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Pain or nociception? Subjective experience mediates the effects of acute noxious heat on autonomic responses

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1. Introduction

The autonomic nervous system (ANS) is remarkably responsive to painful stimulation. More than four decades of research show that nociceptive stimulation elicits autonomic reactions, with studies demonstrating widespread effects across stimulus modalities (e.g. heat, electrical, and pressure stimulation) and physiological outcomes (e.g. cardiovascular reactivity, respiration, skin conductance, and pupil dilatation; see [53], for a review). While nociception refers to neural encoding of impending or actual tissue damage (i.e., noxious stimulation), pain refers to the subjective experience of actual or impending harm [42,43]. Though nociceptive stimulation usually leads to pain, pharmacological and brain lesion research shows that one can exist without the other [30,48,70]. Several human neuroimaging studies support this finding, showing that pain and noxious stimulation intensity are dissociable at the level of brain activity [2,5,24,50,68,95].

However, it remains unknown whether psychological processes, such as pain appraisal, mediate autonomic responses to painful stimulation or whether autonomic responses preliminarily reflect ascending nociceptive signals. Though multiple studies show the sensitivity of the ANS to noxious stimulation [53], few mechanistic studies have investigated the specificity of the ANS response to pain, and most studies in humans have failed to dissociate nociception from pain. Despite the lack of formal investigation, the International Association for the Study of Pain (IASP) refers to autonomic responses as a “consequence of encoding” and links autonomic responses with nociception [42]. Indeed, nociceptive pathways functionally intersect with the autonomic nervous system on multiple subcortical and spinal levels (see [11], for a review), so nociceptive stimuli might evoke an autonomic response automatically as part of a coordinated defensive response, irrespective of awareness or the conscious pain experience. However, research on the nociceptive flexion response indicates that psychological factors such as expectation and affect can shape spinally-mediated reflexive responses (e.g., [78,79,82,92]). Thus, experienced pain might shape the autonomic response to noxious stimulation as cortical regions that regulate pain are also

involved in ANS modulation (see [10], for a review). Physiological arousal can be directly influenced by top-down psychological processes, such as emotional reappraisal [38], implicit and explicit learning [4,34,64,73,94] and stress [47,55]. Consistent with these findings, manipulating attention or emotion can also affect pain experience and the autonomic response to noxious stimulation [18,21,44,54,77]. Thus, taken together, the question remains open whether pain appraisal is necessary for noxious stimulation to activate the ANS.

To address this question, we experimentally manipulated heat stimulation intensity in two tasks and measured the effects on self-reported pain and heat-evoked autonomic response using palmar skin conductance response (SCR). SCR constitutes a well-established marker of the sympathetic threat response [14,32,39,88]. To replicate findings, we collected increased pupil diameter as another marker of physiological arousal [17], though pupil diameter can be influenced by both sympathetic and parasympathetic activity. Both markers are reliably influenced by painful stimulation [53]. We used multi-level modelling to compare the associations of noxious stimulation and pain intensity with evoked autonomic responses and to test a process model in which noxious stimulation predicted autonomic responses through increased pain. Furthermore, we compared this process model for both painful and nonpainful stimulation, to test whether the subjective categorization of thermal stimuli as painful or innocuous regulated the influence of heat on autonomic responses.

2. Method

2.1 Participants

One-hundred eighteen healthy adult volunteers from a community sample at the National Institutes of Health provided informed consent. Procedures were approved by the National Institutes of Health (NIH) ethical review board (protocol number: 15AT0132) and followed the ethical guidelines for human subject research in the Declaration of Helsinki. Eligible participants were required to be between the ages of 18 and 50 years and fluent in English. Participants were not invited if they had: chronic pain or a history of chronic pain or regularly used medication affecting pain; any major neurological or psychiatric conditions; any conditions that affected pain sensitivity or somatosensation; or any dermatological conditions on the testing region. Participants were not enrolled if they used recreational drugs or were pregnant, and urine screens were used to confirm eligibility. Based on a clinical assessment upon arrival in the lab, two participants were deemed ineligible. The remaining 116 participants underwent sensory testing to assess heat-evoked pain and autonomic responses.

Participants completed at least one of two different pain assessment tasks: the two-step pain assessment (TSPA) and the adaptive staircase calibration (ASC). Fifty participants completed both tasks, while 41 completed only the TSPA and 25 completed only the ASC. As the samples were only partially overlapping, and all variables were measured and manipulated within-subjects, we considered the two pain assessment tasks independently for the purpose of the current analyses. Seventy-five participants completed the ASC (52.86% female; $M_{\text{age}} = 27.96$ years, $SD_{\text{age}} = 7.93$; 40.00% Black/African American, 37.14% Caucasian/White, 14.29% Asian, 5.71% Hispanic/Latino, 2.86% mixed race) and ninety-one

participants completed the TSPA (58.24% female; $M_{\text{age}} = 28.02$ years, $SD_{\text{age}} = 7.37$; 39.77% Caucasian/White, 37.50% Black/African American, 12.50% Asian, 6.82% Hispanic/Latino, 3.41% mixed/other race).

2.2 Stimuli and apparatus

Participants received different levels of thermal heat stimulation on eight sites of the non-dominant inner volar forearm via a 16×16 ATS thermode (Medoc Ltd., Ramat Yisha, Israel). During both pain assessment tasks, we recorded skin conductance using the Biopac MP150 EDA-100C module (Biopac Systems, Inc., Goleta, CA, USA) via two shielded silver-silver chloride electrodes. We prepared electrodes with NaCl electrolyte gel (GEL101) as recommended by Biopac Systems for skin conductance measurement. We attached electrodes at the hypothenar muscles of participants' non-dominant hands. During the ASC, we also recorded pupillometry data from the participant's right eye using the Eyelink 1000 Plus eye tracking system (SR Research Ltd., Ottawa, Ontario, Canada). We used a 9-point calibration and validation procedure to calibrate gaze position and pupil measurement. Visual stimuli (e.g. fixations) and behavioral responses (e.g. pain ratings) were presented and collected using Experiment Builder software (SR Research) for ASC and E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) for TSPA.

2.3 Procedures

We first describe the procedures that were common to the ASC and TSPA tasks, followed by the unique procedures associated with each separate task.

General procedures—We recruited participants through flyers posted in NIH buildings and distributed through email list servers, ClinicalTrials.gov, and the NIH patient recruitment office. All potential participants underwent a phone screen to assess eligibility, and eligible participants were invited to the NIH's outpatient clinic. Upon arrival, participants provided informed consent. As per NIH guidelines, participants went through a basic nursing assessment and received a physical examination if they had not received one at the NIH within the past year. Following clinical assessments, participants completed the pain assessment procedures described below (for procedures, see Figure 1). In addition to characterizing autonomic and pain responses to noxious stimuli, we used this session to establish eligibility for subsequent pain experiments. Participants also completed personality and affect questionnaires prior, during, and after the session that we did not analyze for the purpose of the present research questions. Participants received monetary compensation contingent on the individual length of the session.

Thermal stimulation: Participants experienced thermal stimuli delivered via thermode during both tasks. Prior to the tasks, we informed participants that they could stop thermal stimulation at any point if stimulation was intolerable either by asking the experimenter to stop the stimulus or by removing the thermode from their forearm. Target temperatures ranged from 34 to 50°C in 0.5°C increments. Each stimulation trial started with a 1.5 sec on-ramp phase, during which thermal stimulation rose from 32°C to the target temperature level, stayed at the target temperature for 5 or 7 secs, and ended with a 1.5 sec off-ramp phase to return to baseline. The first 12 participants in the ASC experienced 10-second

thermal stimulation, before we switched to 8-second thermal stimulation as it is common in previous research [36,59].¹ All participants in the TSPA experienced 8-second thermal stimulation. Triggers were sent to Biopac to mark the onset and offset of each thermal stimulus, which permitted analyses of time-locked physiological responses. To minimize fear-potentiated startle responses resulting from uncued aversive stimulation (e.g., [16,37]), we signaled heat onset to participants by displaying a fixation cross on the computer screen (see Figure 1). Experimenters were extensively trained to manually deliver heat at fixation onset. Any variation in experimenters' reaction times is likely to be offset by the slow 1.5s ramp from baseline temperature to peak stimulation, thus mitigating the possibility that startle could have contributed to our results.

Perceived intensity ratings: Following the offset of the thermal stimulus, participants rated the perceived intensity using visual analogue scales (VAS) described below. Participants provided ratings using a mouse and stated each rating aloud to facilitate the experimenters' recording of participants' ratings. The verbal ratings allowed experimenters to avoid repeating temperatures participants deemed to be intolerable, and – in the case of the ASC – continuously adjust temperature delivery (see specific procedures below). Experimenters instructed participants to rate pain based on the entire heat trial and checked in with the participants periodically to ensure that participants were using scales as intended. Each VAS had an anchor to denote maximum tolerable pain. If a participant found a specific stimulus to be intolerable, the participant rated the stimulus as higher than this level. Experimenters adjusted subsequent thermal stimuli (irrespective of task) on this skin site to be .5 to 1 degree lower than the temperature of the thermal stimulus rated as intolerable if subsequent temperatures were equal or higher than the stimulus rated as intolerable. To account for such changes, we used the adjusted – not original – temperature variable in all analyses. Furthermore, some participants revised verbal ratings after having provided computer ratings. Sometimes, participants clicked the mouse incorrectly or corrected a rating. However, our computer set-up did not allow participants to change their rating once imputed. Because of these occasional revisions, we analyzed adjusted temperatures and participants' verbalized pain ratings when testing the present research questions. Results and conclusions reported below did not differ substantially when we analyzed responses recorded by computer mouse rather than verbal ratings.

Specific procedures—The ASC and TSPA were counterbalanced across subjects. Because of occasional time constraints and interim changes to our experimental protocol (e.g. the TSPA task was added partway through our protocol as a secondary pain assessment) not all participants completed both pain assessment tasks. We included the ASC because this pain assessment task is an essential part in our clinical protocol to assess participants' eligibility for subsequent experiments. The ASC constitutes an adaptive,

¹We tested in the ASC whether trial length influenced the SCR and PDR to heat stimulation. Trial length (10 vs. 8 sec) did not moderate the effect of temperature ($B = -6.27$, $SE = 170.10$, $t = -0.04$, $p = .971$) or pain ($B = -248.35$, $SE = 198.58$, $t = -1.25$, $p = .216$) on SCR area under the curve (AUC). Intercepts in these analyses indicated that trial length alone did not predict SCR AUC ($Bs = 1759.79$, $SEs = 5038.4$, $ts = 0.35$, $ps = .728$). Similarly, trial length did not moderate the effect of temperature ($B = -7607.60$, $SE = 10685.65$, $t = -0.74$, $p = .479$) or pain ($B = -4505.13$, $SE = 14480.71$, $t = -0.31$, $p = .767$) on PDR AUC. Again, intercepts in these analyses indicated that trial length alone did not predict PDR AUC ($Bs = 47632.12$, $SEs = 281933.80$, $ts = 0.17$, $ps = .866$). Consequently, we combined SCR and PDR data across participants in the ASC.

unidimensional measure of pain, designed to tailor heat stimulus delivery to the pain range of each participant; thus, the ASC is well-suited to quickly and reliably check pain threshold and tolerance levels to determine participation eligibility [13,22]. In addition, we have used this task in our previous research [3,5,6]. However, because the ASC is adaptive, it does not distinguish well between painful and nonpainful temperatures. Furthermore, one concern with a continuous VAS is that it conflates pain and innocuous intensity. Therefore, we also included the TSPA in our experimental protocol, which allowed us to distinguish between painful and nonpainful stimulation [89]. Because we did not have prior data on the direct relationship between the tasks, and because literature suggests that non-adaptive tasks such as the TSPA may be less reliable than adaptive tasks like the ASC, [58], we opted to include both pain assessment tasks in our analyses.

Adaptive staircase calibration: Using an established pain calibration task [3,5,6,89], participants experienced 24 heat stimulation trials on eight skin sites and provided pain ratings on a VAS ranging from 0 (*no sensation at all*) to 10 (*most pain imaginable*). The scale also included anchors for nonpainful warmth (1), pain threshold (2), moderate pain (5), and maximum tolerable pain (8). All participants initially received heat stimulation at 41, 44, and 47 °C (in this order), and then for the remaining 21 trials, we used iterative linear regression to identify and apply temperatures predicted to elicit low, medium, or maximum tolerable pain (i.e., VAS ratings of 2, 5, and 8, respectively). All participants received the same sequence of low, medium, and maximum tolerable pain stimulation (with temperatures based on the iterative fit to each individual). The sequence ensured that each skin site received a low, medium, and maximum painful temperature, and that each stimulus level was followed by every possible stimulus level. Thus, stimulus levels were not randomized across participants, but temperatures varied for each individual. Each skin site received three stimulations over the course of this task.

To facilitate pupillary measurements, we programmed a computer-based task using Experiment Builder (see Figure 1B for trial structure). To begin each trial, the participant fixated on a black square in the center of the computer screen. Following steady fixation of 500 ms, a cross appeared and the experimenter triggered the thermal stimulus through Pathways software at the temperature determined by the iterative regression. Four secs after heat offset, the pain rating scale appeared and the participant provided their rating using a mouse and then stated the rating aloud. An experimenter then moved the thermode to the next skin site. We recorded pupil dilation, gaze position, skin conductance, respiration, heart rate, and electrocardiogram activity during the ASC task. We analyzed heat-evoked skin conductance responses (SCRs) and pupil dilation for the purpose of the current investigation.

Two-step pain assessment: We adapted this task from Wager et al. [89]. Unlike in the ASC, most participants in the TSPA (exceptions see below) received the same fixed sequence of 32 pre-determined temperatures. For each heat stimulus, participants provided both categorical and continuous ratings (see Figure 1C for trial structure). Five seconds after heat offset, participants rated whether the stimulus was “*Not Painful*” or “*Painful*,” and then rated the intensity of each stimulus using a 0–100 VAS. If the stimulus had not been painful, participants rated intensity from 0 (*no sensation at all*) to 100 (*very warm, but not yet*

painful). If the stimulus had been painful, participants rated intensity from 0 (*no pain at all*) through 80 (*most pain tolerable*) to 100 (*worst pain imaginable*).

We applied predetermined temperatures between 34 and 50 °C, with approximately 50% of the thermal stimuli predicted to be non-painful and 50% predicted to be painful, using a pain cut-off of 44 °C. Stimulus lists were pseudorandom and generated using random samples with restrictions, such that each skin site received four stimulations that were at least 1°C apart, with two stimuli from the nonpainful range and two stimuli from the painful range. We changed lists over the course of the study in order to refine thermal stimulus sampling from above and below the pain threshold and to adequately capture the lower bound of the nonpainful temperature interval. As a consequence, 81 participants had the same fixed temperature sequence, while 10 participants had one of two other temperature sequences. Instead of randomizing temperatures within participants, participants received the same sequence of temperatures to ensure that individual participants received stimulation across the targeted temperature range and did not receive a disproportional amount of high or low temperatures. Temperatures only varied across subjects within a sequence if a participant found a stimulation to be intolerable. In this case, all subsequent stimulations on that site were required to be below the intolerable temperature (see general procedures above). We recorded skin conductance, respiration, heart rate, and electrocardiogram activity during the TSPA task. For the current analyses, we focused on heat-evoked SCRs.

2.4 Peripheral autonomic responses

To measure the autonomic response to heat stimulation, we focused on skin conductance responses (SCR) for both tasks, and examined pupil dilation responses (PDR) during the ASC task. Data were preprocessed and extracted using custom code in MATLAB 2015b (MathWorks, Inc., Natick, MA). Technical difficulties prohibited us from collecting autonomic arousal data for a subset of participants (skin conductance for 2 ASC participants; pupil dilation for 4 ASC participants; skin conductance for 3 TSPA participants), reducing sample sizes to: $n = 73$ for analyses of skin conductance during ASC; $n = 71$ for pupil dilation during ASC; $n = 88$ for skin conductance during TSPA. Research participants were blind to temperature levels or reported pain levels when coding for artifacts in individual trials.

Skin conductance—We first preprocessed skin conductance data in AcqKnowledge (Biopac Systems, Inc., Goleta, CA, USA). Data were smoothed with a 1000 samples moving average function and filtered with a 25 Hz FIR low-pass filter. Data were then imported to MATLAB, where we downsampled data to 250 Hz and used event markers to extract and visualize skin conductance levels from one second before heat onset until 4 seconds after offset (12 seconds total) to account for a delayed skin conductance response, similar to previous work [59]. SCRs were baseline-corrected by subtracting the mean skin conductance level over the second prior to heat onset. Finally, trained research assistants visually inspected each trial for artifacts. Based on these inspections, we excluded on average 26.76% of trials per ASC participant and 21.77% of trials per TSPA participant.

Pupil dilation—Since we did not collect data on absolute pupil sizes for all participants, we report changes in pupil dilation in arbitrary units (a. u.). To import ASC pupillary data, we used MATLAB-based algorithms [45]. Initial inspections revealed that extreme values surrounded each period identified as a blink, so we interpolated from 100ms prior to 100ms following each blink. Data were then aligned to event markers, and we used custom MatLab code to visually inspect pupillary data on each trial to both verify interpolation and to identify any artifacts that were not automatically detected. We deleted artifacts and excluded any trials with at least 50% missing data ($M = 1.6\%$ of trials excluded per participant). We then downsampled data to 250 Hz and applied a 25-sample Savitzky-Golay smoothing filter [12,83]. Similar to SCR analyses, we baseline-corrected PDR data for each trial by subtracting the mean pupil dilation level over the 0.5 seconds preceding heat onset.

Heat-evoked autonomic responses—We used custom MATLAB code to align continuous time series data with event markers and extract heat-evoked SCR and PDR data. We calculated different measures of the SCR and PDR to heat stimulation. For each trial, we extracted baseline-corrected responses from 0.5 secs after heat onset to 4 secs after heat offset (to account for delayed autonomic responses). We used the trapezoidal rule-based MATLAB function *trapz.m* to calculate trial-by-trial area under the curve (AUC) across this window as a summary measure of the heat-evoked autonomic response for both outcome measures (SCR and PDR). When calculating AUC in the pupil dilation data, we interpolated across missing data. To gain further insight on the dynamics of heat-evoked autonomic responses, we also computed: a) trial amplitude (difference between overall maximum and preceding minimum); b) response latency (duration between heat onset and maximum amplitude); and AUC for three phases of heat stimulation (*early* = .5 – 4 seconds after onset; *peak* = 4 seconds after onset to heat offset; and *after* = the 4 seconds after offset). Trials with SCRs amplitudes that did not exceed 0.02 μS were set to 0 and considered non-responses, similar to previous work [36]. Unlike the other autonomic response measures, the SCR and PDR amplitude distributions were strongly right-skewed. To reduce non-normalcy, we thus square-root transformed SCR and PDR amplitudes. To better account for multiple fluctuations in pupil dilation and skin conductance across a trial we focused on full trial AUC analyses for the main manuscript; however, we present results using additional autonomic response measures in the Supplementary Materials. Conclusions were similar across autonomic response measures, and we discuss any discrepancies in the main manuscript.

2.5 Analytic strategy

As temperature, pain, and autonomic responses varied within subjects, we tested our hypotheses using multilevel models, which incorporate an intercept and slope for each participant and allow for different numbers of observations across participants. To test main effects and interactions without controlling for competing variables, we used custom-built code in Matlab (the *glmfit_multilevel.m* function, available at <https://github.com/canlab/CanlabCore>) to implement linear mixed models. We used multi-level logistic regression to examine pain categorization in the TSPA (i.e. to predict whether stimuli were labeled painful or innocuous), as implemented with the *glmer* function in R Studio 0.99.473 (R Studio, Inc., Boston, MA, USA). In all analyses, we person-centered predictors and, when testing

interaction effects, also included the main effects of variables comprising interaction terms in our statistical predictor models.

Multi-level mediation and mediated moderation analyses—To examine process models that linked temperature, subjective intensity, and autonomic responses, we used multilevel mediation [9,46,52]. Multilevel mediation and moderated mediation was assessed in Matlab using the Mediation Toolbox (<https://github.com/canlab/MediationToolbox>) [3,90]. See Figure 2 for a graphical depiction of hypothetical mediation and mediated moderation models. We implemented a mediation model with data from the ASC task to test whether stimulus temperature affected the autonomic heat response through pain intensity (see Figure 2A). In this mediation model, path *a* represents the effect of stimulus temperature on pain intensity and path *b* represents the effect of pain intensity on the heat-evoked autonomic response while controlling for temperature. Path *c* represents the overall effect of stimulus temperature on the heat-evoked autonomic response without controlling for pain intensity, while path *c'* represents the direct effect of temperature on the autonomic response, while controlling for the indirect path from temperature through pain intensity to autonomic responses (multiplicative path *ab*).

Somewhat outdated, the traditional approach to mediation has focused on whether controlling for a variable affects the significance of the overall effect, suggesting mediation [8]. Within this framework, a reduced association between temperature and autonomic response to non-significance when controlling for pain means that pain fully explains this association (i.e., suggesting “full” mediation). In contrast, a partial reduction points to process variable(s) not accounted for in addition to pain (i.e., suggests “partial” mediation). However, this approach is problematic because it does not account for sample size, which strongly influences the significance of overall and direct effects [80]. It has thus become customary to test indirect effects to infer mediation instead of interpreting differences in significance levels between overall and direct effects (e.g., [41,46,63]). Consequently, we refrain from interpreting non-significant direct effects between temperature and autonomic responses when controlling for pain, but point out theoretical implications in the case of partial mediation through pain.

In the TSPA task, we used moderated mediation [9] to test whether categorizing stimulation as painful relative to nonpainful influenced this process. As shown in Figure 2B, the mediated moderation model tested whether stimulus categorization (nonpainful vs. painful) interacted with temperature and intensity (experienced warmth or pain) to form path coefficients. The Mediation Toolbox uses non-parametric bootstrapping, which is more robust in handling violations to normality than traditional, parametric approaches [46], and downweights participants based on subject-level variance [90]. We used 5000 bootstrapping samples in each mediation analysis. Results between multilevel mediation and linear mixed effects models (which did not incorporate weighting or bootstraps) may diverge slightly because of this difference. Nevertheless, conclusions were nearly identical across different analytic strategies; we note any substantial differences throughout the paper.

Model constraints—To estimate regression model parameters, we had to restrict analyses to participants who provided sufficient data to estimate first-level regression estimates.

When testing associations with SCR and PDR during the ASC task, we limited analyses to participants with at least three valid measurements in the predictors and predictands. These constraints reduced sample size to 61 participants when testing associations with SCR, to 71 participants when testing associations with PDR, and to 58 participants when testing associations between SCR and PDR indicators.

When testing associations with SCR in the TSPA, we limited analyses to participants who had at least seven valid measurements in predictors and predictands. We also made sure that each participant had at least three thermal stimuli categorized as painful and three thermal stimuli categorized as nonpainful, to be able to test interactions with the thermal stimulus categorization variable. These constraints reduced sample size to 64 participants when testing interaction effects on SCR, to 66 participants in the post-hoc simple slope analyses limited to painful stimulation, and to 68 participants in the post-hoc simple slope analyses limited to nonpainful stimulation.

3. Results

We present results for both pain assessment tasks. First, we report basic relationships between temperature, pain, and autonomic responses separately for each task. Next, we report results of our central analyses testing whether pain intensity mediates the effect of temperature on heat-evoked autonomic responses both in the ASC and TSPA. Finally, we compared this mediation model for temperatures categorized as painful and nonpainful. For bivariate correlations (averaged across participants) between temperature, warmth and/or pain intensity, and autonomic responses, see Tables 2 (ASC) and 3 (TSPA).

3.1 Adaptive Staircase Calibration: Basic relationships

Association between SCR and PDR—In the ASC task, SCR and PDR measures were strongly associated. SCR AUC was associated with PDR AUC ($B = 32.11$, $SE = 9.27$, $t = 3.46$, $p = .001$). We also found significant relations across all additional autonomic response measures, i.e., amplitude, latency, and during all phases of heat stimulation (see Table 1).

Effects of stimulus temperature on pain and autonomic responses—As expected, increases in stimulus temperature were associated with increases in perceived pain intensity ($B = 0.82$, $SE = 0.04$, $t = 23.23$, $p < .001$). Temperature also predicted increased autonomic arousal, with effects on both SCR AUC ($B = 244.79$, $SE = 56.94$, $t = 4.30$, $p < .001$) and PDR AUC ($B = 40127.32$, $SE = 3542.62$, $t = 11.33$, $p < .001$) (for other SCR and PDR measures, see Supplemental Table 1). The upper panel of Figure 3 depicts SCR and PDR across time as a function of temperature. Phase analyses revealed that effects on SCR and PDR were present during peak heat stimulation (AUC from 4 to 8 sec) and after heat stimulation (AUC from 8 to 12 sec), but not during early heat stimulation (AUC .5 to 4 sec) (see Supplemental Table 1).

Effects of pain on autonomic responses—The lower panel of Figure 3 shows the effects of perceived pain (irrespective of temperature) on baseline-corrected SCR and PDR in the ASC task. Analyses revealed that pain intensity predicted both SCR AUC ($B = 346.68$, $SE = 67.35$, $t = 5.15$, $p < .001$) and PDR AUC ($B = 43046.09$, $SE = 4786.61$, $t =$

8.99, $p < .001$). Consistent with these findings, analyses revealed associations between pain and all additional SCR and PDR measures (i.e. amplitude, latency, and during all phases of heat stimulation) although associations during early heat stimulation only trended towards significance (see Supplemental Table 1).

3.2 Two-step pain assessment: Basic relationships

Effects of stimulus temperature and categorization on intensity ratings—

Similar to the ASC task, we found that stimulus temperature predicted perceived intensity during the TSPA ($B = 3.87$, $SE = 0.19$, $t = 20.55$, $p < .001$), when testing the simple association between temperature and perceived intensity without considering stimulus categorization as a moderating variable. Furthermore, a multilevel logistic regression analysis showed that higher temperatures were more likely to be categorized as painful ($B = 1.12$, $SE = 0.08$, $z = 13.77$, $p < .001$). An additional multilevel logistic regression analyses without person-centering temperature allowed us to determine the pain threshold across all participants at 44.8°C. Accordingly, temperatures below that threshold were more likely categorized as nonpainful, while temperatures above were more likely categorized as painful.

However, when testing the moderating role of stimulus categorization, temperature effects on subjective intensity were qualified by a stimulus temperature $\times$ stimulus categorization interaction ($B = 4.73$, $SE = 0.69$, $t = 6.81$, $p < .001$). Post-hoc simple slope analyses revealed that stimulus temperature predicted perceived intensity more when the stimulation was categorized as painful ($B = 8.48$, $SE = 0.52$, $t = 16.29$, $p < .001$) than when the stimulation was categorized as nonpainful ($B = 4.06$, $SE = 0.38$, $t = 10.73$, $p < .001$). These analyses suggest that stimulus temperature and subjective intensity are related, with painful temperatures relating to perceived intensity to a greater extent than to nonpainful temperatures.

Effects of stimulus temperature, perceived intensity, and categorization on autonomic responses—

Figure 4 depicts SCR for painful and nonpainful stimulation across time as a function of temperature (upper panel) and perceived intensity (lower panel). Both stimulus temperature and perceived intensity predicted SCR AUC to a greater extent when temperatures were categorized as painful relative to nonpainful, as painful vs. nonpainful stimulus categorization interacted both with temperature ($B = 655.86$, $SE = 203.28$, $t = 3.23$, $p = .002$) and perceived intensity ($B = 45.58$, $SE = 20.09$, $t = 2.27$, $p = .027$). Interactions on additional SCR measures are reported in Supplemental Table 1. To further probe these interactions, we conducted post-hoc analyses, testing the associations of temperature and perceived intensity with autonomic responses *separately* for stimulation categorized as painful and stimulation categorized as nonpainful.

Autonomic responses to stimuli judged as painful: Replicating findings from the ASC task, both stimulus temperature ($B = 474.33$, $SE = 86.64$, $t = 5.47$, $p < .001$), and pain ($B = 39.59$, $SE = 17.55$, $t = 2.26$, $p = .027$) predicted SCR AUC in separate analyses. These effects were present on all additional SCR measures, with the exception of SCR during early heat stimulation (see Supplemental Table 1).

Autonomic responses to stimuli judged as nonpainful: Associations were much weaker when temperatures were categorized as nonpainful. Neither temperature ($B = 62.87$, $SE = 38.87$, $t = 1.62$, $p = .111$) nor perceived intensity ($B = 6.46$, $SE = 4.86$, $t = 1.33$, $p = .189$) predicted SCR AUC when stimuli were judged as non-painful. It is noteworthy, though, that temperature predicted SCR AUC for nonpainful stimulus when using non-parametric bootstrapping (see analyses below). Associations with other SCR measures were stronger. Additional analyses revealed that stimulus temperature and perceived intensity predicted SCR amplitude and latency, perhaps because objective temperature and subjective intensity predicted SCR after heat offset and marginally during peak heat stimulation, but not during early heat stimulation (see Supplemental Table 1).

3.3 Process models linking autonomic responses with temperature and perceived pain

The above analyses demonstrate that objective stimulus intensity (i.e. temperature) and perceived intensity (i.e. pain) both predict autonomic responses when modeled separately, consistent with previous work [36]. Robust effects of temperature and subjective pain/intensity were present in both tasks, although we found differences based on pain categorization in the TSPA. Next, we tested whether subjective pain/intensity mediated the effect of temperature on the heat-evoked autonomic response, or whether temperature predicted the autonomic response independently from subjective pain/intensity. Unlike the linear mixed models reported above, we tested these hypotheses using multilevel non-parametric bootstrapping [46].

Pain mediates temperature effects on autonomic responses in the ASC task—

In the ASC, we tested mediation models in which actual stimulus intensity (i.e. temperature) indirectly predicted autonomic responses through perceived pain. We found significant mediation of both SCR and PDR AUC (see Figure 5). When controlling for stimulus temperature, pain continued to predict SCR AUC (path $b = 338.18$, $SE = 65.27$, $t = 5.18$, $p < .001$). In contrast, the effect of temperature on SCR AUC became non-significant when controlling for pain, dropping from path $c = 172.39$, $SE = 32.91$, $t = 5.24$, $p < .001$ to $c' = -82.20$, $SE = 69.38$, $t = -1.18$, $p = .265$. As expected, the indirect effect of stimulus temperature through pain on SCR AUC was significant (path $a*b = 237.85$, $SE = 47.42$, $t = 5.02$, $p < .001$). Similarly, when controlling for stimulus temperature, pain continued to predict PDR AUC ($b = 25452.01$, $SE = 5094.77$, $t = 5.00$, $p < .001$). The effect of temperature on PDR AUC dropped significantly when controlling for stimulus temperature, from $c = 32770.45$, $SE = 2366.37$, $t = 13.85$, $p < .001$ to $c' = 11938.93$, $SE = 4550.31$, $t = 2.62$, $p = .008$, as a significant indirect effect from stimulus temperature through pain on PDR AUC indicated ($a*b = 21359.70$, $SE = 3882.48$, $t = 5.50$, $p < .001$). We found the same mediation patterns for all other autonomic response measures (see Supplemental Table 2).

Intensity mediates temperature effects on autonomic responses in the TSPA, depending on pain categorization: Moderated mediation—

Next, we extended the mediation model tested in the ASC. Specifically, we found evidence for a moderated mediation model in which stimulus temperature predicted autonomic responses through perceived stimulation intensity, with the model consistently holding up during painful but not nonpainful stimulation (see Figure 6). When controlling for the temperature $\times$ stimulus

categorization interaction, the perceived intensity $\times$ stimulus categorization interaction continued to predict SCR AUC ($b = 40.05$, $SE = 12.20$, $t = 3.28$, $p < .001$). In contrast, the temperature $\times$ stimulus categorization interaction ceased to predict SCR AUC when controlling for the perceived intensity $\times$ stimulus categorization interaction, dropping from $c = 211.48$, $SE = 63.22$, $t = 3.35$, $p < .001$ to $c' = -8.96$, $SE = 86.70$, $t = -0.10$, $p = .971$. We found the same pattern of mediated moderation for all other SCR measures, except when predicting SCR during early heat stimulation (see Supplemental Table 3). To confirm moderated mediation effects, we decomposed the model and tested separate simple mediation models for stimuli categorized as painful and nonpainful.

When we only modeled trials categorized as painful, we replicated the mediation model from the ASC task: Perceived intensity fully accounted for the association between stimulus temperature and SCR AUC (see Figure 6). When controlling for stimulus temperature, pain predicted SCR AUC ($b = 35.43$, $SE = 10.18$, $t = 3.48$, $p = .002$), while temperature ceased to predict SCR AUC while controlling for pain, dropping from $c = 328.89$, $SE = 43.13$, $t = 7.63$, $p < .001$ to $c' = 51.62$, $SE = 74.47$, $t = 0.69$, $p = .489$. As expected, the indirect effect of stimulus temperature through pain on SCR AUC was significant ($a*b = 302.45$, $SE = 71.87$, $t = 4.21$, $p < .001$). We found the same pattern of mediation for painful trials for all other SCR indicators (see Supplemental Table 3).

In contrast, we did not find consistent evidence for mediation when we tested the mediation model for trials categorized as nonpainful (see Figure 6). When controlling for temperature, perceived warmth did not predict SCR AUC ($b = 1.89$, $SE = 3.14$, $t = 0.60$, $p = .559$). Unlike when testing simple associations above, temperature did predict SCR when using non-parametric bootstrapping: When controlling for perceived warmth, the effect of temperature on SCR AUC dropped from $c = 57.96$, $SE = 21.27$, $t = 2.72$, $p = .007$ to $c' = 35.43$, $SE = 27.96$, $t = 1.27$, $p = .227$, though this drop was not significant, as a non-significant indirect effect from temperature through perceived warmth to SCR AUC ($a*b = 18.91$, $SE = 11.11$, $t = 1.70$, $p = .083$) indicated. However, we note that we did find support for mediation on several other SCR measures, including SCR latency and amplitude, probably because we find mediation when predicting SCR during peak stimulation and after stimulation, but not during early stimulation (see Supplemental Table 3).

3.4. Supplementary analyses

For detailed methods and results, see the online supplement. First, we ruled out the possibility that statistical mediation observed with linear modelling (i.e. intensity as a mediator of temperature effects on ANS responses) was due to nonlinearities in the effects of temperature on intensity and/or ANS responses. However, assuming a power function underlying the sensory response to heat stimulation [76,86] and thus log-transforming model variables to move non-linear associations between these variables into linear space [1,23,76] did not substantially change associations both in the ASC and TSPA (see Supplemental Table 4).

Second, we ruled out the possibility that associations of stimulus categorization were confounded with temperature by testing the associations of stimulus categorization with SCR measures within restricted temperature ranges (see Supplemental Table 5). Overall,

SCR AUC did not differ as a function of categorization within restricted ranges. However, particularly in the medium and high temperature range (44 to 50°C), we found that SCR amplitudes and latencies were elevated when thermal stimuli were characterized as painful relative to nonpainful. By holding temperature intervals constant, we ruled out the possibility that effects of stimulus categorization on the autonomic response are due to a positive association between stimulus categorization and temperature.

The latter finding somewhat explains why visual inspections of the effects of temperature and pain in the ASC (Figures 3A and C) suggested weaker overall effects on SCRs than in the painful trials of the TSPA (Figures 4B and D). The TSPA probably manages better than the ASC to identify painful temperatures which may have led to stronger overall SCRs. When using continuous variables, however, temperature and intensity predicted SCRs in separate analyses to a similar extent regardless of task, suggesting that these tasks despite methodological differences capture similar aspects of the autonomic response to nociception.

4. Discussion

Across two different heat pain assessment tasks, we found that perceived pain consistently predicted autonomic responses over and above objective noxious heat stimulation (i.e. temperature). Furthermore, we found statistical evidence for a mediation model, in which perceived pain mediated the effects of noxious heat on autonomic responses – both SCRs and PDR. Our two-step pain assessment (TSPA) task revealed that this process was in turn moderated by subjective categorization of the stimulus as painful or non-painful. Follow-up analyses revealed that when heat stimulation was perceived as nonpainful, temperature predicted increases in intensity and skin conductance, but intensity did not consistently account for the association between temperature and SCR. In contrast, when heat stimulation was perceived as painful, we observed the same relationships as in the adaptive staircase calibration (ASC) task: subjective pain mediated temperature effects on autonomic responses.

4.1 Theoretical and practical implications

These findings have important theoretical implications, highlighting the importance of pain appraisal in regulating the autonomic response to noxious stimulation. Although there is functional overlap between bottom-up and top-down nociceptive processes and the autonomic nervous system both on subcortical and cortical levels of the central nervous system [10,11], it remained unclear whether conscious appraisals of pain are necessary for noxious stimulation to elicit a defensive autonomic response. Though past research has tested the unique contribution of pain to autonomic responding [66] or tested autonomic responses to both painful and innocuous heat stimulation [59,85], our findings are the first to show that 1) pain statistically mediates the effect of varying noxious stimulation on autonomic responses, 2) this process is reduced for innocuous heat stimulation, and 3) explicit category judgments (i.e. labeling pain vs no-pain) directly modulate autonomic responses, irrespective of objective stimulus intensity. This pattern of findings suggests that consciously experiencing pain is important – if not crucial – for initiating a defensive

autonomic response to tissue threat. Conversely, our findings rule out a purely reflexive account of autonomic responding, in which increased autonomic activity reflects objective properties of noxious stimulation irrespective of the pain experience. In contrast, our findings suggest that experienced pain plays an important role in modulating spinal or supraspinal ANS responses to noxious stimulation. Such findings pose a challenge to accounts linking nociception directly to ANS responses while minimizing the mediating role of pain appraisal [42,43] as well as to important translational work of pain in non-human primates and rodents, as they emphasize the role of language and appraisal in driving autonomic responses in humans. In contrast, our findings are consistent with classic work on the role of emotional appraisal and affective experience in shaping the physiological response to threat [33,35,38,56,57,81,84]. It is noteworthy that pain did not fully account for the association between pain and PDR, which suggest that other spinal or supraspinal processes in addition to pain may also be involved in the autonomic response to noxious stimulation. However, such potential additional processes do not diminish the central role that pain seems to play in the autonomic, nociceptive response.

As a consequence, our findings document the flexibility of the autonomic pain response to quickly adapt to perceived or actual changes in environmental demands. Receiving information about upcoming pain can alter the autonomic pain response [27,28,62,74]. Furthermore, pain sensitivity is malleable and can quickly increase or decrease over time, leading to both sensitization or habituation depending on the level of repeated noxious stimulation [25,51,91]. To respond appropriately, ANS responsiveness needs to be able to adapt to various perceived or actual environmental circumstances. Pain appraisal that adjusts to situational affordances while regulating the autonomic response allows for such autonomic flexibility.

Our results suggest that autonomic responses are highly sensitive to changes in subjective pain, which can be interpreted as support for the use of ANS markers as non-verbal proxies of pain in pharmaceutical, medical, and legal settings. However, biomarkers require not only sensitivity but also specificity [72]. Autonomic responses are known to reflect arousal, which is inherently non-specific: Increased autonomic arousal is associated with other emotionally salient events, such as during anticipation of pain [4,26,71], when experiencing rewarding or surprising outcomes [19,20,61], and during other types of aversive or appetitive stimulation, such as pleasant and unpleasant imagery [15]. Thus, the broad relevance of physiological arousal limits the suitability of these measures for non-verbal biomarkers of pain. An exciting direction is to isolate more fine-grained aspects of autonomic responses that predict pain with model-based methods [7,36] or a combination of autonomic measures [60,87]. However, any measures that are highly sensitive to pain must also be compared to other arousing processes to demonstrate specificity prior to serving as a potential non-verbal biomarker of pain.

4.2 Limitations and future directions

Several avenues for future research remain. Our findings need to be replicated and extended using different pain induction methods, such as cold stimulation, pressure stimulation, and electric shock. When conducting these studies, it is important to include innocuous control

stimulation conditions, in order to compare unique associations between subjective stimulation and autonomic responding both for painful and nonpainful stimulation. Only a fraction of research on the association between acute pain and autonomic response includes adequate innocuous stimulation, which limits conclusions about how unique the contribution of pain to ANS responsivity really is [53]. Furthermore, future research needs to include direct measures of peripheral nociception, to account for intra- and interindividual differences in afferent nociceptive input beyond the effect of temperature. For example, a microneurographic approach would allow to directly measure peripheral nociceptive input stemming from noxious heat stimulation [40,69]. Similarly, the nociceptive flexion response following electric stimulation of the sural nerve captures the pain threshold on the spinal level and correlates well with subjective pain intensity (e.g., [93]).

Similarly, results need to be generalized to other measures of autonomic responding, such as measures of respiration or cardiovascular reactivity. We had to exclude a relatively large amount of trials in the SCR data due to artifacts (> 21% of trials). Fortunately, we mostly replicate findings across SCR and PDR data in the ASC, which gives us confidence that exclusion rates did not unduly influence our findings. However, replication of these findings using other ANS measures is desirable. In general, including multiple autonomic measures allows for extracting a latent autonomic arousal response [36], and thus increases confidence that autonomic measures indeed tap into the same aspect of autonomic responding. Including measures of cardiovascular reactivity in particular would allow for disentangling sympathetic from parasympathetic aspects of the autonomic pain response. Skin conductance and pupil dilation measures in our research likely reflected the sympathetic nervous system's threat response to pain [14,17,88]. Other autonomic measures, such as heart rate variability, are more likely to capture parasympathetic downregulation of the sympathetic pain response [49]. Combining these measures would help to determine whether the association between pain and autonomic response is driven by increased sympathetic activation, decreased parasympathetic activation, or both.

In addition, more research on the causal link between pain and autonomic responses is needed. Our findings provide statistical evidence for the role of pain in regulating the autonomic response to noxious stimulation. However, our findings are correlational and need to be supplemented with experimental manipulations of pain. There is substantial evidence that psychological interventions aimed to alter the pain experience, such as mood inductions, manipulating pain expectations, or hypnosis, affect autonomic responses [53]. It remains unclear, however, whether these interventions reduce ANS responses by directly reducing pain or by reducing other psychological and physiological processes associated with a defensive autonomic response. As a consequence, experimental research on pain and autonomic activation has convincingly documented the power of the mind in changing the autonomic pain response. Nevertheless, direct manipulations of pain and autonomic responses, such as through pharmacological interventions, are needed to complement existing psychological research in order to conclusively pinpoint the role of pain in the autonomic response to noxious stimulation.

Finally, it remains unclear how well autonomic responses track experimentally induced pain for people suffering from chronic pain. A number of studies show that chronic pain

conditions, such as fibromyalgia, irritable bowel syndrome, or painful bladder syndrome, are associated with altered tonic ANS activity (see [29,65], for reviews). Furthermore, people with chronic pain syndromes may have impaired interoceptive access into body and mind processes (see [31], for a review). Altered autonomic responses and a lack of conscious insight into one's pain experience could reduce the functional association between pain and autonomic response. Such a dissociation would in turn affect the diagnostic value of autonomic responding as a pain measure for people suffering from chronic pain conditions. According to recent research, during longer-lasting, tonic, pain episodes in the range of minutes, experienced pain stops predicting autonomic responses above and beyond noxious stimulation [67], perhaps because sensory aspects of noxious stimulation become less important and affective-motivational factors start to dominate the pain experience [75]. Consistent with our findings, however, past research on acute (6-sec) heat pain has shown that variations in pain continue to predict changes in autonomic responses (skin conductance and heart rate) when holding stimulus temperature constant [59]. Thus, more research is needed to probe the relative contribution of pain and noxious stimulation in people suffering from chronic pain conditions and healthy volunteers.

4.3 Conclusion

In summary, our findings show that pain appraisal plays an important role in the defensive autonomic response to noxious heat stimulation. In two pain assessment tasks, we find that autonomic responding is not simply a reflexive reaction to potential or actual tissue damage, but that the individual pain experience is an important predictor of autonomic responses above and beyond objective noxious stimulation intensity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Trial structure. (A) general trial structure, (B) trial in the adaptive staircase pain assessment, and (C) trial in the two-step pain assessment. We measured skin conductance responses (SCR) and pupil dilation responses (PDR) in the adaptive staircase pain assessment and SCR in the two-step pain assessment.

Figure 2.

Theoretical process models. (A) *Mediation model*, in which the effect of stimulus temperature on the Autonomic Nervous System (ANS) response is statistically mediated by pain intensity. (B) *Mediated Moderation model*, in which the interaction effect between stimulus temperature and categorization in predicting the ANS response is statistically mediated by the interaction between stimulus categorization and intensity (experienced warmth or pain). In the mediation model, path c represents the overall effect of temperature on the ANS response, a represents the effect of temperature on intensity, b represents the effect of intensity on the ANS response, and c' represents the direct effect of temperature on the ANS response, while subtracting the multiplicative indirect effect of temperature through intensity on the ANS response (path ab). In the mediated moderation model, paths represent the interaction effects of these model variables with the moderator stimulus categorization (nonpainful vs. painful). Individual-level models (i) are aggregated to the group-level using non-parametric bootstrapping.

Figure 3.

Averaged baseline-centered autonomic arousal responses (SCR and PDR) across heat trials in the adaptive staircase pain assessment. (A) SCR and (B) PDR, both by actual stimulus temperature. (C) SCR and (D) PDR, both by perceived thermal intensity. Pupil dilation is measured in arbitrary units (a. u.). For the purpose of visualization, responses on the thermal intensity VAS are divided up into four categories, to reflect a “No Pain (0–2 VAS)” category, and three pain categories: Low Pain (2–4 VAS), Moderate Pain (4–6 VAS), and High Pain (6–10 VAS). Analyses used continuous, rather than categorical, pain intensity ratings.

Figure 4.

Averaged baseline-centered skin conductance response across heat trials in the two-step pain assessment. SCR by actual stimulus temperature, when thermal stimuli were rated as (A) nonpainful or (B) painful. SCR by perceived thermal intensity, when thermal stimuli were rated as (C) nonpainful or (D) painful. For the purpose of visualization, responses on the thermal intensity VAS are divided up to reflect perceived nonpainful and painful intensity using three warmth categories and three pain categories: Low (0–33), Medium (34–66), and High (67–100). Analyses used continuous, rather than categorical, warmth and pain intensity ratings.

Figure 5.

Modelling the association of actual stimulus intensity with (A) skin conductance response (SCR) and (B) pupil dilation response (PDR) through perceived pain (adaptive staircase pain assessment). Path coefficients are unstandardized regression coefficients and their standard errors, derived using non-parametric bootstrapping. Statistics in square brackets indicate the associations of stimulus temperature with autonomic responses without controlling for pain. We calculated measures of SCR and PDR, calculating area under the curve (AUC) from .5 to 12 secs after heat onset. See Supplemental Table 2 for more comprehensive statistical information. *** $p < .001$, ** $p < .01$

Figure 6.

Modeling the association of actual stimulus intensity with skin conductance response (SCR) through perceived pain (two-step pain assessment). Stimulus categorization (nonpainful vs. painful) moderates this model. The model is decomposed into separate mediation models analyzing stimulation perceived as painful and nonpainful. Path coefficients are unstandardized regression coefficients with their standard errors, derived using non-parametric bootstrapping. Statistics in square brackets indicate associations without controlling for intermediate variables. We calculated measures of SCR, calculating area under the curve (AUC) from .5 to 12 secs after heat onset. See Supplemental Table 3 for more comprehensive statistical information. *** $p < .001$, ** $p < .01$, * $p < .05$

Table 1

Associations between SCR and PDR measures in the adaptive staircase calibration.

Indicator	SCR predicting PDR			
	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i>
AUC	32.11	9.27	3.46	.001
AUC (.5 – 4 sec)	27.48	11.43	2.40	.020
AUC (4 – 8 sec)	36.34	11.01	3.30	.002
AUC (8 – 12 sec)	88.56	17.29	5.12	<.001
Amplitude	5.47	0.70	7.83	<.001
Latency	0.25	0.05	5.44	<.001

Notes. *N* = 58 healthy adult volunteers. Analyses are restricted to participants who provided both at least three valid PDR and SCR measurements. Response amplitudes were square-root transformed to account for non-normalcy in distributions. Regression coefficients are unstandardized. SE are standard errors of unstandardized regression coefficients.

Table 2

Mean bivariate correlations (standard deviations) across participants between temperature, pain, and autonomic response measures in the adaptive staircase calibration.

Measure	1.	2.	3.
1. Temperature	--		
2. Pain	.83 (.15)	--	
3. SCR (AUC)	.23 (.25)	.30 (.23)	--
4. PDR (AUC)	.43 (.19)	.44 (.23)	.21 (.32)

Notes. Correlations are calculated within-person and averaged across participants. Standard deviations of correlations are reported in parentheses. Because of averaging, significance levels of correlations are not calculated. Correlation means and standard deviations are calculated using Fisher's z-transformation, to account for non-normalcy in the distribution of correlations.

Table 3

Mean bivariate correlations (standard deviations) across participants between temperature, intensity (warmth or pain), and SCR for nonpainful (below diagonal) and painful (above diagonal) stimulation in the two-step pain assessment.

Measure	1.	2.	3.
1. Temperature	--	.77 (.19)	.32 (.28)
2. Warmth/Pain	.53 (.29)	--	.36 (.38)
3. SCR (AUC)	.10 (.29)	.06 (.28)	--

Notes. Correlations are calculated within-person and averaged across participants. Standard deviations of correlations are reported in parentheses. Because of averaging, significance levels of correlations are not calculated. Correlation means and standard deviations are calculated using Fisher's z-transformation, to account for non-normalcy in the distribution of correlations.