Virtual Reality to understand Pain-Associated Approach Behaviour: A Proof-of-Concept Study

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Purpose/Aim: Pain-associated approach and avoidance behaviours are critically involved in the development and maintenance of chronic pain. Empirical research suggests a key role of operant learning mechanisms, and first experimental paradigms were developed for their investigation within a controlled laboratory setting. We introduce a new Virtual Reality paradigm to the study of pain-related behaviour and investigate pain experiences on multiple dimensions.

Materials and Methods: The paradigm evaluates the effects of three-tiered heat-pain stimuli applied contingent versus non-contingent with three types of arm movements in naturalistic virtual sceneries. Behaviour, self-reported pain-related fear, pain expectancy and electrodermal activity were assessed in 42 healthy participants during an acquisition phase (movements-pain association) and a modification phase (no movement-pain association).

Results: Pain-associated approach behaviour, as measure by arm movements followed by a severe heat stimuli, quickly decreased in-line with the arm movement pain contingency. Slower effects were observed in fear of movement-related pain and pain expectancy ratings. During the subsequent modification phase, the removal of the pain contingencies modified all three indices. In both phases, skin conductance responses resemble the pattern observed for approach behaviour, while skin conductance levels equal the pattern observed for the self-ratings.

Conclusions: Our findings highlight a fast reduction in approach behaviour in the face of acute pain and inform about accompanying psychological and physiological processes. We discuss strength and limitations of our paradigm for future investigations with the ultimate goal of gaining a comprehensive understanding of the mechanisms involved in chronic pain development, maintenance, and its therapy.

Keywords: Pain-associated approach behaviour, fear of pain, pain expectancy, electrodermal activity, Virtual Reality

Introduction

Chronic pain is a prevalent, complicated, and serious problem. It has a severe impact on the sufferers' everyday lives, psychological well-being, and a noticeable influence on society as a whole (Rice et al. 2016; Mills et al. 2019). In chronic pain conditions, the pain has lost its protective function and becomes a burden by itself; often resulting in disability. In the context of musculoskeletal pain, the Fear-Avoidance Model suggests the emergence of a vicious circle of fear, approach-avoidance conflicts, and pain after an acute or potential tissue damage. This vicious circle is hypothesised to be maintained due to a self-reinforcing mechanisms (Lethem et al. 1983; Vlaeyen and Linton 2012; Vlaeyen et al. 2016).

Fear of movement-related pain, pain expectancy, and overt approach-avoidance behaviour can be examined in controlled laboratory settings. For instance, avoidance behaviour was investigated by introducing the possibility to escaping a painful stimulus and by (negatively) reinforcing this behaviour (van Vliet et al. 2018). In addition, extinction, generalization, reinforcement, and goal conflicts were demonstrated in experimental investigations (Meulders et al. 2013; Claes et al. 2014; den Hollander et al. 2015; Meulders et al. 2016; Biggs et al. 2017). Classical conditioning (Pavlov 1927) was suggested to play a critical role in the acquisition, generalization, and extinction of fear of movement-related pain (Vlaeyen 2015). While, operant learning of avoidance behaviour was proposed as the crucial factor for the persistence of chronic pain and resulting disability (Meulders 2019). From a classical conditioning perspective, pain can be considered as an unconditioned stimulus (US) and the (proprioceptive and visual feedback about the) movement as a conditioned stimulus (CS). The initially neutral CS gains a fear association after multiple pairings with the US. In contrast, operant or instrumental learning characterizes learning about the consequences of one's own behaviour (Skinner 1953). Such operant learning mechanisms might explain the persistence of chronic pain as successful avoidance of movements is negatively reinforced by the absence of pain.

Experimental paradigms have been developed to investigate respective associative (Meulders et al. 2011) and operant (Meulders et al. 2016) mechanisms within controlled laboratory settings. To ensure for sufficient ecological validity of experimental paradigms, three aspects require specific consideration: First, in reality, avoidance is mostly accompanied by non-neglectable costs (e.g. loss of social contacts in chronic pain; Meulders 2019). Thus, introducing realistic costs for reduced approach evolved as a critical factor in laboratory research (e.g. muscle effort; Meulders et al. 2016). Second, in chronic pain, pain-related avoidance behaviour is learned without any explicit instructions. This is not always easy to realize in laboratory research, but might also represent a crucial factor to be considered in the development of experimental paradigms (for a good example see Meulders et al. 2016). Finally, anticipatory fear reactions to movement-related pain become visible across multiple dimensions (e.g. psychological, physiological) that can be assessed using different methodologies (e.g. verbal fear and expectancy ratings, avoidance behaviour, electrodermal activity; see Meulders 2020). To gain a holistic understanding of the mechanisms underlying pain-related behaviour, experimental paradigms should therefore allow for simultaneous assessment of behavioural, psychological, and physiological components.

In recent years, Virtual Reality (VR) developed as a promising tool for pain research and its treatment (Keefe et al. 2012; Pourmand et al. 2018; Ahmadpour et al. 2019; Track 2019). VR creates a simulated 3D environment typically displayed using a head-mounted displays (HMD) or wall screen projections. These techniques aim to achieve presence, i.e. the feeling of being physically present in the virtual world (Bowman et al. 2007; Hudson et al. 2019). Recent pain research demonstrated that VR can not only modulate pain but also affect pain-related physiological factors. For instance, VR has been found to induce clinically significant pain reductions in chronic neck pain (e.g. Chen et al. 2017) and to alleviate movement-related fear in veterans with chronic pain (Fowler, 2019). In the context of acute pain, the analgesic effects

of immersive VR have been associated with smaller increases in brain activity in regions associated with pain stimuli and higher pain tolerances through the modulation of autonomic responses (Hoffman et al., 2006; Colloca et al., 2020).

This proof-of-concept study introduces a new Virtual Reality paradigm to the study of pain-associated approach behaviour. Specifically, the paradigm combines three-tiered heat pain stimulation with three types of arm movements. It prevents any explicit instructions to approach or avoid, induces costs to avoid (i.e. time) that compete with costs to approach (i.e. pain), and allows for simultaneous assessment of behavioural, psychological, and physiological components. The main aim of the study was to evaluate the new paradigm for its further application. Therefore, we hypothesized that a contingent association between specific approach movements and pain stimuli leads to reductions in these movements, while such approach movements increase again when this association is removed. We further expected changes in self-rated fear of movement-related pain and pain expectancy as well as changes in physiological arousal.

Methods

Participants

The current study includes data from 43 healthy adult participants. The sample size was determined by a-priori power calculations for within-subjects designs (G*Power, Faul et al., 2007). Specifically, we intended to detect effect sizes of ~ 0.4 (based on previous work) with a statistical power of 80% and an alpha level of 0.5. This resulted in a required sample size of 41 participants. Prior to participation, the following exclusion criteria were ruled out via telephone interviews: Age < 18 or > 35 ; left-handedness; BMI > 30 or < 18 ; Psychology student (beyond the 2nd semester); vision and hearing disabilities; insufficient German language abilities (to ensure that instructions are understood); regular intake of medication affecting the central nervous system; frequent smoking behaviour (> 15 cigarettes per day); drug consumption (inclusively cannabis); history of or acute diagnosis of chronic pain (e.g. headache); episode of severe pain that required medical treatment within the last six month (e.g. due to an injury); diagnosis of attention-deficit/hyperactivity disorder (ADHD), dyslexia or dyscalculia; acute suffering from any psychological, neurological, cardiovascular, respiratory or endocrinological diseases; disposition for vertigo or fainting. Based on these criteria, the initial pool of 132 participants, which were recruited via local (flyer) and online advertisement (e.g. social media, university platforms), was reduced to 43. Note that many of the exclusion criteria were determined by the fact that the current study is a part of a larger project. This larger project additionally includes a stress induction procedure, the assessment of several physiological (e.g. cortisol) and psychological (e.g. attentional control) variables, and electroencephalographical recordings (EEG) that can be affected by the respective factors in an uncontrollable way (e.g. cortisol by smoking, drugs, and medications; attentional control by ADHD diagnosis; EEG by left-handedness). Furthermore, we excluded participants with any history of chronic pain to prevent any re-activation and harm to a potentially hypersensitive nociceptive system.

All participants were asked to abstain from alcohol for 12 hours before testing, to not drink any coffee two hours prior to measurement, and to contact the study coordinator directly if they had to take any pain medication on the day of testing (to postpone the measurement to a different date or to exclude the participant when regular intake of pain medication follows). All experimental procedures were in accordance with the declaration of Helsinki and approved by the local ethics committee (Psychological Institute, University of Würzburg, Germany, GZEK 2020-18). Informed written consent according to the declaration of Helsinki and to the guidelines of the German Psychological Society was obtained from all participants. Study participation was reimbursed with 17.50€. One participant was excluded afterwards due to technical problems with data saving. Thus, our final sample included 42 healthy adult participants (21 women; age: $M = 24.5$, $SD = 3.5$, range: 19-34).

Experimental paradigm

The current study follows a within-subject design comprising five phases: A preparation phase, a practice phase, two experimental phases (acquisition, modification), and a postprocessing phase. All phases were passed by all participants in identical order. The paradigm is illustrated in detail in Figure 1 and Figure 2 provides a flowchart of acquired measurements. A naturalistic environment was implemented in VR by using a Powerwall, i.e. a computer-created virtual world that was projected on a 2D wall screen (2m x 3.22m) and could be perceived in 3D by wearing customary 3D-glasses (like in the 3D cinema). In this virtual world, participants were instructed to walk along a pre-defined 100m forest path until they reach the end of the path which could be seen from beginning on. To overcome these paths, participants were advised to use an extended self-made joystick apparatus which allows them to induce three types of virtual steps (1m, 5m or 10m) by different arm movements (small ca. 10cm, medium ca. 30cm, large ca. 50cm). During these movements, participants stand upright and wear a thermode (see next paragraph) on their lower inner right forearm. Two electrodes for electrodermal recordings were placed at the inner left hand.

The aim of the practice phase was only to collect experience with moving in the VR environment. Thus, no electrodermal recordings and no application of heat pain stimuli were applied here. The two experimental conditions (acquisition vs. modification phase) differed in respect to the visual characteristics of the virtual worlds (e.g. type of trees, colour of meadow) and, most importantly, in respect to the reinforcement plan of the thermal stimulation. While there was a contingent association between certain movements and certain heat stimuli in the acquisition phase (world A: acquisition of the movement-pain association), no such association was present in the modification phase (world B: modification of the movement-pain association). Specifically, in the acquisition phase (world A) small arm movements (inducing a 1m step in VR) were reinforced with a neutral heat stimulus (CS-, individual pain tolerance minus 10° Celsius), medium arm movements (inducing a 5m step in VR) were reinforced with a medium heat pain stimulus (CS+, individual pain tolerance minus 3° Celsius), and large arm movements (inducing a 10m step in VR) were reinforced with a severe heat pain stimulus (CS++, individual pain tolerance).

The reinforcement rate was 100% in all three cases. In contrast, in the modification phase (world B), the reinforcement with heat stimuli followed a fix plan which was independent of the actually initiated movements and was the same for all participants. This plan was pseudo-randomized by ensuring that applied stimuli included 50% neutral heat stimuli, 40% medium heat pain stimuli, and 10% severe heat pain stimuli (all defined in accordance to the individual pain tolerance as during the acquisition phase, see above). Note that we selected this approach in contrast to no pain application in the modification phase based on the consideration that also in reality pain is seldomly an all or none phenomenon. Recovery from chronic pain (and reductions of pain-related fear) might be characterized by relapses (e.g. reoccurring pain to a movement which was already painless) so that treatments should be robust against these instances of seldom but sudden re-occurring pain perceptions. Note further, that all CS+ laid above individuals pain thresholds, all CS- laid below individual pain thresholds. The heating (and cooling) time of the thermode was the same for all participants and determined by the smallest technically realizable time, i.e. 600ms for CS-, 2s for CS+ and 2600ms for CS++. Response costs to reduced approach behaviour were introduced in the form of time required to overcome the eight paths. Specifically, dependent on the amount of approach behaviour the completion of the acquisition and modification phase could vary between 4min 48s (4 x 1min 12s when taking only 10m steps) and 48min (4 x 12min when taking only 1m steps) each.

Study procedure

At the beginning of the experiment, participants were informed about the study details and the fact that they could quit their participation at any time without any disadvantages. Written

informed consent was obtained from all participants. Next, participants were asked to complete a demographic questionnaire and the exclusion criteria were checked again. Then, a Peltier thermode (Somedic MSA thermal stimulator; Somedic Sales B, Hörby, Sweden) was fixated on the participants left forearm and individual heat pain threshold and heat pain tolerance were determined following the procedure of Horn (Horn et al. 2018). Note that the maximal applicable temperature was automatically limited by the technical system to 49°C (to prevent potential skin irritations) so that potential pain thresholds/tolerances above 49°C could not be recorded.

Participants entered a light-shadowed room and began with the VR experiment (practice phase). All further details about the experimental procedure were provided to the participants via standardized audio instructions and written projections on the wall screen. The practice phase consisted of one 100m path representing one learning trial, while each of the experimental phases comprised four similar looking trials (4 x 100m). Specifically, the environment of world A was used in the practice phase and in all trials of the acquisition phase, while the environment of world B was used in all trials of the modification phase. In the practice phase, participants were instructed to try out each type of movement (1m, 5m, 10m step) at least once and to train the virtual walking procedure. Participants waited for a short peep tone before they began with the first joystick movement. Also, they were instructed to rest the joystick for at least one second in one of the three defined target positions to induce a VR movement. The three target positions were highlighted with different colours and luminous stickers on the Joystick apparatus. After inducing a step, the joystick was placed back in the original position. Participants were instructed to start with the next movement when the next peep tone occurred after a short delay of six seconds. This delay was implemented to ensure that the thermode could cool down completely after each applied thermal stimulation. Although no thermal stimulation was realized in the practice phase, the general procedure and timing were the same in all conditions (practice phase, acquisition phase, modification phase). After finishing the practice phase, the light was switched on and the thermode as well as the electrodes for electrodermal recordings were placed on the participant's right arm and left hand, respectively. The light was turned off again and the experiment started with the acquisition phase (world A). During both experimental conditions, online rating formats were presented before each of the four trials on the wall screen (for an overview of measurements see Figure 2). These were answered via moving a computer mouse placed on the Joystick apparatus.

After completing all three conditions (one trial in the practice phase, four world A trials in the acquisition phase, four world B trials in the modification phase), additional measures were obtained in paper-pencil format (see below and Figure 2). Also, pain thresholds and tolerances were assessed again to rule out potential effects of habituation or sensitization from the beginning to the end of the experiment. Finally, participants were debriefed about the real study subject (cover story: investigation of pain perception in nature) and reimbursed for their participation. Participants were free to choose which movements they executed to complete the nine VR paths (one path in the practice phase, four paths in the acquisition phase, four paths in the modification phase), and by extension, the duration of the experiment varies as a result. On average the whole testing procedure took 1:45h. Finally, participants wore medical masks during all assessments as data acquisition took place during the COVID-19 pandemic (summer and autumn 2020, Germany).

Pain-associated approach behaviour and ratings

As main outcome measure approximating pain-associated approach behaviour, the total number of 10m steps taken to overcome the 100m distance was assessed for each learning trial (each 100m path). For manipulation check and explorative analyses, also the number of 1m and 5m steps were evaluated.

Participants self-reported prospective fear of movement-related pain and prospective pain expectancy were assessed before each learning trial (4 times in each world, Figure 2). More specifically, participants were asked via standardized audio instructions i) to which extent they experience fear when they think of performing the movements to overcome the next path (fear of movement-related pain, aggregated across all movements of the next trial) and ii) to which extent they expect the movements to overcome the next path to be painful (pain expectancy, aggregated across all movements of the next trial). Both answers were assessed online (in the VR) via moving a computer mouse across a numerical rating scale (NRS) with the anchors 1 = “not at all” to 100 = “very strong”.

Beyond these primary outcome measures, multiple additional measures were obtained to check the experimental manipulation and to explore the new paradigm. These measures were assessed twice, i.e. once after each world and include (Figure 2): i) retrospective pain intensity (NRS, 1 = “not painful” to 100 = “very painful”), ii) retrospective pain unpleasantness (NRS, 1 = “not unpleasant” to 100 = “very unpleasant”, iii) affective valence (Self-Assessment Manikin Scale, SAM, Bradley and Lang 1994, nine item version with anchors “happy” and “unhappy”, high internal consistency: $\alpha = .83-.89$; acceptable retest-reliability $r_{tt} = .55-.78$ in Nabizadeh et al. 2012), iv) arousal (SAM, 9 item version with anchors “excited” and “calm”), perceived control (SAM, nine item version with anchors “controlled” and “in control”), v) positive affect (PANAS, Positive and Negative Affect Schedule, Watson et al. 1988, 10 items rated from 1 = “not at all” to 5 = “very strong”, German adaption: Breyer and Bluemke 2016; high internal consistency: $\alpha \geq .84$ but rather low retest-reliability $r_{tt} \leq .66$), and vi) negative affect (10 items rated from 1 = “not at all” to 5 = “very strong”, PANAS). Finally, the subjective experience of the VR environment was assessed with the IPQ (Igroup Presence Questionnaire, 14 Items, Schubert 2003; high internal consistency: $\alpha = .87$; sufficient retest-reliability $r_{tt} = .74$ in Panahi-Shari 2009) and potential feelings of sickness due to the VR were ruled out with the SSQ (Simulator Sickness Questionnaire; 16 Items, Kennedy et al. 1993; acceptable internal consistency: $\alpha \geq .70$; low retest-reliability $r_{tt} \leq .73$). The latter two measures (assessing VR experience) were assessed only once, after finishing the whole VR experiment (results not reported here). All measures were used in the German-adapted version or translated into German.

Electrodermal recordings and preprocessing

Electrodermal activity was recorded with a sample rate of 1,000 Hz during both experimental conditions with Brain Vision Recorder (Brain Products GmbH, München) and a V-Amp Amplifier (Brain Products GmbH, München, Lidberg and Wallin 1981). Therefore, two passive Ag/AgCl surface electrodes (filed with .05 molar NaCl electrode paste) were placed on the participant’s non-dominant (left) hands thenar and hypothenar. Two measures were calculated for each experimental trial: Skin conductance levels (SCL) as tonic indicator of physiological arousal and skin conductance responses (SCR) following 10m steps as phasic behaviour-related arousal measure, i.e. directly linked to the pain-associated movement (CS++).

Data preprocessing was conducted with Brain Vision Analyser 2.0 (Brain Products GmbH, München). After raw data were band-pass filtered between 1 and 45 Hz, data segments were defined from 1,000 ms before to 8,000 ms after movement induction (i.e. the timepoint when participants arm reached its target position and the VR step was initiated). SCRs were calculated as the difference between minima and maxima occurring between 800 ms – 4000 ms and 2000 – 8000ms, respectively, as responses in skin conductance are assumed to take place within this time frame (Boucsein 2012; Boucsein et al. 2012). Automatically determined extrema were manually controlled (removed or changed if required). Bad segments (i.e. maximum occurred before the minimum) were marked with -1 to exclude such segments from further analyses. Finally, all valid SCRs were averaged across segments. This leaves the three SCR measures (electrodermal responses to 1m, 5m, 10m steps) for each of the eight

experimental learning trials (four 100m paths in world A, four 100m paths in world B, Figure 2). Trial-wise SCLs were calculated as mean electrodermal activity within the time frame of each experimental trial, thus providing eight SCL values per subject.

Statistical analyses

First, multiple descriptive statistics were performed to check whether our experimental manipulation was successful. Mean values (e.g. to check if pain tolerances were lower than pain thresholds) were compared using paired *t*-tests when the Shapiro-Wilk test indicates no significant deviations from normality. Otherwise, the Wilcoxon signed-rank test was used instead. The *t*-tests effect sizes were estimated using Cohen's *d*, while for Wilcoxon signed-rank tests the matched rank biserial correlation *r* was used. To assess the primary outcome measures for our main hypotheses we tested for main effects of the factors learning Trial (1-4) and World (A, acquisition phase vs. B, modification phase) as well as for their interaction via two-factorial repeated-measures analyses of variance (rm-ANOVAs). The Greenhouse-Geisser adjustment was applied when the assumption of sphericity was violated (as indicated by the Mauchly test if $p < .05$). Although the factor World has only two levels (A,B), we followed the recent statistical recommendations and refrained from using a non-parametric alternative or additional data transformations as ANOVA has been demonstrated to be sufficiently robust against potential variations in measurement scales (Schmider et al. 2010; Blanca et al. 2017). Effect sizes for rm-ANOVAs were reported using partial Eta squared η^2_p . For skin conductance responses participants were excluded from statistical analyses when no responses could be recorded in the conditions of interest. This concerned eight participants. Note that in this proof-of-concept study we performed no outlier exclusion as we aimed to explore all possible behavioural response patterns to our new experimental paradigm. These decisions were made a priori. Statistical analyses were conducted in R (version 1.3.1056, www.r-project.org), the R-based software packages JASP (version 0.13.1, www.jasp-stats.org), and the R-based program jamovi (version 1.2; the jamovi project; www.jamovi.org). Statistical significance was accepted at $p < .05$. Note that the global results concerning our five main outcome variables (i.e., rm-ANOVAS of pain-associated approach behaviour, fear of movement-related pain and pain expectancy ratings, SCR, and SCL) are reported a) uncorrected for multiple comparisons for exploratory purposes, and b) corrected for multiple (five) comparisons with Bonferroni (adjusted $p < .01$). Results of post-hoc *t*-tests of main outcome variables were also reported a) uncorrected, and b) corrected for multiple (four) trial-wise comparisons with Bonferroni (adjusted $p < .0125$). Manipulation checks were reported uncorrected only.

Results

Experimental manipulation

Individual baseline pain thresholds varied between 35.4°C and 49° ($M = 42.8$, $SD = 4.2$) and were significantly lower than baseline pain tolerances (38.8°C to 49°C; $M = 47.1$, $SD = 2.6$; $t(41) = -9.909$, $p < .001$, Cohens $d = -1.529$). Pain thresholds assessed post-experimentally varied between 35.3°C and 48.9° ($M = 42.4$, $SD = 4.1$) and were also significantly lower than the respective pain tolerances (40.5°C to 49°C; $M = 47.4$, $SD = 2.4$; $t(41) = -11.156$, $p < .001$, Cohens $d = -1.721$; see also Table 1). Of note, neither pain thresholds nor pain tolerances changed significantly from pre to post experimental assessments (pain threshold: $t(41) = 1.399$, $p = .169$, Cohens $d = .216$; pain tolerance: $W(41) = 129.0$, $p = .796$, $r = -.065$). Together, these results support the validity of the individual pain assessments and speak against obvious effects of sensitization or habituation over the course of the experiment.

Positive and negative affect ratings as assessed with the PANAS are depicted in Table 1. While positive affect was similar after the acquisition phase (world A) and after the modification phase (world B) ($t(41) = 0.921$, $p = .362$, Cohens $d = .142$), negative affect was significantly higher

after the acquisition phase compared to after the modification phase ($W(41) = 252.5, p < .001, r = .830$). Pain intensity and pain unpleasantness ratings also decreased significantly from after the acquisition phase to after the modification phase (PI: $t(41) = 5.088, p < .001$, Cohens $d = .785$; PU: $t(41) = 6.074, p < .001$, Cohens $d = .866$; Table 1). In sum, these findings suggest that positive and negative affect can be modified by a change in movement-pain contingencies (for results of additional variables registered to evaluate the experimental manipulation see Supplement).

Finally, in the acquisition phase skin conductance responses (SCRs) to 1m steps (paired with neutral heat stimuli) were significantly lower than SCRs to 5m steps (paired with medium heat pain stimuli) ($W(41) = 29.0, p < .001, r = -.875$), and SCRs to 10m steps (paired with severe heat pain stimuli) were significantly higher than SCRs to 5m steps (paired with medium heat pain stimuli) ($W(41) = 75.0, p < .001, r = -.834$). These physiological responses support the assumption that different pain-movement associations trigger different levels of arousal dependent on the strength of the pain stimulus.

Main outcome variables

The main aim of the current study was to test whether the developed experimental paradigm can be used to comprehensively investigate the acquisition and modification of pain-related behaviour, as well as pain-related psychological and physiological factors. Specifically, we hypothesized that pain-related behaviour decreases in world A (acquisition phase) where a contingent movement-pain association exists, while it increases when this association is removed (world B, modification phase). We further expected changes in self-rated fear of movement-related pain, in pain expectancy, and in physiological arousal.

Pain-associated approach behaviour

Figure 3 illustrates the changes in pain-associated approach behaviour in response to our experimental manipulation. Pain-associated approach behaviour was operationalized as number of 10m steps as those were paired with the most severe heat pain stimuli (CS++) during the acquisition phase. No significant interaction effect was observed ($F(2.05, 83.92) = 1.54, p = .220, \eta^2p = .036$), but a significant main effects of World ($F(1, 41) = 51.72, p < .001, \eta^2p = .558$) and Trial ($F(2.53, 103.73) = 5.53, p = .003, \eta^2p = .119$). Both effects stay significant also when correcting for the number of main outcome variables (five, see Methods) with Bonferroni (adjusted $p < .01$). Post-hoc t -tests (uncorrected for multiple comparisons) revealed significant differences in all trials between both phases (see Figure 3). As all $p < .01$, these effects also hold when correcting for the number of trial-wise (four, see Methods) comparisons with Bonferroni (adjusted $p < .0125$). Together these results suggest reduced pain-related behaviour in the acquisition phase (movement-pain association) compared to the modification phase (no movement-pain association). Further, when averaging across both phases, pain-related behaviour seems to increase slightly over the course of the experiment. Although the increase of approach behaviour in the modification phase was obviously responsible for this main effect of Trial (see Figure 3), the pattern of changes (as indexed by the interaction) did not differ significantly between both phases. For completeness, results for 5m and 1m steps are illustrated in supplementary Table S1 and Figure S1.

Fear of movement-related pain and pain expectancy

Figure 4 depicts the results for the prospective fear of movement-related pain and pain expectancy self-ratings. Concerning fear of movement-related pain, we observed a significant Trial x World interaction ($F(2.01, 82.47) = 14.164, p < .001, \eta^2p = .257$), while no main effects were observed (factor World ($F(1, 41) = 1.220, p = .276, \eta^2p = .029$; factor Trial ($F(1.53, 62.54) = .635, p = .492, \eta^2p = .015$). This effect stays significant when correcting for the number of

main outcome variables (five) with Bonferroni (adjusted $p < .01$). Post-hoc t -tests (uncorrected for multiple comparisons) revealed the existence of two significant trial-specific differences: 1) fear of movement-related pain was lower before trial 1 of the acquisition phase than before trial 1 of the modification phase and 2) fear of movement-related pain was higher before trial 3 of the acquisition phase than before trial 3 of the modification phase (see Figure 4a). As all $p < .01$, these effects also hold when correcting for the number of trial-wise (four) comparisons with Bonferroni (adjusted $p < .0125$). These results suggest that the experimentally-induced change in the movement-pain contingency between acquisition and modification phase led to significant alterations in prospective ratings of fear of movement-related pain.

Concerning pain expectancy, Figure 4b illustrates a significant Trial x World interaction ($F(1.77, 72.38) = 29.00$, $p < .001$, $\eta^2p = .414$) as well as a significant main effect of World ($F(1, 41) = 11.35$, $p = .002$, $\eta^2p = .217$). No main effect was observed for the factor Trial ($F(1.76, 72.17) = 2.49$, $p = .097$, $\eta^2p = .057$). The interaction effect remains significant when Bonferroni corrected for the number of main outcome variables (five) (adjusted $p < .01$). Post-hoc t -tests (uncorrected for multiple comparisons) reveal the existence of significant differences for all trial-wise comparisons. While self-rated pain expectancy was lower before trial 1 of the acquisition phase than before trial 1 of the modification phase, pain expectancy was higher before trial 2, 3, and 4 of the acquisition phase than before trial 2, 3, and 4 of the modification phase, respectively (see Figure 4b). Also these effects hold when correcting for the number of trial-wise comparisons (four) with Bonferroni (adjusted $p < .0125$). These results suggest that the change in contingency between both experimental phases led to significant changes in prospective pain expectancy ratings.

Electrodermal activity

Physiological arousal was assessed via skin conductance levels (SCLs, tonic response over the course of each learning trial, Figure 5a) and skin conductance responses to 10m steps (SCRs, phasic response, Figure 5b). Concerning SCL, a significant World x Trial interaction was observed ($F(1.37, 56.06) = 7.41$, $p = .004$, $\eta^2p = .153$), while no main effects were present for the factors World ($F(1, 41) = 1.94$, $p = .171$, $\eta^2p = .045$) and Trial ($F(1.79, 73.53) = 1.26$, $p = .288$, $\eta^2p = .030$). This interaction stays significant also when correcting for the number of main outcome variables (five) with Bonferroni (adjusted $p < .01$). Figure 5a suggests that physiological arousal increased during the acquisition phase followed by a reduction during the modification phase, however, post-hoc t -tests (uncorrected for multiple comparisons) revealed the absence of any significant difference for all trial-wise comparisons between two phases. Nevertheless, the significant interaction effect suggests that the change in contingency between both experimental phases causes differences in physiological arousal reflected in SCL.

Movement-specific (phasic) changes in physiological arousal were approximated via skin conductance responses to 10m steps. We observed no World x Trial interaction ($F(1.67, 55.04) = 0.500$, $p = .683$, $\eta^2p = .057$) but a significant main effect of World ($F(1, 33) = 5.248$, $p = .028$, $\eta^2p = .137$). No main effect of the factor Trial was found ($F(1.93, 63.78) = 1.419$, $p = .242$, $\eta^2p = .041$). The main effect of World stays significant when correcting for the number of main outcome variables (five) with Bonferroni (adjusted $p < .01$). Post-hoc t -tests (uncorrected for multiple comparisons) revealed the existence of one significant difference for trial-wise comparisons that survives also the Bonferroni correction for the number of trial-wise comparisons (adjusted $p < .0125$). Specifically, skin conductance response to 10m steps in trial 1 of the acquisition phase was significantly higher than in trial 1 of the modification phase (see Figure 5b). Please note that this result pattern resembles the pattern observed for pain-related behaviour. For completeness, results for SCR to 5m and 1m steps are illustrated in Supplementary Table S1 and Figure S2.

Post-hoc control analyses

Temporally-resolved approach behaviour to pain

The results concerning pain-related behaviour (see above) revealed a significant main effect of World. This effect may be driven a) by the existence of per-se difference in the amount of approach behaviour between both phases, or b) by very fast adaptations of approach behaviour within the first trial. To explore both possibilities, we temporally resolved the changes in pain-associated approach behaviour. Specifically, we subdivided the first virtual 100m path (learning trial) into four 25m paths (learning subtrials) and analysed the relative amount of 10m steps taken within each of these 25m subtrials (see Supplementary Figure S3a). Note that we divided the 100m path into four subtrials as more subdivisions provided a less accurate estimate due to higher numbers of overlapping steps, i.e., steps started in one subtrial but finished in another.

The two-factorial rm-ANOVA revealed a significant interaction between the factor World and the factor Subtrial ($F(3,123) = 6.371, p < .001, \eta^2p = .134$) and a significant main effect of the factor World ($F(1,41) = 42.222, p < .001, \eta^2p = .505$), while no main effect was found for the factor Subtrial ($F(2.46,114.39) = .376, p = .731, \eta^2p = .009$). Both effects stay significant also when correcting for the number of main outcome variables (five) with Bonferroni (adjusted $p < .01$). These results reveal that in addition to the average amount of pain-associated approach behaviour (main analysis, see above) also the pattern of changes varied between both experimental phases. In sum, these findings suggest that pain-associated approach behaviour was reduced and enhanced very fast during both the acquisition and modification phase (option 2).

For additional exploratory insights, also the pain-related behaviour of the other three paths was temporally resolved. The patterns over the respective 16 subtrials are illustrated in Supplementary Figure S3b. A two-factorial rm-ANOVA revealed a significant interaction effect between the factor World and the factor Subtrial ($F(8.48,347.69) = 2.72, p = .005, \eta^2p = .062$), a significant main effect of the factor World ($F(1,41) = 50.59, p < .001, \eta^2p = .552$), and a significant main effect of the factor Subtrial ($F(8.33,341.45) = 2.61, p = .008, \eta^2p = .060$). All effects stay significant when correcting for the number of main outcome variables (five) with Bonferroni (adjusted $p < .01$). Therefore, also these results point towards option b. Approach behaviour is quickly reduced when a contingent movement-pain association exists, while it also quickly increases when this contingency is removed.

Skin conductance response: fear vs. physiological reaction to pain

A further and purely exploratory post-hoc analysis was conducted to evaluate the possibility that significant differences between both phases in SCR (see above and Figure 5a) may merely reflect differences in the physiological reaction to pain instead of fear of movement-related pain. This would imply that respective changes in SCR could only be a reflection of the different amounts of painful stimuli applied in both worlds (all 10m steps were paired with CS++ in world A, contingent association while only some 10m steps were paired with CS++ in world B, random association). Therefore, we extracted the SCRs from only those 10m steps in world B that were followed by neural heat stimuli (CS-). Those might reflect the “pure” fear component free of any potential physiological reaction to heat pain. The observed pattern is illustrated in Supplementary Figure S4. It suggests that the SCR observed during our paradigm reflects physiological arousal different from the physiological reaction to the pain itself (e.g. reflecting fear of movement-related pain and pain expectancy).

Discussion

Based on empirical background suggesting critical relevance of approach-avoidance behaviour for the development and maintenance of chronic pain, we propose a new Virtual Reality paradigm to investigate the involved learning mechanisms within a controlled laboratory

setting. We experimentally manipulated the contingency between three types of arm movements and three types of pain stimuli in a sample of $N = 42$ healthy adults. We observed a fast reduction in pain-associated approach behaviour when a contingent movement-pain association existed, while on average approach increased immediately when this contingency was removed. Respective contingency changes manifested also in anticipatory self-ratings capturing fear of movement-related pain and pain expectancy, as well as in physiological arousal (i.e. skin conductance). Manipulation checks further indicate the absence of a) effects of habituation or sensitization over the course of the experiment, b) effects of movement-pain contingency manipulations on negative affect, pain intensity, and pain unpleasantness, and c) effects of the different types of movements as implemented in our paradigm on skin conductance.

The Fear Avoidance Model of chronic pain proposes that psychological factors are critical in the development and maintenance of chronic musculoskeletal pain. More specifically, it describes how an acute or potential harm can create a self-reinforcing vicious circle between fear of movement-related pain and pain-related avoidance behaviours (Lethem et al. 1983; Vlaeyen and Linton, 2012; Vlaeyen et al. 2016;). In the following, a large number of research endeavours addressed associative learning mechanisms involved in the acquisition of fear of movement-related pain. Clever experimental paradigms like the voluntary joystick movement paradigm were developed and adapted extensively (Meulders et al. 2011). Typically, in such paradigms, a specific movement (e.g. hand movement to the right) represents the conditioned stimulus (CS+) that was former neutral but obtains after multiple pairings with an unconditioned stimulus (US, pain) the potential to elicit the conditioned reaction. Research based on these paradigms suggests that the acquisition of fear of movement-related pain can be explained by mechanisms of classical conditioning. This applies also to phenomena of (over-)generalization (Meulders and Vlaeyen, 2013; Meulders et al. 2013) extinction, and return of the fear of movement-related pain (Volders et al. 2012, 2015).

In contrast, reduced approach behaviour and extensive avoidance might be better described by operant learning mechanisms (i.e. instrumental learning; the learning about the avoidance behaviours' consequences; Skinner, 1953). More specifically, the Fear Avoidance Model assumes that successful avoidance is reinforced by the non-occurrence of the feared pain and the prevented catastrophe of acute harm (Vlaeyen and Linton 2012; Vlaeyen et al. 2016). Such operant mechanisms are especially important when trying to understand the persistence of chronic pain (Meulders, 2019). First experimental paradigms were developed to address these mechanisms in the context of movement-related pain (e.g. robotic arm paradigm; Meulders et al. 2016). Our proposed VR paradigm builds directly on this research. Specifically, it combines *learning* of associations between a certain arm movement and a certain pain stimulus with *operant learning* of avoidance behaviour. In our paradigm, participants were neither instructed to approach or avoid nor informed about the contingency, but had to explore and detect the contingency without guidance, most likely via mechanisms of classical conditioning. Specifically, 10m virtual steps performed via hand movements to reach a virtual goal at the end of a virtual path were coupled with heat pain stimuli to induce pain-associated approach behaviour. Furthermore, we implemented costs as the avoidance of such pain-associated behaviour (10 m steps) caused participants to perform more steps (1 or 5 m steps) and thus took longer to reach the goal.

As summarised above, we observed specific effects related to the experimental manipulation of the movement-pain (CS-US) contingency in line with our hypotheses. Changes in the behaviour-pain contingency induced changes in pain-associated approach behaviour, fear of movement-related pain and pain expectancy, as well as in physiological arousal.

The following unexpected observations and shortcomings of the study have to be discussed. First, the change in contingency affected behaviour faster than self-ratings. However, please note that self-ratings were assessed for the three types of movements separately. While

we discarded more detailed ratings as we anticipated a disruption of VR presence, future studies should consider movement specific assessment of fear of movement and pain expectancy. A second observation for which we have currently no explanation is the absence of significant differences in arousal and perceived control between both experimental phases. This is counterintuitive, as participants lost control over which pain stimulus they received in the modification phase (pseudo-random reinforcement). This observation requires further investigation. Third, the generalizability of our proof-of-concept study is also limited due to our strict inclusion criteria. Thus, it is important that future research use larger and more representative samples to obtain more comprehensive insights about the robustness of the unexpected and unexpected findings.

In the following section we outline methodological aspects that require further consideration and suggest promising future adaptations of our paradigm. At first, the self-ratings created to capture fear of movement-related pain were generally low, likely because our participants referenced the German word “Angst” to a very strong inner feeling of threat (e.g. to have an accident). Although, there was still enough variance to observe the respective effects, the framing of the question should be adapted in future studies. Second, all results concerning SCR should be interpreted with caution and as hypotheses-generating as we implemented a rather conservative censoring to the SCR by excluding (instead of replacing) all trials with missing values. This led to an exclusion of up to eight participants in the SCR analysis. Future studies might therefore explore whether different censoring methods come to similar effects.

Third, to optimally investigate how a change in CS-US contingencies manifests in multiple measures, all other factors but the contingency should be held constant. This is, however, not easy to realize in our paradigm. Specifically, although stimuli were presented in a pseudorandomized fixed order, the number of received CS++, CS+, and CS- in world B (modification phase) differed between participants depending on their behaviour. Further, the fixed and for all participants same reinforcement plan induced the possibility that the changes in the contingency were less noticeable for some participants (i.e. those who selected few 10m steps in world A) than for others (i.e. those who selected only 10m steps in world A). The implementation of a yoked control group via a matched-pairs design (for a good example see Glogan et al. 2020) seems promising to address this issue. In respect to our paradigm, this would mean that each participant of one group (contingent movement-pain association) would be paired with a participant of another group (no movement-pain association) and that both receive the same relative amount of heat pain stimulation but with different contingencies. Such a design is, however, complicated to realize as the total number of applied stimuli depends on the participant’s actual behaviour (see above). This behaviour is unknown in the beginning and prevents us from adapting the ratio of the three stimuli in advance. To fix the numbers of movements via overt instructions might solve this issue, however, this would preclude the opportunity to study associative learning mechanisms (Meulders 2019).

Fourth, the use of Virtual Reality requires further consideration. For treatment purposes Virtual Reality has been successfully applied to different chronic pain conditions (e.g. headache, Shiri et al. 2013; fibromyalgia, Morris et al. 2015; for review see Keefe et al. 2012). However, observed reductions in pain intensity were ascribed primarily to one of three mechanisms: distraction, neuromodulation, or graded exposure (Tack, 2019). Whether effects persist beyond the momentary use of the application remained unclear (Gupta et al. 2018; Matheve et al., 2020). In contrast to this line of research that primarily focused on pain intensity, a recent meta-analysis suggests that Virtual Reality paradigms are also able to reduce fear of movements, and disability (e.g. Ahern et al. 2020). In respect to pain-associated approach-avoidance behaviour, Virtual Reality would, for instance, allow researchers to give participants targeted feedback about their own movements. This raises the possibility to modify this feedback in a way that leads to gradual normalization of pathologically restricted movement ranges (Chen et al. 2016). The transfer of our paradigm to groups of chronic pain patients may

represent the next step to gain at first more insights into how associative and operant learning mechanisms differ between chronic pain patients and healthy controls, to then adapt it to treatment purposes. Another important point is that 2D Virtual Reality applications as used in our study (projections on a 2D wall screen) were suggested to induce lower immersion than 3D techniques (mostly implemented with head mounted displays, HDMs, Rose et al. 2018). Thus, especially when it comes to the development of treatments, the use of HDMs might present a further improvement to this paradigm.

A fifth and last promising line of further development of the paradigm is the inclusion of additional trait measures to investigate how individual differences in trait constructs relate to individual differences in the respective associative and operant learning mechanisms. Candidate constructs include trait fear of pain, pain catastrophizing, kinesiophobia, trait anxiety, anxiety sensitivity, and depression all of which can be assessed using standardized questionnaires like the Fear of Pain Questionnaire (FPQ, McNeil and Reinwater, 1998), the Pain Catastrophizing questionnaire (PCS, Sullivan et al. 1995), the Tampa Scale of Kinesiophobia (TSK, Kori 1990), the State Trait-Anxiety-Depression-Inventory (STADI, Laux et al. 2013), the Anxiety Sensitivity Index (ASI, Reiss 1991), and the Beck Depression Inventory (BDI-II, Beck et al. 1996). Although the focus of this proof-of-concept study was the evaluation of our paradigm's potential for further research, and we therefore limited our analyses to group-average effects, a more comprehensive investigation of individual differences in respective mechanisms might be valuable, for instance, to identify individual vulnerability factors (Hilger and Hewig, 2022).

Conclusion

Our study proposes an experimental Virtual Reality paradigm that allows researchers to investigate pain-associated approach behaviour and related psychological and physiological mechanisms in a controlled laboratory setting. We manipulated the contingency between three types of movements and three types of heat pain stimuli in a group of healthy participants and observed that changes in movement-pain contingencies resulted in changes in pain-associated approach behaviour, self-rated fear of movement-related pain and pain expectancy, as well as in alterations of physiological arousal (electrodermal activity). Although the observed effects require replication in a larger and more representative sample, our results provide insights into the fast adaption of approach behaviour in the presence of acute pain. Our new paradigm can be adapted in various ways to gain new insights into the development and maintenance of chronic pain.

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Conflicts of interest

PP is co-founder and shareholder of VTplus GmbH, a company selling VR equipment for research and therapy. The other authors declare no conflicts of interest.

Author's contributions

K.H. and P.P. conceived of the study. K.H. developed and implemented the experimental paradigm. M.J. programmed the experiment in Virtual Reality and provided technical help. K.H., A.S.H., and C.Z. managed the participants, ran the experiment, collected the data, prepared the data and conducted statistical analyses. K.H. wrote the first draft of the manuscript. All authors were involved in results interpretation and provided feedback during manuscript preparation.

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Table 1. Descriptive statistics of manipulation check variables, explorative and primary outcome measures.

	<i>M (SD)</i>	<i>Min</i>	<i>Max</i>	<i>M (SD)</i>	<i>Min</i>	<i>Max</i>
<i>Manipulation checks and exploratively assessed variables</i>						
	Before experiment			After experiment		
Pain threshold	42.8 (4.2)	35.4	49	42.4 (4.1)	35.3	48.9
Pain tolerance	47.1 (2.6)	38.8	49	47.4 (2.4)	40.5	49
	After acquisition phase (World A)			After modification phase (World B)		
Positive affect (PANAS)	28.8 (6.3)	17	44	28.3 (8.0)	14	42
Negative affect (PANAS)	13.1 (3.6)	10	23	11.7 (2.1)	10	19
Pain intensity	49.4 (27.8)	0	89	31.3 (20.4)	0	66
Pain unpleasantness	56.5 (28.8)	0	100	36.1 (22.9)	0	17
Happiness/unhappiness	5.7 (1.4)	3	9	6.3 (1.8)	2.3	10
Arousal	3.7 (2.1)	1	8	3.3 (2.5)	0	8.6
Control	7.2 (1.8)	1	9	6.1 (3.1)	1.2	10
<i>Primary outcome measures</i>						
	During acquisition phase (World A)			During modification phase (World B)		
Number of 10m steps	23.8 (11.2)	2	40	34.9 (5.0)	23	40
Fear of movement-related pain	4.3 (4.7)	0	20.5	3.9 (4.6)	0	19.8
Pain expectancy	16.5 (10.1)	1	35.5	13.8 (9.0)	0	40.0
SCL	12.1 (4.9)	3.4	25.9	12.6 (4.8)	3.8	25.4
SCR to 10m Steps	1.2 (0.8)	0.1	4.6	1.0 (0.6)	0.2	3.7

Pain threshold and pain tolerances are depicted in °C. The maximal applicable temperature was 49°C (technically determined to prevent skin irritations) so that potential pain thresholds/tolerances above 49°C could not be recorded. Positive and negative affect were rated with 10 items from 1 = “not at all” to 5 = “very strong” so that obtained sum values could vary between 10 and 50. Pain intensity and pain unpleasantness were rated on a NRS from 1-100, while happiness/unhappiness, arousal, and control were assessed with the Self-Assessment Manikin Scale (SAM, Bradley and Lang 1994; 9 item version with anchors “happy” and “unhappy”). Note that the 9 visual categories were translated into values ranging from 0-10 for

statistical analyses. Fear of movement-related pain and pain expectancy were rated on a NRS from 1-100. Skin conductance responses (SCR) and skin conductance levels (SCL) are depicted in μS (micro Siemens). Primary outcome measures were averaged across trials. Trial-specific primary outcome measures are depicted in Figure 3-5. For additional exploratory assessed variables (number of 1m and 5m steps, SCR to 1m and 5m steps) see Supplementary Table S1. PANAS, Positive and Negative Affect Schedule (Watson et al. 1988; Breyer et al. 2016).

Figures

Figure 1. Schematic illustration of the experimental paradigm. In addition to the visual details of both worlds (right), acquisition (world A) and modification phase (world B) differed also in their reinforcement plans (left). While there existed a contingent association between certain movements and certain pain stimuli in world A (acquisition phase), no such association was present in world B (modification phase). Specifically, in world A 1m steps induced a neutral heat stimulus (CS-), 5m steps a medium heat pain stimulus (individual heat pain tolerance minus 3°C, CS+), and 10m steps were reinforced with a severe heat pain stimulus (individual heat pain tolerance, CS++). In world B, all movements were reinforced according to a fixed and a priori defined reinforcement plan, which was the same for all participants and ensured via pseudo-randomization that 50% of the applied stimuli were neutral stimuli, 40% were medium heat pain stimuli, and 10% were severe heat pain stimuli (see Methods). All movements were induced via moving a large joystick apparatus with the right arm that was also subject of the heat pain application, while electrodermal recordings were assessed from the left inner hand.

Figure 2. Flowchart of assessed measurements. Heat pain thresholds and heat pain tolerance were assessed in the beginning and at the end of the experiment. Prospective fear of movement-related pain (FoP) and pain expectancy (PE) ratings were obtained before each trial via numerical rating scales (see Methods). Additional measures were retrospectively assessed twice, i.e. once after each world: i) retrospective pain intensity (NRS, 1 = “not painful” to 100 = “very painful”), ii) retrospective pain unpleasantness (NRS, 1 = “not unpleasant” to 100 = “very unpleasant”), iii) affective valence (Self-Assessment Manikin Scale, SAM, Bradley and Lang, 1994, nine item version with anchors “happy” and “unhappy”), iv) arousal (SAM, 9 item version with anchors “excited” and “calm”), perceived control (SAM, nine item version with anchors “controlled” and “in control”), v) positive affect (PANAS, Positive and Negative Affect Schedule, Watson et al. 1988, 10 items rated from 1 = “not at all” to 5 = “very strong”), and vi) negative affect (10 items rated from 1 = “not at all” to 5 = “very strong”, PANAS). Finally, subjective experiences of the VR environment (VR ratings) were assessed with the IPQ (Igroup Presence Questionnaire, 14 Items, Schubert and Bluemke, 2016) and potential feelings of sickness due to the VR were ruled out with the SSQ (Simulator Sickness Questionnaire; 16 Items, Kennedy et al. 1993). Skin conductance levels (SCL) and skin conductance responses (SCR) were assessed during both experimental phases.

Figure 3. Pain-associated approach behaviour (total number of 10m steps) over the four learning trials in the acquisition phase (world A, contingent movement-pain association) and in the modification phases (world B, no movement-pain association). The graphs illustrate the two-factorial repeated-measures ANOVAs conducted as main analyses with factors learning trial and phase (acquisition vs. modification) (see Results section for further details). Error bars indicate 95% confidence intervals. $**p < .01$ indicating statistical significance of post-hoc paired t -tests (uncorrected for multiple comparisons), i.e. directly comparing two learning trials between both phases (acquisition vs. modification phase).

Figure 4. Fear of movement-related pain (a) and pain expectancy (b) ratings over the four learning trials in the acquisition phase (world A, contingent movement-pain association) and in the modification phases (world B, no movement-pain association). The graphs illustrate the two-factorial repeated-measures ANOVAs conducted as main analyses with the factors learning trial and phase (acquisition vs. modification) (see Results section for further details). Error bars indicate 95% confidence intervals. Ratings were assessed on a numerical rating scale (NRS) ranging from 1-100. $**p < .01$ indicating statistical significance of post-hoc paired t -tests (uncorrected for multiple comparisons), i.e. directly comparing two learning trials between both phases (acquisition vs. modification phase).

Figure 5. Skin conductance levels (a) and skin conductance responses (b) over the four learning trials in the acquisition phase (world A, movement-pain association) and in the modification phases (world B, no movement-pain association). The graphs illustrate the two-factorial repeated-measures ANOVAs conducted as main analyses with factors learning trial and phase (acquisition vs. modification) (see Results section for further details). Skin conductance levels (SCL) and skin conductance responses (SCR) are depicted in μS (micro Siemens). Error bars indicate 95% confidence intervals. $**p < .01$ indicating statistical significance of post-hoc paired t -tests (uncorrected for multiple comparisons), i.e. directly comparing two learning trials between both phases (acquisition vs. modification phase).