MRI Evaluation of White Matter Recovery After Brain Injury

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Abstract—We discuss the use of MRI in detecting and staging white matter reorganization after brain injury with and without neurorestorative treatment. Based on variations of diffusion tensor MRI (DTI) methodology, we demonstrate that MRI can detect white matter remodeling after brain injury. In addition, we demonstrate that Q-space DTI can detect early stage axonal remodeling, which involves randomly oriented crossing axons. With the information obtained from conventional and Q-space DTI, it is possible to stage white matter remodeling after brain injury. (Stroke. 2010;41[suppl 1]:S112-S113.)

Key Words: functional recovery imaging stroke recovery

Currently, thrombolytic treatment using intravenous recombinant tissue plasminogen activator is the only effective treatment for the ischemic stroke patient; however, only a small percentage of patients can be treated, despite a window from 3 to 4.5 hours.1 It is important to develop alternate restorative therapies with a less restrictive window that can be applied to the majority of stroke patients, as well as to develop advanced neuroimaging methodologies to monitor recovery. Experimental studies suggest that cell-based or pharmacological-based neurorestorative treatments enhance brain reorganization and significantly improve functional recovery when treatment is initiated up to weeks after stroke or traumatic brain injury (TBI).3 Such neurorestorative treatments amplify endogenous processes of brain plasticity, such as neuronal and vascular remodeling, which likely contribute to improvement in neurological function after stroke and TBI.3 However, the present understanding of neuronal remodeling after stroke derives mainly from regional histological measurements that do not allow dynamic assessment of tissue remodeling.3 In contrast, MRI can noninvasively monitor the temporal profiles of functional recovery and tissue remodeling after brain injury.3,4 Because of the noninvasive nature of MRI measurement, the MRI indices of neuronal remodeling related to neurological outcome in preclinical brain injury models may be translated to clinical application.

The MRI methodologies of neuronal remodeling after brain injury are predominately based on MRI measurement of proton (water) diffusion. Diffusion tensor MRI (DTI) provides a means for delineating the anatomic connectivity of white matter pathways and can be used to detect pathological tract disruption. The utility of DTI in stroke and TBI has been successfully demonstrated in several studies,3,4 and the DTI method has improved diagnosis of stroke and TBI to better understand mechanisms of the progress of the diseases. Previous investigations have primarily focused on the relationships of white matter damage measured by DTI and brain recovery,5 with less attention paid to the effects of white matter reorganization on brain recovery. We have shown that neural progenitor cell treatment of stroke promotes axonal remodeling and remyelination and increases oligodendrocytes.7 White matter reorganization, identified by an increase in axonal density and myelination after neural progenitor cell treatment, is coincident with increases of fractional anisotropy (FA) in the recovery regions of cerebral tissue.3,4 Also, fiber tracking maps derived from diffusion tensor imaging revealed that axonal projections exhibited an overall orientation parallel to the lesion boundary, which was confirmed by histological evaluation of the white matter recovery region after stroke or TBI.3,4 Although conventional DTI using FA and fiber tracking is able to detect white matter damage and recovery after brain injury, DTI produces an anomalous result, showing an overall lowering of FA and erroneous connectivity when white matter fiber tracts cross, because of the inherent assumption of a Gaussian diffusion tensor model.8 In contrast to the single tensor per voxel derived from the Gaussian diffusion tensor model, Q-space diffusion tensor imaging (q-DTI) (eg, diffusion spectrum imaging,9 q-ball,8 and persistent angular structure MRI [PASMRI]10) provides model-independent analysis to obtain multiple tensors per voxel and thereby extracts information on complex tissue structure including crossing fiber tracts. The overall lowering of FA can also be corrected by analysis of the diffusion distance using Q-DTI methods of diffusion kurtosis11 and diffusion standard deviation (SD).12 Direct comparison of fiber orientation between Gaussian DTI, q-ball, PASMRI, and gold standard immunohistochemistry staining has demonstrated that both the PASMRI and orientation distribution function in q-ball clearly show 2 consistent pairs of peaks in the crossing fibers in the layer between corpus callosum and...
cortex, but the Gaussian DTI failed to detect the crossing fibers.\textsuperscript{13}

The early stage of axonal remodeling is associated with less organized, randomly oriented axons that cannot be detected by conventional DTI measurements using the Gaussian diffusion tensor model.\textsuperscript{3,12} Q-space DTI measurements, such as SD DTI\textsuperscript{12} and apparent kurtosis coefficient (AKC) can detect early stage axonal remodeling.\textsuperscript{3,12} Our study of white matter remodeling after TBI after using a cell-based treatment demonstrated that although Gaussian DTI can detect white matter reorganization in the recovery regions where the fiber orientation map exhibited increased single direction–oriented, well-organized fibers, FA did not detect the increase in axons in the recovery region where fiber crossing was detected by the q-ball orientation map.\textsuperscript{3,12} In contrast with FA, the SD or AKC map exhibited increased SD or AKC in the white matter remodeling region with more crossing fibers, which is consistent with histological confirmation of increased axonal density.\textsuperscript{3,12} Because crossing axons are dominant during the early stage of white matter reorganization, our data suggest that we may provide information about the stage of white matter remodeling in the injured brain, with increased SD or AKC alone (without FA elevation) representing an early recovery stage of fiber crossing, whereas the increased FA identifies more mature linear fibers. The patterns of DTI measurements in preclinical studies also apply to clinical stroke patient.\textsuperscript{6} For example, a patient presented with a left striatocapsular stroke 41 days after MRI evaluation and had good functional recovery. His initial NIH Stroke Score (NIHSS) was 20. Follow-up NIHSS at 41 days was 14 with a modified Rankin scale 3. The SD map shows a significant white matter recovery, with increased SD intensity in the ischemic regions that show normally appearing tissues in both the T1 and T2 images 41 days after stroke.\textsuperscript{6} In contrast, the FA map fails to detect white matter recovery in the same regions with crossing fibers, confirmed by the q-ball orientation distribution function map.\textsuperscript{6}

Our data show that Q-space DTI can better detect axonal remodeling, especially early stage remodeling, whereas conventional DTI can only evaluate late stage remodeling generally characterized by single-oriented, well-organized axons. The white matter reorganization is closely related to the status of axons, including axonal density. One promising method for measuring axonal density is the MRI diffusion entropy method.\textsuperscript{14} Diffusion entropy exhibited significant correlation with axonal density measured in different brain structures.\textsuperscript{14} Diffusion entropy also has improved dynamic range and can distinguish between different structures of gray matter.\textsuperscript{14} Our data demonstrate that entropy strongly depends on axonal density rather than axonal orientation and is potentially a very useful measurement for detecting brain structure changes during neurological diseases and recovery.

In summary, MRI can be used to monitor mechanisms related to white matter recovery after brain injury. Neurorestorative therapy can enhance the endogenous restorative mechanisms of the injured brain and amplifies axonal remodeling.\textsuperscript{3,4} We show that MRI methodologies can be used to dynamically measure spatiotemporal events related to white matter remodeling both in experimental animal models and in patients.

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Disclosures
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References
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