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Report

Attention Modulates Spinal Cord Responses to Pain

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Summary

Reduced pain perception while being distracted from pain is an everyday example of how cognitive processes can interfere with pain perception [1–5]. Previous neuroimaging studies showed distraction-related modulations of pain-driven activations in various cortical and subcortical brain regions [6–11], but the precise neuronal mechanism underlying this phenomenon is unclear. Using high-resolution functional magnetic resonance imaging of the human cervical spinal cord in combination with thermal pain stimulation and a well-established working memory task [12], we demonstrate that this phenomenon relies on an inhibition of incoming pain signals in the spinal cord. Neuronal responses to painful stimulation in the dorsal horn of the corresponding spinal segment were significantly reduced under high working memory load compared to low working memory load. At the individual level, reductions of neuronal responses in the spinal cord predicted behavioral pain reductions. In a subsequent behavioral experiment, using the opioid antagonist naloxone in a double-blind crossover design with the same paradigm, we demonstrate a substantial contribution of endogenous opioids to this mechanism. Taken together, our results show that the reduced pain experience during mental distraction is related to a spinal process and involves opioid neurotransmission.

Results and Discussion

Numerous experimental studies as well as clinical observations provide strong evidence that attention is highly effective in modulating the pain experience and demonstrate how cognitive processes can interfere with pain perception [1–8, 10]. Pain is perceived as less intense when a person is distracted from pain, e.g., by a challenging cognitive task [1, 6, 9, 11, 13], even in chronically afflicted patients [14]. Conversely, pain increases when the pain is in the focus of attention [15]. Functional brain imaging and neurophysiological studies have shown that attention- and cognitive distraction-related modulations of nociceptive-driven activations take place in various pain-sensitive cortical und subcortical brain regions, accompanied by concordant changes in pain perception [1, 6–9, 11, 16]. Although a mechanistic explanation of these findings is currently lacking, it is likely that top-down modulation, i.e., the shaping of lower-level sensory signals by higher-order brain circuits [17–20], plays a pivotal role in the cognitive control of pain. Previous studies on pain processing have demonstrated that key regions of the descending pain control system show enhanced responses during attentional distraction [1, 6, 9, 10]. It is, however, unknown how early—i.e., at which stage of the central nervous system (CNS)—this attentional top-down modulation of nociceptive processing occurs in humans. Given that the ultimate target of this modulatory system is the dorsal horn of the spinal cord, we investigated the hypothesis that cognitive processes might alter pain processing already at the level of the spinal cord.

We used high-resolution functional magnetic resonance imaging (fMRI) of the human cervical spinal cord [21] in combination with thermal pain stimulation in the dermatome C6 and a well-established working memory paradigm (1-back versus 2-back letter task). This allowed us to test whether spinal cord blood oxygen level-dependent (BOLD) responses related to painful heat stimulation are reduced during high working memory load compared to low working memory load (see Figure 1).

Pain ratings showed a significant decrease during high working memory load compared to low working memory load [1-back pain condition: 60.3 ± 3.5 (mean ± SEM) versus 2-back pain condition: 48.8 ± 3.6; pain intensity difference ΔP: 11.5 ± 3.1; 19% pain reduction; $t(16) = 3.45$, $p = 0.002$], indicating that the working memory load manipulation successfully decreased perceived pain intensity. The estimated task performance, calculated as the ratio between blocks with a correctly indicated number of n-back targets to the total number of blocks per condition, was 0.80 ± 0.04 for the 1-back condition and 0.51 ± 0.05 for the 2-back condition. Subjects thus performed the 1-back task significantly better than the 2-back task [paired t test: $t(16) = 4.41$, $p < 0.001$], indicating that the intended working memory load manipulation was successful.

We next tested for BOLD responses in the spinal cord related to the main effect of painful thermal stimulation and—in accordance with the functional neuroanatomy of the nociceptive system—observed the strongest BOLD responses ipsilateral to the side of stimulation in the dorsal horn at the upper spinal level C6 [approximately at the junction with segment C5, $t(16) = 3.98$, $p = 0.001$; see Figure S1 available online]. Subsequently, we investigated both pain conditions separately. We observed the most significant BOLD responses to pain during the 1-back condition [$t(16) = 6.29$, $p < 0.001$; Figure 2] approximately at the same site as the main effect of painful stimulation, whereas no significant activations regarding pain during 2-back was observed.

Finally, we directly tested whether the observed BOLD responses in the ipsilateral dorsal horn are reduced under the high working memory load condition. Importantly, a significant reduction of BOLD responses under high working memory load compared to low working memory load was observed at the peak of the main effect of pain [$t(16) = 3.40$, $p = 0.002$, Figure 3; the time course of the response for both working memory conditions separately at this voxel can be obtained from Figure S2]. Furthermore, robust regression revealed that increasing reductions of BOLD responses at the peak voxel of the main effect of pain (coinciding with the peak voxel of the differential contrast, 1-back minus 2-back)

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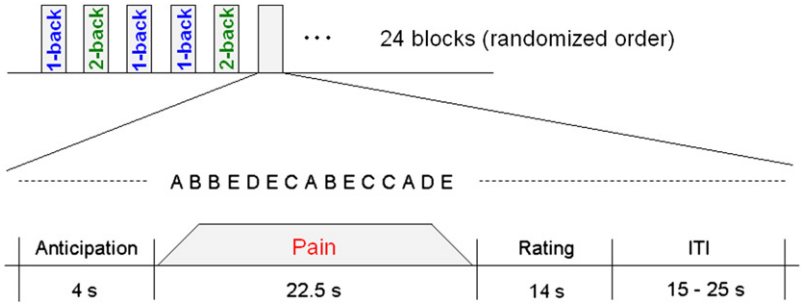

Figure 1. Experimental Paradigm

The experimental paradigm consisted of 1 session comprising 24 blocks. Each block consisted of an anticipation phase (4 s), a painful stimulation accompanied by an n-back task (22.5 s), a rating period (14 s), and a variable intertrial interval (15–25 s). During the anticipation phase, the subjects were visually informed whether they had to perform a 1-back or a 2-back task in the following period ("One-Back" or "Two-Back" was displayed on the screen). During the painful stimulation at the left radial forearm (dermatome C6), a series of 15 letters was presented on the screen and subjects performed the indicated n-back task. Directly after the pain stimulation, subjects indicated the sum of n-back hits and subsequently rated the perceived pain intensity during that block on a visual analogue scale (VAS). During the intertrial interval, a white crosshair was displayed.

was correlated with an increase in behavioral pain reduction [$t(16) = 3.40$, $p = 0.004$].

To investigate whether reduced pain perception during high cognitive load is mediated by endogenous opioid neurotransmission, we performed a second experiment in which we employed the same behavioral paradigm in combination with a pharmacological challenge using the opioid-antagonist naloxone in a double-blind crossover design.

For both working memory conditions, pain ratings under saline showed on average similar intensities as in experiment 1 (1-back pain condition saline: 58.7 ± 2.7 versus 2-back pain condition saline: 45.6 ± 2.8). In agreement with the fMRI experiment, we observed a significant decrease of pain ratings under the 2-back condition in comparison to the 1-back condition [ΔP_NaCl: 13.1 ± 3.8; 22% reduction; $t(14) = 3.45$, $p = 0.002$].

We then analyzed pain intensity ratings during the naloxone treatment. A t test showed that pain ratings regarding the 1-back condition under naloxone did not differ from pain ratings in the 1-back condition under saline application [1-back pain condition naloxone: 58.9 ± 3.9; $t(14) = -0.07$, $p = 0.95$]. Importantly, we observed a selective increase of pain intensity ratings during the 2-back condition under naloxone (2-back pain condition naloxone: 51.1 ± 3.6), leading to a significant reduction of the analgesic effect of working memory load by the opioid antagonist naloxone of 40.5% [ΔP_Nlx: 7.8 ± 3.0 versus ΔP_NaCl: 13.1 ± 3.8; $t(14) = 2.93$, $p = 0.01$]. However, naloxone did not completely abolish the analgesic effect of working memory load on pain perception. Pain ratings during the 2-back condition under naloxone were still reduced in comparison to the 1-back condition under naloxone [$t(14) = 2.62$, $p = 0.01$; see Figure 4].

Similar to the first experiment, subjects performed the 1-back task significantly better than the 2-back task during saline [estimated task performance 1-back: 0.86 ± 0.02, 2-back: 0.56 ± 0.05, $t(14) = 6.52$, $p < 0.001$]. The estimated task performances for both working memory conditions during naloxone did not differ significantly from the corresponding performances during saline (estimated task performance 1-back: 0.79 ± 0.06, 2-back: 0.51 ± 0.06).

Previous imaging studies consistently showed that reduced pain perception during cognitive distraction is paralleled by decreased activity in typical pain-sensitive brain regions, like the thalamus, primary and secondary somatosensory cortices, and insula [1, 6, 9, 11, 22]. Even though these studies were not able to determine whether the observed changes exclusively involved higher-order brain areas or instead reflect a reduced inflow of pain afferences to the brain, it is now clear that these observations rely at least in part on an attenuated nociceptive signal ascending from the spinal cord.

It is important to note that reductions of pain-driven BOLD responses in the dorsal horn of the spinal cord do not merely represent an epiphenomenon, but are of functional significance, because the individual responses in the dorsal horn were related to individual pain reduction.

Previous animal [23] and human data [24, 25] indicated a behaviorally induced inhibition of nociceptive input at the level of the dorsal horn, but the nature of these studies precluded a dissection of cognitive from more general affective-motivational components that might be involved in pain modulation. In contrast, the present study provides direct evidence for a dorsal horn modulation in humans by a purely cognitive task, which is completely unrelated to pain.

One may argue that the observed analgesia does not reflect an effect of working memory on pain perception per se but could also be due to learning where the 2-back task takes on the role of a cue which predicts analgesia. However, for this mechanism to evolve, subjects have to perceive a pain

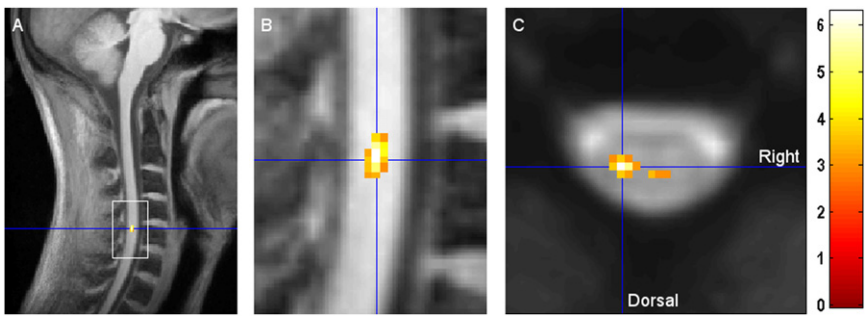

Figure 2. Pain-Related BOLD Responses during the Low Working Memory Load Condition

(A and B) Pain-related BOLD responses are overlaid on the mean structural image of all participants and display the spinal level of pain-related responses (segment C6, approximately at the border to C5). The white box indicates the sagittal section (B) and the blue line indicates the transverse section (C).

(C) The transverse section displays BOLD responses overlaid on the mean functional image and shows that the peak of BOLD responses is located in the dorsal horn, ipsilateral to the side of painful stimulation (left). The color bar indicates t values, and the visualization threshold is set to $p < 0.005$. See also Figure S1.

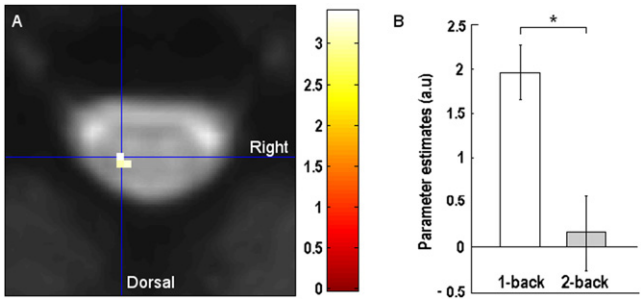

Figure 3. Reduction of Pain-Related Responses in the Spinal Cord by Working Memory Load

(A) The transverse section (mean functional image) shows the effects of the differential contrast (1-back minus 2-back) in the ipsilateral dorsal horn. Interestingly, this peak coincides spatially with the peak of the main effect of pain. The color bar indicates t values and the visualization threshold is set to $p < 0.005$.

(B) The parameter estimates (extracted from the peak voxel of the main effect) show that the BOLD response is significantly reduced under high (gray bar) compared to low working memory load (white bar). Error bars indicate SE. See also Figure S2.

reduction from working memory load during the experiment. Therefore, the observed analgesia cannot be attributed to learning effects alone, although it is possible that learning effects enhance pain reduction.

Although an opioidergic mechanism behind cognition-related pain modulation has been hypothesized previously [26, 27], this is the first study to show a reduction of behavioral analgesia during cognitive demand by naloxone treatment. Importantly, we observed a selective effect of naloxone on behavioral analgesia, whereas the pain ratings to the 1-back condition remained unchanged, indicating that naloxone acted specifically on the antinociceptive mechanisms. Together with previous studies showing enhanced BOLD responses in key regions of the descending pain modulatory system like the rACC and the PAG [6, 9, 10] and enhanced functional connectivity between these structures [6], the current findings point to the descending pain modulatory system as a central nervous network underlying the inhibition of pain during distraction. This phylogenetically highly conserved network is anatomically well-suited to mediate between higher-order brain processes and the spinal cord level through dorsal horn facilitation or inhibition [28, 29]. However, because it is currently not possible to measure cortical and spinal BOLD responses at the same time, our study cannot directly demonstrate the involvement of this system. Furthermore, because we did not apply naloxone during the fMRI measurements, our study cannot reveal the exact site where naloxone exerts its effect.

Although naloxone strongly reduced the analgesic effect of working memory load, it did not completely abolish cognition-related pain reduction, which implies that additional nonopioidergic mechanisms play a role in cognitive pain modulation.

Our findings also have clinical implications, because they demonstrate that cognitive factors, which are well-known predictors of pain perception and chronification [30–35], act not only on a psychological level but are indeed able to modulate pain transmission in the spinal cord, which has been extensively characterized in the animal as a site for central sensitization and chronification processes [36–40]. They therefore establish a tight connection between cognitive factors of pain modulation and basic animal research regarding spinal cord mechanisms of pain processing. As a direct consequence, our findings strengthen the role of cognitive-behavioral therapeutic approaches in the treatment and prevention of pain diseases, because it could be extrapolated that these approaches might have the potential to alter the underlying neurobiological mechanisms as early as in the spinal cord. Furthermore, our results particularly highlight the descending pain modulatory network as a potential pharmacological target to strengthen the cognitive control on spinal cord pain processing. It will be interesting to investigate the contribution of this pain modulatory system and its deficiency on the spinal cord level in different clinical conditions, especially to reveal its predictive value for pain perception in different pain syndromes.

Experimental Procedures

Twenty healthy male subjects (mean age: 27.2 years; range: 23–36 years) participated in experiment 1, and another 15 male subjects (mean age: 25.7 years; range: 23–31 years) participated in experiment 2 of this study. Painful heat stimulation was carried out using a 30 × 30 mm^2 Peltier-Thermode (TSA-II, Medoc, Israel). MRI data were acquired on a 3-Tesla whole body system (Siemens TRIO). The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Council of Hamburg. Further detailed experimental procedures are described in the Supplemental Information.

Supplemental Information

Supplemental Information includes two figures and Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.cub.2012.04.006.

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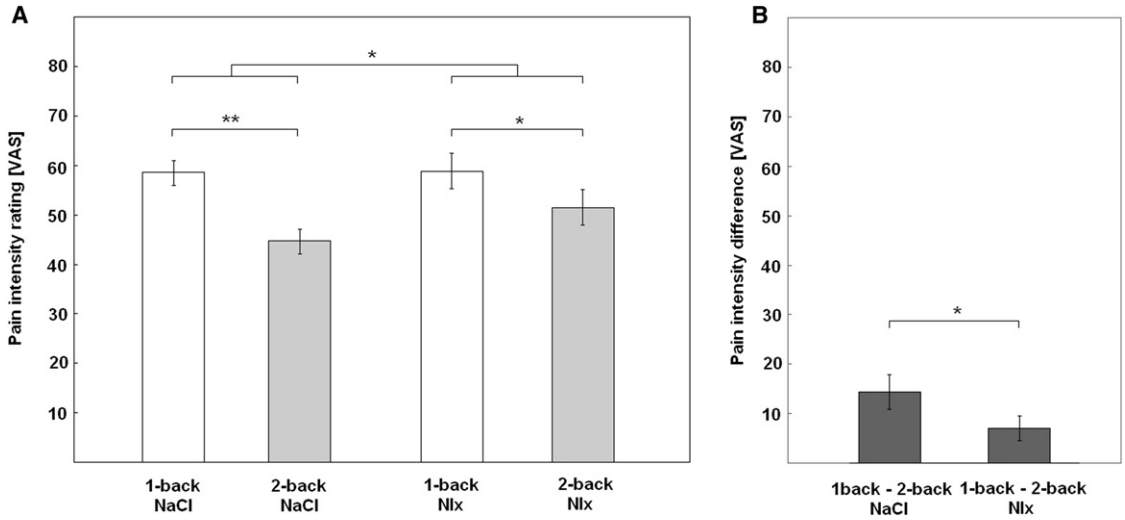

Figure 4. Effects of Naloxone on Pain Ratings and Behavioral Analgesia

(A) Pain intensity ratings obtained on the VAS (0 to 100) for both working memory and pharmacological conditions. Pain ratings during saline application show that increased working memory load led to an effective behavioral analgesia similar to experiment 1. During the naloxone application, we observed a selective increase of pain ratings regarding the high working memory condition, indicating a specific action of naloxone on this mechanism.

(B) Behavioral analgesia as the difference between both working memory conditions was significantly reduced during the naloxone application. NaCl, saline application; Nlx, naloxone application. Error bars indicate SE. *$p < 0.05$, **$p < 0.01$.

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