

Direct Evidence for Spinal Cord Involvement in Placebo Analgesia

Falk Eippert,^{1*} Jürgen Finsterbusch,¹ Ulrike Bingel,² Christian Büchel¹

Placebo analgesia is a prime example of how psychological factors can influence pain perception (1). It refers to a situation where the administration of an inactive treatment has a pain-relieving effect, presumably because of the participant's belief in the analgesic effectiveness of the treatment. Neurobiologically, placebo analgesia is in many cases opioid-dependent and relies on frontal cortical areas and their projections to downstream effectors in the brainstem (1, 2). One possible mechanism of placebo analgesia is thus that cortical areas recruit the opioidergic descending pain control system in the brainstem (3), which ultimately inhibits nociceptive processing in the dorsal horn of the spinal cord in a gate-control manner (4). Behavioral data support the idea that placebo analgesia can act at the level of the spinal cord (5), but there is no direct evidence that nociceptive responses in the spinal cord are reduced under placebo analgesia. We combined high-resolution functional magnetic resonance imaging (fMRI) of the human cervical spinal cord with a robust placebo analgesia paradigm (6) (fig. S1) to test the hypothesis that spinal cord blood oxygen level-dependent (BOLD) responses related to painful heat stimulation are reduced under placebo analgesia.

We first tested for the main effect of painful stimulation and observed the strongest BOLD responses in the dorsal horn ipsilateral to the side of painful stimulation at the expected segmental level [C6, approximately at the junction with C5; $t_{(12)} = 3.51$, $P = 0.002$; Fig. 1A]. Pain ratings, which were obtained after each stimulus during the fMRI exper-

iment, were significantly lower under the placebo condition as compared with the control condition [placebo rating of 52.3 T 5.9 (mean T SEM), control 71.1 T 3.1; 26% reduction; $t_{(12)} = 3.56$, $P = 0.002$], indicating that our placebo induction was successful. We next tested whether the observed BOLD response in the ipsilateral dorsal horn (at the peak voxel of the main effect) would be decreased under the placebo condition. A reduction of BOLD responses under placebo compared with control was evident [$t_{(12)} = 1.81$, $P = 0.046$; Fig. 1B and fig. S2]. To further demonstrate the spatial specificity of our approach, we also tested for motor responses in a reaction time task [middle finger button presses (6)] and found these to be localized more inferiorly and anteriorly (segments C7 and C8; fig. S3), consistent with the functional neuroanatomy of the sensory-motor system.

Our data provide direct evidence that psychological factors can influence nociceptive processing at the earliest stage of the central nervous system, namely the dorsal horn of the spinal cord. They also reveal that one mechanism of placebo analgesia is inhibition of spinal cord nociceptive processing, possibly mediated by the descending pain control system (3) in a gate-control manner (4). It is likely that the decreased BOLD responses we observed are caused by endogenous opioids because opioid antagonists block placebo analgesia (1) and because recent fMRI data from rat spinal cord showed morphine depression of dorsal horn BOLD responses (7). However, our study cannot reveal the exact mechanism of spinal inhibition [i.e., effects on

primary afferents (presynaptic), interneurons, or projection neurons (postsynaptic)] and whether the observed effect is specific for nociception, because we did not measure responses to innocuous stimuli. Nevertheless, the demonstration that modulatory influences on nociceptive spinal cord activity are measurable by fMRI in humans opens up new avenues for assessing the efficacy and possible site of action of new treatments for various forms of pain, including chronic pain.

References and Notes

1. F. Benedetti, H. S. Mayberg, T. D. Wager, C. S. Stohler, J. K. Zubieta, *J. Neurosci.* 25, 10390 (2005).
2. P. Petrovic, E. Kalso, K. M. Petersson, M. Ingvar, *Science* 295, 1737 (2002); published online 7 February 2002 (10.1126/science.1067176).
3. H. L. Fields, A. I. Basbaum, M. M. Heinricher, in *Wall and Melzack's Textbook of Pain*, S. B. McMahon, M. Koltzenburg, Eds. (Elsevier, London, 2006), pp. 125–152.
4. R. Melzack, P. D. Wall, *Science* 150, 971 (1965).
5. D. Matre, K. L. Casey, S. Knardahl, *J. Neurosci.* 26, 559 (2006).
6. Materials and methods are available as supporting material on Science Online.
7. J. Lijla *et al.*, *J. Neurosci.* 26, 6330 (2006).
8. This work was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft BU 1323) and a Bundesministerium für Bildung, Wissenschaft, Forschung, und Technologie grant (01-GO-0510, NeuroImage Nord). We thank K. Müller and K. Wendt for help with MR scanning and C. E. Klinge and E. D. Schoell for comments on previous versions of this manuscript.

¹Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany.

²Department of Neurology, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany.

*To whom correspondence should be addressed. E-mail: f.eippert@uke.uni-hamburg.de

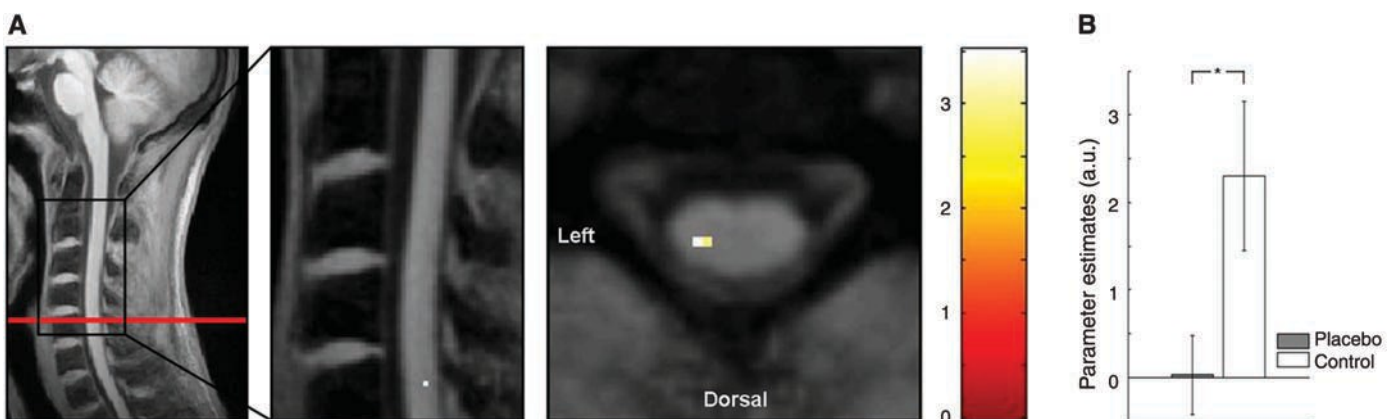


Fig. 1. Pain-related BOLD responses and their reduction by placebo. (A) (Left) The average structural image with the black box indicating the sagittal section (middle image) and the red line indicating the transverse section (right image). The sagittal and transverse sections show that BOLD responses (main effect of pain; visualization threshold $P < 0.01$ uncorrected) are present in the dorsal part of the spinal cord, ipsilateral to the

side of painful stimulation (left). The location corresponds to segment C6. The color bar indicates t values. (B) Parameter estimates were extracted from the peak voxel for the main effect of pain in the ipsilateral spinal cord. The parameter estimates show that the BOLD response is significantly reduced under placebo (gray bar) in comparison with control (white bar). Error bars indicate standard error; $*P \leq 0.05$.