



Cognitive self-regulation influences pain-related physiology

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Abstract

Cognitive self-regulation can shape pain experience, but its effects on autonomic responses to painful events are unclear. In this study, participants (N = 41) deployed a cognitive strategy based on reappraisal and imagination to regulate pain up or down on different trials while skin conductance responses (SCRs) and electrocardiogram activity were recorded. Using a machine learning approach, we first developed stimulus-locked SCR and electrocardiogram physiological markers predictive of pain ratings. The physiological markers demonstrated high sensitivity and moderate specificity in predicting pain across 2 data sets, including an independent test data set (N = 84). When we tested the markers on the cognitive self-regulation data, we found that cognitive self-regulation had significant impacts on both pain ratings and pain-related physiology in accordance with regulatory goals. These findings suggest that self-regulation can impact autonomic nervous system responses to painful stimuli and provide pain-related autonomic profiles for future studies.

Keywords: Pain, Self-regulation, Autonomic nervous system, SCR, ECG

1. Introduction

Cognitive self-regulation is a way of modulating pain and emotion by consciously changing one's thoughts and appraisals of sensations and the context in which they occur.^{1,10,19,26,27,36} Psychological interventions such as hypnosis and placebo have long been documented as effective methods of pain control,³¹ and several cognitive self-regulation techniques have also been documented for their ability to reduce pain (for a review, see Ref. 15). Some of the most prominent include mental imagery^{6,11} and *reappraisal*, which involves contextual reinterpretation of painful sensations.^{39,42} Beliefs and conditioning are known to have strong physiological impacts, such as in the case of placebo effects,^{24,33,47} but the relationship between conscious self-regulation and autonomic responses remains less understood. Here, we studied whether conscious, top-down self-regulation can impact pain-related autonomic physiology.

Painful events induce dramatic changes in the autonomic nervous system. These changes, including increases in blood pressure, heart rate, skin conductance, and pupil dilation,^{4,8,9,18,34} are consistent with sympathetic activation and parasympathetic withdrawal and believed to be mediated by interactions with parabrachial nociceptive pathways in the brainstem.^{5,7,40} However, quantifying pain-related autonomic responses in the context of cognitive pain modulation is challenging because autonomic changes are not specific to pain. During cognitive pain modulation, for example, the autonomic nervous system responds to noxious stimulation, but also to orientation to a stimulus,¹⁶ cognitive load,^{32,35} and stress.²² As a result, it is difficult to isolate cognitive effects on pain-related physiology from those related to other processes, including cognitive regulation itself.^{44,45} For example, regulation-induced reductions in pain-related autonomic responses could be masked by increases due to the cognitive demands of regulation itself, resulting in a null net effect.¹³ Therefore, to quantify the effects of cognitive regulation on pain physiology, there is a need to first identify components of autonomic responses that are as tightly linked to pain as possible, and then test the effects of regulation on these identified component measures. In EEG research, for example, component-based processes (eg, independent components analysis) are routinely used to decompose EEG responses into separate components, some of which reflect artifactual signals and others which reflect multiple task-related signals of interest.³⁰ To the best of our knowledge, however, this approach has not been applied to autonomic responses.

In the current study, we aimed to examine whether self-regulation influences pain-related physiology by developing pain-predictive physiological markers based on skin conductance response (SCR) and electrocardiogram (ECG) data. We reasoned that if pain-related autonomic signals could be isolated by extracting a temporal waveform (component) optimized to predict pain, it could provide a better test of whether cognitive regulation reduces this autonomic signal (**Fig. 1A**). In study 1, 41 participants engaged in self-regulation to increase or decrease

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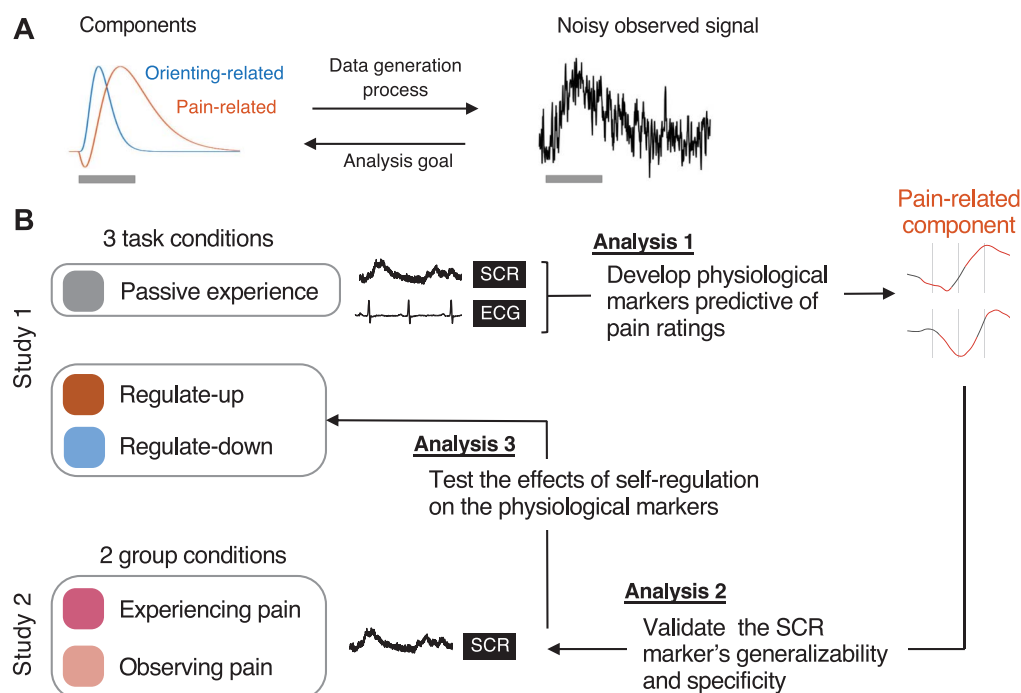


Figure 1. Concept and analysis pipeline. (A) Concept behind component-based analysis. Like other complex signals, autonomic responses may be composed of multiple underlying signals mixed together. Here, 2 components are illustrated, one unrelated and another related to pain reports. The observed signal is a mixture of the 2 plus noise. The gray bar shows the stimulus period. The goal of component-based analysis is to recover the underlying signals. In this case, we aimed to identify a waveform correlated with pain reports, separating this to the extent possible from non-pain-related signal and noise components. This allowed us to test self-regulation effects on the amplitude of the pain-related component for each participant. (B) The analysis plan includes 3 steps. Analysis 1: we developed pain-predictive measures based on SCR and ECG using study 1 ($N = 41$) data from the passive experience condition (no regulation). We used leave-one-subject-out cross-validation to estimate their accuracy in predicting pain when applied to new participants. Analysis 2: we validated the SCR marker with an independent data set (study 2, $N = 84$) to establish its provisional generalizability and specificity. We tested the marker on participants experiencing pain and observing their romantic partner experience pain. Analysis 3: we applied the pain-related autonomic measures to data collected during cognitive self-regulation in study 1, to test whether self-regulation changed pain-predictive physiological responses. We used cross-validation, so that the measures were only applied to subjects not used in measure development. ECG, electrocardiogram; SCR, skin conductance response.

pain while experiencing 6 different levels of painful heat (44.3–49.3°C in 1°C increments). Using data only from trials in which participants passively experienced thermal pain with no regulation instructions, we developed stimulus-locked SCR and ECG models predictive of pain ratings using principal component regression (PCR)²⁰ (analysis 1 in **Fig. 1B**). This first phase was designed to minimize influences of psychological processes (eg, expectations and self-regulation). In study 2, the resulting pain-related SCR measures (the strongest pain-predictive signal) were validated on an independent study data set with 42 pairs of romantic partners (total $N = 84$; analysis 2 in **Fig. 1B**). Here, 3 levels of painful heat (47, 48, and 49°C) were delivered to one participant in each pair (pain receiver), and the other person observed his or her partner experiencing pain (pain observer). Skin conductance responses were simultaneously recorded in both participants throughout. This design allowed us to assess the SCR measure's provisional sensitivity (response to first-person experience of pain) and specificity (response to observed pain, which is a nonpainful, but salient event) in an independent data set.⁴³ Finally, we applied the physiological pain markers to data during cognitive self-regulation in study 1 to test whether cognitive self-regulation affects SCR and ECG-based pain-predictive physiological measures (analysis 3 in **Fig. 1B**). We found that although cognitive regulation had no effect on autonomic responses in traditional analyses of event-related averages, it exerted bidirectional influences on autonomic measures optimized to be pain predictive.

2. Methods

2.1. Participants

2.1.1. Study 1

Forty-two healthy participants with no history of psychiatric, neurological, or pain disorders and no current pain were recruited for this experiment. A sample size of 42 was chosen to both ensure sufficient statistical power and minimize the order effects due to the different condition types (for the randomization procedure, see Task Design). Based on the effect size estimates from the previous study⁵² (Cohen's $d = 0.70$ for the self-regulation effect on self-reported pain), a sample size of 42 was estimated to provide 99.2% power. Participants were recruited through Craigslist.org and advertisements placed on the University of Colorado campus, and further contacted through telephone and email. One participant decided to stop the experiment halfway through because his skin was becoming too sensitive, leaving a final sample size of $N = 41$ (20 females, 21 males; age = 24.3 ± 5.6 [mean \pm SD] years; range: 18–41 years). Thirty-six participants were of Caucasian ethnicity, 2 participants Hispanic, 1 African American, 1 Asian, and 1 participant reported being mixed ethnicity. All participants provided written informed consent and were compensated \$12 an hour for their participation.

2.1.2. Study 2

Forty-eight romantic couples ($N = 96$) with no history of psychiatric, neurological, or pain disorders and no current pain

participated together in this experiment. Six participants from different couples had technical issues in SCR signal acquisition, leaving a final sample size of 42 couples ($N = 84$). One member of each couple experienced pain ($N = 42$, 21 females, age = 27.90 ± 6.29 years, range = 21–47). The other did not experience pain, but observed their partner experiencing pain ($N = 42$, 22 females, age = 27.45 ± 6.20 years, range = 21–47). Thirty eight participants were of Caucasian ethnicity, 7 Hispanic, 1 African American, 3 Native American, and 2 Asian American (and 33 preferred not to respond). All participants provided written informed consent and were compensated \$12 an hour for their participation.

2.2. Thermal stimulation

Thermal stimulation was delivered to participants using an ATS Pathway System (Medoc Ltd., Ramat Yishai, Israel) with a 16-mm Peltier thermode end-plate.

2.2.1. Study 1

Heat stimuli were delivered to 3 sites located on the middle forearm that alternated between runs. Each stimulation lasted 12.5 seconds, with 3-second ramp-up and 2-second ramp-down periods and 7.5 seconds at target temperature. Six levels of temperature were administered to the participants (level 1: 44.3°C ; level 2: 45.3°C ; level 3: 46.3°C ; level 4: 47.3°C ; level 5: 48.3°C ; and level 6: 49.3°C).

2.2.2. Study 2

Heat stimuli were delivered to 3 sites located on the participants' left leg. Each stimulation lasted 12 seconds, with 3.5-second ramp-up and 1-second ramp-down periods and 7.5 seconds at target temperature. Three levels of temperature were administered to the participants (level 1: 47°C ; level 2: 48°C ; and level 3: 49°C).

2.3. Rating scales

In study 1 and study 2, we used the same Generalized Labeled Magnitude Scale (gLMS) to assess pain intensity and unpleasantness.³ We used gLMS because it provides more valid across-group comparisons and more effectively captures variance in the high-pain range than the visual analogue or categorical scales. In the pain intensity gLMS, the anchors began with “No sensation” (0) to the far left of the scale, and continued to the right in a graded fashion with anchors of “Barely detectable” (1.4), “Weak” (6.1), “Moderate” (17.2), “Strong” (35.4), and “Very strong” (53.3), until “Strongest imaginable sensation of any kind” (100) on the far right. Although the pain intensity scale was unipolar, with increasing sensation from left to right, the pain unpleasantness scale was bipolar, with “Neutral” in the center, increasing unpleasantness progressing to the left, and increasing pleasantness progressing to the right. The same increments from the first scale were used in each direction, with the end anchor “Strongest unpleasantness imaginable of any kind” to the left, and “Strongest pleasantness imaginable of any kind” to the far right. The length of the scales was proportional such that the pain intensity scale was exactly half that of the pain unpleasantness scale. During the main task, the intermediate anchors were removed to eliminate anchor effects.²¹

2.4. General procedure

2.4.1. Study 1

Participants were given a brief overview of the experiment, which explained that they were participating in a study on the

physiological effects of cognitive pain regulation. After participants provided informed consent, we explained the gLMS rating scales used throughout the experiment to the participant and allowed them to practice using the scales. After a verbal explanation was given of what each anchor signified, participants were asked to explain the scale back to the experimenter to ensure that the participants understood the scale correctly.

Skin sites were then selected for stimulation based on a calibration procedure. During this procedure, pain intensity ratings were collected from a 47.3 and a 48.3°C stimulation to 8 different sites on the forearm to determine which sites on the arm produced the most reliable and similar pain ratings, and additionally to ensure that the heat was indeed painful, but not intolerable or excessive. The sites of the stimulations were randomized between 8 different locations evenly spaced between the wrist and the elbow on the volar surface of the left forearm. Three sites that the participant rated most similarly were chosen for use in the main procedure.

Following the calibration procedure was a regulation practice session, in which the experimenter asked the participant to relax, close their eyes, and follow along with a script read aloud by the experimenter designed to promote awareness of sensations and cognitive control over one's sensations (see Supplemental Methods, available at <http://links.lww.com/PAIN/A814>, for a full practice script). Participants were informed that an effective way to manipulate pain is to change the meaning of painful sensations, and then led through instructions designed to increase or decrease the experience of pain (see “Cognitive Regulation Instructions” below). These instructions were designed to give participants confidence in their ability to regulate pain because this is essential for any self-regulation technique to be effective. A full practice script can be found in the supplemental materials (available at <http://links.lww.com/PAIN/A814>).

The main task was grouped into 9 runs of 6 thermal stimulations each. There were 3 run conditions: a regulate-up condition, a regulate-down condition, and a passive control condition. Regulation condition for each run was pseudorandomized using a Latin-square method, resulting in 6 different sets of run orders, one of which was assigned to a participant before the experiment began. Each run began with a stimulation at 49.3°C to minimize the effects of within-run sensitization and habituation to heat.²³ After this stimulation, the regulation instructions for the run were shown on screen.

After it was clear that the participant understood the regulation instructions for the run, the stimulations began. The timing of a single trial can be seen in Fig. S1 (available at <http://links.lww.com/PAIN/A814>). Six temperatures between 44.3 and 49.3°C were administered in a randomized order, and after each heat stimulation, pain intensity and unpleasantness ratings were collected. The order in which the 2 rating scales were presented was randomized. After 3 trials, a reminder screen was presented, which provided encouragement and reminded the participant which type of regulation they were supposed to be using.

2.4.2. Study 2

Couples provided informed consent, and then each member of the couple was randomly assigned to be either the main participant, who experienced pain, or the partner, who did not experience pain but provided support. Specifically, partners observed the main participants receiving painful stimulation (“Present” condition) or provided supportive touch (“Hand-holding” or “Gentle stroking” conditions) (see Supplemental Methods, available at <http://links.lww.com/PAIN/A814>, for

a detailed task design for study 2). The current study uses data only from the “Present” condition. The main participants underwent the same rating scale introduction as study 1. Skin site selection was fixed a priori before the experiment and was the same for each person (on the outer left leg, right below the knee, in the center of the leg, and right above the ankle). Temperatures were also determined a priori to be 47, 48, and 49°C.

2.5. Cognitive regulation instructions (study 1)

The regulation instructions (see Supplemental Materials, available at <http://links.lww.com/PAIN/A814>, for full script) combined (1) instructions designed to enhance participants’ pain regulation self-efficacy² (eg, “you can develop a powerful relationship with your sensations,” “it will become much easier to manipulate your experience once you have stronger sensations to work with”) with (2) instructions to engage in specific forms of imagery targeting several aspects of pain, including appraisals of its intensity and harmfulness.

In the regulate-down condition, participants were instructed to engage in imagery and appraisals that minimized danger and enhanced the counterfactual pleasantness of the stimulation, eg, “Focus on the part of the sensation that is pleasantly warm, like a blanket on a cold day, and the aspects of the heat that are calming, soothing, and relaxing”; “...turn down the dial of your pain sensation.” They also emphasized imagery that promotes acceptance and disengagement from negative affect, eg, “allow the pain and heat to be carried away, flowing away from your body”; “visualize the powerful warmth flowing and spreading through you as it gives you energy and life.” In the regulate-up condition, participants were instructed to engage in imagery intended to engage negative affect and enhance appraisals of harm, eg, “Pay attention to the burning, stinging, and shooting sensations”; “imagine how unpleasant the pain is”; “You can use your mind to turn up the dial of the pain”; “visualize your skin sizzling, melting, and bubbling as a result of the intense heat.” In the neutral condition, participants were explicitly instructed not to attempt to regulate the pain, and instead to focus on accurately perceiving the sensations, for example, “Try not to regulate or change your sensation, but instead accurately rate what each sensation was like as you felt it.”

These strategies were chosen because of their effectiveness in published^{6,11,15,52} and ongoing work, and are related to several types of strategies described in the literature. For example, for the regulate-down condition, asking participants to “imagine that the thermal stimulations are less painful than they are” is related to what previous literature has described as *pain acknowledging*⁴⁶ or *reinterpretation*,¹¹ whereas asking participants to focus on aspects of the heat that are “pleasantly warm, like a blanket on a cold day” is similar to *pleasant imagery* or *dramatized coping*, which focuses on the narrative context or situational meaning surrounding stimulation.¹⁵ For the regulate-up condition, asking participants to “focus on how unpleasant the pain is” is a negative form of *pain acknowledging*,⁴⁶ whereas “picture your skin being held up against a glowing hot metal or fire” is related to *dramatized coping*.¹⁵ We intentionally made our self-regulation instructions broad enough to include multiple components of self-regulation strategies because the aim of the current study is to examine the overall effects of self-regulation on pain physiology, and not to compare the effects of various self-regulation strategies. Also, an important commonality between the regulate-up and regulate-down instructions is their emphasis on consciously attending to the stimuli and changing their meaning, instead of directing attention elsewhere, such as in distraction-based pain regulation strategies.

Participants engaged in a postexperiment description of the strategies they actually used, which were coded in relation to 8 common strategies described in the literature. An analysis of the strategies used by participants can be found in Fig. S2 (available at <http://links.lww.com/PAIN/A814>).

2.6. Data acquisition

2.6.1. Electrocardiogram

Electrocardiogram activity was recorded using two 11-mm Ag/AgCl electrodes (Biopac systems, Goleta, CA) placed on the right clavicle and left lower rib area, and sampled at 500 Hz. A maximal overlap discrete wavelet transform (modwt.m, available in the MATLAB wavelet toolbox) was used to enhance ECG signal relevant to the QRS complex, and local maxima corresponding to the R-peak of the ECG signal were isolated using the findpeaks function (findpeaks.m) of the MATLAB signal processing toolbox. Peaks were then checked manually to identify and remove outliers. Interbeat intervals (IBI) were then calculated based on differences between adjacent peaks (Fig. S3a, available at <http://links.lww.com/PAIN/A814>).

2.6.2. Skin conductance response

Skin conductance response activity was recorded using 11-mm Ag/AgCl electrodes (Biopac systems) attached to the medial phalanges of the middle and ring fingers of the left hand. Data were sampled at 500 Hz in study 1, and at 1000 Hz in study 2. The difference in sampling rate between study 1 and study 2 is not expected to affect our findings because the signal of interest and other noise components are located at much lower frequencies.

2.7. Data analysis

2.7.1. Preprocessing

Physiological data (SCR activity and ECG-IBI time-series data) were put through a low-pass filter, 5 Hz for SCR²⁴ and 1 Hz for ECG-IBI,¹⁴ to remove noise, and then downsampled to 25 Hz (Fig. S3a, available at <http://links.lww.com/PAIN/A814>).

2.7.2. Grand average

For each trial, a baseline was created by averaging physiological time-series data from 3 seconds before the thermal stimulation onset. A stimulus-locked physiological response was generated by subtracting the baseline value from the data in the 20-second period after the stimulation onset (Fig. S3b, available at <http://links.lww.com/PAIN/A814>). The stimulus-locked physiological responses were averaged across regulation conditions to create a mean physiological response for each temperature (Figs. 2A and B).

2.7.3. Physiological pain marker development (analysis 1)

To develop SCR and ECG markers for pain, we first created features by averaging the stimulus-locked physiological responses in only the *passive experience* runs. This resulted in a 6 (temperature levels) × 500 (25 Hz × 20 seconds) average time-series matrix for each participant. Mean pain ratings for each participant corresponding to the 6 temperatures were made into a 6 × 1 vector. These data were then concatenated across participants and used for subsequent modeling (see Fig. S3, available at <http://links.lww.com/PAIN/A814>, for more details). Then, PCR was used to create an SCR and ECG time-course model predictive of pain ratings.²⁰ We chose to use PCR because

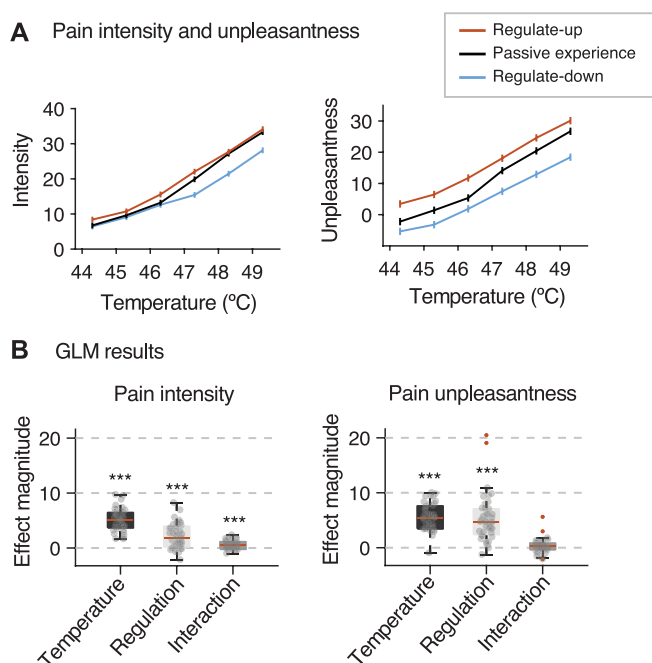


Figure 2. Effects of cognitive self-regulation on pain ratings. (A) Mean intensity and unpleasantness ratings for each temperature in the regulate-up (red), passive experience (black), and regulate-down conditions (blue). Error bars represent within-subject standard errors of the mean (SEM). For pain ratings, we used general labeled magnitude scale (gLMS).³ (B) Effect magnitude (y-axis) represents regression coefficients (β) from a multilevel general linear model. Each dot shows each individual's regression coefficient. The general linear model analyses revealed that temperature (stimulus intensity, °C) and regulation (coded regulate-up, passive experience, and regulate-down as 1, 0, and -1, respectively) had significant main effects on both pain intensity and unpleasantness ratings. In addition, a significant interaction was found between temperature and regulation for the pain intensity ratings, but not for unpleasantness ratings. *** $P < 0.001$; bootstrap tests (10,000 iterations) were used for significance testing.

it works well with the data in which the number of features (or predictors) is greater than the number of observations and the features are intercorrelated. The PCR was achieved in 2 steps: First, principal component analysis was conducted to reduce dimensions of features using covariance information among SCR and ECG time-series data. Second, multiple linear regression was conducted on the component space (ie, using component scores) to predict pain ratings. In this step, we used a reduced number of components (2–3 components depending on the models) based on a leave-one-participant-out cross-validation procedure (see Fig. S4, available at <http://links.lww.com/PAIN/A814>, for details). The regression model was then projected to the time space, yielding a time-series pattern of predictive weights. Bootstrap tests were conducted to identify which time points reliably contributed to the prediction.¹² For each iteration of bootstrap tests, we randomly resampled participants with replacement and trained PCR on each resampled data set. After 10,000 iterations, we calculated the P -values based on the sampling distribution of predictive weights. For the correction for multiple comparisons, we used false discovery rate $q < 0.05$.

2.7.4. Testing the physiological marker (analysis 2 and analysis 3)

For testing the marker on study 1's regulation data, we used a leave-one-participant-out cross-validation procedure. The time-series weights predictive of pain were derived based on

physiological data from passive experience conditions for all participants except for one out-of-sample participant. These weights were then tested on the out-of-sample participant's data in all 3 conditions by calculating the dot product between the time-series weights and stimulus-locked physiological data. This process was done iteratively for each participant. Note that the data from regulation runs were not included in the model developing procedure at all. For testing the marker on study 2 data, which is completely independent from the model developing procedure, we calculated the dot product between the time-series weights and stimulus-locked physiological data.

3. Results

3.1. Behavioral results of cognitive self-regulation

As shown in **Figure 2**, we found that both the stimulus intensity of noxious heat and cognitive self-regulation strongly modulated ratings of both pain intensity and unpleasantness, replicating and extending previous findings.⁵² Stimulus intensity had similar effects on ratings of both pain intensity and unpleasantness (intensity ratings: $\hat{\beta}_{\text{temperature}} = 5.01 \pm 0.31$ [mean \pm SEM], $z = 3.86$, $P < 0.001$ in a bootstrap test with 10,000 times resampling; unpleasantness ratings: $\hat{\beta}_{\text{temperature}} = 5.50 \pm 0.38$, $z = 3.71$, $P < 0.001$). Self-regulation to increase vs decrease pain influenced both intensity and unpleasantness ratings in accordance with regulatory goals, but influenced pain unpleasantness more strongly than intensity (unpleasantness: $\hat{\beta}_{\text{regulation}} = 5.19 \pm 0.68$, $z = 4.54$, $P < 0.0001$; intensity: $\hat{\beta}_{\text{regulation}} = 2.12 \pm 0.36$, $z = 3.94$, $P < 0.0001$). The self-regulation effects on pain unpleasantness ratings were comparable in magnitude with a 1°C change in heat stimulus intensity, $\hat{\beta}_{\text{regulation}} = 5.19$ vs $\hat{\beta}_{\text{temperature}} = 5.50$. Self-regulation effects on pain intensity were larger for more intense stimuli, as evidenced by a small but significant stimulus intensity \times regulation condition interaction, $\hat{\beta}_{\text{interaction}} = 0.54 \pm 0.12$, $z = 3.81$, $P < 0.001$. However, we found only marginal interaction effects for pain unpleasantness ratings, $\hat{\beta}_{\text{interaction}} = 0.30 \pm 0.20$, $z = 1.82$, $P = 0.069$. Significant modulation effects were also observed when regulate-up and regulate-down were separately compared with passive experience (all P values < 0.01 for both intensity and unpleasantness ratings; please see Table S1, available at <http://links.lww.com/PAIN/A814>, for results and statistics).

3.2. Autonomic effects of cognitive self-regulation without isolating the pain-related component

When the stimulus-locked SCR and ECG data (20 seconds after stimulus onset) were averaged for each temperature level, we observed reliable stimulus intensity-related increases in SCR amplitude and heart rate (**Figs. 3A and B**). In addition, when the SCR and ECG data were averaged within each regulation condition and compared, we observed small increases and decreases in SCR amplitude and heart rate for regulate-up and regulate-down, respectively (Fig. S5, available at <http://links.lww.com/PAIN/A814>). Regulation-induced physiological changes were marginally significant or nonsignificant; for example, when using baseline-to-peak amplitudes for regulate-up vs regulate-down, SCR: $\hat{\beta}_{\text{regulation}} = 0.03 \pm 0.01$, $z = 1.93$, $P = 0.053$, ECG: $\hat{\beta}_{\text{regulation}} = -0.002 \pm 0.002$, $z = -0.63$, $P = 0.529$; when using the area-under-the-curve, SCR: $\hat{\beta}_{\text{regulation}} = 4.43 \pm 4.02$, $z = 1.14$, $P = 0.254$, ECG: $\hat{\beta}_{\text{regulation}} = -1.86 \pm 0.92$, $z = -2.03$, $P = 0.043$. These summary measures do not, however, permit a test of whether cognitive self-regulation impacts *pain-related* physiology, due to potential masking by physiological responses to cognitive regulation demand itself, as discussed above.

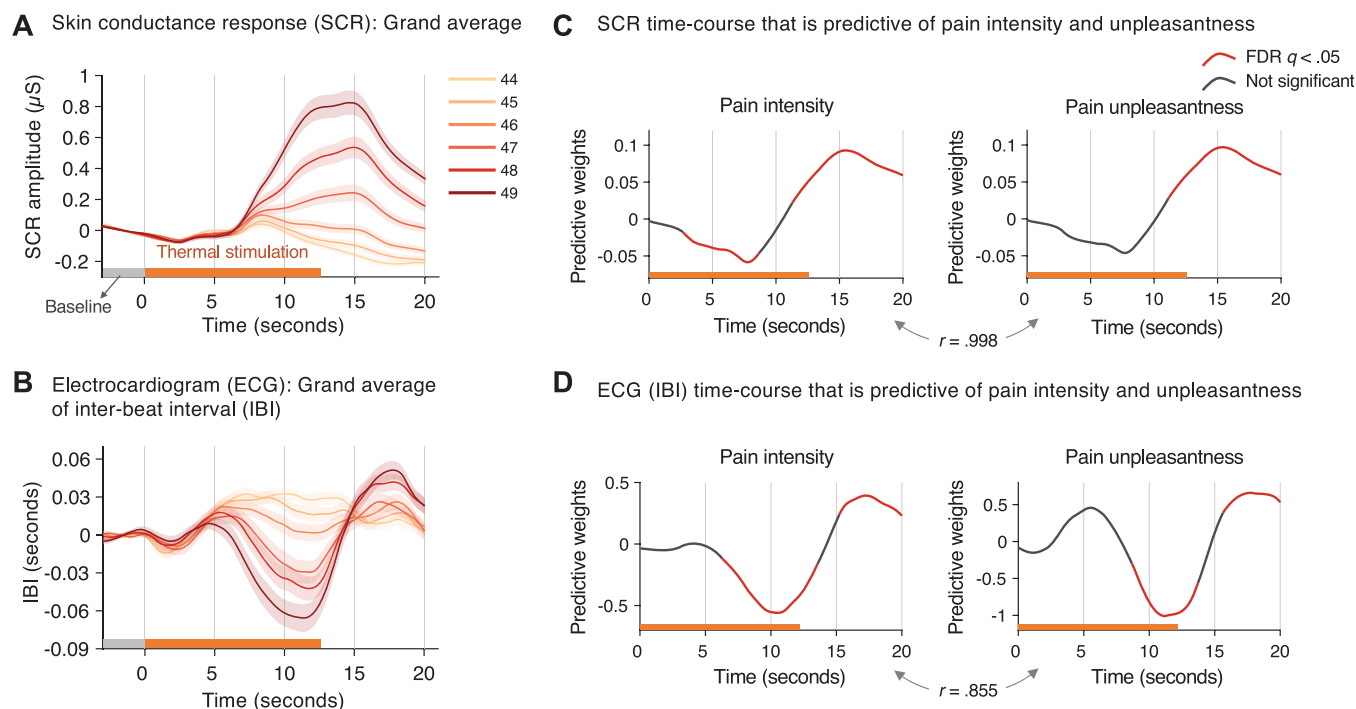


Figure 3. Skin conductance response (SCR) and ECG's IBI time-courses predictive of pain ratings. (A) Stimulus-locked grand average of SCRs across participants for each temperature. Data from 3 seconds before the thermal stimulation onset were used as a baseline (see Methods for details). Shading represents SEM. (B) Grand average of interbeat interval (IBI) calculated from electrocardiogram (ECG). (C) Skin conductance response time-course markers most predictive of pain ratings (left: pain intensity and right: pain unpleasantness). We identified these markers using principal component regression based on data from passive experience runs. Regions in red represent time points that provided significantly reliable contributions to the prediction from bootstrap tests (10,000 iterations) at $q < 0.05$, false discovery rate (FDR). Skin conductance response time courses for pain intensity and unpleasantness were almost identical, $r = 0.998$. (D) Electrocardiogram (IBI) time-course markers most predictive of pain ratings (left: pain intensity and right: pain unpleasantness). The correlation between ECG time courses for pain intensity and unpleasantness was also very high, $r = 0.855$.

3.3. Analysis 1: developing pain-predictive physiology markers based on SCR and electrocardiogram temporal dynamics (study 1)

To examine autonomic changes more directly linked to pain, we first developed pain-predictive SCR and ECG markers using data from passive experience runs (ie, pain without regulation). We then tested these markers on data from the regulation runs using a leave-one-participant-out cross-validation procedure.

As shown in **Figures 3C and D**, the bootstrap test results showed that, for the SCR model, the time points between 2.7 and 8.6 seconds and between 11.3 and 20 seconds after the heat onsets were reliable predictors of pain intensity across participants ($q < 0.05$ false discovery rate corrected), and the time points between 11.1 and 20 seconds made reliable contributions to the prediction of pain unpleasantness. For the ECG model, the time points between 6.3 and 13.5 seconds and between 15.2 and 20 seconds were reliable predictors of pain intensity ratings, and the time points between 8.7 and 13.7 seconds and between 15.6 and 20 seconds were reliable predictors of pain unpleasantness ratings.

Cross-validated test results on the held-out participants' data from passive experience runs showed that the mean within-participant correlations (across averaged trial responses for each stimulus intensity) of predicted with observed pain were $r = 0.83 \pm 0.025$, $P < 0.0001$ (based on a bootstrap test with 10,000 resamples) for the SCR pain intensity model and $r = 0.76 \pm 0.047$, $P < 0.0001$ for the SCR unpleasantness model. For ECG models, the mean prediction–outcome correlations were $r = 0.60 \pm 0.073$, $P < 0.0001$ for the pain intensity model and $r = 0.55 \pm$

0.083 , $P < 0.0001$ for the pain unpleasantness model (Fig. S4, available at <http://links.lww.com/PAIN/A814>). Thus, both SCR and ECG reliably predicted within-person variation in pain reports across trials.

We then tested whether these markers predicted pain reports during regulation runs, using cross-validation to apply the models only to new (held-out) participants (**Fig. 4**). Because the data from held-out participants' regulation runs were never included in the model development process, they provided an unbiased test of whether the SCR and ECG models are predictive of pain ratings in this sample. The mean prediction–outcome correlations were $r = 0.82 \pm 0.020$, $P < 0.0001$, and $r = 0.73 \pm 0.039$, $P < 0.0001$, for SCR pain intensity and unpleasantness models, and $r = 0.67 \pm 0.045$, $P < 0.0001$, and $r = 0.65 \pm 0.046$, $P < 0.0001$, for ECG pain intensity and unpleasantness models, respectively. Thus, the correlations between autonomic responses and pain reports are similar for all regulation conditions. We address effects of regulation on the amplitude of marker responses in analysis 3, below.

3.4. Analysis 2: testing the SCR marker on an independent data set (study 2)

Grand averages and baseline-to-peak amplitudes of stimulus-locked SCR showed enhanced responses to increasing stimulus intensity in both pain receivers and their partners who observed pain (**Figs. 5A–C**). As shown in **Figure 5C**, the baseline-to-peak SCR amplitude significantly increased for 49 vs 47°C and 48 vs 47°C in both pain receivers ($\beta_{49 \text{ vs } 47^\circ\text{C}} = 0.34 \pm 0.08$, $z = 4.98$, $P < 0.0001$, $\beta_{48 \text{ vs } 47^\circ\text{C}} = 0.18 \pm 0.07$, $z = 5.76$, $P < 0.0001$) and

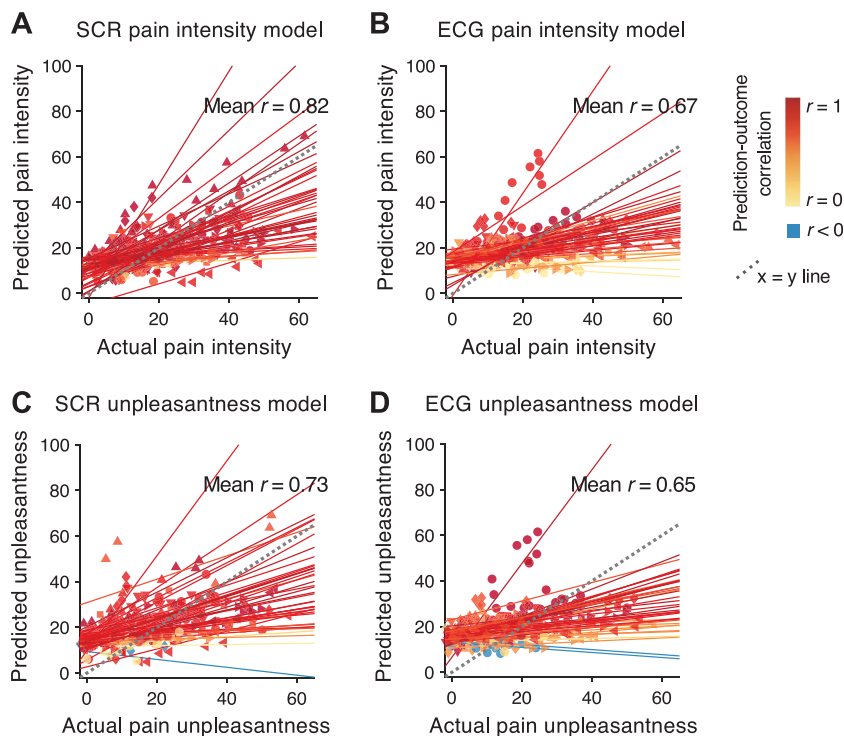


Figure 4. Testing the predictive models on held-out participants' regulation data. Test results of the skin conductance response (SCR) and ECG markers on data from regulation runs (12 trials per person). Note that no data from regulation runs were used for marker development. In addition, leave-one-participant-out cross validation was used to prevent any possibility of overestimation of model performance due to dependency among data from same individuals. Actual pain intensity (A and B) or actual pain unpleasantness (C and D) vs cross-validated predicted pain intensity or unpleasantness are shown in the plots, and each line or symbol represents individual participant's data. The line color represents a correlation level for each participant (red: higher r ; yellow: lower r , and blue: $r < 0$), and the dotted line represents points where the actual pain ratings are same with the predicted ratings (ie, $x = y$). ECG, electrocardiogram.

pain observers ($\hat{\beta}_{49 \text{ vs } 47^\circ\text{C}} = 0.19 \pm 0.05$, $z = 4.79$, $P < 0.0001$, $\hat{\beta}_{48 \text{ vs } 47^\circ\text{C}} = 0.15 \pm 0.05$, $z = 4.12$, $P < 0.0001$). For 49 vs 48°C, the baseline-to-peak amplitude showed significant increases only in pain receivers, $\hat{\beta}_{49 \text{ vs } 48^\circ\text{C}} = 0.16 \pm 0.08$, $z = 2.83$, $P = 0.0046$, not pain observers, $\hat{\beta}_{49 \text{ vs } 48^\circ\text{C}} = 0.04 \pm 0.08$, $z = 0.51$, $P = 0.608$. In addition, experiencing pain induced larger overall SCR changes than observing pain, $\hat{\beta}_{\text{experience vs observe}} = 0.15 \pm 0.06$, $z = 2.66$, $P = 0.0077$. Thus, standard SCR amplitudes showed significant increases proportional to stimulus intensity for both experienced and observed pain, and limited selectivity for pain experience.

When we tested the SCR pain intensity marker from analysis 1, the SCR marker tracked the changes in first-person pain better than in observed pain, demonstrating the marker's differential sensitivity and specificity to first-person pain. The SCR marker showed significant increases for 48 vs 47°C, 49 vs 48°C, and 49 vs 47°C in the participants who experienced pain, $\hat{\beta}_{48 \text{ vs } 47^\circ\text{C}} = 2.84 \pm 0.80$, $z = 5.58$, $P < 0.0001$, $\hat{\beta}_{49 \text{ vs } 48^\circ\text{C}} = 2.53 \pm 1.08$, $z = 4.71$, $P < 0.0001$, and $\hat{\beta}_{49 \text{ vs } 47^\circ\text{C}} = 5.37 \pm 1.17$, $z = 5.44$, $P < 0.0001$, respectively (Fig. 5D). Effect sizes for 1°C increase ranged from Cohen's $d = 0.73$ to $d = 0.86$. These increases were comparable in magnitude with the increases in pain ratings, $\hat{\beta}_{48 \text{ vs } 47^\circ\text{C}} = 3.03 \pm 0.67$, $z = 4.60$, $P < 0.0001$, $\hat{\beta}_{49 \text{ vs } 48^\circ\text{C}} = 1.17 \pm 0.50$, $z = 2.07$, $P = 0.0386$, and $\hat{\beta}_{49 \text{ vs } 47^\circ\text{C}} = 4.21 \pm 0.59$, $z = 3.74$, $P < 0.001$ (Fig. 5E). Effect sizes for 1°C increase on pain ratings were $d = 0.32$ to $d = 0.71$. Conversely, during observed pain, the SCR marker showed nonsignificant or marginal increases for 48 vs 47°C and 49 vs 48°C, $\hat{\beta}_{48 \text{ vs } 47^\circ\text{C}} = 0.54 \pm 0.58$, $z = 0.98$, $P = 0.33$, and $\hat{\beta}_{49 \text{ vs } 48^\circ\text{C}} = 1.68 \pm 0.97$, $z = 1.94$, $P = 0.052$, respectively (Fig. 5D). The SCR marker did show a significant, but

relatively small, increase for 49 vs 47°C during observed pain, $\hat{\beta}_{49 \text{ vs } 47^\circ\text{C}} = 2.22 \pm 0.76$, $z = 3.58$, $P < 0.001$. The effect sizes for observed 1°C increase were $d = 0.15$ and $d = 0.30$, respectively, approximately 3 times lower than those for first-person pain. Overall, our SCR marker showed strong increases for pain experience and weak responses for pain observation, demonstrating good sensitivity, but a moderate level of specificity in this context.

To further characterize stimulus intensity-related increases in the SCR marker, we conducted pairwise classification tests, in which pain ratings and SCR marker responses between 2 levels of stimulus intensity (ie, 49 vs 47°C, 48 vs 47°C, and 49 vs 48°C) were compared, and the condition with the higher levels of pain rating or SCR marker response was predicted to be the more intense (Fig. 5F). During somatic pain experience, the SCR marker demonstrated high accuracy in forced-choice discrimination of different levels of stimulus intensity; for 49 vs 47°C, accuracy = $92.9\% \pm 4.0$, $P < 0.0001$; for 48 vs 47°C, accuracy = $81.0\% \pm 6.1$, $P < 0.0001$; and for 48 vs 49°C, accuracy = $73.8\% \pm 6.8$, $P = 0.0029$. These results were comparable with the performance obtained when using self-reported pain to predict which condition had a more intense stimulus: for 49 vs 47°C, accuracy = $95.2\% \pm 3.3$, $P < 0.0001$; for 48 vs 47°C accuracy = $81.0\% \pm 6.1$, $P < 0.0001$; and for 49 vs 48°C = $81.0\% \pm 6.1$, $P < 0.0001$. For observed pain, the marker response showed worse classification performance than the response to somatic pain, for 49 vs 47°C, accuracy = $71.4\% \pm 7.0$, $P = 0.0079$; for 48 vs 47°C accuracy = $50.0\% \pm 7.7$, $P = 1.00$; and for 49 vs 48°C = $66.7\% \pm 7.3$, $P = 0.0436$. Although some of the contrasts were significantly above the chance level, if we corrected these test

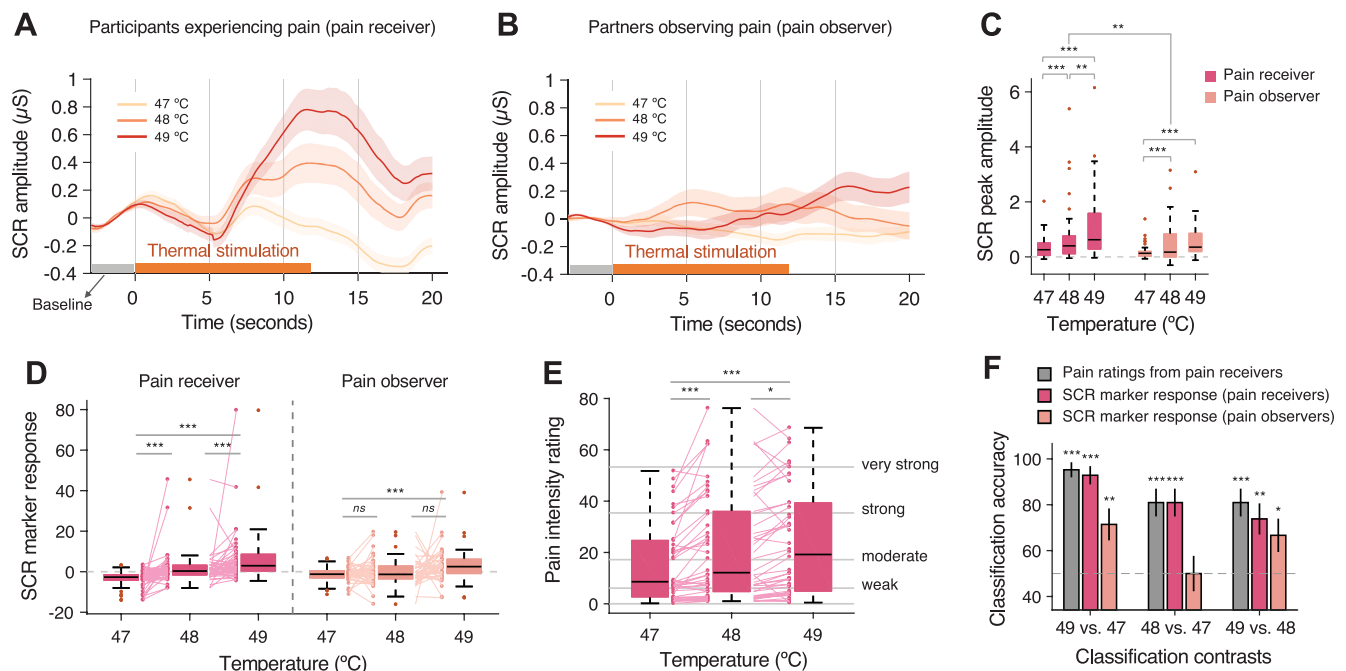


Figure 5. Validation of markers on an independent data set. We tested the sensitivity and specificity of the SCR pain intensity marker using data from study 2. In study 2, participants received thermal heat stimulations on their leg (pain receiver), and their romantic partners observed the main participants experiencing pain (pain observer). (A) Mean SCR amplitudes of pain receivers during 3 different stimulation temperatures. Shading represents SEM. (B) Mean SCR amplitudes of pain observers during the same trials. (C) Baseline-to-peak SCR amplitudes from pain receivers and observers for 3 temperature levels. (D) Skin conductance response marker responses from pain receivers and observers for 3 temperature levels. Lines connect the same individuals' pain ratings. (E) Mean pain intensity ratings from pain receivers for 3 temperatures. Lines connect the same individuals' pain ratings. (F) The 2-choice classification accuracy for stimulus intensity contrasts using (1) pain ratings from pain receivers, (2) SCR marker responses of pain receivers, and (3) SCR marker responses of pain observers. *** $P < 0.001$, ** $P < 0.001$, * $P < 0.05$ (two-tailed); bootstrap (C, D, and E) and binomial tests (F) were used for significance testing.

results for multiple comparisons (9 tests in this classification) using a Bonferroni method (ie, corrected $\alpha = 0.05/9 = 0.0056$), all the classification results for observed pain became non-significant, whereas all first-person pain results remained significant.

3.5. Analysis 3: the effects of cognitive self-regulation on the pain-predictive physiology markers (study 1)

To test whether cognitive self-regulation has significant impacts on pain-related physiology, we conducted multilevel general linear models using the SCR and ECG marker response calculated from study 1 data as outcome measures and tested the effects of stimulus intensity, self-regulation (regulate-up vs regulate-down), and their interaction.

Both stimulus intensity and self-regulation had significant effects on the SCR and ECG pain intensity and unpleasantness markers (Fig. 6 and Fig. S6, available at <http://links.lww.com/PAIN/A814>); for the SCR intensity marker, $\hat{\beta}_{\text{temperature}} = 2.50 \pm 0.32$, $z = 4.99$, $P < 0.0001$, $\hat{\beta}_{\text{regulation}} = 0.61 \pm 0.18$, $z = 4.34$, $P < 0.0001$, for the SCR unpleasantness marker, $\hat{\beta}_{\text{temperature}} = 2.78 \pm 0.38$, $z = 5.04$, $P < 0.0001$, $\hat{\beta}_{\text{regulation}} = 0.61 \pm 0.19$, $z = 4.11$, $P < 0.0001$, for the ECG intensity marker, $\hat{\beta}_{\text{temperature}} = 1.50 \pm 0.23$, $z = 4.95$, $P < 0.0001$, $\hat{\beta}_{\text{regulation}} = 0.62 \pm 0.15$, $z = 4.16$, $P < 0.0001$, and for the ECG unpleasantness marker, $\hat{\beta}_{\text{temperature}} = 2.27 \pm 0.29$, $z = 4.13$, $P < 0.0001$, $\hat{\beta}_{\text{regulation}} = 0.87 \pm 0.23$, $z = 4.09$, $P < 0.0001$. Regulation effect sizes (up vs down) were in the "moderate to large" range, between $d = 0.63$ and $d = 0.67$ for all models.

Similar to the results with pain intensity ratings, the effects of self-regulation on SCR and ECG pain intensity markers showed significant interactions with stimulus intensity, $\hat{\beta}_{\text{interaction}} = 0.34 \pm 0.09$, $z = 3.90$, $P < 0.0001$, and for the ECG intensity marker,

$\hat{\beta}_{\text{interaction}} = 0.13 \pm 0.06$, $z = 2.43$, $P = 0.015$, suggesting that the self-regulation effects on pain intensity-related physiology increase as stimulus intensity increases. For the pain unpleasantness markers, a significant interaction was observed in SCR, $\hat{\beta}_{\text{interaction}} = 0.37 \pm 0.10$, $z = 3.65$, $P < 0.001$, but not in ECG, $\hat{\beta}_{\text{interaction}} = 0.17 \pm 0.11$, $z = 1.71$, $P = 0.087$.

3.6. Estimating regulation effect sizes in terms of effective changes in stimulus intensity

We standardized the beta coefficients of self-regulation relative to those of stimulus temperature, to compare the effect magnitudes of self-regulation on different outcome variables. We used the effect size of a 1°C change in temperature as a reference; for example, the relative effect magnitude of 0.42 for the effects of self-regulation on pain intensity ratings and 0.94 on pain unpleasantness ratings are comparable with the effects of a 0.42 and 0.94°C change in temperature on pain intensity and unpleasantness, respectively. As shown in Figure 7, the self-regulation effects on ECG markers were larger in magnitude than the regulation effects on SCR markers and were comparable with the effects on pain intensity ratings; relative effect magnitude for SCR intensity marker = 0.24°C , SCR unpleasantness marker = 0.22°C , ECG intensity marker = 0.41°C , and ECG unpleasantness marker = 0.38°C . Thus, self-regulation has the largest effects on pain unpleasantness (0.94°C), followed by pain intensity (0.42°C) and heart rate (0.38 – 0.41°C), followed by SCR (0.22 – 0.24°C).

Unlike the effects on pain ratings, the self-regulation effects on physiological markers seem largely driven by the regulate-up condition rather than the regulate-down condition, but the differences in beta coefficients between regulate-up vs passive

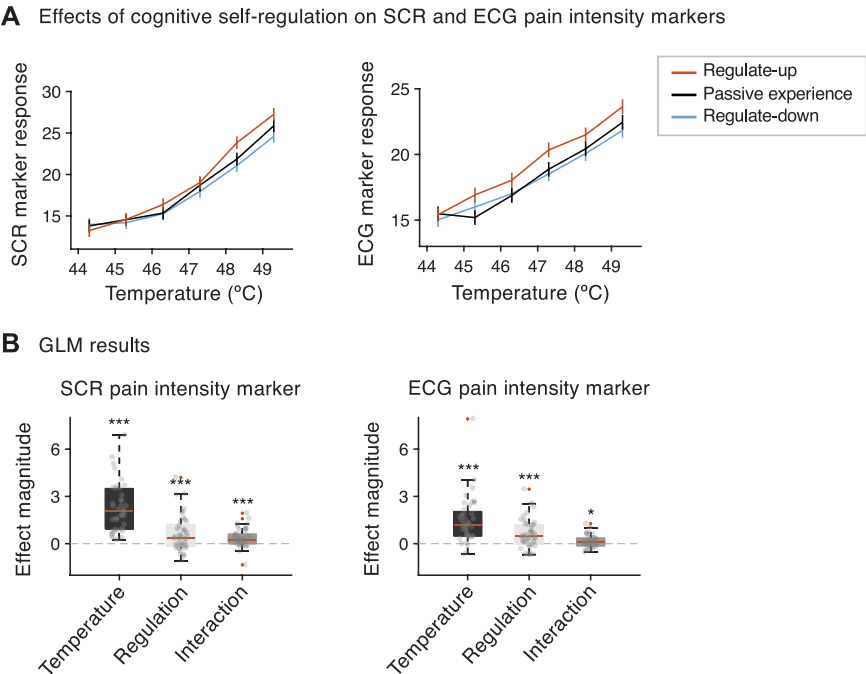


Figure 6. Effects of cognitive self-regulation on skin conductance response (SCR) and ECG markers. (A) This is an analogous plot to Fig. 1A’s left panel, but here we used predicted pain scores based on SCR and ECG pain intensity models. Error bars represent within-subject SEM. (B) Multilevel general linear model results. Similar to the behavioral findings, both stimulus intensity and cognitive self-regulation had significant effects on SCR and ECG marker responses, indicating that cognitive self-regulation has significant effects on pain-related autonomic physiology. *** $P < 0.001$; bootstrap tests (10,000 iterations) were used for significance testing. ECG, electrocardiogram.

experience and passive experience vs regulate-down were not significant; for the SCR intensity marker, mean difference ($\beta_{\text{regulate-up vs passive}} - \beta_{\text{passive vs regulate-down}}$) = 0.18, $t_{40} = 0.30$, $P = 0.762$, for the SCR unpleasantness marker, mean difference = 0.23, $t_{40} = 0.34$, $P = 0.732$, for the ECG intensity marker, mean difference =

0.95, $t_{39} = 1.74$, $P = 0.090$, and for the ECG unpleasantness marker, mean difference = 0.74, $t_{40} = 0.95$, $P = 0.340$ (Table S1, available at <http://links.lww.com/PAIN/A814>).

In sum, increasing the intensity of painful stimuli had a strong effect on autonomic responses, allowing us to identify a pain-

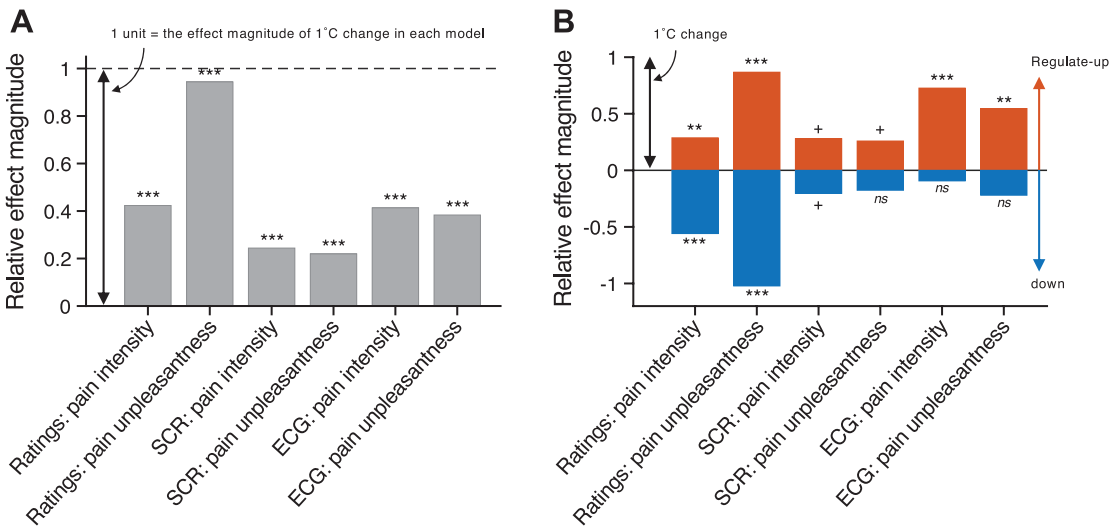


Figure 7. Relative effect magnitudes for different outcome variables. To compare the effect magnitudes across different models, we calculated relative effect magnitudes of self-regulation on different outcome measures by comparing them with the effects of stimulus intensity. In other words, in both of these plots, 1 unit in the y-axis indicates the effect magnitude comparable with the effects of a 1°C change in stimulus intensity. The x-axis shows the various outcome measures assessed in the study; SCR- and ECG-related measures are responses in trained, pain-predictive models. (A) Relative effect magnitude for the average changes by regulate-up vs regulate-down. For example, the relative effect magnitude of 0.94 for pain unpleasantness ratings can be interpreted that regulate-up and regulate-down on average had effects on pain unpleasantness comparable with the effects of 0.94°C change in stimulus intensity. (B) Relative effect magnitude separately for each regulation direction. The significance test results were from bootstrap tests (10,000 iterations) of general linear models for different outcome variables. $^{ns}P > 0.1$, $^{+}P < 0.1$, $^{**}P < 0.01$, $^{***}P < 0.001$. ECG, electrocardiogram.

predictive temporal waveform in both ECG and SCR that can be applied to new individuals and studies to evaluate a pain-related component of responses to noxious stimuli. Cognitive self-regulation significantly modulated these pain-predictive autonomic markers, with effects that appeared strongest for regulating pain up.

4. Discussion

Although the effects of cognitive interventions on self-reported pain are well documented,¹⁵ their effects on autonomic physiology are less clear. A historical problem with assessing autonomic effects is that they reflect a mix of components related to orienting, arousal, and pain. Here, we identified a pain-related component of autonomic responses to noxious stimuli that is distinct from the overall SCR and heart-rate responses to noxious events. The component waveform involves early decreases and late increases just after stimulus offset, effectively subtracting late from early activity during stimulation. This late activity occurs just after peak reported pain, which peaks at the end of the stimulation period in previous studies.^{28,48} Thus, it is less sensitive to the autonomic responses driven by novel stimulus onset and orienting,^{17,50} and more selective for pain. This waveform can be thought of as a link function that averages autonomic activity over a painful stimulation period into a single value optimized to track posttrial pain reports. These functions—one for each of ECG (heart rate) and SCR responses linked to each of pain intensity and affect—can be applied to new individuals to generate testable predictions about pain based on autonomic responses. Turning back to the question of self-regulation, we did not find cognitive regulation effects on standard baseline-to-peak amplitude or area-under-the-curve measures of event-related autonomic responses. However, when we applied the waveforms to isolate a pain-related component of autonomic activity, we observed significant cognitive regulation effects on both heart rate and SCR with meaningful effect sizes. These findings suggest that cognitive strategies have effects on pain-related aspects of autonomic function.

An important aspect of this study is that we developed SCR and ECG physiological markers for pain first, and then applied these markers to examine the effects of cognitive pain modulation on pain-related physiology. These markers can be used in future studies to test relationships with pain and influences of multiple types of interventions. The physiological markers developed here have reasonable levels of sensitivity, specificity, and generalizability in predicting pain across 2 independent data sets. Tests in out-of-sample individuals showed strong correlations with pain reports ($r = 0.55$ – 0.83) and showed the ability to track pain and differentiate first-person pain experience from observation of another person in pain, an experience that activates the autonomic nervous system, but with a different temporal profile. However, testing sensitivity and specificity should be an open-ended process.⁵¹ The current study provided only a limited set of tests for sensitivity and specificity of the markers, and thus further validation with different experimental conditions will be required to precisely characterize them. Despite these challenges, these predictive models have the potential to provide an additional, cost-effective way to objectively assess acute pain besides existing neuroimaging-based pain markers.⁴⁸ In addition, these markers allowed us to examine the effects of self-regulation on pain-related physiology in a more specific manner by isolating pain-related autonomic response from some other nonspecific factors that are present in physiological measurements. Importantly, when we tested an SCR marker from a previous study by

Geuter et al.¹⁸ on our study data set, the SCR marker showed similar predictive performances predicting pain ratings and similar responses to cognitive self-regulation, despite the differences in stimulus duration (Fig. S7, available at <http://links.lww.com/PAIN/A814>). This suggests that the physiological markers could be robust to some changes in stimulus parameters, although future studies could develop more generalizable models across types of stimulation.

Our analysis results revealed some interesting patterns in physiological responses to pain and pain modulation, although we will need additional studies to confirm these to be robust and reproducible. First, the SCR and ECG time points that reliably contributed to the prediction of pain intensity occurred earlier than the time points predictive of pain unpleasantness (Figs. 3C and D). This suggests that the sensory and discriminative processes that are closely related to pain intensity may precede the generation of pain unpleasantness.^{37,38} Second, when comparing the magnitude of self-regulation effects to those of varying stimulus intensity, self-regulation has stronger effects on unpleasantness than intensity, and stronger effects on cardiovascular responses (ECG) than responses in the skin (SCR) (Fig. 7A). For example, the effect of self-regulation on the ECG pain intensity marker was comparable with a 0.41°C change in stimulus intensity, whereas the SCR pain intensity marker showed a regulation effect comparable with a 0.23°C change. The markers for pain unpleasantness showed a similar pattern. An interesting observation from our findings is that the regulate-down condition showed stronger effects on pain ratings as temperature increased, whereas the regulate-up condition showed weaker effects on pain ratings as temperature increased. Although we did not directly assess motivation or beliefs about regulation, this finding suggests that motivation to modulate pain may be an important factor in its efficacy.

Another interesting observation was that the effects of self-regulation on pain-related physiology seem to be largely driven by the regulate-up condition rather than the regulate-down condition, especially for the ECG markers (Fig. 7B). When tested individually against the passive experience condition, the regulate-up condition showed larger effect magnitudes for the SCR and ECG physiological marker responses, a trend not seen for pain ratings. This finding may support for the asymmetric effects of regulating up vs regulating down on pain-related physiology, but direct comparisons between beta coefficients for regulate-up and regulate-down against the passive experience condition yielded null results (all p s > 0.05). It is also possible that we have null effects for passive experience vs regulate-down simply because of the lack of sufficient statistical power to test each regulation direction separately. We need future studies with larger numbers of trials in each condition to get definitive answers for whether asymmetrical effects of regulate-up vs regulate-down on pain-related physiology exist or not.

This study has some additional limitations that should be addressed in future studies. First, our sample was racially homogenous (87% Caucasian), and therefore our findings must be interpreted and generalized with caution. Second, despite our effort to standardize the regulation instructions and strategies across participants (eg, appearance of experimenter, intonation of verbal instructions, and rapport before and during the experiment), we found that participants used a diverse set of regulation strategies from postexperiment questionnaires (Fig. S2, available at <http://links.lww.com/PAIN/A814>). Future studies examining the effects of using different regulation strategies on pain, physiological, and neural outcomes would be very informative. Third, the SCR marker was tested for the specificity

between experienced pain vs observed pain, but not with nonnoxious somatosensory conditions, such as using non-noxious thermal, auditory, visual, or taste stimuli. Finally, although we instructed participants not to regulate pain during the passive experience runs, intrinsic and spontaneous coping responses to pain or carry-over effects from previous regulation runs might influence the conditions and thus were included in our physiological markers.⁴¹ Significant differences in pain ratings between the passive experience vs regulate-down conditions (all p 's < 0.0001 for pain intensity and unpleasantness ratings; see Table S1, available at <http://links.lww.com/PAIN/A814>) suggest that the influences of spontaneous pain regulation on pain during the passive experience runs were small, although they may have influenced the asymmetry between regulate-up and regulate-down effects by reducing autonomic responses under “neutral” instructions to some degree. Nevertheless, examining the physiological effects of spontaneous pain regulation and the temporal dynamics of regulation effects would be important future research topics.

To conclude, in this study, we showed that cognitive self-regulation operates on the level of the autonomic nervous system, producing physiologically meaningful changes. Understanding the nature of the relationship between cognitive regulation and pain physiology has implications for the fields of both basic and clinical pain research. It can provide insight into the neurophysiological mechanisms underlying cognitive and other types of pain regulation. In addition, our study can be useful for clinical pain management because our regulation method shares common elements with techniques such as cognitive behavioral therapy and mindfulness- and acceptance-based therapies.^{25,49} We believe that showing that these techniques can modulate pain physiology has a powerful message for physicians and other caregivers, and for patients.

It has been a long-standing challenge for clinicians and researchers to find physiological markers for pain.²⁹ The predictive modeling approach used here represents a potential avenue through which quantitative biological measures related to pain can be developed and tested across studies. These methods have several potential clinical applications, but creating biomarkers for pain is especially important. The use of biomarkers in place of pain report is unlikely to be viable in the near future, but the U.S. Food and Drug Administration defines biomarkers for multiple other purposes (eg, <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm533161.pdf>). For example, biomarkers for pain are needed to show that interventions engage particular mechanistic targets and track improvements over time (“monitoring” and “pharmacodynamic/response” biomarkers). In this case, the measures we develop can show that treatments engage brainstem generators of autonomic responses, an important part of the overall response to painful events.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Author contributions: study 1: C.-W. Woo and T.D. Wager developed the study concept. G. Matthewson, C.-W. Woo, and T.D. Wager contributed to the study design. G. Matthewson and C.-W. Woo collected data. Study 2: M.C. Reddan and T.D. Wager developed and designed the study, and M.C. Reddan collected data. Study 1 and 2: G. Matthewson and C.-W. Woo analyzed data and drafted the manuscript, and all authors revised the manuscript and provided critical feedbacks. All authors approved the final version of the manuscript for submission.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/A814>.

Supplemental video content

Video content associated with this article can be found online at <http://links.lww.com/PAIN/A815>.

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