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Changes in pain-related fear and pain when avoidance behaviour is no longer effective

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Highlights Journal of Pain – JPAIN-D-19-01105 – Changes in pain-related fear and pain when avoidance behaviour is no longer effective

- Ineffective avoidance behaviour increases pain-related fear
- Ineffective avoidance behaviour decreases pain threshold and tolerance
- Avoidance behaviour continues despite being no longer effective

Abstract

Avoidance is considered key in the development of chronic pain. However, little is known about how avoidance behaviour subsequently affects pain-related fear and pain. We investigated this using a robotic arm reaching avoidance task to investigate this. In a between-subjects design both Experimental Group (n=30) and Yoked Control Group (n=30) participants perform either of three movement trajectories (T1-T3) to reach a target location. During acquisition, only participants of the Experimental Group could partially or fully avoid a painful electrocutaneous stimulus by choosing the intermediate trajectory (T2; 50% reinforcement) or the longest trajectory (T3; 0% reinforcement) versus the shortest trajectory (T1: 100% reinforcement). After acquisition, contingencies changed (all trajectories 50% reinforced), and the acquired avoidance behaviour no longer effectively prevented pain from occurring. The Yoked Control Group received the same reinforcement schedule as the Experimental Group irrespective of their behaviour. When avoidance behaviour became ineffective for the Experimental Group, pain-related fear increased for the previously safe(r) trajectories (T2 and T3) and remained the same for T1, whereas pain threshold and tolerance declined. For the Yoked Group, pain-related fear increased for all trajectories. The Experimental Group persisted in emitting avoidance behaviour following the contingency change, albeit at a lower frequency than during acquisition.

Perspective: Results indicate participants become more afraid of and sensitive to pain, when previously acquired avoidance is no longer effective. Also, participants continue to show avoidance behaviour despite it being not adaptive anymore. These findings suggest that ineffective avoidance may play role in the maintenance and development of chronic pain.

Key words: avoidance behaviour; ineffective avoidance behaviour; pain-related fear; pain; pain sensitization

1. Introduction

When one is confronted with acute pain, trying to avoid subsequent exposure to the presumed nociceptive stimulus is an adaptive strategy potentially preventing (further) injury. The fear-avoidance model describes how chronic pain may develop after an acute pain episode. If an individual appraises the pain experience as threatening, defensive behaviours might spiral into a vicious and self-perpetuating cycle that promotes avoidance behavior, leading to disability, negative affect and pain[28,29]. However, in chronic pain where there is often no objectifiable injury, avoidance becomes maladaptive, and disconnected from its initial function. In addition, avoidance prevents the individual to learn that pain is not a signal of actual bodily harm anymore[30]. Avoidance can be acquired through instrumental conditioning, in which the response prevents an aversive outcome from occurring[20]. Commonly, avoidance is viewed unidirectionally, as instigated by fear, and to result in fear reduction[16,19]. However, van Vliet and colleagues[24] proposed that engaging in pain-avoidance may increase, rather than decrease pain-related fear when the avoidance response is no longer available, suggesting a bidirectional relationship between fear and avoidance. Other studies suggest that engaging in avoidance behaviour may bear threat-inducing properties[9,10]. However, experimental research on the consequences of avoidance behaviour in (chronic) pain is scarce.

Persistent avoidance is a key factor of chronic pain and is often resistant to extinction[21]. When an individual experiences pain when performing a certain movement, they may learn to associate this movement with potential harm and therefore avoid this and similar movements in the future[23]. Due to persistent avoidance, there are fewer opportunities to disconfirm existing expectancies and beliefs about the initial pain-associated movement[7], which can lead to initiating a pathway to functional disability in individuals with chronic pain[28,29].

In chronic pain, pain-avoidance is often ineffective[22]. For example, resting at home, rather than going out with family, may be an attempt to reduce pain. In reality, such avoidance behaviour can be ineffective as it will not necessarily result in pain reduction. Little is known about the consequences of ineffective avoidance attempts on the pain experience itself. Studies suggest that successfully controlling pain through avoidance would reduce pain, whereas failure to control pain would increase pain even more than never having been able to control the pain[6,12].

Here, we aim to investigate (1) the effects of ineffective avoidance of a painful stimulus on subsequent pain-related fear and pain, and (2) whether avoidance behaviour persists despite its ineffectiveness. We operationalize ineffective avoidance as rescheduling the instrumental contingencies such that the emitted avoidance behaviour no longer results in the "no-pain outcome". In other words, the aversive event occurred regardless of responding, which is one form of operant extinction of avoidance[8]. Experimental Group participants acquire avoidance behaviour during a robotic arm reaching avoidance task[18], in which participants can choose to perform movements that are either followed by a painful stimulus in 100% of the trials (T1), in 50% of the trials (T2) or never followed by a painful stimulus (T3). In a subsequent phase, Experimental Group participants can no longer effectively avoid the painful stimulus, because now each movement (T1-T3) was followed by a painful stimulus 50% of the trials. Yoked Control Group participants never have the opportunity to effectively avoid the painful stimulus.

Our first hypothesis is that pain-related fear increases when previously effective avoidance behaviour becomes ineffective. Second, we hypothesize that Experimental Group participants, who have acquired effective avoidance behaviour during the acquisition phase will emit more avoidance behaviour during the ineffective avoidance compared to the Yoked Control Group. Third, we investigate the relation between avoidance and pain measures. We

explore whether pain threshold and tolerance decline when previously acquired avoidance becomes ineffective.

2. Methods

2.1. Participants

A total of 60 healthy, pain-free volunteers participated in this study (33 females; mean (range) ± SD age = 25.45 (18-56) ± 6.81 years). Participants were recruited at KU Leuven, using social media and distribution of flyers around the campus. Psychology students received a course credit for participation; other participants received a monetary compensation of €6. Participants were excluded if they reported to suffer from any cardiovascular disease, chronic pain conditions, pain at the dominant forearm, impaired, uncorrected vision, medical advice to avoid stressful situations, psychiatric disorders (current or in the past), neurological conditions or were pregnant. Participants were assigned to the Experimental Group (n=30, 15 females) or the Yoked Group (n=30, 18 females) via block randomisation, with restriction that the first two participants in the block were always assigned to the Experimental Group.

2.2. Apparatus and stimulus material

2.2.1. HapticMaster

The HapticMaster (HM) is a 3-degrees of freedom, force-controlled robotic arm (Moog Inc. FCS Robotics, East Aurora, New York, USA) and allows for a wide range of movement. Due to the force controlled haptic interface, weight and force can be simulated, mimicking real-life movements. In the current study, movements were restricted to the horizontal plane with depth of 0.35m and a 1m radius. The position of the HM was consistently logged so it could be used as input for the painful stimulus presentation.

2.2.2. Stimulus material

An electrocutaneous stimulus of 2 milliseconds duration served as the painful stimulus. The stimulus was delivered by a commercial stimulator (DS7A, Digitimer, Welwyn Garden City, England), using bar electrodes filled with K-Y gel that were attached to the triceps tendon of the right arm; the same arm was used to perform the reaching task with the robotic arm. Note that a calibration procedure was carried out to determine individual pain threshold and a stimulation that is painful and takes effort to tolerate (from now on referred to as the pain tolerance level) for each participant (see calibration phase). The pain tolerance level during the initial calibration phase was used as the painful stimulus throughout the experiment.

2.2.3. Software

The experiment was run on a Windows 7 Professional (Microsoft Corporation Redmond, WA, USA) 64 bit Dell Latitude 6420 computer (Dell Inc., Round Rock, TX, USA) with 4 GB RAM, CPU: I5-2520M at 2.5GHz and programmed in C/C++. All data recording and processing was performed using a commercial software package (MATLAB version, The MathWorks Inc. Natick, MA, USA, 2000).

2.3. Study protocol

The experiment was conducted during a single 45-min session and consisted of the following phases: preparation, calibration, practice, acquisition, recalibration-I, ineffective avoidance, and recalibration-II. We included the recalibration phases throughout the experiment to explore whether pain threshold and pain tolerance change when previously acquired avoidance becomes ineffective. We used a between-subjects design including an Experimental Group that received the predefined movement trajectories-pain contingencies, and a Yoked Control Group that received the same reinforcement schedule as the Experimental Group irrespective of the chosen movement trajectories. After the experiment, participants completed the fear of pain questionnaire (FPQ-III-NL)[25].

2.3.1. Robotic arm reaching task

Participants executed reaching movements with their right arm using the HM. The reaching task consisted of moving a "green ball" from the starting point to the target location (see Figure 1 for a schematic representation). The task was framed as a movement task, and not as a game in the sense that no reward was provided. Participants could choose one of the three movement trajectories (T1-T3), indicated by separate arches positioned in the middle of the movement plane, to reach the target location. During the task, a painful stimulus was delivered based on the trajectory that was chosen when the "green ball" had just passed through the trajectory arch. The HM is programmed such that there is a linear relationship between the resistive force and the lateral displacement of the robotic arm. When the target location is reached via trajectory T1, which has the least lateral displacement, no force is exerted. When the target location is reached via trajectories T2 and T3, respectively moderate and strong resistance is applied by the HM. In order to standardise the effort needed to perform the movements in the different trajectories, we corrected for participants' maximal arm extensor force with the HM, measured with a hand grip manometer (HHD microFET2; Hoggan Health Industries Inc, Jordan, UT). The strong resistance matched ± 50% of their maximal arm extensor force, while the moderate resistance matched ± 25% of their maximal extensor force.

- Insert FIGURE 1 about here –

Preparation phase. Upon arrival in the lab, participants received oral and written information about the experiment. Participants were informed that they would be exposed to painful electrocutaneous stimuli, but that the stimulus intensity would be individually determined during the calibration phase. All participants provided a written informed consent,

which emphasized that they were allowed to decline participation at any time during the experiment without any consequences. The Social and Societal Ethics Committee of KU Leuven approved the experimental protocol (reg. #: G-2017 01 745).

Calibration phase. Participants were seated in an armchair placed in a sound- and light-attenuated experimental room. After the stimulation electrodes had been attached, the calibration procedure of the electrocutaneous stimulus was initiated. The calibration procedure involved the presentation of a series of stimuli of increasing intensity while participants were asked to indicate the pain intensity of each stimulus on an 11-point Likert scale ranging from 0 to 10 (0 = 'you feel nothing', 1 = 'you feel something but this is not painful, it is merely a sensation', 2 = 'this sensation is unpleasant but not painful', up to 10 = 'the worst tolerable pain'). Two subjective stimuli were targeted: the pain threshold corresponding with 3 (3 = 'the moment that the electrocutaneous stimulus becomes painful') and the pain tolerance corresponding with 8 (8 = 'significantly painful and demanding effort to tolerate'). This stimulus intensity (pain tolerance) was used as the painful stimulus throughout the experiment. Note that all participants were informed that they were free to notify the experimenter at any time if they did not want to receive the stimulus anymore or if they wanted the amplitude to be set back to a lower intensity during the calibration procedure.

Practice phase. During this phase the experimenter instructed the participant to perform each trajectory four times using the robot arm (12 trials in total). Participants were instructed to start one of the three movements as soon as they heard an auditory start signal and saw a visual start signal (=on-screen presentation of a manikin with flag). The end of a trial was indicated by an auditory stop signal together with a visual stop signal (= on-screen presentation of a red stop sign), the latter remained on the screen when the HM repositioned to the starting location and prompted the participant to let go of the HM. After returning to its initial position, the robotic arm remained fixed until the start of the next trial (intertrial

interval = 3 seconds). Participants were also trained to provide verbal ratings using a Windows 7 compatible triple foot switch (USB-3FS-2; Scythe, Tokyo, Japan). During this phase, no painful stimuli were administered, but the resistive force of the HM as described above was applied.

Acquisition phase. Instructions reminded participants to move the HM freely over one of the available trajectories when prompted by the starting signal. Two blocks of 24 movements (ACQ1-2; 48 movements in total) were run. In each phase, a counter on the screen indicated the number of successful movements/trials the participants had completed (i.e. a counter increasing with one unit after each successful movement, starting at 0). During this phase the Experimental Group participants always received a painful stimulus during the shortest trajectory (T1), while for the intermediate trajectory (T2), they only received a painful stimulus in 50% of these movements, and for the longest trajectory (T3) they could avoid the pain stimulus from occurring (i.e. effective avoidance). Participants in the Yoked Control Group were matched with participants in the Experimental Group. When a certain participant in the Experimental Group received a painful stimulation on a given trial, a participant in the Yoked Control Group received a painful stimulation on the same trial, irrespective of which trajectory was chosen. This created an arrangement in which only the Experimental Group learned to avoid the painful stimulus, while the Yoked Control Group did not have that opportunity.

Recalibration phase I. This phase was similar to the initial calibration phase to determine whether pain threshold and pain tolerance had changed. Please note that after the recalibration phase, the original pain tolerance level was again used to continue the conditioning procedure.

Ineffective avoidance phase. The instrumental contingencies were rescheduled for the participants in the Experimental Group. In this phase, participants had a 50% chance of receiving a painful stimulus for each movement trajectory. This contingency change ensured

that the previously effective avoidance behaviour (T3 = 0% reinforcement) now became ineffective (T3 = 50% reinforcement). The reinforcement schedule for the moderately difficult movement trajectory T2 remained the same as before (T2 = 50% reinforcement), and the previous pain-associated trajectory (T1 = 100% reinforcement), became a safer movement trajectory (T1 = 50% reinforcement). As in the previous phases the Yoked Control Group also received the same number of painful stimuli irrespective of the movements they made. Again two blocks of 24 movements were run (IA1-2; 48 movements in total).

Recalibration phase II. This phase was identical to Recalibration phase I.

2.3.2. Extensor strength measurements

Individuals may differ in the force they can produce with their arms. Individuals with greater arm extensor muscle strength need less effort to perform a movement with higher resistance (i.e. T3). In order to standardise the effort needed to perform the movements in the different trajectories, we corrected for participants' maximal arm extensor force with the HM. Before the experiment, we measured the triceps extension force in Newton (N) with a Hand-Held Dynamometer (HHD microFET2; HOGGAN Health Industries Inc., Jordan, UT, USA). The mean force of the current sample was 100.92N (*SD* = 38.86; range = 50-190N).

2.4. Outcome measures

2.4.1. Verbal ratings: pain-related fear, pain expectancy, pain intensity and avoidance

After each block of 24 movements, participants reported pain-related fear, pain expectancy and pain intensity for each of the trajectories. The corresponding trajectory arch was coloured yellow to indicate to which movement trajectory the questions pertained. The questions assessing pain-related fear, pain expectancy and pain intensity were the following: 1) *"How afraid were you to move through the yellow-coloured arch?"*, 2) *"To what extent did you expect an electrical stimulus when moving through the yellow-coloured arch?"*, and 3) *"How painful was moving through the yellow-coloured arch?"*. The pain intensity question

was included to investigate whether participants experienced a 100% reinforced movement as more painful than a 50% reinforced movement. Upon review of the outcome measures, we noted the responses to the question for the pain intensity ratings were difficult to interpret and did not result in a meaningful outcome. The data suggest that Experimental Group participants did not discriminate between T1 and T2 on how painful the movement was during acquisition phase, although we would have expected that participants rate T1 (100% reinforced) as more painful than T2 (50% reinforced). This could be related to the formulation of the question, whereby the participants may have been confused between the pain intensity of the stimulus itself (independent of probability of occurring) and the probability of receiving a painful stimulus during the movement. For now, the results of the pain intensity ratings will be added as supplementary material (see supplementary material, Figure S-1 and Table S-1). Additionally, participants rated to what extent they felt that they could avoid the painful stimulus overall during the block: 4) *"To what extent could you avoid the painful stimulus?"*. Answers were given using the foot switch on a numerical rating scale from 0 to 10 with the respective labels 0 = "not afraid at all" and 10 = "extremely afraid", 0 = "not painful at all" and 10 = "extremely painful", and 0 = "not at all" and 10 = "very much".

2.4.2. Behavioural avoidance: maximal deviation and movement choice

Avoidance behaviour was measured through the maximal deviation from the shortest trajectory T1. Maximal deviation refers to the point on the trajectory furthest away from the shortest trajectory from starting point to the target location. This information was automatically logged by the HM. Because of the continuous nature of this avoidance measure, we also explored the discrete variable movement choice (T1-3). On each movement trial, we recorded which movement trajectory was selected by the participant. We calculated how many times each trajectory was selected per group and phase. This variable indicates the proportions of the chosen movement trajectories per phase.

2.4.3. Pain threshold and pain tolerance

Pain threshold and tolerance were assessed in mA during the (re)calibration phases as described above. ("pre-acquisition" = calibration phase; "avoidance acquisition" = recalibration-I; "ineffective avoidance" = recalibration-II).

2.5. Data analysis overview

First, descriptive statistics of the sample, questionnaire scores (FPQ-III-NL) and reinforcement schedules of the trajectories were computed. Second, as a prerequisite for examining the effects of ineffective avoidance, we tested whether the Experimental Group participants successfully acquired avoidance behaviour. We carried out the following manipulation checks: we performed a series of 2 x 2 x 3 Group (Experimental, Yoked Control) x Block (ACQ1-2) x Trajectory (T1-3) RM ANOVAs on pain expectancy, and pain-related fear ratings. Planned comparisons for the different trajectories were performed within groups to test acquisition of pain expectancy and pain-related fear for T1 > T2 > T3 in the Experimental Group, while for the Yoked Control Group we expected no differentiation between the different trajectories, T1 = T2 = T3. Furthermore, we performed separate 2 x 2 Group (Experimental, Yoked Control) x Block (ACQ1-2) RM ANOVAs on the avoidance ratings and maximal deviation. We expected the Experimental Group to indicate that they could avoid the painful stimulus during acquisition while the Yoked Control Group would indicate they could not avoid the painful stimulus. We expected the Experimental Group to show larger maximal deviation from the shortest trajectory during acquisition compared to the Yoked Control Group.

Second, as manipulation check we performed a 2 x 2 x 3 Group (Experimental, Yoked Control) x Block (IA1-2) x Trajectory (T1-3) RM ANOVA on pain expectancy to investigate whether Experimental and Yoked Control group participants differ. Additionally, we carried

out a 2 x 2 Group (Experimental, Yoked Control) x Block (IA1-2) RM ANOVA on the avoidance ratings to test whether the Experimental and Yoked Control Group did differ in the feeling they could effectively avoid the painful stimulus.

Third, to test our first hypothesis, whether pain-related fear increases when previously acquired avoidance behaviour becomes ineffective, we performed a 2 x 3 x 4 Group (Experimental, Yoked Control) x Trajectory (T1-3) x Block (ACQ1-2, IA1-2) RM ANOVA on the pain-related fear ratings. We assessed the following: (1) Is there an increase in pain-related fear from $T2_{ACQ2}$ (T2=50%-reinforcement) to $T2_{IA1}$ (T2=50%-reinforcement) in the Experimental Group? This is the crucial test of our hypothesis, because the reinforcement schedules for T2 are identical in both phases in the Experimental Group. In other words, an increase in pain-related fear for T2 during the ineffective avoidance phase in the Experimental Group cannot be explained by a change in contingencies from acquisition to ineffective avoidance; (2) Is there a decrease in pain-related fear from $T1_{ACQ2}$ (100%-reinforcement) to $T1_{IA1}$ (50%-reinforcement) in the Experimental Group? We expect this decrease of pain-related fear based on the rescheduling of contingencies; (3) Is there an increase in pain-related fear from $T3_{ACQ2}$ (0%-reinforcement) to $T3_{IA1}$ (50%-reinforcement) in the Experimental Group? We expect this increase of pain-related fear based on the rescheduling of contingencies during the ineffective avoidance phase. We expected the Yoked Control Group to indicate no changes in pain-related fear, because their avoidance behaviour was always ineffective.

To test our second hypothesis, that the Experimental Group participants will persist in emitting avoidance behaviour once the avoidance behaviour is no longer effective, we performed the following analysis: we conducted a 2 x 4 Group (Experimental, Yoked) x Block (ACQ1-2, IA1-2) RM ANOVA on the maximal deviation. We expect the Experimental Group to show larger maximal deviation during ineffective avoidance phase compared to the

Yoked Control Group. Furthermore, we investigated the movement choice of the Experimental and Yoked Control Group. During the ineffective avoidance phase, we compared the proportion of T3 performance (the previously effective avoidance behaviour) between the two groups. We used the chi-squared (χ^2) test statistic to determine if there were significant differences between the proportions of T3 performance during the ineffective avoidance phase, between the groups.

Finally, we explored the effects of effective and ineffective avoidance behaviour on pain threshold and pain tolerance. We performed a 2 x 3 Group (Experimental, Yoked) x Time (pre-acquisition, avoidance acquisition, ineffective avoidance) RM ANOVAs on the pain thresholds and pain tolerance.

For each significant RM ANOVA effect, η_g^2 is reported. η_g^2 is the recommended effect size statistic for repeated measures designs[1]. In case of violation of sphericity, Greenhouse-Geisser corrections were applied by correcting the degrees of freedom. All statistical tests are considered significant at $p < .05$. Holm-Bonferroni corrections were applied to correct for multiple comparison testing. Statistical analyses for all dependent measures were run with R software (RStudio, version 1.0.153).

3. Results

3.1. Descriptive statistics of the sample

Groups did not differ on physical intensity of the painful electrocutaneous stimulus selected during the initial calibration (Threshold Experimental Group: 10.40 ± 4.30 mA; Threshold Yoked Control Group: 10.67 ± 4.26 mA, $t(58) = -.25$, $p = .80$; Tolerance Experimental Group: 25.37 ± 13.41 mA; Tolerance Yoked Control Group: 26.4 ± 11.95 mA, $t(58) = .31$, $p = .75$). Groups also did not differ on the force that was selected for the trajectories based on the triceps extension measure (force Experimental Group: 105.27 ± 39 N; force Yoked Control Group: 96.57 ± 38 N, $t(58) = .45$, $p = .65$). There were no significant

differences in fear of pain as measured by the FPQ-III-NL between groups (see Supplementary Material Table S-2).

During the acquisition phase, the Experimental Group followed a reinforcement schedule with either 100% (T1), 50% (T2) or 0% (T3) reinforcement and in our case, this resulted in the Experimental Group receiving a painful stimulus in 29% of the trials. The Yoked Group was only yoked in matching the same overall number of painful stimuli as the Experimental Group and therefore, they received a painful stimulus in 29% of their trials. During the ineffective avoidance phase, reinforcement schedules for both groups were the same (T1 = T2 = T3 = 50%).

3.2. Manipulation checks

3.2.1 Acquisition phase

The analysis of pain expectancy during acquisition revealed a significant main effect for Group, $F(1, 58) = 14.78$, $p < .001$, $\eta_g^2 = .07$, and Trajectory, $F(2, 116) = 70.67$, $p < .001$, $\eta_g^2 = .30$. Furthermore there was a significant Group x Trajectory interaction, $F(2, 116) = 63.59$, $p < .001$, $\eta_g^2 = .28$, suggesting that pain expectancy ratings for the different trajectories differ between the Experimental Group and the Yoked Control Group. At the end of the second acquisition block (ACQ2) the participants in the Experimental Group expected the painful stimulus more during T1 *vs.* T2, $t(224.4) = 4.1$, $p < .0001$; T1 *vs.* T3, $t(224.4) = 12.81$, $p < .0001$; and T2 *vs.* T3, $t(224.4) = 8.71$, $p < .0001$, whereas there were no differences in pain expectancy between the three trajectories for the Yoked Control Group (see Figure 2).

The analysis of pain-related fear during acquisition revealed a main effect for Trajectory, $F(2, 116) = 38.86$, $p < .001$, $\eta_g^2 = .15$ and a significant Group x Trajectory interaction, $F(2, 116) = 50.65$, $p < .001$, $\eta_g^2 = .19$. At the end of the second acquisition block (ACQ2) the Experimental Group was more afraid of T1 *vs.* T2, $t(220) = 2.41$, $p < .05$; T1 *vs.* T3, $t(220) =$

11.375, $p < .0001$; and T2 *vs*. T3, $t(220) = 8.97$, $p < .0001$, whereas there were no differences in pain-related fear between the three trajectories for the Yoked Control Group (see Figure 3).

The analysis of avoidance ratings during acquisition revealed a significant main effect for Group, $F(1, 58) = 59.29$, $p < .0001$. The Experimental Group reported higher avoidance ratings compared to the Yoked Control Group, $t(235) = 7.70$, $p < .0001$. The analysis of maximal deviation during acquisition revealed a significant main effect for Group, $F(1, 58) = 60.69$, $p < .00001$, $\eta_g^2 = .37$. The Experimental Group avoided more during the two blocks of acquisition phase compared to the Yoked Control Group, $t(151.71) = 10.41$, $p < .0001$.

- insert FIGURE 2 about here –

3.2.2 Ineffective avoidance phase

During the ineffective avoidance phase, the RM ANOVA of pain expectancy ratings did not show any significant main effects or interaction effects (see Figure 2). Additionally, there were no main and interaction effects for the RM ANOVA of avoidance ratings during the ineffective avoidance phase.

In conclusion, the manipulations checks confirmed that Experimental Group participants learned to effectively avoid during acquisition.

3.3. Hypothesis 1: pain-related fear increases when previously effective avoidance behaviour becomes ineffective

The analysis on pain-related fear ratings revealed a significant main effect of Block, $F(2.54, 147.49) = 50.98$, $p <.0001$, $\eta_g^2 = .13$, and a significant main effect of Trajectory, $F(2, 115.90) = 22.90$, $p <.0001$, $\eta_g^2 = .05$. The main effect of Group did not reach statistical significance, $F(1, 58) = 1.95$, $p = .17$. However, the interaction Group x Trajectory x Block was significant, $F(5.31, 308.07) = 19.25$, $p < .0001$, $\eta_g^2 = .07$, suggesting that pain-related fear

for different trajectories evolved differently in the Experimental Group and the Yoked Control Group over time (see Figure 3).

The crucial comparison in the Experimental Group from the acquisition phase to the ineffective avoidance phase, is the expected increase of pain-related fear from $T2_{ACQ2}$ (50%-reinforcement) to $T2_{AI1}$ (50%-reinforcement), reached significance $t(499) = 2.38$, $p < .05$, *Cohen's d* = 0.65. Following the contingencies, we expected a decrease in pain-related fear for the Experimental Group from $T1_{ACQ2}$ (100% reinforcement) to $T1_{AI1}$ (50%-reinforcement), however there was no significant difference between the pain-related fear ratings, $t(499) = -1.63$, $p = .10$. Finally, we did find a significant increase in pain-related fear for the Experimental Group from $T3_{ACQ2}$ (0%-reinforcement) to $T3_{AI1}$ (50%-reinforcement), $t(499) = 15.26$, $p < .0001$. The pain-related fear ratings of the Yoked Control Group, increased from the acquisition phase to ineffective avoidance phase for each trajectory: $T1_{ACQ2}$ to $T1_{AI1}$, $t(499) = 5.84$, $p < .001$; $T2_{ACQ2}$ to $T2_{AI1}$, $t(499) = 4.07$, $p < .001$ and $T3_{ACQ2}$ to $T3_{AI1}$, $t(499) = 3.53$, $p < .001$.

- Insert FIGURE 3 about here –

3.4. Hypothesis 2: Experimental Group participants who have acquired effective avoidance will emit more avoidance behaviour during the ineffective avoidance phase compared to the Yoked Control Group

The analysis on the mean maximal deviation data (see Figure 4) revealed a significant main effect of Group, $F(1, 58) = 60.69$, $p < .00001$, $\eta_g^2 = .37$. There was also a main effect of Phase, $F(3,174) = 31.08$, $p < .00001$, $\eta_g^2 = .19$. Furthermore, a significant interaction between Group and Phase emerged, $F(3,174) = 29.81$, $p < .00001$, $\eta_g^2 = .18$, suggesting that the difference in avoidance behaviour between the Experimental and Yoked Control Group changed over the course of the experiment. In line with our expectations, the Experimental

Group performed more avoidance behaviour during the ineffective avoidance phase compared to the Yoked Control Group, $Experimental_{IA1\text{-}2}$ *vs.* $Yoked_{IA1\text{-}2}$: $t(151.71) = 2.75$, $p < .01$. However, there was a significant decrease in mean maximal deviation for the Experimental Group participants, within-contrast: ACQ2 *vs.* IA1: $t(174) = 9.81$, $p < .0001$. In other words, although there was more avoidance behaviour in the Experimental Group than in the Yoked Control Group, it declined from acquisition to ineffective avoidance phase for the Experimental Group, while no such changes were observed for the Yoked Control Group.

- Insert FIGURE 4 about here –

To test whether the Experimental Group participants perform their previous effective avoidance behaviour more compared to the Yoked Control Group during the ineffective avoidance phase, we also compared the proportion of T3 performance. Proportion T3 trajectory performed during the ineffective avoidance phase for Experimental Group was 0.31 and for the Yoked Control Group 0.22, $\chi^2(1) = 7.551$, $p < .01$. Participants of the Experimental Group performed T3 in 31% of the trials of the ineffective avoidance phase and the Yoked Control Group performed T3 only in 22% of the trials of the ineffective avoidance phase (see supplementary material Figure S-2, for proportion of chosen trajectories for both groups).

3.5. Exploratory analyses: do pain threshold and pain tolerance decline when previously acquired avoidance becomes ineffective?

3.5.1 Pain threshold

The analysis on the pain thresholds (see Figure 5) revealed no main effects of Group or Time. However, the analysis yielded a significant Group x Time interaction, $F(1.80, 104.36) = 4.09$, $p < .05$, $\eta_g^2 = .01$, suggesting that pain thresholds for the two groups evolved differently across time. Within-group comparisons confirmed that by the end of the experiment (ineffective avoidance) the pain threshold in the Experimental Group was significantly lower than at the start of the experiment (pre-acquisition), $t(116) = 2.70$, $p < .05$, and after the acquisition of avoidance behaviour (avoidance acquisition), $t(116) = 3.40$, $p < .01$, whereas no such differences emerged in the Yoked Control Group. However, after the Holm-Bonferroni correction for multiple testing, only the pain threshold at the end of the experiment was significantly lower than the pain threshold after avoidance acquisition (adjusted p-value = 0.017).

- Insert FIGURE 5 about here –

3.5.2 Pain tolerance

The analysis on the pain tolerance levels (see Figure 6) revealed a significant main effect of Time, $F(1.58, 91.83) = 6.45$, $p < .01$, $\eta_g^2 = .02$. The Group x Time interaction just failed to reach significance, $F(1.58, 91.83) = 3.22$, $p = .06$. Again, all comparisons were corrected for multiple testing with the Holm-Bonferroni method and are considered significant with a p-value below .017 .

Within-comparisons confirmed that there was no significant difference in pain tolerance levels for the Experimental Group at the start of the experiment and after acquisition of avoidance behaviour, pre-acquisition *vs.* avoidance acquisition: $t(116) = 0.07$, $p = 0.99$. However, the pain tolerance significantly decreased when measured after the ineffective avoidance phase, when participants of the Experimental Group could not avoid anymore, pre-

acquisition *vs.* ineffective avoidance: $t(116) = 3.10$, $p < .01$ and, avoidance acquisition *vs.* ineffective avoidance: $t(116) = 3.03$, $p < .01$. The Yoked Control Group showed an initial decrease in pain tolerance, pre-acquisition *vs.* avoidance acquisition: $t(116) = 2.46$, $p < .05$, but this did not further decrease in tolerance level after the ineffective avoidance phase (avoidance acquisition *vs.* ineffective avoidance: $t(116) = 1.98$, $p = .12$).

- Insert FIGURE 6 about here –

4. Discussion

This study tested the effects of ineffective avoidance of a painful stimulus on pain-related fear, and pain. Avoidance is mainly intended to reduce anticipatory fear[16,19]. It has been shown that avoidance increases pain-related fear when previously acquired avoidance behaviour ceases to avert a painful stimulus[24]. Here, we: (1) investigated whether pain-related fear increases when avoidance behaviour becomes ineffective; (2) examined whether participants who learned to avoid, persist in emitting avoidance behaviour once the behaviour is ineffective; and (3) explored the effects of ineffective avoidance on pain measures.

First, the results indicate Experimental Group participants learned to avoid painful stimuli by primarily performing the non-painful but most deviating and effortful trajectory(T3), in contrast to Yoked Control participants who primarily performed the shortest and easiest trajectory(T1), hereby demonstrating acquisition of avoidance in the Experimental Group. Additionally, Experimental Group participants expected and feared the painful stimulus more when performing T1 *vs.* T2, and T2 *vs.* T3. No such differences occurred in the Yoked Control Group, as their movements were unrelated to any painful outcomes. The results of acquisition of avoidance behaviour, pain expectancy and pain-related fear replicate previous findings using the same paradigm[18].

Second, our manipulation to render avoidance ineffective was successful. Experimental Group participants showed no differentiation in pain expectancy between trajectories when the contingencies were rescheduled to 50% reinforcement, similar to the Yoked Control participants. Furthermore, both groups reported not being able to effectively avoid painful stimuli during this phase.

As expected, Experimental Group participants reported higher pain-related fear when avoidance became ineffective, after successful avoidance acquisition. Specifically, pain-related fear increased for T2, while the reinforcement of this trajectory remained the same (T2=50% reinforcement). Pain-related fear for T1 remained high, while the chance of getting a painful stimulus during this trajectory decreased from 100% to 50%. Finally, pain-related fear increased for T3, which was now reinforced 50% instead of 0%. This observed increase and maintenance of pain-related fear during ineffective avoidance extends recent studies showing that engaging in avoidance and losing the opportunity to avoid increases fear and adds to prior evidence regarding a bidirectional relationship between fear and avoidance[9,24.] A potential explanation how ineffective avoidance may have maintained and increased pain-related fear could be the tendency to infer danger on the basis of (ineffective) avoidance, known as ex-consequentia reasoning[10]. The availability of avoidance, albeit ineffective, may have led participants to infer danger starting a vicious cycle: avoidance could increase threat perception, resulting in an increase in pain-related fear, which in turn could increase avoidance behaviour, even when it is ineffective.

Furthermore, this increase of pain-related fear during ineffective avoidance is in line with the results of Crombez and colleagues[6], showing that losing control over pain resulted in more fear of the impending pain stimuli. In our study, however, there also was an increase in pain-related fear for the Yoked Control Group during the ineffective avoidance phase. This increase in pain-related fear can be explained by the increase of reinforcement for the

different trajectories from the acquisition to the ineffective avoidance phase. For the Yoked Control Group reinforcement of each trajectory was 29% during acquisition, while during ineffective avoidance, reinforcement was 50%. This change in reinforcement schedule for the different trajectories was due to the matching of participants of the Experimental Group to participants of the Yoked Control Group. Future experiments should consider a slight change in paradigm, for example by using the actual contingencies of the Yoked Control Group during acquisition as the basis for the contingency during the ineffective avoidance phase for the Experimental Group. By doing so, the contingencies of the trajectories for the Yoked Control Group would not have changed, eliminating the potential confound in comparing both groups during the ineffective avoidance phase. Future studies also might consider framing the movement task as a game to maximize participant engagement. Furthermore, we recommend future studies to include psycho-physiological measures of pain-related fear, such as eyeblink startle measurement, skin conductance, or cardiac assessment[2,28], in order to assess whether the increase in pain-related fear can also be found in these measures.

Our results seem to support our second hypothesis, that Experimental Group participants are more persistent in previously acquired, but now ineffective, avoidance despite the extra effort and time this behaviour takes, compared to Yoked Control participants. Although Experimental Group participants explored alternative trajectories during ineffective avoidance phase, they performed the previously learned, but now ineffective avoidance behaviour slightly more. A possible explanation is that the participants continued exploring all three trajectories, given the equal but ambiguous pain contingencies (50%). In addition, the individual's previous learning history (here, acquisition phase) may have influenced current avoidant decision-making[13,30], despite the reduced effectiveness of this behaviour (50%-pain). The participants learned that the costs of performing T3 (effort) are relatively low compared to the more salient cost of T1 (pain). This may have resulted in reduced extinction of

avoidance behaviour[15]. This persistence in avoidance adds to the findings of Meulders and colleagues[18]. They found that participants were persistent in avoidance even though the contingencies no longer held, and no painful stimuli were delivered (extinction). Still, we cannot rule out that the ineffective avoidance behaviour of the Experimental Group would extinguish (i.e., become statistically equivalent to Yoked Control Group) with adding more movements during the ineffective avoidance phase.

Concerning our explorative analyses regarding the effects of ineffective avoidance on pain measures, we found that pain threshold and tolerance declined when avoidance became ineffective in the Experimental Group. These findings suggest that avoidance may be associated with unfavourable pain outcomes and adds to research which proposes that failure to control pain may increase pain or reduce pain tolerance in future circumstances[4,12,17,31]. Interesting is that Yoked Control participants, who never learned to effectively avoid pain, reported a lower pain tolerance during first recalibration, after acquisition phase, which may suggest pain sensitization as a result of uncontrollable pain. This finding corroborates with a study by Bräscher and colleagues[3]. They found that uncontrollability of painful stimuli facilitates pain perception and pain processing. An increased sensitization of pain was reflected by increased activation in pain-processing regions in the brain.

A particular strength is the operationalisation of avoidance. We used a validated paradigm that allowed participants to perform avoidance during a robotic arm reaching task[5,11,18]. Previous studies operationalised avoidance by pressing a stop-button or moving a joystick without associated costs[9,24,26]. Here, to avoid the painful stimuli, Experimental Group participants performed the most deviating and effortful trajectory. The resistance used was tailored to each individual. By doing so, avoidance came with a cost, which is also the case in chronic pain and is more valid than avoidance with no associated costs. We assumed that our paradigm, especially the experimental manipulation of ineffective avoidance and its effects on

pain-related fear and pain, would be a suitable experimental analogue to investigate the mechanisms of avoidance for chronic pain patients. This procedure resembles operant extinction of avoidance by making the aversive event non-eliminable, while the opportunity to engage in avoidance remains[8,14]. In spite of avoidance attempts, pain persists in chronic pain and avoidance now comes with the cost of restrictions in daily life activities. However, our operationalization of avoidance has limited ecological validity. Most of the costs for chronic pain patients are psychosocial in nature (e.g., decreased work/leisure), whereas the cost in the current paradigm is related to the effort needed to perform movements. However, we argue that the face validity and construct validity of our study is high. Not only is there phenomenological similarity between the behaviour in the model and the symptoms of chronic pain, the paradigm also recreates the etiological process of avoidance as a trade-off between lower risk of pain vs. higher risk of costs[27].

The fear-avoidance model proposes that pain-related fear and avoidance play a key role in the development of chronic pain. According to the model, avoidance would eventually lead to disability and disuse, which in turn may lower the threshold at which pain is experienced[28,29]. To our knowledge there are no experimental studies that investigated the effect of (ineffective) avoidance on pain. Here we found some evidence that ineffective avoidance increased pain, thereby providing support for the circular causality typical of the fear-avoidance model. Caution is warranted concerning the interpretation of the results of the pain threshold and tolerance. Participants might have chosen a lower level of pain tolerance throughout the experiment, not because they perceived it as more painful, but because they wished to avoid high pain stimuli in the subsequent trials. To avoid this potential confound, future research might consider using a different pain modality for intermediate pain threshold and tolerance measures than the one used during the conditioning procedure.

In conclusion, and despite these limitations, we replicated the acquisition of avoidance behaviour, pain-expectancy and pain-related fear using a robotic arm reaching task. We demonstrated that when avoidance becomes ineffective, individuals become more afraid, persist in their ineffective avoidance behaviour, and become more sensitive to pain. These findings and procedure can potentially help to further our understanding of how avoidance can develop and maintain pain problems.

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Figure Captions

Figure 1. Robotic arm reaching task, showing the different trajectories: T1, T2, T3, from left to right.

Figure 2. Pain expectancy ratings with standard error bars for the three trajectories (T1, T2, T3) during the acquisition and ineffective avoidance phase for the Experimental group (left) and Yoked Control Group (right).

Figure 3. Pain-related fear ratings with standard error bars for the three trajectories (T1, T2, T3) during the acquisition and ineffective avoidance phase for the Experimental Group (left) and Yoked Control Group (right).

Figure 4. Mean maximal deviation with standard error bars from the shortest trajectory (T1) during acquisition (ACQ1, ACQ2), and ineffective avoidance (IA1, IA2) phase for the Experimental and Yoked Control Group separately.

Figure 5. Pain threshold with standard error bars at the start of the experiment (pre-acquisition), after the acquisition of avoidance (pre-ineffective-avoidance), and after the ineffective avoidance phase (post-ineffective-avoidance) for the Experimental and Yoked Control Group separately.

Figure 6. Pain tolerance with standard error bars at the start of the experiment (pre-acquisition), after the acquisition of avoidance (pre-ineffective-avoidance), and after the ineffective avoidance phase (post-ineffective avoidance) for the Experimental and Yoked Control Group separately.

Figure S-1. Self-reported pain intensity ratings with standard error bars for the three trajectories (T1, T2, T3) during the acquisition and ineffective phase for the Experimental Group (left) and Yoked Control Group (right).

Figure S-2. Proportion of chosen trajectories for Experimental Group and Yoked Control Group with standard error bars for the three trajectories (T1, T2, T3) during acquisition and ineffective avoidance phase.

Figure 1.

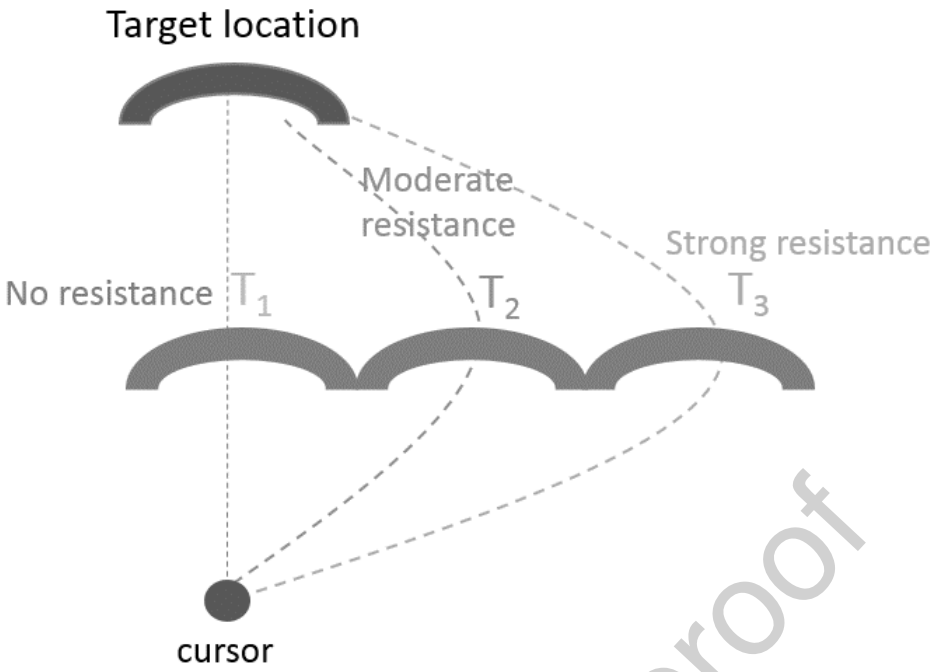

Figure 1. Robotic arm reaching task, showing the different trajectories: T1, T2, T3, from left to right.

Figure 2.

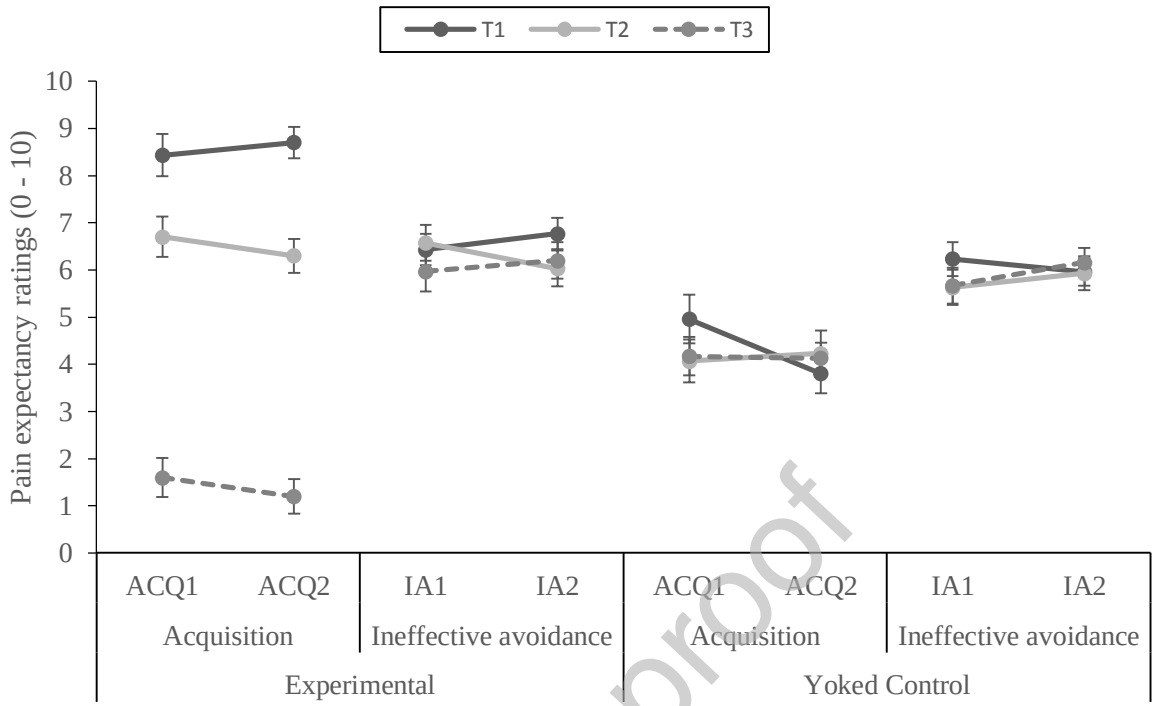

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Figure 3.

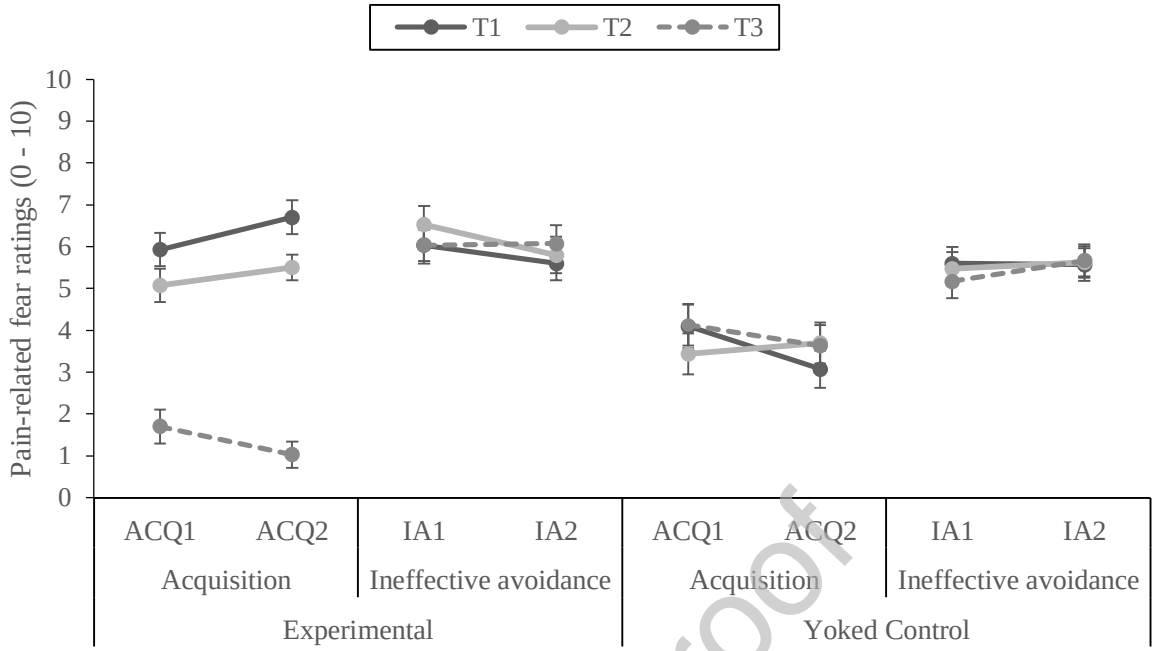

Figure 3. Pain-related fear ratings with standard error bars for the three trajectories (T1, T2, T3) during the acquisition and ineffective avoidance phase for the Experimental group (left) and Yoked Control Group (right).

Figure 4.

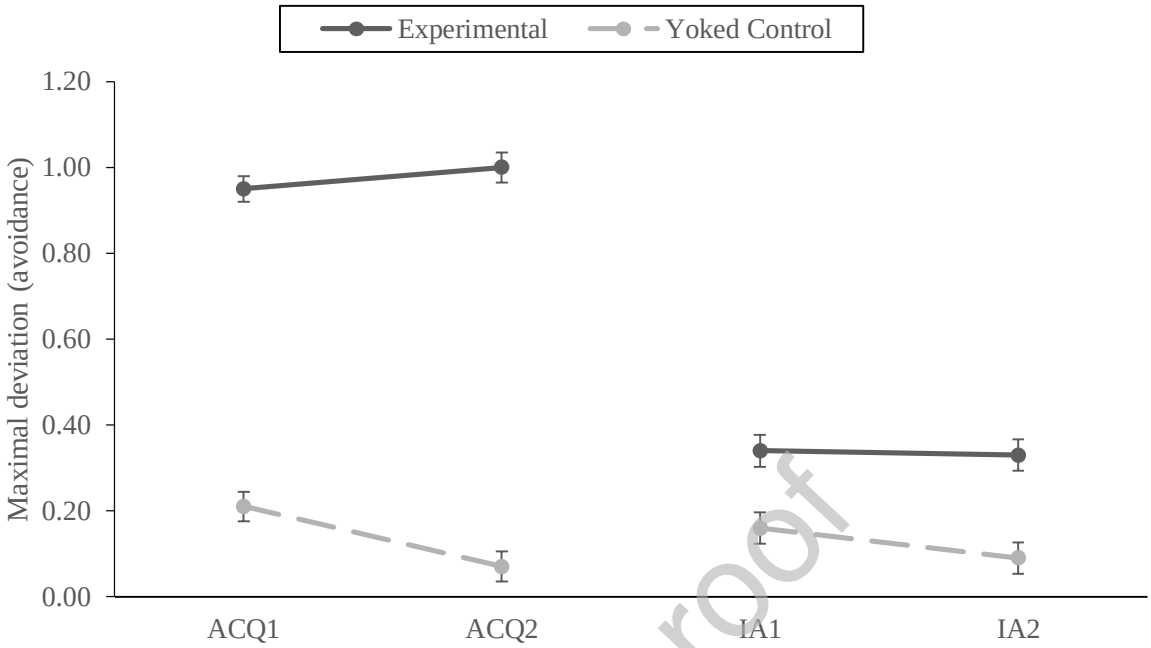

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Figure 5.

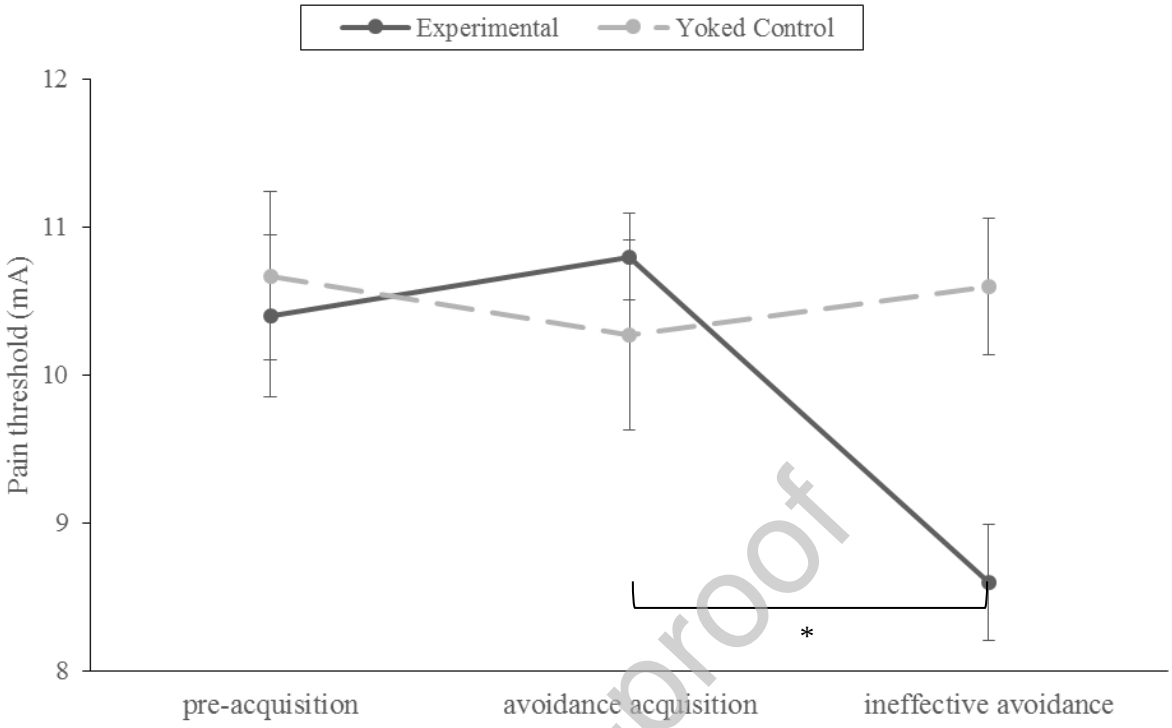

Figure 5. Pain threshold with standard error bars at the start of the experiment (pre-acquisition), after the acquisition of avoidance (pre-ineffective-avoidance), and after the ineffective avoidance phase (post-ineffective-avoidance) for the Experimental and Yoked Control Group separately.

Figure 6.

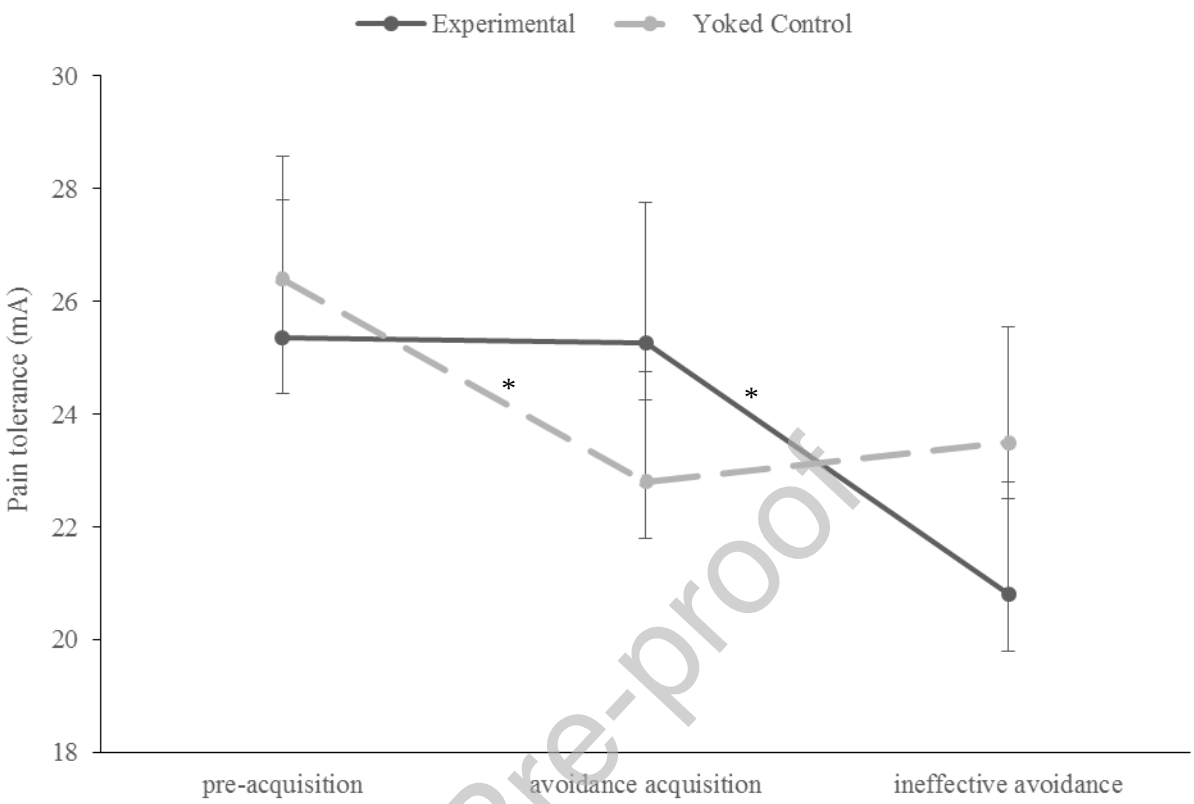

Figure 6. Pain tolerance with standard error bars at the start of the experiment (pre-acquisition), after the acquisition of avoidance (pre-ineffective-avoidance), and after the ineffective avoidance phase (post-ineffective avoidance) for the Experimental and Yoked Control Group separately.

Figure S-1.

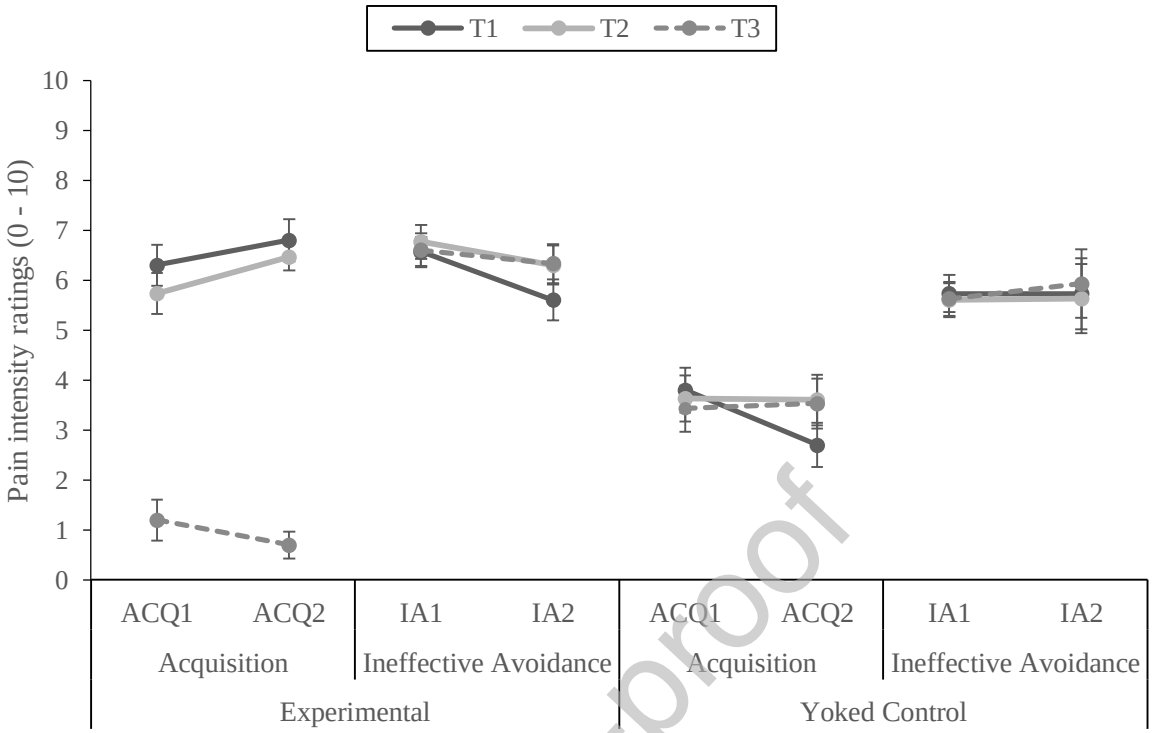

Figure S-1. Self-reported pain intensity ratings with standard error bars for the three trajectories (T1, T2, T3) during the acquisition and ineffective phase for the Experimental group (left) and Yoked Control Group (right).

Figure S-2.

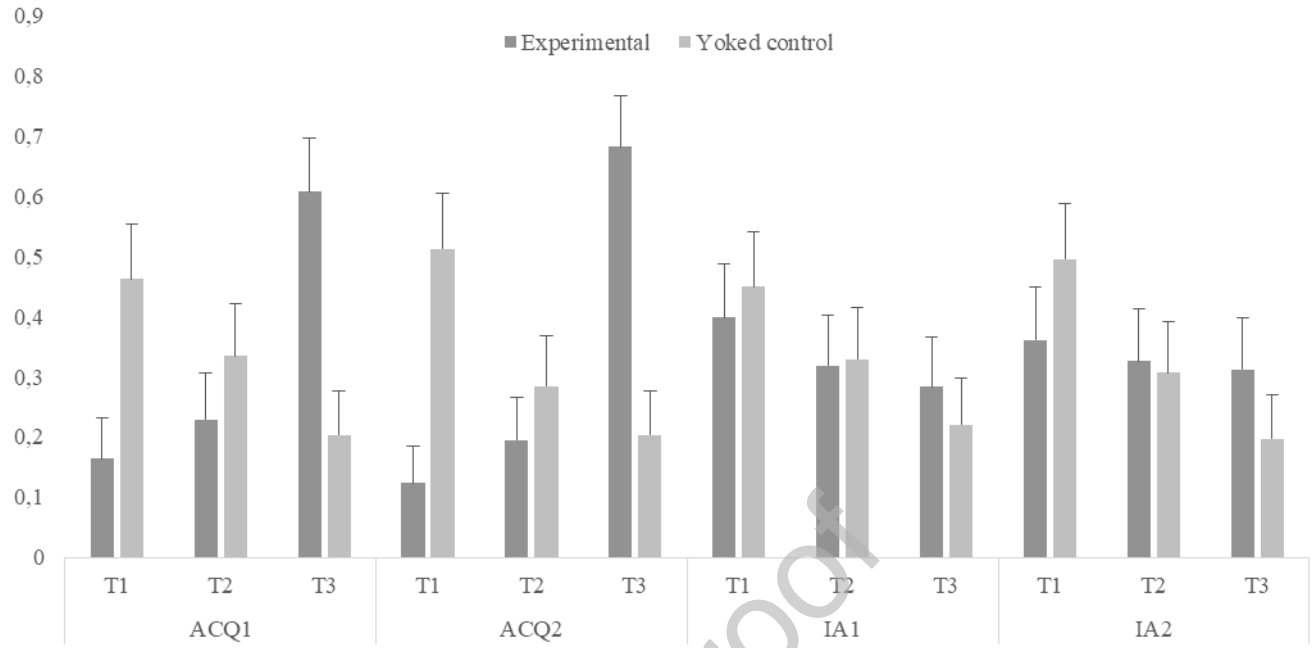

Figure S-2. Proportion of chosen trajectories for Experimental Group and Yoked Control Group with standard error bars for the three trajectories (T1, T2, T3) during acquisition and ineffective avoidance phase.

Table S-1

Means and standard deviations of the pain intensity ratings

Pain intensity *M* (SD)		ACQ1	ACQ2	IA1	IA2
Experimental Group	T1	*6.3* (2.26)	*6.8* (2.32)	*5.6* (2.25)	*6.57* (1.61)
	T2	*5.73* (2.32)	*6.47* (1.72)	*6.3* (2.02)	*6.77* (1.68)
	T3	*1.2* (2.22)	*0.7* (1.47)	*6.33* (2.12)	*6.6* (1.87)
Yoked Control Group	T1	*3.80* (2.46)	*2.70* (2.42)	*5.73* (1.89)	*5.73* (2.05)
	T2	*3.63* (2.37)	*3.60* (2.39)	*5.63* (1.99)	*5.60* (1.81)
	T3	*3.43* (2.51)	*3.53* (2.74)	*5.93* (1.84)	*5.63* (1.85)

Table S-2

FPQ scores

	Experimental group[a]					Yoked control group[b]				
Scale	Mean	*SD*	Median	Min	Max	Mean	*SD*	Median	Min	Max
FPQ										
Minor	17.00	4.31	16.0	10	27	19.03	5.73	18.0	10	29
Severe	34.90	5.22	35.0	25	46	33.37	5.49	35.5	21	42
Medical	23.37	7.19	24.0	13	43	23.53	6.88	22.0	13	41
Total	75.27	14.36	73.5	49	114	76.60	13.62	74.5	53	107

Note. FPQ = Fear of Pain Questionnaire, with subscales minor, severe and medical pain, and with the total

[a] *n = 30*

[b] *n = 30*