Session Title: Diffusion Tensor Imaging (DTI)
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The aim of the discussion was to determine how and to what extent DTI can contribute to research on neurologic impairment, recovery, and rehabilitation. Possible contributions of DTI are the prediction of recovery (prognosis), and the identification of theraputic approaches to maximize recovery given the damage to connections observed with DTI.

Overview of DTI

DTI allows one to examine the diffusivity of water to inform us about the directionality and integrity of white matter, as water diffuses anisotropically (greater diffusion occurs along particular directions) along intact axons, and diffuses relatively isotropically (diffusion occurs equally in all directions) in grey matter or injured white matter. Scalar measures about the diffusion characteristics in each voxel of the brain can be calculated from the diffusion tensor. Mean diffusivity (MD) is a directionally averaged measure of diffusion; whereas, fractional anisotropy (FA) is a measure of how much the diffusion tensor deviates from the isotropic form. One can compare these measures for specified regions of interest or using a voxel-wise approach.

Tractography, a technique that uses information about the predominant direction of diffusion in each voxel to reconstruct fiber trajectories in white matter, was discussed as a useful, albeit relatively user-dependent means of investigating white matter integrity. Though the tracts reconstructed by this method are often referred to as fibers/tubules. it is important to note that streamlines or pathways derived with tractography do not represent individual fibers. This is a consequence of the large size of imaging voxels (usually 1-3 mm in each dimension) relative to individual axons; a single imaging voxel could contain several thousand axons. There are various candidate parameters of structural integrity that can be extracted following reconstruction of tracts. These include total streamline count between target regions, as well as streamline density (i.e., streamline counts per voxel) and mean FA across the reconstructed tract volume.

Methods of Tract Reconstruction

Three dimensional tract reconstruction can be performed using linear (deterministic) or distributed (probabilistic) methods. Linear methods, including Fiber Assignment by Continuous Tracking (FACT), which attempts to determine connectivity utilizing the principal eigenvector of the diffusion tensor to provide a propagation direction for each voxel along a path. The limitation of this approach is that it produces only one reconstructed projection per seed point, when there could be multiple projections that are not accounted for. In addition, these methods do not take into account the uncertainty of the direction information in each voxel, which may lead to generation of erroneous trajectories. This uncertainty information, in the form of probability density functions (PDFs), is incorporated into probabilistic tractography methods, such as the Probabilistic Index of Connectivity (PICo) or the fMRIB Diffusion toolbox. The advantage of these methods is that they can provide a measure of confidence for the connections established, whereas linear tracking methods do not. However, a limitation to these methods is the difficulty in adequately modeling diffusion, and its uncertainty, in each voxel. Modeling areas known to contain multiple tracts propagating in multiple directions is a challenge for three dimensional tract reconstruction methods. However, there are techniques available that model a mixture of diffusion directions to represent intravoxel heterogeneity seen in areas such as crossing fibers and branches that sprout from white matter bundles reaching target cortex.

How Well Validated is DTI as a Measure of Structural Connectivity

DTI has shown concurrent validity as a measure of structural connectivity in stroke. For instance, Judith Schaechter presented tractography work by the Martinos Center showing the number of fibers seen in the ipsilesional cortical-spinal tract (CST) of patients with hemiparetic stroke is highly correlated with ipsilesional peduncular area; such that a lower fiber count in the CST corresponds to lower peduncular area as seen in morphemetric analysis.

Recent findings from published literature were also discussed and consequently highlighted potential confounds in the interpretation of tractography as a measure of structural connectivity. The dependence of propagation of streamlines on anisotropic diffusion was raised as a major issue for the use of tractography in the presence of white matter damage, which can lead to reduced anisotropy. The influence of retrograde and anterograde changes on the ability to reconstruct tracts was also discussed.

More general issues concerning the importance of seed point selection and incorporation of target areas into tractography algorithms were raised. J. Schaechter pointed out that tractography may result in false or aberrant projections which results from the uncertainty in the data given by the partial volume effect. Thus, restriction of the solutions by seed and target points is mandatory and an exploratory analysis driven by the DTI data is hardly possible. Dorothee Saur presented group analyses of intrahemispheric connections in the language system; the use of voxelwise t-tests of tractography-derived probabilistic maps of connectivity at the group level may reduce the influence of false or aberrant streamlines in the reconstruction of white matter tracts across subjects.

Challenges

As with any technology, there are challenges to tractography. For instance, the reconstruction of white matter tracts is user dependent which may introduce error or bias and is dependent on the user's knowledge of neuroanatomy. Insufficient knowledge of neuroanatomy and knowledge of structural connectivity can result in erroneous tracking. Another challenge is determining when it is appropriate to terminate a streamline in the brain. In many tractography algorithms this is determined by FA; however, this may be problematic in injured brains, as FA is reduced in white matter lesions and the reconstruction of tracts terminate far short of where the tract terminates in uninjured brains.

Future Direction

DTI was discussed as a measure with potential utility in combination with fMRI. Such a study might attempt to determine whether the start or end points of damaged white matter tracts correlate spatially with altered BOLD responses. The combination of structural and functional imaging modalities may be a useful method of assessing whether the degree of functional plasticity is related to the degree of structural connectivity.