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The relationship between pain-related avoidance behaviour, pain-related fear, and pain reports

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Chapter 1

General introduction

Why is it that some people develop chronic pain after an injury, while others don't? In this general introduction, we first provide an overview of the evolution in the conceptualisation of pain, moving from a traditional biomedical perspective towards biopsychosocial approaches. Second, we focus on the fear-avoidance model of chronic (musculoskeletal) pain (Lethem, Slade, Troup, & Bentley, 1983; Vlaeyen & Linton, 2000; 2012) and describe how the effects of avoidance behaviour, pain-related fear, and threat appraisals/beliefs, may play a role in the development and maintenance of chronic pain. Third, we take a closer look at current theories of avoidance learning, and the relationship between fear and avoidance. Lastly, we discuss the research aims and the project outline of this dissertation.

1.1 Pain – from biomedical towards biopsychosocial approaches

Ouch! An expression many of us have used when suddenly experiencing acute pain. According to the early biomedical approach, tissue damage on the body periphery activates specialized pain receptors to transfer this nociceptive input via the spinal cord to the brain. Once the brain receives this signal, we feel pain. This theory on the physiology of pain, inspired by the ideas of René Descartes in his book "L'Homme" (1664), assumes a unidirectional, one-to-one relationship between tissue damage and pain. According to this theory, the obvious intervention to alleviate the pain should be the treatment of the underlying tissue damage. However, a number of clinical observations, where pain persisted in the absence of tissue damage, could not be explained by this mechanistic approach. This instigated the formulation of another theory, considering biological, psychological, and social factors of which the latter two had been neglected in the traditional biomedical approach (Gatchel, Peng, Peters, Fuchs, & Turk, 2007).

According to the International Association for the Study of Pain, pain is *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"* (Merskey & Bogduk, 1994). This definition of pain reflects the current understanding of pain where emotions are considered an integral part of the painful experience. From this perspective, how we experience pain can be influenced by beliefs, expectations, motivations, other emotions,

as well as our own behaviour (Arntz & Claassens, 2004; Gatchel, Peng, Peter, Fuchs, & Turk, 2007; Markfelder & Pauli, 2020; Staats, Hekmat, & Staats, 1996). Although experiencing pain is usually unpleasant, it has a clear function for our survival, because it signals potential harm or danger to the body and it promotes behaviours, such as avoidance and escape, to protect ourselves against these dangers (Eccleston & Crombez, 1999; Morley & Eccleston, 2004; Williams, 2016). When one is confronted with acute pain, trying to avoid subsequent exposure to the presumed nociceptive stimulus is an adaptive strategy potentially preventing (further) injury. However, sometimes pain becomes a false alarm, such as in the case of chronic pain, where there is often no objectifiable injury and where pain is disconnected from its original function.

The Gate Control Theory (Melzack & Wall, 1965) was proposed as a new theory of pain mechanisms, postulating that the brain is actively involved in the process of pain perception, rather than only passively receiving information from the periphery. According to this theory, the transmission of information about painful events was not a simple one-way process, but consisted of multiple processes, including cognitions and emotions. A key role is assigned to the spinal cord, where there is a gating system located in the substantia gelatinosa in the dorsal horn of the spinal cord. This gating mechanism controls ascending signals from the periphery and descending signals from the brain. With the Gate Control Theory, the role of the brain became central in creating the pain perception, and this significantly contributed to the idea that this theory "*forced the medical and biological sciences to accept the brain as an active system that filters, selects, and modulates inputs*" (Melzack, 1999, p. S123).

Another important milestone in the understanding of pain was a behaviour model proposed by Fordyce in 1976, highlighting the role of learning processes in the development of problematic pain behaviour. Fordyce drew attention to the importance of observable behaviours (e.g. avoiding activity, expressing pain) in maintaining disability. Fordyce, who was strongly inspired by operant conditioning principles, suggested that pain behaviours are reinforced by repeated associations with specific outcomes. For example, when avoiding lifting heavy objects, because of the fear to hurt one's back (overt pain behaviour), the probability of the reoccurrence of this instrumental behaviour increases because of negative reinforcement (e.g. the absence of pain). Other

operant conditioning principles related to pain behaviours include positive reinforcement (e.g. attention, help), the lack of positive reinforcement of healthy behaviours, and positive (e.g. accusation of exaggeration) or negative (e.g. social exclusion) punishment. Fordyce's operant learning approach fostered considering direct consequences of various pain behaviours in the treatment of pain disability (Fordyce & Steger, 1979; Fordyce, 1976; 1984; 1988). The theoretical basis provided by Fordyce's operant learning approach was followed by increased recognition of the role of cognitions and information processing in the development of the pain problem (Morley, 2011; Turk & Rudy, 1992). Further building on this cognitive approach, a widely used model is the fear-avoidance model of (chronic) pain as put forward by Lethem et al. (1983) and further elaborated by Vlaeyen and Linton (2000, 2012), which emphasizes the importance of pain-related fear in the development and maintenance of chronic pain. Given the importance of this model for this dissertation, we will discuss the fear-avoidance model in detail in section 1.2.2.

1.2 Chronic pain

When does pain become chronic pain? Once pain is disconnected from its acute warning function, and persists past normal healing time, pain is considered as chronic when it lasts or recurs for more than 3 to 6 months (Merskey & Bogduk, 1994). In the next section we will review the impact of chronic pain on the quality of life of individuals who suffer from chronic pain. In addition, we will discuss the fear-avoidance model, which describes the development and maintenance of chronic pain.

1.2.1 The burden of chronic pain

The impact of chronic pain on people's daily activities and quality of life is not to be underestimated. Several studies have shown that chronic pain affects at least 10% to 30% of the adult population in Europe (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Reid, Harker, Bala, Truyers, Kellen, Bekkering, & Kleijnen, 2011). Chronic pain not only affects people's daily activities and quality of life, but there are also influences on the social and family environment of people suffering from chronic pain. For

example, these people do not engage in social activities anymore, they can lose their jobs, get depressed, and they run an increased risk of other somatic and psychological illnesses (Breivik et al., 2006). As a result, there is a significant burden associated with chronic pain, not only related to the costs of the health care system, but also from the loss of productivity and from disability related payments to sufferers from chronic pain (Reid et al., 2011). According to Breivik, Eisenberg and O'Brien (2013), national healthcare and socioeconomic costs of conditions associated with chronic pain represent 3-10% of the gross domestic product in Europe. A recent study by Dieleman and colleagues (2020) revealed that in the USA in 2016 chronic low back and neck pain had the highest amount of health care spending with an estimated $134.5 billion in spending. Other musculoskeletal disorders accounted for the second highest cost to the health care system (estimated at $129.8 billion). Despite the high level of spending in the treatment of pain, the results in terms of addressing the conditions associated with chronic pain are still unsatisfactory. The focus is mainly on biomedical solutions to chronic pain (e.g. prescription of opioids), and 40% of patients report to be dissatisfied with their care (Gatchel, 2004; Gatchel et al., 2007).

There clearly is a need to better understand the development and maintenance of chronic pain and to adopt a multidisciplinary approach to improve the patient's condition and circumstances through both pharmacological and non-pharmacological treatments. Therefore, it will be necessary to develop research initiatives that will include biopsychosocial perspectives to produce new insights into the mechanisms that modulate pain, with an aim to develop effective health policies to prevent and manage chronic pain, thereby increasing daily functioning in individuals suffering from chronic pain.

1.2.2 The fear-avoidance model of chronic pain

The fear-avoidance model introduced by Lethem, Slade, Troup and Bentley (1983), and further elaborated by Vlaeyen and Linton (2000; 2012, see Figure 1.1), describes two pathways in response to pain initiated by an injury. If an individual appraises the pain as non-threatening, the individual will confront the pain and deal with it in an adaptive manner that allows the individual to proceed toward recovery.

If the individual appraises the pain as threatening, it may be dealt with in a maladaptive manner, resulting in a vicious cycle of pain-related fear and avoidance behaviour, which ultimately leads to disability, disuse, and depression.

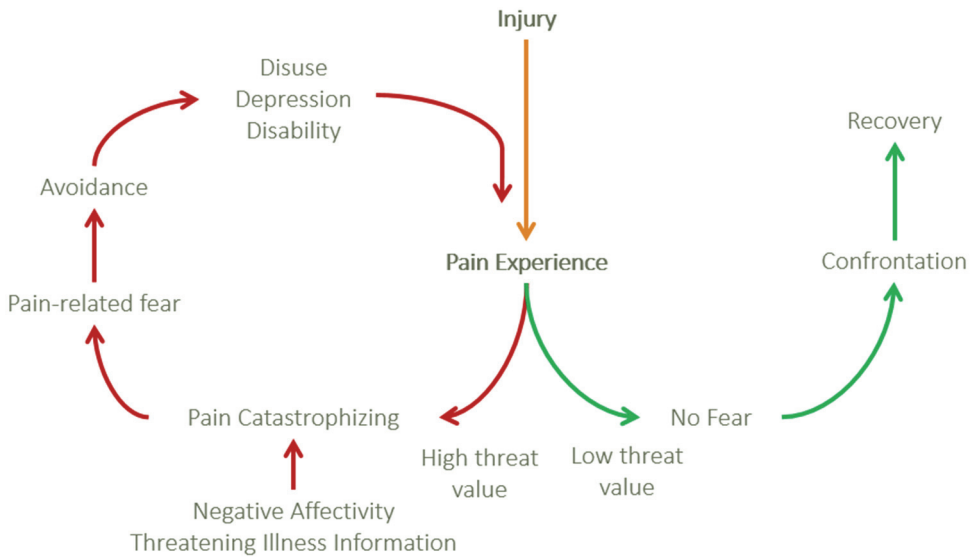

Figure 1.1. Fear-avoidance model of chronic pain (Vlaeyen & Linton, 2000; 2012).

1.2.3 Pain-related fear and avoidance behaviour

Fear and avoidance behaviour have been proposed to account for chronic pain and are the key components of the fear-avoidance model. Pain-related fear is defined as a "*general term to describe different forms of fear with respect to pain*" (Helsen, Leeuw, & Vlaeyen, 2013, p.1267). The different forms of fear may include e.g. fear of pain itself, fear of (re)injury, fear of physical activities. The importance of pain-related fear in the development and maintenance of chronic pain has been extensively demonstrated. Pain-related fear has shown to affect attentional processing of pain, and lead to decreased physical activity, functional disability, and distress (Eccleston & Crombez, 1999; Leeuw, Goossens, Linton, Borsma, & Vlaeyen, 2007; McCracken, Zayfert, & Gross, 1992; van den Hout, Vlaeyen, Houben, Soeters, & Peters, 2001).

Avoidance refers to actions aimed at postponing or preventing an aversive situation (in this case pain) from occurring (Pierce & Cheney, 2008). Avoidance is adaptive when there is a real threat, but when the avoidance response of perceived threats is out of proportion of the actual threat, then the costs of avoiding (e.g. missing out on opportunities) exceed the benefits (Barlow, 2002; Pittig, Treanor, LeBeau, & Craske, 2018). In the case of chronic pain, where pain is typically no longer a sign of actual danger, avoidance behaviour is no longer adaptive and may initiate a pathway towards functional disability (Zale, Lange, Fields, & Ditre, 2013). Furthermore, avoidance behaviours may lead to the misattribution of safety to the avoidance behaviour itself, which prevents disconfirmation of threat beliefs (Lovibond, 2009; Meulders, Van Daele, Volders, & Vlaeyen, 2016; Salkovskis, 1991; Volders, Meulders, De Peuter, Vervliet, & Vlaeyen, 2012).

1.3 The role of associative learning in pain-related fear and avoidance

As is the case in other manifestations of fear, pain-related fear and avoidance are acquired through associative learning (den Hollander, De Jong, Volders, Goossens, Smeets, & Vlaeyen, 2010; Lethem et al., 1983; Philips, 1987; Vlaeyen & Linton, 2000). There are two forms of learning (or conditioning): (1) classical (or Pavlovian) conditioning, and (2) instrumental (or operant) conditioning. We will briefly discuss these two learning principles against the background of chronic pain in the paragraphs below. Lastly, we will review various theoretical models related to the role of learning in the acquisition of avoidance.

1.3.1 Classical conditioning

In a typical classical pain-related fear conditioning procedure, a neutral conditioned stimulus (CS, e.g. a movement) is paired with a biologically relevant unconditioned stimulus (US, e.g. a painful electrocutaneous stimulus) that elicits an unconditioned response (UR, e.g. pain-related fear). Through repeated paired CS-US presentations, an individual learns to predict the occurrence of the US in the presence of the CS. Learning has taken place once the (originally) neutral CS receives motivational properties and comes to elicit conditioned responses (CRs) (see Figure 1.2; Stimulus-Stimulus (S-S) learning). For instance, if pain (US) is present during a certain movement (CS), a person will become more afraid to make the movement. The fear of the movement indicates that the movement has acquired a new meaning, i.e. the movement is now associated with pain, and hence motivates protective behaviour. It is important to note that the conditioned responses (CRs) are often highly adaptive behaviours to the US (Dayan, Niv, Seymour, & Daw, 2006). In the example above, it is adaptive to be afraid of pain, as it usually signals harm to the body.

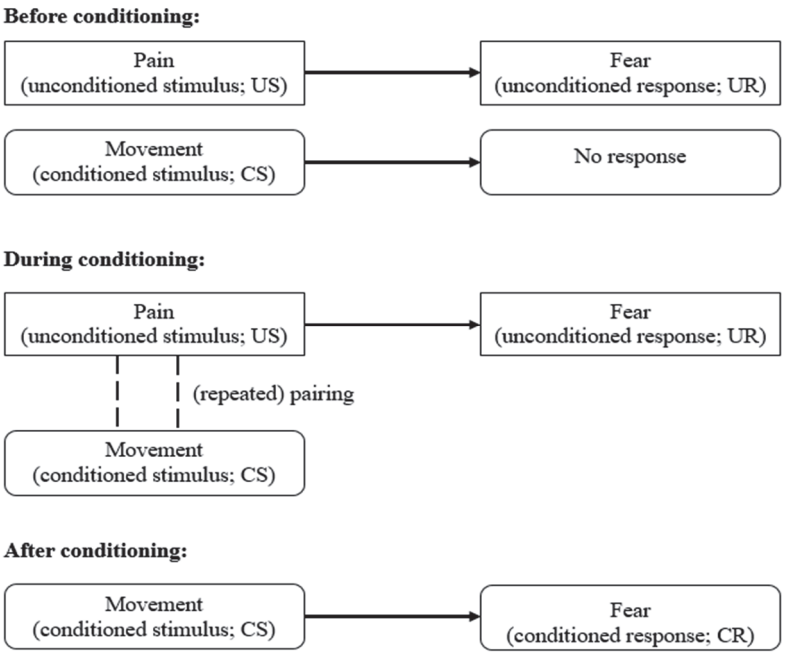

Figure 1.2. Stages of classical conditioning

1.3.2 Instrumental conditioning

Instrumental conditioning of pain behaviour occurs when the probability of the emittance of an individual's action (instrumental response, R, e.g. pain-related avoidance behaviour) has increased as a result of its meaningful consequences (outcome O, e.g. less pain). The outcome is referred to as a reinforcer when the outcome causes an increase in responding, and a punisher when the outcome involves a decrease in responding. The relation between response and outcome can be described as a R-O association. However, there is more to instrumental conditioning than the R-O association. According to Thorndike (1911), the contextual stimulus (S) in the presence of the instrumental response (R) establishes an association between the response R and the contextual stimulus S and not between response and outcome (see Figure 1.3).

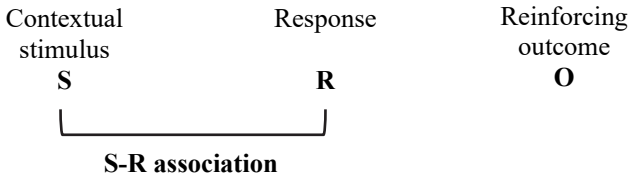

Figure 1.3. S-R associations in instrumental learning

The S-R association is the only thing learned and the outcome (O) is a catalyst for the learning of the S-R association. Other associations can be formed as well in instrumental conditioning; an outcome can be paired with the contextual stimulus (S-O association, Figure 1.4) or a three-term contingency where the outcome is followed by the occurrence of the response (R-O) and that the R-O contingency is only established in the presence of contextual stimulus (S(R-O) association, Figure 1.5). Applied to pain conditions, instrumental conditioning allows a person to control the painful events.

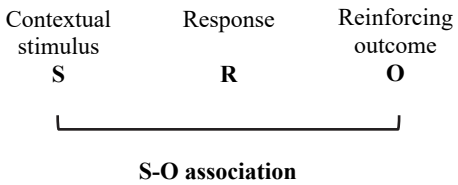

Figure 1.4. S-O associations in instrumental learning

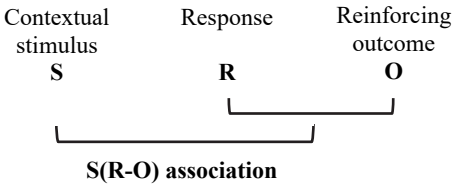

Figure 1.5. S(R-O) associations in instrumental learning

1.3.3 Two-factor theory of Mowrer

Avoidance behaviour is a form of instrumental conditioning in which the response (i.e. avoiding) prevents an aversive outcome (e.g. pain). Most theories propose that the acquisition of avoidance is established by both classical and instrumental conditioning. The two-factor fear-avoidance theory of Mowrer (1951) was one of the first models on avoidance learning, and assumes a dynamic relationship between Pavlovian or classical acquisition of fear and instrumental avoidance behaviour. According to Mowrer, conditioned fear (first factor) is required for avoidance (second factor) to occur, as avoidance behaviour is a response to fear, rather than a response to pain. The two-factor fear-avoidance theory states that avoidance should lead to extinction of fear, which in turn should result in extinction of avoidance behaviour.

Mowrer's theory has also been used as a basis for clinical interventions (Eysenck & Rachman, 1965) and the following example is an illustration of its application: in exposure therapy, patients are repeatedly exposed to a fearful stimulus or situation in order to reduce the fear, e.g. somebody with spider phobia will be confronted with a living spider in a bowl and has to keep looking at the spider till the fear levels go down. This suggestion for a patient to be continued to be exposed to the fearful stimulus until the fear or anxiety has declined, is based on the two-factor theory, i.e. if the exposure to the spider would be terminated while the fear or anxiety levels are still high, then the fear reduction caused by taking the spider away could promote escape or avoidance next time the individual would be exposed to a spider (Emmelkamp, 1982; Mathews, Gelder, & Johnston, 1981).

However, the two-factor fear-avoidance model has been challenged by several studies. For example, Solomon, Kamin and Wynne (1953) showed that avoidance behaviour persists even when shocks are no longer delivered. Also, experimental data have indicated that ending exposure to a fearful stimulus while fear levels were high or low, resulted in similar clinical improvements (De Silva & Rachman, 1984; Rachman, Craske, Tallman &, Solyom, 1986), suggesting that fear-reduction as proposed by the two-factor model is not necessarily the only negative reinforcer of avoidance. These and other findings that were difficult to explain by the two-stage fear avoidance theory encouraged the development of other theories of avoidance.

In the next three paragraphs we will discuss the cognitive theory of Seligman and Johnston (1973), the integrated expectancy-based model of Lovibond (2006), and the model of De Houwer and colleagues (2005) regarding avoidance as a negative occasion setter.

1.3.4 The cognitive theory of Seligman and Johnston

In the cognitive theory of Seligman and Johnston (1973) the role of informational factors on avoidance learning is explicitly addressed. This theory includes two main components: an emotional component and a cognitive component. The emotional component refers to classical (Pavlovian) conditioned fear responses. The cognitive component refers to a decision making process, assessing the trade-off between the expected costs of pain versus the expected costs of avoidance. According to Seligman and Johnston, one of the main principles is that the avoidance response is driven by the expectancies about response-outcome (R-O) contingencies and not by stimulus-response (S-R) associations. As a result, individuals will develop two R-O expectancies during avoidance learning: 1) no painful outcome will occur if an avoidance response is performed; 2) a painful outcome will occur if an avoidance response is not performed. In general, individuals would prefer not to experience a painful outcome and therefore they will decide to perform an avoidance response.

Unlike Mowrer's two-factor theory, where fear motivates avoidance responses and thus it should be expected that avoidance would be extinguished once fear has extinguished, the cognitive theory can explain that avoidance can be maintained despite the potential reduction in fear. To use our earlier example of spider phobia, although the levels of fear for the spider may have been reduced as a result of exposure to the spider, the expectancy of the danger of the spider has not been disconfirmed and therefore avoidance towards spiders can be preserved.

1.3.5 The expectancy model of Lovibond

Lovibond's expectancy model (2006) is an extension of the cognitive theory of Seligman and Johnston (1973). In the expectancy model, like in the cognitive theory, avoidance learning is governed by both classical (Pavlovian) and instrumental (operant) conditioning processes. Also, in both models, during instrumental learning individuals acquire knowledge about the effects of avoidance and non-avoidance (R-O associations; whereby R is avoidance or non-avoidance and O is the outcome, e.g. non-painful/painful outcome). An important deviation from the cognitive theory of Seligman and Johnston (1973) is that according to the expectancy model, expectancies play a crucial role in both instrumental as well as in classical (Pavlovian) conditioning and awareness of the CS-(no)US contingency is crucial for classical (Pavlovian) conditioning. In addition, a deviation from past theories is that the expectancy model assumes that all knowledge during avoidance learning is acquired via propositions (Mitchell, De Houwer, & Lovibond, 2009). This means that according to the expectancy model avoidance behaviour can be acquired not only via direct experience (associative learning), but also via e.g. instruction or observation, whereby higher order, rule-based processes play a role.

With the introduction of the expectancy model, most experimental data regarding avoidance behaviours can be accommodated. For example, the expectancy model can explain how avoidance is acquired, how, despite extinction of fear, avoidance can be maintained and why future avoidance will be reduced as a result of response prevention during extinction. Also, especially because the expectancy model assumes expectancies to play a crucial role in classical (Pavlovian) conditioning, it can better account for the relation between fear and avoidance. For example, the question why does fear return during response prevention, can be explained by the expectancy model: an individual who cannot perform an avoidance response expects an aversive outcome and because of this outcome expectancy, fear will be generated towards the aversive outcome.

1.3.6 Avoidance as a negative occasion setter

In the avoidance learning model of De Houwer and colleagues, an avoidance response serves as a signal that a CS is not going to be followed by an aversive event (De Houwer, Crombez, & Baeyens, 2005). This is referred to as a "negative occasion setter" in associative learning theory (Holland, 1992; Schmajuk & Holland, 1998). To illustrate this with an example, we assume two potential movements to reach a target location. Proprioceptive stimuli, such as movements, can actually serve as CSs as shown by studies of Meulders and colleagues (e.g. Meulders, Vansteenwegen, & Vlaeyen, 2011), evoking fear responses (Vlaeyen, 2015). In our example, one of the movements is always followed by a punisher (e.g. pain), whereas the other movement (avoidance response) is never followed by a punisher. Occasion setting can be seen as the capacity of, in this case, an avoidance response to disambiguate the relation between reaching a target location and an outcome. In negative occasion settings, the presence of the occasion setter (the avoidance response) signals that reaching the target location will not be followed by the punisher, whereas the absence of the occasion setter signals that reaching the target will be punished.

The findings that avoidance responses may have negative occasion setting properties, as proposed by De Houwer and colleagues, were replicated and extended in several of their studies (Declercq & De Houwer, 2008), whereby they compared the properties of avoidance behaviour to functional properties of negative occasion setters identified by Holland (1992). Those properties are: a) trained modulation (i.e. conditioned responding (e.g. fear) towards the target is stronger in the absence of the occasion setter (avoidance response) than in the presence of the occasion setter); b) resistance to counterconditioning (i.e. the presence of a contingency between the occasion setter and the reinforcer does not have an effect on the degree to which the occasion setter influences conditioned responding towards the target); c) selective transfer (i.e. the observation that a negative occasion setter will also influence conditioned responding towards other targets, but in a selective manner. It will more strongly influence conditioned responding towards targets that were previously involved in occasion setting training). However, more recent evidence argues against the negative occasion setting account, as the property of selective transfer of modulation in avoidance learning does

not provide (unique) support for the occasion setting account and the results of this more recent research can be explained by the expectancy model of Lovibond (2006) (Declercq & De Houwer, 2011).

1.4 Avoidance behaviour and fear – a bidirectional relationship?

Avoidance behaviours can be considered a sub-set of safety behaviours, which refer to a range of actions intended to detect, avoid, escape or neutralise a feared outcome (Salkovskis, 1991; Salkovskis, Clark, & Gelder, 1996; Wells, Clark, Salkovskis, Ludgate, Hackmann, & Gelder, 1995; Deacon & Maack, 2008). In daily life contexts, safety precautions are taken against feared outcomes. For example, people wear a helmet when riding bikes to prevent serious head injury in case they would be involved in an accident. Such safety behaviour is functional and can be seen as a rational response to a perceived threat. However, they can also be non-functional, when evoked in the absence of actual threat. Using our example from above, keeping your bike helmet on when going into a restaurant can be considered non-functional, because chances of head injury, even if you would fall during your visit to the restaurant, are rather low and probably not as detrimental as when being involved in an accident whilst biking. Also, when the emitted behaviour is not in line with the actual threat, cognitive dissonance may be induced. Individuals may resolve this dissonance by adjusting their threat attribution to fit their behaviour (Festinger, 1957; van Uijen, Leer, & Engelhard, 2018).

Safety behaviours are common in individuals with anxiety and are assumed to be crucial in the maintenance of irrational fear. Because fear and anxiety are known to contribute to the development and maintenance of chronic pain (Vlaeyen & Linton, 2000; 2012), we propose that pain avoidance in chronic pain has a similar status as safety behaviours in anxiety disorders. Although safety/avoidance behaviours that actually reduce threat are essential for survival and people's well-being (Diener, 2012), excessive and unnecessary avoidance is considered to be a hallmark in anxiety disorders (Clark, 1999; Salkovskis, 1991). Gangemi and colleagues (2012) suggested that safety behaviours are not necessarily the result of threatening information, but that they reversibly can be used as a source of information themselves, as evidence of the danger. In this way, safety behaviours might lead to a misattribution of safety, preventing the

disconfirmation of inaccurate threat beliefs (Salkovskis, 1991). For example, the results from a study by van Uijen and Toffolo (2015) indicated that checking behaviour, which is the most common safety behaviour in obsessive-compulsive disorder (OCD), contributed directly to the exacerbation of OCD symptoms. Similar findings from other studies show that health-related safety behaviours increased health anxiety and hypochondriacal beliefs (Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011), and safety behaviours related to cleaning exacerbated threat perception and contamination anxiety (Deacon & Maack, 2008). In general, these studies showed that engaging in safety behaviour increases anxiety and threat beliefs.

Avoidance is commonly viewed unidirectionally, as instigated by fear, and to result in fear reduction (Maia, 2010; Mowrer, 1947). However, recent studies suggest that engaging in avoidance behaviour may bear threat-inducing properties (Engelhard, van Uijen, van Seters, & Velu, 2015; Gangemi et al., 2012; Pittig, Wong, Glück, & Boschet, 2020). From the above examples from some recent studies in the area of anxiety disorders, anxiety or threat beliefs do lead to safety behaviours (one direction) and in turn, engaging in safety behaviours increases anxiety and threat beliefs (other direction), thereby suggesting a bidirectional relationship. This would also be in line with self-reinforcing "circularity" of the fear-avoidance model. As a result, we decided to investigate if there is also a bidirectional relationship between pain-related fear and pain avoidance behaviour. The results may be relevant to further our understanding of the development and maintenance of chronic pain.

1.5 Research aims and project outline

The primary aim of the present PhD research project was to introduce a new line of experimental work to further investigate the bidirectional relationship between pain-related fear and avoidance behaviour, and, if necessary, to propose a modification of the current fear-avoidance model based on the findings of the studies in the present project. In a series of studies we have experimentally manipulated (the perception of) avoidance behaviour and tested the effects on changes in fear and pain reports.

In *chapter 2* we describe our first experimental study aimed to test the effects of avoidance of a painful heat stimulus on pain-related fear and pain outcomes (intensity/unpleasantness) in healthy, pain-free participants. In this study we hypothesized that engaging in avoidance may (paradoxically) increase rather than decrease pain-related fear (i.e. bidirectionality hypothesis). Participants were randomly assigned to the avoidance group or the control group. Avoidance group participants were instructed to perform an avoidance response by pressing the stop-button upon presentation of a cue to avoid full exposure to a painful heat stimulus, while control group participants were not provided the opportunity to avoid the full painful heat stimulus. However, in reality and unknown to the participants, the intensity and duration of the heat stimulus occurred independently of the avoidance response, and was therefore identical in both groups. This meant that the avoidance was perceived avoidance, because the participants could not really avoid the maximum intensity of the painful stimulus. During the test, the avoidance response (i.e. pressing the stop-button) was no longer available. Self-reported pain-related fear, threat value of the heat stimulus, pain intensity, and pain unpleasantness were assessed. In addition, during the experiment eyeblink startle responses were collected as a physiological measure of pain-related fear.

Our second study, described in *chapter 3*, is a replication of the first study, implementing methodological improvements and minor modifications to the design of the paradigm to test the assumption that avoidance of a painful heat stimulus can be used as a source of threat information, thereby affecting pain-related fear and pain. Also, this second study aimed to provide more insight into the underlying mechanisms of the bidirectional relationship between pain-related fear and avoidance. We hypothesized that avoidance can serve as a source of information that fuels irrational pain-related threat appraisals, which in turn increases pain-related fear, and that the change in threat appraisal of pain mediates the relationship between avoidance behaviour and subsequent increase of pain-related fear. Healthy participants were again randomly assigned to the avoidance or control group and were exposed to a painful heat stimulus. As a methodological improvement relative to the first study, now both groups received the instruction that they could avoid the full heat intensity by pressing a stop-button in the presence of a stop-cue, unlike in the first study, where only the experimental group had

received this instruction. Only avoidance group participants received a stop-cue and were allowed to press the stop-button, while control group participants, although they had received the same instructions, never had the opportunity to avoid the full heat intensity. Again, the same measures as in our first study (chapter 2) were collected.

The third study, described in *chapter 4*, investigated the effects of ineffective avoidance of an electrocutaneous painful stimulus on subsequent pain-related fear and pain, and whether avoidance behaviour persists despite its ineffectiveness. Relative to the previous two studies, described in chapters 2 and 3, where perceived avoidance was operationalised by simply pressing a stop-button with no associated costs, here, to actually avoid the painful stimuli, participants had to perform a more effortful movement. By doing so, avoidance came with a cost, which is also the case in chronic pain and is more ecologically valid than avoidance with no associated costs. More specifically, we examined motor-behavioural characteristics of avoidance behaviours during different movements using the HapticMaster, a 3-degrees of freedom, force-controlled robotic arm. First, we hypothesized that pain-related fear increases when previously effective avoidance behaviour becomes ineffective. Second, we hypothesized that experimental group participants, who have acquired effective avoidance behaviour during the acquisition phase, will emit more avoidance behaviour during the ineffective avoidance compared to the control group. Healthy participants were block randomized and assigned to the experimental group or the control group. Experimental group participants acquired avoidance behaviour during a robotic arm-reaching avoidance task, in which participants could choose to perform trajectory movements that were either followed by a painful stimulus in 100% of the trials (movement T1), in 50% of the trials (movement T2) or never followed by a painful stimulus (movement T3; a measure of avoidance behaviour, i.e this movement T3 had the maximal deviation from the shortest trajectory T1). When the target location was reached via movement T1, which had the least lateral displacement, no force was exerted. When the target location was reached via movements T2 and T3, respectively moderate and strong resistance were applied by the HapticMaster. In a subsequent phase, participants from the experimental group could no longer avoid the painful stimulus effectively, because now each movement (T1, T2, T3) was followed by a painful stimulus 50% of the trials. Control group participants

never had the opportunity to effectively avoid the painful stimulus. Self-reported pain-related fear, pain expectancy, pain intensity and avoidance were assessed. We also collected data on the proportions of the chosen movement trajectories and the pain threshold and pain tolerance of the individual participants to explore the effects of effective and ineffective avoidance behaviour.

Our fourth study, described in *chapter 5*, introduced an innovative aspect relative to the study described in chapter 4, by investigating whether performing a movement to avoid a painful stimulus in the context of a novel, ambiguous movement increases threat and pain-related fear towards this novel movement, and whether avoidance behaviour persists when given the choice between performing the acquired movement or an alternative, novel movement to avoid a painful stimulus. We used a robotic arm-reaching task, where healthy participants were block randomized and assigned to either the experimental group or the control group. During the avoidance acquisition phase, participants could choose between two movement trajectories to reach a target location and they learn that the shortest movement trajectory (T1) was always followed by a painful electrocutaneous stimulus, but they can prevent the painful stimulus by selecting a longer movement trajectory (T3), that is never paired with pain. Next, in the avoidance manipulation phase, we removed the option to perform the shortest trajectory and introduced the option to perform a novel, intermediate trajectory (T2). Performance of T2 was paired with pain only the first time a participant chose this movement trajectory. From the second T2 movement onwards, no painful stimuli were given anymore, but this information was unknown to the participants. The experimental group participants had the free choice to select a novel, intermediate trajectory (T2), or the longest trajectory (T3), whereas the control group participants were only allowed to perform the novel, intermediate trajectory (T2). In a final free-choice test phase, participants of both groups could choose any of the three trajectories (T1, T2, T3). Only movement trajectory T1 was always paired with a painful electrocutaneous stimulus, while T2 and T3 were never paired with a painful electrocutaneous stimulus in this phase. Avoidance was operationalised as the number of times T3 was chosen relative to the alternatives (T1, T2). We collected pain expectancy and pain-related fear ratings for all movements.

The four experimental studies of this present project are described in more detail in the relevant chapters of this dissertation and the main findings of the studies, as well as some suggestions for future research, are provided in *chapter 6*, the general discussion.

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Chapter 2

The opportunity to avoid pain may paradoxically increase fear

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Abstract

Fear-avoidance models propose that pain-related fear may spur avoidance behaviour leading to chronic pain disability. Pain-related fear elicits avoidance behaviour, which is typically aimed at reducing fear. We hypothesized that engaging in avoidance may (paradoxically) increase rather than decrease pain-related fear (i.e. bidirectionality hypothesis). In a between-subject design, participants (N=64) were randomly assigned to the avoidance group or the control group. Avoidance group participants were led to believe they could avoid full exposure to a painful heat stimulus by pressing the stop-button, while control group participants believed they were exposed to the full painful heat stimulus at all times. In reality and unknown to the participants, the intensity and duration of the heat stimulus was independent of the avoidance response, and was identical in both groups. During the test, the avoidance response (i.e. pressing the stop-button) was no longer available. As expected, pain-related fear levels were higher after avoiding the painful heat stimulus. Interestingly, in the avoidance group, pain-related fear increased after receiving instructions that avoidance would be possible, even before actually engaging in avoidance behaviour. In the control group, no significant change was observed in pain-related fear throughout the experiment. The eyeblink startle measures did not corroborate this data pattern.

Perspective: these observations provide partial support for the bidirectionality hypothesis between avoidance behaviour and fear. These findings may have clinical implications and suggest that allowing avoidance behaviours during treatment may thwart fear reduction.

2.1 Introduction

It is commonly accepted that pain can occur in the absence of apparent tissue damage, which is often the case in chronic pain (Loeser & Treede, 2008). Furthermore, beliefs and expectations can influence the experience of pain (Arntz & Claassens, 2004). The fear-avoidance model of chronic pain provides a cognitive-behavioural explanation on how acute pain may turn into chronic pain, and how pain and disability may be maintained (Vlaeyen & Linton, 2000; 2012). The model emphasizes how catastrophic (mis)interpretation of pain elicits pain-related fear that in turn may spur avoidance behaviour leading to chronic pain disability. Recently, it has been proposed that engaging in pain avoidance may paradoxically increase pain-related fear, suggesting that the relationship between avoidance behaviour and fear may be bidirectional (Volders, Boddez, De Peuter, Meulders, & Vlaeyen, 2015).

Fear refers to an immediate alarm reaction to a present threatening stimulus (Barlow, 2000). In the Encyclopedia of Pain, pain-related fear is described as "*a general term to describe different forms of fear with respect to pain*" (Helsen, Leeuw, & Vlaeyen, 2013). Avoidance behaviour can be viewed as safety-seeking behaviour, which refers to a range of actions intended to detect, avoid, escape or neutralise a feared outcome (Cuming, Rapee, Kemp, Abbott, Peters, & Gaston, 2009; Deacon & Maack, 2008). Although safety-seeking behaviours that actually reduce threat are essential for survival and people's well-being (Diener, 2012), studies have shown that anxious individuals often conservatively employ these in the absence of objective danger (Clark, 1999; Salkovskis, 1991). In this way, the absence of expected danger may be erroneously misattributed to the safety-seeking behaviour, which prevents the disconfirmation of dysfunctional threat beliefs (Salkovskis, 1991). Anxious individuals might conclude that their own actions (i.e. their safety-seeking behaviours) prevent feared outcomes, thereby leading them to draw invalid conclusions about the situation, i.e. behaviour as information (Gangemi, Mancini, & van den Hout, 2012). A recent study by Engelhard, van Uijen, van Seters and Velu (2015) showed that safety-seeking behaviour directed towards a stimulus that was never paired with an unpleasant outcome paradoxically increased threat expectations

to that stimulus when it was subsequently presented in the absence of the safety-seeking behaviour. These findings indeed indicate that safety-seeking behaviour itself may bear threat-inducing properties.

The current study investigated the effect of avoidance behaviour on pain-related fear. We designed a between-subject study in which the opportunity to avoid was experimentally manipulated by creating the illusion to avoid a painful stimulus in one group (avoidance group), and not in another (control) group. However, the calibrated pain stimulus intensity or duration was identical for both groups, and did not change throughout the experiment. We hypothesized that (previous) avoidance of a painful stimulus serves as a source of information that further fuels pain-related fear. More specifically, our main hypothesis was that the prior possibility to avoid the pain stimulus increases fear (self-reported and startle), threat value, and intensity/unpleasantness of subsequent pain stimuli when the option to avoid is not available anymore. As our second hypothesis, we expected that the ability to avoid would attenuate pain-related fear and pain, despite identical physical stimulus intensity.

2.2 Methods

2.2.1 Participants

A total of 64 healthy, pain-free volunteers participated in the study (40 females; mean (range) ± SD age = 26.11 (18-59) ± 9.78 years). Participants were recruited at the KU Leuven, using social media and distribution of flyers around the campus. Psychology students received course credits for participation; other participants received a monetary compensation of €8,-. Participants were excluded if they reported to suffer from any cardiovascular disease, chronic pain conditions, pain at the non-dominant forearm, psychiatric disorders (current or in the past), neurological conditions or were pregnant. The Social and Societal Ethics Committee of KU Leuven approved the experimental protocol (registration number: G-2015 12 430). All participants provided a written informed consent, which stated that they were allowed to decline participation at any time during the experiment without any consequences. Participants were randomly assigned to one of two experimental groups: the avoidance group (n=32, 22 females) or the control group (n=32, 18 females).

2.2.2 Apparatus

Phasic painful heat stimuli were generated by a Peltier element-based computer controlled thermal stimulation device (Medoc, TSA, RAMA Yishau, Israel), and delivered through a thermode surface of 30 x 30 mm^2 attached to the non-dominant medial forearm. Acoustic startle probes (white noise delivered at 102 dBA with instantaneous rise time 50 ms) were presented binaurally using headphones (Hoher, Stereo headphones, HF92) to evoke the eyeblink startle responses to measure pain-related fear (Blumenthal, Cuthbert, Filion, Hackley, Lipp, & van Boxtel, 2005).

2.2.3 Study protocol

Heat stimulus intensity was set at individual pain threshold using a calibration procedure based on a temperature protocol provided with Medoc software (previous studies have used a similar procedure; Salomons, Moayedi, Erpelding, & Davis, 2014; Schwedt, Zuniga, & Chong, 2015). During this individual calibration, a series of five heat stimuli were administered, starting at a temperature of 36 °C ramping up at a rate of 0.5 °C/s with a maximum temperature of 49 °C. To avoid temporal summation we used an intertrial interval of 30-35 s during calibration and the experiment, as well as a 2-minute break between the different experimental phases. Participants were instructed to stop the heat stimulus by pressing a stop-button, i.e. clicking the left computer mouse button, at the moment the stimulus became painful. The mean temperature of the last three trials of the calibration procedure was set as the pain threshold (PTH). After calibration, participants received a heat stimulus that was 1 °C higher than the pain threshold (PTH+1°C), and they were told that this was the maximum stimulus intensity they would receive during the remainder of the experiment. The heat stimulus always started at a baseline temperature of 10 °C below the maximum intensity and ramped up with a rate of 0.5 °C/s to the individually determined maximum temperature and remained at that temperature level for 5 s. During each heat stimulus presentation, we provided visual feedback on the computer screen about the progress of the rising temperature of the heat stimulus, consisting of a vertical bar with the labels “baseline” at the bottom of the bar, and “maximum” at the top of the bar (see Figure 2.1 for an overview of the experimental design and trial structure). While the temperature was rising, the bar grew upwards and

gradually coloured red. Depending on group allocation, we manipulated the visual feedback that was provided to the participant. During the *experiential learning phase,* all participants received two trials, during which the heat stimulus reached the maximum PTH+1°C temperature and the visual feedback displayed that the maximum temperature was reached. Next, two trials followed where the heat intensity reached the PTH temperature and the visual feedback stopped before it reached its maximum. This phase was included so participants experienced that the visual feedback on the screen corresponded to the experienced temperature on the arm. During the *full intensity phase*, all participants received three trials, during which the heat stimulus and visual feedback concurrently stopped at maximum intensity and thus at the top of the feedback bar. At the onset of the crucial *intervention phase*, participants in the avoidance group (n=32) were led to believe that they successfully could avoid the pain stimulus peak, and received the following instructions: "*As soon as you see the stop-cue on the screen, press the stop-button immediately to stop the heat stimulation"*. This cue was a stop sign presented next to the visual feedback bar on the screen. Next, three trials followed during which the visual feedback stopped before it reached its maximum when the avoidance response was triggered (i.e. stop-button press). In reality however, the participants in the avoidance group still received the maximum intensity heat stimulus, similar to the control group. Participants in the control group received no stop-cue or any instructions at the start of the intervention phase; they received three trials during which the visual feedback again stopped at its maximum. Finally, during the *test phase*, three additional heat stimulations occurred where participants in the avoidance group were told: "*The stop-cue will no longer be presented, you cannot stop the stimulation anymore"*. Participants in the control group received no instructions during the test phase. Throughout the experimental phases, startle probes were presented during each trial (trial duration: 26.5 s): two during the painful heat stimulus (one in the beginning, between 2-8 s, and one towards the end of the stimulation, between 18-24 s), one startle probe was presented randomly during the intertrial interval (ITI: 30-35 s, between 10 and 20 s).

2.2.4 Outcome measures

Dependent variables were self-reports assessing 1) pain-related fear, 2) threat value of the heat stimulus, 3) pain intensity, and 4) pain unpleasantness on a numerical scale (NRS) from 0 to 100. At the start of each of the three phases, all participants were asked to report how afraid they were of the next heat stimulation on a scale from 0 to 100, with the labels 0 = "not afraid at all" and 100 = "extremely afraid". Participants rated the threat value of the painful heat stimuli twice, i.e. before the experimental phases started (pre), and at the end of the experiment after the last painful heat stimulus (post). The questions assessing threat value were respectively: 1) "*To what extent do you think the heat stimuli will be harmful to the skin?"*, and 2) "*How harmful to the skin did you think the heat stimuli were?"*. On a trial-by-trial basis, participants rated pain intensity and unpleasantness before and after each heat stimulation (i.e. prospective/retrospective ratings). In addition to the self-reports, a psychophysiological correlate of pain-related fear (i.e. the eyeblink startle response) was measured (for an overview of psychophysiological correlates of pain-related fear see Lonsdorf et al., 2017). The startle reflex, which is triggered by startle-evoking stimuli (in this case an acoustic probe), is a cross-species, full-body reflex involved in defensive response mobilisation. The eyeblink response is one component of the startle response. In human fear conditioning research, eyeblink startle responses are generally measured by recording the surface electromyography (EMG) activity on the M. orbicularis oculi beneath the left eye.

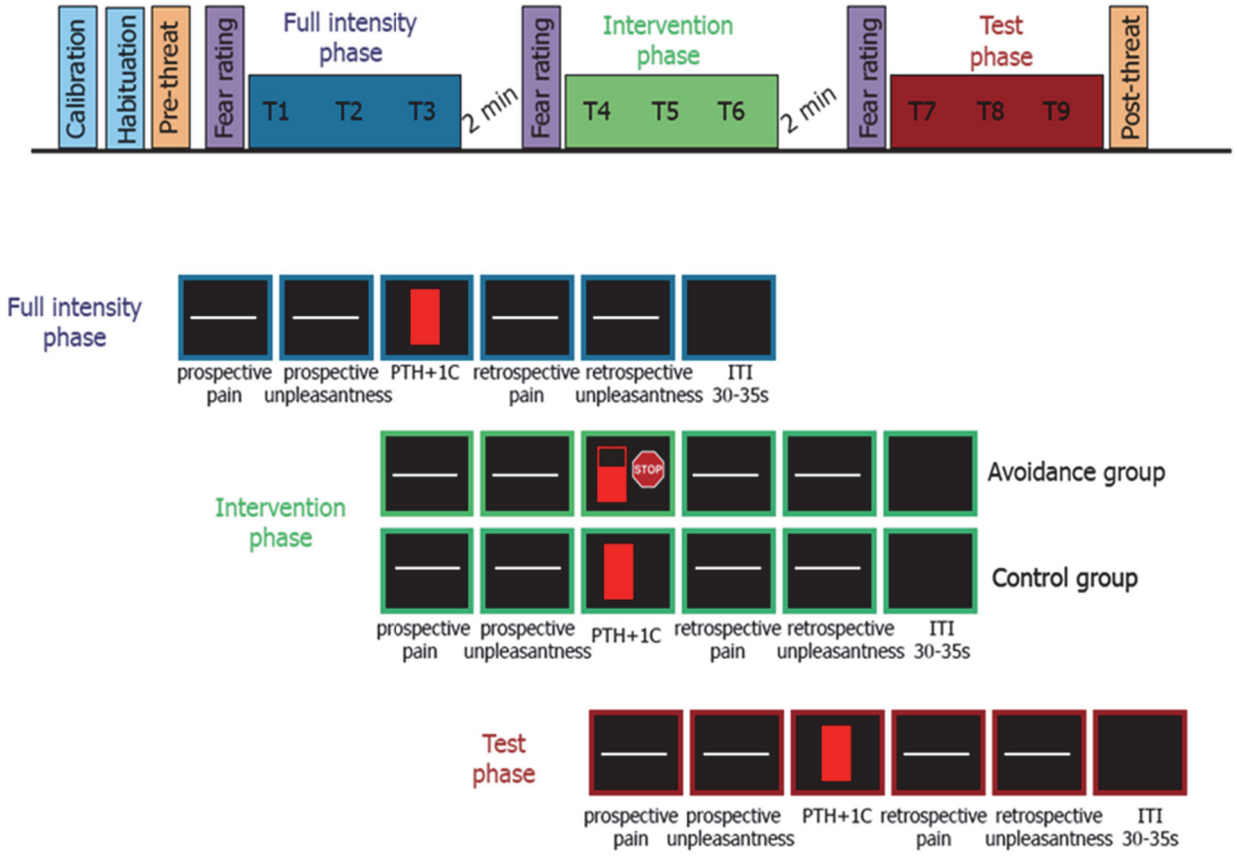

Figure 2.1. Overview experimental design and example trial structure. Presentation of the heat stimulus per phase (full intensity, intervention and test phase).

An increase in startle response occurs during fear states elicited by the anticipation of an aversive stimulus, and is thought to be an index of fear learning (Weike, Schupp, & Hamm, 2007). Electrodes were attached according to the site specifications described by Blumenthal and colleagues (2005). The raw signal was amplified by a Coulbourn isolated bioamplifier with a bandpass filter (LabLinc v75-04). The recording bandwidth of the EMG signal was between 90 Hz and 1 kHz. The signal was rectified online and smoothed by a Coulbourn multifunction integrator (LabLinc v763-23A) with a time constant of 20 ms. The EMG signal was digitized at 1000 Hz from 500 ms before the onset of the auditory startle probe until 1000 ms after probe onset.

2.2.5 Questionnaires

For descriptive purposes, participants completed several questionnaires upon completion of the experiment: the trait version of the State-Trait Anxiety Inventory (STAI; Van der Ploeg, 1980); the Fear of Pain Questionnaire (FPQ-III NL; van Wijk & Hoogstraten, 2006); and the trait version of the Positive Affectivity and Negative Affectivity Scale (PANAS; Engelen, De Peuter, Victoit, Van Diest, & Van Den Berg, 2006).

2.2.6 Manipulation check

At the end of the experiment one question about the perceived control over the heat stimulus was asked as manipulation check in the avoidance group on a 101-NRS ("*When it was possible, to what extend did you feel you could influence the duration and thus also the intensity of the heat stimulus?*").

2.2.7 Data analysis strategy

First, descriptive statistics were computed to describe the sample, and to test for group differences. To test our primary hypothesis that avoidance behaviour increases pain-related fear for subsequent painful stimulations, we performed a Group (2: avoidance/control) x Phase (3: full intensity/intervention/test) RM ANOVA on the pain-related fear measure. Next, planned comparisons were performed to identify expected differences. We primarily expected that avoidance behaviour would lead to increased pain-related fear in the test phase compared to the full-intensity phase. For the threat

value measures, a Group (2: avoidance/control) x Time (2: pre/post) RM ANOVA was performed. We primarily expected that avoidance behaviour would lead to increased threat value of pain in the test phase compared to the full-intensity phase. We expected a similar pattern in the startle data, for which we performed a Group (2: avoidance/control) x Probe (2: during stimulation/ITI) x Phase (3: full intensity/intervention/test) RM ANOVA.

In order to test our second hypothesis, that the avoidance group to report less fear and pain during the intervention phase, a Group (2: avoidance/control) x Phase (3: full intensity/intervention/test) RM ANOVA was performed on pain-related fear and pain intensity/unpleasantness ratings. Planned comparisons between the full-intensity phase and the intervention phase, as well as between the intervention phase and the test phase were performed within each group. For each significant RM ANOVA effect, η_g^2 is reported as the recommended effect size statistic for repeated measures designs (Bakeman, 2005). In case of violation of sphericity, Greenhouse-Geisser corrections were applied. All statistical tests are considered significant at $p < .05$. Holm-Bonferroni corrections were applied to correct for multiple comparison testing. See Appendix 2.A (supplementary material) for the tables of means, and standard errors of all measures.

2.3 Results

2.3.1 Descriptive statistics

Groups did not differ on self-reported pain intensity or temperature (PTH+1 °C) of the stimulation during calibration (on a scale from 0 to 100; $M_{\text{avoidance}} = 72.22$, $SD_{\text{avoidance}} = 17.72$, $M_{control} = 72.38$, $SD_{\text{control}} = 15.42$; $t(61) = -0.04$, $p = .97$; temperature: $M_{\text{avoidance}} = 43.48$ °C, $SD_{\text{avoidance}} = 1.73$, $M_{control} = 43.65$ °C, $SD_{\text{control}} = 1.89$), indicating that the heat stimuli were perceived similar across groups at the onset of the experiment. There were no significant differences in trait anxiety (STAI), fear of pain (FPQ-III-NL), and positive and negative affect (PANAS) between groups. The mean score for STAI was 49.32 (SD = 4.41).

The mean FPQ-III-NL score was 65.9 (SD = 14.88), with 37.15 (SD = 5.64) on the positive affectivity scale and 19.02 (SD = 6.86) on the negative affectivity scale of PANAS. The avoidance group indicated to feel in control of the intensity of the heat stimulus (*M* = 74.72, *SD* = 23.58)

2.3.2 Self-reported pain-related fear

Figure 2.2 displays the mean pain-related fear ratings per group measured before each phase. Testing our first hypothesis, the RM ANOVA on the pain-related fear ratings revealed a main effect of Group, $F(1, 62) = 4.10$, $p < .05$, $\eta_g^2 = .05$, indicating that the avoidance group reported more fear than the control group across all phases. There was a significant main effect of phase, $F(2, 124) = 8.28$, $p < .001$, $\eta_g^2 = .02$, indicating that fear ratings changed during the different experimental phases. Most importantly, the Group x Phase interaction effect was significant, $F(2, 124) = 4.73$, $p < .05$, $\eta_g^2 = .01$, suggesting that fear ratings across the phases of the experiment evolved differently for the avoidance group and the control group. The planned contrast evaluating the change in fear from the full intensity phase to the test phase between groups reached significance, $t(124) = 3.61$, $p < .001$. For the test of our second hypothesis, the planned contrast evaluating the change in fear from the full intensity phase to the intervention phase also reached significance, $t(124)=3.44$, $p < .01$, but not in the expected direction. Participants in the avoidance group paradoxically reported more pain-related fear after they received the instruction to avoid but prior to their actual avoidance behaviour, instead of the expected decrease in pain-related fear. Based on this unexpected finding of the pain-related fear ratings, an additional post-hoc comparison was made to test whether pain-related fear increased from the intervention phase to the test phase, which did not reach statistical significance ($t(124) = 0.17$, $p = .87$).

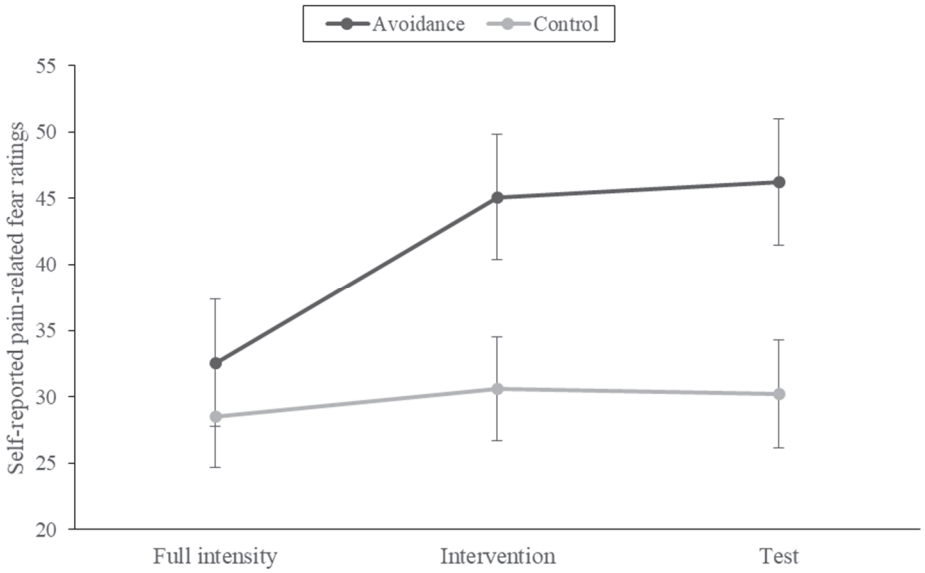

Figure 2.2. Self-reported pain-related fear ratings during the experimental phases for the avoidance and the control group separately.

2.3.3 Eyeblink startle measures

We calculated the peak amplitudes using Psychophysiological Analysis (PSPHA; De Clercq, Verschuere, De Vlieger, & Crombez, 2006). Every peak amplitude was defined as the maximum of the response curve within 21-175 ms after probe onset and was scored by subtracting its baseline score (averaged EMG level between 1 and 20 ms after probe onset). The raw scores were transformed to T-scores to account for inter-individual differences in physiological reactivity. All startle waveforms were visually inspected for technical abnormalities and artifacts. All startle data was included during the analysis, because it did not yield different results.

Figure 2.3 depicts the mean fear potentiated startle amplitudes for both groups separately for the three phases. The RM ANOVA revealed a significant main effect of Phase, $F(2, 124) = 4.58$, $p < .05$, $\eta_g^2 = .03$. Also, a significant main effect of Probe (during stimulation or ITI) was observed, $F(1, 62) = 34.42$, $p < .001$, $\eta_g^2 = .09$. As expected, the startle amplitudes elicited during stimulation, were higher than the startle amplitudes during ITI, suggesting that participants were more fearfully aroused during heat stimulation than in absence of the stimulation. There was no significant main effect of Group. The Probe x Phase interaction was significant, $F(2, 124) = 4.42$, $p < .05$, $\eta_g^2 = .02$. To test our main hypothesis whether pain-related fear would increase after avoidance behaviour, planned contrasts were performed evaluating the changes from the full intensity to the test phase. This comparison did not reveal any significant effects. However, after visual inspection of the data, we noticed an increase in startle amplitudes during the intervention phase for the avoidance group only. In order to test our second hypothesis, we further analysed the startle amplitudes with post-hoc contrasts and found that the startle amplitudes during stimulation were significantly potentiated in the avoidance group during the intervention phase in comparison with the full intensity phase, $t(247) = -2.75$, $p < .01$, and test phase, $t(247) = 4.17$, $p < .001$. There was no such change in startle amplitudes in the control group, $t(247) = -0.37$, $p = .71$; $t(247) = 0.98$, $p = .32$. In sum, the eyeblink startle responses do not seem to corroborate the self-reported increase in pain-related fear during the test phase (after performing the avoidance response). Although there is an initial increase in the mean eyeblink startle response of the avoidance group during the intervention phase, this increase is not maintained during the test phase.

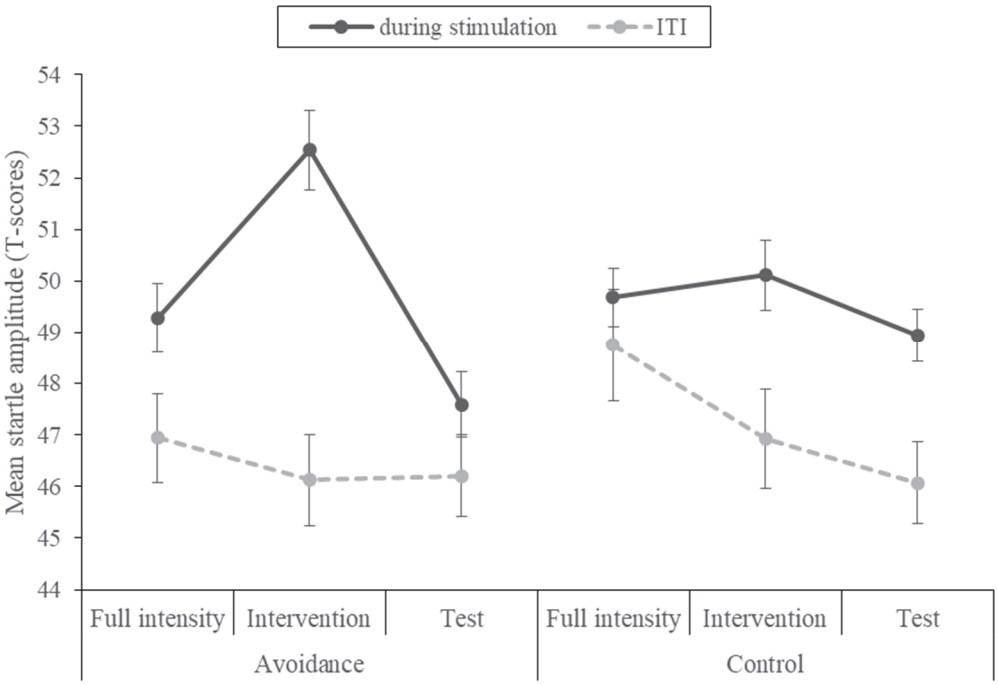

Figure 2.3. Mean startle amplitudes for the avoidance group (left panel) and the control group (right panel) during the full intensity, intervention and test phases during stimulation and during the intertrial interval (ITI). The raw scores from the startle measure were converted to z-scores to account for inter-individual differences. For better visualization of the data, the z-scores were transformed to T-scores, to avoid negative values on the Y-axis. The weighted average of eyeblink startle amplitudes was then calculated for each experimental phase.

2.3.4 Threat value: perceived harmfulness of the painful heat stimulus

The RM ANOVA on threat value ratings revealed significant Group x Time interaction, $F(1, 62) = 7.46$, $p < .001$, $\eta_g^2 = .02$. Mean comparisons indicated that control group participants reported the heat stimulus as less threatening at the end of the experiment, $t(62) = 2.85$, $p < .01$, while no changes were reported in the avoidance group, $t(62) = -1.01$, $p = .32$.

2.3.5 Pain intensity and unpleasantness

The trial-by-trial pain intensity and unpleasantness ratings were merged across the three full intensity, three intervention and three test trials. The RM ANOVA only showed a significant main effect of prospective pain intensity for Phase, $F(2,124) = 8.05$, $p < .001$, $\eta_g^2 = .01$. Participants expected the heat stimulus to be more painful at the end of the experiment compared to the beginning of the experiment, full intensity *vs.* test: $t(124) = -4.03$, $p < .001$. The RM ANOVA for the prospective unpleasantness also only revealed a significant main effect for Phase, $F(2,124) = 4.41$, $p < .05$, $\eta_g^2 = .007$. Participants expected the heat stimulus to be more unpleasant at the end of the experiment compared to the beginning of the experiment, full intensity *vs.* test: $t(124) = -2.96$, $p < .05$. For the retrospective pain intensity ratings, a significant Group x Phase interaction was found, $F(2,124) = 7.36$, $p < .001$, $\eta_g^2 = .006$. We also tested our second hypothesis. Participants in the avoidance group rated an identical heat stimulus as less painful when they thought they were avoiding the maximum stimulus intensity, full intensity *vs.* intervention: $t(124) = 3.74$, $p < .001$, and more painful when they could not avoid the maximum stimulus intensity, intervention *vs.* test: $t(124) = -2.67$, $p < .05$. This was not the case for the control group. The RM ANOVA for retrospective unpleasantness ratings did not reveal any significant effects. For the figure of pain intensity and unpleasantness ratings see Appendix 2.A (supplementary material).

2.4 Discussion

The present study tested the fear ←→ avoidance bidirectionality hypothesis. Although avoidance of a painful stimulus is mainly intended to reduce the accompanying anticipatory fear, it increases pain-related fear when previous avoidance behaviour is no longer available. In line with our expectations, the results showed that self-reported pain-related fear was higher after performing an avoidance response (pressing the stop-button), despite equal intensities and duration of the heat stimulus as in the control condition. The observed increase of pain-related fear as a result of avoidance behaviour is in line with previous research, which was mainly conducted in the field of anxiety disorders, and proposes a bidirectional relationship between fear and avoidance (Deacon

& Maack, 2008; Gangemi et al., 2012; Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011). For example, anxious patients might conclude that their own actions (i.e. their safety-seeking behaviours) prevent feared outcomes, thereby leading them to draw invalid conclusions about the situation (behaviour as information), even in the absence of information about objective danger. This tendency to infer danger on the basis of safety-seeking behaviours may start a vicious circle: safety-seeking behaviour increased threat perception in turn increasing safety-seeking behaviour, and so on.

The increase in pain-related fear as a result of the mere instruction of being able to avoid, is an unexpected but interesting result. We would only have anticipated such an increase in pain-related fear after the participants had actually performed the avoidance behaviour. This early increase in pain-related fear warrants caution in interpreting the results within the context of our main hypothesis, namely that previous avoidance increases pain-related fear when the option to avoid is not available anymore. Since the increase in pain-related fear already happened before engaging in avoidance behaviour, we cannot rule out that the elevated levels of pain-related fear during the test phase might have been due to the instruction of avoidance, instead of the actual engagement of avoidance. Why would the instruction to avoid increase pain-related fear? One possibility is that the instruction to avoid increases attention towards feared stimuli (Lavy & van den Hout, 1994). Increased attention towards pain in turn may have led individuals to view themselves more at risk, leading to an increase in pain-related fear. This explanation is consistent with observations of Powers, Smits and Telch (2004). These researchers found that the availability of a safety aid already had disruptive effects on fear reduction. Our findings add to these observations by showing that the availability of an avoidance response increases pain-related fear. Since we only measured the pain-related fear before each phase, we have no data to determine if the pain-related fear remained high directly after avoiding. Therefore, the maintained increased levels of pain-related fear during test phase cannot solely be ascribed to the engagement in avoidance behaviour, but could also be a consequence of the instruction of avoidance. We can conclude that pain-related fear is at least "maintained" through engagement in avoidance behaviour. As a result, our main hypothesis is only partially supported.

The psychophysiological data from the eyeblink startle responses are not completely in line with the self-reported increase in pain-related fear during the intervention phase (instruction to perform the avoidance response) and test phase (after performing the avoidance response). Although there is an initial increase in eyeblink startle responses of the avoidance group during the intervention phase, this increase is not maintained during the test phase. Eyeblink startle measures may not be well-suited in this paradigm, because responses may have been influenced by preparing to execute an avoidance response (motor preparation) or changes in the attentional processes in the avoidance group (Valls-Solé, Valldeoriola, Tolosa, & Nobbe, 1997). In addition, startle probes were delivered *during* instead of in *anticipation* of the aversive heat stimulation, as is common practice in classical fear conditioning paradigms using fear-potentiated startle measures. This procedural detail may also have rendered the startle measurement less effective/sensitive. Yet, startle responses were higher during stimulation compared to no stimulation for both groups, indicating that participants were more afraid during painful heat stimulation.

Some other observations should be highlighted. The decrease of threat value in the control group is consistent with results of exposure studies (den Hollander, Goossens, Ruijgrok, Oosterhof, Onghena, Smeets, & Vlaeyen, 2016; Sloan & Telch, 2002). Indeed, we expected that avoidance of a painful stimulus would increase the threat values, which then would serve as a source of information to further fuel pain-related fear (Engelhard et al., 2015). Another remarkable observation is the reduction in perceived pain intensity that was achieved by engaging in avoidance behaviour. The data suggests that our experimental manipulation worked, and that avoidance behaviour might indeed have created the expectation that participants avoided the maximum heat intensity (e.g. Reicherts, Gerdes, Pauli, & Wieser, 2016).

This study had various strengths and limitations. An innovative and methodological strength of this study was that we employed an experimental design by creating the illusion that participants could avoid the maximum pain stimulus, such that both received comparable (calibrated) pain intensities throughout the experiment. Therefore, any changes in perceived pain-related fear can be ascribed to the perception of having been able to avoid the maximum heat stimulus intensity. On one side, this is a clear strength

of the study, because pressing the stop-button created the perception for the participants in the avoidance group that they were actually able to avoid a painful stimulus. On the other side, this can also be seen as a limitation, because one may argue that simply pressing a stop-button with no associated cost is not ecologically valid. For example, for chronic pain patients, avoidance behaviour usually comes with a cost of limitations in daily functioning, and those patients have more to lose than to win with their avoidant behavioural patterns. In real-life however, one can argue that avoidance behaviours of chronic pain patients pertain to a combination of low- and high-cost responses. For example, avoiding certain simple movements could be a low-cost response, while not participating in valued life activities to prevent an increase of pain could be considered a high-cost response. Despite the low-cost action of the avoidance response (pressing the stop-button), the study showed effects of the perceived avoidance behaviour on the level of pain-related fear, i.e. the avoidance behaviour induced an increase in pain-related fear. In a similar way, low-cost avoidance behaviours like carrying pills, just in case pain would increase, could create the perception that this specific behaviour effectively prevented serious problems and could likewise increase threat beliefs (Vervliet & Indekeu, 2015). Avoidance precludes the individual the opportunity to experience the feared situation in the absence of pain, and thereby increases fear and may lead to overgeneralisation of avoidance responses (van Meurs, Wiggert, Wicker, & Lissek, 2014). Studies have demonstrated that chronic pain patients overgeneralise pain expectancy and fear to safe situations (Meulders, Harvie, Bowering, Caragianis, Vlaeyen, & Moseley, 2014; Meulders, Jans, & Vlaeyen, 2015; Meulders, Meulders, Stouten, De Bie, & Vlaeyen, 2017). Because of the bidirectional relationship of fear and avoidance, one could speculate that initial low-cost avoidance behaviour could develop into high-cost avoidance response via overgeneralisation of avoidance behaviour, and thereby contributing to the development of chronic pain (Dymond, Schlund, Roche, De Houwer, & Freegard, 2012). For example, when an individual experiences pain while lifting a box, (s)he will avoid to lift this particular box (low-cost avoidance). However, through stimulus generalisation, this person may also become afraid to experience pain

while lifting his/her baby and therefore will avoid holding his/her baby (high-cost avoidance). Future research should focus on potential detrimental effects of avoidance generalisation.

The potential negative effects of pain-related avoidance behaviour may be most prominent in chronic pain patients. Hence, before generalising the findings of the study to patients with chronic pain, future studies need to validate these findings using clinical samples. A better understanding of the dynamics between avoidance behaviour and pain-related fear, including the bidirectionality, could lead to new insights regarding the complexity associated with the development and maintenance of chronic pains.

To address the outstanding issues, future research should include measures of pain-related fear directly after having performed avoidance behaviour, so that further insights of the direct effects of avoidance behaviour on pain-related fear can be obtained. Also, the effects of avoidance behaviours on fear perception using both low- and high-cost responses, including validation in a clinical population await further research.

To conclude, the results of this study do indicate that avoidance behaviour can lead to increased and maintained self-reported pain-related fear, and provide partial support for the hypothesis of a bidirectional relationship between fear and avoidance. This is an important finding, suggesting that avoidance behaviour in itself may play a role in increasing fear, rather than resulting in the intended fear reduction. Interestingly, self-reported pain-related fear in the avoidance group already increased after receiving the instructions that avoidance would be possible, but before actually engaging in avoidance behaviour. Additionally, these findings suggest that allowing avoidance behaviours in clinical therapy may be detrimental for fear reduction and this should be taken into account when providing clinical recommendations.

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Appendix

2.A Supplementary material

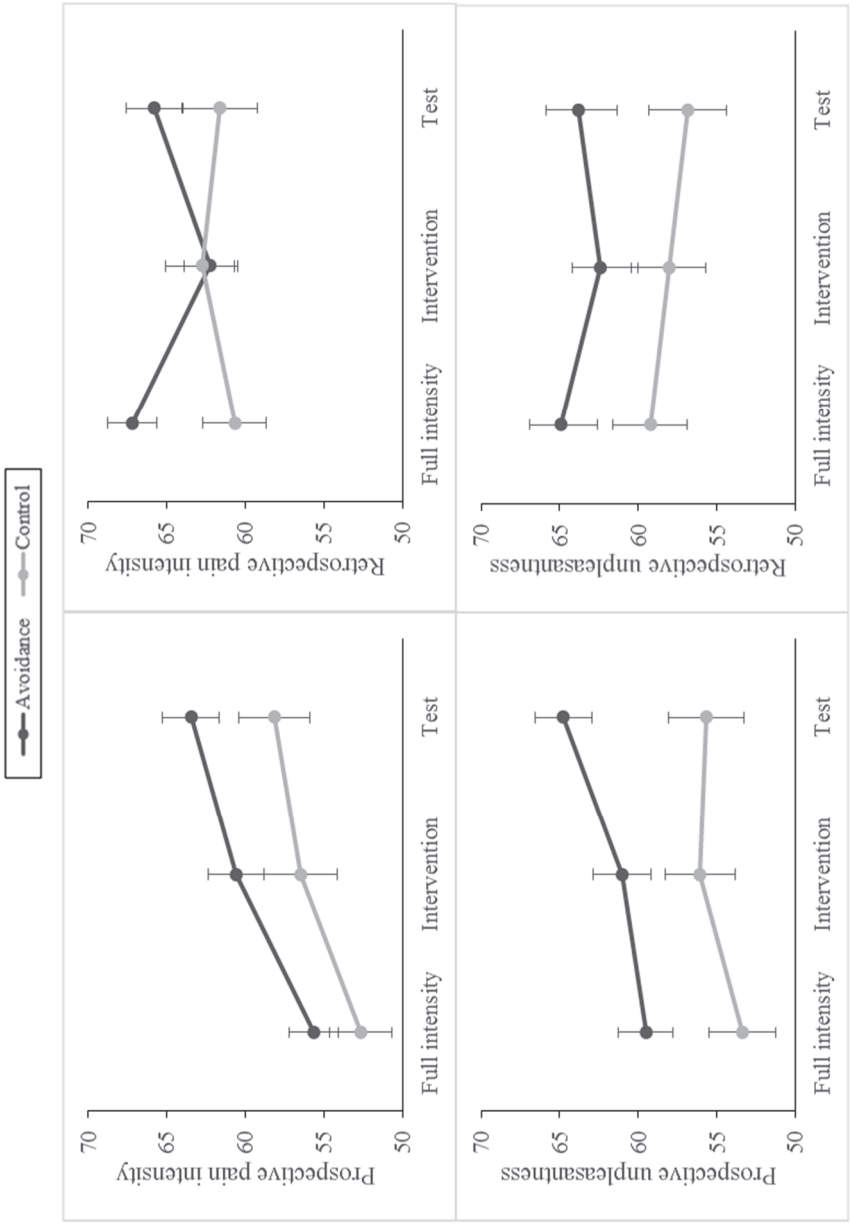

Figure 2.A.1. Self-reported pain intensity and unpleasantness ratings during the experimental phases for the avoidance and control group separately.

Table 2.A.1
Means and standard errors of pain-related fear

Pain-related fear	Full intensity phase *M* (SE)	Intervention phase *M* (SE)	Test phase *M* (SE)
Avoidance group	*32.56* (4.78)	*45.09* (4.71)	*46.22* (4.78)
Control group	*28.53* (3.90)	*30.59* (3.93)	*30.19* (4.06)

Table 2.A.2
Means and standard errors of eyeblink startle measures

Eyeblink startle		Full intensity phase *M* (SE)	Intervention phase *M* (SE)	Test phase *M* (SE)
Avoidance group	during stimulation	*49.28* (0.66)	*52.54* (0.77)	*47.59* (0.64)
	ITI	*46.93* (0.86)	*46.12* (0.90)	*46.21* (0.80)
Control group	during stimulation	*49.67* (0.56)	*50.11* (0.68)	*48.94* (0.50)
	ITI	*48.73* (1.09)	*46.92* (0.97)	*46.07* (0.80)

Table 2.A.3
Means and standard errors threat value

Threat value	Pre experiment *M* (SE)	Post experiment *M* (SE)
Avoidance group	*24.97* (3.79)	*28.31* (4.45)
Control group	*28.84* (4.18)	*19.38* (3.00)

Table 2.A.4
Means and standard errors pain intensity and pain unpleasantness

Pain intensity		Full intensity phase *M* (SE)	Intervention phase *M* (SE)	Test phase *M* (SE)
Avoidance group	Prospective	*59.66* (1.56)	*60.58* (1.76)	*63.47* (1.82)
	Retrospective	*67.20* (1.59)	*62.28* (1.59)	*65.80* (1.78)
Control group	Prospective	*52.67* (2.00)	*56.49* (2.32)	*58.15* (2.29)
	Retrospective	*60.67* (2.03)	*62.77* (2.27)	*61.64* (2.36)
Pain unpleasantness				
Avoidance group	Prospective	*59.53* (1.71)	*61.03* (1.83)	*64.76* (1.79)
	Retrospective	*64.93* (1.96)	*62.40* (1.81)	*63.80* (2.04)
Control group	Prospective	*53.39* (2.13)	*56.07* (2.23)	*55.69* (2.39)
	Retrospective	*59.25* (2.34)	*58.07* (2.39)	*56.86* (2.46)

Chapter 3

The perceived opportunity to avoid pain paradoxically increases pain-related fear through increased threat appraisals

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Abstract

Background: although pain-related avoidance is mainly intended to reduce the accompanying anticipatory fear, avoidance behaviour may paradoxically increase fear when a previous avoidance response is no longer available, suggesting there is a bidirectional relationship between pain-related fear and avoidance.

Purpose: we hypothesized that avoidance can serve as a source of information that fuels irrational pain-related threat appraisals, which in turn increases pain-related fear.

Methods: participants (*N*=66) were exposed to a painful heat stimulus and randomly assigned to the avoidance or control group. They were instructed to avoid the full heat intensity by pressing a stop-button in the presence of a stop-cue. Only avoidance group participants received a stop-cue and were allowed to press the stop-button, while control group participants received the same instructions, but never had the opportunity to avoid the full heat intensity. In reality and unknown to participants, the intensity and duration of the heat stimulus was independent of the avoidance response. In the subsequent test phase, the avoidance response was unavailable for both groups. We measured pain-related fear, threat appraisals/harmfulness, and pain intensity.

Results: in line with our expectations, pain-related fear levels were higher when the avoidance response was no longer available compared to those when the avoidance response was available. Increased threat appraisals mediated the relationship between avoidance behaviour and increased pain-related fear.

Conclusions: the perceived opportunity to avoid increased pain-related fear through threat appraisals, suggesting a more complicated relationship between pain-related fear, threat appraisals, and avoidance behaviour than the unidirectional relationships proposed in the fear-avoidance model. Clinical implications are discussed.

3.1 Introduction

How we experience pain can be influenced by beliefs, expectations, motivations, emotions as well as our own behaviour (Arntz & Claassens, 2004). The fear-avoidance model describes two pathways in response to pain initiated by an injury. If a pain-experience is interpreted as a sign of (impending) harm, pain-related fear may occur and associated avoidance behaviour, which ultimately can lead to disability, disuse, and depression. On the contrary, the non-threatening appraisal of pain will more likely lead to confrontation, and speedy recovery (Meulders, 2019; Vlaeyen & Linton, 2000; 2012). A relatively large body of evidence is in line with this model's assumptions, and a systematic review and meta-analysis concluded that despite the low quality of the investigations, pain-related fear is associated with chronic musculoskeletal pain and disability and is a precursor to chronic pain and disability (Martinez-Calderon, Flores-Cortes, Morales-Asencio, & Luque-Suarez, 2019). In addition, several studies have demonstrated high levels of pain-related fear to result in avoidance behaviour (e.g., Nishi, Osumi, Nobusako, Takeda, & Morioka, 2019; Vlaeyen, Kole-Snijders, Rotteveel, Ruesink, & Heuts, 1995). However, less is known about how avoidance behaviour affects fear and threat appraisals.

The bidirectional relationship between perceived threat and safety-seeking behaviours has been proposed to contribute to the persistence of anxiety disorders (Salkovskis, 1991). Safety-seeking behaviours typically prevent the disconfirmation of imminent threat (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). More recent anxiety research revealed that engaging in avoidance behaviour may bear threat-inducing properties (Engelhard, van Uijen, van Seters, & Velu, 2015; Gangemi, Mancini, & van den Hout, 2012). Van den Hout and colleagues reported that highly anxious people infer higher threat when they avoid more (van den Hout et al., 2014). Lovibond and colleagues showed that threat appraisals (such as the expectancy of an Unconditioned Stimulus; i.e. US-expectancy) regulate fear, and that avoidance aims to reduce the expectancy of a threatening outcome (Lovibond et al., 2009). In that sense, individuals use their avoidance behaviour to infer that the stimulus, which is avoided, might be harmful. For example, because an individual suffering from chronic low-back pain has been avoiding

lifting a heavy object, (s)he might consider lifting that object as a harmful movement, although this might not necessarily be the case. In line with this reasoning, preliminary evidence for the hypothesis that pain avoidance increases pain-related fear was provided in our previous study (van Vliet, Meulders, Vancleef, & Vlaeyen, 2018). We reported increased pain-related fear levels for those avoiding a painful heat stimulus compared to those who did not have the opportunity to avoid that stimulus. In our experimental paradigm, avoidance group participants were led to believe they could avoid the full intensity of the painful heat stimulus by pressing the stop-button, while control group participants believed they were exposed to the maximum heat stimulus at all times. However, the duration and intensity of the heat stimulus were kept equal in both groups, and did not change throughout the experiment. Only for the avoidance group, the visual feedback about the rising temperature of the heat stimulus stopped before it reached its maximum upon instructed button-press, creating the illusion of avoiding the maximal intensity of the painful heat stimulus.

The observation that fear increased after exerting avoidance behaviour provides evidence for the bidirectionality hypothesis. The current study aims to replicate our previous work (van Vliet et al., 2018), and extending this to provide more insight into the underlying mechanisms of the bidirectional relationship between pain-related fear and avoidance. Compared to the earlier study, we include more measurement times for assessing fear, pain intensity and threat appraisal to follow the temporal dynamics, and to investigate the mediating role of threat appraisal in the avoidance-fear relationship. We hypothesized the following: (1) the prior possibility to avoid the painful heat stimulus increases pain-related fear (self-reports and eyeblink startle response) of subsequent pain stimuli when the option to avoid is not available anymore; (2) the perceived avoidance attenuates pain reports despite exposure to identical physical stimulus intensity; (3) the change in threat appraisal of pain mediates the relationship between avoidance behaviour and subsequent increase of pain-related fear.

3.2 Methods

3.2.1 Participants

A total of 66 healthy, pain-free volunteers participated in the study (50 females; mean ± SD (range) age = 22.24 ± 4.75 (18-41) years). Participants were recruited at KU Leuven, using social media and distribution of flyers around the campus. Psychology students received course credits for participation; other participants received a monetary compensation of €8. Participants were excluded if they reported to suffer from any cardiovascular disease, chronic pain condition, pain at the non-dominant forearm, psychiatric disorder (current or in the past), neurological condition or to be pregnant. The Social and Societal Ethics Committee of KU Leuven approved the experimental protocol (Reg #: G-2017-10-960). All participants provided written informed consent, which stated that they were allowed to decline participation at any time during the experiment without any consequences. Participants were randomly assigned, via block randomization, to one of two experimental groups: the avoidance group (n=33, 29 females) or the control group (n=33, 21 females).

3.2.2 Apparatus

Phasic painful heat stimuli were generated by a Peltier element-based computer controlled thermal stimulation device (Medoc, TSA, RAMA Yishau, Israel), and delivered through a thermode surface of 30 x 30 mm^2 attached to the non-dominant medial forearm. Acoustic startle probes (white noise delivered at 102 dBA with instantaneous rise time of 50 ms) were presented binaurally using headphones (Hoher, Stereo headphones, HF92) to elicit the eyeblink startle responses to measure pain-related fear (Blumenthal et al., 2005).

3.2.3 Study protocol

We used a between-subject design with an avoidance group that was presented with the perceived opportunity to avoid, and a control group that never received the opportunity to avoid. The protocol is almost identical to the one reported in our previous study (van Vliet et al., 2018), apart from the following methodological improvements: (1) pain-related fear and threat levels are now measured at trial-level; (2) although the control group is never given the opportunity to avoid (i.e. they are never presented with the stop-cue), instructions to avoid the maximal painful heat stimulus are given to both groups, and not just to the avoidance group. The experiment was conducted during one single 60-minutes session and consisted of the following phases: preparation and calibration, habituation, experiential, full intensity, intervention, and test. After the experiment participants completed a number of questionnaires (see 3.2.5 Questionnaires). This study was preregistered at Open Science Framework (https://osf.io/dwt9y).

3.2.4 Experimental task

Participants observed a red vertical bar filling up on a computer screen during each heat stimulus presentation, providing visual feedback about the progress of the rising temperature of the heat stimulus. The vertical bar depicted the labels “baseline” at the bottom of the bar, and “maximum” at the top of the bar (for an overview of the experimental design and trial structure, see Figure 1). While the temperature was rising, the bar gradually filled up.

Preparation and calibration phase. Participants received oral and written information about the experiment. They were informed that they would be exposed to painful heat stimuli, but that the stimulus intensity would be individually determined during the calibration phase. After signing the informed consent, we attached the thermode to the non-dominant medial forearm. Next, during the calibration phase the heat stimulus intensity was set at individual pain threshold (PTH) and one degree above the pain threshold, which was the maximum intensity (PTH+1°C) (see our previous study for a detailed description of the heat stimulus calibration procedure (van Vliet et al., 2018)).

Once the individual intensity was determined, the presentation of each heat stimulus throughout the experiment was as follows: the heat stimulus always started at a baseline temperature of 10°C below the maximum intensity and ramped up with a rate of 0.5°C/s to the individually determined maximum temperature (PTH+1°C) and remained at that temperature level for 5 s.

Habituation phase. This phase is included to establish a reliable baseline level of startle responding. Participants were instructed that they would be presented with "short, loud noises" throughout the experiment. Next, 10 auditory startle probes were presented with a variable intertrial interval of 10-15 seconds. No painful heat stimuli were given during this phase.

Experiential phase. This phase is included for participants to learn that the visual feedback on the screen actually corresponds to the experienced temperature on the arm. All participants received two trials, during which the heat stimulus reached the maximum PTH+1°C temperature and the visual feedback displayed that the maximum temperature was reached (bar coloured red until label "maximum"). Next, two trials followed where the heat intensity reached the PTH temperature and the visual feedback stopped before it reached its maximum.

Full intensity phase. All participants received three trials, during which the heat stimulus and visual feedback concurrently stopped at maximum heat pain intensity (PTH+1°C) and thus the visual feedback bar filled up until the maximum.

Intervention phase. Both groups received the following instructions: "*As soon as you see the stop-cue on the screen, press the stop-button immediately to stop the heat stimulation"*. The stop-cue was a stop sign presented next to the visual feedback bar on the screen. The stop-cue always appeared at the same time, very close to the end of the stimulation during the intervention phase for the avoidance group. However, participants in the control group never saw the stop-cue during the intervention phase, and thus were never allowed to perform the avoidance response. As a result, they received three trials

during which the visual feedback again stopped at its maximum (PTH+1°C). In contrast, avoidance group participants received the stop-cue during the intervention phase trials. Upon emitting the avoidance response (i.e. pressing the stop-button), the visual feedback stopped before it reached its maximum. In reality however, unknown to the participants in the avoidance group, the bar filled up at a slower pace, as a result of which the participants received the maximum intensity heat stimulus (PTH+1°C), similar to the control group.

Test phase. Both groups received the following instruction: "*The stop-cue will no longer be presented, you cannot stop the stimulation anymore"*. Next, they received three full intensity heat stimuli in which the visual feedback bar also reached its maximum.

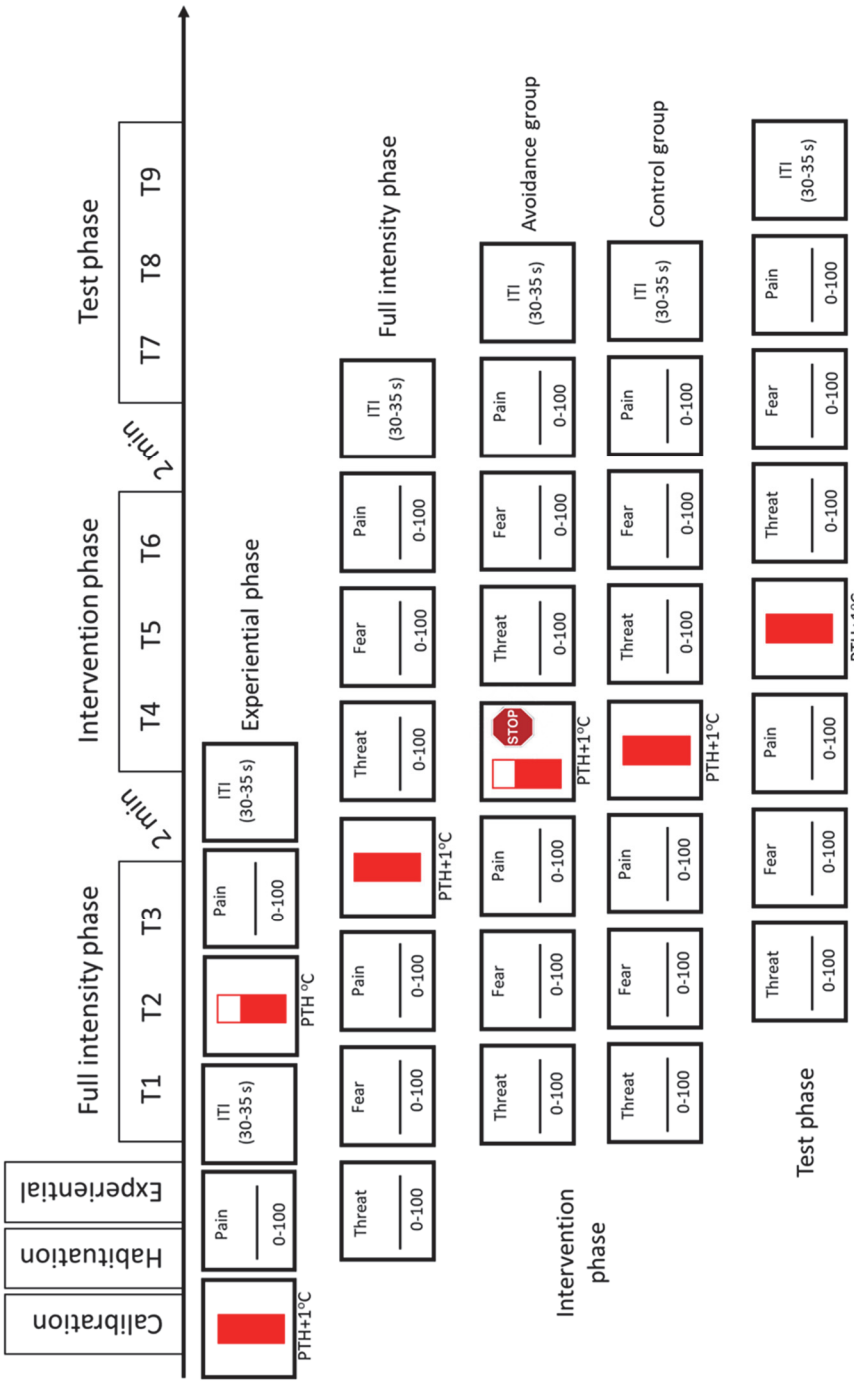

Figure 3.1. Overview of the experimental design and exemplary trial structure. Legend: PTH+1°C = maximum temperature; ITI = inter-trial interval; Calibration = determine individual pain threshold level; Habituation = presentation of 10 startle probes.

3.2.5 Questionnaires

For descriptive purposes, participants completed several questionnaires upon completion of the experiment. We measured trait anxiety with the trait version of the State-Trait Anxiety Inventory (STAI-T) (Van der Ploeg, 1980); fear of pain with the Dutch version of the Fear of Pain Questionnaire (FPQ-III NL) (Van Wijk & Hoogstraten, 2006), and positive and negative affect with the Positive Affectivity and Negative Affectivity Scale (PANAS) (Engelen, De Peuter, Victoir, Van Diest, & Van Den Bergh, 2006).

3.2.6 Manipulation checks

At the end of the experiment two single items on an anchored scale from 0 to 100 assessed the perceived control over the painful heat stimulus ("*When it was possible, to what extent did you feel you could influence the duration and thus also the intensity of the heat stimulus?*"), and the credibility of the visual feedback on the screen respectively, ("*To what extent was the visual feedback on the screen accurate about the stimulus intensity?*"). These questions served as manipulation checks.

3.2.7 Outcome measures

Self-reports

On a trial-by-trial basis, participants rated pain-related fear, the perceived harmfulness of the stimulus (threat appraisal), and pain intensity before and after each heat stimulation (i.e. prospective/retrospective fear and perceived harmfulness ratings; expected/experienced pain intensity ratings) on a scale from 0 to 100, with the following questions: 1) "*How afraid are/were you of the heat stimulus?*"; 2) "*How harmful will the heat stimulus be/ was the heat stimulus?*"; 3) "*How painful will the heat stimulus be/was the heat stimulus?*".

Startle eyeblink modulation

In addition to the self-reports, a psychophysiological correlate of fear (i.e. the eyeblink startle response) was measured (for an overview of psychophysiological correlates of pain-related fear see (Lonsdorf et al., 2017). The startle reflex, which is triggered by startle-evoking stimuli (in this case an acoustic probe), is a cross-species, full-body reflex involved in defensive response mobilisation. The eyeblink response is one component of the startle response. In human fear conditioning research, eyeblink startle responses are generally measured by recording the surface electromyography (EMG) activity on the M. orbicularis oculi beneath the left eye. Electrodes were attached according to the site specifications described by Blumenthal and colleagues (Blumenthal et al., 2005). The raw signal was amplified by a Coulbourn isolated bioamplifier with a bandpass filter (LabLinc v75-04). The recording bandwidth of the EMG signal was between 90 Hz and 1 kHz. The signal was rectified online and smoothed by a Coulbourn multifunction integrator (LabLinc v763-23A) with a time constant of 20 ms. The EMG signal was digitized at 1000 Hz from 500 ms before the onset of the auditory startle probe until 1000 ms after probe onset. Throughout all the experimental phases, startle probes were presented during each trial (trial duration: 26.5 s): two during the heat stimulus (an early probe, between 2-8 s, and a late probe, towards the end of the stimulation, between 18-24 s), and one startle probe was presented randomly during the inter-trial interval (ITI: 30-35 s, between 10-20 s). We included the probe during ITI as a baseline comparison (participants should have learned that no painful stimulations were given during ITI). Pre-processing occurred as follows: we calculated the peak amplitudes using a Matlab script. Every peak amplitude was defined as the maximum of the response curve within 21-175 ms after probe onset and was scored by subtracting its baseline score (averaged EMG level between 1 and 20 ms after probe onset). The raw scores were transformed to T-scores to account for inter-individual differences in physiological reactivity. All startle waveforms were visually inspected for technical abnormalities and artifacts. All startle data was included during the analysis.

3.2.8 Data analysis strategy

First, descriptive statistics were computed to describe the sample, and to test for group differences on the different psychological trait questionnaires. Second, to check whether our manipulation worked, independent-samples t-tests were conducted to compare the perceived control over the heat stimulus and the credibility ratings of the visual feedback on the screen between the avoidance and control group. Third, to test the first hypothesis that prior possibility to avoid the painful heat stimulus increases pain-related fear of subsequent pain stimuli when the option to avoid is not available anymore, we conducted 2 x 9 Group (avoidance, control) x Trial (T1-T9) repeated measures (RM) ANOVAs on prospective and retrospective pain-related fear ratings. Furthermore, we performed planned comparisons between the last trial of the full intensity phase and the first trial of the test phase. We expected larger effects of losing the opportunity to avoid on the prospective pain-related fear ratings than on the retrospective pain-related fear ratings. We assume the ratings to be updated after participants experienced the heat stimulus. In other words, participants feel less afraid after they experienced the "maximum" heat stimulus again during test. Additionally, we performed a 2 Group (avoidance, control) × 2 Probe (during stimulation, ITI) × 9 Trial (T1-T9) RM ANOVA on the startle data. We carried out planned comparisons between the last trial of the full intensity phase and the first trial of the test phase. In addition, because responses to a single probe are not always reliable, we performed a 2 Group (avoidance, control) x 2 Probe (during stimulation, ITI) x 3 Phase (full intensity, intervention, test) RM ANOVA on the startle data to confirm whether similar results emerged as observed in the trial-level analysis. See supplementary material for analysis. Fourth, to test our second hypothesis that perceived avoidance attenuates pain reports despite exposure to identical physical stimulus intensity, we performed a 2 Group (avoidance, control) x 9 Trial (T1-T9) RM ANOVA on expected and experienced pain intensity ratings. Planned comparisons were performed on the pain ratings for the last trial of the full intensity phase *vs.* the last trial of the intervention phase, as well as for the last trial of the intervention phase *vs.* the first trial of the test phase.

For each significant RM ANOVA effect, η_g^2 is reported as the recommended effect size statistic for repeated measures designs (Bakeman, 2005). In case of violation of sphericity, Greenhouse-Geisser corrections were applied. All statistical tests are considered significant at $p < .05$. Holm-Bonferroni corrections were applied to correct for multiple comparison testing. Finally, to test our third hypothesis whether threat appraisal (as measured by harmfulness of the painful heat stimulus) mediates the effect of avoidance on pain-related fear, ordinary least-squares path analysis was employed to estimate coefficients in the model (Hayes, 2017; Meule, 2019). This model was tested using regression (to calculate statistics for specific paths) and bootstrapping (to generate a confidence interval [CI] for the mediation effect/indirect effect). The bootstrapping method is considered the most powerful, most effective method in small samples, and the least vulnerable to Type I errors. In addition, bootstrapping is a nonparametric resampling procedure, which does not assume normal distributions for any variable. We resampled the data 10,000 times. More specifically, we expected that the threat appraisal (measured as the prospective harmfulness of the painful stimulus) increases from the last trial of the intervention phase (trial 6) to the first trial of test phase (trial 7) for participants of the avoidance group, and that this increase in prospective threat appraisal mediates the increase in prospective pain-related fear. To test the mediation, we performed the following steps: we calculated the increase in perceived harmfulness and in pain-related fear by subtracting the first trial of the test phase by the last trial of the intervention phase, which gave us the variables of interest: Δthreat and Δfear. With these two variables, we performed the mediation analysis as described above. Δthreat may be considered a mediator to the extent to which it carries an influence of group allocation (avoidance/control group; independent variable) to the Δfear (dependent variable). Hence, mediation can be said to occur when there is a significant indirect effect. The test on the indirect effect is based on bootstrap 95%-confidence intervals (CI). If 95%-CI of the indirect effect does not contain zero, we would say mediation has occurred.

3.3 Results

3.3.1 Descriptive statistics

Groups did not differ on self-reported pain intensity or temperature (PTH and PTH+1 °C) of the stimulation during calibration (on a scale from 0 to 100), indicating that the heat stimuli were perceived similar across groups at the onset of the experiment. There were no significant differences in trait anxiety (STAI-T), fear of pain (FPQ-III-NL), and positive and negative affect (PANAS) between groups. Please see Table 1 for an overview.

Table 1. *Descriptive statistics and independent samples T-tests for the questionnaires scores for both the Avoidance Group (n=33) and the Control Group (n=33) separately.*

Total	Avoidance Group	Control Group		
N = 66	*M (SD)*	*M (SD)*	*t*(64)	*p*
Temperature PTH (°C)	43.55 (2.74)	43.70 (2.72)	0.22	.82
Pain intensity PTH	57.21 (19.16)	56.03 (18.92)	0.25	.80
Pain intensity PTH+1	72.05 (16.19)	71.53 (16.03)	0.13	.89
STAI-T – total	37.61 (8.29)	40.15 (8.52)	-1.23	.22
FPQ – total	75.33 (14.15)	77.00 (9.46)	-0.56	.58
PANAS – positive	36.09 (4.53)	33.73 (5.60)	1.81	.08
PANAS – negative	19.85 (5.91)	21.27 (5.88)	-0.98	.33

Note. PTH = pain threshold; PTH+1 = 1°C above pain threshold; STAI-T = Trait version of the State-Trait Anxiety Inventory; FPQ = Fear of Pain Questionnaire; PANAS = positive and negative affect

3.3.2 Manipulation checks

The avoidance group indicated they felt more in control over the intensity of the heat stimulus compared to the control group (Avoidance: M = 50.88, SD = 23.60; Control: M= 20.09 , SD= 23.67; $t(64) = 6.95$, $p < .001$). Groups did not differ in how credible they found the visual feedback (Avoidance M= 67.58, SD = 16.45; Control: M = 68.53, SD= 16.29; $t(64) = -0.23$, $p = .82$).

3.3.3 Hypothesis 1: pain-related fear increases when the opportunity to avoid is no longer available.

Self-reported pain-related fear

Figure 3.2 displays the mean pain-related fear ratings per group measured before (prospective fear; panel a) and after (retrospective fear; panel b) each trial.

Prospective pain-related fear. The RM ANOVA on the prospective pain-related fear ratings revealed a main effect of Trial, indicating that the fear ratings changed throughout the experiment, $F(3.75, 239.78) = 15.47$, $p < .001$, $\eta_g^2 = .04$. There was no significant main effect of Group, $F(1, 64) = 0.61$, $p = .44$. Furthermore, the Group x Trial interaction effect for prospective pain-related fear failed to reach significance, $F(3.75, 239.78) = 1.74$, $p = .15$. We tested the hypothesis that prior avoidance behaviour would lead to increased pain-related fear for the avoidance group. The planned contrast compared the last trial of the full intensity phase (trial 3) with the first trial where the avoidance response was no longer available (trial 7). Consequently, the planned contrast evaluating the change in prospective fear reached significance for the avoidance group, $t(512) = 4.32$, $p < .0001$, and not for the control group, $t(512) = 0.55$, $p = .58$. Furthermore, we tested whether prospective pain-related fear increased as a result of the mere instruction of being able to avoid. We compared the last trial of the full intensity phase (trial 3), with the first trial of the intervention phase (just after the instruction was given; trial 4). The change in prospective pain-related fear was not significant, neither for the avoidance group: $t(512) = 0.99$, $p = .32$, nor for the control group: $t(512) = 0.88$, $p = .38$.

Retrospective pain-related fear. The RM ANOVA on the retrospective pain-related fear ratings revealed a main effect of Trial, indicating that the retrospective pain-related fear ratings changed throughout the experiment, $F(3.96, 253.75) = 8.10$, $p < .0001$, $\eta_g^2 = .02$. There was no significant main effect of Group, $F(1, 64) = 0.91$, $p = .33$. Furthermore, the Group x Trial interaction term was not significant, $F(3.96, 253.75) = 0.68$, $p = .61$. The planned contrast evaluating the change from the last trial of the full intensity phase (trial 3) with the first trial of the test phase (trial 7) just failed to reach significance for the avoidance group, $t(512) = 1.93$, $p = .054$, and was not significant for the control group, $t(512) = -0.29$, $p = .77$.

In sum, prior avoidance behaviour leads to a significant increase in prospective pain-related fear ratings, but failed to reach significance in the retrospective pain-related fear ratings (i.e. after participants experienced the painful stimulus). We did not replicate the finding from our previous study that pain-related fear increased as a result of the mere instruction of being able to avoid (van Vliet et al., 2018).

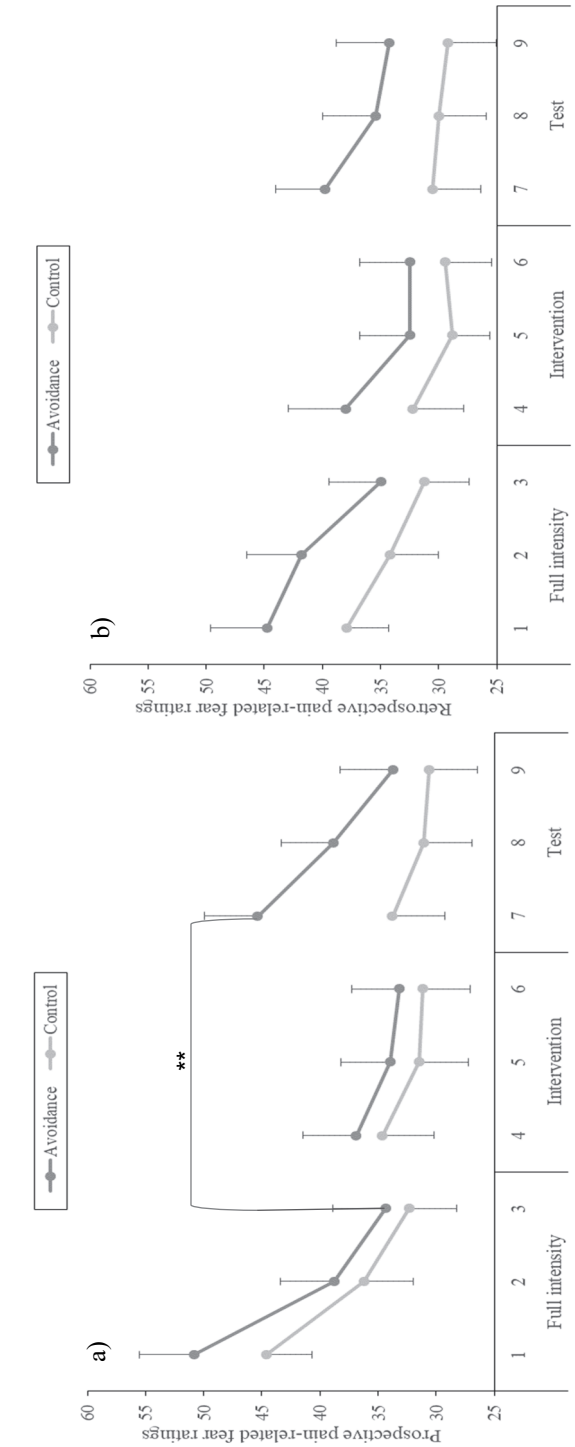

Figure 3.2. Prospective (panel a) and retrospective (panel b) pain-related fear ratings with standard error bars for the avoidance group and the control group during the full intensity, intervention, and test phase. **p< .01

Physiological measure of pain-related fear: startle eyeblink modulation

Figure 3.3 displays the mean fear-potentiated startle amplitudes for both groups separately for each trial. The RM ANOVA revealed a significant main effect of Group, $F(1, 64) = 4.33$, $p < .05$, $\eta_g^2 = .002$. Also, a significant main effect of Trial, $F(8, 512) = 5.68$, $p < .0001$, $\eta_g^2 = .04$, and Probe, $F(1, 64) = 239.33$, $p < .0001$, $\eta_g^2 = .32$, was observed. Furthermore, the Probe x Trial interaction was significant $F(8, 512) = 5.11$, $p < .0001$, $\eta_g^2 = .03$. As a follow up to the significant interaction effect, we examined the effect of Probe at each Trial level, with a one-way ANOVA. All one-way ANOVAs at Trial level were significant. For an overview of the simple main effects, please see supplementary material in appendix 3.A, Table 3.A.1. As expected, the startle amplitudes elicited during stimulation, were higher than the startle amplitudes during ITI, suggesting that participants were more fearfully aroused during heat stimulation than in absence of the stimulation. The following interactions were not significant: Group x Trial interaction, $F(8, 512) = 0.48$, $p = .87$; Group x Probe interaction, $F(1, 64) = 0.0005$, $p = .98$; Group x Trial x Probe interaction, $F(8, 512) = 0.97$, $p = .46$. To test our hypothesis that pain-related fear would increase after avoidance behaviour, planned contrasts were performed evaluating the changes from the last trial of the full intensity phase (trial 3) to the first trial of the test phase (trial 7). We found a significant increase in the startle amplitude for the avoidance group, $t(1024) = 2.26$, $p = .024$, but not for the control group, $t(1024) = -1.17$, $p = .24$. We also observed an increase in startle amplitude during stimulation from the last trial of the full intensity phase (trial 3) to the first trial of the intervention phase (trial 4) for the avoidance group, $t(1024) = 3{,}38$, $p < .001$, as well as for the control group, $t(1024) = 3.26$, $p < .001$. The analysis of the mean startle amplitudes on phase-level can be found in appendix 3.A and Figure 3.A.1.

In sum, the mean startle amplitudes seem to corroborate the self-reported increase in prospective pain-related fear after the avoidance response was no longer available (i.e., during the first trial of the test phase). Furthermore, both groups show an increase in startle responses after the avoidance instructions were delivered.

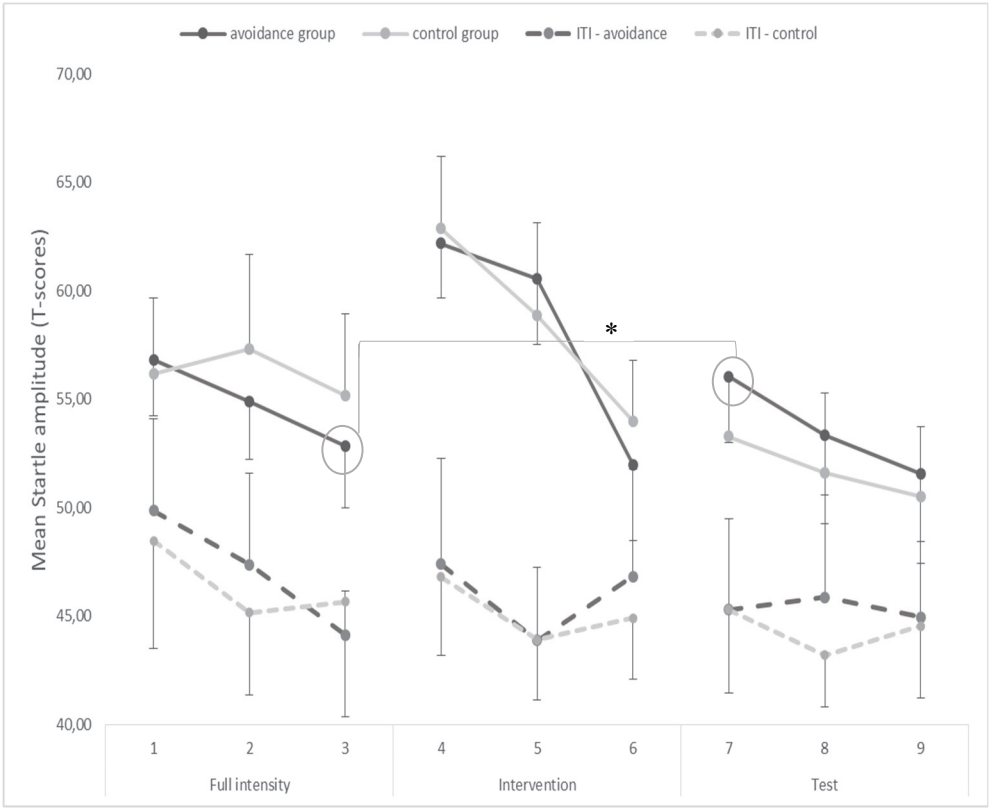

Figure 3.3. Mean startle amplitudes for the avoidance group and control group for all trials during stimulation (solid line) and during ITI (dashed line). The raw scores from the startle measures were converted to Z-scores to account for inter-individual differences. For better visualization of the data, the Z-scores were transformed to T-scores, to avoid negative values on the Y-axis. * $p < .05$

3.3.4 Hypothesis 2: perceived avoidance attenuates pain intensity despite exposure to identical physical stimulus intensity

Figure 3.4 displays the mean pain intensity ratings per group measured before (expected; panel a) and after (experienced; panel b) each trial.

Expected pain intensity. Figure 3.4 (panel a) shows the expected pain intensity ratings for both groups. The RM ANOVA of expected pain intensity showed a significant main effect of Trial only, $F(4.65, 297.39) = 7.75$, $p < .0001$, $\eta_g^2 = .02$. The following effects were not significant: main effect of Group, $F(1, 64) = 0.22$, $p = .64$; Group x Trial interaction, $F(4.65, 297.39) = 0.47$, $p = .78$; Avoidance group participants expected a lower pain intensity when they performed the avoidance response (intervention phase) compared to the beginning of the experiment where they could not perform an avoidance response (full intensity phase): last trial of full intensity (trial 3) *vs*. last trial intervention (trial 6), $t(512) = -1.95$, $p < .05$. This was not the case for the control group, $t(512) = -0.14$, $p = .89$. Participants in the avoidance group expected higher pain intensity during the first trial where they could no longer use the avoidance response (test phase; trial 7) compared to the last trial where the avoidance response was available (intervention phase; trial 6), $t(512) = 1.98$, $p < .05$. This was not the case for the control group, $t(512) = 1.05$, $p = .30$.

Experienced pain intensity. Figure 3.4 (panel b) graphically displays the means of experienced pain intensity ratings for both groups. The RM ANOVA reveals a significant main effect of Trial, $F(5.22, 334.08) = 6.75$, $p < .0001$, $\eta_g^2 = .01$, and just failed to show a significant Group x Trial interaction, $F(5.22, 334.08) = 1.99$, $p = .08$, $\eta_g^2 = .003$. The main effect of Group was not significant, $F(1, 64) = .07$, $p = .80$. The planned contrasts evaluating the change in experienced pain intensity during avoiding and not avoiding revealed similar results as the expected pain intensity.

Experienced pain intensity significantly decreased for the avoidance group when the avoidance response was available: last trial of full intensity (trial 3) *vs*. last trial intervention (trial 6) $t(512) = -2.52$, $p < .05$, and not for the control group, $t(512) = -0.45$, $p = .66$. Experienced pain intensity ratings significantly increased for the avoidance group when avoidance behaviour was no longer available, $t(512) = 4.37$, $p < .001$, but not for the control group $t(512) = 1.20$, $p = .23$. In sum, perceived avoidance behaviour attenuates the expected and experienced pain intensity of physically identical stimuli.

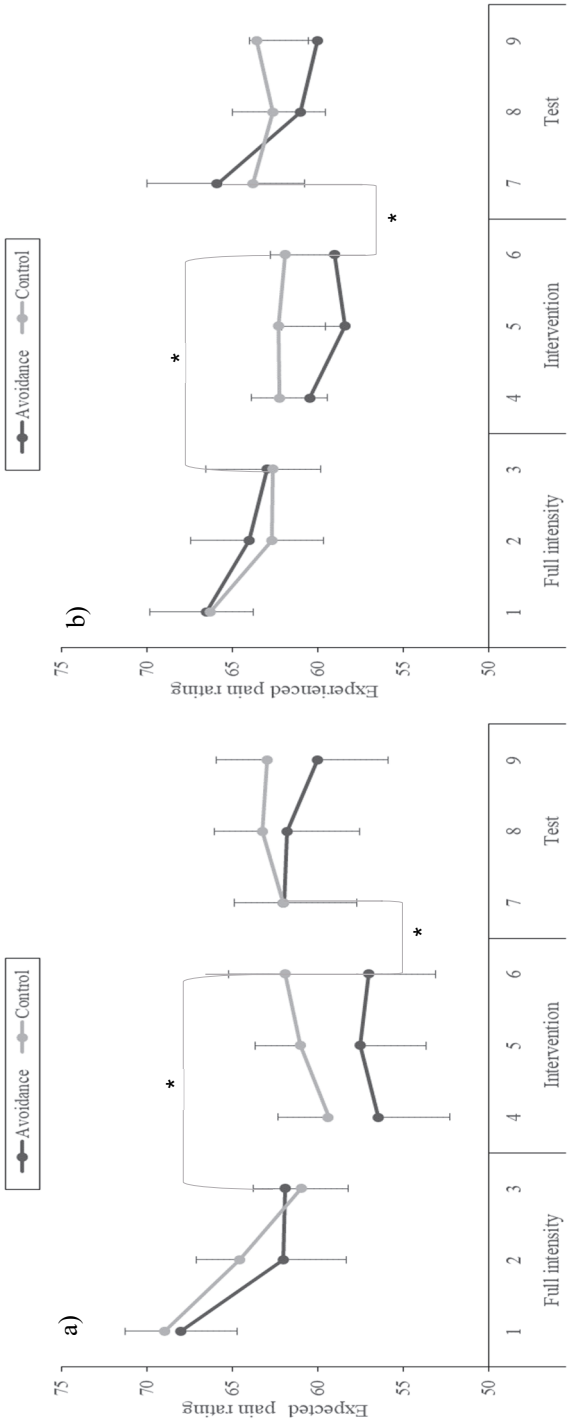

Figure 3.4.. Expected (panel a) and experienced (panel b) pain intensity ratings with standard error bars for the avoidance group and the control group during the full intensity, intervention, and test phase. * $p < .05$; ** $p < .01$

3.3.5 Hypothesis 3: the threat appraisal of pain mediates the relationship between avoidance behaviour and pain-related fear

The paths of the mediation model (see Figure 3.5), were calculated as follows: (1) The regression of avoidance (group allocation) on Δthreat, $b = 5.38$, $t(64) = 2.56$, $p < .05$; (2) The regression of Δthreat on Δfear, $b = .41$, $t(63) = 2.71$, $p < .01$; and finally (3) the regression of avoidance on Δfear, controlling for Δthreat is, $b = 4.88$, $t(63) = 1.84$, $p = .07$. Bootstrapping the indirect effect of the model gave the following results: indirect effect = 2.18, $SE = .87$, 95%-CI[0.67, 4.05]. Since the 95%-CI of the indirect effect does not contain 0, we conclude that mediation has occurred.

In other words, an increase in threat appraisal, measured as the perceived harmfulness of the painful stimulus, mediated the relationship between the perceived ability to avoid the full pain intensity and changes in pain-related fear.

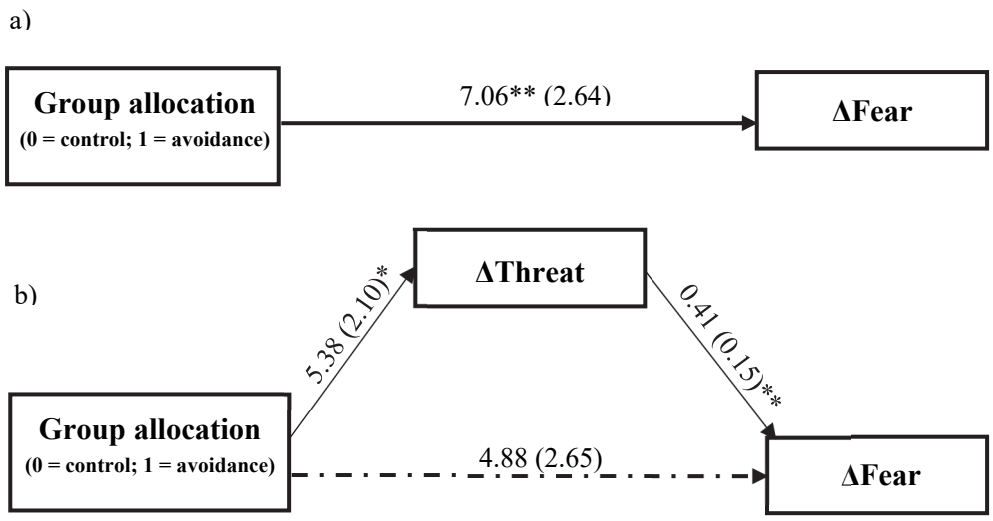

Figure 3.5. Panel a) shows the relation between Group Allocation and ΔFear (without mediation). Panel b) shows ΔThreat as mediator in the relation between Group Allocation and ΔFear. All coefficients represent unstandardized regression coefficients. Solid lines represent significant predictions. Dashed lines represent non-significant predictions. Values in the brackets represent standard errors (SE). Values of group allocation: 0=control group, 1=avoidance group. *$p < .05$, **$p < .01$

3.4 Discussion

The current study was set up to further test the idea that perceived ability to avoid pain affects pain-related fear. According to modern fear-avoidance models, interpreting pain as threatening (a sign of serious harm) results in pain-related fear, may spur avoidance behaviour, and typically maintains chronic pain disability. The initial model proposed a circular, but unidirectional relationship between threat appraisal, pain-related fear, and avoidance behaviour (Vlaeyen et al., 1995). However, the unidirectionality of the fear-avoidance relationship has been challenged. Although avoidance of painful stimuli is aimed at reducing the accompanying anticipatory fear and expected pain, previous research has shown that pain avoidance itself can paradoxically increase pain-related fear. In our previous study (van Vliet et al., 2018), pain-related fear levels increased after avoiding a painful stimulus, suggesting that the relationship between avoidance behaviour and fear may be bidirectional. The current study aimed to replicate these findings, and additionally investigate the mediating role of the threat appraisal of pain (i.e. perceived harmfulness) in the avoidance-fear relationship. Compared to the previous study, the current one is notable for the following methodological improvements: (1) pain-related fear and threat appraisals were measured at trial-level instead of phase-level, enabling the aforementioned mediation analysis; (2) instructions to avoid the maximal painful heat stimulus when a stop-cue is presented are given to both groups instead of to the avoidance group only. This gives us more certainty that the observed increase in pain-related fear in the avoidance group is due to the engagement in avoidance behaviour instead of the mere instruction that avoidance is possible.

Findings of the study were the following: we successfully replicated the findings (1) that the prior perceived ability to avoid the painful stimulus increases pain-related fear; (2) that perceived avoidance attenuates pain reports despite exposure to identical stimulus intensity; and additionally found (3) the threat appraisal of pain mediates the relationship between avoidance behaviour and subsequent pain-related fear.

The prospective pain-related fear ratings and psychophysiological data from the eyeblink startle responses support our first hypothesis. Participants of the avoidance group were more afraid when they no longer could perform their avoidance response.

These findings are in line with previous research, mainly conducted in the field of anxiety disorders (Deacon & Maack, 2008; Engelhard et al., 2015; Gangemi et al., 2012; van den Hout et al., 2014). Avoidance behaviours are assumed to play a role in the development and maintenance of excessive fear. Here, we experimentally show that perceived pain avoidance hinders the disconfirmation of pain-related fear and threat appraisals. In this way, misattribution of safety to the avoidance behaviour itself occurred, which resulted in decreased pain-related fear scores. That is, pain-related fear was low for the avoidance group during the intervention phase. However, during the crucial test phase, when the avoidance behaviour could not be emitted anymore, avoidance group participants reported more pain-related fear, although the stimulus intensity was identical throughout the experiment, compared to the control group participants who never avoided.

Our results seem to support our hypothesis that avoidance behaviour increases the threat appraisal of a painful stimulus, which then serves as a source of information to further fuel pain-related fear. This model is supported by the idea of ex-consequentia reasoning (Arntz, Rauner, & van den Hout, 1995). The avoidance behaviour itself, rather than the painful stimulus, may have led participants to infer danger (e.g. "*I avoid, thus there must be danger"*). These observations are also in line with findings in the field of anxiety research, where avoidance can be seen as counterproductive and can paradoxically enhance or maintain anxiety/fear and self-reported negative experiences (Campbell-Sills, Barlow, Brown, Hofmann, 2006; Cioffi & Holloway, 1993; Dymond et al., 2011; Feldner, Zvolensky, Stickle, Bonn-Miller, Leen-Feldner, 2006; Spira, Zvolensky, Eifert, Feldner, 2004). We suggest that people with persistent pain show a similar tendency to attribute the absence of danger (e.g., re-injury) to their avoidance behaviour, consequently preventing opportunities to disconfirm threat appraisals (Barlow, 2000; Salkovskis, 1991; Volders, Boddez, De Peuter, Meulders, & Vlaeyen, 2015). Also, as can be seen from the mediation analysis, perceived threat mediates the relationship between avoidance behaviour and pain-related fear. These findings suggest an additional avoidance –> threat –> pain-related fear loop as an extension to the fear-avoidance model, which may act as an additional drive propelling the development of fear-related avoidance and disability levels typical for chronic pain.

Although pain usually is considered an unconditioned stimulus (US) in itself, it also serves as a cue signalling another US, which is the actual (re-)injury or bodily harm. In that context, avoiding painful stimuli (or pain increase) is to prevent the (re)injury to occur. Although avoidance behaviour is often described in its passive form, active forms of behaviour do also exist, which often are called safety-seeking behaviours, such as deliberately acting in a certain way. In our study, avoidance group participants had the option to engage in active avoidance behaviour (i.e. pressing a stop-button) and were led to believe by doing so they could avoid pain increase. This paradigm is in line with the fear-avoidance model, even though the avoidance response in question is not refraining from activity (i.e. passive avoidance), but pressing a stop-button (i.e. active avoidance or safety-seeking behaviour).

Concerning our hypothesis that perceived avoidance behaviour attenuates pain intensity reports despite exposure to identical stimulus intensity, we found that the avoidance group participants, but not control group participants, indeed perceived less pain while engaging in avoidance behaviour. We propose that the mechanism driving this hypoalgesia could be placebo-inducing expectancies. Specifically, in the experiential phase, participants felt that the stimulus was less intense (i.e. stimulus intensity at the pain threshold level instead of one degree above the pain threshold level) when the red bar did not reach its maximum. When participants performed the avoidance behaviour, again the red bar did not reach its maximum, creating the (placebo) expectation that the stimulus intensity also would not reach its maximum [Reicherts, Gerdes, Pauli, & Wieser, 2016; van Vliet et al., 2018). In the control group, no such differences in pain intensity were found.

In addition to these results, there are other remarkable observations. For the avoidance group the reduction in pain intensity was not paralleled by reductions in pain-related fear, and this may be due to a bottom effect as the levels of pain-related fear were already quite low. After the instruction to avoid, but prior to actually performing the avoidance response (i.e. pressing the stop-button), the eyeblink startle responses increased for both groups. This observed increase in eyeblink startle responses might be a result of changes in attentional processing (Valls-Solé, Valldeoriola, Tolosa, & Nobbe,

1997) due to the instruction that avoidance behaviour would be available only upon presentation of the stop-cue. For example, eyeblink startle responses may have been influenced by preparing to execute an avoidance response (motor preparation). Another potential explanation for the observed increase in the eyeblink startle response is that the instruction to avoid increases attention towards feared stimuli (Lavy & van den Hout, 1994), which in turn may lead individuals to view themselves more at risk, leading to increased fear levels. As a result, eyeblink startle responses may not be well-suited measures of pain-related fear in this study. Additionally, in our previous study we found an increase in self-reported pain-related fear as a result of the mere instruction to avoid (van Vliet et al., 2018). Although in the current study we did observe an increase in the eyeblink startle responses for both groups, just after the instruction to avoid at the start of the intervention phase, this was not reflected in the self-reported pain-related fear. At this stage, we do not have a plausible explanation for this observation. Furthermore, control participants who were given the same instructions, but never received the opportunity to avoid, displayed significantly lower startle responses during test compared to the start of the experiment, indicating a decrease in fear of the heat stimulus (see supplementary material in appendix 3.A). This was not the case for the avoidance group.

Particular strengths of this study are not only the successful replication of our previous findings (van Vliet et al., 2018), corroborating the validity of the paradigm to investigate the effects of pain avoidance on fear and the underlying mechanisms, but also the mediation analysis confirming the mediating role of perceived harmfulness of pain in the relationship between avoidance behaviour and fear. Another methodological strength of this study is the operationalization of the avoidance behaviour, whereby we created the illusion that participants could avoid the maximum pain by pressing a stop-button, although in reality and unknown to the participants, the intensity and duration of the heat stimulus was independent of the avoidance response. However, there are also some limitations. Firstly, although we mentioned this as one of the strengths of this study, at the same time, the way we operationalised the avoidance can also be seen as a limitation for interpretation of the results in view of the fear-avoidance model of chronic pain, because simply pressing a stop-button with no associated cost is not ecologically

valid. For chronic pain patients, avoidance behaviour typically comes with a cost of limitations in daily functioning, and usually they have more to lose than to gain with their avoidance behaviour. However, one could argue that in real-life both low-cost (e.g. avoiding a simple movement) and high-cost responses (e.g. not participating in valued life activities) are observed in avoidance behaviours of chronic pain patients. We assume the underlying mechanisms of the effects of low- and high-cost responses on pain-related fear and threat to be similar. This study, in which we used a low-cost avoidance response (pressing a stop-button), showed effects of this low-cost response on the levels of pain-related fear and threat. Similarly, in real-life we can also observe low-cost avoidance behaviours of chronic pain patients, like carrying pills, just in case pain would increase. These low-cost avoidance behaviours in chronic pain patients could likewise increase pain-related fear and threat (Vervliet & Indekeu, 2015). Secondly, we chose to give the avoidance instructions to both groups, which might have created frustration in the control group, as they expected the opportunity to avoid the maximal painful stimulation, but never received the opportunity to do so. Unfortunately, we did not include a measure of frustration, and cannot be sure whether and how this may have affected our primary outcomes. However, the results of the control group were similar to our previous study (van Vliet et al., 2018), where no avoidance instructions were given to the control group. Thirdly, this study included pain-free participants. Therefore, one should be cautious in generalizing these findings to individuals with persistent pain. Future studies need to validate these findings using clinical samples. Fourthly, the results of this study are based on a very specific situation. Participants in the avoidance group believed they avoided the maximal pain while the heat stimulus was slowly increasing in temperature. Future studies should consider different experimental pain paradigms to test generality across pain modality. Fifthly, although we gave the instruction to press the stop-button upon the presentation of a cue to avoid receiving increased pain, we did not record these avoidance responses, but based on observation of the participants during the experiment, most of the participants followed the instruction and pressed the stop-button.

Finally, please note in general the effect sizes were relatively small and the results were obtained in a heavily controlled environment. Therefore, some caution is warranted in the interpretation of the results.

In conclusion, we corroborated previous finding that avoidance behaviour reduces pain, but increases pain-related fear when the avoidance option is lost. Additionally, we experimentally demonstrated that the increase of pain-related fear after previous avoidance behaviour is mediated by the threat appraisal of the painful stimulus. These findings suggest a more complicated and interdependent relationship between pain-related fear, avoidance behaviour, and threat than the unidirectional relationships originally proposed in the fear-avoidance model. One of the issues according to the fear-avoidance model is the persistence of avoidance behaviour, even if this behaviour is no longer functional. Indeed, chronic pain patients often continue avoiding movements/activities, because they are afraid that these movements amplify their pain or have detrimental consequences. The results of our study indicate that when the avoidance response is no longer available, initially there is a significant increase of pain-related fear, whereas repeated experience of the pain without the avoidance behaviour significantly reduces pain-related fear. These data support the use of exposure therapy to reduce pain-related fear in chronic pain patients. As a result, allowing avoidance behaviours in clinical therapy for chronic pain may preserve threat and impede fear reduction (Meulders, Van Daele, Volders, & Vlaeyen, 2016). Tackling avoidance behaviour to reduce fear seems as important as reducing fear to halt the process of chronicity in individuals with chronic pain. This can be realized by response prevention during repeated exposure to the painful stimuli as was done in the control condition of the current study, or by introducing rewards for the decision to perform painful movements (Claes, Karos, Meulders, Crombez, & Vlaeyen, 2014).

Finally, the current findings can potentially help to further our understanding of how avoidance can maintain pain problems, and therefore we propose an updated fear-avoidance model with a bidirectional relationship between pain-related fear and avoidance behaviour mediated by threat appraisals of pain.

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Appendix

3.A Supplementary material

Results startle analysis per phase

We performed a 2 Group (avoidance, control) x 2 Probe (during stimulation, ITI) x 3 Phase (full intensity, intervention, test) RM ANOVA on the startle data to check if we would find similar results as when we analysed the startle on trial-level.

Figure 3.A.1 displays the mean fear potentiated startle amplitudes for both groups separately for every phase. The RM ANOVA revealed a significant main effect of Group, $F(1,64) = 4.33$, $p < .05$, $\eta_g^2 = .005$. Also a significant main effect of Phase, $F(1.65, 105.38) = 8.90$, $p < .001$, $\eta_g^2 = .04$, and Probe, $F(1,64) = 239.33$, $p < .0001$, $\eta_g^2 = .54$, was observed. Furthermore, the Probe x Phase interaction reached significance, $F(2, 128) = 8.31$, $p < .001$, $\eta_g^2 = .04$. The following interactions did not reach significance: Group x Phase interaction, $F(2, 128) = 1.24$, $p = .29$; Group x Probe interaction, $F(1, 64) = 0.0005$, $p = .98$; Group x Phase x Probe interaction, $F(2, 128) = 1.33$, $p = .27$.

Similar to the analyses in the main manuscript, the startle amplitudes elicited during stimulation were higher than the startle amplitudes elicited during ITI. To test our hypothesis that pain-related fear would increase after avoidance behaviour, planned contrasts were performed evaluating the changes from the full intensity phase to the test phase. The avoidance group did not show an increase in mean fear potentiated startle amplitudes from the full intensity phase to the test phase, $t(256) = 0.18$, $p = .86$. However, the control group showed a significant decrease in mean startle amplitudes from the full intensity phase to the test phase, $t(256) = -3.01$, $p < .01$.

In sum, we do not find the increase in mean startle amplitudes after avoidance when we analyse the data on phase-level instead of trial-level. However, we do find that participants who never had the opportunity to avoid have a significantly lower mean startle amplitude during the test phase compared to the full intensity phase.

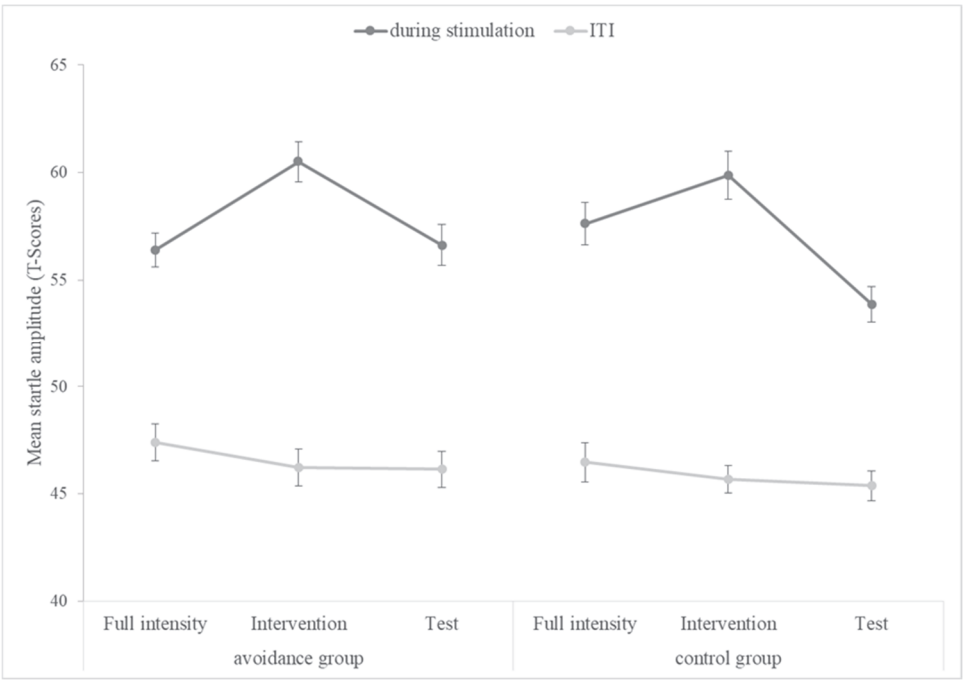

Figure 3.A.1. Mean startle amplitudes for the avoidance group (left panel) and the control group (right panel) for each phase during stimulation and during ITI. The raw scores from the startle measures were converted to Z-scores to account for inter-individual differences. For better visualization of the data, the Z-scores were transformed to T-scores, to avoid negative values on the Y-axis.

Table 3.A.1. *F-statistics of the simple main effects of the Probe x Trial interaction.*

Trial	*df*	*F*-statistic	p-value
1	1, 130	25.42	<.0001
2	1, 130	37.71	<.0001
3	1, 130	80.02	<.0001
4	1, 130	122.30	<.0001
5	1, 130	93.39	<.0001
6	1, 130	51.41	<.0001
7	1, 130	61.20	<.0001
8	1, 130	35.19	<.0001
9	1, 130	37.81	<.0001

Results threat appraisals

Prospective threat appraisals. The RM ANOVA on the prospective threat appraisal ratings revealed a main effect of Trial, indicating that the threat ratings changed throughout the experiment, $F(3.65, 233.60) = 10.09$, $p < .0001$, $\eta_g^2 = .01$. There was no significant main effect of Group, $F(1, 64) = 0.28$, $p = .60$. Furthermore, the Group x Trial interaction effect for prospective threat appraisal ratings failed to reach significance, $F(3.65, 233.60) = 0.56$, $p = .67$.

Retrospective threat appraisals. The RM ANOVA on the retrospective threat appraisals ratings revealed a main effect of Trial, indicating that the retrospective threat appraisal ratings changed throughout the experiment, $F(3.84, 245.61) = 6.20$, $p < .001$, $\eta_g^2 = .004$. There was no significant main effect of Group, $F(1, 64) = 0.35$, $p = .56$. Furthermore, the Group x Trial interaction term was not significant, $F(3.84, 245.61) = 0.94$, $p = .44$.

Chapter 4

Changes in pain-related fear and pain when avoidance behaviour is no longer effective

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Abstract

Avoidance is considered key in the development of chronic pain. However, little is known about how avoidance behavior subsequently affects pain-related fear and pain. We investigated this using a robotic arm-reaching avoidance task. In a between-subjects design both Experimental Group (n = 30) and Yoked Control Group (n = 30) participants perform either of 3 movement trajectories (T1–T3) to reach a target location. During acquisition, only participants of the Experimental Group could partially or fully avoid a painful electrocutaneous stimulus by choosing the intermediate trajectory (T2; 50% reinforcement) or the longest trajectory (T3; 0% reinforcement) versus the shortest trajectory (T1: 100% reinforcement). After acquisition, contingencies changed (all trajectories 50% reinforced), and the acquired avoidance behavior no longer effectively prevented pain from occurring. The Yoked Control Group received the same reinforcement schedule as the Experimental Group irrespective of their behavior. When avoidance behavior became ineffective for the Experimental Group, pain-related fear increased for the previously safe(r) trajectories (T2 and T3) and remained the same for T1, whereas pain threshold and tolerance declined. For the Yoked Group, pain-related fear increased for all trajectories. The Experimental Group persisted in emitting avoidance behavior following the contingency change, albeit at a lower frequency than during acquisition.

Perspective: results indicate participants become more afraid of and sensitive to pain, when previously acquired avoidance is no longer effective. Also, participants continue to show avoidance behavior despite it being not adaptive anymore. These findings suggest that ineffective avoidance may play a role in the maintenance and development of chronic pain.

4.1 Introduction

When one is confronted with acute pain, trying to avoid subsequent exposure to the presumed nociceptive stimulus is an adaptive strategy potentially preventing (further) injury. However, in chronic pain where there is often no objectifiable injury, avoidance becomes maladaptive, and disconnected from its initial function. The fear-avoidance model describes how chronic pain may develop after an acute pain episode. If an individual appraises the pain experience as threatening, defensive behaviours might spiral into a vicious and self-perpetuating cycle that promotes avoidance behavior, leading to disability, negative affect and pain (Vlaeyen & Linton, 2000; 2012). In addition, avoidance prevents the individual to learn that pain is not a signal of actual bodily harm anymore (Zettle et al., 2005). Avoidance can be acquired through instrumental conditioning, in which the response prevents an aversive outcome from occurring (Pierce & Cheney, 2008). Commonly, avoidance is viewed unidirectionally, as instigated by fear, and to result in fear reduction (Maia, 2010; Mowrer, 1947). However, van Vliet and colleagues proposed that engaging in pain-avoidance may increase, rather than decrease pain-related fear when the avoidance response is no longer available, suggesting a bidirectional relationship between fear and avoidance (van Vliet, Meulders, Vancleef, Vlaeyen, 2018). Other studies suggest that engaging in avoidance behaviour may bear threat-inducing properties (Engelhard, van Uijen, van Seters, & Velu, 2015; Gangemi, Manicini, van den Hout, 2012). However, experimental research on the consequences of avoidance behaviour in (chronic) pain is scarce.

Persistent avoidance is a key factor of chronic pain and is often resistant to extinction (Treanor & Barry, 2017). When an individual experiences pain when performing a certain movement, they may learn to associate this movement with potential harm and therefore avoid this and similar movements in the future (van Meurs, Wiggert, Wicker, & Lissek, 2014). Due to persistent avoidance, there are fewer opportunities to disconfirm existing expectancies and beliefs about the initial pain-associated movement (Crombez, Vlaeyen, Heuts, & Lysens, 1999), which can lead to initiating a pathway to functional disability in individuals with chronic pain (Vlaeyen & Linton, 2000; 2012).

In chronic pain, pain-avoidance is often ineffective (Treede et al., 2019). For example, resting at home, rather than going out with family, may be an attempt to reduce pain. In reality, such avoidance behaviour can be ineffective as it will not necessarily result in pain reduction. Little is known about the consequences of ineffective avoidance attempts on the pain experience itself. Studies suggest that successfully controlling pain through avoidance would reduce pain, whereas failure to control pain would increase pain even more than never having been able to control the pain (Crombez, Eccleston, De Vlieger, van Damme, & De Clerq, 2008; Janssen, Spinhoven, & Arntz, 2004).

Here, we aim to investigate (1) the effects of ineffective avoidance of a painful stimulus on subsequent pain-related fear and pain, and (2) whether avoidance behaviour persists despite its ineffectiveness. We operationalize ineffective avoidance as rescheduling the instrumental contingencies such that the emitted avoidance behaviour no longer results in the "no-pain outcome". In other words, the aversive event occurred regardless of responding, which is one form of operant extinction of avoidance (Dymond, 2019). Experimental Group participants acquire avoidance behaviour during a robotic arm-reaching avoidance task (Meulders, Franssen, Fonteyne, & Vlaeyen, 2016), in which participants can choose to perform movements that are either followed by a painful stimulus in 100% of the trials (T1), in 50% of the trials (T2) or never followed by a painful stimulus (T3). In a subsequent phase, Experimental Group participants can no longer effectively avoid the painful stimulus, because now each movement (T1-T3) was followed by a painful stimulus 50% of the trials. Yoked Control Group participants never have the opportunity to effectively avoid the painful stimulus.

Our first hypothesis is that pain-related fear increases when previously effective avoidance behaviour becomes ineffective. Second, we hypothesize that Experimental Group participants, who have acquired effective avoidance behaviour during the acquisition phase will emit more avoidance behaviour during the ineffective avoidance compared to the Yoked Control Group. Third, we investigate the relation between avoidance and pain measures. We explore whether pain threshold and tolerance decline when previously acquired avoidance becomes ineffective.

4.2 Methods

4.2.1 Participants

A total of 60 healthy, pain-free volunteers participated in this study (33 females; mean (range) ± SD age = 25.45 (18-56) ± 6.81 years). Participants were recruited at KU Leuven, using social media and distribution of flyers around the campus. Psychology students received a course credit for participation; other participants received a monetary compensation of €6. Participants were excluded if they reported to suffer from any cardiovascular disease, chronic pain conditions, pain at the dominant forearm, impaired, uncorrected vision, medical advice to avoid stressful situations, psychiatric disorders (current or in the past), neurological conditions or were pregnant. Participants were assigned to the Experimental Group (n=30, 15 females) or the Yoked Group (n=30, 18 females) via block randomisation, with restriction that the first two participants in the block were always assigned to the Experimental Group.

4.2.2 Apparatus and stimulus material

HapticMaster

The HapticMaster (HM) is a 3-degrees of freedom, force-controlled robotic arm (Moog Inc. FCS Robotics, East Aurora, New York, USA) and allows for a wide range of movement. Due to the force controlled haptic interface, weight and force can be simulated, mimicking real-life movements. In the current study, movements were restricted to the horizontal plane with depth of 0.35m and a 1m radius. The position of the HM was consistently logged so it could be used as input for the painful stimulus presentation.

Stimulus material

An electrocutaneous stimulus of 2 milliseconds duration served as the painful stimulus. The stimulus was delivered by a commercial stimulator (DS7A, Digitimer, Welwyn Garden City, England), using bar electrodes filled with K-Y gel that were attached to the triceps tendon of the right arm; the same arm was used to perform the reaching task with the robotic arm. Note that a calibration procedure was carried out to determine individual pain threshold and a stimulation that is painful and takes effort to tolerate (from now on

referred to as the pain tolerance level) for each participant (see calibration phase). The pain tolerance level during the initial calibration phase was used as the painful stimulus throughout the experiment.

Software

The experiment was run on a Windows 7 Professional (Microsoft Corporation Redmond, WA, USA) 64 bit Dell Latitude 6420 computer (Dell Inc., Round Rock, TX, USA) with 4 GB RAM, CPU: I5-2520M at 2.5GHz and programmed in C/C++. All data recording and processing was performed using a commercial software package (MATLAB version, The MathWorks Inc. Natick, MA, USA, 2000).

4.2.3 Study protocol

The experiment was conducted during a single 45-min session and consisted of the following phases: preparation, calibration, practice, acquisition, recalibration-I, ineffective avoidance, and recalibration-II. We included the recalibration phases throughout the experiment to explore whether pain threshold and pain tolerance change when previously acquired avoidance becomes ineffective. We used a between-subjects design including an Experimental Group that received the predefined movement trajectories-pain contingencies, and a Yoked Control Group that received the same reinforcement schedule as the Experimental Group irrespective of the chosen movement trajectories. After the experiment, participants completed the fear of pain questionnaire (FPQ-III-NL; van Wijk & Hoogstraten, 2006).

4.2.4 Robotic arm-reaching task

Participants executed reaching movements with their right arm using the HM. The reaching task consisted of moving a “green ball” from the starting point to the target location (see Figure 4.1 for a schematic representation). The task was framed as a movement task, and not as a game in the sense that no reward was provided. Participants could choose one of the three movement trajectories (T1-T3), indicated by separate arches positioned in the middle of the movement plane, to reach the target location. During the task, a painful stimulus was delivered based on the trajectory that was chosen

when the "green ball" had just passed through the trajectory arch. The HM is programmed such that there is a linear relationship between the resistive force and the lateral displacement of the robotic arm. When the target location is reached via trajectory T1, which has the least lateral displacement, no force is exerted. When the target location is reached via trajectories T2 and T3, respectively moderate and strong resistance is applied by the HM. In order to standardise the effort needed to perform the movements in the different trajectories, we corrected for participants' maximal arm extensor force with the HM, measured with a hand grip manometer (HHD microFET2; Hoggan Health Industries Inc, Jordan, UT). The strong resistance matched their maximal arm extensor force, while the moderate resistance matched half of their maximal extensor force.

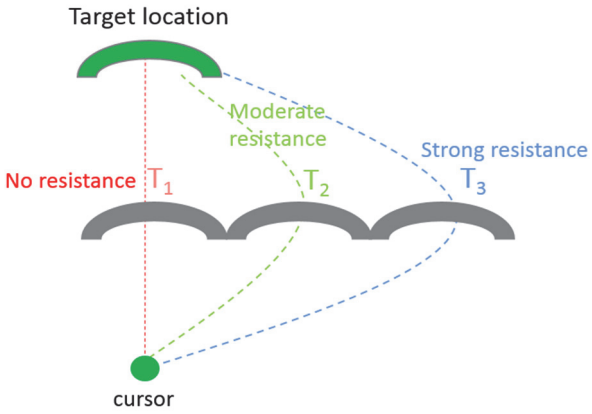

Figure 4.1. Robotic arm-reaching task, showing the different trajectories: T1, T2, T3, from left to right.

Preparation phase. Upon arrival in the lab, participants received oral and written information about the experiment. Participants were informed that they would be exposed to painful electrocutaneous stimuli, but that the stimulus intensity would be individually determined during the calibration phase. All participants provided a written informed consent, which emphasized that they were allowed to decline participation at any time during the experiment without any consequences. The Social and Societal Ethics Committee of KU Leuven approved the experimental protocol (reg. #: G-2017 01 745).

Calibration phase. Participants were seated in an armchair placed in a sound- and light-attenuated experimental room. After the stimulation electrodes had been attached, the calibration procedure of the electrocutaneous stimulus was initiated. The calibration procedure involved the presentation of a series of stimuli of increasing intensity while participants were asked to indicate the pain intensity of each stimulus on an 11-point Likert scale ranging from 0 to 10 (0 = 'you feel nothing', 1 = 'you feel something but this is not painful, it is merely a sensation', 2 = 'this sensation is unpleasant but not painful', up to 10 = 'the worst tolerable pain'). Two subjective stimuli were targeted: the pain threshold corresponding with 3 (3 = 'the moment that the electrocutaneous stimulus becomes painful') and the pain tolerance corresponding with 8 (8 = 'significantly painful and demanding effort to tolerate'). This stimulus intensity (pain tolerance) was used as the painful stimulus throughout the experiment. Note that all participants were informed that they were free to notify the experimenter at any time if they did not want to receive the stimulus anymore or if they wanted the amplitude to be set back to a lower intensity during the calibration procedure.

Practice phase. During this phase the experimenter instructed the participant to perform each trajectory four times using the robot arm (12 trials in total). Participants were instructed to start one of the three movements as soon as they heard an auditory start signal and saw a visual start signal (=on-screen presentation of a manikin with flag). The end of a trial was indicated by an auditory stop signal together with a visual stop signal (= on-screen presentation of a red stop sign), the latter remained on the screen when the HM repositioned to the starting location and prompted the participant to let go of the HM. After returning to its initial position, the robotic arm remained fixed until the start of the next trial (intertrial interval = 3 seconds). Participants were also trained to provide verbal ratings using a Windows 7 compatible triple foot switch (USB-3FS-2; Scythe, Tokyo, Japan). During this phase, no painful stimuli were administered, but the resistive force of the HM as described above was applied.

Acquisition phase. Instructions reminded participants to move the HM freely over one of the available trajectories when prompted by the starting signal. Two blocks of 24 movements (ACQ1-2; 48 movements in total) were run. In each phase, a counter on the screen indicated the number of successful movements/trials the participants had completed (i.e. a counter increasing with one unit after each successful movement, starting at 0). During this phase the Experimental Group participants always received a painful stimulus during the shortest trajectory (T1), while for the intermediate trajectory (T2), they only received a painful stimulus in 50% of these movements, and for the longest trajectory (T3) they could avoid the pain stimulus from occurring (i.e. effective avoidance). Participants in the Yoked Control Group were matched with participants in the Experimental Group. When a certain participant in the Experimental Group received a painful stimulation on a given trial, a participant in the Yoked Control Group received a painful stimulation on the same trial, irrespective of which trajectory was chosen. This created an arrangement in which only the Experimental Group learned to avoid the painful stimulus, while the Yoked Control Group did not have that opportunity.

Recalibration phase I. This phase was similar to the initial calibration phase to determine whether pain threshold and pain tolerance had changed. Please note that after the recalibration phase, the original pain tolerance level was again used to continue the conditioning procedure.

Ineffective avoidance phase. The instrumental contingencies were rescheduled for the participants in the Experimental Group. In this phase, participants had a 50% chance of receiving a painful stimulus for each movement trajectory. This contingency change ensured that the previously effective avoidance behaviour (T3 = 0% reinforcement) now became ineffective (T3 = 50% reinforcement). The reinforcement schedule for the moderately difficult movement trajectory T2 remained the same as before (T2 = 50% reinforcement), and the previous pain-associated trajectory (T1 = 100% reinforcement), became a safer movement trajectory (T1 = 50% reinforcement).

As in the previous phases the Yoked Control Group also received the same number of painful stimuli irrespective of the movements they made. Again two blocks of 24 movements were run (IA1-2; 48 movements in total).

Recalibration phase II. This phase was identical to Recalibration phase I.

Extensor strength measurements

Individuals may differ in the force they can produce with their arms. Individuals with greater arm extensor muscle strength need less effort to perform a movement with higher resistance (i.e. T3). In order to standardise the effort needed to perform the movements in the different trajectories, we corrected for participants' maximal arm extensor force with the HM. Before the experiment, we measured the triceps extension force in Newton (N) with a Hand-Held Dynamometer (HHD microFET2; HOGGAN Health Industries Inc., Jordan, UT, USA). The mean force of the current sample was 100.92N (*SD* = 38.86; range = 50-190N).

4.2.5 Outcome measures

Verbal ratings: pain-related fear, pain expectancy, pain intensity and avoidance

After each block of 24 movements, participants reported pain-related fear, pain expectancy and pain intensity for each of the trajectories. The corresponding trajectory arch was coloured yellow to indicate to which movement trajectory the questions pertained. The questions assessing pain-related fear, pain expectancy and pain intensity were the following: 1) *"How afraid were you to move through the yellow-coloured arch?"*, 2) *"To what extent did you expect an electrical stimulus when moving through the yellow-coloured arch?"*, and 3) *"How painful was moving through the yellow-coloured arch?"*. The pain intensity question was included to investigate whether participants experienced a 100% reinforced movement as more painful than a 50% reinforced movement. Upon review of the outcome measures, we noted the responses to the question for the pain intensity ratings were difficult to interpret and did not result in a meaningful outcome. The data suggest that Experimental Group participants did not discriminate between T1 and T2 on how painful the movement was during acquisition

phase, although we would have expected that participants rate T1 (100% reinforced) as more painful than T2 (50% reinforced). This could be related to the formulation of the question, whereby the participants may have been confused between the pain intensity of the stimulus itself (independent of probability of occurring) and the probability of receiving a painful stimulus during the movement. For now, the results of the pain intensity ratings will be added as supplementary material in Appendix 4.A (Figure 4.A.1 and Table 4.A.1). Additionally, participants rated to what extent they felt that they could avoid the painful stimulus overall during the block: 4) *"To what extent could you avoid the painful stimulus?"*. Answers were given using the foot switch on a numerical rating scale from 0 to 10 with the respective labels 0 = "not afraid at all" and 10 = "extremely afraid", 0 = "not painful at all" and 10 = "extremely painful", and 0 = "not at all" and 10 = "very much".

Behavioural avoidance: maximal deviation and movement choice

Avoidance behaviour was measured through the maximal deviation from the shortest trajectory T1. Maximal deviation refers to the point on the trajectory furthest away from the shortest trajectory from starting point to the target location. This information was automatically logged by the HM. Because of the continuous nature of this avoidance measure, we also explored the discrete variable movement choice (T1-3). On each movement trial, we recorded which movement trajectory was selected by the participant. We calculated how many times each trajectory was selected per group and phase. This variable indicates the proportions of the chosen movement trajectories per phase.

Pain threshold and pain tolerance

Pain threshold and tolerance were assessed in mA during the (re)calibration phases as described above. ("pre-acquisition" = calibration phase; "avoidance acquisition" = recalibration-I; "ineffective avoidance" = recalibration-II).

4.2.6 Data analysis overview

First, descriptive statistics of the sample, questionnaire scores (FPQ-III-NL) and reinforcement schedules of the trajectories were computed. Second, as a prerequisite for examining the effects of ineffective avoidance, we tested whether the Experimental Group participants successfully acquired avoidance behaviour. We carried out the following manipulation checks: we performed a series of 2 x 2 x 3 Group (Experimental, Yoked Control) x Block (ACQ1-2) x Trajectory (T1-3) RM ANOVAs on pain expectancy, and pain-related fear ratings. Planned comparisons for the different trajectories were performed within groups to test acquisition of pain expectancy and pain-related fear for T1 > T2 > T3 in the Experimental Group, while for the Yoked Control Group we expected no differentiation between the different trajectories, T1 = T2 = T3. Furthermore, we performed separate 2 x 2 Group (Experimental, Yoked Control) x Block (ACQ1-2) RM ANOVAs on the avoidance ratings and maximal deviation. We expected the Experimental Group to indicate that they could avoid the painful stimulus during acquisition while the Yoked Control Group would indicate they could not avoid the painful stimulus. We expected the Experimental Group to show larger maximal deviation from the shortest trajectory during acquisition compared to the Yoked Control Group.

Second, as manipulation check we performed a 2 x 2 x 3 Group (Experimental, Yoked Control) x Block (IA1-2) x Trajectory (T1-3) RM ANOVA on pain expectancy to investigate whether Experimental and Yoked Control group participants differ. Additionally, we carried out a 2 x 2 Group (Experimental, Yoked Control) x Block (IA1-2) RM ANOVA on the avoidance ratings to test whether the Experimental and Yoked Control Group did differ in the feeling they could effectively avoid the painful stimulus.

Third, to test our first hypothesis, whether pain-related fear increases when previously acquired avoidance behaviour becomes ineffective, we performed a 2 x 3 x 4 Group (Experimental, Yoked Control) x Trajectory (T1-3) x Block (ACQ1-2, IA1-2) RM ANOVA on the pain-related fear ratings. We assessed the following: (1) Is there an increase in pain-related fear from $T2_{ACQ2}$ (T2=50%-reinforcement) to $T2_{IA1}$ (T2=50%-reinforcement) in the Experimental Group? This is the crucial test of our hypothesis, because the reinforcement schedules for T2 are identical in both phases in the

Experimental Group. In other words, an increase in pain-related fear for T2 during the ineffective avoidance phase in the Experimental Group cannot be explained by a change in contingencies from acquisition to ineffective avoidance; (2) Is there a decrease in pain-related fear from $T1_{ACQ2}$ (100%-reinforcement) to $T1_{IA1}$ (50%-reinforcement) in the Experimental Group? We expect this decrease of pain-related fear based on the rescheduling of contingencies; (3) Is there an increase in pain-related fear from $T3_{ACQ2}$ (0%-reinforcement) to $T3_{IA1}$ (50%-reinforcement) in the Experimental Group? We expect this increase of pain-related fear based on the rescheduling of contingencies during the ineffective avoidance phase. We expected the Yoked Control Group to indicate no changes in pain-related fear, because their avoidance behaviour was always ineffective.

To test our second hypothesis, that the Experimental Group participants will persist in emitting avoidance behaviour once the avoidance behaviour is no longer effective, we performed the following analysis: we conducted a 2 x 4 Group (Experimental, Yoked) x Block (ACQ1-2, IA1-2) RM ANOVA on the maximal deviation. We expect the Experimental Group to show larger maximal deviation during ineffective avoidance phase compared to the Yoked Control Group. Furthermore, we investigated the movement choice of the Experimental and Yoked Control Group. During the ineffective avoidance phase, we compared the proportion of T3 performance (the previously effective avoidance behaviour) between the two groups. We used the chi-squared (χ^2) test statistic to determine if there were significant differences between the proportions of T3 performance during the ineffective avoidance phase, between the groups.

Finally, we explored the effects of effective and ineffective avoidance behaviour on pain threshold and pain tolerance. We performed a 2 x 3 Group (Experimental, Yoked) x Time (pre-acquisition, avoidance acquisition, ineffective avoidance) RM ANOVAs on the pain thresholds and pain tolerance.

For each significant RM ANOVA effect, η_g^2 is reported. η_g^2 is the recommended effect size statistic for repeated measures designs (Bakeman, 2005). In case of violation of sphericity, Greenhouse-Geisser corrections were applied by correcting the degrees of freedom. All statistical tests are considered significant at $p < .05$.

Holm-Bonferroni corrections were applied to correct for multiple comparison testing. Statistical analyses for all dependent measures were run with R software (RStudio, version 1.0.153).

4.3 Results

4.3.1 Descriptive statistics of the sample

Groups did not differ on physical intensity of the painful electrocutaneous stimulus selected during the initial calibration (Threshold Experimental Group: 10.40 ± 4.30 mA; Threshold Yoked Control Group: 10.67 ± 4.26 mA, $t(58) = -0.25$, $p = .80$; Tolerance Experimental Group: 25.37 ± 13.41 mA; Tolerance Yoked Control Group: 26.4 ± 11.95 mA, $t(58) = 0.31$, $p = .75$). Groups also did not differ on the force that was selected for the trajectories based on the triceps extension measure (force Experimental Group: 105.27 ± 39 N; force Yoked Control Group: 96.57 ± 38 N, $t(58) = 0.45$, $p = .65$). There were no significant differences in fear of pain as measured by the FPQ-III-NL between groups (see Appendix 4.A, Table 4.A.2).

During the acquisition phase, the Experimental Group followed a reinforcement schedule with either 100% (T1), 50% (T2) or 0% (T3) reinforcement and in our case, this resulted in the Experimental Group receiving a painful stimulus in 29% of the trials. The Yoked Group was only yoked in matching the same overall number of painful stimuli as the Experimental Group and therefore, they received a painful stimulus in 29% of their trials. During the ineffective avoidance phase, reinforcement schedules for both groups were the same (T1 = T2 = T3 = 50%).

4.3.2 Manipulation checks

Acquisition phase

The analysis of pain expectancy during acquisition revealed a significant main effect for Group, $F(1, 58) = 14.78$, $p < .001$, $\eta_g^2 = .07$, and Trajectory, $F(2, 116) = 70.67$, $p < .001$, $\eta_g^2 = .30$. Furthermore there was a significant Group x Trajectory interaction, $F(2, 116) = 63.59$, $p < .001$, $\eta_g^2 = .28$, suggesting that pain expectancy ratings for the different trajectories differ between the Experimental Group and the Yoked Control Group. At the

end of the second acquisition block (ACQ2) the participants in the Experimental Group expected the painful stimulus more during T1 *vs*. T2, $t(224.4) = 4.1$, $p < .0001$; T1 *vs*. T3, $t(224.4) = 12.81$, $p < .0001$; and T2 *vs*. T3, $t(224.4) = 8.71$, $p < .0001$, whereas there were no differences in pain expectancy between the three trajectories for the Yoked Control Group (see Figure 4.2).

The analysis of pain-related fear during acquisition revealed a main effect for Trajectory, $F(2, 116) = 38.86$, $p < .001$, $\eta_g^2 = .15$ and a significant Group x Trajectory interaction, $F(2, 116) = 50.65$, $p < .001$, $\eta_g^2 = .19$. At the end of the second acquisition block (ACQ2) the Experimental Group was more afraid of T1 *vs*. T2, $t(220) = 2.41$, $p < .05$; T1 *vs*. T3, $t(220) = 11.375$, $p < .0001$; and T2 *vs*. T3, $t(220) = 8.97$, $p < .0001$, whereas there were no differences in pain-related fear between the three trajectories for the Yoked Control Group (see Figure 4.3).

The analysis of avoidance ratings during acquisition revealed a significant main effect for Group, $F(1, 58) = 59.29$, $p < .0001$. The Experimental Group reported higher avoidance ratings compared to the Yoked Control Group, $t(235) = 7.70$, $p < .0001$. The analysis of maximal deviation during acquisition revealed a significant main effect for Group, $F(1, 58) = 60.69$, $p < .00001$, $\eta_g^2 = .37$. The Experimental Group avoided more during the two blocks of acquisition phase compared to the Yoked Control Group, $t(151.71) = 10.41$, $p < .0001$.

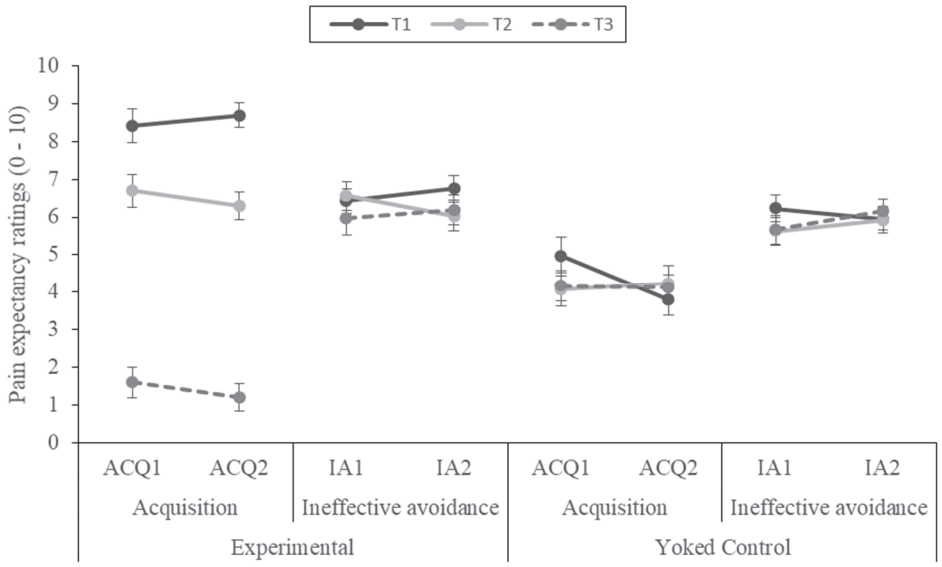

Figure 4.2. Pain expectancy ratings with standard error bars for the three trajectories (T1, T2, T3) during the acquisition and ineffective avoidance phase for the Experimental Group (left) and Yoked Control Group (right).

Ineffective avoidance phase

During the ineffective avoidance phase, the RM ANOVA of pain expectancy ratings did not show any significant main effects or interaction effects (see Figure 2). Additionally, there were no main and interaction effects for the RM ANOVA of avoidance ratings during the ineffective avoidance phase.

In conclusion, the manipulations checks confirmed that Experimental Group participants learned to effectively avoid during acquisition.

4.3.3 Hypothesis 1: pain-related fear increases when previously effective avoidance behaviour becomes ineffective

The analysis on pain-related fear ratings revealed a significant main effect of Block, $F(2.54, 147.49) = 50.98$, $p < .0001$, $\eta_g^2 = .13$, and a significant main effect of Trajectory, $F(2, 115.90) = 22.90$, $p < .0001$, $\eta_g^2 = .05$. The main effect of Group did not reach statistical significance, $F(1, 58) = 1.95$, $p = .17$.

However, the interaction Group x Trajectory x Block was significant, $F(5.31, 308.07) = 19.25$, $p < .0001$, $\eta_g^2 = .07$, suggesting that pain-related fear for different trajectories evolved differently in the Experimental Group and the Yoked Control Group over time (see Figure 4.3).

The crucial comparison in the Experimental Group from the acquisition phase to the ineffective avoidance phase, is the expected increase of pain-related fear from $T2_{ACQ2}$ (50%-reinforcement) to $T2_{AI1}$ (50%-reinforcement), reached significance $t(499) = 2.38$, $p < .05$, *Cohen's d* = 0.65. Following the contingencies, we expected a decrease in pain-related fear for the Experimental Group from $T1_{ACQ2}$ (100% reinforcement) to $T1_{AI1}$ (50%-reinforcement), however there was no significant difference between the pain-related fear ratings, $t(499) = -1.63$, $p = .10$. Finally, we did find a significant increase in pain-related fear for the Experimental Group from $T3_{ACQ2}$ (0%-reinforcement) to $T3_{AI1}$ (50%-reinforcement), $t(499) = 15.26$, $p < .0001$. The pain-related fear ratings of the Yoked Control Group, increased from the acquisition phase to ineffective avoidance phase for each trajectory: $T1_{ACQ2}$ to $T1_{AI1}$, $t(499) = 5.84$, $p < .001$; $T2_{ACQ2}$ to $T2_{AI1}$, $t(499) = 4.07$, $p < .001$ and $T3_{ACQ2}$ to $T3_{AI1}$, $t(499) = 3.53$, $p < .001$.

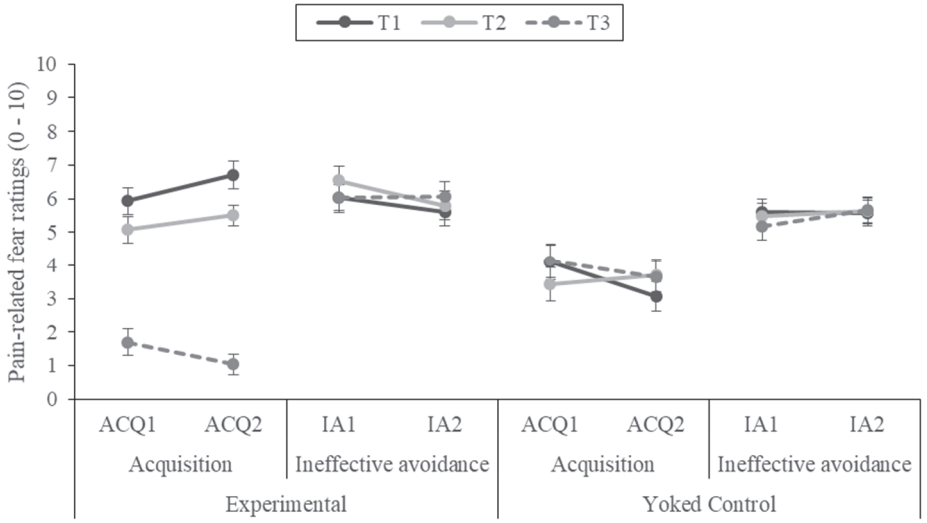

Figure 4.3. Pain-related fear ratings with standard error bars for the three trajectories (T1, T2, T3) during the acquisition and ineffective avoidance phase for the Experimental Group (left) and Yoked Control Group (right).

4.3.4 Hypothesis 2: Experimental Group participants who have acquired effective avoidance will emit more avoidance behaviour during the ineffective avoidance phase compared to the Yoked Control Group

The analysis on the mean maximal deviation data (see Figure 4.4) revealed a significant main effect of Group, $F(1, 58) = 60.69$, $p < .00001$, $\eta_g^2 = .37$. There was also a main effect of Phase, $F(3,174) = 31.08$, $p < .00001$, $\eta_g^2 = .19$. Furthermore, a significant interaction between Group and Phase emerged, $F(3,174) = 29.81$, $p < .00001$, $\eta_g^2 = .18$, suggesting that the difference in avoidance behaviour between the Experimental and Yoked Control Group changed over the course of the experiment. In line with our expectations, the Experimental Group performed more avoidance behaviour during the ineffective avoidance phase compared to the Yoked Control Group, $\text{Experimental}_{\text{IA1-2}}$ *vs.* $\text{Yoked}_{\text{IA1-2}}$: $t(151.71) = 2.75$, $p < .01$. However, there was a significant decrease in mean maximal deviation for the Experimental Group participants, within-contrast: ACQ2 *vs*. IA1: $t(174) = 9.81$, $p < .0001$. In other words, although there was more avoidance behaviour in the Experimental Group than in the Yoked Control Group, it declined from acquisition to ineffective avoidance phase for the Experimental Group, while no such changes were observed for the Yoked Control Group.

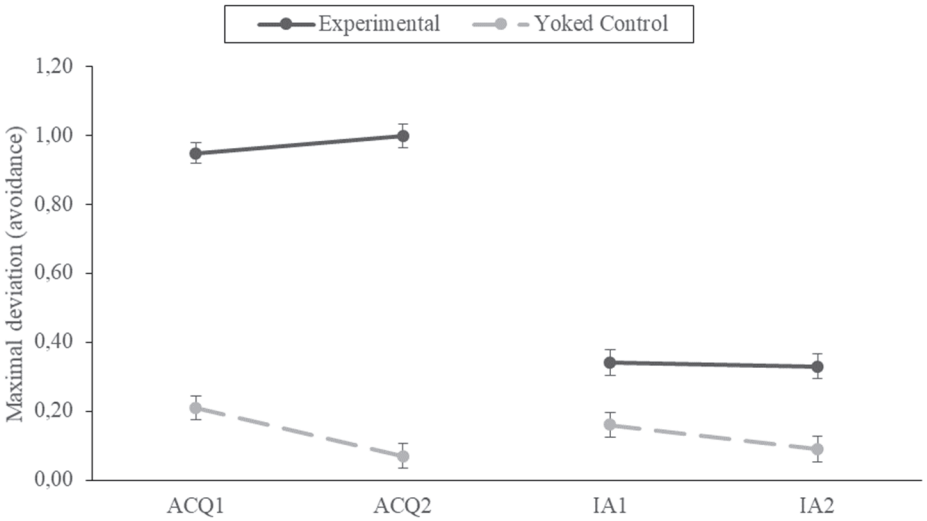

Figure 4.4. Mean maximal deviation with standard error bars from the shortest trajectory (T1) during acquisition (ACQ1, ACQ2), and ineffective avoidance (IA1, IA2) phase for the Experimental and Yoked Control Group separately.

To test whether the Experimental Group participants perform their previous effective avoidance behaviour more compared to the Yoked Control Group during the ineffective avoidance phase, we also compared the proportion of T3 performance. Proportion T3 trajectory performed during the ineffective avoidance phase for Experimental Group was 0.31 and for the Yoked Control Group 0.22, $\chi^2(1) = 7.551$, $p < .01$. Participants of the Experimental Group performed T3 in 31% of the trials of the ineffective avoidance phase and the Yoked Control Group performed T3 only in 22% of the trials of the ineffective avoidance phase (see Appendix 4.A Figure 4.A.2, for proportion of chosen trajectories for both groups).

4.3.5 Exploratory analyses: do pain threshold and pain tolerance decline when previously acquired avoidance becomes ineffective?

Pain threshold

The analysis on the pain thresholds (see Figure 4.5) revealed no main effects of Group or Time. However, the analysis yielded a significant Group x Time interaction, $F(1.80, 104.36) = 4.09$, $p < .05$, $\eta_g^2 = .01$, suggesting that pain thresholds for the two groups

evolved differently across time. Within-group comparisons confirmed that by the end of the experiment (ineffective avoidance) the pain threshold in the Experimental Group was significantly lower than at the start of the experiment (pre-acquisition), $t(116) = 2.70$, $p < .05$, and after the acquisition of avoidance behaviour (avoidance acquisition), $t(116)= 3.40$, $p < .01$, whereas no such differences emerged in the Yoked Control Group. However, after the Holm-Bonferroni correction for multiple testing, only the pain threshold at the end of the experiment was significantly lower than the pain threshold after avoidance acquisition (adjusted p-value = 0.017).

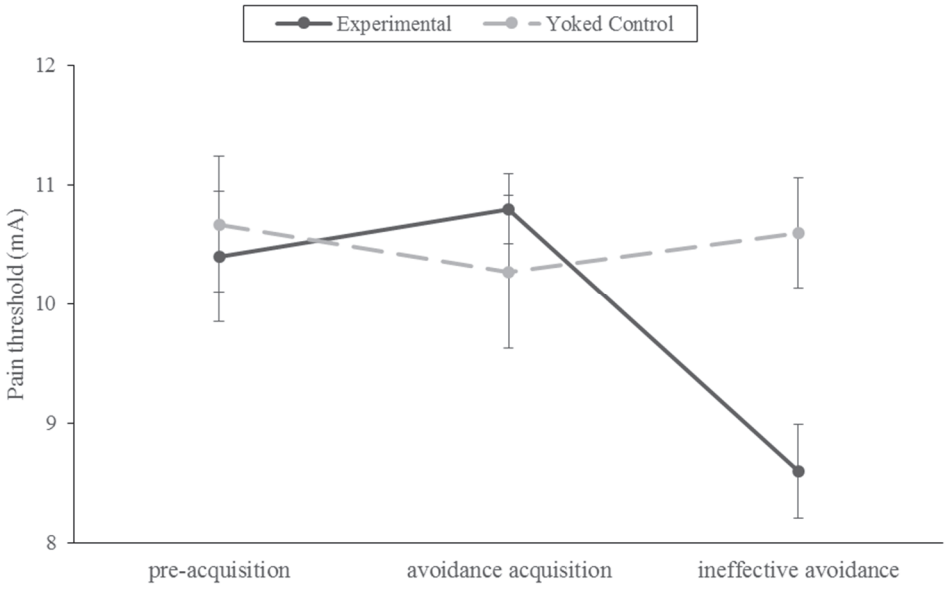

Figure 4.5. Mean maximal deviation with standard error bars from the shortest trajectory (T1) during acquisition (ACQ1, ACQ2), and ineffective avoidance (IA1, IA2) phase for the Experimental and Yoked Control Group separately.

Pain tolerance

The analysis on the pain tolerance levels (see Figure 4.6) revealed a significant main effect of Time, $F(1.58, 91.83) = 6.45$, $p < .01$, $\eta_g^2 = .02$. The Group x Time interaction just failed to reach significance, $F(1.58, 91.83) = 3.22$, $p = .06$. Again, all comparisons were corrected for multiple testing with the Holm-Bonferroni method and are considered significant with a p-value below .017 .

Within-comparisons confirmed that there was no significant difference in pain tolerance levels for the Experimental Group at the start of the experiment and after acquisition of avoidance behaviour, pre-acquisition *vs*. avoidance acquisition: $t(116) = 0.07$, $p = .99$. However, the pain tolerance significantly decreased when measured after the ineffective avoidance phase, when participants of the Experimental Group could not avoid anymore, pre-acquisition *vs*. ineffective avoidance: $t(116) = 3.10$, $p < .01$ and, avoidance acquisition *vs*. ineffective avoidance: $t(116) = 3.03$, $p < .01$. The Yoked Control Group showed an initial decrease in pain tolerance, pre-acquisition *vs*. avoidance acquisition: $t(116) = 2.46$, $p < .05$, but this did not further decrease in tolerance level after the ineffective avoidance phase (avoidance acquisition *vs*. ineffective avoidance: $t(116) = 1.98$, $p = .12$).

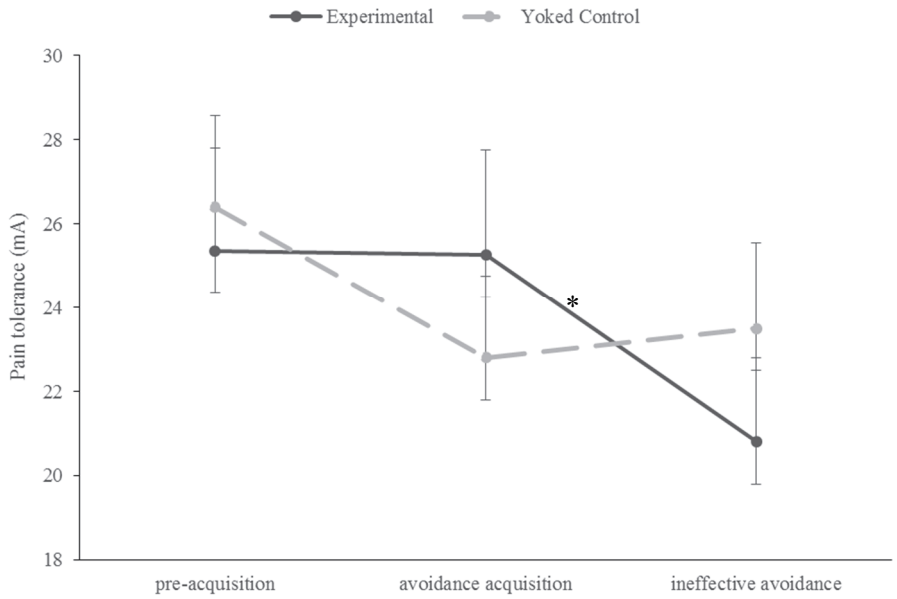

Figure 4.6. Pain tolerance with standard error bars at the start of the experiment (pre-acquisition), after the acquisition of avoidance (pre-ineffective avoidance), and after the ineffective avoidance phase (post-ineffective avoidance) for the Experimental and Yoked Control Group separately. * $p < .01$

4.4 Discussion

This study tested the effects of ineffective avoidance of a painful stimulus on pain-related fear, and pain. Avoidance is mainly intended to reduce anticipatory fear (Maia, 2010; Mowrer, 1947). It has been shown that avoidance increases pain-related fear when previously acquired avoidance behaviour ceases to avert a painful stimulus (van Vliet et al., 2018). Here, we: (1) investigated whether pain-related fear increases when avoidance behaviour becomes ineffective; (2) examined whether participants who learned to avoid, persist in emitting avoidance behaviour once the behaviour is ineffective; and (3) explored the effects of ineffective avoidance on pain measures.

First, the results indicate that Experimental Group participants learned to avoid painful stimuli by primarily performing the non-painful but most deviating and effortful trajectory (T3), in contrast to Yoked Control participants who primarily performed the shortest and easiest trajectory (T1), hereby demonstrating acquisition of avoidance in the

Experimental Group. Additionally, Experimental Group participants expected and feared the painful stimulus more when performing T1 *vs.* T2, and T2 *vs.* T3. No such differences occurred in the Yoked Control Group, as their movements were unrelated to any painful outcomes. The results of acquisition of avoidance behaviour, pain expectancy and pain-related fear replicate previous findings using the same paradigm (Meulders et al., 2016).

Second, our manipulation to render avoidance ineffective was successful. Experimental Group participants showed no differentiation in pain expectancy between trajectories when the contingencies were rescheduled to 50% reinforcement, similar to the Yoked Control participants. Furthermore, both groups reported not being able to effectively avoid painful stimuli during this phase.

In line with our expectations, Experimental Group participants reported higher pain-related fear when avoidance became ineffective, after successful avoidance acquisition. Specifically, pain-related fear increased for T2, while the reinforcement of this trajectory remained the same (T2=50% reinforcement). Pain-related fear for T1 remained high, while the chance of getting a painful stimulus during this trajectory decreased from 100% to 50%. Finally, pain-related fear increased for T3, which was now reinforced 50% instead of 0%. This observed increase and maintenance of pain-related fear during ineffective avoidance extends recent studies showing that engaging in avoidance and losing the opportunity to avoid increases fear and adds to prior evidence regarding a bidirectional relationship between fear and avoidance (Engelhard et al., 2015; van Vliet et al., 2018). A potential explanation for how ineffective avoidance may have maintained and increased pain-related fear could be the tendency to infer danger on the basis of (ineffective) avoidance, which is known as ex-consequentia reasoning (Gangemi et al., 2012). The availability of avoidance, albeit ineffective, may have led participants to infer danger starting a vicious cycle: avoidance could increase threat perception, resulting in an increase in pain-related fear, which in turn could increase avoidance behaviour, even when it is ineffective.

Furthermore, this increase of pain-related fear during ineffective avoidance is in line with the results of Crombez and colleagues, showing that losing control over pain resulted in more fear of the impending pain stimuli (Crombez et al., 2008). In our study, however, there also was an increase in pain-related fear for the Yoked Control Group

during the ineffective avoidance phase. This increase in pain-related fear can be explained by the increase of reinforcement for the different trajectories from the acquisition to the ineffective avoidance phase. For the Yoked Control Group reinforcement of each trajectory was 29% during acquisition, while during ineffective avoidance, reinforcement was 50%. This change in reinforcement schedule for the different trajectories was due to the matching of participants of the Experimental Group to participants of the Yoked Control Group. Future experiments should consider a slight change in paradigm, for example by using the actual contingencies of the Yoked Control Group during acquisition as the basis for the contingency during the ineffective avoidance phase for the Experimental Group. By doing so, the contingencies of the trajectories for the Yoked Control Group would not have changed, eliminating the potential confound in comparing both groups during the ineffective avoidance phase. Furthermore, we recommend future studies to include psycho-physiological measures of pain-related fear, such as eyeblink startle measurement, skin conductance, or cardiac assessment, in order to assess whether the increase in pain-related fear can also be found in these measures (Blumenthal, Cuthbert, Filion, Hackley, Lipp, & Van Boxter, 2005; Vlaeyen & Linton, 2000).

Our results seem to support our second hypothesis, that Experimental Group participants are more persistent in previously acquired, but now ineffective, avoidance despite the extra effort and time this behaviour takes, compared to Yoked Control participants. Although Experimental Group participants explored alternative trajectories during ineffective avoidance phase, they performed the previously learned, but now ineffective avoidance behaviour slightly more. A possible explanation is that the participants continued exploring all three trajectories, given the equal but ambiguous pain contingencies (50%). In addition, the individual's previous learning history (here, acquisition phase) may have influenced current avoidant decision-making (Krypotos, Effting, Arnoudova, Kindt, & Beckers, 2014; Xia, Dymond, Lloyd, & Vervliet, 2017), despite the reduced effectiveness of this behaviour (50%-pain). The participants learned that the costs of performing T3 (effort) are relatively low compared to the more salient cost of T1 (pain). This may have resulted in reduced extinction of avoidance behaviour (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). This persistence in avoidance

adds to the findings of Meulders and colleagues (Meulders et al., 2016). They found that participants were persistent in avoidance even though the contingencies no longer held, and no painful stimuli were delivered (extinction). Still, we cannot rule out that the ineffective avoidance behaviour of the Experimental Group would extinguish (i.e., become statistically equivalent to Yoked Control Group) with adding more movements during the ineffective avoidance phase.

Concerning our explorative analyses regarding the effects of ineffective avoidance on pain measures, we found that pain threshold and tolerance declined when avoidance became ineffective in the Experimental Group. These findings suggest that avoidance may be associated with unfavourable pain outcomes and adds to research which proposes that failure to control pain may increase pain or reduce pain tolerance in future circumstances (Crombez et al., 2008; Janssen et al., 2004; Masedo & Esteve, 2007; Zettle et al., 2005). Of interest is that Yoked Control participants, who never learned to effectively avoid pain, reported a lower pain tolerance during first recalibration, after acquisition phase, which may suggest pain sensitization as a result of uncontrollable pain. This finding corroborates with a study by Bräscher and colleagues (Bräscher, Becker, Hoeppli, & Schweinhardt, 2016). They found that uncontrollability of painful stimuli facilitates pain perception and pain processing. An increased sensitization of pain was reflected by increased activation in pain-processing regions in the brain.

A particular strength is the operationalisation of avoidance. We used a validated paradigm that allowed participants to perform avoidance during a robotic arm-reaching task (Claes, Vlaeyen, & Crombez, 2016; Janssens, Meulders, Cuyvers, Colloca, & Vlaeyen, 2019; Meulders et al., 2016). Previous studies operationalised avoidance by simply pressing a stop-button or moving a joystick with no associated costs (Engelhard et al., 2015; van Vliet et al., 2018; Vervliet & Indekeu, 2015). Here, to avoid the painful stimuli, Experimental Group participants performed the most deviating and effortful trajectory. The resistance used was tailored to each individual. By doing so, avoidance came with a cost, which is also the case in chronic pain and is more valid than avoidance with no associated costs. We assumed that our paradigm, especially the experimental manipulation of ineffective avoidance and its effects on pain-related fear and pain, would be a suitable experimental analogue to investigate the mechanisms of avoidance for

chronic pain patients. This procedure resembles operant extinction of avoidance by making the aversive event non-eliminable, while the opportunity to engage in avoidance remains (Dymond, 2019; Lattal, Peter, & Escobar, 2013). In spite of avoidance attempts, pain persists in chronic pain and avoidance now comes with the cost of restrictions in daily life activities. However, our operationalization of avoidance has limited ecological validity. Most of the costs for chronic pain patients are psychosocial in nature (e.g., decreased work/leisure), whereas the cost in the current paradigm is related to the effort needed to perform movements. However, we argue that the face validity and construct validity of our study is high. Not only is there phenomenological similarity between the behaviour in the model and the symptoms of chronic pain, the paradigm also recreates the etiological process of avoidance as a trade-off between lower risk of pain vs. higher risk of costs (Vervliet & Raes, 2013).

The fear-avoidance model proposes that pain-related fear and avoidance play a key role in the development of chronic pain. According to the model, avoidance would eventually lead to disability and disuse, which in turn may lower the threshold at which pain is experienced (Vlaeyen & Linton, 2000; 2012). To our knowledge there are no experimental studies that investigated the effect of (ineffective) avoidance on pain. Here we found some evidence that ineffective avoidance increased pain, thereby providing support for the circular causality typical of the fear-avoidance model. Caution is warranted concerning the interpretation of the results of the pain threshold and tolerance. Participants might have chosen a lower level of pain tolerance throughout the experiment, not because they perceived it as more painful, but because they wished to avoid high pain stimuli in the subsequent trials. To avoid this potential confound, future research might consider using a different pain modality for intermediate pain threshold and tolerance measures than the one used during the conditioning procedure.

In conclusion, and despite these limitations, we replicated the acquisition of avoidance behaviour, pain-expectancy and pain-related fear using a robotic arm-reaching task. We demonstrated that when avoidance becomes ineffective, individuals become more afraid, persist in their ineffective avoidance behaviour, and become more sensitive to pain. These findings and procedure can potentially help to further our understanding of how avoidance can develop and maintain pain problems.

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Appendix

4.A Supplementary material

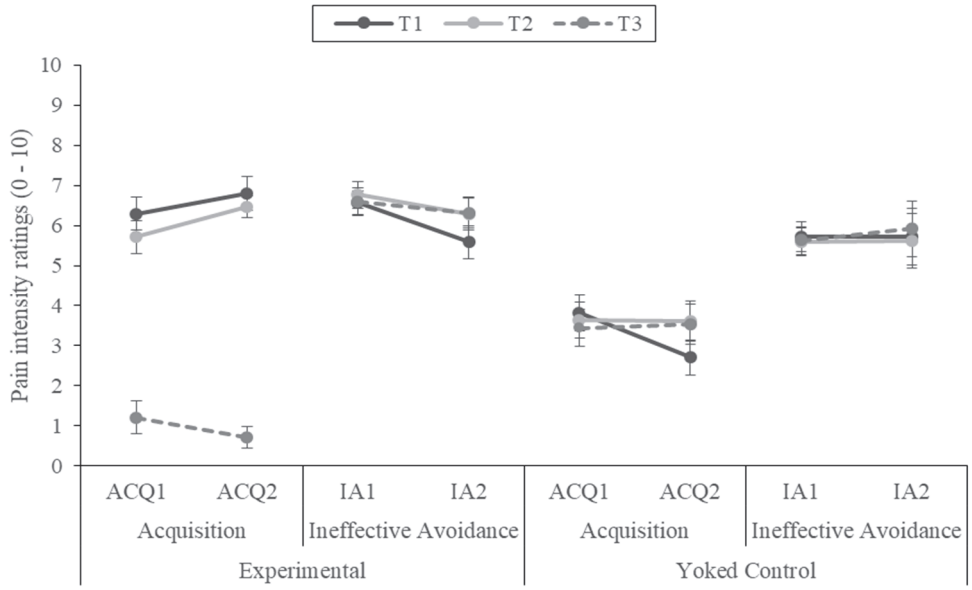

Figure 4.A.1. Self-reported pain intensity ratings with standard error bars for the three trajectories (T1, T2, T3) during the acquisition and ineffective phase for the Experimental group (left) and Yoked Control Group (right).

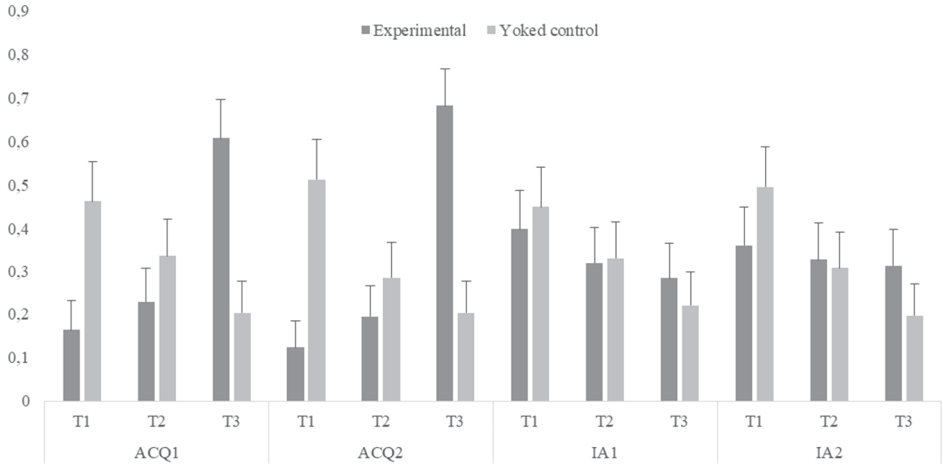

Figure 4.A.2. Proportion of chosen trajectories for Experimental Group and Yoked Control Group with standard error bars for the three trajectories (T1, T2, T3) during acquisition and ineffective avoidance phase.

Table 4.A.1
Means and standard deviations of the pain intensity ratings

Pain intensity *M* (SD)		ACQ1	ACQ2	IA1	IA2
Experimental Group	T1	*6.30* (2.26)	*6.80* (2.32)	*5.60* (2.25)	*6.57* (1.61)
	T2	*5.73* (2.32)	*6.47* (1.72)	*6.30* (2.02)	*6.77* (1.68)
	T3	*1.20* (2.22)	*0.70* (1.47)	*6.33* (2.12)	*6.60* (1.87)
Yoked Control Group	T1	*3.80* (2.46)	*2.70* (2.42)	*5.73* (1.89)	*5.73* (2.05)
	T2	*3.63* (2.37)	*3.60* (2.39)	*5.63* (1.99)	*5.60* (1.81)
	T3	*3.43* (2.51)	*3.53* (2.74)	*5.93* (1.84)	*5.63* (1.85)

Table 4.A.2
FPQ scores

	Experimental group[a]					Yoked control group[b]				
Scale	Mean	*SD*	Median	Min	Max	Mean	*SD*	Median	Min	Max
FPQ										
Minor	17.00	4.31	16.0	10	27	19.03	5.73	18.0	10	29
Severe	34.90	5.22	35.0	25	46	33.37	5.49	35.5	21	42
Medical	23.37	7.19	24.0	13	43	23.53	6.88	22.0	13	41
Total	75.27	14.36	73.5	49	114	76.60	13.62	74.5	53	107

Note. FPQ = Fear of Pain Questionnaire, with subscales minor, severe and medical pain, and with the total score
[a]*n = 30*
[b]*n = 30*

Chapter 5

Avoidance behaviour performed in the context of a novel, ambiguous movement increases threat and pain-related fear

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Abstract

The fear-avoidance model of chronic pain predicts that catastrophic (mis)interpretation of pain elicits pain-related fear that in turn may spur avoidance behaviour leading to chornic pain disability. Here we investigated whether performing a movement to avoid a painful stimulus in the context of a novel movement increases threat and pain-related fear towards this novel movement, and whether avoidance behaviour persisted when given the choice between performing the acquired movement to avoid a painful stimulus or an alternative, novel movement. Applying a robotic arm-reaching task, participants could choose between two movements to reach a target location: a short but painful movement trajectory or a longer non-painful movement trajectory. After avoidance acquisition, the option to choose the painful trajectory was removed. The Experimental Group (n=50) could choose between the longest trajectory, or a novel intermediate trajectory, whereas the Control Group (n=50) was allowed to only perform the novel trajectory. In a final test, participants of both groups were allowed to choose any of the three trajectories. Post-acquisition, Experimental Group participants showed elevated pain-expectancy and pain-related fear towards the novel trajectory, compared to the Control Group. During test, the Experimental Group participants persisted in performing the longest pain-free (avoidance) trajectory, and were less likely to choose the novel trajectory. In addition, these participants maintained higher levels of pain-related fear for the novel trajectory compared to the Control Group. These findings suggest that avoidance in the context of other neutral activities/movements may lead to the development and maintenance of threat appraisals and irrational fears

5.1 Introduction

According to Fear-Avoidance models, pain-related fear and avoidance behaviour have been proposed to account for the transition of a common acute pain episode to chronic disabling pain (Lethem, Slade, Bently, 1983; Meulders, 2020; Vlaeyen & Crombez, 2020; Vlaeyen & Linton, 2000). Individuals avoiding aversive events, may misattribute the perceived safety to the just emitted avoidance response, and therefore they cannot challenge the veracity of the threat that led to the avoidance response (Lovibond, Mitchel, Minard, Brady, & Menzies, 2009; Salkovskis, 1991). In a pain-related fear conditioning experiment, Volders and colleagues (2012) demonstrated that performing an avoidance response during a painful movement and the subsequent removal of the avoidance response, hampered the extinction of fear of movement-related pain. Studies by van Vliet and colleagues (2018; 2019), investigating the bidirectional relationship between avoidance behaviour and pain-related fear, revealed that avoidance behaviour is not only the result of pain-related fear, but that avoidance behaviour in itself may increase fear. Several explanations can be given how a history of avoidance behaviour leads to fear responding. *First*, avoidance behaviour may be used as a source of information of the potential threat (Gangemi, Mancini, & van den Hout, 2012; van den Hout et al., 2014). Therefore, avoiding more frequently could elevate pain expectancies and pain-related fear. *Second*, avoiding safe stimuli may induce cognitive dissonance. Since the emitted behaviour is not in line with the actual threat, individuals may resolve this dissonance by adjusting their threat attribution to fit their behaviour (Festinger, 1957; van Uijen, Leer, & Engelhard, 2018). *Third,* the mere availability of avoiding stimuli with an ambiguous outcome may cause increased threat expectancies (Pittig, 2019; van Uijen et al., 2018). The avoidance response itself may induce transfer of threat and pain-related fear towards the ambiguous stimulus. *Finally*, the availability of an acquired avoidance response may function as a contextual cue indicating the presence of a potential threat (Engelhard, van Uijen, van Seters, & Velu, 2015; Vervliet & Indekeu, 2015).

Does emitting avoidance behaviour in an obvious situation influence the threat value of a novel and ambiguous stimulus that is brought into the same context? To investigate this question, we examined whether (1) acquired avoidance behaviour in the context of a novel ambiguous movement provoked pain expectancy and pain-related fear towards that movement, and (2) whether avoidance behaviour persisted when given the choice to perform either the acquired avoidance behaviour or a novel movement.

In a robotic arm-reaching task, participants learned that the shortest movement trajectory (T1) was followed by a painful stimulus, which they could avoid by choosing a longer trajectory (T3). Next, we removed the option to perform T1 and introduced a novel, intermediate trajectory (T2). Performance of T2 was paired with pain only the first time a participant chose this movement trajectory. The Experimental Group was given the free choice to perform either the avoidance behaviour (T3) or the novel trajectory (T2). The Control Group was allowed to only perform T2. At test, all participants were given the opportunity to freely choose any of the three trajectories (T1, T2, T3). We hypothesized (1) that acquired avoidance behaviour in the presence of a novel movement (T2) would provoke pain expectancy and pain-related fear towards that movement; (2) that pain expectancy and pain-related fear, as well as (3) avoidance behaviour would persist during a free-choice test; (4) that more frequent avoiders would report higher pain expectancy and pain-related fear than less frequent avoiders.

5.2 Methods

5.2.1 Participants

A total of 100 healthy, pain-free volunteers participated in this study (80 women; mean ± SD age = 22 ± 8 years). Participants were recruited at KU Leuven, using social media and distribution of flyers around the campus. Psychology students received half a course credit for participation or a monetary compensation of €4. All participants provided written informed consent, which stated they were allowed to decline participation at any time during the experiment without any consequences. Participants were excluded if they reported to suffer from any cardiovascular disease, chronic pain conditions, pain in the right forearm, impaired uncorrected vision, medical advice to avoid stressful situations, psychiatric disorders (current or in the past), neurological conditions or were pregnant.

Participants were assigned to the Experimental Group (*n*=50, 41 women) or the Control Group (*n*=50, 39 women) via block randomisation. The Social and Societal Ethics Committee of KU Leuven approved the experimental protocol (Reg #: G- 2018 11 1397).

5.2.2 Apparatus and stimulus material

HapticMaster

The HapticMaster (HM) is a 3-degrees of freedom, force-controlled robotic arm (Moog Inc. FCS Robotics, East Aurora, New York, USA) and allows for a wide range of movements (see Figure 5.1). In the current study, movements were restricted to the horizontal plane with depth of 0.35m and a 1m radius (Meulders, Franssen, Fonteyne, & Vlaeyen, 2016). The position of the HM was consistently logged via a computer, such that the coordinates could be used as input for the painful stimulus presentation.

Figure 5.1. Experimental set-up showing the position of the participant in front of the screen, using the HapticMaster for the arm-reaching task.

Stimulus material

An electrocutaneous stimulus of 2 milliseconds duration served as the painful stimulus. The stimulus was delivered by a commercial stimulator (DS7A, Digitimer, Welwyn Garden City, England), using bar electrodes filled with K-Y gel that were attached to the triceps tendon of the right arm, which was used to perform the movements through the reaching task with the robotic arm. Note that a calibration procedure was carried out to select a stimulus intensity that was painful and took some effort to tolerate (see calibration phase).

Hardware and software

The experiment was run on a Windows 7 Professional (Microsoft Corporation Redmond, WA, USA) 64-bit Dell Latitude 6420 computer (Dell Inc., Round Rock, TX, USA) with 4 GB RAM, CPU: I5-2520M at 2.5GHz and programmed in C/C++. All data recording and processing was performed using a commercial software package (MATLAB version, The MathWorks Inc. Natick, MA, USA, 2000).

5.2.3 Study protocol

The experiment was conducted during a single 30-minutes session and consisted of the following phases: preparation, calibration, practice, avoidance acquisition, avoidance manipulation, and free-choice test. We used a between-subjects design including an Experimental (n=50) and Control Group (n=50). After the experiment, participants completed trait questionnaires (Dutch versions) to assess fear of pain (FPQ-III-NL (McNeil & Rainwater, 1998; Roelofs, Peters, Deutz, Spijker, & Vlaeyen, 2005)), trait anxiety (STAI-T (van der Ploeg, 1980)), intolerance of uncertainty (IUS (Helsen, Van den Bussche, Vlaeyen, & Goubert, 2013)), and neuroticism (EPQ-N (Forrest, Lewis, & Shevlin, 2000)).

5.2.4 Robotic arm-reaching task

Participants performed reaching movements with their right arm using the HM. The task consisted of bringing a “green ball” from the starting point (left lower corner of the movement plane) to the target location (left top corner of the movement plane; see Figure

5.2). The ball represented real-time movement and the movement plane was represented on a screen. Participants could freely choose several movement trajectories to reach the target location, and these were indicated by arches positioned in the middle of the movement plane. The trajectories differed in deviation towards the target location. No specific instructions were given to the participants regarding the movements, so they could freely discover which movements led to which outcomes.

Preparation and calibration phase. Participants received oral and written information about the experiment and were told they could decline participation of the experiment at any time without any consequences. After signing the informed consent, stimulation electrodes were attached to the right arm above the elbow and the calibration phase began. During the calibration procedure of the painful stimuli, participants were repeatedly exposed to electrical stimulation of gradually increasing intensity, starting at 2 mA, increasing in increments of 2 mA up to an intensity of 8 mA and then continued in increments of 3 mA up to an intensity of 20 mA, and then continued in increments of 4 mA up to an intensity of 52 mA. Beyond 52 mA, increments were reduced to 2 mA again. Participants selected a stimulus that was painful and demanded some effort to tolerate. Participants were informed that if they did not wish to receive a painful stimulus of a higher intensity, or if they wanted the amplitude to be set back to a lower intensity, they could notify the experimenter who then adjusted the stimulus accordingly. This stimulus intensity was used as the painful stimulus throughout the experiment and was not adjusted anymore after the calibration phase. Following calibration, participants read more specific written instructions on the TV-screen.

Practice phase. During this phase (12 trials) participants were familiarized with the different movement trajectories (T1, T2, T3). Participants performed one of the three movements when a start signal was given (= brief sound simultaneously with on-screen presentation of a manikin raising a flag on the upper right corner of the screen) and participants also practiced the use of the foot switch (USB-3FS-2; Scythe, Tokyo, Japan) to provide ratings. A foot switch was used instead of a manual switch to avoid interference with the arm-reaching movements in this experiment. When participants

reached the target location, a brief sound together with an on-screen red stop-signal was presented, which indicated that the trial ended. The HM robotic arm then returned to its initial starting position, where it remained fixed until the start of the next trial (intertrial interval = 3 s). No painful stimuli were delivered during this phase.

Avoidance acquisition phase. Instructions remained the same as during practice, except that movement trajectory T2 was not available anymore, giving the participants the choice between trajectories T1 or T3. During this phase, T1 was always paired with a painful electrocutaneous stimulus, whereas T3 was not. The painful stimulus was delivered exactly at the point in time when the participant passed the geren ball through the arch of T1. In total 24 trials were run, during which participants acquired pain-related fear for movement T1, but not for movement T3, and could learn to avoid the painful stimulus by performing the longer trajectory movement (T3), i.e. acquisition of the avoidance behaviour.

Avoidance manipulation phase. After the avoidance acquisition phase, the option to perform the shortest trajectory T1 was removed and the intermediate movement trajectory T2 now became available for both groups (12 trials). Performance of T2 was paired with pain only the first time a participant chose this movement trajectory. From the second T2 movement onwards, no painful stimuli were given anymore, but this information was unknown to the participants. The Experimental Group participants could freely choose to move either through T2 or T3, whereas the Control Group was only allowed to perform the novel trajectory T2. The single-trial reinforcement of T2 was applied, because earlier pilot testing had shown that in the absence of this single-trial reinforcement, participants did not avoid anymore (i.e. choose T3) which was crucial for our manipulation.

Free-choice test phase. In the final test, all trajectories were made available for both groups. Again participants performed 12 trials in which they could freely choose which movements they performed. Only movement trajectory T1 was always paired with a painful electrocutaneous stimulus, while T2 and T3 were never paired with a painful electrocutaneous stimulus in this phase.

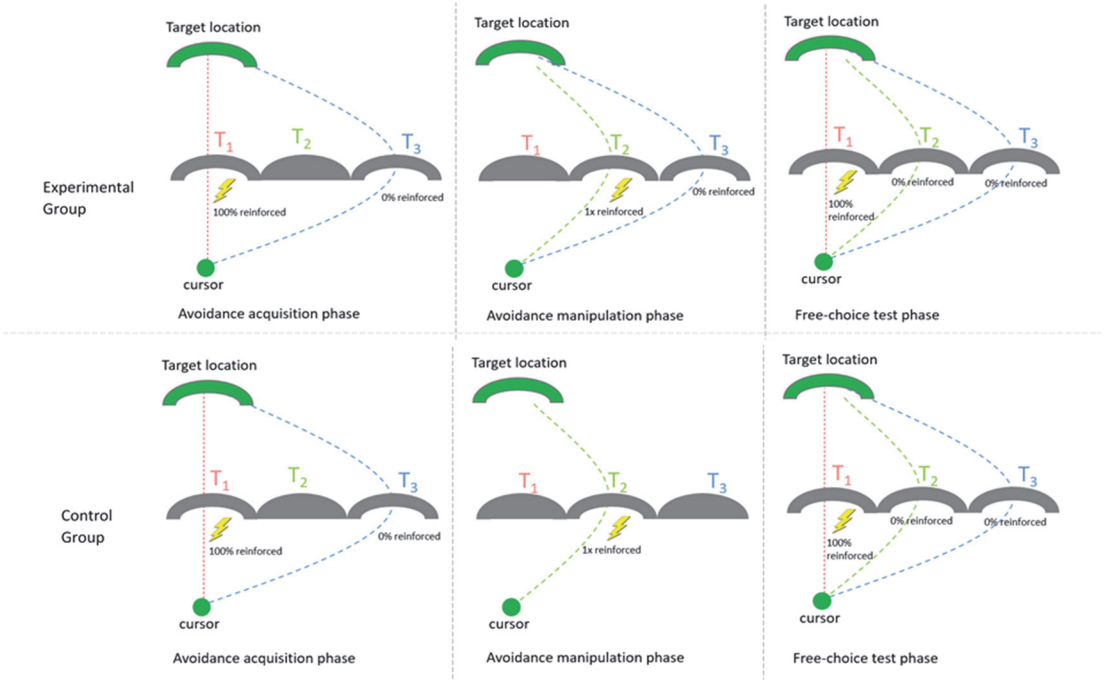

Figure 5.2. Experimental design

5.2.5 Outcome measures

Behavioural avoidance: movement choice

On each movement trial, movement choices were recorded (T1, T2, T3). We calculated the proportion of selected trajectory per group and phase.

Pain expectancy and pain-related fear ratings

Retrospective ratings were obtained during all phases after each block of 4 movements, where participants reported pain expectancy and pain-related fear for each of the trajectories, of which the corresponding arches were highlighted consecutively. The

questions assessing pain expectancy and pain-related fear were the following: 1) "*To what extent did you expect an electrical stimulus when moving through the highlighted arch?"*, and 2) *"How afraid were you to move through the highlighted arch?"*. Ratings were given using the foot switch on a numerical scale from 0 to 10 with respective labels 0 = "*not at all*" and 10 = "*very much*", and 0 = "*not afraid at all*" and 10 = "*extremely afraid*".

Prospective ratings of pain expectancy and pain-related fear for each trajectory were assessed only once before the start of the avoidance manipulation phase and the free-choice test phase.

5.2.6 Data analysis overview

First, descriptive statistics of the sample and questionnaire scores were computed. Second, we tested whether the Experimental and Control Group participants successfully acquired pain-related fear and avoidance behaviour during the avoidance acquisition phase (ACQ). We performed a series of 2 x 3 x 6 Group (Experimental, Control) x Trajectory (T1,T2,T3) x Block (ACQ1-6) RM ANOVAs on pain expectancy, and pain-related fear ratings. Additionally, planned comparisons for the different trajectories were performed to test acquisition of pain expectancy and pain-related fear for T1 > T3 in both groups. We also performed planned comparisons on the behavioural data during the avoidance acquisition phase to check whether Experimental and Control Group participants learned to avoid the painful stimulus by choosing trajectory T3.

In the avoidance manipulation (AM) phase, we tested our first hypothesis, whether acquired avoidance behaviour in the presence of a novel movement (T2) provokes pain expectancy and pain-related fear towards that movement. We performed 2 x 3 x 3 Group (Experimental, Control) x Trajectory (T1, T2, T3) x Block (AM1-3) RM ANOVAs on the retrospective pain expectancy and pain-related fear ratings. With planned comparisons we assessed if the pain expectancy and pain-related fear ratings of T2 for the Experimental Group were higher compared to the Control Group at the start and end of the avoidance phase, i.e. after completion of Block 1 and Block 3 respectively.

To test our second hypothesis, whether elevated pain expectancy and pain-related fear for the novel movement (T2) are preserved for the Experimental Group during the free-choice test (TEST) phase, we performed equivalence tests (Lakens, 2017), based on the retrospective ratings, between the last block of the avoidance manipulation phase and the first block of the free-choice test phase. Furthermore, we performed 2 x 3 x 3 Group (Experimental, Control) x Trajectory (T1, T2, T3) x Block (TEST1-3) RM ANOVAs on pain expectancy and pain-related fear. Planned contrasts assessed whether the pain expectancy and pain-related fear ratings of T2 were higher than T3 for the Experimental Group and the Control Group during the free-choice test phase.

To test our third hypothesis, whether the Experimental Group participants showed proportionally more avoidance behaviour (T3) during the free-choice test phase than the Control Group participants, i.e. persistence in avoidance behaviour, we used the chi-square (χ^2) test statistic on the proportion of the selection of T3 during the free choice test.

To test our fourth hypothesis, whether persistent avoiders (during avoidance manipulation phase) from the Experimental Group reported higher pain expectancy and pain-related fear during the free-choice test phase, we performed linear regression analyses to establish the relationship between the frequency of avoiding (selection of movement T3 during the avoidance phase) and the reported pain expectancy and pain-related fear. These analyses did show the pain expectancy and pain-related fear to be somewhat dependent on the frequency of avoiding, but the explained variance (r^2) was rather low, and we observed bi-modal data, i.e. one group that selected T3 ≤ 6 times out of 12 trials (i.e. ≤ 50% of avoidance) and one group that selected T3 > 6 times out of 12 trials in the avoidance phase (i.e. > 50% of avoidance). As a result, we then decided to divide the Experimental Group in “less frequent avoiders” (n = 14) and “more frequent avoiders” (n = 36). Subsequently, we compared the prospective and retrospective pain expectancy and pain-related fear means of both groups with an unpaired two-sample t-test, when the variances were equal between both groups and a Welch’s unpaired two-sample t-test when the variances between groups were unequal. Please note the selection of more and less frequent avoiders was post-hoc and data-driven.

Table 5.A.1 (supplementary material) includes the descriptive statistics and unpaired two-sample t-tests for the questionnaire scores for the less frequent avoiders and the more frequent avoiders in the Experimental Group.

For each significant RM ANOVA effect, η_g^2 is reported. η_g^2 is the recommended effect size statistic for repeated measures designs (Bakeman, 2005). In case of violation of sphericity, Greenhouse-Geisser corrections were applied by correcting the degrees of freedom. All statistical tests were considered significant at $p < .05$. Holm-Bonferroni corrections were applied to correct for multiple comparison testing. Statistical analyses for all dependent measures were run with R software (RStudio, version 1.0.153).

5.3 Results

5.3.1 Descriptive statistics of the sample and questionnaires

There was no difference in the physical intensity of the painful stimulus chosen by the Experimental Group (24.94 ± 12.17 mA) and the Control Group (22.54 ± 12.37 mA), $t(98) = 0.99$, $p = .33$. Descriptive statistics and questionnaire scores per group are given in Table 5.1. Unpaired two-sample t-test revealed that groups did not differ in their questionnaire scores regarding fear of pain, trait anxiety, intolerance of uncertainty, and neuroticism.

Table 5.1. *Descriptive statistics and independent samples t-tests for the questionnaires scores for both the Experimental Group (n=50) and the Control Group (n=50) separately.*

Total	Experimental Group	Control Group		
N = 100	*M (SD)*	*M (SD)*	*t*(98)	*p*
Age	21.34 (8.45)	22.64 (8.56)	0.76	.45
Pain stimulus (in mA)	24.94 (12.17)	22.54 (12.37)	0.99	.33
FPQ – total	74.90 (14.09)	75.04 (15.65)	-0.05	.96
STAI-T – total	39.66 (9.84)	39.42 (11.05)	0.11	.91
IUS	30.90 (7.40)	31.42 (7.73)	-0.34	.73
EPQ-N	9.58 (4.98)	9.02 (5.52)	0.53	.60

Note. FPQ = Fear of Pain Questionnaire; STAI-T = Trait version of the State-Trait Anxiety Inventory;
IUS = Intolerance of Uncertainty Scale; EPQ-N = Neuroticism scale of the Eysenck Personality Questionnaire

5.3.2 Manipulation checks

Acquisition: behavioural avoidance

As expected, participants of both groups chose T3 more often than T1 during the avoidance acquisition phase: $T1_{exp}$ vs. $T3_{exp}$: $\chi^2(1) = 745.94$, $p < .0001$; $T1_{ctrl}$ vs. $T3_{ctrl}$: $\chi^2(1) = 582.14$, $p < .0001$. Please also see Figure 5.3 panel a.

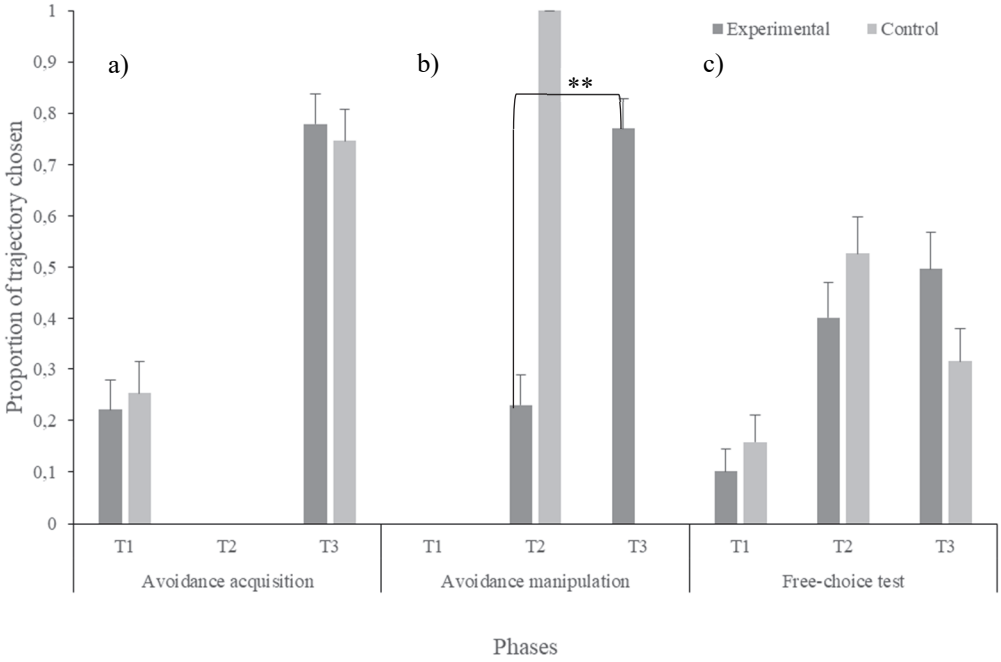

Figure 5.3. Behavioural data on avoidance with standard error bars for all trajectories (T1, T2, T3) during the avoidance acquisition, avoidance manipulation, and free-choice test phase for the Experimental Group and the Control Group, ** $p < .01$

Acquisition: pain expectancy and pain-related fear

Figures 5.4 and 5.5 show the acquisition of pain expectancy and pain-related fear, respectively. The analysis of pain expectancy during avoidance acquisition revealed a significant main effect of Trajectory, $F(2, 196) = 484.61$, $p < .001$, $\eta_g^2 = 0.71$ and a significant Block x Trajectory interaction $F(5.86, 574.53) = 10.35$, $p < .001$, $\eta_g^2 = .02$. As expected, there was neither a main effect of Group, $F(1, 98) = 0.69$, $p = .41$, nor a significant three-way Group x Block x Trajectory interaction, $F(10, 980) = 0.57$, $p = .84$. Planned contrasts confirmed that both groups expected the painful stimulus more to occur during T1 compared to T3 at the end of avoidance acquisition (Experimental Group: $F(1, 98) = 538.3$, $p < .0001$; Control Group: $F(1, 98) = 359.4$, $p < .0001$).

The analysis of pain-related fear during the avoidance acquisition phase revealed similar results: a significant main effect of Trajectory $F(2, 196) = 273.75$, $p < .001$, $\eta_g^2 = 0.55$, and a significant Block x Trajectory interaction $F(4.25, 416.80) = 13.08$, $p < .001$, $\eta_g^2 = .02$. Again, as expected, there was neither a main effect of Group $F(1, 98) = 0.25$, $p = .62$, nor a significant three-way Group x Block x Trajectory interaction, $F(10, 980) = 0.44$, $p = .92$. Planned contrasts confirmed that both groups were more afraid when performing T1 compared to T3 at the end of avoidance acquisition (Experimental Group: $F(1, 98) = 271$, $p < .0001$; Control Group: $F(1, 98) = 191.4$, $p < .0001$).

In conclusion, the manipulation checks confirmed that participants in both groups learned to expect a painful stimulus during the T1 movement and feared to perform this movement by the end of the avoidance acquisition phase. Both groups learned to effectively avoid the painful stimulus by performing the longest trajectory T3.

5.3.3 Hypothesis 1: acquired avoidance behaviour in the presence of a novel movement (T2) provokes pain expectancy and pain-related fear towards that movement

Pain expectancy

Figure 5.4 shows the pain expectancy ratings for both groups. The analysis on pain expectancy during the manipulation phase revealed a significant main effect of Group, $F(1, 98) = 18.99$, $p < .0001$, $\eta_g^2 = .06$, a significant main effect of Trajectory, $F(1.69, 165.66) = 85.27$, $p < .0001$, $\eta_g^2 = .33$, and a significant main effect of Block, $F(1.61, 157.43) = 48.06$, $p < .0001$, $\eta_g^2 = .01$. Furthermore, the Group x Block interaction reached significance, $F(1.61, 157.43) = 6.24$, $p = .005$, $\eta_g^2 = .002$, as well as the Group x Trajectory interaction, $F(1.69, 165.66) = 9.79$, $p < .001$, $\eta_g^2 = .05$, and the Trajectory x Block interaction, $F(1.92, 188.14) = 10.46$, $p < .001$, $\eta_g^2 = .008$. The crucial comparison of the pain expectancy ratings for the novel movement (T2) between the Experimental Group and the Control Group, reached significance at both the start of the avoidance manipulation phase: $T2_{exp}$ *vs.* $T2_{control}$ $F(1, 98) = 17.84$, $p < .001$, as well as the end of the avoidance manipulation phase: $T2_{exp}$ *vs.* $T2_{control}$ $F(1, 98) = 40.01$, $p < .0001$.

In sum, participants of the Experimental Group expected a painful stimulus more during the novel movement (T2) compared to the Control Group.

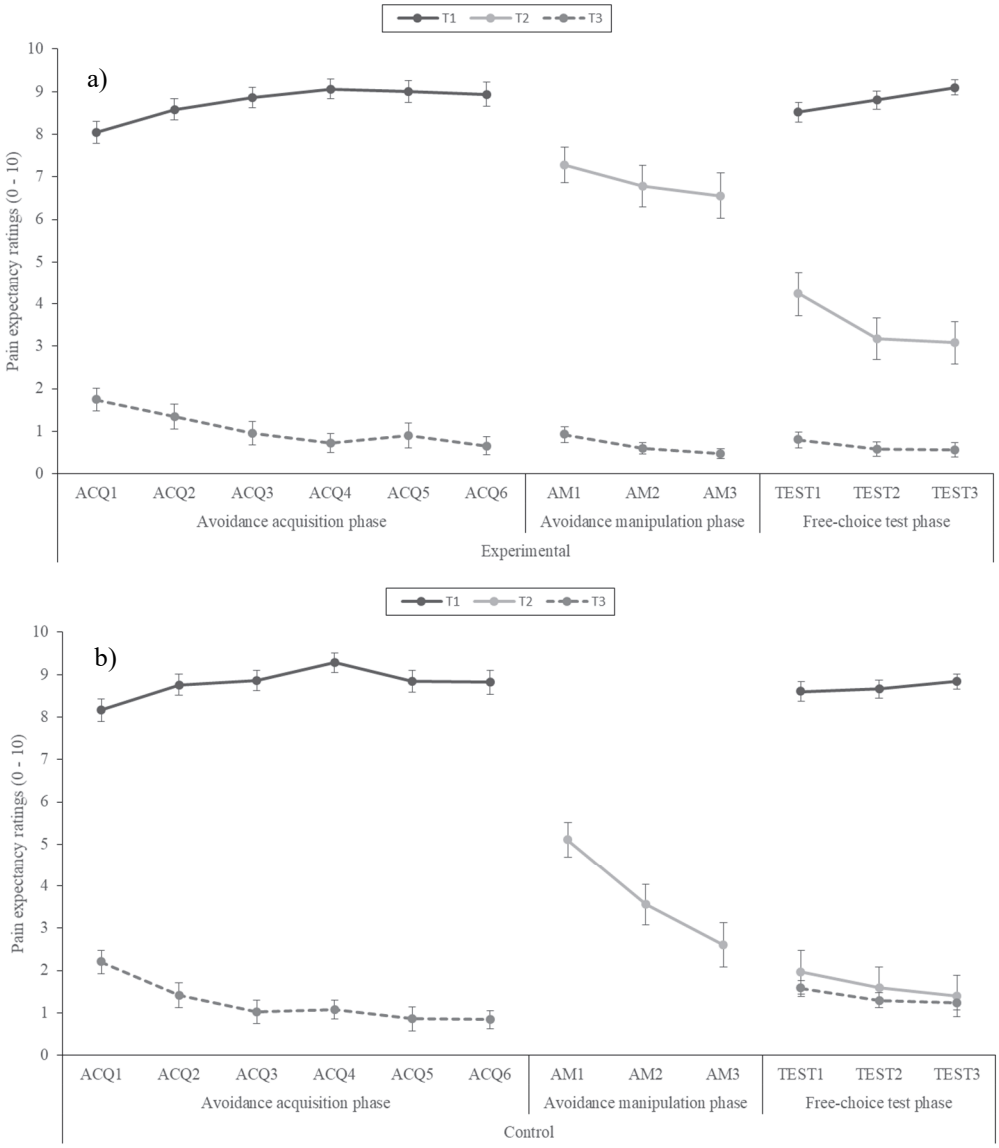

Figure 5.4. Pain expectancy ratings with standard error bars for all trajectories (T1, T2, T3) during the avoidance acquisition, avoidance manipulation, and free-choice test phase for the Experimental Group (panel a) and the Control Group (panel b).

Pain-related fear

In Figure 5.5, the pain-related fear ratings for both groups are displayed. The analysis of pain-related fear during the avoidance manipulation phase showed similar results as the pain expectancy analysis. Following main effects were significant: Group, $F(1, 98) = 12.18$, $p < .001$, $\eta_g^2 = .05$, Trajectory, $F(1.85, 180.96) = 88.48$, $p < .0001$, $\eta_g^2 = .32$, and Block, $F(1.58, 154.39) = 38.99$, $p < .0001$, $\eta_g^2 = .01$. The following interactions were significant as well: Group x Block interaction, $F(1.58, 154.39) = 7.59$, $p < .01$, $\eta_g^2 = .003$; Group x Trajectory interaction, $F(1.85, 180.96) = 3.50$, $p < .05$, $\eta_g^2 = .02$, and the Trajectory x Block interaction, $F(2.59, 253.97) = 10.46$, $p < .0001$, $\eta_g^2 = .006$. The planned comparisons between the Experimental and Control Group were significant at the start of the avoidance phase: $T2_{exp}$ *vs.* $T2_{ctrl}$ $F(1, 98) = 4.56$, $p = .035$, and at the end of the avoidance phase $T2_{exp}$ *vs.* $T2_{ctrl}$ $F(1, 98) = 23.73$, $p < .0001$. These results indicate that participants of the Experimental Group were more afraid to perform T2 compared to the Control Group.

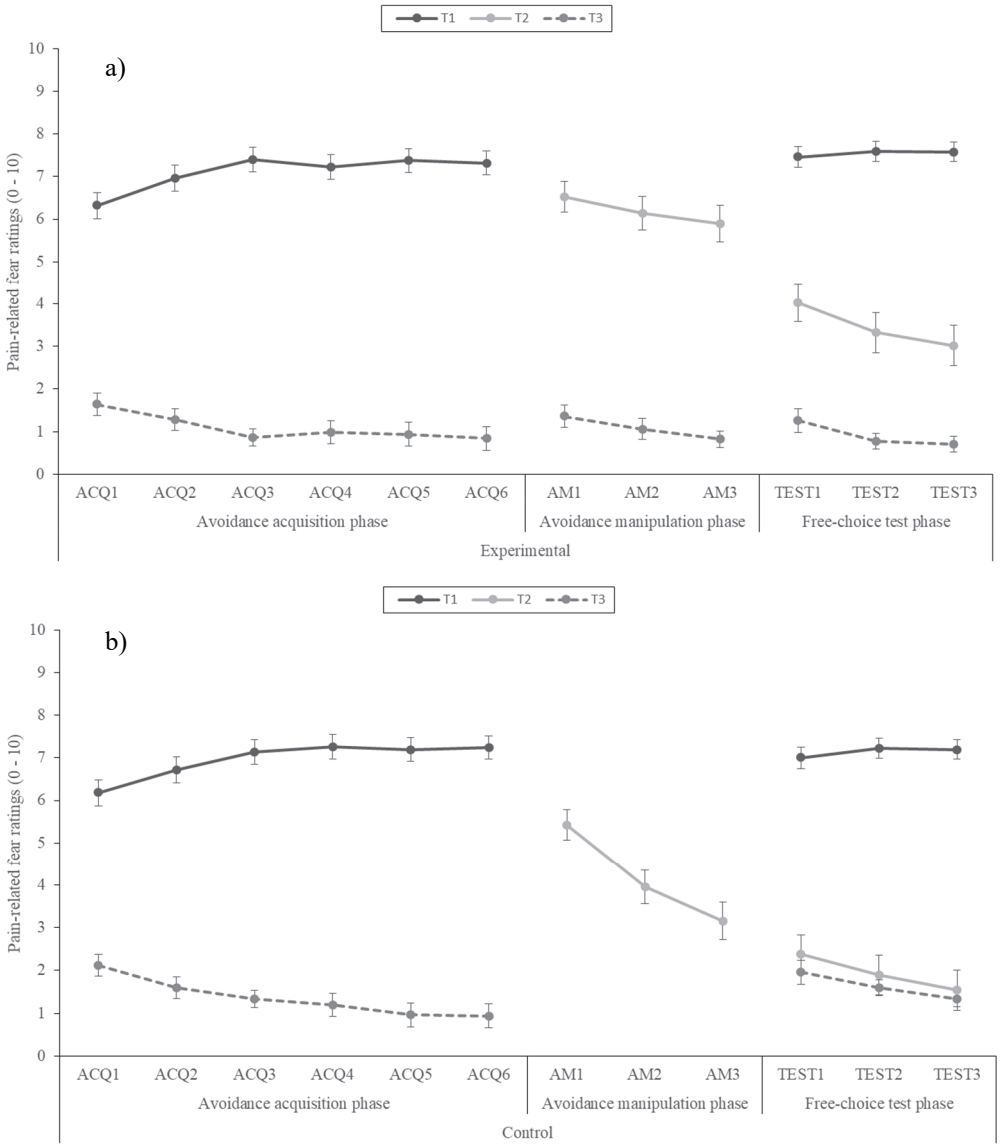

Figure 5.5. Pain-related fear ratings with standard error bars for all trajectories (T1, T2, T3) during the avoidance acquisition, avoidance manipulation, and free-choice test phase for the Experimental Group (panel a) and the Control Group (panel b).

5.3.4 Hypothesis 2: preservation of pain expectancy and pain-related fear during free-choice test phase

Pain expectancy

The analysis on pain expectancy during the free-choice test phase revealed significant main effects of Trajectory, $F(1.82, 178.40) = 364.77$, $p < .0001$, $\eta_g^2 = .71$, and Block, $F(1.42, 138.84) = 10.39$, $p < .001$, $\eta_g^2 = .003$. The main effect of Group failed to reach significance, $F(1, 98) = 3.31$, $p = .07$, $\eta_g^2 = .009$. The Group x Trajectory interaction, $F(1.82, 178.40) = 9.38$, $p < .001$, $\eta_g^2 = .06$, and the Trajectory x Block interaction, $F(2.62, 256.96) = 18.59$, $p < .001$, $\eta_g^2 = .01$, were significant. To test whether pain expectancy for the T2 movement was maintained for the Experimental Group, we performed an equivalence test. The equivalence test revealed that the pain expectancy between the last block of the avoidance phase and first block of the free-choice test phase was not statistically equivalent $t(49) = 4.26$, $p = .99$. In other words, the elevated pain expectancy ratings were not maintained at the same level. However, the Experimental Group still reported higher pain expectancy for T2 during the free-choice test phase compared to T3, $F(1, 48) = 16.39$, $p < 001$, while for the Control Group we did not observe this difference in pain expectancy between T2 and T3, $F(1, 48) = 0.99$, $p = .33$. In sum, Experimental Group participants did not report the same level of pain expectancy for the novel movement (T2) during test compared to during avoidance manipulation phase, however they still expected the pain more than for trajectory T3.

Pain-related fear

The analysis on pain-related fear during the free-choice test phase revealed a significant main effect of Trajectory, $F(2, 196) = 235.29$, $p < .0001$, $\eta_g^2 = .55$, and Block, $F(1.56, 152.99) = 18.86$, $p < .0001$, $\eta_g^2 = .006$. Furthermore, the Group x Trajectory interaction, $F(2, 196) = 7.28$, $p < .001$, $\eta_g^2 = .04$, and the Trajectory x Block interaction, $F(2.83, 277.09) = 11.85$, $p < .0001$, $\eta_g^2 = .007$, reached significance. To test our hypothesis, we compared the pain-related fear ratings of the T2 movement during the last block of the avoidance phase and the first block of the free-choice test phase for the Experimental Group, and found that the pain-related fear reported by the Experimental Group

participants was also not statistically equivalent $t(49) = 3.99$, $p = .99$. However, Experimental Group participants were more afraid to perform T2 compared to T3 during free-choice test phase, $F(1,48) = 19.27$, $p < .001$, while the Control Group participants did not report such difference, $F(1,48) = 1.97$, $p = .17$. In sum, Experimental Group participants did not maintain the same level of pain-related fear to perform T2 during the free-choice test phase. However, they did report higher pain-related fear for T2 compared to T3.

5.3.5 Hypothesis 3: persistence in avoidance behaviour during free-choice test phase

To test whether the Experimental Group avoided more compared to the Control Group during the free-choice test phase, we compared the proportion of T3 choices between both groups. Proportion T3 choices during the free-choice test phase for the Experimental Group was 0.50 and for the Control Group was 0.32, $\chi^2(1) = 40.31$, $p < .0001$. In other words, participants of the Experimental Group avoided on 50% of the trials during the free-choice test phase and Control Group participants only avoided approximately on one third of the trials (32%) during the free-choice test phase (see Figure 5.3, panel c, for the choice data in the free-choice test phase).

5.3.6 Hypothesis 4: more frequent avoiders report higher pain expectancy and pain-related fear than less frequent avoiders

To test the hypothesis that Experimental Group participants, who avoided more during the avoidance phase, would also report higher pain expectancy and pain-related fear during the free-choice test phase, we divided the sample post-hoc into less avoiders (n=14) and more frequent avoiders (n=36).

Pain expectancy

The results of the pain expectancy ratings during the free-choice test phase for the less frequent avoiders and more frequent avoiders of the Experimental Group are shown in Figure 5.6. In all cases the more frequent avoiders group showed higher levels of pain expectancy towards the novel movement T2 compared with the less frequent avoiders: before the free-choice test phase, $t(48) = 4.12$, $p < .001$; block 1, $t(47.92) = 5.56$, $p < .0001$; block 2, $t(41.90) = 5.63$, $p < .0001$; block 3, $t(48) = 2.12$, $p = .039$.

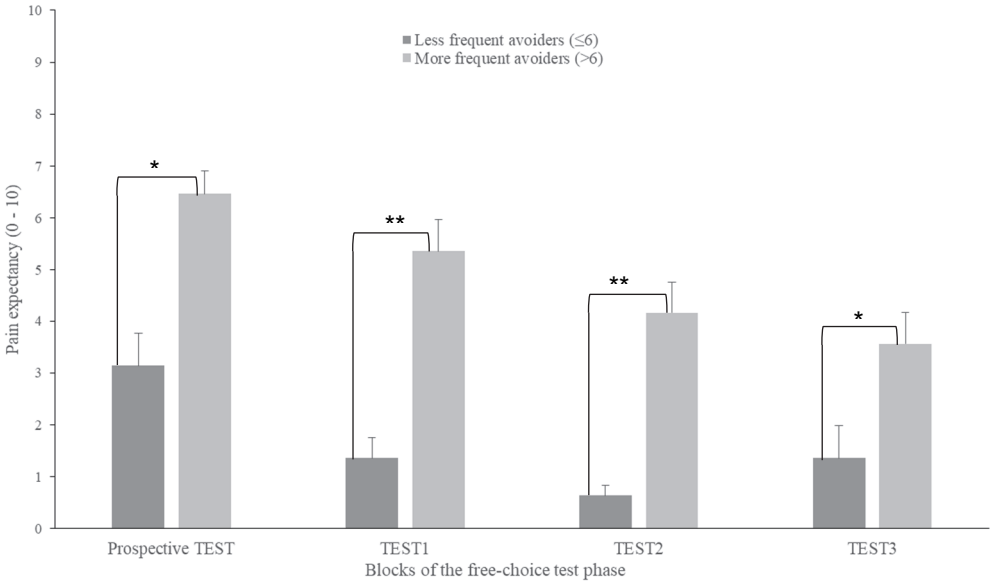

Figure 5.6. Pain expectancy ratings towards the novel movement T2 for less frequent avoiders and more frequent avoiders of the Experimental Group during the free-choice test phase, * $p < .05$; ** $p < .01$

Pain-related fear

The results of the pain-related fear ratings during the free-choice test phase for the less frequent avoiders and more frequent avoiders of the Experimental Group were similar to those of the pain expectancy ratings and are shown in Figure 5.7. In all cases the more frequent avoiders group showed higher levels of pain-related fear towards the novel movement compared with the less frequent avoiders: before the free-choice test phase, $t(48) = 3.65$, $p < .001$; block 1, $t(44.55) = 4.38$, $p < .0001$; block 2, $t(48) = 2.03$, $p = .04$; block 3, $t(48) = 2.11$, $p = .04$.

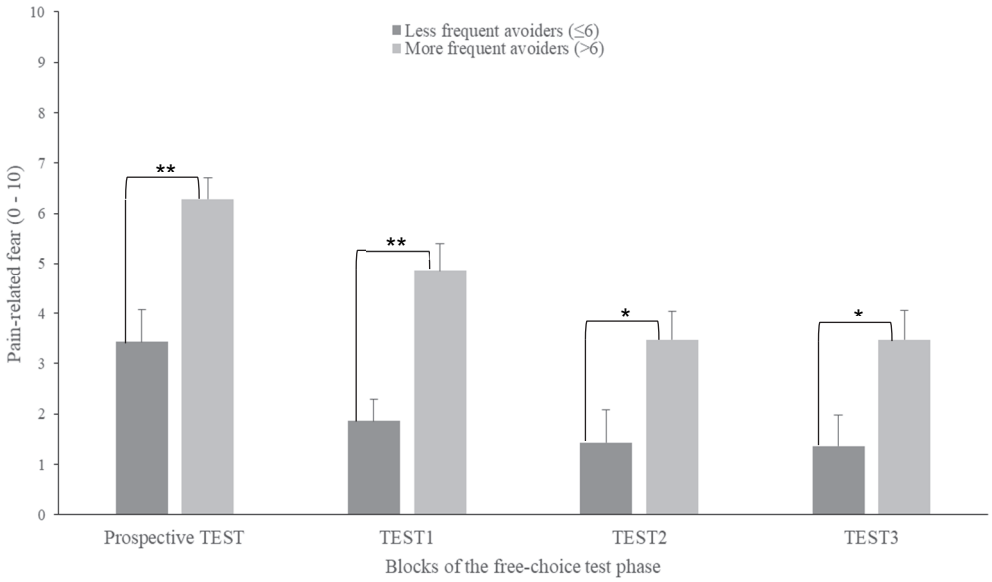

Figure 5.7. Pain-related fear ratings towards the novel movement T2 for less frequent avoiders and more frequent avoiders of the Experimental Group during the free-choice test phase, * $p < .05$; ** $p < .01$

5.4 Discussion

This study addresssed two main questions: 1) whether avoidance behaviour performed in the context of a novel, ambiguous movement increases threat and pain-related fear; 2) whether avoidance behaviour persists when given the choice between performing the known movement to avoid a painful stimulus or an alternative, novel movement. We measured pain expectancies and pain-related fear for three different movements. The Experimental Group and the Control Group learned to avoid a pain-associated movement (T1) by performing a longer, non-painful movement (T3). These findings replicated the results of previous studies of avoidance acquisition, using a similar paradigm, albeit in the absence of associated cost when performing the avoidance movement (Meulders et al., 2016; van Vliet et al., 2019).

In line with our first hypothesis, acquiring avoidance behaviour in the presence of a novel, ambiguous movement (T2) provoked higher pain expectancy and pain-related fear ratings for that movement, thereby extending the findings of Lovibond et al. (2009). In Lovibond's experiment, the experimental group was given the opportunity to perform an avoidance response during extinction, whereas the control group was not given this opportunity. In that study, differences were observed in return of fear between both groups when the extinguished, previously fearful stimulus was tested without an avoidance response being available. Apparently, for the experimental group, the opportunity to perform an avoidance response had prevented fear extinction and maintained threat expectations for the fear-evoking stimulus. As a result, only the control group showed extinction. Potential explanations for the observed role of acquired avoidance behaviour on the transfer of pain expectancy and pain-related fear could be the following. First, the use of "behaviour as information", whereby participants used their own avoidance behaviour to infer threat, i.e. *ex-consequentia reasoning* (Gangemi et al., 2012; van den Hout et al., 2014). In other words, they assumed that the novel movement had to be unsafe/painful, just because they were avoiding, although this was not necessarily a correct conclusion. Second, the mere availability to avoid may cause increased threat expectancies. After acquiring an avoidance response towards a painful movement (T1), the avoidance response itself may induce transfer of threat expectancies and pain-related fear towards a similar, novel movement (T2). The availability of the

acquired avoidance response may function as a contextual cue, indicating the potential threat of T2 that needed to be prevented by performing an avoidance response (Engelhard et al., 2015). Third, earlier findings suggested that risk perception is influenced by intuitive processes and is not only the result of rational analysis (Slovic & Peters, 2006). This intuitive process may lead to misperceptions of the threat of the ambiguous novel movement, because the acquired avoidance behaviour served as a reminder of pain expectancy and pain-related fear.

Our results did not fully support our second hypothesis where we anticipated elevated levels of pain expectancy and pain-related fear for the novel movement (T2) to be maintained from avoidance to free-choice test phase. Experimental Group participants reported lower levels of pain expectancy and pain-related fear for the novel movement T2 in the free-choice test phase compared to the reported levels for T2 in the avoidance manipulation phase. However, Experimental Group participants reported higher pain expectancy and pain-related fear for movement T2 compared to the avoidance movement (T3) in the free-choice test phase, while participants of the Control Group did not differentiate in their pain expectancy and pain-related fear between these movements. Earlier research had suggested a bidirectional relationship between avoidance and pain-related fear (van Vliet et al., 2018; 2019). Avoidance behaviour itself may lead participants to infer danger for a newly introduced movement, assuming this movement may be dangerous as well, merely because it could be avoided. Similar findings have been reported in research about the persistence of anxiety disorders, where safety behaviours have led to excessive and persistent fear of objectively safe stimuli (Rachman, Radomsky, & Shafran, 2008). This could be caused by the misattribution of safety as a result of performing a safety/avoidance behaviour, thereby preserving excessive danger beliefs (Clark, 1999; Pittig, Wong, Glück, & Boschet, 2020; Salkovskis, 1991).

The results of our current study supported our third hypothesis: Experimental Group participants were more persistent in engaging in previously acquired avoidance behaviour (T3) compared to Control Group participants. Although Experimental Group participants explored the novel movement (T2) more during the free-choice test phase than during the avoidance manipulation phase, they mostly performed the previously

acquired avoidance response (T3), thereby preventing disconfirmation of potential threat associated with the novel movement. This finding is in line with earlier research by van Vliet et al. (2019), where persistence of avoidance was observed using a similar movement-related paradigm. Taken together, these observations regarding persisting in avoidance behaviour are important for our understanding of the mechanisms involved in the development of chronic pain. Also, Control Group participants still avoided in approximately thirty percent of the trials in the free-choice test phase, although the pain expectancy and pain-related fear for movement T2 had been extinguished for the Control Group in the avoidance manipulation phase. In other words, there was no logical reason for the Control Group to avoid the safe/non-painful movement T2. This finding is in line with the results reported by Vervliet and Indekeu (2015), who found that avoidance behaviour can re-occur after successful fear extinction, when the avoidance response became available again. Also, the return of the availability to avoid may have acted as a negative occasion setter as described by De Houwer and colleagues (Declercq & De Houwer, 2008; De Hower, Crombez, & Baeyens, 2005).

Regarding our fourth hypothesis we found that more frequent avoiders reported higher pain expectancies and pain-related fear during the free-choice test phase. This result suggested that not only acquired avoidance behaviour by itself can increase pain expectancy and pain-related fear, but also the frequency of performing the avoidance behaviour has an effect on those measures. These findings are supported by the idea of ex-consequentia reasoning (Gangemi et al., 2012; van den Hout et al., 2014); based on their own consequent avoidance behaviour, participants drew invalid conclusions about the outcome associated with T2, and therefore reasoned, “I am avoiding, so it must be dangerous and therefore I am afraid of the movement”.

One of the strengths of this study is the successful operationalisation of movement-related avoidance, further validating a paradigm that allowed participants to perform avoidance during an ecologically valid arm-reaching task (Claes, Vlaeyen, & Crombez, 2016; Janssens, Meulders, Cuyvers, Colloca, & Vlaeyen, 2019; Meulders et al., 2016). Rather than operationalising avoidance by e.g. simply pressing a button upon a cue, here the participants learned to avoid painful stimuli by performing different robotic arm movements. Other strengths are the introduction of a novel movement, after avoidance

acquisition, and the design of the free-choice test phase. Avoidance behaviour can be considered as a decision making process in our paradigm (i.e. choice), taking into account the benefits (averting a painful stimulus) as well as the expected costs of avoidance (Volders, Boddez, De Peuter, Meulders, & Vlaeyen, 2015). An innovative aspect of our study was to investigate the effects of avoidance behaviour in the context of a novel, ambiguous movement, on threat expectancies and fear towards that movement. During the free-choice test phase, we collected data on self-reported pain expectancy and pain-related fear across multiple blocks of trials, allowing us to obtain a trend of the self-reported measures across this phase, compared to other studies where often the test phase consisted of only one trial (Engelhard et al., 2015; Lovibond et al., 2009). One of the limitations of the study is the use of a non-gender-balanced sample for our experiment, which consisted for 80% of female participants. Since females may have enhanced fear acquisition (McClure et al., 2004; Pittig et al., 2020) and pain sensitivity during fear conditioning (Meulders, Vansteenwegen, & Vlaeyen, 2012), future research may benefit from obtaining more gender-balanced samples. Another limitation of the study is the single-trial reinforcement of T2 to induce the avoidance behaviour for T2, because earlier pilot testing had shown Experimental Group participants hardly avoided T2 in the absence of this single-trial reinforcement. This means that transfer of pain-related fear and pan expectancy was not only determined by the acquired avoidance, but also by the single-trial reinforcement. This could have created some ambiguity, because for a number of participants this might have been sufficient evidence that T2 is a dangerous movement, and they refrained from checking further in subsequent trials (Bensi & Giusberti, 2007). Although avoidance may not have been affected, a potential confound in this paradigm is the placement of T2 close to T1 (generalisation of the threat based on perceptual/proprioceptive similarity with T1) and to the left of T3 (rule-based generalization) (Glogan, Gatzounis, Meulders, & Meulders, 2020). Placing T2 to the right of T3 may have been better to control for the potential generalisation. Another limitation is the absence of an additional phase where none of the movements were reinforced. Adding such a phase would enable studying extinction of avoidance behaviour for either the Experimental Group, the Control Group or both groups.

To conclude, the results indicated that avoiding in the context of a novel, ambiguous movement provoked pain expectancy and pain-related fear towards that movement, even in the absence of confirmation of the actual threat level of the movement. Also we observed persistent avoidance in the presence of that novel movement, which can be considered maladaptive and disproportionate to the threat and may have prevented disconfirmation of threat appraisals. The results from this study support the bidirectionality hypothesis between avoidance behaviour and fear, whereby fear leads to avoidance and, in turn, avoidance further increases fear. These findings can potentially help to further our understanding of how persisting in avoidance behaviour may lead to the development and maintenance of irrational fears and threat appraisals.

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Appendix

5.A Supplementary material

Table 5.A.1. *Descriptive statistics and unpaired two-sample t-tests for the questionnaires scores for the less frequent avoiders (n=14) and the more frequent avoiders (n=36) in the Experimental Group.*

Total	Less frequent avoiders	More frequent avoiders		
N = 50	*M (SD)*	*M (SD)*	*t*(48)	*p*
FPQ – total	68.79 (8.41)	77.28 (15.20)	1.96	.054
STAI-T – total	37.29 (8.90)	40.58 (10.15)	1.06	.29
IUS	30.14 (6.26)	31.19 (7.86)	0.45	.66
EPQ-N	8.00 (4.52)	10.19 (5.08)	1.41	.17

Note. FPQ = Fear of Pain Questionnaire; STAI-T = Trait version of the State-Trait Anxiety Inventory; IUS = Intolerance of Uncertainty Scale; EPQ-N = Neuroticism scale of the Eysenck Personality Questionnaire

We observed no significant trait differences between the less frequent avoiders and more frequent avoiders on the scores of the questionnaires.

Chapter 6

General discussion

The main aim of the present PhD research project was to investigate the relationship between pain-related fear and avoidance behaviour, which, according to the fear-avoidance model, plays a pivotal role in the development and maintenance of chronic pain. So far, the fear-avoidance model assumes a unidirectional relationship between pain-related fear and avoidance, i.e. pain-related fear evokes avoidance behaviour. Recent studies in the area of anxiety disorders (Engelhard, van Uijen, van Seters, & Velu, 2015; Gangemi, Mancini, & Van Den Hout, 2012) have shown that anxiety or threat beliefs do lead to safety behaviours (one direction) and in turn, engaging in safety behaviours increases anxiety and threat beliefs (other direction), thereby suggesting a bidirectional relationship. We propose that pain avoidance in chronic pain has a similar status as safety behaviours in anxiety disorders. Therefore the aim of the current research project was testing the bidirectional relationship between fear and avoidance behaviour in the context of pain.

In this chapter we discuss the main results of four experiments. We also integrate our experimental findings within the context of the theory and previous literature from the fields of pain-related fear and avoidance behaviour. Based on these insights, we propose an extension of the theoretical fear-avoidance model introduced by Vlaeyen and Linton (2000, 2012). In addition, we discuss strengths and limitations of the current research project, clinical implications of the findings, and future research directions, to end with some general conclusions.

6.1 Summary of the findings

In our first experimental study, described in *chapter 2*, we tested the effects of avoidance of a painful heat stimulus on pain-related fear and pain outcomes. More specifically, we tested the fear ←→ avoidance bidirectionality hypothesis, whereby engaging in avoidance may (paradoxically) increase rather than decrease pain-related fear. The opportunity to avoid full exposure to a painful heat stimulus, by pressing a stop-button upon presentation of a stop-cue, was experimentally manipulated: we created the illusion to avoid a painful stimulus in one group (avoidance group) and not in another group (control group). However, in reality and unknown to the participants, the calibrated pain stimulus intensity or duration occurred independently of the avoidance response.

Therefore it did not change throughout the experiment and hence was identical for both groups. In that way, both groups were exposed to the same amount of painful stimulation. During the test, the avoidance response was no longer available for the avoidance group. The results showed that the avoidance group reported higher pain-related fear when the avoidance response (pressing the stop-button) was no longer available, in line with our expectations, thereby providing support for the bidirectionality hypothesis. For the control group, no significant change was observed in pain-related fear throughout the experiment. Another interesting observation was that in the avoidance group, pain-related fear already increased after merely receiving the instructions that avoidance was possible, even before actually engaging in avoidance behaviour. The eyeblink startle measures did not corroborate this data pattern. These observations provide partial support for the bidirectionality hypothesis between avoidance behaviour and fear.

Chapter 3 describes our second experimental study, which is a replication of the first study (chapter 2), with some methodological improvements and minor modifications to the design of the paradigm. Here we additionally aimed to test the assumption that avoidance of a painful heat stimulus is used as a source of threat information, thereby affecting pain-related fear and pain for that stimulus. Therefore, we tested whether the avoidance-fear relationship was mediated by threat appraisals. Avoidance group and control group participants both received instructions that they could avoid the full heat intensity of a painful heat stimulus by pressing a stop-button upon presentation of a stop-cue. However, during the experiment, only avoidance group participants received a stop-cue and were allowed to press the stop-button, while control group participants, although they had received the same instructions, never were presented with a stop-cue and therefore never had the opportunity to perform the avoidance response to avoid the full heat intensity. In this study, we successfully replicated the findings of our first study that pain-related fear levels were higher when the avoidance response was no longer available. We also found that perceived avoidance attenuates pain reports despite exposure to identical stimulus intensity. As predicted, the relationship between avoidance behaviour and increased pain-related fear was mediated by increased threat appraisals.

In summary, the perceived avoidance of pain increased pain-related fear through increasing threat appraisals, suggesting a more complicated relationship between pain-related fear, threat appraisals, and avoidance behaviour than the unidirectional relationships proposed in the fear-avoidance model.

Our third experimental study, described in *chapter 4*, examined motor-behavioural characteristics of avoidance behaviours during different movements using the HapticMaster, a 3-degrees of freedom, force-controlled robotic arm. Participants were assigned to either an experimental group or a yoked control group and performed either of three movement trajectories (T1-T3) to reach a target location. During the acquisition phase, only experimental group participants could partially or fully avoid a painful electrocutaneous stimulus by choosing the intermediate trajectory (T2; 50% reinforcement) or the longest trajectory (T3; 0% reinforcement) versus the shortest trajectory (T1; 100% reinforcement). To prevent participants always choosing the non-painful trajectory, a cost in terms of resistive force was introduced. When the target location was reached via movement T1, which had the least lateral displacement, no such force was exerted. When the target location was reached via movements T2 and T3, respectively moderate and strong resistive force was applied by the HapticMaster. In this way a trade-off between pain and resistance was created. Critically, the contingencies changed after acquisition (all trajectories 50% reinforced), and the acquired avoidance behaviour no longer effectively prevented pain from occurring. The results showed that when avoidance behaviour became ineffective for the experimental group, pain-related fear increased for the previously safe(r) trajectories (T2 and T3) and remained the same for T1, whereas pain threshold and tolerance declined. Pain-related fear increased for all trajectories for the yoked control goup. Another result was that the experimental group persisted in emitting avoidance behaviour following the contingency change, albeit at a lower frequency than during acquisition. Results indicated that participants became more afraid of and sensitive to pain, when previously acquired avoidance was no longer effective. Also, participants continued to emit costly avoidance behaviour despite it being not effective anymore. These findings suggest that ineffective avoidance may play a role in the maintenance and development of chronic pain.

Chapter 5 describes our fourth study, aimed to investigate whether performing a movement to avoid a painful stimulus in the context of a novel, ambiguous movement increases threat and pain-related fear towards this novel movement. A second aim was to test whether avoidance behaviour persists when given the choice between performing the acquired movement to avoid a painful stimulus or an alternative, novel movement. As in our third study, here we also used a robotic arm-reaching avoidance task, whereby in the avoidance acquisition phase both experimental group and control group participants performed either a painful movement (T1; 100% reinforcement), or a non-painful movement (T3; 0% reinforcement, i.e. avoidance) to reach a target location. Following the avoidance acquisition, a novel movement (T2) was introduced in the avoidance manipulation phase. In this phase, only the experimental group participants could avoid the novel movement (T2) by selecting T3 over T2, whereas the control group participants could only perform the novel movement (T2). Subsequently, in a final free-choice test phase, participants of both groups could perform all three movements (T1, T2, T3). During the avoidance manipulation phase, experimental group participants showed elevated pain expectancy and pain-related fear towards the novel, ambiguous movement (T2), compared to the control group. During the free-choice test, the experimental group persisted in avoiding the novel, ambiguous movement, thereby preventing disconfirmation of the novel movement threat appraisals. The experimental group also maintained higher levels of pain-related fear for the novel movement compared to the control group. These findings suggest that avoidance in the context of other neutral activities/movements may lead to the development and maintenance of threat appraisals and irrational fears.

Collectively, the results of these four experiments provide support for the bidirectional relationship between pain-related fear and avoidance and constitute an important step in furthering our understanding of the underlying mechanisms in the development and maintenance of chronic pain.

6.2 Does instructed perceived avoidance increase pain-related fear and is the increase in fear mediated by threat?

The designs of the first and the second study, described respectively in chapters 2 and 3, are based on instructed avoidance (i.e. upon presentation of a stop-cue, participants were told to press the stop-button to avoid the maximum painful heat stimulus). In reality and unknown to the participants, the avoidance response had no effect on the physical intensity and duration of the heat stimulus and therefore, rather than actual avoidance, this can be considered perceived avoidance. One of the challenges in these studies was the control for the potentially confounding influence of differential exposure to painful stimuli in both groups. The choice of perceived avoidance, and the introduction of the illusion to avoid, provides the opportunity to expose participants in both groups to exactly the same amount of individually calibrated nociceptive stimulation. Differences between groups found in the outcome measures, such as pain-related fear and threat appraisals, can then be ascribed only to participants' own behaviour as source of information, and not to differences in physical intensity and duration of the heat stimulus. In the test phases of the experiments, the avoidance behaviour would be unavailable to perform.

Together, the findings of the studies described in chapters 2 and 3 suggest that instructed avoidance behaviour increases pain-related fear once the avoidance behaviour is made unavailable, thereby providing support for the bidirectionality hypothesis. One way to explain this finding is e.g. in terms of Lovibond's expectancy model (2006). This model proposes that an individual who cannot perform an avoidance behaviour expects an aversive outcome and because of this expectancy fear will be generated towards the aversive event. Here, the avoidance group participants, who cannot perform their avoidance behaviour anymore (i.e., pressing a stop-button), regarded the pain as more threatening and because of this increased threat appraisal, fear was generated towards the painful stimulus. Avoidance behaviour may thus directly or indirectly (i.e., via threat appraisals) contribute to the intensity of pain-related fear. This is in line with research by Crombez and colleagues (2008) who found that the loss of control over pain is worse than never having control over pain.

Apart from Lovibond's expectancy model, there are also other explanations for the bidirectional relationship between avoidance behaviour and pain-related fear. For example, individuals may infer danger from the use of their own avoidance behaviour (avoidance behaviour as information "*I am avoiding, therefore I must be scared*"; Gangemi et al., 2012; van den Hout et al., 2014). A third explanation might be that the instructed use of the avoidance behaviour in a relatively safe situation may induce cognitive dissonance, because the behaviour is not in line with the perception of threat in that situation (Festinger, 1957). Individuals may reduce this dissonance by bringing their own threat and fear perception in line with their behaviour.

Also, the mediation analysis of the second study reveals that perceived threat totally mediated the relationship between avoidance behaviour and pain-related fear, suggesting an additional avoidance → threat → pain-related fear loop as an extension to the fear-avoidance model. The current study sheds another light on the mediating role of threat appraisals than previously described. For example, studies by Gheldof and colleagues (2006, 2010) have shown that pain-related fear acted as a (partial) mediator between pain intensity and disability, and between negative affectivity and disability. To date, the underlying mechanisms by which various factors in the fear-avoidance model can mediate the relationships between e.g. fear and avoidance, are still largerly unknown and will require further research.

As mentioned at the beginning of this paragraph, the designs of the first and the second study (chapters 2 and 3) were based on instructed avoidance (i.e. the participants were told to press a stop-button upon a cue). One of the drawbacks of this approach is that it may be possible the participants were avoiding the painful stimulus, simply because they were instructed to do so, rather than because of fear for the painful stimulus. This can be overcome by using a design where avoidance behaviour will be acquired through operant learning of pain-related avoidance behaviour, which was applied in studies 3 and 4 (chapters 4 and 5).

6.3 Do pain-related fear and pain change when operantly acquired avoidance becomes ineffective?

The third study, described in chapter 4, which examined motor-behavioural characteristics of avoidance behaviours during different movements, was designed around operant learning of pain-related avoidance behaviour. Participants successfully acquired/learned avoidance behaviour during a robotic arm-reaching task, whereby they were instructed to reach a target location via freely choosing one of three trajectory movements. During acquisition, they learned they could truly avoid a painful electrocutaneous stimulus by selecting one movement trajectory over the other trajectories to reach a target location. A trade-off between pain and resistive force was created such that the partial pain (T2) and no-pain trajectory (T3) was associated with more difficulties to move. In the other phases of the experiment, the avoidance behaviour would still be possible to perform, although it would be ineffective. Here we assumed that our paradigm, especially the manipulation of ineffective avoidance and its effect on pain-related fear and pain, would be a suitable experimental analogue to investigate the mechanisms of avoidance for chronic pain patients.

In this third study, Pavlovian (classical) conditioning and operant (instrumental) conditioning took place within the same phase. We did not follow typical phased learning, where fear is acquired through Pavlovian conditioning, followed by a phase of operant acquisition of avoidance. We observed that conditioned fear resulted in avoidance behaviour and in turn the operantly acquired avoidance behaviour affected the conditioned pain-related fear, even when the avoidance behaviour became ineffective. These results, like in the studies described in chapters 2 and 3, provide support for the bidirectionality hypothesis. Furthermore, the observation of an increase of pain-related fear during ineffective avoidance is in line with the results of Crombez and colleagues (2008), showing that losing control over pain resulted in more fear of the impending pain stimuli. In this case the pain-related avoidance was not completely lost, but became ineffective, so in a way this can also be considered as a loss of control over pain. A potential explanation for the observed increase of pain-related fear during ineffective avoidance may be found in the process of worry, i.e. a dynamic process of humans

engaged in making sense of threat and in attempting to solve problems associated with that threat (Mathews, 1990). For chronic pain patients there are two essential elements for worrying about chronic pain: (1) chronic pain patients experience many forms of threat; (2) patients persevere in attempting to solve the insoluble problem of chronic pain. In our study, the threat value of the pain, which cannot be effectively avoided anymore (the target of worry), increases the pain-related fear and worry may result in persistent attempts to try to avoid the pain, despite avoidance being ineffective (Aldrich, Eccleston, & Crombez, 2000).

When avoidance became ineffective, we also found that pain threshold and tolerance declined, suggesting that failure to control pain may increase pain or reduce pain tolerance in future circumstances (Crombez et al., 2008; Janssen, Spinhoven, & Arntz, 2004; Masedo & Esteve, 2007; Zettle et al., 2005)

6.4 Does operantly acquired avoidance performed in the context of a novel, ambiguous movement increase pain-related fear?

The fourth study, described in chapter 5, used a similar paradigm as the third study, with the exception that (1) no resistance was applied to the three different movement trajectories (i.e. by making the three movements equally effortful, the costs associated with making the movement were taken out as a variable), and (2) the operantly acquired avoidance behaviour did not become ineffective, but could be considered unnecessary, because the novel movement was potentially safe. Also here, the results provide support for the bidirectionality hypothesis. Once avoidance behaviour had been acquired for a pain-related movement, we found evidence that avoiding in the context of a novel, ambiguous movement provokes pain expectancy and pain-related fear towards that movement, even in the absence of confirmation of the actual threat level of the movement. Also, the operantly acquired avoidance response may lead to the misattribution of safety to that response, again resulting in the transfer of pain-related fear and threat.

In addition, the availability of the operantly acquired avoidance response may function as a contextual cue, indicating the potential threat of a novel, potentially safe movement, that needs to be prevented by performing an avoidance response (Engelhard et al., 2015).

6.5 Proposed extension of the fear-avoidance model

The fear-avoidance model introduced by Lethem, Slade, Troup and Bentley (1983), and further elaborated by Vlaeyen and Linton (2000; 2012), has inspired productive research and has become the leading paradigm for understanding disability associated with chronic pain conditions. The fear-avoidance model shows cyclical relationships between risk factors like catastrophizing, fear, depression, and pain-related disability. Several studies have challenged the validity of the cyclical and unidirectional relationships proposed in the fear-avoidance model. For example, studies by Bergbom, Boersma, and Linton (2012) and Wideman, Adams, and Sullivan (2009) failed to show that changes in pain catastrophizing lead to changes in pain-related fear or that changes in fear lead to changes in depression. For a further review regarding the topic of relationships in the fear-avoidance model, please also see Wideman and colleagues (2013).

In this PhD research project, we have investigated the relationships between threat appraisals, pain-related fear, and avoidance behaviour. The results of our studies provide supporting evidence for the bidirectionality hypothesis regarding the relationship between pain-related fear and avoidance behaviour, whereby pain-related fear leads to avoidance behaviour (one direction) and in turn, engaging in avoidance behaviour increases pain-related fear (other direction). The manifestation of the increase in pain-related fear in our studies was observed when the earlier acquired avoidance behaviour became either unavailable or ineffective. Since the current version of the fear-avoidance model assumes a unidirectional relationship between pain-related fear and avoidance, we propose an extension of the fear-avoidance model by including the bidirectional relationship between pain-related fear and avoidance, based on the results of the studies described in this dissertation. In Figure 6.1 we show the proposed extension of the fear-avoidance model. The combination of the red arrow and the newly introduced blue arrow in Figure 6.1 shows the bidirectional relationship between pain-related fear and avoidance. Because of the bidirectional relationship of fear and avoidance, one could

speculate that initial low-cost avoidance behaviour could develop into high-cost avoidance response via overgeneralisation of avoidance behaviour, and thereby contributing to the development of chronic pain (Dymond, Schlund, Roche, De Houwer, & Freegard, 2012). For example, when an individual experiences pain while lifting a box, (s)he will avoid to lift this particular box (low-cost avoidance). However, through stimulus generalisation, this person may also become afraid to experience pain while lifting his/her baby and therefore will avoid holding his/her baby (high-cost avoidance). Also, the findings regarding this bidirectional relationship may have clinical implications and suggest that allowing avoidance behaviours during treatment may thwart fear reduction. These findings can potentially help to further our understanding of how persisting in avoidance behaviour may lead to the development and maintenance of irrational fears and threat appraisals.

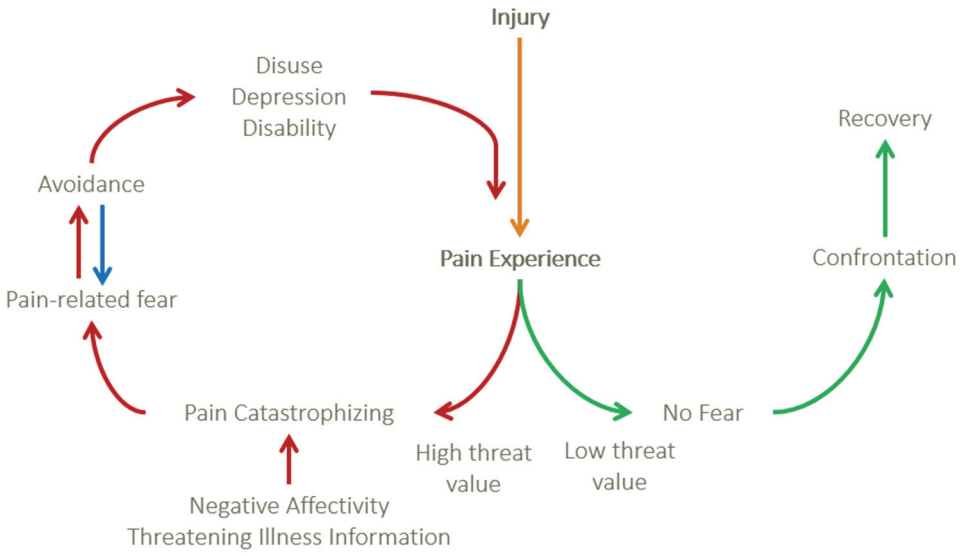

Figure 6.1. Proposed extension (blue arrow) of the fear-avoidance model of chronic pain shows the bidirectional relationship between pain-related fear and avoidance.

6.6 Clinical implications

The experimental studies conducted in the context of the current PhD research project included healthy, pain-free participants and hence, before generalising the findings of the studies to patients with chronic pain, future studies need to validate these findings using clinical samples. However, the results of the studies can still be used to gain a better understanding of the dynamics between avoidance behaviour and pain-related fear, including the bidirectionality, which could lead to new insights regarding the complexity associated with the development and maintenance of chronic pain. We give some examples of the potential clinical implications below.

Traditional exposure therapy for chronic pain patients was aimed at the extinction of fear, not necessarily the extinction of avoidance. This was based on the idea that avoidance would reduce as a result of the extinction of fear. However, a reduction in avoidance is not always observed upon fear extinction, and therefore the situation regarding the effects of exposure treatment is more complex. For example, a recent study by Simons and colleagues (2020), where a group of 27 youth with mixed chronic pain completed a graded in vivo exposure treatment (GET), showed improvements during GET to be superior to the no-treatment randomized baseline period for avoidance, pain acceptance, and pain intensity, whereas fear and pain catastrophizing only improved at 3- and 6-months follow-ups. Avoidance and activity engagement (acceptance) are behavioural measures, whereas fear and catastrophizing are cognitive measures and the results of this GET study do suggest a behaviour → cognition "order of operations" in relation to treatment response. In other words, given the above "order of operations", it seems to be more important to target avoidance behaviour first during exposure therapy, after which a decrease in pain-related fear will follow.

As a result of the bidirectionality relationship, for which we found supporting evidence in our studies, tackling avoidance behaviour to reduce fear in the context of exposure therapy, seems as important as reducing fear to halt the process of chronicity in individuals with chronic pain. This can be realized by response prevention during repeated exposure to the painful stimuli, or by introducing rewards for the decision to perform painful movements. One of our studies (chapter 3) also showed a mediating effect of threat appraisals on the relationship between avoidance behaviour and pain-

related fear. Understanding the effects of mediation of the bidirectional relationship between avoidance and pain-related fear can provide insights into the mechanisms associated with the development of chronic pain, and can help in tailoring individualised treatments. For example, targeting the meaning of the threat appraisals on the relationship between pain-related fear and avoidance behaviour, by cognitive techniques, could have a positive impact on the outcome of exposure therapy for chronic pain patients. These cognitive techniques may include concepts derived from Acceptance and Commitment Therapy (ACT), such as explicit focus on pain willingness and value-based action (Wicksell, Melin, Lekander, & Olsson, 2009). The ACT treatment model is based on awareness and acceptance of both negative and positive experiences. It also identifies valued life directions and provides appropriate actions towards goals that support those values (Wetherell et al., 2011).

We would suggest adopting a multidisciplinary approach to improve the patient's condition and circumstances through both pharmacological and non-pharmacological treatments. The multidisciplinary approach to improve the quality of life of chronic pain patients could be achieved by applying new technologies, like smart phone applications, developed by multiple disciplines, e.g. software engineers, behavioural psychologists, data scientists, fysiotherapists. These applications could trace the activities of chronic pain patients and help in controlling their avoidance behaviours by behavioural techniques. In other words, we would suggest to closely monitor critical (in)activities of pain patients to assess the level of avoidance in order to be able to intervene at an early stage to "break" the relationship between avoidance and fear and thereby prevent the development of chronic pain disability.

6.7 Strengths and limitations

There are several strengths in the present dissertation. First, in the experimental designs, avoidance behaviour was successfully operationalised in two different ways: instructed (pressing a stop-button upon presentation of a stop-cue) and via operant learning (robotic arm-reaching task), so that the effects of the type of avoidance behaviour on the outcome measures could be investigated. Second, the research project included a replication study (chapter 3), confirming the main results of the original study (chapter 2). Third, we used

two different paradigms: one where the avoidance response was simply pressing a stop-button (no associated costs) and another one that allowed participants to perform avoidance during a robotic arm-reaching task, whereby participants performed the most deviating trajectory to avoid the painful stimuli (avoidance came with a cost, which is also the case in chronic pain and is more valid than avoidance with no associated costs). Although we used two different paradigms, the outcome measures were very similar, thereby strengthening the experimental support for the bidirectional relationship between pain-related fear and avoidance behaviour.

There are also several limitations. First, a limitation of the current research project is the use of healthy, pain-free participants, which may make translation of the experimental findings of the current studies to the field of chronic pain less straight forward. Second, the pain modalities which were used in the various paradigms (i.e. painful heat stimulus and electrocutaneous stimulus), are not ecologically valid and differ from the experience of chronic pain patients. Third, the designs of our studies e.g. did not consider competing goals, such as rewards for approach behaviour. As shown in studies by e.g. Claes, Crombez and Vlaeyen (2015; 2016), avoidance of pain-related stimuli is reduced when goal-directed avoidance inflicts costs. Since we did not include rewards for non-avoidance in our paradigms, we were not able to investigate the effects of rewards on the bidirectional relationship between avoidance and fear. Fourth, in our studies, we did not explore resilience factors, which can explain how individuals can successfully adapt to adverse stimuli or situations (Sturgeon & Zautra, 2010). High levels of resilience factors, such as optimism and positive affect, may enhance inhibitory learning and may reduce the generalisation of pain-related fear (Geschwind, Meulders, Peters, Vlaeyen, & Meulders, 2015; Meulders, Meulders, & Vlaeyen, 2014; Zbozinek & Craske, 2017). Fifth, the samples we used for our experiments were not gender-balanced and consisted for more than 50% of female participants. Since females may have enhanced fear acquisition (McClure et al., 2004; Pittig, Wong, Glück, & Boschet, 2020), future research may benefit from obtaining more gender-balanced samples. Sixth, we did not include measures of relief in our experiments, whereby relief refers to a positive affective state that an individual experiences when an expected negative event is omitted (Roseman, 1996; Roseman, Spindel, & Jose, 1990). Relief learning can play a role in the

underlying mechanism that reinforces goal-directed avoidance (Vervliet, Lange, & Milad, 2017). Finally, we want to mention that the effect sizes (generalised eta-squared) for the experiments described in chapters 2 and 3 were relatively small, i.e. generally in the range of approximately 0.01 (small) to 0.13 (medium) (Cohen, 1988).

6.8 Future directions

The main aim of the present PhD research project was to investigate the bidirectional relationship between pain-related fear and avoidance behaviour, in the context of the fear-avoidance model of chronic pain, to better understand the mechanisms associated with the development and maintenance of chronic pain. In addition to the relationship between pain-related fear and avoidance behaviour, there are multiple other parameters that are part of the fear-avoidance model, e.g. threatening illness information, negative affectivity, pain experience. Future research could focus on the relationships between these various parameters, which could also be multi-directional, and their effects on the development and maintenance of chronic pain. Also, little research has targeted the part of the fear-avoidance model that describes the path to recovery and we would recommend future research to examine the mechanisms involved in following this path (please also see Figure 6.1).

Future research may focus more on studying pain-related fear and avoidance behaviour in naturalistic everyday settings, using clinical samples, rather than in laboratory type settings, using healthy, pain-free participants. For example, using a virtual reality setting, whereby chronic pain patients perform certain real-life tasks in an experimental design, like opening cupboards, lifting objects, doing household tasks. In this way, the results could be more ecologically valid. Since chronic pain patients may be reluctant to lift objects in real life as a result of pain-related fear and pain catastrophizing, virtual reality setting may be used to overcome this reluctance and would allow for e.g. graded exposure to fearful movements and to reduce the number of drop-outs during exposure therapy (also see e.g. Trost et al., 2015). Also, to assist with potential improvements in treatment models for chronic pain patients, we would suggest to also include parameters like competing goals, rewards, resilience factors and relief learning in future research.

In the research project described in this dissertation, the focus was mainly on avoiding pain, while chronic pain patients, with persistent pain, do not necessarily try to avoid pain, but their avoidance behaviour could be driven by irrational fears and pain catastrophizing. Future studies should focus on how those irrational fears and their effects on the development and maintenance of chronic pain can be mitigated. For example, helping patients to disconfirm potential irrational expectations regarding pain and harm and challenging them to convert their fearful beliefs (Atlas & Nardin, 2003; Boersma & Linton, 2005).

The bidirectional relationship between pain-related fear and avoidance behaviour can be amplified or dampened by moderating factors (for an overview please also see Pittig et al., 2020). Amplifying and risk factors include e.g. anxiety sensitivity, age, gender, adverse life events and high threat environments, stress, effectiveness of avoidance behaviour. Dampening factors include e.g. distress tolerance (i.e. the capacity to experience and withstand negative psychological states), positive affect (i.e. positive emotions such as determination, enthusiasm, interest and joy), cost of avoidance and incentives for competing behaviour, social demand. The mechanisms whereby these factors moderate the bidirectional relationship between pain-related fear and avoidance behaviour are still largely unknown and therefore future research in these areas would be recommended.

6.9 Conclusion

In conclusion, the findings of the current research project provide support for the bidirectional relationship between pain-related fear and avoidance, whereby pain-related fear leads to avoidance and, in turn, avoidance leads to pain-related fear. The outcome of the studies has been used to suggest an extension of the fear-avoidance model of chronic pain by including the bidirectional relationship between pain-related fear and avoidance into the model. Finally, the present project may initiate future research to study the relationships between other parameters of the fear-avoidance model and can help to further our understanding of the underlying mechanisms in the development and maintenance of chronic pain.

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Summary

To avoid or not to avoid, that's the question

Why is it that some people develop chronic pain after an injury, while others don't? Pain has a clear function for our survival, because it signals potential harm or danger to the body and it promotes behaviours, such as avoidance and escape, to protect ourselves against these dangers. However, pain could also become a false alarm, especially in the case of chronic pain, where there is often no objectifiable injury and where pain is disconnected from its original function.

Avoidance is considered key in the development and maintenance of chronic pain. Fear-avoidance models propose that pain-related fear may spur avoidance behaviour leading to chronic pain disability. So far, the fear-avoidance model assumes a unidirectional relationship between pain-related fear and avoidance, i.e. pain-related fear evokes avoidance behaviour. However, little is known about how avoidance behaviour subsequently affects pain-related fear and pain. In this PhD research project we introduced a new line of experimental work to further investigate the relationship between pain-related avoidance behaviour and pain-related fear. In a series of studies we have experimentally manipulated (the perception of) avoidance behaviour and tested its effects on changes in fear and pain reports. The results of our studies indicated that engaging in avoidance may (paradoxically) increase rather than decrease pain-related fear (i.e. bidirectionality hypothesis, whereby pain-related fear leads to avoidance behaviour (one direction) and in turn, engaging in avoidance behaviour increases pain-related fear (other direction)).

In our first study (see chapter 2) we tested the effects of avoidance of a painful heat stimulus on pain-related fear and pain. The results showed that self-reported pain-related fear was higher after performing an avoidance response (pressing the stop-button), despite equal intensities and duration of the heat stimulus as in the control condition. In our second study (see chapter 3), where we also tested the effects of avoidance of a painful heat stimulus, we replicated the findings of the first study, whereby we observed higher pain-related fear levels when the avoidance response was no longer available compared to those when the avoidance response was available. We also found that perceived avoidance attenuates pain reports despite exposure to identical stimulus intensity. In addition, the results showed that increased threat appraisals mediated the

relationship between avoidance behaviour and increased pain-related fear. Together, these results provide support for a bidirectional relationship between fear and avoidance.

Chapter 4 describes our third experimental study, where we examined motor-behavioural characteristics of avoidance behaviours during different movements, using the HapticMaster, a 3-degrees of freedom, force-controlled robotic arm. We investigated the changes in pain-related fear and pain when avoidance behaviour was no longer effective. The results indicated participants became more afraid of and sensitive to pain, when previously acquired avoidance behaviour was no longer effective. Also, participants continued to show avoidance behaviour despite it being not adaptive anymore. These findings suggest that ineffective avoidance may play a role in the development and maintenance of chronic pain.

In our fourth experimental study (see chapter 5), where we also applied a robotic arm-reaching task, we investigated whether performing a movement to avoid a painful stimulus in the context of a novel, ambiguous movement increased threat and pain-related fear towards this movement, and whether avoidance behaviour persisted when given the choice between performing the acquired movement to avoid a painful stimulus or an alternative, novel movement. The results revealed that acquired avoidance behaviour in the presence of a novel, ambiguous movement elevated pain expectancy and pain-related fear towards that novel movement, even in the absence of confirmation of the actual threat level of the novel movement. We also observed persisting avoidance behaviour towards the novel movement, thereby preventing disconfirmation of the novel movement threat appraisals. These findings suggest that avoidance in the context of other neutral activities/movements may lead to the development and maintenance of threat appraisals and irrational fears.

Taken together, the findings reported in this dissertation provide support for the bidirectional relationship between pain-related fear and avoidance and constitute an important step in furthering our understanding of the underlying mechanisms in the development and maintenance of chronic pain.

Samenvatting

(Dutch summary)

Vermijden of niet vermijden, dat is de vraag

Waarom ontwikkelen sommige mensen chronische pijn na een letsel, terwijl dat bij anderen niet gebeurt? Pijn heeft een duidelijke functie voor ons overleven, omdat pijn potentiële schade of gevaar voor het lichaam signaleert en het bevordert gedragingen, zoals vermijden en ontsnappen, om onszelf te beschermen tegen deze gevaren. Echter, pijn kan ook een vals alarm worden, vooral in het geval van chronische pijn, waar er vaak geen sprake is van een daadwerkelijk letsel en waar pijn niet meer verbonden is met zijn originele functie.

Vermijding wordt beschouwd als zijnde cruciaal in de ontwikkeling en het behoud van chronische pijn. Vreesvermijdingsmodellen gaan ervan uit dat pijngerelateerde vrees vermijdingsgedrag kan aansporen, hetgeen kan leiden tot functiebeperkingen als gevolg van chronische pijn. Tot dusverre veronderstelt het vreesvermijdingsmodel een unidirectionele relatie tussen pijngerelateerde vrees en vermijding, i.e. pijngerelateerde vrees roept op tot vermijdingsgedrag. Echter, er is weinig bekend hoe vermijdingsgedrag vervolgens pijngerelateerde vrees en pijn beïnvloedt. In dit doctoraatsproject introduceerden we een nieuwe reeks van experimenteel onderzoek om de relatie tussen pijngerelateerd vermijdingsgedrag en pijngerelateerde vrees verder te onderzoeken. In een aantal studies hebben we (de perceptie van) vermijdingsgedrag experimenteel gemanipuleerd en de effecten ervan op veranderingen in vrees en pijn getest. De resultaten van onze studies gaven aan dat het uitoefenen van vermijdingsgedrag (paradoxaal) kan leiden tot een toename, in plaats van een afname van pijngerelateerde vrees (i.e. bidirectionaliteitshypothese, waarbij pijngerelateerde vrees leidt tot vermijdingsgedrag (de ene richting) en, op zijn beurt, het uitoefenen van vermijdingsgedrag leidt tot een toename van pijngerelateerde vrees (de andere richting)).

In onze eerste studie (zie hoofdstuk 2) testten we de effecten van vermijding van een pijnlijke warmteprikkel op pijngerelateerde vrees en pijn. De resultaten toonden aan dat zelf-gerapporteerde pijngerelateerde vrees hoger was na het uitvoeren van een vermijdingsreactie (het indrukken van een stopknop), ondanks het feit dat intensiteit en duur van de warmteprikkel in werkelijkheid gelijk waren als in de controle conditie. In onze tweede studie (zie hoofdstuk 3), die ook betrekking had op het vermijden van een warmteprikkel, repliceerden we de bevindingen van onze eerste studie, waarbij we

hogere pijngerelateerde vrees observeerden op het moment dat de vermijdingsreactie niet langer beschikbaar was ten opzichte van de pijngerelateerde vrees toen de vermijdingsreactie nog wel beschikbaar was. We vonden ook dat perceptuele vermijding leidt tot een gerapporteerde lagere pijn, ondanks het feit dat er sprake was van blootstelling aan een identieke intensiteit van de warmteprikkel. Bovendien bleek uit de resultaten dat de relatie tussen vermijdingsgedrag en toegenomen pijngerelateerde vrees werd gemedieerd door een toegenomen dreigingsevaluatie. Tezamen leveren deze resultaten ondersteuning voor een bidirectionele relatie tussen vrees en vermijding.

Hoofdstuk 4 beschrijft onze derde experimentele studie, waar we de motorische vermijdingskarakteristieken onderzochten van verschillende bewegingen, gebruik makend van de HapticMaster, een over 3-vrijheidsgraden beschikkende, krachtgeregelde robotarm. We onderzochten de veranderingen in pijngerelateerde vrees en pijn wanneer het vermijdingsgedrag niet langer effectief was. De resultaten gaven aan dat deelnemers banger van en gevoeliger voor pijn werden, wanneer het eerder aangeleerde vermijdingsgedrag niet langer effectief was. Deelnemers bleven ook het vermijdingsgedrag vertonen ondanks dat het niet meer adaptief was. Deze bevindingen suggereren dat ineffectieve vermijding mogelijk een rol speelt in de ontwikkeling en het behoud van chronische pijn.

In onze vierde experimentele studie (zie hoofdstuk 5), waarin we ook gebruik maakten van de robotarm bewegingstaak, onderzochten we of het uitvoeren van een beweging om een pijnlijke stimulus te vermijden in de context van een nieuwe, ambigue beweging dreiging en pijngerelateerde vrees verhoogde ten aanzien van deze nieuwe beweging, en of het vermijdingsgedrag aanhield wanneer de keuze werd gegeven tussen het uitvoeren van de aangeleerde beweging om een pijnlijke stimulus te vermijden of een alternatieve, nieuwe beweging. De resultaten maakten duidelijk dat aangeleerd vermijdingsgedrag in de aanwezigheid van een nieuwe, ambigue beweging pijnverwachting en pijngerelateerde vrees verhoogde ten opzichte van deze nieuwe beweging, zelfs in de afwezigheid van de bevestiging van de actuele dreiging van de nieuwe beweging. We zagen ook aanhoudend vermijdingsgedrag voor deze nieuwe beweging, hetgeen ontkenning van de dreigingsevaluatie van de nieuwe beweging voorkwam. Deze bevindingen suggereren dat vermijding in de context van andere

neutrale activiteiten/bewegingen kan leiden tot de ontwikkeling en het behoud van dreigingsevaluaties en irrationele vrees.

Samenvattend geven de bevindingen die gerapporteerd worden in deze dissertatie ondersteuning voor de bidirectionele relatie tussen pijngerelateerde vrees en vermijding en zij vormen een belangrijke stap in de richting van het verder begrijpen van de onderliggende mechanismen in de ontwikkeling en het behoud van chronische pijn.

Impact paragraph

Ouch! An expression many of us have used when we suddenly experience pain. Although experiencing pain is usually unpleasant, it has a clear function for our survival, because it signals potential harm or danger to the body and it promotes behaviours, such as avoidance and escape, to protect ourselves against these dangers (Eccleston & Crombez, 1999; Morley & Eccleston, 2004; Williams, 2016). However, pain could also become a false alarm, especially in the case of chronic pain, where there is often no objectifiable injury and where pain is disconnected from its original function.

When does pain become chronic pain? Once pain is disconnected from its acute warning function of physiological nociception, and persists past normal healing time, pain is considered as chronic when it lasts or recurs for more than 3 to 6 months (Merskey & Bogduk, 1994). The impact of chronic pain on people's daily activities and quality of life is not to be underestimated. Several studies have shown that chronic pain affects at least 10% to 30% of the adult population in Europe (Breivik, Collett, Ventafridda, Cohen & Gallacher, 2006; Reid, Harker, Bala, Truyers, Kellen, Bekkering, & Kleijnen, 2011). Chronic pain not only affects people's daily activities and quality of life, but there are also influences on the social and family environment of people suffering from chronic pain. For example, those people do not engage in social activities anymore, they can lose their jobs, get depressed, and they run an increased risk of other somatic and psychological illnesses (Breivik et al., 2006). As a result, there is a significant burden associated with chronic pain, not only related to the costs of the health care system, but also from the loss of productivity and from disability related payments to sufferers from chronic pain (Reid et al., 2011).

Avoidance is considered key in the development of chronic pain. Fear-avoidance models propose that pain-related fear may spur avoidance behaviour leading to chronic pain disability. However, little is known about how avoidance behaviour subsequently affects pain-related fear and pain. In this PhD research project we introduced a new line of experimental work to further investigate the relationship between pain-related avoidance behaviour and pain-related fear. In a series of studies we have experimentally manipulated (the perception of) avoidance behaviour and tested the effects on changes in fear and pain reports. The results of our studies indicated that engaging in avoidance

may (paradoxically) increase rather than decrease pain-related fear (i.e. bidirectionality hypothesis). These results can be of interest to researchers, clinicians, people suffering from chronic pain, and the general public.

The experimental studies conducted in the context of the current PhD research project included healthy, pain-free participants and hence, before generalising the findings of the studies to patients with chronic pain, future studies would need to validate these findings using clinical samples. However, the results of the studies can still be used to gain a better understanding of the dynamics between avoidance behaviour and pain-related fear, including the bidirectionality, which could lead to new insights regarding the complexity associated with the development and maintenance of chronic pain. We give some examples of the potential clinical implications below.

Tackling avoidance behaviour to reduce fear (as a result of the bidirectionality relationship) seems as important as reducing fear to halt the process of chronicity in individuals with chronic pain. This can be realized by response prevention during repeated exposure to the painful stimuli, or by introducing rewards for the decision to perform painful movements. One of our studies also showed a mediating effect of threat appraisals on the relationship between avoidance behaviour and pain-related fear. Understanding the effects of mediation of the bidirectional relationship between avoidance and pain-related fear can provide insights into the mechanisms associated with the development of chronic pain, and can help in tailoring individualised treatments. For example, targeting the meaning of the threat appraisals on the relationship between pain-related fear and avoidance behaviour, by cognitive techniques, could have a positive impact on the outcome of exposure therapy for chronic pain patients.

Future research may focus more on studying pain-related fear and avoidance behaviour in naturalistic everyday settings, using clinical samples, rather than in laboratory type settings, using healthy, pain-free participants. For example, using a virtual reality setting, whereby chronic pain patients get to perform certain real-life tasks in an experimental design, like opening cupboards, lifting objects, doing household tasks. In this way, the results could be more ecologically valid.

In summary, there clearly is a need to better understand the development and maintenance of chronic pain and to adopt a multidisciplinary approach to improve the patient's condition and circumstances through both pharmacological and non-pharmacological treatments. Therefore, it will be necessary to develop research initiatives that will include biopsychosocial perspectives to produce new insights into the mechanisms that modulate pain, with an aim to develop effective health policies to prevent and manage chronic pain, thereby minimizing or avoiding the disability that it causes to the individuals suffering from chronic pain. For example, the multidisciplinary approach to improve the quality of life of chronic pain patients could be achieved by applying new technologies, like smart phone applications, developed by multiple disciplines, e.g. software engineers, behavioural psychologists, data scientists, fysiotherapists. These applications could trace the activities of chronic pain patients and help in controlling their avoidance behaviours by behavioural techniques.

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"There is no great concurrence between learning and wisdom"
Francis Bacon

Curriculum vitae

Christine van Vliet was born on 11 December 1991 in Leiden, the Netherlands. In 1992, she moved with her parents to the United Kingdom and she returned to Oegstgeest, the Netherlands in 1996 and then moved to Keerbergen, Belgium in 1998. She received most of her education in Belgium and in July 2015, she obtained her Master of Science degree (cum laude) in Psychology, Theory and Research, at KU Leuven. During her master's programme, Christine did an internship in the Laboratory for Biological Psychology at KU Leuven, where she conducted experiments to study the neural basis of expertise, comparing the fMRI data of bird experts, mineral experts and novices. For her thesis, she carried out a research project in the Laboratory of Experimental Psychology at KU Leuven in the area of visual perception, studying the characteristics of target appearance changes in visual crowding.

As from 1 October 2015, she started as a PhD student in a joint doctorate between the universities of Leuven and Maastricht, focusing on the paradoxical effects of avoiding pain, under the supervision of prof. dr. Johan Vlaeyen, dr. Ann Meulders and dr. Linda Vancleef. In October 2019, she started an advanced master's programme at KU Leuven and she obtained an additional degree in Clinical Psychology in 2020 (cum laude). During her internship for the advanced master's programme, she worked at a data science company in Antwerp, Belgium, assisting with the development of applications aimed at changing the behaviour of people, e.g. improving well-being, improving driving behaviours.

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