Understanding the fMRI response to thermal stimuli in the human spinal cord

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Introduction
Spinal cord functional magnetic resonance imaging (spinal fMRI) is the only non-invasive, in vivo means available to access neuronal changes that occur as a result of injury. However, in order to achieve its clinical potential, characterization of the fMRI response in healthy subjects along the entire spinal cord is needed to demonstrate the sensitivity and reliability of this technique. A number of studies to date have demonstrated the ability to detect activation of spinal cord neurons with functional MRI. Yet, these studies have all focused on imaging a given region of the cord. Comparisons of results between different segmental levels of the spinal cord are needed because it is unknown if there are systematic differences in functional responses along the cord, to a given stimulus. Moreover, differences between repeated studies with thermal stimulation within an imaging session have been shown to suffer from order effects. This occurs because repeated applications of a thermal stimulus may not produce the same perceived sensation, and significant changes in the level of alertness and attention have been observed to occur as the participants become bored/sleepy, resulting in differences in the detected spinal cord activity. Here, we characterize fMRI signal responses at different levels of the spinal cord within a single experiment, by means of simultaneous thermal stimulation using surface thermodes, and a custom-made thermal stimulation device. Each thermode is heated/cooled with a distinct on-off block paradigm, such that the four paradigms are linearly independent, thus allowing the response to each thermode to be detected. Thermodes were positioned to stimulate cervical, thoracic, and lumbar spinal cord segments in each experiment, in healthy volunteers. The aim of this study was to extend the methods used in our previous experiments to image neuronal activity spanning almost the entire spinal cord. More importantly, the results of this study enable comparisons to be made between responses at different levels of the spinal cord, without the confounding effects caused by differences between repeated studies.

Methods and Materials
Functional MRI studies of the spinal cord were carried out in healthy subjects with no history of spinal injury in a 3T Siemens Magnetom Trio. To examine the neuronal activity thermal stimulation was applied by means of a custom-made device to four distinct dermatomes spanning the length of the spinal cord: more specifically, the C7/C8, T6, T12, and L4 spinal cord segments. These segments were stimulated by thermodes positioned on the anterior-medial area of the hand, 4 cm above the bottom rib, just above the hip bone in the lumbar region, and the medial side of the shin respectively (all on the right side of the body). Thermal stimuli of 44°C were applied in a block paradigm whereby three stimulation periods of 45 s were interspersed with equivalent length baseline periods for a total of 6 min 45 s per experiment. Functional imaging data were acquired with a half-fourier acquisition single-shot turbo spin-echo (HASTE) sequence. TE=38 ms and TR=1 s per slice, in order to obtain primarily proton-density weighted images. Signal intensity changes observed in the image data upon a change in neuronal activity were the result of SEEP and BOLD effects. Sagittal image slices were selected to span from the C7/T1 disc to the bottom of the conus medullaris, with a 384 mm x 288 mm FOV, a 192 x 144 matrix, in nine 2 mm thick contiguous sagittal slices spanning the entire width of the spinal cord. Time series analysis was carried out by means of a general linear model with inclusion of terms to model the cardiac-related confounds. Analysis was completed using custom-made software, written in MatLab². This experiment has been supplemented with further studies implementing stimuli with varying ramp speeds and durations.

Results
Group analysis of the results from all participants shows areas of consistent neuronal activity in the spinal cord at each of the four spinal cord segments, corresponding to the locations of thermal stimulation. Comparing the segmental responses, similar responses were notable in the C7/C8 (cervical enlargement) and L4 (lumbar enlargement) segments, whereas a different response pattern was detected in the upper and lower thoracic regions. The results demonstrate prominent areas of activity in the ipsilateral dorsal horn grey matter (C7/C8, and L4 segment stimulation), and in the contralateral dorsal horn (T6 and T12 segments). The differing patterns in the thoracic segments are attributed to differences in sensitivity to thermal stimuli, and therefore different perceived sensations with stimulation of the chest or hip, as compared to the hand or leg. The observation of contralateral dorsal grey matter activity in the thoracic regions indicates that differences in descending modulation of spinal cord activity also plays a role in the observed differences. The ipsilateral dorsal activity observed in the cervical and the lumbar regions is consistent with the results of previous studies employing thermal stimulation. The areas of activity are observed to extend several millimeters in the superior-inferior direction within the spinal cord segments, and the activity extends into bordering segments. Time-course analysis of the activated voxels, for all levels of the cord, shows spikes of neuronal activity corresponding to the change in temperature of the stimuli as they heat and cool (Fig. 1). Results from supplementary studies conducted also demonstrate neuronal responses associated with a rising and falling of temperature. The target segmental activation sites demonstrate similar patterns of responses between the dorsal right, and dorsal left regions of the cord. Likewise, comparing the signal time-courses between the segments shows a general blueprint for the response pattern to the stimulus involving sharp higher peaks for the first two stimuli, followed by a pair smaller broader signal responses, indicating a desensitization to the stimulus.

Conclusions
The differences in the responses observed in thoracic regions may reflect the sensitivity of the fMRI method, as well as important differences in regional responses. Assessment of spinal cord function in the thoracic region is challenging with standard clinical tests¹, and the observations from this study may provide important reference data for future studies of the effects of spinal cord trauma at all levels of the spinal cord, including the thoracic region. The results to date demonstrate that with this method, it is possible to examine the activity in four different sensory dermatomes spanning the full length of the cord simultaneously. Furthermore, the detection of neuronal response to a change in temperature allows for a more refined model in the analysis to improve spatial accuracy and detection. This has implications for the development of a practical clinical method for assessing spinal cord function by means of spinal fMRI.

References