HHS Public Access

Author manuscript

Curr Phys Med Rehabil Rep. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Curr Phys Med Rehabil Rep. 2017 September ; 5(3): 143–150. doi:10.1007/s40141-017-0161-x.

Advances in Spinal Functional Magnetic Resonance Imaging in the Healthy and Injured Spinal Cords

Ann S. Choe[1,2,*]

[1]Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD 21205 USA

[2]F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD 21205 USA

Abstract

Purpose of Review—This review provides an overview of the current spinal functional magnetic resonance imaging (fMRI) studies that investigate the healthy and injured spinal cords.

Recent Findings—Spinal fMRI-derived outcome measures have previously been suggested to be sensitive to changes in neurological function in the spinal cord. A body of recent task-activated fMRI studies seems to confirm that detecting neural activity in the spinal cord using spinal fMRI may be feasible as well as reliable. Furthermore, a growing number of studies has shown that resting state fMRI in the spinal cord is also feasible, demonstrating that the investigation of changes in neural activity can also be performed in the absence of explicit tasks.

Summary—Current task-activated and resting state fMRI studies suggest that spinal fMRI has a strong potential to provide novel imaging biomarkers that can be used to investigate plastic changes in the injured spinal cord.

Keywords

spinal fMRI; task-activated fMRI; resting state fMRI; spinal cord injury

Introduction

The spinal cord is a conduit for the exchange of information between the brain and the body, and damage to it disrupts conduction of sensory and motor signals across the lesion epicenter (1). The severity of the spinal cord injury (SCI), and the extent of the neurological impairment following the injury, limits the subsequent neurological recovery. Oftentimes, individuals with severe SCI experience only limited neurological recovery that does not

*Corresponding author: Ann S. Choe, Ph.D., F. M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, 707 North Broadway, Baltimore, Maryland 21205 USA, Phone: +1(443) 923-9500, annschoe@gmail.com.

Conflict of Interest

Ann S. Choe declares no conflict of interest.

Compliance with Ethical Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

translate to functional improvements (2,3), and the mechanisms of the plastic neurological changes that occur in the injured spinal cord are not well understood.

The International Standards for Neurological Classification of SCI (ISNCSCI) is the most widely used clinical classification system of SCI that describes neurological injury level and degree of functional preservation in individuals with SCI. However, characterizing and monitoring the plastic neurological changes of the spinal cords in individuals with SCI using ISNCSCI is challenging, because while ISNCSCI is excellent in describing the neurological level of SCI, its ability to describe the degree of functional loss, and therefore the sensitivity to changes in function, is limited (4–6). Other neurological assessment measures are also available, such as neurophysiological tests (e.g., transcranial magnetic stimulation and somatosensory evoked potentials tests (7)), capacity measures (e.g., 10 meter walk test (10MWT) (8)), as well as performance measures (e.g., Spinal Cord Independence Measures (SCIM) (9)). Acquisition of such measures is dependent on intended purpose, which is either describing day to day function (as in SCIM or walking tests) or neurologic function (ISNCSCI). There is a compelling clinical need for new biomarkers that are sensitive to changes in neurological function in the spinal cord per se.

Recently, functional magnetic resonance imaging (fMRI)-derived outcome measures have been proposed as such potential imaging biomarkers (10–12). The term fMRI, when used by itself, conventionally refers more specifically to task-activated fMRI (task-fMRI), which incorporates explicit motor or sensory tasks into its imaging paradigm to elicit neural activity. Several previous task-fMRI studies have shown that the modality can be used to characterize residual neural function in individuals with SCI (13–15). However, translation of task-fMRI into clinics is challenging, as individuals with SCI are often not able to complete the sensory or motor tasks and require the use of modified tasks for different people. In contrast, resting state fMRI (rsfMRI) utilizes the spontaneous fluctuations in blood oxygen-level dependent (BOLD) signal, measured in the absence of explicit tasks (16). This has strong clinical appeal, as it allows the use of an identical imaging protocol for all individuals, regardless of their degree of physical limitations. Consequently, several groups have begun to explore the potential of rsfMRI-derived outcome measures to serve as imaging biomarkers that can be used to study plastic changes in the spinal cord after injury (12).

This review provides an overview of the current spinal fMRI studies that utilized spinal fMRI to investigate the healthy and injured spinal cord. Additionally, potential utility of rsfMRI to investigate the changes in the injured spinal cords is briefly introduced.

Task-activated Functional Magnetic Resonance Imaging in the Spinal Cord

Challenges

Task-fMRI incorporates explicit motor or sensory tasks into its imaging paradigm to elicit neural activity. Such neural activity can then be indirectly measured as the changes in BOLD signal, which is the most commonly used fMRI contrast. Alternatively, signal enhancement by extravascular protons (SEEP) has been suggested to also allow an indirect detection of neural activity, by detecting changes in the intracellular/extracellular volume ratio (10). The

SEEP contrast is often generated using the fast spin echo pulse sequence, which tends to be more resistant to field inhomogeneity-induced imaging artifacts. This is a major advantage especially for spinal imaging, which has to deal with hostile imaging environment in the region of spinal cord. In fact, four out of seven of the spinal fMRI studies listed in Table 1 utilized the SEEP contrast.

Encapsulated in spinal cavity filled with cerebrospinal fluid (CSF), the spinal cord passes through segmented series of bones (vertebrae) that are separated by cartilaginous discs. It is a relatively small structure, with anterior-posterior and transverse diameters reported only as ca. 8.7–14 mm at cervical level (17,18). The coexistence of bones, soft tissues and air in a compact space that pulsate with the flow of CSF creates a hostile imaging environment for spinal imaging. This presents major technical challenges for spinal fMRI, hindering the imaging modality's transition into clinics. The technical challenges include but are not limited to: 1) inhomogeneous magnetic field, 2) physiological motion, and 3) partial volume effect (19). While these challenges are common to all MR imaging applications, they are exacerbated when imaging the spinal cord, due to the cord's small size and the hostile imaging environment around the region.

Large magnetic field inhomogeneity in the spinal cord region created due to the coexistence of bones, soft tissues, and air results in significant image distortion and loss of signal intensity. Fortunately, such image artifacts can be reduced by adopting advanced shimming methods (20–22) and pulse sequences (23,24) that are optimized for spinal imaging. One can also attempt to minimize the magnetic field variation within the imaging field of view itself by obtaining transverse imaging slices – i.e., by placing the imaging plane parallel to the spinal cord's cross-section. Such imaging plane placement ensures that the plane of highest spatial resolution covers the area of spinal cord that contains the most amount of features, thereby reducing partial volume effect, and the amount of imaging artifacts that spread across the spinal cord (25).

As previously stated, the spinal cord and the surrounding structures pulsate with the CSF, making the region vulnerable to motion artifact. To make matters worse, the region is also affected by respiration, and positioned near other pulsating organs such as heart and lungs, making the spinal cord imaging even more vulnerable to the effects of periodic physiological motion. One of the most straightforward solutions to such motion artifacts are to utilize cardiac and respiratory gating techniques (26,27), synchronizing the image acquisition with the cardiac and respiratory cycles. However, utilizing such gating techniques during clinical spinal imaging is challenging, as it can increase the image acquisition time by a factor of two to three. This is a major drawback for imaging of individuals with SCI, as they are often not able to lie still for extended period of time within the MRI scanner. Additionally, gating techniques usually requires variable repetition time (TR) values, which can lead to variable T1-weighting in images that is not appropriate for fMRI.

Finally, the analysis of fMRI involves a complex post-processing pipeline that is often arbitrarily chosen – resulting in different pipelines and statistical tests being used across different groups around the world. Interpreting results of fMRI studies therefore should be done with ample caution. In fact, a recent review of spinal fMRI studies showed that seven

out of the eight reviewed studies made statistical assumptions without correcting for multiple comparisons, leading to potentially biased results (28).

Recent studies

The history of spinal fMRI is a relatively short one, with the first published example by Yoshizawa et al. (29) of the spinal fMRI in healthy spinal cords appearing in 1996, and the first published example of spinal fMRI in injured spinal cords appearing only in 2005 by Stroman et al. (30). Even now, the number of published studies and groups that perform spinal fMRI are, although increasing, limited – demonstrating how difficult performing spinal fMRI in healthy spinal cords, let alone in injured spinal cords, is. As such, the results of the early spinal fMRI studies have initially been met with a healthy dosage of skepticism in the beginning. Over the past few years, however, growing number of spinal fMRI studies started to demonstrate that fMRI in the spinal cord may be feasible, as well as reliable. Notably, a number of recent studies have demonstrated that when a dermatome on one side of the body is stimulated, neural activation is observed on the corresponding spinal cord levels ipsilateral to the side of the stimulation, displaying a high degree of laterality (13–15,31–34). A number of recent task activated fMRI studies are summarized in Table 1.

In a study by Cadotte et al. (13), thermal stimulus were applied to the right and left sides of the body in an interleaved fashion. In response, neural activations were observed in the ipsilateral side of the corresponding levels in the spinal cord. Additionally, it was revealed that compared to healthy controls, individuals with chronic incomplete SCI showed increased number of active voxels in the spinal cord when normal sensory dermatomes were stimulated, and decreased number of active voxels when abnormal sensory dermatomes were stimulated. Similarly, Nash et al. (33) demonstrated that applying noxious thermal stimuli to the left side of the body resulted in neural activation in the corresponding spinal cord levels ipsilateral to the locations of the stimuli. Specifically, painful stimulations of the left side of the body (left deltoid or left thenar eminence) activated the left dorsal horn, whereas painful stimulations of the right side (right deltoid or right thenar eminence) activated the right dorsal horn. More recently, Stroman et al. (14) investigated specifically whether spinal fMRI can be used to characterize changes in pain processing in individuals with SCI. In order to do this, noxious thermal stimuli were again applied to the C8 dermatome. Results showed that while the pain ratings, the location, and magnitude of BOLD activation varied widely across participants, the results varied in relation with perceived pain and the level/severity of injuries. Finally, Kornelsen et al. (32) demonstrated that the spinal fMRI of the entire thoracic spinal cord may be feasible, by applying vibrotectile stimuli on lower thoracic spinal dermatomes on the right side of the body. Results showed that the neural activation was observed in the corresponding lower thoracic spinal cord segments ipsilateral to the side of stimulations, in the dorsal aspect of the spinal cord. Together, this body of research suggests that spinal fMRI can indeed be used to detect neural activity in the spinal cord.

Interestingly, several recent studies have also shown that in certain cases, neural activity of the spinal cord may not lateralize despite similar experimental setup. For example, Xie et al. (31) used Spatial Independent Component Analysis (CORSICA) to assess the method's ability to correct for structured noise, such as cardiac and respiratory function. In the study,

nociceptive transcutaneous electrical stimuli were applied to the subjects' right thumb, and the results showed that the use of CORSICA resulted in increased sensitivity and specificity to the neural activity resulting from the nociceptive stimuli – specifically, fewer voxels showed neural activation in the CSF and outside the spinal region. The neural activation, however, was observed bilaterally instead of being confined to the right (ipsilateral) side of the spinal cord. Similarly, when Rempe et al. (34) attempted to characterize the responses to thermal stimuli applied to the right side of the body, increased activity was observed in both ipsi- and contralateral ventral and dorsal spinal horn. Finally, Zhong et al. (15) used spinal fMRI to assess the neural activity in the spinal cord that was elicited by applying subcutaneous electrical stimulation at the right elbow and thumb. As expected, significant functional activation was observed mainly in the right side of the spinal cord, at the level of C5 to C6. However, some activation in the contralateral dorsal and ventral horn was also observed. One possible explanation for the observed bilateral neural activation in these studies is that the relatively large imaging slice thickness, often employed in spinal fMRI to increase SNR, may have led to unbalanced partial volume effect between the right and left side of the spinal cord (31). Additionally, possible physiological explanations also exist, such as the effect of interneurons crossing to contralateral side of the spinal cord (35) and inhibitory/facilitatory tonic descending control from brainstem regions – in such cases, the observed changes in fMRI signal may be in part explained by the changes in descending modulation (30,34).

Resting state functional magnetic resonance imaging

One of the major goals of the spinal fMRI development in the field of SCI is the modality's successful transition to clinics, where it can be used to provide valuable insight into the pathological changes and residual functions in those with SCI to inform diagnosis and prognosis. However, performing spinal fMRI studies in individuals with SCI is difficult, as the challenges of spinal fMRI are exacerbated to even greater extent in those with injuries. Specifically, extensive atrophy of the spinal cord is often experienced, making the size of the cord even smaller. Also, the images are more prone to motion artifact as many have trouble lying still within the MRI scanner for extended period of time, as well as to susceptibility artifact as many have metal stabilizing hardware installed at and near the site of injuries.

RsfMRI measures the temporal relationships between spontaneous fluctuations in fMRI signal, allowing one to probe intrinsic functional networks in the CNS. There are three major advantages of rsfMRI that are especially relevant to the field of SCI: 1) easy applicability to heterogeneous SCI cohorts – Unlike task-fMRI, which incorporates explicit motor or sensory tasks into its paradigms, rsfMRI is acquired in the absence of explicit tasks, enabling one to probe functional networks based on the hypothesis that "cells that fire together wire together". This has strong clinical appeal, as it allows the use of an identical protocol for individuals not only in various stages of diseases, but also in various stages of interventions – regardless of their degree of cognitive or physical limitations. 2) capacity to observe functional organization within major intrinsic neural networks – through the use of various advanced data analysis methods, several groups have shown that it is possible to localize functionally relevant subdivisions of anatomically defined regions based on the rsfMRI derived measures (6,36–38). 3) high sensitivity to functional changes in CNS –

previous studies have also shown that rsfMRI-derived output measures are sensitive to changes in function, by demonstrating that functional reorganization in CNS could be observed after as little as one week of intervention (39–41). The method's high applicability to heterogeneous cohorts of individuals with SCI, as well as the high sensitivity of the derived measures to functional changes in CNS, suggests that rsfMRI may be an ideal clinical tool for the evaluation of the extent and the pattern of pathological changes in Individuals with SCI. A number of recent resting state fMRI studies are summarized in Table 2.

One of the first published studies of rsfMRI implemented within the spinal cord was performed by Barry et al. (42). The study investigated whether the spontaneous fluctuations of BOLD signal at rest can be used to infer functional connectivity within the neural circuits of spinal cord. Results provided evidence that robust functional connectivity between left and right ventral (motor) horns, and between left and right dorsal (sensory) horns exists within the spinal cord. The study by Barry et al. has exploited the high magnetic field strength of a 7 T magnet and the resulting high signal to noise ratio. Eippert et al. therefore have investigated such functional connectivity within the neural circuits of spinal cord can also be observed in a more clinically relevant field strength of 3 T magnet. Results showed that significant dorsal horn connectivity as well as ventral horn connectivity, but no consistent effects for connectivity between dorsal and ventral horns were observed, thus replicating the human 7T results.

Similarly, Kong et al. (43) have used independent component analysis to investigate whether intrinsically organized and spatially circumscribed resting state networks exist in the spinal cord. Results provided evidence that spatially distinct resting state networks exist within the spinal cord. Specifically, that the resting state networks were clearly separated into dorsal and ventral components, mirroring the functional neuroanatomy of the spinal cord and likely reflecting sensory and motor processing. Vahdat et al. (44) used rsfMRI to investigate the extent to which motor skill acquisition relies on intrinsic spinal cord processes. Interestingly, the spinal and brain fMRI were simultaneously performed, with a goal of separating the spinal local effects from the cortical influences during motor sequence learning. The results revealed learning-related modulation of activity in the C6–C8 spinal region that was independent from that of related cortical sensorimotor structures – suggesting that rsfMRI could be used to investigate local learning-induced plasticity in intact human spinal cord. Finally, studies such as the one performed by Liu et al. (45) show that rsfMRI of the spinal cord can be used to investigate non-traumatic injuries to the spinal cord, such as cervical spondylotic myelopathy (CSM). In this study, the authors measured the amplitude of low frequency fluctuation (ALFF) in the spinal cord, to investigate the regional neural activity level associated with the myelopathic cervical cord. The results showed that ALFF values were higher in the CSM patients at all cervical segments, compared to the healthy controls, and that the severity of myelopathy was associated with the increase of ALFF.

Conclusions

There is growing number of studies that utilizes spinal fMRI to study plastic changes in injured spinal cord that are predictive of progress towards recovery. Major imaging

challenges exist, however, such as magnetic field inhomogeneity and increased vulnerability to physiological motion – hindering the imaging modality's potential to transition into the clinic. Fortunately, the advent of cutting edge shimming methods (20–22) and pulse sequences (23,24) that are optimized for spinal imaging has led to a body of recent research which suggest that detecting neural activity in the spinal cord using spinal fMRI may not only be feasible, but also reliable (13,14,32,33). Furthermore, the technical advances in the field have also enabled the application of rsfMRI in the spinal cord, allowing the use of an identical imaging protocol for all study participants regardless of their degree of cognitive or physical limitations. Collectively, the recent body of task-activated and resting state spinal fMRI studies demonstrates that spinal fMRI has a strong potential to provide novel imaging biomarkers that can be used to investigate plastic changes in the injured spinal cord. As the field of spinal imaging moves forward, however, it should also be recognized that spinal fMRI is especially vulnerable to significant imaging artifacts and the analysis and interpretation of the results must be performed with caution.

Acknowledgments

This work was supported in part by a grant from the Craig H. Neilsen Foundation (338419).

References

Papers of particular interest, published recently, have been highlighted as:

* Of importance

1. Belegu V, Oudega M, Gary DS, McDonald JW. Restoring function after spinal cord injury: promoting spontaneous regeneration with stem cells and activity-based therapies. Neurosurg Clin N Am. 2007 Jan; 18(1):143–68. xi. [PubMed: 17244561]
2. McDonald JW, Sadowsky C. Spinal-cord injury. Lancet. 2002 Feb 2; 359(9304):417–425. [PubMed: 11844532]
3. Kirshblum S, Millis S, McKinley W, Tulsky D. Late neurologic recovery after traumatic spinal cord injury. Arch Phys Med Rehabil. 2004 Nov; 85(11):1811–1817. [PubMed: 15520976]
4. Steeves JD, Lammertse D, Curt A, Fawcett JW, Tuszynski MH, Ditunno JF, et al. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. Spinal Cord. 2007 Mar; 45(3):206–221. [PubMed: 17179972]
5. Ellaway PH, Kuppuswamy A, Balasubramaniam AV, Maksimovic R, Gall A, Craggs MD, et al. Development of quantitative and sensitive assessments of physiological and functional outcome during recovery from spinal cord injury: a clinical initiative. Brain Res Bull. 2011 Mar 10; 84(4–5): 343–357. [PubMed: 20728509]
6. Nebel MB, Joel SE, Muschelli J, Barber AD, Caffo BS, Pekar JJ, et al. Disruption of functional organization within the primary motor cortex in children with autism. Hum Brain Mapp. 2014 Feb; 35(2):567–580. [PubMed: 23118015]
7. Davey NJ, Nowicky AV, Zaman R. Somatopy of perceptual threshold to cutaneous electrical stimulation in man. Exp Physiol. 2001 Jan; 86(1):127–130. [PubMed: 11434326]
8. van Hedel HJ, Wirz M, Dietz V. Assessing walking ability in subjects with spinal cord injury: validity and reliability of 3 walking tests. Arch Phys Med Rehabil. 2005 Feb; 86(2):190–196. [PubMed: 15706542]
9. Catz A, Itzkovich M, Tesio L, Biering-Sorensen F, Weeks C, Laramee MT, et al. A multicenter international study on the Spinal Cord Independence Measure, version III: Rasch psychometric validation. Spinal Cord. 2007 Apr; 45(4):275–291. [PubMed: 16909143]

10. Stroman PW, Krause V, Malisza KL, Frankenstein UN, Tomanek B. Characterization of contrast changes in functional MRI of the human spinal cord at 1.5 T. Magn Reson Imaging. 2001 Jul; 19(6):833–838. [PubMed: 11551724]

11*. Stroman PW, Wheeler-Kingshott C, Bacon M, Schwab JM, Bosma R, Brooks J, et al. The current state-of-the-art of spinal cord imaging: methods. Neuroimage. 2014 Jan 1.84:1070–1081. This paper provides one of the most comprehensive reviews of the spinal cord imaging, including spinal fMRI. [PubMed: 23685159]

12. Choe AS, Belegu V, Yoshida S, Joel S, Sadowsky CL, Smith SA, et al. Extensive neurological recovery from a complete spinal cord injury: a case report and hypothesis on the role of cortical plasticity. Front Hum Neurosci. 2013 Jun 25.7:290. [PubMed: 23805087]

13. Cadotte DW, Bosma R, Mikulis D, Nugaeva N, Smith K, Pokrupa R, et al. Plasticity of the injured human spinal cord: insights revealed by spinal cord functional MRI. PLoS One. 2012; 7(9):e45560. [PubMed: 23029097]

14. Stroman PW, Khan HS, Bosma RL, Cotoi AI, Leung R, Cadotte DW, 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 Aug 1; 33(15):1450–1460. [PubMed: 26801315]

15. Zhong XP, Chen YX, Li ZY, Shen ZW, Kong KM, Wu RH. Cervical spinal functional magnetic resonance imaging of the spinal cord injured patient during electrical stimulation. Eur Spine J. 2017 Jan; 26(1):71–77. [PubMed: 27311305]

16. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995 Oct; 34(4):537–541. [PubMed: 8524021]

17. Sherman JL, Nassaux PY, Citrin CM. Measurements of the normal cervical spinal cord on MR imaging. AJNR Am J Neuroradiol. 1990 Mar-Apr;11(2):369–372. [PubMed: 2107721]

18. Sigmund EE, Suero GA, Hu C, McGorty K, Sodickson DK, Wiggins GC, et al. High-resolution human cervical spinal cord imaging at 7 T. NMR Biomed. 2011 Dec 20; 25(7):891–899. [PubMed: 22183956]

19. Kharbanda HS, Alsop DC, Anderson AW, Filardo G, Hackney DB. Effects of cord motion on diffusion imaging of the spinal cord. Magn Reson Med. 2006 Aug; 56(2):334–339. [PubMed: 16804888]

20. Verma T, Cohen-Adad J. Effect of respiration on the B0 field in the human spinal cord at 3T. Magn Reson Med. 2014 Dec; 72(6):1629–1636. [PubMed: 24390654]

21. Topfer R, Starewicz P, Lo KM, Metzemaekers K, Jette D, Hetherington HP, et al. A 24-channel shim array for the human spinal cord: Design, evaluation, and application. Magn Reson Med. 2016 Nov; 76(5):1604–1611. [PubMed: 27487798]

22. Zhang B, Seifert AC, Kim JW, Borrello J, Xu J. 7 Tesla 22-channel wrap-around coil array for cervical spinal cord and brainstem imaging. Magn Reson Med. 2016 Nov 17.

23. Ellingson BM, Sulaiman O, Kurpad SN. High-resolution in vivo diffusion tensor imaging of the injured cat spinal cord using self-navigated, interleaved, variable-density spiral acquisition (SNAILS-DTI). Magn Reson Imaging. 2010 Nov; 28(9):1353–1360. [PubMed: 20797830]

24. Ben-Eliezer N, Sodickson DK, Shepherd T, Wiggins GC, Block KT. Accelerated and motion-robust in vivo T2 mapping from radially undersampled data using bloch-simulation-based iterative reconstruction. Magn Reson Med. 2016 Mar; 75(3):1346–1354. [PubMed: 25891292]

25. Stroman PW, Ryner LN. Functional MRI of motor and sensory activation in the human spinal cord. Magn Reson Imaging. 2001 Jan; 19(1):27–32. [PubMed: 11295343]

26. Rossi C, Boss A, Steidle G, Martirosian P, Klose U, Capuani S, et al. Water diffusion anisotropy in white and gray matter of the human spinal cord. J Magn Reson Imaging. 2008 Mar; 27(3):476–482. [PubMed: 18224672]

27. Skare S, Andersson JL. On the effects of gating in diffusion imaging of the brain using single shot EPI. Magn Reson Imaging. 2001 Oct; 19(8):1125–1128. [PubMed: 11711237]

28. Martin AR, Aleksanderek I, Cohen-Adad J, Tarmohamed Z, Tetreault L, Smith N, 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, fMRI. Neuroimage Clin. 2015 Dec 4.10:192–238. [PubMed: 26862478]

29. Yoshizawa T, Nose T, Moore GJ, Sillerud LO. Functional magnetic resonance imaging of motor activation in the human cervical spinal cord. Neuroimage. 1996 Dec; 4(3 Pt 1):174–182. [PubMed: 9345507]
30. Stroman PW. Spinal fMRI investigation of human spinal cord function over a range of innocuous thermal sensory stimuli and study-related emotional influences. Magn Reson Imaging. 2009 Dec; 27(10):1333–1346. [PubMed: 19570637]
31. Xie G, Piche M, Khoshnejad M, Perlbarg V, Chen JI, Hoge RD, et al. Reduction of physiological noise with independent component analysis improves the detection of nociceptive responses with fMRI of the human spinal cord. Neuroimage. 2012 Oct 15; 63(1):245–252. [PubMed: 22776463]
32. Kornelsen J, Smith SD, McIver TA, Sboto-Frankenstein U, Latta P, Tomanek B. Functional MRI of the thoracic spinal cord during vibration sensation. J Magn Reson Imaging. 2013 Apr; 37(4):981–985. [PubMed: 23011888]
33. Nash P, Wiley K, Brown J, Shinaman R, Ludlow D, Sawyer AM, et al. Functional magnetic resonance imaging identifies somatotopic organization of nociception in the human spinal cord. Pain. 2013 Jun; 154(6):776–781. [PubMed: 23618495]
34. Rempe T, Wolff S, Riedel C, Baron R, Stroman PW, Jansen O, et al. Spinal and supraspinal processing of thermal stimuli: an fMRI study. J Magn Reson Imaging. 2015 Apr; 41(4):1046–1055. [PubMed: 24737401]
35. Light AR, Perl ER. Spinal termination of functionally identified primary afferent neurons with slowly conducting myelinated fibers. J Comp Neurol. 1979 Jul 15; 186(2):133–150. [PubMed: 109477]
36. Cohen AL, Fair DA, Dosenbach NU, Miezin FM, Dierker D, Van Essen DC, et al. Defining functional areas in individual human brains using resting functional connectivity MRI. Neuroimage. 2008 May 15; 41(1):45–57. [PubMed: 18367410]
37. Kelly C, Uddin LQ, Shehzad Z, Margulies DS, Castellanos FX, Milham MP, et al. Broca's region: linking human brain functional connectivity data and non-human primate tracing anatomy studies. Eur J Neurosci. 2010 Aug; 32(3):383–398. [PubMed: 20662902]
38. Kim JH, Lee JM, Jo HJ, Kim SH, Lee JH, Kim ST, et al. Defining functional SMA and pre-SMA and subregions in human MFC using resting state fMRI: functional connectivity-based parcellation method. Neuroimage. 2010 Feb 1; 49(3):2375–2386. [PubMed: 19837176]
39. Cramer SC, Lastra L, Lacourse MG, Cohen MJ. Brain motor system function after chronic, complete spinal cord injury. Brain. 2005 Dec; 128(Pt 12):2941–2950. [PubMed: 16246866]
40. Winchester P, McColl R, Querry R, Foreman N, Mosby J, Tansey K, et al. Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury. Neurorehabil Neural Repair. 2005 Dec; 19(4):313–324. [PubMed: 16263963]
41. Cramer SC, Orr EL, Cohen MJ, Lacourse MG. Effects of motor imagery training after chronic, complete spinal cord injury. Exp Brain Res. 2007; 177(2):233–242. [PubMed: 16944108]

42*. Barry RL, Smith SA, Dula AN, Gore JC. Resting state functional connectivity in the human spinal cord. Elife. 2014 Aug 5.3:e02812. This is one of the first published studies of rsfMRI implemented within the spinal cord, which demonstrated that low-frequency BOLD fluctuations are inherent in the spinal cord as well as the brain. [PubMed: 25097248]

43*. Kong Y, Eippert F, Beckmann CF, Andersson J, Finsterbusch J, Buchel C, et al. Intrinsically organized resting state networks in the human spinal cord. Proc Natl Acad Sci U S A. 2014 Dec 16; 111(50):18067–18072. This is one of the first published studies of spinal rsfMRI which identified spatially distinct RSNs in the human spinal cord using independent component analysis. [PubMed: 25472845]

44. Vahdat S, Lungu O, Cohen-Adad J, Marchand-Pauvert V, Benali H, Doyon J. Simultaneous Brain-Cervical Cord fMRI Reveals Intrinsic Spinal Cord Plasticity during Motor Sequence Learning. PLoS Biol. 2015 Jun 30.13(6):e1002186. [PubMed: 26125597]
45. Liu X, Qian W, Jin R, Li X, Luk KD, Wu EX, et al. Amplitude of Low Frequency Fluctuation (ALFF) in the Cervical Spinal Cord with Stenosis: A Resting State fMRI Study. PLoS One. 2016 Dec 1.11(12):e0167279. [PubMed: 27907060]

46. Eippert F, Kong Y, Winkler AM, Andersson JL, Finsterbusch J, Buchel C, et al. Investigating resting-state functional connectivity in the cervical spinal cord at 3T. Neuroimage. 2017 Feb 15.147:589–601. [PubMed: 28027960]

Curr Phys Med Rehabil Rep. Author manuscript; available in PMC 2018 September 01.

Table 1

Selection of spinal fMRI studies – task-activated fMRI

Authors (year)	Title	Subjects	B0; vendor	Anatomical region	Pulse sequence	Voxel size; TR/TE (ms); cardiac gating	Clinical outcome measure	Key results
Cadotte et al. (2012) (13)	Plasticity of the injured human spinal cord: insights revealed by spinal cord functional MRI	Cervical SCI (18) vs. HCs (20)	3 T; GE and Siemens	Brainstem and C1-T1	ssTSE (HASTE)	1.5 × 1.5 × 2 mm^3; 9000/38; no	ISNCSCI sensory score	Patients with chronic incomplete SCI, when stimulated in a dermatome of normal sensation, showed an increased number of active voxels relative to controls.
Xie et al. (2012) (31)	Reduction of physiological noise with independent component analysis improves the detection of nociceptive responses with fMRI of the human spinal cord	HCs (14)	3 T; Siemens	C3 – T1	GE-EPI	1.6 × 1.6 × 3 mm^3 2000/20; no	n/a	Correction of Structured noise using spatial Independent Component Analysis increased sensitivity to detect stimulus-related activation in the targeted dorsal segment of the cord
Kornelsen et al. (2013) (32)	Functional MRI of the thoracic spinal cord during vibration sensation	HCs (15)	3 T; Siemens	T1 – T11	ssTSE	1.56 × 1.11 × 2 mm^2; 1000/38; no	n/a	Lower thoracic spinal dermatomes on the right side were stimulated by vibration, leading to signal increases in the ipsilateral side
Nash et al. (2013) (33)	Functional magnetic resonance imaging identifies somatotopic organization of nociception in the human spinal cord	HCs (10)	3 T; GE	C4 – C7	double shot, 3D spiral in-out GE	1.25 × 1.25 × 4 mm^2; 1250/25; no	n/a	fMRI can create high-resolution, neuronal activation maps of the human cervical spinal cord.
Rempe et al. (2015) (34)	Spinal and Supraspinal Processing of Thermal Stimuli: An fMRI Study	HC (16)	3 T; Philips	Thalamus – T7	ssTSE	1 × 1 × 2 mm^3; 9000/38; no	n/a	Increased activity was observed in ipsi- and contralateral ventral and dorsal spinal horn during noxious heat and heat allodynia.
Stroman et al. (2016) (14)	Changes in Pain Processing in the Spinal Cord and Brainstem after Spinal Cord Injury	Cervical (14) and thoracic (2) SCI	3 T Siemens and GE	Thalamus – T1	ssTSE	1.5 × 1.5 × 2 mm^3; 6750/7 6; no	ISNCSCI scores and AIS grade	fMRI may provide sensitive indicators of each individual's pain response, and information about the

Authors (year)	Title	Subjects	B0; vendor	Anatomical region	Pulse sequence	Voxel size; TR/TE (ms); cardiac gating	Clinical outcome measure	Key results
	Characterized by Functional Magnetic Resonance Imaging							mechanisms of altered pain sensitivity
Zhong et al. (2017) (15)	Cervical spinal functional magnetic resonance imaging of the spinal cord injured patient during electrical stimulation	Cervical SCI (7) and HCs (7)	1.5 T; GE	C4 – C7	ssTSE	0.47 × 0.47 × 7 mm^3; 1075.9/43; no	ISNCSCI scores	Significant functional activation was observed mainly in the right side of the spinal cord at the level of the C5–C6 cervical vertebra

SCI: spinal cord injury; HC: healthy control; ssTSE: single shot turbo spin echo; ISNCSCI: international standards for neurological classification of spinal cord injury; GE-EPI: gradient echo echo planar imaging; AIS: American spinal injury association impairment scale

Table 2

Selection of spinal fMRI studies – resting state fMRI

Authors (year)	Title	Subjects	B0; vendor	Anatomical region	Pulse sequence; contrast	Voxel size; TR/TE (ms); cardiac gating	Clinical outcome measure	Key results
Barry et al. (2014) (42)	Resting state functional connectivity in the human spinal cord	HCs (22)	7 T; Philips	C2 – C5	3D multi-shot GE-EPI	0.91 × 0.91 × 4 mm^3; 18/7.8; no	n/a	Low-frequency BOLD fluctuations are inherent in the spinal cord as well as the brain
Kong et al. (2014) (43)	Intrinsically organized resting state networks in the human spinal cord	HCs (24)	3 T; Siemens	C4 – T1	GE-EPI	1 × 1 × 5 mm^3; 1890/44; no	n/a	Spatially distinct RSNs in the human spinal cord were identified, that were clearly separated into dorsal and ventral components
Vahdat et al. (2015) (44)	Simultaneous Brain-Cervical Cord fMRI Reveals Intrinsic Spinal Cord Plasticity during Motor Sequence Learning	HC (25)	3 T Siemens	Brain – T1	GE-EPI	2.5 × 2.5 × 4 mm^3; 2500/30; no	n/a	Learning-related modulation of activity in the C6–C8 spinal region that is independent from that of related supraspinal sensorimotor structures is observed.
Liu et al. (2016) (45)	Amplitude of Low Frequency Fluctuation (ALFF) in the Cervical Spinal Cord with Stenosis: A Resting State fMRI Study	Cervical spondylotic myelopathy (25) and HCs (18)	3 T; Philips	C1 – C7	GE-EPI	1.25 × 1.25 × 4 mm^3; 2000/30; no	JOA score	Amplitude of low frequency fluctuation values were higher in the CSM patients at all cervical segments
Eippert et al. (2017) (46)	Investigating resting-state functional connectivity in the cervical spinal cord at 3T	HCs (20)	3 T Siemens	C6 – T1	GE-EPI	1 × 1x 5 mm^3; 1890/44; no;	n/a	Robust resting-state signals were observed at the clinically more prevalent field strength of 3 T.

HC: healthy control; GE: gradient echo; BOLD: blood oxygenation level dependent; GE-EPI: gradient echo echo planar imaging; RSN: resting state networks; CSM: cervical spondylotic myelopathy; JOA: Japanese orthopedic association