The Enigma of Intermediate and Ventral Spinal Cord Activity with Thermal Sensory Stimulation: A Spinal FMRI Investigation

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Introduction

Background: Functional magnetic resonance imaging (fMRI) of the brain is well established and has proven to be a powerful tool for neuroscience research, but is limited to the cortex and upper brainstem regions. Extension of fMRI to the brainstem and spinal cord requires a modified method in order to overcome significant technical challenges. Nonetheless, a sensitive and reliable method for fMRI of the spinal cord (spinal fMRI) has been developed by using fast spin-echo imaging, with essentially proton-density weighting.[1] Neuronal activity is detected indirectly by means of changes in tissue water content with the "SEEP" contrast mechanism (Signal Enhancement by Extravascular water Protons), as well as a smaller contribution from the BOLD (Blood Oxygenation-Level Dependent) effect. The results have been demonstrated to reflect neuronal activity[1] , and the sensitivity has been demonstrated with studies of motor and sensory stimuli, as well as with interactions between cognitive functions (attention) and sensation. We can now observe the functional neuroanatomy of the human spinal cord with unprecedented detail.

Problem: A number of studies of thermal stimulation of the hand have demonstrated consistent activity in intermediate or ventral areas of the spinal cord gray matter, as well as the expected activity in dorsal gray matter regions. The correct interpretation of the intermediate or ventral activity is unknown.

Solution: Here we investigate neuronal activity in the spinal cord during innocuous thermal sensory stimulation, by systematically varying the stimulation temperature and the order of repeated experiments. From the first experiment to the last, volunteers typically experience a progression from alertness, to boredom and sleepiness. The order of the experiments therefore imposes a systemic variation of cognitive and emotional factors.

Significance: Correct interpretation of the intermediate or ventral activity will enable reliable assessments of spinal cord and brainstem functions and changes with injuries, and may provide new information about normal sensation.

Methods

Functional MRI of the brainstem and spinal cord was carried out in 15 healthy volunteers at 3 tesla (Siemens Magnetom Trio). Volunteers were supine and fMRI data were acquired with a phased-array spine receiver coil, using a half-fourier single-shot, fast spin echo sequence (HASTE) (TE = 38 msec, effective TR = 9 sec, 20 cm x 10 cm FOV, 192 x 96 matrix). Nine contiguous sagittal slices (2mm thick) were imaged spanning from the thalamus to the C7/T1 disc. The resulting voxel size was 1 mm x 1 mm x 2 mm. Thermal stimulation of the C6 dermatome was produced using a Medoc® TSA-II thermal sensory analyzer with the thermal probe placed on the right thenar eminence. Prior to imaging, each volunteer's cold pain threshold was determined, and these fell within a narrow range around 10 °C. In each experiment the stimulator cycled between 32 °C for the baseline condition and one of 5 stimulation temperatures: 29, 25, 22, 18 or 15 °C. Five studies were carried out with each volunteer, one with each of the 5 stimulation temperatures. The order of the experiments was varied so that each of the 5 temperatures was applied 3 times at each point in the order (i.e. 1st, 2nd, 3rd, etc) across the 15 volunteers. Baseline periods were held for 72 seconds and stimulation periods were maintained for 45 seconds. A total of 48 volumes were acquired. During all experiments the volunteers watched a movie to provide an attention focus.

The resulting 3D image data were analyzed using a general linear model, with a basis set consisting of a boxcar model paradigm and models of cardiac-related motion of the spinal cord as confounds. The results were reformatted and normalized to a consistent coordinate space to facilitate group comparisons. Group analyses were carried out using the Partial Least Squares (PLS) method[2] to contrast the signal change responses between stimulation at different temperatures, and at different times in the order of multiple experiments in each volunteer, on a voxel-by-voxel basis. Connectivity between voxels was also assessed by determining the correlation between all responses in the 75 experiments (5 experiments with different stimuli in each of 15 volunteers) between pairs of voxels. Correlations of $R \geq 0.3$ between all responses were identified to show the pattern of apparent connectivity between regions.

Results

Activity in response to thermal sensory stimulation of the right hand was detected in the brainstem and spinal cord in all 15 volunteers. Stimulation at 29 °C elicited a notably different pattern of activity than temperatures of 25 °C or lower. There were consistently larger areas of activity in the right cervical cord, and notable activity in the medulla, possibly cuneate and gracile nuclei. Regions of activity were contrasted with PLS analysis between lower temperatures (15 and 18 °C) and higher temperatures (22 and 25 °C), and between earlier experiments (1st and 2nd) and later experiments (3rd through 5th). Activity in the cervical spinal cord was centered around the 6th cervical segment (C6), as expected. In most of this segment signal changes were lower with lower temperatures in ipsilateral dorsal and contralateral intermediate or ventral regions. At the same rostral-caudal (R/C) levels signal changes were lower with earlier experiments in bilateral dorsal and intermediate or ventral regions. However, a more localized area low in the C6 segment showed only increased signal changes in ipsilateral dorsal and intermediate or ventral regions with lower temperatures, and with earlier studies. Connectivity analyses show correlations between right dorsal areas in C6 and the periaqueductal gray matter (PAG) in the brainstem, and between left intermediate or ventral regions in C6 and the rostral ventromedial medulla (RVM). In the PAG signal changes were observed to be lower with lower temperatures and higher with earlier studies. In the RVM signal changes showed the opposite dependence, they were higher with lower temperatures, and lower with earlier studies.

Discussion

The response observed with stimulation at 29 °C is distinct from that at lower temperatures, and appears to demonstrate sensory facilitation with input from cuneate and gracile regions, as observed with light touch stimuli. The temperatures between 25 °C and 15 °C elicited temperature-dependent responses in spinal cord dorsal and ventral areas. The observed activity in the contralateral intermediate or ventral areas is not consistent with a motor reflex to withdraw from the sensation, because this would involve ipsilateral muscle activity. We observed increases in signal changes with lower temperatures (more intense stimuli) in both dorsal and intermediate or ventral areas in the C6 segment. These were localized within a small R/C range, and were ipsilateral to the stimulus. This indicates greater input to these regions with more intense sensory stimuli. The intermediate or ventral activity in this small range may reflect muscle position sense with the change in temperature, but is not consistent with a withdrawal reflex.

The signal changes in the ipsilateral dorsal gray matter in C6 indicate that the activity shifted in the R/C direction within the segment as a function of temperature, being more rostral with warmer temperatures. This may reflect a difference in the relative inputs from different sensory and pain receptors.

The contralateral activity in C6 in intermediate or ventral increases showed lower signal changes with more intense (colder) stimuli. Connectivity analyses indicate that the contralateral activity is correlated with activity in raphe nuclei in the medulla (RVM and more caudal medial ventral areas as well). The RVM showed the strongest dependence on temperature (higher signal changes with lower temperatures), and the same areas showed a dependence on order (lower with earlier studies). If we interpret the signal changes as reflecting the input to an area, as has been indicated for the BOLD effect[3], then this indicates that colder stimuli result in greater input to the RVM and less input to the contralateral intermediate or ventral regions in C6.

The analyses of connectivity also indicate that the contralateral (left) PAG responses are correlated with those in the ipsilateral dorsal areas centered around C6. The PAG and RVM are part of a descending pathway that modulates the spinal cord responses to thermal and painful stimuli. The results are therefore consistent with the conclusion that the activity observed in all regions of the cervical spinal cord around C6 are linked to the sensory input, and are modulated by emotional or cognitive factors (including attention focus), via the PAG and RVM. The activity in the intermediate or ventral regions does not correspond with a motor reflex, but is concluded to be involved with the modulation of the response to the thermal sensory stimulus.

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