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Functional magnetic resonance imaging of the cervical spinal cord during thermal stimulation across consecutive runs

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ABSTRACT

The spinal cord is the first site of nociceptive processing in the central nervous system and has a role in the development and perpetuation of clinical pain states. Advancements in functional magnetic resonance imaging are providing a means to non-invasively measure spinal cord function, and functional magnetic resonance imaging may provide an objective method to study spinal cord nociceptive processing in humans. In this study, we tested the validity and reliability of functional magnetic resonance imaging using a selective field-of-view gradient-echo echo-planar-imaging sequence to detect activity induced blood oxygenation level-dependent signal changes in the cervical spinal cord of healthy volunteers during warm and painful thermal stimulation across consecutive runs. At the group and subject level, the activity was localized more to the dorsal hemicord, the spatial extent and magnitude of the activity was greater for the painful stimulus than the warm stimulus, and the spatial extent and magnitude of the activity exceeded that of a control analysis. Furthermore, the spatial extent of the activity for the painful stimuli increased across the runs likely reflecting sensitization. Overall, the spatial localization of the activity varied considerably across the runs, but despite this variability, a machine-learning algorithm was able to successfully decode the stimuli in the spinal cord based on the distributed pattern of the activity. In conclusion, we were able to successfully detect and characterize cervical spinal cord activity during thermal stimulation at the group and subject level.

1. Introduction

The central processing of nociceptive information begins in the spinal cord (SC) (Green, 2004; Willis and Westlund, 1997). Through animal studies, we have gained extensive knowledge about SC nociceptive processing including the central projections of primary afferents (Light and Perl, 1979; Sugiura et al., 1986), the SC circuitry that integrates and relays nociceptive signals to other central targets (Apkarian and Hodge, 1989; Willis et al., 1979), and the descending supraspinal control systems that modulate nociceptive processing in the SC (Carstens et al., 1979; Lin et al., 1994). This knowledge has provided the neurophysiological grounds for many clinical pain phenomena (e.g., hyperalgesia, allodynia, referred pain, etc.) and new targets for treatment (Latremoliere and Woolf, 2009). Overall, animal studies have expanded our understanding of the SC pathophysiology in clinical pain states; however, there are limitations in the ability to translate animal research findings to humans (Hackam and Redelmeier, 2006; van der Worp et al., 2010), and an objective method to study SC nociceptive processing in humans would allow for the direct study of the SC pathophysiology in clinical pain states and advance clinical pain research.

A major advancement in pain research has been the application of functional magnetic resonance imaging (fMRI), allowing for the non-invasive, high-spatial resolution mapping of pain-related neural activity. fMRI research has enhanced our understanding of supraspinal nociceptive processing, pain perception, clinical pain states, and the functional changes in the brain underlying the transition from acute to chronic pain (Apkarian et al., 2005; Mansour et al., 2014). Furthermore, the non-invasiveness of fMRI makes it well suited for longitudinal pain research, and the ability to use fMRI in both animal and human studies supports the forward translation of animal findings to clinical research and the

Abbreviations: SC, spinal cord; BOLD, blood oxygen level dependent; MR, magnetic resonance; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; SPACE, sampling perfection with application optimized contrast using different flip angle evolutions; FMRIB, Oxford Center for Functional MRI of the Brain; FSL, FMRIB's Software Library

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reverse translation of clinical findings to animal models (Mao, 2009).

Over the last two decades, a growing base of researchers have been developing increasingly sophisticated methods for SC fMRI, and the means to objectively measure SC nociceptive processing in humans has become more and more practical (for review see Kolesar et al. (2015), Stroman et al. (2014) and Wheeler-Kingshott et al. (2014)). To date, several independent groups have used fMRI to study SC processing in both animals and humans using thermal (Brooks et al., 2012; Cadotte et al., 2012; Cahill and Stroman, 2011; Khan and Stroman, 2015; Nash et al., 2013; Summers et al., 2010; Yang et al., 2015), chemical (Malisza and Stroman, 2002; Porszasz et al., 1997), and electrical (Endo et al., 2008; Lilja et al., 2006; Zhao et al., 2009) experimental pain paradigms. Moreover, some studies have even demonstrated supraspinal influences on SC nociceptive processing (Dobek et al., 2014; Eippert et al., 2009; Geuter and Buchel, 2013; Sprenger et al., 2012).

The purpose of this study was to test the validity of fMRI using a selective field-of-view gradient-echo echo-planar-imaging sequence to detect activity induced blood oxygenation level-dependent (BOLD) signal changes in the SC during warm and painful thermal stimulation. We hypothesized that the SC activity to thermal stimuli would be anatomically specific (located primarily to the ipsilateral dorsal quadrant of the SC), proportional to the stimulus temperature, and exceed a control analysis at both the group and subject level. Furthermore, because the reliability of the SC fMRI signal during noxious thermal stimulation needs to be further assessed (Kolesar et al., 2015), we also evaluated the reliability of the signal across consecutive runs. Finally, in order to quantify the amount of pain-related information present in the SC, we utilized a machine-learning algorithm to decode the thermal stimuli based on the distributed patterns of SC activity.

2. Methods

2.1. Participants

Twelve healthy volunteers (9 male and 3 female; average age $\pm$ one standard deviation (SD) 28.8 ± 2.5 years) were studied. Subjects reported no significant pain, neuromusculoskeletal diseases, or contraindications to MRI. The subjects were informed that the study aimed to investigate pain processing using thermal stimulation and fMRI. The entire study protocol was explained to the subjects, and the subjects provided written informed consent. Northwestern University's Institutional Review Board approved this study.

2.2. Imaging protocol

Imaging was performed with a 3.0 Tesla Siemens Prisma (Erlangen, Germany) magnetic resonance (MR) scanner equipped with a 64-channel head/neck coil. Head coil elements 1–4 were turned off during imaging to minimize motion and flow artifacts from the internal carotid arteries. Head coil elements 5–7 (inferior portion of the head coil) and neck coil elements anterior and posterior (24 channels total) were used to capture the MR signal. To increase the magnetic field homogeneity across the cervical spine and to reduce bulk motion during scanning, a SatPad™ cervical collar was used (Maehara et al., 2014). For the functional images, thirty-one transverse slices of the cervical SC were acquired with a T_2^*-weighted gradient-echo echo-planar-imaging sequence using ZOOMit selective field-of-view imaging (TR = 2500 ms, TE = 30 ms, flip angle = 80°, acquisition matrix = 128×44, field-of-view = 128×44 mm^2, in-plane resolution = 1×1 mm^2, slice thickness = 3 mm) (Pfeuffer et al., 2002; Rieseberg et al., 2002). The imaged volume spanned from the superior endplate of the third cervical vertebra to the superior endplate of the first thoracic vertebra (Fig. 1). For registration of the functional images to template space, a high-resolution T_2-weighted structural image of the entire cervical spine and upper thoracic spine was acquired using a single slab three-dimensional turbo spin echo sequence with a slab selective, variable excitation pulse (SPACE, TR = 1500 ms, TE_{eff} = 115 ms, echo train length = 78, flip angle = 90°/140°, effective resolution = $0.8 \times 0.8 \times 0.8$ mm^3, interpolated resolution = $0.8 \times 0.4 \times 0.4$ mm^3) (Lichy et al., 2005; Mugler et al., 2000). The imaging protocol was the same as used in our previous study exploring SC activity during an upper extremity motor task (Weber et al., 2016).

2.3. Thermal stimulation protocol

Prior to scanning and outside of the scanner room, subjects were familiarized to the thermal stimulation protocol, and pain threshold temperatures and temperature-pain response functions were calculated. Thermal stimuli were applied to the lateral aspect of the ventral proximal right forearm (Advanced Thermal Stimulator with fMRI filter, 900 mm^2 square activation area, Pathway Pain and Sensory Evaluation System, Medoc Ltd., Ramat Yishai, Israel). To familiarize subjects, a range of thermal stimuli were applied in 1.0 °C increments from 43.0 °C up to 50.0 °C as tolerated. For each stimulus, the thermode temperature was increased from a baseline temperature of 30 °C at a rate of 5.0 °C/s to the destination temperature, held for a duration of 7.5 s, and then decreased at a rate of 5.0 °C/s back to a baseline temperature of 30.0 °C. After each stimulus, the subjects were asked to practice rating their pain experience using a 101-point verbal numerical rating scale (NRS) with anchors of “no pain” (0) and “worst imaginable pain” (100) (Hawker et al., 2011).

For the pain threshold temperatures, the thermode temperature was increased from a baseline temperature of 30.0 °C at a rate of 0.5 °C/s. When the sensory experience changed from warmth to pain, the subjects were instructed to press a button, and then the thermode temperature returned to baseline at a rate of 5.0 °C/s. The temperature at the time of the button press was recorded, the procedure was repeated an additional three times, and the last three temperatures were averaged to determine the pain threshold temperature.

Temperature-pain response functions were then calculated. Thermal stimuli were applied with destination temperatures in 1.0 °C increments from the pain threshold temperature –1.0 °C up to the pain threshold temperature +4.0 °C as tolerated (baseline temperature = 30.0 °C, destination rate = 5.0 °C/s, duration = 7.5 s, return rate 5.0 °C/s). Two thermal stimuli at each destination temperature were applied, and the order of the thermal stimuli was randomized. Following each stimulus, the subjects verbally rated their pain experience. The stimulus temperatures and pain ratings were then modeled with a linear function (extreme pain ratings of 0 and 100 were ignored), and the stimulation temperature that provided a pain experience of 65 was calculated.

Subjects were then moved to the scanner room and positioned supine on the scanner bed. The thermode was reattached to the lateral aspect of the ventral proximal right forearm and remained in position for the entire scanning session. For each functional imaging run, ten warm (43.0 °C) and ten painful (temperature producing a moderate pain experience of 65) thermal stimuli were delivered (baseline temperature = 30.0 °C, destination rate = 5.0 °C/s, duration = 7.5 s, return rate 5.0 °C/s) in a randomized order with a varying interstimulus interval (range = 2.5–10.0 s) over a period of 400 s, and each subject completed six runs. No feedback was provided to the subjects for the thermal stimuli, and throughout the imaging session, the subjects were instructed to remain still and not produce any movements. As a safeguard,