**Quantitative Neuro-anatomic and Functional Image Assessment**

**Quantitative Assessment of White Matter**

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White matter is critical for the integration of signals from different brain regions. Injury, disease, abnormal development, or neurodegeneration can lead to impairments in brain circuitry. The axonal bodies are responsible for signal conduction between neurons. Myelin layers surrounding the axons increase the conduction speed and efficiency. Thus, diseases that affect the axon connections, the myelin sheath, or support-cells like oligodendrocytes, which help to produce and maintain myelin, can have adverse effects on brain function. Quantitative imaging biomarkers of axons, myelin, oligodendrocytes, microglia, inflammation and edema would be valuable for the noninvasive detection and characterization of disease, and the monitoring of therapies. In general, conventional structural imaging techniques like T1-, T2-, and PD-weighted MRI offer exquisite anatomical detail, good sensitivity to white matter pathology, but poor specificity. In particular, global white matter abnormalities can make diseased white matter appear normal, hence the term normal appearing white matter (NAWM). Recently, there has been a flurry of research activity to develop quantitative biomarkers of disease progression in white matter. In this presentation, several quantitative MRI methods for assessing white matter will be reviewed – in particular T1 and T2 relaxometry, magnetization transfer, and diffusion imaging will be discussed. Issues related to the measurement, quantification and interpretation of these measures will also be outlined. Examples in both the human brain and animal models of white matter disease will be presented.

**T1 and T2 Relaxometry and the Myelin Water Fraction**

The T1 and T2 relaxation times of water are modulated by the interaction of water with the local environment. In general, increases in the total water concentration increases both T1 and T2, whereas increases in macromolecules (e.g., proteins) associated with myelin generally cause the relaxation times to decrease. Increases in tissue iron concentration (associated with aging and many neurodegenerative diseases) will reduce T2. However, many pathologic processes like demyelination, axonal loss, inflammation, edema, will cause both T1 and T2 to increase, so the specificity is generally poor. One exception, is a water signal component with a very short T2 that is believed to be associated with the water trapped within the myelin bilayers (MacKay et al. 1994). This short T2 component, also called the myelin water fraction (MWF), is usually measured using a multiple spin echo sequence. Studies have shown good correspondence of the WMF signal to the tissue myelin (Moore et al. 2000). Multiple-component T2 measurements with good temporal efficiency have recently been obtained using a 3D steady state sequence (Deoni et al. 2008). To date, the MWF appears to be the most specific imaging measure of myelin.

**Magnetization Transfer**

While imaging water is clearly important, it would be ideal to directly image the macromolecules in myelin and other brain tissues. Unfortunately, the T2 of these macromolecules is generally too short (microseconds time scales) to image directly. However, using magnetization transfer saturation pulses, it is possible to probe the transfer of bound spins on the macromolecules (like myelin proteins) with the spins in the surrounding free water (Wolff and Balaban 1989). By applying off-resonance saturation pulses, this exchange process will partially saturate the on-

resonance water signal. Thus, the higher the macromolecule concentration, the larger the magnetization transfer saturation effect will be. By acquiring a set of images with different magnetization transfer pulse parameters (amplitudes and offset frequencies), it is possible to model the exchange of spins between water and macromolecules (Sled and Pike 2000, Tozer et al. 2003; Yarnykh and Yuan 2004; Portnoy and Stanisz 2007) to estimate measures of the bound pool (macromolecule) signal fraction, the exchange rate, and the T2 of the bound pool. These measurements also require the measurement of T1 and calibration of the RF field.

**Diffusion**

The diffusion of water in tissues is modulated by the interactions with biological membranes, thus it is an ideal probe of the tissue microstructural features. Most of the effects associated with white matter tissue pathology and injury (e.g., axonal injury, demyelination, swelling, cellular proliferation) cause changes to the tissue microstructure, thus diffusion MRI, and diffusion tensor imaging (DTI) in particular has proven to be quite sensitive to white matter changes in a number of white matter diseases and injuries. The diffusion tensor provides information about the mean diffusion (inversely related to tissue density), diffusion anisotropy (a measure of directional variance in the apparent diffusion – generally increased in white matter), and the local orientation of directional tissue (e.g., white matter fiber bundles) components from the eigenvectors (Basser et al. 1994). Recently researchers have also found relationships of the parallel and perpendicular diffusion components in white matter to axonal degeneration and myelin, respectively (Song et al. 2002). However, the diffusion tensor has problems with tissue characterization in regions with crossing white matter fibers. Further, diffusion measurements with high diffusion-weighting also demonstrate non-Gaussian diffusion behavior. Recently, new diffusion imaging methods have been developed to better characterize crossing white matter fibers and the non-Gaussian diffusion behavior (Wedeen et al. 2005; Wu and Alexander 2007.; Assaf and Basser 2005). In general, these methods appear to be more sensitive to restricted diffusion components which are generally higher in white matter relative to gray matter (Wu et al. 2007).

**Other Methods and Strategies**

While these methods are promising, there is a need for correlative studies to better understand the relationship of these quantitative imaging measures to the mechanisms in white matter pathology. This can be performed using both animal models and in patient studies with clinical and behavioral outcome measures. It is possible that complimentary quantitative methods are necessary to improve the overall specificity of pathology in the brain. Further, other methods including MR spectroscopy and contrast agents may also be used to improve the assessment of white matter pathology however they are beyond the scope of this presentation.

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