NEUROSCIENCE

Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia

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Value information about a drug, such as the price tag, can strongly affect its therapeutic effect. We discovered that value information influences adverse treatment outcomes in humans even in the absence of an active substance. Labeling an inert treatment as expensive medication led to stronger nocebo hyperalgesia than labeling it as cheap medication. This effect was mediated by neural interactions between cortex, brainstem, and spinal cord. In particular, activity in the prefrontal cortex mediated the effect of value on nocebo hyperalgesia. Value furthermore modulated coupling between prefrontal areas, brainstem, and spinal cord, which might represent a flexible mechanism through which higher-cognitive representations, such as value, can modulate early pain processing.

Patients in randomized placebo controlled clinical trials frequently discontinue their participation because of side effects. Yet, after unblinding, it turns out that some of these patients were part of the placebo group and thus never received any active medication (*1*). This is a case of the adverse nocebo effect (*2*, *3*) that can be seen in contrast to the placebo effect. The placebo effect with respect to pain involves an opioidergic mechanism (*4*–*7*) and recruits the descending pain modulatory system (*5*), which targets the spinal cord dorsal horn (*8*). Placebo effects can be manipulated by providing value information (e.g., price) about a treatment (*9*–*11*). Although higher-priced treatments lead to higher placebo effects (*11*), they might also lead to an increase in perceived side effects. We thus investigated whether value information about a medical treatment can further modulate behavioral nocebo effects and the underlying neural network dynamics.

How can a medial prefrontal value signal (*10*, *12*) interfere with central pain processing and modulate expectation-induced pain perception? One possibility is that this modulation is mediated through functional interactions between key structures of the descending pain pathway (fig. S8) (*13*). Because nocebo hyperalgesia also modulates activity at the spinal level (*14*), we followed this lead and investigated whether nocebo hyperalgesia is mediated through interactions within a cortico-subcortico-spinal network (*15*), in analogy to other forms of cognitive pain modulation (*16*, *17*). However, simultaneous functional magnetic resonance imaging (fMRI) measurements of neural activity in the brain and spinal cord are technically challenging (*18*). To investigate the dynamics from cortex to spinal cord, we developed an fMRI method (*19*, *20*) that allows the measurement of neural activity in the entire central pain system, comprising the cortex, brainstem, and spinal cord (figs. S2 and S3).

To study the influence of value on nocebo hyperalgesia, we induced negative treatment expectations and experiences in two groups of participants (*21*). As the nocebo treatment, we introduced two alleged medical creams that did not contain any active ingredient and provided different value information by labeling one cream as cheap and the second one as expensive. To support the cheap versus expensive impression, we designed two paper medical-cream boxes that

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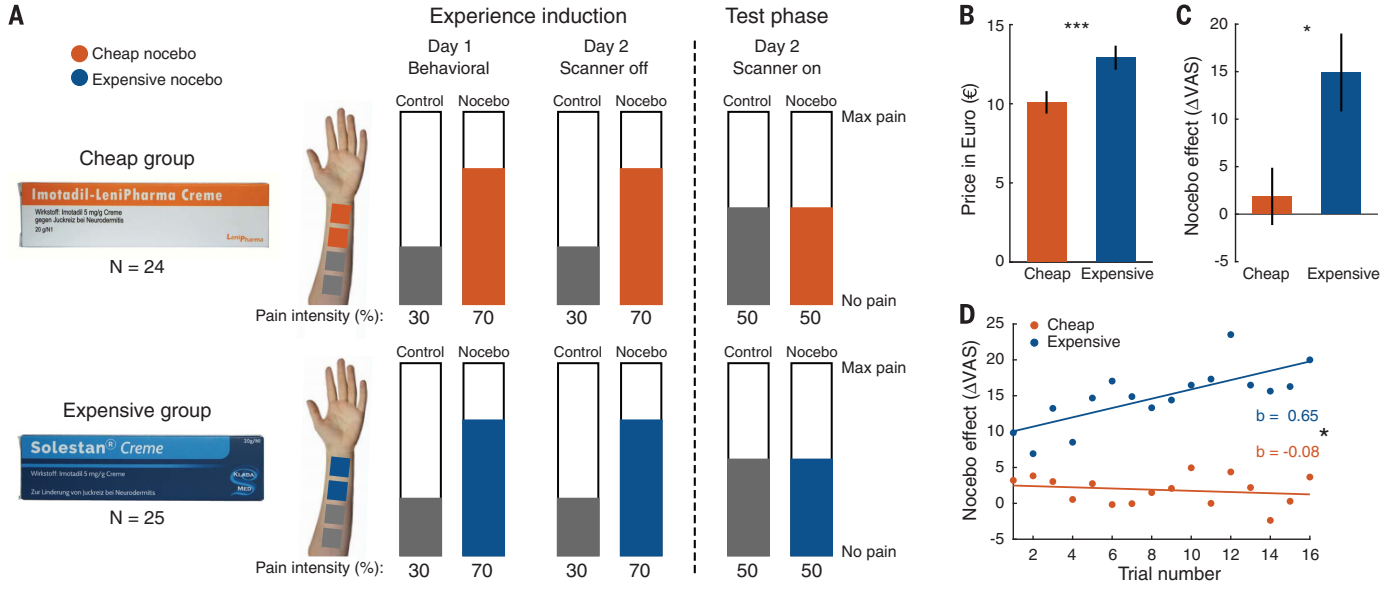

Fig. 1. Study design and behavioral results. (**A**) Experimental design of the nocebo and value manipulation with photos of the designed medical-cream boxes. During the experience induction on day 2, participants were lying in the scanner, but no images were acquired (scanner off). During the test phase, BOLD responses were recorded (scanner on). (**B**) The blue cream box was estimated as being significantly more expensive than the orange box (t_{65} = 5.58, P < 0.001, Cohen's d = 0.69). (**C**) The behavioral nocebo effect was significantly larger in the expensive group than in the cheap group (t_{47} = 2.54, P = 0.014, Cohen's d = 0.74). (**D**) Time courses of the nocebo effect expressed as slope in a linear regression model (b) differed significantly between groups (t_{47} = 2.03, P = 0.048, Cohen's d = 0.58). *P < 0.05; ***P < 0.005; VAS, visual analog scale; bars represent means and error bars represent SEM.

contained design elements for expensive (blue box) and cheap (orange box) medication, respectively (Fig. 1A). A sample of 66 participants that did not take part in the nocebo and value-manipulation experiment estimated actual pharmacy prices of the creams on the basis of the appearance of the boxes. The price of the blue box was estimated to be significantly higher than the price of the orange box (Fig. 1B; for statistical results, see figure captions). Consequently, we used the two boxes in the main experiment to reinforce our value manipulation.

For the main experiment, an independent sample of 49 healthy participants was randomly assigned to either the cheap or the expensive treatment group (table S1). The treatment was introduced as a cream clinically used to treat atopic dermatitis. We induced a nocebo expectation in both groups [(*21*) and table S2]. To implement the value manipulation, we provided different price information about the tested creams. The "cheap group" was told to test a cheap cream and received the nocebo cream from the orange box, whereas the "expensive group" was told to test an expensive cream and received the nocebo cream from the blue box. To compare nocebo responses to baseline pain, an additional control cream was introduced in both groups. In reality, all creams were identical and did not contain any active ingredient. After the nocebo and value expectation induction, participants underwent a heat-pain paradigm on skin patches on the left forearm that were pretreated with either nocebo or control cream (Fig. 1A). During an experience induction phase, temperatures were covertly increased for nocebo and decreased for control conditions to let participants experience the supposed pain-augmenting effect of the treatment. During the test phase, temperatures in nocebo and control conditions were identical while blood oxygen level–dependent (BOLD) responses were recorded.

First, we were interested to see if pain ratings in the nocebo condition differed between cheap and expensive nocebo treatment. The behavioral nocebo effect was significantly greater in the expensive group than in the cheap group (Fig. 1C and fig. S1). Notably, pain ratings did not differ between groups during the experience induction phase, indicating that this significant difference in nocebo effects is unrelated to the experience induction (fig. S1). Expensive treatment thus enhances behavioral expectation effects irrespective of the directionality of the expectation. In analogy to placebo effects (*10*, *11*), the most likely explanation is that participants infer that expensive medication contains a more potent and effective agent and, consequently, produces more side effects.

Furthermore, we analyzed the time course of pain ratings using single-subject linear regression models. Slopes revealed that the nocebo effect increased significantly over time in the expensive group compared to the cheap group (Fig. 1D). This temporal strengthening of the nocebo effect was not influenced by the control condition (fig. S1).

In a first fMRI analysis, we identified a large number of pain-sensitive areas along the central nervous system that were activated during painful stimulation, irrespective of expectation and value (fig. S2). The location of the peak voxel in the spinal cord was within a 1-mm radius of a pain cluster reported in a previous combined imaging study (*20*).

Next, we identified regions that displayed neural representations of nocebo effects irrespective of value. This pooled nocebo effect was represented in the spinal cord at the height of spinal segment C6 (Fig. 2A and fig. S4), slightly more caudal and medial than the pain cluster. Comparing this cluster with results from a previous study that observed nocebo activation within the spinal cord in an independent sample of subjects indicated that both clusters were located at almost identical locations within the spinal cord (fig. S5) (*14*).

Because the behavioral nocebo effect was stronger in the expensive group, we investigated how value-related nocebo effects are reflected at the neural level. The periaqueductal gray (PAG) showed greater activation differences between nocebo and control conditions in the expensive group compared to the cheap group (Fig. 2B). Similar results were observed in prefrontal areas

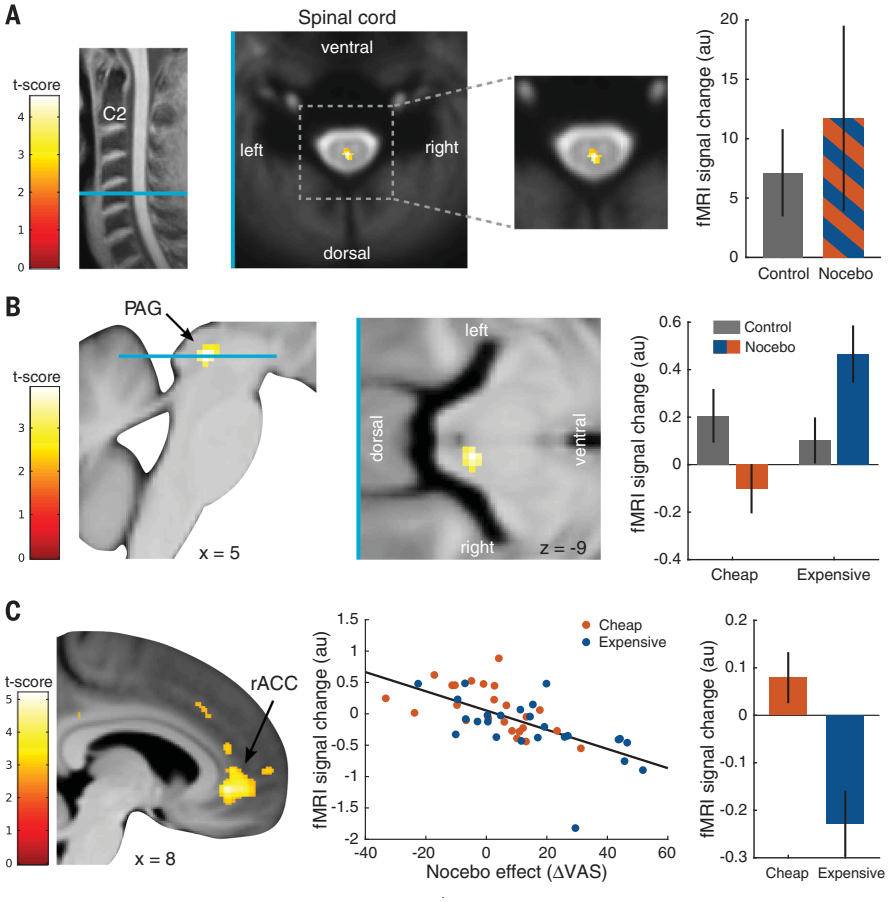

Fig. 2. BOLD responses during nocebo hyperalgesia along the descending pain system. (**A**) Left: Main effect of nocebo pooled across groups (nocebo > control) in the spinal cord at spinal segment C6 (t_{45} = 4.53, P = 0.001, corrected). Right: Respective fMRI signal changes are shown. The statistical t map is overlaid on an average functional image at a visualization threshold of P < 0.01 (uncorrected). au, arbitrary units. (**B**) Left: Interaction effect between groups [(expensive > control) > (cheap > control)] in the PAG (*xyz*: 5,–30,–11; t_{45} = 3.93, P = 0.038, corrected). Right: Respective fMRI signal changes are shown. *xyz* values are MNI coordinates of the template brain in three-dimensional space. (**C**) Left: Correlation between nocebo effects and activation strength in the rACC (*xyz*: 8,38,–5; t_{45} = 4.74, P = 0.008, corrected). Middle: Both groups show a negative correlation. Right: Respective fMRI signal changes are shown. In (B) and (C), statistical t maps are overlaid on an average structural image, and the significance threshold is set to P < 0.005 (uncorrected) for visualization purposes only. Bars represent means and error bars represent SEM.

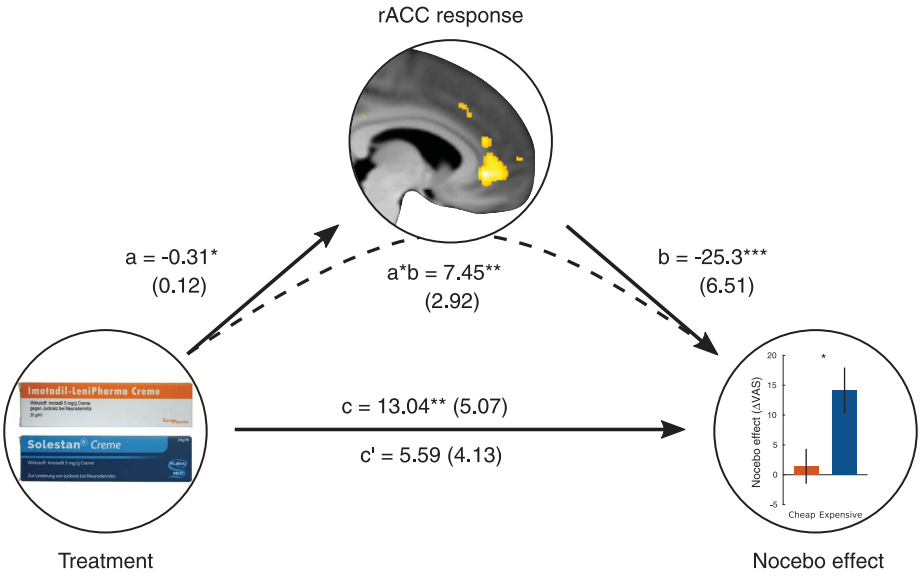

Fig. 3. Mediation analysis in the rACC. The bootstrapped mediation analysis testing the indirect path *a*b* was significant (*ab* = 7.45, SEM = 2.92, *P* = 0.006), indicating that activity in the rACC mediated the treatment effect on behavioral nocebo effects. Numbers indicate path coefficients; numbers in parentheses indicate SEM. **P* < 0.05; ***P* < 0.01; ****P* < 0.005.

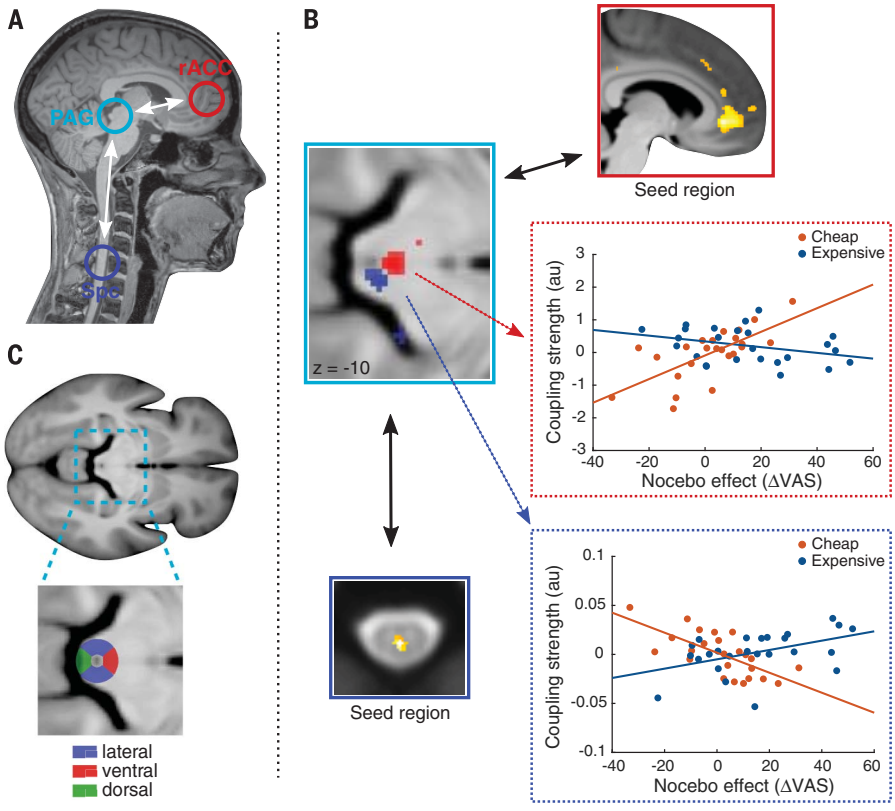

Fig. 4. Connectivity along the descending pain pathway. (**A**) Key candidates for showing expectation-induced modulation in connectivity displayed on a single-subject anatomical image. (**B**) Coupling strength between rACC and ventral PAG (red) and between spinal cord and right lateral PAG (blue) correlated with behavioral nocebo effects (for statistical results, see fig. S7). (**C**) Schematic segregation of anatomical PAG subregions (*27*, *31*) overlaid on an average structural image for illustration purposes: the lateral PAG (blue), the ventral PAG (red), and the dorsal PAG (green).

and the right extended amygdala (fig. S5). Nocebo effects have been conceptualized as the opposite of placebo-related effects (*22*). However, we observed similar activations for nocebo as compared to placebo (*4*, *10*, *23*), indicating that the PAG is engaged during cognitive modulation of pain processing irrespective of the direction of expectation, possibly through activation of on-or-off cells, which either inhibit or facilitate nociceptive transmission in the spinal cord (*24*).

We further examined whether the degree of individual nocebo effects is correlated with BOLD signal changes along the descending pain pathway. Neural activation in the rostral anterior cingulate cortex (rACC) was negatively correlated with behavioral nocebo effects across participants, irrespective of treatment group (Fig. 2C and fig. S6). Thus, the level of rACC deactivation predicted the strength of reported pain increase during nocebo treatment, which suggests that in hypoalgesic or nonpainful conditions, activation in the rACC might subserve an inhibitory function on the descending pain system, and that with increasing levels of deactivation, a descending disinhibition leads to increasing activity at the level of the PAG. Furthermore, this result complements findings in placebo hypoalgesia where the rACC mediates placebo effects (*5*, *6*). The rACC shows a graded response pattern in which increasing activity is related to increased pain reduction (*10*, *25*). Moreover, a pain expectancy signal in the rACC decreases with increasing probabilities for pain, indicating that the rACC shows less activation if more pain is expected (*26*). The negative correlation of rACC activation with individual behavioral nocebo effects further indicates that—with respect to the rACC—placebo and nocebo effects represent a continuum and not opposing entities.

Next, we addressed the hypothesis that the rACC is directly mediating the effect of value. We performed a bootstrapped mediation analysis and tested if the activation strength in the rACC mediates the relationship between cheap and expensive nocebo treatment and behavioral nocebo effects (Fig. 3). This analysis revealed that the effect of our price intervention on the strength of behavioral nocebo effects was mediated by activation in the rACC, indicating that, in addition to economic value (*12*), treatment expectation value is encoded in prefrontal cortex.

To test if value further modulates neural coupling along the descending pain pathway (Fig. 4A) (*5*, *20*), we extracted the fMRI-signal time course from the activation in the spinal cord and rACC (seed regions) and calculated individual coupling strengths between each of these seed regions and other brain regions. Both seed regions revealed coupling with the PAG that correlated significantly with the behavioral nocebo effect (Fig. 4B and fig. S7). However, the correlation pattern differed between treatment group and PAG cluster. The PAG cluster interacting with the rACC was located ventrally, whereas the PAG cluster showing coupling with the spinal cord was located laterally (Fig. 4, B

and C). Overlaying these two PAG clusters onto the previously reported PAG activity revealed that the latter PAG cluster overlapped with both coupling-related PAG subregions (fig. S7). This functional segregation of the PAG is in line with studies showing intrinsic rACC coupling with the ventral PAG (*27*). Conversely, neuronal tracing studies in rats revealed that connections from the spinal cord targeted more lateral aspects of the PAG (*28*). These findings indicate that coupling along the descending pain pathway is a key mechanism to convey value information to early pain-processing areas. Furthermore, distinct subregions within the PAG interact with different pain-processing areas, which might represent a flexible mechanism to modulate pain perception along different levels of the descending pain system.

In summary, we show that expensive medication increases the risk for developing nocebo-related side effects. Moreover, our fMRI protocol allows us to assess how value information about a medical treatment modulates the entire central human pain system. Two regions of the descending pain pathway, namely the rACC and the PAG, facilitated expectation-induced pain modulation and conveyed the difference in nocebo effects between cheap and expensive treatment. Furthermore, modulation of coupling within the rACC-PAG-spinal axis might represent a flexible mechanism through which higher-cognitive representations such as value interact with the descending pain pathway to modulate pain processing between early subcortical areas and nociceptive processing at the spinal level. We did not observe increased activity in other cortical pain-sensitive areas under nocebo, which is in line with another study (*29*) that instead observed increased nocebo activations in subcortical and limbic regions such as the thalamus, amygdala, and hippocampus. This could indicate that expectation modulation might predominantly involve the spinoreticular tract, which comprises regions that showed increased activity in the expensive nocebo group, such as the brainstem, amygdala, and prefrontal cortex (*30*).

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/358/6359/105/suppl/DC1
Materials and Methods
Figs. S1 to S8
Tables S1 and S2
References (*32*–*56*)

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Price modulates early pain processing

Patients in randomized clinical trials frequently stop taking their drug, complaining of side effects. However, it turns out that some of these subjects are part of the placebo group and thus never received any active medication. This is a case of the nocebo effect seriously interfering with medical treatment. Tinnermann *et al.* investigated whether value information such as the price of a medication can further modulate behavioral nocebo effects and the underlying neural network dynamics (see the Perspective by Colloca). They used brain imaging to characterize the circuits involved in nocebo hyperalgesia within the descending pain pathway from the prefrontal cortex to the spinal cord. Their findings revealed how value information increased the nocebo effect.

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