Spinal cord pathology in traumatic and non-traumatic spinal cord injury

Gergely David[1,2], Siawoosh Mohammadi[2,3], Allan R. Martin[4], Julien Cohen-Adad[5], Nikolaus Weiskopf[3,6], Alan Thompson[7], Patrick Freund[1,3,6,7,8]

[1]Spinal Cord Injury Center Balgrist, University Hospital Zurich, University of Zurich, Zurich, Switzerland

[2]Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[3]Wellcome Centre for Human Neuroimaging, UCL Institute of Neurology, London, United Kingdom

[4]Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, Canada

[5]NeuroPoly Lab, Institute of Biomedical Engineering, Polytechnique Montreal, Montreal, Canada

[6]Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

[7]Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, London, United Kingdom

[8]Department of Neurology, University Hospital Zurich, University of Zurich, Switzerland

Abstract

Pathophysiological changes in the white and gray matter resulting from spinal cord injury can be revealed by magnetic resonance imaging (MRI) techniques that provides sensitive markers of macro- and microstructural integrity with important histological correlates. This review highlights spinal cord pathology in traumatic spinal cord injury (tSCI) and in non-traumatic spinal cord injury (i.e. degenerative cervical myelopathy (DCM)), detected by means of cross-sectional area measurements and spinal cord diffusion tensor imaging (DTI), and outlines the current trends and future directions. Cord MRI findings in these pathologies have provided important insights into the pathophysiological processes not just at the focal injury site, but also rostral and caudal to the spinal injury. Interestingly, although tSCI and DCM have different etiologies, they show similar magnitudes of remote tissue specific cord pathology, which suggests similar secondary degenerative mechanisms in tSCI and DCM. Advanced quantitative MRI protocols sensitive to tissue specific cord pathology have the potential to enhance current diagnosis and, more importantly, predict outcome in patients with traumatic and non-traumatic spinal cord injury. It is a promising area of research ripe for further study.

Introduction

Traumatic spinal cord injury (tSCI) and degenerative cervical myelopathy (DCM) (i.e. non-traumatic SCI) cause damage to the spinal cord. tSCI arises from a direct and immediate mechanical insult to the spinal cord (e.g. contusion, compression, laceration) caused by disruption and dislocation of the vertebral column. In the majority of patients, it causes permanent motor (weakness or paralysis) and sensory impairments as well as autonomic dysfunction[1]. Unlike tSCI, DCM is a progressive degenerative disease caused by chronic mechanical compression[2]. Although this condition can be asymptomatic for a lengthy period of time, the degenerative changes often lead to a cervical myelopathy which results in progressive motor and sensory impairments[3].

Despite the differences in etiology, the pathophysiological changes which have been observed after experimental tSCI and DCM share many common features[1,3]. Both of them trigger apoptosis, inflammation, and vascular changes resulting in cell death, axonal degeneration, and myelin changes at the focal injury/compression site[1,3] (Fig. 1). With a certain time lag, secondary neurodegenerative changes spread rostrally and caudally, and these include anterograde as well as retrograde degeneration of axons, but also trans-synaptic changes within the gray matter[3,4] (Fig. 1). However, it remains unclear whether similar pathogenic changes occur in-vivo in patients with tSCI and DCM. Such an understanding is fundamental to the development of surrogate endpoints in clinical trials as well as predictors of outcomes.

Conventional magnetic resonance imaging (MRI) such as T1- or T2-weighted imaging provide rich macrostructural information about the cause, level and extent of spinal cord injury, as well as disc and ligamentous injury, and the presence of edema and hemorrhage[1]. As a result, conventional MRI offers fundamental guidance in the diagnostic work-up of traumatic and non-traumatic SCI that guides surgical intervention[5,6]. In addition, axial T2*-weighted images offer the possibility to measure the cross-sectional area and shape of the gray and white matter, providing quantitative metrics of tissue atrophy[7]. Although these conventional MRI techniques can capture morphological changes of the gray and white matter (including atrophy), they are unspecific and cannot reveal the underlying microstructural changes that might indicate neurodegeneration and compensatory processes.

A number of increasingly sophisticated quantitative MRI (qMRI) techniques have been applied to the spinal cord, which hold potential of being both sensitive and specific markers of spinal cord pathology. These qMRI methods are in various stages of development and diffusion tensor imaging (DTI) is the most mature in terms of clinical utility[8]. DTI belongs to the family of diffusion MRI techniques, and as such, it exploits the self-diffusion of water molecules in biological tissues to create unique contrast of tissue microstructure (Supplementary Fig. 1). The basic assumption of DTI in the white matter (WM) is that the diffusion ellipsoid is aligned with the WM tracts[9]. This assumption generally applies in the spinal cord, which consists of mainly parallel aligned tracts. The DTI metrics are closely related to the WM microstructure, as the diffusion is affected by the cytoskeletal proteins, axonal membranes, myelin sheath, and other cellular and sub-cellular structures acting as physical barriers to the diffusive movements of water molecules. The longitudinal organization of these barriers in the WM causes the water molecules to diffuse in a direction predominantly parallel, rather than perpendicular, to axonal fibers[10]. Investigations found that axonal membranes are the largest contributors to the anisotropy, followed by the myelin sheath and cytoskeletal proteins (neurofilaments and microtubules)[11]. The microstructural information provided by DTI is expected to supplement current approaches to patient assessment, and has the potential to be used for monitoring disease progression and evaluating efficacy of therapies[12]. In addition, spinal cord DTI may facilitate early detection and intervention, as these microstructural changes may precede atrophy (e.g. in DCM[13]).

This review will (i) summarize the findings of the studies involving macrostructural as well as microstructural quantitative MRI (spinal cord DTI) in (a) tSCI and (b) DCM, (ii) compare the findings between the two pathologies, and (iii) outline future directions in spinal cord DTI.

Macrostructural changes in Traumatic Spinal Cord Injury

Trauma site

Conventional T1- and T2-weighted sequences applied in clinical routine provide macrostructural information on the lesion extent, level, the amount of preserved tissue bridges[14,15], and the extent of the cord compression[16]. At the focal injury site, these MRI protocols revealed that – after signs of oedema and haemorrhage resolved[16,17] – the majority of tSCI patients develop a post-traumatic cyst within the first month after injury[14,15]. Next to the posttraumatic cystic cavity, tissue bridges become discernable on the midsagittal slice of T2-weighted scans which are located either dorsally and/or ventrally adjacent to the cyst. Over the course of one year, the extent of the focal injury site remains rather stable and tissue bridges persists[14].

Remote degeneration

Remote from the injury the use of gradient-echo based T2*-weighted sequences allows to assess tissue-specific changes of white and gray matter[7]. In tSCI patients, the cervical spinal cord area above a spinal lesion was found to progressively decrease over the first years after injury[18,19], amounting up to 14% after two years[20]. In chronic tSCI patients this decrease can reach up to 30% (rostral to the lesion)[21–23], indicating that various degenerative processes culminate in measurable tissue atrophy in the chronic stage[24]. In a tissue-specific analysis, Huber et al. showed that both the gray and white matter undergo atrophy at C2/C3 (rostral to the lesion) in chronic tSCI patients, where the relative atrophy was even higher in the gray matter (-30.0% vs. -16.9%)[22]. Interestingly, the same study[22] showed that both the ventral and dorsal horns of the gray matter are affected by above-level degeneration, and their magnitude is associated with motor and sensory outcome, respectively. White matter, ventral and dorsal gray matter were found to atrophy below a cervical lesion as well, even as far as the lumbar enlargement[25].

Microstructural changes in Traumatic Spinal Cord Injury

Although our knowledge about the disease pathophysiology has improved over the past decades, still much remains unknown about the development and progression of secondary degeneration as well as the reorganizational processes taking place after injury[24]. In addition, several new therapeutic interventions have now entered phase I

and II clinical trials (e.g. Anti-Nogo antibody treatment[26,27]), where the evaluation of the safety and efficacy of these treatments requires surrogate endpoint markers. Together, these rationales have triggered much interest in imaging tSCI using DTI. Most spinal cord DTI studies carried out in tSCI patients aimed at (i) better understanding the progressive microstructural damage in the spinal cord and brain, or (ii) identifying predictive imaging markers that correlate with clinical recovery.

Trauma site

The accessibility of the injury site to DTI is limited as the majority of tSCI patients undergo early surgical treatment, and the metallic implants (e.g. fixative orthopaedic implants) subsequently create major artifacts including image distortion and signal loss[28]. Therefore, most DTI investigations have focused on the acute stage, and performed imaging before the patients underwent surgery. DTI studies consistently reported lower FA values at the epicenter of the injury[29,30], while MD was more variable with studies reporting either no change[31] or decreased values[30] at the lesion site. In terms of directional diffusivities, AD was markedly reduced[30]. These in-vivo findings are supported by findings from small animal models of tSCI, which found reduced FA in parallel to reduced AD and increased RD at the lesion site[32,33]. In the chronic stage, FA values continued to be lower at the lesion site, while increased MD and RD have also been reported[34,35].

Remote degeneration

The unique power of DTI lies in the fact that it can non-invasively detect subtle degeneration rostral and caudal to the injury site, in the normal appearing WM, where conventional MRI does not show any abnormality. Studies consistently reported lower FA values in cord segments above and below the lesion in both acute[30,36] and chronic patients[33,34,37]. These findings are in accordance with small animal studies that found reduced FA remote to the lesion as soon as 1 day after injury, which paralleled axonal loss and demyelination in these areas as revealed by histological validation[38]. Parallel to decreased FA, several human studies involving chronic tSCI patients reported decreased AD[39,40] indicative of anterograde and retrograde degeneration of motor and sensory tracts. RD values have been reported to increase above and below the lesion[39,40], providing evidence of demyelination of the affected axons both in the rostral and caudal directions. While most of the studies reported DTI metrics averaged across

the cross-section of the spinal cord, therefore lacking spatial specificity, a voxel-wise analysis performed at C2/3 found decreased FA, AD, and increased RD in overlapping regions in the dorsal and lateral columns, but not in the ventral columns[22] (Fig. 3).

Although small animal studies demonstrated remote secondary degeneration of gray matter (GM) after tSCI[41], GM involvement has been rarely investigated in human studies due to difficulties associated with the small size of GM. However, understanding of tissue-specific cord pathology may improve clinical trial designs by more efficient targeting and monitoring of regenerative and neuroprotective agents. In a voxel-wise analysis, Huber et al.[22] found no evidence of diffusivity changes above the lesion; however, this might have been a consequence of partial volume effects in the very thin GM that reduces the sensitivity for detecting changes.

Investigating degeneration as remote as the lumbar cord has great implications for understanding the pathophysiology of symptoms related to this level, such as degeneration of lower motor neurons, bladder and sexual dysfunctions[42]. However, lumbar cord imaging presents an even higher level of difficulty compared to cervical imaging due to susceptibility and motion artifacts from the lungs and less coil coverage, and the feasibility of performing tissue-specific (both GM and WM) DTI analysis in the lumbar cord on a clinical dataset has been only recently demonstrated[43]. Using this methodology, David et al.[25] conducted the first tissue-specific DTI analysis in the lumbar enlargement of chronic tSCI patients and found decreased FA, AD and increased RD in the WM, and decreased FA and AD in the GM, indicating the involvement of GM in the degenerative processes. Although the pathophysiological correlates of the GM DTI findings are still unclear, it presumably reflects trans-synaptic degeneration of motor neuron pool due to deprivation from supraspinal input[44].

Associations with clinical and electrophysiological measures

Dorsal and ventral midsagittal tissue bridges – detectable early after SCI – transmit tract-specific electrophysiological information[14,15]. The width of dorsal and ventral the tissue bridges predict sensory and motor outcome at 1-year, respectivley[15]. Furthermore, midsagittal tissue bridges were shown to correlate with walking ability[45]. Remote atrophy has also been associated with clinical outcome: above the lesion, dorsal and ventral horn atrophy correlated with sensory and motor outcome, respectively[22]. Caudal to a cervical lesion, in the lumbar enlargement, gray matter

atrophy was associated with lower motor evoked potentials (MEP) of the abductor halluces (extensor) and tibialis anterior (flexor) muscles, which are thought to reflect trans-synaptic changes within both extensor and flexor motor neuron pools[25].

DTI findings have shown to be clinically eloquent as the magnitude of DTI changes correlated with the level of clinical impairment. In cervical tSCI subjects, completeness of neurological injury measured by the ISNCSCI impairment score was found to be correlated with FA in the cervical[46] and in the thoracic and lumbar cord[25,37]. Demonstrating a link between microstructure and function, FA showed correlations with motor and sensory score[39,47], where the dorsal measures of FA explained sensory disability[46]. DTI metrics of the dorsal tracts have been shown to correlate with tibialis SEP amplitudes[37]. Besides, correlations of spinal cord DTI metrics with disability, retrograde degeneration of the cranial corticospinal tract, and the degree of reorganization in the motor cortex have also been demonstrated[48].

Baseline measurements of FA, MD, and AD at the injury site correlated with ISNCSCI motor scores[49] in acute tSCI patients at 1-29 months follow-up[30]. However, this correlation was not present in hemorrhagic patients, as hemorrhage overcasts the diffusivity changes caused by the axonal damage[30]. Vedantam et al.[36] investigated cervical tSCI using pre-surgical DTI and showed that patients with lower FA of the whole cord and the corticospinal tract had lower ISNCSCI upper-limb motor score and lower AIS impairment score. However, both of these studies had a retrospective design and used clinical scores obtained at the acute phase.

For prediction purposes, investigating the association of DTI metrics with clinical scores obtained in the chronic phase is of more interest, as most tSCI patients undergo improvements in the first year after injury. In a recent study, Shanmuganathan et al.[49] investigated the relation between DTI metrics obtained in the acute phase (within 24h of injury) and clinical scores obtained at one year, and found that AD best predicted both neurological (ISNCSCI) and functional (SCIM) outcome. As a close association has been shown between AD and axonal injury[38,50], this might indicate that axonal injury in the cord is the main factor affecting patient recovery, a notion that is supported by small animal studies as well[51].

Macrostructural changes in Degenerative Cervical Myelopathy

Stenosis site

In clinical routine, the same T1- and T2-weighted sequences used in the evaluation of tSCI can be applied in DCM to assess the extent of cervical cord compression, the cause of compression, the number of compressed levels, and the extent of a possible cervical myelopathy[52–54]. The most frequent level of compression can be found at cervical level C5-6, but compression often occurs at multiple levels across the cervical cord in between C3 and C7[52]. At the level of stenosis, studies found lower cross-sectional spinal cord area and increased T2*WI WM/GM ratio[40]. The latter having a good diagnostic accuracy and correlation with clinical impairment[40].

Remote degeneration

Greater decreases in the spinal cord area was found rostral and caudal to the stenosis when compared to healthy controls, suggesting that a focal compression can trigger remote atrophy in DCM patients[55,56]. Further investigations showed that both white and gray matter area at C2/C3 (rostral to the stenosis) are lower than at corresponding levels in healthy controls (gray matter: -7.2%; white matter: -13.9)[55]. Within the gray matter, dorsal horn was affected more by atrophy at C2/C3[55]. Since dorsal horn contains the second-order neurons of the spinothalamic tracts (as opposed to motoneurons in the ventral horn), degeneration of dorsal horn might explain the sensory deficits (but no motor deficits) experienced by DCM patients in the early stages of the disease. In mild non-operative DCM patients, cross-sectional area of the spinal cord was found to decrease at the stenosis site between baseline and 1-year follow-up, while it showed a strong (although non-significant) trend for decrease rostral to the stenosis.

Microstructural changes in Degenerative Cervical Myelopathy

Stenosis site

The rationale behind applying DTI to patients with DCM is compelling. First, DTI studies aim to establish sensitive and specific markers in the early stages of disease progression, which has the potential to improve clinical diagnosis by evaluating the pathophysiological status of the cord early in the clinical course, and subsequently

during rehabilitation[57]. Early diagnosis is very important in DCM as it enables early intervention that may prevent further damage to the spinal cord. Second, the higher sensitivity of DTI to microstructural features (compared to conventional MRI) is expected to provide better prediction of functional outcome compared to conventional MRI[56]. As each WM tract conveys specific functional signals, knowledge about the nature and extent of damage to each WM tract might allow us to predict functional outcome and specific disabilities of affected patients.

There is accumulating evidence that DTI metrics at the stenosis change as myelopathy progresses from early to later stages. The impact of compression has been less well investigated; some studies found decreased MD and slightly increased FA after acute compression[58], which might be the consequence of compression of axon fibers reducing the extra-cellular space but without damaging the axons, a notion that has been supported by diffusion MR simulations[59]. In the later stages, studies consistently reported decreased FA and increased MD at the site of compression[60,61], along with elevated AD and RD[62]. Martin et al.[56] showed that decreased FA values are present at the compression site even in asymptomatic cervical spinal cord compression (ASCC) patients.

Despite the proven sensitivity of DTI metrics to WM damage in DCM, their diagnostic accuracy was shown to be only moderate[61,63], which might be explained by the heterogeneity of DTI metrics even in healthy subjects, the modest test-retest reliability, and limited sensitivity to pathology[57].

Remote degeneration

Similarly to tSCI, applying DTI above and below the stenosis can help improve our understanding of the degenerative changes occurring remotely in DCM patients. Several studies reported decreased FA and increased MD rostral to the stenosis at C2/C3[55,62,64,65]; however, the magnitude of these changes was smaller than at the level of stenosis[64,66]. Similar diffusivity changes with decreased FA and increased MD were also found caudal to the stenosis, extending to the lumbar enlargement[65]. These changes were not uniformly distributed across the WM tracts: FA decrease was more pronounced in the dorsal and lateral columns than in the ventral column[55,67,68] (Fig. 4). In terms of directional diffusivities, RD was consistently found to be increased at and remote to the stenosis[55,62,67], which resembles the findings in tSCI and suggests

remote demyelination triggered by the focal stenosis. However, interestingly, several studies found higher AD above[55,62] and below the stenosis[62,67], which represents a qualitatively different finding compared to tSCI. The most likely explanation for this finding is that compression and loss of surrounding structure leads to denser tissue with elevated fiber density and reduced extra-cellular space[69]. Nevertheless, the increase in RD has been reported to be significantly (nearly two times) higher than the increase in AD, suggesting that demyelination is the dominant process above the level of stenosis (and potentially below as well)[55,62]. Investigating these changes longitudinally, Martin et al.[53] found a further decrease in FA at, above, and below the stenosis in a DCM cohort measured 1 year after baseline.

As with tSCI, gray matter changes have been rarely investigated in DCM. In a cohort of mild-to-moderate DCM with mainly sensory impairment, Grabher et al.[13] found increased MD in the ventral horn but not in the dorsal horn, underlining that even gray matter undergoes extensive degeneration above the level of compression in DCM. Although the exact pathophysiology is unclear, the authors argue that increased MD might be caused by perturbed propriospinal circuitries and corticospinal projections to motor neurons.

Associations with clinical and electrophysiological measures

Macro- and microstructural MRI metrics, measured both at the stenosis and at C2/C3, were found to correlate with baseline clinical scores[56,70]. In particular, the modified Japanese Orthopedics Associations score (mJOA) and Nurick score correlated positively with FA[66,67], while the Nurick score correlated negatively with FA[62,71]. When relating to electrophysiological measures, Wen et al.[67] found that only DCM patients with abnormal SEPs exhibited decrease in FA in the C1/C2 dorsal column (above the stenosis), when compared to healthy subjects.

DTI may hold greater potential to predict surgical outcomes because it can potentially differentiate between reversible (e.g. perfusion deficits) and irreversible (e.g. axonal loss) changes in WM[57]. However, the predictive ability of DTI is not clear as contradictory findings have been reported at the compression site. While Jones et al.[71] found that higher pre-operative FA values site correlate with post-surgical improvement in NDI (Neck Disability Index), but not with Nurick and mJOA scores, Vedantam et al.[66] found that FA at the level of maximum cord compression was significantly correlated with change in mJOA score at 3 months after injury, but not

with NDI. Above the stenosis, Wen et al.[67] also showed that pre-operative FA at C2 correlated with good surgical outcome. MD values have also been assessed to determine their ability to predict clinical recovery after decompression surgery and showed promising results[72].

Discussion

This review describes macro- and microstructural changes in the spinal cords' white and grey matter. It describes how knowledge gained by conventional and quantitative MRI at the focal injury side helps guide clinical decision making and reveals the extent of secondary neurodegeneration that spreads across the entire spinal cord both in tSCI and DCM patients. In particularly, DTI can detect changes even in areas where no abnormality is observed on conventional MRI, and this superior sensitivity makes it an ideal technique to investigate microstructural disease processes triggered by a focal spinal cord injury. Importantly, the spatial extent and temporal profiles of these neurodegenerative processes might offer important targets for clinical trials, both in tSCI and DCM.

Comparison between microstructural changes in tSCI and DCM

Despite obvious difference in the time profile of changes (abrupt onset in traumatic SCI and slowly developing symptoms in DCM), experimental evidence suggests that, tSCI and DCM share several aspects of neurodegenerative changes[73–76]. Indeed, this review outlines, that the order of magnitude of remote secondary neurodegeneration is remarkably similar. For example, the cross-sectional cord area at the C2/C3 level decreases between 15-30% in tSCI[21,22] while it reaches up to 17% in patients with mild DCM[55]. In both spinal cord pathologies, exploratory studies using in-vivo spinal cord DTI revealed diffusivity changes in the WM. These changes are indicators of anterograde (Wallerian) and retrograde degeneration, involving both disintegration of axonal structure and demyelination, as demonstrated by ex-vivo small animal studies[3,38]. In particular, decreased FA was consistently reported in both tSCI and DCM above and below the injury, as far as the lumbar enlargement, although the magnitude of these changes was lower than at the injury site. Radial diffusivity (RD) was found to be increased in both pathologies, which indicates demyelination occurring at and remotely from the lesion/stenosis. Axial diffusivity (AD) showed qualitatively different behavior between tSCI and DCM: it was reported to decrease

after tSCI, while it was found to increase in DCM. This discrepancy may be related to differences in the histopathological correlates of these conflicting findings: while reduced AD has been shown to indicate disintegration of the axonal cytoskeleton (axonal loss), an elevated AD is the sign of increased fiber density with intact axons due to compression. Furthermore, microstructural differences between tSCI and DCM may also be related to the severity of injury, as the majority of tSCI patients have more severe injuries than are observed in DCM. Clearly, further study is required to fully understand the subtle differences in WM degeneration between these conditions. Although the studies cited in this review revealed the spatial pattern of degeneration after tSCI and DCM, the cross-sectional design of these studies did not allow investigating the time course of these changes. Importantly, these microstructural changes also translated to measurable tissue atrophy in both GM and WM, above and below the lesion/stenosis, where the magnitude of atrophy was found to be higher in tSCI patients.

Associations with function and outcome

A large body of evidence demonstrates the association between conventional and quantitative MRI metrics and clinical outcomes. In particular, FA was found to show the highest correlation with clinical scores (ISNCSCI scores in tSCI, mJOA and Nurick scores in DCM), where lower FA values were associated with higher impairment. Importantly, these associations were spatially specific in nature; for example, dorsal measures of FA were more related to sensory disability. When compared with electrophysiological readouts (SEPs and MEPs), the decrease of FA was more pronounced with increasing SEP latencies in both pathologies, indicating a direct link between the microstructure (demyelination) and the function (delayed conduction) of the axons. While the above associations give insights into the structure-function relation of the axons, they were mostly established in the chronic stage of the disease. Investigating the predictive power of DTI requires early measurements, although it can be challenging in DCM where the onset of the injury is not clearly defined. In tSCI, there is moderate evidence that AD in the acute phase predicts functional outcome (measured by ISNCSCI scores) at one year, which may indicate that axonal injury in the cord is the main factor affecting patient recovery[49]. However, the diagnostic and predictive utility of MRI metrics in the clinical settings are still understudied. One limitation is the comparability of the studies due to the small cohort size and

differences in patient characteristics (e.g. level and severity of injury), acquisition, and post-processing techniques. In future, large, prospective studies with a priori hypotheses, stratified patient cohorts, standardized acquisition methods along with cross-vendor validation, and robust automated image processing and analysis techniques are needed to generalize results to the population and to ensure comparability of the results[8,77]. In addition, for MRI metrics to be established as clinical diagnostic tools, they have to be informative about individual patients, not just show significant group differences.

Current trends and advances

Advances in data acquisition:

On the acquisition side, several improvements have been introduced, such as new receive coil designs for spinal cord[78], new generation MR systems with stronger diffusion-imaging gradients[79], or ultra-high field MRI[80], aiming to maximize signal-to-noise ratio and resolution. Other techniques including tailored pulse sequences for the spinal cord[81], dynamic[82] and real-time shimming[83], or retrospective correction for field fluctuations[84] attempt to minimize distortions and other respiratory-related artifacts in DTI.

Advances in data processing:

Advances in image processing techniques[85] include automatic segmentation of the spinal cord[86] and gray matter[7], artifact removal tools[87,88], normalization to spinal cord template[89], and template-based analysis techniques[90]. Automated segmentation techniques can replace time-consuming manual segmentations subject to operator bias, facilitating comparable and reproducible analysis and enabling tissue-specific analysis of DTI metrics. In a gray matter segmentation challenge in 2016, some of these automatic gray matter segmentation techniques could achieve near-human performance[7]. The introduction of PAM50, the first widely-used, multi-contrast, and full spinal cord template, facilitates group and multi-center studies and enables automated tissue-specific and tract-based analysis. Finally, the advances in diffusion-weighted imaging with higher resolution (e.g. ultra-high field imaging) and the recently introduced gray matter atlas[89] are expected to further increase the accessibility and improve the reliability of gray matter spinal cord DTI data.

Advances in diffusion models:

DTI is a simple diffusion MRI technique that offers short acquisition times, wide accessibility and relatively high reliability. However, although DTI metrics such as AD and RD are interpreted as markers of axonal loss and demyelination, respectively, they do not directly represent biological parameters, making DTI metrics inherently non-specific (e.g. see the above-mentioned, opposed changes in AD for DCM and tSCI patients). Instead, DTI metrics are sensitive to a number of biological factors including changes in axonal density, myelination, axonal diameter, and axonal orientation to varying degrees[91]. To increase the specificity of diffusion MRI, more advanced models of the diffusion signal such as Diffusion Kurtosis Imaging (DKI)[92], CHARMED[93], or NODDI[94] have been developed. The latter two fall into the category of biophysical models of the diffusion signal.

In vivo histology using biophysical models and MRI:

In vivo histology using MRI (hMRI[95]) is an emerging field in neuroimaging[96]. It aims to establish the missing link between measured MRI signals and the underlying tissue microstructure by bridging the gap between the micro-scale and the measured mesoscopic MRI voxel size[97]. This is done by developing advanced biophysical models that describe the relationship between MR signal and microscopic tissue properties such as axon density[93,98] or myelin density[99,100]. In recent years, some of the biophysical diffusion models have been tested in the spinal cord, e.g. NODDI has been successfully applied in the cervical spinal cord both in healthy subjects[101] and in multiple sclerosis patients[102]. Another recent development might allow even improved interpretation of classical DTI parameters retrospectively: different groups[103–105] have shown that physical DTI/DKI metrics (e.g. FA or mean kurtosis) are explicitly related to biophysical metrics (e.g. fiber dispersion or axon density).

Although these techniques are potentially more specific markers of microstructure (e.g. axon density as estimated by NODDI or CHARMED), their specificity is still limited. One important reason for this is the fact that diffusion MRI is blind to myelin-water and as a consequence models based solely on diffusion MRI are mostly sensitive to the axonal-water fraction instead of the true axon density. To calculate the axon density, complementary MRI techniques need to be combined[106]. In general, in vivo histology metrics often rely on the fusion of complementary MRI modalities. An important example for such a metric is the g-ratio of fiber pathways[106,107], which

characterizes the relative degree of myelination of an axon and therefore relates to the conduction velocity of information along the fiber pathway. Therefore, it might be particularly interesting to compare g-ratio findings with electrophysiological readouts in tSCI and DCM.

Conclusion

This review emphasizes the role of spinal cord MRI to provide information on the macro- and microstructural integrity of the spinal cord after traumatic and non-traumatic SCI. A large body of evidence demonstrates the sensitivity of MRI metrics, especially FA, to detect focal and remote degeneration occurring after tSCI and in DCM. Directional diffusivities (AD and RD) can give further insights into the nature of the degeneration, with tSCI showing signs of both demyelination and disintegration, and DCM showing only signs of demyelination. Several studies showed associations between MRI metrics, clinical assessments, and recovery in both pathologies. Thus, neuroimaging biomarkers may serve as surrogate endpoints for interventional trials in both tSCI and DCM. The adoption of neuroimaging biomarkers in clinical SCI centres will enable the development of more efficient trials and may eventually lead to individualized patient care approaches. However, large-scale, prospective studies with stratified patient cohorts are needed to establish the role of quantitative MRI as a prognostic marker.

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Figure captions

Figure 1 Schematic illustration of primary and secondary injury mechanisms at, above, and below the injury site after degenerative cervical myelopathy (DCM) and traumatic spinal cord injury (tSCI). The primary injury mechanism is fundamentally different in these conditions, where tSCI is caused by a sudden traumatic event, while DCM results from progressive degeneration of the cervical spine. Following the primary injury, secondary degenerative processes ensue in both tSCI and DCM that propagate remotely, above and below the primary injury site, and involve axonal degeneration and accompanying demyelination. Above the lesion, in the cervical cord, affected sensory tracts (depicted in blue) including dorsal column and spinothalamic tract and motor tracts including corticospinal tract (depicted in red) undergo anterograde and retrograde degeneration, respectively. Below the lesion, in the lumbar cord, similar degenerative processes occur, with sensory and motor tracts undergoing retrograde and anterograde degeneration, respectively. The gray matter can also be affected by means of trans-synaptic degeneration. In the lumbar gray matter, the lower motor neurons located in the ventral horn may undergo trans-synaptic degeneration due to the loss of input from the injured corticospinal tracts. Similarly, the second-order sensory neurons of the spinothalamic and dorsal column medial lemniscus systems located in the dorsal horn can also be affected by retrograde trans-synaptic degeneration.

Figure 2 Cross-sectional areas of white matter (WM) and gray matter (GM) measured at C2/C3 in tSCI (left column) and DCM (right column) as compared to healthy controls. The measurement site at C2/C3 was rostral to the lesion/stenosis in both patient groups. In both tSCI and DCM, WM and GM area were lower compared to healthy controls, indicative of remote tissue atrophy, whereby the magnitude of changes was higher for tSCI patients. [Adapted from Huber et al., 2018 and Grabher et al., 2016]

Figure 3 Voxel-wise analysis of DTI metrics in chronic tSCI patients and healthy controls at C2/C3 level (above the lesion). Compared to healthy controls, tSCI patients exhibited lower FA and higher AD in the lateral and dorsal funiculi, and increased RD in the dorsal and left lateral funiculi. Color bars represent t-values. Clinical scans showed no abnormality in tSCI patients at the corresponding level, apart from

hyperintense signal in the dorsal and lateral funiculi on the T2*-weighted images. These microstructural changes above the level of lesion reflect Wallerian degeneration of the dorsal column, and retrograde degeneration of the motor tracts in the lateral funiculi. [Adapted from Huber et al., 2018]

Figure 4 Voxel-wise analysis of DTI metrics in DCM patients and healthy controls at C2/C3 (above the stenosis). Compared to healthy controls, DCM patients exhibited lower FA in the lateral CST (B) and dorsal column (C), and higher AD, RD, and MD in the dorsal column (D-F). Color bars represent t-values. Clinical scans showed no abnormality in tSCI patients at the corresponding level. These diffusivity changes indicate microstructural changes above the stenosis in DCM patients. [Adapted from Grabher et al., 2016]

Suppl. Fig. 1. The anisotropic diffusion in the white matter can be characterized by a diffusion tensor ($\underline{\boldsymbol{D}}$) that contains six independent diffusivity values. The diffusion tensor can be visualized by an ellipsoid, where the length of the axes ($\lambda_1, \lambda_2, \lambda_3$), corresponding to the eigenvalues of the diffusion tensor, are the diffusion coefficients along the corresponding directions ($\boldsymbol{v_1}, \boldsymbol{v_2}, \boldsymbol{v_3}$). (B) Although in most cases the ellipsoid is not aligned with the laboratory reference frame (x, y, z), the eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) represent rotationally invariant measures, which can be used to derive various shape-related parameters of the ellipsoid (*DTI metrics*) including mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA). On the left side, maps of the corresponding DTI metrics in the cervical spinal cord are illustrated. (C) Schematic illustration of intact and injured myelinated axons with the corresponding diffusion ellipsoid. (i) intact axons with intact myelin sheath exhibit strong diffusion anisotropy, with λ_1 being much larger than λ_2 and λ_3; (ii) disintegration of the axonal structure with (still) intact myelin sheath leads to decreased AD; (iii) demyelination of the axons is characterized by increased RD; (iv) combination of both axonal damage and demyelination results in decreased AD and increased AD.

Declaration of interests

Gergely David has nothing to disclose.

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