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Modeling healthy male white matter and myelin development: 3 through 60 months of age

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ABSTRACT

An emerging hypothesis in developmental and behavioral disorders is that they arise from disorganized brain messaging or reduced connectivity. Given the importance of myelin to efficient brain communication, characterization of myelin development in infancy and childhood may provide salient information related to early connectivity deficits. In this work, we investigate regional and whole brain growth trajectories of the myelin water fraction, a quantitative magnetic resonance imaging measure sensitive and specific to myelin content, in data acquired from 122 healthy male children from 3 to 60 months of age. We examine common growth functions to find the most representative model of myelin maturation and subsequently use the best of these models to develop a continuous population-averaged, four-dimensional model of normative myelination. Through comparisons with an independent sample of 63 male children across the same age span, we show that the developed model is representative of this population. This work contributes to understanding the trajectory of myelination in healthy infants and toddlers, furthering our knowledge of early brain development, and provides a model that may be useful for identifying developmental abnormalities.

Introduction

The elaboration of the myelin sheath around neuronal axons, and the associated white matter maturation, is a cornerstone of human neurodevelopment. Myelinated white matter forms efficient communication pathways that shape the integrated neural systems responsible for higher order functioning (Fornari et al., 2007; Johnson and Munakata, 2005). Given myelin's critical role in brain communication, processes that disrupt its development may result in reduced brain connectivity and inefficient interneuronal communication. In turn, this may lead to altered neuronal functioning, and may contribute to some neurodevelopmental and psychiatric disorders, including autism and attention deficit and hyperactivity disorder (Courchesne, 2004; Haroutunian and Davis, 2007; Konrad and Eickhoff, 2010).

Myelination during the first five years of life is a rapid and dynamic process. Prior histological studies have established that myelination begins in the cerebellum and brainstem in utero (Barkovich et al., 1988; Flechsig, 1901; Paus et al., 2001; Yakovlev and Lecours, 1967). Following birth, myelination proceeds caudocranially from the splenium of the corpus callosum, optic radiations and internal capsule by 3–4 months; occipital and parietal lobes by 5–6 months; temporal and frontal lobes by 9–11 months (Flechsig, 1901; Yakovlev and Lecours, 1967); and continues into the second decade of life (Barnea-Goraly et al., 2005; Bartzokis et al., 2010). However, while retrospective histological studies provide the most faithful characterization of myelin development, they suffer significant limitations. They are i) inherently cross-sectional; ii) difficult to combine into a single temporal timeline, owing to differences in staining techniques and inconsistent brain coverage; iii) difficult to obtain from large specimen pools spanning the infant age-range; iv) preclude investigation of underlying structure–function relationships; and v) labor intensive. Further, they may not necessarily reflect healthy development as these studies are conducted post-mortem.

Recent in vivo magnetic resonance imaging (MRI) techniques, including conventional T_1- and T_2-weighted structural imaging, diffusion tensor (DT)-MRI, and magnetization transfer imaging (MTI), have become popular for investigating early brain development (Giedd and Rapoport, 2010; Giedd et al., 1999; Knickmeyer et al., 2008) and, especially, white matter maturation (Geng et al., 2012; Lebel et al., 2012; van Buchem et al., 2001). These non-invasive techniques provide detailed anatomical tissue contrast and micro-structural insight that affords a more sensitive and direct means of examining white matter development. However, these methods also have their disadvantages.

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While conventional MRI (T_1- and T_2-weighting) have shown alterations in the gray/white matter contrast (Huang et al., 2006; Paus et al., 2001) temporally mirroring myelination, these qualitative observations are influenced by a variety of micro-structural and biochemical elements (MacKay et al., 2009). DT-MRI offers a quantitative approach, with metrics including fractional anisotropy (FA), mean diffusivity (MD), and axonal and radial diffusivity (AD and RD, respectively). Changes in these metrics during development have often been associated with myelination, however these measures are also associated with changes in the local tissue architecture (Jones et al., 2013; Mädler et al., 2008). Many of these measures are also derived directly from the tensor model of diffusion that does not apply to all brain voxels, making the interpretation difficult (Wheeler-Kingshott and Cercignani, 2009). Similarly, while the magnetization transfer ratio (MTR) has been shown to correlate strongly with myelin content (Moll et al., 2011; van Buchem et al., 2001; Zaaraoui et al., 2008), the MTR is also influenced by other processes including edema and/or inflammation (Gareau et al., 2000; Vavasour et al., 2011).

Multi-component analysis of relaxation time data, also termed multi-component relaxometry (MCR), may provide a more sensitive measure of myelin content. MCR decomposes the measured MRI signal into contributions from distinct micro-structural water compartments. Prior MCR studies have consistently reported at least two water compartments: a fast-relaxing water pool attributed to water trapped between the myelin-lipid bilayers; and a slower-relaxing water pool attributed to intra-/extra-cellular water (MacKay et al., 2006; Whittall et al., 1997). Quantification of the signal from the myelin-bound water, termed the myelin water volume fraction (MWF), has been shown to strongly correlate with histological assessments of myelin content (Gareau et al., 2000; Laule et al., 2006, 2008; Odrobina et al., 2005; Webb et al., 2003) and provide improved myelin specificity compared to DT-MRI measures or MTR (Gareau et al., 2000; Mädler et al., 2008; Vavasour et al., 2005).

While MCR has traditionally been performed using multi-echo T2 decay data, a more recent approach, termed mcDESPOT (multi-component driven equilibrium single pulse observation of T_1 and T_2), has been proposed (Deoni et al., 2008). Though at the expense of a more complicated signal model that must include the effects of water exchange, mcDESPOT offers the potential advantages of improved SNR, reduced acquisition times, and increased spatial resolution and volumetric coverage compared to the established T_2 approach. While comparison of multi-echo T_2 and mcDESPOT MWF values present a known discrepancy, with mcDESPOT values being consistently larger (Zhang et al., 2013), they do, however, correspond qualitatively with histological myelin content measures in a Shaking Pup model of dysmyelination (Hurley et al., 2010), and have been used to investigate structure–function impairment in MS (Kitzler et al., 2012; Kolind et al., 2012) and other demyelinating disorders (Kolind et al., 2013). More recently, the mcDESPOT has been applied to the study of white matter maturation and healthy infant neurodevelopment (Deoni et al., 2011, 2012), revealing a strong consistency with the known spatial–temporal pattern of myelination.

A continuous and probabilistic model of myelination could alleviate these concerns. Derivation of an appropriate growth model would allow estimation of the typical mean MWF, and variance, for any age. This work sought to develop such a model by comparing common growth functions fit to measured MWF data. The most appropriate model was then used to generate a continuous, four-dimensional "atlas" of healthy MWF development, allowing calculation of the 'typical' average and standard deviation MWF maps at any desired age. As proof-of-concept, individual and group-averaged MWF maps were statistically compared to the growth model derived MWF maps, with no significant differences found. The developed atlas, therefore, represents the first continuous model of myelin maturation in healthy male infants; provides an important step for understanding the typical myelination trajectory; and provides a framework from which to identify the earliest of white matter changes.

Materials and methods

Subjects

MRI data analyzed in this work are part of an ongoing longitudinal study investigating white matter maturation in healthy, typically developing children and its relationship to behavioral development (Deoni et al., 2012). Informed parental consent was obtained in accordance to ethics approval from the Institutional Review Board of the host institution. Enrolled infants met the following inclusion criteria: uncomplicated single birth between 37 and 42 weeks; no exposure to alcohol or illicit drugs during pregnancy; no familial history of major psychiatric or depressive illness; no diagnosis of major psychiatric, depressive or learning disorder in participant; and no pre-existing neurological conditions or major head trauma. In total, 122 healthy male infants and toddlers between 70 and 1809 days of age (mean = 690.14 days, corrected for a 40-week gestation) were analyzed. Table 1 provides an age-group break down of these participants.

Measuring MWF in infants

Whole-brain MWF maps were acquired using the rapid mcDESPOT (Deoni et al., 2008) imaging technique. Imaging protocols for this age-range, using acoustically-muffled sequences, have been presented previously (Deoni et al., 2011, 2012), and comprise 8 T_1-weighted spoiled gradient echo images (SPGR or spoiled FLASH), 2 inversion-prepared (IR)-SPGR images and 16 T_1/T_2-weighted steady-state free precession (SSFP or TrueFISP) images.

MWF maps were calculated from these data using a three-pool signal model estimating intra/extra-axonal water; myelin-associated water; and a non-exchanging free water pool (Deoni et al., 2013). Corrections for flip angle (B_1) and off-resonance (B_0) inhomogeneities were also performed (Deoni, 2010). Total imaging times ranged from 19 min for the youngest infants to 24 min for older and larger children.

Children under 4 years of age were scanned during natural, non-sedated, sleep; while children over this age were able to watch a favorite TV show or movie. All data was acquired on a 3 T Siemens Tim Trio scanner equipped with a 12 channel head RF array. To minimize intra-scan motion, children were swaddled with an appropriately sized pediatric MedVac vacuum immobilization bag (CFI Medical Solutions, USA) and foam cushions were placed around their head. Scanner noise was reduced by limiting the peak gradient amplitudes and slew-rates to 25 mT/m/s. A noise-insulating insert (Quiet Barrier HD Composite, UltraBarrier, USA) was also fitted to the inside of the scanner bore. MiniMuff pediatric ear covers and electrodynamic headphones (MR Confon, Germany) were used for all scanned children, while a pediatric pulse-oximetry system and infrared camera were used to continuously monitor the sleeping infants during scanning. After acquisition, image data was assessed for motion artifacts (blurring, ghosting, etc).

MR analysis and myelin trajectory modeling

Following calculation of the 122 MWF maps, all maps were non-linearly aligned to a study specific template (Deoni et al., 2012) using the Advanced Normalization Tools software package (Avants et al., 2008) and smoothed with a 3 mm Gaussian kernel. Non-brain parenchyma was removed using FSL's brain extraction tool (BET) (Smith, 2002). Regional masks for bilateral frontal, temporal, parietal, and occipital lobes, cingulum, and cerebellar white matter, as well as the genu, splenium and body of the corpus callosum were derived from the MNI adult template (Mazziotta et al., 2001), co-registered to the study template, and superimposed upon each infant's MWF maps (Deoni et al., 2012). Mean MWF values for each mask were obtained for each infant and plotted against the infant's gestational-corrected age. To examine whether the nonlinear transformation affected the quantitative values, mean MWF values were also extracted from native