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Multiple potential mechanisms for context effects on pain[☆]

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How we experience events is critically dependent on our conceptual knowledge about them. Pain experience is no exception: it is shaped by expectations and beliefs, attentional focus, and social context [1–4]. Some painful events may even be associated with approach behavior and rewarding experiences. In these cases—whether it is habanero sauce on your eggs or the burn of your biceps as you curl a weight—nociceptive signals might even be perceived as pleasurable.

Leknes et al. [5] report upon a fascinating example of meaning-related pain modulation. They manipulated whether a normally painfully hot stimulus was the better or worse of two potential outcomes, thereby assessing effects of the *relative value* of the stimulus on pain and physiology. In the *control context*, moderate-intensity heat was intermixed with non-painful warmth. In the *relative-relief context*, moderate-intensity heat was intermixed with intensely painful stimuli. They compared fMRI, skin conductance, and subjective responses to the identical, moderate-intensity stimulus in each condition. Moderate-intensity stimuli were rated as painful in the control context, but as *pleasant* sensations in the relative-relief context. Both skin conductance and activation in some key pain-processing regions [6–8]—in particular, the anterior cingulate and anterior insula—were reduced in the relative-relief compared to the control context. Conversely, the ventromedial prefrontal cortex (vmPFC), showed increased activation in the relative-relief vs. control context.

Leknes et al. interpret the findings as reflecting a supraspinal mechanism involving descending modulatory control over nociception. They suggest that moderate pain in the relative-relief context activated the brain's reward circuitry, which in turn inhibited activation of pain-processing regions. In support of this view, the vmPFC—which is densely connected with the periaqueductal gray (PAG) and other nuclei that provide descending control of noxious input [9–14]—is activated in a number of studies of context-based pain

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modulation. The VMPFC is also an important contributor to valuation and reward processing [15,16], along with other types of affective meaning [17]. Pain and reward processing also appear to have inhibitory effects on each other [18], perhaps because they engage competing behavioral drives [19]. Some additional findings support this conclusion as well. Though there was no effect of context on PAG activity overall, individuals with larger pain-suppressive context effects activated PAG more strongly in the relative-relief context. Connectivity between the PAG and the nucleus accumbens/ventral striatum was also more positive in the relative-relief context.

While these results are all broadly consistent with activation of a circuit that involves descending inhibition, the results present a curious puzzle to be solved, which motivates the search for additional mechanisms. In Leknes et al.'s study, the least pain was experienced when the greatest pain was expected. In the relative-relief context, participants were essentially conditioned to expect higher pain overall, but they reported less pain in this context. This finding directly contrasts with placebo and expectancy effects in other paradigms, in which high pain expectancy leads to *increased* pain [20–22]. For example, in two recent studies [20,21], high-pain cues were followed by high-intensity or moderate-intensity heat, and low-pain cues were followed by low-intensity or moderate-intensity heat. Just as in Leknes et al.'s study, the two moderate-intensity conditions were compared so as to isolate context effects—but in these studies, the high-pain context caused a reliable *increase* in the painfulness of the moderate-intensity stimuli.

One possible explanation for the opposing findings involves the *temporal dynamics* of pain. Repeated exposure to noxious stimuli can change their painfulness [23], as a result of either peripheral adaptation or affective learning in the central nervous system [24]. For example, pain typically decreases (i.e., habituates) over the course of a series of noxious stimuli. This has been attributed to the suppression of peripheral nociceptive fibers with repeated stimulation [25–29]. Unlike the predictive-cueing studies mentioned above [20,21], the two context conditions in Leknes et al.'s study were run in blocks with systematically different intensities. High-intensity stimuli in the relative-relief condition could have produced greater peripheral adaptation than the warm stimuli in the control condition [27].

The adaptation effects that might underlie Leknes et al.'s effects could be peripheral or central in origin, and might be important phenomena that are distinct from interactions between ‘reward’ and pain. Peripheral habituation occurs with repeated stimulation on the same skin site and appears to be temperature-dependent [30,31]. How much of Leknes et al.'s ‘relief’ effect is peripheral is currently unclear, but assessing its specificity to the site of repeated skin stimulation could provide valuable clues. A second possible cause of Leknes et al.'s effect is *central adaptation* processes distinct from reward. It is well established that noxious stimuli can activate descending opioid and non-opioid regulatory systems, depending on the type, location, and duration of the stimulus [32,33]. In some cases, this effect—termed ‘stress-induced analgesia’—can be accomplished without any contribution from regions rostral to the brainstem [32,34], although forebrain regions may contribute in intact animals. Thus, it is possible that habituation itself could reflect descending control over nociception. Whether peripheral or central, an intriguing possibility is that the effects

observed by Leknes et al. are not related to the meaning context, but to the dynamics of nociception itself.

If this is the case, then how might the fMRI changes in vmPFC, PAG, and ventral striatum—which are plausibly linked to meaning, reward, and forebrain-induced descending control—be explained? This is an important question that the field needs to address. While the vmPFC is activated by a range of studies consistent with conceptual meaning [17,35], vmPFC activation also increases with repeated exposure to noxious stimuli, paralleling the development of habituation effects [36,37]. Increases in vmPFC activation, like context-driven analgesia, could be a feature of nociception or pain itself. The vmPFC is a prominent part of the “default mode network,” which is active at rest and reliably de-activated by tasks that require attention to sensorimotor events [38,39]. A large part of the vmPFC shows a preference for positively valenced events [17] and is de-activated by negative events [20,40]. Thus, relative increases in vmPFC activity could simply be release of deactivation caused by pain itself, rather than “descending control” *per se*. If pain-related deactivation of vmPFC was shown to be much weaker than the increases caused by the relative-relief context, then a case for meaning-related mechanisms might be made.

The connectivity results are helpful in this regard, but are only part of the story. Leknes et al. found stronger connectivity between the PAG and ventral striatum in the relative-relief context, implying greater forebrain control over the brainstem. This finding offers interesting evidence for an active pro-analgesia forebrain process, *if* a common cause (i.e., noxious input itself) can be ruled out. Unfortunately, the linear regression approach used by Leknes et al. (and nearly all neuroimaging studies) cannot capture subtle temporal dynamics, and thus cannot rule out pain/nociception itself as the driver of connectivity. However, once again, if the effects of meaning context on connectivity were much larger than the effects of stimulus intensity, a case could be made for forebrain interactions with brainstem ‘descending control’ systems.

Overall, Leknes et al. present provocative findings on the modulation of pain by the cognitive and physical context surrounding stimulation. Whether the effects are driven by conceptual value or are more akin to stress-induced analgesia, and whether they are created in the forebrain, brainstem, or periphery, the findings are powerful and surprising. The authors have contributed a novel and welcome piece to the puzzle of how context information shapes and regulates pain.

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