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## Investigating pain-related avoidance behavior using a robotic arm-reaching paradigm --Manuscript Draft--

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**TITLE:**

Investigating Pain-Related Avoidance Behavior Using a Robotic Arm-Reaching Paradigm

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**KEYWORDS:**

chronic pain, fear, acquisition, generalization, extinction with response-prevention, associative learning, instrumental conditioning, relapse

**SUMMARY:**

Avoidance is central to chronic pain disability, yet adequate paradigms for examining pain-related avoidance are lacking. Therefore, we developed a paradigm that allows investigating how pain-related avoidance behavior is learned (acquisition), spreads to other stimuli (generalization), can be mitigated (extinction), and how it may subsequently re-emerge (spontaneous recovery).

**ABSTRACT:**

Avoidance behavior is a key contributor to the transition from acute pain to chronic pain disability. Yet, there has been a lack of ecologically valid paradigms to experimentally investigate pain-related avoidance. To fill this gap, we developed a paradigm (the robotic arm-reaching paradigm) to investigate the mechanisms underlying the development of pain-related avoidance behavior. Existing avoidance paradigms (mostly in the context of anxiety research) have often operationalized avoidance as an experimenter-instructed, low-cost response, superimposed on stimuli associated with threat during a Pavlovian fear conditioning procedure. In contrast, the current method offers increased ecological validity in terms of instrumental learning (acquisition) of avoidance, and by adding a cost to the avoidance response. In the paradigm, participants perform arm-reaching movements from a starting point to a target using a robotic arm, and freely choose between three different movement trajectories to do so. The movement trajectories differ in probability of being paired with a painful electrocutaneous stimulus, and in required

effort in terms of deviation and resistance. Specifically, the painful stimulus can be (partly) avoided at the cost of performing movements requiring increased effort. Avoidance behavior is operationalized as the maximal deviation from the shortest trajectory on each trial. In addition to explaining how the new paradigm can help understand the acquisition of avoidance, we describe adaptations of the robotic arm-reaching paradigm for (1) examining the spread of avoidance to other stimuli (generalization), (2) modeling clinical treatment in the lab (extinction of avoidance using response prevention), as well as (3) modeling relapse, and return of avoidance following extinction (spontaneous recovery). Given the increased ecological validity, and numerous possibilities for extensions and/or adaptations, the robotic arm-reaching paradigm offers a promising tool to facilitate the investigation of avoidance behavior and to further our understanding of its underlying processes.

## **INTRODUCTION:**

Avoidance is an adaptive response to pain signaling bodily threat. Yet, when pain becomes chronic, pain and pain-related avoidance lose their adaptive purpose. In line with this, the fear-avoidance model of chronic pain<sup>1-8</sup> posits that erroneous interpretations of pain as catastrophic, trigger increases in fear of pain, which motivate avoidance behavior. Excessive avoidance can lead to the development and maintenance of chronic pain disability, due to physical disuse and decreased engagement in daily activities and aspirations<sup>1-5,9</sup>. Furthermore, given that the absence of pain can be misattributed to avoidance rather than recovery, a self-sustaining cycle of pain-related fear and avoidance can be established<sup>10</sup>.

Despite recent interest in avoidance in the anxiety literature<sup>11,12</sup>, research on avoidance in the pain domain is still in its infancy. Previous anxiety research, guided by the influential two-factor theory<sup>13</sup>, has generally assumed fear to drive avoidance. Correspondingly, traditional avoidance paradigms<sup>12</sup> entail two experimental phases, each corresponding to one factor: the first to establish fear (Pavlovian conditioning<sup>14</sup> phase), and the second to examine avoidance (Instrumental<sup>15</sup> phase). During differential Pavlovian conditioning, a neutral stimulus (conditioned stimulus, CS+; e.g., a circle) is paired with an intrinsically aversive stimulus (unconditioned stimulus, US; e.g., an electric shock), which naturally produces unconditioned responses (URs, e.g., fear). A second control stimulus is never paired with the US (CS-; e.g., a triangle). Following pairings of the CSs with the US, the CS+ will elicit fear in itself (conditioned responses, CRs) in the absence of the US. The CS- comes to signal safety and will not trigger CRs. Afterwards, during instrumental conditioning, participants learn that their own actions (responses, R; e.g., button-press) lead to certain consequences (outcomes; O, e.g., the omission of shock)<sup>15,16</sup>. If the response prevents a negative outcome, the chance of that response recurring increases; this is referred to as negative reinforcement<sup>15</sup>. Thus, in the Pavlovian phase of traditional avoidance paradigms, participants first learn the CS-US association. Subsequently, in the instrumental phase, an experimenter-instructed avoidance response (R) is introduced, canceling the US if performed during CS presentation, establishing a R-O association. Thus, the CS becomes a discriminative stimulus (S<sup>D</sup>), indicating the appropriate moment for, and motivating the performance of, the conditioned R<sup>15</sup>. Apart from some experiments showing instrumental conditioning of pain reports<sup>17</sup> and pain-related facial expressions<sup>18</sup>, investigations into the instrumental learning mechanisms of pain, in general, are limited.

Although the standard avoidance paradigm, described above, has elucidated many of the processes underlying avoidance, it also has several limitations<sup>5,19</sup>. First, it does not allow examining the learning, or acquisition, of avoidance itself, because the experimenter instructs the avoidance response. Having participants freely choose between multiple trajectories, and, therefore, learn which responses are painful/safe and which trajectories to avoid/not avoid, more accurately models real-life, where avoidance emerges as a natural response to pain<sup>9</sup>. Second, in traditional avoidance paradigms, the button-press avoidance response comes at no cost. However, in real life, avoidance can become extremely costly for the individual. Indeed, high-cost avoidance especially disrupts daily functioning<sup>5</sup>. For example, avoidance in chronic pain can severely limit people's social and working lives<sup>9</sup>. Third, dichotomous responses such as pressing/not pressing a button also do not very well represent real life, where different degrees of avoidance occur. In the following sections, we describe how the robotic arm-reaching paradigm<sup>20</sup> addresses these limitations, and how the basic paradigm can be extended to multiple novel research questions.

### **Acquisition of avoidance**

In the paradigm, participants use a robotic arm to perform arm-reaching movements from a starting point to a target. Movements are employed as the instrumental response because they closely resemble pain-specific, fear-evoking stimuli. A ball virtually represents participants' movements on-screen (**Figure 1**), allowing participants to follow their own movements in real-time. During each trial, participants freely choose between three movement trajectories, represented on-screen by three arches (T1–T3), differing from each other in terms of how effortful they are, and in the likelihood that they are paired with a painful electrocutaneous stimulus (i.e., pain stimulus). Effort is manipulated as deviation from the shortest possible trajectory and increased resistance from the robotic arm. Specifically, the robot is programmed such that resistance increases linearly with deviation, meaning that the more participants deviate, the more force they need to exert on the robot. Furthermore, pain administration is programmed such that the shortest, easiest trajectory (T1) is always paired with the pain stimulus (100% pain/no deviation or resistance). A middle trajectory (T2) is paired with a 50% chance of receiving the pain stimulus, but more effort is required (moderate deviation and resistance). The longest, most effortful trajectory (T3) is never paired with the pain stimulus but requires the most effort to reach the target (0% pain/largest deviation, strongest resistance). Avoidance behavior is operationalized as the maximum deviation from the shortest trajectory (T1) per trial, which is a more continuous measure of avoidance, than for example, pressing or not pressing a button. Furthermore, the avoidance response comes at the cost of increased effort. Moreover, given that participants freely choose between the movement trajectories, and are not explicitly informed about the experimental R-O (movement trajectory-pain) contingencies, avoidance behavior is instrumentally acquired. Online self-reported fear of movement-related pain and pain-expectancy have been collected as measures of conditioned fear toward the different movement trajectories. Pain-expectancy is also an index of contingency awareness and threat appraisal<sup>21</sup>. This combination of variables allows scrutinizing the interplay between fear, threat appraisals, and avoidance behavior. Using this paradigm, we have consistently demonstrated the experimental acquisition of avoidance<sup>20,22–24</sup>.

## **Generalization of avoidance**

We have extended the paradigm to investigate generalization of avoidance<sup>23</sup>—a possible mechanism leading to excessive avoidance. Pavlovian fear generalization refers to the spreading of fear to stimuli or situations (generalization stimuli, GSs) resembling the original CS+, with fear declining with decreasing similarity to the CS+ (generalization gradient)<sup>25-28</sup>. Fear generalization minimizes the need to learn relationships between stimuli anew, allowing swift detection of novel threats in ever-changing environments<sup>25-28</sup>. However, excessive generalization leads to fear of safe stimuli (GSs similar to CS-), thus causing unnecessary distress<sup>28,29</sup>. In line with this, studies using Pavlovian fear generalization consistently show that chronic pain patients excessively generalize pain-related fear<sup>30-34</sup>, whereas healthy controls show selective fear generalization. Yet, where excessive fear causes discomfort, excessive avoidance can culminate in functional disability, due to avoidance of safe movements and activities, and increased daily activity disengagement<sup>1-4,9</sup>. Despite its key role in chronic pain disability, research on the generalization of avoidance is scarce. In the paradigm adapted for studying generalization of avoidance, participants first acquire avoidance, following the procedure described above<sup>20</sup>. In a subsequent generalization phase, three novel movement trajectories are introduced in the absence of the pain stimulus. These generalization trajectories (G1–G3) lie on the same continuum as the acquisition trajectories, resembling each of these trajectories, respectively. Specifically, generalization trajectory G1 is situated between T1 and T2, G2 between T2 and T3, and G3 to the right of T3. In this way, generalization of avoidance to novel safe trajectories can be examined. In a previous study, we showed generalization of self-reports, but not avoidance, possibly suggesting different underlying processes for pain-related fear- and avoidance generalization<sup>23</sup>.

## **Extinction of avoidance with response prevention**

The primary method of treating high fear of movement in chronic musculoskeletal pain is exposure therapy<sup>35</sup>—the clinical counterpart to Pavlovian extinction<sup>36</sup>, i.e., the reduction of CRs through repeated experience with the CS+ in the absence of the US<sup>36</sup>. During exposure for chronic pain, patients perform feared activities or movements in order to disconfirm catastrophic beliefs and expectations of harm<sup>34,37</sup>. Since these beliefs do not necessarily concern pain per se, but rather underlying pathology, movements are not always carried out pain-free in the clinic<sup>34</sup>. According to inhibitory learning theory<sup>38,39</sup>, extinction learning does not erase the original fear memory (e.g., movement trajectory-pain); rather, it creates a novel inhibitory extinction memory (e.g., movement trajectory-no pain), which competes with the original fear memory for retrieval<sup>40,41</sup>. The novel inhibitory memory is more context-dependent than the original fear memory<sup>40</sup>, deeming the extinguished fear memory susceptible to re-emergence (return of fear)<sup>40-42</sup>. Patients are often prevented from performing even subtle avoidance behaviors during exposure treatment (extinction with response prevention, RPE), to establish genuine fear extinction by preventing the misattribution of safety to avoidance<sup>10,43</sup>.

## **Return of avoidance**

Relapse in terms of return of avoidance is still common in clinical populations, even after extinction of fear<sup>43-46</sup>. Although multiple mechanisms have been found to result in the return of fear<sup>47</sup>, little is known about those relating to avoidance<sup>22</sup>. In this manuscript, we specifically

describe spontaneous recovery, i.e., return of fear and avoidance due to the passage of time<sup>40,47</sup>. The robotic arm-reaching paradigm has been implemented in a 2-day protocol to investigate return of avoidance. During day 1, participants first receive acquisition training in the paradigm, as described above<sup>20</sup>. In a subsequent RPE phase, participants are prevented from performing the avoidance response, i.e., they can only perform the pain-associated trajectory (T1) under extinction. During day 2, to test for the spontaneous recovery, all trajectories are available again, but in the absence of pain stimuli. Using this paradigm, we showed that, one day after successful extinction, avoidance returned<sup>22</sup>.

## **PROTOCOL:**

The protocols presented here meet the requirements of the Social and Societal Ethics committee of the KU Leuven (registration number: S-56505), and the Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration numbers: 185\_09\_11\_2017\_S1 and 185\_09\_11\_2017\_S2\_A1).

### **1. Preparing the laboratory for a test session**

1.1. Before the test session: Send the participant an e-mail informing him/her about the delivery of pain stimuli, of the general outline of the experiment, and the exclusion criteria. Exclusion criteria for healthy participants comprise: being under 18 years of age; chronic pain; analphabetism or diagnosed dyslexia; pregnancy; left-handedness; current/history of cardiovascular disease, chronic or acute respiratory disease (e.g., asthma, bronchitis), neurological disease (e.g., epilepsy), and/or psychiatric disorder (e.g., clinical depression, panic/anxiety disorder); uncorrected problems with hearing or vision; having pain in the dominant hand, wrist, elbow or shoulder that may hinder performing the reaching task; presence of implanted electronic medical devices (e.g., cardiac pacemaker); and presence of any other severe medical conditions.

1.2. Due to COVID-19 safety precautions, ask the participant to wash/disinfect his/her hands upon arrival at the lab, and do so yourself. Wear a disposable facemask throughout the duration of the test session, and latex gloves whenever physical contact with the participant is required.

1.3. Use two separate rooms or sections for the experimental setting: one for the participant and the other for the experimenter.

1.4. Use one computer with two separate screens: one computer screen for the experimenter, and one larger television screen for the participant.

1.5. To turn on the robotic arm (e.g., HapticMaster), press the power switch in the front of the robot (specific to this robot). Subsequently, turn on the emergency switch, which may later be used to turn off the robot if necessary.

1.6. Recalibrate the robotic arm before each test day. This is done via a direct application programming interface (API) connection with the robotic arm, and only needs to be done once,

at the beginning of the test day.

1.6.1. To establish the API connection, open an internet browser on the computer, and type in the specific API address of the robotic arm.

1.6.2. On the webpage, select **State** under **HapticMASTER**. Subsequently, press the **Start** button next to **Init** (for initialize).

NOTE: This is the standard calibration procedure for this robot. Different robots may require different calibration procedures.

**1.7. Use a constant current stimulator, which is connected to the computer** (see step 1.4). During the experiment, the pain stimulus is delivered via the experimental script, which runs on the computer. The experiment is programmed using a cross-platform game engine (see **Table of Materials**).

1.7.1. For safety reasons, disable the constant current stimulator output by switching down the orange toggle switch in the upper-right corner of the stimulator's front control panel.

1.7.2. Use the orange toggle switch in the middle of the front control panel to set the output range to x 10 mA.

1.7.3. Use the black rotary knob in the upper-left corner of the front control panel to set the pulse duration to 2 ms (2000  $\mu$ s).

1.7.4. To switch on the constant current stimulator, press the power button in the lower-left corner of the front control panel.

## **2. Obtaining informed consent and screening for exclusion criteria**

2.1. Position the participant approximately 2.5 m from the television screen (see step 1.4), at a comfortable distance (~15 cm) from the handle (sensor) of the robotic arm, in a chair with arm rests (**Figure 1**).

2.2. Screen the participant for exclusion criteria by means of self-report (see step 1.1 for exclusion criteria).

2.3. Inform the participant about the delivery of pain stimuli and of the general outline of the experiment. Also, inform him/her that he/she is free to withdraw participation at any point during the experiment, without any repercussions. **Obtain written informed consent.**

2.4. To minimize physical contact with the participant, ensure that the participant section of the lab includes a table on which exclusion and informed consent forms, as well as a Tablet for questionnaires (see step 6.2) are placed before the participant's arrival. The participant should

be able to access and sign the forms independently using this table.

### **3. Attaching the stimulation electrodes**

NOTE: The pain stimulus is a 2 ms square-wave electrical stimulus delivered cutaneously through two stainless steel bar stimulation electrodes (electrode diameter 8 mm, interelectrode distance 30 mm).

3.1. If the participant is wearing long sleeves, ask him/her to roll up the sleeve on his/her right arm at least 10 cm above his/her elbow.

3.2. Fill the center of the stimulation electrodes with conductive electrolyte gel and plug the electrode cables to the emergency switch, which is connected to the constant current stimulator in the experimenter section of the lab.

3.3. Attach the stimulation electrodes over the triceps tendon of the participant's right arm using a strap. Make sure the strap is neither too tight nor too loose. Once the electrodes have been attached, tell the participant to relax his/her arm.

### **4. Calibrating the pain stimulus**

4.1. Explain the pain calibration procedure and corresponding scale by presenting it on the television screen (see step 1.4).

4.1.1. Clarify to the participant that he/she may choose the stimulus which he/she will receive during the experiment, but explain that for data integrity he/she is asked to select a stimulus that he/she would describe as "significantly painful and demanding some effort to tolerate".

4.1.2. Ask the participant to rate each stimulus on the numerical scale presented on the television screen, ranging from 0–10, where 0 is labeled as "I feel nothing"; 1 as "I feel something, but this is not unpleasant; it is only a sensation" (i.e., detection threshold), 2 as "the stimulus is not yet painful, but is beginning to be unpleasant"; 3 as "the stimulus starts being painful" (i.e. pain threshold); and 10 as "this is the worst pain I can imagine".

4.2. Enable the constant current stimulator output by switching up the orange toggle switch (see step 1.7.1).

4.3. During the pain calibration procedure, manually increase the intensity of the pain stimuli using the rotary knob on the front control panel of the constant current stimulator. The intensity of the pain stimulus can be seen above this knob.

4.3.1. Start with an intensity of 1 mA, and gradually increase the intensity in a stepwise manner, with increases of 1, 2, 3, and 4 mA increments. Use the following order of stimulus presentations in mA: 1, 2, 4, 6, 8, 11, 14, 17, 20, 24, 28, 32, 36, 40, 44, 52, etc.



4.4. To deliver the pain stimuli one stimulus at a time, manually trigger the constant current stimulator by pressing the orange trigger button on the front control panel.

4.4.1. Announce each stimulus to the participant before triggering the constant current stimulator.

4.5. Terminate the calibration procedure once the participant reaches a pain intensity level which he/she would describe as “significantly painful and demanding some effort to tolerate”. Ideally, this should correspond to a 7–8 on the pain calibration rating scale.

4.6. Document the participant’s final pain intensity in mA and his/her pain intensity rating (0–10) and maintain this intensity for the remainder of the experiment.

## 5. Running the experimental task

5.1. Verbally inform the participant that he/she will receive instructions about the robotic arm-reaching paradigm on the television screen in front of him/her, after which he/she will be able to practice the task under the supervision of the experimenter.

5.2. Provide the participant with standardized written instructions of the task on-screen.

5.3. Practice: Via the experimental script, on the television screen, present three arches (T1–T3) situated midway through the movement plane. The easiest arm movement (T1) is paired with no deviation or resistance, the middle arm movement (T2) is paired with moderate deviation and resistance, and the furthest arm movement (T3) is paired with the largest deviation and strongest resistance.

5.3.1. Instruct the participant to use his/her dominant hand to operate the sensor of the robotic arm, represented by a green ball on the television screen, and to move the ball/sensor from a starting point at the lower-left corner of the movement plane, to a target at the upper-left corner of the movement plane.

5.3.2. Instruct the participant that he/she can freely choose which one of the available movement trajectories to perform on each trial.

5.4. Do not administer the pain stimulus (see section 3.1 and step 5.7.6) during the practice phase. However, ensure that the relationship between deviation and resistance (see step 5.3) is in place.

5.5. Provide the participant with verbal feedback while they perform the practice phase.

5.5.1. Ensure the participant does not start moving before the visual and auditory “start signals”, and that he/she releases the robotic arm immediately when the visual and auditory

“stop signals” are presented.

NOTE: Two distinct auditory signals (a “start tone” and a “scoring tone”) and two distinct visual signals (the target and a virtual “traffic light” turning green and red, respectively; **Figure 1**) have been used as start and stop signals. Auditory and visual start signals are presented simultaneously, as are auditory and visual stop signals.

5.5.2. Instruct the participant to provide self-report measures of pain-expectancy and fear of movement-related pain on a continuous rating scale, by scrolling to the left and right on the scale using two respective foot pedals on a triple foot switch. Instruct him/her to confirm his/her answer using a third foot pedal.

NOTE: Present self-report questions on fixed, predetermined trials, for each movement trajectory separately. Ensure, via the experimental script, that the robotic arm is immobilized and remains fixed during the time the participant is responding to the questions.

5.6. At the end of the practice phase, respond to the participant’s questions. Leave the experimental section/room and dim the lights. The participant starts the experiment himself/herself by pressing the ‘Confirm’ foot pedal (see step 5.5.2).

5.7. Acquisition: During avoidance acquisition, similarly to the practice phase, let the participant choose which movement trajectory (T1–T3) to perform on each trial.

5.7.1. During avoidance acquisition, subject the participant to the experimental Response-Outcome (movement trajectory-pain) contingencies, and to the avoidance-costs, i.e., the tradeoff between pain and effort, via the experimental script.

5.7.2. Specifically, if the participant performs the easiest movement trajectory (T1), always present the pain stimulus (100% pain/no deviation or resistance).

5.7.3. If he/she performs the middle movement trajectory (T2), present the pain stimulus with a 50% chance, but ensure he/she will have to exert more effort (moderate deviation and resistance).

5.7.4. If the participant performs the furthest, most effortful movement trajectory (T3), do not present the pain stimulus at all, but ensure that he/she will have to exert the most effort to reach the target (0% pain/largest deviation, strongest resistance).

NOTE: If applicable to the design, a Yoked Group can be used as control. In yoked procedures, each control participant is paired with a participant in the experimental group, such that the two receive the same reinforcement schedules<sup>48</sup>. Thus, in the current paradigm, each Yoked Group participant receives pain stimuli on the same trials as his/her Experimental Group counterpart, regardless of the trajectories he/she chooses. No acquisition of avoidance behavior is expected in the Yoked Group, given the lack of manipulated Response-Outcome (movement trajectory-

pain) contingencies.

5.7.5. Where applicable, save data from each Experimental Group participant on the computer (see section 1.4), and use as reference for the reinforcement schedules of each Yoked (control) Group participant.

5.7.5.1. If using a Yoked procedure (i.e., each control participant is paired with a participant in the experimental group, such that the two receive the same reinforcement schedules<sup>48</sup>), allocate participants to groups using a randomization schedule with the rule that the first participant must be in the Experimental Group. Following this, participants are assigned to either group randomly, as long as, at each point, the number of Experimental Group participants exceeds the number of Yoked Group participants.

5.7.6. On trials with a pain stimulus, present the pain stimulus once two-thirds of the movement has been performed, i.e., once the participant has moved through a trajectory arch. The constant current stimulator is automatically triggered via the experimental script.

5.7.7. Successful trial-completion is indicated by the presentation of visual and auditory stop signals. Subsequently, ensure, via the experimental script, that the robotic arm automatically returns to its starting position where it remains fixed. After 3,000 ms, present the visual and auditory start signals, and the participant can start the next trial.

NOTE: Trial duration differs between trials and participants, due to differences in movement speeds. The number of trials per experimental phase can also change between experiments. We recommend a minimum of 2 x 12 trials for successful acquisition of avoidance. Including the steps described above, the acquisition protocol lasts approximately 45 min.

5.8. Generalization: In the generalization protocol, test for generalization of avoidance after the acquisition phase (see section 5.7).

NOTE: When testing for generalization of avoidance, the on-screen trajectory arches are separated during acquisition, to leave room for the generalization trajectory arches, which are positioned between the acquisition trajectory arches (see **Figure 1**).

5.8.1. On the television screen, present three novel movement trajectories instead of the acquisition trajectories T1–T3. Ensure that these “generalization trajectories” (G1–G3) are located adjacent to the acquisition trajectories. Specifically, G1 is situated between T1 and T2, G2 between T2 and T3, and G3 to the right of T3 (see **Figure 1**). Do not pair generalization trajectories with the pain stimulus.

NOTE: Including the steps described above, with a generalization phase of 3 x 12 trials, the avoidance generalization protocol lasts approximately 1.5 h. A Yoked Group<sup>48</sup> is required for testing generalization of avoidance (see step 5.7.5). However, different controls can be used depending on the specific research question (cf. context modulation of avoidance in a within-

subjects design<sup>24</sup>).

5.9. Extinction with response prevention (RPE): In the RPE protocol, after the acquisition phase (see section 5.7), provide the participants with standardized written instructions stating that in the upcoming phase they are only allowed to perform T1.

5.9.1. During the RPE phase, via the experimental script, visually (e.g., blocking the trajectory arches with a gate) and/or haptically (e.g., block participant's arm movement with a haptic wall) block T2 and T3, so that only T1 is available. T1 is not paired with the pain stimulus during this phase. Including the steps described above, with an RPE phase of 4 x 12 trials, this session lasts approximately 60 min.

5.10. Test of spontaneous recovery: For testing spontaneous recovery of avoidance, administer a 2-day protocol with 24 h  $\pm$  3 h in between sessions. On day 1, administer the RPE protocol (see section 5.9).

5.10.1. On day 2, attach the stimulation electrodes (see section 3). Provide brief on-screen refresher instructions of the task. Do not include any information regarding the pain stimuli.

5.10.2. Present the three acquisition trajectories (T1–T3, cf. acquisition phase, see section 5.7), in the absence of the pain stimulus. Including the post-experimental questionnaire (see section 6.2), and a spontaneous recovery phase of 4 x 12 trials, this session lasts approximately 45 min.

NOTE: To prevent reinstatement of fear (i.e., return of fear following unexpected encounters with the pain stimulus<sup>42</sup>; see discussion), do not recalibrate the pain stimulus on day 2.

## 6. Concluding the experiment

6.1. Once the participant has completed the experiment, detach the stimulation electrodes.

6.2. Provide the participant with a Tablet located on the table in the participant's section of the lab (see section 2.4), for responding to an exit questionnaire inquiring about the intensity and unpleasantness of the pain stimulus and avoidance-costs, as well as awareness of the experimental Response-Outcome (movement trajectory-pain) contingencies.

6.3. While the participant completes the psychological trait questionnaires, clean off the electrolyte gel from the stimulation electrodes.

6.4. Once the participant has finished completing the psychological trait questionnaires, provide him/her with a debriefing and reimbursement.

6.5. Clean the stimulation electrodes thoroughly with a disinfectant solution appropriate for cleaning medical instruments; remove all the gel inside and around the electrodes. Dry the electrodes with soft tissue paper. Clean the sensor of the robotic arm with disinfectant wipes or

spray.

## REPRESENTATIVE RESULTS:

Acquisition of avoidance behavior is demonstrated by participants avoiding more (showing larger maximal deviations from the shortest trajectory) at the end of an acquisition phase, compared to the beginning of the acquisition phase (**Figure 2**, indicated by A)<sup>20</sup>, or as compared to a Yoked control group (**Figure 3**)<sup>23,48</sup>.

Acquisition of fear and pain-expectancy is evidenced by participants reporting lower fear for T3 compared to T1 and T2, and expecting the pain stimulus less during T3 compared to T1 and T2<sup>20</sup>. Differential self-reports between T1 and T3 are of primary interest, because T2 is ambiguous. Non-differential self-reports between T1 and T2 have also been found, with both differing from T3<sup>23</sup> (**Figure 4A**, **Figure 5A**, **Figure 6A**, and **Figure 7A**).

Acquisition is a prerequisite for generalization. Generalization of avoidance behavior is indicated by participants in the Experimental Group avoiding (deviating) more than the Yoked Group<sup>48</sup> at the beginning of the generalization phase. Given that generalization is tested in the absence of pain stimuli, avoidance behavior may decrease throughout the generalization phase. Furthermore, a general decrease in avoidance behavior between the end of the acquisition phase and the beginning of the generalization phase (generalization decrement) can be expected. This is a result of the introduction of novel movement trajectories, which may constitute a context-switch<sup>49,50</sup>. In a previous study, we did not find generalization of avoidance, possibly due to specific parameters of the paradigm<sup>23</sup>.

Generalization of fear and pain-expectancy is indicated by a similar pattern to that of the acquisition phase, i.e., by participants in the Experimental Group reporting lower fear to G3 compared to G1 and G2, and expecting the pain stimulus less during G3 compared to G1 and G2, at the beginning of the generalization phase. As in the acquisition phase, differential self-reports between G1 and G3 are of primary interest (**Figure 4B** and **Figure 5B**). Non-differential self-reports between G1 and G2 have been reported so far, with both differing from G3<sup>23</sup>. Furthermore, given that generalization is tested in the absence of pain stimuli, participants may report less fear and pain-expectancies throughout the generalization phase. Furthermore, a general decrease in fear and pain-expectancies toward the novel generalization trajectories, compared to the acquisition trajectories (generalization decrement) can be expected. In a previous study, we found generalization of fear and pain-expectancies, despite avoidance not generalizing<sup>23</sup>.

Acquisition is a prerequisite for extinction. During extinction of avoidance behavior with response prevention, participants are only allowed to perform the previously painful movement trajectory (T1), whereas the other two trajectories (T2 and T3) are prohibited. Therefore, given that participants only have the option of performing T1, and thus the observed data pattern does not reflect their own choices, i.e., genuine extinction of avoidance behavior, extinction of avoidance is not included in the analyses (**Figure 2**).

Extinction of fear and pain-expectancies is evident when participants report lower fear for T1 and expect the pain stimulus less when performing T1, at the end of the RPE phase, compared to the end of the acquisition phase. (**Figure 6B** and **Figure 7B**).

Extinction of self-report measures is a prerequisite for spontaneous recovery. Spontaneous recovery of avoidance behavior is indicated by participants avoiding more at the beginning of the test of spontaneous recovery, compared to the end of the RPE phase (**Figure 2B**).

Spontaneous recovery of fear and pain-expectancy is indicated by participants reporting higher fear and pain-expectancy for T1, during the beginning of the test of spontaneous recovery, compared to the end of the RPE phase (**Figure 6C** and **Figure 7C**).

#### **FIGURE AND TABLE LEGENDS:**

**Figure 1: The experimental set-up and outlook of the experimental task.** The participant is seated in front of the television screen, at reaching distance from the sensor of the robotic arm. The electrodes are placed on the triceps tendon of the right arm, where the pain stimuli are delivered (red circle), and the triple foot switch is used to give fear of movement-related pain and pain-expectancy ratings. The acquisition phase of the experimental task is shown on the television screen and magnified in the white box. The ball is situated in the lower-left corner, and the target in the upper-left corner (green arch). T1–T3 are situated midway through the movement-plane, from left to right, respectively. Spaces are left between T1–T3 specifically in avoidance generalization protocols, in order to leave room for the subsequent generalization trajectory arches (G1–G3).

**Figure 2: Representative data of avoidance behavior during the acquisition, extinction with response prevention, and test of spontaneous recovery phases<sup>22</sup>.** Mean maximum deviation (in centimeters) from the shortest trajectory to the target during acquisition (ACQ1–2), extinction with response prevention (RPE1–4), and spontaneous recovery (TEST1–2). Note that, participants are only allowed to perform the shortest trajectory (T1) during the RPE phase. Error bars represent standard error of the mean (SEM). Data in this figure is from 30 participants (9 men, 21 women; mean age = 21.90)<sup>22</sup>. This figure is modified with permission from ref.<sup>22</sup>.

**Figure 3: Representative data of avoidance behavior during the acquisition phase<sup>20</sup>.** Relative proportions of movements between the Experimental and Yoked<sup>48</sup> Groups, within the experimental movement plane. Top, yellow patterns represent movements predominantly performed by the Experimental Group, and bottom, blue patterns represent movements predominantly performed by the Yoked Group. “Direction from starting point to target” indicates the shortest possible trajectory from the starting point to the target. “Horizontal deviation” indicates deviation from the shortest possible movement trajectory. Data in this figure is from 50 participants (36 men, 14 women; mean age = 24.92)<sup>20</sup>. This figure is reprinted with permission from ref.<sup>20</sup>.

**Figure 4: Representative data of fear of movement-related pain during the acquisition and**

**generalization phases<sup>23</sup>.** Mean fear of movement-related pain toward the acquisition trajectories in the Experimental and Yoked<sup>48</sup> groups during the acquisition blocks (ACQ1–3), and generalization blocks (GEN1–3). Note that during the acquisition phase, self-reports are provided for trajectories T1–T3 and during the generalization phase, for G1–G3. Error bars represent SEM. Data in this figure is from 64 participants (32 per group; Experimental Group: 10 men, 22 women, mean age = 22.88; Yoked Group: 12 men, 20 women; mean age = 23.44)<sup>23</sup>. This figure is modified with permission from ref.<sup>23</sup>.

**Figure 5: Representative data of pain-expectancy during the acquisition and generalization phases<sup>23</sup>.** Mean pain-expectancy toward the acquisition trajectories in the Experimental and Yoked<sup>48</sup> groups during the acquisition blocks (ACQ1–3), and generalization blocks (GEN1–3). Note that during the acquisition phase, self-reports are provided for trajectories T1–T3 and during the generalization phase, for G1–G3. Error bars represent SEM. Data in this figure is from 64 participants (32 per group; Experimental Group: 10 men, 22 women, mean age = 22.88; Yoked Group: 12 men, 20 women; mean age = 23.44)<sup>23</sup>. This figure is modified with permission from ref.<sup>23</sup>.

**Figure 6: Representative data of fear of movement-related pain during the acquisition, extinction with response prevention, and test of spontaneous recovery phases<sup>22</sup>.** Mean fear of movement-related pain toward the different trajectories (T1–T3) during acquisition (ACQ1–2), extinction with response prevention (RPE1–4), and spontaneous recovery (TEST1–2). Error bars represent SEM. Data in this figure is from 30 participants (9 men, 21 women; mean age = 21.90)<sup>22</sup>. This figure is modified with permission from ref.<sup>22</sup>.

**Figure 7: Representative data of pain-expectancy during the acquisition, extinction with response prevention, and test of spontaneous recovery phases<sup>22</sup>.** Mean pain-expectancy toward the different trajectories (T1–T3) during acquisition (ACQ1–2), extinction with response prevention (RPE1–4), and spontaneous recovery (TEST1–2). Error bars represent SEM. Data in this figure is from 30 participants (9 men, 21 women; mean age = 21.90)<sup>22</sup>. This figure is modified with permission from ref.<sup>22</sup>.

## **DISCUSSION:**

Given the key role of avoidance in chronic pain disability<sup>1-5</sup>, and the limitations faced by traditional avoidance paradigms<sup>19</sup>, there is a need for methods to investigate (pain-related) avoidance behavior. The robotic arm-reaching paradigm presented here addresses a number of these limitations. We have employed the paradigm in a series of studies, which have consistently demonstrated acquisition of avoidance, and these effects have extended to our self-report measures of pain-expectancy and fear of movement-related pain<sup>20,22-24</sup>. However, we have also found dissociations between fear and avoidance<sup>23</sup> that may be genuine and informative, suggesting that the two do not always share a one-to-one relationship<sup>5,12,43-45</sup>. Additionally, the paradigm presents multiple opportunities for investigating different aspects of avoidance behavior, such as generalization<sup>23</sup>, extinction with response prevention<sup>22</sup>, and post-extinction return of avoidance<sup>22</sup>, as described in the current manuscript.

The current method offers many advantages over traditional avoidance paradigms. First, instead of performing an experimenter-instructed avoidance response, participants in the robotic arm-reaching paradigm acquire avoidance behavior themselves. The paradigm thus better models real life situations, where avoidance behavior emerges naturally as a response to pain<sup>9</sup>. Understanding the processes underlying how avoidance is acquired, can provide insight into how avoidance can subsequently become pathological, and inspire ways in which these processes can be directly targeted during treatment<sup>51</sup>. For example, methodological modifications, such as manipulating experimental reward to increase approach and reduce avoidance tendencies<sup>52,53</sup>, can allow closer investigation of the behavioral and cognitive processes underlying the acquisition of maladaptive avoidance. With regard to this, the acquisition of avoidance demonstrated with the robotic arm-reaching paradigm can be easily applied to investigate excessive generalization of avoidance to safe stimuli<sup>23</sup>. A second advantage is that the continuous nature of the avoidance response in the current paradigm allows us to examine for whom avoidance might become excessive, as it provides more detailed data than a dichotomous measure. This increased detail in the data allows heightened sensitivity for picking up individual differences, by means of comparing deviation scores between participants. Such a continuous measure is also more ecologically valid, as avoidance in real life can occur at varying degrees. For example, pain-related avoidance can range from subtle (e.g., postural changes or changed breathing when performing a movement) to complete avoidance (e.g., being bedridden). Furthermore, in addition to incorporating a cost to avoidance, the current avoidance response demands some physical effort, meaning that costs increase with time throughout the task. This accurately models real life, where avoidance can become increasingly costly for the individual over a period of time<sup>9</sup>. For example, prolonged or regular absenteeism becomes costly from a financial point of view<sup>54,55</sup>. Finally, given the low cost associated with the previously used instructed button-press response, it is hard to disentangle whether participants in traditional avoidance paradigms avoid due to genuine fear, or simply due to automatic following of task instructions. In contrast, given the high-effort and uninstructed nature of the avoidance response in the current paradigm, it seems likely that any avoidance behavior observed models' genuine self-motivated avoidance.

In addition to addressing limitations of previous methodologies, the robotic arm-reaching paradigm offers many opportunities for investigating further aspects of avoidance behavior, as demonstrated in the current manuscript by the avoidance generalization and RPE protocols. It is noteworthy that, we previously observed a dissociation between self-reports and avoidance, with fear and pain-expectancies generalizing to the novel movement trajectories, while avoidance did not. There are several plausible explanations for the observed discrepancy between fear and avoidance<sup>23</sup>, which we are currently investigating. However, this dissociation may also be a genuine and informative finding, which in fact adds to previous literature suggesting that fear and avoidance do not always occur in synchrony<sup>5,12,43-45</sup>, especially when the avoidance response is costly<sup>56,57</sup>. This finding emphasizes the importance of experimentally investigating avoidance behavior itself, as distinct processes most likely contribute to different aspects of fear learning<sup>58,59</sup>, and these processes would be difficult to uncover by solely measuring self-reports and psychophysiological indices of fear. In addition to generalization of avoidance to novel movements, the robotic arm-reaching paradigm has also been applied to



study generalization of avoidance to novel contexts<sup>24</sup>. So far, context-based generalization of avoidance has been investigated using different colored screens as contextual cues<sup>24</sup>. However, Virtual Reality (VR) could be easily implemented with the current paradigm to increase the ecological validity of the experimental contexts. VR could also be applied to study category-based avoidance generalization, such as generalization of avoidance between different action categories<sup>60,61</sup>. Additional adaptations may also be implemented in the RPE protocol. Besides using a 2-day protocol for the investigation of spontaneous recovery<sup>22</sup>, we have also investigated whether pain-related avoidance behavior returns not with the passage of time, but after unexpected encounters with the pain stimulus (reinstatement)<sup>42</sup> in a 1-day protocol. Furthermore, to examine the proprioceptive underpinnings of pain-related avoidance behavior more closely, the paradigm can be modified to include less or no visual information. This is something we are currently investigating in our lab. Finally, given that physically moving away from an aversive stimulus represents a species-specific defensive response<sup>62</sup>, not unique to fear and pain, this type of operationalization of avoidance permits investigation of many different types of avoidance as well. For example, the paradigm can potentially be applied to examine, not only avoidance of painful stimuli, but also avoidance of other types of aversive stimuli, such as those inducing disgust or embarrassment<sup>63,64</sup>.

The described protocol can also be easily extended to include psychophysiological fear measures. Although not described here, we have incorporated eye-blink startle responses, as well as electroencephalography (EEG), into the robotic arm-reaching paradigm. The eye-blink startle measure offers a fear-specific measure of reflexive defensive responses<sup>65,66</sup>, which can provide additional insight into the mechanisms underlying avoidance behavior and its relationship to fear, whereas implementing EEG to the paradigm enables investigation into specific neural correlates of avoidance behavior<sup>67</sup>. Additionally, the skin-conductance response (SCR)<sup>68</sup>, as well as online self-report ratings of relief-pleasantness<sup>69,70</sup> could be included as measures of relief<sup>71</sup>. SCRs have been previously found to correlate with relief<sup>72</sup>—a proposed reinforcer of avoidance<sup>69,70</sup> given its inherent positive valence in response to the omission of negative events<sup>73,74</sup>. Finally, heart rate (HR) and heart rate variability (HRV) are easily implementable measures that have been linked to multiple aversive emotions associated with avoidance, such as fear, disgust, and embarrassment<sup>75</sup>.

Despite its strengths, we acknowledge that the robotic arm-reaching paradigm also has its limitations. For example, the paradigm is not easily transferable to other laboratories, as the equipment used in, and required for the paradigm (e.g., robot and constant current stimulator) are expensive, limiting the widespread use of the paradigm and its implementation by other laboratories. However, note that similar robots, which are relatively common in rehabilitation clinics, can be programmed in the same way, and more affordable constant current stimulators are available as well. It is also noteworthy that, in the current method the discriminative stimulus ( $S^D$ ) and the instrumental response are intertwined. This is in contrast to traditional avoidance paradigms, where fear is first acquired towards the CS during the Pavlovian phase, and avoidance is examined in a subsequent instrumental phase. However, the temporal relationship between fear and avoidance is not strictly unidirectional<sup>51</sup>. Although the current paradigm allows closer investigation of the temporal dynamics of avoidance-emergence in relation to fear-emergence,

the measures we have employed so far do not allow us to accurately disentangle the temporal dynamics of fear and avoidance. Currently, avoidance behavior in the paradigm can be examined at a trial-by-trial basis, whereas fear and expectancy ratings are only collected at discrete, specific time points during the task, to not interfere with task flow. However, to allow precise comparisons between fear and avoidance, a future study could use a more continuous measure of fear, for example, by means of a dial<sup>76</sup>, single-sensor EEG<sup>77</sup>, or fear-potentiated startle, to allow a detailed understanding of fear-emergence towards the different trajectories, in relation to avoidance. Finally, only electrocutaneous stimuli have so far been used in the robotic arm-reaching paradigm as pain stimuli, for reasons of consistency and comparability with previous studies of pain-related fear<sup>78-80</sup>. However, electrocutaneous stimuli may not fully mimic the more tonic pain experienced by chronic pain patients, given that they produce a relatively phasic, uncommon, and unnatural pain experience<sup>81</sup>. Other pain-induction methods, such as ischemic stimulation<sup>82</sup> and exercise-induced (e.g., delayed onset muscle soreness, DOMS)<sup>83,84</sup> pain have been argued to be better experimental analogues of musculoskeletal pain, given their natural and endogenous nature<sup>81</sup>. These pain-induction methods could be employed in the robotic arm-reaching paradigm in the future. Despite these limitations, the ability of the current paradigm to consistently demonstrate acquisition of fear and avoidance using such entwined S<sup>D</sup>s and R<sup>s</sup> is in itself interesting and novel. Furthermore, we believe that the robotic arm-reaching paradigm can in and of itself further the discussion of the need for more ecologically valid avoidance paradigms<sup>19</sup>. In addition, the paradigm has the potential to pave the way for developing better avoidance paradigms in general, by providing an example of how problems in the field can be tackled in an innovative manner.

In conclusion, the robotic arm-reaching paradigm offers a promising route to improving the ecological validity of investigations into avoidance behavior, and to furthering our understanding of the underlying processes. Using the paradigm, we have already obtained interesting results, which may not have been uncovered by solely assessing passive correlates of fear such as verbal reports and physiological arousal. Yet, extensions to the paradigm have provided some inconclusive results, which require further investigation and refinement of the procedure. Despite this, the robotic arm-reaching paradigm is a huge leap forward with respect to ecological validity in the paradigms used to study avoidance behavior.

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The authors have nothing to disclose.

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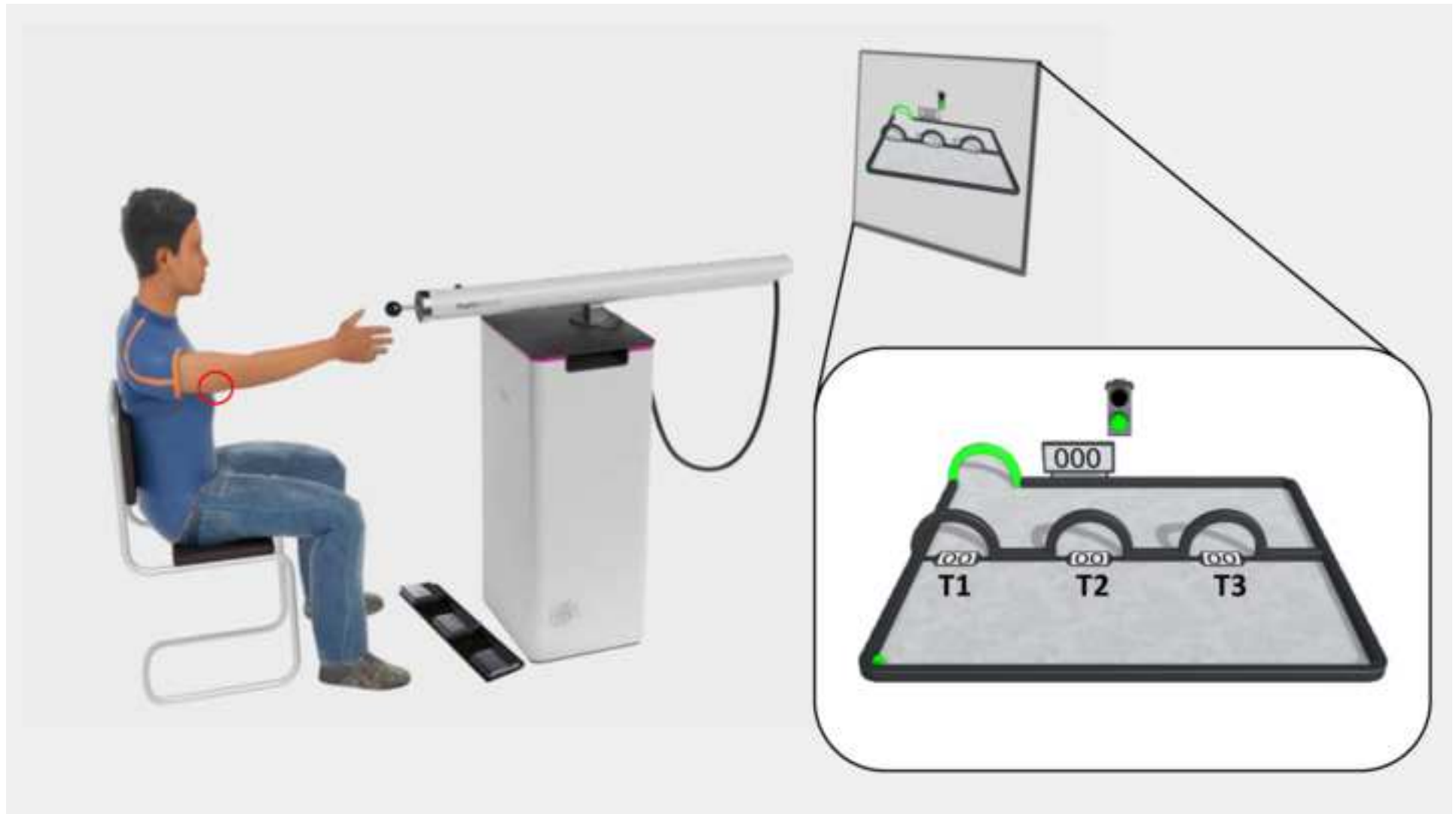
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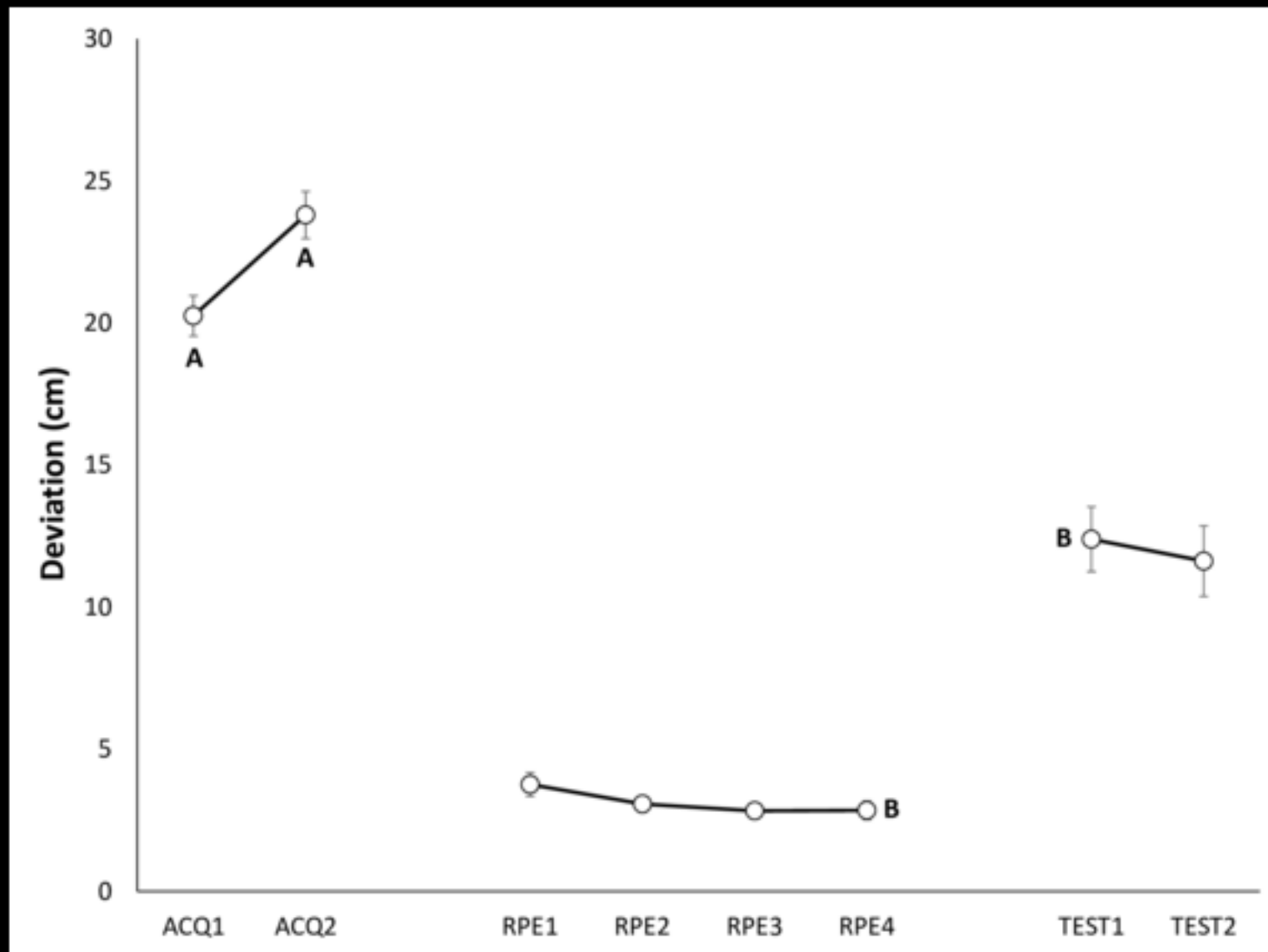
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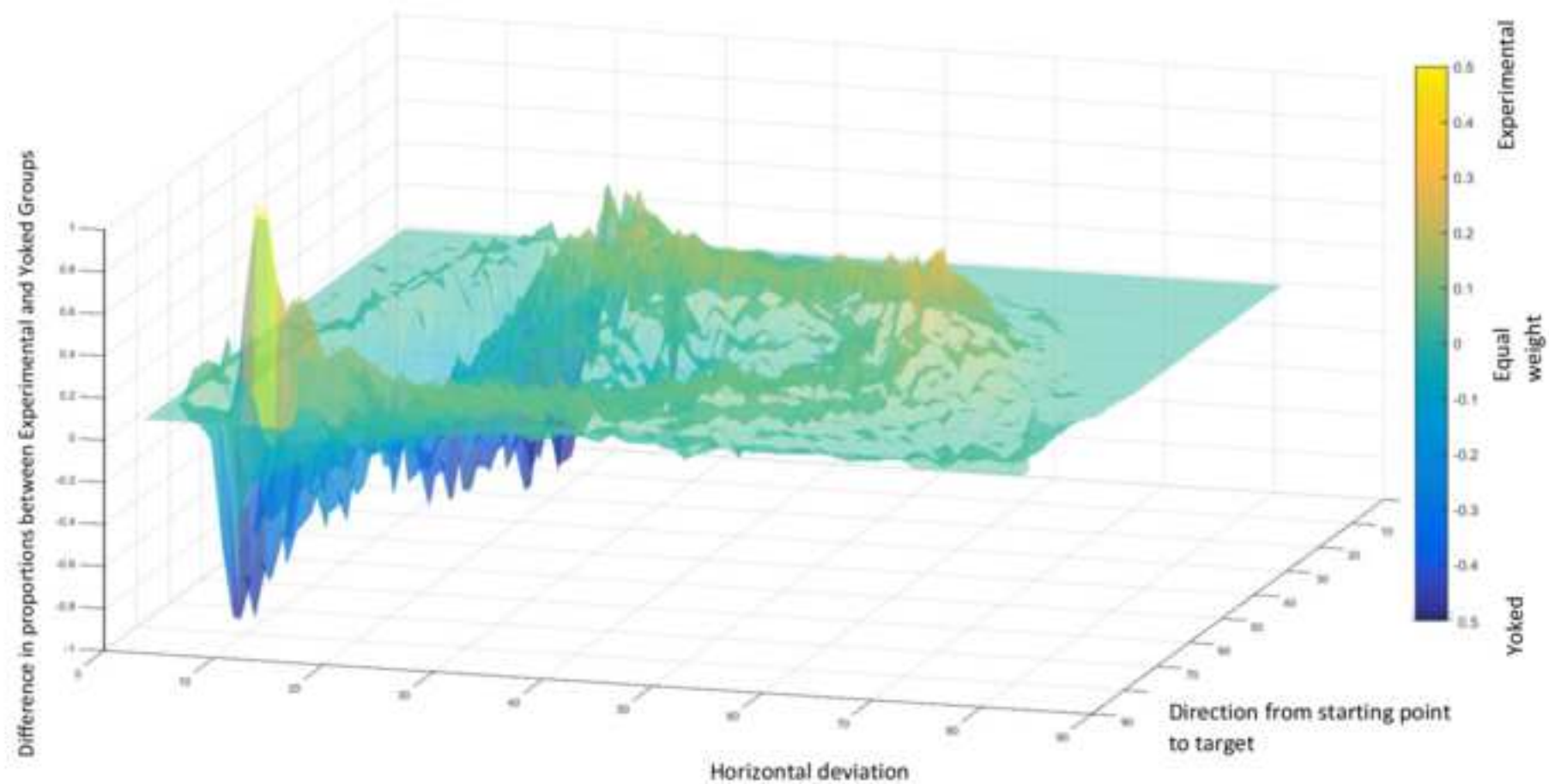
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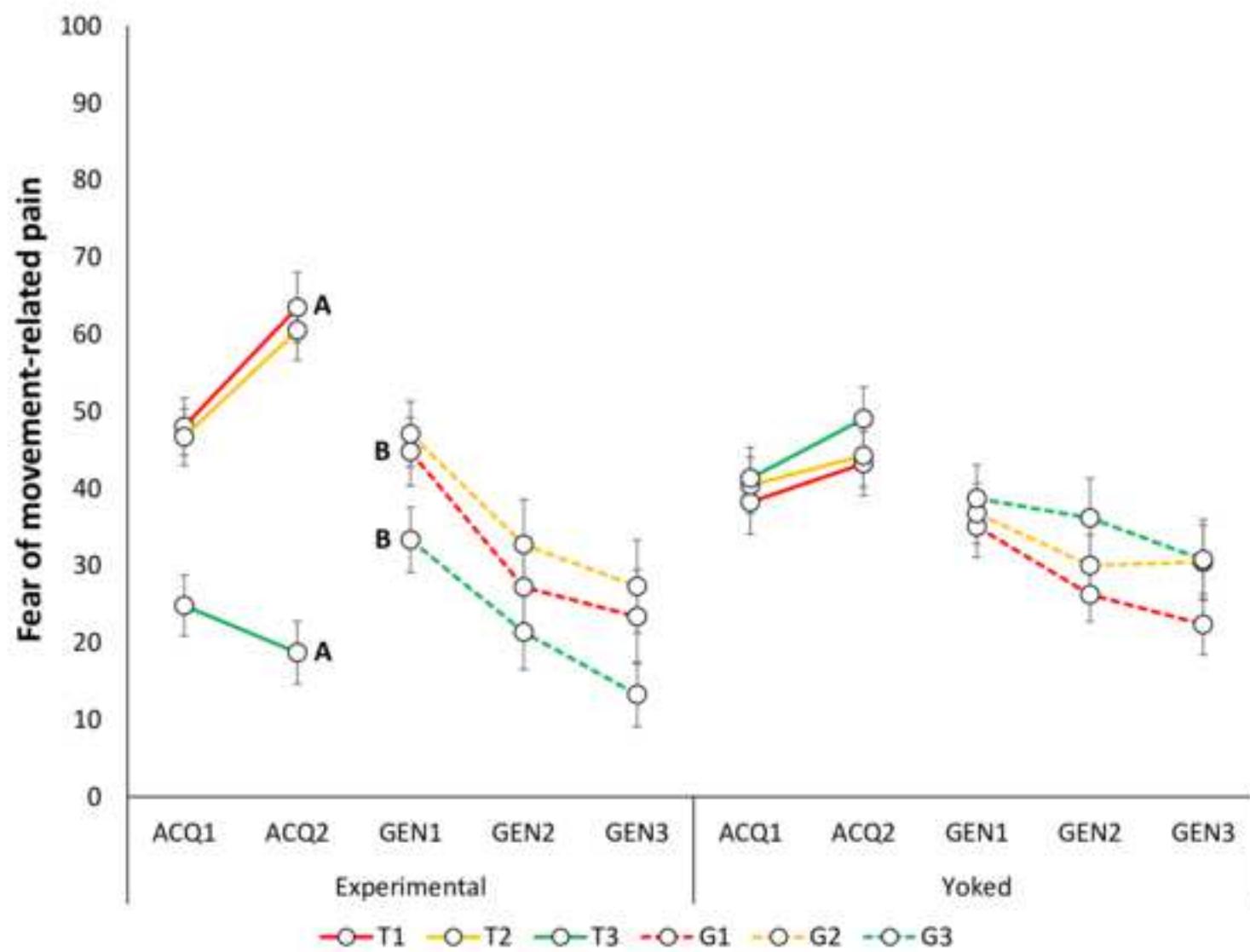
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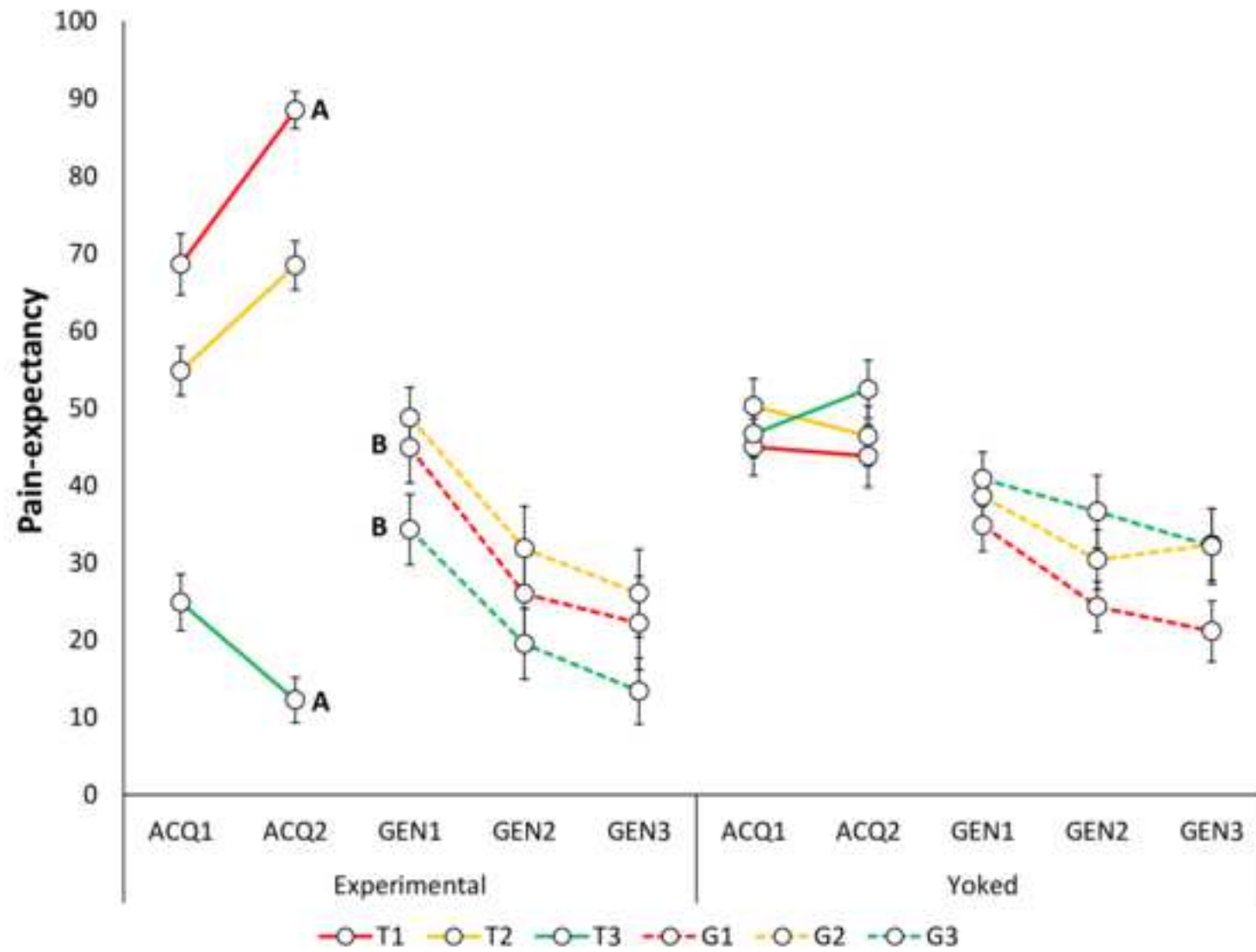


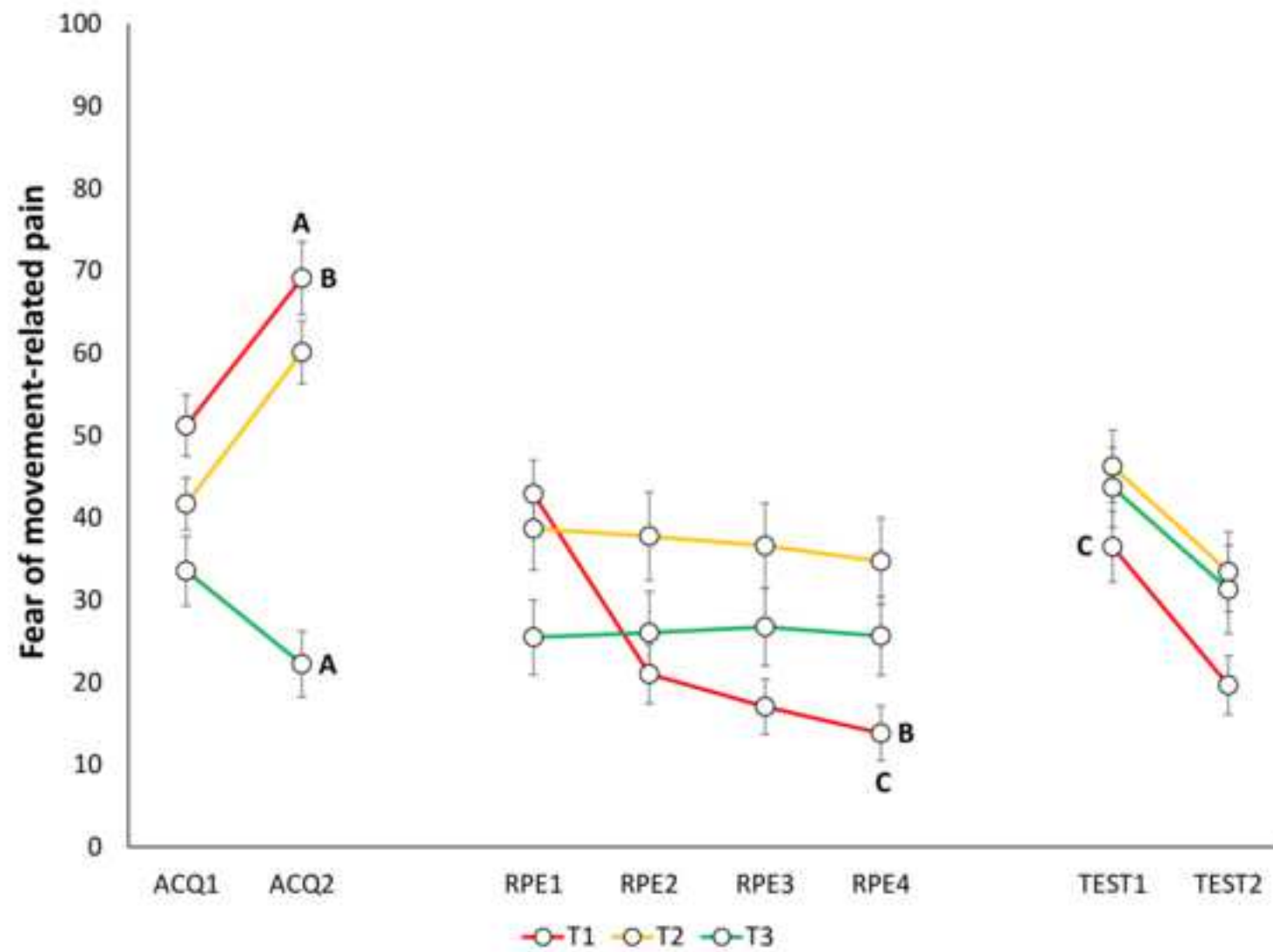


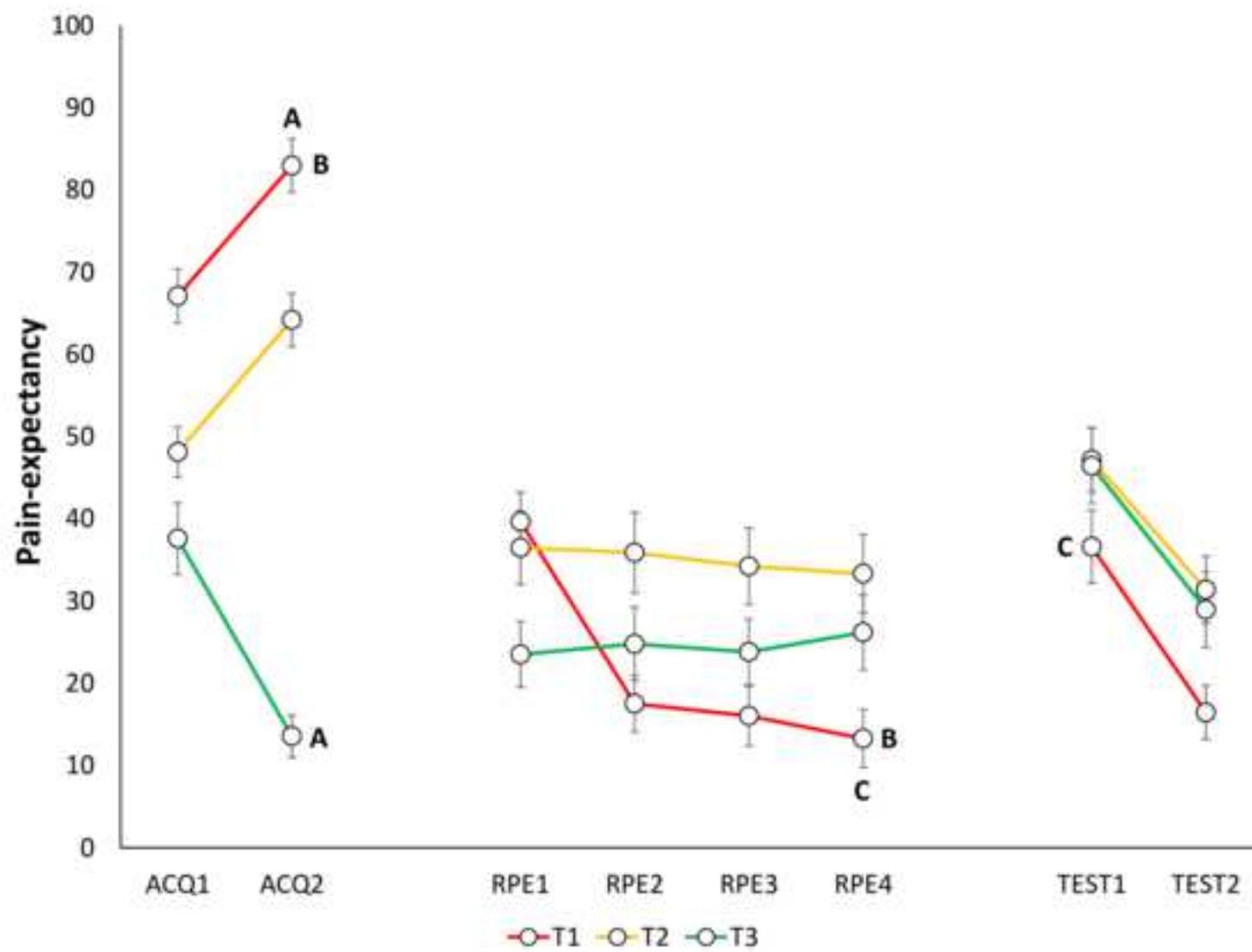












Name of Material/ Equipment	Company	Catalog Number	Comments/Description
1 computer and computer screen	Intel Corporation	64-bit Intel Core	Running the experimental script
40 inch LCD screen	Samsung Group		Presenting the experimental script
Blender 2.79	Blender Foundation		3D graphics software for programming the graphics of the experiment
C#			Programming language used to program the experimental task
Conductive gel	Reckitt Benckiser	K-Y Gel	Facilitates conduction from the skin to the stimulation electrodes
Constant current stimulator	Digitimer Ltd	DS7A	Generates electrical stimulation
HapticMaster	Motekforce Link		Robotic arm
Matlab	MathWorks		For writing scripts for participant randomization schedule, and for extracting maximum deviation from shortest trajectory per trial
Qualtrics	Qualtrics		Web survey tool for psychological questionnaires
Rstudio	Rstudio Inc.		Statistical analyses
Sekusept Plus	Ecolab		Disinfectant solution for cleaning medical instruments
Stimulation electrodes	Digitimer Ltd	Bar stimulating electrode	Two reusable stainless steel disk electrodes; 8mm diameter with 30mm spacing
Tablet	AsusTek Computer Inc.	ASUS ZenPad 8.0	For providing responses to psychological trait questionnaires
Triple foot switch	Scythe	USB-3FS-2	For providing self-report measures on VAS scale
Unity 2017	Unity Technologies		Cross-platform game engine for writing the experimental script including presentations of electrocutaneous stimuli

**2020-07-27**

Dear editor of Journal of Visualized Experiments,

Thank you for your action letter and the opportunity to resubmit our manuscript with revised title “Investigating pain-related avoidance behavior using a robotic arm-reaching paradigm”.

My co-authors and I are pleased that the procedure described in our manuscript has been considered an interesting possible addition to Journal of Visualized Experiments. We would like to thank you and the anonymous reviewers for the elaborate reading, and helpful comments and suggestions to improve our manuscript. We have revised our manuscript accordingly. Attached to this letter, we give a detailed description of how we addressed each of the issues raised by the reviewers. The corrections are indicated using track changes in the manuscript.

We believe that this manuscript has been considerably improved due to the changes made based on recommendations from the reviewers and hope that it merits acceptance in *Journal of Visualized Experiments*. Thank you for your consideration.

Sincerely,

On behalf of all co-authors,

Ann Meulders

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## Revision manuscript JoVE61717 – Rebuttal letter

Investigating pain-related avoidance behavior using a robotic arm-reaching paradigm

*Eveliina Glogan, Rena Gatzounis, Kristof Vandael, Mathijs Franssen, Johan W.S. Vlaeyen, & Ann Meulders*

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### **Editorial comments:**

You will find Editorial comments and Peer-Review comments listed below. Please read this entire email before making edits to your manuscript.

NOTE: Please include a line-by-line response to each of the editorial and reviewer comments in the form of a letter along with the resubmission.

*We have addressed all Peer-Review comments.*

- Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammatical errors.

*We have thoroughly proofread the manuscript.*

- **Protocol Detail:** Please note that your protocol will be used to generate the script for the video, and must contain everything that you would like shown in the video. **Please ensure that all specific details (e.g. button clicks for software actions, numerical values for settings, etc) have been added to your protocol steps.** There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.

*We believe the protocol section of our manuscript includes all relevant information.*

- **Discussion:** JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please ensure that the discussion covers the following in detail and in paragraph form (3-6 paragraphs): 1) modifications and troubleshooting, 2) limitations of the technique, 3) significance with respect to existing methods, 4) future applications and 5) critical steps within the protocol.

*We believe our discussion covers the relevant points.*

- **References:** Please spell out journal names.

*We have edited the references accordingly.*

- If your figures and tables are original and not published previously or you have already obtained figure permissions, please ignore this comment. If you are re-using figures from a

previous publication, you must obtain explicit permission to re-use the figure from the previous publisher (this can be in the form of a letter from an editor or a link to the editorial policies that allows you to re-publish the figure). Please upload the text of the re-print permission (may be copied and pasted from an email/website) as a Word document to the Editorial Manager site in the "Supplemental files (as requested by JoVE)" section. Please also cite the figure appropriately in the figure legend, i.e. "This figure has been modified from [citation]."

*We provide official licenses for, and cite all re-used material.*

### **Reviewers' comments:**

#### **Reviewer #1:**

##### Manuscript Summary:

In this study, the authors proposed a novel paradigm to investigate pain-related avoidance. The manuscript narrative is well conducted to describe current methods to investigate pain-related avoidance and its limitations, as well as the need of a novel and more ecological paradigm to investigate pain-related avoidance. The protocol is well described and there is substantial work conducted by the research group using the novel paradigm.

*We thank the reviewer for his/her overall positive assessment of our manuscript.*

##### Major Concerns:

There are no major concerns in my opinion.

##### Minor Concerns:

One minor concern is, indeed, the fact that the paradigm is not easily accessible to other laboratories. Although this might be a strong barrier for its massification and implementation by other laboratories, I reckon that this should not interfere with the publication of the paradigm protocol.

*We agree that this is a considerable limitation to the method, and have added text to stress this point to lines 508-512 on page 11 of the manuscript: "For example, the paradigm is not easily transferable to other laboratories, as the equipment used in, and required for the paradigm (e.g. robot and constant current stimulator) are expensive, limiting the widespread use of the paradigm and its implementation by other laboratories. However, note that similar robots which are relatively common in rehabilitation clinics, can be programmed in a similar way and more affordable constant current stimulators are available as well."*

#### **Reviewer #2:**

##### Manuscript Summary:

This is a well-written manuscript describing an innovative paradigm used to investigate fear and avoidance of pain. The background literature and key concepts are well defined and clearly laid out. The strengths and limitations of the protocol are described, and the protocol has much to commend it.

*We thank the reviewer for his/her overall positive assessment of our manuscript.*

Major Concerns:

None

Minor Concerns:

The equipment is rather expensive; not just the robot, but even the stimulator. Given that many labs won't have access to the same technical equipment and may use other brands of stimulators, the sequence of shock mA levels given should be prefaced as applying only to the Digitimer equipment.

*We thank the reviewer for pointing out this limitation. We did not add this information before due to the "Instructions to authors" stating that company brand names should be cited in the Materials table only. However, given that the calibration procedure is indeed specific to the Digitimer constant current stimulator, we have specified the type of stimulator in the description of the calibration procedure on lines 234-235 on page 5: "Use the following order of stimulus presentations in mA (sequence is specific to Digitimer constant current stimulators): 1, 2, 4, 6, 8, 11, 14, 17, 20, 24, 28, 32, 36, 40, 44, 48, 52 etc." See also reply to Reviewer #1.*

**Reviewer #3:**

This is very detailed description of the interesting methodology to study pain behaviour in the lab setting. I very like the whole research line, as indeed, it has led to the confirmation of some behavioral concepts previously studied in animals, e.g. acquisition, stimulus generalization, extinction. Authors developed that methodology in the seminal work by Meulders et al. from 2016 and are still continuing exploring pain mechanisms based on behavioral principles. I have some comments that authors should consider prior to publication and recording the video for the JoVE journal.

*We thank the reviewer for his/her overall positive assessment of our manuscript.*

1. A general comment on this manuscript relates to the target group of readers: Do authors want they work to be adopted by researchers from other fields? If so, then the introduction and the way concepts are written should be less „behavioral". Probably, starting from the operant conditioning in a real-life situation (not related to pain) would be a good commencement.

*We agree that expanding the use of the paradigm to other fields is an interesting prospect. However, the paradigm is specifically developed for investigating fear and avoidance in the context of movement, which is particularly relevant to musculoskeletal pain. Furthermore, all experiments performed with the paradigm so far have investigated pain-related avoidance. Therefore, given that the focus of the manuscript should be on the specific method and the results it has produced in the past, we have not deemed it necessary to give an overview of how the paradigm could be of relevance for the broader avoidance literature.*

*However, as we mention on lines 493-496 on page 11 in the discussion of the manuscript, “given that physically moving away from an aversive stimulus represents a species-specific defensive response<sup>2</sup>, not unique to fear and pain, this type of operationalization of avoidance permits investigation of many different types of avoidance as well. For example, the paradigm can potentially be applied to examine, not only avoidance of painful stimuli, but also avoidance of other types of aversive stimuli, such as those inducing disgust or embarrassment.<sup>3,4</sup>”*

*We do not entirely understand the reviewer’s suggestion to make the introduction less “behavioral”, as the described method is in essence a paradigm for conditioning avoidance behavior. Making the introduction and manuscript less behavioral, would only be possible by moving away from the avoidance aspect. Furthermore, starting the manuscript with a real-life operant conditioning situation would also not make the introduction less behavioral. We apologize to the reviewer for not being more responsive to this comment.*

2. Title: Is it a novel procedure? Authors did plenty of studies (starting from 2016) using this methodology so it is not novel anymore. „Novel“ should be deleted.

*We have deleted the word “novel” from the title.*

3. Keywords: What is recommended is to avoid redundancy in terms used in titles and keywords. Databases always are searched according to the words in the title. Keywords can be used as an additional chance for paper to be found by others while searching engines. I would consider adding other terms, and delete redundant.

*We have updated the keywords to: “Chronic pain, fear, acquisition, generalization, extinction, response-prevention, associative learning, instrumental conditioning, robotic arm-reaching paradigm”*

4. Introduction: -86: if authors introduce the classical conditioning terminology they should complete operative definitions: UR is missing. Citations to reference [14] (BF Skinner's book) is not specific, please, cite his original work and others' relevant.

*We have changed the text on lines 84-88 on page 2 to: “During differential Pavlovian conditioning, a neutral stimulus (conditioned stimulus, CS+; e.g. a circle) is paired with an intrinsically aversive stimulus (unconditioned stimulus, US; e.g. an electric shock), which naturally produces unconditioned responses (URs, e.g. fear). A second control stimulus is never paired with the US (CS-; e.g. a triangle). Following repeated pairings of the CSs with the US, the CS+ will elicit fear in its own right (conditioned responses, CRs) in the absence of the US. The CS- comes to signal safety, and will not trigger CRs.”*

*Furthermore, we have specified the references to Skinner’s “Science and human behavior”, by citing the specific chapters in which the referenced concepts (operant conditioning<sup>5</sup>, negative reinforcement<sup>6</sup>, and discriminative stimuli<sup>7</sup>) are introduced. We have also added a reference to*

*Thorndike's "Animal intelligence: An experimental study of the associative processes in animals"<sup>8</sup>, as an additional relevant reference.*

5. -122: „Avoidance behavior is operationalized as the maximum deviation from the shortest trajectory (T1) on each trial, and is therefore a continuous, rather than a dichotomous measure" - it is not entirely correct if one may choose only between three „gates". Furthermore, even though the movement itself might be considered „continuous", it still limited by the space associated with the gates. I would soften this sentence.

*We should note that, although arches delineate the movement trajectories, each of these arches has a width of 7cm. Thus, each coordinate within the 7cm can be an outcome value of maximum deviation for a given trial. Therefore, even if participants move through the same arch, they do not necessarily have the same maximum deviation score. Therefore, we think it is fair to say that it concerns a continuous measure.*

*We have edited the sentence on lines 121-123 on page 3 to read: "Avoidance behavior is operationalized as the maximum deviation from the shortest trajectory (T1) on each trial, which is a more continuous measure of avoidance, than for example pressing or not pressing a button".*

6. -126: Were there any physiological changes reported previously in the robotic paradigm, too? If so, please refer the reader to these findings, too.

*We have recently collected psychophysiological measures of fear by means of the eye-blink startle response and EEG. These studies have not been published yet, and therefore these measures were not included in the introduction. However, we do refer to these studies on lines 498-499 on page 11 in the discussion.*

7. -156: As a clinician, I would say it is important to do feared movements in the way they do not elicit/enhance pain. This is important for fear extinction, isn't?

*Exposure to feared movements is indeed key to exposure therapy for chronic pain in the clinic. However, we would like to note that our lab model of extinction with response prevention is of course simplified, and thus does not encompass the complex fears and catastrophes, which chronic pain patients are trying to avoid. Indeed, although pain is the feared outcome in the experiments described in the manuscript, in chronic pain, pain itself is not always the (only) feared stimulus. Instead, patients may fear that movements and activities will worsen their pain causing harm. Thus, in chronic pain, successful exposure can take place also if pain initially increases, but does not result in the expected harm (i.e. exposure then entails expectancy violation<sup>9,10</sup> of harm rather than pain itself).<sup>11</sup>*

*We have changed the text on lines 155-158 on page 3 to: "During exposure for chronic pain, patients perform feared activities or movements in order to disconfirm catastrophic beliefs and expectations of harm<sup>11,12</sup>. Since these beliefs and expectations do not necessarily concern pain*

*per se*, but rather underlying pathology, movements are not always carried out pain-free in the clinic<sup>11</sup>.”

8. Ethics: Please refer to the document's numbers and dates.

*We have added the registration numbers of the relevant ethical approvals on rows 178-180.*

9. Protocol: -207: „wrist, elbow or shoulder that may hinder performing the reaching task” - This is not specific, I would say that participants with limited range of motion in the upper extremity could not be able to the reaching task. Furthermore, what about screening if the movement *per se* is painful for some participants? I would add this as exclusion criterium.

*The exclusion criteria listed in the manuscript were used in the reported studies and approved by the ethical committees of the respective universities. Therefore, we think it is inappropriate to report them differently in the current manuscript. We do thank the reviewer for the suggestion and will consider changing and specifying the exclusion criteria for future research in healthy samples. In addition, when recruiting chronic pain patients, we will of course reconsider the exclusion criteria with the specific pain conditions in mind. We have added specification to healthy participants to line 210 on page 5.*

10. 3.2: What kind of electrodes? What about equipment being used? Some technical details are missing, unless data in Table 1 includes everything? I think, if other groups would like to replicate the method, everything should be described. Is calibration done automatically, or manually? Which software is used to generate stimuli?

*All equipment and software used in the current experiments are described in the Materials table, as advised in the “Instructions to authors”. We assume that by “Which software is used to generate stimuli?” the reviewer is referring to the electrical stimuli.*

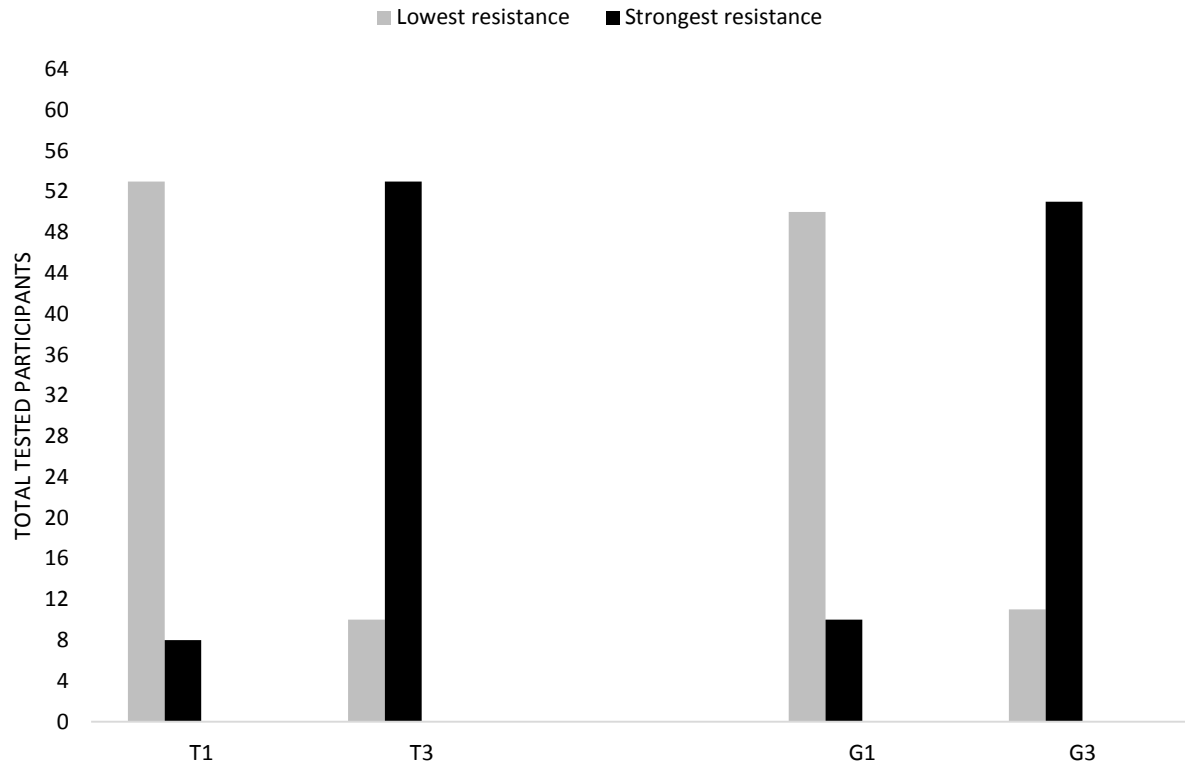
*Calibration of the pain stimulus is done manually, as specified in point 4.1 on page 5 in the manuscript. Specifically, the intensity of the pain stimulus is manually increased and the pain stimuli are manually triggered by the experimenter, using the constant current stimulator. Therefore, no software is used to generate the electrical stimuli during calibration of the stimulus. We have edited the sentence on lines 230-231 on page 5 to read: “During the pain calibration procedure, manually increase the intensity of the pain stimuli, and trigger the constant current stimulator to deliver the pain stimuli, one stimulus at a time.”*

*During the experiment, the electrical stimuli are triggered through the experimental script, which is written in the programming language C#. Furthermore, the script is run with the cross-platform game engine Unity 2017 (Unity Technologies, San Francisco, CA, USA). We have specified this in the Materials table, in the “Comments/Description” column of the C# and Unity 2017 rows. Furthermore, we have added a note to line 260 on page 6 to clarify this: “NOTE: The presentation of pain stimuli takes place via the experimental script.”*

11. -250: Is there any test for linear increase of the resistance one must perform prior to the experiment? I do not fully agree with the linearity assumption: Once you linearly increase the resistance while subject is reaching arm further, you increased the arm lever. If this is the case, less force is required to perform the movement (torque). This violates crucial trade-off assumption. Yet, this depends on the muscle group being involved in the movement. Has the method and movement trajectories been validated biomechanically, or at least, subjectively?

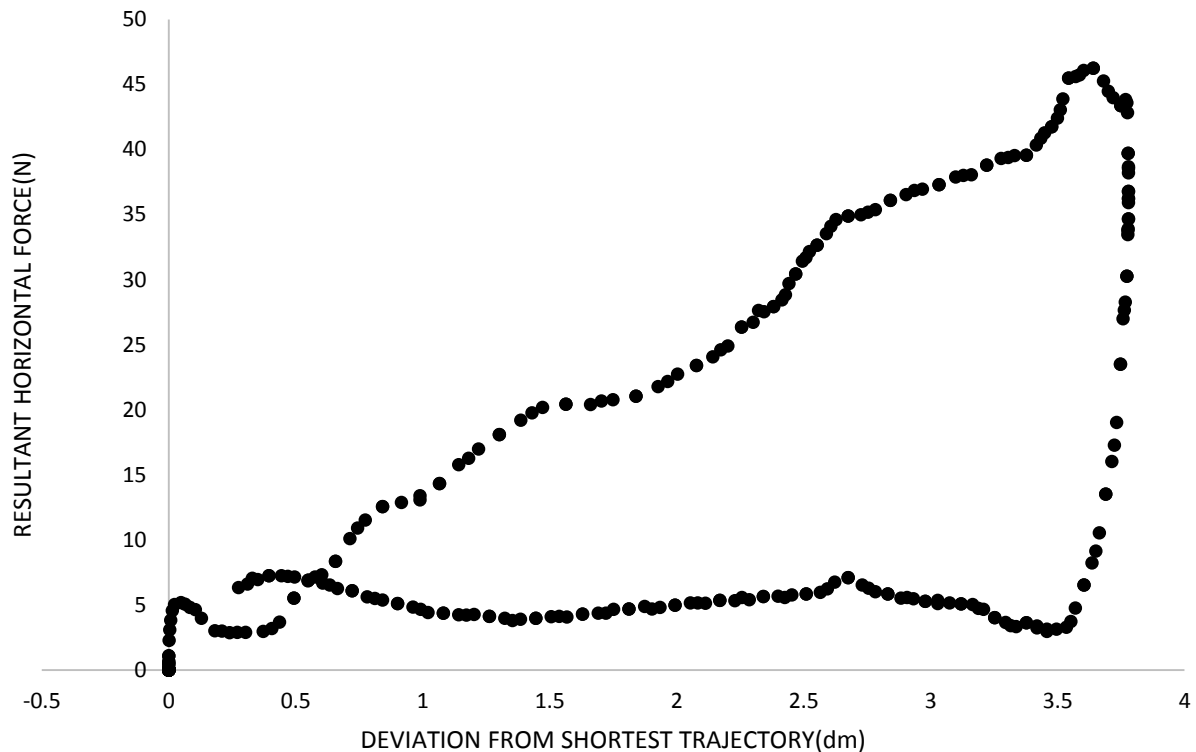
*A variety of haptic effects can be created using the programming interface of the HapticMaster (HM). One of these includes adding the effect of a spring<sup>13,14</sup>. This was used to create the resistance of the robotic arm in the current paradigm. Thus, the further the (sensor of the) arm is moved laterally, the harder the spring will pull in the opposite direction, thus increasing the force needed to perform the furthest movement. We have validated this subjectively with the exit questionnaire, in which participants are asked to post-experimentally report which movements they believed were paired with the strongest and lowest resistance. Participants generally report T1/G1 as being paired with the lowest resistance, and T3/G3 as being paired with the strongest resistance (see fig. 1 below), providing subjective validation of the effort.*

*Furthermore, the HM tracks the force used during each trial, at a 20ms precision. We have visualized the force used by an exemplary participant during one trial, in which the participant performs G3 (the furthest possible movement trajectory), in figure 2 below. During a G3 movement, participants move from the left of the movement plane to the right of the movement plane. Thus, force increases linearly when moving to the right. The width of the movement depicted in figure 2 is approximately 35cm (the width of the entire movement plain is 41cm and the width of each trajectory arch is approx. 7cm). After reaching G3, the participant moves back to the target, which is situated at the upper left corner of the movement plain. Thus, we can see that the force first linearly increases when moving to the right, after which it decreases, due to the participant moving from right to left to reach the target, meaning that the pull of the spring decreases.*



**Figure 1.** Responses to the exit questionnaire of Glogan et al.<sup>1</sup> The question inquired which movement trajectory (T1-3 during acquisition; G1-3 during generalization) is paired with the lowest (grey) and strongest (black) resistance. The graph shows responses collected from all tested participants in Glogan et al.<sup>1</sup> Thus, between 50 and 53 participants out of 64 reported T1/G1 being paired with the lowest and T3/G3 with the strongest resistance.





**Figure 2.** Force used by an exemplary participant during one trial of the robotic arm-reaching task. During the depicted trial, the participant chose the most effortful movement (G3). Thus, 0 on the x-axis represents the participant being at the left-most side of the movement plane, and 4 represents the right-most side of the movement plane.

12. I think control group without painful stimuli solves this problem.

*We agree that having a safe control group could be interesting. In fact, we have found similar effects to those reported in the current manuscript, in a study where a safe context is used as a control (not published yet). See also last paragraph of response to comment 18.*

13. Is there any calibration protocol for the robotic-arm (device calibration) which one must perform?

*1.1. The robot is switched OFF after each test day and is recalibrated once switched ON at the beginning of each test day. We have added this information to lines 187-188 on page 4 (step 1.2.): "Recalibrate the robotic arm before each test day. This is done via a direct application programming interface (API) connection with the robotic arm (specific to the HapticMaster), and only needs to be done once, at the beginning of the test day."*

14. 5.5.1: Yoked procedure should be referenced throughout the manuscript as, I guess, it is not

common in typical pain experiments.

*We have added references to Davis & Bitterman (1971) to lines 288, 305, 348, 358, 408 and 416, as well as to the footnote on page 3.*

15. Can you elaborate how the randomization schedule is maintained if the methodology requires assessment of experimental group first?

*Randomization can be achieved using a randomization schedule based on the rule that the first participant must be in the Experimental Group. Following this, participants are assigned to either group randomly, as long as the number of Experimental Group participants exceeds the number of Yoked Group participants. The reason for this is that, the data from each Experimental Group participant is used to correctly time the presentation of pain stimuli for their Yoked Group counterpart. For this, we have used a MATLAB (MathWorks, Natick, MA, US) script. This information has been added to lines 289-291 on page 6 in the manuscript ("Randomization is achieved using a randomization schedule based on the rule that the first participant must be in the Experimental Group. Following this, participants are assigned to either group randomly, as long as the number of Experimental Group participants exceeds the number of Yoked Group participants."), and to the Materials table in the "Comments/Description" column of the "Matlab" row.*

16. It is not clear from me, if the authors perform resistance calibration. Is the MVC or similar parameter determined? Or is the resistance fixed?

*There are of course differences in the arm strength of participants, which can be measured as a potential covariate, as was done in Meulders et al.<sup>15</sup> where arm extension force was measured and the resistance calibrated.*

*However, given that we are interested in mechanisms of avoidance learning, what is most important is that the urge to avoid pain is greater than the urge to avoid the resistance, but that the resistance is aversive enough to motivate avoidance when pain is unpredictable or cannot be avoided (like in the yoked group).*

*Therefore, when we realized in later experiments, that even with large differences in arm strength the resistance worked for all participants, we decided to keep it constant.*

17. -290: Can you add a reference to the figure, in place where G1-G3 are described?

*We have added a reference to Figure 1 to line 304. We also added labels to T1-3 in Figure 1 in order to avoid any possible confusion regarding the different trajectory arches.*

18. -294: If I understood it correctly, authors argue that two groups are required: yoked and experimental. I think for the validity of the experiment, it is necessary to involve the second control group, without painful stimuli. Should subjects avoid the T3 if the trade-off holds on,

shouldn't? It is not clear how many trials are needed for successful learning? Please, add this detail.

*We should note that, two groups are not necessary for the paradigm. For example, in the RPE protocol, acquisition of avoidance is demonstrated by increased avoidance at the end of the learning (acquisition) phase, compared to the beginning of that phase. This is described on lines 346-348 on page 8 in the “Representative results” section: “Acquisition of avoidance behavior is demonstrated by participants avoiding more (showing larger maximal deviations from the shortest trajectory) at the end of an acquisition phase, compared to the beginning of the acquisition phase”. Furthermore, we have also found similar results to those reported in the manuscript when using a within-subjects design with an avoidance condition and a yoked condition indicated by different experimental backgrounds<sup>16</sup>.*

*In the footnote on page 3 of the manuscript, where we first introduce the yoked control, we explicitly state that: “If applicable to the design, a Yoked Group can be used as control”. This is also the case on lines 286-288 on page 6 (step 5.5.1.) of the manuscript: “Where applicable: The data from each Experimental Group participant are saved on the computer (see Section 1.4.), and used as reference for the reinforcement schedules of each Yoked (control) Group participant.” Furthermore, for the sake of clarity, we have added the following to lines 305-306 on page 7 of the manuscript: “NOTE: A Yoked Group<sup>17</sup> is required for testing generalization of avoidance (see step 5.5.1.). However, different controls can be used depending on the specific research question (cf. context modulation of avoidance in a within-subjects design<sup>16</sup>).”*

*Although it would certainly be interesting to include a second control group, we believe that the Yoked Group provides sufficient control and evidence for the pain-effort trade-off. Specifically, we have consistently found acquisition of avoidance (i.e. significant differences between the Experimental and Yoked Group) using this set-up. In other words, even when participants in the Yoked Group sometimes receive pain during the least effortful (T1) movement, they clearly prefer this to the other trajectories. This suggests that participants who do not have the ability to avoid, reliably prefer the T1 movement to T3, even when T1 is sometimes punished, which we take as strong evidence for their preference of T1.*

19. -364: I know it is not very informative comment, but the description of extinction with its rationale is not very clear in this part.

*We have changed the description on lines 375-380 on page 8 to: “**Extinction of avoidance behavior:** During extinction with response prevention, participants are only allowed to perform the previously most painful movement trajectory (T1), whereas the other two trajectories (T2 and T3) are prohibited. Therefore, given that participants only have the option of performing T1, and thus the observed data pattern does not reflect their own choices, i.e. genuine extinction of avoidance behavior, extinction of *avoidance* is not included in the analyses (fig. 5).”*

20. Discussion: -491: „SCRs have been previously found to correlate with relief [67]" - I think this is the wrong citation as in the study by Lekens et al. only fMRI was conducted. Please check other references for adequacy.

*We thank the reviewer for pointing out this mistake. The reference has been updated to Vervliet et al. (2017)<sup>18</sup>.*

21. The discussion lacks important consideration of the pain model used, authors very often used term „ecologically valid". I agree, and like the paradigm very, however, in my opinion what threatens its internal validity is pain model used. So, I would ask why authors think electrically induced pain should be used in the paradigm? Why not, for example, ischemic pain or heat pain? Both are based on tonic stimulation which force their priority in research application, mostly because of its similarity to clinical pain. This should be discussed. Furthermore, what should be discussed is electrical stimulation itself. Nowadays, electrocutaneous stimuli become more popular because of its potential in activation of nociceptive fibers. I would recommend to use pin-like electrodes and lower intensity (I checked which values are consider in the calibration, e.g. > 40mA - quite high!) as high intensity stimulation suffers from the lack of fibers selectivity. What authors plan to do is a pain induction. If so, it is most likely to happened by stimulating A-delta and C fibers, not A-beta fibers. To reduce possibility of A-beta fibers activation I would suggest to reduce the intensity, change the shape of stimulus and used series of shocks. I think authors did not refer the reader to the pioneered work in the operant conditioning of pain reports by Steven Linton - I would strongly recommend to add it.

*We agree with the reviewer that electrocutaneous pain stimuli lack certain aspects of ecological validity, and thank the reviewer for pointing out this limitation. However, we would like to note that the robotic arm-reaching paradigm is still a relatively novel method, and many of the studies run so far have been the first to investigate basic mechanisms of avoidance-learning. In fact, for validation purposes, the electrocutaneous stimulus is practical, and even ideal given its reproducibility and reliability, brevity (allowing short trials), and ease of application, whereas other pain induction methods, such as ischemic stimulation with longer latencies may interrupt the flow of the task. However, we plan to also investigate pain-related avoidance using different pain-induction methods in the future. Therefore, we have added the following to the limitations section of the manuscript on lines 521-526 on page 11 of the discussion: "Finally, only electrocutaneous stimuli have so far been used in the robotic arm-reaching paradigm as pain stimuli, for reasons of consistency and comparability with previous studies of pain-related fear<sup>19-21</sup>. However, electrocutaneous stimuli may not fully mimic the more tonic pain experienced by chronic pain patients, given that they produce a relatively phasic, uncommon, and unnatural pain experience<sup>22</sup>. Other pain-induction methods, such as ischemic stimulation<sup>23</sup> and exercise-induced<sup>24,25</sup> pain have been argued to be better experimental analogues of musculoskeletal pain, given their natural and endogenous nature<sup>22</sup>. These pain-induction methods could be employed in the robotic arm-reaching paradigm in the future."*

*We agree that the work of Steven Linton is indeed relevant for the current manuscript. We have added a reference to his work to lines 93-94 on page 2: “Apart from Linton’s work on the operant conditioning of pain reports<sup>26</sup>, investigations into the instrumental learning mechanisms relating to pain, in general, are limited.”*

I congratulate authors excellent ideas for the operant conditioning in pain research and I am looking forward to see results of new experiments using this method.

*We thank the reviewer for his/her shared enthusiasm in our research and paradigm.*

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