Spotlight

Towards a taxonomy of pain modulations

Markus Ploner[1], Ulrike Bingel[2], and Katja Wiech[3]

[1] Department of Neurology and TUM-Neuroimaging Center, Technische Universität München, 81675 Munich, Germany
[2] Department of Neurology, Essen University Hospital, 45147 Essen, Germany
[3] Nuffield Department of Clinical Neurosciences and Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), University of Oxford, Oxford, OX3 9DU, UK

The subjective experience of pain is affected by various modulating factors, such as the sufferer's level of anxiety or distraction. A recent study sheds light on the neural underpinnings of pain modulation and illustrates how we can advance towards an integrated psychological, neurobiological and clinical taxonomy of pain modulations.

The experience of pain is not a simple reflection of tissue damage but is influenced by a variety of factors ranging from stimulus characteristics to complex processes such as self-regulation and placebo analgesia. These factors all contribute to the impressive variability of the pain experience, whereby the same stimulus that causes excruciating pain in one situation might be barely noticeable in another. In recent years, a number of studies have investigated many different factors that can modulate the experience of pain [1,2]. Together, they convincingly demonstrate that such modulations can affect all levels of the neural hierarchy, ranging from the spinal cord dorsal horn (e.g., [3]) to higher-level brain areas (e.g., [4]). However, a systematic approach to pain modulations is lacking thus far and a valid psychological, neurobiological, and clinical taxonomy of pain modulations remains to be established.

A recent study by Woo et al. [5] highlights how we can progress towards such a taxonomy. Using fMRI, the authors compared brain mechanisms of two fundamentally different types of pain modulation. In a simple experiment, healthy human subjects were instructed to engage in self-regulation strategies to up- or downregulate pain while they were exposed to different levels of noxious heat. Participants' pain intensity ratings confirmed that both the temperature manipulation and the self-regulation strategy influenced how the heat stimulus was perceived. The analysis of brain imaging data in this study capitalized on the authors' previous definition of a neural signature of pain (NPS) in the brain [6] and on recent observations that a fronto-striatal pathway connecting nucleus accumbens (NAc) and ventromedial prefrontal cortex (vmPFC) plays an important role in pain perception and modulation [7]. The results show that, as expected, variation of the heat level led to a graded response in the NPS. However, the voluntary increase or decrease of the pain experience through a

self-regulation strategy showed no corresponding change in the NPS, but was instead mediated via the frontostriatal vmPFC–NAc pathway. These findings provide compelling evidence that fundamentally distinct brain mechanisms can result in similar modulations of the experience of pain. The study is not the first to compare different modulations of pain, however it showcases how recent conceptual advances in our understanding of the cerebral representation of pain (e.g., its highly distributed representation [6], the lack of specificity of pain-related brain activations [8] and the importance of frontostriatal circuits [7]) can be integrated with state-of-the-art fMRI methodologies. Even more importantly, it highlights that we now have the necessary tools and techniques to allow for the investigation of pain and its modulation in a systematic fashion.

The development of a systematic and integrated psychological, neurobiological and clinical assessment of pain modulations will be conceptually challenging and will require an exchange of ideas and approaches across disciplines. Psychologists have already demonstrated that the experience of pain can be impacted by factors such as stress, anxiety, depression, catastrophizing, reappraisal, attention, distraction, mind-wandering, expectations, uncertainty, anticipation - and depending on the school of thought, the list could be even longer. As necessary as this level of differentiation might seem, it raises the question of commonalities and differences between these concepts. Most likely, the many types of pain modulation are not fully independent but converge on a few common key mechanisms. Sharpening and pruning the terminology might help to identify them. Similarly, neuroscientists might not only investigate different types of pain modulation in isolation but might systematically compare them, as demonstrated by Woo et al. [5]. Such direct comparisons and meta-analytic syntheses of neuroimaging data [9] will be critical for the definition of key neural mechanisms underlying pain modulation at all levels of the neural hierarchy. Thus far, studies have provided evidence for a descending pain-modulatory pathway from cortical brain areas via the brainstem to the spinal cord as well as predominantly intra-cortical pathways. Whether these routes are distinct or share commonalities remains to be clarified. Likewise, clinicians might think about similarities, differences and common key mechanisms of their therapeutic arsenal, ranging from different pharmacological treatments to a variety of psychological approaches. The truly interdisciplinary challenge is to bring the psychological, neurobiological, and clinical concepts together. Ideally, classification on one of these levels will facilitate

Corresponding author: Ploner, M. (ploner@lrz.tum.de).

and inspire classification on the other levels. The final goal is a taxonomy of pain modulations that maps key psychological mechanisms onto neural circuits and therapeutic approaches.

Such a taxonomy of pain modulations is highly desirable and promising from both a basic science and a clinical perspective. As pain is extremely liable to different modulations, basic scientists might harness pain to establish an overarching framework of how the brain integrates sensory, affective and cognitive information into a coherent percept. A taxonomy of pain modulations could, thus, complement activities in other modalities (e.g., [10]) and significantly contribute to our understanding of the brain mechanisms of perception. A taxonomy of this kind would be equally promising from a clinical perspective. To tackle the broad range of factors that influence pain, clinicians commonly address it in an interdisciplinary fashion, combining different interventions. It is, however, largely unknown which patients benefit from which therapeutic strategy. Pain therapy is therefore often difficult and its outcome unsatisfactory. A taxonomy of pain modulations could provide a useful framework for the systematic assessment of an individual's pathologies and preferences and thereby help to target specific psychological mechanisms and neural pathways relevant for the individual patient. Thus, the study by Woo *et al.* [5] demonstrates how new approaches can help establish such a taxonomy, which, in turn, may advance our understanding of the neural mechanisms of perception and open new avenues for the personalized prevention and treatment of chronic pain.

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