Diffusion Techniques to Image Microstructure

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Highlights:

- Diffusion of water molecules by NMR was first described by Stejkal and Tanner in 1965 (Journal of Chemical Physics 42:288, 1965)
- Tissue microstructural properties by diffusion imaging – described in the early '80s
- Diffusion weighted imaging applications in animal models
    a. Stroke
    b. Cancer – response to treatment
    c. Neurodevelopment
- Challenges in diffusion imaging of small animals
    a. Susceptibility artifacts due to EPI based methods
    b. Motion artifacts due to respiratory and cardiac breathing
- Recent Developments
    a. Parallel imaging
    b. Cryo-coils

This introductory lecture is geared towards "beginner" level scientists interested in the application of diffusion imaging methods for assessing tissue microstructure in small animal models. The presentation will provide an overview of the basics of diffusion imaging and its application in assessing tissue microstructure with examples in developmental biology, stroke and cancer. We will also discuss the challenges and potential solutions for high resolution diffusion imaging of small animals.

Diffusion imaging is a highly sensitive method for probing the diffusion of water molecules in a biological system, predominantly within the extra-cellular domain. Unlike true molecular diffusion, diffusion of water molecules in tissues is restricted due to its interactions with membranes, fibers, and macromolecules, making it a sensitive method to assess tissue microstructure. In diffusion imaging, this self-diffusional movement of water molecules is detected by the attenuation of MRI signal using a diffusion weighted sequence. The diffusion weighted MRI signal can be made sensitive to such diffusion by increasing the diffusion time and the degree of diffusion weighting. When unimpeded, water molecules move in a random manner (also known as isotropic diffusion). However, in the presence of obstacles, such as axonal membranes and myelin sheaths in the white matter fiber tracts, the molecular motion is hindered in a particular direction resulting in anisotropic diffusion. Among the several diffusion imaging parameters that can be measured using diffusion imaging, the most commonly used indices are apparent diffusion coefficient (ADC) and fractional anisotropy (FA). ADC is a measure of the directionally averaged magnitude of diffusion and is related to cell density, size and parenchyma permeability, while FA represents the degree of diffusion anisotropy, and reflects the degree of alignment of cellular structure.

Diffusion weighted imaging (DWI) has been established as a reliable method for the early detection of cerebral ischemic stroke. A significant decrease in ADC is noted after the onset of stroke, which has been attributed to energy depletion, ionic imbalance, cellular shrinkage, and a shift of water towards the intra-cellular space (cytotoxic edema). DWI has been used in combination with perfusion imaging methods to detect the ischemic penumbra in animal models of stroke. Small animal DWI studies of cancer models have primarily been used to detect early treatment response to novel therapeutic regimens since an early increase (due to increased extracellular space from cell death) in ADC has been shown to be a marker of response.

Diffusion tensor imaging (DTI) is distinguished from DWI by its sensitivity to anisotropic or directionally dependent diffusion of water molecules. The anisotropic diffusion in the brain is largely attributed to the cyto-architectural compositions of myelin and axons. DTI is also used for fiber tractography, in which the white-matter tract directions are mapped on the assumption that in each imaging voxel, a measure of the local fiber orientation is obtained. High resolution DTI of the rodent brains has been predominantly performed in extracted brains for developmental biology studies as well as in genotypic characterization of mouse models of disease. The drawback for high-resolution DTI is the long acquisition times (> 12h) per sample although, to date, white matter tractography is the only non-invasive technique that provides the morphological connectivity information of the white matter tracts.

Technical advancements in in vivo DTI studies of rodents has lagged behind clinical DTI studies since most rodent studies are performed at relatively higher fields (>4.7T), where increased susceptibility artifacts from echo-planar imaging based diffusion sequences and the need for high resolution images necessitate the need for the much longer spin echo based methods. However, recent hardware and software developments in high-field small animal MRI scanners, such as availability of phased-array coils and parallel imaging methods have led to a substantial reduction in image acquisition times. The reduced scan time can be used to increase the imaging quality by allowing more repetitions or to increase the number of diffusion weighting directions toward Q-ball or diffusion spectrum imaging methods in order to measure the complete 3D pattern of diffusion. Another exciting development is the availability of cryogenic coils to minimize the thermal noise and hence improved signal to noise for in vivo imaging experiments. Improved SNR allows better spatial resolution for small brain structures and also improves the accuracy of diffusion tensor estimation which is sensitive to the noise level. With these exciting developments on the horizon, an increase in the number and quality of DTI studies of rodents is anticipated which will further aid in understanding disease progression and development of therapeutic methods.