Research Paper

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Endogenous opioids contribute to the feeling of pain relief in humans

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Abstract

Endogenous opioids mediate the pleasurable responses to positively reinforcing stimuli such as palatable food. Yet, the reduction or omission of a negative experience can also be rewarding (negative reinforcement). As such, pain relief leads to negative reinforcement and evokes a pleasant feeling in humans. Although it has been shown that the feeling of pleasure associated with positive reinforcement is at least partly mediated through endogenous opioids, it is currently unknown whether similar neurochemical mechanisms are involved in the pleasant feeling evoked by pain relief. In this study, 27 healthy participants completed 2 identical experimental sessions, 1 with placebo and 1 with naltrexone, an endogenous opioid antagonist. Pain relief was induced by superficial cooling after heat stimulation of capsaicin-sensitized skin. Participants rated the relief and pleasantness in response to the cooling. Endogenous opioid blockade by naltrexone decreased relief and pleasantness ratings compared with placebo ($P = 0.0027$). This study provides evidence that endogenous opioids play a role in mediating the pleasant feeling of pain relief in humans. Clinically, the rewarding nature of pain relief and its underlying mechanisms require consideration because of their potential reinforcing effects on behaviors that might be beneficial short-term but maladaptive long-term.

Keywords: Pain relief, Endogenous opioids, Reward, Pain modulation, Pleasantness, Naltrexone, Opioid antagonist

1. Introduction

Endogenous opioids are involved in a multitude of physiological and psychological processes, including an important role in mediating analgesia and pleasure associated with reward [annually reviewed in the "Endogenous Opiates and Behavior" series[12]]. The link between reward-associated pleasure and endogenous opioids is supported by animal studies implementing food or sucrose as the rewarding stimulus leading to positive reinforcement of hedonic "liking" reactions.[15,50] In humans, also the feeling of pleasure in response to positively reinforcing stimuli such as food intake has been shown to involve endogenous opioids signaling.[16,57] In addition to positively reinforcing stimuli, the reduction or omission of an aversive experience, such as pain, can be rewarding, leading to negatively reinforced behavior. Negative reinforcement associated with pain relief has consistently been shown in conditioned place preference paradigms, with rodents favoring locations not previously paired with painful stimuli over those previously paired.[26,38,39] Thus, pain relief seems to have rewarding properties.

In line with the notion that pain relief is rewarding, negative reinforcement might be associated with a similar feeling as positive reinforcement, ie, pleasure. For example, attenuation of experimental pain in healthy volunteers leads to the feeling of pleasure in addition to reduced perceived pain intensity.[29] In rodents, negative reinforcement produced by pain relief has been demonstrated to require supraspinal endogenous opioid signaling,[39] similarly to positive reinforcement. Whether the feeling of pleasure associated with pain relief also depends on endogenous opioid action, however, remains an open question. Therefore, it was tested in this study whether the feeling of pleasure associated with pain relief is mediated by endogenous opioids in healthy humans. Pain relief was achieved by the application of cool stimuli after heat stimulation of capsaicin-sensitized skin, similar to Mohr et al.[36] and Leknes et al.,[29] and the effect of the opioid-receptor antagonist naltrexone on participants' ratings of relief and pleasantness was assessed using a randomized, placebo-controlled, double-blind, counterbalanced, crossover study design. It was hypothesized that blocking endogenous

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opioids with naltrexone, a potent μ-receptor antagonist,[54] decreases subjective relief and pleasantness ratings compared with the placebo condition. Because endogenous opioid blockade can increase perceived pain intensity,[2] which in turn has been shown to influence the magnitude of pain relief,[29] this study used perception-adjusted, rather than temperature-adjusted, painful heat stimulations and analyzed naltrexone effects on pain sensitivity. Furthermore, because pleasure depends on the internal state of an individual,[14] the baseline emotional state of participants between the naltrexone and placebo condition was examined as additional potential confounding factor.

2. Methods

2.1. Participants

Healthy male and female volunteers between 18 and 35 years of age were recruited through advertisement on the internal McGill University web page. Exclusion criteria were any present or past pain condition, psychiatric disorders, substance abuse behaviors, alcohol consumption of more than 100 mL alcohol per week, tobacco use, regular night shifts, sleep disorders, or any medical conditions including neurological diseases. The study was approved by the McGill University Institutional Review Board in accordance with the Declaration of Helsinki (2013). Written informed consent was obtained from all participants before the start of the experiment.

A priori sample size calculation for a similar experimental design yielded a target sample size of 28 participants to detect a desired medium effect size of drug (ie, placebo vs naltrexone) in a 2-way (drug: 2 levels, stimulation type: 3 levels; in this study: 2 levels for all fixed factors) repeated-measures analysis of variance (ANOVA) design with a 5% probability to commit a type I error ($\alpha = 0.95$) and a 20% probability to commit a type II error ($\beta = 0.8$).

For this study, the recruited sample comprised 31 participants. Four participants did not return for the second session, 2 due to nausea (both received naltrexone in the first session) and 2 for unknown reasons. This resulted in a final sample of 27 participants (mean age ± SD 21.70 ± 2.77 years, 14 women). Of this final sample, 3 did not complete the trials at the higher target pain intensity because the temperature safety cutoff (46°C) was exceeded during the calibration procedure. Of these 3 participants, one also reached the temperature safety cutoff during the "self-adjustment phase" in 1 trial at the target pain intensity "170". Because the applied statistical methods (ie, general linear mixed models [GLMMs]) account for missing datapoints, these participants were still included in the analyses.

2.2. General study design

Participants completed 2 identical experimental sessions, 1 with placebo and 1 with naltrexone following a randomized, placebo-controlled, double-blind, counterbalanced, crossover study design. Superficial cooling after heat stimulation of capsaicin-sensitized skin was used to induce pain relief. A timeline of the experimental sessions is shown in **Figure 1A**.

Participants were seated upright throughout the whole session. Before placebo/naltrexone administration, participants filled in the Profile of Mood States Bipolar Scale (POMS-Bi)[32] and a naltrexone side-effect survey. Resting heart rate was recorded for 5 minutes. Subsequently, the participants received 1 of 2 identically looking capsules that was administered orally, containing either placebo (microcrystalline cellulose powder) or naltrexone (both at 1 mg/kg body weight). The order of placebo or naltrexone session was randomized and counterbalanced across participants. Testing started 1 hour after placebo or naltrexone administration to correspond with the peak blood concentration of naltrexone.[21] Immediately after placebo or naltrexone administration in the first session, participants completed the Pain Catastrophizing Scale (PCS)[52] and Temporal Experience of Pleasure Scale (TEPS).[20] Subsequently, heat pain and heat tolerance thresholds were determined in the testing area (ie, volar forearm) using the method of limits[19] to assess whether early naltrexone effects on pain sensitivity occurred. During the remaining waiting period, participants could read or study quietly. A second side-effect survey was performed 35 minutes after placebo/naltrexone administration. One hour after placebo/naltrexone administration, participants completed calibration procedures to determine the individual target temperatures followed by the trials to induce pain and pain relief (at 2 different target pain intensities, 4 trials each, resulting in 8 trials in total) as described in detail in section "Thermal testing procedures". Skin conductance was recorded during pain and pain relief at both target pain intensities. After the last trial, participants filled in a second POMS-Bi and a third naltrexone side-effect survey. In addition, an exit interview was performed assessing the blinding of participants and the experimenter. The experimental sessions lasted approximately 1.5 hours each, with testing occurring between minutes 60 and 90 (half-life of naltrexone: 3.5 hours[21]).

2.3. Thermal testing procedures

Capsaicin was applied topically 40 minutes after placebo/naltrexone administration on a 3 × 3-cm^2 skin area on the nondominant volar forearm 3 cm below the elbow crease using a cream with 0.4% capsaicin, prepared by a compound pharmacy. After 20 minutes, the cream was removed and thermal stimuli were delivered to the sensitized skin area with a 3 × 3-cm^2 thermode (Pathway, Medoc, Israel) to evoke painful hot and relieving/pleasant cooling sensations. The thermode was fixed to the forearm with a Velcro strip. Before testing, participants were instructed regarding all thermal testing procedures. During thermal testing, participants provided ratings on computerized rating scales or controlled the thermode temperature using a computer mouse. Right mouse button presses increased ratings/temperature (by 0.1°C), and left mouse button presses decreased ratings/temperature (by 0.1°C). Short instructions and visual feedback were provided on a computer screen throughout the thermal testing (**Fig. 1B**).

2.3.1. Rating scales

Pain intensity was rated on a horizontal visual analogue scale (VAS) ranging from 0 "no sensation" (left end of the scale) to 200 "most intense pain tolerable" (right end of the scale) with 100 being the pain threshold. Unpleasantness ratings were provided on a VAS ranging from 0 "neutral" to 100 "extremely unpleasant". Relief was rated on a VAS ranging from "no relief" to "intense relief", and the instructions displayed on the computer screen were "press to rate any relief you feel". The pleasantness VAS ranged from "neutral" to "extremely pleasant", and the instructions displayed on the computer screen were "press to rate how pleasant your sensation feels". Because the construct "relief" has rarely been used in human perceptual studies, participants were instructed before testing that relief is considered akin to the sensation of putting something cool on sunburned skin or taking a

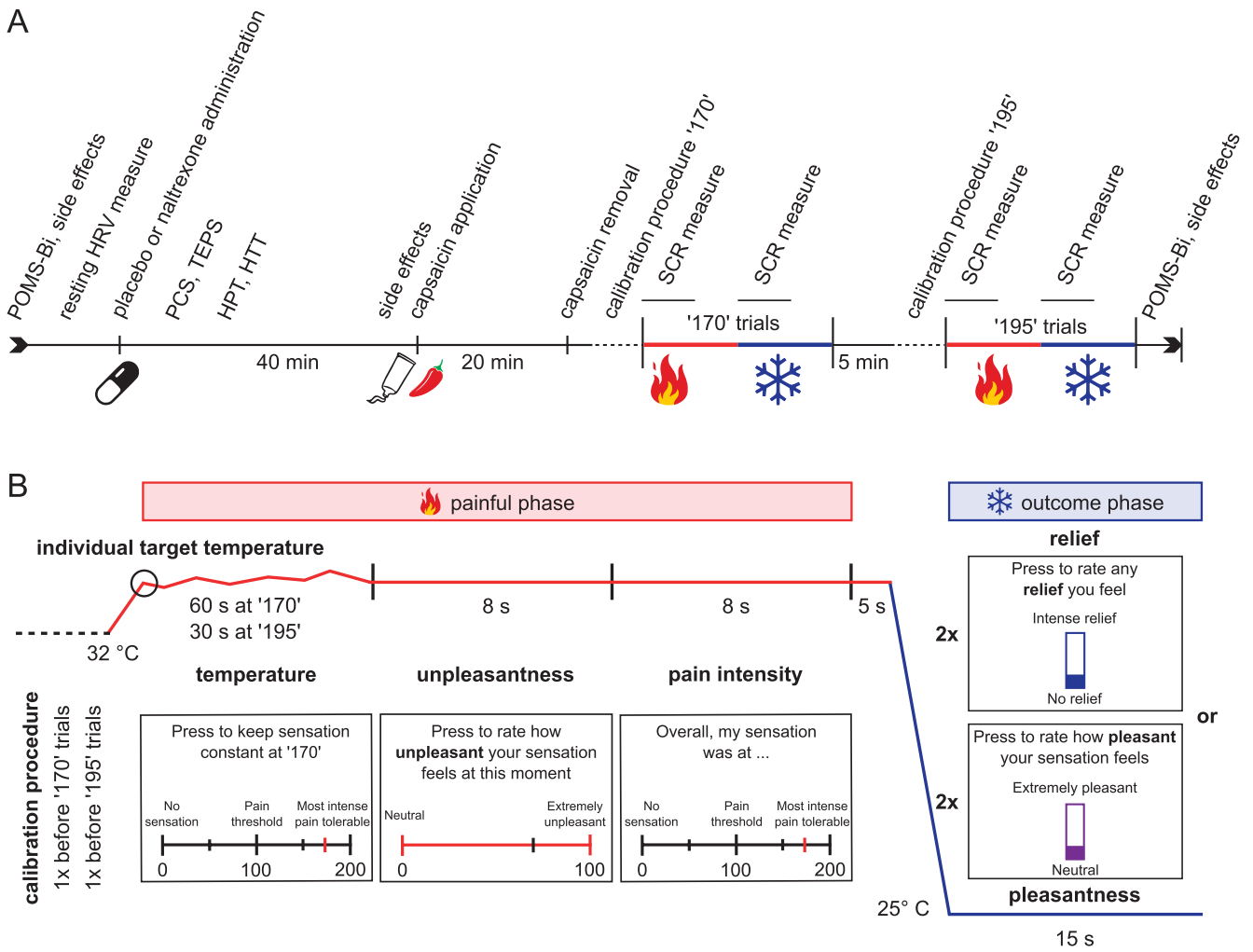

Figure 1. Study design. (A) Timeline of 1 experimental session. (B) Overview of 1 trial. HPT, heat pain threshold; HTT, heat tolerance threshold; HRV, heart rate variability; PCS, Pain Catastrophizing Scale; POMS-Bi, Profile of Mood States Bipolar Scale; SCR, skin conductance response; TEPS, Temporal Experience of Pleasure Scale.

cool shower on a hot day. The experimenter avoided associating words such as "pleasant", "better", or "good" with relief.

2.3.2. Experimental trials

Trials were performed using 2 target pain intensities: "170" and "195". In each session, all trials at "170" were performed before the trials at "195" to reduce sensitization effects. Immediately before the first trial of each target pain intensity, individual temperatures for the respective target pain intensity were determined with the following calibration procedure: The thermode temperature started at 32°C and increased at a rate of 1°C/s. Participants were asked to constantly rate their perceived intensity on the computerized intensity rating scale using the computer mouse. When participants reached the intensities of "170" and "195", the computer adjusted the temperature during 60 seconds for "170" and during 30 seconds for "195", so that the rated intensity stayed constant at "170" or "195" by decreasing the temperature of the thermode if ratings were above the target pain intensity or increasing if ratings were below the target pain intensity. The duration for the target pain intensity of "195" was shorter compared with "170" to decrease the likelihood of participants not tolerating the entire length of the stimulation. The resulting average temperatures for the 2 target pain intensities of "170" and "195" were used as the starting temperatures for all trials of the participant at the respective target pain intensity.

Each trial consisted of 2 phases starting directly after calibration: (1) a painful phase (heating) followed by (2) an outcome phase (cooling). Between the painful and the outcome phase, participants completed a short (5 seconds) motivation task with the thermode temperature remaining at the level of the painful phase. Briefly, participants had to press a mouse button as often as they could while a visual cue was presented on the screen. The motivation task was not part of the present research question and will therefore not be discussed further; important for the current study is that it was identical between the placebo and the naltrexone sessions. Four trials were performed at each target pain intensity (ie, "170" and "195"), resulting in 8 trials in total. An overview of 1 trial is depicted in **Figure 1B**.

2.3.2.1. Painful phase

The thermode temperature increased from baseline (32°C, rate 1°C/s) to the predetermined individual target temperature for the respective target pain intensity (ie, "170" or "195"). During this ramp, participants were presented with a fixation cross on the

computer screen. After reaching the target temperature, the painful phase comprised 3 intervals. First, participants were instructed to control the thermode temperature using the computer mouse to maintain a constant perceived pain intensity, ie, "170" or "195", for 1 minute or 30 seconds, respectively ("self-adjustment phase"). Second, immediately after the "self-adjustment phase", participants were asked to rate the unpleasantness of the perceived pain. The unpleasantness rating scale was displayed for 8 seconds. Subsequently, participants were asked to rate the overall pain intensity (0-200) they had perceived during the "self-adjustment phase". This served as manipulation check if participants had managed to maintain the respective target pain intensity (ie, "170" or "195"). The intensity rating scale was displayed for 8 seconds.

2.3.2.2. Outcome phase

After the painful phase, the thermode temperature decreased to 25°C. The temperature of 25°C was determined to be perceived as nonpainful and pleasant after the same heat-capsaicin stimulation in pilot experiments. During the decrease, a fixation cross was shown on the screen. When the thermode had cooled down to 25°C, the participants were asked to continuously rate the perceived relief in 2 of the 4 trials with the 2 pain intensities ("outcome relief") and perceived pleasantness in the other 2 trials ("outcome pleasantness"). The cooling stimulus was applied for 15 seconds. The order of trials with the "outcome relief" and the "outcome pleasantness" was counterbalanced across participants.

2.4. Autonomic responses

Heart rate and skin conductance were obtained to calculate heart rate variability (HRV) and skin conductance responses (SCR). Heart rate variability can be used to examine the autonomic control of the heart[22] and was used here as a physiological measure of the participants' emotional responding.[3] Skin conductance responses served as measure of physiological responses to painful or relieving thermal stimuli.[30,48] Heart rate and skin conductance were recorded using a Biopac MP150 system (Biopac Systems Inc, Goleta, CA).

Electrocardiograms were measured at rest at the beginning of each session with surface electrodes (type EL503, Biopac Systems Inc, Goleta, CA) for 5 minutes (sampling frequency 1000 Hz). Data were visually inspected, and any artifacts were manually removed. Heart rate variability was calculated from heart rate data through power spectral density analysis using the AcqKnowledge software (Biopac Systems Inc, Goleta, CA) recommended settings. The ratio of low-frequency to high-frequency (LF/HF) components were assessed which is used as index of sympathovagal balance, ie, the balance between the sympathetic and parasympathetic autonomic nervous system.[53]

Skin conductance was recorded during the painful phase and the—relieving—outcome phase at both target pain intensities. Surface electrodes (type EL507, Biopac Systems Inc, Goleta, CA) were placed at the distal phalanx of the index and middle fingers of the participant's nondominant hand. Skin conductance was sampled at 1000 Hz and high-pass filtered (0.05 Hz). Using Ledalab 3.4.9,[10] integrated SCRs (ie, area under the curve) were calculated of identified SCRs (amplitude threshold: 0.01 μS) in the extracted phasic driver between the first 1 to 7 seconds after the onsets of the painful phase and the outcome phase, respectively. Compared with SCR amplitudes, the integration of SCRs reduces bias because of the superposition of SCRs and takes into account their continuous nature.[10]

2.5. Questionnaires

Psychological factors are known to influence pain perception[43,56] and, conceivably, might affect pain relief. To assess the influence of psychological factors, self-report measures were included in this study, specifically the POMS-Bi, the PCS, and the TEPS.

The POMS-Bi was used to evaluate possible naltrexone effects on participants' mood and the participants' mood on the 2 testing days. The POMS-Bi assesses positive and negative affective states, rated on a 4-point rating scale ranging from "much unlike this" to "much like this" (score range: −36 to 252; −36 meaning max. negative affect, 252 max. positive affect, and 108 a balanced negative-positive affect). The total POMS-Bi score and the 2 subscores POMS-Bi "composed-anxious" (score range: 42 to −6) and "elated-depressed" (score range: 42 to −6) were used for further analysis.

The PCS and the TEPS were completed by the participants during the first session immediately after placebo/naltrexone administration with the assumption that naltrexone did not yet exert pharmacodynamic effects. The PCS consists of 13 questions about past painful experiences, each rated with a score between 0 "not at all" to 4 "all the time" (score range: 0-52; 0 meaning no catastrophizing). The TEPS is a measure of the individual pleasure experience and includes 2 subscales for anticipatory (ie, pleasure of forthcoming positive events) and consummatory (ie, "in-the-moment" pleasure) pleasure. Eighteen questions (10 for anticipatory pleasure and 8 for consummatory pleasure) are rated on a 7-point rating scale ranging from 0 "very false for me" to 6 "very true for me" (score range: 0-108; 0 meaning no pleasure). The subscale for consummatory pleasure (score range: 0-54) was used for further analysis.

Potential side effects of placebo or naltrexone were assessed using a side-effect survey at different timepoints throughout each session (**Fig. 1A**). The side-effect survey included 7 items: "dry mouth", "dry skin", "blurred vision", "tiredness", "nausea", "dizziness", and "headache". For each item, participants were asked to choose the best descriptor of how they felt at that moment on a 5-point rating scale ranging from 0 "none" to 4 "extremely strong" (score range: 0-28; 0 meaning no side effects). The sum of all side effects was calculated for each timepoint.

2.6. Exit interview

At the end of each session, the participants and the experimenter were asked whether they believed placebo or naltrexone had been administered in that session (possible answers: "placebo", "drug", or "I do not know"). After the second session, participants were additionally asked what they believed the purpose of the experiment was.

2.7. Data analysis

Statistical analyses were performed using R 3.6.1/RStudio 1.2.5001 for Mac. Statistical significance was set at $\alpha = 0.05$.

2.7.1. Naltrexone effects

Naltrexone effects and between-session differences were analyzed using GLMMs (function lmer() from R package "lme4"). All models included at least drug (2 levels: placebo and naltrexone) and sex (2 levels: female and male) as independent variables. Sex was included

in the model because sex differences are frequently reported in pain-related outcomes [reviewed in Ref. 18], which might also apply for pain relief. Participant identifier was included as a random effects factor. All independent variables were first entered into the model including interaction effects, except for sex, which was included as main effect only. If interactions were not significant, they were removed from the model. Because sex effects were not part of the main research question, sex was removed from the model if its effect was not significant. Model diagnostics (inspection of residual distribution, leverage, and DFBETA values) were used to check requirements for GLMMs. Unless reported otherwise, requirements were met. If potential influential observations were identified (datapoints exceeding a DFBETA value of $2/\sqrt{n}$[9]), the final model was repeated without the respective datapoints (reported in the respective section). If removal of influential observations led to changes of the statistical inference, the model without the influential case is reported. Otherwise, the model with the full data set is reported. Effect sizes are not reported because there exists no agreement on how to calculate standard effect sizes for mixed model structures because of the way variance is partitioned.[45] Nevertheless, GLMMs were used for their advantages in controlling for type I errors compared with alternative approaches, which make results from mixed models more likely to generalize to new observations.[4]

2.7.2. Naltrexone effects on relief/pleasantness

Relief/pleasantness ratings were translated into numerical ratings from 0 "no relief"/"neutral" to 100 "intense relief"/"extremely pleasant". The maximum ratings of the 8 trials (4 trials at "170" and 4 trials at "195") were averaged over the 2 trials ending with the same outcome phase, ie, relief or pleasantness, and used for further analysis. Target pain intensity (2 levels: "170" and "195") and outcome (2 levels: relief and pleasantness) were additionally included as independent variables in the GLMM.

2.7.3. Potential confounders

Endogenous opioid antagonists might have potentially confounding effects on the main outcomes of relief/pleasantness ratings, eg, by influencing pain sensitivity.[42] Pain relief might further be influenced by participants' mood.[31] To investigate such potentially confounding effects, the following exploratory analyses were performed.

2.7.3.1. Naltrexone effect on pain sensitivity

The temperatures as well as the unpleasantness and pain intensity ratings of the painful phase were examined for naltrexone effects. For temperature, the average during the "self-adjustment phase" was used. Target pain intensity (2 levels: "170" and "195") and outcome (2 levels: relief and pleasantness) were included as additional independent variables in the GLMMs.

Furthermore, naltrexone effects on SCRs, as a measure of physiological responses to painful or relieving thermal stimuli,[30,48] were examined. Integrated SCRs were log10 (x + 1)-transformed to meet requirements for GLMMs. The additional independent variables target pain intensity (2 levels: "170" and "195"), phase (2 levels: painful phase and outcome phase), and outcome (2 levels: relief and pleasantness) were included in the GLMM.

2.7.3.2. Participants' mood

It was first analyzed whether naltrexone influenced participants' mood over the course of the sessions. Timepoint (2 levels: start of session and end of session) was included as additional independent variable in the GLMM. Each POMS-Bi score ("composed-anxious" subscore, "elated-depressed" subscore, and total score) was examined for a drug x timepoint interaction effect in a separate GLMM.

Second, potential between-session differences of the participants' emotional state at baseline (ie, start of the session) were examined. General linear mixed models were used to compare each POMS-Bi score ("composed-anxious" subscore, "elated-depressed" subscore, and total score at start of the session) between sessions, as well as the baseline resting HRV LF/HF component, here used as a physiological measure of participants' emotional responding.[3]

2.8. Pain relief: exploring interindividual differences

Correlations with questionnaire scores were performed using Spearman's rho because questionnaire scores are based on an ordinal level of measurement. For all other correlational analyses, data were assessed for normality through visual inspection of histograms and QQ-plots. Pearson's r was used for correlations of normally distributed data, and Spearman's rho was used for non-normally distributed data.

2.8.1. Association with psychological factors

Taking an exploratory approach, it was investigated whether (1) the magnitude of perceived relief/pleasantness is associated with pain catastrophizing or consummatory experience of pleasure and (2) naltrexone effects on relief/pleasantness are associated with these 2 psychological factors.

For (1), Spearman's rho was calculated between maximal relief/pleasantness ratings in the placebo session at both target pain intensities (ie,"170" and "195") and PCS as well as TEPS consummatory scores.

For (2), Spearman's rho was calculated between the differences in maximal relief/pleasantness ratings between the naltrexone and placebo session (ie, naltrexone relief/pleasantness ratings—placebo relief/pleasantness ratings, further referred to as "delta NX-PL") at both target pain intensities (ie,"170" and "195") and PCS as well as TEPS consummatory scores.

2.8.2. Interindividual variability

Because of the observed high interindividual variability of relief/pleasantness ratings, an additional exploratory analysis was performed. Before investigating interindividual differences in rating behavior of relief/pleasantness, the intraindividual stability of participants' relief/pleasantness ratings in the placebo session was examined using a single-measurement, absolute-agreement, 2-way mixed-effect intraclass correlation coefficient analysis.[35] Because the relief ratings were not different from the pleasantness ratings, nor between the trials at target pain intensity "170" and the trials at "195", all 8 trials were included in the analysis. To gain insight into observed interindividual differences in relief/pleasantness ratings, it was investigated whether there was an association between how much relief/pleasantness the participants reported in the placebo session and the magnitude of naltrexone effects on these relief/pleasantness ratings. Maximal relief/pleasantness ratings in the placebo session at both target pain intensities (ie,"170" and "195") were correlated with the respective delta NX-PL (Spearman's rho). Because a random string A (here: relief/pleasantness

ratings in the placebo session) will typically correlate with a random string B-A (here: the respective delta NX-PL), the following statistical analysis was performed to dissociate the observed correlation effects from effects occurring by the flaw A ~ B-A: 10'000 random samples with the same sample size as in this study (N = 27) were created using the same mean values and SDs of the relief and pleasantness ratings (at "170" and "195") of the naltrexone and placebo session, respectively. To account for the inherent correlation of within-subject ratings, the strength of correlations between the random sample A (ie, random relief/pleasantness ratings in the placebo session) and the random sample B (ie, random relief/pleasantness ratings in the naltrexone session) was adjusted to reflect the respective correlations observed in this study. Differences between the random naltrexone and placebo ratings (ie, random delta NX-PL) were calculated and correlated to the random ratings in the placebo session. The resulting distribution of the 10′000 random correlation coefficients represents what could be expected in 10′000 random samples, given the flaw A ~ B-A and an inherent correlation of A and B. From this distribution, the mean, the 97.5% quantile and the 0.25% quantile were calculated. If the observed correlation coefficients fall within the limits of the 0.25% and the 97.5% quantiles of the random distribution, the observed effects are deemed not to be different from an effect expected, given the flaw of A ~ B-A and an inherent correlation of A and B. If the observed correlation coefficients are outside of the limits of the 0.25% and the 97.5% quantiles of the random distribution, the observed effects are deemed to be different from an effect expected by the flaw of A ~ B-A and an inherent correlation of A and B. with the probability of 5% to commit a type I error.

2.9. Side effects and exit interview

Side effects were compared between placebo and naltrexone sessions for each timepoint using the difference to before placebo/naltrexone administration, with Pratt signed-rank tests (an alternative for Wilcoxon signed-rank tests accounting for ties[41]). To assess whether participants and/or experimenter could distinguish placebo and naltrexone sessions better than by chance, a chi-square goodness-of-fit analysis of correct and incorrect responses of the exit interview was performed. If participants or experimenters reported "I do not know", it was assumed that placebo/drug administration could not be distinguished and the answer was excluded from further analysis. "Placebo"/"drug" answers were categorized into correct and incorrect responses and compared with the expected frequency of 0.5 (corresponding to a 50% chance of correct guessing). Two chi-square goodness-of-fit analyses were performed: 1 for participant responses and 1 for experimenter responses. The exit interviews about the experiment's purpose were assessed qualitatively.

2.10. Bayesian analysis of null effects

Several null effects (ie, no statistically significant differences) were observed. Because any null effect of the tests used here (GLMMs, correlation analyses, and Pratt signed-rank tests) only indicates that the null hypothesis (H0) cannot be rejected, Bayesian factors were calculated to assess the strength of the evidence for H0.[24] Bayes factors are usually expressed as the ratio of the likelihood of the alternate hypothesis (H1) to the likelihood of H0 (BF_{10}). A value for BF_{10} between 1 and 3 is considered anecdotal (ie, weak) evidence for H1, while a value between 3 and 10 suggests moderate evidence for H1. BF_{10} values between 1 and 0.33 represent anecdotal evidence for H0, and values between 0.33 and 0.1 are considered moderate evidence for H0.[24,28]

Bayes factors were calculated for all detected null effects. This was deemed particularly important to reduce the likelihood that the main results were influenced by potential confounding factors, foremost different pain sensitivities across sessions.

Bayes factor analysis was performed in R 3.6.1/RStudio 1.2.5001 for Mac using the "BayesFactor" package except for the nonparametric analysis of side effects, which was performed using Jeffreys's Amazing Statistics Program 0.14.0.0. Because the Pratt signed-rank test is unavailable for Bayes factor analysis, a Bayesian Wilcoxon signed-rank test was performed (which, in the conventional analysis confirmed the result of the Pratt signed-rank test). Priors on the effect were specified as Jeffreys-Zellner-Siow priors[5,46] for all ANOVA designs (ie, GLMMs), as shifted, scaled beta priors[34] for all correlational designs, and as zero-centered Cauchy priors[24] for the Bayesian Wilcoxon signed-rank test. Results from analyses with standard medium-width priors (ie, r = 0.71 for ANOVA designs and Bayesian Wilcoxon signed-rank test, r = 0.33 for correlational designs) were used for interpretation (Figures, Supplemental Digital Contents 1 and 2, for details and results for different prior widths, available at http://links.lww.com/PAIN/B355).

3. Results

3.1. Naltrexone decreases relief/pleasantness ratings

Naltrexone intake resulted in reduced relief (mean ± SD at "170": 54.6 ± 21.6, "195": 55.8 ± 23.7) and pleasantness ratings ("170": 58.7 ± 21.2, "195": 53.8 ± 26.3) compared with placebo (relief "170": 61.8 ± 21.4, "195": 64.9 ± 24.6; pleasantness "170": 63.1 ± 25.0, "195": 63.5 ± 24.8) at both target pain intensities ($F[1177.5] = 9.29$, $P = 0.0027$; **Fig. 2A**). The target pain intensity had no effect on relief or pleasantness ratings ($F[1178.4] = 0.0046$, $P = 0.95$), and relief and pleasantness ratings did not differ from each other ($F[1177.2] = 0.034$, $P = 0.85$). Neither interaction effects nor the effect of sex was significant and therefore removed from the model. In the final model, 14 potential influential observations (of 207) were identified. Removal of the respective datapoints did not change the statistical inference of the model.

3.2. Potential confounders

3.2.1. Naltrexone did not affect pain sensitivity

Naltrexone had no influence on participants' self-regulated temperatures as well as pain unpleasantness and pain intensity ratings (**Fig. 3**; Table, Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B355), suggesting no effect on pain sensitivity. The lack of naltrexone effects on the participants' pain sensitivity was supported by an analysis of heat pain thresholds and heat tolerance thresholds (using the same GLMM procedure as described in naltrexone effects), which did not differ between naltrexone and placebo sessions (Figure, Supplemental Digital Content 4; Table, Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B355). Integrated SCRs (after the onset of the painful phase or after the onset of the outcome phase) were neither influenced by naltrexone, in line with the absence of an effect of drug on perceptual pain responses (Figure, Supplemental Digital Content 4; Table, Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B355).

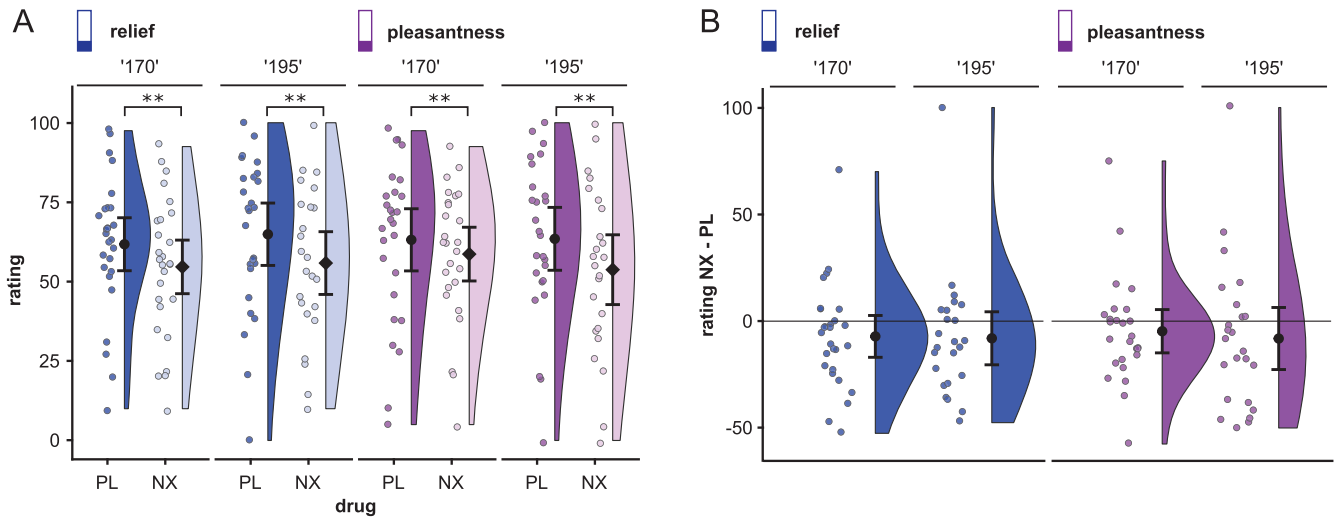

Figure 2. Naltrexone reduces relief/pleasantness ratings. Naltrexone effect on relief/pleasantness ratings at target pain intensities "170" and "195" displayed as raw values in the naltrexone and placebo session (A) and as difference in relief/pleasantness ratings between the naltrexone and the placebo session (negative value denoting a reduction of the ratings by naltrexone) (B). The raincloud plots[1] display the raw data (coloured dots), mean values and 95% confidence intervals (black dots/diamonds and bars) and probability distributions (vertical "clouds"). In (A), each dot represents the maximum relief/pleasantness rating averaged over 2 trials at the respective target pain intensity in the respective condition (PL or NX) for each participant (N = 27). In (B), each dot represents the difference in the averaged maximum relief/pleasantness ratings between the naltrexone and the placebo session for the respective target pain intensity for each participant. $^{**}P < 0.01$. NX, naltrexone; PL, placebo.

Bayes factor analyses supported anecdotal to moderate evidence for H0, ie, the absence of an effect of naltrexone, for all measures of pain sensitivity (Figure, Supplemental Digital Content 1; Table, Supplemental Digital Content 5, available at http://links.lww.com/PAIN/B355).

Despite the absence of a naltrexone effect on perceptual and physiological pain responses, heat pain thresholds and heat tolerance thresholds were lower for women compared with men and integrated SCRs were greater after the onset of the painful phase compared with after the onset of the outcome phase (ie, pain relief) (Table, Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B355), as expected from previous work.[47] During the trials at target pain intensity "195", smaller integrated SCRs were elicited compared with the trials at target pain intensity "170" (Table, Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B355).

3.2.2. Participants' mood was neither affected by naltrexone nor different between testing days

Changes in the POMS-Bi scores were not different between the naltrexone session compared with the placebo session (Figure, Supplemental Digital Content 4; Table, Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B355). Bayes factor analyses supported anecdotal to moderate evidence for H0, ie, the absence of a drug:timepoint interaction effect, for all POMS-Bi scores (Figure, Supplemental Digital Content 1; Table, Supplemental Digital Content 5, available at http://links.lww.com/PAIN/B355).

Participants' mood was also comparable between the 2 testing days because none of the POMS-Bi scores ("composed-anxious" subscore, "elated-depressed" subscore, and total score) was different between the naltrexone and the placebo sessions at baseline (before drug administration) (Figure, Supplemental Digital Content 4; Table, Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B355).

A comparable emotional state of the participants on both testing days was further supported by the baseline resting HRV LF/HF component not differing between the naltrexone and placebo sessions (Figure, Supplemental Digital Content 4; Table, Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B355).

The notion of comparable baselines of participants' mood and emotional state between sessions was additionally supported by the Bayes factor analysis showing anecdotal evidence for H0, ie, no difference between sessions (Figure, Supplemental Digital Content 1; Table, Supplemental Digital Content 5, available at http://links.lww.com/PAIN/B355).

3.3. Pain relief was not associated with psychological factors

There was no correlation between PCS or TEPS consummatory scores and maximal relief and pleasantness ratings in the placebo session at either target pain intensity (rho's ≤ 0.17, P's ≥ 0.38) (Figure, Supplemental Digital Content 6, available at http://links.lww.com/PAIN/B355), a result supported by Bayes factor analyses with anecdotal evidence for H0 for all correlations (Figure, Supplemental Digital Content 2; Table, Supplemental Digital Content 5, available at http://links.lww.com/PAIN/B355). In addition, neither PCS nor TEPS consummatory scores correlated with delta NX-PL relief or pleasantness ratings at either target pain intensity (rho's $\leq |0.20|$, P's ≥ 0.085) (Figure, Supplemental Digital Content 6, available at http://links.lww.com/PAIN/B355). Bayes factor analyses showed mixed evidence for correlations between PCS or TEPS consummatory scores and delta NX-PL relief or pleasantness. For all correlations, anecdotal evidence for H0 was suggested, except the following 5 correlations: PCS with delta NX-PL relief at "170", PCS with delta NX-PL pleasantness at "170", TEPS consummatory score with delta NX-PL relief at "170", TEPS consummatory score with delta NX-PL pleasantness at "195", and TEPS consummatory score with delta NX-PL relief at "195". Despite favoring H1, none of these correlations were significantly different from 0 and were therefore not considered for further interpretation (Figure, Supplemental Digital Content 2; Table, Supplemental Digital Content 5, available at http://links.lww.com/PAIN/B355).

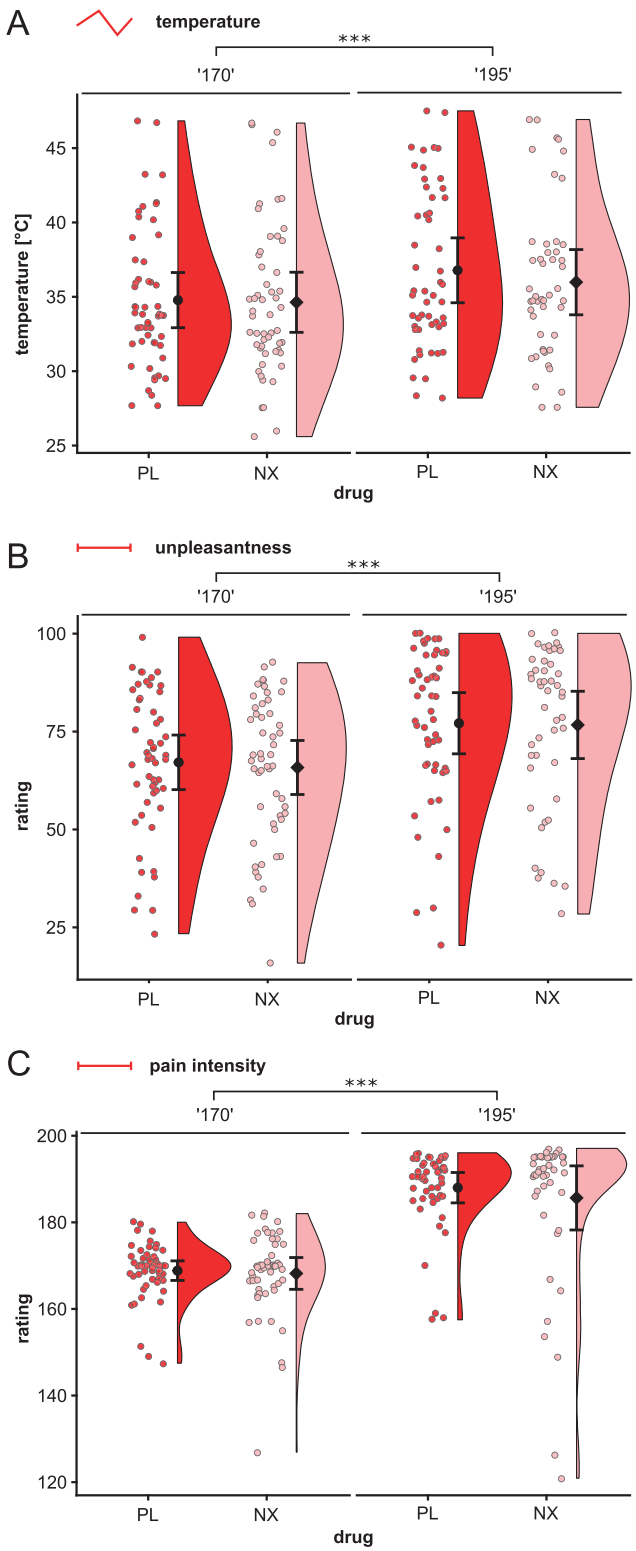

Figure 3. Naltrexone had no effect on participants' self-regulated temperatures (A), pain unpleasantness (B), nor pain intensity ratings (C) at both target pain intensities "170" and "195". The raincloud plots[1] display the raw data (coloured dots), mean values and 95% confidence intervals (black dots/diamonds and bars), and probability distributions (vertical "clouds"). In (A), each dot represents the self-regulated temperature averaged over 2 trials with the same outcome phase (ie, relief or pleasantness) at the respective target pain intensity resulting in 2 datapoints per participant (N = 27) per raincloud plot. The same rule applies for pain unpleasantness ratings in (B) and pain intensity ratings in (C). ***$P < 0.001$. NX, naltrexone; PL, placebo.

3.4. Individual pain relief was not related to individual decrease in pain relief by naltrexone

The high interindividual variability of relief/pleasantness ratings was the reason for exploring first, the intraindividual stability of participants' relief/pleasantness ratings and second, a potential association between how much relief/pleasantness the participants reported in the placebo session and the magnitude of naltrexone effects on these relief/pleasantness ratings. Assessing the intraindividual variance of participants' relief/pleasantness ratings across the 8 trials in the placebo session, a "moderate"-to-"good" test–retest reliability was observed (intraclass correlation coefficient = 0.76, 95% confidence interval = 0.65-0.86), indicating a stable rating behavior of the participants. Correlational analyses showed that individuals reporting higher relief/pleasantness ratings in the placebo session showed greater naltrexone effects on their relief/pleasantness ratings (relief ratings at target pain intensity "170": rho = −0.37, $P = 0.060$; relief ratings at target pain intensity "195": rho = −0.49, $P = 0.016$; pleasantness ratings at target pain intensity "170": rho = −0.56, $P = 0.0027$; pleasantness ratings at target pain intensity "195": rho = −0.43, $P = 0.04$). Because a random string A (here: relief/pleasantness ratings in the placebo session) will typically correlate with a random string B-A (here: the respective delta NX-PL), the observed correlation coefficients were compared with 10′000 randomly created correlation coefficients using inherently correlated samples A and B. All observed correlation coefficients fell within the 97.5% and 2.5% quantiles of the random correlation coefficient distribution, indicating that the observed effects did not differ from what would have been expected, given the flaw of A∼B-A and an inherent correlation of A and B (Table, Supplemental Digital Content 5, available at http://links.lww.com/PAIN/B355).

3.5. No side effects and successful blinding

Side effects (differences after placebo/naltrexone administration to before placebo/naltrexone administration) did not differ between placebo (35 minutes—before: median = 0, range = −4 to 3); end of session—before: median = 0, range = −4 to 4) and naltrexone sessions (35 minutes—before: median = 0, range = −2 to 2; end of session—before: median = 0, range = −3 to 13) (35 minutes after placebo/naltrexone administration—before placebo/naltrexone administration: Z = 0.33, $P = 0.74$; end of session—before placebo/naltrexone administration: Z = −1.50, $P = 0.13$). The absence of an effect of naltrexone on side-effect reports, ie, H0, was supported by Bayes factor analyses with anecdotal to moderate evidence for both timepoints after placebo/naltrexone administration (Figure, Supplemental Digital Content 1; Table, Supplemental Digital Content 5, available at http://links.lww.com/PAIN/B355).

The exit interview revealed that neither participants nor the experimenter identified placebo or naltrexone sessions better than by chance (participants: $X^2 = 0.087$, df = 1, $P = 0.77$; experimenter: $X^2 = 1.85$, df = 1, $P = 0.17$), indicating that blinding of participants as well as the experimenter was successful. Across both experimental sessions, participants correctly guessed placebo/naltrexone administration in 24 cases and incorrectly in 22 cases ("I do not know" in 8 cases). The experimenter was correct in 32 cases and incorrect in 22 cases ("I do not know" in 0 cases).

4. Discussion

This study investigated whether endogenous opioids play a role in mediating the feeling of pain relief in humans. Endogenous opioid blockade using naltrexone diminished self-reported relief in response to cooling after a painful heat stimulation. Pain sensitivity was not influenced by naltrexone. These results provide evidence that the feeling of pain relief in humans involves endogenous opioids.

The omission of an aversive stimulus is accompanied by 2 distinct processes: The negative valence of the stimulus is reduced and a feeling with a positive valence arises.[51] In the case of nociceptive stimulation as an aversive stimulus, these 2 processes correspond to a reduction of perceived pain and an additional feeling of pain relief.[29,49] The positive valence of pain relief has been demonstrated repeatedly[29,30,49] and is reflected in this study by the highly correlated relief and pleasantness ratings (placebo session: $r = 0.93$, $P < 0.001$) in response to the relieving cooling stimulation. Not only is pain relief pleasant, it also has rewarding properties. In conditioned place preference paradigms, rodents prefer locations not previously paired with a painful stimulus over those previously paired, demonstrating that pain relief leads to negative reinforcement.[26,38,39] Recently, Navratilova et al.[39] have shown that this negative reinforcement associated with pain relief requires endogenous opioid activity, similarly to positively reinforced behavior by rewarding stimuli such as food.[25,40] This study adds to these findings by demonstrating that endogenous opioids contribute to the positive feeling of pain relief in humans.

The average magnitude of the endogenous opioid blockade effect across participants (ranging from −8.13 to −4.71 points on the VAS) is comparable with observed reductions in placebo and relative relief-induced analgesia after opioid blockade.[11,17] The exploratory analysis of how much pain relief the individuals reported in the placebo session and the magnitude of naltrexone effects on pain relief first revealed a negative association, ie, the greater the pain relief in the placebo session, the greater the naltrexone reduction of pain relief. However, the comparison to a randomly generated sample of 10′000 correlation coefficients showed that none of the observed correlations was different from what would be expected by the statistical flaw of a random string of numbers A typically correlating with a random string B-A using inherently correlated samples A and B. The observed high interindividual variability of perceived pain relief therefore seems not to be related to how pain relief is modulated by endogenous opioid blockade on an individual level. Nevertheless, interindividual differences in the endogenous opioid system might contribute to differences across individuals in how they perceived pain relief, similar to what has been described for pain perception[37] and clinical opioid effects.[33] It is also conceivable that the feeling of pain relief involves other neurotransmitter systems than endogenous opioids which would not be modulated by naltrexone. Besides, individuals may present with inherently different pain relief rating behaviors, as has been reported for pain ratings.[8] Clinically relevant insights might be gained from future studies investigating the reasons for interindividual differences in the perception of pain relief.

Interestingly, relief/pleasantness ratings were not higher after more intense painful stimuli, in contrast to a previous report.[29] This discrepancy might be explained by differences in the study designs: Leknes et al.[29] used shorter stimuli (ie, 3 seconds compared with 30 seconds and 1 minute here) without capsaicin and subsequent cooling. In another experiment of the same study, cooling after painful heat was shown to increase relief ratings compared with painful heat without subsequent cooling.[29] The combination of relatively long painful stimuli and subsequent cooling in this study might have resulted in a ceiling effect of relief/pleasantness ratings (mean of 62.45 and a 95th percentile of 91.25 at the lower target pain intensity "170" in the placebo session), thereby eliminating a potential association between pain relief and preceding pain intensity.

Nevertheless, care was taken in the study design to avoid that potential differences in perceived pain intensity between placebo and naltrexone sessions might impact relief ratings. For this reason, perception-adjusted, rather than temperature-adjusted, painful heat stimulations were used in this study. Pain intensity ratings did not differ between the naltrexone and placebo sessions, confirming successful pain intensity adjustment. Moreover, the temperatures required to reach the respective pain intensities (ie, "170" and "195") neither differed between sessions, indicating that the participants' pain sensitivity was comparable for naltrexone and placebo. The additional lack of naltrexone effects on pain unpleasantness ratings, heat pain thresholds, and heat tolerance thresholds, as well as autonomic nervous system responses (ie, SCRs), further confirm that naltrexone did not induce hyperalgesia in this study. This finding is in line with most studies assessing opioid antagonist effects on pain sensitivity in experimental pain paradigms [reviewed in Ref. 55]. The observation that SCRs were greater after painful stimuli compared with relieving stimuli is in line with a previous report,[47] indicating that SCR recordings were valid. The finding of smaller SCRs in the trials with higher pain intensity (ie, "195") compared with the "170" trials is probably explained by the order of the trials: The "195" trials were always performed after the "170" trials, which might have resulted in a habituation of the SCRs as demonstrated for repetitive painful electrical stimuli.[13,44]

The participants' emotional state assessed by self-reports (ie, POMS-Bi) and autonomic responses (ie, HRV) did not differ between the naltrexone and the placebo session and could therefore be ruled out as a potential confounder of the finding that naltrexone diminished the feeling of pain relief. Furthermore, no effect of sex was observed, except for heat pain and heat tolerance thresholds being lower for women, in line with the literature on sex differences in pain sensitivity [reviewed in Ref. 18]. None of the assessed psychological factors, ie, pain catastrophizing and consummatory pleasure, was associated with pain relief, possibly because of the sample used here, ie, healthy, young volunteers. Future investigations in patient populations, eg, patients with chronic pain, might be of interest to examine the role of the psychological factors in pain relief.

The rewarding nature of pain relief is an important aspect in the clinical context. For instance, pain relief might reinforce behavioral strategies that are beneficial short-term, but maladaptive long-term. Indeed, operant learning with pain relief as negative reinforcement has been demonstrated in healthy controls and fibromyalgia patients who learned to increase sensitization and habituation responses to painful stimulation.[6,7,23] The effectiveness of operant learning using pain relief as reinforcement might depend on neurochemical systems involved. Conceptually, there is a fundamental difference in whether the termination of an aversive stimulus is neurochemically reflected in a mere reduction in "substance A" (mediating the aversiveness of the stimulus) or by a release of "substance B" (mediating the subsequent pleasure). In the case of pain relief, this study provides evidence that the feeling of pain relief is at least partly mediated by an increase in "substance B", namely endogenous opioids. Consequently, behaviors that provide pain relief may trigger addiction pathways [reviewed in Ref. 27]. This in turn might make the prevention of maladaptive behaviors providing pain relief more difficult. In addition, pain relief and its consequences, beneficial or maladaptive, might vary between individuals. This notion is suggested by the interindividual differences in pain relief and naltrexone effects on pain relief observed here and supported by previous literature on interindividual variability in endogenous opioid systems.[33,37]

5. Conclusion

Pain relief is rewarding and evokes a pleasant feeling in humans. Here, it is shown that the feeling of pain relief involves endogenous opioid signaling. Furthermore, the present results provide evidence of interindividual differences in experienced pain relief which merits closer investigation in future studies. Endogenous opioids mediating pain relief might contribute to its reinforcing properties, which, in a clinical context, are relevant regarding the acquisition and maintenance of behavioral strategies providing pain relief.

Finally, this study demonstrates the involvement of endogenous opioid signaling in the subjective feeling associated with the termination/reduction of nociceptive stimuli as aversive experiences. It would be interesting to investigate whether positive feelings associated with the reduction of aversive stimuli other than nociceptive stimuli are also mediated by endogenous opioids or whether other neurotransmitters are involved.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B355.

Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/B356.

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