Original Report

The Influence of Placebo Analgesia Manipulations on Pain Report, the Nociceptive Flexion Reflex, and Autonomic Responses to Pain

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Abstract: Expectations for pain relief and experience/conditioning are psychological factors that contribute to placebo analgesia, yet few studies have studied the physiological mechanisms underlying their effects. This study randomized 133 participants to 4 groups: an expectation only (E-only) group, a conditioning only (C-only) group, an expectation plus conditioning (E+C) group, and a natural history (NH) control group. Painful electric stimulations were delivered before and after an inert cream was applied to the site of stimulation. Pain-related outcomes (pain ratings, nociceptive flexion reflex [NFR], skin conductance response, and heart rate acceleration) were recorded after each stimulation. NFR (a measure of spinal nociception) assessed if placebo analgesia inhibited spinal processing of pain. E+C was the only manipulation that significantly inhibited pain and skin conductance response. Surprisingly, NFR was facilitated in the E+C and E-only groups. No effects were noted for C-only. Mediation analysis suggested 2 descending processes were engaged during E+C that influenced spinal nociception: 1) descending facilitation and 2) descending inhibition that was also responsible for pain reduction. These results suggest that E+C manipulations produce the strongest analgesia and have a complex influence on spinal nociception involving both inhibitory and facilitatory processes.

Perspective: This study assessed whether placebo analgesia manipulations that include expectations, conditioning, or both modulate the NFR (measure of spinal nociception). Only the manipulation that involved expectations and conditioning inhibited pain, but both expectation manipulations facilitated NFR. This suggests a complex modulation of spinal neurons by placebo manipulations.

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Key words: RII reflex, heart rate, skin conductance, expectations, conditioning, placebo analgesia

Placebo analgesia is pain reduction evoked by sham treatment (eg, inert cream). Because the treatment has no active ingredient, this implies psychosocial processes are involved. Among the processes identified are 1) expectations for pain relief, which is usually induced by verbal suggestion (eg, “This cream is a powerful painkiller”), and 2) experience/conditioning, which is usually induced by pairing the sham treatment with pain reduction (achieved in experiments by surreptitious lowering of the painful test stimulus). To our knowledge, only 2 published studies have independently manipulated expectations and conditioning by randomly assigning participants to expectation without conditioning (E-only), conditioning without expectations (C-only), and expectation plus conditioning (E+C) manipulations within the same study. As a result, there is a limited understanding of how these manipulations compare with one another. Amanzio and Benedetti found that all manipulations evoked analgesia, whereas Reicherts et al found only the E+C manipulation evoked analgesia.

Another understudied issue is what physiological mechanisms relate uniquely to each manipulation. One potential physiological mechanism is descending
inhibition of spinal nociception. Supporting this, a spinal functional magnetic resonance imaging (fMRI) study found that placebo reduced the dorsal horn response and pain from noxious heat. Consistent with this finding, another study found that experimentally induced hyperalgesia (ostensibly a spinal mechanism) and pain were reduced by placebo.31 By contrast, a laser-evoked potential (LEP) study found that the early N1 LEP was not modulated by placebo, although pain perception and the late P2 were modulated by placebo.30 The authors concluded that placebo analgesia does not involve descending spinal inhibition, otherwise their manipulation would have resulted in general (not selective) reduction in LEPs. However, there is some debate about whether these LEPs are specific to nociceptive processing.26 Moreover, the null result could have stemmed from low power. Notably, all 3 studies above used an E+C manipulation.

Another potential method to study whether placebo engages descending inhibition is to measure the effect on the nociceptive flexion reflex (NFR) (a spinally-mediated reflex dependent on activation of A-delta nociceptive fibers34). Given that NFR is inhibited by pharmacological (eg, morphine) and non-pharmacological (eg, hypnotic analgesia) pain interventions,19,29,46,63 the NFR should be inhibited if placebo analgesia engages descending inhibition. Only 1 study has used NFR to this end and found that an E-only manipulation did not inhibit NFR. However, the manipulation also did not result in pain reduction49; thus, the null NFR result could be due to the failure of the E-only manipulation to engage placebo analgesia.

Given the paucity of information on this topic, the aims of the current study were twofold. The primary aim was to examine the influence of expectation and conditioning manipulations on the NFR to assess whether descending inhibition of spinal nociception was engaged by placebo manipulations. The second aim was to compare the effectiveness of expectations and conditioning in producing placebo analgesia. To do so, the current study randomly assigned participants to an E-only, C-only, E+C, or a natural history (NH) condition and assessed the effect on pain ratings and NFR in response to painful, suprathreshold electric stimulations. Pain-evoked skin conductance response (SCR) and heart rate (HR) acceleration were also assessed because SCR is inhibited by placebo manipulations6,23 and both are modulated by other psychological processes.35,41,45,48 We predicted all outcomes would be inhibited by placebo manipulations, but that E+C would produce the greatest analgesia.

**Methods**

**Participants**

Healthy men and women were recruited from the community (using flyers, newspaper advertisements, and email announcements) or from a psychology subject pool. Individuals were excluded if they met the following criteria: being younger than 18 years of age; having health conditions that could interfere with pain testing (neurologic, cardiovascular, or circulatory problems); being currently pregnant; having undergone recent psychological trauma; having a hearing impairment (because intact hearing is necessary for assessment of prepulse inhibition [see procedures]); using medications that could interfere with testing (ie, analgesics, antidepressants, anti-anxiety, stimulants); using narcotic analgesics for 2 weeks before the experiment; using nonnarcotic analgesics (eg, nonsteroidal antiinflammatory drugs, acetaminophen) 24 hours before the experiment; having a body mass index greater than 35 (due to potential difficulties obtaining an NFR in individuals with high adiposity); or having a current diagnosis of chronic pain. Participants recruited from the community who completed the study received a $100 honorarium, whereas those from the psychology subject pool received course credit. A stratified random sampling approach was taken to promote equal sex, race, and ethnicity distributions across the experimental groups. All participants provided written and verbal informed consent and were told that they could discontinue participation at any time. Recruitment took place between August 2012 and July 2015.

Before the study was conducted, a power analysis was used to estimate the needed sample sizes. Cohen’s d effect sizes for the influence of placebo analgesia on pain report were derived from the meta-analysis of Vase et al60 (d = 0.85, d = 0.83, d = 1.45). The natural history control effect size was estimated to be d = 0.21. Based on these effect sizes, 14 participants per group were required in the analysis of pain ratings to achieve power ≥ 0.80 to detect the interaction of interest at α = 0.05. The effect size for placebo analgesia of NFR was unknown due to the problems with the only existing study. Thus the effect size for NFR was estimated from a study on hypnotic suggestion of analgesia (an effect similar to placebo) on NFR by Kiernan et al29 (d = 1.0). Given that the effect size for the placebo effect for E-only on pain ratings discussed above was 58% of the E+C group effect size (ie, 0.85/1.45 = 0.58), d = .58 was used for the effect sizes for the E-only and C-only groups. Based on these effect sizes, 35 participants per group were targeted to achieve power ≥ 0.80 to detect a significant Group X Cream period interaction at α = 0.05. A total of 153 participants were recruited, but due to equipment problems and difficulties evoking NFRs (see Results section), a final sample of 133 participants was available for analysis (see Table 1 for participant characteristics by group).

**Procedures**

To promote believability of the study, each experimenter wore a white lab coat throughout the experiment with a badge that had their photo, name, and a logo that said “Division of Analgesic Trials.” Participants were told that they were participating in a study to examine the effects of a strong pain-relieving cream (ie, Lidocaine) on physiological reactions to painful stimuli. At study entry, participants were screened for inclusion criteria: being younger than 18 years of age; having health conditions that could interfere with pain testing (neurologic, cardiovascular, or circulatory problems); being currently pregnant; having undergone recent psychological trauma; having a hearing impairment (because intact hearing is necessary for assessment of prepulse inhibition [see procedures]); using medications that could interfere with testing (ie, analgesics, antidepressants, anti-anxiety, stimulants); using narcotic analgesics for 2 weeks before the experiment; using nonnarcotic analgesics (eg, nonsteroidal antiinflammatory drugs, acetaminophen) 24 hours before the experiment; having a body mass index greater than 35 (due to potential difficulties obtaining an NFR in individuals with high adiposity); or having a current diagnosis of chronic pain. Participants recruited from the community who completed the study received a $100 honorarium, whereas those from the psychology subject pool received course credit. A stratified random sampling approach was taken to promote equal sex, race, and ethnicity distributions across the experimental groups. All participants provided written and verbal informed consent and were told that they could discontinue participation at any time. Recruitment took place between August 2012 and July 2015.

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criteria, randomized to 1 of the 4 groups, and then instrumented for physiological recording. Some were told they were assigned to a control condition that does not receive the pain-relieving cream (NH, C-only), whereas others were told the painkilling cream would be applied to their ankle (at the site of the painful electric stimulations) at some point, that it is very fast acting, and that the effects last approximately 30 minutes (see Fig 1 for study design). The E-only group was told that the cream would be applied once, whereas the E+C group was told that it would be applied twice to examine the reproducibility of the painkilling effects (the first application allowed for the conditioning phase). All groups were told that 1 experimental group (ie, E+C) would receive the painkilling cream twice and that, to keep procedures consistent for all participants, there needed to be 2 cream applications and thus 2 assessments. Participants then filled out background questionnaires and completed prepulse inhibition of startle eyeblink testing, which is believed to assess individual differences in dopaminergic activity \(^{40,56}\) (reported elsewhere, see details in supplementary material). After prepulse inhibition testing, NFR threshold (and PAIN40 if necessary) were assessed to determine the suprathreshold stimulus intensity to be used during placebo testing.

The rest of the experiment was divided into 2 nearly identical assessment phases separated by a 30-minute break (Fig 1). Each assessment included a pre-cream and post-cream period that involved the delivery of 12 painful, suprathreshold electric stimulations. The actual purpose of assessment 1 (conditioning manipulation phase) was to allow for conditioning trials in the E+C and C-only groups whereby the stimulation intensity was surreptitiously reduced during the post-cream period to produce pain relief. The E+C group was told that the cream applied was a powerful painkiller, but the experimenter actually applied an inert, white electrode gel (EC33; Grass Technologies, West Warwick, RI) from a jar marked “Lidocaine” while wearing rubber medical gloves. The other 3 groups were told that the cream was additional electrode gel that was taken from the same tube used during electrode application. Stimulation intensity was not lowered in the NH and E-only groups. A brief version of prepulse inhibition testing was conducted after the cream application. After the 12 post-cream period stimulations of assessment 1, all groups had a 30-minute break before assessment 2 (test phase) began. They were told the break was necessary to allow the effects of the painkilling cream to wear off in the group that received it during assessment 1.

Placebo analgesia was actually tested during assessment 2 (test phase). During the pre-cream period, a series of 12 painful, suprathreshold stimulations were delivered to assess baseline responsivity. Then the cream was applied again; however, this time both the E+C and the E-only groups were told the cream applied was Lidocaine. The NH and C-only groups were told more electrode gel was applied. During the assessment 2 post-cream period, all groups received painful, suprathreshold stimulations at the same intensity as the pre-cream period to examine changes that result from the placebo manipulations. Prior to each post-cream period, participants were asked to rate the pain that they expected to experience (described below). Additional details about the instructions given to the groups is provided in the supplementary material.
After the study was concluded and data collection was completed, participants were mailed and/or emailed a debriefing letter that explained the study and the rationale for the deception. The letter also explained that the participants were free to withdraw their data, given that the study had now been fully explained to them. No one did so. All procedures were approved by the ethics review board at The University of Tulsa.

### Apparatus, Stimulus Parameters, and Physiological Signals

Stimulus presentation, self-report ratings, and physiological data collection were controlled by a personal computer with dual-monitor capacity, A/D board (PCI-6036E; National Instruments, Austin, TX) and LabVIEW software (National Instruments). One computer monitor was used by the experimenter to monitor physiological signals, and a second computer monitor was used by the participant to complete electronic questionnaires and make ratings of pain stimuli. Testing was completed in a sound-attenuated and electrically shielded testing room. Participants were monitored from an adjacent control room via a video camera connected to a flat panel television. Participants wore sound-attenuating headphones (TDH-49; Telephonics, Farmingdale, NY) that allowed them to hear the experimenter’s instructions. They could speak to the experimenter via the microphone on the video camera.

A medical scale with attached height rod (Detecto, Webb City, MO) was used to assess weight and height to calculate body mass index. Throughout testing, participants were seated in a comfortable reclining chair (PC-6 Perfect Chair; Human Touch, Long Beach, CA) that kept their knee angle at approximately 160 degrees for NFR testing. Electric stimuli to assess pain outcomes were generated by a Digitimer stimulator (DS5; Hertfordshire, UK) and delivered using a bipolar surface stimulating electrode (30-mm interelectrode distance) (Nicolet, Madison, WI) attached to the left leg over the retromalleolar pathway of the sural nerve (stimulating electrode impedance \( \leq 2 \text{k}\)). A computer controlled the timing and intensity of the stimulations, and the maximum stimulation intensity was set at 50 mA to ensure safety.

All physiological signals were amplified and filtered by a Grass Technologies Model 15LT amplifier (with AC Modules 15A54 and DC/AC Module 15A12) and sampled at 1000 Hz. The NFR was assessed from biceps femoris electromyogram (EMG) recorded from 2 active Ag-AgCl electrodes (F-E9-40-5; Grass Technologies) placed 10 cm superior to the popliteal fossa. Biceps femoris EMG was amplified x10,000 and bandpass filtered (10 Hz - 300 Hz). A ground electrode was placed over the lateral epicondyle of the femur. An adaptor (Model SCA1; Grass Technologies) was attached to the Grass Technologies DC/AC Module 15A12 to measure shock-evoked SCR. SCR was recorded from 11-mm reusable disc electrodes.
Rhudy et al

(F-E9-40-5; Grass Technologies) filled with isotonic paste (EC33; Grass Technologies) affixed to the volar surface of the index and middle fingers of the nondominant hand after the participant’s skin had been washed and dried. Electrocardiogram (ECG) was measured using electrodes that were filled with conductive gel (EC60; Grass Technologies) and applied to the left and right forearms. Before NFR and ECG electrodes were applied, the skin was cleaned with alcohol and exfoliated using an abrasive paste (Nuprep; Weaver and Company, Aurora, CO) to reduce impedances below 5 kΩ.

**Questionnaires**

Background information. A custom-built demographics and health status questionnaire was used to obtain standard background information and information regarding health problems. The questionnaire asks about exclusionary criteria such as cardiovascular problems, neurologic disorders, chronic pain, recent trauma, and medications.

Pain catastrophizing. The Pain Catastrophizing Scale was used to assess group differences in this coping style. This scale is a reliable and valid 13-item measure that assesses catastrophic thoughts (rumination, magnification, helplessness) associated with pain. Items were summed to compute a total pain catastrophizing score that ranged from 0 to 52, with higher scores indicating greater catastrophizing.

Mood and anxiety. The Positive and Negative Affect Schedule (PANAS) was used to assess group differences in mood prior to the experiment. The PANAS is a 20-item scale, with 10 items assessing positive affect and 10 items assessing negative affect. Scores were summed to produce subscales that ranged from 0 to 40, with higher scores indicating greater positive and negative affect. The trait subscale of the State-Trait Anxiety Inventory was used to assess group differences in anxiety. Items were summed to produce a subscale that ranged from 20 to 80, with higher scores representing greater trait anxiety.

Pain ratings. To assess pain intensity in response to electric stimuli, participants used a computer-presented visual analog scale (VAS) for pain intensity with the anchors “no pain sensation” and the “the most intense pain sensation imaginable.” Participants used a computer mouse to slide an indicator along the scale to make ratings. A mouse button press was used to submit the rating and return the scale to zero before the next rating. The computer converted the scale to values between 0 and 100, with higher values representing greater pain intensity.

Expectation ratings. To assess expectations for pain relief, the VAS for pain intensity was presented just before each post-cream period with instructions to rate how much the participant expected their pain to change during the upcoming post-cream period. Negative scores represent pain reduction. This change score was used in all analyses of expectations for pain relief.

**Pain-Related Outcomes**

Pain-related outcomes were assessed from the 48 painful, suprathreshold electric stimulations delivered during the pre-cream period and post-cream period of assessment 1 (conditioning manipulation phase) and assessment 2 (test phase). Each electric stimulus was a train of five 1-ms square wave pulses delivered at 250 Hz (ie, 3 ms inter-pulse interval) that lasted 17 ms and was experienced as a single, sharp, shooting painful stimulus that is characteristic of A-δ nociceptor activation.

Pain ratings. VAS pain intensity ratings were used to assess changes in pain experience.

Nociceptive flexion reflex (NFR). NFR is a polysynaptic reflex dependent on activation of A-δ nociceptors that is also referred to as the RII reflex (see Sandrini et al for a thorough review). Following delivery of a noxious stimulus over the sural nerve, the NFR is assessed from biceps femoris EMG in the 90- to 150-ms post-stimulation interval because this interval avoids contamination from nonnociceptive EMG reactions that can occur earlier than 90-ms post-stimulation (eg, RII reflex that is due to A-β fiber activity) and those that can occur after 150-ms post-stimulation (eg, startle, voluntary movements). Furthermore, this interval corresponds to the timing of a reflex that would be due to A-δ fiber activation. Validity studies have shown that 1) the threshold to evoke the NFR is highly correlated with pain threshold, 2) the size of the reflex is correlated with suprathermal threshold intensity and pain ratings, and 3) pharmacologic (eg, morphine, serotonin agonists) and nonpharmacologic (eg, hypnotic analgesia, transcutaneous electrical nerve stimulation, coping strategies, mood induction) pain interventions can modulate the reflex. Moreover, NFR can be elicited in patients with a spinal transection, verifying that it does not require supraspinal input. Although NFR is often modulated in parallel with pain, modulation of the two can be dissociated, indicating that different modulatory circuits contribute to each.

NFR magnitudes in response to painful, suprathreshold electric stimulations were calculated from a d-score (d = [mean rectified EMG during 90- to 150-ms post-stimulus interval minus mean rectified EMG during 60-ms pre-stimulus interval]/ [average of rectified baseline interval standard deviation and 90- to 150-ms interval standard deviation].) This scoring method was used because it produces a stronger correlation with pain ratings and results in a normal-shaped distribution of scores. Individual NFRs were excluded from analysis if the baseline EMG exceeded 3μV, indicating excessive muscle tension prior to the stimulation (2.3% of trials).

Shock-evoked SCR. Shock-evoked SCR can be influenced by placebo manipulations and other psychosocial processes, therefore shock-evoked SCR was used as an outcome in the present study. Shock-evoked
SCR was scored offline using custom software developed in LabVIEW. The peak skin conductance level in the 6-s after electric stimulation onset was found. And then, the mean skin conductance level in the 1-s baseline was subtracted from this value. SCR was z-transformed prior to analyses using the individual’s baseline mean and SD.

**Shock-evoked HR acceleration.** HR acceleration immediately after a painful electric stimulation can also be influenced by psychosocial processes. First, the R-spikes of the ECG were identified and then used to calculate R-R intervals (in ms) that were converted to HR in beats per min (BPM) for each 9-s epoch associated with an electric stimulation (Fig 1). Shock-evoked HR was defined as the mean HR in the 6-s post-stimulation period minus the mean HR in the 1-s pre-stimulation period. If HR decreased on a trial, it was scored zero because only the accelerative component of HR was of interest.

### Determination of Suprathreshold Test Stimulation Intensity

Electric stimulation intensity was individually calibrated for each participant to ensure that stimulations reliably evoked NFRs and pain (ie, were above NFR threshold and pain threshold). NFR threshold was assessed using 3 ascending-descending staircases of electric stimuli according to previously validated methods. The first ascending staircase started at 0 mA and increased in 2-mA steps until an NFR was detected. NFR was said to occur when the mean rectified biceps femoris EMG response in the 90- to 150-ms post-stimulus interval exceeded the mean rectified biceps femoris EMG activity during the 60-ms pre-stimulus baseline interval by at least 1.4 x the baseline EMG standard deviation. After an NFR was detected, the stimulus intensity was decreased in 1-mA steps until an NFR was no longer detected. The second and third ascending-descending staircases used 1-mA steps. The interval between electric stimulations varied randomly from 8 to 12 s to reduce predictability and reflex habituation. After each stimulus, participants rated their pain intensity on the VAS. The stimulus intensity (mA) of the 2 peaks and 2 troughs of the last 2 ascending-descending staircases were averaged and used to define NFR threshold.

In the event that NFR threshold did not produce at least moderate pain (ie, a rating of 40 on the VAS), stimulations were increased in steps of 2 mA until a VAS rating ≥40 was obtained (ie, PAIN40). The suprathreshold stimulation intensity used during placebo testing was set at 120% of NFR threshold or 120% PAIN40, whichever was higher. The stimulation intensity used for conditioning trials (ie, the surreptitiously reduced intensity used to produce pain relief) was PAIN40 intensity or 50% of the suprathreshold stimulation intensity, whichever was lower.

### Ratings Checks

Ratings for expected pain relief during the post-cream period were used to verify that the E+C group expected pain to decrease during assessment 1 (conditioning manipulation phase) and assessment 2 (test phase) and that the E-only group expected pain to decrease only during assessment 2 (test phase). Also, changes in pain, NFR, shock-evoked SCR, and shock-evoked HR acceleration were measured during assessment 1 (conditioning manipulation phase) to determine whether pain and noci-reactivity were reduced in the C-only and E+C groups as a result of surreptitiously reducing the stimulus intensity.

### Data Analysis

SPSS 20.0 (IBM; Armonk, NY) was used for all analyses. Background variables and participant characteristics were analyzed using 1-way analyses of variance (ANOVA) (for continuous variables) or chi-squared tests of independence (for nominal variables), with group as the independent variable. These analyses were conducted to examine whether expectations for placebo analgesia was effective in equalizing groups.

Dependent variables for the primary analyses were pain ratings, NFR magnitudes, shock-evoked SCR, and shock-evoked HR acceleration. Analysis of these variables measured during assessment 2 (test phase) was used to determine whether placebo analgesia was observed. These analyses were conducted using multilevel models (ie, SPSS MIXED procedure). The following variables were entered as independent variables: group (NH, E-only, C-only, E+C), cream period (pre-cream vs post-cream), and stimulus number (stims 1–12 in each cream period). Furthermore, the mean pre-cream value was entered as a covariate to control for any potential baseline differences (except for the analysis of SCR due to the conversion to z scores). The Group X Cream period interaction is the primary effect of interest in these analyses, because it demonstrates whether groups differentially changed from the pre-cream period to the post-cream period as a result of their group assignment and placebo manipulation.

Analyses were also conducted to assess whether placebo manipulations were effective. Pain ratings, NFR magnitudes, shock-evoked SCR, and shock-evoked HR acceleration measured during assessment 1 (conditioning manipulation phase) were analyzed using the same multilevel models described above. These analyses were used to verify that pain relief (eg, reduced pain and noci-reactivity) was experienced by the E+C and C-only groups. Additionally, to verify that expectations for pain relief were affected by the placebo manipulations, an ANOVA was constructed that used the expectation manipulation phase as the dependent variables and group and assessment phase (manipulation phase vs test phase) as independent variables.

Significance was set at $\alpha < .05$ (2-tailed). Follow-up comparisons to significant F-tests were conducted using Bonferroni tests. For most comparisons, this adjusted the alpha level for the 4 possible within-group simple effects of period (ie, adjusted $\alpha < .0125$).
Results

Final Sample and Background Characteristics
A total of 153 participants were eligible for the study; however, NFR threshold was not obtained in 5 participants (2 reached tolerance before NFR achieved, 3 reached max stimulation before NFR achieved), 5 did not complete the study, and 10 were excluded for equipment problems (1 stimulating electrode fell off, 1 signal interference, 8 excessive problems with stimulating electrode impedance). Thus 133 were available for analyses, with 34 in the NH group and 33 in each of the E-only, C-only, and E+C groups. Participant characteristics by group are reported in Table 1. As can be seen, groups did not differ on any background variable or in the stimulus intensity used to evoke pain reactions.

Manipulation Checks
Manipulation check analyses are reported in Table 2. To briefly summarize these results, expectations for pain relief were induced in the E-only and E+C groups (Fig 2). Moreover, surreptitious lowering of the stimulus intensity in the C-only and E+C groups led to reduced pain, NFR, shock-evoked SCR, and shock-evoked HR in those 2 groups only (Fig 3).

Expectation ratings. The significant Group X Assessment phase interaction is depicted in Fig 2. Relative to the NH group, the E+C group expected pain to decrease at assessment 1 (conditioning manipulation phase) and assessment 2 (test phase), whereas the E-only group expected pain to change at assessment 2 (test phase) (all P values < .001).

Pain ratings (manipulation phase). The significant Group X Cream period interaction is depicted in Fig. 3A and 3B. None of the groups differed at the pre-cream period (P = .53); however, pain ratings decreased in the post-cream period for the C-only and the E+C groups due to the surreptitious lowering of the electric stimuli. Moreover, the E+C group experienced even less pain during the post-cream period than the C-only group (P < .001). The other significant interactions (Group X Stimulus number, Cream period X Stimulus number) indicated that pain generally sensitized across the set of 12 stimuli, but less so during the post-cream period because of the habituation trend of the E+C group and the lack of sensitization in the C-only group (see Fig 3A).

NFR magnitudes (manipulation phase). The significant Group X Cream period interaction is depicted in Fig. 3C and 3D. None of the groups differed at the pre-cream period (P = .999); however, NFRs decreased in the post-cream period in the C-only and the E+C groups due to the reduction in stimulus intensity. The significant main effect of stimulus number indicated that NFRs generally habituated across each set of 12 stimulations, especially from the first to second stimulus in the set of 12 (Fig 3C).

Shock-evoked SCR (manipulation phase). The significant Group X Cream period interaction is depicted in Fig. 3E and 3F. None of the groups differed at the pre-
cream period (P = .694); however, SCRs decreased in the post-cream period for the C-only and the E+C groups. The significant main effect of stimulus number indicated that SCRs generally habituated across each set of 12 stimulations, primarily due to the decrease after the first stimulus in the set of 12 (Fig 3E). The significant Cream period X Stimulus number interaction suggested that there were some cream period differences in the general habituation of SCRs over the 12 stimulations; however, these differences were not of general importance (Fig 3E).

Shock-evoked HR acceleration (manipulation phase). The significant Group X Cream period interaction is depicted in Fig. 3G and 3H. None of the groups differed at the pre-cream period (P = .088); however, HR decreased in the post-cream period for the C-only and the E+C groups. The significant main effect of stimulus number indicated shock-evoked HR habituated over time, primarily due to the decrease after the first stimulus in the set of 12 (Fig 3G).

The Effects of Placebo Manipulations on Pain-Related Outcomes (Test Phase)
Analyses associated with the test phase results are reported in Table 3, and means ± standard error of the mean (SEMs) are depicted in Fig 4. To briefly summarize the results, pain ratings and SCR decreased in the E+C group, but NFR increased in the E+C and E-only groups.

Pain ratings (test phase). The significant Group X Cream period interaction is depicted in Fig. 4A and 4B. None of the groups differed at the pre-cream period (P = .99), yet pain ratings for the E+C group decreased during the post-cream period, indicating significant placebo analgesia. The significant main effect of stimulus number indicated that pain ratings generally sensitized across each set of 12 stimulations (Fig 4A).

NFR magnitudes (test phase). The significant Group X Cream period interaction is depicted in Fig. 4C and 4D. Groups did not differ at the pre-cream period (P = .995), yet NFRs for the E-only and the E+C groups increased during the post-cream period. The significant main effect of stimulus number indicated that NFRs generally habituated across each set of 12 stimulations (Fig 4C).

Because NFRs unexpectedly increased, resting EMG activity in the 60-ms pre-stimulus baseline was analyzed to ensure that the changes in NFR were actually due to increases in activity in the 90- to 150-ms post-stimulus period rather than decreases in EMG during the 60-ms pre-stimulus period. As shown in Fig 5, results indicated baseline EMG did not vary by group, cream period, or the Group X Cream period interaction (F values < 1); thus the increases in NFR magnitudes in the E-only and E+C groups cannot be attributed to decreases in EMG baselines.

Shock-evoked SCR (test phase). The significant Group X Stimulus number interaction is depicted in Fig. 4E and 4F. Groups did not differ at the pre-cream period (P = .996), yet SCRs for the E+C group significantly decreased during the post-cream period. The Cream
<table>
<thead>
<tr>
<th>Table 2. Results of Manipulation Check Analyses (Conditioning Phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXPECTATION RATINGS (-100 – +100) ANOVA RESULTS</strong></td>
</tr>
<tr>
<td><strong>FIXED EFFECTS</strong></td>
</tr>
<tr>
<td><strong>DF</strong></td>
</tr>
<tr>
<td>Group 3</td>
</tr>
<tr>
<td>Assessment Phase 1</td>
</tr>
<tr>
<td>Group x Assessment Phase 3</td>
</tr>
</tbody>
</table>

| **PAIN RATINGS (0 – 100) MULTI-LEVEL ANOVA RESULTS**         |
| **FIXED EFFECTS**                                           |
| **DF** | **NUM** | **DENOM** | **F** | **P VALUE** |
| Group 3 | 271.06   | 62.93     | < .001 |
| Cream Period 1 | 478.06   | 308.08    | < .001 |
| Stimulus Number 11 | 2435.91  | 3.58     | < .001 |
| Group x Cream Period 3 | 478.06   | 102.65    | < .001 |
| Group x Stimulus Number 33 | 2435.91  | 1.55     | .2 |
| Cream Period x Stimulus Number 11 | 2216.79  | 1.99     | .03 |
| Group x Cream Period x Stimulus Number 33 | 2217.68  | 0.89     | .66 |
| Mean Baseline (covariate) 1 | 291.65   | 1413.86   | < .001 |

| **NFR MAGNITUDE (d-score) MULTI-LEVEL ANOVA RESULTS**        |
| **FIXED EFFECTS**                                           |
| **DF** | **NUM** | **DENOM** | **F** | **P VALUE** |
| Group 3 | 586.57   | 59.78     | < .001 |
| Cream Period 1 | 696.14   | 232.55    | < .001 |
| Stimulus Number 11 | 1943.72  | 4.88     | < .001 |
| Group x Cream Period 3 | 696.14   | 66.40    | < .001 |
| Group x Stimulus Number 33 | 1944.89  | 1.23     | .18 |
| Cream Period x Stimulus Number 11 | 1898.29  | 1.37     | .18 |
| Group x Cream Period x Stimulus Number 33 | 1899.75  | 0.71     | .89 |
| Mean Baseline (covariate) 1 | 612.56   | 2084.32   | < .001 |

| **SHOCK-EVOKED SCR (z-transformed) MULTI-LEVEL ANOVA RESULTS**|
| **FIXED EFFECTS**                                           |
| **DF** | **NUM** | **DENOM** | **F** | **P VALUE** |
| Group 3 | 461.16   | 61.96     | < .001 |
| Cream Period 1 | 568.88   | 249.77    | < .001 |
| Stimulus Number 11 | 1822.16  | 53.42     | < .001 |
| Group x Cream Period 3 | 568.63   | 70.66    | < .001 |
| Group x Stimulus Number 33 | 1831.62  | 1.22     | .21 |
| Cream Period x Stimulus Number 11 | 1756.96  | 2.20     | .02 |
| Group x Cream Period x Stimulus Number 33 | 1760.13  | 0.91     | .61 |

| **SHOCK-EVOKED HR (bpm) MULTI-LEVEL ANOVA RESULTS**          |
| **FIXED EFFECTS**                                           |
| **DF** | **NUM** | **DENOM** | **F** | **P VALUE** |
| Group 3 | 934.33   | 13.36     | < .001 |
| Cream Period 1 | 1052.58  | 53.60    | < .001 |
| Stimulus Number 11 | 1772.88  | 7.83     | < .001 |
| Group x Cream Period 3 | 1052.58  | 18.18    | < .001 |
| Group x Stimulus Number 33 | 1774.73  | 1.09     | .33 |
| Cream Period x Stimulus Number 11 | 1769.32  | 1.05     | .4 |
| Group x Cream Period x Stimulus Number 33 | 1771.16  | 0.90     | .64 |
| Mean Baseline (covariate) 1 | 953.12   | 1301.83   | < .001 |
post-cream period minus average pre-cream period) during the test phase. The mediator was the change in pain during the test phase (ie, the average post-cream period minus the average pre-cream period). Significance of the indirect (mediation) effect was assessed by generating a 95% confidence interval around the indirect effect from 10,000 bootstrapped samples.

Consistent with the primary analyses, the total effect (Fig 6A, top model) was positive (path c = \(-.1725, P = .0064\) ), indicating facilitated NFR. Moreover, path a (P = .0066), path b (P = .0006) and path c' (P = .0012) were significant (Fig 6A, bottom model). However, the most important result is the bootstrapped test of the indirect effect (ie, path a X path b). The indirect effect from the placebo manipulation to NFR via pain was significant (Fig 6A, path a X path b in lower model = -.0941, 95% confidence interval = \(-.1934, -.0365\)). Notably this indirect effect through pain was negative, indicating that the placebo manipulation was associated with reduced (inhibited) NFR (see Fig 6A). However, the direct effect of the placebo manipulation on NFR was positive (Fig 6A, path c’ of lower model = .2666), indicating that NFR was facilitated through this path.

This model suggests 2 opposing neural mechanisms were acting on NFR: 1) a descending facilitatory mechanism and 2) a descending inhibitory mechanism that also inhibited pain. Thus, the observed effect of placebo manipulations on NFR appears to be the net effect of these 2 mechanisms. Given that the facilitatory effect was stronger, there was a net facilitatory effect (path c = .1725) in the model. Interestingly, after controlling for the inhibitory mechanism on NFR (via modeling the indirect path through pain), the magnitude of descending facilitatory effect was stronger as evidenced by the more positive direct effect (path c’ = .2666) in the model, compared with the total effect (path c = -.1725). This difference is statistically significant (as tested by the significance of the indirect path). Together, these results imply that the E+C manipulation led not only to descending facilitation of NFR but also to placebo analgesia and a weaker simultaneous inhibitory effect on NFR.

**Exploratory Analyses**

**Psychological predictors of changes in pain outcomes.** Correlations were conducted to examine whether changes (post-cream minus pre-cream during the test phase) in pain, NFR, and SCR were associated with expectations for pain relief, mood (PANAS), catastrophizing, and trait anxiety. To do so, participants in the NH, E-only, and E+C groups were selected and Pearson’s correlations were conducted. Expectations for pain relief were related to changes in NFR (r = -.272, P = .007; Fig 7). The more pain relief that participants expected, the more that NFR was increased, suggesting that expectations were associated with the observed increase in NFR. No other correlation was significant.

**Changes in pain/NFR and pain-relief during conditioning.** A second set of exploratory correlations were conducted to examine whether reductions in pain (post-cream period minus pre-cream period) due to
surreptitiously lowering the stimulus intensity during the conditioning manipulation phase (assessment 1) were associated with placebo responses in pain and facilitation of NFR (assessment 2 post-cream period minus pre-cream period). To do so, participants in the NH, C-only, and E+C groups were selected and correlations were conducted. Reductions in pain (pain relief) in response to conditioning trials were significantly correlated with placebo analgesia of pain ratings ($r = .310, P = .002$; Fig 8), but not facilitation of NFR ($r = -.175, P = .083$). This indicates that the more pain relief that participants experienced during the surreptitious lowering of the stimuli, the stronger the placebo analgesia they experienced.

**Discussion**

This study examined E-only, C-only, and E+C manipulations on pain ratings, NFR, SCR, and HR. NFR was measured to determine whether manipulations affected spinal nociception. Although one prior study examined...
the influence of E-only on NFR, they failed to observe placebo analgesia making it difficult to draw conclusions about the lack of change in NFR. For this reason, it is important to consider whether manipulations produced significant reductions in pain.

The Influence of Expectations and Conditioning on Pain

Consistent with the findings of Reicherts et al., only the E+C manipulation produced significant placebo analgesia and also reduced SCR. Expectations alone cannot account for the analgesia because both the E+C and E-only groups expected pain to decrease, but only the E+C group experienced significant analgesia. Moreover, expectation ratings were not significantly correlated with pain reduction. Similarly, conditioning alone cannot explain the analgesia because C-only did not produce significant analgesia. Nonetheless, the significant correlation between pain relief experienced during conditioning and the degree of placebo analgesia suggests that conditioning did contribute. Together these
findings imply a synergy between expectations and conditioning, likely resulting from the sham cream being associated with verbal suggestions for pain relief and the actual pain relief from surreptitious lowering of stimulus intensity. This is consistent with a meta-analysis noting E+C produces the strongest effect size for placebo analgesia.60

By contrast, Amanzio and Benedetti1 found all 3 manipulation types produced analgesia (although E-only and C-only were weaker effects). Their C-only manipulation may have been effective because it involved openly injecting an active painkiller on 2 occasions followed by a test phase in which participants were told they were receiving an injection of a nonpainkiller (eg, antibiotic). Thus their procedure included verbal suggestions to help ensure the participants associated the Conditioned Stimulus (CS) (injection) with pain relief. We did not tell the C-only group that the cream was a powerful painkiller before surreptiously lowering the stimuli. This was done to avoid producing any expectations for pain relief during the test phase. However, it may have weakened the association

Figure 4. The effect of placebo manipulations on pain (A and B), NFR magnitudes (C and D), shock-evoked SCR (E and F), and shock-evoked HR (G and H) acceleration during assessment 2 (test phase). Significant placebo analgesia and reduced shock-evoked SCR were only noted in the E+C group. Surprisingly, E+C and E-only experienced facilitation of NFR. *P < .0125.
Figure 5. Biceps femoris EMG traces during assessment 2 (test phase). The 4 graphs at the top depict the averaged pre-cream and post-cream EMG traces for each group separately. The bottom graph depicts the group averaged EMG traces during the post-cream period. NFR magnitudes (EMG traces during the 90- to 150-ms post-stimulus interval) for E-only and E+C groups were larger during the post-cream period than the pre-cream period and were larger for the E+C and E-only groups relative to the NH group.
between the inert cream (CS) and pain relief. This may have resulted in part from participants having difficulty discriminating the cream CS from other environmental signals (eg, room or experimenter) that could have produced the analgesia. Another difference is that we only provided 1 conditioning trial. As noted elsewhere,10 multiple trials may be needed to evoke conditioning-dependent analgesia.

It is less clear why our E-only manipulation failed to produce analgesia. Amanzio and Benedetti1 injected participants with saline solution during an ischemia tolerance test and told them it was a powerful painkiller. We exposed the participants to the inert cream twice, but only told them it was a powerful painkiller the second time. The first administration without a verbal suggestion for pain relief may have reduced subsequent

Figure 6. Modeling the effect of placebo manipulations on the modulation of pain and NFR. Mediation analysis (A) examined the effect of the placebo manipulation (expectation plus conditioning) on change in NFR, mediated by pain inhibition. The independent variable was dichotomous (0=NH group, 1=E+C group), whereas the mediator is pain inhibitory processes (the post-cream period minus the pre-cream period) and the dependent variable is change in NFR (the post-cream period minus the pre-cream period). The total effect (path c of upper model) of the placebo manipulations indicated the placebo manipulations led to NFR facilitation. The mediated (lower) model indicated that there was a significant indirect (mediated) effect of placebo manipulations on NFR via pain inhibition. This indirect effect was inhibitory, because path a was negative and path b was positive. Nonetheless, the placebo manipulation still led to a significant facilitation of NFR (path c'). In fact, the magnitude of NFR facilitation in the direct effect (path c') was greater than the magnitude of the total effect (path c) when the indirect inhibitory pathway was mathematically controlled. This suggests there is a significant descending inhibition of spinal nociception that reduces the magnitude of the observed NFR facilitation. Light-blue arrows in the mediated model represent the hypothetical underlying mechanisms that are modeled by the mathematical paths. On the right (B) is the hypothetical neural effects proposed by the mediated model. Specifically, NFR is influenced by both descending facilitation and descending inhibition during placebo analgesia. *P < .05, **P < .01, ***P < .001

Figure 7. The relationship between expectations for pain relief and change in NFR magnitudes in the NH, E-only, and E+C groups combined. The more pain relief that was expected (negative pain change scores), the more that NFR was facilitated (positive NFR change scores).
expectations for pain relief during the test phase. Alternatively, E-only manipulations may produce stronger analgesia on tonic measures of pain (ie, ischemia). Indeed, Roelofs et al\textsuperscript{49} also failed to observe a reduction of electric pain after an E-only manipulation, but see Tang and Colagru\textsuperscript{19}, Wager et al.\textsuperscript{51} And finally, we may not have had the statistical power to detect the E-only group effect size due to our Bonferroni adjustment. Whatever the reason, our results are consistent with prior studies showing E+C produces the strongest placebo analgesia.

**Placebo Manipulations and NFR**

Given that placebo analgesia was noted in the E+C group, we expected NFR would also be inhibited. However, NFR was facilitated in E+C and E-only groups, and the degree of facilitation was correlated with ratings of expectations for pain relief (more expected relief = greater facilitation).

Mediation analysis was used to understand this complex modulation of NFR. Results suggested 2 processes were at work: a facilitatory effect but also an inhibitory effect that was also responsible for pain inhibition. Because the facilitatory effect was stronger, the net effect was facilitatory. Although unexpected, this explanation is consistent with the existence of both descending (brain to spinal cord) inhibitory and facilitatory circuits found in animals\textsuperscript{21,33} and humans.\textsuperscript{2,4,36}

Interestingly, our observation of simultaneous pain inhibition and NFR facilitation is consistent with several studies assessing the effects of attention and distraction on NFR. Edwards et al\textsuperscript{54} measured NFR thresholds and pain during rest and a video game and found the video game reduced pain but facilitated NFR (reduced NFR threshold). Similarly, other studies found that mental arithmetic reduces pain but facilitates the NFR.\textsuperscript{1,5,32,37} In another study, Roy et al\textsuperscript{50} found that viewing nonarousing, neutral pictures (vs a fixation point) led to reduced pain but increased NFR. More recently, Bjerre et al\textsuperscript{5} found that a Stroop task distractor enlarged the reflex receptive field (RRF, a putative marker of dorsal horn receptive fields assessed from NFR), whereas attention to the painful stimulus reduced the RRF. Given these findings, a shift in attention away from the painful stimuli may have contributed to the NFR facilitation we observed. This is consistent with the hypothesis of Atlas and Wager\textsuperscript{4} that expectancy effects work in part by directing attention away from pain. This could explain why the degree of NFR facilitation was correlated with expectations for pain relief.

Although our results are consistent with these studies of attention and NFR, they are inconsistent with the findings of Eippert et al.,\textsuperscript{17} who found that spinal neuron activation following noxious heat (assessed by fMRI) was inhibited by an E+C manipulation. Moreover, this same group used spinal imaging to show that distraction reduced heat pain-evoked spinal neuron activation,\textsuperscript{54} thus calling into question the role of attention in our findings. Currently, the reason for the discrepancies with our study is unclear; however, it may reflect that spinal imaging of heat pain (as used by Eippert et al.\textsuperscript{17}) assesses different aspects of spinal nociceptive processing than NFR. Indeed, animal studies have noted that interneurons presynaptic to motoneurons of the spinally-mediated tail-flick (animal reflex similar to NFR) have few long ascending collaterals to supraspinal centers.\textsuperscript{27} So, NFR may not assess the spinal processes that parallel inhibition of pain perception during placebo manipulations. Instead, NFR may assess a different pool of spinal neurons from those assessed by spinal imaging during placebo. Alternatively, as our mediation analysis suggests, NFR may be modulated by descending controls (ie, facilitatory processes) that do not affect the neurons assessed by spinal imaging of heat pain.

At this time, we cannot be sure why NFR diverges from pain and spinal imaging results. However, if our hypothesis is true that attention is involved, it may be advantageous to facilitate limb withdrawal during times when attention is shifted away from danger to help protect limbs while supraspinal processes are engaged by the distracting task. Future studies are needed to address these issues. For example, a study that employs spinal fMRI during NFR assessment could help determine if spinal neurons involved with NFR are inhibited or facilitated by placebo manipulations. Additionally, an NFR study that experimentally manipulates attention toward or away from the painful stimulus during a placebo manipulation could help determine if NFR facilitation is due to attentional processes.

**Placebo Manipulations and Autonomic Responses**

We found that SCR was inhibited, but only by E+C, whereas HR was not modulated by any manipulation. Although both outcomes reflect autonomic responses to painful input, SCR is primarily affected by sympathetic input,\textsuperscript{12} and HR is affected by both sympathetic...
and parasympathetic input. Our finding suggests that pain-evoked sympathetic responses may be more sensitive to placebo manipulations than those that also involve parasympathetic input.

Study Limitations
This study had a number of strengths including measurement of physiological and subjective outcomes, expectation and conditioning manipulations, statistically powerful multilevel models, and a large sample. Nonetheless, a few limitations should be noted beyond those already mentioned. First, we only included pain-free healthy participants, so our results may not generalize to clinical populations. Second, we used electric stimulations so we could measure NFR, but electric pain may not generalize to other types of pain. Despite this, studies that use electric stimuli find similar placebo-related reductions in VAS pain to those using heat and laser stimuli. Also, our use of only 1 stimulus intensity during the test phase may have led to habituation or sensitization that overshadowed placebo effects. Third, we only studied expectation and conditioning, but other processes can also play a role (eg, social modeling). And fourth, because we said we were using Lidocaine, it is possible that there were individual differences in participants’ prior experiences with it that might have affected their placebo responses.

Summary
In sum, E+C was the only manipulation that produced significant pain relief and reduced pain-evoked SCR. By contrast, NFR was facilitated by E+C and E-only manipulations. Mediation analyses suggested NFR facilitation was the sum of 2 opposing mechanisms: a facilitatory mechanism and an inhibitory mechanism responsible for pain inhibition. Because the facilitatory mechanism on NFR was stronger, the net effect was enhanced NFR. Together, these findings suggest placebo manipulations can have a complex effect on spinal nociception.

Disclosures
The project described was supported by the Oklahoma Center for the Advancement of Science and Technology (OCAST; Project Number HR12-100) awarded to Jamie L. Rhudy and by a National Science Foundation (NSF) Graduate Research Fellowship awarded to Yvette Güereca. The content is solely the responsibility of the authors and does not necessarily represent the official views of OCAST or NSF. The authors declare no competing financial interests.

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Jamie L. Rhudy, PhD, designed research, performed research, analyzed data, wrote the paper; Yvette M. Güereca, MA, designed research, performed research, wrote the paper; Bethany L. Kuhn, MA, performed research, wrote the paper; Shreela Palit, MA, performed research, wrote the paper; Magne Arve Flaten, PhD, designed research, wrote the paper.

Supplementary data
Supplementary data related to this article can be found at doi:10.1016/j.jpain.2018.04.012.

References


