Neurodevelopment and Brain Pathology Depicted by Diffusion Spectrum Imaging (DSI)

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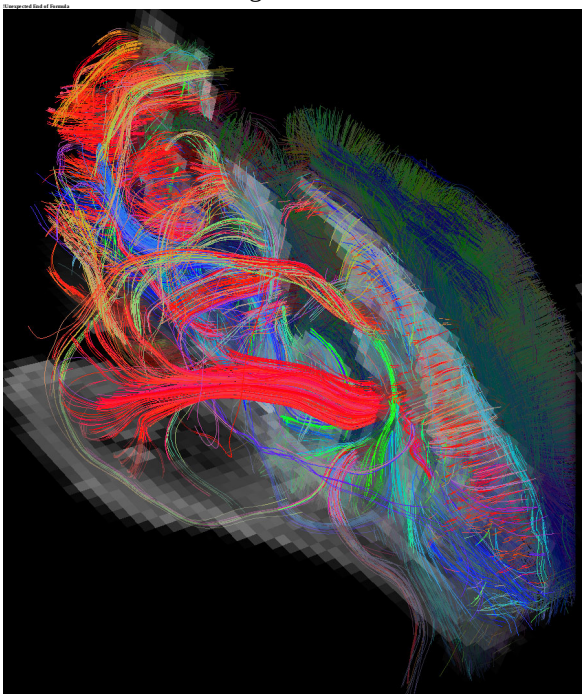
Introduction: Diffusion spectrum imaging (DSI) is a new non-model based approach to measuring the diffusion orientational structure in tissue (1). In addition to resolving fiber crossings in brain white matter tracts (2) this method has the potential to detect complex microstructure in tissues where diffusion is not well described by the simple tensor model, such as the cerebral cortex. This presentation explores the additional information available with DSI, compared to the widespread DTI technique, in the case of neurodevelopment and in two cases of brain pathology: prenatal cocaine exposure and stroke.

Methods: In order to maximize our sensitivity to microstructural changes in the brain, we studied fixed (*ex vivo*) animal brains using a 4.7T Bruker Avance system equipped with actively shielded 40G/cm gradients. Normal brain development was studied in the normal rabbit, comparing adult (50 days old) with juvenile (17 days old) brains. Prenatal cocaine exposure was performed in mice, and the brains harvested when the animals reached adulthood (3). Stroke studies were performed in adult macaques: either transient (3 hr) or permanent ischemia was effected using an endovascular model (4) and the brains harvested at 10 – 31 days after stroke induction. In all cases the brains were fully fixed in 4% paraformaldehyde solution before soaking in phosphate buffered saline solution (PBS) with 1mM GdDTPA. Brains were soaked in the GdDTPA doped PBS for between 2 days (mice) to 2 weeks (monkeys) prior to imaging to rehydrate the tissue and reduce the T_1 relaxation time so as to allow for more rapid imaging. All brains were mounted for MRI scanning in tubes containing a perfluorocarbon liquid (Fomblin LC/8) for susceptibility matching. DSI scanning was performed using a 3D echo planar Stejskal Tanner diffusion sequence: single shot EPI in the axial plane was phase encoded in the Z (i.e. B_0) direction to acquire a whole volume in 1 to 2 minutes. Typical imaging parameters include: 64x64x128 matrix, TE 40-60ms, TR 450ms, 38G/cm max. diffusion gradient, δ=10-14ms, Δ=15-20ms, isotropic spatial resolution of 512μm (monkeys) 320-400μm (rabbits), 175μm (mice). Total scan times were 16-24 hours. We used a 514 point Q-space trajectory covering a 3D Cartesian grid, with maximum b-values from 20,000 to 40,000smm^{-1}. Diffusion data for each voxel was Fourier transformed to generate the 3D diffusion probability density function which was in turn used in the fiber tracking algorithm to calculate all possible tracts within the brain.

Results: Figure 1 shows an example of DSI fiber tracking in an adult rabbit brain (400 μm resolution). Major white matter fiber tracts are apparent extending for a considerable distance through the brain, and also into the cortex. Both radial and some longitudinal fibers are apparent within the cortex itself. In contrast, the juvenile rabbits showed fewer fibers overall and those seen tended to be shorter and extended less clearly into the cortex. Nevertheless, the young animals still revealed a wealth of complex fiber structure which became even more prominent with age. Comparison of control and pre-natally cocaine exposed mice brains yielded a similar pattern of complex white matter fiber architecture, however differences were observed in the cortical fiber structure: cocaine exposure resulted in sparser and less well structured cortical fibers. This is consistent with histological studies in prenatally cocaine exposed mice which show a range of cortical abnormalities including persistent imprecision of cortical lamination, a delayed loss of neurons, and a persistent thinning in the radial domain. Scans of subacute and chronic stroke (>= 10 days post insult) in the nonhuman primates showed an overall reduction in structural contrast in both in white and gray matter in the stroke area, consistent with tissue necrosis.



Conclusion: DSI fiber tracking in these fixed brain samples shows that there is more to be seen than can be revealed by traditional single tensor DTI approaches. DSI can reveal pathology in both cortex and white matter. Most striking are the changes seen with normal development in the rabbit brain. This new method holds great promise for studies of development and cortical plasticity.

References: (1) Wedeen et al., ISMRM Meeting, 2000, p. 38. (2) Lin et al., NeuroImage 19, 2003, 482-495. (3) Wilkins et al. Neurotoxicology & Teratology 20;3, 1998, 215-226. (4) de Crespigny et al., ISMRM Meeting, 2001, p. 345.

Figure 1: DSI fiber tracts in adult rabbit brain. Major interacting white matter tracts such as the cingulum, corpus callosum and fimbria are clearly visible. In addition, some tracts extend into the cortex, which exhibits radial and some horizontal fibers.