

SIMULATION OF DIFFUSION CHANGES IN DIFFERENT PATHOLOGIES AFTER TRAUMATIC BRAIN INJURY

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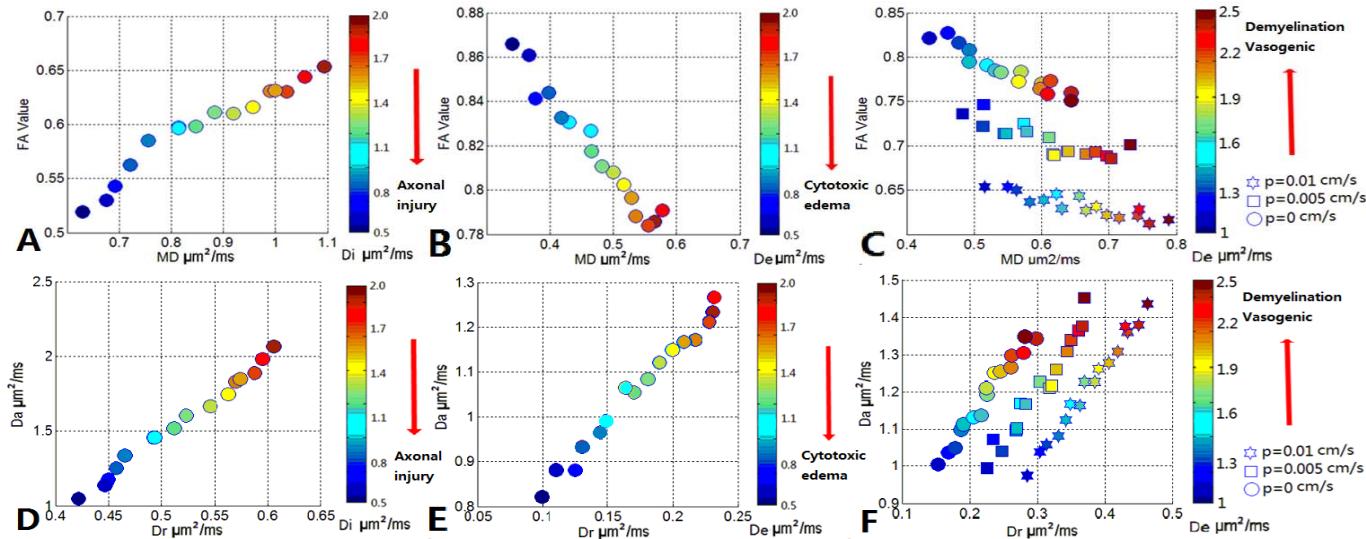
Target audience: Scientists and clinicians who are looking for mechanics behind DTI-detected brain injury changes.

Purpose: Diffusion tensor imaging is able to detect subtle microstructural changes in human brain. Numerous studies have reported changes of DTI parameters, such as mean diffusivity (MD), fractional anisotropy (FA), axial and radial diffusivity (Da and Dr), after traumatic brain injury (TBI). However, the clinical observations are not always consistent as most human studies report decreased FA and elevated MD^[1-3] but a minority reporting increased FA and reduced MD^[4, 5] in the early stage of mild TBI. Recently, new animal models have been proposed to help us understand human TBI^[6]. The discrepancy in findings has not been well understood, even though the differences of severity in TBI and the delay between injury and scanning may count to some degree. In this study, we proposed an evolution course of DTI parameter changes in TBI, and DTI parameters from typical stages of mild and severe TBI were simulated with Monte Carlo method. The preliminary result **supports the observations of both increased and decreased FA/MD values at different time points of TBI evolution course**. And Da and Dr are also evaluated as alternative indicators of TBI.

Methods: We divided TBI into the acute and the subacute stages. In the acute stage, when the injury was relatively mild, axonal injury was the predominant factor determining DTI parameter changes. As injury grew severe, cytotoxic edema became prevalent over axonal injury. In the subacute stage, demyelination and vasogenic edema were the primary driving factors of DTI parameter changes. The present work simulated a tissue model in which axons were regarded as a periodic array of cylinders surrounded by extra-axonal medium, with permeable membranes in between. We chose three variables, i.e. permeability, intra- and extra-axonal diffusivity corresponding to histological changes in TBI. For axonal injury, intra-axonal diffusivity was reduced because accumulated organelles and disrupted neural filaments would hinder water diffusion along axon. Cytotoxic and vasogenic edema would decrease and elevate extra-axonal diffusivity respectively because cellular swelling reduced free water within intercellular space while vasogenic edema increased free water. In demyelination, water molecules could pass axonal membrane more easily as a result of increased membrane permeability. Simulations were conducted in Matlab. We employed a pulsed gradient spin echo sequence, with b-value 1000 s/mm² (gradient duration approximately 0). The number of spins and steps were 10⁴ and 10³ respectively. The simulations were divided into 3 groups with parameters and their ranges in the table below. Then, we fitted the diffusion tensor model to the synthesized data. FA, MD, Da and Dr were calculated and plotted in scatterplots.

Histological event	Stage	Axon density	Axon radius	Extracellular Diffusivity (D _e)	Intracellular diffusivity (D _i)	Axonal membrane permeability
Axonal injury	Acute	300 /mm	1.5 μm	2 $\mu\text{m}^2/\text{ms}$	2 to 0.5 $\mu\text{m}^2/\text{ms}$	P=0.001 cm/s
Cytotoxic edema	Acute	300 /mm	1.5 μm	2 to 0.5 $\mu\text{m}^2/\text{ms}$	1 $\mu\text{m}^2/\text{ms}$	P=0.001 cm/s
Vasogenic edema/ demyelination	Subacute	300 /mm	1.5 μm	1 to 2.5 $\mu\text{m}^2/\text{ms}$	1 $\mu\text{m}^2/\text{ms}$	P=0, 0.005, 0.01 cm/s

Results: When the injury is relatively mild, axonal injury dominates the acute stage. Da, Dr, MD and FA all have a downturn with decreasing intracellular diffusivity in fig. A and D. In case of severe injury, the changes of DTI parameters will be predominated by cytotoxic edema which reduces extracellular diffusivity. As a result, Da, Dr and MD are reduced whereas FA is increased because Dr has a larger reduction than Da (fig. B and E). At subacute stage, the predominant pathology is vasogenic edema and demyelination. Da, Dr and MD will increase beyond the normal (pseudo-normalize) while FA is still lower than the normal (fig. C and F). A higher permeability will further reduce FA and increase Dr and MD because of a reduction of obstacles perpendicular while Da doesn't change with permeability (fig. C and F).



Discussion: Our result shows that axonal injury and cytotoxic edema have opposite effects on FA value in the acute stage, which explains the both increased and reduced FAs reported. Da has a good specificity for pure axonal injury, and Dr can evaluate cytotoxic edema. In the subacute stage, vasogenic edema increases both Da and Dr, but demyelination only increases Dr. So Dr is able to detect demyelination but its sensitivity is easily disturbed by vasogenic edema. The perturbations in the simulated data points is due to limited steps and simulated spins in our Monte Carlo simulation. More convergent data can be expected at cost of huge computation.

Conclusion: The DTI parameter changes are determined by both the severity and timing of injury, and are usually highly related to the pathological events in TBI. DTI is able to detect axonal injury and demyelination sensitively and specifically in acute and subacute stage, but it is more complicated if cytotoxic and vasogenic edema occur, and a combined analysis of all DTI parameters may be helpful in such case.

Keywords: Diffusion tensor imaging, Traumatic brain injury, Monte Carlo simulation

Reference: 1. Arfanakis K, et al., AJNR, 2002; 2. Huisman TAGM, et al., AJNR, 2004; 3. Miles L, et al, Brain Inj, 2008. 4. Wilde E A, et al., Neurology, 2008; 5. Mayer A R, et al., Neurology, 2008; 6. Christine L. Mac Donald, et al., Journal of Neuroscience, 2007