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Perception of repeated pain relief with controllable and uncontrollable pain

Susanne Becker[1,2] | **Karin Schakib-Ekbatan**[3,4,5] | **Daniel Wroblewski**[1] | **Marcel Schweiker**[4,6]

[1]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[2]Integrative Spinal Research Group, Department of Chiropractic Medicine, University Hospital Balgrist, University of Zurich, Zurich, Switzerland

[3]Heidelberg Academy of Sciences and Humanities, Heidelberg, Germany

[4]Building Science Group, Karlsruhe Institute of Technology, Karlsruhe, Germany

[5]Institute for Resource Efficiency and Energy Strategies, Karlsruhe, Germany

[6]Institute for Occupational, Social and Environmental Medicine, Medical Faculty, RWTH Aachen University, Aachen, Germany

Correspondence
Susanne Becker, Department of Chiropractic Medicine, University of Zurich, Balgrist Campus, Lengghalde 5, 8008 Zürich, Switzerland.
Email: susanne.becker@balgrist.ch

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Abstract

Background: The ultimate goal of pain research is to provide effective routes for pain relief. Nevertheless, the perception pain relief as a change in pain intensity and un-/pleasantness has only been rarely investigated. It has been demonstrated that pain relief has rewarding and reinforcing properties, but it remains unknown whether the perception of pain relief changes when pain reductions occur repeatedly. Further, it remains an open question whether the perception of pain relief depends on the controllability of the preceding pain.

Methods: In this study, healthy volunteers ($N = 38$) received five cycles of painful heat stimulation and reduction of this stimulation to a non-painful warm stimulation once in a condition with control of the stimulation and once without control. Participants rated perceived intensity and un-/pleasantness on visual analogue scales during the heat stimulation and immediately after its reduction.

Results: Results showed that perceived pain relief, estimated by the difference in ratings during ongoing heat stimulation and after its reduction, increased with repetitions. However, this increase levelled off after two to four repetitions. Further, perceived pain relief was larger in the condition without control compared to the condition with control.

Conclusion: The perception of pain relief can be modulated similar to the perception of pain by stimulus characteristics and psychological factors. Mechanistic knowledge about such modulating factors is important, because they can determine, e.g., the amount of requested pain killers in clinical settings and the efficacy of pain relief as a reinforcing stimulus.

Significance: When in pain, pain relief can become an all-dominate goal. The perception of such pain relief can vary depending on external and internal characteristics and thus modulate, e.g., requests for pain killers in clinical settings. Here, we show that perceived intensity and pleasantness of pain relief changes with repetitions and whether the preceding pain is perceived as uncontrollable. Such mechanistic knowledge needs to be considered to maximize the effects of pain relief as a rewarding and reinforcing stimulus.

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1 | INTRODUCTION

When in pain, pain relief is almost always much sought after, particularly when suffering from persistent pain. In such a situation, obtaining pain relief can become an all-dominant goal. Correspondingly, the ultimate aim of pain research is to provide effective routes to pain relief in acute and chronic pain states. Despite this focus on pain relief, little is known about the perception associated with pain relief. Only few studies investigated the perception of pain relief directly. Animal research demonstrated that pain relief has rewarding properties and that it can lead to negative reinforcement (König et al., 2018; Navratilova et al., 2012). In human research, it has been shown that (1) pain relief can lead to negative reinforcement as well (Andreatta et al., 2010; Becker et al., 2008, 2011; Hölzl et al., 2005), (2) pain relief obtained in a motivated state can induce endogenous pain inhibition similar to pain combined with an extrinsic reward such as money (Becker et al., 2013, 2017) and (3) pain relief is more than a mere reduction in perceived pain intensity encompassing important emotional–motivational aspects (Leknes et al., 2008). In line with the observation that pain relief is a rewarding process, animal research demonstrated further that negative reinforcement by pain relief requires signalling via endogenous opioids (Navratilova et al., 2015), which are known to specifically mediate liking associated with reward (Berridge & Kringelbach, 2008; Castro & Berridge, 2014; Smith et al., 2011).

Unlike this growing understanding about the rewarding properties of pain relief, it is sparsely investigated how the perception associated with pain relief depends on preceding stimulus characteristics. For instance, it remains unknown whether and how repeated pain relief influences the individual's perception of pain relief. With pain, it is known that repeated stimulation can lead to large changes in the perception of the pain, induced, e.g., by physiological processes such as long-term potentiation or -depression (Adolph et al., 2010; Klein, 2004). Similar processes might also be relevant in the perception of pain relief. Moreover, changes in the perception of repeated pain relief might have a clinical significance. For example, if repeated pain relief is perceived as decreasingly pleasant, increasingly higher doses of pain killers may be used to compensate for this (cf. Finan et al., 2018).

Another factor that affects pain perception and which is relevant in chronic pain is perceived control of the pain (e.g. Aldrich et al., 2000; Bräscher et al., 2016; Tan et al., 2002; Tinti et al., 2011; Wiech et al., 2006). If an individual perceives having control over pain, experimental pain is perceived as less intense and less unpleasant (Arntz & Schmidt, 1989; Müller, 2011). Further, perceived control over pain is associated with better functioning in chronic pain (Tan et al., 2002). Losing control over pain increases fear of pain and impairs task performance (Crombez et al., 2008). Thus, relief from uncontrollable pain might be perceived as larger compared to relief from controllable pain.

Here, we tested in healthy volunteers whether (1) the perception of a repeated pain relief changes in terms of perceived intensity and un-/pleasantness and (2) whether perception of repeated pain relief changes with uncontrollable compared to controllable preceding pain. Participants received repeated experimental painful heat stimuli followed by a non-painful baseline temperature, once in a condition with perceived control of the applied heat stimulation and once in a condition without control. Participants rated perceived intensity and un-/pleasantness of the painful heat stimulation and the subsequent stimulation at baseline temperature.

2 | MATERIAL & METHODS

The Ethics committee and data protection officer of Karlsruhe Institute of Technology (Karlsruhe, Germany) approved the study.

2.1 | Participants

In total, 38 healthy volunteers participated in this study. Participants belonged to two age groups, one younger than 32 years of age ($N = 18$; 9 women, 9 men; $M = 23.9$, $SD = 2.5$ years of age; due to technical error information on the exact age is missing from three participants) and the other older than the age of 50 ($N = 20$; 10 women, 10 men; $M = 61.2$, $SD = 5.0$ years of age). Participants were recruited using announcements placed on a local online job market for students, a free newspaper and on the institutional homepage. Exclusion criteria were age younger than 18, intake of opioid or psychotropic drugs, present or past mental disorders, sleep disorders and any pain present for more than 6 months and more frequently than 1 day every 2 weeks. Inclusion and exclusion criteria were assessed in a telephone interview before participation in the study. During this telephone interview, the interviewer also assessed whether the German language level was sufficient for participation.

2.2 | General procedure

After participants arrived at the testing facility, the experimenter gave them an overview about the procedures and methods upon which written informed consent was obtained. At the beginning of the assessment, participants' pain sensitivity was assessed. After this assessment, the experimental procedure for assessing the perception of repeated pain relief started. This procedure was repeated under two conditions: one in which the perception of having control over the

experimental stimuli was created and the other without such control. Both conditions were performed in counterbalanced order across participants and with a break of a few minutes between both conditions. All testing sessions were performed in the Laboratory for Occupant Behaviour, Thermal comfort, Satisfaction and Environmental Research (LOBSTER; Wagner et al., 2018) belonging to the Building Science Group at the Karlsruhe Institute of Technology, Karlsruhe, Germany.

2.3 | Thermal stimulation

All thermal stimuli were applied with a contact thermode (SENSELab—MSA Thermotest; SOMEDIC Sales AB, Sweden). The thermode size was 2.5 × 5 cm. For safety reasons, the maximal temperature was limited to 50°C. All thermal stimuli were applied to the volar forearm of participants' non-dominant hand. Rate of temperature increase and decrease was set to 10°C/s.

2.4 | Rating scales

Participants rated the perceived intensity and un-/pleasantness of the thermal stimulation using two horizontally oriented visual analogue scales (VASs). The intensity VAS ranged from 'no sensation' at the left end to 'pain threshold' in the middle and 'most intense pain tolerable' at the right end. The un-/pleasantness VAS ranged from 'extremely unpleasant' at the left end to 'neutral' in the middle and 'extremely pleasant' on the right end (Becker et al., 2013; Villemure et al., 2003). These VASs were used to differentiate between non-painful and painful as well as between pleasant and unpleasant sensations. Specifically, a bipolar un-/pleasantness scale was used to allow ratings of pleasant and unpleasant sensations using the same scale and to avoid biasing the participants (cf. Becker et al., 2013; Loggia et al., 2008; Villemure et al., 2003).

To assess potential changes in mood and well-being over the course of the experiment, participants answered seven 5-point scales from 'not at all' to 'extremely' on how excited, externally controlled, stimulated, irritated, relieved, tired and focused they felt at several time points during the experiment. Participants were familiarized with the rating scales prior to the start of the experiments.

2.5 | Assessment of pain sensitivity

To assess participants' pain sensitivity and to determine stimulation intensities for the experimental pain relief procedure, participants' heat-pain threshold and heat-pain tolerance were tested using the methods of limits (Fruhstorfer et al., 1976). For this purpose, stimuli increasing from a baseline temperature of 30°C at a rate of 1°C/s were applied until the participant felt the slightest pain sensation (heat-pain threshold) or could not tolerate the stimulus any longer (heat-pain tolerance). Participants indicated their heat-pain threshold/tolerance levels by a mouse button press. After this mouse press, the temperature of the thermode returned immediately to the baseline temperature. Assessment of pain threshold and tolerance was repeated three times each and the means of the corresponding temperature used as estimators of the individual heat-pain threshold and heat-pain tolerance.

2.6 | Experimental pain relief procedure with and without control

To assess how participants perceive repeated pain relief in terms of reductions of nociceptive thermal stimulation, participants received 5 trials two times with heat stimuli of 30-s duration (see Figure 1). Once these five trials were applied in a condition with simulated control of the thermal stimulation, while the other five trials were applied in a condition without such control.

In each trial, stimulation intensity increased from baseline (38°C) to the target stimulation intensity defined as the heat-pain threshold plus 50% of the difference between the heat-pain threshold and heat-pain tolerance, aiming at a painful sensation (Becker et al., 2020; Flor et al., 2002). After 15 s of stimulation, participants rated perceived intensity followed by a rating of the perceived un-/pleasantness on the VAS described above. In the condition with simulated control (referred to as condition with control), for the last 5 s of stimulation, a button was displayed on the screen in front of the participants. Participants were instructed that they could press the button to stop the stimulation. Independent on whether participants pressed the button or not the stimulation continued for the full remaining 5 s (cf. Borckardt et al., 2011; van Vliet et al., 2018, 2020). In the condition without control, no button was displayed and the stimulation continued after the VAS ratings for further 5 s to ensure the same nociceptive input in both control conditions. After this stimulation of 30 s, the temperature decreased to the baseline temperature of 38°C and after a delay of 2 s, participants rated perceived intensity and un-/pleasantness again on the VASs. After these ratings, participants answered the seven 5-point scales to assess potential changes in mood and well-being across the repetitions and the whole experimental pain relief procedure. In total, the stimulation stayed at the baseline temperature for 2 min, after which the next trial started. During this waiting time before the next trial started, the experimenter was in the room with the participants, ensuring that they did not distract themselves, e.g., by reading or using

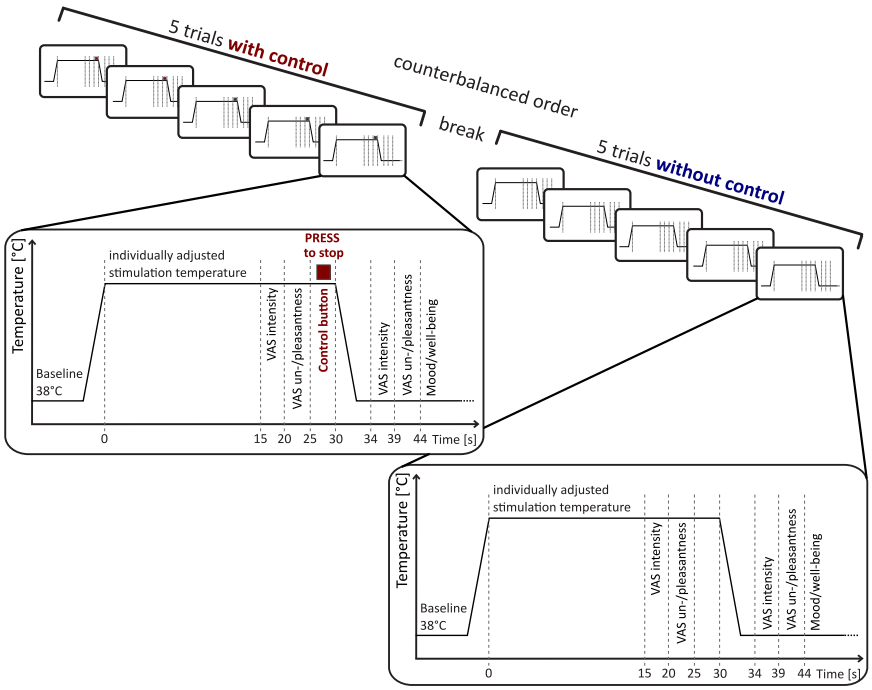

FIGURE 1 Experimental pain relief procedure. Shown is the course of the experiment and the course one experimental trial with and without control (insets). Participants performed five trials of painful heat stimulation and pain relief once in the condition with control and once without control in counterbalanced order. At the beginning of each trial, the stimulation temperature rose from baseline (38°C) to an individually adjusted painful stimulation intensity. After 15 s of stimulation, participants rated perceived intensity and un-/pleasantness of this stimulation on visual analogue scales (VAS). In the condition with control, a button was displayed after the ratings with the instruction to press the button to stop the stimulation whenever participants wanted to. Independent of whether and when participants pressed this button, the total stimulation time was always of the same length (30 s). In the condition without control, no button was shown and the stimulation lasted for the same length (30 s). After 30 s of heat stimulation, the temperature decreased back to baseline and after 2 s participants rated again intensity and un-/pleasantness of the current perception. After these ratings, mood and well-being were assessed and after 120 s the next trial started

their smart phone. Shortly before the next trial started, the experimenter reminded participants to focus on the task again and left the room. After five repetitions, participants removed their arm from the thermode. After a break of a few minutes, the procedure was repeated implementing the second control condition. Repetitions were restricted to five in each of the control conditions (i.e. 10 repetitions of the heat stimulation in total) to reduce the risk of skin burns.

2.7 | Statistical analysis

To test how pain relief was perceived and whether this perception changed across repetitions and control conditions, differences of perceived intensity and un-/pleasantness ratings during and after heat stimulation were calculated and used as an estimate of perceived pain relief. Using linear mixed models (LMM) it was tested whether estimated pain relief differed across repetitions and/or between control conditions with 'repetition' (1–5) and 'control' (with control vs. without control) as within-subject fixed factors and estimated pain relief in terms of perceived intensity and un-/pleasantness as dependent variables in separate LMMs.

To test whether potential changes in estimated pain relief across repetitions and control conditions were driven by changes in perceived intensity and un-/pleasantness during and/or after heat stimulation and between control conditions, full models with the three within-subject fixed factors 'time point' of assessment (during vs. after heat stimulation), 'repetition' (1–5) and 'control' (control vs. no control) were used with ratings of perceived intensity and un-/pleasantness as dependent variables in separate LMMs.

All LMMs included all interactions of the respective fixed factors as well as participant ID as a random intercept factor.

Order of the conditions with and without control for each individual was included in all LMMs as a covariate. Further, in the LMMs on the difference values indicating estimated perceived pain relief, the interaction of this order as a covariate with the fixed factor 'repetition' was included and for the full LMMs for the ratings during and after heat stimulation the interaction with the fixed factor 'time point'. These interactions were included, because separate LMMs testing specifically for the effect of order of the conditions with and without control revealed significant interactions with 'repetition' and 'time point', respectively. In addition, pain threshold was included as a covariate in all LMMs, because individual

pain threshold correlated highly with estimated relief (all r's > ±0.40) and ratings during the heat stimulation (all r's >±0.70). No differences between age groups were found, therefore age groups were pooled in all LMMs.

Ratings of the seven mood and well-being scales were analysed each in separate LMMs all including the within-subject fixed factors 'repetition' (1–5) and 'control' (control vs. no control) and their interaction as well as participant ID as a random intercept factor.

Significant main effects and interactions of the LMMs were followed by planned comparisons, for which Cohen's d as an estimate of effect sizes was calculated. Cohen's d of the means and standard deviations of the respective comparison was calculated by dividing the difference of the means by the pooled standard deviation.

The significance level was set to $\alpha = 0.05$. All statistical analyses were performed using SPSS Statistics 26 (SPSS Inc.).

3 | RESULTS

3.1 | Estimated pain relief increased across repetitions

In a first step, it was tested whether estimated pain relief, indicated by the difference in ratings during and after heat stimulation, changed across repetitions and if this pain relief and its changes across repetitions differed in the conditions with and without control.

With respect to intensity ratings, estimated pain relief changed across repetitions (main effect 'repetition' $F_{4,256} = 2.53$, $p = 0.041$; Figure 2a; Supplementary Table S1 for means and standard deviations). Pain intensity relief was smaller in the first repetition compared to all following repetitions (planned comparisons: repetition 1 vs. 2: mean difference = 14.76, $p = 0.032$, $d = 0.25$; 1 vs. 3: mean difference = 15.75, $p = 0.022$, $d = 0.31$; 1 vs. 4: mean difference = 22.21; $p = 0.001$, $d = 0.44$, 1 vs. 5: mean difference = 23.17, $p = 0.001$, $d = 0.42$), but did not differ significantly from each other in all further repetitions 2–5 (all p's > 0.225; see Figure 2a). These findings indicates that the perceived pain relief in terms of perceived intensity increased from the first to the second repetition, but on average further increases in later repetitions did not reach significance. No differences in estimated pain relief in intensity ratings were found between conditions with and without control (main effect 'control' $F_{1,66} = 1.95$, $p = 0.167$; interaction 'control × repetition' $F_{4,265} = 0.43$, $p = 0.787$).

With respect to un-/pleasantness ratings, estimated pain relief differed across repetitions similar to relief in perceived intensity (main effect 'repetition' $F_{4,265} = 2.93$, $p = 0.021$; Figure 2b; Supplementary Table S1 for means and standard deviations). Planned comparison shows that the difference in estimated pain relief in terms of un-/pleasantness was significant only for repetition 1 compared to 4 (mean difference = 16.75, $p = 0.006$, $d = 0.29$) and repetition 1 compared to 5 (mean difference = 15.11, $p = 0.014$, $d = 0.25$), with no difference between all other comparisons. No differences in estimated pain relief in intensity and un-/pleasantness ratings between conditions with and without control were found (main effect 'control' $F_{1,66} = 1.80$, $p = 0.184$; interaction 'control × repetition' $F_{4,265} = 1.32$, $p = 0.263$).

3.2 | Lower perceived intensity and higher pleasantness after heat stimulation with uncontrollable compared to controllable pain

In a second step, we tested whether changes in estimated pain relief observed in the first step of the analyses were driven

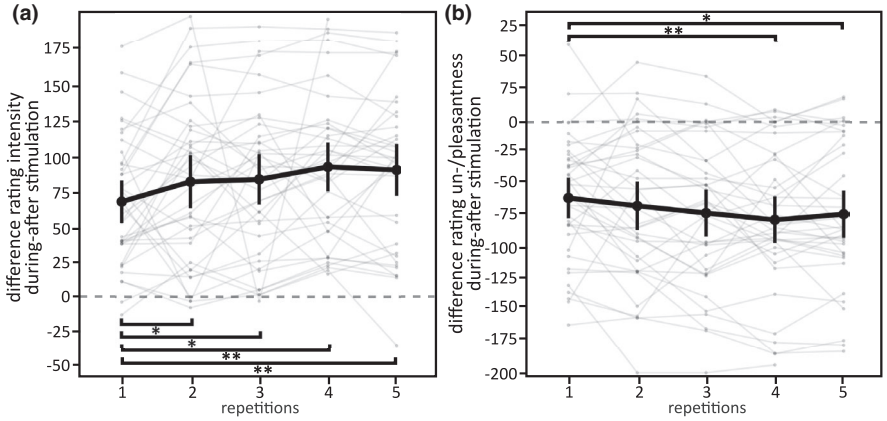

FIGURE 2 Estimated pain relief for perceived intensity (a) and un-/pleasantness (b). Pain relief was estimated by the difference in intensity (a) and un-/pleasantness ratings (b) during and after the heat stimulation for each of the five repetitions. The black line shows means and 95% confidence intervals of the whole group. Thinner grey lines depict estimated pain relief for each individual participant. Conditions with and without control are pooled here because they did not differ statistically. $^{**}p < 0.01$, $^{*}p < 0.05$

by changes in perception during and/or after heat stimulation and if this was different between the two control conditions. For this analyses, the ratings during and after stimulation were both included separately, in contrast to the first analysis step, in which the difference between both was used.

Ratings of perceived intensity during and after the heat stimulation did not change overall across repetitions (main effect 'repetition' $F_{4,638} = 0.28$, $p = .891$; interaction 'time point × repetition' $F_{4,638} = 1.98$, $p = 0.095$; see Figure 3a; Supplementary Table S2 for means and standard deviations). This indicates that there is no clear driver responsible for the change in estimated pain relief across repetitions and that this change appears to be driven by a mixture of processes (e.g. a non-significant decrease in ratings after the heat stimulation together with a non-significant increase in ratings during the heat stimulation). However, after heat stimulation, intensity was perceived differently depending on the conditions with and without control during and (interaction 'condition × time point' $F_{4,638} = 4.89$, $p = 0.027$): After the heat stimulation, intensity was rated lower with no control compared to the control condition (planned comparison: mean difference = 9.98, $p = 0.021$, $d = 0.17$; Figure 3). In contrast, during the stimulation ratings did not differ between control conditions (planned comparison: mean difference = 3.44, $p = 0.424$, $d = 0.11$).

Similar to perceived intensity, ratings of perceived un-/pleasantness during and after the heat stimulation did not change overall across repetitions (main effect 'repetition' $F_{4,638} = 0.23$, $p = 0.921$; interaction 'time point × repetition' $F_{4,638} = 0.82$, $p = 0.513$; see Figure 3b; Supplementary Table S2 for means and standard deviations), indicating again that there is no clear driver responsible for the change in estimated pain relief across repetitions. Yet and similar to perceived intensity, ratings of un-/pleasantness after the heat stimulation were different for uncontrollable compared to controllable pain (interaction 'control × time point' $F_{4,638} = 5.68$, $p = 0.017$): After the stimulation, pleasantness was rated higher without control compared to the control condition (planned comparison: mean difference = 14.15, $p = 0.001$, $d = 0.32$; Figure 3). In contrast, during stimulation ratings of un-/pleasantness did not differ (planned comparison: mean difference = 0.34, $p = 0.934$, $d = 0.03$).

3.3 | Changes in mood and well-being across repetitions and control conditions

For all ratings of mood and well-being, it was tested whether these ratings were different in the conditions with and without control and whether they changed across repetitions.

Participants reported that they felt more externally controlled in the condition without control compared to the condition with control (main effect 'control' $F_{1,316} = 11.57$, $p = 0.001$; Supplementary Table S3 for all means and standard deviations) with no change across repetitions (main effect 'repetition' $F_{4,315} = 0.84$, $p = .503$; interaction 'control × repetition' $F_{4,315} = 0.64$, $p = 0.632$). Differences between control

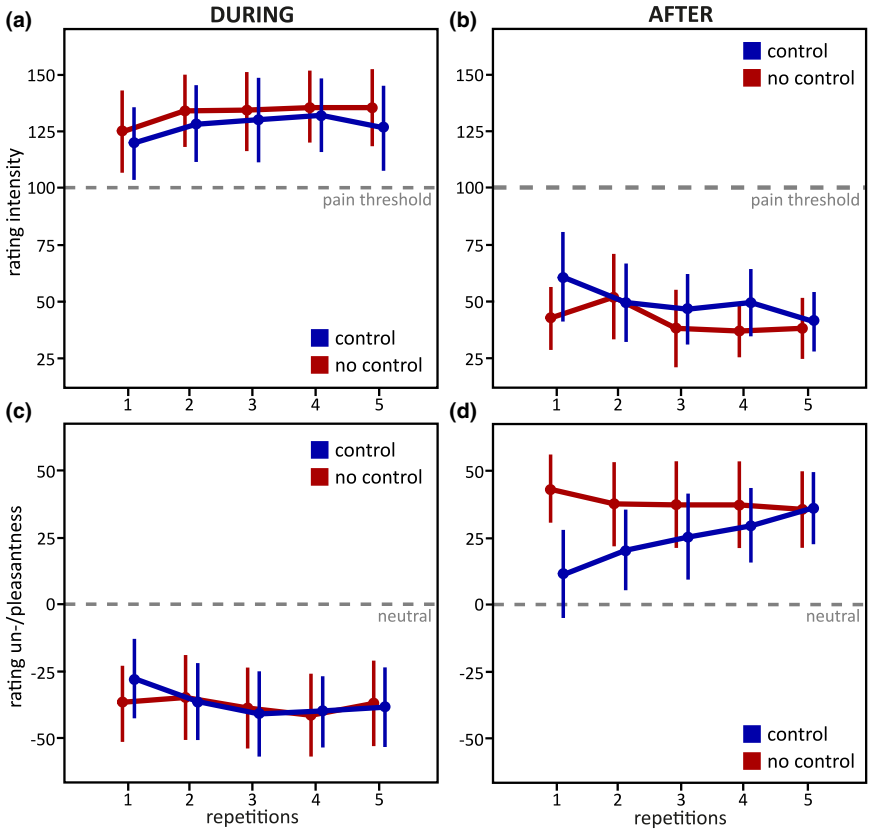

FIGURE 3 Ratings of perceived intensity (a, b) and un-/pleasantness (c, d) during (a, c) and after (b, d) the painful heat stimulation. Means and 95% confidence intervals for intensity and un-/pleasantness ratings during and after the painful heat stimulation in the conditons with (blue) and without control (red) are shown

conditions were also observable for reported tiredness and how focused participants felt: Participants reported to be more tired (main effect 'control' $F_{1, 316} = 4.96$, $p = 0.027$) and less focused (main effect 'control' $F_{1, 317} = 9.89$, $p = 0.002$) in the condition without control compared to the control condition. Further, how focused participants were decreased across repetitions (main effect 'repetition' $F_{4, 315} = 4.13$, $p = 0.003$) independent of control conditions (interaction 'control × repetition' $F_{4,315} = 0.87$, $p = 0.483$), with no changes in tiredness across repetitions (main effect 'repetition $F_{4,315} = 0.37$, $p = 0.819$; interaction 'control × repetition' $4_{, 315} = 0.32$, $p = 0.867$).

The perception of being relieved changed across repetitions dependent on the control condition (interaction 'control × repetition' $F_{4,316} = 2.84$, $p = 0.024$): Feeling relieved was higher in the control condition in the second, third and forth repetition compared to the first repetition (planned comparisons, repetition 1 vs. 2: mean difference = 0.42, $p = 0.003$, $d = 0.47$; 1 vs. 3: mean difference = 0.289, $p = 0.040$, $d = 0.37$; 1 vs. 4: mean difference = 0.40, $p = 0.005$, $d = 0.51$), while in the condition without control the feeling of relief only increased from the fourth to fifth repetition (repetition 4 vs. 5: mean difference = 0.28, $p = 0.047$, $d = 0.32$). Differences between the control conditions were found for the second and fourth repetition (control vs. no control, repetition 2: mean difference = 0.35, $p = 0.012$, $d = 0.35$; repetition 4: mean difference = 0.34, $p = 0.016$, $d = 0.41$).

No changes across repetitions and differences between control conditions were found for how excited, stimulated and irritated participants felt during the experiments (all p's > 0.082).

4 | DISCUSSION

The aim of this study was to test whether perception of pain relief changes with repetitions and whether this perception is different with uncontrollable compared to controllable preceding pain. Differences of intensity and un-/pleasantness ratings during and after painful heat stimulation, used as an indicator of perceived pain relief, increased with repetitions, but this increase levelled off after a few repetitions. Having no control over pain resulted in lower intensity and higher pleasantness ratings after the reduction of the painful stimulation.

While the perception of pain relief at first increased with repetitions, this increase levelled off for perceived intensity after a maximum of four repetitions. This levelling off could be explained by ceiling effects, but on average neither intensity nor un-/pleasantness ratings during and after heat stimulation approached the ends of the rating scales. Rather, it seems that pain relief perception (expressed as the change in intensity and un-/pleasantness ratings) stabilized after a few repetitions. This is an interesting finding because humans show adaptation to repeated stimuli of various modalities—if these stimuli do not represent a danger signal (e.g. visual, auditory, olfactory stimuli). While pain is a danger signal to which humans show adaptation under specific conditions (Kleinböhl et al., 1999, 2006), pain relief is clearly not a danger signal, but rather a rewarding and thus appetitive stimulus (Leknes et al., 2008; Navratilova et al., 2015). In rodents, it has been shown that motivated behaviour induced by pain relief as a negative reinforcement is mediated by activation of mesolimbic reward circuitry—more specifically by activation of dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) and dopamine release in the NAcc (Navratilova et al., 2012). Human research confirmed a central role of the NAcc in processing pain relief, with the NAcc showing activation at the offset of experimentally induced pain (Baliki et al., 2010). Further, a correlation of relief pleasantness ratings with activation in the NAcc, with relief being induced by a safety signals, was described (Leknes et al., 2011). In line with the described role of the NAcc and the mesolimbic dopamine system in processing pain relief and results from addiction showing increased phasic dopamine release with repeated drug exposure as a rewarding stimulus (e.g. Ostlund et al., 2014), it could be speculated that increasing dopamine release with exposure to repeated pain relief resulted in the increasing perception of pain relief.

The present results show that repeated reductions of pain result in an increasing perception of pain relief. Such a change in perceived pain relief across repetitions could be driven by either an increase of perceived intensity and unpleasantness across repetitions during the heat stimulation or decreased perceived intensity and increased pleasantness across repetitions after the heat stimulation or a mixture of both. No significant effects of repetition on the ratings during and after the heat stimulation were found. Therefore, the current results are most likely driven by a mixture of both effects, probably caused by a change in the ratio between perceived intensity and un-/pleasantness during and after the heat stimulation. The lack of significant effects of repetition on the ratings further suggests that changes in perceived pain relief cannot be attributed to sensitization or adaptation processes during and/or after heat stimulation.

Clinically, it is an interesting observation that perceived pain relief does not decrease with repeated presentations of pain reductions. This means that pain relief keeps its perceptual properties or even increases within the first few repetitions. This could be of interest when considering pain relief as a negatively reinforcing stimulus of either maladaptive pain behaviour (e.g. pain-contingent intake of pain killers) or adaptive health behaviour (e.g. paced physical activity; cf. Fordyce, 1982). A lack of adaptation to pain relief might

render this type of reward particularly strong. However, perceived pain relief might change with more repetitions and/or in longer, clinically relevant time frames. Considering strong habituation to daily experimental heat pain stimulation over a time frame of 8–11 days (e.g. Bingel et al., 2007; Rennefeld et al., 2010; Riedl et al., 2011), it could be hypothesized that perceived pain relief decreases as well. In chronic pain, other processes might be relevant. For example, an assumed reward deficiency (Borsook et al., 2016) together with altered dopamine functioning (e.g. Ledermann et al., 2017; Martikainen et al., 2015; Wood et al., 2007) might result in perceptual changes known from addiction research, where increasingly larger amounts of the substance of abuse are needed to result in the same feeling of pleasantness. Such ideas are highly speculative and need to be tested whether in future studies.

No overall effect of controllable versus uncontrollable pain on perceived pain relief could be found. However, ratings after the pain stimulation still suggest differential effects of the control conditions, because intensity ratings were lower and pleasantness ratings higher for uncontrollable compared to controllable pain. It has been repeatedly shown that whether a pain is controllable or not affects how experimental as well as clinical pain is perceived (e.g. Aldrich et al., 2000; Bräscher et al., 2016; Jensen & Karoly, 1991; Wiech et al., 2006)). In pain therapy, rendering clinical pain as controllable is often a declared goal (Gatchel et al., 2007) and it has been shown that increased perceived control is associated with better functioning in chronic pain patients (Tan et al., 2002). In this context, it is interesting that the perception of pain relief appears decreased when the preceding pain is controllable, possibly lowering the rewarding properties of the respective pain relief. From research on reward perception it is known that unpredicted reward leads to stronger release of phasic dopamine compared to expected reward (Fiorillo, 2003), possibly explaining the present results because the pain relief is better predictable with controllable pain. In addition to the possible effects of dopamine release, increased perception of pain relief with uncontrollable pain could be viewed as a compensatory mechanism to counterbalance the negative state induced by the uncontrollable pain. Further, an increase in perceived pain relief with uncontrollable pain could be induced by additional positive affect because the uncertainty related to the perception of uncontrollability is terminated.

Here, we did not investigate perceived pain relief directly, but rather assessed perceived intensity and un-/pleasantness before and after a painful heat stimulus. Other studies on perceived pain relief assessed pain relief directly using a relief VAS (Leknes et al., 2008), which could be considered a more direct assessment. However, the concept of perceived pain relief is rather abstract compared to intensity and un-/pleasantness perception and it could be questioned how well participants are able to evaluate different amounts of pain relief. Interestingly, the opioid-receptor antagonist naloxone blocked endogenous pain inhibition induced by relief elicited by cues signalling lower pain than expected when assessed with intensity and unpleasantness ratings (Berna et al., 2018). In contrast, no effect was found on (retrospective) relief ratings, suggesting that the different scales indeed assess different aspects of perception. However, intensity and/or un-/pleasantness ratings have not been compared directly to pain relief ratings so far, leaving it open how these different ratings relate to each other and whether they potentially reflect different aspects of the perception of pain relief.

In the present paradigm, participants had no real control over the painful stimulation. An illusion of control was created by showing a button with the instruction that pressing the button would end the stimulation but the nociceptive input was kept constant across both the condition with and without control. While this might appear artificial, similar procedures have been used successfully before (Borckardt et al., 2011; van Vliet et al., 2018, 2020). In addition, participants' responses in the ratings of mood and well-being indicated that participants indeed felt less in control in the condition without control (higher scores on how externally controlled they felt) compared to the condition with control. Interestingly, while un-/pleasantness ratings suggested larger pain relief in the first few repetitions in the condition with control, this converged with the ratings in the condition without control in later repetitions. Based on the specifics of the present design with no real control, one might speculate that participants realized with ongoing repetitions that they had no real control over the pain and, thus, ratings approximated those in the uncontrollable condition. However, this hypothesis has to be scrutinized by comparing the present effects to effects of controllability in a study design in which participants truly have control over the pain stimuli.

In sum, the present results show that perceived pain relief increases with repeated pain repetitions and that this pain relief was perceived as larger when the preceding pain was perceived as uncontrollable. These findings highlight the importance of investigating the perceived intensity and pleasantness of pain relief. Future studies should focus on the neurophysiological mechanism underlying the changes in perceived pain relief with repeated stimulation and un-/controllability to enhance our mechanistic understanding of the perception of pain relief.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

SB, MS and KS-E conceptualized and designed the experiment, DW and SB acquired the data, SB analysed the data, all authors discussed the data and were involved in the interpretation of the data, SB drafted the article, MS, KS-E and DW critically revised the article for important intellectual content. All authors approved the final version of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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