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The skin conductance response indicating pain relief is independent of self or social influence on pain

Marthe Gründahl[1] | **Leonie Retzlaff**[1] | **Martin J. Herrmann**[1] | **Grit Hein**[1] | **Marta Andreatta**[2,3]

[1]Center of Mental Health, Department of Psychiatry, Psychosomatic and Psychotherapy, Translational Social Neuroscience Unit, University of Würzburg, Würzburg, Germany

[2]Department of Psychology, Education & Child Studies/Clinical Psychology, Erasmus University of Rotterdam, Rotterdam, The Netherlands

[3]Department of Biological Psychology, Clinical Psychology, and Psychotherapy, University of Würzburg, Würzburg, Germany

Correspondence
Marta Andreatta, Department of Psychology, Education & Child Studies/Clinical Psychology, Erasmus University of Rotterdam, Postbus 1738, 3000 DR Rotterdam, The Netherlands.
Email: andreatta@essb.eur.nl

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Abstract

Pain relief is defined as the ease of pain and is thus highly relevant for clinical applications and everyday life. Given that pain relief is based on the cessation of an aversive pain experience, it is reasonable to assume that pain relief learning would also be shaped by factors that alter subjective and physiological pain responses, such as social presence or a feeling of control. To date, it remains unclear whether and how factors that shape autonomic pain responses might affect pain relief learning. Here, we investigated how pain relief learning is shaped by two important factors known to modulate pain responses, i.e. social influence and controllability of pain. Skin conductance responses (SCRs) were recorded while participants learned to associate a formerly neutral stimulus with pain relief under three different pain conditions. In the social-influence condition ($N = 34$), the pain stimulation could be influenced by another person's decisions. In the self-influence condition ($N = 31$), the participants themselves could influence the pain stimulation. Finally, in the no-influence condition ($N = 32$), pain stimulation was simply delivered without any influence. According to our results, the SCRs elicited by the stimulus that was associated with pain relief were significantly smaller compared to the SCRs elicited by a neutral control stimulus, indicating pain relief learning. However, there was no significant difference in the pain relief learning effect across the groups. These results suggest that physiological pain relief learning in humans is not significantly influenced by social influence and pain controllability.

KEYWORDS
backward conditioning, electrodermal activity, pain relief learning, social modulation

Grit Hein and Marta Andreatta share senior authorship.

1 | INTRODUCTION

Pain relief is defined as the ease of pain as an aversive state (Riebe et al., 2012; Solomon, 1980). The subjective and physiological pain relief responses can be studied using a relief-learning paradigm where a neutral stimulus is repeatedly presented after a painful stimulus (i.e., backward conditioning; Andreatta et al., 2010; Luck & Lipp, 2017). Here, implicit learning processes can be reflected in autonomic responses (Schultz & Helmstetter, 2010). If the neutral stimulus is presented within the pain cessation period, animals (rats, Acosta et al., 2017; honeybees, Kirkerud et al., 2017; drosophilia melanogaster, Yarali et al., 2008) or humans (Andreatta et al., 2016) learn to associate this formerly neutral stimulus with pain relief. As a result, the presence of the pain relief-associated stimulus ($_{relief}$CS) on its own leads to an attenuation of autonomic responses such as startle reflex responses (Andreatta et al., 2010; Luck & Lipp, 2017) and skin conductance responses (SCR; Andreatta et al., 2013) compared to a novel stimulus that is not associated with pain relief.

The SCR is predominantly mediated by the sympathetic cholinergic system (Critchley & Nagai, 2013). In the laboratory setting, at rest and constant temperature, changes in SCRs indicate changes in sympathetic arousal which have been associated with fear and pain learning (Boucsein, 2012; Delgado et al., 2006; Leknes et al., 2008). Experiencing pain is associated with increased SCRs, while relief is associated with reduced SCRs (Leknes et al., 2008). Previous conditioning research have found enhanced SCRs towards fear-conditioned stimuli signaling danger or pain compared to safety signals (Andreatta et al., 2013; Knight et al., 2006). Advancing these findings, signals of pain relief have been associated with reduced SCRs after conditioning, compared to both fear and safety signals (Andreatta et al., 2013).

Recent studies have started to investigate experimental factors that shape pain relief learning in humans. For example, it has been shown that pain relief learning unfolds on the subjective level if the pain is predictable. Neutral stimuli presented after unpredictable pain stimuli are associated with pain (resulting in negative valence) instead of pain relief (resulting in positive valence; Andreatta et al., 2013). A recent study implied that the subjective valence of a relief stimulus depends on the intensity of the aversive stimulation (Green et al., 2020). While pain relief is robustly indexed on the physiological level (indicated by attenuated startle and SCRs), subjective measures such as ratings seem to be additionally influenced by factors related to the presentation of the pain. This demonstrates a discrepancy between implicit and explicit measures (Andreatta et al., 2010, 2012; Green et al., 2020; Luck & Lipp, 2017; Strack & Deutsch, 2004).

Given that pain relief learning is based on the cessation of an aversive pain experience, it is reasonable to assume that factors that alter subjective and physiological pain responses also shape pain relief learning. Supporting this assumption, it has been demonstrated that increases in pain intensity are associated with increased relief ratings (Leknes et al., 2008). There is ample evidence that pain intensity is affected by a number of different factors, most importantly social factors (Che et al., 2018; Krahe et al., 2013) and the controllability of the pain stimulation (Salomons et al., 2004; Stephens et al., 2016; Wiech et al., 2006). With regard to social factors, social support such as helping (Hein et al., 2018) and offering sympathetic comments (Brown et al., 2003; Roberts et al., 2015) have been observed to reduce subjective and physiological pain responses. Overall, previous findings show that clearly expressed social support, like comforting words and touching, has stronger effects than less explicit social support like social presence (Che et al., 2018). Compared to more familiar social partners, for example, a friend, social effects of strangers are often less pronounced (Jackson et al., 2009; Krahe et al., 2013; Master et al., 2009). Nonetheless, recent studies demonstrated a reduction in pain perception (Edwards et al., 2017; Sambo et al., 2010) and autonomic fear responses (e.g., SCRs to an aversive sound, Qi et al., 2020) when another person was present, even if this person was a stranger. However, the results are inconsistent. For example, there is also evidence for an increase in pain responses in association with a social presence, for instance, if the present person shows a strong reaction to the pain stimulation (Hurter et al., 2014), or no social influences on pain processing at all (see e.g., Che et al., 2018; Modić Stanke & Ivanec, 2010). The effects of social influence on pain and subsequent relief learning remain unclear.

With regard to controllability of pain, there are studies showing that perceived control over pain reduced subjective (Wiech et al., 2006) and neural (Mohr et al., 2005; Salomons et al., 2004; Wiech et al., 2006) pain responses in healthy participants. In chronic pain samples, perceived control over pain (Stephens et al., 2016) and the belief in one's functionality despite pain (i.e., "self-efficacy"; Mirjalili et al., 2011; Perry & Francis, 2013) were associated with a reduction in pain severity, pain-related cognitions, and emotionality (e.g., depression). Moreover, participants who actively learned to avoid aversive events showed lower SCRs than a non-avoidance group, both to a conditioned stimulus and during novel threat conditioning (Boeke et al., 2017). Notably, although reporting attenuated physiological pain responses, some studies on pain controllability show no differences in pain severity ratings (Mohr et al., 2012; Salomons et al., 2004). Others

showed changes in perceived suffering, but not physiological responses (Löffler et al., 2018).

Overall, previous studies indicate that social influence and controllability of pain can influence subjective and physiological pain responses. However, it remains unclear whether these factors also affect pain relief learning. Hence, in the present study, we investigated if subjective and autonomic pain relief is modulated by social influence and controllability of pain, that is, two factors that play an essential role in modulating pain.

To do so, we used a relief-learning paradigm. In the learning phase, a pain stimulus was presented, serving as an unconditioned stimulus (US). A visual cue appeared after each pain stimulus and became the conditioned stimulus ($_{relief}$CS). In the test phase, the $_{relief}$CS was again presented, as was a novel control stimulus (control). The US was absent in this phase. Participants were randomly assigned to three different groups that received the pain (i.e., the US) under three different conditions. In one group, the frequency of pain stimulation could ostensibly be influenced by another person (a confederate) that was unknown to the participant and sat in another room (social-influence group). In the second group, the frequency of pain stimulation could be influenced by the participants themselves by actively avoiding the pain via key press (self-influence group). In the third group, the frequency of pain stimulation was determined by the computer program and could not be influenced (no-influence group). Notably, the frequency of pain stimulation and the test phase were similar in all three groups. Participants rated their fear, arousal, and the valence of the stimuli after each phase. Their SCRs were continuously measured. Note that unlike previous studies (e.g., Brown et al., 2003; McClelland & McCubbin, 2008), the social-influence condition did not include active social support. This was chosen to keep the three conditions as similar as possible. Social interactions introduce a high number of additional confounding factors which would have been difficult to reproduce in the non-social conditions.

Based on previous evidence from pain relief learning (Andreatta et al., 2016; Gerber et al., 2014; Luck & Lipp, 2017), we hypothesized that participants learn to associate the neutral stimulus with the prior experience of pain relief. If this is the case, the $_{relief}$CS should be rated as more positive and less arousing and fear-inducing than the control stimulus. Moreover, in the test phase, the SCRs elicited by the $_{relief}$CS should be reduced compared to the SCRs elicited by the control stimulus.

Based on findings that social presence and controllability of pain can decrease pain's aversiveness (Edwards et al., 2017; Mohr et al., 2005; Wiech et al., 2006), and given that pain relief learning is based on the cessation of an aversive pain experience (Gerber et al., 2014), we predicted reduced subjective and autonomic pain responses in the social-influence and self-influence group. If pain (i.e., the US) is perceived as less intense, participants should experience less pain relief (Leknes et al., 2008), resulting in reduced pain relief learning compared to the no-influence group. To reflect the diminished pain relief learning, the difference in SCRs and ratings between the $_{relief}$CS and control in the test phase should be significantly smaller in the social-influence and self-influence compared to the no-influence group.

Alternatively, inspired by studies that showed no effect of social influence and controllability on pain responses (Löffler et al., 2018; Modić Stanke & Ivanec, 2010), it is also possible that we observe comparable subjective and autonomic pain responses in the three experimental conditions (social-influence, self-influence, no-influence). In this case, we would expect no differences in pain relief learning between the experimental conditions, because there are no differences in the pain stimulus (US) that may drive differential pain relief learning. As a result, there should be no significant differences in SCRs and ratings between the $_{relief}$CS and control in the test phase between the social-influence, the self-influence and the no-influence conditions.

2 | METHOD

2.1 | Participants

One-hundred and twenty-five healthy female volunteers participated in the study. They received financial compensation for participating (12 €) and were recruited via university-based and public advertisements. The sample size was chosen based on comparable studies on pain relief learning (Andreatta et al., 2010, 2016). Moreover, we recruited one female student (confederate) trained to act as a partner in the social-influence group. We chose female participants and a female confederate to control for gender and avoid potential cross-gender effects in the social-influence group (which might occur if female participants are paired with a male confederate or vice versa; Hein et al., 2016). Besides age and gender, we controlled for body mass index (BMI; Aldosky, 2019). Ambient temperature (Wilcott, 1963) was kept similar across groups. Participants were asked not to consume nicotine or mind-altering substances prior to the assessment to prevent their cholinergic impact on SCRs (Boucsein et al., 2012). Further exclusion criteria were assessed by self-report or questionnaire (depression: ADS-K, see 2.3 Questionnaires) and included neurological, cardiac and psychiatric illness, epilepsy, chronic pain condition, hearing loss, pregnancy and lactation, and acute depressive symptoms.

We had to exclude 28 participants from the analysis. Twelve participants were excluded because of technical problems, interruption of the experiment, or missing ratings. Sixteen participants were defined as non-responders for the SCRs (mean <0.02 μS, see also 2.6 Data reduction) and consequently excluded from all analyses. In the end, we considered 97 participants for the analysis. 93.8% of participants had the highest German educational level, and 91.8% were students (see Table 1 for characteristics of the final sample). Participants were randomly divided into three groups according to the learning protocol.

Post-hoc power analysis using G*Power (Faul et al., 2009) showed that the final sample size ($N = 97$) had sufficient power to detect pain relief learning in SCRs (Power = 097; based on Phase x Group interaction for SCRs with partial $\eta^2 = 0.079$, see 3.4).

The study was carried out in accordance with the Declaration of Helsinki (World Medical Association, 2001) and the American Psychological Association's ethical principles (American Psychological Association, 2017). The local ethics committee of the University Hospital Würzburg approved the study protocol.

2.2 | Stimulus material

2.2.1 | Pain stimuli

The *painful stimulus* (US) consisted of painful air-pressure-induced stimulation administered to the non-dominant hand's index finger by an Impact Stimulator (Franken Labortechnik) using a compressed air-accelerated projectile. The plastic projectile weighed 612 μg and was shot vertically through a Plexiglas tube attached to the left index finger, approximately 0.5 cm below the proximal nail fold. The stimulus intensity was individually determined using a threshold procedure (Hein et al., 2018; Huskisson, 1974). During pain threshold evaluation, we increased stimulation intensity step by step, starting at the lowest possible intensity (0.25 mg/s). The stimulus intensity was augmented by increasing the compressed air in steps of 0.25 mg/s (range = 2–6 mg/s). Participants rated each stimulation on a ten-level visual analog pain scale (Hein et al., 2018; Huskisson, 1974). The value 0 was defined as "not perceptible", 1 as "barely perceptible", 2–3 as "mild pain", 4–5 as "moderate pain", 6–7 as "severe pain", 8 as "considerably painful but still endurable" and 9–10 as "unbearable pain". The target value 8 on the pain scale marked the upper threshold, and the corresponding painful stimulation delivered by the Impact Stimulator served as the individual stimulation intensity for the experiment. The mean intensity of the US stimulation was 2.86 mA ($SD = 0.65$).

2.2.2 | Visual stimuli

As visual stimuli (training, relief and control stimulus), we used three grey geometrical shapes (RGB: 145, 145, 145) presented at eye level over a black background for 6 s on a 19″ computer screen localized circa 140 cm in front of the participants. Shapes were a triangle (10 cm width × 8.6 cm height), a square (10.3 × 10.3 cm), and a circle (10.5 × 10.5 cm). The three different shapes and their roles as training, relief, and control stimulus were counter-balanced across the participants. In addition, a red (RGB: 255, 0, 0) or blue (RGB: 0, 128, 255) lightning bolt (4.1 cm width × 7.5 cm height) served as a

TABLE 1 Characteristics of experimental groups

	No-influence	Self-influence	Social-influence	Group comparisons
N	32	31	34	
Age (*SD*)	23.94 (3.62)	24.26 (3.36)	23.32 (3.37)	$F(2, 94) = 0.62$, $p = .540$
ASI-3 (*SD*)	19.50 (11.19)	17.68 (10.35)	21.26 (8.67)	$F(2, 94) = 1.03$, $p = .363$
BMI (*SD*)	23.34 (3.45)	21.67 (2.68)	23.51 (3.99)	$F(2, 94) = 0.05$, $p = .827$
High education level[a]	96.9%	100%	94.1%	$F(2, 94) = 0.90$, $p = .410$
STAI-Trait (*SD*)	36.97 (8.47)	35.26 (8.11)	35.56 (7.57)	$F(2, 94) = 0.41$, $p = .664$
STAI-State at start (*SD*)	36.16 (7.60)	34.32 (6.17)	35.41 (5.62)	$F(2, 94) = 0.13$, $p = .878$
STAI-State at end (*SD*)	37.60 (8.74)	38.10 (7.71)	38.32 (7.93)	
ADS-K (*SD*)	8.31 (4.65)	7.00 (3.92)	7.71 (4.41)	$F(2, 94) = 0.72$, $p = .489$
Pain intensity (*SD*)	2.98 (0.60)	2.80 (0.65)	2.80 (0.70)	$F(2, 94) = 0.79$, $p = .457$

[a]Low education level: no certificate, secondary school certificate (Volks-/Hauptschule), or intermediate secondary school certificate (Mittlere Reife).

Abbreviations: ADS-K, Allgemeine Depressionsskala-Kurzform (depression scale); ASI-3, anxiety sensitivity index-3; BMI, body mass index; High education level, vocational technical diploma (Fachhochschulreife) or higher education entrance qualification (Allgemeine Hochschulreife); STAI, state-trait anxiety inventory.

signal stimulus. If the US followed, a rectangular frame (7.2 cm width × 7.9 cm height) in the same color briefly surrounded the lightning bolt (for more details, see 2.4 Procedure).

2.2.3 | Ratings

After each experimental phase (Figure 1a), participants rated the valence ("how unpleasant vs. pleasant was the presented picture?"), arousal ("how strong was your arousal elicited by the presented picture?"), and fear ("how strong is your fear towards this picture?") of the visual stimuli using three different visual analog scales (VAS) ranging from 1 to 9. One indicates "very unpleasant" for the valence, "calm" for the arousal and "no fear" for the fear rating, while 9 indicates "very pleasant", "exciting" and "strong fear", respectively. After both the learning and test phase, we verified participants' contingency awareness by asking them to rate the intensity of the painful stimulation that they associated with each visual stimulus (i.e., US-expectancy ratings). The VAS ranged from 0 (no association) to 100 (perfect association). Both valence and US-expectancy ratings were additionally collected at three times throughout the learning phase for the visual relief stimulus (after 6, 12, and 18 trials, see Figure 1b; results reported in Supplementary Material). At the end of the experiment, all participants rated the painful stimulation's intensity again, as described above. Lastly, the overall tolerability of the experiment ("How tolerable did you find the experiment?") was rated on a 9-point Likert scale ranging from 1 ("easy to tolerate") to 9 ("very difficult to tolerate").

2.3 | Questionnaires

Individual differences in dispositional (trait) anxiety were measured using the German versions of the anxiety sensitivity index-3 (ASI-3; Kemper et al., 2009) and the trait anxiety subscale of the state-trait anxiety inventory (STAI; Laux et al., 1981). We collected the German state subscale of the STAI and the positive and negative affect schedule (PANAS; Krohne et al., 1996) at the beginning and at the end of the experimental session to assess the current emotional state of the participants. For the screening of depressive symptoms, we used the German 15-item short form of the Center for Epidemiologic Studies Depression Scale (Allgemeine Depressionsskala-Kurzform, ADS-K; Hautzinger & Bailer, 1993). In addition, participants of the social-influence group rated their impression of the other person (i.e., the confederate) regarding perceived

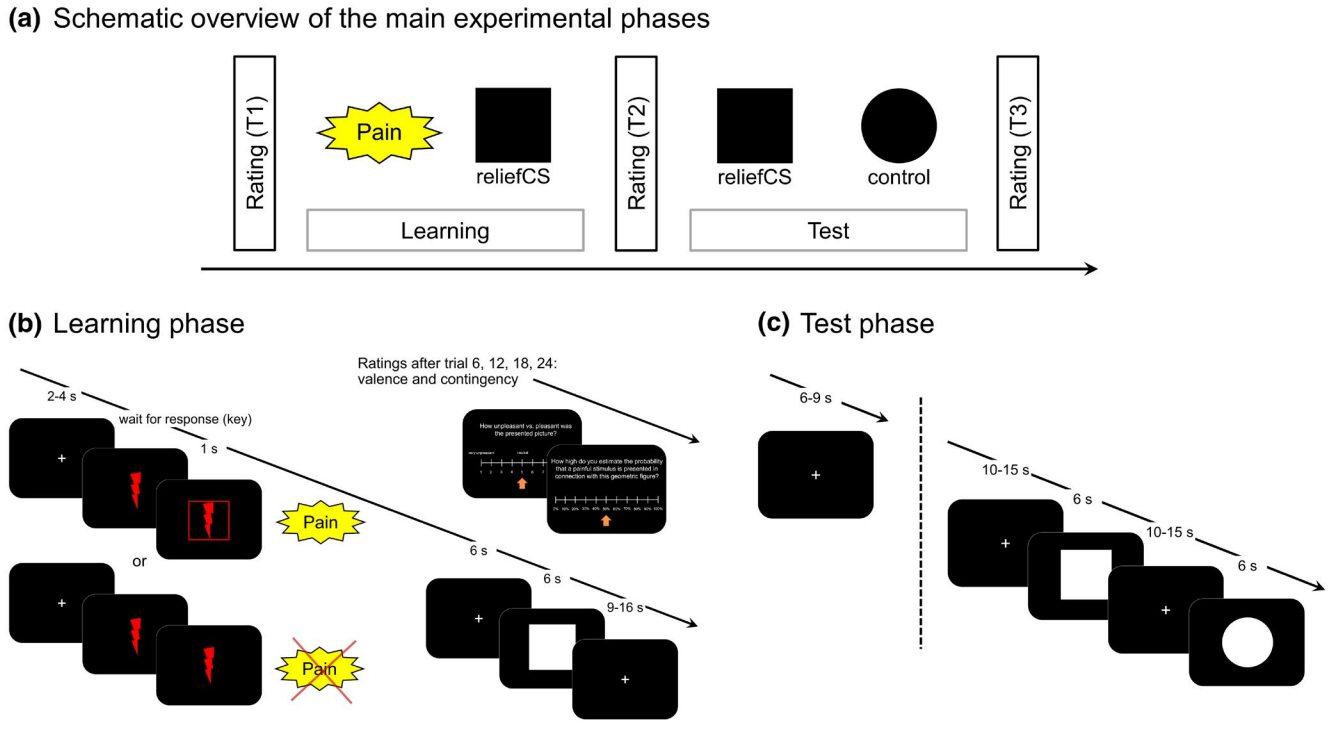

FIGURE 1 Main experimental phases. (a) Schematic overview of ratings, learning phase and test phase. (b) Detailed display of a learning phase trial with call for keypress (lightning bolt), US delivery (Pain) and $_{relief}$CS (here: square), and ratings of valence and contingency. (c) Detailed display of a test phase trial with presentation of $_{relief}$CS and control (here: circle), preceded by seven startle habituation trials

similarity, likability, trustworthiness, supportiveness, and familiarity (Hein et al., 2016).

2.4 | Procedure

After filling in the questionnaires, participants were informed that a series of geometrical shapes, a painful air-puff to the finger and loud white noises would be presented during the experiment and were instructed to fixate on the middle of the screen. We did not mention the contingency between $_{relief}$CS and US. Next, the electrodes were attached, and the pain threshold procedure was performed as described above.

Participants were randomly assigned to three different groups. Participants assigned to the social-influence group briefly met another person (confederate) seated in an adjacent experimental booth without any further contact with the participant. A staged lottery appointed the participant to the role of pain recipient and the confederate to the role of pain influencer. It was explained to both that the pain influencer (confederate) could support the receiver (participant) by learning to press the right one out of two keys on the German keyboard (K or L on a German keyboard) to avert pain stimulation. Thus, pain stimulation was seemingly influenced by another person, although it was in fact fixed. Participants assigned to the self-influence group learned to actively avoid the painful stimulation by pressing the right button out of two keys (K or L, counter-balanced). They were thus able to influence pain stimulation themselves. Participants assigned to the no-influence group had no influence on the delivery of painful stimulation. To keep motor responses comparable across the groups, participants of the social-influence group pressed a key to indicate whether they expected the other person to cancel their pain. Participants of the no-influence group pressed a key to indicate whether they expected a painful stimulus (K or L indicating yes or no, in counter-balanced order).

All participants underwent an identical experimental procedure (Figure 1a).

The experiment started with a habituation phase (7 trials) in which participants familiarized themselves with the trial structure, the response keys, and the geometrical shapes. The first three trials started with a fixation cross (2–4 s, duration varied randomly) followed by a red lightning bolt which lasted until participants pressed one of two keys (K or L). After the response, the lightning bolt remained on the screen for 1 s. A white fixation cross appeared for 6 s (inter-stimulus interval, ISI) followed by a geometrical shape (training). This was followed by a fixation cross (inter-trial interval, ITI, 9–16 s) after 6 s. Each of the remaining four trials started with the presentation of one of the two other geometrical shapes ($_{relief}$CS, control) for 6 s. An ITI of 15–20 s followed. Both shapes were presented twice in a randomized order.

Each trial of the learning phase (Figure 1b) also started with a fixation cross (2–4 s) followed by a red lightning bolt. The lightning bolt lasted until participants pressed one of two keys (K or L). After response, it remained visible for 1 s. In 25% of the cases, a rectangular frame surrounded the lightning bolt during this second, announcing subsequent painful stimulation (no frame = no stimulation). After a 6 s ISI, a geometrical shape ($_{relief}$CS) was presented for 6 s, followed by an ITI (9–16 s; Figure 1b). The learning phase consisted of 24 trials with seven US trials in the social-influence and no-influence group, and 31 or 32 trials with 7 or 8 US trials in the self-influence group. The increased trial number in the self-influence group resulted from additional trials. For fast learners, these trials included additional pain stimulations for the number of pain trials they had successfully avoided to keep the quantity of pain stimuli comparable across groups. Before starting the learning phase, participants of the self-influence group were informed that these trials would occur independently of their performance, indicated by a blue (instead of red) lightning bolt and rectangular frame. After every six trials containing a red lightning bolt, participants gave ratings on US-expectancy and valence of the geometrical shape ($_{relief}$CS). These ratings were included to allow for additional group comparisons in $_{relief}$CS evaluation throughout the learning phase and are reported in the supplementary material.

The test phase (Figure 1c) started with a short startle habituation sequence to decrease initial startle reactivity (Blumenthal et al., 2005). A fixation cross was presented, and seven startle probes were delivered at random intervals of 6–9 s. After startle habituation, each trial of the test phase started with a fixation cross (ITI, 15–20 s). The ITI was followed by the geometrical shape presented in the learning phase ($_{relief}$CS) or another geometrical shape (control) which was never presented during the learning phase, but only twice during habituation phase. Each shape was presented 12 times and in a pseudo-randomized order meaning that each condition was not presented more than twice in a row. The US was never delivered. During half of the trials (i.e., six trials per $_{relief}$CS, control), a startle probe (white noise) was randomly delivered 4 to 5.5 s after stimulus onset. Additionally, six startle probes were delivered during ITI to enhance the startle probes' unpredictability. Startle responses can serve as additional indicators of the learning (Andreatta et al., 2016; see Supplementary Material). In total, the test phase consisted of 24 trials.

2.5 | Physiological data collection and preprocessing

Physiological responses were recorded with a V-Amp 16 amplifier and Vision Recorder V-Amp Edition Software (Version 1.21.0303, BrainProducts GmbH, Gilching, Germany). We applied a sampling rate of 400 Hz. The offline analyses of these responses were conducted with Brain Vision Analyzer Software (Version 2.2.0; BrainProducts GmbH).

SCR was continuously recorded by delivering a constant current of 0.5 V using two 5 mm Ag/AgCl electrodes. These were placed on the palm of the non-dominant hand, the first 2 cm above the hypothenar eminence and the other 2 cm distal. Considering that the startle-eliciting sounds modulate SCRs (de Haan et al., 2018; Sjouwerman et al., 2016), we excluded all trials containing a startle probe for the test phase analysis, which resulted in six trials per condition ($_{relief}$CS, control). In order to remove frequencies linked to other physiological responses (e.g., breathing), the electrodermal activity was offline-filtered, with a 1 Hz high cut-off filter. Data were segmented 1 s before to 8 s after stimulus onset. Following the guidelines (Boucsein et al., 2012), the SCR was defined as the difference (in μS) between the response onset (0.8–4 s after stimulus onset) and the first response peak. Responses below 0.02 μS were coded as zero and included in the analyses. We calculated a mean score for each participant through all the test phase trials for each condition. Those with a mean score lower than 0.02 μS were coded as non-responders and excluded from further analysis (see also Delgado et al., 2011). After having summed 1 to the raw scores, we then transformed the raw data into log to normalize the distribution (Boucsein, 2012). Taking extinction effects into consideration, the log-scores were then averaged for each condition, separately for the first half (early) and the second half (late) of the test phase.

Considering that pain relief strongly depends on the preceding stimulation's painfulness (Leknes et al., 2008), we further verified whether the three groups differed in their responses to the painful stimulation during learning phase. We considered both the responses to the painful stimulation and the responses to the preceding threat signal (i.e., the frame surrounding the lightning bolt for one second) because these two events were very close in time to each other. We calculated separate means for the painful stimulation and threat signal across all the responses. Because of the short ISI (i.e., 1 s), the responses to frame and pain may have overlapped. Therefore, we did three kinds of analysis to disentangle these responses. First, we considered the responses to the frame. Second, we considered the responses to the painful stimulation. Specifically, we averaged all the SCRs to the painful stimulation, meaning both the responses coded as such and the zero responses. However, we had to code numerous pain-responses as zero because the response onset was not visible due to the short delay between pain and frame. Third, we considered only those responses to the pain which were identifiable (i.e., we excluded the zero responses when averaging the SCRs to the US; $N = 84$).

2.6 | Statistical analyses

All data were analyzed with IBM SPSS Statistics for Windows (Version 26). First, using analyses of variances (ANOVAs), we tested for differences in age, BMI, education level, anxiety sensitivity (ASI-3), state and trait anxiety (STAI), depression (ADS-K) and pain intensity ratings between the conditions.

Second, given that our hypotheses are based on a potential effect of social and self-influence on pain processing, we also tested for possible group differences in the response to painful stimulation (US) during the learning phase. To do so, we calculated two one-way ANOVAs with SCRs to the pain stimulus (US) or the symbol signaling pain (frame) as dependent variable and group (no-influence, self-influence, social-influence) as between-subjects factor.

Third, we investigated differences in pain relief learning on the subjective level. To do so, we conducted four separate three-way mixed measures ANOVAs with valence, arousal, fear, and US-expectancy ratings as dependent variables, group (no-influence, self-influence, social-influence) as between-subjects factor, and stimulus ($_{relief}$CS, control, training) and time (before learning [T1], after learning [T2], after test [T3]) as within-subjects factors. The factor time was included to detect change across experimental phases (T1, T2, T3 for valence, arousal and fear ratings; T2 and T3 only for US-expectancy ratings). Post-hoc simple contrasts (Bonferroni-corrected) were conducted to clarify the significant time x stimulus interaction.

Fourth, we investigated group differences in pain relief learning on the physiological level (SCRs), using a three-way mixed-measures ANOVA with SCR as dependent variable, group (no-influence, self-influence, social-influence) as between-subjects factor, and stimulus ($_{relief}$CS, control) and period (early, late) as within-subjects factors. The factor period was included because SCR amplitudes decrease with repeated stimulus presentation, for example, between early and late experimental trials (Boucsein et al., 2012; Qi et al., 2020). It represents averaged SCR log-scores calculated for the first and second half of the test phase. Post-hoc simple contrasts (Bonferroni-corrected) were conducted for the significant period × stimulus

interaction. In response to the significant period × group interaction, we added an explorative analysis using separate two-way ANOVAs for SCRs in the early and late period of the test phase, with group (no-influence, self-influence, social-influence) as between-subjects factor and stimulus ($_{relief}$CS, control) as within-subject factor.

The alpha (α) level was set at 0.05 for all analyses. The effect size is reported as partial η^2. In case of violation of the sphericity assumption, the Greenhouse-Geisser test was applied, and the degree of freedom was consequently corrected. Simple contrasts (Bonferroni-corrected) were calculated as post-hoc tests for significant interactions. The data are available at https://github.com/Marthe-Gruendahl/pain_relief.

3 | RESULTS

3.1 | Group characteristics and questionnaires

There were no significant differences between conditions in age, anxiety sensitivity, state and trait anxiety, depression scores, and pain intensity ratings (see Table 1).

3.2 | SCRs to the painful stimulation (US) and its signal

We tested whether the experimental groups (no-influence, self-influence, social-influence) differed with regard to the responses to the painful stimulation. The ANOVA investigating the SCRs to the frame (which signaled painful stimulation) revealed no significant differences between the experimental groups ($F(2, 94) = 0.593$, $p = .693$, $\eta_p^2 = 0.011$, Figure 2a). The ANOVA investigating the SCRs to the pain stimulation itself (US) also revealed no significant group differences ($F(2, 94) = 1.54$, $p = .220$, partial $\eta_p^2 = 0.032$, Figure 2b).

We conducted an explorative analysis, excluding 13 participants who did not show any evident response to the painful stimulation. Thus, we conducted the same analyses based on $N = 84$ ($n = 25$ for the no-influence group, $n = 30$ for the self-influence group, and $n = 29$ for the social-influence group, respectively). It confirmed the lack of group differences regarding SCRs to the pain stimulus ($F(2, 81) = 0.04$, $p = .959$, $\eta_p^2 = 0.001$; Figure 2c).

3.3 | Ratings of the pain relief stimulus ($_{relief}$CS)

We conducted three-way mixed measures ANOVAs to analyze participants' valence, arousal and fear ratings of the $_{relief}$CS, the control and the training stimulus collected before learning (i.e., after habituation phase; T1), between learning and test (T2), and after the test phase (T3; Figure 3). Another ANOVA investigated expectancy ratings at the last two time points (T2, T3). There were no significant main or interaction effects of group on any rating (all p values >.220), indicating that the three groups did not significantly differ in their ratings of the visual stimuli throughout the experiment .

However, the analyses revealed significant main effects of stimulus ($_{relief}$CS/control/training) on all ratings (valence: $F(2, 188) = 19.21$, $p < .001$, $\eta_p^2 = 0.170$, 95% CI [0.08, 0.26]; arousal: $F(2, 188) = 45.48$, GG-$\varepsilon = 0.912$ $p < .001$, $\eta_p^2 = 0.326$, 95% CI [0.22, 0.42]; fear: $F(2, 188) = 43.42$, GG-$\varepsilon = 0.894$, $p < .001$, $\eta_p^2 = 0.316$, 95% CI [0.21, 0.41]; US-expectancy: $F(2, 188) = 58.97$, GG-$\varepsilon = 0.822$, $p < .001$, $\eta_p^2 = 0.385$, 95% CI [0.28, 0.47]). The ANOVAs

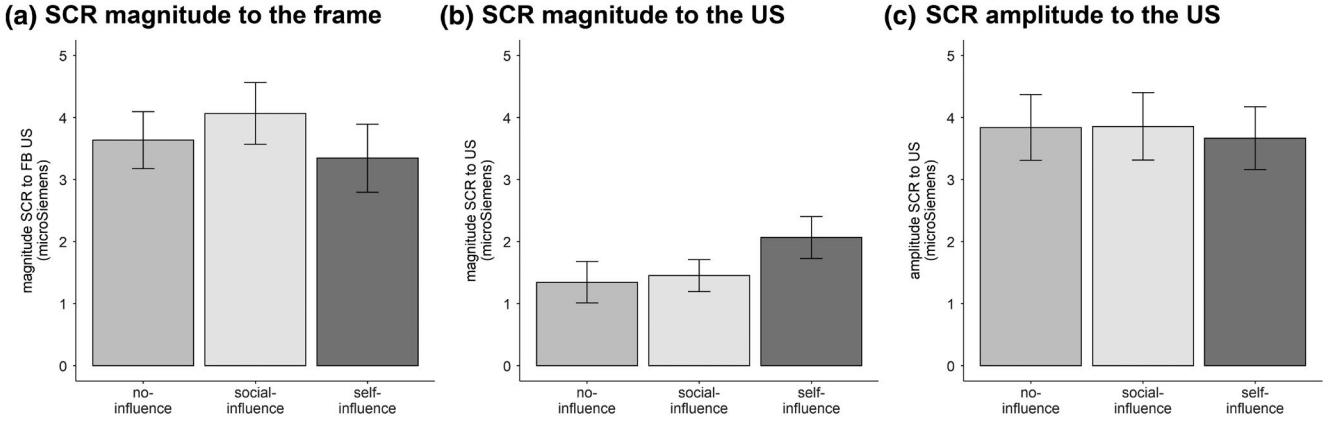

FIGURE 2 Means (with standard errors) of the skin conductance responses (SCRs) to the frame (a) and the US (b and c) separately for the three groups. For the magnitude of the SCR, we considered all responses meaning both those coded as such and the zero responses. For the SCR amplitude, only the responses as such were averaged.

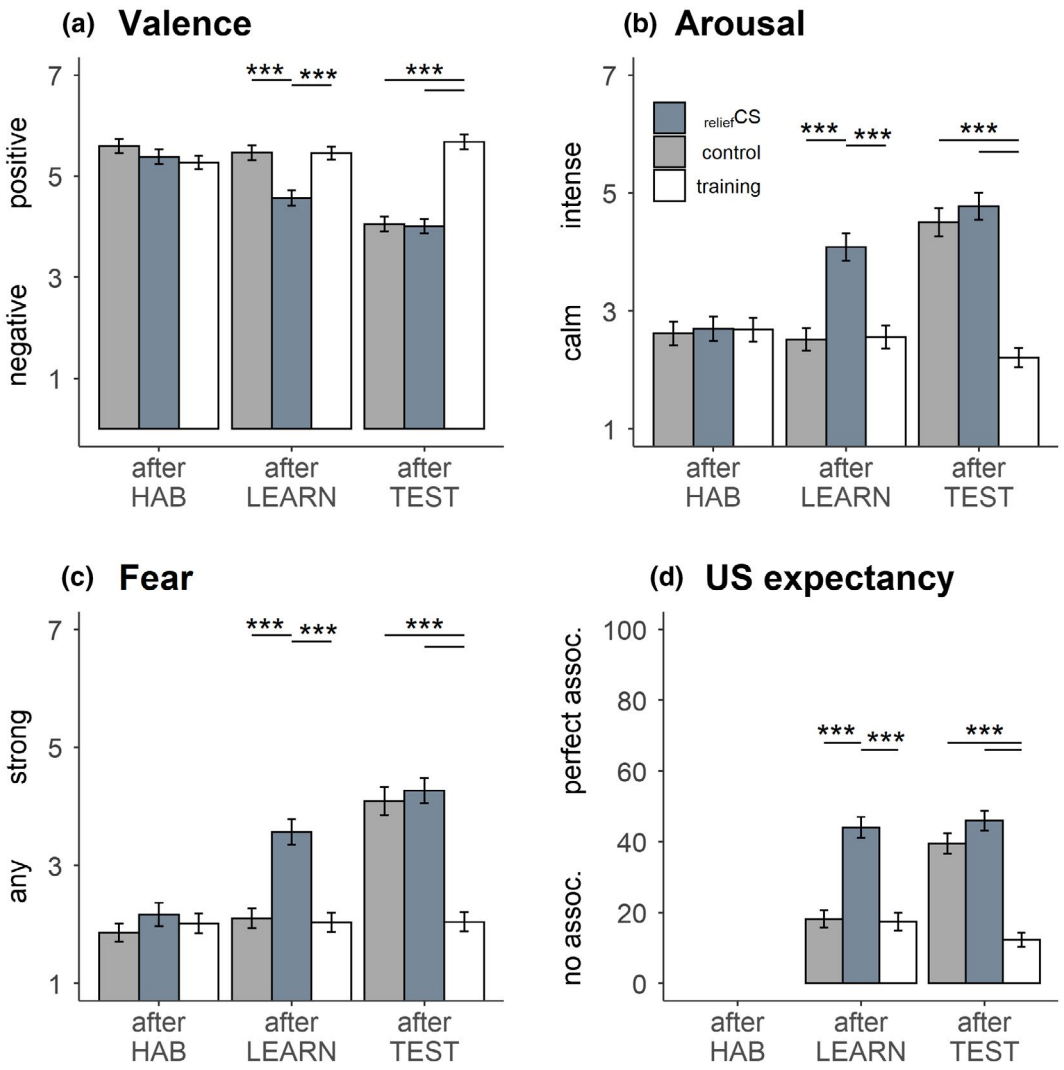

FIGURE 3 Means (with standard errors) of the ratings for (a) valence, (b) arousal, (c) fear, and (d) US-expectancy after the habituation phase (HAB), the learning phase (LEARN), and the test phase. Independently from the group, the $_{relief}$CS (blue-grey bars) was rated as more aversive than both control (grey bars) and training (white bars) after learning protocols. Through the test, the $_{relief}$CS maintained the aversive ratings, while control became more aversive. (***) $p < .001$, post-hoc simple contrasts for significant interactions.

also yielded main effects of time on all ratings (T1/ T2/ T3: valence: $F(2, 188) = 32.00$, $p < .001$, $\eta_p^2 = 0.254$, 95% CI [0.00, 0.06]; arousal: $F(2, 188) = 26.91$, GG-ε = 0.905, $p < .001$, $\eta_p^2 = 0.223$, 95% CI [0.00, 0.07]; fear: $F(2, 188) = 49.62$, GG-ε = 0.910, $p < .001$, $\eta_p^2 = 0.346$, 95% CI [0.00, 0.10]; T2/ T3: US-expectancy: $F(1, 94) = 10.68$, $p = .002$, $\eta_p^2 = 0.102$, 95% CI [0.00, 0.03]). Moreover, there were significant stimulus × time interactions in all four ANOVAs (valence: $F(4, 376) = 32.26$, GG-ε = 0.851, $p < .001$, $\eta_p^2 = 0.256$, 95% CI [0.18, 0.32]; arousal: $F(4, 376) = 32.77$, GG-ε = 0.809, $p < .001$, $\eta_p^2 = 0.258$, 95% CI [0.18, 0.32]; fear: $F(4, 376) = 33.84$, GG-ε = 0.814, $p < .001$, $\eta_p^2 = 0.265$, 95% CI [0.19, 0.33]; US-expectancy: $F(2, 188) = 30.27$, $p < .001$, $\eta_p^2 = 0.244$, 95% CI [0.14, 0.34]; Figure 3), indicating that ratings for $_{relief}$CS and control changed over time.

Post-hoc simple contrasts (Bonferroni-corrected $\alpha < 0.017$) were conducted to investigate the stimulus × time interactions. See Figure 3 for ratings of valence (a), arousal (b), fear (c) and US-expectancy (d) of the three stimuli after each experimental phase.

Prior to learning (T1), results indicated comparable valence (all p values >.054), arousal (all p values >.628) and fear (all p values >.053) across the three visual stimuli.

After learning (T2), $_{relief}$CS was rated as more negative, arousing and threatening than both control (valence: $F(1, 94) = 23.67$, $p < .001$, $\eta_p^2 = 0.201$; arousal: $F(1, 94) = 35.52$, $p < .001$, $\eta_p^2 = 0.274$; fear: $F(1, 94) = 45.65$, $p < .001$, $\eta_p^2 = 0.327$) and training (valence: $F(1, 94) = 25.78$, $p < .001$, η_p^2

= 0.215; arousal: $F(1, 94) = 31.19$, $p < .001$, $\eta_p^2 = 0.249$; fear: $F(1, 94) = 43.84$, $p < .001$, $\eta_p^2 = 0.318$). Moreover, participants expected the painful US more with $_{relief}$CS than with control ($F(1, 94) = 44.60$, $p < .001$, $\eta_p^2 = 0.322$) and training ($F(1, 94) = 45.01$, $p < .001$, $\eta_p^2 = 0.324$). No significant differences were found between control and training (all p values >.679).

After test (T3), $_{relief}$CS was still rated as more negative, arousing and threatening than training (valence: $F(1, 94) = 63.30$, $p < .001$, $\eta_p^2 = 0.402$; arousal: $F(1, 94) = 97.54$, $p < .001$, $\eta_p^2 = 0.509$; fear: $F(1, 94) = 89.05$, $p < .001$, $\eta_p^2 = 0.486$). However, the control stimulus was rated as equally negative, arousing, and threatening as $_{relief}$CS (valence: $F(1, 94) = 0.04$, $p = .842$, $\eta_p^2 < 0.001$; arousal: $F(1, 94) = 2.75$, $p = .101$, $\eta_p^2 = 0.028$; fear: $F(1, 94) = 1.00$, $p = .319$, $\eta_p^2 = 0.011$). Moreover, the control stimulus was rated as more negative, arousing, and threatening than the training stimulus (valence: $F(1, 94) = 68.73$, $p < .001$, $\eta_p^2 = 0.422$; arousal: $F(1, 94) = 82.55$, $p < .001$, $\eta_p^2 = 0.468$; fear: $F(1, 94) = 65.24$, $p < .001$, $\eta_p^2 = 0.410$). This implies that throughout the test phase, the control stimulus was perceived as more aversive than before (T2; see Figure 3a–c). Regarding US-expectancy, the $_{relief}$CS was still more associated with US than training ($F(1, 94) = 101.54$, $p < .001$, $\eta_p^2 = 0.519$) and control ($F(1, 94) = 5.68$, $p = .019$, $\eta_p^2 = 0.057$). Throughout the test phase, control became more associated with the US than training ($F(1, 94) = 77.44$, $p < .001$, $\eta_p^2 = 0.452$; Figure 3d).

3.4 | Skin conductance response to the pain relief stimulus ($_{relief}$CS)

Given that previous studies have shown a general decline of SCRs over time (Qi et al., 2020), repeated-measures ANOVAs tested for differential effects in SCRs in the early and the late period of the test phase, with SCRs as dependent variable, group as between-subject factor, and stimulus ($_{relief}$CS, control) and period (early/late) as within-subject factors.

The stimulus x group x period interaction remained non-significant, $F(2, 94) = 1.22$, $p = .30$, $\eta_p^2 = 0.025$. However, the results revealed significant interactions between period × group ($F(2, 94) = 4.02$, $p = .021$, $\eta_p^2 = 0.079$, 95% CI [0.00, 0.19]) and period × stimulus ($F(1, 94) = 8.38$, $p = .005$, $\eta_p^2 = 0.082$, 95% CI [0.01, 0.20]; Figure 4). There were no other significant results (all $p > .303$).

Post-hoc Bonferroni-corrected ($\alpha < 0.025$) simple contrasts for the period x stimulus interaction suggested successful relief learning as indicated by significantly lower physiological arousal to $_{relief}$CS as compared to control during the early test period ($F(1, 94) = 6.12$, $p = .015$, $\eta_p^2 = 0.061$, Figure 3a), but not during the late test period ($F(1, 94) = 3.30$, $p = .075$, $\eta_p^2 = 0.034$).

Considering that the three groups presented different physiological arousal during early versus late test period, we added separate explorative ANOVAs for SCRs of the early versus late period, with group (no-influence, self-influence, social-influence) as between-subjects factor and stimulus ($_{relief}$CS, control) as within-subjects factor. During the early period, we observed significant main

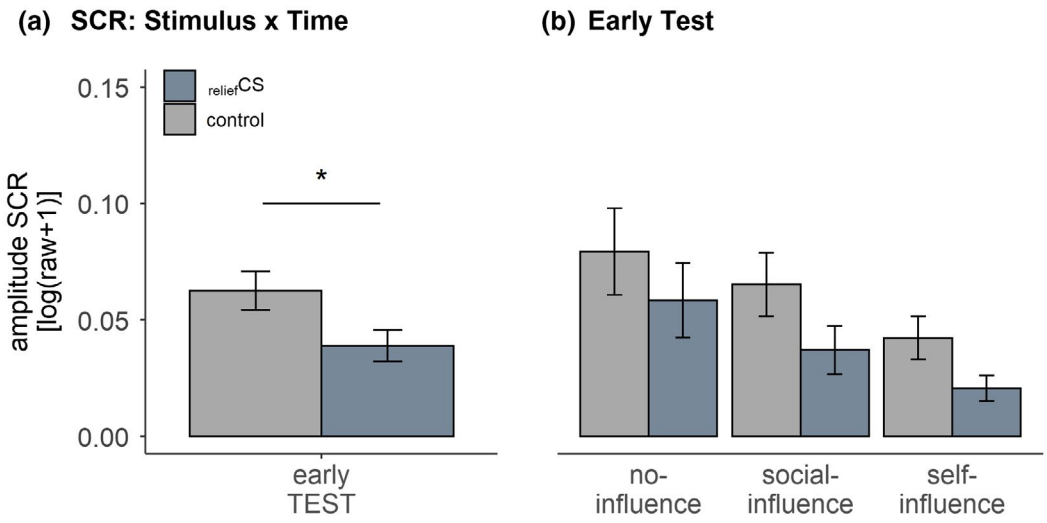

FIGURE 4 Means (with standard errors) of the Skin conductance responses (SCR) for (a) the Stimulus × Time significant interaction, and (b) the SCRs separated for the groups during early test. Independently from the group, the $_{relief}$CS (blue-grey bars) elicited lower physiological arousal than control (grey bars). Self-influence group showed the lowest physiological responses. (*) $p < .05$, post-hoc simple contrasts for significant interactions

effects for stimulus ($F(1, 94) = 6.12$, $p = .015$, $\eta_p^2 = 0.061$) and group ($F(1, 94) = 3.36$, $p = .039$, $\eta_p^2 = 0.067$), but not their interaction. No significant effects were found during the late period (all p values >.072). Again, conditioned pain relief was indicated by significantly reduced physiological arousal towards the $_{\text{relief}}$CS as compared to control. Moreover, post-hoc Bonferroni-corrected ($\alpha < 0.017$) simple contrasts revealed lower physiological arousal for the self-influence group compared to the no-influence group ($F(1, 94) = 6.71$, $p = .011$, $\eta_p^2 = 0.067$), but not to the social-influence group ($F(1, 94) = 1.92$, $p = .170$, $\eta_p^2 = 0.020$). There was no significant difference in physiological arousal between the no-influence and social-influence group ($F(1, 94) = 1.57$, $p = .213$, $\eta_p^2 = 0.016$; Figure 4b).

4 | DISCUSSION

Our study tested whether social influence and controllability of pain affect pain relief learning. Based on studies showing that social influence and controllability of pain influence pain perception (Che et al., 2018; Stephens et al., 2016; Wiech et al., 2006), we hypothesized that these influences on pain perception might also affect pain relief learning, that is, the reduction of physiological responses to a stimulus associated with pain relief compared to a control stimulus. Alternatively, based on studies that showed no effects of social influence and controllability on pain (Modić Stanke & Ivanec, 2010; Mohr et al., 2012), we hypothesized that pain relief learning might be comparable under social-influence, self-influence and no-influence conditions.

Our results showed pain relief learning in the early test period, indicated by a reduction of SCRs to the visual stimulus associated with pain relief compared to a neutral control stimulus. These findings are in line with previous studies (Andreatta et al., 2013; Andreatta & Pauli, 2017; Luck & Lipp, 2017), demonstrating the robustness of pain relief learning in humans. Moreover, they replicate previous results showing similar effects in animals such as honeybees (Kirkerud et al., 2017) and drosophilia melanogaster (Yarali et al., 2008). Extending previous studies, we investigated whether the established effect of pain relief learning is altered by social influence and controllability of the pain stimulus. Our results showed a comparable magnitude of pain relief learning when the pain stimulus was influenced by another person (social-influence group), by the participants themselves (self-influence group), or passively administered by the computer (no-influence group).

Given that pain relief learning is based on the cessation of an aversive pain experience (Gerber et al., 2014), we assumed a lack of group differences in pain relief learning if there are no significant group differences in SCRs to the painful stimulation itself. In line with this assumption, the participants of the social-influence, the self-influence and the no-influence group showed comparable subjective and neural responses to the pain cue and the pain stimulus itself during the learning phase. At first glance, the lack of differential pain responses in the social-influence and the self-influence group compared to the no-influence group seem to be in contrast to previous studies showing that social contact and controllability can reduce pain responses (Boeke et al., 2017; Che et al., 2018; Edwards et al., 2017; Wiech et al., 2006). However, a closer look reveals that there are other studies that reported comparable pain responses in social and controllability conditions compared to passive pain administration (Löffler et al., 2018; Modić Stanke & Ivanec, 2010).

Regarding the effect of social influence on pain, previous findings are in fact heterogeneous. In line with our findings, Modić Stanke and Ivanec (2010) found no effects of a stranger's presence during experimentally induced pain on pain experience compared to being alone. In contrast, other studies found a reducing effect of social presence on pain expression (Karmann et al., 2014), pain perception (Kleck et al., 1976) and physiological arousal to an aversive stimulus (Kleck et al., 1976; Qi et al., 2020). In these studies, however, the other person was not involved in the control over pain. In other studies showing a social modulation of pain responses, the other person was physically present (Karmann et al., 2014; Kleck et al., 1976; McClelland & McCubbin, 2008) and actively offered help or support (Brown et al., 2003; Hein et al., 2018; Roberts et al., 2015). This suggests that social effects are stronger in more explicit expressions of social support (Che et al., 2018). In our study, participants of the social-influence group met the other person only briefly. They were told that this person might influence their pain stimulation, but the person did not actively offer comfort or help and was in a separate room. We deliberately chose the minimal social manipulation to keep the experimental conditions in the social-influence group as comparable as possible to the experimental conditions in the other two groups (i.e., the self-influence and the no-influence group), in which no other person or social cue was present. Although previous studies have shown that minimal social manipulations can reduce responses to aversive events (Edwards et al., 2017; Qi et al., 2020), it is conceivable that these effects are weaker than the effects of social comforting or helping (Che et al., 2018), or not evident as in the current study. Thus, they did

not influence pain relief learning. Future studies should additionally incorporate a more active social condition to increase the comparability with previous findings of social pain modulation.

Regarding the effect of controllability, previous findings suggest moderating factors. For instance, Löffler and colleagues (2018) investigated the effects of pain controllability on physiological pain responses (SCR, heart rate) and found that controllability reduced perceived suffering, but not physiological responses to pain. The authors argue that internal control beliefs induced by different instructions might play an important role here. In line with this, other studies showed attenuated pain and changes in pain-related responses when pain was perceived as controllable rather than uncontrollable (Salomons et al., 2004; Wiech et al., 2006). In our study, participants of the self-influence group could avert the momentary pain stimulation, ostensibly based on their learning performance. Still, they received a number of painful stimulations to ensure comparability between groups. It is possible that this manipulation induced uncertainty, which may have counteracted control beliefs and therefore prevented effects of controllability on pain experience. In light of these results, stronger manipulations of controllability may be needed to trigger a modulation of the pain responses, and consequently, changes in pain relief learning.

That being said, we found a general decline in participants' SCRs to the pain relief stimulus compared to the control stimulus in the self-influence compared to the no-influence condition. This indicates that a certain degree of control over pain later results in a general reduction of physiological arousal, which is in line with previous findings (Boeke et al., 2017; Mohr et al., 2012; Salomons et al., 2004). However, this general effect did not affect pain relief learning. The finding that self-influence reduced the general arousal, but had no effect on pain relief learning suggests that the SCR measures collected with our paradigm can disentangle general arousal effects from effects of pain relief learning.

In the test phase, all three experimental groups showed a comparable and consistent reduction in SCRs to the pain relief stimulus compared to the control stimulus. However, this difference was not evident in participants' ratings. Instead, the pain relief and the control stimuli elicited more negative subjective arousal, valence and fear after the experiment than before the experiment. The discrepancy between a reduction in physiological responses to the pain relief stimulus on the one hand, and an increase in aversiveness ratings on the other hand, resembles previous findings. Other backward conditioning studies with painful stimulation (Andreatta et al., 2010, 2013; Luck & Lipp, 2017) or highly aversive sounds (Green et al., 2020) also showed increased implicit and decreased explicit valence following backward conditioning. This suggests that participants cognitively associated the pain relief stimulus with pain, but physiologically with the experienced pain relief. It is also conceivable that the SCRs and the ratings reflect distinct mechanisms. During the test phase, physiological arousal was continuously recorded and therefore might reflect ongoing learning processes. The ratings were asked at the end of the phase when the learning had terminated and might therefore reflect effects of previous learning (Lonsdorf et al., 2017). In line with this, we observed differences between $_{\text{relief}}$CS and control for the ratings just after the learning phase (T2) and for the SCRs at the beginning of the test phase (early period). These differences disappeared in both responses throughout the test phase, suggesting extinction learning (Milad & Quirk, 2012).

Moreover, in our experimental protocol, startle-eliciting sounds were presented, and these sounds can be quite aversive. Previous studies demonstrated that associative learning mechanisms can be influenced by startle probes (de Haan et al., 2018; Sjouwerman et al., 2016). It is therefore possible that the startle probes had an effect on SCRs in our study. However, given that the startle probes were present in all three groups and our analyses are based on group comparisons, these effects are unlikely to affect our main findings.

There are some limitations which need to be addressed when discussing the present findings. As mentioned above, this study focusses on the evaluation of SCRs as an indicator of sympathetic activity. Future research should include the additional assessment of parasympathetic activity which is associated with self-regulation mechanisms (Laborde et al., 2017). For instance, this could be achieved with heart rate variability (HRV) as an index of vagal tone (Malik et al., 1996), a measure used in both pain (Koenig et al., 2014) and learning research (Pappens et al., 2014; Wendt et al., 2015). Additionally, a variety of factors are known to alter skin conductance levels, including age (Barontini et al., 1997; Gavazzeni et al., 2008), gender (Aldosky, 2019; Lonsdorf et al., 2015), weight (Aldosky, 2019), and mental disorders like depression (Dibbets et al., 2015; Schumann et al., 2017). While we controlled for these factors and found no differences across groups, other possible influences such as physical exercise on a regular basis (Salvador et al., 2001), caffeine consumption (Barry et al., 2005; Davidson & Smith, 1991), and hormonal changes due to the menstrual cycle or hormonal contraceptives (Goldstein et al., 2005; Lonsdorf et al., 2015) were not addressed and their potentially confounding effects cannot be excluded. However, because pain thresholds were individually calibrated, potential differences in pain perception caused by these uncontrolled factors are unlikely to influence our main results.

In sum, future studies should test the modulation of pain relief learning with designs that use stronger manipulations of social influence and controllability of pain, and more reinforced trials in the learning phase. Our current study's results suggest that physiological pain relief learning in humans is not significantly influenced by social influence and pain controllability.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Marthe Gründahl: Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing—original draft; Writing—review & editing. **Leonie Retzlaff:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation; Visualization; Writing—review & editing. **Martin J Herrmann:** Methodology; Resources; Software. **Grit Hein:** Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Validation; Writing—review & editing. **Marta Andreatta:** Conceptualization; Data curation; Formal analysis; Methodology; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

ORCID

Marthe Gründahl https://orcid.org/0000-0003-1824-0523
Marta Andreatta https://orcid.org/0000-0002-1217-8266

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