Investigation of Tract-Specific Myelin Content Measures from a Population Averaged Myelin Water Fraction Atlas

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INTRODUCTION: While much is known regarding the spatial distribution of gross white and gray matter throughout the human brain, specific information related to tissue composition, i.e. myelin content, axonal density, etc., is less readily available and comes principally from post-mortem histological investigations. Consequently, this data is either pathology-specific, or limited to primary brain structures such as the corpus callosum. Given its critical role in normal brain development and neural functioning[1], a reference atlas of myelin content could provide significant insight into brain architecture. Further, as myelination abnormalities are implicated in a number of neurodevelopment, neurodegenerative and psychiatric disorders, such an atlas could provide a reference template for identifying areas or regions of abnormality in patient populations. Multi-component relaxometry (MCR) provides a non-invasive means for quantifying myelin content or, more specifically, the fraction of water trapped within the layers of the myelin sheath[2], by decomposing the measured MR signal into contributions from different micro-anatomical water domains. Multi-component Driven Equilibrium Single Pulse Observation of T_1 and T_2 (mcDESPOT)[3] is a promising new approach to MCR which derives multi-component T_1 and T_2 information from sets of spoiled gradient echo (SPGR) and fully-balanced steady-state free precession (SSFP) data acquired at multiple flip angles. Here, we make use of mcDESPOT to build a population-averaged whole-brain atlas of myelin content and investigate myelin distributions along specific white matter tracts.

METHODS: mcDESPOT data were acquired of 14 healthy right-handed individuals (6 male/ 8 female, 26-43 years of age) with the following parameters: SPGR: TE/TR = 2.4ms/6.7ms, α={3,4,5,6,7,8,11,13,18}°, BW=±19.23kHz; SSFP: TE/TR=1.7ms/3.5ms, α={11,14,19,24,28,34,41,51,67}°, BW=±50kHz. A common 22cm x 22cm x 15cm sagittal FOV was used with a 128 x 96 x 90 (zero-filled to 128 x 128 x 90) matrix for a total scan time of approx. 14 minutes. Following acquisition, data for each volunteer were linearly co-registered to account for intra-scan motion[4], non-brain signal was removed[5], and the myelin water volume fraction (f_M) calculated voxel-wise using mcDESPOT analysis[3]. Data from each volunteer were then non-linearly co-registered to MNI standard space[6], smoothed with a Gaussian kernel (full-width-at-half-maximum value = 2mm) and averaged. The primary white matter tracts were individually masked by superimposing the JHU White Matter Tractography Atlas[7] onto the averaged result and myelin content distributions (histograms) were reconstructed for specific white matter tracts (and normalized with respect to the area under the curve).

RESULTS: Figure 1 contains representative axial, sagittal and coronal slices through the averaged myelin water fraction map. Despite the relatively modest spatial resolution, Fig.1d demonstrates the ability to visually distinguish the cortical spinal tracts as well as other tracts throughout the brainstem. Myelin water fraction histograms for different white matter tracts, including the genium, splenium and body of the corpus callosum (gCC, sCC, bCC), right and left cortical spinal tracts (lCST, rCST), left and right lateral lemnisci (lLM, rLM), anterior, posterior and retrolenticular limbs of the internal capsule (ALIC, PLIC, RLIC), external capsule (EC), inferior, middle, superior and cerebral peduncle (MCP, ICP, SCP, CP), are shown in Fig. 2. Significant disparity in myelin content is observed across the various pathways, specifically the genium, splenium and body of the corpus callosum. Perhaps surprising is the right/left differentiation observed in the cortical spinal tracts and lateral lemnisci. Detailing the corpus callosum further, Fig, 3 contains a comparison between measured myelin water fraction and histology-derived fibre diameter and density values throughout the structure[8]. The observed myelin water gradient qualitatively corresponds closely with decreasing fibre density and increasing fibre diameter. This result may be expected since large diameter fibres have thicker myelin sheaths, implying increased myelin content. These results demonstrates the potential use of the atlas for investigating differences in myelination throughout the brain, both on a gross anatomical level, as well as tract specific level.

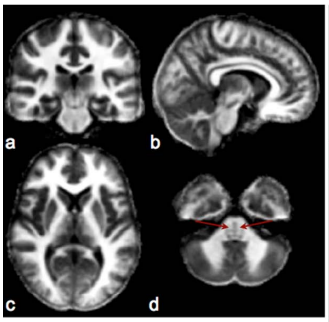

Figure 1: Representative slices through the population average.

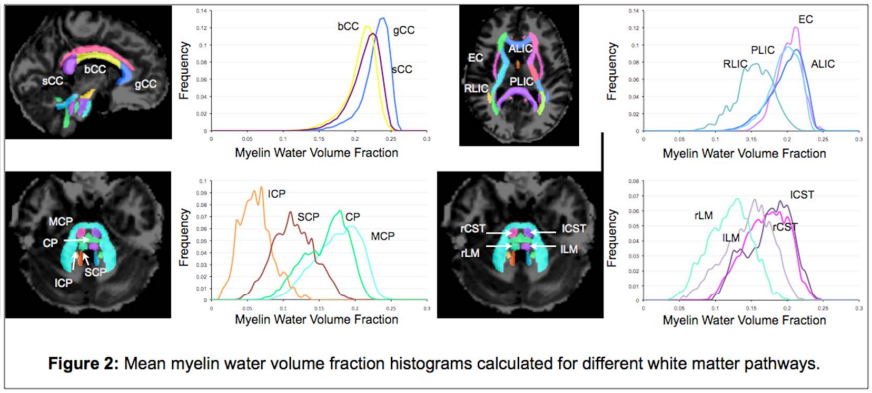

Figure 2: Mean myelin water volume fraction histograms calculated for different white matter pathways.

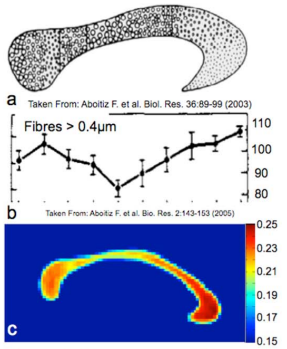

Figure 3: Mean myelin water volume fraction along the corpus callosum compared with histology-derived axonal diameter and density measures.

DISCUSSION / CONCLUSIONS: Myelin plays a critical role normal brain functioning. The ability to distinguish differences in myelin content from normal along specific tracts has application to neuroscience in general, as well as to a broad range of neurological conditions. In this work, we have reported on the development of the first *in vivo* whole-brain atlas of myelin water content in a healthy population. From this datatset, myelin water fraction may be investigated throughout gross brain regions as well as along specific individual white matter pathways. Within healthy brain, we have shown significant disparity across the various pathways, including the right and left cortical spinal tracts and medial lemnisci. It is envisaged that such an atlas will provide a significant resource for investigating disease-related myelin changes.

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