

You'll never know if you never try

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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) (Kryptos 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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