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Functional magnetic resonance imaging identifies somatotopic organization of nociception in the human spinal cord

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ABSTRACT

Functional magnetic resonance imaging (fMRI) is a technique that uses blood oxygen–level–dependent (BOLD) signals to elucidate discrete areas of neuronal activity. Despite the significant number of fMRI human brain studies, few researchers have applied fMRI technology to investigating neuronal activity within the human spinal cord. Our study goals were to demonstrate that fMRI could reveal the following: (i) appropriate somatotopic activations in response to noxious stimuli in the deep and superficial dorsal horn of the human cervical spinal cord, and (ii) lateralization of fMRI activations in response to noxious stimulation in the right and left upper extremity. We subjected healthy participants to noxious stimulation during fMRI scans. Using a spiral in–out image sequence and retrospective correction for physiologic noise, we demonstrated that fMRI can create high-resolution, neuronal activation maps of the human cervical spinal cord. During nociceptive stimulation of all 4 sites (left deltoid, right deltoid, left thenar eminence and right thenar eminence), we found ipsilateral dorsal horn activation. Stimulation of the deltoid activated C5, whereas stimulation of the thenar eminence activated C6. Our study contributes to creating an objective analysis of pain transmission; other investigators can use these results to further study central nervous system changes that occur in patients with acute and chronic pain.

1. Introduction

Functional magnetic resonance imaging (fMRI) is a technique that uses blood oxygen–level–dependent (BOLD) signals to elucidate discrete areas of neuronal activity. Since this technique was first introduced in 1990 [37], it has been used extensively to examine areas of the brain responsible for cognition, emotion, and sensorimotor processing [9,37]. More recently, investigators have used fMRI to assess nociceptive processing in the brain [2,5,40]. As expected, painful experiences activate brain areas, such as the thalamus and the primary and secondary somatosensory cortices. Other investigators have found that the thalamus, anterior cingulate gyrus, insular cortex, and amygdala have been implicated in processing the affective experience of pain and suffering [13,22,23,32,36,38,39].

Despite the significant number of fMRI studies performed on the brain, few researchers have applied this technology to investigating neuronal activity within the human spinal cord. Early human spinal cord studies have revolved around motor tasks and nonpainful sensory stimulation [20,26,30,31,42,43,46]. More recently, studies have imaged the effects of noxious stimulation at a group level [3,4,15,44] and have even shown the effects of placebo analgesia on activity within the spinal cord [10]. The ability to reveal accurate somatotopic maps of nociceptive processing in the spinal cord is essential if the field of spinal cord imaging is to move forward. One study has emerged and attempted to answer the question of somatotopic representation of nociception within spinal cord [3]. Brooks et al. (2012) assessed the effects of stimulus site and modality on activity within the spinal cord, delivering nociceptive thermal and punctate stimuli to the C6 and C8 dermatomes during a single fMRI scan. The authors were able to show lateralization of the dorsal horn BOLD response to noxious stimulation but were unable to discriminate between stimulation of different spinal dermatomes.

Our specific study goals were to further refine the technique and demonstrate that fMRI could reveal: (i) appropriate somatotopic activations in response to noxious stimuli in the deep and superficial dorsal horn of the human cervical spinal cord across

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spinal dermatomes (C5 and C6); and (ii) lateralization of fMRI activations in response to noxious stimulation in the right and left upper extremity of the cervical spine's dorsal horn.

2. Methods

2.1. Subjects

We recruited 10 healthy, undergraduate and graduate volunteers (6 women and 4 men) without any history of neurologic or psychiatric disease or chronic pain. Their ages ranged from 18 to 32 years (mean ± SD, 23 ± 4 years). All subjects were given detailed information about the protocol and were told that they were free to withdraw from the study at any time. All gave their written, informed consent. The protocols were approved by Stanford University's institutional review board.

2.2. Subject set-up before scanning

Before subjects underwent scanning, we had to address 3 issues that could compromise results. The first has to do with the issue of subject movement. The spinal cord is relatively small (<20 mm), and the area of activation is smaller (2 mm). Therefore, even the slightest subject movement is problematic. Even deep breathing or swallowing cause motion of the spinal cord, which can degrade image quality. To minimize these motion artifacts during scanning, we relied on standard methods—placing several straps across the subjects' head and torso, inserting a rigid bite bar into subjects' mouths, and encouraging subjects to be as still as possible by avoiding deep breathing, swallowing, and other subtle movements. In general, each subject moved less than 0.5 mm throughout each scan (as measured with the rigid body motion correction step described in the Image Processing section below).

A second issue that could compromise scanning results relates to the fact that imaging the cervical spine entails obtaining images from a body region the tissues (subcutaneous fat, muscle, lungs, and the spinal cord itself) of which are not homogeneous or equally dense, producing an unfriendly environment for fMRI. To minimize the effects of different tissue densities and improve B_0 homogeneity, we used 2 techniques. First, we placed scanning phantoms around a subject's neck and chest to influence the mean tissue densities [41]. This phantom consisted of a custom saturation pad filled with attapulgite, placed around the subject's head and neck, as indicated in the Cox and Dillon imaging studies [7]. The pad reduced magnetic field heterogeneity while remaining occult in the MRI images. Second, we used the scanner's high-order shim protocol [25], described in detail below, to reduce magnetic field heterogeneity.

The third issue is that physiologic processes such as heart rate and respiration can lead to motion of the spinal cord and degradation of the signal within the images. During scanning, we recorded heart rate and respiration by placing the scanner's photoplethysmograph on a subject's finger and the pneumatic respiration belt on the abdomen. The information collected was then used in RETROIcor software to retrospectively correct for the effects of physiologic noise on image quality [18].

2.3. Stimulation

To ensure that our subjects were familiar with the pain tasks to be used during our scans, they underwent a training session before scanning. During the training session, we applied noxious thermal stimuli to accurately obtain the temperatures correlated to each subject's first report of pain (pain threshold), report of maximum pain, and pain rating of 7 of 10 (visual analogue scale [VAS]), where 0 = no pain and 10 = worst pain imaginable). We applied the temperature found to cause a pain rating of 7 of 10 for all of the pain tasks in the scanner.

Once the subject was in the scanner, we applied thermal stimuli to 2 different sensory dermatomes on both the left and right sides, thereby creating four separate pain tasks in each subject (left and right thenar eminence; n = 7, left deltoid; n = 8, right deltoid; n = 7). Thermal stimuli were delivered with a Peltier thermode (TSA 2001, MEDOC, Haifa, Israel; 3 × 3-cm conducting surface) to the thenar eminence and the deltoid, corresponding to the C6 to C7 and C4 to C5 dermatomes. Our study used a conventional block design consisting of 6 cycles, each comprising a 30-second period of noxious thermal stimulation, alternated with a 40-second period of warm stimulation (32°C). After each subject had undergone scanning, we asked them to rate the pain level to test whether the pain rating remained 7 of 10.

2.4. MRI scans

To collect the scans required to show accurate somatotopic maps of pain processing in the spinal cord we used a GE 3T MRI scanner (GE Healthcare Discovery 750, Milwaukee, WI), and a receive-only cervical spine phased array coil with 8 elements (Nova Medical, Wilmington, MA).

We collected 3 different scans on all subjects during this experiment; each of these served a different purpose toward achieving our goals. An additional 3-dimensional (3D) anatomical scan was collected on a single subject for the purposes of creating a template for normalization, as discussed in more depth below.

First, we collected a localizer scan (gradient echo, repetition time (TR) = 300 ms, echo time (TE) = 14 ms, flip angle = 30°, matrix = 256 × 128) to provide an anatomical image of the general area of interest and to accurately prescribe the other scans. We also used these scans as a way to accurately normalize across a group of subjects. (This normalization procedure is described in more depth below in Section 2.5.)

Second, we collected an axial anatomical image (T2 weighted, spoiled gradient recalled, gradient echo, TR = 3000 ms, TE = 25 ms, flip angle = 30°, voxel size = 0.65 × 0.65 × 4 mm^3, matrix = 256 × 192), prescribed using the identical slice prescriptions as the functional scans, from the top of C4 to the bottom of C6 for the deltoid tasks, and from the top of C5 to the bottom of C7 for the thenar tasks. Functional images of the cervical spinal cord have relatively poor image quality and spatial resolution; we used these axial anatomical images for reference purposes.

The scanner's high-order (2nd order + Z3) shim routine was used to reduce field variations in a region of interest that was carefully chosen to include only the central spinal cord. This iterative shim technique uses a singular value decomposition method to optimize the resistive shim currents within the region of interest [25]. The shim procedure, in combination with the MRI-invisible phantoms placed around the subject's neck as described above, ensured adequate magnetic field homogeneity.

Finally, we collected a series of 4 fMRI scans (double shot, spiral in–out gradient echo sequence [28], TR = 1250 ms, TE = 25 ms, flip angle = 75°, voxel size = 1.25 × 1.25 4 mm^3, matrix = 128 × 128, 212 volumes) which corresponded to noxious stimulation at each of the 4 body sites (left and right deltoid, and left and right thenar eminence). We chose to use a spiral in–out gradient echo sequence over a standard EPI sequence for our fMRI scans because of their decreased susceptibility to motion artifacts, such as those created by physiologic processes including heart rate and respiration [17]. Spiral in–out sequences add additional benefit in having decreased signal dropout associated with tissue interfaces [16].

We also collected a high-resolution 3D anatomical image (T2 weighted, multi-echo recalled gradient echo (MERGE), TR = 30 ms,

TE = 12.2 ms, flip angle = 5°, voxel size = 0.69 × 0.69.1.6 mm^3, matrix = 288 × 288) on a single subject to be used as a template for normalization.

2.5. Image processing

We followed these 6 image-preprocessing steps:

(1) We retrospectively corrected all images for respiratory effects and cardiac pulsatility, using an image-based correction algorithm RETROIcor [18]. These physiological processes can cause noise and can degrade the statistical significance of activation signals; therefore, it is important to remove their possible effects.
(2) Next, we used SPM8 software [12] to process image data. Physiological processes such as heart rate and respiration and the subjects' swallowing can cause the spinal cord to move independently of the neck. To correct for this motion, we created a mask of the spinal cord on the functional images, using the in plane T2 anatomical image as a reference. Using this mask, we extracted only the spinal cord portion from the images and thereby applied rigid-body motion correction to the spinal cord only.
(3) We used software known as ArtRepair [33] to detect and repair any bad slices within the images.
(4) Because no MNI or Talerach template exists for the spinal cord, we used a high-resolution, 3D T2 anatomical image from a single subject as a basis for creating a standard template. We created a mask of the entire spinal column, rostro-caudally from the top of C3 to the bottom of T1 and dorso-ventrally from the ventral aspect of the vertebral column to the dorsal aspect of the spinal cord. We used this image as the template with which to normalize all subjects to a common space. We created an identically masked image covering the same segments of the spinal cord on each subject's localizer scan and normalized this to our template. We used these parameters to normalize the in-plane axial anatomical and all preprocessed functional images. Although this technique aligned and warped the spinal cord across our group of subjects, the images needed further refinements.
(5) To ensure that each subject's spinal cord aligned perfectly, we performed manual co-registration. For example, using 1 subject's normalized left deltoid scan as the reference image, we aligned other subjects' normalized left deltoid functional scans to match that image, thereby perfectly aligning the centers of their spinal cords, ensuring that the same area of the spinal cord was compared in all subjects.
(6) Finally, we resliced and applied a 3-mm (FWHM) Gaussian smoothing kernel to all the functional images. The difficulty normalizing the spinal cord required a slightly larger smoothing kernel than would be ideal. The 3-mm smoothing kernel that we used is still more conservative than the 3 times the raw voxel size that has been used previously in spinal cord imaging [4]. A previous spinal cord imaging study [3] used spatial smoothing to the individual contrast images after the first level analysis instead of smoothing the images before analysis as we have done. This technique has been found to have no significant effect on the size, location, or significance of the result [31]; we therefore believe that our method of smoothing before analysis is appropriate.

2.6. Group statistical analysis

We entered each subject's data into an individual first-level statistical analysis in SPM8 [12]. We used a repeated boxcar model (40 seconds off, 30 seconds on, repeated 6 times), convolved with a specific spinal cord hemodynamic response function [14], to determine significant fMRI signal changes in each individual. We then added each individual's results into a second-level, random effects analysis in the nonparametric version of SPM8, SnPM. We chose to use a nonparametric statistical analysis to account for the small sample size that we have in each of our groups. We added an explicit mask of the spinal cord, taken from the in-plane anatomical, to the analysis to ensure that activation was within the cord and not the cerebrospinal fluid (CSF). We ran a positive 1-sample *t* test on each group (random effects, $P < .01$ uncorrected, 5 voxels).

We created regions of interest (ROIs) of the most significantly activated dorsal horn clusters for each group. From these ROIs, we calculated the average percent signal change, across all voxels in the ROI. We then averaged these together across all subjects to give a group mean, event-related signal change. This mean signal change was then plotted for each of the dorsal horn ROIs during pain at all 4 of our pain locations.

3. Results

3.1. Individual visual analog scale

The temperatures required to yield a 7 of 10 pain rating, on a VAS, ranged from 46.0°C to 48.2°C (mean ± SD = 47.5° ± 0.6°C) for the thenar tasks and 45.8°C to 48.2°C (47.3° ± 0.7°C) for the deltoid tasks. The post-scanning pain ratings that we obtained consistently yielded the same values as those determined at the pre-scanning session. We made no attempt to distinguish the sensory and affective components of the thermal pain.

3.2. Distribution of neuronal activity

As we stated in our study objectives, the primary findings of this study were 2-fold (Fig. 1). First, we found that painful stimulation, regardless of location, predominantly activated the ipsilateral dorsal horn. Painful stimulation of the left side of the body (left deltoid or left thenar eminence) activated the left dorsal horn, whereas pain on the right side (right deltoid or right thenar eminence) activated the right dorsal horn. Second, we found that painful stimulation of the deltoid region activated the dorsal horn at spinal segment C5, and painful stimulation of the thenar eminence activated the dorsal horn at spinal segment C6. We observed that, during painful stimulation of all four sites (left and right thenar eminence, and left and right deltoid) (see Table 1), BOLD signal significantly increased in an event-related manner (Fig. 2).

Although the above results were central to our described aims, we also had an additional finding. We noted that painful stimulation of the thenar eminence significantly increased BOLD signal within the ventral horn of the spinal cord at the C5 level.

4. Discussion

This study fulfilled our objectives and demonstrated that fMRI can be used to create high-resolution activation maps of the human cervical spinal cord. At a group level, we captured activation patterns that agree with the lateralization and rostrocaudal somatotopy of peripheral input to the spinal cord. Deltoid nociceptive stimulation resulted in activations clustered within the ipsilateral dorsal horn of C5; thenar eminence nociceptive stimulation resulted in activations clustered within the ipsilateral dorsal horn of C6.

Historically, animal work has shown that painful stimulation of 1 side of the body results in activation in ipsilateral spinal dorsal horn. This lateralization is reflected in the classic map of the spinothalamic tract, where a noxious stimulus is transmitted by

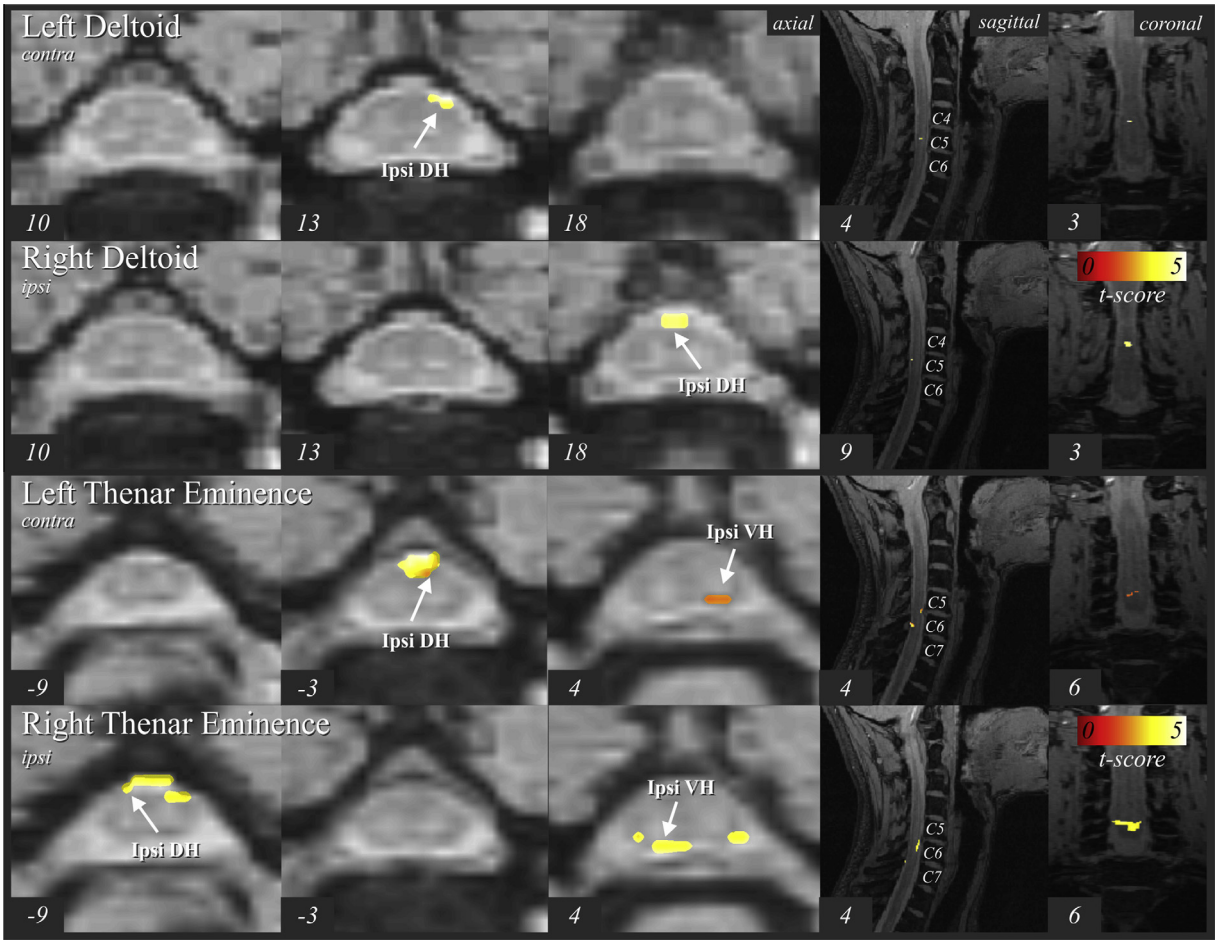

Fig. 1. Spinal cord regions showing significantly increased BOLD signal during heat pain applied to the left deltoid (top), right deltoid, left thenar eminence, and right thenar eminence (bottom). These activation maps have been overlaid onto a single subject's high-resolution anatomical image. Slice locations are listed in the bottom left corner of each image. Ipsi, ipsilateral; DH, dorsal horn. T score color bar graphically shows the statistical significance of each cluster, with brighter colored clusters being more significant.

Table 1
Co-ordinate locations of the most activated voxel in the dorsal horn in response to painful stimuli.

Location of painful stimulation	x	y	z	*z* Score	Cluster size
Deltoid					
Left	2	4	13	2.44	2
Right	2	10	16	2.26	2
Thenar eminence					
Left	4	0	−3	3.30	16
Right	7	−3	−9	2.56	9

Cluster size refers to the number of voxels in the cluster at $P = 0.01$. The *z* score indicates the statistical significance of the most activated voxel within the cluster. Co-ordinate locations (x, y and z), significance and size of reported clusters.

small-diameter peripheral neurons that synapse in the ipsilateral dorsal horn, decussate, and ascend within the anterolateral tract to the brainstem, thalamus, and cortex. Our findings—that heat pain delivered to the deltoid and thenar eminence activates the ipsilateral dorsal horn—agree with those of other investigators who assessed spinal cord activity during painful stimuli [3,4]. They described ipsilateral dorsal horn activation during heat and punctate pressure pain [3,4]. Animal studies support this, showing that heat and chemical pain activates neurons in the dorsal horn using C-fos immunohistochemistry [21,24,45]. Studies have also confirmed this by using electrophysiology and 2-deoxy-glucose imaging techniques [6].

The segmental level of the spinal cord that controls and processes sensory information from different parts of the body is dictated by locations where those peripheral nerves enter the cord. Input of peripheral nerves into the cord occurs as follows: the thenar eminence is innervated by spinal nerves that enter the central nervous system at C6, whereas the deltoid is innervated by nerves entering primarily at C5. This convention was first described in 1933 by Foerster, who anatomically traced individual spinal roots, from their junction with the spinal cord to the their tissue origin, and examined their peripheral receptive fields [11]. A study of the sensory deficits in patients with ruptured disks also supports this, with the authors describing pain in the deltoid region after C5 rupture, and pain in the thenar eminence region after C6 rupture [34]. We found that painful stimulation of the deltoid resulted in activation of the spinal cord at the C5 level, and that painful stimulation of the thenar eminence caused spinal cord activation at the C6 level. Our results agree with the classic sensory dermatomal map.

A recent study by Brooks et al. was unsuccessful in showing rostro-caudal discrimination between nociceptive stimuli applied to the C6 and C8 dermatomes [3]; although their study had similar aims, the different methodology used by their study and ours may account for the difference in results. Brooks et al. used a single, 42-minute scan with nociceptive stimuli of different modalities randomly delivered to the C6 and C8 dermatomes. In addition to this, they used an echo planar, gradient echo sequence

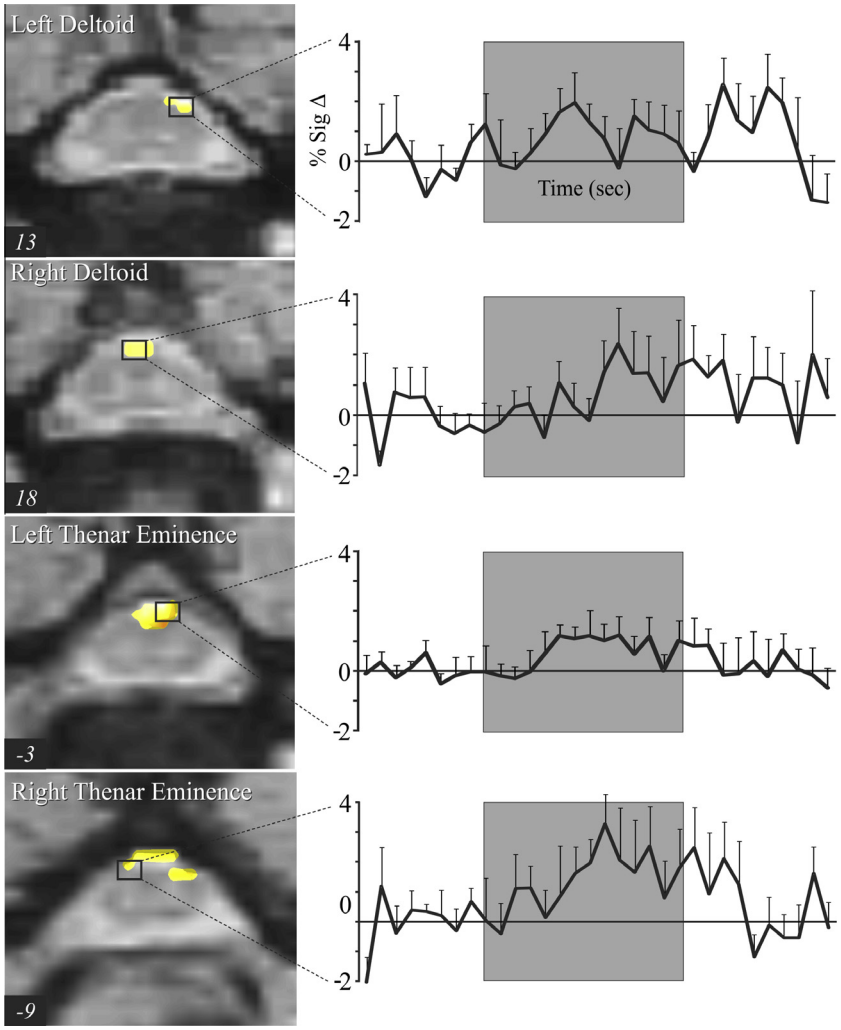

Fig. 2. Plots of signal change over time extracted from the dorsal horn ROIs taken from the group analysis. Activations are overlaid onto an axial section from a single subject's high-resolution anatomical image. ROIs were created from the most activated cluster in the ipsilateral dorsal horn, and mean (±SEM) event-related time courses were calculated from those ROIs. Gray bars indicate the pain period.

and accounted for physiologic noise by adding the respiration and cardiac wave forms as regressors in the final analysis. As described in the Methods section, we collected a different scan for each site of noxious stimulation (C5 and C6 on the left and right sides), we used a spiral gradient echo sequence [17], and used Retroicor software [18] to account for physiologic noise. We believe that the differences in methodology may account for the differences in results described in these 2 studies.

Although the pattern of dorsal horn activity was the focus of this study, a secondary finding that emerged was activity within the ventral cord. During heat pain delivered to the thenar eminence, we found BOLD signal significantly increased within the ventral aspect of the cord at the C5 segmental level. The ventral horn of the spinal cord is where the cell bodies of alpha motor neurons, which innervate skeletal muscle, are located, and is therefore thought to control voluntary and reflexive movement. This study did not involve a motor task, but activation of motor regions during pain tasks is common [1,19,27,31,35]. Furthermore, ventral horn activity has been recorded in anesthetized rats during a pain task [29], indicating that ventral horn activity due to pain is possible in the absence of any movement.

Interestingly, during noxious stimulation of the thenar eminence, we found ventral horn activity at C5, 1 segment above the level at which we found dorsal horn activity. Activation of motor areas is common during pain tasks and is hypothesized to be a safety mechanism to escape the noxious stimulus and to guard the injured area from further injury. It is possible that the activation that we are seeing at the C5 level during noxious stimulation of the hand is caused by this guarding or escape mechanism. The fact that neurons from the ventral horn at C5 are known to innervate muscles that support the hand and arm, such as Serratus anterior, Deltoid, Ifraspinatus, Teres minor, Teres major, Pectoralis major, Supraspinatus, Biceps, Brachialis, Brachioradialis, and Supinator supports this theory, as these are the muscles that would be involved in a reflexive movement to remove the hand from a possibly noxious event.

This study aimed to provide high-resolution maps of pain processing in the dorsal horn of the spinal cord; however, 2 limitations exist with regard to the current study. First, the limited spatial resolution of fMRI prevented us from being able to completely achieve our goal. We collected images with a raw voxel size of $1.25 \times 1.25 \times 4\ mm^3$, a satisfactory size for scanning the spinal cord. However, the dorsal horn is a laminated structure that receives nociceptive input preferentially to lamina I, II, and V [6,8]. Our results show clear BOLD activation within the dorsal aspect of the cord, within the region that we believe to be the dorsal horn. Commentary on any specific lamina activation is outside the scope of this study, because of the above-mentioned limitations of fMRI

as well as our need to spatially smooth our images for statistical analysis. Second, we used a statistical analysis that is not corrected for multiple comparisons, making it susceptible to false-positive results. However, the significant clusters that we report here have a 5-voxel minimum size, and are laterally and somatotopically accurate. It is also worth noting that there are fewer voxels within the spinal cord and therefore fewer comparisons, decreasing the chances of finding false-positive results. Although we understand the risks of using an uncorrected statistical threshold, we believe that the results that we have presented here are accurate.

Overall, our study contributes to creating an objective analysis of pain transmission in the spinal cord. The study revealed consistent, accurate patterns of neuronal activity within the cervical spinal cord, consequent to noxious stimulation. Functional MRI, combined with spiral k-space fMRI acquisitions and retrospective correction for physiologic noise, can be used to create accurate, somatotopically correct representations of pain transmission and processing in the human spinal cord.

Conflict of interest statement

None of the authors have any financial relationships that may lead to a conflict of interest.

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