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Quantitative histological validation of NODDI MRI indices of neurite morphology in multiple sclerosis spinal cord

Introduction Neurite orientation dispersion and density imaging (NODDI) is a recent diffusion magnetic resonance imaging (MRI) method mapping neurite morphology, potentially able to detect specific features of tissue microstructure changes in multiple sclerosis (MS).

Objectives To investigate the validity and specificity of NODDI in MS via comparison of its metrics to quantitative histology.

Methods MRI Two samples of formalin-fixed post-mortem MS spinal cord (one lumbar, secondary progressive MS, expanded disability status scale (EDSS) 10, length 2cm; one thoracic, primary progressive MS, EDSS 7, length 3.5cm) were scanned at 9.4T. MRI images were analysed to derive NODDI free water fraction (FWF), neurite density index (NDI) and orientation dispersion index (ODI, 0 for parallel, 1 for dispersed neurites) and diffusion tensor imaging (DTI) fractional anisotropy (FA), axial, radial and mean diffusivities (AD, RD, MD). FA quantifies the spatial anisotropy of diffusion; AD/RD the amount of diffusion parallel/orthogonal to the main diffusion direction; MD the average amount of diffusion. Histology Sections from the lumbar case were stained for axons and myelin. Digital processing of their images provided circular variance (CV, spread of neurite orientations) and myelin staining intensity (MSI). Statistics Univariable linear regression models identified associations between mean values of histology and MRI metrics within manually drawn regions of interest.

Results Metrics In both cases, NDI, ODI and FA were hypointense in white matter (WM) focal lesions (FLs) compared to surrounding WM, whereas FWF, AD, RD, MD hyperintense. In the lumbar case, CV was hypointense in WM FLs, where MSI showed demyelination. NDI and MSI were hypointense in grey matter (GM) FLs compared to GM. Statistics For NODDI, higher CV was strongly associated with higher ODI ($p< 0.001$); higher MSI with higher NDI ($p< 0.001$) and weakly with lower ODI ($p=0.02$). For DTI, higher CV was associated with lower FA ($p=0.03$); higher MSI with higher FA ($p=0.01$) and lower AD ($p=0.003$), RD ($p=0.01$), MD ($p=0.01$).

Conclusions NODDI metrics in post-mortem MS spinal cord agree with histology. While pathological

decreases in neurite orientation dispersion and myelin can be selectively detected with NODDI ODI and NDI, the two cause opposite effects on DTI FA, a conventional but non-specific index of tissue integrity. In conclusion, NODDI provides sensitive and specific promising biomarkers of tissue injury in MS.

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