European Journal of Radiology 85 (2016) 25–30

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Diffusion MRI: Pitfalls, literature review and future directions of research in mild traumatic brain injury

Aurélie Delouche[a], Arnaud Attyé[a,b,c,*], Olivier Heck[a,b,c], Sylvie Grand[a,b,c], Adrian Kastler[a,b,c], Laurent Lamalle[b,c], Felix Renard[a,c], Alexandre Krainik[a,b,c]

[a] Department of Neuroradiology and MRI, Grenoble University Hospital—SFR RMN Neurosciences, Grenoble, France
[b] Univ. Grenoble Alpes, IRMaGe, F-38000 Grenoble, France
[c] UMS IRMaGe, Grenoble, France

ARTICLE INFO

Article history:
Received 15 July 2015
Received in revised form 6 October 2015
Accepted 1 November 2015

Keywords:
Brain injury
Diffusion tractography
Post-concussion syndrome
Magnetic resonance imaging

ABSTRACT

Mild traumatic brain injury (mTBI) is a leading cause of disability in adults, many of whom report a distressing combination of physical, emotional and cognitive symptoms, collectively known as post-concussion syndrome, that persist after the injury. Significant developments in magnetic resonance diffusion imaging, involving voxel-based quantitative analysis through the measurement of fractional anisotropy or mean diffusivity, have enhanced our knowledge on the different stages of mTBI pathophysiology. Other diffusion imaging-derived techniques, including diffusion kurtosis imaging with multi-shell diffusion and high-order tractography models, have recently demonstrated their usefulness in mTBI. Our review starts by briefly outlining the physical basis of diffusion tensor imaging including the pitfalls for use in brain trauma, before discussing findings from diagnostic trials testing its usefulness in assessing brain structural changes in patients with mTBI. Use of different post-processing techniques for the diffusion imaging data, identified the corpus callosum as the most frequently injured structure in mTBI, particularly at sub-acute and chronic stages, and a crucial location for evaluating functional outcome. However, structural changes appear too subtle for identification using traditional diffusion biomarkers, thus disallowing expansion of these techniques into clinical practice. In this regard, more advanced diffusion techniques are promising in the assessment of this complex disease.

1. Introduction

Traumatic brain injury (TBI) is a major cause of disability and death in adults aged between 15 and 45 years and thus represents a significant public health burden with high socio-economic impact. Patients are classified using the Glasgow coma scale (GCS) as being mildly (GCS 13–15), moderately (GCS 9–12) or severely injured (GCS < 8). Seventy to ninety percent of all treated brain injuries are mild (mTBI), corresponding to an estimated incidence of 100-300/100,000 according to the WHO Task Force [1]. Nevertheless, after the mTBI, a significant proportion of patients report suffering a distressing combination of physical, emotional and cognitive symptoms, collectively known as post-concussion disorder [2], that persist well after the injury event and thus hinder their return to work or cause resumption of social activities. Depression [3] and vestibular complaints [4] are also frequently reported.

Computed tomography offers only a limited view of the subtle intracranial abnormalities that occur in acute brain injury. Magnetic resonance imaging (MRI) on the other hand has become a major tool for use in diagnosing neurological impairment. Indeed, recent morphological MRI sequences such as susceptibility-weighted imaging (SWI) [5] or contrast-enhanced fluid-attenuated inversion recovery (FLAIR) [6], have considerably improved the assessment of macroscopic lesions. However, diffusion-weighted imaging (DWI) is the only tool capable of mapping the complex fiber architecture of tissues at a submillimetric level [7,8]. This tool was mainly used to diagnose ischemic brain tissue at early stages after TBI [9]. Today, the development of diffusion tensor imaging (DTI) techniques now enables brain voxel-based quantitative analysis through the measurement of fractional anisotropy (FA) or mean diffusivity (MD) [10]. Diffusion imaging and consecutive fiber

Abbreviations: GCS, Glasgow coma scale; mTBI, mild traumatic brain injury; SWI, susceptibility-weighted imaging; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; DKI, diffusion kurtosis imaging; RD, radial diffusivity; WM, white matter; CC, corpus callosum; CST, corticospinal tracts.

* Corresponding author at: Neuroradiology and MR Unit, CS 10217-Grenoble University Hospital, F-38043 Grenoble Cedex 9, France. Fax: +33 4 76 76 52 86.
E-mail address: aattye@chu-grenoble.fr (A. Attyé).

http://dx.doi.org/10.1016/j.ejrad.2015.11.004
0720-048X/

tractography in post-processing have also been used inside the brain to highlight white matter (WM) bundles, providing new insight into post-traumatic structural connectivity [11]. The main advantage of tractography, from a clinical research perspective, is the possibility to evaluate the whole fiber bundle, as opposed to just one of its segments. Many methods have been proposed for tractography, and the results vary depending on the chosen method. Recently, other techniques derived from diffusion imaging, including diffusion kurtosis imaging (DKI), multi-shell diffusion [12,13] and high-order tractography models with super-resolution properties were assessed in terms of their capacity to better detect diagnostic and prognostic biomarkers [14,15].

In this review, we will briefly outline the physical basis of these techniques including their pitfalls for use in brain trauma, before discussing findings from their use in diagnostic trials assessing brain structural changes in patients with mTBI. To conclude, we will discuss the future direction of research with advanced diffusion acquisition.

2. Search criteria

A structured search using PubMed was performed on the 15th of March 2015, and included all relevant articles published in and after 2005. The search used the following key word combinations: "DTI" AND "mild traumatic brain injury" ($n = 319$); "Tractography" AND "mild traumatic brain injury" ($n = 104$); "Kurtosis diffusion imaging" AND "mild traumatic brain injury" ($n = 9$). The search resulted in 330 individual articles from which additional relevant articles were identified upon examination of the cited references. After having eliminated 274 articles on the basis of our exclusion criteria; 56 articles were assessed and included in the review. Exclusion criteria were as follows: language other than English ($n = 6$); animal or in vitro studies ($n = 45$); studies of diseases other than mTBI ($n = 68$); case reports ($n = 55$); and no use of diffusion-weighted imaging ($n = 16$). Studies that regrouped moderate or severe TBI categories together with the mTBI for analysis were excluded ($n = 86$). Studies concerning MR technical development ($n = 12$) were included regardless of their publication date.

3. Diffusion MR techniques

3.1. DTI physical basis

In WM fibers, the diffusion parallel to the direction of the axons is assumed to be unrestricted while that occurring perpendicularly to this is constrained by membranes. This anisotropic behavior is described by the diffusion tensor model [16] that is based on a Gaussian distribution of the water molecule motion in tissue. DTI is now a well-documented technique for assessing WM integrity, either on a regional or a whole-brain level, via the measurement of FA, a scalar value that describes the anisotropy of water diffusion. The FA is estimated within the brain for subsequent analysis, yet the degree of anisotropy is influenced in the brain by many factors such as axon diameter, inter-axon spacing, membrane permeability, myelination and the coherence of axon orientations [17]. Thus, FA is highly sensitive to microstructural changes, with no tissue compartment specificity. The inter-group comparison of FA may be achieved using the traditional voxel-based method. The MD measures the average distance a water molecule traverses within a given observation time and also displays sensitivity in both extra-cellular (edema) and intra-cellular (cellularity, necrosis) compartments. Axial diffusivity (AD) and radial diffusivity (RD) correspond to the diffusivity in the principal and perpendicular direction respectively and may more specifically describe the direction and magnitude of tissue water diffusion. Yet, similar to FA, these coefficients may be influenced by axonal diameters or density [10]. Another voxel-wise comparison, known as tract-based spatial statistics and that is specific to DTI, aims to solve the inaccuracy issues encountered in aligning FA images from numerous patients, through the crafting of a mean FA skeleton [18]. This method involves the non-linear registration of multiple images followed by projection onto an alignment-invariant tract representation i.e the mean FA skeleton. Anatomical alignment in diffusion studies is a crucial point that affects the quality of the dataset upon which tract-based spatial statistics rely in a graded and predictable manner. It allows the transformation of tract data that are consistent into a common space [19].

Brain WM bundles of neuronal axons are coherently oriented along the lengths of the fibers, resulting in an orientation dependence of the measured diffusion-weighted MR signal. In large WM tracts, the properties of diffusion can be well described by the diffusion tensor model [16] prior to tractography post-processing.

3.2. Pitfalls of their use in traumatic brain injury

The most common primary lesion in TBI is diffuse axonal injury, perhaps due to the selective vulnerability of WM axons during rapid head accelerations and decelerations [20], and was recently shown by SWI to occur frequently in patients with mTBI [5].

Such focal hemorrhagic injuries lead to wide heterogeneity in the spatial distribution of damage, and to difficulties analyzing the average value of FA within a large region of WM. If the effects of the mTBI are local, then the detection power will be limited by averaging values with those of unaffected tissue. "Pothole" analysis was developed to overcome this limitation, and involves comparing clusters of voxels with reduced FA values against corresponding voxels in a control group. Use of FA measurement as a biomarker should however be with caution since it may introduce bias due to the lack of independent data and cross-validation methods [21]. The effect of age on diffusion measures has been demonstrated for both FA and MD [22]. In addition, sex was shown to be a strong predictor of persistent post-concussion symptoms in patients with mTBI when using FA values [23]. Indeed, relative sparing of the uncinate fasciculus was found in women compared with men following mTBI in this study.

Tractographic approaches may be useful to evaluate clinically relevant white matter fascicles, such as corpus callosum (CC) or uncinate fasciculus, in post-traumatic conditions. Yet, there is marked variability in tract volume among healthy subjects, and injuries can lead to a reduced connectivity thereby changing the analysis volume [24]. Thus, DTI, based on tractography, can potentially yield misleading information regarding the actual pathways of WM in the brain and should therefore be used with caution [25]. Despite this drawback, DTI tractography models have been proposed as gold standard for clinical trials, either for their robustness or scan time feasibility. To overcome the above issue, high angular resolution diffusion-weighted imaging [26] has been suggested as a method more suitable for acquiring data close to anatomical reality.

4. Advances in knowledge

4.1. Altered areas

Pathophysiological modifications after mTBI are time-dependent, and thus render chronology a crucial factor in the interpretation of diffusion imaging findings [11].

When focusing on acute stages, results from voxel-based diffusion analyses appear conflicting: mTBI was recently found not to be associated with white matter changes in a rigorous and large

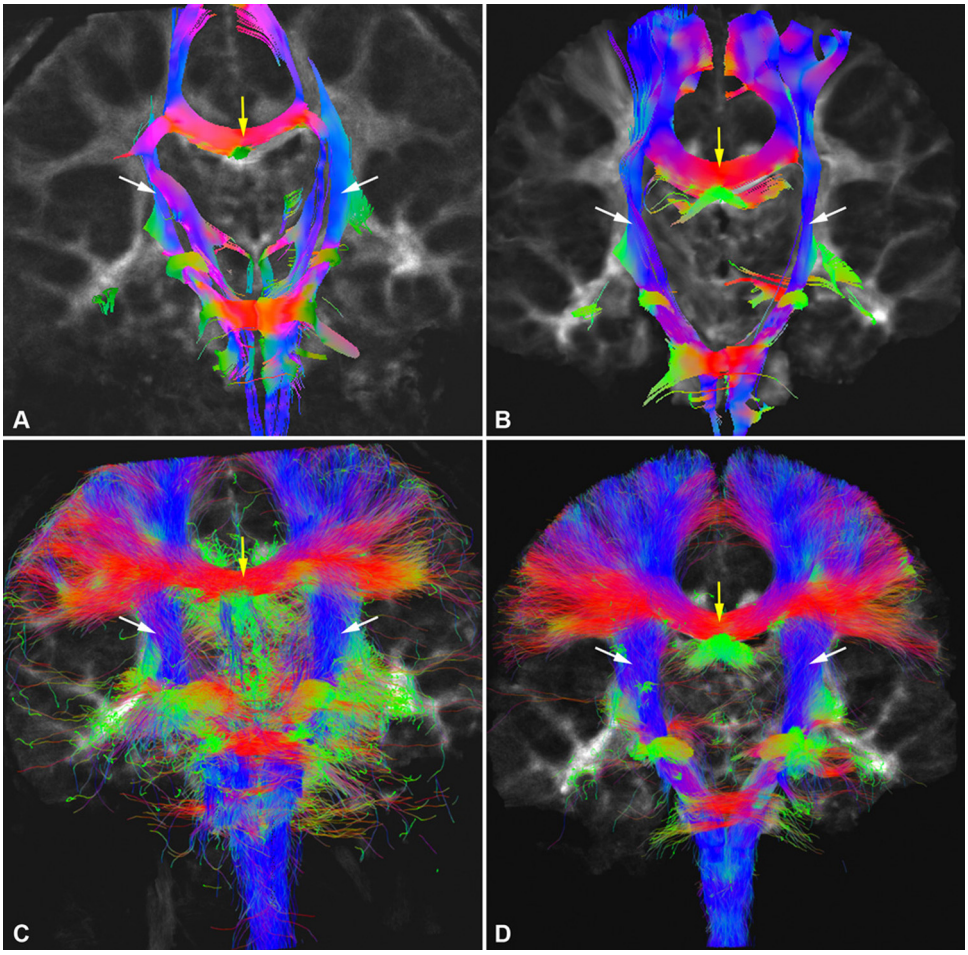

Fig. 1. Example of a patient diagnosed with secondary post-concussion syndrome after mTBI (A and C) in comparison with a healthy subject (B and D). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Reconstructions of the corpus callosum and corticospinal tracts were performed with DTI-based tractography using a deterministic algorithm (A and B) and with CSD-based tractography combined with a probabilistic algorithm (C and D) using diffusion acquisition with 60 directions and post-processing with MRtrix package software [14] (J-D Tournier, Brain Research Institute, Melbourne, Australia http://www.brain.org.au/software/).
In the healthy subject, the DTI-based method produced only a narrow set of tracks starting from the sensorimotor cortex and ending in the brainstem for CST pathways (white arrows), while CSD-based tractography successfully reconstructed fascicles closely resembling known anatomy [25]. The same findings were obtained with corpus callosum tracts (yellow arrow). In the mTBI patient, disorganization of CST and CC tracts was better highlighted with the high-order tractography method.

controlled study [22] while previous studies showed significant differences in the mean FA for the CC and internal and external capsules [27,28].

At semi-acute or chronic stages following mTBI, FA was shown to be altered in several brain areas including CC [29–32], centrum semiovale or internal capsule [29,31,33]. One meta-analysis revealed the posterior part of the CC to be more vulnerable to mTBI than the anterior part, and suggested the potential utility of DTI to detect WM damage in the CC of patients with mTBI [34]. Concerning the parameter MD, while some studies reported it to be normal in comparison with healthy subjects [26], others described it as increased in the splenium of the CC [28,29]. In addition to these commonly used parameters, an increased radial diffusivity has been demonstrated in the genu and splenium of the CC in mTBI compared with controls [35].

Besides diffusion biomarker quantitative measurements, use of tractography based on DTI models led to similar results when assessing whole WM bundles. The most common locations of abnormal FA are midline structures, including the CC [36,37], the cingulum bundle [36,38] and the fornix [37]. Developments in tractography should allow investigation of a more detailed anatomy and hence permit greater accuracy and precision in tracing the WM pathways and an improved detection of focal lesions. The consequential increase in use of tractography in clinical studies will encourage the testing of new hypotheses to obtain important new insight into the functional organization of the normal and damaged or diseased brain.

4.2. Functional outcomes after mTBI

At an early stage, an increase in FA and a decrease in MD may indicate an injury-induced cytotoxic edema with potentially poor clinical outcome [33]. One longitudinal study [39] highlighted that measurements of diffusion (FA and radial diffusivity) within the CC genu could be used to classify patients. Furthermore, in their holistic approach, Yuh et al. showed that a diminished FA was more predictive of poor clinical outcome than neuropsychiatric history, age or years of education [40].

Interestingly, a decrease in FA values has also been found in gray matter areas [41]. Locations of interest included superior frontal cortex in patients with cognitive and emotional complaints in the semi-acute phase following mTBI. The authors concluded that such FA alterations without MD abnormalities suggested the presence of cytotoxic edema in these areas, arising from mechanical forces. Patients with persistent post-concussive symptoms were also found to display increased gray matter diffusion anisotropy

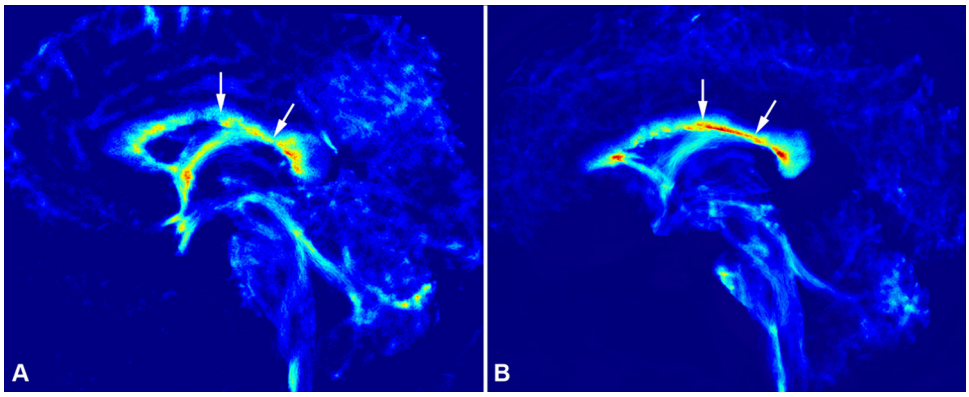

Fig. 2. Track-density imaging of a patient referred for mTBI despite normal morphological MR sequences (A), in comparison with a healthy subject (B).
In track-density imaging, the intensity of the image is proportional to the number of streamlines traversing each voxel. Ten million tracks were generated with the same software on the whole brain volume using a probabilistic algorithm after MRI diffusion acquisition with 60 directions, before TDI maps were then displayed with super-resolution on a grid-size of 0.3 mm [50]. This novel contrast image taken in a sagittal plane clearly shows less streamline per voxel in this patient's corpus callosum (white arrows) by comparison with the healthy subject.

when compared to the normative atlas [42]. Post-traumatic gliosis could explain such findings, as explained by Bouix et al.

Secondary apparition of vasogenic edema can be revealed by a decrease in FA and was found to positively correlate with secondary post-concussive syndrome [29,43], especially when concerning the corona radiata, uncinate fasciculus or CC. A reduced FA, especially that found in the CC [44], was also found to be correlated with major depression and with executive function impairment in the frontal white matter [45].

The implications of diffusion biomarker modifications on patient outcome need further investigation. A longitudinal study would enable the monitoring over time of the damage to the brain following mTBI, in order to determine the significance of increased versus decreased FA and MD values observed following injury.

5. Future research directions

5.1. High-order tractography

Beyond the DTI-tractography model, two principal methods exist to describe the orientation dependence of the diffusion-weighted MR signal: the diffusion orientation distribution function (ODF) and the estimation of fiber ODF. The former essentially describes the diffusion within a voxel, as for instance in the composite hindered and restricted model of diffusion (CHARMED) [13]. This model consists of two parts: one accounting for hindered diffusion in the extracellular space and the other for restricted diffusion in the intra-axonal space. A multi-compartmental model of diffusion may help better characterize neuronal injury following mTBI yet may also lead to less accurate tractography reconstructions in comparison with the fODF approach [46]. Several fODF models have been suggested over the past few years, the most promising being the constrained spherical deconvolution (CSD) method [14,25] in the assessment of injured WM fascicles (Fig. 1). CSD allows the estimation of fiber orientation distribution, directly from diffusion-weighted MR data, without the need for prior assumptions regarding the number of fiber populations, and has been used to resolve crossing fibers on imaging phantom data [47]. It has also produced representations close to anatomical findings [48] of the corticospinal and arcuate fasciculus tracts, and those of the cranial nerve correlating with surgical in vivo findings [49]. An interesting method derived from CSD is super-resolution track-density imaging [50], which theoretically provides quantitative tractography-based metrics of WM, such as average path-length maps that were recently used in a patient with a post-traumatic condition to assess streamline length in the genu of the CC [51] (Fig. 2).

5.2. Diffusion kurtosis imaging

DKI [12] is another technique that may in future clinical trials prove useful in mTBI diagnostic imaging. DTI measures water diffusion parameters based on the assumption that the spin displacement distribution is a Gaussian function. However, water movement in brain tissue is often non-Gaussian and yet its accurate measurement would provide useful information relating to tissue structure and pathophysiology. One sensitive technique allowing for the more accurate estimation of diffusion tensor parameters [52] is DKI, which uses multi-shell diffusion imaging measurements based on the non-Gaussian behavior of water diffusion. Multi-shell imaging has been proposed as an alternative to the compartmental model that describes the diffusion signal as resulting from both a fast and a slow compartment of water diffusion [53]. This model makes no presumption of compartmentalization and has been shown to fit the diffusion-weighted signal well, using multi b-value acquisition. The acquisition time is directly proportional to the number of gradient direction acquisitions. The original DKI protocol (6 b-values and 30 motion-probing gradient directions) required more than 10 min of scanning time however a shorter protocol was recently proposed for clinical use [54] with only 3 b-values. DKI has also proven to be more sensitive than other diffusion methods in the characterization of gray matter injuries [55], a potentially crucial advantage in a context of TBI. Initially, the mean kurtosis was assessed as a quantitative measure, and was favored for its apparent increased specificity for changes in the integrity of tissue by comparison with FA, despite being seemingly limited for studying single direction [56]. DKI was then suggested [57] to overcome the direction-related issues and was found to be sensitive to structure size when assessing focal areas of the brain, with inter-subject differences contributing more than imaging noise to the overall variability [53]. A correlation between mean kurtosis, radial kurtosis and healthy brain age was found in gray matter and WM areas [58].

From a post-traumatic point of view, while Szczepankiewicz et al. [59] demonstrated a strong correlation between DKI parameters and structure size for the cingulum and CC, Zhuo et al. [60] highlighted structural changes contralateral to the side affected by a mild controlled cortical impact in an animal model. Interestingly, these abnormalities were not observed on either FA or MD maps. The authors also demonstrated that mean kurtosis (MK)

was significantly elevated at the sub-acute stages in all ipsilateral regions, scaled inversely with the distance from the impacted site, and was significantly related to increased reactive astrogliosis from immunohistochemistry analysis. In a recent longitudinal multimodal MRI study, Grossman et al. associated DTI, DKI and arterial spin labeling perfusion to assess the role of the thalamus among patients with cognitive impairment after mTBI [61].

Finally, DKI was found to be a sensitive method for tracking pathophysiological changes following mTBI, especially in anterior and posterior capsula areas [62] where a correlation was displayed between cognitive improvement and the MK and the radial kurtosis evolution between follow up visits at 1 month and 6 months following mTBI.

To conclude, combining diffusion acquisition with MR biomarkers may lead to the discovery of more specific biomarkers to assess prognosis in mTBI. However, lack of homogeneity among inclusion criteria and acquisition parameters has to date produced conflicting results. Advanced diffusion techniques with robust statistics may provide more reliable radiological evidence of mTBI, and may further elucidate its underlying neurophysiologial mechanisms.

Conflict of interest

None.

References

[1] L. Holm, J.D. Cassidy, L.J. Carroll, J. Borg, Neurotrauma Task Force on Mild Traumatic Brain Injury of the WHO Collaborating Centre, Summary of the WHO Collaborating Centre for neurotrauma task force on mild traumatic brain injury, J. Rehabil. Med. 37 (2005) 137–141, http://dx.doi.org/10.1080/16501970510027321.

[2] H.G. Belanger, G. Curtiss, J.A. Demery, B.K. Lebowitz, R.D. Vanderploeg, Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis, J. Int. Neuropsychol. Soc. 11 (2005) 215–227, http://dx.doi.org/10.1017/s1355617705050277.

[3] V. Rao, M. Bertrand, P. Rosenberg, M. Makley, D.J. Schretlen, J. Brandt, et al., Predictors of new-onset depression after mild traumatic brain injury, J. Neuropsychiatry Clin. Neurosci. 22 (2010) 100–104, http://dx.doi.org/10.1176/appi.neuropsych.22.1.100.

[4] K. Gottshall, Vestibular rehabilitation after mild traumatic brain injury with vestibular pathology, NeuroRehabilitation 29 (2011) 167–171, http://dx.doi.org/10.3233/NRE-2011-0691.

[5] X. Wang, X.-E. Wei, M.-H. Li, W.-B. Li, Y.-J. Zhou, B. Zhang, et al., Microbleeds on susceptibility-weighted MRI in depressive and non-depressive patients after mild traumatic brain injury, Neurol. Sci. 35 (2014) 1533–1539, http://dx.doi.org/10.1007/s10072-014-1788-3.

[6] S.C. Kim, S.-W. Park, I. Ryoo, S.C. Jung, T.J. Yun, S.H. Choi, et al., Contrast-enhanced FLAIR (fluid-attenuated inversion recovery) for evaluating mild traumatic brain injury, PLoS One 9 (2014), http://dx.doi.org/10.1371/journal.pone.0102229, e102229.

[7] D. Le Bihan, E. Breton, D. Lallemand, P. Grenier, E. Cabanis, M. Laval-Jeantet, MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders, Radiology 161 (1986) 401–407, http://dx.doi.org/10.1148/radiology.161.2.3763909.

[8] C. Pierpaoli, P.J. Basser, Toward a quantitative assessment of diffusion anisotropy, Magn. Reson. Med. 36 (1996) 893–906.

[9] C.C. Hanstock, A.I. Faden, M.R. Bendall, R. Vink, Diffusion-weighted imaging differentiates ischemic tissue from traumatized tissue, Stroke 25 (1994) 843–848.

[10] P.J. Basser, Inferring microstructural features and the physiological state of tissues from diffusion-weighted images, NMR Biomed. 8 (1995) 333–344.

[11] M.B. Hulkower, D.B. Poliak, S.B. Rosenbaum, M.E. Zimmerman, M.L. Lipton, A decade of DTI in traumatic brain injury: 10 years and 100 articles later, AJNR Am. J. Neuroradiol. 34 (2013) 2064–2074, http://dx.doi.org/10.3174/ajnr.a3395.

[12] J.H. Jensen, J.A. Helpern, A. Ramani, H. Lu, K. Kaczynski, Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging, Magn. Reson. Med. 53 (2005) 1432–1440, http://dx.doi.org/10.1002/mrm.20508.

[13] Y. Assaf, P.J. Basser, Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain, Neuroimage 27 (2005) 48–58, http://dx.doi.org/10.1016/j.neuroimage.2005.03.042.

[14] J.-D. Tournier, F. Calamante, A. Connelly, Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution, Neuroimage 35 (2007) 1459–1472, http://dx.doi.org/10.1016/j.neuroimage.2007.02.016.

[15] F. Calamante, S.-H. Oh, J.-D. Tournier, S.-Y. Park, Y.-D. Son, J.-Y. Chung, et al., Super-resolution track-density imaging of thalamic substructures: comparison with high-resolution anatomical magnetic resonance imaging at 7.0T, Hum. Brain Mapp. 34 (2013) 2538–2548, http://dx.doi.org/10.1002/hbm.22083.

[16] P.J. Basser, J. Mattiello, D. LeBihan, MR diffusion tensor spectroscopy and imaging, Biophys. J. 66 (1994) 259–267, http://dx.doi.org/10.1016/s0006-3495(94)80775-1.

[17] C. Beaulieu, A. De Crespigny, D.C. Tong, M.E. Moseley, G.W. Albers, M.P. Marks, Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: evolution of lesion volume and correlation with clinical outcome, Ann. Neurol. 46 (1999) 568–578, http://dx.doi.org/10.1002/1531-8249(199910)46:4<568::AID-ANA4>3.0.CO;2-R.

[18] S.M. Smith, M. Jenkinson, H. Johansen-Berg, D. Rueckert, T.E. Nichols, C.E. Mackay, et al., Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data, Neuroimage 31 (2006) 1487–1505, http://dx.doi.org/10.1016/j.neuroimage.2006.02.024.

[19] M. de Groot, M.W. Vernooij, S. Klein, M.A. Ikram, F.M. Vos, S.M. Smith, et al., Improving alignment in tract-based spatial statistics: evaluation and optimization of image registration, Neuroimage 76 (2013) 400–411, http://dx.doi.org/10.1016/j.neuroimage.2013.03.015.

[20] J.H. Adams, D. Doyle, I. Ford, T.A. Gennarelli, D.I. Graham, D.R. McLellan, Diffuse axonal injury in head injury: definition, diagnosis and grading, Histopathology 15 (1989) 49–59.

[21] R. Watts, A. Thomas, C.G. Filippi, J.P. Nickerson, K. Freeman, Potholes and molehills: bias in the diagnostic performance of diffusion-tensor imaging in concussion, Radiology 272 (2014) 217–223, http://dx.doi.org/10.1148/radiol.14131856.

[22] T. Ilvesmäki, T.M. Luoto, U. Hakulinen, A. Brander, P. Ryymin, H. Eskola, et al., Acute mild traumatic brain injury is not associated with white matter change on diffusion tensor imaging, Brain 137 (2014) 1876–1882, http://dx.doi.org/10.1093/brain/awu095.

[23] S. Fakhran, K. Yaeger, M. Collins, L. Alhilali, Sex differences in white matter abnormalities after mild traumatic brain injury: localization and correlation with outcome, Radiology 272 (2014) 815–823, http://dx.doi.org/10.1148/radiol.14132512.

[24] T. Kurki, L. Himanen, E. Vuorinen, A. Myllyniemi, A.-R. Saarenketo, T. Kauko, et al., Diffusion tensor tractography-based analysis of the cingulum: clinical utility and findings in traumatic brain injury with chronic sequels, Neuroradiology 56 (2014) 833–841, http://dx.doi.org/10.1007/s00234-014-1410-7.

[25] S. Farquharson, J.-D. Tournier, F. Calamante, G. Fabinyi, M. Schneider-Kolsky, G.D. Jackson, et al., White matter fiber tractography: why we need to move beyond DTI, J. Neurosurg. 118 (2013) 1367–1377, http://dx.doi.org/10.3171/2013.2.jns121294.

[26] D.S. Tuch, T.G. Reese, M.R. Wiegell, N. Makris, J.W. Belliveau, V.J. Wedeen, High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity, Magn. Reson. Med. 48 (2002) 577–582, http://dx.doi.org/10.1002/mrm.10268.

[27] K. Arfanakis, V.M. Haughton, J.D. Carew, B.P. Rogers, R.J. Dempsey, M.E. Meyerand, Diffusion tensor MR imaging in diffuse axonal injury, AJNR Am. J. Neuroradiol. 23 (2002) 794–802.

[28] M. Inglese, S. Makani, G. Johnson, B.A. Cohen, J.A. Silver, O. Gonen, et al., Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study, J. Neurosurg. 103 (2005) 298–303, http://dx.doi.org/10.3171/jns.2005.103.2.0298.

[29] L. Miles, R.I. Grossman, G. Johnson, J.S. Babb, L. Diller, M. Inglese, Short-term DTI predictors of cognitive dysfunction in mild traumatic brain injury, Brain Inj. 22 (2008) 115–122, http://dx.doi.org/10.1080/02699050801888816.

[30] J.J. Bazarian, K. Donnelly, D.R. Peterson, G.C. Warner, T. Zhu, J. Zhong, The relation between posttraumatic stress disorder and mild traumatic brain injury acquired during Operations Enduring Freedom and Iraqi Freedom, J. Head Trauma Rehabil. 28 (2013) 1–12, http://dx.doi.org/10.1097/htr.0b013e318256d3d3.

[31] A.R. Mayer, J. Ling, M.V. Mannell, C. Gasparovic, J.P. Phillips, D. Doezema, et al., A prospective diffusion tensor imaging study in mild traumatic brain injury, Neurology 74 (2010) 643–650, http://dx.doi.org/10.1212/wnl.0b013e3181d0ccdd.

[32] L.C. Henry, J. Tremblay, S. Tremblay, A. Lee, C. Brun, N. Lepore, et al., Acute and chronic changes in diffusivity measures after sports concussion, J. Neurotrauma 28 (2011) 2049–2059, http://dx.doi.org/10.1089/neu.2011.1836.

[33] J.J. Bazarian, J. Zhong, B. Blyth, T. Zhu, V. Kavcic, D. Peterson, Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study, J. Neurotrauma 24 (2007) 1447–1459, http://dx.doi.org/10.1089/neu.2007.0241.

[34] Y. Aoki, R. Inokuchi, M. Gunshin, N. Yahagi, H. Suwa, Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis, J. Neurol. Neurosurg. Psychiatry 83 (2012) 870–876, http://dx.doi.org/10.1136/jnnp-2012-302742.

[35] R. Kumar, R.K. Gupta, M. Husain, C. Chaudhry, A. Srivastava, S. Saksena, et al., Comparative evaluation of corpus callosum DTI metrics in acute mild and moderate traumatic brain injury: its correlation with neuropsychometric tests, Brain Inj. 23 (2009) 675–685, http://dx.doi.org/10.1080/02699050903014915.

[36] D.R. Rutgers, P. Fillard, G. Paradot, M. Tadié, P. Lasjaunias, D. Ducreux, Diffusion tensor imaging characteristics of the corpus callosum in mild,

moderate, and severe traumatic brain injury, AJNR Am. J. Neuroradiol. 29 (2008) 1730–1735, http://dx.doi.org/10.3174/ajnr.a1213.
[37] N. Nakayama, A. Okumura, J. Shinoda, Y.-T. Yasokawa, K. Miwa, S.-I. Yoshimura, et al., Evidence for white matter disruption in traumatic brain injury without macroscopic lesions, J. Neurol. Neurosurg. Psychiatry 77 (2006) 850–855, http://dx.doi.org/10.1136/jnnp.2005.077875.
[38] H.S. Levin, E.A. Wilde, Z. Chu, R. Yallampalli, G.R. Hanten, X. Li, et al., Diffusion tensor imaging in relation to cognitive and functional outcome of traumatic brain injury in children, J. Head Trauma Rehabil. 23 (2008) 197–208, http://dx.doi.org/10.1097/01 HTR.0000327252.54128.7c.
[39] J.M. Ling, A. Peña, R.A. Yeo, F.L. Merideth, S. Klimaj, C. Gasparovic, et al., Biomarkers of increased diffusion anisotropy in semi-acute mild traumatic brain injury: a longitudinal perspective, Brain 135 (2012) 1281–1292, http://dx.doi.org/10.1093/brain/aws073.
[40] E.L. Yuh, S.R. Cooper, P. Mukherjee, J.K. Yue, H.F. Lingsma, W.A. Gordon, et al., Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study, J. Neurotrauma 31 (2014) 1457–1477, http://dx.doi.org/10.1089/neu.2013.3171.
[41] J.M. Ling, S. Klimaj, T. Toulouse, A.R. Mayer, A prospective study of gray matter abnormalities in mild traumatic brain injury, Neurology 81 (2013) 2121–2127, http://dx.doi.org/10.1212/01.wnl.0000437302.36064.b1.
[42] S. Bouix, O. Pasternak, Y. Rathi, P.E. Pelavin, R. Zafonte, M.E. Shenton, Increased gray matter diffusion anisotropy in patients with persistent post-concussive symptoms following mild traumatic brain injury, PLoS One 8 (2013) e66205, http://dx.doi.org/10.1371/journal.pone.0066205.
[43] S.N. Niogi, P. Mukherjee, J. Ghajar, C. Johnson, R.A. Kolster, R. Sarkar, et al., Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury, AJNR Am. J. Neuroradiol. 29 (2008) 967–973, http://dx.doi.org/10.3174/ajnr.a0970.
[44] S.C. Matthews, I.A. Strigo, A.N. Simmons, R.M. O'Connell, L.E. Reinhardt, S.A. Moseley, A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion, Neuroimage 54 (Suppl. 1) (2011) S69–S75, http://dx.doi.org/10.1016/j.neuroimage.2010.04.269.
[45] M.L. Lipton, E. Gulko, M.E. Zimmerman, B.W. Friedman, M. Kim, E. Gellella, et al., Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury, Radiology 252 (2009) 816–824, http://dx.doi.org/10.1148/radiol.2523081584.
[46] M. Descoteaux, R. Deriche, T.R. Knösche, A. Anwander, Deterministic and probabilistic tractography based on complex fibre orientation distributions, IEEE Trans. Med. Imaging 28 (2009) 269–286, http://dx.doi.org/10.1109/TMI.2008.
[47] J.-D. Tournier, C.-H. Yeh, F. Calamante, K.-H. Cho, A. Connelly, C.-P. Lin, Resolving crossing fibres using constrained spherical deconvolution: validation using diffusion-weighted imaging phantom data, Neuroimage 42 (2008) 617–625, http://dx.doi.org/10.1016/j.neuroimage.2008.05.002.
[48] G. Kristo, A. Leemans, M. Raemaekers, G.-J. Rutten, B. de Gelder, N.F. Ramsey, Reliability of two clinically relevant fiber pathways reconstructed with constrained spherical deconvolution, Magn. Reson. Med. 70 (2013) 1544–1556, http://dx.doi.org/10.1002/mrm.24602.
[49] A. Attyé, A. Karkas, I. Troprès, M. Roustit, A. Kastler, G. Bettega, et al., Parotid gland tumors MR tractography to assess contact with the facial nerve, Eur. Radiol. (2015), http://dx.doi.org/10.1007/s00330-015-4049-9.
[50] F. Calamante, J.-D. Tournier, D. Nyoman, Z. Kurniawan, E. Yang, E. Gyengesi, G.J. Galloway, et al., Super-resolution track-density imaging studies of mouse brain: comparison to histology, Neuroimage 59 (2012) 286–296, http://dx.doi.org/10.1016/j.neuroimage.2011.07.014.
[51] K. Pannek, J.L. Mathias, E.D. Bigler, G. Brown, J.D. Taylor, S.E. Rose, The average pathlength map: a diffusion MRI tractography-derived index for studying brain pathology, Neuroimage 55 (2011) 133–141, http://dx.doi.org/10.1016/j.neuroimage.2010.12.010.
[52] J. Veraart, D.H.J. Poot, W. Van Hecke, I. Blockx, A. Van der Linden, M. Verhoye, et al., More accurate estimation of diffusion tensor parameters using diffusion kurtosis imaging, Magn. Reson. Med. 65 (2011) 138–145, http://dx.doi.org/10.1002/mrm.22603.
[53] S.E. Maier, R.V. Mulkern, Biexponential analysis of diffusion-related signal decay in normal human cortical and deep gray matter, Magn. Reson. Imaging 26 (2008) 897–904, http://dx.doi.org/10.1016/j.mri.2008.01.042.
[54] I. Fukunaga, M. Hori, Y. Masutani, N. Hamasaki, S. Sato, Y. Suzuki, et al., Effects of diffusional kurtosis imaging parameters on diffusion quantification, Radiol. Phys. Technol. 6 (2013) 343–348, http://dx.doi.org/10.1007/s12194-013-0206-5.
[55] A. Paydar, Diffusional kurtosis imaging: a promising technique for detecting microstructural changes in neural development and regeneration, Neural Regen. Res. 9 (2014) 1108–1109, http://dx.doi.org/10.4103/1673-5374.135309.
[56] E.S. Hui, M.M. Cheung, L. Qi, E.X. Wu, Towards better MR characterization of neural tissues using directional diffusion kurtosis analysis, Neuroimage 42 (2008) 122–134, http://dx.doi.org/10.1016/j.neuroimage.2008.04.237.
[57] E.S. Hui, M.M. Cheung, L. Qi, E.X. Wu, Advanced MR diffusion characterization of neural tissue using directional diffusion kurtosis analysis, Conf. Proc. IEEE Eng. Med. Biol. Soc. 2008 (2008) 3941–3944, http://dx.doi.org/10.1109/IEMBS.2008.4650072.
[58] J. Lätt, M. Nilsson, R. Wirestam, F. Ståhlberg, N. Karlsson, M. Johansson, et al., Regional values of diffusional kurtosis estimates in the healthy brain, J. Magn. Reson. Imaging 37 (2013) 610–618, http://dx.doi.org/10.1002/jmri.23857.
[59] F. Szczepankiewicz, J. Lätt, R. Wirestam, A. Leemans, P. Sundgren, D. van Westen, et al., Variability in diffusion kurtosis imaging: impact on study design, statistical power and interpretation, Neuroimage 76 (2013) 145–154, http://dx.doi.org/10.1016/j.neuroimage.2013.02.078.
[60] J. Zhuo, S. Xu, J.L. Proctor, R.J. Mullins, J.Z. Simon, G. Fiskum, et al., Diffusion kurtosis as an in vivo imaging marker for reactive astrogliosis in traumatic brain injury, Neuroimage 59 (2012) 467–477, http://dx.doi.org/10.1016/j.neuroimage.2011.07.050.
[61] E.J. Grossman, J.H. Jensen, J.S. Babb, Q. Chen, A. Tabesh, E. Fieremans, et al., Cognitive impairment in mild traumatic brain injury: a longitudinal diffusional kurtosis and perfusion imaging study, AJNR Am. J. Neuroradiol. 34 (2013) 951–957, http://dx.doi.org/10.3174/ajnr.a3358, S1-3.
[62] J.A. Stokum, C. Sours, J. Zhuo, R. Kane, K. Shanmuganathan, R.P. Gullapalli, A longitudinal evaluation of diffusion kurtosis imaging in patients with mild traumatic brain injury, Brain Inj. 29 (2015) 47–57, http://dx.doi.org/10.3109/02699052.2014.947628.