of four were imaged during natural (non-sedated) sleep, while children over four were imaged while watching a favorite movie or TV show (Dean et al., 2014). To attenuate noise levels in the scanner, and keep the youngest participants asleep for the duration of the session, peak gradient amplitudes and slew rates were reduced to 25 mT/m/s, foam inserts (Quiet Barrier HD Composite, UltraBarrier USA) were secured inside the scanner bore, and headphones (MR Confon, Germany) were positioned to cover the ears. To limit the possibility of movement during the scan, all children were swaddled in age-appropriate MedVac vacuum immobilization bags (CFI Medical Solutions, USA) and their heads were kept in place with foam pads. A research assistant watched over infants from inside the scanner room, and additional monitoring was possible using a pediatric pulse-oximetry system and infrared camera. During acquisition, image data was evaluated for motion artifacts including blurring and ghosting. Presentation of these artifacts on an image necessitated repeated acquisition of that image using the original FOV positioning and sequence parameters until higher quality data was obtained. These motion-free images were then incorporated into the child's data set as replacements for artifact-laden images prior to image processing (Dean et al., 2014).