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Uncertainty in a context of pain: disliked but also more painful?

Jonas Zaman\textsuperscript{a,*}, Lukas Van Oudenhove\textsuperscript{b,c}, Johan W.S. Vlaeyen\textsuperscript{b,d}

1. Introduction

Pain is part of a motivational system that urges the individual to take action when the integrity of the body is challenged.\textsuperscript{37} Although regularly updated information available from the internal and external environment is used to estimate the risk for such bodily threat, this process is fraught with uncertainties. Indeed, patients may dwell on the cause of their pain, its meaning, their future, when the next pain episode will occur, the intensity of their pain, or how to control it.\textsuperscript{8} Uncertainty denotes “a lack of sureness about someone or something and may range from a falling short of certainty to an almost complete lack of conviction or knowledge, especially about an outcome or result” (Merriam-Webster.com Dictionary, s.v. “uncertainty,” accessed July 15, 2020, https://www.merriam-webster.com/dictionary/uncertainty). Many different situations may give rise to uncertainty, of which unpredictability and uncontrollability are the most pertinent.\textsuperscript{23} When living with pain, uncertainty can emerge at different levels and through different origins that can affect the experience and impact of chronic pain.\textsuperscript{23} For instance, patients with pain might experience high levels of uncertainty because of the ambiguity of their pain (eg, is it a sign of a life-threatening condition or not?), because of an inability to explain its origin (ie, lack of knowledge), or because of conflicting treatment information (ie, inconsistency, rest on keeping on moving). In clinical studies, uncertainty has been related to various negative behavioral outcomes.\textsuperscript{16–20,28,38} It is often suggested that uncertainty also aggravates pain perception, yet endeavors to investigate the relationship between uncertainty and pain perception in experimental settings have yielded mixed findings. This article aims to summarize research on this matter in an attempt to identify potential methodological and conceptual challenges to inspire future research.

2. Unpredictability

Uncertainty is a broad concept that transcends a single source of origin. Nevertheless, endeavors to investigate its effect on pain perception have often reduced it to the issue of unpredictability. It is well known that both humans and animals have a strong preference for situations that enable them to predict aversive events,\textsuperscript{1,25} and that the inability to do so can have an extensive impact on an emotional, behavioral, and motivational level.\textsuperscript{1,10,22,25,27} Unpredictable pain can result in increased stress, a general state of arousal, and sustained levels of anxiety.\textsuperscript{15,34} In an attempt to refine the concept of anxiety, Imada and Nagelish\textsuperscript{17} proposed 9 different manipulations to alter uncertainty (Table 1), some of which can be grouped into 2 classes as proposed by Miller: those that foster prediction accuracy about the exact moment of occurrence (called onset predictability) and those that manipulate information about the characteristics of the aversive stimulus, such as its location, duration, or intensity (termed event predictability).\textsuperscript{25}

3. Uncertainty in a Bayesian framework

Efforts to investigate the effects of uncertainty on pain perception predominantly used a dichotomous approach comparing pain ratings between predictable and unpredictable conditions. The assumption in those studies is that the compared conditions differ only in terms of uncertainty levels. However, as we will argue, this is often not the case, especially for studies that relied on manipulations of event predictability. Before elaborating hereupon, we first introduce the concept of perception as a Bayesian process.\textsuperscript{16,30} Here, perception is considered the active inference of sensory input based on prior beliefs (Fig. 1). Specific sensory inputs are more likely than others for a given physical stimulus, resulting in a probability distribution called the likelihood. Here, the issue of uncertainty is implemented by assigning different probabilities to a set of possible stimuli. This probability distribution captures that different stimuli could have caused the sensory input and that this is more likely for some stimuli than others. Furthermore, expectations about which stimuli are more likely are represented by another probability distribution called the prior. It is the combination of sensory input (likelihood) with prior information (prior) that drives perception (ie, the posterior). For example, a high-intensity pain cue will shift the prior to the expected sensation. When the expectation corresponds with the sensory input (ie, the prior strongly overlaps with the likelihood), the perception will become more certain (ie, the posterior becomes narrower). However, when the expectation does not match the sensory input, the perception will shift in the direction of the prior (Fig. 1).

4. The role of expectancies

Prior beliefs do not remain naive and stable because they incorporate the experience gained across subsequent events, where the posterior becomes the prior for the next pain episode.

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Because of this generative updating process, humans do not remain naive in most experimental, unpredictable conditions but acquire expectations about upcoming pain. That is, the prior will evolve towards a wide distribution reflecting some degree of uncertainty with a peak that centers around the mean pain intensity resulting in a regression-to-the-mean effect.\textsuperscript{16,30} In several experimental studies, a custom method is to compare pain ratings between predictable and unpredictable pain using cues. The predictable cue reliably signals the same stimulus intensity (stimulus A), whereas the unpredictable cue is followed by stimuli of different pain intensities (stimulus A or B). Depending on the intensity of stimulus B in the unpredictable condition, the mean of the prior for the unpredictable cue will be positioned at a higher (or lower) location compared with the prior for the predictable cue, reflecting differences in acquired expectations (Fig. 1). Next, if a test stimulus is presented that is below the mean of the prior in the uncertain context, it will be perceived as more intense compared with the certain condition (where the prior and likelihood overlap). The opposite can be expected when the test stimulus is located above the prior in the uncertain context. Hence, depending on which stimulus intensities are used and which stimuli are compared between conditions, inferences can be opposite with the apparent conclusion that uncertainty is related to more or less pain or no difference at all (Fig. 1).

Thus, the contrasted conditions not only differ regarding uncertainty levels but, more importantly, can also differ on the acquired expectations. As a consequence of this methodological intertwining of 2 processes, it is impossible to disentangle the effects attributed to uncertainty vs those due to differences in expectations. In other words, the effects of uncertainty on pain perception are confounded by expectancies. For instance, Brown et al.\textsuperscript{4} included 3 stimulation intensities that were preceded by either a cue that correctly signaled the intensity or a cue that signaled a 33\% probability of receiving a low-, a moderate-, or a high-intensity stimulus. From a Bayesian perspective, the prior of the unpredictable cue is expected to

<table>
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<tr>
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<td>Event</td>
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<td>Fixed vs variable cue quality, pattern, and locus</td>
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Table 1. Taxonomy of manipulations to make a situation uncertain.

Figure 1. Perception as a Bayesian inference process: Expectations (the prior) and sensory input (the likelihood) are precision averaged into a percept (the posterior). Depending on which 2 conditions are compared, conclusions about the role of uncertainty differ. In this theoretical example, the uncertain cue had an equal probability of being followed by either a low- or a high-noxious stimulus (NSL [upper row] or NSH [lower row]). As a consequence, more pain is expected in the uncertain condition when a low-noxious stimulus is presented, and less pain is expected when a high-noxious stimulus is presented compared with when both stimuli are correctly cued. When another stimulus is presented than those used during training (ie, medium-noxious stimulus), again differential effects are expected depending on whether the uncertain condition is compared with cued low or high pain. Note that in these scenarios, the effects originate because of a shift in the posterior in both cued (predictable) conditions.
be centered around the moderate-intensity stimulus, reflecting the average of all possible stimuli intensities. The priors for each predictable cue are expected to be located at the corresponding stimulus intensities. As a consequence, the expected average pain level (the mean of the prior) will be (1) higher in the unpredictable cue compared with the low-intensity cue, (2) similar to the expected pain level for the moderate-intensity cue, and (3) lower compared with the high-intensity cue. They found (1) higher ratings for the non-noxious stimulus when preceded by the 33% cue compared with the low-intensity cue, (2) equal pain ratings for the moderate-intensity noxious stimulus between both cues, and (3) lower pain ratings for the high-intensity noxious stimulus when preceded by the unpredictable cue.4 Attributing the differential effects to an aggravating pain effect of uncertainty is difficult, whereas they can be easily understood from a Bayesian perspective. In a conditioning experiment by Lin et al., one of 2 cues was always followed by a low-intensity noxious stimulus. The other cue was followed by either the same stimulus or a high-intensity noxious stimulus (ratio 50%–50%), which should result in a prior with a higher mean pain expectancy. They found that the low-intensity noxious stimulus was perceived as more painful when uncertainty was high.21 In yet another study, participants received innocuous and noxious stimuli in a predictable and unpredictable manner. Higher ratings were found for the noxious and lower ratings for the innocuous stimulus when their intensity was predictable.42 Given the precise prior expectations, these results are in line with the proposed framework. However, other studies found overall higher pain ratings when stimuli were presented in blocks of variable compared with fixed intensities.29,32 In this context, model extensions such as the recent 2-process model of Press et al. may be especially interesting. Here, a Bayesian account is combined with a learning process where prediction errors (determined by the overlap between the prior and posterior) influence the perception of certain events depending on its size.31

Within the Bayesian framework, uncertainty regarding future outcomes is reflected by the width of the prior. The more uncertain we are about a future event, the wider the prior, and the lower its influence on the posterior will be. That is, following the principles of Bayes’ rule, information is combined optimally. Both sensory input and expectations are precision weighted such that information with the lowest uncertainty will have the most substantial influence on the posterior. In the most extreme scenario, a uniform prior exists such that all events have an equal probability. As a consequence, perception (the posterior) will be solely determined by the sensory input (the likelihood). Only a few studies have tried to investigate the effects of uncertainty by only affecting the width (and not the mean of the distribution) of the prior. Yoshida et al. attempted to investigate the effects of uncertainty while ensuring similar average expectations between conditions using a vicarious learning paradigm in a small sample (N = 13).43 Before the stimulus presentation, participants saw 8 fictitious pain ratings of previous participants as a cover story. The authors found that high levels of uncertainty (i.e., fictitious ratings with large variation) led to higher pain ratings regardless of in which direction the vicarious information was manipulated.40 However, a recent study failed to replicate their finding in a larger sample (N = 40).41

Another way to induce uncertainty, where differences in expected pain levels between conditions are less likely to occur, is to manipulate onset predictability. In those paradigms, participants have information about the stimulus intensity, but their ability to predict its onset varies between conditions. The bulk of onset predictability studies did not found any effect of unpredictability on pain perception,2,6,7,11–15,33,39 with a few exceptions.5,9,24 However, in one of those studies, pain ratings were only obtained in between blocks instead of after each stimulus presentation, which may have affected intensity ratings.38 Also, these studies did not control for differences in anticipation duration, which seems to be an important factor, as effects of onset predictability disappeared when ensuring similar periods of pain anticipation between conditions.45 Collectively, and contrary to the common idea that uncertainty amplifies the perception of pain, there is currently little experimental evidence for a direct influence of uncertainty on self-reported pain ratings.

5. Uncertainty is more than unpredictability
Furthermore, as already mentioned, uncertainty cannot be reduced to unpredictability and encompasses several other components. For example, patients with chronic pain can differ not only in the extent to which they perceive pain as unpredictable but also in how they conceive the origin of their pain. For instance, a patient with low back pain might have learned that the execution of a certain movement will trigger pain onset but may lead him to worry about his future (e.g., ability to continue hobbies and maintenance of job). In other patients, the uncertainty originates from the absence of clear cues signaling pain increases or the inability to predict the course and the duration of a pain episode. However, systematic research on these different aspects is currently lacking. Furthermore, a conceptual challenge that may limit the generalizability of experimental work on uncertainty to real life is the issue of controllability. Persons do not volunteer to develop a chronic pain state, with little control over their pain or the ability to escape the situation. Participants in experiments, on the contrary, volunteer to experience pain, knowing that they can escape from the situation at any time point (for a review on the effects of controllability, see Ref. 26). Besides, experimentally induced pain differs in many more aspects that affect uncertainty levels compared with the pain in real life. For instance, pain in an experimental context does not lead to ambiguity over its meaning, its origin, or its implications. Furthermore, participants receive explicit information (for ethical reasons) that their pain will be within the threshold of tolerance and safety, which is not the case outside of experimental situations.

At this point, it seems that pain uncertainty in experimental settings does not directly affect pain perception, although there is evidence that uncertainty aggravates the overall impact of chronic pain on patients’ lives. Furthermore, researchers should be aware that certain manipulations of uncertainty can simultaneously affect expectations that also influence the reported pain intensities. In addition, not only have few studies considered pain expectancies on whether and how uncertainty impacts pain reports, the research so far has neglected the influence of expected vs unexpected uncertainty itself. Based on prior information, individuals may expect the course of pain to be uncertain, which may have different consequences as compared to unexpected uncertainty. The research on such meta-uncertainty is an emerging field that still has to be explored in pain science.30 Finally, the relationship between pain uncertainty (both overall levels and different types) and pain reports, as well as focus on other outcomes (e.g., disability levels and quality of life) in daily contexts requires further scientific attention, to better understand how individuals protect themselves against bodily threat in an uncertain environment.

Conflict of interest statement
The authors have no conflicts of interest to declare.
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