NODDI: a practical technique for in vivo neurite orientation dispersion and density imaging of the human brain

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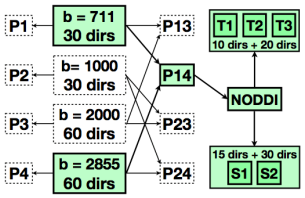

Fig 1: HARDI shells and the protocols

INTRODUCTION This work introduces neurite orientation dispersion and density imaging (NODDI), a practical diffusion MRI technique for estimating microstructural complexity of dendrites and axons *in vivo* on clinical MRI systems. Dendrites and axons, collectively known as neurites, are the cellular building blocks of the brain's computational circuitry. Quantifying neurite morphology, in terms of its density and orientation dispersion, provides a window into the structural basis of brain function. Diffusion-tensor imaging provides measures such as fractional anisotropy (FA) that are sensitive to neurite density and orientation dispersion but can not isolate their individual contributions [1]. Recent advances in diffusion MRI have shown great promise in measuring such microstructural features directly [2-10]. In particular, it has been shown to provide estimates of neurite density [8] and orientation dispersion [10] consistent with independent histological measures. Nevertheless, none of the existing techniques are practical for routine clinical applications. We address this problem by developing NODDI, a novel neurite imaging and analysis framework, that achieves clinical feasibility with an optimized two-shell HARDI protocol. We demonstrate NODDI for *in vivo* whole-brain imaging of neurite characteristics for the first time, which enables the disentanglement of the two key factors contributing to FA and allows them to be separately examined in clinical studies.

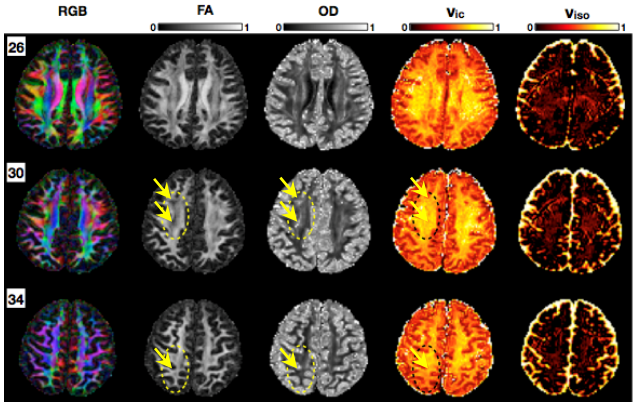

Fig 2: Parameter maps of NODDI estimates and FA

METHODS Tissue and signal model: NODDI adopts a simple three-compartment model to support the estimation of neurite density and orientation dispersion while accounting for CSF contamination. It represents neurites as a collection of impermeable sticks (cylinders with zero radii) with dispersed orientations embedded in a homogeneous medium. The intracellular (IC) compartment has a volume fraction v_{ic}, which quantifies neurite density; the extracellular (EC) compartment has a volume fraction $(1-v_{ic})$. The IC and EC signals are computed using the orientation-dispersed axonal model [9]. It captures orientation dispersion with a Watson distribution specified by dominant orientation $\boldsymbol{\mu}$ and concentration parameter κ [11]. CSF contamination is modeled as an isotropic compartment with a volume fraction of v_{iso}. Orientation dispersion index: Because the concentration parameter κ is *inversely* proportional to angular variance, we define OD, the orientation dispersion index, as $(2/\pi)\arctan(1/\kappa)$. OD varies from 0, for no dispersion, to 1, for maximum dispersion. Optimized Protocol: The NODDI protocol is generated with the experiment design optimization procedure [6] by optimizing for the NODDI tissue model and the hardware settings (see Imaging), with an acquisition time constraint of 30 minutes. The optimized protocol consists of a 711 s/mm^2 shell of 30 directions and a 2855 s/mm^2 shell of 60 directions, as well as 9 b=0 measurements. Protocols for comparison: We additionally acquire a 1000 s/mm^2 shell of 30 directions and a 2000 s/mm^2 shell of 60 directions to construct additional protocols which we compare the NODDI protocol to. These protocols are shown in Fig.1, which includes: 1) the one-shell protocols P1-4; 2) the two-shell protocols generated by choosing one 30-direction and one 60-direction shell; 3) the reduced-orientation-sampling (ROS) NODDI protocols, including S1-2, created by dividing the orientations of each of its two shells uniformly into two equal halves, and T1-3, created similarly to S1-2 but into three equal parts; 4) the four-shell protocol by choosing all the shells. The ROS-NODDI protocols are determined with the uniform orientation splitting algorithm [12] implemented in Camino [13]. Imaging: We acquired diffusion imaging data of a healthy adult male on a clinical 3T Philips Achieva system with $|G|_{max}$ = 60 mT/m. The protocols are acquired using axial EPI with matrix size 112x112, FOV 224x224 mm^2, slice thickness 2mm. A total of 50 slices were acquired to cover the whole brain, with TE = 78 ms and TR = 12.5 s. The scanning time is about 25 minutes for the NODDI protocol and the same for the two additional shells. Parameter estimation: We adapt the fitting procedure in [7] to fit the NODDI model to data. It uses grid-search to find a good starting point and subsequently refines the estimation with maximum-likelihood gradient descent. Evaluation: We evaluate the NODDI protocol in terms of the accuracy and precision of its parameter estimates, using the estimates from the four-shell protocol as the pseudo ground-truth. Its performance is evaluated against the one-shell and the alternative two-shell protocols.

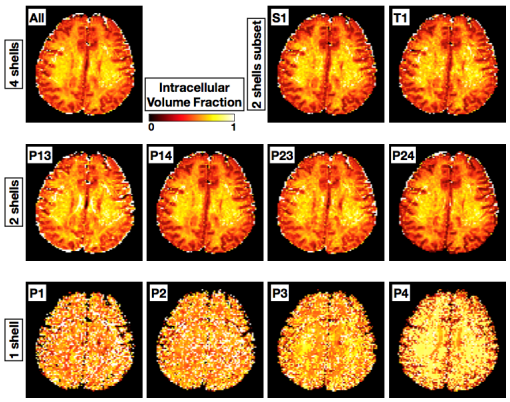

Fig 3: Neurite density estimates from different protocols

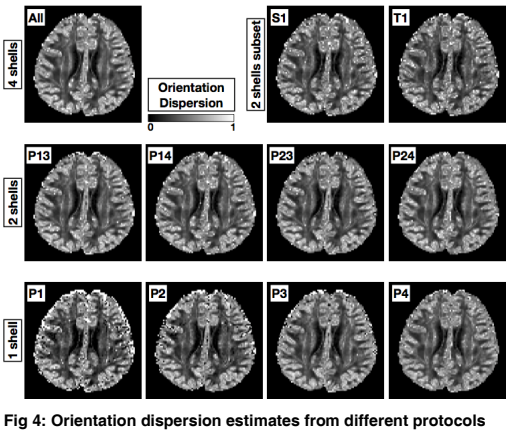

Fig 4: Orientation dispersion estimates from different protocols

RESULTS Parameter maps: Fig.2 provides the maps of the pseudo ground-truth NODDI estimates alongside the FA map from tensor fitting. Firstly, it demonstrates that the estimates from NODDI are sensible. Neurite density is high in white matter (WM) but low in gray matter (GM), consistent with ex vivo findings [10]. Orientation dispersion is high in GM but low in WM and the lowest in the corpus callosum, consistent with known anatomy. Secondly, it illustrates that disentangling the two main factors contributing to FA provides more specific information about the underlying tissue. For example, FA variation in the highlighted region on slice 30 can be attributed primarily to the variation in orientation dispersion, while in the highlighted region on slice 34, FA fails to reveal the underlying variation in neurite density. Protocol comparison: Comparing the estimates from the protocols in Fig.1 to the pseudo ground-truth estimates, we show that i) the two-shell protocols estimate neurite density accurately (Fig.3 middle) but the one-shell protocols do not (Fig.3 bottom); ii) all the protocols can estimate orientation dispersion accurately (Fig.4); iii) the ROS-NODDI protocols show similar performance to the full NODDI protocol (Fig.3&4 top right). Finally, quantitative analysis further shows that the NODDI protocol outperforms the other alternative two-shell protocols (not shown).

DISCUSSION We show that NODDI provides sensible estimates of neurite density and orientation dispersion and enables the separate quantification of the two key microstructural factors contributing to FA. Clinical feasibility of NODDI is demonstrated by the excellent performance of its reduced-orientation-sampling versions that take as little as 10 minutes to acquire.

ACKNOWLEDGEMENT This work is supported by the future and emerging technologies (FET) program of the EU FP7 framework through the CONNECT consortium, and the MS Society of Great Britain and Northern Ireland, the ISRT and the CBRC.

REFERENCE 1. Pierpaoli et al, Radiology96; 2. Assaf et al, NIMG05; 3. Jespersen et al, NIMG07; 4. Assaf et al, MRM08; 5. Barazany et al, BRAIN09; 6. Alexander, MRM08; 7. Alexander et al, NIMG10; 8. Jespersen et al, NIMG10; 9. Zhang et al. NIMG11; 10. Jespersen et al, TMI11; 11. Mardia & Jupp. Directional statistics 90; 12. Cook et al, JMRI07; 13. Cook et al, ISMRM06.