pISSN 2384-1095
eISSN 2384-1109

iMRI 2021;25:76-80

https://doi.org/10.13104/imri.2021.25.2.76

iMRI
Investigative Magnetic Resonance Imaging

The Emerging Role of Fast MR Techniques in Traumatic Brain Injury

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Post-concussion syndrome (PCS) following mild traumatic brain injury (mTBI) is a major factor that contributes to the increased socioeconomic burden caused by TBI. Myelin loss has been implicated in the development of PCS following mTBI. Diffusion tensor imaging (DTI), a traditional imaging modality for the evaluation of axonal and myelin integrity in mTBI, has intrinsic limitations, including its lack of specificity and its time-consuming and labor-intensive post-processing analysis. More recently, various fast MR techniques based on multicomponent relaxometry (MCR), including QRAPMASTER, mcDESPOT, and MDME sequences, have been developed. These MCR-based sequences can provide myelin water fraction/myelin volume fraction, a quantitative parameter more specific to myelin, which might serve as a surrogate marker of myelin volume, in a clinically feasible time. In this review, we summarize the clinical application of the MCR-based fast MR techniques in mTBI patients.

Keywords: Post-concussion syndrome; Mild traumatic brain injury; Myelin; Diffusion tensor imaging; Multi-component relaxometry

Review Article

Received: February 27, 2021
Revised: March 31, 2021
Accepted: March 31, 2021

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Clinical Importance of Traumatic Brain Injury

Today, mild traumatic brain injury (mTBI) is a relatively common disease entity worldwide. In the United States, TBI accounts for approximately 1.1 million emergency department visits and 235,000 hospital admissions per year, most of which are mTBI (1). The clinical diagnosis of mTBI is made when a person has loss of consciousness for 0-30 minutes, posttraumatic amnesia for less than 24 hours, or alteration of the mental state at the time of accident, and the Glasgow Coma Scale (GCS) does not fall below 13 after 30 minutes following the injury (2). Although mTBI itself does not contribute to the overall death rate from TBI, it may lead to the pathological condition termed 'post-concussion syndrome (PCS)', which is characterized by a variety of somatic, cognitive, and behavioral deficits (3). PCS is a major factor that contributes to the increased socioeconomic burden, because the symptoms may persist up to several months or years (4, 5).

Traditional MR Imaging Techniques in Traumatic Brain Imaging

Although MR imaging is often not part of the diagnostic work-up in mTBI patients, conventional MR imaging and widely used advanced MR imaging techniques, including diffusion-weighted imaging (DWI) and susceptibility-weighted imaging (SWI), may be

used for patients with persisting PCS symptoms in order to exclude any structural abnormality. However, these images often fail to reveal microstructural changes in mTBI patients with PCS; such changes may account for the apparent cognitive, somatic, or behavioral symptoms experienced by the patients.

Over the past several decades, efforts have been made to develop advanced MR imaging techniques that can detect these subtle microstructural changes. Among the various MR imaging techniques, diffusion tensor imaging (DTI) has been traditionally used to evaluate the axonal and myelin integrity in mTBI patients with PCS, given the growing evidence that underscores the loss of WM integrity as the important pathophysiology for the poor long-term prognosis of TBI patients (6, 7). DTI enables both qualitative (visual) and quantitative assessment of the WM integrity. Following the acquisition, images are post-processed to generate diffusion tensor tractography, which provides a visual representation of the overall anisotropic diffusion, with color coding for the three different directions of diffusion. In addition, various anisotropy indices, such as fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD), are calculated to represent the direction and magnitude of diffusion within a voxel.

Decreased FA values (especially at the anterior corona radiata, cingulum bundle, and e uncinate fasciculus) and increased RD values have been reported in TBI patients and are thought to reflect more isotropic (i.e., less restricted) diffusion caused by the WM injury and increased diffusion perpendicular to the predominant orientation of axonal fibers caused by the myelin injury (8-11). Meanwhile, increased FA values and decreased RD values have also been noted in the corpus callosum and several left-hemisphere tracts in semi-acute mTBI patients, compared to those of healthy controls (12).

Nonetheless, clinical application of DTI is limited by its following major drawbacks:

1) DTI lacks specificity and cannot identify which specific WM microstructure (e.g., axonal membranes, neurofilaments, or myelin sheath) is injured (13),
2) other factors, such as gliosis and inflammation, can also influence the DTI metrics (14-16), and
3) the post-processing analysis of DTI is a time-consuming and labor-intensive process, which in turn limits its routine use in daily practice.

Emerging Fast MR Techniques in Imaging Myelin Loss in Traumatic Brain Injury

Preclinical studies have demonstrated that mTBI can also result in myelin loss, which can persist chronically, in particular after repetitive injury (17, 18). More recently, in parallel with the general trend towards acceleration of MRI acquisition (19, 20), various techniques based on multicomponent relaxometry (MCR) have been developed to derive myelin water fraction (MWF), a quantitative parameter that is more specific to myelin and that might serve as a surrogate marker of myelin volume, in a clinically feasible time.

Specifically, MWF can be derived using the 'Multicomponent-Driven Equilibrium Single-Pulse Observation (mcDESPOT)' technique, which is based on conventional MR acquisition sequences (fast Spoiled Gradient Echo [SPGR] and balanced Steady-State Free Precession [bSSFP] sequences). Previous studies have reported that high-resolution whole-brain mapping of multicomponent T1 and T2 can be achieved with the use of mcDESPOT within 12 (21) to 15 minutes (22). Jurick et al. (21), using MWF derived from mcDESPOT, have shown that veterans with a history of mTBI had lower myelin volume than did controls. A positive association was found between MWF in several regions and speeded attention task performance. The results agree with those of a previous study, in which myelin loss, as compared with the baseline, was depicted in several WM tracts, such as the superior longitudinal fasciculus, corona radiata, internal capsule, and corpus callosum, at the subacute stage in concussed athletes (hockey players), using MWF obtained from MCR with a 32 echo T2 scan (23).

On the other hand, increased myelination has also been shown in contact-sport (football and rugby) players with mTBI in a prospective study that assessed MWF obtained with mcDESPOT (24). In particular, increased myelination was observed in various brain regions, including the corpus callosum, corticospinal tract, temporal lobe, and basal ganglia, at the time of injury, and the remyelination was even more profound at 3 months after the injury.

An estimate of myelin volume, i.e., myelin volume fraction (MVF), can also be obtained with a multidynamic multiecho (MDME) sequence. In the multislice, multisaturation delay, multiecho, fast spin-echo sequence, four automatically calculated saturation delays (inversion times) and two echo times produce T1, T2, and proton density (PD) maps. Subsequently, a 4-compartment model comprising myelin,

excess parenchymal water, cellular water, and free-water volume fractions is adopted to estimate MVF in each voxel (25). According to the model, the effective T1, T2, and PD values of a given voxel as a whole are thought to be attributable to the T1, T2, and PD value of each volume fraction. The intrascanner repeatability and interscanner reproducibility of MVF derived using various MDME sequences are reported to be high across different scanners (26). Furthermore, previous studies have shown good correlations between MVF obtained with an MDME sequence and histological measures (27) or other myelin estimation methods (28).

In our unpublished study, we obtained MVF in 41 consecutive mTBI patients with PCS and in 29 controls, using an MDME sequence acquired within 6 min and 27 sec. We post-processed the MDME data within a minute, using SyMRI software (version 8.0.4; SyntheticMRAB). We did automatic whole-brain segmentation based on 3D T1-weighted images with FreeSurfer software (version 6.0; Laboratory for Computational Neuroimaging), and calculated MVF at the bilateral cerebral GM/WM, corpus callosum, and brainstem afterward. Our study demonstrated that the mean MVF at the bilateral cerebral WM was lower in PCS patients than in controls (25.2% vs. 26.8%; P = 0.004). No significant difference in the mean MVF was noted at other regions, including the bilateral cerebral GM, corpus callosum, and brainstem, between the two groups. Of note, MVF was not correlated with any of the neuropsychological tests, but we found a significant positive correlation between the total myelin volume at the bilateral cerebral WM and a verbal learning test (delayed recall) (P = 0.425; P = 0.048).

Furthermore, it has also been reported that a pulse sequence called 'quantification of relaxation times and proton density by multiecho acquisition of a saturation recovery using turbo spin-echo readout (QRAPMASTER)' enables quantification of R1, R2, and PD along with the amplitude of the local radiofrequency B1 field in a single acquisition within 5 minutes (29, 30). Although no studies have yet discovered its potential use in delineating myelin alteration in mTBI, the sequence has been shown to be useful in detecting the myelin loss in multiple sclerosis (31) and hyperglycemia-induced hemichorea (32).

Clinical Implications

In routine practice, the clinical diagnosis of mTBI with PCS is hindered by a considerable overlap in the symptoms and neuropsychological test results between PCS and other psychiatric disorders. These MCR-based fast MR techniques for imaging myelin provide a quantitative and objective measure with a greater specificity to the underlying pathology than do WM T2 hyperintensities, which encompass a wide range of pathological processes, including inflammation, gliosis, edema, and demyelination. Also, the quantitative myelin volume measure could facilitate early diagnosis by allowing the detection of subtle microstructural changes prior to overt changes visible on conventional structural imaging and could enable grading of the disease severity. More importantly, unlike signal intensities, MWF/MVF are absolute values, and thus are more advantageous for therapeutic response monitoring in general, because they are less susceptible to the variations in MR scanners and acquisition parameters. Nonetheless, in routine practice, MWF/MVF alone is not sufficient in the imaging work-up of mTBI with PCS. We will probably still need additional information from susceptibility-weighted imaging with superiority in delineating hemorrhage (33), multi-planar imaging, and multiple contrast-weighted images (T1-weighted, T2-weighted, proton-weighted, and T2 fluid-attenuated inversion recovery images) readily synthesized from quantitative relaxometric parameters in order to delineate overt structural changes and hemorrhages.

In conclusion, PCS following mild TBI is a major factor contributing to the increased socioeconomic burden caused by TBI. DTI, a traditional imaging modality for the evaluation of axonal and myelin integrity in mTBI, has intrinsic limitations, including its lack of specificity and its time-consuming and labor-intensive post-processing analysis. Meanwhile, various MCR-based fast MR techniques, including QRAPMASTER, mcDESPOT, and MDME sequences, followed by rapid post-processing using dedicated software (SyMRI software), can provide a quantitative parameter, MWF/MVF, which is more specific to myelin and may serve as a surrogate marker of myelin volume, in a clinically feasible time. This quantitative and objective measure can facilitate not only early diagnosis but also grading of the disease severity in various central nervous system (CNS) diseases with myelin pathology, including but not limited to mTBI with PCS. Moreover, myelin imaging is likely to have value in longitudinal evaluation, in particular therapeutic response monitoring, in those diseases, given that MWF/MVF, unlike conventional T2 signal intensity, is an absolute measure and thus is less susceptible to scanner and imaging

parameter variations.

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