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Doubling your pay-off: Winning pain relief engages endogenous pain inhibition

Pain relief as reward

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17 SB, WG, PS developed the study concept and design. Data collection was performed
18 by SK, AKA, and SB. SB performed the data analysis under the supervision of PS. SB,
19 WG and PS contributed critically to the interpretation of the experiment and results.
20 SB drafted the manuscript, PS provided critical revisions. All authors approved the
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Abstract

When in pain, pain relief is much sought-after, particularly for individuals with chronic pain. In analogy to augmentation of the hedonic experience ('liking') of a reward by the motivation to obtain reward ('wanting'), the seeking of pain relief in a motivated state might increase the experience of pain relief when obtained. We tested this hypothesis in a psychophysical experiment in healthy human subjects, by assessing potential pain-inhibitory effects of pain relief 'won' in a wheel of fortune game compared to pain relief without winning, exploiting that the mere chance of winning induces a motivated state. The results show pain-inhibitory effects of pain relief obtained by winning in behaviorally assessed pain perception and ratings of pain intensity. Further, the higher participants scored on the personality trait novelty seeking, the more pain inhibition was induced. These results provide evidence that pain relief, when obtained in a motivated state, engages endogenous pain inhibitory systems beyond the pain reduction that underlies the relief in the first place. Consequently, such pain relief might be used to improve behavioral pain therapy, inducing a positive, perhaps self-amplifying feedback loop of reduced pain and improved functionality.

Significance statement

When in pain, pain relief is relevant to everyone. For individuals with chronic pain, pain relief can be an all-dominant goal. Although it is clear that pain relief is a fundamental motivator, it is unknown whether pain relief gained in a motivated state alters the perception of the remaining pain. It is demonstrated here that pain relief that is obtained in a motivated state engages endogenous pain inhibition compared to pain

relief unrelated to individuals' behavior. High novelty seeking as a personality trait was associated with more endogenous pain inhibition. This knowledge is highly relevant for pain therapy as it could be used to create a self-sustaining and perhaps self-amplifying positive feedback loop of pain-inhibition and improved functionality.

Introduction

The pleasure of pain relief is known to everyone – satisfying, soothing, and much sought-after when one is in pain. Particularly for individuals with chronic pain, pain relief is a major, sometimes all-dominant goal. Such a motivated state, i.e. the seeking of pain relief, might induce a change in the perception of relief when obtained, because the motivation to obtain reward ('wanting') and the hedonic experience ('liking') of an reward are closely linked and typically, enhance each other (Barbano and Cador, 2006; Sherdell et al., 2012; Barbano and Cador, 2007, for review). Enhanced motivation depends on opioid release in response to reward, increasing the hedonic properties of the reward, which is incorporated in future anticipatory evaluation of reward (i.e. incentive salience; Smith et al., 2011). In turn, increased dopamine release in states of heightened motivation (Berridge et al., 2009, for review) probably leads to increased release of endogenous opioids (Morgan and Franklin, 1990), thereby enhancing liking.

The interaction between pain and reward, specifically reward associated with positive stimuli, is conceptualized in the Motivation-Decision-Model (Fields, 2007). This model predicts pain inhibition via endogenous opioidergic systems when the motivation to obtain reward is prioritized over pain avoidance. Confirming the model and the interaction between dopaminergic and opioidergic systems, rewards such as food or

money have been shown to induce endogenous pain inhibition through opioid release (Dum and Herz, 1984) and to reduce the perceived intensity of painful stimuli (Becker et al., 2013). Outside the laboratory, interactions between pain relief as the offset of a negative stimulus associated with reward (Franklin et al., 2013) and pain might be particularly important because many chronic pain patients can achieve some pain relief by certain behaviors such as a change in body posture or pacing. Despite potentially being more important than positive stimuli such as money or food, pain relief as a reward is not discussed in the Motivation-Decision-Model and it remains unknown whether pain relief gained in a motivated state induces endogenous pain inhibition, thereby augmenting pain relief.

Here, we exploited that the mere chance of winning induces motivated states even with purely random outcomes (Clark et al., 2009; Martinez et al., 2009; Dong et al., 2014). To test potential pain-inhibitory effects of pain relief that is gained by the individual in a motivated state, we compared pain relief 'won' in a wheel of fortune game to pain relief that occurred unrelated to participants' behavior. Further, we tested whether the hypothesized pain inhibition is related to personality traits associated with reward sensitivity, specifically novelty seeking and reward dependence, and inversely related to harm avoidance.

Material & Methods

Participants

Thirty-five healthy volunteers (18 female, 17 male; age *M*=23.6 yrs, *SD*=6.0 yrs) participated in one testing session each. Exclusion criteria were any present or past pain

condition, psychiatric disorders, excessive gambling, substance abuse behaviors, alcohol consumption of more than 100 ml alcohol per week, tobacco use, regular night shifts or sleep disorders. Because no comparable studies were available, expected effect sizes could not be estimated and accordingly an a priori sample size calculation could not be performed. We therefore decided a priori to test 40 participants, allowing finding small to medium effects (f = 0.16 estimated with G*Power 3.1, Faul et al., 2007); repeated measures ANOVA with within-subject factors) with a significance level of 0.05, and an assumed power of 80%. Five recruited participants were excluded before commencing the wheel of fortune game because they did not develop skin sensitization with capsaicin. The study was approved by the McGill University Institutional Review Board and informed consent was obtained from all participants according to the revised Declaration of Helsinki (2008).

Thermal stimulation

While participants were playing a wheel of fortune game (see below) they received heat stimuli using a 27 mm diameter contact thermode (Contact Heat Evoked Potentials, CHEPS; PATHWAY Pain & Sensory Evaluation System, Medoc Ltd. Advanced Medical System, Israel). Baseline temperature was 32°C; rise rate 20°C/s, and return rate 30°C/s. Thermal stimuli were applied to the inner forearm of participants' non-dominant hand after sensitization of the skin using 0.075% topical capsaicin cream. The cream was applied to a 3 x 3 cm area on the forearm. Capsaicin is the active ingredient of chili pepper that induces heat sensitization by activating temperature-dependent TRPV1 ion-channels (Holzer, 1991). The cream was removed after 20 min (Dirks et al., 2003; Gandhi et al., 2013) and the thermode applied at the location on the forearm. Capsaicin-induced sensitization of the skin was used to allow for potent pain relief as reward and

pain increase as punishment without the risk of skin damage (c.f. Gandhi et al., 2013). Participants' pain thresholds were assessed before the wheel of fortune game. Participants were exposed to stimuli of 30 sec duration with target temperatures starting at 35 °C and increasing by 1 °C for each subsequent stimulus. Participants rated the peak of the perceived pain intensity at the end of the stimulation. If their rating was lower than 130 on the pain rating scale (see below; mildly painful), more stimuli were applied with increasing temperatures by steps of 1 °C or 0.5 °C, depending on the participant's rating. In case of ratings higher than 130, more stimuli were applied with decreased temperatures resembling a staircase method. The temperature rated consistently around 130 on the pain rating scale was used to determine the stimulation intensities for the wheel of fortune game.

Rating scales

Participants rated the perceived intensity and pleasantness/unpleasantness of the thermal stimuli using two horizontally orientated Visual Analogue Scales (VASs). The intensity VAS ranged from 0 "no sensation" to 200 "most intense pain tolerable" with 100 being the pain threshold. The pleasantness/unpleasantness VAS ranged from -100 "extremely unpleasant" to +100 "extremely pleasant", with the midpoint qualifying the stimuli as hedonically neutral (Villemure et al., 2003; Becker et al., 2013). These VASs were used to differentiate between non-painful and painful as well as between pleasant and unpleasant sensations. Before commencing with testing, participants were familiarized with the rating scales to ensure that they used the scales appropriately.

Wheel of fortune game

A wheel of fortune game, adapted from previous versions (Breiter et al., 2001; Ernst et al., 2004; Becker et al., 2013), was used to provide participants with the possibility to win pain relief. The game comprised two types of trials: the *test* trials, in which participants played the wheel of fortune game and the *control* trials, in which participants did not play the game. In both trial types, thermal stimulation started and when the target temperature was reach participants were instructed to memorize the temperature perceived at this moment (interval of 2 sec: see Figure 1). After this memorization interval, participants were presented on a computer screen with a wheel of fortune that was divided into three sections of equal size but different color.

In the *test trials*, participants selected one of two colors by pressing a corresponding button on a keyboard, which started spinning the wheel. When the wheel came to a stop, the color under the pointer determined the outcome. If the wheel landed on the color the participant had selected, the participant won pain relief; if the wheel landed on the color the participant had not selected, the participant lost and received a pain increase; if the wheel landed on the color that could not be chosen (white), the participant neither won nor lost and the thermal stimulation stayed constant. Both the losing and the no change outcomes served as control conditions for comparison with the pain relief outcome. The no change outcome served as a control for unspecific effects for which the difference between test and control trials should not differ for the pain relief and the 'no change' outcomes, such as distraction. The losing outcome was included because winning has been associated with arousal. Losing is similarly associated with arousal (Sokol-Hessner et al., 2009; 2013) and therefore ensured that any finding regarding winning is not simply caused by arousal. Losing trials also made the game more realistic, which was important to increase participants' engagement. It was expected that

perceived intensities in losing trials would be high, thereby possibly leading to a ceiling effect between test and control conditions for this outcome.

In the *control trials*, participants could not choose a color of the wheel but had to press a button of unrelated color (black), which started the wheel spinning as in the test trials. In contrast to the test trials, the wheel displayed in the control trials had no pointer. After the wheel came to a stop, the temperature of the thermode either decreased, increased, or stayed the same just as in the test trials but because the participant had not selected a color, there was no winning or losing component and the temperature change occurred unrelated to participants' behavior. Stimulation intensities in these control trials followed the same course as in the test trials (yoked control) to allow testing specifically for endogenous pain inhibition induced by pain relief that is obtained through winning in a wheel of fortune game.

Unbeknownst to the participants, the outcome of a trial was not related to their color selection because outcomes for each trial occurred in a predetermined, pseudorandom order. This purposefully excluded other processes such as learning and associated meaningful choice behavior, as the aim of the experiments was to test whether pain relief that is won leads to engagement of endogenous pain inhibition compared to pain relief that occurs unrelated to participants' behavior.

While the outcome temperature of the trial was applied, participants rated the perceived intensity and the pleasantness/unpleasantness of the thermal stimulation using the previously described VASs (Figure 1). Immediately after these ratings, participants adjusted the stimulation intensity themselves to match the temperature they memorized at the beginning of the trial to implement a behavioral assessment of pain perception. Participants adjusted the temperature by using a response unit with two

buttons, one to increase the temperature and one to decrease the temperature. Self-adjusted temperatures lower than the stimulation intensity at the beginning of the trial indicate sensitization across the trial, while higher temperatures indicate habituation.

Participants played in total 18 trials of the wheel of fortune game, three trials per condition (test trials: winning, losing, no change; control trials: temperature decrease, temperature increase, no change). Conditions were applied in predetermined pseudorandom order. Each outcome (pain relief, pain increase, no change) occurred with a fixed probability of 1/3.

++insert Figure 1 here++

Pain relief was implemented by a reduction of the stimulation intensity of -7°C, pain increase by a rise of +5°C. The magnitude of these temperature steps was determined and optimized in pilot experiments with the aim to induce potent pain relief and pain increase. The magnitude of these temperature steps was the same in test and control trials to ensure that the only difference between test and control trials was whether participants played the wheel of fortune game or not.

Skin conductance measurements

Skin conductance was recorded at the third phalanx of the index and middle finger of the participant's non-dominant hand with Ag-AgCl surface electrodes (Type EL-507) using a BIOPAC MP150 system (BIOPAC Systems Inc., Goleta, USA). Skin conductance was sampled at 1000 Hz and high-pass filtered (0.05 Hz). To quantify skin conductance

responses (SCR), onset-to-peak amplitude within 1-8 seconds after the display of the outcome was analyzed. SCRs were averaged across outcomes (pain relief, pain increase, and no change) and trial type (test and control) for each participant. Skin conductance was analyzed using Ledalab V3.4.6c (Benedek and Kaernbach, 2010).

Questionnaire and exit interview

The personality traits novelty seeking, harm avoidance, and reward dependence were assessed after the experiment using the Temperament and Character Inventory (TCI; (Cloninger, 1987). In addition, an exit interview was performed, asking for the following information: whether participants (1) had difficulties using the VAS or adjusting the temperature; (2) used a strategy for playing the wheel of fortune; (3) thought the wheel was more likely to land on one color than another; (4) thought that the wheel followed a pattern on which color it landed; (5) were motivated to play the wheel of fortune; (6) tried to get as much pain relief as possible while playing the game. Participants gave first yes/no answers and were then asked in open-ended question to specify their answers.

Statistical analysis

For the statistical analysis, nine participants were excluded because they did not perceive the thermal stimulation during the wheel of fortune game as painful (i.e. ratings <100 in the no change condition) possibly due to the distraction by playing the game. Before testing the effects of pain relief on the perception of thermal stimuli, it was ensured that the wheel of fortune game did not allow meaningful choice behavior by analyzing the frequencies of choice repetitions after each condition. Frequencies were compared using a repeated measures analysis of variance (ANOVA) design with the two within-subjects factors 'outcome' (with the levels pain relief, pain increase, no change)

and 'trial type' (with the levels test and control) by mixed model procedures. A second repeated measures ANOVA with the same factors was used to test for possible differences in trial durations because trial durations could vary depending on participants speed of responding (see Figure 1).

The effects of pain relief on the perception of thermal stimuli, behaviorally assessed pain perception (adjustment of the temperature) and VAS ratings (perceived intensity and pleasantness/unpleasantness) were analyzed after confirming normality (kurtosis and skewness <1). Onset-to-peak amplitude of skin conductance responses were squared to correct for non-normality (kurtosis and skewness after correction <1). Behaviorally assessed pain perception, VAS ratings, and squared skin conductance responses were analyzed with a repeated measurement ANOVA design using mixed model procedures with the factors 'outcome' and 'trial type'. To account for possible ceiling effects in the pain increase outcome, this ANOVA analysis was repeated only for the pain relief and the no change outcomes. ANOVA analyses were followed by post-hoc pairwise comparisons and calculation of Cohen's d as a measure of effect size (Cohen, 1988) when appropriate.

To test whether the magnitude of pain-inhibition due to winning pain relief was related to participants' personality traits of novelty seeking, harm avoidance, and reward dependence, the differences in behaviorally assessed pain perception, perceived intensity und pleasantness/unpleasantness between the test and control trials for the pain relief outcome were correlated with the TCI scores.

To assess whether the variables assessed in the exit interview affected the result of the wheel of fortune game, yes/no answers of the participants were included into the analysis as covariates, calculating separate ANCOVA analysis with mixed model

procedures for each variable. If the covariate explained a significant amount of variance in the model, it was tested whether this covariate interacted with the factors of interest.

The significance level was set to 5% for all analysis and Bonferroni corrected for multiple testing. All statistical analyses were performed using PASW Statistics 17 (SPSS Inc. Chicago, USA). Table 1 provides a summary of the statistical analyses (rows in the table refer to values referenced by superscript letters in results section). Observed power was calculated post hoc with G*Power 3.1 (Faul et al., 2007).

++insert Table 1 here++

Results

Effects of pain relief obtained by winning on behaviorally assessed pain perception

As expected with approximately 20 second-long heat pain stimuli of moderate to high intensity, participants sensitized within trials to the thermal stimulation. In the no change condition, the self-adjusted temperature was on average 0.8° C lower at the end of the trial compared to the beginning of the trial (M = -0.80˚C, SD = 1.40˚C). The self-adjusted temperature was across trial types lower for the pain relief outcome and higher for the pain increase outcome compared to the no change outcome (Figure 2; main effect 'outcome' F_{25} = 162.97, p < 0.001[a]; post-hoc comparison wining vs. no change p < 0.001. Cohen's d=1.72[b]; losing vs. no change p < 0.001, Cohen's d=1.42[c], both significant after Bonferroni correction), probably induced by the temperature decrease

and increase in the outcome interval of wheel of fortune game. Differences in sensitization or habituation across conditions could not be explained by different durations of the trials (mixed model ANOVA, interaction 'outcome' x 'trial type' F_{150} = 0.23, p = 0.80[d]; all post-hoc comparisons p > 0.25).

However, when compared to pain relief without winning, pain relief obtained by winning resulted in reduced sensitization in response to the thermal stimulation, indicating endogenous inhibition of the nociceptive input and confirming our hypothesis (Figure 2; main effect 'trial type' F_{25} = 8.46, p = 0.004[e]; interaction 'outcome x trial type' F_{25} = 0.97, p > 0.25[f]; post-hoc comparison p=0.007, significant after Bonferroni correction; Cohen's d=0.47[g]; because the interaction did not reach significance the post-hoc tests were Bonferroni corrected; as both the pain increase and the no change outcome were designed as control conditions, no interaction was expected). Behaviorally assessed pain perception did not differ for the pain increase (p = 0.410[h]) and no change outcome (p = 0.151[i]) between test and control trials. Repeating the analysis without the pain increase outcome to account for possible ceiling effects confirmed the results (main effect 'trial type' F_{75} = 7.15, p = 0.009[j]; interaction 'outcome x trial type' F_{75} = 0.70, p > 0.25[k]; post-hoc comparisons: pain relief outcome p=0.015, significant after Bonferroni correction; Cohen's d=2.42[l], no change p=0.197).

++insert Figure 2 here++

Effects of pain relief obtained by winning on pain ratings

Similar to the effects of pain relief obtained by winning on behaviorally assessed pain perception, perceived pain intensity was rated as less intense when pain relief was won compared to the respective control trials without winning (Figure 3; main effect 'outcome' F_{25} = 155.68, p < 0.001[m]; main effect 'trial type' F_{25} = 5.16, p = 0.032[n]; interaction 'outcome x trial type' F_{25} = 55.67, p < 0.001[o]; post-hoc comparison p=0.011 significant after Bonferroni correction; Cohen's d=0.23[p]). However, the effect was smaller for subjectively perceived pain intensity compared to behaviorally assessed pain perception (Cohen's d=0.23 vs. Cohen's d=0.47). In contrast to the behaviorally assessed pain perception, perceived pain intensity differed for the no change outcome between test and control trials: when participants could choose between two colors of the wheel of fortune (test trials) they perceived the thermal stimulation as more intense when the wheel landed on the color that could not be chosen compared to when participants were not allowed to chose a color (control trials; Figure 3; post-hoc comparison p < 0.001 significant after Bonferroni correction; Cohen's d=1.13[q]). For the pain increase outcome, ratings of perceived pain intensity did not differ between test and control trials (p = 0.932[r]). Repeating the analysis without the pain increase outcome confirmed the results (main effect 'outcome' F_{25} = 52.52, p < 0.001[s]; main effect 'trial type' F_{25} = 8.40, p = 0.008[t]; interaction 'outcome x trial type' F_{25} = 94.08, p < 0.001[u]; post-hoc comparisons: pain relief outcome p=0.011, significant after Bonferroni correction, Cohen's d=1.14[v]; no change <0.001, Cohen's d=5.75[w]).

No differences in perceived unpleasantness of the thermal stimulation were found for the pain relief (p = 0.759[x]) and pain increase outcomes (p = 0.791[y]) between test and control trials. But similar to the perceived intensity, the stimulation was perceived as

more unpleasant when participants were allowed to choose between two colors of the wheel but it landed on the third color (no change outcome) compared to the respective control trials (main effect 'outcome' $F_{25} = 294.82$, $p < 0.001$[z]; main effect 'trial type' $F_{25} = 3.46$, $p < 0.001$[aa]; interaction 'outcome x trial type' $F_{25} = 5.55$, $p = 0.005$[ab]; post-hoc comparison p<.001 significant after Bonferroni correction, Cohen's d=0.88[ac]). The analysis without the pain increase outcome confirmed the results (main effect 'outcome' $F_{25} = 43.02$, $p < 0.001$[ad]; main effect 'trial type' $F_{25} = 18.25$, $p < 0.001$[ae]; interaction 'outcome x trial type' $F_{25} = 25.62$, $p < 0.001$[af]; post-hoc comparisons: pain relief outcome p=0.573; no change <0.001, Cohen's d=4.48[ag]).

++insert Figure 3 here++

Reductions in pain sensitization and reductions in perceived pain intensity due to pain relief obtained by winning were not correlated (r=0.20, p=0.33[ah]), indicating that pain relief that is won may have differential effects on different components of pain processing.

Association of novelty seeking and pain-inhibition by pain relief obtained by winning

Participants showed more endogenous pain-inhibition by pain relief obtained by winning the more novelty seeking they were: the amount of pain-inhibition by pain relief that was won in the test compared to the control trials correlated negatively with novelty seeking assessed with the TCI questionnaire (Figure 4; r = -0.54 p=0.005[ai]). Because pain-inhibition by pain relief obtained by winning was calculated as the

382 difference between VAS ratings of perceived intensity in the test and control trials,
383 negative values indicate successful pain-inhibition. Novelty seeking was specifically
384 related to induced pain inhibition obtained by winning pain relief and not to the level of
385 the perceived pain in neither the test nor the control trials, demonstrated by computing
386 separate correlations of the pain ratings with the novelty seeking scores in the test trials
387 (r=-0.15, p=0.48[aj]) and control trials (r=0.08, p=0.72[ak]). No correlations were found with
388 harm avoidance and reward dependence.

389

390 ++insert Figure 4 here++

391

392 ***Skin conductance responses***

393 Further, as expected for the different thermal stimulation intensities, skin conductance
394 responses differed for the difference outcomes (pain relief, no change, pain increase) of
395 the wheel of fortune, irrespective of the trials type (test, control) indicated by a main
396 effect of outcome (F_{62} = 7.22, p = 0.002[al]). Post-hoc tests revealed higher skin
397 conductance responses with the pain increase outcome compared to the no change
398 (p=.001 significant after Bonferroni correction, Cohen's d=0.82[am]) and the pain relief
399 outcome (p=.002 significant after Bonferroni correction, Cohen's d=1.04[an]; comparison
400 no change – win: p = 0.641[ao]).

401 Skin conductance responses were higher in the test compared to the control trials
402 across outcomes, indicated by a main effect of trial type (F_{60} = 11.20, p = 0.01[ap]). Further,
403 skin conductance responses showed an interaction effect of outcome and trial type
404 (F_{54}=6.79, p=0.02[aq]). Post-hoc comparisons showed a significant difference between test

and control trials for the no change outcome, with higher skin conductance responses in test compared to control trials (Figure 5; post-hoc comparison p<.001 significant after Bonferroni correction, Cohen's d=0.96[ar]). In addition, a trend for differences in skin conductance responses for the pain increase outcome between test and control trials was observed, with higher responses in test compared to control trials (Figure 5; post-hoc comparison p=0.07, Cohen's d=0.42[as]) but no difference for the pain relief outcome (p = 0.308[at]). These results indicate that participants were more aroused in the test trials compared to the control trials for the no change outcome with a similar tendency for the pain increase outcome, but not the pain relief outcome.

++insert Figure 5 here++

Exit interview

The exit interview revealed that four participants had difficulties using the VAS scales and one had difficulties memorizing the temperature at the beginning of each trial. Although this variable explained a significant amount of variance as a covariate in an ANCOVA analysis of perceived pain intensities (F_{25} = 4.04, p = 0.046[au]), none of the factors of interest was affected by these difficulties, indicating that the covariate had no direct effects on the effects of pain relief obtained by winning. In addition, the covariate had no effects on the other outcome measures (behaviorally assessed pain perception and perceived unpleasantness). No other variable from the exit interview had any effect on any of the outcome measures.

Manipulation check

As intended by the design of the wheel of fortune game, the different outcomes of the game in the previous trial had no effect on choice behavior, indicating that reward-dependent learning and meaningful choice behavior were successfully eliminated.

Discussion

In this study, we show for the first time that pain relief that is gained in a motivated state induces endogenous pain inhibition, thereby augmenting pain relief. Exploiting that the mere chance of winning induces motivated states even with purely random outcomes, we used a wheel of fortune task to induce such a motivated state. These pain-inhibiting effects of pain relief linked to increased motivation were observed in behaviorally assessed pain perception and in ratings of perceived pain intensity. The amount of endogenous pain inhibition was related to the personality trait of novelty seeking: the higher participants scored on novelty seeking, the more their pain was decreased when they won pain relief compared to the control condition.

The present results demonstrate clearly that pain relief when obtained in a motivated state, engages endogenous pain inhibitory systems beyond the pain reduction that underlies the relief in the first place. It had been shown previously that monetary reward inhibits pain perception (Becker et al., 2013), but no data existed on pain relief as a reward. Although winning pain relief, as implemented in this study, is not necessarily based on instrumental, contingent behavior, the mere chance of winning induces motivated states, thoughtful decision-making and the illusion of control, even with purely random outcomes (Clark et al., 2009; Martinez et al., 2009; Dong et al., 2014). Also, winning is inherently associated with positive emotions. Because

motivational and emotional pain modulation cannot be separated in the present study, mechanisms of affective pain modulation might have contributed to the pain inhibition observed (c.f. Kenntner-Mabiala et al, 2008; Roy et al., 2008; Villemure et al., 2003). Nevertheless, pain relief typically occurs in motivated states, i.e. when someone is in pain seeking to decrease his or her pain. Particularly in chronic pain patients, pain relief is sometimes an all-dominant goal. Some pain relief can be achieved by many chronic pain patients, for example by a change in body posture. Therefore, we posit that pain relief is particularly relevant in natural settings. The motivational component of pain relief shapes future behavior through operant learning (Becker et al., 2011; Navratilova et al., 2012), increasing the likelihood of repeating the behavior that led to the pain relief. Thereby, a positive feedback loop of behavior and pain inhibition that is perhaps self-amplifying might be created.

In the present study, pain inhibition induced by pain relief gained in a motivated state was stronger in the behaviorally assessed pain perception compared to participants' ratings of perceived intensity. Similarly, operant learning by pain relief as negative reinforcement in behaviorally assessed pain perception but not in pain ratings has been found previously (Hölzl et al., 2005; Becker et al., 2011). The effects of pain relief might be better captured by perceptual assessments such as the behavioral assessment of pain perception used here (cf. Kleinböhl et al., 1999) because such behavioral assessments are less influenced by social and cognitive confounds compared to verbal ratings (Cowey, 2004). In addition, it has been shown that even reductions in nociceptive input that are not consciously perceived can act as negative reinforcement (Becker et al., 2012), perhaps indicating that behaviorally assessed pain perception is a more sensitive measure than pain ratings. Further, in contrast to perceived pain intensity, perceived

475 unpleasantness was not modulated when pain relief was obtained in a motivated state.
476 While it is not obvious why such dissociation occurred (we excluded higher variance in
477 the unpleasantness ratings as a possible factor), similar findings have been reported
478 before. For example, it has been reported that attention modulates predominately
479 perceived pain intensity and emotion perceived unpleasantness (Villemure and
480 Bushnell, 2009), but also that emotion modulates both perceived intensity and
481 unpleasantness (e.g. Kenntner-Mabiala et al., 2008).

482 Individuals who are more reactive to reward might benefit more from pain relief in
483 terms of endogenous pain inhibition. This was indicated by the correlation of the
484 personality trait novelty seeking and endogenous pain inhibition: the higher the novelty
485 seeking scores, the higher the pain inhibition by pain relief that was won. Reward
486 sensitivity, and in particular novelty seeking, has been related to the neurotransmitter
487 dopamine (Leyton et al., 2002; Zald et al., 2008). Thus, the finding that the pain-
488 inhibitory effects of pain relief gained in a motivated state were related to novelty
489 seeking might indicate that dopamine mediated endogenous pain inhibition. In support
490 of this notion, placebo analgesia, in which the anticipation of clinical benefit can be
491 conceptualized as a special case of reward anticipation (de la Fuente-Fernandez et al.,
492 2001), has been shown to be associated with higher scores in personality traits related
493 to reward sensitivity, including novelty seeking (Schweinhardt et al., 2009). Also, direct
494 evidence indicates that dopamine mediates pain-inhibitory effects of monetary reward
495 (Becker et al., 2013). It is conceivable that the motivation to obtain pain relief increases
496 with increasing pain intensity, which in turn is related to increased dopamine release in
497 the basal ganglia (Wood et al., 2007; Scott et al., 2008). Thus, increasing dopamine
498 release might bias an organism more and more towards escape or avoidance behavior to

increase the likelihood of pain relief. Obtaining pain relief in such a state of heightened motivation probably increases release of endogenous opioids (Morgan and Franklin, 1990), augmenting the pain relief and the hedonic experience ('liking'). The hedonic experience of relief is associated with reward (Franklin et al., 2013), inducing approach behavior and, if applied in a learning context as negative reinforcement, a strengthening of behavior. Nevertheless, relief and reward can be conceptualized as different entities and relief learning and reward learning appear to be mediated by different neurophysiological mechanisms (Gerber et al., 2014, for review). Future studies should assess and specify the neurophysiological mechanisms underlying pain inhibition induced by pain relief gained in motivated states.

Participants were more aroused when they played the wheel of fortune game (test trials) compared to the control trials of the game, indicated by higher skin conductance responses. This effect was particularly strong in the no change condition. A similar trend was observed in the pain increase condition; stronger differential skin conductance responses between test and control trials were possibly precluded by a ceiling effect. In the pain relief condition, skin conductance responses did not differ between test and control trials. This could be explained by a soothing effect of pain relief, reducing arousal and thereby reducing the difference in arousal between test and control trials. For the no change condition, higher arousal in the test trials might explain the higher ratings of perceived pain intensity of the test trials compared to the control trials. As proposed by the "two-factor theory of emotion" (or "Schachter-Singer theory"; Schachter and Singer, 1962; Friedman, 2010), arousal might have been cognitively evaluated, resulting in the interpretation that the higher arousal might be caused by higher pain, leading in turn to higher ratings of perceived pain intensity. No such differential effects of arousal would

be expected for implicit behavioral measures (cf. Cowey, 2004; Hölzl et al., 2005); and indeed, there was no difference between test and control trials in the no change condition when pain was behaviorally assessed. An alternative interpretation to the Schachter-Singer theory is that playing the game without winning in the test trials of the no change condition induced negative emotions, contributing to pain facilitation in these trials (c.f. Kenntner-Mabiala et al., 2008; Roy et al., 2008; Villemure et al., 2003).

Endogenous pain inhibition induced by pain relief gained in a motivated state occurred over and above the well-known effects of distraction (Duncan et al., 1987; Miron et al., 1989; Villemure and Bushnell, 2009), offset-analgesia (Yelle et al., 2008; Martucci et al., 2012), and stimulus controllability (Arntz and Schmidt, 1989; Müller, 2011). Distraction reduces short-term pain to such a degree that it is used in clinical settings, e.g. when children undergo minor medical interventions. Offset analgesia describes the phenomenon that pain reduction is consistently reported as bigger than suggested by the actual change in nociceptive input. Stimulus controllability is associated with reduced pain perception (Arntz and Schmidt, 1989; Müller, 2011) and playing the wheel of fortune game might have induced a feeling of control (c.f. Martinez et al., 2009). The effects offset analgesia, and controllability should be present in the test and control trials of the wheel of fortune game and can therefore not have confounded the findings of the present study. Further, attention or distraction effects can neither explain our findings because heighted attention to the thermal stimulation in the test trials, leading to increased pain perception, or distraction by the wheel of fortune, leading to decreased pain perception, would have similarly influenced the pain relief outcome as well as the no change outcome.

Reinforcement is an important principle that is already used successfully in operant pain therapy. Using reinforcement to improve health behavior and to reduce maladaptive pain behavior results in substantial and long-lasting improved functionality and reduced clinical pain in chronic pain patients (Flor and Diers, 2007; Gatzounis et al., 2012), for review). Based on the influential work by W.E. Fordyce, positive reinforcement based on social interaction (e.g. verbal feedback or attention) is applied in operant pain therapy (Fordyce and Staff, 2014). Using pain relief as a negative reinforcement might be of particular benefit in this context because pain relief is a prominent and fundamental motivator for chronic pain patients. As discussed above, pain relief occurs frequently in chronic pain, although such relief might be incomplete. Importantly, even if reductions in nociceptive input are very small and possibly below the discrimination threshold (i.e. they cannot be reported) they can shape future behavior through their rewarding properties (Becker et al., 2008). Further, it has been shown that after partial pain relief even moderate pain can be perceived as pleasurable, demonstrating the strong motivational and emotional components of reduced pain (Leknes et al., 2013). Using pain relief in operant pain therapy could create a self-sustaining and perhaps self-amplifying positive feedback loop of pain-inhibition and improved functionality, possibly enhancing the effectiveness operant pain therapy.

In summary, our results indicate that pain relief gained in a motivated state induces endogenous pain inhibition and that the amount of this pain inhibition depends on an individual's degree of novelty seeking. These results highlight that pain relief is a fundamental motivator that can modulate our pain perception. Surprisingly, in clinical contexts, pain relief is commonly viewed as a simple reduction in perceived pain intensity (Farrar et al., 2001). Consequently, clinical trials typically measure only

reductions in perceived pain intensity (Dahan et al., 2011; Martini et al., 2013), neglecting important factors; re-gaining functionality and improving quality of life is often more important for chronic pain patients and, at least partially, independent of an actual change in pain magnitude. To further expand the present findings and to allow implementation in pain therapy, future studies should investigate whether chronic pain patients show similar responses to pain relief obtained in a motivated state.

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725

Legends

Figure 1: Time line of one test trial of the wheel of fortune game. The green line in the outcome interval indicates pain relief as outcome of the game, the red line indicates pain increase as an outcome, and the black line the no change outcome. Thermal stimulation followed the same temperature time course in both the test and the control trials. Instead of playing the game by choosing a color in the button press interval in the test trials, participants had to press a black button and the wheel stopped at a random position with no pointer in the control trials.

Figure 2: Means and 95% confidence intervals of behaviorally assessed pain perception for test and control trials in the pain relief, pain increase and no change outcome. Negative values indicate pain sensitization relative to the beginning of each trial, positive values habituation. Post-hoc comparisons: * $p < 0.017$, significant after Bonferroni correction for multiple testing.

Figure 3: Means and 95% confidence intervals of perceived pain intensity for test and control trials in the pain relief, pain increase and no change outcome. Post-hoc comparisons: ** $p < 0.003$, * $p < 0.017$, significant after Bonferroni correction for multiple testing.

Figure 4: Correlation of participants' scores on the novelty seeking subscale of the TCI and pain modulation by pain relief obtained by winning calculated as the difference between intensity ratings in the test minus the control trials of the pain relief outcome.

Figure 5: Means amplitude and 95% confidence intervals of skin conductance responses in the test and control trials in the pain relief, pain increase and no change outcome. Post-hoc comparisons: ^{t} $p < 0.10$; ** $p < 0.003$ after Bonferroni correction for multiple testing.

Table 1: Summary of statistical analyses. Letters (left) refer to values within the results section.

Tables

Table 1: Summary of statistical analyses

	Data structure	Type of test	Power
a	normally distributed	repeated measures mixed model ANOVA, main effect	1
b	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
c	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
d	normally distributed	repeated measures mixed model ANOVA, main effect	0.09
e	normally distributed	repeated measures mixed model ANOVA, main effect	0.90
f	normally distributed	repeated measures mixed model ANOVA, interaction	0.05
g	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.84
h	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.30

i	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.84
j	normally distributed	repeated measures mixed model ANOVA, main effect	0.97
k	normally distributed	repeated measures mixed model ANOVA, interaction	0.19
l	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
m	normally distributed	repeated measures mixed model ANOVA, main effect	1
n	normally distributed	repeated measures mixed model ANOVA, main effect	0.71
o	normally distributed	repeated measures mixed model ANOVA, interaction	1
p	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.30
q	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
r	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc	0.05

		comparison	
s	normally distributed	repeated measures mixed model ANOVA, main effect	1
t	normally distributed	repeated measures mixed model ANOVA, main effect	1
u	normally distributed	repeated measures mixed model ANOVA, interaction	1
v	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
w	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
x	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.06
y	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.06
z	normally distributed	repeated measures mixed model ANOVA, main effect	=1
aa	normally distributed	repeated measures mixed model ANOVA, main effect	0.50
ab	normally distributed	repeated measures mixed model	0.97

		ANOVA, interaction	
ac	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
ac	normally distributed	repeated measures mixed model ANOVA, main effect	1
ad	normally distributed	repeated measures mixed model ANOVA, main effect	1
ae	normally distributed	repeated measures mixed model ANOVA, interaction	1
af	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
ag	normally distributed	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
ah	normally distributed	Pearson correlation	0.26
ai	normally distributed	Pearson correlation	0.91
aj	normally distributed	Pearson correlation	0.19
ak	normally distributed	Pearson correlation	0.11
al	normally distributed after transformation	repeated measures mixed model ANOVA, main effect	1
am	normally distributed after transformation	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc	1

		comparison	
an	normally distributed after transformation	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
ao	normally distributed after transformation	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.08
ap	normally distributed after transformation	repeated measures mixed model ANOVA, main effect	1
aq	normally distributed after transformation	repeated measures mixed model ANOVA, interaction	1
ar	normally distributed after transformation	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	1
as	normally distributed after transformation	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.71
at	normally distributed after transformation	repeated measures mixed model ANOVA, Bonferroni corrected post-hoc comparison	0.99
au	normally distributed	repeated measures mixed model ANOVA with covariate	1

760