Altered spinal cord and brainstem activation in response to peripheral sensitization to sensory stimuli: a spinal fMRI study

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Introduction

Functional magnetic resonance imaging (fMRI) studies have identified multiple brain structures involved in the pain experience. However, most of the imaging studies performed to date have focused on brain structures rostral to the thalamus, although the first level of sensory information and pain transmission occurs at the spinal cord. The primary goal of the present study is to map activity using fMRI, from the entire cervical spinal cord and brainstem following innocuous and noxious stimuli before and after peripheral sensitization in normal human volunteers. This study is unique in that it focuses on determining the functional activity induced by sensory and painful stimulation within the spinal cord and lower supraspinal structures in human subjects who can simultaneously report their pain experience. Using these findings, we can then assess the various components of touch and pain experiences, enabling detection of differences in activity between normal nociceptive pain and abnormal pain responses.

Materials and Methods

Functional MRI studies of the spinal cord were carried out in 26 healthy individuals in a 3T Siemens Magnetom Trio. We examined the activity of innocuous touch (n=8), brush (n=8) and noxious touch (n=10) before and after peripheral sensitization. Touch and brush stimuli consisted of von Frey filaments of varying force or a 2 cm wide artist brush applied to the right volar forearm at a frequency of 1 Hz. Stimuli were randomly applied in a block paradigm consisting of three stimulation periods of 56 seconds, interleaved with baseline periods of 140 seconds, for a total of 11 min 12 seconds for each experiment. After each block, volunteers were asked to rate the pain and unpleasantness on a numerical 11 point scale, where 0 indicates no pain and 10 indicates worst possible pain[1]. Peripheral sensitization was induced by topical application of capsaicin (0.075%) for 30 minutes.

Functional image data were acquired with a half-fourier single-shot fast spin-echo (HASTE) sequence. TE=38 msec and TR=1 sec 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 signal enhancement by extravascular water protons (SEEP)[2,3], as well as a contribution from BOLD. Sagittal image slices were selected to span from the C7/T1 disc to the superior edge of the thalamus, with a 20 cm x 10 cm FOV, a 192 x 96 matrix, in fourteen 2 mm thick contiguous sagittal slices to span the entire width of the spinal cord and brainstem. Spatial suppression pulses were applied to eliminate aliasing and signal anterior to the spine. The peripheral pulse was recorded continuously during each study and was used with a general linear model approach to improve the discrimination between physiological motion and signal intensity changes arising from neuronal activity[4].

The resulting 3D image data were reformatted to permit smoothing only along the long axis of the cord anatomy, and were normalized to a consistent coordinate space for all subjects to facilitate group comparisons of results. Analysis was done with custom-made software written in MatLab. Normalized results were combined to demonstrate the number of volunteers showing activity at each location on a voxel-by-voxel basis. The primary areas of activity were detected in a minimum of 5 (n=8) or 6 (n=10) of the volunteers. Areas of activity were superimposed onto anatomical transverse drawings and identified visually with comparison to a stereotaxic atlas.

Results and Discussion

The results from this study strongly indicate that a non-noxious stimulus translates into a pain response after peripheral sensitization. A touch response, examined by the brush stimuli, before sensitization activated typical areas expected of non-painful sensory transmission. These include the ipsilateral dorsal horn, gracile and cuneate nuclei in the medulla and areas surrounding the dorsal column medial lemniscal pathway. Peripheral sensitization produced activation patterns typical of a pain response, such as the contralateral ventral horn which is thought to be due to activation of descending pain-modulating systems. The touch stimulus (pain score = 1) produced activity in typical sensory centres in the dorsal horn and brainstem before sensitization, but after sensitization, we observed a pain response as evidenced by the activity in the spinal cord and higher brainstem structures. Interestingly, stimuli that produced the same pain ratings before and after peripheral sensitization (pain score = 4-6) showed similar activation patterns even though the force of the von Frey filament used to evoke these responses were different. In all experiments there was indication of descending modulation as activity was observed in and around areas of the periaqueductal gray, midbrain red nuclei and pontine reticular formation. This research demonstrates how sensory and pain information is transmitted from the first synapse in the dorsal spinal horn to the brain in healthy individuals and how peripheral sensitization induces changes in non-noxious stimuli-induced activation patterns that correlate with pain sensory transmission.

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