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Pathways to the generalization of pain-related avoidance behavior

Eveliina Glogan

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Pathways to the generalization of pain-related avoidance behavior

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CHAPTER 1

AN INTRODUCTION TO THE GENERALIZATION OF PAIN-RELATED AVOIDANCE BEHAVIOR

Chronic pain: definition, prevalence, and burden

Pain, nowadays, is understood as *"[an] unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (Raja et al., 2020, p. 2), and is thus just as much an emotional experience as a physical one. A large body of literature shows that pain and emotion are inextricably linked (Linton, 2013), with some authors calling for pain to be viewed as a homeostatic emotion in and of itself, implicating pain as a basic behavioral drive, similar to hunger or thirst (Craig, 2003). Indeed, acute pain has the important function of alerting us to imminent or actual threat to the body, and thus motivates certain reflexes (e.g. attention to the site of injury) or behaviors (e.g. avoidance) in order to minimize further harm. In contrast, chronic pain can occur even in the absence of any apparent tissue damage. Therefore, these protective behaviors are often no longer necessary when pain becomes chronic. Clinically, pain is considered chronic when it persists beyond normal healing time – most often 3 months post-injury (Merskey & Bogduk, 1994). Recent classifications recognize different types of chronic pain (Treede et al., 2015; World Health Organization, 2018). In some cases, the anatomical cause of pain can be easily pinpointed (e.g. chronic post-surgical pain or chronic pain following an injury) (Treede et al., 2015), while in other chronic pain conditions, the source of pain cannot be traced back to any clear pathophysiology (e.g. fibromyalgia) (Nicholas et al., 2019), leaving their exact etiology unknown. Yet, in both cases, pain often has lost its acute warning function and has thus transitioned to a state that is not proportionate to the degree of tissue damage (Merskey & Bogduk, 1994).

For a decade, pain-related conditions have been the leading cause of disability and disease burden worldwide (Vos et al., 2017). For example, low back- and neck pain have consistently been among the top global causes of years lived with disability, with other chronic pain conditions featuring eminently in the top 10 causes of disability (Vos et al., 2017). The population prevalence estimates of chronic pain (i.e. proportion of the at-risk population affected by a condition) vary widely due to differences in employed research methodologies, and in the time point, place and populations studied (Mills et al., 2019). Some studies estimate that chronic pain affects approximately 20% of the global population (Breivik et al., 2006; Goldberg & McGee, 2011;

Institute of Medicine, 2011), and accounts for 15-20% of doctor visits (Koleva et al., 2005; Mäntyselkä et al., 2001). In the Netherlands, moderate to severe chronic non-cancer pain was found to affect 18% of adults, 79% of whom reported receiving inadequate treatment of their pain, and 43% of whom reported receiving no treatment (Bekkering et al., 2011). Staggeringly, a recent meta-analysis suggests that chronic pain affects as many as 35-50% of UK adults, 10.4-14.3% of those reporting moderate-to-severely disabling chronic pain (Fayaz et al., 2016).

The economic impact of pain is greater than that of most other health conditions (Maniadakis & Gray, 2000), including heart disease, cancer, and diabetes (Gaskin & Richard, 2012), due to the impact of chronic pain on rates of absenteeism and reduced levels of productivity at work (presenteeism), as well as the risk of leaving the labor market (Phillips, 2009). For instance, people with chronic pain were found to be seven times more likely to quit their jobs due to ill health compared to gender- and age adjusted pain-free controls (Eriksen et al., 2003). However, the real burden of chronic pain resides within the suffering and reduced quality of life experienced by people with chronic pain, as well as their families. Indeed, chronic pain disorders are associated with some of the poorest quality-of-life indices (Becker et al., 1997; Sprangers et al., 2000), with calls being made for pain relief to be considered a basic human right (Cousins et al., 2004).

Unfortunately, traditional views (Nafe, 1934; Sinclair, 1955; Weddell, 1955) of pain have reduced it to simple nerve stimulation caused by tissue damage. This has resulted in pain being primarily treated from a biomedical perspective, often with painkillers such as opioids, contributing to the current US opioid crisis (Volkow et al., 2018; Volkow et al., 2019). In the Netherlands, more than 80% of opioids are prescribed by general practitioners, indicating that they are still the standard first line treatment for chronic pain (Kalkman et al., 2019). However, not only do opioid-analgesics induce tolerance but they can even increase pain (Chu et al., 2006; Hayhurst & Durieux, 2016). Given the side effects and risks of such drugs (Kornick et al., 2003), as well as their inefficiency to combat chronic pain in the long run, the need for non-drug based treatments of chronic pain is impossible to ignore.

Beyond tissue damage: the biopsychosocial perspective

Traditionally, pain has been understood from a mechanistic point of view, and thus conceptualized as a reflex of the mind in response to damage to the body (Gatchel et al., 2007b). This approach posits that damage to body tissue activates specialized pain receptors (*nociceptors*), which transfer nociceptive input via the spinal cord to the brain, resulting in nociception, i.e. the experience of pain. Thus, pain has conventionally been attributed exclusively to biomedical causes, that is, an underlying pathophysiology, where the extent of tissue damage equals the extent of pain.

According to this view, any treatment that reduces the underlying tissue damage or inhibits nociception, should be sufficient to also reduce pain. However, a number of chronic pain conditions and clinical observations, such as pain experienced in an amputated region of the body (i.e. phantom limb pain; Subedi & Grossberg, 2011), cannot be explained simply in terms of tissue damage.

The Gate Control Theory of Melzack and Wall (1965) fundamentally changed the understanding of pain. The theory was able to provide a physiological explanation for observations of psychological factors affecting pain perception. Specifically, it proposed that a gating system in the dorsal horn of the spinal cord controls both *ascending* signals from the body periphery, as well as *descending* signals from the brain. Due to these bidirectional connections between the brain and the body periphery, the brain was seen as playing an active part in the process of pain perception, rather than passively receiving information from peripheral nociceptors (Melzack & Wall, 1965). The Gate Control Theory paved the way for the biopsychosocial model of Engel (1977), which prompted recognition of psychosocial factors in the reporting of illness, and pain perception in specific, implicating pain as the result of a complex interplay between biological, psychological, and social factors (Engel, 1977).

Subsequently, Loeser (1982) proposed a model explaining pain in terms of four levels, described in terms of concentric rings (see Figure 1.1). Most importantly, Loeser made a distinction between nociception and pain. Specifically, *nociception* resides at the center, on the first level of the model, and refers to the event of sensory nerve-endings being stimulated, conveying information about tissue damage to the brain. In contrast, *pain*, surrounding nociception on the second level, refers to the sensory (nociceptive) information arriving at the brain, producing the *subjective experience* of pain. The third level represents *suffering*, which involves the emotional response to pain, and surrounding this on the fourth and final level, is *pain behavior*. This includes observable pain behaviors, such as attempts to control pain (e.g. avoidance of movements believed to result in pain) (Loeser, 1982). This work integrated psychosocial factors with biological ones to provide a coherent model of the different factors involved in the subjective pain experience.

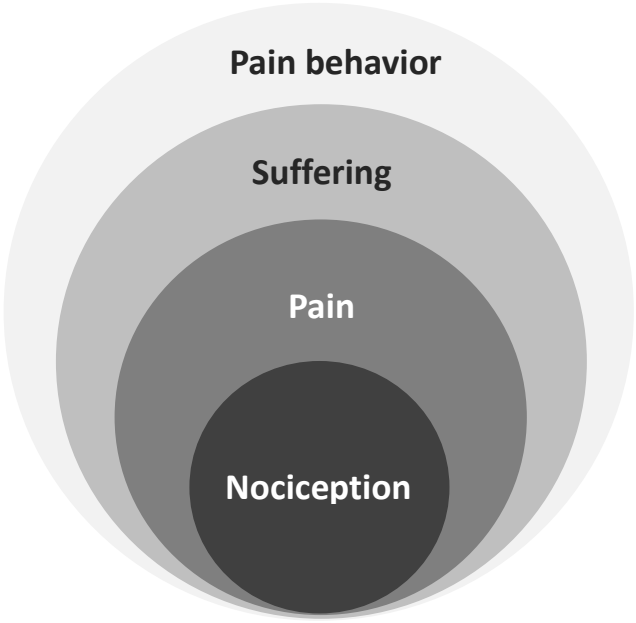

Figure 1.1. Loeser's (1982) multifaceted model of pain components.

In line with this, Fordyce had already previously (1976) highlighted the relevance of overt behaviors, such as activity-avoidance, in the maintenance of chronic pain disability. In line with *instrumental*, or *operant*, learning principles (Skinner, 1953), Fordyce suggested that pain behaviors become established through repeated pairings with specific outcomes (Fordyce, 1976). In the case of avoidance, Fordyce gives the example of a "*limp, established because it avoided or minimized the distress experiences soon after [pain] onset, [continuing] when the person anticipates that walking without the limp would again lead to severe distress*" (Fordyce et al., 1982, p. 3). Fordyce believed that the levels of disability exhibited by people with chronic pain were disproportionate to their actual pain problem, and proposed that, rather than alleviating pain, treatments should focus on reducing disability (Fordyce et al., 1985), thus implicating pain behaviors as the targets of treatment.

Fordyce thus pioneered the use of instrumental methods in the treatment of chronic pain, while simultaneously drawing attention to the roles of cognition and information processing in the development of persistent pain conditions (Morley, 2004, 2011; Turk & Rudy, 1992). Further building on this behavioral approach, Lethem et al. (1983) proposed the fear-avoidance model of chronic pain, which emphasizes the importance of pain-related fear and avoidance in the development and maintenance of chronic pain disability (Lethem et al., 1983). Since then, the model has been further elaborated upon by Vlaeyen and Linton (2000, 2012), and Crombez et al. (2012).

Given pain's essential protective function, it makes sense that it evokes defensive responses, such as some degree of fear. However, there are great individual differences in the extent to which pain evokes fear (Ochsner et al., 2006; Vambheim & Øien, 2017). According to the fear-avoidance model, the way in which people interpret pain is integral to how their pain condition will develop (Vlaeyen & Linton, 2000, 2012). If pain is interpreted as nonthreatening (e.g. just a temporary nuisance, which one is physically and mentally equipped to deal with), people will reduce activity levels for a period of time, after which they will begin to test and correct expectations of pain, for instance, by carefully beginning to use the injured body part. Alternatively, pain can be interpreted *catastrophically*, meaning that it is disproportionately evaluated as a sign of serious injury or pathology, which one has little or no ability to control. The model proposes that these catastrophic misinterpretations lead to excessive fear of pain and/or (re)injury, motivating avoidance of movements believed to worsen the pain or to pose risk of re-injury (Crombez et al., 2012; Vlaeyen & Linton, 2000, 2012).

Although decreased activity levels may promote healing in the short term, if feared movements and activities are not confronted, avoidance precludes any opportunity to test and correct pain expectations, possibly resulting in overestimations of future pain and its negative consequences. In the long-term, if people stop pursuing daily activities and thus become physically less active, they risk increasing physical and psychological deterioration, which makes them more vulnerable to pain, disability, and suffering (Meulders, 2019; Vlaeyen & Linton, 2000, 2012). Furthermore, persistent avoidance may lead to degradation of a person's muscular system and general fitness (*disuse syndrome*) (Verbunt et al., 2003), and this can ultimately increase their susceptibility to pain (Vlaeyen & Linton, 2000). The fear-avoidance model thus explains how pain-related fear and avoidance may culminate into chronic pain disability.

A final theoretical development implicates pain, like any percept, as an outcome of active inference (Tabor, Keogh, et al., 2017; Tabor, Thacker, et al., 2017). All perception relies on the integration of previous experiences with current sensory information (de Lange et al., 2018). Because the brain receives such a vast amount of information, we can only access a portion of it. Thus, the information ultimately available to us is always, to an extent, incomplete, noisy, and ambiguous (Chater et al., 2010; Knill & Pouget, 2004; Körding et al., 2007). For this reason, our brain must filter the sensory signals it receives, to arrive at an estimation of the most likely properties of the outside world, based on current information and existing knowledge (Clark, 2013). The perception of pain, therefore, varies depending on multiple factors, such as present cues (e.g. cues signaling danger vs. safety), expectations (e.g. expectations of danger vs. safety), and prior learning (Tabor, Thacker, et al., 2017). For example, experimental evidence suggests that pain

perception increases when accompanied by credible evidence of imminent tissue damage, and vice versa – credible indication of safety can have pain-reducing effects (Anchisi & Zanon, 2015; Büchel et al., 2014; Moseley & Arntz, 2007). This suggests that the extent to which a person infers threat from pain, their previous experiences with pain, and their prior learning, can all affect the extent to which they experience pain.

Learning to predict painful events: Pain-related fear

Fear-related and anxiety disorders have been predominantly described in terms of learning principles for decades (Mineka & Zinbarg, 2006). Fear and avoidance are core symptoms of fear-related and anxiety disorders (American Psychiatric Association, 2013; World Health Organization, 2018), and according to the National Institute of Mental Health Research Domain Criteria, avoidance behavior is a transdiagnostic behavioral mechanism contributing to a wide array of psychopathologies (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/units/behaviors). Therefore, the recognition of fear and avoidance as central to the etiology of chronic pain disability has resulted in the pain literature being inspired by the learning approach as well (Meulders, 2020).

Pain is a powerful motivator of learning, given its important protective function: if someone accidentally places their hand on a hot stove once, they are very unlikely to make the same mistake again. Pain-related fear can be learned through classical, or Pavlovian, conditioning (Meulders et al., 2011; Meulders & Vlaeyen, 2013). Specifically, pain, as a naturally aversive stimulus, is considered an unconditioned stimulus (US). In other words, without any prior learning, pain evokes defensive reactions, such as fear. These innate defensive reactions are referred to as unconditioned responses (UR). In contrast, if an initially neutral stimulus (conditioned stimulus, CS; e.g. a movement) is (repeatedly) experienced with a US (e.g. pain), the CS may come to be perceived as a predictor of the occurrence of the US. Learning has occurred once the CS receives motivational properties of its own, and comes to elicit defensive reactions (conditioned responses, CR; e.g. fear) even in the absence of the US (Pavlov, 1927). An example of this could be a person experiencing a shooting back pain (US) when performing a yoga pose (CS), and hence becoming fearful (CR) of the yoga pose itself (Vlaeyen, 2015).

Fear acquisition

Classical conditioning of pain-related fear has been consistently demonstrated in the lab (Meulders et al., 2011; Meulders & Vlaeyen, 2013; Vlaeyen, 2015). In a study with a voluntary joystick movement (VJM) paradigm (Meulders et al., 2011), participants performed joystick movements to

the right and left. One of these movements (e.g. to the left; CS+; counterbalanced across participants) was paired with a painful electrical stimulus (US), whereas the other movement (e.g. to the right; CS-) was not. After repeated pairings, the CS+ elicited higher fear responses (self-reported pain-related fear, eye-blink startle responses, i.e. a reflexive cross-species reaction to startle-evoking stimuli (Blumenthal et al., 2005; Davis et al., 2010), and movement latencies, i.e. a proxy of behavioral avoidance), compared to the CS-, which had come to signal safety (Meulders et al., 2011). This type of fear conditioning procedure, where one stimulus is reinforced and the other (control stimulus) is not, is referred to as a *differential* fear conditioning procedure.

Furthermore, this type of learning, where someone develops fear after painful experience, is referred to as learning from *direct experience*. However, it is only one of the pathways in which (pain-related) fear can be learned. One can also learn to fear (pain) based on negative verbal information (Muris et al., 2003; Olsson & Phelps, 2007), for example, by being told that a certain movement will be painful (*instructional learning*). In contrast, positive information about an activity can reduce fear. Finally, fear can also be learned indirectly by observing someone else experiencing pain (*vicarious/observational learning*) (Goubert et al., 2011; Helsen et al., 2011).

Fear generalization

Perceptual fear generalization

No two aversive learning experiences are identical. Therefore, when confronted with a novel, potentially threatening situation, one must select an appropriate defensive response based on prior experience. Extrapolating knowledge from a previous learning event facilitates employment of appropriate defensive responses without needing to experience the possible harmful outcomes of that novel situation. Conditioned fear can thus spread to a range of stimuli similar to the CS, a phenomenon known as *fear generalization* (Dymond et al., 2015; Ghirlanda & Enquist, 2003; Honig & Urcuioli, 1981; Kalish, 1969). Fear generalization is adaptive, but it relies on an intricate balance between differentiation between and generalization to the different stimuli (Ghirlanda & Enquist, 2003; Pavlov, 1941). Indeed, if fear generalization becomes excessive, it poses the risk of fearful responding to false alarms, i.e. objectively safe stimuli, and thus unnecessary distress (Dymond et al., 2015; Lissek & Grillon, 2010). For example, the fear associated with a yoga pose may spread to a range of similar, yet objectively safe, movements.

Fear generalization is experimentally investigated using fear conditioning protocols. In such protocols, fear conditioning is first induced (i.e. the acquisition phase), after which novel stimuli are introduced during the test phase (i.e. the generalization phase), to examine whether they also evoke conditioned fear responses. Typically, these novel stimuli linearly decrease in similarity

on a continuum from the CS+ to the CS-. Importantly, these *generalization stimuli* (GSs) are never paired with the US. The strength of CRs typically declines with decreasing similarity to the CS+ (Dymond et al., 2015; Lissek et al., 2008). In other words, fear exhibits a *generalization gradient* (Lissek et al., 2008) (see Fig. 1.2). Using the VJM paradigm, Meulders et al. (Meulders et al., 2013) found that intermediate movements between the CS+ and CS- came to elicit fear responses, which were highest for the CS+, and linearly diminished in intensity when similarity decreased from the CS+. This type of fear generalization, based on physical similarity between stimuli, is referred to as *perceptual fear generalization* (Dymond et al., 2015).

Interestingly, if a GS is introduced, which is (physically) an extreme version of the CS+, that extreme GS may evoke even higher fear responses than the CS+ (Purtle, 1973). For example, if participants learn that a green-blue stimulus (CS+) predicts an aversive US, and that a blue stimulus (CS-) is safe, a GS slightly greener in hue than the CS+ will be feared even more than the CS+ (Dunsmoor & LaBar, 2013). Thus, the peak of the generalization gradient shifts to this more extreme GS (see Fig. 1.2). This phenomenon is known as the *peak shift effect*, and is typical of generalization protocols employing a differential fear conditioning protocol (Guttman & Kalish, 1956; Lee et al., 2018). The peak shift has typically been explained as the result of excitation on the side of the CS+, and inhibition on the side of the CS-, resulting in net excitation towards a generalization stimulus beyond the CS+, in a direction opposite to the CS- (Spence, 1937). Responses can also be generally elevated towards novel stimuli on the side of the CS+ away from the CS-, even in the absence of a peak shift (i.e. *area shift* (Honig & Urcuioli, 1981)).

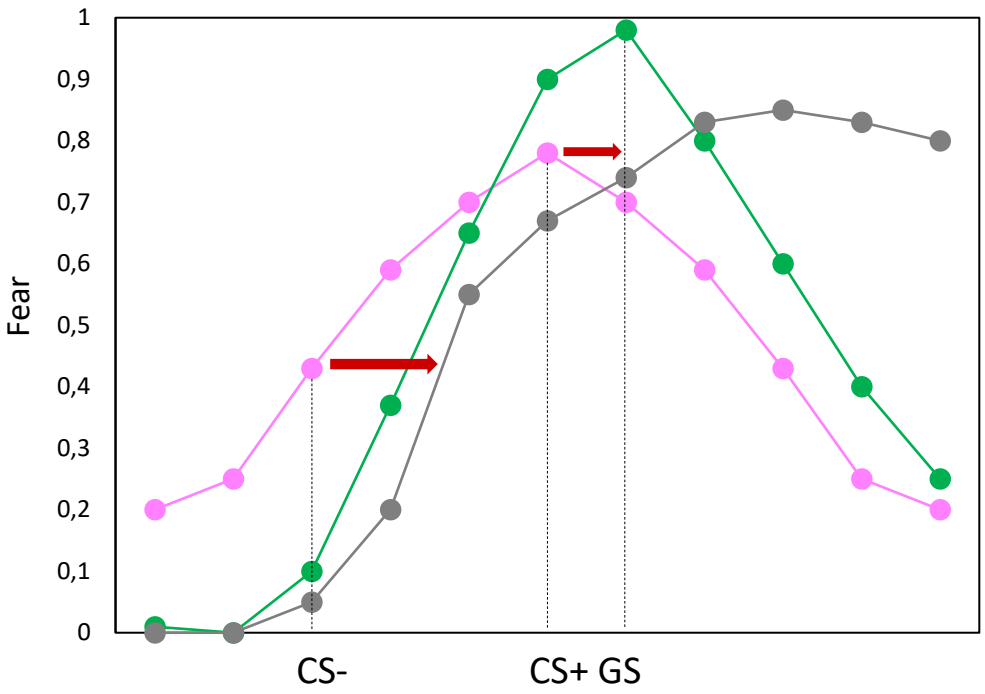

Figure 1.2. Example of a typical fear generalization gradient (pink), peak shift (green), and area shift (grey) following (differential) Pavlovian fear conditioning. CS+ is the conditioned stimulus paired with a feared outcome, and CS- is the conditioned stimulus not paired with the feared outcome. GS is the generalization stimulus, which is an extreme version of the CS+.

Increased generalization of pain-related fear seems to be a pathological marker of anxiety pathology (Lissek & Grillon, 2010; Lissek et al., 2014; Lissek et al., 2010) and chronic pain (Harvie et al., 2017; Meulders et al., 2014; Meulders et al., 2015) alike. For example, generalization of fear to safe stimuli has been observed in several clinical populations such as people with panic disorder (Lissek et al., 2010), generalized anxiety disorder (Lissek et al., 2014), and post-traumatic stress disorder (Lissek & Grillon, 2012). Similarly, whereas healthy participants were found to exhibit the expected fear generalization gradient, which decreases from the CS+ to CS-, people with fibromyalgia (Meulders, Meulders, et al., 2017a), chronic unilateral hand pain (Meulders et al., 2014) and chronic neck pain (Harvie et al., 2020), have been shown to exhibit flatter gradients with higher pain-expectancy towards GSs similar to the CS-. In another study, people with fibromyalgia showed less differential fear generalization between GSs similar to the CS+ and those similar to the CS-, in comparison to healthy control participants (Meulders et al., 2015). Together, these findings indicate that, compared to control participants, people with anxiety and pain conditions generalize fear more to novel stimuli resembling a conditioned safe stimulus.

Category-based fear generalization

Humans also have the ability to organize knowledge about the world into categories and higher-order concepts (Sloutsky & Wei, 2019). Being able to consider different stimuli or events as belonging to the same category, allows us to infer the properties of a novel stimulus based on the properties of familiar, categorically related stimuli. In line with this, fear does not only generalize based on physical similarity between stimuli, but can also generalize based on higher-order reasoning (*concept- or category-based generalization*; (Dunsmoor & Murphy, 2015; Dunsmoor et al., 2011)). For example, a person who experiences a shooting back pain in a specific yoga pose may begin to fear this pose. The person may subsequently generalize fear of that specific yoga pose to other yoga poses or the entire activity of yoga, even if on a physical (proprioceptive) level, these behaviors are all very different. Ultimately, fear may generalize to all physical exercise because the person places the feared activity "yoga" under the category "exercise".

In line with this, previous research has shown that fear of movement can generalize based on real-life action categories in the lab (Glogan et al., 2018; Meulders, Vandael, et al., 2017). Pain-related fear has also been shown to generalize based on de novo categories created experimentally using a matching-to-sample (MTS) task (Skinner, 1950). In an MTS task, participants learn to group perceptually dissimilar stimuli together, such that previously untrained categories are formed through trial-and-error, with the help of corrective feedback. Using such a task, Bennett et al. (2015) trained participants to form two categories where specific nonsense words were trained to be equivalent to specific joystick movements. During a subsequent fear conditioning phase, nonsense words from one of the categories were paired with a painful electrical stimulus, but those from the other were not. Subsequently, pain-related fear spread to the joystick movements from the category of the pain-associated nonsense words, despite the joystick movements *themselves* never being experienced with pain (Bennett et al., 2015). Because category-based generalization is not bound by perceptual stimulus features, but can be affected by any prior learning of a specific person, concept-based generalization introduces an additional level of complexity to understanding the ways in which an individual may learn to fear safe stimuli and situations (Dunsmoor & Murphy, 2015; Dymond et al., 2015).

Fear extinction

The preeminent approach to fear reduction is exposure-in-vivo (Pittig et al., 2016), which is the clinical counterpart to Pavlovian extinction (Scheveneels et al., 2016). Extinction refers to the reduction of fear via repeated presentation of the CS+ in the absence of the US (Pavlov, 1927). For example, if the person who became fearful of a pain-associated yoga pose, performs the same

yoga pose again, this time not paired with a shooting back pain, they may become less fearful of performing that yoga pose again. Experiencing the CS+ without the US is believed to result in the creation of a novel *extinction memory* (e.g. movement-no pain), which competes with the initial learning memory (e.g. movement-pain) for retrieval, that is, it inhibits this memory (Bouton, 2002; Craske, 2015). This inhibitory extinction memory is often more context-dependent that the original memory, thus deeming fear susceptible to re-emergence when the extinction context is changed (Bouton, 2002; Vervliet et al., 2013). Using the VJM paradigm (Meulders et al., 2011), Meulders & Vlaeyen (2012) showed that fear responses towards the movement trained to be CS+ during an acquisition phase, extinguished once it was no longer paired with the pain-US (Meulders & Vlaeyen, 2012). Furthermore, compared to healthy controls, people with fibromyalgia exhibited less extinction of fear towards unreinforced GSs, suggesting that people with chronic pain show slower "safety learning", and are slower in updating their fearful beliefs compared to healthy participants (Meulders, Meulders, et al., 2017). Nevertheless, exposure has been successfully applied in individuals with various chronic pain syndromes, including chronic low back pain (Vlaeyen et al, 2001), complex regional pain syndrome (Den Hollander et al., 2016) and pediatric pain (Simons et al., 2020).

Learning to control harmful events: Pain-related avoidance

Unlike fear, avoidance is learned via instrumental (or operant) conditioning, whereby one learns that their own actions have consequences, which in turn shapes future behavior (Skinner, 1953). In an operant conditioning procedure, three elements play a crucial role. These are the discriminative stimulus (S^D), the behavior (or response, R), and the consequence (or outcome, O) of the behavior. The operant R is a behavior, which is influenced by a certain outcome related to that behavior. The O is what results from performing that behavior. Finally, the S^D indicates whether a specific R will be followed by the O (Skinner, 1953). For example, *touching* (R) a ceramic stove will only result in *pain* (O) when its ring is *red* (S^D).

If the response (e.g. avoidance) prevents a negative outcome (e.g. pain exacerbation, re-injury), the chance of that response recurring in the future, or becoming more frequent, increases; this is referred to as *negative reinforcement* (Skinner, 1953). Alternatively, if the response (e.g. bending down) results in a negative outcome, such as pain, the chance of that response recurring will decrease; this is referred to as *positive punishment*. In this way, instrumental learning shapes behavior and allows a person to learn to control harmful (e.g. painful) events. To return to our previous example of the person who experiences pain when performing a yoga pose: the person may become fearful of performing that yoga pose, and consequently begin to avoid it. If the pain does

not occur again, or does not get worse, the person may attribute this to not performing that specific pose anymore (even if in reality the cause of pain has simply healed), causing a self-sustaining cycle of avoidance (Gatzounis et al., 2012).

Furthermore, the response can also result in a valued outcome (*positive reinforcement*), such as attention from a partner or a healthcare provider, or in the absence of a positive outcome (*negative punishment*), such as missing a social event. In other words, the outcome is referred to as a reinforcer when it causes an increase in responding, and as a punishment when it causes a decrease in responding. Furthermore, conditioning with negative outcomes is known as *aversive* conditioning, whereas conditioning with positive outcomes is referred to as *appetitive* conditioning (Andreatta & Pauli, 2015).

The relationship between fear and avoidance

Although avoidance these days is recognized as a fundamental symptom of anxiety disorders and other fear-related disorders (American Psychiatric Association, 2013), research was long focused mainly on understanding the mechanisms underlying fear, leaving many of the mechanisms underlying avoidance poorly understood. This was partly due to the prominent Two-Factor Theory of Mowrer (Mowrer, 1951), which put forth fear reduction as the sole reinforcer of avoidance. According to Mowrer, following classical fear conditioning (first factor), avoidance arouses as a means to reduce the unpleasantness of fear. That is, avoidance is negatively reinforced (instrumental phase; second factor) by the disappearance of, or increased physical distance to, the CS, resulting in fear reduction. Thus, according to Mowrer, it would be the reduction of pain-related fear, rather than the omission of pain (or other feared outcomes), that reinforces avoidance. Importantly, the theory posits that any reductions in fear would automatically also result in reductions in avoidance, given that fear is the main motivator of avoidance (Mowrer, 1951).

Two-Factor Theory has since, however, struggled to explain many avoidance phenomena (Krypotos et al., 2015). For example, avoidance does not necessarily reduce fear, but can in fact increase it (Engelhard et al., 2015; Pittig et al., 2020; van Vliet et al., 2018). For example, people may infer from their own behavior, that threat is present (van den Hout et al., 2014), contributing to a vicious cycle of fear and avoidance. Furthermore, experimental data and clinical observations indicate that avoidance does not always automatically follow fear, but the two can occasionally dissociate (e.g. (Rachman & Hodgson, 1974)). Fear learning is expressed on multiple different levels, including the physiological (e.g. startle), cognitive (e.g. pain-expectancies), and behavioral (e.g. avoidance) (Bradley & Lang, 2000; Lonsdorf et al., 2017). Often, outcomes on different

response levels can diverge (Sevenster et al., 2012, 2014), and behavioral responses can be affected by multiple circumstances.

For example, avoidance, but not fear, is inherently influenced by approach-avoidance conflicts. In approach-avoidance conflicts, one behavioral option is simultaneously linked to positive and negative outcomes (e.g. attending a social event is rewarding but may come at the cost of pain exacerbation, whereas staying home may relieve pain but will come at the cost of missing out on social rewards) (Corr, 2013; Talmi & Pine, 2012), with the positive ones motivating approach, and the negative ones motivating avoidance (Sierra-Mercado et al., 2015). Indeed, people in pain often need to weigh the value of avoiding pain against the costs that come with avoiding. For instance, avoidance behavior can be accompanied by financial problems from absenteeism, missing out on rewarding experiences such as social activities, or being unable to achieve certain life-goals (e.g. (Breivik et al., 2013; Deyo et al., 1991; Volders et al., 2015)). Therefore, adding costs to experimental avoidance may more accurately tap into pathological forms of avoidance; after all, it is the substantial cost of avoidance, which limits people's daily lives, and thus gives it its problematic quality (American Psychiatric Association, 2013). Because of these costs, healthy behavior is often characterized by prioritizing other behaviors over avoidance, such that valued goals are still reached, whereas in chronic pain, the balance between reward and punishment seems to be shifted in the direction of pain-avoidance at the cost of rewards (Rizvi et al., 2021; Van Damme et al., 2010). In support of this, high and low anxious individuals have been shown to demonstrate comparable levels of *low-cost* avoidance, whereas *costly* avoidance was found to be elevated only in high trait-anxious individuals (Pittig & Scherbaum, 2020).

This also aligns with other experimental findings from previous pain (Claes et al., 2016; Claes et al., 2015; Claes et al., 2014; Van Damme et al., 2012) and anxiety literature (e.g. (Pittig & Dehler, 2019)), which show that healthy people are willing to approach feared stimuli, when valued goals (e.g. rewards) competing with avoidance, are introduced. For example, Pittig et al. (2019) directly manipulated the effect of rewards on fear and avoidance by dividing their sample into three groups with differing reward schedules. Specifically, in two groups, the CS+ was simultaneously associated with both an aversive US and rewards, during acquisition. During a subsequent test phase where the US was discontinued, *rewards* remained present in one of the groups, whereas in the other, rewards were only present during acquisition, and were discontinued in the test phase. The third group never received rewards. For this group, the CS+ was only paired with the US. The authors reported that avoidance was attenuated in both reward groups, and remained such in these groups, even after rewards were discontinued in the other group. The group that received no rewards, on the other hand, exhibited persistent avoidance throughout the

experiment. Interestingly, rewards did not affect *fear levels*, which remained high in all groups, even when *avoidance* was attenuated (Pittig & Dehler, 2019).

A study by Claes et al. (2014) showed similar findings in the context of pain. In the study, a joystick movement in one direction (CS+, e.g. to the left) was simultaneously paired with pain and reward, whereas a movement in the opposite direction (CS-, e.g. to the right) was paired with neither. In the control condition, the CS+ movement (e.g. upward), was only paired with pain, and the CS- (e.g. downward) was not. Authors found that in both conditions the CS+ was feared more than the CS-. However, when participants were given the chance to choose between the joystick movements, they chose the CS+ more in the experimental condition, where the CS+ was also paired with reward, compared to the control condition where the CS+ was only paired with pain (Claes et al., 2014). Thus, it seems that adding costs to, or rewards competing with, experimental avoidance, can cause fear and avoidance to dissociate by mitigating avoidance.

Limitations of previous avoidance paradigms and a way forward

Despite being widely recognized as a limited model, much of avoidance research to date has employed variations of a paradigm inspired by the two factors of Two-Factor Theory (Krypotos et al., 2018). Traditional avoidance paradigms thus entail two phases: the first phase (classical conditioning) to establish fear, and the second (instrumental phase) to investigate avoidance. In the first phase of traditional avoidance paradigms, participants learn the CS-US association. Subsequently, in the instrumental phase, an experimenter-instructed avoidance response (such as pressing a computer key) is introduced, cancelling the US if performed during CS presentation, establishing an R (e.g. key press)-O (e.g. US-omission) association (Krypotos et al., 2018).

Although this paradigm has elucidated many of the processes underlying avoidance, it also has several limitations in terms of how well it reflects real life (i.e. ecological validity) (Krypotos et al., 2018; A. Meulders, 2019). First, because the experimenter instructs the avoidance response, the paradigm does not allow participants to sort out themselves which response cancels the aversive outcome, thus obstructing examination of the natural learning of avoidance. Using an operant procedure, where participants freely choose between available responses, and thus learn which responses are painful/safe, models real life more accurately, where avoidance emerges as a natural response to pain (Volders et al., 2015). Second, dichotomous responses such as pressing/not pressing a button are not a very accurate representation of real life, where different degrees of avoidance occur. Finally, previous studies have only investigated avoidance generalization using classical-operant methods where the same avoidance response (e.g. pressing a computer button) generalizes to classically conditioned stimuli (e.g. circles of different sizes). Yet, no study to date

has investigated whether (pain-related) avoidance generalizes from one *operant response* to another. This type of operant-based generalization is known as *response-generalization*, where the outcome associated with one response (the R-O contingency) generalizes to other, similar responses, thus increasing/decreasing the likelihood of their occurrence (Skinner, 1953). This is an important question because people with chronic pain often fear and avoid operant responses (e.g. bending down to pick something, doing physical labor).

The robotic arm-reaching paradigm, developed by Meulders and colleagues (Meulders et al., 2016) to investigate pain-related avoidance, attempted to address these limitations. In the paradigm, participants use a robotic arm to perform arm-reaching movements from a starting point to a target. Movements are employed as the instrumental response because they are highly relevant for chronic pain, where movement is often feared. Participants' movements are typically represented by a virtual ball on an LCD screen, allowing participants to follow their own movements in real-time. In the basic paradigm, participants freely choose between three movement trajectories, represented on-screen by three arches (trajectories T1-3), differing from each other in terms of effort and likelihood of being paired with a painful electrical stimulus (i.e. pain). Effort is manipulated as increasing deviation from the shortest possible movement trajectory (T1) and increased resistance from the robotic arm. That is, the robot is programmed such that resistance increases linearly with deviation to the right, meaning that the more participants deviate from T1, the more force they need to exert on the robot in order to reach the target. Furthermore, pain administration is programmed such that the shortest, easiest trajectory (T1) is always paired with pain (100% pain/no deviation or resistance). The middle trajectory (T2) is paired with a 50% chance of receiving pain, but more effort is required (moderate deviation and resistance). The longest, most effortful trajectory (T3) is never paired with pain but requires the most effort to reach the target (0% pain/largest deviation, strongest resistance). Avoidance behavior is operationalized as the maximum deviation from the shortest trajectory (T1) per trial, which is a more continuous measure of avoidance than the typical button press/no button press. Furthermore, the avoidance response comes at the cost of increased effort. Finally, given that participants freely choose between the movement trajectories, and are not explicitly informed about the experimental R-O (movement trajectory-pain) contingencies, avoidance behavior is individually, instrumentally acquired. Online self-reported fear of pain and pain-expectancy are collected as measures of conditioned fear towards the different movement trajectories. Pain-expectancy is also an index of contingency awareness and threat appraisal (Boddez et al., 2013). This combination of variables thus allows scrutinizing the interplay between fear, threat appraisals,

and avoidance behavior. Using this paradigm, Meulders et al. have demonstrated operant learning of avoidance behavior in healthy participants (Meulders et al., 2016).

Generalization of avoidance

Like fear, avoidance can generalize from one feared movement to other, similar movements. Problematically, since avoidance does not allow for fearful beliefs to be challenged (Krypotos et al., 2015), any perceived safety can be misattributed to avoidance behavior, making it difficult to evaluate whether avoidance was necessary or not (Lovibond et al., 2009b; Rescorla, 2003). Thus, it also becomes difficult to assess whether avoidance is necessary. For instance, following a painful episode with one yoga pose, a number of different yoga poses, similar to the original pain-associated one, may be avoided, even if these are objectively safe.

Traditional avoidance paradigms have elucidated many of the processes underlying avoidance (Krypotos et al., 2015; Krypotos et al., 2018), and have also been adapted to investigate the generalization of avoidance, albeit mainly in the anxiety domain. A study by Lommen et al. (2010) is one of few to have investigated perceptual avoidance generalization. Using a white and black circle as CS+ and CS-, respectively, the authors first classically conditioned fear. The CS+ was always paired with an aversive electrical stimulus. During the generalization test, circles in differing grey hues ranging between black and white were presented as ambiguous GSs. Additionally, before the start of the generalization phase, participants were instructed that on different trials (depending on the color of a flickering light), they had either 1 or 5 seconds to avoid the electrical stimulus by pressing the computer's space bar. Results showed that a preselected group who scored high on neuroticism, avoided electrical stimuli during more GSs compared to a group scoring low on neuroticism, but only on the 5-s latency trials. The authors interpreted this finding as indicating a more elaborate thought process taking place in the longer trials, suggesting that the high neuroticism group used a "better safe than sorry" strategy to decide whether or not to avoid during the ambiguous GSs (Lommen et al., 2010).

Recently, San Martín et al. (2020) investigated avoidance generalization along a dimension of "avoidability". Specifically, there were two CSs+, indicated by different colored lamps in an office environment presented on the computer screen. A third color served as the CS-. During one of the CSs+ (CS+av), a button press effectively omitted the US (an aversive electrical stimulus), whereas during the other CS+ (CS+unav), the button press was ineffective. That is, the US was presented irrespective of the avoidance response. During generalization, morphed colors between the CS+av and CS+unav, as well as the CS+ av and CS- were presented. The authors reported generalization gradients of (proportions of) avoidance, that is, higher rates of avoidance

to the CS+av, decreasing towards the CS+unav on one dimension, and from the CS+av to the CS- on the other. Furthermore, participants reported feeling increasingly relieved (in terms of "relief pleasantness") to have avoided the US during GSs similar to CS+unav, with reports decreasing towards to the CS- (San Martín et al., 2020).

A larger number of studies have investigated conceptual forms of avoidance generalization. The first evidence for this came from a seminal study by Augustson and Dougher (1997), where participants were taught two stimulus equivalence categories (A1-B1-C1-D1 and A2-B2-C2-D2), after which differential fear conditioning with aversive electrical stimuli as USs was employed to establish B1 and B2 as CS+ and CS-, respectively. During a following avoidance phase, electrical stimuli could be avoided by performing a fixed-ratio 20-response (button press) requirement in the presence of B1, whereas B2 was never followed by an electrical stimulus. After this, symbolic generalization of avoidance was tested by presenting the other members from the two categories, in the absence of the US. All eight participants avoided C1 and D1 but not C2 and D2, indicating that they transferred the directly trained avoidance response from B1 to the symbolically related C1 and D1 without these being ever paired with the electrical stimulus (Augustson & Dougher, 1997).

Multiple studies have since replicated and/or extended these findings. For example, Dymond et al. (2011) replicated the findings of Augustson and Dougher with a larger sample, and using aversive images and sounds, instead of electrical stimuli, as USs (Dymond et al., 2011). These findings aligned with relational frame theory (RFT), which posits that avoidance often occurs in the presence of a wide range of situations, based on the *inferred* presence of an aversive event (Dymond & Roche, 2013). Similarly, arbitrarily applicable relational responding (AAAR) is a form of generalized operant behavior in which novel, untrained responses emerge from a subset of directly trained responses due to being symbolically related with the trained response (Dymond et al., 2018).

Boyle, Roche, Dymond, and Hermans (2014) also demonstrated avoidance generalization based on real-life categories. During the initial fear conditioning phase, one word was the CS+ (e.g., broth), and another word was the CS- (e.g., assist). In the subsequent instrumental phase, participants learned to press the space bar in order to avoid presentation of an aversive electrical stimulus. During the generalization test, synonyms of the CS+ (e.g., soup) and CS- (e.g., help) were presented in the absence of electrical stimuli. Results showed that the CS+ and its synonyms were avoided more, and evoked elevated skin conductance responses (SCRs; a measure of fearful arousal (Esteves et al., 1994)) and higher self-reported US-expectancies compared to members of the CS- category (Boyle et al., 2014).

Recently, Bennett et al. (2020) found that, following an MTS task, participants learned to avoid (by pressing a computer key) a negative outcome (negative feedback) in the presence of a CS+. Avoidance subsequently generalized to other members of the same category, established during the MTS task. However, this was only the case when avoidance generalization was tested in the same "context" (e.g. green colored screen) where avoidance learning occurred, but not when tested in a different context (e.g. blue colored screen). Furthermore, this effect was specific to groups who had also learned different behaviors, which competed with the avoidance response. Those participants who had not learned a competing behavior, generalized avoidance in both contexts. Thus, the behavior competing with avoidance seemed to attenuate its generalization (Bennett et al., 2020).

The generalization of *costly* avoidance was first demonstrated in a study by Van Meurs et al. (2014). In the experiment, participants first underwent classical fear conditioning, where one circle served as CS+ (e.g. large circle), another as CS- (e.g. small circle), and circles linearly varying in size between the CSs served as GSs. Subsequently, in a computer game, participants chose whether to avoid an aversive electrical stimulus at the cost of poorer performance in the game. Specifically, a trial of the game started with the presentation of one of the CSs or GSs, after which the participant was required to choose between two pathways, to send a virtual farmer cycling between a tool shed and garden, to plant and harvest crops. Each path was paired with different costs and benefits: a short road resulted in the aversive US but assured a successful harvest. Conversely, a long road was never paired with the US, but came with the risk of the farmer losing his crop because of birds consuming it. Because the GSs were never paired with the US, and avoidance came at a cost, avoiding during these stimuli was considered maladaptive. The authors reported that greater fear corresponded to more avoidance. However, whereas US-expectancy and eye-blink startle were elevated towards the GS2 (second closest approximation of the CS+), avoidance only occurred towards the GS3 (closest approximation of the CS+). This suggests that the costs associated with avoidance, attenuated its generalization in comparison to fear (van Meurs et al., 2014).

Finally, a recent study showed generalization of costly avoidance based on (real-life) *categorical knowledge* (Wong & Pittig, 2020). Participants in this study learned that exemplars from one category (e.g. animal) were paired with an aversive electrical stimulation (US), whereas those from another category (e.g. fruit) were not. Subsequently, in the absence of the US, participants underwent an avoidance test where, if they chose cards from a high-reward deck, they were presented with exemplars from the pain-associated category. Conversely, if participants chose cards from a low-reward deck, they were presented with an exemplar from the safe category.

Results showed that participants avoided the high-reward deck more than a control group for whom the avoidance test did not involve exemplars from either of the fear conditioning categories. These findings indicate that costly avoidance generalizes also based on categorical knowledge (Wong & Pittig, 2020).

Extinction of avoidance

In accordance with how they are learned, fear and avoidance are also extinguished differently (Dymond, 2019; Urcelay & Prével, 2019): whereas fear is acquired and extinguished purely based on classical conditioning (presenting the CS in the absence of the US), avoidance usually requires also an operant component (although see (Krypotos et al., 2014)). Because avoidance impedes the opportunity to encounter feared stimuli, thus precluding the disconfirmation of fearful beliefs, it is often prevented during treatment (*extinction with response prevention*, RPE; (Gatzounis et al., 2021; Mineka, 1979). However, avoidance often returns following RPE. Using the robotic arm-reaching paradigm, Gatzounis and Meulders demonstrated extinction of pain-related fear and pain-expectancies, when costly avoidance (performing T3 and T2) was prevented, thus allowing performance of T1 only. However, at one-day follow-up, pain-related fear, pain-expectancies, and avoidance all returned, albeit not to pre-extinction levels (Gatzounis & Meulders, 2020). Similar results were reported by Vervliet and Indekeu in terms of *low-cost* avoidance of aversive electrical stimuli (Vervliet & Indekeu, 2015). It has been suggested that entirely restricting avoidance during exposure treatment represents a significant context change compared to daily life, where avoidance is always possible (Bouton, 2002) likely resulting in the original fear memory being released from inhibition, causing that memory to take over.

Summary and Research aims

To date, there have been no investigations into the generalization of costly avoidance in the context of (chronic) pain. The behavioral research that has been done has mostly used procedures where the experimenter instructs participants on how to avoid, precluding the opportunity to study spontaneous avoidance acquisition and generalization. Furthermore, due to the low costs and instructions associated with the typically employed avoidance responses, it is difficult to decipher whether avoidance generalization is genuinely motivated by fear, or by participants simply attempting to follow task instructions. Finally, even when costs are included, as in the virtual farmer paradigm (van Meurs et al., 2014), the binary nature of the button-press avoidance response does not capture very well the different degrees at which avoidance may occur, nor do they allow investigation of response-based avoidance generalization (Skinner, 1953). In order to optimize the

ecological validity of avoidance generalization paradigms for chronic pain, we argue that participants should be given the opportunity to learn avoidance generalization themselves. Furthermore, this approach, together with avoidance costs, will leave less room for the possibility of avoidance generalization being motivated by anything other than a genuine desire to avoid a pain stimulus. Finally, in real life, people with chronic pain may generalize fear and avoidance from one pain-associated movement or action, to other (safe) movements and actions. Thus, research on pain-related avoidance generalization should aim to use such pain-relevant "stimuli" as responses.

There is substantial research supporting the role of pain-related fear and its generalization in the development and maintenance of chronic pain (Wertli et al., 2014). Furthermore, a new wave of avoidance research (see Fig. 1.3) has begun to elucidate the mechanisms of avoidance generalization (Dymond et al., 2015; Krypotos et al., 2015), as well as some of the previously less understood modulators of avoidance, such as the avoidance-attenuating effects of avoidance-costs and competing rewards (Pittig & Dehler, 2019; van Meurs et al., 2014). However, most of this research has taken place in the anxiety domain. Although some studies have directly explored the effects of rewards on *pain-related* avoidance (Claes et al., 2016; Claes et al., 2015; Claes et al., 2014; Van Damme et al., 2012), our understanding of the effects of avoidance costs, especially on excessive (e.g. generalized) pain-related avoidance, is still limited. *First*, whether pain-related avoidance can generalize from one operant response (i.e. movement) to another has not been investigated before. However, this is an important question, given that people with chronic pain may generalize avoidance of one response (e.g. bending down) to a range of other perceptually similar responses (e.g. sitting at a desk). *Furthermore*, such operant generalization of perceptually dissimilar but categorically related responses would help us understand the mechanisms underlying all the complex forms in which fear and avoidance might generalize to safe behaviors (Dymond et al., 2015). Better understanding the mechanisms underlying both perceptual and category-based avoidance generalization will enable treatments to be as effective as possible, by allowing in-depth analyses of the fears faced by people with chronic pain. *Finally*, given that much of the anxiety and pain literature has focused on fear instead of avoidance due to the tacit assumption that fear would automatically motivate avoidance, much of our understanding of the mechanisms of generalization come from Pavlovian (fear) generalization. For example, the generalization gradient is typically used as an index of the extent of fear generalization (Hanson, 1957; Lissek et al., 2008). However, such characteristics of fear generalization have not been investigated in operant avoidance. A clear understanding of how closely fear and avoidance generalization correspond, would inform how much inspiration can be drawn from existing knowledge of fear generalization, in order to apply

it to research on avoidance generalization. Thus, the primary aim of the current research project was to investigate the mechanisms underlying the generalization of costly pain-related avoidance using an ecologically valid paradigm. We used an operant avoidance-conditioning paradigm, in which the trade-off between avoiding and approaching was modeled by employing a costly pain-avoidance response.

More specifically, we aimed to address the following questions: 1) Do pain-free participants generalize costly pain-related avoidance based on perceptual (proprioceptive) similarity between movements (**Study 1, Chapter 2**)? 2) What are the boundary conditions of costly pain-related avoidance generalization in healthy participants (**Studies 2 and 3, Chapter 3**)? 3) How closely do concurrently measured pain-related fear- and costly pain-related avoidance generalization correspond in one task (**Study 4, Chapter 4**)? 4) Do healthy participants generalize pain-related avoidance based on conceptual knowledge (**Study 5, Chapter 5**)?

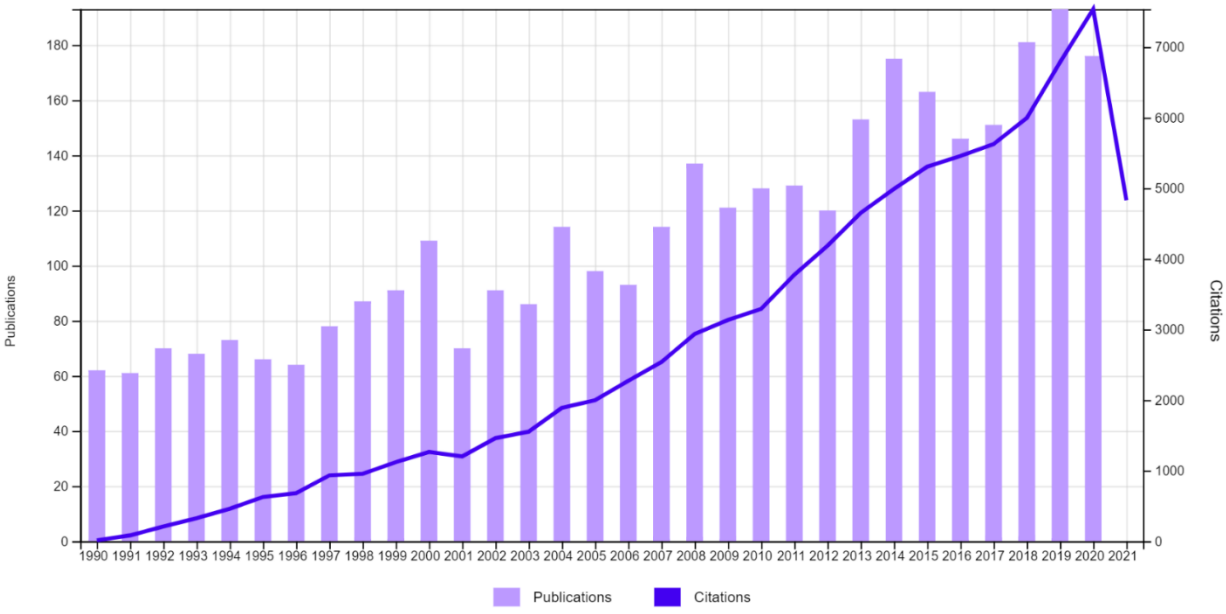

Figure 1.3. Number of publications (lilac) and citations (purple) indexed in Clarivate's Web of Science, for the research areas of psychology, psychiatry, and neuroscience, in which "avoidance" was included in their title, from the year 1990 to the year 2020 (as of August 27th, 2021).

To address the first question, we used a novel, pain-related avoidance paradigm (the robotic arm-reaching paradigm (Meulders et al., 2016) described above) to investigate *perceptual generalization of pain-related avoidance* (**Chapter 2**). Briefly, during the acquisition phase, participants in an *Experimental Group* learned that they can (partly) avoid a pain-associated movement (T1) by performing increasingly costly movements (T2 and T3). During a subsequent generalization test,

the acquisition trajectories disappeared and were replaced by three novel generalization trajectories (G1-3), which were positioned between the acquisition trajectories. None of the generalization trajectories were paired with pain. We also collected self-reports of pain-related fear and pain-expectancy. We expected that the Experimental Group would show larger deviations compared to the Yoked Group during the acquisition and generalization phases, and that self-reports would follow the pattern T1/G1 > T2/G2 > T3/G3 in the Experimental Group but not the Yoked Group. Surprisingly, self-reports generalized from T1-3 to G1-3, respectively, but avoidance did not. We suspected the absence of avoidance generalization to have resulted from a perceived context switch between the acquisition and generalization phases. Alternatively, the high expectations of pain for T1/G1 may have resulted in avoidance behavior rapidly extinguishing when these expectations were disconfirmed.

In two extended replications of **Study 1** (described in **Chapter 3**), were aimed to investigate these post-hoc interpretations. In **Experiment 1**, we reduced visual (context) changes between the acquisition and generalization phases. In **Experiment 2** we attempted to increase pain uncertainty (and thus reduce disconfirmation of threat beliefs) by lowering the likelihoods of pain for T1 and T2 during acquisition. Our hypotheses for both experiments were the same as for **Study 1**. In a fourth study, described in **Chapter 4**, we sought to investigate whether concurrently measured generalization of pain-related fear and of costly avoidance correspond in one task. We also explored whether healthy participants would show excessive avoidance despite associated costs, and if avoidance would decrease as a function of dissimilarity from a pain-associated movement (an avoidance generalization "gradient"). Thus, we aimed to obtain a better understanding of how closely fear and avoidance generalization correspond, to inform how much inspiration can be drawn from existing knowledge of fear generalization, in order to apply it to research on avoidance generalization. In line with studies of differential *fear* conditioning, participants were presented with only two movement trajectories instead of three, and could avoid the low-cost, pain-associated movement trajectory (T+), by choosing the high-cost non-painful movement trajectory (T-). T+ and T- were located at opposite ends of the movement plane. Subsequently, in the absence of pain, we introduced three movement trajectories (G1-3) between T+ and T-, and one movement trajectory on the side of T- further away from T+ (G4). In addition to pain-related fear and pain-expectancies, we also measured startle EMG as a psychophysiological indicator of fear. We expected fear measures to show a generalization gradient decreasing with increasing distance from T+. We also explored whether avoidance would decrease (i.e. *approach* of a movement trajectory would *increase*) with increasing distance from T+. Finally, we also explored

whether G4 would be preferred over the closest generalization trajectory (G3), thus indicating unnecessary effort to avoid pain.

The fifth study, described in **Chapter 5**, investigated category-based generalization of avoidance using de novo categories. In the robotic arm-reaching paradigm, participants in two groups learned different categorical relationships between T1-3 and G1-3 in an MTS task, and subsequently underwent avoidance acquisition, as described above (with T1-3). Self-reports of pain-related fear and pain-expectancies were also collected. Subsequently, during the generalization phase, G1-3 were made available in the absence of pain. For one group, based on category learning, avoidance generalization would correspond to choosing G1, whereas in the other group it would correspond to choosing G3. During the generalization phase, we expected the groups to show opposite patterns of generalization in avoidance, pain-related fear, and pain-expectancies, based on the categories they learned during the MTS task.

In **Chapter 6**, we provide a methodological outline of the robotic arm-reaching paradigm and its potential for future research in the context of pain-related avoidance behavior, as well as in other research domains, such as anxiety disorders. Finally, in the general discussion, **Chapter 7**, we will summarize the findings of this PhD project, discuss and integrate them in relation to previous literature, give suggestions for future research, mention strengths and limitations, and discuss the theoretical implications of our findings.

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CHAPTER 2
INVESTIGATING THE GENERALIZATION OF PERCEPTUAL PAIN-RELATED AVOIDANCE BEHAVIOR

Abstract

Avoidance is considered a key contributor to the development and maintenance of chronic pain disability, likely through its excessive generalization. This study investigated whether acquired avoidance behavior generalizes to novel but similar movements. Using a robotic arm, participants moved their arm from a starting to a target location via one of three possible movement trajectories. For the Experimental Group, the shortest, easiest trajectory was always paired with pain (T1 = 100% reinforcement/no resistance and deviation). Pain could be partly or completely avoided by choosing increasingly effortful movements (T2 = 50% reinforcement, moderate resistance/deviation; T3 = 0% reinforcement, strongest resistance/largest deviation). A Yoked Group received the same number of painful stimuli irrespective of their own behavior. Outcomes were self-reported fear of movement-related pain, pain-expectancy, avoidance behavior, (maximal deviation from the shortest trajectory), and trajectory choice behavior. We tested generalization to three novel, unreinforced trajectories (G1-3) positioned next to the acquisition trajectories. Whereas acquired fear of movement-related pain and pain-expectancy generalized in the Experimental Group, avoidance behavior did not, suggesting that threat beliefs and high-cost avoidance may not be directly related. The lack of avoidance generalization may be due to a perceived context-switch in the configurations of the acquisition and the generalization phases.

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Introduction

Acute pain warns us of immediate or impending physical threat, and often dissipates once injury has healed. Chronic pain, on the other hand, persists even in the absence of evident physical damage, and thus ceases to be adaptive (Institute of Medicine Committee on Advancing Pain Research & Education, 2011; Treede et al., 2015). Further, chronic pain is a widespread health concern posing significant individual and societal burden (Breivik et al., 2006; Breivik et al., 2013; Gaskin & Richard, 2012; Phillips, 2009), with calls being made to increase our knowledge, and improve the quality of care for chronic pain (Breivik et al., 2013).

Pain-related fear and avoidance are considered to play a key role in the chronification of acute pain (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen & Linton, 2000, 2012). According to the fear-avoidance model of chronic pain, catastrophic misinterpretations of pain (e.g. pain representing re-injury or a catastrophe such as the spine snapping) may result in increased pain-related fear (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen & Linton, 2000, 2012). To alleviate fear, individuals avoid movements and activities they believe will worsen their pain. Though avoidance is adaptive when pain is acute, in chronic pain it becomes maladaptive and can lead to functional disability, via disuse and decreased daily activity (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen & Linton, 2000, 2012).

Fear of movement-related pain can be learned through classical conditioning (Meulders et al., 2011; Meulders & Vlaeyen, 2013; Vlaeyen, 2015). In a study with a voluntary joystick movement (VJM) paradigm (Meulders et al., 2011), participants performed joystick movements to the right and left. One of these movements (e.g. to the left; conditioned stimulus CS+) was associated with a painful electrocutaneous stimulus (unconditioned stimulus, US), whereas the other movement (e.g. to the right; CS-) was not. The CS+ came to elicit higher conditioned responses (CRs; self-reported fear of movement-related pain, eye-blink startle responses, and movement latencies (a proxy measure of behavioral avoidance)), in comparison to the CS- (Meulders et al., 2011). In clinical terms, this might mean that a person who experiences shooting back pain (pain-US) when bending forward (CS+) to lift their child, may come to associate bending forward with pain, and to consequently fear (CR) lifting their child in future situations.

Conditioned fear can spread to a range of stimuli or events related to the original fear experience - a phenomenon known as *fear generalization* (Dymond et al., 2015; Ghirlanda & Enquist, 2003; Honig & Urcuioli, 1981; Kalish, 1969). Specifically, generalization stimuli (GSs) that are similar to the original fear-evoking stimulus, but never experienced in the presence of the US, can also come to trigger conditioned fear responses. Fear generalization is adaptive, as it minimizes the necessity to always learn anew. However, excessive fear generalization comes with the risk of

fearful responding to false alarms (Dymond et al., 2015; Lissek & Grillon, 2010). For example, the fear associated with bending forward to pick up a child might spread to a range of other safe bending-related movements and activities (e.g. yoga or household chores).

Generalization of fear of movement-related pain has been demonstrated in the lab (Meulders et al., 2013; Meulders & Vlaeyen, 2013). For example, using the VJM paradigm, Meulders et al. (Meulders et al., 2013) found that intermediate movements between the CS+ (GSs+) and CS- (GSs-) came to elicit eye-blink startle responses, which linearly decreased in intensity with decreasing similarity with the CS+ (i.e. generalization *gradient*). Moreover, evidence suggests that chronic pain patients excessively generalize fear and expectancies of pain (Meulders et al., 2014; Meulders et al., 2015). For example, it was found that whereas healthy participants exhibited a clear generalization gradient, chronic hand pain patients showed flatter gradients with higher pain-expectancy towards GSs similar to the CS- (Meulders et al., 2014). In another study, fibromyalgia patients showed less differential fear generalization between GSs+ and GSs-, in comparison to healthy control participants (Meulders et al., 2015). These results suggest that chronic pain patients do not differentiate between safe and harmful stimuli as accurately as healthy individuals.

Although a considerable amount of research has been dedicated to understanding pain-related fear, pain-related avoidance behavior is largely unexplored. This is surprising given the central role of avoidance behavior in theoretical and clinical models of chronic pain disability (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen & Linton, 2000, 2012); namely, where fear merely induces discomfort, avoidance behavior is a potential pathway to functional disability.

Avoidance behavior can be learned through operant conditioning, whereby a behavior that results in the omission of a negative event (e.g. pain) will be negatively *reinforced*, i.e. the likelihood of that behavior occurring again in the future is increased (Skinner, 1953). For example, the person who begins to fear bending movements after experiencing pain in the back may begin to avoid bending forward to prevent pain from occurring again (i.e. omission of a negative event). When the pain does not occur, he/she might (mis)attribute this outcome to avoidance behavior (even if in reality, the injury has simply healed), and persistently avoid bending forward. Given that fear can be accompanied by avoidance behavior, and also has the potential to generalize (excessively) (Dymond et al., 2015; Ghirlanda & Enquist, 2003; Honig & Urcuioli, 1981; Kalish, 1969), this person may also generalize his/her avoidance behavior, and begin to avoid a range of bending-related movements and activities, even if these are safe. This, in turn, may lead to decreased engagement in daily activity, ultimately resulting in chronic pain disability.

One reason for the scarcity of research on this clinically relevant but challenging topic is the a lack of valid paradigms to study avoidance behavior in humans (Krypotos et al., 2018). To address this problem, Meulders et al. (Meulders et al., 2016) developed a novel operant conditioning paradigm (robotic arm-reaching paradigm) to investigate pain-related avoidance behavior. In this paradigm, participants perform three different arm-reaching movements using a robotic arm. The movements differ in the effort they require, as well as their likelihood of being paired with a painful electrocutaneous stimulus. Specifically, the least effortful movement (in terms of distance and resistive force; T1) is always paired with pain, a moderately effortful one (T2) is paired with a 50% chance of receiving pain, and the most effortful trajectory (T3) is never paired with pain, in the Experimental Group. Thus, participants in the Experimental Group can avoid the pain stimulus, but have to exert more effort. A Yoked Group receives the same number of painful stimuli, irrespective of the movement trajectories they choose. Avoidance behavior is operationalized as the maximal deviation from the shortest trajectory. In the study of Meulders et al. (Meulders et al., 2016), self-reported fear of movement-related pain, and pain-expectancy reflected the experimental contingencies (T1>T2>T3) in the Experimental Group, whereas there were no differences in ratings between trajectories in the Yoked Group. Furthermore, the Experimental Group showed more avoidance, that is, they showed larger deviations from the shortest trajectory, compared to the Yoked Group (Meulders et al., 2016).

In the current study, we extended the robotic arm-reaching paradigm (Meulders et al., 2016), to investigate whether acquired avoidance behavior would also generalize to novel movements that had never been paired with pain. To do this we included a generalization phase, during which three novel movement trajectories (generalization trajectories G1-3) were performed under extinction (intermixed with blocks where the original trajectories (T1-3) were performed, under reinforcement (reminder-of-acquisition)). Dependent measures were avoidance behavior, self-reported fear of movement-related pain-, and pain-expectancy ratings. We expected (1) to replicate acquisition of avoidance behavior, fear of movement-related pain, and pain-expectancy (Meulders et al., 2016), and crucially, (2) that acquired fear and avoidance would generalize to the novel movement trajectories, i.e. the Experimental Group would avoid more (show larger maximal deviation), compared to the Yoked Group, during the generalization phase, and fear of movement-related pain and pain-expectancy would vary along with the different trajectories (G1>G2>G3) in the Experimental Group. No such differences were expected in self-reports for the different trajectories in the Yoked Group.

Methods and materials

Participants

Sixty-four (sample size replicated from (Meulders et al., 2016)) healthy, pain-free volunteers participated in the study (42 females, mean ± *SD* age = 23 ± 6, range = 18-57). They were assigned either to the Experimental (*n* = 32) or to the Yoked (*n* = 32) Group, based on an alternating schedule depending on the order in which they arrived at the laboratory. The matching procedure was replicated from Meulders et al. (Meulders et al., 2016). We did not match participants based on gender, and given the general homogeneity in age in the student population from which we recruited, we did not deem it necessary to explicitly match participants based on age. Participants were recruited by the experimenter (EG) through the research participation system of Maastricht University (Sona; Sona Systems, Nijmegen, The Netherlands), as well as advertisements distributed around the university campus, and through social media. Recruitment and data collection took place during May and June of 2018.

Exclusion criteria comprised chronic pain; analphabetism or diagnosed dyslexia; pregnancy; left-handedness; current/history of cardiovascular disease; chronic or acute respiratory disease (e.g., asthma, bronchitis); neurological disease (e.g., epilepsy); current/history of psychiatric disorder (e.g., clinical depression, panic/anxiety disorder); uncorrected problems with hearing or vision; having pain at the dominant hand, wrist, elbow or shoulder that may hinder performing the reaching task; presence of implanted electronic medical devices (e.g., cardiac pacemaker); and presence of any other severe medical conditions. All participants completed an exclusion criteria checklist, and provided informed consent. Participants were informed that they could freely terminate participation at any time without any negative consequences. Participants received either 1.5 course credit, or €12.50 in gift vouchers. The study was approved by the Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration number: 185 09 11 2017 S1).

Apparatus and stimulus material

HapticMaster. The HapticMaster (HM; Motekforce Link, Amsterdam, the Netherlands) is a 3 degrees-of-freedom force-controlled robotic arm. More specifically, it is an admittance-controlled robot, which means that when the individual exerts a certain force, the device reacts with a corresponding movement. The volumetric workspace of the HM consists of a depth of 0.36m, a height of 0.40m, and a radius of 1m. In the current experiment, movements were confined to a 2-dimensional horizontal movement plane with a depth of 0.36m and a width of 0.41m. The HM records exerted force, velocity, and positions of displacement over time during a movement.

This information can be fed back to other devices, and used as input to trigger other stimulus presentations. In the current study, information about participants' movements was used to correctly time presentations of the painful electrocutaneous stimulus.

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

Pain stimulus. The pain stimulus was an electrocutaneous stimulus (square-wave, 2ms duration), delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, United Kingdom), through two reusable stainless steel disk electrodes (8mm diameter with 30mm spacing; Digitimer, Welwyn Garden City, United Kingdom) filled with K-Y gel (Reckitt Benckiser, Slough, United Kingdom), and attached around the triceps tendon of the right (dominant) arm, using a Velcro strap. In order to increase spatial contiguity of the movement and the pain, the electrodes were attached to the right arm, with which the task was performed.

Protocol

The session lasted approximately 1.5 hours, during which participants were tested individually. Participants were informed that the experiment involved the presentation of painful electrocutaneous stimuli. After completion of exclusion criteria- and informed consent forms, the experimenter attached the electrodes, the pain calibration procedure was carried out (see '*Calibration of the pain stimulus*'), and participants completed the task (see '*Robotic arm-reaching task*'). After completing the task, participants filled in an exit questionnaire and six psychological trait questionnaires (for meta-analytical reasons), after which they were thanked for their participation, received the compensation of choice, and were dismissed.

Calibration of the pain stimulus. Intensity of the pain was individually calibrated for each participant. Participants were administered a series of electrocutaneous stimuli, starting with an intensity of 1mA and increasing stepwise. They were asked to rate each pain stimulus on a numerical scale ranging from 0-10, where 0 was labelled as "*I feel nothing*"; 1 as "*I feel something, but this is not unpleasant; it is only a sensation*", 2 as "*the stimulus is not yet painful, but is beginning to be unpleasant*"; and 10 as "*this is the worst pain I can imagine*" (e.g., (Meulders et al., 2013; Meulders & Vlaeyen, 2013)).

Participants were asked to select a stimulus that they would describe as "*significantly painful and demanding some effort to tolerate*". The mean physical intensity of the pain stimulus chosen during the calibration procedure was 34.5 mA (± *SD* = 21.6, range = 4-99), and the mean self-reported stimulus intensity was 7.8 (± *SD* = 0.76, range = 5-9).

Robotic arm-reaching task. The robotic arm-reaching task was adapted from Meulders et al. (Meulders et al., 2016). Participants were seated in a chair, at an approximate distance of 2.5m from the LCD screen, and a comfortable distance (~15cm) from the handle (sensor) of the HM (see Fig. 2.1). Participants were required to hold the sensor of the HM in their right hand, and to move it from a starting location to a target location. Feedback regarding movements performed within the experimental movement plane was provided visually on the LCD screen. The sensor was visualized on the screen as a "green ball", which allowed participants to track their movements on-screen. The start and target locations were situated at the lower and upper left corners of the movement plane, respectively. The target location was visualized as a green arch, through which the green ball had to pass in order for the movement to be completed (see Fig. 2.2, Panel 2 for a flow-chart of the experimental task; see here: https://maastrichtuniversity.bbvms.com/view/um/4112993.html for a video of the task). Participants could reach the target via three different movement trajectories (T1-3) represented on screen as three arches situated midway through the movement plane. The trajectory arches were separated, in order to leave room for the generalization trajectory arches, which were positioned between the acquisition trajectory arches during the generalization phase (G1-3, see Fig. 2.2, Panel 2, "Generalization"). The trajectory arches, as well as the target arch, each had their own counter, which increased by 1 unit when the green ball had successfully passed through the corresponding arch; the given trajectory counter was set back to 0 once the target was successfully reached, and the target counter increased by 1 unit. On each trial, participants freely chose one of the three the movement trajectories to reach the target location.

To indicate that the participant could initiate the movement, the target arch and a "traffic light" positioned at the top of the movement plane, turned green, and an auditory "starting signal" was presented. A movement was successfully completed when (1) the green ball passed through the target arch at the end of the movement plane, (2) the overall trial counter placed next to the target arch increased by 1 unit, (3) an auditory "scoring signal" was presented, and (4) both the target arch and traffic light turned red. Upon successful movement completion, participants were required to release the HM, which repositioned itself to the starting position automatically. While the HM was repositioning, the target arch and traffic light remained red, indicating that moving

the HM was prohibited at that point. After returning to its starting position, the HM remained fixed for 3s (inter-trial interval; ITI) before the start of the next trial.

Figure 2.1. The experimental setup. The participant is seated in front of the LCD screen, at reaching distance from the sensor of the HM. The electrodes for delivering electrical stimuli, are placed on the triceps tendon of the right arm (yellow circle), and the triple foot switch is used to give pain-related fear and pain-expectancy ratings. Figure modified with permission from Glogan, Gatzounis, Vandael, et al. (2020).

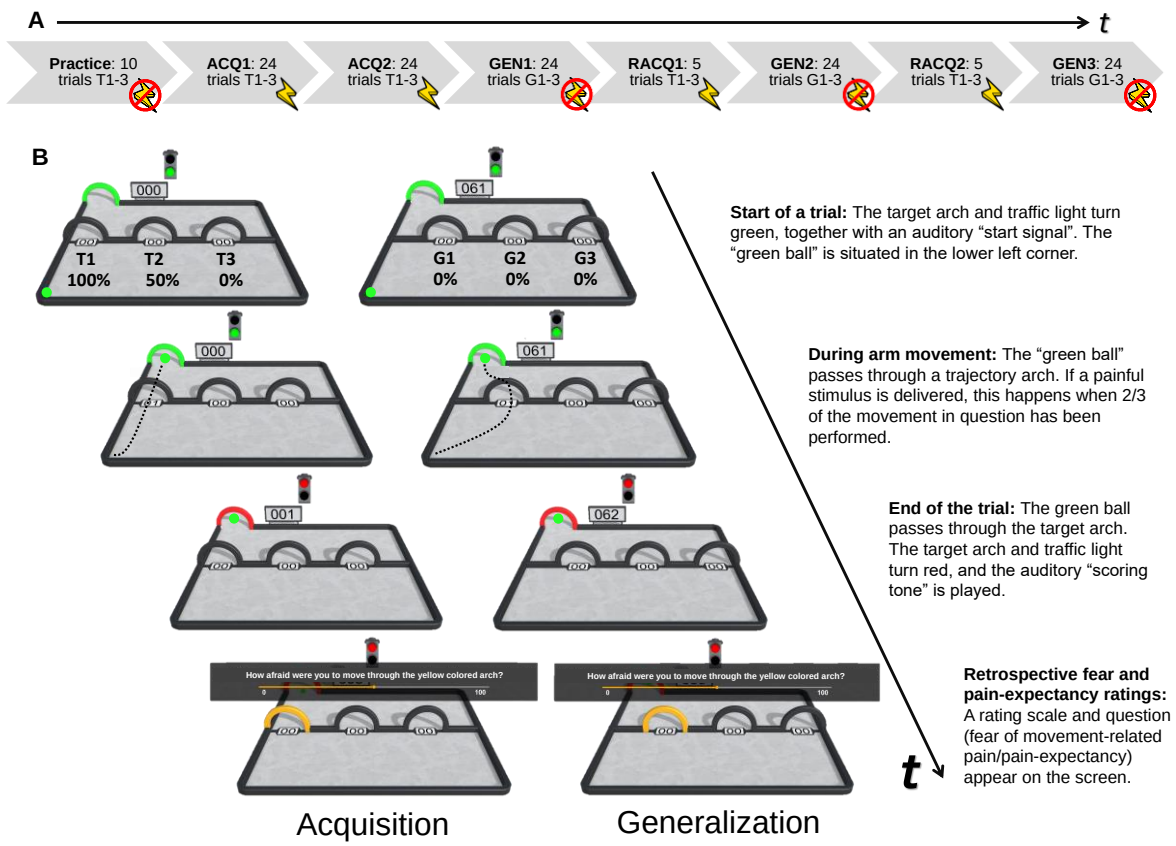

Figure 2.2. Experimental design and schematic overview of the experimental task. Panel A: The design of the experimental task. ACQ1-2 – blocks 1 and 2 of the acquisition phase, GEN1-3 – blocks 1-3 of the generalization phase, RACQ1-2 – blocks 1 and 2 of reminder-of-acquisition. T1-3 and G1-3 refer to acquisition trajectory arches and generalization trajectory arches, respectively. Lightning bolts with and without stop sign refer to blocks where the pain stimulus was not and was present, respectively. **Panel B:** Schematic overview of the experimental task. Labels T1-3, G1-3, and percentages (100%, 50%, 0%) refer to the trajectory arches and their corresponding probabilities of pain, respectively. Note – labels for arches and reinforcement rates have been added to the figure for clarification and were not part of the visual representation of the experimental paradigm.

The HM was programmed such that there was a linear relationship between resistive force and the lateral displacement of the robotic arm. This means that, when the shortest trajectory (T1) was chosen, minimal effort was needed to reach the target (in terms of distance and resistive force), when the middle trajectory (T2) was chosen, moderate effort was needed, and when the target was reached via the longest trajectory (T3), the most effort was needed to reach the target. Participants completed four phases: the practice phase, the acquisition phase, and the generalization phase that was interspersed by short reminder-of-acquisition blocks (Fig. 2.1, Panel 1.).

Practice phase. Participants read on-screen instructions about the task and then performed 10 practice trials, during which the participant was trained to operate the HM correctly. The first trial was performed by the experimenter as an example, after which the participant was asked to try each trajectory a few times. Only acquisition trajectory arches (T1-3) were shown during the practice phase. During this phase, the experimenter also ensured that participants did not start moving before the starting signals were presented, and that they released the HM immediately when the scoring signal appeared. Participants were also trained to provide self-report measures (see '*2.4.2 Self-reports: fear of movement-related pain and pain-expectancy*') using a Windows 10 compatible triple foot switch (USB-3FS-2; Tokyo, Japan). A foot switch instead of a manual switch was used in order to not interfere with the arm-reaching movements. During this phase, no painful stimuli were presented, but the above-mentioned relationship between the resistive force and lateral displacement of the HM was already in operation.

Acquisition phase. The acquisition phase consisted of 2 blocks of 24 trials. For participants in the *Experimental Group*, the easiest and shortest trajectory was always paired with the pain (T1 = 100% reinforcement; no resistance or deviation). The pain was delivered when 2/3 of the movement was completed. By choosing one of the other trajectories, participants were able to either partly (T2 = 50% reinforcement; moderate resistance and deviation) or completely (T3 = 0% reinforcement; strongest resistance and largest deviation) avoid the pain, but more effort was required. Each participant in the *Yoked Group* was matched to a participant in the Experimental Group, meaning that they received pain on the same trials as their Experimental Group counterpart, irrespective of their chosen movement trajectory. For example, if a participant in the Experimental Group chose T1 on trial 14 of the acquisition phase, and thus received pain on that trial, their yoked control also received pain on trial 14, even if the yoked participant chose T3. During the acquisition phase, fear of movement-related pain, and pain-expectancy for all trajectories were assessed three times during each block. Pain intensity and unpleasantness ratings were collected at the end of each block.

Generalization phase. This phase was similar to the acquisition phase, except that the generalization trajectories (G1-3) were now available instead of T1-3. G1 was positioned between T1 and T2, G2 was positioned between T2 and T3, and G3 was positioned to the right of T3 (see Fig. 2.1, Panel 2, "Generalization"). Thus, G1 was similar to both pain-associated trajectories (T1 and T2). G2 represented an ambiguous trajectory, as it was between a trajectory partially associated with pain, and a safe trajectory. G3 represented "overgeneralization" of avoidance behavior, as performing this movement required more effort than performing the movement that previously completely averted the pain. Again, retrospective fear of movement-related pain, and pain-

expectancy questions were asked three times during each block of the generalization phase. The generalization phase was identical for both groups and was interspersed with brief reminder-of-acquisition blocks (see '*Reminder-of-acquisition*').

Reminder-of-acquisition. In order to prevent extinction during the generalization phase, the three blocks of generalization were interspersed with two brief reminder-of-acquisition blocks, during which the acquisition trajectories were once again available along with the related contingencies. These blocks comprised 5 trials. Fear of movement-related pain, and pain-expectancy questions were asked once in the middle of both reminder-of-acquisition blocks.

Primary outcome measures

Behavioral avoidance. Avoidance behavior was operationalized as the maximal deviation from the shortest trajectory, from the start location to the target location, on each trial of the robotic arm-reaching task. This information was extracted using the co-ordinates of each performed movement, which were automatically logged by the HM.

Self-reports: retrospective pain-expectancy and fear of movement-related pain. During the acquisition and generalization phases, fear of movement-related pain and pain-expectancy reports were collected three times for each trajectory during each block on fixed, predefined trials. During the shorter reminder-of-acquisition blocks, reports were collected once for each trajectory. Questions were presented on-screen. To indicate the movement trajectory to which the question was referring to, the corresponding arch turned yellow (Fig. 2.1). Participants rated the questions *"To what extent did you expect an electrical stimulus when moving through the yellow-colored arch?"* (i.e. pain-expectancy) and "*How afraid were you to move through the yellow-colored arch?"* (i.e. fear of movement-related pain) retrospectively for each of the movement trajectories. Answers were provided on a Visual Analogue Scale (VAS) ranging from 0-100 (0 = "not at all" and 100 = "very much"), using the foot pedals. The left and middle foot pedals were used to scroll to the left and right on the rating scale, respectively, and the right foot pedal was used to confirm the participant's answer. During the time that participants responded to these questions, the HM was immobilized.

Secondary outcome measures

Trajectory choice. Frequencies of choices for all movement trajectories were calculated for both groups. This information was automatically logged by the HM.

Exit questionnaire. Immediately after completing the robotic arm-reaching task, participants completed an exit questionnaire, which included the following questions: (1) "*How intense did you find the electrical stimulus during the robotic arm task?*", (2) "*How unpleasant did you find the electrical*

stimulus?", (3) "*How much did you want to avoid the electrical stimulus?*", (4) "*How threatening did you find the electrical stimulus?*" (5) "*How intense did you find the resistance of the robotic arm?*", (6) "*How unpleasant did you find the resistance?*", and (7) "*How much did you want to avoid the resistance?*". These questions were responded to on an 11-point scale ranging from 0 to 10 (0 = not at all, and 10 = very much). Furthermore, participants responded to contingency-awareness questions inquiring which arches they believed to be paired with the least and most resistance, and which arches they believed were least and most likely to predict the pain.

Psychological trait questionnaires. Participants completed six psychological questionnaires to measure individual differences in (1) positive and negative affect (PANAS; the Positive and Negative Affect Schedule [(Engelen et al., 2006; Watson et al., 1988)]), (2) pain catastrophizing (PCS; Pain Catastrophizing Scale [(Sullivan et al., 1995)]), (3) fear of pain (FPQ; Fear of Pain Questionnaire [(McNeil & Rainwater, 1998; Roelofs et al., 2005)]), (4) experiential avoidance (MEAQ; the Multidimensional Experiential Avoidance Questionnaire [(Gamez et al., 2011)]), and (5) distress tolerance (DTS; the Distress Tolerance Scale [(Simons & Gaher, 2005)]). Questionnaires were presented using a web survey tool (Qualtrics; Qualtrics, Provo, Utah, USA; Seattle, Washington, USA), and completed on a tablet (ASUS ZenPad 8.0, AsusTek Computer Inc., Taipei, Taiwan).

Statistical analysis overview

Paired samples *t*-tests between groups were performed on sample characteristics data (age, physical pain intensity (in mA), self-reported pain intensity, and scores of the psychological trait questionnaires), as well as exit questionnaire data. The acquisition phase was included in the analysis as a manipulation check, since acquisition of avoidance behavior, fear of movement-related pain and pain-expectancy are required to test for generalization effects. The reminder-of-acquisition phase was also analyzed as a manipulation check, given that its function was to refresh the originally acquired fear and avoidance responses. To test the hypothesis that self-report measures would differ significantly between the different trajectories (T1>T2>T3; G1>G2>G3), in the Experimental but not the Yoked Group, responses were averaged over blocks, and repeated measures (RM) Analyses of Variance (ANOVAs) with "Group" as the between-subjects factor, and "Block" and "Trajectory" as the within-subjects factors, were performed on the mean fear of movement-related pain, and mean pain-expectancy reports, respectively, and separately for each experimental phase. We also ran exploratory equivalence tests on mean self-reports in the Yoked Group during all experimental blocks (see Appendix A for the descriptions and complete results of these analyses).

For analyses of avoidance behavior, maximum deviation from the shortest trajectory on each trial was calculated using a MatLab (MathWorks, Natick, MA, US) script. Furthermore, to increase comparability of avoidance data between the acquisition and generalization phases, the deviation data from the generalization phase were linearly transformed to share the same co-ordinates as the acquisition data. These values were averaged for each participant over each block. To compare avoidance behavior between groups, separate RM ANOVAs were performed with "Group" as the between-subjects factor, and "Block" as the within-subjects factor, separately for each phase. For all measures, we expected the largest generalization effects during the first generalization block, and for these to gradually decrease.

Furthermore, as an exploratory analysis to investigate the effect of group on trajectory choice, we ran multinomial ordered logistic regression analyses for each experimental phase separately, with Trajectory Choice (T1-3/G1-3) as the ordered categorical dependent variable, and Group, Block, and the Group x Block interaction as predictors. Specifically, for each experimental phase, a model including a normally distributed random shift effect to account for the dependence between observations within participants was estimated. The model consisted of two simultaneously estimated cumulative logit models. The first logit modelled the probability of choosing T/G3, and the second logit modelled the probability of choosing T/G2 or higher. The proportional odds assumption implies that the coefficients of the predictors (and hence the corresponding odds) are assumed to be equal in the two logit equations. See Appendix A for a detailed description of these models.

The α level was set at .05. To control for violations of sphericity, Greenhouse-Geisser corrections were applied when necessary. To control for multiple comparison testing, Bonferroni-Holm corrections were applied to all planned comparisons, and Bonferroni corrections to multiple independent samples *t*-tests. Pooled (Welch-Satterthwaite) degrees of freedom, and corrected *p*-values are reported. The indication of effect size η_p^2 is reported for significant ANOVA effects, and Cohen's *d* for planned comparisons. RM ANOVAs and planned comparisons were performed using the free software environment RStudio (RStudio Inc. Boston, MA, USA). Exploratory multinomial logistic regressions were estimated using the GLIMMIX Procedure in the statistical software SAS (SAS Institute Inc., Cary, NC, USA).

Results

Sample demographics and characteristics of the pain stimulus and questionnaires

There were no differences between the Experimental and Yoked Groups in age, $t(62) = .37$, $p = .71$, chosen physical pain intensity, $t(62) = .65$, $p = .52$, or self-reported intensity of the pain

stimulus, $t(62) = 1.07$, $p = .29$. No differences occurred in any of the exit questionnaire items or psychological trait variables (all p-values > .05).

Manipulation checks

Acquisition of self-reported pain-expectancy. A 2 x 2 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: ACQ1-2) x (Trajectory: T1-3) revealed a significant main effect of Block, $F(1, 62) = 4.89$, $p = .03$, $\eta_p^2 = .07$, and Trajectory, $F(1.87, 116.19) = 63.4$, $p < .0001$, $\eta_p^2 = .51$. These were qualified by a significant 3-way interaction, $F(1.97, 121.91) = 21.21$, $p < .0001$, $\eta_p^2 = .26$, suggesting that pain-expectancies for the different trajectories changed differently in the two groups over time. Planned comparisons showed that by the end of the acquisition phase (ACQ2), the Experimental Group expected the pain stimulus to occur more when performing T1 compared to T3, $t(215) = 17.71$, $p < .0001$, $d = 4.41$, and compared to T2, $t(215) = 4.67$, $p < .0001$, $d = 1.10$ (see Fig. 2.3, Panel A). In line with our hypothesis, pain-expectancy reports were also significantly higher for T2 compared to T3, $t(215) = 13.04$, $p < .0001$, $d = 2.82$. These results confirm that participants in the Experimental Group successfully acquired the experimental response-outcome contingencies. Please refer to Appendix A for the results of equivalence testing on pain-expectancies in the Yoked Group.

Acquisition of self-reported pain-related fear. We performed a similar 2 x 2 x 3 RM ANOVA on the fear ratings during the acquisition phase. This analysis yielded significant main effects for Block, $F(1, 62) = 16.25$, $p < .001$, $\eta_p^2 = .21$, and Trajectory, $F(1.5, 93.27) = 28.79$, $p < .0001$, $\eta_p^2 = .32$. A significant three-way interaction emerged, $F(1.84, 113.97) = 10.74$, $p < .0001$, $\eta_p^2 = .15$, suggesting that fear of the respective trajectories evolved differently for the two groups during acquisition. Planned comparisons confirmed that by ACQ2, the Experimental Group was more afraid to perform T1, $t(217) = 11.8$, $p < .0001$, $d = 1.76$, and T2, $t(217) = 11.02$, $p < .0001$, $d = 1.76$, compared to T3. In contrast with the pain-expectancy ratings, no differences in fear ratings were observed between trajectories T1 and T2, $t(217) = .78$, $p = .44$ (see Fig. 2.3, Panel B), despite T1 having a higher probability to be followed by a pain stimulus than T2. These findings corroborate the pain-expectancy results for T3, that is, this trajectory was perceived as a safe trajectory, and consequently, participants reported less fear of performing this trajectory. In contrast, a discrepancy was observed between pain-expectancy ratings and fear ratings for T1 and T2; although these trajectories elicited differential pain-expectancy ratings (T1 > T2), they produced similar levels of fear (T1 = T2). Please refer to Appendix A for the results of equivalence testing on pain-related fear reports in the Yoked Group.

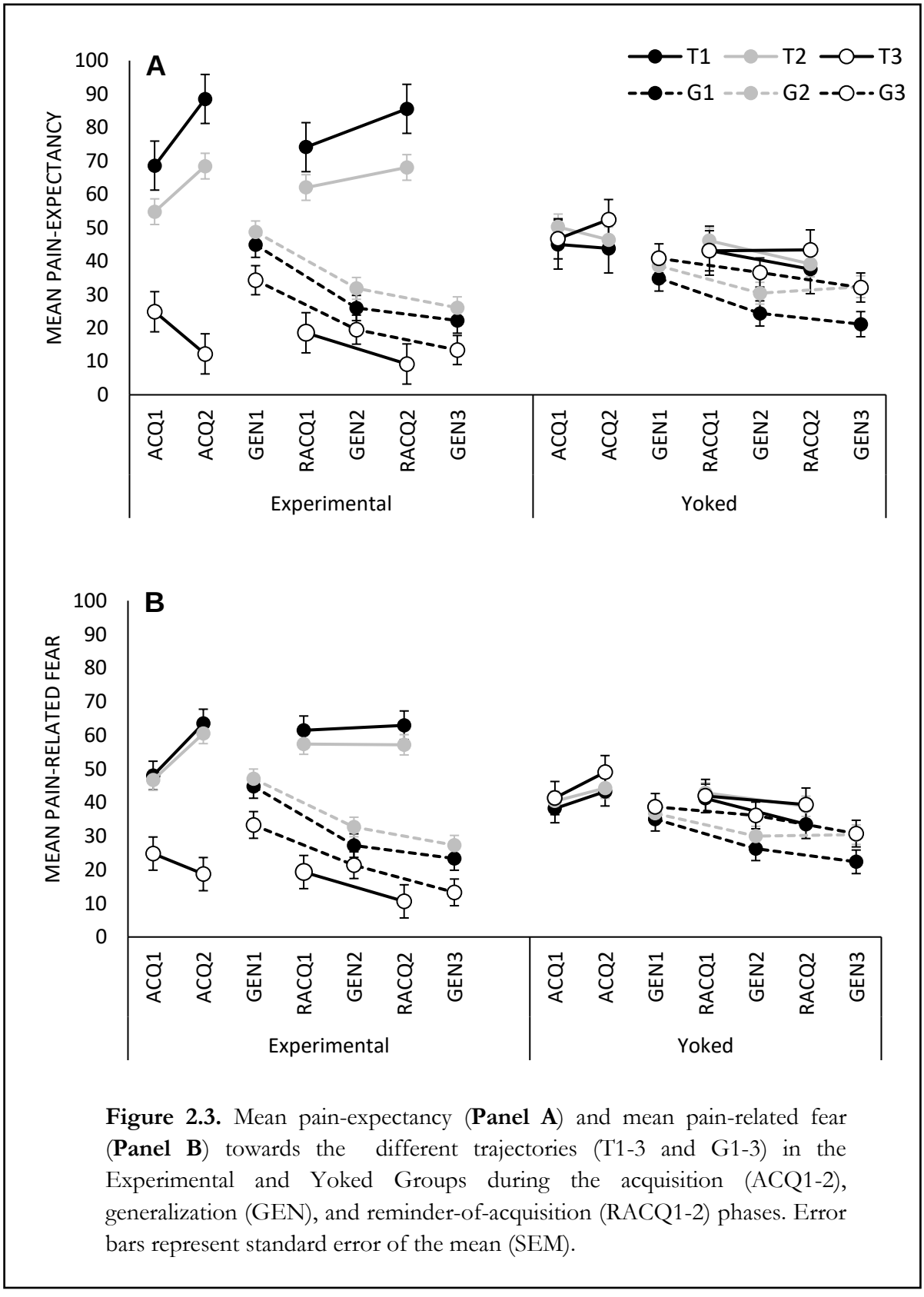

Figure 2.3. Mean pain-expectancy (**Panel A**) and mean pain-related fear (**Panel B**) towards the different trajectories (T1-3 and G1-3) in the Experimental and Yoked Groups during the acquisition (ACQ1-2), generalization (GEN), and reminder-of-acquisition (RACQ1-2) phases. Error bars represent standard error of the mean (SEM).

Acquisition of behavioral avoidance. A 2 x 2 RM ANOVA (Group: Experimental, Yoked) x 2 (Block: ACQ1-2) was carried out on the maximal deviation data during acquisition.[1] There was a significant main effect of Group, $F(1, 62) = 60.18$, $p < .0001$, $\eta_p^2 = .49$, and of Block, $F(1, 62) = 7.13$, $p = .01$, $\eta_p^2 = .10$, which were accommodated by a significant Group x Block interaction, $F(1, 62) = 20.55$, $p < .0001$, $\eta_p^2 = .25$. Planned comparisons confirmed that participants in the Experimental Group showed significantly larger deviations than the Yoked Group, during ACQ2, $t(91.70) = 8.97$, $p < .0001$, $d = .84$ (see Fig. 2.4). These findings confirm that participants in the Experimental Group acquired avoidance behavior.

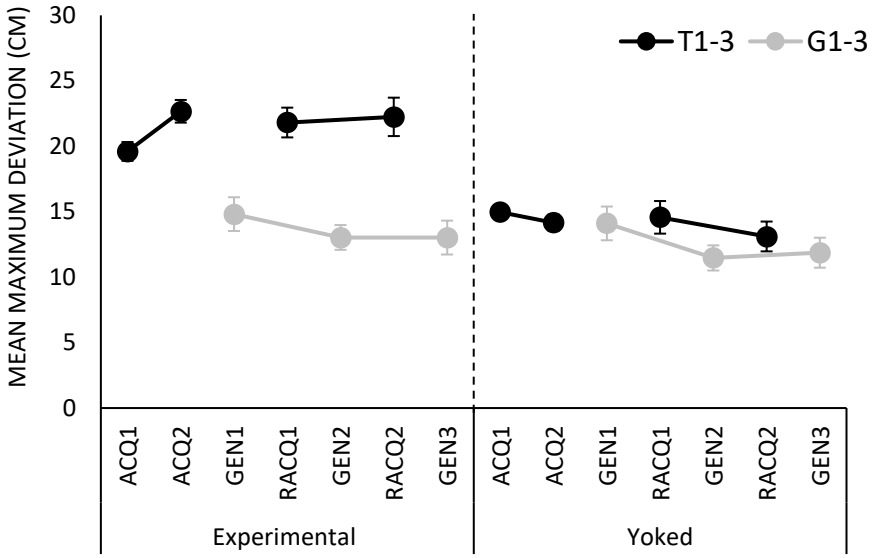

Figure 2.4. Mean maximum deviation from T1, from the starting position to the target during acquisition (ACQ1-2), generalization (GEN1-3), and reminder-of-acquisition (RACQ1-2), in the Experimental and Yoked Groups. Error bars represent SEM. Note – To increase comparability between phases, deviation data from the generalization phase have been linearly transformed to share same co-ordinates as acquisition data.

[1] Trial-wise analyses were also run for the sake of completeness. However, these analyses did not yield differing results from the block-wise analysis.

Trajectory choice. During the first block of the acquisition (ACQ1) phase, participants in the Experimental Group were 2.42 times more likely to choose T3 rather than T1 or T2 (or, T3 or T2 rather than T1) than participants of the Yoked Group, ($\exp(\hat{\beta}_G)$, $p < .0001$, for $\hat{\beta}$ values see Table 2.1; see Fig. 2.5). During ACQ2, Experimental Group participants were 5.30 times more likely to choose T3 compared to T1 and T2 (or, T3 or T2 rather than T1) compared to participants in the Yoked Group, ($\exp(\hat{\beta}_G + \hat{\beta}_{GxB2})$, $p < .0001$). A significant Group x Block interaction emerged, showing that the odds ratio for choosing T3 rather than T1 or T2 (or T3 or T2 rather than T1) in the Experimental Group, compared to the Yoked Group, was significantly higher during the second block of the acquisition phase, than during the first block of the acquisition phase (5.30 versus 2.42, $p < .001$). Thus, compared to the Yoked Group, the propensity of the Experimental Group to choose the avoidance trajectory, increased from ACQ1 to ACQ2, suggesting that avoidance behavior was gradually acquired.

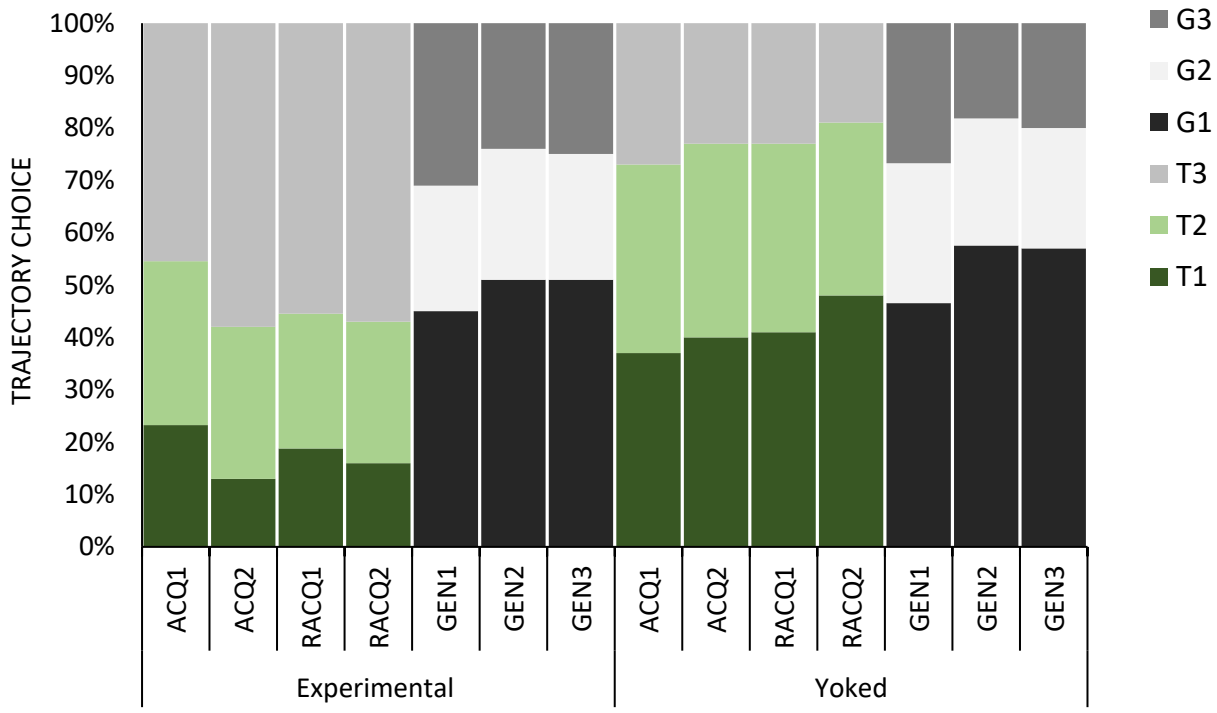

Figure 2.5. Percentages of trajectory choice for all movement trajectories (T1-3 and G1-3) during the acquisition phase (ACQ1-2), reminder-of-acquisition phase (RACQ1-2), and generalization phase (GEN1-3) for the Experimental and Yoked Groups.

Table 2.1. Regression coefficients ($\hat{\beta}$) and odds ($\exp(\hat{\beta})$) for the variables included in the random proportional odds models for the different experimental phases.

		Acquisition		Reminder-of-acquisition		Generalization	
		$\hat{\beta}$	$\exp(\hat{\beta})$	$\hat{\beta}$	$\exp(\hat{\beta})$	$(\hat{\beta})$	$\exp(\hat{\beta})$
Intercept T3/G3	a_3	-1.071***	0.34	-1.342***	0.26	-1.487***	0.23
Intercept T2/G2	a_2	.548***	1.73	.352	1.42	-.008	0.99
Group	β_G	.885***	2.42	1.603***	4.97	.451	1.57
Block 2	β_{B2}	-.171	0.84	-.262	0.77	-.584***	0.56
Block 3	β_{B3}					-.524***	.59
Group x Block 2	β_{GxB2}	.783***	2.19	.363	1.44	.181	1.20
Group x Block 3	β_{GxB3}					.125	1.13

*= significant at .05 **= significant at .01 ***= significant at .001

Note – Group refers to a dummy variable that equals 1 for the Experimental Group and 0 for the Yoked Group. Block 2 refers to a dummy variable that equals 1 for Block 2, and 0 in other cases. Block 3 refers to dummy variable that equals 1 for Block 3, and 0 in other cases.

Reminder-of-acquisition: Self-reported pain-expectancy. A 2 x 2 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: RACQ1-2) x (Trajectory: T1-3) revealed a significant main effect of Group, $F(1, 62) = 5.64$, $p = .02$, $\eta_p^2 = .08$, and of Trajectory, $F(1.67, 103.43) = 80.68$, $p < .0001$, $\eta_p^2 = .57$. These were accommodated by a significant Group x Block x Trajectory interaction, $F(1.76, 108.83) = 12.51$, $p < .0001$, $\eta_p^2 = .17$, suggesting that pain-expectancy towards the different trajectories evolved differently in both groups during the reminder-of-acquisition phase.

Planned comparisons confirmed that participants in the Experimental Group still expected the pain stimulus more when performing T1, compared to T2, (RACQ1: $t(192) = 2.85$, $p = .005$, $d = .57$; RACQ2: $t(192) = 4.14$, $p = .0001$, $d = .69$, and T3, (RACQ1: $t(192) = 13.12$, $p < .0001$, $d = 2.61$; RACQ2: $t(192) = 18.03$, $p < .0001$, $d = 3.64$), during the reminder-of-acquisition phase. Furthermore, T2 also evoked significantly higher pain-expectancy reports, compared to T3, (RACQ1: $t(192) = 10.27$, $p < .0001$, $d = 2.06$; RACQ2: $t(192) = 13.89$, $p < .0001$, $d = 2.54$ (see Fig. 2.3, Panel A). These findings indicate that the test of generalization under extinction did not affect the acquired differential pain-expectancy ratings for the original trajectories (T1-3). Please refer to Appendix A for results of equivalence tests on data from the Yoked Group.

Reminder-of-acquisition: Self-reported pain-related fear. A similar RM ANOVA was carried out on the fear ratings during the reminder-of-acquisition phase. There was a significant main effect of Trajectory, $F(1.6, 99.26) = 51.41$, $p < .0001$, $\eta_p^2 = .45$, as well as a significant three-way interaction, $F(1.89, 117.42) = 3.78$, $p = .03$, $\eta_p^2 = .06$, suggesting that fear towards the different trajectories evolved differently within the two groups during the reminder-of-acquisition phase. Planned comparisons showed that participants in the Experimental Group were still more afraid to perform T1, (RACQ1: $t(198) = 10.49$, $p < .0001$, $d = 1.72$, RACQ2: $t(198) = 13.04$, $p < .0001$, $d = 1.96$,) and T2, (RACQ1: $t(198) = 9.47$, $p < .0001$, $d = 1.54$, RACQ2: $t(198) = 11.59$, $p < .0001$, $d = 1.79$), compared to T3 (see Fig. 2.3, Panel B). In line with the acquisition data pattern, no such differences occurred between T1 and T2 (RACQ1: $t(198) = 1.03$, $p = .56$; RACQ2: $t(198) = 1.45$, $p = .32$). These findings show that the acquired differential fear in response to the original trajectories (T1-3) was preserved after participants were exposed to the non-painful generalization trajectories (G1-3).

Avoidance behavior. A 2 x 2 RM ANOVA (Group: Experimental, Yoked) x 2 (Block: RACQ1-2) was run on the maximal deviation data during the reminder-of-acquisition phase. There was a significant main effect of Group, $F(1, 62) = 34.33$, $p < .0001$, $\eta_p^2 = .36$, suggesting overall group differences in avoidance behavior during the reminder-of-acquisition blocks. Planned comparisons revealed that participants in the Experimental Group showed larger deviations from the shortest trajectory compared to the Yoked Group during the first ($t(85.10) = 4.74$, $p < .0001$,

d = .67) and second, t(85.10) = 5.99, p < .0001, d = .84 blocks of this phase. Thus, acquired avoidance behavior toward the original acquisition trajectories did not extinguish during the generalization phase (see Fig. 2.4).

Trajectory choice. During RACQ1, participants in the Experimental Group were 4.97 times more likely to choose T3 compared to T2 or T1 (or, T3 or T2 compared to T1) than participants in the Yoked Group, ($\exp(\hat{\beta}_G)$, p < .0001; Fig. 2.4). During RACQ2, Experimental Group participants were 7.1 times more likely to choose T3 rather than T2 and T1 (or, T3 or T2 rather than T1) than participants in the Yoked group, ($\exp(\hat{\beta}_G + \hat{\beta}_{GxB2})$, p < .0001) (Fig. 2.5). The Group x Block interaction was not significant, suggesting that the odds ratio comparing the odds of the Experimental and the Yoked Groups did not change between blocks, indicating that no additional learning occurred during the reminder-of-acquisition phase.

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

Self-reported pain-expectancy. A 2 x 3 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) x (Trajectory: G1-3) was carried out. There was a significant main effect of Block, F(1.85, 114.65) = 43.89, p < .0001, η_p^2 = .41. Significant Group x Block, F(1.85, 114.65) = 6.77, p = .002, η_p^2 = .10, and Group x Trajectory interactions, F(1.38, 85.73) = 5.99, p = .009, η_p^2 = .09, also emerged, suggesting that pain-expectancy changed between groups with time, and that overall pain-expectancy for the trajectories differed between groups. During the first generalization block (GEN1), the Experimental Group expected the pain to occur significantly more for G1, t(203) = 2.27, p = .05, d = .30, and G2, t(203) = 3.10, p = .007, d = .45, compared to G3. No significant differences occurred between G1 and G2, t(203) = .83, p = .41. During the second (GEN2) and third (GEN3) generalization blocks, G2 continued to evoke higher pain-expectancy reports compared to G3, t(203) = 2.65, p = .03, d = .40, and t(203) = 2.75, p = .02, d = .41 (see Fig. 2.3, Panel A). During these blocks there were no differences between G1 and G2, or G1 and G3 (all p-values > .05). Surprisingly, the Yoked Group reported expecting pain more during G3 compared to G1 during GEN2, t(203) = 2.63, p = .03, d = .23 (i.e. opposite direction of experimental manipulation; see Appendix A for results of equivalence tests).

Self-reported pain-related fear. A similar RM ANOVA run on self-reported fear in response to the generalization trajectories revealed a significant main effect of Block, F(1.71, 106.30) = 37.12, p < .0001, η_p^2 = .37. Furthermore, significant Group x Block, F(1.71, 106.30) = 5.78, p = .006, η_p^2 = .09, and Group x Trajectory interactions emerged, F(1.42, 88.03) = 5.48, p = .01, η_p^2 = .08, suggesting that fear levels changed between groups with time, and that fear for the different

trajectories differed between groups. Planned comparisons revealed significantly higher fear ratings for G1, $t(196) = 2.54$, $p = .02$, $d = .36$ and G2, $t(196) = 3.04$, $p = .008$, $d = .45$, compared to G3 in the Experimental Group during the first generalization block. In line with the acquisition phase, no differences emerged between G1 and G2, $t(196) = .51$, $p = .61$ (see. Fig. 2.3, Panel B). The difference between G3 and G2 remained significant during GEN2 and GEN3, $t(196) = 2.52$, $p = .04$, $d = .35$, $t(196) = 3.11$, $p = .006$, $d = .45$. However, no significant differences were observed between G1 and G3, or G1 and G2 during the rest of the generalization phase (all p-values > .05). Together with the pain-expectancy reports, these results suggest that pain-expectancy and fear of movement-related pain initially generalized from acquisition to generalization trajectories, but decreased rapidly.

Avoidance behavior. A 2 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: Gen1-3) was carried out.[2] There was a significant main effect of Block, $F(1.88, 116.42) = 6.70$, $p = .002$, $\eta_p^2 = .10$, but not of Group, $F(1, 62) = .50$, $p = .48$, nor was there a significant Group x Block interaction, $F(1.88, 116.42) = .23$, $p = .78$, $\eta_p^2 = .004$. In contrast with the verbal reports, no generalization of avoidance behavior was observed (see Fig. 2.4).

Trajectory choice. There was no significant effect of Group, neither was there a significant Group x Block interaction. However, a significant effect of Block emerged in the Yoked Group, whereby the odds of choosing G3 rather than G2 or G1 (or, G3 or G2 rather than G1), were 1.79 times lower for Block 2 than for Block 1 ($1/\exp(\hat{\beta}_{B2})$, $p < .0001$). Similarly, the odds were 1.69 times lower for Block 3 than for Block 1 ($1/\exp(\hat{\beta}_{B3})$, $p < .0001$). These results suggest that in the Yoked Group, the likelihood of choosing the avoidance trajectory (G3) decreased from GEN1 to GEN2 and GEN3 (see Fig. 2.5).

Discussion

The present experiment used a sample of healthy participants, who performed an operant arm-reaching task, to test whether acquired avoidance behavior, as well as fear of movement-related pain and pain-expectancy, would generalize to novel, similar movements that were never paired with pain. As expected, participants in the Experimental Group successfully acquired the experimental response-outcome contingencies. This was evidenced by pain-expectancy reports, which were highest for T1 (100% reinforcement) and lowest for T3 (0% reinforcement), with T2 (50% reinforcement) in the middle. Furthermore, participants also learned to fear the pain-associated trajectories but not the safe trajectory, as shown by significantly higher fear of

[2] Again, trial-wise analyses were also run for the sake of completeness. These analyses did not yield differing results from the block-wise analysis.

movement-related pain reported for T1 and T2 compared to T3. However, in contrast to pain-expectancy reports, participants did not show differential fear levels for the two reinforced trajectories, despite T1 and T2 having different probabilities of being followed by pain (100% vs. 50%). We also successfully replicated acquisition of avoidance behavior (Meulders et al., 2016), as evidenced by significantly larger deviation from the shortest trajectory in the Experimental Group compared to the Yoked Group.

Second, the described acquisition effects remained present during the reminder-of-acquisition blocks, suggesting that avoidance behavior, as well as differential self-reported fear of movement-related pain and pain-expectancy towards the acquisition trajectories did not extinguish during generalization under extinction.

Third, and in line with our main hypothesis, both fear of movement-related pain and pain-expectancy generalized to the novel, similar trajectories during the generalization phase, as shown by significantly higher self-reported fear and pain-expectancy for G1 and G2 in comparison to G3 at the beginning of the generalization phase. However, a generalization decrement was observed for both threat and safety learning. That is, there was a decrease in self-reported fear and pain-expectancy from T1 to G1 (G1 < T1) and T2 to G2 (G2 < T2), whereas these increased from T3 to G3 (G3 > T3), suggesting that participants were generally less certain about the contingencies following the change from the acquisition to the generalization phase. Interestingly, in line with fear of movement-related pain reports during the acquisition phase, participants did not show differential fear- or pain-expectancy reports for G1 and G2. Finally, and contrary to our hypothesis, avoidance behavior did not generalize to the novel, similar movement trajectories during the generalization phase.

Some of these findings deserve further attention. First, there was a discrepancy between self-reports and the observed avoidance behavior in the generalization phase. Namely, self-reported fear of movement-related pain and pain-expectancy generalized to the novel trajectories, whereas instrumentally acquired avoidance behavior did not. Our exploratory analyses on the trajectory choice data corroborated our findings of avoidance as a continuous measure. The lack of avoidance generalization in the current study is in contrast with previous research reporting generalization of both self-reports and operant avoidance behavior (Boyle et al., 2014; Cameron et al., 2015; Dymond et al., 2012; Dymond et al., 2011; Norbury et al., 2018; van Meurs et al., 2014). It must be noted, however, that all of these previous studies employed a simple, low-cost button press as the avoidance-response. This is a critical methodological difference from the current study, in which avoidance behavior was effortful. This seems to suggest that the

generalization of operant avoidance behavior in healthy participants may depend on whether or not the avoidance-response comes at a cost.

In line with this, manipulating the cost (Van Damme et al., 2012) or value (Pittig & Dehler, 2019) of avoidance has been found to disentangle fear and operant avoidance. Indeed, our preliminary finding of dissociated self-reports and avoidance behavior corroborates previous literature (Bravo-Rivera et al., 2015; Krypotos et al., 2015; Meulders, 2019; Mineka, 1979; Vervliet & Indekeu, 2015) reporting that fear and avoidance do not share a one-to-one relationship. For example, avoidance behavior is commonly found to persist even when fear has been extinguished (Bravo-Rivera et al., 2015; Mineka, 1979; Solomon et al., 1953; Vervliet & Indekeu, 2015).

Avoidance behavior in real life occurs in a context with many other competing, concomitant personally valued goals (Claes et al., 2016; Volders et al., 2015), which may influence the relationship between fear and avoidance. For example, chronic pain patients are likely to sometimes perform valued behaviors (e.g. playing with one's children, going to work), even if they are afraid of these worsening the pain. The choice whether or not to perform a specific behavior (e.g. avoidance) often depends on the value and probability of success of each available behavioral option (Eccles & Wigfield, 2002; Fishbach & Ferguson, 2007). In the current study, participants had to choose between avoiding pain and avoiding effort. The Experimental Group learned that during the acquisition phase, they could successfully avoid pain by deviating from the shortest trajectory. However, the switch from the acquisition phase to the generalization phase may have decreased participants' trust in this avoidance response. Indeed, it has been suggested (Bouton et al., 2014; Bouton et al., 2011) that during operant appetitive conditioning, a direct context-response association is produced, deeming the response less supported when the context is changed. In the present paradigm, the change from the acquisition phase to the generalization phase was operationalized by visually removing the acquisition arches and displaying the novel, intermediate generalization arches. These visual changes may have been interpreted as a *context-switch* (Bouton & Todd, 2014) leading participants to believe that potentially new response-outcome contingencies would be in place. This interpretation is supported by our data, which show a clear generalization decrement for both threat- and safety learning (i.e. fear and pain-expectancy = G1 < T1, G2 < T2, G3 > T3), suggesting a general uncertainty about the acquisition contingencies. This uncertainty also seems evident in the pain-expectancy reports, which differed between T1 and T2 during acquisition (T1 > T2), but did not do so between G1 and G2 during generalization (G1 = G2). This general uncertainty regarding the experimental contingencies during the generalization phase may have decreased the perceived probability of success of the avoidance response, and increased participants' propensity to perform the less effortful movements.

However, even in this case generalization of avoidance may have occurred if participants' fear beliefs had not been disconfirmed immediately after they tested G1. Indeed, methodological characteristics may also explain the lack of generalization of avoidance behavior. For example, a perceived context-switch between the acquisition and generalization phases, due to changes in the task configuration, may have stimulated exploratory behavior. Participants may have felt more inclined to try G1 at the beginning of generalization in order to verify whether this novel trajectory, similar to the previous pain-associated trajectory, would still be paired with pain. Our data support this post-hoc interpretation, as 15/32 participants in the Experimental Group chose G1 already on the first generalization trial (in comparison to 5/32 and 12/32 for G2 and G3, respectively). Because of the 100% reinforcement schedule of T1 during acquisition, participants learned that T1 was *always* accompanied by pain. Therefore, successful generalization of avoidance from T1 to G1 would mean that participants also expected G1 to be paired with pain on a majority of trials. For example, it is possible that participants still expected G1 to be followed by pain at the beginning of the generalization phase, but due to the 100% reinforcement rate of T1, this expectation was immediately disconfirmed when performing a G1 movement. The change in task configuration may have functioned as an *occasion setter* (Baeyens et al., 2004; Holland, 1992), i.e. participants may have learned that the task configuration (the position of the arches) modulates the response-outcome contingencies. This interpretation is also in line with our results from the reminder-of-acquisition blocks, where the trajectory arches shifted back to the left, and conditioned responding returned.

Our findings of generalization in fear of movement-related pain and pain-expectancy reports are in line with previous research on operant avoidance generalization (Boyle et al., 2014; Cameron et al., 2015; Dymond et al., 2011; Dymond et al., 2012; Norbury et al., 2018; van Meurs et al., 2014), where generalization of self-report measures has also been reported. However, fear and expectancy reports declined rapidly in the current study, and only the middle (G2), but not the short (G1), generalization trajectory continued to evoke significantly higher self-reports in comparison to the "safe" generalization trajectory (G3) throughout the generalization phase. This finding parallels previous reports in the fear conditioning literature. In the current study, G2 represented an ambiguous trajectory, given that it was situated between a trajectory sometimes paired with pain (T2) and a trajectory never paired with pain (T3). Abad, Ramos-Alvarez and Rosas (Abad et al., 2009) found that a switch in contexts did not affect responding to a partially reinforced CS (ambiguous), whereas responding to a concurrently trained, continuously reinforced CS (unambiguous) decreased (Abad et al., 2009). Thus, our results are similar to those of Abad et al. (Abad et al., 2009); the change in contexts from acquisition to generalization seemed to have a

greater diminishing effect on responding towards G1 than G2. As stated above, 100% reinforcement schedules often lead to a rapid decrease (e.g. extinction) of fear. Thus to slow down the rate of extinction, partial reinforcement schedules are traditionally used in operant conditioning research (Finger, 1942; Pennes & Ison, 1967). Given that T2 was only sometimes paired with pain during acquisition, the absence of reinforcement during G2 had a more ambiguous meaning. In contrast to this, and in line with our data, it is likely that due to the 100% reinforcement rate of T1, the absence of pain during G1 had a more profound meaning, and deleterious effect on fear and expectancy reports.

We observed a divergence between pain-expectancy and fear of movement-related pain measures; where pain-expectancy reports during the acquisition phase differed between all trajectories in the Experimental Group, fear reports for the two pain-associated trajectories did not, despite differing reinforcement rates (T1 = 100% vs. T2 = 50%). This divergence is in contrast to Meulders et al. (Meulders et al., 2016), where both self-report measures reflected the experimental contingencies of the acquisition phase. The current finding is, however, in line with the notion of expectancy and fear-reports reflecting different processes; namely, whereas pain-expectancy ratings have been suggested to represent a *cognitive component* of fear learning, and a proxy of contingency-awareness (Boddez et al., 2013), fear-reports are believed to reflect a more the *emotional component* of fear learning (Soeter & Kindt, 2010). This suggests that, although participants in the current study were *aware* that T2 was less likely to be followed by pain than T1, the two pathways evoked similar levels of *emotional* (fearful) responding. Unpredictability commonly leads to increased anticipatory anxiety and physiological arousal (Carlsson et al., 2006; Davis et al., 2010; de Berker et al., 2016; Grillon et al., 2006; Machida et al., 2013; Yoshida et al., 2013). Thus, despite apparent contingency awareness expressed in pain-expectancy reports, participants may have found the unpredictable pain associated with T2 similarly threatening as the predictable pain associated with T1.

However, this explanation only sheds light on the non-differential fear reports between T1 and T2, but not the difference in fear report results between the current study, and that of Meulders et al. (Meulders et al., 2016) (non-differential and differential fear-reports for T1 and T2, respectively). This finding may be explained by differences in samples. For example, the sample of Meulders et al. consisted of a majority of male participants (36 males, 14 females), whereas the current sample was mostly female (20 males, 42 females). Women have been found to score higher on the FPQ, and to report higher fear of pain in general (Vambheim & Øien, 2017). In line with this, the current Experimental Group reported noticeably higher fear of pain, as measured by the FPQ (McNeil & Rainwater, 1998; Roelofs et al., 2005) (mean FPQ: 85.63, *SD* = 18.31), compared

to that of Meulders et al. (mean FPQ: 59.56 *SD* = 12.75) (Meulders et al., 2016). Subjective fear of pain is closely linked to emotional reactions in response to the anticipation of pain (Lyby et al., 2011). Furthermore, ambiguous stimuli allow increased variance in individual responses to emerge (Lommen et al., 2010). Thus, overall higher levels of trait fear of pain in the current sample could have resulted in increased fear-reports for T2, and thus non-differential fear between T1 and T2.

Some limitations should be discussed. The current results suggest that the absence of generalization of avoidance behavior may be due to specific features in the design. First, in our study, T1 was paired with pain on 100% of trials, for reasons of replication (Meulders et al., 2016). Yet, a partial reinforcement schedule may have been better suited for investigating generalization, for reasons described above. Future research should replicate the present study with partial reinforcement rates during acquisition, to increase ambiguity, and minimize the possibility of immediate disconfirmation of participants' acquired fear beliefs. It should also be mentioned that, on closer inspection of individual response patterns, a subset of participants in the current study (4/32) did generalize avoidance. These participants chose G3 on all, or a clear majority of generalization trials, they reported higher fear for G1 and G2 compared to G3, and in the exit questionnaire they reported believing the probability of pain to follow the pattern G1 > G2 > G3. This suggests that the current paradigm has the potential to capture generalization of avoidance behavior. Given that individual differences tend to emerge with more ambiguous stimuli (Lommen et al., 2010), increasing the ambiguity of the movement trajectories in the current paradigm may increase participants' tendency to generalize avoidance behavior. Second, our results suggest that there are a variety of ways in which participants in the Experimental Group may have interpreted the change from the acquisition phase to the generalization phase (e.g. context-switch), that were not accounted for by the current design. Thus, future research should attempt to minimize the possibility of any perceived context-switch by, for example, having all trajectory arches visible throughout the entire experiment, but making explicit that only the acquisition arches can be moved through during the acquisition phase, and vice versa during the generalization phase. Finally, our sample consisted of only healthy participants, which limits the generalizability of the results to chronic pain populations. Specifically, exploratory behavior is to be expected of healthy individuals, whereas rigid behavior patterns (e.g. persistent avoidance) may be more characteristic of chronic pain patients. Indeed, cognitive and mental inflexibility has been observed in chronic pain patients both retrospectively (Karp et al., 2006; Moriarty et al., 2017), and prospectively (preceding surgery) (Attal et al., 2014). Therefore, a replication of the current study in a sample of chronic pain patients is required to further validate the paradigm and present results.

Despite these limitations, some strengths also deserve to be mentioned. First, the current data provide further support for the experimental acquisition of operant pain-related avoidance behavior in healthy participants. Second, the robotic arm-reaching paradigm offers increased ecological validity for the investigation of avoidance behavior in comparison to traditional avoidance paradigms, because it enables participants to acquire a costly avoidance response instead of simply performing an arbitrary, low-cost avoidance response, instructed by the experimenter. Exploratory analyses of avoidance as trajectory choice behavior corroborated our findings of avoidance behavior as a continuous measure, further adding to the validity of the paradigm. Furthermore, traditional avoidance paradigms in the anxiety literature usually only measure adaptive avoidance, given that the avoidance-response, such as a button press, effectively cancels the aversive stimulus. In contrast, the current paradigm provides a means to investigate maladaptive avoidance, because performing G3 requires more effort than was previously needed to completely avoid pain, thus representing overgeneralization. To our best knowledge, the current study is the first to investigate avoidance generalization using such a paradigm, and thus offers novel preliminary data on the mechanisms possibly underlying avoidance generalization in healthy humans.

In conclusion, the present study demonstrates that fear and pain-expectancies can generalize even in the absence of overt avoidance behavior. These findings add to a growing literature suggesting that pain-related avoidance behavior and pain-related fear may not always share a direct relationship. Instead, at least in healthy participants, this relationship can be affected by such factors as the effort required to perform an avoidance response; when avoidance behavior is effortful, healthy people may be more likely to explore other behavioral options, especially so when the effectiveness of avoidance is not certain. Given the crucial role avoidance behavior plays in disability, the generalization of pain-related avoidance remains and interesting topic of investigation, and potential pathway into the development and maintenance of chronic pain.

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CHAPTER 3
INVESTIGATING THE BOUNDARY CONDITIONS OF COSTLY PAIN-RELATED AVOIDANCE GENERALIZATION

Abstract

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

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Introduction

Avoidance of objectively safe movements and activities is central to chronic pain disability (Vlaeyen & Linton, 2000), which often profits from psychological treatments, such as Cognitive Behavioral Therapy (Morley et al., 1999), rather than purely biomedical ones (Gatchel & Okifuji, 2006; Gatchel et al., 2007a). Avoidance of pain-associated movements/activities after healing prevents disconfirmation of threat, leading to a self-sustaining cycle of fear and avoidance (Vlaeyen & Linton, 2000). Furthermore, avoidance often spreads to movements resembling the original pain-associated movement, that were never paired with pain themselves (avoidance *generalization*) (Dymond et al., 2015). Generalization is adaptive, allowing extrapolation of once-learned protective responses to similar, potentially harmful situations. Yet, generalization of avoidance to safe movements (*excessive generalization*) bears the risk of disproportionate activity-withdrawal. Given its self-reinforcing nature, avoidance may lead to a negative cycle of physical disengagement, culminating into functional disability.

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

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

We recently reported such dissociation between pain-related fear and costly avoidance (Glogan, Gatzounis, Meulders, et al., 2020). Using a pain-related avoidance-conditioning paradigm, healthy participants learned to avoid pain at the cost of performing increasingly effortful arm-movements (acquisition trajectories). During a subsequent generalization test, three novel, similar movements (generalization trajectories) were tested in the absence of the acquisition trajectories and pain. Pain-expectancy and pain-related fear generalized to the novel movements, but avoidance did not (Glogan, Gatzounis, Meulders, et al., 2020), sparking the question under which conditions costly avoidance generalizes.

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

Here we report on two experiments with altered methodologies to, respectively, minimize visual (context) changes (Bouton & Todd, 2014) between acquisition and generalization (Experiment 1), and prevent rapid extinction of avoidance during generalization (Experiment 2) (Craske et al., 2018). We hypothesized that these modifications would result in avoidance and differential self-reports (pain-expectancies and pain-related fear) generalizing from the acquisition trajectories to the novel, similar generalization trajectories.

General methods and materials

Apparatus and stimulus material

HapticMaster. The HapticMaster (HM; Motekforce Link, Amsterdam, the Netherlands) is a 3-degrees of freedom, admittance-controlled robot, i.e. when operated by an external force, the robot reacts with a corresponding movement. Under operation, the HM registers and records the force, position, velocity, and acceleration exerted onto it. This information can be fed back to other devices, and used for triggering the presentations of stimuli, such as the electrocutaneous

stimuli in the current experiments. Additionally, the HM can be programmed to exert resistive force itself. In the current studies, the available movement range was delineated by a 2-dimensional horizontal movement plane with a depth of 0.36 m and radius of 0.41 m.

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

Pain stimulus. The pain stimulus was a 2 ms square-wave electrocutaneous stimulus, delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, United Kingdom), through two reusable stainless steel disk electrodes (8mm diameter with 30mm spacing; Digitimer, Welwyn Garden City, United Kingdom) filled with K-Y gel (Reckitt Benckiser, Slough, United Kingdom). Intensity of the pain stimulus was individually calibrated: participants were administered a series of electrical stimuli of increasing intensity, according to a standard protocol (e.g.(Meulders et al., 2011)). Participants were asked to rate each stimulus on a numerical rating scale ranging from 0-10, where 0 was labelled as "*I feel nothing*"; 1 as "*I feel something, but this is not unpleasant; it is only a sensation*", 2 as "*the stimulus is not yet painful, but is beginning to be unpleasant*"; and 10 as "*this is the worst pain I can imagine*". Participants were asked to select a stimulus they would describe as "*significantly painful and demanding some effort to tolerate*", corresponding to a 7-8 on the numerical rating scale.

The basic paradigm: Robotic arm-reaching task

Both experiments used variations of the same basic paradigm as Glogan et al. (2020; **Study 1** in this dissertation). On each trial, participants were required to move from a start location to a target location by operating the HM with their right (dominant) hand (see Fig. 3.1, Panel A). Participants' movements were visualized on the LCD screen by a green ball, allowing them to track their movements in real-time (see Fig. 3.1, Panel B). The start and target locations were situated at the lower and upper left corners of the movement plane, respectively. The target location was visualized as a green arch, through which the green ball had to be moved. Participants could reach the target via three different movement trajectories (T1-3) represented on screen as three arches situated midway through the movement plane. The trajectory arches were separated by spaces

where the generalization trajectory arches (G1-3) would appear during the generalization phase (see Fig. 3.1, Panels B and C: Experiment 2). On each trial, participants freely chose one of the three available movement trajectories to reach the target location.

The HM was programmed such that there was a linear relationship between lateral displacement (deviation) and resistive force (resistance). This meant that, when the shortest trajectory (T1) was chosen, participants needed to exert minimal effort regarding deviation and force. When the middle trajectory (T2) was chosen, moderate effort was needed, and when the target was reached via the longest trajectory (T3), the most effort was needed (see Fig. 3.1, Panel B).

The experiment was preceded by a *practice phase*, during which participants performed the task and familiarized themselves with self-reports. During this phase no pain was delivered. During the *acquisition phase*, participants in the *Experimental Group*, were able to avoid the pain stimulus by exerting more effort, that is, T1 was always paired with pain (T1 = 100% punishment/no deviation or resistance), but by choosing one of the alternative, more effortful trajectories, participants were able to avoid the pain stimulus (T2 = 50% punishment/moderate deviation and resistance; T3 = 0% punishment/largest deviation and most resistance). In this way, costly avoidance was modeled (i.e. avoidance at the cost of effort). Note that, conceptualizing these responses as avoidance means that, by choosing T3, participants in the Experimental Group could avoid pain 100% of the time, by choosing T2 50% of the time, and never, by choosing T1 (i.e. negative reinforcement; Skinner, 1953).

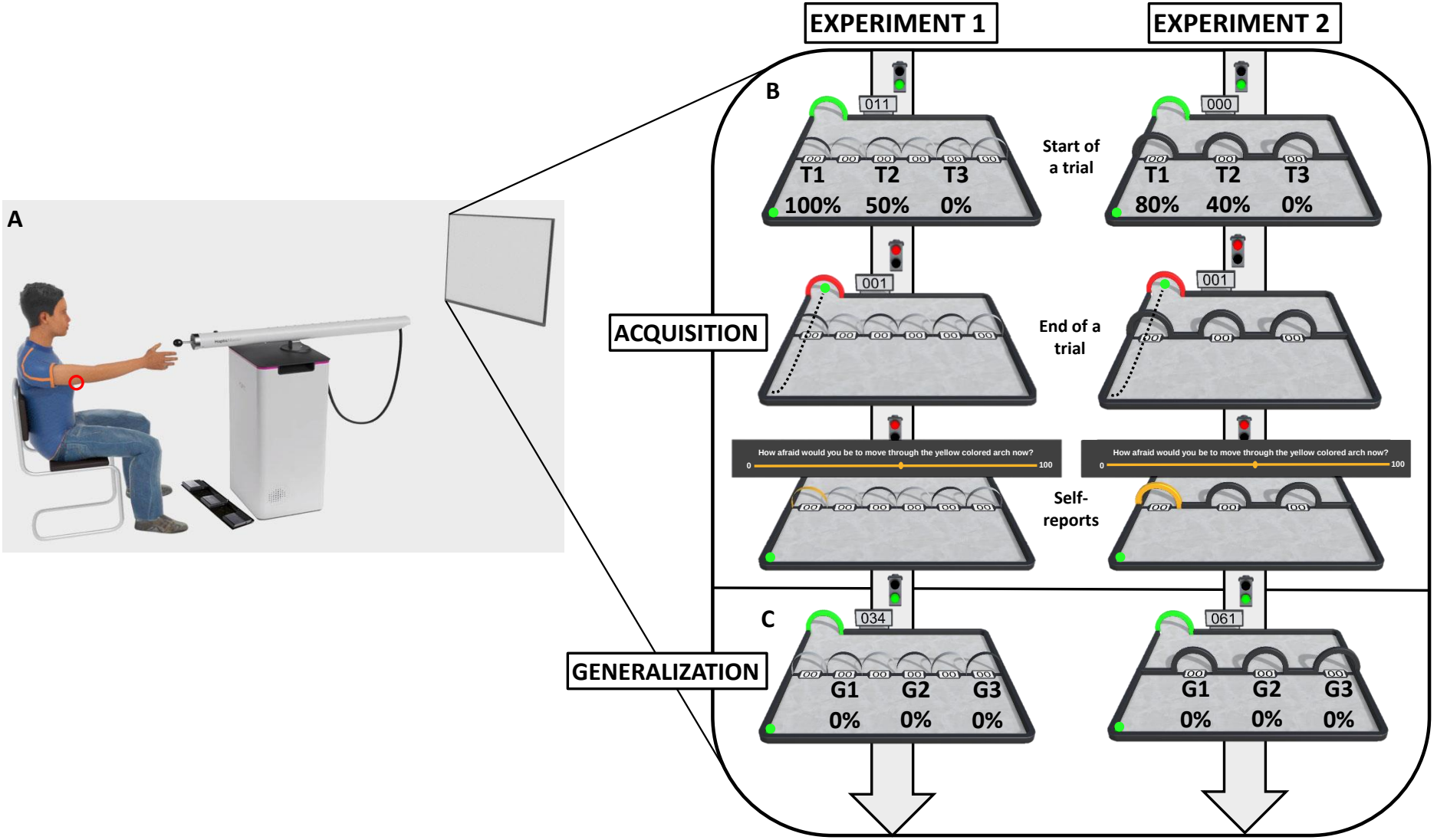
A
EXPERIMENT 1
EXPERIMENT 2
B
011
000
T1
T2
T3
100%
50%
0%
80%
40%
0%
Start of a trial
ACQUISITION
001
001
End of a trial
How afraid would you be to move through the yellow colored arch now?
0
100
Self-reports
C
034
061
GENERALIZATION
G1
G2
G3
0%
0%
0%

Figure 3.1. The experimental setup and schematic overview of the experimental tasks during the acquisition and generalization phases. **Panel A:** The participant is seated in front of the LCD screen, at reaching distance from the sensor of the robotic arm. The electrodes for delivering electrical stimuli, are placed on the triceps tendon of the right arm (red circle), and the triple foot switch is used to give pain-related fear and pain-expectancy ratings. **Panels B and C**: the acquisition (B) and generalization (C) phases of Experiment 1 and Experiment 2. T1-3 and G1-3 refer to acquisition and generalization movement trajectories, respectively. Percentages refer to respective punishment rates in each experiment. Note that, signs for movement trajectories and punishment rates were not part of the visual representations of the experimental tasks. Also note that, in Experiment 1, T1-3 were black during the acquisition phase, and G1-3 during generalization, whereas in **Study 1**, and Experiment 2, only trajectory arches T1-3 were visible during the acquisition phase, and conversely, only G1-3 during the generalization phase. **Start of a trial*:*** The target arch and traffic light turn green together with the auditory start tone. The green ball is situated in the lower left corner. *Acquisition in Experiment 1*: If the green ball was moved through T1, the pain stimulus was always presented. If it passes through T2, the pain stimulus was presented 50% of the time. T3 was always safe. *Acquisition in Experiment 2:* If the green ball was moved through T1, the pain stimulus was presented 80% of the time. If it passed through T2, the pain stimulus was presented 40% of the time. T3 was always safe. There were no such contingencies in the Yoked Group. **End of a trial*:*** The green ball passes through the target arch. The target arch and traffic light turn red, and the auditory stop tone is played. **Self-reports*:*** On some trials, a rating scale and question (pain-expectancy/pain-related fear) appear on the screen. After both ratings have been given for all trajectories (T1-3 during acquisition, G1-3 during generalization), the HM automatically returns to its starting position, remains fixed for 3s, after which the start signals are presented again, and the next trial starts. The trial structure during the generalization phase was the same as during acquisition. This figure is adapted with permission from Glogan, Gatzounis, Vandael, et al. (2020).

Each participant in the *Yoked Group* (Davis & Bitterman, 1971) was matched to a participant in the Experimental Group, and thus received pain on the same trials as their Experimental Group counterpart, irrespective of their chosen movement trajectories. In yoked control procedures, each participant in the yoked (control) group is matched to a participant in the experimental group, such that the control participant receives the same schedule of punishment/reinforcement as their corresponding experimental group participant, irrespective of their own behavior (Davis & Bitterman, 1971). Thus, the experimental movement-pain contingencies of the current studies did not apply to the Yoked Group, and therefore no avoidance learning was expected to occur in this group. However, the yoked procedure controls for the number of electrical stimuli received in each group.

The *generalization phase* was similar to the acquisition phase, except that now three novel generalization trajectories (G1-3; Fig 3.1, Panel C: Experiment 2), were presented. None of the generalization trajectories were paired with pain. Furthermore, to prevent extinction, this phase was interspersed by short *reminder-of-acquisition* blocks, during which the original acquisition trajectories (T1-3) and their corresponding outcomes were once again presented.

Primary outcome measures

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

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

Secondary outcome measures

Exit questionnaire and psychological trait questionnaires. Immediately after completing the robotic arm-reaching task, participants completed an exit questionnaire as a manipulation check, and a series of questionnaires for meta-analytical reasons, and to map potential group differences in psychological trait variables.

Data analysis overview

The hypotheses and analysis plans of Experiment 1 (https://osf.io/jpu42/?view_only=ff15ab4ac7e94b64a880be888bf73fe9) and Experiment 2 (https://osf.io/yvx6c/?view_only=5a7bc4b1d5374efba71f90f29bb09f20) were pre-registered on Open Science Framework (OSF). There were slight differences in the pre-registered analysis plans of both studies, but for the sake of consistency and comparability, the analyses were run based on the pre-registration with more stringent corrections. We will explicitly report these deviations below. Independent samples *t*-tests between groups were performed on sample characteristics data (age, selected intensity of the pain stimulus (in mA), and self-reported pain intensity during calibration. Data from the acquisition, and reminder-of-acquisition phases were analyzed as manipulation checks (see Appendix B for the full descriptions and results of these analyses).

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

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

The α level was set at .05. For RM ANOVAs, Greenhouse-Geisser corrections were applied to correct for sphericity violations. Degrees of freedom, and *p*-values are reported. Holm-Bonferroni corrected *p*-values are reported for significant planned comparisons. The indication of effect size η_p^2 is reported for significant ANOVA effects, and Cohen's *d* for significant planned comparisons. Data-analyses were crosschecked by EG and KV using RStudio (RStudio Inc. Boston, MA, USA; Package "afex" (Singmann et al., 2021)), and SPSS 25.0 (IBM, Armonk, NY, USA), yielding the same results.

Experiment 1

Instrumental responses may become directly associated with the learning context (Rosas et al., 2013), leading to diminished responding when the context is changed (Bouton et al., 2014). How generalization was operationalized (absence of T1-3 and appearance of G1-3) in Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020) may have been experienced by participants as a context-switch (Bouton & Todd, 2014), stimulating exploration of the novel trajectories similar to the previously pain-associated ones (G1 and G2), resulting in participants quickly learning that these novel generalization movements were not paired with the pain stimulus. Therefore, the goal of Experiment 1 was to reduce visual context changes by presenting all trajectory arches simultaneously (Fig. 3.1: Panel B, Experiment 1), in accordance with previous studies of pain-related *fear* generalization (Meulders et al., 2013).

Methods

Thus, all six trajectory arches were visible throughout Experiment 1, but only T1-3 were available during the acquisition phase and only G1-3 during the generalization phase. When trajectories were available, their corresponding arches were colored black, and when they were unavailable, their arches were colored grey. Therefore the *acquisition phase* was similar to that of Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020), (contingencies: T1 = 100% punishment, T2 = 50% punishment, T3 = 0% punishment) except that all six movement trajectories were presented simultaneously. The acquisition phase consisted of two blocks of 12 trials. The *generalization phase* followed, and was similar to, the acquisition phase, except that only G1-3 were now available and no pain was presented. This phase consisted of three blocks of 12 trials. The three generalization blocks were interspersed by the brief *reminder-of-acquisition* blocks, comprising five trials each. During the acquisition and generalization phases, self-reports of pain-expectancy and pain-related fear were collected three times for each trajectory during each block on fixed, predefined trials, and once during the shorter reminder-of-acquisition blocks.

Participants

Sixty-five pain-free volunteers participated in this study. One participant was excluded prior to data analysis due to technical difficulties during data collection, amounting to 64 participants being included in the analyses (52 female, $M \pm SD$ (range) age = 22 ± 4 years, (18-37)). The sample size was based on the same a priori power calculation as that of Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020) (using G*Power; $\alpha = .05$, $d = .80$, power = .80) for an independent *t*-test (two-tailed), which yielded a sample size of 52. A large effect size was chosen based on the

acquisition effect found in a previous study (Meulders et al., 2016) when comparing the Experimental and Yoked groups at the end of acquisition. The sample size was then increased with roughly 20% because a reduced effect size was anticipated for generalization, accumulating to 64 participants.

Participants were assigned either to the Experimental or Yoked Groups based on an alternating schedule depending on the order in which they arrived at the laboratory, and were naïve to this allocation. The reason for using an alternating schedule was that the sequence of electrical stimuli received by each Experimental Group participant (based on their movement trajectory choices), was saved on the computer, and administered to their corresponding Yoked Group participant. Participants were recruited through the research participation system of Maastricht University (Sona; Sona Systems, Nijmegen, The Netherlands), advertisements distributed around the university campus, and through social media.

Exclusion criteria comprised chronic pain; analphabetism or diagnosed dyslexia; pregnancy; left-handedness; current/history of cardiovascular disease; chronic or acute respiratory disease (e.g., asthma, bronchitis); neurological disease (e.g., epilepsy); current/history of psychiatric disorder (e.g., clinical depression, panic/anxiety disorder); uncorrected problems with hearing or vision; pain in the dominant hand, wrist, elbow or shoulder that may hinder performing the reaching task; presence of implanted electronic medical devices (e.g., cardiac pacemaker); and presence of any other severe medical conditions. All participants provided informed consent and completed an exclusion criteria checklist. Participants were informed that they could freely terminate participation at any time without any negative consequences, and received either 1.5 course credit, or €12.50 in gift vouchers as compensation. The study was approved by the Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration number: 185_09_11_2017_S5).

Results

Sample characteristics, pain stimulus, and baseline group differences

There were no differences between the Experimental and Yoked Groups in age, intensity of the pain stimulus (in mA) chosen during calibration, or self-reported intensity of the pain stimulus (see Table 3.1). Furthermore, no differences arose in the items of the exit questionnaire, nor in psychological trait variables (all p-values > .05).

Table 3.1. Sample characteristics of Experiments 1 (Experimental and Yoked Groups n = 32) and 2 (Experimental and Yoked Groups n = 35).

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

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

Manipulation checks

Acquisition: pain-expectancy, pain-related fear, and avoidance behavior. Participants in the Experimental Group learned to expect (Fig. 3.2: Panel A) the pain stimulus more during, and to fear (Fig. 3.3: Panel A), the pain-associated movements (T1-2) compared to the safe movement (T3). Furthermore, participants in the Experimental Group showed significantly larger deviations than the Yoked Group during the acquisition phase, demonstrating successful avoidance learning (Fig. 3.4: Panel A). For the complete results, see Appendix B.

Reminder-of-acquisition: pain-expectancy, pain-related fear, and avoidance behavior. During the reminder-of-acquisition blocks, the data pattern of all measures reflected the acquisition phase, confirming that the test of generalization (under extinction) did not affect the acquired differential pain-expectancy and pain-related fear ratings for the acquisition trajectories, nor did it affect previously acquired avoidance behavior.

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

A 2 x 3 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) x (Trajectory: G1-3) on the mean *pain-expectancy ratings* during generalization revealed no 3-way interaction, $F(3.94, 216.60) = .69$, $p = .580$, but a significant Group x Trajectory interaction, $F(1.61, 100.11) = 8.75$, $p < .001$, $\eta_p^2 = .12$, suggesting that groups showed distinct patterns of pain-expectancies for the different trajectories during the generalization phase. During the first generalization block (GEN1), the Experimental Group expected the pain stimulus to occur more during G1 and G2, compared to G3 (G1 *vs.* G3: $t(62) = 3.14$, $p = .005$, $d = .59$; G2 *vs.* G3: $t(62) = 3.61$, $p = .002$, $d = .53$). In contrast to T1 and T2 during the acquisition phase, G1 did not evoke higher pain-expectancies than G2, $t(62) = .44$, $p = .664$ (Fig. 3.2: Panel A). Thus, pain-expectancies generalized towards the trajectories resembling the previously pain-associated ones (G1-2), whereas G3 continued to be appraised as comparatively safe in the Experimental Group.

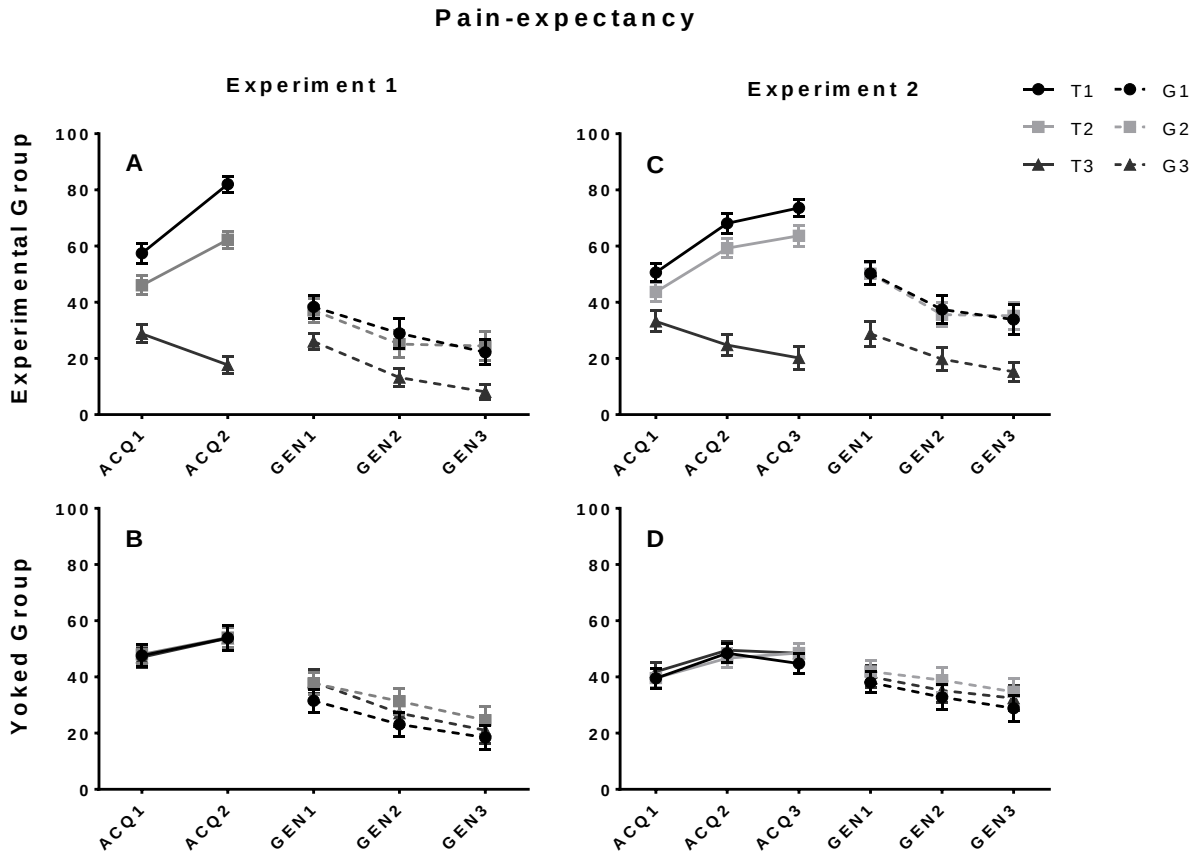

Figure 3.2. Mean pain-expectancy ratings towards the acquisition trajectories (T1-3) and generalization trajectories (G1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiment 1 (panels A and B) and Experiment 2 (panels C and D), during the acquisition blocks (Experiment 1: ACQ1-2, Experiment 2: ACQ1-3), and generalization blocks (GEN1-3). Error bars represent standard deviations (SD).

A similar RM ANOVA on the mean *fear ratings* during generalization also showed no 3-way interaction, $F(3.30, 204.62) = .67$, $p = .580$, but revealed a significant Group x Trajectory interaction, $F(1.43, 88.52) = 5.18$, $p = .010$, $\eta_p^2 = .08$. Unexpectedly, planned comparisons revealed that neither G1, $t(62) = 2.33$, $p = .069$ nor G2, $t(62) = 2.22$, $p = .060$ was feared more than G3 during GEN1, although the difference between G1 and G3 was significant prior to Holm-Bonferroni correction, $p = .023$. However, following visual inspection of the data, which suggested that the expected differences appeared later in the generalization phase, and because the Group x Trajectory interaction was not modulated by Block, we ran the same comparisons for the subsequent generalization blocks, although these were not pre-registered. During these blocks, G1 and G2 were feared more than G3 (see Appendix B for the complete results of pain-related fear

reports during the generalization phases) (Fig. 3.3: Panel A). Thus, fear did not generalize in the hypothesized manner, although the effect emerged in the later blocks.

A 2 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) on mean *maximal deviation* data during generalization yielded no significant effects (Group, $F(1, 62) = .52$, $p = .47$; Block, $F(1.56, 96.63) = 1.88$, $p = .17$; Group x Block, $F(1.56, 96.63) = .08$, $p = .88$). Thus, no generalization of avoidance behavior was observed in Experiment 1 (Fig. 3.4: Panel A).

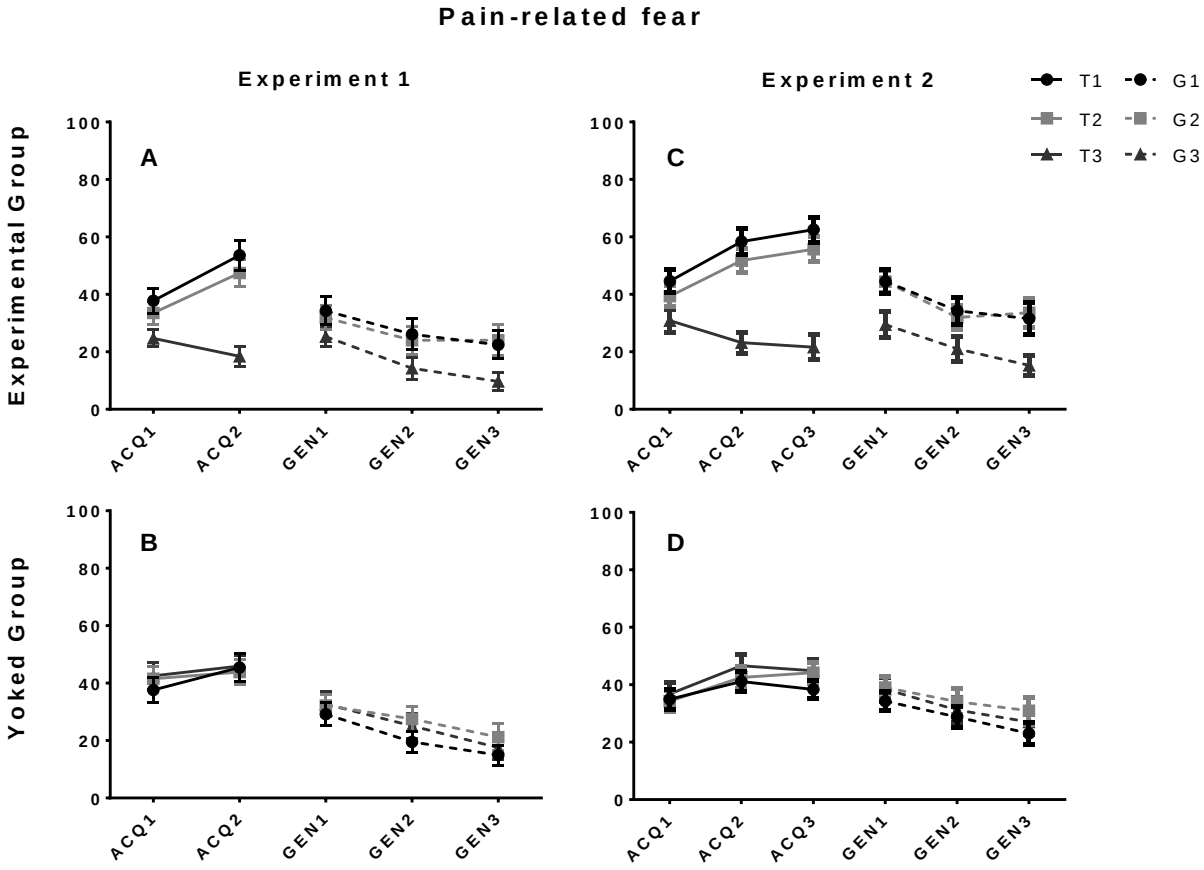

Figure 3.3. Mean pain-related fear ratings towards the acquisition trajectories (T1-3) and generalization trajectories (G1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiment 1 (panels A and B) and Experiment 2 (panels C and D), during the acquisition blocks (Experiment 1: ACQ1-2, Experiment 2: ACQ1-3), and generalization blocks (GEN1-3). Error bars represent SDs.

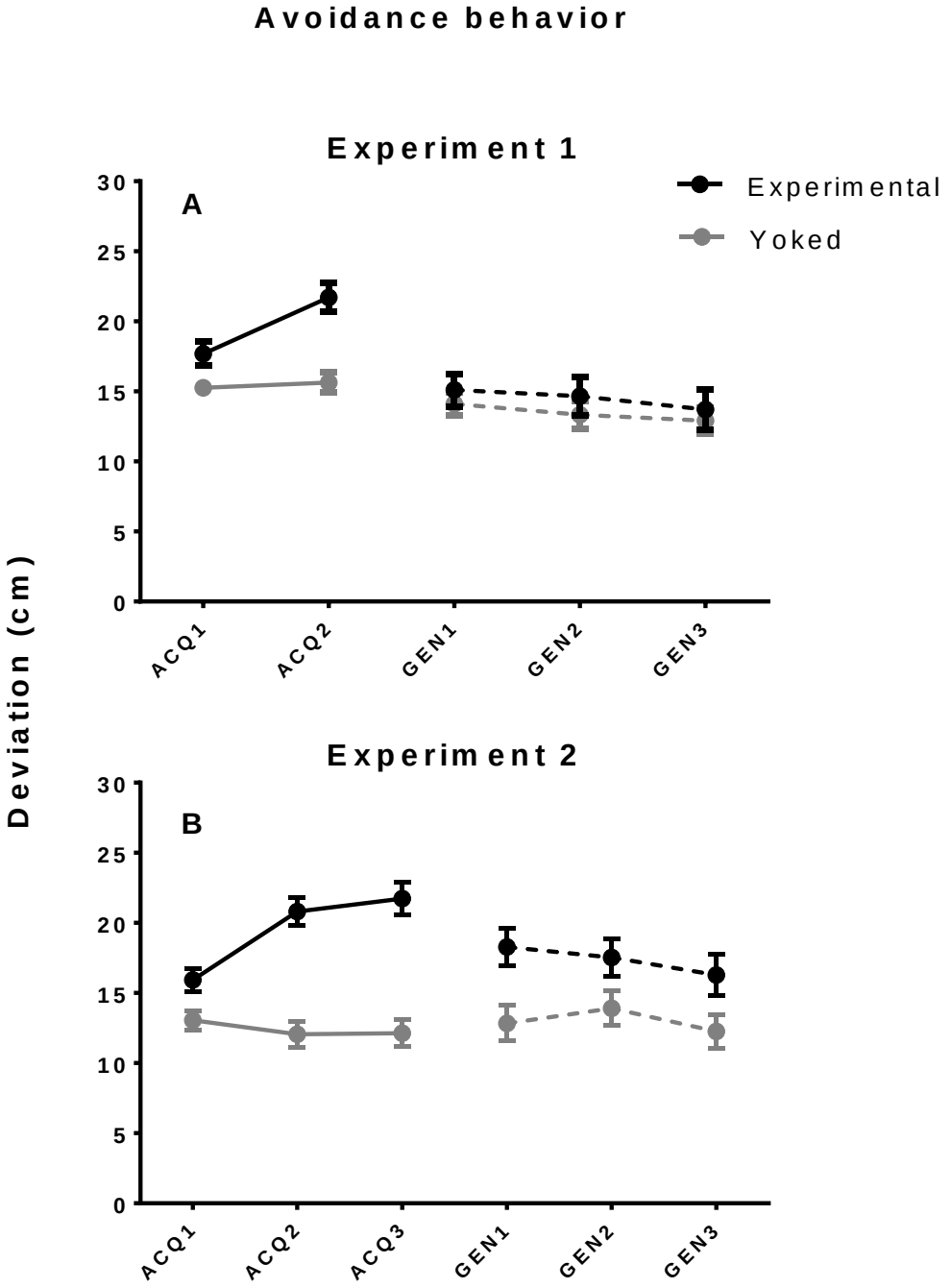

Figure 3.4. Mean maximal deviation (in cm) from the shortest trajectory, from the starting position to the target during the acquisition blocks (Experiment 1: ACQ1-2, Experiment 2: ACQ1-3), and generalization blocks (GEN1-3), in the Experimental and Yoked Groups of Experiments 1 (panel A) and 2 (panel B). Error bars represent SDs. Note – To increase comparability between phases, deviation data from the generalization phase have been linearly transformed to share the same co-ordinates as the acquisition data.

Experiment 2

The 100% punishment rate for T1 in Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020) may have resulted in high expectations of punishment also for G1. Thus, the absence of pain when exploring G1 at the beginning of generalization would have been surprising, leading to rapid disconfirmation of acquired threat beliefs (extinction) (Craske et al., 2018). In Experiment 2, we therefore aimed to reduce or delay rapid extinction by decreasing the punishment rates associated with the acquisition trajectories, and to thus increase the uncertainty associated with the painful movements (T1-2), and their generalization counterparts (G1-2).

Methods

The current paradigm was similar to that of Experiment 1, except that only available trajectory arches were visible during the given experimental phase (T1-3 during acquisition, G1-3 during generalization; as in Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020)). Furthermore, T1 was now paired with an 80% instead of 100% punishment rate, and T2 with a 40% instead of 50%, punishment rate (Fig. 3.1: Panel B, Experiment 2). T3 remained 0% punished. The acquisition and generalization phases both consisted of three blocks of 12 trials, and the generalization blocks were again interspersed by reminder-of-acquisition blocks (5 trials each). Self-reports were collected in a similar manner to Experiment 1.

Participants

Seventy-eight pain-free volunteers participated in this study. Eight participants were excluded prior to data analysis due to technical difficulties during data collection. Thus, 70 participants were included in the analyses (48 female, $M \pm SD$ (range) age = 22 $\pm$ 3 years (18-31)). The sample size was based on the same a priori power calculation as those of Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020) and Experiment 1 (N = 64). However, given that Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020) showed no effect of avoidance generalization, and because we reduced punishment rates in the current study (possibly resulting in more variation between participants (Lissek et al., 2006)), we increased the sample size for detecting a medium-to-large effect size. Participants were randomly assigned either to the Experimental or Yoked groups, based on a randomization schedule created in MATLAB, with the rule that the first participant must be assigned to the Experimental Group. Participants were naïve to this allocation. Exclusion criteria were the same as in Experiment 1. The study was approved by the Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration number: 185_09_11_2017_S1_A1).

Results

Sample characteristics, pain stimulus, and baseline group differences

There were no differences between the Experimental and Yoked Groups in age, intensity of the pain stimulus (in mA) chosen during calibration, or self-reported intensity of the pain stimulus (see Table 3.1). There were no differences in psychological trait variables between groups (all *p*-values > .05). However, in the exit-questionnaire, the Yoked Group reported significantly higher desire than the Experimental Group, to avoid the effort related to G3 (the avoidance response in the Experimental Group), $t(68) = 2.89$, $p = .005$.

Manipulation checks

Acquisition: pain-expectancy, pain-related fear, and avoidance behavior. During the acquisition phase, the Experimental Group successfully acquired the movement-pain contingencies, shown by differential pain-expectancy (Fig. 3.2: Panel C) and fear (Fig. 3.3: Panel C) ratings, and successfully learned to avoid the pain stimulus (Fig. 3.4: Panel B). For the complete results, see Appendix B.

Reminder-of-acquisition: pain-expectancy, pain-related fear, and avoidance behavior. Similarly to Experiment 1, the data patterns during the reminder-of-acquisition blocks for all measures reflected the acquisition phase, confirming that the test of generalization (under extinction) did not affect the originally acquired differential pain-expectancy and pain-related fear nor did it affect acquired avoidance behavior.

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

A 2 x 3 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) x (Trajectory: G1-3) of mean *pain-expectancy ratings* during the generalization phase yielded no significant 3-way interaction, $F(3.08, 209.73) = .79$, $p = .50$, but a significant Group x Trajectory interaction, $F(1.55, 105.16) = 7.76$, $p = .002$, $\eta_p^2 = .10$. This suggests that patterns of pain-expectancy for the different trajectories differed between groups. During the first generalization block (GEN1), the Experimental Group expected the pain stimulus more during G1, $t(68) = 4.08$, $p < .0001$, $d = .86$, and G2, $t(68) = 4.75$, $p < .0001$, $d = .87$, compared to G3. In contrast to pain-expectancies toward T1 and T2, however, pain was not expected more during G1 compared to G2, $t(68) = .03$, $p = .978$ (Fig. 3.2: Panel C). Thus, pain-expectancy beliefs generalized to some extent from the acquisition trajectories to the novel generalization trajectories in the Experimental Group.

A similar RM ANOVA of mean *fear ratings* during generalization did not show a significant 3-way interaction, $F(3.17, 215.89) = .74$, $p = .54$, but revealed a Group x Trajectory interaction, $F(1.62, 109.91) = 6.52$, $p = .004$, $\eta_p^2 = .09$, suggesting that fear for the different trajectories differed between groups. The Experimental Group reported significantly higher fear for G1, $t(68) = 3.25$, $p = .004$, $d = .58$, and G2, $t(68) = 3.97$, $p = .001$, $d = .59$, compared to G3. Again, in contrast to fear reported toward T1 and T2 during acquisition, G1 was not feared more than G2, $t(68) = .01$, $p = .991$. Furthermore, to be consistent with Experiment 1 (although not pre-registered), exploratory comparisons of fear ratings towards all generalization trajectories were run on the subsequent generalization blocks, during which the effects from GEN1 persisted (Fig. 3.3: Panel C) (see Appendix B). Together with the pain-expectancy reports, these results indicate that pain-expectancy and pain-related fear generalized to some extent towards the novel trajectories resembling the previously pain-associated ones (G1-2), whereas acquired safety generalized to G3 in the Experimental Group.

A 2 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: GEN1-3) on mean *maximal deviation* during generalization yielded a significant main effect of Group, $F(1, 68) = 7.63$, $p = .007$, $\eta_p^2 = .10$, but not of Block, $F(1.88, 128.06) = 1.92$, $p = .150$, nor was there a significant 2-way interaction, $F(3.08, 209.73) = .79$, $p = .500$. Planned comparisons confirmed that, in line with our hypothesis, the Experimental Group avoided more compared to the Yoked Group during the first generalization block, $t(68) = 2.98$, $p = .004$, $d = .71$, demonstrating generalization of avoidance to the novel trajectories in the Experimental Group (Fig. 3.4: Panel B).

General discussion

The present experiments aimed to investigate the conditions under which costly pain-related avoidance generalizes in healthy participants. We previously observed generalization in self-reports (pain-expectancy and pain-related fear), but not in costly avoidance (Glogan, Gatzounis, Meulders, et al., 2020). Experiment 1 aimed to reduce exploration by decreasing visual contextual changes. Experiment 2 attempted to prevent rapid extinction of avoidance by increasing the uncertainty of punishment.

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

Importantly, where Experiment 1 did not show generalization of avoidance, Experiment 2 did; the Experimental Group deviated more than the Yoked Group during generalization.

The results of Experiment 1 replicate those of Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020), where self-reports generalized, but avoidance did not. This suggests that participants in the Experimental Groups of these studies explored the novel, less-effortful movement trajectories during generalization, despite fear, and despite us minimizing visual changes between phases in Experiment 1. Furthermore, they imply that avoidance rapidly extinguished due to this exploration - effects that were successfully countered in Experiment 2 by increasing the uncertainty associated with the pain-associated acquisition trajectories; participants likely needed more information to disconfirm their previously acquired fear beliefs, resulting in less (rapid) extinction of avoidance.

This aligns with reinforcement learning models, which define exploration as choosing options with uncertain outcomes (e.g. movement possibly followed by pain), with the goal of obtaining future rewards (e.g. needing to exert less effort) (Lee et al., 2011). Furthermore, the more one's expectations are violated (e.g. surprising absence of pain), the more they will learn from exploration (Dayan & Angela, 2003), and the more likely they will be to re-evaluate current behavior (e.g. stop avoiding) (Mehlhorn et al., 2015). On the other hand, if one's expectations are not violated, or they are uncertain from the get-go (e.g. uncertain expectations of pain), less learning, and thus less behavior change will occur (i.e. *exploitation* of a behavior with known outcomes (Mehlhorn et al., 2015); e.g. sustained avoidance) (see also (Rescorla & Wagner, 1972)).

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

In Experiment 2, uncertainty associated with the acquisition movements may have therefore directly *decreased* exploration, rather than simply countering its effects (rapid extinction), motivating participants to behave anxiously (Grillon et al., 2006; Grupe & Nitschke, 2013), leading to less exploration and instead excessive avoidance. In line with this, visualization, and a post-hoc *t*-test on choice behavior, in the current experiments shows that participants in Experiment 2 exhibited less exploration at the beginning of the generalization phase, compared to participants in Experiment 1 (see Appendix B). This indeed suggests that in some participants, uncertainty directly reduced exploration, implying that uncertainty about movements resulting in pain may hinder recovery due to decreased exploration and less disconfirmation of fearful beliefs. In agreement with this, a recent study (Hunt et al., 2019) incorporating a costly avoidance response, showed that both anxiety sensitivity and intolerance of uncertainty increase the synchrony between generalized fear and avoidance in healthy participants. Given that uncertainty is accompanied by uncontrollability (Van den Bergh et al., 2021), future research could investigate ways in which treatments can increase people's experience of control over their pain. In support of this, controllability over pain was recently shown to selectively reduce pain-related suffering, but not pain intensity or pain unpleasantness, in healthy participants (Löffler et al., 2018). This is especially relevant for chronic pain, in which targeting the management and psychosocial concomitants of pain, is often more effective than targeting the pain itself (Gatchel & Okifuji, 2006; Gatchel et al., 2007a).

Importantly, the results of Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020) and Experiment 1 indicate that adding a *cost* to experimental avoidance increases exploration. Previous studies of avoidance generalization in the anxiety domain reported synchronized generalization of self-reported fear and operant low-, or no-cost, avoidance (e.g. (Boyle et al., 2014; Dymond et al., 2012)). This is an important distinction from an ecological validity perspective, since real-life avoidance is often extremely costly (Volders et al., 2015), and people with pain or anxiety often weigh the value of avoidance against that of alternative, competing behaviors (Claes et al., 2014; Van Damme et al., 2012). Thus, people with chronic pain, for example, may go to work, or play with their children, despite fear of pain (Van Damme et al., 2010; Volders et al., 2015). In fact, the presently reported dissociations between self-reports and avoidance align with literature demonstrating attenuated avoidance, but not fear, when alternative goals (e.g., gaining rewards) compete with avoidance of both aversive (Pittig & Dehler, 2019; Pittig et al., 2018) and painful (Claes et al., 2015; Claes et al., 2014; Van Damme et al., 2012) stimuli. These findings highlight the importance of clinical interventions targeting disability by emphasizing the value of pursuing life

goals (e.g. Acceptance and Commitment Therapy (Hughes et al., 2017; Pielech et al., 2017; Vowles et al., 2014)).

It should be noted that, with the robotic arm-reaching paradigm, avoidance was recently found to be modulated by context (Meulders et al., 2020), demonstrating that context-switches, *per se*, do not eliminate avoidance in the paradigm. However, in Meulders et al. (Meulders et al., 2020), the avoidance response itself did not change. Indeed, although some contextual change is inherent to generalization studies, the critical change in the current studies is in fact *response-based*, i.e. generalizing the avoidance response to a similar, yet different response. In response generalization, the contingency (e.g. punishment rate) related to one response, generalizes to other similar responses, increasing or decreasing the recurrence of these similar behaviors(Skinner, 1953). However, there is scarcely any literature investigating avoidance generalization from the perspective of response generalization. Instead, avoidance generalization is often examined using the same avoidance response (often pressing a computer key), to stimuli differing from each other along perceptual (Hunt et al., 2019; Norbury et al., 2018; van Meurs et al., 2014) or semantic (Boyle et al., 2014; Dymond et al., 2012) continua. Since in chronic pain both the feared stimulus and avoidance response often are movements themselves, it is important to investigate avoidance generalization in the pain domain as generalization between responses.

Some limitations should be discussed. First, the aim of showing all movement trajectories simultaneously in Experiment 1 was to decrease context-changes between phases. However, generalization relies on a balance between differentiation and generalization between stimuli (Ghirlanda & Enquist, 2003; Pavlov, 1941). Simultaneously presenting all trajectory arches may have facilitated discrimination between movements, thus reducing the likelihood of generalization. Second, computational models could enable detailed examination of individual response patterns in the present data (Krypotos et al., 2020). However, given the unbalanced designs of Experiments 1 and 2 (different numbers of trials and participants), the fitted models would have been difficult to compare. Third, we speculate that the observed dissociations between fear and avoidance in Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020) and Experiment 1 resulted from avoidance-costs. However, in order to confirm this hypothesis, these experiments should be replicated with no, or decreased costs. Fourth, to better understand the relationship between uncertainty and avoidance generalization, intolerance of uncertainty could be added as a psychological trait measure in future studies (Carleton et al., 2007; Dugas et al., 2004). Furthermore, a mechanism of chronic pain that may contribute to excessive avoidance, is deficient safety learning (heightened fearful reactivity to objectively safe conditions) (Harvie et al., 2017). To directly test whether people with chronic pain show impaired learning in comparison to healthy

people in the current paradigm, avoidance generalization should be compared between people with chronic pain and healthy controls, using objectively predictable punishment (T1 = 100%) during acquisition. Finally, where traditional fear generalization studies only employ two extreme stimuli (CS+ and CS-) during acquisition, between which generalization stimuli (GSs) lie on a perceptual continuum during generalization, we also trained an ambiguous trajectory (T2), lying between the two extreme trajectories (T3 and T1). This was to increase ecological validity, since in real life there is rarely only one painful, and one entirely safe movement. However, this way of operationalizing generalization may limit the comparability of the current studies to previous fear generalization studies.

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

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CHAPTER 4

COMPARING THE GENERALIZATION OF PAIN-RELATED FEAR AND COSTLY PAIN-RELATED AVOIDANCE

Abstract

Pain-related fear and avoidance crucially contribute to pain chronification. People with chronic pain may adopt costly avoidance strategies above and beyond what is necessary, aligning with experimental findings of excessive fear generalization to safe movements in these populations. Furthermore, recent evidence suggests that, when avoidance is costly, it can dissociate from fear. Here, we investigated whether concurrently measured pain-related fear and costly avoidance generalization correspond in one task. We also explored whether healthy participants avoid excessively despite associated costs, and if avoidance would decrease as a function of dissimilarity from a pain-associated movement. In a robotic arm-reaching task, participants could avoid a low-cost, pain-associated movement trajectory (T+), by choosing a high-cost non-painful movement trajectory (T-), at opposite ends of a movement plane. Subsequently, in the absence of pain, we introduced three movement trajectories (G1-3) between T+ and T-, and one movement trajectory on the side of T- opposite to T+ (G4), linearly increasing in costs from T+ to T-. Avoidance was operationalized as the maximal deviation from T+, and trajectory choice. Fear learning was measured using self-reported pain-expectancy, pain-related fear, and startle eyeblink EMG. Where self-reports generalized, both decreasing with increasing distance from T+, avoidance generalized only transiently. Generally, all generalization trajectories were chosen equally, indicating healthy exploration. No such effects emerged in the EMG measures. These results add to a growing body of literature showing that (pain-related) avoidance can be attenuated even when fear is not, calling for a better understanding of the factors motivating, and mitigating, disabling avoidance.

Introduction

Fear-avoidance models posit pain-related fear and -avoidance as crucial contributors to the transition from acute to chronic pain (Crombez et al., 2012; A. Meulders, 2019). In order to *predict* physical harm, individuals learn to fear movements and activities experienced as painful (e.g. Meulders et al., 2011; Meulders & Vlaeyen, 2013), and may subsequently adopt various behaviors, such as avoidance of the feared movements/activities, in an attempt to *control* possible harm to the body (Vlaeyen, 2015). Albeit protective when pain is acute, pain-related fear and avoidance can become debilitating in chronic pain (Crombez et al., 1999; A. Meulders, 2019). Despite its core role in disability, avoidance is understudied compared to fear, given the tacit assumption of fear being a valid proxy of avoidance (Krypotos et al., 2015; A. Meulders, 2019). Yet, avoidance behavior does not occur in a void of competing motivations and goals, but individuals may choose not to avoid, even when they are afraid, particularly when avoidance is costly (Claes et al., 2014; Glogan, Gatzounis, Vandael, et al., 2020). This is highly relevant, since avoidance can become extremely costly in chronic pain (e.g. financial problems from absenteeism (Breivik et al., 2013; Deyo et al., 1991)).

Pain-related fear and -avoidance typically become problematic when excessive (A. Meulders, 2019). For instance, fear can spread from one painful movement to similar movements never paired with pain (*fear generalization*; Dymond et al., 2015). Although generalization is adaptive, sparing organisms the need to always learn anew, unrestricted fear and avoidance generalization may lead to needless distress and excessive activity disengagement (Dymond et al., 2015). Thus, people in pain must establish an intricate balance between safety-seeking and preserving daily functioning. In line with this, fear generalization in healthy people often decreases as a function of dissimilarity from the original painful movement (*generalization gradient*; Lissek et al., 2008), whereas people with chronic pain tend to also generalize fear to movements dissimilar from the painful movement (Meulders et al., 2015), suggesting excessive pain-related fear generalization as a pathogenic marker for chronic pain.

Like fear, avoidance can generalize to a range of movements never paired with pain (*avoidance generalization*; Dymond et al., 2015) (Glogan et al., In press). Problematically, avoidance does not allow for fearful beliefs to be challenged (Krypotos et al., 2015). Thus, any perceived safety can be misattributed to avoidance behavior, making it difficult to evaluate whether avoidance was necessary or not. Since people with chronic pain often cannot avoid pain, they may adopt increasingly costly, yet ineffective, avoidance strategies (e.g. absenteeism), which all pursue the same outcome (e.g. pain/harm reduction). For example, a person who experiences pain when bending down may initially perform this movement with reduced spinal motion, in an attempt to

avoid further damage to the spine (Thomas & France, 2007). However, additional avoidance strategies may subsequently be adopted, such as wearing a lumbar corset, increasing pain medication, and/or spending more time in bed.

This type of avoidance, which goes above and beyond what is necessary, and can become detrimental (e.g. side effects from painkillers), has never been experimentally investigated before. Yet, it bears similarity to a common phenomenon in *fear* generalization, whereby stimuli, which are extreme versions of an original threat-associated stimulus, are feared even more than that stimulus (*peak shift*; Hanson, 1957; Purtle, 1973). In this experiment, we aimed to investigate whether (1) concurrently measured pain-related fear and costly pain-related avoidance generalization correspond in one task, (2) whether avoidance, like fear, would decrease as a function of dissimilarity from an original pain-associated movement, and (3) whether healthy participants would exhibit excessive avoidance (i.e. a peak shift effect), beyond a safe movement, despite associated costs.

Methods and materials

Participants

Sixty-two healthy, pain-free volunteers participated in the current study. Two participants' data were excluded prior to data analysis due to technical difficulties experienced during data collection. Thus, 60 participants were included in the analyses (34 female, $M \pm SD$ (range) age = 24.25 $\pm$ 5 years (18-36)). The sample size was determined by a previous *a priori* power calculation (using G*Power; $\alpha = .05$, $d = .80$, power = .80) for an independent *t*-test (two-tailed), yielding a sample size of 52. The effect size was based on the avoidance acquisition effect found in a previous study (Meulders et al., 2016). The sample size was increased by roughly 20% because a reduced effect size was anticipated for generalization. Participants were randomly assigned to an Experimental or Yoked group, based on a randomization schedule created in MATLAB (MathWorks, Natick, MA, US), with the rule that the first participant must be assigned to the Experimental Group, after which groups are assigned randomly as long as the number of Experimental Group participants exceeds the number of Yoked Group participants. Participants were naïve to this allocation.

Participants were recruited through the research participation system of Maastricht University (Sona; Sona Systems, Nijmegen, The Netherlands), advertisements distributed around the university campus, as well as word of mouth and social media by EG and LP. Exclusion criteria comprised: pregnancy, left-handedness, chronic pain, acute pain in dominant shoulder/arm/elbow/wrist/hand, current/history of cardiovascular disease, current/history of

psychiatric disorder (e.g., clinical depression and panic/anxiety disorder), use of electronic implants (e.g. cardiac pacemaker), uncorrected hearing and/or vision problems, presence of any other serious medical conditions, and having been advised by one's GP to avoid stressful situations.

Participants performed the experiment individually during a single test session. They were informed that they could freely terminate participation at any time without any negative consequences, completed an exclusion criterial checklist, and signed an informed consent from before the protocol was started. Finally, participants received either 1.5 course credit or €12.50 in gift vouchers as compensation. All data were collected in a laboratory at the Faculty of Psychology and Neuroscience of Maastricht University by EG and LP. The Ethics Review Committee Psychology and Neuroscience of Maastricht University approved the study protocol (registration number: 185_09_11_2017_S7_A1).

Apparatus and stimulus material

HapticMaster. The HapticMaster (HM; Motekforce Link, Amsterdam, the Netherlands) is a robotic arm, which allows force-controlled movement within a three-dimensional space. Movements can be programmed to include a location-specific resistance to manipulate physical effort. By recording relative displacement from the starting position, the HM provides an outcome measure that allows quantification of the movement trajectories. For the current study, the HM was programmed to allow movement along a two-dimensional, horizontal plane (depth = 0.36m, radius = 0.41m) with a linear increase in resistance for lateral displacement. In other words, movement along the lateral axis of the horizontal plane required increasing effort towards the right. Displacement from the starting position can also be used to trigger presentations of stimuli, and was used in the current experiment for delivering pain stimuli (see '*2.3. Stimulus materials: Pain stimulus*').

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

Pain stimulus. The pain stimulus was a 2 ms square-wave electrocutaneous stimulus, delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, United Kingdom), through two reusable stainless steel disk electrodes (8mm diameter with 30mm spacing; Digitimer, Welwyn Garden City, United Kingdom) filled with K-Y gel (Reckitt Benckiser, Slough, United Kingdom), to the triceps tendon of the right arm. The intensity of the pain stimulus was individually determined within a standard calibration procedure (e.g. (Meulders et al., 2011)), in which stimuli were administered at intensities increasing in 1, 2, 3, or 4 mA increments, from 1mA to 99 mA (maximum of the constant current stimulator). Participants were asked to rate the intensity of each stimulus on a scale from 0 to 10. Ratings were described as "*I feel nothing*" at a rating of 0, "*I feel something, but this is not unpleasant; it is only a sensation*" at 1, "*the stimulus is not yet painful, but is beginning to be unpleasant*", at 2, "*the stimulus is beginning to be painful*" at 3, ending at "*this is the worst pain I can imagine*" at a rating of 10. Participants were asked to reach a level they would describe as "*significantly painful and demanding some effort to tolerate*" approximating an 8 on the rating scale.

Startle probe. The startle probe was a 50ms, 95dBA burst of white noise with instantaneous rise time, presented binaurally through headphones (MDR-7510; Sony Corp., Tokyo, Japan) (Blumenthal et al., 2005).

Robotic arm-reaching paradigm

We used an adapted version of the robotic arm-reaching paradigm, described elsewhere (Glogan, Gatzounis, Vandael, et al., 2020; Meulders et al., 2016). Participants' main task was to move a "green ball" from a start location to a target location by operating the HM with their right (dominant) hand (Fig. 4.1: panel B). Participants could visually track their movements, represented by the movement of the green ball, on-screen in real-time. The start and target locations were situated at the lower and upper left corners of the movement plane, respectively. The target location was visualized as a green arch, through which the green ball had to be moved.

The experiment started with a *practice phase* (see Fig. 4.1: Panel A for a summary of the design), during which participants were presented with two movement trajectory arches, colored black, situated midway through the movement plane. One of the arches corresponded to the shortest movement to reach the target (T+), and was thus paired with no cost (i.e. deviation or resistance). The other arch (T-) was located at the side of the movement plane opposite to T+, and thus required a longer movement and more effort to overcome the resistance (Fig. 4.1: panel C). During 6 practice trials, participants had the chance to acquaint themselves with the HM and

the task, and to practice providing self-reports using foot pedals (see *Self-reports: pain-expectancy and pain-related fear*). During each of these trials, participants could freely choose between T+ and T-. Trial onset was indicated by auditory and visual start signals (a "start tone", as well as an on-screen traffic light and the target arch turning green). Successful completion of a movement was signaled by auditory and visual stop signals (a "stop tone", and the traffic light and target arch turning red). When stop signals were presented, participants were required to release the HM, which repositioned to its starting position automatically. After returning to the starting position, the HM remained fixed for 3s (inter-trial interval; ITI) before the start of the next trial. During the practice phase, no pain stimuli or startle probes were presented.

The *acquisition phase* was similar to the practice phase, except that pain stimuli were now presented according to the experimental contingencies, at 2/3 of movement completion. Specifically, in the Experimental Group, performing T+ was paired with the pain stimulus with an 80% likelihood, whereas T- was never paired with the pain stimulus. Therefore, this group could learn to avoid the pain stimulus at the cost of performing a longer and more effortful movement. In the Yoked Group, each participant was matched to a specific participant of the Experimental Group, such that they received a pain stimulus on the same trials as their Experimental Group counterpart, irrespective of the movements they chose. Therefore, the movement-pain contingencies of the acquisition phase did not hold in the Yoked Group, and no avoidance learning was expected to occur in this group. However, this procedure controls for the number of pain stimuli received in each group. The acquisition phase comprised two blocks of 12 trials, and self-reports were collected three times per block on fixed, predetermined trials. No startle probes were presented during this phase.

To prevent confounding by comparatively high initial startle responses, the acquisition phase was followed by a *startle habituation phase* during which 10 startle probes were presented consecutively with ITIs ranging between 18-25s (jittered and randomized). During this phase, there were no pain stimuli, and the LCD screen was black.

To assess startle responses towards both acquisition trajectories (T+ and T-), a *startle acquisition test* of 6 trials was included. This phase was similar to the acquisition phase, except that participants were now instructed to perform both acquisition movements 3 times, and the ITI was 10s, to allow for the EMG signal to return to baseline (Dimberg, 1990). The phase was preceded by instructions stating that from now on participants could only move through an arch if it was highlighted in blue (Fig. 4.1: panel D). Movements were instructed in a randomized order, and highlighted at the start of each 10s ITI. The startle probe was presented 500ms before the start signals prompted the participant to initiate the new trial, allowing a 9500-ms anticipation period

between the highlighting of the to-be-performed movement, and the startle probe. Once participants had performed the instructed movement, the HM returned normally to its starting position, after which the new ITI started, and the next movement was immediately signaled. Because participants' movement speeds vary considerably, and since startle EMG is a measure of anticipatory fear (Grillon, 2002; Lang et al., 2000), the startle probe was presented during the ITI, in order to minimize confounding with the pain stimulus.

During the *generalization phase,* four novel movement trajectories were introduced, and presented for the first time as three additional arches placed on-screen between T+ and T- (generalization trajectories G1-3), as well as one arch to the right of T- (G4). All generalization trajectory arches were colored blue to signal their availability. T+ and T- were also still visible but haptically blocked, and colored black to signal their unavailability (Fig. 4.1: panel E). The generalization test comprised 12 trials during which participants could freely choose between G1-4, and self-reports were collected three times on predetermined trials. Note that, since T- was not available during this phase, we could not compare preference of G4 to T- (i.e. avoidance peak shift). Thus, we could only investigate an *area shift* of avoidance, that is, generally increased preference to responses on the side of T-, away from T+ (Honig & Urcuioli, 1981).

To examine generalization in startle responses, the task ended with a *startle generalization test*, comprising 2 blocks of 6 trials. During this phase, all movements were performed once per block in a randomized order. Movements were instructed, and startle probes were presented, in a similar manner as during the startle acquisition test. Furthermore, the acquisition contingencies were again effective during this phase, i.e. T+ was paired with the pain stimulus with a probability of 80% (Fig. 4.1: panel F).

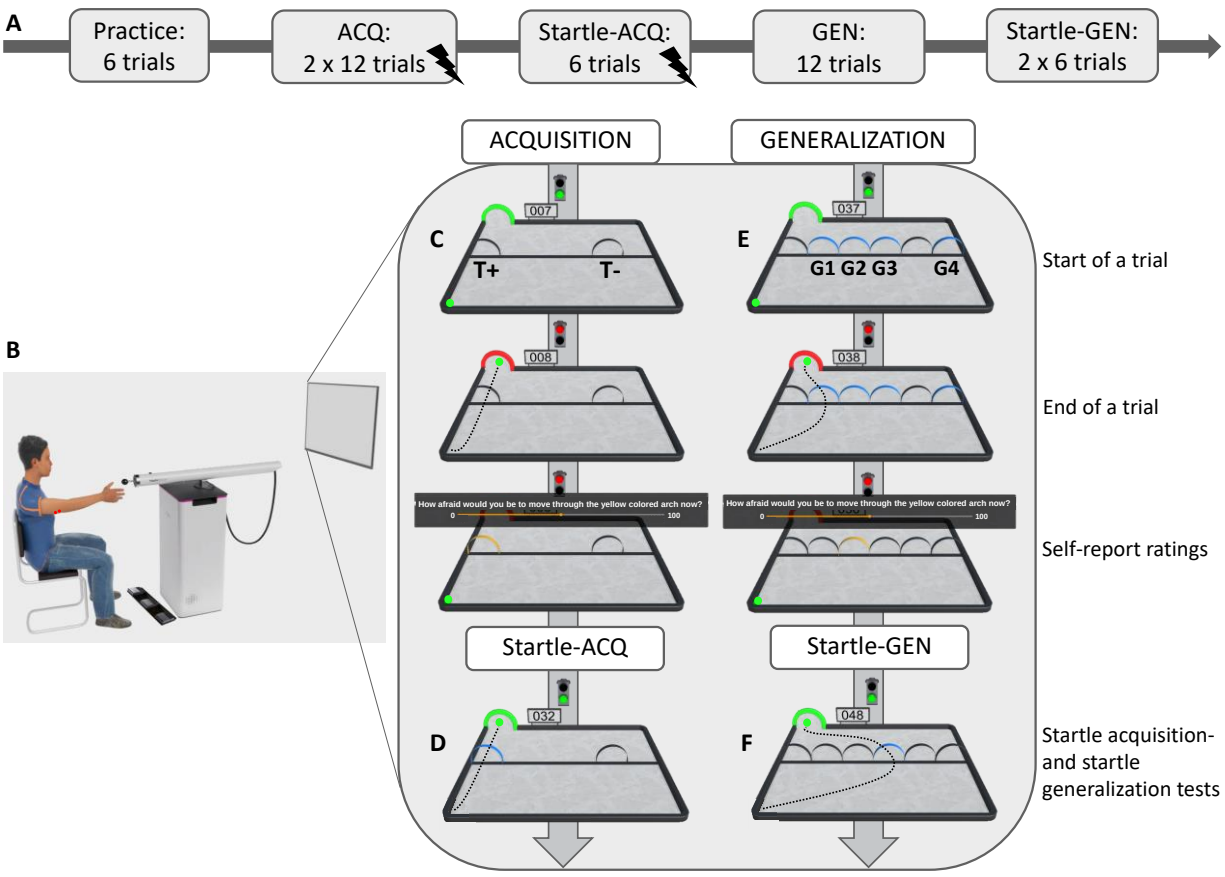


Figure 4.1. The experimental design, the experimental setup, and a schematic overview of the experimental task. Panel A: The design of the experimental task. ACQ – acquisition phase, Startle-ACQ – startle-acquisition test, GEN – generalization phase, Startle-GEN – startle-generalization test. Lightning bolts refer to phases where pain stimuli were presented. **Panel B:** The participant is seated in front of the LCD screen, at reaching distance from the sensor of the HM. The electrodes for delivering pain stimuli are placed on the triceps tendon of the right arm (red dots), and the triple foot switch is used to give pain-related fear and pain-expectancy ratings. **Panel C:** The acquisition phase of the current experiment. **Panel D:** An example trial of the startle-acquisition test, where T+ is being instructed. **Panel E:** The generalization phase of the current experiment. G1-4 were colored blue throughout this phase, and participants could freely choose between them. **Panel F:** An example trial of the startle-generalization test, where G3 is being instructed. **Start of a trial***:* The target arch and traffic light turn green together with the auditory start tone. The green ball is situated in the lower left corner. *Only for Acquisition*: If the ball passes through T+, the pain stimulus is presented 80% of the time. There were no contingencies in the Yoked Group. **End of a trial***:* The green ball passes through the target arch. The target arch and traffic light turn red, and the auditory stop tone is played. **Self-report ratings***:* On some trials, a rating scale and question (pain-expectancy/pain-related fear) appear on the screen. After both ratings have been given for all trajectories (T+ and T- during acquisition and startle-acquisition; T+, T-, and G1-4 during generalization and startle-generalization), the HM automatically returns to its starting position, remains fixed for 3s, after which the start signals are presented again, and the next trial starts. **Startle acquisition- and startle generalization tests:** The trial structure during the startle-acquisition- and startle-

generalization tests was the same as during ACQ and GEN, except that, the ITI was 10s, movements were instructed in a randomized order at the beginning of the ITI, and startle probes were presented 500ms before the start signals were presented. This figure is adapted with permission from (Glogan, Gatzounis, Vandael, et al., 2020).

Primary outcome measures

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

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

Trajectory choice. Frequencies of choices of all movement trajectories were calculated for both groups. This information was automatically logged by the HM.

Startle modulation. The startle response is a reflexive cross-species reaction to startle-evoking stimuli, such as sudden loud noises (often operationalized as acoustic startle probes), and is measured as action potentials from the orbicularis oculi muscle, using electromyographic (EMG) electrodes (Blumenthal et al., 2005; Davis et al., 2010). *Startle modulation*, which refers to potentiation of the startle reflex during states of aversive anticipation, is a widely accepted proxy of conditioned fear (Grillon, 2002; Lang et al., 2000).

Startle responses were measured using three, 3mm Ag/AgCl electrodes (Gereonics Inc., Irvine, CA, USA) filled with microlyte gel. Two of these electrodes were placed under the right eye, and one on the forehead to act as ground (Blumenthal et al., 2005). The EMG signal was digitized at 1000Hz, and digitally filtered offline using BrainVision Analyzer (Brain Products GmbH, Gilching, Germany; 4^{th} order Butterworth filter, rolloff 24 dB/octave; 28-400 Hz passband). A MATLAB script was used to rectify and smooth the signal (moving average 20ms). The baseline score was defined as the mean EMG amplitude between 1 and 20ms after probe onset for the given movement trajectory. The MATLAB script was also used to extract peak EMG

amplitudes, which were defined as the maximum of the response curve within 21-175ms after startle probe onset. Subsequently, EMG data of all participants were visually inspected, resulting in a total of 34 (3.31%) trials (Experimental Group: 25, Yoked Group: 9) being determined non-responses, and thus being excluded from the analyses. Finally, all EMG data were standardized and transformed into *T*-scores.

Data analysis overview

The hypotheses and analysis plan were pre-registered on Open Science Framework (follow this link https://osf.io/cr5b6/?view_only=89d1a9636b624aee8b7ee24fb5bbc610 for pre-registration). We hypothesized (1) that pain-related fear would generalize, indicated by self-reports (pain-related fear, pain-expectancies), and EMG amplitudes linearly decreasing from T+ to G4, and (2) that avoidance behavior would generalize, indicated by larger deviations in the Experimental Group compared to the Yoked Group, during the generalization phase. Furthermore, we aimed to explore whether pain-related fear would exhibit a peak shift, indicated by lower responses for G4 compared to T-, and/or and area shift, indicated by lower responses for G4 compared to G3. To test for acquisition and generalization of pain-related fear and avoidance behavior, we performed a series of repeated measures (RM) analyses of variance (ANOVAs), and follow-up contrasts to examine our *a priori* hypotheses. Furthermore, linear and quadratic trend analyses were conducted over the six movement trajectories to respectively test for the presence of generalization gradients and peak/area shifts in pain-related fear and pain-expectancies. We also ran equivalence tests on mean self-reports in the Yoked Group during the acquisition and generalization phases (see Appendix C for the descriptions and results of these analyses). RM ANOVAs and planned contrasts were performed in RStudio (version 1.4.1106; RStudio Inc., Boston, MA, USA, 2009-2021), using R (version 3.6.2.; The R Foundation for Statistical Computing, 2019), with package afex (version 0.28-1; (Singmann et al., 2021)).

Finally, we also aimed to explore whether avoidance behavior would show a "generalization gradient" and "area shift", that is, trajectory choices decreasing from G4 to G1, and being higher for G4 compared to G3 (i.e. preference of G4), respectively. To investigate this "avoidance generalization gradient", we implemented a proportional odds model on trajectory choice data during the generalization phase (see Appendix C for detailed descriptions of the models used for analysing trajectory choice data). These analyses were pre-registered as exploratory, depending on whether or not the maximal deviation data revealed generalization effects. We ran these analyses using the R package brms (version 2.15.0; (Bürkner, 2017)), which fits Bayesian general linear multivariate multilevel models using the probabilistic programming

language Stan (Stan Development Team, 2021), to estimate random effects proportional odds models. More specifically, the brm() function uses Markov Chain Monte Carlo methods to compute a sample of the posterior distribution of the model parameters. As the posterior sample allows to compute the distribution of any function of the model parameters, it can be used to simulate the distribution of the choice probabilities in each group (Bürkner, 2017). Thus, the odds of the Experimental Group to choose G4 rather than G1-3 (or, G4 or G3 rather than G2 or G1, or, G4 or G3 or G2 rather than G1) compared to the Yoked Group, was calculated as an odds ratio. To test whether participants in the Experimental Group were more likely to choose G4/G3 rather than G2/G1, we tested $H_0 : \beta_G \leq 0$ against $H_0 : \beta_G > 0$, using the "hypothesis" function of the brms package. Since we had clear *a priori* hypotheses, we also performed planned contrasts to examine the median of the posterior odds of Experimental Group participants to choose G4 over G3, G3 over G2, and G2 over G1, which is possible with brms. If the odds equal 1, both trajectories have the same probability of being chosen, and odds greater than 1 indicate that the first trajectory (e.g. G4) is more likely to be chosen than the second trajectory (e.g. G3). To account for the repeated-measures nature of the data, the models included a random intercept for each participant. The precision of results obtained from our proportional odds models were estimated using 90% confidence intervals (CI). A regression coefficient was deemed statistically significant when the specific posterior credible intervals did not cross 0. Similarly, odds can be considered as statistically significant when the specific posterior credible intervals did not cross 1.

Results

Sample characteristics and pain stimulus

We ran paired-samples *t*-tests to check for baseline group differences. There were no differences between the Experimental and Yoked Groups in age, $t(58) = 1.234$, $p = .222$, physical intensity (mA) of the pain stimulus chosen during calibration, $t(58) = .610$, $p = .545$, or self-reported intensity of the pain stimulus, $t(58) = .174$, $p = .862$.

Acquisition: Self-reported pain-expectancy and pain-related fear

We ran a 2 x 2 x 2 RM ANOVA with Group (Experimental, Yoked) as the between-subjects factor, and Block (ACQ1-2) and Trajectory (T+, T-) as the within-subjects factors, on mean pain-expectancies during the acquisition phase. This analysis revealed a significant 3-way interaction, $F(1, 58) = 19.38$, $p < .001$, $\eta_p^2 = .250$, suggesting that pain-expectancies for the trajectories evolved differently in the two groups throughout the acquisition phase. Planned contrasts showed that, in

line with our hypotheses, the Experimental Group reported significantly lower pain-expectancy for T- compared to T+, at the end of the acquisition phase (ACQ2), $t(58) = 10.880$, $p < .0001$, $d = 2.778$. No such differences occurred in the Yoked Group, $t(58) = .473$, $p = .638$ (Fig. 4.2: Panel A).

A similar RM ANOVA on mean pain-related fear ratings also revealed a significant 3-way interaction, $F(1, 58) = 13.64$, $p < .001$, $\eta_p^2 = .190$. Pain-related fear developed in a similar manner as pain-expectancies during the acquisition phase, that is, by the end of the acquisition phase, the Experimental Group reported significantly lower fear for T- compared to T+, $t(58) = 6.980$, $p < .0001$, $d = 1.217$. No such differences occurred in the Yoked Group, $t(58) = .907$, $p = .368$ (Fig. 4.2: Panel B).

Acquisition of avoidance behavior: maximal deviation

A 2 x 2 RM ANOVA on maximal deviation, with Group as the between-subjects factor, and Block as the within-subjects factor, during the acquisition phase, yielded a significant 2-way interaction, $F(1, 58) = 4.85$, $p = .032$, $\eta_p^2 = .077$, suggesting that avoidance behavior developed differently for the two groups during acquisition. As expected, planned contrasts confirmed that participants in the Experimental Group successfully acquired avoidance behavior by the end of the acquisition phase, indicated by larger maximal deviations from the shortest trajectory in this group compared to the Yoked Group, , $t(58) = 4.637$, $p < .0001$, $d = 1.197$ (Fig. 4.3).

Acquisition of startle modulation

EMG data of three participants were excluded or not recorded due to technical difficulties during their test sessions. This resulted in data from 57 participants being included in the EMG data analyses. A 2 x 2 RM ANOVA with Group (Experimental, Yoked) as the between-subjects factor, and Trajectory (T+, T-) as the within-subjects factor, on mean EMG amplitudes during the startle acquisition test, revealed no significant effects (2-way interaction, $F(1, 55) = 0.00$, $p = .981$). Thus, there was no differential learning effect in the startle data.

Generalization of self-reported pain-expectancy and pain-related fear

A 2 x 6 RM ANOVA with Group (Experimental, Yoked) as the between-subjects factor, and Trajectory (T+, G1, G2, G3, T-, G4) as the within-subjects factor, on mean pain-expectancy reports during the generalization phase, showed a significant 2-way interaction, $F(3.11, 180.36) = 22.65$, $p < .001$, $\eta_p^2 = .281$, indicating different patterns of pain-expectancies for the six trajectories between groups. In line with our expectations, linear trend analysis revealed a significant linear

decrease in pain-expectancies, $F(1, 29) = 53.41, p < .0001, \eta_p^2 = .648$, whereby they decreased with increasing distance from T+, in the Experimental Group. Planned contrasts confirmed that, during the generalization phase in the Experimental Group, T+ evoked higher pain-expectancies compared to all of the other movement trajectories, whereas T- evoked lower pain-expectancies than G1-3. G4 did not evoke lower pain-expectancies compared to T- (i.e. no peak shift), but did do so compared to G3 (and all other trajectories), suggesting an area shift in pain-expectancies. In line with this, trend analysis also revealed a significant quadratic trend, $F(1, 29) = 23.77, p < .0001, \eta_p^2 = .450$, in the Experimental Group. However, excluding T+ from the analysis eliminated this effect, $F(1, 29) = .959, p = .336$, suggesting that the quadratic trend was mainly driven by high pain-expectancy reports for T+, rather than low expectancy for G4 (Fig. 4.2: Panel A).

A similar RM ANOVA on mean pain-related fear reports revealed comparable effects to pain-expectancy reports. There was a significant 2-way interaction, $F(3.08, 178.69) = 13.24, p < .001, \eta_p^2 = .186$, and linear decrease in fear from T+ to G4, $F(1, 29) = 32.27, p < .0001, \eta_p^2 = .527$, further supported by planned contrasts, which showed significantly lower fear for all other trajectories compared to T+. All trajectories, except for G4, were feared more than T-. Similarly to pain-expectancies, G4 did not evoke less fear than T-, but did so compared to G3 (and all other trajectories), suggesting an area shift in pain-related fear reports. Again, although trend analyses revealed a significant quadratic trend, $F(1, 29) = 6.69, p = .015, \eta_p^2 = .187$, this effect disappeared when T+ was excluded from the analysis, $F(1, 29) = .153, p = .698$. Together, these results indicate generalization gradients in pain-expectancies and pain-related fear. Although the quadratic trends seemed to be mainly driven by high self-reports for T+, rather than low reports for G4, there was evidence for an area shift, given that G4 evoked lower pain-expectancies and less pain-related fear compared to G3 (Fig. 4.2: Panel B).

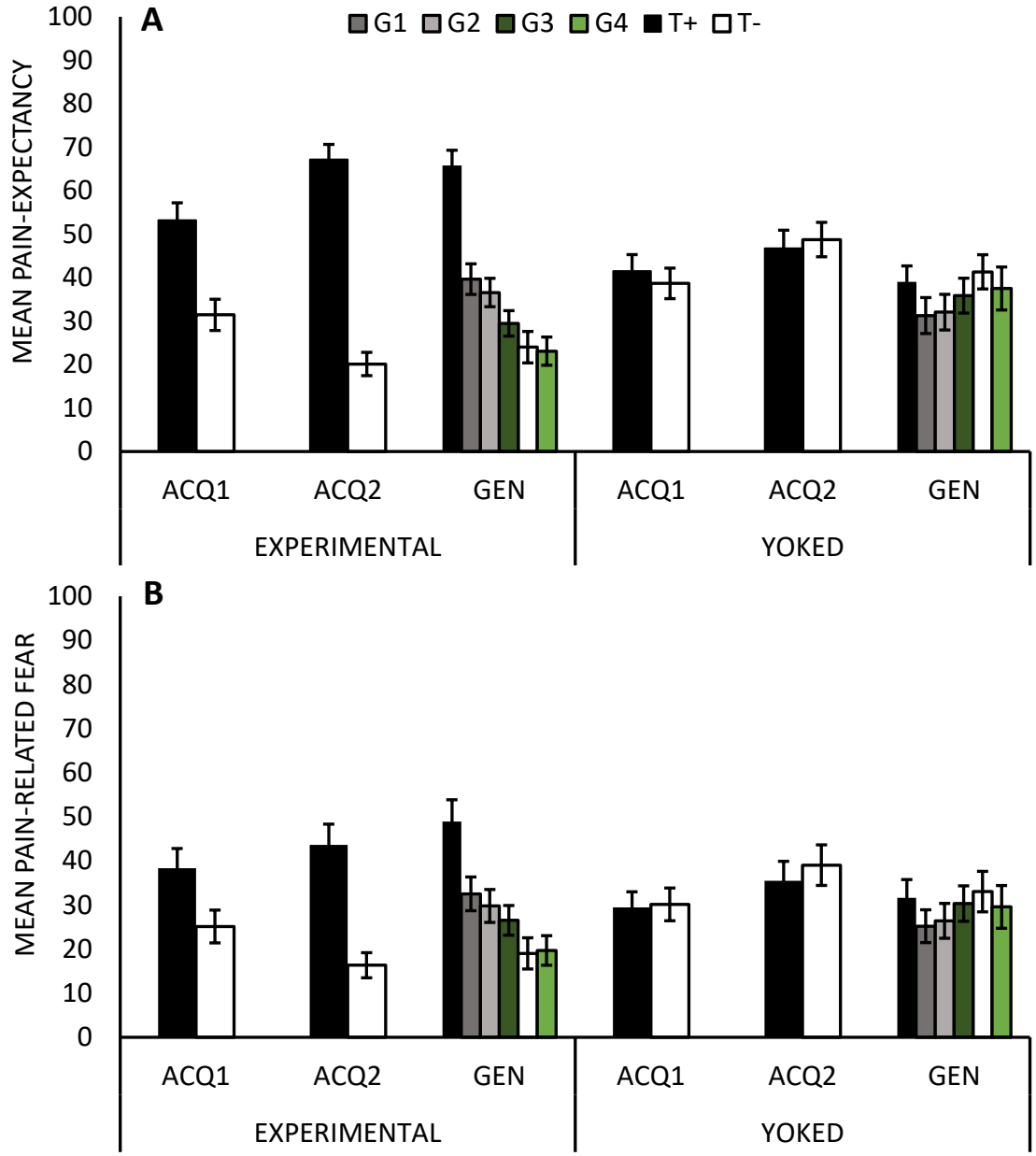


Figure 4.2. Mean pain-expectancy (**Panel A**) and mean pain-related fear (**Panel B**) towards the different trajectories in the Experimental and Yoked Groups during the acquisition (ACQ1-2), and generalization (GEN) phases. Error bars represent standard error of the mean (SEM).

Generalization of avoidance behavior: maximal deviation

In line with our hypotheses, a 2 x 12 RM ANOVA with Group (Experimental, Yoked) as the between-subjects factor, and Trial (T1-12) as the within-subjects factor revealed a significant main effect of Group, $F(1, 58) = 6.80$, $p = .012$, $\eta_p^2 = .105$, indicating overall differences in deviation between groups. Since the Group x Trial interaction was also significant, $F(7.80, 452.53) = 2.04$, $p = .042$, $\eta_p^2 = .034$, suggesting that avoidance behavior developed differently for the two groups with time, we decided to further explore this effect. Exploratory contrasts showed that maximal deviation was significantly higher for the Experimental Group compared to the Yoked Group during the first, $t(58) = 3.27$, $p = .0018$, $d = .845$, and second, $t(58) = 4.31$, $p = .0001$, $d = 1.114$, trials of the generalization phase. However, this difference did not persist, and during the remainder of the generalization trials (apart from trial 5, $t(58) = 2.21$, $p = .031$, $d = .571$), the groups did not differ in their maximal deviation scores (Fig. 4.3).

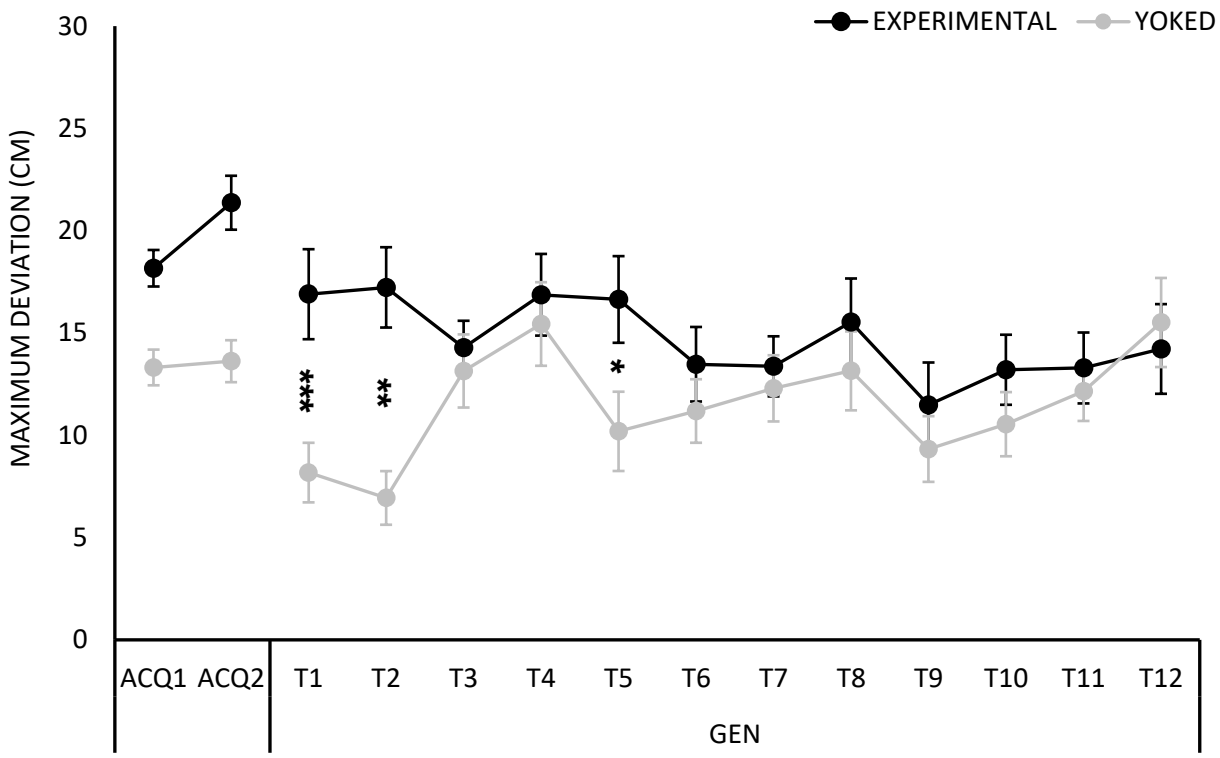


Figure 4.3. Mean maximum deviation from the shortest trajectory from the starting position to the target during the acquisition phase (ACQ1-2), and all trials of the generalization phase (GEN: T1-12), in the Experimental and Yoked Groups. Error bars represent SEM. *<.05, **<.01, ***<.001.

Generalization of startle modulation

Since there were no acquisition effects in the startle data, no generalization effects could be expected, and these data will thus not be further reported.

Avoidance generalization gradient and -area shift: trajectory choice

We estimated a random intercept proportional odds model (Model 1) on trajectory choice data during the generalization phase, with Trajectory Choice (G1-4) as the categorical dependent variable, and Group (Experimental, Yoked) as the predictor. Note that, because T+ and T- were not available during the generalization phase, G4 was compared to the closest generalization trajectory (G3) (i.e. area shift). The Group effect was significant, whereby participants in the Experimental Group were 2.08 times more likely to choose G4 rather than G1-3 (or, G4 or G3 rather than G2 or G1, or, G4 or G3 or G2 rather than G1), compared to participants in the Yoked Group, exp(.73), 90% CI [1.31, 3.31]. The test of whether participants in the Experimental Group were more likely to choose G4/G3 rather than G2/G1 yielded an evidence ratio of 175.99. This indicates that the evidence in favor of the alternative hypothesis was 175.99 times larger than the evidence in favor of the null hypothesis, 90% CI of β_G [.27, 1.20]. Thus, Experimental Group participants overall, were more likely to choose an effortful generalization trajectory (G4 and G3), similar to a previously safe one (T-), compared to Yoked Group participants.

One-sided follow-up contrasts (based on the median of the odds across participants) revealed that participants in the Experimental Group were 1.15 times more likely to choose G1 than G2 during the entire generalization phase, 90% CI [.94, 1.40], 1.01 times more likely to choose G2 compared to G3, 90% CI [.81, 1.24], and 1.11 times more likely to choose G3 than G4, 90% CI [.89, 1.36]. Since odds of 1 indicate that the two options are equally likely to occur, these results suggest that the Experimental Group chose all generalization trajectories relatively equally. Thus, we did not observe the hypothesized "avoidance generalization gradient", nor "area shift", in the Experimental Group. Although not pre-registered, but for the sake of comparison with the Experimental Group, we ran the same analysis on an exploratory basis, on trajectory choice data from the Yoked Group. Yoked Group participants were 1.52 times more likely to choose G1 than G2, 90% CI [1.22, 1.86], 1.26 times more likely to choose G2 rather than G3, 90% CI [1.01, 1.55], and 1.34 times more likely to choose G3 compared to G4, 90% CI [1.08, 1.65]. Thus, the Yoked Group exhibited a gradient based on level of effort associated with the trajectories, that is, they favored the less effortful generalization trajectories over the more effortful ones (Fig. 4.4).

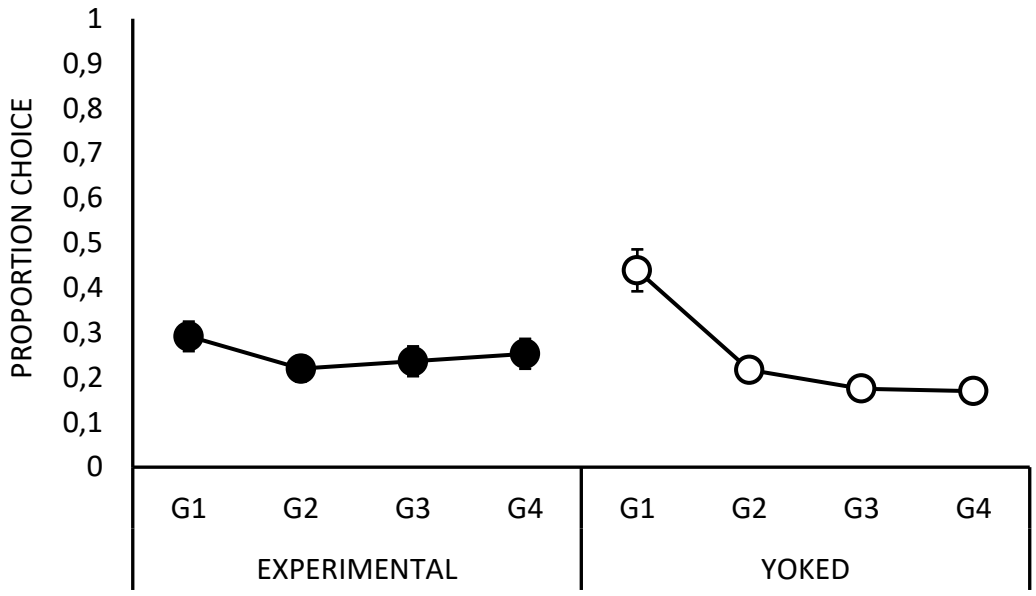
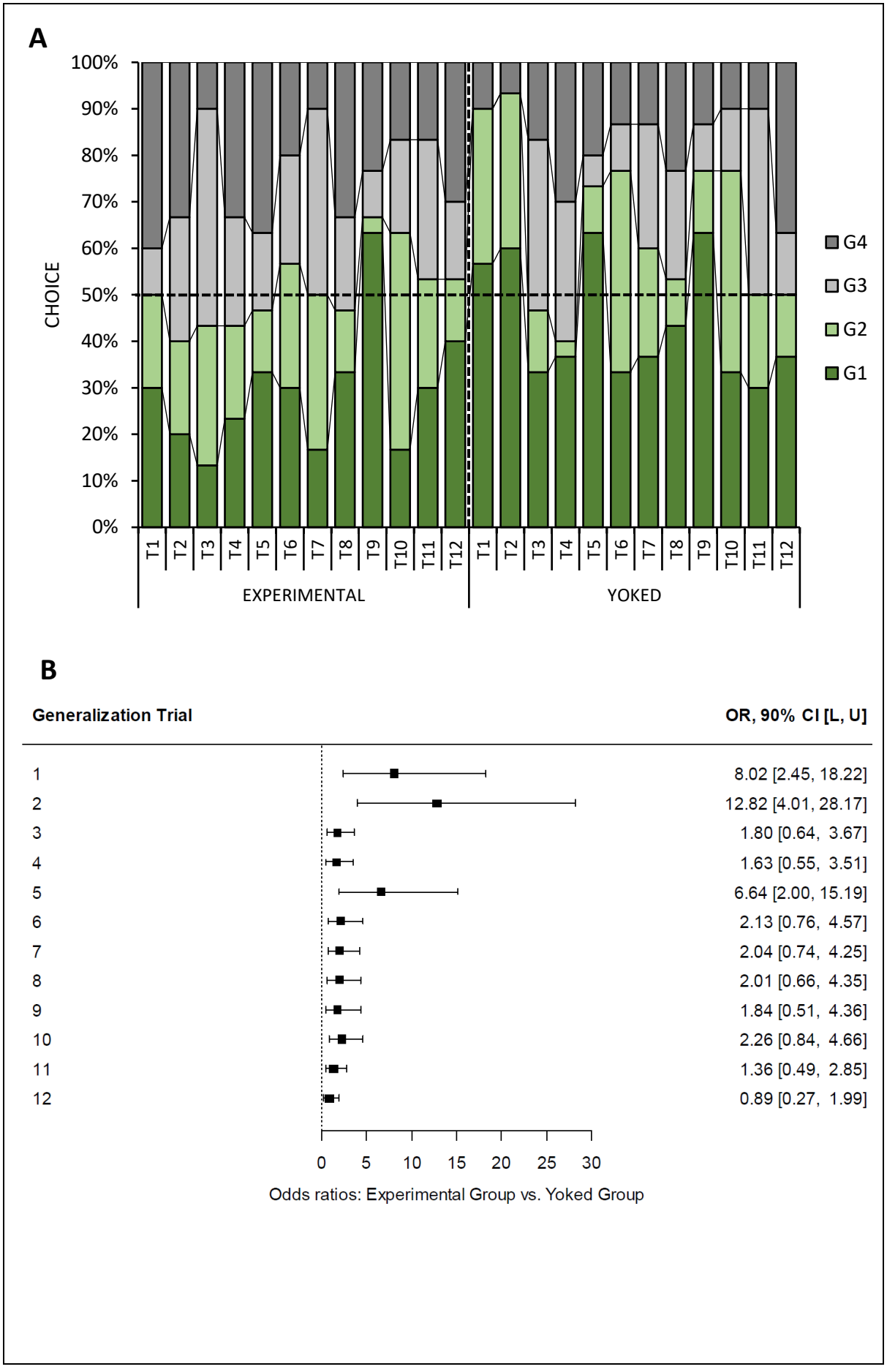


Figure 4.4. Average proportions of choices of each generalization trajectory in the Experimental and Yoked Groups during the entire generalization phase (averages of 12 trials). Error bars represent SEM.

Finally, although not pre-registered, but to explore differences in choices between groups on a trial-by-trial basis, we ran another random intercept proportional odds model (Model 2), with Trajectory Choice (G1-4) as the categorical dependent variable, and Group (Experimental, Yoked) and Trial (T1-12) as predictors. In line with the maximal deviation data, the Experimental Group was only slightly more likely to choose G4 rather than G1-3 (or, G4 or G3 rather than G2 or G1, or, G4 or G3 or G2 rather than G1), compared to the Yoked Group, throughout the generalization phase overall. However, as with the maximal deviation data, during the first, second, and fifth trials of the generalization phase, the Experimental Group was 8.02, 90% CI [2.45, 18.22], 12.82, 90% CI [4.01, 28.17], and 6.64, 90% CI [2.00, 15.19], times more likely to choose a more effortful movement trajectory (rather than a less effortful one), compared to the Yoked Group, respectively (Fig. 4.5; see Appendix C for estimated model coefficients and 90% credible intervals for Models 1 and 2).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Generalization Trial
OR, 90% CI [L, U]
1 8.02 [2.45, 18.22]
2 12.82 [4.01, 28.17]
3 1.80 [0.64, 3.67]
4 1.63 [0.55, 3.51]
5 6.64 [2.00, 15.19]
6 2.13 [0.76, 4.57]
7 2.04 [0.74, 4.25]
8 2.01 [0.66, 4.35]
9 1.84 [0.51, 4.36]
10 2.26 [0.84, 4.66]
11 1.36 [0.49, 2.85]
12 0.89 [0.27, 1.99]
0
5
10
15
20
25
30
Odds ratios: Experimental Group vs. Yoked Group

Figure 4.5. Panel A: Proportions of trajectory choices in the Experimental and Yoked Groups during each trial (T1-12) of the generalization phase. **Panel B:** Odds ratios (OR; i.e. the ratios of the odds of the Experimental Group choosing G4 rather than G1-3 (or, G4 or G3 rather than G2 or G1, or, G4 or G3 or G2 rather than G1) compared to the Yoked Group) during each trial of the generalization phase, together with 90% confidence intervals (CI). 90% CIs indicate the estimated precision of the results. Horizontal bars indicate confidence interval bounds. An odds ratio of 1 indicates that the likelihood to choose a more effortful movement trajectory is equal in both groups. Any value greater than 1 indicates that the likelihood to choose a more effortful movement trajectory is higher in the Experimental Group than the Yoked Group, and any value less than 1 indicates that the likelihood to choose a more effortful movement trajectory is lower in the Experimental Group than the Yoked Group. A coefficient is deemed statistically significant when the specific posterior credible intervals, i.e. the lower (L) and upper (U) bounds do not cross 0.

Discussion

The current experiment aimed to investigate whether (1) concurrently measured pain-related fear and costly pain-related avoidance generalization correspond in one task, (2) avoidance, like fear, can decrease as a function of dissimilarity from a pain-associated movement, and (3) healthy people exhibit excessive avoidance, despite associated costs. Aligning with previous research (Meulders et al., 2013), we found generalization gradients in pain-related fear and pain-expectancies: both ratings linearly decreased with increasing distance from the pain-associated movement (T+). Although we did not observe peak shifts in our self-report measures, we did find area shifts. Specifically, the extreme version (G4) of the safe movement (T-) was feared less than the movement (G3) on the *other* side of T-, suggesting a general decrease in conditioned fear to stimuli on the side of T-, away from T+. Finally, avoidance behavior generalized initially: the Experimental Group deviated more from the shortest available trajectory than the Yoked Group, at the beginning of generalization. Throughout generalization, the Experimental Group was more inclined than the Yoked Group to choose the *more* effortful generalization trajectories (G4 and G3), similar to the previously safe one (T-), indicative of avoidance generalization. A closer look at participants' choices of generalization trajectories suggests that the difference between groups was driven by the Experimental Group performing all generalization trajectories relatively equally, whereas the Yoked Group preferred the shortest, least effortful movement trajectory (G1) over the other trajectories. Since preference of the generalization trajectories in the Experimental Group did not decrease from the "safest" generalization trajectory (G4) to the "most threatening" one (G1), no *avoidance generalization gradient*, or area shift (i.e. preference for G4 over G3) was observed.

Therefore, although participants labeled G4 as the safest generalization trajectory, they did not prefer this movement.

The current findings align with previous studies investigating generalization of costly pain-related avoidance in healthy people. In Glogan et al. (Glogan, Gatzounis, Meulders, et al., 2020), and Glogan, Vandael, et al. (Glogan et al., In press), pain-related fear and pain-expectancies generalized, but costly pain-related avoidance did not. Fear learning is expressed on different levels, including physiological- (e.g. startle), cognitive- (e.g. pain-expectancies), and behavioral (e.g. avoidance) response systems (Bradley & Lang, 2000; Lonsdorf et al., 2017). Oftentimes outcomes in different response systems can diverge (Sevenster et al., 2012, 2014), and behavioral responses in particular are affected by multiple factors, including social demands (Karos et al., 2015; Volders et al., 2015), competing goals (Pittig & Dehler, 2019; Pittig et al., 2018; Van Damme et al., 2012), motivations (Van Damme et al., 2010), and costs (Claes et al., 2015; Claes et al., 2014; Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., In press). Therefore, especially in healthy people, fear does not necessarily result in avoidance, as in the current experiment.

One obvious situation attenuating avoidance (but not fear) is approach-avoidance conflict, wherein one behavioral option is simultaneously linked to positive and negative outcomes (Corr, 2013; Talmi & Pine, 2012). In the current experiment, participants were faced with the conflict of avoiding pain (or effort; positive outcome) at the cost of effort (or pain; negative outcome). Experimental Group participants chose all generalization trajectories relatively equally, suggesting that the costs associated with the "safe" movement trajectories (G3 and G4) motivated participants to also approach the "less safe" ones (G1 and G2), rather than simply sticking to G3 and G4. This is in line with past reports of avoidance decreasing as a function of costs associated with avoidance (Rattel et al., 2017), and with previous pain (Claes et al., 2014; Van Damme et al., 2012) and anxiety literature (e.g.(Pittig & Dehler, 2019)) showing that healthy people approach feared stimuli, when valued goals competing with avoidance, are introduced. In contrast, people with chronic pain seem to put increased weight on pain-control (e.g. avoidance), despite high costs (Volders et al., 2015).

An approach-avoidance conflict necessarily involves decision-making processes, which are often influenced by the anticipation of reward and/or punishment (LeDoux, 2012a, 2012b; Schultz, 2006; Sierra-Mercado et al., 2015). During acquisition, Experimental Group participants persisted in costly avoidance (choosing T-) because they learned that the less effortful movement (T+) reliably predicted pain. However, when novel movements (G1-4) were introduced, and the familiar options were no longer available, participants had to re-evaluate the risk of punishment against the costs of avoiding, prompting exploration (i.e. *approach* of an option with uncertain

outcomes, but possible gains (Lee et al., 2011; Mehlhorn et al., 2015)) of the less effortful movements.

Thus, it is not entirely surprising that healthy people would *not* prefer the even more effortful version of the safe movement (G4). In chronic pain, however, the balance between reward and punishment is likely shifted in the direction of pain-avoidance at the cost of rewards (Rizvi et al., 2021; Van Damme et al., 2010). Indeed, negative biases about pain (Crombez et al., 2013; Schoth & Liossi, 2016) can complicate the updating of pain-related expectations in situations where pain-related outcomes are more positive than expected (Van den Bergh et al., 2021), possibly resulting in deficient safety learning (Meulders, Meulders, et al., 2017c), which in turn can lead to excessive avoidance, and ultimately, chronic pain disability (A. Meulders, 2019). Therefore, although healthy participants did not prefer the costly, "safer" movements in the current paradigm, it is possible that some people with chronic pain may disregard costs, and exhibit increased avoidance, compared to healthy participants. This intriguing hypothesis remains to be tested.

Contrary to most avoidance studies (Krypotos et al., 2018), participants in this experiment were given no instructions regarding the experimental movement-pain contingencies, and they thus learned the acquisition contingencies through trial-and-error. When presented with a set of entirely novel movement trajectories (G1-4), participants were again required to learn the contingencies themselves. One's decision to approach or avoid is fundamentally affected by their motivations (i.e. energization of behavior towards, or away from, a stimulus (Elliot, 2006)) and goals (i.e. aims that an individual strives for (Elliot & Fryer, 2008)) (Elliot, 2006). The current sample of healthy people may have valued information (learning the contingencies) more than preserving safety at all times. This post-hoc interpretation is supported by the data: the Experimental Group chose all generalization trajectories relatively equally, which implies trying to learn which movement was now paired with pain. Further inspection of trajectory choice data also shows that participants mostly switched from one generalization trajectory to another between trials. This is in line with previous results from our lab, showing that healthy participants explore novel movement trajectories, even when they report being fearful of these (Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., In press). Exploration can be interpreted as healthy behavior, promoting disconfirmation of threat beliefs (Glogan et al., In press), leading to eventual recovery. Of note, since none of the generalization trajectories were punished, but were increasingly costly, this could also be interpreted as delayed safety learning compared with the Yoked Group, who preferred the least effortful trajectory, thus exhibiting the more cost-effective behavior.

Pain is only one among many basic drivers of behavior (Craig, 2003), and especially in healthy people, competing drives may take over the need to avoid pain. In fact, healthy behavior

is characterized by curiosity (Peterson & Seligman, 2004), which is an intrinsic drive in itself (Oudeyer & Kaplan, 2007), and motivates exploration (Spielberger & Starr, 1994; Voss & Keller, 1983). It is suggested (Spielberger & Starr, 1994) that when curiosity is stronger than anxiety, individuals will explore their environment, but when anxiety is stronger than curiosity, goals will be disengaged from to reduce stimulation. Participants here knew that the pain stimulus did not pose real danger, and for this reason, the motivation to explore may have overridden the need to avoid pain. In contrast, a reduction in curiosity can be a symptom of psychopathology, such as depression (Kidd & Hayden, 2015; Rodrigue et al., 1987), highly comorbid with chronic pain (Demyttenaere et al., 2007; Ohayon & Schatzberg, 2010; Radat et al., 2013; Von Korff et al., 2005). It seems feasible that in chronic pain, the need for pain-control may trump curiosity, leading to less exploration of novel movements, and to sustained avoidance. This aligns with previous findings from our lab, showing that increased exploration of novel movements leads to rapid extinction of avoidance (Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., In press), whereas less exploration causes sustained, generalized avoidance (Glogan et al., In press). Relatedly, curiosity has been shown to improve coping efficacy (Denneson et al., 2017), and has been linked to tolerance of uncertainty and -anxiety, suggesting it can buffer distress (Kashdan et al., 2013). Thus, curiosity may prove an interesting topic of investigation for the pain-avoidance literature.

Some limitations should be discussed. First, it would be interesting to include more than one generalization trajectory for investigating peak- and area shifts (i.e. a trajectory to the right of G4, or to the left of T+), and having only one generalization trajectory for this purpose limits the interpretation of the current area shifts in fear and expectancies. However, we were limited by the available movement area of the HM. Second, we did not observe any effects in our startle measures. This is surprising, given that a previous study investigating generalization of movement-based pain-related fear did find gradients in this measure (Meulders et al., 2013). However, because in the current experiment, the to-be-performed movement was highlighted at the beginning of the 10s ITI, anticipation of pain may have simply waned, possibly explaining the lack of differential startle responses. Third, we opted for making the acquisition movement trajectories (T+ and T-) unavailable during generalization, thus partly restricting the natural choices of participants. However, participants may have otherwise stuck to the known safe option (T-), preventing examination of avoidance generalization. Finally, given the healthy status of our sample, we can only speculate on the behavior of chronic pain populations in the current paradigm.

In conclusion, the current results provide one of the first direct comparisons of pain-related fear- and costly pain-related avoidance generalization in one single study, and add to increasing literature demonstrating that pain-related fear and avoidance do not always converge,

especially when avoidance is costly. However, similar investigations in clinical populations are still lacking. Thus, replication of the current study in a clinical sample is needed for furthering the understanding of how normally adaptive fear and avoidance interact, diverge, and ultimately come to contribute to the development of chronic pain disability.

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CHAPTER 5

THE GENERALIZATION OF PAIN-RELATED AVOIDANCE BASED ON DE NOVO CATEGORICAL KNOWLEDGE

Abstract

People with chronic pain often fear and avoid movements and activities that were never experienced with pain. Safe behaviors may be feared and avoided because they belong to the same category as a pain-associated behavior. The current study investigated whether instrumental pain-relevant responses (movements) can be arbitrarily associated with physically dissimilar behaviors, and thus motivate avoidance of safe movements - a phenomenon known as category-based avoidance generalization. Two groups learned to categorize two sets of movement trajectories (T1-3 and G1-3) in different ways (MTS-Congruent: T1 = G1, T2 = G2, T3 = G3; MTS-Incongruent: T1 = G3, T2 = G2, and T3 = G1). Subsequently, participants learned that T1 (the shortest trajectory) was paired with the highest chance of emitting a painful electrical stimulus, whereas T2 (the middle trajectory) was less likely to do so, and T3 (the longest trajectory) was never paired with pain. Avoidance learning was thus measured as deviation from T1. Self-reports of pain-related fear and pain-expectancies were collected as indices of fear. Finally, during the generalization phase, G1-3 were made available, but in the absence of pain. The results showed that avoidance and self-reports generalized differently in the two groups, based on the categories learned during the MTS task, suggesting that pain-related avoidance can generalize to safe behaviors that are not physically, but categorically similar to a pain-associated behavior. This form of generalization is problematic because category-based relations can be extremely wide-reaching and idiosyncratic. Thus, the category-based generalization of operant pain-related avoidance merits further investigation.

Introduction

Fear and avoidance are adaptive responses to pain, which normally signals bodily threat (Vlaeyen & Linton, 2000, 2012). However, since there often is no sign of remaining injury in chronic pain, pain-related fear and avoidance become uncoupled from their protective function (Merskey & Bogduk, 1994), and thus cause unnecessary distress. Avoidance specifically can culminate in disability, because it directly causes physical disuse and decreases engagement in daily activities (A. Meulders, 2019). Unfortunately, any transient pain relief, or the absence of a feared outcome (e.g. pain exacerbation or re-injury) may be misattributed to avoidance, resulting in a self-sustaining cycle of avoidance, which in turn can further increase pain-related fear (by suggesting that threat is truly present) (Krypotos et al., 2015; A. Meulders, 2019; van Vliet et al., 2018).

The fear-avoidance model of chronic pain draws from theories of learning and cognition to explain how chronic pain disability develops and is maintained (Vlaeyen & Linton, 2000, 2012). According to the model, pain-related fear is learned through classical (Pavlovian) conditioning, whereby a stimulus (e.g. a movement; conditioned stimulus; CS+) that is paired with pain (unconditioned stimulus; US), becomes associated with pain, and thus begins to elicit fear (conditioned response; CR) in its own right (Meulders et al., 2011; Pavlov, 1927; Vlaeyen, 2015). Another movement that is never paired with pain will not elicit such CRs but becomes a signal of safety instead (CS-). Later, fear motivates avoidance behavior through a process of operant (instrumental) conditioning. That is, avoidance actions (R; e.g. moving with reduced spinal motion (Thomas & France, 2007)) that omit a negative outcome (a feared outcome, O; e.g. pain) will increase in frequency (*negative reinforcement*) (Skinner, 1953). Problematically, people with chronic pain often fear and avoid movements and activities that never featured in a painful event. This spreading of fear and avoidance from a pain-associated movement to similar, albeit safe movements, is known as fear/avoidance *generalization* (Dymond et al., 2015), and has been posited as an etiological pathway within anxiety disorders (Lissek & Grillon, 2010) and chronic pain (Meulders et al., 2015). This pathway has been widely studied in the context of physically similar, pain-relevant stimuli (Meulders et al., 2013; Meulders & Vlaeyen, 2013) and operant responses (i.e. movements) (Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., In press). For example, participants who associate an easy movement with highly probable pain avoid that movement by performing an effortful but safe movement (Glogan, Vandael et al. (In press; Experiment 2). Furthermore, in a subsequent pain-free phase, these participants also persisted in avoiding a novel movement, similar to the easy and pain-associated one from the previous phase. That is, they continued to perform a novel movement that was proprioceptively similar to the effortful, pain-free movement, even though the novel *easy* movement was also pain-free in this phase.

Fear and avoidance can generalize not only based on perceptual similarity between stimuli and responses, but also based on higher-order reasoning, such as knowledge about the different categories a stimulus might belong to (Dunsmoor & Murphy, 2015; Dymond et al., 2015). To give a real-life example, a person who experiences a shooting back pain when performing a specific yoga pose may begin to fear and avoid this pose. The person may subsequently generalize avoidance to other yoga poses, or the entire activity of yoga, even if on a physical (proprioceptive) level, these behaviors are all different. Ultimately, fear may even generalize to all physical exercise if the person categorizes the activity "yoga" as similar to "exercise".

Previous experiments have demonstrated this type of *concept, or category-based* generalization of pain-related *fear* using de novo stimulus categories in a matching-to-sample (MTS) task (Bennett et al., 2015). In an MTS task, participants learn to group perceptually dissimilar stimuli together, such that novel categories are formed through trial-and-error with the help of corrective feedback (Skinner, 1950). For example, Bennett et al. (2015), trained participants to form two categories where specific nonsense words were equivalent to respective joystick movements. During a subsequent fear conditioning phase, nonsense words from one of the categories were paired with a painful electrical stimulus, whereas nonsense words from the other category were not. Subsequently, pain-related fear spread to joystick movements from the category of the pain-associated nonsense words, but not to those from the other category, despite the joystick movements *themselves* never being experienced with pain (Bennett et al., 2015). Since the nonsense words bore no resemblance to the joystick movements, the formed associations between the two could have only arisen due to categorical knowledge created in the MTS task. Other studies have demonstrated pain-related fear generalization based on *real-life* action categories (i.e. opening/closing boxes) (Glogan et al., 2018; Meulders, Vandael, et al., 2017).

Research has also demonstrated category-based generalization of *avoidance*. These experiments often employ a classical-operant approach to examine avoidance. Following creation of de novo categories in an MTS task, participants first complete a classical fear conditioning phase before learning to avoid the US by employing an experimenter-defined avoidance response to one of the de novo categories. Critically, during a subsequent generalization test, presentations of other members from the category of the CS+ elicit avoidance, even though none of these are paired with the US (e.g. Augustson & Dougher, 1997; Dymond et al., 2011; Bennett et al., 2020). Category membership has thus been experimentally shown to prompt the spreading of avoidance to objectively safe stimuli.

Because category-based generalization is not bound by the perceptual features of movements and actions, but can be affected by any prior learning of a specific person, category-

based generalization introduces another level of complexity to understanding the ways in which an individual may learn to fear safe stimuli and situations (Dunsmoor & Murphy, 2015). For treatments to be as effective as possible, in-depth analyses are needed of the fears faced by people with chronic pain, and it is therefore important to understand the mechanisms underlying all the complex forms in which fear and avoidance might be acquired and generalized (Dymond et al., 2015).

However, no study to date has investigated category-based generalization of *pain-related* avoidance. Perhaps even more importantly, previous studies have only investigated category-based avoidance generalization using classical-operant methods where the same avoidance response (e.g. pressing a computer button) generalizes to classically conditioned stimuli. Yet, no study has yet investigated whether (pain-relevant) responses, such as movements, can become categorically associated with one another, and thus also motivate avoidance in the absence of real threat. This is an important question because people with chronic pain, more often than not, fear and avoid operant *responses* (e.g. bending down, doing physical labor), rather than Pavlovian *stimuli* (e.g. spiders). This type of operant-based generalization is known as *response-generalization*, where the outcome associated with one *response* generalizes to other, similar responses, thus increasing/decreasing the likelihood of their occurrence (Skinner, 1953).

Therefore, in the current study, we aimed to investigate if pain-related avoidance would generalize based on de novo categorical relationships between pain-relevant responses (i.e. movements). Employing a robotic arm-reaching paradigm (Meulders et al., 2016), participants in two groups were trained to categorize the same arm-movements in two different ways during an MTS task. Subsequently, the groups underwent an operant avoidance acquisition phase; a movement from one of the categories was paired with a high probability of pain, while the others were paired with a medium probability, and no pain, respectively. During the following generalization phase, the movements categorically related to those from the acquisition phase were made available, but no pain was presented. Self-reports of pain-related fear and pain-expectancies were collected as indices of *fear* learning. We expected avoidance and fear to generalize differently in both groups, based on the respective categories learnt during the MTS task.

Method and materials

Participants

Sixty-six healthy, pain-free volunteers participated in this study. One participant was excluded prior to data analysis because they did not fulfill the inclusion criteria. Thus, 65 participants were included in the final analyses (48 women, $M \pm SD$ (range) age = 25.82 $\pm$ 8.12 years (18-65)). The

sample size was based on the generalization effect size from Glogan, Vandael et al. (In press; d = 0.71), and an *a priori* power analysis conducted in G*Power (independent-samples *t*-test, two-tailed, a = .05, power = .80). Participants were randomly assigned to one of two groups: MTS-Congruent (n = 33) or MTS-Incongruent (n = 32). Participants were recruited via the research participation system of Maastricht University (Sona; Sona Systems, Nijmegen, The Netherlands), and the study was promoted via posters distributed around the university campus, social media, and word of mouth. Exclusion criteria comprised: under 18/over 65 years of age; pregnancy; left-handedness; chronic pain; acute pain in dominant shoulder/arm/elbow/wrist/hand; current/history of cardiovascular disease and/or psychiatric disorders; electronic implants (e.g. pacemaker); uncorrected hearing and/or vision problems; analphabetism or diagnosed dyslexia; other serious medical conditions; and being advised to avoid stressful situations by one's GP. Before the experiment, participants were informed that they could freely terminate participation at any time without any negative consequences, after which they completed an exclusion criteria checklist and an informed consent form. Participants were compensated either with €12.50 in gift vouchers or 1.5 course credit. Ethical approval was provided by The Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration number: 185_09_11_2017_S12).

Apparatus and stimulus materials

HapticMaster. The HapticMaster (HM; Motekforce Link, Amsterdam, the Netherlands) is a 3-degrees of freedom, admittance-controlled robotic arm. When operated by an external force, the robot reacts with a corresponding movement. By recording relative displacement from the starting position, the HM also provides an outcome measure to quantify each performed movement. For the current study, the HM was programmed to allow movement along a two-dimensional, horizontal movement plane (depth = 0.36m, radius = 0.41m). The movement coordinates can also be used to trigger presentations of stimuli. This was used in the current experiment for delivering pain stimuli (see '*2.3. Pain stimulus*').

Software and hardware. The experiment was programmed in C#, using cross-platform game engine Unity 2019 (Unity Technologies, San Francisco, CA, USA), and 3D graphics software, Blender 2.8 (Blender Foundation, Amsterdam, The Netherlands). The experimental script was run on a Windows 10 Enterprise (Microsoft Corporation, Redmond, WA, USA) 64-bit Intel Core desktop computer (Intel Corporation, Santa Clara, CA, USA) with 8GB RAM and CPU: i7-7700 at 3.600GHz. Communication between the computer and HM took place via a direct application programming interface connection. The experimental script was presented on a 40-inch LCD screen (Samsung UE40ES5500; Samsung Group, Seoul, South Korea).

Pain stimulus. The pain stimulus was a 2-ms square-wave electrocutaneous stimulus, delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, United Kingdom) through two reusable stainless steel disk electrodes (8mm diameter with 30mm spacing; Digitimer, Welwyn Garden City, United Kingdom) filled with K-Y gel (Reckitt Benckiser, Slough, United Kingdom), attached to the triceps tendon of the participant's right arm. The intensity of the pain stimulus was calibrated individually for each participant, using a standard calibration procedure (e.g. (Meulders et al., 2011). The procedure consisted of the presentation of a series of electrical stimuli increasing in intensity (Glogan, Gatzounis, Vandael, et al., 2020). Participants were asked to reach an intensity that they would describe as "*significantly painful and demanding some effort to tolerate*", corresponding to an 8 on a numeric rating scale ranging from 0 to 10. On this scale, 0 corresponded to "*I feel nothing*", 1 to "*I feel something, but it is not unpleasant; it is only a sensation*", 2 to "*the stimulus is not yet painful, but is beginning to be unpleasant*", 3 to "*the stimulus is starting to be painful*", and 10 to "*this is the worst pain I can imagine*".

Experimental paradigm

The study employed an adaptation of the robotic arm-reaching paradigm, described elsewhere (Glogan, Gatzounis, Meulders, et al., 2020; Meulders et al., 2016), which was extended to also include an MTS task (Skinner, 1950). The participants' task was to move a "green ball" from a start location in the center of the lower end of the movement plane, to a target location directly opposite to the start location, at the upper end of the movement plane (see Fig. 5.1, panels B and C). Participants achieved this by operating the HM with their right (dominant) hand. Participants could visually track their movements, which were represented by the movement of the green ball on-screen, in real-time. The target location was visualized as a green arch, through which the green ball was to be moved for a trial to be completed.

Participants could reach the target via six movement trajectories. The movement trajectories were indicated by six arches placed side-by-side, midway through the movement plane. Three trajectories (acquisition trajectories, T1-3) were located on the right side of the start location (i.e. the center of the movement plane), and the other three trajectories were located on the left side of the start location (generalisation trajectories, G1-3). T1 and G1 were the trajectories closest to the center of the movement plane, and thus the shortest trajectories to the target. T2 and G2 were placed next to T1 and G1, respectively, and thus included slightly more deviation to reach the target. Finally, T3 and G3 were placed at the far right and far left sides of the movement plane, respectively. Thus, they were the trajectories furthest away from the center, and required the largest deviation to reach the target.

Practice phase. The experiment started with a 6-trial practice phase, during which participants got acquainted with the HM and the task. The participant was presented with all movement trajectories. During the first 3 trials, only T1-3 were available, and during the last 3 trials, only G1-3 were available. On each trial, participants could freely choose between the available movement trajectories. When movement trajectories were available, their trajectory arches were colored black, and when they were unavailable, their corresponding arches were colored grey (see Fig. 5.1). The start of a trial was indicated by visual and auditory start signals, i.e. the target arch and a "traffic light" located next to the target, turned green, and a "start tone" was played. The trial ended when the green ball had passed through the target arch. At this point, visual and auditory stop signals were presented, i.e. the target arch and the traffic light turned red, and a "stop tone" was played. Participants were asked to release the robot and wait for it to automatically return to its starting position. Participants were also able to practice providing self-reports of pain-related fear and pain-expectancies using a triple foot switch (USB-3FS-2; Tokyo, Japan). A foot switch was used in order for the self-reports to not interfere with the arm-reaching task. There were no pain stimuli during this phase.

MTS task. In the next phase, participants learned which acquisition trajectories were related to which generalization trajectories (i.e. the trajectory categories). For the MTS-Congruent group, the trajectory categories were, T1 = G1, T2 = G2, T3 = G3, whereas for the MTS-Incongruent group, the categories were, T1 = G3, T2 = G2, T3 = G1 (see Fig. 5.2). During this phase, participants received feedback after each trial, indicating whether or not they had correctly matched the movement trajectories. The trial started with all six movement trajectories visible, and colored grey. Following the start signals, the participant was instructed to perform an acquisition trajectory (i.e. T1, T2, or T3). The to-be-performed movement (i.e. the sample trajectory) was indicated by highlighting its trajectory arch in a specific color. For T1, this was pink, for T2 it was purple, and for T3, it was blue. After the participant had performed the instructed movement, the message "Is equal to…" was presented on-screen, following which the generalization trajectory arches (G1-3) turned black (i.e., became available) and question marks appeared below all of them, prompting the participant to perform a generalization trajectory of their choice (i.e. the comparison trajectory). If the participant selected the *correct* movement trajectory, the following feedback was presented: an on-screen message saying, "CORRECT", the chosen generalization trajectory arch highlighting in the same color as the corresponding acquisition trajectory arch, and a counter at the top of the movement plane increasing by one unit (see Fig. 5.3). If the participant selected an *incorrect* generalization trajectory, a written message saying, "WRONG", was presented, the generalization trajectory arch remained black, and the counter was reset to 0. After this, a new trial

with a new, randomly assigned sample trajectory began. That is, if a participant incorrectly matched the trajectories, the next trial did not necessarily involve the same trajectory category. This phase ended when the participant had performed 21 correctly matched trials in a row. In the following phase, category learning was tested. Twelve correctly matched trials in a row were required, during which no feedback was presented, and the counter was no longer visible.

Acquisition phase. The next phase was similar to the practice phase, except that pain stimuli were now presented according to the experimental contingencies, at 2/3 of movement completion. Only T1-3 were available, and thus colored black. The generalization trajectory arches were also visible, but colored grey to signal their unavailability. Participants could freely choose between T1-3. Choosing T1 was paired with an 80% chance of the participant receiving a pain stimulus, T2 was paired with a 40% chance, and T3 was never paired with the pain stimulus. Thus, participants could partly, or completely, avoid the pain stimulus by choosing T2 or T3, respectively. Avoidance behavior was operationalized as maximum deviation from the shortest possible movement (i.e. a straight line from start to target) for both groups. The acquisition phase comprised three blocks of 12 trials. On two fixed, pre-determined trials of each block, self-report questions (see *2.5. Primary outcome measures*) were presented at the bottom of the screen.

Generalization phase. This phase was similar to the acquisition phase except that only G1-3 were available and no pain stimuli were presented. The generalization phase consisted of two blocks of 12 trials. Similarly to the acquisition phase, self-reports were collected on two fixed, pre-determined trials per block.

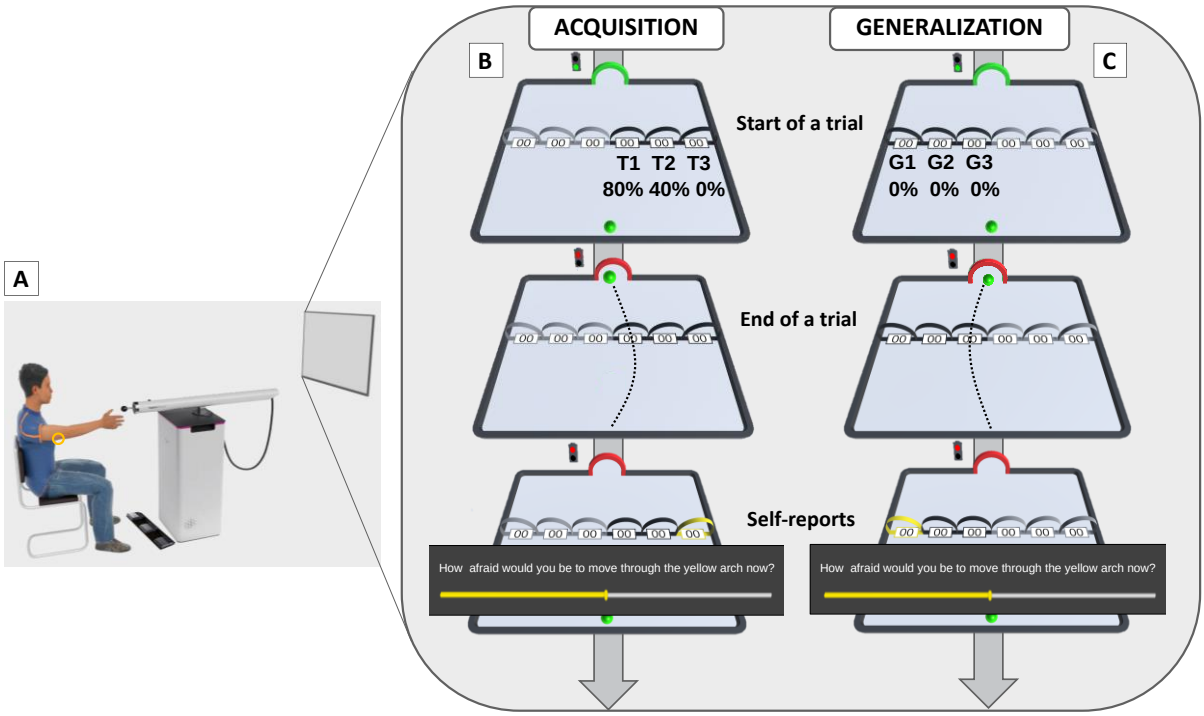

Figure 5.1. The experimental setup and a schematic overview of the experimental task. **Panel A:** The participant is seated in front of the LCD screen, at reaching distance from the sensor of the HM. The electrodes for delivering pain stimuli are placed on the triceps tendon of the right arm (yellow circle), and the triple foot switch is used to give pain-related fear and pain-expectancy ratings. **Panel B:** The acquisition phase of the current experiment, with T1-3 colored black and G1-3 colored grey. **Panel C:** The generalization phase of the current experiment, with G1-3 colored black and T1-3 colored grey. **Start of a trial:** The target arch and traffic light turn green together with the auditory start tone. The green ball is situated at the center of the lower end of the movement plane. *Only for Acquisition*: If the ball passes through T1, the pain stimulus is presented 80% of the time, and 40% of the time if moved through T2. T3 is never paired with a pain stimulus. **End of a trial:** The green ball passes through the target arch. The target arch and traffic light turn red, and the auditory stop tone is played. **Self-report ratings:** On some trials, a rating scale and question (pain-expectancy/pain-related fear) appear on the screen. After both ratings have been given for all trajectories (T1-3 during acquisition and G1-3 during generalization), the HM automatically returns to its starting position, remains fixed for 3s, after which the start signals are presented again, and the next trial starts. This figure is adapted with permission from Glogan, Gatzounis, Vandael, et al. (2020).

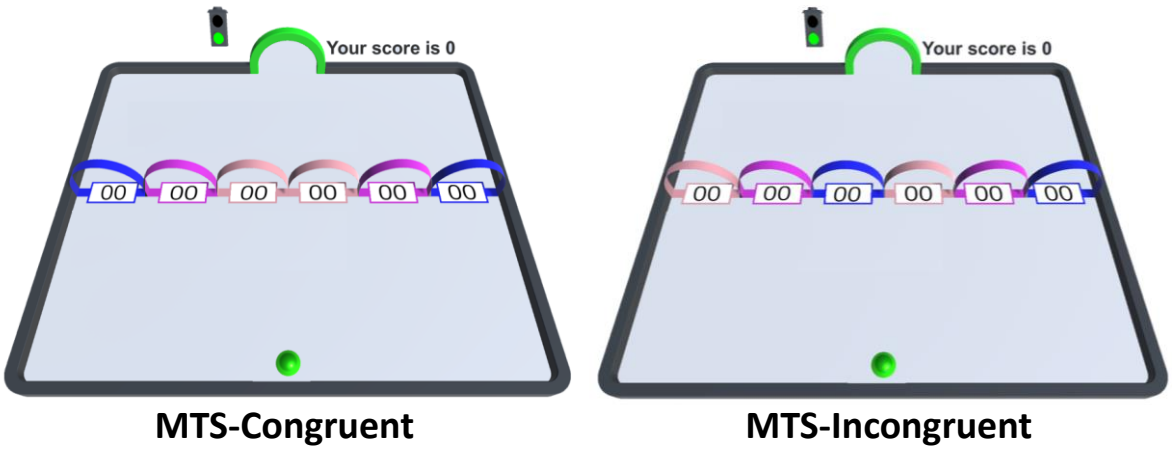

Figure 5.2. The movement trajectory categories of groups MTS-Congruent and MTS-Incongruent. Note that, this figure has been created for visualization purposes, and the categories were never displayed to participants as such.

Primary outcome measures

Avoidance behavior. Avoidance behavior was operationalized as the maximal deviation from the shortest possible movement trajectory within the available movement plane, per trial. This information was extracted from the coordinates of each performed movement, automatically logged by the HM.

Self-reports: pain-expectancy and pain-related fear. Self-reports were collected on specific predetermined trials during the acquisition and generalization phases, always for all available movement trajectories. Questions were presented on-screen using a visual analogue scale (VAS) ranging from 0-100 (0 = "not at all" and 100 = "very much"), and answered using the triple foot switch. To indicate which movement trajectory the question referred to, the corresponding trajectory arch was highlighted in yellow. Participants answered the following questions *"To what extent do you expect an electrical stimulus when moving through the yellow arch?"* (i.e. pain-expectancy) and "*How afraid are you to move through the yellow arch?"* (i.e. pain-related fear).

Secondary outcome measures

Trajectory choice. Frequencies of choices of all movement trajectories were calculated. This information was automatically logged by the HM.

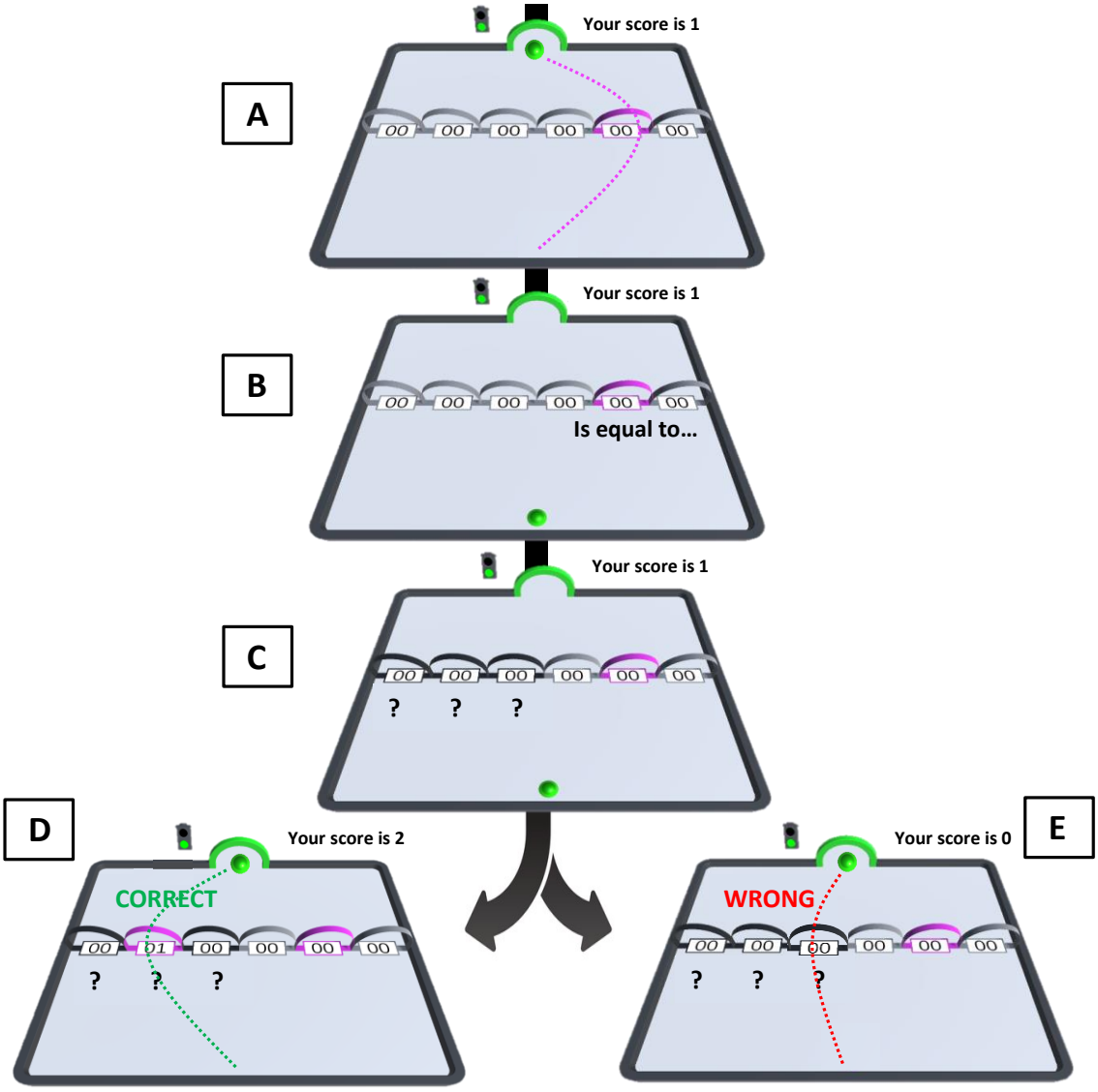

Figure 5.3. An example trial of the MTS task. (A) One of the acquisition trajectory arches (T1-3) is highlighted in its respective color (here, T2 in purple; i.e. the sample movement). The highlighted movement is performed, after which **(B)** the message "Is equal to…" is presented. Subsequently, **(C)** question marks appear under the generalization trajectory arches. Simultaneously, the generalization movement trajectories (i.e. the comparison movements) become available to be performed. **(D)** The participant performs one of the generalization movements; If the performed generalization movement is correctly matched with the previously highlighted and performed sample movement, the generalization trajectory arch is highlighted in the same color as the previously performed sample movement, the message "CORRECT" appears on the screen, and the counter increases by 1 unit. **(E)** If the movement trajectories are not correctly matched, the performed generalization movement trajectory arch is not highlighted, the message "WRONG" appears on the screen, and the counter is reset to 0.

Data Analysis overview

The hypotheses and analysis plan were pre-registered on Open Science Framework (https://osf.io/wtypx/?view_only=b03c45b30ec940f3ab74bd52fd783751). During the acquisition phase, we expected self-reports to follow the pattern T1 > T2 > T3 in both groups, with the effect of interest being T1 > T3 (i.e. acquisition of fear and pain-expectancies), given that T2 was ambiguous. Furthermore, we expected maximal deviations to be larger during the last acquisition block (ACQ3), compared to the first acquisition block (ACQ1) in both groups, indicating acquisition of avoidance. During the generalization phase, we expected self-reports to follow the pattern G1 > G2 > G3, in MTS-Congruent, and G3 > G2 > G1 in MTS-Incongruent (again with the main interest being between G1 and G3), indicating generalization of fear and pain-expectancies. Furthermore, we expected maximal deviations to be larger in MTS-Congruent compared to MTS-Incongruent, indicating generalization of avoidance. To test for acquisition and generalization of self-reports and avoidance behavior, we performed a series of repeated measures (RM) analyses of variance (ANOVAs), and follow-up contrasts to examine our *a priori* hypotheses. RM ANOVAs and planned contrasts were performed in RStudio (version 1.4.1106; RStudio Inc., Boston, MA, USA, 2009-2021), using R (version 3.6.2.; The R Foundation for Statistical Computing, 2019), with package afex (version 0.28-1; (Singmann et al., 2021)) [3].

Results

Demographics

We ran paired-samples *t*-tests to check for baseline group differences. There were no group differences in age, $t(63) = .28$, $p = .78$, physical intensity (mA) of the pain stimulus chosen during calibration, $t(63) = 1.44$, $p = .16$, or self-reported intensity of the pain stimulus, $t(63) = 1.67$, $p = .10$.

Acquisition of pain-expectancies and pain-related fear

We ran a 2 x 3 x 3 RM ANOVA with Group (MTS-Congruent, MTS-Incongruent) as the between-subjects factor, and acquisition Block (ACQ1-3) and Trajectory (T1-3) as the within-subjects factors, on mean *pain-expectancies* during the acquisition phase. As expected, this analysis revealed no effect of Group, $F(1, 64) = .11$, $p = .74$, $\eta_p^2 = .002$, but a main effect of Trajectory, $F(1.41, 88.77) = 168.87$, $p < .001$, $\eta_p^2 = .73$, and a Block x Trajectory interaction, $F(3.69, 232.45) = 49.29$,

[3] Note that, we also pre-registered proportional odds models on our trajectory choice data. However, given that these data are simply a different way of looking at the maximal deviation data, in which we found our effect of interest, we did not report these analyses in the current chapter.

$p < .001$, $\eta_p^2 = .44$. This indicates that the differences in pain-expectancies for the acquisition trajectories changed throughout the acquisition phase, similarly in both groups. Planned contrasts showed that, in line with our hypotheses, both groups reported significantly lower pain-expectancy for T3 compared to T1, at the end of the acquisition phase (ACQ3), MTS-Congruent: $t(63) = 9.89$, $p < .0001$, $d = 2.36$; MTS-Incongruent: $t(63) = 11.20$, $p < .0001$, $d = 3.88$ (Fig. 5.3: Panel A).

A similar RM ANOVA on pain-related *fear* ratings also revealed no effect of Group, $F(1, 63) = .00$, $p = .99$, $\eta_p^2 < .001$, but a significant effect of Trajectory, $F(1.28, 80.83) = 124.10$, $p < .001$, $\eta_p^2 = .66$, and a Block x Trajectory interaction, $F(3.03, 190.58) = 53.25$, $p < .001$, $\eta_p^2 = .46$. Planned contrasts specified that both groups reported significantly lower fear for T3 compared to T1 at ACQ3, MTS-Congruent: $t(63) = 8.25$, $p < .0001$, $d = 1.96$; MTS-Incongruent: $t(63) = 8.91$, $p < .0001$, $d = 2.16$. Thus, both groups successfully learned the acquisition contingencies, and showed differential fear reports reflecting these contingencies (Fig. 5.3: Panel B).

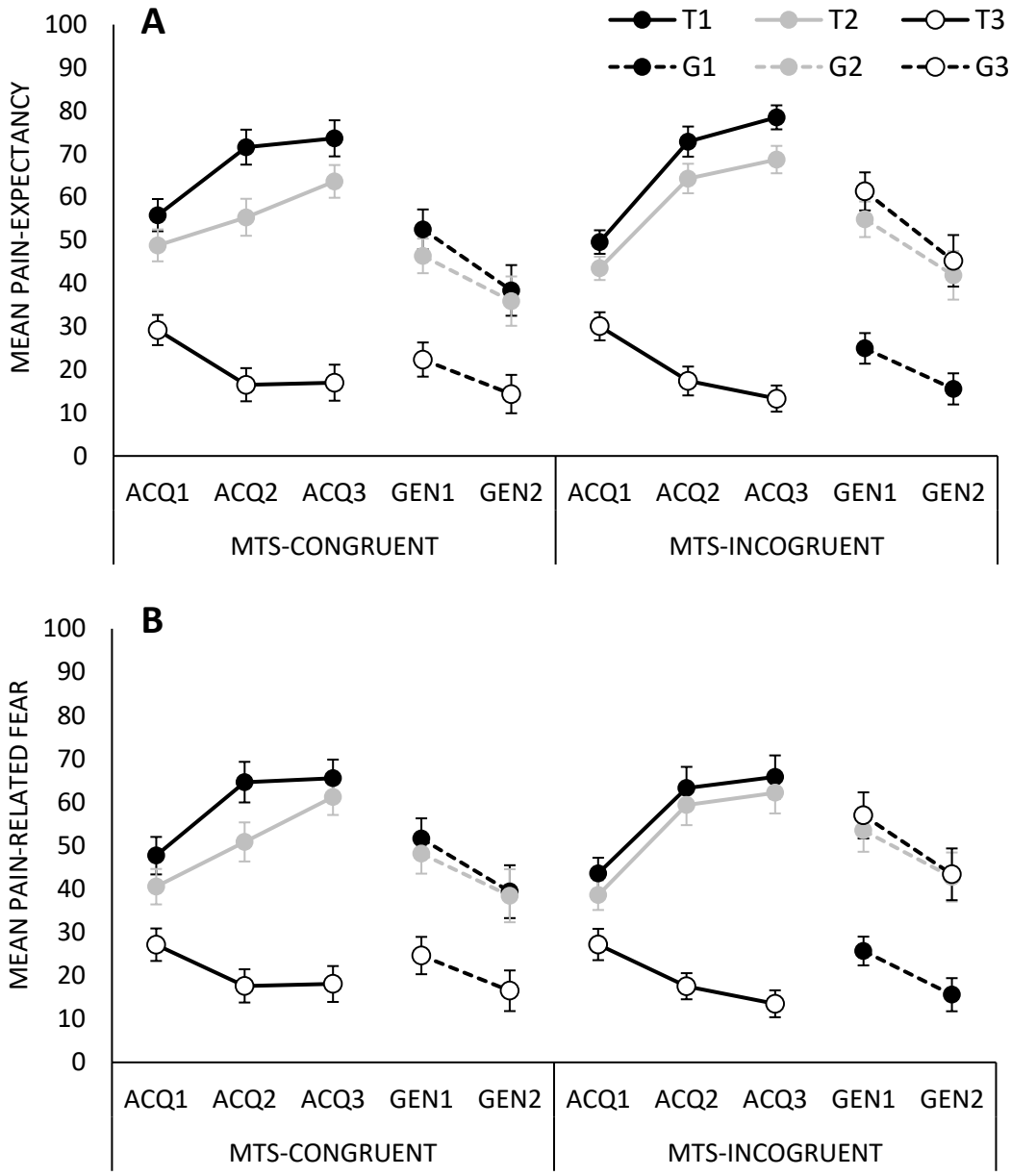

Figure 5.3. Mean pain-expectancy (**Panel A**) and mean pain-related fear (**Panel B**) towards the different trajectories in the MTS-Congruent and MTS-Incongruent Groups during the acquisition (ACQ1-3), and generalization (GEN1-2) phases. Error bars represent ± standard error of the mean (SEM).

Acquisition of voidance behavior

A 2 x 3 RM ANOVA on maximal deviation, with Group (MTS-Congruent, MTS-Incongruent) as the between-subjects factor, and acquisition Block (ACQ1-3) as the within-subjects factor, yielded no effect of Group, $F(1, 63) = .11$, $p = .75$, $\eta_p^2 = .002$, but the expected significant main effect of Block, $F(1.82, 114.90) = 45.98$, $p < .001$, $\eta_p^2 = .42$, suggesting that avoidance behavior, in general, increased throughout the acquisition phase. Planned contrasts confirmed that both groups showed larger deviations by the end of the acquisition phase (ACQ3), compared to the beginning of this phase (ACQ1), MTS-Congruent: $t(63) = 4.39$, $p = .0001$, $d = .60$; MTS-Incongruent: $t(63) = 6.60$, $p < .0001$, $d = 1.03$, indicating successful acquisition of avoidance behavior (see Fig. 5.4).

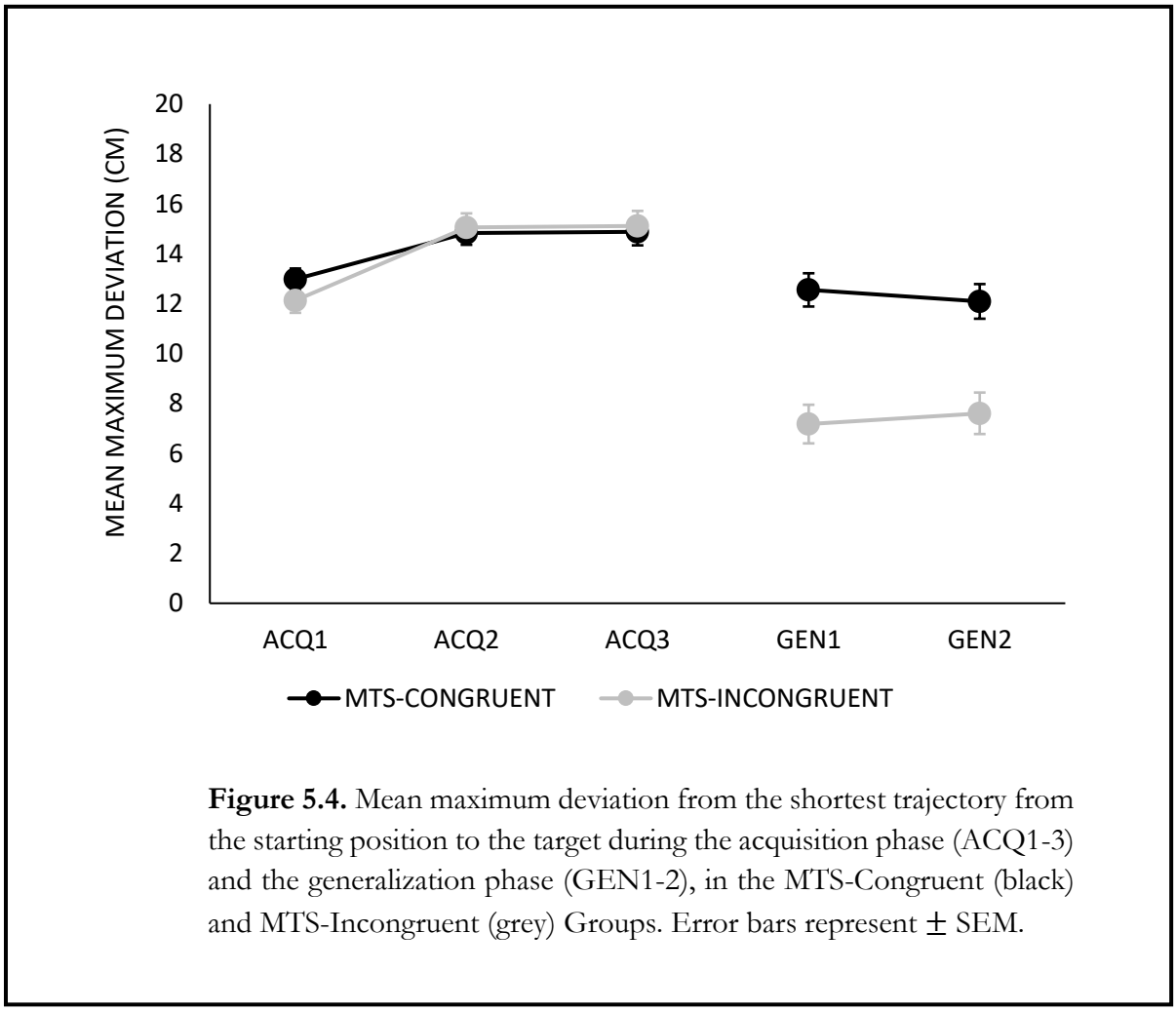

Figure 5.4. Mean maximum deviation from the shortest trajectory from the starting position to the target during the acquisition phase (ACQ1-3) and the generalization phase (GEN1-2), in the MTS-Congruent (black) and MTS-Incongruent (grey) Groups. Error bars represent ± SEM.

Generalisation of pain-expectancies and pain-related fear

A 2 x 2 x 3 RM ANOVA with Group (MTS-Congruent, MTS-Incongruent) as the between-subjects factor, and Block (GEN1-2) and Trajectory (G1-3) as the within-subjects factors, on *pain-expectancy* reports during the generalization phase, revealed the expected Group x Trajectory interaction, $F(1.51, 95.43) = 39.96$, $p < .001$, $\eta_p^2 = .39$, indicating that the generalization trajectories evoked different patterns of pain-expectancies in the two groups. In line with our expectations, MTS-Congruent expected pain more during G1 compared to G3, $t(63) = 5.07$, $p < .0001$, $d = 1.22$, whereas MTS-Incongruent expected pain more during G3 compared to G1, $t(63) = 6.17$, $p < .0001$, $d = 1.62$, during the first generalization block (GEN1).

A similar RM ANOVA on *pain-related fear* reports revealed comparable effects to pain-expectancy reports. There was a significant Group x Trajectory interaction, $F(1.46, 92.06) = 32.63$, $p < .001$, $\eta_p^2 = 34$, and planned contrasts showed significantly more fear for G1 compared to G3 in MTS-Congruent, $t(63) = 4.81$, $p < .0001$, $d = 1.04$, and the opposite effect (G3 > G1) in MTS-Incongruent, $t(63) = 5.60$, $p < .0001$, $d = 1.25$, at GEN1. These results indicate that participants generalized their pain-expectancies and pain-related fear based on the artificial categories learned during the MTS task.

Generalization of avoidance behavior

As expected, a 2 x 2 RM ANOVA with Group (MTS-Congruent, MTS-Incongruent) as the between-subjects factor and Block (GEN1-2) as the within-subjects factor revealed a significant main effect of Group, $F(1, 63) = 23.48$, $p < .001$, $\eta_p^2 = .27$, indicating overall differences in maximal deviation between groups during this phase. Planned contrasts confirmed that deviations were larger in MTS-Congruent compared to MTS-Incongruent, $t(63) = 5.35$, $p < .0001$, $d = 1.33$, at the beginning of the generalization phase, suggesting that both groups generalized avoidance based on the different categories they had learned during the MTS task.

Discussion

In the current experiment, we investigated category-based generalization of pain-related avoidance using de novo categories of operant-based movements. In a robotic arm-reaching paradigm, participants in two groups were trained to place the same movements in distinct categories. Then, participants underwent an operant avoidance acquisition phase wherein a movement (T1) from one of the categories was paired with a high probability of pain (80%) –other movements were paired with a medium probability (40%) and no pain (T2 and T3, respectively). During the following generalization phase, the movements (G1-3) categorically related to those from the

acquisition phase, were made available but no pain was presented. Self-reports of pain-related fear and pain-expectancies were collected as indices of fear learning. We expected the groups to show opposite patterns of generalization in avoidance (maximal deviation MTS-Congruent > MTS-Incongruent), pain-related fear, and pain-expectancies (MTS-Congruent: G1 > G2 > G3, MTS-Incongruent: G3 > G2 > G1) based on the movement trajectory categories they learned during the MTS task.

The results aligned with these hypotheses. First, both groups acquired pain-related fear and pain-expectancies; that is, both groups feared T1 more and expected pain more during T1 compared to T3 during the acquisition phase. Second, both groups also learned to avoid the pain stimulus; in both groups, maximal deviations were larger at the end of the acquisition phase, compared to the beginning of this phase. Thus, the current findings further replicate the acquisition of pain-related fear and avoidance in the robotic arm-reaching paradigm (Gatzounis & Meulders, 2020; Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., In press; Meulders et al., 2016). Importantly, and relating to our main hypotheses, both groups also *generalized* responses in all measures in line with the categories they learned during the MTS task. Specifically, MTS-Congruent feared and expected pain more during G1 compared to G3. The opposite pattern was evident in the MTS-Incongruent group (G3 > G1). Critically, both groups also generalized avoidance in line with the categories they learned during the MTS task. That is, given that MTS-Congruent had learned that the longest generalization trajectory (G3) was associated with the original avoidance response (T3), this group showed larger deviations compared to MTS-Incongruent, who had learned that the shortest generalization trajectory (G1) was related to T3. These results are the first to show that pain-related avoidance behavior can generalize based on de novo relationships between pain-relevant responses, i.e. movements. Indeed, participants generalized pain-related fear and avoidance to movements never paired with pain, based simply on arbitrary categories created in the earlier MTS task, between the acquisition responses and the generalization responses. These findings implicate a unique way for behaviors to evoke pain-related fear and avoidance in the absence of a painful experience.

The current results are in line with previous research reporting generalization of category-based pain-related *fear*. For example, in the study of Bennett et al. (2015), two equivalence categories of nonsense words and joystick movements were created, after which pain-related fear spread to the joystick movements from the category of the pain-associated nonsense words, despite the joystick movements never having been experienced with pain. The current results also align with those of Meulders et al. (2017) and Glogan et al. (2018) who demonstrated generalization of pain-related fear based on real-life categories. Similarly, the current study also showed

generalization of pain-related fear to movements never paired with pain, due to de novo categorical knowledge.

The results of the current study also extend the findings of Bennett et al. (2015), Meulders et al. (2017), and Glogan et al. (2018) by showing that not only pain-related fear, but also pain-related *avoidance* can generalize in this manner. This finding is in line with previous research from the anxiety domain. For example, Augustson and Dougher (1997), and Dymond et al. (2011) also demonstrated category-based avoidance generalization. In these studies, avoidance generalized to stimuli (C1 and D1) from one category, after a member (B1) of this category was paired with an avoidance response that cancelled an electrical stimulus, despite C1 and D1 never having been experienced with B1 directly. Given that these previous studies did not use a *painful* electrical stimulus as US, the current results extend these findings to apply to *pain-related* avoidance as well. Furthermore, due to the differences between classical-operant and operant avoidance procedures, the current findings also extend previous ones by showing that not only Pavlovian stimuli, but also operant responses, can become categorically related to one another based on arbitrary associations formed by individuals. In the real world, this might mean that experiencing pain during one activity (e.g. a yoga pose) can spread to a multitude of other, physically different, but categorically related, activities (e.g. yoga as a whole).

It is worth noting that, in the current study, we created *symmetry relations* (Hayes & Hayes, 1992). This means that the sample movement (e.g. T1) was directly paired with the comparison movement (e.g. G1), but not with other stimuli. Thus, the comparison movement (e.g. G1) was indirectly paired with the *pain stimulus*, via the sample movement (e.g. T1). In contrast, previous studies (Augustson & Dougher, 1997; Bennett et al., 2015; Dymond et al., 2011) created *equivalence relations*, meaning that their sample stimulus (e.g. an abstract symbol; Bennett et al., 2015) was paired with multiple comparison stimuli (e.g. nonsense words *and* joystick movements), which became indirectly associated also with each other (Hayes & Hayes, 1992). A benefit of this approach is that one stimulus could be part of both derived symmetry relations (abstract symbol – nonsense word, abstract symbol – joystick movement), as well as derived equivalence relations (nonsense word - joystick). That is, in the study of Bennett et al. (2015), for example, the nonsense words were never explicitly paired with the joystick movements, but instead participants derived the equivalence of these stimuli via the mutually related abstract symbols. This type of equivalence-based avoidance generalization arguably explains the more wide reaching generalizations of fear and avoidance (Dymond et al., 2011). That is, to stimuli that, not only were never paired with a US, but were also never directly experienced with the original fear inducing event (CS).

Given that avoidance often comes at great personal costs (e.g. disability, missing out on important life events, financial costs from absenteeism) to people with chronic pain (Phillips, 2009; Sprangers et al., 2000; Vos et al., 2017), research in our lab has typically focused on costly avoidance. Indeed, the current findings are in contrast to previous experiments from our lab where *costly* perceptual avoidance did *not* generalize in the robotic arm-reaching paradigm (Glogan, Gatzounis, Meulders, et al., 2020; Glogan et al., In press): Experiment 1), suggesting that the minimized costs in the current study may have enabled avoidance to generalize. Other studies have, however, reported generalization of costly *category-based* avoidance. For example, participants in a study by Wong and Pittig (2020) learned that exemplars from one category (e.g. animal) were paired with an aversive electrical stimulation (US), whereas those from another category (e.g. fruit) were not. Subsequently, in the absence of the US, participants underwent an avoidance test where, if they chose cards from a high-reward deck, they were presented with exemplars from the pain-associated category. Conversely, if participants chose cards from a low-reward deck, they were presented with an exemplar from the safe category. Results showed that participants avoided the high-reward deck more than a control group for whom the avoidance test did not involve exemplars from either of the fear conditioning categories. Thus, avoidance generalized categorically, at the cost of rewards (Wong & Pittig, 2020). Given the inconsistent findings of costly/low-cost, perceptual/category-based avoidance generalization in some studies (e.g. Wong & Pittig, 2020; Glogan, Vandael et al., In press; Experiment 2) and not others (e.g. Glogan et al., 2020; Glogan, Vandael et al., In press; Experiment 1), the differences between perpetual and category-based avoidance generalization warrant further investigation.

In a similar vein, the current results also partly align with those of Bennett et al. (2020), who demonstrated avoidance generalization to other members of an aversive category, based on de novo relationships established during an MTS task. However, complete avoidance generalization (i.e. avoidance generalization between contexts) was specific to groups who had *not* learned behaviors that competed with the avoidance response. Those participants who *had* learned a competing behavior, generalized avoidance only in the same context where avoidance was acquired. Thus, the behavior competing with avoidance seemed to attenuate its generalization (Bennett et al., 2020), suggesting that reinforcing new categories of behaviors may be an effective strategy to reduce the generalization of avoidance. It would be interesting to investigate how such behaviors or rewards competing with avoidance would affect the current results. A future study could, for example, include two more groups, which, in addition to undergoing the same paradigm as the current groups, would learn that the middle movement trajectory (T2) is paired with reward (e.g. every choice of T2 increases the chance of winning a monetary prize). In this way, we could

investigate the attenuation of pain-related avoidance generalization by rewarding an alternative behavior.

Some limitations deserve attention. Firstly, we did not counterbalance the colors of the movement trajectory arches during the MTS task, which may have confounded the category learning effects. Furthermore, during the MTS task we prompted participants to select the comparison movement "equal" to the sample movement, although strictly speaking, we did not create equivalence relations during this task. Indeed, in the current experiment we investigated *symmetry* relations rather than *equivalence* relations (Hayes & Hayes, 1992). This can also be perceived as a limitation, given that equivalence relations arguably explain the more far-reaching generalizations of fear and avoidance, given that they involve an even more indirect form of learning (Bennett et al., 2015; Dymond et al., 2011). Unfortunately, we were limited by the available movement space of the HapticMaster robot in the current study, and thus also had a limited space available for different movements. It would be interesting to extend the current findings by increasing the number of movement trajectories, such that some would become associated with each other indirectly, via a mutually related trajectory. This would enable the formation and investigation of response-based equivalence relations as well as symmetry relations (Hayes & Hayes, 1992). Nonetheless, we perceive the current results as a significant first step into investigating this important pathway to the generalization of operant pain-related avoidance.

Furthermore, in the current experiment we employed only a low-cost avoidance response. However, real-life avoidance is often costly, and the fact that there was no cost in the current study suggests that there also was no reason for participants *not* to avoid during the generalization phase. While this may reduce the ecological validity of the results, it is important to note that people with anxiety disorders and chronic pain also use subtle and low-cost safety behaviors (e.g. performing a feared movement with reduced spinal flexibility or keeping pain medication at hand at all times). Safety behaviors may be especially resistant to treatment (Lovibond et al., 2009b), given that they do not hinder daily functioning (as much), and may go unnoticed by patients and therapists. Thus, we believe these findings are still clinically relevant. Furthermore, given that this is the first experiment of its kind, we aimed to focus mainly on the category learning aspect – something, which might have been disrupted by adding costs. A future study should aim to replicate the current findings with avoidance costs. One way to do this could be to adjust the starting point of the movement such that, rather than it being in the middle of the general movement plane, it would be in the middle of the respective acquisition and generalization movement planes. Thus, T1/G1 and T3/G3 would be the same length, but T3 could be paired with increased resistance

from the robot, and subsequently G1 and G3 would be paired with resistance as well, depending on the MTS group.

With this in mind, a third limitation is that for the MTS-Congruent group, avoidance generalization was operationalized as longer deviations to reach the target (choice of G3), whereas for the MTS-Incongruent group, avoidance generalization was represented as shorter deviations to reach the target (choice of G1). This slightly complicates the interpretation of the behavior of the MTS-Incongruent group. Specifically, given that G1 is the most direct movement trajectory to the target, it is difficult to exclude that the MTS-Incongruent group was not simply behaving in the most energy-efficient way by taking the shortest path to the target (rather than, or in addition to, generalizing). In line with this suggestion, post-hoc *t*-tests performed on mean movement durations during the generalization phase, indicated that the MTS-Incongruent group was significantly faster at performing the arm-movements during the generalization phase, compared to the MTS-Congruent group (GEN1: $t(64) = 3.16$, $p. = .002$; GEN2: $t(64) = 3.43$, $p. = .001$). Unfortunately, whether or not participants perceived this as a cost, cannot be reliably confirmed from the data we collected. Nonetheless, given that self-reports in the current study reflected our hypotheses, we do maintain that the most likely explanation for the group differences in avoidance behavior are the differing learning histories between groups.

To conclude, the results of the current study suggest that category knowledge can be engaged during the learning of operant pain-related avoidance, causing an entire category to become related to threat, and to evoke avoidance. This form of generalization is highly problematic, given that category-based relations can be extremely wide-reaching, and can be highly idiosyncratic, due to their abstract nature and them not being restricted by physical form (Dunsmoor & Murphy, 2015). Therefore, the category-based generalization of operant pain-related avoidance merits further investigation.

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CHAPTER 6
METHODOLOGICAL OUTLINE OF THE ROBOTIC ARM-REACHING PARADIGM

Abstract

Avoidance behavior is a key contributor to the transition from acute pain to chronic pain disability. Yet, there has been a lack of ecologically valid paradigms to experimentally investigate pain-related avoidance. To fill this gap, we developed a paradigm (the robotic arm-reaching paradigm) to investigate the mechanisms underlying the development of pain-related avoidance behavior. Existing avoidance paradigms (mostly in the context of anxiety research) have often operationalized avoidance as an experimenter-instructed, low-cost response, superimposed on stimuli associated with threat during a Pavlovian fear conditioning procedure. In contrast, the current method offers increased ecological validity in terms of instrumental learning (acquisition) of avoidance, and by adding a cost to the avoidance response. In the paradigm, participants perform arm-reaching movements from a starting point to a target using a robotic arm, and freely choose between three different movement trajectories to do so. The movement trajectories differ in probability of being paired with a painful electrocutaneous stimulus, and in required effort in terms of deviation and resistance. Specifically, the painful stimulus can be (partly) avoided at the cost of performing movements requiring increased effort. Avoidance behavior is operationalized as the maximal deviation from the shortest trajectory on each trial. In addition to explaining how the new paradigm can help understand the acquisition of avoidance, we describe adaptations of the robotic arm-reaching paradigm for (1) examining the spreading of avoidance to other stimuli (generalization), (2) modelling clinical treatment in the lab (extinction of avoidance using response prevention), as well as (3) modelling relapse, and return of avoidance following extinction (spontaneous recovery). Given the increased ecological validity, and numerous possibilities for extensions and/or adaptations, the robotic arm-reaching paradigm offers a promising tool to facilitate the investigation of avoidance behavior and to further our understanding of its underlying processes.

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Introduction

Avoidance is an adaptive response to pain signaling bodily threat. Yet, when pain becomes chronic, pain and pain-related avoidance lose their adaptive purpose. In line with this, the fear-avoidance model of chronic pain (Crombez et al., 2012; Kori et al., 1990; Leeuw et al., 2007; Lethem et al., 1983; A. Meulders, 2019; Vlaeyen & Linton, 2000, 2012; Waddell et al., 1993) posits that erroneous interpretations of pain as catastrophic, trigger increases in fear of pain, which motivate avoidance behavior. Excessive avoidance can lead to the development and maintenance of chronic pain disability, due to physical disuse and decreased engagement in daily activities and aspirations (Crombez et al., 2012; Leeuw et al., 2007; A. Meulders, 2019; Vlaeyen & Linton, 2000, 2012; Volders et al., 2015). Furthermore, given that the absence of pain can be misattributed to avoidance rather than recovery, a self-sustaining cycle of pain-related fear and avoidance can be established (Lovibond et al., 2009a).

Despite recent interest in avoidance in the anxiety literature (Hofmann & Hay, 2018; Krypotos et al., 2015), research on avoidance in the pain domain is still in its infancy. Previous anxiety research, guided by the influential two-factor theory (Mowrer, 1951), has generally assumed fear to drive avoidance. Correspondingly, traditional avoidance paradigms (Krypotos et al., 2015) entail two experimental phases, each corresponding to one factor: the first to establish fear (Pavlovian conditioning (Pavlov, 1927) phase), and the second to examine avoidance (Instrumental (Skinner, 1953) phase). During differential Pavlovian conditioning, a neutral stimulus (conditioned stimulus, CS+; e.g., a circle) is paired with an intrinsically aversive stimulus (unconditioned stimulus, US; e.g., an electric shock), which naturally produces unconditioned responses (URs, e.g., fear). A second control stimulus is never paired with the US (CS-; e.g., a triangle). Following pairings of the CSs with the US, the CS+ will elicit fear in itself (conditioned responses, CRs) in the absence of the US. The CS- comes to signal safety and will not trigger CRs. Afterwards, during instrumental conditioning, participants learn that their own actions (responses, R; e.g., button-press) lead to certain consequences (outcomes; O, e.g., the omission of shock) (Skinner, 1953; Thorndike, 1898). If the response prevents a negative outcome, the chance of that response recurring increases; this is referred to as negative reinforcement (Skinner, 1953). Thus, in the Pavlovian phase of traditional avoidance paradigms, participants first learn the CS-US association. Subsequently, in the instrumental phase, an experimenter-instructed avoidance response (R) is introduced, canceling the US if performed during CS presentation, establishing a R-O association. Thus, the CS becomes a discriminative stimulus (S^D), indicating the appropriate moment for, and motivating the performance of, the conditioned R (Skinner, 1953). Apart from some experiments showing instrumental conditioning of pain reports (Linton & Götestam, 1985) and pain-related

facial expressions (Gatzounis et al., 2012), investigations into the instrumental learning mechanisms of pain, in general, are limited.

Although the standard avoidance paradigm, described above, has elucidated many of the processes underlying avoidance, it also has several limitations (Krypotos et al., 2018; A. Meulders, 2019). First, it does not allow examining the learning, or acquisition, of avoidance itself, because the experimenter instructs the avoidance response. Having participants freely choose between multiple trajectories, and, therefore, learn which responses are painful/safe and which trajectories to avoid/not avoid, more accurately models real-life, where avoidance emerges as a natural response to pain (Volders et al., 2015). Second, in traditional avoidance paradigms, the button-press avoidance response comes at no cost. However, in real life, avoidance can become extremely costly for the individual. Indeed, high-cost avoidance especially disrupts daily functioning (A. Meulders, 2019). For example, avoidance in chronic pain can severely limit people's social and working lives (Volders et al., 2015). Third, dichotomous responses such as pressing/not pressing a button also do not very well represent real life, where different degrees of avoidance occur. In the following sections, we describe how the robotic arm-reaching paradigm (Meulders et al., 2016) addresses these limitations, and how the basic paradigm can be extended to multiple novel research questions.

Acquisition of avoidance

In the paradigm, participants use a robotic arm to perform arm-reaching movements from a starting point to a target. Movements are employed as the instrumental response because they closely resemble pain-specific, fear-evoking stimuli. A ball virtually represents participants' movements on-screen (Fig. 6.1), allowing participants to follow their own movements in real-time. During each trial, participants freely choose between three movement trajectories, represented on-screen by three arches (T1–T3), differing from each other in terms of how effortful they are, and in the likelihood that they are paired with a painful electrocutaneous stimulus (i.e., pain stimulus). Effort is manipulated as deviation from the shortest possible trajectory and increased resistance from the robotic arm. Specifically, the robot is programmed such that resistance increases linearly with deviation, meaning that the more participants deviate, the more force they need to exert on the robot. Furthermore, pain administration is programmed such that the shortest, easiest trajectory (T1) is always paired with the pain stimulus (100% pain/no deviation or resistance). A middle trajectory (T2) is paired with a 50% chance of receiving the pain stimulus, but more effort is required (moderate deviation and resistance). The longest, most effortful trajectory (T3) is never paired with the pain stimulus but requires the most effort to reach the target (0% pain/largest

deviation, strongest resistance). Avoidance behavior is operationalized as the maximum deviation from the shortest trajectory (T1) per trial, which is a more continuous measure of avoidance, than for example, pressing or not pressing a button. Furthermore, the avoidance response comes at the cost of increased effort. Moreover, given that participants freely choose between the movement trajectories, and are not explicitly informed about the experimental R-O (movement trajectory-pain) contingencies, avoidance behavior is instrumentally acquired. Online self-reported fear of movement-related pain and pain-expectancy have been collected as measures of conditioned fear toward the different movement trajectories. Pain-expectancy is also an index of contingency awareness and threat appraisal (Boddez et al., 2013). This combination of variables allows scrutinizing the interplay between fear, threat appraisals, and avoidance behavior. Using this paradigm, we have consistently demonstrated the experimental acquisition of avoidance (Gatzounis & Meulders, 2020; Glogan, Gatzounis, Meulders, et al., 2020; Meulders et al., 2020; Meulders et al., 2016).

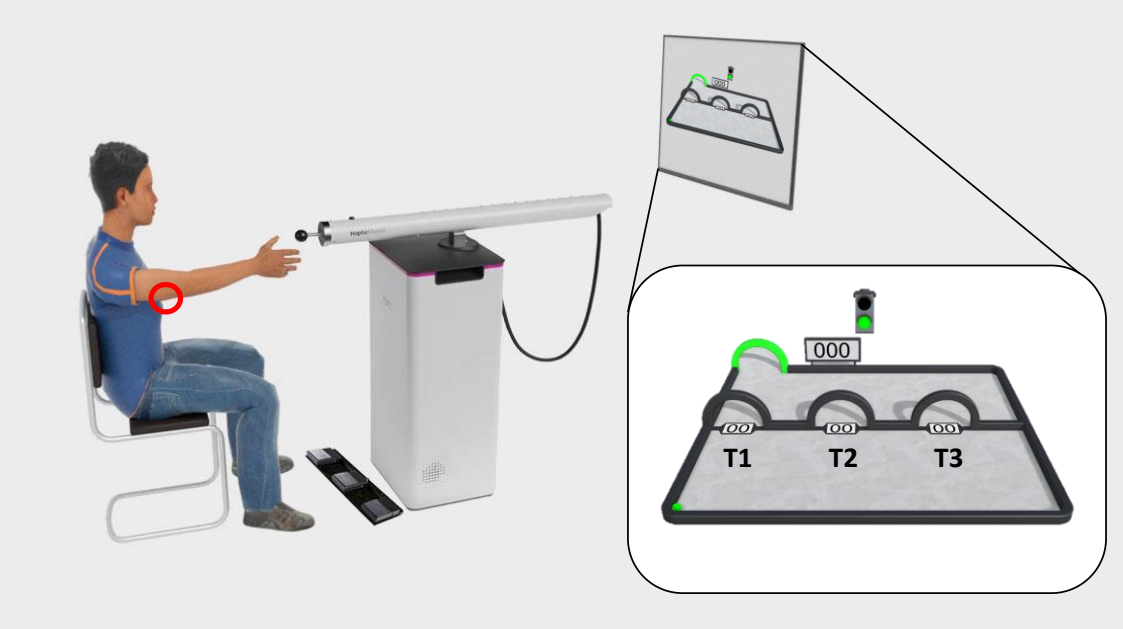

Figure 6.1: The experimental set-up and outlook of the experimental task. The participant is seated in front of a television screen, at reaching distance from the sensor of the robotic arm. Stimulation electrodes are placed on the triceps tendon of the right arm, where the pain stimuli are delivered (red circle), and a triple foot switch is used to give fear of movement-related pain and pain-expectancy ratings. The acquisition phase of the experimental task is shown on the television screen and magnified in the white box. The ball is situated in the lower-left corner, and the target in the upper-left corner (green arch). T1–T3 are situated midway through the movement-plane, from left to right, respectively. Spaces are left between T1–T3 specifically in avoidance generalization protocols, in order to leave room for the subsequent generalization trajectory arches (G1–G3).

Generalization of avoidance

We have extended the paradigm to investigate generalization of avoidance (Glogan, Gatzounis, Meulders, et al., 2020)—a possible mechanism leading to excessive avoidance. Pavlovian fear generalization refers to the spreading of fear to stimuli or situations (generalization stimuli, GSs) resembling the original CS+, with fear declining with decreasing similarity to the CS+ (generalization gradient) (Dymond et al., 2015; Ghirlanda & Enquist, 2003; Honig & Urcuioli, 1981; Kalish, 1969). Fear generalization minimizes the need to learn relationships between stimuli anew, allowing swift detection of novel threats in ever-changing environments (Dymond et al., 2015; Ghirlanda & Enquist, 2003; Honig & Urcuioli, 1981; Kalish, 1969). However, excessive generalization leads to fear of safe stimuli (GSs similar to CS-), thus causing unnecessary distress (Dymond et al., 2015; Lissek & Grillon, 2010). In line with this, studies using Pavlovian fear generalization consistently show that chronic pain patients excessively generalize pain-related fear (Harvie et al., 2017; Meulders, 2020; Meulders et al., 2014; Meulders et al., 2015; Meulders, Meulders, et al., 2017b), whereas healthy controls show selective fear generalization. Yet, where excessive fear causes discomfort, excessive avoidance can culminate in functional disability, due to avoidance of safe movements and activities, and increased daily activity disengagement (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen & Linton, 2000, 2012; Volders et al., 2015). Despite its key role in chronic pain disability, research on the generalization of avoidance is scarce. In the paradigm adapted for studying generalization of avoidance, participants first acquire avoidance, following the procedure described above (Meulders et al., 2016). In a subsequent generalization phase, three novel movement trajectories are introduced in the absence of the pain stimulus. These generalization trajectories (G1–G3) lie on the same continuum as the acquisition trajectories, resembling each of these trajectories, respectively. Specifically, generalization trajectory G1 is situated between T1 and T2, G2 between T2 and T3, and G3 to the right of T3. In this way, generalization of avoidance to novel safe trajectories can be examined. In a previous study, we showed generalization of self-reports, but not avoidance, possibly suggesting different underlying processes for pain-related fear- and avoidance generalization (Glogan, Gatzounis, Meulders, et al., 2020).

Extinction of avoidance with response prevention

The primary method of treating high fear of movement in chronic musculoskeletal pain is exposure therapy (Vlaeyen et al., 2012)—the clinical counterpart to Pavlovian extinction (Scheveneels et al., 2016), i.e., the reduction of CRs through repeated experience with the CS+ in the absence of the US (Scheveneels et al., 2016). During exposure for chronic pain, patients perform feared activities

or movements in order to disconfirm catastrophic beliefs and expectations of harm (den Hollander et al., 2010; Meulders, 2020). Since these beliefs do not necessarily concern pain per se, but rather underlying pathology, movements are not always carried out pain-free in the clinic (Meulders, 2020). According to inhibitory learning theory (Craske et al., 2008; Quirk & Mueller, 2008), extinction learning does not erase the original fear memory (e.g., movement trajectory-pain); rather, it creates a novel inhibitory extinction memory (e.g., movement trajectory-no pain), which competes with the original fear memory for retrieval (Bouton, 2002; Bouton et al., 2012). The novel inhibitory memory is more context-dependent than the original fear memory (Bouton, 2002), deeming the extinguished fear memory susceptible to re-emergence (return of fear) (Bouton, 2002; Bouton et al., 2012; Haaker et al., 2014). Patients are often prevented from performing even subtle avoidance behaviors during exposure treatment (extinction with response prevention, RPE), to establish genuine fear extinction by preventing the misattribution of safety to avoidance (Lovibond et al., 2009a; Mineka, 1979).

Return of avoidance

Relapse in terms of return of avoidance is still common in clinical populations, even after extinction of fear (Bravo-Rivera et al., 2015; Mineka, 1979; Solomon et al., 1953; Vervliet & Indekeu, 2015). Although multiple mechanisms have been found to result in the return of fear (Bouton & Swartzentruber, 1991), little is known about those relating to avoidance (Gatzounis & Meulders, 2020). In this manuscript, we specifically describe spontaneous recovery, i.e., return of fear and avoidance due to the passage of time (Bouton, 2002; Bouton & Swartzentruber, 1991). The robotic arm-reaching paradigm has been implemented in a 2-day protocol to investigate return of avoidance. During day 1, participants first receive acquisition training in the paradigm, as described above (Meulders et al., 2016). In a subsequent RPE phase, participants are prevented from performing the avoidance response, i.e., they can only perform the pain-associated trajectory (T1) under extinction. During day 2, to test for the spontaneous recovery, all trajectories are available again, but in the absence of pain stimuli. Using this paradigm, we showed that, one day after successful extinction, avoidance returned (Gatzounis & Meulders, 2020).

Protocol

The protocols presented here meet the requirements of the Social and Societal Ethics committee of the KU Leuven (registration number: S-56505), and the Ethics Review Committee Psychology and Neuroscience of Maastricht University (registration numbers: 185_09_11_2017_S1 and 185_09_11_2017_S2_A1).

1. Preparing the laboratory for a test session

1.1. Before the test session: Send the participant an e-mail informing him/her about the delivery of pain stimuli, of the general outline of the experiment, and the exclusion criteria. Exclusion criteria for healthy participants comprise: being under 18 years of age; chronic pain; analphabetism or diagnosed dyslexia; pregnancy; left-handedness; current/history of cardiovascular disease, chronic or acute respiratory disease (e.g., asthma, bronchitis), neurological disease (e.g., epilepsy), and/or psychiatric disorder (e.g., clinical depression, panic/anxiety disorder); uncorrected problems with hearing or vision; having pain in the dominant hand, wrist, elbow or shoulder that may hinder performing the reaching task; presence of implanted electronic medical devices (e.g., cardiac pacemaker); and presence of any other severe medical conditions.

1.2. Aligning with COVID-19 safety precautions, ask the participant to wash/disinfect his/her hands upon arrival at the lab, and do so yourself. Wear a disposable facemask throughout the duration of the test session, and latex gloves whenever physical contact with the participant is required.

1.3. Use two separate rooms or sections for the experimental setting: one for the participant and the other for the experimenter.

1.4. Use one computer with two separate screens: one computer screen for the experimenter, and one larger television screen for the participant.

1.5. To turn on the robotic arm (e.g., HapticMaster), press the power switch in the front of the robot (specific to this robot). Subsequently, turn on the emergency switch, which may later be used to turn off the robot if necessary.

1.6. Recalibrate the robotic arm before each test day. This is done via a direct application programming interface (API) connection with the robotic arm, and only needs to be done once, at the beginning of the test day.
1.6.1. To establish the API connection, open an internet browser on the computer, and type in the specific API address of the robotic arm.
1.6.2. On the webpage, select **State** under **HapticMASTER**. Subsequently, press the **Start** button next to **Init** (for initialize).

NOTE: This is the standard calibration procedure for this robot. Different robots may require different calibration procedures.

1.7. Use a constant current stimulator, which is connected to the computer (see step 1.4). During the experiment, the pain stimulus is delivered via the experimental script, which runs on the computer. The experiment is programmed using a cross-platform game engine (see Table of Materials in Appendix D).
1.7.1. For safety reasons, disable the constant current stimulator output by switching down the orange toggle switch in the upper-right corner of the stimulator's front control panel.
1.7.2. Use the orange toggle switch in the middle of the front control panel to set the output range to x 10 mA.
1.7.3. Use the black rotary knob in the upper-left corner of the front control panel to set the pulse duration to 2 ms (2000 μs).
1.7.4. To switch on the constant current stimulator, press the power button in the lower-left corner of the front control panel.

2. Obtaining informed consent and screening for exclusion criteria

2.1. Position the participant approximately 2.5 m from the television screen (see step 1.4), at a comfortable distance (~15 cm) from the handle (sensor) of the robotic arm, in a chair with arm rests (Fig. 6.1).

2.2. Screen the participant for exclusion criteria by means of self-report (see step 1.1 for exclusion criteria).

2.3. Inform the participant about the delivery of pain stimuli and of the general outline of the experiment. Also, inform him/her that he/she is free to withdraw participation at any point during the experiment, without any repercussions. Obtain written informed consent.

2.4. To minimize physical contact with the participant, ensure that the participant section of the lab includes a table on which exclusion and informed consent forms, as well as a Tablet for questionnaires (see step 6.2) are placed before the participant's arrival. The participant should be able to access and sign the forms independently using this table.

3. Attaching the stimulation electrodes

NOTE: The pain stimulus is a 2 ms square-wave electrical stimulus delivered cutaneously through two stainless steel bar stimulation electrodes (electrode diameter 8 mm, interelectrode distance 30 mm).

3.1. If the participant is wearing long sleeves, ask him/her to roll up the sleeve on his/her right arm at least 10 cm above his/her elbow.

3.2. Fill the center of the stimulation electrodes with conductive electrolyte gel and plug the electrode cables to the emergency switch, which is connected to the constant current stimulator in the experimenter section of the lab.

3.3. Attach the stimulation electrodes over the triceps tendon of the participant's right arm using a strap. Make sure the strap is neither too tight nor too loose. Once the electrodes have been attached, tell the participant to relax his/her arm.

4. Calibrating the pain stimulus

4.1. Explain the pain calibration procedure and corresponding scale by presenting it on the television screen (see step 1.4).

4.1.1. Clarify to the participant that he/she may choose the stimulus which he/she will receive during the experiment, but explain that for data integrity he/she is asked to select a stimulus that he/she would describe as "significantly painful and demanding some effort to tolerate".

4.1.2. Ask the participant to rate each stimulus on the numerical scale presented on the television screen, ranging from 0–10, where 0 is labeled as "I feel nothing"; 1 as "I feel something, but this is not unpleasant; it is only a sensation" (i.e., detection threshold), 2 as "the stimulus is not yet painful, but is beginning to be unpleasant"; 3 as "the stimulus starts being painful" (i.e. pain threshold); and 10 as "this is the worst pain I can imagine".

4.2. Enable the constant current stimulator output by switching up the orange toggle switch (see step 1.7.1).

4.3. During the pain calibration procedure, manually increase the intensity of the pain stimuli using the rotary knob on the front control panel of the constant current stimulator. The intensity of the pain stimulus can be seen above this knob.

4.3.1. Start with an intensity of 1 mA, and gradually increase the intensity in a stepwise manner, with increases of 1, 2, 3, and 4 mA increments. Use the following order of stimulus presentations in mA: 1, 2, 4, 6, 8, 11, 14, 17, 20, 24, 28, 32, 36, 40, 44, 48, 52, etc.

4.4. To deliver the pain stimuli one stimulus at a time, manually trigger the constant current stimulator by pressing the orange trigger button on the front control panel.

4.4.1. Announce each stimulus to the participant before triggering the constant current stimulator.

4.5. Terminate the calibration procedure once the participant reaches a pain intensity level which he/she would describe as "significantly painful and demanding some effort to tolerate". Ideally, this should correspond to a 7–8 on the pain calibration rating scale.

4.6. Document the participant's final pain intensity in mA and his/her pain intensity rating (0–10) and maintain this intensity for the remainder of the experiment.

5. Running the experimental task

5.1. Verbally inform the participant that he/she will receive instructions about the robotic arm-reaching paradigm on the television screen in front of him/her, after which he/she will be able to practice the task under the supervision of the experimenter.

5.2. Provide the participant with standardized written instructions of the task on-screen.

5.3. Practice: Via the experimental script, on the television screen, present three arches (T1–T3) situated midway through the movement plane. The easiest arm movement (T1) is paired with no deviation or resistance, the middle arm movement (T2) is paired with moderate deviation and resistance, and the furthest arm movement (T3) is paired with the largest deviation and strongest resistance.

5.3.1. Instruct the participant to use his/her dominant hand to operate the sensor of the robotic arm, represented by a green ball on the television screen, and to move the ball/sensor from

a starting point at the lower-left corner of the movement plane, to a target at the upper-left corner of the movement plane.

5.3.2. Instruct the participant that he/she can freely choose which one of the available movement trajectories to perform on each trial.

5.4. Do not administer the pain stimulus (see section 3.1 and step 5.7.6) during the practice phase. However, ensure that the relationship between deviation and resistance (see step 5.3) is in place.

5.5. Provide the participant with verbal feedback while they perform the practice phase.

5.5.1. Ensure the participant does not start moving before the visual and auditory "start signals", and that he/she releases the robotic arm immediately when the visual and auditory "stop signals" are presented.

NOTE: Two distinct auditory signals (a "start tone" and a "scoring tone") and two distinct visual signals (the target and a virtual "traffic light" turning green and red, respectively; Fig. 6.1) have been used as start and stop signals. Auditory and visual start signals are presented simultaneously, as are auditory and visual stop signals.

5.5.2. Instruct the participant to provide self-report measures of pain-expectancy and fear of movement-related pain on a continuous rating scale, by scrolling to the left and right on the scale using two respective foot pedals on a triple foot switch. Instruct him/her to confirm his/her answer using a third foot pedal.

NOTE: Present self-report questions on fixed, predetermined trials, for each movement trajectory separately. Ensure, via the experimental script, that the robotic arm is immobilized and remains fixed during the time the participant is responding to the questions.

5.6. At the end of the practice phase, respond to the participant's questions. Leave the experimental section/room and dim the lights. The participant starts the experiment himself/herself by pressing the 'Confirm' foot pedal (see step 5.5.2).

5.7. Acquisition: During avoidance acquisition, similarly to the practice phase, let the participant choose which movement trajectory (T1–T3) to perform on each trial.

5.7.1. During avoidance acquisition, subject the participant to the experimental Response-Outcome (movement trajectory-pain) contingencies, and to the avoidance-costs, i.e., the tradeoff between pain and effort, via the experimental script.

5.7.2. Specifically, if the participant performs the easiest movement trajectory (T1), always present the pain stimulus (100% pain/no deviation or resistance).

5.7.3. If he/she performs the middle movement trajectory (T2), present the pain stimulus with a 50% chance, but ensure he/she will have to exert more effort (moderate deviation and resistance).

5.7.4. If the participant performs the furthest, most effortful movement trajectory (T3), do not present the pain stimulus at all, but ensure that he/she will have to exert the most effort to reach the target (0% pain/largest deviation, strongest resistance).

NOTE: If applicable to the design, a Yoked Group can be used as control. In yoked procedures, each control participant is paired with a participant in the experimental group, such that the two receive the same reinforcement schedules (Davis & Bitterman, 1971). Thus, in the current paradigm, each Yoked Group participant receives pain stimuli on the same trials as his/her Experimental Group counterpart, regardless of the trajectories he/she chooses. No acquisition of avoidance behavior is expected in the Yoked Group, given the lack of manipulated Response-Outcome (movement trajectory-pain) contingencies.

5.7.5. Where applicable, save data from each Experimental Group participant on the computer (see section 1.4), and use as reference for the reinforcement schedules of each Yoked (control) Group participant.

5.7.5.1. If using a Yoked procedure (i.e., each control participant is paired with a participant in the experimental group, such that the two receive the same reinforcement schedules (Davis & Bitterman, 1971)), allocate participants to groups using a randomization schedule with the rule that the first participant must be in the Experimental Group. Following this, participants are assigned to either group randomly, as long as, at each point, the number of Experimental Group participants exceeds the number of Yoked Group participants.

5.7.6. On trials with a pain stimulus, present the pain stimulus once two-thirds of the movement has been performed, i.e., once the participant has moved through a trajectory arch. The constant current stimulator is automatically triggered via the experimental script.

5.7.7. Successful trial-completion is indicated by the presentation of visual and auditory stop signals. Subsequently, ensure, via the experimental script, that the robotic arm

automatically returns to its starting position where it remains fixed. After 3,000 ms, present the visual and auditory start signals, and the participant can start the next trial.

NOTE: Trial duration differs between trials and participants, due to differences in movement speeds. The number of trials per experimental phase can also change between experiments. We recommend a minimum of 2 x 12 trials for successful acquisition of avoidance. Including the steps described above, the acquisition protocol lasts approximately 45 min.

5.8. Generalization: In the generalization protocol, test for generalization of avoidance after the acquisition phase (see section 5.7).

NOTE: When testing for generalization of avoidance, the on-screen trajectory arches are separated during acquisition, to leave room for the generalization trajectory arches, which are positioned between the acquisition trajectory arches (see Fig. 6.1).

5.8.1. On the television screen, present three novel movement trajectories instead of the acquisition trajectories T1–T3. Ensure that these "generalization trajectories" (G1–G3) are located adjacent to the acquisition trajectories. Specifically, G1 is situated between T1 and T2, G2 between T2 and T3, and G3 to the right of T3 (see Fig. 6.1). Do not pair generalization trajectories with the pain stimulus.

NOTE: Including the steps described above, with a generalization phase of 3 x 12 trials, the avoidance generalization protocol lasts approximately 1.5 h. A Yoked Group (Davis & Bitterman, 1971) is required for testing generalization of avoidance (see step 5.7.5). However, different controls can be used depending on the specific research question (cf. context modulation of avoidance in a within-subjects design (Meulders et al., 2020)).

5.9. Extinction with response prevention (RPE): In the RPE protocol, after the acquisition phase (see section 5.7), provide the participants with standardized written instructions stating that in the upcoming phase they are only allowed to perform T1.

5.9.1. During the RPE phase, via the experimental script, visually (e.g., blocking the trajectory arches with a gate) and/or haptically (e.g., block participant's arm movement with a haptic wall) block T2 and T3, so that only T1 is available. T1 is not paired with the pain stimulus

during this phase. Including the steps described above, with an RPE phase of 4 x 12 trials, this session lasts approximately 60 min.

5.10. Test of spontaneous recovery: For testing spontaneous recovery of avoidance, administer a 2-day protocol with 24 h ± 3 h in between sessions. On day 1, administer the RPE protocol (see section 5.9).

5.10.1. On day 2, attach the stimulation electrodes (see section 3). Provide brief on-screen refresher instructions of the task. Do not include any information regarding the pain stimuli.

5.10.2. Present the three acquisition trajectories (T1–T3, cf. acquisition phase, see section 5.7), in the absence of the pain stimulus. Including the post-experimental questionnaire (see section 6.2), and a spontaneous recovery phase of 4 x 12 trials, this session lasts approximately 45 min.

NOTE: To prevent reinstatement of fear (i.e., return of fear following unexpected encounters with the pain stimulus(Haaker et al., 2014); see discussion), do not recalibrate the pain stimulus on day 2.

6. Concluding the experiment

6.1. Once the participant has completed the experiment, detach the stimulation electrodes.

6.2. Provide the participant with a Tablet located on the table in the participant's section of the lab (see section 2.4), for responding to an exit questionnaire inquiring about the intensity and unpleasantness of the pain stimulus and avoidance-costs, as well as awareness of the experimental Response-Outcome (movement trajectory-pain) contingencies.

6.3. While the participant completes the psychological trait questionnaires, clean off the electrolyte gel from the stimulation electrodes.

6.4. Once the participant has finished completing the psychological trait questionnaires, provide him/her with a debriefing and reimbursement.

6.5. Clean the stimulation electrodes thoroughly with a disinfectant solution appropriate for cleaning medical instruments; remove all the gel inside and around the electrodes. Dry the electrodes with soft tissue paper. Clean the sensor of the robotic arm with disinfectant wipes or spray.

Representative results: avoidance behavior

Acquisition of avoidance behavior is demonstrated by participants avoiding more (showing larger maximal deviations from the shortest trajectory) at the end of an acquisition phase, compared to the beginning of the acquisition phase (Fig. 6.2, indicated by A) (Gatzounis & Meulders, 2020), or as compared to a Yoked control group (Fig. 6.3) (Davis & Bitterman, 1971; Glogan, Gatzounis, Meulders, et al., 2020).

Acquisition is a prerequisite for *generalization*. Generalization of avoidance behavior is indicated by participants in the Experimental Group avoiding (deviating) more than the Yoked Group (Davis & Bitterman, 1971) at the beginning of the generalization phase (similar data pattern as in Fig. 6.3). Given that generalization is tested in the absence of pain stimuli, avoidance behavior may decrease throughout the generalization phase. Furthermore, a general decrease in avoidance behavior between the end of the acquisition phase and the beginning of the generalization phase (generalization decrement) can be expected. This is a result of the introduction of novel movement trajectories, which may constitute a context-switch (Bouton et al., 2014; Bouton & Todd, 2014). In a previous study, we did not find generalization of avoidance, possibly due to specific parameters of the paradigm (Glogan, Gatzounis, Meulders, et al., 2020).

Acquisition is a prerequisite for *extinction*. During extinction of avoidance behavior with response prevention, participants are only allowed to perform the previously painful movement trajectory (T1), whereas the other two trajectories (T2 and T3) are prohibited. Therefore, given that participants only have the option of performing T1, and thus the observed data pattern does not reflect their own choices, i.e., genuine extinction of avoidance behavior, extinction of avoidance is not included in the analyses (Fig. 6.2). *Spontaneous recovery* of avoidance behavior is indicated by participants avoiding more at the beginning of the test of spontaneous recovery, compared to the end of the RPE phase (Fig. 6.2B).

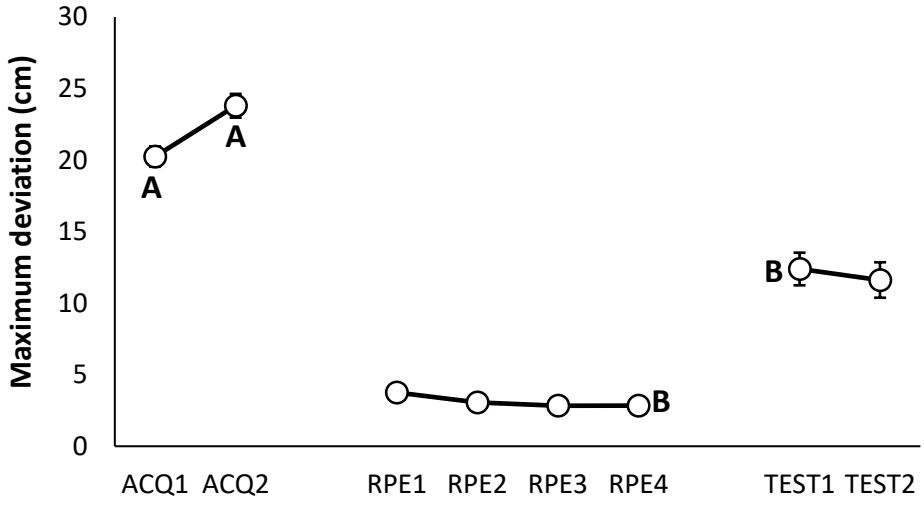

Figure 6.2: Representative data of avoidance behavior during the acquisition, extinction with response prevention, and test of spontaneous recovery phases (Gatzounis & Meulders, 2020). Mean maximum deviation (in centimeters) from the shortest trajectory to the target during acquisition (ACQ1–2), extinction with response prevention (RPE1–4), and spontaneous recovery (TEST1–2). Note that, participants are only allowed to perform the shortest trajectory (T1) during the RPE phase. Error bars represent standard error of the mean (SEM). Data in this figure is from 30 participants (9 men, 21 women; mean age = 21.90; Gatzounis & Meulders, 2020). This figure is modified with permission from (Gatzounis & Meulders, 2020).

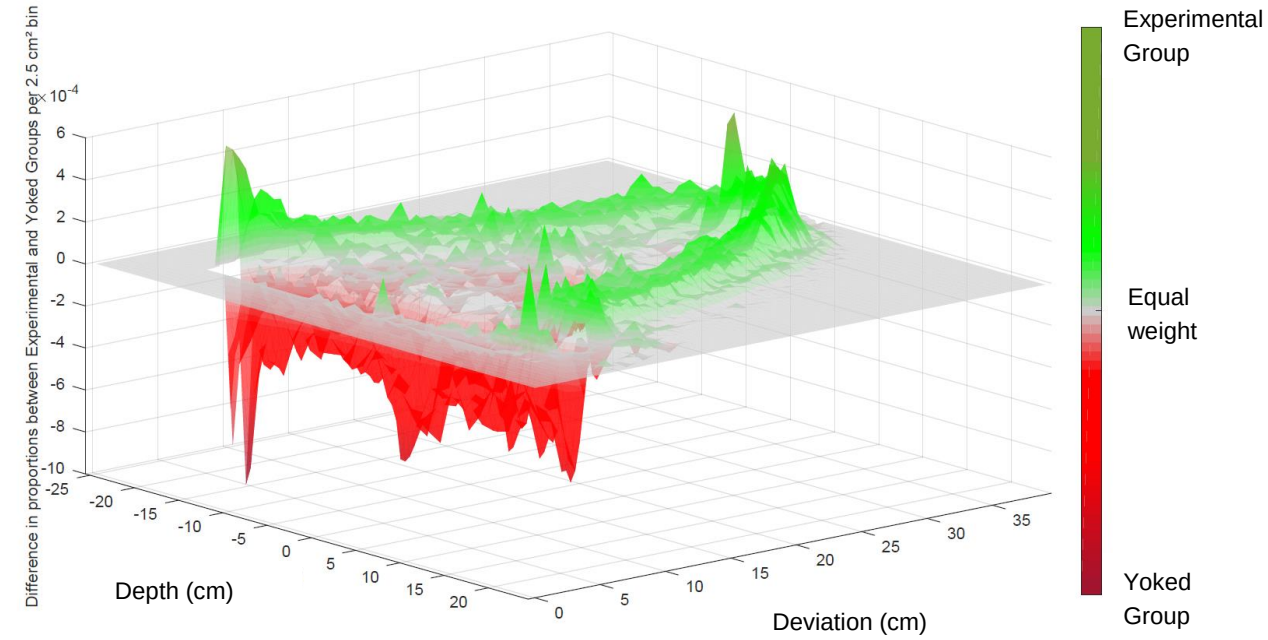

Figure 6.3: Representative data of avoidance behavior during the acquisition phase. Relative proportions of movements between the Experimental and Yoked Groups, within the experimental movement plane. Top, green patterns represent movements predominantly performed by the Experimental Group, and bottom, red patterns represent movements predominantly performed by the Yoked Group. "Depth" indicates the direction from starting point to target, i.e. the shortest possible trajectory from the starting point to the target. "Deviation" indicates horizontal deviation from the shortest possible movement trajectory to the longest possible movement trajectory. Data in this figure are from 70 participants (48 female, mean age = 22 years; **Study 3**).

Representative results: self-reports

Acquisition of fear and pain-expectancy is evidenced by participants reporting lower fear for T3 compared to T1 and T2, and expecting the pain stimulus less during T3 compared to T1 and T2 (Meulders et al., 2016). Differential self-reports between T1 and T3 are of primary interest, because T2 is ambiguous. Non-differential self-reports between T1 and T2 have also been found, with both differing from T3 (Glogan, Gatzounis, Meulders, et al., 2020) (Fig. 6.4A, and Fig. 6.5A).

Generalization of fear and pain-expectancy is indicated by a similar pattern to that of the acquisition phase, i.e., by participants in the Experimental Group reporting lower fear to G3 compared to G1 and G2, and expecting the pain stimulus less during G3 compared to G1 and G2, at the beginning of the generalization phase. As in the acquisition phase, differential self-reports between G1 and G3 are of primary interest (Fig. 6.4B). Non-differential pain-related fear between G1 and G2 have been reported so far, with both differing from G3 (Glogan, Gatzounis, Meulders, et al., 2020). Furthermore, given that generalization is tested in the absence of pain stimuli, participants may report less fear and pain-expectancies throughout the generalization phase. Furthermore, a general decrease in fear and pain-expectancies toward the novel generalization trajectories, compared to the acquisition trajectories (generalization decrement) can be expected. In a previous study, we found generalization of fear and pain-expectancies, despite avoidance not generalizing (Glogan, Gatzounis, Meulders, et al., 2020).

Extinction of fear and pain-expectancies is evident when participants report lower fear for T1 and expect the pain stimulus less when performing T1, at the end of the RPE phase, compared to the end of the acquisition phase. (Fig. 6.5B).

Extinction of self-report measures is a prerequisite for spontaneous recovery. Spontaneous recovery of fear and pain-expectancy is indicated by participants reporting higher fear and pain-expectancy for T1, during the beginning of the test of spontaneous recovery, compared to the end of the RPE phase (Fig. 6.5C).

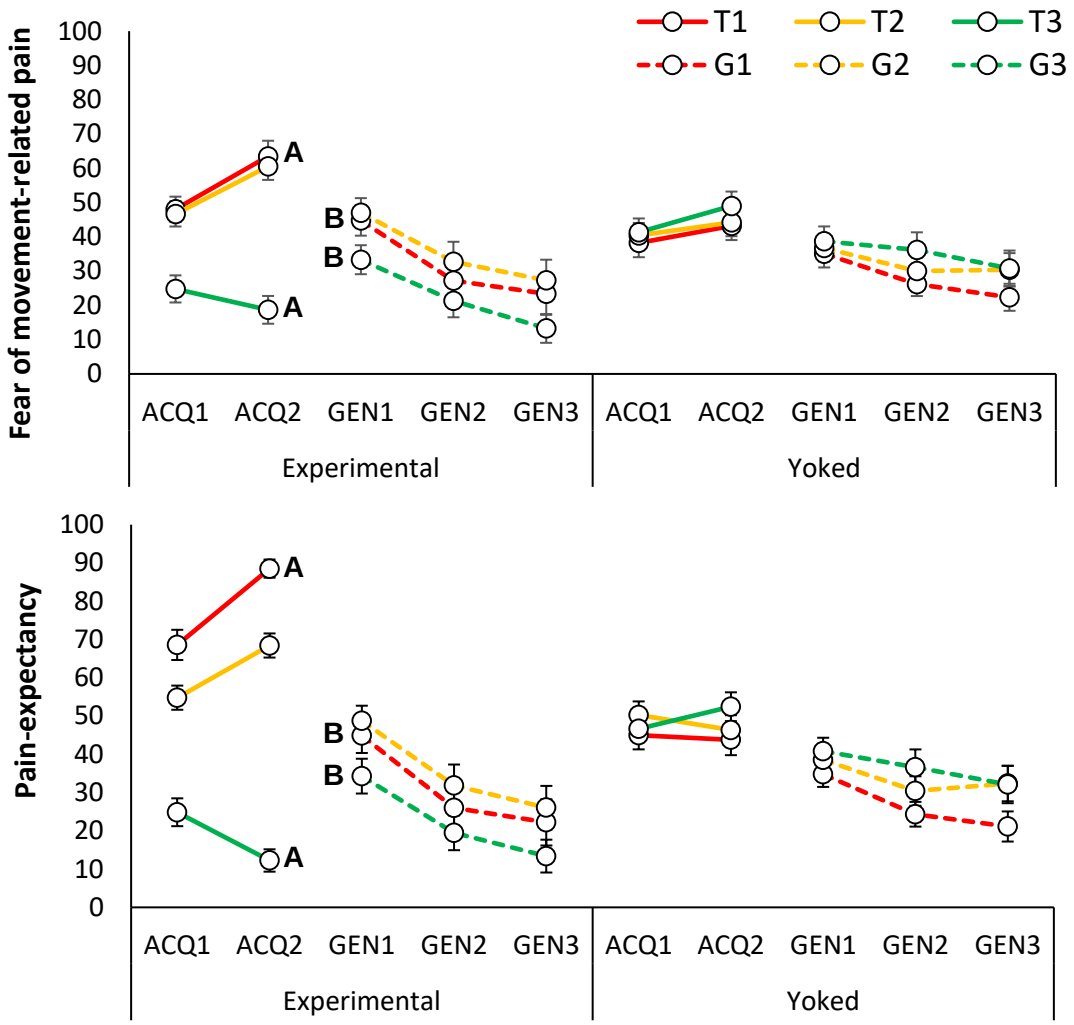

Figure 6.4: Representative data of fear of movement-related pain (top panel) and pain-expectancies (bottom panel) during the acquisition and generalization phases (Glogan, Gatzounis, Meulders, et al., 2020). Mean fear of movement-related pain towards the acquisition trajectories in the Experimental and Yoked (Davis & Bitterman, 1971) groups during the acquisition blocks (ACQ1–3), and generalization blocks (GEN1–3). Note that during the acquisition phase, self-reports are provided for trajectories T1–T3 and during the generalization phase, for G1–G3. Error bars represent SEM. Data in this figure are from 64 participants (32 per group; Experimental Group: 10 men, 22 women, mean age = 22.88; Yoked Group: 12 men, 20 women; mean age = 23.44; Glogan, Gatzounis, Meulders, et al., 2020). This figure is modified with permission from (Glogan, Gatzounis, Meulders, et al., 2020).

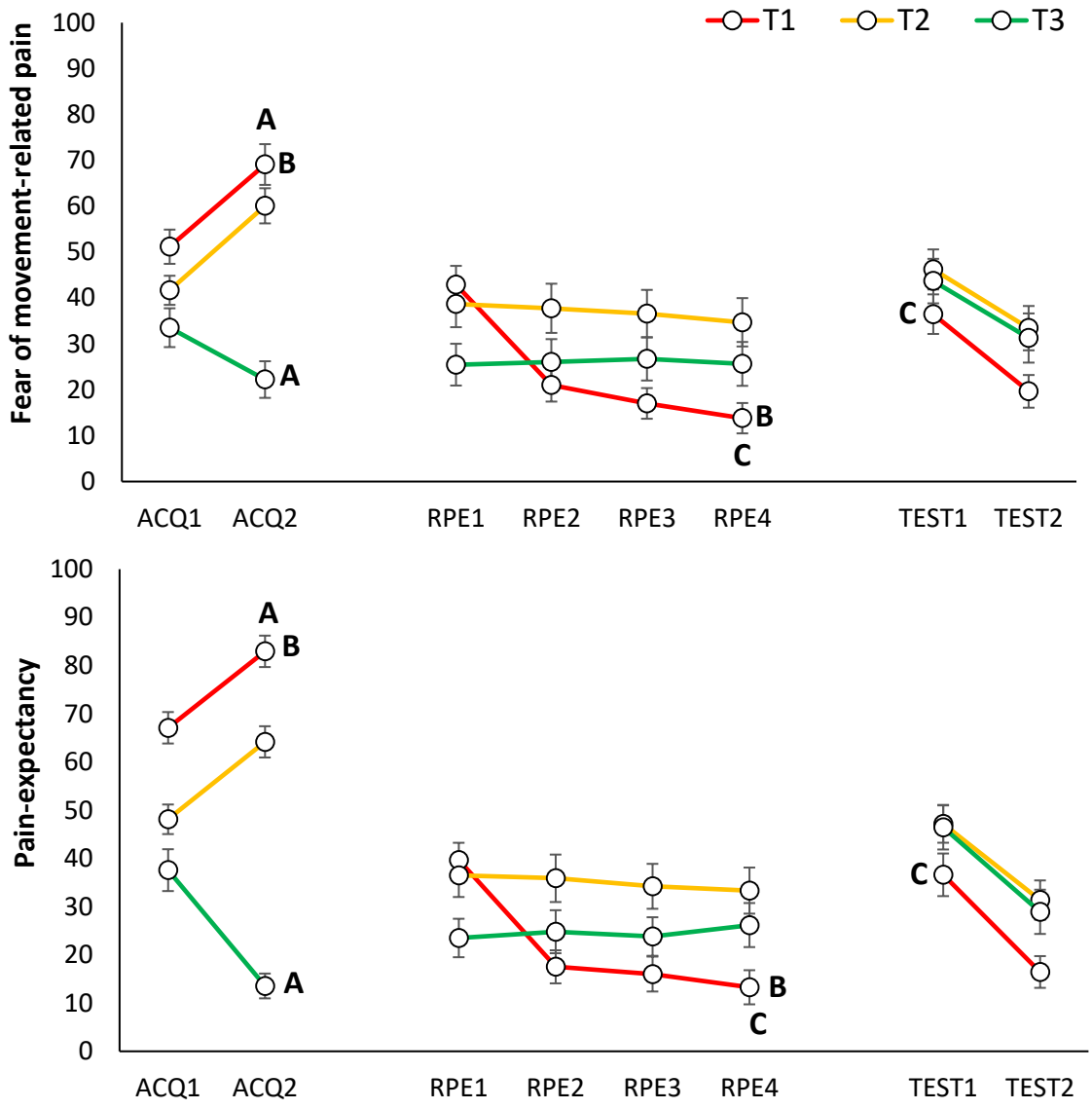

Figure 6.5: Representative data of fear of movement-related pain (top panel) and pain-expectancy (bottom panel) during the acquisition, extinction with response prevention, and test of spontaneous recovery phases (Gatzounis & Meulders, 2020). Mean fear of movement-related pain toward the different trajectories (T1–T3) during acquisition (ACQ1–2), extinction with response prevention (RPE1–4), and spontaneous recovery (TEST1–2). Error bars represent SEM. Data in this figure are from 30 participants (9 men, 21 women; mean age = 21.90; Gatzounis & Meulders, 2020). This figure is modified with permission from (Gatzounis & Meulders, 2020).

Discussion

Given the key role of avoidance in chronic pain disability (Crombez et al., 2012; Leeuw et al., 2007; A. Meulders, 2019; Vlaeyen & Linton, 2000, 2012), and the limitations faced by traditional avoidance paradigms (Krypotos et al., 2018), there is a need for methods to investigate (pain-related) avoidance behavior. The robotic arm-reaching paradigm presented here addresses a number of these limitations. We have employed the paradigm in a series of studies, which have consistently demonstrated acquisition of avoidance, and these effects have extended to our self-report measures of pain-expectancy and fear of movement-related pain (Gatzounis & Meulders, 2020; Glogan, Gatzounis, Meulders, et al., 2020; Meulders et al., 2020; Meulders et al., 2016). However, we have also found dissociations between fear and avoidance (Glogan, Gatzounis, Meulders, et al., 2020) that may be genuine and informative, suggesting that the two do not always share a one-to-one relationship (Bravo-Rivera et al., 2015; Krypotos et al., 2015; A. Meulders, 2019; Mineka, 1979; Vervliet & Indekeu, 2015). Additionally, the paradigm presents multiple opportunities for investigating different aspects of avoidance behavior, such as generalization (Glogan, Gatzounis, Meulders, et al., 2020), extinction with response prevention (Gatzounis & Meulders, 2020), and post-extinction return of avoidance (Gatzounis & Meulders, 2020), as described in the current manuscript.

The current method offers many advantages over traditional avoidance paradigms. First, instead of performing an experimenter-instructed avoidance response, participants in the robotic arm-reaching paradigm acquire avoidance behavior themselves. The paradigm thus better models real life situations, where avoidance behavior emerges naturally as a response to pain (Volders et al., 2015). Understanding the processes underlying how avoidance is acquired, can provide insight into how avoidance can subsequently become pathological, and inspire ways in which these processes can be directly targeted during treatment (Pittig et al., 2020). For example, methodological modifications, such as manipulating experimental reward to increase approach and reduce avoidance tendencies (Pittig & Dehler, 2019; Van Damme et al., 2012), can allow closer investigation of the behavioral and cognitive processes underlying the acquisition of maladaptive avoidance. With regard to this, the acquisition of avoidance demonstrated with the robotic arm-reaching paradigm can be easily applied to investigate excessive generalization of avoidance to safe stimuli (Glogan, Gatzounis, Meulders, et al., 2020). A second advantage is that the continuous nature of the avoidance response in the current paradigm allows us to examine for whom avoidance might become excessive, as it provides more detailed data than a dichotomous measure. This increased detail in the data allows heightened sensitivity for picking up individual differences, by means of comparing deviation scores between participants. Such a continuous measure is also

more ecologically valid, as avoidance in real life can occur at varying degrees. For example, pain-related avoidance can range from subtle (e.g., postural changes or changed breathing when performing a movement) to complete avoidance (e.g., being bedridden). Furthermore, in addition to incorporating a cost to avoidance, the current avoidance response demands some physical effort, meaning that costs increase with time throughout the task. This accurately models real life, where avoidance can become increasingly costly for the individual over a period of time (Volders et al., 2015). For example, prolonged or regular absenteeism becomes costly from a financial point of view (Breivik et al., 2006; Langley et al., 2010). Finally, given the low cost associated with the previously used instructed button-press response, it is hard to disentangle whether participants in traditional avoidance paradigms avoid due to genuine fear, or simply due to automatic following of task instructions. In contrast, given the high-effort and uninstructed nature of the avoidance response in the current paradigm, it seems likely that any avoidance behavior observed models' genuine self-motivated avoidance.

In addition to addressing limitations of previous methodologies, the robotic arm-reaching paradigm offers many opportunities for investigating further aspects of avoidance behavior, as demonstrated in the current manuscript by the avoidance generalization and RPE protocols. It is noteworthy that, we previously observed a dissociation between self-reports and avoidance, with fear and pain-expectancies generalizing to the novel movement trajectories, while avoidance did not. There are several plausible explanations for the observed discrepancy between fear and avoidance (Glogan, Gatzounis, Meulders, et al., 2020), which we are currently investigating. However, this dissociation may also be a genuine and informative finding, which in fact adds to previous literature suggesting that fear and avoidance do not always occur in synchrony (Bravo-Rivera et al., 2015; Krypotos et al., 2015; A. Meulders, 2019; Mineka, 1979; Vervliet & Indekeu, 2015), especially when the avoidance response is costly (Claes et al., 2015; Claes et al., 2014). This finding emphasizes the importance of experimentally investigating avoidance behavior itself, as distinct processes most likely contribute to different aspects of fear learning (Soeter & Kindt, 2010)·(LeDoux & Daw, 2018), and these processes would be difficult to uncover by solely measuring self-reports and psychophysiological indices of fear. In addition to generalization of avoidance to novel movements, the robotic arm-reaching paradigm has also been applied to study generalization of avoidance to novel contexts (Meulders et al., 2020). So far, context-based generalization of avoidance has been investigated using different colored screens as contextual cues (Meulders et al., 2020). However, Virtual Reality (VR) could be easily implemented with the current paradigm to increase the ecological validity of the experimental contexts. VR could also be

applied to study category-based avoidance generalization, such as generalization of avoidance between different action categories (Glogan et al., 2018; Meulders, Vandael, et al., 2017).

Additional adaptations may also be implemented in the RPE protocol. Besides using a 2-day protocol for the investigation of spontaneous recovery (Gatzounis & Meulders, 2020), we have also investigated whether pain-related avoidance behavior returns not with the passage of time, but after unexpected encounters with the pain stimulus (reinstatement) (Haaker et al., 2014) in a 1-day protocol. Furthermore, to examine the proprioceptive underpinnings of pain-related avoidance behavior more closely, the paradigm can be modified to include less or no visual information. This is something we are currently investigating in our lab.

Finally, given that physically moving away from an aversive stimulus represents a species-specific defensive response (Bolles, 1970), not unique to fear and pain, this type of operationalization of avoidance permits investigation of many different types of avoidance as well. For example, the paradigm can potentially be applied to examine, not only avoidance of painful stimuli, but also avoidance of other types of aversive stimuli, such as those inducing disgust or embarrassment (McCambridge & Consedine, 2014; Shook et al., 2019).

The described protocol can also be easily extended to include psychophysiological fear measures. Although not described here, we have incorporated eye-blink startle responses, as well as electroencephalography (EEG), into the robotic arm-reaching paradigm. The eye-blink startle measure offers a fear-specific measure of reflexive defensive responses (Lipp et al., 1994; van Well et al., 2012), which can provide additional insight into the mechanisms underlying avoidance behavior and its relationship to fear, whereas implementing EEG to the paradigm enables investigation into specific neural correlates of avoidance behavior (Davidson et al., 2000). Additionally, the skin-conductance response (SCR) (Benedek & Kaernbach, 2010), as well as online self-report ratings of relief-pleasantness (Leknes et al., 2011; Vervliet et al., 2017a) could be included as measures of relief (Leknes et al., 2013). SCRs have been previously found to correlate with relief (Vervliet et al., 2017b)—a proposed reinforcer of avoidance (Leknes et al., 2011; Vervliet et al., 2017a) given its inherent positive valence in response to the omission of negative events (Deutsch et al., 2015; Vlemincx et al., 2009). Finally, heart rate (HR) and heart rate variability (HRV) are easily implementable measures that have been linked to multiple aversive emotions associated with avoidance, such as fear, disgust, and embarrassment (Kreibig, 2010).

Despite its strengths, we acknowledge that the robotic arm-reaching paradigm also has its limitations. For example, the paradigm is not easily transferable to other laboratories, as the equipment used in, and required for the paradigm (e.g., robot and constant current stimulator) are expensive, limiting the widespread use of the paradigm and its implementation by other

laboratories. However, note that similar robots, which are relatively common in rehabilitation clinics, can be programmed in the same way, and more affordable constant current stimulators are available as well. It is also noteworthy that, in the current method the discriminative stimulus (S^D) and the instrumental response are intertwined. This is in contrast to traditional avoidance paradigms, where fear is first acquired towards the CS during the Pavlovian phase, and avoidance is examined in a subsequent instrumental phase. However, the temporal relationship between fear and avoidance is not strictly unidirectional (Pittig et al., 2020). Although the current paradigm allows closer investigation of the temporal dynamics of avoidance-emergence in relation to fear-emergence, the measures we have employed so far do not allow us to accurately disentangle the temporal dynamics of fear and avoidance. Currently, avoidance behavior in the paradigm can be examined at a trial-by-trial basis, whereas fear and expectancy ratings are only collected at discrete, specific time points during the task, to not interfere with task flow. However, to allow precise comparisons between fear and avoidance, a future study could use a more continuous measure of fear, for example, by means of a dial (Pappens et al., 2012), single-sensor EEG (de Man & Stassen, 2016), or fear-potentiated startle, to allow a detailed understanding of fear-emergence towards the different trajectories, in relation to avoidance. Finally, only electrocutaneous stimuli have so far been used in the robotic arm-reaching paradigm as pain stimuli, for reasons of consistency and comparability with previous studies of pain-related fear (Meulders et al., 2013; Meulders et al., 2011; Meulders & Vlaeyen, 2013). However, electrocutaneous stimuli may not fully mimic the more tonic pain experienced by chronic pain patients, given that they produce a relatively phasic, uncommon, and unnatural pain experience (Moore et al., 2013). Other pain-induction methods, such as ischemic stimulation (Lewis, 1932) and exercise-induced (e.g., delayed onset muscle soreness, DOMS) (Niederstrasser et al., 2015; Niederstrasser et al., 2014) pain have been argued to be better experimental analogues of musculoskeletal pain, given their natural and endogenous nature (Moore et al., 2013). These pain-induction methods could be employed in the robotic arm-reaching paradigm in the future. Despite these limitations, the ability of the current paradigm to consistently demonstrate acquisition of fear and avoidance using such entwined S^Ds and Rs is in itself interesting and novel. Furthermore, we believe that the robotic arm-reaching paradigm can in and of itself further the discussion of the need for more ecologically valid avoidance paradigms (Krypotos et al., 2018). In addition, the paradigm has the potential to pave the way for developing better avoidance paradigms in general, by providing an example of how problems in the field can be tackled in an innovative manner.

In conclusion, the robotic arm-reaching paradigm offers a promising route to improving the ecological validity of investigations into avoidance behavior, and to furthering our

understanding of the underlying processes. Using the paradigm, we have already obtained interesting results, which may not have been uncovered by solely assessing passive correlates of fear such as verbal reports and physiological arousal. Yet, extensions to the paradigm have provided some inconclusive results, which require further investigation and refinement of the procedure. Despite this, the robotic arm-reaching paradigm is a huge leap forward with respect to ecological validity in the paradigms used to study avoidance behavior.

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CHAPTER 7
GENERAL DISCUSSION

Research aims and methodology

Fear and avoidance are adaptive responses to pain, which normally signals bodily threat. Yet in chronic pain, pain-related fear and avoidance seem to come uncoupled from their protective function (Merskey & Bogduk, 1994), thus causing interference with daily life activities, and unnecessary distress. Furthermore, fear and avoidance can become excessive if they generalize to safe movements and behaviors (Dymond et al., 2015). Importantly, avoidance in particular, can culminate in disability, because it may directly lead to reduced physical fitness and engagement in daily activities (A. Meulders, 2019; Vlaeyen & Linton, 2000). In this PhD project, we aimed to investigate the mechanisms underlying the generalization of pain-related avoidance behavior. Using a novel pain-related avoidance paradigm, we aimed to address the following research questions: 1) Do pain-free participants generalize costly pain-related avoidance based on physical similarity between movements (**Chapter 2**)? 2) What are the boundary conditions of costly pain-related avoidance generalization in healthy participants (**Chapter 3**)? 3) How closely do concurrently measured pain-related fear- and costly pain-related avoidance generalization correspond in one task (**Chapter 4**)? 4) Do healthy participants generalize pain-related avoidance based on conceptual knowledge (**Chapter 5**)?

Our primary methodology to investigate these questions was a novel pain-related avoidance conditioning paradigm, in which participants learned to avoid pain through trial-and-error. Participants could avoid pain by moving away from a painful movement trajectory. However, the further they moved from the painful movement trajectory, the more effort they needed to exert (acquisition phase). Subsequently, participants were presented with novel movement options resembling the original acquisition movement trajectories (generalization phase). Unbeknown to participants, none of these novel movements were paired with pain. Thus, we aimed to model how people in pain might generalize pain-related avoidance from one pain-associated movement to other, similar yet safe movements. This question is relevant because, although judicious avoidance is adaptive when pain is acute, when avoidance becomes excessive, i.e. when it generalizes to objectively safe behaviors, it can disrupt daily functioning and cause unnecessary suffering (Dymond et al., 2015; A. Meulders, 2019).

In the paradigm, participants used a robotic arm to perform arm-reaching movements from a starting point to a target, and freely chose between three possible movement trajectories (operant responses) to do so. The movement trajectories were represented on-screen by three arches (trajectories T1-3) situated midway through the movement plane. The movement trajectories differed from each other in terms of effort, and likelihood of being paired with a painful electrical stimulus (the negative outcome). Effort was manipulated as deviation from the shortest possible movement trajectory (T1; a straight line from start to target) and force needed to overcome resistance from the robotic arm. Furthermore, pain administration was programmed such that the shortest, easiest movement trajectory (T1), positioned to the extreme left of the movement plane, was always paired with pain (100% pain/no deviation or resistance). A middle trajectory (T2) was paired with a 50% chance of pain, but more effort was required to perform it. The longest, most effortful movement trajectory (T3) was never paired with pain but required the most effort to reach the target (0% pain/largest deviation, strongest resistance). Costly avoidance behavior was operationalized as the maximum deviation from the straight line from start to target, per trial. Furthermore, as a control, each participant in a Yoked Group was matched to a participant in the Experimental Group, and thus received pain on the same trials as their Experimental Group counterpart, irrespective of their chosen movement trajectories. Thus, the experimental movement-pain contingencies of the current studies did not apply to the Yoked Group, and therefore no avoidance learning was expected to occur in this group. Online self-reported fear of pain and pain-expectancies were collected as measures of conditioned fear (and contingency-awareness) regarding the different movement trajectories. In a subsequent generalization phase, three novel movement trajectories were introduced in the absence of the pain stimulus. These generalization trajectories (G1-3) lay on the same continuum as the acquisition trajectories, resembling each of these trajectories, respectively. That is, generalization trajectory G1 was situated between T1 and T2, G2 between T2 and T3, and G3 to the right of T3. In this way, generalization of avoidance to novel, safe movements were examined.

Summary and discussion of the findings

Perceptual generalization of pain-related avoidance

In **Study 1** (see Chapter 2), we investigated the generalization of (perceptual) pain-related avoidance, using the paradigm described above. Participants in the Experimental Group successfully acquired the experimental response-outcome contingencies, that is, pain-expectancy reports were highest for T1 (100% punishment) and lowest for T3 (0% punishment), with T2 (50% punishment) in the middle. Participants also learned to fear the pain-associated movement

trajectories in comparison to the safe one, as shown by significantly higher pain-related fear for T1 and T2 compared to T3. We also successfully replicated the acquisition of avoidance behavior, first demonstrated by Meulders and colleagues (2016). Specifically, the Experimental Group deviated more from the shortest acquisition trajectory compared to the Yoked Group, during the acquisition phase (Meulders et al., 2016). Of importance, pain-related fear and pain-expectancies also generalized to the novel generalization trajectories. That is, participants feared and expected the pain stimulus to occur more during G1 and G2 movements, compared to G3, at the beginning of the generalization phase. Finally, and contrary to our main hypothesis, transfer of avoidance behavior to the generalization movement trajectories was absent, that is, there were no differences in avoidance behavior between the Experimental and Yoked Groups during the generalization phase. Trial-level analyses showed that the avoidance effect was absent already on the first trial of the generalization phase (see Figure 7.1.). Thus, avoidance behavior did not generalize in this study.

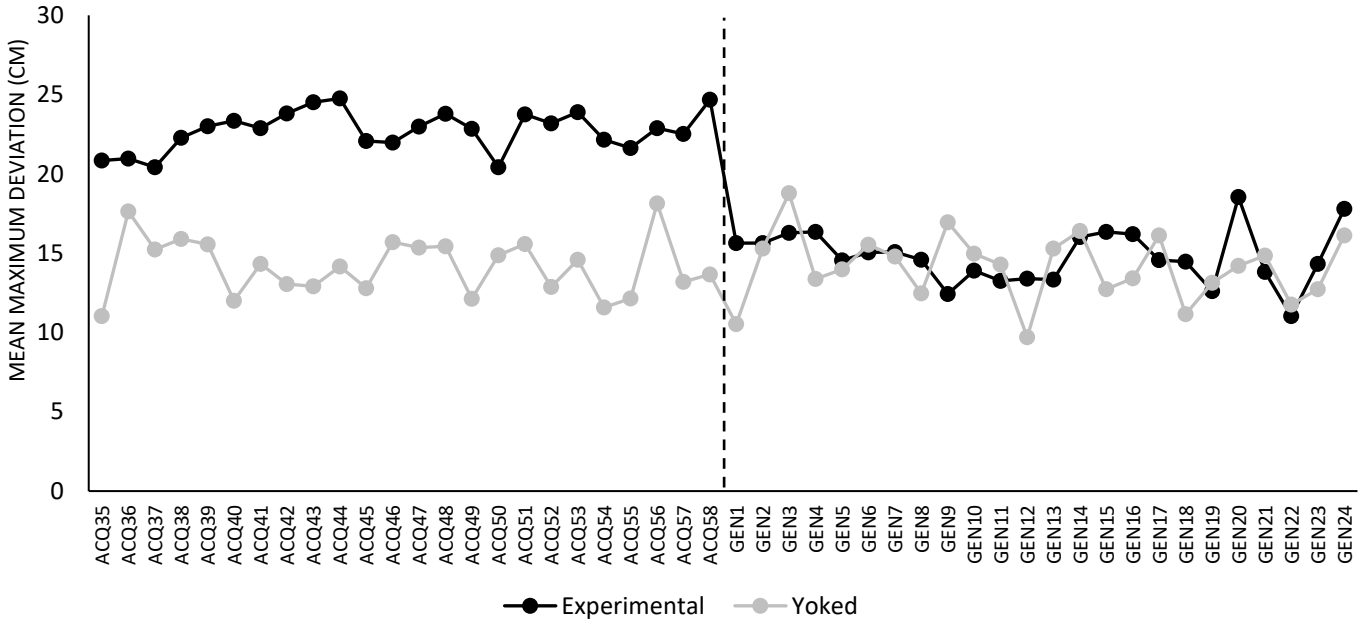

Figure 7.1. Mean maximum deviations from the shortest possible movement during each trial of the final block of the acquisition phase and first block of the generalization phase, in the Experimental and Yoked Groups of Study 1.

Only a few previous studies to date have investigated perceptual generalization of avoidance. These studies have all been outside the pain field, and have used very different methodologies to **Study 1**. A major difference is that these previous experiments used classical-operant procedures, in which participants first complete a classical fear conditioning phase. After this, they learn to avoid the US by employing an experimenter-defined avoidance response during the CS+ or GSs. In the study of Lommen and colleagues (2010), people high in neuroticism avoided more GSs (circles differing in grey hues between a white CS+ and black CS-) than a group low in neuroticism, on trials where they had 5 seconds (evoking a more elaborate thought process) to decide whether or not to avoid. On 1-s trials (indicating spontaneous responding), there were no group differences (Lommen et al., 2010). However, these authors did not describe the extent of avoidance generalization, *per se* (only the group comparison). Given this, and the fact that we did not investigate the effects of pre-screened anxiety traits on avoidance generalization, these results are not directly comparable to the current results.

The present findings are partly in line with those of van Meurs and colleagues (2014). In this study, participants first underwent classical fear conditioning, where one circle served as CS+, another as CS-, and circles linearly varying in similarity (size) between the CSs served as GSs. Subsequently, in a computer game, participants learned to avoid the US at the cost of poorer performance in the game. Costly avoidance generalized along with self-reported risk ratings (i.e. US-expectancy), yet was slightly attenuated compared to those ratings (van Meurs et al., 2014). This result was replicated by Hunt et al. (2017) who extended these findings by showing that distress endurance and distraction suppression (defined as healthy distress-coping strategies) decrease the synchronization between generalization of Pavlovian fear (measured using fear-potentiated startle EMG), and costly avoidance (Hunt et al., 2017). Together, these results suggest that healthy behavior is characterized by reductions in avoidance compared to fear, in situations where avoidance is costly.

Yet, it must be noted that, in **Study 1**, avoidance did not generalize at all, whereas in the studies of van Meurs et al. (2014) and Hunt et al. (2017) avoidance still mostly generalized in line with fear measures. That is, risk ratings generalized to *more* dissimilar GSs than avoidance, but avoidance still generalized. However, the methodologies of these previous studies differed from that of **Study 1** in some significant ways. Importantly, these previous studies used a two-phase (or classical-operant) setup. Participants first underwent a Pavlovian conditioning phase where they learned that one circle was paired with a US (e.g. large circle; CS+) and that another circle was not (e.g. small circle; CS-), followed by a Pavlovian generalization phase, where circles differing in size between the CS+ and CS- were presented. Finally, during the instrumental phase, participants were

instructed that they could avoid the US at the cost of poorer performance in the task. Conversely, the robotic arm-reaching paradigm employs an operant approach to avoidance conditioning. In **Study 1**, there was no separate fear-learning phase, but instead participants learned to fear and avoid the operant responses (movements) through trial-and-error, and also learned the costs of avoiding without instruction.

Due to these differences between classical and operant conditioning, avoidance generalization in the previous studies was examined based on similarity between stimuli (i.e. Pavlovian CSs and GSs), whereas the response itself stayed the same. Contrary to this, in **Study 1**, avoidance generalization was *response-based*, that is, avoidance (was meant to be) generalized from one operant R to similar, yet different Rs (e.g. from T3 to G3). In response generalization, the outcome (e.g. punishment rate) related to one response (e.g. movement) (i.e. the R-O contingency), generalizes to other similar responses, increasing or decreasing the likelihood of these similar behaviors occurring (Skinner, 1953). However, there is scarcely any literature investigating avoidance generalization from this perspective, likely due to the difficulties to conceptualize and operationalize avoidance behavior (LeDoux et al., 2017).

The context-dependent nature of operant responses

One possible explanation for the difference between classical and operant generalization stems from the appetitive operant conditioning literature. Specifically, this research suggests that operant responses do not readily generalize between contexts, i.e. they are *context-dependent* (Rosas et al., 2013). In contrast, Pavlovian conditioning typically transfers easily across contexts (Lonsdorf et al., 2017; Rosas et al., 2013). Almost anything can come to be regarded as a context. For example, a space, a point in time, or an internal state can be perceived as a context (Bouton, 2010). In **Study 1**, the change from the acquisition phase to the generalization phase was operationalized by visually removing the acquisition trajectory arches and displaying the novel, intermediate generalization trajectory arches. Although this context-specificity effect is more prominent in the operant *extinction* literature (i.e. operant extinction often does not generalize between contexts) (Rosas et al., 2013), results from the Bouton lab suggest that operant behavior, in general, may be "*inherently under contextual control*" (Rosas et al., 2013; p. 7). For example, research from this lab has demonstrated that rats trained to perform a specific response (e.g. lever pressing) to receive a reward (food pellet) in one context (Context A) will show decreased responding in a novel context (Context B) (Bouton et al., 2011; Todd, 2013). This was also the case when the behavior was trained to apply only under the control of a discriminative stimulus (a light) (Bouton et al., 2014). Interestingly, these authors also found that, if Context B was trained to be as familiar as Context

A before conditioning in Context A, responding decreased in Context B only when the response changed between Context A (e.g. lever pressing) and Context B (e.g. chain pulling) (Bouton et al., 2014). That is, in this study, there was no context-specificity effect as long as the response stayed the same between contexts.

Based on these pieces of evidence, Rosas et al. (2013) proposed that during operant conditioning, the response becomes specifically associated with the learning context. More specifically, these authors suggested, based on Gibson's theory of affordances (Gibson, 1977), that the specific combination of contextual features comes to "afford" the response, just as a concrete, instead of a fluid, surface comes to afford being stepped on due its unique features (e.g. supportiveness). Thus, in a similar way, a response may become specifically associated with its learning context, deeming the response less supported when the context is changed. Context, therefore, seems to play an important role in operant behavior, and this effect may be especially strong when also the responses are different between contexts (Bouton et al., 2014). This may have explained the difference in findings (avoidance generalization vs. no avoidance generalization) between the previous studies where the avoidance response itself stayed the same (Hunt et al., 2017; Lommen et al., 2010; van Meurs et al., 2014), and **Study 1**, where avoidance generalization was response-based. However, given the lack of research on response-generalization, firm conclusions are difficult to draw. It must also be noted, that lever pressing and. chain pulling are comparatively more different than the acquisition and generalization responses employed in **Study 1**.

Nonetheless, the visual changes between the acquisition and generalization phases in **Study 1** may have been interpreted by participants as a context-switch, deeming the costly avoidance response less supported in the novel context. Because the avoidance response (T3) and the response similar to it (G3) were costly, this context-switch may have motivated exploration of the novel, less effortful generalization trajectories (G1 and G2). *Exploration* can be defined as choosing novel options (e.g. a movement similar to a previously painful one) at risk of negative outcomes (e.g. pain), with the goal of obtaining future rewards (e.g. needing to exert less effort) (Lee et al., 2011). In contrast, *exploitation* is the process of choosing a known good alternative (e.g. avoidance) with the risk of missing out on rewards (e.g. needing to exert less effort). This trade-off is known as the exploration-exploitation dilemma (Krypotos et al., 2021; Mehlhorn et al., 2015). Integral to the exploration-exploitation dilemma is the need to ascertain the best course of action in a novel environment (Mehlhorn et al., 2015). Thus, the change in contexts along with the avoidance costs likely motivated participants to stop exploiting the known safe, but costly behavior, and to explore the novel, less costly ones in the hopes of needing to exert less effort in

the future. This exploration may have reduced avoidance behavior during the generalization phase of **Study 1**.

Surprising events and operant responses: The Rescorla-Wagner model

However, even if exploratory behavior occurred, avoidance in **Study 1** may have generalized had participants' fear beliefs not been disconfirmed immediately when they explored (tested G1). To elaborate, the Rescorla-Wagner model (1972), posits that learning is a function of the discrepancy between what is predicted and what actually occurs, i.e. *expectancy violation*. The model describes the possible changes in associative strength (V) between a signal (CS) and its reinforcement (US) that follows conditioning. In other words, the model uses the CS-US contingency as a parameter, which predicts the associative strength between the CS and US. The stronger the contingency (and thus the association) between a stimulus and its reinforcement, the stronger the learning effect when that association is disconfirmed (e.g. when a movement highly associated with pain is no longer paired with pain) (Rescorla & Wagner, 1972; Wagner & Rescorla, 1972). In line with this, 100% reinforcement schedules during learning, often lead to a rapid decrease of fear (e.g. fear extinction), when reinforcement is discontinued (Craske, 2015). To slow down the rate of extinction, partial reinforcement schedules are traditionally used in operant conditioning research (Finger, 1942; Pennes & Ison, 1967). In **Study 1**, the shortest movement trajectory (T1) had always been paired with pain during the acquisition phase, which may have resulted in high expectations of pain for G1 as well (e.g. "the shortest movement was always punished before, thus the movement similar to that one must also (almost) always be punished"). The absence of pain when exploring G1 at the beginning of the generalization phase would have therefore been surprising, resulting in a large expectancy violation, rapid disconfirmation of acquired threat beliefs, and thus rapid extinction of avoidance during the pain-free generalization phase. In line with this reasoning, the studies of van Meurs et al. (2014) and Hunt et al. (2017) also reinforced the CS+ on only 50% of the Pavlovian learning trials. Therefore, the lack of avoidance generalization in **Study 1** may have resulted from *a combination* of exploring (testing G1) and a resultant rapid disconfirmation of threat beliefs.

Could the type of cost matter?

Finally, an additional intriguing explanation for the difference in findings between these previous studies and **Study 1** is the difference in the nature of the costs employed. Specifically, **Study 1** used a biologically significant cost (physical effort), whereas the previous studies used a representation of costs, that is, poorer task performance. This type of "hypothetical" cost arguably relies on more higher-order cognitive processes than an innate, physical cost. For example, the physical costs in

Study 1 may have been perceived by participants as more aversive than the hypothetical costs in the studies of van Meurs et al. (2014) and Hunt et al. (2017). This, in turn may have more strongly motivated participants to not avoid when novel responses were presented, whose outcomes were still unknown. However, the use of hypothetical *rewards* in avoidance studies is relatively common (e.g. (Pittig et al., 2014; Wong & Pittig, 2020), and research comparing the use of these with real rewards has found no differences in decision-making (Bowman & Turnbull, 2003; Jenkinson et al., 2008). Thus, this explanation remains highly speculative.

Does costly avoidance generalize with minimized context changes and/or expectancy violation?

It seemed that the absence of avoidance generalization in **Study 1** could be explained by multiple plausible explanations, or a combination of these. In **Studies 2 and 3** (see Chapter 3), with methodological adaptations, we thus aimed to investigate the hypotheses that avoidance in **Study 1** did not generalize due to 1) exploration resulting from contextual changes between the acquisition and generalization phases (**Study 2**), and/or 2) rapid extinction of avoidance due to the surprising absence of pain during generalization (**Study 3**). Thus, in **Study 2** (Experiment 1 of Chapter 3), we aimed to reduce visual context changes between the acquisition and generalization phases by presenting all trajectory arches (T1-3 and G1-3) simultaneously. However, only T1-3 were available during the acquisition phase, and only G1-3 were available during the generalization phase. Thus, we also aimed to increase familiarity with the generalization trajectory arches before the generalization phase (Bouton et al., 2014), and to reduce the surprise associated with the sudden change between phases (Rescorla & Wagner, 1972; Wagner & Rescorla, 1972). When trajectories were available, their corresponding arches were colored black, and when they were unavailable, their arches were colored grey. The acquisition phase of **Study 2** was thus similar to that of **Study 1** (contingencies: T1 = 100% pain, T2 = 50% pain, T3 = 0% pain), except that all six movement trajectories were presented simultaneously. The generalization phase followed, and was similar to, the acquisition phase, except that only G1-3 were available and no pain was presented. In **Study 3** (Experiment 2 of Chapter 3), we aimed to delay rapid extinction of avoidance by decreasing the probability of pain associated with the acquisition trajectories, thus attempting to increase the uncertainty associated with the painful movements (T1-2) (and their generalization counterparts; G1-2). The paradigm and visual configuration in **Study 3** were similar to that of **Study 1**. However, T1 was now paired with an 80% instead of 100% chance of pain, and T2 with a 40% instead of 50%, chance of pain. T3 remained entirely pain-free.

In **Study 2**, we replicated the results of **Study 1**: self-reports of pain-related fear and pain-expectancies generalized, but avoidance did not. In contrast, **Study 3** demonstrated generalization

of all measures, including avoidance. That is, in this study, the Experimental Group deviated more than the Yoked Group during the generalization phase. Together, these results indicate that, regardless of our attempts to minimize visual changes between phases in **Study 2**, participants in the Experimental Groups of **Studies 1 and 2** explored the novel, less-effortful movement trajectories (G1 and G2) during generalization, even when they reported being fearful of these. It is worth noting, however, that although we attempted to reduce contextual changes between the acquisition and generalization phases in **Study 2** (by having all movement trajectory arches visible throughout the experiment), the indication of the availability of the movement trajectories (color of arches changing between black and grey) necessarily caused *some* contextual change.

The total absence of avoidance in these studies thus argued in favor of a (rapid) extinction explanation. In other words, that continuous punishment of T1 resulted in avoidance quickly extinguishing when G1 was explored and not punished. It is slightly perplexing, however, that this extinction was not reflected in fear and pain-expectancies, especially so when previous findings typically show reductions in fear even when avoidance remains high (Krypotos et al., 2015; Lovibond, 2006; Melzig et al., 2009; Solomon et al., 1953). On the other hand, a number of previous studies show that avoidance becomes attenuated compared to fear when avoidance comes at a cost (Claes et al., 2015; Claes et al., 2014; Pittig & Dehler, 2019; Pittig et al., 2018; Van Damme et al., 2012). Since avoidance is certainly motivated by fear, but also by other factors, such as costs, the avoidance costs (and possibly the fear generalization decrement) may have simply caused participants to be less motivated to continue avoiding after the responses and the context changed. Indeed, the absence of avoidance does not necessarily imply an absence of fear. In fact, it is exactly the absence of avoidance in the presence of fear (e.g. testing and correcting of one's fearful expectations), that may ultimately lead someone onto the path of recovery, and is therefore indicative of healthy behavior (Crombez et al., 2012; Vlaeyen & Linton, 2000, 2012).

The results of **Study 3** further argued in favor of a (rapid) extinction explanation, since increased uncertainty during the acquisition phase of this study (acquisition contingencies: T1 = 80%, T2 = 40% chance of pain), seemed to allow avoidance to generalize. That is, when the presentation of pain was made less predictable during the acquisition phase, avoidance generalized along with pain-related fear and pain-expectancies. Together with the results of **Studies 1 and 2**, this finding aligned nicely with previous literature. For example, the *partial reinforcement extinction effect* postulates that unpredictable cue/response-outcome associations are more resistant to fear extinction than predictable ones (Sheffield, 1949; Weinstock, 1954). According to this theory, the detection of a context-change (e.g. the sudden discontinuation of reinforcement) primes learners to quickly become aware of novel contingencies in the environment, thus resulting in behavior

change. Conversely, if no context shift is detected (e.g. the discontinuation of reinforcement is not noticed) the rate of learning remains low, and behavior changes slowly (Harris & Bouton, 2020). This also aligns with the Rescorla-Wagner model: less certain expectations of an outcome (e.g. pain) result in less learning (e.g. of safety), and thus sustained responding (e.g. avoidance) (Rescorla & Wagner, 1972).

Uncertainty, expectations, and their effect on exploration and avoidance generalization

Uncertainty is said to occur when one is not able to accurately evaluate events or predict outcomes (Mishel, 1988). It is inherently aversive (Carleton, 2016; Zaman et al., 2021), and central to anxiety pathology (Grupe & Nitschke, 2013). Anxiety has been defined as "*anticipatory affective, cognitive, and behavioral changes in response to uncertainty about potential future threat*" (Grupe & Nitschke, 2013), p. 2). Previous research indicates that difficulty tolerating uncertainty (*intolerance of uncertainty, IU*; (Buhr & Dugas, 2002)), as well as attempts to cognitively and behaviorally reduce uncertainty, are associated with a number of anxiety and mood disorders (Boelen & Reijntjes, 2009; Boswell et al., 2013; Gentes & Ruscio, 2011; Jacoby, 2020). Furthermore, uncertainty precludes one's ability to exert control and thus complicates the process of balancing the efficiency (e.g. exploration) and effectiveness (e.g. exploitation) of threat-related preparatory behaviors. Therefore, it can increase the likelihood that one will make overly prudent and costly choices, in an effort to gain back control (Grupe & Nitschke, 2013).

The choice to explore/exploit is further moderated by expectations. For example, Cohen, McClure, and Yu (2007) suggest that people will behave differently depending on whether uncertainty itself is expected or whether it is unexpected. The reason is that sudden changes in one's environment (i.e. unexpected uncertainty) indicate that changes in behavior may be necessary in order to adapt, thus promoting exploration. On the contrary, if the environment is predictably variable (i.e. expected uncertainty), there is less reason to believe that something has changed, and thus less information to be gained from exploring (Cohen et al., 2007). This also aligns nicely with the partial reinforcement extinction effect (Sheffield, 1949; Weinstock, 1954). Walker et al. (2021) recently showed that, in a group where participants learned that one behavior predictably resulted in a favorable outcome, whereas another predictably did not (Phase 1), exploration increased significantly when R-O relationships were made unpredictable (Phase 2). In contrast, another group for which the relationships had been unpredictable from the beginning, continued to exhibit the same (exploitative) behavior in Phase 2. These authors have coined this effect "*protection from uncertainty*" (Walker et al., 2021). It thus seems that the unexpected absence of pain in **Studies 1 and 2** resulted in exploration, and thus behavior change (less avoidance), whereas the

uncertainty associated with pain in **Study 3**, likely "protected" participants from the novel uncertainty of the generalization phase. Uncertainty about the presentation of pain during T1 (and thus G1) may have buffered against the effects of exploration (i.e. rapid extinction of avoidance; e.g. "the shortest movement (T1) before was not always punished. Thus, the absence of punishment during the similar movement (G1) does not mean it will not be punished if I try it again"). In real life, a person with chronic pain may not continue to perform an unfamiliar activity, despite it not resulting in pain once, because the absence of pain is interpreted not as rule, but a lucky exception. In contrast, absence of pain following a movement, highly expected to be painful, may lead to more learning and less avoidance of that movement (Craske et al., 2008).

It is worth noting that uncertainty is typically used to experimentally induce anxiety-like states in classical conditioning studies. In these studies, uncertainty is operationalized by presenting USs in the absence of any explicit cue (CS) (Meulders et al., 2013; Meulders & Vlaeyen, 2013). In the absence of a predictable relationship between the CS and US, the entire experimental context becomes associated with threat (i.e. context conditioning), thus producing diffuse and sustained anxiety-like responding (Davis et al., 2010; Grillon et al., 2004). In contrast, in **Study 3**, only the pain-associated movements (T1 and T2), but not the context as whole, were made less predictable. That is, pain could still be reliably avoided by choosing T3. Thus, the presence of any pain-related fear in **Study 3** would have been specifically related to T1 (and T2), but not the entire experimental context. Some evidence for this uncertainty-induced response-specific anxiety comes from the results of **Study 1**, where G2 continued to evoke more pain-related fear and pain-expectancies compared to G3 throughout the generalization phase, whereas G1 did so only during the first block of this phase. T1 had been paired with predictable pain (100%), and T2 with unpredictable pain (50%), which may have caused sustained fear and pain-expectancies towards G2.

Recent theories may be able to provide a mechanism to explain the finding of increased avoidance in the presence of uncertainty. Specifically, Van den Bergh et al. (2021) have proposed a persistent "better safe than sorry" strategy as an underlying vulnerability factor for developing psychopathology. The theory draws from predictive processing accounts and is thus also in line with active inference models of chronic pain (Tabor, Keogh, et al., 2017; Tabor, Thacker, et al., 2017). Predictive processing theories view the brain as an organ that actively constructs internal models to explain the world around it, by combining incoming sensory evidence with its own predictions (Clark, 2015). These predictions do not always exactly reflect the real world but are imbued by a person's prior beliefs. Because there is always some difference between the brain's predictions and the incoming sensory information, this process results in prediction errors, which the brain uses to improve the accuracy of its models (*error reduction*), and to update them to best

explain the world. Thus, the uncertainty associated with the acquisition movements in **Study 3** may have complicated the process of reducing errors, even when evidence disconfirming previous beliefs was available (no pain during a G1 movement). This may have motivated participants to adopt a "better safe than sorry" strategy, resulting in exploitation of G3, which further prevented disconfirmation of the safety of G1.

In the lives of people with chronic pain, uncertainty can occur on many different levels (McCormick, 2002; Zaman et al., 2021), such as not knowing the cause, meaning, and/or best course of action relating to their pain. It is not hard to see how pain, perceived as uncertain and uncontrollable, may motivate someone to control excessively, i.e. avoid a wider array of movements and activities, in order to "stay on the safe side". Thus, taken together, the results of **Studies 1, 2, and 3** suggest that, making people feel less uncertain about their pain may reduce the spreading of avoidance to safe movements and activities. For example, if a person feels that they can easily predict which movements and activities will exacerbate their pain, or to what extent these activities will do so (e.g. "skateboarding for more than two hours will make my back pain worse"), they may be less likely to generalize avoidance, because they feel in control of pain. In contrast, someone who feels that anything might make their pain worse, may be more likely to avoid a wider array of movements and activities. However, the current results require replication, and this interpretation therefore warrants caution. Nonetheless, in support of this interpretation, controllability over pain was recently shown to selectively reduce pain-related suffering, but not pain intensity or pain unpleasantness, in healthy participants (Löffler et al., 2018). This is especially relevant for chronic pain, in which targeting the management and psychosocial concomitants of pain is often more effective than targeting the pain itself (Gatchel & Okifuji, 2006; Gatchel et al., 2007a).

How closely do pain-related fear and avoidance generalization correspond to one another?

The results of **Studies 1 and 2** added to evidence suggesting that (pain-related) fear and avoidance do not always share a one-to-one relationship (Claes et al., 2014; Mineka, 1979; Pittig & Dehler, 2019), and extended these findings by demonstrating that in some cases the two may only dissociate at the point where they would become unnecessary, i.e. during generalization. Given that theoretical models assumed that avoidance would always align with fear, most of our understanding of the mechanisms of generalization stems from research on fear (Dymond et al., 2015). Thus, a clear understanding of how closely fear and avoidance generalization correspond to one another would inform how much inspiration can be drawn from existing knowledge of fear

generalization, in order to apply it to research on the generalization of operant avoidance. In **Study 4** (see Chapter 4), we thus sought to investigate whether healthy participants would generalize avoidance similarly to how they generalize fear. That is, whether avoidance would also decrease (or, *approach* would *increase*) as a function of dissimilarity to a pain-associated movement, indicating an avoidance "generalization gradient". We also explored whether participants would prefer an extreme version of the safe movement, indicative of an avoidance "area shift". In a simplified acquisition phase of the robotic arm-reaching paradigm, and in line with differential *fear* conditioning paradigms (Lissek et al., 2008; Meulders et al., 2013), participants were presented with only two movement trajectories (T+ and T-) instead of three (T1-3). Participants could avoid the pain, which was paired with T+ (80% chance of pain/low-cost movement trajectory), by choosing T- (0% chance of pain/high-cost movement trajectory). T+ and T- were located at opposite ends of the movement plane. Subsequently, in the absence of pain, we introduced three movement trajectories (G1-3) between T+ and T-, and one movement trajectory on the side of T- away from T+ (G4). Thus, G1-4 linearly increased in costs from T+ to T-. As an additional measure, we collected startle EMG amplitudes in response to the different movement trajectories. During the blocks where fear-potentiated eyeblink startle EMG was measured, movements were instructed, in order to allow us to collect these responses for all movement trajectories (which participants otherwise might not have chosen).

Lack of startle EMG findings: Effect of classical vs. operant conditioning?

Our startle EMG measure showed no differences between movement trajectories. This was a surprising finding, given that previous research investigating generalization of movement-based pain-related fear did find gradients in this measure, albeit in a classical fear conditioning paradigm (Meulders et al., 2013). The absence of startle EMG effects in **Study 4** may have been due to the timings of the startle probes and the signaling of the to-be-performed movement. Because participants' movement speeds vary widely in the robotic arm-reaching paradigm, EMG responses may have been confounded by the pain stimulus, which was presented during the movement. Thus, we decided to present the startle probes during the ITI. Furthermore, we wanted to eliminate the chance of unnecessary noise in the EMG signal during movements. However, because the to-be-performed movement was highlighted at the beginning of the 10-s ITI, whereas the startle probe was presented at the end of the ITI, anticipation of pain may have simply waned, possibly explaining the lack of differential startle responses. Alternatively, it is possible that startle EMG simply does not present in the same way in the robotic arm-reaching paradigm, as it does in classical fear conditioning paradigms. Indeed, startle EMG is a common measure of classical fear

conditioning (Lonsdorf et al., 2017), but has rarely been used in operant conditioning research. An interesting psychophysiological measure to use in the robotic arm-reaching paradigm in the future, could be pupil dilation, which has been linked to both decision-making and expectancy violation (de Gee et al., 2014; Preuschoff et al., 2011).

Generalization gradients and peak/area shifts

Aligning with previous research (Meulders et al., 2013), we found generalization gradients in pain-related fear and pain-expectancies: both ratings linearly decreased with increasing distance from the pain-associated movement (T+). There was also a general decrease in conditioned fear to the extreme version (G4) of the safe movement (T-), compared to the other generalization movements (G1-3). We interpreted this as an "area shift" of fear (G3 feared more than G4). However, this was not entirely in line with our expectations, given that we hypothesized that G4 would be feared less than T- (a "peak shift"). Interestingly, avoidance briefly generalized at the beginning of the generalization phase (maximal deviation in Experimental Group > Yoked Group), but swiftly disappeared. Our proportional odds models further revealed that, throughout generalization, the Experimental Group was more inclined than the Yoked Group to choose the *more* effortful generalization trajectories (G4 and G3), which were similar to the previously safe one (T-), indicative of avoidance generalization. Exploration of this effect at trial-level suggested that the difference between groups was driven by the Experimental Group choosing all generalization trajectories relatively equally throughout the generalization phase, whereas the Yoked Group preferred the shortest, least effortful movement trajectory (G1) over the others. Since approach of the generalization trajectories in the Experimental Group did not decrease from the "safest" generalization trajectory (G4) to the "most threatening" one (G1), no "avoidance generalization gradient" was observed. Therefore, although participants labeled G4 as the safest generalization trajectory (in self-reports), they did not approach this movement more than the other generalization movements. Furthermore, where pain-related fear and pain-expectancies showed generalization gradients, thus aligning with consistent findings in the classical fear generalization literature (Dymond et al., 2015; Honig & Urcuioli, 1981; Lee et al., 2018; Lissek et al., 2008; Meulders et al., 2013; Purtle, 1973), avoidance did not. These results add to growing literature, including **Studies 1 and 2**, suggesting that avoidance does not always directly map onto fear.

Given that our hypothesized "avoidance generalization gradient" was the opposite of a fear generalization gradient, peak responding was investigated towards an extremely safe movement (G4) (i.e. *increased approach* of a *safe* movement, rather than *fear* of a *painful* movement).

Typically, however, peak shifts arise as *increased* responding to an extreme version of a *reinforced* (CS+), and not a safe (CS-) stimulus, following differential fear conditioning (Lee et al., 2018). Traditional accounts of the peak shift effect posit that it results from excitation on the side of the CS+, and inhibition on the side of the CS-, resulting in net excitation towards a generalization stimulus beyond the CS+, in a direction opposite to the CS- (Spence, 1937). Therefore, the safe nature of this extreme movement trajectory may have lacked integral, excitatory properties required for a peak shift effect, and framing reduced responding towards G4 as a "peak" or "area shift" may not have been the most accurate way of describing this behavior. Indeed, **Study 4** is, to our knowledge, the first to investigate such a "safety" peak shift effect, and this point of investigation was thus very exploratory. Nonetheless, given that a safe movement (T-) likely acquires inhibitory, and a painful movement (T+) excitatory properties, it does not seem entirely impossible for this to cause less excitation at an extremely safe movement (G4) compared to a less extreme version of the safe movement (G3), resulting in lower responding to G4 compared to G3. Furthermore, people with chronic pain often cannot avoid pain, and may thus not be able ascertain when avoidance becomes unnecessary. Thus, they may come to adopt increasingly costly but ineffective avoidance strategies (such as G4 in **Study 4**) over and above what is necessary for safety (e.g. preventing re-injury or pain exacerbation). Therefore, we maintain that this is an intriguing topic of further investigation.

In contrast to San Martín and colleagues (2020), who reported avoidance generalization gradients, decreasing from an *avoidable* CS+ to an *unavoidable* CS+ and a CS-, we did not observe such a gradient in **Study 4**. These authors investigated avoidance generalization along a dimension of "avoidability", where during one CS+ (CS+av), a button press effectively omitted the US (an aversive electrical stimulus), whereas during another CS+ (CS+unav), the button press was ineffective (San Martín et al., 2020). Thus, one reason for the different findings between this previous study and **Study 4** is that, during the generalization phase in **Study 4**, pain was always avoidable. That is, although participants in **Study 4** had not been informed about the absence of pain stimuli during the generalization phase, they had learned during the acquisition phase that they could choose their own responses, and that they could thus always avoid if they wanted to. This is in contrast to the study of San Martín et al. (2020), in which participants had the ability to choose whether or not to respond to a stimulus presented to them, and during one stimulus avoidance was not possible. Thus, participants' freedom to choose their own responses in **Study 4** may have provided a level of control, which participants in the study of San Martín et al. (2020) did not have. Not being able to avoid one CS+ may have increased excitation towards that CS and those GSs similar to it, resulting in this previous study finding an avoidance generalization gradient,

where **Study 4** did not. It should also be noted that San Martín et al. (2020) investigated low-cost avoidance, whereas in **Study 4**, an avoidance generalization gradient would have meant approach increasing as a function of increasing costs. The differences in avoidance-costs may thus explain the differences in avoidance generalization between these two studies.

Deciding to approach or avoid

Another consequence of the differential use of classical-operant and operant procedures is that the former typically employs an *instructed* avoidance response. This means that participants first learn the CS-US association and are subsequently instructed that a certain response (e.g. pressing a computer button) will omit the US if performed during the CS. In the current studies, however, participants were given no instructions regarding the experimental movement-pain contingencies, and they thus learned these independently through trial-and-error. They also had to independently decide between multiple behavioral options during the generalization phase, when presented with a set of entirely novel movement trajectories. This type of task arguably involves more active decision-making than deciding whether or not to press a computer key in response to different stimuli.

Decision-making processes are integral to approach-avoidance conflicts (e.g. the decision to approach a movement similar to a previously safe one, or to avoid a movement similar to a painful one), and are influenced by the anticipation of rewards and/or punishment (Krypotos et al., 2021). For example, the balance between magnitude of reward and probability of receiving punishment affects choice behavior, such that when the risk of punishment is high, smaller rewards will be rejected in favor of a safe option, whereas if the risk of punishment is low, even small rewards will prompt approach (Sierra-Mercado et al., 2015). In the current studies, the Experimental Groups persisted in costly avoidance during the acquisition phases, once they had reliably learned that the least effortful movement (T1/T+) predicted pain. However, when the familiar movements were replaced by novel options, participants had to re-evaluate their perceived risk of punishment, prompting approach (i.e. exploration) of the novel, less effortful movements.

One's decision to approach or avoid is further affected by their motivations and goals (Elliot, 2006; Schrooten et al., 2014). For example, a person with back pain may choose to sit on a hard floor in order to play with their children (a valued activity), even if it might lead to a later increase in pain. Participants in **Study 4** may have valued attaining information (i.e. learning the contingencies) more than preserving safety (i.e. avoiding) at all times, leading to less generalization of avoidance. The data also supported this interpretation: the Experimental Group in **Study 4** chose all generalization trajectories relatively equally, possibly indicating that these participants

were trying to learn which of the novel generalization movement trajectories were (not) paired with pain. Further (post-hoc) inspection of trajectory choice data also showed that participants in **Study 4** switched between the generalization movement trajectories on most trials of the generalization phase (see Figure 7.2). This type of behavior is indicative of healthy exploration (Krypotos et al., 2021) resembling the results from **Studies 1 and 2**. However, more inflexible behavior may be characteristic of people with chronic pain (Thomas & France, 2007; van Dieën et al., 2017), who have been suggested to persistently choose actions (e.g. avoidance) that (they believe will) result in less pain and/or its exacerbation. This may often come at the cost of pursuing other valued life goals (an example of exploiting current expectation about pain) (Apkarian et al., 2004; Hess et al., 2014; Krypotos et al., 2021; Verdejo-García et al., 2009; Walteros et al., 2011).

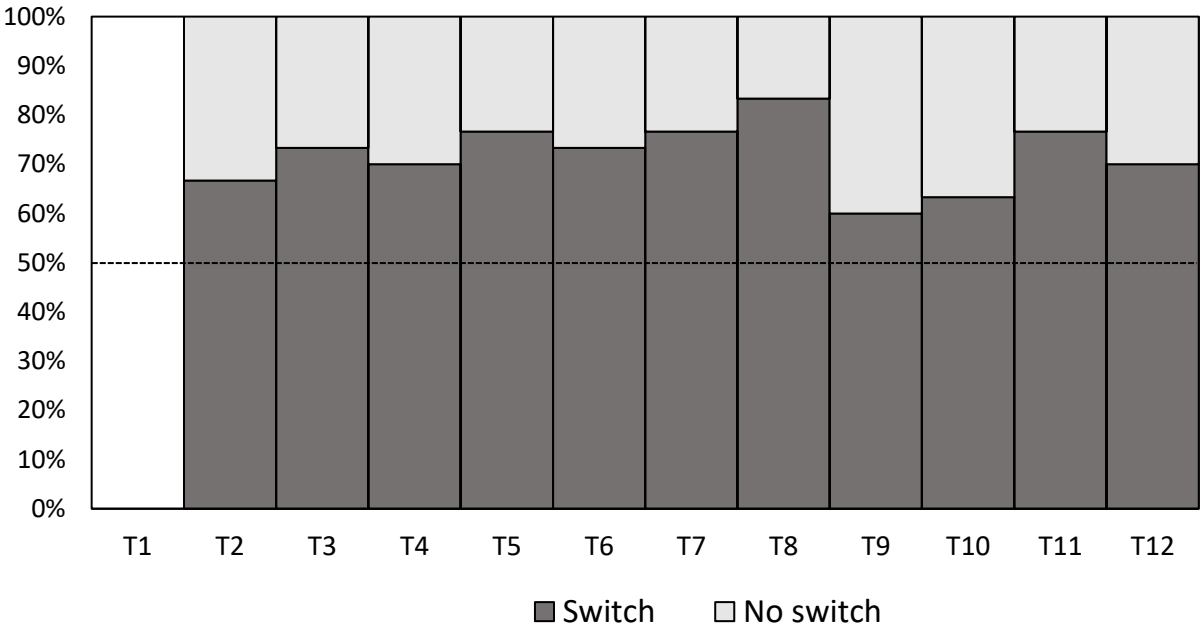

Figure 7.2. Proportions of switching behavior during each trial of the generalization phase in the Experimental Group of Study 4.

Summary and implications

The finding that stands out when combining the results of **Studies 1, 2, and 4** is that, compared to fear, healthy people seem to not generalize avoidance behavior (**Studies 1 and 2**), or they generalize avoidance less (**Study 4**), if a cost is involved. Indeed, in three of four studies, pain-related fear and pain-expectancies generalized, but costly pain-related avoidance did not, or was attenuated. Furthermore, avoidance always aligned with pain-related fear and pain-expectancies during the acquisition phases, that is, when there was a real threat and avoidance was therefore adaptive. This strengthens the notion that, in healthy behavior, avoidance dissociates from fear mainly at the point where it becomes unnecessary, such as in objectively safe situations.

Given the basic nature of the current research, any clinical implications should be considered with caution. However, the findings of costs attenuating unnecessary avoidance, underline the importance of treatments emphasizing the value of alternative behaviors. For example, Acceptance and Commitment Therapy (ACT), has shown promising results as a treatment of treating chronic pain (Scott & McCracken, 2015). ACT aims to help people increase acceptance of their present state, and thus attempts to promote psychological flexibility. ACT does not attempt to alter the intensity of pain, pain-related emotions, or the content of pain-related cognitions, but aims to encourage people to directly see and follow new options for behavior, other than control and avoidance of pain and other difficult experiences (Scott & McCracken, 2015).

In summary, the present results suggest that avoidance-costs can motivate healthy people to explore behaviors perceptually (proprioceptively) similar to previously painful ones, rather than exploiting costly behaviors, similar to previously safe ones. However, uncertainty about those behaviors resulting in pain may prolong recovery, due to reduced disconfirmation of threat beliefs when exploring.

Generalization of category-based pain-related avoidance

In **Study 5** (see Chapter 5), we investigated category-based generalization of pain-related avoidance using de novo categories of operant responses (movements). In a robotic arm-reaching paradigm, participants in two groups were trained to categorize the same movements in two different ways, respectively. For the MTS-Congruent group, the movement trajectory categories were: T1 = G1, T2 = G2, and T3= G3, and for the MTS-Incongruent group they were: T1 = G3, T2 = G2, and T3= G1. Subsequently, during an operant acquisition phase, participants learned that T1 was paired with a painful electrical stimulus (80% likelihood of pain), and that the likelihood of the pain stimulus could be partly or completely reduced by choosing T2 (40% likelihood of pain) or T3 (0% likelihood of pain), respectively. Finally, to investigate whether avoidance would generalize based on the categories previously learned during the MTS task, G1-3 were made available, in the absence of the pain stimulus. Self-reports of pain-related fear and pain-expectancies were collected as indices of fear learning. We expected the groups to show opposite patterns of generalization in avoidance (maximal deviation MTS-Congruent > MTS-Incongruent), pain-related fear, and pain-expectancies (MTS-Congruent: G1 > G3, MTS-Incongruent: G3 > G1), based on the movement trajectory categories they learned during the MTS task.

The results of **Study 5** aligned with these hypotheses. First, participants successfully acquired avoidance, pain-related fear and pain-expectancies, thus replicating these findings in the

robotic arm-reaching paradigm (Meulders et al., 2016); **Studies 1-5**). Specifically, both groups feared T1 more, and expected pain more during T1 compared to T3 during the acquisition phase. Second, both groups also learned to avoid pain: maximal deviations were larger at the end of the acquisition phase compared to the beginning of this phase, in both groups. Importantly, and relating to our main hypotheses, both groups also *generalized* responses in all measures, in line with the categories they learned during the MTS task. Specifically, MTS-Congruent feared, and expected pain more during G1 compared to G3, whereas MTS-Incongruent showed the opposite pattern (G3 > G1). Critically, both groups also generalized avoidance in line with the categories they learned during the MTS task. That is, MTS-Congruent had learned to categorize the furthest generalization trajectory (G3) with the original avoidance response (T3), and this group thus showed larger maximal deviations compared to MTS-Incongruent, who had learned to categorize the shortest generalization trajectory (G1) with T3. This indicates successful generalization of categorical pain-related avoidance. These results are the first to show that pain-related avoidance behavior can generalize based on de novo relationships between pain-relevant responses, i.e. movements, thus suggesting a unique way for behaviors to evoke pain-related fear and avoidance in the absence of a painful experience.

The results of **Study 5** are in line with those of Bennett et al. (2015), in which two equivalence categories of nonsense words and joystick movements were created. After this, pain-related fear spread to the joystick movements from the category of the pain-associated nonsense words, despite the joystick movements never being experienced with pain. Similarly, **Study 5** also showed generalization of pain-related fear to movements never paired with pain, due to de novo relationships learned within the context of the experiment. Furthermore, the results of **Study 5** extended the findings of Bennett et al. (2015) by showing that also pain-related *avoidance* can generalize in this manner. This finding is in line with previous research from the anxiety domain. For example, Augustson and Dougher (1997), and Dymond and colleagues (2011) also demonstrated category-based avoidance generalization. In these studies, avoidance generalized to stimuli (C1 and D1) from one category, after a member (B1) of this category was paired with an avoidance response, which cancelled an aversive electrical stimulus, despite C1 and D1 never being experienced with B1 (or the US) directly. Given that these previous studies did not use a *painful* electrical stimulus as US, the results of **Study 5** extend these findings to apply to *pain-related* avoidance as well. Furthermore, the results of **Study 5** also extend previous results by showing that avoidance does not only generalize between categorically related *stimuli*, but also between categorically related operant *responses*. In the real world, this might mean that experiencing pain

during one activity (e.g. a yoga pose) can spread to a multitude of other, physically unrelated, but categorically associated, activities (e.g. yoga as a whole).

It is worth noting that, in **Study 5** we created *symmetry relations*. This means that the sample movement (e.g. T1) was directly paired with the comparison movement (e.g. G1), which thus became indirectly paired with the *pain stimulus*, but not any other movement trajectories, via the sample movement (e.g. T1). In contrast, the previous studies (Augustson & Dougher, 1997; Bennett et al., 2015; Dymond et al., 2011) created *equivalence relations*, meaning that their sample stimulus (e.g. an abstract symbol; Bennett et al., 2015) was paired with multiple comparison stimuli (e.g. nonsense words *and* joystick movements), which became indirectly associated also with each other. A benefit of creating equivalence categories is that one stimulus could be part of both derived symmetry relations (abstract symbol – nonsense word, abstract symbol – joystick movement), as well as derived equivalence relations (nonsense word - joystick). For example, in the study of Bennett and colleagues (2015), the nonsense words were never explicitly paired with the joystick movements, but instead participants derived the equivalence of these stimuli via the mutually related abstract symbols. This type of equivalence-based avoidance generalization arguably explains the more wide reaching generalizations of fear and avoidance (Dymond et al., 2011). That is, to stimuli that, not only were never paired with a US, but were also never directly experienced with the original fear inducing event (CS). It would be interesting to extend the current findings by adding one or more movement trajectories in each category (by employing the third dimension of the HM, i.e. upward and downward movements), to enable the formation and investigation of response-based, operant equivalence relations as well as symmetry relations. In the real world, this might mean that, following pain during a yoga pose, the person may not only generalize avoidance to activities directly related to the yoga pose, such as yoga, but to activities also related to yoga as whole (e.g. all exercise). Nonetheless, we perceive **Study 5** as a significant first step to investigating this important pathway to the generalization of operant pain-related avoidance.

Avoidance costs and category-based generalization

The results of **Study 5** are in contrast to those of **Studies 1, 2 and 4**, where (perceptual) avoidance did not generalize (or was attenuated compared to self-reports). One relatively obvious explanation for this difference is that the earlier studies involved avoidance-costs, whereas in **Study 5**, these costs were minimized. That is, although avoidance behavior during the acquisition phase of **Study 5** was operationalized as the *longest* movement (T3) to reach the target, it was not paired with any extra additional, such as resistance from the robotic arm. Indeed, **Study 5** was the first of this PhD

project to employ the robotic arm-reaching paradigm with low costs. The finding of avoidance generalization in this study corroborates our previous prediction that avoidance behavior in healthy people does not generalize as readily as fear, when avoidance is associated with costs, but does so even in healthy people when avoidance is not costly, since arguably there is no reason not to avoid. This would also explain why avoidance generalization is relatively more common in the anxiety literature, where low-cost avoidance is often used (San Martín et al., 2020; Vervliet & Indekeu, 2015), yet has remained elusive in the current PhD project.

However, the difference between findings of **Study 5** and **Studies 1, 2, and 4**, could also be due to the difference in the generalization pathways under investigation (category-based vs. perceptual). Indeed, other studies have reported generalization of *costly* avoidance based on (real-life) categorical knowledge. Participants in the study of Wong and Pittig (2020) learned that exemplars from one category (e.g. animal) were paired with a high reward, but also an aversive electrical stimulation (US), whereas those from another category (e.g. fruit) were paired with a low reward, but no US. Subsequently, in the absence of the US, participants avoided the high-reward deck more than a control group for whom the avoidance test did not involve exemplars from either of the fear conditioning categories. Thus, avoidance generalized categorically, at the cost of rewards (Wong & Pittig, 2020).

In another study from our lab (Glogan et al., In preparation; see Box 1), category-based pain-related avoidance also generalized despite associated costs. In this study, participants used joystick movements to perform activities from two categories (gardening and cleaning), in a virtual environment. Pain could be avoided, but at the cost of task progress, during exemplars from one category (e.g. gardening). The other category (e.g. cleaning) was always safe. In a subsequent generalization phase, in the absence of the pain-stimulus, participants continued to avoid more during novel exemplars from the previously pain-associated category (e.g. gardening activities), compared to those from the previously safe category (e.g. cleaning activities), despite the costs associated with avoiding. Thus, it seems that even with associated costs, (pain-related) avoidance generalizes readily based on categorical knowledge. However, given that costly *perceptual* pain-related avoidance did not generalize in some previous studies (**1, 2, and 4**), but did in others (**Study 3**), the differences between perpetual and conceptual avoidance generalization warrant further investigation.

Box 1. Generalization of pain-related avoidance based on existing categorical knowledge

Research on pain-related avoidance generalization based on real-life categories is scarce, if not non-existent. Therefore, we aimed to investigate whether costly pain-related avoidance generalizes based on categorical relationships between real-life activities, in a pain-relevant paradigm. Participants were required to perform arm-reaching movements with a joystick in order to carry out everyday activities from two different categories (gardening and cleaning), within a computer environment. Movements representing everyday activities were used as instrumental responses, in order to reflect the clinical reality of a person with chronic pain as closely as possible. Specifically, on each trial, participants moved either a gardening or a cleaning tool (e.g. rake or mop) via one of two possible movement trajectories (T+/T-), in order to collect items matching the tools (e.g. pile of leaves or puddle of water), and were required to carry the items into a target. The shortest trajectory (T+) was paired with an 80% chance of the participant receiving a painful electrical stimulus, but only in one of the categories (*avoidance condition*). Furthermore, T+ always resulted in the entire matching item (e.g. pile of leaves or puddle of water) being moved into the target. The other category was entirely safe (*safe condition*). Which category served as the avoidance condition was counterbalanced across participants. Furthermore, participants could always avoid the electrical stimulus by choosing the more effortful trajectory (T-), which came at the cost of movement length and task progress. That is, there was an 80% chance that during the T- movement, only half of the item would be moved into the target, thus meaning that this movement needed to be performed twice (and a 20% chance that one movement would suffice). Lastly, we tested for categorical generalization of avoidance, by introducing novel exemplars from each of the two categories (e.g. shovel/pile of dirt or dish brush/pile of dirty dishes), in the absence of the pain stimulus. Measures included avoidance behavior (maximal deviation from the shortest trajectory, T+), and self-reported pain-expectancy and pain-related fear.

We expected participants to (1) avoid the pain stimulus in the avoidance condition, despite avoidance-costs, and (2) for avoidance to subsequently generalize to novel exemplars from the avoidance condition, despite these not being paired with the pain stimulus. Furthermore, we expected (3) self-reports to be higher for the pain-associated response (T+), compared to the avoidance-response (T-) in the avoidance condition, and these to not differ in the safe condition, throughout the experiment.

Figures 7.3 and 7.4 summarize the results of this study. Separate 2 x 2 RM ANOVAs (Condition: Avoidance, Safe) x (Trajectory: T+, T-) on self-reported pain-expectancies and pain-

related fear during the generalization phase, revealed significant Condition x Trajectory interactions: pain-expectancy, $F(1, 39) = 10.70$, $p = .002$, $\eta_p^2 = 0.22$; pain-related fear, $F(1, 39) = 9.44$, $p = .004$, $\eta_p^2 = 0.20$. As expected, planned contrasts confirmed that participants showed higher pain-expectancies towards T+ than T-, and feared T+ more than T-, in the avoidance condition: pain-expectancy, $t(39) = 10.20$, $p < .0001$, $d = 2.32$; pain-related fear, $t(39) = 9.36$, $p < .0001$, $d = 2.04$. Surprisingly, these differences also occurred in the safe condition: pain-expectancy, $t(39) = 3.40$, $p = .002$, $d = .86$; pain-related fear, $t(39) = 3.30$, $p = .002$, $d = .81$. The reason for this unexpected finding may be that the contingencies associated with the movement trajectories were more salient than those associated with the different conditions. That is, since the conditions and tool/item exemplars were constantly changing, while the two movement trajectories were fixed, participants likely first learned the difference between the trajectories (choosing the shorter trajectory is usually followed by pain, and choosing the longer one is always safe). Only after that would they have learned the differences between categories. Furthermore, even when they chose T+ in the avoidance condition, this response sometimes did not result in pain. Thus, participants may have been generally uncertain about the R-O contingencies they had learned, resulting in some suspicion of pain possibly being presented even during the safe condition.

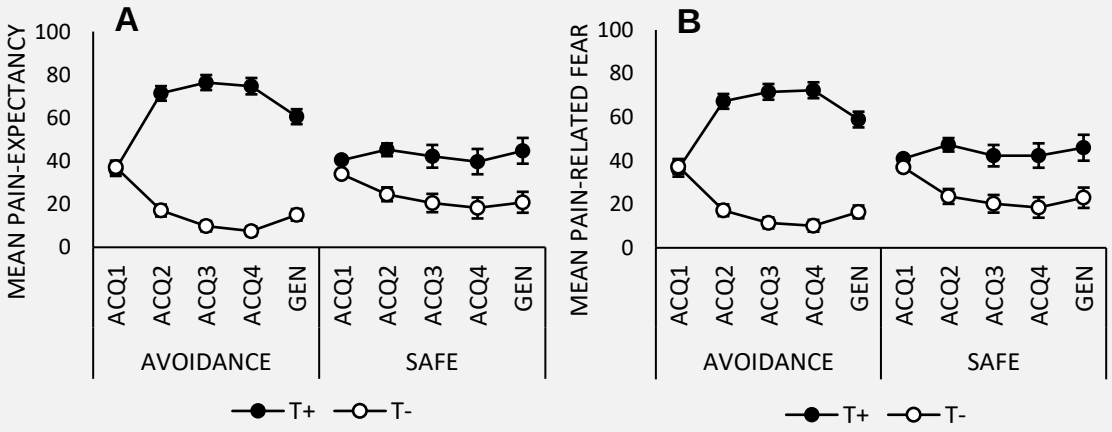

Figure 7.3. Panel A: Mean self-reported pain-expectancy, and **Panel B:** Mean self-reported pain-related fear towards T+ (black) and T- (white) in the avoidance and safe conditions during the acquisition (ACQ1-4) and generalization (GEN) phases.

Importantly, as hypothesized, a paired samples *t*-test on mean avoidance behavior during the one block of the generalization phase, showed that participants also avoided more during novel exemplars of the avoidance category, compared to the safe category, $t(39) = 3.99$, $p < .001$, $d = 0.63$. Given that we did not train these categories in any way, we conclude that costly pain-related avoidance in this study generalized based on existing categorical knowledge (about gardening and cleaning activities).

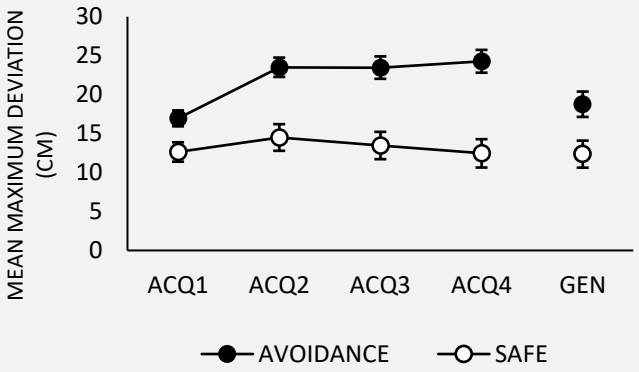

Figure 7.4. Mean maximum deviations during the avoidance (black) and safe (grey) conditions during the acquisition and generalization phases. Error bars represent standard error of the mean.

It is worth noting that, for the MTS-Incongruent group, avoidance generalization was operationalized as shorter deviations to reach the target (choice of G1), which slightly complicates the interpretation of the behavior observed in this group, given that G1 was the most direct movement trajectory to the target. Therefore, it is difficult to exclude that the MTS-Incongruent group was not simply behaving in the most energy-efficient way rather than, or in addition to, generalizing. In line with this suggestion, post-hoc analyses of mean movement durations during the generalization phase, indicated that the MTS-Incongruent group was significantly faster at performing the arm-movements during the generalization phase, compared to the MTS-Congruent group. However, given that the self-reports still aligned with our hypotheses of group differences in generalization, we do maintain that the most likely explanation for the difference observed between groups in **Study 5** was their differing learning histories.

In summary, the results of **Study 5** suggest that category knowledge can be engaged when pain-related avoidance is learned, implying that entire categories of behaviors may become related to threat, and evoke avoidance. Thus, the ability to learn that different pain-associated stimuli or

activities are similar, may result in fear and avoidance generalizing to a wide network of categorically connected events. This form of generalization is highly problematic because category-based relations can have a substantial scope, and can be highly idiosyncratic, given their abstract nature and lack of reliance on physical form (Dunsmoor & Murphy, 2015). Therefore, the category-based generalization of avoidance is worthy of further investigation.

Limitations and future directions

Need for replication in (sub)clinical populations

One limitation of the current project is its lack of clinical data. The original outline of the current PhD project included a study comparing pain-related avoidance generalization between people with chronic pain, and healthy controls. However, due to delays and complications caused by the COVID-19 pandemic, we were not able to run such a study. Indeed, all the samples of the studies described in this thesis were healthy and pain-free, which limits the generalizability of the current findings to chronic pain populations. Nonetheless, the scientific process naturally requires starting out with healthy participants before any clinical populations can ethically be recruited. Thus, the current data offer a starting point for future research looking more closely at the differences in avoidance (generalization) between healthy people and people with chronic pain.

A future study could investigate whether people with chronic pain generalize avoidance in experimental protocols where healthy people in the current project did *not*. We hypothesize that the healthy participants in **Studies 1 and 2** did not generalize avoidance due to 1) rapid extinction of avoidance following 100% chance of pain for T1, and 2) avoidance-costs. We also expect that people with chronic pain may generalize avoidance more (Harvie et al., 2017; Meulders et al., 2014; Meulders et al., 2015), and show slowed down extinction compared to healthy people (Meulders, Meulders, et al., 2017a). Furthermore, we hypothesize that people with chronic pain may persist in choosing actions with short-term gains (less pain/pain exacerbation), at the cost of long-term goals (being active) (Apkarian et al., 2004; Hess et al., 2014; Verdejo-García et al., 2009; Walteros et al., 2011). Thus, a future study could investigate whether people with chronic pain generalize avoidance compared to pain-free controls, using the same paradigm as **Study 1**. That is, with objectively predictable pain for T1 during acquisition, we could compare (rapid) extinction of avoidance between pain-free participants and participants with chronic pain, and by including avoidance costs, we could examine whether people with chronic pain indeed disregard these costs, and avoid excessively, compared to pain-free participants. A related limitation is that we collected psychological trait measures in all the studies described in this thesis but did not find any effects on avoidance based on these. This could be due to the sample sizes of the respective studies not

allowing adequate power for detecting such effects. Alternatively, given that the samples were all healthy, the ranges in questionnaire scores may have been restricted. An interesting future prospect would be to run a meta-analysis on all these individual differences data to investigate if we then may find any effects of psychological traits on avoidance generalization.

Exploring exploration

In **Studies 1, 2, and 4**, we proposed that avoidance did not generalize as expected due to exploration of the novel generalization movement trajectories. This suggests that exploratory behavior may have a moderating effect on avoidance generalization. Given that uncertainty seemed to increase avoidance generalization in **Study 3**, we suggested that uncertainty may act on exploratory behavior by buffering its effects (i.e. extinction from expectancy violation). Another possibility is that uncertainty during acquisition directly reduces the rates of exploration due to a less noticeable difference between contexts (e.g. "contingencies were uncertain during the previous phase, therefore they will probably continue to be uncertain in this mew phase") (Cohen et al., 2007), or possibly due to increased anxiety (Grupe & Nitschke, 2013). However, apart from post-hoc visualizations and *t*-tests, we did not directly investigate this effect, nor did we attempt to replicate it yet.

Future research should attempt to directly investigate the effect of uncertainty on exploration, and its effect on avoidance generalization. This could be done, for example, by investigating the effect of Intolerance of Uncertainty (i.e. the personal tendency to experience uncertain situations as inherently aversive and anxiety provoking (Buhr & Dugas, 2002)) on exploration and avoidance generalization (in a quasi-experimental setup). Alternatively, the level of uncertainty could be directly manipulated in different groups, allowing observation of its effect on exploration. As in previous research (Krypotos et al., 2021), exploration could be operationalized as switching behavior, similar also to the post-hoc tests performed in **Studies 2, 3, and 4**. *Less exploration* could be quantified as less switching behavior altogether at the beginning of a generalization phase, whereas *less learning* from exploration could be evidenced by slower extinction of avoidance during the generalization phase, despite the presence of exploration. We further posited that exploration is characteristic of healthy behavior, especially due to the costs associated with avoidance. However, we cannot confirm this without comparisons with clinical populations, that is, we do not know whether people with chronic pain would not also explore. Although some evidence suggests that people with chronic pain may exhibit inflexible motor behavior patterns (Thomas & France, 2007; van Dieën et al., 2017), whether or not this translates

to exploring/exploiting novel behaviors remains to be tested, by directly comparing exploratory behavior between pain-free controls and people with chronic pain.

Direct investigation of the effects of costs/rewards on avoidance generalization

A further limitation is that we have thus far only speculated that the findings of dissociations between fear and avoidance were due to the costs associated with avoidance. However, in order to confirm this hypothesis, we would need to replicate the studies where avoidance did not generalize, using an additional group with no, or decreased costs. Furthermore, in the current project we focused on investigating avoidance generalization by taking into account the costs associated with avoidance. However, avoidance behavior in the real world is affected not only by costs, but also by other valued goals (e.g. obtaining rewards) competing with avoidance (Van Damme et al., 2010; Volders et al., 2015). In fact, to the best of our knowledge, goals competing with avoidance have not been investigated before in the context of pain-related avoidance *generalization*. A future study could directly manipulate costs (effort) and rewards (e.g. monetary), and investigate whether one has a greater reducing effect on avoidance generalization than the other does. This type of procedure would also enable comparison between direct (reward) and indirect (avoidance-costs) *approach* of a feared movement (T1/G1), which may prove helpful for developing future treatments.

The temporal dynamics of fear and avoidance

Finally, it is also noteworthy that, in the robotic arm-reaching paradigm (Meulders et al., 2016), Pavlovian fear and instrumental avoidance are acquired more-or-less simultaneously, making it difficult to disentangle the Pavlovian and instrumental aspects of the avoidance learning process. Although not necessarily a limitation, this is in contrast to traditional avoidance paradigms, in which fear is first acquired towards the CS during the Pavlovian phase and avoidance is examined in a subsequent instrumental phase (Krypotos et al., 2018). Although it would be possible to investigate the temporal dynamics of avoidance-emergence in relation to fear-emergence in the robotic arm-reaching paradigm, the measures we employed in the current project did not allow us to do so trial-by-trial. Indeed, avoidance behavior in the current studies was examined at a trial-by-trial basis, whereas fear- and expectancy ratings were only collected at discrete, specific time points during the task, in order to not interfere with task flow. However, to allow mapping the temporal dynamics between fear and avoidance, a future study could use a more continuous measure of fear, for example, by means of a custom-made pain-expectancy dial (Pappens et al.,

2012) to allow a detailed understanding of fear acquisition towards the different trajectories, in relation to avoidance.

Clinical and theoretical implications

With the current studies, we set out to investigate whether costly pain-related avoidance generalizes experimentally between operant pain-relevant responses (movements). The findings imply that, although costly avoidance can generalize in healthy, pain-free participants, this is often not the case. Indeed, given that avoidance generalization was attenuated compared to fear generalization in three of five studies (**Studies 1, 2, and 4**), the current findings suggest that healthy people do not readily avoid unnecessarily, especially when avoidance is costly. Therefore, the current results are in line with the fear-avoidance model of chronic pain (Crombez et al., 2012; Vlaeyen & Linton, 2000, 2012). According to the model, healthy behavior is characterized by testing and correcting pain-related fear beliefs and expectations, such that they remain in sync with the current state of injury. This allows fear and avoidance to stay checked and not become excessive (i.e. generalize). Given that participants in **Studies 1, 2, and 4**, quickly stopped avoiding, or began to avoid less, when novel responses were presented, can be interpreted as such testing and correcting of pain-related expectations, helping to keep them in line with reality. This type of behavior may be exactly what sets apart the people who recover from acute pain from those who go on to develop chronic pain disability (for example, due to avoidance generalization). Yet, the current results also imply that when the pain associated with a response is more uncertain, even healthy people may be more inclined to generalize avoidance. This finding requires replication.

Given the experimental nature of the current studies, clinical implications cannot readily be drawn. However, avoidance did generalize in **Studies 3 and 5**, indicating that pain-related avoidance can generalize from one pain-associated response to another in healthy people, highlighting the importance of avoidance in maintaining and increasing the scope of disability (A. Meulders, 2019). Furthermore, given the observed dissociations between pain-related fear and avoidance, the current findings highlight the need for research focusing on avoidance itself, rather than as a behavioral expression of fear. These findings thus corroborate the work of Fordyce, by further stressing that targeting avoidance behaviors during treatment may be especially important (Fordyce, 1976).

The current results further imply that multiple avoidance responses may need to be considered during treatment. The finding that avoidance can also generalize based on categorical relationships between operant responses, suggests that the scope of avoidance-inducing behaviors may be increasingly vast. During exposure for chronic pain, avoidance is typically prevented

because it precludes the opportunity to confirm safety (i.e. *extinction with response prevention*) (Gatzounis et al., 2021; Mineka, 1979). The empirical evidence to date has provided inconsistent results regarding the ability of extinction effects to generalize from one response to another. One study showed that the information from extinguishing one pain-associated movement generalizes to other movements in people with complex regional pain syndrome (CRPS-I), and people with chronic back pain (den Hollander et al., 2020; Trost et al., 2008). In contrast, other similar studies found no such effects (Crombez et al., 2002; Goubert et al., 2002). Research from the anxiety domain suggests that extinguishing the original CS+ may generalize to (categorically related) GSs, but extinction of a GS does not generalize to the CS+ or other GSs (Vervoort et al., 2014). Because in chronic pain the original fear learning event is not always possible to recreate, or may not be known, targeting multiple avoidance responses during exposure may prove most effective. In line with this, a recent single-case study demonstrated that when people with CRPS-I were exposed to a wide variety of movements, they exhibited greater reductions in pain-related fear, compared to people with CRPS-I who were exposed to a smaller variety of different movements. However, this greater variation in exposure did not increase the generalization of extinction learning to a larger number of novel movements (den Hollander et al., 2020). Since the results of **Studies 3 and 5** imply that avoidance can generalize from one response to another, future research should further investigate ways in which to promote the generalization of extinction effects from one movement or activity to another.

A final clinical implication relates to pain education – a strategy often employed at the beginning of exposure treatment for chronic pain, during which the therapist educates the client on the difference between acute and chronic pain, and how chronic pain may develop (e.g. the fear-avoidance model) (den Hollander et al., 2010). The aim of pain education is to prepare the client for treatment via a variety of pathways, such as reducing fear and increasing self-efficacy (den Hollander et al., 2010). Although only a first step so far, the current findings imply that avoidance generalization may be a viable topic of discussion in such pain education strategies. For example, educating clients on the possibility that avoidance may generalize to a variety of safe movements and activities may help prepare them for the possibility of multiple activities being targeted in treatment, thus giving them a sense of control during treatment (Gatzounis et al., 2021). So far, such a potential benefit for pain education remains speculative, however.

Finally, where most modern theories of avoidance behavior agree that Mowrer's Two Factor Theory does not explain all observations relating to avoidance, they still accept the two factors proposed by the theory (Krypotos et al., 2018). That is, that avoidance learning requires fear to be first acquired via Pavlovian conditioning, and only after that avoidance to be learned as

an instrumental response to fear (Krypotos et al., 2015). However, all the studies in the current research project exhibited acquisition of avoidance behavior without a separate Pavlovian learning phase. Thus, theoretically, the current findings challenge the notion that Pavlovian and instrumental fear need to be learned sequentially and suggest that they can in fact be learned more-or-less simultaneously, and that avoidance, acquired in this way, also has the potential to generalize. However, further disentangling the exact contributions of Pavlovian and instrumental processes in the robotic arm-reaching paradigm are needed before the exact contributions of both to avoidance generalization can be determined.

Conclusions

Modern biopsychosocial models of chronic pain, such as the fear-avoidance model, posit that increased pain-related fear and avoidance play critical roles in the development and maintenance of the disability exhibited by people with chronic pain (Crombez et al., 2012; Vlaeyen & Linton, 2000, 2012). However, in contrast to theoretical models assuming avoidance would always follow fear, recent findings show that fear and avoidance may dissociate when avoidance is costly (Claes et al., 2014; Pittig & Dehler, 2019). Because avoidance is a direct pathway to disability, it merits research in its own right. One of the mechanisms by which avoidance becomes excessive is when it generalizes to safe behaviors (Dymond et al., 2015). Therefore, by means of an operant avoidance-conditioning paradigm, our aim was to investigate whether costly avoidance behavior generalizes from one pain-associated movement to another. We found that costly avoidance does not necessarily generalize from one movement to another in healthy participants, even when they generalize *fear* (**Studies 1 and 2**). However, we did find (preliminary) evidence that when the pain associated with one movement is uncertain, healthy participants will persistently perform a novel movement similar to a previously safe movement, despite costs, indicating avoidance generalization (**Study 3**). Further research is needed to confirm the reliability of this finding. In order to better understand the relationship between pain-related fear and costly avoidance, we investigated whether avoidance would show a generalization gradient, typically used to indicate the extent of *fear* generalization (Dymond et al., 2015). We found that costly avoidance did not show the same pattern as pain-related fear in a task where the two were concurrently measured (**Study 4**). Taken together, these results suggest that costly avoidance does not readily generalize amongst operant avoidance responses in healthy people, even if fear remains high. Finally, we demonstrated that avoidance generalizes between operant behaviors, based on categorical knowledge (**Study 5**), suggesting that fear and avoidance of one behavior may result in an entire category of behaviors

being associated with fear and thus being avoided. Given the minimal avoidance costs in this study, it is difficult to compare these findings to the rest of the project.

Given the experimental nature of this research, the clinical implications of our findings are limited and should be interpreted with caution. Indeed, we used a novel paradigm to investigate a topic scarcely examined in humans (*operant* avoidance generalization). Thus, our findings necessarily have their limitations. However, we can relatively safely conclude that our innovative methods and findings provide a framework for further research to tap into. The fundamental research conducted in this project clearly demonstrates that such operant conditioning methods are promising as experimental models for pain-related avoidance learning. Furthermore, they add to evidence suggesting that there are differences between the generalization of pain-related fear and pain-related avoidance that require further investigation. However, based on the current data, we cannot sufficiently explain why these differences occur. Ultimately, we hope that using the methods we have developed, and building on our preliminary findings, future research may contribute to a better understanding of chronic pain disability in order to improve the lives of those suffering from such conditions.

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SUMMARY

Contemporary models of chronic pain (Vlaeyen et al., 2016; Vlaeyen and Linton, 2012, 2000) posit that pain-related fear and -avoidance play key roles in the development and maintenance of chronic pain. Although initially adaptive, when they spread (generalize) to safe movements/behaviors, fear and avoidance of pain may come at extreme individual costs, such as stigma or financial losses, and can culminate in disability (Meulders, 2019). Although fear unarguably causes discomfort, avoidance is a direct pathway to disability, and thus deserves investigation in its own right. Yet, as discussed in **Chapter 1**, research on avoidance generalization, especially in the pain domain, is scarce. Thus, we used an innovative operant avoidance-conditioning paradigm to investigate the mechanisms underlying the generalization of costly pain-related avoidance. In the paradigm, participants learned to avoid pain by performing increasingly costly arm-movements, using a robotic arm (acquisition). Subsequently (generalization), novel pain-free movements were presented, respectively similar (physically and in terms of costs) to the acquisition movements. Self-reports of pain-related fear and pain-expectancies were also measured. With this paradigm, we addressed the following questions: 1) Do healthy participants generalize costly pain-related avoidance based on perceptual (proprioceptive) similarity between pain-relevant responses (i.e. movements; **Chapter 2**)? 2) What are the boundary conditions of costly pain-related avoidance generalization in healthy participants (**Chapter 3**)? 3) How closely do concurrently measured pain-related fear- and costly pain-related avoidance generalization correspond to one another in one task (**Chapter 4**)? 4) Do healthy participants generalize pain-related avoidance from one behavior to a proprioceptively different, but categorically similar, behavior (**Chapter 5**)?

In a first study, we found that healthy people did not generalize costly pain-related avoidance based on proprioceptive similarity between movements, even though pain-related fear did generalize (**Chapter 2**). In two subsequent studies (**Chapter 3**), we aimed to further investigate this finding by making slight modifications to the original paradigm. Because operant responses may become directly related to the context in which they are learned (Rosas et al., 2013), in one of the studies, we reduced visual differences between phases, thus aiming to reduce contextual changes. We replicated the finding of fear generalizing but not avoidance. Because high expectations of punishment (e.g. pain) may lead to a large expectancy violation when punishment is discontinued (Rescorla & Wagner, 1972), in the other study we reduced the probability of pain during the acquisition movement trajectory paired with the highest probability of pain. We thus aimed to increase the uncertainty associated with this movement trajectory, and the generalization

movement trajectory similar to it. Here, costly pain-related avoidance *did* generalize along with pain-related fear.

Given that the extent of generalization is often measured in terms of generalization gradients, in **Chapter 4**, we further modified the paradigm to allow investigation of such gradients, in both fear and avoidance. We found that avoidance generalized, but only transiently. Critically, avoidance did not follow the same pattern as fear, which decreased with increasing dissimilarity to the pain-associated movement (indicative of a generalization gradient). This finding added to a growing body of literature suggesting that, when costly, avoidance in healthy people is attenuated compared to fear. However, in **Chapter 5** we showed that healthy participants do generalize pain-related avoidance (and -fear) based not on physical, but on categorical similarity between movements. Given that no costs were used in this study, it is difficult to disentangle why avoidance generalized here but not in most of the previous studies; does avoidance generalize more readily based on categorical, rather than proprioceptive similarity, or did participants simply not perceive a reason *not* to avoid due to low avoidance costs? This question requires further investigation.

In **Chapter 6**, we provide a methodological outline of the paradigm used in this project and discuss its potential for future research on the topic of avoidance. Finally, in the general discussion (**Chapter 7**), we summarize these findings, and discuss them in relation to previous literature, future research, and clinical implications. Taken together, the findings of this PhD project corroborate the notion that healthy participants do not readily avoid unnecessarily, that is, they do not exhibit generalized avoidance to safe behaviors. However, even healthy people seem to generalize avoidance to safe movements when they are not entirely certain if the original pain-associated movement will or will not be followed by pain, suggesting such uncertainty as a potential pathway to persistent and costly generalized avoidance. However, further research is required to confirm whether or not such uncertainty may be a factor worth considering in future research, and potentially in treatments targeting generalized pain-related fear and avoidance. Nevertheless, the current project provides a sound basis for further investigations into pain-related avoidance generalization in healthy populations, and a starting point for such research in clinical populations.

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SAMENVATTING

Hedendaagse modellen van chronische pijn (Vlaeyen et al., 2016; Vlaeyen en Linton, 2012, 2000) stellen dat pijngerelateerde vrees en -vermijding een sleutelrol spelen bij de ontwikkeling en instandhouding van chronische pijn. Hoewel ze aanvankelijk adaptief zijn, kunnen vrees en vermijding van pijn zich verspreiden (generaliseren) naar veilige bewegingen/gedragingen waardoor ze grote kosten voor het individu met zich meebrengen, zoals stigmatisering of financiële verliezen, en uiteindelijk kunnen leiden tot invaliditeit (Meulders, 2019). Hoewel vrees onbetwistbaar ongemak veroorzaakt, is vermijding een directe weg naar invaliditeit en verdient het daarom op zichzelf onderzoek. Maar zoals besproken in **Hoofdstuk 1**, is onderzoek naar generalisatie van vermijding schaars, vooral in het domein van pijn. Daarom hebben we een innovatief operante vermijding-conditioneringsparadigma gebruikt om de mechanismen te onderzoeken die ten grondslag liggen aan de generalisatie van kostelijke pijngerelateerde vermijding. In het paradigma leerden deelnemers pijn te vermijden door steeds kostelijker wordende armbewegingen uit te voeren met behulp van een robotarm (acquisitie). Vervolgens (generalisatie) werden nieuwe, pijnloze bewegingen gepresenteerd, respectievelijk vergelijkbaar (fysiek en qua kosten) met de acquisitiebewegingen. Zelf-gerapporteerde pijngerelateerde vrees en pijnverwachtingen werden ook gemeten. Met dit paradigma hebben we volgende vragen proberen beantwoorden: 1) Generaliseren gezonde deelnemers kostelijke pijngerelateerde vermijding op basis van perceptuele (proprioceptieve) overeenkomsten tussen pijnrelevante responsen (d.w.z. bewegingen; **Hoofdstuk 2**)? 2) Wat zijn de randvoorwaarden voor generalisatie van kostelijke pijngerelateerde vermijding bij gezonde deelnemers (**Hoofdstuk 3**)? 3) Hoe goed komen generalisatie van pijngerelateerde vrees en kostelijke pijngerelateerde vermijding overeen wanneer gelijktijdig gemeten in één taak (**Hoofdstuk 4**)? 4) Generaliseren gezonde deelnemers pijngerelateerde vermijding van het ene gedrag naar een proprioceptief verschillend, maar categorisch gelijkaardig gedrag (**Hoofdstuk 5**)?

In een eerste studie vonden we dat gezonde mensen kostelijke pijngerelateerde vermijding niet generaliseerden op basis van proprioceptieve gelijkenissen tussen bewegingen, hoewel pijngerelateerde vrees wel generaliseerde (**Hoofdstuk 2**). In twee daaropvolgende studies (**Hoofdstuk 3**) wilden we deze bevinding verder onderzoeken door kleine wijzigingen aan te brengen in het oorspronkelijke paradigma. Omdat operante responsen direct gerelateerd kunnen worden aan de context waarin ze worden geleerd (Rosas et al., 2013), hebben we in het ene onderzoek de visuele verschillen tussen fasen verminderd, om zo contextuele veranderingen te proberen verminderen. We repliceerden de bevinding dat vrees generaliseert, maar vermijding niet.

Omdat een hoge verwachting van een straf (bv. pijn) kan leiden tot een sterke schending van deze verwachting wanneer de straf niet langer volgt (Rescorla & Wagner, 1972), hebben we in de andere studie de kans op pijn verlaagd bij het acquisitiebewegingstraject met de hoogste kans op pijn. We wilden dus de onzekerheid vergroten die gepaard gaat met dit bewegingstraject en het gelijkaardige bewegingstraject voor generalisatie. Hier generaliseerde kostbare pijngerelateerde vermijding *wel* samen met pijngerelateerde angst.

Gezien de mate van generalisatie vaak wordt gemeten in termen van generalisatiegradiënten hebben we in **Hoofdstuk 4** het paradigma verder aangepast om onderzoek van dergelijke gradiënten mogelijk te maken in zowel angst als vermijding. We vonden dat vermijding generaliseerde, maar slechts tijdelijk. Cruciaal was dat vermijding niet hetzelfde patroon volgde als vrees, dat afnam met afnemende gelijkenis met de met pijngeassocieerde beweging (indicatief voor een generalisatiegradiënt). Deze bevinding droeg bij aan een groeiende literatuur die suggereert dat, in vergelijking met vrees, vermijding bij gezonde mensen wordt verminderd wanneer het kostelijk is. In **Hoofdstuk 5** hebben we echter laten zien dat gezonde deelnemers pijngerelateerde vermijding (en vrees) wel generaliseren, niet op basis van fysieke, maar op basis van categorische gelijkenissen tussen bewegingen. Gezien er in deze studie geen kosten zijn gebruikt, is het moeilijk te ontrafelen waarom vermijding hier wel gegeneraliseerde, maar niet in de meeste eerdere studies; generaliseert vermijding makkelijker op basis van categorische in plaats van proprioceptieve gelijkenis, of zagen deelnemers gewoon geen reden om niet te vermijden vanwege de lage vermijdingskosten? Deze vraag vereist nader onderzoek.

In **Hoofdstuk 6** geven we een methodologisch overzicht van het paradigma dat in dit project wordt gebruikt en bespreken we het potentieel voor toekomstig onderzoek naar vermijding. Tot slot vatten we deze bevindingen samen in de algemene discussie (**Hoofdstuk 7**) en bespreken ze in relatie tot bestaande literatuur, toekomstig onderzoek en klinische implicaties. Samengenomen bevestigen de bevindingen van dit doctoraatsproject het idee dat gezonde deelnemers niet snel onnodig vermijden en dus geen gegeneraliseerde vermijding van veilig gedrag vertonen. Zelfs gezonde mensen lijken vermijding echter te generaliseren naar veilige bewegingen wanneer ze niet helemaal zeker zijn of de oorspronkelijke pijngerelateerde beweging al dan niet zal gevolgd worden door pijn, wat wijst op onzekerheid als een mogelijk pad tot aanhoudende en kostelijke gegeneraliseerde vermijding. Er is echter verder onderzoek nodig om te bevestigen of dergelijke onzekerheid al dan niet een belangrijke factor kan zijn voor toekomstig onderzoek, en mogelijks in behandelingen gericht op gegeneraliseerde pijngerelateerde vrees en vermijding. Desalniettemin biedt het huidige project een solide basis voor verder onderzoek naar

pijngerelateerde vermijdingsgeneralisatie in gezonde populaties en een startpunt voor dergelijk onderzoek in klinische populaties.

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IMPACT PARAGRAPH

Acute pain is a universal experience with the important protective function of signaling bodily threat. However, when pain persists beyond healing time and becomes chronic, it ceases to be protective. Nearly 20% of adult Europeans suffer from chronic pain. Staggeringly, half of these people receive inadequate pain management, resulting in significant personal suffering and huge societal costs (Breivik et al., 2006; Breivik et al., 2013). Indeed, the economic impact of pain is greater than that of most other health conditions (Maniadakis & Gray, 2000), including heart disease, cancer, and diabetes (Gaskin & Richard, 2012).

Modern biopsychosocial models of chronic pain, such as the fear-avoidance model, posit that increased pain-related avoidance, motivated by pain-related fear, plays a critical role in the development and maintenance of the disability exhibited by people with chronic pain (Crombez et al., 2012; Vlaeyen & Linton, 2000, 2012). However, in contrast to theoretical models assuming avoidance would always follow fear, recent findings show that fear and avoidance may dissociate when avoidance is costly (Claes et al., 2014; Pittig & Dehler, 2019). Because avoidance is a direct pathway to disability, it merits research in its own right. One of the mechanisms by which avoidance becomes excessive is when it generalizes to safe behaviors (Dymond et al., 2015). Therefore, by means of an operant avoidance-conditioning paradigm, our aim was to investigate whether costly avoidance behavior generalizes from one pain-associated movement to another.

While chronic pain and its associated disability clearly are topics with broad societal relevance due to their high cost for our health care system and society at large, as well as the burden they put on the individual sufferer and those close to them, our approach to the topic was mainly fundamental in nature. Although fundamental research is often not easily expressed in terms of knowledge utilization, this project has the potential to contribute to science and society in several ways.

Potential theoretical impact

Avoidance generalization has traditionally been investigated by first inducing Pavlovian fear (e.g. tone-shock pairings), after which avoidance behavior is examined using an (often instructed) avoidance response (e.g. pressing a computer key) to different stimuli (e.g. tones) (Krypotos et al., 2018). Contrary to this, all the studies in the current PhD project used a paradigm where avoidance was instrumentally learnt without any preceding fear learning or instructions on how pain could be avoided. Thus, the findings of current PhD project challenges the traditional view that fear must be learned before avoidance can emerge (Mowrer, 1951), and indeed suggest that avoidance

can emerge spontaneously and more-or-less simultaneously to fear. However, the validity and underlying processes of this suggestion cannot be deciphered based on the current studies.

In a similar vein, and in contrast to traditional theories of avoidance, the findings of **Studies 1, 2 and 4** suggest that even when healthy people generalize *fear* from a pain-associated movement to a similar safe one, they do not automatically generalize *costly avoidance* of that movement to the other movement. In other words, it seems that healthy people do not let their emotions (fear) take control of their behavior (avoidance) when that behavior is costly and unnecessary. These findings add to a growing literature challenging the view that avoidance automatically follows fear (e.g. (Claes et al., 2014; Pittig & Dehler, 2019; Pittig et al., 2020), and instead show that the two can become decoupled under certain situations. This aligns with the notion that, although some degree of avoidance behavior is adaptive and necessary, avoidance becomes problematic at the point where it becomes excessive, that is, when it spreads to objectively safe behaviors, despite being increasingly costly.

Together these findings certainly have the potential to inspire a novel way of understanding and researching avoidance behavior. Given that, the basic mechanisms under investigation here are presumably shared with other forms of pathological anxiety-related avoidance behavior (Meulders, 2020), these findings potentially have impacts across domains (e.g. pain, anxiety, instrumental learning theories) and across disciplines (e.g. behavioral sciences, clinical psychology). Based on the results of the current PhD project, we can relatively safely conclude that the fundamental research conducted in this project demonstrates that operant-based conditioning methods are promising as experimental models for pain-related avoidance generalization.

Potential clinical impact

Given the experimental nature of this research, the clinical implications of our findings are limited and should be interpreted with caution. However, given that the current PhD project has allowed us to establish generalization of operant-based pain-related avoidance in the lab, the findings do contribute to our scientific knowledge about the transition from adaptive avoidance behavior in acute pain to persistent and excessive (generalized) avoidance behavior. In the future, this may help in identifying possible targets for the prevention of chronic pain disability. Specifically, the findings of **Study 3** suggest that *costly* pain-related avoidance does indeed have the potential to generalize from one pain-associated behavior (movement) to another, even in a sample of healthy people, whereas **Study 5** implied that avoidance can also generalize between operant behaviors based on more higher order reasoning, that is, knowledge about behaviors' category membership. Thus, these findings suggest that learning to avoid one behavior may result in a variety of

proprioceptively similar behaviors, or an entire category of behaviors, being associated with fear and thus being avoided. This is highly relevant for chronic pain, where people often fear physical actions rather than external stimuli (such as in Pavlovian fear generalization).

Furthermore, avoidance in **Study 3** generalized when the presentation of pain was uncertain, whereas it did not generalize in **Studies 1 and 2**, which had otherwise similar methodologies. These results offer preliminary evidence suggesting that when the pain associated with one action is uncertain, even healthy participants may generalize avoidance, that is, continue to perform a behavior, similar to a previously safe one, despite it being costly. This implies that reducing the uncertainty of pain associated with certain behaviors, may be an effective treatment strategy, aligning with recent experimental findings suggesting that controllability over pain reduces pain-related suffering (Löffler et al., 2018).

Although these findings are certainly intriguing, further research is needed to confirm their reliabilities. However, they do offer experimental evidence suggesting that in the prevention and treatment of chronic pain, it may be relevant to take into account that multiple instrumental behaviors can potentially become associated with the same feared outcome (e.g. pain exacerbation, a slipped disc) and also evoke fear and avoidance, and may thus need to be targeted as well. Ultimately, any knowledge that makes a contribution to the understanding of chronic pain disability and its mitigation, can have a great positive impact not only on the person suffering from pain, but to their social surroundings, health care systems and society as whole.

Current impact

The current findings have been presented at various international academic conferences across the pain (e.g. Pain research meeting), learning (e.g. Australian learning group conference), and anxiety (e.g. European meeting on human fear conditioning) fields (despite almost half of the PhD project taking place during the COVID-19 pandemic). Furthermore, they have been published by high impact journals (The Journal of Pain, impact factor = 4.621; Behaviour Research and Therapy, impact factor = 4.500), and through up-and-coming visual mediums (Journal of Visualized Experiments, impact factor = 1.392). Additionally, the findings have been shared across popular social platforms (e.g. Twitter, ResearchGate) and have been covered by various publications (The Academic Times, UMagazine). We plan to continue such efforts also with the so far unpublished studies in **Chapters 4 and 5**, and to share the findings among the scientific community as well as the general public.

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ABOUT THE AUTHOR

Eveliina Glogan was born on March 6th, 1992, in Turku, Finland. She completed her high school education at Puolalanmäki music oriented upper secondary school, during which her interest in psychology first sparked. In 2015, she graduated from The University of Glasgow with a Bachelor of Science in Psychology. Her interest in the psychological and neural mechanisms of pain was first piqued during her gap year in London when, on a commute, she read about the potential of rewiring the brain via novel behaviors, for treating seemingly incurable pain-conditions (Doidge, 2007). She immediately knew she wanted to investigate such neural mechanisms of persistent pain, with the aim of informing ways in which pain could be treated without, or with less, medication. In 2016 she thus enrolled in a Master of Science program in Cognitive Neuroscience at Maastricht University.

During her master thesis research internship, Eveliina chose to work with Prof. Amanda Kaas on an fMRI study within the PhD project of Emma Biggs, looking at the neural underpinnings of predictable vs. unpredictable pain. This research experience cemented her passion for the topics of pain and the related learning mechanisms, and she was thus delighted to hear of an opening for a PhD position in the lab of Dr. Ann Meulders, investigating the generalization of pain-related avoidance using an innovative robotic arm-reaching paradigm. She was subsequently hired as a PhD student on this project, which she started working on in 2017, directly after finishing her Master's degree. During her PhD, she used operant conditioning methods to investigate how chronic pain disability might develop. Specifically, she investigated the ways in which people learn to avoid pain, and painful movements and behaviors, and how avoidance of pain might subsequently spread to a range of safe movements and behaviors never paired with pain, but which somehow resemble the original painful movement or behavior. In 2021, Eveliina was rewarded the Postdoctoral mandate from KU Leuven, which will allow her to continue her research on the topic of behavioral learning mechanisms of chronic pain and its related disability.

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OUTPUT
List of publications

Articles published as part of this dissertation:

Glogan, E., Gatzounis, R., Meulders, M., & Meulders, A. (2020). Generalization of instrumentally acquired pain-related avoidance to novel but similar movements using a robotic arm-reaching paradigm. *Behaviour research and therapy*, *124*, 103525.

Glogan, E., Gatzounis, R., Vandael, K., Franssen, M., Vlaeyen, J. W., & Meulders, A. (2020). Investigating pain-related avoidance behavior using a robotic arm-reaching paradigm. *JoVE*.

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Articles published not as part of this dissertation:

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Glogan, E., Gatzounis, R., & Meulders, A. Perceptual Generalization of Operant Avoidance Behavior. Pain Research Meeting. 2018. 3.-4.09.2018, Lanaken, Belgium.

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Glogan, E. Generalization of pain-related avoidance behavior. EPP symposium: Lifestyle and Mental Health. 13.-14.02.2020, The Hague, The Netherlands.

Glogan E. Comparing generalization gradients and area shifts of pain-related fear and costly pain-related avoidance. (Online) European Meeting on Human Fear Conditioning @ Home. 17.-19.05.2021, organized by Ruhr University Bochum.

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Glogan, E., van Vliet, C., Roelandt, R., & Meulders, A. Generalization and Extinction of Concept-based Pain-related Fear. 10th European Meeting on Human Fear Conditioning. 16.-18.04.2018, Cardiff, Wales, UK.

Glogan, E., Gatzounis, R., & Meulders, A. Generalization of instrumentally acquired avoidance to novel but similar movements using a robotic arm-reaching paradigm. Expert Meeting on Avoidance, Pain and Fear. 27.-29.03.2019, Leuven, Belgium.

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Grants and Awards:

Postdoctoral Mandate (PDM). Received in June 2021 to fund a post-doctoral position at KU Leuven for the duration of one year.

APPENDIX A: Supplementary materials to Chapter 2

Chapter 2: Results of equivalence tests

We ran Two-One-Sided *T*-tests (TOST, Lakens, 2017; Lakens et al., 2018) to test for equivalence in self-reports towards the different trajectories in the Yoked Group. According to this procedure, results that fall within the range of a pre-specified upper and lower bound are considered statistically equivalent (Lakens, 2017). Equivalence bounds were set at dz = ± .51, which was determined through a sensitivity power calculation in G*Power (Heinrich-Heine-Universität, Düsseldorf, Germany), using group sample size n = 32. The desired level of statistical power was .80 and alpha, .05. We report the results of these analyses below. For the sake of brevity and clarity, tables are provided for sets of tests with multiple comparisons.

Acquisition phase

Pain-expectancy. Equivalence testing indicated that Yoked Group participants reported equivalent pain-expectancies for T1 and T2 during the final acquisition block (ACQ2), upper bound: $t(31) = 3.47$, $p = .0008$, lower bound: $t(31) = 2.30$, $p = .01$. However, ratings for T1, upper bound: $t(31) = 5.21$, $p < .0001$; lower bound: $t(31) = .56$, $p = .29$, and T2, upper bound: $t(31) = 5.21$, $p < .0001$; lower bound: $t(31) = 1.41$, $p = .08$ were not statistically equivalent to T3, due to higher expectancy ratings for T3, compared to T1 and T2 (i.e., opposite of experimental manipulation).

Pain-related fear. Similarly to pain-expectancies, equivalence testing indicated that Yoked Group participants reported equivalent pain-expectancies for T1 and T2 during the final acquisition block (ACQ2), upper bound: $t(31) = 3.21$, $p = .002$, lower bound: $t(31) = 2.56$, $p = .008$. However, ratings for T1 were not statistically equivalent to T3, upper bound: $t(31) = 4.88$, $p < .0001$; lower bound: $t(31) = .89$, $p = .19$, nor were they equivalent between T2 and T3, upper bound: $t(31) = 4.54$, $p < .0001$; lower bound: $t(31) = 1.23$, $p = .11$. Again, this effect was due to higher expectancy ratings for T3, compared to T1 and T2 (i.e., opposite of experimental manipulation).

Reminder-of-acquisition

Pain-expectancy. Equivalence testing indicated that, during the reminder-of-acquisition phase, pain-expectancy ratings for all movement trajectories were statistically equal (*p*-values for upper and lower bounds < .05; see Table S2.1), except for ratings between T1 and T3 during the second block (RACQ2), upper bound: $t(31) = 4.08$, $p = .0001$, lower bound: $t(31) = 1.69$, $p = .051$.

Table S2.1 Results of TOST equivalence testing on *pain-expectancy* reports between T1-3 in the Yoked Group during the first reminder-of-acquisition block of Study 1.

RACQ1		*t*(31)	*p*
T1 vs. T2	Upper bound	-3.64	.0005
	Lower bound	2.13	.0206
T1 vs. T3	Upper bound	-2.88	.0036
	Lower bound	2.89	.0035
T2 vs. T3	Upper bound	-1.91	.0324
	Lower bound	3.86	.0003

Table S2.2. Results of TOST equivalence testing on *pain-expectancy* reports between T1-3 in the Yoked Group during the second reminder-of-acquisition block of Study 1.

RACQ2		*t*(31)	*p*
T1 vs. T2	Upper bound	-3.31	.0012
	Lower bound	2.46	.0099
T1 vs. T3	Upper bound	-4.08	.0001
	Lower bound	1.69	.0509
T2 vs. T3	Upper bound	-3.97	.0002
	Lower bound	1.80	.0407

Pain-related fear. Similarly, all comparisons of pain-related fear ratings were equivalent (see Table S2.3), except for ratings between T1 and T3, $t(31) = 4.44$, $p < .0001$, lower bound: $t(31) = 1.33$, $p = .096$, during RACQ2. This lack of equivalence was again due to higher pain-expectancies for T3 compared to T1 (i.e., opposite of experimental manipulation). During RACQ2 (see Table S2.4), the difference in fear ratings between T1 and T2 was also not statistically equivalent, upper bound: $t(31) = 4.53$, $p < .0001$, lower bound: $t(31) = 1.24$, $p = .112$, due to higher fear towards T2 compared to T1.

Table S2.3. Results of TOST equivalence testing on *pain-related fear* reports between T1-3 in the Yoked Group during the first reminder-of-acquisition block of Study 1.

RACQ1		*t*(31)	*p*
T1 vs. T2	Upper bound	-3.36	.0010
	Lower bound	2.41	.0111
T1 vs. T3	Upper bound	-3.04	.0024
	Lower bound	2.73	.0052
T2 vs. T3	Upper bound	-2.57	.0076
	Lower bound	3.20	.0016

Table S2.4. Results of TOST equivalence testing on *pain-related fear* reports between T1-3 in the Yoked Group during the first reminder-of-acquisition block of Study 1.

RACQ2		*t*(31)	*p*
T1 vs. T2	Upper bound	-4.53	< .0001
	Lower bound	1.24	.1122
T1 vs. T3	Upper bound	-4.44	< .0001
	Lower bound	1.33	.0962
T2 vs. T3	Upper bound	-3.06	.0023
	Lower bound	2.71	.0054

Generalization

Pain-expectancy. We did not test for equivalence between G1 and G3 during the second generalization block (GEN2), given that planned comparisons showed that ratings for G3 were significantly higher than for G1 during this block. Equivalence testing for the rest of the comparisons indicated that Yoked Group participants reported equivalent pain-expectancies for G2 and G3 during the first (GEN1), upper bound: $t(31) = 3.63$, $p = .0005$, lower bound: $t(31) = 2.14$, $p = .020$, and final (GEN3), upper bound: $t(31) = 2.83$, $p = .004$, lower bound: $t(31) = 2.94$, $p = .003$, generalization blocks. During the rest of the generalization phase, pain-expectancies between the different trajectories were not statistically equivalent, due to low ratings for G1, compared to G2 and G3.

Table S2.5. Results of TOST equivalence testing on *pain-expectancies* between G1-3 in the Yoked Group during the first generalization block of Study 1**.**

GEN1		*t*(31)	*p*
G1 vs. G2	Upper bound	-4.39	< .0001
	Lower bound	1.38	.0883
G1 vs. G3	Upper bound	-4.42	< .0001
	Lower bound	1.35	.0940
G2 vs. G3	Upper bound	-3.63	.0005
	Lower bound	2.14	.0203

Table S2.6 Results of TOST equivalence testing on *pain-expectancies* between G1-3 in the Yoked Group during the second generalization block of Study 1.

GEN2		*t*(31)	*p*
G1 vs. G2	Upper bound	-4.82	< .0001
	Lower bound	.95	.1750
G2 vs. G3	Upper bound	-4.99	< .0001
	Lower bound	.78	.2195

Table S2.7 Results of TOST equivalence testing on *pain-expectancies* between G1-3 in the Yoked Group during the last generalization block of Study 1.

GEN3		*t*(31)	*p*
G1 vs. G2	Upper bound	-6.23	< .0001
	Lower bound	-.46	.6750
G1 vs. G3	Upper bound	-4.94	< .0001
	Lower bound	.83	.2058
G2 vs. G3	Upper bound	-2.83	.0041
	Lower bound	2.94	.0031

Pain-related fear. Equivalence testing indicated that pain-related fear for all the different trajectories during GEN1 were statistically equivalent. However, during the rest of the generalization phase, none of the comparisons were equivalent, except for that between G2 and G3 during GEN3, upper bound: $t(31) = 2.96$, $p = .003$, lower bound: $t(31) = 2.81$, $p = .004$.

Table S2.8 Results of TOST equivalence testing on *pain-related fear* between G1-3 in the Yoked Group during the first generalization block of Study 1.

GEN1		*t*(31)	*p*
G1 vs. G2	Upper bound	-3.68	.0004
	Lower bound	2.09	.0226
G1 vs. G3	Upper bound	-3.96	.0002
	Lower bound	1.81	.0398
G2 vs. G3	Upper bound	-3.59	.0006
	Lower bound	2.18	.0187

Table S2.9 Results of TOST equivalence testing on *pain-related fear* between G1-3 in the Yoked Group during the second generalization block of Study 1.

GEN2		*t*(31)	*p*
G1 vs. G2	Upper bound	-4.20	.0001
	Lower bound	1.57	.0636
G1 vs. G3	Upper bound	-5.44	< .0001
	Lower bound	.33	.3728
G2 vs. G3	Upper bound	-4.74	< .0001
	Lower bound	1.03	.1551

Table S2.10 Results of TOST equivalence testing on *pain-related fear* between G1-3 in the Yoked Group during the final generalization block of Study 1.

GEN2		*t*(31)	*p*
G1 vs. G2	Upper bound	-5.20	< .0001
	Lower bound	.57	.2876
G1 vs. G3	Upper bound	-4.50	< .0001
	Lower bound	1.27	.1064
G2 vs. G3	Upper bound	-2.96	.0029
	Lower bound	2.81	.0042

Taken together, equivalence tests did not indicate a clear pattern of statistical equivalence between the acquisition or generalization trajectories in the Yoked Group of Study 1. Pain-expectancies and pain-related fear to T1 and T2 were consistently equal during the acquisition

phase, whereas responses to T1 and T2 in comparison to T3 were not statistically equivalent. This effect seemed to arise from higher responding to T3 in comparison to the other two trajectories. During the generalization phase, he results were slightly different. In this phase, self-reports for G3 and G2 were consistently equivalent, whereas those for G1 and G2, and G1 and G3 were not. Again, this effect was due to lowest responding to G1. Findings from the reminder-of-acquisition phase were mixed, with the comparisons mostly being equivalent. However, T1 and T3 were not always equal during these blocks, reflecting the same pattern as the rest of the phases. In other words, self-reports in the Yoked Group showed the opposite pattern to the experimental manipulation of the Experimental Group. This finding is likely due to the Yoked Group being most exposed to T1/G1, given that participants in the Yoked Groups could not avoid the electrical stimulus, and T1/G1 was the least effortful movement trajectory.

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Chapter 2: Description of models used for ordinal logistic regression models.

Let Y_{ijkg} be the choice of person i in group g on trial j of block k. The ordinal categorical variable Y is coded as 1,2,3 for choices T1, T2 and T3. To model Y, we use a proportional odds model with a person-specific random shift in the threshold, and as predictors group, block, and a group x block interaction. The predictors are coded using dummy coding:
Group: G=0 for yoked group and G=1 for experimental group

Block: B_2 equals 1 for block=2 and 0 otherwise; B_3 equals 1 for block=3 and 0 otherwise.

The random shift effect is used to account for dependencies among the responses of the same person.

The model for the acquisition data (which includes only 2 blocks) can be formulated as follows:

$$\log\left(\frac{P(Y_{ijkg} \geq m)}{P(Y_{ijkg} < m)}\right) = \theta_i + \alpha_m + \beta_1 G_i + \beta_2 B_{2k} + \beta_3 G_i B_{2k} \quad (m = 2,3)$$

With $\theta_i \sim N(0, \sigma^2)$ a Normally distributed random shift effect of person i.

The coefficients of the model can be interpreted as follows:

- For trials in the first block (i.e. with $B_{21} = 0$), the odds to choose 3 rather than 1,2 (or the odds to choose 1 rather than 2,3) are $\exp(\beta_1)$ times higher for persons in the experimental group than for persons in the yoked group.
- For trials in the second block (i.e. with $B_{22} = 1$), the odds to choose 3 rather than 1,2 (or the odds to choose 1 rather than 2,3) are $\exp(\beta_1 + \beta_3)$ times higher for persons in the experimental group than for persons in the yoked group.
- For persons of the yoked group (i.e. with $G_i = 0$), the odds to choose 3 rather than 1,2 (or the odds to choose 1 rather than 2,3) are $\exp(\beta_2)$ times higher for trials of block 2 compared to trials of block 1.
- For persons of the experimental group (i.e. with $G_i = 1$), the odds to choose 3 rather than 1,2 (or the odds to choose 1 rather than 2,3) are $\exp(\beta_2 + \beta_3)$ times higher for trials of block 2 compared to trials of block 1.

- the odds ratio to choose 3 rather than 1,2 (or the odds to choose 1 rather than 2,3) for the experimental group compared to the yoked group is $\exp(\beta_3)$ times higher for trials of block 2 than for trials in block 1.

Explanation:

we start from:

$$\log\left(\frac{P(Y_{ijkg} \geq m)}{P(Y_{ijkg} < m)}\right) = \theta_i + \alpha_m + \beta_1 G_i + \beta_2 B_{2k} + \beta_3 G_i B_{2k}$$

Taking the exp() of both sides we get

$$\frac{P(Y_{ijkg} \geq m)}{P(Y_{ijkg} < m)} = \exp(\theta_i)\exp(\alpha_m)\exp(\beta_1 G_i)\exp(\beta_2 B_{2k})\exp(\beta_3 G_i B_{2k})$$

We can now see that the odds **for the experimental group at block 1** are:

$$\frac{P(Y_{ij11} \geq m \mid G_i = 1, B_{21} = 0)}{P(Y_{ij11} < m \mid G_i = 1, B_{21} = 0)} = \exp(\theta_i)\exp(\alpha_m)\exp(\beta_1 * 1)\exp(\beta_2 * 0)\exp(\beta_3 * 0 * 1)$$
$$= \exp(\theta_i)\exp(\alpha_m)\exp(\beta_1)$$

and that the odds for the Yoked group at block 1 are

$$\frac{P(Y_{ij10} \geq m \mid G_i = 0, B_{21} = 0)}{P(Y_{ij10} < m \mid G_i = 0, B_{21} = 0)} = \exp(\theta_i)\exp(\alpha_m)\exp(\beta_1 * 0)\exp(\beta_2 * 0)\exp(\beta_3 * 0 * 0)$$
$$= \exp(\theta_i)\exp(\alpha_m)$$

The odds-ratio is obtained by dividing the odds of the experimental group by those of the yoked group, we then get

Odds-ratio = $\exp(\beta_1)$

In other words

- For trials in the first block (i.e. with $B_{21} = 0$), the odds to choose 3 rather than 1,2 (or the odds to choose 1 rather than 2,3) are $\exp(\beta_1)$ times higher for persons in the experimental group than for persons in the yoked group.

APPENDIX B: Supplementary materials to Chapter 3

Chapter 3: Results of acquisition phases

Data analysis overview

Acquisition of self-report measures was indicated by significant differences between the different trajectories (T1 > T2 > T3), in the Experimental, but not the Yoked Group. To test these hypotheses, self-reports were averaged over blocks for all participants, and repeated measures analyses of variance (RM ANOVAs) were calculated separately for each experimental block, with Group as the between-subjects factor, and Block and Trajectory as the within-subjects factors. Comparisons of T1 *vs.* T3 were of primary interest, given that T2 was an ambiguously punished movement trajectory. Note that, for Experiment 1, only comparisons between T1 and T3 were pre-registered. However, given that all comparisons (T1 *vs.* T2, T2 *vs.* T3 and T1 *vs.* T3) were pre-registered for Experiment 2, we will report all comparisons for Experiment 1 as well.

For analyses of avoidance behavior, a MATLAB (MathWorks, Natick, MA, US) script was used to extract the maximal deviation data per trial. These values were averaged per block for each participant, and used to compare avoidance behavior between groups (RM ANOVAs) with Group as the between-subjects factor, and Block as the within-subjects factor.

Results

Experiment 1

Acquisition of pain-expectancy, pain-related fear, and avoidance behavior. A 2 x 2 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: ACQ1-2) x (Trajectory: T1-3) on the mean *pain-expectancy ratings* per acquisition block revealed a significant 3-way interaction, $F(1.77, 109.73) = 22.90$, $p < .0001$, $\eta_p^2 = .27$, indicating that pain-expectancies for the three trajectories evolved differently for the two groups. Planned comparisons confirmed that by the end of the acquisition phase (ACQ2), the Experimental Group expected the pain stimulus to occur more during T1, $t(62) = 13.38$, $p < .0001$, $d = 3.76$, and T2, $t(62) = 10.74$, $p < .0001$, $d = 2.05$, compared to T3, showing that the Experimental Group successfully acquired the experimental movement-pain contingencies (T1 > T2 > T3) (Fig. 3.2: panel A in manuscript). Furthermore, the pain stimulus was expected more during T1 than T2, $t(62) = 5.08$, $p < .0001$, $d = 1.17$. No such differences occurred in the Yoked Group (all p-values > .05) (Fig. 3.2: panel B).

A similar RM ANOVA of the mean *fear ratings* per acquisition block revealed a significant 3-way interaction, $F(1.67, 103.61) = 9.92$, $p < .001$, $\eta_p^2 = .14$. Planned comparisons confirmed similar differences as in pain-expectancy for the Experimental group at ACQ2: T1 *vs.* T3, $t(62) = 7.00$, $p < .0001$, $d = 1.38$, T2 *vs.* T3, $t(62) = 6.94$, $p < .0001$, $d = 1.21$, although the difference between T1 and T2 did not reach significance, $t(62) = 1.90$, $p = .062$ (Fig. 3.3: panel A). No such differences occurred in the Yoked Group (all *p*-values > .05) (Fig. 3.3: panel B). Thus, participants in the Experimental Group learned to expect the pain stimulus more during, and to fear, the pain-associated movements (T1-2) compared to the safe movement (T3).

A 2 x 2 RM ANOVA (Group: Experimental, Yoked) x (Block: ACQ1-2) on the mean *maximal deviation* per acquisition block revealed a significant 2-way interaction, $F(1, 62) = 12.72$, $p = < .001$, $\eta_p^2 = .17$, indicating differences in avoidance behavior over time in the two groups. As expected, planned comparisons confirmed that participants in the Experimental Group showed significantly larger deviations than the Yoked Group at ACQ2, $t(62) = 4.87$, $p < .0001$, $d = 1.22$, demonstrating successful avoidance learning (Fig. 3.4: panel A).

Experiment 2

Acquisition of pain-expectancy, pain-related fear, and avoidance behavior. A 2 x 3 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: ACQ1-3) x (Trajectory: T1-3) of mean *pain-expectancy reports* during the acquisition phase revealed a significant 3-way interaction, $F(2.90, 197.36) = 15.37$, $p < .0001$, $\eta_p^2 = .18$, suggesting that pain-expectancies for the three trajectories evolved differently in the two groups. Planned comparisons confirmed that by the end of the acquisition phase (ACQ3), the Experimental Group expected the pain stimulus to occur more during T1, $t(68) = 11.33$, $p < .0001$, $d = 2.45$, and T2, $t(68) = 10.14$, $p < .0001$, $d = 1.85$ compared to T3. Furthermore, participants also expected the pain stimulus more during T1 compared to T2, $t(68) = 3.33$, $p = .001$, $d = .72$ (Fig. 3.2: panel C). No such differences occurred in the Yoked Group (all *p*-values > .05) (Fig. 3.2: panel D).

A similar RM ANOVA of mean *fear reports* during acquisition revealed comparable effects to pain-expectancy. Namely, a significant 3-way interaction, $F(3.50, 238.11) = 15.05$, $p < .0001$, $\eta_p^2 = .18$, and planned comparisons showed that both T1, $t(68) = 9.48$, $p < .0001$, $d = 1.61$, and T2, $t(68) = 8.55$, $p < .0001$, $d = 1.33$ were feared more than T3 during ACQ3, as was T1 more than T2, $t(68) = 2.49$, $p = .015$, $d = .27$ (Fig. 3.3: panel C). No such differences occurred in the Yoked Group (all *p*-values > .05) (Fig. 3.3: panel D).

A 2 x 2 RM ANOVA (Group: Experimental, Yoked) x (Block: ACQ1-2) on mean *maximal deviation* during acquisition revealed a significant 2-way interaction, $F(1.92, 130.35) = 14.93$, $p < .0001$, $\eta_p^2 = .18$, indicating that avoidance developed differently for the two groups. Planned comparisons confirmed that the Experimental Group demonstrated larger deviations than the Yoked Group by ACQ3, $t(68) = 6.46$, $p < .0001$, $d = 1.54$ (Fig.3.4: panel B). Together these results indicate that the Experimental Group successfully acquired the movement-pain contingencies, shown by differential pain-expectancy and fear ratings, and successfully learned to avoid the pain stimulus.

Chapter 3: Results of reminder-of-acquisition

Given that generalization was tested in the absence of painful stimuli (generalization under extinction), extinction of self-reports (pain-expectancy and pain-related fear), and avoidance behavior towards the original acquisition trajectories (T1-3) was tested during brief reminder-of-acquisition blocks. In these blocks, the acquisition trajectories were once again available along with the acquisition punishment schemata.

Data analysis overview

Retention of the acquisition effects was indicated by a similar data pattern to that of the acquisition phase (Self-reports: significant differences between the different trajectories (T1 > T2 > T3), in the Experimental, but not the Yoked Group; Avoidance: significantly larger deviations in the Experimental compared to the Yoked Group). The analyses of the reminder-of-acquisition blocks were similar to those performed on the data from the acquisition phases.

Results

Experiment 1

Acquisition of pain-expectancy, pain-related fear, and avoidance behavior. A 2 x 2 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: RACQ1-2) x (Trajectory: T1-3) on the mean *pain-expectancy ratings* during the reminder-of-acquisition blocks revealed a significant Group x Trajectory interaction, $F(1.91, 118.39) = 59.41$, $p < .0001$, $\eta_p^2 = .49$, indicating that pain-expectancies for the different trajectories differed between groups during these blocks. Planned comparisons confirmed that the Experimental Group still expected the pain to occur more for T1, $t(62) = 10.66$, $p < .0001$ $d = 2.83$, and T2, $t(62) = 7.81$, $p < .0001$, $d = 1.85$, compared to T3, during the first reminder-of-acquisition block (RACQ1). Pain was also expected more for T1 compared to T2 in this block, $t(62) = 3.48$, $p = .001$, $d = .75$. The same pattern emerged in the second reminder-of-acquisition block (RACQ2: T1 *vs.* T3, $t(62) = 14.32$, $p < .0001$ $d = 3.55$; T2 *vs.* T3, $t(62) = 10.02$, $p < .0001$, $d = 1.82$; T1 *vs.* T2, $t(62) = 5.60$, $p < .0001$, $d = 1.08$) (see Fig. S3.1: panel A below). No such differences emerged in the Yoked Group (all p-values > .05) (Fig. S3.1: panel B).

A similar RM ANOVA on the mean *fear ratings* during the reminder-of-acquisition blocks also showed a significant Group x Trajectory interaction, $F(1.56, 96.64) = 23.15$, $p < .0001$, $\eta_p^2 =$

.27, suggesting that fear for the different trajectories differed between groups during these blocks. Planned comparisons confirmed that in line with the acquisition phase, the Experimental Group still feared T1, $t(62) = 7.10$, $p < .0001$, $d = 1.56$, and T2, $t(62) = 6.34$, $p < .0001$, $d = 1.36$, more than T3 during RACQ1, but fear reports did not differ between T1 and T2, $t(62) = 1.54$, $p = .128$. During RACQ2, both T1, $t(62) = 8.21$, $p < .0001$, $d = 1.91$, and T2, $t(62) = 7.26$, $p < .0001$, $d = 1.41$, continued to evoke more fear than T3. Furthermore, T1 also evoked more fear than T2, $t(62) = 2.60$, $p = .012$, $d = .32$ (Fig. S3.2: panel A). No such differences emerged in the Yoked Group (all p-values > .05) (Fig. S3.2: panel B). Taken together, these results indicate that the test of generalization (under extinction) did not affect the acquired differential pain-expectancy and fear ratings for the acquisition trajectories.

A 2 x 2 RM ANOVA (Group: Experimental, Yoked) x 2 (Block: RACQ1-2) on *maximal deviation* data yielded a significant main effect of Group, $F(1, 62) = 10.96$, $p = .002$, $\eta_p^2 = .15$. Planned comparisons confirmed that the Experimental Group avoided more than the Yoked Group, during RACQ1, $t(62) = 2.755$, $p = .008$, $d = .69$, and RACQ2, $t(62) = 3.36$, $p = .001$, $d = .84$, suggesting that acquired avoidance behavior did not extinguish during the generalization phase (Fig. S3.3: panel A).

Experiment 2

Acquisition of pain-expectancy, pain-related fear, and avoidance behavior. A 2 x 2 x 3 RM ANOVA (Group: Experimental, Yoked) x (Block: RACQ1-2) x (Trajectory: T1-3) on mean *pain-expectancy ratings* during the reminder-of-acquisition phase revealed a significant Group x Trajectory interaction, $F(1.61, 109.56) = 34.93$, $p < .0001$, $\eta_p^2 = .34$, indicating different patterns of pain-expectancies for the different trajectories between groups. Planned comparisons revealed similar effects to the acquisition phase both reminder-of-acquisition blocks in the Experimental Group (RACQ1: T1 *vs.* T3, $t(68) = 7.77$, $p < .0001$, $d = 1.77$; T2 *vs.* T3, $t(68) = 5.82$, $p < .0001$, $d = 1.13$; T1 *vs.* T2, $t(68) = 3.76$, $p < .001$, $d = .60$; RACQ2: T1 *vs.* T3, $t(68) = 8.27$, $p < .0001$, $d = 1.74$; T2 *vs.* T3, $t(68) = 6.73$, $p < .0001$, $d = 1.27$; T1 *vs.* T2, $t(68) = 3.39$, $p = .001$, $d = .44$) (Fig. S3.1: panel C). No such differences emerged in the Yoked Group (all p-values > .05) (Fig. S3.1: panel D).

A similar RM ANOVA of mean *fear ratings* during the reminder-of-acquisition blocks also showed a significant Group x Trajectory interaction, $F(1.59, 108.11) = 27.15$, $p < .0001$, $\eta_p^2 = .29$, indicating that fear for the different trajectories differed between groups during these blocks. Furthermore, the Experimental Group still feared T1, $t(68) = 6.14$, $p < .0001$, $d = 1.22$, and T2, $t(68) = 5.21$, $p < .0001$, $d = .97$, more than T3 during RACQ1, although not T1 more than T2,

$t(68) = 1.88$, $p = .065$. During RACQ2, however, in line with the acquisition phase, all comparisons were significant: T1 *vs.* T3, $t(68) = 7.39$, $p < .0001$, $d = 1.34$; T2 *vs.* T3, $t(68) = 6.33$, $p < .0001$, $d = 1.07$; T1 *vs.* T2, $t(68) = 2.27$, $p = .026$, $d = .27$ (Fig. S3.2: panel C). No differences occurred for any of the pairs in the Yoked Group (all p-values > .05) (Fig. S3.2: panel D).

A 2 x 2 RM ANOVA (Group: Experimental, Yoked) x (Block: RACQ1-2) on mean *maximal deviation* data during the reminder-of-acquisition blocks yielded a significant main effect of Group, $F(1, 68) = 26.39$, $p < .0001$, $\eta_p^2 = .28$. Planned comparisons confirmed that avoidance behavior persisted during the reminder-of-acquisition blocks: the Experimental Group avoided more than the Yoked Group during RACQ1, $t(68) = 4.83$, $p < .0001$, $d = 1.15$, and RACQ2, $t(68) = 4.13$, $p < .001$, $d = .99$ (Fig. S3.3: panel B). Thus, acquired pain-expectancies, pain-related fear, and acquired avoidance behavior did not extinguish due to the test of generalization under extinction.

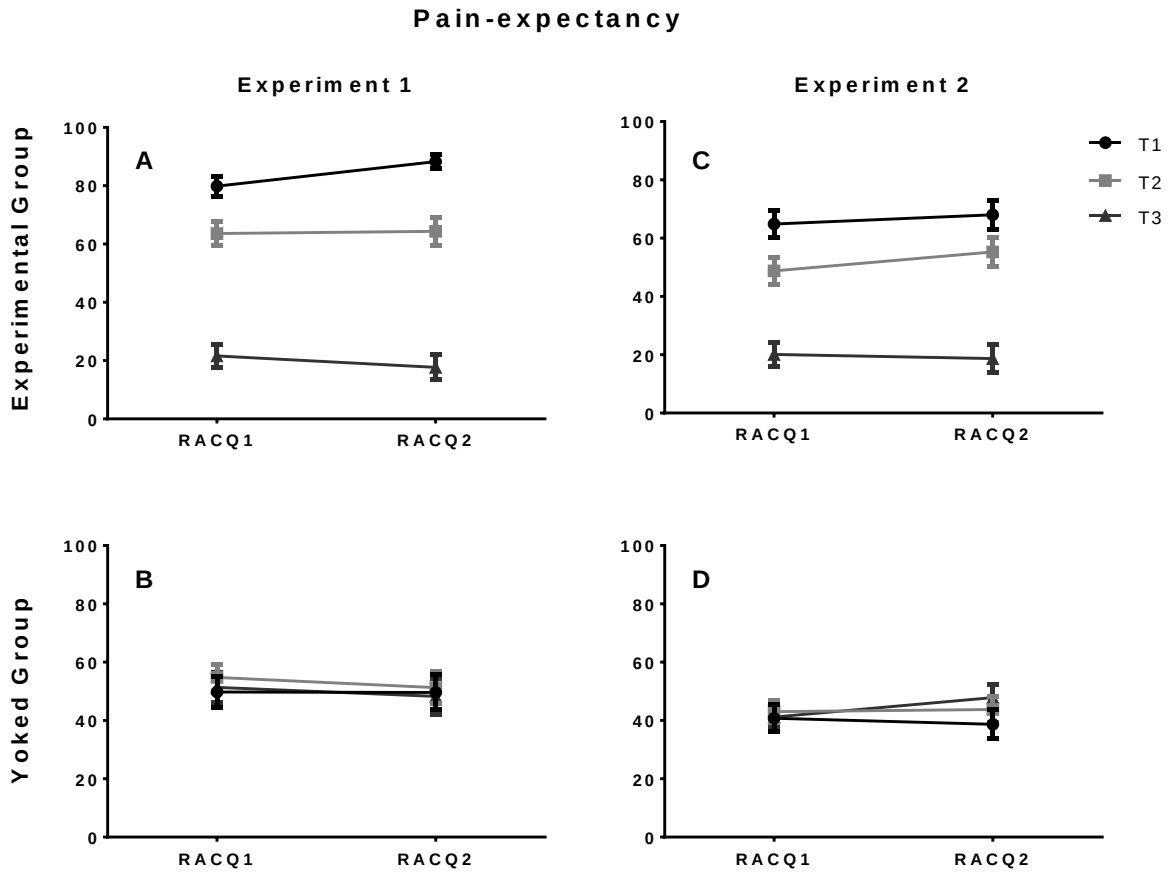

Figure S3.1. Mean pain-expectancy ratings towards the acquisition trajectories (T1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiments 1 (panels A and B) and 2 (panels C and D), during the reminder-of-acquisition blocks (RACQ1 and RACQ2).

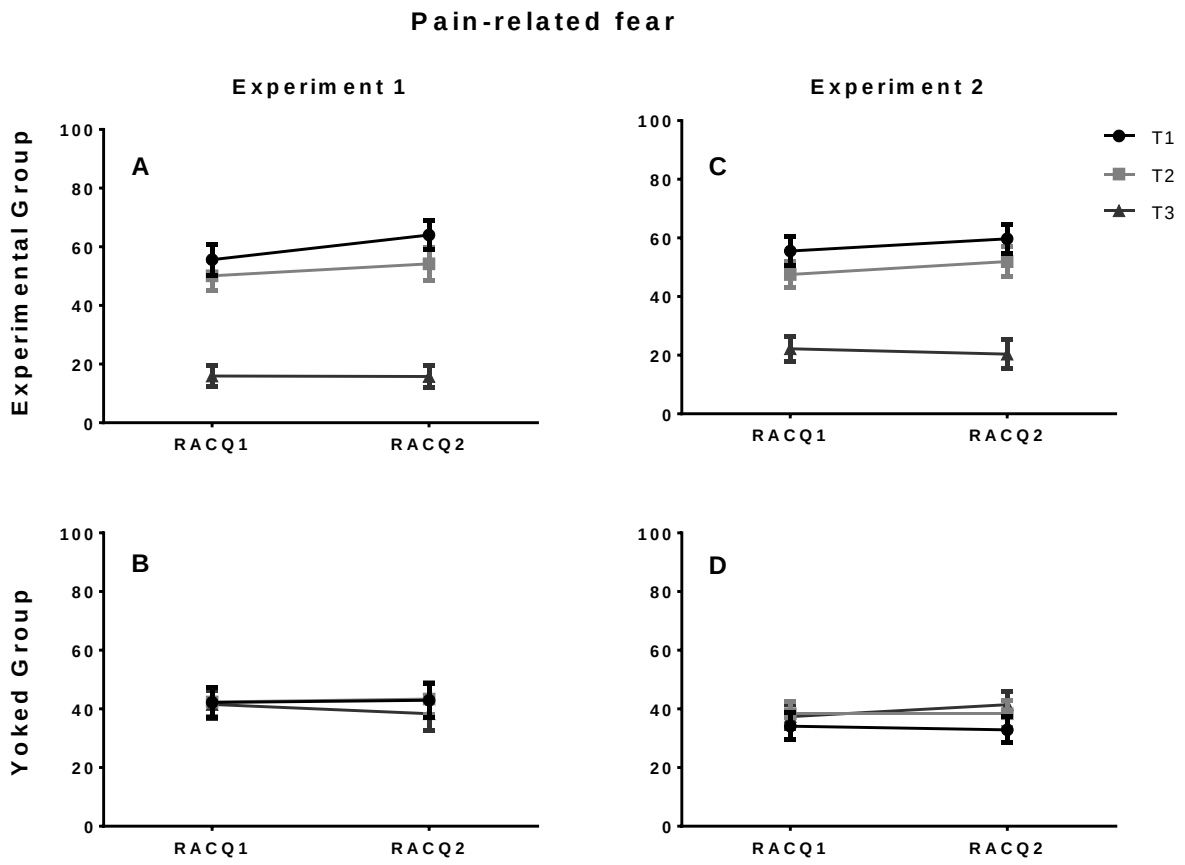

Figure S3.2. Mean pain-related fear ratings towards the acquisition trajectories (T1-3) in the Experimental (panels A and C) and Yoked (panels B and D) Groups of Experiments 1 (panels A and B) and 2 (panels C and D), during the reminder-of-acquisition blocks.

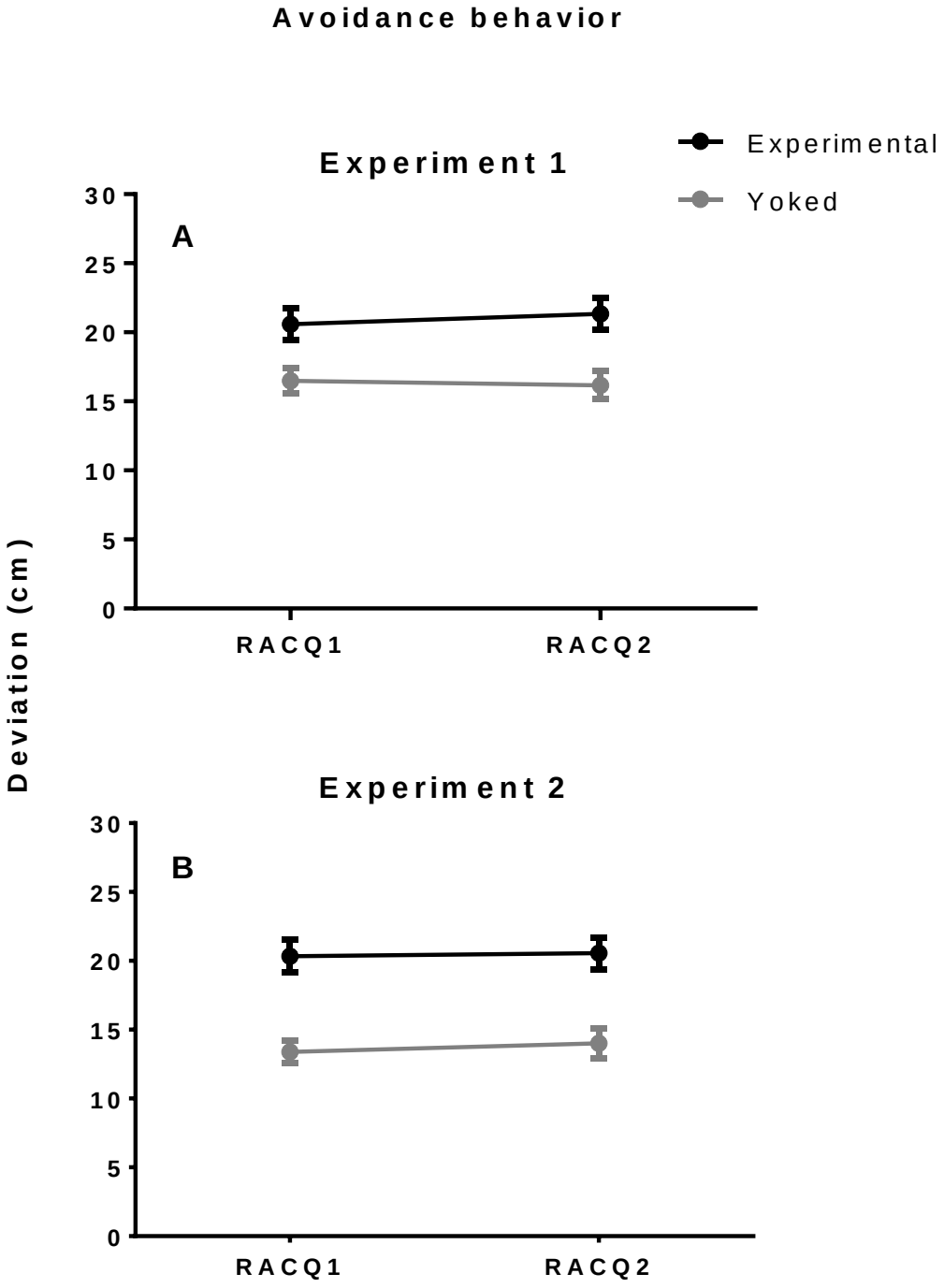

Figure S3.3. Mean maximum deviation (in cm) from the shortest trajectory from the starting position to the target during the reminder-of-acquisition blocks (RACQ1 and RACQ2) in the Experimental and Yoked Groups of Experiments 1 (panel A) and 2 (panel B).

Chapter 3: Complete fear generalization results

Results of planned comparisons of pain-related fear during the generalization phases of Experiments 1 and 2.

Results

Experiment 1

Table S3.1. Results of planned comparisons (G1 *vs.* G2, G1 *vs.* G3, G2 *vs.* G3) of pain-related fear in the Experimental Group of Experiment 1 during the first (GEN1), second (GEN2), and third (GEN3) generalization blocks.

Comparison	$t(62)$	p	Cohen's d
GEN1			
G1 *vs.* G2	1.03	.307	.09
G1 *vs.* G3	2.33	.069	.36
G2 *vs.* G3	2.22	.060	.30
GEN2			
G1 *vs.* G2	.64	.527	.07
G1 *vs.* G3	2.42	.037	.45
G2 *vs.* G3	2.63	.032	.39
GEN3			
G1 *vs.* G2	-.46	.646	-.05
G1 *vs.* G3	2.73	.017	.55
G2 *vs.* G3	3.55	.002	.56

p-values are Holm-Bonferroni corrected.

Experiment 2

Table S3.2. Results of planned comparisons (G1 *vs.* G2, G1 *vs.* G3, G2 *vs.* G3) of pain-related fear in the Experimental Group of Experiment 2 during the first (GEN1), second (GEN2), and third (GEN3) generalization blocks.

Comparison	$t(68)$	p	Cohen's d
GEN1			
G1 *vs.* G2	.011	.991	.00
G1 *vs.* G3	3.253	.004	.58
G2 *vs.* G3	3.966	< .001	.59
GEN2			
G1 *vs.* G2	.755	.453	.09
G1 *vs.* G3	2.679	.028	.49
G2 *vs.* G3	2.601	.023	.44
GEN3			
G1 *vs.* G2	-.546	.587	-.06
G1 *vs.* G3	3.182	.004	.58
G2 *vs.* G3	4.604	< .001	.68

p-values are Holm-Bonferroni corrected.

Chapter 3: Switching Behavior

Switching behavior (visualized in Fig. S3.4) was operationalized as choosing a movement trajectory different from the one on the previous trial. This gives a rough estimate of exploratory behavior, as more switching indicates more exploration. The visualization suggests that switching behavior gradually decreased throughout acquisition phases in both Experiments 1 and 2. This decrease indicates that participants learned the experimental contingencies and switched from exploring all trajectories to exploiting the avoidance trajectory (as shown by manipulation checks of avoidance acquisition in the manuscript). Comparing the first generalization blocks of both experiments, an increase in switching behavior can be observed in Experiment 1, whereas this increase seems absent or at least attenuated in Experiment 2. In other words, in Experiment 1 participants seemed to explore the novel generalization trajectories at the start of the generalization test, whereas in Experiment 2, participants tended to exploit the trajectory similar to the original avoidance response. A post-hoc independent samples *t*-test comparing the relative frequencies in switching behavior in the Experimental Groups of Experiments 1 and 2, during the first generalization blocks of both experiments, confirmed that there was more switching in Experiment 1, $t(20) = 2.10$, $p = .049$, $d = .94$. It is worth noting that, Experiment 2 had a longer acquisition phase than Experiment 1 (Experiment 2: 36 trials; Experiment 1: 24 trials). However, in **Study 1**, where avoidance also did not generalize, the acquisition phase was even longer (48 trials). Therefore, we do not believe that the longer acquisition phase in Experiment 2 can explain the current finding of avoidance generalization in Experiment 2, but not Experiment 1.

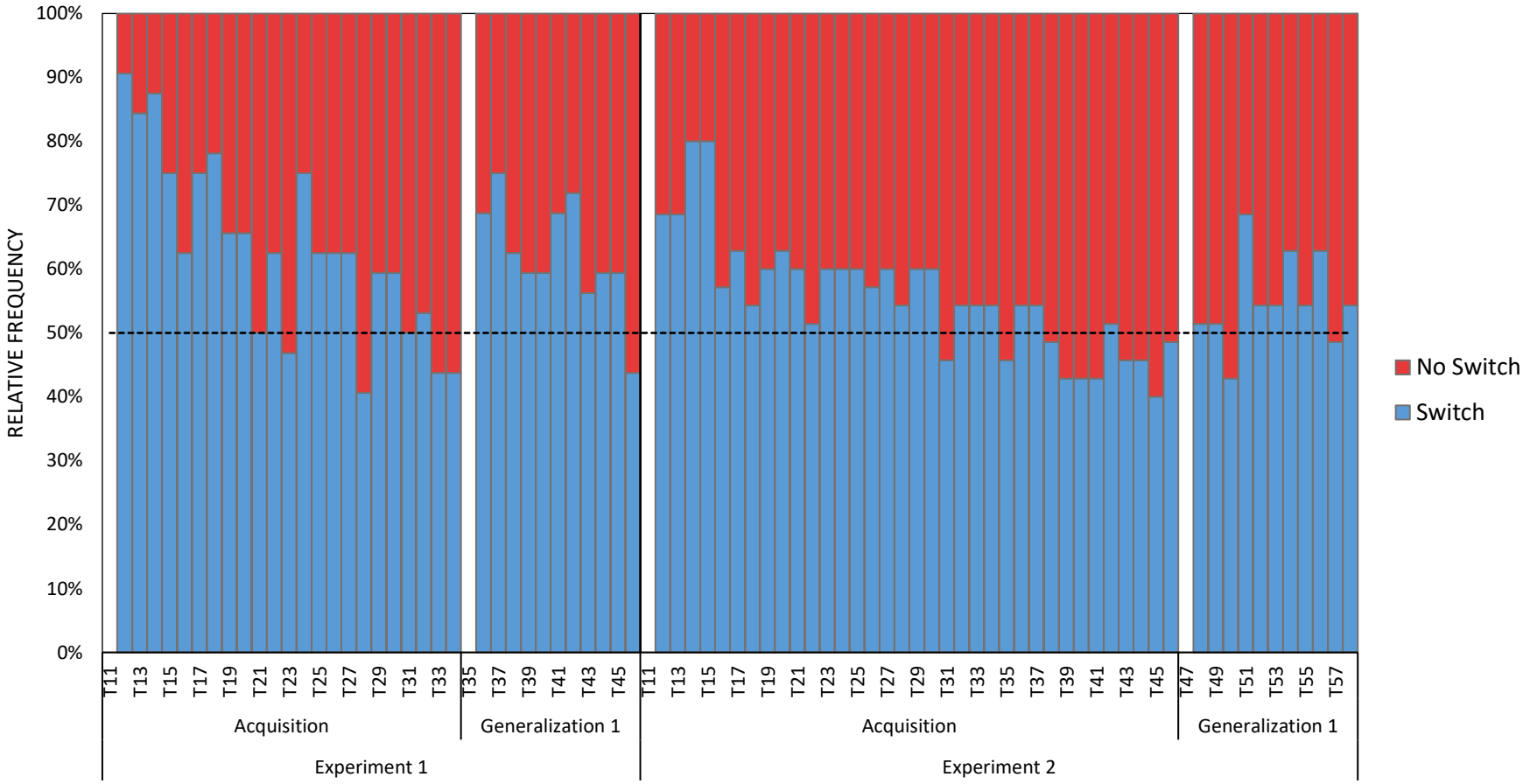

Figure S3.4. Switching behavior in the Experimental Groups of Experiments 1 and 2. Left panel: Experiment 1, right panel: Experiment 2. Switching behavior is operationalized as choosing a movement trajectory different from the one on the previous trial (T). Note that this implies that the first trial of each phase is a missing value. Choice-switches are shown during the entire acquisition phase (Experiment 1: T11-T34; Experiment 2: T11-T46), and the first block of the generalization phase (Experiment 1: T35-T46; Experiment 2: T47-T58) for both experiments. Note that, the acquisition phase in Experiment 2 included one extra block of 12 trials, compared to Experiment 1.

Chapter 3: Results of equivalence tests

Similarly to **Study 1**, we performed TOSTs (Lakens et al., 2018) to test for equivalence in self-reports towards the different trajectories in the Yoked Group. Equivalence bounds were set at dz = ± .51, which was determined through a sensitivity power calculation in G*Power (Heinrich-Heine-Universität, Düsseldorf, Germany), using group sample sizes n = 32 (Experiment 1) and n = 35 (Experiment 2). The desired level of statistical power was .80 and alpha, .05. We report the results of these analyses below.

Experiment 1

Generalization of pain-expectancies. Equivalence testing indicated that Yoked Group participants reported equivalent pain-expectancies for G2 and G3 during the first generalization block (GEN1; p-values for upper and lower bounds < .05). However, ratings for G1 were not statistically equivalent to G2 (upper bound: t(31) = -5.56, p < .001; lower bound: t(31) = .22, p = .416), nor G3 (upper bound: t(31) = -4.82, p < .001; lower bound: t(31) = .94, p = .176), due to lower expectancy ratings for G1 (i.e., opposite of experimental manipulation).

Generalization of pain-related fear. We did not perform equivalence tests on these data, given that they did not follow our alternative hypotheses.

Experiment 2

Generalization of pain-expectancies. Equivalence testing indicated that Yoked Group participants reported equivalent pain-expectancies for G1 and G3, and G2 and G3 during GEN1 (p-values for upper and lower bounds < .05). However, ratings for G1 were not statistically equivalent to G2 (upper bound: t(34) = -4.52, p < .001; lower bound: t(34) = 1.52, p = .069), due to lower expectancy ratings for G1 (i.e., opposite of experimental manipulation).

Generalization of pain-related fear. Equivalence testing indicated that in the Yoked Group, fear reports for G2 and G3 were equivalent during GEN1 (p-values for upper and lower bounds < .05). However, reports for G1 were not statistically equivalent to G2 (upper bound: t(34) = -4.92, p < .001; lower bound: t(34) = 1.12, p = .136), nor G3 (upper bound: t(34) = -4.36, p < .001; lower bound: t(34) = 1.68, p = .051), due to lower fear reports for G1 (i.e., opposite of experimental manipulation).

In sum, equivalence tests did not indicate a clear pattern of statistical equivalence between the generalization trajectories in the Yoked Groups of Experiments 1 and 2. Pain-expectancies and pain-related fear to G2 and G3 were consistently equal in both Experiments, and in both

measures. However, responding to G1 was not equal to G2 or G3 (apart from pain-expectancies in Experiment 2; G1 = G3), due to self-reports being lower for G1 than the other trajectories. In other words, and in line with equivalence testing in Study 1, self-reports in the Yoked Groups showed the opposite pattern to the experimental manipulation of the Experimental Group. This finding is likely due to the Yoked Group being most exposed to G1, given that participants in the Yoked Groups could not avoid the electrical stimulus, and G1 was the least effortful movement trajectory.

References

Lakens, D., Scheel, A. M., & Isager, P. M. (2018). Equivalence testing for psychological research: A tutorial. *Advances in Methods and Practices in Psychological Science*, *1*(2), 259-269.

APPENDIX C: Supplementary materials to Chapter 4

Chapter 4: Results of equivalence tests

Similarly to **Studies 1, 2, and 3**, we performed TOSTs (Lakens et al., 2018) to test for equivalence in self-reports towards the different trajectories in the Yoked Group. Equivalence bounds were set at dz = ± .53, which was determined through a sensitivity power calculation in G*Power (Heinrich-Heine-Universität, Düsseldorf, Germany), using group sample size n = 30. The desired level of statistical power was .80 and alpha, .05. We report the results of these analyses below.

Acquisition

Pain-expectancy. Equivalence testing indicated that Yoked Group participants reported equivalent pain-expectancies for T+ and T- during the final acquisition block (ACQ2), upper bound: $t(29) = 3.42$, $p = .0009$, lower bound: $t(29) = 2.39$, $p = .012$.

Pain-related fear. Similarly to pain-expectancies, equivalence testing indicated that Yoked Group participants reported equivalent pain-expectancies for T+ and T- during ACQ2, upper bound: $t(29) = 3.90$, $p = .0002$, lower bound: $t(29) = 1.90$, $p = .033$.

Generalization

Pain-expectancy. The planned comparisons from our main analyses showed that the Yoked Group expected pain more during **T+** compared to **G1**, $t(29) = 2.11$, $p = .039$, $d = .361$. Furthermore, they also expected pain more during **T-** compared to **G1**, $t(29) = 2.75$, $p = .008$, $d = .454$, and **G2**, $t(29) = 2.81$, $p = .007$, $d = .421$. Thus, we did not run equivalence tests on these comparisons.

Equivalence testing for the rest of the comparisons indicated that Yoked Group participants continued to expect pain equally for **T+** and **T-** during the generalization phase, upper bound: $t(29) = 3.56$, $p = .0006$, lower bound: $t(29) = 2.24$, $p = .016$. Furthermore, they reported equivalent pain-expectancies for **T+** and **G3**, upper bound: $t(29) = 1.98$, $p = .028$, lower bound: $t(29) = 3.82$, $p = .0003$, and **T+** and **G4**, upper bound: $t(29) = 2.38$, $p = .0079$, lower bound: $t(29) = 3.24$, $p = .0015$. **G1** and **G2** also evoked similar levels of pain-expectancies, upper bound: $t(29) = 3.46$, $p = .0008$, lower bound: $t(29) = 2.34$, $p = .013$, as did **G3** and **G4**, upper bound: $t(29) = 3.53$, $p = .0007$, lower bound: $t(29) = 2.27$, $p = .015$, and **T-** and **G4**, upper bound: $t(29) = 1.80$, $p = .041$, lower bound: $t(29) = 4.00$, $p = .0002$. None of the other comparisons were statistically equivalent (see Table S4.1).

Table S4.1. Results of TOST equivalence testing on *pain-expectancies* between all movement trajectories in the Yoked Group during the generalization phase of Study 4**.**

		G1		**G2**		**G3**		**T-**		**G4**	
		***t*(29)**	***p***	***t*(29)**	***p***	***t*(29)**	***p***	***t*(29)**	***p***	***t*(29)**	***p***
T+	Upper bound	N/A	N/A	-.57	.2860	-1.98	.0283	-3.56	.0006	-2.56	.0079
	Lower bound	N/A	N/A	5.23	< .0001	3.82	.0003	2.24	.0163	3.24	.0015
G1	Upper bound			-3.46	.0008	-5.25	< .0001	N/A	N/A	-5.15	< .0001
	Lower bound			2.344	.0131	.55	.2919	N/A	N/A	.66	.2571
G2	Upper bound					-4.74	< .0001	N/A	N/A	-4.94	< .0001
	Lower bound					1.06	.1487	N/A	N/A	.87	.1964
G3	Upper bound							-4.86	< .0001	-3.53	.0007
	Lower bound							.9430	.1767	2.27	.0152
T-	Upper bound									-1.80	.0410
	Lower bound									4.00	.0002

Note – N/A refers to the comparisons that were significantly different in the follow-up planned comparisons from our RM ANOVAs.

Pain-related fear. The planned comparisons from our main analyses showed that the Yoked Group feared **T-** more than **G1**, $t(29) = 2.60$, $p = .012$, $d = .329$, and **G2**, $t(29) = 2.359$, $p = .022$, $d = .277$. Furthermore, **G3** was feared more than **G1** in this group, $t(29) = 2.04$, $p = .046$, $d = .236$. Thus, we did not run equivalence tests on these comparisons.

Equivalence testing for the rest of the comparisons indicated that, similarly to pain-expectancies, Yoked Group participants reported equivalent pain-expectancies for **T+** and **G3**, upper bound: $t(29) = 1.98$, $p = .028$, lower bound: $t(29) = 3.82$, $p = .0003$, and **T+** and **G4**, upper bound: $t(29) = 2.38$, $p = .012$, lower bound: $t(29) = 3.42$, $p = .0009$. Furthermore, in line with pain-expectancies, Yoked Group participants continued to expect pain equally for **T+** and **T-** during the generalization phase, upper bound: $t(29) = 3.33$, $p = .0011$, lower bound: $t(29) = 2.48$, $p = .0096$.

Again, in line with pain-expectancies, **G1** and **G2** were also feared equally, upper bound: $t(29) = 3.81$, $p = .0003$, lower bound: $t(29) = 2.00$, $p = .028$, as were **G3** and **T-**, upper bound: $t(29) = 3.96$, $p = .0002$, lower bound: $t(29) = 1.85$, $p = .037$, and **G3** and **G4**, upper bound: $t(29) = 2.56$, $p = .0080$, lower bound: $t(29) = 3.25$, $p = .0014$. None of the other comparisons were statistically equivalent (see Table S4.2).

In sum, aligning with Studies 1, 2, and 3, equivalence tests did not indicate a clear pattern of statistical equivalence between the acquisition or generalization trajectories in the Yoked Group of Study 4. During the generalization phase, the results of equivalence testing were very mixed, suggesting that responding, in general, was relatively random. Indeed, this unclear pattern of responding reflects the experience of the Yoked Group, for which the pain stimulus was presented in the absence of any contingencies.

References

Lakens, D., Scheel, A. M., & Isager, P. M. (2018). Equivalence testing for psychological research: A tutorial. *Advances in Methods and Practices in Psychological Science*, *1*(2), 259-269.

Table S4.2. Results of TOST equivalence testing on *pain-related fear* between all movement trajectories in the Yoked Group during the generalization phase of Study 4**.**

		G1		**G2**		**G3**		**T-**		**G4**	
		***t*(29)**	***p***	***t*(29)**	***p***	***t*(29)**	***p***	***t*(29)**	***p***	***t*(29)**	***p***
T+	Upper bound	-.27	.3964	-.85	.2003	-2.45	.0103	-3.33	.0012	-2.38	.0120
	Lower bound	5.54	< .0001	4.95	< .0001	3.35	.0011	2.48	.0097	3.42	.0009
G1	Upper bound			-3.81	.0003	N/A	N/A	N/A	N/A	-4.76	< .0001
	Lower bound			2.00	.0277	N/A	N/A	N/A	N/A	1.04	.1531
G2	Upper bound					-4.93	< .0001	N/A	N/A	-4.13	.0001
	Lower bound					.8763	.1940	N/A	N/A	1.68	.0518
G3	Upper bound							-3.96	.0002	-2.56	.0080
	Lower bound							1.85	.0373	3.25	.0015
T-	Upper bound									-1.63	.0570
	Lower bound									4.18	.0001

Note – N/A refers to the comparisons that were significantly different in the follow-up planned comparisons from our RM ANOVAs.

Chapter 4: Description of models generalization phase

Let Y_{ij} be the choice of person i on trial j. The ordinal categorical variable Y is coded as 1,2,3,4 for choices G1, G2, G3 and G4. Group is dummy coded using $G_i = 0$ if person i belongs to the yoked group and $G_i = 1$ if person i belongs to the experimental group.

Model 1: proportional odds model with group-effect

To model Y, we use a proportional odds model with a person-specific random shift in the threshold and group as predictor.

The model can be formulated as follows:

$$\log\left(\frac{P(Y_{ij} \geq m)}{P(Y_{ij} < m)}\right) = \theta_i + \alpha_m + \beta_G G_i \quad (m = 2,3,4)$$

With $\theta_i \sim N(0, \sigma^2)$ a Normally distributed random shift effect of person i. The random shift effect is used to account for dependencies among the responses of the same person.

The coefficients of the model can be interpreted as follows:

- For persons of the Yoked group (i.e. $G_i = 0$) with an average value of the random intercept (i.e. $\theta_i = 0$), the odds to choose G4 rather than G1,G2,G3 equal $\exp(\alpha_4)$.
- For persons of the Yoked group with an average value of the random intercept, the odds to choose G4,G3 rather than G1,G2 equal $\exp(\alpha_3)$.
- For persons of the Yoked group with an average value of the random intercept, the odds to choose G4,G3,G2 rather than G1 equal $\exp(\alpha_2)$.
- For persons of the experimental group (i.e. with $G_i = 1$), the odds to choose G4 rather than G1,G2,G3 (or the odds to choose G3,G4 rather than G1,G2; or the odds to choose G2,G3,G4 rather than G1) are $\exp(\beta_G)$ times higher compared to persons of the Yoked group.

  To test whether persons of the experimental group are more likely to choose G3,G4 rather than G1, G2 we test $H_0 : \beta_G \leq 0$ against $H_A : \beta_G > 0$.

Category probabilities for a person with a value of θ_i for the random intercept can be derived from the cumulative probabilities as follows:

$$P(Y_{ij} \geq 4) = P(Y_{ij} = 4) = \frac{\exp(\theta_i + \alpha_4 + \beta_G G_i)}{1 + \exp(\theta_i + \alpha_4 + \beta_G G_i)}$$

$$P(Y_{ij} = 3) = P(Y_{ij} \geq 3) - P(Y_{ij} \geq 4) = \frac{\exp(\theta_i + \alpha_3 + \beta_G G_i)}{1 + \exp(\theta_i + \alpha_3 + \beta_G G_i)} - \frac{\exp(\theta_i + \alpha_4 + \beta_G G_i)}{1 + \exp(\theta_i + \alpha_4 + \beta_G G_i)}$$

$$P(Y_{ij} = 2) = P(Y_{ij} \geq 2) - P(Y_{ij} \geq 3) = \frac{\exp(\theta_i + \alpha_2 + \beta_G G_i)}{1 + \exp(\theta_i + \alpha_2 + \beta_G G_i)} - \frac{\exp(\theta_i + \alpha_3 + \beta_G G_i)}{1 + \exp(\theta_i + \alpha_3 + \beta_G G_i)}$$

$$P(Y_{ij} = 1) = 1 - P(Y_{ij} \geq 2)$$

Model 2: proportional odds model with group x trial interaction

To model Y, we use a proportional odds model with a person-specific random shift in the threshold and group, trial and group x trial interaction as predictors. Trial is coded with dummies T_j $(j = 2, \ldots, 12)$ that equal 1 for trial j and 0 otherwise. The first trial is used as the reference category.

The model can be formulated as follows:

$$\log\left(\frac{P(Y_{ij} \geq m)}{P(Y_{ij} < m)}\right) = \theta_i + \alpha_m + \beta_G G_i \ (m = 2, 3, 4;\ j = 1)$$

and

$$\log\left(\frac{P(Y_{ij} \geq m)}{P(Y_{ij} < m)}\right) = \theta_i + \alpha_m + \beta_G G_i + \beta_j T_j + \beta_{Gxj} G_i T_j \ \ (m = 2, 3, 4;\ j = 2, \ldots, 12)$$

With $\theta_i \sim N(0, \sigma^2)$ a Normally distributed random shift effect of person i. The random shift effect is used to account for dependencies among the responses of the same person.

The coefficients of the model can be interpreted as follows:

- For persons of the Yoked group (i.e. $G_i = 0$) with an average value of the random intercept (i.e. $\theta_i = 0$), the odds to choose G4 rather than G1,G2,G3 in the first trial (i.e. $T_1 = 0$) equal $\exp(\alpha_4)$.

- For persons of the Yoked group with an average value of the random intercept, the odds to choose G4,G3 rather than G1,G2 in the first trial equal $\exp(\alpha_3)$.
- For persons of the Yoked group with an average value of the random intercept, the odds to choose G4,G3,G2 rather than G1 in the first trial equal $\exp(\alpha_2)$.
- For persons of the experimental group (i.e. with $G_i = 1$), the odds to choose G4 rather than G1,G2,G3 (or the odds to choose G3,G4 rather than G1,G2; or the odds to choose G2,G3,G4 rather than 1) in the first trial are $\exp(\beta_G)$ times higher compared to persons of the Yoked group.
- For persons of the experimental group (i.e. with $G_i = 1$), the odds to choose G4 rather than G1,G2,G3 (or the odds to choose G3,G4 rather than G1,G2; or the odds to choose G2,G3,G4 rather than 1) in trial j $(j = 2,\ldots,12)$ are $\exp(\beta_G + \beta_{Gxj})$ times higher compared to persons of the Yoked group.

As with model 1 category probabilities can be computed from the cumulative probabilities.

Table S4.1. Estimated model coefficients and 90% credible intervals for model 1 and model 2.

		Model 1		Model 2	
Effect	**Parameter**	**Estimate**	**90% CI**	**Estimate**	**90% CI**
Threshold	α_2	.26	[-.09, .59]	-.56	[-1.26, .14]
	α_3	-0.80	[-1.14, -.46]	-1.70	[-2.39, -.99]
	α_4	-1.92	[-2.29, -1.57]	-2.89	[-3.61, -2.17]
Group	β_G	.73	[.27, 1.20]	1.90	[.90, 2.90]
Trial	β_2			-.24	[-1.13, .64]
	β_3			1.34	[.51, 2.19]
	β_4			1.68	[.83, 2.51]
	β_5			.14	[-.79, 1.06]
	β_6			.80	[-.04, 1.64]
	β_7			1.04	[.19, 1.86]
	β_8			1.19	[.34, 2.05]
	β_9			-.01	[-.95, .93]
	β_{10}			.81	[-.02, 1.64]
	β_{11}			1.31	[.48, 2.15]
	β_{12}			1.67	[.79, 2.56]
Group x Trial	β_{Gx2}			.48	[-.74, 1.71]
	β_{Gx3}			-1.45	[-2.62, -.30]
	β_{Gx4}			-1.57	[-2.78, -.40]
	β_{Gx5}			-.20	[-1.48, 1.11]
	β_{Gx6}			-1.29	[-2.48, -.10]
	β_{Gx7}			-1.33	[-2.52, -.14]
	β_{Gx8}			-1.37	[-2.58, -.17]

	β_{Gx9}			-1.50	[-2.79, -.20]
	β_{Gx10}			-1.22	[-2.37, -.07]
	β_{Gx11}			-1.74	[-2.92, -.56]
	β_{Gx12}			-2.20	[-3.43, -.97]
Random shift	σ	.93	[.72, 1.18]	1.02	[.79, 1.28]

APPENDIX D: Supplementary materials to Chapter 6

Chapter 6: Table of Materials

Name of Material/ Equipment	Company	Catalog Number	Comments/Description
1 computer and computer screen	Intel Corporation	64-bit Intel Core	Running the experimental script
40 inch LCD screen	Samsung Group		Presenting the experimental script
Blender 2.79	Blender Foundation		3D graphics software for programming the graphics of the experiment
Conductive gel	Reckitt Benckiser	K-Y Gel	Facilitates conduction from the skin to the stimulation electrodes
Constant current stimulator	Digitimer Ltd	DS7A	Generates electrical stimulation
HapticMaster	Motekforce Link		Robotic arm
Matlab	MathWorks		For writing scripts for participant randomization schedule, and for extracting maximum deviation from shortest trajectory per trial
Qualtrics	Qualtrics		Web survey tool for psychological questionnaires
Rstudio	Rstudio Inc.		Statistical analyses
Stimulation electrodes	Digitimer Ltd	Bar stimulating electrode	Two reusable stainless steel disk electrodes; 8mm diameter with 30mm spacing

Tablet	AsusTek Computer Inc.	ASUS ZenPad 8.0	For providing responses to psychological trait questinnaires
Triple foot switch	Scythe	USB-3FS-2	For providing self-report measures on VAS scale
Unity 2017	Unity Technologies		Cross-platform game engine for writing the experimental script including presentations of electrocutaneous stimuli
C#			Programming language used to program the experimental task
Sekusept Plus	Ecolab		Disinfectant solution for cleaning medical instruments