Paper accepted in Behaviour Research and Therapy

Pavlovian-to-Instrumental Transfer in Individuals with Chronic Pain

Angelos-Miltiadis Krypotos[1,2], Rachel Sjouwerman[3], Mathijs Teppers[4,5], & Johan W.S. Vlaeyen[1,3]

[1] Research group of Healthy Psychology, KU Leuven, Belgium

[2] Department of Clinical Psychology, Utrecht University, Netherlands

[3] Experimental Health Psychology, Maastricht University, Netherlands

[4]Ziekenhuis Oost-Limburg, Lanaken, Belgium

[5] TRACE (Centre for Translational Psychological Research), Belgium

Author note

Angelos-Miltiadis Krypotos was supported by an FWO grant (Reg. # 12X5320N) and is now supported by an NWO grant (Reg. # 401.18.056) grant. Johan W.S. Vlaeyen is supported by the 'Asthenes' long-term structural funding–Methusalem grant by the Flemish Government, Belgium (METH/15/011) and the National Institute for Health and Disability Insurance (NIHDI: #2018-00047). Rachel Sjouwerman is supported by an NWO Open Competition grant (nr. 406.20.GO.032) awarded to Johan W.S. Vlaeyen. This study was supported by an infrastructure grant from the FWO and the Research Fund KU Leuven, Belgium (AKUL/19/06; I011320N).

Correspondence concerning this article should be addressed to Angelos-Miltiadis Krypotos, Tiensestraat 102, 3000 Leuven, Belgium. E-mail: amkrypotos@gmail.com.

Abstract

Avoidance of pain has been argued to be key factor leading pain events to chronic disability. In this respect, research has focused on investigating the working mechanisms of avoidance's acquisition. Avoidance of painful stimuli has been traditionally studied using a combination of Pavlovian and Instrumental procedures. However, such approach seems to go against real-life scenarios where avoidance is commonly acquired more readily. Using a novel pain avoidance paradigm, we tested whether pain avoidance can be installed in absence of associations between a cue and pain omission, and whether such avoidance differs between pain patients and healthy controls. Participants first learned to avoid painful stimuli by pressing a grip bar. Then, they passively encountered pairings of one geometrical shape with pain and of another geometrical shape without pain. Lastly, participants encountered the geometrical shapes while being able to use the grip bar. Results showed that participants pressed the bar more vigorously when encountering the previously pain-related shape compared to the pain-unrelated shape. This effect did not seem to differ between pain patients and healthy control. Our study could inspire a new way in measuring avoidance in pain, possibly paving the way to better understanding how avoidance is installed in chronic pain.

Keywords: Pavlovian learning, instrumental learning, conditioning, therapy, pain

Pavlovian-to-Instrumental Transfer in Patients with Chronic Pain

Avoidance of potentially painful stimuli is an adaptive response, often motivated by the fear that pain potentially signals a bodily harm (Crombez et al., 2012; Meulders, 2019). The learning of pain avoidance is frequently studied in experimental research by using a combination of *Pavlovian* and *Instrumental* learning procedures (Krypotos, 2015; Pittig et al., 2020; Vlaeyen, 2015). In Pavlovian learning procedures, cues (e.g., picture of a square; Conditioned Stimulus or CS+) are paired with a painful stimulus (e.g., an electrocutaneous stimulus; Unconditional Stimulus or US) while some other cues (CS-) are not. During Instrumental learning procedures, participants can avoid the US presentation by performing an experimenter-defined action (e.g., pressing a grip bar). Despite the insights gained, the current experimental procedures assume a two-step learning (i.e., Pavlovian and Instrumental learning both involving the same CS)(Krypotos, 2015). However, it would seem evolutionary advantageous that pain avoidance is acquired rapidly, rather than being a result of two-stages (Bouton & Fanselow, 1997). As such, avoidance learning towards a CS+ can be better addressed by procedures that assume avoidance towards a CS+, but without avoidance being associated with that CS+.

This goal can be achieved by a procedure called Pavlovian-to-Instrumental Transfer (PIT). During PIT, individuals exhibit instrumental responses towards a CS+, but without that instrumental response ever being associated with the cancellation of the US in presence of the CS+.. Specifically, participants first learn to actively perform an experimenter-defined response to avoid a US (*Instrumental* phase), in *absence* of any CS. Then, during the passive *Pavlovian* phase, individuals encounter new stimuli (CSs) with some of them being followed by the US. The result of learning is tested during the *Transfer phase*, were individuals can perform the experimenter-defined response again but in the presence of the new CSs. Typically, participants

emit a stronger avoidance response in the presence of the CS+ and not the CS-, although such response has never been directly associated with the CS+.

To date, the PIT effects in humans have been mainly tested using appetitive stimuli as USs (e.g., Sekutowicz et al., 2019), with only a few studies using aversive stimuli (Lewis et al., 2013). In addition, none of the studies so far have tested PIT in the context of pain. However, such a study is deemed relevant given that successful pain avoidance is a key characteristic of both acute and chronic pain (Linton et al., 2018; Vlaeyen, 2015). Studying PIT within a pain context could prove useful for uncovering how avoidance may maintain chronic pain and disability.

In this study we tested an aversive PIT paradigm with a painful US, and whether PIT-related avoidance responses differ between individuals reporting chronic pain and those with no chronic pain. In the Instrumental phase, participants received a painful stimulus (US) unless they press a grip bar with their dominant hand, in the absence of any CS. Then, in a subsequent Pavlovian phase, two CSs (i.e., a picture of a square or a triangle) were presented on screen, with one of them being paired with the pain-US while another with the pain-US absent. Participants were not allowed to use the grip bar during this phase. Lastly, in the Transfer phase, the CSs were presented while participants were able to press the grip bar again. To prevent further learning, no pain-USs are delivered in this phase. Given that in chronic pain patients, excessive avoidance behaviour is often observed, as compared to people not in chronic pain, we expect stronger avoidance responses in the chronic pain group in our study as well. Specifically, we hypothesized stronger grip responses towards the CS+, and not the CS-, in both groups. We also expected that

these stronger CS+ responses, compared to the CS-, will be stronger in the chronic pain group as compared to the non-pain control group." [1]

Methods

Participants. Ninety-seven participants were included, of whom individuals with chronic pain (N = 50) and no pain controls (N = 47). No pain controls were matched on age and sex with the chronic pain group. A power analysis showed that for a repeated measures ANOVA with 1 within subject factor with 2 levels (CS+ vs. CS-), 1 between subject factor with 2 levels (chronic pain vs. no pain control group), an alpha level of 0.05, power of 0.8, a correlation between measures of 0.5, a non-sphericity correction of 1, and an effect size of 0.2 (between small and medium), a sample of 52 participants in total was needed (Faul et al., 2009). However, we opted for a higher sample due to potential attrition and drop-outs. As for practical reasons the testing of the patient population started earlier than that of the control group, we were able to age-match the latter group by selecting participants with a similar age as that of the patient population. The inclusion criteria for the chronic pain group were: over 18 years old and reporting pain for longer than 3 months. The exclusion criteria based on self-report were: (a) not speaking Dutch at a native level, (b) not able to move their arms, shoulders, or hands due to pain (c) reporting heart or cardiovascular problems or disease, (d) lung problems or a lung disease, (e) a neurological disorder, (f) a psychiatric disorder, (g) any other serious medical condition (excluding chronic pain) (h) pregnancy, (i) using recreational drugs (such as cannabis), (j) recovering from severe trauma or an operation, (k) having taken any medicine which could influence the intestines or the

[1] Please note that our hypothesis do not stem from an assumption that avoidance is necessarily maladaptive in chronic pain, but only that in chronic pain often avoidance exceeds the relevant benefits.

central nervous system, (l) not to get involved in stressful situations as required by their doctors, (m) having had an electronic implant (such as pace-maker), (n) hearing problems, and (o) poor vision and not corrected by glasses or contact lenses. Mentally and physically healthy individuals should have been either above 18 years old and were excluded from the study by the same criteria of the chronic pain group and also if (p) they reported problems moving arms, shoulders, or hands, (q) acute or chronic pain on wrists, hands, shoulders, or related areas. Participants were tested either in a regional hospital in the east of Belgium or the psychology labs at KU Leuven, in the city of Leuven, Belgium. The group of chronic pain patients that was included in this study participated in the David Back Concept rehabilitation program at the 'Ziekenhuis Oost-Limburg', or were recruited via social media, unions, and patient organizations. The control participants were recruited from the city of Leuven, Belgium. As for practical reasons the testing of the patient population started earlier than that of the control group, we were able to age-match the latter group by selecting participants with a similar age as that of the patient population. The study was preregistered at the Open Science Framework website: https://osf.io/zrswu

Stimuli. A triangle and square shape – presented on the middle of the screen -- served as CSs. Which shape served as the CS+ and the CS- was counterbalanced across participants. Electrocutaneous pain was delivered at the wrist (styloid process of the left ulnar bone) with two reusable electrodes placed on the forearm of the non-dominant hand (Digitimer Ltd, Hertfordshire, UK). These electrodes were filled with KY-gel (Johnson & Johnson, New Brunswick, NJ) and connected to the DS7 Isolated Bipolar Constant Current stimulator (Digitimer Ltd, Hertfordshire, UK). This pain stimulus served as the US.

Rating scales. As in our previous studies (Krypotos et al., 2022), participants rated the painfulness of the electrocutaneous stimulus using a 10-point painfulness rating scale with the question "*How painful did you find this stimulus?*" and anchors to "no sensation at all" (1) to

"worst pain imaginable" (10). Participants also rated the electrocutaneous stimulus based on its unpleasantness (i.e., *How unpleasant do you find this stimulus?* 1: not unpleasant at all; 10: extremely unpleasant) and their tolerance to it (i.e., *How difficult was it for you to endure the electrocutaneous stimulus*? 1: not difficult at all; 10: extremely difficult). Participants rated the contingencies between each CS and the US presentation with the rating "*To what extent do you expect to receive an electrocutaneous stimulus after this geometrical shape?*" (anchors: 1: not at all; 10: very much). They also rated their fear of each CS (i.e., *How afraid were you of the geometrical shape above?* 1: not at all; 10: very much).

Questionnaires. Both groups filled in the following questionnaires for descriptive reasons: The Intolerance of Uncertainty Scale (Buhr & Dugas, 2002), the Neuroticism scale of the Eysenck's Personality Questionnaire (Eysenck and Eysenck, 1964), the Fear of Pain Questionnaire (Roelofs et al., 2005), and the Behavioral Inhibition/Activation scales (Franken & Muris, 2005).

Avoidance response

The avoidance response was measured with a hand grip (Vernier *isometric hand dynamometer*, Vernier Beaverton, OR 97005 USA). The participants took the grip in their dominant hand, and when the force with which the grip was squeezed exceeded a predetermined threshold (see grip force calibration), the pain stimulus was delayed by 5 seconds.

Procedure. Participants first read the information brochure and signed the informed consent. Then, the electrodes were fitted and the calibration staircase procedure took place to determine per participant the intensity of the electrocutaneous stimulation. The starting point was an intensity of 1 mA, which was then gradually increased with 2 mA at each step. At each step,

participants rated the intensity of the electrocutaneous stimulus using the numerical rating scale (see "Ratings" section). We stopped increasing the intensity when the stimulus was judged to be "moderately painful and demanded some effort to tolerate" (i.e., rating of 8) using the painfulness rating scale presented in the "Ratings" section. Participants were asked to rate verbally to the experimenter each stimulus on a pain scale, an unpleasantness scale, and a tolerance scale, with the final intensity of the stimulus being determined based on the tolerance scale. The intensity of the stimulus and ratings on the question were filled in a calibration form. Please note that the intensity of the stimulus was set to a painful level and not to an 'unpleasant but non-painful' level as typically done in fear conditioning studies (Gazendam et al., 2020)

The calibration of the hand grip followed, during which participants were asked to press the hand grip as hard as they could so the maximum intensity of the handgrip could be determined. The experimenter explained that a hand grip was going to be used during the experiment to decrease the chance of receiving the painful stimulus and demonstrated the use of the hand grip to the participant. Unbeknown to the participants, to avoid the electrocutaneous stimulus during the experimental procedure, participants needed to exert at least 50% of their maximum pressure on the hand grip. This calibration procedure took about 10 seconds. The main PIT procedure followed. The procedure of the PIT-paradigm of this study was based on the protocol of Lewis et al., 2013 and the experiment was programmed in PsychoPy.37 (Peirce, 2007). Participants underwent three phases: an instrumental learning phase, a Pavlovian learning phase, and a transfer phase.

Instrumental phase: Participants saw a square on the screen that represented an electrical circuit (Fig. 1). When the circuit was closed, it meant that there was a chance the electrocutaneous stimulus would follow. By squeezing the hand grip forcefully enough, participants could break the circuit, and as such avoid receiving the electrocutaneous stimulus.

Participants received the electrocutaneous stimulus every 3 seconds unless they put enough pressures on the hand grip. In case they exhibited at least 50% of their maximum force, the electrocutaneous stimulus was postponed for 5 seconds. If within these 5 seconds they put enough pressure again on the hand grip, the electrocutaneous stimulus was again postponed for 5 seconds, and so on. The instrumental phase was stopped after 180 seconds.

Pavlovian phase: Participants saw two different geometrical shapes (a square and a triangle) on the screen in front of them. They were informed that they may, at some point, receive a painful electrocutaneous stimulus and that they could figure out the association between the geometric figure and the painful stimulus. In this phase, participants were not allowed use the hand grip. On each trial, the CS was displayed on the screen for 4 seconds, 18 times in total (nine times per CS). The CS+ was always followed by the pain-US whereas the CS- was never followed by a US. After each presentation of the stimuli, a random intertrial interval of 7, 9, or 11 seconds was presented with a fixation cross in the middle of the screen. At the end of the phase, the CSs were shown on the computer screen one by one, and participants were asked to rate how afraid they were of each geometrical figure, and how unpleasant they perceived the figure.

Transfer phase: During the Transfer phase, participants were informed that they could use the hand grip again after the fixation cross that was presented between trials, to interrupt the electrical circuit that was displayed on the screen together with one of the two geometrical shapes they had seen before.. The two geometrical shapes with the electrical circuit were presented on the screen for 4 seconds 12 times in total (six times per CS). Participants were reminded that squeezing the bar hard enough reduced the chance of receiving a painful stimulus. To prevent further learning, no US was delivered during the transfer phase. After each presentation of the stimuli, a random intertrial interval of 7, 9, or 11 seconds was presented with a fixation cross in the middle of the screen. At the end of this transfer phase, the CSs were displayed again on the

computer screen, and participants were asked to rate fearfulness and unpleasantness of each geometrical shape.

Upon completion of the experimental procedure the equipment was disconnected from the participants. The participants were asked to fill out the questionnaires. Then, the participants were compensated and thanked for taking part in the study.

Data reduction and statistical analyses. For extracting the avoidance data for transfer phase, we computed mean force per trial and then centered the data per participant. Then we computed mean responding separately for each CS.

Between group sex differences were evaluated using chi-square analysis. Also, groups were compared in terms of questionnaire scores and age using separate one-way Analysis of Variance (ANOVA). Fear and unpleasantness ratings, as well as PIT effect, here as the force exerted on the grip bar, were compared using separate 2 (CS: CS+ vs. CS-) x 2 (Group: Pain Group vs. Healthy Controls) repeated measures ANOVAs, separately for each phase with CS serving as the within-subject factor and Group as the between-subject factor. We followed up these tests with post-hoc comparisons, using Bonferroni corrections. The number of electrocutaneous stimuli participants received in the instrumental phase was computed, with a maximum of 60 stimuli (180sec/3sec). In line with our previous studies (e.g., Krypotos et al., 2017) we conducted our analysis within both a frequentist framework, using an alpha level of 0.05, as well as using Bayes factors. For estimating the Bayes Factors we used the software program JASP and we used the default options for all our analyses. For more information about Bayesian analyses, we point to relevant resources (Krypotos et al., 2017, 2017).

Results

Demographics and Questionnaires. There were no group differences in terms of sex (χ^2 (1) = 0.005, p = .946), or age differences, t(95) = -0.002, p = .998; BF_{10} = 0.214). Groups did not differ in terms of the intolerance of uncertainty sum scores (t(78) = -1.826, p = 0.072; BF_{10} = 0.976), the Behavioral Activation (t(95) = 0.304, p = .762; BF_{10} = 0.223) or Behavioral Inhibition scores (t(95) = -0.070, p = .945; BF_{10} = 0.214), and neuroticism (t(95) = 0.350, p = .727; although BF_{10} = 12.125) or the fear of pain questionnaire (t(95) = 1.940, p = 0.055; BF_{10} = 1.115).

Fear ratings. During the Pavlovian phase participants in both groups rated the CS+ as more fearful than the CS-, CS main effect: F(1, 95) = 95.874, p < .001, η^2_p = 0.502; BF_{10} > 1000, CS x group interaction: F(1, 95) = 0.681, p = .411, η^2_p = 0.007; BF_{10} = 0.406. Similar results arose during the transfer phase: CS main effect: F(1, 95) = 49.490, p < .001, η^2_p = 0.343; BF_{10} > 1000, CS x group interaction: F(1, 95) = 3.037, p = .085, η^2_p = 0.031; BF_{10} = 1.775, see Fig. 2.

Avoidance responses.

During the instrumental phase, participants learned to press the grip bar to avoid the US, t(96) = 11.051, p < .001, d = 1.122, BF_{10} > 1000, an effect that was not different per group, t(95) = 0.640, p = .640, d = .095, BF_{10} = .236, see Fig. 3.

During the transfer phase, participants pressed the grip bar stronger when encountering the CS+ than the CS-, CS main effect: F(1, 95) = 107.453, p < .001, η^2_p = 0.531; BF_{10} > 1000. However, the group, CS x group interaction did not reach statistical significance: F(1, 95) = 3.868, p = .052, η^2_p = 0.039, although the Bayesian results showed good evidence for differences between groups, BF_{10} = 5.247. The difference arose with the control group showing more CS differentiation compared to the patient group, evident from stronger grip force in presence of the CS+ and weaker grip force in presence of the CS-.

Discussion

We tested whether pain avoidance towards conditioned cues can be installed in the absence of learned associations between behavior and the conditioned cue, and if this behavior differs between individuals with chronic pain and no pain controls. By including a novel pain avoidance procedure, which has not been used before, we found the expected Pavlovian-to-Instrumental Transfer (PIT) effect, namely that participants exhibit avoidance behaviors more vigorously (here operationalized as force on a hand grip) towards conditioned cues that have been previously associated with pain, compared to stimuli that have not been associated with pain. However, this pattern of results did not differ between groups, with both groups exhibiting similar responses towards the CS+ and the CS-.

First, our results call for an update of current pain avoidance learning models. To date, the dominant models of avoidance learning argue that avoidance acquisition takes part by relying in two factors (Bolles, 1972; Krypotos, 2015; LeDoux et al., 2017), namely via Pavlovian and Instrumental Learning. As it has been argued before (Bolles, 1972) this two-factor learning could be particularly time consuming and against real environments, where avoidance needs to be acquired rapidly. By adopting this PIT paradigm, we have shown that the two-stage learning need not take place. In our study, participants exhibited avoidance responses, more towards the CS+ than the CS-, despite being learned independently of these CSs. In other words, Pavlovian learning was sufficient for participants to exhibit more vigorous avoidance responses. Importantly, instrumental responses in two-factor avoidance protocols are exhibited to the CS after the completion of an instrumental phase where the CS is associated with the US absence after the performance of the instrumental response. This was not the case in our instrumental phase here where no CS was presented during the instrumental phase. Although in human Pavlovian pain conditioning traditionally subjective (e.g., reported fear learning levels) and physiological responses are usually tested (Lonsdorf et al., 2017), here we showed that it is

possible to also test instrumental responses. This also extends previous findings showing that Pavlovian associations result only in avoidance tendencies (i..e, tendencies as precursous of instrumental behaviour) but not actual avoidance (Krypotos, 2015; Krypotos et al., 2014).

Second, although the p-value was on cusp of significance, Bayes factors showed that there were between group differences where participants in the pain group showed less CS avoidance differentiation, in the transfer phase, compared to the healthy controls. Although this finding was against our predictions, it is in line with the robust finding in the anxiety literature showing that individuals suffering from anxiety-related disorders show less CS differentiation compared to healthy individuals (Duits et al., 2015). A common explanation for such findings is that patients although being able to learn to associate neutral cues with threatening events (e.g., pain), they do not acquire associations between different cues and the absence of threat as readily as healthy individuals. This limited ability to acquire safety could be an explanation of the long time that therapies take for the reduction of anxiety symptomatology or chronic pain. Our findings may show that similar safety learning limitations may hold also for chronic pain patients.

Our paradigm provides a new way for studying avoidance in pain. Future studies could, for example, test not only avoidance to the CS (specific PIT) but also to other types of stimuli that resemble the CSs (general PIT). This could be an explanation of the spreading of pain avoidance from a specific spot (e.g., left arm) to more body areas (e.g., the whole left side). Additionally, if Pavlovian associations are sufficient in establishing pain avoidance, it remains a challenge to detect how such avoidance can be subsequently reduced. In this direction, conditioning procedures for reducing avoidance (e.g., extinction with response prevention (Meulders et al., 2016) or counterconditioning (Meulders et al., 2015) or reinforcing non-pain goals (Claes et al., 2014) could prove particularly insightful. Lastly, our sample size did not allow

us to test potential individual differences that could moderate the obtained effects. Future studies with larger samples could potentially be informative in this direction.

Our study also has limitations. First, since this was the first time we used this paradigm, we did not include any physiological measures of fear (e.g., skin conductance or startle reflex), and we decided to focus on our main outcome, which was the avoidance strength. Second, as any original effect and given that our between group differences were on the cusp of significance, and Bayesian analyses showing some evidence for group differences, our study needs independent replication. Lastly, and although unlikely, it is possible that the ratings collected during before the beginning of the last phase could have influenced participants' performance during the transfer phase.

Taken together, by using a novel avoidance learning procedure, we showed for the first time that avoidance in pain can be directly envigored via Pavlovian learning, without being directly associated with the Pavlovian cues. These findings show that learning to avoid pain is much easier acquired than previously thought. Given the central role of avoidance in the transition between single pain episodes to chronic pain disability (Crombez et al., 2012), more research with PIT procedures seem to be timely.

Acknowledgements

We are grateful to Lotte Bamelis, PhD for organizing data collection at Ziekenhuis Oost-Limburg, Lanaken, Belgium. We also thank Katoo Maes, Clara van Looy, and Noa Constandt for helping with the data collection.

Declarations of interest

None.

Author contribution

AMK: Conseptualization, Methodology, Software, Formal Analysis, Data Curation, Wring – First draft, Writing - Review & Editing, Visualization, Project administration, Supervision. RS: Writing - Review & Editing. MT: Resources, Writing - Review & Editing. JWSV: Conseptualization, Methodology, Writing - Review & Editing, Project administration, Supervision.

References

Bolles, R. C. (1972). The Avoidance Learning Problem. In G. H. Bower (Ed.), *Psychology of Learning and Motivation* (Vol. 6, pp. 97–145). Academic Press. https://doi.org/10.1016/S0079-7421(08)60385-0

Buhr, K., & Dugas, M. J. (2002). The intolerance of uncertainty scale: Psychometric properties of the English version. *Behaviour Research and Therapy*, *40*(8), 931–945. https://doi.org/10.1016/S0005-7967(01)00092-4

Claes, N., Karos, K., Meulders, A., Crombez, G., & Vlaeyen, J. W. S. (2014). Competing Goals Attenuate Avoidance Behavior in the Context of Pain. *The Journal of Pain*, *15*(11), 1120–1129. https://doi.org/10.1016/j.jpain.2014.08.003

Crombez, G., Eccleston, C., Van Damme, S., Vlaeyen, J. W. S., & Karoly, P. (2012). Fear-avoidance model of chronic pain: The next generation. *The Clinical Journal of Pain*, *28*(6), 475–483. https://doi.org/10.1097/AJP.0b013e3182385392

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., van den Hout, M. A., & Baas, J. M. P. (2015). Updated Meta-Analysis of Classical Fear Conditioning in the Anxiety Disorders. *Depression and Anxiety*, *32*(4), 239–253. https://doi.org/10.1002/da.22353

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149

Franken, I. H. A., & Muris, P. (2005). Individual differences in decision-making. *Personality and Individual Differences*, *39*(5), 991–998. https://doi.org/10.1016/j.paid.2005.04.004

Gazendam, F. J., Krypotos, A.-M., Kamphuis, J. H., van der Leij, A. R., Huizenga, H. M. H., Eigenhuis, A., & Kindt, M. (2020). From adaptive to maladaptive fear: Heterogeneity in threat and safety learning across response systems in a representative sample. *International Journal of Psychophysiology*, *158*, 271–287. https://doi.org/10.1016/j.ijpsycho.2020.09.017

Krypotos, A.-M. (2015). Avoidance learning: A review of theoretical models and recent developments. *Frontiers in Behavioral Neuroscience*, *9*. https://doi.org/10.3389/fnbeh.2015.00189

Krypotos, A.-M., Blanken, T. F., Arnaudova, I., Matzke, D., & Beckers, T. (2017). A Primer on Bayesian Analysis for Experimental Psychopathologists. *Journal of Experimental Psychopathology*, *8*(2), 140–157. https://doi.org/10.5127/jep.057316

Krypotos, A.-M., Effting, M., Arnaudova, I., Kindt, M., & Beckers, T. (2014). Avoided by Association: Acquisition, Extinction, and Renewal of Avoidance Tendencies Toward Conditioned Fear Stimuli. *Clinical Psychological Science*, *2*(3), 336–343. https://doi.org/10.1177/2167702613503139

LeDoux, J. E., Moscarello, J., Sears, R., & Campese, V. (2017). The birth, death and resurrection of avoidance: A reconceptualization of a troubled paradigm. *Molecular Psychiatry*, *22*(1), Article 1. https://doi.org/10.1038/mp.2016.166

Lewis, A. H., Niznikiewicz, M. A., Delamater, A. R., & Delgado, M. R. (2013). Avoidance-based human Pavlovian-to-instrumental transfer. *European Journal of Neuroscience*, *38*(12), 3740–3748. https://doi.org/10.1111/ejn.12377

Linton, S. J., Flink, I. K., & Vlaeyen, J. W. S. (2018). Understanding the Etiology of Chronic Pain From a Psychological Perspective. *Physical Therapy*, *98*(5), 315–324. https://doi.org/10.1093/ptj/pzy027

Lonsdorf, T. B., Menz, M. M., Andreatta, M., Fullana, M. A., Golkar, A., Haaker, J., Heitland, I., Hermann, A., Kuhn, M., Kruse, O., Meir Drexler, S., Meulders, A., Nees, F., Pittig, A., Richter, J., Römer, S., Shiban, Y., Schmitz, A., Straube, B., … Merz, C. J. (2017). Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neuroscience & Biobehavioral Reviews*, *77*, 247–285. https://doi.org/10.1016/j.neubiorev.2017.02.026

Meulders, A. (2019). From fear of movement-related pain and avoidance to chronic pain disability: A state-of-the-art review. *Current Opinion in Behavioral Sciences*, *26*, 130–136. https://doi.org/10.1016/j.cobeha.2018.12.007

Meulders, A., Franssen, M., Fonteyne, R., & Vlaeyen, J. W. S. (2016). Acquisition and extinction of operant pain-related avoidance behavior using a 3 degrees-of-freedom robotic arm. *PAIN*, *157*(5), 1094. https://doi.org/10.1097/j.pain.0000000000000483

Meulders, A., Jans, A., & Vlaeyen, J. W. S. (2015). Differences in pain-related fear acquisition and generalization: An experimental study comparing patients with fibromyalgia and healthy controls. *PAIN*, *156*(1), 108–122. https://doi.org/10.1016/j.pain.0000000000000016

Peirce, J. W. (2007). PsychoPy—Psychophysics software in Python. *Journal of Neuroscience Methods*, *162*(1), 8–13. https://doi.org/10.1016/j.jneumeth.2006.11.017

Pittig, A., Wong, A. H. K., Glück, V. M., & Boschet, J. M. (2020). Avoidance and its bi-directional relationship with conditioned fear: Mechanisms, moderators, and clinical

implications. *Behaviour Research and Therapy*, *126*, 103550. https://doi.org/10.1016/j.brat.2020.103550

Roelofs, J., Peters, M. L., Deutz, J., Spijker, C., & Vlaeyen, J. W. S. (2005). The Fear of Pain Questionnaire (FPQ): Further psychometric examination in a non-clinical sample. *Pain*, *116*(3), 339–346. https://doi.org/10.1016/j.pain.2005.05.003

Sekutowicz, M., Guggenmos, M., Kuitunen-Paul, S., Garbusow, M., Sebold, M., Pelz, P., Priller, J., Wittchen, H.-U., Smolka, M. N., Zimmermann, U. S., Heinz, A., Sterzer, P., & Schmack, K. (2019). Neural Response Patterns During Pavlovian-to-Instrumental Transfer Predict Alcohol Relapse and Young Adult Drinking. *Biological Psychiatry*, *86*(11), 857–863. https://doi.org/10.1016/j.biopsych.2019.06.028

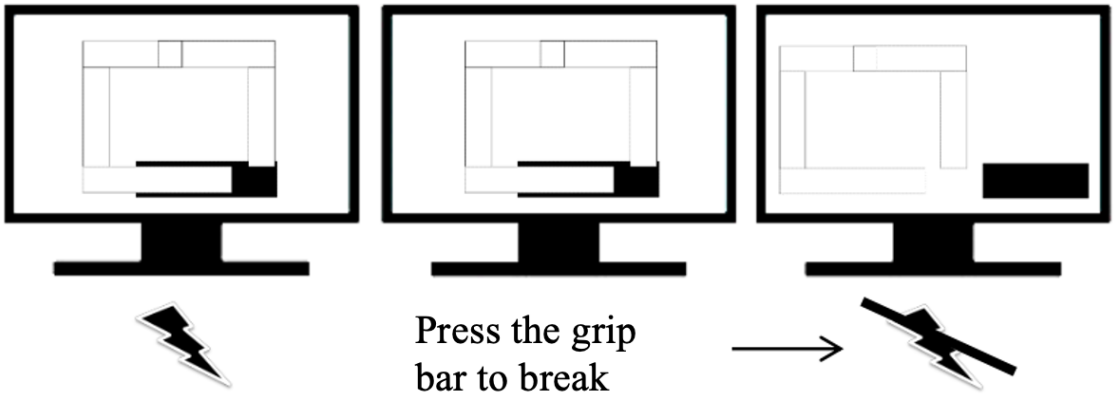
Vlaeyen, J. W. S. (2015). Learning to predict and control harmful events: Chronic pain and conditioning. *Pain*, *156*(Supplement 1), S86–S93. https://doi.org/10.1097/j.pain.0000000000000107

Fig 1. Visualization of the experimental design.

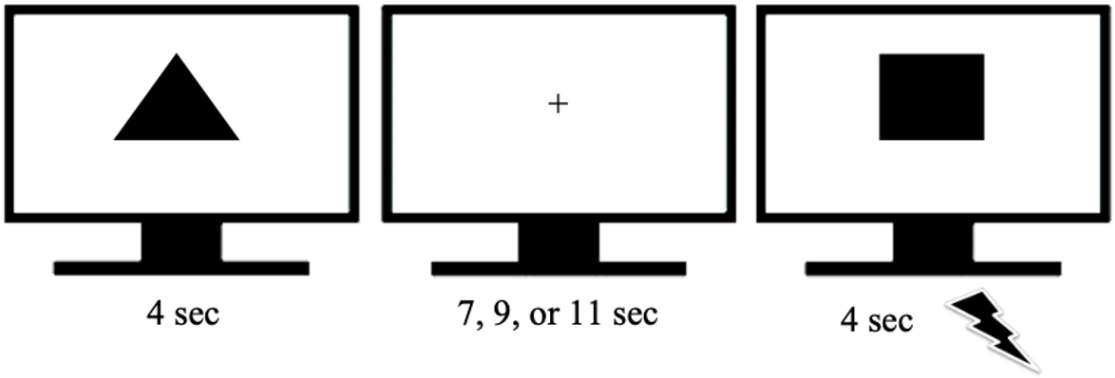
Fig 2. Results of the fear and ratings for the Pavlovian and the transfer phase.

Fig 3. Results of the avoidance data for the Transfer phase.

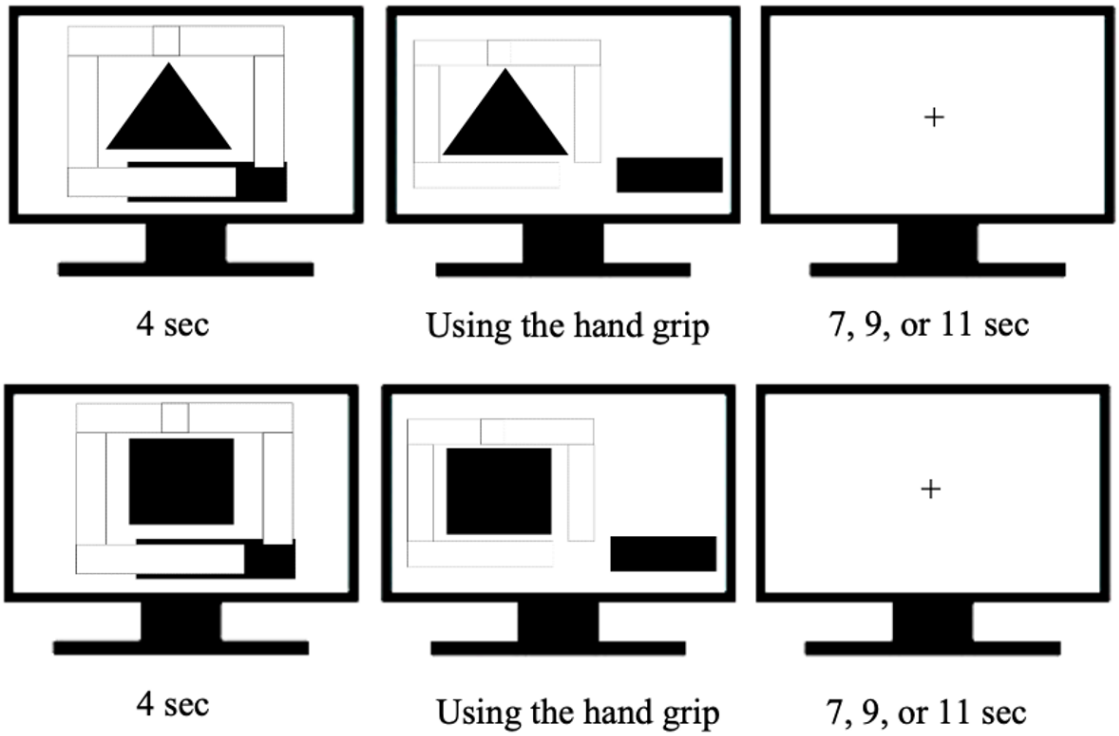
Instrumental Phase.

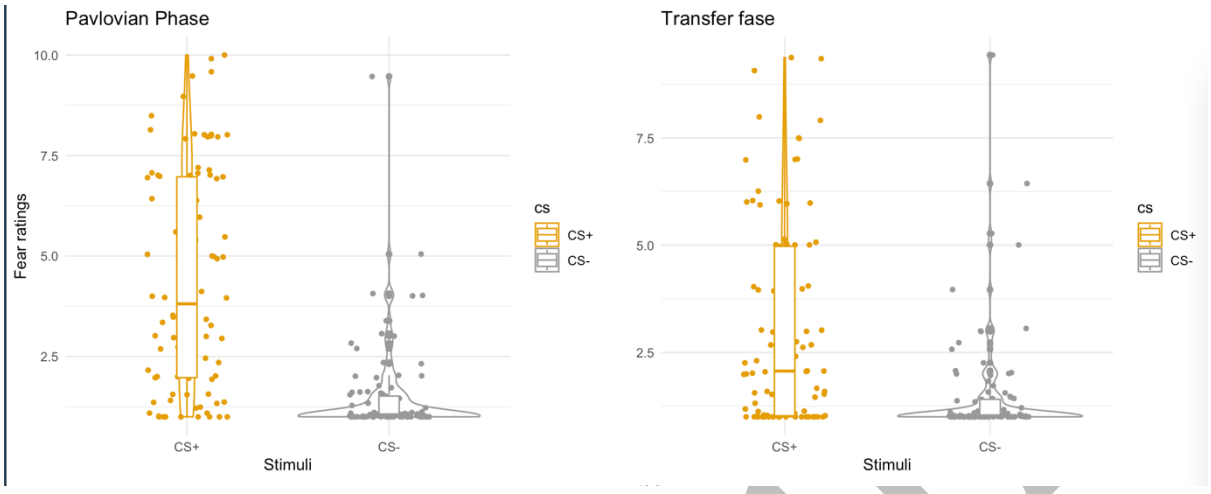


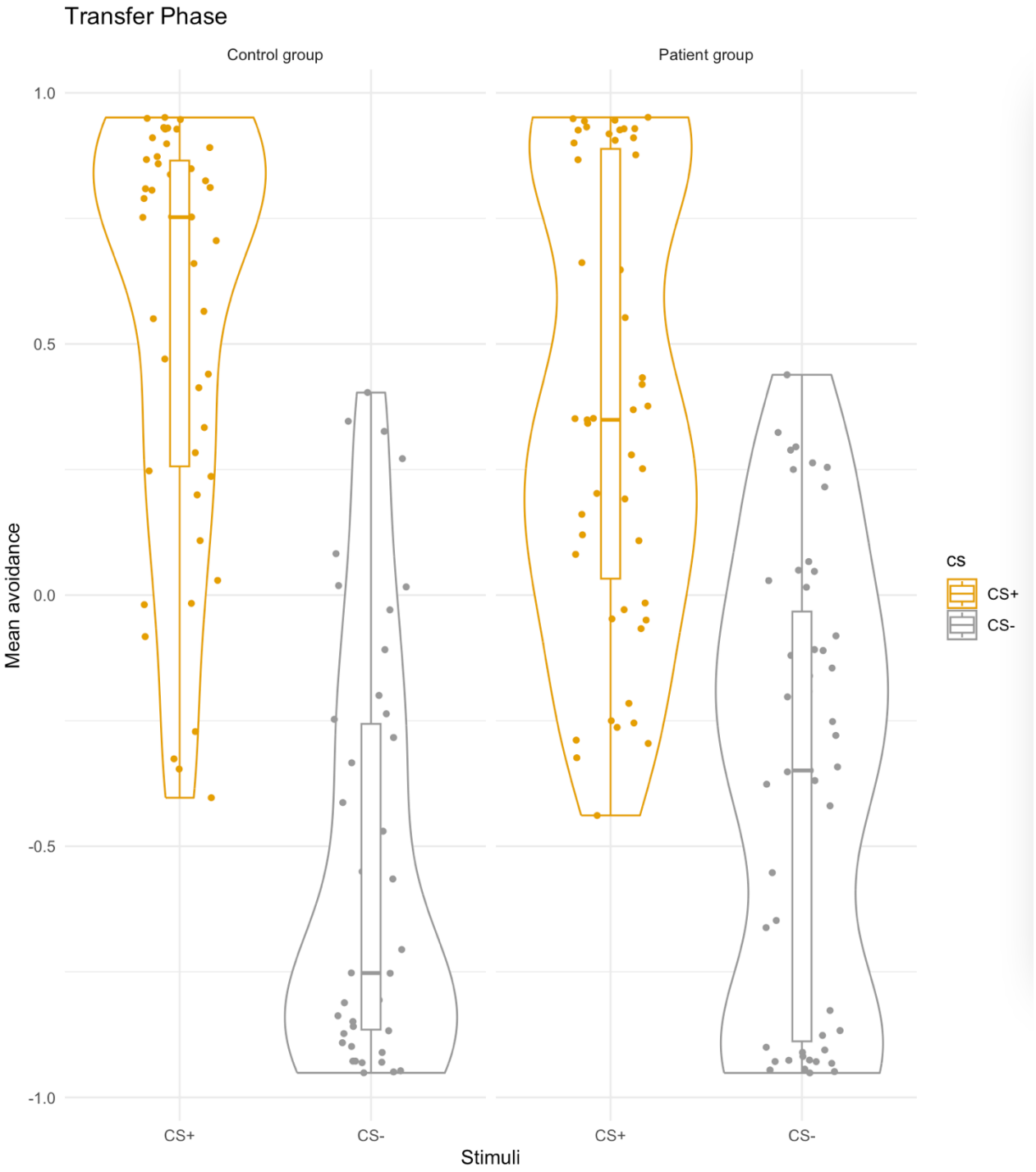
Pavlovian Phase.



Transfer Phase.




Pavlovian Phase
Fear ratings
10.0
7.5
5.0
2.5
CS+
CS-
Stimuli
cs
CS+
CS-
Transfer fase
7.5
5.0
2.5
CS+
CS-
Stimuli
cs
CS+
CS-


Transfer Phase
Control group
Patient group
1.0
0.5
0.0
-0.5
-1.0
Mean avoidance
CS+
CS-
CS+
CS-
Stimuli
CS
CS+
CS-