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Applying functional MRI to the spinal cord and brainstem

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Abstract

Functional magnetic resonance imaging of the spinal cord (spinal fMRI) has facilitated the noninvasive visualization of neural activity in the spinal cord (SC) and brainstem of both animals and humans. This technique has yet to gain the widespread usage of brain fMRI, due in part to the intrinsic technical challenges spinal fMRI presents and to the narrower scope of applications it fulfills. Nonetheless, methodological progress has been considerable and rapid. To date, spinal fMRI studies have investigated SC function during sensory or motor task paradigms in spinal cord injury (SCI), multiple sclerosis (MS) and neuropathic pain (NP) patient populations, all of which have yielded consistent and sensitive results. The most recent study in our laboratory has successfully used spinal fMRI to examine cervical SC activity in a SCI patient with a metallic fixation device spanning the C_4 to C_6 vertebrae, a critical step in realizing the clinical utility of the technique. The literature reviewed in this article suggests that spinal fMRI is poised for usage in a wide range of patient populations, as multiple groups have observed intriguing, yet consistent, results using standard, readily available MR systems and hardware. The next step is the implementation of this technique in the clinic to supplement standard qualitative behavioral assessments of SCI. Spinal fMRI may offer insight into the subtleties of function in the injured and diseased SC, and support the development of new methods for treatment and monitoring.

Keywords: Magnetic resonance imaging; fMRI; Brainstem; Spinal cord; Human; Animal

1. Introduction

Functional magnetic resonance imaging of the spinal cord (spinal fMRI) has been under development, and its use expanding, almost as long as fMRI of the brain, with the first article on spinal fMRI being published in 1996 [1]. Its use has not expanded at the explosive pace of brain fMRI, however, partly because it meets a narrower scope of applications for the broad fields of neuroscience and because of the inherent technical challenges, which will be discussed below. Nonetheless, the rate of advances has been rapid, facilitated by adaptations of technological developments for brain fMRI, and, to date, there have been nearly 50 articles published on spinal fMRI in humans and in animals. The current methods may prove useful for clinical trials aimed at assessing the effects of spinal cord injury (SCI) and disease, and for use as a tool for spinal cord (SC) research. Here we outline the recent methodological developments and the applications that have been realized as support for this conclusion.

The need for a noninvasive method of mapping neural function in the SC, such as fMRI, is demonstrated by the fact that clinical decisions about the best treatment course to take following trauma to the SC, or after the effects of diseases such as multiple sclerosis (MS), etc., require knowledge of how the cord is functioning. This knowledge is obtained from tests that must be applied without causing additional damage to the cord or undue pain or stress to the patient [2]. Current standard clinical tests for SC function include the American Spinal Injury Association (ASIA) International Standards for Neurological Classification [3], which involves pin-prick tests across dermatomes and motor tests of various muscle groups. Electrophysiological tests involving stimulation of cortical areas and recording of motor- and

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sensory-evoked potentials are also used to reveal functional connections. Other assessments include surveys of the patient's abilities and quality-of-life factors, such as Functional Independence Measure, Functional Assessment Measure, the Spinal Cord Independence Measure and the Walking Index for Spinal Cord Injury [2]. These tests are limited because they do not reveal information about SC function below the most rostral point of damage, thoracic regions of the cord are difficult to assess and the assessments are subjective. Moreover, none of these tests reveal information about the causes of bowel, bladder or sexual dysfunction, and they rarely reveal multiple sites of damage. Functional MRI of the human SC has been shown to demonstrate activity caudal to sites of SCI at any level of the cord [4,5], the effects of MS [6,7] and peripheral nerve damage [8], and can also demonstrate SC activity related to sexual function [9], potentially providing information that may be missed with current clinical assessments.

2. Methodological developments

Key technical challenges for spinal fMRI that were identified in a previous review [10] include motion of the SC within the spinal canal and variability of the results across repeated experiments. Additional challenges include the lack of a standardized coordinate system, such as that defined by Talairach and Tournoux [11] for the brain, in order to enable objective comparisons of results between different people and group analyses. In the past 4 years, significant developments have addressed these issues and are described below.

2.1. Choice of contrast mechanism for spinal fMRI: SEEP or BOLD

Two different approaches have emerged for fMRI of the SC, one based on the established brain fMRI method employing blood oxygenation level-dependent (BOLD) contrast, and the other based on signal enhancement by extravascular water protons (SEEP). The physiological changes underlying the SEEP contrast mechanism are discussed in detail in a separate review in this issue [12] and so are not repeated here. The BOLD contrast mechanism is well known from brain fMRI [13–15] and also occurs in the SC [16]. Each method has been shown to have specific benefits and drawbacks. SEEP contrast is based on detection of changes in tissue water content and can therefore be obtained with proton density-weighted spin-echo parameters which provide high-quality images of the SC [16–18]. However, this method deposits relatively high amounts of energy in the tissues [i.e., specific absorption ratio (SAR)] and its speed is limited to about 1 s per slice. BOLD contrast can be obtained with gradient-echo imaging methods which produce much lower SAR and can be applied at a faster rate. Most spinal fMRI studies employing BOLD contrast to date have employed echo-planar spatial encoding to achieve the highest imaging speed [19–21]. However, echo-planar imaging methods suffer from significant distortion and signal loss in the SC, and so the gain in imaging speed is at the expense of image quality. Also, BOLD fMRI methods in the SC have not been verified to exclusively demonstrate sites of neuronal activity in the SC, as a recent study by Cohen-Adad et al. [22] indicates that spinal fMRI with BOLD contrast demonstrates predominantly the draining veins on the surface of the cord and therefore has low spatial specificity. Spinal fMRI based on SEEP contrast, on the other hand, has been shown to have high spatial precision and sensitivity to neural function, as detailed below.

2.2. Reduction of variability in spinal fMRI results

Two sources of variability in spinal fMRI results have been identified [22,23], one being Type I and Type II errors, arising from physiological motion and random noise, and the second being actual variation in the neuronal activity between repeated experiments. The problem of physiological motion in brain fMRI has been addressed by modeling the motion and retrospectively accounting for the consequent MR signal changes in a general linear model (GLM) analysis [24], and the method was termed "RETROICOR." This method allows reliable detection of neuronal activity-related signal changes in spite of the confounding motion. A similar approach has been investigated for spinal fMRI data acquired with neuronal activity detected with SEEP contrast [25]. This study demonstrated that GLM analysis produces reliable results for spinal fMRI data and that inclusion of recordings of cardiac, but not respiratory, movement during the fMRI time series improves the reliability of the results. An analysis by Valsasina et al. [26] similarly demonstrated that the GLM is effective for spinal fMRI data acquired with SEEP contrast and also that the sensitivity may be improved by also including terms obtained by independent component analysis in the GLM basis set. Brooks et al. [27] then used the RETROICOR approach for spinal fMRI data acquired with BOLD contrast. Their study showed that by including in the GLM basis functions the cardiac and respiratory motion, interactions between them, and low frequency terms, the rates of detection of false-positive activity were reduced. In two separate studies, Figley et al. [28,29] measured the SC motion within the spinal canal as a function of the cardiac cycle and developed a model of the motion at any level of the cord. This model was then used in a GLM with a method analogous to RETROICOR and was termed "retrospective spinal cord motion time-course estimates (RESPITE)" [30]. In this study, 100 spinal fMRI data sets acquired with SEEP contrast were analyzed and the results showed that the addition of the RESPITE terms to the GLM improved the sensitivity by 15–20% and the specificity by 5–6%. Overall, these studies demonstrate that the GLM approach for analysis of spinal fMRI data is

highly effective and that physiological motion terms can significantly improve the quality of the results. We propose that the disagreement between these studies as to whether or not respiratory terms need to be included in the GLM can be explained by the higher sensitivity of GE-EPI (BOLD fMRI) to breathing-related magnetic field fluctuations than fast spin-echo (SEEP fMRI) methods.

2.3. True physiological variation

A key source of variation in fMRI results is the true differences in neuronal activity that can occur between repeated studies. While this variability cannot be considered an error, per se, because its detection demonstrates the reliability and sensitivity of the fMRI method, it can present a challenge for repeated or group studies.

It is well known [31,32] that activity in the SC in both ventral and dorsal regions is modulated by descending input from the brainstem and cortex, and depends on factors of awareness, alertness and attention, as well as control of motor reflex responses. Studies of emotional and cognitive influences on activity in the SC have been carried out by systematically varying participants' attention focus, whether toward a thermal sensation on the hand, toward a movie or toward mentally challenging tasks [33]. The results showed that activity in the cord, in response to a thermal sensory stimulus, did indeed depend on the participant's attention focus in each study. A separate study demonstrated that the activity in the SC, in response to thermal stimuli applied to the hand, depends on both the stimulus temperature and the order of experiments [23]. This result again implicates factors of emotion and attention. The overall conclusions from these studies are that emotional and attention factors need to be controlled, as much as possible, in spinal fMRI studies of any specific function. Even changes in anxiety or alertness over time, as participants become accustomed to being inside the MRI system, and potentially become bored with the study, were seen to affect spinal fMRI results [23]. These observations demonstrate that spinal fMRI results are sensitive to subtle response variations which may be features of true neuronal activity.

2.4. Spatial normalization

A means of spatially normalizing spinal fMRI results acquired in sagittal slices has been developed [34] by first defining a three-dimensional coordinate system, with the primary axis parallel to the long axis of the SC at every position along the rostral–caudal direction, and orthogonal axes in the right–left and anterior–posterior directions. For data spanning the cervical SC and brainstem in sagittal slices, rostral–caudal position reference points were selected to be at the caudal edge of the pons (the pontomedullary junction) and at the C_7/T_1 disc, and are spaced 140 mm apart in the normalized space [34]. For images of the lumbar SC, reference points were chosen to be the T_8/T_9 disc and the tip of the conus, with a normalized spacing of 157 mm [9]. In order to complete the entire span of the SC, the thoracic region is spanned with reference points at the C_7/T_1 disc and the T_8/T_9 disc spaced 176 mm apart (unpublished results). The three reference volumes therefore overlap and span the entire SC and brainstem, as shown in Fig. 1, with a total normalized span of 448 mm from the top of the C_1 vertebra to the bottom of the conus, consistent with the average expected SC length of 45 cm in adults. The definition of this normalized space, analogous to the Talairach space for the brain, has been shown to enable voxel-by-voxel group analyses in the SC and brainstem, and allows side-by-side comparisons of results from patients after trauma and reference results from healthy subjects [23].

3. Applications of spinal fMRI

The combined improvements provided by the methodological developments to date have resulted in a more sensitive and reliable method for spinal fMRI. The value of this method is the detailed information that it can potentially provide about the injured or diseased SC to researchers and clinicians. This has been demonstrated by a number of studies that have been carried out by approximately 16 different research groups since 1996 to investigate the reliability, sensitivity and validity of spinal fMRI in animal models and in humans. Recent studies of the injured [4,5] and diseased [6,7] SC also provide evidence of the utility of spinal fMRI for clinical applications, as described below.

3.1. Animal studies

Spinal fMRI studies using animal models have provided some key evidence of the reliability and sensitivity of the method by linking fMRI responses with known markers of neuronal activity. In 1997, Pórszász et al. [35] observed an immediate response in the ipsilateral SC following injection of formalin into the hindpaw of the rat. This response was characterized by a 12.7±3.7% (mean±S.E.M.) decrease in signal intensity in L_4 and L_5 SC segments ipsilateral to the site of injection. Although the direction of signal change (decrease) was unexpected, the correlation of the signal change to the peripheral noxious stimulus was verified by administering lidocaine prior to formalin injection. The lidocaine effectively eliminated the observed signal change response. Similarly, noxious stimulation of a rat's forepaw by means of capsaicin injection and electrical stimulation was shown to produce a signal increase in the ipsilateral dorsal horn of SC segments C_6 to C_8. Electrical stimulation produced an additional response in the ipsilateral ventral gray matter, attributed to a reflexive motor response [36].

An investigation of the correspondence between fMRI responses and neural activity was carried out in rats by comparing functional activity maps from fMRI with well-established markers of neuronal activity such as the early gene *c-fos* [37–39]. When noxious electrical stimulation

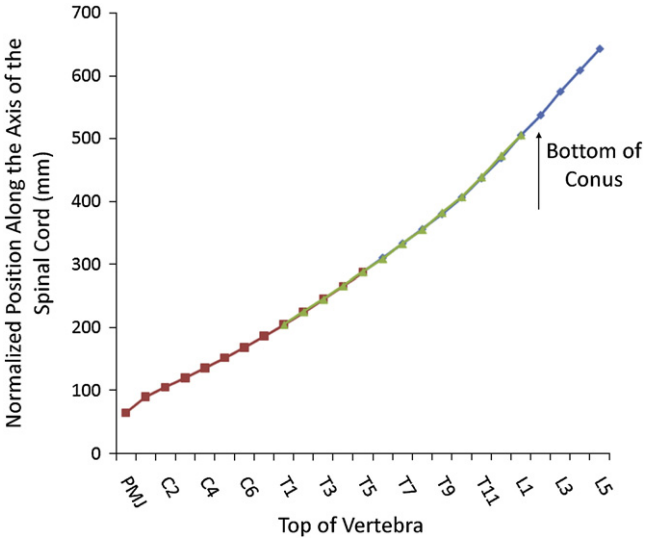

Fig. 1. Plot of the positions adopted for spatial normalization of the SC anatomy. The positions are fixed based on the pontomedullary junction (PMJ) being placed at 65 mm along the primary axis (parallel to the long axis of the SC at all points along the cord), and fixed spans of 140 mm between the PMJ and C_7/T_1 intervertebral disc, 176 mm between the C_7/T_1 disc and the T_8/T_9 disc, and 157 mm between the T_8/T_9 disc and the caudal tip of the conus (approximately in line with the L_1/L_2 disc). The positions of each intervertebral disc have been selected based on multiple sagittal MR images spanning different ranges of the spinal column in healthy volunteers, and the positions were scaled and aligned to be consistent across each overlapping span. Data from each volunteer are shown with a different symbol and color.

(15 V) was applied to the right forepaw and right hindpaw, activity was observed with both fMRI analysis and *c-fos* staining which was localized to the ipsilateral dorsal gray matter [40]. This link is further reinforced by the correspondence between the observed locations of the fMRI responses and the known anatomy of the SC. When 0.5 mA of electrical stimulation was applied to the rat hindlimb, localized signal intensity changes were detected in the ipsilateral medulla oblongata (the first synaptic relay station in the dorsal column pathway) [41]. However, when the stimulus was increased to 2 mA, the fMRI responses were observed in the ipsilateral dorsal and intermediate gray matter in lamina II–VI (indicative of the first synapse in the spinothalamic pathway, implicated in transmission of painful sensations) [42]. In a separate study, the expected ipsilateral dorsal horn response was seen in SC segments L_2 to L_4 with fMRI when the rat hindpaw was electrically stimulated, but when the spinal nerve L_3 was transected, the signal change was observed to be significantly reduced. Moreover, when spinal nerve L_4 was also transected (resulting in severe loss of axonal connectivity), the signal changes were even further reduced [43]. While these examples do not represent the entirety of the published spinal fMRI studies in animal models, they demonstrate and highlight evidence for the link between neural function and fMRI results.

3.2. Human studies and clinical applications

Our understanding of SC physiology has improved over the past several years by applying spinal fMRI in human subjects. Although this understanding is important, another goal of spinal fMRI research is to provide a means of observing function in the injured and diseased SC to assist in diagnosis, treatment planning, and follow-up. To this end, a number of clinically related studies have been carried out to date in patient populations with SCI [4,5], neuropathic pain (NP) [8] and MS [6,7], using a variety of sensory stimuli and motor or proprioceptive tasks.

3.2.1. Sensory stimuli

Sensory-related neural activity in the SC has been consistently observed with fMRI in a number of studies involving healthy and clinical subject populations since 2002 [5,6,23,44–52]. Early studies of patients with SCI investigated the functional response in the lumbar SC to thermal stimulation of the fourth lumbar dermatome [5,44]. The thermal probe was placed against the inner skin of the calf, and the temperature was ramped from skin temperature (32°C) to 10°C several times. Neural activity was consistently observed in the lumbar SC caudal to the site of injury, regardless of whether the subject could consciously feel the stimulus or not. Although the percent signal change was similar between healthy controls and SCI patients (2–3% when the temperature ranged from 29°C to 15°C and approximately 8% at 10°C, which subjects reported as a noxious sensation, discussed below), the spatial distribution of activity was notably different. While healthy controls show predominantly ipsilateral dorsal gray matter activity in response to sensory stimuli, absent or diminished dorsal gray matter and enhanced contralateral ventral gray matter activity is observed in subjects with complete SCI (patients who were unable to feel the stimulus). Results from patients with incomplete SCI are essentially divided based on the degree to which subjects were able to perceive the stimulus. For subjects with preserved sensation, the observed activity pattern was similar to that of healthy controls (consistent ipsilateral dorsal gray matter activity, in addition to central and bilateral ventral gray matter activity). Conversely, patients with decreased sensation exhibited diminished ipsilateral dorsal gray matter activity (similar to complete SCI), yet bilateral ventral gray matter activity was similar (in some cases even diminished) compared to healthy controls. The ability of spinal fMRI to distinguish subtle functional differences between well-established classes of SCI lends credence to its capacity to quantitatively assess the function of the SC.

SC and brainstem fMRI responses to noxious stimuli have been investigated in both healthy and NP patient populations [8,44]. In healthy controls, when a thermal stimulus was ramped from 29°C to 15°C, the percent signal changes ranged between 2% and 3%. However, when the stimulus was further ramped to 10°C (reported as noxious), the

percent signal change more than doubled to approximately 8% and the observed activity became concentrated in superficial regions of the ipsilateral dorsal horn [44], corresponding to Rexed's laminae I and II, which is consistent with known pain pathways. A recent study focusing specifically on pain pathways in NP patients yields further insight into the normal and pathological processing of noxious stimuli [8]. When painful pressure is applied to the median nerve of both healthy controls and patients diagnosed with carpal tunnel syndrome (CTS, a common neuropathy caused by compression of the median nerve), several differences are observed. The controls tended toward positive signal intensity changes, while the CTS patients tended toward negative signal intensity changes. Furthermore, increasingly painful stimuli produced greater differences in the distribution of neuronal activity between controls and CTS patients, which may indicate various adaptations that have occurred in the CNS of patients experiencing neuropathic (or chronic) pain.

Spinal fMRI has also been used to assess and compare the functional differences in the SC gray matter between healthy controls and patients with relapsing–remitting MS (RRMS). Neural activity in the cervical SC was investigated following tactile stimulation of the palm of the right hand and was found from C_5 to C_8 in all patients and controls [6], which corresponds to the expected regions of neuronal recruitment. In general, MS patients showed approximately 20% greater signal intensity changes than controls (3.9% compared to 3.2%), with activity dispersed throughout the dorsal, central and ventral cord, most likely attributable to the interneuronal systems of the SC [41,53,54]. Interestingly, MS patients tend to show an over-recruitment of dorsal gray matter (i.e., show bilateral dorsal activity, whereas healthy controls show predominantly ipsilateral dorsal activity), which is indicative of reduced functional lateralization in the SC. This result appears to support SC gray matter reorganization (previously found in the cortex [55]), as well as postmortem [56–59] and in vivo MRI studies [60] of the SC, which suggest that gray matter is not spared by MS pathology. The purpose of this gray matter reorganization is not yet clear. However, spinal fMRI could be the tool needed to assess changes in the functional activity of gray matter throughout the evolution of the disease and may yield insight as to whether these changes are predictive of clinical outcome.

3.2.2. Motor tasks

Neuronal activity in the SC related to various motor tasks has been demonstrated by a number of groups [1,4,7,20,46,61–66]. Twelve patients with SCI, classified as ASIA A [3] (no sensory or motor function preserved, n=4), ASIA B (sensory but no motor function preserved, n=3), ASIA C (weak motor function is preserved, n=3) or ASIA D (motor function preserved in a condition sufficient for near-normal use n=2), were studied while performing a pedaling motor task [4]. All subjects participated in the passive task (researcher manually moved pedals and subjects' feet moved in pedaling motion), but only ASIA C and D patients performed the active task (autonomous alternating pedaling). Consistent with results from studies in SCI patients using sensory stimuli, neuronal activity was detected caudal to the site of injury in all subjects, regardless of the extent or level of injury. The number of active voxels in the lumbar SC was greater during active compared to passive participation; however, the overall percent signal change was greater during passive (15.0%) compared to active (13.6%) pedaling. The spatial distribution of neural activity in SCI patients was similar to healthy controls for each task. Active participation resulted in bilateral activity in both dorsal and ventral horns, corresponding to a neural response to sensory and motor stimulation, typical of purposeful movement. Passive participation yielded some ventral horn activity, but most activity was seen in the dorsal horn, typical of a neuronal response to proprioceptive and mechanical information produced by this type of movement. Also, the number of active voxels detected in the SC of each subject population mirrors the severity of the impairment. That is, fewer active voxels were detected in the SC of ASIA C/D SCI patients than in the healthy control group [63]. Likewise, still fewer active voxels were observed in the SC of ASIA A SCI subjects compared to ASIA C/D SCI subjects. Perhaps most intriguingly, six subjects were only able to use one limb during active participation (unilateral movement generation), as opposed to typical pedaling with both feet (bilateral movement generation). The latter results in neuronal activity distributed across both sides of the cord. In this study, it was found that during unilateral movement generation, neuronal activity appeared to be prominent in the contralateral ventral horn. This corresponds with known physiology [5,67–70] and suggests once again that spinal fMRI is able to detect subtle differences in neural function. Although spinal fMRI cannot determine the cause of the observed activity patterns, it may be used to supplement the ASIA diagnosis with functional activity maps, providing additional insight into SC physiology and enhancing the design of rehabilitation programs. Neuronal function could be investigated before, during and after rehabilitation to provide a quantitative measure of progress in addition to the qualitative measures provided by ASIA and other subjective (outcome-based) tests.

A study similar to the passive participation pedaling task has been carried out in an MS patient population as well, investigating the extent of cervical SC functional activity in healthy controls and patients with RRMS or secondary progressive course MS (SPMS) [7]. Passive and calibrated 45° flexion/extension was repetitively administered (by the researcher) to the relaxed, prone, right hand of the patient. Activity was observed in the cervical SC from C_5 to C_8 in all subjects, but several differences between controls and patients were noted. Approximately 20% greater signal intensity changes were observed in the cervical SC of MS patients (3.4%) compared to controls (2.7%), analogous to results from the study investigating the spinal fMRI effects

of tactile stimulation of the palm in MS patients and healthy controls [6]. Also, increased bilateral ventral gray matter activity was observed in MS patients compared to controls.

Not only has spinal fMRI been used to detect differences between patient and control populations, but also has been used to investigate functional differences between various classifications of MS severity. This study has also shown that patients with less severe MS (RRMS) had a task-related spinal fMRI activity pattern similar to healthy controls, while patients with more severe MS (SPMS) show a pattern of cord activity more similar to SCI patients. If cervical cord functional activity varies over the course of the disease, spinal fMRI may be useful in assessing the nature and evolution of MS within individual patients.

4. Conclusions and future directions

An important goal of spinal fMRI research is to develop a practical, quantitative tool to improve the diagnosis, treatment and prognosis of SCI and disease. Because this method can reveal SC function below the site of injury, spinal fMRI may provide objective information which can be used for assessing retained function, designing rehabilitation programs, predicting the potential for recovery of function in SCI patients and also for assessing new experimental treatment strategies. A recent study in our laboratory employed a custom-made apparatus to apply multipoint thermal stimulation in a patient with an incomplete (ASIA C) C_5 SCI, with a

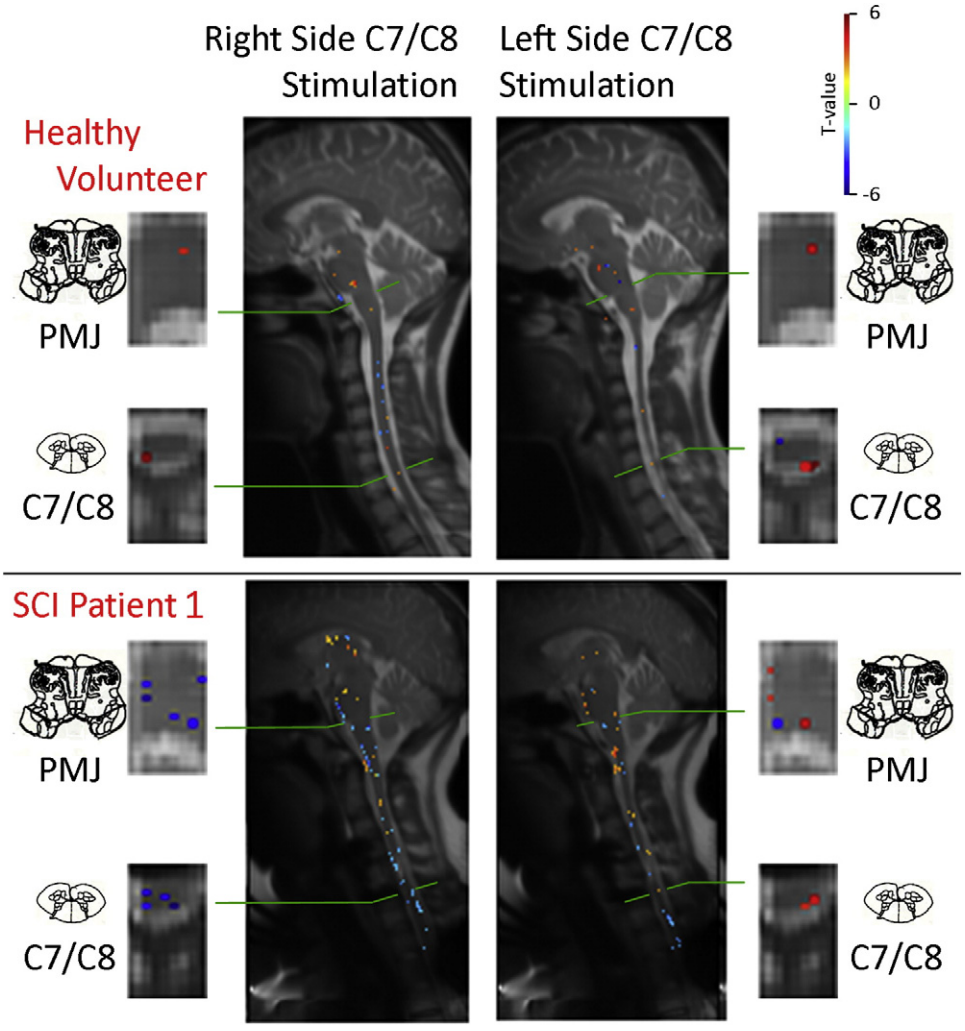

Fig. 2. Comparison of fMRI results obtained from a healthy age- and sex-matched control and a person with a cervical spinal cord injury (SCI), with a metal fixation plate spanning the injury site and metal screws in the C4 and C6 vertebral bodies. In each participant, thermal stimuli at 44°C were applied to four different dermatomes in distinguishable patterns in time so that the response to each could be identified. Stimulation was applied symmetrically at multiple sites on the right and left sides, including the little-finger side of the palm in both participants, and the upper arm of the healthy control and the shoulder of the SCI patient. The results are shown only for stimulation of the right and left palms in both people, in selected 2-mm-thick sagittal slices showing the right-side and left-side activity, and in selected 1-mm-thick transverse slices at the level of the pontomedullary junction (PMJ) and at the level of the C7 or C8 SC segments. The results show clearly symmetric responses to right- and left-side stimulation in the healthy participant with activity in the right and left dorsal horn of the gray matter, respectively. The responses detected in the injured participant show an almost normal-appearing response to left-side stimulation, but a very different response with stimulation of the right side, indicating preserved pathways through the injury site, consistent with clinical assessments using the ASIA standard.

metallic fixation device spanning the C_4 to C_6 vertebrae [71]. Functional activity was observed in the SC both rostral and caudal to the site of injury, despite the fact that the patient did not consciously perceive stimuli below the injury (Fig. 2). The fMRI data took only 7 min to acquire and we were able to detect functional activity in the SC in close proximity to the metallic fixation device. Acquiring fMRI data within a practical time frame and in the presence of fixation devices are two critical steps toward implementing spinal fMRI as a routine clinical tool. This particular case study revealed a nearly normal-appearing response to thermal stimulation on the left side of the body below the injury level, although with altered brainstem responses, such as in the rostral medulla (near the PMJ as shown in Fig. 2), and with significant negative responses to stimulation on the right side of the body below the level of injury. These observations indicate that there are some preserved white matter pathways spanning the injury level, and preserved sensory function below the injury, in agreement with clinical assessments based on the ASIA standard. However, the fMRI results further suggest that descending input from the brainstem on both the right and left sides is present but altered compared to the healthy volunteer and that ascending input from the SC is also present but altered on both sides. Although this is a single-case study, the results present an intriguing example of the information that may be made available when planning rehabilitation therapy and monitoring progressive changes over time.

Regardless of the stimulus or the health of the SC in question, spinal fMRI has been shown to detect neuronal activity in the SC. Thus, without the need for invasive procedures or any changes to existing clinical MRI facilities, this method makes it possible to observe SC function in both patients and healthy subjects.

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