Cognitive self-regulation influences pain-related physiology

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Abstract

Cognitive self-regulation can shape pain experience, but little is known about whether it affects autonomic responses to painful events. 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 (SCR) and electrocardiogram (ECG) activity were recorded. Using a machine learning approach, we developed stimulus-locked SCR and ECG physiological markers predictive of pain ratings. The markers demonstrated high sensitivity when predicting pain ratings, r = 0.55-0.83. In an independent dataset (N = 84), they discriminated different levels of painful heat with 74-93% accuracy and showed some specificity relative to discriminating levels of vicarious pain (50-71% accuracy; chance is 50%). Cognitive self-regulation increased and decreased both pain ratings and physiology in accordance with regulatory goals. These findings suggest that self-regulation can impact autonomic nervous system responses to painful stimuli and provide pain-selective autonomic profiles for future studies.

Keywords: pain, self-regulation, autonomic nervous system, SCR, ECG

Author Summary

It is well known that cognitive self-regulation can modulate pain perception in humans, yet its physiological consequences are difficult to quantify, as the pain- and task-related physiological responses are intricately intertwined. Here, we developed physiological markers predictive of pain report from skin conductance response (SCR) and electrocardiogram (ECG) data collected from 41 participants while they experienced painful thermal stimulations without regulating their pain. These markers were validated on an independent dataset, and then tested for effects of reappraisal-based cognitive self-regulation. When participants were instructed to use this strategy to increase the amount of pain they experienced, expression of the pain-predictive physiological markers increased, and when participants were instructed to reduce the amount of pain they felt, expression of the physiological markers decreased. These results demonstrate that cognitive pain regulation using a conscious, reappraisal-based strategy not only impacts the way participants report pain, but also the way their autonomic physiology responds to pain.

Introduction

Cognitive self-regulation is a way of modulating pain and emotion by consciously changing one's own thoughts and appraisals of sensations and the context in which they occur (1-6). Psychological interventions such as hypnosis and placebo have long been documented as effective methods of pain control (7), and several cognitive self-regulation techniques have also been documented for their ability to reduce pain (for a review, see (8)), such as use of mental imagery (9, 10) and contextual reinterpretation of painful sensations (11, 12). Conscious beliefs and conditioning are known to have strong physiological impacts, such as in the case of placebo effects (13-15), but the relationship between self-regulation and autonomic responses remains to be 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 (16-20), are consistent with sympathetic activation and parasympathetic withdrawal and thought to be mediated by interactions with parabrachial nociceptive pathways in the brainstem (21-23). However, quantifying pain-related autonomic responses in the context of cognitive pain modulation is challenging because autonomic changes are elicited by a wide variety of cognitive and affective processes besides pain. During cognitive pain modulation, for example, the autonomic nervous system responds to noxious stimulation, but also to orientation to a stimulus (24), cognitive load (25, 26), and stress (27). As a result, it is difficult to isolate changes in pain-related physiology from those related to cognitive events surrounding pain, including cognitive regulation itself (28, 29). For example, cognitive regulation effects on pain physiology could be masked by regulatory engagement, resulting in a null net effect (30). Therefore, to quantify the effects of cognitive regulation on pain physiology, it is desirable to identify components of physiological responses that are tightly linked to pain without regulation first, and then test the effects of regulation on these identified physiological components.

In the current study, we first sought to develop a pain-predictive physiological marker by adopting a machine-learning approach (Analysis 1 in **Fig. 1**). Using principal component regression, we developed stimulus-locked pain physiology models predictive of

pain intensity and unpleasantness ratings from skin conductance response (SCR) and electrocardiogram (ECG) data. We used Study 1 (N = 41) data only from trials in which participants passively experienced thermal pain with no regulation instruction. The physiological data in these trials were minimally influenced by psychological processes related to regulation. The SCR marker for pain was then validated on an independent dataset (Study 2; N = 84) to establish its provisional specificity and sensitivity to pain experience, as well as its generalizability to new individuals. This independent test dataset was comprised of participants both experiencing pain and observing pain (in their romantic partner; Analysis 2 in **Fig. 1**).

Finally, we applied the physiological markers for pain to data during cognitive self-regulation in Study 1 to test whether self-regulation changed pain-predictive physiological responses (Analysis 3 in **Fig. 1**). For cognitive self-regulation, we instructed participants to use a strategy of mental reframing of the context surrounding pain, including elements of strategies described as "pain acknowledging," "imaginative transformation," (11) and "dramatized coping" (8, 31) in previous work (see **Supplemental Materials** for full script). These strategies were chosen because of their effectiveness in published (8-10, 32) and ongoing work. 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, not to compare the effects of various self-regulation strategies (see **Fig. S1** for the analyses on the different self-regulation strategies used by participants). The results showed that the cognitive self-regulation of pain significantly impacted pain-predictive SCR and ECG responses, indicating that cognitive regulation not only changes the way participants experience and report pain, but the way in which they respond physiologically to painful events.

Results

Behavioral results of cognitive self-regulation

As shown in **Fig. 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 (32). Stimulus intensity had

similar effects on ratings of both pain intensity and unpleasantness (intensity ratings: $\hat{\beta}_{\text{temperature}}$ = 5.01 ± 0.31 [mean ± s.e.m.], z = 3.86, p < .001 in a bootstrap test with 10,000 times resampling; unpleasantness ratings: $\hat{\beta}_{\text{temperature}}$ = 5.50 ± 0.38, z = 3.71, p < .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 ± 0.68, z = 4.54, p < .0001; intensity: $\hat{\beta}_{\text{regulation}}$ = 2.12 ± 0.36, z = 3.94, p < .0001). The self-regulation effects on pain unpleasantness ratings were comparable in magnitude to a 1˚C change in heat stimulus intensity, $\hat{\beta}_{\text{regulation}}$ = 5.19 vs. $\hat{\beta}_{\text{temperature}}$ = 5.50. The effects of self-regulation on pain intensity ratings were larger for more intense stimuli, as evidenced by a small but significant stimulus intensity × regulation condition interaction, $\hat{\beta}_{\text{interaction}}$ = 0.54 ± 0.12, z = 3.81, p < .001. However, we found only marginal interaction effects for pain unpleasantness ratings, $\hat{\beta}_{\text{interaction}}$ = 0.30 ± 0.20, z = 1.82, p = .069. Significant modulation effects were also observed when regulate-up and regulate-down were separately compared with passive experience (all p values < .01 for both intensity and unpleasantness ratings; please see **Table S1** for results and statistics).

Analysis 1: Developing pain-predictive physiology markers based on SCR and ECG temporal dynamics (Study 1)

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-b**). In addition, when the SCR and ECG data were averaged within each regulation condition, we observed small increases and decreases in SCR amplitude and heart rate for regulate-up and regulate-down, respectively (**Fig. S2**). These physiological changes were marginally significant or non-significant; for example, when using baseline-to-peak amplitudes, SCR: $\hat{\beta}_{\text{regulation}}$ = 0.03 ± 0.01, z = 1.93, p = .053, ECG: $\hat{\beta}_{\text{regulation}}$ = -0.002 ± 0.002, z = -0.63, p = .529; when using the area-under-the-curve, SCR: $\hat{\beta}_{\text{regulation}}$ = 4.43 ± 4.02, z = 1.14, p = .254, ECG: $\hat{\beta}_{\text{regulation}}$ = -1.86 ± 0.92, z = -2.03, p = .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. In order to examine autonomic changes more directly linked to pain, we need to develop pain-predictive SCR and ECG markers using data from passive experience runs (i.e., pain without regulation) first and test these markers on data from the regulation runs.

To develop physiological markers, we used principal component regression with a reduced number of components (two or three principal components depending on the models; see **Fig. S3**) that provided the best performance in leave-one-participant-out cross-validation tests. The input features were created by averaging the stimulus-locked SCR and ECG responses for each temperature (for details, see **Fig. S4** and **Methods**). We then identified temporal profiles of stimulus-locked SCR and ECG responses that reliably contributed to the prediction of pain ratings using bootstrap tests (**Figs. 3c-d**). For prediction purposes, the entire temporal profiles were used as a pattern of predictive weights. These predictive markers reduce the time series of autonomic responses into a single predicted intensity or unpleasantness value for each trial or condition. In the training data, the performance was examined using within-participant prediction-outcome correlations (i.e., correlations between the actual outcome values, y, and predicted values, $\hat{y}$) across different experimental conditions using leave-one-participant-out cross-validation.

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, 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 (i.e., training data) showed that the mean within-participant prediction-outcome correlations were $r = .83 \pm 0.025$, $p < .0001$ (based on a bootstrap test with 10,000 times resampling) for the SCR pain intensity model and $r = .76 \pm 0.047$, $p < .0001$ for the

SCR unpleasantness model. For ECG models, the mean prediction-outcome correlations were $r = .60 \pm 0.073$, $p < .0001$ for the pain intensity model and $r = .55 \pm 0.083$, $p < .0001$ for the pain unpleasantness model (**Fig. S3**). Thus, both SCR and ECG reliably predicted within-person variation in pain reports across trials. We then tested the models on the data from regulation runs of the 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 $r = .82 \pm 0.020$, $p < .0001$ and $r = .73 \pm 0.039$, $p < .0001$ for SCR pain intensity and unpleasantness models, and $r = .67 \pm 0.045$, $p < .0001$ and $r = .65 \pm 0.046$, $p < .0001$ for ECG pain intensity and unpleasantness models, respectively.

Analysis 2: Testing the SCR marker on an independent dataset (Study 2)

To validate our physiological markers' generalizability and specificity, we tested our SCR marker on an independent study dataset with 42 pairs of romantic partners (total $N = 84$). In the experiment, three different levels of heat stimuli (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). SCRs were simultaneously recorded in both participants throughout. This design allowed us to test whether the SCR marker increases in response to first-person experience of somatic pain (i.e., sensitivity), and assess specificity against SCR responses to observed pain.

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 **Fig. 5c**, the baseline-to-peak SCR amplitude significantly increased for 49 vs. 47˚C and 48 vs. 47˚C in both pain receivers ($\hat{\beta}_{49 \text{ vs. } 47^{\circ}C} = 0.34 \pm 0.08$, $z = 4.98$, $p < .0001$, $\hat{\beta}_{48 \text{ vs. } 47^{\circ}C} = 0.18 \pm 0.07$, $z = 5.76$, $p < .0001$) and pain observers ($\hat{\beta}_{49 \text{ vs. } 47^{\circ}C} = 0.19 \pm 0.05$, $z = 4.79$, $p < .0001$, $\hat{\beta}_{48 \text{ vs. } 47^{\circ}C} = 0.15 \pm 0.05$, $z = 4.12$, $p < .0001$). For 49 vs. 48˚C, the baseline-to-peak amplitude showed significant increases only in pain receivers, $\hat{\beta}_{49 \text{ vs. } 48^{\circ}C} = 0.16 \pm 0.08$, $z = 2.83$, $p = .0046$, not pain observers, $\hat{\beta}_{49 \text{ vs. } 48^{\circ}C} = 0.04 \pm 0.08$, $z = 0.51$, $p = .608$. In addition, experiencing pain induced larger overall SCR

changes than observing pain, $\hat{\beta}_{\text{experience vs. observe}} = 0.15 \pm 0.06$, $z = 2.66$, $p = .0077$. Thus, standard SCR and ECG 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 better tracked the changes in first-person pain than observed pain, demonstrating the marker's 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, $\hat{\beta}_{48 \text{ vs. } 47^{\circ}\text{C}} = 2.84 \pm 0.80$, $z = 5.58$, $p < .0001$, $\hat{\beta}_{49 \text{ vs. } 48^{\circ}\text{C}} = 2.53 \pm 1.08$, $z = 4.71$, $p < .0001$, and $\hat{\beta}_{49 \text{ vs. } 47^{\circ}\text{C}} = 5.37 \pm 1.17$, $z = 5.44$, $p < .0001$ (**Fig. 5e**). These increases were comparable in magnitude to the increases in pain ratings, $\hat{\beta}_{48 \text{ vs. } 47^{\circ}\text{C}} = 3.03 \pm 0.67$, $z = 4.60$, $p < .0001$, $\hat{\beta}_{49 \text{ vs. } 48^{\circ}\text{C}} = 1.17 \pm 0.50$, $z = 2.07$, $p = .0386$, and $\hat{\beta}_{49 \text{ vs. } 47^{\circ}\text{C}} = 4.21 \pm 0.59$, $z = 3.74$, $p < .001$ (**Fig. 5d**). Conversely, during observed pain, the SCR marker showed non-significant or marginal increases for 48 vs. 47˚C and 49 vs. 48˚C, $\hat{\beta}_{48 \text{ vs. } 47^{\circ}\text{C}} = 0.54 \pm 0.58$, $z = 0.98$, $p = .33$, $\hat{\beta}_{49 \text{ vs. } 48^{\circ}\text{C}} = 1.68 \pm 0.97$, $z = 1.94$, $p = .052$ (**Fig. 5e**). However, the SCR marker showed a significant, but relatively small, increase for 49 vs. 47˚C during observed pain, $\hat{\beta}_{49 \text{ vs. } 47^{\circ}\text{C}} = 2.22 \pm 0.76$, $z = 3.58$, $p < .001$. 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 two levels of stimulus intensity (i.e., 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% ± 4.0, $p < .0001$, for 48 vs. 47 ˚C, accuracy = 81.0% ± 6.1, $p < .0001$, for 48 vs. 49 ˚C, accuracy = 73.8% ± 6.8, $p = .0029$. These results were comparable to 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% ±

3.3, $p < .0001$, for 48 vs. 47 ˚C accuracy = 81.0% ± 6.1, $p < .0001$, for 49 vs. 48 ˚C = 81.0% ± 6.1, $p < .0001$. For observed pain, the marker response showed worse classification performance than the response to somatic pain, for 49 vs. 47 ˚C, accuracy = 71.4% ± 7.0, $p = .0079$, for 48 vs. 47 ˚C accuracy = 50.0% ± 7.7, $p = 1.00$, for 49 vs. 48 ˚C = 66.7% ± 7.3, $p = .0436$. Though some of the contrasts were significantly above the chance level, if we corrected these test results for multiple comparisons (9 tests in this classification) using a Bonferroni method (i.e., corrected $\alpha = 0.05/9 = 0.0056$), all the classification results for observed pain became non-significant, while other results remained significant.

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 multi-level 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. down), and their interaction.

Both stimulus intensity and self-regulation had significant effects on the SCR and ECG pain intensity and unpleasantness markers (**Fig. 7** and **Fig. S5**); for the SCR intensity marker, $\hat{\beta}_{\text{temperature}} = 2.50 \pm 0.32$, $z = 4.99$, $p < .0001$, $\hat{\beta}_{\text{regulation}} = 0.61 \pm 0.18$, $z = 4.34$, $p < .0001$, for the SCR unpleasantness marker, $\hat{\beta}_{\text{temperature}} = 2.78 \pm 0.38$, $z = 5.04$, $p < .0001$, $\hat{\beta}_{\text{regulation}} = 0.61 \pm 0.19$, $z = 4.11$, $p < .0001$, for the ECG intensity marker, $\hat{\beta}_{\text{temperature}} = 1.50 \pm 0.23$, $z = 4.95$, $p < .0001$, $\hat{\beta}_{\text{regulation}} = 0.62 \pm 0.15$, $z = 4.16$, $p < .0001$, and for the ECG unpleasantness marker, $\hat{\beta}_{\text{temperature}} = 2.27 \pm 0.29$, $z = 4.13$, $p < .0001$, $\hat{\beta}_{\text{regulation}} = 0.87 \pm 0.23$, $z = 4.09$, $p < .0001$.

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, $\hat{\beta}_{\text{interaction}} = 0.34 \pm 0.09$, $z = 3.90$, $p < .0001$, and for the ECG intensity marker, $\hat{\beta}_{\text{interaction}} = 0.13 \pm 0.06$, $z = 2.43$, $p = .015$, 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, $\hat{\beta}_{\text{interaction}} = 0.37 \pm 0.10$, $z = 3.65$, $p < .001$, but not in ECG, $\hat{\beta}_{\text{interaction}} = 0.17 \pm 0.11$, $z = 1.71$, $p = .087$.

Next, we standardized the beta coefficients of self-regulation relative to those of stimulus temperature, in order 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 to the effects of a 0.42˚C and 0.94˚C change in temperature on pain intensity and unpleasantness, respectively. As shown in **Fig. 7**, the self-regulation effects on ECG markers were larger in magnitude than the regulation effects on SCR markers and were comparable to 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, ECG unpleasantness marker = 0.38˚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 experience and passive experience vs. regulate-down were not significant; for the SCR intensity marker, mean difference ($\hat{\beta}_{\text{regulate-up vs. passive}} - \hat{\beta}_{\text{passive vs. regulate-down}}$) = 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, $t_{39} = 1.74$, $p = 0.090$, for the ECG unpleasantness marker, mean difference = 0.74, $t_{40} = 0.95$, $p = 0.340$ (**Table S1**). In sum, cognitive self-regulation showed significant modulation of pain-predictive physiology marker responses, though the detailed patterns of the modulation effects for regulate-up and regulate-down conditions were somewhat different between pain ratings and the physiological markers.

Discussion

Although the effects of cognitive interventions on self-reported pain are well-documented (8), an open question addressed by this study is whether cognitive self-

regulation influences autonomic nervous system activity in addition to pain report. Here, we found significant effects of cognitive self-regulation on ECG and SCR markers for pain in a manner consistent with the direction of regulation, suggesting that cognitive regulation can modulate not only the subjective experience of pain, but also pain-related autonomic physiology. However, these self-regulation effects only emerged clearly when we tested autonomic markers based on pattern information across multiple time points trained to predict pain report. Thus, when testing the component of autonomic responses most closely related to pain, self-regulation effects are clear. However, when summary information such as baseline-to-peak amplitude or area-under-the-curve was used, the effects become equivocal, suggesting that autonomic activity related to the cognitive demands of self-regulation could mask the regulation effects on pain-related physiology.

An innovative aspect of this study is that we developed SCR and ECG physiological markers for pain using a machine learning approach first, and then applied these markers to examine the effects of cognitive pain modulation on pain-related physiology. We showed that the physiological markers developed here have reasonable levels of sensitivity, specificity, and generalizability in predicting pain across two independent datasets. These predictive models provide an additional, cost-effective way to objectively assess acute pain besides existing neuroimaging-based pain markers (e.g., ref. (33)). 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 a variety of other non-specific factors that are present in physiological measurements.

Our analysis results revealed some interesting patterns in physiological responses to pain and pain modulation, though 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-d**). This suggests that the sensory and discriminative processes that are closely related to pain intensity may precede the generation of pain unpleasantness (34, 35). 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 to a 0.41 ˚C change in stimulus intensity, whereas the SCR pain intensity marker showed a regulation effect comparable to 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, while the regulate-up condition showed weaker effects on pain ratings as temperature increased. While 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 up vs. down-regulation on pain-related physiology, but direct comparisons between beta coefficients for regulate-up and -down against the passive experience condition yielded null results (all *p*s > .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. down on pain-related physiology exist or not.

This study has some 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 (e.g., appearance of experimenter, intonation of verbal instructions, rapport before and during the experiment), we found that participants used a diverse set of regulation strategies from post-experiment questionnaires (**Fig. S1**). Future studies examining the effects of using different regulation strategies on pain, physiological, and neural outcomes would be very informative.

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. Additionally, our study can be useful for clinical pain management, as our regulation method shares common elements with techniques such as cognitive behavioral therapy and mindfulness- and acceptance-based therapies (36, 37). 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 (38). 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. Use as a surrogate biomarker in place of pain is unlikely to be viable in the near future, but the United States Food and Drug Administration (FDA) defines biomarkers for multiple other purposes (e.g., 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.

Materials and Methods

Participants

Study 1. 42 healthy participants with no history of psychiatric, neurological, or pain disorders and no currentpain 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 study (32) (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 ± SD] years; range: 18-41 years). 36 participants were of Caucasian ethnicity, 2 participants Hispanic, 1 African-American, 1 Asian, and 1 participant reported being mixed ethnicity. All participants gave written informed consent and were compensated $12 an hour for their participation.

Study 2. 48 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) as either the main participant of *N* = 42 (21 females, age = 27.90 ± 6.29 years, range = 21 - 47), who experienced pain, or the partner *N* = 42 (22 females, age = 27.45 ± 6.20 years, range = 21 - 47), who did not experience pain, but observed their partners experiencing pain. 38 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 gave written informed consent and were compensated $12 an hour for their participation.

Thermal stimulation

Thermal stimulation was delivered to the volar surface of the left inner forearm applied using an ATS Pathway System (Medoc Ltd.) with a 16-mm Peltier thermode end-plate.

Study 1. Heat stimulations were delivered to three 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; level 6: 49.3°C).

Study 2. Heat stimulations were delivered to three 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; level 3: 49°C).

Rating scales

In Study 1 and 2, we used the same general Labeled Magnitude Scale (gLMS) to assess pain intensity and unpleasantness (39). We used gLMS because it provides more valid across-group comparisons and more effectively captures variance in the high-pain range than the visual analog 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. Whereas the pain intensity scale progressed in a unidirectional fashion from left to right, the pain unpleasantness scale was used in a bidirectional fashion, 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 (40).

General procedure

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 upon a calibration procedure. During this procedure, pain intensity ratings were collected from a 47.3°C and a 48.3° C stimulation to eight 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 eight 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** 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, as this is essential for any self-regulation technique to be effective. A full practice script can be found in the supplemental material.

The main task was grouped as 9 runs of 6 thermal stimulations each. There were three run conditions: an up-regulation condition, a down-regulation condition, and a passive control condition. Regulation condition for each run was pseudorandomized using a Latin-square method, resulting in six different sets of run orders, one of which was assigned to a participant before the experiment began. Each run began with a stimulation of 49.3° C to minimize the effects of within-run sensitization and habituation to heat (41). 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. S6**. Six temperatures between 44.3-49.3°C were administered in a randomized order, and after each heat stimulation pain intensity and unpleasantness ratings were collected. The order

in which the two rating scales were presented was randomized. After three trials, a reminder screen was presented, which provided encouragement and reminded the participant which type of regulation they were supposed to be using.

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** 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.

Cognitive Regulation Instructions (Study 1)

In order to examine the effects of a generic form of self-regulation on pain physiology, we created our regulation instructions by combining several different self-regulation strategies. For example, for down-regulation of pain, asking participants to "imagine as hard as they can that the thermal stimulations are less painful than they are" (see below) could be considered pain acknowledging (31) or a non-imaginal reinterpretation strategy (10), whereas asking participants to focus on aspects of the heat that are "pleasantly warm, like a blanket on a cold day" is similar to regulation techniques such as pleasant imagery or dramatized coping (8). For up-regulation of pain, asking participants to "try and focus on how unpleasant the pain is" is similar to pain acknowledging (31), whereas "picture your skin being held up against a glowing hot metal or fire" is more similar to a "dramatized coping" strategy (8).

Although the instructions were a mixture of pain regulation strategies, an important commonality between both the up-regulation and down-regulation instructions is that they guided participants to manipulate painful experiences by consciously attending to the stimuli and changing their meaning, instead of by directing attention elsewhere, such as in

distraction-based pain regulation strategies. A post-hoc analysis of which specific types of strategies participants used can be found in **Fig. S1.**

Regulate-down. To down-regulate pain, participants were instructed to minimize the amount of pain felt by focusing on their sensations and cognitively changing the context in which they were experienced. Full instructions are as follows:

> *During this section, we are going to ask you to try to imagine as hard as you can that the thermal stimulations are less painful than they are. 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. You can use your mind to turn down the dial of your pain sensation, much like turning down the volume dial on a stereo. As you feel the stimulation rise, let it numb your arm, so any pain you feel simply washes away. Picture your skin being very cool from walking outside on a snowy day, and focus on how comforting the stimulation feels on your arm as it warms you up. Think of how you would like to keep your arm on the heat, and visualize the powerful warmth flowing and spreading through you as it gives you energy and life.*

Regulate-up. Instructions to up-regulate pain were designed to be similar in content to down-regulation instructions, but instead maximize the amount of pain felt. Full instructions are as follows:

> *During this section, we are going to ask you to try to imagine as hard as you can that the thermal stimulations are more painful than they are. Try to focus on how unpleasant the pain is, for instance, how strongly you would like to remove your arm from it. Pay attention to the burning, stinging and shooting sensations. You can use your mind to turn up the dial of the pain, much like turning up the volume dial on a stereo. As you feel the pain rise in intensity, imagine it rising faster and faster and going higher and higher. Picture your skin being held up against a glowing hot metal or fire. Think of how disturbing it is to be burned, and visualize your skin sizzling, melting and bubbling as a result of the intense heat.*

Passive experience. Participants were asked to focus on the fixation cross on the screen, and rate intensity and unpleasantness of pain without regulating it up or down. This condition was loosely matched in length and word count to both the regulate-up and regulate down conditions. Full instructions are as follows:

During this section, we are going to ask you to stare at the fixation cross, and rate how intense and pleasant/unpleasant each stimulation is. Try not to regulate or change your sensation, but instead accurately rate what each sensation was like as you felt it. Focus on the fixation cross during each heat stimulation, and try and keep your eyes open and your face aligned towards the computer screen. As you feel the stimulation rise, try and sit as still as possible, and keep your eyes and face oriented towards the camera in front of you.

Data acquisition

Electrocardiogram (ECG). ECG 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 maximums 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. Inter-beat intervals (IBI) were then calculated based on differences between adjacent peaks (See **Fig. S4a**).

Skin conductance response (SCR). SCR activity was recorded using 11-mm Ag/AgCl electrodes (Biopac systems, Goleta, CA) attached to the medial phalanges of the middle and ring fingers of the left hand. Data was sampled at 500 Hz in Study 1, and at 1000 Hz in Study 2. The difference in sampling rate between Study 1 and 2 should have no effects on our findings because the signal-of-interest and other noise components should be located in the much lower frequency domain.

Data analysis

Preprocessing. Physiological data (SCR activity and ECG-IBI time-series data) was put through a low-pass filter, 5 Hz for SCR (15), and 1 Hz for ECG-IBI (42), to remove noise, and then downsampled to 25 Hz (See **Fig. S4a**).

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 (See **Fig. S4b**). The stimulus-locked physiological responses were averaged across regulation conditions to create a mean physiological response for each temperature (**Figs. 2a-b**).

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 six temperatures were made into a 6 × 1 vector. SCR and ECG time-series data were then concatenated across participants so that they could be used as features for subsequent modeling, and pain ratings were used as an outcome variable (see **Fig. S4** for more details). Then, principal component regression (PCR) was used to create a SCR and ECG time-course model predictive of pain ratings. This was achieved in two 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 (i.e., using component scores) to predict pain ratings. In this step, only the first two components were used except for the ECG model for pain unpleasantness (for this model, three components were used). We chose the number of components based on a leave-one-participant-out cross-validation procedure, where we compared the mean correlation values between actual and predicted outcomes from models with different numbers of principal components (from 2 to 10 components) and chose the one that yielded the best cross-validated results (see **Fig. S3** 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 contribute to the prediction. We constructed 10,000 bootstrap sample sets (with replacement) and ran PCR on each.

Testing the physiological marker (Analysis 2 and 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 three

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.

Acknowledgements

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Data Availability Statement

De-identified data for Study 1 and the data analysis scripts for reproducing all figures and results will be publicly available at github.com and osf.io immediately upon publication. For the peer review, the data and codes are available via a view-only link: https://osf.io/sujpx/?view_only=4a17fecb55504665b9a6d8fba925cc12

Author contributions

Study 1: CWW and TDW developed the study concept. GM, CWW, and TDW contributed to the study design. GM and CWW collected data. Study 2: MCR and TDW developed and designed the study, and MCR collected data. Study 1 and 2: GM and CWW 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.

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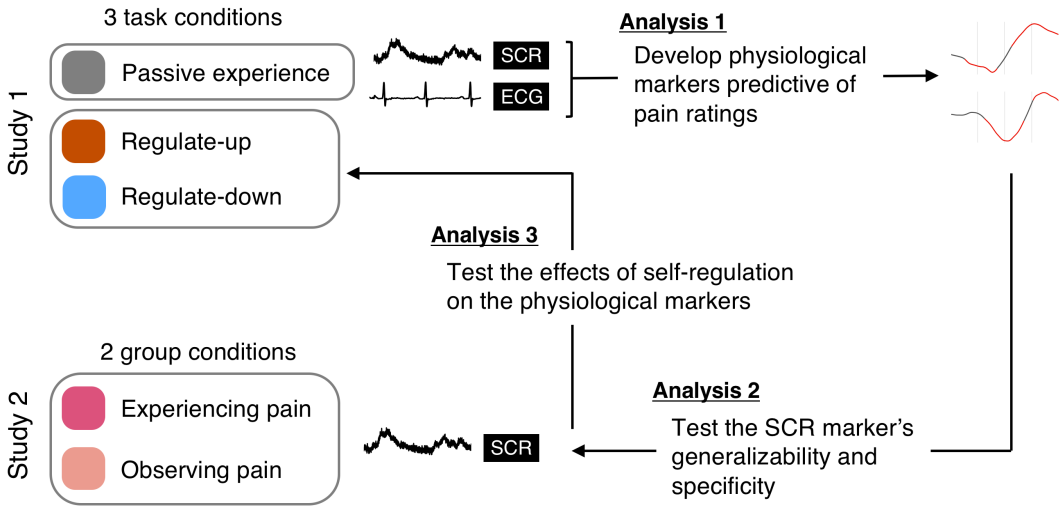

Figure 1. Analysis pipeline. The current study consists of three analysis steps. **Analysis 1:** We first developed a pain-predictive physiological marker using Study 1 ($N = 41$) data from the passive experience condition (no regulation). **Analysis 2:** We validated the SCR marker with an independent dataset (Study 2, $N = 84$) to establish its provisional generalizability and specificity by testing the marker on participants experiencing pain and observing their romantic partner experience pain. **Analysis 3:** We applied the physiological markers for pain to data during cognitive self-regulation in Study 1 to test whether self-regulation changed pain-predictive physiological responses.

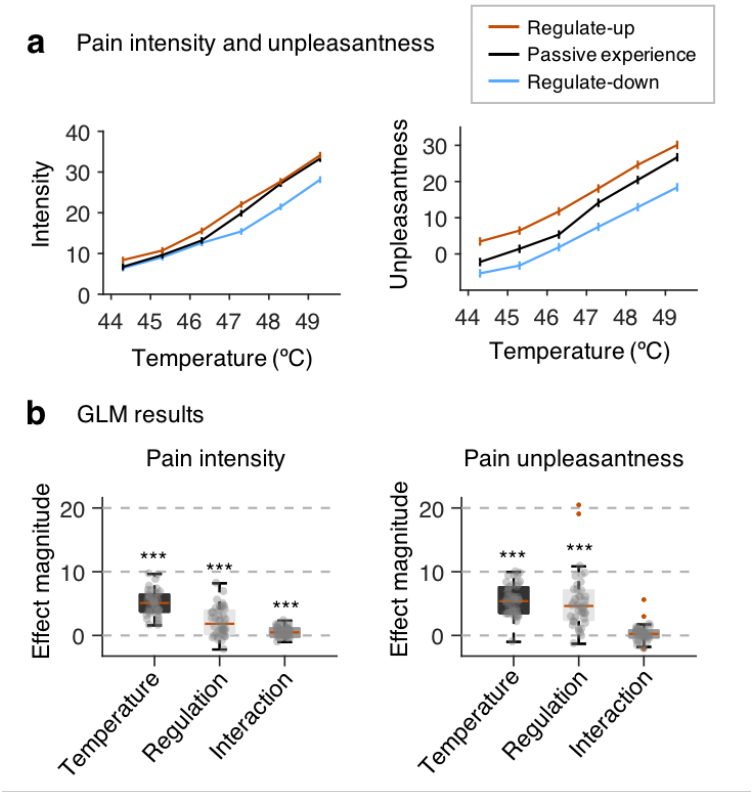

Figure 2. Effects of cognitive self-regulation on pain ratings. **(a)** Mean intensity and unpleasantness ratings for each temperature in the Regulate-up (red), Passive experience (black), and Regulate-down conditions (blue). Error bars represent within-subject standard errors of the mean (S.E.M.). For pain ratings, we used general Labeled Magnitude Scale (gLMS) (39). **(b)** Effect magnitude (y-axis) represents regression coefficients ($\hat{\beta}$) from a multi-level general linear model. Each dot shows each individual's regression coefficient. The GLM analyses revealed that temperature (stimulus intensity, ˚C) and regulation (coded regulate-up, passive experience, and regulate-down as 1, 0, and -1) 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. $^{***}p < .001$; Bootstrap tests (10,000 iterations) were used for significance testing.

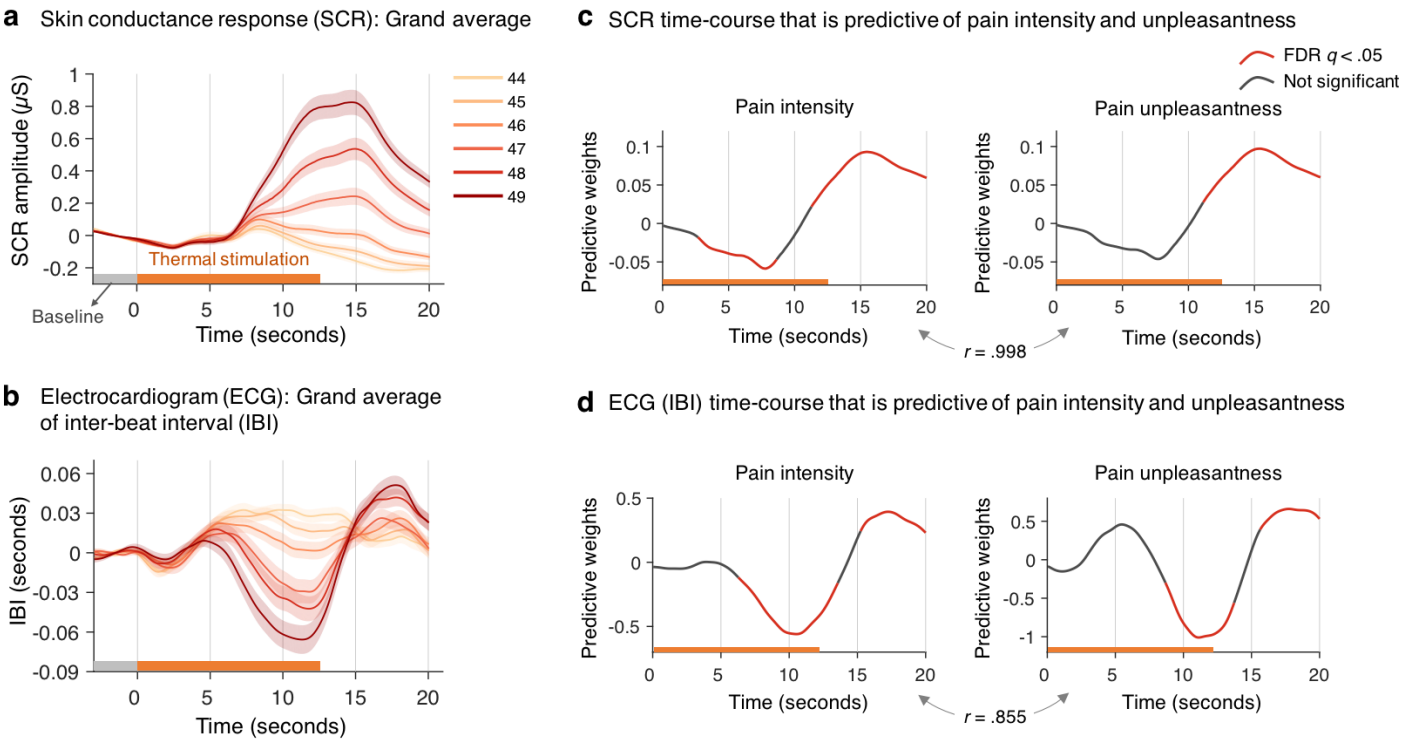

Figure 3. SCR and ECG's IBI time-courses predictive of pain ratings. (a) Stimulus-locked grand average of skin conductance responses (SCR) across participants for each temperature. Data from 3 seconds prior to the thermal stimulation onset were used as a baseline (see **Methods** for details). Shading represents S.E.M. **(b)** Grand average of inter-beat interval (IBI) calculated from electrocardiogram (ECG). **(c)** SCR time-course markers most predictive of pain ratings (left: pain intensity, 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 $q < .05$, false discovery rate (FDR). SCR time courses for pain intensity and unpleasantness were almost identical, $r = .998$. **(d)** ECG (IBI) time-course markers most predictive of pain ratings (left: pain intensity, right: pain unpleasantness). The correlation between ECG time courses for pain intensity and unpleasantness was also very high, $r = .855$.

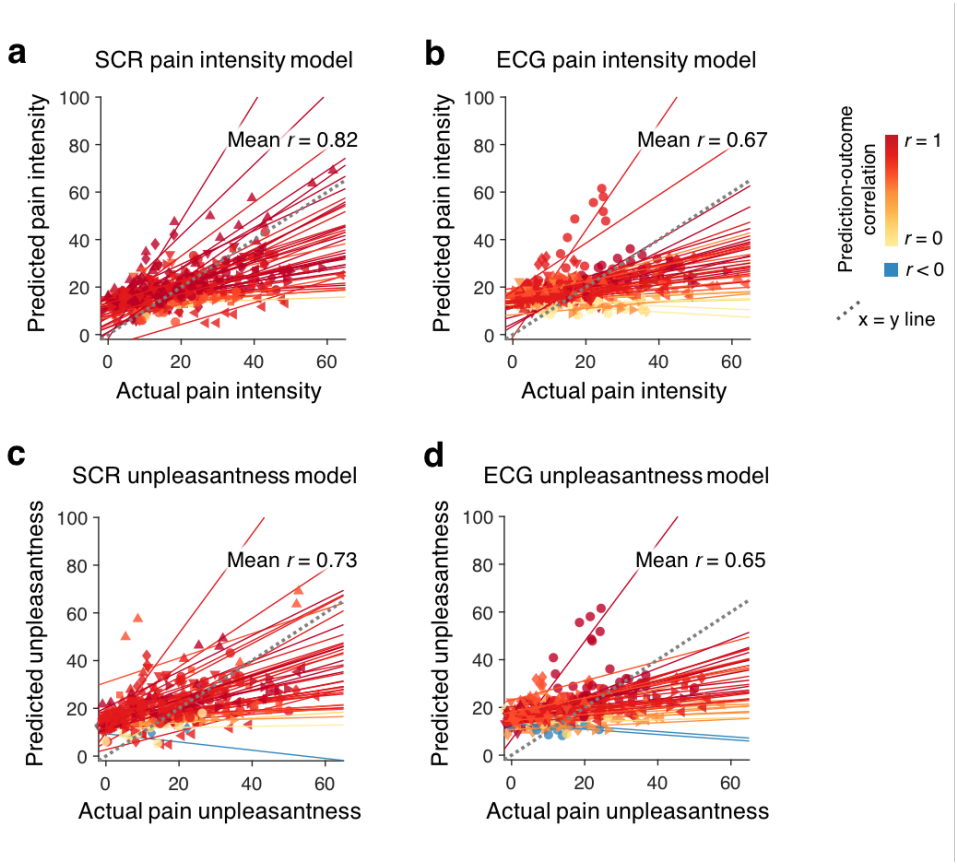

Figure 4. Testing the predictive models on held-out participants' regulation data. Test results of the SCR and ECG markers on data from regulation runs (12 trials per person). Note that no data from regulation runs were used for marker development. Additionally, leave-one-participant-out cross validation 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**) versus 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,* blue: $r < 0$), and the dotted line represents points where the actual pain ratings are same with the predicted ratings (i.e., x = y).

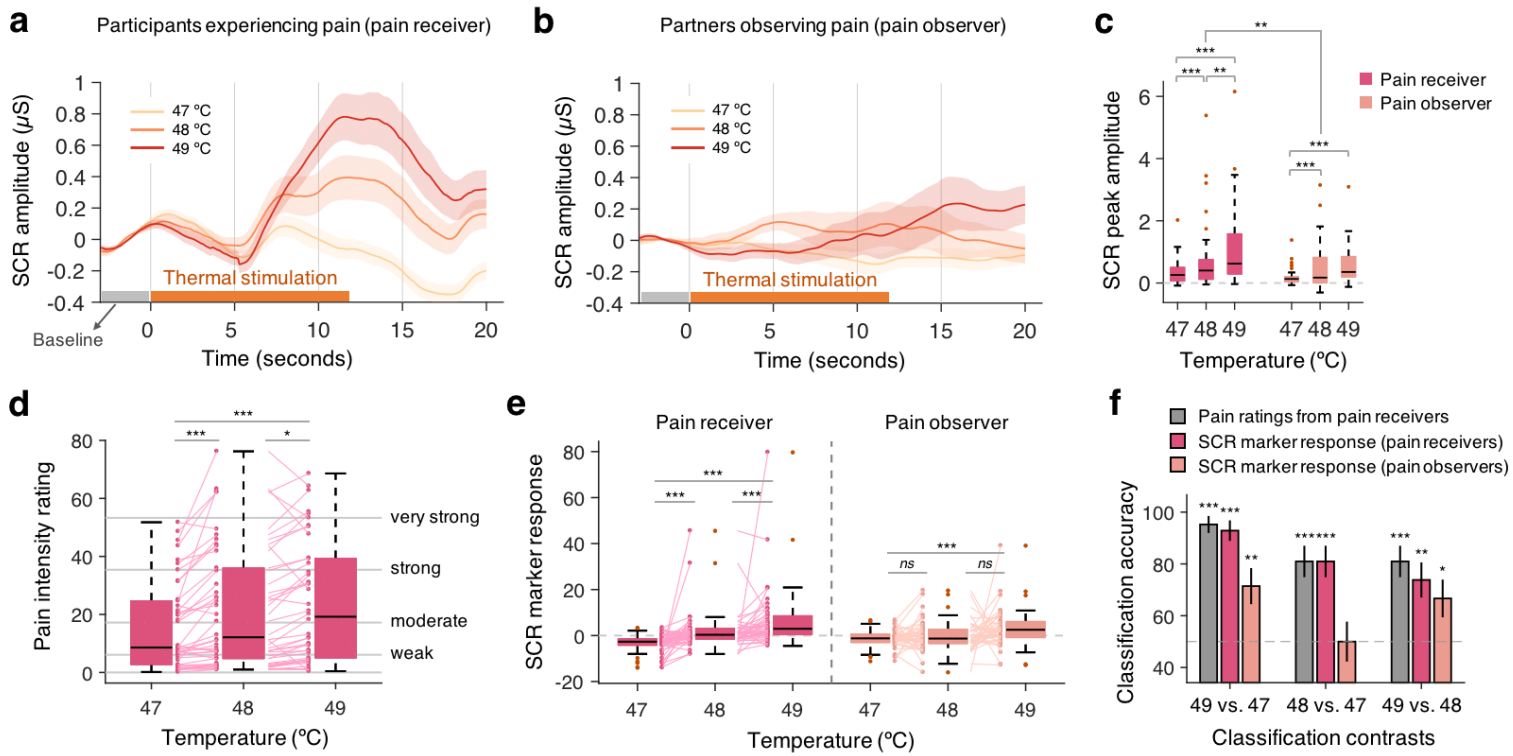

Figure 5. Validation of markers on an independent data set. We tested the sensitivity and specificity of the SCR pain intensity marker using data from Study 2. In Study 2, participants received thermal heat stimulations on their leg (pain receiver), and their romantic partners observed the main participants experiencing pain (pain observer). **(a)** Mean SCR amplitudes of pain receivers during three different stimulation temperatures. Shading represents S.E.M. **(b)** Mean SCR amplitudes of pain observers during the same trials. **(c)** Baseline-to-peak SCR amplitudes from pain receivers and observers for three temperature levels. **(d)** Mean pain intensity ratings from pain receivers for three temperatures. Lines connect the same individuals' pain ratings. **(e)** SCR marker responses from pain receivers and observers for three temperature levels. Lines connect the same individuals' marker responses. **(f)** The two-choice classification accuracy for stimulus intensity contrasts using (i) pain ratings from pain receivers, (ii) SCR marker responses of pain receivers, and (iii) SCR marker responses of pain observers. $^{***}p < .001$, $^{**}p < .001$, $^{*}p < .05$ (two-tailed); Bootstrap (c, d, and e) and binomial test (f) was used for significance testing.

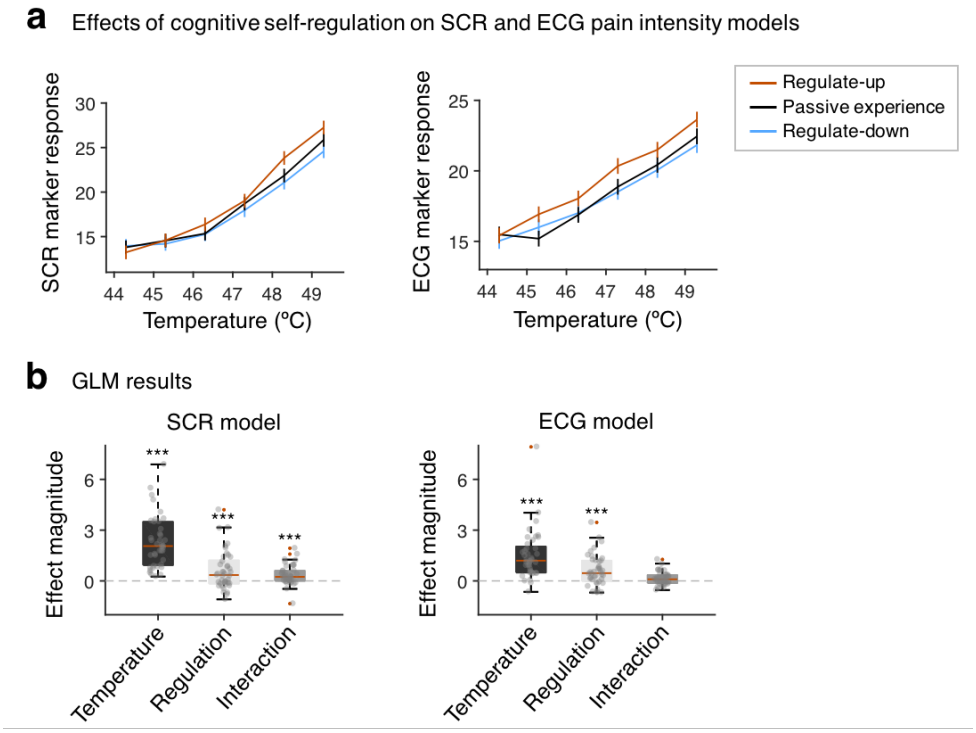

Figure 6. Effects of cognitive self-regulation on SCR and ECG markers. (a) This is an analogous plot to Fig. 1a's left panel, but here we used predicted pain scores based on SCR and ECG pain intensity models. Error bars represent within-subject S.E.M. **(b)** Multi-level general linear model results. 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. $^{***}p < .001$; Bootstrap tests (10,000 iterations) were used for significance testing.

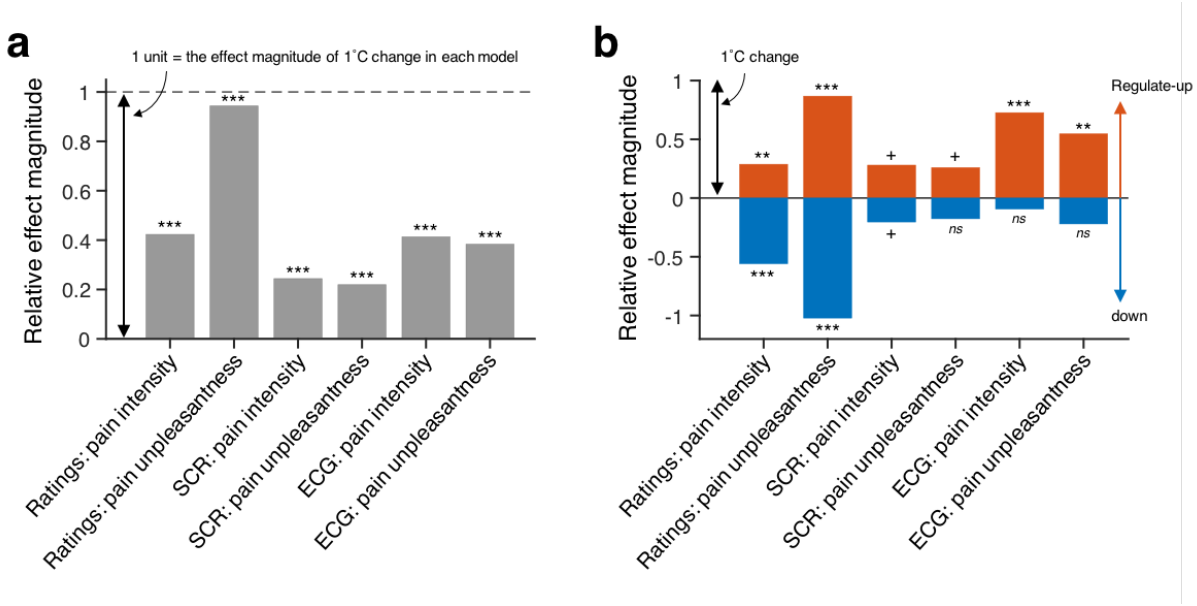

Figure 7. Relative effect magnitudes for different outcome variables. To compare the effect magnitudes across different models, we calculated relative effect magnitudes of self-regulation on different outcome measures by comparing them to the effects of stimulus intensity. In other words, in both of these plots, 1 unit in the y-axis indicates the effect magnitude comparable to 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 to 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. $^{ns}p > .1$, $^{+}p < .1$, $^{**}p < .01$, $^{***}p < .001$.