USASP
US ASSOCIATION FOR THE STUDY OF PAIN

PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol 00, No 00 (), 2021: pp 1–12
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

When Do We Not Face Our Fears? Investigating the Boundary Conditions of Costly Pain-Related Avoidance Generalization

Eveliina Glogan,[*,†,#] Kristof Vandael,[*,‡,#] Rena Gatzounis,[*] and Ann Meulders[*,†]

[*]*Experimental Health Psychology, Maastricht University, Maastricht, The Netherlands,* [†]*Research Group Health Psychology, KU Leuven, Leuven, Belgium,* [‡]*Laboratory of Biological Psychology, KU Leuven, Leuven, Belgium*

Abstract: **Excessive generalization of fear and avoidance are hallmark symptoms of chronic pain disability, yet research focusing on the mechanisms underlying generalization of avoidance specifically, is scarce. Two experiments investigated the boundary conditions of costly pain-related avoidance generalization in healthy participants who learned to avoid pain by performing increasingly effortful (in terms of deviation and force) arm-movements using a robot-arm (acquisition). During generalization, novel, but similar arm-movements, without pain, were tested. Experiment 1 (*N* = 64) aimed to facilitate generalization to these movements by reducing visual contextual changes between acquisition and generalization, whereas Experiment 2 (*N* = 70) aimed to prevent extinction by increasing pain uncertainty. Both experiments showed generalization of pain-expectancies and pain-related fear. However, Experiment 2 was the first and only to also demonstrate generalization of avoidance, ie, choosing the novel effortful arm-movements in the absence of pain. These results suggest that uncertainty about the occurrence of pain may delay recovery, due to reduced disconfirmation of threat beliefs when exploring, resulting in persistent avoidance.**

Perspective: ***This article demonstrates generalization of instrumentally acquired costly pain-related avoidance in healthy people under conditions of uncertainty. The results suggest that targeting pain-related uncertainty may be a useful tool for clinicians adopting a psychological approach to treating excessive pain-related avoidance in chronic pain.***

Key words: *Avoidance behavior, fear generalization, avoidance generalization, chronic pain, operant conditioning.*

Avoidance of objectively safe movements and activities is central to chronic pain disability,[55] which often profits from psychological treatments, such as Cognitive Behavioral Therapy,[39] rather than purely biomedical ones.[14,15] Avoidance of pain-associated movements/activities after healing prevents disconfirmation of threat, leading to a self-sustaining cycle of fear and avoidance.[55] Furthermore, avoidance often spreads to movements resembling the original pain-associated movement, that were never paired with pain themselves (avoidance *generalization*).[12] Generalization is adaptive, allowing extrapolation of once-learned protective responses to similar, potentially harmful situations. Yet, generalization of avoidance to safe movements (*excessive generalization*) bears the risk of disproportionate activity-withdrawal. Given its self-reinforcing nature, avoidance may lead to a negative cycle of physical disengagement, culminating into functional disability.

Received October 29, 2020; Revised March 24, 2021; Accepted March 26, 2021.
[#]E.G. and K.V. contributed equally to this manuscript.
Funding: This research was supported by a Vidi grant from The Netherlands Organization for Scientific Research (NWO), The Netherlands (grant ID 452-17-002) granted to Ann Meulders.
Conflicts of interest: The authors have no conflicts of interest to declare.
Data statement: The data from this manuscript are available upon request.
Address reprint requests to Ann Meulders, PhD, Maastricht University, Faculty of Psychology and Neuroscience, Experimental Health Psychology, P.O. Box 616, 6200 MD Maastricht, The Netherlands.
E-mail: ann.meulders@kuleuven.be
1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2021.03.149

According to the fear-avoidance model of chronic pain,[55] misinterpreting pain as harmful, induces pain-related fear, motivating avoidance of movements/activities associated with pain. Specifically, pain-related fear is learned through *Pavlovian conditioning,*[41] where a neutral movement (conditioned stimulus; CS) experienced with pain (unconditioned stimulus; US), comes to elicit fear (conditioned response; CR).[38,41] Due to pain-related fear, and following *operant conditioning,*[48] any behavior (response, R; eg, a movement) believed to predict pain (ie, a negative outcome, O) will decrease (ie, *punishment*). Alternatively, an avoidance response (eg, moving in an unnatural manner), which omits a negative outcome (eg, pain) will increase (ie, *negative reinforcement*), and thus be strengthened.[48]

Because avoidance was traditionally believed to directly follow fear,[26,49] previous research in the anxiety and pain domains focused mainly on (pain-related) *fear* generalization,[12,37] assuming avoidance would align.[49] This research demonstrated that compared to healthy controls, people with chronic pain overgeneralize pain-related fear.[36] However, in the daily life of a person with chronic pain, controlling pain (eg, by avoiding) is only one among numerous competing goals (eg, socializing).[56] Therefore, despite fear, avoidance may not always be prioritized if the associated costs (eg, stigma) are too high, promoting dissociation between fear and avoidance.[6] Because the ultimate goal is to understand and sustainably change pain *behavior*, more research is needed on avoidance behavior itself.[27]

We recently reported such dissociation between pain-related fear and costly avoidance.[17] Using a pain-related avoidance-conditioning paradigm, healthy participants learned to avoid pain at the cost of performing increasingly effortful arm-movements (acquisition trajectories). During a subsequent generalization test, 3 novel, similar movements (generalization trajectories) were tested in the absence of the acquisition trajectories and pain. Pain-expectancy and pain-related fear generalized to the novel movements, but avoidance did not,[17] sparking the question under which conditions costly avoidance generalizes.

There are several plausible explanations for this dissociation.[17] *First*, the way in which generalization was operationalized (absence of acquisition trajectories and appearance of generalization trajectories) may have been experienced as a context-switch, generating doubt about the acquisition movement-pain contingencies still holding during the generalization phase,[1,2] and thus uncertainty about the continued need for effort. That is, since avoidance was costly, the change in available responses may have motivated exploration (ie, choosing an option with possible gains, but uncertain outcomes[28,32]) of the novel movement trajectories, similar to those previously paired with pain, with the goal of minimizing effort.[28] *Second*, the absence of highly expected pain during generalization may have resulted in rapid safety learning when exploring the less effortful generalization trajectories, thus extinguishing avoidance.[8,46]

Here we report on 2 experiments with altered methodologies to, respectively, minimize visual (context) changes[2] between acquisition and generalization (Experiment 1), and prevent rapid extinction of avoidance during generalization (Experiment 2).[7] We hypothesized that these modifications would result in avoidance and differential self-reports (pain-expectancies and pain-related fear) generalizing from the acquisition trajectories to the novel, similar generalization trajectories.

Methods

Apparatus

HapticMaster. The HapticMaster (HM; Motekforce Link, Amsterdam, the Netherlands) is a 3 degrees of freedom, admittance-controlled robot, ie, when operated by an external force, the robot reacts with a corresponding movement. Under operation, the HM registers and records the force, position, velocity, and acceleration exerted onto it. This information can be fed back to other devices, and used for triggering the presentations of stimuli, such as the electrocutaneous stimuli in the current experiments. Additionally, the HM can be programmed to exert resistive force itself. In the current studies, the available movement range was delineated by a 2-dimensional horizontal movement plane with a depth of 0.36 m and radius of 0.41 m.

Software and Hardware. The experiment was programmed in C#, using cross-platform game engine, Unity 2017 (Unity Technologies, San Francisco, CA, USA), and 3D graphics software, Blender 2.79 (Blender Foundation, Amsterdam, The Netherlands). The experimental script was run on a Windows 10 Enterprise (Microsoft Corporation, Redmond, WA, USA) 64-bit Intel Core desktop computer (Intel Corporation, Santa Clara, CA, USA) with 8GB RAM, CPU: i7-7700 at 3.600GHz. Communication between the computer and HM took place via a direct application programming interface connection. The experimental script was presented on a 40-inch LCD screen (Samsung UE40ES5500; Samsung Group, Seoul, South Korea).

Stimulus Material

Pain Stimulus. The pain stimulus (pain) was a 2 ms square-wave electrocutaneous stimulus, delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, United Kingdom), through 2 reusable stainless steel disk electrodes (8mm diameter with 30mm spacing; Digitimer) filled with K-Y gel (Reckitt Benckiser, Slough, United Kingdom). Intensity of the electrical stimulus was individually calibrated: participants were administered a series of electrical stimuli of increasing intensity, according to a standard protocol (eg,[38]). Participants were asked to rate each stimulus on a numerical rating scale ranging from 0-10, where 0 was labelled as "*I feel nothing*"; 1 as "*I feel something, but this is not unpleasant; it is only a sensation*", 2 as "*the stimulus is not yet painful, but is beginning to be unpleasant*"; and 10 as "*this is the worst pain I can imagine*". Participants were asked to select a stimulus they would describe as "*significantly painful and demanding*

some effort to tolerate", corresponding to a 7-8 on the numerical rating scale.

The Basic Paradigm: Robotic Arm-Reaching Task

Both experiments used variations of the same basic paradigm as Glogan et al.[17] On each trial, participants were required to move from a start location to a target location by operating the HM with their right (dominant) hand (see Fig 1, panel A). Participants' movements were visualized on the LCD screen by a green ball, allowing them to track their movements in real-time (see Fig 1, panel B; see Supplementary Materials 1: Video, for a visualization of the paradigm's trial structure). The start and target locations were situated at the lower and upper left corners of the movement plane, respectively. The target location was visualized as a green arch, through which the green ball had to be moved. Participants could reach the target via 3 different movement trajectories (T1-3) represented on screen as 3 arches situated midway through the movement plane. The trajectory arches were separated by spaces where the generalization trajectory arches (G1-3) would appear during the generalization phase (see Fig 1, panels B and C: Experiment 2). On each trial, participants freely chose 1 of the 3 available movement trajectories to reach the target location.

The HM was programmed such that there was a linear relationship between lateral displacement (deviation) and resistive force (resistance). This meant that, when the shortest trajectory (T1) was chosen, participants needed to exert minimal effort regarding deviation and force. When the middle trajectory (T2) was chosen, moderate effort was needed, and when the target was reached via the longest trajectory (T3), the most effort was needed (Fig 1, panel B).

The experiment was preceded by a *practice phase*, during which participants learned to perform the task and familiarized themselves with self-reports. During this phase no electrical stimuli were delivered. During the *acquisition phase*, participants in the *Experimental Group*, were able to avoid the electrical stimulus by exerting more effort, that is, T1 was always paired with pain (T1 = 100% punishment/no deviation or resistance), but by choosing one of the alternative, more effortful trajectories, participants were able to avoid the electrical stimulus (T2 = 50% punishment/moderate deviation and resistance; T3 = 0% punishment/largest deviation and most resistance). In this way, costly avoidance was modeled (ie, avoidance at the cost of effort). Note that, conceptualizing these responses as avoidance means that, by choosing T3, participants in the Experimental Group could avoid pain 100% of the time, by choosing T2 50% of the time, and never, by choosing T1 (ie, negative reinforcement[48]). Each participant in the *Yoked Group*[9] was matched to a participant in the Experimental Group, and thus received pain on the same trials as their Experimental Group counterpart, irrespective of their chosen movement trajectories. In yoked control procedures, each participant in the yoked (control) group is matched to a participant in the experimental group, such that the control participant receives the same schedule of punishment/reinforcement as their corresponding experimental group participant, irrespective of their own behavior.[9] Thus, the experimental movement-pain contingencies of the current studies did not apply to the Yoked Group, and therefore no avoidance learning was expected to occur in this group. However, the yoked procedure controls for the number of electrical stimuli received in each group.

The *generalization phase* was similar to the acquisition phase, except that now 3 novel generalization trajectories (G1-3; Fig 1, panel C: Experiment 2), were

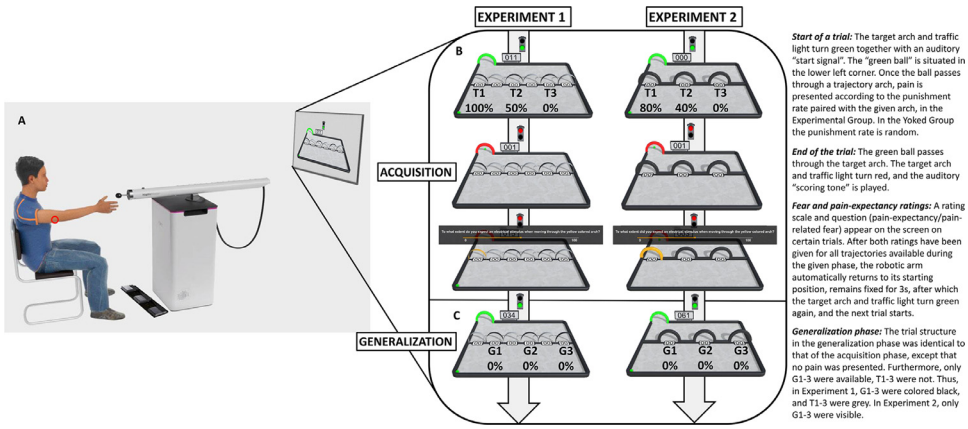

Figure 1. The experimental setup and schematic overview of the experimental tasks during the acquisition and generalization phases. Panel A: The participant is seated in front of the television screen, at reaching distance from the sensor of the robotic arm. The electrodes for delivering electrical stimuli are placed on the triceps tendon of the right arm (red circle), and the triple foot switch is used to give pain-related fear-, and pain-expectancy ratings. Panels B and C: the acquisition (B) and generalization (C) phases of Experiment 1 and Experiment 2. T1-3 and G1-3 refer to acquisition and generalization movement trajectories, respectively. Percentages refer to respective punishment rates of each experiment. Note that, signs for movement trajectories and punishment rates were not part of the visual representations of the experimental tasks. Also note that, in Experiment 1, T1-3 were black during the acquisition phase, and G1-3 during generalization, whereas in Glogan et al,[17] and Experiment 2, only trajectory arches T1-3 were visible during the acquisition phase, and conversely, only G1-3 during the generalization phase. Figure modified with permission from ref. 18

presented. None of the generalization trajectories were paired with pain. Furthermore, to prevent extinction, this phase was interspersed by short *reminder-of-acquisition* blocks, during which the original acquisition trajectories (T1-3) and their corresponding outcomes were once again presented.

Trial onset was indicated by auditory ("start sound") and visual (green traffic light and the target arch turning green) start signals. Upon successful trial completion, auditory ("scoring tone") and visual (red traffic light and the target arch turning red) stop signals were presented. When stop signals were presented, participants were required to release the HM, which repositioned to its starting position automatically. After returning to the starting position, the HM remained fixed for 3s (inter-trial interval; ITI) before the start of the next trial (see Supplementary Materials 1).

Primary Outcome Measures

Behavioral Avoidance

Avoidance behavior was operationalized as the maximal deviation from the shortest trajectory within the 0.36×0.41 m horizontal movement plane, per trial. This information was extracted using the coordinates of each performed movement, which were automatically logged by the HM.

Self-Reports: Pain-Expectancy and Pain-Related Fear

Questions were presented on-screen using a visual analogue scale (VAS) ranging from 0-100 (0 = "not at all" and 100 = "very much"), and answered using a triple foot switch (USB-3FS-2; Tokyo, Japan). To indicate which movement trajectory the question related to, the corresponding arch turned yellow. Participants rated the questions *"To what extent do you expect an electrical stimulus when moving through the yellow-colored arch?"* (ie, pain-expectancy) and "*How afraid are you to move through the yellow-colored arch?"* (ie, pain-related fear) for each of the movement trajectories.

Secondary Outcome Measures

Exit Questionnaire and Psychological Trait Questionnaires

Immediately after completing the robotic arm-reaching task, participants completed an exit questionnaire as a manipulation check (see Supplementary Materials 2: Exit questionnaires, for the description and results of these questionnaires), and a series of questionnaires to map potential group differences in psychological trait variables (see Supplementary Materials 3: Trait questionnaires, for the description and results of these questionnaires).

Data Analysis Overview

The hypotheses and analysis plans of Experiment 1 (https://osf.io/jpu42/?view_only=ff15ab4ac7e94b64a880be888bf73fe9) and Experiment 2 (https://osf.io/yvx6c/?view_only=5a7bc4b1d5374efba71f90f29bb09f20) were pre-registered on Open Science Framework (OSF). There were slight differences in the pre-registered analysis plans of both studies, but for the sake of consistency and comparability, the analyses were run based on the pre-registration with more stringent corrections. We will explicitly report these deviations below.

Independent samples *t*-tests between groups were performed on sample characteristics data (age, selected intensity of the electrical stimulus (in mA), self-reported pain intensity during calibration (Table 1)), and secondary outcome measures (see Supplementary Materials 2 and 3: Exit questionnaires and Trait questionnaires), to test baseline group differences. Data from the acquisition,

Table 1. Sample Characteristics of Experiments 1 (Experimental and Yoked Groups *n* = 32) and 2 (Experimental and Yoked Groups *n* = 35)

	Experimental (78% Female)		Yoked (84% Female)				
Experiment 1 N = *64*	M	SD	M	SD	DF	T	P
Age (18+)	22.25	3.79	22.42	4.08	62	-.171	.865
Intensity of the electrical stimulus (1-99 mA)	34.81	20.10	33.75	16.50	62	.231	.818
Self-reported pain intensity (0-10)	7.34	.87	7.47	1.11	62	-.503	.617
	Experimental (71% female)		Yoked (66% female)				
Experiment 2 N = *70*	M	SD	M	SD	DF	T	P
Age (18+)	21.86	3.27	22.66	3.15	68	-1.042	.301
Intensity of the electrical stimulus (1-99 mA)	41.00	25.30	37.09	23.75	68	.667	.507
Self-reported pain intensity (0-10)	7.51	1.25	7.89	0.99	68	-1.300	.198

Note - *P* – indication of significance at .002 (Bonferroni-corrected).

and reminder-of-acquisition phases were analyzed as manipulation checks (see Supplementary Materials 4 and 5: Results of acquisition phases, and Reminder-of-acquisition, for the analyses and results of these phases).

Generalization of self-reports was indicated by differences between the generalization trajectories (G1 > G2 > G3) in the Experimental, but not the Yoked Group. To test these hypotheses, self-reports were averaged over blocks for all participants, and repeated measures analyses of variance (RM ANOVAs) were calculated, with Group as the between-subjects factor, and Block and Trajectory as the within-subjects factors. Comparisons of G1 *vs.* G3 were of primary interest and were the only comparisons pre-registered for Experiment 1, given that G2 was similar to an ambiguously punished trajectory (T2). However, since all comparisons (G1 *vs.* G2, G2 *vs.* G3 and G1 *vs.* G3) were pre-registered for Experiment 2, we will report all comparisons for Experiment 1 as well.

For analyses of avoidance behavior, a MATLAB (MathWorks, Natick, MA) script was used to extract the maximal deviation data per trial. These values were averaged per block for each participant, and used to compare avoidance behavior between groups (RM ANOVAs) with Group as the between-subjects factor, and Block as the within-subjects factor. Given that, no pain was present during the generalization phase (test under extinction), we expected the largest generalization effects during the first generalization block, for all measures.

The α level was set at .05. For RM ANOVAs, Greenhouse-Geisser corrections were applied to correct for sphericity violations. Degrees of freedom, and *P* values are reported. Holm-Bonferroni corrected *P* values are reported for significant planned comparisons. The indication of effect size η_ρ^2 is reported for significant ANOVA effects, and Cohen's *d* for significant planned comparisons. Data analyses were crosschecked by EG and KV using RStudio (RStudio Inc., Boston, MA; Package "afex"[47]), and SPSS 25.0 (IBM, Armonk, NY), yielding the same results.

Experiment 1

Instrumental responses may become directly associated with the learning context,[23] leading to diminished responding when the context is changed.[1] How generalization was operationalized (absence of T1-3 and appearance of G1-3) in Glogan et al[17] may have been experienced by participants as a context-switch,[2] stimulating exploration of the novel trajectories similar to the previously pain-associated ones (G1 and G2), resulting in participants quickly learning that these novel generalization movements were not paired with the electrical stimulus. Therefore, the goal of Experiment 1 was to reduce visual context changes by presenting all trajectory arches simultaneously (Fig 1: panel B, Experiment 1), in accordance with previous studies of pain-related *fear* generalization.[37]

Methods

Thus, all 6 trajectory arches were visible throughout Experiment 1, but only T1-3 were available during the acquisition phase and only G1-3 during the generalization phase. When trajectories were available, their corresponding arches were colored black, and when they were unavailable, their arches were colored grey. Therefore the *acquisition phase* was similar to that of Glogan et al,[17] (contingencies: T1 = 100% punishment, T2 = 50% punishment, T3 = 0% punishment) except that all 6 movement trajectories were presented simultaneously. The acquisition phase consisted of 2 blocks of 12 trials. The *generalization phase* followed, and was similar to, the acquisition phase, except that only G1-3 were now available and no pain was presented. This phase consisted of 3 blocks of 12 trials. The 3 generalization blocks were interspersed by the brief *reminder-of-acquisition* blocks, comprising 5 trials each. During the acquisition and generalization phases, self-reports of pain-expectancy and pain-related fear were collected 3 times for each trajectory during each block on fixed, predefined trials, and once during the shorter reminder-of-acquisition blocks.

Participants

Sixty-five pain-free volunteers participated in this study. One participant was excluded prior to data analysis due to technical difficulties during data collection, amounting to 64 participants being included in the analyses (52 female, $M \pm SD$ (range) age = 22 $\pm$ 4 years, (18-37)). The sample size was based on the same a priori power calculation as that of Glogan et al[17] (using G*Power; α = .05, *d* = .80, power = .80) for an independent *t*-test (2-tailed), which yielded a sample size of 52. A large effect size was chosen based on the acquisition effect found in a previous study[35] when comparing the Experimental and Yoked groups at the end of acquisition. The sample size was then increased with roughly 20% because a reduced effect size was anticipated for generalization, accumulating to 64 participants. Participants were assigned either to the Experimental or Yoked Groups based on an alternating schedule depending on the order in which they arrived at the laboratory, and were naÿve to this allocation. The reason for using an alternating schedule was that the sequence of electrical stimuli received by each Experimental Group participant (based on their movement trajectory choices), was saved on the computer, and administered to their corresponding Yoked Group participant. Participants were recruited by KV through the research participation system of Maastricht University (Sona; Sona Systems, Nijmegen, The Netherlands), advertisements distributed around the university campus, and through social media. Exclusion criteria comprised chronic pain; analphabetism or diagnosed dyslexia; pregnancy; left-handedness; current/history of cardiovascular disease; chronic or acute respiratory disease (eg, asthma, bronchitis); neurological disease (eg, epilepsy); current/history of psychiatric disorder (eg, clinical depression, panic/anxiety disorder); uncorrected problems with hearing or vision; pain in the dominant hand, wrist, elbow or shoulder that may hinder performing the reaching task; presence of implanted electronic medical devices (eg, cardiac pacemaker); and presence of any

other severe medical conditions. All participants provided informed consent and completed an exclusion criteria checklist. Participants were informed that they could freely terminate participation at any time without any negative consequences, and received either 1.5 course credit, or €12.50 in gift vouchers as compensation. The data were collected in Maastricht between July and December of 2019, and the study was approved by the Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration number: 185_09_11_2017_S5).

Results

Sample Characteristics, Pain Stimulus, and Baseline Group Differences

There were no differences between the Experimental and Yoked Groups in age, intensity of the electrical stimulus (in mA) chosen during calibration, self-reported intensity of the electrical stimulus (see Table 1), or any of the scores on the psychological trait questionnaires (see Supplementary Materials 3: Trait questionnaires, Table S3.1).

Manipulation Checks

Acquisition: Pain-Expectancy, Pain-Related Fear, and Avoidance Behavior. Participants in the Experimental Group learned to expect (Fig 2: panel A) the electrical stimulus more during, and to fear (Fig 3: panel A), the pain-associated movements (T1-2) compared to the safe movement (T3). Furthermore, participants in the Experimental Group showed significantly larger deviations than the Yoked Group during the acquisition phase, demonstrating successful avoidance learning (Fig 4: panel A). For the complete results, see Supplementary Materials 4: Results of acquisition phases, Experiment 1.

Reminder-of-Acquisition: Pain-Expectancy, Pain-Related Fear, and Avoidance Behavior. During the reminder-of-acquisition blocks, the data pattern of all measures reflected the acquisition phase, confirming that the test of generalization (under extinction) did not affect the acquired differential pain-expectancy (Fig S5.1: panel A) and pain-related fear (Fig. S5.2: panel A) ratings for the acquisition trajectories, nor did it affect previously acquired avoidance behavior (Fig. S5.3: panel A). For the complete results, see Supplementary Materials 5: Reminder-of-acquisition, Experiment 1.

Testing Our Main Hypotheses: Generalization of Pain-Expectancy, Pain-Related Fear, and Avoidance Behavior

A 2×3×3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) x (Trajectory: G1-3) on the mean *pain-expectancy ratings* during generalization revealed no 3-way interaction, $F(3.94, 216.60) = .69$, $p = .580$, but a significant Group x Trajectory interaction, $F(1.61, 100.11) = 8.75$, $P < .001$, $\eta_p^2 = .12$, suggesting that groups showed distinct patterns of pain-expectancies for the different trajectories during the generalization phase. During the first generalization block (GEN1), the

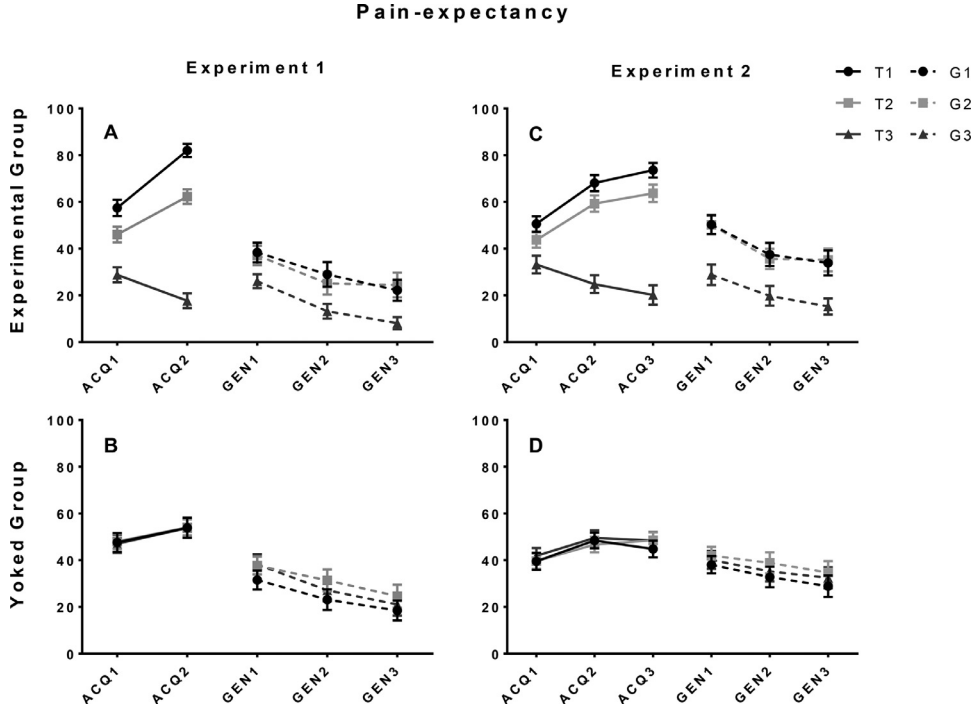

Figure 2. Mean pain-expectancy ratings towards the acquisition trajectories (T1-3) and generalization trajectories (G1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiment 1 (panels A and B) and Experiment 2 (panels C and D), during the acquisition blocks (Experiment 1: ACQ1-2, Experiment 2: ACQ1-3), and generalization blocks (GEN1-3). Error bars represent SDs.

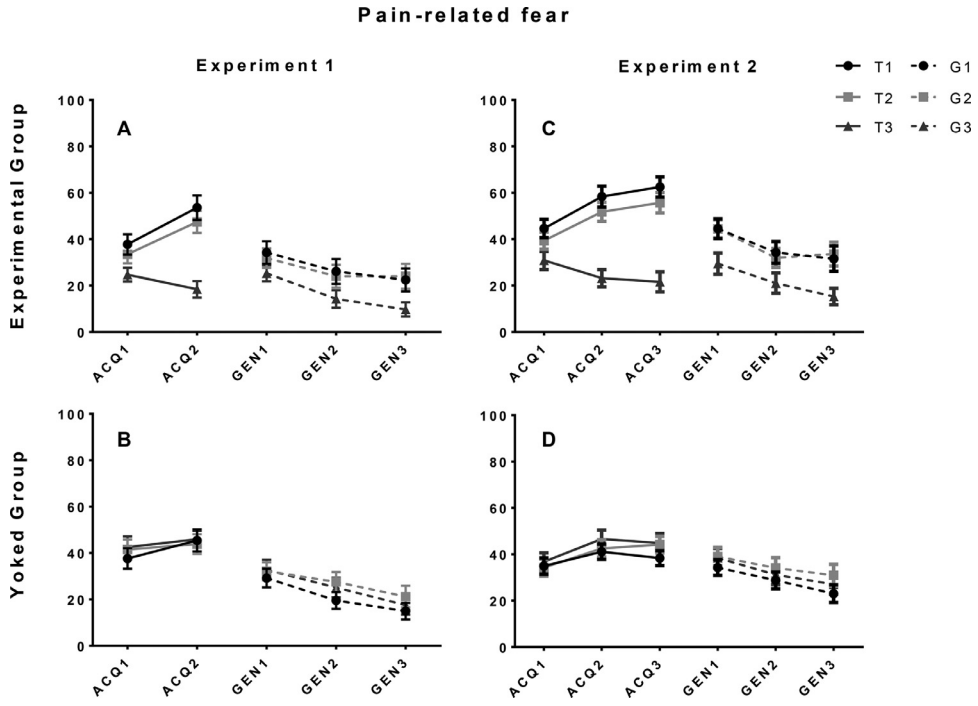

Figure 3. Mean pain-related fear ratings toward the acquisition trajectories (T1-3) and generalization trajectories (G1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiment 1 (panels A and B) and Experiment 2 (panels C and D), during the acquisition blocks (Experiment 1: ACQ1-2, Experiment 2: ACQ1-3), and generalization blocks (GEN1-3). Error bars represent SDs.

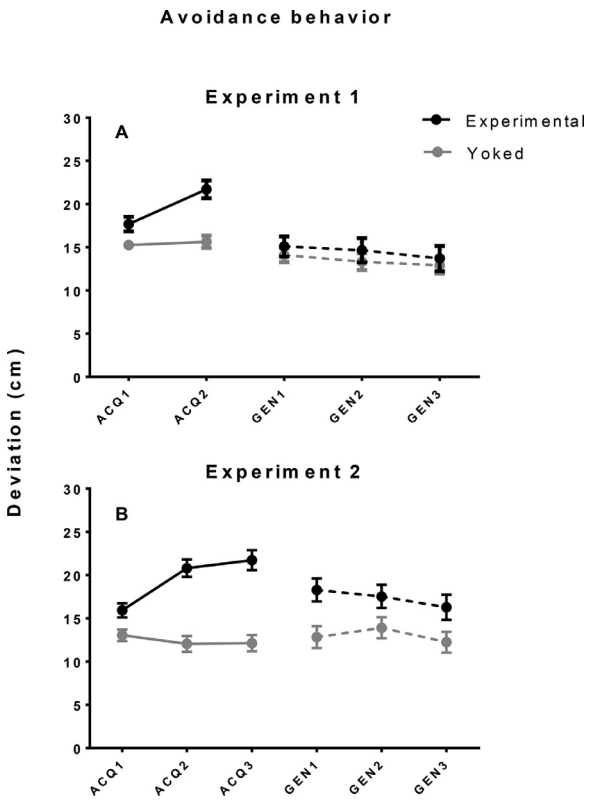

Figure 4. Mean maximal deviation (in cm) from the shortest trajectory, from the starting position to the target during the acquisition blocks (Experiment 1: ACQ1-2, Experiment 2: ACQ1-3), and generalization blocks (GEN1-3), in the Experimental and Yoked Groups of Experiments 1 (panel A) and 2 (panel B). Error bars represent SDs. Note – To increase comparability between phases, deviation data from the generalization phase have been linearly transformed to share the same co-ordinates as the acquisition data.

Experimental Group expected the electrical stimulus to occur more during G1 and G2, compared to G3 (G1 *vs.* G3: $t(62) = 3.14$, $P = .005$, $d = .59$; G2 *vs.* G3: $t(62) = 3.61$, $P = .002$, $d = .53$). In contrast to T1 and T2 during the acquisition phase, G1 did not evoke higher pain-expectancies than G2, $t(62) = .44$, $P = .664$ (Fig 2: panel A). Thus, pain-expectancies generalized towards the trajectories resembling the previously pain-associated ones (G1-2), whereas G3 continued to be appraised as comparatively safe in the Experimental Group. No significant differences in pain-expectancies were found between trajectories in the Yoked group (all P values $> .05$).

A similar RM ANOVA on the mean *fear ratings* during generalization also showed no 3-way interaction, $F(3.30, 204.62) = .67$, $P = .580$, but revealed a significant Group x Trajectory interaction, $F(1.43, 88.52) = 5.18$, $P = .010$, $\eta_\rho^2 = .08$. Unexpectedly, planned comparisons revealed that neither G1, $t(62) = 2.33$, $P = .069$ nor G2, $t(62) = 2.22$, $P = .060$ was feared more than G3 during GEN1, although the difference between G1 and G3 was significant prior to Holm-Bonferroni correction, $P = .023$. However, following visual inspection of the data, which suggested that the expected differences appeared later in the generalization phase, and because the Group x Trajectory interaction was not modulated by Block, we ran the same comparisons for the subsequent generalization blocks, although these were not pre-registered. During these blocks, G1 and G2 were feared more than G3 (see Supplementary Materials 6: Fear Generalization, Table S6.1, for the complete results of pain-related fear reports during the generalization phases) (Fig 3: panel A). No significant differences occurred between any of the pairs in the Yoked Group (all P values $> .05$) (Fig 3: panel B). Thus, fear did not

generalize in the hypothesized manner, although the effect emerged in the later blocks.

A 2×3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) on mean *maximal deviation* data during generalization yielded no significant effects (Group, $F(1, 62) = .52$, $P = .47$; Block, $F(1.56, 96.63) = 1.88$, $P = .17$; Group x Block, $F(1.56, 96.63) = .08$, $P = .88$). Thus, no generalization of avoidance behavior was observed in Experiment 1 (Fig 4: panel A).

Experiment 2

The 100% punishment rate for T1 in Glogan et al[17] may have resulted in high expectations of punishment also for G1. Thus, the absence of pain when exploring G1 at the beginning of generalization would have been surprising, leading to rapid disconfirmation of acquired threat beliefs (extinction).[7] In Experiment 2, we therefore aimed to reduce or delay rapid extinction by decreasing the punishment rates associated with the acquisition trajectories, and to thus increase the uncertainty associated with the painful movements (T1-2), and their generalization counterparts (G1-2).

Methods

The current paradigm was similar to that of Experiment 1, except that only available trajectory arches were visible during the given experimental phase (T1-3 during acquisition, G1-3 during generalization; as in Glogan et al[17]). Furthermore, T1 was now paired with an 80% instead of 100% punishment rate, and T2 with a 40% instead of 50%, punishment rate (Fig 1: panel B, Experiment 2). T3 remained 0% punished. The acquisition and generalization phases both consisted of 3 blocks of 12 trials, and the generalization blocks were again interspersed by reminder-of-acquisition blocks (5 trials each). Self-reports were collected in a similar manner to Experiment 1.

Participants

Seventy-eight pain-free volunteers participated in this study. Eight participants were excluded prior to data analysis due to technical difficulties during data collection. Thus, 70 participants were included in the analyses (48 female, $M \pm SD$ (range) age = 22 ± 3 years (18-31)). The sample size was based on the same a priori power calculation as those of Glogan et al[17] and Experiment 1 ($N = 64$). However, given that Glogan et al[17] showed no effect of avoidance generalization, and because we reduced punishment rates in the current study (possibly resulting in more variation between participants[30]), we increased the sample size for detecting a medium-to-large effect size. Participants were randomly assigned either to the Experimental or Yoked groups, based on a randomization schedule created in MATLAB, with the rule that the first participant must be assigned to the Experimental Group. Participants were naÿve to this allocation. Exclusion criteria were the same as in Experiment 1. Participants were recruited and tested in Maastricht by EG between July and December of 2019. The study was approved by the Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration number: 185_09_11_2017_S1_A1).

Results

Sample Characteristics, Pain Stimulus, and Baseline Group Differences

There were no differences between the Experimental and Yoked Groups in age, intensity of the electrical stimulus (in mA) chosen during calibration, self-reported intensity of the electrical stimulus (see Table 1), or any of the scores on the psychological trait questionnaires (see Supplementary Materials 3: Trait questionnaires, Table S3.2).

Manipulation Checks

Acquisition: Pain-Expectancy, Pain-Related Fear, and Avoidance Behavior. During the acquisition phase, the Experimental Group successfully acquired the movement-pain contingencies, shown by differential pain-expectancy (Fig 2: panel C) and fear (Fig 3: panel C) ratings, and successfully learned to avoid the electrical stimulus (Fig 4: panel B). For the complete results, see Supplementary Materials 4: Results of Acquisition Phases, Experiment 2.

Reminder-of-Acquisition: Pain-Expectancy, Pain-Related Fear, and Avoidance Behavior. Similarly to Experiment 1, the data patterns during the reminder-of-acquisition blocks for all measures reflected the acquisition phase, confirming that the test of generalization (under extinction) did not affect the originally acquired differential pain-expectancy (Fig S5.1: panel C) and pain-related fear (Fig S5.2: panel C), nor did it affect acquired avoidance behavior (Fig S5.3: panel B). For the complete results, see Supplementary Materials 5: Reminder-of-acquisition, Experiment 2.

Testing Our Main Hypotheses: Generalization of Pain-Expectancy, Pain-Related Fear, and Avoidance Behavior

A 2×3×3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) x (Trajectory: G1-3) of mean *pain-expectancy ratings* during the generalization phase yielded no significant 3-way interaction, $F(3.08, 209.73) = .79$, $P = .50$, but a significant Group x Trajectory interaction, $F(1.55, 105.16) = 7.76$, $P = .002$, $\eta_p^2 = .10$. This suggests that patterns of pain-expectancy for the different trajectories differed between groups. During the first generalization block (GEN1), the Experimental Group expected the electrical stimulus more during G1, $t(68) = 4.08$, $P < .0001$, $d = .86$, and G2, $t(68) = 4.75$, $P < .0001$, $d = .87$, compared to G3. In contrast to pain-expectancies toward T1 and T2, however, pain was not expected more during G1 compared to G2, $t(68) = .03$,

P = .978 (Fig 2: panel C). Thus, pain-expectancy beliefs generalized to some extent from the acquisition trajectories to the novel generalization trajectories in the Experimental Group. No significant differences were found between trajectories in the Yoked group (all P values > .05).

A similar RM ANOVA of mean *fear ratings* during generalization did not show a significant 3-way interaction, $F(3.17, 215.89) = .74$, $P = .54$, but revealed a Group x Trajectory interaction, $F(1.62, 109.91) = 6.52$, $P = .004$, $\eta_\rho^2 = .09$, suggesting that fear for the different trajectories differed between groups. The Experimental Group reported significantly higher fear for G1, $t(68) = 3.25$, $P = .004$, $d = .58$, and G2, $t(68) = 3.97$, $P = .001$, $d = .59$, compared to G3. Again, in contrast to fear reported toward T1 and T2 during acquisition, G1 was not feared more than G2, $t(68) = .01$, $P = .991$. Furthermore, to be consistent with Experiment 1 (although not pre-registered), exploratory comparisons of fear ratings towards all generalization trajectories were run on the subsequent generalization blocks, during which the effects from GEN1 persisted (Fig 3: panel C) (see Supplementary Materials 6: Fear Generalization, Table S6.2). No significant differences occurred for any of the pairs in the Yoked Group (all P values > .05) (Fig 3: panel D). Together with the pain-expectancy reports, these results indicate that pain-expectancy and pain-related fear generalized to some extent towards the novel trajectories resembling the previously pain-associated ones (G1-2), whereas acquired safety generalized to G3 in the Experimental Group.

A 2×3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) on mean *maximal deviation* during generalization yielded a significant main effect of Group, $F(1, 68) = 7.63$, $P = .007$, $\eta_\rho^2 = .10$, but not of Block, $F(1.88, 128.06) = 1.92$, $P = .150$, nor was there a significant 2-way interaction, $F(3.08, 209.73) = .79$, $P = .500$. Planned comparisons confirmed that, in line with our hypothesis, the Experimental Group avoided more compared to the Yoked Group during the first generalization block, $t(68) = 2.98$, $P = .004$, $d = .71$, demonstrating generalization of avoidance to the novel trajectories in the Experimental Group (Fig 4: panel B).

General Discussion

The present experiments aimed to investigate the conditions under which costly pain-related avoidance generalizes in healthy participants. We previously observed generalization in self-reports (pain-expectancy and pain-related fear), but not in costly avoidance.[17] Experiment 1 aimed to reduce exploration by decreasing visual contextual changes. Experiment 2 attempted to prevent rapid extinction of avoidance by increasing the uncertainty of punishment.

Self-reports of pain-expectancy and pain-related fear generalized in both experiments, that is, the Experimental Groups reported higher pain-expectancy for the generalization trajectories similar to the previously pain-associated ones (G1-2), compared to the trajectory resembling the previously safe one (G3). Although differential fear in Experiment 1 did not reach significance at the beginning of generalization (following P value adjustment), it emerged later during this phase. Importantly, where Experiment 1 did not show generalization of avoidance, Experiment 2 did; the Experimental Group deviated more than the Yoked Group during generalization.

The results of Experiment 1 replicate those of Glogan et al,[17] where self-reports generalized, but avoidance did not. This suggests that participants in the Experimental Groups of these studies explored the novel, less-effortful movement trajectories during generalization, despite fear, and despite us minimizing visual changes between phases in Experiment 1. Furthermore, they imply that avoidance rapidly extinguished due to this exploration - effects that were successfully countered in Experiment 2 by increasing the uncertainty associated with the pain-associated acquisition trajectories; participants likely needed more information to disconfirm their previously acquired fear beliefs, resulting in less (rapid) extinction of avoidance.

This aligns with reinforcement learning models, which define exploration as choosing options with uncertain outcomes (eg, movement possibly followed by pain), with the goal of obtaining future rewards (eg, needing to exert less effort).[28] Furthermore, the more one's expectations are violated (eg, surprising absence of pain), the more they will learn from exploration,[10] and the more likely they will be to re-evaluate current behavior (eg, stop avoiding).[32] On the other hand, if one's expectations are not violated, or they are uncertain from the get-go (eg, uncertain expectations of pain), less learning, and thus less behavior change will occur (ie, *exploitation* of a behavior with known outcomes[32]; eg, sustained avoidance) (see also[46]).

In line with Glogan et al[17] and Experiment 1, healthy people tend to explore, whereas inflexible behavior is more characteristic of people with chronic pain.[53] Thus, the current findings corroborate the fear-avoidance model of chronic pain,[55] which proposes that most people in acute pain test and correct pain expectations (ie, explore), which facilitates recovery.[29] However, if pain is interpreted as a sign of serious harm over which one has limited control, fear of pain and re-injury will evoke sustained avoidance.[33] Furthermore, psychological and neurobiological theories of anxiety place uncertainty at the center of anxiety pathology[20]: Uncertainty complicates the process of balancing the efficiency (eg, exploration) and effectiveness (eg, exploitation) of threat-related preparatory behaviors, thus increasing the likelihood of making overly prudent choices (eg, by adopting a "better safe than sorry" approach[52]). Furthermore, uncertainty impedes one's ability to *control* aversive events, which results in diffuse, costly, and ineffective preparatory behaviors.[52]

In Experiment 2, uncertainty associated with the acquisition movements may have therefore directly *decreased* exploration, rather than simply countering its effects (rapid extinction), motivating participants to behave anxiously,[19,20] leading to less exploration and instead excessive avoidance. In line with this,

visualization, and a post-hoc *t*-test on choice behavior, in the current experiments shows that participants in Experiment 2 exhibited less exploration at the beginning of the generalization phase, compared to participants in Experiment 1 (see Supplementary Materials 7: Switching Behavior, Fig S7). This indeed suggests that in some participants, uncertainty directly reduced exploration, implying that uncertainty about movements resulting in pain may hinder recovery due to decreased exploration and less disconfirmation of fearful beliefs. In agreement with this, a recent study[24] incorporating a costly avoidance response, showed that both anxiety sensitivity and intolerance of uncertainty increase the synchrony between generalized fear and avoidance in healthy participants. Given that uncertainty is accompanied by uncontrollability,[52] future research could investigate ways in which treatments can increase people's experience of control over their pain. In support of this, controllability over pain was recently shown to selectively reduce pain-related suffering, but not pain intensity or pain unpleasantness, in healthy participants.[31] This is especially relevant for chronic pain, in which targeting the management and psychosocial concomitants of pain, is often more effective than targeting the pain itself.[14,15]

Importantly, the results of Glogan et al[17] and Experiment 1 indicate that adding a *cost* to experimental avoidance increases exploration. Previous studies of avoidance generalization in the anxiety domain reported synchronized generalization of self-reported fear and operant low-, or no-cost, avoidance (eg,[3,13]). This is an important distinction from an ecological validity perspective, since real-life avoidance is often extremely costly,[56] and people with pain or anxiety often weigh the value of avoidance against that of alternative, competing behaviors.[6,51] Thus, people with chronic pain, for example, may go to work, or play with their children, despite fear of pain.[50,56] In fact, the presently reported dissociations between self-reports and avoidance align with literature demonstrating attenuated avoidance, but not fear, when alternative goals (eg, gaining rewards) compete with avoidance of both aversive[44, 45] and painful[5,6,51] stimuli. These findings highlight the importance of clinical interventions targeting disability by emphasizing the value of pursuing life goals (eg, Acceptance and Commitment Therapy[22,43,57]).

It should be noted that, with the robotic arm-reaching paradigm, avoidance was recently found to be modulated by context,[34] demonstrating that context-switches, *per se*, do not eliminate avoidance in the paradigm. However, in Meulders et al,[34] the avoidance response itself did not change. Indeed, although some contextual change is inherent to generalization studies, the critical change in the current studies is in fact *response-based*, ie, generalizing the avoidance response to a similar, yet different response. In response generalization, the contingency (eg, punishment rate) related to one response, generalizes to other similar responses, increasing or decreasing the recurrence of these similar behaviors.[48] However, there is scarcely any literature investigating avoidance generalization from the perspective of response generalization. Instead, avoidance generalization is often examined using the same avoidance response (often pressing a computer key), to stimuli differing from each other along perceptual[24,40,54] or semantic[3,13] continua. Since in chronic pain both the feared stimulus and avoidance response often are movements themselves, it is important to investigate avoidance generalization in the pain domain as generalization between responses.

Some limitations should be discussed. First, the aim of showing all movement trajectories simultaneously in Experiment 1 was to decrease context-changes between phases. However, generalization relies on a balance between differentiation and generalization between stimuli.[16,42] Simultaneously presenting all trajectory arches may have facilitated discrimination between movements, thus reducing the likelihood of generalization. Second, computational models could enable detailed examination of individual response patterns in the present data.[25] However, given the unbalanced designs of Experiments 1 and 2 (different numbers of trials and participants), the fitted models would have been difficult to compare. Third, we speculate that the observed dissociations between fear and avoidance in Glogan et al[17] and Experiment 1 resulted from avoidance-costs. However, in order to confirm this hypothesis, these experiments should be replicated with no, or decreased costs. Fourth, to better understand the relationship between uncertainty and avoidance generalization, intolerance of uncertainty could be added as a psychological trait measure in future studies.[4,11] Furthermore, a mechanism of chronic pain that may contribute to excessive avoidance, is deficient safety learning (heightened fearful reactivity to objectively safe conditions).[21] To directly test whether people with chronic pain show impaired learning in comparison to healthy people in the current paradigm, avoidance generalization should be compared between people with chronic pain and healthy controls, using objectively predictable punishment (T1 = 100%) during acquisition. Finally, where traditional fear generalization studies only employ 2 extreme stimuli (CS+ and CS-) during acquisition, between which generalization stimuli (GSs) lie on a perceptual continuum during generalization, we also trained an ambiguous trajectory (T2), lying between the 2 extreme trajectories (T3 and T1). This was to increase ecological validity, since in real life there is rarely only one painful, and one entirely safe movement. However, this way of operationalizing generalization may limit the comparability of the current studies to previous fear generalization studies.

Taken together, the present results suggest that, avoidance-costs can motivate healthy people to explore alternative behaviors. However, uncertainty about those behaviors resulting in pain may prolong recovery, due to reduced disconfirmation of threat beliefs when exploring. The current results also offer preliminary evidence suggesting that uncertainty may directly decrease healthy exploration, causing people to behave more anxiously, and rigidly avoid pain-free movements similar to previously painful ones. Yet, further research is needed to

determine the exact mechanism by which pain-related avoidance generalizes to a disabling degree.

Acknowledgments

The authors wish to thank Jacco Ronner for programming the experiment, Richard Benning for designing and creating the graphics of the experiment, Thom Frijns for filming and editing the video of the experiment, and Angelos Krypotos for helpful input.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2021.03.149.

References

1. Bouton ME, Todd TP, Leon SP: Contextual control of discriminated operant behavior. J Exp Psychol Animal Learn Cogn 40:92-105, 2014

2. Bouton ME, Todd TP: A fundamental role for context in instrumental learning and extinction. Behav Process 104:13-19, 2014

3. Boyle S, Roche B, Dymond S, Hermans D: Generalisation of fear and avoidance along a semantic continuum. Cognit Emot 30:340-352, 2015

4. Carleton RN, Norton MA, Asmundson GJ: Fearing the unknown: A short version of the intolerance of uncertainty scale. J Anxiety Dis 21:105-117, 2007

5. Claes N, Crombez G, Vlaeyen JW: Pain-avoidance versus reward-seeking: An experimental investigation. Pain 156:1449-1457, 2015

6. Claes N, Karos K, Meulders A, Crombez G, Vlaeyen JWS: Competing goals attenuate avoidance behavior in the context of pain. J Pain 15:1120-1129, 2014

7. Craske MG, Hermans D, Vervliet B: State-of-the-art and future directions for extinction as a translational model for fear and anxiety. in Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 373; 2018

8. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B: Maximizing exposure therapy: An inhibitory learning approach. Behav Res Ther 58:10-23, 2014

9. Davis J, Bitterman ME: Differential reinforcement of other behavior (DRO): A yoked-control comparison. J Exp Anal Behav 15:237-241, 1971

10. Dayan P, Angela JY: Expected and unexpected uncertainty: ACh and NE in the neocortex. Advances in Neural Information Processing Systems; 2003173-180

11. Dugas MJ, Buhr K, Ladouceur R: The role of intolerance of uncertainty in etiology and maintenance. Generalized Anxiety Disorder: Advances in Research and Practice. New York, NY, Guilford Press, 2004, pp 143-163

12. Dymond S, Dunsmoor JE, Vervliet B, Roche B, Hermans D: Fear generalization in humans: Systematic review and implications for anxiety disorder research. Behav Ther 46:561-582, 2015

13. Dymond S, Schlund MW, Roche B, De Houwer J, Freegard GP: Safe from harm: Learned, instructed, and symbolic generalization pathways of human threat-avoidance. PLoS One 7, 2012

14. Gatchel RJ, Okifuji A: Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. J Pain 7:779-793, 2006

15. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC: The biopsychosocial approach to chronic pain: Scientific advances and future directions. Psychol Bull 133:581-624, 2007

16. Ghirlanda S, Enquist M: A century of generalization. Anim Behav 66:15-36, 2003

17. Glogan E, Gatzounis R, Meulders M, Meulders A: Generalization of instrumentally acquired pain-related avoidance to novel but similar movements using a robotic arm-reaching paradigm. Behav Res Ther 124:103525, 2020

18. Glogan E, Gatzounis R, Vandael K, Franssen M, Vlaeyen JWS, Meulders A: Investigating pain-related avoidance behavior using a robotic arm-reaching paradigm. JoVE, 2020. https://doi.org/10.3791/61717

19. Grillon C, Baas JM, Cornwell B, Johnson L: Context conditioning and behavioral avoidance in a virtual reality environment: Effect of predictability. Biol Psychiatry 60:752-759, 2006

20. Grupe DW, Nitschke JB: Uncertainty and anticipation in anxiety: An integrated neurobiological and psychological perspective. Nat Rev Neurosci 14:488-501, 2013

21. Harvie DS, Moseley GL, Hillier SL, Meulders A: Classical conditioning differences associated with chronic pain: A systematic review. J Pain 18:889-898, 2017

22. Hughes LS, Clark J, Colclough JA, Dale E, McMillan D: Acceptance and commitment therapy (ACT) for chronic pain: A systematic review and meta-analyses. Clin J Pain 33:552-568, 2017

23. Hull CL: Principles of Behavior: An Introduction to Behavior Theory. Oxford, England, Appleton-Century, 1943

24. Hunt C, Cooper SE, Hartnell MP, Lissek S: Anxiety sensitivity and intolerance of uncertainty facilitate associations between generalized Pavlovian fear and maladaptive avoidance decisions. J Abnorm Psychol 128:315-326, 2019

25. Krypotos AM, Crombez G, Meulders A, Claes N, Vlaeyen JWS: Decomposing conditioned avoidance performance with computational models. Behav Res Ther 133:103712, 2020

26. Krypotos AM, Effting M, Kindt M, Beckers T: Avoidance learning: A review of theoretical models and recent developments. Front Behav Neurosci 9:189, 2015

27. Krypotos AM, Vervliet B, Engelhard IM: The validity of human avoidance paradigms. Behav Res Ther 111:99-105, 2018

28. Lee MD, Zhang S, Munro M, Steyvers M: Psychological models of human and optimal performance in bandit problems. Cogn Syst Res 12:164-174, 2011

29. Lethem J, Slade PD, Troup JD, Bentley G: Outline of a fear-avoidance model of exaggerated pain perception-I. Behav Res Ther 21:401-408, 1983

30. Lissek S, Pine DS, Grillon C: The strong situation: A potential impediment to studying the psychobiology and pharmacology of anxiety disorders. Biol Psychol 72:265-270, 2006

31. Löffler M, Kamping S, Brunner M, Bustan S, Kleinböhl D, Anton F, Flor H: Impact of controllability on pain and suffering. Pain Rep 3, 2018. e694-e694

32. Mehlhorn K, Newell B, Todd P, Lee M, Morgan K, Braithwaite V, Hausmann D, Fiedler K, Gonzalez C: Unpacking the exploration–exploitation tradeoff: A synthesis of human and animal literatures. Decision 2:191-215, 2015

33. Meulders A: From fear of movement-related pain and avoidance to chronic pain disability: A state-of-the-art review. Curr Opin Behav Sci 26:130-136, 2019

34. Meulders A, Franssen M, Claes J: Avoiding based on shades of gray: Generalization of pain-related avoidance behavior to novel contexts. J Pain 21:1212-1223, 2020

35. Meulders A, Franssen M, Fonteyne R, Vlaeyen JWS: Acquisition and extinction of operant pain-related avoidance behavior using a 3 degrees-of-freedom robotic arm. Pain 157:1094-1104, 2016

36. Meulders A, Jans A, Vlaeyen JWS: Differences in pain-related fear acquisition and generalization: an experimental study comparing patients with fibromyalgia and healthy controls. Pain 156:108-122, 2015

37. Meulders A, Vandebroek N, Vervliet B, Vlaeyen JWS: Generalization gradients in cued and contextual pain-related fear: An experimental study in healthy participants. Front Human Neurosci 7:345, 2013. https://doi.org/10.3389/fnhum.2013.00345

38. Meulders A, Vansteenwegen D, Vlaeyen JWS: The acquisition of fear of movement-related pain and associative learning: A novel pain-relevant human fear conditioning paradigm. Pain 152:2460-2469, 2011

39. Morley S, Eccleston C, Williams A: Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain 80:1-13, 1999

40. Norbury A, Robbins TW, Seymour B: Value generalization in human avoidance learning. eLife 7:e34779, 2018. https://doi.org/10.7554/eLife.34779

41. Pavlov IP: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. London, Oxford University Press, 1927

42. Pavlov IP: Lectures on Conditioned Reflexes. Vol. II. Conditioned Reflexes and Psychiatry. New York, NY, US, International Publishers, 1941

43. Pielech M, Vowles KE, Wicksell R: Acceptance and commitment therapy for pediatric chronic pain: Theory and application. Children (Basel, Switzerland) 4:10, 2017

44. Pittig A, Dehler J: Same fear responses, less avoidance: Rewards competing with aversive outcomes do not buffer fear acquisition, but attenuate avoidance to accelerate subsequent fear extinction. Behav Res Ther 112:1-11, 2019

45. Pittig A, Hengen K, Bublatzky F, Alpers GW: Social and monetary incentives counteract fear-driven avoidance: Evidence from approach-avoidance decisions. J Behav Ther Exp Psychiatry 60:69-77, 2018

46. Rescorla RA, Wagner AR: A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. Classical Conditioning II: Current Research and Theory. New York, NY, Appleton-Century-Crofts, 1972, pp 64-99

47. Singmann H, Bolker B, Westfall J, Aust F, Ben-Shachar MS: Afex: Analysis of Factorial Experiments [R package version 0.25-1]. R Package Version 0.25-1. 2019

48. Skinner BF: Science and Human Behavior. New York, NY, Macmillan, 1953

49. Urcelay GP, Prével A: Extinction of instrumental avoidance. Curr Opin Behav Sci 26:165-171, 2019

50. Van Damme S, Legrain V, Vogt J, Crombez G: Keeping pain in mind: A motivational account of attention to pain. Neurosci Biobehav Rev 34:204-213, 2010

51. Van Damme S, Van Ryckeghem DM, Wyffels F, Van Hulle L, Crombez G: No pain no gain? Pursuing a competing goal inhibits avoidance behavior. Pain 153:800-804, 2012

52. Van den Bergh O, Brosschot JF, Critchley H, Thayer JF, Ottaviani C: Better safe than sorry: A common signature of general vulnerability for psychopathology. Perspect Psychol Sci 16:225-246, 2021

53. van Dieën JH, Flor H, Hodges PW: Low-back pain patients learn to adapt motor behavior with adverse secondary consequences. Exerc Sport Sci Rev 45:223-229, 2017

54. van Meurs B, Wiggert N, Wicker I, Lissek S: Maladaptive behavioral consequences of conditioned fear-generalization: A pronounced, yet sparsely studied, feature of anxiety pathology. Behav Res Ther 57:29-37, 2014

55. Vlaeyen J, Linton S: Fear-avoidance and its consequences in chronic musculoskeletal pain: A state of the art. Pain 85:317-332, 2000

56. Volders S, Boddez Y, De Peuter S, Meulders A, Vlaeyen JWS: Avoidance behavior in chronic pain research: A cold case revisited. Behav Res Ther 64:31-37, 2015

57. Vowles KE, Fink BC, Cohen LL: Acceptance and Commitment Therapy for chronic pain: A diary study of treatment process in relation to reliable change in disability. J Contextual Behav Sci 3:74-80, 2014