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Pathways to attenuate the spreading of pain-related avoidance behavior

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DISSERTATION

To obtain the degree of Doctor at Maastricht University, on the authority of Rector Magnificus, prof. dr. Pamela Habibović, and the degree of Doctor of Psychology (PhD) at KU Leuven, on the authority of Rector prof. dr. Luc Sels, in accordance with the decision of the Board of Deans, to be defended in public on Monday 7th of November 2022 at 10:00 hours.

by

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General introduction

Chronic pain

It sounds counterintuitive, but experiencing pain can be very helpful. Imagine touching a tray that just came out of the oven with your hand; the pain you would experience would make you pull back your hand quickly, thus preventing (further) tissue damage, and it would make you think twice before touching that tray again. Such *acute pain* is something most of us experience from time to time. As the example illustrates, it has an important function: it signals potential or actual tissue damage, and motivates escaping and avoiding potentially harmful situations. Indeed, individuals who are unable to experience pain – a condition named congenital insensitivity to pain – often die young because they fail to notice the presence of injuries or diseases (Nagasako et al., 2003).

However, also in people not suffering from congenital insensitivity there is no one-to-one relationship between tissue damage and pain. Sometimes people suffer severe injuries, for example due to a car crash, but they experience no pain in that moment – a phenomenon named stress-induced analgesia (Butler & Finn, 2009). This again can be extremely helpful, as the priority in such moments is to get oneself to safety. Only later, pain experience will motivate attending to injuries. The opposite is also true; sometimes people experience pain, while there is no (potential) tissue damage. In that case, pain is no longer helpful: it signals potential damage and may motivate escaping and avoiding certain situations, while there is no actual threat. This complicated relationship between pain and tissue damage is reflected in contemporary definitions of pain. The International Association for the Study of Pain for example defines pain as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (Raja et al., 2020, p. 14).

When acute pain is caused by an injury or underlying medical condition, treatment of this condition usually leads to resolution. This means that pain generally disappears within a few weeks. However, it may also persist despite successful treatment of its initial cause. When it persists or recurs beyond healing time – i.e., for longer than three months –, it is referred to as *chronic pain* (Treede et al., 2019). Furthermore, in cases such as fibromyalgia, chronic pain can be present without a clear underlying condition that explains pain onset. Approximately 20% of the adult European population is affected by chronic pain (Breivik et al., 2006). Similar rates have been reported in other Western countries such as the USA and Canada (Kennedy et al., 2014; Schopflocher et al., 2011). Importantly, chronic pain can interfere significantly with daily activities and lead to reduced participation in social roles (Nicholas et al., 2019). In a majority of sufferers, it affects the ability to sleep, exercise, walk, do household chores, attend social activities, and maintain an independent lifestyle (Breivik et al., 2006). In other words, chronic pain is often a seriously debilitating condition. Moreover, it is frequently associated with significant emotional distress, including anxiety and depressive feelings (Van Hecke et al., 2013). In addition to the individual burden, the financial costs to society are considered substantial,

with estimates usually in the billions of euros per year (Dagenais et al., 2008). Unfortunately, despite these findings, people with chronic pain often report receiving inadequate treatment (Breivik et al., 2006).

Fear-avoidance models of chronic pain

Pain is traditionally considered a direct sign of injury or disease and its intensity is thought to reflect the inflicted bodily harm (Vlaeyen & Crombez, 2020). This view has been influential for a long time and is often still adhered to in society (De Ruddere et al., 2012). However, it is unable to explain clinical and scientific observations in which there is no clear association between pain reports and evidence of tissue damage, such as chronic pain. Moreover, reducing pain to a signal of tissue damage can have detrimental effects in clinical practice. For example, spine degeneration detected through imaging is often considered causal in the experience of low back pain, potentially leading to surgical intervention. Importantly, such degeneration is common in – mainly older – individuals that do not experience pain, with evidence for disk degeneration being found in nearly 90% of individuals 60 years of age or older (Brinjikji et al., 2015). In other words, the inappropriate use of imaging techniques and narrow focus on organic pathology in pain can lead to unnecessary, yet risky surgeries (Flynn et al., 2011).

Contemporary views on pain acknowledge the importance of other factors than biomedical ones; generally, these models emphasize that next to biological factors – such as tissue damage –, psychological and social factors play important roles in pain experience. Such views are in line with the biopsychosocial models of illness that were developed as a reaction to the dominant biomedical models (Engel, 1977). A striking illustration of the role of psychological factors in pain is the case of placebo analgesia: the *expectation* that a treatment will result in pain relief causes pain reduction, even when the treatment is inert (Atlas & Wager, 2012). Importantly, it also works the other way around. In the case of nocebo hyperalgesia, the belief that a treatment will cause pain results in increased pain (Petersen et al., 2014). Note that the interest in associations between pain and psychological and social factors was already present before the introduction of the biopsychosocial approach. In particular, Fordyce et al. (1968) emphasized the role of overt behaviors such as resting in chronic pain; he argued that such responses can be disproportionate, and actually contribute to the development and maintenance of chronic pain (Fordyce, 1973). According to Fordyce, these behaviors can persist because they result in favorable outcomes in the short term, such as reductions in pain. Moreover, he emphasized that such behaviors should be the focus of treatment; for example, he described the role that responses of others, such as attention and praise, can play in increasing activity levels again, and reducing chronic pain complaints (Fordyce et al., 1968).

Building on such insights, the first theoretical model describing interactions between fear, avoidance and pain was introduced by Lethem et al. (1983): the fear-avoidance model. Central to this model is pain-related fear (or 'fear of pain'), which is assumed to lead to varying behavioral responses. One such response is *avoidance* of pain, which is argued to lead to the maintenance and exacerbation of pain-related fear, restricted activity levels, and eventually chronic pain. In this case, the activity reductions aimed at preventing pain are disproportional to the initial underlying pathology. Alternatively, *confrontation* (or approach) leads to reductions in pain-related fear, resumption of (physical) activities, and eventually recovery. In this case, people undertake an increasing range of activities as tissues heal, which eventually allows them to resume daily activities. Since its introduction, findings have corroborated the assumptions of the fear-avoidance model, and it has been further refined – for example by including cognitive factors such as pain catastrophizing (Leeuw et al., 2007; Meulders, 2019; Vlaeyen et al., 2016; Vlaeyen & Linton, 2000, 2012). Generally, the pathway of avoidance is considered a vicious cycle: disproportionate avoidance significantly interferes with daily life and leads to increases in negative affect, which can maintain pain experience, thereby fueling the vicious cycle of increasing pain-related fear and avoidance (Vlaeyen & Linton, 2000). Moreover, long-term avoidance of movements and activities may lead to deterioration of the musculoskeletal system, such as muscle atrophy due to disuse, thus further contributing to pain and disability (Van Dieën et al., 2017; Verbunt et al., 2003). However, a crucial question in this is how pain-related fear and avoidance are acquired in the first place.

Pain-related fear

Because of its intrinsically alarming function, pain is an important motivator for learning: it fosters the detection of stimuli that predict the occurrence of pain and potential harm (Meulders, 2019). Once pain and harm can be predicted, they can be minimized or avoided. *Pavlovian or classical conditioning* is a key mechanism in threat prediction: when an initially neutral stimulus (conditional stimulus; CS), such as a movement, is repeatedly paired with an aversive outcome (unconditional stimulus; US), such as pain, it will start eliciting defensive responses such as pain-related fear (conditional response). An experimental lab study by Meulders et al. (2011) employed joystick movements as CSs and a painful electrical stimulus as US to investigate this mechanism in healthy, pain-free participants. During the experimental task, one joystick movement – e.g., movement to the right – was repeatedly paired with the US (CS+), while another – e.g., movement to the left – was never paired with the US (CS-). As expected, both self-report and psychophysiological measures of pain-related fear were higher for the CS+ compared to the CS-. These results have been repeatedly replicated, including in experimental paradigms with more complex movements, thus confirming that

pain-related fear can be acquired through classical conditioning in musculoskeletal pain (Karos et al., 2017; Meulders & Vlaeyen, 2013).

Interestingly, pain-related fear can spread toward movements and activities that are perceptually similar to a pain-associated one. Such *stimulus generalization* has been repeatedly observed in lab studies using healthy, pain-free participants: after fear conditioning, movements resembling the CS+ (generalization stimuli; GSs) can elicit pain-related fear as well, even though they were never paired with the US (Dymond et al., 2015; Meulders et al., 2013; Meulders & Vlaeyen, 2013). In case of the joystick task, where movements to the left and right serve as CSs, diagonal movements have been used as GSs for example (Meulders & Vlaeyen, 2013). In such studies, generalization gradients can be observed: GSs usually elicit less pain-related fear as similarity to the CS+ decreases (Meulders et al., 2013). Furthermore, pain-related fear has been shown to spread towards perceptually similar contexts and along a dimension of categorical relatedness (Glogan et al., 2018; Kloos et al., 2022; Meulders et al., 2020; Meulders, Vandael, et al., 2017). For example, pain-related fear can spread toward movements and activities that belong to the same functional category as the pain-associated movement – such as household chores, sports, etc.

Generalization is usually adaptive, because we do not need to learn about each movement or activity separately. However, it can become maladaptive when movements and activities that bear little similarity to the pain-associated one elicit pain-related fear as well. For example, when bending the back to pick up a pencil elicits fear, this is maladaptive if pain was initially experienced while lifting a heavy bag of sand during construction work. Contemporary fear-avoidance models consider such *overgeneralization* to play an important role in the transition from acute to chronic pain (Meulders, 2019; Vlaeyen et al., 2016). This view is corroborated by experimental studies in various chronic pain conditions (Harvie et al., 2017). Using a classical conditioning paradigm with joystick movements as CSs and GSs, Meulders et al. (2015) observed overgeneralization of pain-related fear in people with fibromyalgia. This finding was replicated by Meulders, Meulders, et al. (2017), albeit only in the pain-expectancy – which can be considered a proxy of pain-related fear. Furthermore, overgeneralization in pain-expectancy was observed by Meulders, Harvie, et al. (2014) in chronic unilateral hand pain patients. These studies generally show that, compared to pain-free controls, people with chronic pain show elevated responding to novel stimuli that resemble the CS-, rather than to those that resemble the CS+ (Meulders, 2020) – however, note that reduced threat learning (i.e., reduced responding to the CS+) has been observed as well (Harvie et al., 2020; Schlitt et al., 2021). In other words, these studies confirm that people with chronic pain conditions show excessive pain-related fear for stimuli that bear minimal similarity to the CS+.

Pain-related avoidance

Whereas pain-related fear is key in predicting pain and harm, pain-related avoidance behavior is key in preventing them (Vlaeyen & Crombez, 2020). Avoidance can be acquired through *instrumental or operant learning*: people learn that certain movements or activities (responses) reduce or prevent pain (outcome). In this case, a response leads to the non-occurrence of an aversive event (negative reinforcement), which makes this response more likely to occur in the future (Domjan, 2018). For example, if resting leads to pain reductions, this behavior is likely to occur again. The acquisition of pain-related avoidance behavior has been studied in the lab by Meulders et al. (2016) using a robotic arm-reaching paradigm: healthy, pain-free participants learned that certain arm movements led to pain (i.e., a painful electrical stimulus) and that another – avoidance – movement did not. Consequently, the avoidance movement was indeed performed more. Multiple factors have been argued to reinforce avoidance (Krypotos et al., 2015). Mowrer (1951) for example introduced the idea that fear reductions following avoidance behavior play a reinforcing role. However, avoidance can persist despite fear no longer being present (Vervliet & Indekeu, 2015). Therefore, other factors have been introduced since then, such as relief – the positive feeling in reaction to the absence of an anticipated aversive event (Vervliet et al., 2017).

Avoidance behavior is very adaptive in acute pain, because it can prevent further harm and promote recovery. For example, performing alternative movements after experiencing intense pain while bending the back can prevent exacerbating an injury. However, when injury is not, or no longer, present, avoidance prevents learning that movements or activities are safe. Moreover, recent evidence shows that avoidance can exacerbate pain-related fear (van Vliet et al., 2018). In other words, avoidance behavior can be self-sustaining, making it difficult to treat. Avoidance may also generalize toward movements and activities that are similar to the one associated with pain. As with generalization of pain-related fear, this is adaptive because it prevents having to learn anew. However, when avoidance spreads excessively to safe movements and activities, it can interfere severely with daily activities. For example, it can prevent a person from participating in valued social activities, thus causing isolation. (Over)generalized avoidance can again be sustained by reinforcing factors such as relief (San Martín et al., 2020). Contemporary fear-avoidance models therefore emphasize the importance of excessive spreading of avoidance in the development and maintenance of chronic pain disability (Meulders, 2019; Vlaeyen et al., 2016).

Experimental investigations into the generalization of pain-related avoidance behavior can provide crucial insights to help counter its overgeneralization. Because there is no one-to-one relationship between fear and avoidance, research on avoidance (generalization) specifically is required (Meulders, 2019; Pittig, Wong, et al., 2020); even though fear-avoidance models assume that

fear motivates avoidance, the two can dissociate when there are costs or competing goals involved (Crombez et al., 2012). For example, a person that is afraid of lifting may still pick up their child, because interacting with their child overrules the pain-avoidance goal. Lab studies in the anxiety field have already investigated avoidance generalization in healthy participants – i.e., participants without clinical anxiety symptoms. These studies confirm that avoidance generalizes (San Martín et al., 2020), even when it is associated with a cost (Hunt et al., 2019; van Meurs et al., 2014). However, these paradigms generally involve visual stimuli as CSs and GSs; when it comes to learning in pain conditions, proprioceptive cues – i.e., the sense of position and movement of the body and body segments in space – for example may be more relevant. Moreover, paradigms from the anxiety field often employ simple button presses as avoidance responses, meaning that there is either avoidance or not (San Martín et al., 2020; van Meurs et al., 2014); such dichotomous responses do not allow capturing more subtle differences in avoidance. Therefore, more ecologically valid and sensitive paradigms are required to model generalization of pain-related avoidance.

A promising paradigm is the robotic arm-reaching task introduced by Meulders et al. (2016), which conditions arm movements and uses a continuous measure of avoidance, meaning that it allows different degrees of avoidance. Moreover, avoidance movements are associated with a cost, as they require more physical effort. Using this paradigm, Glogan, Gatzounis, Meulders, et al. (2020) investigated the generalization of pain-related avoidance toward perceptually similar movements in healthy, pain-free participants. Interestingly, results showed that pain-related fear indeed generalized – thus corroborating previous work –, but avoidance did not. This dissociation sparks the question under which conditions generalization of pain-related avoidance can be observed in healthy, pain-free participants; understanding these conditions may inspire interventions to counter overgeneralization.

Despite the pivotal role of overgeneralization of avoidance in the development and maintenance of chronic pain disability, experimental studies on interventions to attenuate it are lacking in the pain field. However, Geschwind et al. (2015) investigated the potential of experimentally inducing positive affect to reduce generalization of pain-related *fear*, using joystick movements as CSs and GSs; results showed that increases in positive affect were indeed associated with less generalization, specifically toward stimuli similar to the CS-. Although these results are promising, the question is whether this approach also affects pain-related avoidance generalization, as there is no straightforward relationship between fear and avoidance. In the anxiety field, there has been some investigation of interventions to reduce avoidance generalization, albeit limited. The potential of perceptual discrimination training – i.e., improving the capacity to differentiate between similar stimuli – has been tested for example (Lommen et al., 2017). However, it is an open question whether these principles apply in the context of chronic pain, as such trainings have mainly focused on visual

information, and not on movements for example. Once such interventions show potential to reduce generalization in healthy, pain free – or subclinical – participants, they can be tested in clinical populations to counter overgeneralization. However, this requires evidence that experimental avoidance paradigms can indeed observe overgeneralization – i.e., diagnostic validity should be established (Vervliet & Raes, 2013). Unfortunately, experimental studies on avoidance overgeneralization in clinical conditions are lacking, both in the field of pain and anxiety.

Insights from experimental investigations into the attenuation of avoidance (over)generalization can be used to inform and optimize evidence-based treatment of chronic pain conditions. The fear-avoidance model has already given rise to cognitive behavioral treatments for people reporting substantial pain-related fear (den Hollander et al., 2010). These include exposure interventions in which people with chronic pain perform – or expose themselves to – movements and activities, which they expect to be harmful, and which they are afraid of (Gatzounis et al., 2021). This presumably leads to fear reductions, and thus less avoidance, as erroneous threat beliefs are disconfirmed. However, a recent meta-analysis evaluating psychological therapies for the management of chronic pain, such as cognitive behavioral therapy, indicated that these treatments generally result in small to very small beneficial effects in terms of reducing pain, disability and distress (Williams et al., 2020). In other words, there is significant room for improvement. Moreover, research into the prevention of chronic pain is scarce (Gewandter et al., 2015). Knowledge on attenuating avoidance generalization specifically can be an important source for the development or improvement of preventive interventions.

Aims and outline of this thesis

The goal of the current PhD project was to investigate potential pathways to attenuate the generalization of pain-related avoidance behavior. Because the study by Glogan, Gatzounis, Meulders, et al. (2020) showed a dissociation between generalized pain-related fear and avoidance using the robotic arm-reaching paradigm, we first set out to investigate the **boundary conditions under which generalization of pain-related avoidance can be observed in healthy, pain-free participants**, using this paradigm (**Chapter 1**). Once generalization of avoidance toward perceptually similar movements can be reliably established, this would provide an experimental framework to investigate the effects of experimental interventions on generalization.

Although experimental research on **potential ways to reduce generalization of avoidance** is limited, we reviewed the existing literature from both the pain and anxiety field (**Chapter 2**). Because fear and avoidance are closely linked – despite dissociations occurring –, we reviewed both studies that showed attenuated fear generalization and attenuated avoidance generalization following

experimental intervention, and discussed future directions for this domain of research. In particular, we focused on the potential of training *proprioceptive accuracy*, inducing *positive affect*, and *reinforcing competing goals*. The current PhD project further investigated the former two pathways in an experimental lab context.

To investigate proprioceptive accuracy training as a potential way to attenuate generalization, we first needed to develop a **reliable task to quantify proprioceptive function of the upper limb**, as the robotic-arm reaching paradigm involves arm movements. Therefore, we developed a novel dynamic movement reproduction (DMR) task, evaluated its test-retest reliability, and compared it to an existing measure of proprioceptive function, using healthy, pain-free participants (**Chapter 3**). Furthermore, we adapted the robotic arm-reaching paradigm to increase its reliance on proprioceptive information (rather than visual information), and tested whether avoidance as measured in this adapted version was associated with proprioceptive accuracy as measured by the DMR task; in other words, we **tested whether poor proprioceptive accuracy was indeed associated with excessive pain-related avoidance in healthy, pain-free participants** (**Chapter 4**). Once an association is established between the two, this would clearly indicate the potential of training proprioceptive accuracy to counter overgeneralization.

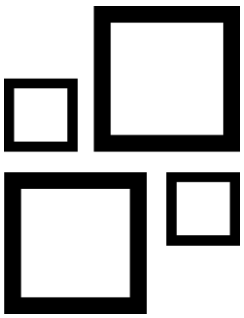
Next, we investigated whether inducing positive affect might be an effective way to reduce generalization of pain-related avoidance in healthy, pain-free participants. To this end, we employed two different experimental paradigms. First, the robotic arm-reaching task from Chapter 1 – which showed generalization of pain-related avoidance in healthy, pain-free participants – was used to **test whether experimentally induced positive affect reduces pain-related fear and avoidance generalization** (**Chapter 5**). Second, we used a previously validated paradigm that allows investigation of relief generalization next to avoidance (San Martín et al., 2020). Because there is no one-to-one relationship between fear and avoidance, and avoidance can be reinforced by other factors such as relief, investigation of such factors is crucial. Moreover, cross-validating results regarding avoidance attenuation across experimental paradigms would form a clear basis for investigating positive affect induction in chronic pain conditions. Therefore, we **investigated whether experimentally induced positive affect reduces generalization of pain-related avoidance and relief** (**Chapter 6**).

Due to the lack of investigations into **overgeneralization of pain-related avoidance behavior in chronic pain conditions**, we aimed to investigate this in people with chronic shoulder, arm and/or hand pain (**Chapter 7**). To this end, we employed a robotic arm-reaching task in which generalization of an acquired avoidance behavior toward novel, perceptually similar contexts is assessed. This task was previously validated in participants with low versus high anxiety levels: high anxiety was associated with excessive generalization of avoidance (Meulders et al., in preparation). Additionally,

the goal was to investigate diagnostic validity of the DMR task. Because previous research repeatedly showed proprioceptive impairments in chronic pain conditions, we wanted to test whether participants with chronic pain indeed showed poor proprioceptive accuracy as measured by the DMR task (Juul-Kristensen et al., 2008a; Knoop et al., 2011; Stanton et al., 2016; Tong et al., 2017). However, due to the COVID-19 pandemic and persistent technical difficulties, data collection for this study was not finished before writing this thesis. Therefore, we present the preregistration including the background, hypotheses, sample size and analysis plan of this study.

Chapter 1

Generalization of pain-related avoidance



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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 robotic device (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 pain-related avoidance, i.e., 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.

Introduction

Avoidance of objectively safe movements and activities is central to chronic pain disability, which often profits from psychological treatments, such as cognitive behavioral therapy (Morley et al., 1999), rather than purely biomedical ones (Gatchel & Okifuji, 2006; Gatchel et al., 2007; Vlaeyen & Linton, 2000). Avoidance of pain-associated movements/activities after healing prevents disconfirmation of threat, leading to a self-sustaining cycle of fear and avoidance (Vlaeyen & Linton, 2000). Furthermore, avoidance often spreads to movements resembling the original pain-associated movement, that were never paired with pain themselves (avoidance generalization; Dymond et al., 2015). 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.

According to the fear-avoidance model of chronic pain, misinterpreting pain as harmful induces pain-related fear, motivating avoidance of movements/activities associated with pain (Vlaeyen & Linton, 2000). Specifically, pain-related fear is learned through *Pavlovian conditioning*, where a neutral movement (conditional stimulus) experienced with pain (unconditional stimulus; US), comes to elicit fear (conditional response; Meulders et al., 2011; Pavlov, 1927). Due to pain-related fear, and following *operant conditioning*, any behavior (response; e.g., a movement) believed to predict pain (outcome) will decrease (i.e., punishment; Skinner, 1953). Alternatively, an avoidance response (e.g., moving in an unnatural manner), which omits a negative outcome such as pain, will increase, and thus be strengthened (i.e., negative reinforcement; Skinner, 1953).

Because avoidance was traditionally believed to directly follow fear (Krypotos et al., 2015; Urcelay & Prével, 2019), previous research in the anxiety and pain domains focused mainly on (pain-related) *fear* generalization (Dymond et al., 2015; Meulders et al., 2013), assuming avoidance would align. This research demonstrated that compared to healthy controls, people with chronic pain overgeneralize pain-related fear (Meulders et al., 2015). However, in the daily life of a person with chronic pain, controlling pain (by avoiding for example) is only one among numerous competing goals (such as socializing for example; Volders et al., 2015). Therefore, despite fear, avoidance may not always be prioritized if the associated costs (e.g., stigma) are too high, promoting dissociation between fear and avoidance (Claes et al., 2014). Because the ultimate goal is to understand and sustainably change pain *behavior*, more research is needed on avoidance behavior itself (Krypotos et al., 2018).

We recently reported such dissociation between pain-related fear and costly avoidance (Glogan, Gatzounis, Meulders, et al., 2020). 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, three 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, sparking the question under which conditions costly avoidance generalizes (Glogan, Gatzounis, Meulders, et al., 2020).

There are several plausible explanations for this dissociation (Glogan, Gatzounis, Meulders, et al., 2020). *First*, the way in which generalization was operationalized – i.e., the absence of acquisition trajectories and appearance of generalization trajectories – may have been experienced as a context-switch, generating doubt whether the movement-pain contingencies still hold during the generalization phase (Bouton & Todd, 2014; Bouton et al., 2014), and thus generating uncertainty about the continued need for effort. That is, since avoidance was costly, the change in available responses may have motivated exploration – i.e., choosing an option with possible gains, but uncertain outcomes – of the novel movement trajectories similar to those previously paired with pain, with the goal of minimizing effort (Lee et al., 2011; Mehlhorn et al., 2015). *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 (Craske et al., 2014; Rescorla & Wagner, 1972).

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

General methods and materials

Apparatus

HapticMaster

The HapticMaster (Motekforce Link, Amsterdam, the Netherlands) is a 3-degrees of freedom, admittance-controlled robot; when operated by an external force, the robot reacts with a corresponding movement. Under operation, the HapticMaster records its position, velocity, and acceleration, as well as the force exerted onto it. This information can be fed back to other devices and used for triggering the presentations of stimuli, such as the electrical stimuli in the current experiments. Additionally, the HapticMaster 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 task 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 HapticMaster took place via a direct application programming interface connection. The experimental task was presented on a 40-inch LCD screen (Samsung UE40ES5500; Samsung Group, Seoul, South Korea). Participants navigated through instructions and answered questions using a foot switch (USB-3FS-2; Scythe Co., Ltd., Tokyo, Japan).

Pain stimulus

The pain stimulus was a 2 ms square-wave electrical stimulus, delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, UK), through two reusable stainless steel disk electrodes (8mm diameter with 30mm spacing; Digitimer, Welwyn Garden City, UK) filled with K-Y gel (Reckitt Benckiser, Slough, UK). Intensity of the electrical stimulus was individually calibrated: participants were given a series of electrical stimuli of increasing intensity, according to a standard protocol (e.g., Meulders et al., 2011). 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, Gatzounis, Meulders, et al. (2020). On each trial, participants were required to move from a start location to a target location by operating the HapticMaster with their right (dominant) hand (Figure 1.1, panel A). Participants' movements were visualized on the LCD screen by a green ball, allowing them to track their movements in real-time (Figure 1.1, panel B). 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 three different movement trajectories (T1-3) represented on screen as three arches situated midway through the

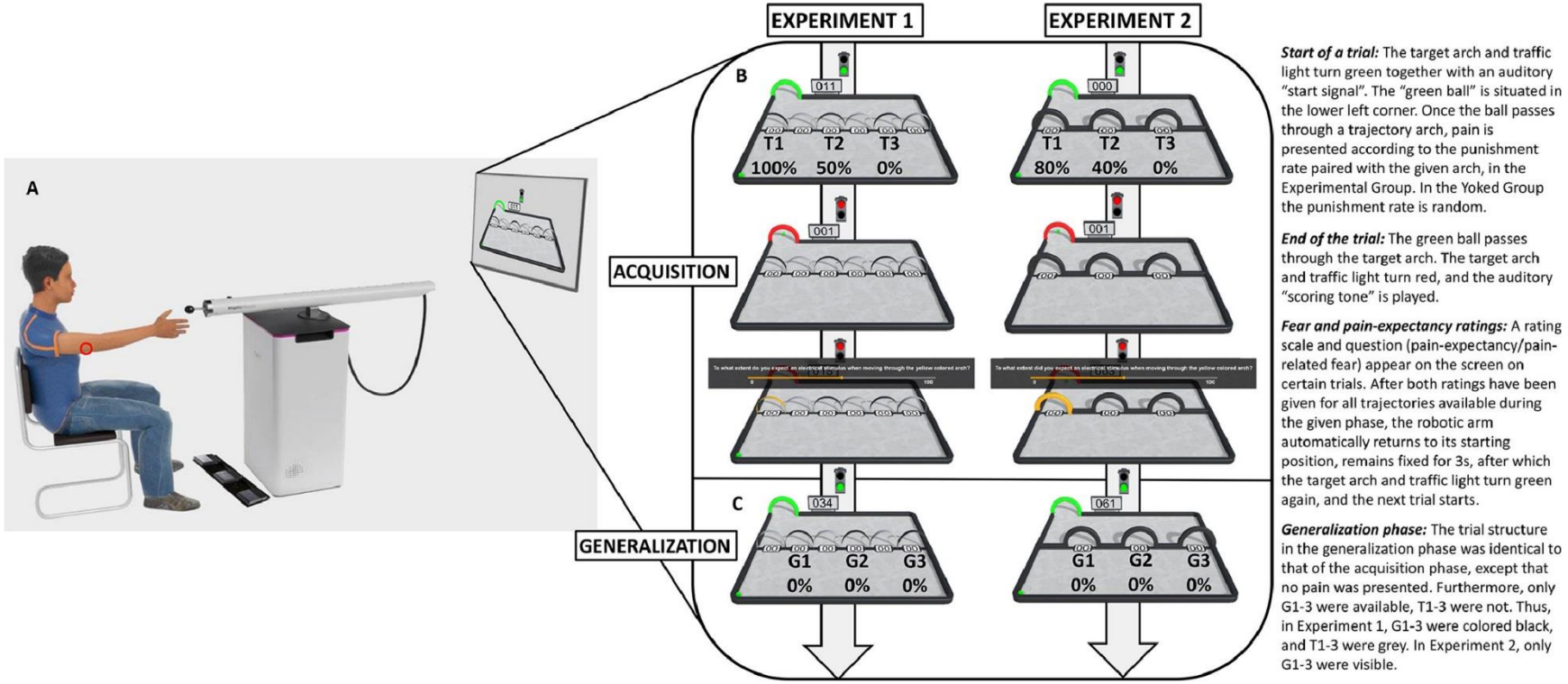
movement plane. The trajectory arches were separated by spaces where the generalization trajectory arches (G1-3) would appear during the generalization phase (Figure 1.1, panel B: Experiment 2). On each trial, participants freely chose one of the three available movement trajectories to reach the target location.

The HapticMaster 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 (Figure 1.1, panel B).

The experiment was preceded by a *practice phase*, during which participants performed the task and familiarized themselves with self-reports. During this phase no pain stimulus was 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 the pain stimulus (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 (i.e., avoidance at the cost of effort). Note that conceptualizing these responses as avoidance means that participants in the Experimental Group could avoid the pain stimulus 100% of the time by choosing T3, 50% of the time by choosing T2, and never by choosing T1 (i.e., negative reinforcement; Skinner, 1953). Each participant in the *Yoked Group* was matched to a participant in the Experimental Group, and thus received the pain stimulus 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 (Davis & Bitterman, 1971). 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.

Figure 1.1

Experimental setup and schematic overview of experimental tasks



Note. Panel A: the participant sits in front of the television screen, at reaching distance from the robotic device's handle; the electrodes for delivering electrical stimuli are on the right arm (red circle); the foot switch is used to provide ratings. Panels B (acquisition) and C (generalization): T1-3 and G1-3 refer to acquisition and generalization trajectories respectively, and percentages refer to respective punishment rates (both not visualized during task). Figure modified with permission from Glogan, Gatzounis, Vandael, et al. (2020).

The *generalization phase* was similar to the acquisition phase, except that now three novel generalization trajectories (G1-3; Figure 1.1, panel C: Experiment 2), were presented. None of the generalization trajectories were paired with the pain stimulus. 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 robotic device's handle, which repositioned to its starting position automatically. After returning to the starting position, the robotic device remained fixed for 3 s (inter-trial interval) before the start of the next trial.

Primary outcome measures

Avoidance behavior

Avoidance behavior was operationalized as the maximal deviation from the shortest trajectory within the 0.36 x 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 robotic device.

Self-reports: pain-expectancy and pain-related fear

Questions were presented on-screen using a visual analogue scale ranging from 0-100 (0 = "*not at all*" and 100 = "*very much*"), and answered using the foot switch. 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?"* (i.e., pain-expectancy) and "*How afraid are you to move through the yellow-colored arch?"* (i.e., pain-related fear) for each of the movement trajectories.

Exit questionnaire and psychological trait questionnaires

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

Data analysis overview

The hypotheses and analysis plans of Experiment 1 (https://osf.io/q7nj8) and Experiment 2 (https://osf.io/yvx6c/?view_only=5a7bc4b1d5374efba71f90f29bb09f20) were pre-registered on Open Science Framework. 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 explicitly report these deviations below.

Independent samples *t*-tests between groups were performed on sample characteristics (i.e., age, intensity of the electrical stimulus, and self-reported pain intensity during calibration), and exit and psychological trait questionnaires (see Appendix A) to test for group differences. Data from the acquisition and reminder-of-acquisition phases were analyzed as manipulation checks (see Appendix A 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 per trajectory for all participants, and repeated measures analyses of variance (RM ANOVAs) were calculated; Group served as between-subjects factor, and Block and Trajectory as 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 report all comparisons for Experiment 1 as well.

For analyses of avoidance behavior, a MATLAB (MathWorks, Natick, MA, US) script was used to extract the maximal deviation per trial. These values were averaged per block for each participant, and used to compare avoidance behavior between groups (RM ANOVAs); Group served as between-subjects factor, and Block as within-subjects factor. Given that no pain stimuli were presented 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. Holm-Bonferroni corrected *p*-values are reported in case of multiple testing. The indication of effect size η_p^2 is reported for significant ANOVA effects, and Cohen's *d* for significant planned comparisons. Data-analyses were crosschecked using RStudio (RStudio Inc. Boston, MA, USA; Package "afex"; Singmann et al., 2019) and SPSS 25.0 (IBM, Armonk, NY, USA) – yielding the same results.

Experiment 1

Instrumental responses may become directly associated with the learning context (Hull, 1943), leading to diminished responding when the context is changed (Bouton et al., 2014). How generalization was operationalized (absence of T1-3 and appearance of G1-3) in Glogan, Gatzounis, Meulders, et al. (2020) may have been experienced by participants as a context-switch (Bouton & Todd, 2014). This may have stimulated 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 pain stimulus. Therefore, the goal of Experiment 1 was to reduce visual context changes by presenting all trajectory arches simultaneously (Figure 1.1, panel B, Experiment 1), in accordance with previous studies of pain-related *fear* generalization (Meulders et al., 2013).

Methods

Thus, all six 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. When trajectories were unavailable, their arches were colored grey. Therefore the *acquisition phase* was similar to that of Glogan, Gatzounis, Meulders, et al. (2020; contingencies: T1 = 100% punishment, T2 = 50% punishment, T3 = 0% punishment), except that all six movement trajectories were presented simultaneously. The acquisition phase consisted of two blocks of 12 trials. The subsequent *generalization phase* was similar to the acquisition phase, except that only G1-3 were now available and no pain stimuli were presented. This phase consisted of three blocks of 12 trials. The three generalization blocks were interspersed by the brief *reminder-of-acquisition* blocks, comprising five trials each. During the acquisition and generalization phases, self-reports of pain-expectancy and pain-related fear were collected three 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; $M \pm SD$ age = 22 $\pm$ 4 years, range: 18-37). The sample size was based on the same a priori power calculation as that of Glogan, Gatzounis, Meulders, et al. (2020) for an independent *t*-test (two-tailed), which yielded a sample size of 52 (using G*Power; $\alpha = .05$, d = .80, power = .80; Faul et al., 2007). A large effect size was chosen based on the acquisition effect found in a previous study when comparing the Experimental and Yoked groups at the end of acquisition

(Meulders et al., 2016). 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 naïve to this allocation. This approach was used because 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 the corresponding Yoked Group participant. Participants were recruited through the research participation system of Maastricht University (Sona Systems Ltd., Tallinn, Estonia), 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 (e.g., asthma, bronchitis); neurological disease (e.g., epilepsy); current/history of psychiatric disorder (e.g., 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 (e.g., 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 EUR in gift vouchers as compensation. The data were collected in Maastricht 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_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 (Table 1.1), or any of the scores on the psychological trait questionnaires (Table S1.3 in Appendix A).

Table 1.1

Sample characteristics

Experiment 1	**Experimental**		**Yoked**				
***N* = 64**	**(78% female)**		**(84% female)**				
	M	***SD***	***M***	***SD***	***df***	***t***	***p***
Age	22.25	3.79	22.42	4.08	62	-0.17	.865
Intensity of the electrical stimulus	34.81	20.10	33.75	16.50	62	0.23	.818
Self-reported pain intensity	7.34	.87	7.47	1.11	62	-0.50	.617
Experiment 2	**Experimental**		**Yoked**				
***N* = 70**	**(71% female)**		**(66% female)**				
	M	***SD***	***M***	***SD***	***df***	***t***	***p***
Age	21.86	3.27	22.66	3.15	68	-1.04	.301
Intensity of the electrical stimulus	41.00	25.30	37.09	23.75	68	0.67	.507
Self-reported pain intensity	7.51	1.25	7.89	0.99	68	-1.30	.198

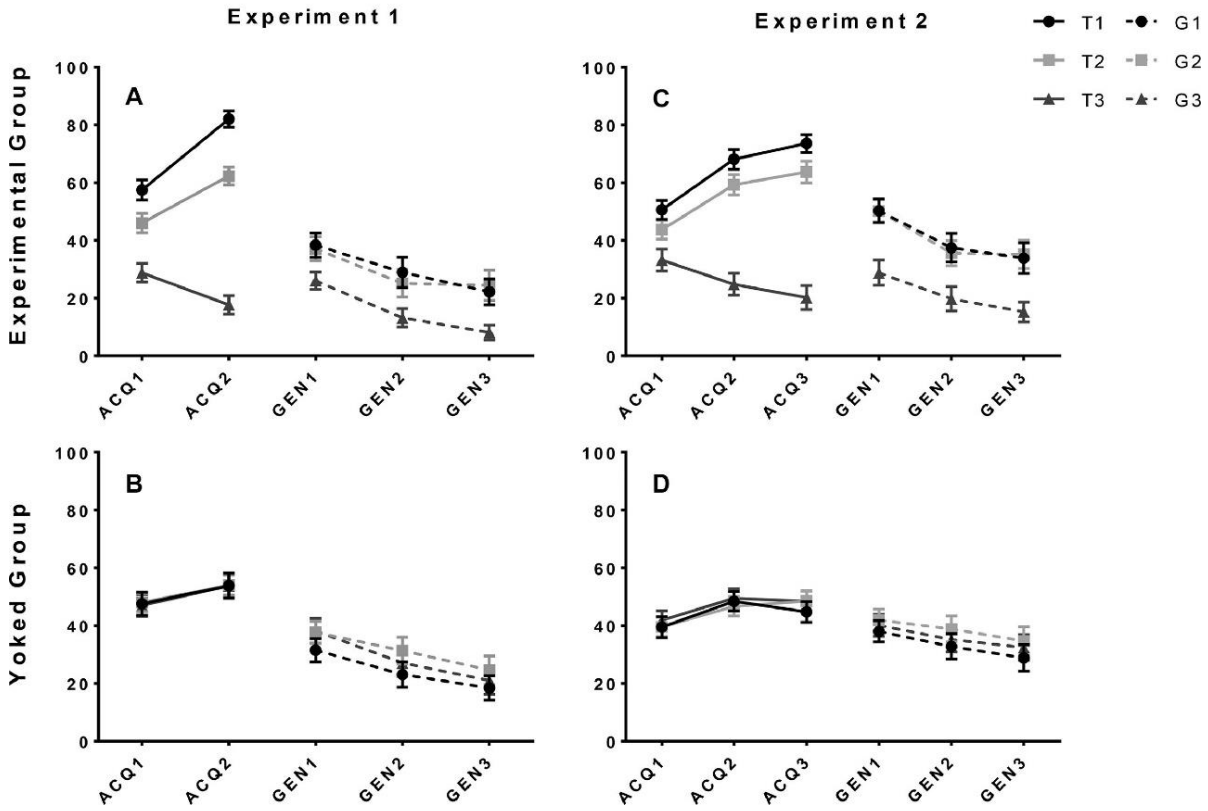
Note. Experiment 1: *n* = 32; Experiment 2: *n* = 35. The minimum age was 18 years; the intensity of the electrical stimulus could range between 1 and 99 mA; self-reported pain intensity could range between 0 and 10. *P*-values are not corrected for multiple testing (Bonferroni corrected threshold = .017).

Manipulation checks

Acquisition: pain-expectancy, pain-related fear, and avoidance behavior. Participants in the Experimental Group learned to expect the pain stimulus more during the pain-associated movements (T1-2) compared to the safe movement (T3; Figure 1.2, panel A). The same pattern was present in the pain-related fear ratings (Figure 1.3, panel A). Furthermore, participants in the Experimental Group showed significantly larger deviations than the Yoked Group during the acquisition phase, demonstrating successful avoidance learning (Figure 1.4, panel A). For the complete results, see Appendix A.

Figure 1.2

Pain-expectancy ratings

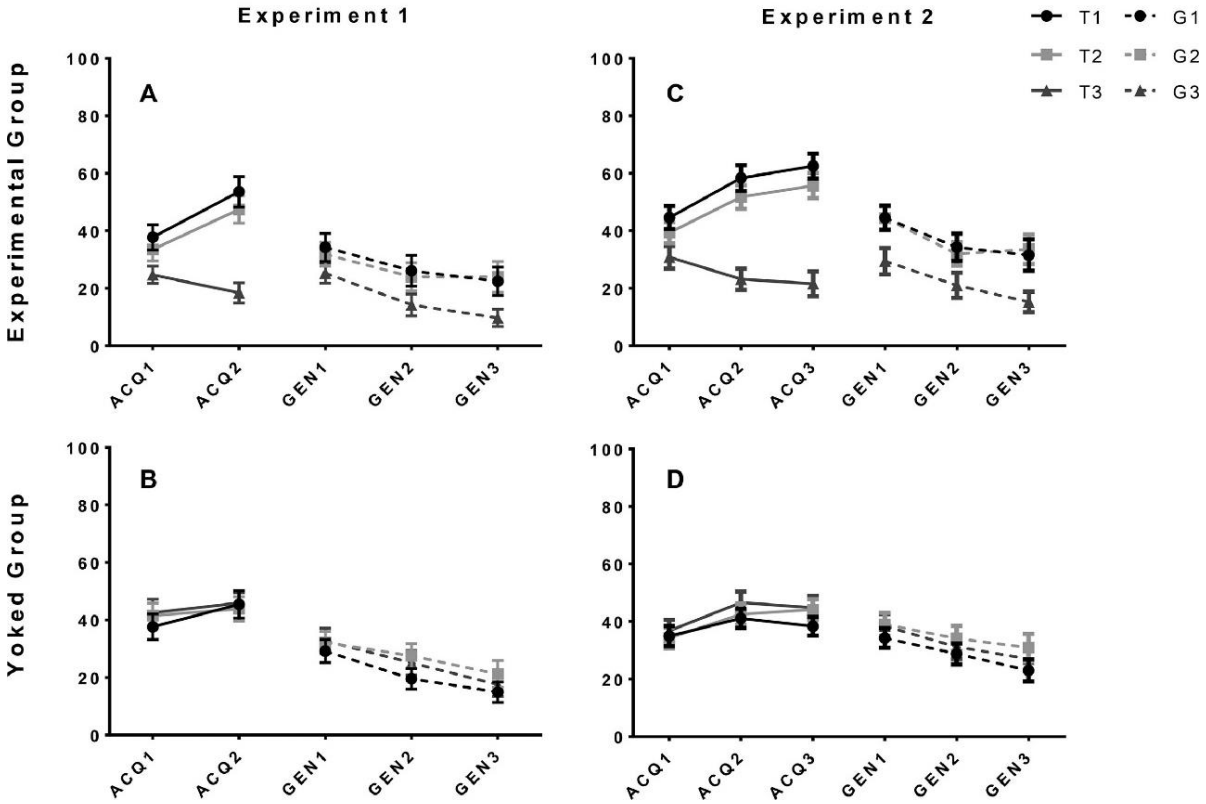


Note. Mean pain-expectancy ratings towards the acquisition trajectories (T1-3) and generalization trajectories (G1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiment 1 (panels A and B) and Experiment 2 (panels C and D), during the acquisition blocks (Experiment 1: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

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. This confirmed that the test of generalization (under extinction) did not affect the acquired differential pain-expectancy (Figure S1.1, panel A in Appendix A) and pain-related fear (Figure S1.2, panel A in Appendix A) ratings for the acquisition trajectories, nor did it affect previously acquired avoidance behavior (Figure S1.3, panel A in Appendix A). For the complete results, see Appendix A.

Figure 1.3

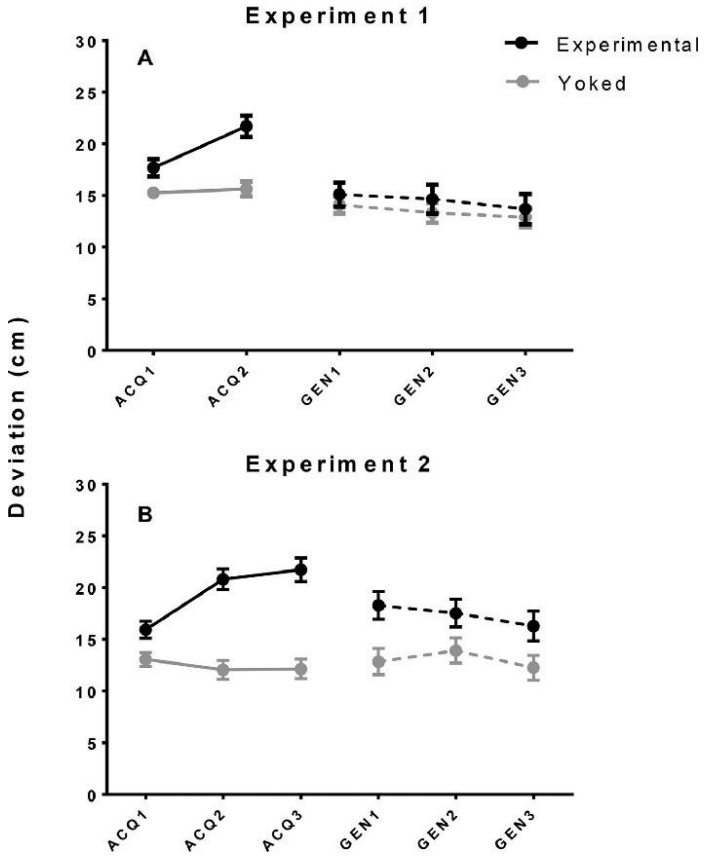
Pain-related fear ratings



Note. 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 standard deviations.

Figure 1.4

Avoidance behavior



Note. 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 standard deviations. To increase comparability between phases, a linear transformation was performed: the acquisition and generalization trajectories share the same coordinates.

Testing our main hypotheses: Generalization of pain-expectancy, pain-related fear, and avoidance behavior

A 2 (Group: Experimental, Yoked) x 3 (Block: GEN1-3) x 3 (Trajectory: G1-3) RM ANOVA on the mean *pain-expectancy ratings* during generalization showed no significant 3-way interaction, $F(3.94, 216.60) = 0.69$, $p = .580$, but a significant Group x Trajectory interaction, $F(1.61, 100.11) = 8.75$, $p < .001$, $\eta_p^2 = .12$. This suggests that groups showed distinct patterns of pain-expectancies for the different trajectories during the generalization phase (Figure 1.2, panel A). During the first generalization block (GEN1), the 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) = 0.44, *p* = .664. 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; Figure 1.2, panel B).

A similar RM ANOVA on the mean *pain-related fear ratings* during generalization also showed no significant 3-way interaction, *F*(3.30, 204.62) = 0.67, *p* = .580, but a significant Group x Trajectory interaction, *F*(1.43, 88.52) = 5.18, *p* = .010, η_p^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 (Figure 1.3, panel A), 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 Table S1.5 in Appendix A for the complete results of pain-related fear reports during the generalization phase). No significant differences occurred between any of the pairs in the Yoked Group (all *p*-values > .05; Figure 1.3, panel B). Thus, fear did not generalize in the hypothesized manner, although the effect was present in the later blocks.

A 2 (Group: Experimental, Yoked) x 3 (Block: GEN1-3) RM ANOVA on mean *maximal deviation* data during generalization yielded no significant effects (Group: *F*(1, 62) = 0.52, *p* = .472; Block, *F*(1.56, 96.63) = 1.88, *p* = .167; Group x Block, *F*(1.56, 96.63) = 0.08, *p* = .884). Thus, no generalization of avoidance behavior was observed in Experiment 1 (Figure 1.4, panel A).

Experiment 2

The 100% punishment rate for T1 in Glogan, Gatzounis, Meulders, et al. (2020) may have resulted in high expectations of punishment also for G1. Thus, the absence of the pain stimulus when exploring G1 at the beginning of generalization would have been surprising, leading to rapid disconfirmation of acquired threat beliefs (extinction; Craske et al., 2018). 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 pain-associated 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 and G1-3 during generalization, as in Glogan, Gatzounis, Meulders, et al. (2020). Furthermore, T1 was now paired with an 80% instead of 100% punishment rate, and T2 with a 40% instead of 50% punishment rate (Figure 1.1, panel B, Experiment 2). T3 remained 0% punished. The acquisition and generalization phases both consisted of three blocks of 12 trials. 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; $M \pm SD$ age = 22 $\pm$ 3 years, range: 18-31). The sample size was based on the same a priori power calculations as those of Glogan, Gatzounis, Meulders, et al. (2020) and Experiment 1 (N = 64). However, given that Glogan, Gatzounis, Meulders, et al. (2020) showed no effect of avoidance generalization, and because we reduced punishment rates in the current study – possibly resulting in more variation between participants (Lissek et al., 2006) –, 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 naïve to this allocation. Exclusion criteria were the same as in Experiment 1. Participants were recruited and tested in Maastricht 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), self-reported intensity of the electrical stimulus (see Table 1.1), or any of the scores on the psychological trait questionnaires (Table S1.4 in Appendix A).

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 (Figure 1.2, panel C) and fear (Figure 1.3, panel C) ratings, and

successfully learned to avoid the electrical stimulus (Figure 1.4, panel B). For the complete results, see Appendix A.

Reminder-of-acquisition: pain-expectancy, pain-related fear, and avoidance behavior. Similar 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 (Figure S1.1, panel C in Appendix A) and pain-related fear (Figure S1.2, panel C in Appendix A), nor did it affect acquired avoidance behavior (Figure S1.3, panel B in Appendix A). For the complete results, see Appendix A.

Testing our main hypotheses: Generalization of pain-expectancy, pain-related fear, and avoidance behavior

A 2 (Group: Experimental, Yoked) x 3 (Block: GEN1-3) x 3 (Trajectory: G1-3) RM ANOVA of mean *pain-expectancy ratings* during the generalization phase yielded no significant 3-way interaction, $F(3.08, 209.73) = 0.79$, $p = .50$, 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 (Figure 1.2, panel C). During the first generalization block (GEN1), the Experimental Group expected the electrical stimulus more during G1, $t(68) = 4.08$, $p < .001$, $d = .86$, and G2, $t(68) = 4.75$, $p < .001$, $d = .87$, compared to G3. In contrast to pain-expectancies toward T1 and T2 however, the pain stimulus was not expected more during G1 compared to G2, $t(68) = 0.03$, $p = .978$. 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; Figure 1.2, panel D).

A similar RM ANOVA of mean *pain-related fear ratings* during generalization did not show a significant 3-way interaction, $F(3.17, 215.89) = 0.74$, $p = .540$, but the Group x Trajectory interaction did reach significance, $F(1.62, 109.91) = 6.52$, $p = .004$, $\eta_p^2 = .09$, 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 (Figure 1.3, panel C). Again, in contrast to fear reported toward T1 and T2 during acquisition, G1 was not feared more than G2, $t(68) = 0.01$, $p = .991$. 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 (Table S1.6 in Appendix A). No significant differences were present for any of the pairs in the Yoked Group (all *p*-values > .05; Figure 1.3, panel D). Together with the pain-expectancy reports, these results indicate that in the Experimental Group, 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.

A 2 (Group: Experimental, Yoked) x 3 (Block: GEN1-3) RM ANOVA on mean *maximal deviation* during generalization yielded a significant main effect of Group, $F(1, 68) = 7.63$, $p = .007$, $\eta_p^2 = .10$, 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 (Figure 1.4, panel B).

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 (Glogan, Gatzounis, Meulders, et al., 2020). 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: 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, Gatzounis, Meulders, et al. (2020), 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, these results imply that avoidance rapidly extinguished due to this exploration. These effects 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 (e.g., a movement possibly followed by pain), with the goal of obtaining

future rewards (e.g., needing to exert less effort; Lee et al., 2011). Furthermore, the more one's expectations are violated (e.g., surprising absence of pain), the more they will learn from exploration, and the more likely they will be to re-evaluate current behavior (e.g., stop avoiding; Mehlhorn et al., 2015; Rescorla & Wagner, 1972). On the other hand, if one's expectations are not violated, or they are uncertain from the get-go (e.g., uncertain expectations of pain), less learning, and thus less behavior change will occur – i.e., *exploitation* of a behavior with known outcomes (e.g., sustained avoidance; Mehlhorn et al., 2015; Rescorla & Wagner, 1972).

In line with Glogan, Gatzounis, Meulders, et al. (2020) and Experiment 1, healthy people tend to explore, whereas inflexible behavior is more characteristic of people with chronic pain (Van Dieën et al., 2017). Thus, the current findings corroborate the fear-avoidance model of chronic pain, which proposes that most people in acute pain test and correct pain expectations (i.e., explore), which facilitates recovery (Lethem et al., 1983; Vlaeyen & Linton, 2000). 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 (Meulders, 2019). Furthermore, psychological and neurobiological theories of anxiety place uncertainty at the center of anxiety pathology (Grupe & Nitschke, 2013); uncertainty complicates the process of balancing the efficiency (e.g., exploration) and effectiveness (e.g., exploitation) of threat-related preparatory behaviors, thus increasing the likelihood of making overly prudent choices (e.g., by adopting a "better safe than sorry" approach; Van den Bergh et al., 2021). Furthermore, uncertainty impedes one's ability to *control* aversive events, which results in diffuse, costly, and ineffective preparatory behaviors (Van den Bergh et al., 2021).

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 (Grillon et al., 2006; Grupe & Nitschke, 2013), 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 showed that participants in Experiment 2 exhibited less exploration at the beginning of the generalization phase, compared to participants in Experiment 1 (see Appendix A). This indeed suggests that for 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 – 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 (Hunt et al., 2019). Given that uncertainty is accompanied by uncontrollability (Van den Bergh et al., 2021), 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 (Löffler et al., 2018). 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 (Gatchel & Okifuji, 2006; Gatchel et al., 2007).

Importantly, the results of Glogan, Gatzounis, Meulders, et al. (2020) 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 (e.g., Boyle et al., 2016; Dymond et al., 2012). This is an important distinction from an ecological validity perspective, since real-life avoidance is often extremely costly (Volders et al., 2015), and people with pain or anxiety often weigh the value of avoidance against that of alternative, competing behaviors (Claes et al., 2014; Van Damme et al., 2012). Thus, people with chronic pain may for example go to work or play with their children, despite fear of pain (Van Damme et al., 2010; Volders et al., 2015). In fact, the presently reported dissociations between self-reports and avoidance align with literature demonstrating attenuated avoidance, but not fear, when alternative goals (e.g., gaining rewards) compete with avoidance of both aversive (Pittig & Dehler, 2019; Pittig et al., 2018) and painful (Claes et al., 2015; Claes et al., 2014; Van Damme et al., 2012) stimuli. These findings highlight the importance of clinical interventions targeting disability by emphasizing the value of pursuing life goals (e.g., Acceptance and Commitment Therapy; Hughes et al., 2017; Pielech et al., 2017; Vowles et al., 2014).

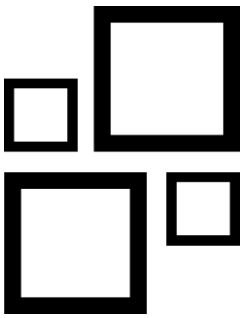
It should be noted that, using the robotic arm-reaching paradigm, avoidance was recently found to be modulated by context (Meulders et al., 2020), demonstrating that context-switches, *per se*, do not eliminate avoidance in the paradigm. However, in Meulders et al. (2020), the avoidance response itself 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*: i.e., generalizing the avoidance response to a similar, yet different response. In response generalization, the contingency (e.g., punishment rate) related to one response, generalizes to other similar responses, increasing or decreasing the recurrence of these similar behaviors (Skinner, 1953). 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) in the presence of stimuli differing from each other along perceptual (Hunt et al., 2019; Norbury et al., 2018; van Meurs et al., 2014) or semantic (Boyle et al., 2016; Dymond et al., 2012) 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 (Ghirlanda & Enquist, 2003; Pavlov, 1941). 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 (Krypotos et al., 2020). 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, Gatzounis, Meulders, et al. (2020) and Experiment 1 resulted from avoidance-costs. However, 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 (Carleton et al., 2007). Furthermore, a mechanism of chronic pain that may contribute to excessive avoidance is deficient safety learning (heightened fearful reactivity to objectively safe conditions; Harvie et al., 2017). 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 two extreme stimuli (i.e., one stimulus associated with an aversive outcome and one safe stimulus) during acquisition, between which generalization stimuli lie on a perceptual continuum during generalization, we also trained an ambiguous trajectory (T2), lying between the two extreme trajectories (T1 and T3). 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.

Chapter 2

Targets for intervention



This chapter is under revision as Vandael, K., Vervliet, B., Peters, M., & Meulders, A. Excessive generalization of pain-related avoidance behavior: mechanisms, targets for intervention, and future directions. *Pain*.

Abstract

Contemporary fear-avoidance models assign a key role to excessive pain-related avoidance in the development and maintenance of chronic pain disability. Avoiding pain-associated activities is adaptive as it prevents bodily harm. However, when avoidance spreads (generalizes) excessively toward safe activities, it can lead to disproportional withdrawal from harmless and valued daily activities, which may culminate into disability. Hence, the systematic investigation of methods to reduce excessive avoidance generalization is warranted. The current topical review first provides an overview of conditioning studies investigating the acquisition and generalization of pain-related fear and avoidance behavior. Based on empirical evidence from both pain and anxiety research, we then provide an overview of potential pathways to intervene on fear generalization and/or the fear-avoidance relation – as fear can motivate avoidance behavior, but there is no one-to-one relation between the two. We highlight perceptual accuracy, positive affect, and competing goals specifically, and discuss additional pathways based on preliminary evidence. Future directions for this field of research are discussed.

Introduction

Avoidance of pain-associated activities is adaptive in acute pain because it prevents harm; for example, when shooting pain is experienced while bending, not repeating this movement may prevent exacerbating an injury. However, when tissues have healed, avoidance prevents learning that these activities are actually safe. Furthermore, avoidance can spread toward activities similar to those previously associated with pain, even if these were never paired with pain (i.e., avoidance generalization; Glogan et al., 2021). This again is adaptive as a learned protective behavior can be applied to similar instances, without needing to learn about each separately. However, when applied to safe activities, it bears the risk of increased withdrawal from harmless daily activities. According to contemporary fear-avoidance models, such excessive generalization (or overgeneralization) may instigate a self-sustaining cycle of activity disengagement, resulting in chronic pain disability (Crombez et al., 2012; Leeuw et al., 2007; Meulders, 2019; Vlaeyen et al., 2016).

Due to the central role of avoidance in chronic pain disability, gaining insight into factors that tackle its excessive generalization can help to develop and optimize interventions reducing pain-related suffering. According to fear-avoidance models, pain-related fear can initiate avoidance behavior intended to avert bodily threat. Therefore, we first review experimental studies on (over)generalization of pain-related fear before moving to avoidance studies. Next, targets for intervention are discussed in light of empirical evidence from both the field of chronic pain and anxiety disorders. Note that the current review focuses on behavioral interventions, and excludes for example neural stimulation methods (e.g., Burger et al., 2019).

Generalization of pain-related fear

Pavlovian or classical conditioning plays a key role in learning to predict potential harm (Meulders, 2019). Lab studies show that an initially neutral movement (conditional stimulus; CS+) paired with pain (unconditional stimulus; US; e.g., a painful electrical stimulus) comes to elicit pain-related fear (conditional response; Karos et al., 2017; Meulders, 2020; Meulders et al., 2011). Fear can then spread towards stimuli perceptually similar to the CS+ (stimulus generalization; Dymond et al., 2015; Lissek et al., 2008): movements resembling the pain-associated movement (generalization stimuli; GSs) can elicit pain-related fear as well, even though they were never paired with pain (Meulders et al., 2013; Meulders & Vlaeyen, 2013). GSs that are less similar to the CS+ typically elicit less fear. Additionally, pain-related fear can spread towards perceptually similar contexts and along a dimension of conceptual relatedness, that is, pain-related fear can spread towards movements that have the same function or belong to the same category as the pain-associated movement (e.g., household chores; Glogan et al., 2018; Meulders et al., 2020; Meulders, Vandael, et al., 2017).

Generalization is adaptive because we do not need to learn everything anew. However, this process becomes maladaptive when stimuli bearing only minimal similarity to the CS+ elicit fear. Such overgeneralization is considered a transdiagnostic pathogenic marker in anxiety disorders (Dunsmoor & Paz, 2015; Lissek et al., 2014; Lissek et al., 2010) and recently the same argument has been made for chronic pain disorders (Meulders, 2019, 2020; Vlaeyen et al., 2016). For example, when someone is afraid of slightly bending the back, this is maladaptive if they originally experienced pain during a very different movement – such as bending over a 90-degree angle while lifting a heavy object. Using a Pavlovian conditioning paradigm in which joystick movements served as CSs and GSs, Meulders et al. (2015) showed overgeneralization of pain-related fear in people with fibromyalgia compared to healthy, pain-free controls, corroborating the role of overgeneralization in chronic pain. Moreover, these results have been replicated in various chronic pain conditions (Harvie et al., 2020; Meulders, Harvie, et al., 2014).

Generalization of pain-related avoidance

Next to pain-related fear, contemporary fear-avoidance models emphasize the role of avoidance in the development and maintenance of chronic pain disability (Vlaeyen et al., 2016). Avoidance can be particularly disruptive in daily life and prevent individuals from participating in social activities for example. Moreover, it is self-sustaining, as it prevents learning that activities are safe. Operant conditioning paradigms are commonly used to study the acquisition and generalization of avoidance in the lab (e.g., Glogan, Gatzounis, Vandael, et al., 2020; van Meurs et al., 2014). Through operant conditioning, participants learn that certain behaviors or movements (responses) lead to the non-occurrence of a feared event such as pain (outcome). This learning strengthens avoidance behaviors, making them more likely to occur. Besides the non-occurrence of the feared event, other factors have been argued to reinforce avoidance behavior, such as fear reduction and relief – the positive feeling in reaction to the absence of an anticipated aversive event (Krypotos et al., 2015; Mowrer, 1951; Vervliet et al., 2017). Importantly, a recent study confirmed that avoidance of pain-associated movements can generalize toward perceptually similar movements in healthy, pain-free participants (Glogan et al., 2021).

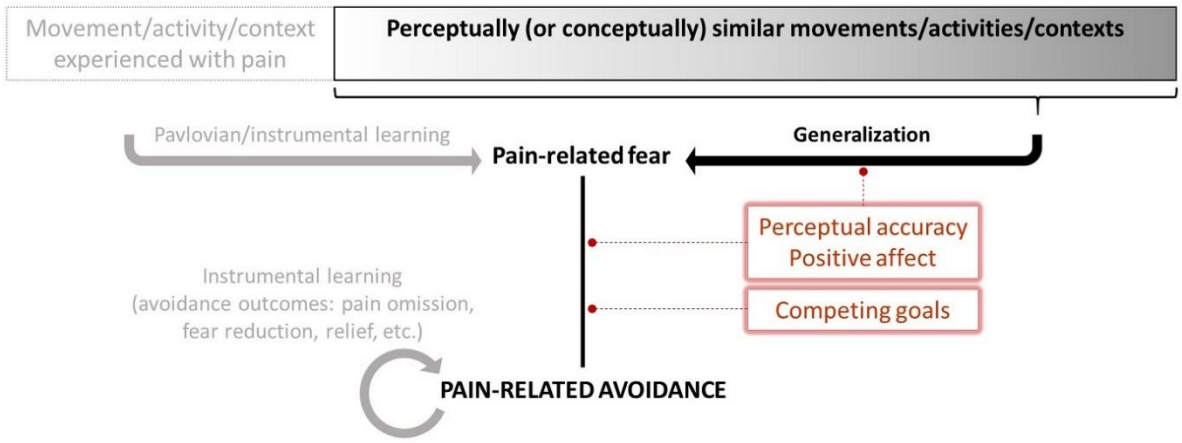
Currently, studies on overgeneralization of avoidance behavior in clinical anxiety and chronic pain disorders are lacking. Contemporary emotion theories consider avoidance as a component of fear, as emotions are viewed as a compound of cognitions, action tendencies, physiological responses, motor actions, and subjective feelings (Krypotos et al., 2015; Moors, 2009). In other words, when fear overgeneralizes, it is likely to be accompanied by overgeneralization of avoidance. However, there is no one-to-one relationship between (generalized) fear and behavioral avoidance, emphasizing the

need for research on overgeneralization of avoidance specifically (Glogan, Gatzounis, Meulders, et al., 2020; Pittig, Wong, et al., 2020). For example, while avoidance behaviors are strengthened when a feared outcome does not occur (among other factors), they can simultaneously be weakened by costs – such as not being able to participate in valued activities. This can lead to fear and avoidance dissociating, as activities are performed despite fear (Claes et al., 2014; Van Damme et al., 2012). However, it should be noted that a study by Hunt et al. (2019) showed that anxiety traits moderate the relation between fear and avoidance. Specifically, high intolerance of uncertainty and anxiety sensitivity were associated with generalized fear being accompanied by more avoidance. In other words, a stronger fear-avoidance relation seems present in high anxious individuals, indicating that when fear overgeneralizes, avoidance will indeed overgeneralize as well.

Next, we describe potential intervention targets to reduce avoidance overgeneralization: perceptual accuracy, positive affect, and goals competing with avoidance. For each factor, we review empirical evidence supporting that intervention affects fear generalization and/or the fear-avoidance relation in human subjects (Figure 2.1). We also discuss other potential factors to intervene on, based on observational studies indicating their implication in fear generalization and/or the fear-avoidance relation.

Figure 2.1

Potential intervention targets to reduce excessive generalization of pain-related avoidance.



Note. Potential intervention targets are displayed in red as evidence indicates they attenuate fear generalization and/or the fear-avoidance relation. Note that the acquisition of pain-related fear and the reinforcement of avoidance behavior through associative learning are not the focus of intervention in the current review, and are therefore displayed in gray.

Intervention targets to attenuate avoidance generalization

Perceptual accuracy

Moseley and Vlaeyen (2015) advanced the idea that perceptual inaccuracy could lead to overgeneralization of protective responses, as generalization negatively relates to the degree to which one stimulus can be differentiated from another (Ghirlanda & Enquist, 2003; Struyf et al., 2017; Zaman, Ceulemans, et al., 2019). For example, when movements that were never paired with pain are not accurately perceived, they may be more likely to elicit pain-related fear and avoidance as well. This implies that perceptual discrimination training potentially reduces generalization. Ginat-Frolich et al. (2017) provided evidence for this in healthy participants that were trained on perceptual discrimination during a fear conditioning procedure. Participants performed a decision-making task in which they discriminated between visual stimuli – which were different from the CSs and GSs. During the subsequent generalization test, participants that performed the discrimination training reported less generalized fear. Additionally, Herzog et al. (2021) showed stronger reduction of generalization when using the CSs and GSs versus a novel stimulus set during discrimination training. Moreover, Lommen et al. (2017) observed attenuated generalization of avoidance behavior following perceptual discrimination training (using visual stimuli), which indicates that such training also affects the behavioral component of fear. Interestingly, generalization of US-expectancy (as a proxy of fear) was unaffected, which indicates a dissociation between generalized fear and avoidance. In other words, it was rather the relation between fear and avoidance that was weakened. Furthermore, Ginat-Frolich et al. (2019) trained perceptual discrimination in highly spider-fearful participants, which resulted in reduced avoidance of stimuli ranging from fake to real spiders. This suggests that perceptual training is a promising method to reduce excessive avoidance in clinical populations.

In the context of pain, somatosensory and proprioceptive information is as important as visual information for fear and avoidance learning, and subsequent generalization (Van Dieën et al., 2017). Studies indeed show that tactile acuity – the accuracy of sense of touch – affects pain-related fear learning (Harvie et al., 2016). Moreover, improving tactile acuity reduces pain intensity in chronic pain conditions (e.g., Moseley et al., 2008). When learning about movements specifically, proprioceptive information plays a key role; i.e., the perception of motion and position of the body or body segments in space (Proske & Gandevia, 2012). A wide range of pain conditions present with impaired proprioceptive accuracy (Juul-Kristensen et al., 2008a; Knoop et al., 2011; Stanton et al., 2016; Tong et al., 2017), and evidence again suggests that targeting this specific impairment may improve pain outcomes (Jull et al., 2007). Moreover, a recent experimental study showed an association between poor proprioceptive accuracy and excessive avoidance of pain-associated movements in healthy, pain-

free participants, suggesting that proprioceptive training might indeed be a pathway to counter overgeneralization of pain-related avoidance behavior (Vandael et al., 2022).

Positive affect

Fear-avoidance models acknowledge the importance of vulnerability factors such as negative affect in the development and maintenance of chronic pain disability. Additionally, evidence for the role of resilience factors such as positive affect has accumulated (Finan & Garland, 2015; Hanssen et al., 2017; Ong et al., 2015; Sturgeon & Zautra, 2010). Studies in people with chronic pain show that positive affect may be depleted during pain and stress, and that positive affect inversely predicts pain reports (Zautra, Fasman, et al., 2005; Zautra, Johnson, et al., 2005). Moreover, positive psychology interventions have been shown to successfully promote positive affect, wellbeing and functioning, and reduce pain severity and depression in individuals suffering from chronic pain [see Ong et al. (2020) and Braunwalder et al. (2022) for systematic reviews].

Evidence suggests that positive affect facilitates learning that certain stimuli are safe and thus inhibits fear from spreading to novel safe stimuli (Zbozinek & Craske, 2017). Geschwind et al. (2015) tested whether experimentally induced positive affect indeed has the potential to reduce overgeneralization. This study with healthy, pain-free participants employed joystick movements as CSs and GSs, and a visualization exercise to induce positive affect. Results showed that increases in positive affect were associated with less generalization of pain-related fear to the movements that were more similar to the CS-. Furthermore, positive affect may increase willingness to approach fear-evoking stimuli (i.e., to not avoid them), thus potentially affecting the fear-avoidance relation as well (Zbozinek & Craske, 2017).

Competing goals

As avoidance occurs in a dynamic environment of concurrent, potentially competing, goals, the motivational context should be taken into account (Van Damme et al., 2012). Some individuals prioritize controlling pain as a goal at the cost of competing valued goals, thus instigating the vicious cycle of disability described by fear-avoidance models (Vlaeyen et al., 2016). Goals are the focus in certain psychological interventions for chronic pain (e.g., Muller et al., 2016). For example, Acceptance and Commitment Therapy encourages participants to identify and pursue valued life goals, and has been shown to reduce the extent to which pain interferes with daily functioning in chronic pain (Wetherell et al., 2011). Experimental studies in both the field of anxiety and pain indeed show that the presence of competing goals (e.g., obtaining monetary reward) attenuates avoidance (Claes et al., 2014; Pittig & Dehler, 2019; Pittig et al., 2018). Moreover, such goals do not necessarily reduce fear

directly, but rather affect the fear-avoidance relation (Pittig & Dehler, 2019). Based on these results, an operant-based approach in which behaviors competing with avoidance are reinforced could be applied to reduce excessive avoidance generalization.

Evidence supporting this approach comes from a study with healthy subjects by Bennett et al. (2020), showing that reinforcing competing behaviors may be an effective means to mitigate generalization of avoidance along a conceptual dimension. Specifically, participants performed a conditioning procedure during which they learned to avoid an aversive stimulus upon CS presentation. Next, a group of participants received positive feedback when performing responses that were incompatible with the avoidance response – potentially activating task adherence (i.e., maximizing task performance) as a goal. When GSs conceptually related to the CSs were presented, avoidance of GSs was significantly reduced when participants had acquired competing behaviors.

Further potential avenues

Executive functions such as working memory and attentional control are also impaired in chronic pain conditions, indicating potential for intervention (Berryman et al., 2013; Todd et al., 2018). Moreover, evidence shows that working memory plays a role in generalization, although research attempting to experimentally improve working memory to attenuate generalization is currently lacking (Lenaert et al., 2016; Wills et al., 2015). Intriguingly, inducing positive affect improves executive functions, including working memory, indicating that cognitive processes may mediate the effect of positive affect induction on generalization (Boselie et al., 2017; Boselie et al., 2014; Yang et al., 2013). Therefore, it would be interesting to compare – or combine – interventions targeting positive affect and executive functioning to evaluate their (combined) effects.

Anxious traits such as anxiety sensitivity and intolerance of uncertainty are associated with more fear generalization as well as with a stronger fear-avoidance relation, indicating another avenue for intervention (Hunt et al., 2019; Morriss et al., 2016). The idea of intervening on traits is compatible with a dynamic view on personality, as behaviors are not assumed stable across situations, but dependent on specific situations (Mischel & Shoda, 1998). Furthermore, traits may be of interest to identify at-risk individuals, who potentially benefit most from interventions. For example, individuals with high intolerance of uncertainty may benefit from proprioceptive accuracy training as it could help reduce uncertainty about movements.

Future directions

Although paradigms have been developed to study generalization of avoidance behavior in both anxiety (e.g., van Meurs et al., 2014) and pain research (e.g., Glogan et al., 2021), diagnostic

validity still needs to be established in both fields (Vervliet & Raes, 2013). In other words, we need evidence showing overgeneralization of avoidance in clinical samples. Next, validated paradigms can be used to test experimental interventions, both in healthy, subclinical, and clinical samples. It should be noted that the listed interventions theoretically could be applied to counter overgeneralization along a perceptual dimension (i.e., perceptually similar stimuli/responses/ contexts), as well as a conceptual dimension. It may be counterintuitive to train perceptual accuracy to reduce generalization along a conceptual dimension. However, from a predictive processing perspective, fear overgeneralization results from giving more weight to the affective-motivational aspects of input at the expense of detailed sensory-perceptual input (Van den Bergh et al., 2021). Training proprioceptive accuracy may lead to increased weighing of sensory-perceptual input and decreased weighing of affective-motivational aspects, meaning less emphasis on inferences based on conceptual relationships, thus attenuating overgeneralization.

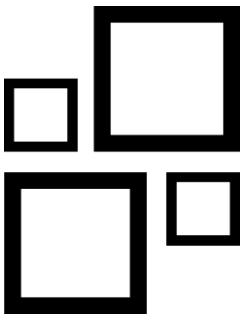
Investigation of experimental interventions to counter overgeneralization is crucial to inform evidence-based treatment. Note that proprioceptive accuracy training (e.g., Jull et al., 2007), positive psychology interventions (e.g., Peters et al., 2017), and goal-directed interventions (e.g., Wetherell et al., 2011) have already been implemented as clinical treatments in chronic pain, and other existing interventions may unintendedly utilize the discussed mechanisms (e.g., overcoming fear during exposure therapy may lead to positive affect). Experimental studies can provide insights into underlying mechanisms of such interventions and ways to optimize treatments, or identify novel targets for treatment. Furthermore, the preventive potential of interventions in the acute pain stage currently remains under-investigated. Note that the experimental model should reflect whether the interest is in prevention before or during the acute stage (e.g., before/after surgery), or in treatment during the chronic stage. For example, interventions can be inserted before conditioning to model the former (e.g., Lommen et al., 2017), or in between generalization tests to model the latter (e.g., Herzog et al., 2021).

A final consideration is that what works in the lab, might not work in clinical reality. Figuring out ‘what works for whom’ may be crucial in this, as patients present with specific problems: for example, poor proprioceptive accuracy may be an indication for proprioceptive training, while reduced reward responsivity may be a counter indication for goal-directed approaches. Indeed, altered reward responsivity has been observed in people with chronic pain, resulting in limited reward learning (Rizvi et al., 2021). Furthermore, certain intervention aspects may be combined to improve clinical outcomes: for example, positive psychology interventions may be used to motivate physical exercise to increase perceptual accuracy, or the performance of valued activities in goal-directed approaches.

In summary, excessive avoidance can be extremely debilitating in daily life; reducing the spreading of such overprotective behavior therefore deserves further scrutiny. However, lab studies providing insight into potential interventions are currently scarce. We reviewed promising pathways to intervene on fear/avoidance generalization and/or the fear-avoidance relation, inspired by both pain and anxiety research.

Chapter 3

Assessing kinesthetic proprioceptive function of the upper limb



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Abstract

Proprioception refers to the perception of motion and position of the body or body segments in space. A wide range of proprioceptive tests exists, although tests dynamically evaluating sensorimotor integration during upper limb movement are scarce. We introduce a novel task to evaluate kinesthetic proprioceptive function during complex upper limb movements using a robotic device. We aimed to evaluate the test-retest reliability of this newly developed dynamic movement reproduction (DMR) task. Furthermore, we assessed reliability of the commonly used joint reposition (JR) task of the elbow, evaluated the association between both tasks, and explored the influence of visual information (i.e., viewing arm movement or not) on performance during both tasks. During the DMR task, participants actively reproduced movement patterns while holding a handle attached to the robotic device, with the device encoding actual position throughout movement. In the JR task, participants actively reproduced forearm positions; with the final arm position evaluated using an angle measurement tool. The difference between target movement pattern/position and reproduced movement pattern/position served as measures of accuracy. In Study 1 (N = 23), pain-free participants performed both tasks at two test sessions, 24-hours apart, both with and without visual information available (i.e., vision occluded using a blindfold). In Study 2 (N = 64), an independent sample of pain-free participants performed the same tasks in a single session to replicate findings regarding the association between both tasks and the influence of visual information. Accuracy as measured by the DMR task showed good-to-excellent test-retest reliability, while the JR task showed poor reliability: measurements did not remain sufficiently stable over testing days. The DMR and JR tasks were only weakly associated. Adding visual information (i.e., watching arm movement) had different performance effects on the tasks: it increased JR accuracy but decreased DMR accuracy, though only when the DMR task started with visual information available (i.e., an order effect was present). The DMR task's highly standardized protocol (i.e., largely automated), precise measurement and involvement of the entire upper limb kinetic chain (i.e., shoulder, elbow and wrist joints) make it a promising tool. Moreover, the poor association between the JR and DMR tasks indicates that they likely capture unique aspects of proprioceptive function. While the former mainly captures position sense, the latter appears to capture sensorimotor integration processes underlying kinesthesia, largely independent of position sense. Finally, our results show that the integration of visual and proprioceptive information is not straightforward: additional visual information of arm movement does not necessarily make active movement reproduction more accurate; on the contrary, when movement is complex, vision appears to make it worse.

Introduction

When we perform controlled voluntary movements, such as reaching for a glass of water, we rely heavily upon sensory information elicited from the movement to successfully perform and control that movement. A key source of sensory information is proprioceptive input, as it allows for the perception of motion and position of the body or body segments in space (Proske & Gandevia, 2012). Proprioceptive input consists of an ensemble of sensory information from various receptors that detect and encode the mechanical changes in tissues (e.g., muscles, skin) during movement; during active movement, muscle spindles are considered the primary source of proprioceptive information (Proske & Gandevia, 2012). Proprioceptive input then undergoes processing within the spinal cord, cephalad transmission up the sensory neuraxis, finally leading to a proprioceptive representation within the brain (area 2 of the primary somatosensory cortex in case of arm movement; Chowdhury et al., 2020). During movement, proprioceptive (and tactile) input is used to inform motor planning (Wolpert et al., 1998). It is also used to determine whether or not the movement has occurred as intended: a motor efferent copy is generated and compared to the sensory input that has resulted as a consequence of this movement (Wolpert & Ghahramani, 2000; Wolpert et al., 1995). Such a process of sensorimotor integration ultimately allows for accurate, controlled movement.

A large variety of tests exist to quantify proprioceptive function, which differ in the required motor and memory capacity to perform the test, but importantly, also vary in the aspect of proprioception that they evaluate (Hillier et al., 2015). One aspect of proprioceptive function involves the perception of motion (i.e., kinesthesia), which is typically evaluated using a task in which the joint of interest is passively moved until the subject indicates they sense the movement and/or its direction (Juul-Kristensen et al., 2008b). Alternatively, to assess perception of spatial location or position (i.e., position sense), limb position reproduction tasks, such as the joint repositioning (JR) task, are commonly used (Han et al., 2016). In the active variant, participants have their vision occluded and reproduce target *positions* using the body part of interest; for example, various target positions of the forearm are reproduced to assess position sense at the elbow joint. The average difference between target and reproduced position then serves as a measure of accuracy.

A limitation of these proprioceptive tasks is that they generally do not allow for evaluation of more complex processes that are essential for accurate and controlled movement (i.e., kinesthesia during functional movement), such as integration of sensory and motor information. This is an important limitation because goal-directed movement requires dynamic updating of motor output based on proprioceptively encoded (and changing) body position (i.e., sensorimotor integration; Proske & Gandevia, 2012). Evaluation of such processes underlying kinesthesia during active movement may provide unique and important information, given that there are known dynamic

modulations that occur during movement (e.g., sensory gating; Saradjian, 2015). Capturing processes of dynamic modulation may also be important because proprioceptive tasks evaluating position sense or passively evaluating kinesthesia provide little insight into dynamic movement; that is, they are not always associated with actual motor performance (Davies et al., 2006; Dukelow et al., 2012; Helsen et al., 2016; Kitchen & Miall, 2019). Here we introduce a novel task in which movement *patterns* are reproduced to dynamically assess kinesthetic proprioceptive function: the dynamic movement reproduction (DMR) task. This task uses a 3 degrees-of-freedom, force-controlled robotic device, and involves continuous (i.e., online) assessment of an actively reproduced arm movement, thus including aspects of both limb position sense and sensorimotor integration to support kinesthetic function. The ability to accurately assess kinesthetic proprioceptive function during complex movement processes is clinically relevant given that a wide range of clinical conditions are characterized by impaired proprioception (Goble, 2010; Proske & Gandevia, 2012; Röijezon et al., 2015) and that the type of proprioceptive deficit can vary (Kenzie et al., 2017), meaning that it may be integration processes (versus position sense) that are of crucial importance in certain clinical conditions.

A key feature for both research and clinical relevance of a proprioceptive function task is adequate test-retest reliability. Past work shows that the reliability of traditional, active JR tests ranges widely depending on the device used and the extremity joint measured (Clark et al., 2015; Elangovan et al., 2014). Equipment measurement error likely influences these reliability findings. Use of more sophisticated equipment during testing, such as robotic devices (which are becoming increasingly prevalent in research and clinical practice), may have higher sensitivity and precision (Maggioni et al., 2016). Such properties also affect the ability to detect proprioceptive impairment. This is essential given that even slight impairments might be of clinical relevance, particularly for complex sensorimotor integration processes. Therefore, the primary aims of the current study were to evaluate (1) test-retest reliability of the DMR task and (2) a JR test of the elbow, and (3) the association between performance on both tasks. Understanding the association between the tasks is important; if highly associated, then a complex task (such as the DMR task) might not be needed; if only weakly associated, then it would provide evidence that these tasks capture different aspects of proprioceptive function. Thus to evaluate these aims, in Study 1, healthy participants performed the DMR and JR tasks at two different test sessions, 24-hours apart. Since the use of a robotic device allows for a highly standardized protocol and precise measurement, i.e., features shown to increase test-retest reliability (Maggioni et al., 2016), we hypothesised that (1) the DMR task would be highly reliable (good-to-excellent range). Furthermore, consistent with findings from Juul-Kristensen et al. (2008b), we hypothesised that (2) JR accuracy at the elbow would have fair-to-good reliability. Finally, we predicted (3) a weak association between DMR and JR accuracy. Both tasks involve active elbow

movements and involve aspects of joint position sense; however, the continuous measurement of error during the DMR task likely also captures complex sensorimotor integration processes, thus only a weak association was anticipated.

In addition, to better understand the various sensory contributions to task performance, our secondary aim was to evaluate the influence of visual information on both proprioceptive measures. Movements typically involve integration of visual and proprioceptive information, which may be combined in differing ways based on the nature of movement (e.g., differing between trajectory control and final position regulation; Scheidt et al., 2005). Testing both tasks with and without visual information of limb movement allows us to determine the relative visual versus proprioceptive weighting in task performance. We hypothesised that there would be increased accuracy with visual information for both tasks, given that vision provides an extra source of sensory information that may assist in movement and joint position accuracy. Given that recent calls to improve research rigor recommend undertaking validation of study findings in an independent sample (Laraway et al., 2019), we also evaluated the two proprioceptive tasks (with and without visual information available) in a second independent sample (Study 2) to ensure reproducibility of our findings.

Study 1: Materials and methods

Participants

Twenty-nine pain-free volunteers [sample size based on Juul-Kristensen et al. (2008b)] were recruited through word-of-mouth and the participant recruitment system of Maastricht University (Sona Systems Ltd., Tallinn, Estonia). Six participants were excluded: four due to equipment failure and two because they confused movement directions (e.g., performing clockwise movements, when counterclockwise movements were requested). Statistical analyses were run on the final sample of *N* = 23 [mean (*SD)* age = 24.39 (3.12) years, ranging from 18-32, 11 women]. Exclusion criteria were: chronic pain; left-handedness; uncorrected problems with hearing or vision; current pain at the dominant hand, wrist, elbow, or shoulder that may hinder task performance. Participants received 7.50 EUR in gift vouchers as compensation for their time and effort.

Pre-registration of the protocol and ethical approval

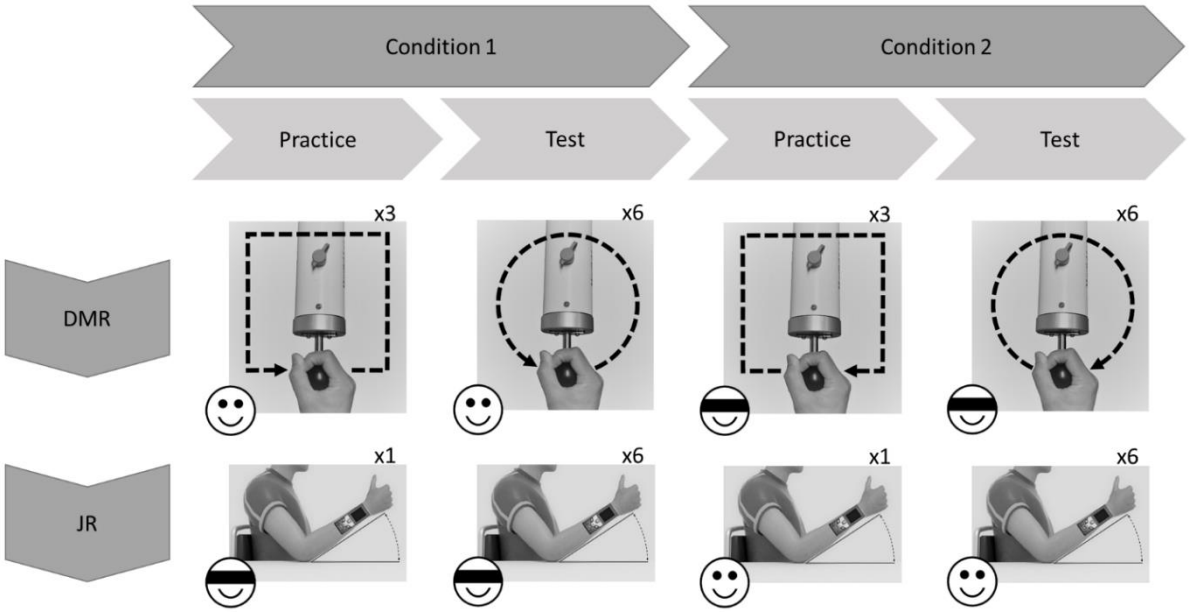
The experimental protocol was approved by the Ethics Review Committee Psychology and Neuroscience of Maastricht University (185 09 11 2017 S5) and pre-registered on AsPredicted (https://aspredicted.org/blind.php?x=c7g8bp). Prior to the start of the experiment, all participants read an information sheet, completed an exclusion criteria checklist, and provided written informed consent.

Study design

All participants performed both the JR and the DMR tasks using the dominant (right) arm. Each task comprised two conditions: Visual Information (i.e., without blindfold) and No Visual Information (i.e., with blindfold). In the Visual Information condition, participants directly watched the movement of their own limb. The order of the tasks and conditions was randomized across participants (using random.org). The same tasks were performed 24 hours later, in the same order as during the first test session (Figure 3.1).

Figure 3.1

Exemplary flowchart of a single test session



Note. The order of tasks and conditions (i.e., with or without visual information; indicated by emoji) was randomized across participants. In this example, the dynamic movement reproduction (DMR) task is first, and the joint reposition (JR) task is second. For the DMR task, movement direction (i.e., clockwise or counterclockwise; indicated by arrows) was counterbalanced across conditions, and practice movements were squares, while test movements were circles (to minimize training effects).

Apparatus

Angle measurement tool (JR task)

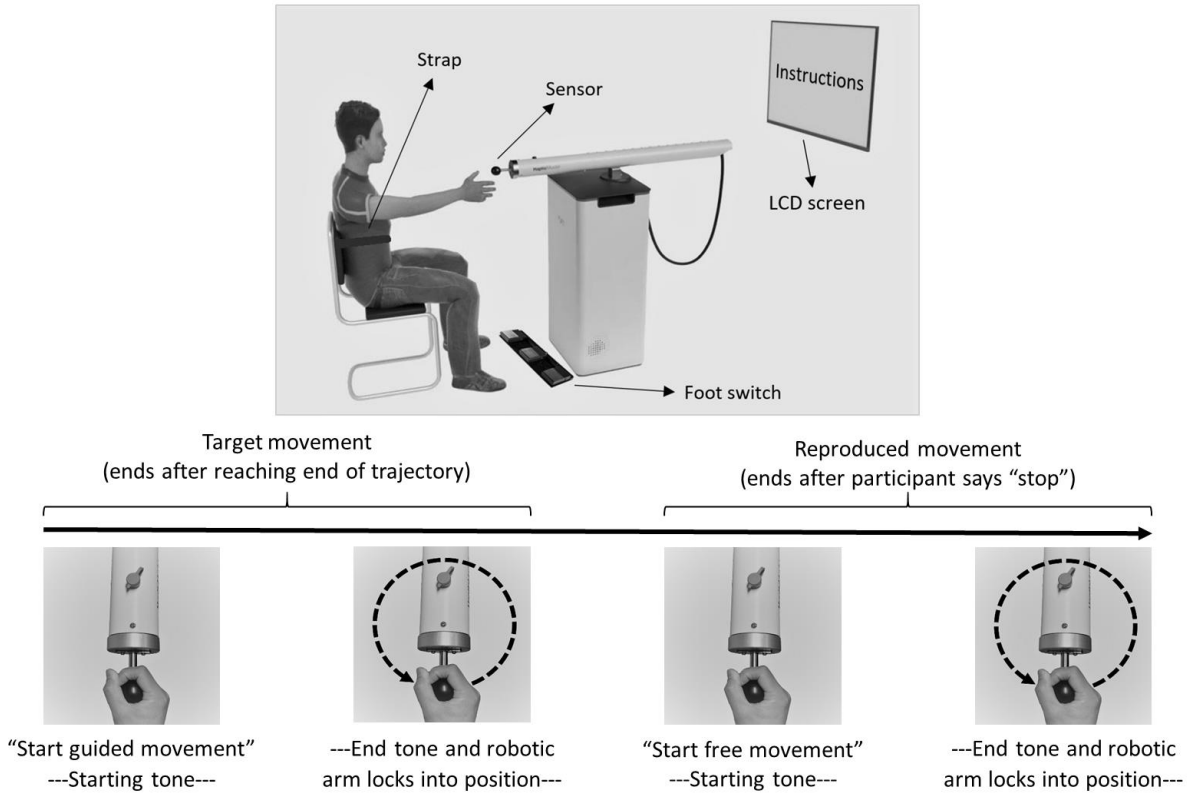
The Bosch GLM 80 Professional measuring tool (Robert Bosch GmbH, Gerlingen-Schillerhoehe, Germany) was used to measure arm positions (in degrees; precision = 0.1°; accuracy = ±0.2°). The device was attached to participants' wrist using a Velcro strap and measured the angle of the forearm relative to the horizontal surface.

HapticMaster (DMR task)

The HapticMaster (Motekforce Link, Amsterdam, the Netherlands; Figure 3.2) is a 3 degrees-of-freedom, force-controlled robotic device. Participants hold the handle of the device and can move it in all directions within a specific volume of space. The HapticMaster allows forward/backward movement with a depth of 40 cm, upward/downward movement with a height of 40 cm, and 60 degrees of rotation around its vertical axis (with smallest radius 46 cm). In the current task, movements were confined to a 2-dimensional horizontal movement plane (i.e., height remained constant). The HapticMaster automatically logs position along all three dimensions every 2 ms, with a resolution of 10^-6 m.

Figure 3.2

Experimental setup and trial flow of dynamic movement reproduction task



Note. During target movements, the robotic device haptically delineated the trajectory, while during movement reproduction there was no guidance. On the right side of the participant, a partition (not displayed here) separated the experimenter and participant to prevent potential distractions during performance of the task.

Computer software and hardware (DMR task)

The DMR task was programmed in C# using Unity 2017 (Unity Technologies, San Francisco, CA, USA). The experimental task was run on a Windows 10 Enterprise (Microsoft Corporation, Redmond, WA, USA) 64-bit Intel Core desktop computer (Intel Corporation, Santa Clara, CA, USA) and instructions were presented on a 40-inch LCD screen (Samsung UE40ES5500; Samsung Group, Seoul, South Korea). A Windows 10 compatible foot switch (USB Triple Foot Switch II; Scythe Co., Ltd., Tokyo, Japan) was used to navigate through instructions.

Experimental setting

In both tasks, participants sat with their back against the chair and a strap encircling their torso to ensure their position remained fixed. For the DMR task, participants sat in front of the HapticMaster within reaching distance of the handle (Figure 3.2). The LCD screen was mounted on the wall in front of them; the foot switch was placed on the floor at their feet. The experimenter sat on the opposite side of a partition and observed participants via a webcam. For the JR task, participants sat with their right elbow resting on a marked position on a desk. During this task, the experimenter sat next to them to read the angles of the forearm positions.

Procedure

Dynamic movement reproduction task

During the DMR task, participants replicated square (practice) and circular movement patterns while holding the handle of the robotic device. Movement direction was counterbalanced: some participants moved in clockwise direction during the entire Visual Information condition and counterclockwise during the entire No Visual Information condition (Figure 3.1), other participants received the reversed combinations. Therefore, none of the findings can be attributed to specific combinations of stimuli. Each condition started with three practice trials to familiarize participants with the procedure, followed by six test trials.

Practice phase. Instructions on how to operate the robotic device and the procedure of the task were presented on-screen, including movement direction (and pattern shape; Figure 3.1), and whether or not a blindfold would be worn. Additionally, participants were informed that all movements would occur in the horizontal plane. On each trial, the robotic device first restricted movement to a single trajectory to show participants what movement was to be reproduced (i.e., *target movement*). The participants actively explored the trajectory; the robotic device was programmed to haptically block certain areas of its workspace, thus restricting the movement to specific patterns. During practice, this pattern was a square with a side length of 16 cm. Note that on

all practice trials the shape of this pattern was the same and starting positions were always in the middle of the side closest to the participant. Participants began movement when they heard a starting tone after the automated audio message "*start guided movement"* (Figure 3.2). If participants moved in the wrong direction, an error message was played and the trial restarted. After being guided through the target movement once, participants were asked to reproduce this movement as accurately as possible, while having the entire range of the robotic device – within the horizontal plane – available. Participants began moving when they heard a starting tone after the automated audio message "*start free movement"*, and they verbally said "*stop"* when they finished reproducing the movement, at which time the experimenter manually ended the trial. The robotic device then moved to a new starting position for the next trial. Six different starting positions within the same horizontal plane were used to limit potential spatial learning effects (random order; shoulder angles along the frontal plane approximately between 0 and 90 degrees; shoulder angles along the longitudinal plane approximately between 0 and 45 degrees; elbow angle approximately between 30 and 160 degrees). No feedback regarding participants' performance was given.

Test phase. Identical procedures to the practice phase were used during the test phase. However, the shape of the target movements was changed to a circle with a radius of 8 cm – to limit potential training effects. The shape of this pattern was the same on all test trials. The starting position was always on the point of the circular pattern closest to the participant.

Joint reposition task

Each condition started with one practice trial to familiarize participants with the procedure, followed by six test trials. During the task, participants' elbow rested on a marked spot on a horizontal surface (shoulder angle along the frontal plane at approximately 0 degrees; elbow angle at approximately 135 degrees; wrist in neutral position, with thumb pointing upwards; Figure 3.1). Prompted verbally by the experimenter, participants actively moved their forearm to a target position, moved back to the resting position on the horizontal surface, and then actively reproduced the target position (Figure 3.3). Participants were allowed to adjust the position of the forearm until they felt it reached the correct position and verbally indicated when this was the case. Both the target and reproduced angle were recorded by the experimenter. Three different target angles were presented in random order and were assessed twice (30°, 45° and 60°; between forearm and horizontal surface). No feedback regarding participants' performance was given.

Figure 3.3

Trial flowchart with experimenter's verbal instructions during joint reposition task

"*Slowly, flex your arm, until I say 'stop'.*"

"*Stop; hold and remember this position.*"
--Experimenter registers angle--
"*Return your arm to the table and keep it there.*"

"*Slowly flex your arm again to the same position as before and say 'stop' when you think you reached it.*"

--Experimenter registers angle after participant says "*stop*"--

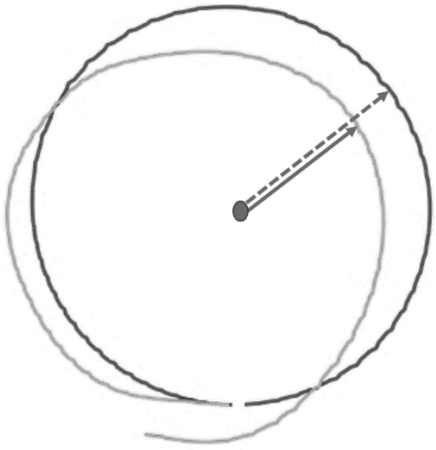
Main outcome variables

Dynamic movement reproduction error

DMR error was operationalized as the mean absolute difference (in cm) between the reproduced and the target circular movement pattern (i.e., radius) on each trial (see Appendix B for an alternative measure considering direction of errors). Larger errors reflect poorer accuracy. The reproduced radius was calculated using the coordinates of each performed movement, as logged by the robotic device (Figure 3.4).

Figure 3.4

Visualization of raw data from a single test trial of the dynamic movement reproduction task



Note. Both the target (black line) and reproduced (gray line) movement pattern are visualized. Note that the dashed arrow represents the target radius, while the solid arrow represents the reproduced radius, which is calculated for each coordinate logged by the robotic device.

Joint reposition error

JR error is operationalized as the absolute difference between the target angle and the reproduced angle on each trial. Again, larger errors reflect poorer accuracy. The recorded target angles were approximately 30, 45 or 60 degrees (in most participants the recorded target angles were not exactly these values due to delay in stopping movement).

Data preparation and statistical analysis overview

First, data were checked to determine if participants moved in the correct direction during the DMR task. This was assessed using the number of mistakes during guided movements, which was automatically logged by the experimental task. Next, data were visually inspected for other artifacts such as participants reaching the end of the movement plane of the robotic device.

The mean of each outcome variable was calculated per condition (over six trials) and is referred to as *accuracy*. The standard deviation of the measurements per condition is referred to as *consistency*, as it indicates whether subjects are consistent in their size/range of error (Juul-Kristensen et al., 2008b). Bland Altmann plots were used to visually inspect test-retest data of both tasks. Paired *t*-tests and repeated measures (RM) analyses of variance (ANOVAs) were calculated to check for systematic differences between sessions and trials. Intraclass correlation coefficients (ICCs; two-way mixed; McGraw & Wong, 1996; Shrout & Fleiss, 1979) were used to test the absolute agreement between the test and retest sessions for accuracy and consistency (average measures). The categories

of reliability used for reference were .00 – .40 (poor), .40 – .75 (fair-to-good), and .75 – 1.00 (good-to-excellent; Fleiss, 1986). We quantified measurement error of the DMR accuracy measure with the smallest real difference (SRD; Beckerman et al., 2001). The *SRD* of a test is useful for both researchers and clinicians to determine whether a change in accuracy on the individual level is of significance at the 95% confidence level. First, the standard error of measurement (*SEM*) was calculated using the standard deviation (*SD*) of all test-retest scores and the ICCs: $SEM = SD \times \sqrt{1 - ICC}$ (Chen et al., 2009). Next, the *SEM* was used to calculate the *SRD*: $SRD = 1.96 \times SEM \times \sqrt{2}$. To evaluate if associations existed between task performance on both tasks, Spearman rank-order correlations (ρ) were calculated between DMR and JR accuracy and consistency (DMR accuracy in Session 2, and JR accuracy and consistency in Session 1 were not normally distributed; Shapiro Wilk test $p < .05$). All correlations were calculated with and without outliers (> +3*SD* or < -3*SD*). All analyses were performed on data from the No Visual Information condition, as this is the preferred way to test proprioceptive function. To test the influence of visual information on task performance, RM ANOVAs were conducted on DMR and JR accuracy. The family-wise α was kept at .05. Bonferroni corrections were used to account for multiple testing. All statistical analyses were performed using SPSS 25 (IBM, Armonk, NY, USA). HapticMaster data was pre-processed using a custom-made MATLAB script (The MathWorks Inc., Natick, MA, USA).

Study 1: Results

Test-retest reliability

Dynamic movement reproduction accuracy (no visual information)

Bland Altmann plots suggest that there is sufficient test-retest reliability for DMR accuracy and consistency (Figure 3.5). There was no statistically significant difference between sessions for accuracy, $t(22) = 1.54$, $p = .138$, nor consistency, $t(22) = -0.12$, $p = .904$. Adding trial as a factor in a RM ANOVA on DMR accuracy indicated no systematic differences on this level, $F(3.11, 62.12) = .62$, $p = .611$. DMR accuracy had good-to-excellent reliability, *ICC* = .80, $F(22, 22) = 5.35$, $p < .001$, *95% CI* = [.55-.92]. The *SRD* value for DMR accuracy is 0.76 cm. In other words, a change between two measurements of the same subject exceeding 0.76 cm can be interpreted as a true change at the 95% confidence level. Consistency showed fair-to-good reliability, *ICC* = .63, $F(22, 22) = 2.64$, $p = .014$, *95% CI* = [.11-.85]. Sensitivity analyses without outliers yielded similar results.

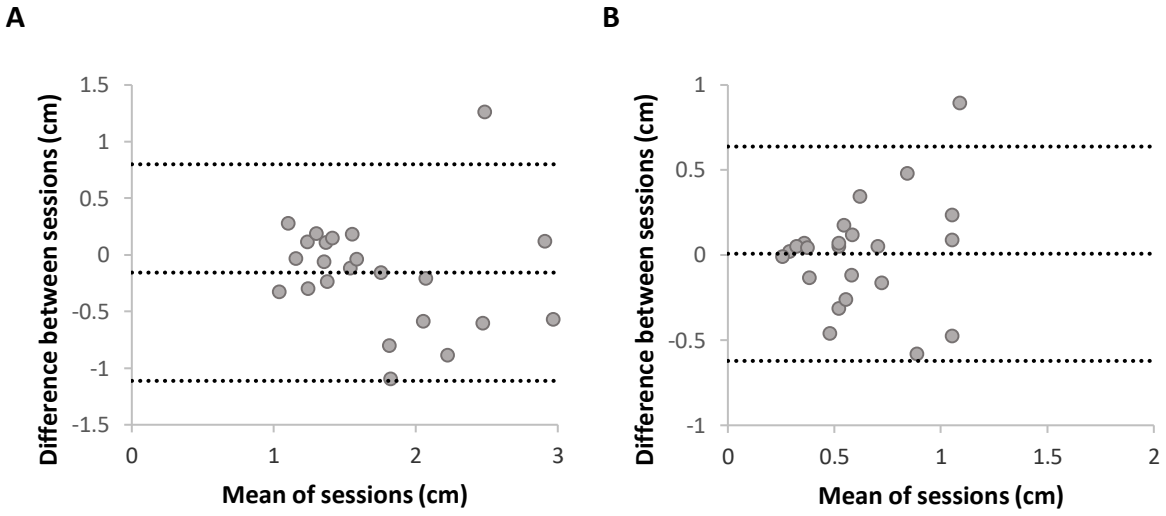
Joint reposition accuracy (no visual information)

Bland Altmann plots (Figure 3.6) suggest poor test-retest reliability for JR accuracy and consistency, as variation in means of sessions (i.e., between-subjects) seems lower than variation in differences between sessions (i.e., within-subjects). No systematic differences between sessions were present; Accuracy: $t(22) = -0.61$, $p = .548$; Consistency: $t(22) = -0.01$, $p = .993$. Adding trial as a factor

in a RM ANOVA on JR accuracy indicated no systematic differences on this level, $F(5,110) = 1.06$, $p = .389$. JR accuracy had fair-to-good reliability, *ICC* = .46, $F(22, 22) = 1.83$, $p = .081$, *95% CI* = [-.29-.77], but this was not statistically significant (i.e., *ICC* did not significantly differ from zero). Analysis without outliers confirmed the poor reliability: the *ICC* dropped to -.76 ($F < 1$). JR consistency had poor reliability, *ICC* = .33, $F(22, 22) = 1.46$, $p = .190$, *95% CI* = [-.66-.72] and was not statistically significant. Analysis without outliers confirmed the poor reliability for consistency, *ICC* = -.26, $F < 1$.

Figure 3.5

Plots of test-retest data of dynamic movement reproduction accuracy (panel A) and consistency (panel B) with no visual information



Note. The difference between Sessions 1 and 2 is plotted against the mean of both sessions. The mean difference between sessions is presented as a horizontal line (middle line), and the upper and lower lines represent the 95% upper and lower limits of these differences. Note that sufficient test-retest reliability corresponds with differences between sessions (y-axis) being closer to zero (i.e., roughly the same accuracy and consistency in both sessions), and variation in means between sessions (x-direction) being larger than variation in differences between sessions (y-direction; i.e., larger between-subjects variation than within-subjects variation).

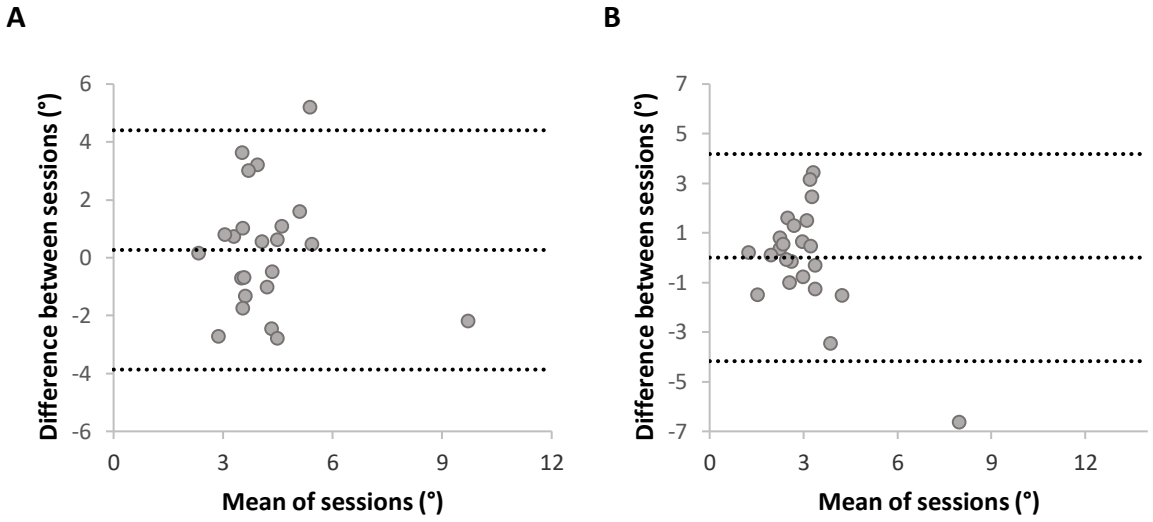
Association between performance accuracy on the dynamic movement reproduction and the joint reposition tasks (no visual information)

The Spearman correlations showed no relationship between DMR and JR accuracy during initial test sessions (Table 3.1). The retest sessions did show a significant positive correlation of moderate strength. This correlation remained significant when correcting for multiple testing, though

no longer when conducting the analyses without outliers, ρ = .32, p = .18. Analyses of consistency yielded similar results.

Figure 3.6

Plots of test-retest data of joint reposition accuracy (panel A) and consistency (panel B) with no visual information



Note. The difference between Sessions 1 and 2 is plotted against the mean of sessions. The mean difference between sessions is presented as a horizontal line (middle line), and the upper and lower lines represent the 95% upper and lower limits of these differences. Note that sufficient test-retest reliability corresponds with differences between sessions (y-axis) being closer to zero (i.e., roughly the same accuracy and consistency in both sessions), and variation in means between sessions (x-direction) being larger than variation in differences between sessions (y-direction; i.e., larger between-subjects variation than within-subjects variation).

The effect of visual information

Dynamic movement reproduction accuracy

The 2 (Session: 1-2) x 2 (Visual Information: No visual information vs. Visual information) RM ANOVA analysis showed a significant effect of Session, $F(1, 22) = 4.57$, $p = .044$, $\eta_p^2 = 0.17$, but no effect of Visual Information, $F(1, 22) = 0.21$, $p = .649$, and no interaction, $F(1, 22) = 0.82$, $p = .375$. Thus, visual information did not significantly influence DMR accuracy (Figure 3.7). The significant effect of Session suggests a potential learning effect (i.e., increased accuracy over sessions), as mean errors were significantly higher for Session 1 (M = 1.86; SE = 0.14) than Session 2 (M = 1.64; SE = 0.11).

Table 3.1

Correlations between dynamic movement reproduction and joint reposition accuracies, and consistencies

ρ (p-value)		JR accuracy		JR consistency	
		Test	Retest	Test	Retest
Study 1					
DMR accuracy	Test	.08 (.723)	.39 (.068)		
	Retest	.05 (.809)	**.52* (.011)**		
DMR consistency	Test			.06 (.774)	**.54* (.008)**
	Retest			.02 (.929)	.27 (.220)
Study 2					
DMR accuracy	Test	**.25* (.047)**			
DMR consistency	Test			.22 (.078)	

Note. DMR = dynamic movement reproduction; JR = joint reposition. *Spearman rank correlation (*ρ*) is significant at the .05 level (2-tailed). No corrections for multiple testing. These correlations are calculated using only data from the condition without visual information (i.e., while participants wore a blindfold).

Joint reposition accuracy

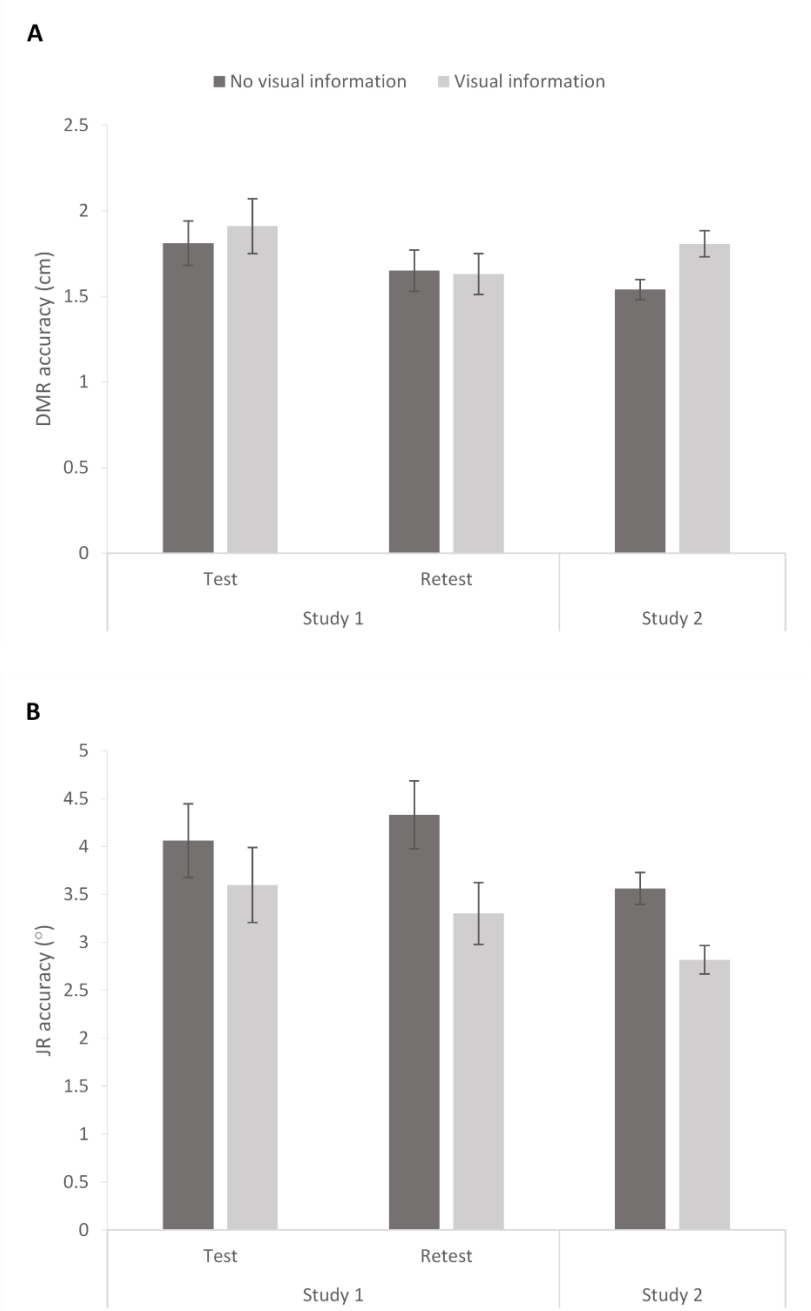
The 2 (Session: 1-2) x 2 (Visual Information: No visual information vs. Visual information) RM ANOVA analysis showed an effect of Visual Information, $F(1, 22) = 7.42$, $p = .012$, $\eta_p^2 = .25$, and no effect of Session, $F(1, 22) < 0.01$, $p = .964$, or interaction, $F(1, 22) = 1.12$, $p = .302$. Including visual information increased accuracy (i.e., smaller mean errors; No visual information: $M = 4.20$, $SE = 0.30$; Visual information: $M = 3.45$, $SE = 0.30$; Figure 3.7).

Study 2: Materials and methods

The aim of the second study was to evaluate the reproducibility of findings regarding the association between both tasks and the influence of visual information using a larger, independent sample. Additionally, given the large sample, we considered the effect that visual condition order might have on performance (i.e., first performing proprioceptive task with vision vs. first performing the task without vision). The apparatus**,** setting, procedure, and main outcome variables were identical to the first study, with the exception that this study was comprised of only one test session. In other words, participants performed both tasks only once, with the order of the tasks and conditions again randomized across participants.

Figure 3.7

Dynamic movement reproduction and joint reposition accuracy with and without visual information



Note. Dynamic movement reproduction (DMR; panel A) and joint reposition (JR; panel B) accuracy with and without visual information are displayed separately for studies 1 (test and retest) and 2. Higher values correspond with poorer accuracy. Error bars represent standard errors.

Participants

A convenience sample of sixty-four healthy volunteers was recruited (recruitment sources and eligibility criteria identical to Study 1; sample size based on power calculations for another – separately

preregistered – research question). Statistical analyses were run on the complete sample of *N* = 64 [mean (*SD)* age = 22.33 (3.90) years, ranging from 18-37, 52 women]. Participants received 12.50 EUR in gift vouchers as compensation (part of a longer testing session).

Data preparation and statistical analysis overview

Data were checked and prepared as described above. Note that DMR consistency, and JR accuracy and consistency data were not normally distributed. Analyses and inference criteria were also identical, with the exception that paired *t*-tests were used to test for the effect of visual information. Additional RM ANOVAs were used to explore order effects (Visual information versus No visual information performed first).

Study 2: Results

Association between performance accuracy on the dynamic movement reproduction and joint reposition tasks (no visual information)

Spearman correlations suggest a weak positive relationship between DMR and JR accuracy (Table 3.1). Excluding outliers reduced the correlation further rendering it non-significant, ρ = .22, p = .09. Analyses of consistency yielded comparable results (excluding outliers: ρ = .17, p= .19).

The effect of visual information

Dynamic movement reproduction accuracy

DMR accuracy differed significantly between conditions, $t(63) = -3.33$, $p = .001$, $d = 0.49$, showing higher errors when visual information was present ($M = 1.81$, $SE = 0.08$) than when no visual information was present ($M = 1.54$, $SE = 0.06$). These findings suggest poorer accuracy when vision was available. However, further exploratory analysis showed that condition order moderated the effect (Visual Information x Order: $F(1, 62) = 7.16$, $p = .010$, $\eta_p^2 = 0.10$). Specifically, there was no significant difference between conditions when performing the task *without* visual information first ($p = .520$), but there was a difference between conditions when performing the task *with* visual information first ($p < .001$). In sum, visual information decreased accuracy, but only when the task started with visual information available.

Joint reposition accuracy

JR accuracy differed significantly between conditions, $t(63) = 3.49$, $p < .001$, $d = .59$, with lower errors when visual information was present ($M = 2.82$, $SE = 0.15$) than when no visual information was present ($M = 3.56$, $SE = 0.17$). Thus, participants showed poorer accuracy without visual information

available. Adding the order of conditions as a factor in a RM ANOVA did not change the results (Visual Information x Order: $F(1, 62) = 0.51$, $p = .478$).

Discussion

We developed a new task to dynamically assess sensorimotor integration underlying kinesthetic proprioceptive function during upper limb movement, and evaluated test-retest reliability, associations with a JR task, and the influence of visual input on task performance. Our first hypothesis, that the DMR task test-retest reliability would be good to excellent, was supported. However, our second hypothesis was not, as the JR task showed poor reliability. Our third hypothesis was confirmed: there were weak associations between the DMR task and the JR task. Interestingly, allowing the use of vision during the DMR task was different than we hypothesized: vision only improved task performance for the JR task, not the DMR task. Importantly, our findings on associations between tasks and the influence of vision on task performance were largely reproducible in a larger independent sample, although the effect of vision on DMR task performance was not.

An important implication of the present study is that our new DMR task evaluating kinesthetic proprioceptive function exhibits sufficient test-retest reliability to support its use in research and clinical settings. That is, DMR accuracy showed good-to-excellent reliability, and fair-to-good test-retest reliability was found for consistency (i.e., variation in error throughout the task). These results are comparable to other studies evaluating test-retest reliability of tasks assessing proprioceptive function using robotic devices (e.g., Cappello et al., 2015; Rinderknecht et al., 2018; Rinderknecht et al., 2016). Furthermore, this reliability was notably higher than that of the traditional JR task tested here. However, it is of interest that our findings of poor test-retest reliability for JR accuracy differed from that of Juul-Kristensen et al. (2008b), who found fair-to-good reliability. There could be numerous reasons underlying these differences between our studies. While device precision appears comparable, it is possible that use of differing forearm repositioning angles (smaller angles in our task which may increase task ease, reducing between-subjects variability and thus reliability), differing duration between test sessions (1 hour *vs*. 24 hours in present study, enhancing memory of the task and increased reliability in former work), participants' age range (18-57 years *vs.* 18-32 years in present study, reducing between-subjects variability), and examiner experience (highly trained physiotherapists in past work, psychology student here) all contributed to differing findings. Together, our differing reliability findings for the JR task support past work showing that reliability varies widely (Clark et al., 2015; Elangovan et al., 2014). Regardless, it is important to highlight that potential memory and/or examiner effects did not influence the DMR measure to the same extent, thus

highlighting the benefit of using a highly standardized protocol and a device allowing for precise measurement such as the HapticMaster.

The second implication of this study is that the DMR task measure of proprioceptive accuracy captures a unique aspect of proprioceptive function; that is, distinct from the JR task. Indeed, the association between DMR and JR accuracy was weak. Importantly, we replicated this finding in our second study using a larger sample, collected to remove any concerns about low statistical power in Study 1. Note that both tasks involve active reproductions involving the elbow joint of the dominant (right) arm, which might suggest stronger association. However, measures of proprioceptive function correlate weakly in general as they assess different aspects of proprioception (De Jong et al., 2005; Elangovan et al., 2014). In the DMR task, participants perform a specific movement *pattern* (i.e., a circle) and then reproduce this pattern. This is similar to the JR task where participants move their arm to a certain *position* and then reproduce it. That is, the DMR task involves remembering the position and size of the circle and using (combined) limb position sense to replicate that circular movement, as well as sensorimotor integration to ensure accurate performance of the intended action. The latter integration is likely underpinned via generation of a motor efferent copy, which is then compared to sensory input that has resulted as a consequence of the movement (Wolpert & Ghahramani, 2000; Wolpert et al., 1995). However, the purposeful complex movements during the DMR task require higher levels of sensorimotor integration compared to the JR task. Furthermore, the error measure in the DMR task is not only looking at an 'end position' but the accuracy of the entire movement (i.e., dynamic assessment). Our findings suggest then that the DMR task mainly captures sensorimotor integration processes underlying kinesthetic proprioceptive function, rather than joint position sense. Furthermore, it is relevant to note that the DMR task involves the entire upper limb kinetic chain (shoulder, elbow and wrist joints) while the JR task only involves elbow movement, which may also contribute to poor associations. Together, these results support our hypothesis that the DMR task indeed captures a unique aspect of proprioceptive function compared to JR tasks, and emphasize the importance of considering and appropriately assessing the proprioceptive feature of interest as well as the relevant joints for that condition.

Finally, our results suggest that the contribution of visual information to proprioceptive accuracy is complex. It appears dependent on the proprioceptive task, and for the DMR task, was opposite of what we expected. That is, while our first study found no difference between visual conditions when performing the DMR task, exploration of this in a larger sample showed lower accuracy when performing the task with visual information. Additionally, the condition order moderated this effect, as it was only present when participants started the task with visual information present. In contrast, JR results were consistent with expectations, indicating that visual information

increased accuracy (Scheidt et al., 2005). These contradicting results of vision for the JR versus DMR task may be explained by task differences. For example, in the JR task, simple forearm positions are reproduced (i.e., allowing the use of visual reference points), while in the DMR task more complex movements (including movement of a robotic device) using multiple joints are performed, potentially making reliance upon visual information a disadvantage. Further, order effects for the DMR task may be explained by the influence of visual information while learning a task. For example, if visual information is absent while learning a complex task, it is learned proprioceptively; the visual information that is available afterwards is then an adjunct to the proprioceptively learned task. The same may not occur if visual information is present while learning a complex task, as it may provide less reliable information for a complex movement than the proprioceptive input. This emphasizes that the integration of visual and proprioceptive information is not straightforward (Sarlegna & Sainburg, 2009; Scheidt et al., 2005), and supports that proprioceptive and visual information are weighted based on their reliability (van Beers et al., 1999).

Some limitations of the current study should be outlined as well. First, analysis of the effect of visual information on the DMR task revealed the presence of a potential learning effect between sessions (i.e., higher accuracy in the second session), even though our initial analysis did not show this effect and test-retest reliability was in the good-to-excellent range. However, this may have led to an underestimation of test-retest reliability. Increasing practice or familiarization when using tasks that are more complex may be advisable. Second, we did not fully standardize movement kinematics of the upper limb during the DMR task, allowing some variation in use of different joints during movements (i.e., only movement of the handle of the robotic device was recorded). When comparing accuracy within or between participants, this should be standardized to prevent compensation for joint-specific deficits. Third, the sample size of our first study may not have provided sufficient statistical power for the JR test-retest analysis, although it was sufficient for the DMR measures. Fourth, since the average age of our sample is relatively low, the present findings are limited in generalizability toward older adults. Finally, as with all assessments of active proprioceptive function, factors other than proprioception can influence the outcomes. For example, both the DMR and the JR methods are less suitable for people with severe cognitive impairments since the tasks depend on working memory (Han et al., 2016). Another factor is motor control: the precision of movement limits the precision of the measured proprioceptive accuracy (Elangovan et al., 2014). However, motor control and proprioception are closely related as both are integrated to perform movements (Proske & Gandevia, 2012).

The DMR task's highly automated (i.e., requiring limited operator input) and brief (around 15 min) protocol makes it straightforward to use in a clinical setting. Our results indicate that a change

of 0.76 cm or more in DMR accuracy (i.e., the difference between two measurements) is meaningful, and not merely due to measurement error (Beckerman et al., 2001), highlighting its precision. It should be noted that the task presented here is not necessarily limited to use of HapticMaster devices, as similar devices, commonly found in research and rehabilitation settings (e.g., motor cortex retraining in stroke patients; Timmermans et al., 2009), could be used. Further, our DMR task using a robotic device, while not the first, extends previous work in this area. For example, in contrast to our DMR task, past active robotic tasks have depended on visual guidance (Dukelow et al., 2012), or used mirror-matching (Kenzie et al., 2014). Additionally, Kitchen and Miall (2019) have used a robotic device in older adults to evaluate arm-reaching movements, though their task involves reaching a position along a straight line as quickly as possible, and thus does not require complex sensorimotor integration. Rather, the DMR is the first to use vision occluded complex movements, particularly emphasizing sensory guidance by using replication of a circular pattern and not emphasizing speed, making it more appropriate to assess kinesthetic proprioceptive function and the sensorimotor integration processes required for accurate arm movement pattern reproduction.

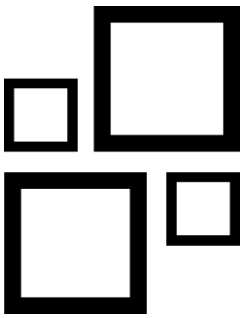
The innovative aspect of our DMR task is that it dynamically assesses sensorimotor integration processes of the entire upper limb kinetic chain, potentially allowing capture of more complex kinesthetic proprioceptive deficits. In addition to the device's precise measurement, this could help capture deficits in certain conditions that involve multi-joint impairment more accurately, which is of importance in both research and practice (Röijezon et al., 2015; Stasinopoulos, 2019). For example, lateral epicondylalgia, or 'tennis elbow' is characterized by symptoms of persistent pain and sensorimotor dysfunction, and people with lateral epicondylalgia present with impaired proprioceptive function at the elbow (Juul-Kristensen et al., 2008a). However, recent work has shown that sensorimotor dysfunction also occurs at the shoulder, the scapula, and the wrist (Alizadehkhaiyat et al., 2007; Day et al., 2015; Lucado et al., 2012), and that it may be the combination of impairment within this dynamic upper extremity kinetic chain that impedes treatment (Lucado et al., 2019). However, reliable, valid proprioceptive tests to evaluate the entirety of the upper limb kinetic chain are currently lacking, limiting detection of impairment and provision of appropriate treatment (Stasinopoulos, 2019). Future research is warranted to explore use of the DMR task in clinical populations such as lateral epicondylalgia, evaluating test-retest reliability as well as exploring the predictive validity of the DMR measure for clinical improvement via proprioceptive or movement retraining. Visual inspection of the reproduced (versus target) movement pattern data may also prove useful in clinical application, as it may allow identification of what aspect of proprioceptive function to target (see Appendix B for examples of relatively impaired position sense, but intact sensorimotor integration and vice versa). Further work exploring combination of the DMR task with movement

capture systems to explore differences in the way movement occurs during the task might provide interesting insights.

In conclusion, the DMR task seems a promising new tool for reliably testing kinesthetic proprioceptive function of the upper limb. It showed high test-retest reliability and appears to capture a unique aspect of proprioceptive function, as it dynamically evaluates sensorimotor integration processes of the entire upper limb. This may make the DMR task particularly relevant for certain clinical conditions with multiple-joint involvement. Additionally, this study shows that the integration of visual and proprioceptive information is not straightforward, with vision of arm movement beneficial during simple movements, but not when learning complex movements, and supports the idea that proprioceptive and visual information are weighted based on their task-specific reliability.

Chapter 4

The association between proprioceptive accuracy and pain-related avoidance



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Abstract

Pain-related avoidance of movements that are actually safe (i.e., overprotective behavior) plays a key role in chronic pain disability. Avoidance is reinforced through operant learning: after learning that a certain movement elicits pain, movements that prevent pain are more likely to be performed. Proprioceptive accuracy importantly contributes to motor learning and memory. Interestingly, reduced accuracy has been documented in various chronic pain conditions, prompting the question whether this relates to avoidance becoming excessive. Using robotic arm-reaching movements, we tested the hypothesis that poor proprioceptive accuracy is associated with excessive pain-related avoidance in pain-free participants. Participants first performed a task to assess proprioceptive accuracy, followed by an operant avoidance training during which a pain stimulus was presented when they performed one movement trajectory, but not when they performed another trajectory. During a test phase, movements were no longer restricted to two trajectories, but participants were instructed to avoid pain. Unbeknownst to the participants, the pain stimulus was never presented during this phase. Results supported our hypothesis. Furthermore, exploratory analyses indicated a reduction in proprioceptive accuracy after avoidance learning, which was associated with excessive avoidance and higher trait fear of pain.

Introduction

Avoidance of pain-associated movements is an adaptive response to acute pain as it may protect against (further) injury. For example, if a shooting pain is experienced while bending the back, not repeating this movement can prevent exacerbating an injury. However, when injury is not, or no longer, present, avoidance may prevent learning that these movements are actually safe. Moreover, avoidance can spread toward movements similar to a pain-associated one, regardless of whether these were experienced with pain (i.e., generalization; Glogan et al., 2021). This again is an adaptive mechanism that may become maladaptive when applied excessively to safe movements (i.e., overgeneralization). Such overprotective behavior may instigate a self-sustaining cycle of disengagement from harmless daily and valued activities (e.g., household chores, social activities), contributing to chronic pain disability (fear-avoidance models of pain; Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen et al., 2016).

Pain-related avoidance of movements can be acquired through operant learning (Meulders et al., 2016): avoidance behaviors are reinforced by the omission of pain (among other factors; Krypotos et al., 2015), making them more likely to occur in the future. Proprioceptive accuracy plays a key role in this, as accurate perception of motion and position of the body, and body segments, in space contributes to motor learning and memory (Proske & Gandevia, 2012). Interestingly, reduced proprioceptive accuracy has been observed in a range of chronic pain conditions (Juul-Kristensen et al., 2008a; Knoop et al., 2011; Stanton et al., 2016; Tong et al., 2017), suggesting this may play a role in avoidance becoming excessive, thus contributing to disability. Not being able to accurately perceive and encode technically safe movements may lead to these movements being avoided as well, leading to a reduced movement repertoire. Yet to date, research investigating the relationship between proprioception and avoidance is lacking.

Support for a potential link comes from conditioning studies in the field of anxiety disorders. These studies show that, after pairing a (visual) stimulus with an aversive outcome, the spreading of fear responses toward perceptually similar stimuli that were never paired with this outcome (i.e., fear generalization) is modulated by perceptual accuracy (Struyf et al., 2017; Zaman, Ceulemans, et al., 2019; Zaman, Struyf, et al., 2019). Specifically, fear generalization is negatively related to the degree to which one stimulus can be differentiated from another (Ghirlanda & Enquist, 2003; Moseley & Vlaeyen, 2015). Moreover, evidence suggests that aversive conditioning itself has the potential to decrease perceptual accuracy (Laufer et al., 2016; Shalev et al., 2018; Zaman et al., 2015). From a predictive processing perspective, this may be due to a “better safe than sorry” processing strategy. This perspective posits that the brain generates a model of internal and external environments by comparing sensory input to predicted input. It could be that reduced proprioceptive accuracy is a

result of increased weighting of the affective-motivational aspects of input at the expense of detailed sensory-discriminative input (Van den Bergh et al., 2021).

As avoidance is a key characteristic of fear (Krypotos et al., 2015), it can be expected that perceptual accuracy modulates avoidance as well. However, whether this is true, and whether proprioceptive accuracy specifically can play a modulating role, remains to be investigated. The current study tested the hypothesis that poor proprioceptive accuracy is associated with overprotective avoidance behavior, using the dynamic movement reproduction (DMR) task – a recently developed measure for proprioceptive accuracy (Vandael et al., 2021) – and an operant avoidance task consisting of robotic arm-reaching movements. During the avoidance training, one movement trajectory was paired with a pain stimulus, while another was not. During the avoidance test, movements were no longer limited to two trajectories, but participants were instructed to avoid the pain stimulus. We expected participants with poorer proprioceptive accuracy to show excessive avoidance in terms of increased deviation from the avoidance trajectory, away from the pain-associated trajectory.

Methods

Ethical approval and preregistration

The experimental protocol was approved by the Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration number: 185 09 11 2017 S9). Before starting the experiment, all participants read an information sheet, completed an exclusion criteria checklist, and provided written informed consent. Because this study was conducted during the COVID-19 pandemic, additional safety measures were used according to institutional guidelines (e.g., both experimenter and participant wore facemasks, the experimenter wore gloves while attaching electrodes). The experimental protocol and analysis plan were registered prior to data collection at Open Science Framework (https://osf.io/f38je).

Participants

A registered a priori power analysis using G*Power (Faul et al., 2007) for our main hypothesis (bivariate correlation) indicated a sample of 46 participants would allow .80 power to detect a medium correlation of .40, at .05 alpha error probability (two-tailed). We decided to test 48 participants to balance counterbalancing conditions. Participants were recruited using the research participation system of Maastricht University (Sona Systems Ltd., Tallinn, Estonia), advertisements distributed around the university campus, and through social media. Seven participants were excluded during data preparation, resulting in a final sample size of 41 participants [11 male, 30 female, $M \pm SD$ (range)

age = 24 ± 4 years (18-35)], allowing detection of a .42 correlation according to a sensitivity analysis with G*Power – using the same input as the a priori analysis. Participants received either 1 course credit or 7.50 EUR in gift vouchers as a compensation. Exclusion criteria were chronic pain; analphabetism or diagnosed dyslexia; pregnancy; left-handedness; current/history of cardiovascular disease; current/history of psychiatric disorder (e.g., clinical depression, panic/anxiety disorder); uncorrected problems with hearing or vision; having pain at the dominant hand, wrist, elbow or shoulder that may hinder performing the reaching task; presence of implanted electronic medical devices (e.g., cardiac pacemaker); and presence of any other severe medical conditions.

Apparatus and software

Movements were performed using the HapticMaster (Motekforce Link, Amsterdam, the Netherlands; Figure 4.1), a 3 degrees-of-freedom, force-controlled robotic device that can be moved in all directions within a specific volume of space by exerting force on its handle, which is a sensor attached at the end of the arm. It allows horizontal movement with a depth of 40 cm, vertical movement with a height of 40 cm, and 60 degrees of rotation around its vertical axis with minimum radius 46 cm. Position is automatically logged along all three dimensions every 2 ms, with a resolution of 10^-4 cm. In the current task, height remained constant: movements were confined to a 2-dimensional horizontal plane. The experimental task was programmed in C#, using cross-platform game engine Unity 2017 (Unity Technologies, San Francisco, CA, USA), and 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. A direct application programming interface (API) connection was used for communication between the computer and HapticMaster. The experimental task was presented on a 40-inch LCD screen (Samsung UE40ES5500; Samsung Group, Seoul, South Korea). Participants used a foot switch (USB Triple Foot Switch II; Scythe Co., Ltd., Tokyo, Japan) to navigate through instructions and answer questions.

A 2 ms square-wave electrical stimulus was used as pain stimulus, which was delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, UK) through two reusable stainless steel disk electrodes (8mm diameter with 30mm spacing; Digitimer, Welwyn Garden City, UK) filled with K-Y gel (Reckitt Benckiser, Slough, UK). The electrodes were placed on the triceps tendon of the right arm. The physical intensity of the stimulus was individually calibrated to be significantly painful and demanding some effort to tolerate.

Figure 4.1

Experimental setup

Note. Reproduced with permission from Glogan, Gatzounis, Vandael, et al. (2020).

Procedure

We employed a repeated measures design in which all participants performed the DMR task followed by the operant avoidance task. In both tasks, all movements were carried out in the same horizontal plane and were performed actively by participants, meaning that participants exerted force to move the robotic device. The experimental session took approximately 1 hour. After the experiment, participants completed a number of questionnaires.

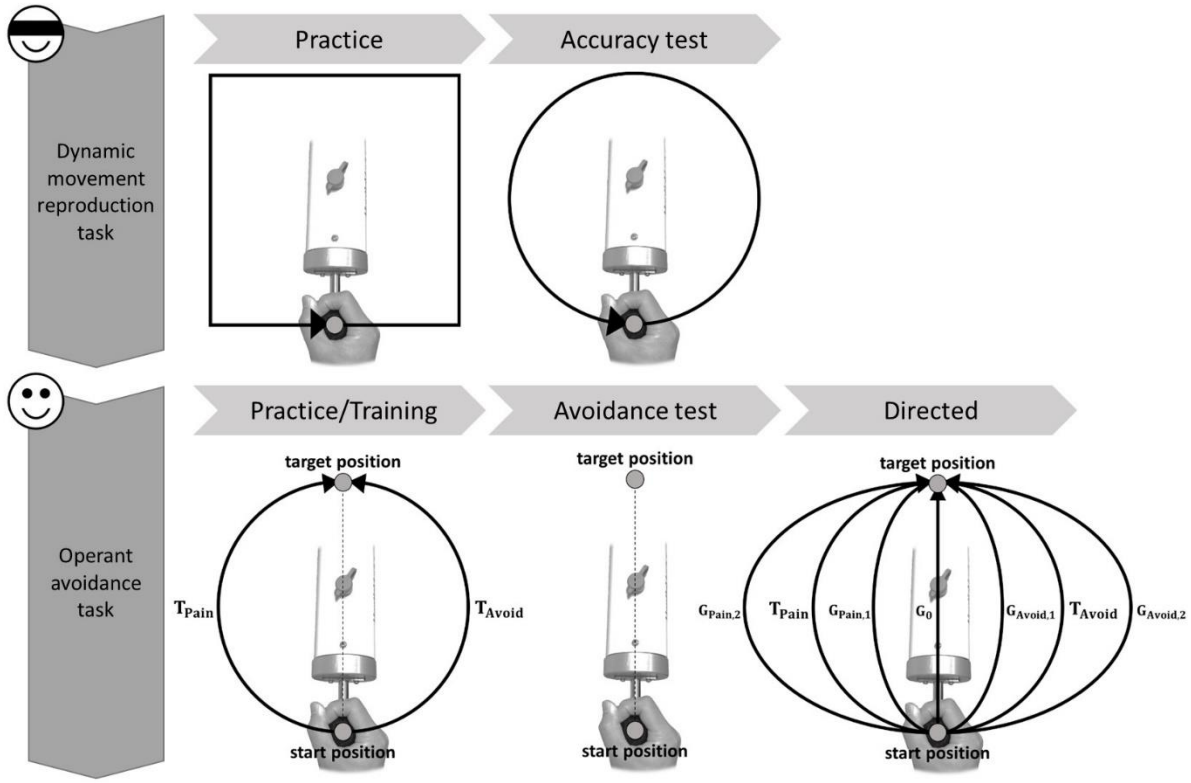
Dynamic movement reproduction task

Practice. Instructions on how to operate the robotic device and the task procedure were presented on-screen, which included movement direction and pattern shape (Figure 4.2). After reading these, participants wore a blindfold for the remainder of the task, which is standard practice when assessing proprioceptive accuracy (e.g., Christensen et al., 2020). On each trial, the robotic device first restricted movement to a single trajectory, i.e. the target movement. During all practice trials, this was a square with a side length of 16 cm, with the starting position always in the middle of the side closest to the participant. The movement direction (i.e., clockwise or counterclockwise) was counterbalanced between participants (order based on pre-made list). A starting tone together with the automated audio message "*start guided movement*" prompted participants to start moving. Movement in the wrong direction resulted in an error message and restart of the trial. After performing the target movement once, participants were instructed to reproduce this movement as accurately as possible. A starting tone together with the automated audio message "*start free movement*" prompted participants to start moving. Participants indicated when they finished movement reproduction by saying "*stop*", which prompted the experimenter to end the trial manually. An end tone was presented upon trial termination and the robotic device then moved to the starting position of the next trial. This phase consisted of four trials. The entire range of the robotic

device – within the horizontal plane – was available during reproduction. Six different starting positions within the horizontal plane were used in random order and no feedback regarding participants' performance was provided.

Figure 4.2

Movement trajectories presented during phases of the dynamic movement reproduction and operant avoidance tasks



Note. Movement directions were counterbalanced. Emoji indicate whether participants wore a blindfold. During the operant avoidance task, two trajectories were presented during practice (without pain stimuli) and avoidance training. During the latter, one trajectory was paired with the pain stimulus (80% chance; T_{Pain}), while the other trajectory was never followed by the pain stimulus (T_{Avoid}). The dotted line indicates the shortest trajectory (used as reference, see Primary outcome measures section), but was not available during practice and training. The entire horizontal movement plane was available during the avoidance test. Seven trajectories were presented in random order (one per trial) during the directed phase: the shortest trajectory between start and target position (G_0), the pain-associated trajectory (T_{Pain}), the avoidance trajectory (T_{Avoid}), and a trajectory on each side of the training trajectories (i.e., between the shortest trajectory and the training trajectories, $G_{Pain,1}$ and $G_{Avoid,1}$ respectively; on the outside of the training trajectories, $G_{Pain,2}$ and $G_{Avoid,2}$ respectively).

Accuracy test. The procedure during the test phase was identical to the practice phase, except that the shape of the target movements was changed to a circle with a radius of 8 cm for all test trials. Again, six different starting positions within the horizontal plane were used in random order, which were always positioned on the point of the circle closest to the participant. This phase consisted of six trials.

Pain calibration

To individually calibrate the intensity of the electrical stimulus, we followed a standard protocol (e.g., Glogan et al., 2021) in which participants received a series of stimuli of increasing intensity (starting at 1.00 mA). Participants rated each stimulus on a numerical scale ranging from 0-10, with 0 labeled 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*", 3 as "*the stimulus starts being painful*" 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 or 8 on the numerical pain scale.

Operant avoidance task

The operant avoidance task consisted of an arm-reaching task in which participants moved the handle of the robotic device from a start position to a target position. Note that these positions remained the same during the entire task. Participants no longer wore a blindfold, and contrary to previous operant avoidance tasks using the HapticMaster in our lab (e.g., Glogan et al., 2021), no on-screen visual feedback on movements was provided.

Practice. During this phase, the robotic device restricted movement along two trajectories to reach the target position, each consisting of half a circle (radius = 8cm; identical to DMR task): one to the left of the middle line connecting start and target position (i.e., clockwise), and one to the right (i.e., counterclockwise; Figure 4.2). A starting tone together with the written message "*Start movement!*" prompted participants to start moving. When reaching the target, an end tone was presented together with the written message "*Target reached!*". The robotic device then returned to the start position and the next trial started. This phase consisted of six trials. On the first two trials, movement direction was instructed to guarantee that participants experienced both trajectories. For the remaining (four) trials, participants could freely choose which trajectory they performed. Note that only two trajectories were available during the entire phase. Participants also practiced providing anticipatory pain-expectancy and pain-related fear ratings for each trajectory; no pain stimuli were presented.

Avoidance training. This phase was identical to the practice phase, except that participants could now freely choose between the two trajectories on all trials, and pain stimuli were presented.

One movement trajectory was followed by the pain stimulus with 80% probability, while the other was never paired with the pain stimulus (avoidance movement; counterbalanced between participants; order based on pre-made list). The pain stimulus was triggered automatically when two-thirds of the movement trajectory was performed. Participants were not informed of these contingencies before starting the training. This phase consisted of two blocks of 12 trials. Participants provided anticipatory pain-expectancy and pain-related fear ratings at the start (trial one of block one), middle (trial 12 of block one), and end (trial 12 of block two) of the phase.

Avoidance test. The main difference in this phase was that movements were no longer restricted along two trajectories, meaning that participants were free to perform any movement – within the predefined horizontal plane – to reach the target position. However, they were explicitly instructed to avoid the pain stimulus. This phase consisted of 12 trials, and no pain stimuli or questions were presented. Participants were not informed of the change in contingencies before starting the test.

Directed phase. During this phase, movements were restricted to one trajectory per trial. Seven trajectories were performed in random order: the shortest trajectory between start and target position (a straight line; G_0), the pain-associated trajectory (T_{Pain}), the avoidance trajectory (T_{Avoid}), and a trajectory on each side of these trajectories (i.e., between the shortest trajectory and the training trajectories, $G_{Pain,1}$ and $G_{Avoid,1}$ respectively; on the outside of the training trajectories, $G_{Pain,2}$ and $G_{Avoid,2}$ respectively). Participants performed each of these trajectories once (i.e., seven trials) and provided retrospective pain-expectancy and pain-related fear ratings after each movement. No pain stimuli were presented, but participants were again not informed of this.

Primary outcome measures

Proprioceptive accuracy was operationalized as the absolute difference (in cm) between the target and the reproduced circular movement pattern (i.e., difference between radiuses), averaged over the six test trials of the DMR task. Larger values reflect poorer accuracy. The reproduced radius was calculated using the coordinates of each performed movement, as logged by the robotic device, and the coordinates of the center of the target circle. This measure has shown sufficient test-retest reliability (Vandael et al., 2021).

Pain-expectancy and pain-related fear ratings were provided using the on-screen questions, "*To what extent do you expect an electrical stimulus when moving to the left/right?*" and "*How afraid are you to move to the left/right?*", which were answered using a visual analogue scale ranging from 0-100 (0 = "*not at all*" and 100 = "*very much*").

Avoidance proportion was operationalized as the proportion of avoidance movements per block of the operant avoidance task, using the shortest trajectory – a straight line from start to target – as reference (i.e., average orthogonal deviation from this line). On each trial, movements on the side of the avoidance trajectory were coded as avoidance movement; movements on the side of the pain-associated trajectory were coded as non-avoidance movement. Note that this dichotomization is based on a rather arbitrary cut-off (i.e. the middle line), meaning that this measure is a rough approximation of avoidance vs. approach behavior.

Avoidance behavior was operationalized as the (orthogonal) deviation from the avoidance trajectory during the avoidance test of the operant avoidance task, averaged over the entire block. This information was again extracted using the coordinates of each performed movement. The avoidance trajectory serves as zero value: negative values indicate deviations away from the avoidance trajectory in the direction of the pain-associated trajectory; positive values indicate deviations in the opposite direction, indicating excessive (i.e., overprotective) avoidance.

Secondary outcome measures and psychological trait questionnaires

Retrospective pain-expectancy and pain-related fear ratings collected during the directed phase are described in Appendix C.

Avoidance behavior accuracy was operationalized as the *absolute* (orthogonal) deviation from the avoidance trajectory during the avoidance test of the operant avoidance task, averaged over the entire block. Note that this method is identical to the proprioceptive accuracy measure.

Post-experimental questions regarding the experimental procedure were presented at the end of the session. To assess whether participants tried to reproduce the avoidance movement during the avoidance test, they answered the question "*Did you try to perform exactly the same avoidance trajectory from the previous phase?*" with answer options "*Yes*"/"*No*". If yes, the question "*How often did you try to perform exactly the same avoidance trajectory from the previous phase?*" was answered using a visual analogue scale ranging from "*Never*" to "*Always*". See Appendix C for a description of further post-experimental questions.

Psychological trait questionnaires were administered after the experimental procedure to assess fear of pain (the Fear of Pain Questionnaire; Roelofs et al., 2005), positive and negative affect (trait version of Positive And Negative Affect Schedule; Watson et al., 1988), intolerance of uncertainty (Intolerance of Uncertainty Scale, 12 item version; Carleton et al., 2007), distress tolerance (Distress Tolerance Scale; Simons & Gaher, 2005), and sensation seeking (Brief Sensation Seeking Scale; Hoyle et al., 2002).

Data preparation and analysis

First, data from the DMR task were visually inspected for artifacts. Two participants were excluded for not adhering to task instructions, as they only moved along the edge of the movement plane. Additionally, five test trials were excluded (over four participants) for reaching the end of the movement plane or initially moving in the wrong direction. Proprioceptive accuracy was calculated using the remaining test trials for these four participants. To calculate the avoidance behavior measure, we excluded trials from the first non-avoidance movement onward per participant – using the average orthogonal deviation from the middle line as described for the avoidance proportion measure – because our main interest was in avoidance behavior, and not in exploratory behavior. This decision was preregistered and was based on pilot data where participants reported exploration of the novel movements to find out movement-outcome contingencies, even though they were instructed to avoid. This led to the exclusion of an additional five participants who did not avoid on the first trial of the avoidance test, resulting in a final sample size of 41 participants to test our main hypothesis.

Before testing our main hypothesis, we performed a number of manipulation checks. *First,* to test for acquisition of pain-expectancy and pain-related fear, repeated measures (RM) analyses of variance (ANOVAs) with within-subjects factors Trajectory (T_{Pain}, T_{Avoid}) and Time (Start, Middle, End) were conducted on ratings during avoidance training. A pairwise comparison between both trajectories at the end of training was used to confirm successful acquisition. *Second*, to check whether participants learned to avoid the pain stimulus, we tested whether they performed the avoidance trajectory significantly more than the pain-associated trajectory during the second training block using a one-sample *t*-test on avoidance proportion (with test value .50, which indicates random movement). *Third*, the same test was run on the avoidance test to check whether participants generalized their avoidance behavior, meaning that we checked whether they performed movements similar to the avoidance trajectory more frequently than movements similar to the pain-associated trajectory.

To test our main hypothesis stating that poorer proprioceptive accuracy is associated with excessive avoidance behavior, we calculated Spearman rank correlation coefficient ρ, as proprioceptive accuracy was not normally distributed (Shapiro-Wilk test $p < .05$). A one-sample *t*-test was added to check whether movements indeed significantly deviated from the avoidance trajectory (with test value 0, which corresponds with the avoidance trajectory), away from the pain-associated trajectory. Furthermore, we explored how proprioceptive accuracy evolved from the DMR task to the avoidance test (i.e., avoidance behavior accuracy minus proprioceptive accuracy) in a subsample of participants who reported attempting to reproduce the exact avoidance trajectory during the avoidance test. We used a paired samples *t*-test for this, and additionally tested whether this change

was associated with any psychological traits using Spearman rank correlations (as change in accuracy was not normally distributed; Shapiro-Wilk test $p < .05$).

Additionally, in Appendix C, we provided a summary of psychological trait questionnaire scores, physical stimulus intensity and subjective stimulus ratings (during calibration and after the experiment), and compared these between the subsample of participants that reported only reproducing the avoidance trajectory during the avoidance test, and the rest of the sample. Furthermore, we analyzed the tendency to move on the outside of the target circle/avoidance trajectory (i.e., overshooting) in both the DMR and avoidance tasks and performed preregistered exploratory analyses (see Appendix C).

For all analyses, the family-wise alpha level was set at .05. Greenhouse-Geisser corrections were applied to control for violations of sphericity in RM ANOVAs, and corrected degrees of freedom are reported together with ε. To control for multiple testing, Holm-Bonferroni corrections were applied. The indication of effect size η_p^2 is reported for significant ANOVA effects, and Cohen's *d* for *t*-tests. All statistical analyses were performed using jamovi 1.6.23 (*jamovi*, 2021). HapticMaster data was processed using custom-made MATLAB scripts (The MathWorks Inc., Natick, MA, USA).

Results

Confirmatory analyses

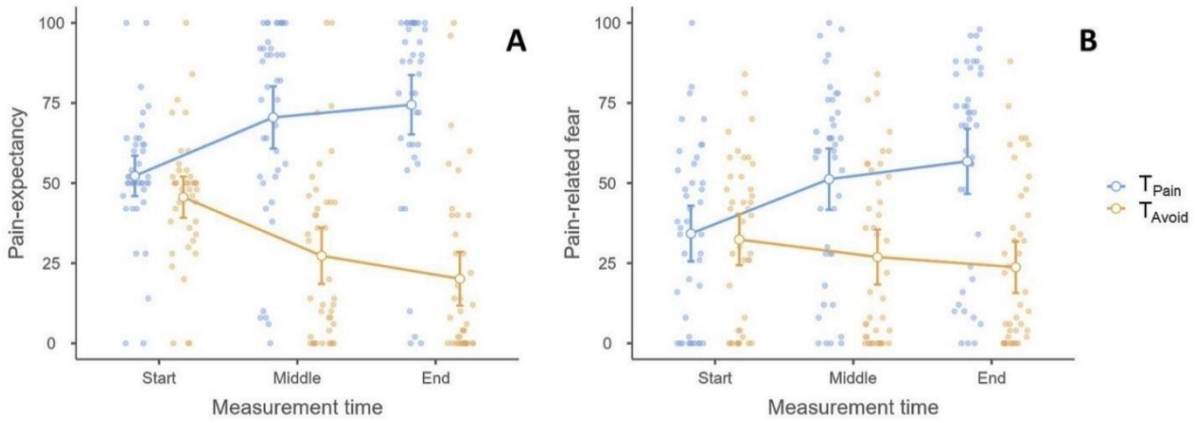
Manipulation checks

Acquisition of pain-expectancy. Analysis of pain-expectancy ratings during avoidance training showed a main effect of Trajectory, $F(1, 40) = 45.28$, $p < .001$, $\eta_p^2 = .53$, but not Time, $F(1.67, 66.81) = .27$, $p = .726$, $\varepsilon = .84$. As expected, there was a significant two-way interaction, $F(2, 80) = 20.02$, $p < .001$, $\eta_p^2 = .33$, indicating that pain-expectancy ratings evolved differently per trajectory during the training phase (Figure 4.3, panel A). At the end of training, participants expected the pain stimulus to occur more before performing the pain-associated trajectory compared to the avoidance trajectory, $t(40) = 6.80$, $p < .001$, $d = 1.94$.

Acquisition of pain-related fear. Analysis of pain-related fear ratings during avoidance training showed main effects of Trajectory, $F(1, 40) = 19.61$, $p < .001$, $\eta_p^2 = .33$, and Time, $F(1.38, 55.00) = 4.22$, $p = .033$, $\eta_p^2 = .10$, $\varepsilon = .69$, as well as a significant two-way interaction, $F(1.57, 62.71) = 14.72$, $p < .001$, $\eta_p^2 = .27$, $\varepsilon = .78$. A pairwise comparison at the end of avoidance training confirmed that participants were more afraid to perform the pain-associated trajectory than the avoidance trajectory, confirming successful differential fear learning (Figure 4.3, panel B), $t(40) = 4.70$, $p < .001$, $d = 1.14$.

Figure 4.3

Pain-expectancy and pain-related fear ratings during avoidance training



Note. Observed ratings, estimated marginal means, and 95% confidence intervals of pain-expectancy (panel A) and pain-related fear (panel B) ratings for the pain-associated (T_{Pain}) and avoidance trajectories (T_{Avoid}) during the three measurement times (Start, Middle, and End) of the avoidance training phase.

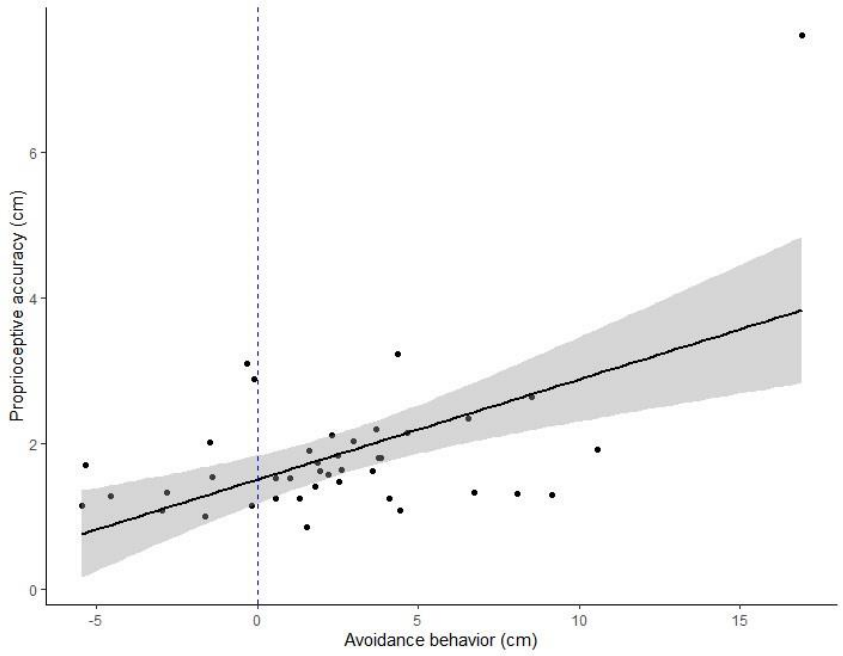
*Avoidance proportions during avoidance training and test***.** As expected, participants performed the avoidance trajectory significantly more (*M* = .77, *SD* = .21) than the pain-associated trajectory during the second block of the training phase, $t(40) = 8.07$, $p < .001$, $d = 1.26$, meaning that participants learned to avoid the pain stimulus. Moreover, during the avoidance test, participants generally performed movements similar to the avoidance trajectory (*M* = .81, *SD* = .23), $t(40) = 8.69$, $p < .001$, $d = 1.36$, indicating that participants generalized what they learned during training to this phase.

Testing our main hypothesis: is poorer proprioceptive accuracy associated with excessive avoidance behavior?

The correlation between proprioceptive accuracy and avoidance behavior during the avoidance test was significant, $\rho(41) = .35$, $p = .024$. Furthermore, participants significantly deviated from the avoidance trajectory, away from the pain-associated trajectory (i.e., outward; *M* = 2.44, *SD* = 4.35), $t(40) = 3.58$, $p < .001$, $d = 0.56$, indicating a general tendency to be overprotective. These results support our hypothesis that poorer proprioceptive accuracy is associated with excessive avoidance (Figure 4.4).

Figure 4.4

Scatterplot of the association between avoidance behavior and proprioceptive accuracy during the avoidance test



Note. The black line represents a regression line and the gray area a 95% confidence interval. For the avoidance behavior measure, the avoidance trajectory serves as zero value (represented by the dotted line): negative values indicate deviations away from the avoidance trajectory in the direction of the pain-associated trajectory; positive values indicate deviations in the opposite direction, indicating excessive (i.e., overprotective) avoidance. For the proprioceptive accuracy measure, larger values reflect poorer accuracy.

Exploratory analyses

Change in proprioceptive accuracy after avoidance conditioning

Thirteen of 41 participants (31.71 %) reported attempting to *exactly reproduce the avoidance trajectory* during the entire avoidance test. In this subsample, avoidance behavior accuracy during the avoidance test was significantly reduced compared to proprioceptive accuracy during the DMR task, $t(12) = 2.29$, $p = .041$, $d = .63$. Reductions in accuracy were significantly correlated with avoidance behavior, $\rho(13) = .86$, $p < .001$, indicating they were generally directed away from the pain-associated trajectory. Moreover, reduced proprioceptive accuracy was significantly correlated with trait fear of pain scores, $\rho(13) = .75$, $p = .018$: higher reductions in accuracy were associated with higher trait fear of pain. Correlations between accuracy reductions and other traits did not reach significance (negative affect, $\rho(13) = .60$, $p = .144$; positive affect, $\rho(13) = -.29$, $p = 1.00$; intolerance of uncertainty, $\rho(13) = .24$, $p = .861$; distress tolerance, $\rho(13) = -.18$, $p = .547$; sensation seeking, $\rho(13) = -.27$, $p = 1.00$).

Discussion

The current study investigated the intriguing question whether poorer proprioceptive accuracy is associated with overprotective pain-related avoidance behavior using robotic arm-reaching tasks. First, our manipulation checks showed successful acquisition of self-reported pain-expectancy and pain-related fear, as well as avoidance behavior, confirming that participants learned the movement-outcome contingencies. Furthermore, the learned avoidance behavior successfully generalized toward the avoidance test. Testing of our main hypothesis supported that poor proprioceptive accuracy was associated with excessive avoidance in terms of increased deviation from an avoidance trajectory, away from a pain-associated trajectory. Moreover, exploratory analyses – using a subsample of participants who reported the strategy to exactly reproduce the avoidance trajectory during the avoidance test – showed reduced accuracy during the avoidance test compared to the proprioceptive accuracy test before conditioning. Interestingly, reduced proprioceptive accuracy was associated with overprotective avoidance behavior and higher trait fear of pain.

The finding that poorer proprioceptive accuracy was indeed associated with excessive pain-related avoidance behavior is an innovative and important contribution to the field of chronic pain disability, because poor proprioceptive accuracy has been observed in a wide range of chronic pain conditions (Juul-Kristensen et al., 2008a; Knoop et al., 2011; Stanton et al., 2016; Tong et al., 2017). Although we did not establish causality, the found association suggests that such poor accuracy may contribute to disability, as excessive avoidance is considered key in the development and maintenance of chronic pain disability (Vlaeyen et al., 2016). Because avoidance is a key behavioral correlate of fear (Krypotos et al., 2015), this finding also extends previous work in the field of anxiety disorders, which showed – using visual stimuli – that poor perceptual accuracy is associated with more fear generalization (Struyf et al., 2017; Zaman, Ceulemans, et al., 2019; Zaman, Struyf, et al., 2019). However, such studies mainly focused on the relationship between perceptual accuracy and fear responding toward stimuli resembling a threat-associated stimulus, whereas the current study looked at safe avoidance movements.

Our exploratory finding that avoidance learning is associated with a reduction in proprioceptive accuracy extends previous work showing that aversive classical conditioning reduces perceptual accuracy in a number of modalities (e.g., visual, auditory stimuli; Laufer et al., 2016; Shalev et al., 2018; Zaman et al., 2015). For example, Schechtman et al. (2010) showed increased misperception of novel tones as a conditioned tone after aversive conditioning. Previous work however solely focused on classical conditioning, in which participants passively experience associations between stimuli, and not on operant conditioning, where participants actively adapt their behavior based on learned associations, as in the current study. Furthermore, these studies mainly

focused on perceptual changes in stimuli similar to an aversively conditioned stimulus, and to a lesser extent in stimuli similar to a safe stimulus, such as the avoidance trajectory in the current study. However, a study by Shalev et al. (2018) showed no change (or even improvement) in perceptual discrimination thresholds when testing stimuli similar to a safe stimulus. The current study however provides evidence for a reduction in proprioceptive accuracy when trying to reproduce a learned safe movement. Importantly, reductions were associated with avoidance behavior, indicating that it may contribute to avoidance becoming excessive, thus contributing to disability. Moreover, higher reductions were associated with higher trait fear of pain scores. From a predictive processing perspective, this may be due to a "better safe than sorry" processing strategy underlying such traits. This perspective views the brain as a prediction machine that continuously strives to reduce prediction errors (Clark, 2013). Specifically, the brain attempts to generate a model of the internal and external world using prior knowledge and sensory evidence as input. However, these inputs are weighted (precision weighting); therefore, reduced proprioceptive accuracy may be a result of increased weighting of the affective-motivational aspects of input at the expense of detailed sensory-discriminative input, leading to a stagnated error-reduction process (Van den Bergh et al., 2021).

Some limitations of the current findings and implications for future studies deserve attention. *First*, the DMR and the operant avoidance tasks both require performance of circular movement trajectories. Future studies may employ unique movements in the operant avoidance task to establish that the effect generalizes to other movements. *Second*, our avoidance behavior measure captures multiple processes, such as variation in generalization of avoidance, proprioceptive accuracy, and exploratory behavior (i.e., figuring out movement-outcome contingencies). Proprioceptive accuracy inherently plays a role in such a task, however, future versions could limit exploratory behavior by improving instructions, for example by instructing participants to select a trajectory that is most likely to avoid the aversive outcome, and stick to this trajectory. To limit the role of exploratory behavior in the current study (which was present according to post-experimental questioning), we excluded movements from the avoidance test, starting from the first movement that objectively resembled the pain-associated trajectory more than the avoidance trajectory. However, this approach may have unintentionally omitted movements that actually had an avoidance function, because our cut-off (i.e., the middle line) was rather arbitrary, and we did not assess underlying motivations for each movement. The same holds for movements that were included as avoidance movements. *Third*, our measure of proprioceptive accuracy also depends on factors such as recall and motor control, as is often the case when assessing active proprioceptive function (Elangovan et al., 2014; Goble et al., 2010). Future studies may benefit from assessing the influence of these specific factors in the association between proprioceptive accuracy and avoidance behavior as found in the current study.

Fourth, some caution is warranted in interpreting the general tendency to move on the outside of the avoidance trajectory during the avoidance test as excessive avoidance behavior, as this tendency is also present in the DMR task. In other words, there is a general tendency to move on the outside of the target circle during reproduction (overshooting; see Appendix C). Future studies using the current paradigm need to control for this effect. However, movements deviated significantly further in the avoidance test compared to overshooting during the DMR task, indeed indicating the presence of overprotective behavior. *Fifth*, regarding our exploratory analyses, the subsample of participants that attempted to replicate the avoidance trajectory was rather small and 'self-selected', as they decided on this movement strategy. It may be that these participants were generally more anxious, thus showing the association between reduced accuracy and trait fear of pain – although exploratory analyses showed no statistical difference with the rest of the sample in trait fear of pain (see Appendix C). Whether the findings regarding change in accuracy still hold when explicitly instructing the full sample to replicate the avoidance trajectory deserves further investigation. *Finally*, the reduction in accuracy could also be due to other factors such as the addition of vision in the operant avoidance task, as the DMR task was performed blindfolded, thus limiting causal inferences. However, previous work from our lab indicates that the addition of visual cues does not significantly reduce accuracy (Vandael et al., 2021).

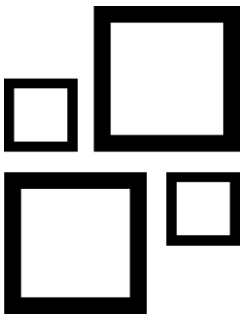
Given the key role of excessive avoidance behavior in chronic pain conditions (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen et al., 2016), gaining insight into factors that contribute to such behavior is imperative for treatment. The current study is the very first to show that there is an association between proprioceptive accuracy and excessive pain-related avoidance of movements. It should be noted that the sample on which this conclusion is based consisted mostly of bachelor students – thus limiting generalizability – and observed movement deviations were in the order of centimeters. Therefore, these results need validation in clinical populations. Given that excessive spreading (i.e., overgeneralization) of pain-related fear and pain-expectancy has been observed in chronic pain samples (Meulders, Harvie, et al., 2014; Meulders et al., 2015; Meulders, Meulders, et al., 2017), we expect to observe excessive avoidance in such samples compared to pain-free participants. Furthermore, we expect poorer proprioceptive accuracy, and a significant association between accuracy and avoidance. If this association is indeed present in chronic pain samples, the effect of training proprioceptive accuracy on avoidance behavior deserves investigation to see whether clinically relevant effects can be obtained. There is preliminary evidence for beneficial effects of proprioceptive accuracy training in chronic neck pain (Jull et al., 2007), though underlying mechanisms deserve further attention to inform and optimize treatment. Studies in the field of anxiety disorders have already indicated that training (visual) perceptual accuracy indeed leads to attenuated

generalization of fear (Ginat-Frolich et al., 2017; Herzog et al., 2021) and avoidance (Ginat-Frolich et al., 2019; Lommen et al., 2017), thus indicating potential for the field of chronic pain as well.

In conclusion, the current study is the very first to show that poorer proprioceptive accuracy is associated with excessive pain-related avoidance of movements. Furthermore, explorative analyses suggest that avoidance learning leads to reduced proprioceptive accuracy, and that reductions in accuracy are associated with excessive avoidance and trait fear of pain. These findings have important implications for future research as well as clinical practice, as they highlight the potential of targeting proprioceptive accuracy to attenuate excessive avoidance of movements.

Chapter 5

Positive affect and generalization of pain-related avoidance and fear



This chapter has been published as Vandael, K., Meulders, M., zur Mühlen, K., Peters, M., & Meulders, A. (2022). Increased positive affect is associated with less generalization of pain-related avoidance. *Behaviour Research and Therapy*, *185*, 104199.

Abstract

Fear-avoidance models of chronic pain consider excessive spreading (or overgeneralization) of pain-related avoidance toward safe activities to play a crucial role in chronic pain disability. This study (*N* = 96) investigated whether avoidance generalization is mitigated by positive affect induction. Pain-free, healthy participants performed an arm-reaching task during which certain movements were followed by pain, while another was not. One group then performed an exercise to induce positive affect (positive affect group), while another group performed a neutral exercise (neutral group). A third group also performed the neutral exercise, but did not learn to avoid pain during the arm-reaching task (yoked neutral group). To test generalization, we introduced novel but similar movements that were never followed by pain in all groups. Results showed no differences in generalization between the positive affect and neutral groups; however, across groups, higher increases in positive affect were associated with less generalization of avoidance, and less generalization of pain-expectancy and pain-related fear. Compared to the yoked neutral group, the neutral group showed no generalization of avoidance, while pain-expectancy and pain-related fear did generalize. These results point toward the potential of positive affect interventions in attenuating maladaptive spreading of pain-related avoidance behavior to safe activities.

Introduction

According to contemporary fear-avoidance models of chronic pain, pain-related avoidance of safe activities plays a crucial role in the development and maintenance of chronic pain disability (Meulders, 2019; Vlaeyen et al., 2016; Vlaeyen & Linton, 2012). Lab research using robotic arm-reaching movements repeatedly showed that pain-related avoidance can be acquired through operant conditioning: pain-free participants learn that certain movements lead to pain (i.e., a painful electrical stimulus), and that another – avoidance – movement does not (Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., 2021; Meulders et al., 2016). Consequently, the avoidance movement is more likely to be performed. Glogan et al. (2021) tested *generalization of avoidance* using the robotic arm-reaching paradigm: novel movements that were proprioceptively similar to the pain-associated and avoidance movements were introduced after avoidance acquisition. Even though none of these movements were paired with pain, avoidance spread to them (Glogan et al., 2021). Such generalization is adaptive to a certain extent in daily life because it prevents having to learn about each activity separately. However, it may turn maladaptive when applied excessively to safe activities (i.e., *overgeneralization*), as this leads to disproportional withdrawal from valued activities (Vlaeyen et al., 2016).

Because of its assumed contribution to chronic pain disability, investigating ways to mitigate avoidance overgeneralization may help optimize therapies. Increasing evidence shows that it may be beneficial to target positive affect in pain treatment (Finan & Garland, 2015; Hanssen et al., 2017); positive psychology interventions successfully augment positive affect, wellbeing and functioning, and reduce pain severity and depression in individuals with chronic pain (Braunwalder et al., 2022; Ong et al., 2020). Geschwind et al. (2015) showed that experimentally induced positive affect is associated with less generalization of *pain-related fear*. Interestingly, positive affect preserved adaptive generalization of fear toward movements similar to a pain-associated movement, but reduced maladaptive overgeneralization toward movements similar to a safe movement. However, whether positive affect has the potential to reduce *pain-related avoidance* remains an important open question, because fear alone does not lead to disability, whereas avoidance does. Although research in the field of anxiety disorders shows that fear and avoidance are closely linked, there is no one-to-one relationship (Pittig, Wong, et al., 2020; van Meurs et al., 2014).

The current study investigated the effect of experimentally inducing positive affect on the generalization of pain-related avoidance, pain-expectancy and pain-related fear, using the paradigm of Glogan et al. (2021). One group of participants performed a visualization exercise to induce positive affect before the generalization test (positive affect group), while another group performed a control visualization exercise (neutral group; Geschwind et al., 2015). We hypothesized that compared to the

neutral group, the positive affect group would show (1) less generalization of pain-related avoidance and (2) less generalization of self-reported pain-expectancy and pain-related fear toward movements similar to the original safe movement. Additionally, we wanted to investigate whether the finding that pain-related avoidance behavior generalizes in pain-free participants could be replicated (Glogan et al., 2021), so we included another control group that could not learn to avoid pain and performed the control visualization exercise (yoked neutral group). We hypothesized that compared to the yoked neutral group, the neutral group would show (3) generalization of pain-related avoidance and (4) generalization of self-reported pain-expectancy and pain-related fear toward novel movements similar to the original pain-associated movements.

Methods

Ethical approval and preregistration

The Ethics Review Committee Psychology and Neuroscience of Maastricht University approved the experimental protocol (registration number: 185 09 11 2017 S8). All participants provided written informed consent before the experiment and could terminate their participation at any point during the session without loss of compensation. Because the experiment ran during the COVID-19 pandemic, additional safety measures were employed according to institutional guidelines (e.g., both participant and experimenter wore a facemask). The study protocol and analyses were registered prior to data collection at the Open Science Framework (https://osf.io/sqrxc/?view_only=11c2fd47cf8744dca77ffb4812124951).

Participants

A power analysis using the R package "SIMR" and data from the study by Glogan et al. (2021) showed 84% power to detect a group effect on avoidance behavior during the generalization test when using a linear mixed model (i.e., experimental versus yoked contingencies; based on 100 simulations; Green & MacLeod, 2016). In the current study, 96 pain-free, healthy volunteers participated [73 women, 23 men; $M \pm SD$ (range) age = 24 ± 8 years (17-56); 32 per group]. Participants received either 2 course credits or a 15 EUR gift voucher and were recruited through Maastricht University's research participation system, as well as advertisements distributed around the university campus and on social media. Prior to participation, everyone completed a checklist to confirm that none of the following exclusion criteria applied: chronic pain, pregnancy, left-handedness, analphabetism, diagnosed dyslexia, (history of) cardiovascular disease, (history of) psychiatric disorder (e.g., clinical depression, anxiety disorder), uncorrected problems with hearing/vision, pain in the dominant hand/wrist/elbow/shoulder that may hinder performing the reaching task, presence of

implanted electronic medical devices (e.g., cardiac pacemaker), and presence of any other severe medical conditions.

Apparatus and software

Arm-reaching movements were performed using the HapticMaster, a 3 degrees-of-freedom, force-controlled robotic device (Motekforce Link, Amsterdam, the Netherlands; Figure 5.1). Participants used their right hand to exert force on the HapticMaster's handle (i.e., force sensor), which resulted in corresponding movement of the robotic device. The device logged the position of its handle every 2 ms along all three axes (resolution 10^-4 cm) and allowed movements within a horizontal plane with 40 cm depth and 40 cm width. Height remained constant in the current setup.

The experimental task was programmed in Unity 2017 (Unity Technologies, San Francisco, CA, USA) and 3D graphics were created in Blender 2.79 (Blender Foundation, Amsterdam, The Netherlands). The task was run on a Windows 10 Enterprise (Microsoft Corporation, Redmond, WA, USA) 64-bit Intel Core desktop computer (with 8GB RAM, CPU: i7-7700 at 3.600GHz; Intel Corporation, Santa Clara, CA, USA) and was presented on a 40-inch LCD screen (Samsung UE40ES5500; Samsung Group, Seoul, South Korea) that was mounted on the wall in front of the participant. A direct application programming interface connection enabled communication between the HapticMaster and desktop computer. Participants used a foot switch (USB Triple Foot Switch II; Scythe Co., Ltd., Tokyo, Japan) to navigate through instructions and answer questions during the experimental task. Questionnaires were presented on a tablet (ASUS ZenPad 8.0; AsusTek Computer Inc., Taipei, Taiwan) using Qualtrics (Qualtrics, Seattle, Washington, USA).

The pain stimulus was a 2 ms square-wave electrical stimulus administered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, UK) via two reusable stainless steel disk electrodes (8mm diameter with 30mm spacing; Digitimer, Welwyn Garden City, UK). These electrodes were filled with K-Y gel (Reckitt Benckiser, Slough, UK) and attached to the right arm of the participant (approximately 5 cm above the elbow).

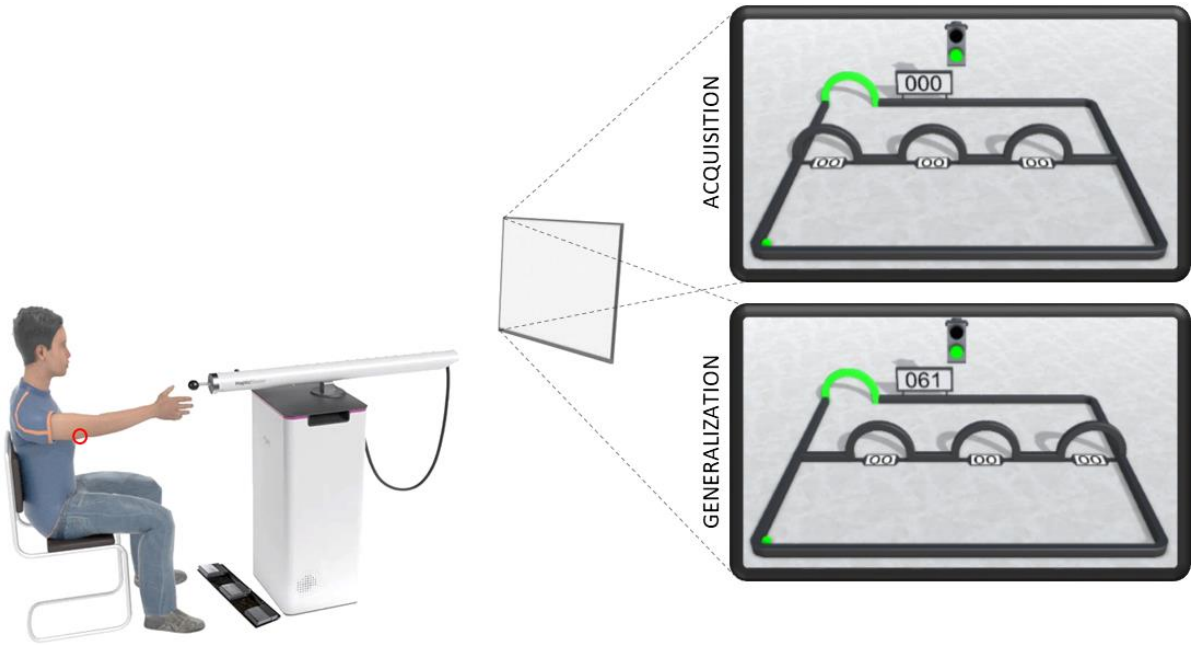
Procedure

Participants were invited to the lab and – unbeknownst to them – assigned to one of three groups: the positive affect, neutral, or yoked neutral group. Groups were assigned in an alternating fashion, based on the order in which participants arrived at the lab, because the sequence of electrical stimuli received by a participant in the yoked neutral group was identical to the sequence of electrical stimuli received by the previous participant in the neutral group. The robotic arm-reaching task was identical to the one described by Glogan et al. (2021; experiment 2). However, the current study used

a positive affect/neutral manipulation before the generalization test. State positive affect was assessed before starting the experimental procedure (pre-experiment measurement).

Figure 5.1

Experimental setup



Note. Participants were seated in front of the robotic device. The electrodes for the pain stimuli were placed on the triceps tendon of the right arm (red circle). The footswitch to navigate through instructions and answer questions was on the floor in front of the robotic device and the television screen was mounted on a wall behind the robotic device. During the acquisition phase, trajectories T1-3 (from left to right) were available, while during generalization, trajectories G1-3 (from left to right) were available. The stoplight served as start signal (green light) and stop signal (red light). This figure was adapted from Glogan, Gatzounis, Vandael, et al. (2020).

Pain calibration

After applying the electrodes, the intensity of the pain stimulus was individually calibrated according to a standard protocol (e.g., Glogan et al., 2021). Electrical stimuli with increasing intensity were delivered and participants rated each stimulus on a numerical scale ranging from 0-10; 0 represented "*I feel nothing*", 1 "*I feel something, but this is not unpleasant*", 2 "*the stimulus is not yet painful, but it is beginning to be unpleasant*", 3 "*the stimulus starts being painful*" and 10 "*this is the worst pain I can imagine*". Participants were asked to select a stimulus they would describe as "*definitely painful and demanding some effort to tolerate*", corresponding to a 7-8 on the rating scale.

Practice

Participants first practiced operating the robotic device and performing the arm-reaching task. They were instructed to move the handle of the robotic device from a start position to a target position. The handle was represented on-screen by a green ball and its start position was in the bottom left corner of the movement plane (Figure 5.1). After an auditory and visual start signal, participants moved the green ball to the target position, which was represented by a green arch in the upper left corner. To reach this position, participants moved along one of three trajectories, which were represented on-screen as arches positioned in the middle of the movement plane (i.e., halfway between start and target position). Lateral deviation from the shortest trajectory between the start and target position was associated with an increase in resistance generated by the robotic arm: the first trajectory (from the left; T1) required minimal effort, the middle trajectory (T2) required medium effort, and the third trajectory (T3) required most effort. Participants chose freely which trajectory they used throughout the entire experiment. The practice phase consisted of 10 trials and no pain stimuli were administered. Participants practiced providing pain-expectancy and pain-related fear ratings on trial 5.

Acquisition

This phase was identical to practice, with the crucial difference that pain stimuli were now presented. For participants in the positive affect and neutral groups, movements along trajectory T1 had an 80% chance of being paired with the pain stimulus, T2 movements had a 40% chance, and T3 movements were never paired with the pain stimulus. However, T3 still required the most effort, meaning that there was a trade-off between pain-avoidance and effort. Participants in the yoked neutral group received a pain stimulus on each trial that their matched counterpart in the neutral group received a stimulus, to control for the number of pain stimuli received by each participant. This meant that participants in the yoked neutral group could not avoid pain, as there was no contingency between movement trajectories and the pain stimulus. The acquisition phase consisted of three blocks of 12 trials. Participants provided pain-expectancy and pain-related fear ratings for each trajectory on trials 1, 6 and 12 of each block. Additionally, they provided pain-intensity and -unpleasantness ratings at the end of each block.

Positive affect manipulation

The experimenter removed the electrodes at the start of this phase and state positive affect was assessed again (pre-visualization measurement). The current study employed the best possible self exercise to induce positive affect, as used by Geschwind et al. (2015): the experimenter verbally instructed participants in the positive affect group to think about (1 min), write about (15 min) and visualize (5 min) a future in which everything went well and in which they realized their dreams. In the

neutral and yoked neutral groups, equivalent instructions to think about, write about, and visualize a typical day were used (Geschwind et al., 2015; see Appendix D for verbatim instructions). A third affect measurement occurred at the end of this phase (post-visualization measurement), and electrodes were reapplied.

Generalization

During this phase, new trajectory arches were introduced: G1 was positioned between T1 and T2, G2 between T2 and T3, and G3 to the right of T3 (Figure 5.1). The acquisition trajectories (T1-3) were no longer available and none of the generalization trajectories were paired with the pain stimulus, but the third trajectory (from the left; G3) still required the most effort (i.e., lateral deviation was still associated with increased resistance). This phase consisted of three blocks of 12 trials. Participants again provided pain-expectancy and pain-related fear ratings for each available trajectory on trials 1, 6 and 12 of each block. After the third generalization block, participants completed the final state positive affect assessment (post-experiment measurement), followed by post-experimental questions and trait questionnaires.

Reminder-of-acquisition

The generalization blocks were interspersed with reminder-of-acquisition blocks to hamper extinction: one block between generalization blocks 1 and 2, and one block between generalization blocks 2 and 3. During these blocks, the acquisition trajectory arches (T1-3) were presented again with the original pain stimulus contingencies, while the generalization trajectories were unavailable. These blocks consisted of five trials and participants provided pain-expectancy and pain-related fear ratings for the available trajectories on trial 3 of each block.

Primary outcome measures

Avoidance behavior

Avoidance behavior was operationalized as the maximal, orthogonal deviation from the shortest trajectory between the start and target position per trial (range: 0 – 40 cm). The maximal deviation was extracted using the coordinates of each movement as registered by the HapticMaster. These values were averaged per block. For comparability of avoidance data between the acquisition phase and generalization test, a linear transformation was performed: the acquisition and generalization trajectories share the same coordinates. This means that the width of acquisition trajectory T1 was subtracted from all maximal deviations of the generalization test.

Pain-expectancy and pain-related fear

Throughout the arm-reaching task, participants rated their pain-expectancy and pain-related fear for each trajectory available during that phase. To indicate to which trajectory questions

pertained, the corresponding arch turned yellow. Participants rated the questions *"How much do you expect the pain to occur when moving through the yellow colored arch?"* (pain-expectancy) and *"How afraid are you to move through the yellow colored arch?"* (pain-related fear) using an on-screen visual analogue scale ranging from 0 to 100. Ratings were averaged per block.

Positive affect

To assess state positive affect, the modified Differential Emotions Scale was employed (Fredrickson et al., 2003). This questionnaire contains 15 items, which consist of words describing feelings, with five items relating to positive affect (*"joyful, happy, amused"*; *"warm hearted, gleeful, elated"*; *"loving, affectionate, friendly"*; *"moved"*; *"satisfied, pleased"*). Participants rated the degree to which they experienced these feelings in the present moment on a numerical scale ranging from 1 (*"not at all"*) to 7 (*"very intense"*). The five items relating to positive affect were averaged.

Secondary outcome measures and trait questionnaires

See Appendix D for a full description of the pain-intensity/unpleasantness and negative affect measures, the post-experimental questions, and psychological trait questionnaires.

Analysis plan

Manipulation checks were performed before testing our main hypotheses. To analyze our *positive affect* measure, we used a linear mixed model including predictors Group (Positive affect, Neutral, Yoked neutral) and Time (Pre-experiment, Pre-visualization, Post-visualization, Post-experiment), and the interaction between both. Note that the pre-visualization affect measurement was missing for one participant due to technical difficulties; this participant was excluded from analyses involving state positive affect. See Appendix D for the full description of additional manipulation and randomization checks.

To test our *first hypothesis* – that the positive affect group would avoid less in the generalization test compared to the neutral group –, we defined a linear mixed model with predictors Group (Positive affect, Neutral) and Block (1-3), and the interaction between both predictors. As preregistered, this analysis was followed by a responder analysis in case the expected main effect of Group did not reach significance. In this model, the Group predictor was substituted with Positive affect change as predictor – i.e., post- minus pre-visualization positive affect, independent of group. This continuous variable increases statistical power [see Geschwind et al. (2015) for a similar approach]. For the *second hypothesis* – that the positive affect group would show reduced generalization in pain-expectancy and pain-related fear ratings for G2/3 compared to the neutral group – we defined two separate linear mixed models with predictors Group (Positive affect, Neutral),

Trajectory (G1-3) and Block (1-3), and the interaction between Group and Trajectory. Similar to the previous hypothesis, we substituted Group for continuous predictor Positive affect change in case the interactions between Group and Trajectory did not reach significance. To test our *third hypothesis* – that the neutral group would avoid more than the yoked neutral group during the generalization test –, we used a linear mixed model on avoidance behavior, which included predictors Group (Neutral, Yoked neutral), Block (1-3) and the interaction between both predictors. For our *fourth hypothesis* – that ratings would differ significantly between generalization trajectories (G1 > G3) in the neutral group, but not the yoked neutral group –, two separate linear mixed models were used for pain-related fear and pain-expectancy ratings during the generalization test. These included predictors Group (Neutral, Yoked neutral), Trajectory (G1-3) and Block (1-3), and all corresponding interactions between these predictors.

All linear mixed models included a participant-specific random intercept. Pairwise comparisons were used to investigate significant interaction effects. Whenever no difference was expected between measures, we used an equivalence test: the two-one-sided *t*-test (Lakens et al., 2018). Equivalence bounds were set using the smallest effect size of interest, given our sample size (n = 32 per group), desired level of statistical power (.80) and alpha (.05). A sensitivity analysis in G*Power (Faul et al., 2007) returned a Cohen's *dz* value of 0.51 for within-subjects testing (i.e., between trajectories), and a Cohen's *d* value of 0.71 for between-subjects testing (i.e., between groups). Median splits were employed to investigate and visualize interactions involving continuous variable Positive affect change. For all analyses, the family-wise α-level was set at .05. Satterthwaite's method was used for degrees of freedom. To control for multiple comparison testing, Holm-Bonferroni corrections were applied. Effect sizes partial eta squared (η_p^2) and Cohen's *d* are reported for *F*- and *t*-tests respectively. All analyses were performed using RStudio (RStudio, Boston, MA, USA).

Results

Manipulation checks

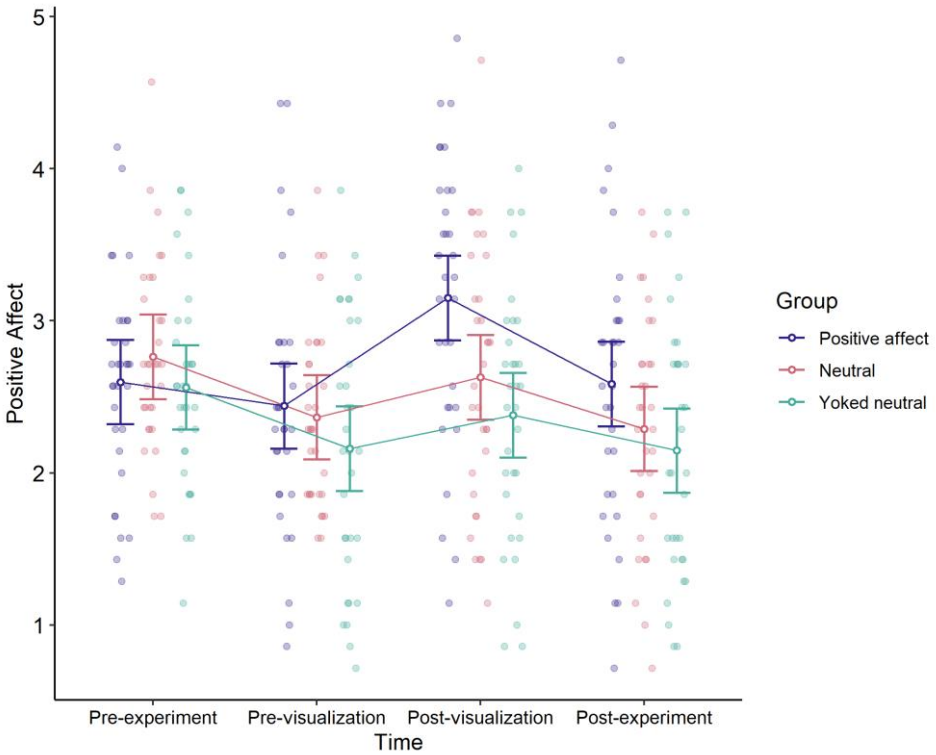
Positive affect

As expected, the analysis of positive affect yielded a significant interaction between Group and Time, $F(6, 278.14) = 4.43$, $p < .001$, $\eta_p^2 = 0.09$, indicating that positive affect evolved differently in groups during the experiment (Figure 5.2). Participants in the positive affect group reported more positive affect immediately after the visualization exercise than before, $t(278) = 5.99$, $p < .001$, $d = 0.77$, while participants in the neutral group, $t(278) = 2.24$, $p = .078$, $d = 0.34$, and the yoked neutral group, $t(278) = 1.86$, $p = .197$, $d = 0.26$, showed no significant increase. This change resulted in significantly higher positive affect ratings in the positive affect group compared to both the neutral

group, $t(164) = 2.62$, $p = .019$, $d = 0.59$, and the yoked neutral group, $t(164) = 3.88$, $p < .001$, $d = 0.88$, immediately after the visualization exercise. Additionally, positive affect scores in the positive affect group were statistically equivalent to scores in both the neutral and yoked neutral group right before the visualization exercise (p-values for both upper and lower bounds < .05). These results confirm that the positive affect manipulation was successful. It should be noted that the effects were transient; groups no longer differed significantly after the generalization test (Positive affect group versus Neutral group: $t(164) = 1.48$, $p = .282$, $d = 0.35$; Positive affect group versus Yoked neutral group: $t(164) = 2.20$, $p = .088$, $d = 0.49$).

Figure 5.2

Positive affect during the different experimental phases



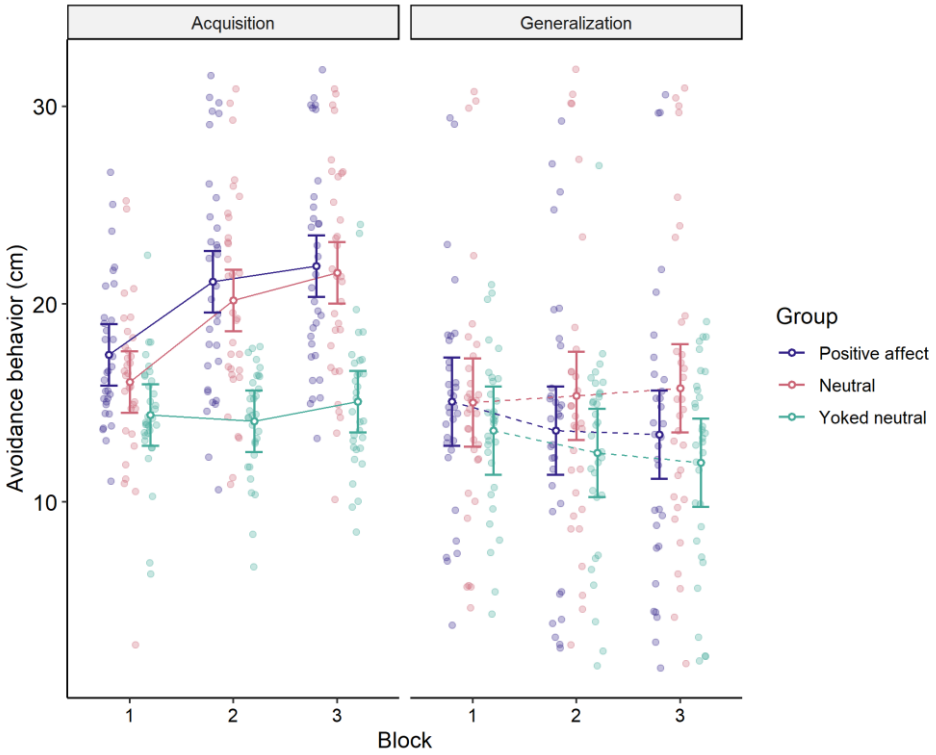
Note. Observed average scores, estimated marginal means and 95% confidence intervals of positive affect are displayed for the positive affect, neutral, and yoked neutral groups at the four measurement times (i.e., pre-experiment, pre-visualization, post-visualization and post-experiment).

Acquisition of avoidance, pain-expectancy and pain-related fear

The avoidance (Figure 5.3), pain-expectancy (Figure 5.4), and pain-related fear (Figure 5.5) measures all indicated successful acquisition. See Appendix D for a detailed description of the results.

Figure 5.3

Acquisition and generalization of pain-related avoidance behavior



Note. Observed average maximal deviations, estimated marginal means and 95% confidence intervals of avoidance behavior are displayed for the positive affect, neutral, and yoked neutral groups during the acquisition blocks (full lines) and generalization blocks (dashed lines). To increase comparability between phases, a linear transformation was performed: the acquisition and generalization trajectories share the same coordinates.

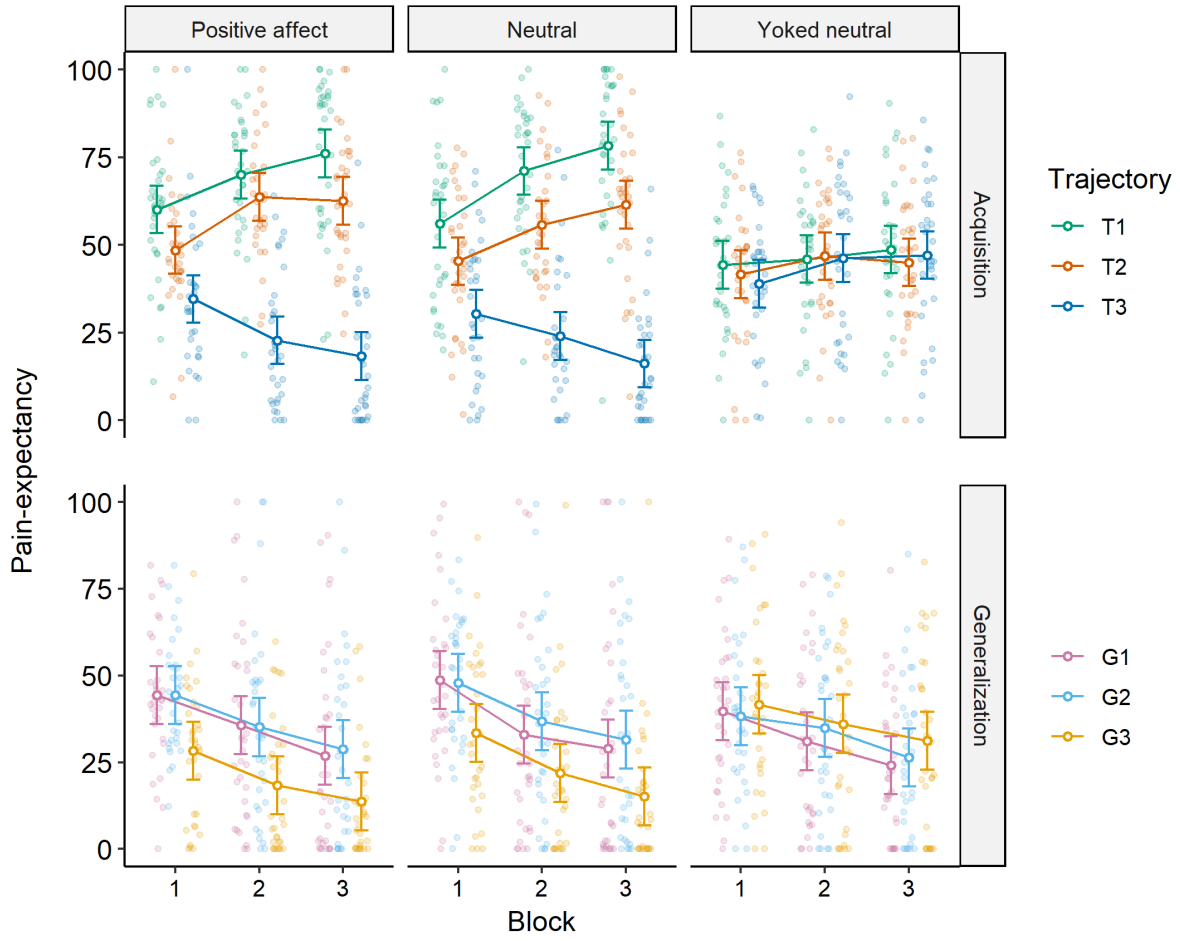
Main analyses

Hypothesis 1: Is pain-related avoidance generalization reduced after positive affect induction?

Contrary to our expectations, the analysis of avoidance behavior in the positive affect and neutral groups showed no significant main effect of Group (Figure 5.3), $F(1, 62) = 0.72$, $p = .399$, $\eta_p^2 = 0.01$. The interaction between Group and Block also did not reach significance, $F(2, 124) = 1.79$, $p = .171$, $\eta_p^2 = 0.03$. Interestingly, when Positive affect change was used as predictor instead of the Group factor, the analysis did indicate a main effect of this predictor, $F(1, 61) = 10.91$, $p = .002$, $\eta_p^2 = 0.15$. As expected, higher increases of positive affect – across groups – were associated with less avoidance generalization (Figure 5.6).

Figure 5.4

Acquisition and generalization of pain-expectancy



Note. Observed average ratings, estimated marginal means and 95% confidence intervals of pain-expectancy are displayed for each trajectory (T/G1-3) during the acquisition and generalization blocks, separately for the positive affect, neutral, and yoked neutral groups.

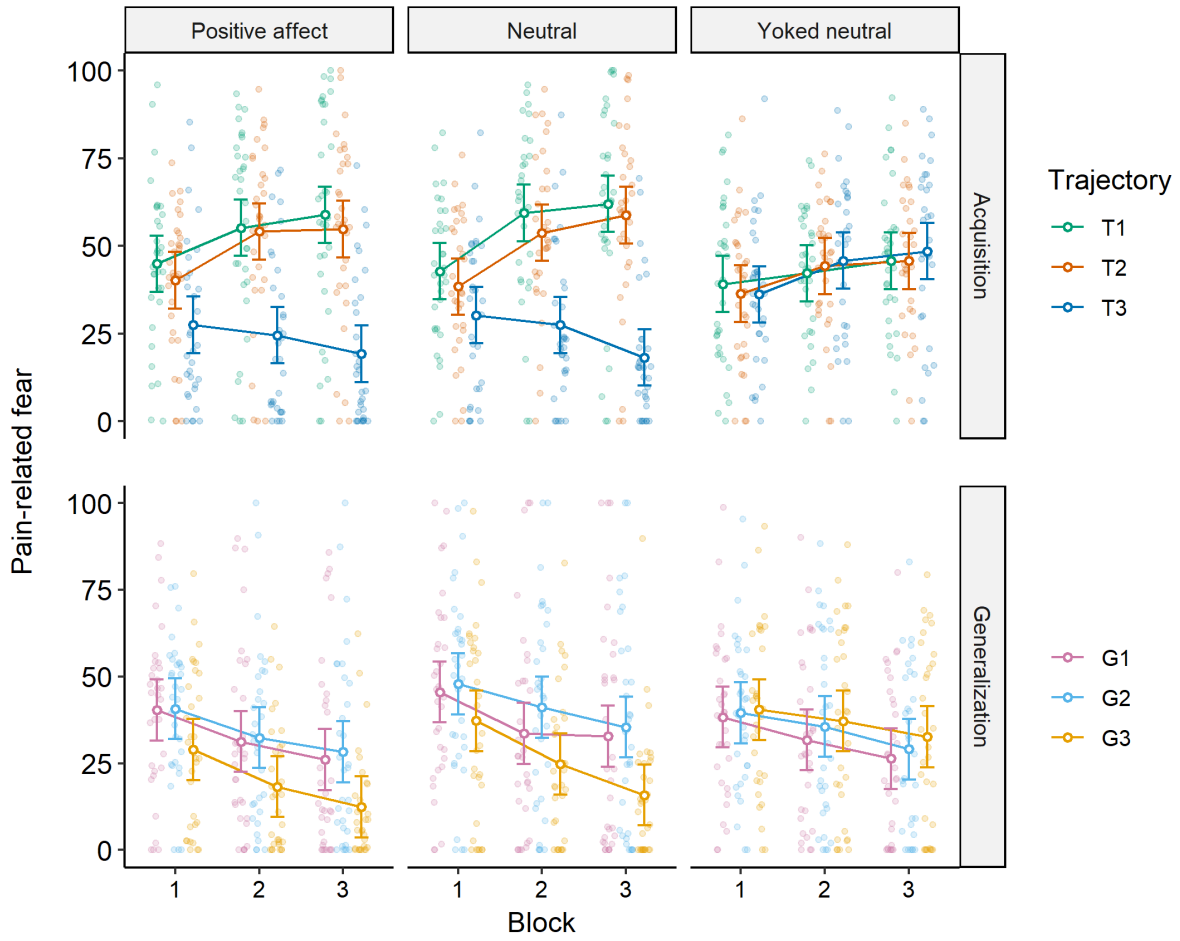
Hypothesis 2: Is pain-expectancy and pain-related fear generalization reduced after positive affect induction?

Contrary to our expectations, analysis of *pain-expectancy ratings* in the positive affect and neutral groups during the generalization test showed no significant interaction between Group and Trajectory, $F(2, 506) = 0.16$, $p = .850$, $\eta_p^2 < 0.01$, indicating that rating patterns did not differ between groups (Figure 5.4). However, when using Positive affect change as predictor instead of Group, results did show a significant interaction between Positive affect change and Trajectory, $F(2, 498) = 4.77$, $p = .009$, $\eta_p^2 = 0.02$. Contrary to our expectations, further analysis of the two-way interaction – using a median split for changes in positive affect – indicated that higher increases in positive affect were associated with lower ratings on trajectory G1, $t(101) = -2.01$, $p = .047$, $d = -0.16$, while no significant

associations were present for G2, $t(101) = -0.97$, $p = .333$, $d = 0.08$, and G3, $t(101) = 0.52$, $p = .604$, $d = 0.12$ (Figure 5.7, upper panel). In other words, increases in positive affect across groups were mainly associated with lower pain-expectancy for the trajectory most similar to the pain-associated trajectories.

Figure 5.5

Acquisition and generalization of pain-related fear



Note. Observed average ratings, estimated marginal means and 95% confidence intervals of pain-related fear are displayed for each trajectory (T/G1-3) during the acquisition and generalization blocks, separately for the positive affect, neutral, and yoked neutral groups.

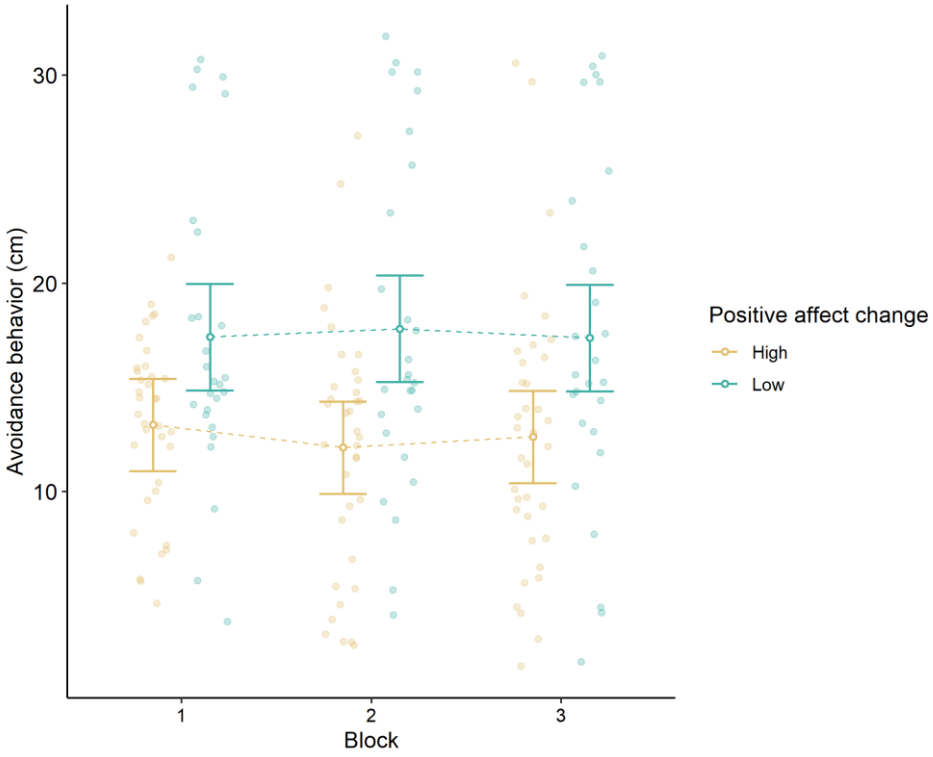
Similarly, the analysis of *pain-related fear ratings* showed no significant interaction between Group and Trajectory (Figure 5.5), $F(2, 506) = 0.33$, $p = .722$, $\eta_p^2 < 0.01$. When using Positive affect change as predictor, the two-way interaction again reached significance, $F(2, 498) = 5.39$, $p = .005$, $\eta_p^2 = 0.02$. Visualization of this interaction – using a median split for changes in positive affect – suggests a pattern similar to pain-expectancy ratings, with higher increases in positive affect associated mainly

with lower ratings for trajectory G1, although the pairwise comparison did not reach significance (G1: $t(84.90) = -1.90$, $p = .060$, $d = -0.20$; G2: $t(84.90) = -1.09$, $p = .278$, $d = 0.01$; G3: $t(84.90) = 0.55$, $p = .586$, $d = 0.11$; Figure 5.7, lower panel).

Note that we used dummy coding for the generalization trajectories instead of the preregistered linear trend variable to model pain-expectancy and pain-related fear. This decision was made because ratings for trajectories – per block – did not follow a linear trend (Figures 5.4, 5.5). However, both models resulted in the same conclusions and performed similarly in terms of explained variance (pain-expectancy: 53.02% with dummy coding, 50.69 % with linear trend variable; pain-related fear: 61.44% with dummy coding, 59.07 % with linear trend variable). See Appendix D for the results when using the linear trend variable.

Figure 5.6

Association between change in positive affect and generalization of pain-related avoidance behavior



Note. Observed average maximal deviations, estimated marginal means and 95% confidence intervals of avoidance behavior are displayed for participants showing high versus low increases in positive affect (median split) during generalization blocks.

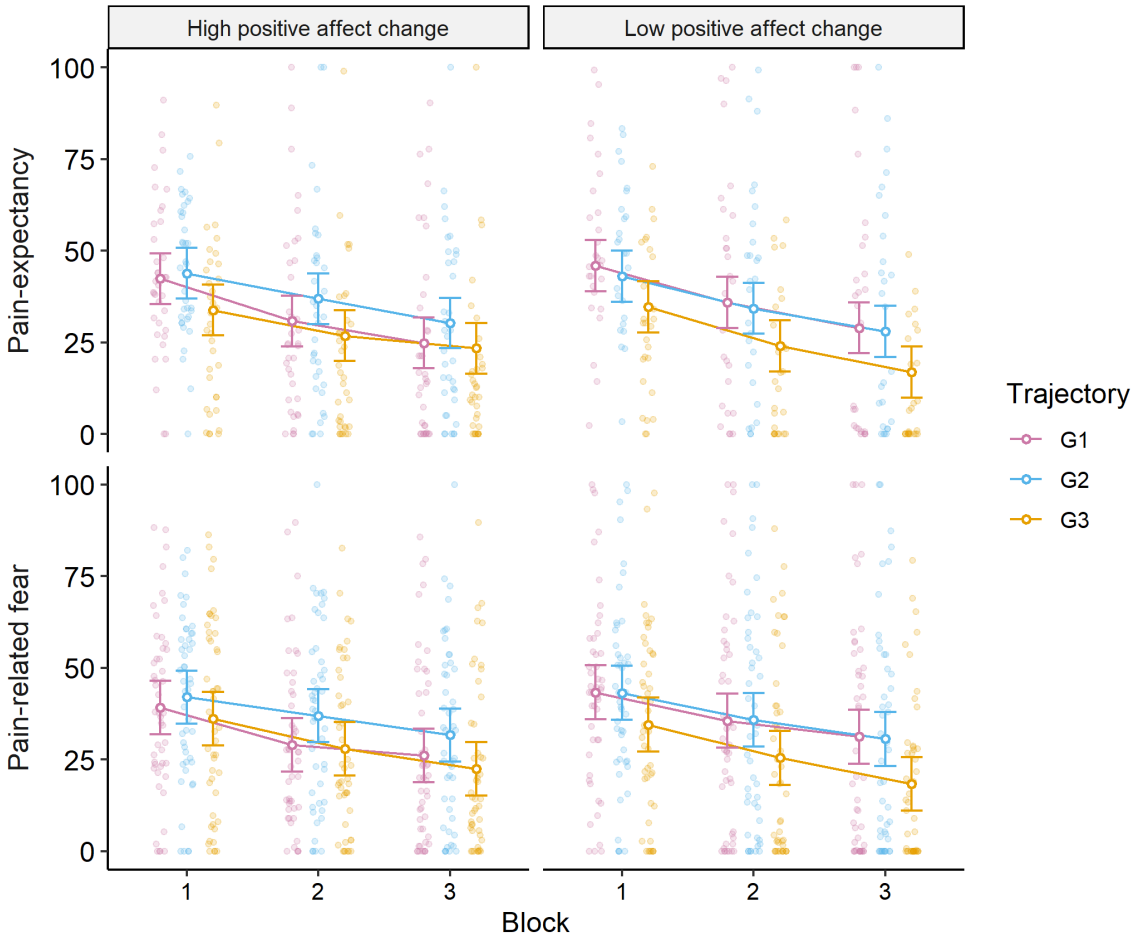
Hypothesis 3: Replication of generalization of pain-related avoidance

Contrary to our expectations, the analysis of avoidance behavior in the neutral and yoked neutral groups during the generalization test showed no significant main effect of Group, $F(1, 62) =$

3.92, p = .052, η_p^2 = 0.06 (Figure 5.3). These results indicate a lack of generalization of pain-related avoidance. The Group by Block interaction also did not reach significance, $F(2, 124) = 1.74$, p = .179, η_p^2 = 0.03.

Figure 5.7

Associations between change in positive affect and generalization of pain-expectancy and pain-related fear



Note. Observed average ratings, estimated marginal means and 95% confidence intervals of pain-expectancy and pain-related fear ratings are displayed for each trajectory (T/G1-3) during the generalization blocks separately for participants demonstrating high versus low increases in positive affect (median split).

Hypothesis 4: Replication of generalization of pain-expectancy and pain-related fear

The analysis of *pain-expectancy ratings* in the neutral and yoked neutral groups during the generalization test resulted in no significant three-way interaction between Group, Block and Trajectory, $F(4, 496) = 0.12$, p = .977, η_p^2 < 0.01. However, as expected, the two-way interaction

between Group and Trajectory reached significance, $F(2, 496) = 17.94$, $p < .001$, $\eta_p^2 = 0.07$, indicating that the neutral and yoked neutral groups exhibited different rating patterns (Figure 5.4). Further analysis of this interaction showed that the neutral group expected the pain stimulus significantly more for trajectory G1 than G3, $t(496) = 5.38$, $p < .001$, $d = 0.50$, thus confirming generalization of pain-expectancy. In the yoked neutral group there was no significant difference between these trajectories, $t(496) = -1.89$, $p = .178$, $d = -0.19$; ratings were indeed statistically equivalent in the first generalization block (p-values for upper and lower bounds < .05), but not in blocks 2 and 3. However, ratings for G1 were lower compared to G3 in these later blocks, which is opposite of the experimental contingencies in the neutral group (Figure 5.4; lower bounds: block two, $t(31) = 1.35$, $p = .094$, and block three, $t(31) = 0.17$, $p = .432$).

Similarly, analysis of *pain-related fear ratings* showed no significant three-way interaction, $F(4, 496) = 0.78$, $p = .539$, $\eta_p^2 < 0.01$, but the interaction between Group and Trajectory did reach significance as expected, $F(2, 496) = 16.36$, $p < .001$, $\eta_p^2 = 0.06$. The neutral group again showed significantly higher ratings for G1 compared to G3 (Figure 5.5), $t(496) = 4.73$, $p < .001$, $d = 0.41$, whereas the yoked neutral group showed no significant difference, $t(496) = -1.93$, $p = .161$, $d = -0.19$. Ratings between these trajectories were statistically equivalent in the first generalization block in the yoked neutral group (p-values for upper and lower bounds < .05), while ratings for G1 were lower compared to G3 in later blocks (Figure 5.5; lower bounds: block two, $t(31) = 0.93$, $p = .179$, and block three, $t(31) = 0.31$, $p = .380$).

Exploratory analyses

Avoidance, pain-expectancy, and pain-related fear during reminder-of-acquisition

Analysis of avoidance during the reminder-of-acquisition blocks showed that participants in the positive affect and neutral groups continued to avoid more compared to the yoked neutral group. Furthermore, both the positive affect and neutral groups continued to give higher fear/expectancy ratings for T1 compared to T3; as expected, the yoked neutral group did not show this pattern. There were no differences between the positive affect and neutral groups regarding neither avoidance nor self-reports. See Appendix D for a detailed description of the results.

Negative affect

Analysis of state negative affect showed no differences between groups; however, there was an unexpected decrease in negative affect in all groups from pre- to post-visualization. See Appendix D for a full description.

Associations between avoidance/ratings and positive affect change at the start of the generalization test

To investigate whether higher increases in positive affect were already associated with less avoidance and/or lower ratings at the start of the generalization test, we analyzed these associations using only the first part of the first generalization block using simple linear regression models (i.e., means for trials 1-6 of generalization block 1). These analyses included the positive affect and neutral groups, and expectancy/fear ratings for trajectory G1. Analysis of avoidance showed a significant association with positive affect change, $F(1, 61) = 4.54$, $p = .037$, $\eta_p^2 = 0.07$; higher increases in positive affect were already associated with less avoidance (β = -0.21). Pain-expectancy ratings on the other hand were not significantly associated with positive affect change, $F(1, 61) = 0.12$, $p = .731$, $\eta_p^2 < 0.01$. Similarly, pain-related fear ratings showed no significant association with positive affect change, $F(1, 61) = 1.09$, $p = .301$, $\eta_p^2 = 0.02$. These results indicate that higher increases in positive affect were initially associated with less avoidance, but not yet with lower ratings.

Discussion

Excessive generalization of pain-related avoidance is considered to play a crucial role in chronic pain disability (Meulders, 2019). This makes investigation of potential pathways to reduce such overgeneralization imperative. Positive affect is a promising target in pain treatment and experimental research showed that induced positive affect is associated with less generalization of *pain-related fear* (Geschwind et al., 2015). However, as there is no one-to-one relationship between fear and avoidance, an important open question is whether positive affect has the potential to mitigate overgeneralization of *pain-related avoidance*. Therefore, the current study investigated whether experimentally induced positive affect leads to less generalization of (1) pain-related avoidance behavior, and (2) self-reported pain-expectancy and pain-related fear in pain-free participants. Additionally, we aimed to replicate the findings of Glogan et al. (2021) that (3) pain-related avoidance, and (4) pain-expectancy and pain-related fear generalize to novel movements (Glogan et al., 2021).

Our *first hypothesis* was partially supported; the positive affect group did not show reduced generalization of pain-related avoidance compared to the neutral group, but higher increases in positive affect were associated with less avoidance generalization across groups. This novel finding was in line with our expectations, and indicates that positive affect indeed has the potential to attenuate the spreading of pain-related avoidance toward safe activities. Our *second hypothesis* was not supported; results showed no reduction in generalization of pain-expectancy and pain-related fear ratings in the positive affect group compared to the neutral group. However, higher increases in

positive affect were associated with less generalization of these ratings across groups, albeit not according to the expected pattern. In line with results from Geschwind et al. (2015), we expected induced positive affect to preserve adaptive generalization toward movements similar to the pain-associated movements, but reduce overgeneralization toward movements similar to the safe movement. However, in the current study, increased positive affect was associated with decreased generalization of pain-expectancy and pain-related fear toward the movement most similar to the pain-associated movements. This finding may be due to an important methodological difference between the two studies. In the current paradigm, participants always chose which movements to perform and thus decided whether to avoid or not. The paradigm used by Geschwind et al. (2015) did not allow such decisions: all movements were instructed after the positive affect induction. A reduction in avoidance may have led to extinction of generalized pain-expectancy and pain-related fear in the current study, thus resulting in lower ratings for the trajectory most similar to the pain-associated trajectories. This interpretation is supported by exploratory analyses, which showed that increases in positive affect were associated with less avoidance early in the generalization test, but showed no association with pain-expectancy and pain-related fear – for the movement most similar to the pain-associated movements – at this point. In other words, participants with larger increases in positive affect after the visualization exercise initially showed less avoidance generalization, but not less generalization of expectancy/fear. This finding is in line with the idea that positive affect increases willingness to approach fear associated stimuli (Zbozinek & Craske, 2017).

In addition to investigating the effects of positive affect induction on generalization, the current study aimed to replicate the findings by Glogan et al. (2021). Surprisingly, our *third hypothesis* was not supported: although there was a trend in the expected direction, the neutral group did not show significantly more avoidance behavior during the generalization test compared to the yoked neutral group. This means that we did not replicate the finding from Glogan et al. (2021) that costly pain-related avoidance generalizes in pain-free participants. Our result is also not in line with work from the anxiety field showing generalization of avoidance (San Martín et al., 2020), even when avoidance is costly (van Meurs et al., 2014). However, it should be noted that previous versions of the current paradigm – using a higher chance to receive the painful stimulus when performing the pain-associated trajectories – also did not show generalization of avoidance (Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., 2021). This indicates a need to further investigate the boundary conditions under which generalization of pain-related avoidance behavior can be observed. In the current study, the typical day exercise may have caused some participants to show an unintended increase in positive affect (although statistical testing did not show significant increases, the neutral and yoked neutral groups did show a trend toward increased positive affect). Such increases may have bolstered

exploration of the less effortful movements. Finally, our *fourth hypothesis* was supported; pain-expectancy and pain-related fear ratings generalized toward movements similar to the original pain-associated movement in the neutral group, corroborating the findings by Glogan et al. (2021). These results are also in line with previous work using variations of the current paradigm (Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., 2021).

Some limitations should be considered when interpreting our results. *First*, in line with Geschwind et al. (2015), we analyzed associations between increases in positive affect and generalization across groups. However, the causal inferences we can make based on this approach are limited, as these analyses are not based on the experimental groups. In other words, other factors such as psychological traits may have influenced both generalization and changes in state positive affect. *Second*, we powered this study to replicate generalization of costly pain-related avoidance (Glogan et al., 2021). Therefore, it may have been underpowered to detect effects of the positive affect manipulation on a group level. *Third*, a general decrease in negative affect was observed from pre- to post-visualization across groups – i.e., regardless of performing the best possible self or typical day exercise. This unintended change may have affected the current results as previous research for example showed a positive association between state anxiety and avoidance (van Meurs et al., 2014). *Fourth*, next to decreased negative affect, performing the typical day exercise may have caused some participants to show an unintended increase in positive affect. Therefore, future research may benefit from reconsidering the typical day visualization as a control exercise.

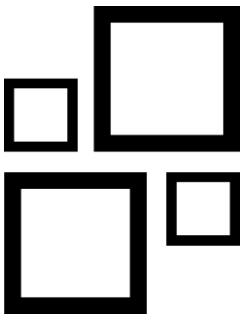
Despite these limitations, the current results have important implications. Contemporary fear-avoidance models of chronic pain emphasize excessive pain-related avoidance as playing a crucial role in the development and maintenance of chronic pain disability (Meulders, 2019; Vlaeyen et al., 2016; Vlaeyen & Linton, 2012). Avoiding a pain-associated activity is highly adaptive in acute pain, because it prevents bodily harm. For example, when intense pain is experienced while lifting a heavy box with a bent back, not repeating this activity can prevent (exacerbating an) injury. Subsequently generalizing avoidance to similar activities is highly adaptive, because it helps to avoid other potentially harmful activities, without the need to learn about each activity separately. However, when pain-related avoidance spreads toward a range of safe activities, it can lead to disproportional withdrawal from valued life activities such as participating in social events. For example, avoiding all activities that require slightly bending the back after experiencing pain while lifting a heavy object can quickly become debilitating. Such excessive pain-related avoidance may culminate into functional disability (Vlaeyen et al., 2016). Therefore, it is crucial to study ways to attenuate generalization of pain-related avoidance. The current results contribute to a growing literature showing evidence for the potential of positive affect in treatment of chronic pain disability (Finan & Garland, 2015; Hanssen et al., 2017).

Positive psychology interventions – such as the best possible self exercise – indeed may be particularly relevant for people with chronic pain (Molinari et al., 2018; Molinari et al., 2020), as studies show that positive affect can be depleted during episodes of pain and stress in this population (Zautra, Fasman, et al., 2005). However, the current results require replication – also on group level. Furthermore, it remains to be investigated whether experimentally inducing positive affect has the potential to reduce overgeneralization of pain-related avoidance in participants with chronic pain. Such investigations will be beneficial to inform and optimize existing therapies.

In conclusion, the current study is the first to report an association between experimentally induced positive affect and generalization of avoidance behavior: higher increases in positive affect were associated with less generalization. Although further investigation is required, these results point toward the potential of positive affect interventions in attenuating maladaptive spreading of pain-related avoidance behavior to safe activities.

Chapter 6

Positive affect and generalization of pain-related avoidance and relief



This chapter has been submitted as Vandael, K., Meulders, A., Peters, M., & Vervliet, B. The effect of experimentally induced positive affect on the generalization of pain-related avoidance and relief.

Abstract

Avoiding pain-associated activities can prevent tissue damage. However, when avoidance spreads excessively (or overgeneralizes) to safe activities, it may culminate into chronic pain disability. Gaining insight into ways to reduce overgeneralization is therefore crucial. An important factor to consider in this is relief, as it reinforces avoidance behavior and therefore may be pivotal in making avoidance persist. The current study investigated whether experimentally induced positive affect can reduce generalization of pain-related avoidance and relief. We used a conditioning task in which participants (*N* = 50) learned that certain stimuli were followed by pain, while another was not. Subsequently, they learned an avoidance response that effectively omitted pain with one stimulus, but was ineffective with another. Next, one group of participants performed an exercise to induce positive affect, while another group performed a control exercise. During the critical generalization test, novel stimuli that were perceptually similar to the original stimuli were presented. Results showed that both avoidance and relief generalized to novel stimuli, thus replicating previous work. However, increasing positive affect did not reduce generalization.

Introduction

Avoiding pain-associated activities is adaptive because it can prevent harm to the body. For example, when intense pain is experienced while lifting a child with a bent back, not repeating this activity may prevent (exacerbating an) injury. Avoidance behavior may then spread toward perceptually similar activities, such as bending the back during yoga class (avoidance generalization; Glogan et al., 2021). This again is adaptive because a protective behavior is applied to similar activities, without needing to learn about each activity separately. However, when applied to safe activities, it may cause increased withdrawal from harmless valued activities, such as playing sports with friends. Contemporary fear-avoidance models consider such *overgeneralization* of avoidance behavior to play a key role in the development and maintenance of chronic pain disability (Meulders, 2019; Vlaeyen et al., 2016; Vlaeyen & Linton, 2012).

Conditioning paradigms are commonly used to model the generalization of avoidance behavior in the lab (e.g., van Meurs et al., 2014). Such paradigms often start with a Pavlovian fear conditioning phase in which a certain stimulus (e.g., an image; conditional threat stimulus; CS+) is paired with an aversive event (unconditional stimulus; US), while another stimulus is not (conditional safe stimulus; CS-). To model acute pain, a painful electrical stimulus is commonly used as US (e.g., Meulders et al., 2011). Because of its previous pairing with the US, the CS+ will start eliciting conditional responses, such as fear. After fear conditioning, participants learn that a certain behavior leads to the non-occurrence of the US (e.g., button press; avoidance conditioning). Novel stimuli, which are never paired with the US, are then introduced to test whether avoidance behavior generalizes to these stimuli (generalization stimuli; GSs; San Martín et al., 2020; van Meurs et al., 2014). Typically, generalization gradients are observed during such tests: the frequency of avoidance toward the GSs increases with their similarity to the CS+.

Due to the central role of avoidance in the trajectory towards chronic pain disability, an important question is how to buffer against excessive generalization of acquired avoidance behavior. Fear-avoidance models acknowledge the role of negative affect as a vulnerability factor in the development and maintenance of chronic pain disability, however, the importance of positive affect has been emphasized as well (Finan & Garland, 2015; Hanssen et al., 2017). Evidence suggests that positive affect facilitates learning that certain stimuli are safe (Zbozinek & Craske, 2017); this may in turn inhibit fear from spreading to novel safe stimuli. Geschwind et al. (2015) provided empirical evidence that increasing positive affect may indeed mitigate overgeneralization. After a fear conditioning procedure, one group of participants performed a visualization exercise to experimentally induce positive affect, while a second group performed a control exercise that did not change affect. Results from the subsequent generalization test showed that higher increases in

positive affect were associated with less generalization of fear and US-expectancy toward GSs similar to the CS-, while it preserved generalization toward GSs similar to the CS+. Moreover, as there is no one-to-one relationship between fear and avoidance (Meulders, 2019; Pittig, Wong, et al., 2020), Vandael et al. (under revision) investigated whether experimentally induced positive affect can attenuate generalization of pain-related avoidance specifically; results confirmed that higher increases in positive affect were indeed associated with less avoidance generalization.

An important question is via which mechanisms generalized avoidance is maintained, as avoidance is not merely a product of fear; for example, avoidance behavior can persist despite fear extinction (Vervliet & Indekeu, 2015). Therefore, research is needed on the reinforcing mechanisms of avoidance behavior, as these may be key in avoidance turning maladaptive (Krypotos et al., 2015). An important factor to consider is the relief experienced when avoiding: the positive feeling in reaction to the absence of an anticipated negative event (Vervliet et al., 2017). Vulnerable individuals may show more avoidance because they enjoy more relief. This implies that whether generalized avoidance is maintained depends on the extent to which relief generalizes. San Martín et al. (2020) provided empirical evidence that relief indeed generalizes following avoidance conditioning.

The aims of this study where two-fold: we aimed to (1) replicate that experimentally inducing positive affect attenuates generalization of avoidance (Vandael et al., under revision), and (2) investigate whether induced positive affect also attenuates relief generalization. To this end, we used the conditioning procedure by San Martín et al. (2020); one group of participants performed a visualization exercise to induce positive affect before the generalization test (positive affect group), while another group performed a control visualization exercise (control group; Geschwind et al., 2015). As in standard generalization protocols, the procedure by San Martín et al. (2020) allows investigating generalization toward GSs over a threat-safety dimension, with a GS similar to the CS+ and one similar to the CS-. We hypothesized (1) reduced generalization of avoidance behavior along this dimension toward the stimulus perceptually similar to the CS- in the positive affect group, thus resulting in a steeper generalization gradient compared to the control group. Similarly, we hypothesized (2) reduced generalization of self-reported relief pleasantness toward the stimulus perceptually similar to the CS- in the positive affect group compared to the control group, as relief is modulated by threat expectancy (San Martín et al., 2020). Additionally, the procedure by San Martín et al. (2020) allows exploration of generalization over a dimension of avoidability; next to the stimulus where the avoidance response is effective (i.e., leads to omission of US; avoidable CS+), it also includes a stimulus where the avoidance response is ineffective (i.e., no omission of US; unavoidable CS+), and GSs similar to this stimulus. This allows disentangling generalization of the CS-US and response-omission associations.

Methods

Ethical approval and preregistration

The Social and Societal Ethics Committee of the KU Leuven approved the experimental protocol (registration number: G-2020-2757). All participants read an information sheet, completed an exclusion criteria checklist, and provided written informed consent before starting the experiment. Additional safety measures were used according to institutional guidelines due to the COVID-19 pandemic (e.g., both participant and experimenter wore a facemask). The experimental protocol and analyses were registered prior to conducting the research at Open Science Framework (https://osf.io/qh5v3/?view_only=7517fe8927c241f3b627477131f69687).

Participants

A registered a priori power analysis using G*Power (Faul et al., 2007) indicated that a sample size of 50 participants (25 per group) would allow detection of a within-between interaction with effect size f = 0.17 when applying a repeated measures (RM) analysis of variance (ANOVA; alpha = .05; power = .80; 2 groups; 4 measurements; 0.50 correlation among repeated measurements; nonsphericity correction epsilon 1). This analysis pertains to our hypothesis on avoidance behavior, where we expected an interaction between factors Group and Stimulus on the threat-safety dimension. We recruited 50 participants [7 men, 43 women; $M \pm SD$ (range) age = 21 ± 4 years (18-40)] using the online Experiment Management System (Sona Systems Ltd., Tallinn, Estonia) of the Faculty of Psychology and Educational Sciences of KU Leuven, as well as advertisements distributed around the university campus and through social media. Participants received either 1.75 course credit or 14 EUR as compensation. Exclusion criteria consisted of the presence of: chronic pain, pain or any other condition at hands or wrists, pregnancy, any cardiovascular condition, any respiratory condition, any neurological condition (e.g., epilepsy), an electronic implant (e.g., cardiac pacemaker), any current and past psychiatric disorder (e.g., clinical depression), any other serious medical condition, or physician's advice to avoid stressful situations.

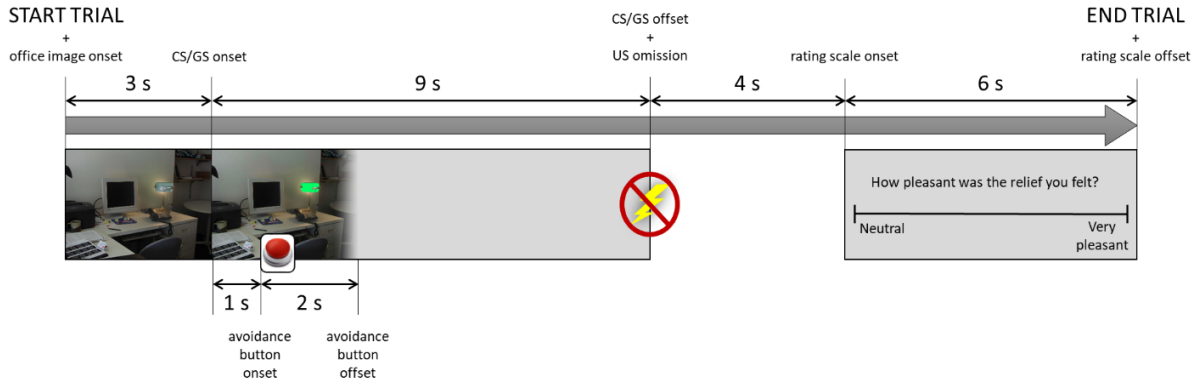
Apparatus and experimental stimuli

The US was a 2 ms square-wave electrical stimulus delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, UK) through two reusable stainless steel disk electrodes (8 mm diameter with 30 mm spacing; Digitimer, Welwyn Garden City, UK). The electrodes were filled with K-Y gel (Reckitt Benckiser, Slough, UK) and placed on top of the non-dominant forearm, approximately 50 mm below the wrist. The physical intensity of the stimulus was calibrated individually to be painful and demanding some effort to tolerate.

Three CSs were used, which consisted of images of a lamp with varying colors (green, yellow or red) presented within an image of an office (Figure 6.1). The four GSs consisted of intermediate lamp colors: two between green and yellow, and two between yellow and red. These CSs and GSs were identical to the study by San Martín et al. (2020). All pictures were presented on a computer screen, positioned at eye level at approximately 500 mm distance, using Affect 4.0 (Spruyt et al., 2010). The avoidance response was operationalized as mouse clicking on an image of a red button presented in the upper left corner of the office image (the avoidance button; Figure 6.1).

Figure 6.1

Example of trial flow including timings



Note. CS = conditional stimulus; GS = generalization stimulus; US = unconditional stimulus. The avoidance button was presented on each trial during avoidance conditioning and the generalization test, never during fear conditioning. The US was not presented on CS- trials, GS trials, and when the avoidance response was emitted on avoidable CS+ trials. US presentation occurred on all other trials, meaning on unavoidable CS+ trials and when the avoidance response was not emitted on avoidable CS+ trials. The relief pleasantness rating scale was presented on all trials on which the US was not presented.

A Coulbourn Instruments skin conductance coupler (model V71- 23, Holliston, MA, USA) was employed to measure skin conductance levels. The coupler applied a constant voltage of 0.5 V across a pair of disposable electrodes (11 mm diameter; EL507; Biopac Systems, Inc., Goleta, CA, USA) placed approximately 10 mm apart on the palm of the non-dominant hand. A Labmaster DMA 12-bit analog-to-digital converter (Scientific Solutions, Solon, OH, USA) digitized the recorded signal at 10 Hz.

Procedure

Trait questionnaires and US calibration

Participants first completed a number of trait questionnaires. Next, electrodes for delivering the US and measuring skin conductance levels were attached. A standard protocol was used to calibrate the intensity of the US individually (Meulders et al., 2011). Participants received a series of electrical stimuli of increasing intensity – starting at 1.00 mA – and rated each stimulus on a numerical scale ranging from 0-10; with 0 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*", 3 as "*the stimulus starts being painful*" and 10 as "*this is the worst pain I can imagine*". Participants were asked to select a stimulus that was "*painful and demanding some effort to tolerate*", corresponding to a 7 or 8 on the numerical scale.

Fear conditioning

The conditioning task was identical to the one used by San Martín et al. (2020). On each trial of the fear conditioning phase, the office space image was presented first, followed by a CS (i.e., one of three lamp colors). Note that there were two types of CS+: an avoidable CS+ and an unavoidable CS+. In the current phase, both were always followed by the US, meaning they were functionally equivalent during this phase. The CS- was never followed by the US. The red and green lamp colors were counterbalanced as CS- and unavoidable CS+ between participants, while the yellow lamp color always served as avoidable CS+. Participants were not informed of contingencies between CSs and the US, and provided relief pleasantness ratings at the end of the trial each time no US was presented (i.e., on all CS- trials). Note that one trial with only the image of an office space – without CS or US – was presented before the start of fear conditioning, which allowed participants to practice using the relief pleasantness rating scale. The next trial started after an inter-trial interval of 5 s on average (range: 3-7 s). Table 6.1 provides an overview of the number of trials per phase. At the end of the fear conditioning phase, participants provided retrospective US-expectancy ratings for each CS.

Avoidance conditioning

Trials during this phase were the same as during fear conditioning, with one crucial difference: the avoidance button was presented on all trials. This meant that the US again always followed the unavoidable CS+ and never the CS-; however, during this phase the US only followed the avoidable CS+ in case no avoidance response was emitted. In other words, clicking the avoidance button always cancelled US presentation on avoidable CS+ trials. Participants were informed that clicking the avoidance button may or may not cancel the US and they provided relief pleasantness ratings when no US was presented, meaning on avoidable CS+ trials on which the avoidance response was emitted and all CS- trials.

Table 6.1

Design of the conditioning task

Fear conditioning[a]	**Avoidance conditioning**[b]	**Generalization test**[b]
2 blocks of 8 trials	**2 blocks of 12 trials**	**3 blocks of 7 trials**
2 x 4 (un)avoidable CS+*	2 x 4 avoidable CS+	3 x 1 avoidable CS+
2 x 4 CS-	2 x 4 unavoidable CS+	3 x 1 unavoidable CS+
	2 x 4 CS-	3 x 1 CS-
		3 x 4 GS

Note. CS = conditional stimulus; GS = generalization stimulus. The vertical double line between avoidance conditioning and the generalization test indicates the break during which the visualization exercise was performed. The order of trials was semi-randomized within each block with no more than two consecutive presentations of the same stimulus. [a]Avoidance response unavailable; [b]Avoidance response available; *Order of blocks counterbalanced with either only the avoidable or unavoidable CS+ in the first block.

Visualization exercise

The experimenter removed US electrodes at the start of this phase and participants completed a questionnaire assessing positive affect (pre-visualization measurement). Participants were randomly assigned to either the positive affect or control group (based on the order in which they arrived in the lab using a pre-defined randomization list). Participants in the positive affect group performed the best possible self visualization exercise (Peters et al., 2010); they were verbally instructed to think about (1 min), write about (15 min) and visualize (5 min) a future in which everything went well and in which they realized their dreams. In the control group, equivalent instructions to think, write about, and visualize a typical day were used (Typical Day exercise; see Appendix E for verbatim instructions). A second affect measurement was completed at the end of this phase (post-visualization).

Generalization test and post-experimental questionnaire

First, the experimenter reattached US electrodes. Trials during this phase were the same as during avoidance conditioning, but now included the four GSs as well. These novel stimuli were always accompanied by the avoidance button – as were the CSs again – but were never followed by the US. Note that on the threat-safety dimension (i.e., CS-, GS1, GS2, avoidable CS+), GS1 was perceptually most similar to the CS- and GS2 was similar to the avoidable CS+; on the dimension of avoidability (i.e., avoidable CS+, GS3, GS4, unavoidable CS+), GS3 was similar to the avoidable CS+ and GS4 was similar to the unavoidable CS+. Contingencies between CSs and the US remained the same as during previous

phases and the avoidance response remained effective on avoidable CS+ trials. Participants were again not informed of contingencies and provided relief pleasantness ratings when no US was presented, meaning on all CS- trials, all GS trials, and avoidable CS+ trials on which the avoidance response was emitted. Participants completed a third affect measurement (post-generalization) as well as a post-experimental questionnaire at the end of this phase.

Outcome measures

Avoidance behavior

As a measure of avoidance behavior, the proportion of trials on which an avoidance response was emitted was calculated per CS and GS (generalization phase only). Proportions were calculated per phase, except for the avoidance conditioning phase where they were calculated per block.

Relief pleasantness

On every trial where no US was presented, participants rated the pleasantness of the experienced relief using a visual analogue scale ranging from "*neutral*" to "*very pleasant*". Ratings were averaged per CS and GS (generalization phase only). Averages were calculated per phase, except for the avoidance conditioning phase where they were calculated per block.

Positive affect

The Positive Affect subscale of the Positive and Negative Affect Schedule was used to assess state positive affect (Watson et al., 1988). This subscale consists of 10 adjectives describing positive emotions. Participants rated the extent to which they experienced each emotion in the current moment on a 5-point Likert scale ranging from "*very little*" to "*very much*".

Trait questionnaires and secondary outcome measures

Trait questionnaires, state negative affect, stimulus-elicited skin conductance responses (SCRs), omission-elicited SCRs, retrospective US-expectancy ratings and post-experimental questions are described in Appendix E.

Data analysis

RM ANOVAs were run as manipulation checks on positive affect, and on avoidance behavior and relief pleasantness during avoidance conditioning. A Group factor (Positive affect, Control) was added to the analyses on avoidance and relief to check for pre-visualization group differences. Our main hypotheses were tested using RM ANOVAs on avoidance behavior and relief pleasantness during the generalization test. The analysis of avoidance was run on the threat-safety dimension, meaning that it included the CS-, avoidable CS+ and their intermediate GSs: GS1 and GS2; see Appendix E for an exploratory analysis on the dimension of avoidability. The analysis of relief pleasantness included

all stimuli on which relief ratings were provided (i.e., excluding the unavoidable CS+). Furthermore, we tested for the presence of linear and quadratic trends to check whether a generalization gradient was present. Interaction effects and trends were further explored using pairwise comparisons. Given that we were interested in the relief consequences of avoidance, an additional RM ANOVA was conducted on relief pleasantness during generalization that only included trials on which the avoidance response was emitted. For this particular analysis, average relief ratings were calculated over the two adjacent GSs (GS1+2 and GS3+4) to compensate for the anticipated reduction in number of data points, while the CS- was excluded from this analysis because a low level of avoidance to this stimulus was expected. As preregistered, responder analyses were conducted in case of non-significant interaction effects with Group during the generalization test, which used change in positive affect instead of the Group factor. In other words, these analyses used the difference in positive affect between post- and pre-visualization as (continuous) covariate, as this increases statistical power [see Geschwind et al. (2015) for a similar approach]. Sample characteristics and analyses of secondary outcome measures are described and reported in Appendix E.

For all analyses, the family-wise α-level was set at .05. Greenhouser-Geisser corrections were applied for RM ANOVA effects when Mauchly's test of sphericity was significant, and corrected degrees of freedom are reported together with epsilon values. Holm-Bonferroni corrections were applied to correct for multiple testing. The indication of effect size partial eta squared (η_p^2) is reported for *F*-tests, and Cohen's *d* for *t*-tests. Raw data files were processed using custom-made MATLAB scripts (The MathWorks Inc., Natick, MA, USA) and statistical analyses were performed using jamovi 1.6.23 (*jamovi*, 2021).

Results

Manipulation checks

Fear conditioning

The stimulus-elicited SCRs and retrospective US-expectancy ratings both confirmed successful fear acquisition. See Appendix E for a detailed description of the results.

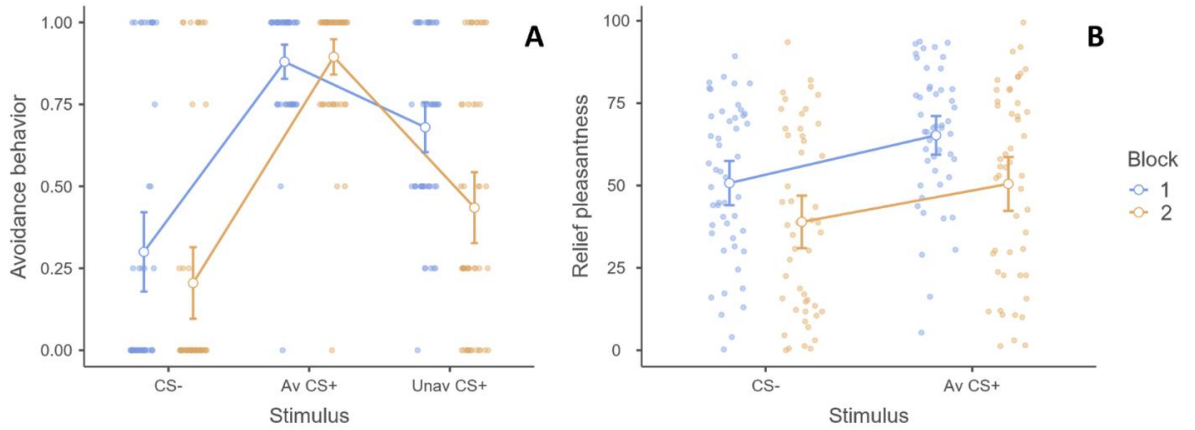
Avoidance conditioning

A 3 (Stimulus: CS-, avoidable CS+, unavoidable CS+) x 2 (Block: 1-2) RM ANOVA on *avoidance behavior* during avoidance conditioning showed significant main effects of Stimulus, $F(2, 98) = 76.06$, $p < .001$, $\eta_p^2 = 0.61$, and Block, $F(1, 49) = 32.22$, $p < .001$, $\eta_p^2 = 0.40$. The interaction between both factors was significant as well, indicating that avoidance toward the different stimuli evolved differently across blocks (Figure 6.2, panel A), $F(2, 98) = 18.36$, $p < .001$, $\eta_p^2 = 0.27$. Pairwise comparisons showed that avoidance significantly decreased between blocks for the CS-, $t(49) = -2.91$,

p = .016, *d* = -0.23, and unavoidable CS+ , *t*(49) = -6.54, *p* < .001, *d* = -0.74, but not for the avoidable CS+, *t*(49) = .68, *p* = .497, *d* = 0.11. In block 2 of avoidance conditioning, the avoidable CS+ was avoided significantly more than both the CS-, *t*(49) = 11.19, *p* < .001, *d* = 2.28, and unavoidable CS+, *t*(49) = 7.52, *p* < .001, *d* = 1.53, indicating successful avoidance conditioning. When Group was added to these analyses as a factor to check for pre-visualization differences between groups, no significant main or interaction effects of this factor were observed, confirming that avoidance patterns did not significantly differ between groups at this stage.

Figure 6.2

Avoidance behavior and relief pleasantness during avoidance conditioning



Note. Observed proportions/averages, estimated marginal means and 95% confidence intervals of avoidance behavior (panel A) and relief pleasantness (panel B) during both blocks of the avoidance conditioning phase. CS = conditional stimulus; Av = avoidable; Unav = unavoidable.

A 2 (Stimulus: CS-, Avoidable CS+) x 2 (Block: 1-2) RM ANOVA run on *relief pleasantness* during avoidance conditioning showed significant main effects of both Stimulus, *F*(1, 48) = 63.01, *p* < .001, η_p^2 = 0.57, and Block, *F*(1, 48) = 35.20, *p* < .001, η_p^2 = 0.42, and no significant interaction effect, *F*(1, 48) = 1.79, *p* = .188, η_p^2 = 0.04. As expected, these results indicate higher relief ratings for the avoidable CS+ compared to the CS- (Figure 6.2, panel B), and a general decrease in relief ratings over blocks while differential ratings were maintained. However, adding the Group factor showed a significant three-way interaction between Stimulus, Block and Group, *F*(1, 47) = 4.51, *p* = .039, η_p^2 = 0.09. This indicates a difference in relief patterns between groups before the visualization exercise. Further investigation of this interaction showed no significant Group effects in the first block, but a significant main effect of Group in the second block, with overall higher relief pleasantness in the positive affect group compared to the control group, *F*(1, 47) = 7.91, *p* = .029, η_p^2 = .14.

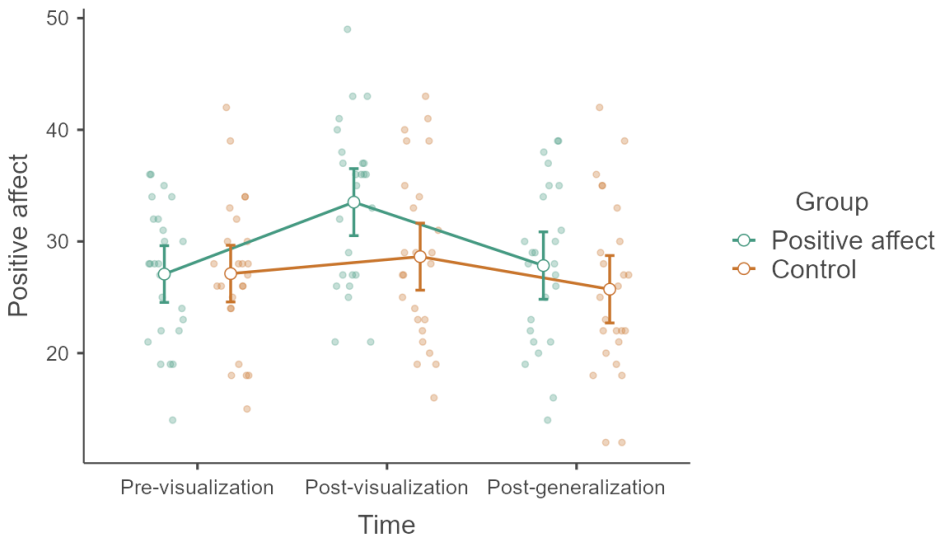
Successful avoidance conditioning was also reflected in stimulus-elicited SCRs, omission-elicited SCRs and retrospective US-expectancy ratings; see Appendix E for a detailed description of the results.

Positive affect

A 3 (Time: pre-visualization, post-visualization, post-generalization) x 2 (Group: Positive affect, Control) RM ANOVA run on state positive affect showed a significant main effect of Time, $F(2, 96) = 20.25$, $p < .001$, $\eta_p^2 = .30$, but not of Group, $F(1, 48) = 1.63$, $p = .207$, $\eta_p^2 = 0.03$. As expected, the interaction effect was significant, indicating that positive affect evolved differently for both groups (Figure 6.3), $F(2, 96) = 5.37$, $p = .006$, $\eta_p^2 = .10$. Pairwise comparisons showed a significant increase in positive affect from pre-visualization ($M = 27.08$, $SD = 6.08$) to post-visualization ($M = 33.52$, $SD = 7.22$) in the positive affect group, $t(48) = 5.74$, $p < .001$, $d = 0.96$. Moreover, post-visualization there was a significant difference between the positive affect and control ($M = 28.64$, $SD = 7.70$) groups, $t(48) = 2.31$, $p = .025$, $d = 0.66$. These results confirm that the positive affect manipulation was successful. Further exploration showed that the difference between groups was no longer significant post-generalization, $t(48) = 1.00$, $p = 1.00$, $d = 0.28$.

Figure 6.3

Positive affect



Note. Observed scores, estimated marginal means and 95% confidence intervals of state positive affect before and after performing the visualization exercise (pre- and post-visualization) and after performing the generalization test of the conditioning task (post-generalization).

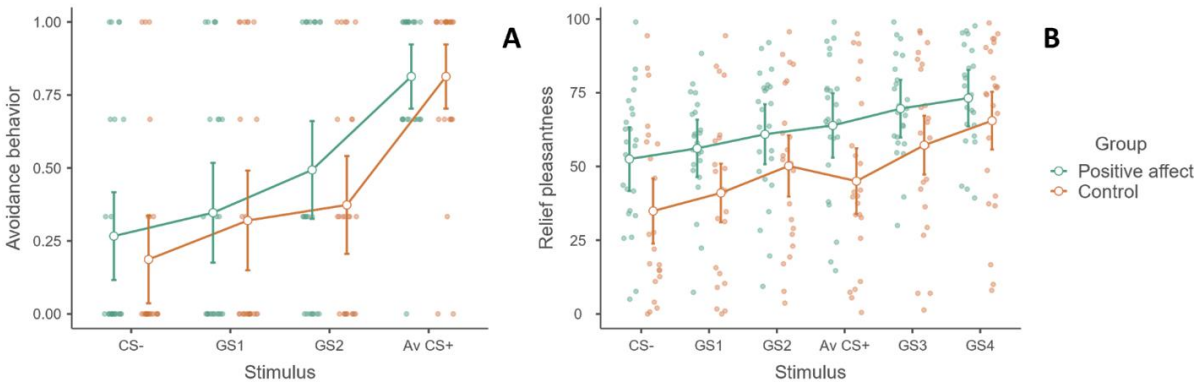
Hypothesis testing

Avoidance generalization along threat-safety dimension

A 4 (Stimulus: CS-, GS1, GS2, Avoidable CS+) x 2 (Group: Positive affect, Control) RM ANOVA run on avoidance behavior during the generalization test showed a main effect of Stimulus, $F(2.27, 108.94) = 45.87$, $p < .001$, $\eta_p^2 = 0.49$, $\varepsilon = .76$, but not of Group, $F(1, 48) = 0.45$, $p = .504$, $\eta_p^2 = 0.01$. The interaction effect did not reach significance either, $F(3, 144) = 0.51$, $p = .678$, $\eta_p^2 = 0.01$, indicating that the visualization exercises did not affect avoidance responding differentially during the generalization test (Figure 6.4, panel A). Both the linear, $F(1, 48) = 97.84$, $p < .001$, $\eta_p^2 = 0.67$, and quadratic trend, $F(1, 48) = 9.33$, $p = .004$, $\eta_p^2 = 0.16$, in the effect of Stimulus did reach significance, indicating the presence of a generalization gradient. Further exploration of this gradient showed significantly more avoidance responding to GS1, $t(48) = 2.25$, $p = .029$, $d = 0.27$, GS2, $t(48) = 4.15$, $p < .001$, $d = 0.52$, and the avoidable CS+, $t(48) = 10.13$, $p < .001$, $d = 1.80$, compared to the CS-. Furthermore, avoidance responding to both GS1, $t(48) = 7.19$, $p < .001$, $d = 1.36$, and GS2, $t(48) = 6.56$, $p < .001$, $d = 1.08$, was significantly lower than to the avoidable CS+. When the RM ANOVA was conducted with change in positive affect as covariate instead of the Group factor, conclusions remained the same.

Figure 6.4

Avoidance behavior and relief pleasantness during generalization test



Note. Observed proportions/averages, estimated marginal means and 95% confidence intervals of avoidance behavior (panel A) and average relief pleasantness (panel B) during the generalization test. CS = conditional stimulus; GS = generalization stimulus; Av = avoidable.

Relief pleasantness generalization

A 6 (Stimulus: CS-, GS1, GS2, Avoidable CS+, GS3, GS4) x 2 (Group: Positive affect, Control) RM ANOVA run on relief pleasantness during the generalization test showed a significant main effect of Stimulus, $F(3.66, 164.78) = 32.55$, $p < .001$, $\eta_p^2 = 0.42$, $\varepsilon = .73$, and of Group, $F(1, 45) = 4.39$, $p = .042$, $\eta_p^2 = 0.09$. The interaction effect was not significant, $F(5, 225) = 1.68$, $p = .140$, $\eta_p^2 = 0.04$, indicating

elevated relief ratings for all stimuli in the positive affect group compared to the control group (Figure 6.4, panel B). Moreover, a significant linear trend was present for Stimulus, $F(1, 45) = 80.79$, $p < .001$, $\eta_p^2 = 0.64$, indicating the presence of a generalization gradient, though the quadratic trend did not reach significance, $F(1, 45) = 1.02$, $p = .319$, $\eta_p^2 = 0.02$. Further exploration of this gradient showed significantly higher ratings for GS1, $t(45) = 2.76$, $p = .008$, $d = 0.18$, GS2, $t(45) = 4.60$, $p < .001$, $d = 0.44$, the avoidable CS+, $t(45) = 4.95$, $p < .001$, $d = 0.36$, GS3, $t(45) = 7.47$, $p < .001$, $d = 0.73$, and GS4, $t(45) = 8.56$, $p < .001$, $d = 0.95$, compared to the CS-. Furthermore, ratings for the avoidable CS+ were significantly higher compared to GS1, $t(45) = 2.42$, $p = .040$, $d = 0.20$, but lower compared to GS3, $t(45) = -3.80$, $p = .003$, $d = -0.35$, and GS4, $t(45) = -5.87$, $p < .001$, $d = -0.57$. Results showed no significant difference between the avoidable CS+ and GS2, $t(45) = -0.50$, $p = .620$, $d = -0.07$. Together, this means that relief pleasantness ratings were generally higher for GSs on the dimension of avoidability compared to those on the threat-safety dimension.

Because the interaction effect of interest did not reach significance, we conducted the same analysis with positive affect change as covariate instead of the Group factor; however, conclusions remained the same. Furthermore, due to the observed Group effect in relief ratings during avoidance conditioning, we added average relief pleasantness during the avoidance conditioning phase (i.e., averaged over all stimuli and blocks) as a covariate to the original analysis (i.e., using the Group factor), which resulted in a non-significant effect of Group, $F(1, 44) = 0.05$, $p = .823$, $\eta_p^2 < 0.01$. This suggests that the group difference in relief was not actually due to the visualization exercises, but rather due to pre-existing differences between groups.

An additional 3 (Stimulus: GS1+2, Avoidable CS+, GS3+4) x 2 (Group: Positive affect, Control) RM ANOVA with relief ratings on avoided trials showed a significant main effect of Stimulus, $F(2, 60) = 8.77$, $p < .001$, $\eta_p^2 = 0.23$, but not of Group, $F(1, 30) = 1.60$, $p = .216$, $\eta_p^2 = 0.05$, and no significant interaction effect $F(2, 60) = 1.29$, $p = .282$, $\eta_p^2 = 0.04$, indicating no differential effect of visualization exercises. The effect of Stimulus again showed a significant linear trend, $F(1, 30) = 10.48$, $p = .003$, $\eta_p^2 = 0.26$, that was accompanied by a significant quadratic trend this time, $F(1, 30) = 7.97$, $p = .008$, $\eta_p^2 = 0.21$. Ratings for GS3+4 were significantly higher compared to the avoidable CS+, $t(30) = 4.00$, $p = .001$, $d = 0.43$, while results showed no significant difference between the avoidable CS+ and GS1+2, $t(30) = 1.37$, $p = .179$, $d = 0.24$, indicating that relief pleasantness ratings were generally higher for GSs on the dimension of avoidability. Controlling for average relief pleasantness during avoidance conditioning did not change these results. In addition, when this RM ANOVA was conducted with change in positive affect as covariate instead of the Group factor, conclusions remained the same.

Exploratory analyses

Avoidance generalization along the dimension of avoidability

Analysis of avoidance behavior along the avoidability dimension during the generalization test showed no significant differences between the positive affect and control groups. However, results showed a generalization gradient along this dimension as well, with increased avoidance as similarity to the avoidable CS+ increased; see Appendix E for a full report of the results.

Generalization of stimulus- and omission-elicited SCRs

Analyses of the stimulus- and omission-elicited SCRs during the generalization test again indicated no differences between groups. Furthermore, no generalization gradients were observed in these measures; results are provided in Appendix E.

Negative affect

Analysis of state negative affect showed no differences between groups. However, there was a decrease in negative affect in both groups from pre- to post-visualization. See Appendix E for the results in detail.

Discussion

Contemporary fear-avoidance models consider overgeneralization of pain-related avoidance key in the development and maintenance of chronic pain disability (Meulders, 2019; Vlaeyen et al., 2016; Vlaeyen & Linton, 2012). Therefore, an important question is how to attenuate such excessive generalization. Evidence shows that positive affect is a potential target for interventions, as it may improve safety learning (Hanssen et al., 2017). Moreover, Vandael et al. (under revision) provided empirical evidence that induced positive affect is indeed associated with less generalization of pain-related avoidance. However, as avoidance is not merely a product of fear, research into reinforcing mechanisms of avoidance specifically is required (Krypotos et al., 2015; Vervliet & Indekeu, 2015). An important reinforcing factor to consider is relief, as excessive relief may be pivotal in avoidance turning maladaptive (Vervliet et al., 2017). The current study aimed to (1) replicate that experimentally induced positive affect attenuates the generalization of avoidance and (2) investigate whether positive affect also has the potential to attenuate relief.

Results did not provide support for our first hypothesis: generalization of pain-related avoidance was not attenuated following positive affect induction. We expected reduced avoidance generalization based on Geschwind et al. (2015) showing that increases in positive affect were associated with less fear generalization, and Vandael et al. (under revision) showing that increases in positive affect were associated with less avoidance generalization. It should be noted that both Geschwind et al. (2015) and Vandael et al. (under revision) did not report significant group differences,

i.e., when comparing the positive affect and control groups. However, analyzing their data across groups using positive affect change as covariate showed associations between increases in positive affect and less generalization of pain-related fear and avoidance. Yet, using a similar approach in the current study did not show any significant associations.

Our second hypothesis was also not supported: generalization of pain-related relief was not attenuated following positive affect induction. Relief has shown to be modulated by US-expectancy, with higher relief as expectancy is higher (San Martín et al., 2020). Moreover, Geschwind et al. (2015) showed that increases in positive affect were associated with less generalization of pain-expectancy. Therefore, we expected reduced relief generalization following positive affect induction. Surprisingly, the positive affect group showed generally higher relief pleasantness ratings – for all stimuli – compared to the control group during the generalization test. However, further analysis showed that this pattern was already present before the crucial affect manipulation. There was no longer a significant difference between both groups when controlling for pre-visualization relief pleasantness levels. Furthermore, when analyzing relief following avoidance behavior specifically, there was no significant difference between groups either. Taken together, it seems that generalized avoidance behavior was reinforced by relief to the same extent in both groups, which resulted in similar levels of avoidance.

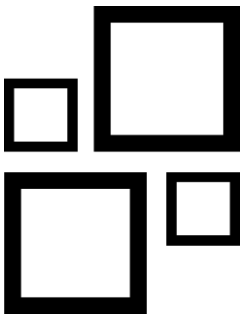
Although our hypotheses were not supported, it is important to note that the current study replicated the findings by San Martín et al. (2020); both avoidance and relief generalized to novel stimuli. Regarding *avoidance behavior*, the current study replicated the presence of a generalization gradient along the threat-safety dimension: the frequency of avoidance toward GSs varied along with their similarity to the avoidable CS+, with more avoidance toward the stimulus most similar to the avoidable CS+. This finding also corroborates previous work on avoidance generalization (Hunt et al., 2019; van Meurs et al., 2014). Additionally, the current study replicated the presence of a generalization gradient on the dimension of avoidability, again with increased avoidance as similarity to the avoidable CS+ increased (see Appendix E; San Martín et al., 2020). This gradient was flattened compared to the threat-safety dimension, with overall more avoidance on the dimension of avoidability. In other words, avoidance behavior seems more likely to generalize toward instances where it is ineffective, than to instances where threat is absent. Regarding *relief pleasantness*, the current study showed a generalization gradient with lowest relief levels for the GS most similar to the CS- and highest relief for the GS most similar to the unavoidable CS+. In other words, relief was higher when surprise was allegedly higher, thus suggesting that relief is indeed modulated by US-expectancy (San Martín et al., 2020).

A number of limitations need consideration when interpreting these results. *First*, avoidance was not associated with a cost in the current paradigm; costs may attenuate the performance of (ineffective) avoidance behavior in healthy, pain-free participants (Pittig, Wong, et al., 2020). Individuals suffering from chronic pain on the other hand may show persistent avoidance behavior despite costs, as they may prioritize pain control (Vlaeyen et al., 2016). Including a cost could therefore be crucial to separate adaptive from maladaptive avoidance. Moreover, this would increase the ecological validity of the paradigm, because pain-related avoidance behavior can be associated with substantial costs in daily life – e.g., not participating in social activities (Meulders, 2019). A *second* limitation is the fact that the avoidance response consisted of a single mouse click. Allowing different degrees of avoidance may make this measure more sensitive to effects of manipulations and individual differences. This can mean using a continuous response (e.g., applying pressure) or multiple clicks. *Third*, the positive affect group showed higher relief ratings compared to the control group before the crucial affect manipulation, which may have obscured effects of the manipulation on generalization. Note that we did not find statistically significant differences between both groups on other (trait) variables assessed in the current study (see Appendix E). However, a plausible explanation for the difference in relief pleasantness levels is that there was a difference between these groups – despite random allocation of participants – in terms of a certain state/trait that was not captured by our measures. *Finally*, the current study was performed using healthy, pain-free participants. This may have limited the effect of the positive affect manipulation for example – although there was a significant increase. Furthermore, traits such as anxiety sensitivity are known to modulate avoidance generalization (Hunt et al., 2019); participants with higher levels of such anxious traits show flattened generalization gradients, leaving more room for attenuation by affect induction. Therefore, future studies may benefit from investigating subclinical samples – e.g., preselecting on anxious traits – to increase the potential effect of the intervention.

In conclusion, the current study replicated previous work on the generalization of avoidance and relief. However, despite previous studies showing evidence for the role of positive affect in safety learning and generalization, our results did not support that experimentally inducing positive affect reduces avoidance and relief generalization.

Chapter 7

Generalization of pain-related avoidance in people with chronic pain (preregistration)



Abstract

Contemporary models of pain advance pain-related fear and avoidance as key contributors to the transition from acute to chronic pain. Despite the high prevalence of avoidance in chronic pain conditions and its key role in contemporary fear-avoidance models, surprisingly little systematic research has been dedicated to the development, spreading, and persistence of pain-related avoidance behavior. Here we present the preregistration of a study that will investigate the excessive spreading (or overgeneralization) of pain-related avoidance behavior toward novel, but perceptually similar contexts. We will recruit people with chronic pain at the upper limb (i.e., hand, arm, or shoulder complex) and age- and gender-matched healthy, pain-free controls. We expect that participants with chronic pain show more avoidance behavior in novel (generalization) contexts that are perceptually similar to a context that signals safety in comparison with control participants. Additionally, the goal is to investigate the diagnostic validity of our newly developed dynamic movement reproduction (DMR) task. Since people with chronic pain conditions often present with impaired proprioception, we expect participants with chronic pain to show poorer proprioceptive accuracy in the DMR task compared to the control group.

Introduction

Acute pain is a universal experience serving a protective function. When pain persists beyond healing time and turns chronic, it ceases to be protective and increases suffering and disability. Modern models of chronic pain advance pain-related fear and avoidance as key contributors to the transition from acute to chronic pain (Vlaeyen et al., 2016). Catastrophic misinterpretations of pain as a sign of bodily harm may give rise to pain-related fear, which can initiate avoidance behavior intended to avert bodily threat. When avoidance behavior serves to reduce or eliminate genuine threat to the body, it is highly adaptive. However, in chronic pain, and in the absence of actual danger, avoidance behavior is no longer adaptive as a protective strategy. Moreover, it can spread excessively toward safe activities and situations, thus interfering severely with daily life and potentially initiating a pathway toward functional disability (Meulders, 2019). Despite the high prevalence of avoidance in chronic pain conditions and its cardinal role in contemporary fear-avoidance models, surprisingly little systematic research has been dedicated to the development, spreading, and persistence of pain-related avoidance behavior.

The current study will investigate the excessive spreading (or overgeneralization) of pain-related avoidance behavior toward novel, but similar contexts – i.e., contexts in which no pain has been experienced. A previous study in our lab has shown that healthy participants with high levels of trait anxiety show more avoidance behavior in novel (generalization) contexts that are perceptually similar to a context that signals safety in comparison with participants with low levels of trait anxiety (Meulders et al., in preparation). In the current study, our main aim is to replicate these findings in a sample of people with chronic pain at the upper limb (i.e., hand, arm, or shoulder complex) and an age- and gender-matched healthy, pain-free control group. We hypothesize that during the generalization phase, participants with chronic pain will show more avoidance behavior in (1) the safe context (i.e. impaired safety learning) and (2) the generalization context perceptually most similar to the safe context (i.e., overgeneralization) compared to healthy controls.

Additionally, the goal is to provide evidence for the diagnostic validity of our newly developed dynamic movement reproduction (DMR) task (Vandael et al., 2021). Since people with chronic pain conditions often present with impaired proprioception, we expect participants with chronic pain to show poorer accuracy in the DMR task compared to the control group (Juul-Kristensen et al., 2008a; Knoop et al., 2011; Stanton et al., 2016; Tong et al., 2017).

Method

The hypotheses, sample size, procedure and analysis plan regarding avoidance behavior have been registered prior to data collection at Open Science Framework (https://osf.io/db93u/?view_only=c63e004c371348298da4487e1db745ce). The validation of the DMR task was registered separately on the same platform (https://osf.io/vqb7y/?view_only=161a9a9946904c488a5dab02ca4bd56f).

Participants

We will test 60 participants in total: 30 participants with chronic upper limb pain and 30 age- and gender-matched healthy, pain-free controls. According to our power calculations using G*Power (Faul et al., 2007), a sample size of 60 will allow us to detect a two-way interaction effect of $f = 0.155$ (between Group and Context, see data analysis plan; with Power = .80; Number of groups = 2; Number of measurements = 4; Correlation among rep measures = 0.50; Nonsphericity correction = 1). The age range will be set between 17 and 65 years old. Participants will be excluded from both groups if any of the following criteria (based on self-report) is met: left-handedness (participants will perform the experimental task with their right arm), not fluent in Dutch, diagnosed dyslexia or analphabetism, pregnancy, history or current state of any heart- or cardiovascular problems, neurological problems (e.g., epilepsy), other severe medical problems, any type of electronic implant (e.g., pacemaker) or uncorrected hearing or vision problems. The most important inclusion criterion for the patient group is that they experience chronic pain (present for more than 3 months) at the hand, arm or shoulder and that they experience interference in their daily life because of their pain condition. The key exclusion criterion for the healthy control group is any chronic pain diagnosis. Furthermore, controls will be excluded if one of the following criteria is met: clinical depression, panic or anxiety disorder, or any other psychiatric problem (at present or in the past). Participation in this study will be voluntary, and participants will receive remuneration of 16 EUR (plus reimbursement of travel costs).

Procedure

DMR task

First, participants will reproduce movements with their right arm while wearing a blindfold, using the HapticMaster – a 3-degrees of freedom robotic device (Motekforce Link, Amsterdam, the Netherlands). The task starts with four practice trials to get familiarized with the procedure, followed by six test trials. In the practice phase, the HapticMaster first restricts movement to a single square trajectory to show participants what movement is to be reproduced. After performing this target movement once, participants are asked to reproduce it as accurately as possible, while having the

entire range of the robotic device – within the horizontal plane – available. The test phase is the same as practice, except for the shape of the movements; the target movement is a circle. Note that movement direction (i.e., clockwise or counterclockwise) will remain constant throughout the task, and will be counterbalanced between participants.

Robotic arm-reaching task

The avoidance task will be a modified version of an established pain-related avoidance paradigm in which participants are requested to move the HapticMaster from a start to a target location, using their right hand (Meulders et al., 2016). The handle of the HapticMaster is represented as a ball on-screen, thus allowing participants to track their own movements. There are three different trajectories to reach the target, which are represented as arches positioned between the start and target location. The first trajectory, T1, is short and easy (no resistive force on the robotic device), but is always followed by an electrical pain stimulus. The second trajectory, T2, is longer and more effortful to perform (the robotic device generates resistive force), and is followed by the pain stimulus in 50% of movements. The last trajectory, T3, is the longest and most effortful, but is never followed by the pain stimulus. Participants will first perform this arm-reaching task in two different contexts. In the threat context (e.g., black background color), they will be able to avoid pain stimuli by performing the more effortful trajectories; in the safe context (e.g., white background color) no pain stimuli will be presented, and thus there will be no need to avoid. In other words, the same movement trajectories will be performed in both contexts, but the contingencies between trajectories and the pain stimulus will differ. Background colors will be counterbalanced between participants. Next, we will test the generalization of avoidance behavior in two novel contexts with varying similarity to the original safe and threat contexts (G_safe and G_threat respectively; i.e. dark or light grey background colors). The same movement trajectories will again be presented in these contexts, but as in the safe context, none of them will be followed by the pain stimulus. Participants will not be informed about the contingencies between movement trajectories and the pain stimulus – and their dependence on context – before starting the experiment.

The avoidance task will consist of six consecutive phases, each consisting of a certain number of blocks of trials: practice, acquisition (ACQ), test-of-acquisition (TACQ), reminder-of-acquisition (RACQ), generalization (GEN), and test-of-generalization (TGEN). In the practice, acquisition, test-of-acquisition and reminder-of-acquisition phases, the safe and threat contexts will be presented, while in the generalization and test-of-generalization phases, the novel G_safe and G_threat contexts will be introduced (in addition to the original contexts). No pain stimuli will be presented during the practice phase, regardless of context. During the test-of-acquisition and test-of-generalization blocks, participants will not be free to choose which trajectory to use, as the task will signal which one to take;

this approach is used to measure eyeblink startle responses (see outcome measures section) for each trajectory. See Table 7.1 for an overview of the design.

Pain calibration. Prior to the avoidance task, intensity of the electrical stimulus will be calibrated for each participant. They will receive a series of electrical stimuli of increasing intensity, according to a standard protocol – see for example Meulders et al. (2011). Participants will rate each stimulus on a numerical rating scale ranging from 0-10, where 0 is 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*". They will be asked to select a stimulus that is "*significantly painful and demanding some effort to tolerate*", corresponding to a 7-8 on the rating scale.

Resistance calibration. Contingencies between the movement trajectories and resistive force generated by the robotic device will be the same throughout the entire avoidance task. Resistance levels will be determined prior to the experiment using a calibration phase where participants are asked to move the HapticMaster several times, each time with increasing resistive force. They will rate each movement in terms of whether it was painful or not ("*yes*"/"*no*"), how much effort the movement required (on a rating scale from 0 to 10), and to what extent they would like to avoid this effort (on a rating scale from 0 to 10). Note that we do not want the most effortful movements to be experienced as painful by participants with chronic upper limb pain, because in that case, both the avoidance trajectory and the pain-associated trajectory would induce pain – albeit from a different quality. In other words, this would interfere with the trade-off between pain and effort in the avoidance task. Once the rating regarding avoidance of the effortful movement reaches a minimum of 4, this movement will be presented together with the pain stimulus that was previously calibrated. Participants will be asked to judge whether they would rather avoid the pain stimulus or the effort. This check is included to ensure that participants want to avoid the pain stimulus more than the effort. If the participant answers in the opposite direction, the resistance calibration procedure continues with decreased resistance until a fitting resistance is reached. This way we make sure that the avoidance movement is indeed costly in terms of effort, and that the cost does not overrule pain-avoidance.

Table 7.1

Design overview for robotic arm-reaching task

Practice[1]	**Acquisition**[2]	**Test-of-acquisition**[3]	**Reminder-of-acquisition**	**Generalization**	**Test-of-generalization**[3]
2 blocks of 5 trials	**6 blocks of 12 trials**	**2 blocks of 9 trials**	**2 blocks of 12 trials**	**4 blocks of 6 trials**	**4 blocks of 9 trials**
5 Threat	3 x 12 Threat	9 Threat	12 Threat	6 Threat	9 Threat
5 Safe	3 x 12 Safe	9 Safe	12 Safe	6 Safe	9 Safe
				6 G_threat	9 G_threat
				6 G_safe	9 G_safe

Note. The chronic pain and control group perform the same experimental phases. Pain stimuli are only delivered – according to the experimental contingencies – in the threat context (e.g., black background color); no pain stimuli are delivered in the safe (e.g., white background color), G_threat (e.g., dark grey background color) and G_safe (e.g., light grey background color) contexts. Presentation order of contexts is semi-randomized with a maximum of two consecutive blocks of same context. [1]No pain stimuli or startle probes are presented. [2]A block of trials in the safe context is run first to counter strong generalization of acquired avoidance behavior from the threat context. [3]Participants are instructed which movement to perform, with each movement performed three times per block; startle probes are presented on each trial.

Outcome measures

Regarding the DMR task, *proprioceptive accuracy* is operationalized as the absolute difference between the target and the reproduced circular movement (i.e., the difference between the target and reproduced radius), averaged over the six test trials. This means that larger values correspond with poorer accuracy. The reproduced radius will be calculated using the coordinates of each movement reproduction and the coordinates of the target circle (Vandael et al., 2021).

During the avoidance task, participants will repeatedly answer questions concerning *pain-related fear and pain-expectancy* for each movement trajectory. To answer these questions, a visual analogue scale with anchors 0 = "*Not at all*" and 10 = "*Very much*" will be used. Ratings will be averaged per block for each trajectory.

Avoidance behavior will be operationalized as the maximal deviation (i.e. lateral displacement) from the shortest trajectory, which is a straight line from the start to the target location. Deviations will be averaged per block.

Eyeblink startle responses will be measured as a psychophysiological index of conditioned fear using surface electromyography (EMG) recordings. An acoustic startle probe (white noise, 100dB, instantaneous rise, duration 50ms) will be presented binaurally via headphones following movement onset. The EMG signal will be digitized at 1000Hz from 500ms before the onset of the startle probe until 1000ms after. Averages will be calculated per block for each trajectory. Note that non-responders – i.e. participants with no reliable startle response in more than 50% of the trials – will be excluded from analyses.

At the end of the experiment, participants will be asked to fill in the following *questionnaires* to check for group and individual differences: Disability of the Arm, Shoulder and Hand (Angst et al., 2011), Chronic Pain Grade Scale (Vonkorff et al., 1992), Pain Cognition List (Van Breukelen & Vlaeyen, 2005), Tampa Scale of Kinesiophobia (Roelofs et al., 2011), Hospital Anxiety Depression Scale (Spinhoven et al., 1997), and the trait version of the Positive And Negative Affect Schedule (Watson et al., 1988).

Data analysis plan

Testing our hypotheses

DMR task. An independent *t*-test will be employed to compare the chronic pain group to the healthy control group. We expect proprioceptive accuracy to be significantly poorer (i.e., higher values) in the chronic upper limb pain group than in the healthy, pain-free control group.

Avoidance task. A 2 (Group: Chronic pain, Healthy control) x 4 (Context: Threat, G_threat, G_safe, Safe) repeated measures (RM) analysis of variance (ANOVA) will be run on avoidance behavior

during generalization. We expect a significant two-way interaction between Group and Context, indicating a difference in context modulation between both groups. Planned comparisons will be used to further investigate differences between the chronic pain and healthy control groups in the different contexts: we expect significant differences in (1) the safe context and (2) the G_safe context, indicating that participants with chronic pain avoid more in these contexts compared to the healthy controls.

Manipulation checks for the avoidance task

Acquisition. We will carry out a 2 (Group: Chronic pain, Healthy control) x 2 (Context: Threat, Safe) x 3 (Block: ACQ1-3) RM ANOVA on avoidance behavior during acquisition. We will conduct planned comparisons to confirm that at the end of acquisition (ACQ3), both groups avoid more in the threat context compared to the safe context. Furthermore, we expect a three-way interaction between Group, Context and Block, indicating slower differential learning over blocks between contexts in the chronic pain group. On the pain-expectancies and pain-related fear ratings, a 2 (Group: Chronic pain, Healthy control) x 2 (Context: Threat, Safe) x 3 (Block: ACQ1-3) x 3 (Trajectory: T1-3) RM ANOVA will be run. Planned comparisons will be used to confirm that by the end of acquisition (ACQ3), participants in both groups give higher ratings for T1 compared to T3 in the threat context. Furthermore, we expect a four-way interaction indicating slower differential learning over blocks between trajectories and contexts in the chronic pain group.

Test-of-Acquisition. A 2 (Group: Chronic pain, Healthy control) x 2 (Context: Threat, Safe) x 3 (Trajectory: T1-3) RM ANOVA will be run on the startle responses during the test-of-acquisition. We will use planned comparisons to confirm that in both groups, startle responses for T1 are higher compared to responses for T3 in the threat context. Furthermore, we expect a three-way interaction indicating different response patterns in the safe context between groups (i.e., impaired safety learning in the chronic pain group), with elevated responses for T1 in the chronic pain group compared to the control group.

Reminder-of-acquisition. We will carry out a 2 (Group: Chronic pain, Healthy control) x 2 (Context: Threat, Safe) RM ANOVA on avoidance behavior during reminder-of-acquisition. We will conduct planned comparisons to confirm that both groups still avoid more in the threat context compared to the safe context. On the pain-related fear and pain-expectancy ratings, a 2 (Group: Chronic pain, Healthy control) x 2 (Context: Threat, Safe) x 3 (Trajectory: T1-3) RM ANOVA will be run. Planned comparisons will be used to confirm that participants in both groups still give higher ratings for T1 compared to T3 in the threat context.

Generalization. We will use a 2 (Group: Chronic pain, Healthy control) x 3 (Trajectory: T1-3) x 4 (Context: Threat, G_threat, G_safe, Safe) RM ANOVA on pain-expectancies and pain-related fear ratings. We expect a significant three-way interaction, indicating that ratings for the respective

trajectories vary across contexts, though not in the same way for both groups (i.e., impaired safety learning and overgeneralization in chronic pain group).

Test-of-generalization. A 2 (Group: Chronic pain, Healthy control) x 3 (Trajectory: T1-3) x 4 (Context: Threat, G_threat, G_safe, Safe) RM ANOVA will be run on the eyeblink startle responses. We expect a significant Group x Trajectory x Context interaction, indicating that responses for the respective trajectories vary across contexts, though not in the same way for both groups (i.e., impaired safety learning and overgeneralization in chronic pain group).

Inference criteria

For all analyses, the family-wise α-level will be set at .05. Greenhouse-Geisser corrections will be applied for RM ANOVA effects when Mauchly's test of sphericity is significant. Holm-Bonferroni corrections will be applied to multiple comparisons.

General discussion

Chronic pain is an important cause of disability and sufferers often receive inadequate treatment (Breivik et al., 2006; Kennedy et al., 2014; Nicholas et al., 2019; Schopflocher et al., 2011; Van Hecke et al., 2013). Pain researchers and clinicians recognize chronic pain as a complex and challenging condition in which biological, psychological as well as social factors play important roles (Gatchel et al., 2007). Contemporary fear-avoidance models emphasize excessive pain-related avoidance as a crucial factor in the development and maintenance of chronic pain disability (Crombez et al., 2012; Leeuw et al., 2007; Meulders, 2019; Vlaeyen et al., 2016). However, despite its supposed central role, relatively little experimental research has systematically investigated ways to reduce the spreading (or generalization) of avoidance behavior toward safe activities (Meulders, 2019). Such research can help optimize treatments tackling chronic pain disability or identify new targets for treatment. Therefore, the current PhD project set out to investigate potential intervention targets to attenuate the generalization of pain-related avoidance.

To this end, we first aimed to demonstrate that avoidance behavior can generalize toward proprioceptively similar movements in healthy, pain-free participants, using an operant conditioning task (the robotic arm-reaching paradigm; Meulders et al., 2016; Chapter 1). This could then provide an experimental framework to investigate factors that can attenuate excessive generalization. Next, we reviewed existing experimental research on potential attenuating factors from both the field of pain and anxiety (Chapter 2). To investigate proprioceptive accuracy training as a potential pathway toward reduced generalization, we first developed a task to quantify proprioceptive function of the upper limb, and evaluated its test-retest reliability (the DMR task; Chapter 3). Next, we investigated whether an association exists between proprioceptive accuracy and pain-related avoidance in healthy, pain-free participants (Chapter 4). Such an association would confirm the potential of training accuracy to reduce overprotective avoidance. Furthermore, we investigated the effect of experimentally induced positive affect on generalization of pain-related avoidance in healthy, pain-free participants, using the robotic arm-reaching paradigm (Chapter 5). Additionally, we investigated the effect of induced positive affect on avoidance and the consequent experience of relief – as excessive relief may contribute to avoidance becoming excessive (Chapter 6). Finally, we included the preregistration of an experimental protocol to test overgeneralization of pain-related avoidance behavior in chronic pain conditions, because diagnostic validity of current avoidance generalization paradigms requires evaluation (Chapter 7). Once this paradigm has shown to observe overgeneralization in chronic pain, it can be used to continue experimental research into factors attenuating overgeneralization.

Generalization of pain-related avoidance behavior

Previous experimental studies have repeatedly shown that pain-related fear generalizes toward movements perceptually similar to a pain-associated one (Meulders et al., 2013; Meulders & Vlaeyen, 2013). However, as fear and avoidance do not show a one-to-one relationship, research into the generalization of avoidance specifically is required (Meulders, 2019; Pittig, Wong, et al., 2020). Glogan, Gatzounis, Meulders, et al. (2020) investigated generalization of costly pain-related avoidance in healthy, pain-free participants using the robotic arm-reaching paradigm, and showed a dissociation between pain-related fear and avoidance: fear generalized toward perceptually similar but safe movements, while avoidance did not. However, the physical effort associated with avoidance movements (making them costly) may have prompted the healthy, pain-free participants to explore generalization movements similar to the pain-associated ones, as these required less effort.

In Chapter 1, we tested two factors that could reduce such exploration in healthy, pain-free participants, using adapted versions of the robotic arm-reaching paradigm. In a first study, we minimized visual (context) changes between the avoidance acquisition phase and the generalization test, because context changes may lead to diminished expression of a learned response (Bouton et al., 2014). In a second study, we investigated whether less certain movement-pain contingencies would lead to generalization of pain-related avoidance; in the original study, exploration of the generalization trajectories may have led to strong expectancy-violations because one of the pain-associated trajectories was *always* followed by pain during avoidance acquisition, leading to rapid safety learning (Craske et al., 2014; Rescorla & Wagner, 1972). In other words, the absence of highly expected pain during generalization may have quickly extinguished avoidance. Results showed that minimizing visual changes did not lead to generalization of pain-related avoidance, whereas reducing movement-pain contingencies did. This finding suggests an important role for uncertainty in the pathway toward excessive costly avoidance, and thus chronic pain disability. This idea is in line with previous work on the role of uncertainty in chronic pain conditions, which has linked various types of uncertainty to negative behavioral outcomes (Johnson et al., 2006; Serbic et al., 2016).

In Chapter 5, we investigated whether the finding that costly pain-related avoidance generalizes under conditions of uncertainty could be replicated (in healthy, pain-free volunteers). Surprisingly, results did not support that avoidance generalized, although a trend toward generalization was present. An important procedural difference was that, unlike the original study, there was a gap of approximately 20 min between avoidance acquisition and the generalization test, during which participants performed the typical day visualization exercise (as a control for the positive affect-inducing best possible self exercise). Results showed that during this break, there was a significant decrease in negative affect. Although speculative, this was probably because, contrary to

the acquisition phase, participants could no longer receive pain stimuli during the visualization exercise (i.e., electrodes were detached). The change in negative affect may have attenuated avoidance generalization, as previous research showed a positive association between negative affective states such as anxiety and avoidance (van Meurs et al., 2014).

Interestingly, the non-significant avoidance generalization effects in Chapters 1 (Study 1) and 5, and previous studies, are at odds with work from the anxiety field (e.g., Klein et al., 2020). San Martín et al. (2020) for example showed generalization of avoidance behavior toward perceptually similar (visual) stimuli, and we replicated this finding in Chapter 6 – using a pain-US instead of a merely aversive US. However, this paradigm did not involve any response costs; such costs are an important addition in terms of ecological validity, because excessive avoidance can come at a high cost for both individuals with clinical anxiety and individuals with chronic pain (e.g., withdrawal from valued social activities). Importantly, van Meurs et al. (2014) showed generalization of avoidance while also including a (virtual) cost [replicated by Hunt et al. (2019)]. A consideration to make is that studies in the anxiety field – including the study from Chapter 6 – generally are methodologically distinct from the robotic arm-reaching paradigm, as they use a Pavlovian conditioning phase followed by an instrumental phase. In other words, participants first passively experience associations between the CS and US, and then learn that a simple avoidance response (e.g., a button press) upon CS presentation cancels the US. The generalization test then consists of presentation of GSs, with the same avoidance response available. In the robotic arm-reaching paradigm on the other hand, participants can always choose between three different responses (i.e., trajectories) – and can show variation in the way they perform these responses (e.g., the three trajectories allow variation in lateral deviation; movements can be performed with varying speeds; etc.). Although speculative, having such a range of responses available throughout the entire procedure may lead to an increased sense of control (i.e., the perceived ability to affect the outcome of situations and events), which may bolster exploratory behavior in the generalization test, thus leading to less avoidance generalization. Indeed, higher perceived control has been linked to less anxious responding (Endler et al., 2000).

The dissociations between pain-related fear and avoidance observed in previous research (e.g., Glogan, Gatzounis, Meulders, et al., 2020), and in Chapters 1 (Study 1) and 5, emphasize that avoidance is not merely a by-product of fear: fear does not necessarily lead to avoidance. Alternatively, avoidance can persist in the absence of fear; for example, avoidance behavior has been observed after extinguishing fear (Vervliet & Indekeu, 2015). Therefore, research is required on the mechanisms that maintain (generalized) avoidance and potentially turn it maladaptive (Krypotos et al., 2015). An important factor to consider is the relief experienced when avoiding, as vulnerable individuals may show more avoidance because they enjoy higher levels of relief (Vervliet et al., 2017).

Importantly, San Martín et al. (2020) showed that relief generalizes toward novel stimuli, a finding we replicated in Chapter 6. In other words, also generalized avoidance may persist because of excessive relief.

Research into overgeneralization of pain-related avoidance in chronic pain conditions is currently lacking. Previous research has repeatedly shown that people with chronic pain overgeneralize pain-related *fear* compared to healthy, pain-free controls (Harvie et al., 2020; Meulders, Harvie, et al., 2014; Meulders et al., 2015). Because there is no straightforward relationship between fear and avoidance, research on avoidance specifically is necessary in this population as well. In Chapter 7 we introduced a study to investigate overgeneralization of avoidance in participants with chronic upper limb pain (i.e., at the shoulder, arm and/or hand) compared to gender- and age-matched healthy, pain-free controls. This study employs a version of the robotic arm-reaching task in which generalization of an acquired avoidance behavior toward novel, perceptually similar contexts is assessed (i.e., varying background colors). This task was previously validated in participants with varying levels of anxiety: high trait anxiety was associated with excessive generalization of avoidance (Meulders et al., in preparation). As chronic pain conditions are often associated with elevated anxiety levels (Van Hecke et al., 2013), this suggests that a similar pattern may be present in this population. Note that we can also expect a pattern of excessive generalization toward proprioceptively similar *movements* when using the robotic arm-reaching paradigm introduced in Chapter 1 (Study 2) in chronic pain conditions. Despite difficulties replicating the avoidance generalization effect in healthy, pain-free participants (Chapter 5), we can expect people with chronic pain to prioritize pain-control over avoiding costs (Meulders, 2019), and thus show overgeneralization of pain-related avoidance towards similar movements as well.

Pathways toward attenuated pain-related avoidance generalization

Proprioceptive accuracy

In Chapter 2, we identified improving proprioceptive accuracy as a potential pathway toward attenuated generalization of avoidance. Impaired proprioceptive accuracy has been observed in a range of pain conditions, and evidence suggests that interventions targeting this impairment can improve outcomes in such conditions (Jull et al., 2007; Juul-Kristensen et al., 2008a; Knoop et al., 2011; Stanton et al., 2016; Tong et al., 2017). Interestingly, studies show that fear generalization is negatively related to (visual) perceptual accuracy (Struyf et al., 2017; Zaman, Ceulemans, et al., 2019). In the context of pain, this could mean that movements are more likely to elicit pain-related fear and avoidance if they are not accurately perceived, even if these movements were never experienced with pain. In other words, poor proprioceptive accuracy may lead to a wide range of movements being

avoided, thus leading to a restricted movement repertoire, and contributing to the development and maintenance of chronic pain disability.

To investigate this intriguing question, we needed a reliable measure to quantify proprioceptive function of the upper limb, as the robotic arm-reaching paradigm requires upper limb movement (Meulders et al., 2016). A large variety of proprioceptive tests exists; they differ in the required motor and memory capacity, but importantly, also in the aspect of proprioception that they evaluate (Hillier et al., 2015). Unfortunately, existing tasks generally did not allow for evaluation of more complex processes that are essential for accurate and controlled movement (i.e., kinesthesia during functional movement), such as integration of sensory and motor information – i.e., the dynamic updating of motor output based on proprioceptively encoded (and changing) body position (Proske & Gandevia, 2012). Therefore, in Chapter 3 we developed the DMR task, which captures such sensorimotor integration processes, and established that it has sufficient test-retest reliability. The diagnostic validity of this task still needs to be evaluated; in Chapter 7, we presented the preregistration of a study investigating whether participants with chronic pain indeed show poor proprioceptive accuracy as measured by the DMR task, compared to pain-free controls.

Because the original robotic arm-reaching task relies heavily on visual information (e.g., the handle of the robotic device is visualized on-screen to track movements online), we adapted this task to rely more on proprioceptive information. In Chapter 4, we introduced an adapted version in which participants were no longer guided by on-screen visual aids while learning to avoid the pain stimulus. Using this task in combination with the DMR task introduced in Chapter 3, we showed an association between poor proprioceptive accuracy and excessive avoidance behavior. This innovative finding suggests that poor accuracy may indeed contribute to disability, as excessive avoidance is considered key in the development and maintenance of chronic pain disability (Vlaeyen et al., 2016). However, whether there is a causal relationship between proprioceptive accuracy and avoidance still needs to be established. The observed association also extends previous work showing that poor (visual) perceptual accuracy is associated with more fear generalization (Struyf et al., 2017; Zaman, Ceulemans, et al., 2019; Zaman, Struyf, et al., 2019). However, these studies mainly focused on generalization toward stimuli resembling a threat-associated stimulus, whereas the current study looked at safe avoidance movements.

Positive affect

Besides improving proprioceptive accuracy, positive affect induction was identified as a promising pathway to attenuate generalization of pain-related avoidance behavior (Chapter 2). Evidence for the potential of positive psychology interventions in pain treatment has been

accumulating (Finan & Garland, 2015; Hanssen et al., 2017; Ong et al., 2015; Sturgeon & Zautra, 2010); they have been shown to successfully promote positive affect, optimism, wellbeing and functioning in people with chronic pain (Braunwalder et al., 2022; Ong et al., 2020). Importantly, Geschwind et al. (2015) showed that experimentally induced positive affect was associated with generalization of pain-related *fear*: higher increases in positive affect were associated with less fear generalization. In Chapter 5, we extended this work by investigating whether positive affect induction also has the potential to reduce generalization of pain-related *avoidance*. Using the robotic arm-reaching paradigm introduced in Chapter 1 (Study 2), one group of participants performed a visualization exercise to induce positive affect before the generalization test, while another group performed a control visualization exercise. Results showed no difference between both groups in terms of generalization. However, when analyzing data *across* groups (i.e., using positive affect change as covariate), results showed that increases in positive affect were indeed associated with less generalization of both pain-related avoidance and fear. Even though such analyses limit causal inferences, because they are not based on the experimental groups, these results confirm that positive affect induction is a promising way to attenuate excessive generalization.

In Chapter 6, we investigated whether we could replicate this finding, using a different paradigm. Specifically, we used the procedure by San Martín et al. (2020), which allowed us to investigate the effect of positive affect induction on relief in addition to avoidance. As in the study with the robotic arm-reaching task (Chapter 5), one group of participants performed a visualization exercise to induce positive affect before the generalization test, while another group performed a control exercise. Results showed no differences between groups in terms of pain-related avoidance, nor relief. Also when performing analyses across groups (i.e., using positive affect change as covariate), results showed no associations between increases in positive affect and avoidance or relief. This unexpected finding could be explained by an important methodological difference between the two avoidance paradigms. The procedure by San Martín et al. (2020) employed a simple button press as avoidance response, as is often the case in the anxiety field (e.g., Lommen et al., 2017; van Meurs et al., 2014); however, such dichotomous responses may prevent capturing more subtle differences in avoidance. The robotic arm-reaching paradigm on the other hand allows varying degrees of avoidance behavior: avoidance is operationalized as lateral deviation from the shortest (and easiest) trajectory. Using such a continuous measure may have allowed for the effects of positive affect induction to manifest themselves. This operationalization is also an important improvement in terms of ecological validity, as varying degrees of avoidance can be observed in clinical reality.

Challenges and future directions

Validating current findings

In the operant avoidance task used in Chapter 4, to test the association between proprioceptive accuracy and avoidance, movements on the outside of the semi-circular avoidance trajectory were interpreted as excessive avoidance behavior, as such movements are directed away from the pain-associated trajectory. However, in the DMR task, which also employs circular movement trajectories (but involves no pain stimuli), there was a general tendency to move on the outside of the target circle during movement reproduction as well (i.e., systematic overshooting). This may be due to the fact that circular movements produce an outward directed force, which results in the movement deviating outward if this force is not counteracted sufficiently. Importantly, this means that during the operant avoidance task, the observed tendency to move on the outside of the avoidance trajectory probably did not solely result from overprotective behavior, but also from overshooting. Further analyses showed that movements during this task deviated significantly further compared to the DMR task, indicating that outward deviations were not *only* a result of overshooting. However, to firmly establish that deviations reflect excessive avoidance, follow-up research is required. In Box 1, we present a study that investigates whether the association between poor proprioceptive accuracy and excessive pain-related avoidance behavior can be replicated while controlling for overshooting tendencies. This study is being conducted at the time of writing (preregistered at Open Science Framework: https://osf.io/6yxaj/?view_only=7a768ccc48324e5eaab85c3b091228aa).

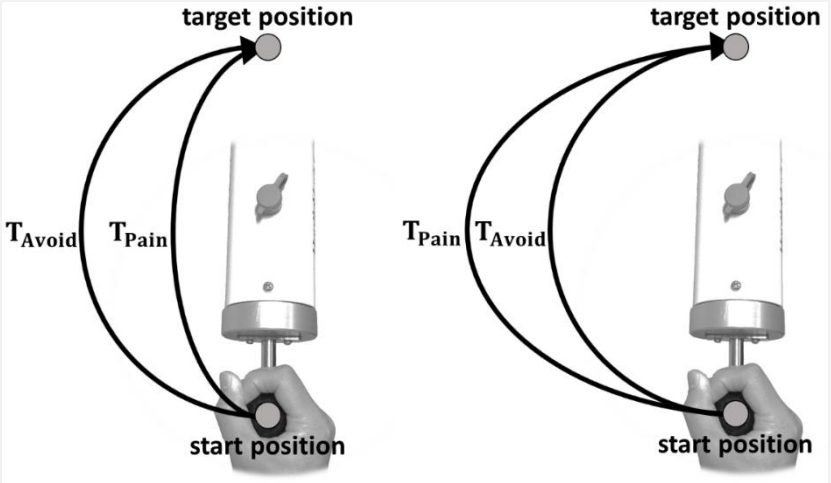
In Chapter 5, we reported evidence for an association between experimentally increased positive affect and less generalization of avoidance. However, to confirm the causal influence of the affect manipulation, follow-up research is required. Our study tested this manipulation in healthy, pain-free participants as a first step. However, these individuals generally do not show deficits in positive affect, thus limiting the potential to increase it – even though we found significant increases in positive affect in both Chapters 5 and 6. Larger increases in positive affect may result in stronger differences in behavior between experimental and control groups. Furthermore, anxious traits modulate avoidance generalization (Hunt et al., 2019); participants with higher levels of such traits show more avoidance generalization, meaning that there is more potential to attenuate it. Follow-up studies can for example select participants based on low trait positive affect and high trait anxiety scores. Investigations using (sub)clinical samples may result in larger effect sizes, which may also result in group-based differences (i.e., statistically significant differences between positive affect and control groups). Such work could confirm the causal role of positive affect induction in tackling excessive spreading of avoidance.

Box 1: *Replicating the association between poor proprioceptive accuracy and excessive pain-related avoidance behavior while controlling for overshooting tendencies*

The procedure starts with the DMR task to assess proprioceptive accuracy. Next, participants perform an adapted version of the operant avoidance task. Similar to Chapter 4, two trajectories can be used to reach the target position during this task. One is a semi-circle with an 8 cm radius; this trajectory is never followed by the pain stimulus. Contrary to Chapter 4, the pain-associated trajectory is no longer a semi-circle positioned on the opposite side, but a curved trajectory positioned either on the in- or outside of the semi-circular avoidance trajectory (counterbalanced between participants; Figure B1.1). This means that when the pain-associated trajectory is positioned on the outside, excessive avoidance (during the avoidance test) is operationalized as movement on the *inside* of the semi-circular avoidance trajectory. In other words, excessive avoidance cannot be explained by overshooting in this case.

Figure B1.1

Movement trajectories presented during adapted operant avoidance task



Note. One trajectory is paired with the pain stimulus (80% chance; T_{Pain}), while the pain stimulus can be avoided by performing the other trajectory (T_{Avoid}). Position of T_{Pain} and whether movements are performed to the left or right (not displayed here) are counterbalanced between participants.

Further investigating experimental interventions

Because Chapter 4 showed an association between proprioceptive accuracy and pain-related avoidance behavior, an important next step is to test whether improving proprioceptive accuracy attenuates excessive avoidance. Interestingly, as emphasized in Chapter 2, research in the domain of anxiety already showed that perceptual – i.e., visual – discrimination training reduces generalization of fear/expectancy (Ginat-Frolich et al., 2017; Herzog et al., 2021) and avoidance behavior (Ginat-Frolich et al., 2019; Lommen et al., 2017). However, it remains to be investigated whether this applies to movements and activities in the context of pain as well.

The activation of competing goals was identified as another potential way to attenuate excessive generalization of avoidance in Chapter 2. Experimental studies in both the field of anxiety and pain indeed show that competing goals (e.g., obtaining money) attenuate avoidance (Claes et al., 2014; Pittig & Dehler, 2019; Pittig et al., 2018). Moreover, Bennett et al. (2020) showed that reinforcing behaviors that compete with avoidance leads to reduced generalization along a dimension of conceptual relatedness. In experimental settings, competing goals are often activated by introducing monetary or even virtual reward (Pittig & Dehler, 2019; Pittig et al., 2018). However, such outcomes may not be experienced as rewarding or motivating to the same extent for all participants (Pittig, Boschet, et al., 2020; Pittig & Scherbaum, 2020). Therefore, personalizing the rewards to account for individual variation may be necessary. This could be particularly relevant in chronic pain patients as reduced reward responsivity has been observed in this population (Rizvi et al., 2021). Though challenging, a lab analogue to clinical methods in which participants are encouraged to identify their personal values and set goals consistent with those values, as used for example in Acceptance and Commitment Therapy for chronic pain (Wetherell et al., 2011), may prove fruitful.

When testing interventions to attenuate avoidance generalization, the timing within the experimental procedure deserves consideration. In Chapters 5 and 6, the experimental design reflected an intervention approach: positive affect was induced *after* avoidance acquisition. However, an important question is whether interventions such as positive affect induction are also viable prevention strategies in the context of chronic pain. A preventive approach can be employed for example when at-risk individuals – e.g., showing high pain catastrophizing – are faced with surgery, as these individuals may be more likely to develop chronic pain disability (Khan et al., 2011). In other words, when investigating interventions to counter overgeneralization, effects on learning itself also deserve attention. The observation that overgeneralization may be driven by impaired safety learning in particular is important to consider (Meulders, 2020; Meulders, Harvie, et al., 2014; Meulders et al., 2015). Positive affect for example not only has the potential to reduce generalization of pain-related fear and avoidance, but also to protect against deficient pain-related safety learning (Meulders,

Meulders, et al., 2014). The same may be true for other interventions, as proprioceptive accuracy training for example could improve encoding of the response-omission memory. Improving safety learning may steepen generalization gradients, meaning that stimuli, responses and contexts similar to a safe one elicit less fear and avoidance as well, assuming that such learning will generalize. From a clinical perspective, generalizing safety for example corresponds with systematically performing movements that are similar to ones that are known not to increase pain, thus leading to a wider range of movements being performed, breaking the potential vicious cycle described by fear-avoidance models (Vlaeyen et al., 2016).

Effects on learning may not only be relevant from the perspective of preventive approaches, but also for interventions during the acute pain stage; exploratory analyses in Chapter 5 suggested that positive affect reduced avoidance generalization, while fear generalization was initially unaffected. This means that for a sustained behavior change to occur, safety learning would be required (i.e., extinction of generalized pain-related fear). Importantly, impaired extinction of generalized pain-related fear has been observed in chronic pain (Meulders, Meulders, et al., 2017). However, positive affect interventions for example can facilitate extinction learning (Zbozinek & Craske, 2017). Whether sustained behavior changes are achieved following positive affect induction in the lab can be examined by including a follow-up test session (e.g., 24 hours later). This does not necessarily mean that positive affect increases are maintained in follow-up tests when using healthy, pain-free participants; Chapter 5 for example showed that effects on positive affect were rather transient during a single lab session, while a maintained change in behavior seemed present. However, when using positive affect induction in treatment settings (i.e., outside the lab), both sustained positive affect and behavior changes may be expected; according to the broaden-and-build theory, positive emotions lead to enduring change because they instigate an upward spiral in which positive emotions lead to behavioral changes, which in turn lead to increased positive emotions (Fredrickson, 2001, 2003).

Underlying mechanisms

In Chapter 1, we suggested that uncertainty might play a role in the generalization of pain-related avoidance behavior: increased uncertainty regarding movement-pain associations seems to lead to more avoidance generalization. The role of uncertainty is important to consider in chronic pain conditions, as it can arise on different levels; sufferers can for example experience uncertainty regarding the occurrence, origin, meaning and intensity of their pain (Zaman et al., 2021). Moreover, uncertainty may arise in case of poor proprioceptive accuracy, meaning that it could play a role in the association between proprioceptive accuracy and avoidance behavior (Chapter 4). This means that

proprioceptive accuracy training could lead to less uncertainty regarding performed movements, and therefore less avoidance generalization. However, experimental research systematically investigating the role of uncertainty is required to confirm its role in generalization (e.g., comparing groups with varying degrees of uncertainty), and in interventions such as proprioceptive accuracy training. Individual differences in intolerance of uncertainty deserve attention here as well: individuals highly intolerant of uncertainty are more likely to show excessive avoidance (Hunt et al., 2019), and may benefit most from reducing uncertainty.

Positive affect on the other hand has been found to improve executive functions such as working memory, indicating that cognitive processes may mediate the effect of positive affect induction on generalization (Boselie et al., 2017; Boselie et al., 2014; Yang et al., 2013). As discussed in Chapter 2, evidence indeed shows that better working memory is associated with less generalization (Lenaert et al., 2016; Wills et al., 2015). Moreover, executive functions such as working memory and attentional control are impaired in chronic pain conditions (Berryman et al., 2013; Todd et al., 2018). Therefore, it might prove fruitful to investigate whether improved working memory underlies the association between higher positive affect increases and less generalization of avoidance behavior. However, in Chapter 5, improvements in working memory seem unlikely to have played a mediating role, because the movement trajectories used here were easily distinguishable; working memory is probably more relevant for complex stimuli.

Another aspect to consider in Chapter 5 is that positive affect induction may have led to more positive evaluations of the movement trajectories similar to the pain-associated ones, thus leading to approach behavior (Zbozinek & Craske, 2017). Additionally, affect induction may have influenced approach motivation directly; some positive affect states have been argued to be low in approach motivation (e.g., joy when seeing a funny video), while others are high in approach motivation (e.g., desire when seeing chocolate; Gable & Harmon-Jones, 2008). The best possible self exercise used to induce positive affect in Chapter 5 entails visualizing the achievement of one's goals (Peters et al., 2010), and therefore arguably induces positive affect that is high in approach motivation. Although the induced approach motivation was probably not directly related to the experimental task, it may have increased approach behavior here as well (i.e., approach of novel movements similar to the pain-associated ones that required less effort). Future studies can investigate this further by varying and assessing the approach motivation of induced positive affect for example. Such studies are important because gaining insight into the underlying mechanisms of experimental interventions can further inform and optimize treatment; it may for example help treatment focus specifically on aspects such as approach motivation to increase effectiveness.

Generalizability of findings

In the current experimental studies we only focused on generalization along perceptual dimensions (i.e., we tested perceptually similar movements and stimuli). However, studies have shown that pain-related fear generalizes along dimensions of categorical relatedness (Bennett et al., 2015; Glogan et al., 2018; Meulders, Vandael, et al., 2017). Moreover, research in the anxiety field has shown that avoidance behavior can generalize along such dimensions as well (Bennett et al., 2020; Dymond et al., 2011). Whether the interventions discussed and tested in this thesis affect (over)generalization along dimensions of categorical relatedness deserves further investigation. As noted in Chapter 2, proprioceptive accuracy training may affect such generalization as well: it could lead to increased weighing of sensory-perceptual input and decreased weighing of affective-motivational aspects of activities, meaning less emphasis on inferences based on conceptual relationships, thus attenuating overgeneralization.

Furthermore, it is important to consider that avoidance takes different forms in chronic pain conditions: it can be passive (i.e., refraining from performing movements or activities altogether; e.g., resting) or active (i.e., performing movements or activities in a particular way; e.g., rigid, unnatural movement). Both types of avoidance behavior can be modeled in the lab by either suppressing a threat-associated response – e.g., not performing a pain-associated movement – or performing a safety-associated response respectively – e.g., performing an alternative, safe movement (Krypotos et al., 2015). In the current PhD project, we focused on active avoidance behavior; whether the discussed interventions are also effective in case of passive avoidance is an open question. In case of passive avoidance, it may be for example that behavioral inhibition following pain experience is of relevance rather than generalization of learned avoidance behavior (Jensen et al., 2016). Furthermore, we used predictable pain in the current experiments: certain stimuli and movements were paired with pain (with varying probabilities), while others were not. This approach models regional pain syndromes (e.g., low back pain), rather than widespread pain (e.g., fibromyalgia; Meulders & Vlaeyen, 2013). In other words, whether the discussed interventions result in improved outcomes in widespread pain (i.e., unpredictable pain) deserves further investigation as well.

Finally, it is important to take into account that all findings in the current thesis are based on samples that consisted of healthy, pain-free participants, which were mainly European students. Whether our findings generalize toward clinical populations with varying ages, ethnicities, etc. requires further research. For example, the role of relief in overgeneralization of avoidance in chronic pain conditions needs investigation, because impaired reward learning has been observed in this population: people with chronic pain show deficits in improving their performance on reward-dependent learning tasks (Rizvi et al., 2021). A plausible explanation for this is impaired updating of

expectancies (e.g., pain is expected) based on outcomes (e.g., no pain is experienced) in chronic pain conditions (i.e., a stagnated error-reduction process; Van den Bergh et al., 2021). This implies maintained expectancy-violations when avoidance is not followed by pain, which results in persistent relief experience when avoiding, as relief is suggested to track expectancy-violations (Willems & Vervliet, 2021). Such persistent relief may result in persistent avoidance, turning avoidance maladaptive (Vervliet et al., 2017). However, this is speculative and therefore needs further scrutiny.

Once experimental interventions to attenuate generalization of pain-related avoidance behavior have been validated in pain-free samples, they can be tested in chronic pain conditions to reduce overgeneralization in the lab. Additionally, to bridge the gap between the lab and daily life, such studies could also explore whether behavior as measured in the lab is linked to functioning in daily life, as this would importantly contribute to the external validity of paradigms – an important aspect that is often overlooked (Vervliet & Raes, 2013).

Clinical implications

Systematic investigation of experimental interventions to counter overgeneralization is crucial to inform and optimize evidence-based treatment of chronic pain conditions. Proprioceptive accuracy training (e.g., Jull et al., 2007) and positive psychology interventions (e.g., Peters et al., 2017) are already being used as treatments in chronic pain conditions – and other treatments may unintendedly target proprioceptive accuracy and positive affect (e.g., overcoming fear during exposure therapy may lead to positive affect). Experimental studies can provide insights into underlying mechanisms of such treatments, and therefore help fine-tune them and boost their application. Evidence for the role of proprioceptive accuracy in excessive avoidance can for example prompt clinicians to screen for proprioceptive impairments, and provide accuracy training if necessary. Furthermore, low levels of positive affect may be an indication for the use of positive psychology interventions. Moreover, interventions may be combined to improve clinical outcomes: for example, positive psychology interventions could motivate (avoided) physical exercise to increase proprioceptive accuracy. However, these clinical applications first need systematic investigation before promoting their use in general practice – for example starting with single-case designs (Onghena & Edgington, 2005). Finally, it needs to be emphasized that research into the prevention of chronic pain is scarce (Gewandter et al., 2015). Experimental research on the preventive potential of interventions may inspire this important field of research.

Conclusion

Pain and protective responses such as avoidance can be very helpful when they prevent bodily harm. However, when tissues have healed, they are no longer helpful. In the current PhD project, we used innovative experimental paradigms to investigate factors that may counter excessive spreading (or overgeneralization) of pain-related avoidance behavior toward safe activities. Gaining insight into these factors is crucial because overgeneralization of avoidance can be extremely debilitating and contribute to chronic pain disability. We investigated the potential of proprioceptive accuracy and positive affect, and paved the road for future studies to advance knowledge in this field. Continued experimental research efforts can eventually help optimize existing, and potentially develop new, treatment strategies to break the self-sustaining cycle of activity disengagement and reduce suffering.

Appendix A

Supplemental material Chapter 1

Methods

Exit questionnaires

In both experiments, immediately after completing the robotic arm-reaching task, participants completed an exit questionnaire including the following questions: (1) "*How intense did you find the electrical stimulus during the robotic arm task?*", (2) "*How unpleasant did you find the electrical stimulus?*", (3) "*How much did you want to avoid the electrical stimulus?*", (4) "*How threatening did you find the electrical stimulus?*", and (5) "*How intense did you find the resistance of the robotic arm?*". Participants responded on an 11-point scale ranging from 0 ("*not at all*") to 10 ("*very much*"). In addition to these questions, Experiment 2 included the questions: (6) "*How unpleasant did you find the resistance?*", and (7) "*How much did you want to avoid the resistance?*".

Trait questionnaires

In both experiments, participants completed trait questionnaires to measure individual differences in (1) positive and negative affect (the Positive and Negative Affect Schedule; Watson et al., 1988), (2) pain catastrophizing (Pain Catastrophizing Scale; Sullivan et al., 1995), (3) fear of pain (Fear of Pain Questionnaire; McNeil & Rainwater, 1998; Roelofs et al., 2005), (4) experiential avoidance (the Multidimensional Experiential Avoidance Questionnaire; Gámez et al., 2011), (5) distress tolerance (the Distress Tolerance Scale; Simons & Gaher, 2005), and (6) trait anxiety (the State-Trait Anxiety Inventory; Spielberger, 1983). In addition to these traits, in Experiment 2 we assessed cognitive flexibility (Cognitive Flexibility Inventory; Portoghese et al., 2020). Questionnaires were filled in using a web survey tool (Qualtrics; Qualtrics, Provo, Utah, USA) presented on a tablet (ASUS ZenPad 8.0; AsusTek Computer Inc., Taipei, Taiwan).

Switching behavior

Switching behavior was operationalized as choosing a movement trajectory different from the one on the previous trial. This gives a rough estimate of exploratory behavior, as more switching indicates more exploration.

Data analysis

Independent samples *t*-tests were performed to test for differences between groups on scores of the *exit and trait questionnaires*.

To check for the successful acquisition of pain-related fear and avoidance, we analyzed data from the acquisition phases of both experiments. In the *self-report measures* (i.e., pain-expectancy and pain-related fear ratings), acquisition was indicated by significant differences between the different trajectories (T1 > T2 > T3) in the Experimental, but not the Yoked Group. To test these hypotheses, self-reports were averaged over blocks per trajectory for all participants, and RM ANOVAs were calculated separately for each experimental block; Group served as between-subjects factor, and Block and Trajectory as within-subjects factors. Comparisons of T1 *vs.* T3 were of primary interest, given that T2 was an ambiguously punished movement trajectory. Note that for Experiment 1, only comparisons between T1 and T3 were pre-registered. However, given that all comparisons (T1 *vs.* T2, T2 *vs.* T3, and T1 *vs.* T3) were pre-registered for Experiment 2, we report all comparisons for Experiment 1 as well. For analyses of *avoidance behavior*, a MATLAB (MathWorks, Natick, MA, US) script was used to extract the maximal deviation per trial. These values were averaged per block for each participant and used to compare avoidance behavior between groups (RM ANOVAs); Group served as between-subjects factor and Block as within-subjects factor.

Given that generalization was tested in the absence of pain stimuli (generalization under extinction), extinction of self-reports (i.e., pain-expectancy and pain-related fear), and avoidance behavior towards the original acquisition trajectories (T1-3) was tested during the *reminder-of-acquisition blocks*. In these blocks, the acquisition trajectories were once again available along with the acquisition punishment schemata. Retention of the acquisition effects was indicated by a similar data pattern to that of the acquisition phase (Self-reports: significant differences between the different trajectories (T1 > T2 > T3), in the Experimental, but not the Yoked Group; Avoidance: significantly larger deviations in the Experimental compared to the Yoked Group). The analyses of the reminder-of-acquisition blocks were similar to those performed on the data from the acquisition phases.

For the sake of completeness, we report all *pairwise comparison of pain-related fear ratings during all generalization blocks* of both experiments.

Finally, we visualized the relative frequency of *switching behavior* for the Experimental Groups of Experiments 1 and 2 during the acquisition phases (Experiment 1: T11-T34; Experiment 2: T11-T46) and the first generalization blocks (Experiment 1: T35-T46; Experiment 2: T47-T58).

Results

Exit and trait questionnaires

See tables for results regarding exit questionnaires (Experiment 1: Table S1.1; Experiment 2: Table S1.2). Only one of these tests was significant: in Experiment 2 the Yoked group reported a significantly higher desire to avoid the effort compared to the Experimental Group, $t(68) = -2.89$, $p = .005$ (Bonferroni corrected threshold for significance = .007). This suggests that the ability and incentive to avoid pain decreased the aversiveness of needing to exert effort in the Experimental Group of Experiment 2. In other words, avoidance was perceived as less costly when it resulted in the omission of pain. Note that, the question pertaining to the desire to avoid effort was only included in the exit questionnaire of Experiment 2, and not Experiment 1.

See tables for results regarding trait questionnaires (Experiment 1: Table S1.3; Experiment 2: Table S1.4).

Table S1.1

Group differences on exit questionnaires Experiment 1

N = 64	Experimental Group		Yoked Group			
	M	*SD*	*M*	*SD*	*t*(62)	*p*
Pain intensity	6.69	1.47	7.03	1.38	-0.96	.338
Pain unpleasantness	7.19	2.39	7.59	1.93	-0.75	.457
Pain threat	5.31	2.66	5.34	3.31	-0.04	.967
Desire to avoid pain	7.28	2.47	7.56	2.55	-0.45	.656
Resistance intensity	5.28	2.04	5.56	2.35	-0.51	.611

Note. Differences between the Experimental Group (n = 32) and the Yoked Group (n = 32) in retrospective ratings of intensity, unpleasantness, and threat value of the pain stimulus, intensity of resistance of the robotic device, and the extent to which participants wanted to avoid the pain stimulus. *P*-values are not corrected for multiple testing (Bonferroni corrected significance threshold is .01).

Acquisition phases

Experiment 1

A 2 (Group: Experimental, Yoked) x 2 (Block: ACQ1-2) x 3 (Trajectory: T1-3) RM ANOVA on the mean *pain-expectancy ratings* per acquisition block revealed a significant 3-way interaction, $F(1.77, 109.73) = 22.90$, $p < .001$, $\eta_p^2 = .27$, indicating that pain-expectancies for the three trajectories evolved differently for the two groups. Planned comparisons confirmed that by the end of the acquisition

phase (ACQ2), the Experimental Group expected the pain stimulus to occur more during T1, $t(62) = 13.38$, $p < .001$, $d = 3.76$, and T2, $t(62) = 10.74$, $p < .001$, $d = 2.05$, compared to T3, showing that the Experimental Group successfully acquired the experimental movement-pain contingencies (T1 > T2 > T3; Figure 1.2, panel A in Chapter 1). Furthermore, the pain stimulus was expected more during T1 than T2, $t(62) = 5.08$, $p < .001$, $d = 1.17$. No such differences occurred in the Yoked Group (all *p*-values > .05; Figure 1.2, panel B in Chapter 1).

Table S1.2

Group differences on exit questionnaires Experiment 2

N = 70	Experimental Group		Yoked Group			
	M	*SD*	*M*	*SD*	*t*(68)	*p*
Pain intensity	6.91	1.15	6.60	1.82	0.86	.390
Pain unpleasantness	7.37	1.78	7.23	2.09	0.31	.759
Pain threat	6.20	2.81	5.46	2.76	1.12	.268
Desire to avoid pain	7.91	2.31	7.51	2.78	0.65	.516
Resistance intensity	5.34	2.33	5.09	2.33	0.46	.646
Resistance unpleasantness	3.77	2.54	5.03	2.47	-2.10	.040
Desire to avoid resistance	2.94	2.89	4.97	2.99	-2.89	.005

Note. Differences between the Experimental Group (n = 35) and the Yoked Group (n = 35) in retrospective ratings of intensity, unpleasantness, and threat value (pain stimulus only) of the pain stimulus and resistance of the robotic device, as well as the extent to which participants wanted to avoid the pain and the effort. *P*-values are not corrected for multiple testing (Bonferroni corrected significance threshold is .007).

A similar RM ANOVA on the mean *pain-related fear ratings* during acquisition revealed a significant 3-way interaction, $F(1.67, 103.61) = 9.92$, $p < .001$, $\eta_p^2 = .14$. Planned comparisons confirmed similar differences as in pain-expectancy for the Experimental group at ACQ2 (T1 *vs.* T3: $t(62) = 7.00$, $p < .0001$, $d = 1.38$; T2 *vs.* T3: $t(62) = 6.94$, $p < .0001$, $d = 1.21$), although the difference between T1 and T2 did not reach significance, $t(62) = 1.90$, $p = .062$ (Figure 1.3, panel A in Chapter 1). No such differences occurred in the Yoked Group (all *p*-values > .05; Figure 1.3, panel B in Chapter 1). Thus, participants in the Experimental Group learned to fear and expect the pain stimulus more during the pain-associated movements (T1-2) compared to the safe movement (T3).

Table S1.3

Group differences on trait questionnaires Experiment 1

N = 64	Experimental Group (78% female)		Yoked Group (84% female)			
	M	*SD*	*M*	*SD*	*t(62)*	*p*
PANAS – negative affect	16.56	5.12	18.56	4.75	-1.62	.111
PANAS – positive affect	30.38	5.84	31.00	8.11	-0.35	.725
PCS – rumination	7.03	3.87	6.59	4.07	0.44	.661
PCS – magnification	4.19	2.61	3.56	2.38	1.00	.321
PCS – helplessness	7.03	4.37	6.91	4.78	0.11	.913
PCS – total	18.25	9.81	17.06	10.07	0.48	.634
FPQ – medical pain	27.69	7.24	26.75	6.18	0.56	.579
FPQ – minor pain	19.53	5.02	20.25	5.16	-0.56	.574
FPQ – severe pain	36.94	7.25	37.56	7.95	-0.33	.744
FPQ – total	84.16	16.24	84.56	15.83	-0.10	.920
MEAQ – behavioral avoidance	28.94	7.06	29.34	9.19	-0.20	.843
MEAQ – distress aversion	40.19	10.53	38.31	10.61	0.71	.481
MEAQ – procrastination	22.63	7.67	20.72	7.26	1.02	.311
MEAQ – distraction	25.59	5.56	23.75	5.56	1.33	.189
MEAQ – repression	31.16	7.64	32.63	10.31	-0.65	.520
MEAQ – distress endurance	49.13	6.31	50.03	7.74	-0.51	.610
MEAQ – total	176.38	27.80	171.72	34.38	0.60	.554
DTS – total	57.53	10.28	59.13	8.52	-0.68	.502
STAI-T	40.16	8.32	42.06	7.73	-0.95	.346

Note. PANAS = Positive and Negative Affect scale; PCS = Pain Catastrophizing Scale; FPQ = Fear of Pain Questionnaire; MEAQ = Multidimensional Experiential Avoidance Questionnaire; DTS = Distress Tolerance Scale; STAI-T = State-Trait Anxiety Inventory: trait version. Bonferroni corrected threshold for significance is $p < .003$.

Table S1.4

Group differences on trait questionnaires Experiment 2

N = 70	Experimental Group (71% female)		Yoked Group (66% female)			
	M	*SD*	*M*	*SD*	*t(67)*	*p*
PANAS – positive affect	26.29	5.95	26.09	5.88	0.14	.890
PANAS – negative affect	21.29	5.39	21.79	5.09	-0.40	.688
PCS – rumination	7.31	4.38	6.44	4.22	0.84	.402
PCS – magnification	3.46	2.43	3.68	2.50	-0.37	.713
PCS – helplessness	6.40	3.99	6.21	4.50	0.19	.850
PCS – total	17.17	9.39	16.32	9.80	0.37	.715
FPQ – severe pain	38.74	6.45	36.21	7.69	1.49	.142
FPQ – minor pain	22.71	6.30	21.68	6.13	0.69	.491
FPQ – medical pain	30.06	6.84	27.79	8.73	1.20	.234
FPQ – total	91.51	16.26	85.68	16.86	1.46	.148
MEAQ – behavioral avoidance	31.49	8.93	32.44	8.09	-0.46	.643
MEAQ – distress aversion	43.82	10.97	39.59	12.54	1.77	.081
MEAQ – procrastination	23.20	7.34	24.71	7.52	-0.84	.403
MEAQ – distraction	26.23	7.24	25.47	6.34	0.46	.646
MEAQ – repression	32.60	10.76	35.24	12.44	-0.94	.349
MEAQ – distress endurance	49.43	7.45	47.88	5.69	0.97	.337
MEAQ – total	206.37	33.52	205.50	33.32	0.11	.914
DTS	53.80	12.71	55.67	10.66	-0.65	.515
STAI-T	40.60	8.87	43.03	7.70	-1.21	.229
CFI	106.85	12.45	103.06	11.51	1.29	.200

Note. PANAS = Positive and Negative Affect scale; PCS = Pain Catastrophizing Scale; FPQ = Fear of Pain Questionnaire; MEAQ = Multidimensional Experiential Avoidance Questionnaire; DTS = Distress Tolerance Scale; STAI-T = State-Trait Anxiety Inventory: trait version; CFI = Cognitive Flexibility Inventory. Bonferroni corrected threshold for significance is $p < .002$.

A 2 (Group: Experimental, Yoked) x 2 (Block: ACQ1-2) RM ANOVA on the mean *maximal deviations* during acquisition revealed a significant 2-way interaction, $F(1, 62) = 12.72$, $p < .001$, $\eta_p^2 = .17$, indicating differences in avoidance behavior over time in the two groups. As expected, planned

comparisons confirmed that participants in the Experimental Group showed significantly larger deviations than the Yoked Group at ACQ2, $t(62) = 4.87$, $p < .001$, $d = 1.22$, demonstrating successful avoidance learning (Figure 1.4, panel A in Chapter 1).

Experiment 2

A 2 (Group: Experimental, Yoked) x 3 (Block: ACQ1-3) x 3 (Trajectory: T1-3) RM ANOVA on mean *pain-expectancy reports* during the acquisition phase revealed a significant 3-way interaction, $F(2.90, 197.36) = 15.37$, $p < .001$, $\eta_p^2 = .18$, suggesting that pain-expectancies for the three trajectories evolved differently in the two groups. Planned comparisons confirmed that by the end of the acquisition phase (ACQ3), the Experimental Group expected the pain stimulus to occur more during T1, $t(68) = 11.33$, $p < .001$, $d = 2.45$, and T2, $t(68) = 10.14$, $p < .001$, $d = 1.85$ compared to T3. Furthermore, participants also expected the pain stimulus more during T1 compared to T2, $t(68) = 3.33$, $p = .001$, $d = .72$ (Figure 1.2, panel C in Chapter 1). No such differences occurred in the Yoked Group (all *p*-values > .05; Figure 1.2, panel D in Chapter 1).

A similar RM ANOVA on mean *pain-related fear reports* during acquisition revealed comparable effects to pain-expectancy; there was a significant 3-way interaction, $F(3.50, 238.11) = 15.05$, $p < .001$, $\eta_p^2 = .18$, and planned comparisons showed that both T1, $t(68) = 9.48$, $p < .001$, $d = 1.61$, and T2, $t(68) = 8.55$, $p < .001$, $d = 1.33$ were feared more than T3 during ACQ3. Furthermore, T1 was feared more than T2 in this block, $t(68) = 2.49$, $p = .015$, $d = .27$ (Figure 1.3, panel C in Chapter 1). No such differences occurred in the Yoked Group (all *p*-values > .05; Figure 1.3, panel D in Chapter 1).

A 2 (Group: Experimental, Yoked) x 2 (Block: ACQ1-2) RM ANOVA on mean *maximal deviations* during acquisition revealed a significant 2-way interaction, $F(1.92, 130.35) = 14.93$, $p < .001$, $\eta_p^2 = .18$, indicating that avoidance developed differently for the two groups. Planned comparisons confirmed that the Experimental Group demonstrated larger deviations than the Yoked Group during ACQ3, $t(68) = 6.46$, $p < .001$, $d = 1.54$ (Figure 1.4, panel B in Chapter 1). Together these results indicate that the Experimental Group successfully acquired the movement-pain contingencies, shown by differential pain-expectancy and fear ratings, and successfully learned to avoid the pain stimulus.

Reminder-of-acquisition phases

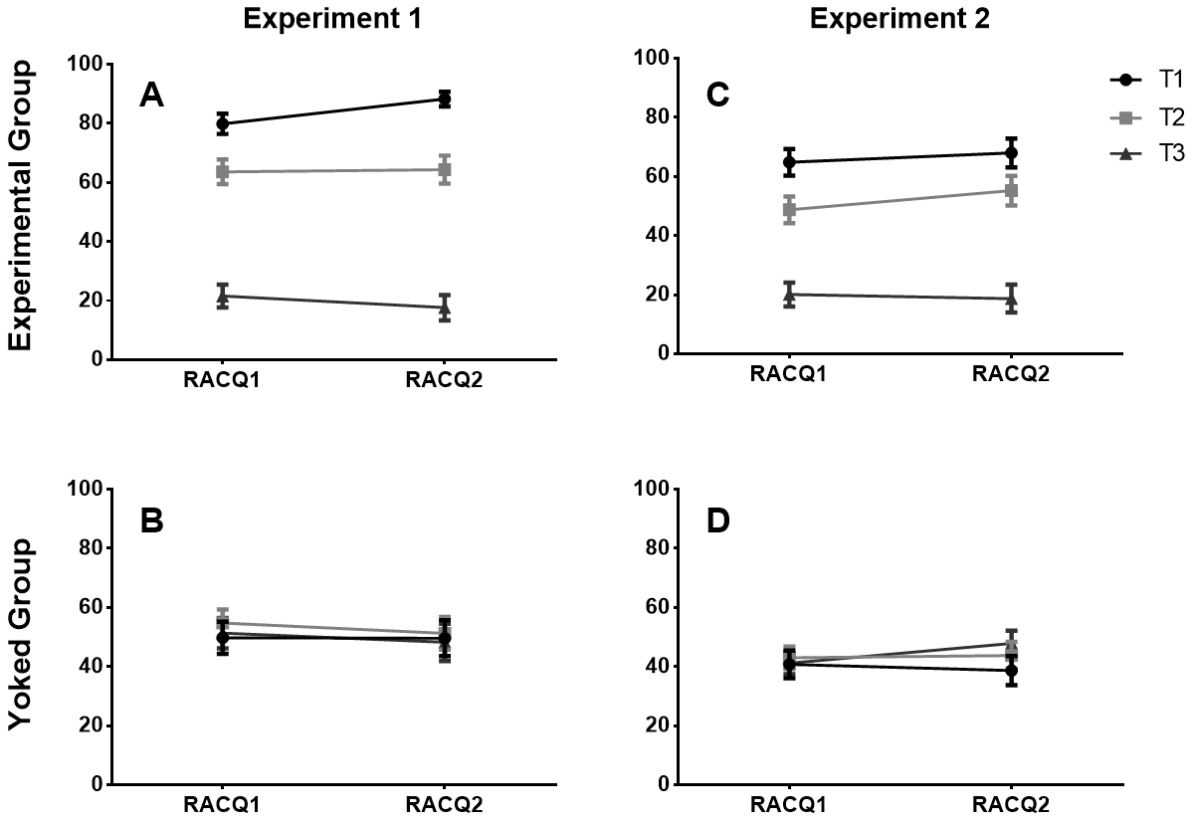
Experiment 1

A 2 (Group: Experimental, Yoked) x 2 (Block: RACQ1-2) x 3 (Trajectory: T1-3) RM ANOVA on the mean *pain-expectancy ratings* during the reminder-of-acquisition blocks revealed a significant Group x Trajectory interaction, $F(1.91, 118.39) = 59.41$, $p < .001$, $\eta_p^2 = .49$, indicating that pain-expectancies for the different trajectories differed between groups during these blocks. Planned comparisons confirmed that the Experimental Group still expected the pain to occur more for T1, $t(62)$

= 10.66, $p < .001$ $d = 2.83$, and T2, $t(62) = 7.81$, $p < .001$, $d = 1.85$, compared to T3 during the first reminder-of-acquisition block (RACQ1). Pain was also expected more for T1 compared to T2 in this block, $t(62) = 3.48$, $p = .001$, $d = 0.75$. The same pattern was present in the second reminder-of-acquisition block (RACQ2: T1 *vs.* T3, $t(62) = 14.32$, $p < .001$ $d = 3.55$; T2 *vs.* T3, $t(62) = 10.02$, $p < .001$, $d = 1.82$; T1 *vs.* T2, $t(62) = 5.60$, $p < .001$, $d = 1.08$; Figure S1.1, panel A). No such differences emerged in the Yoked Group (all *p*-values > .05; Figure S1.1, panel B).

Figure S1.1

Pain-expectancy ratings during reminder-of-acquisition



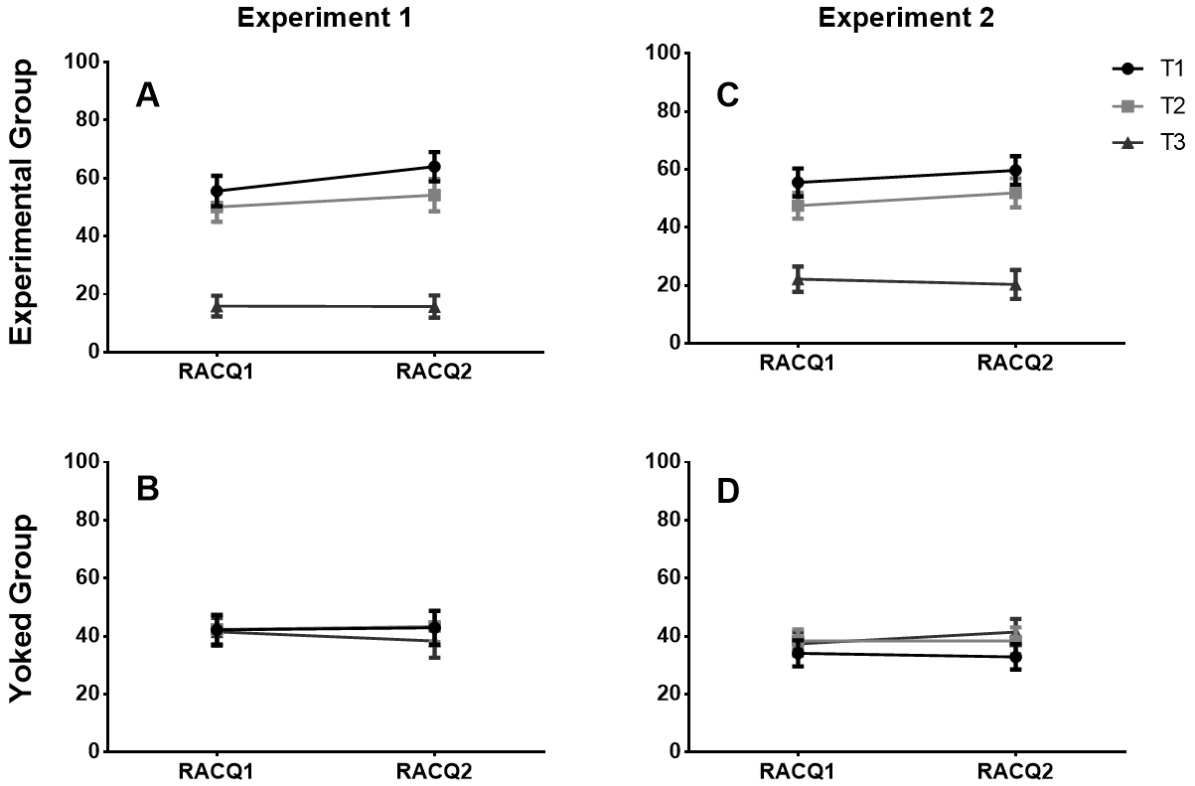
Note. Mean pain-expectancy ratings towards the acquisition trajectories (T1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiments 1 (panels A and B) and 2 (panels C and D), during the reminder-of-acquisition blocks (RACQ1 and RACQ2). Error bars represent standard deviations.

A similar RM ANOVA on the mean *pain-related fear ratings* during the reminder-of-acquisition blocks also showed a significant Group x Trajectory interaction, $F(1.56, 96.64) = 23.15$, $p < .001$, $\eta_p^2 = .27$, suggesting that fear for the different trajectories differed between groups during these blocks. Planned comparisons confirmed that in line with the acquisition phase, the Experimental Group still feared T1, $t(62) = 7.10$, $p < .001$, $d = 1.56$, and T2, $t(62) = 6.34$, $p < .001$, $d = 1.36$, more than T3 during

RACQ1, but fear reports did not differ between T1 and T2, $t(62) = 1.54$, $p = .128$. During RACQ2, both T1, $t(62) = 8.21$, $p < .001$, $d = 1.91$, and T2, $t(62) = 7.26$, $p < .001$, $d = 1.41$, continued to evoke more fear than T3. Furthermore, T1 also evoked more fear than T2, $t(62) = 2.60$, $p = .012$, $d = .32$ (Figure S1.2, panel A). No such differences emerged in the Yoked Group (all *p*-values > .05) (Figure S1.2, panel B). Taken together, these results indicate that the test of generalization (under extinction) did not affect the acquired differential pain-expectancy and fear ratings for the acquisition trajectories.

Figure S1.2

Pain-related fear ratings during reminder-of-acquisition

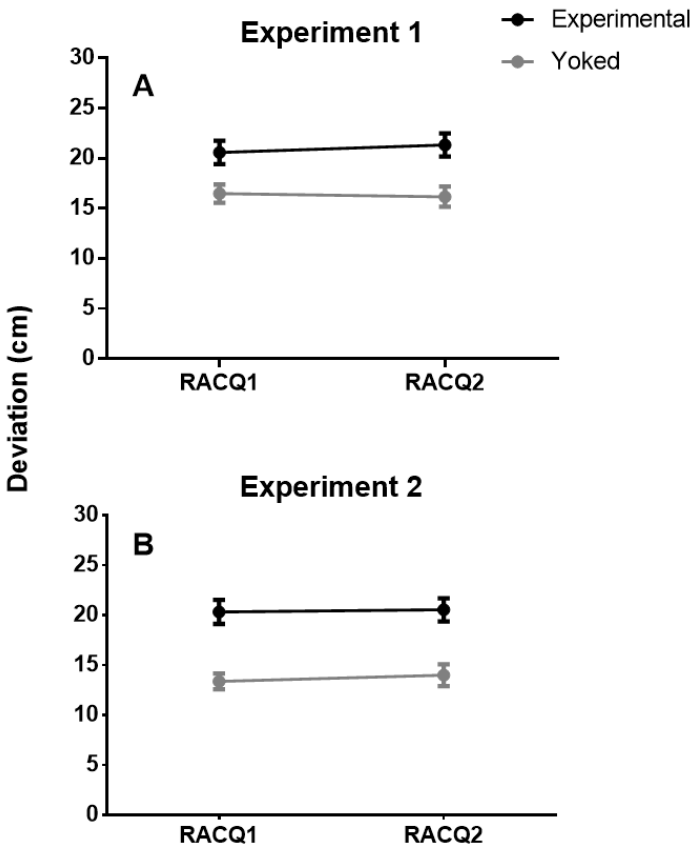


Note. Mean pain-related fear ratings towards the acquisition trajectories (T1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiments 1 (panels A and B) and 2 (panels C and D), during the reminder-of-acquisition blocks. Error bars represent standard deviations.

A 2 (Group: Experimental, Yoked) x 2 (Block: RACQ1-2) RM ANOVA on *maximal deviation* data yielded a significant main effect of Group, $F(1, 62) = 10.96$, $p = .002$, $\eta_p^2 = .15$. Planned comparisons confirmed that the Experimental Group avoided more than the Yoked Group, during RACQ1, $t(62) = 2.755$, $p = .008$, $d = .69$, and RACQ2, $t(62) = 3.36$, $p = .001$, $d = .84$, suggesting that acquired avoidance behavior did not extinguish during the generalization phase (Figure S1.3, panel A).

Figure S1.3

Avoidance behavior during reminder-of-acquisition



Note. Mean maximum deviation (in cm) from the shortest trajectory from the starting position to the target during the reminder-of-acquisition blocks (RACQ1 and RACQ2) in the Experimental and Yoked Groups of Experiments 1 (panel A) and 2 (panel B). Error bars represent standard deviations.

Experiment 2

A 2 (Group: Experimental, Yoked) x 2 (Block: RACQ1-2) x 3 (Trajectory: T1-3) RM ANOVA on mean *pain-expectancy ratings* during the reminder-of-acquisition phase revealed a significant Group x Trajectory interaction, $F(1.61, 109.56) = 34.93$, $p < .001$, $\eta_p^2 = .34$, indicating different patterns of pain-expectancies for the different trajectories between groups. Planned comparisons revealed similar effects to the acquisition phase during both reminder-of-acquisition blocks in the Experimental Group (RACQ1: T1 *vs.* T3, $t(68) = 7.77$, $p < .001$, $d = 1.77$; T2 *vs.* T3, $t(68) = 5.82$, $p < .001$, $d = 1.13$; T1 *vs.* T2, $t(68) = 3.76$, $p < .001$, $d = .60$; RACQ2: T1 *vs.* T3, $t(68) = 8.27$, $p < .001$, $d = 1.74$; T2 *vs.* T3, $t(68) = 6.73$, $p < .001$, $d = 1.27$; T1 *vs.* T2, $t(68) = 3.39$, $p = .001$, $d = .44$) (Figure S1.1, panel C). No such differences were present in the Yoked Group (all *p*-values > .05; Figure S1.1, panel D).

A similar RM ANOVA on mean *pain-related fear ratings* during the reminder-of-acquisition blocks also showed a significant Group x Trajectory interaction, $F(1.59, 108.11) = 27.15$, $p < .001$, $\eta_p^2 =$

.29, indicating that fear for the different trajectories differed between groups during these blocks. Furthermore, the Experimental Group still feared T1, $t(68) = 6.14$, $p < .001$, $d = 1.22$, and T2, $t(68) = 5.21$, $p < .001$, $d = .97$, more than T3 during RACQ1, but not T1 more than T2, $t(68) = 1.88$, $p = .065$. During RACQ2, however, in line with the acquisition phase, all comparisons were significant: T1 *vs.* T3, $t(68) = 7.39$, $p < .001$, $d = 1.34$; T2 *vs.* T3, $t(68) = 6.33$, $p < .001$, $d = 1.07$; T1 *vs.* T2, $t(68) = 2.27$, $p = .026$, $d = .27$ (Figure S1.2, panel C). No differences occurred for any of the pairs in the Yoked Group (all *p*-values > .05; Figure S1.2, panel D).

A 2 x 2 RM ANOVA (Group: Experimental, Yoked) x (Block: RACQ1-2) on mean *maximal deviation* data during the reminder-of-acquisition blocks yielded a significant main effect of Group, $F(1, 68) = 26.39$, $p < .001$, $\eta_p^2 = .28$. Planned comparisons confirmed that avoidance behavior persisted during the reminder-of-acquisition blocks: the Experimental Group avoided more than the Yoked Group during RACQ1, $t(68) = 4.83$, $p < .001$, $d = 1.15$, and RACQ2, $t(68) = 4.13$, $p < .001$, $d = .99$ (Figure S1.3, panel B). Thus, acquired pain-expectancies, pain-related fear, and avoidance did not extinguish due to the test of generalization under extinction.

Generalization phase: pain-related fear

Results of comparisons of pain-related fear between trajectories during the generalization phases of Experiments 1 and 2 are shown in Tables S1.5 and S1.6 respectively.

Switching Behavior

The visualization suggests that switching behavior gradually decreased throughout acquisition phases in both Experiments 1 and 2 (Figure S1.4). This decrease indicates that participants learned the experimental contingencies and switched from exploring all trajectories to exploiting the avoidance trajectory – as shown by manipulation checks of avoidance acquisition in Chapter 1. Comparing the first generalization blocks of both experiments, an increase in switching behavior can be observed in Experiment 1, whereas this increase seems absent, or at least attenuated, in Experiment 2. In other words, participants seemed to explore the novel generalization trajectories at the start of the generalization test in Experiment 1, whereas participants tended to exploit the trajectory similar to the original avoidance response in Experiment 2. A post-hoc independent samples *t*-test comparing the relative frequencies in switching behavior during the first generalization blocks of both experiments confirmed more switching in Experiment 1, $t(20) = 2.10$, $p = .049$, $d = .94$. It is worth noting that Experiment 2 had a longer acquisition phase than Experiment 1 (Experiment 2: 36 trials; Experiment 1: 24 trials). However, in the study of Glogan, Gatzounis, Meulders, et al. (2020), where avoidance also did not generalize, the acquisition phase was even longer (48 trials). Therefore, we do

not believe that the longer acquisition phase can explain the finding of avoidance generalization in Experiment 2.

Table S1.5

Pain-related fear ratings during the generalization phase of Experiment 1

Comparison	*t*(62)	*p*	Cohen's *d*
GEN1			
G1 *vs.* G2	1.03	.307	0.09
G1 *vs.* G3	2.33	.069	0.36
G2 *vs.* G3	2.22	.060	0.30
GEN2			
G1 *vs.* G2	0.64	.527	0.07
G1 *vs.* G3	2.42	.037	0.45
G2 *vs.* G3	2.63	.032	0.39
GEN3			
G1 *vs.* G2	-0.46	.646	-0.05
G1 *vs.* G3	2.73	.017	0.55
G2 *vs.* G3	3.55	.002	0.56

Note. P-values are Holm-Bonferroni corrected. Results of comparisons (G1 *vs.* G2, G1 *vs.* G3, G2 *vs.* G3) of pain-related fear in the Experimental Group of Experiment 1 during the first (GEN1), second (GEN2), and third (GEN3) generalization blocks.

Table S1.6

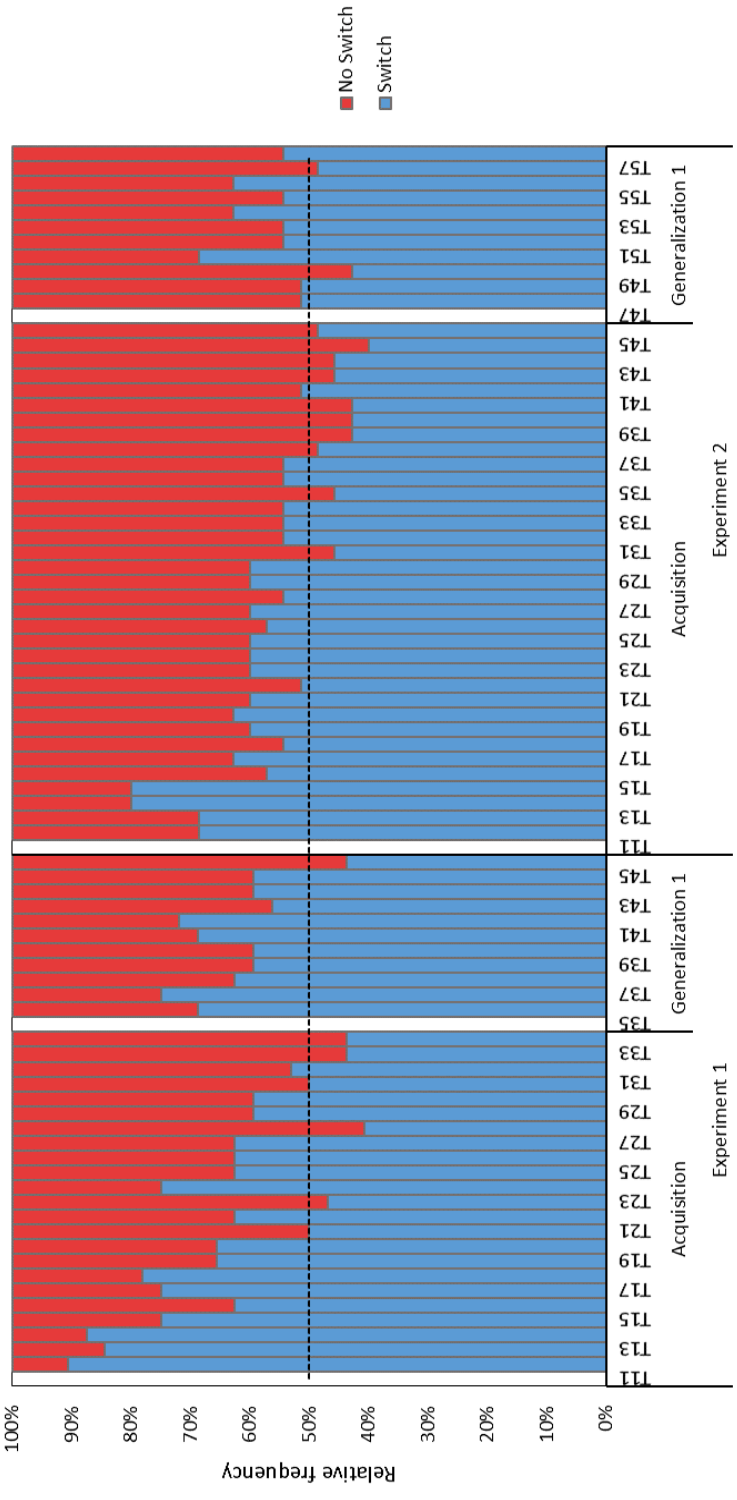
Pain-related fear ratings during the generalization phase of Experiment 2

Comparison	*t*(68)	*p*	Cohen's *d*
GEN1			
G1 *vs.* G2	0.01	.991	0.00
G1 *vs.* G3	3.25	.004	0.58
G2 *vs.* G3	3.97	< .001	0.59
GEN2			
G1 *vs.* G2	0.76	.453	0.09
G1 *vs.* G3	2.68	.028	0.49
G2 *vs.* G3	2.60	.023	0.44
GEN3			
G1 *vs.* G2	0.76	.453	-0.06
G1 *vs.* G3	2.68	.028	0.59
G2 *vs.* G3	2.60	.023	0.68

Note. P-values are Holm-Bonferroni corrected. Results of planned comparisons (G1 *vs.* G2, G1 *vs.* G3, G2 *vs.* G3) of pain-related fear in the Experimental Group of Experiment 2 during the first (GEN1), second (GEN2), and third (GEN3) generalization blocks.

Figure S1.4

Switching behavior



Note. Switching behavior is operationalized as choosing a trajectory different from the one on the previous trial (T); therefore, the first trial of each phase is a missing value. Relative frequency of switching behavior is displayed for the Experimental Groups of Experiments 1 and 2 during the acquisition phases (Experiment 1: T11-T34; Experiment 2: T11-T46) and the first generalization blocks (Experiment 1: T35-T46; Experiment 2: T47-T58).

Appendix B

Supplemental material Chapter 3

Dynamic movement reproduction (DMR) directional error

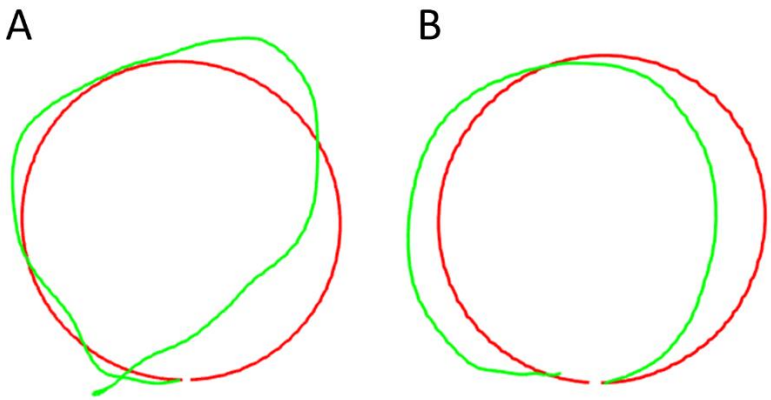
As described in the Chapter 3, the HapticMaster automatically logs position along all three dimensions every 2 ms during the DMR task. For each logged position, the distance between the middle point of the circular movement pattern and the current coordinates was calculated (i.e., reproduced radius). Subsequently, the target radius (i.e., 8 cm) was subtracted from this, and the absolute value served as the error (i.e., direction was not taken into account). Next, the mean of all errors was calculated per trial, and served as the DMR error, which is used to calculate DMR accuracy (Figure 3.4 in Chapter 3). Note that the zero value of this measure means that there was absolutely no deviation (error) from the target movement pattern.

Here we introduce an additional measure that may be of interest to evaluate, DMR directional error, in which the difference between the target radius and reproduced radius is used to calculate error, but the direction of this error (negative or positive) is taken into account. Such errors would allow us to determine if a participant is systematically overshooting or undershooting relative to the target movement during the DMR task (positive versus negative average DMR directional error, respectively), as is commonly reported in JR tasks. However, it is probable that most people will not systematically over- or undershoot entire target movement patterns, but may vary in their performance errors throughout the movement pattern. This may create a situation where absolute DMR task error will be high (low accuracy), but DMR directional error may be low (high accuracy) because the errors 'even out'. Here we explore whether the combination of DMR directional error, with or without visual inspection of the movement pattern data, is sufficient to delineate the type of movement pattern impairment (e.g., due to altered position sense, altered sensorimotor integration, or both).

During the DMR task, some participants may have impairments with sensorimotor integration, while position sense is intact. For example, a participant may be overshooting (reproduced radius > 8 cm) at some point, while undershooting at another (reproduced radius < 8 cm), but roughly placing the circle in the correct spatial position. Panel A of Figure S3.1 shows an example of this as performed by one of the study participants. In this situation, absolute DMR error was relatively high (1.06 cm) compared to DMR directional error (0.02 cm), suggesting non-systematic over- and undershooting errors.

Figure S3.1

Visualizations of raw data from single test trials of the Dynamic Movement Reproduction task



Note. Both the target (red line) and reproduced (green line) movement pattern are visualized. Panel A: in this participant, position sense appears relatively intact, while the sensorimotor integration is more impaired; Panel B: in this participant, sensorimotor integration appears relatively intact, while position sense is more impaired.

Alternatively, a participant's sensorimotor integration may be relatively intact, while position sense is impaired. For example, a participant may be capable of performing a circular movement with the correct radius, though not in the correct position. Panel B of Figure S3.1 shows an example of this as performed by one of the study participants. In this case, absolute DMR error was again relatively high (1.05 cm) compared to DMR directional error (0.04 cm).

Note that the DMR directional error measure mainly differs from absolute DMR error in the meaning of the zero value. While a value of zero for absolute DMR error indicates that *both* sensorimotor integration and position sense are intact, a value of zero for the DMR directional error indicates that there are no systematic errors, with *either* sensorimotor integration and/or position sense intact. That DMR directional error could be zero for either situation means that additional visual inspection of the data is necessary. Indeed, the two DMR measures are highly correlated (using data from Study 2 – No Visual Information condition – for sufficient statistical power: $\rho = .68$, $p < .001$), suggesting that the DMR directional error does not add to data interpretation unless also accompanied by visual inspection of the data. Furthermore, similar to DMR accuracy, DMR directional accuracy (i.e., the average DMR directional error over six test trials) showed fair-to-good test-retest reliability (using test-retest data from Study 1 – No Visual Information condition: *ICC* = .73, $F(22, 22) = 3.55$, $p = .002$, *95% CI* = [.35 - .88]) and a weak association with JR accuracy (using data from Study 2 – No Visual Information condition – for sufficient statistical power: $\rho = .25$, $p = .040$).

Appendix C

Supplemental material Chapter 4

Methods

Secondary outcome measures

Directional proprioceptive accuracy was operationalized as the difference (in cm) between the reproduced and the target circular movement pattern (i.e., difference in radiuses), averaged over the six test trials of the DMR task. Positive values reflect 'overshooting': movement on the outside of the target circle; negative values reflect the opposite. This measure has shown to have fair-to-good test-retest reliability (Vandael et al., 2021).

Retrospective pain-expectancy and pain-related fear ratings were collected on each trial during the directed phase of the operant avoidance task (i.e., for all seven trajectories). Participants rated the on-screen questions, "*Regardless of whether you actually received an electrical stimulus, to what extent did you expect an electrical stimulus during this movement?*" and "*How afraid were you during this movement?*", using a visual analogue scale ranging from 0-100 (0 = "*not at all*" and 100 = "*very much*").

Post-experimental questions regarding the experimental procedure were presented at the end of the session. These included intensity of the electrical stimulus ["*How intense did you find the electrical stimulus?*"; numerical rating scale: "*Not at all intense*" (0) – "*Very intense*" (10)], unpleasantness of the electrical stimulus ["*How unpleasant did you find the electrical stimulus?*"; numerical rating scale: "*Not at all unpleasant*" (0) – "*Very unpleasant*" (10)], tendency to avoid the electrical stimulus ["*How much did you want to avoid the electrical stimulus?*"; numerical rating scale: "*Not at all*" (0) – "*Very much*" (10)], and threat value of the electrical stimulus ["*How threatening did you find the electrical stimulus?*"; numerical rating scale: "*Not at all threatening*" (0) – "*Very threatening*" (10)].

Data analysis

First, a summary ($M \pm SD$) of movement deviation measures, trait questionnaire scores, physical stimulus intensity and subjective stimulus ratings (during calibration and after the experiment) is provided. We compared these characteristics between participants that reported only replicating the avoidance trajectory during the avoidance test and the rest of the sample using independent samples *t*-tests. Next, we analyzed the tendency to move on the outside of the target

circle/avoidance trajectory (overshoot) in both the DMR and operant avoidance tasks using one sample *t*-tests on the directional proprioceptive accuracy and avoidance behavior measures respectively (test value 0 representing the target circle/avoidance trajectory respectively), and compared these tendencies between tasks using a paired samples *t*-test. Furthermore, as preregistered, we explored the interaction between trait intolerance of uncertainty/distress tolerance and proprioceptive accuracy: we expected that people scoring high on trait intolerance of uncertainty/low on distress tolerance show a stronger association between proprioceptive accuracy and avoidance behavior. We used linear regression analyses including intolerance of uncertainty/distress tolerance, proprioceptive accuracy, and the interaction between these variables as predictors. Finally, using the full sample of 48 participants [16 male, 32 female, *M* ± *SD* (range) age = 24 ± 5 years (18-44)], we analyzed the associations between psychological trait questionnaire scores and avoidance proportion using Spearman rank correlations, and generalization gradients in the retrospective pain-expectancy and pain-related fear ratings using RM ANOVAs with within-subjects factor Trajectory ($G_{Pain,2}$, T_{Pain}, $G_{Pain,1}$, G_0, $G_{Avoid,1}$, T_{Avoid}, $G_{Avoid,2}$). Note that the full sample was used for these analyses to improve statistical power as the proprioceptive accuracy and avoidance measures were not employed here.

Results

Trait scores, physical stimulus intensity and stimulus ratings

A summary of movement deviation measures, trait scores, physical stimulus intensity and stimulus ratings is provided in Table S4.1.

Interactions between proprioceptive accuracy and intolerance of uncertainty/ distress tolerance in predicting avoidance behavior

The linear regression model containing an interaction between proprioceptive accuracy and intolerance of uncertainty (R^2 = .32) indicated no significant interaction (p = .69), and neither did the model containing an interaction between proprioceptive accuracy and distress tolerance (R^2 = .32, p = .78).

Table S4.1

Summary of movement deviation measures, trait scores, physical stimulus intensity and stimulus ratings

	Test sample (N = 41)	Avoidance trajectory replicators (n = 13)	Avoidance trajectory replicators vs. rest of test sample *t*-test
	M ± *SD*	*M* ± *SD*	*p*-value
Movement deviation measures (cm)			
Proprioceptive accuracy[1]	1.84 ± 1.08	2.04 ± 1.71	.41
Directional proprioceptive accuracy[2]	0.89 ± 1.39	1.22 ± 1.99	.32
Avoidance behavior[2]	2.44 ± 4.35	3.16 ± 5.24	.47
Avoidance behavior accuracy[1]	4.24 ± 3.30	4.15 ± 4.69	.90
Trait scores			
Fear of pain	84.61 ± 16.10	90.00 ± 9.66	.73
Positive affect	33.83 ± 5.31	36.62 ± 4.72	.12
Negative affect	20.85 ± 7.18	20.46 ± 7.64	1.00
Intolerance of uncertainty	29.32 ± 7.74	30.92 ± 6.64	1.00
Distress tolerance	53.98 ± 8.83	53.62 ± 4.72	.86
Sensation seeking	3.62 ± 0.70	3.67 ± 0.79	1.00
Physical stimulus intensity (mA; calibration)	45.93 ± 25.41	45.00 ± 28.24	.88
Stimulus ratings			
Intensity (calibration)	7.61 ± 1.59	7.15 ± 1.68	.88
Intensity (post-experimental)	6.85 ± 1.75	6.54 ± 1.98	1.00
Unpleasantness (post-experimental)	7.07 ± 2.42	7.38 ± 2.57	.58
Avoidance (post-experimental)	7.27 ± 2.47	7.69 ± 3.09	.92
Threat (post-experimental)	5.29 ± 2.84	6.15 ± 3.36	.95

Note. [1]These measures were operationalized as the ***absolute*** (orthogonal) deviation from the target/avoidance trajectory to quantify proprioceptive accuracy/avoidance behavior. [2]These measures took the direction of the deviation into account.

Overshooting tendencies: comparing directional proprioceptive accuracy and avoidance behavior

Participants tended to overshoot in both the DMR task, $t(40) = 4.11$, $p < .001$, $d = 0.64$, and the operant avoidance task, $t(40) = 3.58$, $p < .001$, $d = 0.56$. In other words, participants tended to move more on the outside than on the inside of both the target circle and the semi-circular avoidance trajectory in the respective tasks. However, deviations were significantly higher in the operant avoidance task ($M = 2.44$, $SD = 4.35$) compared to the DMR task ($M = 0.89$, $SD = 1.39$), $t(40) = 2.54$, $p = .015$, $d = 0.40$, showing that deviations during the avoidance task were not merely a result of overshooting, thus indicating overprotective avoidance behavior.

Associations between psychological trait scores and avoidance proportion

Manipulation checks as reported in the manuscript were similar in this sample (i.e., successful acquisition of pain-related fear and avoidance when $N = 48$). There were no significant associations between avoidance proportion and the traits fear of pain [$\rho(48) = .04$, $p = .78$], positive affect [$\rho(48) = .12$, $p = .41$], negative affect [$\rho(48) = -.10$, $p = .50$], intolerance of uncertainty [$\rho(48) = -.01$, $p = .94$], distress tolerance [$\rho(48) = -.04$, $p = .78$], nor sensation seeking [$\rho(48) = -.07$, $p = .62$]. Using the orthogonal deviation from the middle line as dependent variable (on which avoidance proportion is based, see Primary outcomes section in manuscript) led to the same conclusions.

Generalization gradients in retrospective pain-expectancy and pain-related fear ratings

Results showed a significant main effect of Trajectory on retrospective pain-expectancy ratings, $F(4.35, 204.40) = 16.60$, $p < .001$, $\eta_p^2 = .26$, $\varepsilon = .72$. Furthermore, there was a significant linear trend, $F(1, 47) = 41.89$, $p < .001$, $\eta_p^2 = .47$, indicating the presence of a generalization gradient, although the quadratic trend was not significant, $F(1, 47) = 3.05$, $p = .087$. Pairwise comparisons were employed to analyze this gradient (Table S4.2). These showed that pain-expectancy generalized toward the two trajectories most similar to the pain-associated trajectory (i.e., $G_{Pain,2}$ and $G_{Pain,1}$).

Regarding pain-related fear ratings, results again showed a significant main effect of Trajectory, $F(4.29, 201.86) = 12.63$, $p < .001$, $\eta_p^2 = .21$, $\varepsilon = .72$, and a linear trend, $F(1, 47) = 31.98$, $p < .001$, $\eta_p^2 = .40$, but no quadratic trend, $F(1, 47) = 1.59$, $p = .214$. Pairwise comparisons showed a generalization pattern similar to pain-expectancy ratings (Table S4.2).

Table S4.2

Pairwise comparisons between retrospective pain-expectancy and pain-related fear ratings for movement trajectories during directed phase

	Generalization trajectories					
p-values	$G_{Pain,2}$	$G_{Pain,1}$	G_0	$G_{Avoid,1}$	$G_{Avoid,2}$	T_{Avoid}
Retrospective pain-expectancy						
T_{Pain}	.752	.129	**.002***	**<.001***	**<.001***	**<.001***
T_{Avoid}	**.001***	**.031***	.494	.752	.752	
Retrospective pain-related fear						
T_{Pain}	1.00	.740	**.044***	**<.001***	**<.001***	**<.001***
T_{Avoid}	**.002***	**.008***	.153	1.00	1.00	

Note. *significant at .05 alpha level. Holm-Bonferroni corrections were applied. Total degrees of freedom are 47 for all comparisons. Trajectories: the shortest trajectory between start and target position (G_0), the pain-associated trajectory (T_{Pain}), the avoidance trajectory (T_{Avoid}), and a trajectory on each side of the training trajectories (i.e., between the shortest trajectory and the training trajectories, $G_{Pain,1}$ and $G_{Avoid,1}$ respectively; on the outside of the training trajectories, $G_{Pain,2}$ and $G_{Avoid,2}$ respectively).

Appendix D

Supplemental material Chapter 5

Methods

Procedure

Verbatim instructions for the best possible self exercise

Instruction 1: *"During this exercise, we ask you to think about your best possible self for one minute and then write down your thoughts. 'Thinking about your best possible self' means that you imagine yourself in the future, after everything has gone as well as it possibly could have. You have worked hard and succeeded at accomplishing all the goals of your life. Think of this as the realization of your dreams, and that you have reached your full potential. So, you identify the best possible way that things might turn out in your life. You can start thinking of your Best Possible Self now, and after one minute I will tell you it is time to start writing."*

[Participant thinks 1 minute]

Instruction 2: *"Now, I will ask you to write about your best possible self for 15 minutes. The only rule we have about writing is that you write continuously for the entire time. If you run out of things to say, just repeat what you have already written before. Don't worry about grammar, spelling or sentence structure. Don't worry about erasing or crossing things out. Just write. If English is not your native language, you can also write in your native language if you prefer. If you need to repeat the instructions for the exercise, you can read them on the piece of paper in front of you. Again, I will tell you when it is time to stop. You can start now."*

[Participant writes 15 minutes]

Instruction 3: *"You can finish your final sentence now.* [wait until participant indicates they are ready] *Now, I want you to imagine as vividly as possible the things you have been writing about. So, think about your best possible self, and do that for 5 minutes. Imagine your best possible self with as much detail as you can. Again, I will tell you when it is time to stop. For this part, you can just sit back and start visualizing. You can close your eyes if you want to."*

[Participant visualizes 5 minutes]

Verbatim instructions for the typical day exercise

Instruction 1: *"During this exercise, we ask you to think about a typical day in your life for one minute and then write down your thoughts. 'Thinking about your typical day' means that you take notice of ordinary details of your day that you usually don't think about. These might include particular*

classes or meetings you attend to, people you meet, things you do, typical thoughts you have during the day. Think of this as moving through your typical day, hour after hour. So, you identify what such a day looks like for you. You can start thinking of your typical day now, and after one minute I will tell you it is time to start writing."

[Participant thinks 1 minute]

Instruction 2: *"Now, I will ask you to write about a typical day in your life for 15 minutes. The only rule we have about writing is that you write continuously for the entire time. If you run out of things to say, just repeat what you have already written before. Don't worry about grammar, spelling or sentence structure. Don't worry about erasing or crossing things out. Just write. If English is not your native language, you can also write in your native language if you prefer. If you need to repeat the instructions for the exercise, you can read them on the piece of paper in front of you. Again, I will tell you when it is time to stop. You can start now."*

[Participant writes 15 minutes]

Instruction 3: *"You can finish your final sentence now.* [wait until participant indicates they are ready] *Now, I want you to imagine as vividly as possible the things you have been writing about. So, think about a typical day in your life, and do that for 5 minutes. Imagine your typical day with as much detail as you can. Again, I will tell you when it is time to stop. For this part, you can just sit back and start visualizing. You can close your eyes if you want to."*

[Participant visualizes 5 minutes]

Secondary outcome measures

Pain intensity and unpleasantness

At the end of each acquisition block of the arm-reaching task, participants answered the questions "*How painful did you find the electrocutaneous stimulus in the previous phase?*" (pain intensity) and "*How unpleasant did you find the electrocutaneous stimulus in the previous phase?*" (pain unpleasantness) using a visual analogue scale ranging from "*not at all*" to "*very much*".

Negative affect

To assess state negative affect, the modified Differential Emotions Scale was employed (Fredrickson et al., 2003). This questionnaire contains 15 items which consist of words describing feelings, with seven items relating to negative affect ("*sad, downhearted, blue*"; "*angry, irritated, mad*"; "*fearful, scared, afraid*"; "*disgusted, turned off, repulsed*"; "*disdainful, scornful, contemptuous*"; "*guilty, remorseful*"; and "*ashamed, embarrassed*"). Participants rated the degree to which they experienced these feelings in the present moment on a numerical scale ranging from 1 (*"not at all"*) to 7 (*"very intense"*). The five items relating to negative affect were averaged.

Post-experimental questions and psychological trait questionnaires

After the post-experiment affect measurement, participants completed a questionnaire regarding the arm-reaching task, which consisted of the following questions: (1) "*How intense did you find the electrical stimulus during the robotic arm task?*", (2) "*How unpleasant did you find the electrical stimulus?*", (3) "*How much did you want to avoid the electrical stimulus?*", (4) "*How threatening did you find the electrical stimulus?*", (5) "*How intense did you find the resistance of the robotic arm?*". These questions were answered using an 11-point scale ranging from 0 ("*not at all*") to 10 ("*very much*"). Next, they completed trait questionnaires assessing fear of pain (Fear of Pain Questionnaire; Roelofs et al., 2005), pain catastrophizing (Pain Catastrophizing Scale; Van Damme et al., 2002), positive and negative affect (Positive and Negative Affect Schedule; Watson et al., 1988), anxiety (Trait version of the State-Trait Anxiety Inventory; Spielberger, 1983), distress tolerance (Distress Tolerance Scale; Simons & Gaher, 2005) and avoidance (Multidimensional Experiential Avoidance Questionnaire; Gámez et al., 2011).

Analysis plan

As a randomization check, ratings during the stimulus calibration procedure, post-experimental ratings and trait scores were modeled using a linear model with Group as predictor (Positive affect, Neutral, Yoked neutral). Pain intensity and unpleasantness ratings during the experiment were modeled using two separate linear mixed models with predictors Group (Positive affect, Neutral, Yoked neutral) and Block (1-2), and the interaction between both.

To model *avoidance behavior during acquisition*, we used a linear mixed model with predictors Group (Positive affect, Neutral, Yoked neutral) and Block (1-3), and the interaction between both predictors. To model *pain-related fear and pain-expectancy during acquisition*, we used two separate linear mixed models including predictors Group (Positive affect, Neutral, Yoked neutral), Block (1-3) and Trajectory (T1-3), and all corresponding interactions between these predictors. Because we were interested in comparing generalization of self-reported pain-expectancy and pain-related fear between the positive affect and neutral groups (hypothesis 2), we also modelled pain-expectancy and pain-related fear ratings in these groups during the third acquisition block specifically to test for significant differences before the visualization exercise. These two additional linear mixed models included predictors Group (Positive affect, Neutral) and Trajectory (T1-3), and the interaction between both predictors.

To test our *second hypothesis using a linear trend variable* (as preregistered), we defined two separate linear mixed models for pain-expectancy and pain-related fear. These included predictors Group (Positive affect, Neutral), Linear trend (which equals 0, 1, 2 for trajectories G1, G2, G3) and

Block (1-3), and the interaction between Group and Linear trend. As preregistered, these analyses were followed by responder analyses when the expected interaction between Group and Trajectory did not reach significance. In these models, the Group predictor was substituted with Positive affect change (i.e., post- minus pre-visualization positive affect).

To model *avoidance behavior during reminder-of-acquisition*, we used a linear mixed model including predictors Group (Positive affect, Neutral, Yoked neutral) and Block (1-2), and the interaction between both predictors. To model *pain-related fear and pain-expectancy during reminder-of-acquisition*, we used two separate linear mixed models including predictors Group (Positive affect, Neutral, Yoked neutral), Block (1-2) and Trajectory (T1-3), and all corresponding interactions between these predictors.

Finally, to model our *negative affect* measure, we used a linear mixed model including predictors Group (Positive affect, Neutral, Yoked neutral) and Time (Pre-experiment, Pre-visualization, Post-visualization, Post-experiment), and the interaction between both. Note that we did not obtain a pre-visualization affect measurement for one participant due to technical difficulties; this participant was excluded from the current analysis.

Results

Descriptive variables

An overview of descriptive statistics is provided in Table S5.1. Additionally, we tested for group differences on these variables. None of these tests reached significance. Also, note that for the analyses of pain unpleasantness and intensity, the interaction effects between Block and Group did not reach significance either.

Manipulation checks

Acquisition of pain-related avoidance

As expected, analysis of pain-related avoidance behavior during the acquisition phase showed a significant interaction between Group and Block, $F(4, 186) = 7.95$, $p < .001$, $\eta_p^2 = 0.15$, indicating that avoidance evolved differently in groups (Figure 5.3 in Chapter 5). Both the positive affect group, $t(167) = 6.13$, $p < .001$, $d = 1.52$, and the neutral group, $t(167) = 5.83$, $p < .001$, $d = 1.41$, showed significantly more avoidance compared to the yoked neutral group in the third acquisition block, confirming successful avoidance learning. Additionally, avoidance behavior in the positive affect and neutral group were statistically equivalent (*p*-values for both upper and lower bound < .05).

Table S5.1

Descriptive statistics per group

	M (*SD*)			*F*	η_p^2
	Positive affect	Neutral	Yoked neutral		
Stimulus calibration					
Physical intensity (mA)	35.97 (21.04)	42.68 (25.99)	33.78 (17.90)	1.44	0.03
Subjective intensity	7.59 (0.91)	7.78 (0.49)	7.81 (0.74)	0.83	0.02
Acquisition					
Pain unpleasantness	61.58 (21.02)	65.60 (18.21)	66.09 (19.57)	0.65	0.01
Pain intensity	72.22 (24.63)	77.78 (20.14)	77.66 (21.61)	0.76	0.02
Post-experimental					
Pain unpleasantness	7.12 (2.09)	7.81 (1.57)	8.03 (1.73)	2.18	0.03
Pain intensity	6.56 (1.56)	6.91 (1.28)	6.97 (1.51)	0.72	0.02
Pain avoidance	7.69 (2.90)	7.34 (2.31)	7.69 (2.72)	0.18	<0.01
Pain threat	4.91 (3.37)	5.22 (2.62)	5.12 (2.98)	0.09	<0.01
Resistance intensity	4.91 (2.32)	4.63 (1.98)	4.62 (1.83)	0.20	<0.01
Trait scores					
Fear of pain	81.69 (14.31)	80.09 (16.94)	82.41 (18.79)	0.16	<0.01
Pain catastrophizing	30.47 (8.75)	29.69 (10.22)	32.28 (8.28)	0.68	0.01
Positive affect	32.97 (5.63)	31.16 (6.09)	31.75 (6.54)	0.74	0.02
Negative affect	16.47 (4.44)	17.06 (6.46)	18.19 (6.38)	0.72	0.02
Anxiety	41.56 (8.52)	44.41 (11.11)	42.44 (9.97)	0.69	0.01
Distress tolerance	57.28 (10.20)	54.88 (10.35)	53.28 (11.47)	1.14	0.02
Avoidance	185.03 (30.11)	192.22 (35.88)	186.00 (35.91)	0.42	<0.01

Note. None of the *F*-tests reached significance.

Acquisition of pain-expectancy and pain-related fear

As expected, analysis of *pain-expectancy* ratings during acquisition showed a significant three-way interaction between Group, Block and Trajectory, $F(8, 744) = 5.17$, $p < .001$, $\eta_p^2 = 0.05$, indicating that ratings evolved differently over blocks in groups (Figure 5.4 in Chapter 5). Pairwise comparisons confirmed that ratings for T1 were significantly higher compared to T3 during the third block in both

the positive affect group, *t*(744) = 14.32, *p* < .001, *d* = 2.82, and the neutral group, *t*(744) = 15.39, *p* < .001, *d* = 3.29. The difference between ratings for T1 and T3 was not significant during the third block in the yoked neutral group, *t*(744) = 0.40, *p* = 1.00, *d* = 0.08, and further analysis confirmed statistical equivalence of these ratings (*p*-values for both upper and lower bound < .05). Additionally, rating patterns in the positive affect and neutral groups did not significantly differ in the third acquisition block, *F*(2, 124) = 0.23, *p* = .797, η_p^2 < 0.01.

Similarly, analysis of *pain-related fear ratings* during acquisition showed a significant three-way interaction, *F*(8, 744) = 3.82, *p* < .001, η_p^2 = 0.04, with significantly higher ratings for T1 compared to T3 during the third block in both the positive affect group (Figure 5.5 in Chapter 5), *t*(744) = 9.78, *p* < .001, *d* = 1.50, and the neutral group, *t*(744) = 10.81, *p* < .001, *d* = 1.79. There was no significant difference between these trajectories during the third block in the yoked neutral group, *t*(744) = -0.68, *p* = 1.00, *d* = -0.11, and again these ratings were statistically equivalent (*p*-values for both upper and lower bound < .05). Rating patterns between the positive affect and neutral groups again did not significantly differ in the third block, *F*(2, 124) = 0.25, *p* = .776, η_p^2 < 0.01.

Testing reductions in generalization of pain-expectancy and pain-related fear (hypothesis 2) using linear trend variable

Analysis of *pain-expectancy ratings* in the positive affect and neutral groups during the generalization phase showed no significant interaction between Group and Linear trend, *F*(1, 508) = .30, *p* = .583, η_p^2 < .01, indicating that generalization patterns did not significantly differ between groups. However, when using Positive affect change as predictor instead of Group, results did show a significant interaction between Positive affect change and Linear trend, *F*(1, 500) = 9.08, *p* = .003, η_p^2 = 0.02. Similarly, when analyzing *pain-related fear ratings*, the interaction between Group and Linear trend did not reach significance, *F*(1, 508) = 0.13, *p* = .723, η_p^2 < .01, while the interaction between Positive affect change and Linear trend did, *F*(1, 500) = 9.92, *p* = .002, η_p^2 = 0.02. Note that these models resulted in the same conclusions as reported in the manuscript.

Exploratory analyses

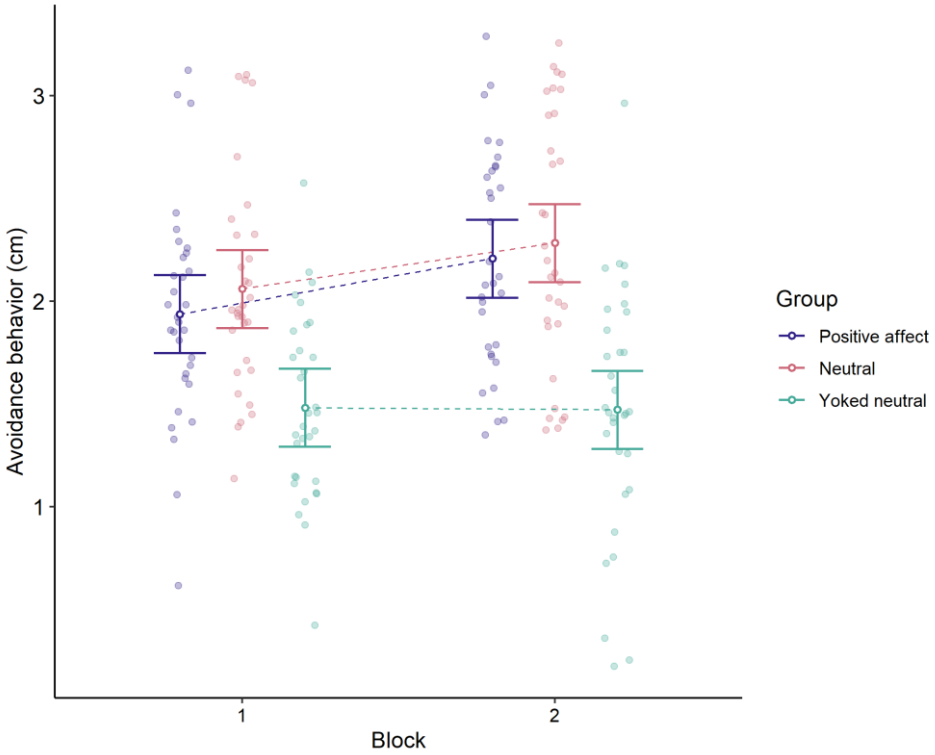
Avoidance behavior during reminder-of-acquisition

Analysis of avoidance behavior during the reminder-of-acquisition blocks showed a significant main effect of Group, *F*(2, 93) = 21.54, *p* <.001, η_p^2 = 0.32. Specifically, the positive affect group showed significantly more avoidance compared to the yoked neutral group (Figure S5.1), *t*(93) = 5.20, *p* < .001 , *d* = 1.12, and so did the neutral group, *t*(93) = 6.07, *p* < .001 , *d* = 1.26. There was no significant

difference when comparing the positive affect group to the neutral group, *t*(93) = -0.87, *p* = .389, *d* = -0.18.

Figure S5.1

Avoidance behavior during reminder-of-acquisition



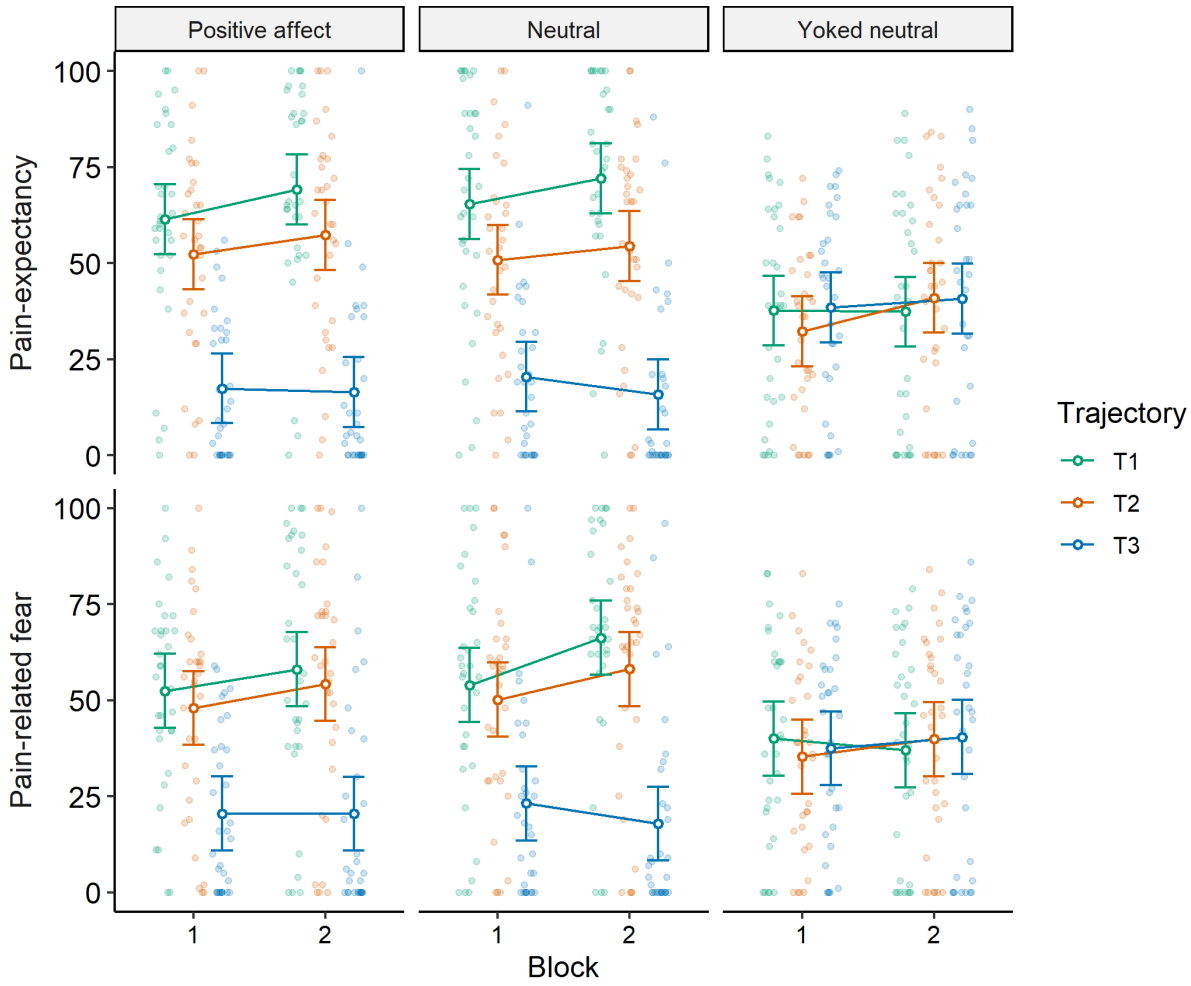
Note. Observed average deviations, estimated marginal means and 95% confidence intervals of avoidance behavior are displayed separately for the positive affect, neutral and yoked neutral groups during reminder-of-acquisition blocks.

Pain-expectancy and pain-related fear during reminder-of-acquisition

Analysis of *pain-expectancy ratings* during the reminder-of-acquisition phase showed a significant interaction between Group and Trajectory, *F*(4, 465) = 40.69, *p* <.001, η_p^2 = 0.26, indicating that rating patterns differed between groups (Figure S5.2). The three-way interaction between Group, Block and Trajectory did not reach significance, *F*(4, 465) = 0.72, *p* = .577, η_p^2 < 0.01. Further exploration of the two-way interaction showed that T1 still elicited significantly higher ratings than T3 in both the positive affect, *t*(465) = 13.97, *p* < .001 , *d* = 2.00, and the neutral group, *t*(465) = 14.63, *p* < .001 , *d* = 1.98, but not in the yoked neutral group, *t*(465) = -0.61, *p* = 1.00, *d* = -0.08. No significant differences were present when comparing the positive affect to the neutral group (T1: *t*(166) = -0.63, *p* = .530, *d* = -0.12; T3: *t*(166) = -0.22, *p* = .828, *d* = -0.06).

Figure S5.2

Pain-expectancy and pain-related fear ratings during reminder-of-acquisition



Note. Observed average ratings, estimated marginal means and 95% confidence intervals of pain-expectancy and pain-related fear ratings are displayed for each trajectory (T1-3) during the reminder-of-acquisition blocks (1-3), separately for the positive affect, neutral, yoked neutral groups.

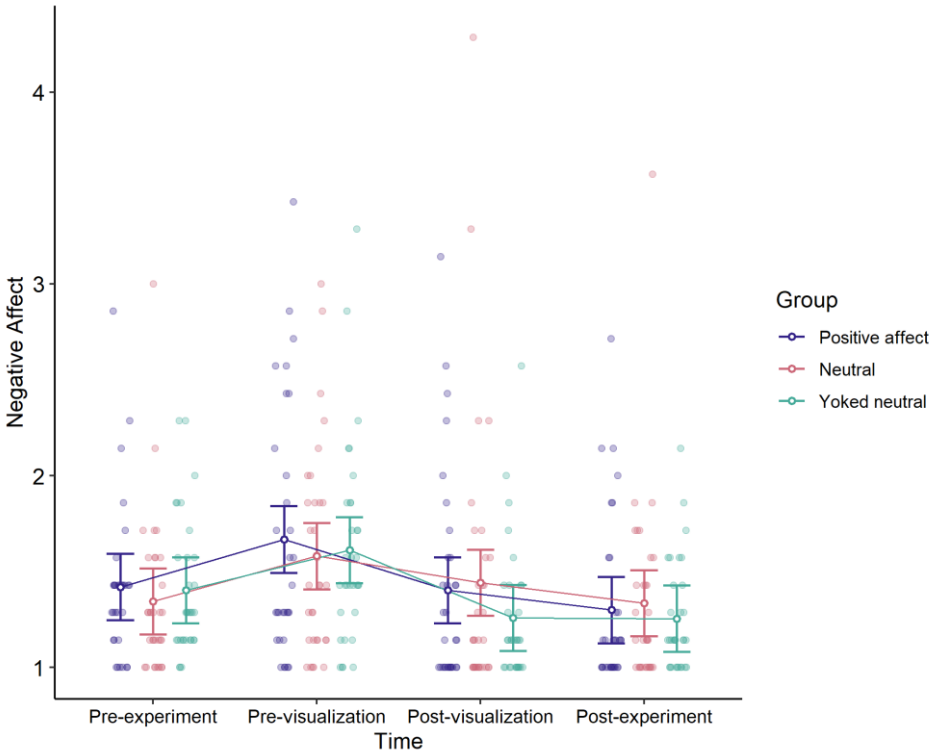
Analysis of *pain-related fear* during the reminder-of-acquisition phase again showed a significant interaction between Group and Trajectory (Figure S5.2), $F(4, 465) = 25.82$, $p < .001$, $\eta_p^2 = 0.18$. The three-way interaction between Group, Block and Trajectory did not reach significance, $F(4, 465) = 1.57$, $p = .181$, $\eta_p^2 = 0.01$. Analysis of the two-way interaction showed that trajectory T1 still elicited significantly higher ratings than T3 in both the positive affect, $t(465) = 10.43$, $p < .001$, $d = 1.29$, and neutral group, $t(465) = 11.88$, $p < .001$, $d = 1.41$, but not in the yoked neutral group, $t(465) = -0.13$, $p = 1.00$, $d = -0.02$. No significant differences were present when comparing the positive affect and neutral groups (T1: $t(144) = -0.81$, $p = .422$, $d = -0.17$; T3: $t(144) < .01$, $p = 1.00$, $d < .01$).

Negative affect

As expected, analysis of negative affect showed no significant interaction between Group and Time, $F(6, 278.21) = 0.93$, $p = .473$, $\eta_p^2 = 0.02$, indicating that negative affect did not evolve differently in groups (Figure S5.3). The main effect of Group did not reach significance either, $F(2, 93.10) = 0.22$, $p = .802$, $\eta_p^2 < 0.01$, however, the effect of Time did, $F(3, 278.21) = 16.38$, $p < .001$, $\eta_p^2 = 0.15$. Pairwise comparisons showed a significant increase in negative affect from pre-experiment to pre-visualization, $t(278) = 4.73$, $p < .001$, $d = 0.46$, followed by a decrease from pre- to post-visualization, $t(278) = -5.15$, $p < .001$, $d = -0.44$. There was no significant change from post-visualization to post-experiment, $t(278) = -1.46$, $p = .288$, $d = -0.14$.

Figure S5.3

Negative affect during experimental session



Note. Observed average scores, estimated marginal means and 95% confidence intervals of negative affect are displayed for the positive affect, neutral, yoked neutral groups at the four measurement times (i.e., pre-experiment, pre-visualization, post-visualization and post-experiment).

Appendix E

Supplemental material Chapter 6

Methods

Procedure

Verbatim instructions for the best possible self exercise

Instruction 1: *"During this exercise we ask you to think about your best possible self for one minute and then write down your thoughts. 'Thinking about your best possible self' means that you imagine yourself in the future, after everything has gone as well as it possibly could have. You have worked hard and succeeded at accomplishing all the goals of your life. Think of this as the realization of your dreams, and that you have reached your full potential. So, you identify the best possible way that things might turn out in your life. You can start thinking of your Best Possible Self now, and after one minute I will tell you it is time to start writing."*

[Participant thinks 1 minute]

Instruction 2: *"Now, I will ask you to write about your best possible self for 15 minutes. The only rule we have about writing is that you write continuously for the entire time. If you run out of things to say, just repeat what you have already written before. Don't worry about grammar, spelling or sentence structure. Don't worry about erasing or crossing things out. Just write. If English is not your native language, you can also write in your native language if you prefer. If you need to repeat the instructions for the exercise, you can read them on the piece of paper in front of you. Again, I will tell you when it is time to stop. You can start now."*

[Participant writes 15 minutes]

Instruction 3: *"You can finish your final sentence now.* [wait until participant indicates they are ready] *Now, I want you to imagine as vividly as possible the things you have been writing about. So, think about your best possible self, and do that for 5 minutes. Imagine your best possible self with as much detail as you can. Again, I will tell you when it is time to stop. For this part, you can just sit back and start visualizing. You can close your eyes if you want to."*

[Participant visualizes 5 minutes]

Verbatim instructions for the typical day exercise

Instruction 1: *"During this exercise we ask you to think about a typical day in your life for one minute and then write down your thoughts. 'Thinking about your typical day' means that you take notice of ordinary details of your day that you usually don't think about. These might include particular*

classes or meetings you attend to, people you meet, things you do, typical thoughts you have during the day. Think of this as moving through your typical day, hour after hour. Think of a day in which nothing particularly stressful or joyful happens, a normal day. You can start thinking of your typical day now, and after one minute I will tell you it is time to start writing."

[Participant thinks 1 minute]

Instruction 2: *"Now, I will ask you to write about a typical day in your life for 15 minutes. The only rule we have about writing is that you write continuously for the entire time. If you run out of things to say, just repeat what you have already written before. Don't worry about grammar, spelling or sentence structure. Don't worry about erasing or crossing things out. Just write. If English is not your native language, you can also write in your native language if you prefer. If you need to repeat the instructions for the exercise, you can read them on the piece of paper in front of you. Again, I will tell you when it is time to stop. You can start now."*

[Participant writes 15 minutes]

Instruction 3: *"You can finish your final sentence now. [wait until participant indicates they are ready] Now, I want you to imagine as vividly as possible the things you have been writing about. So, think about a typical day in your life, and do that for 5 minutes. Imagine your typical day with as much detail as you can. Again, I will tell you when it is time to stop. For this part, you can just sit back and start visualizing. You can close your eyes if you want to."*

[Participant visualizes 5 minutes]

Trait questionnaires

Before starting the experimental task, participants completed the Distress Tolerance Scale (Simons & Gaher, 2005), Intolerance of Uncertainty Scale (12 item version; Carleton et al., 2007), and Fear of Pain Questionnaire (Roelofs et al., 2005).

Secondary outcome measures

Stimulus-elicited SCRs

Stimulus-elicited SCRs were calculated on a trial-by-trial basis by subtracting the average skin conductance level during 2 s prior to CS/GS onset from the peak skin conductance level during the 6 s CS/GS window after offset of the avoidance cue (i.e., starting 3 s after CS/GS onset). Negative changes were scored as zero, while remaining positive values were square root transformed to reduce skewness of the distribution. Average stimulus-elicited SCRs were calculated per CS and GS (generalization phase only). Averages were calculated per phase, except for the avoidance conditioning phase where they were calculated per block.

Omission-elicited SCRs

Omission-elicited SCRs were calculated on trials that contained no US by subtracting the average skin conductance level during 2 s prior to CS/GS offset from the peak skin conductance level during the 4 s post-CS/GS window. Negative changes were scored as zero, while remaining positive values were square root transformed to reduce skewness of the distribution. Average omission-elicited SCRs were calculated for each CS and GS (generalization phase only). Averages were calculated per phase, except for the avoidance conditioning phase where they were calculated per block.

Retrospective US-expectancy

After both the fear and avoidance conditioning phase, a five-point scale was used to rate the expectancy of the US occurring after each CS, ranging from "*certainly no shock*" to "*certainly shock*". Questions after the fear conditioning phase differentiated between the first and last trial of the phase, while questions after the avoidance conditioning phase differentiated between clicking and not clicking the avoidance button (i.e., emitting the avoidance response or not).

Post-experimental questions

Five visual analogue scales ranging from 0 to 100 with anchors "*not at all*" to "*very much*" were used to assess unpleasantness of the US, the three CSs, and the avoidance cue. An additional visual analogue scale with the same anchors assessed the degree to which participants wanted to avoid the US.

Negative affect

The Negative Affect subscale of the Positive and Negative Affect Schedule was used to assess state negative affect (Watson et al., 1988). This subscale consists of 10 adjectives describing negative emotions. Participants rated the extent to which they experienced each emotion in the current moment on a 5-point Likert scale ranging from "*very little*" to "*very much*".

Data analysis

First, a summary [$M \pm SD$ (range)] of trait questionnaire scores, US intensity (self-reported and physical), and post-experimental ratings is provided. We compared these variables between both groups using independent samples *t*-test. Separate RM ANOVAs were run on stimulus-elicited SCRs and retrospective US-expectancy ratings during both fear conditioning and avoidance conditioning, and on omission-elicited SCRs during avoidance conditioning as additional manipulation checks. Further RM ANOVAs were used to explore avoidance behavior along the dimension of avoidability (i.e., including avoidable CS+, GS3, GS4, and the unavoidable CS+), and stimulus- and omission-elicited SCRs during the generalization test. Given that we were interested in the relief consequences of avoidance, an additional RM ANOVA was conducted on omission-elicited SCRs that only included trials

on which the avoidance response was emitted. For this particular analysis, average SCRs were calculated over the two adjacent GSs (GS1+2 and GS 3+4) to compensate for the anticipated reduction in number of data points, and the CS- was excluded from this analysis as a low level of avoidance to this stimulus was expected. Responder analyses were conducted in case of non-significant interaction effects with Group, which used the actual change in positive affect as covariate instead of the group factor (i.e., difference in positive affect between post- and pre-visualization, across groups). Finally, a RM ANOVA was run on our state negative affect measure. Raw skin conductance data were processed using Psychophysiological Analysis (De Clercq et al., 2006).

Results

Trait scores, self-reported and physical US intensity, and post-experimental ratings

A summary of trait scores, US intensity (self-reported and physical) and post-experimental ratings is provided in Table S6.1. There were no significant differences between groups regarding these variables.

Manipulation checks

Fear conditioning

A 3 level (Stimulus: CS-, Avoidable CS+, Unavoidable CS+) RM ANOVA was run on *stimulus-elicited SCRs* and showed a significant main effect, $F(1.73, 84.65) = 24.10$, $p < .001$, $\eta_p^2 = 0.33$, $\varepsilon = .86$. Pairwise comparisons showed significantly higher responding toward both the avoidable CS+, $t(49) = 6.43$, $p < .001$, $d = 0.80$, and unavoidable CS+, $t(49) = 6.60$, $p < .001$, $d = 0.88$, compared to the CS- (Figure S6.1, panel A), confirming successful differential fear conditioning. Adding Group (Positive affect, Control) as between-subjects factor to this analysis showed a significant Stimulus by Group interaction, $F(2, 96) = 14.46$, $p < .001$, $\eta_p^2 = 0.23$, however, none of the pairwise comparisons between groups per stimulus reached significance.

A 3 (Stimulus: CS-, Avoidable CS+, Unavoidable CS+) x 2 (Trial: First, Last) RM ANOVA run on *retrospective US-expectancy* ratings showed significant main effects of Stimulus, $F(1.64, 80.27) = 94.19$, $p < .001$, $\eta_p^2 = 0.66$, $\varepsilon = .82$, and Trial, $F(1, 49) = 8.70$, $p = .005$, $\eta_p^2 = 0.15$. The interaction effect reached significance as well, $F(1.59, 77.75) = 71.64$, $p < .001$, $\eta_p^2 = 0.59$, $\varepsilon = .79$, indicating that rating patterns changed between the first and last trial of the fear conditioning phase (Figure S6.2, panel A). US-expectancies significantly decreased for the CS-, $t(49) = -8.14$, $p < .001$, $d = -1.56$, while they increased for both the avoidable CS+, $t(49) = 7.96$, $p < .001$, $d = 1.53$, and unavoidable CS+, $t(49) = 6.00$, $p < .001$, $d = 1.16$. This resulted in significantly higher ratings for the avoidable CS+, $t(49) = 15.44$, $p < .001$, $d = 3.62$, and unavoidable CS+, $t(49) = 16.84$, $p < .001$, $d = 4.20$, compared to the CS- on the

last trial, confirming successful fear conditioning. The difference between the avoidable and unavoidable CS+ did not reach significance, $t(49) = -1.48$, $p = 0.292$, $d = -0.20$. Adding Group (Positive affect, Control) to this RM ANOVA resulted in no main or interaction effects involving Group.

Table S6.1

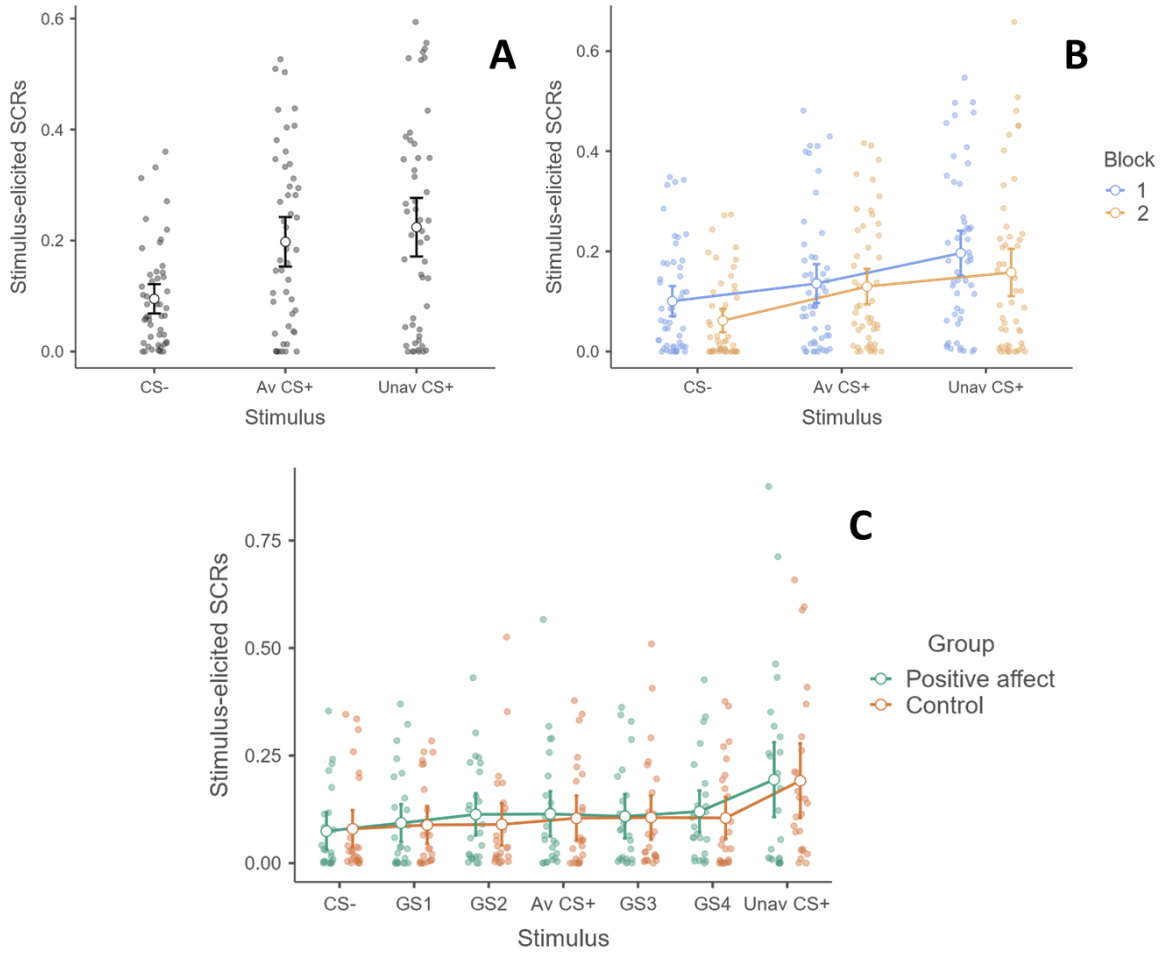
Summary of trait scores, US intensity (self-reported and physical) and post-experimental ratings

	Positive affect (n = 25)	Control (n = 25)	Positive affect vs. Control *t*-test	
	M ± *SD*	*M* ± *SD*	*p*-value	Cohen's *d*
Trait scores				
Distress tolerance	53.32 ± 9.72	50.20 ± 11.91	.315	0.29
Intolerance of uncertainty	31.68 ± 6.70	32.60 ± 7.64	.653	-0.13
Fear of pain	74.92 ± 16.26	76.04 ± 14.77	.800	-0.07
US calibration				
Self-reported intensity	7.58 ± 0.84	7.40 ± 0.69	.921	0.23
Physical intensity (mA)	31.36 ± 20.15	31.92 ± 19.79	.412	-0.03
Unpleasantness (post-exp)				
US	68.48 ± 23.15	74.56 ± 17.16	.297	-0.30
CS-	13.76 ± 28.55	12.48 ± 25.84	.869	0.05
Avoidable CS+	38.76 ± 24.79	30.44 ± 24.87	.242	0.34
Unavoidable CS+	74.76 ± 28.72	81.40 ± 24.06	.380	-0.25
Avoidance button	26.76 ± 25.81	26.44 ± 30.40	.968	0.01
Avoidance (post-exp)				
Avoidance tendency	80.44 ± 17.72	80.52 ± 14.54	.986	<0.01

Note. US = unconditional stimulus; CS = conditional stimulus; Post-exp = post-experimental. None of the independent *t*-tests reached significance.

Figure S6.1

Stimulus-elicited skin conductance responses



Note. Observed averages, estimated marginal means and 95% confidence intervals of stimulus-elicited skin conductance responses (SCRs) during fear conditioning (panel A), blocks 1 and 2 of avoidance conditioning (panel B) and the generalization test (panel C). CS = conditional stimulus; GS = generalization stimulus; Av = avoidable; Unav = unavoidable.

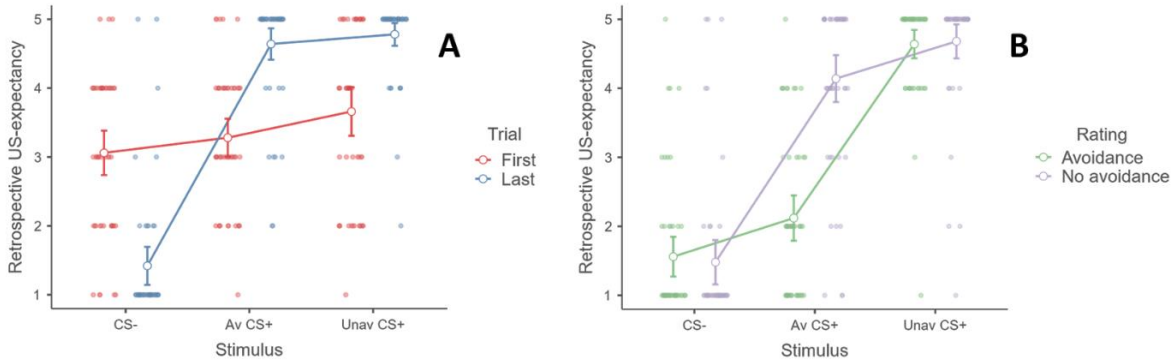
Avoidance conditioning

A 3 (Stimulus: CS-, Avoidable CS+, Unavoidable CS+) x 2 (Block: 1-2) RM ANOVA was run on *stimulus-elicited SCRs* during avoidance conditioning and showed both significant main effects of Stimulus, $F(2, 98) = 18.27$, $p < .001$, $\eta_p^2 = 0.27$, and Block, $F(1, 49) = 6.22$, $p = .016$, $\eta_p^2 = 0.11$, and no significant interaction effect, $F(1.73, 84.70) = 1.60$, $p = .211$, $\eta_p^2 = 0.03$, $\varepsilon = .86$. This indicates differential responding to stimuli and a general decrease in responding between blocks, while differential responding was maintained (Figure S6.1, panel B). Pairwise comparisons showed significantly higher responding to both the avoidable CS+, $t(49) = 3.73$, $p < .001$, $d = 0.45$, and unavoidable CS+, $t(49) = 5.72$, $p < .001$, $d = 0.72$, compared to the CS-. Moreover, responding to the avoidable CS+ was

significantly higher compared to the unavoidable CS+, $t(49) = 2.63$, $p = .011$, $d = 0.30$, indicating successful avoidance conditioning. Adding Group (Positive affect, Control) to this RM ANOVA resulted in no main or interaction effects involving Group.

Figure S6.2

Retrospective US-expectancy ratings



Note. Observed ratings, estimated marginal means and 95% confidence intervals of retrospective US-expectancy ratings after fear conditioning (differentiating between first and last trial; panel A) and avoidance conditioning (differentiating between emitting and not emitting the avoidance response; panel B). CS = conditional stimulus; Av = avoidable; Unav = unavoidable.

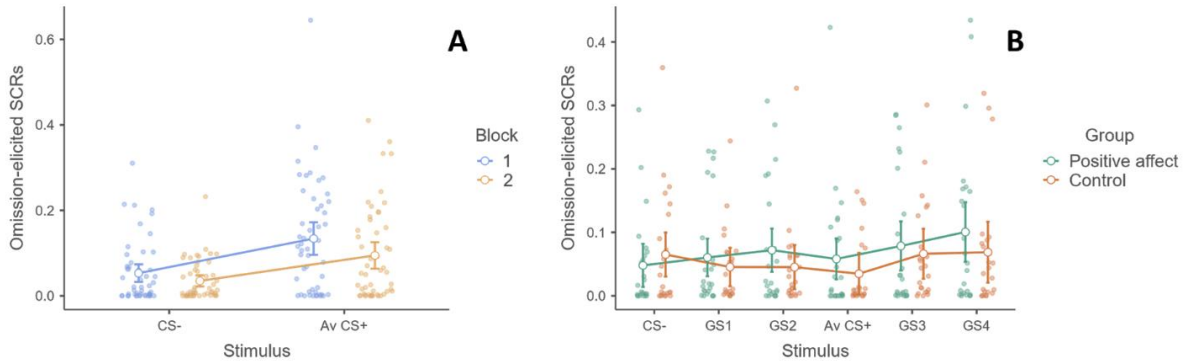
A 2 (Stimulus: CS-, Avoidable CS+) x 2 (Block: 1-2) RM ANOVA on *omission-elicited SCRs* during avoidance conditioning showed both significant main effects of Stimulus, $F(1, 49) = 30.77$, $p < .001$, $\eta_p^2 = 0.39$, and Block, $F(1, 49) = 8.39$, $p = .006$, $\eta_p^2 = 0.15$, and no significant interaction, $F(1, 49) = 1.84$, $p = .182$, $\eta_p^2 = 0.04$. As expected, these results indicate higher responding to the avoidable CS+ compared to the CS- and a general decrease in responding across blocks while differential responding was maintained (Figure S6.3, panel A). Adding Group (Positive affect, Control) to this RM ANOVA resulted in no main or interaction effects involving Group.

A 3 (Stimulus: CS-, Avoidable CS+, Unavoidable CS+) x 2 (Rating: Avoidance, No Avoidance) RM ANOVA on *retrospective US-expectancy* ratings was used to test whether participants acquired the action-omission contingencies. This analysis showed significant main effects of both Stimulus, $F(2, 98) = 244.27$, $p < .001$, $\eta_p^2 = 0.83$, and Rating, $F(1, 49) = 40.88$, $p < .001$, $\eta_p^2 = 0.45$. The interaction effect reached significance as well, $F(2, 98) = 25.60$, $p < .001$, $\eta_p^2 = 0.34$, indicating different US-expectancy patterns when avoiding versus when not avoiding (Figure S6.2, panel B). A pairwise comparison confirmed significantly lower expectancies when avoiding versus when not avoiding on the avoidable CS+, $t(49) = -7.60$, $p < .001$, $d = -1.72$. Adding Group (Positive affect, Control) to this RM ANOVA showed a significant three-way interaction, $F(2, 96) = 3.60$, $p = .031$, $\eta_p^2 = 0.07$. Further exploration of this effect

showed a significant Stimulus by Group interaction when avoiding, $F(2, 96) = 3.32$, $p = .040$, $\eta_p^2 = 0.06$, though pairwise comparisons between groups for each stimulus separately did not reach significance.

Figure S6.3

Omission-elicited skin conductance responses



Note. Observed averages, estimated marginal means and 95% confidence intervals of average omission-elicited skin conductance responses (SCRs) during blocks 1 and 2 of avoidance conditioning (panel A) and during the generalization test (panel B). CS = conditional stimulus; GS = generalization stimulus; Av = avoidable; Unav = unavoidable.

Exploratory analyses

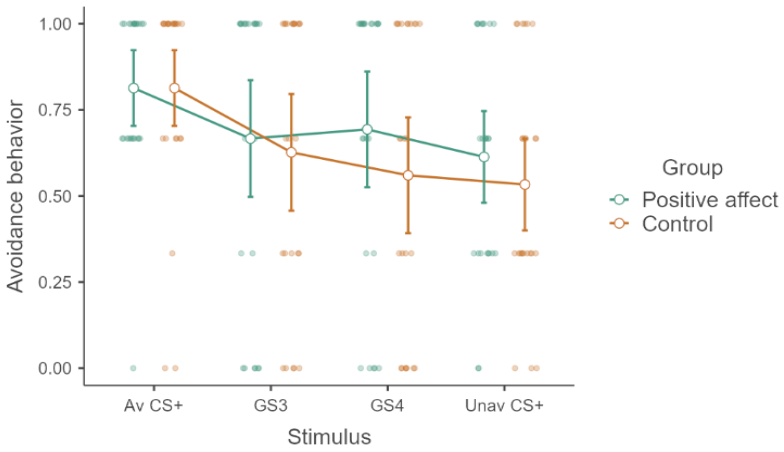
Generalization test

A 4 (Stimulus: Avoidable CS+, GS3, GS4, Unavoidable CS+) x 2 (Group: Positive affect, Control) RM ANOVA was used to explore the effect of the visualization exercises on *avoidance behavior over the dimension of avoidability* during the generalization test. This analysis showed a significant main effect of Stimulus, $F(3, 144) = 8.32$, $p < .001$, $\eta_p^2 = 0.15$, though no significant effect of Group, $F(1, 48) = 0.59$, $p = .448$, $\eta_p^2 = 0.01$, or interaction effect, $F(3, 144) = 0.63$, $p = .598$, $\eta_p^2 = 0.01$, indicating no differential effect of the visualization exercises on avoidance behavior (Figure S6.4). The Stimulus effect showed a significant linear trend, $F(1, 48) = 22.40$, $p < .001$, $\eta_p^2 = 0.32$, and no quadratic trend, $F(1, 48) = 1.82$, $p = .183$, $\eta_p^2 = 0.04$. Further analysis of this generalization gradient showed significantly more avoidance toward the avoidable CS+, $t(48) = 4.74$, $p < .001$, $d = 0.79$, but not GS3, $t(48) = 1.49$, $p = .429$, $d = 0.21$, nor GS4, $t(48) = 1.03$, $p = .620$, $d = 0.16$, compared to the unavoidable CS+. Responding to both GS3, $t(48) = -3.05$, $p = .015$, $d = -0.47$, and GS4, $t(48) = -3.32$, $p = .009$, $d = -0.53$, was significantly lower compared to the avoidable CS+. These results indicate a flattened generalization gradient compared to avoidance along the threat-safety dimension (see manuscript). An additional 7 (Stimulus: CS-, GS1, GS2, Avoidable CS+, GS3, GS4, Unavoidable CS+) x 2 (Group: Positive affect, Control) RM ANOVA on avoidance behavior again showed a significant main effect of Stimulus, $F(3.46, 165.91) =$

24.60, $p < .001$, $\eta_p^2 = 0.34$, $\varepsilon = .58$, but not of Group, $F(1, 48) = 0.77$, $p = .383$, $\eta_p^2 = 0.02$, and no significant interaction, $F(6, 288) = 0.36$, $p = .903$, $\eta_p^2 = 0.01$. A pairwise comparison showed significantly lower avoidance responding to the CS- compared to the unavoidable CS+, $t(48) = -6.81$, $p < .001$, $d = -0.98$, confirming a flattened generalization gradient on the dimension of avoidability. When these analyses were conducted with change in positive affect as covariate instead of the Group factor, conclusions remained the same.

Figure S6.4

Avoidance behavior along the dimension of avoidability during the generalization test



Note. Observed proportions, estimated marginal means and 95% confidence intervals of avoidance proportion during the generalization test. CS = conditional stimulus; GS = generalization stimulus. Av = avoidable; Unav = unavoidable.

A 7 (Stimulus: CS-, GS1, GS2, Avoidable CS+, GS3, GS4, Unavoidable CS+) x 2 (Group: Positive affect, Control) RM ANOVA on *stimulus-elicited SCRs* during the generalization test showed a significant main effect of Stimulus, $F(3.89, 186.65) = 6.26$, $p < .001$, $\eta_p^2 = 0.12$, $\varepsilon = .65$, but not of Group, $F(1, 48) = 0.08$, $p = .785$, $\eta_p^2 < 0.01$, and no significant interaction, $F(6, 288) = 0.10$, $p = .996$, $\eta_p^2 < 0.01$. These results indicate that visualization exercises did not affect stimulus-elicited SCRs differentially (Figure S6.1, panel C). The linear trend in the Stimulus effect reached significance, $F(1, 48) = 12.88$, $p = .001$, $\eta_p^2 = 0.21$, but not the quadratic trend, $F(1, 48) = 3.69$, $p = .061$, $\eta_p^2 = 0.07$. Further exploration of this trend revealed it was mainly driven by responding to the unavoidable CS+, with significantly higher responding to this stimulus compared to both the CS-, $t(48) = 3.56$, $p = .016$, $d = 0.69$, and avoidable CS+, $t(48) = 4.15$, $p = .003$, $d = 0.48$, while none of the GSs significantly differed from the CS- or avoidable CS+. The CS- and avoidable CS+ did not significantly differ either, $t(48) = 1.49$, $p = 1.00$, d

= 0.25. When these analyses were conducted with change in positive affect as covariate instead of the Group factor, conclusions remained the same.

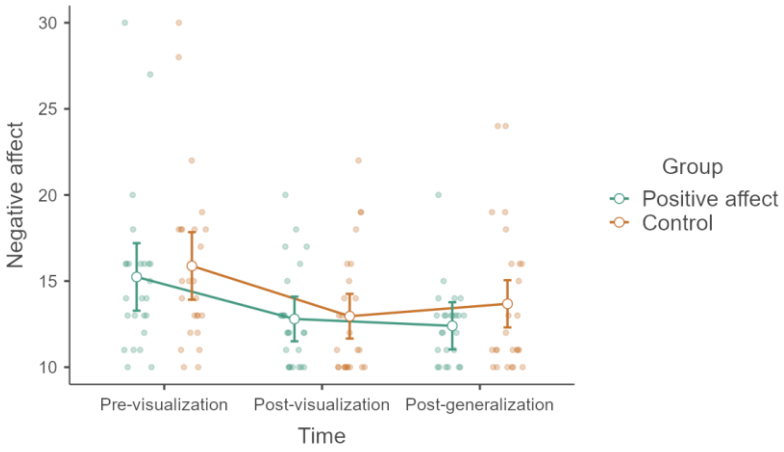
Effects of the visualization exercises on *omission-elicited SCRs* during generalization were tested using a 6 (Stimulus: CS-, GS1, GS2, Avoidable CS+, GS3, GS4) x 2 (Group: Positive affect, Control) RM ANOVA. Results showed a significant main effect of Stimulus, $F(5, 225) = 2.41$, $p = .038$, $\eta_p^2 = 0.05$, but not of Group, $F(1, 45) = 0.60$, $p = .442$, $\eta_p^2 = 0.01$, and no significant interaction effect, $F(5, 225) = 0.93$, $p = .461$, $\eta_p^2 = 0.02$, indicating no differential effects of visualization exercises on omission-elicited SCRs (Figure S6.3, panel B). Furthermore, no significant linear, $F(1, 45) = 3.73$, $p = .060$, $\eta_p^2 = 0.08$, or quadratic trend, $F(1, 45) = 3.74$, $p = .060$, $\eta_p^2 = 0.08$, was present in the Stimulus effect. In addition, none of the GSs differed significantly from the CSs, nor did the CSs differ significantly from one another, indicating the lack of a generalization gradient. Removing the Group factor and using change in positive affect as covariate did not result in any effects involving group, and the Stimulus effect no longer reached significance. An additional 3 (Stimulus: GS1+2, Avoidable CS+, GS3+4) x 2 (Group: Positive affect, Control) RM ANOVA only including trials on which an avoidance response was emitted showed no significant main effect of Stimulus, $F(3, 39) = 2.12$, $p = .113$, $\eta_p^2 = 0.14$, nor of Group, $F(1, 13) < 0.01$, $p = .954$, $\eta_p^2 < 0.01$, nor a significant interaction effect, $F(3, 39) = 0.49$, $p = .693$, $\eta_p^2 = 0.04$. Conclusions remained the same when using change in positive affect as covariate instead of the Group factor.

Negative affect

A 3 (Time: pre-visualization, post-visualization, post-generalization) x 2 (Group: Positive affect, Control) RM ANOVA run on state negative affect showed a significant main effect of Time (Figure S6.5), $F(2, 96) = 18.80$, $p < .001$, $\eta_p^2 = 0.28$, but not of Group, $F(1, 48) = 0.53$, $p = .469$, $\eta_p^2 = 0.01$. The interaction effect did not reach significance, $F(2, 96) = 0.66$, $p = .521$, $\eta_p^2 = 0.01$. Further exploration of the Time effect using pairwise comparisons showed a significant decrease in negative affect from pre-visualization ($M = 15.56$, $SD = 4.84$) to post-visualization ($M = 12.88$, $SD = 3.19$), $t(48) = -5.07$, $p < .001$, $d = -0.65$, while there was no significant difference between post-visualization and post-generalization, $t(48) = 0.47$, $p = .639$, $d = 0.05$.

Figure S6.5

Negative affect



Note. Observed scores, estimated marginal means and 95% confidence intervals of negative affect before and after performing the visualization exercise (pre- and post-visualization) and after performing the generalization test of the conditioning task (post-generalization).

Bibliography

Alizadehkhaiyat, O., Fisher, A. C., Kemp, G. J., Vishwanathan, K., & Frostick, S. P. (2007). Upper Limb Muscle Imbalance in Tennis Elbow: A Functional and Electromyographic Assessment Omid. *Journal of Orthopaedic Research*, *25*, 1651-1657. https://doi.org/10.1002/jor.20458

Angst, F., Schwyzer, H. K., Aeschlimann, A., Simmen, B. R., & Goldhahn, J. (2011). Measures of adult shoulder function: Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) and its short version (QuickDASH), Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons (ASES) Society standardized shoulder assessment form, Constant (Murley) Score (CS), Simple Shoulder Test (SST), Oxford Shoulder Score (OSS), Shoulder Disability Questionnaire (SDQ), and Western Ontario Shoulder Instability Index (WOSI). *Arthritis Care & Research*, *63* (S11), S174-S188. https://doi.org/10.1002/acr.20630

Atlas, L. Y., & Wager, T. D. (2012). How expectations shape pain. *Neuroscience Letters*, *520*, 140-148. https://doi.org/10.1016/j.neulet.2012.03.039

Beckerman, H., Roebroeck, M. E., Lankhorst, G. J., Becher, J. G., Bezemer, P. D., & Verbeek, A. L. M. (2001). Smallest real difference, a link between reproducibility and responsiveness. *Quality of Life Research*, *10*, 571-578. https://doi.org/10.1023/A:1013138911638

Bennett, M. P., Meulders, A., Baeyens, F., & Vlaeyen, J. W. S. (2015). Words putting pain in motion: The generalization of pain-related fear within an artificial stimulus category. *Frontiers in Psychology*, *6*, 1-12. https://doi.org/10.3389/fpsyg.2015.00520

Bennett, M. P., Roche, B., Dymond, S., Baeyens, F., Vervliet, B., & Hermans, D. (2020). Transitions from avoidance: Reinforcing competing behaviours reduces generalised avoidance in new contexts. *Quarterly Journal of Experimental Psychology*, *73*(12), 2119-2131. https://doi.org/10.1177/1747021820943148

Berryman, C., Stanton, T. R., Jane Bowering, K., Tabor, A., McFarlane, A., & Lorimer Moseley, G. (2013). Evidence for working memory deficits in chronic pain: A systematic review and meta-analysis. *Pain*, *154*, 1181-1196. https://doi.org/10.1016/j.pain.2013.03.002

Boselie, J. J. L. M., Vancleef, L. M. G., & Peters, M. L. (2017). Increasing Optimism Protects Against Pain-Induced Impairment in Task-Shifting Performance. *Journal of Pain*, *18*(4), 446-455. https://doi.org/10.1016/j.jpain.2016.12.007

Boselie, J. J. L. M., Vancleef, L. M. G., Smeets, T., & Peters, M. L. (2014). Increasing optimism abolishes pain-induced impairments in executive task performance. *Pain*, *155*, 334-340. https://doi.org/10.1016/j.pain.2013.10.014

Bouton, M. E., & Todd, T. P. (2014). A fundamental role for context in instrumental learning and extinction. *Behavioural Processes*, *104*, 13-19. https://doi.org/10.1016/j.beproc.2014.02.012

Bouton, M. E., Todd, T. P., & Leon, S. P. (2014). Contextual control of discriminated operant behavior. *Journal of Experimental Psychology: Animal Learning and Cognition*, *40*(1), 92-105. https://doi.org/10.1037/xan0000002

Boyle, S., Roche, B., Dymond, S., & Hermans, D. (2016). Generalisation of fear and avoidance along a semantic continuum. *Cognition and Emotion*, *30*(2), 340-352. https://doi.org/10.1080/02699931.2014.1000831

Braunwalder, C., Muller, R., Glisic, M., & Fekete, C. (2022). Are Positive Psychology Interventions Efficacious in Chronic Pain Treatment? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain Medicine*, *23*(1), 122-136. https://doi.org/10.1093/pm/pnab247

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain*, *10*, 287-333. https://doi.org/10.1016/j.ejpain.2005.06.009

Brinjikji, W., Luetmer, P. H., Comstock, B., Bresnahan, B. W., Chen, L. E., Deyo, R. A., . . . Jarvik, J. G. (2015). Systematic Literature Review of Imaging Features of Spinal Degeneration in Asymptomatic Populations. *American Journal of Neuroradiology*, *36*(4), 811-816. https://doi.org/10.3174/ajnr.A4173

Burger, A. M., Van Diest, I., Van der Does, W., Korbee, J. N., Waziri, N., Brosschot, J. F., & Verkuil, B. (2019). The effect of transcutaneous vagus nerve stimulation on fear generalization and subsequent fear extinction. *Neurobiology of Learning and Memory*, *161*, 192-201. https://doi.org/10.1016/j.nlm.2019.04.006

Butler, R. K., & Finn, D. P. (2009). Stress-induced analgesia. *Progress in Neurobiology*, *88*(3), 184-202. https://doi.org/10.1016/j.pneurobio.2009.04.003

Cappello, L., Elangovan, N., Contu, S., Khosravani, S., Konczak, J., & Masia, L. (2015). Robot-aided assessment of wrist proprioception. *Frontiers in Human Neuroscience*, *9*, 1-8. https://doi.org/10.3389/fnhum.2015.00198

Carleton, R. N., Norton, M. A. P. J., & Asmundson, G. J. G. (2007). Fearing the unknown: A short version of the Intolerance of Uncertainty Scale. *Journal of Anxiety Disorders*, *21*, 105-117. https://doi.org/10.1016/j.janxdis.2006.03.014

Chen, H. M., Chen, C., Hsueh, I. P., Huang, S. I., & Hsieh, C. L. (2009). Test-Retest Reproducibility and Smallest Real Difference of 5 Hand Function Tests in Patients With Stroke. *Neurorehabilitation and Neural Repair*, *23*(5), 435-440. https://doi.org/10.1177%2F1545968308331146

Chowdhury, R. H., Glaser, J. I., & Miller, L. E. (2020). Area 2 of primary somatosensory cortex encodes kinematics of the whole arm. *eLife*, *9*, e48198. https://doi.org/10.1101/643205

Christensen, S. W. M., Peolsson, A., Agger, S. M., Svindt, M., Graven-Nielsen, T., & Hirata, R. P. (2020). Head repositioning accuracy is influenced by experimental neck pain in those most accurate but not when adding a cognitive task. *Scandinavian Journal of Pain*, *20*(1), 191–203. https://doi.org/10.1515/sjpain-2019-0093

Claes, N., Crombez, G., & Vlaeyen, J. W. (2015). Pain-avoidance versus reward-seeking: an experimental investigation. *Pain*, *156*(8), 1449-1457. https://doi.org/10.1097/j.pain.0000000000000116

Claes, N., Karos, K., Meulders, A., Crombez, G., & Vlaeyen, J. W. S. (2014). Competing goals attenuate avoidance behavior in the context of pain. *Journal of Pain*, *15*, 1120-1129. https://doi.org/10.1016/j.jpain.2014.08.003

Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behavioral and brain sciences*, *36*(3), 181-204. https://doi.org/10.1017/S0140525X12000477

Clark, N. C., Röijezon, U., & Treleaven, J. (2015). Proprioception in musculoskeletal rehabilitation. Part 2: Clinical assessment and intervention. *Manual Therapy*, *20*, 378-387. https://doi.org/10.1016/j.math.2015.01.009

Craske, M. G., Hermans, D., & Vervliet, B. (2018). State-of-the-art and future directions for extinction as a translational model for fear and anxiety. *Philosophical Transactions of the Royal Society B-Biological Sciences*, *373*(1742). https://doi.org/10.1098/rstb.2017.0025

Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014). Maximizing exposure therapy: An inhibitory learning approach. *Behaviour research and therapy*, *58*, 10-23. https://doi.org/https://doi.org/10.1016/j.brat.2014.04.006

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*, 475-483. https://doi.org/10.1097/AJP.0b013e3182385392

Dagenais, S., Caro, J., & Haldeman, S. (2008). A systematic review of low back pain cost of illness studies in the United States and internationally. *The Spine Journal*, *8*, 8-20. https://doi.org/10.1016/j.spinee.2007.10.005

Davies, G. J., Krauschaar, D. J. R., Brinks, K. F., & Jennings, J. (2006). Neuromuscular Static and Dynamic Stability of the Shoulder: The Key to Functional Performance. In *Postsurgical Orthopedic Sports Rehabilitation: Knee & Shoulder* (pp. 133-155). https://doi.org/10.1016/B978-032302702-1.50010-7

Davis, J., & Bitterman, M. E. (1971). Differential reinforcement of other behavior (DRO): a yoked-control comparison. *Journal of the experimental analysis of behavior*, *15*(2), 237-241. https://doi.org/10.1901/jeab.1971.15-237

Day, J. M., Bush, H., Nitz, A. J., & Uhl, T. L. (2015). Scapular muscle performance in individuals with lateral epicondylalgia. *Journal of Orthopaedic and Sports Physical Therapy*, *45*, 414-424. https://doi.org/10.2519/jospt.2015.5290

De Clercq, A., Verschuere, B., De Vlieger, P., & Crombez, G. (2006). Psychophysiological Analysis (PSPHA): A modular script-based program for analyzing psychophysiological data. *Behavior Research Methods*, *38*, 504-510. https://doi.org/10.3758/BF03192805

De Jong, A., Kilbreath, S. L., Refshauge, K. M., & Adams, R. (2005). Performance in Different Proprioceptive Tests Does Not Correlate in Ankles With Recurrent Sprain. *Archives of Physical Medicine and Rehabilitation*, *86*, 2101-2105. https://doi.org/10.1016/j.apmr.2005.05.015

De Ruddere, L., Goubert, L., Vervoort, T., Prkachin, K. M., & Crombez, G. (2012). We Discount the Pain of Others When Pain Has No Medical Explanation. *Journal of Pain*, *13*(12), 1198-1205. https://doi.org/10.1016/j.jpain.2012.09.002

den Hollander, M., de Jong, J. R., Volders, S., Goossens, M. E., Smeets, R. J., & Vlaeyen, J. W. (2010). Fear reduction in patients with chronic pain: a learning theory perspective. *Expert Review of Neurotherapeutics*, *10*(11), 1733-1745. https://doi.org/10.1586/ern.10.115

Domjan, M. (2018). *The essentials of conditioning and learning* (Fourth Edition. ed.). American Psychological Association.

Dukelow, S. P., Herter, T. M., Bagg, S. D., & Scott, S. H. (2012). The independence of deficits in position sense and visually guided reaching following stroke. *Journal of NeuroEngineering and Rehabilitation*, *9*, 1-13. https://doi.org/10.1186/1743-0003-9-72

Dunsmoor, J. E., & Paz, R. (2015). Fear Generalization and Anxiety: Behavioral and Neural Mechanisms. *Biological Psychiatry*, *78*, 336-343. https://doi.org/10.1016/j.biopsych.2015.04.010

Dymond, S., Dunsmoor, J. E., Vervliet, B., Roche, B., & Hermans, D. (2015). Fear Generalization in Humans: Systematic Review and Implications for Anxiety Disorder Research. *Behavior Therapy*, *46*, 561-582. https://doi.org/10.1016/j.beth.2014.10.001

Dymond, S., Schlund, M. W., Roche, B., De Houwer, J., & Freegard, G. P. (2012). Safe from harm: Learned, instructed, and symbolic generalization pathways of human threat-avoidance. *PLoS One*, *7*(10). https://doi.org/10.1371/journal.pone.0047539

Dymond, S., Schlund, M. W., Roche, B., Whelan, R., Richards, J., & Davies, C. (2011). Inferred threat and safety: symbolic generalization of human avoidance learning. *Behaviour Research And Therapy*, *49*(10), 614-621. https://doi.org/10.1016/j.brat.2011.06.007

Elangovan, N., Herrmann, A., & Konczak, J. (2014). Assessing Proprioceptive Function: Evaluating Joint Position Matching Methods Against Psychophysical Thresholds. *Physical therapy*, *94*(4), 553-561. https://doi.org/10.2522/ptj.20130103

Endler, N. S., Macrodimitris, S. D., & Kocovski, N. L. (2000). Controllability in cognitive and interpersonal tasks: is control good for you? *Personality and Individual Differences*, *29*(5), 951-962. https://doi.org/10.1016/S0191-8869(99)00246-9

Engel, G. L. (1977). The need for a new medical model: a challenge for biomedicine. *Science*, *196*(4286), 129-136. https://doi.org/10.1126/science.847460

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*, 175-191. https://doi.org/10.3758/BF03193146

Finan, P. H., & Garland, E. L. (2015). The Role of Positive Affect in Pain and its Treatment. *The Clinical journal of pain*, *31*, 177-187. https://doi.org/10.1038/jid.2014.371

Fleiss, J. L. (1986). *Design and analysis of clinical experiments*. John Wiley & Sons.

Flynn, T. W., Smith, B., & Chou, R. (2011). Appropriate Use of Diagnostic Imaging in Low Back Pain: A Reminder That Unnecessary Imaging May Do as Much Harm as Good. *Journal of Orthopaedic & Sports Physical Therapy*, *41*(11), 838-846. https://doi.org/10.2519/jospt.2011.3618

Fordyce, W. E. (1973). An operant conditioning method for managing chronic pain. *Postgraduate Medicine*, *53*(6), 123-128. https://doi.org/10.1080/00325481.1973.11713462

Fordyce, W. E., Fowler, R. S., & DeLateur, B. (1968). An application of behavior modification technique to a problem of chronic pain. *Behaviour Research And Therapy*, *6*(1), 105-107. https://doi.org/10.1016/0005-7967(68)90048-x

Fredrickson, B. L. (2001). The Role of Positive Emotions in Positive Psychology. *The American psychologist*, *56*, 218-226. https://doi.org/10.1037/0003-066x.56.3.218

Fredrickson, B. L. (2003). The Value of Positive Emotions: The emerging science of positive psychology is coming to understand why it's good to feel good. *American Scientist*, *91*, 330-335. https://doi.org/10.1511/2003.4.330

Fredrickson, B. L., Tugade, M. M., Waugh, C. E., & Larkin, G. R. (2003). What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. *Journal of Personality and Social Psychology*, *84*(2), 365-376. https://doi.org/10.1037/0022-3514.84.2.365

Gable, P. A., & Harmon-Jones, E. (2008). Approach-motivated positive affect reduces breadth of attention. *Psychological Science*, *19*(5), 476-482. https://doi.org/10.1111/j.1467-9280.2008.02112.x

Gámez, W., Chmielewski, M., Kotov, R., Ruggero, C., & Watson, D. (2011). Development of a Measure of Experiential Avoidance: The Multidimensional Experiential Avoidance Questionnaire. *Psychological Assessment*, *23*, 692-713. https://doi.org/10.1037/a0023242

Gatchel, R. J., & Okifuji, A. (2006). Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. *The Journal of Pain*, *7*(11), 779-793. https://doi.org/10.1016/j.jpain.2006.08.005

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological Bulletin*, *133*(4), 581-624. https://doi.org/10.1037/0033-2909.133.4.581

Gatzounis, R., den Hollander, M., & Meulders, A. (2021). Optimizing Long-term Outcomes of Exposure for Chronic Primary Pain from the Lens of Learning Theory. *Journal of Pain*, *22*(11), 1315-1327. https://doi.org/10.1016/j.jpain.2021.04.012

Geschwind, N., Meulders, M., Peters, M. L., Vlaeyen, J. W. S., & Meulders, A. (2015). Can experimentally induced positive affect attenuate generalization of fear of movement-related pain? *Journal of Pain*, *16*, 258-269. https://doi.org/10.1016/j.jpain.2014.12.003

Gewandter, J. S., Dworkin, R. H., Turk, D. C., Farrar, J. T., Fillingim, R. B., Gilron, I., . . . Walco, G. A. (2015). Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations. *Pain*, *156*(7), 1184-1197. https://doi.org/10.1097/j.pain.0000000000000191

Ghirlanda, S., & Enquist, M. (2003). A century of generalization. *Animal Behaviour*, *66*, 15-36. https://doi.org/10.1006/anbe.2003.2174

Ginat-Frolich, R., Klein, Z., Aderka, I. M., & Shechner, T. (2019). Reducing avoidance in adults with high spider fear using perceptual discrimination training. *Depression and Anxiety*, *36*, 859-865. https://doi.org/10.1002/da.22930

Ginat-Frolich, R., Klein, Z., Katz, O., & Shechner, T. (2017). A novel perceptual discrimination training task: Reducing fear overgeneralization in the context of fear learning. *Behaviour Research And Therapy*, *93*, 29-37. https://doi.org/10.1016/j.brat.2017.03.010

Glogan, E., Gatzounis, R., Meulders, M., & Meulders, A. (2020). Generalization of instrumentally acquired pain-related avoidance to novel but similar movements using a robotic arm-reaching paradigm. *Behaviour Research And Therapy*, *124*, 103525. https://doi.org/10.1016/j.brat.2019.103525

Glogan, E., Gatzounis, R., Vandael, K., Franssen, M., Vlaeyen, J. W. S., & Meulders, A. (2020). Investigating pain-related avoidance behavior using a robotic arm-reaching paradigm. *Journal of Visualized Experiments*, *164*, e61717. https://doi.org/10.3791/61717

Glogan, E., van Vliet, C., Roelandt, R., & Meulders, A. (2018). Generalization and extinction of concept-based pain-related fear. *The Journal of Pain*, *20*(3). https://doi.org/10.1016/j.jpain.2018.09.010

Glogan, E., Vandael, K., Gatzounis, I., & Meulders, A. (2021). When do we not face our fears? Investigating the boundary conditions of costly pain-related avoidance generalization. *The Journal of Pain*, *22*(10), 1221-1232. https://doi.org/10.1016/j.jpain.2021.03.149

Goble, D. J. (2010). Proprioceptive Acuity Assessment Via Joint Position Matching: From Basic Science to General Practice. *Physical Therapy*, *90*, 1176-1184. https://doi.org/10.2522/ptj.20090399

Goble, D. J., Noble, B. C., & Brown, S. H. (2010). Where was my arm again? Memory-based matching of proprioceptive targets is enhanced by increased target presentation time. *Neuroscience Letters*, *481*(1), 54-58. https://doi.org/10.1016/j.neulet.2010.06.053

Green, P., & MacLeod, C. J. (2016). SIMR: an R package for power analysis of generalized linear mixed models by simulation. *Methods in Ecology and Evolution*, *7*(4), 493-498. https://doi.org/10.1111/2041-210x.12504

Grillon, C., Baas, J. M., Cornwell, B., & Johnson, L. (2006). Context conditioning and behavioral avoidance in a virtual reality environment: effect of predictability. *Biological Psychiatry*, *60*(7), 752-759. https://doi.org/10.1016/j.biopsych.2006.03.072

Grupe, D. W., & Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience*, *14*, 488-501. https://doi.org/10.1038/nrn3524

Han, J., Waddington, G., Adams, R., Anson, J., & Liu, Y. (2016). Assessing proprioception: A critical review of methods. *Journal of Sport and Health Science*, *5*, 80-90. https://doi.org/10.1016/j.jshs.2014.10.004

Hanssen, M. M., Peters, M. L., Boselie, J. J., & Meulders, A. (2017). Can positive affect attenuate (persistent) pain? State of the art and clinical implications. *Current Rheumatology Reports*, *19*, 80. https://doi.org/10.1007/s11926-017-0703-3

Harvie, D. S., Meulders, A., Reid, E., Camfferman, D., Brinkworth, R. S. A., & Moseley, G. L. (2016). Selectivity of conditioned fear of touch is modulated by somatosensory precision. *Psychophysiology*, *53*, 921-929. https://doi.org/10.1111/psyp.12631

Harvie, D. S., Moseley, G. L., Hillier, S. L., & Meulders, A. (2017). Classical Conditioning Differences Associated With Chronic Pain: A Systematic Review. *Journal of Pain*, *18*, 889-898. https://doi.org/10.1016/j.jpain.2017.02.430

Harvie, D. S., Weermeijer, J. D., Olthof, N. A., & Meulders, A. (2020). Learning to predict pain : differences in people with persistent neck pain and pain-free controls. *Peerj*, *8*, e9345. https://doi.org/10.7717/peerj.9345

Helsen, W. F., Van Halewyck, F., Levin, O., Boisgontier, M. P., Lavrysen, A., & Elliott, D. (2016). Manual aiming in healthy aging: does proprioceptive acuity make the difference? *AGE*, *38*, 45. https://doi.org/10.1007/s11357-016-9908-z

Herzog, K., Andreatta, M., Schneider, K., Schiele, M. A., Domschke, K., Romanos, M., . . . Pauli, P. (2021). Reducing Generalization of Conditioned Fear: Beneficial Impact of Fear Relevance and Feedback in Discrimination Training. *Frontiers in Psychology*, *12*, 665711. https://doi.org/10.3389%2Ffpsyg.2021.665711

Hillier, S., Immink, M., & Thewlis, D. (2015). Assessing Proprioception : A Systematic Review of Possibilities. *Neurorehabilitation and Neural Repair*, *29*, 933-949. https://doi.org/10.1177/1545968315573055

Hoyle, R. H., Stephenson, M. T., Palmgreen, P., Lorch, E. P., & Donohew, R. L. (2002). Reliability and validity of a brief measure of sensation seeking. *Personality and Individual Differences*, *32*, 401-414. https://doi.org/10.1016/S0191-8869(01)00032-0

Hughes, L. S., Clark, J., Colclough, J. A., Dale, E., & McMillan, D. (2017). Acceptance and Commitment Therapy (ACT) for Chronic Pain: A Systematic Review and Meta-Analyses. *The Clinical journal of pain*, *33*(6), 552-568. https://doi.org/10.1097/ajp.0000000000000425

Hull, C. L. (1943). *Principles of behavior: an introduction to behavior theory*. Appleton-Century.

Hunt, C., Cooper, S. E., Hartnell, M. P., & Lissek, S. (2019). Anxiety sensitivity and intolerance of uncertainty facilitate associations between generalized pavlovian fear and maladaptive avoidance decisions. *Journal of Abnormal Psychology*, *128*, 315-326. https://doi.org/10.1037/abn0000422

jamovi. In. (2021). (Version 1.6) The jamovi project. https://www.jamovi.org

Jensen, M. P., Ehde, D. M., & Day, M. A. (2016). The Behavioral Activation and Inhibition Systems: Implications for Understanding and Treating Chronic Pain. *Journal of Pain*, *17*(5), 529-529. https://doi.org/10.1016/j.jpain.2016.02.001

Johnson, L. M., Zautra, A. J., & Davis, M. C. (2006). The role of illness uncertainty on coping with fibromyalgia symptoms. *Health Psychology*, *25*(6), 696-703. https://doi.org/10.1037/0278-6133.25.6.696

Jull, G., Falla, D., Treleaven, J., Hodges, P., & Vicenzino, B. (2007). Retraining Cervical Joint Position Sense: The Effect of Two Exercise Regimes. *Journal of Orthopaedic Research*, *25*, 404-412. https://doi.org/10.1002/jor

Juul-Kristensen, B., Lund, H., Hansen, K., Christensen, H., Danneskiold-Samsøe, B., & Bliddal, H. (2008a). Poorer elbow proprioception in patients with lateral epicondylitis than in healthy controls: A cross-sectional study. *Journal of Shoulder and Elbow Surgery*, *17*, 72-81. https://doi.org/10.1016/j.jse.2007.07.003

Juul-Kristensen, B., Lund, H., Hansen, K., Christensen, H., Danneskiold-Samsøe, B., & Bliddal, H. (2008b). Test-retest reliability of joint position and kinesthetic sense in the elbow of healthy subjects. *Physiotherapy Theory and Practice*, *24*, 65-72. https://doi.org/10.1080/09593980701378173

Karos, K., Meulders, A., Gatzounis, R., Seelen, H. A. M., Geers, R. P. G., & Vlaeyen, J. W. S. (2017). Fear of pain changes movement: Motor behaviour following the acquisition of pain-related fear. *European Journal of Pain*, *21*(8), 1432-1442. https://doi.org/10.1002/ejp.1044

Kennedy, J., Roll, J. M., Schraudner, T., Murphy, S., & McPherson, S. (2014). Prevalence of persistent pain in the U.S. adult population: new data from the 2010 national health interview survey. *Journal of Pain*, *15*(10), 979-984. https://doi.org/10.1016/j.jpain.2014.05.009

Kenzie, J. M., Semrau, J. A., Findlater, S. E., Herter, T. M., Hill, M. D., Scott, S. H., & Dukelow, S. P. (2014). Anatomical correlates of proprioceptive impairments following acute stroke: A case series. *Journal of the Neurological Sciences*, *342*, 52-61. https://doi.org/10.1016/j.jns.2014.04.025

Kenzie, J. M., Semrau, J. A., Hill, M. D., Scott, S. H., & Dukelow, S. P. (2017). A composite robotic-based measure of upper limb proprioception. *Journal of NeuroEngineering and Rehabilitation*, *14*, 1-12. https://doi.org/10.1186/s12984-017-0329-8

Khan, R. S., Ahmed, K., Blakeway, E., Skapinakis, P., Nihoyannopoulos, L., Macleod, K., . . . Athanasiou, T. (2011). Catastrophizing: a predictive factor for postoperative pain. *American Journal of Surgery*, *201*(1), 122-131. https://doi.org/10.1016/j.amjsurg.2010.02.007

Kitchen, N. M., & Miall, R. C. (2019). Proprioceptive deficits in inactive older adults are not reflected in fast targeted reaching movements. *Experimental Brain Research*, *237*, 531-545. https://doi.org/10.1007/s00221-018-5440-y

Klein, Z., Shner, G., Ginat-Frolich, R., Vervliet, B., & Shechner, T. (2020). The effects of age and trait anxiety on avoidance learning and its generalization. *Behaviour Research And Therapy*, *129*. https://doi.org/10.1016/j.brat.2020.103611

Kloos, T., van Vliet, C., Riecke, J., & Meulders, A. (2022). Indoor or Outdoor? Generalization of Costly Pain-Related Avoidance Behavior to Conceptually Related Contexts. *Journal of Pain*, *23*(4), 657-668. https://doi.org/10.1016/j.jpain.2021.10.010

Knoop, J., Steultjens, M. P. M., van der Leeden, M., van der Esch, M., Thorstensson, C. A., Roorda, L. D., . . . Dekker, J. (2011). Proprioception in knee osteoarthritis: A narrative review. *Osteoarthritis and Cartilage*, *19*, 381-388. https://doi.org/10.1016/j.joca.2011.01.003

Krypotos, A. M., Crombez, G., Meulders, A., Claes, N., & Vlaeyen, J. (2020). Decomposing conditioned avoidance performance with computational models. *Behaviour Research And Therapy*, *133*, 103712. https://doi.org/10.1016/j.brat.2020.103712

Krypotos, A. M., Effting, M., Kindt, M., & Beckers, T. (2015). Avoidance learning: a review of theoretical models and recent developments. *Frontiers in Behavioral Neuroscience*, *9*, 189. https://doi.org/10.3389/fnbeh.2015.00189

Krypotos, A. M., Vervliet, B., & Engelhard, I. M. (2018). The validity of human avoidance paradigms. *Behaviour Research And Therapy*, *111*, 99-105. https://doi.org/10.1016/j.brat.2018.10.011

Lakens, D., Scheel, A. M., & Isager, P. M. (2018). Equivalence Testing for Psychological Research: A Tutorial. *Advances in Methods and Practices in Psychological Science*, *1*, 259-269. https://doi.org/10.1177/2515245918770963

Laraway, S., Snycerski, S., Pradhan, S., & Huitema, B. E. (2019). An Overview of Scientific Reproducibility: Consideration of Relevant Issues for Behavior Science/Analysis. *Perspectives on Behavior Science*, *42*, 33-57. https://doi.org/10.1007/s40614-019-00193-3

Laufer, O., Israeli, D., & Paz, R. (2016). Behavioral and neural mechanisms of overgeneralization in anxiety. *Current Biology*, *26*, 713-722. https://doi.org/10.1016/j.cub.2016.01.023

Lee, M. D., Zhang, S. N., Munro, M., & Steyvers, M. (2011). Psychological models of human and optimal performance in bandit problems. *Cognitive Systems Research*, *12*(2), 164-174. https://doi.org/10.1016/j.cogsys.2010.07.007

Leeuw, M., Goossens, M. E. J. B., Linton, S. J., Crombez, G., Boersma, K., & Vlaeyen, J. W. S. (2007). The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *Journal of Behavioral Medicine*, *30*, 77-94. https://doi.org/10.1007/s10865-006-9085-0

Lenaert, B., van de Ven, V., Kaas, A. L., & Vlaeyen, J. W. S. (2016). Generalization on the Basis of Prior Experience Is Predicted by Individual Differences in Working Memory. *Behavior Therapy*, *47*, 130-140. https://doi.org/10.1016/j.beth.2015.10.001

Lethem, J., Slade, P. D., Troup, J. D., & Bentley, G. (1983). Outline of a Fear-Avoidance Model of exaggerated pain perception-I. *Behaviour Research And Therapy*, *21*(4), 401-408. https://doi.org/10.1016/0005-7967(83)90009-8

Lissek, S., Biggs, A. L., Rabin, S. J., Cornwell, B. R., Alvarez, R. P., Pine, D. S., & Grillon, C. (2008). Generalization of conditioned fear-potentiated startle in humans: Experimental validation and clinical relevance. *Behaviour Research And Therapy*, *46*, 678-687. https://doi.org/10.1016/j.brat.2008.02.005

Lissek, S., Kaczkurkin, A. N., Rabin, S., Geraci, M., Pine, D. S., & Grillon, C. (2014). Generalized anxiety disorder is associated with overgeneralization of classically conditioned fear. *Biological Psychiatry*, *75*, 909-915. https://doi.org/10.1016/j.biopsych.2013.07.025

Lissek, S., Pine, D. S., & Grillon, C. (2006). The strong situation: A potential impediment to studying the psychobiology and pharmacology of anxiety disorders. *Biological Psychology*, *72*(3), 265-270. https://doi.org/10.1016/j.biopsycho.2005.11.004

Lissek, S., Rabin, S., Heller, R. E., Lukenbaugh, D., Geraci, M., Pine, D. S., & Grillon, C. (2010). Overgeneralization of Conditioned Fear as a Pathogenic Marker of Panic Disorder. *American Journal of Psychiatry*, *167*, 47-55. https://doi.org/10.1176/appi.ajp.2009.09030410

Löffler, M., Kamping, S., Brunner, M., Bustan, S., Kleinböhl, D., Anton, F., & Flor, H. (2018). Impact of controllability on pain and suffering. *Pain reports*, *3*(6), e694-e694. https://doi.org/10.1097/PR9.0000000000000694

Lommen, M. J. J., Duta, M., Vanbrabant, K., De Jong, R., Juechems, K., & Ehlers, A. (2017). Training discrimination diminishes maladaptive avoidance of innocuous stimuli in a fear conditioning paradigm. *PLoS ONE*, *12*, 1-14. https://doi.org/10.1371/journal.pone.0184485

Lucado, A. M., Kolber, M. J., Cheng, M. S., & Echternach, J. L. (2012). Upper extremity strength characteristics in female recreational tennis players with and without lateral epicondylalgia. *Journal of Orthopaedic and Sports Physical Therapy*, *42*, 1025-1031. https://doi.org/10.2519/jospt.2012.4095

Lucado, A. M., Vincent, J., & Day, J. M. (2019). Response letter to the role of proprioception of lateral elbow tendinopathy. *Journal of Hand Therapy*, *32*, e4-e5. https://doi.org/10.1016/j.jht.2018.04.002

Maggioni, S., Melendez-Calderon, A., Van Asseldonk, E., Klamroth-Marganska, V., Lünenburger, L., Riener, R., & Van Der Kooij, H. (2016). Robot-aided assessment of lower extremity functions: A review. *Journal of NeuroEngineering and Rehabilitation*, *13*, 1-25. https://doi.org/10.1186/s12984-016-0180-3

McGraw, K. O., & Wong, S. P. (1996). Forming Inferences about Some Intraclass Correlation Coefficients. *Psychological Methods*, *1*, 30-46. https://doi.org/10.1037/1082-989X.1.1.30

McNeil, D. W., & Rainwater, A. J. (1998). Development of the Fear of Pain Questionnaire—III. *Journal of Behavioral Medicine*, *21*, 389-410. https://doi.org/10.1023/A:1018782831217

Mehlhorn, K., Newell, B., Todd, P., Lee, M., Morgan, K., Braithwaite, V., . . . Gonzalez, C. (2015). Unpacking the Exploration–Exploitation Tradeoff: A Synthesis of Human and Animal Literatures. *Decision*, *2*. https://doi.org/10.1037/dec0000033

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. (2020). Fear in the context of pain: Lessons learned from 100 years of fear conditioning research. *Behaviour Research And Therapy*, *131*, 103635. https://doi.org/10.1016/j.brat.2020.103635

Meulders, A., Franssen, M., & Claes, J. (2020). Avoiding Based on Shades of Gray: Generalization of Pain-Related Avoidance Behavior to Novel Contexts. *Journal of Pain*, *21*(11-12), 1212-1223. https://doi.org/10.1016/j.jpain.2020.02.002

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*, 1094-1104. https://doi.org/10.1097/j.pain.0000000000000483

Meulders, A., Harvie, D. S., Bowering, J. K., Caragianis, S., Vlaeyen, J. W. S., & Moseley, G. L. (2014). Contingency learning deficits and generalization in chronic unilateral hand pain patients. *Journal of Pain*, *15*, 1046-1056. https://doi.org/10.1016/j.jpain.2014.07.005

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*, 108-122. https://doi.org/10.1016/j.pain.0000000000000016

Meulders, A., Meulders, M., Stouten, I., De Bie, J., & Vlaeyen, J. W. S. (2017). Extinction of Fear Generalization: A Comparison Between Fibromyalgia Patients and Healthy Control Participants. *Journal of Pain*, *18*, 79-95. https://doi.org/10.1016/j.jpain.2016.10.004

Meulders, A., Meulders, M., & Vlaeyen, J. W. S. (2014). Positive affect protects against deficient safety learning during extinction of fear of movement-related pain in healthy individuals scoring relatively high on trait anxiety. *Journal of Pain*, *15*, 632-644. https://doi.org/10.1016/j.jpain.2014.02.009

Meulders, A., Traxler, J., & Scheepers, S. (in preparation). The effect of trait anxiety on generalization of avoidance behavior to novel safe contexts.

Meulders, A., Vandael, K., & Vlaeyen, J. W. S. (2017). Generalization of Pain-Related Fear Based on Conceptual Knowledge. *Behavior Therapy*, *48*, 295-310. https://doi.org/10.1016/j.beth.2016.11.014

Meulders, A., Vandebroek, N., Vervliet, B., & Vlaeyen, J. W. S. (2013). Generalization gradients in cued and contextual pain-related fear: an experimental study in healthy participants. *Frontiers in Human Neuroscience*, *7*, 345. https://doi.org/10.1016/j.pain.2012.10.025

Meulders, A., Vansteenwegen, D., & Vlaeyen, J. W. S. (2011). The acquisition of fear of movement-related pain and associative learning: A novel pain-relevant human fear conditioning paradigm. *Pain*, *152*, 2460-2469. https://doi.org/10.1016/j.pain.2011.05.015

Meulders, A., & Vlaeyen, J. W. S. (2013). The acquisition and generalization of cued and contextual pain-related fear: An experimental study using a voluntary movement paradigm. *Pain*, *154*, 272-282. https://doi.org/10.1016/j.pain.2012.10.025

Mischel, W., & Shoda, Y. (1998). Reconciling processing dynamics and personality dispositions. *Annual Review of Psychology*, *49*, 229-258. https://doi.org/10.1146/annurev.psych.49.1.229

Molinari, G., García-Palacios, A., Enrique, Á., Roca, P., Comella, N. F. L., & Botella, C. (2018). The power of visualization: Back to the future for pain management in fibromyalgia syndrome. *Pain Medicine*, *19*, 1451-1468. https://doi.org/10.1093/pm/pnx298

Molinari, G., Miragall, M., Enrique, A., Botella, C., Banos, R. M., & Garcia-Palacios, A. (2020). How and for whom does a positive affect intervention work in fibromyalgia: An analysis of mediators and moderators. *European Journal of Pain*, *24*(1), 248-262. https://doi.org/10.1002/ejp.1481

Moors, A. (2009). Theories of emotion causation: A review. *Cognition and Emotion*, *23*, 625-662. https://doi.org/10.1080/02699930802645739

Morley, S., Eccleston, C., & Williams, A. (1999). 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*(1-2), 1-13. https://doi.org/10.1016/s0304-3959(98)00255-3

Morriss, J., Macdonald, B., & Van Reekum, C. M. (2016). What is going on around here? Intolerance of uncertainty predicts threat generalization. *PLoS ONE*, *11*(5), e0154494. https://doi.org/10.1371/journal.pone.0154494

Moseley, G. L., & Vlaeyen, J. W. S. (2015). Beyond nociception: The imprecision hypothesis of chronic pain. *Pain*, *156*, 35-38. https://doi.org/10.1016/j.pain.0000000000000014

Moseley, G. L., Zalucki, N. M., & Wiech, K. (2008). Tactile discrimination, but not tactile stimulation alone, reduces chronic limb pain. *Pain*, *137*(3), 600-608. https://doi.org/10.1016/j.pain.2007.10.021

Mowrer, O. H. (1951). Two-factor learning theory: summary and comment. *Psychological Review*, *58*(5), 350-354. https://doi.org/10.1037/h0058956

Muller, R., Gertz, K. J., Molton, I. R., Terrill, A. L., Bombardier, C. H., Ehde, D. M., & Jensen, M. P. (2016). Effects of a Tailored Positive Psychology Intervention on Well-Being and Pain in Individuals With Chronic Pain and a Physical Disability A Feasibility Trial. *Clinical Journal of Pain*, *32*(1), 32-44. https://doi.org/10.1097/Ajp.0000000000000225

Nagasako, E. M., Oaklander, A. L., & Dworkin, R. H. (2003). Congenital insensitivity to pain: an update. *Pain*, *101*(3), 213-219. https://doi.org/10.1016/S0304-3959(02)00482-7

Nicholas, M., Vlaeyen, J. W. S., Rief, W., Barke, A., Aziz, Q., Benoliel, R., . . . Chro, I. T. C. (2019). The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*, *160*(1), 28-37. https://doi.org/10.1097/j.pain.0000000000001390

Norbury, A., Robbins, T. W., & Seymour, B. (2018). Value generalization in human avoidance learning. *Elife*, *7*. https://doi.org/10.7554/eLife.34779

Ong, A. D., Thoemmes, F., Ratner, K., Ghezzi-Kopel, K., & Reid, M. C. (2020). Positive affect and chronic pain: a preregistered systematic review and meta-analysis. *Pain*, *161*(6), 1140-1149. https://doi.org/10.1097/j.pain.0000000000001828

Ong, A. D., Zautra, A. J., & Reid, M. C. (2015). Chronic pain and the adaptive significance of positive emotions. *American Psychologist*, *70*, 283-284. https://doi.org/10.1037/a0038816

Onghena, P., & Edgington, E. S. (2005). Customization of pain treatments: Single-case design and analysis. *Clinical Journal of Pain*, *21*, 56-68. https://doi.org/10.1097/00002508-200501000-00007

Pavlov, I. P. (1927). *Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex*. Oxford University Press.

Pavlov, I. P. (1941). *Lectures on conditioned reflexes. Vol. II. Conditioned reflexes and psychiatry*. International Publishers.

Peters, M. L., Flink, I. K., Boersma, K., & Linton, S. J. (2010). Manipulating optimism: Can imagining a best possible self be used to increase positive future expectancies? *Journal of Positive Psychology*, *5*(3), 204-211. https://doi.org/10.1080/17439761003790963

Peters, M. L., Smeets, E., Feijge, M., Van Breukelen, G., Andersson, G., Buhrman, M., & Linton, S. J. (2017). Happy Despite Pain: A Randomized Controlled Trial of an 8-Week Internet-delivered Positive Psychology Intervention for Enhancing Well-being in Patients with Chronic Pain. *Clinical Journal of Pain*, *33*, 962-975. https://doi.org/10.1097/AJP.0000000000000494

Petersen, G. L., Finnerup, N. B., Colloca, L., Amanzio, M., Price, D. D., Jensen, T. S., & Vase, L. (2014). The magnitude of nocebo effects in pain: A meta-analysis. *Pain*, *155*(8), 1426-1434. https://doi.org/10.1016/j.pain.2014.04.016

Pielech, M., Vowles, K. E., & Wicksell, R. (2017). Acceptance and Commitment Therapy for Pediatric Chronic Pain: Theory and Application. *Children*, *4*(2), 10. https://doi.org/10.3390/children4020010

Pittig, A., Boschet, J. M., Schneider, K., & Glück, V. M. (2020). Elevated costly avoidance in anxiety disorders : Patients show little downregulation of acquired avoidance in face of competing rewards for approach. *Depression and Anxiety*, 1-11. https://doi.org/10.1002/da.23119

Pittig, A., & Dehler, J. (2019). Same fear responses, less avoidance: Rewards competing with aversive outcomes do not buffer fear acquisition, but attenuate avoidance to accelerate subsequent fear extinction. *Behaviour Research And Therapy*, *112*, 1-11. https://doi.org/10.1016/j.brat.2018.11.003

Pittig, A., Hengen, K., Bublatzky, F., & Alpers, G. W. (2018). Social and monetary incentives counteract fear-driven avoidance: Evidence from approach-avoidance decisions. *Journal of Behavior Therapy and Experimental Psychiatry*, *60*, 69-77. https://doi.org/10.1016/j.jbtep.2018.04.002

Pittig, A., & Scherbaum, S. (2020). Costly avoidance in anxious individuals: Elevated threat avoidance in anxious individuals under high, but not low competing rewards. *Journal of Behavior Therapy and Experimental Psychiatry*, *66*. https://doi.org/10.1016/j.jbtep.2019.101524

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

Portoghese, I., Lasio, M., Conti, R., Mascia, M. L., Hitchcott, P., Agus, M., . . . Penna, M. P. (2020). Cognitive Flexibility Inventory: Factor structure, invariance, reliability, convergent, and discriminant validity among Italian university students. *PsyCH Journal*, *9*(6), 934-941. https://doi.org/10.1002/pchj.401

Proske, U., & Gandevia, S. C. (2012). The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. *Physiological reviews*, *92*, 1651-1697. https://doi.org/10.1152/physrev.00048.2011

Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., . . . Vader, K. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*, *161*(9), 1976-1982. https://doi.org/10.1097/j.pain.0000000000001939

Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In *Classical conditioning II: Current research and theory* (Vol. 2, pp. 64-99). Appleton-Century-Crofts.

Rinderknecht, M. D., Lambercy, O., Raible, V., Büsching, I., Sehle, A., Liepert, J., & Gassert, R. (2018). Reliability, validity, and clinical feasibility of a rapid and objective assessment of post-stroke deficits in hand proprioception. *Journal of NeuroEngineering and Rehabilitation*, *15*, 1-15. https://doi.org/10.1186/s12984-018-0387-6

Rinderknecht, M. D., Popp, W. L., Lambercy, O., & Gassert, R. (2016). Reliable and rapid robotic assessment of wrist proprioception using a gauge position matching paradigm. *Frontiers in Human Neuroscience*, *10*, 1-12. https://doi.org/10.3389/fnhum.2016.00316

Rizvi, S. J., Gandhi, W., & Salomons, T. (2021). Reward processing as a common diathesis for chronic pain and depression. *Neuroscience & Biobehavioral Reviews*, *127*, 749-760. https://doi.org/10.1016/j.neubiorev.2021.04.033

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*, 339-346. https://doi.org/10.1016/j.pain.2005.05.003

Roelofs, J., van Breukelen, G., Sluiter, J., Frings-Dresen, M. H. W., Goossens, M., Thibault, P., . . . Vlaeyen, J. W. S. (2011). Norming of the Tampa Scale for Kinesiophobia across pain diagnoses and various countries. *Pain*, *152*(5), 1090-1095. https://doi.org/10.1016/j.pain.2011.01.028

Röijezon, U., Clark, N. C., & Treleaven, J. (2015). Proprioception in musculoskeletal rehabilitation: Part 1: Basic science and principles of assessment and clinical interventions. *Manual Therapy*, *20*, 368-377. https://doi.org/10.1016/j.math.2015.01.008

San Martín, C., Jacobs, B., & Vervliet, B. (2020). Further characterization of relief dynamics in the conditioning and generalization of avoidance: Effects of distress tolerance and intolerance of uncertainty. *Behaviour Research And Therapy*, *124*, 103526. https://doi.org/10.1016/j.brat.2019.103526

Saradjian, A. H. (2015). Sensory modulation of movement, posture and locomotion. *Clinical Neurophysiology*, *45*, 255-267. https://doi.org/10.1016/j.neucli.2015.09.004

Sarlegna, F. R., & Sainburg, R. L. (2009). The Roles of Vision and Proprioception in the Planning of Reaching Movements. In D. Sternad (Ed.), *Progress in motor control* (pp. 317-335). Springer. https://doi.org/10.1007/978-0-387-77064-2_16

Schechtman, E., Laufer, O., & Paz, R. (2010). Negative Valence Widens Generalization of Learning. *Journal of Neuroscience*, *30*(31), 10460-10464. https://doi.org/10.1523/Jneurosci.2377-10.2010

Scheidt, R. A., Conditt, M. A., Secco, E. L., & Mussa-Ivaldi, F. A. (2005). Interaction of visual and proprioceptive feedback during adaptation of human reaching movements. *Journal of Neurophysiology*, *93*, 3200-3213. https://doi.org/10.1152/jn.00947.2004

Schlitt, F., Schmidt, K., Merz, C. J., Wolf, O. T., Kleine-Borgmann, J., Elsenbruch, S., . . . Bingel, U. (2021). Impaired pain-related threat and safety learning in patients with chronic back pain. *Pain*. https://doi.org/10.1097/j.pain.0000000000002544

Schopflocher, D., Taenzer, P., & Jovey, R. (2011). The prevalence of chronic pain in Canada. *Pain Research and Management*, *16*(6), 445-450. https://doi.org/10.1155/2011/876306

Serbic, D., Pincus, T., Fife-Schaw, C., & Dawson, H. (2016). Diagnostic uncertainty, guilt, mood, and disability in back pain. *Health Psychology*, *35*(1), 50-59. https://doi.org/10.1037/hea0000272

Shalev, L., Paz, R., & Avidan, G. (2018). Visual Aversive Learning Compromises Sensory Discrimination. *Journal of Neuroscience*, *38*(11), 2766-2779. https://doi.org/10.1523/Jneurosci.0889-17.2017

Shrout, P. E., & Fleiss, J. L. (1979). Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin*, *86*, 420-428. https://doi.org/10.1037/0033-2909.86.2.420

Simons, J. S., & Gaher, R. M. (2005). The distress tolerance scale: Development and validation of a self-report measure. *Motivation and Emotion*, *29*, 83-102. https://doi.org/10.1007/s11031-005-7955-3

Singmann, H., Bolker, B., Westfall, J., Aust, F., & Ben-Shachar, M. S. (2019). Afex: Analysis of factorial experiments [R package version 0.25-1]. R package version 0.25-1. In.

Skinner, B. F. (1953). *Science and human behavior*. Macmillan.

Spielberger, C. D. (1983). *Manual for the State-Trait Anxiety Inventory (STAI)*. Consulting Psychologists Press.

Spinhoven, P., Ormel, J., Sloekers, P. P. A., Kempen, G. I. J. M., Speckens, A. E. M., & VanHemert, A. M. (1997). A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological Medicine*, *27*(2), 363-370. https://doi.org/10.1017/S0033291796004382

Spruyt, A., Clarysse, J., Vansteenwegen, D., Baeyens, F., & Hermans, D. (2010). Affect 4.0: A free software package for implementing psychological and psychophysiological experiments. *Experimental Psychology*, *57*, 36-45. https://doi.org/10.1027/1618-3169/a000005

Stanton, T. R., Leake, H. B., Chalmers, K. J., & Moseley, G. L. (2016). Evidence of Impaired Proprioception in Chronic, Idiopathic Neck Pain: Systematic Review and Meta-Analysis. *Physical Therapy*, *96*, 876-887. https://doi.org/10.2522/ptj.20150241

Stasinopoulos, D. (2019). The role of proprioception in the management of lateral elbow tendinopathy. *Journal of Hand Therapy*, *32*, e2-e3. https://doi.org/10.1016/j.jht.2018.02.010

Struyf, D., Zaman, J., Hermans, D., & Vervliet, B. (2017). Gradients of fear: How perception influences fear generalization. *Behaviour Research And Therapy*, *93*, 116-122. https://doi.org/10.1016/j.brat.2017.04.001

Sturgeon, J. A., & Zautra, A. J. (2010). Resilience: A new paradigm for adaptation to chronic pain. *Current Pain and Headache Reports*, *14*, 105-112. https://doi.org/10.1007/s11916-010-0095-9

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and Validation. *Psychological Assessment*, *7*, 524-532. https://doi.org/10.1037//1040-3590.7.4.524

Timmermans, A. A., Seelen, H. A., Willmann, R. D., & Kingma, H. (2009). Technology-assisted training of arm-hand skills in stroke: Concepts on reacquisition of motor control and therapist guidelines for rehabilitation technology design. *Journal of NeuroEngineering and Rehabilitation*, *6*, 1. https://doi.org/10.1186/1743-0003-6-1

Todd, J., van Ryckeghem, D. M. L., Sharpe, L., & Crombez, G. (2018). Attentional bias to pain-related information: a meta-analysis of dot-probe studies. *Health Psychology Review*, *12*, 419-436. https://doi.org/10.1080/17437199.2018.1521729

Tong, M. H., Mousavi, S. J., Kiers, H., Ferreira, P., Refshauge, K., & van Dieën, J. (2017). Is There a Relationship Between Lumbar Proprioception and Low Back Pain? A Systematic Review With Meta-Analysis. *Archives of Physical Medicine and Rehabilitation*, *98*, 120-136. https://doi.org/10.1016/j.apmr.2016.05.016

Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., . . . Wang, S. J. (2019). Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*, *160*, 19-27. https://doi.org/10.1097/j.pain.0000000000001384

Urcelay, G. P., & Prével, A. (2019). Extinction of instrumental avoidance. *Current Opinion in Behavioral Sciences*, *26*, 165-171. https://doi.org/https://doi.org/10.1016/j.cobeha.2019.01.018

van Beers, R. J., Sittig, A. C., & van der Gon, J. J. D. (1999). Integration of Proprioceptive and Visual Position-Information: An Experimentally Supported Model. *Journal of Neurophysiology*, *81*, 1355-1364. https://doi.org/10.1152/jn.1999.81.3.1355

Van Breukelen, G. J. P., & Vlaeyen, J. W. S. (2005). Norming clinical questionnaires with multiple regression: The pain cognition list. *Psychological Assessment*, *17*(3), 336-344. https://doi.org/10.1037/1040-3590.17.3.336

Van Damme, S., Crombez, G., Bijttebier, P., Goubert, L., & Van Houdenhove, B. (2002). A confirmatory factor analysis of the Pain Catastrophizing Scale invariant factor structure across clinical and non-clinical populations. *Pain*, *96*(3), 319-324. https://doi.org/10.1016/S0304-3959(01)00463-8

Van Damme, S., Legrain, V., Vogt, J., & Crombez, G. (2010). Keeping pain in mind: A motivational account of attention to pain. *Neuroscience and Biobehavioral Reviews*, *34*(2), 204-213. https://doi.org/10.1016/j.neubiorev.2009.01.005

Van Damme, S., Van Ryckeghem, D. M. L., Wyffels, F., Van Hulle, L., & Crombez, G. (2012). No pain no gain? Pursuing a competing goal inhibits avoidance behavior. *Pain*, *153*, 800-804. https://doi.org/10.1016/j.pain.2011.12.015

Van den Bergh, O., Brosschot, J., Critchley, H., Thayer, J. F., & Ottaviani, C. (2021). Better Safe Than Sorry: A Common Signature of General Vulnerability for Psychopathology. *Perspectives on Psychological Science*, *16*(2), 225-246. https://doi.org/10.1177/1745691620950690

Van Dieën, J. H., Flor, H., & Hodges, P. W. (2017). Low-Back Pain Patients Learn to Adapt Motor Behavior With Adverse Secondary Consequences. *Exercise and Sport Sciences Reviews*, *45*, 223-229. https://doi.org/10.1249/JES.0000000000000121

Van Hecke, O., Torrance, N., & Smith, B. H. (2013). Chronic pain epidemiology and its clinical relevance. *British Journal of Anaesthesia*, *111*, 13-18. https://doi.org/10.1093/bja/aet123

van Meurs, B., Wiggert, N., Wicker, I., & Lissek, S. (2014). Maladaptive behavioral consequences of conditioned fear-generalization: A pronounced, yet sparsely studied, feature of anxiety pathology. *Behaviour Research And Therapy*, *57*, 29-37. https://doi.org/10.1016/j.brat.2014.03.009

van Vliet, C. M., Meulders, A., Vancleef, L. M. G., & Vlaeyen, J. W. S. (2018). The Opportunity to Avoid Pain May Paradoxically Increase Fear. *Journal of Pain*, *19*, 1222-1230. https://doi.org/10.1016/j.jpain.2018.05.003

Vandael, K., Meulders, M., zur Mühlen, K., Peters, M., & Meulders, A. (under revision). Increased positive affect is associated with less generalization of pain-related avoidance. *Behaviour Research And Therapy*.

Vandael, K., Stanton, T. R., & Meulders, A. (2021). Assessing kinesthetic proprioceptive function of the upper limb: A novel dynamic movement reproduction task using a robotic arm. *Peerj*, *9*, e11301. https://doi.org/10.7717/peerj.11301

Vandael, K., Vasilache, A., & Meulders, A. (2022). Know Your Movements: Poorer Proprioceptive Accuracy is Associated With Overprotective Avoidance Behavior. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2022.03.233

Verbunt, J. A., Seelen, H. A., Vlaeyen, J. W., van de Heijden, G. J., Heuts, P. H., Pons, K., & Knottnerus, J. A. (2003). Disuse and deconditioning in chronic low back pain: concepts and hypotheses on contributing mechanisms. *European Journal of Pain*, *7*(1), 9-21. https://doi.org/10.1016/s1090-3801(02)00071-x

Vervliet, B., & Indekeu, E. (2015). Low-cost avoidance behaviors are resistant to fear extinction in humans. *Frontiers in Behavioral Neuroscience*, *9*, 1-12. https://doi.org/10.3389/fnbeh.2015.00351

Vervliet, B., Lange, I., & Milad, M. R. (2017). Temporal dynamics of relief in avoidance conditioning and fear extinction: Experimental validation and clinical relevance. *Behaviour Research And Therapy*, *96*, 66-78. https://doi.org/10.1016/j.brat.2017.04.011

Vervliet, B., & Raes, F. (2013). Criteria of validity in experimental psychopathology:Application to models of anxiety and depression. *Psychological Medicine*, *43*, 2241-2244. https://doi.org/10.1017/S0033291712002267

Vlaeyen, J. W. S., & Crombez, G. (2020). Behavioral Conceptualization and Treatment of Chronic Pain. *Annual Review of Clinical Psychology*, *16*, 187-212. https://doi.org/10.1146/annurev-clinpsy-050718-095744

Vlaeyen, J. W. S., Crombez, G., & Linton, S. J. (2016). The fear-avoidance model of pain. *Pain*, *157*, 1588-1589. https://doi.org/10.1097/j.pain.0000000000000574

Vlaeyen, J. W. S., & Linton, S. J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*, *85*, 317-332. https://doi.org/10.1145/2994143

Vlaeyen, J. W. S., & Linton, S. J. (2012). Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain*, *153*, 1144-1147. https://doi.org/10.1016/j.pain.2011.12.009

Volders, S., Boddez, Y., De Peuter, S., Meulders, A., & Vlaeyen, J. W. S. (2015). Avoidance behavior in chronic pain research: a cold case revisited. *Behaviour research and therapy*, *64*, 31-37. https://doi.org/10.1016/j.brat.2014.11.003

Vonkorff, M., Ormel, J., Keefe, F. J., & Dworkin, S. F. (1992). Grading the Severity of Chronic Pain. *Pain*, *50*(2), 133-149. https://doi.org/10.1016/0304-3959(92)90154-4

Vowles, K. E., Fink, B. C., & Cohen, L. L. (2014). Acceptance and Commitment Therapy for chronic pain: A diary study of treatment process in relation to reliable change in disability. *Journal of contextual behavioral science*, *3*(2), 74-80. https://doi.org/10.1016/j.jcbs.2014.04.003

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and Validation of Brief Measures of Positive and Negative Affect: The PANAS Scales. *Journal of Personality and Social Psychology*, *54*(6), 1063-1070. https://doi.org/10.1037/0022-3514.54.6.1063

Wetherell, J. L., Afari, N., Rutledge, T., Sorrell, J. T., Stoddard, J. A., Petkus, A. J., . . . Atkinson, J. H. (2011). A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain*, *152*(9), 2098-2107. https://doi.org/10.1016/j.pain.2011.05.016

Willems, A. L., & Vervliet, B. (2021). When nothing matters: Assessing markers of expectancy violation during omissions of threat. *Behaviour Research And Therapy*, *136*, 103764. https://doi.org/10.1016/j.brat.2020.103764

Williams, A. C. C., Fisher, E., Hearn, L., & Eccleston, C. (2020). Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database of Systematic Reviews*, *8*, CD007407. https://doi.org/10.1002/14651858.CD007407.pub4

Wills, A. J., Graham, S., Koh, Z., McLaren, I. P. L., & Rolland, M. D. (2015). Effects of Concurrent Load on Feature- and Rule-based Generalization in Human Contingency Learning. *Journal of Experimental Psychology: Animal Behavior Processes*, *37*(3), 308-316. https://doi.org/10.1037/a0023120

Wolpert, D. M., & Ghahramani, Z. (2000). Computational principles of motor neuroscience. *Nature Neuroscience*, *3*, 1212-1217. https://doi.org/10.1038/81497

Wolpert, D. M., Ghahramani, Z., Jordan, M. I., Wolpert, D. M., Ghahramani, Z., & Jordan, M. (1995). An Internal Model for Sensorimotor Integration. *Science*, *269*(5232), 1880-1882. https://doi.org/10.1126/science.756993

Wolpert, D. M., Goodbody, S. J., & Husain, M. (1998). Maintaining internal representations: The role of the human superior parietal lobe. *Nature Neuroscience*, *1*, 529-533. https://doi.org/10.1038/2245

Yang, H., Yang, S., & Isen, A. M. (2013). Positive affect improves working memory: Implications for controlled cognitive processing. *Cognition and Emotion*, *27*, 474-482. https://doi.org/10.1080/02699931.2012.713325

Zaman, J., Ceulemans, E., Hermans, D., & Beckers, T. (2019). Direct and indirect effects of perception on generalization gradients. *Behaviour Research And Therapy*, *114*, 44-50. https://doi.org/10.1016/j.brat.2019.01.006

Zaman, J., Struyf, D., Ceulemans, E., Beckers, T., & Vervliet, B. (2019). Probing the role of perception in fear generalization. *Scientific Reports*, *9*, 10026. https://doi.org/10.1038/s41598-019-46176-x

Zaman, J., Van Oudenhove, L., & Vlaeyen, J. W. S. (2021). Uncertainty in a context of pain: disliked but also more painful? *Pain*, *162*(4), 995-998. https://doi.org/10.1097/j.pain.0000000000002106

Zaman, J., Vlaeyen, J. W. S., Van Oudenhove, L., Wiech, K., & Van Diest, I. (2015). Associative fear learning and perceptual discrimination: A perceptual pathway in the development of chronic pain. *Neuroscience and Biobehavioral Reviews*, *51*, 118-125. https://doi.org/10.1016/j.neubiorev.2015.01.009

Zautra, A. J., Fasman, R., Reich, J. W., Harakas, P., Johnson, L. M., Olmsted, M. E., & Davis, M. C. (2005). Fibromyalgia: Evidence for deficits in positive affect regulation. *Psychosomatic Medicine*, *67*, 147-155. https://doi.org/10.1097/01.psy.0000146328.52009.23

Zautra, A. J., Johnson, L. M., & Davis, M. C. (2005). Positive affect as a source of resilience for women in chronic pain. *Journal of Consulting and Clinical Psychology*, *73*, 212-220. https://doi.org/10.1037/0022-006X.73.2.212

Zbozinek, T. D., & Craske, M. G. (2017). The Role of Positive Affect in Enhancing Extinction Learning and Exposure Therapy for Anxiety Disorders. *Journal of Experimental Psychopathology*, *8*, 13-39. https://doi.org/10.5127/jep.052615

Summary

Chronic pain can be seriously debilitating. Unfortunately, sufferers often receive inadequate treatment. Contemporary fear-avoidance models of pain emphasize excessive pain-related avoidance as a crucial factor in the development and maintenance of chronic pain disability. However, despite its central role, surprisingly little experimental research has systematically investigated ways to reduce the spreading (or generalization) of avoidance behavior toward safe activities. Therefore, the current PhD project set out to investigate potential intervention targets to attenuate such excessive generalization. To this end, we first demonstrated that avoidance behavior indeed generalizes to a certain degree in healthy, pain-free participants, using an innovative operant conditioning task (the robotic arm-reaching paradigm; **Chapter 1**). Next, we reviewed existing experimental research on factors that can attenuate generalization (**Chapter 2**). In the current project, we investigated two factors further: proprioceptive accuracy and positive affect. To investigate the potential of proprioceptive accuracy as an intervention target, we first developed a task to quantify proprioceptive function of the upper limb, and established that it has sufficient test-retest reliability (**Chapter 3**). Next, we tested whether there is an association between proprioceptive accuracy – as measured by our novel task – and avoidance behavior: results confirmed that poor proprioceptive accuracy was associated with overprotective avoidance in healthy, pain-free participants (**Chapter 4**). This association confirms the potential of training accuracy to reduce excessive avoidance. To investigate positive affect as another potential intervention target, we tested the effect of experimentally induced positive affect on generalization of pain-related avoidance in healthy, pain-free participants, using the robotic arm-reaching paradigm (**Chapter 5**). Results confirmed that increases in positive affect were associated with less avoidance generalization. Next, we tested whether we could replicate this finding in another established avoidance paradigm (**Chapter 6**) – which allowed investigation of relief generalization as well, a factor that can reinforce avoidance behavior. Surprisingly, the association between positive affect and avoidance was not replicated, nor was there an association between positive affect and relief. Finally, we included the preregistration of an experimental protocol testing generalization of pain-related avoidance behavior in chronic pain conditions (**Chapter 7**). Once the proposed paradigm has shown to capture excessive generalization in chronic pain, it can be used to continue experimental research into factors attenuating generalization. Such research is crucial to help optimize existing, and potentially develop new, treatment strategies to tackle chronic pain disability.

Samenvatting

Chronische pijn kan een ernstige beperking vormen. Helaas worden mensen die hieraan lijden vaak onvoldoende behandeld. Hedendaagse vrees-vermijdingsmodellen van pijn benadrukken overmatig pijn-gerelateerd vermijdingsgedrag als een cruciale factor in de ontwikkeling en instandhouding van chronische pijnbeperkingen. Ondanks deze centrale rol heeft verrassend weinig experimenteel onderzoek zich systematisch gericht op manieren om de verspreiding (of generalisatie) van vermijdingsgedrag naar veilige activiteiten te verminderen. Daarom was het doel van het huidige PhD-project om potentiële interventiedoelwitten te onderzoeken om zulke buitensporige generalisatie te verminderen. Hiertoe hebben we eerst aangetoond dat vermijdingsgedrag inderdaad in zekere mate generaliseert in gezonde, pijnvrije deelnemers, met behulp van een innovatieve operante conditioneringstaak (het robotarm-bewegingsparadigma; **Hoofdstuk 1**). Vervolgens hebben we een overzicht gemaakt van bestaand experimenteel onderzoek naar factoren die generalisatie kunnen verminderen (**Hoofdstuk 2**). In het huidige project hebben we twee factoren verder onderzocht: proprioceptieve accuraatheid en positief affect. Om het potentieel van proprioceptieve accuraatheid als interventiedoelwit te onderzoeken hebben we eerst een taak ontwikkeld om de proprioceptieve functie van de bovenste ledematen te kwantificeren, en vastgesteld dat deze voldoende test-hertest betrouwbaarheid heeft (**Hoofdstuk 3**). Vervolgens hebben we getest of er een verband is tussen proprioceptieve accuraatheid – gemeten door onze nieuwe taak – en vermijdingsgedrag: de resultaten bevestigden dat lage proprioceptieve accuraatheid geassocieerd was met over-beschermende vermijding bij gezonde, pijnvrije deelnemers (**Hoofdstuk 4**). Deze associatie bevestigt het potentieel van het trainen van accuraatheid om overmatige vermijding te verminderen. Om positief affect als een ander potentieel interventiedoelwit te onderzoeken hebben we het effect van experimenteel geïnduceerd positief affect op de generalisatie van pijn-gerelateerde vermijding getest bij gezonde, pijnvrije deelnemers, met behulp van het robotarm-bewegingsparadigma (**Hoofdstuk 5**). Resultaten bevestigden dat toenames in positief affect geassocieerd waren met minder vermijdingsgeneralisatie. Vervolgens hebben we getest of deze bevinding repliceerbaar was in een ander gevestigd vermijdingsparadigma (**Hoofdstuk 6**) – wat het ook mogelijk maakte om de generalisatie van opluchting te onderzoeken, een factor die vermijdingsgedrag kan versterken. Tegen verwachtingen in werd de associatie tussen positief affect en vermijding niet gerepliceerd, en evenmin was er een associatie tussen positief affect en opluchting. Ten slotte hebben we de preregistratie van een experimenteel protocol om de generalisatie van pijn-gerelateerd vermijdingsgedrag bij chronische pijnaandoeningen te testen geïncludeerd (**Hoofdstuk 7**). Zodra het voorgestelde paradigma heeft getoond dat het excessieve generalisatie in chronische pijn

kan vaststellen, kan het gebruikt worden voor verder experimenteel onderzoek naar factoren die generalisatie afzwakken. Dergelijk onderzoek is cruciaal om bestaande, en mogelijk nieuwe, behandelingsstrategieën voor chronische pijnbeperkingen te helpen optimaliseren.

Impact

Chronic pain affects approximately 20% of the population and can be seriously debilitating. Scientists and clinicians alike consider biological, psychological as well as social factors to play important roles in the development and maintenance of chronic pain disability. Contemporary fear-avoidance models of pain emphasize the importance of excessive avoidance behaviors specifically. For example, when pain is experienced while lifting a heavy box with a bent back, not repeating this movement could prevent harm to the body. However, when avoidance spreads to harmless movements and activities, such as bending over slightly to pick up a piece of paper, this can be seriously disruptive in daily life, as this may interfere with valued activities. The main objective of the current research project was to investigate potential intervention targets to reduce the spreading (or generalization) of pain-related avoidance behavior in an experimental lab setting.

First, we provided evidence that pain-related avoidance can spread (or generalize) to a certain degree toward safe movements that are similar to pain-associated ones in healthy, pain-free participants. This provides evidence for the idea that generalization could contribute to avoidance becoming excessive in the context of pain, as proposed by contemporary fear-avoidance models of chronic pain. Moreover, we provided further evidence that the experience of relief when pain is avoided may play a role in generalized avoidance persisting. Next, we provided evidence for an association between proprioception – the sense of movement and position of the body (segments) – and pain-related avoidance behavior, indicating that proprioceptive accuracy is a potential intervention target. This is an important finding because impaired proprioception has been documented in various chronic pain conditions. This work has mostly been published in the field of physiotherapy and exists largely separated from the pain-related fear and avoidance conditioning literature. The current PhD project bridged this gap between the fields of physiotherapy and pain psychology by proposing that excessive avoidance behavior may be the missing link between impaired proprioception and chronic pain disability. Moreover, in the process of researching this link, we developed the dynamic movement reproduction task, a reliable task to assess proprioceptive function of the upper limb with high precision. This task can be a useful tool for both researchers and clinicians to quantify proprioceptive function. Finally, we showed that experimentally induced positive affect is associated with less generalization of pain-related avoidance, thus confirming that positive affect is a promising intervention target. This finding contributes to a growing literature showing the important role of positive affect in pain treatment.

Results from the current PhD project have been presented at various international conferences in the fields of pain (e.g., Annual Pain Research Meeting) and psychology (e.g., Annual

Convention of the Association for Psychological Science). Furthermore, they have been published in scientific journals with significant impact (e.g., The Journal of Pain), and these publications have been promoted through social media platforms (e.g., Twitter). Such efforts will be continued and findings that are currently unpublished will be submitted to scientific journals as well (i.e., Chapter 6). Informing the scientific community about our findings is crucial to push research into intervention targets forward; for example, replication and further investigation (e.g., underlying mechanisms) of our findings is essential. Importantly, our findings are not only relevant for chronic pain, but also for other disorders where avoidance is considered to play a key role (e.g., anxiety disorders). Furthermore, impact beyond the scientific community could be achieved by integrating our findings into teaching activities and disseminating them to a broader audience (e.g., practitioner conferences, patient societies).

A fundamental understanding of how avoidance becomes excessive and how this may be countered can help develop and optimize treatment strategies, and boost their application in clinical practice. Current treatments have shown to be effective, albeit only to a certain extent. Novel insights may improve effectivity and therefore help reduce suffering further. For example, proprioceptive deficits could indicate that proprioceptive accuracy training leads to improved outcomes. However, adapted treatment strategies based on novel insights need systematic investigation before they are implemented widely in clinical practice. To bridge the gap between the lab and clinical practice, close collaboration between scientists, practitioners as well as patients could prove fruitful. Such collaborations can help to translate experimental findings effectively into clinical interventions, and generate novel questions for experimental research to tackle.

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Curriculum Vitae

Kristof Vandael was born on 27 September 1991 in Hasselt, Belgium. He completed his high school education at the Sint-Jan Berchmansinstituut in Zonhoven. In 2016, the KU Leuven awarded him the degree of Master of Psychology, with major subject Clinical and Health Psychology. His interest in the role of psychological factors in chronic pain conditions was sparked during his master thesis, which was supervised by dr. Ann Meulders, and which focused on the spreading of pain-related fear through conceptual similarity. In 2018, he started a joint PhD at Maastricht University and KU Leuven under supervision of dr. Ann Meulders, prof. dr. Madelon Peters and prof. dr. Bram Vervliet; his project focused on attenuating the spreading of pain-related avoidance behavior. In 2022, Kristof was awarded a one-year Postdoctoral Mandate (PDM) by KU Leuven, which will allow him to continue research on this topic.

Journal articles

Vandael, K., Meulders, A., Peters, M., & Vervliet, B. (under review). The effect of experimentally induced positive affect on the generalization of pain-related avoidance and relief.

Vandael, K., Vervliet, B., Peters, M., & Meulders, A. (under revision). Excessive generalization of pain-related avoidance behavior: mechanisms, targets for intervention, and future directions.

Vandael, K., Meulders, M., zur Mühlen, K., Peters, M., & Meulders, A. (2022). Increased positive affect is associated with less generalization of pain-related avoidance. *Behaviour Research and Therapy*, *185*, 104199. https://doi.org/10.1016/j.brat.2022.104199

Vandael, K., Vasilache, A., & Meulders, A. (2022). Know your movements: poorer proprioceptive accuracy is associated with overprotective avoidance behavior. *The Journal of Pain, 23*(8), 1400-1409. https://doi.org/10.1016/j.jpain.2022.03.233

Glogan, E.*, **Vandael, K.***, Gatzounis, R., & Meulders, A. (2021). When do we not face our fears? Investigating the boundary conditions of costly pain-related avoidance generalization. *The Journal of Pain, 22*(10), 1221-1232. https://doi.org/10.1016/j.jpain.2021.03.149
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Vandael, K., Stanton, T. R., & Meulders, A. (2021). Assessing kinesthetic proprioceptive function of the upper limb: A novel dynamic movement reproduction task using a robotic arm. *PeerJ, 9*, e11301. https://doi.org/10.7717/peerj.11301

Dewaele, A., **Vandael, K.**, Meysman, S., & Buysse, A. (2021). Understanding collaborative interactions in relation to research impact in social sciences and humanities: A meta-ethnography. *Research Evaluation, 30*(2), 179-190. https://doi.org/10.1093/reseval/rvaa033

Glogan, E., Gatzounis, R., **Vandael, K.**, Franssen, M., Vlaeyen, J. W. S., & Meulders, A. (2020). Investigating Pain-Related Avoidance Behavior using a Robotic Arm-Reaching Paradigm. *Journal of visualized experiment, 164*, e61717. https://doi.org/10.3791/61717

Vandael, K., Meulders, M., Vanden Boer, C., & Meulders, A. (2020). The relationship between fear generalization and pain modulation: an investigation in healthy participants. *Scandinavian Journal of Pain, 20*(1), 151-165. https://doi.org/10.1515/sjpain-2019-0065

Meulders, A., **Vandael, K.**, & Vlaeyen, J. W. S. (2017). Generalization of pain-related fear based on conceptual knowledge. *Behavior Therapy, 48*(3), 295-310. https://doi.org/10.1016/j.beth.2016.11.014

Oral and poster presentations

Vandael, K. (2022). Reducing generalization of pain-related avoidance. Presented at the annual Pain Research Meeting, Annweiler am Trifels, Germany, 7 Sep 2022.

Vandael, K., Meulders M., zur Mühlen K., Peters M., Meulders, A. Increased positive affect is associated with less generalization of pain-related avoidance. Oral presentation at the Association for Psychological Science (APS) Annual Convention, Chicago, USA, 26 May 2022 – 29 May 2022.

Vandael, K., Meulders, A. (2021). Is proprioceptive accuracy associated with pain-related avoidance behavior? Poster presented at the annual Experimental Psychopathology (EPP) day, Egmond aan Zee, Netherlands, 17 Sep 2021.

Vandael, K. (2021). PhD pitch: pathways to attenuate generalization of pain-related avoidance. Presented at the annual Pain Research Meeting, online event, 13 Sep 2021.

Vandael, K., Meulders, A. (2019). The relationship between proprioceptive accuracy and generalization of pain-related avoidance behavior. Presented at the annual Pain Research Meeting, Dilbeek, Belgium, 12 Sep 2019 – 13 Sep 2019.

Vandael, K., Meulders, M., Vanden Boer, C., Meulders, A. (2019). The relationship between fear generalization and pain modulation: An investigation in healthy participants. Poster presented at the European Meeting of Human Fear Conditioning (EMHFC), Würzburg, Germany, 06 May 2019 – 08 May 2019.

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