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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,