Clinical utility of NODDI in assessing patients with epilepsy due to focal cortical dysplasia

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Purpose: To apply NODDI (neural orientation dispersion and density imaging) in a clinical population of patients with epilepsy due to focal cortical dysplasia (FCD) to show that the parameter estimates are compatible with underlying disrupted tissue microstructure and provide useful additional clinical information.

Methods: Patients with FCD were scanned on a 3T GE Signa HDx scanner with a full clinical protocol and a NODDI protocol optimized for the scanner consisting of two high angular resolution diffusion imaging shells (single-shot EPI, 50x2.5mm axial slices, 96x96 matrix zero-filled to 128x128, FOV 24x24cm, TE 85ms, TR 13s; 9 non-diffusion weighted acquisitions, 24 directions with b-value 700s mm⁻², 48 directions with b-value 2000s mm⁻², maximum gradient strength 40mTm⁻¹, slew rate 150Tm⁻¹s⁻¹, total scan time 20 minutes). Optimised gradient directions from the Camino software package generated using electrostatic energy minimization were used3. Fitting was performed with the NODDI Matlab Toolbox4.

The NODDI tissue model has 3 compartments: intracellular (sticks with zero radius with an orientation distribution modeled by a Watson distribution); extracellular (simple Gaussian anisotropic diffusion); cerebrospinal fluid (isotropic Gaussian diffusion). Four parameters are fitted - intracellular volume fraction νc, mean orientation of Watson distribution μ, concentration parameter of Watson distribution κ, isotropic volume fraction νiso. For details see this paper5.

Results: In patients with FCD, intracellular volume fraction was reduced (Figure 1) compatible with iontophoretic studies of resected human tissue6. The same was true in tuberous sclerosis which has the same pathology as FCD (Figure 2). The affected area was easier to identify than on corresponding fractional anisotropy (FA) or mean diffusivity (MD) images and was clearly seen even when it was hard to identify on anatomical images (Figure 3).

Discussion: DTI indices such as FA reflect many underlying parameters including neuronal density, fibre orientation dispersion, axonal diameter and degree of myelination. DTI assumes Gaussian diffusion within a single compartment and does not adequately reflect the microstructure within a voxel. Multi-compartment models more accurately reflect the diffusion MR signal by distinguishing restricted non-Gaussian diffusion (intracellular) and hindered Gaussian diffusion (extracellular space)6 but typically require scans times far longer than clinically feasible or make invalid assumptions (e.g. no axonal dispersion). The NODDI model distinguishes two key variables contributing to FA changes - neurite density and orientation dispersion - with a clinically feasible scan protocol1 (20 minutes, which can be reduced further).

In patients with epilepsy, identifying the location of the epileptogenic zone is critical in planning surgical treatment but up to 20-30% have normal MRI scans. Many patients have undetected FCD, a developmental anomaly characterized by disrupted laminar architecture/columnar organisation and abnormal cells7. The classical neuroimaging findings described on T1- and T2-weighted images are not always present8. DTI changes including reduced FA and increased MD in underlying white matter are non-specific, extend beyond the area of abnormality9 and cannot evaluate dysplastic grey matter due to the low FA and CSF contamination.

The NODDI model is suitable for both grey and white matter and by modeling CSF as a separate compartment avoids CSF contamination. A key fitted parameter is the intracellular volume fraction. Iontophoretic studies have shown that the extracellular volume fraction is increased (and thus intracellular volume fraction is reduced) in human neocortical tissue removed during surgery in patients with FCD8. Findings consistent with this have been demonstrated on NODDI scans and can be more clearly demonstrated than on other clinical or diffusion sequences.

Conclusion: NODDI is viable to apply to a clinical population and the findings of reduced intracellular volume fraction are compatible with the known pathology of FCD. NODDI may assist in patients with epilepsy the clinical identification of areas of FCD not seen on other imaging sequences.