Placebo improves pleasure and pain through opposite modulation of sensory processing

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Placebo analgesia is often conceptualized as a reward mechanism. However, by targeting only negative experiences, such as pain, placebo research may tell only half the story. We compared placebo improvement of painful touch (analgesia) with placebo improvement of pleasant touch (hyperhedonia) using functional MRI and a crossover design. Somatosensory processing was decreased during placebo analgesia and increased during placebo hyperhedonia. Both placebo responses were associated with similar patterns of activation increase in circuitry involved in emotion appraisal, including the pregenual anterior cingulate, medial orbitofrontal cortex, amygdala, accumbens, and midbrain structures. Importantly, placebo-induced coupling between the ventromedial prefrontal cortex and periaqueductal gray correlated with somatosensory decreases to painful touch and somatosensory increases to pleasant touch. These findings suggest that placebo analgesia and hyperhedonia are mediated by activation of shared emotion appraisal neurocircuitry, which down- or up-regulates early sensory processing, depending on whether the expectation is reduced pain or increased pleasure.

expectancy | neuroimaging | hedonic feelings

Medical treatments aim to provide relief from pain and aversive states. Consequently, research on placebo effects has focused on relief of negative hedonic feelings, like pain and displeasure (1). In contrast, placebo improvement of positive hedonics has received little attention. However, pain and pleasure processes are tightly linked. Relief from pain can induce a pleasant experience underpinned by activation of reward neurocircuitry (2–4). Moreover, a painful stimulus can even be perceived as pleasant when it represents relief from a more severe outcome (5). In line with this pain–pleasure link, placebo analgesia can be conceptualized as a type of reward mechanism; pain relief is a better outcome than the alternative (6–8) and is typically framed as a gain (improvement of pain) (9).

Like pain, pleasure is greatly affected by context and expectation (10). Manipulation of people's beliefs about the price of a wine (11), the amount of fruit in a sweet drink (12), the richness of a skin cream (13), and who is caressing them (14) alters the experienced pleasantness of these stimuli.

Placebo-induced improvement of aversive experiences (e.g., pain, anxiety, unpleasant taste) is often underpinned by a decrease in central sensory processing. Placebo analgesia is characterized by decreases in the thalamus, posterior insula (pINS), and primary and secondary somatosensory areas (SI and SII) (15–17). Placebo reduction of affective responses to unpleasant visual stimuli is similarly underpinned by suppression of visual processing (8). It is not, however, known whether placebo-enhanced pleasantness (i.e., hyperhedonia) also alters early stages of sensory processing, or if this change is encoded in higher-level valuation areas.

Functional neuroimaging studies have revealed that the ventromedial prefrontal cortex (vmPFC), amygdala, ventral striatum, and the midbrain are important for mediating placebo analgesia (16, 18–21). Activity in these regions predicts individual placebo analgesia more accurately than regions involved in cognitive control or pain processing (21). This network is dependent on endogenous opioids (16, 19, 22) and interacts with the mesolimbic dopamine system (23–25) to reduce pain by inhibiting nociceptive signaling (15). Because these regions collectively are involved in valuation and reward-related processing more generally (26, 27), and for reasons of clarity and brevity, we will refer to this set of regions as "emotion appraisal circuitry."

Pleasure and pain show similarities both in terms of neurochemistry and systems neurophysiology (10, 28). If placebo responses build on a generalized mechanism of reward prediction (6–8), a negatively reinforcing effect (e.g., pain relief) should involve processes similar to those encoding positive reinforcement. We hypothesized that placebo improvement of pleasant touch would recruit the same emotion appraisal circuitry that underpins placebo analgesia. Moreover, we investigated whether placebo hyperhedonia, like placebo analgesia, involves modulation of somatosensory processing. Specifically, while expectation of pain relief (placebo analgesia) would reduce sensory processing, we hypothesized that expectation of enhanced pleasantness of an already pleasant touch (placebo hyperhedonia) would increase sensory processing.

To compare brain processing of placebo hyperhedonia and placebo analgesia, we conducted a crossover study using functional MRI (fMRI). Thirty healthy participants received gentle brush strokes, moderately pleasant warmth stimuli, and moderately painful heat stimuli on 2 separate days. These stimuli were

Significance

Placebo effects illustrate the power of the human brain; simply expecting an improvement can alter pain processing and produce analgesia. We induced placebo improvement of both negative and positive feelings (painful and pleasant touch) in healthy humans, and compared the brain processing using functional MRI. Pain reduction dampened sensory processing in the brain, whereas increased touch pleasantness increased sensory processing. Neurocircuitry associated with emotion and reward underpinned improvement of both pain and pleasant touch. Our findings suggest that expectation of improvement can recruit common neurocircuitry, which up- or down-regulates sensory processing, depending on whether the starting point is painful or pleasant. These results promote widening the scope of medical research to improvement of positive experiences and pleasure.

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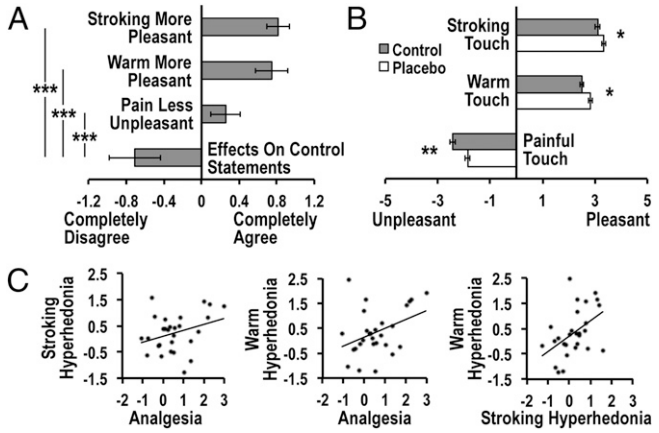

Fig. 1. Behavioral results. (*A*) After watching the documentary, participants indicated a positive expectation that intranasal oxytocin treatment would induce stroking touch and warm touch hyperhedonia, as well as analgesia, but no expectation of oxytocin effects on irrelevant control statements. (*B*) Compared with the control condition, placebo treatment increased pleasantness of stroking and warm touch, and decreased unpleasantness of painful touch. (*C*) The magnitude of placebo responses [defined as the (placebo > control) difference in VAS scores] correlated across stimulus types. Error bars represent SEM; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

applied on the left arm for 10 s in a pseudorandomized order. In the placebo session, participants self-administered an inert nasal spray before the experimental protocol. They were informed that the nasal spray could contain oxytocin, and could thereby: (*i*) increase the pleasantness of stroking and (*ii*) warm touch, and (*iii*) reduce the unpleasantness of painful touch. To strengthen the participants' belief in the effects of the nasal spray, they were shown a short video documentary summarizing scientific findings of such oxytocin effects. The control session was identical to the placebo session except that there was no nasal spray administration. Session order was counterbalanced, and the experimenter who administered the tactile stimuli was blinded to whether it was the placebo or the control session.

Results

Expectations of Treatment Benefit on Pleasant and Painful Touch. To assess expectations about the effects of the nasal spray administration, participants were asked to indicate on a Likert scale of −3 to 3 how much they agreed with a set of task-relevant and control statements before testing (see *SI Materials and Methods*). As confirmed by a repeated-measures ANOVA, there was a significant difference in expectation across the different statements [$F(3.9, 78.7) = 31.1$, $P < 0.001$]. Planned t tests revealed that ratings of expectations on relevant items [treatment-induced improvement of stroking touch (0.81 ± 0.63, mean rating ± SD, partial eta squared (η^2) = 0.62]; warm touch (0.75 ± 0.89, $\eta^2 = 0.59$); and decreased unpleasantness of painful touch (0.26 ± 0.82, $\eta^2 = 0.43$) were significantly higher than expectation on irrelevant control items (-0.71 ± 1.42; all P's < 0.001, one-tailed) (Fig. 1*A*), confirming the efficacy of the placebo manipulation.

Placebo Manipulation Induced Hyperhedonia and Analgesia. Ratings of pleasantness recorded after each stimulus using a visual analog scale (VAS, unpleasant to pleasant, −5 to 5) confirmed placebo improvement for all three touch stimuli [$F(1, 24) = 7.2$, $P = 0.01$, $\eta^2 = 0.22$] (Fig. 1*B*). Stroking touch and warm touch were rated as significantly more pleasant after placebo treatment (stroking: 3.3 ± 0.2; warm: 2.8 ± 0.2) compared with the control condition (stroking: 3.1 ± 0.2, $P = 0.049$; warm: 2.5 ± 0.2, $P = 0.03$). Correspondingly, painful touch was less unpleasant in the placebo (-1.9 ± 0.2) than in the control condition (-2.4 ± 0.2, $P = 0.003$). The placebo response magnitude did not significantly differ across stimuli [treatment*stimulus interaction: $F(1.9,46.4) = 1.4$, $P = 0.25$, $\eta^2 = 0.06$].

Magnitude of Placebo Improvement Correlated Across Touch Stimuli. The placebo response [calculated as the individual (placebo minus control) difference in VAS scores within each stimulus type] correlated across the three stimulus types (all r's > 0.32, P's < 0.05) (Fig. 1*C*).

Opposite Effects on Pleasant and Painful Touch Processing in Sensory Circuitry. To compare the effects of placebo hyperhedonia and analgesia on somatosensory processing, we first compared placebo-induced (placebo > control) blood-oxygen level-dependent (BOLD) signal changes within each participant for each of the three stimulus types. The group analyses were limited to a priori, independently defined regions of interest (ROI) involved in somatosensory processing (contralateral pINS, SI, SII, and the sensory thalamus). Voxel-wise comparison controlling for multiple comparisons within these regions revealed significant placebo-induced increases in BOLD responses to stroking (pINS: $Z = 3.96$; SII: $Z = 3.25$) and warm touch (pINS: $Z = 3.26$; SII: $Z = 2.33$), and decreases in responses to painful touch (SI: $Z = -4.29$; SII: $Z = -3.56$). Specific contrasts between stimulus types confirmed that placebo-induced BOLD responses to stroking and warm touch differed from those to painful touch in pINS (stroking > pain: $Z = 2.27$; warm > pain: $Z = 2.27$), SI (stroking > pain: $Z = 3.13$; warm > pain: $Z = 3.44$), and SII (stroking > pain: $Z = 3.39$; warm > pain: $Z = 2.57$) (Fig. 2 and Table S1). There were no significant changes in the sensory thalamus ROI.

Placebo Hyperhedonia and Analgesia Recruited Similar Emotion Appraisal Circuitry. To investigate placebo-induced processing changes in emotion appraisal circuitry, we performed voxel-wise comparisons within each stimulus type, controlling for multiple comparisons within a priori-defined ROIs encompassing emotion appraisal circuitry. The results revealed a significant placebo-induced increase in activation for the whole group (placebo > control) in the nucleus accumbens (NAc) during stroking ($Z =$

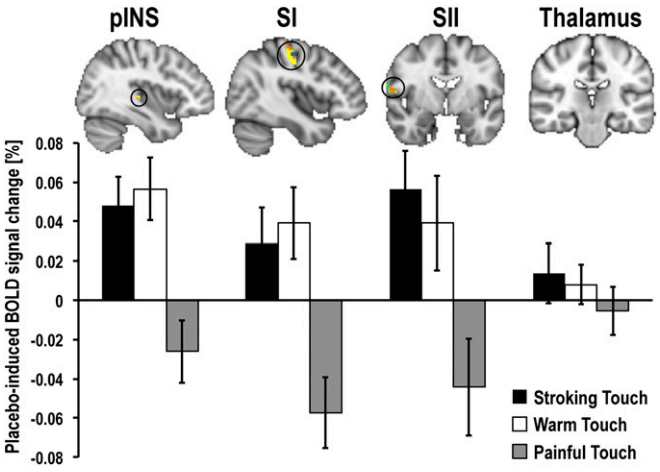

Fig. 2. Placebo-induced BOLD responses in somatosensory circuitry. Placebo improvement of painful and pleasant touch experiences was underpinned by opposite BOLD effects in contralateral somatosensory areas (pINS, SI, and SII). After placebo treatment, BOLD responses to pleasant touch were increased, but BOLD responses to painful touch were decreased. Averaged activation maps [$Z > 2$, uncorrected for illustration purposes, superimposed on the Montreal Neurological Institute (MNI) standard template brain] show voxels where placebo-induced BOLD changes during stroking touch (green) and warm touch (yellow) were significantly more positive than during painful touch (orange represents overlap between stroking and warm touch). Averaged percent signal change values (placebo > control) from the ROIs (bottom) are plotted for illustration purposes. Error bars represent SEM.

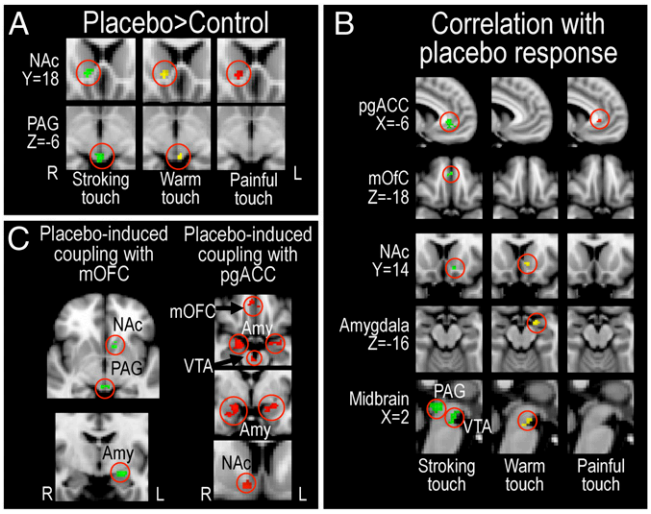

Fig. 3. Placebo-induced BOLD responses in a priori-defined emotion appraisal neurocircuitry. (*A*) The group contrast (placebo > control) revealed overlapping placebo-induced BOLD increases in the NAc during stroking, warm, and painful touch (as revealed by conjunction analysis), and in the PAG during stroking and warm touch. (*B*) Regions where individual placebo response (placebo > control) correlated with placebo-induced (placebo > control) BOLD increase. High placebo responses correlated with high placebo-induced increases in these regions. (*C*) Magnitude of stroking touch hyperhedonia correlated with increased functional coupling between the mOFC, left NAc, left amygdala, and the PAG. Magnitude of placebo analgesia correlated with increased functional coupling between pgACC and mOFC, and bilateral amygdalae as well as mesolimbic reward regions (right NAc and VTA). Green represents stroking touch; yellow represents warm touch; red represents painful touch. Averaged activation maps ($Z > 2$, uncorrected for illustration purposes) were superimposed on the MNI standard template brain.

2.92), warm ($Z = 4.69$), and painful touch ($Z = 3.51$) (Fig. 3*A*), shown by a conjunction analysis to involve overlapping parts of the NAc ($Z = 2.9$) (see *SI Materials and Methods* for details). A significant increase was also found in the periaqueductal gray (PAG) during stroking ($Z = 3.16$) and warm touch ($Z = 2.59$) (Fig. 3*A* and Table S2). Further placebo-induced BOLD increases were found in the amygdala for warm touch ($Z = 2.06$), and in the ventral tegmental area (VTA) for warm ($Z = 2.31$) and painful touch ($Z = 2.29$). Placebo-induced recruitment of emotion appraisal circuitry did not significantly differ between the three touch stimuli, as assessed by voxel-wise comparisons between placebo > control parameter estimates of the three stimuli [e.g., painful (placebo > control) > stroking (placebo > control)].

Placebo Responses Correlated with BOLD Signal Increases in Emotion Appraisal Circuitry. A well-known feature of placebo treatment is individual variability in the magnitude of the placebo response. These behavioral differences are known to reflect differences in central placebo processing (15, 23). We identified covariance with the behavioral placebo response within emotion appraisal circuitry by adding a regressor with each subject's average placebo improvement (placebo > control) for each stimulus type to the fMRI group analysis setup (placebo > control) for each stimulus. This correlation analysis confirmed that the larger the reported benefit of placebo treatment, the higher placebo-induced BOLD increases in the medial orbitofrontal cortex (mOFC, stroking: $Z = 2.78$), pregenual anterior cingulate cortex (pgACC, stroking: $Z = 3.69$; pain: $Z = 3.18$), NAc (stroking: $Z = 3.24$; warm: $Z = 2.98$), amygdala (warm: $Z = 2.9$), PAG (stroking: $Z = 4.13$), and VTA (stroking: $Z = 3.75$; warm: $Z = 2.75$) (Fig. 3*B* and Table S2).

Placebo Responses Correlated with Increases in Functional Connectivity Within Emotion Appraisal Circuitry. Previous studies showed that placebo analgesia increases functional connectivity of the pgACC and mOFC with PAG and amygdala (16, 20, 22). We used a psychophysiological interaction (PPI) analysis (29, 30) to assess whether placebo-induced functional coupling between these prefrontal regions and subcortical emotion appraisal circuitry increased in proportion to the behavioral placebo effect. We extracted the mean time series from pgACC and mOFC from each individual run, and added these as regressors in separate first-level generalized linear model (GLM) analyses for each subject. Statistical maps based on interactions between the time series and each stimulus regressor were included in group-level analyses assessing the correlation between the placebo-induced (placebo – control) change in PPI parameter estimates and the individual behavioral placebo response. As above, this analysis controlled for multiple comparisons within the a priori-defined ROIs. We confirmed significant placebo-related increases in functional connectivity between prefrontal and subcortical emotion appraisal regions. Specifically, the stronger the placebo-induced increases in functional connectivity between the mOFC and the amygdala ($Z = 2.94$), PAG ($Z = 2.98$), and NAc ($Z = 2.35$), the larger the reported benefit of placebo treatment on stroking touch pleasantness (Fig. 3*C* and Table S2). Similarly, placebo-induced increases in functional connectivity between the pgACC and the mOFC ($Z = 3.18$), amygdala (left: $Z = 2.84$; right: $Z = 3.24$), NAc ($Z = 3.46$), and VTA ($Z = 3.04$) correlated with the magnitude of the placebo analgesic response (Fig. 3*C*).

Placebo-Induced Functional Coupling Strength Correlated with Opposite Modulation of Sensory Processing During Placebo Hyperhedonia and Analgesia. To investigate how placebo-induced functional coupling within this circuitry related to sensory processing, we first extracted each individual's mean parameter estimate within the PAG from the PPI-analysis (placebo > control) seeded in the mOFC for each stimulus type. This value, reflecting individual placebo-induced functional coupling between the mOFC and PAG, was then added as a regressor in the group level GLM (placebo > control) for each stimulus. This correlation analysis revealed that placebo-induced (placebo > control) functional coupling between the mOFC and PAG correlated with placebo-induced (placebo > control) modulation of sensory regions in opposite directions during hyperhedonia and analgesia. Specifically, participants with high placebo-induced increases in mOFC–PAG coupling strength had larger increases in SII responses to stroking touch ($Z = 3.01$), but larger decreases in SII responses to painful touch ($Z = -2.85$) (Fig. 4). To formally test whether these relationships differed between placebo hyperhedonia and placebo analgesia, we calculated the corresponding correlation coefficients (based on mean placebo-induced OFC–PAG functional coupling vs. mean percent BOLD signal change within sensory

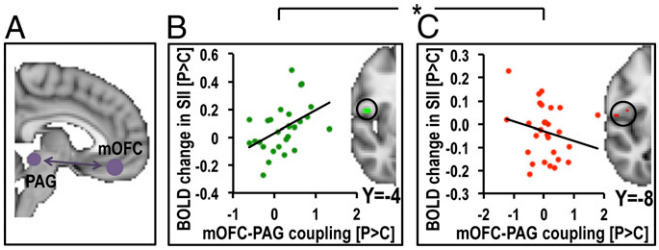

Fig. 4. mOFC–PAG coupling strength was associated with opposite modulation of SII in placebo analgesia and hyperhedonia. Strong placebo-induced functional coupling between mOFC and PAG (*A*) correlated with increased SII responses to stroking touch (*B*) but decreased SII responses to painful touch (*C*), a pattern that was replicated also for the pINS. Averaged activation maps were thresholded at $Z > 2$, uncorrected, for illustrational purposes. The scatterplots illustrate the correlations, which are significantly different from each other. *$P > 0.05$.

regions). Direct comparison between these correlation coefficients confirmed that the correlation during stroking touch was significantly more positive than the correlation during painful touch for SII ($r_{stroking} = 0.31$, $r_{pain} = -0.25$; $Z = 2.04$; $P = 0.02$) and for pINS (stroking: $Z = 2.37$; pain: $Z = -2.51$; stroking > pain: $r_{stroking} = 0.43$, $r_{pain} = -0.27$; $Z = 2.6$, $P < 0.001$).

A similar pattern was revealed for the functional coupling between pgACC and PAG. High placebo-induced pgACC–PAG coupling correlated significantly with increases in SII responses to stroking ($Z = 2.79$) and warm ($Z = 2.38$) touch, and decreases in SI responses to painful touch ($Z = -4.77$). These findings are consistent with a general pattern of modulation across sensory circuitry.

Discussion

This study investigated the central mechanisms by which positive expectations to the same inert nasal spray enhance the pleasantness of stroking and warm touch, and reduce the unpleasantness of painful touch. These beneficial placebo effects were reflected in opposite modulation of sensory processing. Specifically, placebo-induced improvement of pleasant experiences involved an up-regulation of activity in the pINS, SI, and SII, the earliest cortical targets of somatosensory processing, and placebo-induced analgesia involved a down-regulation of activity in these areas. Our results indicate that increased sensory processing of a stimulus of positive valence (e.g., pleasant touch) underpins hyperhedonia, in a similar manner as reduced processing of an aversive stimulus (e.g., painful touch) underpins analgesia.

Individual differences in behavioral placebo hyperhedonia and analgesia responses correlated with placebo-induced activity increases and functional coupling strength within circuitry involved in reward, valuation, and emotion appraisal. Moreover, placebo-induced functional coupling between the vmPFC and PAG correlated with increased sensory processing to stroking touch but decreased processing to painful touch. We suggest that similar modulatory circuits can up- and down-regulate early sensory processing, depending on whether the expectation is improvement of positive or negative hedonic feelings.

Opposite Modulation of Sensory Processing. The placebo-related decrease in sensory regions (pINS, SI, and SII) during painful touch confirmed previous findings (15–17). A unique finding is the increase in sensory processing when placebo treatment increased the pleasantness of pleasant touch. Thus, a cognitively induced increase in pleasantness was underpinned by modulation of the earliest cortical relay stations of somatosensory processing, and not only in higher-level valuation areas. This modulation affected cortical targets of both myelinated A-fibers (SI and SII) and unmyelinated C-fibers (pINS). This result is consistent with recent findings that modulation of touch affect is reflected in both pINS and SI (14, 31).

The somatosensory cortices are also prone to attentional modulation (32). However, the opposite effects during pleasant and painful stimuli indicate that placebo treatment did not induce a general effect of attention. Moreover, recent evidence suggests that placebo treatment and distraction work additively in reducing pain when combined in the same challenge, supporting the view that placebo responses and attention provide analgesia through independent mechanisms (33).

Common Emotion Appraisal Circuitry Mediated Behavioral and BOLD Placebo Responses of Hyperhedonia and Analgesia. Placebo treatment increased BOLD responses in the NAc for stroking, warm, and painful touch, and in the VTA for painful and warm touch, potentially constituting a common component of placebo hyperhedonia and analgesia. The NAc is a key structure of the mesolimbic reward network and receives heavy dopaminergic projections from the VTA. Dopaminergic and opioidergic NAc activity underpins placebo analgesia responses (22–25). The ventral striatum (including the NAc) is involved in a variety of expectation effects: motor improvement in patients with Parkinson disease (34), anxiety reduction (8), and enhanced pleasantness of a sweet drink (35). Moreover, dopamine release in the ventral striatum is related to motivational and learning aspects of rewards (1). Placebo responses across conditions are mediated by expectations and desire for a benefit from the treatment. The dopamine and opioid systems have thus been proposed to be motors of placebo modulation across different conditions (6, 36).

We observed that individuals with the largest placebo hyperhedonia responses also had the largest placebo-related increases in the pgACC, mOFC, NAc, amygdala, VTA, and PAG processing: regions where placebo analgesia is underpinned by opioid release (18, 19, 22, 24). Stroking touch hyperhedonia and analgesia responses both correlated with increases in the pgACC. In addition to its role in pain modulation and placebo responses, this region is paramount for emotion appraisal and valuation processing (27), and is activated by pleasant tactile stimuli, such as warmth (37), massage (38), and soft gentle strokes to the skin (39).

Placebo analgesia is characterized by increases in functional connectivity between the the pgACC, mOFC, and the PAG and amygdala (16, 20, 22). We found that high placebo analgesia responders had the greatest increases in functional coupling between the pgACC and mOFC, amygdala, NAc, and VTA. These findings extend upon previous research because this modulatory network was also functionally connected with the NAc and VTA, parts of the mesolimbic reward system. Intriguingly, stroking touch hyperhedonia responses correlated positively with functional connectivity strength in a similar network, comprising the mOFC, amygdala, PAG, and NAc.

Proposed Mechanisms of Placebo Hyperhedonia and Analgesia. Positive expectations, conditioning, or desire for pain relief activates an opioid network involving the vmPFC and amygdala, which in turn engages the antinociceptive brainstem-spinal cord/dorsal horn circuit (40), resulting in placebo analgesia. We found that placebo-induced functional coupling between the vmPFC and PAG correlated with modulation of sensory processing of pleasant and painful touch in an opposite manner. Although a large increase in mOFC–PAG coupling strength was associated with reduced SII responses to painful touch, it was associated with greater SII responses to stroking touch. A similar pattern was found for the posterior insula, as well as for the modulation of sensory responses by placebo-induced coupling of the pgACC to the PAG.

This influence of vmPFC–PAG coupling on sensory processing may potentially reflect a descending modulatory mechanism acting at the spinal cord level, facilitating "positive" touch signals and suppressing nociceptive signals (7, 41). However, the PAG has bidirectional connections to a wide range of cortical and subcortical structures (42), and the modulation of sensory circuitry may be entirely central in origin. For example, bidirectional modulation of one central region by another region has been reported in studies of reappraisal of negative affect (43). Further research is needed to pinpoint the exact mechanism whereby placebo-induced engagement of cortical and subcortical circuitry modulates sensory systems, but it is likely to emerge from a synergy of both descending action at the spinal cord level (40), and interaction of dopaminergic (23–25) and opioidergic (16, 19, 22, 36) cortico-limbic networks.

The opposite influence of vmPFC–PAG connectivity on sensory processing of pleasant and painful touch points to a potential shared mechanism of placebo improvement of positive and negative hedonic feelings. Mu opioid signaling in this circuitry induces powerful analgesia, but also has reinforcing effects, promoting reward seeking (28). In the framework of the motivation–decision model of pain, opioid inhibition of pain reduces the motivation to escape pain, allowing the individual to endure the pain to survive a threat or to seek a reward (41). In a pain context, successful opioid and dopamine activation in the vmPFC, amygdala, NAc, PAG, and VTA is associated with a large placebo analgesic response (22, 24). We show here that activation of this circuitry also correlates with an increase in pleasantness of

appetitive stimuli, likely through corresponding influences on sensory processing. It will be interesting to see, in future studies, whether placebo hyperhedonia, similarly to analgesia, relies on opioid or dopaminergic transmission.

Note that activity patterns in emotion appraisal circuitry were similar, but not identical for placebo analgesia and hyperhedonia, consistent with nonidentical top-down mechanisms for these two placebo modulations. For example, a significant conjunction was found only in the NAc, and basic contrasts (placebo-control) showed significant activations in the PAG during stroking and warm touch, but not pain. Nevertheless, there were no significant differences between analgesia and hyperhedonia within emotion appraisal circuitry. Moreover, the observation that placebo-induced vmPFC–PAG coupling correlated with reduction in sensory processing during pain supports a role of the PAG in the current study consistent with previous investigations of placebo analgesia (15, 16).

We suggest that expectation of treatment benefit, whether increased pleasantness or reduced unpleasantness, engages shared modulatory neurocircuitry, consistent with investigations of placebo suppression of pain (15) and negative emotions (8). The consequence is top-down modulation of processing in sensory areas in an opposite manner, with expectation of hyperhedonia leading to up-regulation of sensory processing, and expectation of analgesia leading to down-regulation of sensory processing (Fig. 5).

Placebo Hyperhedonia and Analgesia in the Clinic. In clinical settings, placebo responses can confound assumptions about the physical or "true" effects of the treatment, but can also be used to optimize a treatment (44–46). Although the amount of expectancy, desirability (47), personality traits (48), and biomarkers, like gray matter density of the NAc (25), sometimes correlate with placebo responses, it has been notoriously difficult to predict placebo responses across different contexts (49, 50). Most placebo research has addressed the effect of a treatment on one clinical outcome in isolation (e.g., reduction of pain). However, in randomized controlled trials, it has been proposed that the severity of side effects may give rise to larger placebo effects, because this increases the participants' confidence that they are receiving a potent treatment (51). Here, individuals with large placebo analgesia responses also had large placebo hyperhedonia responses. This finding could reflect a placebo-induced hyperhedonic and analgesic state affecting both positive and negative hedonic feelings. If so, one would predict hyperhedonic responses after treatment that is presented as purely analgesic (i.e., without conscious expectation of hyperhedonia) and vice versa.

Furthermore, if hyperhedonia and analgesia share common mechanisms, it is possible that one contributed to the other, and that inducing hyperhedonia bolstered the analgesic effect. Such an account would highlight the importance of focusing on positive effects of a treatment (e.g., regained ability to enjoy pleasures, or increased life quality), analogous to the importance of avoiding focus on negative side effects to reduce nocebo effects (46). Future studies should address these questions.

In conclusion, this study demonstrated that placebo improvement of pleasant and painful touch involved opposite modulation of somatosensory processing. Placebo increases in touch pleasantness increased sensory activation, whereas placebo reductions in pain unpleasantness decreased sensory activation. Furthermore, similar emotion appraisal neurocircuitry was recruited during both analgesia and hyperhedonia. Increases in functional coupling between the vmPFC and PAG specifically correlated with increased sensory processing of stroking touch, but reduced sensory processing of painful touch, potentially constituting a shared mechanism of placebo hyperhedonia and analgesia. Overall, our results suggest that emotion appraisal circuitry is recruited by expectations of a benefit, whether it is pain relief or enhanced pleasantness of a positive stimulus, and modulates sensory processing accordingly to meet these predictions.

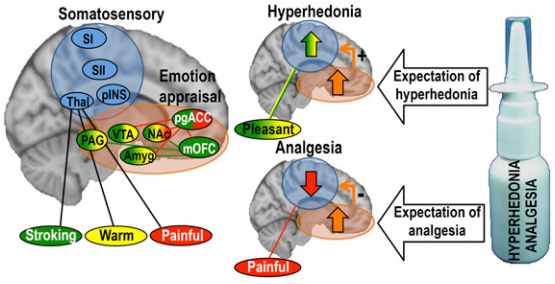

Fig. 5. Proposed mechanism of placebo analgesia and hyperhedonia. During expectation of hyperhedonia and analgesia, a shared modulatory network up-regulates pleasant touch processing and down-regulates painful touch processing in somatosensory areas, possibly through similar dopaminergic/opioidergic connections. Color-coding of the regions represent areas where placebo treatment induced activation for stroking touch (green), warm touch (yellow), and painful touch (red). Connecting lines represent placebo-related increases in functional connectivity for stroking touch (green) and painful touch (red). Somatosensory regions are shown in blue.

Materials and Methods

Subjects. Thirty healthy volunteers (mean age 25.5 ± 4.5 y; range 20–41 y; 10 females) participated. Two datasets were incomplete, leaving a final sample size of 28 participants. All participants gave informed written consent and were paid 400 NOK (~70 USD). The study was approved by the Regional Committee for Medical and Health Research Ethics (2009/208/REK sør-øst C) and followed the guidelines of the Declaration of Helsinki (1996).

Study Design. Each volunteer participated in two sessions on separate days, with and without intranasal placebo treatment (counterbalanced order), but identical in every other manner. To induce expectation of intranasal oxytocin's beneficial effects on painful and pleasant touch experience, participants viewed a 6-min locally developed video documentary about oxytocin's putative prosocial effects, such as involvement in bonding, love, grooming, affective touch, and healing (see *SI Materials and Methods* for details). Following this presentation, the subjects either self-administered 10 puffs (five in each nostril) of a saline nasal spray that they were told could contain oxytocin (placebo session), or directly moved on to the next part of the procedure (control session). Next, fMRI data were collected throughout the 15-min experiment, in which the participants received a total of 27 10-s tactile stimuli: stroking touch, warm touch, and painful touch presented in a pseudorandomized order (no more than two of the same stimulus in a row; at least 1 min between each painful touch stimulus to avoid skin sensitization). Eight seconds after each stimulus, the subjects rated their subjective experience on a VAS.

Stroking Touch. Gentle strokes were delivered to the dorsum of the left forearm (20 cm distance) at a velocity of ~5 cm/s using a 7-cm-wide soft artist's goat hair brush (31). The brush strokes were administered for 10 s (two strokes) in proximal-to-distal direction. This type of tactile stimulation is consistently perceived as pleasant and effectively activates C-tactile afferents, which signal affective aspects of touch (52).

Warm Touch. A soft, gel-filled "heat pad" (ColdHot Pack, 3M Health Care) was heated for 60 s in a microwave oven (~42.5 °C surface temperature) immediately before the experiment. The ColdHot Pack, wrapped in thin nylon cloth, was placed gently on the dorsum of the left forearm for 10 s and then removed, resembling the touch of a warm human hand.

Painful Touch. Heat stimuli were delivered using an MRI compatible peltier thermode (Pathway model ATS, 30 × 30 mm, Medoc). A moderately painful temperature, which was selected for each participant before the first fMRI session (5 on a numeric rating scale, NRS, with anchors 0 = no pain; 1 = pain threshold; 10 = intense pain), was used in both fMRI sessions (mean temperature = 47.1 ± 0.73 °C). An experimenter placed the thermode on the dorsum of the left hand for 10 s, and then removed it. Participants were not informed that the same temperature was used for all stimuli in the fMRI sessions, and were instructed to focus on their experience of each individual stimulus. To avoid skin sensitization that could affect the positive touch experience, painful touch was applied on a location adjacent to the pleasant touch stimuli.

Hedonic Ratings. A VAS (−5 to +5) with anchors "unpleasant" and "pleasant" was presented on a screen 8 s after each stimulus, and remained on the screen

for 6 s. Participants used a button-box to indicate their rating. Average per-session ratings for each stimulus were calculated and analyzed using repeated-measures ANOVA (Greenhouse–Geisser correction) with the within-subjects factors treatment (placebo, control) and stimulus type (stroking, warm, pain), and between-subjects factors treatment order (placebo first, control first) and sex (male, female). Planned paired *t* tests (one-tailed) between placebo and control were calculated within each stimulus type. See *SI Results* and Figs. S1–S3 for details about temporal characteristics of ratings, effects of order and sex, and the relationship between expectation and hedonic ratings.

fMRI Preprocessing and Analysis. Imaging was performed using a Philips Achieva 3 Tesla whole-body MR unit (Philips Medical Systems). See *SI Materials and Methods* for image-acquisition details. fMRI data analysis was performed in a multistage process using FEAT (fMRI Expert Analysis Tool) v5.98, part of FSL [Functional MRI of the Brain (FMRIB)'s Software Library]. Prestatistics processing was applied within each individual run (see *SI Materials and Methods*, Fig. S4, and Table S3 for details). A unique input stimulus function was defined for each stimulus type (stroking, warm, and pain), and for the VAS rating intervals. Input stimulus functions were convolved with the γHRF to yield regressors for the GLM. Time-series statistical analysis was carried out using FILM with local autocorrelation correction (53). Registration to high-resolution structural and standard space images was carried out using FLIRT (54, 55). Higher-level (group) analyses were performed using FLAME 1+2 (FMRIB's Local Analysis of Mixed Effects) (see *SI Materials and Methods*, Fig. S5, and Table S4). All a priori ROIs were defined from independent sources (*SI Materials and Methods* and Fig. S6).

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Supporting Information

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SI Results

Behavioral Results. ***Relationship between initial expectations and placebo responses.*** Expectation of treatment benefit is often an important factor in shaping placebo responses. We therefore calculated correlation coefficients between the agreement with questionnaire statements suggesting nasal spray benefit, and the placebo-induced change in visual analog scale (VAS) hedonic ratings, within each stimulus type (Fig. S1). Expectation of increased warm pleasantness significantly correlated with placebo warm hyperhedonia ($r = 0.33$; $P = 0.04$, one-tailed), and expectation of reduced pain unpleasantness significantly correlated with placebo analgesia ($r = 0.55$; $P = 0.001$, one-tailed). The correlation between expectation of increased stroking touch pleasantness and placebo stroking hyperhedonia was also positive, but did not reach statistical significance ($r = 0.1$; $P = 0.32$, one-tailed).

Effects of order and sex. As confirmed by repeated-measures ANOVAs, there were no significant effects of treatment order or sex on expectation ratings (all P's > 0.5) or hedonic ratings (all P's > 0.42).

Temporal characteristics of hedonic ratings. To investigate whether VAS reports stayed consistent throughout the experimental sessions, we first calculated mean values from the first and the last half of the experimental sessions for each individual. We then performed a repeated-measures ANOVA with the factors stimulus type (stroking, warm, pain), and time (first half, last half). There was no significant main effect of time [$F(1, 27) = 2.1$, $P = 0.16$] and no significant interaction between time and stimulus type [$F(1.3, 36) = 0.85$, $P = 0.4$]. In post hoc t tests (paired, two-tailed) comparing the first and last halves within each stimulus type, we found no significant differences of time for the ratings of stroking ($P = 0.29$) and painful touch ($P = 0.85$). However, the ratings of warm touch were significantly higher in the first half compared with the last half of the experimental sessions ($P = 0.02$), which may be related to the decrease in temperature (the HotCold pack decreased slightly in temperature from ∼42.5 °C at the start, to ∼40 °C at the end), satiety of the stimulus, or other effects of lying in an MRI scanner for this period. The effects did not significantly differ between placebo and control sessions (all $P = 0.2$). Nor did the decline in warm ratings differ significantly from decline in stroking touch ($P = 0.3$) or pain ratings ($P = 0.1$).

Functional MRI Results. ***Relationship between initial expectations and placebo-induced blood-oxygen level-dependent change.*** To explore the relationship between initial expectation and placebo-induced (placebo-control) blood-oxygen level-dependent (BOLD) changes, we added a regressor with the expectation of treatment benefit (demeaned) for each stimulus type for the functional MRI (fMRI) analysis setup (placebo > control) for each stimulus, controlling for multiple comparisons within regions of interest (ROIs) encompassing emotion appraisal and sensory circuitry (Fig. S6). There was a correlation between expectation of treatment benefit on stroking touch and placebo-induced increase in the posterior insula (pINS) during stroking touch ($Z = 2.45$, contralateral to the stimulus site), but nothing else survived significance threshold. However, an activation pattern generally comparable (but weaker) to analyses using placebo response as a regressor, was observed when thresholding at $P = 0.05$ (uncorrected) (Fig. S3).

Outlier correction. Two subjects in the comparison between [placebo-induced medial orbitofrontal cortex (mOFC)–periaqueductal gray (PAG) coupling] and [placebo-induced BOLD change in the secondary somatosensory area (SII)] during pain (Fig. 4), are outside of ±1.5-times the interquartile range: −0.94 to 1.1; they can be considered mild outliers according to the guidelines of ref. 1. If these subjects are both excluded from analysis, the effect remains comparable to the original analysis ($r_{stroking} = 0.31$, $r_{pain} = -0.21$; $Z = 1.9$, $P = 0.03$). Furthermore, the results remain the same when conducting the voxel-based analysis using robust outlier deweighting (as implemented in FLAME [Functional MRI of the Brain's (FMRIB) Local Analysis of Mixed Effects], FSL) ($Z = 2.85$).

SI Materials and Methods

Balance of the Conditions. The placebo and control conditions were carried out on separate days to keep the sessions as short as possible, to maximize participants' comfort. To ensure experimental balance, the two sessions were kept as identical as possible, both before and during the experimental procedure. Before both experimental sessions, the participants went through the exact same sequence of temperatures during pain thresholding, watched the video documentary, and filled out the expectation and mood questionnaires. During both experiments the participants received the same tactile stimuli, which were administered by an experimenter who was blinded to which session it was (placebo or control). The only aspect that differed was the nasal spray administration, which was done in the placebo session only. Although there was no sensory stimulation of the nostrils in the control session, we consider it an unlikely cause of the hyperhedonic and analgesic effects that were observed in the experiment, which started ∼10 min after nasal spray administration.

Video Documentary About Oxytocin. To induce expectation of intranasal oxytocin's beneficial effects on painful and pleasant touch experience, participants viewed a 6-min locally developed video documentary about oxytocin's putative prosocial effects such as involvement in bonding, love, grooming, affective touch, and healing. As all of the material was based on published research, there was no deception. The video concluded that a nasal spray of oxytocin might enhance the pleasantness of: (*i*) stroking and (*ii*) warm touch, and (*iii*) reduce the unpleasantness of pain. The video was introduced using a scripted explanation: "Due to the recent surge in scientific and media interest in oxytocin's positive effects in humans, how much people know about oxytocin varies greatly. Thus, we show everyone this film to even out the differences." Participants viewed the video in both sessions.

Mood Assessment. Mood was measured at three time points during each session: (*i*) after informed consent, (*ii*) immediately before scanning, and (*iii*) immediately after scanning. Participants rated their current level of fear, sadness, irritability, happiness, calmness, and anxiety using VAS with anchors "not at all" and "very much so." These scores were analyzed using repeated-measures ANOVA with the within-subjects factors treatment (placebo, control), time of rating (*i*, *ii*, *iii*), and questionnaire item, and between-subjects factors treatment order (placebo first, control first) and sex (male, female). There were no significant main effects or interactions (all Fs < 2.23; all Ps > 0.06).

Assessment of Expectations. After watching the video documentary about oxytocin, participants filled in a questionnaire (−3 to +3 Likert scale, with the anchors "completely disagree" and "completely agree") addressing specific expectations about effects of intranasal oxytocin. This questionnaire included 10 items, all starting with "I believe a nasal spray containing oxytocin will make me…" and ending either with relevant statements (experience

touch as more pleasant, warmth as more pleasant, pain as less unpleasant) or with control items (feel more outgoing and social, feel less patient, discriminate better between moving touch velocities, feel touch as unpleasant, feel happier, more relaxed, feel generally more delighted). Participants filled in the same questionnaire in both sessions. Expectation data were analyzed used repeated-measures ANOVA (Greenhouse–Geisser correction) with the within-subjects factors session number (session 1, session 2) and questionnaire item (each of the 10 items), and the between-subjects factors treatment order (placebo first, control first) and sex (male, female). The reports did not differ between the two sessions [$F(1,20) = 1.2$, $P = 0.3$]. We performed direct comparisons between relevant and irrelevant statements using averaged values from both sessions. Planned paired t tests (one-tailed) between the response on each relevant item (expectation of increased stroking and warm touch pleasantness, and reduced unpleasantness of pain) and the averaged responses on the irrelevant items, were calculated.

MRI Acquisition and Preprocessing. Imaging was performed using a Philips Achieva 3 Tesla whole-body MR unit equipped with an eight-channel Philips SENSE (reduction factor = 2) head coil (Philips Medical Systems). Functional images were acquired with a gradient-echo echo-planar imaging (EPI) sequence: TR = 2000 ms; TE = 30 ms; flip angle = 80°; field-of-view = 240 × 240; in-plane resolution = 3 × 3 mm; slice thickness = 3 mm; gap spacing between slices = 0.3 mm; number of axial slices (placed on the ac-pc line) = 34; number of volumes = 510. A high-resolution T1-weighted scan was acquired directly after the fMRI sequence in session two, to aid registration of the EPI images to standard space: TR = 7.1 ms; TE = 3.2 ms; flip angle = 8°; field-of-view = 256 × 256; in-plane resolution = 1 × 1 mm; slice thickness = 1 mm (no gap); number of axial slices = 160.

Prestatistics processing was applied within each individual run: motion correction using MCFLIRT (2); nonbrain removal using BET (3); spatial smoothing using a Gaussian kernel of full-width half-maxim 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line fitting with a high pass filter cutoff of 120.0 s).

We applied a denoising procedure using probabilistic independent component analysis (ICA) (4) as implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) v3.10. Independent components were visually inspected, and labeled noise-components or signal-components, following the guidelines presented by Kelly, et al. (5). The time courses of noise-components were filtered out from the preprocessed data, and the resulting denoised data were used in the statistical analyses. An example of the effect of denoising on pain signal in the PAG/colliculi is illustrated in Fig. S4 and Table S3.

Registration of small structures in the brainstem to a standard template is not straight-forward. We therefore compared the registration procedure (FLIRT) used in this study with an alternative procedure (FLIRT plus FMRIB's nonlinear registration technique, FNIRT). The two procedures provided comparable registration quality and statistical effects.

fMRI Analysis. ***Regions of interest.*** All a priori ROIs were defined from independent sources. ROIs in contralateral parts of the sensory circuitry comprised: (*i*) posterior insula (pINS/Ig2, $P > 30\%$); (*ii*) primary somatosensory area (SI/area 3b, $P > 50\%$); (*iii*) secondary somatosensory area (SII/OP4, $P > 50\%$): Jülich histological atlas (6); and (*iv*) sensory thalamus Oxford thalamic connectivity probability atlas ($P > 10\%$) (7). Very few voxels are more than 50% probable of being in the pINS/Ig2 and the sensory thalamus in the Montreal Neurological Institute (MNI)152 standard map. Therefore, to ensure enough space was provided for detecting effects within these structures, thresholds for these ROIs were lowered to 30% and 10%, respectively, thereby reducing the risk of type II errors (see Fig. S6 for illustrations of all ROIs overlaid on a MNI152 standard brain).

ROIs defined within emotion appraisal circuitry comprised: (*i*) the pregenual anterior cingulate cortex (pgACC) and (*ii*) mOFC [spheres (8-mm radius) around peak activations from a meta-analysis of placebo analgesia (8)]; (*iii*) the nucleus accumbens (NAc) and (*iv*) amygdala (Harvard-Oxford subcortical atlas, $P > 50\%$); (v) the PAG (mask used by ref. 9); and (*vi*) the ventral tegmental area [VTA; manually drawn based on anatomical landmarks from the Duvernoy's Brainstem atlas (10), ranging from MNI152 coordinates z (−10) to z (−18)]. Selection of the regions (mOFC, pgACC, PAG) for the comparison between placebo-induced ventromedial prefrontal cortex (vmPFC)–PAG functional coupling and placebo-induced change in sensory regions was based on a priori predictions derived from this circuit's involvement in placebo analgesia (9, 11, 12). This selection was made irrespective of these regions' activation in the basic contrast (placebo > control) because of the individual variability in placebo response magnitude.

To investigate whether structures outside the hypothesized circuitry were important for placebo hyperhedonia or analgesia, we performed voxel-based analyses using a whole-brain approach with a corrected cluster significance threshold of $P = 0.05$ (13). Because we did not observe any additional activations that furthered our understanding of the current findings, these results are presented in Table S4 without further discussion.

Conjunction analysis. To formally test whether any voxels were significantly activated (placebo > control) during both stroking, warm, and painful touch, we calculated a minimum Z image to test the "conjunction null" hypothesis (14).

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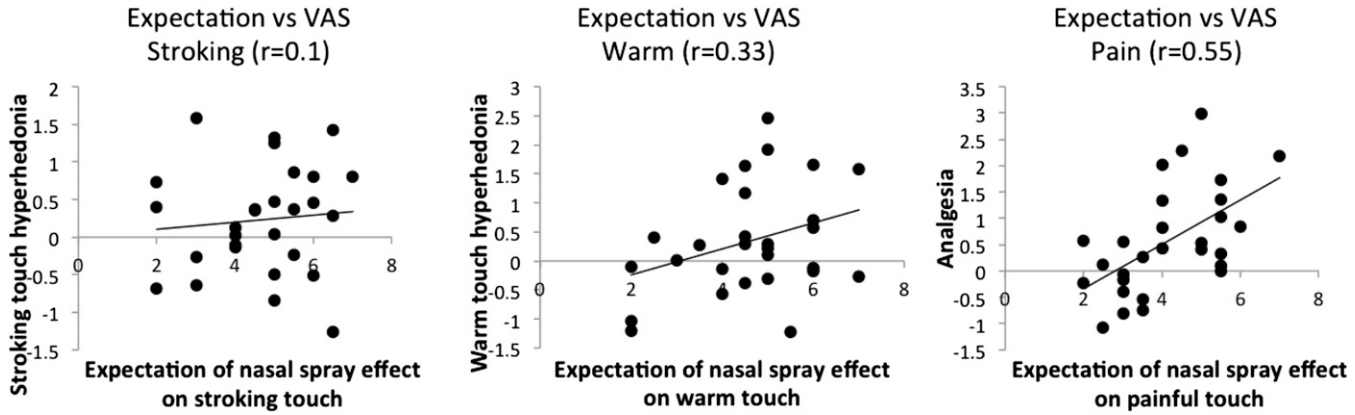

Fig. S1. Relationship between expectations and placebo responses. Expectations of nasal spray benefit on tactile stimuli had a positive relationship with placebo response (defined as the placebo minus control difference in VAS scores) for stroking (nonsignificant), warm, and painful touch.

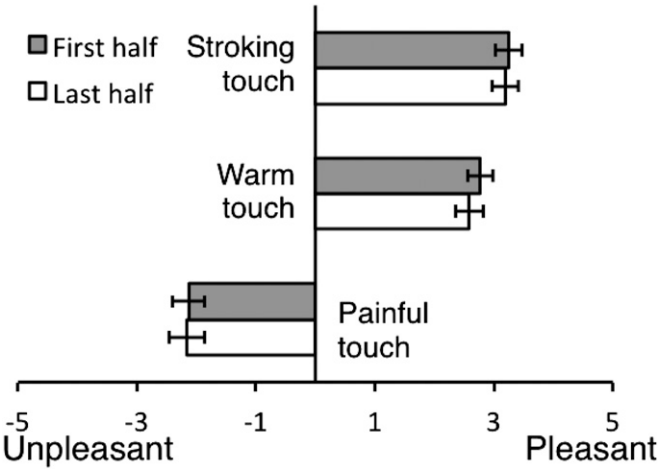

Fig. S2. Temporal characteristics of hedonic ratings. There was no main effect of time (first half vs. last half of the experiment) on ratings. Post hoc *t* tests indicated that although ratings of stroking and painful touch did not differ significantly over time, ratings of warm touch were significantly higher in the first half. However, the decline in warm touch ratings did not differ significantly between placebo and control sessions, nor did it differ significantly from decline in stroking or painful touch. Error bars indicate SEM.

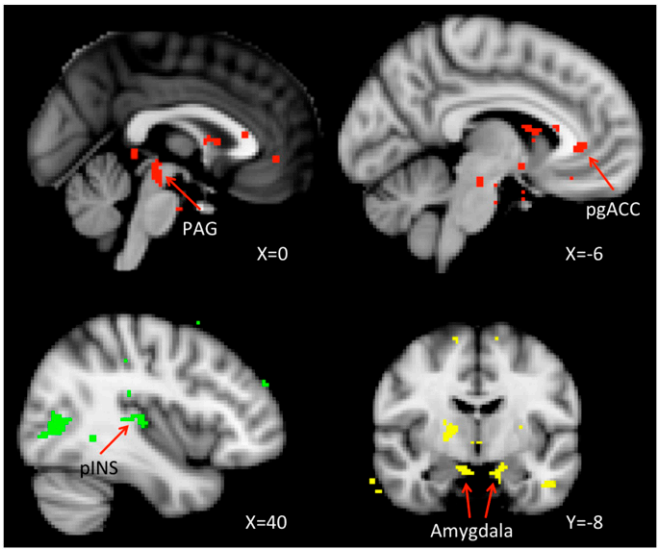

Fig. S3. Exploratory analyses using expectation of nasal spray benefit as a regressor. Averaged group activation maps ($P > 0.05$ uncorrected, whole-brain), with the expectation of nasal spray benefit as a regressor, are superimposed on the MNI standard template brain. Green, stroking touch; yellow, warm touch; red, painful touch.

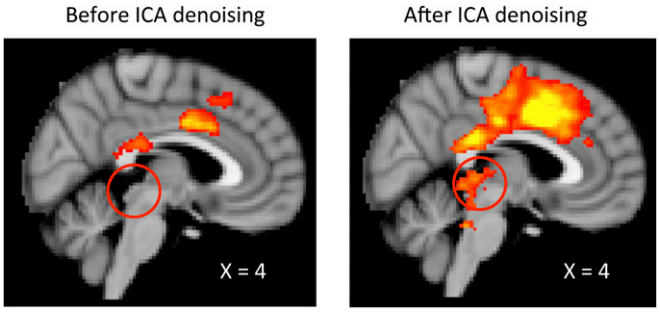

Fig. S4. Effect of ICA denoising on baseline pain signal. Stimulus signal increased substantially after denoising using ICA, here illustrated by increased signal in PAG/colliculi. Significant voxels from the group contrast pain > rest, in the control session, are shown (whole-brain search, cluster-thresholded at $Z = 2.3$).

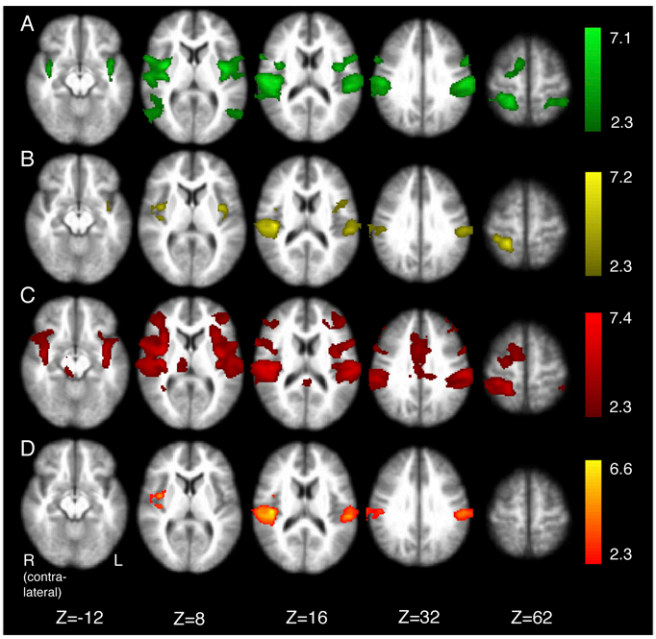

Fig. S5. Baseline stimulus activation maps. BOLD responses (stimulus > rest, control condition) during stroking touch (*A*), warm touch (*B*), and painful touch (*C*), and voxels overlapping between all three touch stimuli, as revealed by conjunction analysis (*D*). Color bars to the right indicate *Z*-scores (ranging from minimum value to maximum value in the contrast), and MNI-coordinates are shown in millimeters. Averaged group activation maps (cluster-thresholded, whole-brain) are superimposed on the MNI-registered (group average) structural image (T1-weighted).

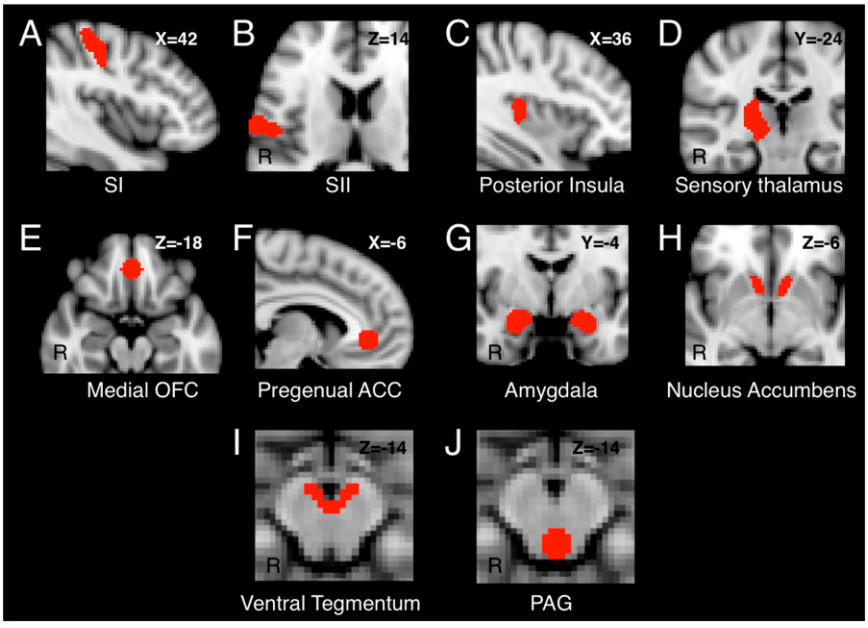

Fig. S6. A priori regions of interest. Masks used for analyses assessing sensory circuitry were right primary somatosensory area (*A*), right secondary somatosensory area (*B*), right pINS (*C*), and right sensory thalamus (*D*), all contralateral to the stimulus site. Masks used for analyses assessing emotion appraisal circuitry were medial orbitofrontal cortex (*E*), pregenual anterior cingulate (*F*), amygdala (*G*), nucleus accumbens (*H*), ventral tegmentum (*I*), and periaqueductal gray (*J*). Masks are superimposed on the MNI standard template brain, and MNI coordinates are shown in millimeters.

Table S1. BOLD responses in sensory circuitry

Analysis	pINS	SI	SII	Sensory thalamus
Group contrast ($P > C$)				
Stroking	3.96 (40 −20 10)	—	3.25 (54 −12 12)	—
Warm	3.26 (40 −20 6)	—	2.33 (68 −14 18)	—
Painful	—	−4.29 (20 −34 60)	−3.56 (56 −4 12)	—
Pleasant touch ($P > C$) > Painful touch ($P > C$)				
Stroking ($P > C$) > Pain ($P > C$)	2.27 (40 −22 16)	3.13 (42 −24 60)	3.39 (52 −12 18)	—
Warm ($P > C$) > Pain ($P > C$)	2.27 (36 −22 4)	3.44 (46 −20 50)	2.57 (60 −4 12)	—
Correlation with behavioral placebo response				
Stroking	3.1 (34 −24 12)	3.11 (20 −34 66)	—	—
Warm	—	—	—	—
Painful	—	—	—	—
Correlation with placebo-induced vmPFC-PAG coupling				
Stroking	mOFC-PAG: 2.37 (34 −20 6)	—	mOFC-PAG: 3.01 (56 −6 14) pgACC-PAG: 2.79 (54 −8 10)	—
Warm	—	—	pgACC-PAG: 2.38 (52 −12 16)	—
Painful	mOFC-PAG: 2.51 (36 −24 18)	pgACC-PAG: 4.77 (56 −4 24)	mOFC-PAG: 2.85 (60 −10 10)	—

The strength of activation is expressed in maximum (peak) *Z* scores, and coordinates in MNI-space are denoted by *x*, *y*, *z* in millimeters [*Z* (*x y z*)]. The listed *Z* scores survived significance threshold ($P = 0.05$, corrected for small volumes). C, control; L, left; mOFC, medial orbitofrontal cortex; P, placebo; PAG, periaqueductal gray; pgACC, pregenual anterior cingulate cortex; R, right; SI, primary somatosensory area; SII, secondary somatosensory area.

Table S2. BOLD responses in emotion appraisal circuitry

Analysis	pgACC	mOFC	NAc	Amygdala	PAG	VTA
Group contrast ($P > C$)						
Stroking	—	—	2.92 (12 18 −4)	—	3.16 (−6 −32 −2)	—
Warm	—	—	4.69 (12 18 −6)	2.06 (−16 −2 −19)	2.59 (−4 −30 −6)	2.31 (−6 −14 −16)
Painful	—	—	3.51 (14 18 −4)	—	—	2.29 (−8 −14 −16)
Correlation with behavioral placebo response						
Stroking	3.7 (−6 10 −4)	2.8 (4 46 −20)	3.2 (−10 10 −12)	—	4.1 (−2 −30 −8)	3.8 (4 −16 −14)
Warm	—	—	2.98 (−6 10 −4)	2.9 (−16 −8 −18)	—	2.75 (−2 −20 −16)
Painful	3.18 (−6 36 2)	—	—	—	—	—
PPI Group contrast ($P > C$)						
Stroking (mOFC seed)	—	—	—	—	2.4 (2 −30 −14)	—
Warm	—	—	—	—	—	—
Painful (pgACC seed)	—	—	—	—	3.3 (−2 −30 −8)	—
PPI correlation with placebo response						
Stroking (mOFC seed)	—	—	2.35 (−12 14 −6)	2.94 (−22 −8 −14)	2.98 (4 −30 −6)	—
Warm	—	—	—	—	—	—
Painful (pgACC seed)	—	3.18 (8 44 −18)	3.46 (12 10 −10)	2.84 (−26 −2 −16) (L) 3.24 (18 −6 −18) (R)	—	3.04 (4 −20 −20)

The strength of activation is expressed in maximum (peak) *Z* scores, and coordinates in MNI-space are denoted by *x*, *y*, *z* in millimeters [*Z* (*x y z*)]. The listed *Z* scores survived significance threshold ($P = 0.05$, corrected for small volumes). pgACC, pregenual anterior cingulate cortex; mOFC, medial orbitofrontal cortex; NAc, nucleus accumbens; PAG, periaqueductal gray; VTA, ventral tegmental area; PPI, psychophysiological interaction analysis; P, placebo; C, control; R, right; L, left.

Table S3. Comparison between *Z*-scores before and after ICA denoising

Contrast	Peak *Z* (PAG ROI)	
	Before ICA	After ICA
Pain > Rest (Control session)	1.46	3.33
Group contrast (Placebo > Control)	0.49	0.94

PAG, periaqueductal gray; ROI, region of interest; ICA, independent component analysis.

Table S4. BOLD responses (whole-brain searches)

Analysis	*Z* (*x y z*)
Group contrast (*P* > C)	
Stroking touch	
Superior temporal gyrus	3.74 (−70 −24 10)
Correlation (*P* > C)	
Stroking touch	
Subcallosal cortex	4.00 (−6 22 −8)
Cuneal cortex	3.78 (−20 −72 24)
Precuneous	3.86 (−6 −50 46)
Painful touch	
Superior temporal gyrus	4.21 (−56 −36 12)
PPI mOFC (*P* > C)	
Stroking touch	
Anterior cingulate cortex	3.45 (−10 10 38)
PPI pgACC (*P* > C)	
Warm touch	
Precuneous	3.38 (8 −56 34)
Painful touch	
Frontal pole	3.72 (2 70 −18)
Occipital cortex	3.43 (-4 −98 24)

The strength of activation is expressed in maximum (peak) *Z* scores, and coordinates in MNI-space are denoted by *x*, *y*, *z* in millimeters [*Z* (*x y z*)]. The listed *Z* scores survived significance threshold (*P* = 0.05, whole-brain cluster corrected). P, placebo; C, control; PPI, psychophysiological interaction analysis; mOFC, medial orbitofrontal cortex; pgACC, pregenual anterior cingulate cortex.