Linking Myelination with Behavioural Development in Healthy Infants

S. C. Deoni[1], D. Dean[1], C. Quigley[1], F. Liu[1], and B. A. Jerskey[2]
[1]School of Engineering, Brown University, Providence, RI, United States, [2]Department of Psychiatry and Human Behavior, Butler Hospital, Providence, RI, United States

INTRODUCTION: The myelination of white matter is a cornerstone of human neurodevelopment, allowing the establishment and refinement of efficient neural systems underpinning behaviour, cognition and emotion. Prior post-mortem histological studies have presented myelination as a well-defined spatial and temporal sequence[1], proceeding from deep to superficial brain regions. However, this work prohibits the investigation of structure-function relationships and, by nature, does not reflect healthy development. As an adjunct to histology, MRI has revealed a progressive reduction in white matter T_1 and T_2 relaxation times[2] and increase in diffusion fractional anisotropy[3], which broadly parallel the histologically defined myelination pattern. This work has provided indirect support for the hypothesis that behaviour and other cognitive functions mature as myelination progresses in the sub-serving brain regions[4]. Unfortunately, to date, direct investigation of myelination, in relation to behavioural maturation, has yet to be addressed. This dearth reflects both the difficulty of directly and non-invasively measuring myelin content in vivo; as well as the difficulty in imaging healthy young infants and toddlers. Imaging techniques such as T_1 and T_2 *weighted* and diffusion tensor imaging provide non-specific information related to white matter microstructure, reflecting not only myelin content, but also free water content; axonal size and fibre density; fibre membrane permeability; etc. To directly investigate myelin content in healthy infants, we have previously demonstrated a novel and silent variant of the mcDESPOT multi-component relaxation (MCR) technique[4], faithfully reproducing the histologically established spatio-temporal myelination sequence[5]. In this work, we provide our first results investigating the relationships between myelination and evolving fine and gross motor control, visual reception, and expressive and receptive language in healthy infants and toddlers 4 months through 2 years of age.

METHODS: MRI Whole-brain myelin water fraction maps were acquired of 16 healthy infants (5 female) 106 to 689 days of age (corrected to a 40 week gestation). Specific ages were (106, 113, 170, 181, 224, 228, 240, 245, 311, 383, 489, 568, 573, 664, and 689) days. Data were acquired on a Siemens Tim Trio scanner with installed noise proofing and sound attenuating headphones. Infants were scanned during non-sedated natural sleep. Sequence specifics were: For infants under 10months: a common (14x14x14)cm^3 sagittal FOV, 80x80x80 matrix, SPGR: TE/TR/α=5.4ms/14ms/(2,3,4,5,6,7,10,14)degrees, BW=350Hz/pixel; SSFP: TE/TR/α=5.7ms/11.4ms/(12,15,19,23,27,35,50,70)degrees, BW=350Hz/pixel. Two SSFP phase-cycling patterns (0 and 180degrees) were acquired to correct for off-resonance effects[6]. Two reduced resolution IR-SPGR images were also acquired (TE/TR/TI/α=5.4ms/14ms/(650 and 900ms)/5degrees, BW=350Hz/pixel) to correct for flip angle heterogeneity[7]. For toddlers up to 2years: a common (16x16x14)cm^3 sagittal FOV, 96x96x80 matrix. Other imaging parameters were the same. Following acquisition and normal mcDESPOT post-processing[4] to derive the myelin water fraction maps, infant and toddler data were registered to a study-specific 6 or 18month template image. These template images were created by non-linearly registering and averaging the 106-311day old data and 383-689 day old data, respectively. The transformation between the two age-group templates was also calculated, allowing the infant and toddler data to be aligned. This two step process was necessary given the limited contrast within the youngest participant data. **NEUROBEHAVIOR ASSESSMENT** Within 7 days of scanning, each participant also underwent a broad neurobehavioural assessment using the Mullen Scales of Early Learning[8], assessing fine and gross motor control, visual reception, and expressive and receptive language. **CORRELATION ANALYSIS** Non-parametric analysis was performed (Randomise, www.fmrib.ox.ac.uk/fsl) to identify areas of significant ($p<0.05$FDR) correlation between raw neurobehavioural scores in each of the 5 tested domains and measures of myelin water fraction. Participant age (at scan) and age^2 were included as co-variates. Resultant maps were corrected for multiple comparisons using threshold free cluster enhancement.

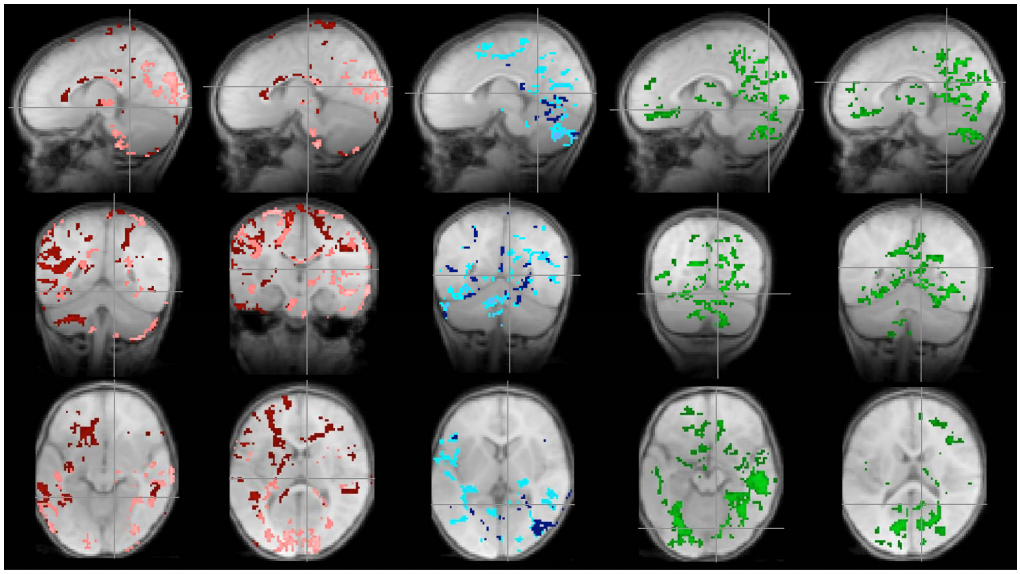

Figure 1: Areas showing significant correlation between myelin water fraction and fine motor control (pink); gross motor control (red); receptive language (dark blue); expressive language (light blue); and visual reception (green).

RESULTS: Figure 1 displays areas of significant correlation between myelin water fraction and fine (pink) and gross (red) motor control, expressive (light blue) and receptive (dark blue) language, and visual reception (green). Images are shown in radiological convention; R=R. Areas associated with gross motor included left cerebellum, left frontal, bilateral internal capsule and motor cortex, and the genu, splenium and body of the corpus callosum. Areas associated with fine motor included bilateral occipital lobe, bilateral internal capsule and motor cortex, and the body and splenium of the corpus callosum. Areas associated with visual reception included bilateral cerebellum, bilateral occipital lobe, bilateral optic radiations, bilateral frontal lobe and bilateral temporal lobe. Areas associated with expressive and receptive language included bilateral cerebellum and left temporal lobe. These results are consistent with brain regions known to be involved in each specific domain.

DISCUSSION: Our results present the first in vivo association between myelin maturation and evolving behaviour in healthy human infants. Though preliminary, reflecting data from 16 healthy infants and toddlers, the results are encouraging; overlapping with brain regions known to be involved the assessed behavioural domains and providing the first evidence of the structure-function relationships associated with neurodevelopment. Through the continued accrual of participants across the age-range, it is expected that the presented results will become more spatially localized, and the associations of additional brain regions, particularly within the frontal and temporal lobes will become more evident. These areas are likely under-represented in the presented data as they are amongst the last to mature (with myelination not beginning in ernest until 8-11 months of age). Further, it will be desirable to investigate male / female differences in development. In the current data, both male and female data were combined to achieve sufficient sample size. Despite these considerations, the results are encouraging, and represent an important first step in understanding behavioral development and the associations with structural maturation. By understanding these relationships in healthy infants and during typical development, we will be well positioned to identify deficits hypothesized to underly psychiatric disorders, such as autism and developmental delay.

REFERENCES: [1] PI Yakovlev, AR Leours. In *Regional Development of the Brain in Early Life*. Blackwell Scientific Publications, Oxford. 1967. [2] Lippert IR et al. JMRI. 29; 258-267 (2009). [3] Mukherjee P et al. AJNR. 23; 1445-1456 (2002). [4] Deoni SCL et al. MRM. 60; 1372-1387 (2008). [5] Deoni SCL et al. J. Neurosci. (In Press). [6] Deoni SCL et al. ISMRM pp 4609. (2009). [7] Deoni SCL et al. JMRI. 26; 1106-1111 (2007). [8] Mullen, EM. Mullen Scales of Early Learning. Circle Pines, MN: American Guidance Services, Inc., 1995.