Imaging Myelination in Infant Neurodevelopment

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INTRODUCTION: Myelination, or the development of the myelin lipid bilayer surrounding neuronal axons, is a fundamental cornerstone of human neurodevelopment. Essential for normative brain function, the myelin sheath facilitates rapid information transfer between disparate brain regions that comprise the integrated neural systems required for coordinated movement, decision-making and other higher order cognitive, behavioral and emotive functions. Post-mortem histological studies have presented myelination as a well-defined spatial and temporal sequence (1), proceeding from deep to superficial brain regions, with myelinating regions corresponding to developing neural systems and behaviour (2). Unfortunately, histological investigations preclude longitudinal investigations of development, as well studies of structure-function relationships. The onset of 'adult-like' grey and white matter contrast on conventional T_1 or T_2-weighted MR images (3,4) and progressive increases in water diffusion fraction anisotropy (FA) measured by DT-MRI (5) both parallel the biochemical and biophysical tissue changes associated with brain maturation and myelination. However, these measures reflect several characteristics of neural maturation, including gross tissue and fibre architecture changes and are not specific to myelin. Thus, to date, no quantitative description of myelin development in human infants has been presented. In this work, we re-construct myelin development in healthy infants using a novel, silent and myelin-specific MRI-based technique (6). We reveal a spatio-temporal sequence of myelination that faithfully reproduces the established post-mortem findings and, for the first time, allows non-invasive and quantitative visualization of myelin development during human infancy.

METHODS: To quantitatively image myelin development, we used the rapid multi-component relaxation (MCR) technique, mcDESPOT - multi-component Driven Equilibrium Single Pulse Observation of T_1 and T_2 - which models the spoiled gradient recalled echo (SPGR) and fully-balanced steady-state free precession (SSFP) MR signals as summations from two physically separate but exchanging water pools: 1) restricted water trapped within the hydrophobic bilayers of the myelin sheath; and 2) the less restricted intra and extra cellular and axonal water. Using mcDESPOT, whole-brain myelin water volume fraction (MWF) maps were acquired from 8 healthy infants (3 females) between 3 and 8 months of age during non-sedated natural sleep. Acquisition parameters were: SPGR: TE/TR = 4.1/11.2ms, α = {3,4,5,6,7,9,11,14}°, BW = 93Hz/voxel; SSFP: TE/TR = 5.6/11.2ms, α = {14,20,25,30,37,46,58,80}°, BW = 244Hz/voxel. SSFP data were acquired with phase-cycling increments of 0 and 180°. Scan time was minimized through partial k-space acquisition (NEX=0.5) plus parallel imaging with an acceleration factor of 1.5. Total acquisition time per infant was 10 minutes on a GE Signa 1.5T clinical scanner with an 8-channel head RF coil. Following acquisition, data for each infant were linearly co-registered (7) and non-brain parenchyma removed (8). Voxel-wise MWF estimates were calculated as detailed in (6). All infant data were non-linearly co-registered (9) and averaged to create a study template, to which each infant's data were subsequently co-registered for visualization and comparative analysis. Developmental trajectories (MWF vs. age) were calculated for the genu, body and splenium of the corpus callosum; internal capsule; frontal, temporal, parietal, and occipital lobe white matter, using spatially-normalized tissue masks for curves were fitted to these data to reconstruct interpolated myelin development 00 through 225 days of age.

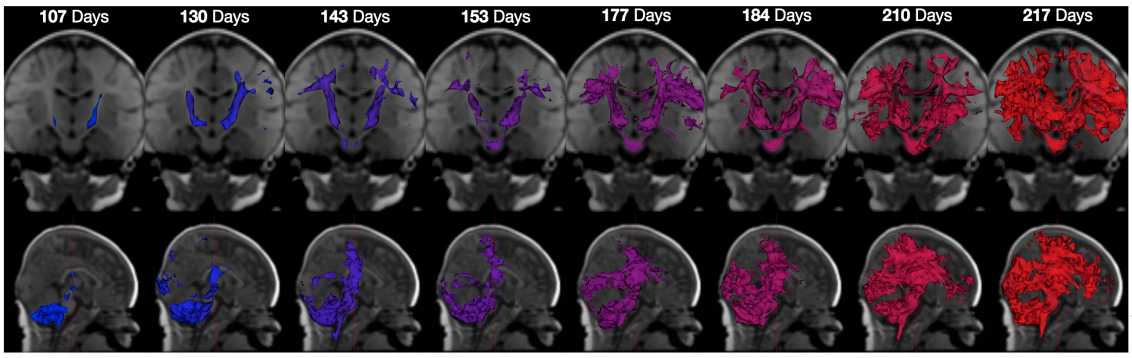

Figure 1: Three-dimensional volume renderings depicting myelin development across the imaged infants. 3D surfaces correspond to voxels with at least 3.5% MWF. The progression from deep white matter (cerebellar, internal capsules) to superficial regions (optic radiations, corpus callosum and frontal white matter) is easily followed and corresponds with the histologically-established sequence of myelination.

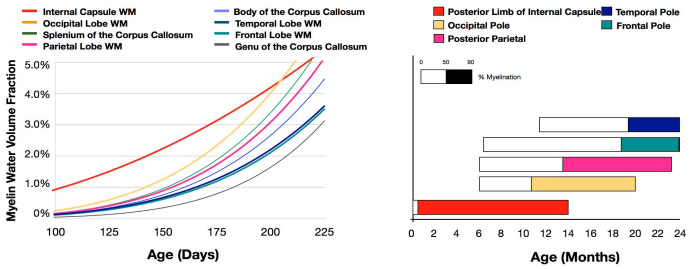

Figure 2: Reconstructed myelin development trajectories (*left*) for various white matter regions, revealing the temporal onset of myelination, beginning with the internal capsule, followed sequentially by occipital, parietal, frontal and temporal regions. This sequence reproduces known histology (*right*), with onset of myelination in the internal capsule before birth (beginning of the box), and 50% of the region myelinated just after birth (beginning of the colored portion of box). Occipital, parietal and temporal regions achieve 50% myelination by 11, 14 and 18 months, respectively.

ESULTS: A 3D appreciation of the spatio-temporal course of myelination is esented in Fig. 1. Here, the spatially aligned MWF maps of each infant were tered to remove voxels with less than 3.5% MWF and a 3D surface fitted to the ing voxels. Qualitatively, our data replicates the histological spatial course of yelination, beginning in the cerebellum, pons and internal capsule before birth; the proceeding caudocranially to the splenium of the corps callosum and optic radiations (by 2-4 months); and occipital and parietal lobes (by approximately 4 through 6 months), to the genu of the corpus callosum and frontal and temporal lobes by 6 to 8 months of age (1). The spatial and temporal consistency between our data and prior histological studies, in both the presence and absence of myelin, attest to the validity of the mcDESPOT method. Figure 3a displays calculated myelin development trajectories reconstructed from 100 through 225 days post-birth. Comparison of these curves with histologically established milestones (Fig. 3b) reveals a strong correspondence in the sequential onset of myelination: beginning with the internal capsule, followed by occipital, parietal, frontal and temporal white matter.

DISCUSSION / CONCLUSIONS: In this work we have non-invasively quantified myelin development in healthy infants, detecting a spatio-temporal sequence of myelination that faithfully reproduces established post-mortem findings and, for the first time, allows non-invasive and quantitative visualization of myelin development during infancy. Quantitative, assessment and visualization of myelination, coupled with non-invasive reconstruction of myelin development trajectories offers a significant advance in our ability to investigate a crucial aspect of neurodevelopment in the earliest stages of life. Increasingly, abnormal or atypical white matter maturation and myelination is being proposed as a potential substrate to neurological and psychiatric disorders, including autism and schizophrenia; and there is increasing consensus that these and others are disorders of brain 'connectivity', mediated by myelin. The ability to compare developmental trajectories in at-risk and typically developing children represents a new avenue for investigating the early neurobiological events that contribute to, or underlie, these devastating disorders.

REFERENCES: [1] PI Yakovlev, AR Leours. In *Regional Development of the Brain in Early Life*. Blackwell Scientific Publications, Oxford. 1967. [2] RB Dietrich *et al. AJNR.* 150, 889-896, 1987. [3] HC Kinney *et al. J. Neuropathol. Exp. Neurol.* 47, 217–234, 1988. [4] T Paus, *et. al. Brain Res. Bull.* 54, 255-266, 2001. [5] L Zhang *et al. AJNR.* 26, 45-49, 2005. [6] SCL Deoni *et al. Magn. Reson. Med.* 60, 1372-1387, 2008. [7] M Jenkinson *et al. NeuroImage.* 17, 825-841, 2002. [8] SM Smith. *Hum. Brain. Mapp.* 17, 143-155, 2002. [9] CJ Holmes *et al. J. comput. Assist. Tomogr.* 22, 324-333, 1998.