

Quantitative Magnetic Susceptibility Mapping of the developing mouse brain

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INTRODUCTION: Cerebral development involves a complex cascade of events which are difficult to visualize in vivo. In this study we combine information from Diffusion Tensor Imaging (DTI) and Quantitative Susceptibility Mapping (QSM) on developing mouse brains at four stages, for three central regions. Values of the Fractional Anisotropy (FA), Apparent Diffusion Coefficient (ADC) and quantitative susceptibility maps were analyzed to provide inferred information on developing neuron architecture. Also, a novel approach, susceptibility anisotropy suggests that neuronal fibers are paramagnetic. We show the potential of this method to study early brain development.

METHODS: Four healthy C57BL/6 mice of the same mother were anesthetized and imaged on a 9.4T with the following parameters: For the QSM maps: 3D Gradient Echo Sequence (GRE), TE 20ms, TR 200ms, FOV=368x184x184 mm³, flip angle 40°. For the DTI maps Spin Echo Sequence, FOV=165x82x82 mm³. Six encoding directions were used. The animal study was approved by the Institutional Animal Care and Use Committee (IACUC) of our institution.

The pixel size was adjusted with k-space manipulation to isotropic 60μm for all maps to increase Signal-to-Noise Ratio (SNR) for the QSM maps and to make comparison easier. Phase data from the GRE were reconstructed and large background phase was removed with the sphere-mean-value filter followed by a deconvolution operation (1). Quantitative magnetic susceptibility value was computed for each voxel iteratively using the LSQR algorithm (2). Regions-of-interest (ROI) of three structures -Corpus Callosum (CC), Anterior Commissure (AC), Fornix System (FS)- were manually and conservatively segmented using ITK-SNAP (3) with respect to FA maps. These ROI were then scaled onto the QSM maps to match their resolution using Convert3D (part of ITK-SNAP). The weighted average of each ROI and its standard deviation was calculated. The same brain was scanned with different angles to the main magnetic field. The resulting QSM maps were linearly registered using a transformation matrix that was computed from the magnitude maps of each using FSL-FLIRT(4). The same ROI were extracted across the maps.

RESULTS: Fig. 2 shows weighted average of ROI for various contrast mechanisms for P2, P7, P14, P22. Fig. 2A shows the monotonically increasing trend of the FA regardless of structure. Fig. 2B shows the mean ADC decreasing then increasing which agrees with data from others (5,6) on human and rat brains respectively. While the axial diffusivity (or eigenvector) decreases and radial diffusivity increases resulting in the dip at P7 in the mean ADC graph. These temporal changes in the DTI metrics were related to the neuronal and axonal pruning and myelination that are known to occur in the developing brain. Fig. 2C depicts the QSM of various structures. AC shows a monotonic decline as it has a well defined small homogeneous ROI. In contrast CC and FS are close to other structures with much different susceptibility, are poorly defined and are more complicated both in their macro- and micro-architecture leading to appreciable standard deviations. Contrast in QSM images is solely created by myelin and iron concentrations as demonstrated recently by Liu et al(7). However, high resolution phase imaging at even higher field strengths is essential to improve SNR and will help in the understanding of the exact cause of these variations as well as a wide range of pathologies. Expected histological examinations will also verify the cause but are limited to in-vitro applications. Fig. 3 reveals the orientation dependence of the QSM to the angle (θ) between the main magnetic field and the main neuronal axons in the FS ROI. We observe an increase in the slope of the fitted trend line as we progress through days, signifying that in the early days with no myelin formed the axon itself is paramagnetic, while as myelin is formed around it, the angle of the trend line increases so the axon becomes diamagnetic.

DISCUSSIONS & CONCLUSIONS: Sensitive assessment of brain myelination is important for the diagnosis of brain white matter degenerative diseases. Previous studies (6,7) have shown that both diffusion and susceptibility imaging provide useful information regarding the brain white matter myelination. However, since their underlying molecular underpinnings is completely different, i.e. diffusion imaging relies on signal attenuation caused by random diffusion of free water molecules, while susceptibility contrast is originated mainly from the myelin structure, these imaging methods show different changes during the normal development of the neuronal network in mouse, as shown in this study. The combination of this information may allow for a more comprehensive picture of the development processes or in degenerative neurological diseases. Further, we have evaluated the variation of susceptibility of selected white matter fibers among different orientations with respect to the main magnetic field (Fig.3). The susceptibility anisotropy is changing during brain development, which provides a new, different kind of information that relates both the level of myelination and direction of the fiber to the B_0 , to the measured anisotropy of the susceptibility.

ACKNOWLEDGMENTS: NIH R00EB007182.

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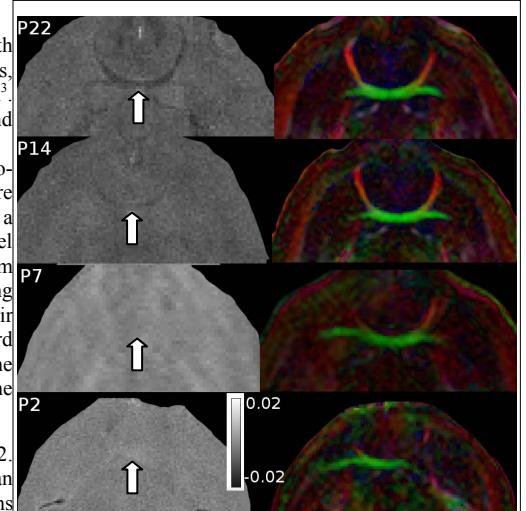


Fig. 1 A comparison between QSM and FA as a function of age. AC is not visible in the early days in QSM maps, hence the need to use registered FA maps for ROI segmentation.

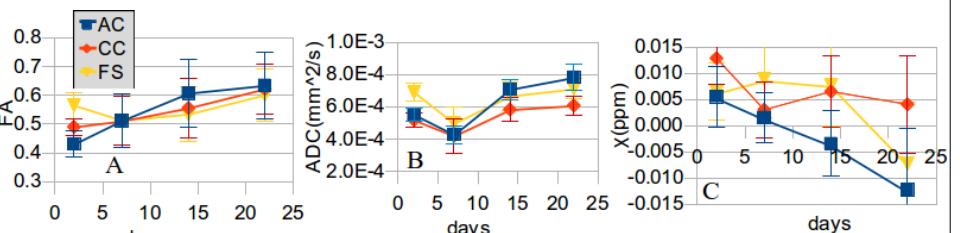


Fig. 2 Quantitative comparison between DTI and QSM. Each method provides different information on neuronal development..

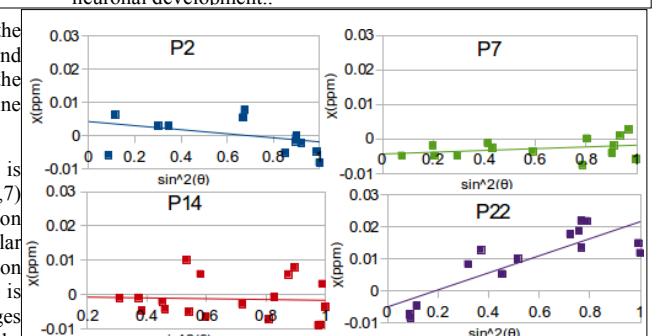


Fig. 3 Age-dependent susceptibility anisotropy. As the age increases, the slope (anisotropy) is rising.