In vivo mouse brain NODDI acquired at 9.4T using cryogenic probe

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Target audience: Neuroimaging scientists interested in studying mouse brain tissue microstructures using diffusion MRI.

Purpose: Diffusion-weighted Imaging (DWI) with the conventional technique of Diffusion Tensor Imaging (DTI) has been widely used to characterize the microstructural organization and wiring of the brain by utilizing the diffusion of water molecules in the brain[1]. However, DTI parameters provide incomplete description of tissue microstructure. A reduction in FA (fractional anisotropy) may either indicate reduced neurite (dendrites and axons) density or the presence of bending and fanning axon[2]. Additionally, several studies showed that DTI failed in quantifying regions of crossing fibers as it traces only one direction in a voxel[3,4]. NODDI (**N**eurite **O**rientation **D**ispersion and **D**ensity **I**maging) provides additional and more specific information of brain tissue morphology compared to DTI, in terms of compartmentalization, neurite density and their orientation dispersion. NODDI models three types of brain microstructural compartments: intra-cellular, extra-cellular, and CSF environments[2].

While rodents have been widely used in preclinical studies as translational models, there has not been any NODDI processing for *in vivo* rodent brains. *This study aims at using NODDI to identify subtle microscopic brain structures in adult mouse mice.*

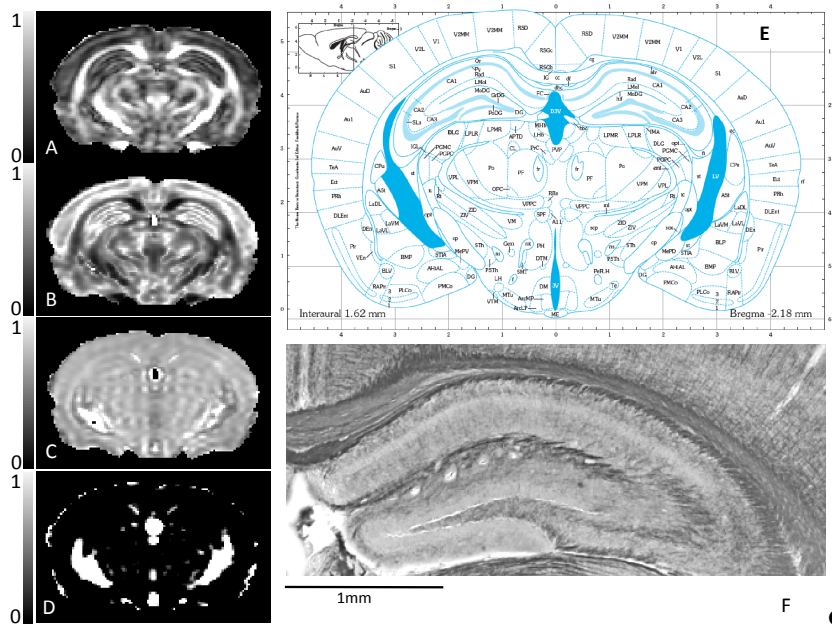
Method: *Animal preparation and preprocessing* Specimens used are C57Bl/6J mice (N = 6). MR scans were performed using Bruker Biospin 9.4T Biospec equipped with mouse brain cryoprobe. Mice were anaesthetized using 1.5% isoflurane with oxygen flow at 1L/min. Diffusion data were obtained with two HARDI (High-angular Resolution Diffusion-weighted Imaging) shells using 2D Stejskal-Tanner DWI-EPI sequence with b-values of 1000 and 2000 s/mm^2, 30 diffusion gradient encoding directions with TR of 1500 ms, TE of 22 ms, δ/Δ of 4/10 ms. The FOV is 1.28 cm × 0.96 cm, resolution 0.1 × 0.1 × 0.3 mm^3, with the acquisition time of 24 minutes. Before the model described by Zhang et al.[2] was fitted to the data, the brain was masked with a binary mask so that all the non-brain tissue was removed using ITKSNAP[5]. The DTI parameters were calculated using MRTrix 0.2.11[6].

NODDI model The intra-cellular compartment, indicating the space confined by the membrane of neurites, is modeled as a set of sticks with diffusion highly restricted perpendicularly to neurites and unhindered along neurites. Neurites are used to characterize highly coherently oriented white matter structures (such as the corpus callosum), white matter structures composed of bending and fanning axons (such as the human centrum semiovale), and the cerebral cortex and subcortical gray matter structures with dendrites spreading out in all directions. The extra-cellular compartment defines the space around the neurites, which is occupied by many types of glial cells and additionally somas (i.e. cell bodies) in gray matter. The diffusion process in this space is hindered but not restricted, and can be characterized with Gaussian distribution. The CSF compartment is modeled as isotropic Gaussian diffusion.

Collectively, a normalized signal A characterized with NODDI can be written as $A = (1 - v_{iso})(v_{ic}A_{ic} + (1 - v_{ic})A_{ec}) + v_{iso}A_{iso}$, where A_{ic} and v_{ic} are the normalized signal and volume fraction of the intra-cellular compartment; A_{ec} is the normalized signal of the extra-cellular compartment; and A_{iso} and v_{iso} are the normalized signal and volume fraction of the CSF compartment. The following NODDI parameters were fitted into the 2-shell HARDI data using the NODDI Matlab script[2]:

- v_{ic}: intra-cellular volume fraction.
- v_{iso}: isotropic volume fraction, reaching highest values in the CSF region where the diffusion is considered isotropic.
- κ: concentration parameter that measures the extent of orientation dispersion about the mean orientation μ of Watson distribution.
- OD values range from 0 to 1, characterizing the angular variation of neurites. An OD of 1 indicates neurites being at maximum dispersion.

κ and OD are inversely proportional, and the characteristics of κ may be considered similar to FA.



Results & Discussion:

Figure 1 illustrates DTI FA (**A**) and NODDI parameters (**B**) OD, (**C**) v_{ic}, (**D**) v_{iso} maps from the same dataset. For reference, a coronal section of brain atlas[7] (**E**) and myelin histology of the hippocampus (**F**) are also shown to illustrate the spatial locations of brain structures and characteristic fiber dispersions.

NODDI maps are found to be largely consistent with known anatomy and provide additional information of microstructure features of the mouse brain compared to DTI. For example, the corpus callosum (CC), the most highly oriented white matter structure[2], has medium-high FA values (0.4–0.7), which is reflected by low OD values (0.02–0.25). Another main white matter tract, the internal capsule, also showed similar characteristics with FA (0.5) and low OD (0.19).

Hippocampus (HC), which plays important roles in memory and learning[7], contains regions with high density of neurons such as CA1-3 and dentate gyrus. These gray matter structures have low FA (0.1– 0.2), high OD values (0.4–0.7) and low κ (0.04 – 0.1, map not shown). The high-density neurons of HC produce moderate v_{ic} of 0.4–0.5, with the v_{iso} being almost 0.

However, NODDI may show regions with unexpected high v_{iso} values (not shown), which appeared to be artifacts. These appear to be exacerbated by animal respiratory and low SNR in the ventral area of the brain far from the cryoprobe surface coils.

Conclusion: Compared to the traditional DTI model, NODDI provides more insight into microscopic brain structures both in gray and white matters. Like other diffusion techniques, NODDI suffers from motion artifacts and low SNR, in which corrections need to be made to eliminate fitting error in the analysis.

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