Diffusion Tensor Imaging / Tractography

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The possibility of detecting and measuring the diffusivity of water with Nuclear Magnetic Resonance (NMR) methods was reported in the early work of pioneers of NMR in the early fifties (e.g. E. L. Hahn' Phys. Rev. 80, 580–594 (1950). In the seventies the first spectroscopic investigations of diffusion in biological tissues took place, followed in the mid eighties by the first clinical demonstration of diffusion weighted MRI (DWI). The investigation of diffusion in anisotropic and heterogeneous tissues has been facilitated by the introduction of diffusion tensor MRI (DTI). From diffusion tensor data one can compute quantities that characterize specific features of the diffusion process, such as the principal diffusivities (eigenvalues of D), the trace of the diffusion tensor (Trace(D)), indices of diffusion anisotropy, and the principal directions of diffusion (eigenvectors of D). Diffusion tensor MRI (DTI) has been extensively used for probing features related to composition, microstructure, and organization of tissues in the brain and other organs of human subjects. There is a large amount of data indicating that DT-MRI could improve the clinical assessment of several neurological and psychiatric disorders. Promising clinical applications of DT-MRI have been proposed also in organs other than the brain, such as kidney, liver, prostate, skeletal muscle.

Diffusion MRI methods can be used to infer the trajectories of white matter fibers in the brain. Since the initial DTI “tractography” studies published more than 10 years ago, several more sophisticated methods have been proposed generating a lot of enthusiasm in the neuroscience community in the hope that these tools could help elucidating anatomical connectivity in the central nervous system.

Despite the large body of clinical and experimental studies published using Diffusion MRI, this methodology has still very little penetration into clinical practice. In this talk we will review some of the obstacles that have hindered a larger dissemination of Diffusion MRI.
In particular we identify the following aspects that may need additional work:

1) ***Quality of Diffusion MRI acquisition***. The quality of Diffusion MRI is generally poor compared to that of other structural MRI acquisitions because clinical DWIs are acquired using single shot echo planar imaging (EPI). EPI has the advantage of being efficient (high SNR per unit time) and it is relatively immune from motion related-ghosting. However, the spatial resolution and anatomical accuracy of EPI is suboptimal in most clinical scanners. We will discuss the impact of EPI artifacts on DT-MRI and review strategies for correcting residual EPI related distortions via non-linear image registration.

2) ***Artifacts affecting accuracy and reproducibility of Diffusion MRI***. Although DT-MRI is a quantitative technique (i.e. it measures a physical quantity

that is reported in absolute units), several factors adversely affect the accuracy and precision of DTI measures. Such factors can be broadly classified as originating from thermal noise, system induced artifacts, and physiological noise. Physiological noise originates from subject motion, cardiac pulsation, partial volume contamination from cerebral-spinal fluid, and, possibly, respiratory motion and blood flow induced pseudo-diffusion effects. These factors affect the reproducibility of clinical DTI scans and negatively impact clinical studies in several ways. Not knowing the overall variability of DTI measurements precludes computing the number of subjects necessary to be able to detect a given effect.

Moreover, longitudinal data and data from different centers cannot be compared reliably. Sources of variability also act as confounds in assessing differences between different groups of subjects. For example, DT-MRI differences found between healthy controls and patients may be due to artifacts originating from physiological noise, such as heart rate and subject motion, rather than to true anatomical differences. There is clearly a need for improving the resolution, reliability, and overall quality of diffusion tensor MRI acquisitions. The challenge is to achieve this goal by maintaining a reasonably short scan time.

3) ***Biological specificity and Validation of Diffusion MRI.*** In general, understanding the relationship between a measured water diffusion pattern and the underlying histological features of the tissue is not simple. We lack a robust and comprehensive model that relates water diffusivity to specific biological features. Essentially, we do not know how “specific” diffusion metrics are as biomarkers. For example, the main problem in inferring white matter trajectories from diffusion MRI measurements is that the diffusion properties measured in a voxel are affected by the presence of a large quantity of axons.

The measured diffusion displacement profile is essentially a voxel-averaged quantity which provides a good estimate of fiber orientation only if the axons are oriented collinearly. In heterogeneous tissue, inferring the intravoxel architecture of white matter becomes a complicated inverse problem which we believe is essentially unsolvable with the limited information gathered by Diffusion MRI. One other obstacle is related to noise in the measurement. The water diffusion displacement profile we measure in each voxel is affected by both instrumental and physiological noise. In diffusion-based tractography the effect of noise is magnified because errors are propagated from one voxel to the next in the tractography chain.

Ultimately the penetration of a technique into clinical practice is related to its ability to answer reliably, quickly, and inexpensively questions such as: 1) Does this technique have good sensitivity and specificity in detecting disease; Is it useful for staging the disease?; Is it sensitive to hidden pathology not revealed by other techniques (e.g. lesion load in in "normal appearing" white matter)? 2) Can this technique help differentiating between different clinical subgroups ? 3) Is there a relationship between changes in imaging parameters and clinical disability? Is this technique a reliable biomarker? 4) Would the information I gain with the examination alter treatment choices and/or provide prognostic

information?
The current lack of widespread clinical application of Diffusion MRI does not imply that the technique could not provide a positive response for most of this questions in the future, but it clearly indicates that we need to put more effort in overcoming standing obstacles.