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

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Author Questionnaire

1. **Microscopy**: Does your protocol require the use of a dissecting or stereomicroscope for performing a complex dissection, microinjection technique, or similar? **N**

2. **Software:** Does the part of your protocol being filmed demonstrate software usage? **Y**

Videographer: All screen captures provided, do not film

3. **Interview statements:** Considering the Covid-19-imposed mask-wearing and social distancing recommendations, which interview statement filming option is the most appropriate for your group? **Please select one**.

☒ Interviewees wear masks until the videographer steps away (≥6 ft/2 m) and begins filming. The interviewee then removes the mask for line delivery only. When the shot is acquired, the interviewee puts the mask back on. Statements can be filmed outside if weather permits.

4. **Filming location:** Will the filming need to take place in multiple locations (greater than walking distance)? **N**

Protocol Length
Number of Shots: **39**

Introduction

1. **Introductory Interview Statements**

REQUIRED:

1.1. **Eveliina Glogan**: Pain-related avoidance behavior majorly contributes to chronic pain disability, yet existing paradigms often lack ecological and construct validity by employing an instructed and low or no cost avoidance response **[1]**.

1.1.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

REQUIRED:

1.2. **Kristof Vandael**: Our paradigm tackles these limitations by allowing investigation of the ways in which avoidance is naturally learned and reinforced and by incorporating a cost to the avoidance response **[1]**.

1.2.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

OPTIONAL:

1.3. **Ann Meulders**: Our paradigm can be uniquely used to explain the processes underlying the learning of pain-related avoidance behavior, how this behavior becomes disabling in chronic pain, and how the behavior can be mitigated **[1]**.

1.3.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

Ethics Title Card

1.4. Procedures involving human subjects have been approved by the Social and Societal Ethics committee (SMEC) of the KU Leuven and/or Ethics Review Committee Psychology and Neuroscience (ERCPN) of Maastricht University.

Protocol

2. Test Session Preparation

2.1. To prepare for a test session, have everyone disinfect their hands upon arrival to the lab **[1]**.

2.1.1. WIDE: Talent and/or Participant disinfecting hands. NOTE: Please move voiceover 2.1. and shot 2.1.1. after shot 2.2.2. (2.2., 2.2.1., and 2.2.2. are first steps of protocol)

2.2. Place a computer in one room or section for the Researcher **[1]** and place a large television in a separate room or section for the Participant **[2]**.

2.2.1. Talent turning on computer

2.2.2. Talent turning on television

2.3. Have the Participant sit in a chair with arm rests, approximately 2.5 meters from the television screen at a comfortable distance of approximately 15 centimeters from the sensor of the robotic arm **[1-TXT]**.

2.3.1. Talent wearing facemask gesturing/Participant sitting **TEXT: Take appropriate precautions during Covid-19 (*e.g.*, wear a facemask, gloves)**

2.4. After obtaining written informed consent from Participant, fill the center of each electrode with conductive electrolyte gel **[1]** and use a strap to attach the stimulation electrodes over the triceps tendon of the Participant's right arm **[2-TXT]**.

2.4.1. Talent filling electrode(s)

2.4.2. Talent strapping electrodes over triceps **TEXT: Strap should be neither too tight nor too loose**

3. Pain Stimulus Calibration

3.1. After explaining the calibration procedure **[1]**, ask the Participant to rate each stimulus on a numerical scale from 0-10, with 0 representing "I feel nothing" and 10 representing "the worst pain imaginable" **[2]**.

3.1.1. WIDE: Talent explaining procedure~~, with scale on television screen visible in frame~~

3.1.2. Talent indicating 0-10 on pain scale/Participant nodding/acknowledging

3.2. Turn on the stimulator **[1],** set the intensity to 1 milliamp to start **[2]**, and announce that a pain stimulus is about to be delivered **[3]**.

3.2.1. Talent turning on stimulator

3.2.2. Talent setting knob to 1 mA

3.2.3. Talent telling Participant to expect stimulus

3.3. When the Participant acknowledges the announcement **[1]**, press the orange trigger button on the constant current stimulator to deliver the stimulus **[2]**.

3.3.1. Participant indicating awareness/consent

3.3.2. Talent pressing button/Participant reacting (or not)

3.4. After obtaining the participant's pain rating, apply the stimulus at the next level of intensity as demonstrated, gradually increasing the intensity of the pain stimulus in a stepwise manner in 1-, 2-, 3-, and 4-milliamp increments **[1-TXT]**.

3.4.1. Talent turning knob and pressing trigger/Participant reacting (or not) **TEXT: *e.g.*, 1, 2, 4, 6, 8, 11, 14, 17, 20, 24, 28, 32, 36, 40, 44, 48, 52, *etc*.**

3.5. When the Participant reaches a pain intensity that they would describe as "significantly painful and demanding some effort to tolerate", terminate the calibration procedure **[1-TXT]** and document the final pain intensity in milliamps and the pain intensity rating of the Participant **[2]**.

3.5.1. Participant reacting in response to significant pain **TEXT: *i.e.*, 7-8 on pain calibration rating scale**

3.5.2. Talent recording the selected intensity in mA and pain scale number

4. Experimental Task: Practice Phase

4.1. Before starting the robotic arm-reaching pain-related avoidance task, provide the Participant with on-screen standardized written instructions of the task **[1]** before presenting three arches situated midway through the movement plane **[2]**.

4.1.1. WIDE: Talent indicating instructions to Participant, with screen visible in frame

4.1.2. SCREEN: 4.1.2.

4.2. Ensure that the shortest arm movement is paired with no deviation or resistance **[1]**, the middle arm movement is paired with moderate deviation and resistance **[2]**, and the furthest arm movement is paired with the largest deviation and strongest resistance **[3-TXT]**.

4.2.1. SCREEN: 4.1.2. *Video Editor: please emphasize left arch*

4.2.2. SCREEN: 4.1.2. *Video Editor: please emphasize middle arch*

4.2.3. SCREEN: 4.1.2. *Video Editor: please emphasize right arch*

4.3. Instruct the Participant to use the dominant hand to operate the robotic arm by moving its sensor **[1]**, which is represented by a green ball on the television screen **[2]**, and to move the 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 **[3][4-TXT]**.

4.3.1. Talent indicating sensor

4.3.2. SCREEN: 4.3.2. *Video Editor: please emphasize green ball*

4.3.3. Participant using sensor to move ball *Videographer: Important step; please capture to allow 4.3.4. to be included as inset* **TEXT: Do not administer pain stimulus during practice phase**

4.3.4. SCREEN: 4.3.4._43sec_to_47sec: 00:43-00:48 *Video Editor: please include as inset in 4.3.3.*

4.4. Inform the Participant that they can freely choose which of the available movement trajectories to perform on each trial **[1]** and 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 **[2][3]**.

4.4.1. Talent indicating movement trajectories

4.4.2. Participant using foot pedals to scroll through scale *Videographer: Please capture to allow 4.4.3. to be included as inset*

4.4.3. SCREEN: Screen_4.4.4._Self_reports: 09:23-09:50 *Video Editor: please include as inset in 4.4.2* NOTE: 4.4.4._Self_reports directly corresponds to shot 4.4.2. of the foot pedals

4.5. At the end of the practice phase, after answering any questions, leave the room and dim the lights **[1-TXT]**. Observe the participant from the Researcher's section or room **[2]**.

4.5.1. Talent answering questions and leaving the experimental section, lights dimming **TEXT: lights during experiment have not been dimmed for purpose of the video**

4.5.2. Talent sitting in researcher's section, observing participant.

5. ~~Basic Experimental Task:~~ Acquisition and Generalization Protocols

5.1. To execute the acquisition protocol, have the Participant press the **Confirm** foot pedal to initiate the experiment **[1]**.

5.1.1. WIDE: Participant pressing confirm foot pedal

5.2. During the avoidance acquisition phase, if the Participant performs the shortest movement trajectory, program the constant current stimulator to always deliver the pain stimulus once two thirds of the movement has been completed **[1-TXT]**.

5.2.1. Participant performing shortest trajectory with pain stimulus *Videographer: Important step* **TEXT: *i.e.*, deliver pain once ball moves through trajectory arch**

5.3. If the Participant selects the middle movement trajectory, present the pain stimulus 50% of the time, while ensuring that the Participant will have to exert more effort **[1]**.

5.3.1. Participant performing medium trajectory, with 50% chance of receiving a pain stimulus *Videographer: Important step*

5.4. If the Participant performs the furthest, most effortful movement trajectory, do not present the pain stimulus but ensure that the Participant will have to exert the most effort to reach the target **[1]**.

5.4.1. Participant performing furthest trajectory, with 0% chance of receiving a pain stimulus *Videographer: Important step*

5.5. A successfully completed trial will be indicated by the presentation of visual and auditory stop signals **[1]**.

5.5.1. Participant finishing trial, with visual stop signal visible in frame *Videographer/Video Editor: please include auditory signal*

5.6. The robotic arm should be programmed to automatically return to its starting position at the end of a trial **[1]**. After 3000 milliseconds, present the visual and auditory start signals that indicate that the Participant can start the next trial **[2]**.

5.6.1. Robotic arm returning to starting position, with ball moving to starting position on monitor visible in frame as possible OR SCREEN: 4.3.4._ 43sec_to_47sec: 0:00:47-0:00:51

5.6.2. Visual and auditory signals indicating that the next trial can begin Videographer NOTE: 5.6.2 should be included in shot 5.5.1 *Videographer/Video Editor: please include auditory signal*

5.7. When testing for generalization of avoidance, the on-screen trajectory arches are separated during the acquisition phase to leave room for the generalization trajectory arches **[1]**.

5.7.1. SCREEN: 6.1.1.

5.8. To test for the generalization of avoidance, after the acquisition phase, present three novel, generalization movement trajectories adjacent to the acquisition trajectories. **[1-TXT]**.

5.8.1. SCREEN: 6.2.1. **TEXT: Do not deliver pain stimulus during generalization phase**

6. Extinction with Response Prevention and Spontaneous Recovery Protocols

6.1. To investigate the extinction of avoidance with response prevention, after the acquisition phase **[1]**, provide the Participant with standardized written instructions stating that, in the upcoming phase, they can only perform T1 **[2]**.

6.1.1. WIDE: Participant in front of television screen, reading instructions on screen

6.1.2. SCREEN: Screen_6.1.3._forced_RPE

6.2. During the response prevention phase, visually and haptically block T2 and T3 so that only T1 is available **[1-TXT]**.

6.2.1. Participant attempting to perform T2 and T3, but being stopped by barriers **TEXT: Do not pair T1 with a pain stimulus during the RPE phase** NOTE: Use Take 2

6.3. Thus, you ensure that during the RPE phase, the participant only performs T1 **[1]**.

6.3.1. Participant performing T1

6.4. Approximately 24 hours later, attach the stimulation electrodes **[1-TXT]** and provide brief, on-screen refresher instructions of the task without including any information regarding the pain stimulus **[2]**.

6.4.1. Talent attaching electrode(s) **TEXT: Do not recalibrate the pain stimulus on day 2**

6.4.2. SCREEN: 8.2.2.

6.5. Then present the three acquisition trajectories in the absence of the pain stimulus **[1]**.

6.5.1. Participant performing task with all trajectories available

6.6. Upon completion of the experiment, detach the stimulation electrodes **[1]** and thoroughly clean the stimulation electrodes with a disinfectant solution **[2]**.

6.6.1. Talent detaching electrodes

6.6.2. Talent cleaning electrodes

6.7. Then dry the electrodes with soft tissue paper **[1]** and clean the sensor of the robotic arm with disinfectant wipes or spray **[2]**.

6.7.1. Talent drying electrode(s)

6.7.2. Talent cleaning sensor

Protocol Script Questions

A. Which steps from the protocol are the most important for viewers to see?
4.3.3., 5.2.1., 5.3.1., and 5.4.1.

B. What is the single most difficult aspect of this procedure and what do you do to ensure success?
4.3.3. The first few trials of the practice phase. Participants often find the task counterintuitive, given that the green ball on the screen follows the sensor/their hand, rather than the front of the robot. Explaining this to participants often speeds up their learning of operating the robot.

Results

7. Results: Acquisition, Generalization, Extinction and Return of Avoidance, Pain-Related Fear, and Pain-Expectancies

7.1. Acquisition of avoidance behavior **[1]** is demonstrated by participants avoiding pain more **[2]** at the end of an acquisition phase, compared to the beginning of the acquisition phase **[3]** or as compared to a Yoked control group **[4-TXT]**.

7.1.1. LAB MEDIA: Figure 2
7.1.2. LAB MEDIA: Figure 2 *Video Editor: please emphasize 2nd/higher A data point*
7.1.3. LAB MEDIA: Figure 2 *Video Editor: please emphasize 1st/lower A data point*
7.1.4. LAB MEDIA: Figure 3 *Video Editor: please emphasize bottom blue peaks* **TEXT: A similar pattern is expected for avoidance generalization**

7.2. The acquisition of fear and pain-expectancy is evidenced by participants reporting lower fear for, and expecting the pain stimulus less during, T3 **[1]** compared to T1 and T2 **[2]**.

7.2.1. LAB MEDIA: Figures 4, 5, 6, and 7 *Video Editor: please emphasize green A data lines in all graphs*
7.2.2. LAB MEDIA: Figures 4, 5, 6, and 7 *Video Editor: please emphasize red and yellow A data lines in all graphs*

7.3. Generalization of fear and pain-expectancy is indicated by participants in the Experimental Group reporting lower fear to, and expecting the pain stimulus less during, G3 **[1]** compared to G1 and G2 **[2]**

7.3.1. LAB MEDIA: Figures 4, 5, 6, and 7 *Video Editor: please emphasize green dashed B data lines in Figures 4 and 5*
7.3.2. LAB MEDIA: Figures 4, 5, 6, and 7 *Video Editor: please emphasize red and yellow dashed B data lines in Figures 4 and 5*

7.4. The extinction of fear and pain-expectancies is evident when participants report lower fear and expect the pain-stimulus less during T1 **[1]** at the end of the response prevention phase, compared to the end of the acquisition phase **[2]**.

7.4.1. LAB MEDIA: Figures 4, 5, 6, and 7 *Video Editor: please emphasize red B/C data lines in Figures 6 and 7*

7.4.2. LAB MEDIA: Figures 4, 5, 6, and 7 *Video Editor: please emphasize Red A data lines in Figures 6 and 7*

7.5. The spontaneous recovery of avoidance behavior is indicated by participants avoiding more at the beginning of the test of spontaneous recovery **[1]**, compared to the end of the response prevention phase **[2]**.

7.5.1. LAB MEDIA: Figure 2 *Video Editor: please emphasize B Test data line*
7.5.2. LAB MEDIA: Figure 2 *Video Editor: please emphasize B RPE data line*

7.6. The spontaneous recovery of fear and pain-expectancy is indicated by participants reporting higher fear and pain-expectancy for T1 **[1]** during the beginning of the test of spontaneous recovery, compared to the end of the response prevention phase **[2]**.

7.6.1. LAB MEDIA: Figures 4, 5, 6, and 7 *Video Editor: please emphasize red C Test data lines in Figures 6 and 7*
7.6.2. LAB MEDIA: Figures 4, 5, 6, and 7 *Video Editor: please emphasize red B/C RPE data lines in Figures 6 and 7*

Conclusion

8. Conclusion Interview Statements

8.1. **Eveliina Glogan**: Moving away from aversive stimuli is not a pain-specific defensive response. This method could also be applied to investigate avoidance of disgust or embarrassment, which are relevant for anxiety disorders **[1]**.

8.1.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

8.2. **Ann Meulders**: Our paradigm enables testing potential differences in avoidance learning in chronic pain, compared to healthy populations. Deeper understanding of the mechanisms underlying avoidance could optimize, or offer novel, treatment possibilities **[1]**.

8.2.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera