● PERSPECTIVES

Diffusional kurtosis imaging: a promising technique for detecting microstructural changes in neural development and regeneration

Brain development is one of the most fascinating subjects in the field of biological sciences. Nonetheless, our scientific community still faces challenges in trying to understand the concepts that define the underlying mechanisms of neural tissue development. After all, it is a very complex subject to grasp and many of the processes that take place during central nervous system maturation are yet to be ascertained. Despite this challenge, we have come to recognize that understanding the natural course of normal brain tissue development on both microscopic and macroscopic scales is the key to deciphering the mechanisms through which these neural networks also heal and regenerate.

Realizing this concept, my good friend and colleague, Dr. Sarah Milla, and I decided to take on a human study to investigate brain maturation using non-invasive imaging techniques in the pediatric population at New York University (NYU) School of Medicine (Paydar et al., 2013). Our research subjects included 59 normal infants with an age spectrum ranging from birth to approximately 5 years of age, when the brain is in its most active stage of development. We implemented a Magnetic Resonance Imaging (MRI) diffusion technique called Diffusional Kurtosis Imaging (DKI) to investigate the microstructural changes that occur in both the white matter (WM) and gray matter (GM) in the developing brain.

Macrostructural changes that take place within the brain during the course of maturation have been well documented by conventional MRI techniques in both normal and pathologic states. However, these conventional techniques are limited in their ability to quantify developmental changes that occur at the microstructural level. Therefore, *in vivo* characterization and accurate diagnosis of microstructural abnormalities currently remains challenging.

Diffusion imaging, including Diffusion-Weighted Imaging (DWI), has been utilized for evaluation of microstructural changes that are difficult to detect using conventional MRI techniques (Basser and Jones, 2002). In particular, the widely used Diffusion Tensor Imaging (DTI) has been shown to be sensitive to age-related microstructural changes during rodent and human brain development in both physiologic and pathologic states (Takeda et al., 1997; Mukherjee et al., 2002; Deipolyi et al., 2005; Lebel et al., 2008; Cheung et al., 2009; Huang et al., 2009; Treit et al., 2013; Yoshida et al., 2013). As a quantitative measuring tool, DTI has also been implemented in studies investigating the degree of neuronal damage due to both acute and chronic injury (Erjian et al., 2013; Guojie et al., 2014) as well as progressive neurodegeneration (Thomalla et al., 2004; Zhang et al., 2009).

Fractional Anisotropy (FA), the DTI metric that is the primary index of diffusional directionality, can be used to evaluate the anisotropic neuroarchitectural orientation of WM fiber tracts. FA has demonstrated its sensitivity to certain processes that contribute to tissue organization and increase in anisotropic complexity, particularly myelination, which predominantly occurs in the WM (Beaulieu, 2002; Mukherjee et al., 2002; Lebel et al., 2008). Accordingly, DTI is an excellent tool for investigating the age-related increase in anisotropy that occurs within the network of WM tracks as a result of myelination.

However, DTI is based on a Gaussian approximation of water diffusion, which limits its sensitivity to diffusional and micro-structural properties of biological tissues (Veraart et al., 2011). Several years ago, DKI diffusion weighted technique, which exploits diffusional non-Gaussianity, was developed at NYU by our colleagues, Drs. Jens Jensen and Joseph Helpern. This technique takes into account the non-Gaussian diffusional properties of water motion in complex media and is therefore more comprehensive in evaluating brain tissue microstructural complexity (Jensen et al., 2005; Lu et al., 2006; Jensen and Helpern, 2010).

The DKI method is basically a clinically feasible extension of the traditional DTI model, maintaining the ability to estimate all of DTI's standard diffusion tensor metrics, although with improved accuracy (Veraart et al., 2011). Moreover, DKI provides an additional parameter that quantifies non-Gaussian diffusion called diffusional kurtosis, K. By using the K parameter, multiple additional kurtosis metrics, most importantly, mean kurtosis (MK), can be generated.

In our study, we hypothesized that, owing to its potentially higher sensitivity for detection of age-related microstructural changes, MK may provide additional information about brain maturation when compared to that obtainable with the conventional FA metric in both WM and GM. And our results were quite conclusive.

We demonstrated a progressive rise in both FA and MK throughout seven WM regions (splenium and genu of corpus callosum, frontal and parietal WM, anterior and posterior limbs of the internal capsule, and external capsule) that we examined in the first 2 years of life. This finding suggested that both DTI and DKI can reflect the age-related increase in diffusional anisotropy in WM tracts, predominantly as a function of myelination in the first 2 years. However, our data also showed that MK continues to rise beyond the FA plateau at the 2-year mark in all WM regions, showing its ability to resolve the more delayed microstructural changes that occur in the WM beyond 2 years of age. In other words, compared to DTI, DKI offers additional characterization of the isotropic diffusion barriers that continue to develop in the WM even after myelination and axonal packing have already peaked.

Our study also supported the hypothesis that DKI is sensitive to age-related microstructural changes that occur in the isotropic GM, for which DTI has previously shown to have limited sensitivity (Mukherjee et al., 2002; Cheung et al., 2009). Our results proved that, unlike FA, MK showed a steady rise in signal in the interrogated GM regions (putamen and thalamus) overtime, accounting for specific isotropic GM changes to which FA is not as sensitive. Therefore, when compared to FA, MK can better resolve the progression of GM organization with respect to age by accounting for other isotropic microstructural barriers that form at the cellular level.

Finally, we generated three-dimentional DKI tractography images at various stages of development. These tractography images, as illustrated in **Figure 1** courtesy of Paydar and colleagues (2013), qualitatively display DKI's ability to detect the progressive age-related increase in volume and coherent orientation of central WM tracts throughout development.

In summary, DKI is an innovative diffusion MRI technique that can provide a more comprehensive evaluation of age-related changes in the microstructural complexity of both WM and GM when compared to DTI. Indeed, both DTI and DKI can detect the anisotropic WM changes which occur predominantly during the first 2 years of life as a result of myelination. However, DKI is able to identify other isotropic WM changes that occur beyond the first 2 years. It also provides greater characterization of GM maturation. Accordingly, DKI offers sensitive and comprehensive measures for the quantitative evaluation of age-related microstructural changes in both WM and GM.

So, our investigation has demonstrated the potential utility of a valuable MRI technique for detection of microstructural changes within neural tissues, particularly in the setting of normal brain
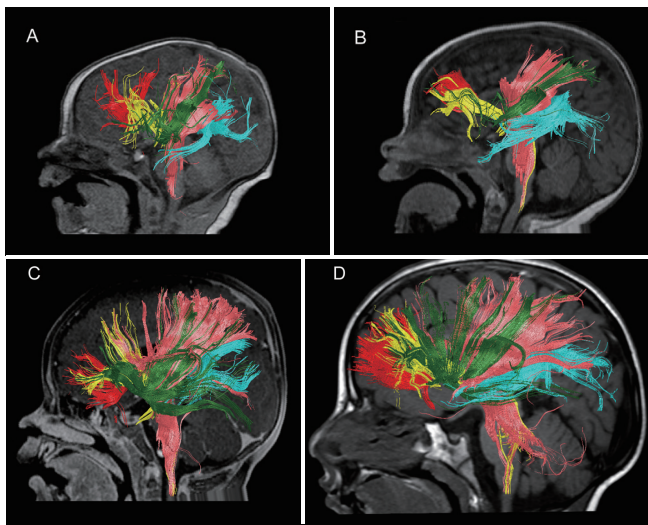
Figure 1 Diffusional Kurtosis Imaging (DKI) tractography at various stages of development, including at birth (A), 6 months (B), 11 months (C), and 2 years 1 month (D) of age.
Fiber tracking is displayed for the genu (red), splenium (cyan), anterior limb of internal capsule (yellow), posterior limb of internal capsule (pink), and external capsule (dark green).

development. But what is the relevance of this discovery for neural regeneration research? The answer to this question is clear.

Speculatively, the diffusion barriers which may form due to the progressive increase in macromolecular reorganization during neural maturation are probably similar to ones that take shape during the course of neural regeneration. These barriers may partly result from many cytoarchitectural changes that take place at the microstructural level during both neural development and regeneration. For example, these changes may include the overall increase in the complexity of intrinsic cellular processes (*e.g.*, proliferation of cell membranes, organelles, and extracellular matrix), axonal pruning and cell packing, myelination and functional reorganization of myelin, as well as addition of basal dendrites and transition of radial glial cells to astrocytic neuropil (Truwit, 2001; Mukherjee et al., 2002; Huppi and Dubois, 2006; Lu et al., 2006; Cheung et al., 2009; Jensen and Helpern, 2010; Veraart et al., 2011; Provenzale et al., 2012; Yoshida et al., 2013).

Therefore, since the increase in tissue complexity that occurs during development may be similar to regeneration, DKI may potentially serve as a valuable measuring tool for detection of cellular processes that alter microstructural complexity of tissues in the setting of neural regeneration. We are optimistic about this great prospect and hope that our neuroscience community will effectively use this non-invasive MRI diffusion technique in both *in vivo* and *in vitro* settings for neural regeneration research in the near future.

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