Neurite Density Imaging (NDI): rapid acquisition and estimation of the intracellular volume fraction.

Björn Lampinen[1], Danielle van Westen[2,3], Freddy Ståhlberg[1,2], Jimmy Lätt[3], Oskar Hansson[4], and Markus Nilsson[5]

[1]*Dpt. of Medical Radiation Physics, Lund University, Lund, Sweden,* [2]*Dpt. of Diagnostic Radiology, Lund University, Lund, Sweden,* [3]*Imaging and function, Skane University Health Care, Lund, Sweden,* [4]*Clinical Memory Research Unit, Clinical Sciences, Malmö, Lund University, Lund, Sweden,* [5]*Lund University Bioimaging Center, Lund University, Lund, Sweden*

Introduction – Neurite orientation dispersion and density imaging (NODDI) provides estimates of the intracellular volume fraction, or neurite density. It is superior to DTI in terms of parameter specificity, but it also requires more advanced modeling and extended data acquisitions.[1] In this work we show that by averaging the diffusion-weighted data across multiple directions, it is possible to obtain the neurite density using a simplified NODDI model from data acquired with a simplified protocol, which reduces the acquisition and analysis time. We validate the technique, which we refer to as neurite density imaging (NDI), by investigating whether the reduced acquisition time results in increased bias and reduced precision. To demonstrate the value of NDI, we employ the method to disambiguate the cause of an unexpected finding, i.e., elevated FA in the hippocampal cingulum of patients with Parkinson's disease dementia (PDD).

Theory – In NODDI, the diffusion-encoded signal is modeled by an intracellular, or neurite, compartment (f_{ic}), an extracellular compartment in which the diffusion is hindered, and a CSF compartment (f_{iso}) with freely diffusing water. The orientation distribution of the neurite compartment is modeled by the Watson distribution, parameterized by the direction $\boldsymbol{\mu}$ and concentration κ. Neurites are assumed to have zero radial diffusivity (RD) and a fixed axial diffusivity (AD_0), and thus the intra-axonal diffusion is described by f_{ic}, $\boldsymbol{\mu}$ and κ. In the extracellular compartment, AD and RD are modeled as functions of κ. The isotropic diffusivity (D_{iso}) is fixed.[2]

The NODDI model can be simplified by assuming full orientation dispersion. This assumption is valid if data is averaged across diffusion encoding directions before model fitting; so-called powder averaging. In the limit of infinitely dense sampling, the attenuations of the intra- and extracellular compartments (A_{ic} and A_{ec}) are given by

$$A = \exp(-b\,\mathrm{MD}) \cdot f(\alpha), \quad \text{where} \quad f(\alpha) = (\pi/2\alpha)^{1/2} \cdot \exp(\alpha/3) \cdot \mathrm{erf}(\alpha), \qquad (1)$$

and b is the diffusion encoding strength, erf is the error function, and $\alpha = b(\mathrm{AD} - \mathrm{RD})$, using the values of MD, RD, and AD associated to the intra- or extracellular compartments, respectively. Provided that fibers are parallel on a microstructural scale, we know that $AD_{ec} = AD_0$ and $RD_{ec} = (1 - f_{ic})\,AD_0$.[2] The remaining free parameters are S_0, f_{iso} and f_{ic}, which can be estimated by fitting $S = S_0[\,(1-f_{iso})(f_{ic}A_{ic} + (1-f_{ic})A_{ec}) + f_{iso}\exp(-bD_{iso})]$ to the data.

Methods – Multi-shell diffusion MRI data were acquired using a Siemens Skyra 3T scanner equipped with a 32-channel head coil. In total 99 DWI volumes with 52 contiguous slices were acquired, using b-values of 0, 250, 500, 1000 and 2750 s/mm^2, distributed over 3, 6, 6, 20, and 64 directions, respectively. This is hereafter referred to as the full protocol. A single-shot spin-echo with EPI read-out was used, having TR = 8100 ms, TE = 103 ms, voxel size = 2.3×2.3×2.3 mm^3 and a total acquisition time of 15 minutes. Patients with Parkinson's disease dementia (PDD, age 73.2 ± 6.1 years, n = 12) and age-matched controls (HC, age 72.3 ± 2.0 years, n = 12) were scanned. Written informed consent was obtained. Based on a previous analysis of the data, we chose to test for diffusion changes between PDD and controls in the parahippocampal cingulum, extracted based on the scheme proposed by Jones *et al*.[3]

Finite directional sampling may violate a key assumption of NDI, and could cause a bias in f_{ic}. The maximal magnitude of the bias was thus investigated for a range of subsampled protocols. All protocols used a single b_0-measurement, but a varying number of measurements in the $b = 1000$ and 2750 s/mm^2 shells, from 3 to 32, with the directions spread out evenly on the sphere. In order to simulate a worst-case scenario, the generative tissue model was chosen to be parallel fibers ($\kappa = \infty$ in the NODDI model). The NDI model was fitted repeatedly to the signal simulated for multiple rotations of the fibers, after which the largest absolute bias found in f_{ic} was stored. The precision in f_{ic} was studied by comparing the f_{ic} maps estimated using NODDI vs. NDI, where in the case of NDI both a full and a reduced dataset was used.

Results – Table 1 lists the maximum bias in f_{ic} found when varying the number of directions used in the $b = 1000$ and $b = 2750$ shells. It approaches zero for the full protocol, and is only a few percent for most protocols having at least 15 directions in the high b-value shell. Figure 1 shows f_{ic} maps computed with NODDI and NDI on data obtained with the full protocol as well as a map computed with NDI on data from a subsampled protocol, using only 30 out of 99 volumes. The 30 volumes were distributed across 1, 4, 4, 6 and 15 directions for the different b-value shells of the full protocol. Visually, the maps have essentially the same contrast without clear difference in variability, despite the scan time of the rightmost case being reduced by two thirds from 15 minutes to 5 minutes. Furthermore, the analysis time for NODDI was around 24 hours, but only 1 hour for NDI, on a 2.6 GHz dual-core Intel Core i7 Mac mini. Finally, the results from comparing PDD patients to healthy controls are shown in Figure 2. FA was significantly higher in the hippocampal cingulum of the PDD group ($p < 0.01$), but no difference in f_{ic} was observed.

Table 1. Maximal bias in f_{ic} from subsampling a full protocol, measured in percent. Rows and columns show a varying number of directions in the low and high b-value shell (b = 1000 and 2750 s/mm^2), respectively. The combination of directions used for the subsampled map presented in Figure 1 is shown in bold.

b = 1000 s/mm^2 \ b = 2750 s/mm^2	#dir	3	6	12	**15**	32
	3	67	12	20	6	5
	6	54	6	12	**2**	1
	12	53	8	11	4	2
	15	51	7	13	2	0
	32	50	7	13	2	0

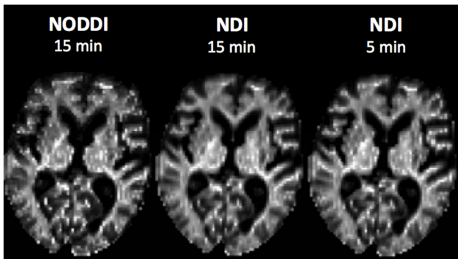

Figure 1. Comparison of maps showing the intracellular volume fraction (f_{ic}) obtained using NODDI and NDI, where the latter was applied to data obtained in either 15 or 5 minutes. NDI simplifies the acquisition and analysis, compared to NODDI.

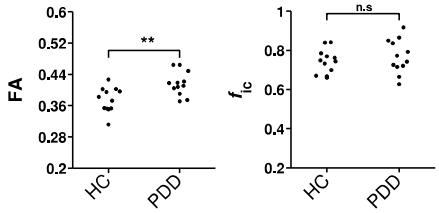

Figure 2. Higher FA was observed in the parahippocampal cingulum in PDD patients compared to in healthy controls (left). This counter-intuitive finding may be explained by reduced axonal sprouting in PDD leading to lower orientation dispersion. Such an interpretation is supported by the absence of a difference in f_{ic} (right).

Discussion – By using powder averaging to induce full orientation dispersion, NDI reduce the number of free parameters compared to the NODDI model, and yield accurate f_{ic} maps from data acquired in only 5 minutes, compared to 10 minutes as the minimal time recommended by Zhang *et al*.[1] The analysis time is also drastically shorter for NDI than for NODDI, although recent NODDI developments are promising.[4] When comparing diffusion MRI metrics in the parahippocampal cingulum between PDD patients to age-matched controls, we were surprised to find an elevated FA (Figure 2). Similar unexpected findings has been reported in the parahippocampal cingulum before by Bracht *et al.* in ageing, who suggested reduced sprouting of hippocampal axons as the cause for the elevated FA where a reduction was expected.[5] Reduced orientation dispersion is in agreement with our results, since no difference was found in the axon density between the HC and PDD group.

Conclusions – Neurite Density Imaging is enables estimation of the neurite density from data acquired in only 5 minutes compared 10 minutes for NODDI. Thus, NDI can be the preferred choice for clinical applications where short acquisition times are crucial.

References – [1]Zhang *et al.* Neuroimage 2012;61:1000-1016 [2]Jones *et al.* Neuropsychologia 2013;51(1):67–78 [4]Daducci *et al.* Neuroimage 2014;15:32-44. [5]Brach *et al.* Journal of affective disorders 2015;170:143-149