Tissue bridges predict neuropathic pain emergence after spinal cord injury

Pfyffer, Dario; Vallotton, Kevin; Curt, Armin; Freund, Patrick

Abstract: OBJECTIVE: To assess associations between preserved spinal cord tissue quantified by the width of ventral and dorsal tissue bridges and neuropathic pain development after spinal cord injury. METHODS: This retrospective longitudinal study includes 44 patients (35 men; mean (SD) age, 50.05 (18.88) years) with subacute (ie, 1 month) spinal cord injury (25 patients with neuropathic pain, 19 pain-free patients) and neuroimaging data who had a follow-up clinical assessment at 12 months. Widths of tissue bridges were calculated from midsagittal T2-weighted images and compared across groups. Regression analyses were used to identify relationships between these neuroimaging measures and previously assessed pain intensity and pin-prick score. RESULTS: Pin-prick score of the 25 patients with neuropathic pain increased from 1 to 12 months (Δmean=10.08, 95% CI 2.66 to 17.50, p=0.010), while it stayed similar in pain-free patients (Δmean=2.74, 95% CI -7.36 to 12.84, p=0.576). They also had larger ventral tissue bridges (Δmedian=0.80, 95% CI 0.20 to 1.71, p=0.008) at 1 month when compared with pain-free patients. Conditional inference tree analysis revealed that ventral tissue bridges' width (>2.1 mm) at 1 month is the strongest predictor for 12 months neuropathic pain intensity (1.90±2.26 and 3.83±1.19, p=0.042) and 12 months pin-prick score (63.84±28.26 and 92.67±19.43, p=0.025). INTERPRETATION: Larger width of ventral tissue bridges—a proxy for spinothalamic tract function—at 1 month post-spinal cord injury is associated with the emergence and maintenance of neuropathic pain and increased pin-prick sensation. Spared ventral tissue bridges could serve as neuroimaging biomarkers of neuropathic pain and might be used for prediction and monitoring of pain outcomes and stratification of patients in interventional trials.

DOI: https://doi.org/10.1136/jnnp-2020-323150
ORIGINAL RESEARCH

Tissue bridges predict neuropathic pain emergence after spinal cord injury

Dario Pfyffer, Kevin Vallotton, Armin Curt, Patrick Freund, DP and KV contributed equally.

ABSTRACT

Objective To assess associations between preserved spinal cord tissue quantified by the width of ventral and dorsal tissue bridges and neuropathic pain development after spinal cord injury.

Methods This retrospective longitudinal study includes 44 patients (35 men; mean (SD) age, 50.05 (18.88) years) with subacute (ie, 1 month) spinal cord injury (25 patients with neuropathic pain, 19 pain-free patients) and neuroimaging data who had a follow-up clinical assessment at 12 months. Widths of tissue bridges were calculated from midsagittal T2-weighted images and compared across groups. Regression analyses were used to identify relationships between these neuroimaging measures and previously assessed pain intensity and pin-prick score.

Results Pin-prick score of the 25 patients with neuropathic pain increased from 1 to 12 months (Δmean=10.08, 95% CI 2.66 to 17.50, p=0.010), while it stayed similar in pain-free patients (Δ=2.74, 95% CI −7.36 to 12.84, p=0.576). They also had larger ventral tissue bridges (Δmedian=0.80, 95% CI 0.20 to 1.71, p=0.008) at 1 month when compared with pain-free patients. Conditional inference tree analysis revealed that ventral tissue bridges’ width (≤2.1 or >2.1 mm) at 1 month is the strongest predictor for 12 months neuropathic pain intensity (1.90±2.26 and 3.83±1.19, p=0.042) and 12-months pin-prick score (63.84±28.26 and 92.67±19.43, p=0.025).

Interpretation Larger width of ventral tissue bridges—a proxy for spinothalamic tract function—at 1 month post spinal cord injury is associated with the emergence and maintenance of neuropathic pain and increased pin-prick sensation. Spared ventral tissue bridges could serve as neuroimaging biomarkers of neuropathic pain and might be used for prediction and monitoring of pain outcomes and stratification of patients in interventional trials.

INTRODUCTION

Spinal cord injury (SCI) is a devastating and life-changing event. In most cases, it produces immediate and permanent sensory, motor and autonomic dysfunction below the level of injury, resulting in a reduced quality of life. Along with the functional deficits, the majority of patients develops neuropathic pain (NP) at and/or below the level of injury. NP usually arises early after SCI and is often refractory to treatment and normally persists over years with a potentially increasing intensity. Although the origin of NP is largely unknown, it is thought to arise at least partially in the spinal cord. Preserved tissue bridges adjacent to the intramedullary lesion cavity, which can be identified in all patients with incomplete SCI, are permissive for electrophysiological information flow and the size of which is predictive of functional recovery. Importantly, NP below the level of injury develops over time. This suggests that fractions of sensory pathways within preserved tissue bridges become active over time and may affect both ascending and descending modulatory systems. Moreover, hyperactive dorsal horn neurons of the spinothalamic tract have been identified as a possible pathobiological substrate. Interestingly, recovery of spinothalamic tract function (eg, pin-prick score) is enhanced in patients with SCI suffering from NP and its magnitude has been associated with pain intensity.

Based on neuroimaging, the location and width of spared midsagittal tissue bridges have been shown to be critically involved in the recovery of sensorimotor function. For example, dorsal tissue bridges covering the dorsal columns are predictive of sensory evoked potentials and recovery of light-touch function and may transmit pain signals evoked by normally non-painful stimuli (ie, allo-dynia). Ventral tissue bridges have been linked to recovery of motor function and cover, next to the anterior corticospinal tract, also portions of the anterior spinothalamic tract. Thus, the question arises whether width of ventral and dorsal tissue bridges can predict the emergence and/or maintenance of NP after SCI.

This study aimed to explore the value of spared midsagittal tissue bridges (ventral and dorsal) derived from conventional T2-weighted (T2w) serial scans in predicting the emergence and maintenance of SCI-related NP. Therefore, we investigated the relationships between the width of ventral and dorsal tissue bridges and pain intensity as well as its clinical characteristics.

METHODS

Experimental design

In this retrospective study, we included 44 patients with subacute SCI (28 tetraplegic and 16 paraplegic patients) who were admitted consecutively to the Balgrist University Hospital (Zurich, Switzerland) between May 1996 and January 2019. Of these 44 patients, all had a follow-up clinical assessment and 32 had a neuroimaging follow-up visit at 12 months post-SCI (figure 1).

We used 1 month and 12 months neuroimaging, neuropathic pain and clinical data from these patients to investigate group differences and clinicopathological relationships as well as outcome predictions by means of regression analysis and unbiased recursive partitioning (URP). Variables...
of interest included were lesion parameters as well as pain and clinical outcome measures at 1 month and 12 months follow-up.

We excluded patients with pre-existing neurological or mental disorders or brain lesions, as well as patients with MRI contraindications.

Tissue bridge data from a small subset of the study population was previously reported in a different context.9-11

Clinical assessments
All patients were clinically examined using a comprehensive clinical protocol including 1) the International Standards for Neurological Classification of Spinal Cord Injury protocol22 and 2) the European Multicenter Study about Spinal Cord Injury (EMSCI) pain questionnaire (V4.2, http://www.emsci.org/). On the EMSCI questionnaire, patients rate various aspects of pain (eg, current pain intensity, mean and maximal pain intensity during the last week before the assessment, location and quality of pain, intensity of allodynia and paraesthesia). The pain intensity was quantified using an 11-point numeric rating scale with ‘0’ indicating no pain and ‘10’ indicating the worst imaginable pain. Data from the EMSCI pain questionnaire was available for 43 patients with SCI at 1 month (24 patients with NP, 19 pain-free patients) and 42 patients at 12 months post-SCI (28 patients with NP, 14 pain-free patients). One patient and two patients without EMSCI pain questionnaire at 1 month and 12 months, respectively, reported to suffer from NP.

Image acquisition
All study participants underwent MRI on 1.5 or 3 T Philips (Philips Healthcare, Best, The Netherlands), Siemens (Siemens Healthcare, Erlangen, Germany) or GE (GE Medical Systems, Waukesha, Wisconsin, USA) scanners. A 32-channel receive spine coil integrated in the table was used with all scanners. The anatomical MRI protocol consisted of standard sagittal T1-weighted, sagittal T2w and axial T2w clinical scans obtained at the lesion level. Repetition time (TR), echo time (TE) and flip angle (FA) of the sagittal T2w clinical sequences were used as follows: at 1.5 T (TR=4138 ms; TE=109 ms; FA=149 degrees) and at 3 T (TR=3938 ms; TE=97 ms; FA=153 degrees). The echo train length was 19 at 1.5 T and 17 at 3 T. At 1.5 and 3 T, the field of view was set to 330 mm×330 mm and 220 mm×220 mm, respectively. To reduce metal artefacts, readout bandwidths were increased at 1.5 T (415 Hz/pixel) and at 3 T (751 Hz/pixel). The spatial resolution of sagittal T2w images was 0.55 mm×0.55 mm×2.75 mm at 1.5 T and 0.57 mm×0.57 mm×2.75 mm at 3 T. The midsagittal slices of sagittal T2w scans were the ones used for lesion segmentation analysis.9-11

Image analysis
Together with oedema and haemorrhage, intramedullary damage manifests as changes of signal intensity on T2w scans.21 Crucially, hyperintense signal changes in the subacute phase reliably reflect neural damage within the spinal cord9-10 rather than oedema and haemorrhage which is harder to differentiate in the acute phase after SCI. Patients’ neuroimaging data were only included if T2w scans showed a clearly visible lesion (ie, hyperintense signal)—if present—on the midsagittal slice whereas scans with insufficient image quality or lesion visibility due to metal artefacts were excluded.9-14 Neuroimaging data with appropriate image quality and lesion visibility was available for 44 patients with subacute SCI of which 32 had a follow-up scan at 12 months post-SCI.

Lesion segmentation was performed manually and blinded to patient identity and scan time point by rater DP. We used the Jim software (V7.0, Xinapse Systems, Aldwincle, UK) to delineate the lesion on the midsagittal slice from sagittal T2w scans. This enabled us to assess the lesion area, its rostro-caudal lesion length, anterior-posterior lesion width and ventral and dorsal tissue bridges, the sum of both reflecting the total width of tissue bridges (ie, hypointense regions between the relatively hyperintense adjacent cystic cavity within the spinal cord and the cerebrospinal fluid).9-10

Statistical analysis
Statistical analysis was performed using Stata software (V4.2; StataCorp, College Station, Texas, USA). We used unpaired two-tailed t-tests to compare patients with SCI with NP and pain-free patients with SCI regarding their age at 1 month scanning time point and the time interval between injury and 1 month scan. Paired two-tailed t-tests were used for comparison of midsagittal tissue bridges (ie, total, ventral and dorsal), pin-prick score and mean pain intensity at 1 month and 12 months post-SCI.

We applied Mann-Whitney U tests for pairwise comparisons of patient groups regarding their pin-prick score and width of midsagittal tissue bridges (ie, total, ventral and dorsal) at 1 month and 12 months post-SCI as well as rate of change in pin-prick score from 1 month to 12 months.

We used multivariable linear regression analysis to investigate associations between imaging measures (ie, width of ventral midsagittal tissue bridges) and mean pain intensity at 1 month. One month quantitative lesion measures were also used with the same model to predict mean NP intensity and recovery of pain sensation (ie, pin-prick score) at 12 months follow-up. Age and sex were included as covariates of no interest in the regression models to adjust for linear age and sex dependency. Models including ventral tissue bridges were also corrected for dorsal
Spinal cord injury

tissue bridges. Prediction models were furthermore adjusted for 1 month clinical scores (eg, pin-prick score at 1 month). Potential confounders were only retained if the covariates were significant or if they had a substantial effect on the correlation coefficient of interest. Results were regarded as significant when the p values were ≤0.05 and CIs were set to 95%.

We further used a widely used24-28 unbiased recursive partitioning technique called conditional inference tree (URP-CTREE)29 implemented in the ‘party’ package within R30 (V.3.4.3). URP-CTREE performs a prospective prediction-based stratification of a patient population with regard to predefined outcome variables. URP-CTREE is a tree-structured regression model for independence tests between sets of predictors (eg, early imaging parameters) and specified future clinical end points (eg, pain sensation measures). We used 1 month ventral and dorsal midsagittal tissue bridges’ widths as predictors for mean neuropathic pain intensity and pin-prick score at 1 month and 12 months. The URP-CTREE algorithm dichotomously separates an initial heterogeneous patient population into more homogeneous and well-defined pairs of subgroups (ie, nodes) with respect to the future clinical outcomes specified. Subgroups that will be further separated are referred to as inner nodes. Separation goes on as long as one of the predictor variables is found to be associated with the predefined clinical end point and to split the group into two disjoint subgroups with a p value ≤0.05. The algorithm is designed in a way that every separation is based on the singular most significant predictor with the aim to maximise the difference between the newly formed subgroups. Splitting groups is continued as long as there is any significant predictor value.

Data availability
Anonymised data of this study are available on request from the corresponding author.

RESULTS

Demographics and clinical characteristics

Forty-four patients with SCI (n=35 men (79.5%)) with a mean (±SD) age of 50.05±18.88 years were included. Patients with NP (50.40±17.38 years, n=25) and pain-free patients (49.58±21.17 years, n=19) did not differ in their age at 1 month (Δmean=−0.82, 95% CI −12.55 to 10.91, p=0.888).

The patients’ time interval between injury and 1 month scan (ie, subacute stage) was 32.95±16.85 days. There was no difference in time since injury (Δmean=4.80, 95% CI −5.56 to 15.17, p=0.355) between patients with NP (30.88±17.55 days, n=25) and pain-free patients (35.68±15.93 days, n=19).

Over time, NP developed in six initially pain-free patients whereas one patient with NP at baseline reported to be NP-free at follow-up. Patients with NP at 1 month (56.8%) and dorsal tissue bridges at 1 month were associated with a higher mean pain intensity at 1 month (coefficient=0.23, 95% CI 0.07 to 0.39, p=0.005, R²=0.179, n=43, figure 3A), adjusted for dorsal tissue bridges and age.

Within the pain-free group, width of total tissue bridges was similar at 1 month and 12 months follow-up (Δmean=−0.48 mm, 95% CI −1.02 to 0.07 mm, p=0.081). Width of ventral tissue bridges was comparable at 1 month and 12 months in patients with NP (Δmean=−0.04 mm, 95% CI −0.39 to 0.31 mm, p=0.816, figure 2C) and pain-free patients (Δmean=−0.33 mm, 95% CI −0.73 to 0.07 mm, p=0.097). Similarly, the rate of change in width of dorsal tissue bridges over time was similar for patients with NP (Δmean=−0.32 mm, 95% CI 0.00 to 0.65 mm, p=0.053, figure 2D) and pain-free patients (Δmean=−0.15 mm, 95% CI −0.43 to 0.13 mm, p=0.280).

Association of tissue bridges and clinical pain measures at 1 month

Larger ventral tissue bridges at 1 month were associated with a higher mean pain intensity at 1 month (coefficient=0.23, 95% CI 0.07 to 0.39, p=0.005, R²=0.179, n=43, figure 3A), adjusted for dorsal tissue bridges and age.

URP-CTREE analysis led to a partition of the entire cohort (p=0.013, n=43, figure 3B) into two terminal nodes with regard to the patients’ mean pain intensities (ranging from 0 to 10) at 1 month, according to the 1 month width of ventral tissue bridges being ≤2.1 mm (n=31, node 2) or >2.1 mm (n=12, node 3). The two subgroups presented 1 month mean NP intensities of 1.45±2.05 and 3.58±1.83, respectively.

Association of tissue bridges and clinical pain measures at 12 months

Larger ventral tissue bridges at 1 month were associated with a higher mean NP intensity (coefficient=0.20, 95% CI 0.03 to 0.36, p=0.022, R²=0.131, n=42) and higher pin-prick score at 12 months (coefficient=0.03, 95% CI 0.01 to 0.04, p<0.001, R²=0.355, n=44), independent of dorsal tissue bridges, age and 1 month clinical score. When looking at subgroups separately,
patients with NP (coefficient=0.03, 95% CI 0.01 to 0.04, p=0.007, R2=0.385, n=30, figure 4A), but not pain-free patients (coefficient=−0.01, 95% CI −0.03 to 0.02, p=0.525, R2=−0.386, n=14) showed a positive relationship between width of ventral tissue bridges at 1 month and pin-prick score at 12 months.

URP-CTREE analysis separated the entire cohort (p=0.042, n=42) into two terminal nodes with regard to the patients' mean pain intensities at 12 months, according to the 1 month width of ventral tissue bridges being ≤2.1 mm (n=30, node 2) or >2.1 mm (n=12, node 3). The two subgroups presented 12 months mean pain intensities of 1.90±2.26 and 3.83±1.19, respectively. The URP-CTREE algorithm also identified 1 month ventral tissue bridges as a predictor for 12 months pin-prick score, its width separating the initial group (p=0.025, n=44, figure 4B) into two nodes with ≤2.1 mm (n=32, node 2) and >2.1 mm (n=12, node 3) in ventral tissue bridges’ width. The two subgroups presented 12 months pin-prick scores of 63.84±28.26 and 92.67±19.43, respectively.

In a second step, the algorithm identified width of dorsal tissue bridges as a second predictor variable (p=0.030) for the subgroup showing a width of ventral tissue bridges ≤2.1 mm and separated it into two more nodes with ≤1.62 mm (n=24, node 3) and >1.62 mm (n=8, node 4) in dorsal tissue bridges’ width. The two subgroups presented 12 months pin-prick scores of 56.58±27.18 and 85.63±19.66, respectively.

DISCUSSION

This study demonstrates the potential involvement of spared ventral tissue bridges in the development and maintenance of NP following SCI. In particular, patients with NP had larger total and ventral tissue bridges when compared with pain-free patients, their width at 1 month being a predictor for a higher NP intensity and higher pin-prick score at 12 months.

As expected, about two-third (68.2%) of the patients with SCI enrolled in this study developed NP of which more than half had already NP at the subacute stage (56.8%). Hari et al reported that enhanced recovery of spinothalamic tract function (ie, pin-prick) is associated with NP after SCI, and Hatem et al showed that there were less spinothalamic tract impairments in patients with syringomyelia with both spontaneous and evoked pain when compared with patients with spontaneous pain only. In our study, recovery of pin-prick score (ie, clinical measure for pain) at 12 months post-SCI was significantly related to the width of ventral tissue bridges at 1 month.

Table 1  Dynamic change of width of total, ventral and dorsal tissue bridges

|                      | Patients with SCI with NP (n=17) | Pain-free patients with SCI (n=15) |
|----------------------|----------------------------------|-----------------------------------|
| Width of tissue bridges | 1 month                          | 12 months                         | 1 month                          | 12 months                      |
| Total, mean (SD), mm  | 2.45 (1.64)                      | 2.73 (1.48)                       | 1.60 (1.33)                      | 1.12 (1.17)                    |
| Ventral, mean (SD), mm| 1.46 (1.29)                      | 1.42 (0.94)                       | 0.75 (0.86)                      | 0.42 (0.68)                    |
| Dorsal, mean (SD), mm | 0.99 (1.20)                      | 1.31 (1.29)                       | 0.85 (0.74)                      | 0.70 (0.66)                    |

NP, neuropathic pain; SCI, spinal cord injury.
Spinal cord injury pain sensation) paralleled the emergence of NP and its intensity while no substantial change was observed in the pain-free group. This supports the notion that recovery of spinothalamic function is involved in the emergence and/or maintenance of NP.

Ventral tissue bridge measures are likely to cover the anterior spinothalamic tract. Interestingly, patients with NP had greater width of ventral tissue bridges at baseline and follow-up, while the width of dorsal tissue bridges was similar between groups at both time points. Crucially, larger ventral tissue bridges at 1 month are associated with higher mean pain intensities at 1 month.
month and 12 months, independent of dorsal tissue bridges. By means of URP-CTREE analysis, we further identified ventral tissue bridges at 1 month as predictors of recovery of pin-prick scores at 12 months with a cut-off value of 2.1 mm. Next to the implication of ventral tissue bridges, dorsal tissue bridges might also be involved in the generation of Ne. To examine pin-prick sensation (ie, clinical pain measure), the patient needs to distinguish a sharp and a dull end of a pin when blindfolded. Thus, next to spinothalamic tract function, the medial lemniscal system running through the dorsal columns (ie, dorsal tissue bridges) is also involved as it conveys the information for tactile discrimination. Thus, dorsal tissue bridges likely involve second-order neurons of the spinothalamic tract within the substantia gelatinosa of the spinal cord dorsal horn. Sparing of these neurons could be of high importance for maintenance or recovery of clinical pain sensation (ie, pin-prick score) at dermatomes corresponding to the lesioned spinal cord levels. Finnerup et al reported that patients with SCI with NP, when compared with pain-free patients with SCI, showed more sensory hypersensitivity in lesion level-related dermatomes, suggesting a key role of sensory neuronal hyperexcitability in NP following SCI.

This study has limitations. First of all, this study is a retrospective monocentric study with specified inclusion criteria. This likely represents a bias source as the study design resulted in a homogeneous data set, but might not reflect the general SCI population. Future studies would therefore benefit from a prospective multicentric design including larger patient numbers. Furthermore, women and men were not equally distributed in our patient cohort. However, this is also not the case for the general SCI population. Quantification of tissue bridges was only performed on midsagittal but not parasagittal slices. Further quantification of lateral tissue bridges on T2w axial slices was also not possible due to a low spatial resolution. This limits information about specific spared tracts and potential correlations with their corresponding functions. These points should be addressed in future studies to further explore the already promising method of tissue bridges characterisation with its reliable quantification already at early stages after SCI and even in the presence of metal artefacts near the lesion. The EMSCI pain questionnaire rather crudely assesses NP characteristics. Future studies would benefit from using more detailed pain assessments including drawings of the body with the extent, quality and intensity of the perceived pain at different body parts. Finally, even though our sample size was rather large, including more patients in the URP-CTREE analysis would increase the chances of reliably predicting future clinical end points and stratifying a heterogeneous patient cohort into homogeneous subgroups via multilevel inference trees and corresponding predictor variables.

This study identifies spared tissue bridges as quantifiable neuroimaging biomarkers assessed by conventional MRI addressing the emergence and maintenance of NP. Specifically, we identified 1 month width of ventral tissue bridges as the strongest predictor of NP intensity and pin-prick score at 12 months post-SCI. Thus, ventral tissue bridges represent MRI metrics, which could be readily implemented in the daily clinical routine to serve as promising, reliable and time-saving neuroimaging biomarkers for the monitoring of NP and for stratification of patient subgroups in interventional clinical trials.

Acknowledgements The authors would like to thank the whole European Multicenter study about Spinal Cord Injury (EMSCI) Study Group and in particular René Koller for the assistance with the EMSCI database. The authors would like to thank the staff of the Department of Neurology and Radiology at the Balgrist University Hospital for their great help. The authors would also like to thank all study participants for their time spent and contribution and DP, Balgrist University Hospital, ETH and University of Zurich and Kevin Vallotton, MD, Balgrist University Hospital, University of Zurich for conducting statistical analysis.

Contributors DP: study concept and design; acquisition, analysis and interpretation of data; writing the manuscript. KV: study concept and design; acquisition, analysis and interpretation of data; writing the manuscript. AC: critical revision of manuscript for intellectual content. PF: study concept and design; study supervision; critical revision of manuscript for intellectual content.

Funding This research was supported by Wings for Life, Austria (WFL-CH-007/14), the International Foundation for Research in Paraplegia (IRP-P158), the EU project (Horizon2020 ‘NSFC’ grant agreement no. 681094) and the framework of ERA-NET NEURON (BMMP 01EW1711A and B). PF is funded by an SNF Excellenza Professorial Fellowship grant (PCEFP3_181362/1). Open access of this publication is supported by the Swiss National Science Foundation (Grant 091593/210/2).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The local ethics committee approved the study protocol (EK-2010-0271), which was conducted in accordance with the Declaration of Helsinki and all patients gave informed, written consent prior to study enrolment.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Anonymised data of this study are available on request from the corresponding author.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Dario Pfyffer http://orcid.org/0000-0002-2406-9251

REFERENCES

1 Ahuja CS, Wilson JR, Nori S, et al. Traumatic spinal cord injury. Nat Rev Dis Primers 2017;3:17018.
2 Burke D, Fullen BM, Stokes D, et al. Neuropathic pain prevalence following spinal cord injury: a systematic review and meta-analysis. Eur J Pain 2017;21:29–44.
3 Störmer S, Gerner H, Grüninger W, et al. Chronic pain dysaesthesiae in spinal cord injury patients: results of a multicentre study. Spinal Cord 1997;35:446–55.
4 Mehta S, Orenzuck K, McIntyre A, et al. Neuropathic pain post spinal cord injury Part 1: systematic review of physical and behavioral treatment. Top Spinal Cord Inj Rehabil 2013;19:61–77.
5 Gruener H, Zeilig G, Gaidukov E, et al. Biomarkers for predicting central neuropathic pain occurrence and severity after spinal cord injury: results of a long-term longitudinal study. Pain 2020;161:545–56.
6 Knüfer D, Callaghan MJ, et al. Tracking sensory system atrophy and interpretation of pain outcome in spinal cord injury. Ann Neurol 2015;78:751–61.
7 Tsuda M. Microglia in the spinal cord and neuropathic pain. J Diabetes Investig 2016;7:17–26.
8 Gwak YS, Hulsebosch CE, Leem JW. Neuronal-Glia-interactions maintain chronic neuropathic pain after spinal cord injury. Neural Plast 2017;2017:2406089.
9 Huber E, Lachappelle P, Sutter R, et al. Are midsagittal tissue bridges predictive of outcome after cervical spinal cord injury? Ann Neurol 2017;81:740–8.
10 Pfyffer D, Huber E, Sutter R, et al. Tissue bridges predict recovery after traumatic and ischemic thoracic spinal cord injury. Neurology 2019;93:e1550–60.
11 Vallotton K, Huber E, Sutter R, et al. Width and neurophysiologic properties of tissue bridges predict recovery after cervical injury. Neurology 2019;92:e2733–802.
12 Finnerup NB, Norritink C, Trok K, et al. Phenotypes and predictors of pain following traumatic spinal cord injury: a prospective study. J Pain 2014;15:40–4.
13 Watson G, Lee BB, Engel S, et al. Residual spinthalamic tract pathways predict development of central pain after spinal cord injury. Brain 2008;131:2387–400.
14 Wrigley PJ, Siddall PJ, Gustin SM. New evidence for preserved somatosensory pathways in complete spinal cord injury: a fMRI study. Hum Brain Mapp 2016;39:588–98.
15 Wrigley PJ, Press SR, Gustin SM, et al. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain 2009;141:52–9.
16 Hari AR, Wydendoller K, Dokkoldal P, et al. Enhanced recovery of human spinthalamic function is associated with central neuropathic pain after SCI. Exp Neurol 2009;216:428–30.
17 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 2020;43:268–71.
**Spinal cord injury**

18 Kim J, Back SK, Yoon YW, et al. Dorsal column lesion reduces mechanical allodynia in the induction, but not the maintenance, phase in spinal hemisection rats. *Neurosci Lett* 2005;379:218–22.

19 Sun H, Ren K, Zhong CM, et al. Nerve injury-induced tactile allodynia is mediated via ascending spinal dorsal column projections. *Pain* 2001;90:105–11.

20 Welniarz Q, Dusart I, Rosé E. The corticospinal tract: evolution, development, and human disorders. *Dev Neurobiol* 2017;77:810–29.

21 Saliani A, Peraud B, Duval T, et al. Axon and myelin morphology in animal and human spinal cord. *Front Neuroanat* 2017;11:129.

22 Kirshblum SC, Burns SP, Biering-Sørensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). *J Spinal Cord Med* 2011;34:535–46.

23 Goldberg AL, Daffner RH, Schapiro RL. Imaging of acute spinal trauma: an evolving multi-modality approach. *Clin Imaging* 1990;14:11–16.

24 De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective Consortium analysis. *Lancet Oncol* 2010;11:753–62.

25 Brown AW, Malec JF, Hothorn T, et al. Toward inclusive trial protocols in heterogeneous neurological disorders: Prediction-Based stratification of participants with incomplete spinal cord injury. *Neurorehabil Neural Repair* 2015;29:867–77.

26 Tanadini LG, Hothorn T, Jones LAT, et al. Toward inclusive trial protocols in heterogeneous neurological disorders: Prediction-Based stratification of participants with incomplete spinal cord injury. *Neurorehabil Neural Repair* 2015;29:867–77.

27 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.

28 Velstra IM, 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.

29 Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. *J Comput Graph Stat* 2006;15:651–74.

30 R Core Team. *R: A Language and Environment for Statistical Computing* [program]. Vienna, Austria: R Foundation for Statistical Computing, 2016.

31 van Gorp S, Kessels AG, Joosten EA, et al. Pain prevalence and its determinants after spinal cord injury: a systematic review. *Eur J Pain* 2015;19:5–14.

32 Hatem SM, Attal N, Ducoux D, et al. Clinical, functional and structural determinants of central pain in syringomyelia. *Brain* 2010;133:3409–22.

33 Cruz-Almeida Y, Felix ER, Martinez-Arizala A, et al. Decreased spinothalamic and dorsal column medial lemniscus-mediated function is associated with neuropathic pain after spinal cord injury. *J Neurotrauma* 2012;29:2706–15.

34 Widerström-Noga E, Cruz-Almeida Y, Felix ER, et al. Somatosensory phenotype is associated with thalamic metabolites and pain intensity after spinal cord injury. *Pain* 2015;156:166–74.

35 Ozdemir RA, Perez MA. Afferent input and sensory function after human spinal cord injury. *J Neurophysiol* 2018;119:134–44.

36 Al-Chalabi M, Gupta S. Neuroanatomy, spinothalamic tract. Treasure Island, FL: StatPearls, 2019.

37 Finnerup N, Sørensen L, Biering-Sørensen F, et al. Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. *Exp Neurol* 2007;207:139–49.

38 Onifer SM, Smith GM, Fouad K. Plasticity after spinal cord injury: relevance to recovery and approaches to facilitate it. *Neurotherapeutics* 2011;8:283–93.

39 Tsuda M, Koga K, Chen T, et al. Neuronal and microglial mechanisms for neuropathic pain in the spinal dorsal horn and anterior cingulate cortex. *J Neurochem* 2017;141:486–98.

40 Masuda T, Ozono Y, Mikuniya S, et al. Dorsal horn neurons release extracellular ATP in a V1NUT-dependent manner that underlies neuropathic pain. *Nat Commun* 2016;7:12529.

41 Jackson AB, Dijkers M, Devivo MJ, et al. A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. *Arch Phys Med Rehabil* 2004;85:1740–8.

42 Finnerup NB, Gylensten C, Nielsen E, et al. MRI in chronic spinal cord injury patients with and without central pain. *Neurology* 2003;61:1569–75.