Combined NODDI and qMT for full-brain g-ratio mapping with complex subvoxel microstructure

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Target Audience: This work will be of interest to imaging scientists interested in diffusion and magnetization transfer imaging, scientists interested in white matter microstructure, and clinicians investigating white matter disease.

Introduction: The myelin g-ratio[1], which is the ratio of the inner to the outer diameter of a myelinated axon, is a fundamental metric that can be computed from combined diffusion and quantitative magnetization transfer (qMT) imaging. Together, these complementary imaging technologies can provide measures of fiber volume fraction (FVF) and myelin volume fraction (MVF), from which the g-ratio can be computed using a simple formula[2]. Previous work[2] has used the fractional anisotropy (FA) from diffusion tensor imaging (DTI)[3] to infer the FVF using a quadratic relationship. However, the correlation between FA and FVF applies only in the case where the MRI voxels contain a single fiber system with parallel, straight fibers, and breaks down in the presence of partial volume averaging of fiber orientations, such as curvature, splay, and crossing fiber systems. This makes the FA an unsuitable measure of FVF for full-brain quantitative maps. Recently, several models have been developed that allow for partial volume averaging of fiber orientations and provide measures of axonal volume[4,5,6,7]. Here, we apply the Neurite Orientation Dispersion and Density Imaging (NODDI) model[4] to obtain a full brain axon signal fraction. We compute whole-brain maps of the g-ratio in one healthy human subject, and we compare the performance of the NODDI-based FVF measure to the DTI-based approach.

Theory: The g-ratio has been shown[2] to be a function of the MVF and the FVF, $g = \sqrt{1 - \frac{MVF}{FVF}}$. The MVF is linearly related to the macromolecular pool size F from qMT[8,9,10]. The FVF from NODDI is given by FVF=MVF+(1-MVF)(1- v_{iso}) v_{ic} , with v_{iso} and v_{ic} as described by Zhang et al.[4]. This formula arises because the myelin signal in a typical diffusion acquisition with long TE is negligible due to the short T_2 and low proton density of myelin water. Among the parameters from the NODDI model are the fractions of the non-myelin volume for the isotropic, unhindered, compartment (v_{iso}) and the anisotropically restricted compartment ((1- v_{iso}) v_{ic}). The anisotropically restricted compartment is a surrogate for the intra-axonal compartment in white matter. Scaling by (1-MVF) gives the true axon volume fraction, and the fiber volume fraction is the sum of the axon and myelin volume fractions. The NODDI model uses a Watson distribution of fiber orientations, and has been shown to be robust to fanning fibers[4], hence, robustness to fiber curvature is also expected because fanning and curvature are indistinguishable at the voxel scale[11].

Methods: Whole-brain diffusion and qMT imaging were performed *in vivo* in one healthy human using a 3T Siemens Trio MRI scanner (Erlangen, Germany) equipped with a 32 channel array coil. A two-shell NODDI diffusion protocol was used. One signal average of both 700 s/mm^2 (30 directions) and 2000 s/mm^2 (64 directions) and nine b=0 s/mm^2 images were acquired using a twice-refocused balanced echo single-shot spin-echo EPI sequence[12] with 2 mm isotropic voxels and TE=101 ms. An additional diffusion dataset optimized for FA calculation was acquired, with 99 b=1000 s/mm^2 encoding directions, ten b=0 s/mm^2 images, and TE=87 ms. For qMT, a 3D SPGR protocol was used with the same imaging resolution as the diffusion scanning, one signal average, variable flip angle (VFA) T1 mapping[13], actual flip angle imaging (AFI) B1 mapping[14], and 10-point uniform sampling of the z-spectrum[8]. The FVF, MVF, and g-ratio were computed from the diffusion and qMT data as described above, using both DTI and NODDI for the FVF. The corpus callosum was skeletonized and a voxel-wise correlation between the FVF computed from DTI and from NODDI was performed. Additionally, in order to check the NODDI model's robustness to crossing fibers, we performed simulations of diffusion in systems of straight, parallel fibers and compared to the identical fibers with 50% of the fibers rotated 90 degrees, for fiber volume fractions from 0.3 to 0.7 and g-ratios from 0.7 to 0.9. The simulations were performed using the dSim diffusion simulator[15]. The FVF was computed from the simulated data using both DTI and NODDI for the parallel and crossing fiber configurations.

Results:

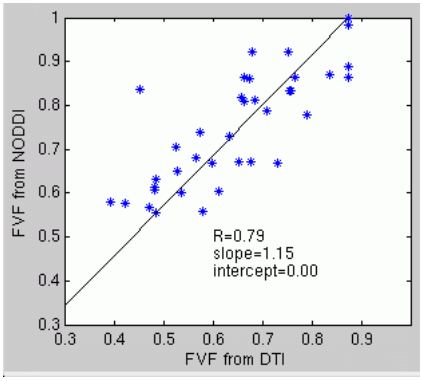


Fig. 1: Correlation between DTI-based and NODDI-based FVF in the skeleton of the corpus callosum.

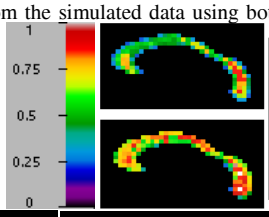
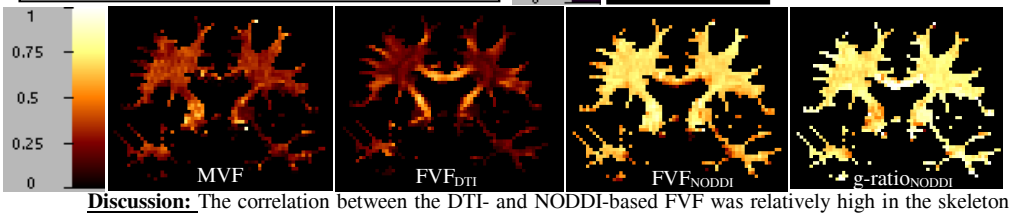


Fig. 2: Maps of (top) FVF from DTI and (bottom) FVF from NODDI in the corpus callosum.

Fig. 3: Full brain white matter maps of, from left to right, MVF from qMT, FVF from DTI, FVF from NODDI, and g-ratio from NODDI and qMT.



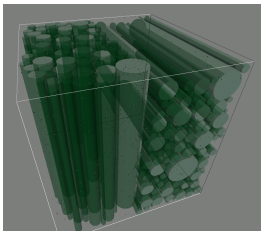


Fig. 4: In simulations, the computed FVF was 3.8±0.3% lower for crossing versus parallel fibers for NODDI, and 58.7±3.2% lower for the DTI-based FVF calculation. (Values reported are percent error.)

Discussion: The correlation between the DTI- and NODDI-based FVF was relatively high in the skeleton of the corpus callosum, where the voxels are expected to contain relatively straight, parallel white matter fibers, as required by the DTI-based FVF model (Fig.s 1 and 2). The DTI-based FVF is, however, lower than that from NODDI even in the corpus callosum, probably due to partial volume averaging with cerebrospinal fluid, or slight curvature or splay of fibers. There are voxels in which the FVF is lower than the MVF, which is not physically possible. Elsewhere in the brain, the DTI-based FVF drops significantly due to partial volume averaging of fiber orientations (Fig. 3). Simulation corroborated this observation (Fig. 4), and it indicated that the NODDI Watson model of fiber dispersion is robust to crossing fibers for the estimation of fiber volume fraction. NODDI can therefore be expected to work for all subvoxel distributions of fibers. Using NODDI, the g-ratio map for the full brain is relatively constant (Fig. 3). A flat g-ratio profile in healthy brain is expected, as the g-ratio has been shown to have an optimal value for signal conduction[16,17]. g-ratio mapping in humans *in vivo* has the potential to be a sensitive marker of pathology in myelinated axons. Using a combination of qMT and NODDI acquisition and processing provides an imaging protocol for full-brain g-ratio computation without explicit calculation of the axon diameter distribution.

References: [1] Rushton et al. J. Physiol. 1951. [2] Stikov et al. NeuroImage 2011. [3] Basser et al. JMR 1994. [4] Zhang et al. NeuroImage 2012. [5] Assaf et al. NeuroImage 2005. [6] Jespersen et al. NeuroImage 2010. [7] Wang et al. Brain 2011. [8] Levesque et al. MRM 2011. [9] Thiessen et al. NMR Biomed 2013. [10] Campbell et al. ISMRM Diffusion Workshop 2013. [11] Savadjiev et al. NeuroImage 2008. [12] Reese et al. MRM 2003. [13] Fram et al. MRI 1987. [14] Yarnykh et al. MRM 2007. [15] Sveinsson et al. Technical Report CNITR-001 2011. [16] Chomiak et al. PLoS ONE 2009. [17] Pajevic et al. PLoS ONE 2013.