Specialty Area: Imaging Microstructure in Neurology/Neuroradiology

Target Audience: Physicists and clinicians interested in clinical applications of microstructure imaging.

Purpose/Outcome: Understand the clinical relevance of tissue microstructure metrics and the issues arising from application of these metrics towards neurologic disease.

Methods: It is desirable to place studies of microstructure in the context of macrostructure. Macrostructural imaging encompasses volumetric imaging, which can be qualitative (i.e. rater assessment of intracranial volume, hippocampal volume, or white matter lesions) or quantitative (segmentation of the brain and measurement of volume/thickness with FreeSurfer [1], FSL [2], ASHS [3], etc.)

Microstructural imaging generally involves obtaining a quantitative metric from each voxel. With diffusion tensor imaging, a tensor is fit to the diffusion-weighted images, and from the tensor, one obtains the metrics of fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. The tensor model is optimal in regions in which a single primary fiber bundle of relatively homogeneous axonal diameter is present. Under this condition, each of the above metrics has a predictable pattern correlating with integrity or lack thereof in the fiber bundle. After these multi-parametric maps are made, they can be compared between subjects using programs such as AFQ [4] and TBSS [5]. Many other advanced diffusion processing methods can deal with crossing fibers and non-gaussian diffusion components of the signal decay (e.g. NODDI [6] , DKI) that require multi TE-matched b-shell acquisitions and sophisticated data processing and modeling.

Magnetic susceptibility can be measured in multiple ways from within a voxel. T2* or R2* measurement has a long history of use, but more recently, quantitative magnetic susceptibility has shown great promise in quantifying the contribution of iron and myelin to susceptibility.

For a microstructural clinical study, the key data is the clinical population of interest and an age-matched control population. Key analyses are comparison of the two populations, as well as correlation of severity of disease within the clinical population (which requires measurement of disease severity). Longitudinal analyses hold the promise of better defining the nature of these correlations. Many caveats exist, the most prominent of which is if the differences found are incidental or unrelated. Other caveats I will cover include many significant statistical issues that can “make or break” any study, and despite their well-documented nature, are still essentially errors that are routinely done (i.e. how to normalize for intracranial volume [7], issues of multiple comparisons, handedness, the proper statistical use of control populations [8].)

Results: I will illustrate the issues in microstructural imaging by describing a study on chronic fatigue syndrome [9] as well as a few other relevant research studies. We imaged a clinical cohort as well as an age and gender-matched control group with both macrostructural and microstructural imaging. The macrostructural imaging showed a

decrease in the size of the white matter compartment supratentorially. There were several concomitant foci of right-hemispheric increases in cortical thickness. Thus the macrostructural backdrop to consider was one of diffuse white matter decreases and unilateral gray matter increases. The microstructural imaging showed an increase in FA in the right arcuate fasciculus, and this increase correlated with disease severity. A receiver-operator characteristic suggested possible clinical application. The nature of the FA increase will require future studies to fully delineate.

Discussion/Conclusion: Impressive methodological advances in microstructural imaging present a great opportunity to improve our scientific and diagnostic capabilities. Taking advantage of this opportunity requires the following: (1) applying sound scientific methodology to avoid potential confounders, and (2) embedding these findings in a larger context of macroscopic imaging and clinical context.

References:

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