

MRI in traumatic spinal cord injury: from clinical assessment to neuroimaging biomarkers



Patrick Freund, Maryam Seif, Nikolaus Weiskopf, Karl Friston, Michael G Fehlings, Alan J Thompson, Armin Curt

Traumatic spinal cord injury occurs when an external physical impact damages the spinal cord and leads to permanent neurological dysfunction and disability, and it is associated with a high socioeconomic burden. Conventional MRI plays a crucial role in the diagnostic workup as it reveals extrinsic compression of the spinal cord and disruption of the discoligamentous complex. Additionally, it can reveal macrostructural evidence of primary intramedullary damage such as haemorrhage, oedema, post-traumatic cystic cavities, and tissue bridges. Quantitative MRI, such as magnetisation transfer, magnetic resonance relaxation mapping, and diffusion imaging, enables the tracking of secondary changes across the neuraxis at the microstructural level. Both conventional MRI and quantitative MRI metrics, obtained early after spinal cord injury, are predictive of clinical outcome. Thus, neuroimaging biomarkers could serve as surrogate endpoints for more efficient future trials targeting acute and chronic spinal cord injury. The adoption of neuroimaging biomarkers in centres for spinal cord injury might lead to personalised patient care.

Introduction

Conventional MRI of the spinal cord is an essential component in the diagnostic investigation, surgical treatment, and rehabilitation of patients with spinal cord injury.¹ Spinal MRI is the gold standard for the evaluation of any damage to the discoligamentous complex (ie, spine instability and spinal canal encroachment) and neural structures (ie, intramedullary damage of the spinal cord) induced by mechanical trauma.² In clinical practice, T1-weighted and T2-weighted MRI sequences are usually applied.³ These conventional MRI sequences reveal the level of the damage and the extent of intramedullary or extramedullary abnormalities (oedema and haemorrhage), the degree of spinal cord compression, extent of disk herniation, and the amount of ligamentous instability at the level of the injury.³ Coupled with the clinical examination, these imaging findings, obtained within hours of the trauma, guide decision making and can lead to a timely and appropriate decompression of the spinal cord.⁴

Despite their importance in clinical management, these conventional MRI sequences provide little information about the evolving neurodegenerative changes of the immediate and adjacent spinal cord segments and, subsequently, of the brain. Thus, there is an urgent need for a more in-depth understanding of the complex processes of neural plasticity involved in spinal cord injury recovery.⁵ Spinal imaging studies using advanced quantitative MRI techniques, such as magnetisation transfer, magnetic resonance relaxation mapping, and diffusion imaging can improve detection and quantification of microstructural features of trauma-induced pathology both at, and remotely from, the site of injury.^{6–14} These quantitative MRI protocols provide measures of spinal cord^{15,16} and brain integrity¹⁷ that reflect atrophy, demyelination, and iron deposition. They have been used to demonstrate widespread^{6–14} and progressive neurodegeneration,^{7–9} the magnitude of which can predict clinical recovery.^{9,10} Quantitative MRI therefore offers improved assessment of underlying neural integrity

and can provide insights into the relationship between clinical recovery and neural plasticity.¹⁸ Additionally, task-based functional MRI and resting-state functional MRI (rs-fMRI), although non-quantitative, can probe plasticity in the brain^{19–21} and spinal cord.^{22–25} In clinical practice, sensorimotor impairments assessed by means of the International Standards for Neurological Classification of Spinal Cord Injury²⁶ are commonly used as outcome predictors following spinal cord injury (panel 1). Conventional MRI markers such as the Brain and Spinal Injury Center (BASIC) score³⁷ and intramedullary lesion length³⁸ are also considered useful predictors of outcome. However, the future portends a better understanding of trauma-induced microstructural changes by means of neuroimaging biomarkers, and a potential use of neuroimaging biomarkers as an indicator of outcome in clinical trials.

In this Review, we evaluate findings from conventional MRI and discuss the insights they have provided concerning the primary pathological features of the injury epicentre. We then assess developments in quantitative MRI imaging studies that have revealed new information on secondary pathological changes affecting the entire neuraxis. We discuss the relevance and implications of these advances in quantitative MRI for improving the ability to predict recovery are discussed, and we follow that discussion with an assessment of their application as biomarkers in spinal cord injury trials. We review studies assessing cortical and spinal functional plasticity by means of fMRI and rs-fMRI are reviewed before discussing the application of MRI protocols in clinical and research settings. Finally, we suggest directions for future research.

Conventional MRI

Immediate changes at the epicentre

Most patients with spinal cord injury undergo decompression surgery and receive spinal fixation devices (ie, metallic implants) to manage spinal instability. The presence of metallic implants causes substantial MRI artifacts such as signal-loss, signal-pileup, geometric distortion, and

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Panel 1: Clinical and electrophysiological assessment of patients with spinal cord injury

The symptoms and signs of myelopathy (ie, the degree of sensorimotor deficit and the presence of neuropathic pain) can be assessed clinically and by electrophysiological tests. The gold standard in assessing clinical impairment is by means of the International Standards for the Neurological Classification of Spinal Cord Injury protocol.²⁷ This test is routinely performed at admission by a qualified clinician who tests key muscles for strength and all dermatomes for light-touch and pin-prick sensation. A score is then calculated and used to classify the patient's overall impairment on the American Spinal Injury Association Impairment (AIS) scale with five ranked categories—A to E. Category A corresponds to the most severely damaged spinal cord, with no motor and sensory function below the level of injury, whereas category E features no clinically relevant impairment. Although defining AIS categories is a fairly easy process, it does not capture the entire extent of primary and secondary injury mechanisms. Consequently, there is considerable heterogeneity within an AIS category, which limits the applicability of this classification to guide stratification in clinical trials. Thus, large clinical trials are needed to distinguish a treatment effect from natural history. To address this drawback, dedicated prediction models (ie, unbiased recursive partitioning) have been developed.^{28,29} These models aim to reduce the heterogeneity within spinal cord injury cohorts, thereby improving patient stratification.

For upper limb function, manual dexterity is assessed by the Graded Redefined Assessment of Strength, Sensibility, and Prehension score,^{30,31} and functional independence by the Spinal Cord Independence Measure score,³² while neuropathic pain intensity is commonly assessed with pain questionnaires.³³ Neurophysiological recordings, such as motor and sensory-evoked potentials³⁴ and contact heat evoked potentials,³⁵ can provide additional information about the integrity of impulse conductance of motor and distinct sensory pathways.³⁶ However, these examinations report on impaired function related to focal injury, and they do not reflect remote neurodegeneration and functional reorganisational processes that occur with distinct (delayed) temporal profiles.⁵

failure of fat suppression,³⁹ which worsen with increasing magnetic field strength.⁴⁰ These image artifacts limit MRI diagnostic utility and reduce the quality of the quantitative MRI metrics. Current strategies for metal artifact suppression that allow scan acquisitions in a clinically feasible duration include slice-encoding for metal artifact correction⁴¹ with dual-source parallel radiofrequency,⁴² as well as compressed sensing multi-spectral imaging techniques.⁴³ By taking advantage of such techniques, MRI studies have investigated primary (ie, macrostructural) changes immediately following the injury, focally at the injury site,

and on the basis of hyperintensity signal changes of sagittal and axial T2-weighted MRI scans and hypointensity signal changes of T1-weighted MRI scans.^{38,44–49} The most prominent features on sagittal T2-weighted MRI scans include haemorrhage, cytotoxic oedema, and spinal cord swelling.^{38,47} Serial quantification of the sagittal T2-weighted hyperintensity revealed that the intramedullary damage dynamically expands rostrally and caudally, with injury severity substantially affecting the rate of expansion.^{37,38,47} On the basis of T2-weighted signal abnormalities, a five-point ordinal MRI score—referred to as the BASIC score—has been proposed for MRI-based diagnostic and prognostic classification in patients with spinal cord injury in the first days after injury.³⁷ The BASIC score quantifies five distinct patterns of intramedullary T2-weighted signal abnormality in the axial plane at the injury epicentre of the spinal cord (figure 1). These patterns range from no abnormalities to the most severe abnormalities, consisting of a mix of haemorrhage and oedema. The feasibility and prognostic validity of the BASIC score have been demonstrated for patients with acute cervical^{37,50} and thoracic⁵¹ spinal cord injury, in whom MRI had been performed within days after injury. Moreover, the intramedullary lesion size, measured on sagittal T2-weighted scans (figure 2), might be a good predictor of recovery as its size is influenced by injury severity^{44–48} and the outcome of surgical decompression.³⁸

A caveat to quantifying intramedullary damage by conventional MRI scans is that the T2-weighted signal changes are non-specific to the underlying pathophysiology. T2-weighted signal changes can reflect various processes, including oedema, inflammation, demyelination, cyst cavitation, or the development of myelomalacia.³⁷ Moreover, interpretation should be dependent on the timing of MRI assessments, as the evolution of the signal can change considerably (eg, oedema and haemorrhage) over time and is highly variable across patients.³⁸ Finally, since fully automated methods that can reliably distinguish artifact induced signal changes at the epicentre of a traumatic lesion are not available, the quantification of changes in T2-weighted MRI scans is usually performed by a user with experience in assessing conventional MRI. Thus, the utility of the BASIC score as suitable outcome predictor, and the quantification of the intramedullary lesion length require further validation. Multicentre studies, at both early and later time points, would be ideal—for example, during rehabilitation when the T2-weighted signal abnormalities have evolved—for the validation of these neuroimaging biomarkers.⁵²

Evolution of changes at the epicentre

A longitudinal study employing conventional MRI has investigated the natural sequelae of macrostructural intramedullary changes during the first year after cervical spinal cord injury in 13 patients.⁵² This study found that T2-weighted MRI scans showed a transition from the acute oedema and haemorrhage⁵³ to subacute intramedullary

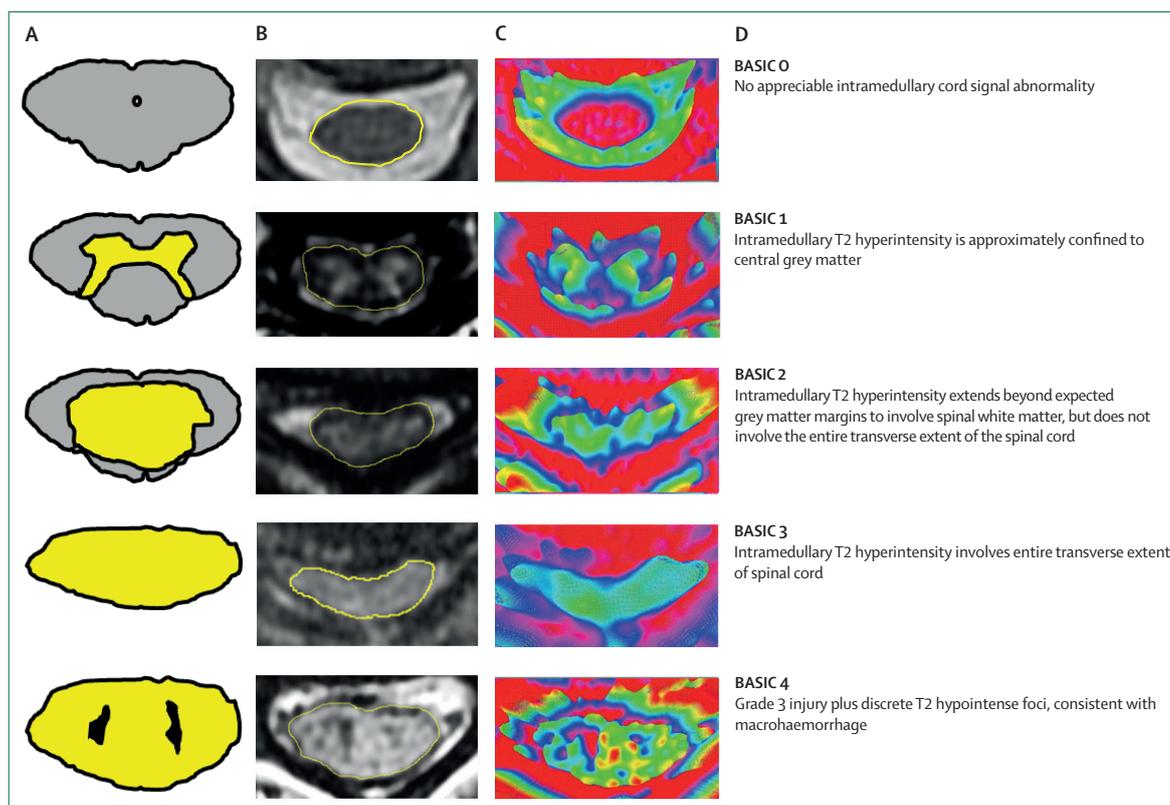


Figure 1: Classification of acute spinal cord injury according to the BASIC score

BASIC comprises a five-point ordinal MRI score for classifying acute spinal cord injuries on the basis of conventional axial T2-weighted MRI scans. The score stratifies spinal cord injury according to the extent of transverse T2-weighted signal abnormality during the acute phase of the injury. The figure shows cartoon schematics (A), representative axial T2-weighted MRI scans with the external contour of the spinal cord outlined in yellow for better delineation (B), 3D-colour surface plots based on the axial T2-weighted MRI scan (C), and brief definitions (D) for each of the five BASIC scores (ranging from 0 to 4). Reproduced from Talbott et al,³⁷ by permission of the American Association of Neurological Surgeons. BASIC=Brain and Spinal Cord Injury Score.

lesion expansion^{44,47} (figure 3). After signs of oedema and haemorrhage slowly evolved on the T2-weighted MRI scans, a post-traumatic cyst appeared in all patients within the first month after spinal cord injury.⁵² At one month after spinal cord injury it is possible to detect small tissue bridges around the post-traumatic cyst that can be measured at the dorsal and ventral aspect of the cord, on midsagittal T2-weighted scans (figure 2).^{52,54} Crucially, the width and location of these tissue bridges might predict tract-specific electrophysiological information flow⁵² and long-term functional recovery.^{52,54,55} Thus, the quantification of spared midsagittal tissue bridges on T2-weighted MRI scans, at 1 month after spinal cord injury, holds potential as an important prognostic outcome tool.

The prognostic ability of MRI markers of lesion characteristics and tissue bridges emphasises the importance of conventional MRI protocols to be applied in clinical routine.⁵⁶ In particular, T2-weighted MRI scans can detect dynamic intramedullary signal changes and preserved midsagittal tissue bridges.⁵² Being potentially sensitive to therapeutic interventions, these neuroimaging biomarkers can serve both as a diagnostic and prognostic tool. Conventional MRI protocols are also easily applied in

longitudinal study designs at any stage of spinal cord injury, and thus could serve as neuroimaging biomarkers for clinical trials.⁵²

Progressive spinal cord atrophy

Automated and unbiased quantification of trauma-induced changes at the level of the injury are still not feasible because of the artifacts induced by metal implants at the lesion site. One strategy to measure structural changes free of metal artifacts that can be performed fully or semi-automatically is to target the artifact-free spinal cord above and below the level of injury. A prospective, longitudinal MRI investigation of 15 patients with traumatic spinal cord injury, tracking changes to the cross-sectional cord area (measured in mm²) on the basis of a T1-weighted MPRAGE sequence at the cervical spinal cord level (C2/C3), showed signs of remote spinal cord atrophy within 2 months of the spinal cord injury.^{8,57} One year after spinal cord injury, atrophy continued to progress,^{7,8} at the level of the cervical spinal cord, reaching 14% at 2 years after spinal cord injury compared with 2 months after spinal cord injury.^{6,9} In patients with long-standing spinal cord injury, high-resolution multi-echo gradient echo MRI

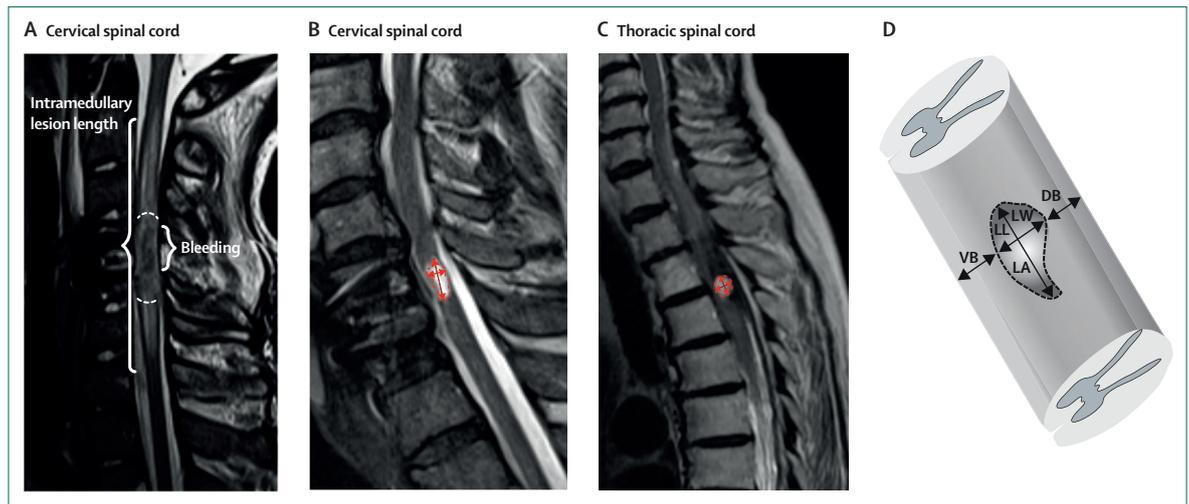


Figure 2: Extent of lesion and tissue bridges in patients with spinal cord injury
 (A) Postoperative T2-weighted MRI of the cervical spinal cord of a 17-year-old patient with traumatic spinal cord injury (male, American Spinal Injury Association Impairment Scale [AIS] grade A [complete]). Postoperative MRI at 32.5 h after decompression surgery indicated an intramedullary lesion length of 102 mm (long bracket) with bleeding (short bracket) and myelomalacia (dotted lines) at the injury epicentre. Reproduced from Aarabi and colleagues, 2017,³⁸ with permission from the American Association for the Advancement of Science. (B) Demonstration of the lesion segmentation using mid-sagittal T2-weighted MRI within the cervical cord of a 51-year-old patient with incomplete spinal cord injury (male, tetraplegic, AIS grade C, and with scan finding of central T2-weighted hyperintense cervical spinal cord defect at the C6/C7 level). (C) Demonstration of the lesion segmentation using mid-sagittal T2-weighted MRI within the thoracic spinal cord of an 80-year-old patient with an incomplete spinal cord injury (female, paraplegic, AIS grade C, and with scan finding of subdural haemorrhage on T4 level). (D) Schematic drawing of the lesion on the spinal cord for analysing the lesion parameters: dorsal midsagittal tissue bridges (DB), lesion area (LA), lesion length (LL), lesion width (LW), ventral midsagittal tissue bridges (VB).

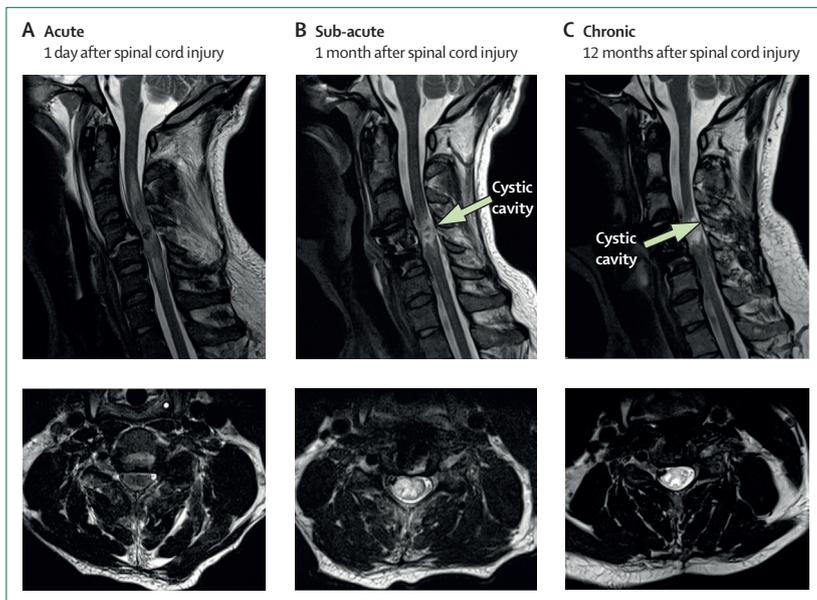


Figure 3: Overview of the lesion evolution over time in a patient with spinal cord injury
 Longitudinal T2-weighted axial MRI scans showing the evolution of the cervical lesion epicentre in a 27-year-old patient with spinal cord injury (male, tetraplegic, American Spinal Injury Association Impairment Scale [AIS] grade A [complete]) in the acute, subacute, and chronic phases after spinal cord injury.

scans, which allow to segment the grey and white matter of the spinal cord,³⁸ showed that remote neurodegeneration occurs within the dorsal and ventral horns as well as in white matter within the cervical spinal cord⁶ and lumbar enlargement.⁵⁹ While dorsal horn atrophy at

the cervical level was associated with sensory outcome (eg, pain sensation, ie, pin-prick score), ventral horn atrophy was associated with motor muscle strength score.⁶ It is still not clear whether the rate of spinal cord atrophy is related to the lesion level or the severity of the injury.^{7,10,57}

Progressive brain atrophy

The conventional T1-weighted MPRAGE sequence that covers the brain and cervical spinal cord has also provided insights into remote brain atrophy. Trauma-induced brain atrophy is particularly prominent across the cranial projections of the corticospinal tracts, primary motor cortex, insula, anterior cingulate gyrus, and thalamus.^{7-9,60-63} As in the spinal cord, brain atrophy starts to evolve within the first months after spinal cord injury and continues for at least 2 years after injury.^{9,64} The resulting changes in tissue volume are clinically relevant. For example, greater volume reductions in the brainstem during the first 6 months after spinal cord injury were associated with poorer recovery of lower limb motor function.⁶⁵ Likewise neuropathic pain intensity has been shown to be associated with reductions in volumes of primary sensory cortices and thalamus,⁶⁰ as well as increases (ie, potentially reflecting reorganisational processes) in grey matter volume within the anterior cingulate gyrus and primary motor cortices.⁶⁶ Performance improvements due to lower limb training in nine patients with incomplete chronic spinal injury (time since injury >1 year) led to volume increases within the atrophied brainstem—indicating reorganisation processes.⁶⁴

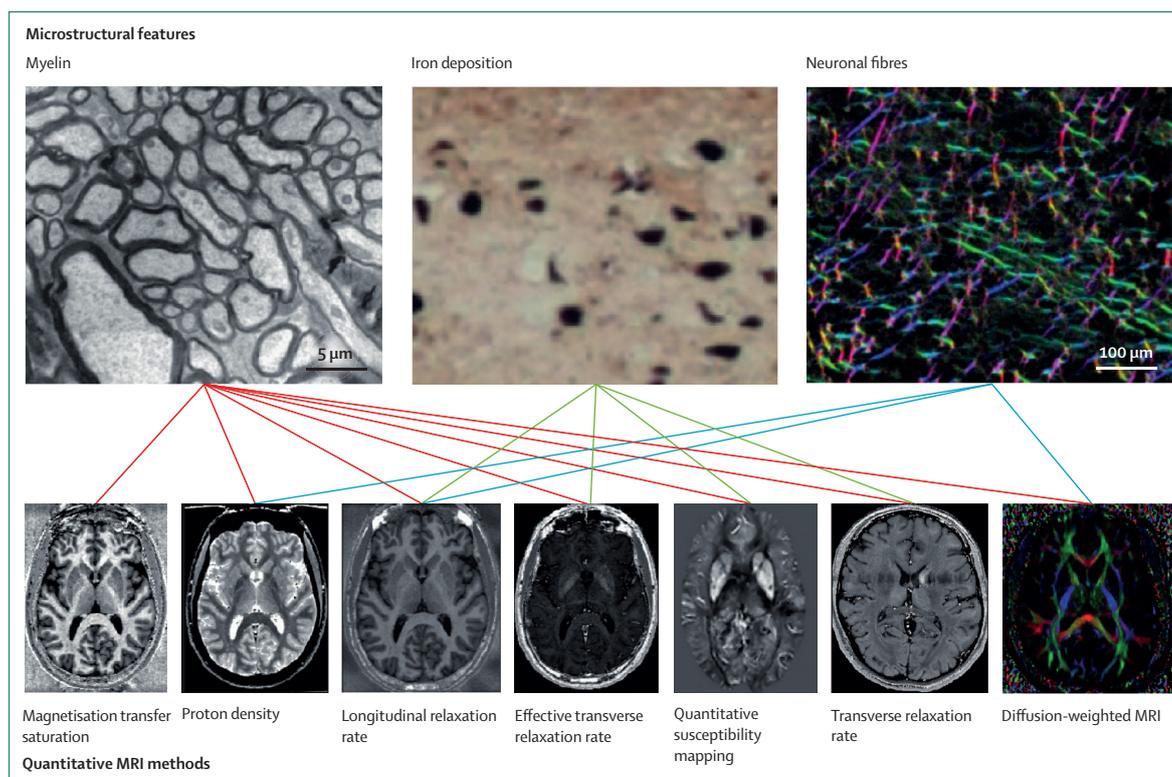


Figure 4: Schematic representation of potential connections between quantitative MRI methods and neocortical microstructural features

The figure shows relationships between different quantitative MRI readouts and the microstructural features based on post-mortem brain tissue^{72,73}. A coloured line between a quantitative MRI readout and a microstructural feature implies that this readout has been empirically linked to this feature. The relationships between magnetic resonance contrast and microstructural features makes microstructural mapping via the combination of complementary quantitative MRI possible. Reproduced from Edwards et al,⁶⁸ under the terms of the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

Quantitative MRI

Advances in MRI technology

Novel quantitative MRI protocols of the spinal cord^{15,67} and the brain^{17,68} have the potential to measure neural changes at the microstructural level. This quantification is feasible because the degree of myelination, iron content, and neuronal microstructure are reflected in magnetic resonance relaxation times, magnetisation transfer, and diffusion of water molecules, which can be measured at the voxel level in the spinal cord^{15,67} and the brain.^{17,68} Quantitative MRI aims at providing values that can be compared between individuals and that are sensitive to particular structural states, for example, axonal degeneration or demyelination.⁶⁷

The most common quantitative MRI technique is diffusion-weighted imaging, which probes the directional diffusivity of water molecules and shows sensitivity and specificity to the axon and myelin pathology.⁶⁹ Diffusion-imaging data are commonly analysed using a tensor model (ie, applying diffusion tensor imaging [DTI]).⁷⁰ However, the tensor model makes several restricting assumptions, which complicate the interpretation of key DTI indices (eg, fractional anisotropy) with respect to the underlying pathology. Novel biophysical models of diffusion contrast are being developed on the basis

of different mathematical models and could alleviate this issue. However, these modelling approaches have yet to be validated—partially due to acquisition or modelling variability versus biological variability.⁷¹ The quantitative measurement of relaxation and magnetisation transfer parameters has been an area of substantial development, making these approaches more accessible to clinical and preclinical research applications. For example, the multi-parametric mapping approach combines different MRI modalities in one protocol quantifying magnetic resonance parameter measures of magnetisation transfer, and longitudinal and effective transverse relaxation rates (R1, R2*)⁷² (figure 4). The link between these quantitative MRI metrics and histology has been studied to probe the microstructure of the human neocortex, focusing specifically on myelin, iron deposition, and neuronal fibre mapping.⁶⁸ Magnetisation transfer measures correlate with histologically measured myelin content,⁷⁵ whereas certain quantitative relaxation rate measurements, such as R2*, correlate with iron content.⁷⁶ These results might provide useful and specific biomarkers such as measurements of oligodendrocyte, glial cells, and iron rich fibres, with potential clinical impact in different pathologies, including spinal cord injury.⁶⁸

Clinical quantitative MRI studies

Building on advances of quantitative MRI methods, studies in patients with spinal cord injury have focused on improving the detection and quantification of tissue-specific spinal cord and brain pathology and on elucidating its relationship with clinical impairment. DTI applied to the white matter of the injured spinal cord showed lower than healthy controls fractional anisotropy (sensitive to axon degeneration) values above and below the lesion, both in acute⁷⁷ and in chronic patients.^{6,12} For processing diffusion-weighted images, the advent of a spinal cord template⁷⁷ and post-processing tools^{79,80} included in the spinal cord toolbox⁸¹ now offer the opportunity to assess tract-specific DTI changes at the voxel level across the entire spinal cord. At both the cervical cord⁶ and lumbar enlargement,⁵⁹ DTI has shown tissue specific decreased fractional anisotropy and axial diffusivities (associated with axonal degeneration⁶⁹) and increased radial diffusivities (associated with demyelination⁶⁹) in the corticospinal tract and the dorsal columns. The results are suggestive of retrograde and anterograde degeneration of descending motor pathways and ascending afferent spinal projections, respectively. Moreover, the grey matter of the lumbar enlargement featured decreased fractional anisotropy and axial diffusivity, indicating trans-synaptic degeneration of motor neuron pools deprived of supraspinal input.⁵⁹ Brain DTI showed impaired microstructure along the cranial projection of the corticospinal tract,^{13,14} and other brain areas (eg, the corpus callosum) and fibre tracts (eg, inferior and superior longitudinal fasciculi)¹¹ suggesting large-scale structural degeneration and reorganisation across the brain after spinal cord injury.

The multi-parametric mapping protocol^{74,82} (figure 4), applied to patients with acute spinal cord injury (<2 months), revealed that spinal cord atrophy was paralleled by myelin-sensitive magnetisation transfer decreases,⁷ while in brain areas undergoing progressive atrophy, myelin content decreased and iron content increased.⁸⁻⁹ Specifically, compared with values derived from healthy controls, the atrophying primary motor cortex showed lower myelin content (reflected by decreased magnetisation transfer and R1⁸), while the atrophying thalamus showed iron deposition (reflected by increased R2*⁸). Moreover, within the cerebellum, accelerating atrophy was paralleled by a deceleration of myelin-sensitive magnetisation transfer.⁹ These bidirectional effects suggest that the changes in myelination⁷⁵ and iron content⁸³ reflect dynamic processes in the context of compensation, decompensation, and the compounding of functional deficits.⁵

Predicting outcome

Clinical recovery occurs most rapidly within the first 6 months and plateaus at approximately 2 years after spinal cord injury.⁸⁴ At present, neurorehabilitation shows the strongest evidence to foster functional recovery. Neurorehabilitation per se is believed to promote neurological

changes such as cortical and spinal cord neural circuit reorganisation, which are assumed to translate into improved function.⁶⁵ A few longitudinal quantitative MRI studies, within the range of 1–2 years after spinal cord injury follow-up, have found that better motor recovery was predicted by less cervical spinal cord atrophy^{9,10} and cord diffusion alterations.⁸⁵ Early after spinal cord injury (less than 2 months after injury) and at the level of the brain, greater motor recovery was associated with less cranial corticospinal tract atrophy.⁹ At the microstructural level, an absent or impaired pain sensation (eg, altered pin-prick score) was associated with a greater increase in grey matter R2* in the thalamus,⁹ a better motor recovery was predicted by a smaller decrease in magnetisation transfer in the somatosensory cortex,⁹ a greater decrease in R2* in the cerebellum,¹⁰ and increased functional connectivity between primary motor cortex and supplementary motor and premotor cortices.⁵⁷ Greater grey matter atrophy in the cerebellum was associated with impaired light-touch sensation,¹⁰ while greater increases in neuropathic pain intensity were associated with increased iron-sensitive R2* in the secondary sensory cortex, anterior cingulate cortex, and cerebellum.⁹

These longitudinal quantitative MRI studies within a 2-year follow-up point to three important and clinically relevant findings: while clinical recovery stops improving at about 2 years after spinal cord injury, progressive changes in macroscopic and microstructural markers continue; although macrostructural changes slow down at the level of the spinal cord, both macroscopic and microstructural measures of neurodegeneration show sustained changes in the brain; the changes that have the greatest predictive validity in relation to clinical outcome appear to be those observed at the level of the spinal cord, brainstem, and cortex (eg, spinal cord atrophy, cranial corticospinal tract atrophy, and lower magnetisation transfer in the primary motor cortex) over the first 6 months.^{9,10}

Implication for clinical trials

The usual primary endpoint of choice in spinal cord injury trials is an improvement in clinical outcome. However, neuroimaging biomarkers have the potential to supplement these clinical measures, as they are sensitive to neuronal changes even when they do not yet translate into clinical benefit. Clinical trials employ conventional MRI—eg, T2-weighted signal characteristics of the spinal cord (table)—to account for gross macrostructural changes at the lesion site in the spinal cord—for example, after stem cell interventions.⁸⁶⁻⁸⁹ However, signal intensity changes in conventional MRI do not correspond with the specific and quantitative measures of microstructural deficits—eg, demyelination and axonal degeneration.¹⁵ With potential treatments targeting repair of the injured spinal cord, it is imperative to improve clinical trial design and efficiency, optimise patient stratification in the context of disease heterogeneity, and identify sensitive outcome measures.

Study name	Intervention	Patients	Primary MRI outcome	Secondary MRI outcome	MRI techniques	
NCT01325103 ⁸⁶	Evaluation of autologous mesenchymal stem cell transplantation in patients with chronic spinal cord injury	Autologous mesenchymal stem cells	14 participants with chronic spinal cord injury	..	Lesion volume (before transplantation [baseline], and 3 months and 6 months after the transplantation)	Conventional MRI scan (T1-weighted and T2-weighted MRI)
NCT01624779 ⁸⁷	Intrathecal transplantation of autologous adipose tissue derived mesenchymal stem cells in patients with spinal cord injury	Autologous adipose tissue derived mesenchymal stem cells	15 participants with chronic spinal cord injury	Qualitative lesion assessment (at baseline and 8 months after the transplantation)	..	Conventional MRI scan (T1-weighted and T2-weighted axial and sagittal MRI)
NCT01739023 ⁸⁸	Safety of autologous human Schwann cells in subjects with subacute spinal cord injury	Autologous human Schwann cells	9 participants with subacute spinal cord injury (30 days after the injury)	..	Lesion volume (immediately after the injury, 1–2 days before the transplantation [baseline], day 1, 6 months, and 12 months after the transplantation)	Conventional MRI scan (T1-weighted and T2-weighted)
NCT03935321 ⁸⁹	Nogo inhibition in spinal cord injury (NISCI)	Antibodies against Nogo-A infusion in sub-acute spinal cord injury	132 patients with acute tetraplegic spinal cord injury (4–28 days after the injury)	..	Lesion volume, tissue bridges, and voxel-wise (microstructural) changes above the lesion (at baseline, 3 months, and 6 months after the intervention)	Conventional and quantitative MRI scan

We searched clinicaltrials.gov for clinical trials in spinal cord injury with MRI as an outcome measure.

Table: Clinical trials assessing treatments for patients with spinal cord injury with MRI as an outcome measure

Based on the advances in MRI, the application of neuroimaging biomarkers for spinal cord injury trials, which combine conventional MRI and quantitative MRI assessments, is now feasible. The application of neuroimaging biomarkers requires measures sensitive to the earliest changes following injury, which are quantifiable, and capture neural damage and plasticity. As quantitative MRI^{15,67,90} is sensitive to microstructural aspects of specific tissue classes of the CNS, these neuroimaging biomarkers are potentially sensitive to recovery processes and treatment responses.^{15,17,68} Moreover, they have the potential to provide short-term surrogate endpoints (ie, changes over 6–12 months), which may reduce the time and cost associated with novel drug development.^{91,92} Even if a therapeutic intervention would have an effect on an imaging outcome, such as halting atrophy, there is still some disconnect between changes in imaging outcomes and clinically meaningful recovery—the ultimate goal of a successful clinical trial. Thus, it might be useful to employ more than one imaging outcome in future trials to maximise understanding and interpretation of clinically meaningful findings.

Deploying advanced quantitative MRI methods in multicentre trials is challenging, however, requiring high-quality quantitative MRI techniques such as high-field MRI scanner (eg, 3 Tesla), advanced software versions, and sophisticated image post-processing pipelines to be implemented on the different scanner platforms from different manufacturers and at different clinical sites. Any

resulting differences or performance issues might reduce the potential benefits for evaluating new therapies. Moreover, clinical trials usually run over years, and hence scanner software and hardware upgrades, as well as scanner replacements, cannot always be avoided. Thus, there is a need to further improve intra-scanner and inter-scanner comparability of the quantitative MRI protocols. The feasibility of combining multicentre DTI data has been shown using different 3T MRI scanner models, software versions, and pulse sequences.^{93,94} However, critical parameters—such as noise, floor level and signal-to-noise floor ratio—have to be monitored and adjusted to increase the statistical power estimates.⁹³ Likewise, the multi-parametric mapping protocol was validated at 3T MRI scanner for use in multicentre studies based on standard FLASH sequences.⁷⁴ The multi-parametric mapping protocol is currently used in a phase 2 multicentre clinical trial (NCT03935321) investigating the neutralising effects of an anti-Nogo-A antibody treatment for spinal cord injury.⁸⁹ Hypothetical treatment effects, defined by slower longitudinal structural changes in these imaging measures, could be detectable over a realistic timescale (6 months after the injury) with potentially lower sample sizes (fewer than 50 participants per arm) than required for traditional clinical readouts.⁶⁴

Task-based and resting-state functional MRI

Much of the discussion above concerns the assessment of trauma-induced neurodegenerative changes in the brain

and spinal cord during recovery. Just as important is the ability to assess functional reorganisation associated with spinal cord injury. Functional reorganisation can be indirectly quantified, both in the brain and spinal cord, by means of fMRI that tracks task-dependent oxygen

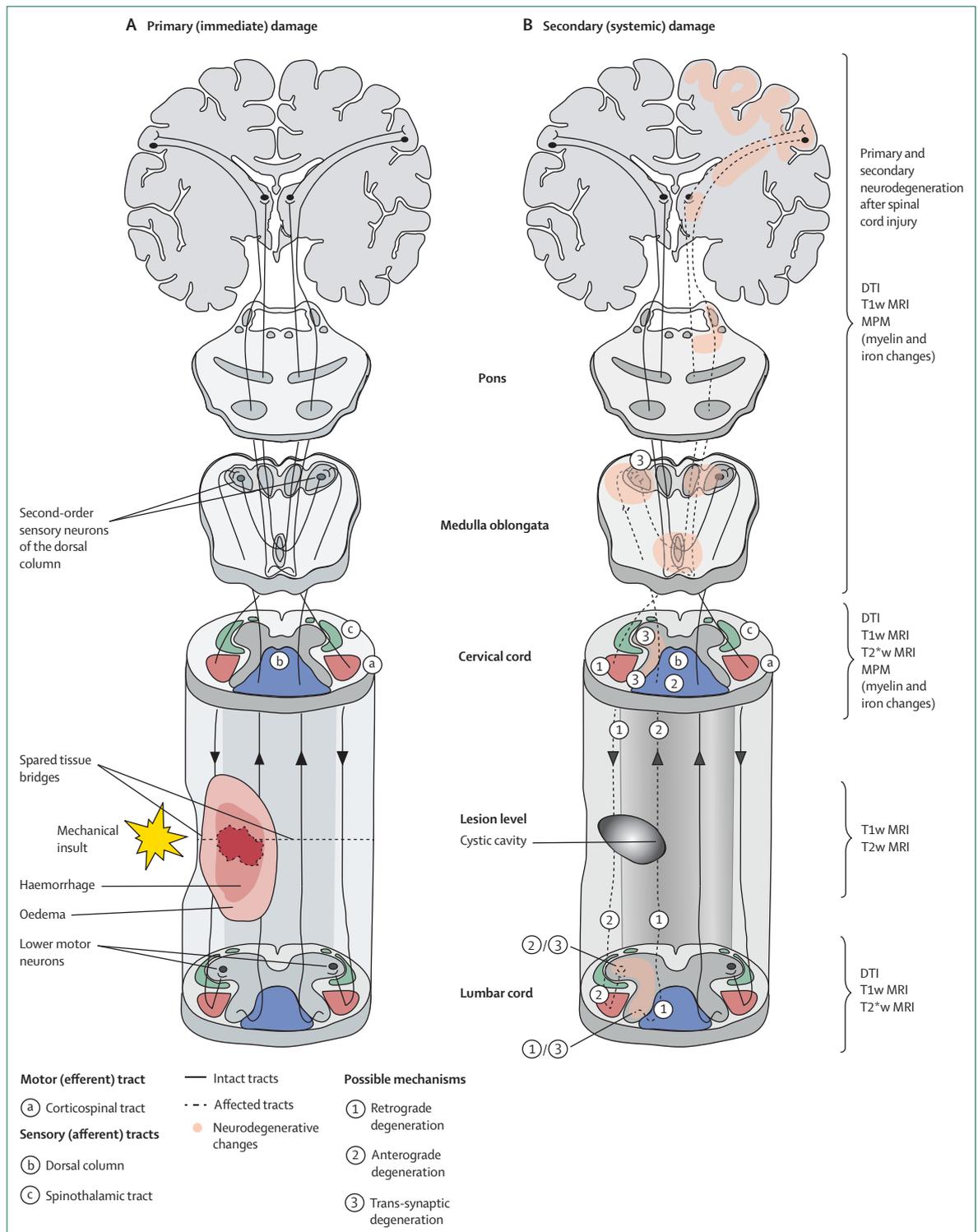
consumption that is indirectly related to neuronal activity (eg, blood oxygen dependent signal). In the absence of an explicit task, neuronal activity can also be studied by means of rs-fMRI analysis, which is based on low frequency spontaneous fluctuations in the blood oxygen

Figure 5: Overview of primary and secondary neurodegenerative processes occurring after spinal cord injury

Primary damage at the epicentre of the lesion occurs within hours after injury (A), and secondary (systemic) degenerative processes occur remotely (B), above, below, and at the primary injury site.

Sensory and motor tracts affected by the injury undergo anterograde or retrograde (depending on the location) axonal degeneration and accompanying demyelination.^{6,12,77} Lesion site shows the macrostructural evidence of primary intramedullary damage (eg, oedema and haemorrhage) and secondary changes, such as post-traumatic cyst cavities and spared tissue bridges.^{52,54} In the lumbar cord, 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.⁵⁹ Similarly, second-order sensory neurons of the spinothalamic and dorsal column medial lemniscus systems can also be affected by trans-synaptic degeneration.

At the brain level, atrophic changes are located within the brainstem,⁶² cranial corticospinal tracts, primary motor cortices, insula, anterior cingulate cortex, and thalamus.^{78,14} Some of these brain areas (eg, cortical and subcortical regions) present also with changes in myelin and iron content which are suggestive of demyelination and iron accumulation.⁹ Reproduced from David et al,⁵⁹ by permission of the American Academy of Neurology. DTI=diffusion tensor imaging. MPM=multi-parameter mapping. T1wMRI=T1-weighted MRI. T2wMRI=T2-weighted MRI. T2*w MRI=T2*-weighted MRI.



dependent signal. rs-fMRI provides an indirect measurement of connectivity that allows for characterisation of distinct functional networks in the brain or spinal cord.⁹⁵

Motor and sensory recovery after spinal cord injury are associated with functional reorganisation of the sensorimotor networks.^{96–98} fMRI studies after chronic spinal cord injury (time since injury > 2 years) have inferred cortical reorganisation through increased task-dependent activation in the primary motor cortex, cerebellum, and parietal lobe.⁹⁶ In 23 patients with chronic spinal cord injury, stimulation below the level of the injury resulted in activation in the relevant somatosensory cortices.⁹⁸ This observation suggests that preserved tissue bridges⁵² continue to carry functional information, but that they are insufficient to produce clinically meaningful activations or functions.

Spinal cord fMRI studies have also found that substantial task-related spinal activity, in response to stimuli, is retained above and below the injury site.^{22–24} This finding suggests that the spinal cord is actively engaged in plastic processes that can result in recovery of function. This retained activity might also contribute to the presence of neuropathic pain conditions,⁹⁷ which have been associated with maladaptive plasticity.⁶⁰ Thus, spinal fMRI is feasible in the clinical setting⁹⁹ and can identify changes in neural processing in relation to the location and extent of injury. Although the task-based fMRI and rs-fMRI are readily available on clinical MRI systems with a good spatial resolution, the analysis requires sophisticated post-processing tools⁸¹ and the interpretation of the functionally activated voxels remains challenging.¹⁶ Further advances in MRI hardware (sensitive MRI coils¹⁰⁰), MRI software (optimised localised shimming¹⁰¹), and other areas (eg, image postprocessing) are expected to increase the value of spinal cord fMRI as an imaging biomarker, in the near future, for probing reorganisation and plasticity induced by injury.

The application of rs-fMRI has gained momentum as it does not require an explicit task or active participation of the individual. Both in patients with acute^{19–21} spinal cord injury and in those with chronic^{102–104} spinal cord injury, connectivity changes occur across the motor system and in areas of cognitive control (eg, dorsal anterior cingulate cortex); the magnitude of change, in both groups, relates to the recovery of function.^{19–21} Thus, connectivity changes in brain networks might reflect compensatory strategies to overcome functional deficit. However, rs-fMRI is an emerging field featuring a wide range of pre-processing and analytical approaches, which make it difficult to compare the outcomes of the different studies. Although rs-fMRI studies in patients with spinal cord injury are technically feasible,^{25,95,105} such studies have not been conducted yet due to various technical issues, such as the influence of physiological noise and metallic implants. Nonetheless, rs-fMRI results obtained in healthy controls have consistently shown robust networks with extensive connectivity between spinal cord regions and across the

Panel 2: Overview of MRI techniques used in clinical practice or research and their corresponding outcome measures in spinal cord injury

- Sagittal and axial conventional T2-weighted MRI of the spinal cord at the injury level: extent of the intramedullary injury and lesion length;^{37,38,48} presence of haemorrhage,⁴⁴ oedema,⁴⁶ spinal cord compression²⁸
- Sagittal conventional T2-weighted MRI of the spinal cord at the injury level: preserved midsagittal tissue bridges^{52,54}
- T1-weighted MRI (above the injury level, cervical cord and brain): presence of cervical spinal cord and brain atrophy^{78,10,57,60,63}
- T2*-weighted MRI of the cervical and lumbar cord (remote from the injury site): presence of grey and white matter atrophy of the spinal cord^{6,59}
- Diffusion tensor imaging of the spinal cord and brain (remote from the injury site): presence of axonal degeneration and demyelination^{6,11,12,14,77}
- Multiparameter mapping of the cervical spinal cord and brain (above the injury level): Presence of demyelination and iron deposition^{7–10}
- Functional MRI of brain and spinal cord (remote from injury level): Integrity of functional networks and plasticity in the brain^{19–21} and spinal cord^{22–25}

brainstem and the spinal cord.^{89,106} On the basis of these results, rs-fMRI of the injured spinal cord would be expected to show regions with altered or absent connectivity to other spinal cord regions, as well as dynamic connectivity changes during recovery. This imaging biomarker would allow monitoring of functionally relevant changes within the spinal cord during the process of recovery.

Conclusions and future directions

Traumatic spinal cord injury causes permanent disability, and yet, despite advances in clinical management, many patients are left with substantial neurological impairment. Currently, intensive care measures, including blood pressure augmentation, neuroprotective approaches with anti-inflammatories, neurosurgical decompression and stabilisation, and intensive neurorehabilitation are the only interventions applied to promote partial recovery.⁸⁴ Understanding the pathophysiological sequelae would help to prevent and reduce disease burden and would facilitate the development of effective regenerative and neuroprotective treatments.

Both conventional MRI and quantitative MRI of the spinal cord and brain can guide diagnostic workup, identify predictors of recovery, elucidate spinal cord injury pathogenesis, and provide surrogate endpoints in future clinical trials (figure 5).^{16,56} Conventional T2-weighted sagittal and axial MRI scans are key methods to identify the extent of the intramedullary injury^{37,38} and to identify prognostic parameters such as intramedullary lesion length and preserved midsagittal tissue bridges.^{47,52,54}

Advanced quantitative MRI sequences, such as DTI and multi-parametric mapping, applied remotely from the injury, can identify microstructural changes such as axonal degeneration, demyelination, and iron deposition across the entire neuraxis.^{15,9} Combinations of serial conventional MRI and quantitative MRI represent key modalities for a better assessment of spinal cord function than clinical assessment, and further, for elucidating the relationship between clinical impairment and remote secondary changes in the spinal cord and brain. In addition, these quantifiable changes appear to have predictive validity, rendering them viable outcomes for interventional trials.^{9,64}

Neuroimaging of the spinal cord should be routinely performed in clinical practice and in interventional trials (panel 2). Conventional MRI should include both sagittal and axial views to assess the level and extent of injury within the first 48 hours (eg, BASIC score). These scans should be repeated 3–4 weeks later to quantify the dynamics of intramedullary lesion length and to identify the amount of preserved midsagittal tissue bridges. To investigate pathophysiological changes in the research setting, quantitative MRI methods, such as DTI and multi-parametric mapping, should be used, as these methods can probe microstructural changes of the spinal cord and brain. Neuroimaging outcome measures derived from both conventional MRI and quantitative MRI protocols should be considered as predictors of recovery.^{9,64} However, a careful evaluation of the variance caused by differences between MRI scanners and an assessment of reproducibility is required, adding to the complexity of multicentre trials.

Understanding of trauma-induced changes across the neuraxis remains incomplete (figure 5). A key requirement to assess plasticity in vivo is ultra-high spatial resolution on the order of hundreds of microns. To visualise and quantify ultra-scale tissue properties of grey and white matter, biophysical models that exploit symmetries in the organisation of microstructure are required. Emerging technological and imaging developments at higher field strengths (eg, 7T MRI scanner), such as improvements in radio frequency coil designs, pulse-sequence design, improved localised magnetic field shimming methods,¹⁰¹ suppression of MRI artifacts induced by orthopaedic implants,⁴³ and changes in data sampling schemes⁶⁷ will provide the necessary means for these biophysical models in future research. These models can combine multiple different MRI contrasts with different views on the underlying microstructure. Thus, addressing the intractable problem of accurately making inferences concerning the microstructure from single contrasts, by modelling the relative myelination of axons (eg, g-ratio mapping^{107,108}). The integration and unifying across the different contrasts and spatial scales (from micrometres to centimetres) is the subject of intensive and ongoing research in the MRI community.^{15,68} However, MRI contrasts remain indirect measures of changes in the microstructure and composition of the tissue. Therefore, knowledge about the

Search strategy and selection criteria

We searched PubMed for articles in English from Jan 1, 2013, to Jan 31, 2019. The search terms were “traumatic spinal cord injury” in combination with the terms “atrophy”, “demyelination”, “diffusion”, “conventional MRI”, “quantitative MRI”, “neurodegeneration”, “clinical trial”, “longitudinal”, and “MRI prediction”. Further articles were identified by searching the list of references cited in the articles that were reviewed. The final reference list was generated on the basis of relevance to the topics covered in this Review.

underlying changes is needed for interpretation of the non-invasive quantitative MRI data and for improving the biophysical models. Quantitative MRI data will need to undergo histological validation. Cross-validation of the multi-parametric mapping contrasts is currently performed in a multi-national ERA-NET funded consortium (understanding the mechanisms of atrophy associated with spinal cord injury: the application of MRI-based in vivo histology and ex vivo histology, known as hMRIofSCI) of tissue samples from experimental spinal cord injury models to shed light on the mechanistic underpinnings of changes observed with different MRI contrasts. Finally, multicentre and longitudinal studies, with large patient cohorts, that employ quantitative MRI of the spinal cord and brain, would be useful to better characterise primary and secondary disease changes, along with their dynamics, and also to support and extend current monocentric and mainly cross-sectional studies. Increasing our understanding of the sequelae after spinal cord injury will eventually allow prediction of individual trajectories of recovery.

Contributors

PF, MS, NW, KF, MF, AT, and AC contributed to the literature search and writing of the manuscript. PF and MS created the figures and table.

Declaration of interests

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References

- Ellingson BM, Salamon N, Holly LT. Imaging techniques in spinal cord injury. *World Neurosurg* 2014; **82**: 1351–58.
- Kumar Y, Hayashi D. Role of magnetic resonance imaging in acute spinal trauma: a pictorial review. *BMC Musculoskelet Disord* 2016; **17**: 310.
- Shah LM, Ross JS. Imaging of spine trauma. *Neurosurgery* 2016; **79**: 626–42.
- Fehlings MG, Martin AR, Tetreault LA, et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the role of baseline magnetic resonance imaging in clinical decision making and outcome prediction. *Glob Spine J* 2017; **7** (suppl): S221–30.
- Freund P, Friston K, Thompson AJ, et al. Embodied neurology: an integrative framework for neurological disorders. *Brain* 2016; **139**: 1855–61.
- Huber E, David G, Thompson AJ, Weiskopf N, Mohammadi S, Freund P. Dorsal and ventral horn atrophy is associated with clinical outcome after spinal cord injury. *Neurology* 2018; **90**: e1510–22.
- Grabher P, Callaghan MF, Ashburner J, et al. Tracking sensory system atrophy and outcome prediction in spinal cord injury. *Ann Neurol* 2015; **78**: 751–61.
- Freund P, Weiskopf N, Ashburner J, et al. MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: a prospective longitudinal study. *Lancet Neurol* 2013; **12**: 873–81.
- Ziegler G, Grabher P, Thompson A, et al. Progressive neurodegeneration following spinal cord injury. *Neurology* 2018; **90**: e1257–66.
- Seif M, Curt A, Thompson AJ, Grabher P, Weiskopf N, Freund P. Quantitative MRI of rostral spinal cord and brain regions is predictive of functional recovery in acute Spinal cord injury. *Neuroimage Clin* 2018; **20**: 556–63.
- Ilvesmäki T, Koskinen E, Brander A, Luoto T, Öhman J, Eskola H. Spinal cord injury induces widespread chronic changes in cerebral white matter. *Hum Brain Mapp* 2017; **38**: 3637–47.
- Koskinen E, Brander A, Hakulinen U, et al. assessing the state of chronic spinal cord injury using diffusion tensor imaging. *J Neurotrauma* 2013; **30**: 1587–95.
- Koskinen EA, Hakulinen U, Brander AE, Luoto TM, Ylinen A, Öhman JE. Clinical correlates of cerebral diffusion tensor imaging findings in chronic traumatic spinal cord injury. *Spinal Cord* 2014; **52**: 202–28.
- Jirjis MB, Vedantam A, Budde MD, Kalinosky B, Kurpad SN, Schmit BD. Severity of spinal cord injury influences diffusion tensor imaging of the brain. *J Magn Reson Imaging* 2016; **43**: 63–74.
- Cohen-Adad J. Microstructural imaging in the spinal cord and validation strategies. *Neuroimage* 2018; **182**: 169–83.
- Cadotte DW, Akbar MA, Fehlings MG, Stroman PW, Cohen-Adad J. What has been learned from magnetic resonance imaging examination of the injured human spinal cord: a canadian perspective. *J Neurotrauma* 2018; **35**: 1942–57.
- Trampel R, Bazin P-L, Pine K, Weiskopf N. In-vivo magnetic resonance imaging (MRI) of laminae in the human cortex. *Neuroimage* 2017; published online Sept 20. DOI:10.1016/j.neuroimage.2017.09.037.
- Lerch JP, van der Kouwe AJW, Raznahan A, et al. Studying neuroanatomy using MRI. *Nat Neurosci* 2017; **20**: 314–26.
- Hou J-M, Sun T-S, Xiang Z-M, et al. Alterations of resting-state regional and network-level neural function after acute spinal cord injury. *Neuroscience* 2014; **277**: 446–54.
- Zhu L, Wu G, Zhou X, Li J, Wen Z, Lin F. Altered spontaneous brain activity in patients with acute spinal cord injury revealed by resting-state functional MRI. *PLoS One* 2015; **10**: e0118816.
- Hawasli AH, Rutlin J, Roland JL, et al. Spinal cord injury disrupts resting-state networks in the human brain. *J Neurotrauma* 2018; **35**: 864–73.
- Stroman PW, Khan HS, Bosma RL, et al. Changes in pain processing in the spinal cord and brainstem after spinal cord injury characterized by functional magnetic resonance imaging. *J Neurotrauma* 2016; **33**: 1450–60.
- Zhong X-P, Chen Y-X, Li Z-Y, Shen Z-W, Kong K-M, Wu R-H. Cervical spinal functional magnetic resonance imaging of the spinal cord injured patient during electrical stimulation. *Eur Spine J* 2017; **26**: 71–77.
- Alexander M, Kozyrev N, Fingley CR, Richards JS. Altered spinal cord activity during sexual stimulation in women with SCI: a pilot fMRI study. *Spinal Cord Ser Cases* 2017; **3**: 16041.
- Barry RL, Conrad BN, Smith SA, Gore JC. A practical protocol for measurements of spinal cord functional connectivity. *Sci Rep* 2018; **8**: 16512.
- Kirshblum SC, Waring W, Biering-Sorensen F, et al. Reference for the 2011 revision of the international standards for neurological classification of spinal cord injury. *J Spinal Cord Med* 2011; **34**: 547–54.
- Kirshblum S, Waring W. Updates for the international standards for neurological classification of spinal cord injury. *Phys Med Rehabil Clin N Am* 2014; **25**: 505–17, vii.
- Tanadini LG, Hothorn T, Jones LAT, et al. Toward inclusive trial protocols in heterogeneous neurological disorders: prediction-based stratification of participants with incomplete cervical spinal cord injury. *Neurorehabil Neural Repair* 2015; **29**: 867–77.
- Tanadini LG, Steeves JD, Hothorn T, et al. Identifying homogeneous subgroups in neurological disorders: unbiased recursive partitioning in cervical complete spinal cord injury. *Neurorehabil Neural Repair* 2014; **28**: 507–15.
- Velstra I-M, Bolliger M, Tanadini LG, et al. Prediction and stratification of upper limb function and self-care in acute cervical spinal cord injury with the graded redefined assessment of strength, sensibility, and prehension (GRASSP). *Neurorehabil Neural Repair* 2014; **28**: 632–42.
- Velstra I-M, Curt A, Frotzler A, et al. Changes in strength, sensation, and prehension in acute cervical spinal cord injury. *Neurorehabil Neural Repair* 2015; **29**: 755–66.
- Itzkovich M, Shefler H, Front L, et al. SCIM III (spinal cord independence measure version III): reliability of assessment by interview and comparison with assessment by observation. *Spinal Cord* 2018; **56**: 46–51.
- Hatch MN, Cushing TR, Carlson GD, Chang EY. Neuropathic pain and SCI: identification and treatment strategies in the 21st century. *J Neurol Sci* 2018; **384**: 75–83.
- Petersen JA, Spiess M, Curt A, et al. Upper limb recovery in spinal cord injury: involvement of central and peripheral motor pathways. *Neurorehabil Neural Repair* 2017; **31**: 432–41.
- Jutzeler CR, Ulrich A, Huber B, Rosner J, Kramer JLK, Curt A. Improved diagnosis of cervical spondylotic myelopathy with contact heat evoked potentials. *J Neurotrauma* 2017; **34**: 2045–53.
- Hupp M, Pavese C, Bachmann LM, Koller R, Schubert M. Electrophysiological multimodal assessments improve outcome prediction in traumatic cervical spinal cord injury. *J Neurotrauma* 2018; **35**: 2916–23.
- Talbot JF, Whetstone WD, Readdy WJ, et al. The brain and spinal injury center score: a novel, simple, and reproducible method for assessing the severity of acute cervical spinal cord injury with axial T2-weighted MRI findings. *J Neurosurg Spine* 2015; **23**: 495–504.
- Aarabi B, Sansur CA, Ibrahim DM, et al. Intramedullary lesion length on postoperative magnetic resonance imaging is a strong predictor of ASIA impairment scale grade conversion following decompressive surgery in cervical spinal cord injury. *Neurosurgery* 2017; **80**: 610–20.

- 39 Jungmann PM, Agten CA, Pfirrmann CW, Sutter R. Advances in MRI around metal. *J Magn Reson Imaging* 2017; **46**: 972–91.
- 40 Sundseth J, Jacobsen EA, Kolstad F, Nygaard OP, Zwart JA, Hol PK. Magnetic resonance imaging evaluation after implantation of a titanium cervical disc prosthesis: a comparison of 1.5 and 3 Tesla magnet strength. *Eur Spine J* 2013; **22**: 2296–302.
- 41 Lee YH, Lim D, Kim E, Kim S, Song H-T, Suh J-S. Feasibility of fat-saturated T2-weighted magnetic resonance imaging with slice encoding for metal artifact correction (SEMAC) at 3T. *Magn Reson Imaging* 2014; **32**: 1001–15.
- 42 Song KD, Yoon YC, Park J. Reducing metallic artefacts in post-operative spinal imaging: slice encoding for metal artifact correction with dual-source parallel radiofrequency excitation MRI at 3.0T. *Br J Radiol* 2013; **86**: 20120524.
- 43 Worters PW, Sung K, Stevens KJ, Koch KM, Hargreaves BA. Compressed-sensing multispectral imaging of the postoperative spine. *J Magn Reson Imaging* 2013; **37**: 243–48.
- 44 Dalkilic T, Fallah N, Noonan VK, et al. Predicting injury severity and neurological recovery after acute cervical spinal cord injury: a comparison of cerebrospinal fluid and magnetic resonance imaging biomarkers. *J Neurotrauma* 2018; **35**: 435–45.
- 45 Martínez-Pérez R, Cepeda S, Paredes I, Alen JF, Lagares A. MRI prognostication factors in the setting of cervical spinal cord injury secondary to trauma. *World Neurosurg* 2017; **101**: 623–32.
- 46 Matsushita A, Maeda T, Mori E, et al. Subacute T1-low intensity area reflects neurological prognosis for patients with cervical spinal cord injury without major bone injury. *Spinal Cord* 2016; **54**: 24–28.
- 47 Le E, Aarabi B, Hersh DS, et al. Predictors of intramedullary lesion expansion rate on MR images of patients with subaxial spinal cord injury. *J Neurosurg Spine* 2015; **22**: 611–21.
- 48 Farhadi HF, Kukreja S, Minnema A, et al. Impact of admission imaging findings on neurological outcomes in acute cervical traumatic spinal cord injury. *J Neurotrauma* 2018; **35**: 1398–406.
- 49 Aarabi B, Olexa J, Chryssikos T, et al. Extent of spinal cord decompression in motor complete (American Spinal Injury Association Impairment Scale grades A and B) traumatic spinal cord injury patients: post-operative magnetic resonance imaging analysis of standard operative approaches. *J Neurotrauma* 2018; **36**: 862–76.
- 50 Haefeli J, Mabray MC, Whetstone WD, et al. Multivariate analysis of MRI biomarkers for predicting neurological impairment in cervical spinal cord injury. *Am J Neuroradiol* 2017; **38**: 648–55.
- 51 Mabray MC, Talbott JF, Whetstone WD, et al. Multidimensional analysis of magnetic resonance imaging predicts early impairment in thoracic and thoracolumbar spinal cord injury. *J Neurotrauma* 2016; **33**: 954–62.
- 52 Huber E, Lachappelle P, Sutter R, Curt A, Freund P. Are midsagittal tissue bridges predictive of outcome after cervical spinal cord injury? *Ann Neurol* 2017; **81**: 740–48.
- 53 Dhall SS, Haefeli J, Talbott JF, et al. Motor evoked potentials correlate with magnetic resonance imaging and early recovery after acute spinal cord injury. *Neurosurgery* 2018; **82**: 870–76.
- 54 O'Dell DR, Weber KA, Berliner JC, et al. Midsagittal tissue bridges are associated with walking ability in incomplete spinal cord injury: a magnetic resonance imaging case series. *J Spinal Cord Med* 2018; published online Oct 22. DOI:10.1080/10790268.2018.1527079.
- 55 Valloton K, Hubert E, Sutter R, Curt A, Hupp M, Freund P. Width and neurophysiologic properties of tissue bridges predict recovery after cervical injury. *Neurology* 2019; **92**: e2793–e802.
- 56 Farhadi HF, Minnema AJ, Talbott JF, Aarabi B. Letter to the editor: what has been learned from magnetic resonance imaging examination of the injured human spinal cord: a Canadian perspective. *J Neurotrauma* 2018; **36**: 1942–57.
- 57 Hou J, Xiang Z, Yan R, et al. Motor recovery at 6 months after admission is related to structural and functional reorganization of the spine and brain in patients with spinal cord injury. *Hum Brain Mapp* 2016; **37**: 2195–209.
- 58 Prados F, Ashburner J, Blaiotta C, et al. Spinal cord grey matter segmentation challenge. *Neuroimage* 2017; **152**: 312–29.
- 59 David G, Seif M, Huber E, et al. In vivo evidence of remote neural degeneration in the lumbar enlargement after cervical injury. *Neurology* 2019; **92**: e1367–77.
- 60 Jutzeler CR, Huber E, Callaghan MFMF, et al. Association of pain and CNS structural changes after spinal cord injury. *Sci Rep* 2016; **6**: 18534.
- 61 Chen Q, Zheng W, Chen X, et al. Brain gray matter atrophy after spinal cord injury: a voxel-based morphometry study. *Front Hum Neurosci* 2017; **11**: 211.
- 62 Grabher P, Blaiotta C, Ashburner J, Freund P. Relationship between brainstem neurodegeneration and clinical impairment in traumatic spinal cord injury. *NeuroImage Clin* 2017; **15**: 494–501.
- 63 Mole TB, MacIver K, Sluming V, Ridgway GR, Nurmikko TJ. Specific brain morphometric changes in spinal cord injury with and without neuropathic pain. *NeuroImage Clin* 2014; **5**: 28–35.
- 64 Seif M, Ziegler G, Freund P. Progressive ventricles enlargement and CSF volume increases as a marker of neurodegeneration in SCI patients: a longitudinal MRI study. *J Neurotrauma* 2018; **35**: 2941–2946.
- 65 Villiger M, Grabher P, Hepp-Reymond M-CM-C, et al. Relationship between structural brainstem and brain plasticity and lower-limb training in spinal cord injury: A longitudinal pilot study. *Front Hum Neurosci* 2015; **9**: 254.
- 66 Jutzeler CR, Freund P, Huber E, Curt A, Kramer JLK. neuropathic pain and functional reorganization in the primary sensorimotor cortex after spinal cord injury. *J Pain* 2015; **16**: 1256–126.
- 67 Stroman PW, Wheeler-Kingshott C, Bacon M, et al. The current state-of-the-art of spinal cord imaging: methods. *Neuroimage* 2014; **84**: 1070–81.
- 68 Edwards LJ, Kirilina E, Mohammadi S, Weiskopf N. Microstructural imaging of human neocortex in vivo. *Neuroimage* 2018; **182**: 184–206.
- 69 Brennan FH, Cowin GJ, Kurniawan ND, Ruitenber MJ. Longitudinal assessment of white matter pathology in the injured mouse spinal cord through ultra-high field (16.4T) in vivo diffusion tensor imaging. *Neuroimage* 2013; **82**: 574–85.
- 70 Vedantam A, Jirjis MB, Schmit BD, Wang MC, Ulmer JL, Kurpad SN. Diffusion tensor imaging of the spinal cord: insights from animal and human studies. *Neurosurgery* 2014; **74**: 1–8.
- 71 Novikov DS, Kiselev VG, Jespersen SN. On modeling. *Magn Reson Med* 2018; **79**: 3172–93.
- 72 Morawski M, Kirilina E, Scherf N, et al. Developing 3D microscopy with CLARITY on human brain tissue: Towards a tool for informing and validating MRI-based histology. *Neuroimage* 2018; **182**: 417–28.
- 73 Liewald D, Miller R, Logothetis N, Wagner H-J, Schüz A. Distribution of axon diameters in cortical white matter: an electron-microscopic study on three human brains and a macaque. *Biol Cybern* 2014; **108**: 541–57.
- 74 Weiskopf N, Suckling J, Williams G, et al. Quantitative multi-parameter mapping of R1, PD*, MT, and R2* at 3T: a multi-center validation. *Front Neurosci* 2013; **7**: 95.
- 75 Wang F, Li K, Mishra A, Gochberg D, Min Chen L, Gore JC. Longitudinal assessment of spinal cord injuries in nonhuman primates with quantitative magnetisation transfer. *Magn Reson Med* 2016; **75**: 1685–96.
- 76 Langkammer C, Krebs N, Goessler W, et al. Quantitative MR imaging of brain iron: a postmortem validation study. *Radiology* 2010; **257**: 455–62.
- 77 Vedantam A, Eckardt G, Wang MC, Schmit BD, Kurpad SN. clinical correlates of high cervical fractional anisotropy in acute cervical spinal cord injury. *World Neurosurg* 2015; **83**: 824–28.
- 78 De Leener B, Fonov VS, Collins DL, Callot V, Stikov N, Cohen-Adad J. PAM50: Unbiased multimodal template of the brainstem and spinal cord aligned with the ICBM152 space. *Neuroimage* 2018; **165**: 170–79.
- 79 David G, Freund P, Mohammadi S. The efficiency of retrospective artifact correction methods in improving the statistical power of between-group differences in spinal cord DTI. *Neuroimage* 2017; **158**: 296–307.
- 80 Mohammadi S, Freund P, Feiweier T, Curt A, Weiskopf N. The impact of post-processing on spinal cord diffusion tensor imaging. *Neuroimage* 2013; **70**: 377–85.
- 81 De Leener B, Lévy S, Dupont SM, et al. SCT: Spinal Cord Toolbox, an open-source software for processing spinal cord MRI data. *Neuroimage* 2017; **145**: 24–43.
- 82 Callaghan MF, Freund P, Draganski B, et al. Widespread age-related differences in the human brain microstructure revealed by quantitative magnetic resonance imaging. *Neurobiol Aging* 2014; **35**: 1862–72.

- 83 Sauerbeck A, Schonberg DL, Laws JL, McTigue DM. Systemic iron chelation results in limited functional and histological recovery after traumatic spinal cord injury in rats. *Exp Neurol* 2013; **248**: 53–61.
- 84 Ahuja CS, Wilson JR, Nori S, et al. Traumatic spinal cord injury. *Nat Rev Dis Prim* 2017; **3**: 17018.
- 85 Shanmuganathan K, Zhuo J, Chen HH, et al. Diffusion tensor imaging parameter obtained during acute blunt cervical spinal cord injury in predicting long-term outcome. *J Neurotrauma* 2017; **34**: 2964–71.
- 86 Mendonça MV, Larocca T, de Freitas Souza B, et al. Safety and neurological assessments after autologous transplantation of bone marrow mesenchymal stem cells in subjects with chronic spinal cord injury. *Stem Cell Res Ther* 2014; **5**: 126.
- 87 Hur JW, Cho T-H, Park D-H, Lee J-B, Park J-Y, Chung Y-G. Intrathecal transplantation of autologous adipose-derived mesenchymal stem cells for treating spinal cord injury: a human trial. *J Spinal Cord Med* 2016; **39**: 655–64.
- 88 Anderson KD, Guest JD, Dietrich WD, et al. Safety of autologous human Schwann cell transplantation in subacute thoracic spinal cord injury. *J Neurotrauma* 2017; **34**: neu.2016.4895.
- 89 Kucher K, Johns D, Maier D, et al. First-in-man intrathecal application of neurite growth-promoting anti-Nogo-A antibodies in acute spinal cord injury. *Neurorehabil Neural Repair* 2018; **32**: 578–89.
- 90 Zhou X, Sakaie KE, Debbins JP, et al. Quantitative quality assurance in a multicenter HARDI clinical trial at 3T. *Magn Reson Imaging* 2017; **35**: 81–90.
- 91 Martin AR, Aleksanderek I, Cohen-Adad J, et al. Translating state-of-the-art spinal cord MRI techniques to clinical use: a systematic review of clinical studies utilizing DTI, MT, MWF, MRS, and fMRI. *Neuroimage Clin* 2016; **10**: 192–238.
- 92 Cadotte DW, Fehlings MG. Will imaging biomarkers transform spinal cord injury trials? *Lancet Neurol* 2013; **12**: 843–44.
- 93 Zhou X, Sakaie KE, Debbins JP, Narayanan S, Fox RJ, Lowe MJ. Scan-rescan repeatability and cross-scanner comparability of DTI metrics in healthy subjects in the SPRINT-MS multicenter trial. *Magn Reson Imaging* 2018; **53**: 105–11.
- 94 Samson RS, Lévy S, Schneider T, et al. ZOOM or Non-ZOOM? Assessing spinal cord diffusion tensor imaging protocols for multi-centre studies. *PLoS One* 2016; **11**: e0155557.
- 95 Eippert F, Kong Y, Winkler AM, et al. Investigating resting-state functional connectivity in the cervical spinal cord at 3T. *Neuroimage* 2017; **147**: 589–601.
- 96 Solstrand Dahlberg L, Becerra L, Borsook D, Linnman C. Brain changes after spinal cord injury, a quantitative meta-analysis and review. *Neurosci Biobehav Rev* 2018; **90**: 272–93.
- 97 Jutzeler CR, Curt A, Kramer JLK. Relationship between chronic pain and brain reorganization after deafferentation: a systematic review of functional MRI findings. *Neuroimage Clin* 2015; **9**: 599–606.
- 98 Wrigley PJ, Siddall PJ, Gustin SM. New evidence for preserved somatosensory pathways in complete spinal cord injury: A fMRI study. *Hum Brain Mapp* 2018; **39**: 588–98.
- 99 Powers JM, Ioachim G, Stroman PW. Ten key insights into the use of spinal cord fMRI. *Brain Sci* 2018; **8**: 173.
- 100 Zhao W, Cohen-Adad J, Polimeni JR, et al. Nineteen-channel receive array and four-channel transmit array coil for cervical spinal cord imaging at 7T. *Magn Reson Med* 2014; **72**: 291–300.
- 101 Finsterbusch J, Sprenger C, Büchel C. Combined T2*-weighted measurements of the human brain and cervical spinal cord with a dynamic shim update. *Neuroimage* 2013; **79**: 153–61.
- 102 Min Y-S, Park JW, Jin SU, et al. Alteration of resting-state brain sensorimotor connectivity following spinal cord injury: a resting-state functional magnetic resonance imaging study. *J Neurotrauma* 2015; **32**: 1422–27.
- 103 Oni-Orisan A, Kaushal M, Li W, et al. Alterations in cortical sensorimotor connectivity following complete cervical spinal cord injury: a prospective resting-state fMRI Study. *PLoS One* 2016; **11**: e0150351.
- 104 Kaushal M, Oni-Orisan A, Chen G, et al. Evaluation of whole-brain resting-state functional connectivity in spinal cord injury: a large-scale network analysis using network-based statistic. *J Neurotrauma* 2017; **34**: 1278–82.
- 105 Barry RL, Smith SA, Dula AN, Gore JC. Resting-state functional connectivity in the human spinal cord. *Elife* 2014; **3**: e02812.
- 106 Sprenger C, Finsterbusch J, Buchel C. Spinal cord-midbrain functional connectivity is related to perceived pain intensity: a combined spino-cortical fMRI Study. *J Neurosci* 2015; **35**: 4248–57.
- 107 Duval T, Lévy S, Stikov N, et al. g-Ratio weighted imaging of the human spinal cord in vivo. *Neuroimage* 2017; **145**: 11–23.
- 108 Mohammadi S, Carey D, Dick F, et al. Whole-brain in-vivo measurements of the axonal G-Ratio in a group of 37 healthy volunteers. *Front Neurosci* 2015; **9**: 441.

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