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Influence of attention focus on neural activity in the human spinal cord during thermal sensory stimulation

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Abstract

Perceptions of sensation and pain in healthy people are believed to be the net result of sensory input and descending modulation from brainstem and cortical regions depending on emotional and cognitive factors. Here, the influence of attention on neural activity in the spinal cord during thermal sensory stimulation of the hand was investigated with functional magnetic resonance imaging by systematically varying the participants' attention focus across and within repeated studies. Attention states included (1) attention to the stimulus by rating the sensation and (2) attention away from the stimulus by performing various mental tasks of watching a movie and identifying characters, detecting the direction of coherently moving dots within a randomly moving visual field and answering mentally-challenging questions. Functional MRI results spanning the cervical spinal cord and brainstem consistently demonstrated that the attention state had a significant influence on the activity detected in the cervical spinal cord, as well as in brainstem regions involved with the descending analgesia system. These findings have important implications for the detection and study of pain, and improved characterization of the effects of injury or disease.

Keywords: Functional magnetic resonance imaging; MRI; fMRI; Sensation; Pain; Brainstem; Spinal cord; Human

1. Introduction

Understanding how normal perceptions of sensation or pain are produced is a prerequisite for understanding how these functions are altered by trauma or disease. After a spinal cord injury 60% to 80% of patients suffer chronic pain [1], so understanding the genesis and propagation of this pain is of great importance [2]. However, pain and sensation are difficult to quantify because they are subjective perceptions of sensory inputs, and not the inputs themselves [3,4]. In healthy people, these perceptions are the result of a network integrating the sensory spino-thalamo-cortical pathway and the descending pain modulatory system that arises in the frontal cortex, anterior cingulate cortex, amygdala and hypothalamus, which connects via the periaqueductal gray matter (PAG), dorsolateral pontine tegmentum (DLPT) and rostral ventromedial medulla (RVM) to control spinal pain transmission neurons directly [5–7]. This descending modulation and the consequent perception of pain or sensation have been shown to be influenced strongly by factors such as attention, anticipation and emotion [8–10].

Functional magnetic resonance imaging (fMRI) of the spinal cord (spinal fMRI) is currently the only noninvasive means of mapping neural function and the effects of the descending control in the human spinal cord. This method has the potential to be an extremely important clinical tool because it has been shown to be sensitive to differences in neural function between painful and nonpainful sensory stimuli [11–13] and has demonstrated spinal cord activity involved with sexual function [14], differences in pain

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responses in patients with carpal tunnel syndrome compared to healthy controls [15], the effects of multiple-sclerosis on spinal cord function [16,17], and also sensory and motor functions caudal to sites of spinal cord trauma [18,19]. The effects of the descending control from the brainstem and higher cortical structures are as important to the overall spinal cord function and determination of the effects of injury, as are the ascending neural inputs from the periphery. The importance of understanding both the ascending and descending inputs to the cord is demonstrated by the fact that one likely mechanism for the chronic pain experienced after spinal cord injury is the result of a change or imbalance of the descending modulation relative to the ascending signals [20–22].

An important missing link in our understanding, however, arises from the fact that normal sensory and pain processing have rarely been studied in the intact human spinal cord. The spinal cord inputs from the brainstem have only been inferred from detailed animal studies [20,23] and from observing the effects of injury and of therapy [24,25]. The areas of the brain and rostral portions of the brainstem that play a key role in pain/sensation perception and descending modulation have been observed in humans by means of fMRI and positron emission tomography and by microstimulation during surgical procedures [8,9,26–29]. Spinal cord neural responses to descending modulation have only been observed in healthy humans in a single previous study as a result of changes in emotional status, alertness, or attention across repeated spinal fMRI studies [11].

Here, we investigate how, or if, activity in the human cervical spinal cord is modulated by changing the focus of the person's attention (i.e., their "attention state") at the same time that a sensory stimulus is applied. We hypothesize that activity in the cervical spinal cord during thermal stimulation of the hand, is influenced by the attention state, as it is in the cortex and brainstem [8,9].

2. Materials and methods

2.1. FMRI data acquisition

This study consisted of three protocols which were carried out with separate groups of healthy adult volunteers with no previous history of neurological trauma or disease. Three different protocols were employed in order to determine the influence of the "attention state" on the activity elicited by cooling the hand, distinct from other task-related effects such as motor and visual responses, as described below. For the purposes of this study, we use the term attention state to mean the state of all of the cognitive processes that are involved with (1) attending to a thermal sensation and providing instantaneous subjective ratings or (2) attending to tasks of watching a movie, detecting the direction of a subset of moving dots in a randomly moving visual field or responding to mentally-challenging puzzles or questions.

fMRI data were acquired in a 3 T Siemens Magnetom Trio using a phased-array spine receiver coil, and posterior neck coil, using a half-Fourier single-shot fast spin-echo sequence with the echo time set at minimum (38 ms). Signal intensity changes observed in the image data were the result of signal enhancement by extravascular water protons (SEEP), reflecting a change in neural activity, as described previously [13,30]. Data were acquired with a 20×10 cm FOV, spanning from the T1/C7 disc to the rostral limit of the thalamus for protocols 1 and 2 (see "Behavioural Protocols"). For protocol 3 the FOV was 28×14 cm and spanned from the T1/C7 disc to above the cingulate gyrus. In all cases the images were acquired with a 192×96 matrix, in 2 mm thick contiguous sagittal slices. Spatial suppression pulses were applied to eliminate signal from anterior to the spine. The peripheral pulse was recorded continuously during each study. Subjects entered the MRI system head first and supine and viewed a rear-projection screen via a mirror attached to the head coil, with images projected onto the screen with a DLP projector (NEC model LT265). Audio was presented via overhead speakers incorporated into the MRI system. In all 3 protocols, thermal stimulation of the palm of the right hand was used to elicit activity in the cervical spinal cord, by means of a Medoc TSA-II thermal sensory analyzer with a 3×3 cm flat surface probe (the "thermode"). In Protocols 1 and 2, subject responses were recorded from the left hand with an MR-compatible four-button keypad (Current Designs) and custom software written in MatLab (The MathWorks Inc.). In Protocol 3, the responses were instead recorded by means of an MR-compatible eye-tracking system (ISCAN ETL-400 camera running DQW software v1.10×, sampling the eye position at 120 Hz). The participants indicated their responses by fixing their gaze on the written choice of responses on the visual display (described below).

2.2. Behavioural protocols

The three protocols differed primarily by the tasks that were performed to draw attention away from the thermal sensation, whereas the thermal stimulation was consistent across experiments, except for a few minor variations, as indicated in Fig. 1. In every protocol, a task of rating the thermal sensations (attention to the stimulus) was compared with a cognitive task (attention away from the stimulus).

Protocol 1 (Fig. 1A) involved 11 volunteers [4 males, 7 females; 25.5±16.2 years old (mean±S.D.)] who participated in 2 repeated experiments (four experiments total) in one imaging session. In each fMRI experiment the participant either (a) provided subjective instantaneous ratings of the discomfort caused by the thermal stimulation in the right hand ("Rating" task), or (b) watched a movie throughout the experiment ("Movie" task). Regardless of the attention state, each fMRI experiment consisted of thermal stimulation of the palm of the right hand in a block design, with four thermal stimulation blocks at 15°C with durations of 45 s

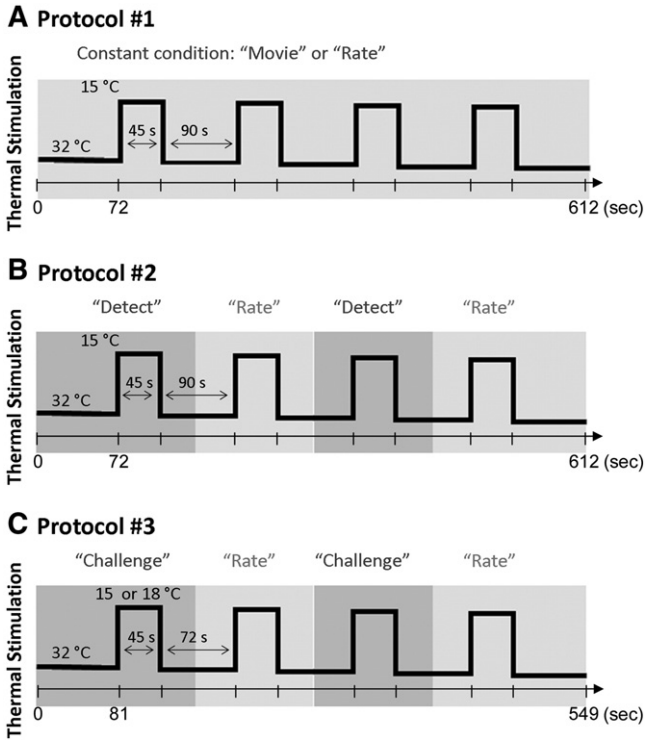

Fig. 1. Thermal stimulation and cognitive interaction paradigms for the three protocols employed in this study. The "Rating" tasks, and mental tasks of "Movie," "Detect," or "Challenge" are described in the text. (A) In Protocol 1, a constant cognitive task was applied throughout acquisition of an fMRI time series, and different tasks were applied in separate experiments with each volunteer. For Protocols 2 (B) and 3 (C), the cognitive tasks were instead alternated during the thermal sensory stimulation paradigm, as indicated.

each, interleaved with baseline conditions at 32°C, with durations of 63 s. For the "Rating" task, the volunteer was prompted via the visual display to focus on the cold sensation and was asked to rate the discomfort on a 1–4 scale with the four-button keypad with the left hand, every 15 s. The meaning of the buttons was described to the participants as being "no discomfort" for the lowest button, to "mild discomfort," "strong discomfort" and "worst discomfort possible" for the highest button. For the "Movie" task, participants watched an audio-visual presentation of the movie "Finding Nemo" (Disney/Pixar), and were instructed to press any button on the keypad each time a new character with a speaking role appeared. Button presses occurred throughout stimulation and baseline conditions. The two "Rating" experiments (denoted Rating1 and Rating2) were alternated with two "Movie" experiments (denoted Movie1 and Movie2) with each volunteer. In each experiment the button responses and the thermal stimuli were asynchronous, occurring at different frequencies and durations, so that in the subsequent fMRI data analysis, the button-press and thermal sensation responses could not be confused.

Protocol 2 (Fig. 1B) was similar except that "Rating" tasks (as in Protocol 1) were interleaved with "Detect" tasks in each experiment, and five people participated (one male, four females, 26.2±9.8 years old). The attention state was changed within each experiment in Protocol 2 in order to enable comparisons of fMRI results acquired only minutes apart, to reduce the potential influences of systematic changes if participants became tired or bored over the span of the entire MRI session. For the "Rating" task, the participant was asked to provide a rating of their instantaneous level of discomfort due to the temperature applied to their right hand, on a 1–4 scale, every 15 s. Again, the rating was registered by pressing one of 4 buttons with the fingers on their left hand. The "Detect" task (based on the task described in [9]) consisted of viewing a dynamic image of moving dots, with a random allocation of 10–50% of the dots moving coherently to the right or left, and the allocation and direction of the dots was changed every 7 s. The field of moving dots spanned approximately 35 cm and was viewed at a distance of 1 meter (angle of 20°, dots moving at 3°/s). The participant was instructed to indicate which direction the coherent dots were moving by pressing buttons with the fingers of their left hand. The transition between "Rate" and "Detect" tasks occurred during baseline periods midway between stimulation periods. The different rates of registering responses for the two tasks in this protocol were unavoidable because of different timing requirements. It was necessary to provide a reasonable amount of time for the participant to focus on the sensation and think about the rating and also to have the field of dots moving at a suitable speed across the display [9].

Protocol 3 (Fig. 1C) also involved interleaved cognitive conditions, this time between the "Rating" task, and a "Challenge" task consisting of mentally-challenging multiple-choice questions. Nine people participated in this protocol (four males, five females, 21.4±2.0 years old). In each experiment (while the attention state was alternated), thermal stimulation was applied at 18°C or 15°C (one stimulation temperature for each experiment), and the thermode was held at 32°C during baseline periods. Participants were told prior to entering the MRI system that they would feel different cold sensations during the experiments, but they were not told that only two different temperatures would be used. This was to avoid any preconceptions that the ratings of discomfort should be the same every time they felt a cold sensation on their hand. During all parts of protocol 3, the responses were recorded by means of gaze position instead of button presses. Questions, or prompts to rate the sensation, were presented at the center of the visual display and a choice of responses was presented in the four corners of the display. The "Challenge" task questions spanned a range of problem types including arithmetic with two or three operators, logic, vocabulary, geometric rotation and symmetry, and completion of number patterns (example questions are listed in Table 1). The questions were presented in a random order and were not duplicated across all of the fMRI experiments for each participant. For the "Rating" task, the choice of rating descriptors were "No Discomfort," "Mild

Table 1
Examples of mentally challenging multiple-choice questions used in Protocol 3

Questions	Answer choices			
Solve the equation: 6 × 0.5 = 0.25 × ?	*7*	*16*	*5*	*12*
Pillow is to pillowcase as hand is to _____	*Elbow*	*Glove*	*Glasses*	*Ring*
Choose the image that mirrors the same shape 				
Solve the equation: (1 + 2) × (3 × 4) = ?	*33*	*10*	*36*	*24*
Which number is next in the sequence?1 1 2 3 5 ?	*8*	*7*	*9*	*4*
If Leon is taller than Sarah, Sarah is taller than Marcel, and Leslie is taller than Leon, then who is tallest?	*Leon*	*Sarah*	*Marcel*	*Leslie*
Closest word in meaning to: Obviate	*Make Obvious*	*Avert*	*Obscure*	*Destroy*
Which number should come next? 144 121 100 81 64 ___	*17*	*36*	*49*	*50*
Two girls caught 25 frogs. Jill caught 4 times as many as Lisa. How many did Lisa catch?	*8*	*4*	*5*	*10*

Discomfort," "Strong Discomfort" and "Worst Discomfort Possible." Each rating choice was pseudo-randomized among the four corners of the display between prompts, so that regardless of the attention state the participant had to follow the same process of reading the question or prompt, searching for their selected answer and fixing their gaze on the answer to indicate their choice. The prompts and answers were changed every 18 s. The transition in attention state between "Challenge" and "Rating" occurred during the baseline conditions, midway between the thermal stimulation blocks. At the same time (midway between the stimulation blocks), the participants were asked to rate the discomfort caused by the preceding stimulation block on a visual-analog scale, by fixing their gaze on a point along a continuous line marked with "No Discomfort" at one end and "Worst Discomfort Possible" at the other end. This scale was calibrated immediately prior to obtaining each rating by presenting fixation crosses at each end of the scale, one at a time, for 1 s each. Participants were instructed prior to the imaging session to look at these fixation crosses when they appeared.

2.3. Data analysis

The resulting 3D image data were analyzed using a general linear model (GLM), with custom-made software written in MatLab as described previously [11,31]. The GLM in this analysis is implemented as described by Worsely et al. [32] and is essentially identical to that used in the SPM (Statistical Parametric Mapping) software package. The basis set for the GLM consisted of a boxcar model paradigm convolved with the SEEP tissue response function [33] (similar to the BOLD response but with the peak occurring 7 s after onset and no poststimulus undershoot), a constant function, a linear ramp and models of cardiac-related motion of the spinal cord as confounds [34,35]. The results demonstrate the required weighting factors (i.e., β values) for each element in the basis set to sum to the observed signal intensity time course. The value of β_1 is the magnitude of the pattern matching the stimulation paradigm convolved with the tissue response function, and β_0 is that of the constant function (i.e., the average intensity of the voxel). The individual results are expressed as the significance (T value) that β_1/β_0 is not equal to zero, for each voxel spanned by the image data. The results were then reformatted and normalized to a consistent coordinate space, defined for the brainstem and spinal cord, to facilitate group comparisons [35]. Briefly, the normalization procedure consists of interpolating the image data to 1-mm cubic voxels and reslicing the volume into axial sections every 1 mm along a manually-defined reference line along the anterior edge of the spinal cord in a mid-line sagittal slice. The point where the reference line passes through each resulting axial section is positioned at the center of each axial image, producing an apparently straight spinal cord in sagittal views. Two reference points; the caudal edge of the pons (the pontomedullary junction), and the intervertebral disc between the C7 and T1 vertebrae, were then used to linearly shift and scale the volume to a normalized coordinate system with axes along the long axis of the cord, right-left and anterior-posterior, relative to the spinal cord anatomy. This method has been shown to align the spinal cord and brainstem anatomy from different people to within 2 mm or less in 93% of the voxels and to have a mean accuracy of 0.3 mm. In the present study, a additional left/right correction was applied by manually defining a reference line down the center of the cord in a coronal slice that was extracted parallel to the sagittal reference line, in order to further refine the normalization procedure. Combined group results were determined using a random-effects analysis as described by McGonigle et al [36]. This consisted of calculating the mean and standard error of the ratio of β_1/β_0 across the participants in each group, to determine the significance of the activity detected in each voxel. Contrasts between responses to different stimuli, or during different mental states, were determined in a similar

manner based on the mean and standard error of the differences between β-values between contrasted conditions.

Significant group responses, or contrasted responses, were inferred at $P<.01$, corrected for multiple comparisons by thresholding at a minimum cluster extent as determined with the MatLab function "stat_threshold" written by K. Worsely [37,38]. The extent thresholds were set at 8.8 mm^3, 9.5 mm^3 and 8.9 mm^3, respectively, for Protocols 1, 2 and 3, with the differences in threshold sizes arising from the different numbers of studies and subjects in each group. The cluster thresholds were determined based on a total volume of the cervical spinal cord and brainstem of 27,400 mm^3, as determined from a spatially normalized region-of-interest mask.

3. Results

3.1. Ratings of sensations and question responses during fMRI experiments

The subjective ratings obtained during "Rating" tasks, and the responses provided during "Movie," "Detect," or "Challenge" tasks indicate that the participants performed the tasks correctly, and that their attention states and experiences of the thermal stimuli were successfully altered by the tasks. These results are summarized in Table 2.

In Protocol 1 (Fig. 1A, Table 2A), during the experiments with "Rating" conditions, the correlation between the subjects' responses and the stimulation temperature had a mean value of 0.78±0.16 (S.D.) (median: 0.83), and a mean reaction time of 920 ms±310 ms (median: 900 ms). During the experiments with participants watching a movie, the subjects reported new characters appearing in the movie 11±6 times with the first movie clip (Movie1), and 10±3 times with the second movie clip (Movie2). The number of new characters appearing in each clip was 8. Some variability can be attributed to each subject's interpretation of what should be considered "a character with a speaking role" as per the instructions prior to the experiment, and that the movie has many background characters.

In Protocol 2 (Fig. 1B, Table 2B), with alternating "Rating" and "Detect" conditions within each experiment, responses were correlated with the 15°C stimulus temperature and the 32°C baseline temperature (R=0.71±0.20, median 0.79) during "Rating," and were correlated with the proportion and direction of moving dots (R=0.51±0.11, median 0.48) during "Detect" conditions.

In Protocol 3 (Fig. 1C, Table 2C), participants responded during the mentally challenging task ("Challenge" condition) with correct answers to 71%±46% and 66%±48% of the questions while stimuli were applied at 18°C and 15°C, respectively. Before and after each stimulus, during baseline conditions, the correct answer rates were 62%±49% and 60%±49%, respectively. Confidence intervals of the correct answer rates exclude the chance answer rate of 25% at $P<.05$ in all cases, and the correct answer rates were not significantly different between all cases (Student t test, n=9, df=7, $T<0.7$, $P>.25$). Ratings of discomfort were enumerated 1–4, for each of the choices of "No Discomfort,"

Table 2
Summary of subjective ratings and question responses

A) Protocol 1

"Movie" tasks	New Characters Reported	Number of New Characters Appearing in the Movie Clip
First movie clip (Movie1)	11±6	8
Second movie clip (Movie2)	10±3	8

"Rating" tasks	Correlation Between Ratings and Thermode Temperature:
All "Rating" blocks	0.78±0.16 (S.D.)

B) Protocol 2

	Correlation Between Ratings and Thermode Temperature:	Correlation Between Responses and Direction of Coherently Moving Dots:
All "Rating" or "Detect" blocks	0.71±0.20	0.51±0.11

C) Protocol 3

	18°C	15°C	32°C (baseline)
"Rating" tasks 1–4 scale *	2.1±0.8	2.3±0.9 †	1.3±0.8
"Challenge" tasks Rate of correct answers	71%±46%	66%±48%	62%±49%
"Rating" tasks Ratings, 0–10 scale ‡	1.0±1.4	1.4±2.0	
"Challenge" tasks Ratings, 0–10 scale ‡	2.0±2.5	3.0±2.7 §	

* Ratings correspond to descriptors: "No Discomfort," "Mild Discomfort," "Strong Discomfort," and "Worst Discomfort Possible," respectively.

† Significantly different (t-test, $P<.05$) between stimulation at 18°C and 15°C.

‡ Ratings of discomfort caused by the thermal stimulus, reported after each stimulation block, on a visual-analog scale from 0 (no discomfort) to 10 (worst discomfort possible).

§ Significantly different (t-test, $P=.01$) between "Rating" and "Challenge" conditions.

"Mild Discomfort," "Strong Discomfort" and "Worst Discomfort Possible," respectively. During baseline conditions at 32°C the average ratings were 1.3±0.8 and 1.4±0.8 for experiments with stimulation at 18°C and 15°C, respectively, and during thermal stimulation conditions, the participants' ratings averaged 2.1±0.8 and 2.3±0.9, respectively, and were significantly different (paired Student's *t* test, *P*=.03, *T*=2.3, *df*=77) between the two temperatures. Ratings of the discomfort caused by the thermal stimuli, on a Visual Analog Scale from 0 (No Discomfort) to 10 (Worst Discomfort Possible), were provided during baseline conditions after each stimulus. In 26% of the ratings obtained (37 out of 144 ratings, across 9 participants) problems with the calibration step did not permit reliable recording of the ratings on the visual-analog scale and were excluded for being less than −1, and one value was also excluded for being greater than 10. With "Rating" conditions the average ratings were 1.0±1.4 and 1.4±2.0 for the 18°C and 15°C conditions, respectively, whereas during the "Challenge" conditions the ratings were higher at 2.0±2.5 and 3.0±2.7, respectively. These ratings were significantly different between "Rating" and "Challenge" conditions with stimulation at 15°C (student's t-test, *P*=.01, *T*=2.7, *df*=25), but only showed a strong tendency with stimulation at 18°C (Student's *t* test, *P*=.06, *T*=1.9, *df*=25).

3.2. Anatomical locations of activity with fMRI

Activity was detected in the cervical spinal cord and regions of the brainstem in every participant, across the three protocols. There were consistent features regarding the locations of activity across studies, as well as differences depending on the attention state. Fig. 2 shows the anatomical locations of activity detected in response to thermal stimulation of the right hand in Protocols 1, 2 and 3. These are group results obtained with a random-effects analysis [36] and are shown for selected rostro-caudal spans for clarity.

With all "Rating" tasks across the three protocols, activity was consistently observed in localized regions of the ipsilateral dorsal gray matter (dGM) and in the ipsilateral ventral gray matter (vGM) in the sixth to eighth cervical spinal cord segments (C6–C8) (Fig. 2). This activity involved predominantly negative signal changes. During the rating tasks, activity was also consistently observed in the

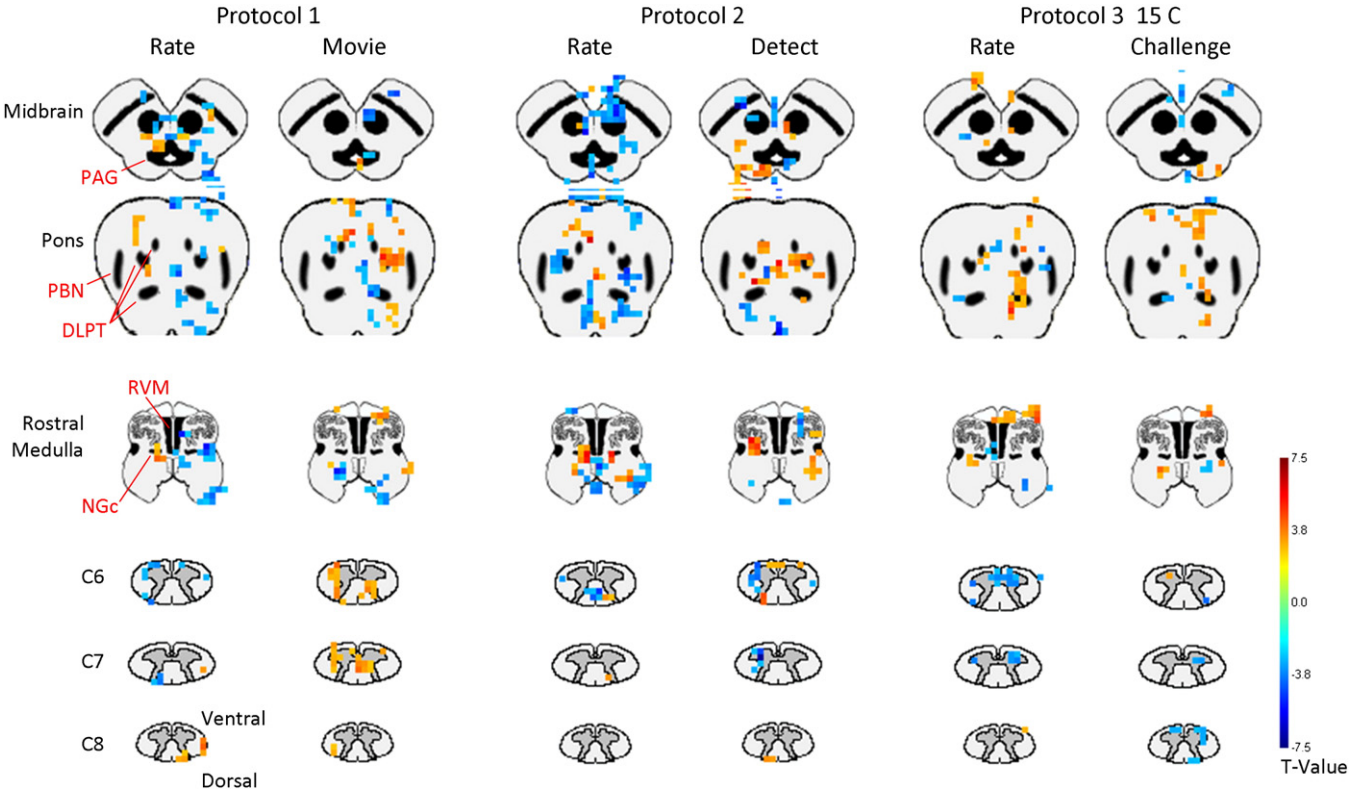

Fig. 2. Group fMRI results spanning the brainstem and spinal cord with the 3 experimental protocols, computed by means of a random effects analysis after spatially normalizing the individual results. Active regions are shown with a significance level of *P*<.01 corrected for multiple comparisons with a cluster-size threshold as described in the text. The largest magnitude responses along each span are projected onto a single axial section, and the rostro-caudal extent of active regions is therefore not indicated. The colours within the cross-sectional anatomical drawings reflect the significance (*T* value), corresponding to the color bar on the right. Each panel is in radiological orientation, as indicated by the schematic diagram on the far right side of the figure. Labelled regions include the periaqueductal gray matter (PAG); parabrachial nucleus (PBN); dorsolateral pontine tegmentum (DLPT), which includes the Kölliker-Fuse nucleus, subcoeruleus and locus coeruleus; the rostral ventromedial medulla (RVM) which includes the nucleus raphe magnus (NRM) and adjacent reticular formation and the nucleus gigantocellularis (NGc).

medulla in the vicinity of the RVM and nucleus gigantocellularis (NGc) as well as in the vicinity of the locus coeruleus and nuclei of the DLPT in the pons. In the midbrain, activity was observed in the vicinity of the periaqueductal gray matter (PAG) and the midbrain reticular formation. While the vicinity of the NGc showed predominantly positive activity, the vicinity of the DLPT, RVM and PAG showed both positive and negative areas of activity in response to thermal stimulation of the hand at 18°C or 15°C during rating conditions.

When participants answered mentally challenging multiple-choice questions (Protocol 3), detected the subset of coherently moving dots (Protocol 2), or watched a movie (Protocol 1) while thermal stimulation was applied to the hand, similar regions of activity were observed as with the "Rating" conditions. Most importantly, however, the direction of the signal changes (i.e., positive or negative) was not the same between the "Rating" and cognitive tasks (Fig. 2). In the cervical spinal cord, ipsilateral dGM activity was observed at C6–C8, as well as ipsilateral and contralateral vGM activity, depending on the task and stimulus. Both positive and negative areas of activity were again observed in the spinal cord, rostral medulla and midbrain with the "Movie," "Detect" and "Challenge" conditions, but more areas of positive activity were observed than during the "Rating" conditions. Most notably, the ipsilateral NGc in the rostral medulla again showed consistently positive activity, as during "Rating" conditions, and the contralateral DLPT showed more areas of positive activity, as did the cervical spinal cord between C6–C8. The only exception is during the "Challenge" condition, which did not show as much change from the "Rating" condition as did the other tasks.

Overall, the anatomical locations of activity that were detected in response to thermal stimulation were relatively consistent across the 3 study protocols. However, the magnitude (and direction) of the MRI signal change responses in these areas depended on the attention state that was imposed.

3.3. Contrasts between conditions

Contrasts between responses to thermal stimuli during different attention states, or between different temperature stimuli, demonstrated significant differences between the states that were imposed in these studies (Fig. 3) and support the observations from the group results. The most notable differences in salient regions of the brainstem and spinal cord have predominantly lower responses during "Rating" conditions than the "Movie," "Detect" or "Challenge" conditions.

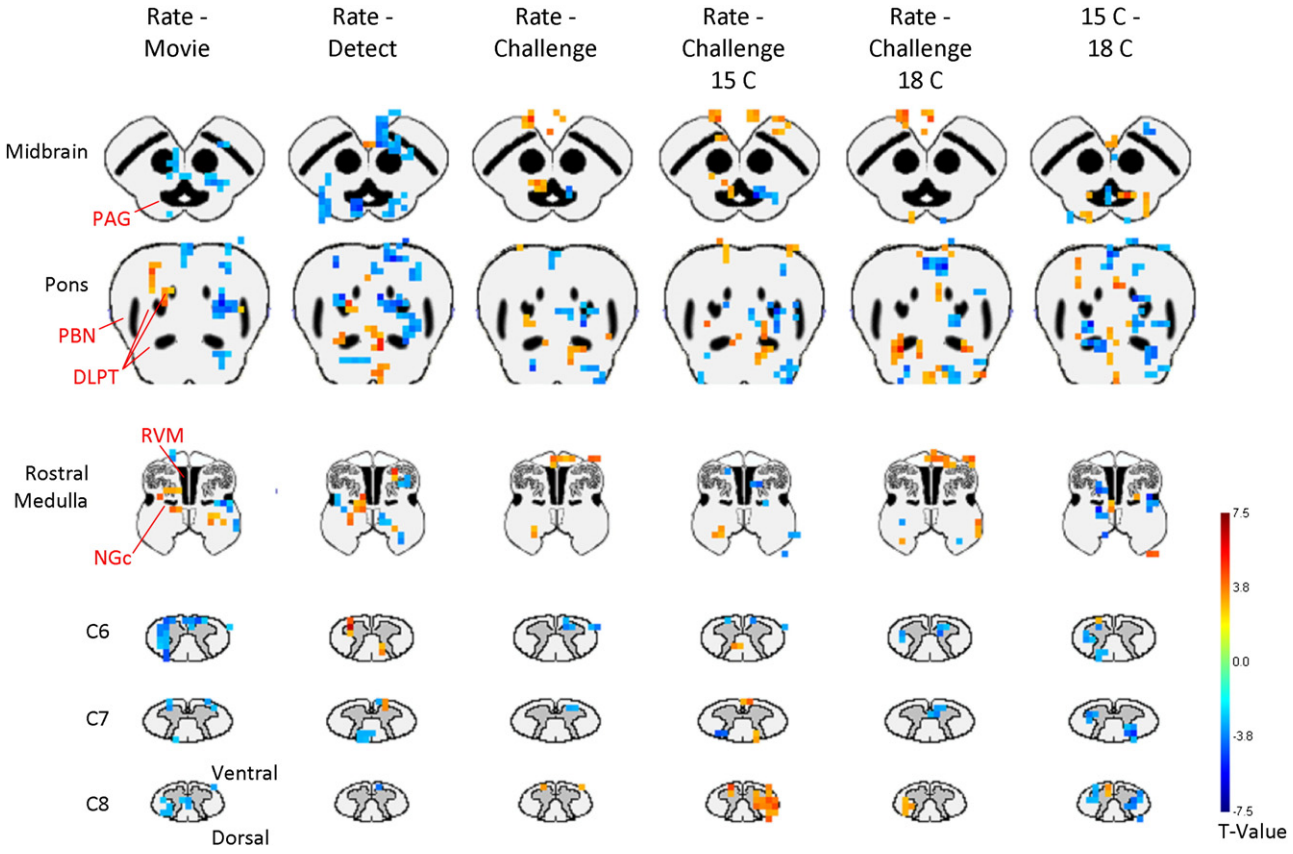

Fig. 3. Contrasts between experiments carried out with thermal sensory stimulation of the hand, while different cognitive tasks were performed, for the regions shown in Fig. 2. Differences in responses were computed between results of individual experiments, and significance was determined with a random-effects analysis across participants. Significance is indicated by the *T* value for the differences between responses, with the color scale shown on the right. A cluster-size threshold was applied to achieve a corrected significance level of $P<.01$.

The activity in the cervical spinal cord is confirmed to be significantly negative (i.e., lower or more negative signal changes) in the ipsilateral dorsal gray matter of the spinal cord during all "Rating" conditions than during any of the "Movie," "Detect" or "Challenge" conditions. While lower signal changes were also detected in both ipsilateral and contralateral ventral gray matter regions during "Rating" than during the "Movie" condition, higher signal changes were detected in ventral and contralateral dorsal gray matter areas during "Rating," than during the "Detect" and "Challenge" conditions, particularly with stimulation at 15°C, as opposed to at 18°C.

In brainstem regions, signal changes were observed to be significantly lower during "Rating" conditions than during "Movie," "Detect" or "Challenge" conditions in the vicinity of the contralateral DLPT in the pons, and PAG in the midbrain. Higher signal changes were detected with the "Rating" conditions primarily in the ipsilateral DLPT and PAG. The exception was the vicinity of the locus coeruleus (which is included in the DLPT), which showed more positive activity on either side during "Rating" conditions than during the "Detect" or "Challenge" conditions, depending on the condition.

The contrasted responses between stimuli at 15°C and 18°C, determined across different cognitive conditions, shows lower activity in the ipsilateral dGM at 15°C, and in bilateral locus coeruleus. Higher signal change responses however are seen in the bilateral PAG, and in the RVM with stimulation at 15°C. A region of higher signal response is also seen in the ipsilateral vGM.

4. Discussion

The key finding of this study is that activity in the human cervical spinal cord in response to a thermal sensory stimulus, as detected by spinal fMRI, depended on the participant's attention state. Contrasted results between task conditions (Fig. 3) demonstrated significantly lower signal in the ipsilateral dGM of the spinal cord in response to thermal stimulation while "Rating" conditions were applied, as compared to during any of the cognitive tasks (i.e. "Movie," "Detect," or "Challenge"). Group fMRI results (Fig. 2) showed predominantly negative responses in the ipsilateral dGM at C6/C7 (the level of primary input to the cord) with "Rating" tasks, and generally no response or positive response, while the participants performed the cognitive tasks. The dGM is known to be involved with sensory input, and these results therefore indicate that the total net change of neural input to the dGM upon thermal sensory stimulation, was zero, or at least small, while the participants performed one of the cognitive tasks. The total net change during the rating tasks was a reduction in neural input to the dGM, compared to the tonic input from the brainstem [20] and little sensory input from the skin, which presumably occurred during baseline conditions with 32°C applied to the skin.

This interpretation of the results is supported by the observed activity in the medulla, pons, and midbrain. Contrasted results between "Rating" and each of "Movie," "Detect" or "Challenge" conditions showed significantly higher responses with "Rating" tasks predominantly in the ipsilateral NGc and DLPT, and lower responses in areas within the contralateral DLPT. Differential responses were also observed in the vicinity of the PAG but depended on which of the three cognitive tasks was applied, in comparison with rating tasks. The differences between 15°C and 18°C in Protocol 3, demonstrated differences primarily in bilateral PAG and in the RVM, as well as bilateral locus coeruleus. The key differences in the observed responses that depend specifically on the cognitive states, therefore identify the NGc and DLPT.

The PAG and RVM exert bidirectional control, and both pain inhibition and facilitation are major components of their function [7]. The RVM is the main source of modulation of the spinal cord, whereas ascending projections to the RVM from the spinal cord are sparse. Another source of descending control, however, is the noradrenergic neurons of the DLPT which contribute significantly to pain modulation. The DLPT is an important part of the descending pathways that modulate nociception, and includes the Kölliker-Fuse nucleus, subcoeruleus, and locus coeruleus, and this region receives input from both the PAG and RVM [7,39]. The NGc, on the other hand, receives ascending input from the spinal cord, and plays a role in the affective component of perceived pain. In the present study, no significant activity was observed in the RVM in the group results, with any of the cognitive tasks, and the PAG had no change or lower activity during rating tasks compared to the cognitive tasks. These observations indicate that there was little or no net total change in neural input to these regions. This may be a result of the thermal stimuli used in this study being relatively innocuous, producing only mild discomfort, as indicated by the subjective pain ratings provided by the participants (Table 2). Nonetheless, areas of the DLPT, particularly the locus coeruleus, and also the NGc, demonstrated significant changes in neural input in response to cold thermal stimulation, during all of the conditions. The activity in the DLPT was expected to reflect the net ascending and descending input ipsilateral to the stimulus, whereas the contralateral activity likely indicated only the descending input because the input from the spinal cord was ipsilateral [7]. The contrast between rating and cognitive conditions therefore indicated lower neural input to the contralateral DLPT during rating conditions. This was consistent with the interpretation that the total input to the dGM, including input from the contralateral DLPT, was lower during rating conditions. An exception was observed with the contrast between "Rating" and "Challenge" tasks in Protocol 3, which demonstrated higher activity during the rating condition in the contralateral locus coeruleus, and lower activity in the other regions of

the DLPT. In this case, there was no net change in activity detected in the ipsilateral dGM.

The subjective ratings provided by the 25 participants during thermal stimulation of the hand showed that the two attention states that were imposed successfully altered the perceived sensations. It was somewhat surprising that the ratings of discomfort felt during "Rating" tasks were significantly lower than during the "Challenge" tasks (Protocol 3). Based on previous studies [9,10,40], having the participants' attention focus on the sensations during "Rating" tasks, was expected to elicit greater discomfort. The results we obtained may be a consequence of the fact that the participants rated the sensations in retrospect, during the baseline periods after each stimulation block. It was not possible to obtain ratings during the stimulation blocks when the cognitive tasks were being performed. The thermal stimuli may have been an annoyance (a distraction) while the participants were trying to answer the mentally challenging multiple-choice questions, leading to higher retrospective ratings of discomfort. Another important distinction between the present study and previous investigations of descending modulation was that the stimuli we used were uncomfortable, but not painful. Such thermal sensory stimuli are necessary for this study because of the need to investigate the interactions between cognitive conditions and sensory responses in the human spinal cord, and in order to relate to previous spinal fMRI studies.

Overall, these results indicate that during "Rating" tasks, while the participants were focusing their attention on the thermal sensations on the hand, input to the ipsilateral dGM was lower than when subjects focused their attention on performing a cognitive task. This reduction in input to the spinal cord dGM was attributed to a change in descending modulatory input from the DLPT, particularly the locus coeruleus.

5. Conclusions

Here, we demonstrate that the attention state can modulate neural function in the human spinal cord during thermal sensory stimulation, as detected by spinal fMRI. The results support our hypothesis that activity in the cervical spinal cord during thermal stimulation of the hand was influenced by what the participant was thinking about while the stimulus was applied. This means that, in healthy humans, the ability to play through the pain in sports or to focus on responding to danger in spite of a painful injury involves local processing and modulation of outputs at the level of the spinal cord, as well as in brainstem and cortical regions. This information and the ability to detect this function in humans may also provide important new insight into the mechanisms of chronic pain after spinal cord trauma. The ability to influence the descending modulation of spinal cord activity by changing attention states also demonstrates a means of separately assessing the effects of injury or disease on ascending and descending pathways in the human spinal cord.

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