American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 18, No 8 (August), 2017: pp 889-898
Available online at www.jpain.org and www.sciencedirect.com

Critical Review

Classical Conditioning Differences Associated With Chronic Pain: A Systematic Review

Daniel S. Harvie,[*,†] G. Lorimer Moseley,[*,‡] Susan L. Hillier,[*] and Ann Meulders[§,¶]

**Body in Mind Research Group, Sansom Institute for Health Research, University of South Australia, Adelaide, Australia.*
[†]Recover Injury Research Centre, Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia.
[‡]Neuroscience Research Australia, Sydney, Australia.
[§]Research Group on Health Psychology, University of Leuven, Leuven, Belgium.
[¶]Center for Excellence on Generalization Research in Health and Psychopathology, University of Leuven, Leuven, Belgium.

Abstract: **Prominent clinical models of chronic pain propose a fundamental role of classical conditioning in the development of pain-related disability. If classical conditioning is key to this process, then people with chronic pain may show a different response to pain-related conditioned stimuli than healthy control subjects. We set out to determine whether this is the case by undertaking a comprehensive and systematic review of the literature. To identify studies comparing classical conditioning between people with chronic pain and healthy control subjects, the databases MEDLINE, PsychINFO, PsychARTICLES, Scopus, and CINAHL were searched using key words and medical subject headings consistent with 'classical conditioning' and 'pain.' Articles were included when: 1) pain-free control and chronic pain groups were included, and 2) a differential classical conditioning design was used. The systematic search revealed 7 studies investigating differences in classical conditioning between people with chronic pain and healthy control participants. The included studies involved a total of 129 people with chronic pain (fibromyalgia syndrome, spinal pain, hand pain, irritable bowel syndrome), and 104 healthy control participants. Outcomes included indices of pain-related conditioning such as unconditioned stimulus (US) expectancy and contingency awareness, self-report and physiological measures of pain-related fear, evaluative judgements of conditioned stimulus pleasantness, and muscular and cortical responses. Because of variability in outcomes, meta-analyses included a maximum of 4 studies. People with chronic pain tended to show reduced differential learning and flatter generalization gradients with respect to US expectancy and fear-potentiated eyeblink startle responses. Some studies showed a propensity for greater muscular responses and perceptions of unpleasantness in response to pain-associated cues, relative to control cues.**

Perspective: ***The review revealed preliminary evidence that people with chronic pain may exhibit less differential US expectancy and fear learning. This characteristic may contribute to widespread fear-avoidance behavior. The assumption that altered classical conditioning may be a predisposing or maintaining factor for chronic pain remains to be verified.***

Key words: *Classical conditioning, learning deficits, chronic pain, associative learning.*

A.M. is a postdoctoral researcher of the Research Foundation Flanders (FWO-Vlaanderen), Belgium, (grant ID: 12E3714N). G.L.M. is supported by a National Health and Medical Research Council Senior Research Fellowship. This work is supported by National Health and Medical Research Council project grant ID 1047137.

The authors acknowledge that 3 of the included articles were led by coauthor A.M. and that this presents a potential conflict. A.M. was not involved in the search/inclusion process, and was not involved in assessing risk of bias of her own work. The authors have no further conflicts of interest to declare.

Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.

Address reprint requests to Daniel S. Harvie, Griffith University, Gold Coast Campus, Southport, QLD 4222, Australia. E-mail: d.harvie@griffith.edu.au

1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2017.02.430

Identification of the cues in our environment that predict threatening events may be one of the most important adaptations serving survival—it enables early initiation of defensive behavior.[37] The predominant learning paradigm by which certain stimuli become associated with others is that of classical conditioning. The outcome of classical conditioning is apparent when a stimulus that is initially inert (the 'conditioned stimulus' [CS]), results to elicit a behavioral response (the 'conditioned response') because of its repeated pairing with a stimulus (the 'unconditioned stimulus' [US]) that innately elicits a response (the 'unconditioned response').

Classical Conditioning in Theories of Chronic Pain

Although the development of chronic pain is undoubtedly complex and involving a range of biological and behavioral mechanisms summarized elsewhere,[9] a number of prominent theories assign a central role to classical conditioning. Fordyce was the first to propose a role of associative learning in chronic pain, although he mainly focused on the effect of reinforcement on pain behavior (ie, operant conditioning).[10] Gentry and Bernal[12] were the first to present a classical conditioning model of chronic pain (the 'respondent model'), which was later extended by Linton et al.[25] This model starts off with the observation that acute pain, an US, elicits a number of unconditioned responses such as fear and muscle tension, which renders it an important motivator for learning. The model then proposes that stimuli (such as movements) repeatedly paired with pain can function as conditioned stimuli that in turn start to elicit conditioned responses. The model further suggests that if the conditioned responding manifests as elevated anxiety, then people become more sensitive to noxious stimuli.[25] If the conditioned responding manifests as protective muscle activity, then pain is evoked by secondary activation of nociceptive pathways.[12,25]

Today, several prominent models outlining the development and maintenance of chronic pain continue to attribute a fundamental role to classical conditioning. The fear-avoidance model (FAM), for example, emphasizes the role of conditioned fear responding in driving avoidance behavior, to which it attributes the deconditioning, disability, and distress components of the chronic pain problem.[50,51] The FAM is one of the most influential chronic pain-related models of our time, with citations of seminal papers surpassing 2,800.[50] The biobehavioral model incorporates the FAM, and also assigns a role for classical conditioning driving long-term protective muscle activity, which in turn causes pain via nociceptive pathways.[9] Two recent models propose a role for classical conditioning in altering perceptual processes, leading to a more direct effect on pain (the imprecision hypothesis[41]; failed perceptual discrimination pathway[52]). These models suggest that pain itself might become a conditioned response[41]; or that conditioned stimuli themselves might be perceived as aversive in a way no longer perceptibly distinct to painful, noxious unconditioned stimuli.[52] Although both models were only released in 2015, each has been cited more than 20 times. Further demonstrating the perceived relevance of classical conditioning to chronic pain, a recent survey of more than 1,000 clinicians suggested that 83% of clinicians believe classical conditioning can result in pain in the absence of nociception.[28]

The Directional Hypothesis

The nature or intensity of a painful event does not strongly relate to the development of chronic pain,[5] suggesting that it is not the event, but an individual's biological and behavioral response to the event, that contributes to chronicity. Because responses to painful events may be seen as adaptive or nonadaptive, it follows that only nonadaptive responses should contribute to nonadaptive outcomes like chronic pain. The theory being tested by this review suggests that if altered classical conditioning is one of the keys to chronicity, as it is often purported to be, then people with chronic pain should show a conditioning response that is different and less adaptive than that observed in healthy control subjects. The critical component of adaptive pain-related classical conditioning is the ability to effectively learn and respond to predictors of harm but refrain from responding to cues that are not predictive of impending harm (ie, safety cues). Failure to discriminate between cues of harm and safety has been shown to result in prolonged, free-floating, threat-related anticipation.[1,13,34,36,48] Thus, maladaptive pain-related classical conditioning may not be a result of exaggerated conditioned responses to threat-related cues, but rather a failure to inhibit fear responding in the presence of safety cues. Well controlled fear conditioning studies use a 'differential' design, whereby 2 conditioned stimuli are used, one stimulus (CS+) is paired with the aversive stimulus and the other (the CS−) is not. After conditioning, the difference between CS+ and CS− responses can be used to evaluate the subject's ability to identify and respond to discrete predictors of harm, and to inhibit responding to safety cues also present in the experimental context. Among the anxiety literature, initial predictions that anxious individuals would show enhanced conditioning, as defined by higher responses to the CS+, have generally not been supported. Rather, with some exceptions,[42] anxious individuals have instead shown greater responding to conditioned safety cues, manifesting as reduced selective or 'differential' conditioning.[4,26]

The primary aim of this review therefore, was to evaluate the evidence for altered differential classical conditioning in people with chronic pain relative to healthy control subjects. We hypothesized that, relative to healthy control subjects, chronic pain patients would show impaired ability to selectively learn and respond to threat-related cues (CS+) and not safety cues (CS−), whether evaluated using contingency awareness (operationalized as one's ability to verbalize the relationship